

Basic things to know about phenols*

1. Nomenclature – p-chlorophenol, p-cresol
2. Phenols are acidic ($pK_a=10$)
 1. HOAc=5 EtOH 15
 2. p-nitrophenol = 7
3. Synthesis – diazotization, then Cu_2O , Cu^{+2} , H_2O
4. Strong o,p-directing group
5. Makes ethers and esters just like an alcohol
 1. But no reaction that cleaves the C-O bond

*in lieu of including Chapter 21

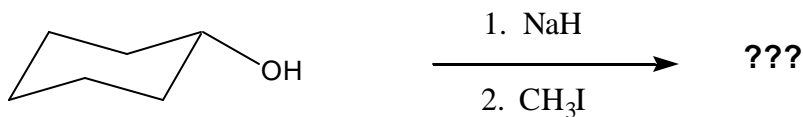
Overview & Review

Two things important in organic chemistry

1. Structure and physical properties of a compound
2. Chemical transformations

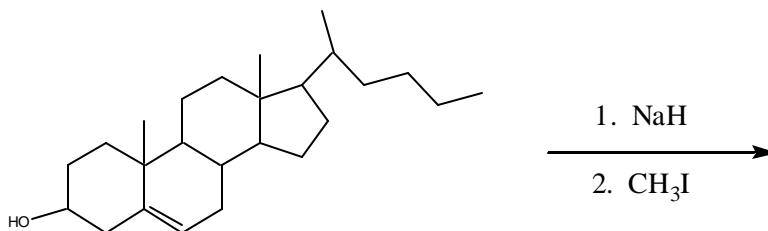
Structure and Physical Properties

- Geometry of any functional group
- Solubility and boiling point trends
- Basic principles of mass spec
 - M, M+1, M+2
- IR – the six major regions discussed
- NMR
 - numbers of signals (equivalent H or C's)
 - Trends in chem shift
 - Splitting (coupling) in ^1H NMR
- UV/Visible – reflects conjugated systems
- Aromaticity – $4n+2$ rule



1. What is the starting material? What functional group(s)?
2. What kind of reagent is used in first step?
3. Product of first step??
4. Any special circumstances (stereochemistry, regioselectivity, isomers, catalyst, competing reactions) in first step
5. What kind of reagent for second step?
6. Repeat questions 3 and 4 for second step

Give the product



Types of reagents

- Acid
- Base
- Nucleophile
- Electrophile
- Oxidizing Agent
- Reducing Agent
- Free radicals
- Dehydrating agents
- Concerted reactions

Acids (illustrative, *not* comprehensive)

- Acids without nucleophiles
 - Sulfuric and sulfonic acids
- Acids with weak nucleophiles
 - HCl
 - HCN
 - H₂O
- Lewis Acids
 - AlCl₃, BF₃, FeCl₃

Bases

- Weak
 - Amines
 - Bicarbonate
 - Acetate and other acid salts
- Standard bases
 - OH, OR
- Strong bases
 - NaH, NaNH₂, LDA
 - Organometals (BuLi, RMgX)

Oxidizing Agents

- Oxygen – everything burns
- Ozone – cleaves double bonds
- Permanganate
 - Alcohols to acids or ketones
 - Aromatic side chains to acid
 - Alkenes to diols (mild) (also OsO_4) or cleave to two acids
- Chromate
 - Alcohols to acids or ketones
 - PCC = primary alcohol
- Hydrogen Peroxide
 - Used to finish oxymercuration, hydroboration, selenium reaction
- Organic peroxides
 - Free radical initiator (eg, anti Mark addition of HBr)
- Peroxyacids
 - Epoxides

Reducing Agents

- Hydrogen
 - Alkenes and alkynes
 - Nitro groups
 - Reductive amination
- Hydride reduction
 - LAH strongest, NaBH_4 more selective
 - $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ or DIBALH: acid chlorides to aldehydes
 - NaBH_3CN for reductive amination
- Metals
 - Sodium in ammonia or amines – alkynes to trans alkenes
 - Zn amalgam + Cl = Clemmenson reduction
 - Fe + HCl - nitro groups

Functional groups

Alkanes – free radical halogenation

Alkenes

- electrophiles to double bond
 - Markovnikov, stereochemistry?
- radical additions
- concerted – Diels-Alder, oxidation, hydrogenation
- allylic reactions
- Conjugated dienes -1,2 vs 1,4 addition. Diels-Alder

Alkynes

- Acidity of terminal alkynes and reactions
- Hydrogenation – may be selective
- Same electrophilic additions
 - Addition product from water (or BH_3) tautomerizes to $\text{C}=\text{O}$

Alcohols

- Oxidation
- Acidity
- As nucleophile
 - Formation of esters and ethers
- As leaving group
 - Dehydration
 - Conversion to alkyl halide

Aldehydes and Ketones

- Oxidation of aldehydes
- Reduction
- Addition of nucleophiles to form adducts
 - Grignard, acetals, cyanohydrins
- Addition of nucleophile followed by loss of O.
 - Imines and enamines, Wittig reaction
- Reactions at the alpha carbon (via enolates or enols)
 - Aldol and related condensations
 - Alkylations
 - Special case of β -dicarbonyls
- α,β -unsaturated C=O can have 1,2 or 1,4 addition

• Acids (Carboxylic)

- Acidity
- Reduction
- Replacement of OH (chlorides, esters, amides)
- Decarboxylation of β -carbonyl acids

• Acid derivatives

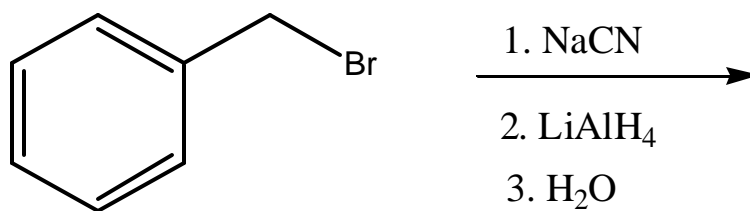
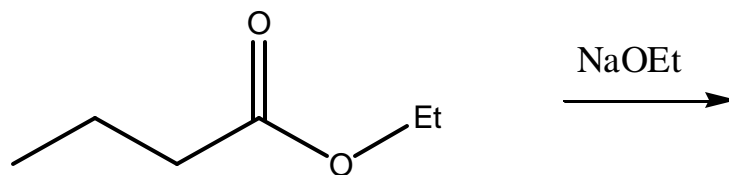
- Reductions
- Nucleophilic addition-elimination
 - interconversion to other acid derivatives
- Addition of carbon nucleophiles – Grignard, Claisen condensation
- Reactions at α -carbon – Claisen

Amines

- Basicity
- Activation of aromatic rings
- Nucleophile
 - Alkylation, acylation
 - Addition to carbonyls followed by dehydration
- Diazotization with nitrous acid

Aromatic Compounds

- Stability and $4n+2$ rule
- Electrophilic substitutions
- E-donating groups = activating and o,p-directing
- E-withdrawing groups = deactivating and m-
- Benzylic position activated
 - Oxidation
 - Radical substitution
 - Conjugation of C=C favored
- Diazotization



Name reactions

1. Grignard
2. Diels-Alder
3. Wittig
4. Friedel Crafts
5. Aldol
6. Claisen
7. Acetoacetic ester and malonic ester reactions
8. Diazotization (and Sandmeyer)
9. More specialized
 1. Michael addition (1,4-addition)
 2. Mannich reaction
 3. Enamine reaction (Stork)
 4. Robinson annelation
 5. Hofmann and Curtius rearrangements

Syntheses

- Know simple conversions
 - alcohol to alkyl halide
 - alcohol to aldehyde or ketone
- Use retrosynthesis principles
- Focus on change in number in carbon skeleton if applicable
- Consider any special requirements
 - Regioselectivity
 - Directing effects, e.g., on aromatic ring
 - stereochemistry

To lengthen carbon chains

- Grignards
 - 1 C – CO₂ or H₂CO
 - 2 C – epoxide
 - Any alcohol – versatile
- Terminal alkynes
- Friedel Crafts
- Wittig Reaction
- Alkylation at α -carbons of carbonyls
 - Direct
 - Aldol and similar condensations
 - β -dicarbonyl
 - Enamines
- Cyanide ion – 1 C

How to make cyclic compounds

- Diels-Alder – always 6, at least 1 C=C
- Intramolecular condensations
- Robinson annelation – always 6, with $\alpha\beta$ -unsaturated ketone
- Heterocyclics – lactones, lactams, hemiacetals, acetals, acid anhydrides, imides
- Three membered rings – epoxidation, carbenes

Typical multi-step syntheses

From any alcohol of 4 carbons or less, plus benzene, cyclohexane, acetoacetic ester, and malonic ester, how would you make....

2-hexanol

Pentylamine

Butylbenzene

Butyl butanoate

Cis-1,2-cyclohexanediol

Methyl 2-Cyclohexylethyl ether

m-bromochlorobenzene