Week 9

Nucleophilic Substitutions and Elimination

9.1 Nucleophilic Substitutions (cont.)

11/30:

- Choosing between the mechanisms (cont.).
  4. Solvent.

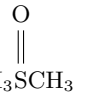
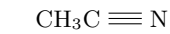
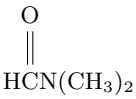
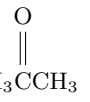
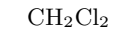
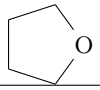
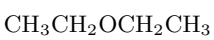
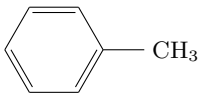
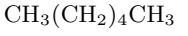
Solvent	**Structure**
Polar	
Dimethyl sulfoxide (DMSO)	
Acetonitrile	
N,N-Dimethylformamide (DMF)	
Acetone	
Moderately polar	
Dichloromethane	
Tetrahydrofuran (THF)	
Nonpolar	
Diethyl ether	
Toluene	
Hexane	

Table 9.1: Common aprotic solvents.

  - Critical for borderline cases.
  - The solvent is important for dissolving things/providing an environment for the reaction.
  - There are two types of solvents: **protic** and **aprotic**.
  - We need to know all of the common solvents (a table will be uploaded).
  - Key difference between protic and aprotic solvents.
    - Protic solvents can do hydrogen bonding with anions (LGs), stabilizing them.
    - Aprotic solvents cannot do this.
  - Protic solvents can stabilize X^-, easing the self-ionization step in S_N1.
  - Protic solvents stabilize both the nucleophile and LG in S_N2.
    - With the nucleophile retarded, the rate of S_N2 goes down.
  - In an aprotic solvent, the nucleophile is even more reactive.
  - Take-home message: For secondary alkyl halides (the borderline cases), protic solvents promote S_N1 and aprotic solvents promote S_N2.

- **Protic** (solvent): A solvent with an acidic proton.
- **Aprotic** (solvent): A solvent without an acidic proton.
- If you see a nucleophilic substitution-type reaction with just one compound surrounding the arrow, assume it is both the nucleophile *and* the solvent.
- **Allylic** (carbocation): A carbocation on a carbon adjacent to an alkene.
  - Extra stable due to resonance stabilization.

9.2 β-Elimination

- β-elimination is a form of dehydrohalogenation.
- General form.

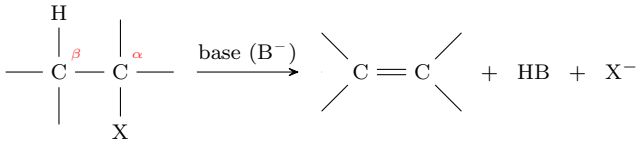
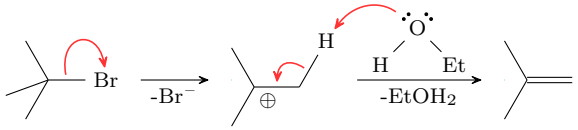
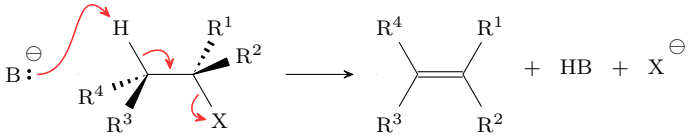


Figure 9.1: Elimination.

- Mechanisms.



(a) E1.



(b) E2.

Figure 9.2: Elimination mechanisms.

- **E1**: Unimolecular elimination.
  - Not a clean reaction — E1 and S_N1 often happen together.
  - They will not ask us to tell which pathway is more favored.
  - Features.
    1. Tertiary alkyl halides are favored (secondary sometimes).
    2. Protic solvents are needed.
    3. We need a weak base/poor nucleophile.
    4. Selectivity: Determined by the alkene stability; we favor forming the more stable alkene (as per **Zaitsev's Rule**).
  - E1 is not a useful reaction to prepare alkenes from alkyl halides since we get a mixture of products and there are selectivity issues.
- **Zaitsev's Rule**: More substituted alkenes are more stable.
  - For secondary carbons, *cis* < *trans* < geminal in terms of stability.
  - Since sp^2 is more electronegative than sp^3 and R is an EDG, more R groups can provide more electrons to stabilize the sp^2 carbons.
- **E2**: Bimolecular elimination.
  - Often very selective, and you can make it very selective.
    - The lack of a carbocation intermediate and the fact that it's a concerted mechanism both contribute to the higher yield.
  - In order to realize E2, the conformation *must* adopt **anti-periplanar geometry**.
    - E2 is a stereospecific reaction.
  - A bulky base (such as Bu^tO^-) is preferred since such a base reduces competition from S_N2.
- **Anti-periplanar geometry**: Two groups of importance are opposite each other and lie in the same plane.
  - Consider the H and X in Figure 9.2b.
- Example: Consider *cis*-1-chloro-2-isopropylcyclohexane in solution with MeONa and MeOH.
  - Only the more stable cyclohexane conformation (with Cl axial and Pr^i equatorial) has hydrogens anti to the chlorine.
  - Both of these hydrogens will undergo E2 elimination with the chlorine, and the trisubstituted product will be the major product (as per Zaitsev's rule).
  - However, if we use *t*-butoxide instead of methoxide, the disubstituted product would be the major product due to sterics.
- Example: Consider *trans*-1-chloro-2-isopropylcyclohexane in solution with MeONa and MeOH.
  - Since the less stable conformation is the reactive one, the reaction will still go, but it will be very slow.
- Take-home summary: For E2, the first priority is anti-periplanar, and then Zaitsev.

12/6:
- Deciding between S_N2 and E2 in secondary cases.

Good	Br^-, I^-
	CH_3S^-, RS^-
	HO^-, CH_3O^-, RO^-, $R-C\equiv C^-$
	CN^-, N_3^-, H_2N-
Moderate	Cl^-, F^-
	CH_3COO^-, $RCOO^-$
	CH_3SH, RSH, R_2S
	$NaHSO_3$, RNH_2, R_2NH, R_3N
Poor	H_2O
	CH_3OH, ROH
	CH_3COOH, RCOOH

Table 9.2: Nucleophilicities in alcohol or water.

  - When you have a strong base, E2 is favored.
    - Examples: OH^-, MeO^-, EtO^-, Bu^tO^-.
  - When you have a good nucleophile that is not too basic, S_N2 is favored.
    - Examples: Br^-, I^-, RS^-, $N\equiv C^-$, N_3^-, PPh_3.

- Deciding between E2 and E1/S_N1.
  - For E2, the role of the base is critical — without a strong base, it will not take place.
  - For E1, the role of the base is not important; ionization is more important.
  - Since ionization is a very slow process, if there is competition between E2 and E1 and a strong base is present, E2 will usually win out because it's so much faster.
  - Primary alkyl halides lead to E2 only.
  - Secondary and tertiary alkyl halides lead to E2 in the presence of a strong base, and E1/S_N1 in the presence of a weak base/solvent.

9.3 Alkyl Halide Equivalents

- Other species that can behave with the above chemistry.
- Consider the following sulfonate ester.

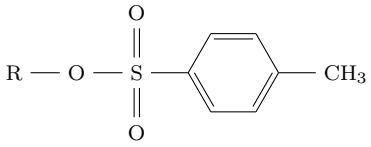


Figure 9.3: A sulfonate ester.

  - Often abbreviated OTs and called tosylate.

- This species is important because we can make it from alcohols with stereoretension.

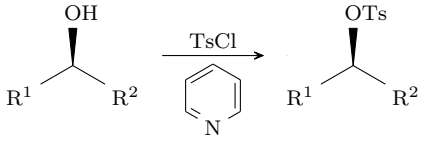


Figure 9.4: Making tosylate species.

  - The species below the arrow above is called pyridine and is often abbreviated Py.
  - The mechanism of the above reaction is not needed.

- You can then hit the product in Figure 9.4 with a nucleophile to perform S_N2.
- Note that like RX, ROTs can also undergo β-elimination (such as E2).

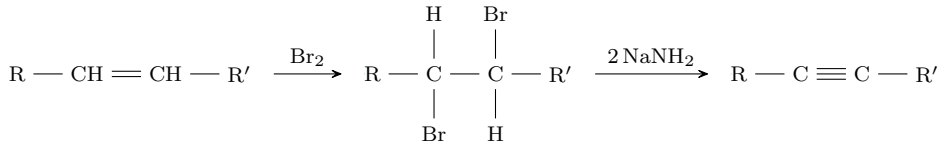
9.4 Alkyne Synthesis

- You can form alkynes from simpler alkynes, alkenes, and ketones (though we don't have to know the last one for this class).
- Alkylation of acetylides with RX via S_N2.

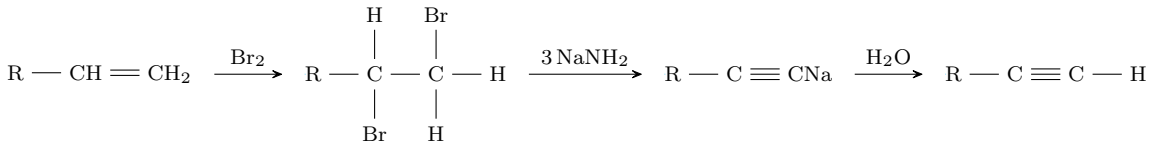
$$\mathrm{H{-}C{\equiv}C{-}H} \xrightarrow[\text{2. R{-}Br}]{\text{1. NaNH}_2} \mathrm{H{-}C{\equiv}C{-}R} \xrightarrow[\text{2. R'{-}Br}]{\text{1. NaNH}_2} \mathrm{R'{-}C{\equiv}C{-}R}$$

  - Start with an acetylide such as $\mathrm{NaC{\equiv}C{-}H}$.
  - React it with an alkyl bromide (RBr) in THF to attach it to that alkyl species at the former bromium site with inverted stereochemistry (yielding $\mathrm{RC{\equiv}C{-}H}$ and NaBr).
  - React the terminal alkyne species with a strong base (e.g., NaH, $NaNH_2$, LDA) to generate a species such as $\mathrm{NaC{\equiv}CR}$.
  - React this with another alkyl bromide ($\mathrm{R'Br}$) to yield the final $\mathrm{RC{\equiv}CR'}$ species.

- **Synthesis**: Making a large and more useful molecule from readily available small molecules.
  - Using alkynes is a very important approach to make carbon-carbon bonds.
- From alkenes.



(a) Internal alkene.



(b) Terminal alkene.

Figure 9.5: Synthesis of alkynes from alkenes.

  - The elimination mechanism for the two pairs of HBr in Figure 9.5a is different from E1 and E2, and we do not need to know it.
  - In Figure 9.5b, we need the third equivalent of base in the second step because once an alkyne species is formed, its acidic proton will react with any base in solution. Thus, if we used only two equivalents, some of the reactant would get converted all of the way to the $\mathrm{R{-}C{\equiv}CNa}$ species, and some would not get converted at all. Therefore, we push all of the reactant to be converted, and then work with the product, quenching with H_2O to get our final desired product.
  - Note that various byproducts are generated that are not shown (they are the predictable ones, though).
  - We can also use chloride here.

9.5 Multi-Step Synthesis

- These problems are the core of organic chemistry, using both our imagination and our knowledge to construct *a* right answer (there are often more than one).
- Tip: Think backwards!
  - Formally, "retro-synthetic analysis," as coined by E. J. Corey, a Nobel laureate at Harvard.
- Example: Construct cyclohexane-1,2-diol from cyclohexanol.

$$\mathrm{C_6H_{11}OH} \xrightarrow{\mathrm{TsCl,\,Py}} \mathrm{C_6H_{11}OTs} \xrightarrow[-\mathrm{Bu^tOH,\,OTs^-}]{\mathrm{Bu^tO^-}} \mathrm{C_6H_{10}} \xrightarrow[2.\,\mathrm{NaHSO_3}]{1.\,\mathrm{OsO_4}} \mathrm{C_6H_{10}(OH)_2}$$

- More examples given.