18-1 H α to a C=O is much more acidic than other C-H bonds

pK_a $CH_3-H \approx CH_2=CH-H \approx 45-50$

pK_a $HC\equiv C-H = 25$

but

pK_a of $-\overset{|}{C}-\overset{\|}{C}-$ ranges from [redacted] 17-30

α-hydrogen → (H) β-dicarbonyl compound

pK_a of $-\overset{\|}{C}-\overset{|}{C}-\overset{\|}{C}-$ ranges from [redacted] 6-13

(H)

Reason: resonance stabilization of the carbanion

18.2 Keto-enol tautomers

we've seen this before:

$$R-C\equiv CH + H_2O \xrightarrow[H^+]{Hg^{2+}} \left(R-\overset{\oplus OH}{\overset{|}{C}}=CH_2\right) \rightarrow R\overset{O}{\overset{\|}{C}}CH_3$$

18.3 "Enolization" is rapid & reversible

So that ENOL is ALWAYS present for any* carbonyl compound with α-H

18.4 Enols & enolates are electron-rich at carbon, and are good carbon nucleophiles

18.5 Halogenation of the α-carbon using X_2 (dihalogen) is promoted by acid or base.
This is a common motif in carbonyl α-substitution: it can be either acid- or base-catalyzed.
However, base catalysis is more important (and common) because enolate ions are better nucleophiles than enols.
(And also because, with the appropriate base, the population of enolate is large, while the population of enol is always small.)

18.6 The H-V-Z reaction is just another acyl α-halogenation reaction, with a twist.
Study the mechanism!

18.7 Tells how to use α-halo carbonyl compounds in synthesis with S_N2 nucleophiles, and for E2 reactions

18.8 Lithium Diisopropyl Amide = LDA

most common base for generating enolate ions.

Why? pKa (LDA) = 35

pKa of most aldehydes & ketones (and esters and amides) is less than 30.

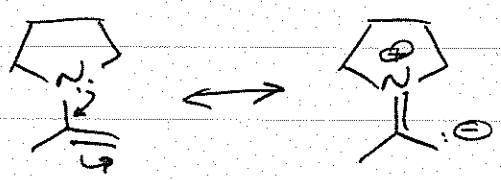
(NOT used with β-dicarbonyl compounds; too strong)

18.9. Enolates can react as S_N2 nucleophiles (seldom S_N1 — why?)

Product: α-alkyl carbonyl compounds of various sorts.

18.10 The ~~Stork~~ Enamine Reaction

Enamines are "neutral enolates":



Advantage: less reactive than enolate reactions; typically only mono-alkyl product

See top of p. 868

Advantage: can be used to acylate; this would not work with strong base enolates.

18.11 The Michael reaction

Conjugate addition (17.16) of a β-dicarbonyl (enolate) to an α,β-~~unsat~~unsaturated carbonyl compound.

Conjugate addition of any nucleophile is sometimes called "Michael addition."

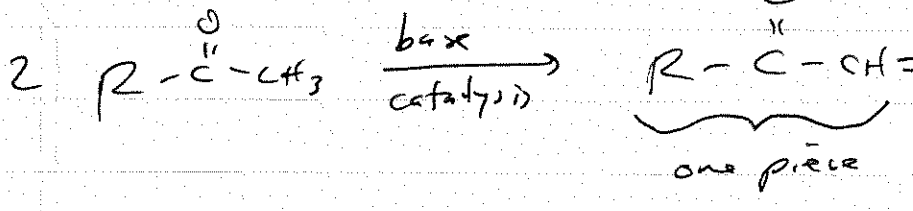
The Stork Enamine Reaction is the enamine version of the Michael reaction.

18.12 The Aldol addition reaction forms an "aldol" (aldehyde - alcohol) product.

Know the mechanism. The product is a β-hydroxy carbonyl compound...

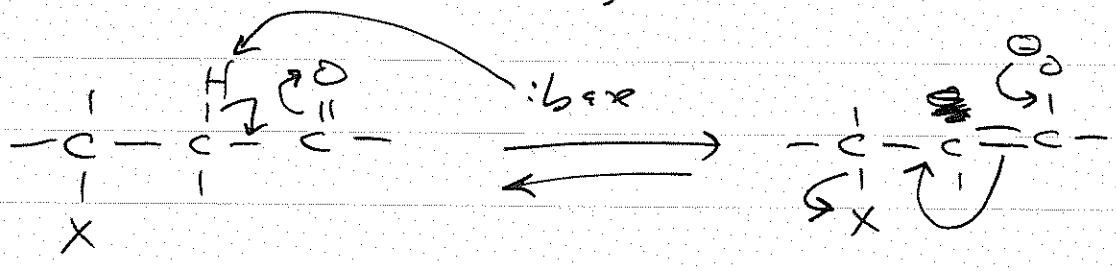
18.13 ... that can eliminate to form an α,β-unsaturated carbonyl compound. (Works because of the α-H acidity) - E1cb

The combination is "the aldol condensation" which converts an aldehyde or ketone to a "dimer" that is an α,β-unsaturated carbonyl:



$E1_{cB}$ = "E1 - conjugate base"

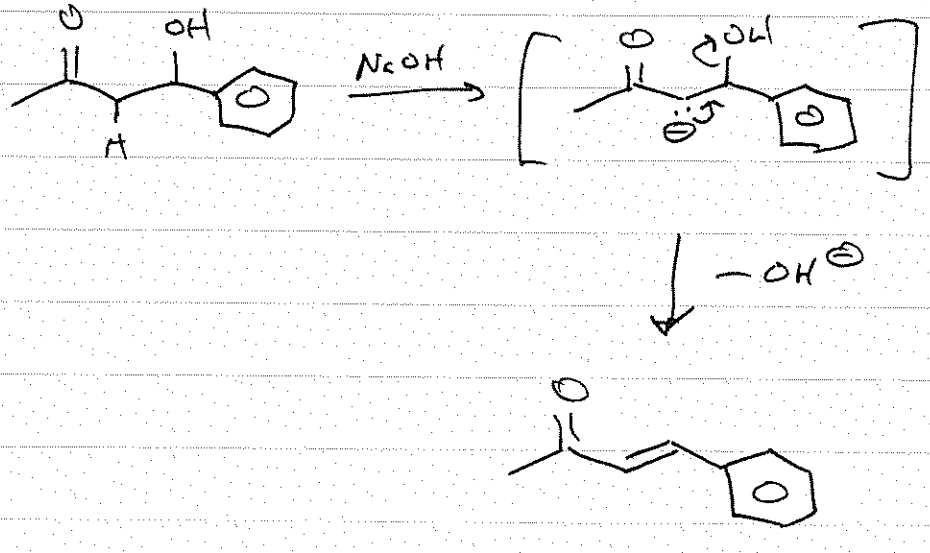
This is a common mechanism for elimination beta to a carbonyl group:



Notice this: good leaving groups for E2 or S_N2 reactions must have pK_a lower than about 6 or 7.
But good leaving groups for $E1_{CB}$ can have pK_a up to 25 or 30!!

α,β-unsaturated carbonyl compound

ex.



18.14 The mixed Aldol reaction produces 4 possible products
Careful synthetic design can limit the
number of possible products to one or two.
Two possible ways are shown on p. 875

18.15 The Claisen condensation

Differs from the Aldol in that ~~the~~
an ester has a leaving group: an
aldehyde or ketone does not. (p. 877, top)

Product:
2 ester ⟶ β-Ketoester ("dimer")

18.16 Mixed Claisen condensations have considerations
similar to the mixed Aldol condensation.
Use only one ester with α-H to limit
the possible products.

KNOW THE MECHANISMS
of the Aldol & Claisen
condensation reactions!

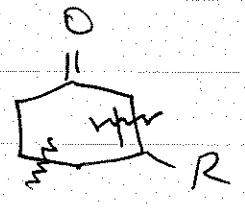
18.17 Aldol & Claisen reactions can be used between two ends of the same molecule to form a ring. "Intramolecular"

Intramolecular Claisen = "Dieckmann condensation"
Intramolecular Aldol = "Intramolecular Aldol"

These reactions favor the formation of 5 and 6-membered rings because they are reversible; 5 and 6-membered rings are more stable / less strained (as you calculated a month ago)

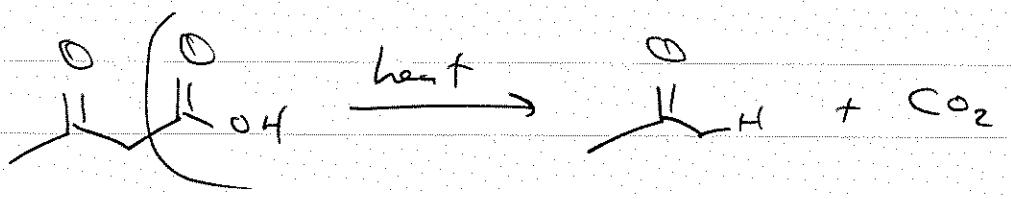
p. 883 The Robinson Annulation combines a Michael addition with an intramolecular Aldol to form a ring from two molecules.

The product is always a cyclohexenone:



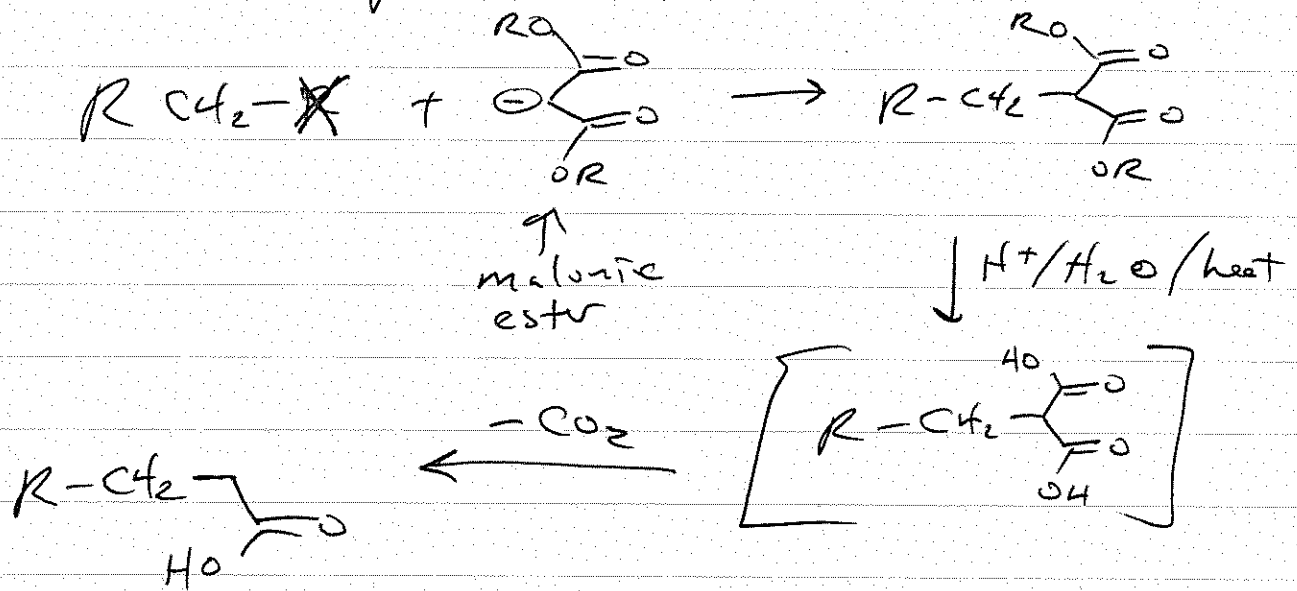
Know the mechanism!

18.18 Decarboxylation of β-keto acids

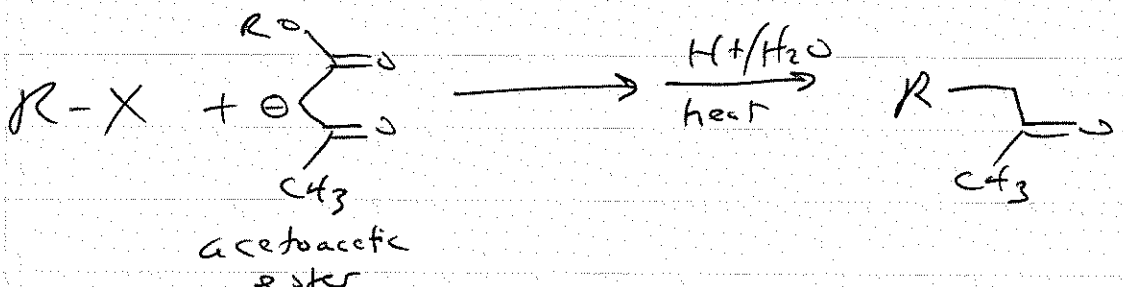


This allows us to use 18.19 & 18.20

18.19 The Malonic ester synthesis allows synthesis of a carboxylic acid from a primary alkyl halide



18.20 The acetoacetic ester synthesis allows synthesis of a methyl ketone in the same way:



18.22 Designing syntheses

You ~~must~~ need to go through the reactions in Ch. 18 (see the summary pp. 896 etc) and carefully list what the reaction starts with and how the pieces end up put together.

All of Ch. 18 has been about putting small molecules together into bigger ones.

Note how (for example) the product of an Aldol & the product of a Claisen can get together in a Michael reaction, or the fact that the Claisen reaction of ethyl ethanoate forms an acetoacetic ester that can be used in the acetoacetic ester synthesis!

Also, go back to 18.10 Activation of an enamine reduces a β-dicarbonyl compound.

18.22 Is FYI