Objective 15. Develop synthesis strategies for organic synthesis.
Skills: Draw structure, ID structural features and reactive sites (alpha C, beta C, LG, etc.), ID Nu^- and E^+, use curved arrows to show bonds breaking and forming, show delocalized electrons with resonance structures.
Key ideas: Starting material --> target compound.
Count # of C's – bigger or smaller compound.
ID functional groups in starting material and target compound. How does functional group in starting material react? How is functional group in target compound formed?
What part(s) of the starting material and target compound are the same?
ID bonds that break/form.
Brainstorm possible reactions.
Synthesis:
1 step
2 steps
3 steps

Practice problems solutions:
You've been doing organic synthesis in organic lab this semester.
Organic synthesis strategies include:

- converting one functional group to another,
- moving a functional group from one carbon to an adjacent carbon,
- making a carbon-carbon bond to make a bigger molecule, and
- making a compound with two or more functional groups.

You want to identify the Reaction Type to accomplish your desired synthesis. Structural features help you figure out the reaction type. Identifying the structural feature as a nucleophile or electrophile tells you how the reaction occurs.
Table 1. Synthesis Strategies Summary

Structure Change	Reaction Type	Structural Features	What Happens
Make an acid or base	Proton transfer	Acid and base. See pKa table.	H^+ (only) is transferred from acid to base.
Make a better Leaving Group (LG)	Proton transfer	LG and Acid. See pKa table.	H^+ (only) is transferred from acid to base.
Make a C=C pi bond	Elimination	H bonded to beta C (or carbocation), LG, and $Nu:^-$.	$Nu:^-$ reacts at H, pi bond forms, LG leaves
Add atoms or groups to each atom in a pi bond	Electrophilic Addition	C=C pi bond $Nu:^-$ reacts with E^+.	Atoms or group add to each vinylic C.
	Nucleophilic Addition	C=O bond. $Nu:^-$ reacts at carbonyl C.	Atoms or groups add to carbonyl C and O.
Convert or exchange one functional group for another at one carbon	Nucleophilic Substitution	alpha carbon, LG, and $Nu:^-$.	Leaving group exchanges with another atom or group at alpha C.
	Nucleophilic Acyl Substitution	carbonyl C bonded to a LG, $Nu:^-$.	Leaving group exchanges with another atom or group at carbonyl C.
	Electrophilic Aromatic Substitution (addition/elimination)	aromatic pi bond and strong E^+.	H exchanges with another atom or group at aromatic C. See o, p vs. m directors.
Convert or exchange one functional group for another at one carbon	Oxidation/Reduction	Carbon-oxygen bond, carbon-nitrogen bond, nitrogen-hydrogen bond, nitrogen-oxygen bond	gain or loss of O or H at one C or N.

Structural features:
C=C pi bond (including conjugated diene and aromatic)
C-O, C-X, C-N compounds: alpha carbon, leaving group (HOH, ROH, NH_3, X^-), H bonded to beta carbon, epoxide
C=O compounds: carbonyl carbon, carbonyl oxygen, alpha carbon (C next to carbonyl C), beta carbon

TWO structural features:
β-hydroxy aldehyde/ketone (see enolates)

α,β-unsaturated aldehyde/ketone (see enolates)
β-keto ester (see ester enolates)

Table 2. Nucleophiles and Electrophiles by Atom Type

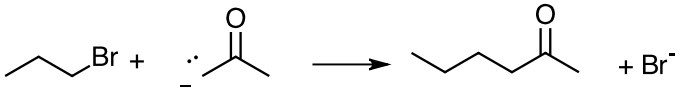
Atom Type	Nucleophile	Electrophile
hydrogen	Acid (H^+, RCOOH, ROH, etc.) See pK_a table.	Hydride (H^-), H bonded to beta carbon
carbon	CN^-, acetylide, Grignard, enolate, ester enolate	Carbocation, carbonyl carbon, alpha carbon on LG
nitrogen	Lone pair N: NH_3, NH_2^-, NRH_2, NRH^-, imine N	NH_4^+, NH_3, ..
oxygen	Lone pair O: H_2O, OH^-, ROH, RO^-, ROR, $RCOO^-$,	H_2O, H_3O^+, ROH, ROH_2^+, $ROHR^+$,
X (Cl, Br, I)	X^-	X_2
Bond	C=C pi bond, C≡C bond pi bond	

Many organic reactions are reversible.
Table 3. Reversible Reaction Types

Forward Reaction	Example:	Reverse Reaction
Acid-Base	ROH + H^+ -- ROH_2^+	Base-Acid
Substitution	ROH + HBr --> RBr	Substitution
Addition	ethylene + HBr --> ethyl bromide	Elimination
Oxidation	1^o ROH --> RCHO or RCOOH	Reduction

Example: ethanol reacts in several ways:
Substitution with HX to form ethyl bromide. (Or substitution with RX to form ether.)
Elimination to form ethylene.
Oxidation to form acetic acid.
This means there are at least three ways to synthesize ethanol (look at reverse reaction).

1. Make a C-C bond. (Make a big molecule from a small molecule.)
See Table 1. What reaction types would you use to make a carbon-carbon bond? Give an example for each type. (Hint: there are at least 4 different reaction types.)
Example: Nucleophilic substitution. RBr + carbon nucleophile.



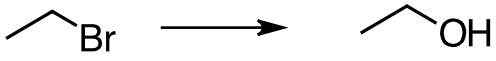
Answers:
1. acetylide ion + RX (nucleophilic substitution)
2. Grignard reaction + RCOR or RCHO (nucleophilic addition)
3. Aldol condensation reaction: aldehyde/ketone + base --> enolate ion -- aldehyde/ketone --> β-hydroxy aldehyde/ketone or α,β-unsaturated aldehyde/ketone
4. Claisen condenstion reaction: ester + base --> ester enolate ion – ester --> β-keto ester

2. Move a functional group, e.g., -OH or pi bond, over one carbon.
See Table 1. What reaction type
a. To move a –OH or –X group over one carbon, you can use an elimination reaction to make a ____ followed by an addition reaction (2 step synthesis). Describe how you would make 2-propyl bromide from 1-propyl bromide.
b. To move a pi bond over one carbon, you can use a _____ reaction reaction followed by a ____ reaction (2 step synthesis). Describe how you would make 2-butene from 1-butene.
c. To move a C=O bond over one carbon, you can convert the C=O to another group first. Then, do a 2 step synthesis from part a or b. Describe how you would make acetone from propanal.
Answers:
a. elimination and then addition reaction
1-propyl bromide --> 2-propyl bromide
1-propyl bromide + $C_2H_5O^-$ --> propene
propene + HBr --> 2-propyl bromide
b. addition and then elimination reaction
1-butene --> 2- butene
1- butene + HBr --> 2-bromobutane
2-bromobutane + $C_2H_5O^-$ --> 2- butene

c. propanal --> acetone
propanal + $NaBH_4$ (reducing agent) —> 1-propanol
1-propanol + H_2SO_4 --> propene
propene + H_2SO_4 --> 2-propanol
2-propanol + $KMnO_4$ (oxidizing agent) --> acetone

3. Here is a method you can use to determine how to synthesize a target compound from a starting material.
   i. Draw the structures of the reactant (starting material) and product (target compound).
   ii. How does the starting material differ from the target compound? At which atom does the reaction occur? Which bond breaks/forms?
   iii. Is the number of carbons in the starting material the same as the number of carbons in the target compound? Does a C-C bond form? If yes, then you'll have to make a C-C bond by using a carbon Nu:$^-$ (CN^-, acetylide ion, RMgX, enolate ion). Or break a C-C bond by ozonolysis or decarboxylation.
   iv. Identify the structural features in the starting material the and target compound. Identify each structural feature as a nucleophile or electrophile. This tells you the possible reaction types.
   v. What is the reaction type?
   vi. What reagent will accomplish this reaction and reaction type?

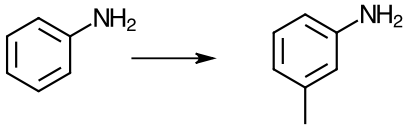
a. Describe how to make ethanol from ethyl bromide.

i. 

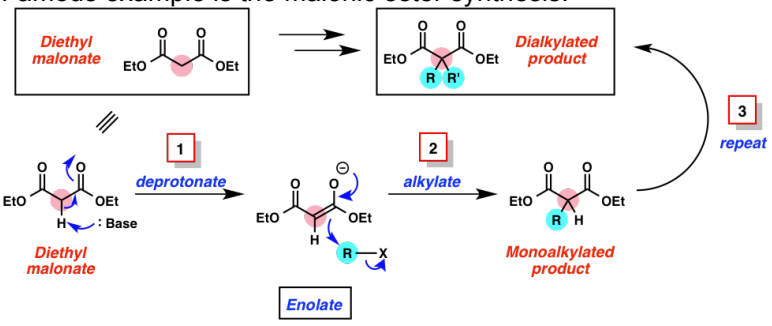
ii. Alkyl halide ----> alcohol. Reaction occurs at alpha C. C-Br bond breaks. C-O bond forms.
iii. 2 carbons -----> 2 carbons. A C-C bond does not form.
iv. Br LG (Nu:$^-$), alpha C (E^+), H bonded to beta C (E^+) -----> OH LG (Nu:$^-$), alpha C (E^+), H bonded to beta C (E^+), acidic H on O (E^+), basic O (Nu:$^-$). Possible reaction types: substitution, elimination.
v. Reaction type = nucleophilic substitution. Don't want elimination because no pi bond forms.
vi. Use OH^- as Nu:$^-$ to react at alpha C to substitute OH for Br.

b. Describe how to make acetaldehyde from ethanol.
c. Describe how to make 2-butene from 1-butene.
d. Describe how to make 2-propanol from 1-propanol.
e. Describe how to make isopropanol from acetaldehyde.
f. Describe how to make C_4H_{10} from C_2H_5Br.
g. Describe how to make C_2H_5COOH from C_2H_5Br.
h. Describe how to make

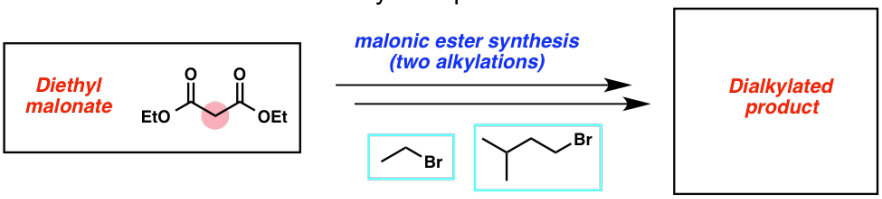
i.

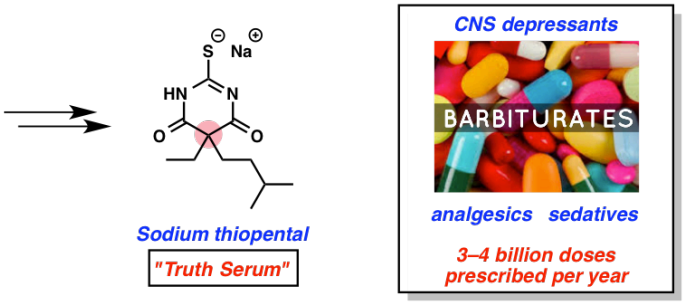


j. (From LearnBacon.com) Enolate alkylation
Famous example is the malonic ester synthesis.

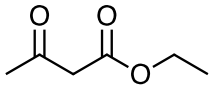


Malonic ester synthesis is used to make countless bioactive molecules, e.g., barbituates (sedative-hypnotic drugs which can cause death by depressing the central nervous system).
Famous barbituate is sodium thiopental (used in psychiatry, lethal injections, truth serums).
Predict the structure of the dialkylated product formed in the malonic ester synthesis of sodium thiopental.

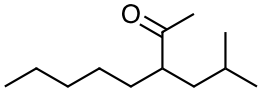




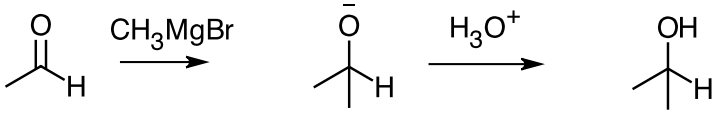
k. Starting from ethyl acetate, describe a synthesis of:



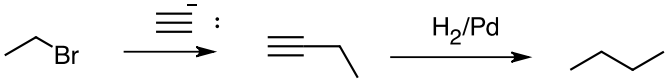
l. Starting from acetone, $C_5H_{11}Br$, and $(CH_3)_2CHCH_2Br$, describe a synthesis of:



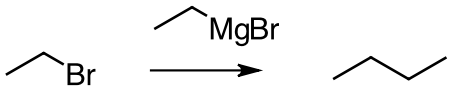
Answers:
b. Describe how to make acetaldehyde from ethanol.
Oxidation: Ethanol – PCC --> acetaldehyde
c. Describe how to make 2-butene from 1-butene.
Move pi bond by HX addition to form RX and then elimination to form pi bond. 1-butene – HBr --> 2-bromobutane – $NaOC_2H_5$ --> 2-butene
d. Describe how to make 2-propanol from 1-propanol.
Move OH group by elimination followed by addition.
1-propanol – H_2SO_4 --> propene -- H_2SO_4 --> 2-propanol
e. Describe how to make isopropanol from acetaldehyde.
Acetaldehyde has 2 carbons and isopropanol has 3 carbons so have to use a reaction that forms a C-C bond.
Use Grignard reaction to add 1 carbon. Acetylide ion adds 2 carbons.



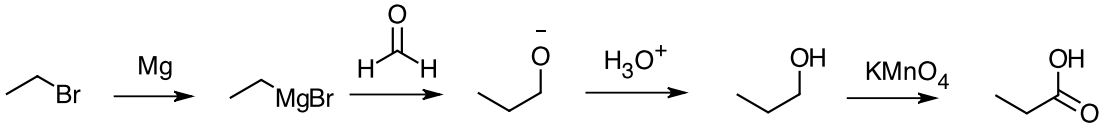
f. Describe how to make C_4H_{10} from C_2H_5Br.
C_2H_5Br has 2 carbons and C_4H_{10} has 4 carbons so have to use a reaction that forms a C-C bond.
Use acetylide ion.



Or use Grignard reagent: $C_2H_5Br + C_2H_5MgBr$ --> C_4H_{10}.

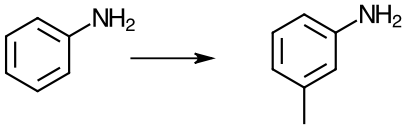


g. Describe how to make C_2H_5COOH from C_2H_5Br.
C_2H_5Br has 2 carbons and C_2H_5COOH has 3 carbons so have to use a reaction that forms a C-C bond.
Use Grignard reagent: C_2H_5Br --> C_2H_5MgBr. Then, C_2H_5MgBr + H_2CO to form alcohol. Then oxidize alcohol to acid.

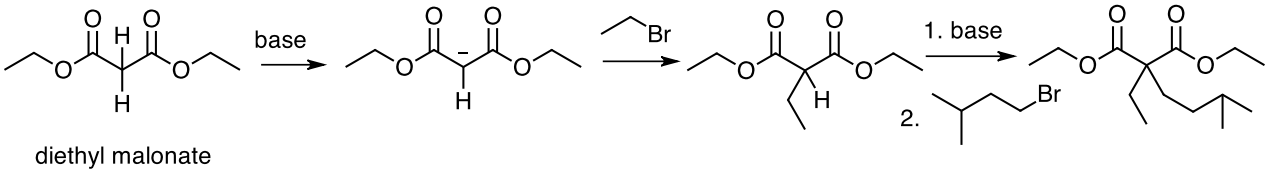


h. The starting compound and target compound have 4 carbons
Move the OH group in t-butanol over one carbon.
So do an elimination reaction to convert t-butanol to an alkene: t-butanol + H_2SO_4 ---> 2-methylpropene.
Then, do an addition reaction to place the OH group on carbon 1: 2-methylpropene – 1. BH_3, 2. H_2O_2, OH^- --> 2-methyl-1-propanol
Then, oxidize the 1°C to an acid: 2-methyl-1-propanol – $KMnO_4$ --> 2-methylpropanoic acid

i. Do an electrophilic aromatic substitution (EAS) reaction to substitute CH_3 group meta to NH_2 group.
NH_2 group is an ortho, para director.
Oxidize NH_2 group to NO_2 group, which is a meta director. Aniline – $KMnO_4$ --> nitrobenzene
Then treat nitrobenzene with $CH_3Cl/AlCl_3$ to make m-nitrotoluene: nitrobenzene -- $CH_3Cl/AlCl_3$ --> m-nitrotoluene
Then, reduce the NO_2 group back to NH_2 group: m-nitrotoluene – $NaBH_4$ --> m-methyl aniline

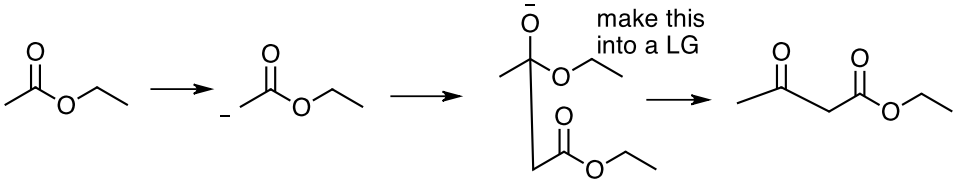


j. Diethyl malonate has two ester groups. Remove the alpha proton to form an ester enolate ion ==> a strong nucleophile that reacts at the alpha C in the RBr in a CHM 12A substitution reaction.
Repeat: remove 2nd alpha proton to form an ester enolate ion ==> reacts at the alpha C in the 2nd RBr in a CHM 12A substitution reaction.

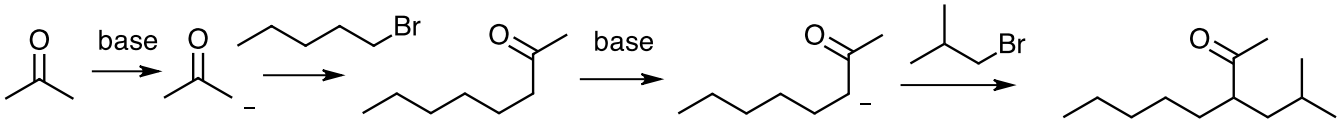


diethyl malonate

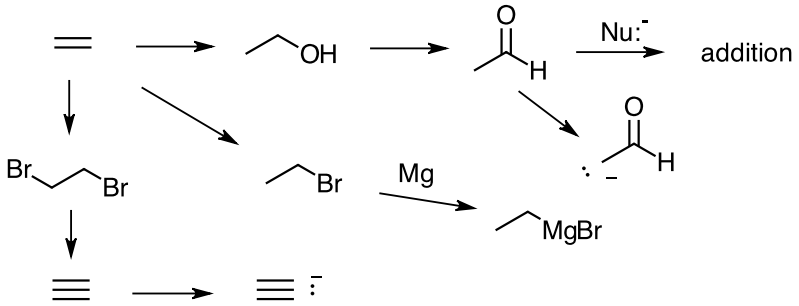
k. The target compound is a beta-keto ester. A beta-keto ester is made by Claisen condensation (nucleophilic acyl substitution of ester with ester enolate ion).
Ethyl acetate --> ester enolate ion -- Ethyl acetate --> tetrahedral intermediate --> beta-keto ester.



l. RBr has an alpha C and LG so it can be used in a substitution reaction.
Acetone has an alpha C so can make an enolate ion, which is a $Nu:^-$.
React enolate ion with RBr to make C-C bond and a bigger molecule.
acetone + NaOEt --> enolate ion -- $C_5H_{11}Br$ --> -- NaOEt --> enolate ion -- $(CH_3)_2CHCH_2Br$ --> product

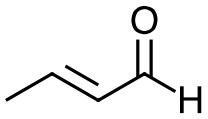


4. The chemical industry uses ethylene, acetylene, or benzene as the starting materials to make bigger molecules. Examples:

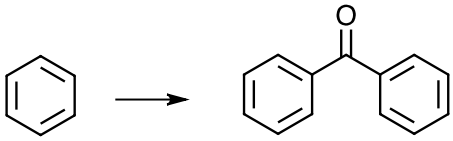


Note acetylide, C_2H_5MgBr, and the enolate ion are nucleophiles to make C-C bonds.

a. Starting from ethylene, describe a synthesis of 1,3-butadiene.
b. Starting from ethylene, describe a synthesis of acetone.
c. Starting from ethylene, describe a synthesis of ethyl acetate.
d. Starting from ethylene, describe a synthesis of:



e. Starting from benzene, describe a synthesis of aspirin.
f. Starting from benzene, describe a synthesis of benzophenone.



g. Using toluene, NaCN, and CO_2 as the sources of carbon atoms, describe a synthesis of:
(i) phenylacetic acid
(ii) benzoyl chloride

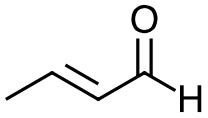
Answers:
a. ethylene has 2 carbons; 1,3-butadiene has 4 carbons so you have to make a C-C bond.
1,3-butadiene has 2 C=C bonds – make pi bond with elimination reaction, e.g., C-C-Br – strong base --> C=C
Use Grignard reagent to make C-C bond:
(i) make RBr: ethylene + HBr --> C_2H_5Br
(ii) make RMgBr: C_2H_5Br + Mg --> C_2H_5MgBr
(iii) make C-C bond (substitution reaction): C_2H_5MgBr + C_2H_5Br --> C_4H_{10}.
Make RBr:
(iv) C_4H_{10} – Br_2/light --> $CH_3CHBrCHBrCH_3$
Make pi bonds:
(v) $CH_3CHBrCHBrCH_3$ -- NaOEt --> 1,3-butadiene
OR another Grignard:
(i) ethylene + Br_2 --> 1,2-dibromoethane
(ii) 1,2-dibromoethane -- NaOEt --> acetylene
(iii) acetylene + HBr --> C_2H_3Br
(iv) C_2H_3Br + Mg --> C_2H_3MgBr
(v) C_2H_3MgBr + C_2H_3Br --> 1,3-butadiene
OR Use acetylide ion to make C-C bond:
(i) ethylene + Br_2 --> 1,2-dibromoethane

(ii) 1,2-dibromoethane -- NaOEt --> acetylene
(iii) acetylene – $NaNH_2$ --> acetylide ion
(iv) acetylide ion + 1,2-dibromoethane --> $CHCCH_2CH_2Br$
(v) eliminate Br to make C=C: $CHCCH_2CH_2Br$ -- NaOEt --> $CHCCHCH_2$
(vi) convert carbon-carbon triple bond to C=C: $CHCCHCH_2$ -- H_2/Lindlar's catalyst --> 1,3-butadiene

b. ethylene --> acetone
ethylene has 2 carbons; acetone has 3 carbons so you have to make a C-C bond.
Make ketone by oxidizing 2^o ROH.
Use Grignard reagent to make C-C bond: RMgBr + aldehyde or ketone --> 2^o ROH – [O] --> ketone
e.g., CH_3CHO + CH_3MgBr --> 2-propanol – $KMnO_4$ --> acetone
Make CH_3CHO: ethylene + H_2SO_4 --> ethanol – PCC --> CH_3CHO. Need to use weak [O] to convert 1^o ROH to aldehyde. Stronger [O] oxidizes 1^o ROH to acid.

c. ethylene ---> ethyl acetate.
ethyl acetate is an ester. Can do a nucleophilic acyl substitution: acid + alcohol --> ester + water
acetic acid + ethanol --> ethyl acetate + water
Make ethanol: ethylene + H_2SO_4 --> ethanol
Make acetic acid: ethanol – $KMnO_4$ --> CH_3COOH
Make ethyl acetate: acetic acid + ethanol -- H_2SO_4 catalyst --> ethyl acetate + water

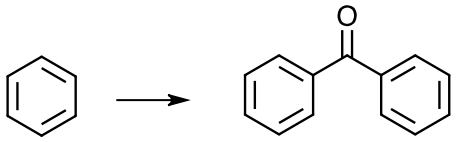
d. ethylene --->



Note structural feature: Target compound is an α, β-unsaturated aldehyde – use aldol condensation reaction (nucleophilic addition of nucleophile to carbony carbon).
Make alcohol from ethylene by electrophilic addition: Ethylene (C_2H_4) – H_2SO_4 --> ethanol
Oxidize ethanol to aldehyde: ethanol – PCC --> CH_3CHO
Acid-base: CH_3CHO + NaOH or NaOEt --> CH_2CHO^- enolate ion
nucleophilic addition: CH_3CHO + CH_2CHO^- ---> 2-butenal

e. benzene ---> aspirin.
Do an electrophilic aromatic substitution (EAS) reactions to substitute the two groups on ring.
Do a nucleophilic acyl substitution to convert alcohol to ester.
Benzene – $CH_3Cl/AlCl_3$ --> toluene ($C_6H_5CH_3$) – $KMnO_4$ --> benzoic acid (C_6H_5COOH)
To substitute OH, need to make aryl diazonium ion. See Objective 14 Practice Problem 8.
Benzene – HNO_3/H_2SO_4 --> nitrobenzene ($C_6H_5NO_2$) – [Reducing agent = $NaBH_4$] --> aniline ($C_6H_5NH_2$) – $NaNO_2$, HCl --> aryl diazonium ion ($C_6H_5N_2^+$) -- H_2O --> phenol
COOH group is a meta director; OH group is an ortho, para director so make phenol first, and then substitute methyl group and then oxidize methyl group to –COOH group.
(i) EAS: Benzene – HNO_3/H_2SO_4 --> nitrobenzene ($C_6H_5NO_2$)
(ii) Reduction reaction: $C_6H_5NO_2$ – [Reducing agent = $NaBH_4$] --> aniline ($C_6H_5NH_2$)
(iii) Oxidation reaction: $C_6H_5NH_2$ – $NaNO_2$, HCl --> aryl diazonium ion ($C_6H_5N_2^+$)
(iv) Substitution: aryl diazonium ion ($C_6H_5N_2^+$) -- H_2O --> phenol
(v) EAS: phenol -- $CH_3Cl/AlCl_3$ --> 2-methyl phenol
(vi) Oxidation reaction: 2-methyl phenol – $KMnO_4$ --> 2-hydroxy benzoic acid (commonn name = salicylic acid)
(vii) nucleophilic acyl substitution: salicylic acid + acetic acid -- H_2SO_4 catalyst --> aspirin + water

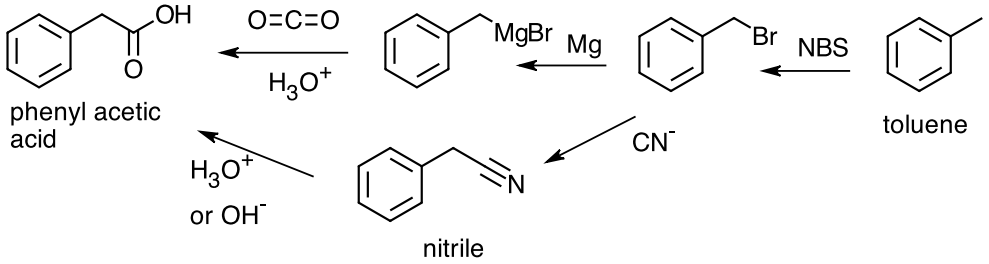
f. benzene ---> benzophenone.



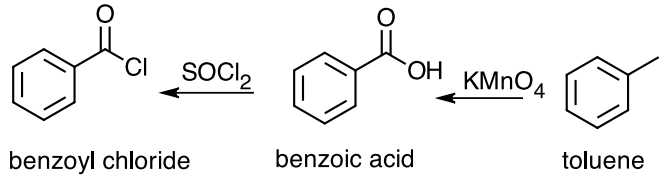
Ketone is made by oxidizing an alcohol.
Alcohol is made by Grignard reaction (RMgX + aldehyde/ketone) and makes a C-C bond.

Grignard reagent is made from RBr: RBr + Mg --> RMgBr
Do an electrophilic aromatic substitution (EAS) reaction:
(i) Benzene + $Br_2/FeBr_3$ ---> bromobenzene (C_6H_5Br)
(ii) Make Grignard reagent: C_6H_5Br – Mg --> C_6H_5MgBr
(iii) For aldehyde (to react with Grignard reagent to make C-C bond), make benzaldehyde: Benzene – $HCOCl/AlCl_3$ --> benzaldehyde (C_6H_5CHO)
(iv) Do Grignard reaction to make C-C bond: C_6H_5CHO – 1. C_6H_5MgBr, 2. H_3O^+ --> diphenylmethanol
(v) Oxidize OH to ketone with $KMnO_4$: diphenylmethanol -- $KMnO_4$ --> benzophenone

g. Using toluene, NaCN, and CO_2 as the sources of carbon atoms, describe a synthesis of:
(i) phenylacetic acid



Phenylacetic acid has acid group.
Can make an acid by oxidation of alcohol or Grignard reaction with CO_2.
OR make an acid by nitrile hydrolysis (see Objective 12).
(ii) benzoyl chloride



Benzoyl chloride is an acid derivative (acyl halide).
Do a nucleophilic acyl substitution to make acyl halide from benzoic acid. $SOCl_2$ is often used as a source of Cl^-.
Benzoic acid is made by oxidizing toluene.