Outline Lecture 1 Thursday, January 13, 2000

1. See the Web go to http://www.chem.uky.edu
   a) Click on courses then find 535.
   b) I have also included previous problem sets and tests in this page as well.

2. Various text sources
   ii) R. C. LaRock, *Comprehensive Organic Transformations*
   iii) J. March, *Advanced Organic Chemistry*
   v) journal articles.

3. What is Organic Synthesis?
   a) Cornforth’s definition: Intentional construction of molecules by means of chemical reactions.
   b) Cammers’ 3-part definition
      i) **plan** intentional construction of molecules— retrosynthesis
      ii) **convince** a funding agency or a supervisor that the work can be done and is worth doing
      iii) **carry out** the laboratory work
         a) The last step does not happen until the first two do.
         b) This part is very labor intensive
   c) The main focus of this course is on the planning and the convincing (2.b.i & 2.b.ii above). We will not be in the laboratory.

4. Synthesis is
   a) championship chess -> human against nature, the order you do things in is all important
   b) The profession of architecture -> economical construction with known methods
   c) The profession of the law -> precedent is very important in both fields

5. I can not teach you this whole subject
   a) It is too vast
   b) Synthetic O-chem is something you can pursue for the rest of your life and still feel inadequate. No one knows it all
   c) We are going to skim the surface
      i) Will not talk about reaction after reaction usually used to accomplish some transformation — this stuff is catalogued in books and the literature, and there’s no need for you to memorize it because you can go look it up whenever you want.
      ii) Instead will focus on general strategies and mechanistic rationale
   d) the only way you will be able to pick this stuff up is if you are interested
      i) sorry but I am going to have to work you
      ii) If you are here for an easy grade, **drop the course**!
   e) What does it take to be a good synthetic chemist?
      i) I have seen it pursued in at least two ways.
         a) read the literature and memorized particular xformations
            (1) know who did what when to which molecule.
            (2) keep a deck of index cards on interesting reactions
            (3) memorize which reactions to use for retro{}synthetic transformations


b) have a general interest in chemical transformations  
   (1) care about how mechanisms are determined  
   (2) know the principles of stereochemical control  
   (3) know something about biochemistry and why people make molecules in the 90's.  
   (4) consider concepts like molecular strain and topology and what this means for reactivity.  

ii) invariable synthetic chemist #2 is the better chemist  
   a) physical and inorganic chemists chuckle about syn chem #1  
   b) I am going to teach this course with syn chem #2 in mind  

6. Why do people synthesize organic molecules?  
   a) 1930-1975  
      i) prove structure of a natural product  
      ii) prove it can be done  
      iii) gain insights to reactivity based on structure  
      iv) test synthetic methodology  
      v) physical organic chemical studies  
   b) synthesis in the nineties is done for all of the above reasons and to  
      i) construct nanostructure  
      ii) apply or test a biological utility or theory  
      iii) gain enough synthetic knowledge of the molecular architecture of natural product x to be able to make analogues for drug testing  
   c) knowing how to make molecules is not enough just like knowing how to speak and write is not enough — you have to have something worthwhile about which to speak or write  
   d) to do this you need to know something about chemistry and science that can often be far away from synthesis  

7. A few more historical notes on synthesis  
   a) The art and science of synthesis expanded greatly during 1945-1970 because  
      i) formulation of detailed electronic mechanisms  
      ii) study of molecular conformations (1960's)  
      iii) development of spectroscopic and other physical methods, especially NMR  
      iv) chromatography  
      v) discovery of selective reagents for organic transformations  
   b) the mechanics of retrosynthetic analysis is affect by the above developments  
      i) hey what is retrosynthetic analysis? ... we will get to this later  
      ii) mechanistic formulation, the language developed  
         a) searched for the appropriate starting material in old days (~pre 1945)  
         b) ~post 1945 could talk about organic transformations and what should happen ... synthesis planned based on mechanistic considerations.  
      iii) the invention of chromatography meant that the synthetic chemist no longer has to plan syntheses around molecules that are more likely to crystallize ... great! Meant also that oils were recovered and oils are inherently less pure than crystals ... bummer!  

8. Retrosynthetic thinking  
   a) Working the problem in reverse  
   b) Each step has a sole criterion: the problem should get more simple
c) Conformation and molecular shape cannot be ignored in retrosynthetic analysis
   i) you need to know what you are up against
   ii) don’t underestimate the problem! Evaluate the structural complexity at the appropriate level!
      a) you want to render the structure in a conformational drawing
      b) build a ball and stick model
      c) perhaps model the structure computationally
      d) consider strain in the structure!
   iii) Simplicity versus complexity
      a) in order to know which direction to go in you must know what makes a molecule complex.
      b) We are going to spend the next class time discussing molecular complexity and then retrosynthesis
   d) We will use molecular modeling in here to solve synthetic problems
      i) I will tell you the basics about molecular modeling
      ii) Molecular models are essential in this class

9. The terminology of stereochemistry — Review the Cahn, Ingold, Prelog rules in a textbook if you think this is necessary. Also, see stereochemical glossary on Web.
   a) Chiral, achiral compounds.
   b) Stereogenic, nonstereogenic centers.
   c) Enantiomers, diastereomers.
   d) Prochiral, prostereogenic.
   e) Enantiotopic, diastereotopic atoms and faces. Si and Re faces of C(sp^2).
   f) Ways of drawing stereochemistry: tapered and untapered bold and hashed lines.
   g) For two adjacent stereocenters, we can use
      i) \((R^*,R)\) and \((R^*,S)\) (the * means relative, not absolute)
      ii) for cyclic structures, cis and trans
      iii) threo and erythro (very old-fashioned)
      iv) syn and anti (for a chain drawn in zigzag fashion)
      v) like and unlike (only Europeans use this one)

10. The importance of the literature
   a) You can’t know it all. Don’t even begin to think you can.
   b) Precedent is incredibly important
      i) best way to shut up a critic is to prove it’s been done before.
      ii) But make sure your precedent is relevant and as close to what you want to do as possible!
   c) How do you find precedent?
      i) Computer searches
         a) Beilstein
         b) Chemical Abstracts
         c) Science Citation Index (Web of Science)
         d) ACS journals can be searched electronically
         e) Don’t use generic search services like Yahoo or Altavista
      ii) Encyclopedias
         a) *Comprehensive Organic Synthesis*
         b) *Comprehensive Organic Functional Group Transformations*
c) *Encyclopedia of Reagents for Organic Synthesis*

   d) Houben–Weyl’s *Methoden* (latest volumes are in English, but organic chemists cannot be afraid of German!)

   (1) organized by functional groups — discusses preparation (*herstellung*) and transformations (*umwandlung*)

   (2) hard to find some of the articles, but more recent volumes show the functional groups on the spine

iii) Reference monographs

   a) March
   b) Larock
   c) Carey & Sundberg
   d) Michael B. Smith
   e) Greene’s *Protective Groups in Organic Synthesis*
   f) All of these works have limitations

iv) Book series

   a) *Organic Reactions*

      (1) absolutely the best place to find info about a reaction, if there’s an article

      (2) look in most recent volume for subject index for all volumes

      (3) discusses scope and limitations of particular methods and gives exhaustive list of all examples to date of article

   b) Patai’s *Chemistry of the Functional Groups* (very dated now)

v) Monographs

vi) Review articles (not referenced in Beilstein!)

   a) *Chemical Reviews*
   b) *Synthesis*
   c) *Tetrahedron*
   d) *Angewandte Chemie*
   e) *J. Org. Chem* lists recent reviews quarterly

vii) Aldrich catalog

   a) Find out what’s commercially available.
   b) Cost makes a difference, too! $1/g or less is considered cheap. $10/g or more is considered expensive.
   c) The catalog itself is free
   d) There are other catalogs, but Aldrich is about as comprehensive as they come