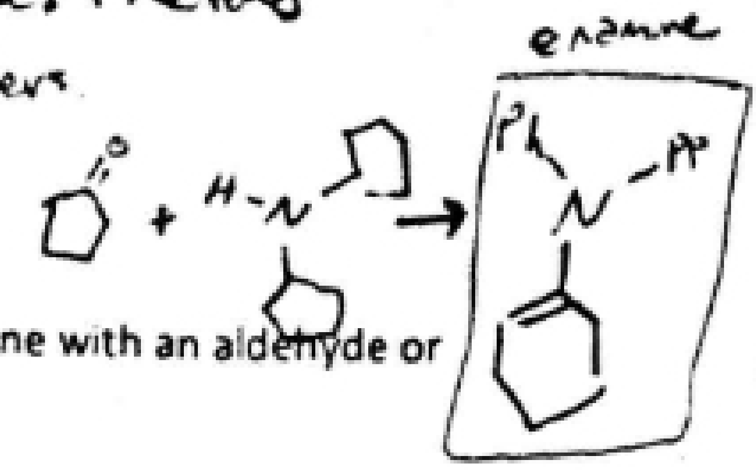
Difference Between: Aldol + Claison + Dieckman.

- Adol only works for aldehydes + ketones
- Claison + Dieckman work for Esters.

IV. Enamines

-What is an Enamine eg



A. **Enamines** are formed by the reaction of a secondary amine with an aldehyde or ketone. Is also called a schiff base.

1. The most common secondary amines used for the formation of an enamine are pyrrolidine and morpholine.

2. Why is making an enamine a good thing?

a. the β-carbon of an enamine is a nucleophile by virtue of the conjugation of the C=C w/ the electron pair on N.

b. That means that they resemble enolates in their reaction.

c. This was first piorneered by Gilbert Stork (Columbia University) and are sometimes called the Stork enamine reaction.

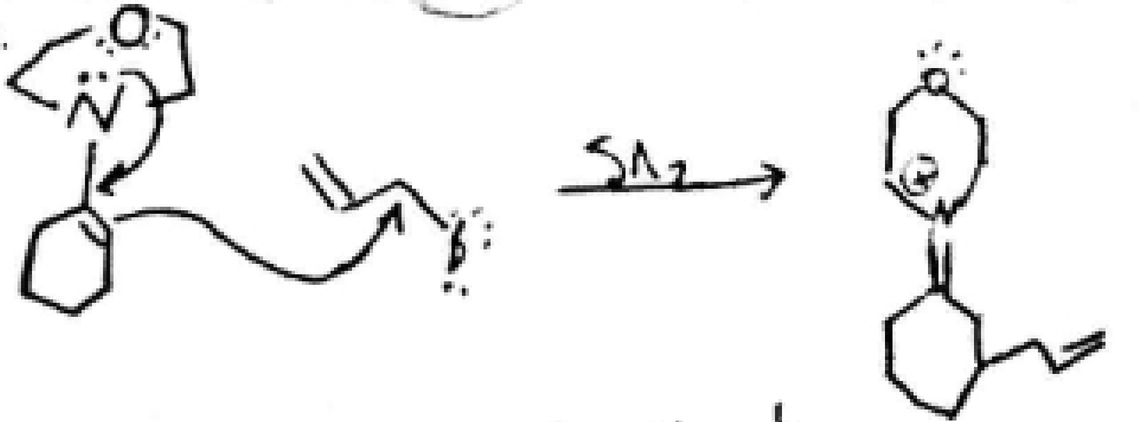
B. Enamines readily undergo S_N2 reactions with methyl and primary alkyl halides, α-haloketones, and α-haloesters.

1. They work bette4r than enolates because they are less basic and give higher ratios of substitution to elimatino products.

Mechanism #5: Alkylation of an Enamine

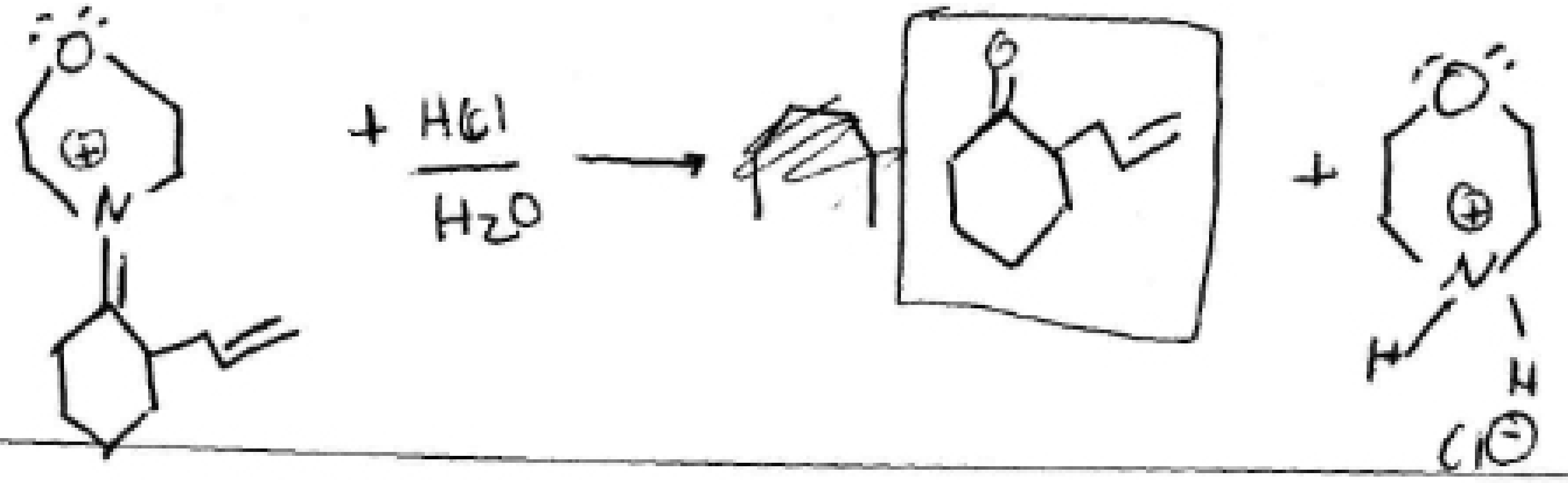
Assuming we already have enamine. should be able to make it!

Step 1: Treatment of the enamine with one equivalent of an alkylating agent gives an iminium halide.

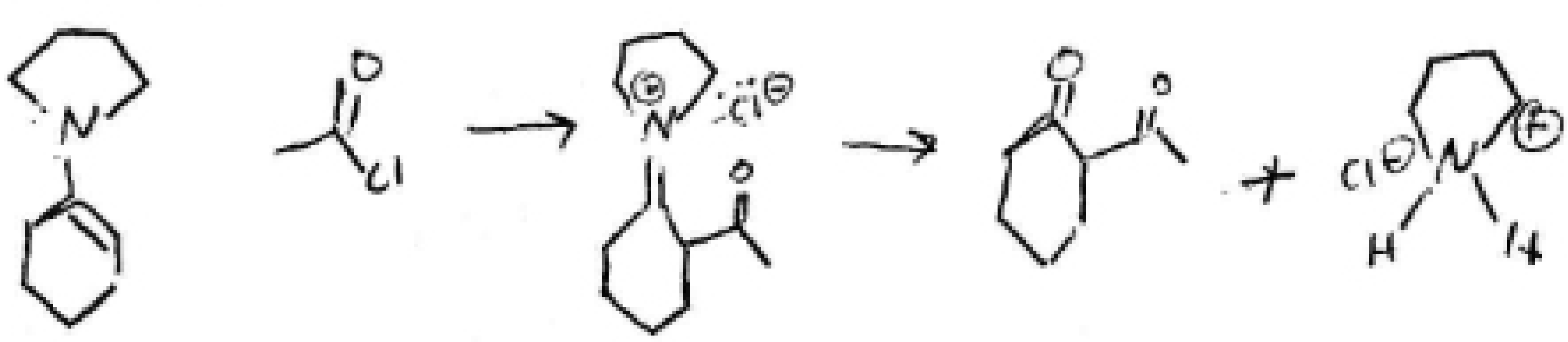


This only react with the halide so if you take an acid Chloride, the ketone won't be harmed!!

Step 2: Hydrolysis of the iminium salt gives the alkylated ketones and regenerates morpholine as its hydrochloride salt.



C. Enamines undergo acylation when treated with acid chlorides and acid anhydrides.



1. We can attach an acyl group to the α-carbon of an aldehyde or ketone using its enamine as an intermediate – this process is called **acylation**.

WILL BE ON EXAM. ☆

V. Acetoacetic Ester Synthesis

A. Why are β-ketoesters (like acetoacetic ester) great starting materials for the formation of new carbon-carbon bonds?

1. The acidity of α-hydrogens (pK_a 10-11) between the two carbonyl groups
2. The nucleophilicity of the enolate anion resulting from the loss of an α-hydrogen.
3. The ability of the product to undergo decarboxylation after hydrolyzing the ester.

B. We can use the **acetoacetic ester synthesis** to synthesize monosubstituted and disubstituted acetones. e.g

from

1. We've seen all of these reactions separately, but now we're just putting all of them together for the first time.

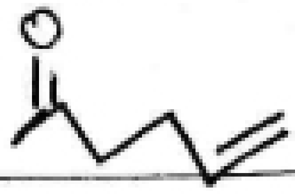
2. Let's use 5-hexen-2-one as our target molecule.

ON EXAM FOR SURE

Just Know these 5 steps

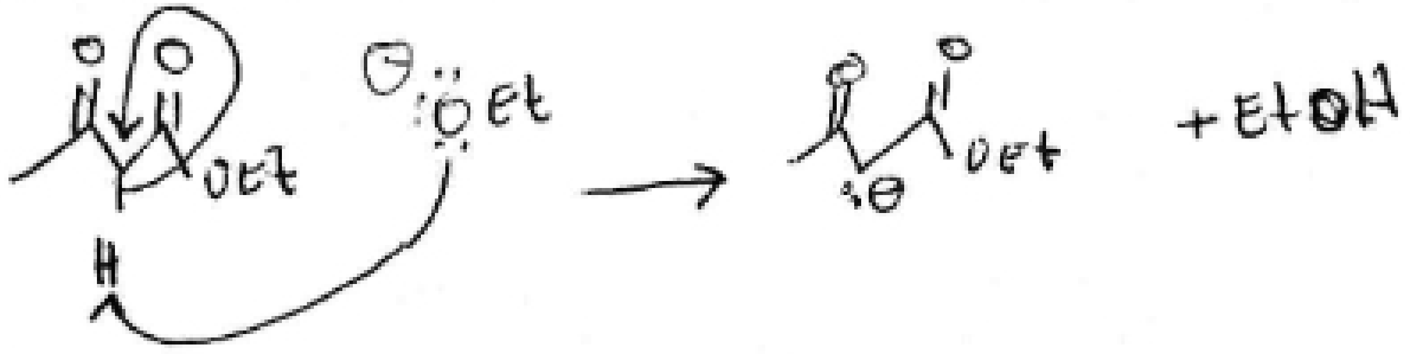
Know this synthesis

Goal Compound

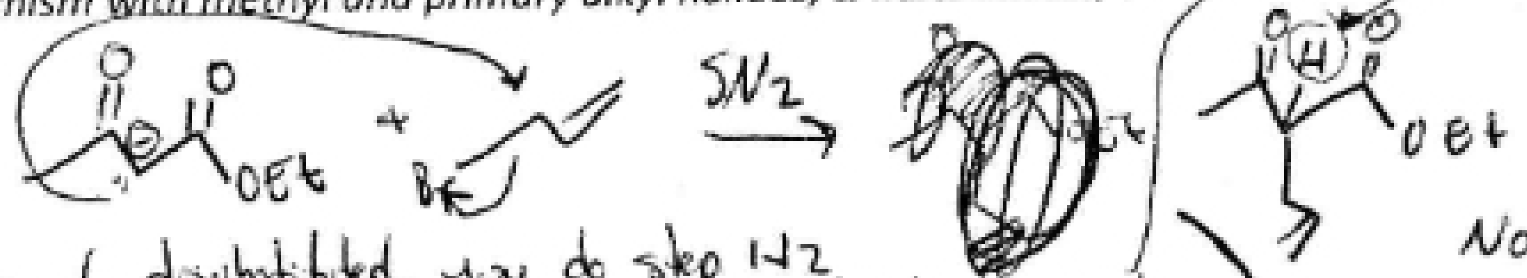


Synthesis #1: Synthesis of 5-hexen-2-one

Step 1: The methylene hydrogens of ethyl acetoacetate (pK$_a$ 10.7) are more acidic than those of ehtnaol (pK$_a$ 15.9); therefore, ethyl acetoacetate is converted completely to its anion by sodium ethoxide (you coud use another alkali metal alkoxide).



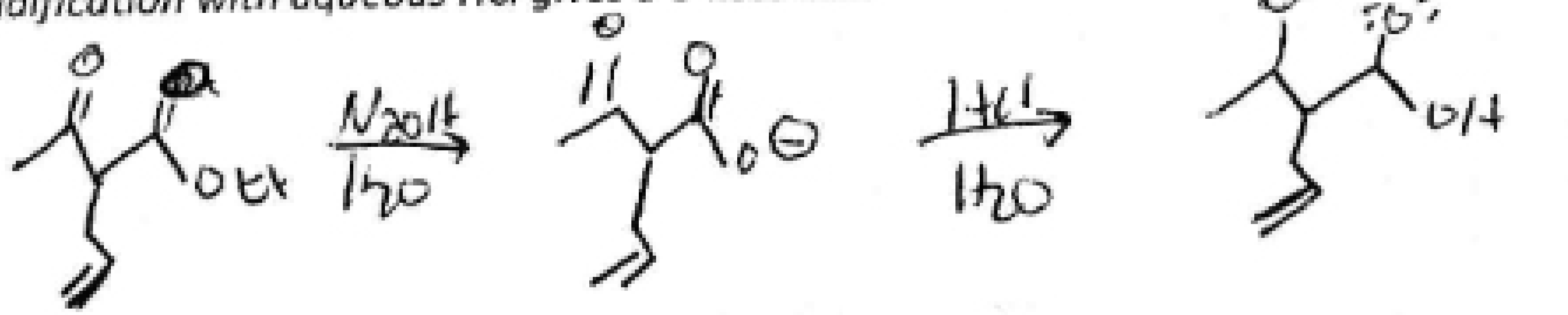
Step 2: The enolate anion of ethyl acetoacetate is a nucleophile and reacts by an S$_N$2 mechanism with methyl and primary alkyl halides, α-haloketones, and α-haloesters.



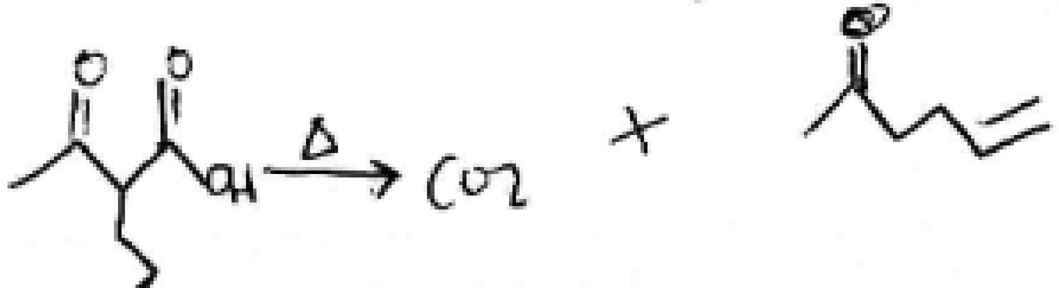
(* To get disubstituted, you do step 1+2 twice, get rid of the final center α-hydrogen)

Now we must get rid of the ester.

Steps 3 and 4: Hydrolysis of the alkylated acetoacetic ester in aqueous NaOH followed by acidification with aqueous HCl gives a β-ketoacid.



Step 5: Heating the β-ketoacid brings about decarboxylation to give 5-hexen-2-one.



decarboxylation removes carboxylic Acid group.

3. What if we wanted to create a di-substituted acetone?
   a. We could interrupt this process at the end of step 2 by reacting it with a second equivalent of base to give a second enolate anion, then treat with an alkyl halide.

* ON BACK OF Chap 18 NOTES!