The Tandem Grignard-Oppenauer Oxidation

A Greener Synthesis of α-Trimethylsilyl Phenyl Vinyl Ketone

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Outline

- Introduction to green chemistry
- Baylis-Hillman reaction
- My research
- Continuing research

What is Green Chemistry?

"The utilization of a set of principles that reduces or eliminates the use or generation of hazardous substance in the design, manufacture and application of chemical products."

– Doxsee, K.M. and Hutchison, J.E. *Green Chemistry: Strategies, Tools, and Laboratory Experiments.* Thomson, Brookes, and Cole. **2003.**

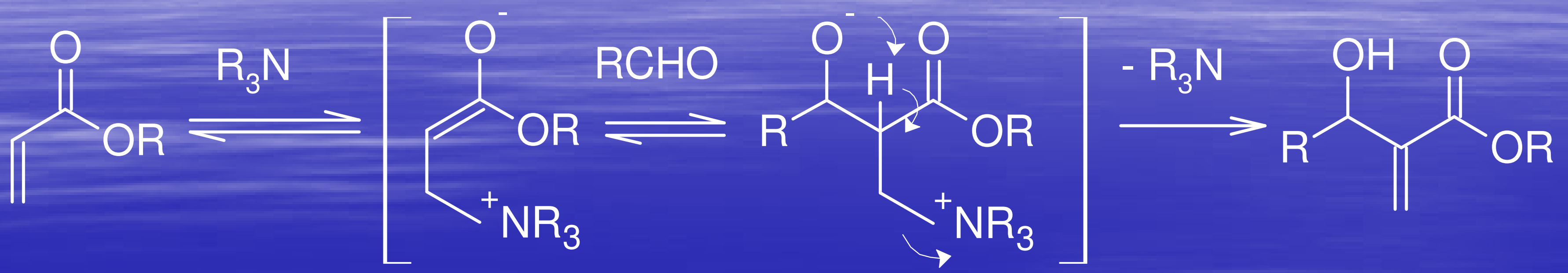
Green Chemistry is:

- An emerging field within organic chemistry
- Pollution prevention at the most fundamental level, atoms and molecules
- Focuses on reducing intrinsic hazards of reactions and making them more efficient

Applying Green Chemistry to Undergraduate Research

- Assess reactions for the “greenness” of the reaction
- Propose safer methods or chemicals that could be used
- Implement proposed changes in lab to determine effectiveness
- Development of new methodology

Baylis-Hillman Reaction



Utility of Baylis-Hillman Adduct

- Densely functionalized
- Broad use as substrate in other reactions

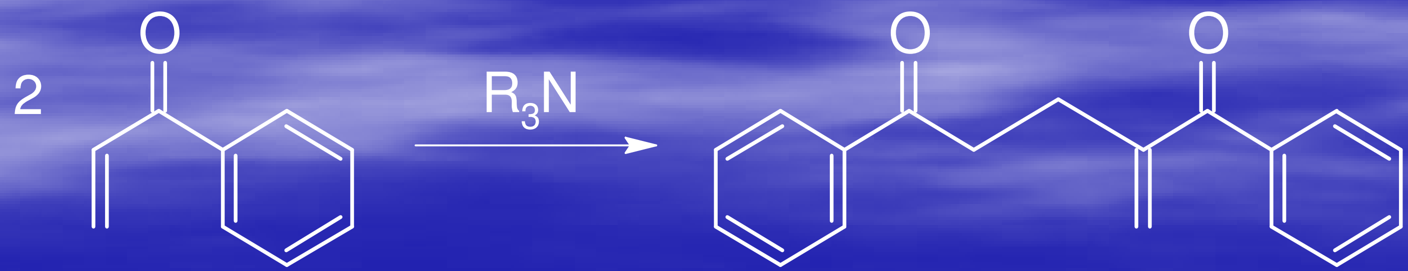
How "Green" is the Baylis-Hillman Reaction?

- Mild reaction conditions
- Very little waste formed
- Atom efficient
- No need for solvent
- No aqueous quench
- Easily recovered catalysts
- Reagents and products low in toxicity

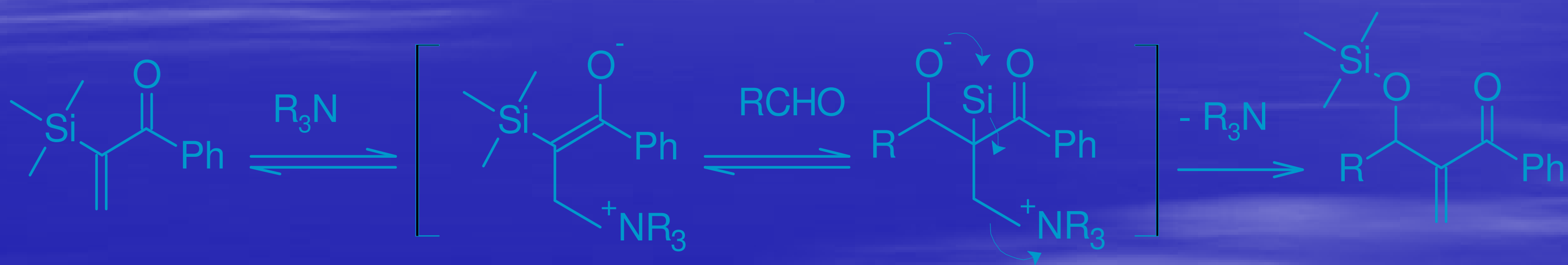
Limitations of the Baylis-Hillman Reaction

- Limited number of activated olefins suitable for the reaction due to competitive dimerization.
- Phenyl vinyl ketone (PVK), which dimerizes rapidly under Baylis-Hillman conditions, is essentially unsuitable as a substrate.

PVK Dimer Formation



Silicon-Mediated Baylis-Hillman Reaction



The addition of a silicon group prevents the PVK from forming a dimer.

How Can the Silicon-Mediated Reaction be Improved?

- Assessing substrate preparation

Synthesis of Trimethylsilyl Phenyl Vinyl Ketone

- I will refer to this as TMS-PVK for short

Synthesis of TMS-PVK

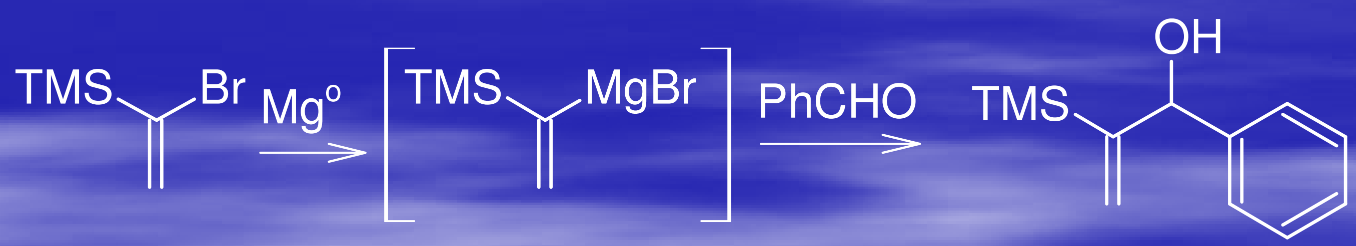
- Pyridinium chlorochromate (PCC) is used to make Trimethylsilyl Phenyl Vinyl Ketone
  - PCC is a known carcinogen
  - Chromium waste products are formed

Goal of Research

- To find a “greener” route for the synthesis of TMS-PVK

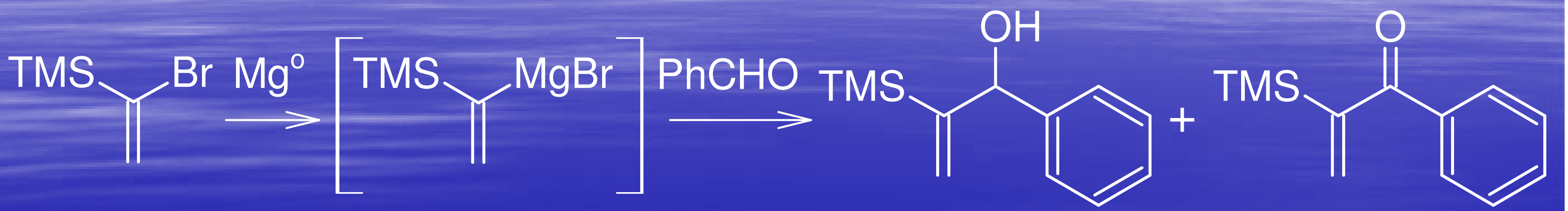
Getting Started

- Our original plan was to create the alcohol precursor and attempt greener oxidation conditions



Synthesis of Alcohol Precursor

Surprising Result



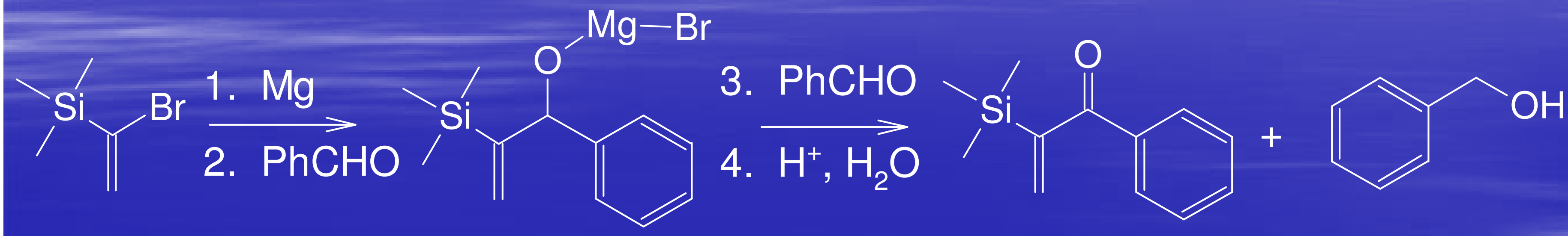
- Grignard addition followed by workup and isolation afforded the alcohol precursor
- ^{1}H NMR indicated that a small amount of TMS-PVK was also present in the crude reaction mixture

How Did This Happen?

- A search on the oxidation of magnesium alkoxide salts indicated the possible occurrence of a Magnesium-Oppenauer Oxidation
- We proposed that the oxidation was working in tandem with the Grignard Addition reaction

Byrne, B.; Karras, M. *Tetrahedron* **1987,** *28,* 769-772.

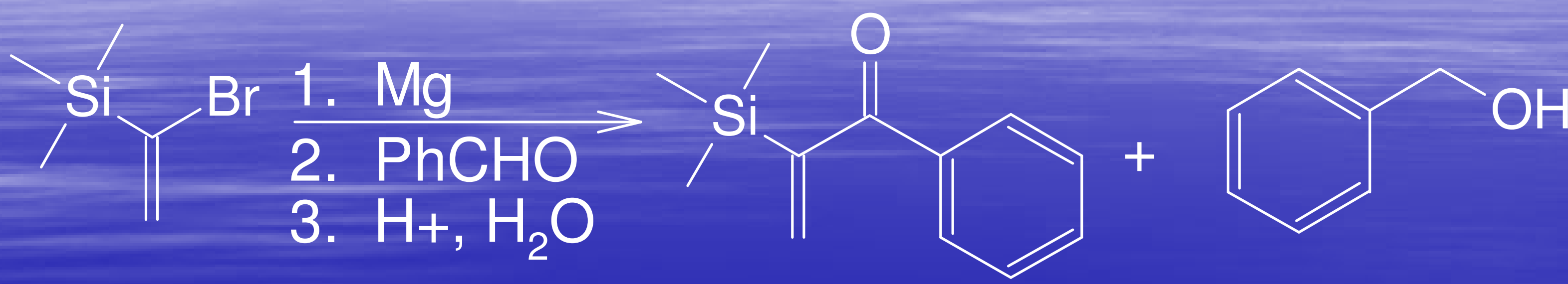
Proposed Tandem Grignard-Oppenauer Oxidation



The 1st equivalent of benzaldhyde is for the Grignard Addition

The 2nd equivalent of benzaldehyde is for the Oppenauer Oxidation

Results



- 80% yield of TMS-PVK
- 100% yield of benzyl alcohol
- No alcohol precursor observed in ^{1}H NMR spectra
- Results demonstrate successful Grignard addition and complete oxidation

Success

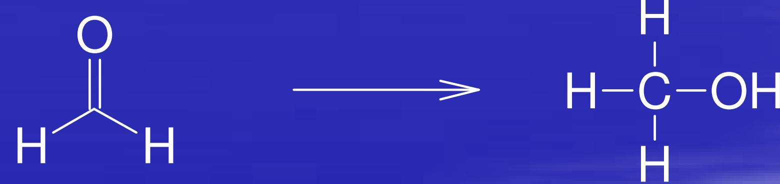
- Magnesium-Oppenauer oxidation is greener than previous synthetic route of TMS-PVK
  - Reduces synthesis by one step and utilizes oxidizing potential of the magnesium alkoxide salt
  - Eliminates the use of PCC
- Can more improvements can be made?

Improvements on the Reaction

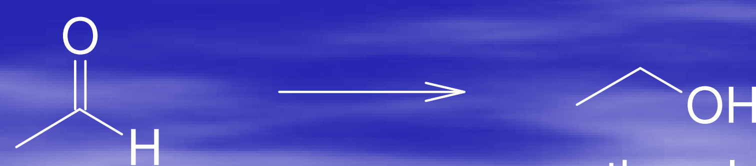
- Replacement of oxidizing equivalent of benzaldehyde with smaller ketones or aldehydes would improve atom economy.
- Additionally, use of small ketones or aldehydes would eliminate the need for column chromatography to separate the TMS-PVK from excess benzaldehyde and benzyl alcohol.

Oxidizing Agents and Their Waste Products

benzaldehyde → benzyl alcohol



formaldehyde → methanol

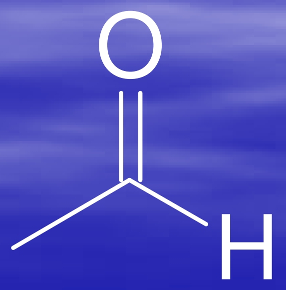


acetaldehyde → ethanol

acetone → isopropanol

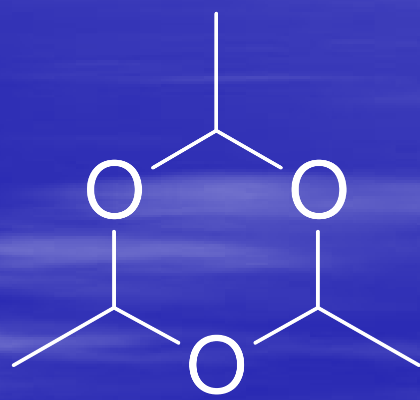
Reagents Utilized

- Grignard-Oppenauer protocol repeated using acetaldehyde as oxidizing agent
- Acetaldehyde proved too volatile to use
- Evaporated immediately when added to the refluxing reaction mixture
  - Boiling point = 21 °C



Reagents Utilized

- Grignard-Oppenauer protocol repeated using paraldehyde as oxidizing agent
  - Trimer of acetaldehyde
  - Boiling point = 124℃



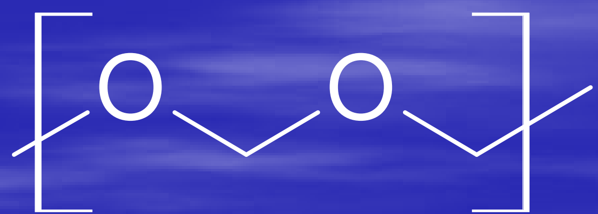
- No TMS-PVK observed in ^{1}H NMR spectrum of crude product

Reagents Utilized

- Also tried using trimer as the both the solvent and oxidizing agent
  - eliminated use of THF as solvent
- No TMS-PVK observed in ^{1}H NMR spectrum of crude product

Continuing Research

- Paraformaldehyde (polymer of formaldehyde) is being explored as the oxidizing agent in the Grignard-Oppenauer protocol



  – Formaldehdye is a gas at room temperature
  – Also comes in aqueous solution, but reaction conditions must be dry

Paraformaldehyde

- Preliminary results indicate that TMS-PVK was synthesized, but some alcohol precursor still remained (~2:1 ratio)
- Needs to be explored further

Acknowledgements

- Thanks to:
  - Marian College Department of Natural and Behavioral Sciences
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  - Dr. Carl Lecher

Questions?