Synthesis In Brief - Feynman Liang
CHEM231 - Spring 2012
Amherst College

I Designing Syntheses

Consider the target's:

- Molecular size/density
- Number of stereocenters
- Elements present
- Functional groups present
- Chemical reactivity

Synthesis Considerations

- Must be selective to be useful (protecting groups, solvent choice)
- Other functional groups on the molecule
- Be aware of limitations of proposed transformations

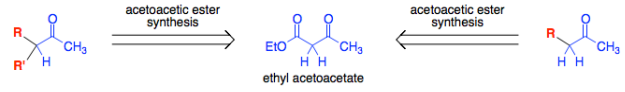
Retrosynthesis

Basically disconnect groups one by one and work backwards from target to start.

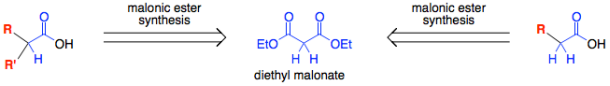
II Common retrosynthetic patterns

Carbonyl patterns

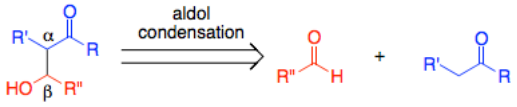
- Methyl ketones with alkyl groups attached to α-carbon



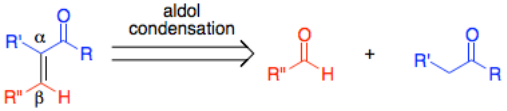
- Carboxylic acid with alkyl groups attached to α-carbon



- β-hydroxy carbonyl

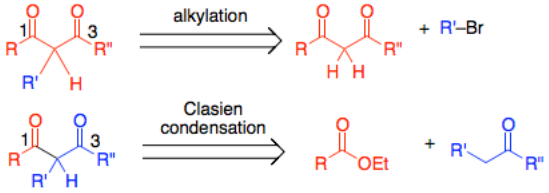


- α,β-unsaturated aldehyde/ketone: E1cb (removal of α-proton followed by elimination of β-hydroxy with - charge)

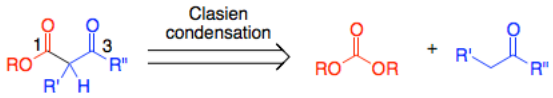


Dicarbonyl patterns

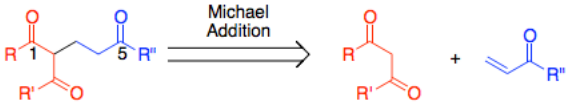
- 1,3-dicarbonyl



- 1,3-β-ketoester

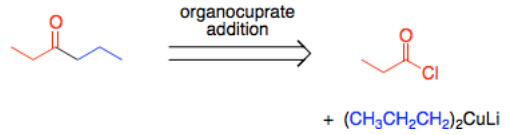


- 1,5-dicarbonyl



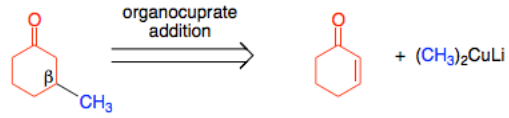
Enolate patterns

- Non-methyl ketone

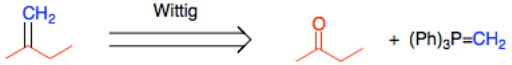


- Non-methyl ketone (branching at α)

- Non-methyl ketone (branching at β)

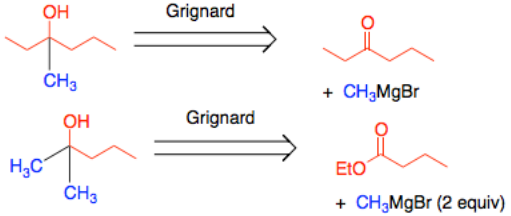


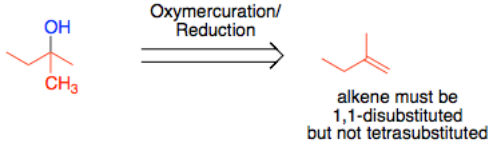
Unconjugated alkenes



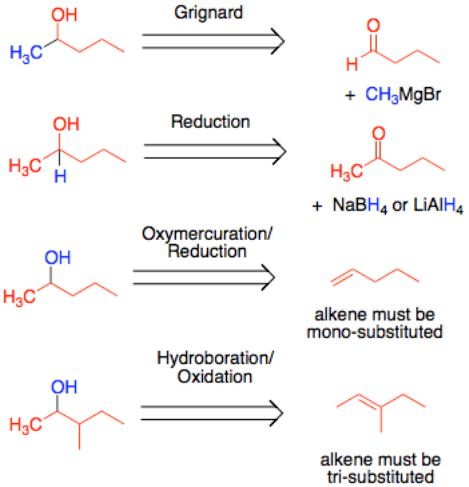
Alcohol patterns

- Tertiary alcohol

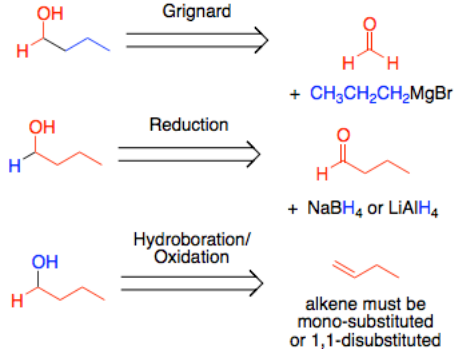




- Secondary alcohol

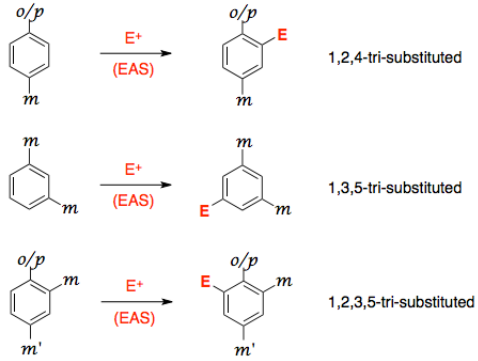


- Primary alcohol



EAS

- Must proceed through **privileged systems**:



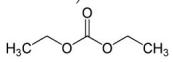
- **EAS Rules:**
  - Can stop each EAS after one reaction
  - Only o/p di-substituted isomers can be seperates (no tri/tetra separation)
  - Proceed only through **privileged systems**: substituents symmetric or all direct to same positions
  - No Friedel Crafts alkyl/acylation (alkyl and acyl halide rxn through carbocation/acylium intermediate) if R-NO_2 present (too deactivating)
  - No Friedel Crafts alkylation (alkyl halide rxn through carbocation) if carbocation rearrangements are possible
- Strategies:
  - **Sulfonation/sulfonation is reversible**, can block 5 position of 1,2,3-trisub
  - NO_2 directs m, reduction (and Sandmeyer) converts to o/p director NH_2 (or from Sandmeyer: OH, Cl, Br, I)
  - Alkyl directs o/p, converted to acyl via **$KMnO_4$ oxidation**
  - Acyl directs m, can be converted to corresponding alkyl via **Clemmenson reduction**

III Ground Rules for Synthesis

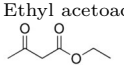
- Any inorganic starting materials
- Any organometallic reagent (RMgX or R_2CuLi) where R=
  a) Allyl group
  b) Phenyl ring
  c) Saturated alkyl chain with $\leq$4 carbons
- Organic reagents:
  a) Any saturated alcohol, aldehyde, ketone, carboxylic acid, alkyl halide with $\leq$4 carbons
  b) Any ylide with $\leq$4 carbons (phenyls in PPh_3 don't count)
  c) Any ester which acid component contains $\leq$4 carbons (don't count ester's carbons)
- ONLY ONE functional group per molecule. ex. no Michael acceptors b/c contains both alkene and carbonyl, no vinyl halides (allyl permitted)

Allowed reagents:

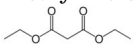
- **Diethyl carbonate** - starting ester (to make diesters from ketones)



- Ethyl acetoacetate - acetoacetic ester synthesis

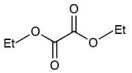


- **Diethyl malonate** - malonic ester synthesis

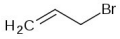


- 1,2-ethanediol - carbonyl protecting group

- **Diethyl oxalate** - only 1,2-dicarbonyl, not too sure...



- **Allyl bromide** - substitution/alkene

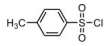


- **Benzyl bromide** - substitution

- **Cyclohexanone** - ketone, 6-ring

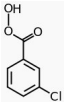
- **Cycloopentanone** - ketone, 5-ring

- **Tosyl Chloride** - TsCl, alcohols → R-OTs



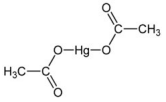
- **Pyridine** - weak base/proton sink

- **mCPBA** - epoxidation rxn agent

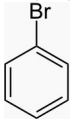


- **Dimethyl sulfide** - ozonolysis reducing agent

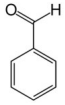
- **Mercuric acetate** - oxymercuration rxn agent



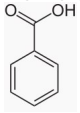
- **Bromobenzene** - EAS



- **Benzaldehyde** - EAS



- **Benzoic acid** - EAS



- **Benzene** - EAS

- **Toluene** - EAS