27. A Solvent Free Wittig Reaction

A. Background

The ability to prepare alkenes is an extremely valuable reaction in organic synthesis. There are a number of reactions that can be used to prepare alkenes, but one of the most important is the Wittig reaction. In fact, the discoverer of this reaction, George Wittig, was awarded the 1979 Nobel Prize in Chemistry for his work.

The Wittig reaction involves the reaction of an aldehyde or ketone with a phosphorus ylide. An ylide is a species that has negatively charged carbon adjacent to a positively charged heteroatom. Ylides have a second resonance structure that can be drawn in which the charges are minimized. The driving force for the Wittig reaction is formation of triphenylphosphine oxide, which has an extremely strong phosphorus/oxygen double bond. (Figure 1)

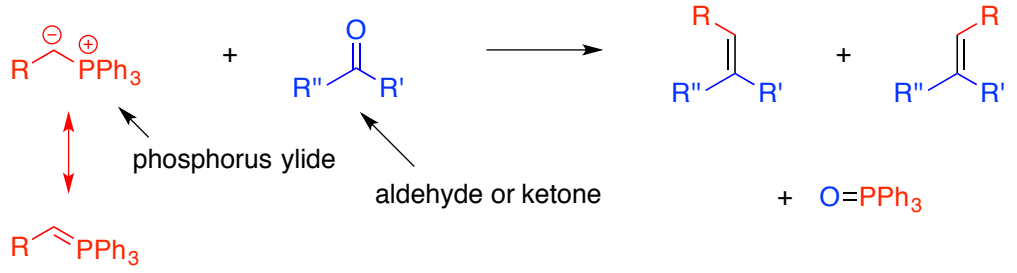

Figure 1. A General Wittig Reaction

Ylides are prepared by reacting an organohalide with triphenylphosphine to provide a phosphonium salt. The positively charged phosphorus in the phosphonium salt greatly increases the acidity of the adjacent methylene group. The phosphonium salt is then converted to the ylide by reaction with a base as shown in figure 2. Some ylides are commercially available, however, it is most common to prepare the desired ylide in the lab just prior to use.

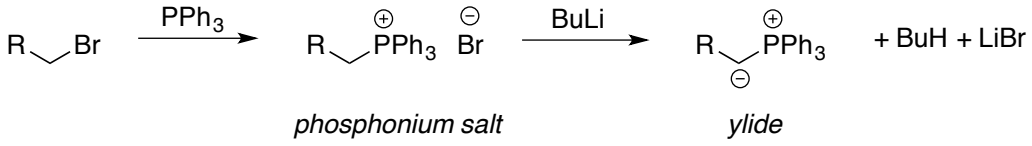

Figure 2. Preparation of an Ylide from an Organohalide

The mechanism of the Wittig reaction involves initial cycloaddition of the ylide and carbonyl group. This can be thought of as the negatively charged carbon of the ylide acting as a nucleophile at the carbonyl carbon. The electrons in the C=O π-bond simultaneously attack the positively charged phosphorus. The resulting intermediate is a four membered ring called an oxaphosphetane. The oxaphosphetane then fragments, eliminating triphenylphosphine oxide and providing the desired alkene product. (Figure 3)

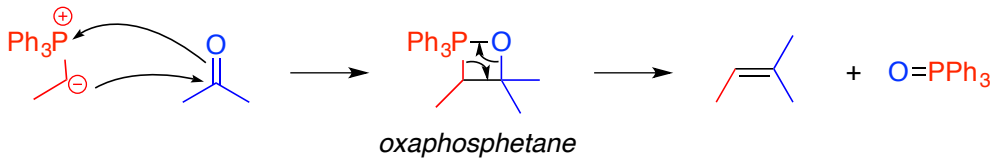

Figure 3. Mechanism of the Wittig Reaction

The *E/Z* selectivity of the Wittig reaction depends upon the structure of the ylide that is used. When the R group of the ylide is a simple alkyl, the species is called an **unstabilized ylide** and the *Z* double bond isomer predominates in the products. When R is an aryl, alkenyl, or $-CO_2R$ group, the species is called a **stabilized ylide** because the carbanion has additional resonance stabilization. Stabilized ylides give products with predominately *E* stereochemistry. (Figure 4)

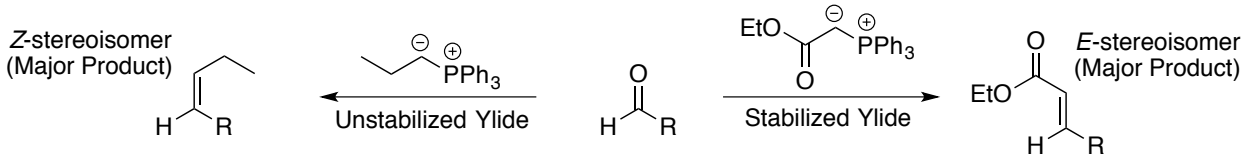

Figure 4. Stabilized Versus Unstabilized Ylides

In today's laboratory experiment you will be reacting benzaldehyde with the Wittig reagent (carboxymethylene)triphenylphosphorane to produce ethyl cinnamate as shown in figure 5. Both the *E* and *Z* double bond isomers are produced, however, because a stabilized ylide is used in this reaction, the *E*-stereoisomer is the major product. The ylide used in this experiment is commercially available and will be provided. (Figure 5)

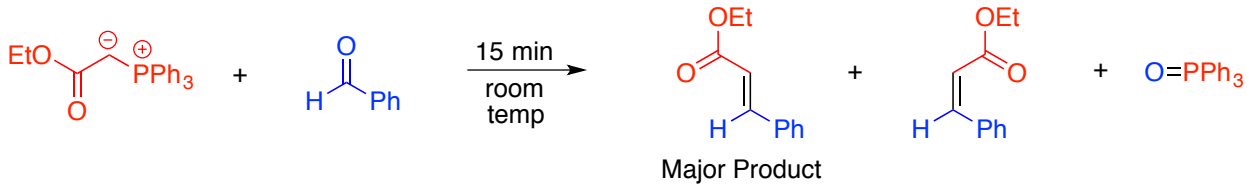

Figure 5. Wittig Reaction to form Ethyl Cinnamate

Green Chemistry – A Solvent Free Reaction

The Wittig reaction that you will perform is typically carried out in the solvent methylene chloride. Organic solvents are very useful for dissolving organic substrates, however, they do impose additional health risks, environmental impact, and expensive waste disposal costs. In this experiment, we will eliminate the reaction solvent. Typically when a reaction solvent is eliminated, one or both of the reactants should be in the liquid state so that the liquid can act as a "pseudo-solvent." In this experiment, the phosphorane ylide is a solid and benzaldehyde is a liquid. It should be noted that following the reaction, the solvent hexane is used to extract the organic product from the solid byproduct. Ideally, for the most "green" process, no solvent is used at any point in the reaction, workup, or isolation steps. Despite this drawback, hexane is a relatively safe solvent that has little evidence of negative health effects or environmental damage.

B. Experimental Procedure[i]

Reagent	Mol. Wt.	Mass	Mmol	Equiv.
Benzaldehyde	106			1
(carboxymethylene)triphenylphosphorane	348			1.15

Place a clean 5 mL conical reaction vial on a balance and tare the balance. Add benzaldehyde dropwise to the vial until the mass reaches ~60 mg (this should require 4-5 drops from a pipet). **Record the actual mass that you measure out**. Based on the mass of benzaldehyde, calculate the mass of the phosphorane reagent that you will need for the reaction.

Add a spin vane to the conical vial and begin stirring. Weigh out the necessary amount of phosphorane reagent in a weigh boat and add this solid to the stirring benzaldehyde in the conical vial. Stir the mixture for 15 min at room temperature. You may need to periodically scrape the solids from the vial walls down into the mixture. After 15 min of stirring, the reaction should be complete. Add hexanes to bring the vial volume to 3 mL and stir rapidly to extract the product into the organic solvent.

Prepare a filtering pipet by plugging a pipet with a small wad of cotton. Filter the hexanes solution through the pipet into a clean, **weighed**, conical vial. Add a second 1.5 mL portion of hexanes to the reaction vial and stir rapidly to extract any remaining product. Filter this second portion of solution through the filter pipet and collect it with the first portion.

TLC: You should check the reaction by TLC to ensure that it went to completion. *Refer to experiment 7 from Chem 235 to review TLC*. Prepare a TLC plate as shown in figure 6. Using a spotter, spot the product solution at C (co-spot) and P (product). The solution is sufficiently concentrated that you should only need to spot once. Prepare a starting material solution by dissolving 1 drop of benzaldehyde in 1 mL of hexanes. Place one spot of this solution at S (starting material) and at C (co-spot). Place the TLC plate in a developing chamber containing a 10% ethyl acetate/hexanes mobile phase. Visualize the developed TLC using a UV lamp.

Product Isolation: Place a clean spin vane in the vial containing the product dissolved in hexanes. Heat the vial on the hot-plate with stirring to boil off the hexanes. Aim for a 90-100 °C block temperature. This process will take ~20 min. Allow the vial to cool, remove the spin-vane, and weigh the vial containing product to determine the yield. Record an IR spectrum of your product.

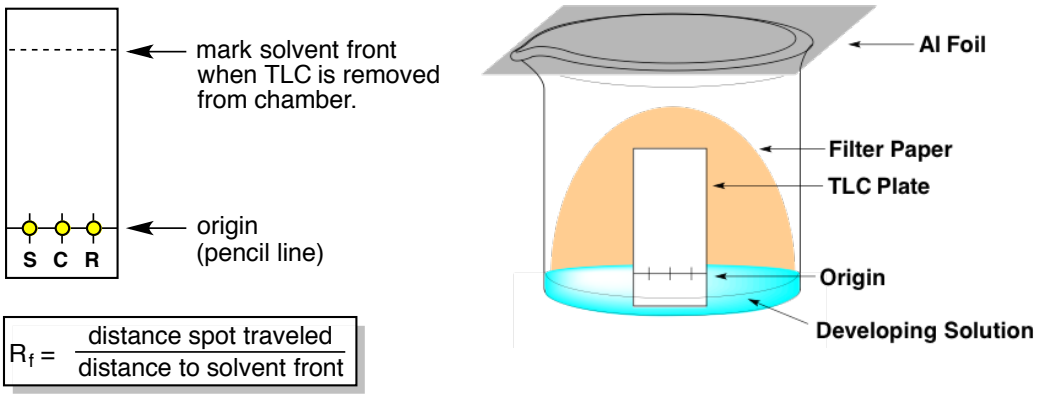

Figure 6. Thin Layer Chromatography

C. Prelab Questions

1) A general ylide preparation is described in figure 2. Show how the ylide that is used in this laboratory experiment could be prepared in the lab.

2) The ylide used in this experiment is considered a stabilized ylide. Use resonance to explain how this ylide has additional stability compared to an unstabilized ylide.

3) Using the mechanism in figure 3 as a guide, show the complete electron pushing mechanism for the Wittig reaction that you be performing in lab.

4) Look at the 12 principles of green chemistry listed at http://goo.gl/1zdmDy and describe which of these principles are accomplished in this laboratory experiment.

5) Considering the 12 principles of green chemistry from the previous question, is there one principle that is most definitely not achieved in the reaction? *Hint: consider the byproduct of the reaction*.

D. Postlab Questions

1) The ^{1}H NMR spectrum shown below in figure 7 corresponds to the products isolated from the same Wittig reaction that you performed in lab. Using this NMR, answer the following questions.
   a. The peaks labeled a-d correspond to the alkene protons in the *cis* & *trans* alkene isomers. Which peaks correspond to the *trans* product: a & c or b & d?
   b. Draw the structure that corresponds to signals a & c. Assign these two signals to the corresponding alkene protons in the molecule. Explain your reasoning.
   c. Using the integration values provided, calculate ratio of *trans* to *cis* product produced.

2) Besides NMR, what is another technique that could be used to determine the relative percentages of *cis*- and *trans*-stereoisomers produced following the reaction? *Hint: think back to the experiments from Chem 235.*

3) Calculate the R_f values of the starting material (benzaldehyde) and product (ethyl cinnamate) from your TLC data.

4) Based on the IR data that you collected, how can you confirm that the desired alkene product was formed?

5) Following the reaction a white solid remained in the vial. What is this substance?

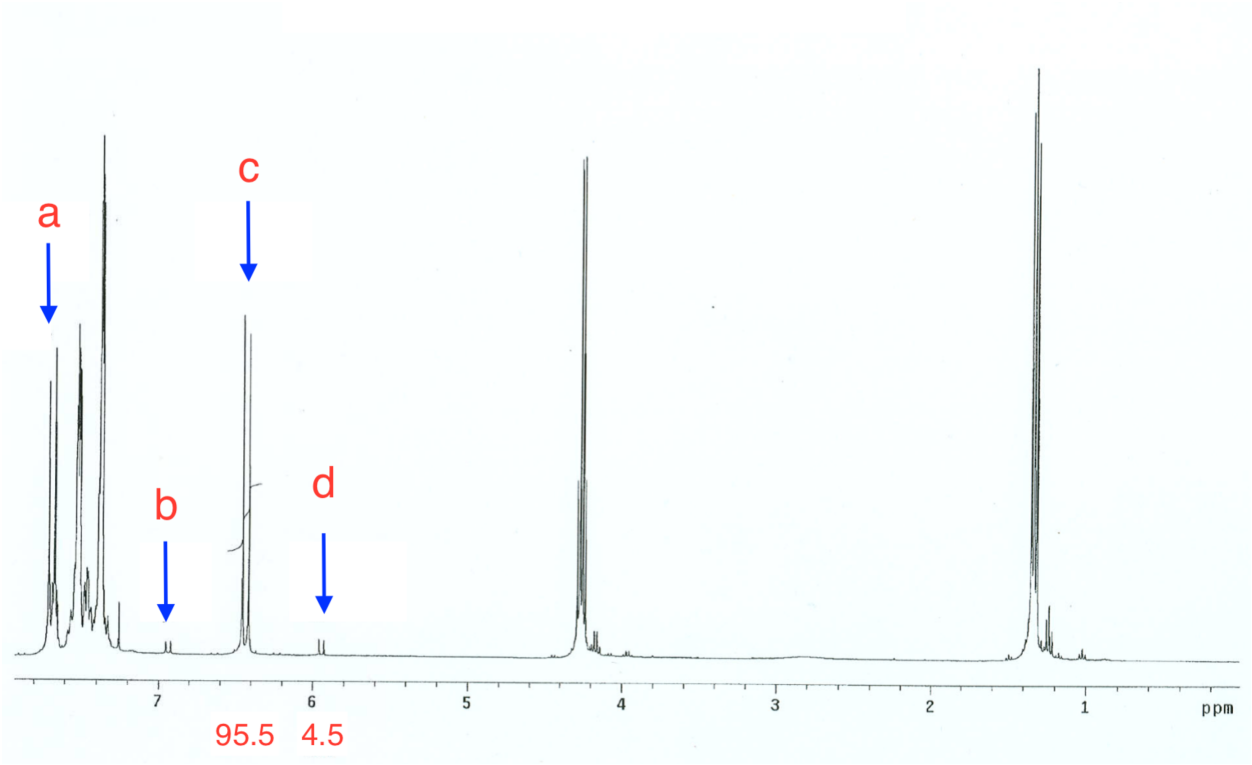

Figure 7. NMR Spectrum of Cis and Trans Ethyl Cinnamate

[i] Procedure adapted from: *J. Chem. Ed.* **2007**, 119