

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

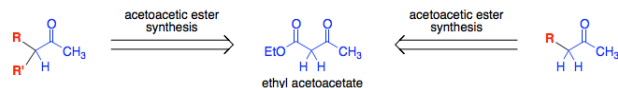
Retrosynthesis

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

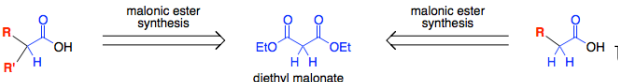
II Common reaction patterns

Carbonyl patterns

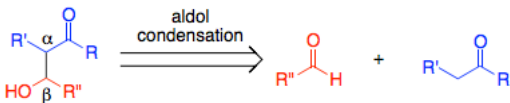
- Methyl ketones with alkyl groups attached to α -carbon



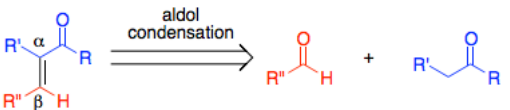
- Carboxylic acid with alkyl groups attached to α -carbon



- β -hydroxy carbonyl

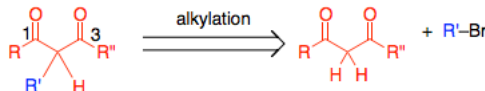


- α, β -unsaturated aldehyde/ketone: E1cb (removal of α -proton followed by elimination of β -hydroxy with - charge)

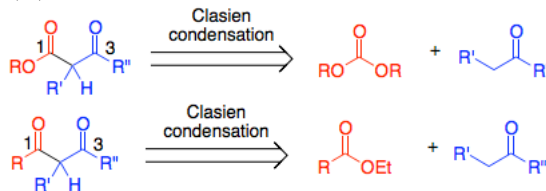


Dicarbonyl patterns

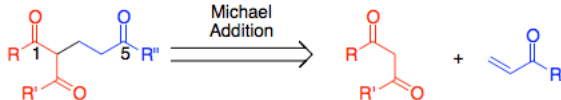
- 1,3-dicarbonyl



- 1,3- β -ketoester

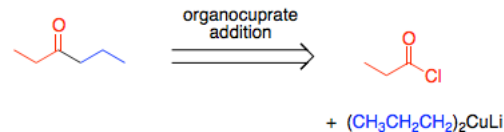


- 1,5-dicarbonyl

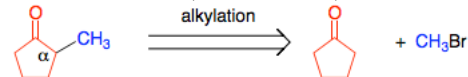


Enolate patterns

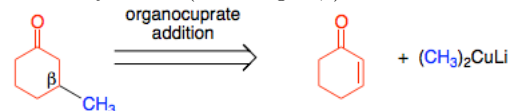
- Non-methyl ketone



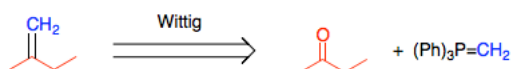
- Non-methyl ketone (branching at α)



- Non-methyl ketone (branching at β)

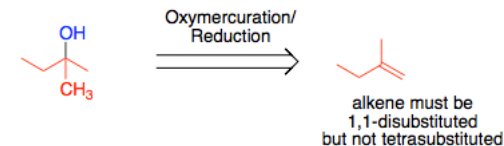
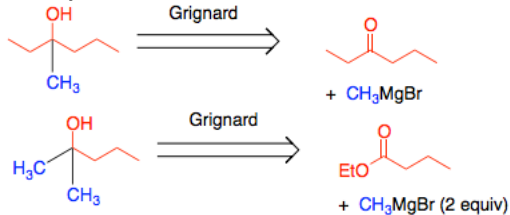


Unconjugated alkenes

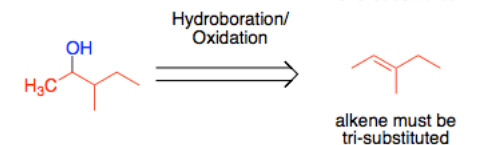
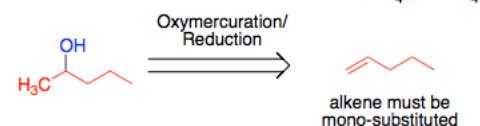
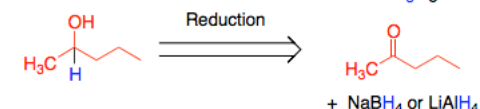
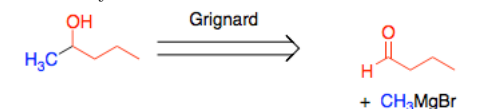


Alcohol patterns

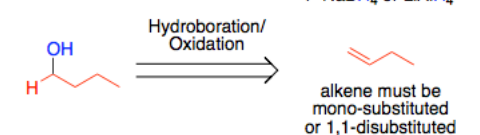
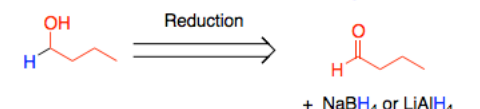
- Tertiary alcohol



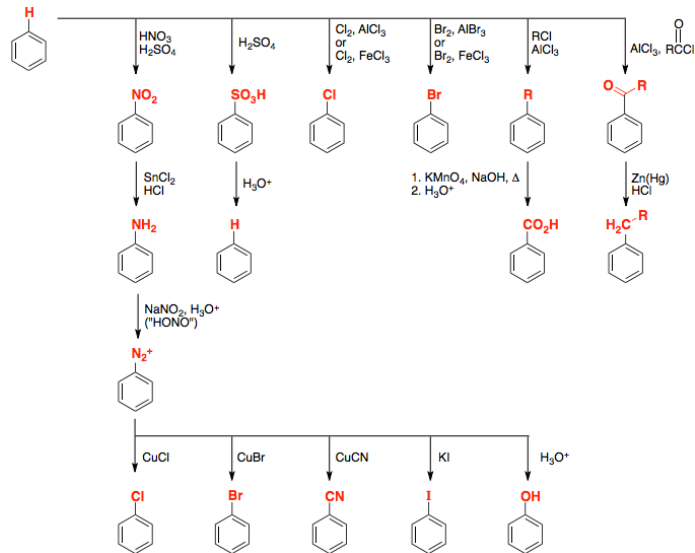
- Secondary alcohol



- Primary alcohol

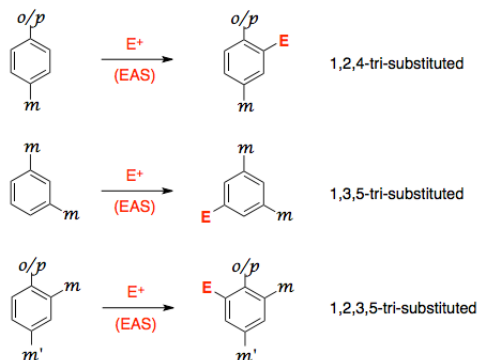


EAS



EAS Rules:

- Can stop each EAS after one reaction
- Only o/p di-substituted isomers can be separated (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/acylum intermediate) if R-NO₂ present (too deactivating)
- No Friedel Crafts alkylation (alkyl halide rxn through carbocation) if carbocation rearrangements are possible
- EAS privileged systems (use for retro and fw):



Strategies:

- Sulfonation/sulfonation is reversible**, can block 5 position of 1,2,3-trisub
- NO₂ directs m, reduction (and Sandmeyer) converts to o/p director NH₂ (or from Sandmeyer: OH, Cl, Br, I)
- Alkyl directs o/p, converted to acyl via **KMnO₄ 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 R₂CuLi) where R=
 - Allyl group
 - Phenyl ring
 - Saturated alkyl chain with ≤4 carbons
- Organic reagents:
 - Any saturated alcohol, aldehyde, ketone, carboxylic acid, alkyl halide with ≤4 carbons
 - Any ylide with ≤4 carbons (phenyls in PPh₃ don't count)
 - Any ester which acid component contains ≤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
- Allowed reagents:

Ethyl acetoacetate Diethyl malonate 1,2-ethanediol Diethyl carbonate Diethyl oxalate Bromobenzene Benzaldehyde Benzoic acid Allyl bromide Benzyl bromide Cyclohexanone Cyclopentanone Tosyl Chloride Pyridine mCPBA Dimethyl sulfide Mercuric acetate Benzene Toluene	Acetoacetic ester synthesis Malonic ester synthesis Carbonyl protecting group Diol protecting group 1,2-dicarboxylic ester, used for polymer Ph-Br, aromatic substitution target Ph-COH, aromatic aldehyde Ph-COOH, aromatic carboxylic acid C=C-C-Br, starting alkene Ph-CH ₂ -Br, starting aromatic Hexane=O, ketone Pentane=O, ketone Convert alcohols → R-OTs → R-X Weak base/proton sink Epoxidation Reducing agent for ozonolysis Oxymercuration Starting EAS Starting EAS
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