

# The Tandem Grignard Addition-Oppenauer Oxidation

A Greener Synthesis of  
 $\alpha$ -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.

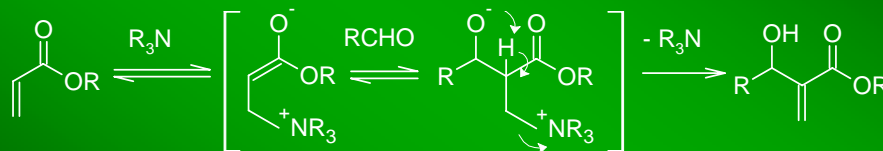
## Green Chemistry is:

- 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

## Baylis-Hillman Reaction



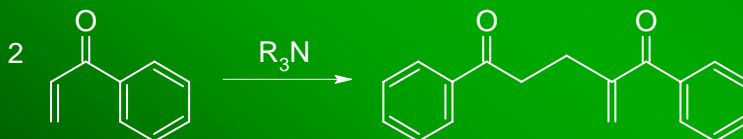
## How “Green” is the Baylis-Hillman Reaction?

- 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

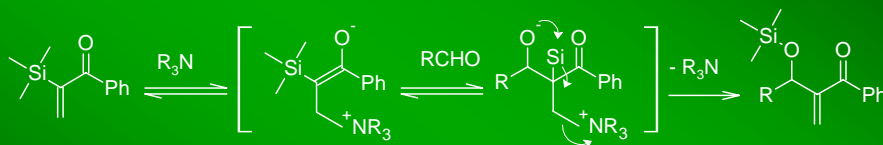
## Limitations of the Baylis-Hillman Reaction

- 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



## How Can the Silicon-Mediated Reaction be Improved?

- Assessing substrate preparation



Synthesis of Trimethylsilyl Phenyl Vinyl Ketone

## 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

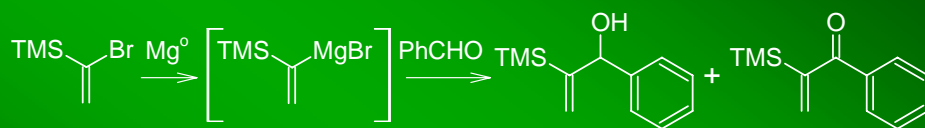
## Getting Started

- In order to try alternative oxidation reactions, the alcohol precursor to TMS-PVK must be synthesized



Synthesis of Alcohol Precursor

## Surprising Result



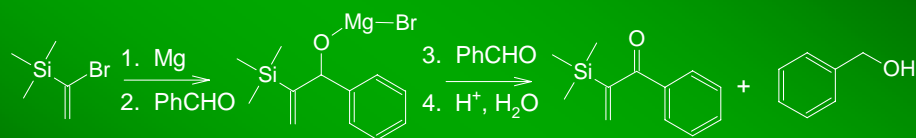
- Grignard addition followed by workup and isolation afforded the alcohol precursor of TMS-PVK
- But, a small amount of our target TMS-PVK was already observed in the  $^1\text{H}$  NMR spectrum

## How Did This Happen?

- A literature search revealed the possible occurrence of a Magnesium-Oppenauer Oxidation
  - Oxidation of a magnesium alkoxide salt to a ketone
- Oxidation was working in tandem with the Grignard reaction

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

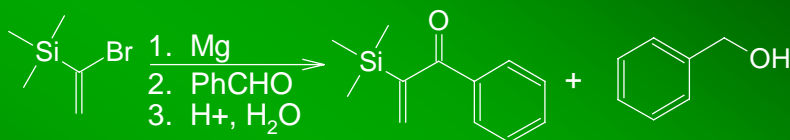
## Proposed Tandem Grignard-Oppenauer Oxidation



## Testing the Tandem Grignard-Oppenauer Oxidation

- 3 equivalents of benzaldehyde were added to the Grignard reaction
  - 1st equivalent was electrophile for Grignard
  - 2nd equivalent was oxidizing agent for the Oppenauer Oxidation
  - Excess used to ensure that the reaction went to completion

## Results



- 80% yield of TMS-PVK
- 100% yield of benzyl alcohol
- No alcohol precursor observed in <sup>1</sup>H NMR spectra
- Results demonstrate successful Grignard addition and complete oxidation

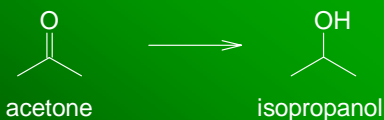
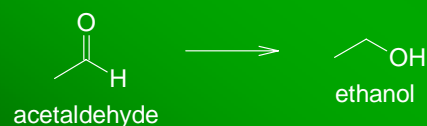
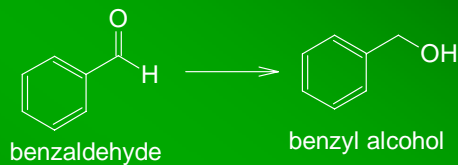
## Success?

- Magnesium-Oppenauer oxidation 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
- BUT more improvements can be made

## Improvements on the Reaction

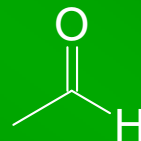
- Replacement of benzaldehyde with smaller ketones or aldehydes would improve atom economy.
- Additionally, use of small ketones or aldehydes would eliminate the need for column chromatography to separate the TMS-PVK from excess benzaldehyde.

## Potential Oxidizing Agents



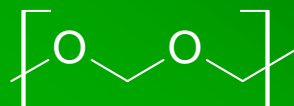
## Continuing Research

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



## Continuing Research

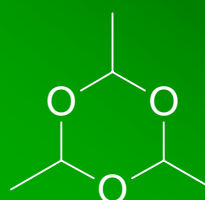
- Paraformaldehyde (polymer of formaldehyde) is being explored as the oxidizing agent in the Grignard-Oppenauer protocol



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

## Other Reagents to be Utilized

- Trimer of acetaldehyde
  - Boiling point = 124°C



## Acknowledgements

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

Questions?