A Guide to Green Chemistry Experiments for Undergraduate Organic Chemistry Labs

Brought to you by Beyond Benign and My Green Lab through the generous support of MilliporeSigma

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Introduction

Overview of Resource Guide

In the organic chemistry laboratory, green chemistry serves as a means for reducing hazards and waste in the laboratory course, while maintaining the necessary rigor for teaching the subject. Through a partnership with Beyond Benign, My Green Lab, and MilliporeSigma, a resource guide has been developed for integrating green chemistry in the organic chemistry laboratory course. It is our hope this will facilitate the widespread adoption of green chemistry in the standard undergraduate curriculum.

The purpose of this guide is to provide examples of green chemistry experiments that may serve as substitutions for classic undergraduate organic chemistry laboratory experiments. Discussions pertaining to the measurable benefits resulting from implementing greener alternative organic chemistry labs are provided, which include waste reduction, economic benefits, and hazard reduction.

For each experiment, a detailed experimental protocol is provided, along with an explanation as to why the substitution is considered to be more sustainable, and a TA guide complete with example lab questions. It provides multiple pathways for adopting greener labs and points faculty members to options that can be tailored to suit the needs of their own department, and their own courses. The guide also provides an assessment of some qualitative benefits of green chemistry implementation, including energy efficiency, use of renewable resources, and use of safer solvents.

While each experiment may stand on its own, they were designed to be highly modular to allow for facile adoption into existing curricula. We encourage you to use this guide as a starting point, and build upon this framework to suit the needs and unique format of your teaching laboratory.

Acknowledgements

The resource guide has been developed through a collaboration of Beyond Benign, MilliporeSigma, My Green Lab, and a network of chemistry faculty from throughout North America. All experiments are adapted directly from the literature publications, and have not been created or are not owned by any of the organizations that created this guide. Some text included in the introduction and teaching assistant guide, and select example quiz questions have also been adapted directly from the original publication introduction, discussion, and supporting information. Full credit is given to the author and journal of each, and references are provided accordingly.

About Beyond Benign

Beyond Benign is a non-profit organization dedicated to green chemistry education. We disseminate green chemistry concepts and best practices globally to science educators, scientists and the public at large through our education programs that are designed to teach and demonstrate green chemistry principles. Beyond Benign would like to thank Amy Cannon, Alicia McCarthy, and Derrick Ward for their contributions to this guide.

About My Green Lab

My Green Lab works to reduce the environmental impact of laboratories by fostering collaboration between scientists, students, sustainability directors, environmental health and safety personnel, procurement, vendors, and regulatory agencies. A 501c3 non-profit, My Green Lab has set standards for labs across North America with a Green Lab Certification program, and for products sold into labs through work with the EPA, ENERGY STAR®, and creation of the ACT Label. My Green Lab would like to thank Erika Daley for her contributions to this guide.

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Methodology used for Quantitative and Qualitative Assessment

Each reaction has been measured by quantitative and qualitative means. The quantitative assessment includes a volume of waste estimate, and an environmental, health and safety assessment. The qualitative assessment includes the flagging of the reaction for the following green chemistry principles: use of renewable feedstocks, energy efficiency, catalysis, safer solvents and auxiliaries, and accident prevention. Each estimate includes assumptions and are based on widely available data-sets and/or resources, which are outlined further below.

Qualitative Assessment

Chemicals and chemical reactions are flagged for the following qualitative benefits: less hazardous chemical synthesis, use of renewable feedstocks, energy efficiency, catalysis, safer solvents and auxiliaries, and accident prevention. Each qualitative endpoint is described further:

Qualitative Endpoint	Icon	Criteria
Less Hazardous Chemical Synthesis	⚠	Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
Renewable Feedstocks	🌿	The chemical can be derived from a renewable feedstock. For example: ethanol can be derived from bio-based feedstocks
Energy Efficiency	🔌	The reaction uses comparatively less energy than the traditional reaction procedure. For example: the grinding of two reagents at room temperature using a mortar and pestle versus heating to reflux.
Catalysis	🕒	The use of catalytic reagents as opposed to stoichiometric reagents.
Safer Solvents and Auxiliaries	⚗	The use of safer solvents as compared to traditional alternatives (see Safer Solvent section).
Accident Prevention	✚	The avoidance of the use of substances that have potential for chemical accidents, including releases, explosions and fires. For example: avoiding the use of a pyrophoric reagent

Volume of Waste Estimate

This analysis is based on the assumption that all solvents, reagents and products will be transformed to waste products. We understand that some products will be used as starting materials for a subsequent reaction. However, in our assessment, we are assuming that the product will be minimal in relation to the waste created and that the products are eventually discarded as waste. We have made note of where aqueous waste is created that can be neutralized before disposal, which may decrease the amount of liquid waste disposed.

Environmental, Health and Safety (EH&S) Assessment

While EH&S assessments can typically be viewed as qualitative, we have attempted to use "quantifiable" tools, such as the National Fire Protection Association (NFPA)[1] categories, Global Harmonized System (GHS), Registry of Toxic Effects of Chemical Substances through ToxPlanet Database[2], Pharos[3], and GreenScreen® for Safer Chemicals[4] as metrics for more rigorously measuring the environmental, health and safety hazards of each chemical. The environmental, health and safety assessment is broken into three categories: physical hazards (including skin corrosion), human health hazards (including both chronic and acute mammalian toxicity), and PBT (persistence, bioaccumulation, and aquatic toxicity). These three categories are used as indicators of the health and safety of the chemical.

EHS Key:

🟨	**Physical hazard**	🟥 *	**Very high hazard**
🟨	**Toxicity/Health hazard**	🟥	**High hazard**
⬜	**Persistent Bioaccumulative Toxic (PBT) Chemicals**	🟨	**Moderate hazard**
		🟩	**Low hazard**
		⬜	**No data**

An example of the EH&S chart included with each experiment is below.

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Ethanol 459836	(varies)	🟥 🟨 🟩
Water n/a	(varies)	🟩 🟩 🟩

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[1] NFPA, Flammable and Combustible Liquids Code, http://www.nfpa.org/codes-and-standards/all-codes-and-standards/list-of-codes-and-standards?mode=code&code=30 [Accessed February 2017]

[2] ToxPlanet; https://toxplanet.com/ [Accessed February 2017]

[3] Pharos, https://www.pharosproject.net/ [Accessed February 2017]

[4] GreenScreen® for Safer Chemicals, http://www.greenscreenchemicals.org/ [Accessed February 2017]

Physical Hazards

The physical hazards include the flammability, reactivity, and corrosive nature of the chemical as indicators of the physical hazards the chemicals present.

Flammability

This assessment is based on the NFPA categories for flammability as follows:

Human Health Rating	NFPA Rating	Degree of Flammability
Low	0	Materials that will not burn (materials that will not burn in air when exposed to a temperature of 820 °C for a period of 5 minutes)
Low	1	Materials that must be preheated before they will ignite (flash point at or above 93.3 °C)
Moderate	2	Materials that must be moderately heated or exposed to relatively high ambient temperatures before they will ignite (flash point between 37.8 and 93.3 °C)
High	3	Liquids and solids that can ignite under almost all temperature conditions (Liquids having a flash point below 22.8 °C and having a boiling point at or above 37.8 °C or having a flash point between 22.8 and 37.8 °C)
Very High	4	Materials which will rapidly vaporize at atmospheric pressure and normal temperatures, or are readily dispersed in air and which burn readily (includes pyrophoric substances. Flash point below room temperature at 22.8 °C)

Reactivity

This assessment is based on the NFPA categories as follows:[5]

Human Health Rating	NFPA Rating	Degree of Reactivity
Low	0	Materials that are stable even under exposure to fire. Technical Criteria: Materials that have an instantaneous power density (product of heat of reaction and reaction rate) at 250°C below 0.01 W/mL
Low	1	Materials that are normally stable, but become explosive at elevated temperatures and pressure. Technical Criteria: Materials that have an instantaneous power density (product of heat of reaction and reaction rate) at 250°C at or above 0.01 W/mL and below 10 W/mL
Moderate	2	Materials that readily undergo a violent reaction, but do not explosively decompose. Technical Criteria: Materials that have an instantaneous power density (product of heat of reaction and reaction rate) at 250°C at or above 10 W/mL and below 100 W/mL
High	3	Materials that are prone to explosive decomposition, but require an ignition source or will react explosively with water. Technical Criteria: Materials that have an instantaneous power density (product of heat of reaction and reaction rate) at 250°C at or above 100 W/mL and below 1000 W/mL. Materials that are sensitive to thermal or mechanical shock at elevated temperatures and pressures.
Very High	4	Materials that are prone to explosive decomposition at normal temperatures and pressure. Technical Criteria: Materials that have an instantaneous power density (product of heat of reaction and reaction rate) at 250°C at 1000 W/mL or greater. Materials that are sensitive to localized thermal or mechanical shock at normal temperatures and pressures.

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[5] National Fire Protection Association (NFPA), Codes and Standards, https://www.nfpa.org/codes-and-standards/all-codes-and-standards/list-of-codes-and-standards/detail?code=704 [Accessed January 2018]

Corrosivity (Skin)

This assessment is based on the GHS categories for Skin Corrosivity as follows:

Human Health Rating	GHS Rating	Degree of Corrosivity
Low	N/A	No listing or phrases
Moderate	Category 1C	> 1 hour and ≤ 4 hours exposures and ≤ 14 days observations; pH extremes of ≤2 and ≥ 11.5 including acid/alkali reserve capacity.
High	Category 1B	>3 minutes ≤ 1 hour exposure and ≤ 14 days observations; pH extremes of ≤2 and ≥ 11.5 including acid/alkali reserve capacity.
Very High	Category 1A	≤ 3 minutes exposure and ≤ 1 hour observation; pH extremes of ≤2 and ≥ 11.5 including acid/alkali reserve capacity. Hazard Phrase: H314

Human Health Hazard

Human health hazard data can be gathered from SECTION 11 (Toxicological Information) on Globally Harmonized Safety Data Sheets, which can be obtained from Sigma-Aldrich [http://www.sigmaaldrich.com/united-states.html]. Both acute and chronic toxicity endpoints are listed. The human health hazard is assessed based on a selection of data from the GreenScreen® for Safer Chemicals[3] criteria for acute human health, and chronic human health hazards. The European Union Risk and Hazard Statements[6] are also used to determine low, moderate, high and very high hazard.

Hazard Level	Acute Mammalian Toxicity Criteria:
Very High	GHS Category 1 or 2; Risk Phrases R26, R27, R28; Hazard Phrases H300, H310, H330; Technical Criteria: Oral LD50 ≤ 50 mg/kg; Dermal LD50 ≤ 200 mg/kg; Inhalation (g) LC50 ≤ 500 ppm; Inhalation (v) LC50 ≤ 2 mg/l; Inhalation (dust, mist) LC50 ≤ 0.5 mg/l; NFPA Health 4
High	GHS Category 3; Risk Phrases R23, R24, R25; Hazard Phrases H301, H311, H331; Technical Criteria: Oral LD50 > 50 but ≤ 300 mg/kg; Dermal LD50 > 200 but ≤ 1,000 mg/kg; Inhalation (g) LC50 > 500 but ≤ 2,500 ppm; Inhalation (v) LC50 > 2.0 but ≤ 10.0 mg/l; Inhalation (dust, mist) LC50 > 0.5 but ≤ 1.0 mg/l; NFPA Health 3
Moderate	GHS Category 4; Risk Phrases R20, R21, R22; Hazard Phrases H302, H312, H332; Tech. Criteria: Oral LD50 > 300 but ≤ 2,000 mg/kg; Dermal LD50 > 1,000 but ≤ 2,000 mg/kg; Inh. (g) LC50 > 2,500 but ≤ 20,000 ppm; Inh. (v) LC50 > 10.0 but ≤ 20.0 mg/l; Inh. (dust, mist) LC50 > 1.0 but ≤ 5.0 mg/l; NFPA
Low	GHS Category 5; Hazard Phrases H303, H313, H333; Technical Criteria: Oral LD50 > 2,000 mg/kg; Dermal LD50 > 2,000 mg/kg; Inh. (g) LC50 > 20,000 ppm; Inh. (v) LC50 > 20.0 mg/l; Inh. (dust, mist) LC50 > 5.0 mg/l

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[6] Sigma-Aldrich, GHS Hazard Statements, https://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/promo_NOT_INDEXED/General_Information/1/h_overview.pdf [Accessed February 2017]

The following chronic toxicity endpoints are flagged for toxicity based on risk and hazard statements, as well as Globally Harmonized System (GHS) categories: carcinogenicity (C), mutagenicity/genotoxicity (M), neurotoxicity (N), sensitization (S), reproductive toxicity (R), developmental toxicity (D), and endocrine activity (E).

Hazard Level	**Chronic Toxicity Criteria:**
High	*Carcinogenicity:* Risk Phrases - R45 or R49; Hazard Phrases - H350 or H350i; *Mutagenicity/Genotoxicity:* GHS Category 1A or 1B; Risk Phrases - R46; Hazard Phrases - H340; *Reproductive Toxicity:* GHS Category 1A or 1B; Risk Phrases - R60; Hazard Phrases - H360F, H360FD, H360Fd; *Developmental Toxicity:* GHS Category 1A or 1B; Risk Phrases - R61 or R64; Hazard Phrases - H360D, H360FD, HD360Df, H362; *Sensitization, Respiration*: GHS Category 1A and 1B; Hazard Phrase- H334; *Sensitization, Skin* Category 1A; Hazard Phrases – H317; *Neurotoxicity (Repeated exposure)*- GHS CNS Category 1 or 2; 90-day rat inhalation (vapor) study < 0.2 (mg/L/6h/day); *Endocrine*- Substances listed on the EU – SVHC Authorization List for Endocrine Activity
Moderate	*Carcinogenicity:* Risk Phrases - R40; Hazard Phrases - H351; *Mutagenicity/Genotoxicity:* GHS Category 2; Risk Phrases - R68; Hazard Phrases - H341; *Reproductive Toxicity:* GHS Category 2; Risk Phrases - R62; Hazard Phrases - H360, H361f, H361fd; *Developmental Toxicity:* GHS Category 2; Risk Phrases R63; Hazard Phrases H360Fd, H361d, H361fd; *Sensitization, Respiration*: Risk Phrases – R42; *Sensitization, Skin* Category 1B Risk Phrases- R43; *Neurotoxicity (Repeated exposure)*- GHS CNS Category 3, 90-day rat inhalation (vapor) study 0.2—1.0 (mg/L/6h/day); Risk Phrase R67; Hazard Phrase – H336; *Endocrine* - indication of Endocrine Activity in the scientific literature; Substitute It Now (SIN) List or TEDX Potential List
Low	*Carcinogenicity:* no risk or hazard phrases; *Mutagenicity/Genotoxicity*: No listings or phrases; *Reproductive Toxicity:* No listings or phrases; *Developmental Toxicity:* No listings or phrases; *Sensitization, Respiration*: No listings or phrases; *Sensitization, Skin*: No listings or phrases; *Neurotoxicity* – No listings or phrases; 90-day rat inhalation (vapor) study > 1.0 (mg/L/6h/day); *Endocrine Activity*- no listing.

Aquatic Toxicity

The aquatic toxicity endpoint is used as an indicator for environmental hazard and is based on acute aquatic toxicity data. If chronic and acute toxicity had different GHS categories, the worst-case scenario was taken as the final score. The criteria are based on a selection of the GreenScreen® for Safer Chemicals criteria for acute aquatic toxicity and includes GHS categories, risk and hazard phrases, and technical data as follows:

Hazard Level	**Acute Aquatic Toxicity Criteria:**
Very High	GHS Category 1; Risk Phrases R50, Hazard Phrases H400; Technical Criteria: 96 hr LC50 (fish) ≤ 1 mg/l, 48 hr EC50 (crustacea) ≤ 1 mg/l, 72 or 96 ErC50 (algae) ≤ 1 mg/l
High	GHS Category 2; Risk Phrases R51, Hazard Phrases H401; Technical Criteria: 96 hr LC50 (fish) > 1 but ≤ 10 mg/l, 48 hr EC50 (crustacea) > 1 but ≤ 10 mg/l, 72 or 96 ErC50 (algae)> 1 but ≤ 10 mg/l
Moderate	GHS Category 3; Risk Phrases R52, Hazard Phrases H402; Technical Criteria: 96 hr LC50 (fish) > 10 but ≤ 100 mg/l, 48 hr EC50 (crustacea) > 10 but ≤ 100 mg/l, 72 or 96 ErC50 (algae) > 1 but ≤ 100 mg/l
Low	Technical Criteria: 96 hr LC50 (fish) > 100 mg/l, 48 hr EC50 (crustacea) > 100 mg/l, 72 or 96 ErC50 (algae)> 100 mg/l

The following criteria for PBTs endpoints are based on the Environmental Protection Agency's (EPA) 1999 "Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances" policy statement and criteria developed in EPA's New Chemical Program for toxicity to fish. The technical data as follows:

Hazard Level	**PBT Criteria:**[7]
Very High	EPA Standards Persistence: Water, Soil, and sediment Half-life > 6 months (> 180 days); Bioaccumulation: BCF > 5,000; Fish ChV <0.1 mg/l
High	EPA Standards Persistence: Water, Soil, and sediment Half-life >= 2 months (>= 60 days); Half-life in Air >2 days; Bioaccumulation: BCF > = 1,000; Fish ChV <0.1mg/l
Moderate	Suspected PB (modeling); Fish ChV 0.1-10 mg/l
Low	Listed as not persistent or bioaccumulative; Fish ChV >10 mg/l

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[7] Based on EPA Standards: http://www.pbtprofiler.net/criteria.asp [Accessed February 2017]

Acid/Base Molarity Hazard Level Adjustment

Acids and bases used by the students within these experiments are often diluted from the original concentrate. To account for this, solutions with smaller molarity were decreased by one human health score to acknowledge the reduction in hazard. Laboratory experiment scores do not replace the necessity of reading the safety data sheets. Criteria on acid/base molarity of reagents were taken from the Sigma-Aldrich Molarity of Concd. Reagent chart. An example of a scoring adjustment on an acid based on criteria from Sigma-Aldrich Molarity of Concd. Reagent chart is provided:

Chemical Name	**Molarity of Reagent[8]**	**Human Health**	
		Original Hazard Score	**Adjusted Hazard Score**
Hydrochloric Acid	12.1*	High	High
	6 >	High	Moderate
	1 >	High	Low

*Max molarity of Hydrochloric Acid reagent.

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[8] Based on Millipore Sigma Molarity of Concd. Reagent for Acids and Bases Chart

Solvent Substitution Resources

The use of safer solvents is oftentimes the ‘low hanging fruit’ for implementing green chemistry principles into traditional organic chemistry experiments. There are many solvent selection guides that have been published within the pharmaceutical sector and are being used as a basis for guiding the selection of safer solvent choices for chemical reactions, extractions, and separations. The following summary provides an overview of these guides, along with guidance towards safer solvent substitution.

Pfizer Solvent Selection Tool

Pfizer created an internal solvent selection tool[9] that has been widely publicized. The tool categorizes solvents based on worker safety (acute and chronic toxicity), process safety (flammability, and reactivity), and environmental and regulatory considerations. Solvents are categorized into "preferred", "usable" and "undesirable" solvents and are also presented in a solvent replacement table that can be used to guide "greener" choices for solvents (Table 1). Through internal use of the solvent selection tool, Pfizer realized a 50% reduction in chlorinated solvent use, the reduction of undesirable ether usage by 97%, and the shifting of the use of less harmful heptane over hexane and pentane across their research division during 2004-2006.[5]

Table 1. Pfizer solvent replacement table

Undesirable Solvent	Alternative
Pentane	**Heptane**
Hexane(s)	**Heptane**
Di-isopropyl ether or diethyl ether	**2-MeTHF or *tert*-butyl methyl ether**
Dioxane or dimethoxyethane	**2-MeTHF or *tert*-butyl methyl ether**
Chloroform, dichloroethane or carbon tetrachloride	**Dichloromethane**
Dimethyl formamide, dimethyl acetamide or N-methylpyrrolidinone	**Acetonitrile**
Pyridine	**Et_3N (if pyridine is used as a base)**
Dichloromethane (extractions)	**EtOAc, MTBE, toluene, 2-MeTHF**
Dichloromethane (chromatography)	**EtOAc/heptane**
Benzene	**Toluene**

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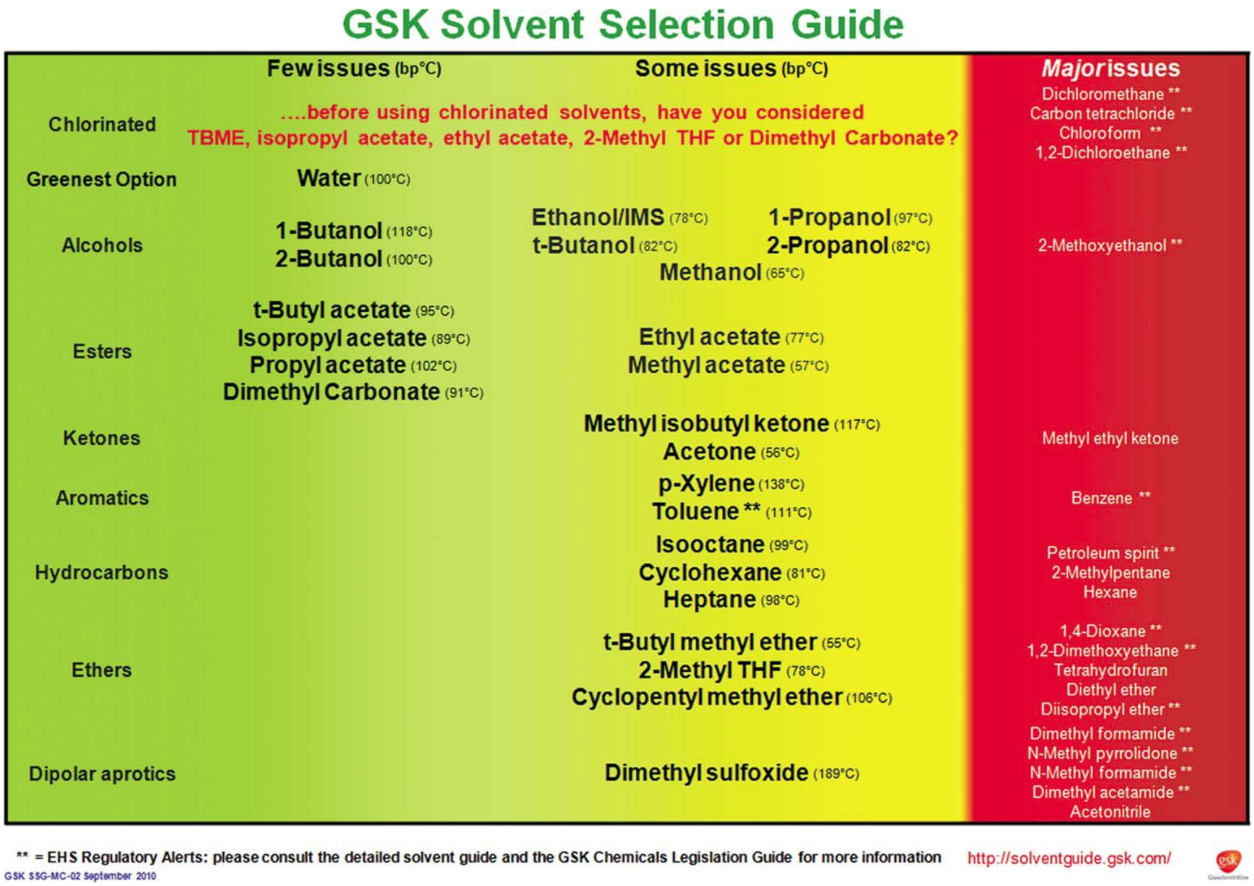
[9] Dunn, P. J., *et. al.*, Green Chemistry, 2008, 10, 31-36.

GlaxoSmithKline (GSK) Solvent Selection Guide

GSK has developed a solvent selection guide[10] for use by their medicinal chemists. This solvent guide, shown below, is a quick reference tool for practicing chemists to quickly identify solvents of concern. The guide is supported by a table which identifies the areas of concern in the following categories: waste, environmental impact, health hazards, flammability and explosion hazard, reactivity and stability, life cycle score and a legislation flag that alerts the user of any regulatory restrictions. The complete guide provides different levels of detail depending on the requirements by the user and the application.



GSK Solvent Selection Guide

	Few issues (bp°C)	**Some issues** (bp°C)	***Major* issues**
Chlorinated	....before using chlorinated solvents, have you considered TBME, isopropyl acetate, ethyl acetate, 2-Methyl THF or Dimethyl Carbonate?		Dichloromethane ** Carbon tetrachloride ** Chloroform ** 1,2-Dichloroethane **
Greenest Option	**Water** (100°C)		
Alcohols	**1-Butanol** (118°C) **2-Butanol** (100°C)	**Ethanol/IMS** (78°C) **t-Butanol** (82°C) **1-Propanol** (97°C) **2-Propanol** (82°C) **Methanol** (65°C)	2-Methoxyethanol **
Esters	**t-Butyl acetate** (95°C) **Isopropyl acetate** (89°C) **Propyl acetate** (102°C) **Dimethyl Carbonate** (91°C)	**Ethyl acetate** (77°C) **Methyl acetate** (57°C)	
Ketones		**Methyl isobutyl ketone** (117°C) **Acetone** (56°C)	Methyl ethyl ketone
Aromatics		**p-Xylene** (138°C) **Toluene** ** (111°C)	Benzene **
Hydrocarbons		**Isooctane** (99°C) **Cyclohexane** (81°C) **Heptane** (98°C)	Petroleum spirit ** 2-Methylpentane Hexane
Ethers		**t-Butyl methyl ether** (55°C) **2-Methyl THF** (78°C) **Cyclopentyl methyl ether** (106°C)	1,4-Dioxane ** 1,2-Dimethoxyethane ** Tetrahydrofuran Diethyl ether Diisopropyl ether **
Dipolar aprotics		**Dimethyl sulfoxide** (189°C)	Dimethyl formamide ** N-Methyl pyrrolidone ** N-Methyl formamide ** Dimethyl acetamide ** Acetonitrile

** = EHS Regulatory Alerts: please consult the detailed solvent guide and the GSK Chemicals Legislation Guide for more information http://solventguide.gsk.com/

GSK SSG-MC-02 September 2010

Figure 1: GlaxoSmithKline (GSK) Solvent Selection Guide.

Figure reproduced from Henderson, R. K., et. al, Green Chemistry, 2011, 13, 854-862 with permission of The Royal Society of Chemistry.

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[10] Henderson, R. K., *et. al.*, Green Chemistry, 2011, 13, 854-862.

American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable Solvent Selection Guide

The ACS GCI pharma roundtable have collaboratively developed a solvent selection guide[11] for pharma companies. The guide rates solvents against 5 categories: safety, health, environment (air), environment (water), and environment (waste). Each category is scored between 1-10, with 10 being the highest concern.

Additional Solvent Replacement Resources

There are many other solvent substitution resources and guides within the pharmaceutical sector.[12] Additionally, there are substitution tools that have been developed within academia, such as the MIT Green Alternatives Wizard.[13] The Green Alternatives Wizard is an online tool that allows the user to search for alternative chemicals or chemical processes. Users are guided to potential substitutes, which include the pros and cons of the substitution and links to the primary literature.

An excellent review and compilation of solvent selection guides by Prat *et. al.* has also been published in Green Chemistry[14]. Furthermore, the CHEM21 consortium used the solvent selection guides developed by Pfizer, GSK, Sanofi, and ACS GCI as a basis to develop a unified CHEM21 solvent selection guide[15]. The CHEM21 guide ranked a number of bioderived solvents, to give a clearer picture of how well they performed when scrutinized in the same manner as classical solvents.

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[11] ACS GCI Pharma Roundtable Solvent Selection Guide [http://www.acs.org/content/acs/en/greenchemistry/industry-business/pharmaceutical.html]

[12] Prat, D., et. al., Organic Process Research & Development, 2013, 17, 1517-1525.

[13] MIT Green Alternatives Wizard [http://ehs.mit.edu/greenchem]

[14] Prat, D.; Hayler, J.; Wells, A. Green Chem., 2014, 16, 4546.

[15] CHEM21 Solvent Selection Guide [http://pubs.rsc.org/en/content/articlelanding/gc/2016/c5gc01008j#!divAbstract]

Alternatives to Dichloromethane in Chromatography

"A convenient guide to help select replacement solvents for dichloromethane in chromatography"[11]

A 3:1 (v/v) solution of ethyl acetate/ethanol has been found to a viable alternative for dichloromethane (DCM) in flash chromatography and HPLC. This alternative is based on a publication in the journal *Green Chemistry* by Taygerly and Peterson titled "A convenient guide to help select replacement solvents for dichloromethane in chromatography".[16] The chromatography guide is experimentally-derived, and provides chemists options for choosing greener options, with a particular focus on the use of DCM. The guide itself was developed for use by medicinal chemists looking for alternatives to DCM and methanol, which is widely used by chemists to purify their compounds. The quick-reference guide provides chemists with a reference tool for guiding the substitution according to solvent polarity and eluting ability. The tool cross-references these properties to guide users towards the following greener options for solvents: heptanes, ethyl acetate: ethanol, isopropanol, and methyl t-butyl ether. Sigma-Aldrich offers a greener alternative to chlorinated solvents (in particular, DCM) in chromatography (Sigma-Aldrich SKU 745588).

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[16] Taygerly, J.P., Peterson, E.A., *et. al.*, Green Chemistry, 2012, 14, 3020-3025.

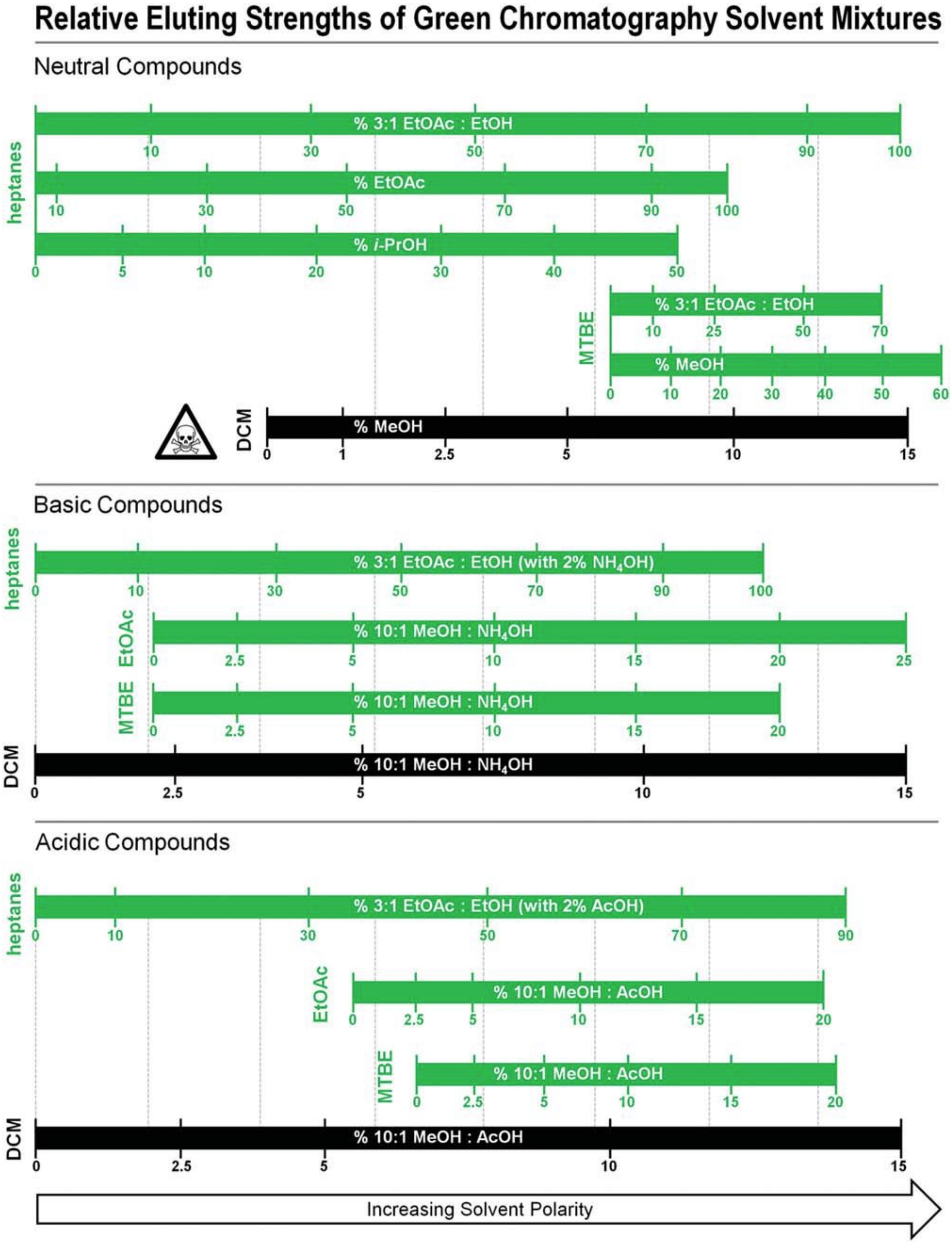

Figure 2: Green Chromatography Solvent Selection Guide. Starting from the appropriate DCM–MeOH concentration, compare vertically across the bar chart to identify greener solvent mixtures of similar eluting ability. For example, if a compound suitably elutes in 5% DCM–MeOH in the absence of an additive, the "Neutral Compounds" bar chart predicts that 60% 3:1 EtOAc : EtOH in heptanes or 40% *i*-PrOH in heptanes would be suitable starting points to evaluate greener solvent alternatives.

Figure reproduced from Taygerly, J.P., Peterson, E.A., *et. al.*, Green Chemistry, 2012, 14, 3020-3025 with permission of The Royal Society of Chemistry.

Reagent and Reaction Selection Resources

Greener alternatives to organic chemistry reactions have been on the rise since the early 2000's, when new publications began to appear that presented easily adoptable options for greener organic chemistry experiments. Select resources have been identified within this guide to facilitate the adoption of greener alternatives.

Key publications and websites for greener alternative organic laboratory exercises include:

1. University of Oregon Greener Education Materials Database [http://greenchem.uoregon.edu/gems.html]
2. Doxsee, K., Hutchison, J. Green Organic Chemistry: Strategies, Tools, and Laboratory Experiments, Brooks/Cole, Pacific Grove, CA, 2004.
3. Kirchhoff, M., Ryan, M.A., Eds., Greener Approaches to Undergraduate Chemistry Experiments, American Chemical Society, Washington, DC, 2002.
4. Roesky, H., Kennepohl, D., Eds., Experiments in Green and Sustainable Chemistry, Wiley-VCH, Weinheim, 2009.
5. Dicks, A.P., Ed., Green Organic Chemistry in Lecture and Laboratory, CRC Press Taylor & Francis Group, Boca Raton, FL, 2012.

ACS GCI Reagent Guides

The ACS GCI Pharma roundtable has developed an online tool to guide chemists towards the greener selection of reagents in chemical transformations.[17] The tool presents the user with a Venn diagram representing three factors for the selection of reagents: wide utility, scalability, and greenness. The ideal reagent is centrally located at the intersection of all three circles. Each reagent within the Venn diagrams are hyperlinked to further information and lists the primary references.

The Greener Organic Chemistry Reaction Index

Green Organic Chemistry in Lecture and Laboratory (#5 in the key publications list above), edited by Dr. Andrew Dicks, includes an appendix of greener organic chemistry reactions. The appendix profiles 178 reactions covering the typical reactions taught within the organic laboratory course, and includes the primary literature reference, experimental technique employed, and greener principles highlighted.

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[17] ACS GCI Pharmaceutical Reagent Guides [http://www.reagentguides.com]

Laboratory Techniques

A Brief Overview of Greener Recommendations to Common Synthetic Techniques

Distillation: Simple and Fractional

Simple and fractional distillations are commonly taught techniques in the organic chemistry laboratory, most notably for use in purifications and in boiling point determination. Organic solvents such as toluene and cyclohexane are commonly used to demonstrate the separation of solvent mixtures through distillation[18]. Ethanol-water mixtures can also be used and the purified ethanol tested for purity through an ignition test[19].

Laboratory experiments demonstrating acetone recovery are also being performed as means for teaching students the importance and potential of solvent recycling[20, 21]. The table below lists commonly used distillation solvents and their relative EH&S information.

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Cyclohexane	(varies)	🟥 🟥 🟥
Toluene 244511	(varies)	🟥 🟥 🟥
Acetone 650501	(varies)	🟥 🟨 🟩
Ethanol 459836	(varies)	🟥 🟨 🟩
Water n/a	(varies)	🟩 🟩 🟩

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[18] Simple and Fractional Distillation of a Cyclohexane-Toluene Mixture, Macroscale and Microscale Organic Exp., Williamson, K.L., Masters, K.M., 6th Ed, Brooks/Cole Cengage Learning, 2011, pp. 92-95.

[19] Simple Distillation of an Ethanol-Water Mixture, Macroscale and Microscale Organic Experiments, Williamson, K.L., Masters, K.M., 6th Edition, Brooks/Cole Cengage Learning, 2011, pp. 93-95.

[20] Simple Distillation: Purification and Reuse of Acetone, Lecher, C.S., Marian College, Greener Educational Materials for Chemists, 2007, http://greenchem.uoregon.edu/PDFs/GEMsID91.pdf [Accessed February 2017]

[21] Recycling of Waste Acetone by Fractional Distillation, McDougal, O.M., *et. al.*, J. Chem. Educ., 2011, 88 (12), pp. 1724–1726.

Chromatography: TLC and Column

Chromatography techniques are essential in the organic chemistry laboratory for identifying whether or not the desired reaction has occurred, if starting materials are present, for testing the purity of a product, and product purification. The choice of chromatography solvent can be limited due to the required solvent properties for the eluting solvent. There are many available resources for guiding chemists towards greener solvent choices, the majority of which were outlined in the above introduction section *Solvent Selection Resources*. Simple solvent substitutions can have considerable impact, especially minimizing the use of chlorinated solvents[22,23].

Greener chromatography experiments often involve the separation of pigments from plants and include the use of recycled solvents in the extraction process[24] and the use of alternative media for use within column chromatography[25].

The table below lists commonly used solvents in chromatography and their relative EH&S information. Please refer to the solvent selection resources in the introduction of this resource for further information regarding solvent substitution.

Chemical Name Aldrich Catalog #	**Amount per 100 students (g or mL)**	**EH&S**
Hexane 296090	(varies)	🟥 🟥 🟥
Heptane 246654	(varies)	🟥 🟨 🟥 *
Dichloromethane 676853	(varies)	🟩 🟥 🟥
Ethyl acetate 270989	(varies)	🟥 🟨 🟨

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[22] A convenient guide to help select replacement solvents for dichloromethane in chromatography, Taygerly, J. P., Miller, L. M., Yee, A., Peterson, E. A., Green Chem., 2012, 14, 3020.

[23] Green chemistry tools to influence a medicinal chemistry and research chemistry-based organization, Dunn, P. J., *et. al.*, Green Chemistry, 2008, 10, 31-36.

[24] A Green Approach To Separate Spinach Pigments by Column Chromatography, McDougal, O.M., et. al., J. Chem. Educ., 2013, 90 (6), pp 796–798.

[25] Supermarket Column Chromatography of Leaf Pigments Revisited: Simple and Ecofriendly Separation of Plant Carotenoids, Chlorophylls, and Flavonoids from Green and Red Leaves, J. Chem. Educ. 2015, 92(1), 189-192.

Extraction

Extraction techniques are commonly performed as means for isolating and purifying a product (i.e., essential oil or natural product extraction). Solvents commonly used in extractions include methylene chloride, petroleum ether, or hexanes. Greener solvent choices can be explored for solvents that have similar properties (e.g. miscibility, boiling point), and can often seamlessly replace traditional solvents. See the Solvent Selection Resources section for further information.

A greener extraction procedure for use within the organic chemistry laboratory involves the extraction of avocado oil using ethyl acetate and isopropanol. The oil is then used in the making of an avocado soap[26].

Please refer to the Solvent Selection Resources in the introduction of this resource for further information regarding solvent substitution.

The table below lists commonly used solvents in extraction and their relative EH&S information.

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Dichloromethane 676853	(varies)	🟩 🟥 🟥
Petroleum ether 320447	(varies)	🟥 *F 🟨 🟥
Hexanes 296090	(varies)	🟥 🟥 🟥
Heptane 246654	(varies)	🟥 🟨 🟥 *
Ethyl acetate 270989	(varies)	🟥 🟨 🟨
Isopropanol 278475	(varies)	🟥 🟨 🟩

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[26] Green Soap: An Extraction and Saponification of Avocado Oil, Sutheimer, S., Caster, J. M., Smith, S. H., J. Chem. Ed., 2015, 92, 1763-1765.

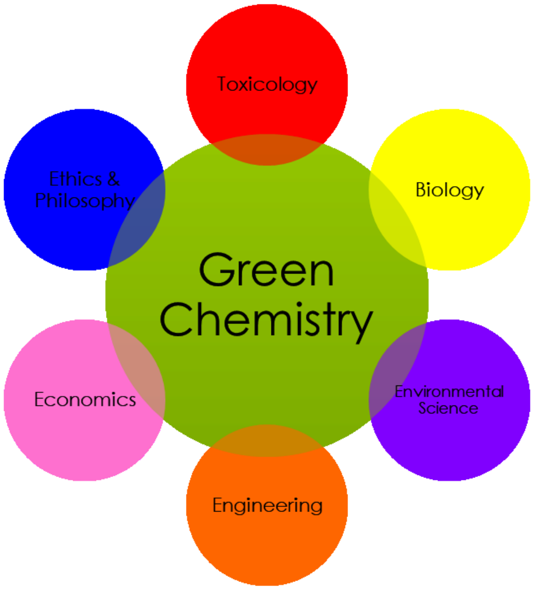
Introduction to Green Chemistry for TA's

Green chemistry is a fundamental approach to evaluating chemical processes and products, focusing on protecting human health and the environment. The 12 Principles of Green Chemistry[27]are a common reference point for evaluating environmental and health impacts of chemical processes, and are used for the design of safer reactions and products. We encourage you to reference these principles and relate back to them throughout lessons and experiments in the teaching lab.

Various metrics have been developed to evaluate environmental and health impacts including amount of waste generated, toxicity of reagents, and energy use at each stage of product development. For example, Process Mass Intensity (PMI) is a metric developed to standardize and quantify improvements leading to sustainable manufacturing methods. It focuses on decreasing the amount of materials used to make a product, which reduces the environmental footprint of the product, all while making the process more cost effective. The American Chemical Society Green Chemistry Institute® (ACS GCI) has created a PMI Calculation Tool on the Microsoft Excel platform, that can be downloaded and used for free here.

A complete evaluation of a chemical process is termed a Life Cycle Analysis (LCA), which considers everything from extraction of feedstocks to disposal and fate of the final product. Scientists in all disciplines are uniting to embrace challenges in the environmental and sustainability sector through LCAs, and use these analyses to drive research and innovation. The adoption of a holistic life-cycle perspective can build upon the existing foundation and framework for all divisions of chemistry. An article from the ACS on Sustainability and the Chemical Enterprise on the use and importance of LCAs can be found here.

Green chemistry is not a sub-discipline of chemistry – it is an umbrella that encompasses not only all divisions of chemistry, but virtually all divisions of science, business, and arts. Examples of interconnected divisions of green chemistry are shown on the left.



This should not be overwhelming – you do not need to be an expert in each to be successful in using and applying green chemistry principles. Collaboration is key! It encourages partnerships and working with colleagues and other departments to help each other make research and science as efficient and sustainable as possible.

Thinking holistically and looking at problems with a big picture perspective, especially with sustainability in mind, is an increasingly valuable skill to have in the modern workplace. Many companies have energy, waste, hazard reduction, and other aggressive sustainability goals in place and are seeking scientists that know how to collaborate to implement such measures.

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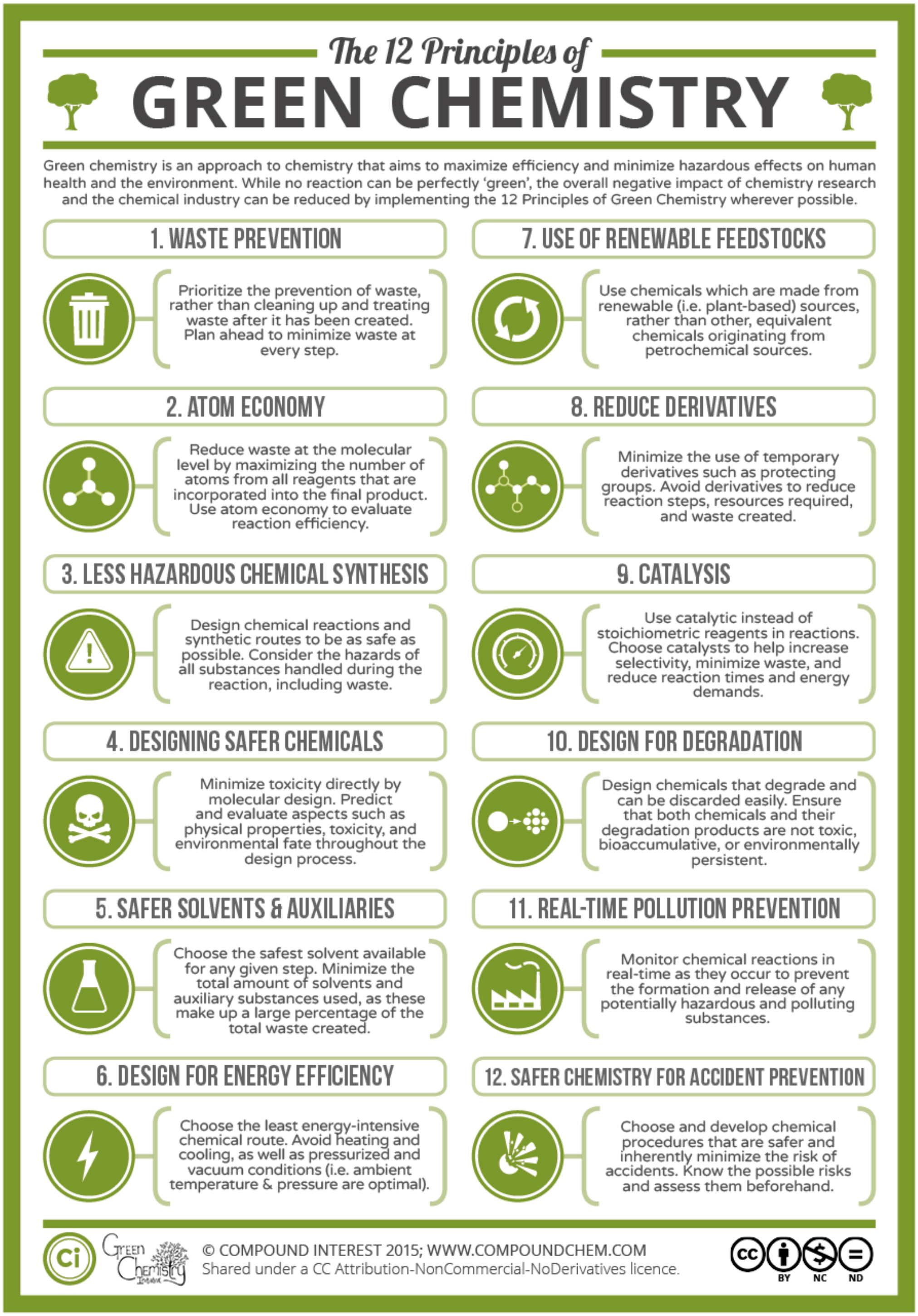
[27] Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998, p.30

The 12 Principles of Green Chemistry

The following infographic describes each of the principles. The graphic was designed by Compound Interest and the Green Chemistry Initiative at the University of Toronto. This student group has also created a YouTube video series (GreenChemUofT) around each of the principles.



The 12 Principles of GREEN CHEMISTRY

Green chemistry is an approach to chemistry that aims to maximize efficiency and minimize hazardous effects on human health and the environment. While no reaction can be perfectly 'green', the overall negative impact of chemistry research and the chemical industry can be reduced by implementing the 12 Principles of Green Chemistry wherever possible.

1. WASTE PREVENTION

Prioritize the prevention of waste, rather than cleaning up and treating waste after it has been created. Plan ahead to minimize waste at every step.

2. ATOM ECONOMY

Reduce waste at the molecular level by maximizing the number of atoms from all reagents that are incorporated into the final product. Use atom economy to evaluate reaction efficiency.

3. LESS HAZARDOUS CHEMICAL SYNTHESIS

Design chemical reactions and synthetic routes to be as safe as possible. Consider the hazards of all substances handled during the reaction, including waste.

4. DESIGNING SAFER CHEMICALS

Minimize toxicity directly by molecular design. Predict and evaluate aspects such as physical properties, toxicity, and environmental fate throughout the design process.

5. SAFER SOLVENTS & AUXILIARIES

Choose the safest solvent available for any given step. Minimize the total amount of solvents and auxiliary substances used, as these make up a large percentage of the total waste created.

6. DESIGN FOR ENERGY EFFICIENCY

Choose the least energy-intensive chemical route. Avoid heating and cooling, as well as pressurized and vacuum conditions (i.e. ambient temperature & pressure are optimal).

7. USE OF RENEWABLE FEEDSTOCKS

Use chemicals which are made from renewable (i.e. plant-based) sources, rather than other, equivalent chemicals originating from petrochemical sources.

8. REDUCE DERIVATIVES

Minimize the use of temporary derivatives such as protecting groups. Avoid derivatives to reduce reaction steps, resources required, and waste created.

9. CATALYSIS

Use catalytic instead of stoichiometric reagents in reactions. Choose catalysts to help increase selectivity, minimize waste, and reduce reaction times and energy demands.

10. DESIGN FOR DEGRADATION

Design chemicals that degrade and can be discarded easily. Ensure that both chemicals and their degradation products are not toxic, bioaccumulative, or environmentally persistent.

11. REAL-TIME POLLUTION PREVENTION

Monitor chemical reactions in real-time as they occur to prevent the formation and release of any potentially hazardous and polluting substances.

12. SAFER CHEMISTRY FOR ACCIDENT PREVENTION

Choose and develop chemical procedures that are safer and inherently minimize the risk of accidents. Know the possible risks and assess them beforehand.

Experiment 1: The Grignard Reaction

Introduction

A Grignard reagent is formed by reacting an alkyl or aryl halide with magnesium, and is characterized by the presence of a carbon-magnesium bond.

$$\mathrm{R{-}X} \xrightarrow{\mathrm{Mg}} \mathrm{R{-}MgX}$$

Victor Grignard, whom these reagents are named after, was awarded the Nobel Prize in Chemistry in 1912 for demonstrating the broad utility of these carbon nucleophiles. Since carbon is significantly more electronegative than magnesium, it withdraws electron density in the C-Mg bond to such an extent that this bond may now be treated as ionic, thus the formation of Grignard reagents represent an example of an Umpolung reaction. The resulting delta negative carbon can subsequently react with a variety of electrophiles, such as the carbonyl group of aldehydes and ketones, to create new C-C bonds.

However, this classic demonstration of a Grignard reaction is not always the most practical in a teaching-lab setting as it is typically carried out in anhydrous solvents in dry glassware given the reactive nature of the reagents. If care isn't taken to achieve anhydrous conditions, undesired reaction of the magnesium salt with moisture will compete with reaction with the carbonyl.

As the chemistry lab continues to become a more environmentally-conscious space, the recent design of chemical processes has increasingly focused on alternative solvents and neat (i.e. solvent free) reactions.

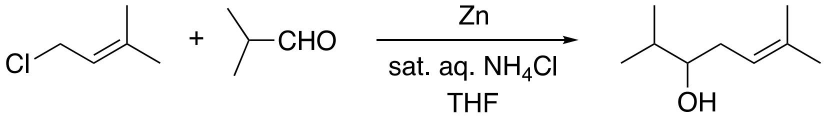
This lab illustrates an example of Barbier-Grignard zinc-mediated C-C bond forming reaction in an aqueous medium, alleviating the need for anhydrous conditions. The Barbier reaction is a one-pot synthesis, whereas the Grignard reaction requires preparation of the Grignard reagent prior to addition of the carbonyl substrate. The Barbier reaction mechanism has not been definitively established, however a radical-based pathway is often suggested in literature reports.

The following principles of green chemistry are employed in the alternative experiment described herein:

- Safer Solvents & Auxiliaries
- Catalysis
- Safer Chemistry for Accident Prevention

Grignard Reaction – A Greener Alternative (1)

An analogue to a Grignard reaction that offers a greener option and calls for aqueous reaction conditions. This zinc-mediated reaction inserts zinc into a carbon-chlorine bond, generating a carbon-based nucleophile. The organozinc reagent then adds to the carbonyl to generate a substituted alcohol.



Reference

Water-Soluble Catalysis: Aqueous Analogue of the Grignard Reaction, Warner, J.C., in Greener Approaches to Undergraduate Chemistry Experiments, American Chemical Society, 1999, 23-24.

Experimental

1. In a 50 mL Erlenmeyer flask equipped with a magnetic stir bar, combine 0.78 g of untreated, commercially available zinc powder and 10mL of a saturated aqueous NH_4Cl solution.
2. Combine 0.91 mL of isobutyraldehyde and 1 mL of THF in a small test tube, and add it to the solution in the flask. Stir the mixture vigorously while adding 1.4 mL of 1-chloro-3-methyl-2-butene, dropwise. An immediate reaction takes place with the loss of zinc powder.
3. Stir the mixture for 45 min. The progress of the reaction can be monitored by using thin-layer chromatography, IR spectroscopy, or NMR spectroscopy.
4. At the end of the 45-minute period, add 2 mL of ether. Filter the mixture through a plug of glass wool to remove excess zinc and any precipitate (e.g. zinc salts) that may have formed. Rinse the precipitate with 2 mL of fresh ether.
5. Transfer the filtrate to a small separatory funnel, and separate the organic and aqueous layers. Wash the aqueous phase with 2 mL of ether. Combine the organic phases and dry over anhydrous sodium sulfate. Filter, and remove the ether to yield 3-hydroxy-2,6-dimethyl-5-heptane.
6. Analyze the product by NMR and IR spectroscopy.

Optional Activity

Students may work in teams to investigate the effect on the reaction of varying the amount of THF used. For example, each group could be tasked with conducting the reaction at varied concentrations (i.e. as written above, with no THF, with 0.5 mL THF, etc.), and the results can be pooled so students can assess the effect of concentration on observed reactivity.

It is suggested to employ the following greener alternatives:

- **THF**: A greener alternative is 2-Me-THF (MilliporeSigma product numbers: 414247 & 673277).
- **Diethyl Ether**: A greener alternative is cyclopentylmethyl ether (CPME) (MilliporeSigma product numbers: 675970, 675989 & 791962). Ethyl ether can also be substituted with 2-Me-THF.

Health and Safety

EHS Key:

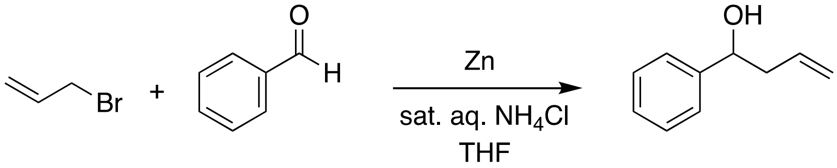
🟨	**Physical hazard**
🟨	**Toxicity/Health hazard**
⬜	**Persistent Bioaccumulative Toxic (PBT) Chemicals**
🟥 *	**Very high hazard**
🟥	**High hazard**
🟨	**Moderate hazard**
🟩	**Low hazard**
⬜	**No data**

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
1-chloro-3-methyl-2-butene 303259	70 mL	🟥 🟨 🟨
Isobutyraldehyde 320358	45.5 mL	🟥 🟨 🟥
Zinc powder 243469	39 g	🟥 *R 🟩 🟥 *
Ammonium chloride solution, saturated 213330	500 mL	🟨 🟨 🟥
Tetrahydrofuran 401757	50 mL	🟥 🟨 🟩
Diethyl ether 346136	100 mL	🟥 *F 🟨 🟨
Sodium sulfate, anhydrous 239313	100 g	🟩 🟩 🟩

Grignard Reaction – A Greener Alternative (2)

Another analogue to the Grignard reaction that offers a greener option and utilizes aqueous reaction conditions is described herein. This zinc-mediated reaction inserts zinc into a carbon-bromine bond. The organozinc reagent then adds to the carbonyl to generate a substituted alcohol.



Reference

A Grignard-like Organic Reaction in Water, Breton, G.W., Hughey, C.A., J. Chem. Educ. 1998, 75, 85.

Experimental[28]

Caution: Allyl bromide is a toxic, flammable liquid. Gloves should be worn at all times during its handling, and all manipulations should be carried out in an efficient hood.

1. To a mixture of 0.078 g (1.20 mmol) of untreated, commercially available zinc powder and 1 mL of a saturated aqueous NH_4Cl solution in a 25-mL round-bottomed flask equipped with a magnetic stir bar is added a solution of 0.102 mL (1.00 mmol) of benzaldehyde in 0.5 mL of THF.
2. The flask is fitted with a condenser and the mixture is stirred vigorously while 0.104 mL (1.20 mmol) of allyl bromide is added dropwise via a calibrated pipet, through the condenser. An immediate reaction takes place, with loss of the zinc powder. The mixture is stirred for 0.5 h.
3. At the end of this 0.5 h period, 1 mL of ether is added. The mixture is filtered through a plug of glass wool to remove excess zinc and any precipitate (e.g. zinc salts) that may have formed. The precipitate is rinsed with 1 mL of fresh ether.
4. The organic phase is separated, and the aqueous phase is washed once with a fresh aliquot (1 mL) of ether. The combined organic phases are dried over sodium sulfate (Na_2SO_4), filtered, and concentrated to afford 1-phenyl-3-buten-1-ol as a colorless liquid.

Notes

- It is important to use a round-bottomed flask for this step. Little or no reaction occurred when we used a conical reaction vial (and spin vane), owing to inefficient mixing of the dense zinc powder with the liquid phases. Effective mixing of the zinc is essential to afford good yields of product.
- The bromide should be carefully added so that each drop falls directly into the stirring mixture. Loss of compound as a result of running the liquid down the side of the condenser lowers the product yield.

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[28] Experimental procedure reprinted with permission from Breton, G.W., Hughey, C.A., J. Chem. Ed., 1998, 75, 85. Copyright 1998 American Chemical Society.

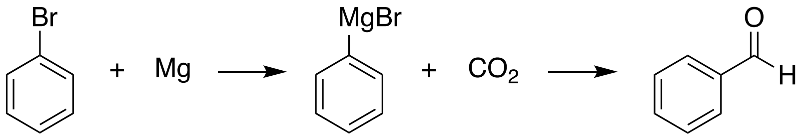
Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Benzaldehyde B1334	5.1 mL	🟨 🟨 🟥
Allyl bromide 337528	5.2 mL	🟥 *F 🟨 🟥 *
Zinc powder 243469	3.9 g	🟥 *R 🟩 🟥 *
Ammonium chloride solution, saturated 213330	50 mL	🟨 🟨 🟥
Tetrahydrofuran 401757	25 mL	🟥 🟨 🟩
Diethyl ether 346136	50 mL	🟥 *F 🟨 🟨
Sodium sulfate, anhydrous 239313	50 g	🟩 🟩 🟩

Traditional Grignard Reaction

The formation of carbon-carbon double bonds is perhaps one of the most important synthetic transformations in organic chemistry. The Grignard reaction is a classic example of a C-C forming reaction where magnesium is inserted into a carbon-halogen bond. The nucleophilic carbon then adds to the electrophilic carbonyl, producing a substituted alcohol.

In the example below, benzoic acid is produced via a Grignard reaction.



Reference

Grignard Synthesis of Benzoic Acid, K. L. Williamson, Macroscale and Microscale Organic Experiments, 2nd Ed. 1994, Houghton Mifflin, Boston, p. 364.

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Magnesium 254118	2.5 g	🟥 *R 🟨 🟨
Bromobenzene B57702	16.5 g	🟨 🟨 🟥
Diethyl ether 346136	135 mL	🟥 *F 🟨 🟨
Dry ice (carbon dioxide)	50 g	🟩 🟩 🟥
Hydrochloric acid, 3M 320331	100 mL	🟨 🟨 🟨
Sodium hydroxide, 3M 221465	60 mL	🟨 🟨 🟩
Water n/a	60 mL	🟩 🟩 🟩

Comparative Analysis of Traditional vs. Suggested Experiments

- Greener methods reduce the use of diethyl ether
- Greener methods do not require anhydrous conditions and therefore decreases the amount of unnecessary waste resulting from experiments contaminated with moisture
- Greener method (1) still requires use of hazardous substances (i.e., THF, diethyl ether)
- Greener method (2) still requires use of hazardous substances (i.e., allyl bromide, THF, diethyl ether)
- The comparative costs for all reagents per 100 students for this experiment is $587 for the Greener method (1), $19 for the Greener method (2) and $20 for the Traditional method. Actual cost will vary.

	Waste Reduction (per 100 students)	**"Greener" Benefits**
Greener method (1)	800 mL liquid 100 g solid waste	⚗
Greener method (2)	135 mL liquid 50 g solid waste	⚗
Traditional method	375 mL	

Additional Resources & Further Reading

The following are additional greener alternative laboratory experiment options:

- Microwave-Assisted Carbonyl Chemistry for the Undergraduate Chemistry Laboratory, J. Chem. Educ. 2009, 86, 227-229.
- The Question-Driven Laboratory Exercise: A New Pedagogy Applied to a Green Modification of Grignard Reagent Formation and Reaction, J. Chem. Educ. 2010, 87, 714-716.

TA Guide

This lab illustrates an example of Barbier-Grignard zinc-mediated C-C bond forming reaction in an aqueous medium, alleviating the need for anhydrous conditions required in conventional Grignard reactions. The Barbier reaction is similar to the Grignard reaction, but is carried out in a one-pot synthesis whereas the Grignard reaction requires preparation of the Grignard reagent before addition of the carbonyl substrate. The preponderance of empirical evidence suggests a radical-based mechanistic pathway; however other mechanistic scenarios have also been proposed in the literature.

In this experiment, a mixture of zinc powder and the aldehyde are prepared, followed by dropwise addition of an alkyl halide. There is a 30-45 minute reaction period during which students may prepare for the subsequent filtration and separation work up procedure. This period may also be used to discuss the green chemistry principles that apply to the experiment at hand.

The following principles of green chemistry are employed:

- Safer Solvents & Auxiliaries
- Catalysis
- Safer Chemistry for Accident Prevention

Tips & Tricks

- Take caution when using alkyl halide reagents as they may be toxic, flammable, or have other hazards. As always, please review the MSDS prior to instructing on hazardous materials.
- Remind students how to determine which is the organic and which is the aqueous layer, and not to discard these layers until products are obtained.

Fun Facts

- Did you know the Barbier reaction is named after Philippe Barbier, who supervised Victor Grignard (yes…the Grignard reaction) during his PhD?

Example Quiz Questions

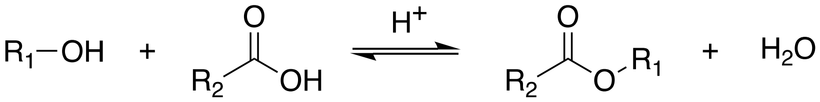
The following are examples of questions that may be used on pre- or post-lab quizzes, assignments, etc. or as discussion points during a lecture.

1. What are some key differences between the Grignard and Barbier reactions?
2. Describe the Barbier reaction and suggest a plausible mechanism.
3. What are the benefits and drawbacks of using water as a solvent? Please list 2 of each and explain.

Experiment 2: The Esterification Reaction

Introduction

Esters may be prepared via a number of different processes, with one classic example being the Fischer esterification – an acid-catalyzed reaction between a carboxylic acid and an alcohol, which undergoes nucleophilic acyl substitution.



The substitution mechanism is supported by isotopic labeling studies, wherein employing $MeO^{18}H$ gives rise to the corresponding ester with O^{18} incorporated into the acyl -OR unit. Fischer esterification is a reversible process and this reaction is therefore governed by Le Châtelier's principle. As such, the alcohol is often employed as the solvent to shift equilibrium to product formation.

Transesterification is slightly different than Fischer esterification in that the starting material is an ester, instead of an aldehyde, ketone, or acyl halide typically employed in other esterification reactions. The initial ester is trans-esterified to yield a 'new' ester with a different R group on the alcohol moiety.

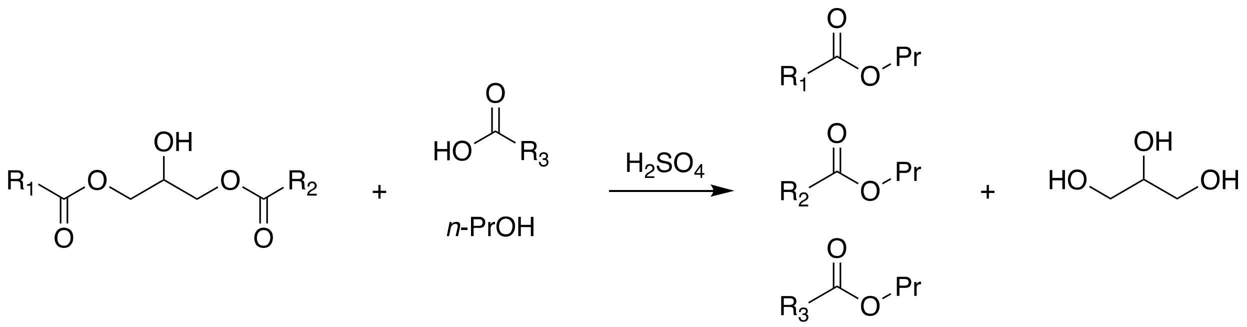
Not only does this lab function as a synthetic example of Fischer esterification and transesterification, but also serves to unite the chemistry laboratory with the real world. Vegetable oil undergoes partial hydrolysis in typical cooking conditions to yield a mixture of glycerides and free fatty acids. For this experiment, waste vegetable oil undergoes a simple, one-pot acid-catalyzed transesterification in 1-propanol to yield biodiesel. This procedure simultaneously converts both the free fatty-acids and glycerides, avoids messy emulsions associated with base-catalyzed reactions, and reduces the transesterification reaction time to make this a practical experiment for a 3-hour lab period.

The following principles of green chemistry are employed in the alternative experiment described herein:

- Use of Renewable Feedstocks
- Safer Solvents & Auxiliaries

Esterification Reaction – A Greener Alternative

Waste vegetable oil is a mixture of products that result from the hydrolysis of triglycerides, creating a raw waste product that is suitable starting material for the reaction at hand. This preparation of biodiesel from vegetable oil involves acid-catalyzed Fischer esterification of free fatty acids and transesterification of glycerides. The reaction is carried out in 1-propanol, instead of the more traditionally employed methanol, as its higher boiling point allows for a significant decrease in reaction time. This serves as a real-world example to introduce students to the concept of bio-based, renewable fuel feedstocks. The product from this experiment is suitable for use in diesel engines.



Reference

Acid-Catalyzed Preparation of Biodiesel from Waste Vegetable Oil: An Experiment for the Undergraduate Organic Chemistry Laboratory, J. Chem. Educ. 2011, 88, 201–203.

Experimental[29]

Caution: Sulfuric acid is extremely corrosive and sodium hydroxide is caustic – do not allow them to come into contact with your skin. If they do come into contact, wash with water immediately.

1. Combine 1-propanol (8.0 mL) with concentrated sulfuric acid (0.15 mL) in a 125 mL reaction flask equipped with a magnetic stir bar. Allow the mixture to stir for 2 min.
2. Add waste vegetable oil (20 mL) and equip flask with a reflux condenser. Heat the mixture to reflux for 1 h.
3. Allow the reaction mixture to cool. Transfer to a separatory funnel and allow the layers to separate for several minutes.
4. Drain the clear brown glycerin layer off the bottom. Wash the top layer with 3 x 15 mL portions of 1M NaCl solution, being careful to avoid emulsions. Check the final washing with pH paper to ensure the pH is neutral.
5. Drain the ester layer into a flask and dry with anhydrous calcium chloride or magnesium sulfate. Obtain the biodiesel product via gravity filtration.

Analysis of Biodiesel

1. Create two oil lamps with 2-dram vials, cotton string, and aluminum foil. Wrap the foil around the top of the vial to support the cotton string. Leave approximately 5 mm of string sticking out the top of the vial and enough of a tail to stay submerged in the oil. Place 1 mL biodiesel into one vial and 1 mL vegetable oil into the other. Be sure to coat the entire string with the liquid. In the designated section of the laboratory away from the flammable solvents, check the ease of lighting each lamp, quality of flame, and time required for the flame to extinguish itself.
2. Fill one Pasteur pipette with vegetable oil and another with biodiesel, and allow them to drain without the bulb simultaneously. Record the time it takes each pipette to empty.

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[29] Experimental procedure reprinted with permission from Bladt, D., Murray, S., Gitch, B., *et. al.*, J. Chem. Ed., 2011, 88, 201-203. Copyright 2011 American Chemical Society.

Health and Safety

EHS Key:

🟨 Physical hazard
🟨 Toxicity/Health hazard
⬜ Persistent Bioaccumulative Toxic (PBT) Chemicals

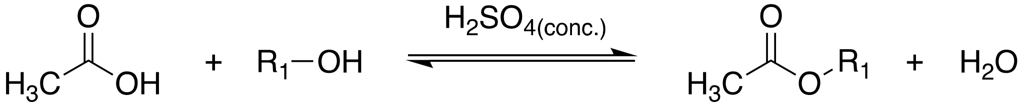
🟥 * Very high hazard
🟥 High hazard
🟨 Moderate hazard
🟩 Low hazard
⬜ No data

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Vegetable Oil n/a	1000 mL	🟩 🟩 🟩
1-propanol 402893	400 mL	🟥 🟨 🟩
Sulfuric acid, conc. 258105	7.5 mL	🟨 🟥 🟨
Sodium chloride, 1M sol 746398	2250 mL	🟩 🟩 🟩
Magnesium sulfate, anhydrous 793612	100g	🟩 🟨 🟩

Traditional Esterification Reaction

This experiment features a traditional acid-catalyzed Fischer esterification to yield a range of esters that are primarily responsible for the diversity of odors used in the flavoring and perfume industry. The esterification reaction proceeds through the reaction of a carboxylic acid and an alcohol in the presence of concentrated sulfuric acid.



Reference

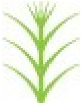
Fischer Esterification, Organic Chemistry Laboratory Manual, A. B. Padfas, Hayden-McNeil, 2013.

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
1-pentanol 398268	15 mL	🟨 🟨 🟨
2-pentanol P8017	15 mL	🟨 🟨 🟨
Isopentyl alcohol W205702	15 mL	🟨 🟨 🟩
Hexyl alcohol W256706	15 mL	🟨 🟨 🟩
4-methyl-2-pentanol 109916	15 mL	🟨 🟨 🟩
Glacial acetic acid 695092	150 mL	🟨 🟥 🟨
Sodium bicarbonate (5%) S6014	300 mL	🟩 🟩 🟩
Sulfuric acid, conc 258105	5 mL	🟨 🟥 🟨
Sodium sulfate, anhyd. 258105	25 g	🟩 🟩 🟩

Comparative Analysis of Traditional vs. Suggested Experiments

- Greener method introduces the concepts of bio-based resources and renewable raw materials
- Greener method produces the product, which can be used in diesel engines, along with aqueous waste
- Traditional esterification reaction uses various alcohols which all have moderate EH&S profiles
- The comparative costs for all reagents per 100 students for this experiment is $41 for the Greener method and $21 for the Traditional method. Actual cost will vary.

	Waste Reduction (per 100 students)	**"Greener" Benefits**
Greener method	1400 mL biodiesel product 2.3 mL aq. waste 100 g solid waste	
Traditional method	525 mL aq. waste 25 g solid waste	

Additional Resources & Further Reading

The following are additional greener alternative laboratory experiment options:

- Replacing Mineral Acids in the Laboratory: Nafion-Catalyzed Dehydration and Esterification, J. Chem. Educ. 1993, 70, 493-495.
- Methyl benzoate by Fischer Esterification, Macroscale and Microscale Organic Experiments, Williamson, K.L., Masters, K.M., 6th Edition, 2011, p. 524-525.

TA Guide

Triglycerides are the primary component of vegetable oil, and have a high calorie count owing to extremely efficient energy storage. Just as the human body uses these for fuel in metabolic processes, fats can also serve as fuel sources for combustion engines in automobiles. However, unlike the human body, vegetable oil cannot directly fuel the engine efficiently due to high viscosity, particularly at low temperatures, and low volatility resulting in incomplete combustion. Conveniently, triglycerides can easily be broken down into glycerol and fatty acid esters via transesterification to produce what is commonly known as biodiesel.

Vegetable oil undergoes partial hydrolysis under standard cooking conditions, and is broken down into free fatty acids and glycerides. In an effort to turn this waste product into a useful commodity, synthetic methods have been optimized and refined to an elegant one-pot reaction demonstrated herein. This lab illustrates synthetic examples of acid-catalyzed Fisher esterification and transesterification reactions, and a real-world example of renewable fuel feedstocks.

Students will carry out the reaction by mixing the reagents, which stir for 1 hour, followed by separation and subsequent work up. Biodiesel and new vegetable oil cannot be easily distinguished by visual inspection. Both a flame test and viscosity can be used to identify the product, and serve to demonstrate the importance of physical properties of motor fuels.

The following principles of green chemistry are employed:

- Use of Renewable Feedstocks
- Safer Solvents & Auxiliaries

Tips & Tricks

- Ensure all students are wearing full splash goggles. Concentrated sulfuric acid is corrosive and safety measures to avoid contact with eyes and skin should be prioritized.
- 1-Propanol is flammable and adequate precautions should be taken.
- Concentrated sulfuric acid combined directly with an unsaturated oil will result in decomposition. Ensure the sulfuric acid is first added to the alcohol, and then add this mixture to the oil.

Fun Facts

- Due to their extremely efficient storage of energy, triglycerides can be used as a source of fuel in the human body as well as modified diesel engines.
- When gasoline supplies were sparse during WWI and WWII, coconut oil was used as fuel.

Example Quiz Questions

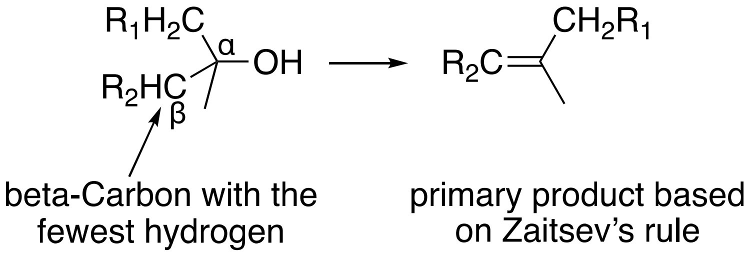
The following are examples of questions that may be used on pre- or post-lab quizzes, assignments, etc. or as discussion points during a lecture.

1. What is the mechanistic difference between acid and base catalyzed transesterification?
2. Define esterification and transesterification. Identify similarities and differences.
3. Why are triglycerides efficient at storing energy?
4. Explain two features of this teaching lab that make it unsuitable for large-scale production.

Experiment 3: The Alcohol Dehydration Reaction – Zaitsev Elimination

Introduction

Elimination reactions represent a powerful methodology for synthesizing a wide range of alkenes. A hydrogen in the beta (β) position, together with the leaving group, is removed to yield a double bond. According to Zaitsev's rule, the alkene formed in greatest amount is the one that corresponds to the removal of the hydrogen from the β carbon having the fewest hydrogens, i.e. the reaction is selective for the more substituted alkene.



This beta elimination, also known as a 1,2-elimination, can be carried out with any good leaving group (e.g. -Cl, -Br, $-H_2O$, -OTs, etc.). Before this unifying mechanism was understood, chemists described individual classes of beta eliminations that are still common today. For example, a dehydrohalogenation is beta elimination with a halide leaving group. Similarly, a dehydration is beta elimination with water as the leaving group.

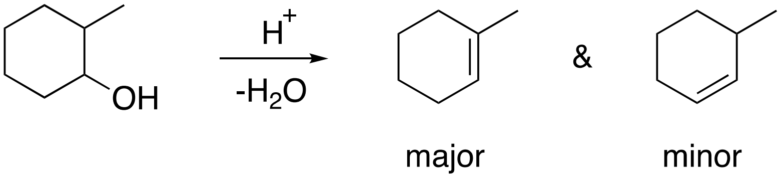
Molecules in which the beta positions are not identical present the opportunity for the double bond to form in two different regions of the molecule. There are various driving factors that can favor the formation of one isomer over another, a phenomenon known as regioselectivity. Alexander M. Zaitsev was the first to document the regioselective trend when he observed preferential formation of the most substituted alkene comprising the major product, and hence the Zaitsev product, as we know it today.

The following principles of green chemistry are employed in the alternative experiment described herein:

- Less Hazardous Chemical Synthesis
- Safer Solvents & Auxiliaries
- Use of Renewable Feedstocks
- Catalysis
- Real-Time Pollution Prevention
- Safer Chemistry for Accident Prevention
- Waste Prevention

Alcohol Dehydration: Zaitsev Elimination – A Greener Alternative

Most undergraduate organic chemistry labs study the preparation of alkenes via the dehydration reaction of alcohols. Traditionally, concentrated sulfuric or phosphoric acid is used as a catalyst for this reaction. These concentrated acids are corrosive and cause unnecessary waste that can be harmful to humans and the environment. An alternative greener method is proposed, using Montmorillonite KSF clay, a nontoxic and reusable catalyst.



Reference

Alternative Greener Method for Preparation of Alkenes from Alcohol, Warnock, L., Coll, S., Githui, M. and Asonganyie, E., http://www.cs.gordon.edu/courses/organic/salem/Montmorillonite-alkene.pdf [Accessed January 2018]

Experimental

1. To a 25 mL round bottom flask, add 5 mL of 2-methylcyclohexanol and 0.25 g of Montmorillonite KSF clay, along with a magnetic stirring bar.
2. Attach a condenser and reflux the solution with stirring for 90 min.
3. Remove the flask from the heating source and allow it to cool. Attach a distillation apparatus, and distill the product from the unreacted alcohol and the catalyst. Collect approximately 2 mL of the product.
4. Analyze the product via gas chromatography, and determine the percentages of different isomers in the product mixture.

Health and Safety

EHS Key:

🟨	Physical hazard	🟥 *	Very high hazard
🟨	Toxicity/Health hazard	🟥	High hazard
⬜	Persistent Bioaccumulative Toxic (PBT) Chemicals	🟨	Moderate hazard
		🟩	Low hazard
		⬜	No data

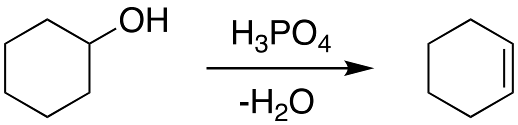
Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
2-methylcyclohexanol 153087	100 mL	🟨 🟨 🟨
Montmorillonite KSF* 281530	12.5 g	🟥 🟥 🟩
Poly(ethylene glycol), avg. M_n 400 (PEG 400) 202398	150 mL	🟩 🟩 🟩
Sodium sulfate 798592	100 g	🟩 🟩 🟩

Note: The high human toxicity hazard is associated with an inhalation hazard for silicon dioxide. The conditions of this procedure have very low potential for inhalation of the Montmorillonite KSF clay.

Alcohol Dehydration – Zaitsev Elimination

Most undergraduate organic chemistry labs study the preparation of alkenes via the dehydration reaction of alcohols. Traditionally, concentrated sulfuric or phosphoric acid is used as a catalyst for this reaction. These concentrated acids are corrosive and cause unnecessary waste that can be harmful to humans and the environment.



Reference

Dehydration of cyclohexanol to cyclohexene with phosphoric acid, Macroscale and Microscale Organic Experiments, 6e; Brooks/Cole, 2011; p. 335-357.

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Cyclohexanol 105899	100 mL	🟨 🟨 🟩
Phosphoric acid, conc. W290017	25 mL	🟥 🟥 🟩
Toluene 179418	150 mL	🟥 🟥 🟨
Sodium chloride 793566	42 g	🟩 🟩 🟩
Calcium chloride C1016	25 g	🟩 🟨 🟩
Ethanol E7023	250 mL	🟥 🟨 🟩
Acetone 34850	250 mL	🟥 🟨 🟩
Water N/A	250 mL	🟩 🟩 🟩

Comparative Analysis of Traditional vs. Suggested Experiments

- Greener method eliminates the use or organic solvents toluene and acetone
- Greener method eliminates the use of concentrated phosphoric acid
- Greener method includes the use of a catalyst that can be re-used
- Greener method uses a safer solvent, poly(ethylene) glycol, avoiding the use of toluene
- The comparative costs for all reagents per 100 students for this experiment is $47 for the greener method versus $76 for the traditional method. Actual cost will vary.

	Waste Reduction (per 100 students)	**“Greener” Benefits**
Greener method	375 mL	🕒 ⚗
Traditional method	1100 mL	

Additional Resources & Further Reading

The following are additional greener alternative laboratory experiment options:

- Synthesis and Spectroscopic Analysis of a Cyclic Acetal: A Dehydration Performed in Aqueous Solution, J. Chem. Educ., 2001, 78 (1), 70.
- Green Synthesis of a Fluorescent Natural Product, J. Chem. Educ., 2011, 88 (3), 319–332.

TA Guide

Alkenes prepared via the dehydration of alcohols traditionally employ concentrated sulfuric or phosphoric acid as a catalyst. These are corrosive and the resulting waste can be harmful to humans and the environment.

The reaction demonstrated in this lab employs Montmorillonite KSF clay as the catalyst. This non-toxic, reusable alternative makes this experiment safer and more environmentally benign. In this experiment, students will stir the reagents under reflux for 90 minutes, followed by a simple distillation to obtain the product as a mixture of isomers. The product is analyzed by gas chromatography to establish the yield of each isomer.

The following principles of green chemistry are employed:

- Less Hazardous Chemical Synthesis
- Safer Solvents & Auxiliaries
- Use of Renewable Feedstocks
- Catalysis
- Real-Time Pollution Prevention
- Safer Chemistry for Accident Prevention
- Waste Prevention

Fun Facts

- Montmorillonite is comprised of parallel sheets of Si_2O_5, and part of a larger group of compounds that have this common structure known as phyllosilicate
- More specifically, Montmorillonite is a 2:1 ratio of these tetrahedral Si_2O_5 sheets to a central octahedral sheet of Al_2O_3, also known as alumina
- Montmorillonite is used in the oil drilling industry, water wells, animal feed, paper making, cosmetics, medicine, and as a catalyst in various other chemical reactions

Example Quiz Questions

The following are examples of questions that may be used on pre- or post-lab quizzes, assignments, etc. or as discussion points during a lecture.

1. Is there a mechanistic difference between the traditional acid-catalyzed reaction and the greener alternative employed in this lab? Explain.
2. Describe Zaitsev's rule and explain what type of reaction this is.
3. List and explain two of the 12 Principles of Green Chemistry that are applied in this greener alternative experiment.

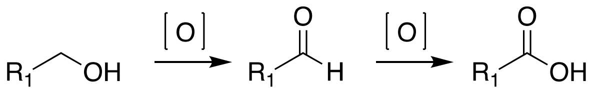
Experiment 4: The Oxidation Reaction

Introduction

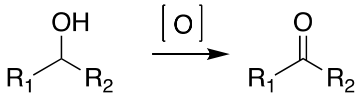
The oxidation of alcohols is a very versatile transformation, which is widely used in organic synthesis for the preparation of functionalized carbonyl-containing compounds. The product depends on the type of alcohol starting material – primary, secondary, or tertiary, as illustrated below.

Primary (1°) alcohols have two hydrogens at the α position and can therefore undergo two consecutive oxidations. The first oxidation produces an aldehyde, which may be subsequently oxidized to a carboxylic acid. Secondary alcohols (2°) have one hydrogen at the α position and only undergo a single oxidation to produce a ketone. Tertiary alcohols (3°) generally do not undergo oxidation.

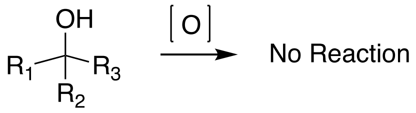
Primary Alcohol



Secondary Alcohol



Tertiary Alcohol



Chromium-based reagents have traditionally been used to oxidize 1° and 2° alcohols. These are hazardous, expensive, heavy-metal compounds that pose both environmental and health risks, and produce toxic waste that requires special handling. Moreover, such reactions are generally carried out in chlorinated hydrocarbon solvents, which furthers the safety concerns and environmental impact. Only some Cr-based reagents are selective for single oxidation of 1° alcohols to yield the aldehyde, whereas others will go on to react with the aldehyde and produce a carboxylic acid, which is not always the desired product.

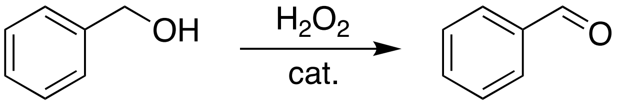
Pyridinium chlorochromate (PCC), a hazardous, heavy-metal reagent, is often regarded as the only feasible reagent for transforming alcohols to aldehydes in most undergraduate textbooks. Fortunately, this is not the case. Safer alternatives that employ more environmentally benign reagents have been developed using sodium molybdate and aqueous hydrogen peroxide to achieve the selective oxidation of alcohol to aldehyde.

The following principles of green chemistry are employed in the alternative experiment described herein:

- Less Hazardous Chemical Synthesis
- Safer Solvents & Auxiliaries
- Catalysis
- Real-Time Pollution Prevention
- Safer Chemistry for Accident Prevention

Oxidation Reaction – A Greener Alternative

The greener approach uses a molybdenum catalyst as a replacement for the traditional reagents. In this reaction, the oxidizing agent is formed from sodium molybdate to make an efficient catalyst that is activated by aqueous hydrogen peroxide.



Reference

Selective Oxidation of Benzyl Alcohol to Benzaldehyde, Levy, I., Assor, K., Thames, E., and Walker, R., Gordon College Organic Chemistry Laboratory Experiment, laboratory exercise inspired by Guo, Ming-Lin; Li, Hui-Zhen Li., Selective oxidation of benzyl alcohol to benzaldehyde with hydrogen peroxide over tetraalkylpyridinium octamolybdate catalysts, Green Chem., 2007, 9, 421-423.

Experimental

Preparation of Tetrakis(benzyltriethylammonium) Octamolybdate Catalyst

1. To prepare the catalyst, add sodium molybdate dihydrate (0.30 g; 1.2 mmol), and 4 M HCl (0.5 mL; 2.0 mmol) to a vial. Add 1 mL of water to complete the dissolution.
2. To a second vial, stir benzyl triethyl ammonium chloride (BTEAC) (0.525 g; 2.30 mmol) and ca. 3 mL water until dissolved. Heat the BTEAC solution to 70 °C with stirring.
3. Add the molybdate solution, dropwise, to the BTEAC solution, and stir for an additional 5 minutes.
4. Remove from heat and obtain the solid product by vacuum filtration. Wash the solid with ca. 5 mL water while on the filter under vacuum.

Preparation of Benzaldehyde

1. Add benzyl alcohol (5 mL; 50 mmol) to a 50 mL round bottom flask containing dry catalyst (0.25 g; 0.2 mol%).
2. Add 15 wt% hydrogen peroxide (12 mL; 60 mmol) to the flask. Heat the mixture to reflux for 60 minutes.
3. Allow the reaction flask to cool to room temperature. Isolate the product by simple distillation to yield benzaldehyde and water in the distillate.
4. Remove water with a pipet and dry the product over sodium sulfate.
5. Weigh the product and calculate yield, and record IR spectrum.

Health and Safety

EHS Key:

🟨	**Physical hazard**
🟨	**Toxicity/Health hazard**
⬜	**Persistent Bioaccumulative Toxic (PBT) Chemicals**

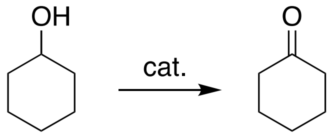
🟥 *	**Very high hazard**
🟥	**High hazard**
🟨	**Moderate hazard**
🟩	**Low hazard**
⬜	**No data**

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Sodium molybdate dihydrate 331058	15 g	🟩 🟩 🟩
Hydrochloric acid, 4 M 320331	75 mL	🟨 🟨 🟨
Benzyl triethyl ammonium chloride 146552	26.25 g	🟩 🟨 🟩
Water n/a	400 mL	🟩 🟩 🟩
Benzyl alcohol 305197	250 mL	🟩 🟨 🟨
Hydrogen peroxide, 3% 216763	3000 mL	🟩 🟩 🟩
Sodium sulfate 239313	250 g	🟩 🟩 🟩

Traditional Oxidation Reaction

Most organic chemistry laboratory procedures for the oxidation of alcohols to aldehydes or ketones involve the use of hazardous oxidizing agents, such as chromium compounds. Some of the most ubiquitous of these compounds are pyridinium chlorochromate (PCC) and sodium dichromate dihydrate, which have high human toxicities.



Reference

The Oxidation of a Ketone to a Carboxylic Acid: Cyclohexanone from Cyclohexanol, Macroscale and Microscale Organic Experiments, Williamson, K.L., Masters, K.M., 6th Edition, Brooks/Cole Cengage Learning, 2011, pp. 358-359.

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Sodium dichromate dihydrate 398063	375 g	🟥 🟥 🟥 *
Acetic acid, 1M 965092	1000 mL	🟩 🟩 🟩
Cyclohexanol 105899	375 g	🟨 🟨 🟩
Water n/a	2500 mL	🟩 🟩 🟩
Sodium chloride 746398	400 g	🟩 🟩 🟩
Anhydrous diethyl ether 346136	750 mL	🟥 * 🟨 🟨
Sodium hydroxide, 3M 221465	500 mL	🟨 🟨 🟩
Sodium chloride, sat. solution 746398	750 mL	🟩 🟩 🟩
Calcium chloride 793639	125 g	🟩 🟨 🟩

Comparative Analysis of Traditional vs. Suggested Experiments

- Greener method avoids the use of chromium compounds, which have high human toxicities
- Greener method avoids the use of diethyl ether, which is highly flammable
- Greener method generates less solvent waste and has reduced purchasing costs
- The comparative estimated costs for all reagents per 100 students for this experiment is $110 for the Greener method versus $339 for the Traditional method. Actual costs will vary.

	Waste Reduction (per 100 students)	**"Greener" Benefits**
Greener method	3800 mL liquid waste 250 g solid waste	⚠ 🕒
Traditional method	6600 mL liquid waste 125 g solid waste	

Additional Resources & Further Reading

The following are additional greener alternative laboratory experiment options:

- Oxidation of Aromatic Aldehydes Using Oxone, J. Chem. Educ., 2007, 84 (5), 852. (aldehyde-acid)
- Environmentally Responsible Redox Chemistry: An Example of Convenient Oxidation Methodology without Chromium Waste, J. Chem. Educ., 2006, 83 (2), 268. (alcohol oxidation)
- pH-Controlled Oxidation of an Aromatic Ketone: Structural Elucidation of the Products of Two Green Chemical Reactions, J. Chem. Educ., 2010, 87 (2), 190–193. (ketone oxidation)
- Oxidation of Borneol to Camphor Using Oxone and Catalytic Sodium Chloride: A Green Experiment for the Undergraduate Organic Chemistry Laboratory, J. Chem. Educ., 2011, 88 (5), 652–656. (alcohol oxidation)
- Oxidation of Cyclododecanol to Cyclododecanone, Experimental Organic Chemistry, Gilbert and Martin, 5th Edition, 2011, p. 543-544.

TA Guide

Oxidation of alcohols to aldehydes has been traditionally demonstrated using pyridinium chlorochromate (PCC), a hazardous, heavy-metal reagent. PCC is the textbook standard for the alcohol to aldehyde transformation, and has even been cited as the only reagent to carry out this reaction. Moreover, dichloromethane (DCM) has been the recommended solvent to carry out this reaction. Both PCC and DCM are hazardous and potential carcinogens.

The greener alternative reaction to achieve the same transformation demonstrated in this lab employs an environmentally benign oxidizing agent formed from sodium molybdate activated by hydrogen peroxide, which serves as an efficient catalyst. Hydrogen peroxide also lends itself as the solvent for this reaction.

The following principles of green chemistry are employed:

- Less Hazardous Chemical Synthesis
- Safer Solvents & Auxiliaries
- Catalysis
- Real-Time Pollution Prevention
- Safer Chemistry for Accident Prevention

Fun Facts

- There are several solvent selection guides that can help you transition to safer solvents for reactions and in column chromatography. Pfizer, GSK, and Sanofi have all published guides according to their own standard, and many papers have been published comparing these three guides and ranking solvents overall from preferred to major issues.
- Approximately 1 million pounds per year of sodium molybdate are used in the agriculture industry as a fertilizer
- Sodium molybdate is also used in industry for corrosion inhibition

Example Quiz Questions

The following are examples of questions that may be used on pre- or post-lab quizzes, assignments, etc. or as discussion points during a lecture.

1. Explain the mechanism by which sodium molybdate is activated by hydrogen peroxide, and subsequent catalytic activity.
2. Describe why the benzaldehyde oxidation reaction is selective for the carboxylic acid.
3. What is one thing you could change in this reaction to make it even greener?

Experiment 5: The Polymerization Reaction

Introduction

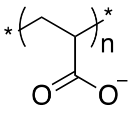
The chemical industry has flourished over the last 150 years, primarily on the manufacturing of synthetic dyes, pharmaceuticals, and polymers. As much as half of all professional chemists will work in polymer science to some extent during their career, making this a very broad and diverse branch of the chemical industry. In fact, synthetic polymers comprise over half of the compounds produced by the chemical industry.

A polymer is a molecule that is comprised of repeating subunits called monomers. These are most typically thought of as plastics, but also include proteins such as collagen, keratin, enzymes, and hormones; polysaccharides such as cellulose, chitin, starch, and glycogen; DNA and RNA; and materials such as Teflon, rubber, polystyrene, polyester, nylon, and rayon.

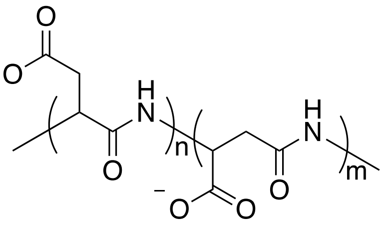
Polymerization is the chemical conversion of monomers into a polymer chain or network. Chain-reaction (or addition) polymerization typically involves reactive species such as radicals, and takes place through three defined steps: initiation, propagation, and termination. Conversely, step-reaction (or condensation) polymerization proceeds by conventional functional group transformations, often with the loss of a by-product such as water.

Polymers have proven to be of great use in the water treatment industry. The accumulation of insoluble materials in water-handling infrastructure can lead to a number of issues. Scale inhibitors are typically added to industrial water to help prevent buildup of these materials. The scale inhibitor additive is eventually removed in a wastewater treatment facility along with other contaminants, which creates a sludge that is disposed of in a landfill.

One of the most widely used scale inhibitors is a polymer called poly(acrylate) (PAC). Although PAC is relatively non-toxic and environmentally benign, it is not biodegradable.



PAC



TPA

Thermal poly(aspartate) (TPA) is a biodegradable polymer alternative that is just as effective in preventing scale, but can be broken down by microorganisms in wastewater treatment plants. It has also been shown to enhance nutrient uptake in crops, and thereby decreases quantity of fertilizer necessary in the agricultural industry.

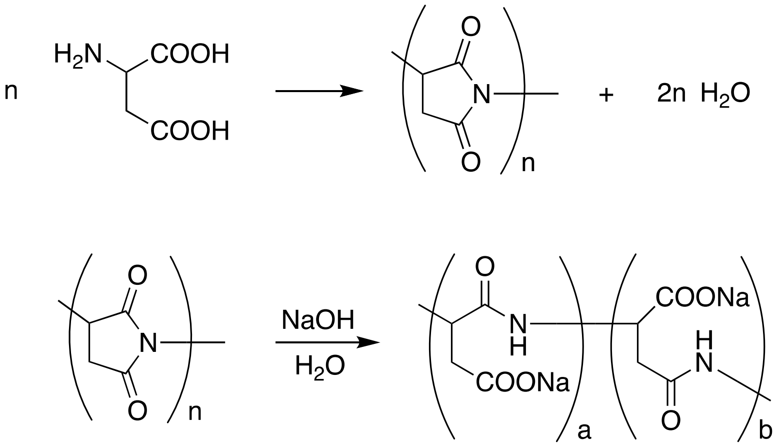
This teaching experiment is similar to the commercial method developed by Donlar Corp., which uses no organic solvents and produces little to no waste.

The following principles of green chemistry are employed in the alternative experiment described herein:

- Prevent Waste
- Less Hazardous Chemical Synthesis
- Design Benign Chemicals
- Use of Renewable Feedstocks
- Design for Degradation
- Real-Time Pollution Prevention
- Safer Chemistry for Accident Prevention

Polymerization Reaction – A Greener Alternative (1)

This greener reaction involves the polymerization of aspartic acid to create poly(aspartate), which has similar applications to poly(acrylate) polymers.



Reference

A Green Polymerization of Aspartic Acid for the Undergraduate Organic Laboratory, J. Chem. Educ., 2005, 82, 1380–1381.

Experimental[30]

Caution: High temperatures used during heating pose a burn hazard. Glass beakers that are cooled too quickly can crack from thermal shock. Sodium hydroxide solutions can cause severe eye and skin damage. Aqueous solutions of hydrochloric acid can be corrosive. Take all necessary precautions to avoid these hazards and prevent accidents.

1. Weigh 1.33 g (0.0100) mol of L-aspartic acid into a 150-mL beaker.
2. Place the beaker into a sand bath (in a 500-mL thermowell) such that the sand covers most of the bottom half of the outside of the beaker. Use a thermometer to monitor the temperature of the sand bath, and heat to ~250 °C. Maintain the sand bath at that temperature until all of the solid has turned to a tan or yellow color or for 2 hours, whichever comes first. During the period of heating, a glass stirring rod should be used to agitate the contents of the beaker every minute or so to prevent charring.
3. Allow the beaker to cool to room temperature on a cork ring. Place the cooled solid on a suction filter and wash with sat. aq. $NaHCO_3$ (3 x 5 mL), water (5 mL), 1% HCl (5 mL), and water (5 mL).
4. Dry the solid in the oven for at least 30 minutes, and then weigh the dried solid. Calculate the polymer percent yield.
5. Place the solid into a dry, pre-weighed 250-mL beaker. Add 0.1 M aqueous NaOH to the beaker of polysuccinimide. The volume in mL should be the same as the polymer percent yield or 100, whichever is lower.
6. Stir the mixture until all of the solid dissolves. You might need to warm the contents of the beaker. Place the beaker on a hot plate, and bring the solution to a boil. Use a glass stirring rod to break up surface tension (rather than a magnetic stir bar or boiling chips). Continue heating until the water has almost completely evaporated. [Note: If the contents of the beaker start to splatter, remove the beaker from the hot plate.]
7. Remove the beaker from the hot plate, and allow it to cool on a cork ring.
8. Cover the beaker with a watch glass or petri dish, and place it in the oven for at least 30 minutes to complete the drying and then weigh the dried solid. Calculate the polymer percent yield of your sodium poly(aspartate). Calculate the approximate molecular weight, PW, of your polymer.
9. Use a pH meter to determine the pH of 50-100 mL of magnetically stirred distilled water in a 150-250 mL beaker. Weigh about 0.5 g of the polymer to at least three figures on an analytical balance, and dissolve the sample in the water. Titrate this solution with standardized HCl solution (the molarity will be ~0.2 and will be listed to at least three significant figures) until the pH of the solution matches the initial pH of the water.
10. Calculate the weight of the repeating unit (UW) according to the equation:

    $$\mathbf{UW = (sample\ mass\ in\ g)(volume\ HCl\ solution\ in\ L)^{-1}(conc.\ HCl\ solution\ in\ moles/L)^{-1}}$$

    Each time a monomer of sodium aspartate (molar mass = 155) adds to the growing polymer chain, a molecule of water (molar mass = 18) is lost, and a titratable acid is added. Therefore, for a chain of n monomers:

    $$\mathbf{UW = [155n-18(n-1)]/n = (137n+18)/n}$$

    Solve for n by using the rearranged equation:

    $$\mathbf{n = 18/(UW-137)}$$

    $$\mathbf{PW = n(UW)}$$

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[30] Experimental procedure reprinted with permission from Bennett, G., J. Chem. Educ., 2005, 82, 1380–1381. Copyright 2005 American Chemical Society.

Health and Safety

EHS Key:

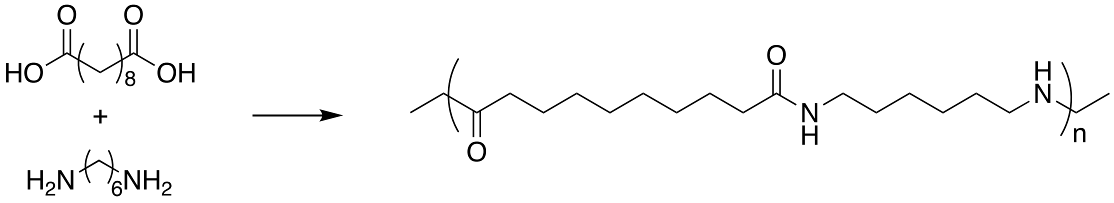
🟨	**Physical hazard**	🟥*	**Very high hazard**
🟨	**Toxicity/Health hazard**	🟥	**High hazard**
⬜	**Persistent Bioaccumulative Toxic (PBT) Chemicals**	🟨	**Moderate hazard**
		🟩	**Low hazard**
		⬜	**No data**

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
L-Aspartic acid A9256	67 g	🟩 🟩 🟩
Sodium bicarbonate, sat. sol’n S6014	750 mL	🟩 🟩 🟩
Hydrochloric acid, 1% 320331	250 mL	🟩 🟩 🟩
Water N/A	250 mL	🟩 🟩 🟩
Sodium hydroxide, 0.1M 221465	5000 mL	🟩 🟩 🟩

Traditional Polymerization Reaction

Polymerizations are commonly taught within organic chemistry laboratory courses, with one of the most common being the polymerization of nylon. Procedures typically involve the use of chlorinated solvents and hazardous reagents. In this procedure, sebacic acid and 1,6-hexanediamine are used to create a nylon polymer in a condensation polymerization.



Reference

Synthesis of nylon by interfacial polymerization, Macroscale and Microscale Organic Experiments, 6e; Brooks/Cole, 2011; pp. 763-765.

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Sebacic acid 283258	100 g	🟩 🟩 🟨
Thionyl chloride 320536	100 mL	🟩 🟥 🟨
Dimethylformamide 227056	5 mL	🟨 🟥 * 🟨
Dichloromethane 676853	2500 mL	🟩 🟥 🟥
1,6-Hexanediamine H11696	100 g	🟨 🟥 🟨
Sodium hydroxide 221465	50 g	🟥 *C 🟥 🟨
Water n/a	3750 mL	🟩 🟩 🟩

Comparative Analysis of Traditional vs. Suggested Experiments

- Greener method avoids the use of hazardous solvents such as dichloromethane and dimethylformamide
- Greener method avoids the use of thionyl chloride
- The comparative estimated costs for all reagents per 100 students for this experiment is $22 for the Greener method versus $164 for the Traditional method. Actual costs will vary.

	Waste Reduction (per 100 students)	**“Greener” Benefits**
Greener method	6600 mL liquid waste (6000 mL aqueous waste)	🌿 ⚗
Traditional method	6600 mL liquid waste (3700 mL aqueous waste)	

Additional Resources & Further Reading

The following are additional greener alternative laboratory experiment options:

- Sustainable Polymers in the Organic Chemistry Laboratory: Synthesis and Characterization of a Renewable Polymer from δ-Decalactone and l-Lactide, J. Chem. Educ. 2014, 91, 131-135. (renewable triblock copolymers)
- The Cyclohexanol Cycle and Synthesis of Nylon 6,6: Green Chemistry in the Undergraduate Organic Laboratory, J. Chem. Educ., 2012, 89 (2), 262–264.
- Ring-Opening Polymerization of Lactide To Form a Biodegradable Polymer, J. Chem. Educ. 2008, 85, 258–260. (polylactic acid)

TA Guide

Sodium poly(acrylate) is a superabsorbent polymer, and has broad applications in consumer products such as an anti-scaling agent, potting soil, and disposable diapers. It is made from petroleum-based feedstocks, and is either precipitated or absorbed during wastewater treatment and disposed of in a landfill. Sodium poly(aspartate) functions in a similar manner, but is biodegradable, and made from a readily-available, biodegradable amino acid.

A more sustainable way to incorporate polymers in the teaching lab is the polymerization of aspartic acid, demonstrated in the lab at hand.

The following principles of green chemistry are employed:

- Prevent Waste
- Less Hazardous Chemical Synthesis
- Design Benign Chemicals
- Safer Solvents & Auxiliaries
- Use of Renewable Feedstocks
- Design for Degradation
- Real-Time Pollution Prevention
- Safer Chemistry for Accident Prevention

Tips and Tricks

- Have students agitate the aspartic acid/poly(succinimide) periodically (every minute or so) during the heating period to prevent charring. A glass stir rod is preferred over a magnetic stir bar.
- Washing the poly(succinimide) with sodium hydrogen carbonate will remove unpolymerized aspartic acid and small oligomers.
- Water and HCl washes remove residual $NaHCO_3$, and the final water wash helps remove remaining HCl.
- When boiling away water after hydrolysis is complete, the solution may splatter when volume is reduced. Prepare a cork ring and tongs to remove the beaker from the hot plate should this occur.
- Special precautions need to be taken due to high temperatures used during this reaction. Glass beakers can crack from thermal shock if cooled too quickly.
- When performing the titration to determine molecular weight of the polymer, the amount of titrant will vary depending on the amount of sodium poly(aspartate) dissolved, concentration of standardized HCl, and size of the polymer.
- The product may be disposed of in the drain as an aqueous solution, and the anti-scaling properties may leave the plumbing cleaner.

Example Quiz Questions

The following are examples of questions that may be used on pre- or post-lab quizzes, assignments, etc. or as discussion points during a lecture.

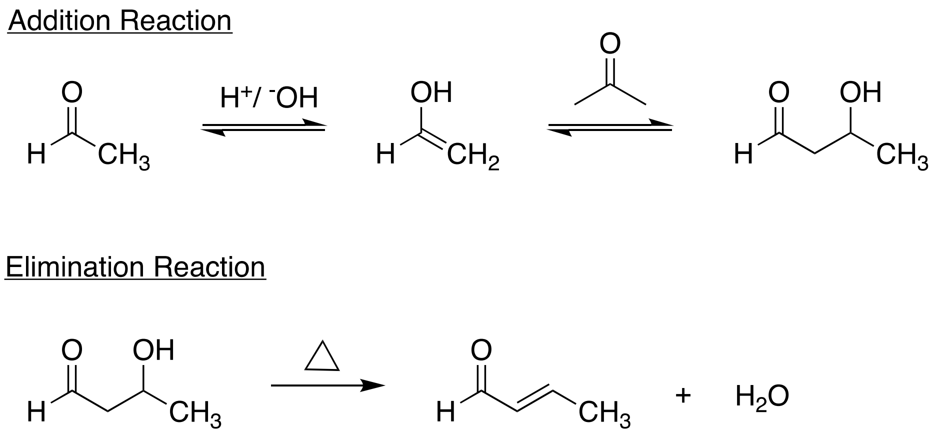
1. Propose a mechanism for each of the two steps involved in this reaction?
2. The product is a polymer of an amino acid. Is it, therefore, considered a protein? Why or why not?
3. What is the purpose of the four washing steps in the procedure between the thermal polymerization of aspartic acid and the hydrolysis with NaOH?
4. What is green about this procedure?
5. What is not green about this procedure?
6. How can this procedure be made greener?
7. If you wanted to try to polymerize glutamic acid by this method, what, if anything, would you change about the procedure? (Hint: Compare the melting points of L-aspartic acid and L-glutamic acid.)

Experiment 6: The Aldol Condensation Reaction

Introduction

A condensation reaction refers to reactions in which an addition reaction between two molecules takes place, followed by loss of a small molecule such as water, carbon dioxide, or nitrogen gas.

One of the most powerful synthetic pathways to generate carbon-carbon bonds, a central focus in organic chemistry, is the aldol condensation. An aldol possesses both an aldehydic group and a hydroxyl group, and hence the name aldol – *ald* for aldehyde, and *ol* for alcohol. When heated in acidic or basic conditions, the product of an aldol addition reaction will undergo elimination to yield an α,β-unsaturated aldehyde or ketone with concomitant loss of water.



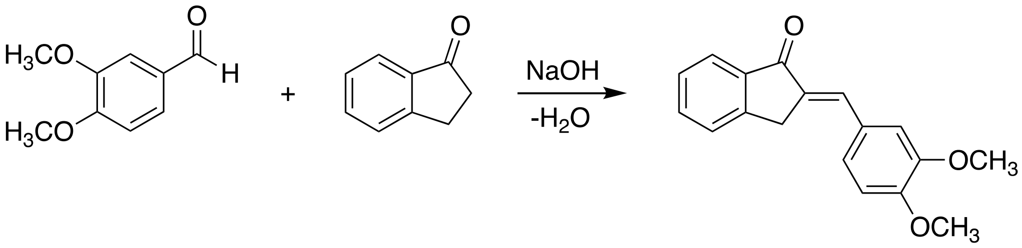
These lab experiments illustrate examples of neat (i.e. solventless) aldol condensation reactions. They proceed with high atom economy and are relatively simple reactions to carry out. By avoiding the use of a solvent, these experiments are an excellent demonstration of greener synthetic routes and practices that may be extended into research settings.

The following principles of green chemistry are employed in the alternative experiment described herein:

- Safer Solvents & Auxiliaries
- Waste prevention
- Atom Economy
- Real-Time Pollution Prevention
- Safer Chemistry for Accident Prevention

Aldol Condensation Reaction – A Greener Alternative (1)

This neat aldol condensation of 3,4-dimethoxybenzaldehyde and 1-indanone allows students to perform a based-catalyzed reaction by grinding two raw materials together and witnessing the melting of the reactants for the reaction to occur. The product is produced through aqueous work-up and recrystallized in ethanol/water.



Reference

Solventless Reactions: The Aldol Reaction, Green Organic Chemistry – Strategies, Tools, and Laboratory Experiments, Doxsee, K.M. And Hutchison, J.E., Tompson Brooks/Cole, 2004, p. 115-119.

Experimental

1. Place 0.25 g of 3,4-dimethoxybenzaldehyde and 0.20 g of 1-indanone in a test tube. Use care to avoid breaking the test tube. Using a metal spatula, scrape and crush the two solids together until a brown oil is observed.
2. Using a mortar and pestle, grind 0.05 g solid NaOH to a fine texture, and add this to the reaction mixture. Continue scraping until the mixture becomes solid.
3. Allow the mixture to stand for 15 minutes, then add 2 mL of 10% aqueous HCl solution. Scrape well in order to dislodge the product from the walls of the test tube. Check the pH of the solution to make sure it is acidic.
4. Isolate the solid product by vacuum filtration, continuing to pull air through the solid to facilitate drying. Determine the mass of the crude product.
5. Recrystallize the product from 90% ethanol/10% water, using the hot solvent first to rinse any remaining product from the test tube. You should not require more than 20 mL of solvent to effect this recrystallization.
6. Determine the mass and melting point of the recrystallized product.

Health and Safety

EHS Key:

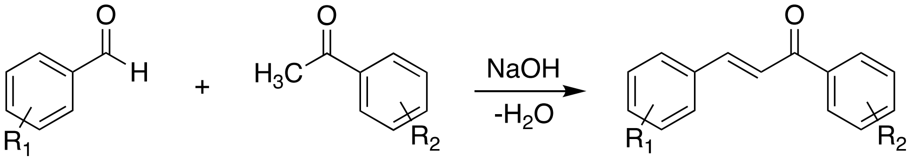
🟨	Physical hazard	🟥 *	Very high hazard
🟨	Toxicity/Health hazard	🟥	High hazard
⬜	Persistent Bioaccumulative Toxic (PBT) Chemicals	🟨	Moderate hazard
		🟩	Low hazard
		⬜	No data

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
3,4-dimethoxybenzaldehyde 143758	12.5 g	🟩 🟨 🟨
1-indanone I2304	10 g	🟩 🟩 🟨
sodium hydroxide 221465	2.5 g	🟥 *C 🟥 🟨
Hydrochloric acid, 3M 320331	100 mL	🟩 🟨 🟨
Ethanol, 90% 792799	750 mL	🟥 🟨 🟩

Aldol Condensation Reaction – A Greener Alternative (2)

This solventless aldol condensation is the solventless synthesis of chalcones, made by mixing and matching various aldehydes and acetophenones (see literature reference for corresponding tables). The reactions are promoted by grinding the reagents in a mortar and pestle. The work-up of the chalcones is simple, which requires only water. The final product can be recrystallized in ethanol, ethanol-water, or ethanol-toluene, depending on the product (see primary literature for typical yields and tables with properties of the product).



Reference

Solventless Synthesis of Chalcones, J. Chem. Educ., 2004, 81, 1345.

Experimental

1. To a 3-inch porcelain mortar, add 5 mmol of benzaldehyde, 5 mmol of acetophenone, and 200 mg of solid NaOH. Grind with the pestle for 5-10 minutes. The mixture may quickly become pasty. Continue grinding until the mixture solidifies and breaks into small particles.
2. Add 10 mL distilled water and mix with the pestle and a spatula to dislodge the solid from the wall of the mortar.
3. Obtain the solid via suction filtration using a Buchner funnel. Rinse the mortar and pestle with 5 mL water and collect the rinses on the same filter.
4. Wash the product on the filter with an additional 5 mL water and allow to dry.
5. Obtain the mass of the product, determine the melting point, and analyze by melting point and NMR spectroscopy.

Optional

Recrystallize the crude product from 95% ethanol. However, this may be eliminated as the crude product typically consists of >90% chalcone.

There are 20 variations of this reaction in the original publication, which follow the same procedure and slightly modified work ups, by simply alternating the starting materials. It is anticipated that 3-4 may be completed in a 3-hour lab period.

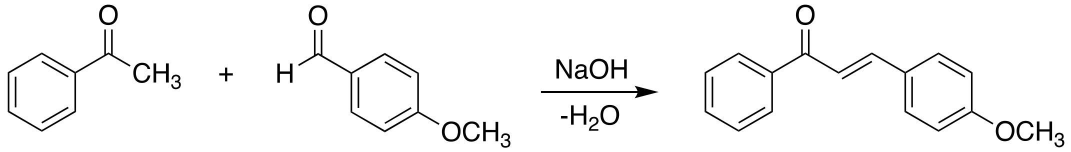
Health & Safety Evaluation

	Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
One of the following aldehydes are used (the amounts listed are the total amounts for each aldehyde needed if only that aldehyde was selected):	p-anisaldehyde A88107	34 g	🟩 🟩 🟨
	p-tolualdehyde T35602	30 g	🟨 🟨 🟨
	4-chlorobenzaldehyde 112216	35 g	🟨 🟨 🟥
	3-chlorobenzaldehyde C23403	35 g	🟨 🟨 🟥
	Benzaldehyde B1334	26.5 g	🟨 🟥 🟥
One of the following acetophenones are used (the amounts listed are the total amounts for each acetophenone needed if only that acetophenone was selected):	Acetophenone A10701	29 mL	🟨 🟨 🟨
	4’-methylacetophenone M26615	37.5 g	🟨 🟩 🟨
	4’-bromoacetophenone B56404	50 g	🟩 🟨 🟨
	4’-methoxyacetophenone 117374	33.5 g	🟩 🟩 🟩

Continued from above	Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
	Sodium hydroxide 221465	10 g	🟥 *C 🟥 🟨
	Water n/a	1000 mL	🟩 🟩 🟩
	Ethanol, 95% 459836	500 mL	🟥 🟨 🟩
	Toluene 244511	250 mL	🟥 🟥 🟨

Traditional Aldol Condensation Reaction

The Aldol Condensation is an important carbon-carbon bond forming reaction. In this classic reaction, an α,β-unsaturated carbonyl compound is formed by a crossed-aldol condensation.



Reference

Preparation of trans-p-Anisalacetophenone, Experimental Organic chemistry, 2011, 5th Edition, Gilbert and Martin, p. 620.

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
p-anisaldehyde A88107	10 mL	🟩 🟩 🟨
Acetophenone A10701	10 mL	🟨 🟨 🟩
Sodium hydroxide 221465	25 g	🟥 *C 🟥 🟨
Water n/a	25 mL	🟩 🟩 🟩
Ethanol, 95% 459836	50 mL	🟥 🟨 🟩
Methanol 322415	500 mL	🟥 🟥 🟥

Comparative Analysis of Traditional vs. Suggested Experiments

- Greener methods introduce the concepts of solventless synthesis. However, solvents are required in the work-up of the reaction to produce the product.
- Greener processes avoid the use of methanol.
- The comparative estimated costs for all reagents per 100 students for this experiment is $46 for the Greener method (1) and $134 for the Greener method (2), versus $38 for the Traditional method. Actual costs will vary.

	Waste Reduction (per 100 students)	**"Greener" Benefits**
Greener method (1): solventless aldol	875 mL liquid waste	⚗
Greener method (2): solventless synthesis of chalcones	1000 mL liquid aqueous waste ~500 mL solvent waste (recrystallization)	⚗
Traditional method	620 mL liquid waste	

Additional Resources & Further Reading

The following are additional greener alternative laboratory experiment options:

- Green Chemistry Laboratory: Benign Synthesis of 4,6-Diphenyl[2,2']bipyridine via Sequential Solventless Aldol and Michael Additions, J. Chem. Educ. 2005, 82, 468-469.
- A Green Enantioselective Aldol Condensation for the Undergraduate Organic Laboratory, J. Chem. Educ. 2006, 83, 1871-1872.
- The Aldol Addition and Condensation: The Effect of Conditions on the Reaction Pathway, J. Chem. Educ. 2007, 84, 475-476.

TA Guide

Proteins are fundamental biological compounds. One of the most abundant of such is collagen, which can be found in bones and skin, and is often associated with the aging process. Individual collagen units can be isolated from younger animals. However, collagen undergoes an aldol condensation reaction to cross-link with one another and, as an animal ages, the number of these cross-linked proteins increase.

These lab experiments illustrate an example of solventless aldol condensation reactions. They proceed with high atom economy and are relatively simple reactions to carry out. Students will use a mortar and pestle to grind the starting materials, and either transfer to a test tube, or carry out the reaction in the mortar. Given the high yields and simple purification of the desired product, the scale of these reactions can be easily modified to suit the needs of your group.

You should familiarize yourself with the hazards, toxicity, and proper disposal of the chemicals being used in the experiments you will be teaching. Please note, none of the acetophenones in the second greener alternative reaction are lachrymators. The starting materials are irritants and NaOH is caustic. Skin and eye contact of all chemicals should be avoided, especially of the chalcone products. The experiments should be carried out in a fume hood, and the use of gloves is highly recommended. Please discuss proper use of gloves with your students.

The following principles of green chemistry are employed:

- Safer Solvents & Auxiliaries
- Waste prevention
- Atom Economy
- Real-Time Pollution Prevention
- Safer Chemistry for Accident Prevention

Tips & Tricks

- Remind students of proper recrystallization technique, including minimal solvent use and scratching the flask with a glass rod, if necessary.

Fun Facts

- In the late 1980's, Toda and coworkers studied a number of solventless reactions. They found that the absence of solvent usually leads to faster and cleaner processes for select transformations.
- Retro-aldol condensation reactions are an essential part of many biochemical processes, including energy generation for muscles. For example, glycolysis uses a retro-aldol condensation catalyzed by the enzyme aldolase.

Example Quiz Questions

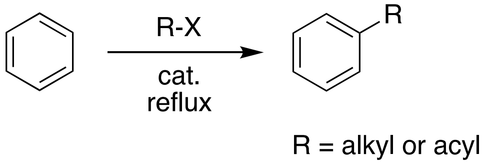
The following are examples of questions that may be used on pre- or post-lab quizzes, assignments. or as discussion points during a lecture.

1. What is the atom economy for the reaction?
2. Explain the melting point depression phenomenon.
3. What are the advantages of eliminating the reaction solvent? Are there any drawbacks to eliminating the solvent? If so, explain.
4. Propose a plausible mechanism for a base-catalyzed aldol reaction.
5. Which protons in the ^1H NMR spectrum would be the most diagnostic in determining if you've formed the chalcone product?

Experiment 7: The Friedel-Crafts Alkylation and Acylation Reactions

Introduction

It was in 1877 that Charles Friedel and James Crafts discovered what is now known as the Friedel-Crafts reactions. This set of reactions allow for the installation of alkyl and acyl substituents on an aromatic ring. There are two types of Friedel-Crafts reactions in this guide: alkylation and acylation. Both proceed by electrophilic aromatic substitution-type mechanisms.



The key to these reactions is the Lewis acid catalyst, which facilitates the conversion of the alkyl or acyl halide electrophile into a reactive carbocation. Aluminum trichloride is traditionally employed as the Lewis acid catalyst. However, a greener approach has been developed which employs graphite. While an alkyl halide is electrophilic, without the conversion to a carbocation it is not sufficiently electrophilic to react with an aromatic ring such as benzene.

It is also important to note that, in practice, a Friedel-Crafts alkylation should be carried out with a secondary or tertiary halide substrate, as to generate a more stable carbocation for which rearrangement is unlikely. Otherwise, a mixture of products will be obtained. However, Friedel-Crafts alkylations are not limited to alkyl halides and can be carried out using a variety of carbocationic intermediates, such as those obtained from alkenes and a protic acid, Lewis acid, enones, and epoxides.

A challenging component of this reaction is that the ensuing product is more nucleophilic than the reagents due to the electron donating nature of the alkyl chain. This can result in polyalkylation of the same molecule. Although not always the most practical solution, the selectivity of the reaction can be improved by modifying the steric profile of the substrates.

An acyl group may also be installed on an aromatic ring through a Friedel-Crafts acylation. This reaction has advantages over the alkylation reaction. The ketone product is less reactive than the starting material due to the electron withdrawing nature of the carbonyl group, diminishing the potential for undesired polyacylations. Moreover, carbocation rearrangements do not occur, as the carbonium ion is resonance stabilized.

The mechanism is very similar to that of the alkylation reaction. An acyl halide, in the presence of a Lewis acid catalyst, forms a cationic acylium ion. This intermediate ion is resonance stabilized and therefore not prone to rearrangement, as resonance would be lost if a carbocation rearrangement were to occur. The acylium ion is an excellent electrophile, and undergoes an electrophilic aromatic substation with benzene to yield the final product – an aryl ketone. It should be noted that a significant driving force for these reactions following initial reaction with the Lewis acid, is the re-establishment of aromaticity, which is temporarily lost in the first step.

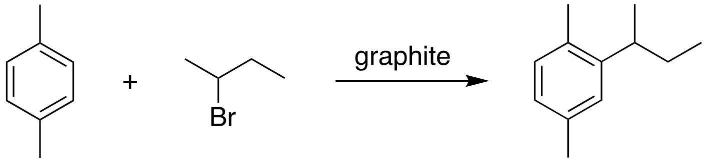
These reactions are related to a number of classic named reactions including the Clemmensen reduction, Gattermann-Koch reaction, Gattermann reaction, Houben-Hoesch reaction, Fries rearrangement, Scholl reaction or Friedel-Crafts arylation, and many more. The Friedel-Crafts reactions are fundamental to a number of industrial processes and have been employed in modern chemistry, such as ionic liquid-based syntheses and beyond.

The following principles of green chemistry are employed in the alternative experiment described herein:

- Safer Solvents and Auxiliaries
- Reduce Derivatives
- Catalysis
- Safer Chemistry for Accident Prevention

Friedel-Crafts Alkylation Reaction – A Greener Alternative

This alternative Friedel-Crafts Alkylation reaction uses graphite to catalyze the alkylation of *p*-xylene by 2-bromobutane. This procedure avoids the use of aluminum chloride and the associated aqueous work-up of the product.



Reference

A Greener Alternative to Aluminum Chloride Alkylation of Xylene, Sereda, G.A. And Rajpara, V.B., J. Chem. Ed., 2007, 84(4), 692.

Experimental[31]

Caution: *p*-Xylene and 2-bromobutane are flammable.

1. Place 5 mL of *p*-xylene, 0.44 mL (4 mmol) of 2-bromobutane and 0.5 g of graphite in a round-bottom flask.
2. Reflux the reaction mixture for 1.5 h with a water-cooled condenser.
3. Cool the reaction flask to room temperature, filter out graphite on a fritted funnel, rinse the reaction flask and wash the graphite with 15 mL of hexane, dry on air for 10 min (use the aspirator to pass air through the filter cake for 10 min) and turn in to the instructor.
4. Combine all filtrates in a pre-weighed round-bottom flask; evaporate hexane and excess xylene on a rotary evaporator.
5. Weigh the liquid 2-sec-butyl-1,4-dimethylbenzene, calculate the yield.
6. Record ^{1}H- and COSY NMR-spectra of the obtained product.
7. Repeat steps 1-5, but use 0.1 g of graphite instead of 0.5 g.

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[31] Experimental procedure reprinted within permission from Sereda, G.A. And Rajpara, V.B., J. Chem. Ed., 2007, 84(4), 692. Copyright 2007 American Chemical Society.

Health and Safety

EHS Key:

🟨 **Physical hazard**
🟨 **Toxicity/Health hazard**
⬜ **Persistent Bioaccumulative Toxic (PBT) Chemicals**

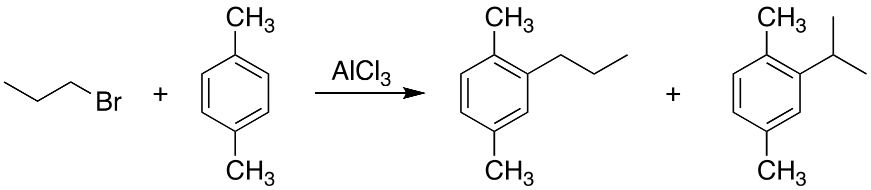
🟥 * **Very high hazard**
🟥 **High hazard**
🟨 **Moderate hazard**
🟩 **Low hazard**
⬜ **No data**

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
p-xylene 134449	250 mL	🟥 🟩 🟥
2-bromobutane B59500	22 mL	🟥 🟩 🟨
Graphite (<20 micron particles) 282863	25 g	🟩 🟩 🟨
Heptane 246654	750 mL	🟥 🟨 🟥 *

Traditional Friedel-Crafts Alkylation Reaction

The Friedel-Crafts alkylation reaction proceeds similarly to the acylation reaction, but uses an alkyl halide to attach an alkyl group to an aromatic ring. Anhydrous aluminum chloride is used in this classic example and is extremely hygroscopic and reacts rapidly with water to produce hydrogen chloride fumes.



Reference

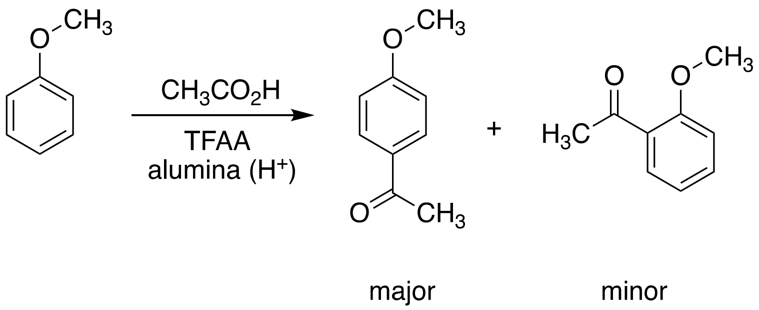
Friedel-Crafts Alkylation of *p*-xylene, Experimental Organic Chemistry, Gilbert & Martin, 5th edition, 2011, p. 495-496.

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
p-xylene 134449	750 mL	🟥 🟩 🟥
Aluminum chloride, anhydrous 237051	35 g	🟥 🟥 🟨
1-bromopropane B78106	425 mL	🟥 🟥 🟨
Crushed ice n/a	500 g	🟩 🟩 🟩
Sodium sulfate, anhydrous 239313	250 g	🟩 🟩 🟩

Friedel-Crafts Acylation Reaction – A Greener Alternative

This greener approach to a Friedel-Crafts acylation avoids the use of aluminum chloride by using an activated alumina catalyst and trifluoroacetic anhydride (TFAA). The solventless reaction is the first step in a 2-step synthesis of *p*-anisic acid.



Reference

Introducing environmentally benign synthesis into the introductory organic lab - a greener Friedel-Crafts acylation, The Chemical Educator. 2001, 6(1), 25–27.

Experimental

Caution: Trifluoroacetic anhydride is highly volatile, corrosive and reacts violently with water. This reagent should be dispensed only into dry glassware in a fume hood. Formation of the mixed anhydride in part 1 is exothermic. Ensure glassware is dry by placing in an oven overnight or by flame-dry technique.

Part 1

1. Place 3.0 g of dry acidic alumina and a magnetic stirring bar into a clean, dry 25 mL round bottom flask capped with a septum. Using a disposable syringe, add 0.33 mL of anisole slowly, dropwise to the alumina with efficient stirring. Periodic agitation on a vortex-type shaker can also assist in accomplishing an even distribution of the substrate over the entire catalytic surface of the alumina.
2. To a 3 or 5 mL conical vial equipped with a spin vane, add 1.25 mL of trifluoroacetic anhydride and cap the vial with a septum. To this capped vial deliver with a syringe 0.35 mL of acetic acid dropwise with stirring.
3. Add the mixed anhydride to the substrate coated alumina in the round bottom flask while stirring efficiently. Continue to stir and periodically shake the reaction mixture for about 40 minutes. The reaction mixture will turn pink and then purple.
4. After the 40-minute reaction period, add 15 mL of diethyl ether to the flask and stir thoroughly for at least 5 minutes to extract organic product. Filter or decant, saving the ether, and repeat the process one more time.
5. Combine the ether layers (30 mL total) and place in a separatory funnel. Wash with saturated sodium bicarbonate (30 mL) with care as foam will form due to gas evolution. Shake the funnel gently and open to vent gas. Repeat 2-3 times.
6. Allow layers to separate and drain off and discard the lower aqueous layer. Add saturated brine (30 mL) and gently shake for a minute or two to free the ether solution of gross quantities of water. Drain and discard the lower aqueous layer and dry the ether layer over sodium sulfate in a small Erlenmeyer flask, decant the dry ether solution into another small, pre-weighed Erlenmeyer and evaporate the ether on a steam bath in the hood.
7. Weigh the flask containing the crude product and determine the percent yield for the first step. An IR spectrum can be obtained as a thin film between salt plates.

Part 2

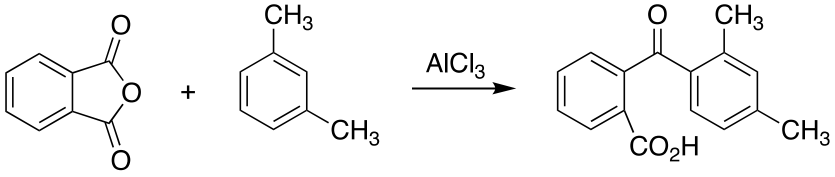
1. This reaction is run in the Erlenmeyer flask containing the first product. The exact amounts used in Part 2 depend upon the quantity of crude methoxyacetophenone carried forward from Part 1. For every 100 mg of product from the first step, add 4 ml of 5% NaOCl (commercial bleach) and approximately 0.25 mL of 10% NaOH.
2. Heat the reaction mixture on a steam bath or in a hot water bath for 20 or 30 minutes or until all of the organic material dissolves. If at the end of this time material remains undissolved, an additional 4 mL of bleach and 0.25 mL of 10% NaOH should be added and heating continued for 10 more minutes.
3. When the reaction is complete, add acetone (5 mL) dropwise to destroy excess hypochlorite. Allow the solution to cool and then carefully acidify by the dropwise addition of concentrated HCl until pH paper indicates a pH of 2-3.
4. Collect the white precipitate of p-anisic acid by suction filtration using a Hirsch funnel. The crude solid can be recrystallized from 95% ethanol. Allow the material to dry and determine the weight and melting point.

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Anisole 123226	16.5 mL	🟨 🟩 🟨
Activated acidic aluminum oxide (Brockmann 1) 199966	150 g	🟩 🟩 ⬜
Trifluoroacetic anhydride 106232	62.5 mL	🟥 *C 🟥 🟨
Glacial acetic acid 695092	17.5 mL	🟨 🟥 🟨
Diethyl ether 346136	1500 mL	🟥 *F 🟨 🟩
Sodium bicarbonate, sat. solution S6014	1500 mL	🟩 🟩 🟩
Brine solution 746398	1500 mL	🟩 🟩 🟩
Sodium sulfate, anhyd. 239313	250 g	🟩 🟩 🟩

Traditional Friedel-Crafts Acylation Reaction

The Friedel-Crafts acylation is a classic electrophilic aromatic substitution reaction that typically uses anhydrous aluminum chloride, a strong Lewis acid, to produce acylonium ions, which function as electrophiles in the reaction. Anhydrous aluminum chloride is extremely hygroscopic and reacts rapidly with water to produce hydrogen chloride fumes.



Reference

Friedel-Crafts Acylation of m-Xylene with Phthalic Anhydride, Experimental Organic Chemistry, Gilbert and Martin, 5th Edition, 2011, p. 505-506.

Health & Safety Evaluation

Chemical Name **Aldrich Catalog #**	**Amount per 100 students (g or mL)**	**EH&S**
Phthalic anhydride 320064	50 g	🟩 🟨 🟨
Aluminum chloride, anhydrous 237051	100 g	🟥 🟥 🟨
m-xylene 185566	300 mL	🟥 🟥 🟨
Hydrochloric acid, conc. 320331	100 mL	🟥 🟥 🟥 *
Water n/a	500 mL	🟩 🟩 🟩
Diethyl ether 346136	1400 mL	🟥 * 🟨 🟩
Hydrochloric acid, 6M 320331	250 mL	🟨 🟨 🟥
Sodium sulfate 239313	500 g	🟩 🟩 🟩
Ethanol, 50% 459836	500 mL	🟥 🟨 🟩

Comparative Analysis of Traditional vs. Suggested Experiments

Friedel-Crafts Alkylation

- Greener method eliminates the use of aluminum chloride, which is extremely hygroscopic and reacts rapidly with water to produce hydrogen chloride fumes
- Greener method uses a graphite catalyst which can be re-used to reduce waste
- The comparative costs for all reagents per 100 students for this experiment is $70 for the Greener method versus $132 for the Traditional method. Actual costs will vary.

	Waste Reduction (per 100 students)	**"Greener" Benefits**
Greener method	1000 mL liquid waste	🕒 ✚
Traditional method	1700 mL liquid waste 250 g solid waste	

Friedel-Crafts Acylation

- Greener method avoids the use of aluminum chloride, which is highly reactive to moisture, producing hydrogen chloride fumes
- Both methods utilize diethyl ether as a solvent in the work-up procedures, which is highly flammable
- Greener method can be used as part of a multi-step synthesis as product can be used to create *p*-anisic acid in a second reaction
- Greener method avoids the use of concentrated hydrochloric acid
- The comparative costs for all reagents per 100 students for this experiment is $265 for the Greener method versus $246 for the Traditional method. Actual costs will vary.

	Waste Reduction (per 100 students)	**"Greener" Benefits**
Greener method	4600 mL liquid waste (3000 mL aqueous waste) 500 g solid waste	⚠
Traditional method	3200 mL liquid waste 250 g solid waste	

Additional Resources & Further Reading

The following are additional greener alternative laboratory experiment options:

- A Research-Based Undergraduate Organic Laboratory Project: Investigation of a One-Pot, Multicomponent, Environmentally Friendly Prins–Friedel–Crafts-Type Reaction, J. Chem. Educ. 2012, 89, 265-267.
- A Microwave-Assisted Friedel–Crafts Acylation of Toluene with Anhydrides, J. Chem. Educ., 2013, 90 (3), 390–392.
- The Friedel-Crafts reaction: Acetylation of Ferrocene, Doxsee, K. M., Hutchison, J.E., Green Organic Chemistry – Strategies, Tools, and Laboratory Experiments, Print 2004, p. 225-230.

TA Guide

Discovered in the late 1800's, alkylation and acylation of aromatic compounds continues to be a prominent methodology used in basic and applied research. The Friedel-Crafts alkylation and acylation reactions proceed by a Lewis acid catalyzed electrophilic aromatic substitution, and yield alkylated aromatics and aryl ketones.

The greener alternative Friedel-Crafts alkylation reaction proceeds without the use of a solvent. However, the reagents are flammable and necessary precautions should be taken. Furthermore, aluminum chloride is replaced by graphite, which can be reused, in the greener alternative suggested herein – $AlCl_3$ reacts rapidly with water to produce hydrogen chloride fumes.

The traditional Friedel-Crafts acylation employs hazardous solvents such as dichloromethane and carbon disulfide. Aluminum chloride is used stoichiometrically or a slight excess, and therefore requires a tedious workup that generates large quantities of acidic aqueous waste and aluminum salts.

The greener alternative Friedel-Crafts acylation reaction also avoids the use of aluminum trichloride, and concentrated HCl. It should be noted that trifluoroacetic anhydride (TFAA) is used and is highly volatile, corrosive, and reacts violently with water and is only to be used in clean, dry glassware in the fume hood. Formation of the mixed anhydride in part 1 is exothermic and necessary precautions should be taken. The atom economy of the greener reaction is significantly better than the traditional method, and is carried out without the use of a solvent, on the surface of acidic alumina. A simple workup gives a highly pure product.

It is recommended that TA's engage students in discussions comparing the traditional experiments with the greener alternatives, and this could be a potential quiz question, as suggested in the following section. For example, the acylation reaction uses TFAA which needs to be handled in a specific manner and is not considered a mild reagent. The subsequent chlorine-based oxidation has a low atom economy and produces chloroform as a by-product. While the overall reaction is a net greener reaction with improvements to the environmental profile compared to the traditional experiment, this serves as a real-life example of the often-difficult task of deeming processes as 'green' or 'greener' than another one.

The following principles of green chemistry are employed:

- Safer Solvents and Auxiliaries
- Reduce Derivatives
- Catalysis
- Safer Chemistry for Accident Prevention

Tips & Tricks

- Be sure students are aware of the necessary precautions and proper synthetic techniques, especially for the acylation reaction.
- Alkylation
    - The reaction produces a small, insignificant amount of HBr. If the reaction is used for a large laboratory section, HBR should be trapped with a tube filled with sodium carbonate.
    - Using *p*-xylene as the solvent makes the second alkylation unlikely, and ensures excellent purity of the reaction product.
- Acylation
    - Some of the crude acylation products retain highly colored purple impurities through the workup. This will not affect the subsequent oxidation reaction.
    - Alumina should be disposed of in a properly labeled container.
    - The aqueous waste obtained upon filtration of the carboxylic acid product will contain small quantities of chloroform, and should be placed in a labeled waste container in the fume hood.
- The trifluoroacetic acid by-product can be recovered and reconverted into the starting anhydride.

Example Quiz Questions

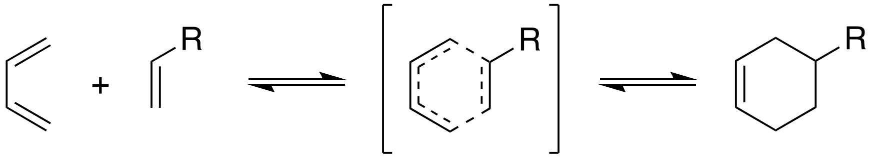
The following are examples of questions that may be used on pre- or post-lab quizzes, assignments, etc. or as discussion points during a lecture.

1. What is the mechanism for a Friedel Crafts electrophilic aromatic substation?
2. Are primary halides reactive in a Friedel-Crafts alkylation with a graphite catalyst? Why or why not?
3. The Friedel-Crafts acylation reaction has a more benign environmental profile than the traditional Friedel-Crafts acylation, but still employs and produces compounds that are hazardous and challenging to work with. Explain in detail three downfalls of the greener alternative Friedel-Crafts acylation reaction.

Experiment 8: The Diels-Alder Reaction

Introduction

The Diels-Alder reaction is an atom economical carbon-carbon bond forming reaction, wherein two C-C sigma bonds are formed simultaneously to create a ring structure. Therefore, this is an example of a pericyclic reaction, specifically a [4+2]-cycloaddition, that takes place between the π systems of a donor and acceptor molecule. The Diels-Alder transformation is also described as the one-step, concerted reaction of a diene and a dienophile to yield a substituted cyclohexene. Otto Diels and Kurt Alder first described this reaction in 1928, and were awarded the 1950 Nobel Prize in Chemistry for their discovery of this incredibly useful transformation.



Traditional Diels-Alder teaching experiments employ extremely reactive reagents and are carried out in aromatic solvents. These reagents require specific preparation and careful handling, and present safety concerns. Due to the extremely valuable nature of this reaction, it is almost always demonstrated in the teaching laboratory. In an effort to decrease the hazardous and environmental impact of such a widely used reaction, recent efforts have seen drastic improvements to the experimental design of the Diels-Alder reaction.

The Diels-Alder reaction suggested in this guide uses water as the solvent, which also serves to enhance the reaction rate by reason of the hydrophobic effect. Due to the insoluble nature of the reaction products, the hydrophobic effect favors precipitation out of the aqueous media. It also demonstrates the importance of solvent selection, if one is necessary.

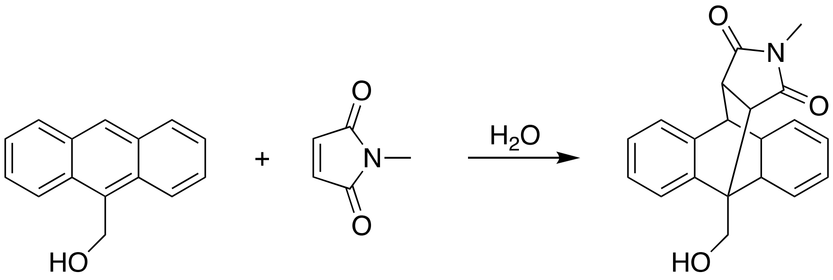
The two main reagents in a Diels-Alder reaction are known as a diene and dienophile. A diene is a hydrocarbon with two carbon-carbon double bonds, while a dienophile is an electrophilic alkene or alkyne. In traditional Diels-Alder reactions involving select diene and dienophiles, a number of stereoisomers can be formed. The suggested greener reaction herein favors the production of a single product due to the plane of symmetry in the dienophile.

The following principles of green chemistry are employed in the alternative experiment described herein:

- Waste Prevention
- Atom Economy
- Less Hazardous Chemical Synthesis
- Safer Solvents and Auxiliaries
- Design for Energy Efficiency
- Real-Time Pollution Prevention
- Safer Chemistry for Accident Prevention

Diels-Alder Reaction – A Greener Alternative

This Diels-Alder reaction is performed in water and eliminates the requirement to prepare the starting material (thermal decomposition is required in the traditional approach). This approach takes advantage of the hydrophobic effect, which increases the reaction rate. As such, the reaction can be completed in an hour, even though the reagents are significantly less reactive than the traditional cyclopentadiene and 1,3-butadiene starting materials.



Reference

Greener Solutions for the Organic Chemistry Teaching Lab: Exploring the Advantages of Alternative Reaction Media, McKenzie, L.C., Huffman, L.M., Hutchison, J.E., Rogers, C.E., Goodwin, T.E., Spessard, G.O., J. Chem. Educ. 2009, 86, 488–493.

Experimental[32]

Caution: *N*-Methylmaleimide is corrosive and must be handled with care. Wear gloves and safety glasses at all times.

1. Weigh 65 mg of 9-anthracenemthanol into a 100 mL round bottom flask.
2. Add 50 mL of water and a magnetic stir bar.
3. Add 3 equivalents of *N*-methylmaleimide (0.104 g) to the reaction flask.
4. Fit the reaction flask with a reflux condenser and heat the reaction to reflux while stirring.
5. Monitor the progress of the reaction by TLC, eluting with 1:1 ethyl acetate/hexanes. Be sure to let all of the water evaporate before developing the TLC.
6. When the reaction is complete, after approximately one hour, allow the reaction to cool to room temperature, and then cool further in an ice-water bath.
7. Collect the product by vacuum filtration.
8. Record the weight, melting point, and IR spectrum in a KBr pellet of your final product.

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[32] Experimental procedure reprinted with permission from McKenzie, L.C., Huffman, L.M., Hutchison, J.E., Rogers, C.E., Goodwin, T.E., Spessard, G.O., J. Chem. Educ. 2009, 86, 488–493. Copyright 2009 American Chemical Society.

Health and Safety

EHS Key:

- 🟨 Physical hazard
- 🟨 Toxicity/Health hazard
- ⬜ Persistent Bioaccumulative Toxic (PBT) Chemicals

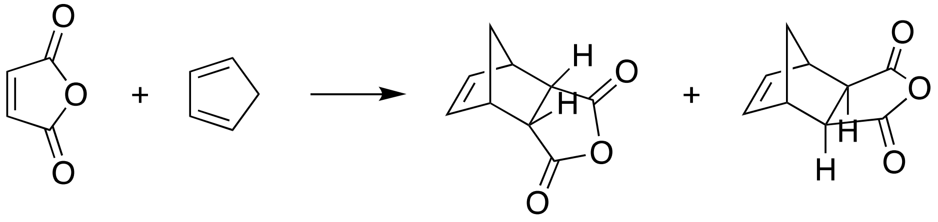
- 🟥 * Very high hazard
- 🟥 High hazard
- 🟨 Moderate hazard
- 🟩 Low hazard
- ⬜ No data

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
9-Anthracenemethanol 187240	3.25 g	🟩 🟩 🟨
N-methylmaleimide 389412	5.2 g	🟩 🟥 🟩
Water n/a	2500 mL	🟩 🟩 🟩

Traditional Diels-Alder Reaction

The Diels-Alder reaction remains one of the most important reactions for constructing 6-membered rings, involving the reaction of a 1,3-diene with an alkene (dienophile). A traditional Diels-Alder reaction involves a simple diene such as 1,3-cyclopentadiene and maleic anhydride. The reaction proceeds by the thermal decomposition of dicyclopentadiene.



Endo Exo

Reference

Reaction of 1,3-cyclopentadiene and maleic anhydride, Experimental Organic Chemistry, 5th Edition, Gilbert and Martin, 2011, p. 429-430.

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Dicyclopentadiene 454338	345 g	🟥 🟨 🟥
Maleic anhydride M188	5 g	🟥 🟥 🟨
Ethyl acetate 270989	20 mL	🟥 🟨 🟨
Petroleum ether 320447	20 mL	🟥 *F 🟨 🟥
Calcium chloride, anhyd. 793639	25 g	🟩 🟨 🟩

Comparative Analysis of Traditional vs. Suggested Experiments

- Greener method uses water as a solvent and eliminates the need for hazardous organic solvents.
- Greener method has overall lower EH&S hazard profile.
- The comparative costs for all reagents per 100 students for this experiment is $54 for the Greener method versus $37 for the Traditional method. Actual costs will vary.

	Waste Reduction (per 100 students)	**"Greener" Benefits**
Greener method	2500 mL aqueous waste	⚗
Traditional method	390 mL liquid waste 25 g solid waste	

Additional Resources & Further Reading

The following are additional greener alternative laboratory experiment options:

- Diels–Alder Cycloadditions: A MORE Experiment in the Organic Laboratory Including A Diene Identification Exercise Involving NMR Spectroscopy and Molecular Modeling, J. Chem. Educ., 2005, 82 (4), 625.
- Microwave-Enhanced Organic Syntheses for the Undergraduate Laboratory: Diels–Alder Cycloaddition, Wittig Reaction, and Williamson Ether Synthesis, J. Chem. Educ., 2010, 87 (1), 84–86.
- Microwave-Assisted Synthesis of a Natural Insecticide on Basic Montmorillonite K10 Clay. Green Chemistry in the Undergraduate Organic Laboratory, J. Chem. Educ. 2006, 83, 270–272. (hetero)

TA Guide

The Diels-Alder reaction is an atom economical carbon-carbon bond formation, wherein two C-C sigma bonds are formed simultaneously to create a substituted cyclohexene system. Otto Diels and Kurt Alder were awarded the 1950 Nobel Prize in Chemistry for their discovery of this incredibly useful transformation.

This greener Diels-Alder experiment allows students to employ greener solvents and methods, that also improve the safety and outcome of the reaction. The starting materials are less reactive and safer to handle. There is also an energy savings as there is less energy input needed due to reaction rate enhancement by the water solvent. Not only does water enhance the rate of reaction, it is also an environmentally benign solvent, provides easy separation of the product, and can be recycled along with excess starting material.

The Diels-Alder adduct is not soluble in water and therefore precipitates out of solution and can be obtained by suction filtration. The filtrate can be reused as solvent in a subsequent reaction – two equivalents of *N*-methylmaleimide remain dissolved in the water, and the reaction will go to completion with the addition of equimolar amounts of 9-anthracenemethanol and *N*-methylmaleimide. There is a 100% atom economy for this Diels-Alder transformation.

The following principles of green chemistry are employed:

- Waste Prevention
- Atom Economy
- Less Hazardous Chemical Synthesis
- Safer Solvents and Auxiliaries
- Design for Energy Efficiency
- Real-Time Pollution Prevention
- Safer Chemistry for Accident Prevention

Tips & Tricks

- The filtrate obtained during product isolation is largely water, but also contains two equivalents of *N*-methylmaleimide, and potentially small concentrations of 9-anthracenemethanol and the target product. As such, this filtrate should be disposed of in a labeled aqueous waste container or reused in a subsequent repeat of this reaction in which case only one equivalent of *N*-methylmaleimide to the solvent.
- Consider using heptanes instead of hexanes for eluting the TLC for an even safer, and greener process.
- The ethyl acetate-hexanes mixtures used for TLC should be disposed of as non-halogenated solvent waste or reused for a subsequent lab section.
- Be sure to have students add the 9-anthracenemethanol to the flask before the water. It is extremely hydrophobic and will be more likely to stay submerged and dissolve.
- The product is typically an off-white solid with a melting point range of 237-239 °C and a yield of approximately 80%.

Fun Facts

- In a Diels-Alder reaction that yields a bicyclic compound, the *endo* position is *syn* to the larger bridge, while the *exo* position is *anti* to the larger bridge.
- At elevated temperatures, generally above 200 °C, the Diels-Alder reaction is reversible. This is known as the retro-Diels-Alder reaction.
- The product of the Diels-Alder reaction, an unsaturated 6-member ring, is a common framework of many natural products.

Example Quiz Questions

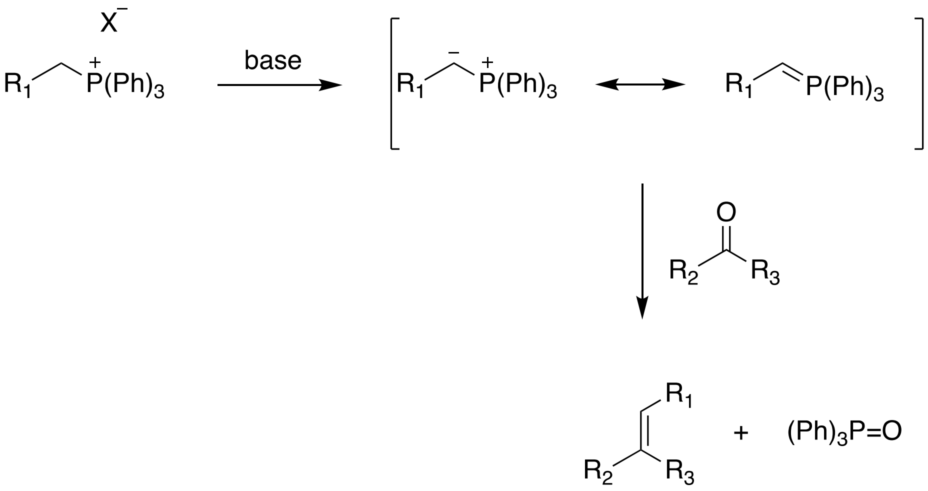
The following are examples of questions that may be used on pre- or post-lab quizzes, assignments, etc. or as discussion points during a lecture.

1. Draw an energy diagram and include structures of the starting material, transition state, and final product. Be sure to label both axes appropriately and include relevant thermochemical paramters (e.g., $\Delta_r E^\circ$ and $\Delta_r E^{\neq}$).
2. Is the Diels-Alder reaction a step-wise or concerted process?
3. Is the Diels-Alder reaction reversible? Explain the thermodynamic considerations in terms of enthalpy and entropy.
4. What are the drawbacks of using water as a solvent? Explain.

Experiment 9: The Wittig Reaction

Introduction

The Wittig (pronounced Vit-tig) reaction is used to convert ketones or aldehydes into alkenes by formation of a carbon-carbon bond at the carbonyl moiety. Georg Witting was awarded the 1979 Nobel Prize in Chemistry for his research on phosphorous-based compounds and discovery of this important reaction. A phosphorus ylide is generation by the reaction of a phosphonium salt and a base. The ylide then reacts with a carbonyl compound to give an alkene product and triphenylphosphine oxide.



Like most organic chemical reactions in the laboratory, the Wittig reaction is traditionally done in an organic solvent. However, in the present experiment, a solventless Wittig reaction is carried out in a mortar and pestle by grinding the reactants together. Solventless reactions help reduce the amounts of organic waste produced in a laboratory. This in turn minimizes health and environmental hazards.

In this experiment, (*E*)- and (*Z*)-1-(4-bromophenyl)-2-phenylethene are synthesized by a Wittig reaction of benzyltriphenylphosphonium chloride, 4-bromobenzaldehyde, and potassium phosphate (tribasic). These chemicals are placed in a mortar and ground up with a pestle for about 20 minutes to carry out the reaction. Although both the *E* and *Z* isomers of 1-(4-bromophenyl)-2-phenylethene are produced in this reaction, only the *E* isomer will be isolated by crystallization in ethanol.

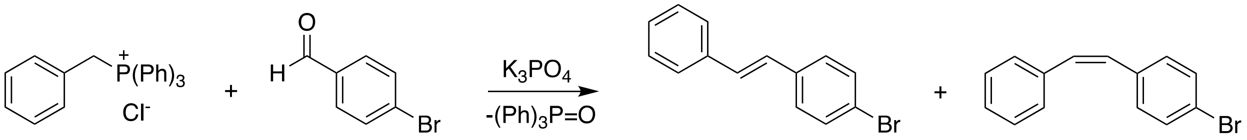
The following principles of green chemistry are employed in the alternative experiment described herein:

- Waste Prevention
- Atom Economy
- Real-Time Pollution Prevention

*Note: The introduction was adapted directly from the SI of the Witting Reaction – Greener Alternative reference, listed below.

Wittig Reaction – A Greener Alternative

This solventless Wittig Reaction utilizes a potassium phosphate (tribasic) base to catalyze the reaction, which forms both the *E* and *Z* isomers of the alkene product. This reaction eliminates the use of methylene chloride in the traditional reaction.



Reference

Solventless Wittig Reaction: A Green Organic Chemistry Laboratory Experiment, Leung, S. H., Angel, S. A., J. Chem. Educ., 2004, 81 (10), p 1492.

Experimental[33]

Caution: Benzyltriphenylphosphonium chloride, 4-bromobenzaldehyde, and potassium phosphate can cause eye and skin irritation. Ethanol is flammable. Denatured ethanol contains small quantities of organic compounds such as ethyl acetate and methyl isobutyl ketone. Students should avoid breathing the vapor.

1. Mix benzyltriphenylphosphonium chloride (200 mg), 4-bromobenzaldehyde (95 mg), and potassium phosphate (425 mg) in a porcelain mortar (80 mm outer diameter).
2. Grind the mixture with a pestle for 20 minutes. During this time, periodically stop grinding and, using a spatula, gently scrape the chemicals off the inside walls of the mortar and off the pestle into the center of the mortar. Resume grinding. The reaction will become pasty during the grinding process. The actual grinding time should be at least 15 minutes to ensure the completion of the reaction, but does not need to be done absolutely continuously.
3. Thin-layer chromatography (TLC) may be used at this point to analyze the mixture to determine if the reaction is complete. Mix a small sample (~ 2 mg) with a few drops of ethanol in a watch glass. Not all the solid will dissolve.
4. Spot the solution on a silica gel TLC plate. Also spot a solution of 4-bromobenzaldehyde in ethanol on the same TLC plate for comparison.
5. Develop the TLC plate in 1:4 ethyl acetate/hexanes. The absence of 4-bromobenzaldehyde in the reaction mixture on the TLC plate indicates the completion of the reaction.
6. After the completion of the reaction is determined, add 10 mL of water to the mortar and scrape loose all the solid. Also scrape off all the solid on the pestle into the mortar.
7. Filter this suspension to collect the solid.
8. Add 5 mL of water to the mortar and transfer any remaining solid into the funnel. The solid contains a mixture of the *E* and *Z* isomers of the product and triphenylphosphine oxide.
9. Isolate the *E* isomer by crystallization in ethanol. Transfer the solid mixture into a test tube and add 2 mL of ethanol (denatured or absolute). Heat the test tube in a warm water bath (70-80 °C) until almost all of the solid is dissolved. Allow the solution to cool to room temperature. Crystallization should occur. Cool the test tube further in an ice bath, and filter the contents to collect the (*E*)-1-(4-bromophenyl)-2-phenylethene as white (or off-white) crystals.
10. Weigh the product, and analyze the product by ^{1}H-NMR spectroscopy and melting point. Confirm that it is the *E* isomer by determining the coupling constant for the alkenyl protons and comparing against values reported in the literature.

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[33] Experimental procedure reprinted with permission from Leung, S. H., Angel, S. A., J. Chem. Educ., 2004, 81 (10), 1492. Copyright 2004 American Chemical Society.

Health and Safety

EHS Key:

🟨	Physical hazard
🟨	Toxicity/Health hazard
⬜	Persistent Bioaccumulative Toxic (PBT) Chemicals

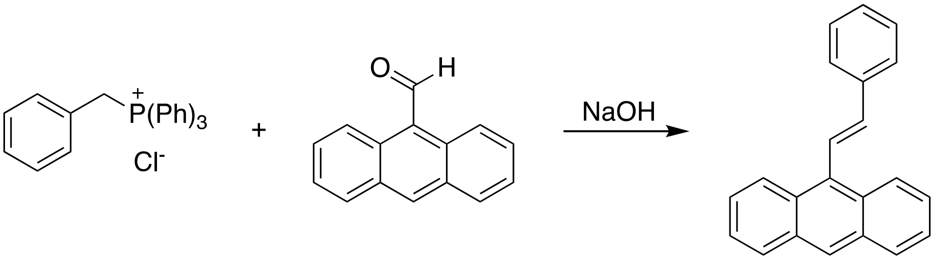
🟥 *	Very high hazard
🟥	High hazard
🟨	Moderate hazard
🟩	Low hazard
⬜	No data

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Benzyltriphenylphosphonium chloride B32807	10 g	🟩 🟥 🟥
4-bromobenzaldehyde B57400	4.75 g	🟩 🟥 🟨
Ethyl acetate 270989	100 mL	🟥 🟨 🟨
Ethanol 459836	100 mL	🟥 🟨 🟩
Heptane 246654	400 mL	🟥 🟨 🟥 *
Potassium phosphate, tribasic P5629	21.3 g	🟩 🟨 ⬜
Water n/a	750 mL	🟩 🟩 🟩

Traditional Wittig Reaction

The Wittig reaction is a classic reaction for converting a carbonyl compound to an olefin through a four-centered intermediate. This reaction traditionally proceeds using a hazardous solvent, such as dichloromethane or dimethyl formamide.



Reference

Synthesis of trans-9-(2-phenylethenyl) anthracene (microscale), Macroscale and Microscale Organic Experiments, 6e; Brooks/Cole, 2011; pp. 509-510.

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Benzyltriphenylphosphonium chloride B32807	10 g	🟩 🟥 🟥
9-anthraldehyde 8.2011	5.75 g	🟩 🟩 🟥
Dichloromethane 676853	155mL	🟩 🟥 🟥
Sodium hydroxide, 50% 221465	13 mL	🟥 🟨 🟨
Water n/a	75 mL	🟩 🟩 🟩
Calcium chloride 793639	50 g	🟩 🟨 🟩
2-propanol 278475	150 mL	🟥 🟨 🟩

Comparative Analysis of Traditional vs. Suggested Experiments

- Greener method avoids the use of chlorinated solvent – dichloromethane.
- Greener method still requires solvent in the work-up of the product.
- The comparative costs for all reagents per 100 students for this experiment is $49 for the Greener method versus $56 for the Traditional method. Actual costs will vary.

	Waste Reduction (per 100 students)	**"Greener" Benefits**
Greener method	1400 mL liquid waste (750 mL aqueous waste)	⚗
Traditional method	500 mL liquid waste	

Additional Resources & Further Reading

The following are additional greener alternative laboratory experiment options:

- Greening Wittig Reactions: Solventless Synthesis of Ethyl trans-Cinnamate and trans-3-(9-Anthryl)-2-Propenoic Acid Ethyl Ester, J. Chem. Educ., 2007, 84 (1), 119.
- *p*-Carboxystyrene. A Wittig procedure in aqueous medium, J. Chem. Educ., 1978, 55 (12), 813.
- Solventless Synthesis and Fluorescence of a Thiol-Reactive Sensor for Undergraduate Organic Laboratories, J. Chem. Educ., 2013, 90 (12), 1685–1687.

TA Guide

The Wittig (pronounced Vit-tig) reaction has enormous synthetic utility and facilitates access to a broad range of important compounds. Georg Witting was awarded the 1979 Nobel Prize in Chemistry for his discovery of this reaction and work in this branch of chemistry. The Wittig reagent, a phosphonium ylide, reacts with an aldehyde or ketone to yield an alkene and triphenylphosphine oxide. Witting reagents are easily prepared in an S_N2 reaction by treating triphenylphosphine with an alkyl halide (CH_3I) followed by addition of a strong base (e.g. *n*-BuLi).

With the recent focus on green chemistry alternatives in industry, research, and teaching laboratories, a number of modified Wittig reactions have emerged in the literature. A solventless experiment is suggested herein as the greener alternative. Reagents are ground in a mortar and pestle for approximately 20 minutes, and the reaction readily proceeds. Two isomers are formed. Isolation of the *E* isomer is achieved by washing the crude product with water, followed by recrystallization in ethanol.

The following principles of green chemistry are employed:

- Waste Prevention
- Atom Economy
- Real-Time Pollution Prevention

Tips and Tricks

- Encourage students to gently scrape the inside walls of the mortar and off the pestle to avoid abrasion of the metal spatula on the porcelain surface. The abrasion of the metal spatula may add a grayish tint to the final product.
- Two different melting points have been reported in the literature for the *E* isomer product: 139-141 °C and 132-133 °C. The product from this experiment typically gives a melting point of 134-135 °C.
- The ethanol filtrate from the crystallization of the *E*-isomer is expected to contain both isomers of the products and triphenylphosphine oxide. This filtrate should be collected in a waste bottle with proper label.
- The NMR sample can be prepared by dissolving 10 mg of the product in 1 mL of $CDCl_3$ in a 10 mL beaker or small vial. Not all solid will dissolve. The insoluble solid is assumed to contain potassium chloride and the unreacted potassium phosphate. Filter the suspension through a Pasteur pipet into the NMR tube.

Example Quiz Questions

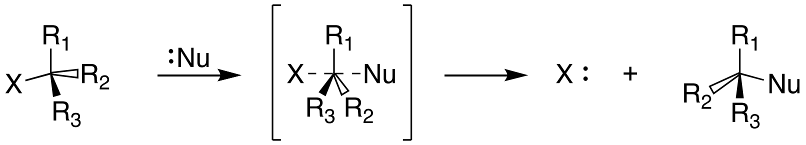
The following are examples of questions that may be used on pre- or post-lab quizzes, assignments, etc. or as discussion points during a lecture.

1. In Thin Layer Chromatography (TLC), what is the R_f value and how is it determined?
2. Why do the *E* and *Z* isomers have different R_f values, and do not crystallize together?
3. Which isomer has a larger R_f value? What does this tell you about the polarity of the two isomers? Explain.
4. List and explain three principles of green chemistry and how they apply to the greener alternate Wittig experiment.

Experiment 10: The Substitution (S_N2) Reaction

Introduction

Substitution reactions involve the exchange of one functional group for another, and are very important transformations in organic and biological syntheses. In the 1930s, Christopher Ingold and Edward Hughes studied substitution reactions extensively. They coined the S_N2 reaction to reference bimolecular nucleophilic substitution reactions, wherein two molecules (the nucleophile and substrate) react in one concerted step. This results in an inversion of configuration at the stereocenter, which is known as a Walden inversion.



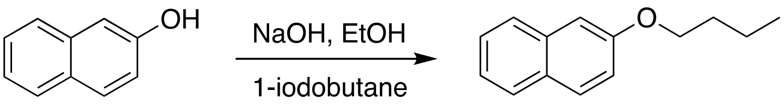
Substitution reactions are almost always part of the organic chemistry teaching lab experiments, but routinely involve hazardous solvents and lachrymator reagents. An easy, safe, and more environmentally benign demonstration of the S_N2 reaction is presented herein. A solid product is formed in the reaction and precipitates from solution. The ability of a primary alkyl halide to undergo a S_N2 reaction despite the atypical polar protic solvent is also included in this demonstration.

The following principles of green chemistry are employed in the alternative experiment described herein:

- Less hazardous chemical synthesis
- Safer solvents and auxiliaries
- Safer chemistry for accident prevention

Substitution (S_N2) Reaction – A Greener Alternative

In this greener approach, 1-iodobutane and 2-naphthol are utilized in this S_N2 reaction to produce 2-butoxynaphthalene. Ethanol is used as the solvent, minimizing the use of hazardous solvents.



Reference

A Simple S_N2 Reaction for the Undergraduate Organic Laboratory, J. Chem. Educ. 2009, 86, 850.

Experimental[34]

Caution: 2-Naphthol and 1-iodobutane are irritants and are harmful to the environment. In addition, 1-iodobutane is flammable. Sodium hydroxide is corrosive. Ethanol causes eye and respiratory tract irritation and is flammable.

1. To a 100 mL round bottom flask, add 0.56 g (14.0 mmol) of NaOH (about 5 or 6 pellets) and 1.0 g (6.8 mmol) of 2-naphthol.
2. Add 20 mL ethanol and a few boiling chips to the flask. Swirl the flask. Reflux the solution for 15 minutes or until all the solids have dissolved.
3. Remove the heat source and allow the solution to cool slightly. Ensure the solution has stopped boiling before removing the reflux condenser.
4. Remove the reflux condenser and add 1.0 mL 1-iodobutane (8.8 mmol) to the flask. Replace the condenser and reflux for an additional hour.
5. Before stopping the reaction, place about 50 mL of water in an ice bath for later use.
6. After 1 hour of refluxing, remove the heat source and carefully pour the contents of the round bottom flask over about 25 g of ice in a 250 mL beaker. Using the water that has been cooling, rinse the round bottom flask and add this to the beaker containing the ice and your product.
7. Swirl the contents of the beaker until all of the ice has melted. Carefully collect the product by suction filtration. Wash the product with ice-cold water. Draw air through the product for 5 – 10 minutes. If additional product crystallizes out of the filtrate, collect it by suction filtration and combine all the product. Allow your product to dry over the next week. Take the melting point and calculate the percent yield. Analyze the product by ^{1}H NMR spectroscopy.

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[34] Reprinted with permission from Esteb, J.J., Magers, J. R., McNulty, L., et. al., J. Chem. Educ. 2009, 86, 850. Copyright 2009 American Chemical Society.

Health and Safety

EHS Key:

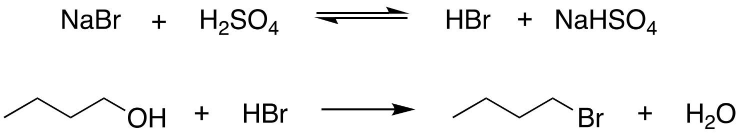
🟨	Physical hazard	🟥 *	Very high hazard
🟨	Toxicity/Health hazard	🟥	High hazard
⬜	Persistent Bioaccumulative Toxic (PBT) Chemicals	🟨	Moderate hazard
		🟩	Low hazard
		⬜	No data

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Sodium hydroxide 221465	28 g	🟥 *C 🟥 🟨
2-Naphthol 185507	50 mL	🟩 🟨 🟥 *
Ethanol 459836	1000 mL	🟥 🟨 🟩
1-Iodobutane 167304	50 mL	🟥 🟩 🟨
Water n/a	3750 mL	🟩 🟩 🟩

Traditional Substitution (S_N2) Reaction

A commonly performed reaction for converting a primary alcohol to an alkyl halide involves the treating of an alcohol with a hydrogen halide. In this reaction, hydrobromic acid is generated in situ from sodium bromide and concentrated sulfuric acid.



Reference

Preparation of 1-bromobutane: An S_N2 Reaction, Experimental Organic Chemistry, Gilbert and Martin, 5th Edition, 2011, p. 465-466. (Miniscale Procedure)

Health & Safety Evaluation

Chemical Name Aldrich Catalog #	Amount per 100 students (g or mL)	EH&S
Sodium bromide 793574	555 g	🟩 🟨 🟩
Water n/a	1500 mL	🟩 🟩 🟩
1-Butanol B7906	500 mL	🟥 🟨 🟩
Sulfuric acid, conc. 258105	500 mL	🟨 🟥 🟨
Sodium hydroxide, 2M 221465	500 mL	🟨 🟨 🟨
Sodium chloride, sat. sol’n 746398	500 mL	🟩 🟩 🟩
Sodium sulfate 239313	250 g	🟩 🟩 🟩

Comparative Analysis of Traditional vs. Suggested Experiments

- Greener method avoids the use of concentrated sulfuric acid
- Greener method utilizes a safer solvent, ethanol
- The comparative costs for all reagents per 100 students for this experiment is $114 for the Greener method versus $180 for the Traditional method. Actual costs will vary.

	Waste Reduction (per 100 students)	**"Greener" Benefits**
Greener method	4900 mL liquid waste (3750 mL aqueous waste)	⚗ ⚠
Traditional method	4000 mL liquid waste 250 g solid waste	

Please note that there is not a "greener" approach for the S_N1 reaction provided in this evaluation. To date, we have not found a greener version that avoids the use of concentrated hydrochloric acid, as described in many standard procedures.

TA Guide

In the 1930s, Christopher Ingold and Edward Hughes studied substitution reactions extensively. They coined the S_N2 reaction to reference bimolecular nucleophilic substitution reactions, wherein two molecules (the nucleophile and substrate) react in one concerted step.

The greener alternative S_N2 reaction presented herein is an easy, safe, and more environmentally benign demonstration of this transformation. The reaction is run in refluxing ethanol and monitored by TLC. Owing to the high UV activity of 2-naphthol, trace quantities are visible by TLC. Product isolation is generally facile as crystallization occurs rapidly when poured over ice.

This laboratory is intended to teach students that the ideal conditions given in lecture for a reaction may not always be the conditions chosen. For example, this experiment is run in ethanol, whereas the students are typically taught that polar aprotic solvents are optimal for S_N2 reactions. The understanding of acidity is fundamental to the understanding of reactivity. In this case, the students must learn why the deprotonation of 2-naphthol is more facile than the deprotonation of the solvent for the reaction. In addition, the need for deprotonation of the 2-naphthol to generate a better nucleophile reinforces the understanding of trends in nucleophile strength.

The following principles of green chemistry are employed:

- Less hazardous chemical synthesis
- Safer solvents and auxiliaries
- Safer chemistry for accident prevention

Tips & Tricks

- Ensure safety glasses are worn at all times in the laboratory.
- The following are citations from the Sigma-Aldrich catalog: 2-Naphthol is harmful and an irritant that is harmful to the environment, 1-iodobutane is harmful or an irritant, sodium hydroxide is corrosive.
- For optimal product yields, it is important for students to sufficiently cool the product in ice water prior to isolation by suction filtration. Likewise, the students need to wash the product with ice cold water to avoid dissolution of the desired product. The isolation of a second crop of crystals from the filtrate may be necessary.

Fun Facts

- The human body makes use of an S_N2 reaction to produce *S*-adenosylmethionine from ATP and methionine. This product acts as a methylating agent in the biosynthesis of important biological compounds, such as adrenaline.

Example Quiz Questions

The following are examples of questions that may be used on pre- or post-lab quizzes, assignments, etc. or as discussion points during a lecture.

1. What is the difference between S_N1 and S_N2 reactions? Provide an example arrow-pushing mechanism.
2. Identify the nucleophile, electrophile, and leaving group in the reaction.
3. Ethanol is not usually a solvent used for S_N2 reactions – why not? Describe an undesirable side reaction that might occur using ethanol as a solvent that would not occur if THF was used as the solvent.
4. Why is it important to mix naphthol with sodium hydroxide before adding the electrophile? What happens during this time?
5. What is the better nucleophile – sodium naphthoxide or naphthol? Why?