Chapter 9 – The Chemistry of Alkyl Halides (partial)

Introduction

Chapter 9 follows directly on the heels of topics introduced in chapter 8 by examining three kinds of chemical reactions that alkyl halides engage in:

- Nucleophilic substitution
- β-Elimination (to form alkenes)
- α-Elimination (to form unstable carbenes)

Of course, alkyl halides do other things (for example, we learned in chapter 8 that they can be converted into Grignard and alkyl lithium reagents), but these reactions are *central* to organic chemistry (and much more so than the addition reactions studied in chapter 4 and 5). The principles of chemical reactivity that are learned here will be used on a weekly basis for the rest of the year.

Checklist

When you have finished studying Chapter 9, you should be able to:

1. name and draw alkyl halides
   a. recognize *primary* (1^o), *secondary* (2^o), and *tertiary* (3^o) halides
   b. recognize *alkyl* halides (as compared to *vinyl* and *aryl* halides)
   c. recognize C_α and C_β in an alkyl halide
2. plan and predict the outcomes of the following chemical reactons:
   a. bimolecular nucleophilic substitution (S_N2)
   b. unimolecular nucleophilic substitution (S_N1)
   c. bimolecular base-assisted β-elimination (E2)
   d. unimolecular β-elimination (E1)
   e. base-assisted α-elimination in $CHCl_3$ (leads to a carbine that is captured by an alkene)
3. describe and interpret phenomena associated with the chemical reactions listed in item #2
   a. by drawing detailed mechanisms, complete with curved arrows, stereochemistry (when called for), and alternative resonance structures (when called for)
   b. by drawing reaction energy diagrams
   c. by referring to reaction rate laws
   d. by referring to the structure and energy of key transition states
   e. by referring to the structure and energy of key intermediates, particular *carbocations* and *carbenes*
      i) and by referring to the Hammond postulate
   f. and by referring to other effects (strain, hindrance, resonance, solvent, etc.) that might affect reaction rate or favorability

Top xx Problems for Chapter 9 (incomplete)

All of these problems are drawn from the *Additional Problems* located at the end of the chapter 9.

The top x for chapter 9 are **(incomplete - sorry)**

Supplement

Synthetic planning

S_N2 and E2 reactions are much more useful for making new molecules than are S_N1 or E1 reactions. The results of S_N2 and E2 reactions are more predictable in that we have a good idea where the new functionality will be located (no rearrangements) and what the product stereochemistry will be. S_N1 reactions are used mainly when the substrate has a particularly simple structure and the nucleophile is derived from a protic solvent (H_2O, ROH, RCO_2H). E1 reactions of alkyl halides are almost never employed since the substrates (3^o RX and 2^o RX also lend themselves to the more reliable E2 reactions.)

S_N2 planning. Know what functional groups can be produced from alkyl halides by *functional group transformations*. See Table 9.1. Know what nucleophiles can be used to make these functional groups. Know the base strength of these nucleophiles (or the acid strength of their conjugate acids) so that you can anticipate when E2 elimination might be a competing reaction. E2 mainly competes when S_N2 is slow, i.e., for secondary alkyl halides + basic nucleophiles, and when the nucleophile's conjugate acid has a $pK_a \geq 10$. (Note: <u>None</u> of the *anionic* nucleophiles in Table 9.1 are used in S_N1 reactions because they are all much too basic. *Amines*, though neutral, are too basic too.)

E2 planning. Know what bases and experimental conditions reliably produce elimination instead of substitution. Ch. 9.1B mentions alkoxide salts dissolved in the conjugate acid (alcohol) as frequently used bases. Typical com-

binations include: CH_3CH_2ONa in CH_3CH_2OH, and $(CH_3)_3COK$ in $(CH_3)_3COH$.

Remember to identify all *beta* CH groups in your substrate. Elimination might involve any of these groups. Zaitsev's rule is followed in both E2 and E1 eliminations.

S_N1 planning. This kind of reaction is most successful when the nucleophile is the solvent (neutral, non-basic), i.e., when a solvolysis occurs. Never invoke a carbocation as a starting material; these are too unstable. The electrophile must be an alkyl halide. Likewise, never invoke an anion as a nucleophile because these are too basic (important exceptions are I^-, Br^-, Cl^-; these anions are not basic at all). Therefore, to make ROEt, don't start with R^+ (not available) + EtO^- (much too basic). Instead, combine RX + EtOH and wait for a multi-step S_N1 mechanism to work its magic.

Stereochemical planning. S_N2 reactions always proceed with inversion of configuration at the electrophilic carbon. S_N1 reactions, on the other hand, generally yield a mixture of products. If an S_N1 starting material is an optically active chiral molecule, the product will usually be partially racemized. To simplify things, we often assume that the product will be completely racemic, but this outcome is rarely achieved in practice.

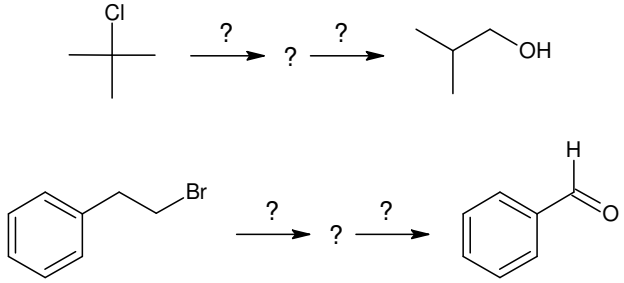
Functional group planning. Eliminations lead to alkenes which can then undergo the transformations that were described in chapters 4 and 5. This means that all sorts of two-step synthetic plans are possible:

$$RX \rightarrow >C=C< \rightarrow \text{you name it}^1$$

Likewise, many functional groups can be introduced by nucleophilic substitutions:

$$RX \rightarrow \text{you name it}^2$$

The upshot of these equations is somewhat daunting: alkyl halides can be the starting point for making all kinds of other molecules. Practice "traveling" the routes that connect different functional groups together until you have a good grasp of the "chemical map" and can find your way around easily. Here are some "simple" two-step problems for you to think about (you need to fill in reagents for each step and draw the molecule that could be isolated after the first transformation):



Some general considerations. A few more seeds to plant:

Water is rarely used as a reaction solvent because most organics are insoluble in water.

Strong acids and bases are always incompatible. When both are present, they neutralize each other before any other interesting chemistry (S_Nx, Ex) can commence. No mechanism and no synthetic plan should combine these reagents.

The best synthetic plan is one that relies on chemical reactions that are favorable, reasonably fast, and *have no competing side reactions*.

Predictions and rationales

Chapter 9 contains an exceptionally long list of end-of-chapter problems. This reflects the fact that nucleophilic substitution and elimination are "tricky" reactions that show up in many contexts. Practice solving as many problems as you can.

Two types of phenomena stand out as being especially important:

- **Relative reactivity** (starting with structural formulas). All kinds of "rules" need to be considered, but you won't know which "rules" to use unless you can smoothly negotiate the next point;
- **Competing reactions** (multiple reaction sites, multiple modes of reactivity, multiple stereoisomers, etc.) When you see an alkyl halide and some reaction conditions, does your mind pick out the most likely mode of reaction?

Here's a study tip. This chapter introduces many "effects" on chemical reactivity. Go through the chapter and list

[1] See chapters 4-5 for ideas.

[2] See table 9.1.

them. Group the "effects" in logical ways, for example, list structural factors that:

- Make one *nucleophile* more reactive than another
- Make one *base* more reactive than another
- Make a reagent more likely to act either as a base or as a nucleophile (this is a *selectivity* effect)
- Make an *alkyl halide* more reactive in S_N2 reactions
- Make an *alkyl halide* more likely to undergo S_N2 reactions (*selectivity* effect)
- Repeat the previous two items for E2, S_N1, and E1 reactions

Obviously, some lists will be longer than others. Another important point: edit and extend them as you work end-of-chapter problems. Each time you work a problem, review the relevant list of effects. Are you thinking about everything you need to think about? Each time you come across another useful effect, reactivity or selectivity, add it to your list. It might even be worthwhile to reference your list to the source material (textbook page, equation, problem, figure) that illustrates this effect.

Another study tip: as you work each problem, make a habit of identifying the mechanism(s) that probably operate. What was your basis for choosing one mechanism? What was your basis for ruling out the others? (Really spend some time thinking about why the other mechanisms are probably irrelevant.) The map on the next page may also prove useful.

Substitution/Elimination Decision Map

(with apologies to 2° RX – you are just too complicated)