Objective 15: Develop synthesis strategies for organic synthesis.

Quiz Practice problems

Key ideas:

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.

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

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.
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.

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	Carbocation, alpha carbon on LG
nitrogen	Lone pair N: NH_3, NH_2^-, NRH_2, NRH^-	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, CΞC 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 HBr to form ethyl bromide. (Or substitution with RX to form ether.)

Elimination to form ethylene.

Oxidation to form acetic acid (CHM 12B reaction).

This means there are at least three ways to synthesize ethanol. In other words, look at ethanol reactions in reverse or backwards.

Skills:

Given target compound and starting materials, identify structural features.

Given target compound and starting materials, identify functional groups.

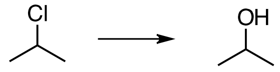
Given target compound and starting materials, identify bonds that break and form.

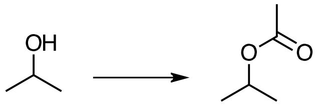
Given target compound and starting materials, design a synthesis to

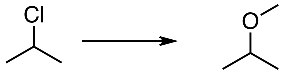
- convert one functional group to another,
- move a functional group from one carbon to an adjacent carbon,

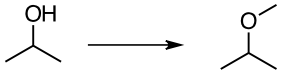
- make a carbon-carbon bond to make a bigger molecule, and
- make a compound with two or more functional groups.

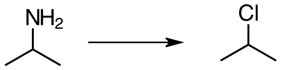
1. Convert one functional group to another.
a. See Table 1. Use a substitution reaction. You need a ____ and ____ and ___ for a substitution reaction. Use your pKa table.
Describe a one or two step synthesis of the target compound from the starting material. (In other words, Determine the reaction conditions for each reaction.) Use reactions we have covered in Chem 12A.

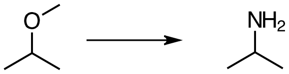






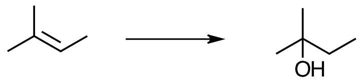


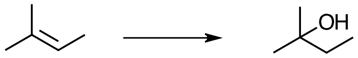


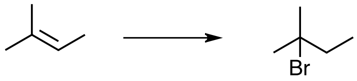


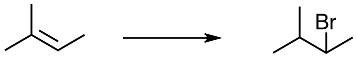
Answers:
Reaction 1: use a substitution reaction with $Nu:^-$ = OH^-.
Reaction 2: use a substitution reaction. Make OH into a better leaving group so use CH_3COOH. The conjugate base of CH_3COOH is the nucleophile in the substitution step.
Reaction 3: use a substitution reaction with $Nu:^-$ = CH_3O^-.
Reaction 4: use a substitution reaction. Make OH into a better leaving group so use CH_3OH. The conjugate base of CH_3OH is the nucleophile in the substitution step.
Reaction 5: use a substitution reaction. Make NH_2 into a better leaving group so use HCl. The conjugate base of HCl is the nucleophile in the substitution step.
Reaction 6: use a substitution reaction. Make OCH_3 into a better leaving group so use NH_4^+. The conjugate base of NH_4^+ is the nucleophile in the substitution step.

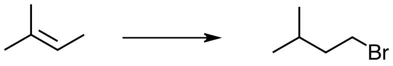
b. See Table 1. Use an addition reaction. Convert a C=C pi bond to a functional group.
Describe a one step synthesis of the target compound from the starting material. Use reactions we have covered in Chem 12A.

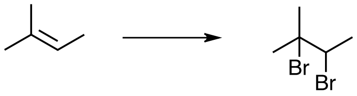


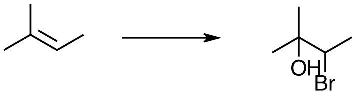








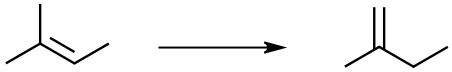




Answers:
Reaction 1: use an addition reaction with E$^+$ = H_2SO_4. Markovnikov addition.
Reaction 2: use an addition reaction with E$^+$ = H_2SO_4. (Same as reaction 1)
Reaction 3: use an addition reaction with E$^+$ = HBr. Markovnikov addition.
Reaction 4: use an addition reaction with HBr and peroxides in a radical reaction. non-Markovnikov addition.
Reaction 5: Br substitutes in allylic position so use NBS or Br_2/light in a radical reaction.
Reaction 6: use an addition reaction with E$^+$ = Br_2.
Reaction 7: use an addition reaction with E$^+$ = Br_2 in 1st step and H_2O in 2nd step. See bromohydrin formation.

2. Move a functional group, e.g., -OH or pi bond, over one carbon.
See Table 1.
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). Use reactions we have covered in Chem 12A.
(i) Describe how you would make 2-propyl bromide from 1-propyl bromide.
(ii) Describe how you would make 1-butanol from 2-butanol.

b. To move a pi bond over one carbon, you can use a ______ reaction reaction followed by a ____ reaction (2 step synthesis). Use reactions we have covered in Chem 12A.
(i) Describe how you would make 2-butene from 1-butene.
(ii)



Answers:
a. To move a –OH or –X group over one carbon, you can use an elimination reaction to make a C=C pi bond followed by an addition reaction (2 step synthesis). Use reactions we have covered in Chem 12A.
(i) Describe how you would make 2-propyl bromide from 1-propyl bromide.
Step 1: 1-propyl bromide + $(CH_3)_3CO^-$ (large, strong base) --> propene
Step 2: propene + HBr --> 2-propyl bromide
(ii) Describe how you would make 1-butanol from 2-butanol.
Step 1: 2-butanol + H_2SO_4 --> 1-butene. (Reaction produces mostly 2-butene.)
Step 2: 1-butene + BH_3/H_2O_2, OH^- --> 1-butanol

3. Make a big molecule from a small molecule. Make a C-C bond.
See Table 1. To make a carbon-carbon bond,
(i) use acetylide ion as Nu:$^-$ and RX as substrate in a substitution reaction. FOCUS on THIS ONE.
(ii) use CN$^-$ ion as Nu:$^-$ and RX as substrate in a substitution reaction. (We will use this reaction in CHM 12B.)
(iii) Use C=C pi bond and carbocation in an Addition reaction.
Propose an efficient synthesis. Use reactions we have covered in Chem 12A.
a. acetylene --> propene

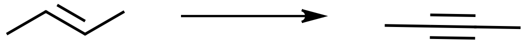
b. acetylene --> 1-butyne
c. acetylene --> 2-butyne
c. propene --> 2-pentyne
Answers:
a. Step 1: acetylene + NH_2^- --> acetylide ion
Step 2: acetylide ion + CH_3Br --> propyne
Step 3: Propyne + H_2/Lindlar's catalyst --> propene

b. Step 1: acetylene + NH_2^- --> acetylide ion
Step 2: acetylide ion + C_2H_5Br --> 1-butyne

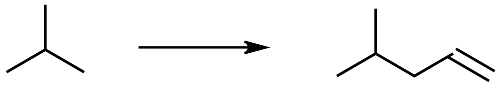
c. Step 1: acetylene + NH_2^- --> acetylide ion
Step 2: acetylide ion + CH_3Br --> propyne
Step 3: propyne + NH_2^- --> propylide ion
Step 4: propylide ion + CH_3Br --> 2-butyne

d. Step 1: acetylene + NH_2^- --> acetylide ion
Step 2: acetylide ion + CH_3Br --> propyne
Step 3: propyne + NH_2^- --> propylide ion
Step 4: propylide ion + C_2H_5Br --> 2-pentyne

4. Propose an efficient synthesis: Combine ideas from Problems 1, 2, and 3. Use reactions we have covered in Chem 12A.
a. acetylene --> isopropanol
b. acetylene --> 2-butene
c. acetylene --> 1,3-butadiene
d.



e.



Answers:
a. 2 carbon reactant --> 3 carbon product so you want to make a C-C bond.
Step 1: acetylene + NH_2^- --> acetylide ion
Step 2: acetylide ion + CH_3Br --> propyne
Step 3: Propyne + H_2/Lindlar's catalyst --> propene
Step 4: propene + H_2SO_4 --> isopropanol

b. 2 carbon reactant --> 4 carbon product so you want to make a C-C bond.
Step 1: acetylene + NH_2^- --> acetylide ion
Step 2: acetylide ion + CH_3Br --> propyne
Step 3: propyne + NH_2^- --> propylide ion
Step 4: propylide ion + CH_3Br --> 2-butyne
Step 5: 2-butyne + H_2/Lindlar's catalyst --> 2-butene

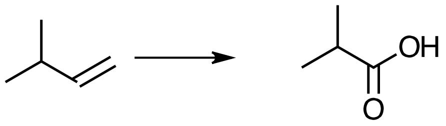
c. 2 carbon reactant --> 4 carbon product so you want to make a C-C bond.
Step 1: acetylene + NH_2^- --> acetylide ion
Step 2: acetylide ion + C_2H_5Br --> 1-butyne
Step 3: 1-butyne + H_2/Lindlar's catalyst --> 1-butene
1-butene has an allylic C.
Step 4: 1-butene + NBS --> 3-bromo-1-butene
Eliminate Br to form pi bond.
Step 5: 3-bromo-1-butene + $(CH_3)_3CO^-$ (large, strong base) --> 1,3-butadiene

d. 4 carbon reactant --> 4 carbon product.
Make a C-C pi bond with an elimination reaction. Need a H on beta C and leaving group.
Do an addition reaction first to add a leaving group to starting compound.
Step 1: 2-butene + Br_2 --> 2,3-dibromobutane
Step 2: 2,3-dibromobutane + $(CH_3)_3CO^-$ (large, strong base) --> 2-butyne

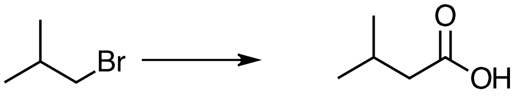
e. 4 carbon reactant --> 6 carbon product so you want to make a C-C bond.
Alkanes undergo radical halogenation reaction.
Use Cl2/light (random Cl substitution gives a mixture of products so you will have to separate and isolate the product you want.
Step 1: 2-methayl propane + Cl_2/light --> 1-chloro-2-methyl propane
Step 2: acetylene + NH_2^- --> acetylide ion
Step 3: acetylide ion + 1-chloro-2-methyl propane --> 4-methyl-1-pentyne
Step 4: 4-methyl-1-pentyne + H_2/Lindlar's catalyst --> 4-methyl-1-pentene

5. Propose an efficient synthesis. Hint: the only reaction we covered in Chem 12A that makes an acid is ozonolysis of alkynes.

a.



b.



Answers:
a. 5 carbon reactant --> 4 carbon product. Need to break a C-C triple bond to make an acid. Use ozonolysis.
Convert alkene to alkyne – see Question 4d.
Step 1: 3-methyl-1-butene + Br_2 --> 1,2-dibromo-3-methyl butane
Step 2: 1,2-dibromo-3-methyl butane + $(CH_3)_3CO^-$ (large, strong base) --> 3-methyl-1-butyne
Step 3: 3-methyl-1-butyne – 1. O_3, 2. Zn, HCl --> 2-methyl propanoic acid

b. 4 carbon reactant --> 5 carbon product so you want to make a C-C bond.
Use alkynes ozonolysis --> acid.
Ozonolysis breaks a C-C triple bond.
Step 1: acetylene + NH_2^- --> acetylide ion
Step 2: acetylide ion + 1-bromo-2-methyl propane --> 4-methyl-1-pentyne
Step 3: 4-methyl-1-pentyne – 1. O_3, 2. Zn, HCl --> 3-methyl propanoic acid (isobutyric acid)