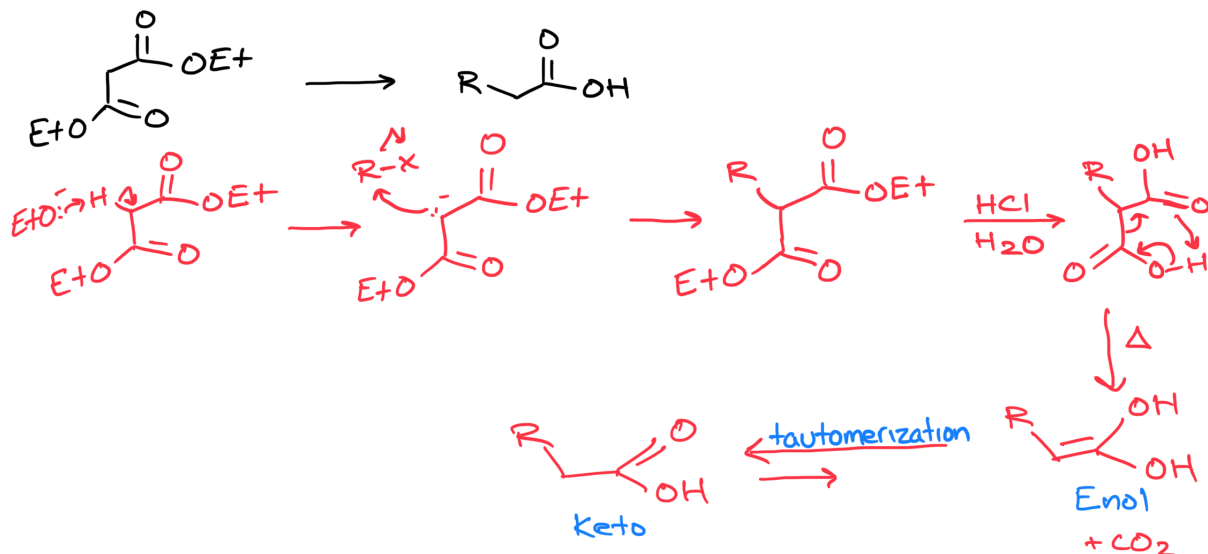


Midterm 3 Review Packet Key

1. Draw the mechanism for the following reaction



Malonic Ester Synthesis: produces carboxylic acids from diethyl malonate

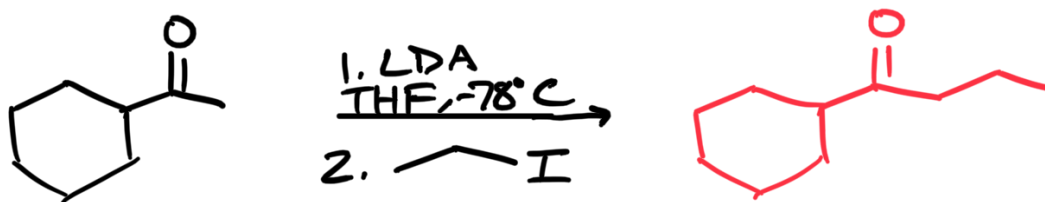
- Heating with acid and water hydrolyzes both esters to carboxy groups forming β -diacid.
- Decarboxylation readily occurs whenever a carboxy group is bonded to the α carbon of another carbonyl group.

Mechanism steps:

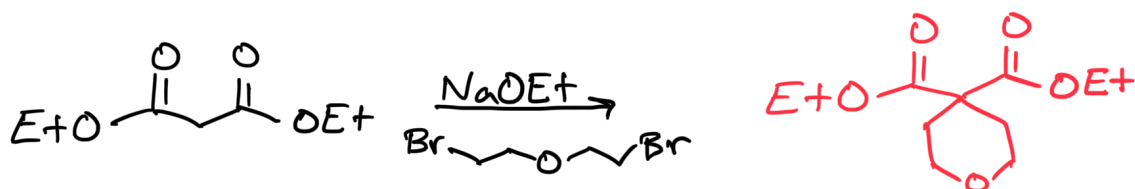
1. Deprotonation removes acidic α proton
2. Alkylation: nucleophilic enolate reacts with alkyl halide (S_N2 mechanism)
3. Hydrolysis and decarboxylation

2. Draw the products for the following reactions

A.

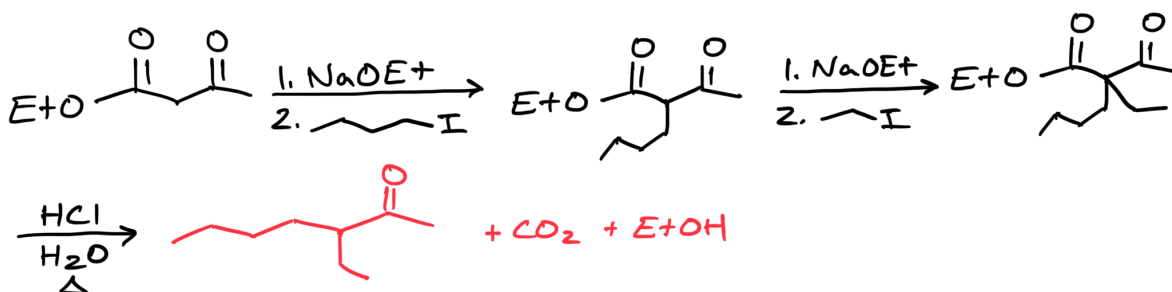


LDA is a strong, non nucleophilic base that removes a proton on the less substituted α carbon to form the kinetic enolate.



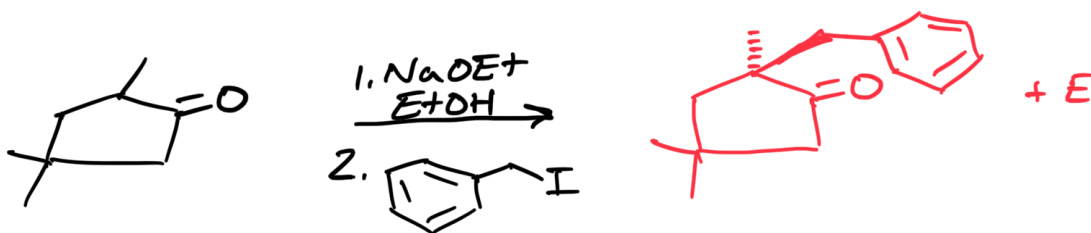
Intramolecular malonic ester synthesis used to form cyclic structure. Follows the same enolate chemistry as before but done twice (two bromine atoms).

C.



Acetoacetic Ester Synthesis: converts ethyl acetoacetate (β -keto ester) to ketone. Follows same process as shown in problem #1.

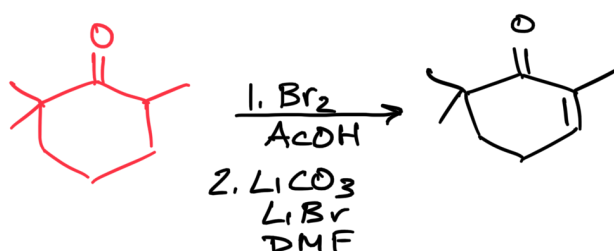
D.



Alkoxide bases in a protic solvent favor removal of a proton from the more substituted α carbon to form the thermodynamic enolate.

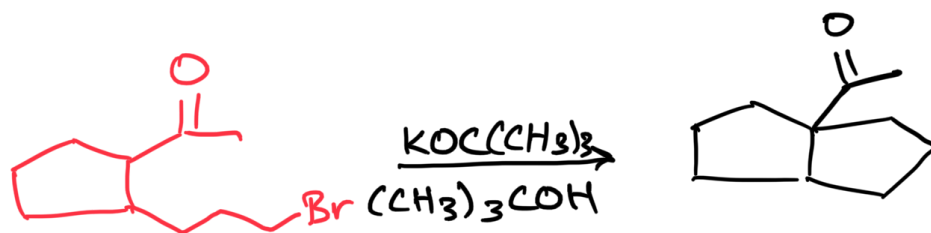
3. Draw the starting material for each of the reactions

A.



In order to work backwards you need to know what each of the reagents do. Br_2 & AcOH will add a bromine at the α carbon to produce the intermediate. The next set of reagents cause elimination of the Br and H from the α and β position to form a double bond. Going backwards would simply remove the double bond to produce the starting material required.

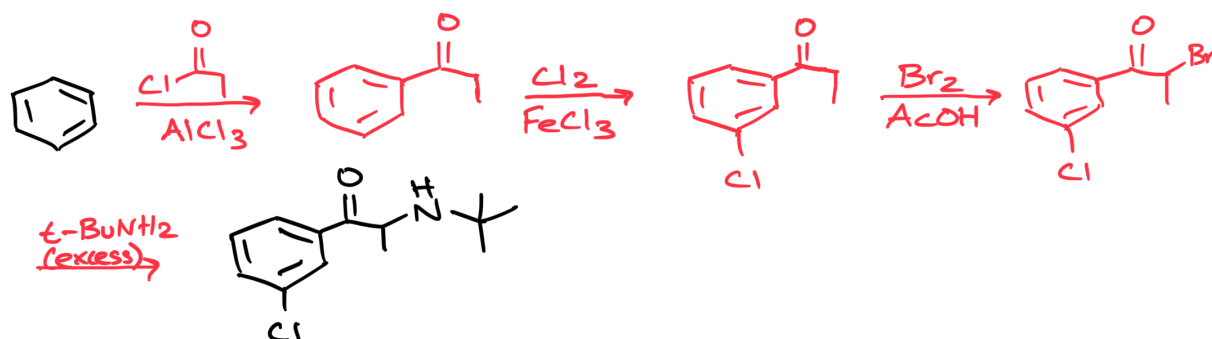
B.



Alkoxide bases will form a cyclic structure at the most substituted carbon. Cleaving the bond and adding a leaving group (such as Br) to perform an $\text{S}_{\text{N}}2$ reaction will produce the starting material.

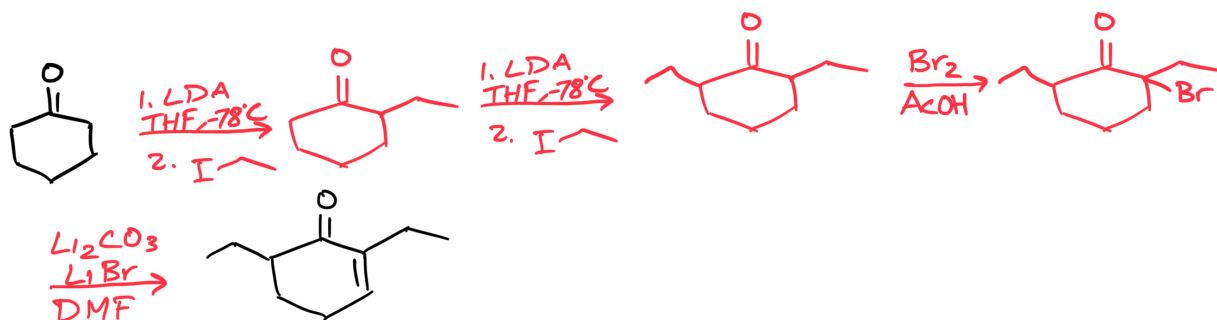
4. Provide the necessary reagents to produce the products from the starting material. Draw all intermediates.

A.



Review chapter 16 reagents! In order to add a carbonyl group to the benzene, we use Friedel-Crafts acylation followed by halogenation to add a chloride group at the meta position (the carbonyl group is a meta director). Now that you have a carbonyl group, you can create an enolate at the α carbon for a halogenation reaction. α -halo carbonyl compounds react with nucleophiles (in this case we use t-BuNH_2) by an $\text{S}_{\text{N}}2$ mechanism.

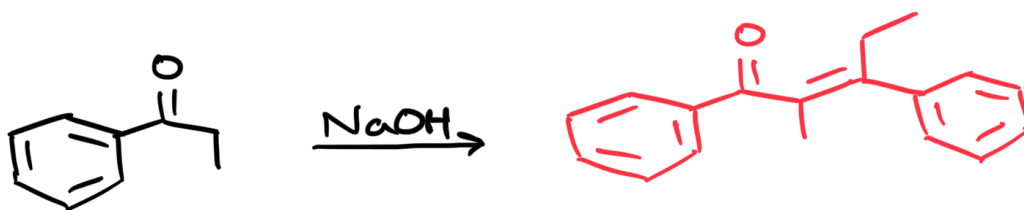
B.



Use of LDA and primary alkyl halide to produce the intermediate (do this twice), followed by halogenation and then an elimination reaction.

5. Draw the products for the following reactions

A.



Aldol reaction: two molecules of aldehyde or ketone react with each other in base. Forms new C-C bonds.

Step 1: Base removes proton from enolate

Step 2: nucleophilic attack of enolate on electrophilic carbonyl

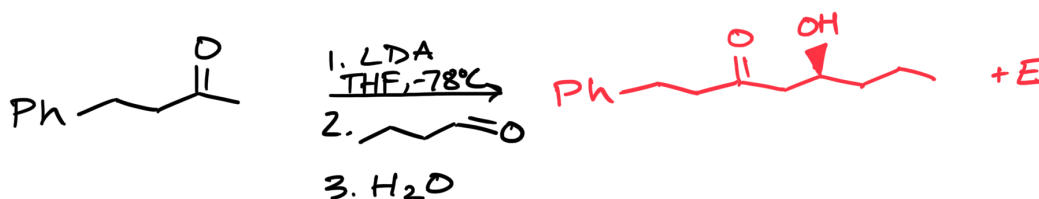
Step 3: protonation of alkoxide

Step 4-5: These are steps if you are performing aldol condensation. Dehydration occurs: Base removes a proton on α carbon, and OH^- is eliminated to form a new pi bond.

This question will have a spontaneous condensation reaction due to the conjugated group (benzene ring)

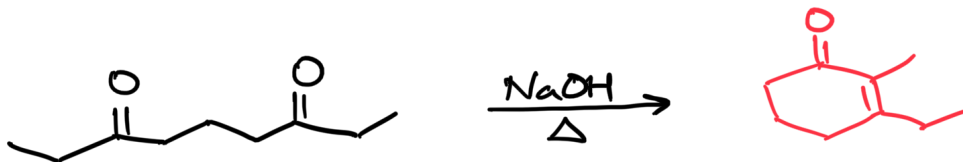
Rule: When the α, β unsaturated carbonyl compound is also conjugated with a C=C or benzene ring, H₂O elimination is spontaneous. If it isn't conjugated and you want condensation to occur, you need to add heat.

B.



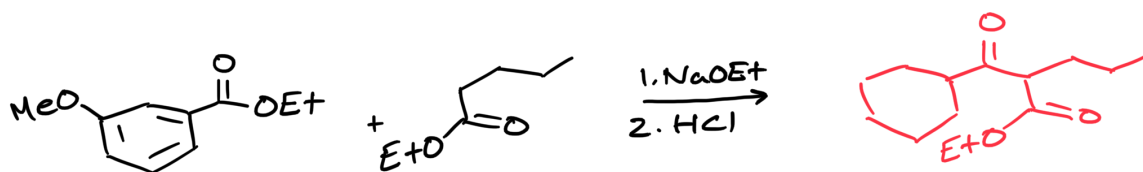
Another example of an aldol reaction. Follow steps 1-3 listed above.

C.



Intramolecular aldol reaction. I recommend redrawing the structure in a more cyclic starting material so it's easy to visualize and count your carbons so you don't mess up. Otherwise it does the same process as before but since heat is added, a condensation will occur (follow steps 1-5).

D.



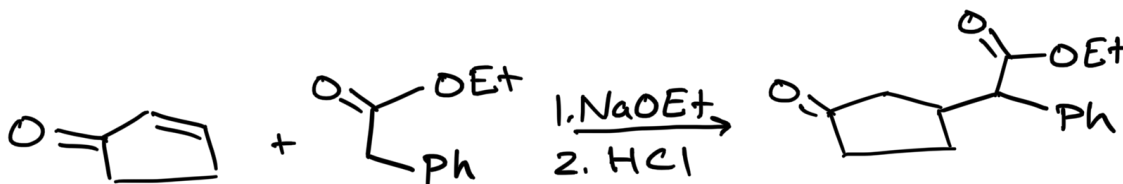
This is a crossed claisen reaction.

In order for a crossed claisen reaction to occur you need either:

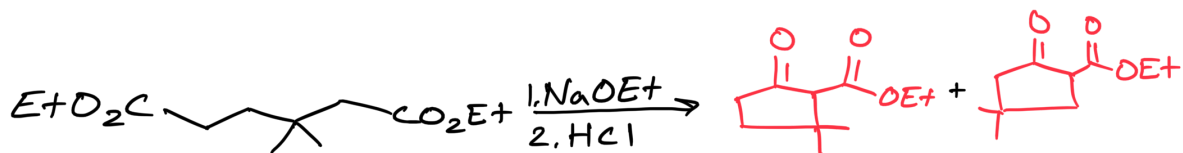
1. Two esters where only one has α hydrogens
2. A ketone and an ester. The enolate is mostly formed by the ketone so it's beneficial if the ester doesn't have any α hydrogens so that there is no mixture of products.

If you have a tough time drawing the product of these reactions, I gave a useful tip in the recording.

E.



This is a Michael reaction: conjugate addition (1,4 addition) of **resonance stabilized** enolate to the β carbon of Michael acceptor. You would form the enolate and perform 1,4 addition similar to cuprate reactions from chapter 17.



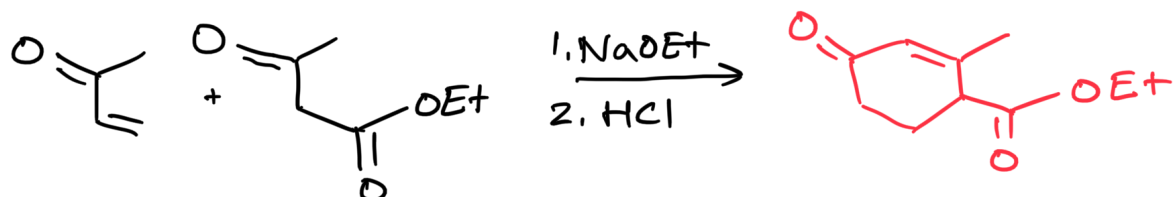
This is a Dieckmann reaction (intramolecular Claisen). If you have an ester starting material you should be thinking about either Claisen or Dieckmann

1,6 diesters → produce 5 membered ring

1,7 diesters → produce 6 membered ring

Depending on which side you form the enolate, it will form a mixture of products since they are not equidistant from the two methyl groups.

G.



This is a Robinson Annulation which consists of a Michael reaction and an intramolecular aldol reaction. It is used to form ring products. You do not need to know the mechanism for this reaction.

Simplified process:

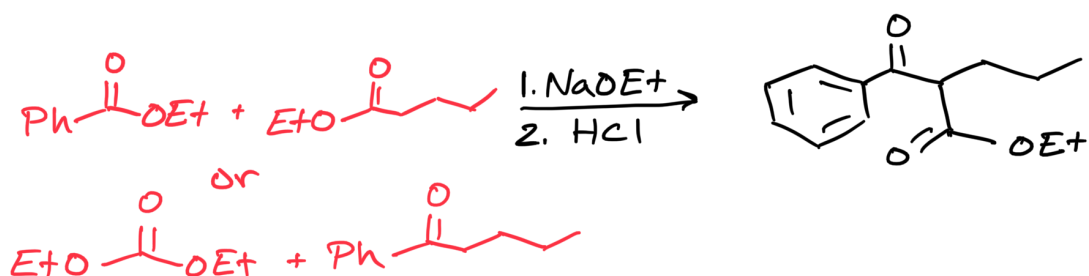
Step 1: Michael Addition (enolate does 1,4 addition)

Step 2: Intramolecular aldol (form enolate to attack carbonyl to form ring structure, dehydration causes elimination of OH^- and loss of proton to form pi bond).

Full explanation can be found in the textbook.

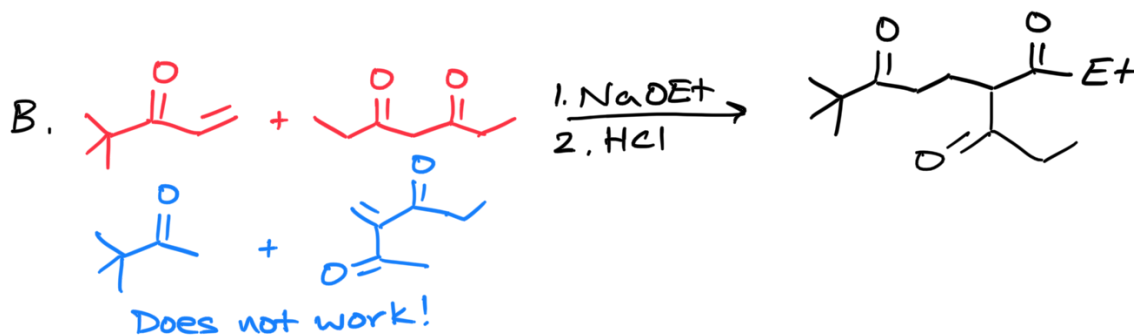
6. Draw the starting material for each of the reactions

A.



Since you see an ester in the product, you should be thinking about a Claisen reaction, specifically a crossed Claisen reaction. You can cleave the bond at two different locations and therefore have two sets of starting materials. You add a OR group to the group that was cleaved.

B.



Retrosynthesis of a Michael reaction:

1. Break β - γ bond
2. Add a double bond to the α - β position \rightarrow this forms your Michael acceptor. The remaining part is the enolate. The other possible starting material written in blue does not work because it is not a stabilized enolate which is needed for a Michael reaction.

C.

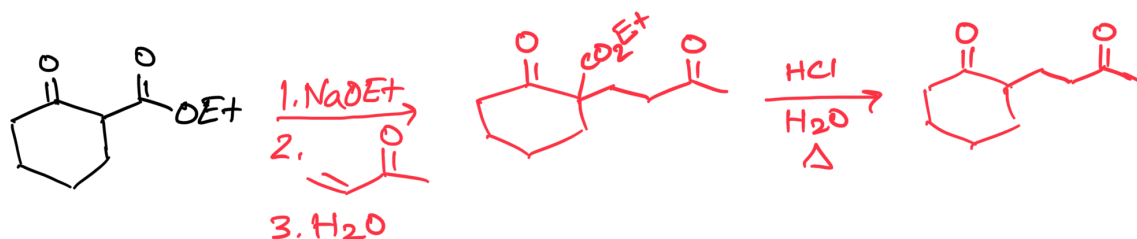


Retrosynthesis of Robinson Annulation:

1. Break $\text{C}=\text{C}$ bond, one half will become the carbonyl group of the enolate (add in oxygen atom)
2. Break the bond between the β carbon and the carbon it's attached to, and add a pi bond to the α - β position.

7. Provide the necessary reagents to produce the product from the starting material. Draw all intermediates.

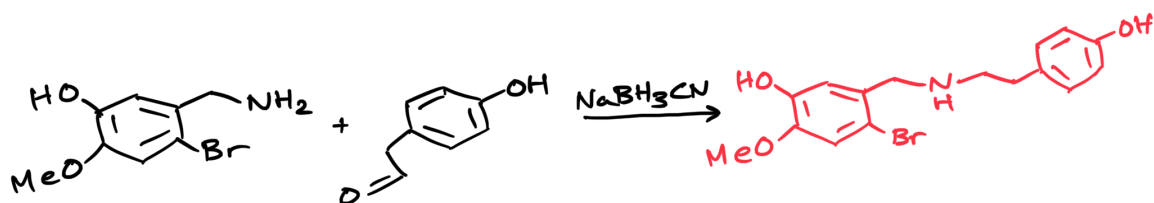
A.



Perform a Michael reaction; 1,4 addition allows the addition of this long carbonyl chain. To remove the ester functional group, you perform hydrolysis and decarboxylation.

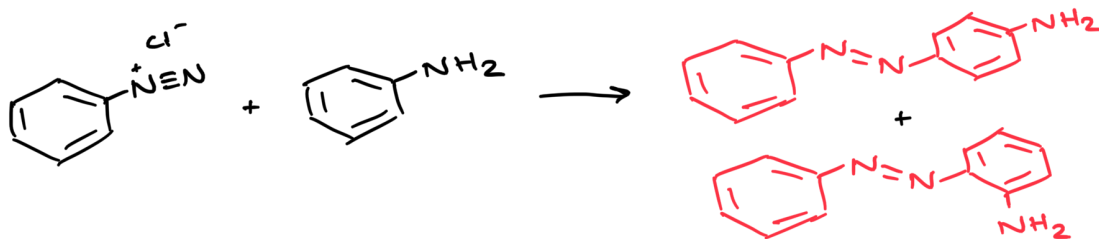
8. Draw the products for the following reactions

A.



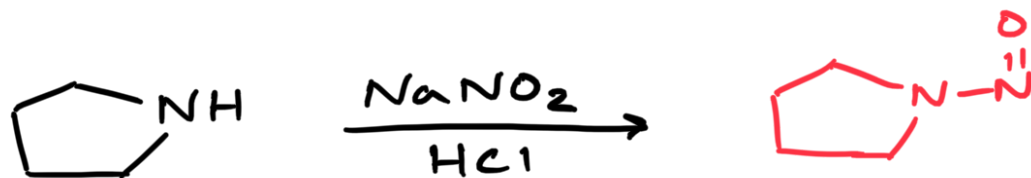
NaBH₃CN is used for reductive amination. It converts aldehydes and ketones to amines. If you have trouble visualizing this reaction, I provide a tip in the recording.

B.



Formation of an azo compound: requires strong electron donating groups on the benzene (ex. NH₂, NR₂, NHR, OH). Two products are formed - ortho and para.

C.



Reaction of an amine with nitrous acid (HNO_2)

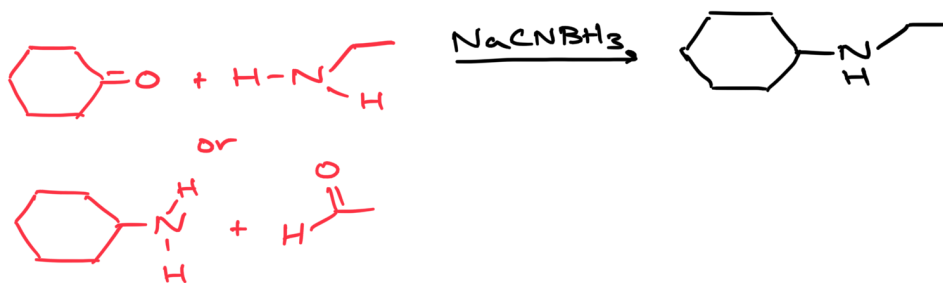
1° amines will form diazonium salts (N_2)

2° amines will form N-nitrosamines ($\text{R}_2\text{N}-\text{N}=\text{O}$)

This question contains a secondary amine so therefore it will form a nitrosamine. You should know the mechanism for both of these reactions.

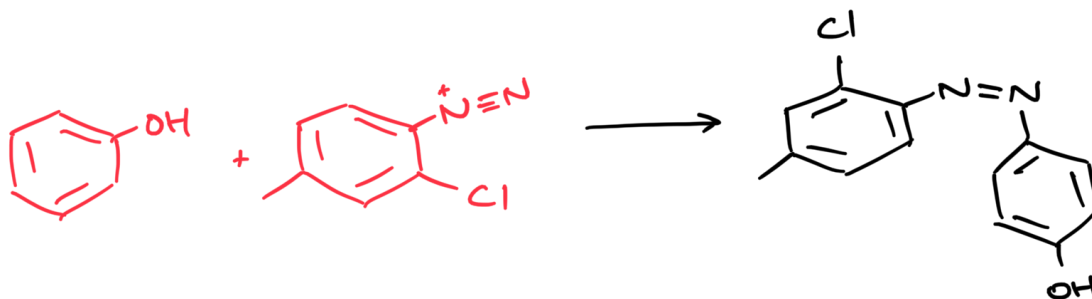
9. Draw the starting material for each of the reactions

A.



Two different ways to cleave the product. Starting material required for these reactions is an aldehyde or ketone and an amine.

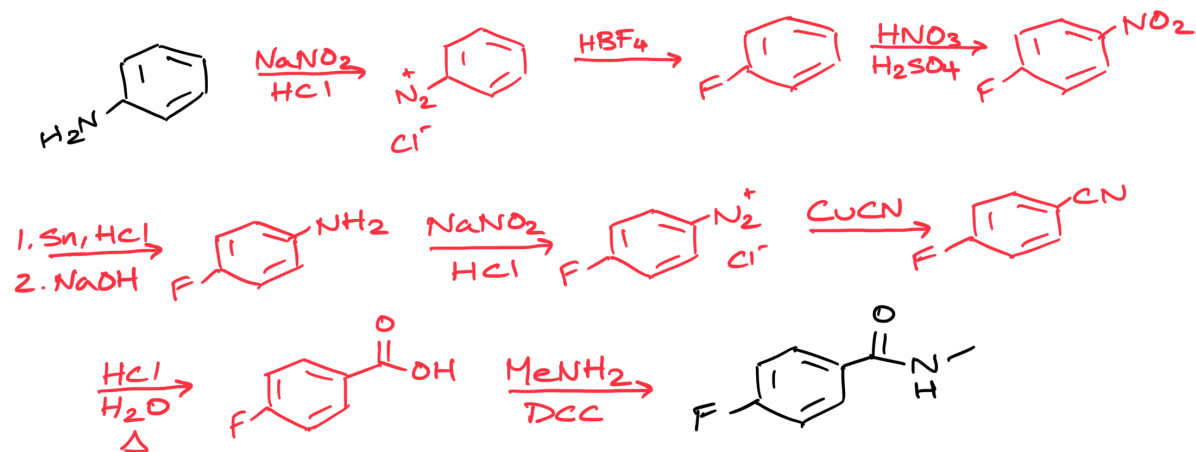
B.



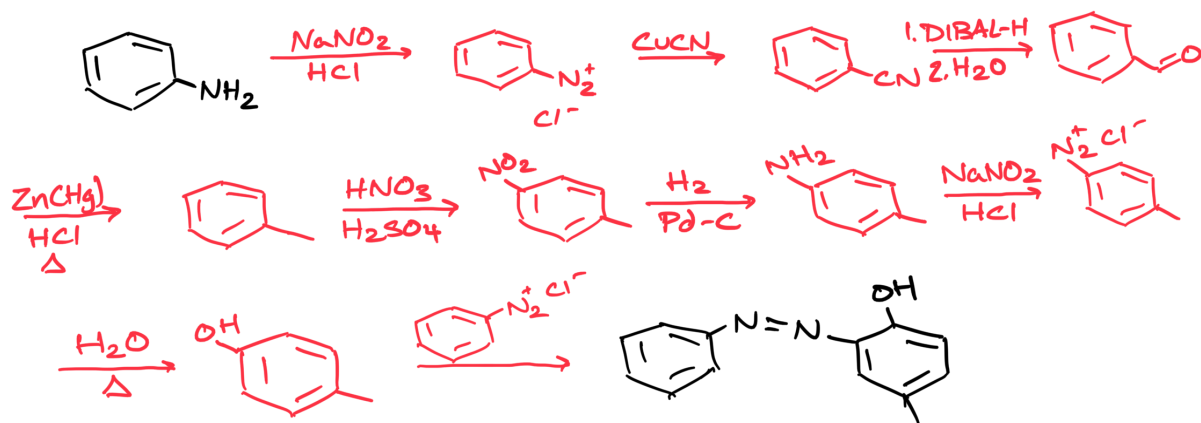
Diazonium salt acts as electrophile (this is another example of electrophilic aromatic substitution). You want to divide the molecule so that one portion has a benzene ring with the diazonium ion and the other portion has a benzene ring with a strong electron donor group.

10. Provide the necessary reagents to produce the products from the starting material. Draw all intermediates.

A.



B.



These synthesis reactions don't need much of an explanation, it's just showcasing the importance of knowing reagents from previous chapters. Highly unlikely you would have something this long on exams but it's important to know all of these methods in case you do need to use them.