The Robinson Annulation

The Robinson Annulation is the name for a process that combines two key reactions you've learned previously into one longer sequence.

The reaction begins with a **Michael reaction**, followed by an **intramolecular aldol condensation** to give a new six-membered ring containing an alpha, beta unsaturated ketone. This post goes into all the details!



1. Revisiting Intramolecular Reactions

There's something about intramolecular reactions that often trips students up.

Conceptually, understanding an intramolecular reaction is not much different than understanding what happens when you fasten a belt, making a loop in the process.

This is despite the fact that exactly the same bonds form and break!

It's OK. Organic chemistry can seem very abstract at first. It can take time to appreciate that all these symbols we draw for molecules are proxies for three-dimensional objects, and follow many of their familiar principles!



2. The Aldol Condensation

The base-catalyzed version of the Aldol Condensation begins with formation of a nucleophilic **enolate** through deprotonation of the "alpha-carbon" of an aldehyde or ketone, and the subsequent addition of this nucleophile to the electrophilic **carbonyl** carbon of a second aldehyde or ketone, forming a new C-C bond.

Upon heating, the resulting **aldol addition** product is deprotonated to give a *new* enolate, which then displaces the hydroxide ion, resulting in a carbon-carbon double bond accompanied by the net loss of water (H₂O). [*note this is an example of elimination through an* $E1_{cb}$ *mechanism*] The resulting product containing an alpha, beta unsaturated ketone (or aldehyde) is the **aldol condensation** product.

This picture shows the result of aldol condensation between two molecules of 2-propanone (aka "acetone").



3. The Intramolecular Aldol Condensation

No, not drastically different. Actually, all we need to do is replace two of the C–H bonds with a C–C bond that links the two ketones. *That's it!*

Now our nucleophile happens to be on the same molecule as our electrophile. So, just like fastening a belt, when the two combine, we obtain a "loop", or ring.



Change one thing: put a bond between two carbons, and a 5-membered ring is formed

The mechanism is exactly the same. Upon treatment with base (e.g. NaOH) an enolate still forms, and it still adds to a ketone. And after the net loss of H_2O , the exact same sequence of bonds has formed and broken. The only difference is that since the two ketones are linked, we now we have a ring!

Full mechanism here (link)

4. Intramolecular Reactions Favor Five- and Six-Membered Ring Formation

The best candidates for ring closure tend to be **five and six-membered rings**, which combine low ring strain with a reasonable reaction rate.

Three- and four-membered rings tend to suffer from **ring strain**. It's not *impossible* for 3- and 4membered rings to form (*intramolecular reactions to form epoxides exist, after all – see this post*) but in a process where the steps are in equilibrium (and thus potentially reversible), a process that forms an unstrained five- or six-membered ring will be thermodynamically favored over one that forms a three- or four-membered ring. [Note 2]

Seven- and higher-membered rings tend to be **slower to form**, due to a lower "effective concentration" of the nucleophile in the vicinity of the electrophile.

An example for the formation of a six-membered ring through the intramolecular reaction of a "1,5-diketone" is shown below. [Note: the 1 and 5 here don't refer to the IUPAC numbering, but to the fact that the second ketone is 4 carbons over from the first one]. The pattern of bonds that form and break is exactly the same as above.

In formation of rings, 5- and 6- membered rings are favored

- 3- and 4-membered rings are strained;
- 7- and higher-membered rings form too slowly
- · 5- and 6- membered rings are relatively unstrained, and also form quickly

Six-membered rings can be formed from "1,5-diketones"



5. The Michael Reaction Gives 1,5-Diketones

We've actually already seen a reaction that makes 1,5-diketones: the Michael reaction.

To recap: the Michael reaction involves the addition of a nucleophilic **enolate** to the "beta" (β) carbon in the double bond of an alpha,beta-unsaturated ketone in a process called "conjugate addition" or "1,4-addition" [also a prominent reaction of Gilman reagents (organocuprates): see Gilman Reagents: What They're Used For]. This results in a new enolate. Protonation of this enolate then gives the 1,5-diketone:

The Michael Reaction Gives 1,5-Diketones



Hover for mechanism (link)

6. The Robinson Annulation

Now let's join these two threads together. *Pattern recognition is a key skill in organic chemistry!*

- **Since** 1,5-diketones can form six-membered rings through an intramolecular Aldol condensation...
- ...and 1,5 diketones can be made through the Michael reaction...
- ...and furthermore, they both require the same reagent (base, e.g. NaOH)...

then what would happen if we were to stir together a ketone, an alpha,beta-unsaturated ketone, NaOH, and then heat the mixture? Would we end up with an intramolecular aldol condensation product?

Yes! In a 1935 paper, Robert Robinson and collaborator William Rapson reported that a substituted methyl vinyl ketone and cyclohexanone gave a product with a new six membered ring containing an alpha,beta unsaturated ketone:

The Robinson Annulation (1935)

Combining a ketone and an (alpha,beta) unsaturated ketone in the presence of base resulted in a new unsaturated six-membered ring:



This has become known as the Robinson Annulation, and it still finds use today. The process begins with a Michael reaction and ends with an intramolecular aldol condensation to give the new ring. It is a classic example of a **tandem (or cascade) reaction**, where an initial reaction provides the starting material for a successive reaction.

7. Mechanism Of The Robinson Annulation

Let's walk through the whole mechanism, using the simplified example of 2-propanone and methyl vinyl ketone.

The Michael Reaction segment involves three steps:

- 1. formation of the enolate
- 2. conjugate addition, and
- 3. protonation of the new enolate.

The Robinson Annulation, Part 1: Michael Reaction



The 1,5-diketone produced by the Michael reaction then becomes the starting material for the next segment of the Robinson annulation, **the intramolecular aldol condensation**.

- The aldol condensation begins with deprotonation of the 1,5-diketone to give an enolate on C-1 [Note that there are two enolates that could be formed, on C-1 and C-3 (since the molecule is symmetrical, these are equivalent to C-7 and C-5, respectively). However, the C-3 enolate is a dead-end; formation of the (strained) 4-membered ring is reversible, and equilibrium will eventually drive the reaction toward formation of the six-membered aldol condensation product]
- Formation of the enolate on C-1 is followed by attack at the ketone five carbons away, giving the six-membered ring.
- Protonation of the negatively charged oxygen, followed by deprotonation at the adjacent carbon, gives a new enolate.
- This enolate then expels a hydroxide ion (HO-) from the adjacent carbon, forming a new carbon-carbon double bond, resulting in the aldol condensation product.

The Robinson Annulation, Part 2: Intramolecular Aldol Condensation



8. Robinson Annulation Retrosynthesis: Working Backwards

It's extremely important to be able to look at the structure of a product of the Robinson annulation and work backwards to the two components.

- The first step is to recognize the **key pattern** in the product of a Robinson: a six-membered ring containing a double bond adjacent to a ketone (an alpha, beta unsaturated ketone).
- Next, work backwards from the Aldol condensation: so in the reverse direction, break the C=C bond and place two C-H bonds on one end (the alpha carbon of the ketone) and a C=O bond on the other end.
- Finally, work backwards on the **Michael**: break the C-C bond, and replace with a C-C pi bond on one component and a C-H bond on the other.



As an exercise, try working backwards from the following examples:

Exercise: How could each of these molecules be synthesized through a Robinson annulation?

