

Synthesis of an Alkene via the Wittig Reaction

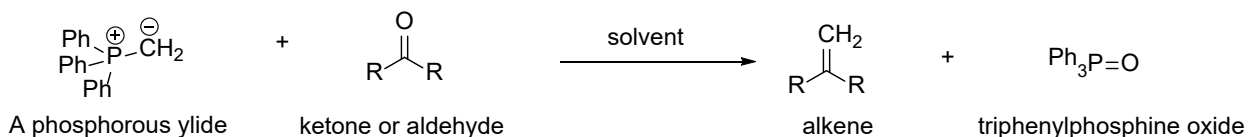
I. Introduction

In 1953, the synthesis world was forever changed. Before this, the controlled installation of an alkene into an organic moiety was arbitrary, difficult, and sometimes just down right impossible. Prof. George Wittig and his graduate students developed a very effective and operationally simple method of incorporating an alkene where once was present a ketone or aldehyde. This process is now known as the Wittig reaction. For this work, George Wittig was awarded the Nobel Prize in chemistry in 1979 (co-recipient H.C. Brown). For an extensive review on this reaction, see: Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* **1989**, 89, 863-927. This review is also posted on the course website.

II. The Overall Process

The Wittig reaction generates an alkene via the reaction between a stabilized carbon nucleophile and a ketone or aldehyde (most other carbonyl groups are unreactive). Figure 1 shows the overall process. Notice the carbon anion is attached to a formally positive charged heteroatom but the species is overall uncharged. This is called an ylide and is discussed further in section III. The reaction also produces triphenylphosphine oxide, which is separated from the desired alkene.

Figure 1. The Wittig reaction converts a ketone or aldehyde to a new alkene.



III. The Ylide

The original, most widely utilized version of the Wittig reaction makes use of a species known as an ylide (pronounced yl-id). This is a dipolar, overall neutral species, but contains a formal negative atom (generally carbon) and a formal positive heteroatom (see Figure 1). There are a few variations of the ylide, but the phosphorous species is the most widely known. For example, Figure 2 shows a phosphorous ylide and a sulfur ylide as the formally charged version. More commonly, however, their resonance forms (Figure 3) are shown to reduce clutter within the structure. These dipolar species are fairly powerful nucleophiles.

Figure 2. Phosphorous and sulfur ylides with positive and negative charges

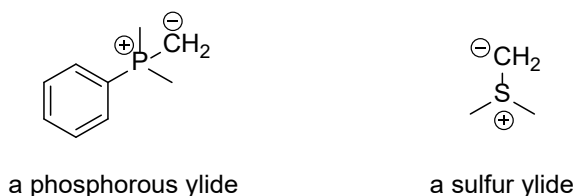
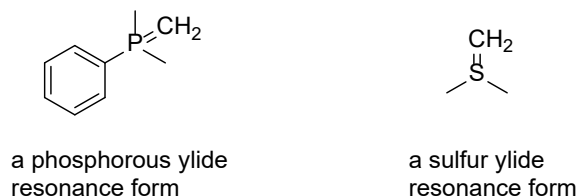


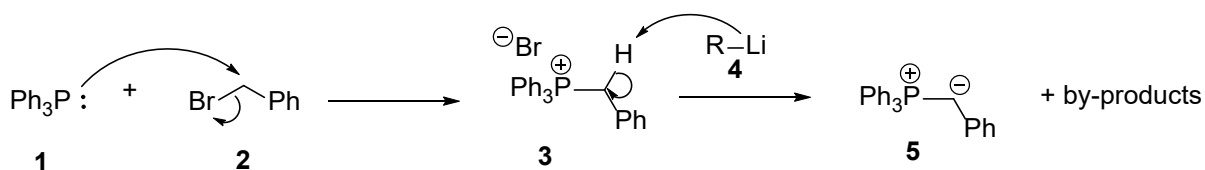
Figure 3. Phosphorous and sulfur ylides shown without formal charges



IV. The Reaction and Mechanism

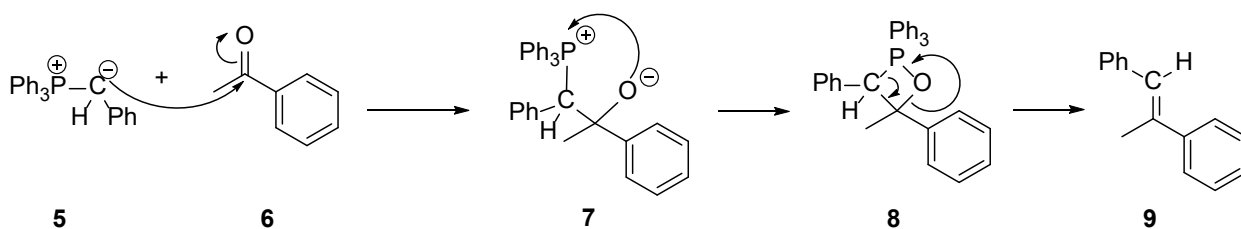
Ylides are stabilized carbanions, but most are not stable enough to be commercially available. They must be prepared via an S_N2 reaction (Scheme 1) between triphenylphosphine (**1**) and a suitable electrophile (**2**). The electrophile (**2**) is generally a primary alkyl halide (here the electrophile is a primary alkyl bromide) or halide equivalent (a tosylate, for example). What re-

Scheme 1. Generation of a phosphonium salt and conversion to the ylide.



sults is a phosphonium salt (**3**), which is then treated with a strong base (generally an alkyl lithium, **4**) to abstract a proton to form ylide (**5**) and other by-products. Ylide (**5**) then attacks carbonyl compound **6** (Scheme 2, here a ketone) to form a betaine (**7**). The opposite charges of oxygen and phosphorous, along with a very strong bond formed between these two atoms, yields

Scheme 2. Attack of a ketone by an ylide to yield an alkene via the two intermediates discussed in the text.

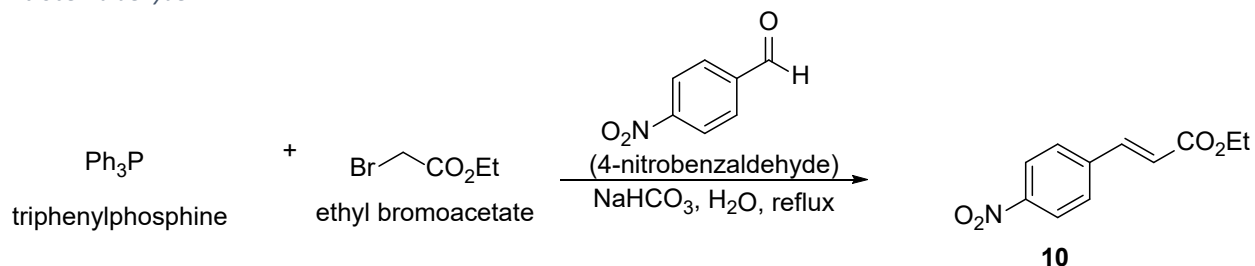


the four-membered ring compound **8**, known as an oxaphosphetane, which collapses almost as soon as it is formed due to ring strain. After collapsing, alkene **9** is formed along with the by-product triphenylphosphine oxide (not shown). This oxide is an extraordinarily stable compound, and as such, provides the thermodynamic driving force for the Wittig reaction.

V. Our Experiment

We will be performing a safer, greener version of the Wittig reaction. Instead of using organic solvent, we will utilize water as the reaction medium. The overall reaction performed in this experiment is shown in Scheme 3. We will utilize a one-pot procedure where all reactants and

Scheme 3. The Wittig reaction performed in this experiment between triphenylphosphine, ethyl bromoacetate and 4-nitrobenzaldehyde



reagents are placed into a single round bottom flask and then allowed to react. As previously discussed in Section IV, the base used to generate the ylide from the phosphonium salt was an alkyl lithium. These bases are extremely pyrophoric and dangerous to handle. Instead, we will employ sodium bicarbonate (baking soda).

VI. Pre-Lab Questions

1. In scheme 1, what are the two by-products not shown? This should be very easy.
2. Provide a complete mechanism, from start to finish, for the formation of the α,β -unsaturated ester **10**.
3. Trimethylphosphine is a much stronger nucleophile than triphenylphosphine, but it is never used to make ylides. Why is the former phosphine unsuitable for making ylides?
4. Look up the MSDS for all compounds used in this experiment (not the workup procedure), excluding water, and list at least one hazard for each in your TOR.

VII. Precautions

Ethyl bromoacetate is a toxic lachrymator. Wear gloves at all times during this experiment. As always, perform all work in the fume hood.

VIII. Experimental Procedure

- Turn on hot plate with aluminum block immediately upon entering the lab. Put on safety glasses/goggles and a lab coat.
- Obtain from the reagent bench the following equipment: 25 mL round bottom flask (RBF), water jacketed condenser, blue Keck clip, separatory funnel and ground glass stopper, magnetic stir bar, and two lengths of condenser tubing.

- To the RBF add 3.3 mmol of 4-nitrobenzaldehyde, 5.0 mmol of triphenylphosphine and the stir bar.
- Add 10 mL of saturated, aqueous sodium bicarbonate.
- To this solution add 6.6 mmol of ethyl bromoacetate via a syringe.
- Clamp water jacketed condenser to the ring stand. Attach tubing to inlets. Water goes in the bottom and out of the top.
- Attach RBF to condenser and secure with the blue Keck clip. Turn on water. If water is trickling out of the drain tubing, the flow rate is fine.
- Lower apparatus into the bowl-shaped well that fits the RBF. Turn on stirring to establish a good stir rate. When solution begins refluxing, continue for 35 minutes.
- When time expires, cool until you can easily handle the RBF.
- Transfer contents of RBF to separatory funnel, being certain the stopcock is closed. You will, most likely, notice a solid particulate in the RBF.
- To the RBF with the solid, add 10 mL ethyl acetate and stir until complete dissolution of the solid. Add this to the separatory funnel. Cap sep funnel with glass stopper.
- Invert sep funnel and vent via the stopcock. Invert, shake, and get those layers to mix (remember lidocaine?). Make sure to periodically vent via the stopcock, not the glass stopper.
- Allow layers to separate and drain lower aqueous layer. Drain organic layer into a separate vessel.
- Add aqueous layer back to funnel. Add 5 mL ethyl acetate and repeat the invert, vent, shake, invert, vent process. Drain aqueous layer into the same vessel as you previously used for the aqueous layer.
- Combine the organic layer with the previous organics.
- Repeat above two more times. What you are doing is called extracting the aqueous layer with ethyl acetate, 4 x 5 mL.
- Add combined organics back to the empty separatory funnel. Add 15 mL of brine. Shake, invert, vent, etc. Drain aqueous layer and discard.
- Remove the combined organics into a new 50 mL Erlenmeyer flask and dry with calcium chloride. Gently swirl and let dry for 5 minutes. Remove drying agent via suction filtration using a clean, 25 mL filter flask.
- Remember, your product is in solution (the filtrate).
- Evaporate organic solvent via a gentle stream of air.
- Recrystallize the resulting solid from 95% ethanol/water and isolate via suction filtration.
- With help from your TA, obtain an IR using the ATR (**A**ttenuated **T**otal **R**eflection) instrument attachment.
- Prepare a sample for $^1\text{H-NMR}$: dissolve ~20 mg of sample in deuterated chloroform (CDCl_3) spiked with 1% tetramethylsilane (TMS) reference. This TMS is already added to the stock solution of CDCl_3 . You should run YOUR OWN NMR.

IX. Clean Up

Dispose of all waste in the halogenated liquid waste container as there may be some ethyl bromoacetate leftover.

X. Postlab Data Analysis

You must be able to justify that you have made the product. Use the IR, NMR of starting material and product. Justify by what you learned in lecture. What protons are responsible for each peak or set of peaks?

In your experimental procedure it is standard to report your NMR peaks at the end. You must look up how to do report this. Use the supporting information from any *Organic Letters* article that describes the synthesis of a compound and mimic the style within.