Final Review Worksheet KEY

Objectives:

Chapter 7

➢ Draw mechanisms for, and differentiate between, $S_N^1$ and $S_N^2$ reactions.
➢ Explain trends in nucleophilicity, basicity, carbocation stability, reactivity of alkyl halide reagents, and either polar protic or polar aprotic solvent choices.
➢ Utilize alkyl halides and various other organic reagents for organic synthesis of novel compounds.

Chapter 8

➢ Rank alkenes based on their inherent stability and predict elimination reaction products based on the Zaitsev rule.
➢ Differentiate between E1, E2, $S_N^1$ and $S_N^2$ reactions in regards to their favorability in a given reaction, their mechanisms, and the products formed.

Chapter 9

➢ Predict products, and draw mechanisms, for reactions involving alcohols.
  ○ Alkene formation via a dehydration reaction with $\text{H}_2\text{SO}_4$
➢ Predict, and draw mechanisms for, the various ways in which an -OH group may be made into a good leaving group.
  ○ Alkyl Halide formation via strong acid (H-X), $\text{SOCl}_2$ and pyridine, or $\text{PBr}_3$ and pyridine
  ○ Tosylation of an alcohol via $\text{TosCl}$ and pyridine
➢ Account for carbocation shifts (1,2 alkyl and hydride shifts) when predicting product formation.
➢ Synthesize ethers via the Williamson ether synthesis
➢ Describe ways to either synthesize or cleave ethers and epoxides
  ○ Distinguish between the products formed when reacting ethers with 1 vs 2 equivalents of H-X
➢ Draw mechanisms and predict product formation of both acid and base catalyzed ring openings of epoxides
Chapter 10

➢ Draw mechanisms and predict products for the following reactions:
  ○ Electrophilic Addition of either H-X or H₂O to alkenes
  ○ Halogenation via addition of X₂ to alkenes
  ○ Halohydrin formation via addition of X₂ and H₂O to alkenes
  ○ Hydroboration-Oxidation via addition of either 9-BBN or BH₃, followed by H₂O₂ and HO⁻
➢ Utilization of known reactions for the synthesis of novel compounds

Chapter 11

➢ Draw mechanisms and predict products for the following reactions:
  ○ Double Elimination formation of alkynes via addition of either 2 equivalents (non-terminal) or 3 equivalents (terminal) of NaNH₂
  ○ Electrophilic Addition of H-X to alkynes
  ○ Halogenation via addition of X₂ to alkynes
  ○ Hydration via the Keto-Enol tautomerization mechanism when adding H₂O and H₂SO₄ to alkynes
  ○ Hydroboration-Oxidation of alkynes via addition of either 9-BBN or BH₃, followed by H₂O₂ and HO⁻
➢ Utilization of known reactions for the synthesis of novel compounds

Chapter 12

➢ Distinguished between Oxidation and Reduction reactions
  ○ Distinguished between the products formed when reacting alkynes with either H₂ and Lindlar’s Catalyst or Na and NH₃ (l)
➢ Predict products for the following reactions:
  ○ Alkyne reduction with either H₂/Lindlar’s Catalyst or Na/NH₃ (l)
  ○ Reduction of alkyl halides and epoxides with LiAlH₄
  ○ Oxidation of alkenes with peroxyacids like mCPBA to form epoxides
  ○ Dihydroxylation with KMnO₄ of an alkene to form syn-products
  ○ Ozonolysis with O₃, followed by an oxidative or reductive workup, to form aldehydes, ketones, or carboxylic acids
  ○ Alcohol oxidation with either CrO₃/H₂SO₄ or PCC to form carboxylic acids, aldehydes, or ketones
➢ Utilization of known reactions for the synthesis of novel compounds
Chapter 15

➢ Draw mechanisms for reactions involving radicals.
   ○ Treatment of alkane chains and alkenes with Br₂ and hv
➢ Predict products for the following reactions:
   ○ Treatment of alkanes with Br₂ and hv
   ○ Treatment of alkenes with NBS, ROOR, and hv
➢ Rank radicals based on their stability and have a general understanding why treatment with Br₂ and hv is more selective than Cl₂ and hv in product formation
➢ Utilization of known reactions for the synthesis of novel compounds

Chapter 16

➢ Draw mechanisms for reactions involving the formation of 1,2 and 1,4 products.
   ○ Differentiate between thermodynamic (Zaitsev) and kinetic (Hoffman) products, and the conditions that favor their formation
➢ Predict major products formed in the Diels-Alder reaction

Chapter 17

➢ Determine if a compound is aromatic, antiaromatic, or non-aromatic based on Huckel’s rules of aromaticity

Problem Set:

1. Predict the following reactant(s) or product(s) for each reaction below.

   a. (9.61 c)

   \[
   \text{[reactant]} \xrightarrow{\text{HBr (2 equiv.)}} \text{[product]} \quad \text{Br} \\
   \text{H}_2\text{O}
   \]

   Recall that adding two equivalents of strong H-X acid to an ether (at high temperatures) will cause cleavage of the ether into 2 alkyl halides alongside water byproduct. Adding only one equivalent of H-X will form an alcohol and alkyl halide. The alkyl halide that forms with one equivalent depends on the nature of the ether’s
R groups. If a stable carbocation (secondary, tertiary, resonance stabilized) can be formed, then the first alkyl halide will form under the $S_N1$ reaction mechanism (which is a surprisingly fast reaction!) over a potential $S_N2$ reaction mechanism with the ether’s other R group.

In Chem 51B, treatment of ethers with H-X acid and ozonolysis, followed by either reductive or oxidative workup, are the two main ways of making fragments from larger starting materials.

b. (Ch 15 Practice Test 5)

Route A

The formation of an alkyl halide at the most substituted carbon directly from an alkyl ring without any functional groups suggests the use of a radical reaction. Therefore, either NBS or Br$_2$, followed by peroxide (ROOR) and light (hv), will yield the desired alkyl halide product. Since the carbon receiving the radical bromine is achiral, identical compounds are formed regardless of the radical attack pathway (frontside or backside).

Route B

The formation of an alkene from a tertiary alkyl halide is best accomplished through an E2 reaction with a strong base, such as sodium ethoxide. Note that potassium tert-butoxide is too bulky to attack the sterically hindered alkyl halide and yield the Zaitsev product (Hoffman product is formed instead).
**Route C**

The addition of an -OH group to the less-substituted side of an alkene can be accomplished via the hydroboration oxidation reaction. In the first step, either BH$_3$ or 9-BBN is added. In a second step, hydrogen peroxide and the hydroxide ion is added. Recall that this reaction leads to syn-addition of an -OH and -H to the alkene.

**Route D**

Recall that the formation of an epoxide directly from an alkene can be accomplished through the addition of the mCPBA reagent (or the addition of Cl$_2$ and H$_2$O, followed by NaH, for an intramolecular epoxide-forming S$_N$2 reaction). The formation of the epoxide results in a racemic mixture of two enantiomeric products (one where the epoxide is on wedges and another on dashes).

**Route E**

The conversion of a secondary alcohol to a ketone can be accomplished through an oxidation reaction with either PCC or CrO$_3$ and H$_2$SO$_4$.

**Route F**

The product of this reaction suggests the opening of a base-catalyzed epoxide ring opening, as given by the -CN substituent on the less substituted side of the initial epoxide. Therefore, the addition of NaCN (as the nucleophile) and H$_2$O (to protonate the oxygen AFTER the ring opening) would result in product formation. Note that a racemic mixture of products (where the -CN and -OH substituents are in the anti-configuration) would form.

2. (Variation of 16.55 c) You are a Chem 199 student studying the Diels-Alder reaction and have decided to use the following compounds as your reactants.
a. Determine which compound represents the diene and dienophile. Then, predict the product that would form if both compounds were placed in a heated reaction vessel.

\[
\text{H} \quad \text{C} = \text{C} \quad \text{H} \\
\text{O} \quad \text{C} = \text{C} \quad \text{C} \quad \text{H}
\]

The reaction above is an example of the \textbf{Diels-Alder reaction}, where a \textit{diene} (in red) and \textit{dienophile} (in black) are combined at high temperatures to form ringed products. The product above is a \textbf{bicyclic ring} formed from \textit{pent-2-ene}, whose contributions to the final product have been marked in red, and the \textit{dienophile} with an aldehyde (an electron withdrawing group that \textit{helps increase reactivity} of the dienophile with the diene). Recall that the Diels-Alder reaction primarily \textit{forms endo- products}, where the \textbf{EWG is closer to the 2C bridge} (where newly formed pi bond is) in this particular product (selectivity stems from a \textit{stabilizing transition state configuration}).

b. Devise a synthesis of compound A starting from ethane. You may use any necessary organic or inorganic reagents.

\textbf{DISCLAIMER:} Synthesis problems will 99.999\% of the time have more than one solution. The pathway described below is merely one of the many possible manners to synthesize the compound presented above.

\textbf{Retrosynthetic Approach:}
Given the starting compound is ethane, and the final product has more than 2 initial carbons, a synthesis route involving acetylene is likely (a key carbon chain creator in Chem 51B). Likewise, the inclusion of oxygen in the final product from starting materials that do not initially contain it also suggests the addition of ethylene oxide (which, with some forward thinking and knowledge of reagents from Chem 51B that make aldehydes, can be utilized later on if a primary alcohol can be formed). To form the acetylide anion, addition of Br₂ and hv to ethane will create an alkyl halide which can undergo elimination, to make an alkene, with strong base. Then, after the addition of Br₂ to the alkene, a double elimination reaction with 3 equivalents of strong base (either NaNH₂ or NaH) will form the acetylide anion that subsequently acts as a good nucleophile for an S₉₉₂ base-catalyzed epoxide ring opening after the addition of ethylene oxide and water. Then, reduce the alkyne to an alkene with H₂ and Lindlar’s catalyst (Na/NH₃ would also work). Finally, treat the compound with PCC to convert the primary alcohol into an aldehyde.

c. Devise a synthesis of compound B starting from cyclopentane. You may use any necessary organic or inorganic reagents.

DISCLAIMER: Synthesis problems will 99.999% of the time have more than one solution. The pathway described below is merely one of the many possible manners to synthesize the compound presented above.

Retrosynthetic Approach:
The formation of two double bonds is the result of two individual elimination reactions. Starting off from cyclopentane, the addition of Br₂ and hv can form an alkyl halide that undergoes E2 elimination in the presence of strong base. To add another leaving group necessary for a second elimination, add NBS, ROOR, and hv. Finally, perform another E2 elimination with a second equivalent of strong base.

Recall that the addition of Br₂ and hv to an alkene will lead to a much faster halogenation reaction instead of the intended radical addition reaction. This problem can be solved by using NBS, which does not have the chance of adding bromine directly to the alkene pi bond.

3. (W3 Practice Problems 1) Determine the compound number(s) which correctly answers the questions that follow.

   a. Which compound undergoes an E2 but no Sₐ,2 with NaOCH₃ in methanol?

   Tertiary, aryl and vinylic alkyl halides are incapable of undergoing the Sₐ,2 reaction mechanism. Likewise, sodium methoxide is a strong base that also promotes the E2 reaction. Therefore, Compound 3 is the most likely to undergo an exclusive E2 reaction, despite the presence of a polar protic solvent.
b. Which compound(s) form(s) a resonance stabilized carbocation after ionization?

Despite seeming not having any reactivity if treated with a poor base and nucleophile, like \( \text{H}_2\text{O} \), **Compound 2** can actually form a resonance-stabilized carbocation after its leaving group is removed. The potential resonance structures have been highlighted below.

![Resonance structures](image)

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c. Which compound(s) are not expected to undergo the \( \text{S}_\text{N}1 \) reaction?

Primary alkyl halides generally do not undergo the \( \text{S}_\text{N}1 \) reaction, unless resonance stabilized carbocations are formed (as in Compound 2). Likewise, allylic and vinylic alkyl halides are also incapable of \( \text{S}_\text{N}1, \text{S}_\text{N}2, \text{E}1, \) or \( \text{E}2 \) reactivity. Thus, **Compounds 4 and 5** are not expected to undergo the \( \text{S}_\text{N}1 \) reaction.

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d. Which compound gives the fastest reaction with \( \text{NaN}_3 \) in DMSO?

Sodium azide is a notable good nucleophile with relatively low basicity. Furthermore, the fastest reaction would occur under the \( \text{S}_\text{N}2 \) reaction with a non-sterically hindered primary alkyl halide where backside attack is easily attainable. Therefore, **Compound 2** would have the fastest reaction with \( \text{NaN}_3 \) in DMSO.

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4. (Variation of Dr. King’s Ch 15, Pg. 134 Example and 15.56) Draw a detailed stepwise mechanism for the following reaction.

\[
\text{[Scheme Image]}
\]
Dr. King has mentioned in lecture that one of two radical addition mechanisms will appear on the final exam. The example shown above is one of these two mechanisms. The other involves treatment of either an alkane or alkene with Br₂ and hv.

Recall that radical reactions have three distinct steps in their mechanism: initiation, propagation, and termination. In the initiation step, the primary radical reagent (bromide radical) is formed via dissociation of ROOR alkyl peroxide and subsequent reaction with HBr. The newly formed bromine radical will then react with the pi bond of the alkene reactant and form a secondary radical that reacts with HBr to subsequently form another bromine radical (often described as a radical chain reaction). Under the propagation phase, the reaction “loops” in its formation of primary alkyl halide product and bromine radicals while competing with the termination step, where excess bromine radicals can combine to form bromine gas.

Note that radicals are NOT subject to rearrangements like carbocations and more than one termination reaction is possible (with any two radicals in the propagation step). Likewise, MOVEMENT OF RADICALS USE FISH HOOK ARROWS and not double headed arrows.
For mechanisms, make sure all reacting atoms have lone pairs, arrows begin from areas of electron density (lone pairs, pi bonds, etc), land on areas with electron deficiency, and all bond angles are accurate (alkene substituents are 120° apart, etc).

5. (12.69 b) Devise a synthesis of the following compound using ethanol as the only source of carbon. You may use any other needed inorganic reagents.

![Diagram of the target compound]

**DISCLAIMER:** Synthesis problems will 99.999% of the time have more than one solution. The pathway described below is merely one of the many possible manners to synthesize the compound presented above.

**Retrosynthetic Approach:**

An epoxide with **syn- substituents** can be formed from the addition of the mCPBA reagent to a **cis- alkene**. Secondly, the **cis- alkene** can be formed via **reduction** of a symmetrical 6 carbon alkyne with H₂ and Lindar’s Catalyst. Given the limitations of this problem to possessing ethanol as the sole source of carbon atoms, **ethyl bromide** (which can be formed from **ethanol** with **PBr₃ and pyridine**) can be added to a **deprotonated 4 carbon alkyne** (achievable via initial addition of NaH or NaNH₂) in an S₉² reaction. This step is repeated to subsequently form the 6-carbon chain from the **acetylide anion**. To form the acetylide anion, add 3 **equivalents of NaNH₂ to a dibromide alkyl chain for double elimination**. To form the dibromo alkyl chain, recall the reaction involving **Br₂ addition to an alkene**. The **alkene can be formed from an E2 reaction with tert-butoxide base and ethyl bromide**. Finally, recall that earlier in
the synthesis, the initial formation of ethyl bromide from ethanol was mentioned via addition of PBr$_3$ and pyridine.

*Note that the retrosynthetic pathway depicted above is NOT required on an exam and is merely a reflection of thought processes trying to dissect the synthetic pathway to the target compound.*

**Synthesis Pathway:**

![Chemical reaction diagram](image)

*To consider:* Would treatment of the cis- alkene (in the final step of this synthesis) with Br$_2$ and H$_2$O, followed by NaH, also lead the correct target product?

6. Consider the following (Variation of Dr. King Winter 2021 Final Review):

![Chemical structures](image)

Rank the following structures in order of decreasing reactivity in a free radical bromination reaction (greatest to least).
Determining the reactivity of radical structures is very similar to determining stability of carbocation. This is due to the fact both have two open p-orbitals, sp², and planar. Nevertheless, the more R groups the radical or the hydrogen highlighted, the more stable it is, therefore, more reactive in a radical bromination reaction. HOWEVER, THE PRIMARY ALLYLIC AND BENZYLIC RADICALS ARE MORE STABLE THAN A TERTIARY RADICAL. Below I have included Dr. King’s Notes regarding stability of radicals as a reference:

**Stability:** Free radicals and carbocations are both electron deficient and they follow a similar order of stability:

\[
\text{[Ar]]} > \text{[allyl]} > R\text{C}^- > R\text{C}^- > R\text{C}^- > \text{H}\text{C}^- 
\]

7. Label each compound as aromatic, antiaromatic, or not aromatic. Assume all completely conjugated rings are planar (Variation of 17.35 3rd edition).
Guidelines for Aromaticity:

1. Structure must be cyclic (is it a ring or not?)
2. Each atom in the ring must have an unhybridized p-orbital (If there is a sp³ atom, it is neither)
3. Structure must be planar (Any ring with 6 carbons or below is planar)
4. Delocalization of pi-electrons must result in a lowering of electronic energy
   a. If $(4n + 2)\pi = AROMATIC$
   b. $4n\pi = ANTIAROMATIC$

MUST SATISFY ALL FOUR RULES TO BE CONSIDER AROMATIC OR ANTIAROMATIC!!

Note: When count hydrogens for Rule #4, count only 1 pair of lone pairs for oxygen & sulfur.
8. Consider the following reaction (Variation of 16.62 3rd edition):

![Reaction diagram]

a. Show the detailed mechanisms for the following transformation to both the 1,2-product and 1,4-product. Clearly show all lone pairs, charges, and curvy arrows, and show mechanism in a stepwise manner.

b. Which product formed from the reaction is the thermodynamic product? Why?

The **1,4 product is the thermodynamic product** because the alkene produced is trisubstituted, therefore, a more stable alkene from the monosubstituted alkene produced in the 1,2 product.

With the electrophilic addition reactions of conjugated dienes, there will always be the possibility of two products: **1,2-product & 1,4-product**. Now, which alkene will attack the HBr? It will be the **most substituted alkene to provide the most stable carbocation**. Therefore, the left trisubstituted alkene will attack the HBr. Now since there is an additional alkene with a
carbocation which can do resonance structures; that's where the two products come into play. Finally, the Br will attack the carbocation. To know if you got an 1,2-product or 1,4-product, see where the hydrogen and bromine end up. If the bromine and hydrogen are on adjacent carbons, it is 1,2-product and if the hydrogen and bromine are four carbons apart, it is 1,4-product.

9. Provide a synthesis for the following compound from the given starting material. If required, number individual steps.

For this particular synthesis problem, if you see a pattern where it starts with a ring and find that the ring opened up in the final product, it is a HUGE INDICATION that an ozonolysis occurs. Now with the final product, there is a ketone and an aldehyde, therefore it is an indication that a reduction workup occurs after the ozonolysis. Zn, H₂O or CH₃SCH₃ could work!!
Now you started with a simple alkane, the **most easiest method of adding a functional group would be Br₂, hv**. Now with your tertiary alkyl halide and knowing that an ozonolysis must occur, you need an alkene. An E2 elimination reaction could work!! **BE CAREFUL BECAUSE A LARGE STERIC HINDERED BASE SUCH AS KO(CH₃)₃ WILL PRODUCE A DISUBSTITUTED ALKENE, NOT THE TRISUBSTITUTED ALKENE NEEDED FOR THE SYNTHESIS.** Therefore, a small base such as NaOH will work in this situation.

As mentioned before, **Br₂, hv will be your best friend when adding a functional group to a simple alkane**. Now you might notice how the aldehyde is on the least substituted side, therefore, it is **very possible that 9-BBN and H₂O₂, NaOH** is one of the reagents. However, this reaction could occur with a less substituted alkene. This is only possible with an **E2 reaction with a sterically hindered base such as KOC(CH₃)₃**. Now with those 4 reagents listed, you have an anti-markovnikov alcohol, but need an aldehyde. **PCC will work best in this situation.**
Initially looking at this synthesis, you might want to do a simple dehydration and \( \text{KMnO}_4, \text{H}_2\text{O}, \text{KOH}, \text{cold} \). THAT IS WRONG!! Doing that, will provide a SYN dihydroxylation only. The final product here is anti-dihydroxylation. Instead, use mCPBA to produce an epoxide and \( \text{NaOH, H}_2\text{O} \) because it does inversion of configuration at the carbon attacked by the \( \text{NaOH} \).
For this synthesis, a pattern you should be able to recognize is going from an alkyne to a structure where a -CH₂CH₂OH is added. That is an indication that an epoxide is added in the synthesis. Since a terminal alkyne is a great nucleophile, deprotonate it with NaNH₂ and adding epoxide will do a job. However, remember that with good nucleophiles, add water to protonate the oxygen. Afterwards, to get from -OH to an aldehyde, use PCC to accomplish it. **NOTE:** DON'T ADD Na, NH₃ BEFORE THE EPOXIDE BECAUSE AN ALKENE CANNOT BE ADDED TO AN EPOXIDE. ORDER DOES MATTER IN SYNTHESIS!!!
For this synthesis, recognize the pattern where going from an alkyne to a cis alkene is an indication of using \( \text{H}_2 \), Lindlar’s Catalyst. Therefore, start with \( \text{H}_2 \), Lindlar’s Catalyst. Now you should notice how a strong nucleophile, but weak base is added allylically from the alkene. Therefore, that should demonstrate to you that a halide was added using NBS, heat, and peroxide. DO NOT USE \( \text{Br}_2 \), hv because an addition reaction could occur too!! Nevertheless, end it with a simple SN2 reaction with NaSH.

10. Fill in the major product in the following reactions, showing stereochemistry where known. If an enantiomer is formed, you can write +E (Variations of 15.48, 12.37).

a. 

\[
\text{NBS} \quad \text{hv}
\]
For this problem, a free radical provides two open p-orbitals, therefore, the NBS can attack from top or bottom of the radical. Therefore, enantiomers are definitely possible. For allylic compounds, resonance structures are possible where the double bond moves towards the left of the structure, therefore producing a primary allylic free radical. However, enantiomers are not possible because the carbon itself is not chiral.
mCPBA will provide an epoxide, but there are no enantiomers because the initial structure is achiral. Therefore, do not automatically put + E everytime you use mCPBA. LiAlH₄ is a strong nucleophile that can attack the epoxide, but on the least substituted side. Do not forget water to protonate the negatively charged oxygen.

c.

NaH will deprotonate the alcohol group and with the negatively charged oxygen, it will do intramolecular SN2 to kick out the bromine. It will produce an epoxide. LiAlH₄ is a strong nucleophile, therefore, it can attack the least substituted of the epoxide. Finally, PCC will produce an aldehyde since it is a primary alcohol compound.

d.
As mentioned many times, start with a Br₂, hv to add a functional group first at the most substituted carbon. The steric hindered base will make a less substituted alkene where mCPBA comes in to make an epoxide. The strong base, NaOCH₃ will attack the least substituted side of the epoxide. HOWEVER, water is not added so do not assume to protonate the oxygen. The CH₃Br will come in for a Williamson ether synthesis reaction.

Challenge Problem:
11. Show the detailed mechanisms for the following transformation. Clearly show all lone pairs, charges, and curvy arrows, and show mechanism in a stepwise manner. (This is a mechanism you have never seen before!)
Even though this is something you have never seen before, do not be too scared. Look at what is given: an epoxide and a strong nucleophile. You should know a strong nucleophile will attack the least substituted side of an epoxide. Now, be careful because there is no source of hydrogen to protonate the oxygen, therefore, leave it negatively charged. HOWEVER, there is an alkyl halide within the structure and a negatively charged oxygen. Therefore, an intramolecular SN2 should be the next step. There you go, you got the product.