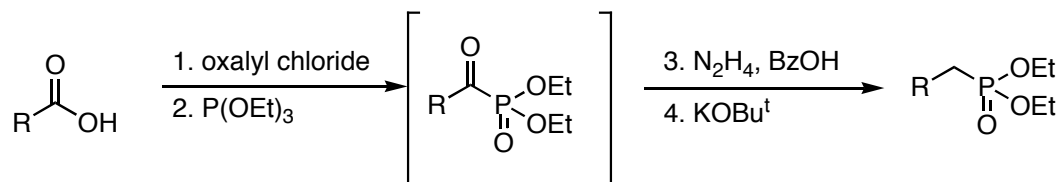


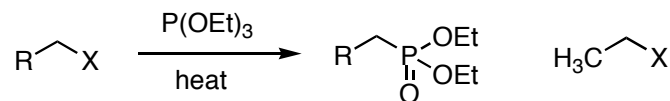
# Room-Temperature Alternative to the Arbuzov Reaction: The Reductive Deoxygenation of Acyl Phosphonates



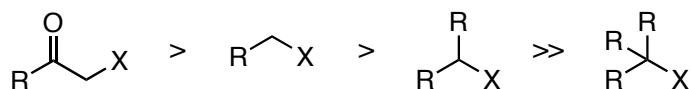
Kedrowski, S. M. A.; Dougherty, D. A.  
*Org. Lett.* **2010** ASAP

John Maciejewski  
*Wipf Group - Current Literature*  
4 September 2010

# Michaelis-Arbuzov Reaction



- Trialkylphosphite displaces alkyl halide to form phosphonate ester
- Discovered by Michaelis in 1898, but the scope and limitations explored by Arbuzov
- Ethyl halide produced considered a reactive byproduct; can undergo undesired side reactions

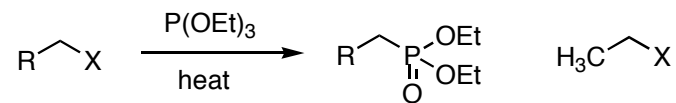


Reactivity of alkyl halides toward phosphites decreases with branching

Kurti, Laszlo, and Barbara Czako. Strategic Applications of Named Reactions in Organic Synthesis. Boston: Elsevier, 2005.

*Chem. Rev.* **1981**, *81*, 415-430.

# Michaelis-Arbuzov Reaction



Limitations include:

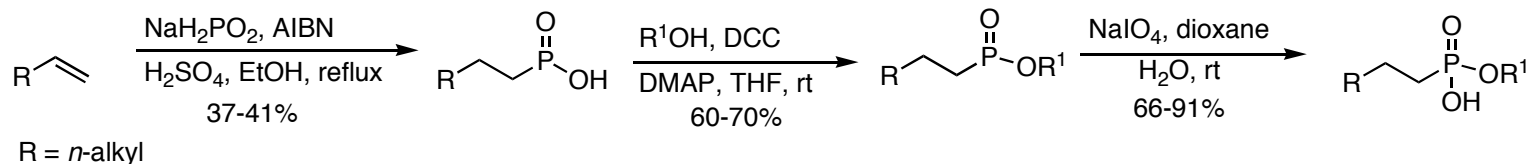
- high temperatures may not be tolerated by sensitive substrates
- phosphonate esters are usually purified by fractional distillation (multiple products)
- phosphite reagent is often used as the solvent

Kurti, Laszlo, and Barbara Czako. Strategic Applications of Named Reactions in Organic Synthesis. Boston: Elsevier, 2005.

*Chem. Rev.* **1981**, *81*, 415-430.

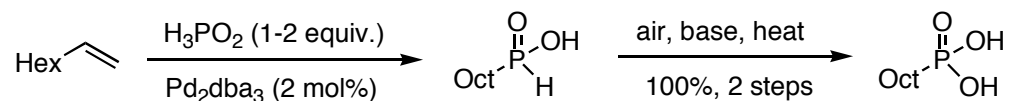
# Preparation of Alkyl phosphonates

3 step protocol to generate alkyl phosphonates



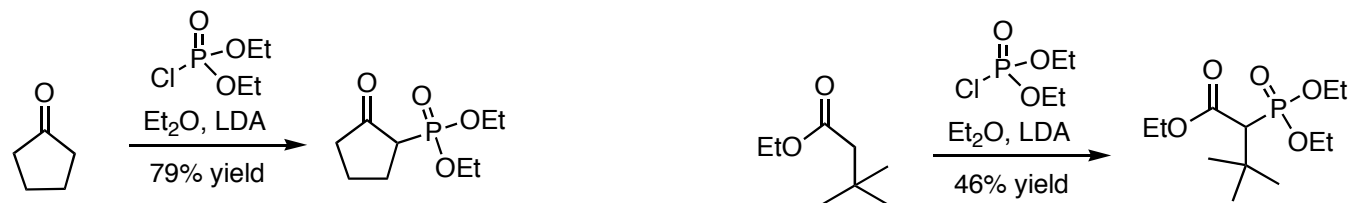
*Bioorg. Med. Chem. Lett.* **1996**, 6, 1951-1954.

Tandem hydrophosphinylation/oxidation to produce phosphonic acid



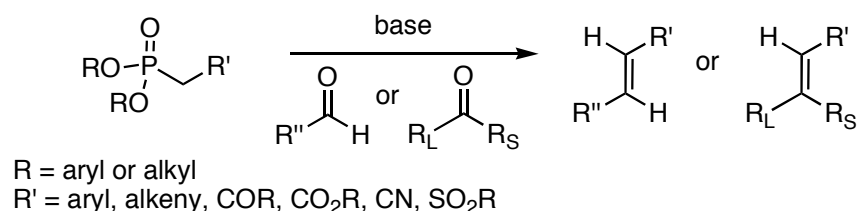
*Tetrahedron Lett.* **2007**, 48, 5755-5759.

Enolate trap with phosphonyl chloride provides alkyl phosphonate



*J. Org. Chem.* **1996**, 56, 5556-5560.

# Horner-Wadsworth-Emmons (HWE) Reaction



Developed to improve the Wittig olefination by:

- allows further functionalization of  $\alpha$ -carbon to phosphonate
- water soluble phosphate anions are easier to remove than phosphine oxides

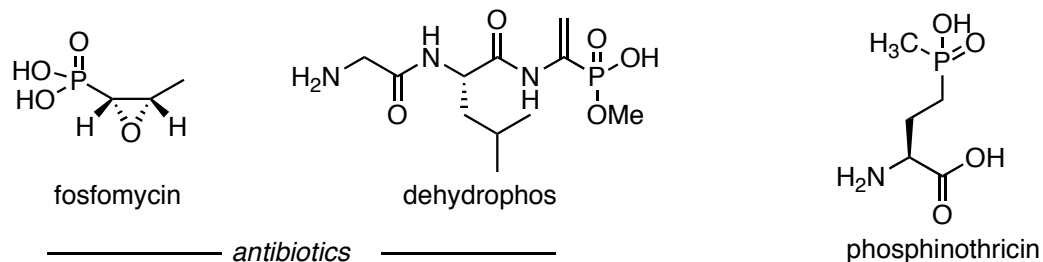
HWE produces *E*-alkene as major isomer

Still-Gennari modification produces *Z*-alkene as major

- R = CH<sub>2</sub>CF<sub>3</sub>
- R''/R<sub>L</sub> lies *anti* to phosphonate in transition state

Kurti, Laszlo, and Barbara Czako. Strategic Applications of Named Reactions in Organic Synthesis. Boston: Elsevier, 2005. *Chem. Rev.* **1974**, 74, 87.

# Therapeutics and Agrochemicals



Small molecules with C-P bonds find applications in both pharmaceutical and agrochemical industries

Fosfomycin:

- activity against methicillin- and vancomycin-resistant *Staphylococcus aureus*
- deactivates essential enzyme (MurA) which is essential in the first step of cell wall biosynthesis

Dehydrophos:

- isolated by Eli Lilly; shown to have broad antibiotic activity
- structure confirmed by synthesis
- mode of action of enamine not fully understood
- hydrolysis of C-terminus of peptide may produce methyl acetophosphonate, a pyruvate mimic

Phosphinothricin:

- widely used herbicide

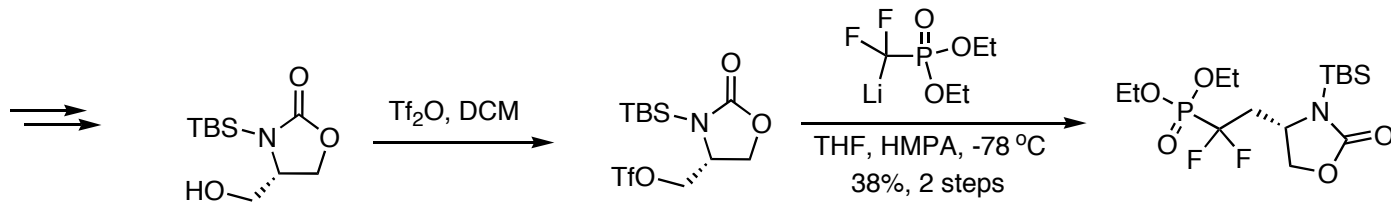
*Annu. Rev. Biochem.* **2009**, 78, 65-94.

*Annu. Rev. Biochem.* **2007**, 61, 379-400.

# Therapeutics

## Phosphoserine mimic

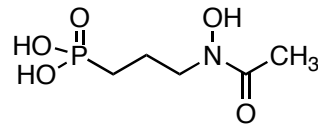
- used to study kinase signal transduction
- C-P bonds are not hydrolyzed under physiological conditions



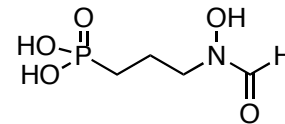
*Chem. Biol.* **2009**, *16*, 928

## Anti-malaria activity

- small molecules containing phosphonic acid moiety show promising antimalarial activity



FR-900098

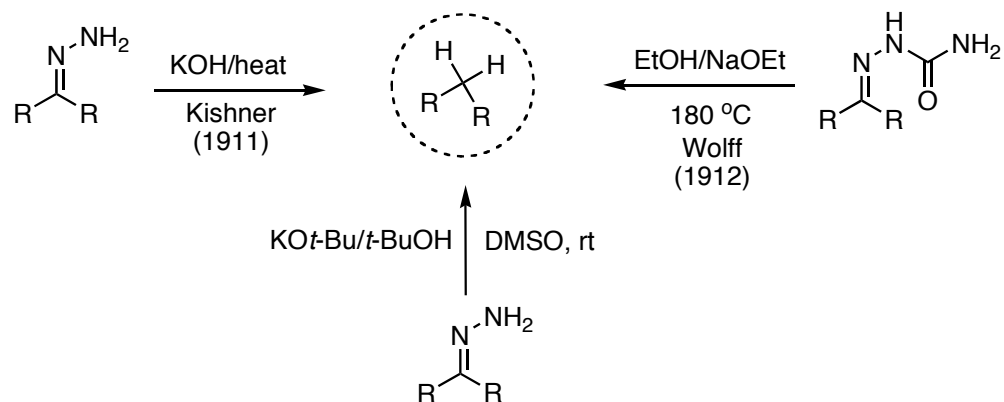


fosmidomycin

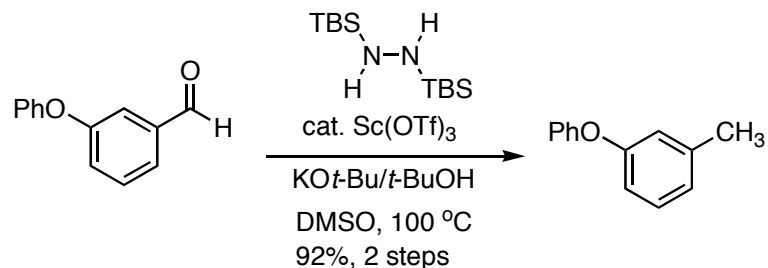
*Annu. Rev. Biochem.* **2009**, *78*, 65-94.

*Annu. Rev. Biochem.* **2007**, *61*, 379-400.

# Wolff-Kishner Reduction



Standard conditions for Wolff-Kishner reduction are harsh  
 Cram modification proceeds at rt; yields are variable on small scale

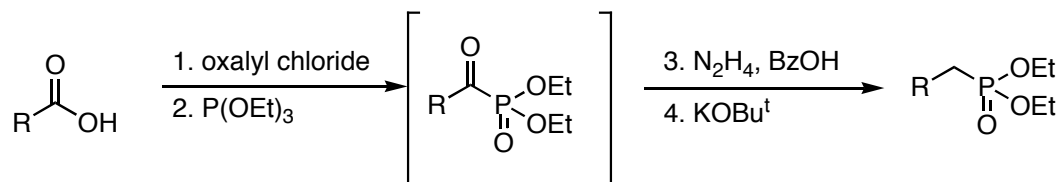


Recent example of Lewis acid catalyzed hydrazone formation proceeds in good yield

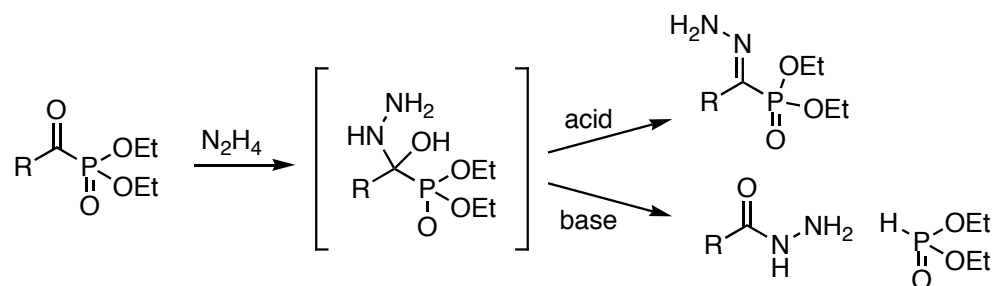
Kurti, Laszlo, and Barbara Czako. Strategic Applications of Named Reactions in Organic Synthesis. Boston: Elsevier, 2005.  
*J. Am. Chem. Soc.* **2004**, *126*, 5436-5445.



# Title Paper: Preparation of Acyl Phosphates

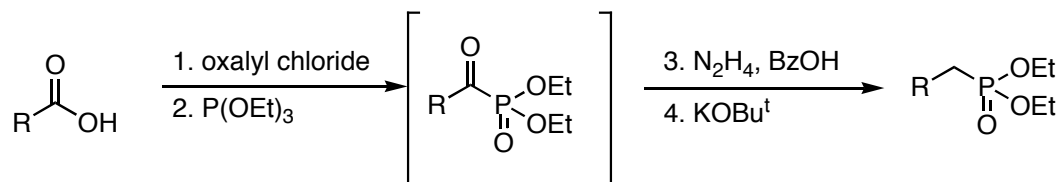


- Phosphine addition to acyl halide occurs under mild conditions over the traditional alkyl halide displacement
- Hydrazones of acyl phosphonates can be isolated

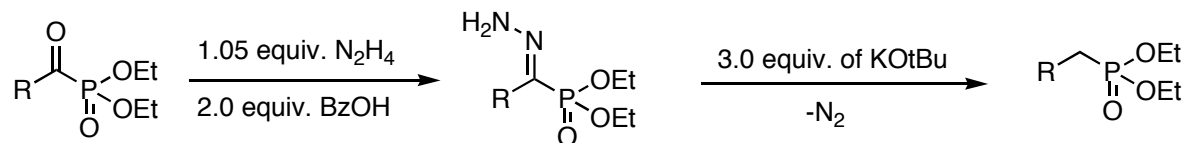


- pH neutral and basic pH leads to decomposition to hydrazide and phosphite
- “Moderately acidic” conditions worked the best, where low pH promoted no reaction

# Title Paper: Deoxygenation of Acyl Phosphates

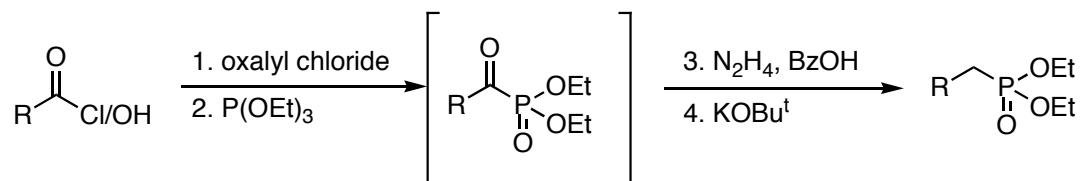


Hydrazones of acyl phosphonates can be deoxygenated *via* a Wolff-Kishner pathway



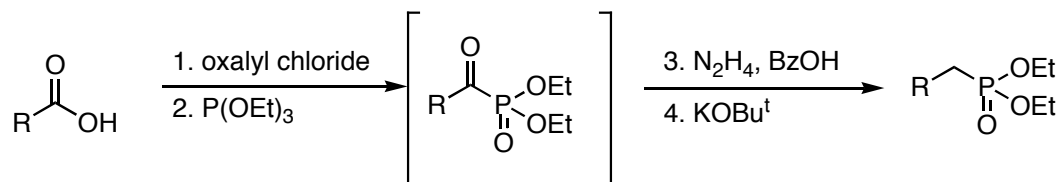
After hydrazone formation, all residual water was removed through lyophilization before adding base  
Stabilized carbanion  $\alpha$  to phosphonate facilitates reaction under mild conditions

# Title Paper: Substrate Scope



entry	starting material	product	yield (%) (over 3 or 4 step sequence)
1			58
2			35
3			< 5
4			21
5			< 5
6			65

# Conclusions



Uses two classical reactions to formulate a new methodology

Mild conditions offer attractive method to prepare alkyl phosphonates over classical methods

Methodology should be applied to sensitive molecules to demonstrate synthetic utility