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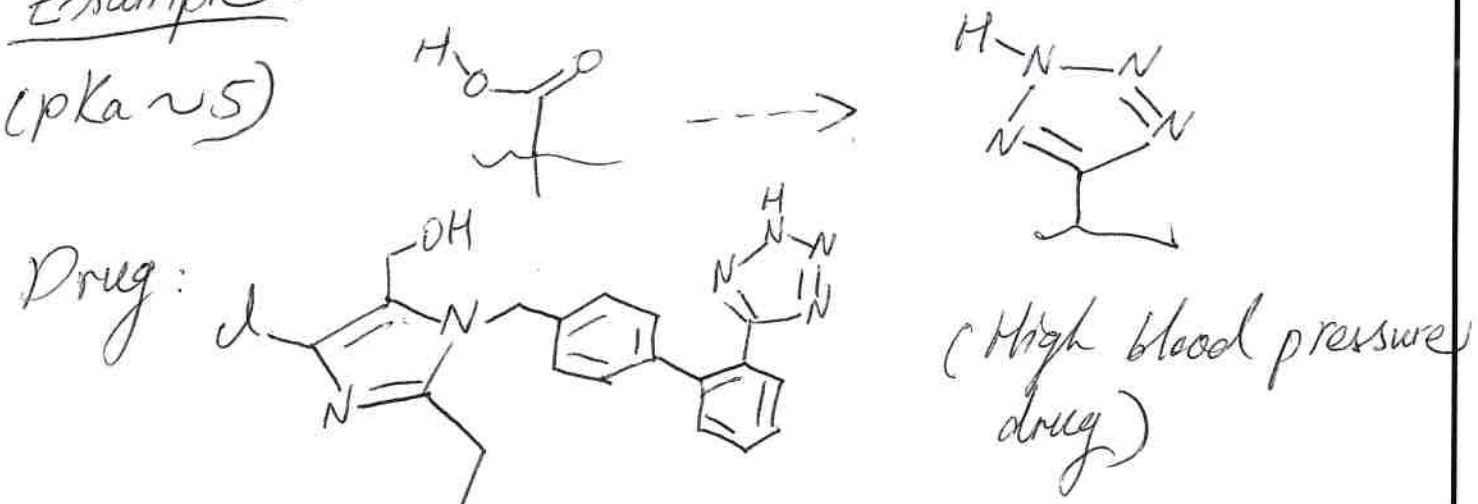
What I learned @ U. Penn.

"Bioisostere" = Replacement fragment

→ Medicinal chemistry & Drug Design

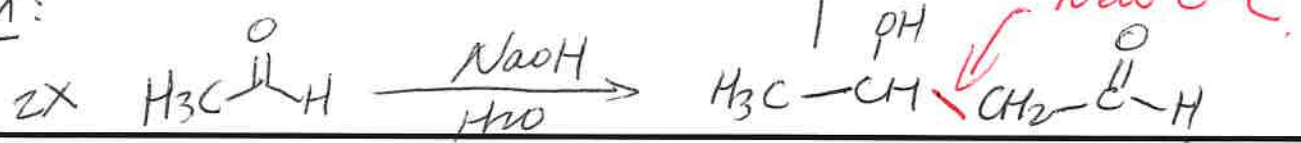
Example:



Recall: Aldol condensation

Combine electrophilic reactivity of  w/ nucleophilic reactivity of  (enolate)

Ex:



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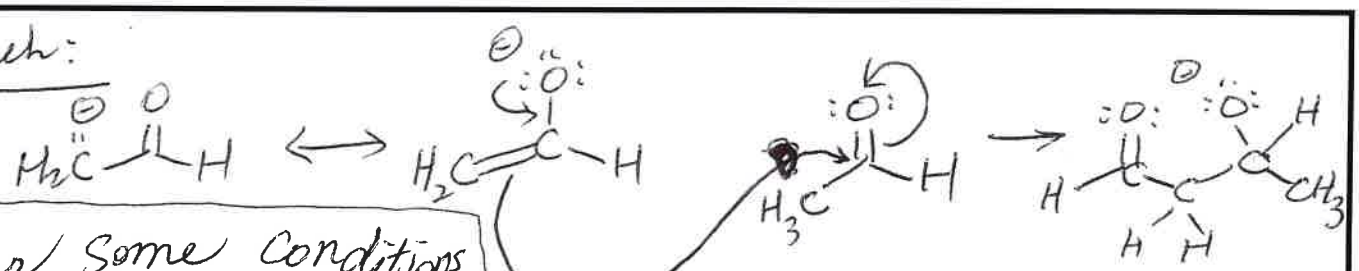
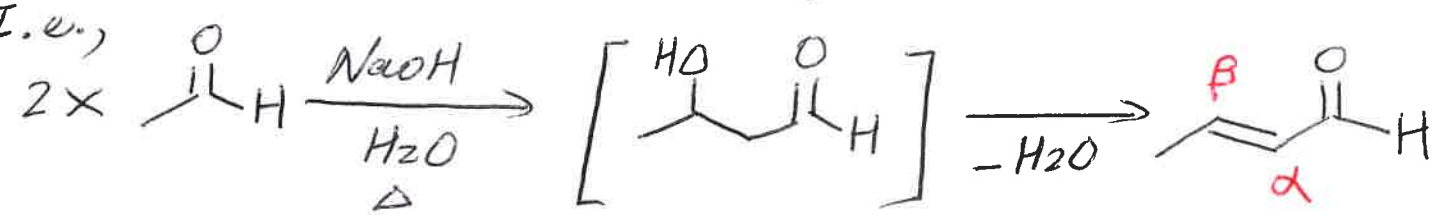
Mech:

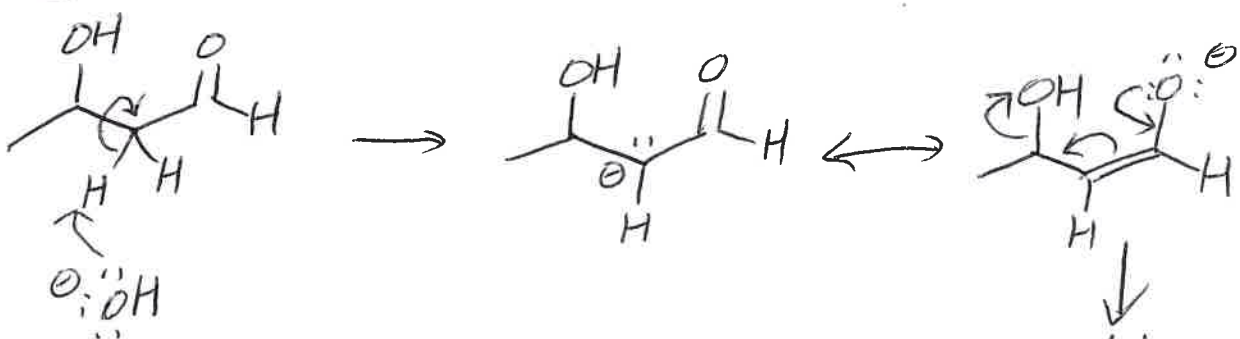


Under some conditions, the "aldol" product undergoes further rxn (elimination) to form an "α,β-unsaturated aldehyde".

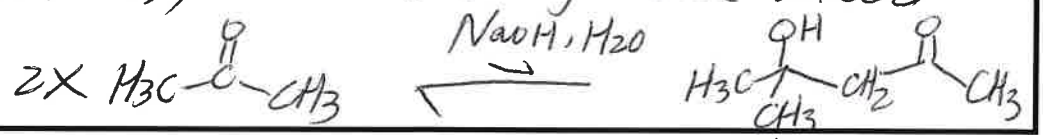
I.e.,



Mech: NOT E2.



All steps in aldol mechanism are reversible. For ketones, reverse rxn is favored under basic conditions.



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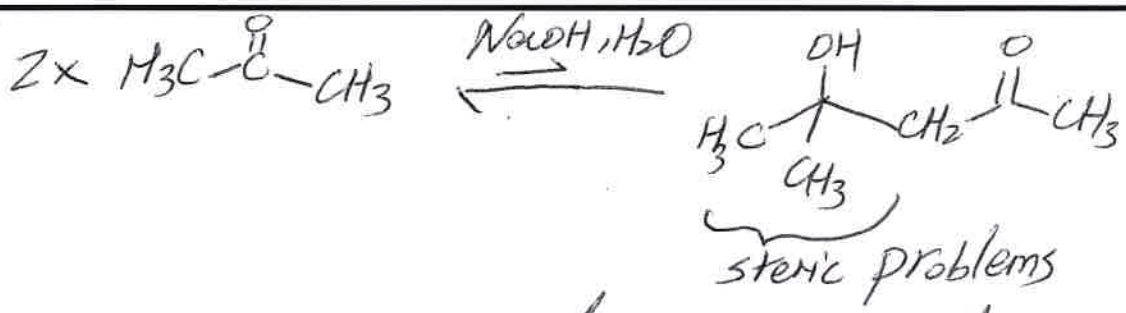
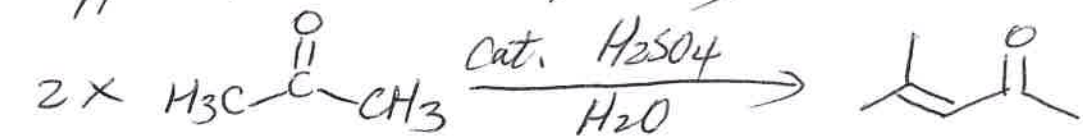


Aldol rxns can occur under acidic conditions, too, w/ a different (but comparable) mechanism ...

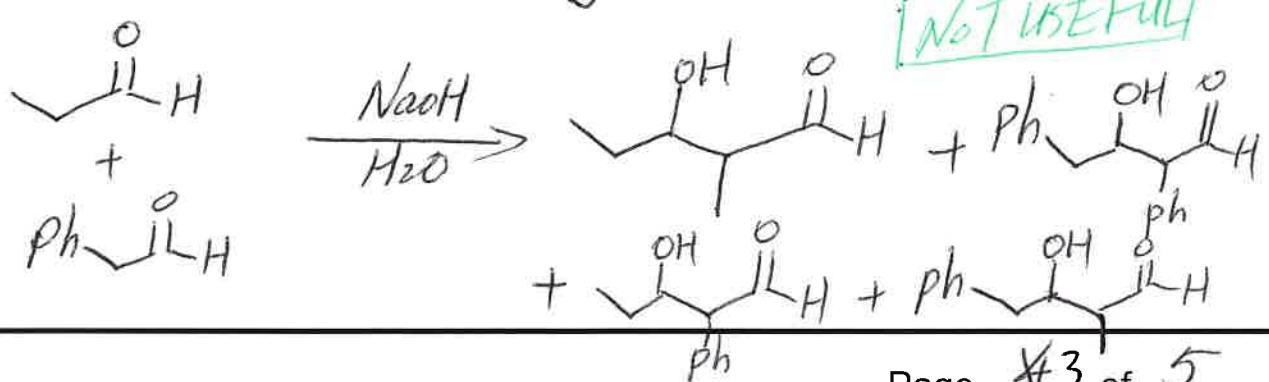
Ex: 

Note: always observe elimination under acidic conditions

Note: Ketone rxn is efficient in acid; elimination prevents reverse aldol.

"Cross aldol" — attractive from synthetic perspective, but how accomplish?

In many cases, crossed aldol is not preparatively useful because mixtures are generated.

Ex: 

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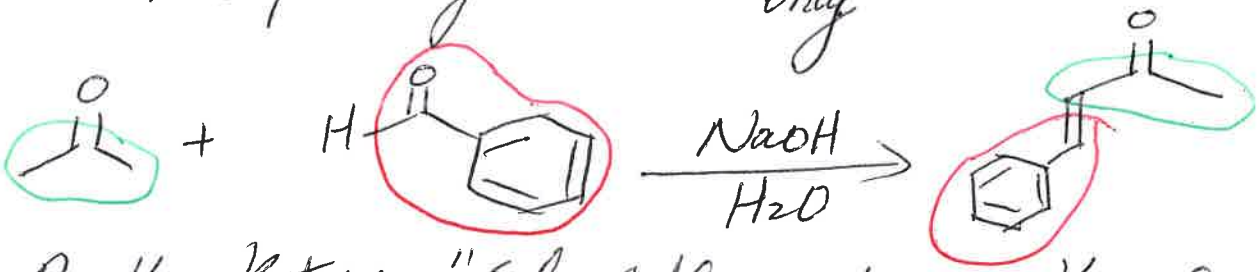
Special case:

Ketone + aldehyde w/o α H's

↓ nucleophile only

→ electrophile only

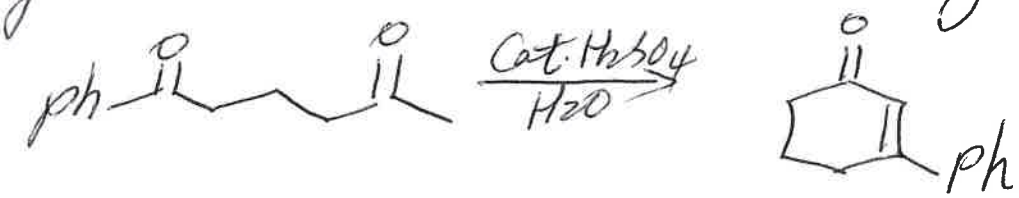


Recall: Ketone "~~Self~~ self-condensation" unfavorable.

∴ Ketone won't serve as ~~electrophile~~ electrophile.

Observe: Aldehyde lacks α H's, thus, cannot serve as ~~elect~~ nucleophile.

Another special case: Intramolecular condensation, leading to a 5- or 6-membered ring.



(Consider sources of selectivity ...)

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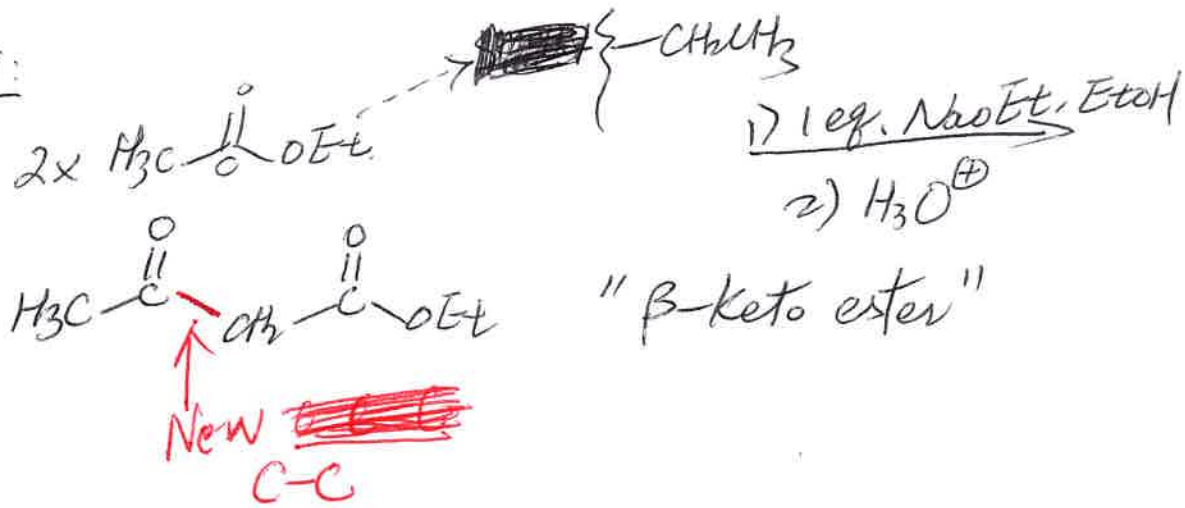
Analogous rxns involving ester rather than aldehyde/ketones.

[C(+3) vs. C(+2)] "claisen condensenti"

Ex:



Mech: