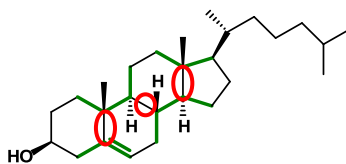


Practice Questions for Chapters 1-8
CHEM 4000A – Medicinal Chemistry

1. The structure of cholesterol is shown below:



- (a) Identify all of the endoendo bonds in cholesterol. *circled in red*
- (b) Identify all of the exendo bonds in cholesterol. *see thick green bonds*
- (c) If we were performing a retrosynthetic analysis on cholesterol and began by making a single disconnection, it should not be one of the endoendo bonds. Why not?

Making a disconnection at any of the endoendo bonds would mean that we would need to make a synthetic intermediate containing a medium sized ring – a nine-membered ring if the bond between the five- and six-membered rings is chosen, or a ten-membered ring if one of the other two endoendo bonds is chosen. Medium sized rings are difficult to form and should be avoided as synthetic intermediates.

- (d) Generally speaking, what would be a better approach to a retrosynthetic analysis of cholesterol?

Instead of making a series of one-bond disconnections, some sort of tandem reaction in which several bonds are formed in a single reaction would be preferable.

2.

- (a) There are hundreds (possibly thousands?) of ways to oxidize a secondary alcohol to a ketone. Give two examples of reaction conditions that can accomplish this.

Oxidizing reagent that you likely saw in CHEM 2600 would include:

- *PCC (pyridinium chlorochromate = pyridine + HCl + CrO₃),*
- *PDC (pyridinium dichromate = pyridine + H₂Cr₂O₇),*
- *Jones oxidation (sulfuric acid + CrO₃), and*
- *Swern oxidation (oxalyl chloride + DMSO then add alcohol then add Et₃N).*

A few of you also mentioned :

- *Dess Martin oxidations (contain an iodine atom in a high oxidation state) or*
- *TPAP/NMO (catalytic tetrapropylammonium perruthenate = Pr₄N⁺ RuO₄⁻ in the presence of stoichiometric N-methylmorpholine oxide)*

in your assignments.

- (b) Which of your two examples is greener? Explain.

Of the examples listed above, PCC and PDC are the least green (in my opinion). Cr(VI) salts are highly toxic and they're being used stoichiometrically. Pyridine is not a particularly green substance either (with the potential to cause a number of medical issues including male sterility). Jones isn't much better (if at all). It may not have the pyridine, but it still uses a Cr(VI) salt and concentrated strong acid.

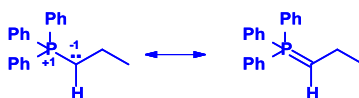
The Swern oxidation requires cooling below -60 °C for the first step – which is not particularly green.

Dess Martin reagent is made from 2-iodobenzoic acid, so a large number of atoms are “wasted” since none of the atoms in the 2-iodobenzoic acid are actually incorporated into the ketone.

TPAP-NMO uses a transition metal (Ru) but in catalytic amounts. It does get reoxidized using stoichiometric NMO, so the reaction is not perfectly green but at least it runs at room temperature.

A few of you referenced oxidizing agents bound to beads in your assignments. They would also be arguably green choices.

3. We saw two different reactions involving ylides as reagents.
- (a) The Wittig reaction involved a phosphonium ylide reacting with a carbonyl. Draw both resonance structures of one example of a phosphonium ylide.



- (b) We also saw a reaction involving a sulfonium ylide reacting with a carbonyl. Draw both resonance structures of the sulfonium ylide.

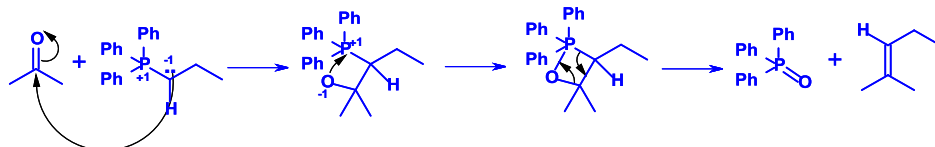


- (c) Looking at your answers to (a) and (b), define the term “ylide”.

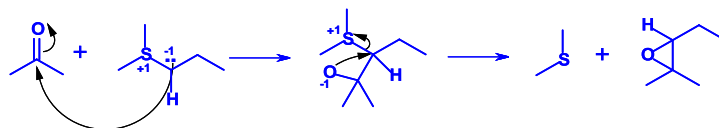
An ylide is a molecule which, in its octet-rule-obeying resonance structure is a Zwitterion with a negative charge on carbon and a positive charge on an adjacent heteroatom.

- (d) What is the main difference between the reaction of a carbonyl with a phosphonium ylide vs. with a sulfonium ylide?

A phosphonium ylide reacts with a carbonyl to give an alkene:



A sulfonium ylide reacts with a carbonyl to give an epoxide:



4. Diethylzinc (Et_2Zn) is often used a source of nucleophilic carbon.
- (a) Would you expect this to be a hard nucleophile or a soft nucleophile? Explain.

I would expect diethylzinc to be a soft nucleophile.

As a point of reference, we know that organocopper compounds act as soft nucleophiles.

Zinc is immediately to the right of copper on the periodic table so zinc is expected to be slightly more electronegative than copper. As such, a C-Zn bond should be slightly less polar than a C-Cu bond (since C is more electronegative than both metal), giving a carbon atom with a slightly less negative charge. Because the charge density of the nucleophilic carbon atom is therefore quite low, it will be a soft nucleophile.

- (b) Diethylzinc is pyrophoric (catches fire easily in the presence of water or air). Why?

Compounds containing nucleophilic carbon atoms are usually also strong bases.* When exposed to water (even moisture in the air), the diethylzinc deprotonates it in an exothermic reaction producing ethane gas and zinc(II) oxide. Heat + volatile alkane = potential for fire. ☺

* Cyanide anion is an exception. It would be considered a weak-to-moderate base since it has a conjugate acid with a pKa of 9.

5. In this course, we discussed three of the four main approaches influencing choice of bond-set. (The fourth approach was “use synthetic methods in which you already have expertise”.)

(a) What is a bond-set?

A bond-set is the set of bonds in a target molecule that are disconnected in a retrosynthetic analysis.

In the forward synthesis, these are the bonds that will be created by reactions (rather than being brought in as parts of pre-existing starting materials).

(b) What were the three approaches we discussed? Briefly describe each.

1. Functional group oriented approach to synthesis

Use the heteroatoms in the target molecule to choose a bond-set consisting of (where possible) natural synthons (a^1 , d^2 , a^3 , d^4). This approach takes advantage of natural reactivity patterns of carbonyl groups, nitriles, etc. (carbon attached to heteroatom is δ^+ therefore electrophilic; next carbon can be deprotonated to give anion since negative charge will be delocalized onto heteroatom, etc.)

2. Skeleton oriented approach to synthesis

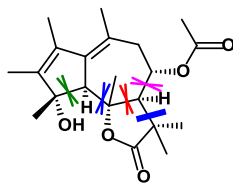
Choose a bond-set that breaks the molecule into fragments with simpler shapes. In molecules with branches, this will tend to involve breaking at the branching point so that two linear synthetic intermediates (or a ring and a linear synthetic intermediate) are obtained.

3. Building block oriented approach to synthesis

This usually means one of two things:

- Repeating units are identified within the target molecule (or a precursor to the target molecule). A bond-set is chosen to break the target molecule into these repeating units. Thus, a single starting material can be used to make multiple fragments of the target molecule, simplifying the synthesis (since there are fewer starting materials or synthetic intermediates to make).
- Units resembling widely available materials (often sugars, amino acids or natural products such as menthol, camphor, etc.) are identified within a molecule. A bond-set is chosen to break the target molecule into units that either are or can be made from these widely available materials. This approach was often used as a means to introduce chirality centers.

6. The structure of matricin is shown below.



(a) Identify a disconnection that would give an a^1 and a d^2 synthon. *see X on figure above*

(b) If I'm counting correctly, there are four possible answers to part (a).

Which is/are best? Which is worst? Why?

The red X represents the worst disconnection. Disconnection of this endo-endo bond gives a 10-membered ring as a synthetic intermediate, and medium sized rings are to be avoided.

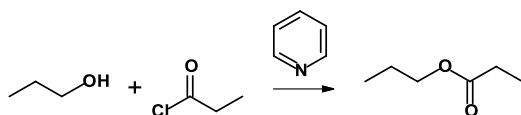
I would tend to prefer the blue X since that gives two five-membered rings connected by a chain. That looks to me like the least complex synthetic intermediate.

An argument could probably be made for either the pink or green X as being good alternatives. Whichever your choice, I'd want to see what type of synthetic intermediate was produced by each disconnection and you should be looking to minimize complexity of the synthetic intermediates.

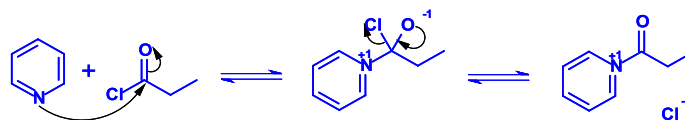
(c) Identify a disconnection that would give an a^2 and a d^2 synthon. *see thick blue line*

- (d) Why is an a^2-d^2 disconnection usually considered inferior to an a^1-d^2 synthon?
 a^1 and d^2 are natural synthons. If we consider that any heteroatom can be generated from the oxygen of a carbonyl compound, the carbonyl carbon is naturally electrophilic (i.e. natural a^1 synthon), the α carbon is nucleophilic in enol or enolate form (i.e. natural d^2 synthon).
 a^2 is an umpoled synthon. To generate an electrophilic site at the α carbon, we must attach a leaving group. This usually requires extra synthetic steps.
 So, the natural-natural synthon pairing is favoured over the natural-umpolung synthon pairing.

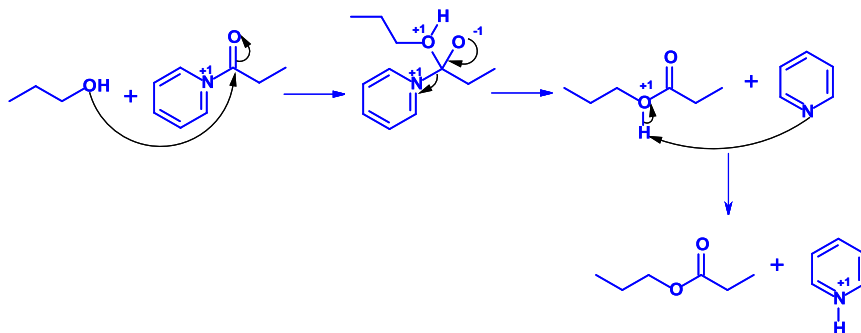
7. When an alcohol is reacted with an acid chloride, an amine such as pyridine is usually included as a nucleophilic catalyst. Propose a mechanism for the reaction below and explain how the inclusion of pyridine accelerates the reaction.



Pyridine is a better nucleophile than the alcohol (because N is less electronegative than O, so neutral N is a better electron donor than neutral O). So, it attacks the electrophilic carbon of the acid chloride. This gives a tetrahedral intermediate which collapses, kicking out one of the two good leaving groups. (If it kicks out the pyridine, the starting materials are regenerated. If it kicks out the chloride, the product shown results.)

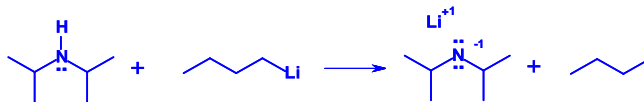


The N^+ bonded to the carbonyl makes the carbonyl carbon a better electrophilic site (compared to the carbon of the acid chloride), so now it is better able to react with the alcohol. Pyridine is still an excellent leaving group (if not quite as good as chloride; weaker bases make better leaving groups), so the reaction proceeds as follows.



Thus, the pyridine is regenerated (see second arrow in second part of mechanism), making it a catalyst. Unusually, it is a catalyst that is typically used in stoichiometry quantities because of its secondary role – deprotonating the final product. Its catalytic role, however, is to generate a better electrophile to react with the not-very-nucleophilic alcohol.

8. LDA is made by reacting diisopropylamine with butyllithium.
 (a) Write a balanced chemical reaction for this reaction (including structures of all reactants and products).

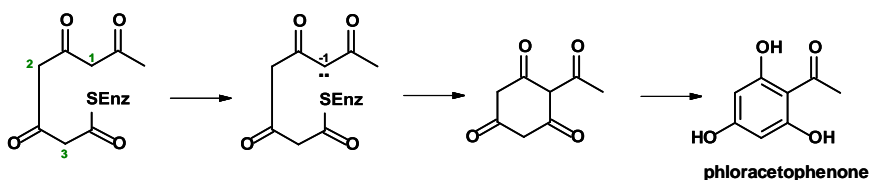


- (b) Both LDA and butyllithium are strong bases. So, why would we ever want to make LDA instead of just using butyllithium?

Butyllithium is a nucleophilic strong base. This means that, in some cases, it will act as a nucleophile instead of a strong base. For example, it cannot be used to deprotonate α to a carbonyl to make an enolate. This is because it will act as a nucleophile, attacking the carbonyl carbon instead.

LDA is a non-nucleophilic strong base. Even though it is a slightly weaker base than butyllithium, the bulky isopropyl groups prevent it from acting as a nucleophile, so it is a better choice for making enolates (or for other reactions in which there is an electrophilic site in addition to the acidic hydrogen).

9. The biosynthesis of phloracetophenone is shown below.



SEnz stands for a sulfur atom that is part of an enzyme.

Explain what is going on in each step of this biosynthesis. You may use generic acids (HA) and bases (B) in any mechanism as it is reasonable to assume that there are enzymes present with both acidic and basic sites.

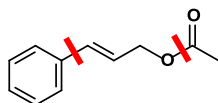
In the first step, a relatively acidic site ($pK_a \sim 10$) is deprotonated. The negative charge is delocalized onto two different oxygen atoms, stabilizing the anion shown.

In the second step, the nucleophilic carbanion attacks the electrophilic carbon of the thioester. A tetrahedral intermediate is formed, and EnzS^- is the eventual leaving group. (It's a good leaving group since S is large so the charge density is fairly low. Also, S is a reasonably electronegative atom.)

The final step is a tautomerization. All three ketones in the ring tautomerize to enols, giving an aromatic ring. The generation of aromaticity is what drives this step forward.

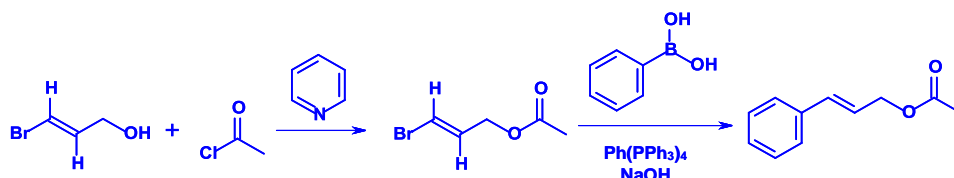
Note that there are three different carbons with acidic hydrogens in the initial starting material (numbered 1, 2 and 3 on the original reaction equation). There is likely an equilibrium involving the three different carbanions that can be formed (unless enzyme geometry controls this step). The carbanion formed at carbon 2 cannot attack any of the electrophilic carbonyl carbons as that would lead to an unfavourable 4-membered ring. The carbanion formed at carbon 3 can and will attack the top righthand carbonyl carbon to give a different six-membered ring leading to a different natural product.

10. Propose a synthesis of cinnamyl acetate (shown below). You may use any starting materials that you might reasonably expect to be commercially available as long as no single starting material contributes more than four carbon atoms or one benzene ring to the final product.

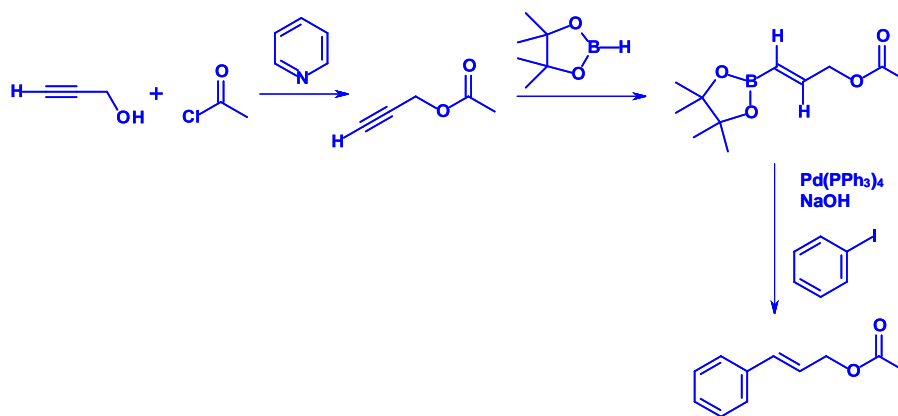


I would probably go with the bond-set shown above. The ester should be fairly straightforward to prepare from an alcohol and an acid chloride (or anhydride) using the method described in question 7. I have a wide variety of options for attaching the benzene ring to the alkene:

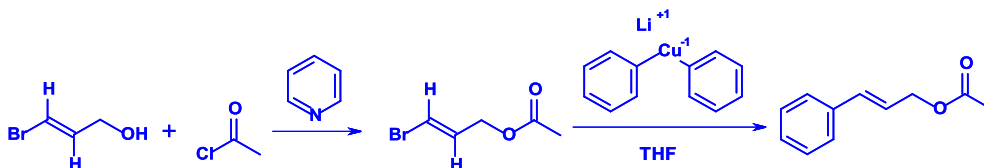
- I could do a Suzuki coupling. If I choose this option, I'd want to make the ester first since an alcohol may interfere with the reaction. (I could protect the alcohol, do the coupling, remove the protecting group then make the ester, but that's more work and less efficient.) From a practical perspective, I'd have the boronic acid (or boronate ester) on the benzene ring and the bromide or iodide on the alkene because I suspect those materials are more likely to be commercially available. Use of NaOH would have to be carefully controlled so that it doesn't saponify the ester (convert it back to alcohol + carboxylic acid). If that turned out to be implausible, I'd be back to the "protect the alcohol" approach.*



- If I couldn't find the right bromide or iodide, I could make a boronate ester by hydroboration of the alkyne instead:*



- I could make a cuprate from phenyllithium and add that to the vinyl bromide (or vinyl iodide). Again, I'd want to make the ester first so that I don't run into problems with the alcohol (which will get deprotonated by the cuprate). This assumes that the vinyl bromide (or iodide) is commercially available.*



- I could make a Grignard from bromobenzene and use that to attack an aldehyde, giving an alcohol followed by elimination of water to give the double bond (E1 reaction – use H_2SO_4). If I take this approach, I should not make the ester first as the Grignard might attack it as well. (The aldehyde *is* more reactive, but it would be risky to try adding such a reactive nucleophile to one in the presence of the other.) So, I have to protect the alcohol then do the Grignard addition followed by dehydration. I could choose a protecting group that is acid-sensitive so that it falls off during the dehydration step. Finally, I make the ester as shown in the syntheses above. The main drawback to this approach is that, while the trans double bond should be the major product, there may be some cis double bond as a contaminant (since the elimination step is not stereospecific).

