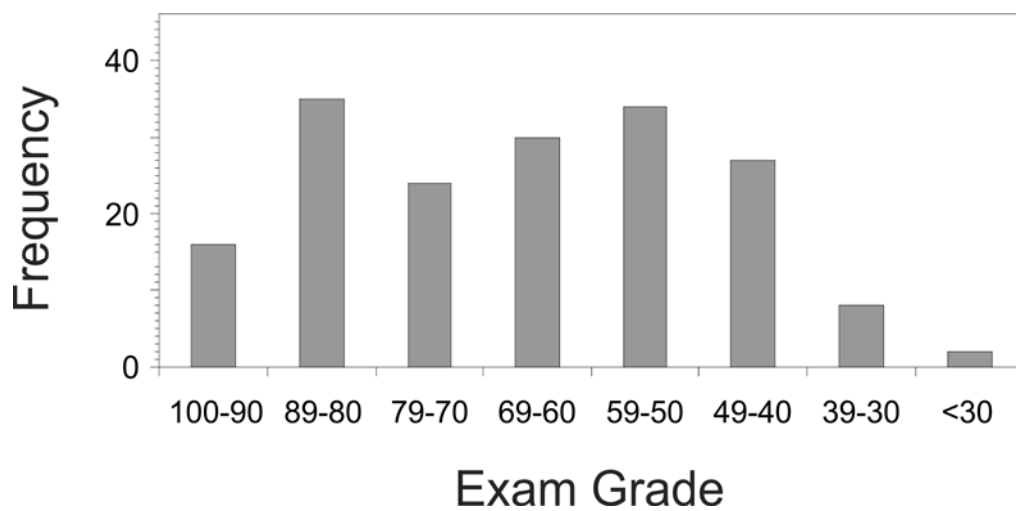
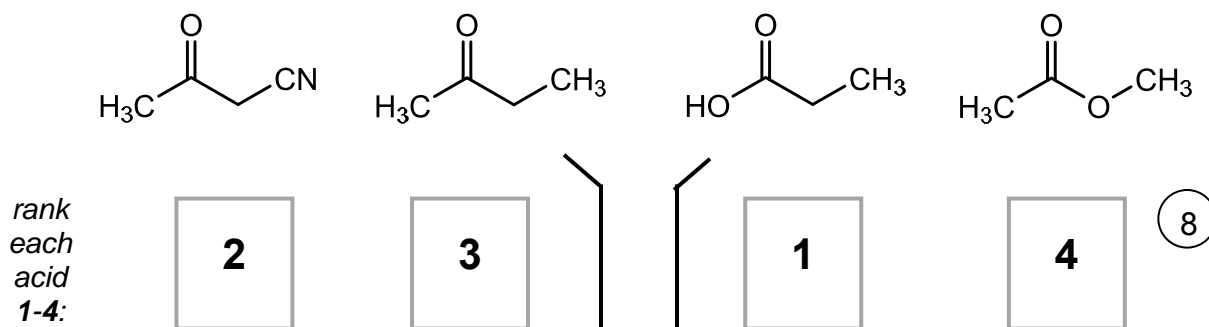


**Exam 3
Answer Key**

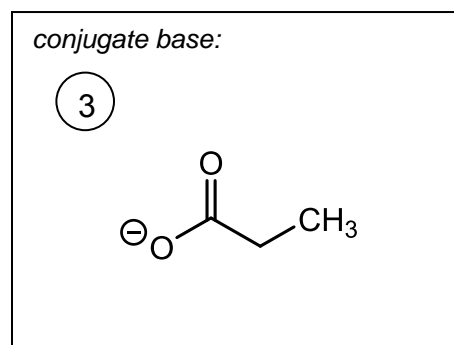
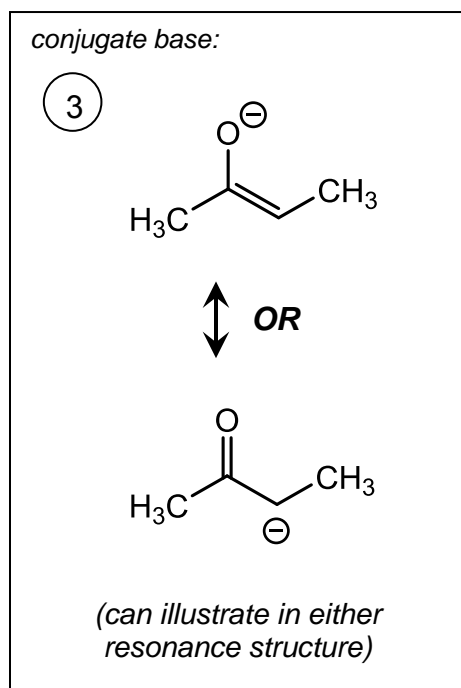
Exam 3 Mean: 67
Exam 3 Median: 67
Exam 3 St. Dev.: 17



1. (14 pts) Each of the four carbonyl-containing compounds below is acidic, and would be deprotonated by a strong base like amide anion (NH_2^-). Rank each molecule **1** through **4** in terms of its acidity, from most acidic (**1**) to least acidic (**4**). Then, for the two acids in the middle, draw the preferred conjugate base structure that would be generated by deprotonation with sodium amide (NaNH_2).



NaNH_2 deprotonates these to:



Given the choice between giving up a proton at the α -carbon or oxygen, a carboxylic acid will lose the proton at oxygen.

The ketone also has a choice; it can be deprotonated at the less substituted carbon on the left, or the more substituted carbon on the right. Here, deprotonation occurs on the right. Unless deprotonation occurs under a very narrow set of conditions intended to generate a kinetic enolate, α -deprotonation will make the most stable (thermodynamic) enolate. In this case, that's the (*Z*)-enolate that puts the two methyl groups opposite each other.

Rubric:

8 points for the correct acidity sequence.

4 points partial if two numbers are switched (but the other two are correct).

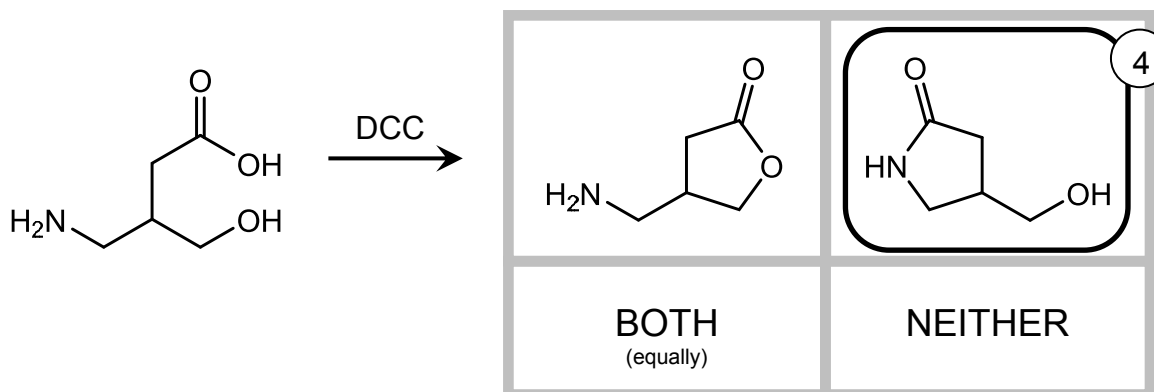
4 points partial for a transposed endpoint. This is true for 1-2-4-3, or 3-4-2-1.

2 points partial for just one number correct.

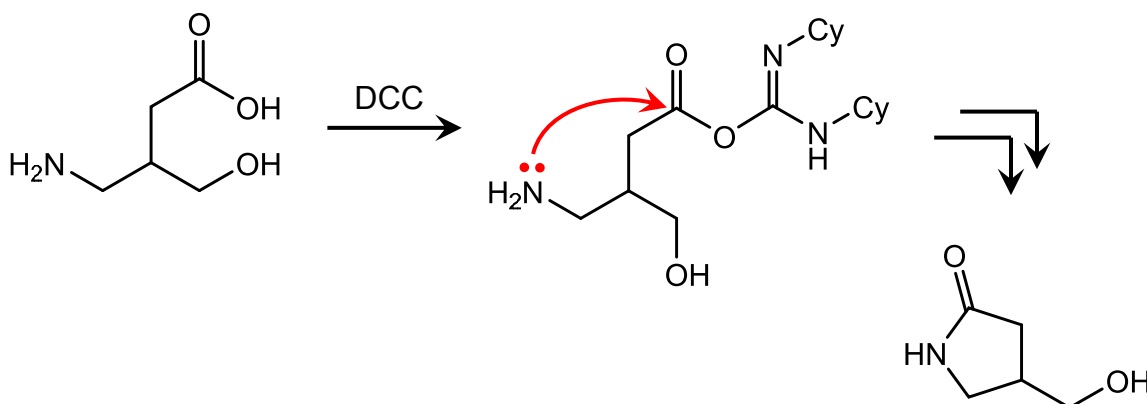
3 points for each correct conjugate base.

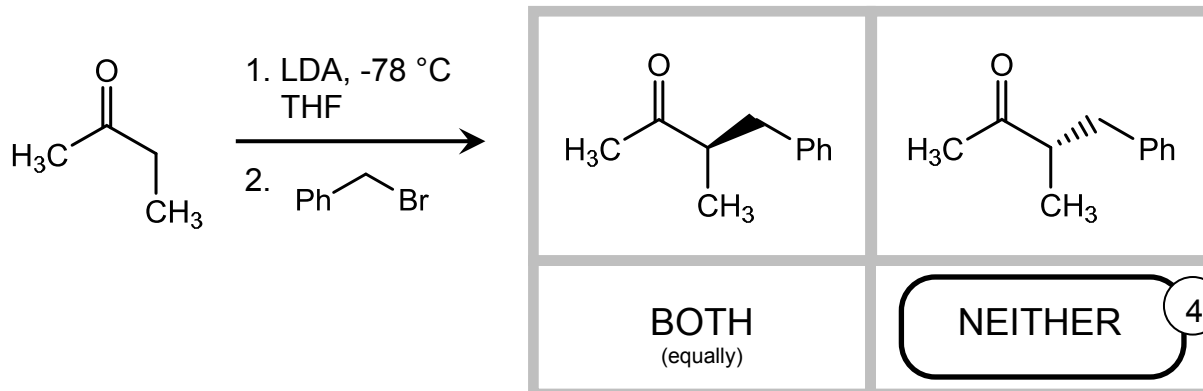
1 points partial for (E)-enolate of ketone rather than (Z). If the structure of the enolate is drawn as its carbanion resonance structure, the (Z)-geometry still needs to be correct. 1 point partial if it's not.

2. (20 pts) Each of the reactions on the following pages is drawn with two possible products. If one of the two products predominates, circle that preferred product. If the two products are produced equally, circle "BOTH". If neither product would result from the reaction, circle "NEITHER". **Circle one answer only.**

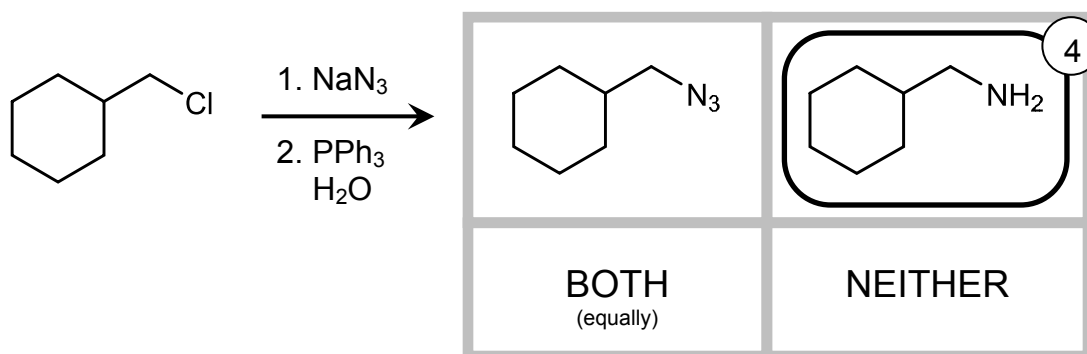


DCC activates carboxylic acids to react with nucleophiles. In this case, our molecule has two nucleophiles—an amine, and an alcohol. As we discussed in class, the activated, DCC intermediate is choosy about the nucleophiles it reacts with; it can discriminate better nucleophiles, like amines, from worse ones, like water or alcohols. In this case the DCC intermediate will react with the amine.

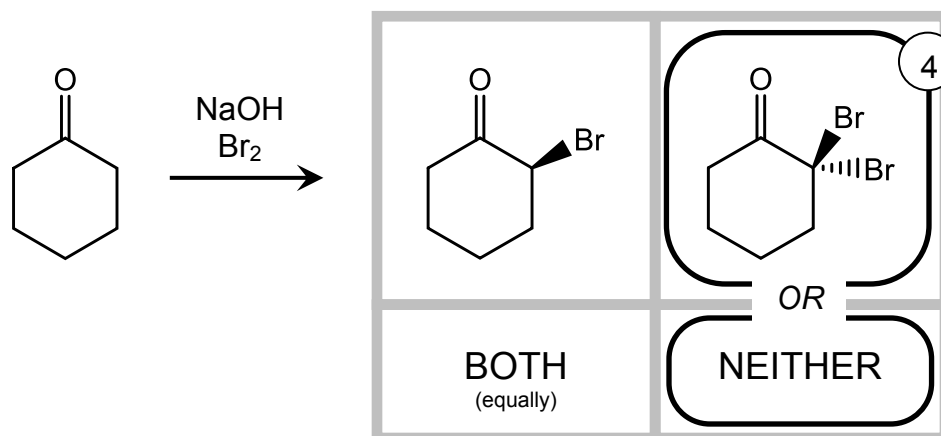




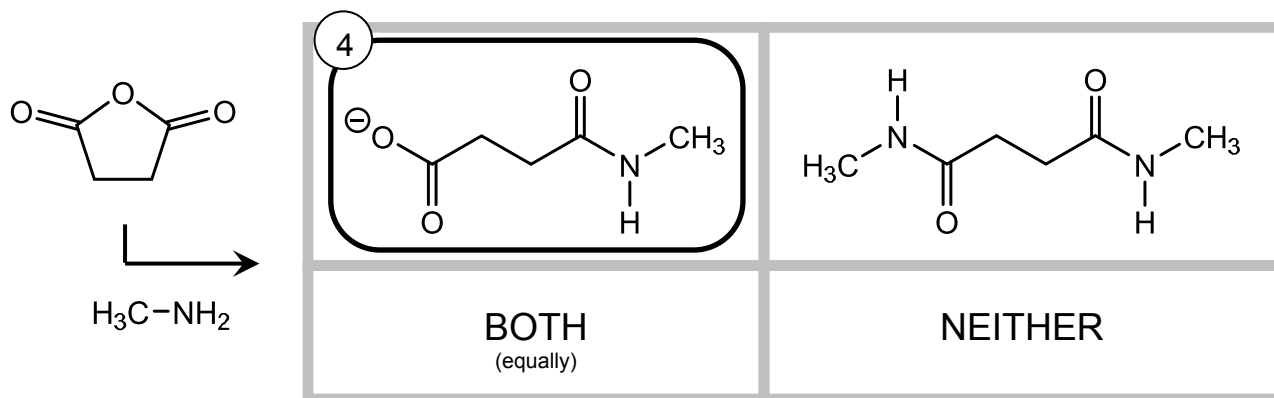
This problem was a little tricky, but it is related to problem #1 on the exam, in that the starting material is the same as one of the molecules you considered in that problem. In this case, the conditions for deprotonation—low temperature, sterically hindered base, polar aprotic solvent—are the conditions for generating the less substituted enolate on the left-hand side of the molecule. Neither of the products shown would be formed.



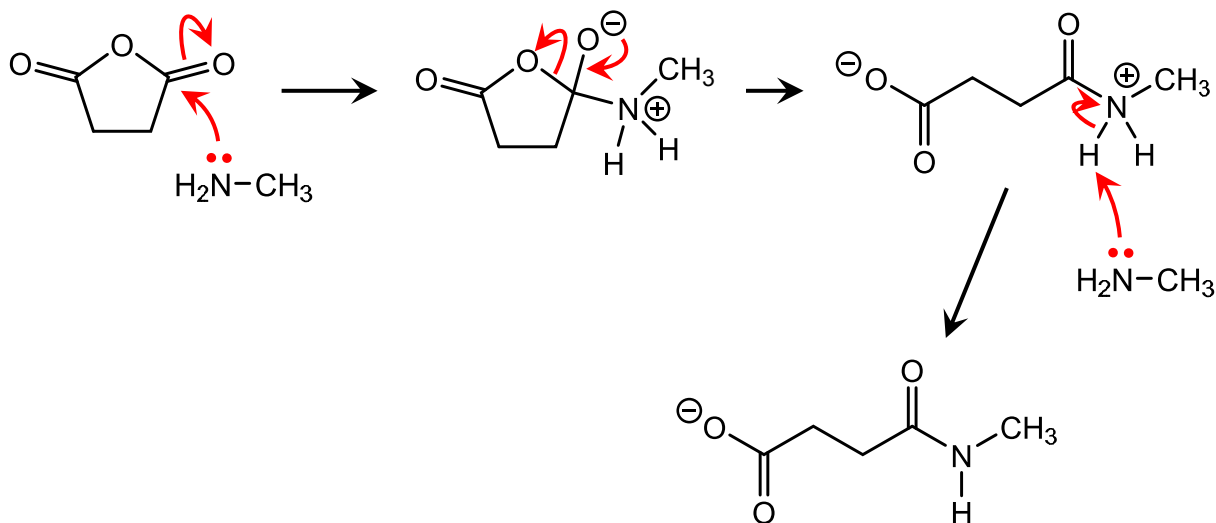
These reaction conditions yield a primary amine. The azide on the left is generated by the first step of the recipe, and then the second, reduction step converts the azide to an amine.



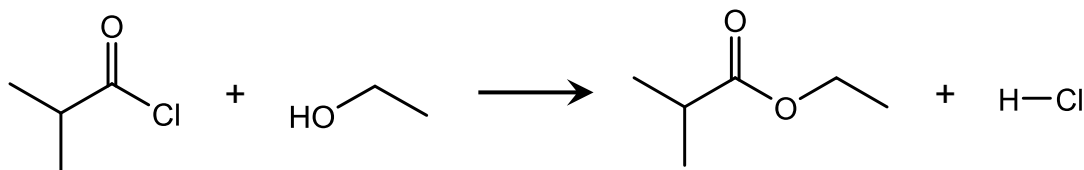
In base, multiple α -halogenations occur at the same carbon adjacent to a carbonyl, to yield a multiply halogenated product. (This makes this reaction different from halogenation in acid, which occurs just once.) The problem, however, doesn't make it clear whether the reaction only lasts long enough to halogenate one side of the molecule, or whether it is allowed to go on and halogenate both. Both the dihalogenated product or "NEITHER" should be acceptable answers to this problem.



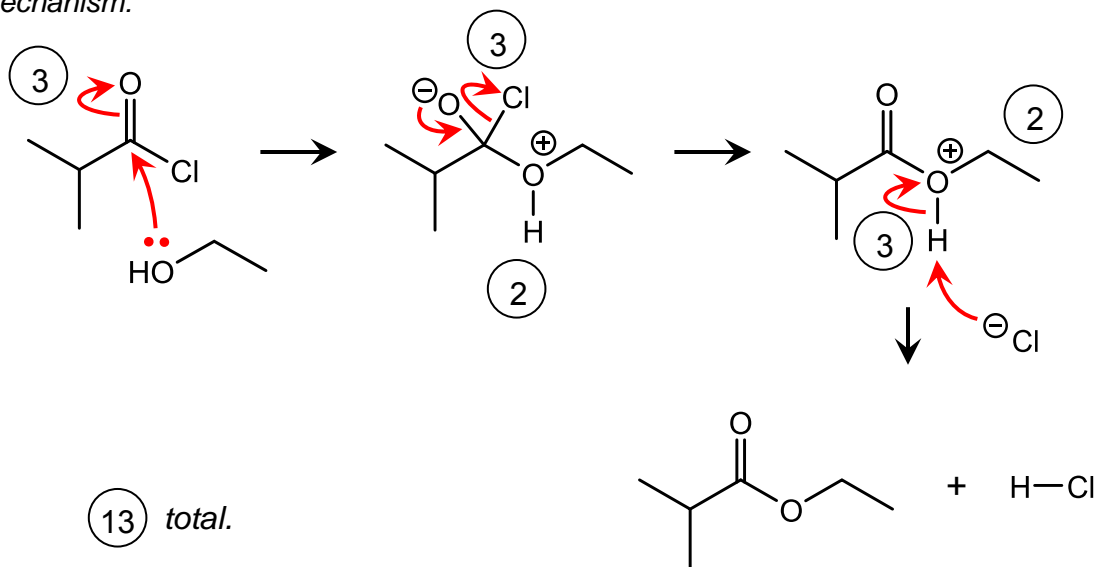
Our starting material in this problem is an acid anhydride. Anhydrides react with nucleophiles on just one side, to give a carboxylic acid derivative and a carboxylate:



3. (26 pts) For each reaction shown below, draw a mechanism that explains how the product is generated from the starting material. In your answer, make sure that you:
- Draw each step of the mechanism separately;
 - Use "electron pushing" to show where the electrons in each step go;
 - Use only the molecules that you are given; do not invoke reactants or solvents that aren't in the problem.



Mechanism:



Acyl halides are extremely reactive, and so they undergo nucleophilic acyl substitution via an initial zwitterion intermediate, without the need for any help from acid or base catalysts. (In this way, they are different from the more stable carboxylic acid derivatives found in nature, like esters, that typically need the help of a catalyst to react.) If you invoked an acid or base helper in your mechanism, you did not receive credit for steps involving that acid or base.

Rubric: (13 points for this part.)

3 points for each electron-pushing step.

2 points for each intermediate.

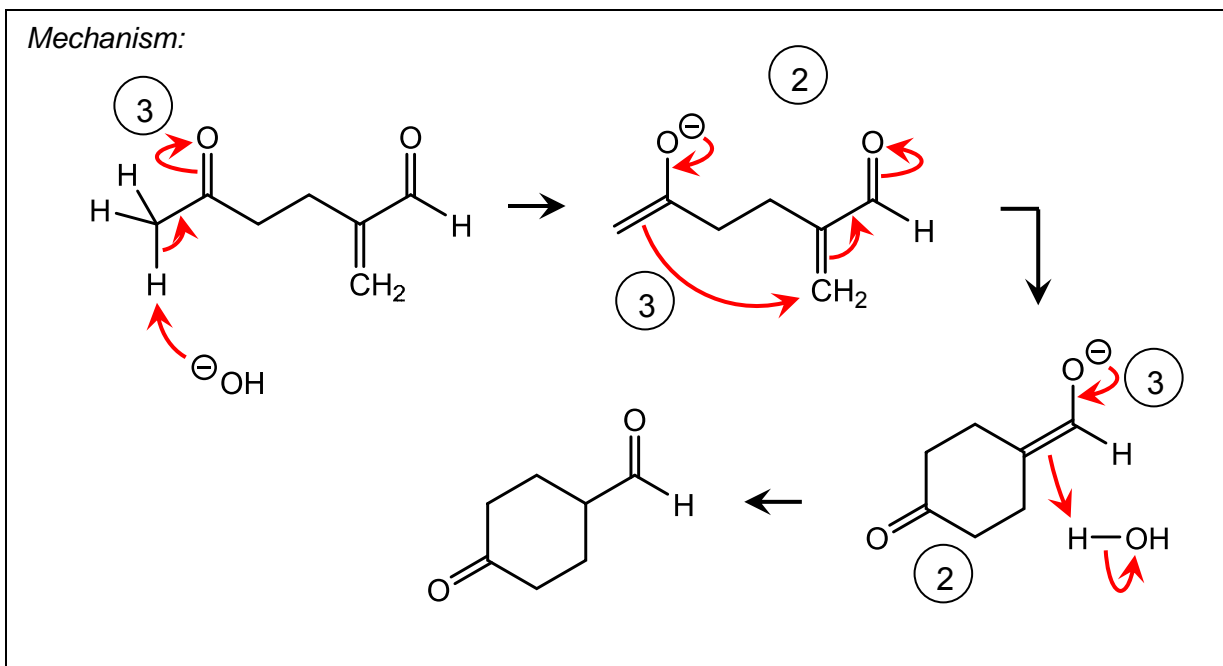
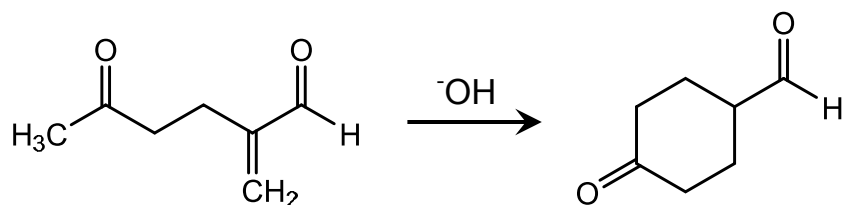
Overall notes:

Overall, the minimum score for each step is zero; errors in a step cannot earn you negative points that count against another, correct step.

Things that have left for good and spectators may be omitted.

Resonance is NOT a mechanistic step; it is just multiple ways of drawing the same intermediate. As a result, we did not evaluate electron-pushing that showed resonance—you can push electrons for resonance, or not, your choice. In addition, resonance does not have to be shown as an explicit “step”—it can be combined with adjacent steps, for full credit. Any molecule in your mechanism can be illustrated in any resonance form, for full credit.

- 1 point, for each arrow in each step, for errors in drawing arrows. Arrow must start at an electron pair, and end at nucleus where electrons will newly interact. Can only lose points if you get them.
 - 1 point for each minor error in charge, valency, structure, etc.; if error propagates, points are taken off only for initial error.
 - 2 points for each use of a generic or incorrect acid/nucleophile/base.
- If you combine steps that can't be combined, you can get points for arrows that are in the rubric, but not for the intermediate you skipped.



Rubric: (13 points for this part.)

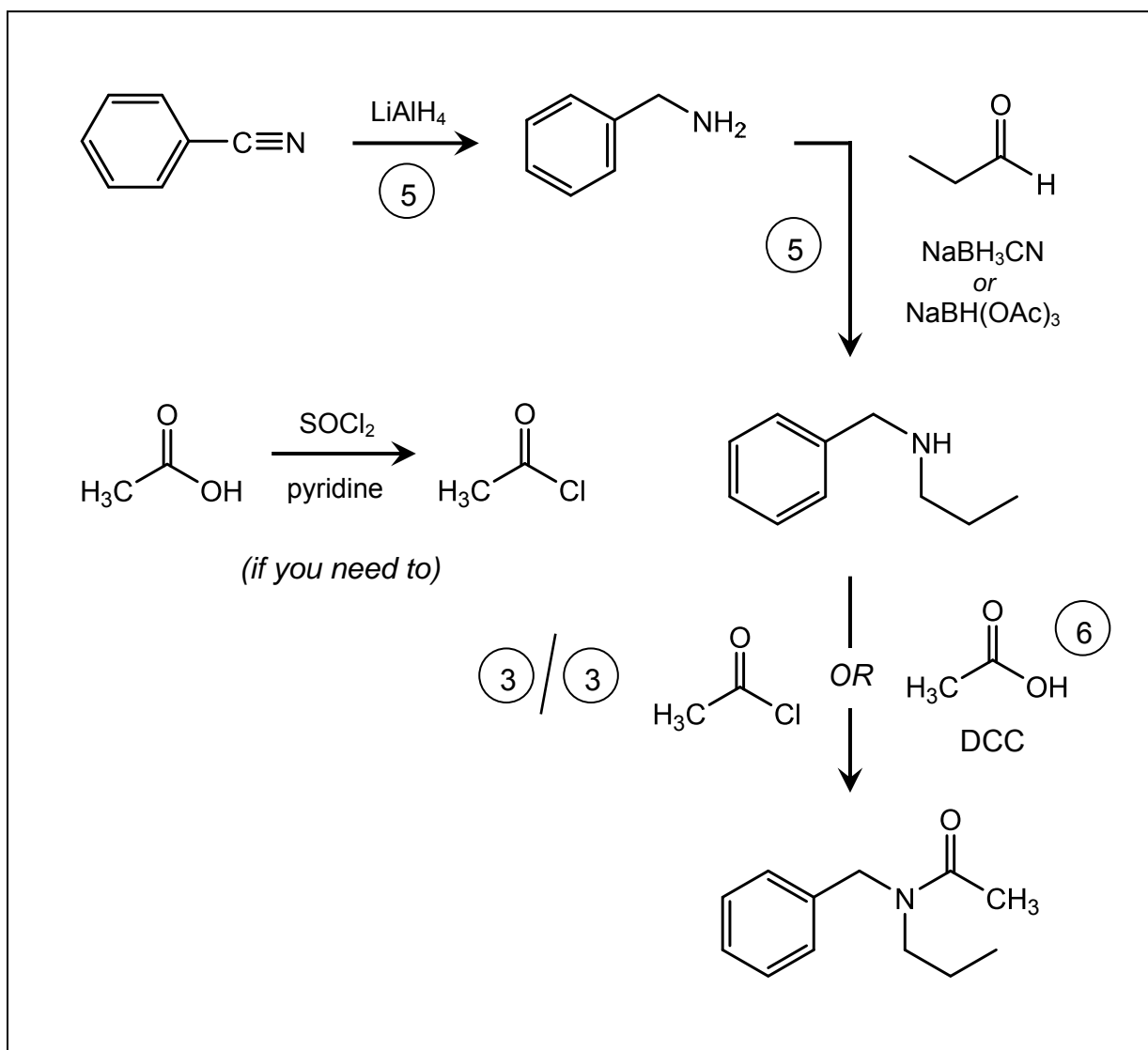
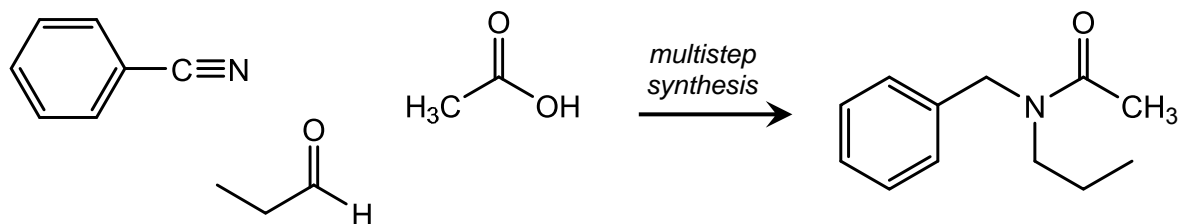
Same as previous problem.

3 points for each electron-pushing step.

2 points for each intermediate.

Again, resonance is NOT a mechanistic step. Enolates can be illustrated as either oxyanion or carbanion resonance forms.

4. (16 pts) In the box on the next page, propose a multistep synthesis of the product below, beginning with the starting materials given. In addition to these organic starting materials, you can use any reagents and reactions we've learned about in class. You might discover multiple answers to this problem; draw only your best (one) synthetic route. Feel free to draw an incomplete route—we will give you partial credit where we can.



Rubric:

General notes:

Each task is judged separately, and does not require that the synthesis makes sense, or that other tasks are correct.

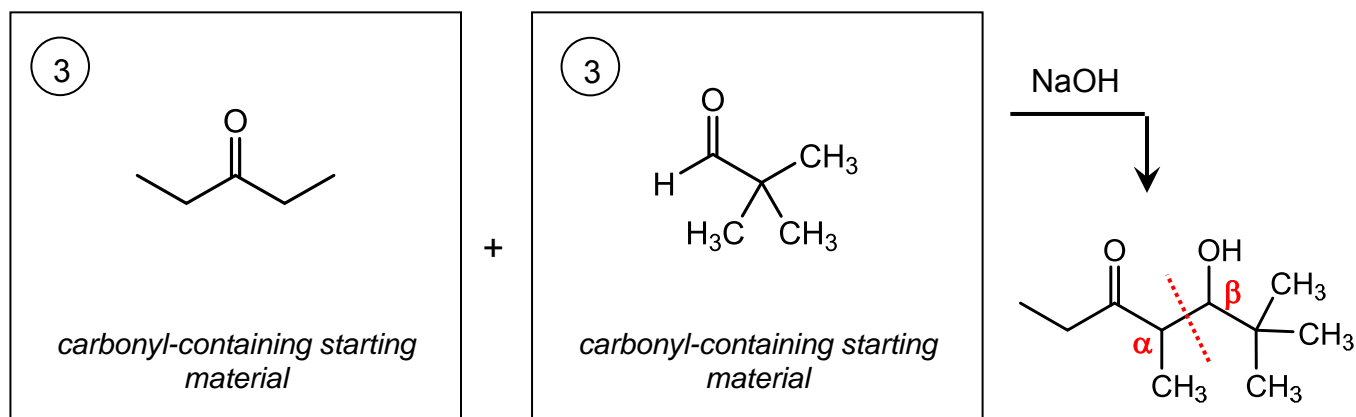
-1 point for each minor, trivial error in structures or reagents; if error propagates, points are taken off only for initial error.

-2 points if step reagents are incorrect, but reaction could otherwise be accomplished with correct reagents.

-2 points if reagents are correct, but product is wrong. If this happened, and you were led down an incorrect synthetic path by your mistake, you can also lose later points.

We only gave points for reagents if they connected a starting material and a product in an understandable way. So, for example, just writing a change in the starting material, by itself, isn't worth any points.

1. Reduction of nitrile with LiAlH_4 (5 points).
 2. Reductive amination to secondary amine (5 points).
3 points partial for alkylation via $\text{S}_{\text{N}}2$. This would result in overalkylation.
2 points for reaction with amide instead of amine. Reductive amination only works between an aldehyde/ketone and an amine. Some exams proposed to connect an aldehyde and an amide using the same chemistry—to make an amide first, and then attach an alkyl group via reductive amination. That won't work.
 3. Combination of amine and carboxylic acid to form amide (6 points).
There are a few ways to do this, including combining the two with DCC, or converting the acid to an acyl halide or anhydride first, then combining.
5. (24 pts) For each of the reactions below, fill in the empty box corresponding to reactants, reagents, or products. Give only one answer in each box. For reactions that you expect to yield multiple products, draw one major product. For reactions that yield multiple enantiomers, draw only one enantiomer in the box, and include the note "+ enantiomer".



used in excess?

YES or NO ?

(circle one)

used in excess?

YES or NO ?

Our product is an β -hydroxyketone, which is a synthon for the aldol reaction. We can go backwards, from product to reactants, by applying the retrosynthetic disconnect for the aldol reaction, which cuts through the α - β bond. The α -carbon comes from a ketone enolate, which originates as a ketone; and the β -carbon comes from a C=O bond.

In a crossed aldol, two reacting aldehyde/ketone starting materials can be combined directly if one of them cannot make an enolate, and that starting material is used in excess.

Rubric:

Either answer can be in either box.

3 points for diethyl ketone.

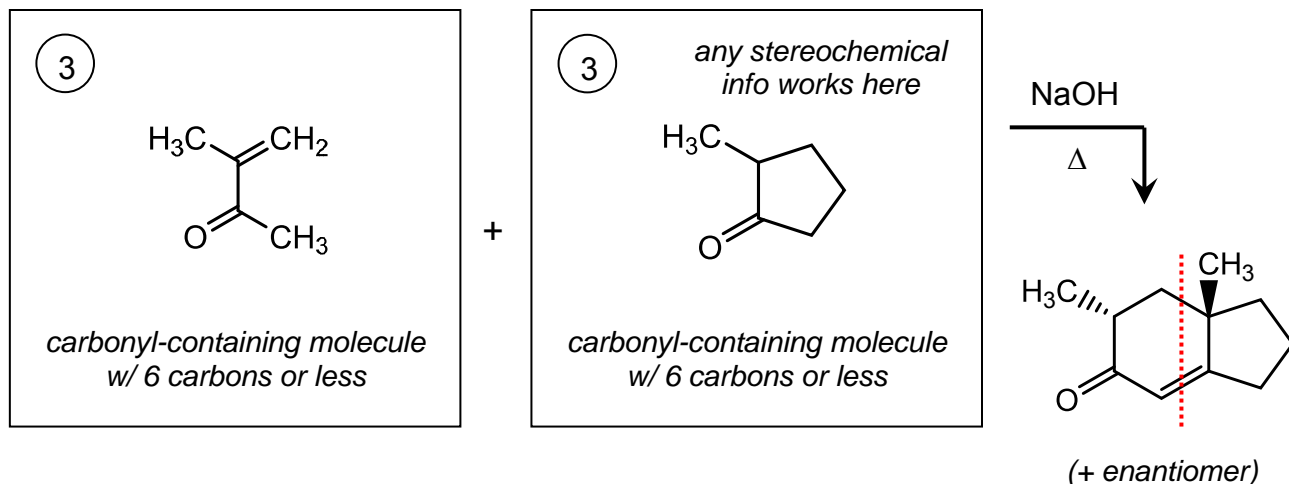
2 points partial for diethyl ketone enolate. The NaOH base will form this for you—you don't need to start with it.

3 points for tert-butyl aldehyde

-2 points for minor errors.

1 point for each correctly circled answer.

Can only score this point if box answer is correct; answer is relative to what is in the box.



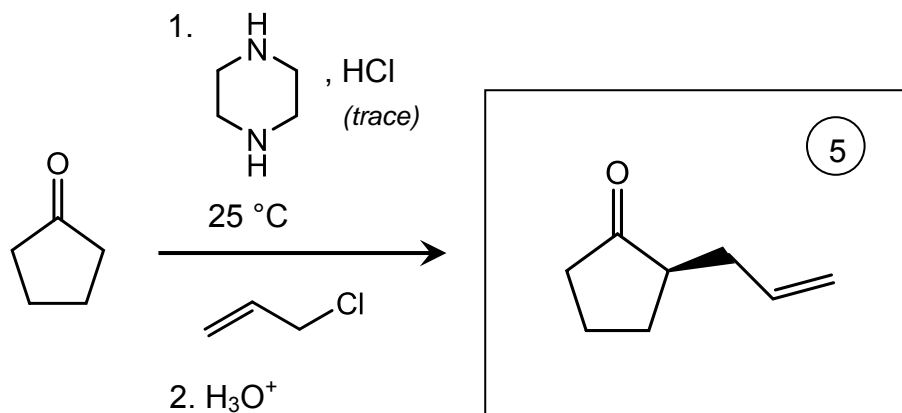
Our product contains a cyclohexanone ring, which is a synthon for the Robinson annulation. We can use the retrosynthetic disconnect for the Robinson annulation (shown above) as a way of visualizing the two starting materials required. The four-carbon section of the six-membered ring inherits a double bond, and the two-carbon section has a C=O bond where it used to have a C=C bond.

Rubric:

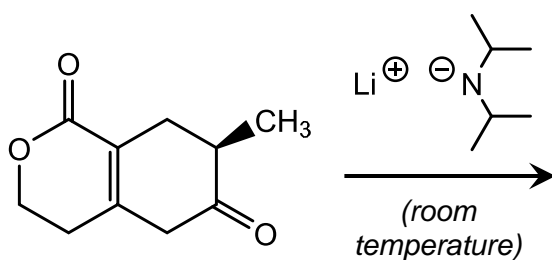
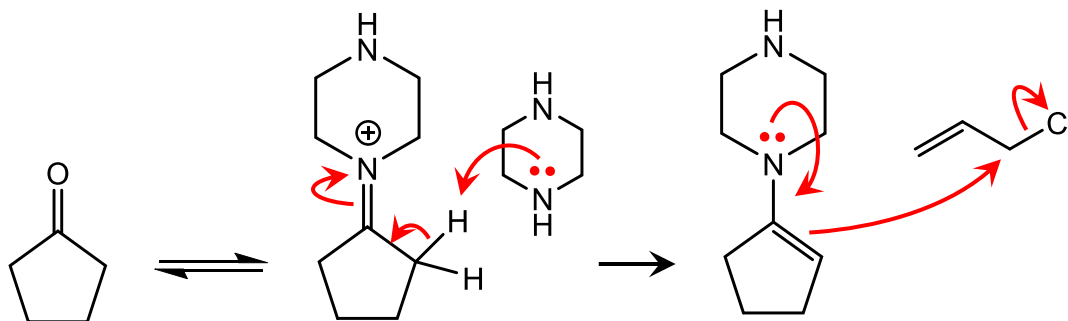
Either answer can be in either box.

3 points each answer.

-2 points for a minor error, such as omitting the double bond, or omitting a ring or -CH₃ carbon.



This set of reagents causes the starting ketone to react as an enamine, and undergo enamine alkylation:



At room temperature, LDA will deprotonate the starting material to generate the thermodynamically most stable enolate. Normally, that will be the most substituted enolate. However, in this case, the less substituted carbon forms an enolate that has lots of resonance structures, including two major oxyanion resonance structures. In this way, the enolate on the left is like a β -diketone enolate, doubly stabilized by resonance.

