**Supporting Information**

Green Aqueous Wittig Reaction: Teaching Green Chemistry in Organic Teaching Laboratories

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**1. Student Instructions**

**Green Wittig Reaction for the Undergraduate Organic Chemistry Lab**

*University of Illinois Springfield*

*Dr. Layne Morsch, PhD.*



**Background**

The Wittig reaction has been used as a good general method for preparing alkenes from aldehydes or ketones. A phosphine ylide is formed *in situ* by treating the stable triphenylphosphonium chloride with a base that can deprotonate the carbon bonded to phosphorus.



The ylide will then react with aromatic aldehydes to form a 4 membered ring – oxaphosphetane- intermediate. This intermediate then eliminates triphenylphosphine oxide to give an alkene.



Both the E and Z forms of the alkene will form in this reaction. *If you only take into account product stability,* *which one would you expect to be the major product?*



Green chemistry techniques and processes can be applied to a Wittig reaction to make it safer for the environment and efficient for Organic Chemistry labs. Various changes made to the traditional procedure include using less harmful chemicals, lowering stir times, no reflux, along with replacing the organic solvent with water. The products can be analyzed via 1H Nuclear Magnetic Resonance Spectroscopy (1H NMR), Infrared Spectroscopy (IR), Thin Layer Chromatography (TLC), and Gas Chromatography—Mass Spectrometry (GCMS). Most products have sufficient yields to be acceptable for both analysis and identification in an Undergraduate Organic Chemistry lab setting.

Pre-lab Case-Study:

For this case study, you will play the part of chemists working for a company that produces stilbene derivatives. This case study will expose you to the topic of green chemical synthesis as well as helping you understand some of the value of green chemistry in industry.

Your lab has been using a traditional Wittig reaction to make stilbene derivatives for several years. Your lab manager tells you that she has found a recently published method that could improve on your product production time and potential cost to produce. She would like you to submit an analysis of the two processes to help her decide whether or not to change your production plan.

Traditional Wittig: The aldehyde and benzyltriphenylphosphine are stirred for 4 hours at room temperature in N,N-dimethylformamide with n-butyllithium as the base. The mixture is then heated to reflux overnight. Upon completion, the product is extracted with diethyl ether and recrystallized from propanol.

New Method overview: The aldehyde is mixed with the benzyltriphenylphosphonium chloride. Sodium hydroxide is added and the suspension is stirred for 30 minutes. The product is filtered, washed with water and recrystallized from ethanol.

The following are some questions you should address to help your manager understand the potential effects of this new green methodology.

1. *What are the 12 principles of green chemistry? (if you are not familiar with them, they can be found on the American Chemical Society’s ACE Green Chemistry Institute website) (accessed April 30, 2013)* [*http://portal.acs.org/portal/acs/corg/content?\_nfpb=true&\_pageLabel=PP\_ARTICLEMAIN&node\_id=1415&content\_id=WPCP\_007504&use\_sec=true&sec\_url\_var=region1&\_\_uuid=7f174e78-d85f-486f-b801-e17b77cc6df9*](http://portal.acs.org/portal/acs/corg/content?_nfpb=true&_pageLabel=PP_ARTICLEMAIN&node_id=1415&content_id=WPCP_007504&use_sec=true&sec_url_var=region1&__uuid=7f174e78-d85f-486f-b801-e17b77cc6df9)
2. *Identify 3 of the principles that are present in this experiment. Give a short explanation of how they are being applied.*
3. *Identify 3 of the principles that are not present in this experiment.*
4. *Is this experiment still a good example of green chemistry?*
5. *Contrast this with the traditional Wittig reaction.*

**Required Materials**

Aromatic Aldehyde (*o*-nitrobenzaldehyde, *p*-anisaldehyde, benzaldehyde, 4-chlorobenzaldehyde, *p*-tolualdehyde, mesitaldehyde, N,N-demithylaminobenzaldedhyde, cinnamaldehyde (structure is a bit different from the others)

Benzyltriphenylphosphonium chloride

10 N sodium hydroxide

Magnetic Stir Bar/ Plate

Vacuum Filtration Apparatus (Buchner funnel, filter flask, filter paper)

Two (2) 25mL Erlenmeyer Flasks

Ethanol

Ice Bath

NMR tube + CDCl3 if running NMR

Ethyl acetate and heptane TLC plates if performing TLC analysis

Heptane (for GCMS)

Potassium bromide (for IR)

Mortar and Pestle (for IR)

GC vials (2 mL)

**Hazards**

Wear eye protection and protective gloves during this experiment. All work should be done in a fume hood and no open flames should be used in lab. All starting aldehydes and products are considered eye and skin irritants and should not be ingested. Benzaldehyde is a repiratory and skin sensitizer. *P*-tolualdehyde is combustible. Benzyltriphenylphosphonium chloride is highly toxic by ingestion. Heptane is highly flammable and may be fatal if swallowed and enters airways. Deuterochloroform causes irritation of the skin and respiratory system, may cause chemical burns and is a possible carcinogen. Ethanol and ethyl acetate are highly flammable and toxic by ingestion. Sodium hydroxide (10 N) is extremely damaging to the eyes and skin.

**Reaction**

Obtain amounts of the starting aromatic aldehyde and the benzyltriphenylphosphonium chloride in a 1.0:1.1 equivalent mole ratio. Start with 500 mg of the aldehyde and calculate the amount of the phosphonium salt needed. To do this, you need to determine the moles of the aldehyde, and then calculate the slight excess (1.1 times the moles of aldehyde) of the phosphonium material. Combine materials in 25 mL Erlenmeyer flask along with a magnetic stir bar. Measure 5 mL 10 N sodium hydroxide (NaOH). Add the NaOH to the reaction flask, place on a stir plate and stir for 30 minutes.

Filtering

When the 30 minutes is nearly complete, obtain 20mL ethanol and begin to heat to boiling for recrystallization. Assemble a vacuum filtration apparatus and filter product. Wash the crude product with water until the filtrate is no longer basic.

At this point you could analyze the crude product mixture via TLC (10% ethyl acetate in heptane). GCMS could also be run in heptane to determine if any product has formed as well as the ratio of E to Z isomers.

Recrystallization

Transfer the crude product to a 25 mL Erlenmeyer flask. Add a minimum amount of boiling ethanol to the product until it is completely dissolved. Let the solution cool to room temperature on the counter without disturbing, and then place in an ice bath for about 30 minutes. Vacuum filter and weigh the crystalline product.

***Analysis***

TLC

The recrystallized product can be analyzed by thin layer chromatography using 10/90 ethyl acetate/ heptane. It should be possible to see both the Z and E isomers on the TLC plate.

*Do you see a pronounced difference between the TLC of the crude and recrystallized in terms of Z/E products?*

IR

Add a small spatula full of your product to about 10x as much KBr and grind with a mortar and pestle. Place a small amount into a die and compress. After 1-2 minutes, open the die and check to see if you have a window in the middle of the die that light will pass through. Analyze your sample by infrared spectrophotometry.

*Where do carbonyl peaks typically appear in IR?*

*Where is the aldehyde peak in your starting material?*

*Does the product have a peak in the same area?*

1H NMR

Dissolve a small amount of your product in CDCl3 for analysis by 1H NMR.

*Where do aldehydes show up in 1H NMR?*

*Is there still an aldehyde peak present in the spectra?*

*Where do alkenes typically show up in 1H NMR?*

When alkenes are conjugated to aromatic rings, the proton signals shift downfield. *Which signal do you think is resulting from the alkene protons?*

Make a table of your NMR data assigning signals to protons on your product.

GCMS

Prepare a sample of your product for GCMS analysis (1 small crystal of material dissolved in 1-2 mL heptane).

*What is the molecular weight of your starting aldehyde?*

*Does the aldehyde appear in your recrystallized product?*

*What is the molecular weight of your predicted product?*

*Does the molecular ion match this molecular weight?*

*What is a potential structure for any fragments in the mass spectrum?*

*If you analyze the crude product by GCMS as well:*

*Will the E or Z isomer have greater van der Waals forces? If you are not sure about this, consider that Z-stilbene is a liquid, while E-stilbene is a solid.*

*Which isomer will elute from the column first?*

*What ratio of E:Z isomers do you see in your crude product?*

*How does that differ from your recrystallized product?*

Make a table of your GCMS data assigning fragments from your product and E:Z isomers if analyzing the crude product.

**Disposal of Waste**

No waste from this lab should be poured down the sink. There will be appropriate waste disposal vessels available for you in the lab. There will be a waste container for the basic aqueous waste from the initial filtering and rinsing. There will be another waste container for the recrystallization solvent waste. There will be a separate waste container for the NMR solvent since it is halogenated and should not be placed in the same container as the recrystallization solvent.

1. **Instructions with notes for instructors**

**Green Wittig Reaction for the Undergraduate Organic Chemistry Lab**

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**Background**

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The ylide will then react with aromatic aldehydes to form a 4 membered ring – oxaphosphetane- intermediate. This intermediate then eliminates triphenylphosphine oxide to give an alkene.



Both the E and Z forms of the alkene will form in this reaction. *If you only take into account product stability,* *which one would you expect to be the major product? E, due to sterics*



Green chemistry techniques and processes can be applied to a Wittig reaction to make it safer for the environment and efficient for Organic Chemistry labs. Various changes made to the traditional procedure include using less harmful chemicals, lowering stir times, no reflux, along with replacing the organic solvent with water. The products can be analyzed via 1H Nuclear Magnetic Resonance Spectroscopy (1H NMR), Infrared Spectroscopy (IR), Thin Layer Chromatography (TLC), and Gas Chromatography—Mass Spectrometry (GCMS). Most products have sufficient yields to be acceptable for both analysis and identification in an Undergraduate Organic Chemistry lab setting.

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*Prevention, Atom Economy, Less Hazardous Chemical Synthesis, Designing Safer Chemicals, Safer Solvents, Design for Energy Efficiency, Use of Renewable Feedstocks, Reduce Derivatives, Catalysis, Design for Degradation, Real-time Analysis, Inherently Safer Chemistry for Accident Prevention*

1. *Identify 3 of the principles that are present in this experiment. Give a short explanation of how they are being applied.*

*Prevention, Less Hazardous Chemical Synthesis, Safer Solvents, Design for Energy Efficiency, Use of Renewable Feedstocks, Inherently Safer Chemistry for Accident Prevention*

1. *Identify 3 of the principles that are not present in this experiment.*

*Atom Economy, Designing Safer Chemicals, Reduce Derivatives, Catalysis, Design for Degradation, Real-time Analysis*

1. *Is this experiment still a good example of green chemistry? Explain why or why not.*

*Yes, no reaction can be perfect. The goal is to incorporate as many green principles as possible.*

1. *Contrast this with the traditional Wittig reaction.*

*It uses milder base- sodium hydroxide instead of n-butyllithium, no solvent in place of N, N-dimethylformamide, reduced reaction time 30 minutes instead of overnight, the extraction with diethyl ether is eliminated and solvent from renewable feedstock for recrystallization.*

**Required Materials**

Aromatic Aldehyde:

*o*-nitrobenzaldehyde (Aldrich) CAS: 99-61-6

*p*-anisaldehyde (Acros Organics) CAS: 123-11-5

benzaldehyde (Alfa Aesar) CAS: 100-52-7

4-chlorobenzaldehyde (Acros) CAS 104-88-1

*p*-tolualdehyde (Aldrich) CAS 104-87-0

mesitaldehyde (Aldrich) CAS 487-68-3

4-(dimethylamino)benzaldehyde CAS 100-10-7

*trans*-cinnamaldehyde (structure is a bit different from the others since the product will have 2 alkenes) (Eastman) CAS 104-55-2

10 N sodium hydroxide prepared from solid (Fisher) CAS 1310-73-2 prepared by dissolving 40 g sodium hydroxide in 100 mL deionized water – caution this solution will become quite hot and will require cooling with a water or ice water bath during preparation.

benzyltriphenylphosphonium chloride (Acros Organics) CAS 15853-35-7

magnetic stir bar/ plate

vacuum filtration apparatus (Buchner funnel, filter flask, filter paper)

two (2) 25mL Erlenmeyer flasks

ethanol (Fisher) CAS 64-17-5

ice bath

NMR tube + deuterochloroform(Acros Organics) CAS 865-49-6 if running NMR

ethyl acetate (Fisher) CAS 141-78-6 and heptane (Acros Organics) CAS 142-82-5

TLC plates if performing TLC analysis

heptane (for GCMS) (Acros Organics) CAS 142-82-5

potassium bromide (for IR) (International Crystal Labs) CAS 7758-02-3

mortar and pestle (for IR)

GC vials (2 mL)

**Hazards**

Wear eye protection and protective gloves during this experiment. All work should be done in a fume hood. All chemicals used in this experiment should be considered harmful by ingestion and skin irritants. Benzaldehyde is a repiratory and skin sensitizer. P-tolualdehyde is combustible. Benzyltriphenylphosphonium chloride is highly toxic by ingestion. Heptane is highly flammable and may be fatal if swallowed and enters airways. Deuterochloroform causes irritation of the skin and respiratory system, may cause chemical burns and is a possible carcinogen. Ethanol and ethyl acetate are highly flammable and toxic by ingestion.

**Reaction**

Obtain amounts of the starting aromatic aldehyde and the benzyltriphenylphosphonium chloride in a 1.0:1.1 equivalent mole ratio. Start with 500 mg of the aldehyde and calculate the amount of the phosphonium salt needed. To do this, you need to determine the moles of the aldehyde, and then calculate the slight excess (1.1 times the moles of aldehyde) of the phosphonium material. Combine materials in 25 mL Erlenmeyer flask along with a magnetic stir bar. Measure 5 mL 10 N sodium hydroxide (NaOH). Add the NaOH to the reaction flask, place on a stir plate and stir for 30 minutes.

*(Instructor’s note: Using 500 mg of starting aldehyde will require approximately 1.8 g of the ylide. The experiment can be performed successfully on smaller amounts, though smaller glassware can be helpful (e.g. 6 mL vials). With 200 mg of starting aldehyde, students have been able to recrystallize the products with enough material for instrumental analysis. If the reaction is being used as part of a multi-week)*

Filtering

When the 30 minutes is nearly complete, obtain 20mL ethanol and begin to heat to boiling for recrystallization. Assemble a vacuum filtration apparatus and filter product. Wash the crude product with water until the filtrate is no longer basic.

At this point you could analyze the crude product mixture via TLC (10% ethyl acetate in heptane). GCMS could also be run in heptane to determine if any product has formed as well as the ratio of *E* to *Z* isomers.

Recrystallization

Transfer the crude product to a 25 mL Erlenmeyer flask. Add a minimum amount of boiling ethanol to the product until it is completely dissolved. Let the solution cool to room temperature on the counter without disturbing, and then place in an ice bath for about 30 minutes. Vacuum filter and weigh the crystalline product.

*(Instructor’s note: The triphenylphosphine oxide byproduct is removed during the recrystallization process).*

***Analysis***

TLC

The recrystallized product can be analyzed by thin layer chromatography using 10/90 ethyl acetate/ heptane. It should be possible to see both the Z and E isomers on the TLC plate.

*Do you see a pronounced difference between the TLC of the crude and recrystallized in terms of Z/E products? The crude should have a mix of E and Z, while the recrystallized is primarily E isomer.*

IR

Add a small spatula full of your product to about 10x as much KBr and grind with a mortar and pestle. Place a small amount into a die and compress. After 1-2 minutes, open the die and check to see if you have a window in the middle of the die that light will pass through. Analyze your sample by infrared spectrophotometry.

*Where do carbonyl peaks typically appear in IR? ~1700 cm-1*

*Where is the aldehyde peak in your starting material? 1675 - 1710 cm-1*

*Does the product have a peak in the same area? Not unless the reaction doesn’t proceed and they are analyzing the aldehyde reactant*

1H NMR

Dissolve a small amount of your product in CDCl3 for analysis by 1H NMR.

*Where do aldehydes show up in 1H NMR? 9.68-10.55 ppm for the reactants*

*Is there still an aldehyde peak present in the spectra? Not unless the reaction doesn’t proceed and they are analyzing the aldehyde reactant*

*Where do alkenes typically show up in 1H NMR? 5-6ppm*

When alkenes are conjugated to aromatic rings, the proton signals shift downfield. *Which signal do you think is resulting from the alkene protons? 6.75-7.26 ppm for the new alkene.*

Make a table of your NMR data assigning signals to protons on your product.

*Instructor’s Note: the aromatic region will be difficult to assign unless high-field NMR is available. With a 60MHz NMR, it is still possible to see side chains, lack of aldehyde and appearance of the alkene protons.*

GCMS

Prepare a sample of your product for GCMS analysis (1 small crystal of material dissolved in 1-2 mL heptane).

*Instructor’s Note: In testing the experiment, the product was analyzed by GCMS using a 30m Rtx-5 column with the following temperature program: 40oC hold for 2 minutes, ramp at 10oC per minute to 200oC and hold for 2 minutes, ramp 20oC per minute to 280oC and hold for one minute. Dichloromethane or hexanes can also be used as GCM S solvents but heptane are preferable due to reduced toxicity.*

*What is the molecular weight of your starting aldehyde?*

*Does the aldehyde appear in your recrystallized product?*

*What is the molecular weight of your predicted product?*

*Does the molecular ion match this molecular weight?*

*What is a potential structure for any fragments in the mass spectrum?*

*If you analyze the crude product by GCMS as well:*

*Will the E or Z isomer have greater van der Waals forces? If you are not sure about this, consider that Z-stilbene is a liquid, while E-stilbene is a solid. More spread out molecules have greater vdw forces, therefore E has greater vdw.*

*Which isomer will elute from the column first? Z will come out first.*

*What ratio of E:Z isomers do you see in your crude product?*

*How does that differ from your recrystallized product?*

Make a table of your GCMS data assigning fragments from your product and E:Z isomers if analyzing the crude product.

**Disposal of Waste**

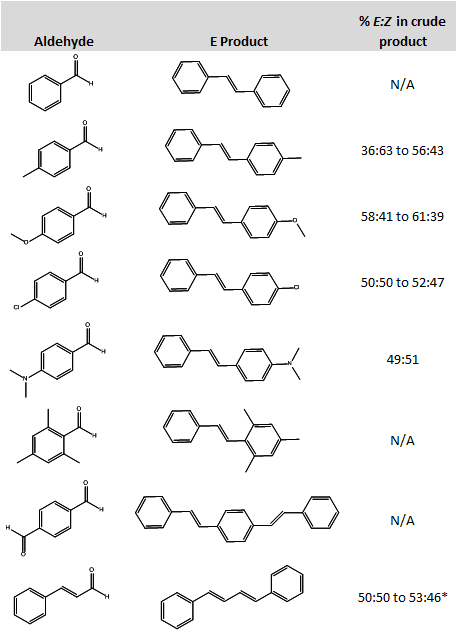
No waste from this lab should be poured down the sink. There will be appropriate waste disposal vessels available for you in the lab. There will be a waste container for the basic aqueous waste from the initial filtering and rinsing. There will be another waste container for the recrystallization solvent waste. There will be a separate waste container for the NMR solvent since it is halogenated and should not be placed in the same container as the recrystallization solvent.

**3. Summary of Product Yields and Experimental Data**

Table 1. Summary of Product Yields and Experimental Data



Table 2. Summary of *E-Z* percentages in crude products

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Some samples were not analyzed by the students in lab before recrystallization. For those, there is no crude stereochemical breakdown (marked N/A). \* The cinnamaldehyde starting material was *E*-cinnamaldehyde, so the product after recrystallization was (1E,3E)-1,4-diphenylbuta-1,3-diene. The product of the terephthalaldehyde could be in s-cis conformation as shown or s-trans conformation.

**4. Additional Spectra**

Crude 4-chlorobenzaldehyde GCMS



The crude 1-chloro-4-styrylbenzene chromatogram shows 47:52 E:Z ratio. The peak at 15.662 corresponds to the Z isomer. The mass spectrum of this isomer is shown here with the molecular ion at 214 m/z with the 37Cl isotope peak at 216 m/z.

E isomer MS



The peak at 17.758 corresponds to the E isomer. The mass spectrum of this isomer also clearly shows the molecular ion of the expected product.

Recrystallized E isomer chromatogram and MS



(*E*)-1-chloro-4-styrylbenzene after recrystalliztion, the Z isomer is gone as evidenced by the loss of the peak at 15.66 in the chromatogram.



The anisaldehyde starting material clearly shows the methoxy peak at 3.8 ppm, the aldehyde at 9.8 ppm and the expected doublet of doublets for a para substituted benzene ring at 6.9-7.8 ppm.



The (*E*)-1-methoxy-4-styrylbenzene product still shows the methoxy peak at 3.8 ppm, while the aldehyde at 9.8 ppm is now missing and the aromatic region includes the three additional signal from the additional benzene ring as well as the alkene protons that are conjugated to both rings (6.8-7.6 ppm).