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Chemistry

Organic Chemistry Laboratory Experiments

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Wittig Reaction

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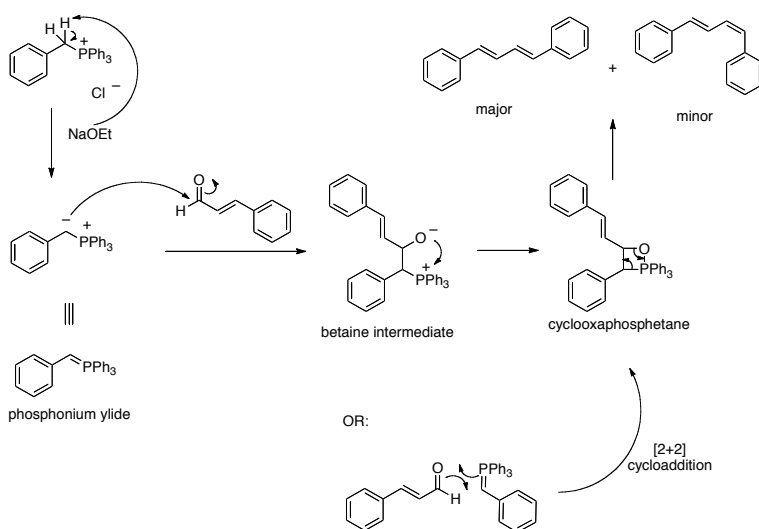
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The Wittig Reaction

Introduction:

The Wittig reaction is one of the most famous reactions in all of organic chemistry, so much so that its discoverer, Georg Wittig, who reported the reaction in 1954, received the Nobel Prize in Chemistry in 1979. It is one of the easiest and least expensive ways to create alkenes from ketones and aldehydes. This reactive species in this reaction, as well as in related procedures such as the Horner-Wadsworth-Emmons reaction, is a unique intermediate known as the *ylide*. An ylide is an overall neutral species that has adjacent atoms with opposite charges, often made possible by the fact that one of those atoms has an expanded valence shell. For example, elements like phosphorus and sulfur readily form ylides due to the presence of *d* orbitals which can stabilize adjacent negative charges. In terms of reactivity, the ylide functions like a carbanion, and thus it is nucleophilic. Overall, a phosphorous ylide reacts with an aldehyde or ketone to generate an alkene.

The mechanism for the Wittig reaction is shown below. Deprotonation of a phosphonium salt generates the phosphorus ylide. Since the ylide is nucleophilic at carbon and in the presence of an aldehyde, it will add to the π^* orbital of the carbonyl to generate a betaine intermediate. Phosphorus is oxophilic, and thus cyclization of the betaine occurs to give a cyclooxaphosphetane, a four-membered ring containing both oxygen and phosphorus. Alternatively, a concerted [2+2] cycloaddition between the ylide and the carbonyl group of the ketone or aldehyde to give the cyclooxaphosphatane directly. Today it is believed that this latter pathway operates in most carbonyl olefination reactions. Cycloreversion results in formation of the alkene and the byproduct triphenylphosphine oxide. Since nucleophilic addition of the ylide on the carbonyl can be reversible depending on the exact composition of the ylide, the reaction can be under thermodynamic control and the *trans*-isomer is the predominant product. In other cases, the reaction conditions may give the *Z*-isomer, the kinetic product.

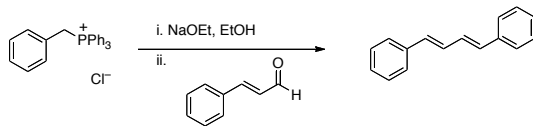


For your experiment, we will generate an ylide by deprotonating a phosphonium salt with sodium ethoxide solution. The ylide will then be allowed to react with an aldehyde to generate a mixture of *cis*- and *trans*-isomers. You will isolate the major product by recrystallization. Comparing the melting point of this synthetic compound to its literature value provides a measure of its purity. Since other analytical techniques (NMR, LC-MS) provide more information on purity, melting point determination is waning as an analytical technique. Nevertheless, it is an important skill to learn in an undergraduate setting. Finally, we will review how to run a TLC and reinforce UPLC-MS analysis.

References:

1. Pavia, D. L.; Lampman, G. M.; Kriz, G. S.; Engel, R. G. *Introduction to Laboratory Techniques*, 4th Ed. Thomson Brooks/Cole: Mason, OH, 2006; pp 359-364.

Wittig Reaction



Equipment:

Microscale glassware kit
25 and 50 mL beakers
10 mL graduated cylinder
1 mL syringes and needles
Pasteur pipets
Capillary tubes
Cotton
Scintillation vials and caps
NMR tubes
HPLC vials
MeltTemp apparatus
Stir bars

Chemicals:

Benzyltriphenylphosphonium chloride
2.5 M sodium ethoxide solution in ethanol
Cinnamaldehyde (other cinnamaldehydes may also work to create substituted dienes)
Ethanol (2 x 200 mL)
Acetone
Hexanes
Deionized water
Methanol (2 x 500 mL)
 CDCl_3

Procedure: adapted from Pavia, D. L.; Lampman, G. M.; Kriz, G. S.; Engel, R. G. *Introduction to Laboratory Techniques*, 4th Ed. Thomson Brooks/Cole: Mason, OH, 2006; pp 359-364.

Wittig Reaction: Place 480 mg of benzyltriphenylphosphonium chloride in an oven-dried 5 mL conical vial containing a magnetic spin vane. The vial can be placed in the oven for 10 minutes before use. Dissolve the Wittig salt in 2 mL anhydrous ethanol and then add 0.75 mL of 2.5 M sodium ethoxide solution via syringe. Cap the vial and stir for 15 minutes. Note any changes in the composition of your sample. While your ylide is forming, dissolve 0.15 mL of cinnamaldehyde in 0.5 mL anhydrous ethanol in another conical vial. After the 15 minutes has elapsed, add the cinnamaldehyde solution to the ylide mixture and observe any changes in the reaction mixture. Stir the reaction for 15 minutes and take a TLC to ensure that your reaction is complete. Use cinnamaldehyde as your reference and hexanes as your elution solvent. Be sure to dilute your reaction mixture and reference sample prior to developing the TLC and that you have a co-spot on your TLC plate!

Workup: Cool the reaction mixture in an ice bath for 10 minutes and then filter the product mixture, collecting the solid on a Hirsch funnel. Wash the crystals with 2 x 1 mL ice-cold ethanol. Recrystallize your product with 3 mL water and vacuum filter. Let air run through the sample for 10 minutes, then transfer the solid to a tared vial and dry in the oven 20 minutes prior to analysis.

Analysis: Obtain a ¹H NMR, IR, UPLC/MS (*t_R* only), and melting point to fully characterize your data. Obtain a weight of your diene and record your yield. Place your sample in a tared scintillation vial and submit a labeled sample to your TF for storage.

Pre-Lab Exercise:

These questions do not need to be explicitly answered in writing, but you should be able to answer them prior to your arrival in lab.

1. The sodium ethoxide solution is prepared by dissolving sodium metal in ethanol. Why would this reagent need to be prepared fresh each time it is used?
2. What is an ylide? How does it behave?
3. A pheromone of the female housefly is called muscalure. Look up the structure of muscalure and devise a synthesis using the Wittig reaction.
4. What is the relationship between melting point and purity? (i.e. What happens to the melting point if a sample isn't pure? and Why?)
5. What side products are generated during this reaction? During your analysis of the filtrate, how many of these will you observe on the TLC plate?
6. Why is it necessary to keep the glassware extremely dry during this experiment?
7. What is the geometry about the double bond for the major product in this reaction? Assign the E/Z designation to each double bond.

Post-Lab Assignment: Ask your instructor.