

CHEMISTRY 4000

Topic #2: Functional Group Oriented Bond-Sets

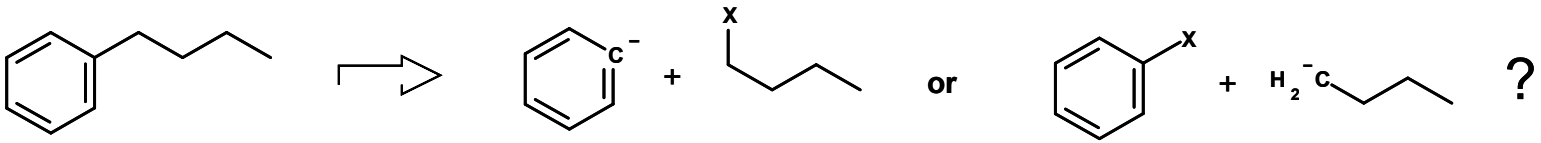
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Synthons for Polar Bond Formation

- Once we identify a bond-set, we have to generate a corresponding set of forward reactions. Knowledge of an available set of forward reactions tends to strongly influence choice of bond-set.

- Often, the forward reaction is a polar bond formation so it involves a nucleophile and an electrophile. First, identify which of the two pieces will serve as nucleophile and which will serve as electrophile.



- In this example, one option should appear substantially better than the other. In some cases, both options are feasible – but you still have to choose one to try first!

Synthons for Polar Bond Formation

- The functional groups in the target will tend to dictate which piece serves as the nucleophile and which serves as the electrophile (hence the term 'functional group oriented bond-set').

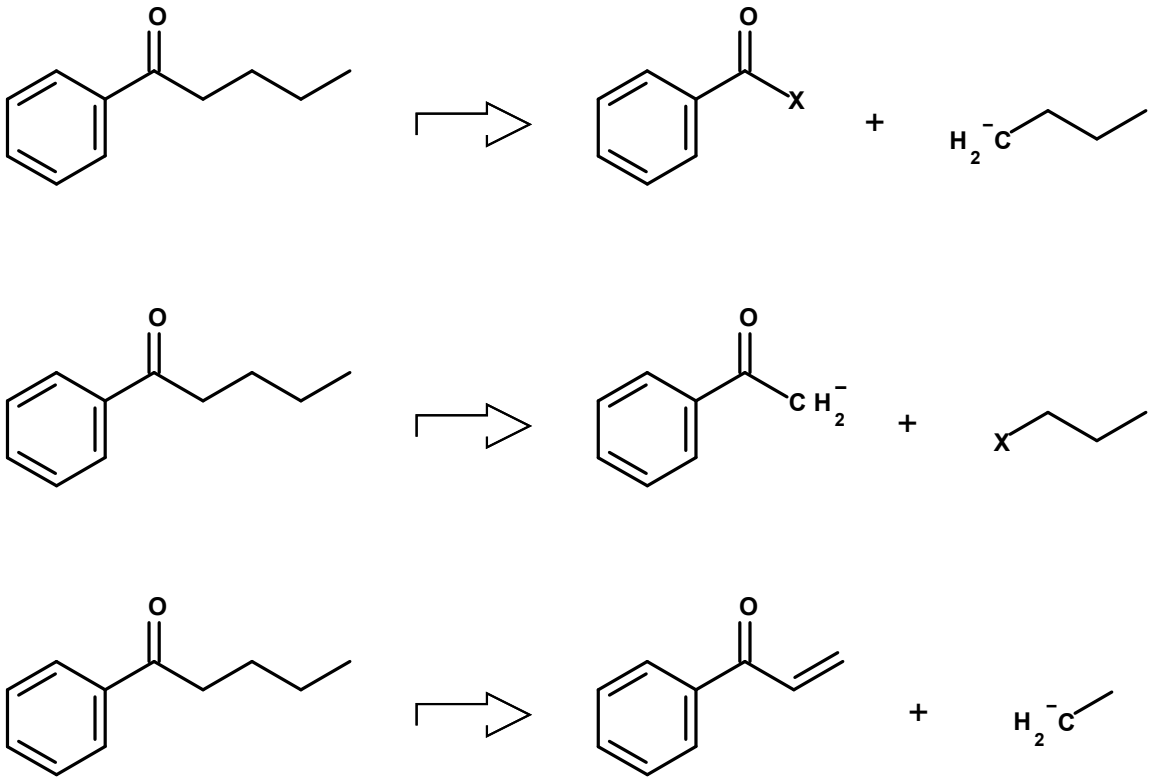
- Each piece is referred to as a **synthon**.
  - The nucleophilic piece is the donor synthon (or d-synthon).
  - The electrophilic piece is the acceptor synthon (or a-synthon).

Synthons for Polar Bond Formation

- In the example on page 2, the aromatic ring dictated the choice of donor and acceptor synthons. What if, instead of disconnecting next to the aromatic ring, we had chosen to disconnect at the next C-C bond in the chain?

Synthons for Polar Bond Formation

- Consider the influence of a carbonyl group on a nearby retrosynthetic disconnection. There are three reasonable choices for disconnections in the vicinity of a carbonyl:



See the end of this set of notes for more on reactions corresponding to the third disconnection.

Synthons for Polar Bond Formation

- Information about how close a synthon is to the functional group in question can also be encoded in the synthon name.
  - A donor synthon which donates electrons from a carbon directly attached to a heteroatom is a d^1-synthon.
  - A donor synthon which donates electrons from a carbon 2 bonds away from the heteroatom is a d^2-synthon.
  - A donor synthon which donates electrons from a carbon 3 bonds away from the heteroatom is a d^3-synthon.

  - An acceptor synthon which accepts electrons at a carbon directly attached to a heteroatom is an a^1-synthon.
  - An acceptor synthon which accepts electrons at a carbon 2 bonds away from the heteroatom is an a^2-synthon.
  - An acceptor synthon which accepts electrons at a carbon 3 bonds away from the heteroatom is an a^3-synthon.

- Classify the 3 carbonyl-containing synthons on the previous page.

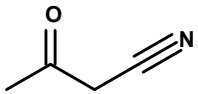
Synthons for Polar Bond Formation

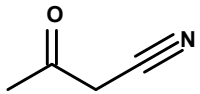
- Of course, there will be a variety of different ways to achieve each desired connection – hence the use of the generic X in place of heteroatoms in many synthons. Functional group interchanges (FGI) allow for alternate approaches using the same bond-set. These alternate approaches are not always as elegant but, if Plan A fails, it's nice to have Plans B, C, D, etc.

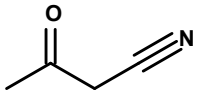
Synthons for Polar Bond Formation

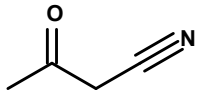
Synthons for Polar Bond Formation

- If there are two (or more) functional groups near a proposed retrosynthetic disconnection, they will each influence one synthon. We must still have one electron donor and one electron acceptor:

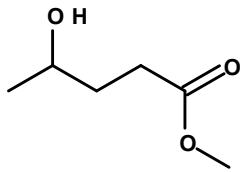


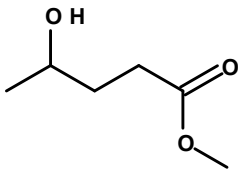


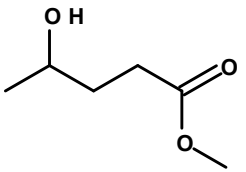


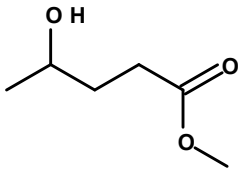


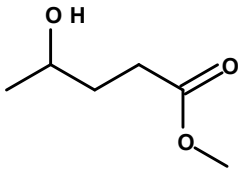
Synthons for Polar Bond Formation

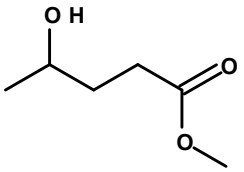












Synthons for Polar Bond Formation

- It is ideal if each of the closest functional groups enhances the reactivity of one of the synthons. This is the case for a^1, d^2, a^3 and d^4 synthons. These are the natural synthons.

- If the distance between the two functional groups means that it is not possible for both synthons to be natural, the non-natural one will require special attention.

- When we go against natural reactivity patterns in organic chemistry, we have to create an Umpolung effect – making an atom that is usually electrophilic be nucleophilic or making an atom that is usually nucleophilic be electrophilic. So, a non-natural synthon will be an **umpoled** synthon.

Synthons for Polar Bond Formation

- Use of two umpoled synthons would not normally be first choice. That's usually too much work! ☺ Considering this, re-evaluate the disconnection options for the examples on pages 9 and 10.

- When might a double umpolung approach be useful?

Umpoled Synthons for Polar Bond Formation

- There are lots of different functional groups which could correspond to an a^1-synthon:

After all, most heteroatoms are more electronegative than carbon, so a carbon atom with one or more bonds to heteroatoms is usually partially positive and therefore electrophilic.

Umpoled Synthons for Polar Bond Formation

- How do we choose a molecule that will correspond to a d^1-synthon?
  - It will have to be a carbanion (to overcome the effect of the polar bonds noted on the previous page).
  - We know that you can't deprotonate an aldehyde or on the same carbon as a leaving group. Those hydrogens aren't acidic enough!
  - So, what anions *can* we make in which the anionic carbon has one or more bonds to heteroatom(s)?

Umpoled Synthons for Polar Bond Formation

- How do we choose a molecule that will correspond to an a^2-synthon?
  - We have to make sure that the planned electrophilic carbon atom is *more* electrophilic than the one attached to the heteroatom.
  - We might be able to have Br or I attached to the planned electrophilic carbon atom:

Umpoled Synthons for Polar Bond Formation

- We might have to use a "protecting group" as well in order to reduce the reactivity of the functional group thereby favouring reaction at the planned electrophilic carbon atom:

Umpoled Synthons for Polar Bond Formation

- An epoxide an also function as an a^2-synthon:

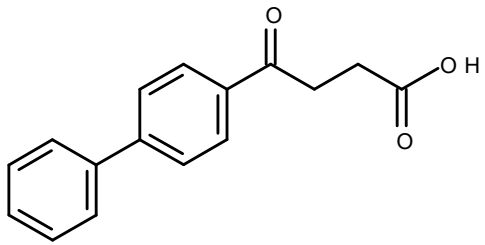
Umpoled Synthons for Polar Bond Formation

- How do we choose a molecule that will correspond to a d^3-synthon?
  - Usually, the planned nucleophilic carbon atom is far enough away from the functional group that a protecting group strategy is viable:

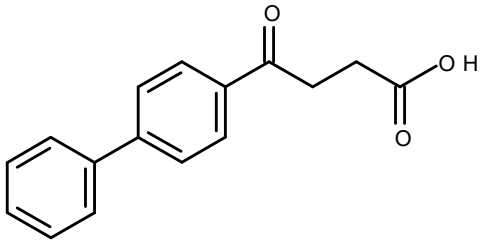
Umpoled Synthons for Polar Bond Formation

- Given that making an umpoled synthon tends to require extra steps, we usually try to have the more complex synthon be natural and the simpler/smaller/more-readily-available synthon be umpoled in cases where they can't both be natural.

- It is impossible to create a 1,4-relationship between functional groups using only natural synthons. Consider the molecule below (fenbufen, a non-steroidal anti-inflammatory drug). If we want to disconnect between the two carbonyl groups, what are our options? Which are preferable?



Umpoled Synthons for Polar Bond Formation



Alternatives to Umpoled Synthons

- It is also impossible to create a 1,2-relationship between functional groups using only natural synthons. Retrosynthetic disconnection leads to a d^1-synthon and an a^1-synthon.

- It can, however, be possible to create the 1,2-relationship by introducing one or both functional groups after making the skeleton.
  - If one of the two groups is a carbonyl *and* if it is possible to selectively form an enolate on the desired side only, the enolate can be used to introduce a heteroatom bonded to the adjacent carbon atom:

Alternatives to Umpoled Synthons

- Similarly, oxidation of an enol can be used to introduce an alcohol next to a carbonyl:

Alternatives to Umpoled Synthons

- If the two functional groups are the same, a double bond between the two carbon atoms can be used to attach one heteroatom to each:

This strategy can be attempted if the functional groups are different, but control of regiochemistry may be difficult.

- A third alternative is to simply choose a starting material that already has functional groups with a 1,2-relationship so that the disconnection is unnecessary…

Sidenote – Conjugate Addition Reactions

- Recall that pi systems react as a unit. An α,β–unsaturated carbonyl has two electrophilic sites:

- This gives rise to two possible reactions:
  - A 1,2-addition (e.g. most additions of RMgX or RLi)

  - A 1,4-addition (e.g. most additions of R_2CuLi or R_2CuMgX)

Sidenote – Conjugate Addition Reactions

- What determines whether a nucleophile attacks an α,β–unsaturated carbonyl in a 1,2-addition or a 1,4-addition?
  - Thus far, you have defined nucleophiles (and electrophiles) as being 'good' vs. 'bad' (or 'strong' vs. 'weak'). There is another property of a nucleophile that comes into play in this situation. A nucleophile is either 'hard' or 'soft'. An electrophile is also either 'hard' or 'soft'.
  - What do you imagine would be the difference between a hard nucleophile and a soft nucleophile?

Sidenote – Conjugate Addition Reactions

- What do you imagine would be the difference between a hard electrophile and a soft electrophile?

Sidenote – Conjugate Addition Reactions

- Consider CH_3Li and $(CH_3)_2CuLi$:

  - Which nucleophile would be the harder nucleophile?
  - Which nucleophile would be the softer nucleophile?
  - Why?

Sidenote – Conjugate Addition Reactions

- Consider propenal:

  - Which electrophilic carbon would be the harder electrophilic site?
  - Which electrophilic carbon would be the softer electrophilic site?
  - Why?

Sidenote – Conjugate Addition Reactions

- Hard nucleophiles tend to attack hard electrophilic sites while soft electrophiles tend to attack soft electrophilic sites.
  - Hard nucleophile + hard electrophilic site:
  - Soft nucleophile + soft electrophilic site:

This is why we observe 1,2-additions with organolithium and organomagnesium reagents but 1,4-additions with organocopper reagents (also called organocuprates).

Sidenote – Conjugate Addition Reactions

- More examples of 1,4-addition reactions of organocuprates:

It only requires addition of a catalytic amount of a copper(I) salt to a Grignard reagent to give 1,4-addition instead of 1,2-addition.

Sidenote – Conjugate Addition Reactions

- Organocuprates are not the only nucleophiles that will attack an α,β–unsaturated carbonyl to give a 1,4-addition.
- The hydrogen atoms between the two carbonyls in a β–dicarbonyl compound are quite acidic (pK_a 9-13). Treatment of a β–dicarbonyl compound with base gives the conjugate base:

Sidenote – Conjugate Addition Reactions

- This conjugate base is a good nucleophile which readily attacks α,β–unsaturated carbonyl compounds to give a 1,4-addition:

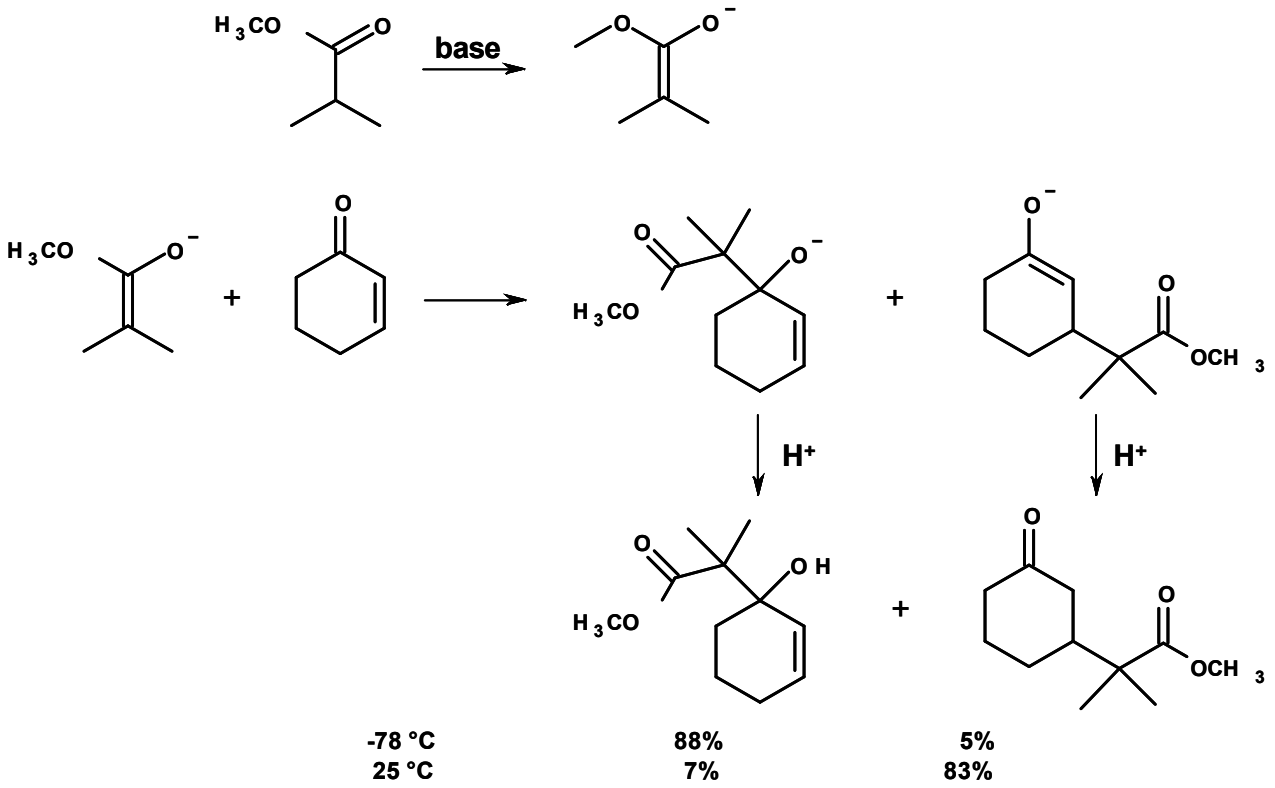
This is called a Michael addition.

Sidenote – Conjugate Addition Reactions

- Why does this nucleophile give 1,4-addition instead of 1,2-addition?

Sidenote – Conjugate Addition Reactions

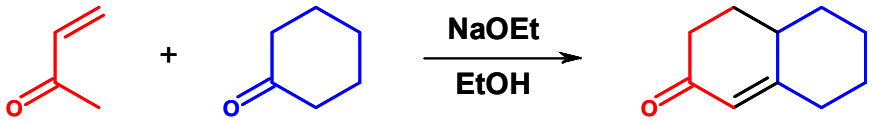
- Formation of an enolate from a monocarbonyl compound is less selective and, in many cases, solvent choice, temperature, etc. determine whether 1,4-addition or 1,2-addition is observed:



- Why is the 1,4-addition not as strongly favoured with this enolate?

Sidenote – Conjugate Addition Reactions

- One more example of conjugate addition is in the Robinson annelation. A Michael addition is followed by an aldol reaction, making a new ring. ('annelation' = 'annealing' = 'making a ring')



Sidenote – Conjugate Addition Reactions