

## COMMON SYNTHETIC SEQUENCES FOR OCHEM I

Students frequently get overwhelmed by the increasingly large number of organic reactions and mechanisms they must learn. This task is made particularly difficult by the perception that it is just “busy work,” and that it serves no purpose other than to meet an academic requirement. It is true that a lot of organic reactions seem to lack meaning in and of themselves, but obviously they are not useless. Unfortunately students do not get exposed to the contexts in which this information comes to life until later, or sometimes never. The context of most immediate relevance from the point of view of the organic chemistry student is in the application of these reactions in synthesis.

**A synthesis is a series of two or more reactions designed to obtain a specific final product.** A synthetic step (not to be confused with a mechanistic step, which is something entirely different) is a single reaction that must be conducted separately from the others in a synthesis. Therefore the number of steps in a synthetic sequence is the same as the number of reactions that must be conducted separately, that is to say, the number of reactions that make up the sequence. The concept of synthetic strategy refers to the design of the most efficient combination of reactions that will yield the desired final product. This concept is widely used in R&D departments in the pharmaceutical industry to obtain synthetic drugs of many kinds. This type of research brings together widely different fields of science such as biochemistry, organic chemistry, biology, and even computer science into a single integrated task: the task of drug discovery.

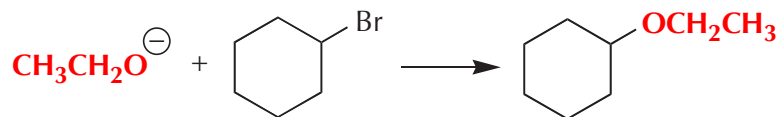
Another context in which organic reactions acquire meaning is in biochemistry. Many of the reaction types discussed in introductory organic chemistry, such as nucleophilic substitutions, eliminations, and oxidations and reductions actually take place in biological systems. There are some differences in the way these reactions happen in biological systems as opposed to the organic chemistry lab. For example most biological reactions take place in water as the medium, not in organic solvents like methylene chloride. Another difference is in the catalysis. In the vast majority of biological systems reactions are catalyzed by enzymes, which are organic macromolecules that have a high degree of specificity and precision. For example, at the stereochemical level they are capable of distinguishing one enantiomer from another. They can catalyze the formation of a specific stereoisomer with 100% efficiency. By way of contrast, one can use many catalysts in the organic chemistry lab that could not possibly be used in biological systems. However, it is surprising that the same mechanistic principles studied in organic chemistry courses, such as the rules of proton transfers, nucleophilic attacks, and steric interactions actually apply in almost the same form in bioorganic mechanisms. Thus, an understanding of the physiology of an organism at the molecular level requires a solid understanding of organic mechanisms and reaction types.

With that in mind, we now turn to the task of learning a few basic synthetic sequences that a beginning organic chemistry student can use to get started in the art of synthetic design. A typical synthetic problem requires the design of a specific molecule or functional group from simple starting materials that can be obtained commercially, or which are readily available in the lab. It is then up to the synthetic chemist to choose from a variety of organic reactions those that will accomplish the task most effectively. Needless to say, this is an art as much as it is a science, and only experience can bring about improved synthetic skills.

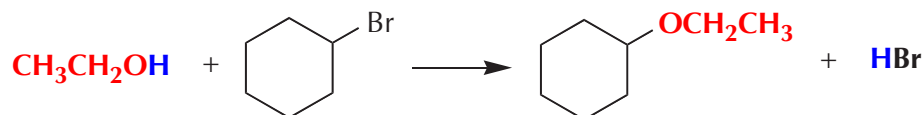
## 1. STARTING WITH AN ALKANE, PROVIDE A SYNTHESIS FOR A MOLECULE THAT HAS A FUNCTIONAL GROUP Z, WHERE Z IS A NUCLEOPHILE.

First thing to remember is that in nucleophilic reactions, the nucleophile replaces the leaving group unchanged only if it originally carried a negative charge. A neutral nucleophile, typically water or an alcohol, will lose a proton in the process of replacing the leaving group. Therefore, it is the conjugate base of such nucleophile that actually replaces the leaving group.

### Sn2 reaction with a negatively charged nucleophile



### Sn1 reaction with a neutral nucleophile (most frequently $\text{H}_2\text{O}$ or $\text{ROH}$ )

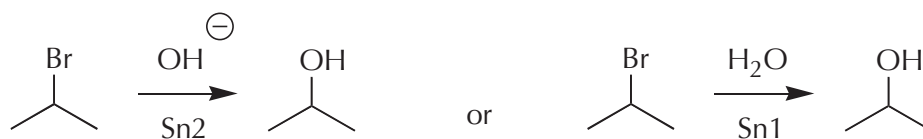


At this level we are acquainted with only one major type of leaving groups, which are the halogens (Cl, Br, and I). So if we're supposed to start the synthesis from an alkane, we must first fit it with a good leaving group, namely a halogen. Once we have a leaving group in place we can bring in a number of different nucleophiles to replace it, depending on which functional group we're trying to obtain at the end.

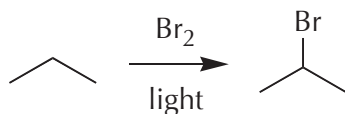
**EXAMPLE 1.** From propane, make 2-propanol (isopropanol). In other words, how can the following transformation be accomplished?



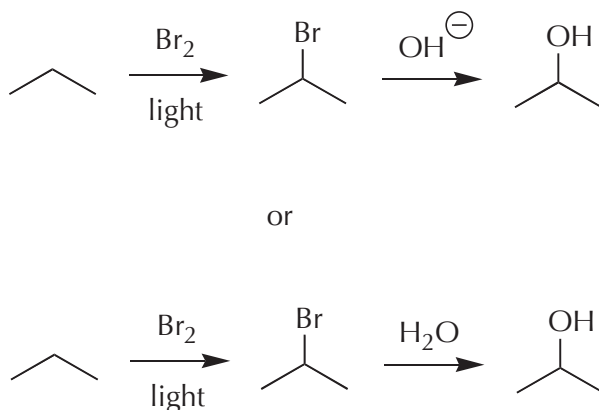
Obviously we don't have the tools to do this in one step. So we'll need at least two steps to do it. A **retrosynthetic analysis starts from the target product and works backwards step by step until it arrives at the desired starting material.** In a retrosynthesis we start from the end and worry only about the step we're working on, momentarily forgetting the rest of the requirements. In this case, we notice that the target product is an alcohol, and alcohols contain the OH group, which can be a nucleophile. To use a nucleophile we must first have a molecule with a good leaving group (halogen). Therefore the last step in the synthesis can look something like this:



Having solved the last step, now we worry about how we're going to obtain the bromide (isopropyl bromide). In a flash of insight, we recall that in a previous part of the course we learned how to make bromides from alkanes (free radical halogenation reaction – bingo!). Feverishly, we try to recall the conditions that led to it, and suddenly we recall that all we need is an alkane and bromine in the presence of light. We desperately scramble for a pencil to jot that down before we forget it and come up with the following:



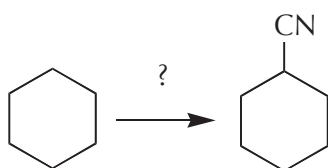
Not bad, we pat ourselves on the back. Now we're through with the second to the last step of the synthesis. With a rush of adrenaline now pumping through our veins, we now ask what the next step would be. How can we obtain propane from...? Wait a minute! We're supposed to start the synthesis with propane. Does that mean we're done? You betcha! The complete synthesis would then look something like this:



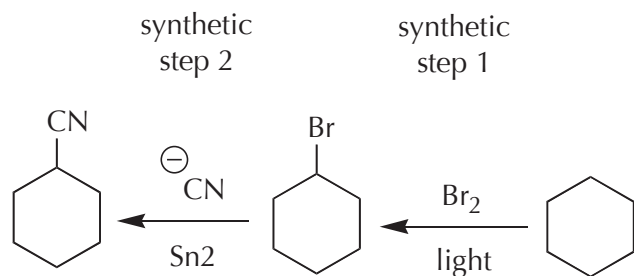
Notice that a synthetic sequence does not show all the substances that are actually present in the reaction medium, especially not the inorganic ones such as HBr. For the sake of clarity, the sequence shows only those materials of direct relevance to the task at hand, namely those organic substances whose fate we're interested in following due to their relationship to the end product.

Also notice that a synthetic problem typically has many solutions. For example, in the synthesis above we could've used chlorine as the leaving group instead of bromine. We can use water as the nucleophile or OH ion. These are all equally effective solutions. The final choice is therefore frequently based on factors other than those directly related to the chemistry, for example price and availability of the substances required, their toxicity, etc.

**EXAMPLE 2.** From cyclohexane prepare cyclohexane nitrile:

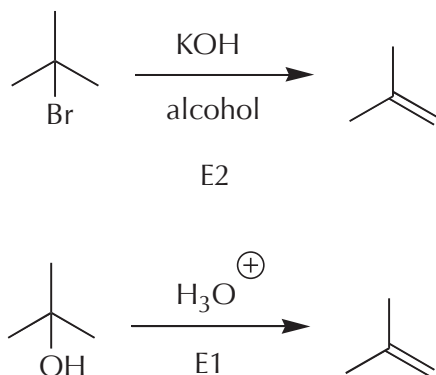


Nothing can stop us now. We immediately realize that CN is one of the nucleophiles we learned about in the chapter on nucleophilic substitutions. After a quick retrosynthetic analysis we whip out the following scheme (shown in reverse because we're working backwards, remember?):



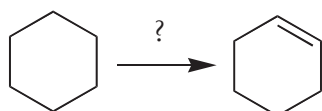
## 2. STARTING WITH AN ALKANE, PROVIDE A SYNTHESIS FOR AN ALKENE WITH THE SAME NUMBER OF CARBONS.

First question to ask in a lot of synthetic problems is, given the functional group I'm supposed to prepare, how many ways do I know right now that I can use to form that particular functional group? In this case I'm supposed to prepare an alkene. At this point the only way I know to prepare alkenes is by means of elimination reactions. According to the lecture notes, the most efficient approaches are the E2 reaction (dehydrohalogenation of bulky halides in the presence of strong bases), and the acid-catalyzed E1 dehydration of secondary and tertiary alcohols.

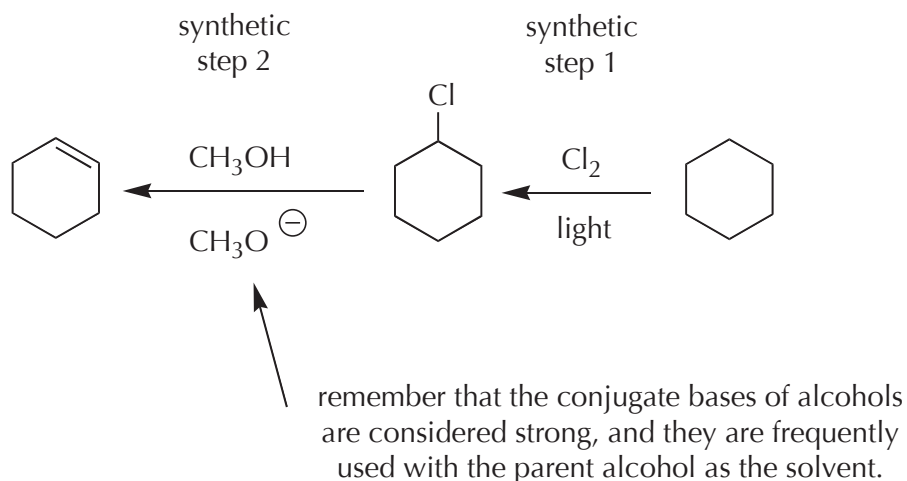


The E2 reaction requires a halogen as the leaving group, so I can prepare an alkyl halide from the required alkane by the free radical halogenation reaction, just as I did before. The E1 reaction on the other hand requires the preparation of an alcohol as the starting material. However, I find that at this point the only preparations of alcohols that I know start with alkenes (acid catalyzed addition of water, oxymercuration reaction, and hydroboration sequence). It would be redundant to start with an alkene to prepare an alcohol, only to dehydrate it back to alkene. Therefore, at this point, I will stick with the E2 reaction because it is more compatible with the requirements of the problem.

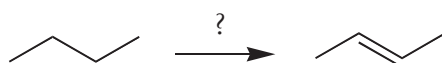
**EXAMPLE 3.** Starting with cyclohexane, provide a synthesis for cyclohexene.



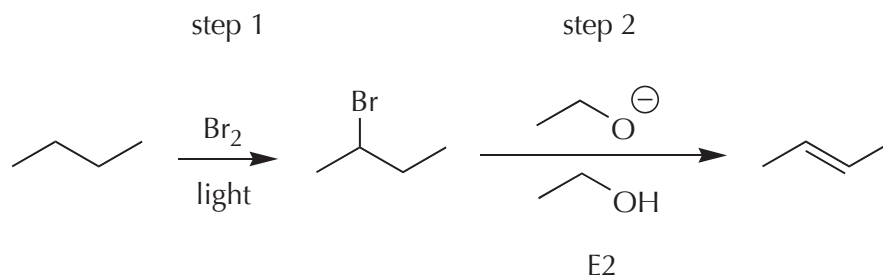
No problemo. By now I'm a whiz of organic synthesis. so here is the quick solution.



**EXAMPLE 4.** From *n*-butane, prepare 2-butene.



Again, no problem. A retrosynthetic analysis yields the following solution.



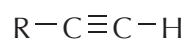
The only thing to note in this approach is that the last step above would yield a mixture of *cis* and *trans* isomers, since in this particular case, that step would not involve a stereospecific reaction.

### 3. PREPARE A SUBSTITUTED ACETYLENE.

A monosubstituted acetylene can be prepared from acetylene by a combination of acid-base reaction followed by an  $S_N2$  displacement. A disubstituted acetylene can be prepared from a monosubstituted acetylene by a similar reaction sequence. Before proceeding, make sure you understand this nomenclature by consulting the relevant section in the chapter on alkynes.



acetylene

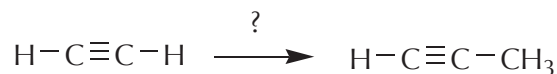


monosubstituted  
acetylene

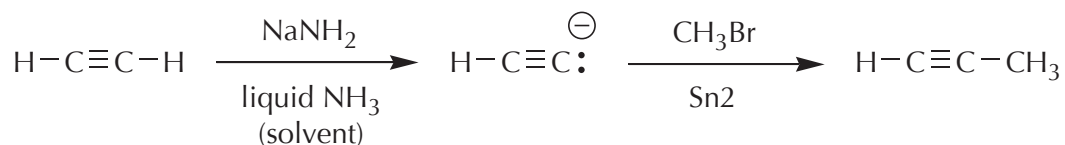


disubstituted  
acetylene

**EXAMPLE 5.** From acetylene prepare methylacetylene.

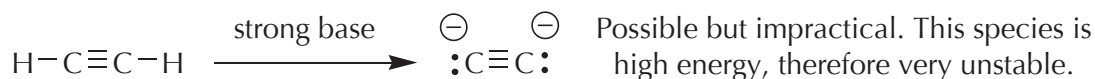


My first task is to remove the acidic proton from acetylene to convert it into its conjugate base. I can then use this conjugate base as a nucleophile in an  $\text{S}_{\text{N}}2$  reaction with the relevant alkyl halide to yield the desired product.

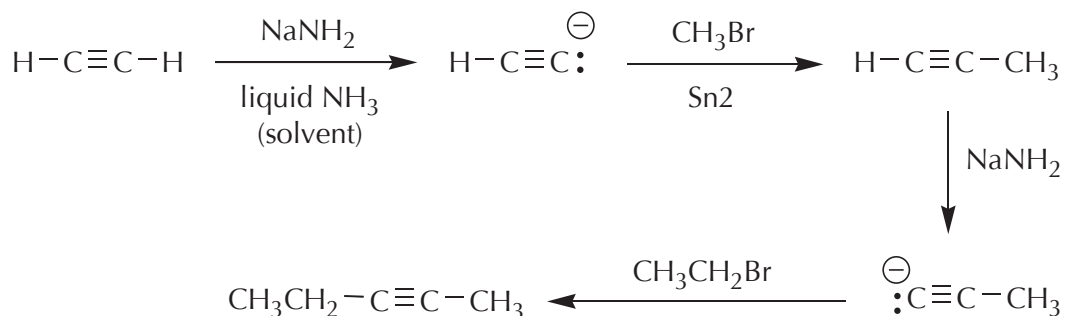


Something to note here:  $\text{NaNH}_2$  is an ionic salt. The actual base is  $\text{NH}_2^-$  (amide ion). Sodium remains a spectator ion and as such does not directly participate in the process. Second thing to note is that **to perform the first step efficiently, a base whose  $\text{pK}_{\text{a}}$  is higher than the  $\text{pK}_{\text{a}}$  of acetylene must be used. Otherwise equilibrium would not be favorable to formation of the conjugate base.** In this case, acetylene has a  $\text{pK}_{\text{a}}$  of 25, and  $\text{NH}_2^-$  has a  $\text{pK}_{\text{a}}$  of about 38 (as measured by the  $\text{pK}_{\text{a}}$  of its conjugate acid, ammonia). Because 38 is greater than 25,  $\text{NH}_2^-$  can be effectively used to deprotonate acetylene.

Disubstituted acetylenes follow a similar reaction sequence, but the deprotonation steps must be conducted separately. Trying to remove both protons from acetylene simultaneously would not work very well because the potential energy of the resulting species is too high. That is to say, it's not very stable.



**EXAMPLE 6.** From acetylene prepare methylethylacetylene.



The synthetic sequence has four steps total.

#### 4. SPECIFICALLY PREPARE PRIMARY, SECONDARY, OR TERTIARY ALCOHOLS USING CARBON NUCLEOPHILES SUCH AS ALKYNIDE IONS AND GRIGNARD REAGENTS..

These sequences are extensively discussed in the notes and in the Wade textbook (5th ed.). Please refer to the following sections and exercises from the textbook to illustrate this type of synthetic problem.

**Chapter 9:** Section 9–7B. See solved problem 9–2, and problem 9–8.

**Chapter 10:** Section 10–9. See solved problem 10–2, and problems 10–13 through 10–15.

In addition, work as many related problems as possible from the end of the chapters, such as problem 10–39.