Chapter 2 Writing a Correct Mechanism

1) Balancing Equations

2) Using Arrows to show Electron Movement

3) Mechanisms in Acidic and Basic Media

4) Electron rich Species: Nucleophile or Base?

5) Trimolecular Steps

6) Stability of Intermediates

7) Driving Forces for Reactions (a) Leaving Groups
(b) Forming a small stable molecule

8) Structural Relationship between Starting Materials and Products

9) Effect of Solvent

10) Occam's Razor

Mechanisms are the step by step account of the electron movement (which consequently gives the bond reorganization) for a given transformation.

It should be stated that mechanisms don't really have any objective existence, they are just our attempt to represent what is going on during a reaction.

Experiments can suggest which mechanisms are reasonable, and which are not.

Often there is no experimental evidence of a mechanism, just these SM/reagents gave this product.

YOU CANNOT PROVE A MECHANISM

You can disprove an incorrect mechanism experimentally.

At best, all you can say is that a mechanism is consistent with experimental evidence.

Often you will disprove all other mechanistic possibilities, leaving just one mechanism which fits the experimental facts.

Actually we are free to write any mechanism we choose, constrained only by good fundamental mechanistic principles.

Actually you are all already aware of these principles (= Org I and Org II).

This course will teach you how to apply these mechanistic principles.

Specifically you will develop the skill to figure out how a reaction (that you have never seen before) proceeds.

How do you get from A to B, using only good organic principles?

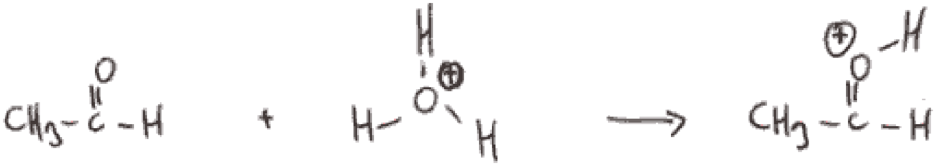
It is like a big jigsaw puzzle / cross word puzzle / logic / brain teaser problem.

(There are no magical chemical pixies moving atoms around, everything obeys the rules of good organic chemistry).

1) Balancing Equations

Organic chemists often only care about the carbon atoms when they write equations.

So they will often write equations such as:



Obviously this is not a balanced equation as far as the H and O atoms are concerned.

The balanced equation is:

Be aware that many journal papers / text books will not write fully complete balanced equations for every transformation. This does not mean that the “missing” components vanish / are destroyed / don’t exist.

You have to understand what is *implied*.

Besides the atoms, you also must pay attention to the charges, ensuring they are:

a) correct

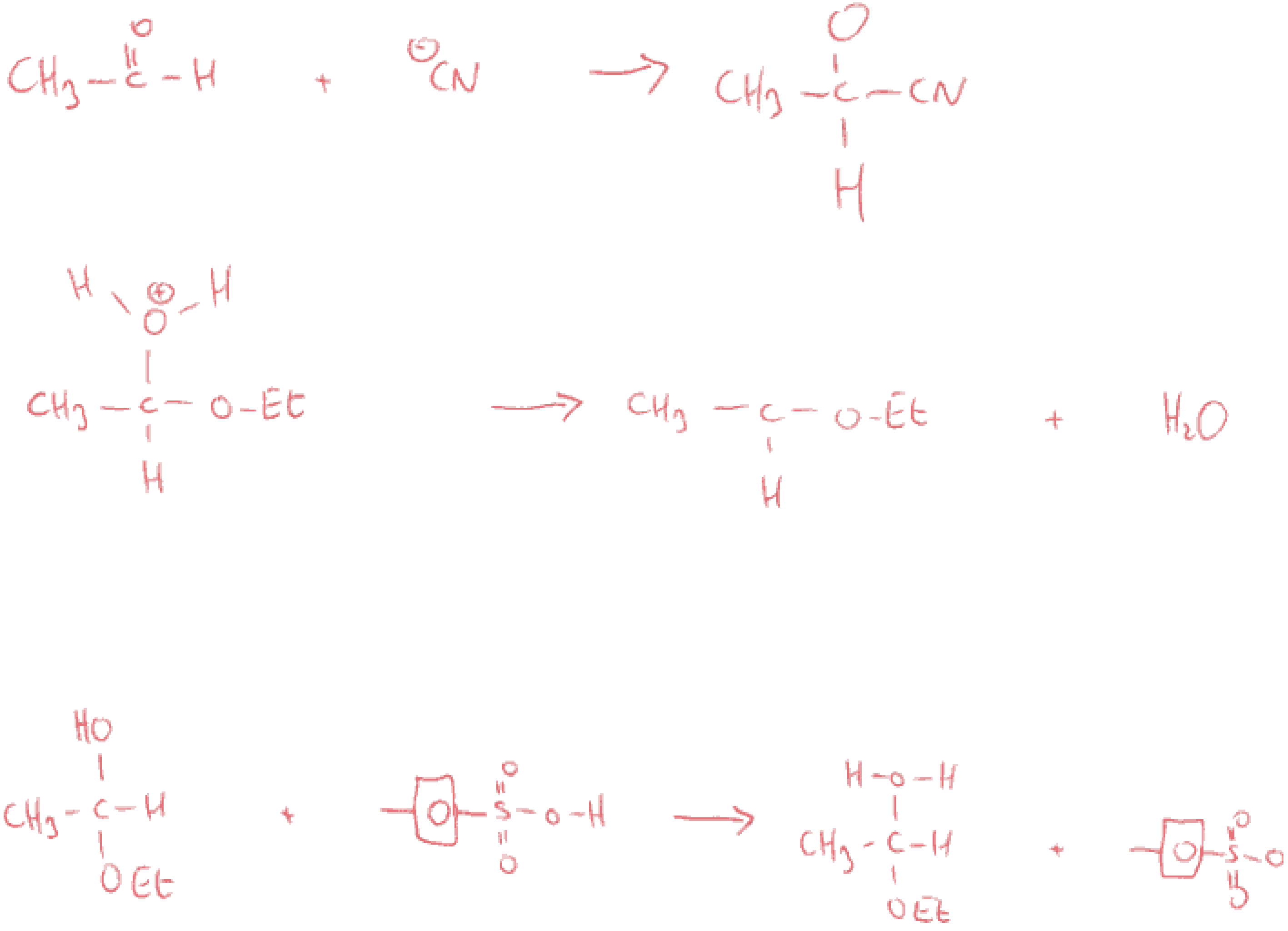
b) balanced.

Balanced but Wrong

Balanced and Correct.

Problems

Fill In the Charges



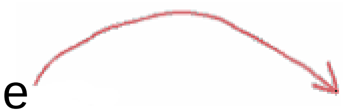
2) Using Arrows to show Electron Movement

Atoms don’t move.

It is the electrons that move, which results in bond reorganization, which connects previously unconnected atoms.

Curly arrow = movement of 2 electrons.

Arrows go from electron rich species to electron poor species.



Nucleophile Electrophile

CURLY ARROW RULES

i) Start of arrow must unambiguously indicate which 2 electrons are moving

ii) End of arrow must show exactly where the 2 electrons are going.

iii) Check the direction of the arrow, and that is makes “organic sense”

EVERY CURLY ARROW I SEE YOU DRAW, I WILL CRITICALLY EVALUTE USING THE ABOVE CRITERIA.

Hints

Draw out correct Lewis structures for your species. (Pay attention to lone pairs and charges).

Arrows will usually start at lone pairs or bonds. The nucleophilic part is normally partially or fully negatively charged.

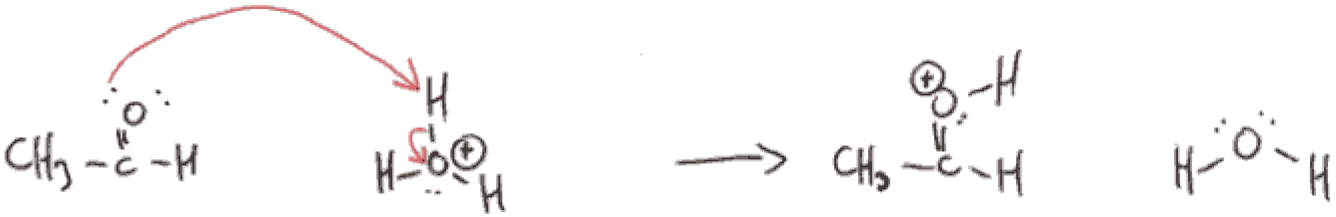
The arrows attack the electrophilic center / atom, which is partially or fully positively charged.

Remember dipoles (partial charges) arise from bonds of atoms with different Electronegativities.

It is rare to see two arrows coming to (or going from) the same atom in the one step.

Examples

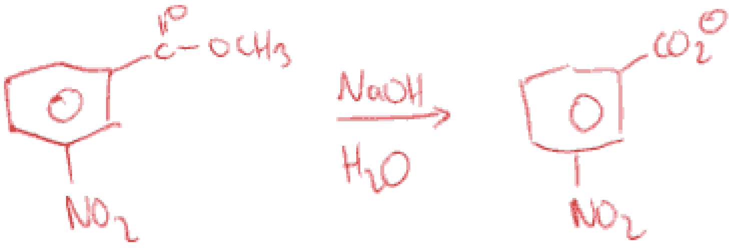
Mechanisms for the examples we saw earlier:



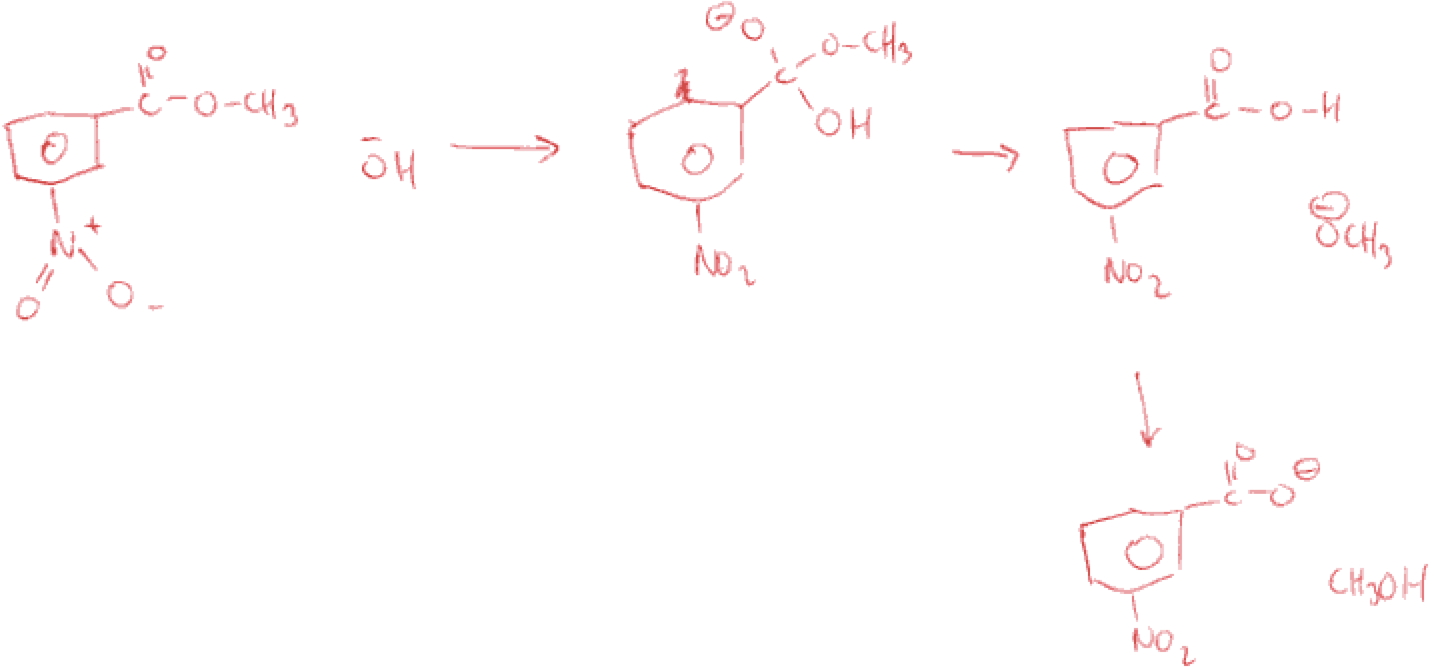
PROBLEM (a)

For these reactions, draw in the curly arrows:

(a)

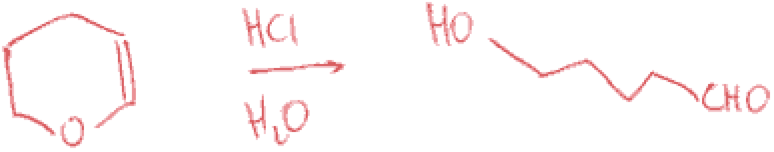


is the transformation.

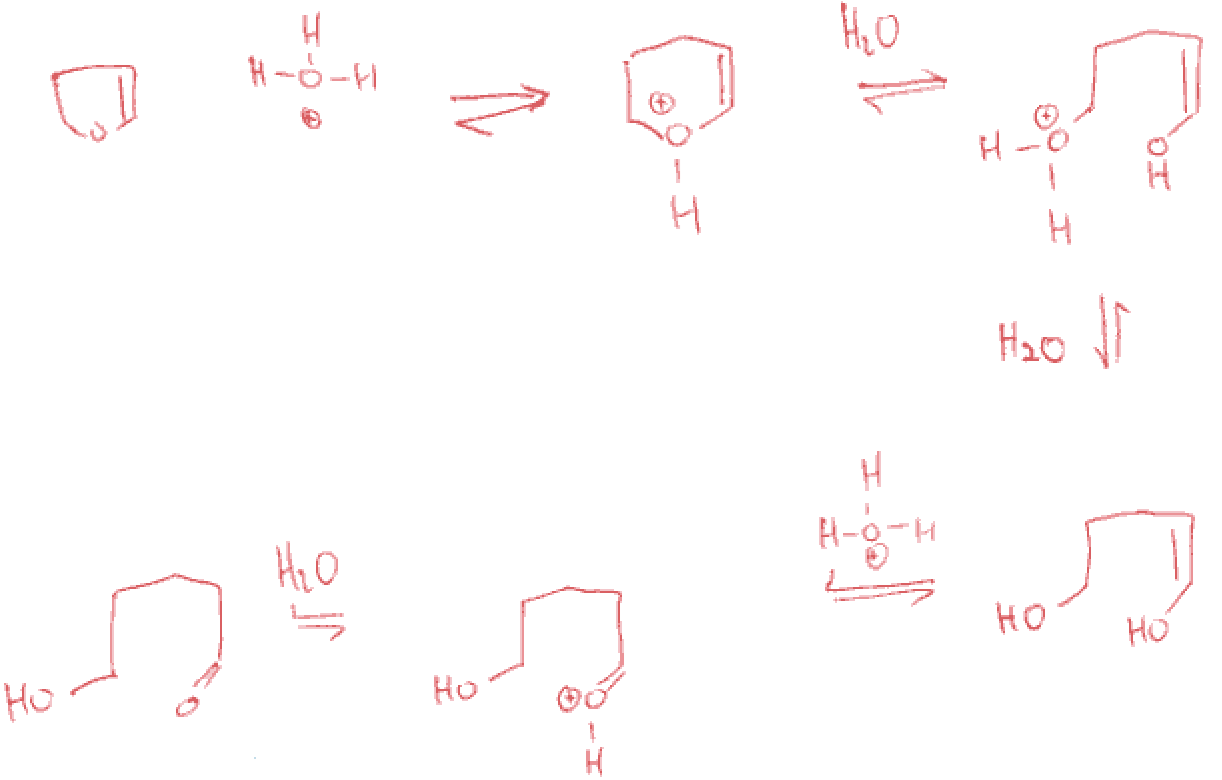


PROBLEM (b)

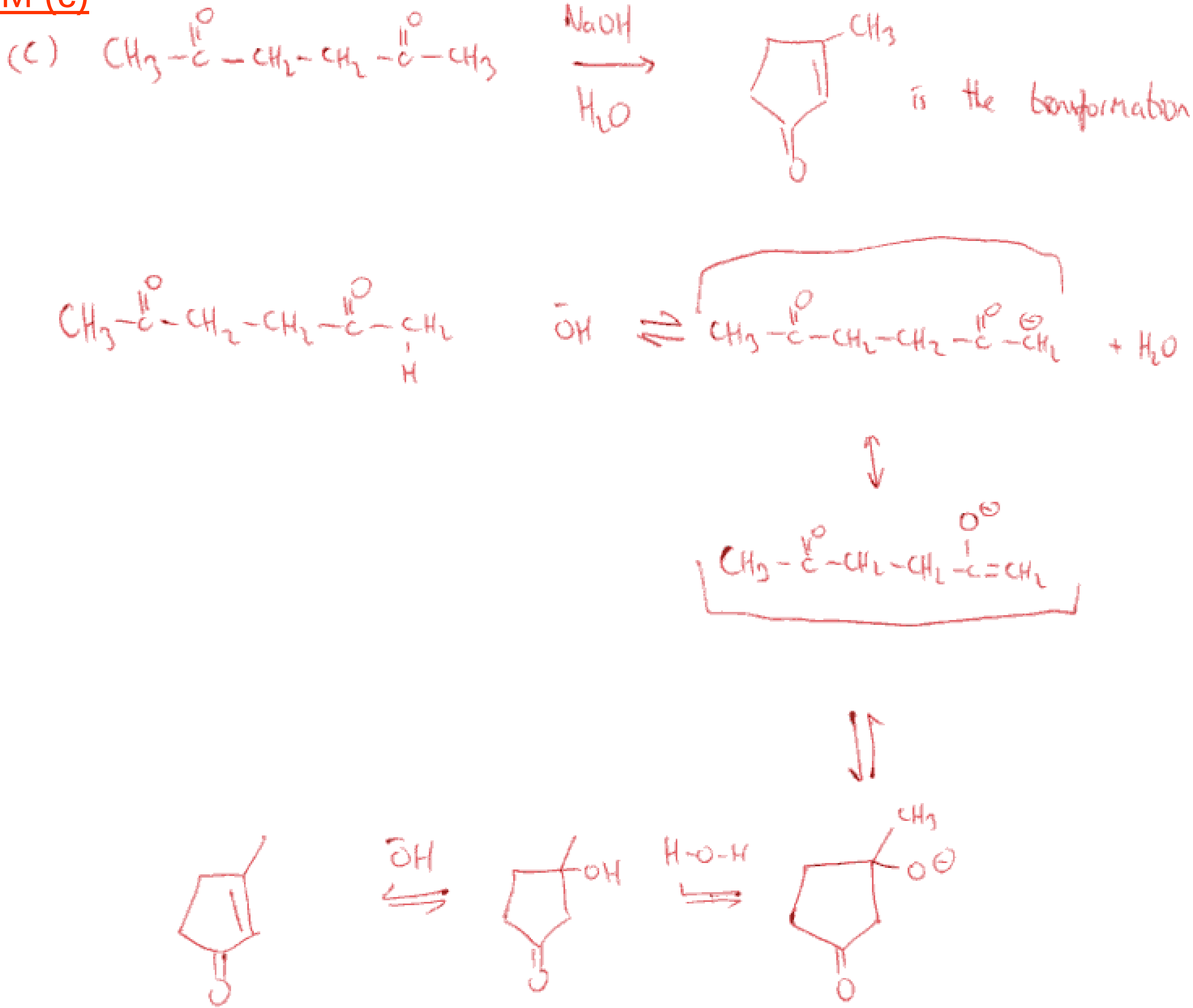
(b)



is the transformation



PROBLEM (c)


(c)
CH3–C(=O)–CH2–CH2–C(=O)–CH3
NaOH
H2O
CH3
is the transformation
CH3–C(=O)–CH2–CH2–C(=O)–CH2–H
⁻OH
CH3–C(=O)–CH2–CH2–C(=O)–CH2⁻
+ H2O
CH3–C(=O)–CH2–CH2–C(O⁻)=CH2
CH3
O⁻
H–O–H
OH
⁻OH

3) Mechanisms in Acidic and Basic Media

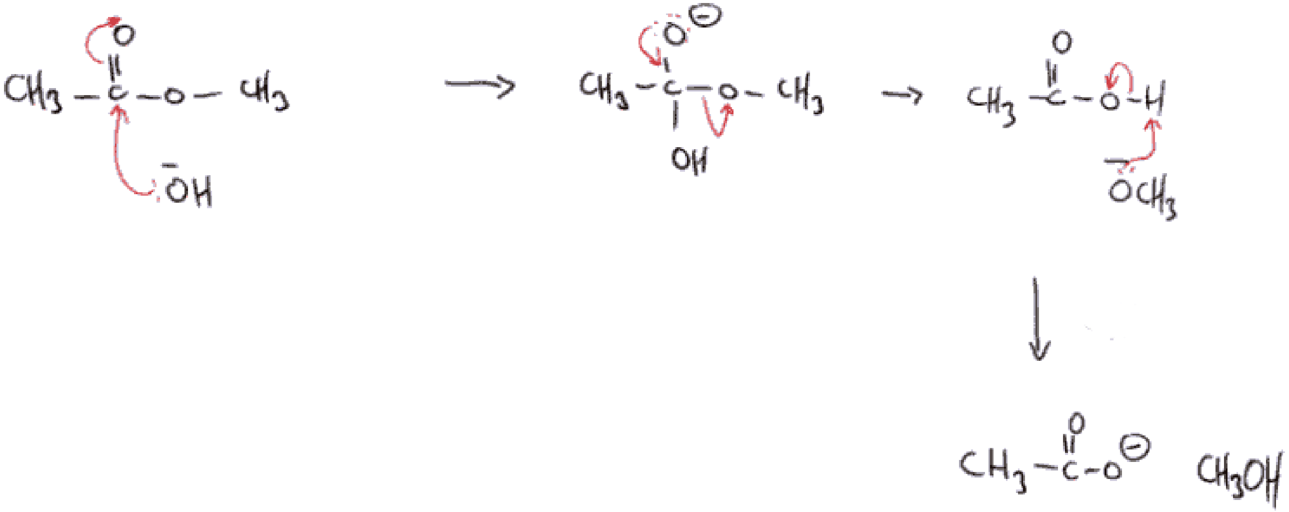
Rule

If a reaction is run in a strongly basic medium, any positively charged species must be weak acids. Equally, if a reaction in run in strongly acidic medium, any negatively charged species must be weak bases. In neutral media, both strongly acidic and basic species may be written in the mechanism.

This means you cannot write strongly acidic species existing in basic media, and vice versa.

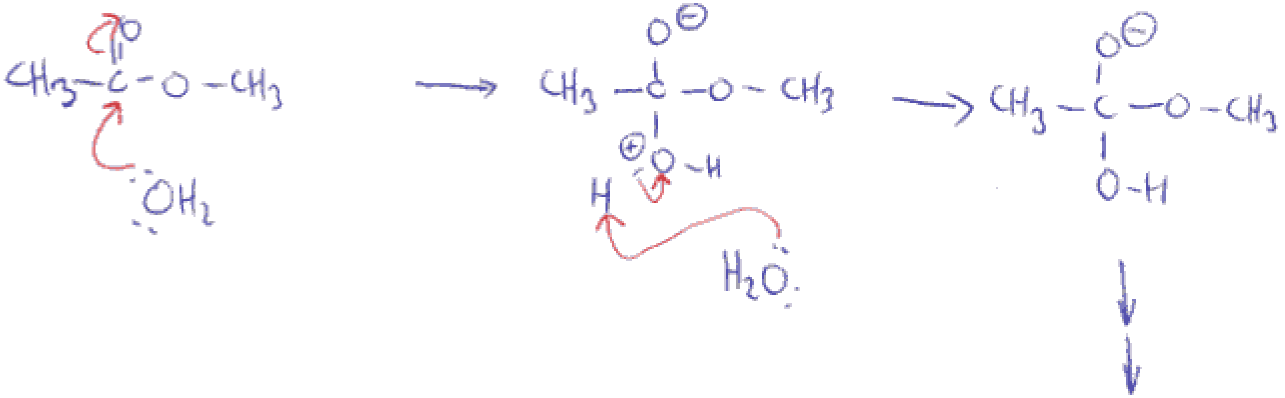
(....Because they won’t exist!)

Consider the hydrolysis of ester to carboxylic acid:

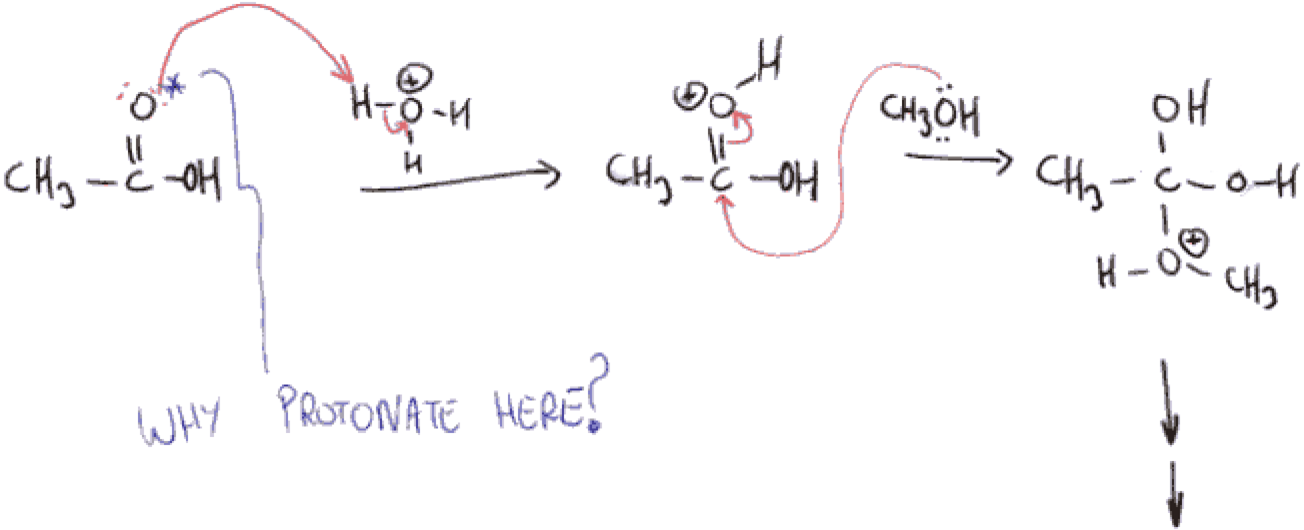


In strongly basic solution, the below mechanism is INCORRECT.

IN BASE this mechanism is WRONG.

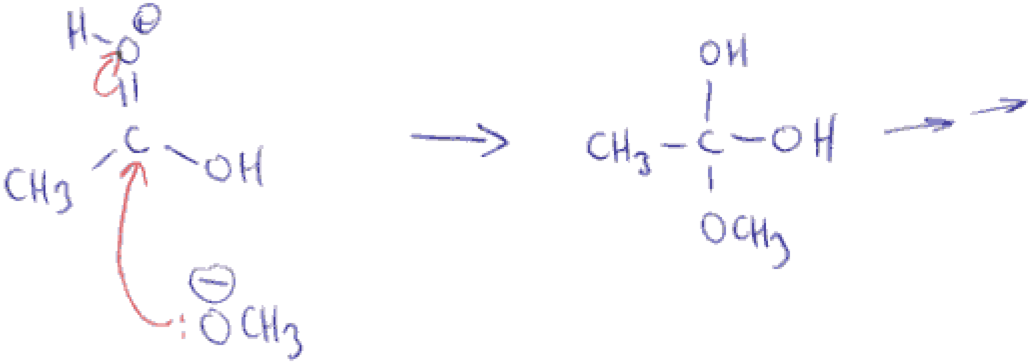


What about acid catalyzed esterification?

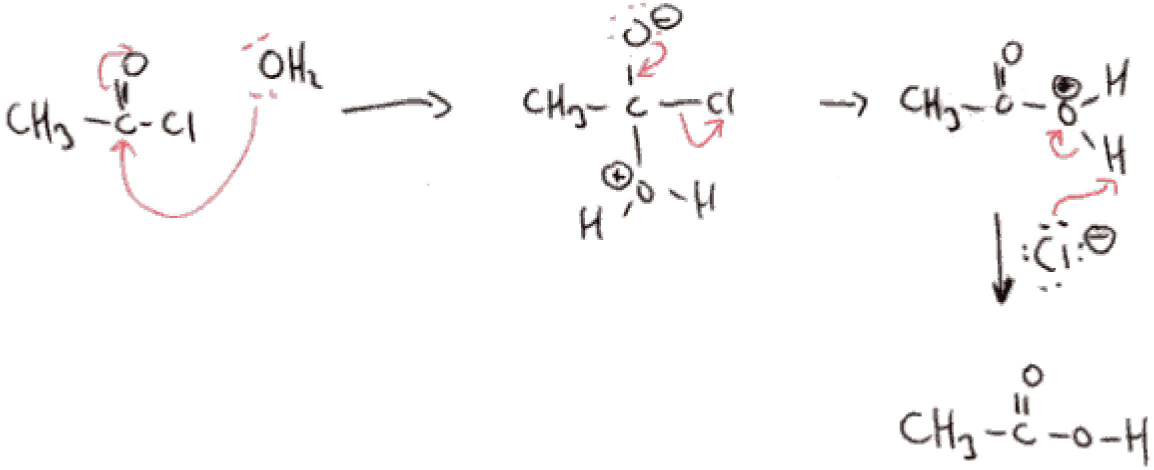


The below mechanism in acidic media is INCORRECT.

IN Acid this is INCORRECT.



What about neutral (weakly acidic or basic) media?



Hints

Approach writing a mechanism in a logical fashion: if a reagent is a strong base (e.g. NaOH), then look for an acidic hydrogen in your substrate, to generate an anion. Then the anion is going to do something that anions do (maybe do a Nuc attack, or expel a suitable leaving group, etc)

Chemists don't add random reagents.

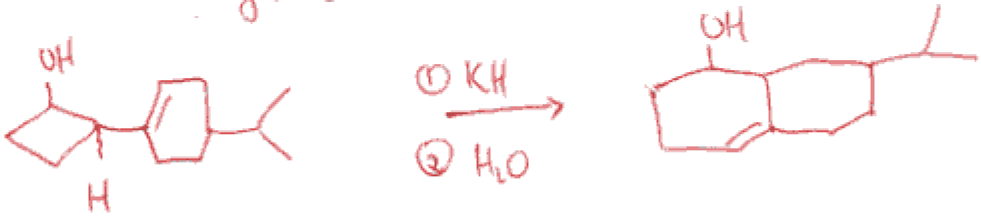
If they add an acid, there is a very good chance that something is going to get protonated...etc.

(You should be aware that sometimes removal of the most acidic hydrogen does NOT lead to a product. Such *unproductive* steps can occur, but through equilibrium, other *productive* hydrogens can be eventually removed, thus allowing product to form).

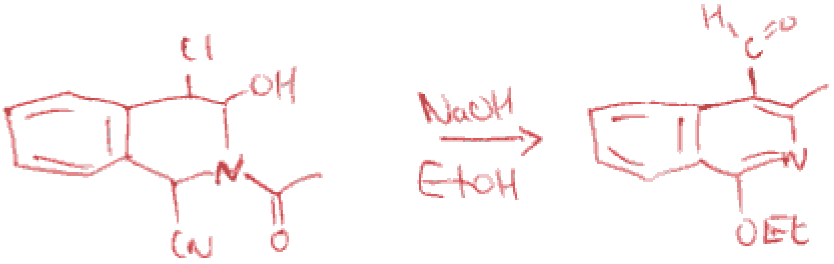
Problem (bases)

Circle the most acidic proton (also indicate the 2nd most acidic) in the starting material.

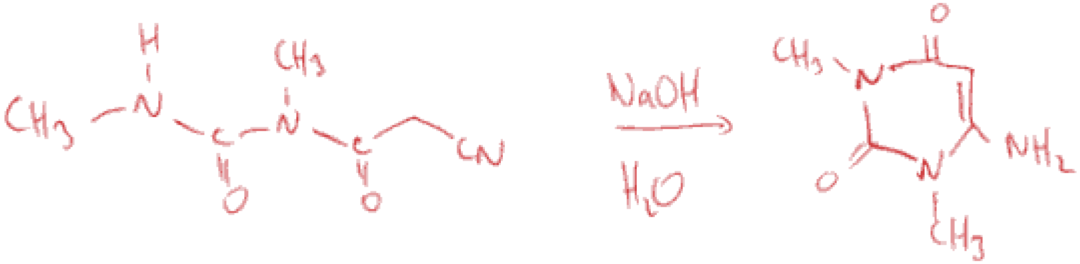
(a)



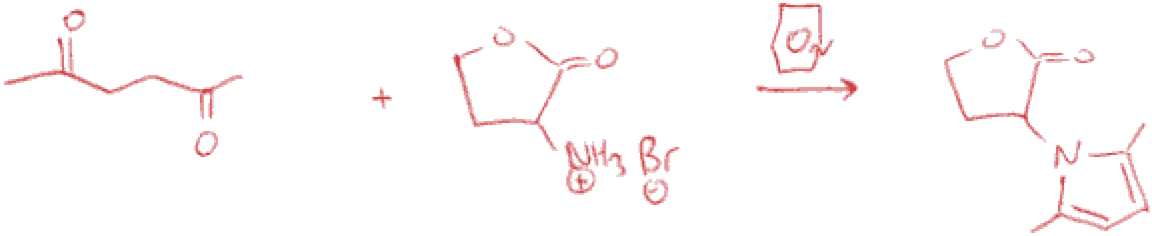
(b)



(c)



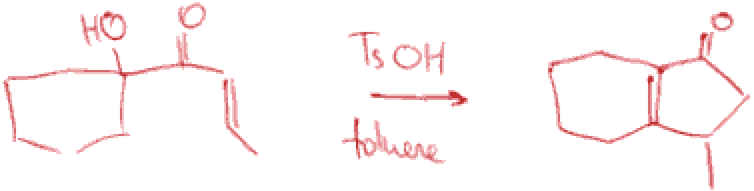
(d)



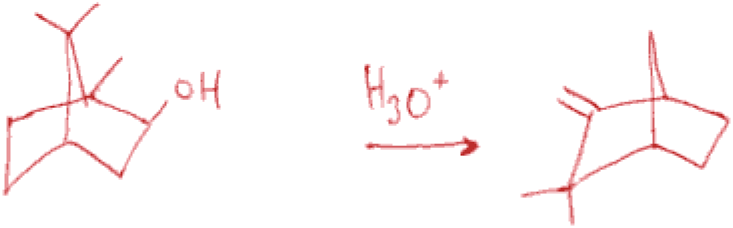
Problem (acids)

For these reactions, circle the atom most likely protonated in the S.M.

(a)



(b)



(c)

4) Electron rich Species: Nucleophile or Base?

An electron rich species, like a Lewis Base, can function as a nucleophile, and / or a base.

The dominant process depends on factors such as:

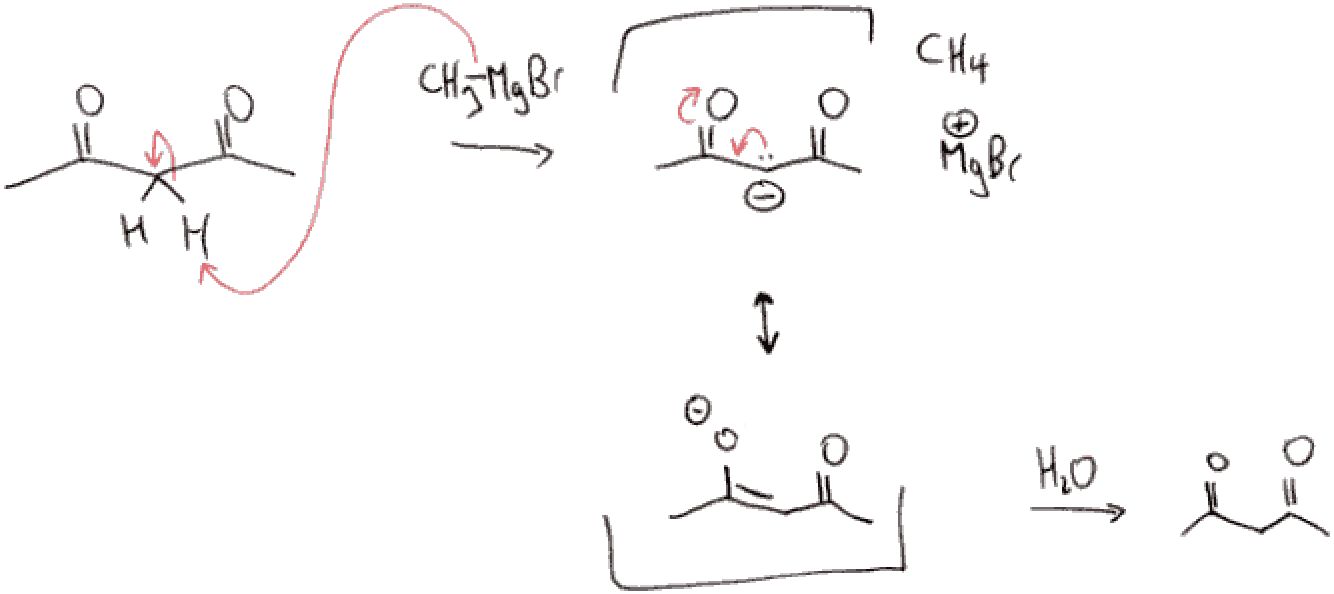
- i) the structure of the Lewis Base
- ii) the structure of the substrate
- iii) solvent
- iv) temperature.

Organometallics

Organometallic reagents function as bases 1st (faster) and nucleophiles 2nd (slower).

Common organometallics include Organolithiums (e.g. methyl lithium / CH_3Li / MeLi, butyl lithium, phenyl lithium) and Grignards (methyl magnesium bromide, phenyl magnesium bromide / PhMgBr / C_6H_5MgBr, etc).

Hence CH_3MgBr reacting with this diketone preferentially yields deprotonation as opposed to nucleophilic attack at the carbonyl.

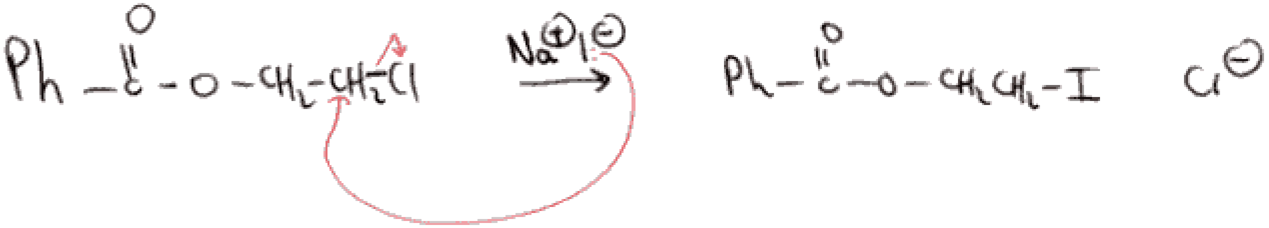


Halides

Halides are excellent nucleophiles but poor bases.

(I$^-$ better Nuc than Br$^-$ better than Cl$^-$ better than F$^-$)

Hence I$^-$ gives *predominant* substitution.



Alkoxides

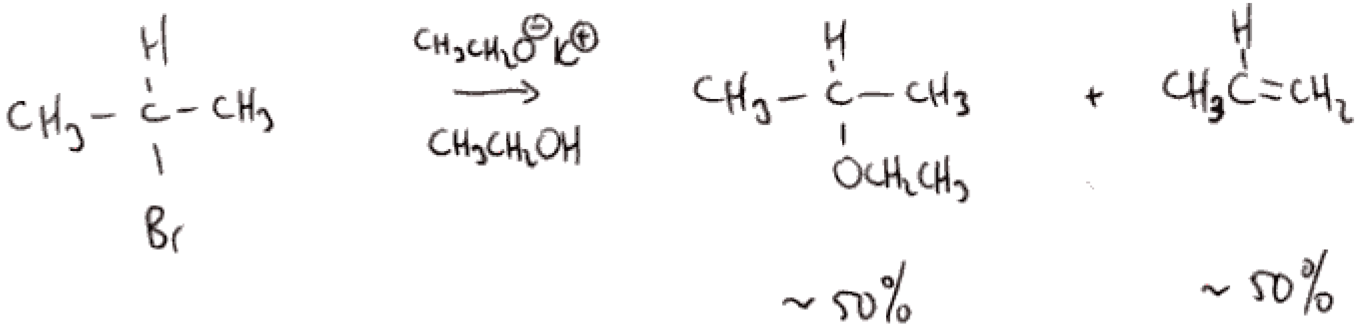
Alkoxides are good bases AND nucleophiles.

Steric bulk can discourage nucleophilicity

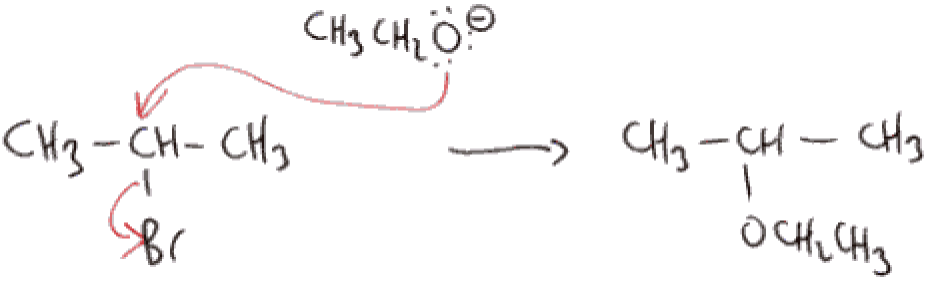
(^{t}Butoxide is less nucleophilic than Ethoxide).

Often you get both processes occuring in comparable amounts.

E.g.



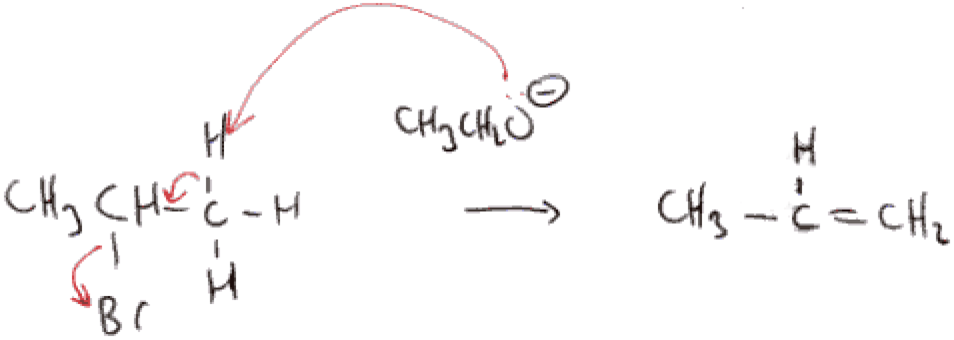
Substitution



SUBSTN.

(SN2)

Elimination



ELIMN

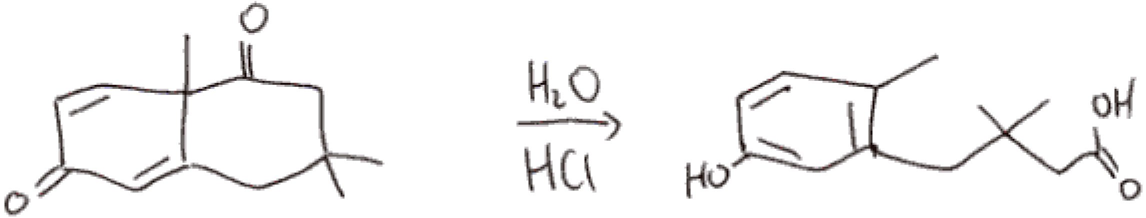
(E2)

Be aware that if you are given the product of a reaction, it should be obvious to determine if the electron rich reagent functioned as a base or a nucleophile.

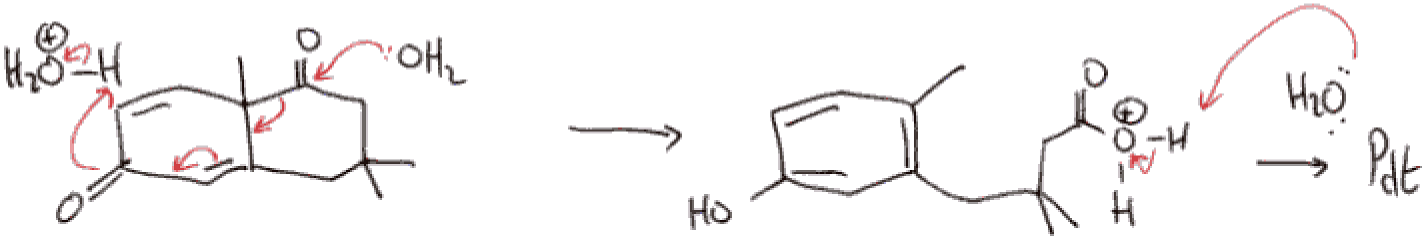
5) Trimolecular Steps

Despite lazy / inaccurate chemists writing such steps, these are in reality, very rare (entropy and orientation concerns).

E.g. this ring opening reaction in acidic conditions.



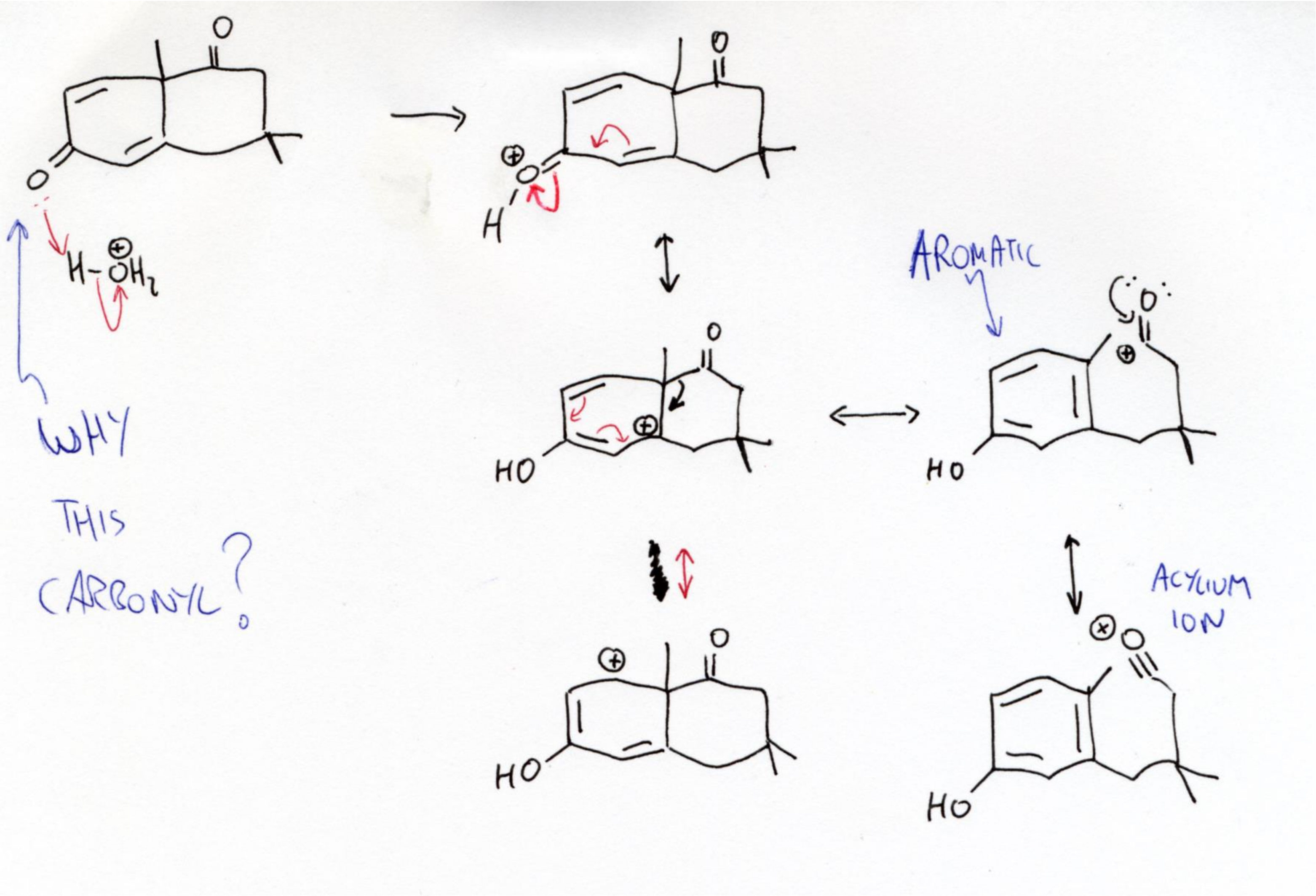
This mechanism could be proposed which includes a trimolecular step.



AVOID TRIMOLECULAR STEPS!!!

Ignoring other errors, it is unlikely that this all happens at the same time.

It would be better / more likely / more accurate to write an initial protonation, followed by a series of steps based on good organic science.



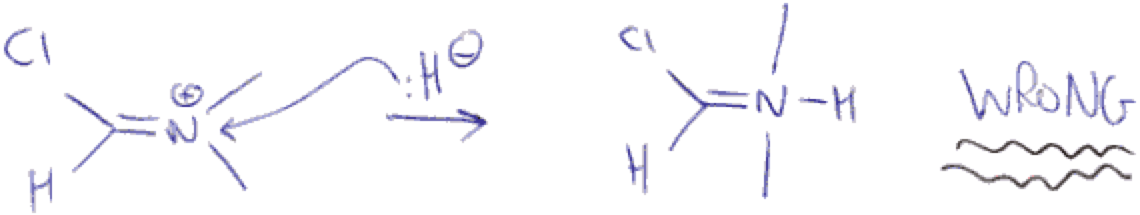
6) Stability of Intermediates

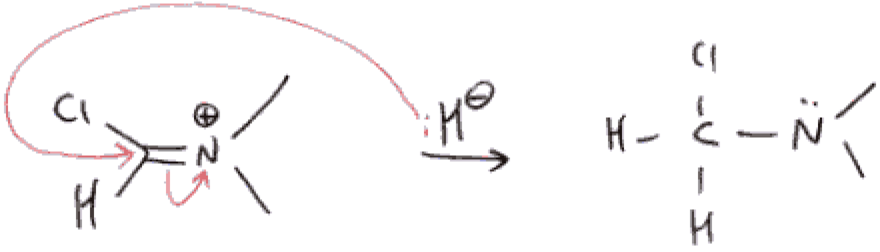
The intermediates you write during a mechanism must:

i) be able to physically exist

ii) have a reasonable stability.

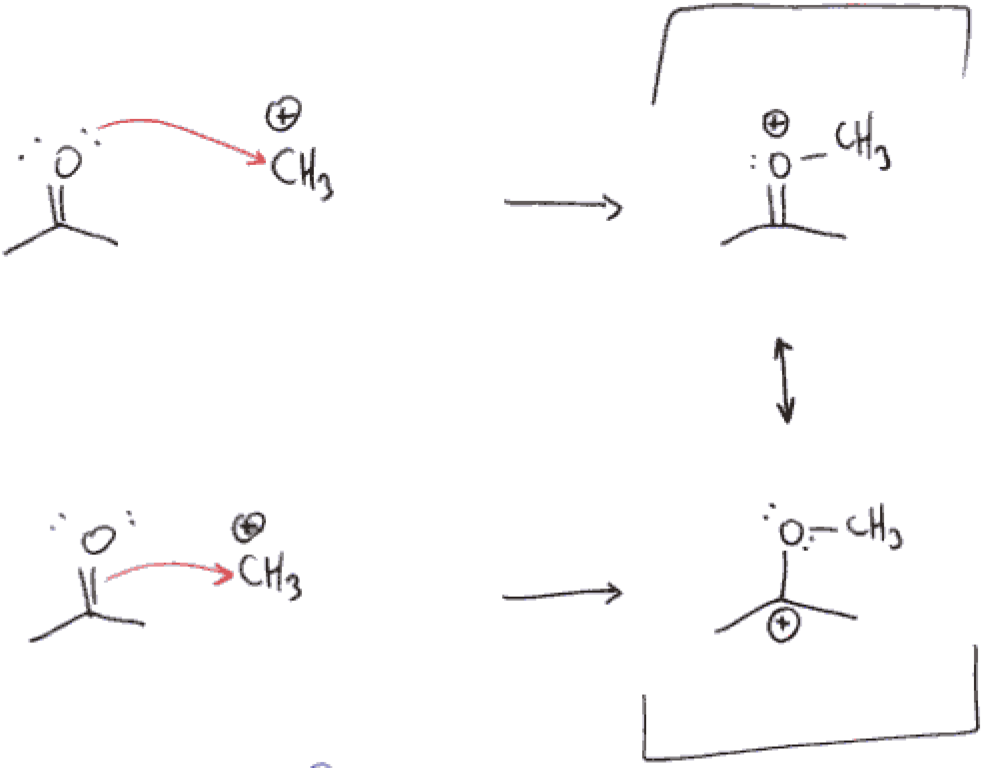
for example, Hydride reduction of imine derivatives.





Be aware that if your species has a positive N or O with only 6 electrons around it (nitrenium / oxenium ion), you are probably doing something wrong.

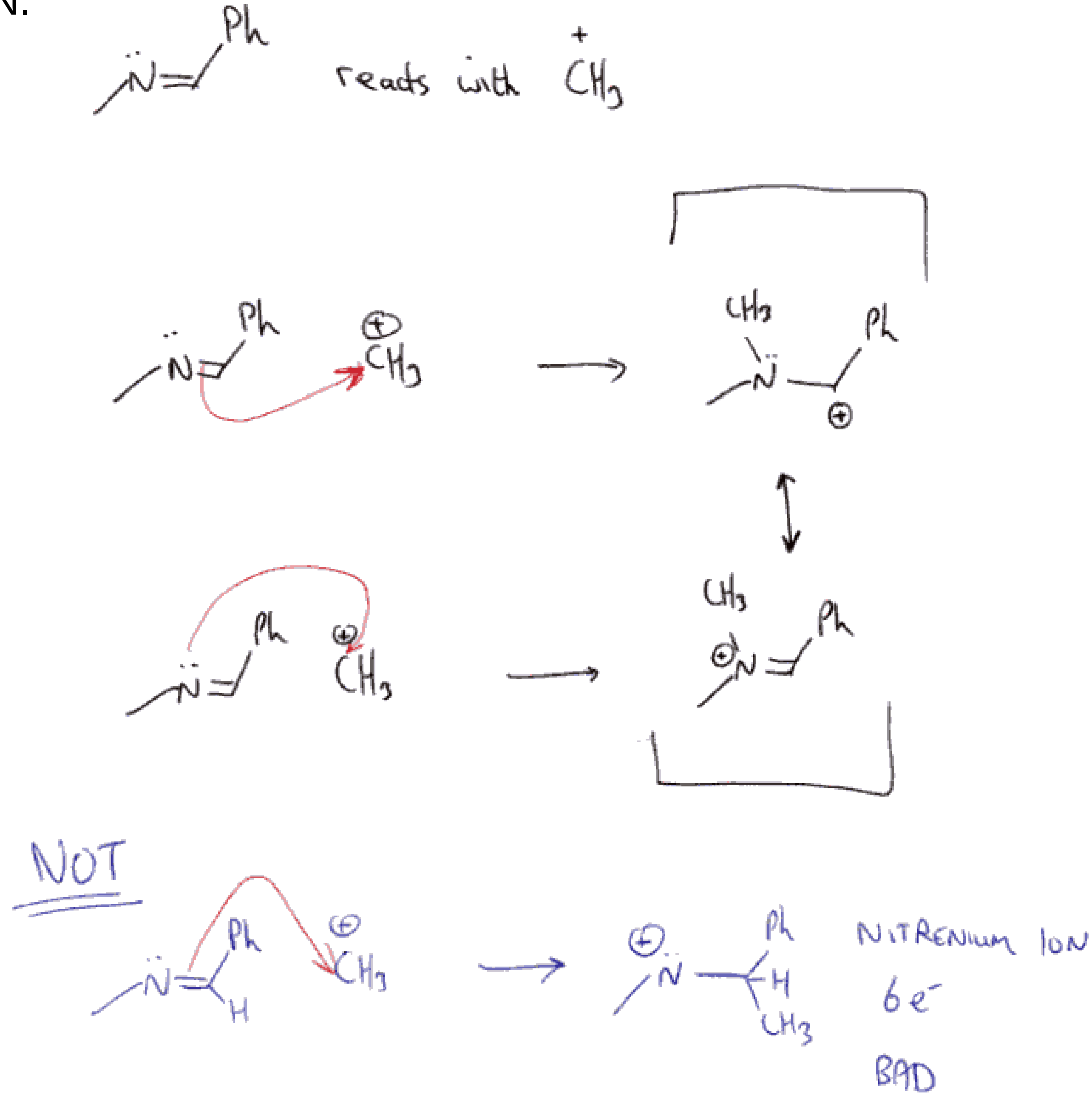
E.g.  reacts with $^{\oplus}CH_3$



OXENIUM
ION
6 e⁻
BAD

WRONG

Similarly with N.



7) Driving Forces for Reactions

Viable reaction steps should have some energetic driving force.

For example, formation of a:

(a) stable inorganic product
(b) stable double bond (conjugation / aromaticity even better)
(c) stable carbocation / anion / radical (resonance helps)
(d) stable small molecule (liberated gas means *irreversible*).

Decrease in enthalpy (forming stronger bonds = lower energy) is good.

Increase in entropy (forming more species) is also good.

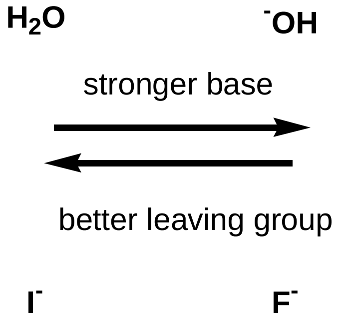
When writing a mechanism, constantly ask yourself ***"WHY would this step occur?"***

(Especially because I will be constantly asking you this question!!)

(a) Leaving Groups

If a reaction involves a nucleophilic substitution, the nature of the leaving group is fundamental to the success (or failure) of the reaction.

Typically leaving group ability is inversely related to base strength.



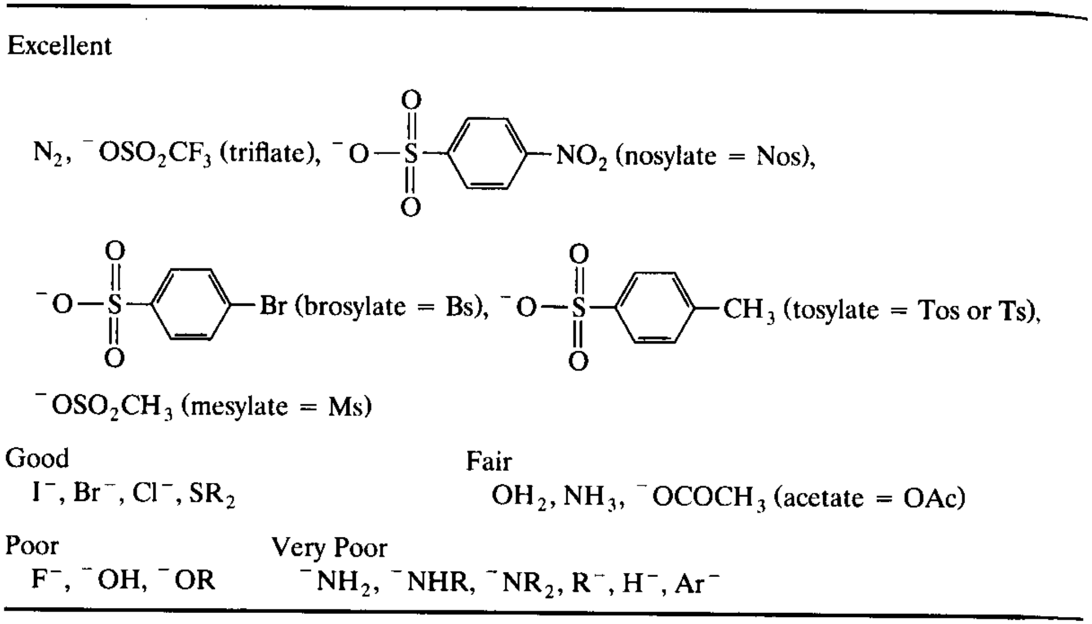
H_2O ^{-}OH

stronger base

better leaving group

I^{-} F^{-}

Common Leaving groups



Excellent

N_2, $^{-}OSO_2CF_3$ (triflate), $^{-}O-\overset{O}{\underset{O}{S}}-C_6H_4-NO_2$ (nosylate = Nos),

$^{-}O-\overset{O}{\underset{O}{S}}-C_6H_4-Br$ (brosylate = Bs), $^{-}O-\overset{O}{\underset{O}{S}}-C_6H_4-CH_3$ (tosylate = Tos or Ts),

$^{-}OSO_2CH_3$ (mesylate = Ms)

Good

I^{-}, Br^{-}, Cl^{-}, SR_2

Fair

OH_2, NH_3, $^{-}OCOCH_3$ (acetate = OAc)

Poor

F^{-}, ^{-}OH, ^{-}OR

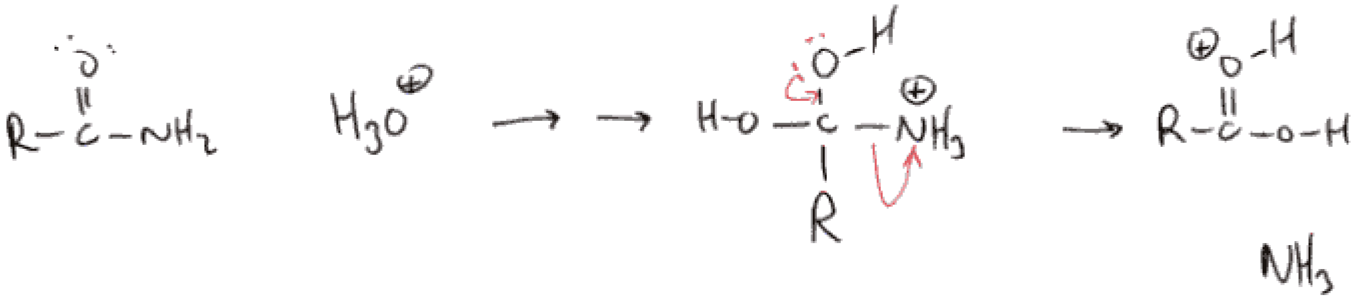
Very Poor

$^{-}NH_2$, ^{-}NHR, $^{-}NR_2$, R^{-}, H^{-}, Ar^{-}

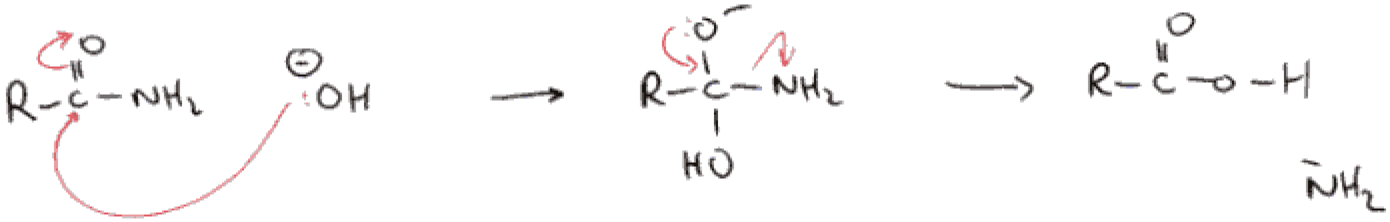
The worse the leaving group, the better the nucleophile required to expel it.

For example in the hydrolysis of amides.

HOH (weaker nuc) can expel NH_3 (good LG)



Whereas HO^- (stronger nuc) required to expel $^-NH_2$ (poor LG).

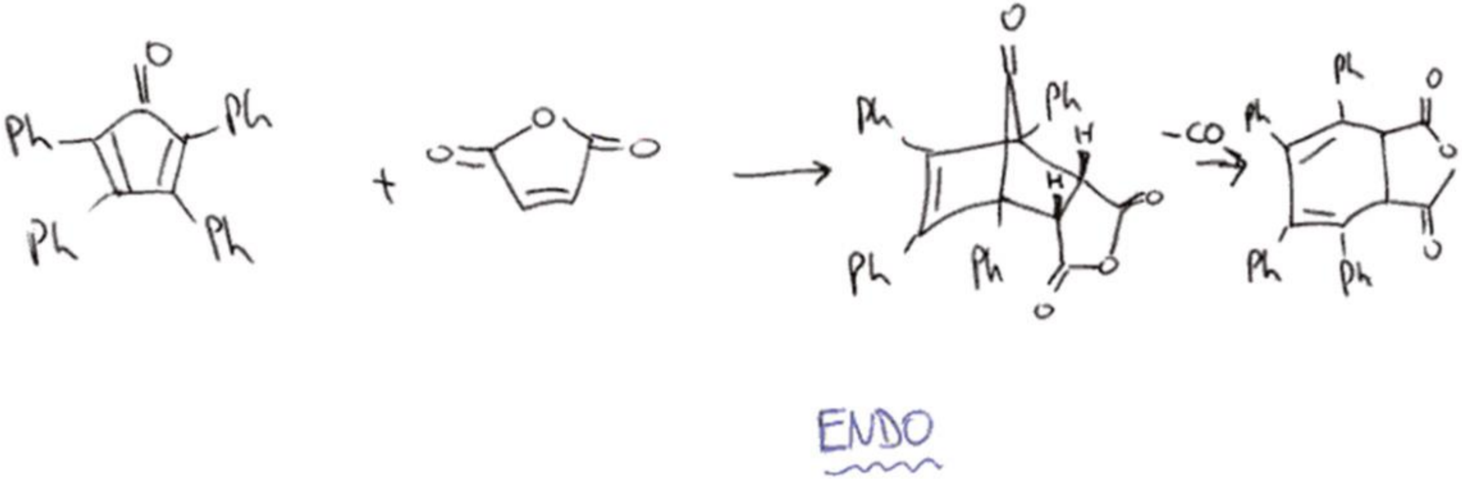


(b) Forming a small stable molecule

This is a very significant driving force for a reaction for entropic and enthalpic reasons.

Common small molecules which are formed / expelled include N_2, CO_2, CO, H_2O, SO_2...etc.

E.g. extrusion of carbon monoxide.



8) Structural Relationship between Starting Materials and Products

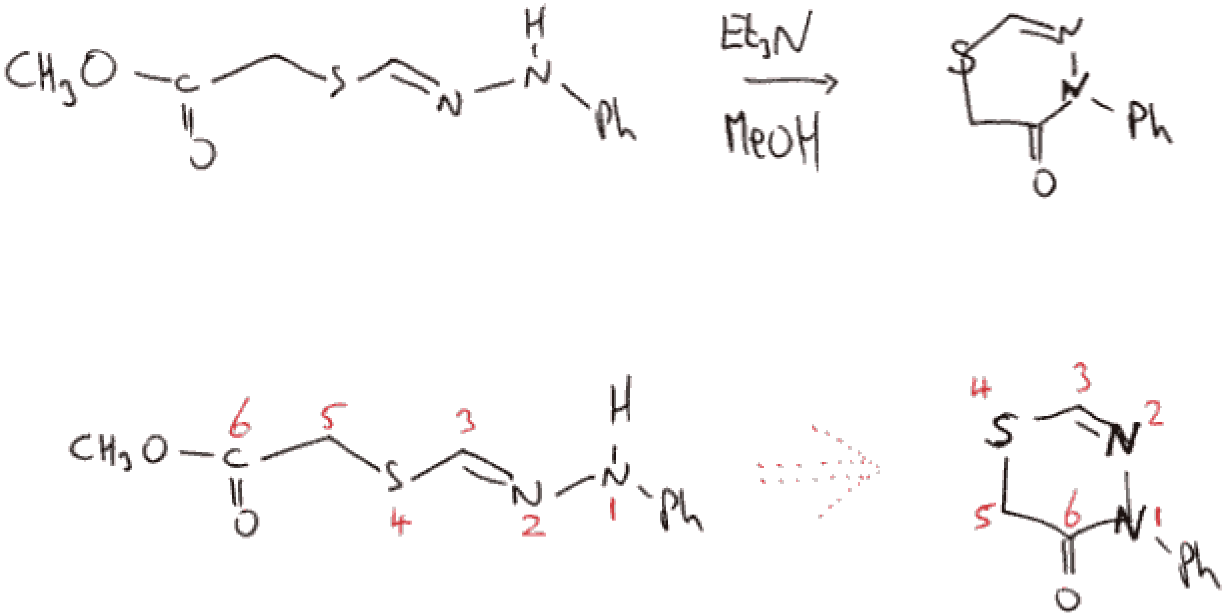
One of the most helpful strategies for elucidating a reaction mechanism is recognizing / identifying the structural relationship between the starting material and the product.

This is most easily done by numbering (or labeling) the SM in any **logical** order.

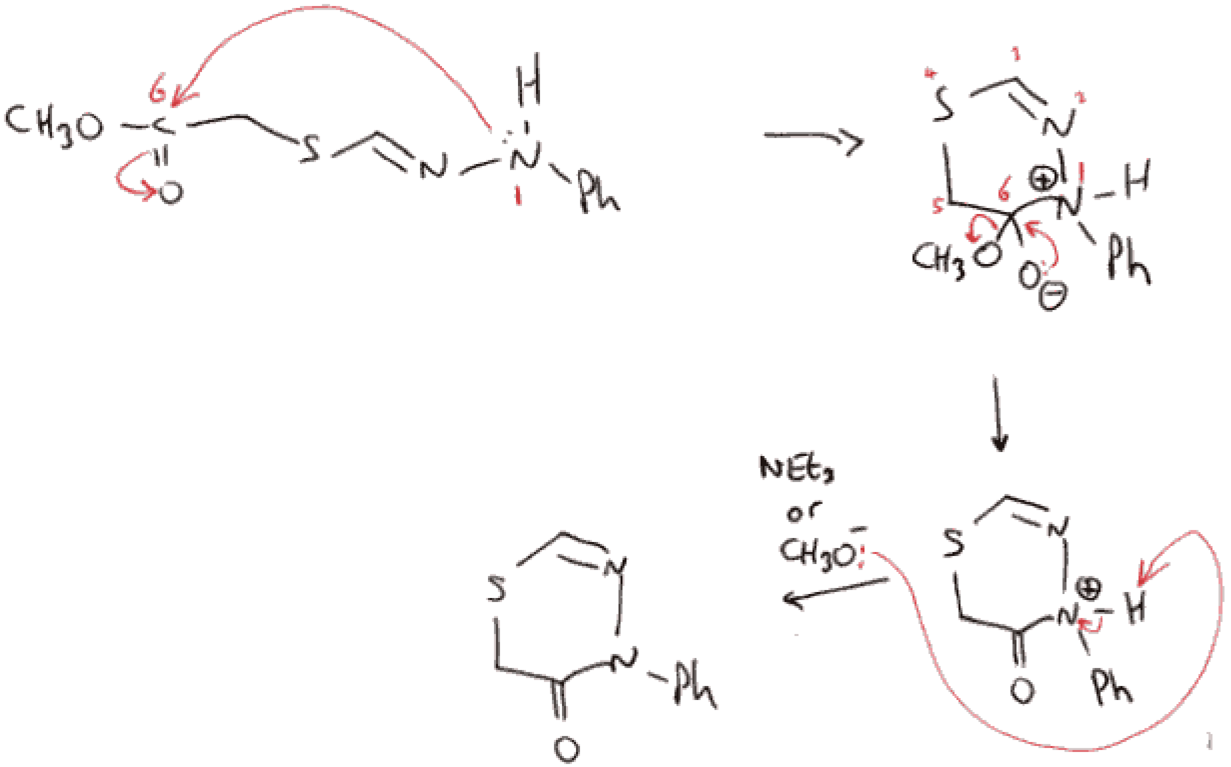
Then look for common sequences of atoms and bonding patterns in the product, and assign the obvious corresponding atoms in the product.

The rest of the assignments usually follow on from the smallest possible number of bond changes.

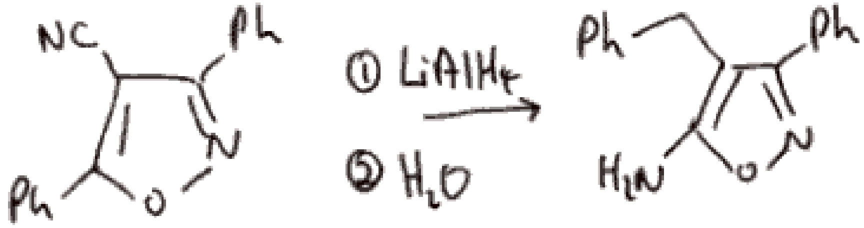
For example:



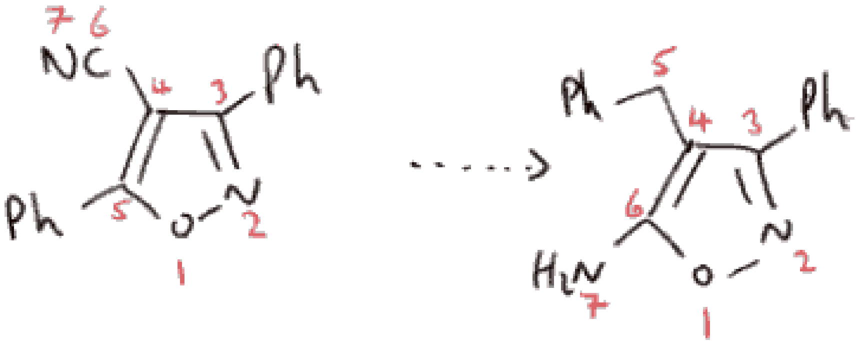
This tells us that N-1 gets connected to C-6, which helps us start writing a good mechanism.



The same approach would helps us in this example:



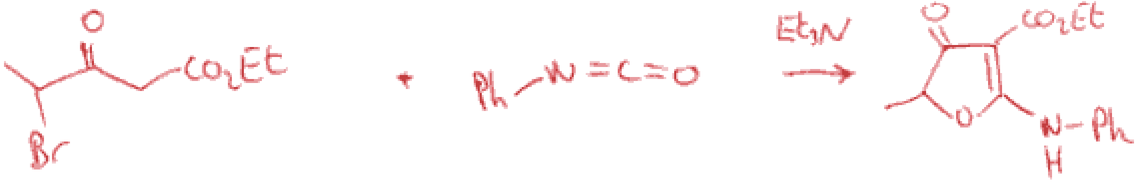
Numbering the SM, and then the product tells us that O-1 and C-5 have disconnected, and O-1 and C-6 need to be connected.



PROBLEMS

Number the starting material atoms, & label the same atoms in the product

(a)



(b)

9) Effect of Solvent

Normally the primary effect of a solvent is to provide a medium in which the reactant and SM can all come in contact with one another, and thus react.

Therefore the SOLUBILITY is a major consideration for solvent choice.

However, solvent can subtly influence the mechanism of a reaction.

Solvents are broadly classified into 3 types:

(1) Polar, protic solvents (water, alcohols, acids, ...)
(2) Polar, aprotic solvents (DMF, DMSO, CH_3CN, acetone, HMPA, [very polar]).
(3) Non-polar solvents (hexane, benzene, CCl_4 [very non-polar];
then chloroform, THF, ethyl ether [more polar]).

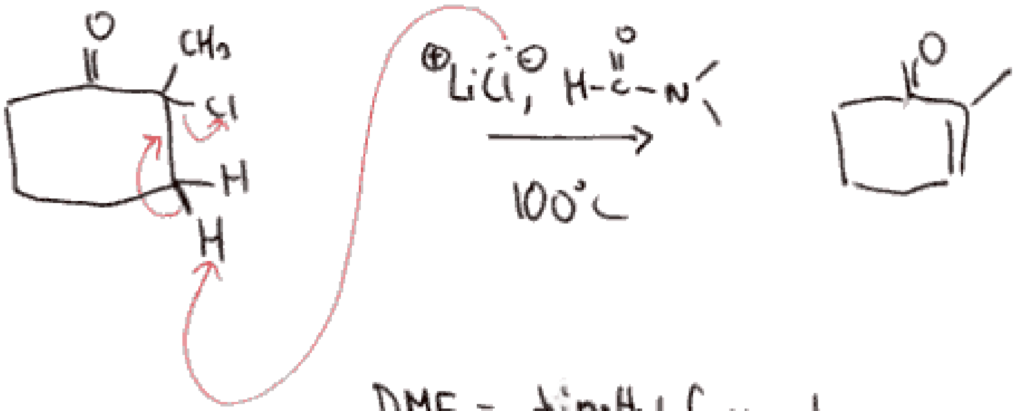
Interactions between polar solvents and charged species are stabilizing.
Polar, protic solvents can stabilize anions and cations.
Polar, aprotic solvents can stabilize cations.

Thus S_N1 reactions are encouraged by polar solvents.

Influence of solvent on basicity

Chloride ion is usually thought of as a weak base.

Below Cl^- acts as a base since the polar, aprotic solvent solvates the Li^+, leaving the Cl^- naked, and thus of enhanced reactivity.



DMF = dimethyl formamide

= Polar Aprotic Solvent

10) Occam’s Razor

A famous 14th century English philosopher William of Occam came up with a principle know as “Occam’s Razor”.

“One should not increase, beyond what is necessary, the number of entities required to explain anything”.

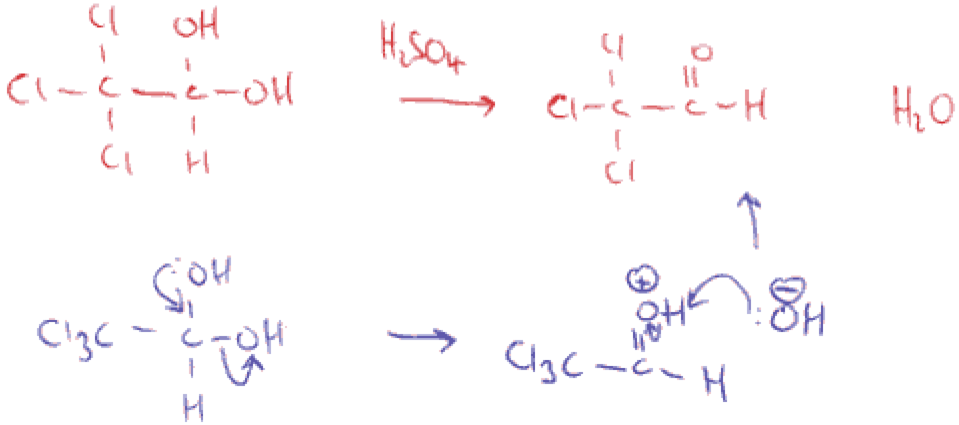
When we are dealing with mechanisms, often we will be confronted with several possible mechanistic solutions.

Occam’s Razor tells us *the **simplest** one is usually the **best** one.*

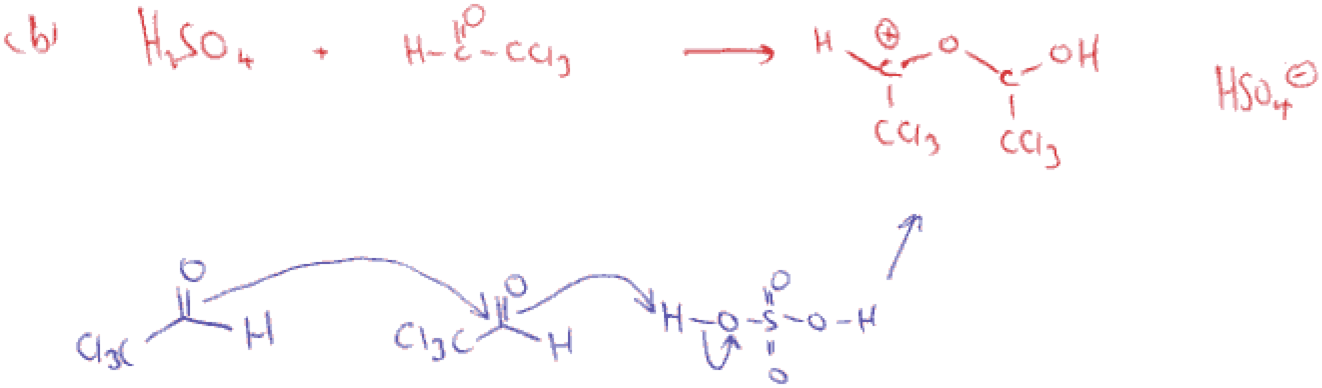
Last Four Problems in Ch2

For each transformation, a "bad" mechanism is provided.
Highlight the errors, & write a "good" mechanism.

(a)

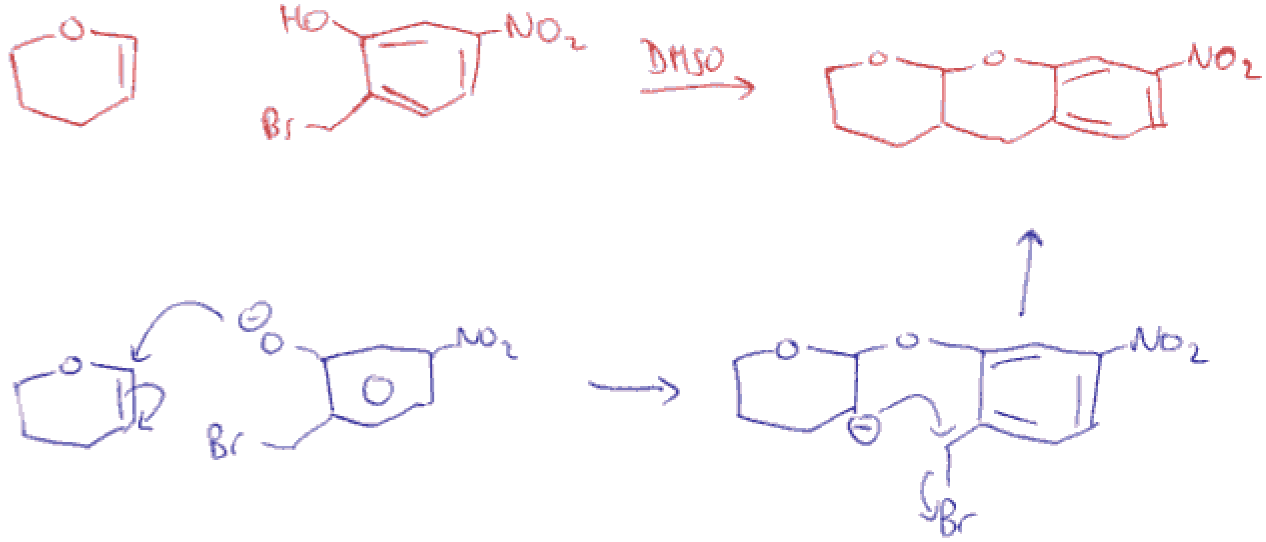


Last Problems in Ch2



Last Problems in Ch2

(c)



Last Problems in Ch2

(d)