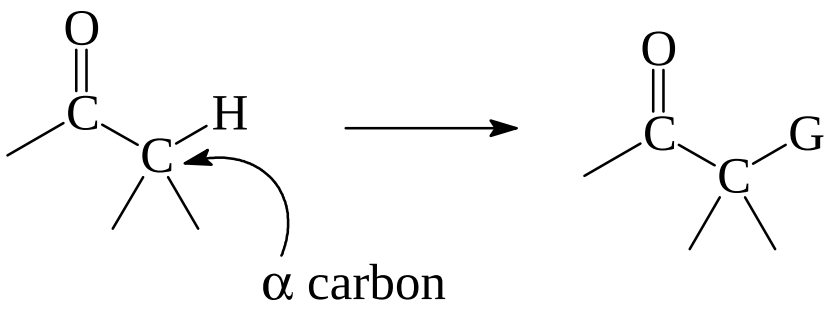
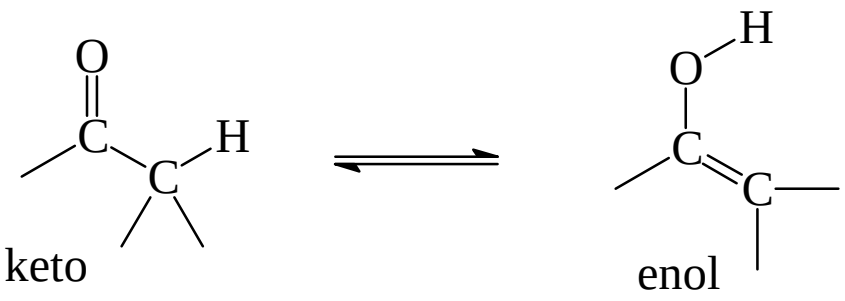
Carbonyl α-Substitution Reactions



These reactions often occur *via enols* or *enolate anions.*

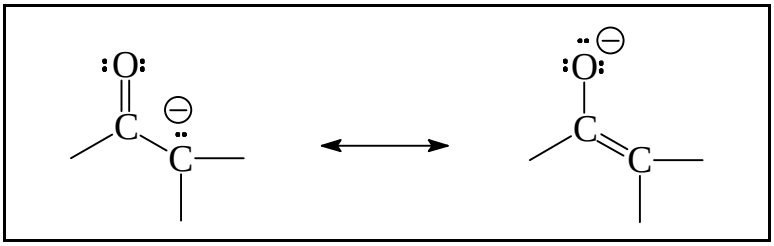
An aside on keto-enol tautomerism —



For most aldehydes, ketones, and acid chlorides K_{eq} is very small, but some enol is present. For esters, amides and carboxylic acids the amount of enol present is usually negligible.

The keto-enol tautomerization is catalyzed by acid: the carbonyl oxygen is protonated and the resulting cation loses an α hydrogen to give the enol.

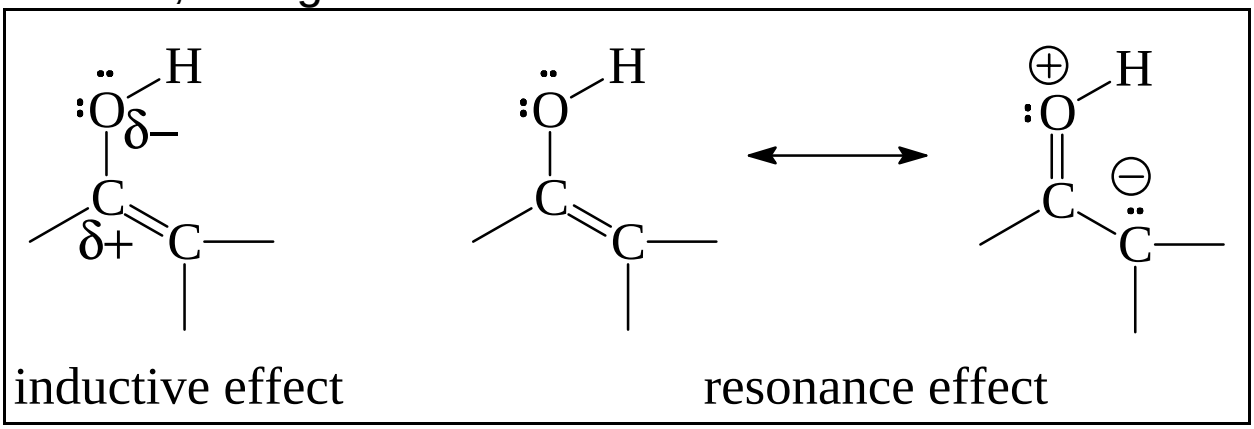
This tautomerization is also catalyzed by base: the base removes an α hydrogen forming a resonance stabilized enolate anion which accepts a proton at the oxygen to give the enol.



Enolate Anion

The Chemistry of Enols —

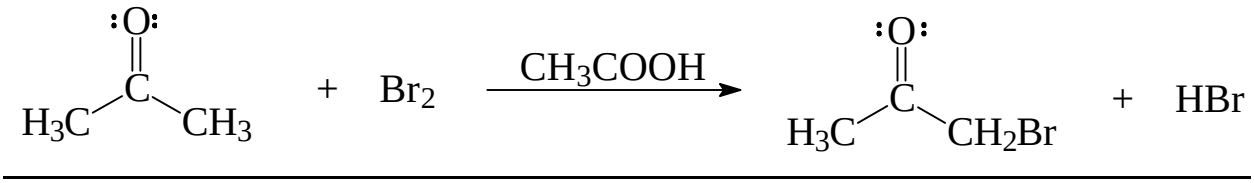
Enols have a C=C double bond. C=C double bonds are susceptible to electrophilic attack. The carbon <u>not</u> attached to the oxygen is more electron rich than the one which is, owing to inductive and resonance effects.



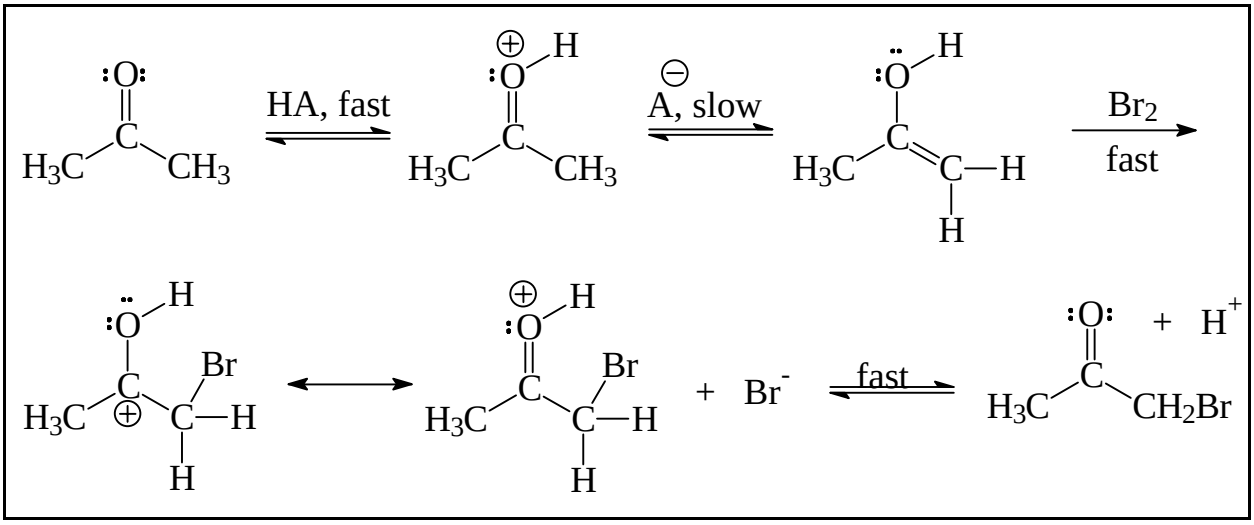
inductive effect resonance effect

The electron rich carbon will undergo electrophilic attack.

Alpha Halogenation (Cl, Br, I) of Aldehydes and Ketones —



Mechanism —



Note that the site of the attack by Br_2 on the enol (the regioselectivity) is governed not only by the site of attack being the more electron rich carbon, but is also the result of the formation of the more stable (resonance stabilized) carbocation.

Evidence —

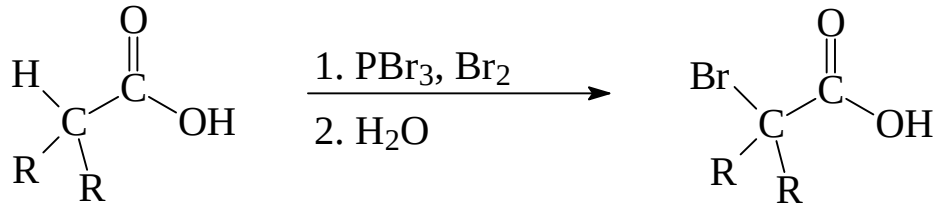
❄ reaction rate = k[ketone][H^+], indicating that the rate limiting step involves H^+, or H^+ is involved before the rls.

❄ Chlorination, bromination and iodination of a given ketone all occur at the same rate. This means that the same rate limiting step is involved for all three halogens. This also suggests that this step does not involve the halogens (because they would very likely react at different rates).

❄ If a ketone is treated with D_3O^+, the α-hydrogens are replaced by deuteriums at the same rate as this ketone is halogenated. This suggests that the same intermediate is involved in deuteration and halogenation, namely, the enol.

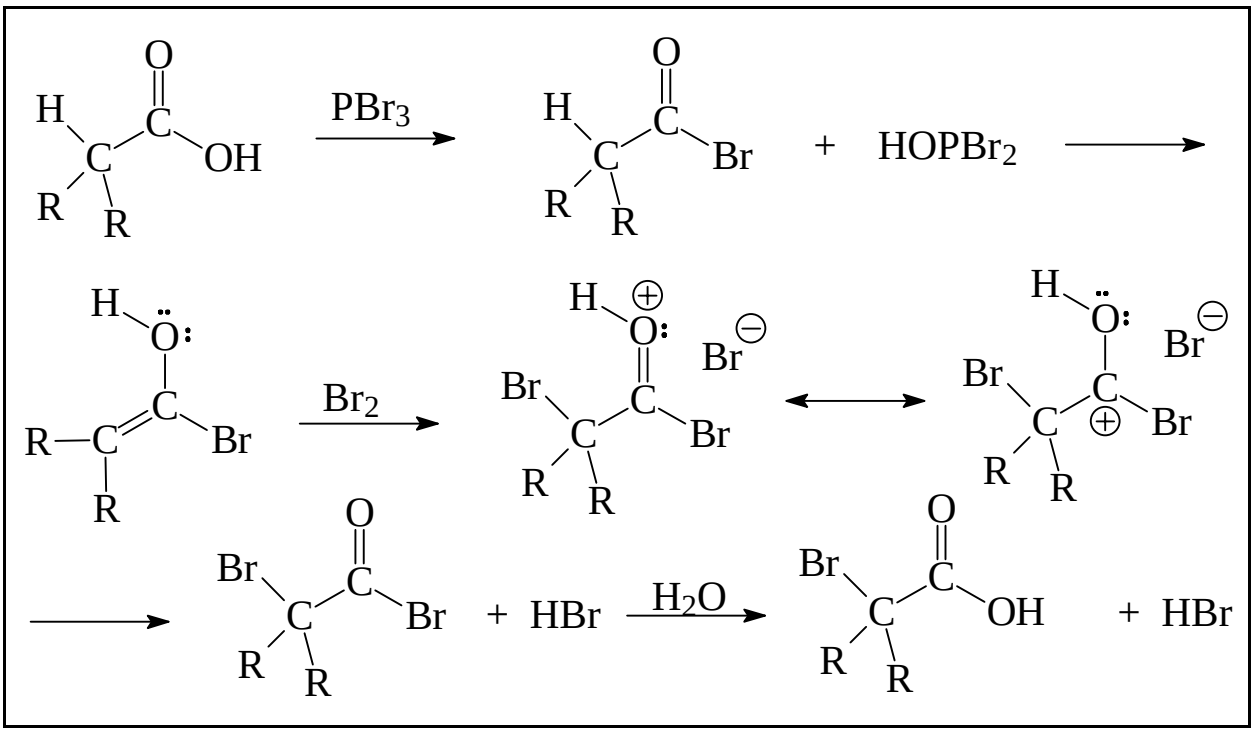
Alpha Bromination of Carboxylic Acids:

The Hell-Volhard-Zelinskii Reaction —



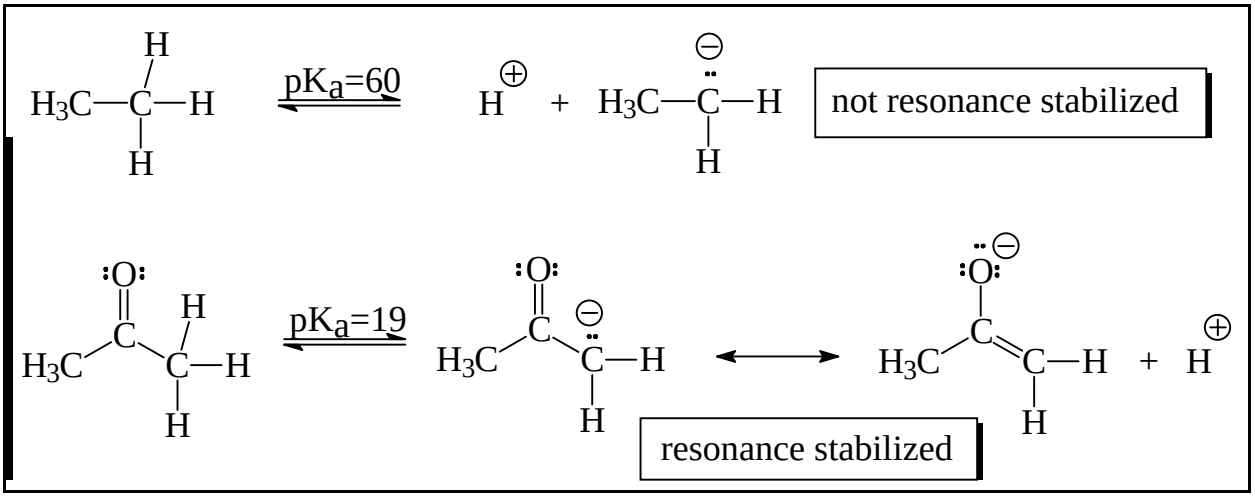
In cases where the bromine is on a 2° carbon the α-bromo acid can be converted to an α-amino acid or an α,β-unsaturated acid.

Mechanism (condensed) —



Acidity of Hydrogens α to a Carbonyl

These hydrogens are more acidic than hydrogens attached to other sp^3 carbons because the enolate anion which results is resonance stabilized.

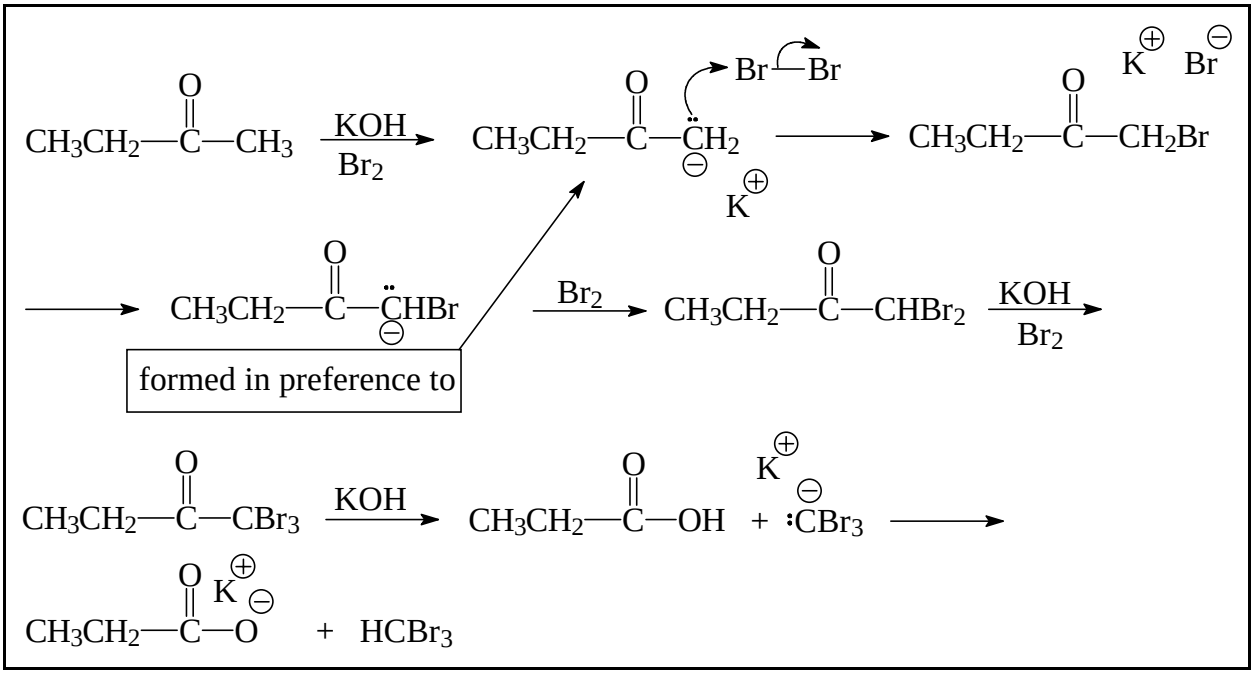


When a carbonyl compound forms an enolate anion the α carbon from which the proton is removed goes from sp^3 to sp^2; thus, a chiral center at this position loses its chirality.

Enolates are *ambident* nucleophiles: they have two nucleophilic sites — C and O — but usually attack from carbon resulting in a new bond to the carbon.

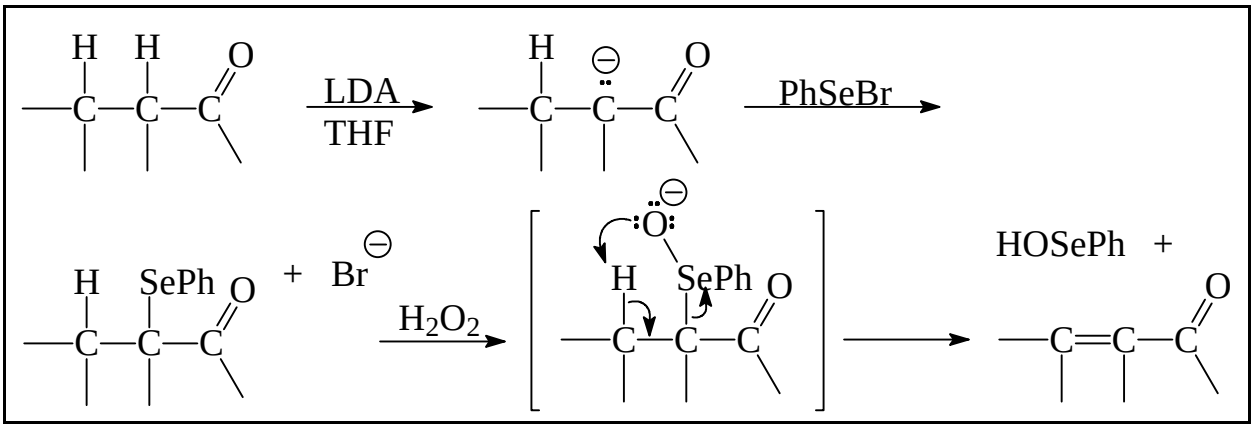
Carbonyl compounds with α hydrogens can be partially converted into enolate anion by use of hydroxide ion and almost completely converted using a stronger base, such as, sodium hydride, sodamide ($NaNH_2$), or lithium diisopropylamide, LDA ($LiNH(CH(CH_3)_2)_2$. Although sodium hydroxide is convenient, it is a powerful nucleophile and can interfere in some reactions. Although LDA is a stronger base it is a weaker nucleophile, owing to its bulk, and less likely to interfere.

The Haloform Reaction —

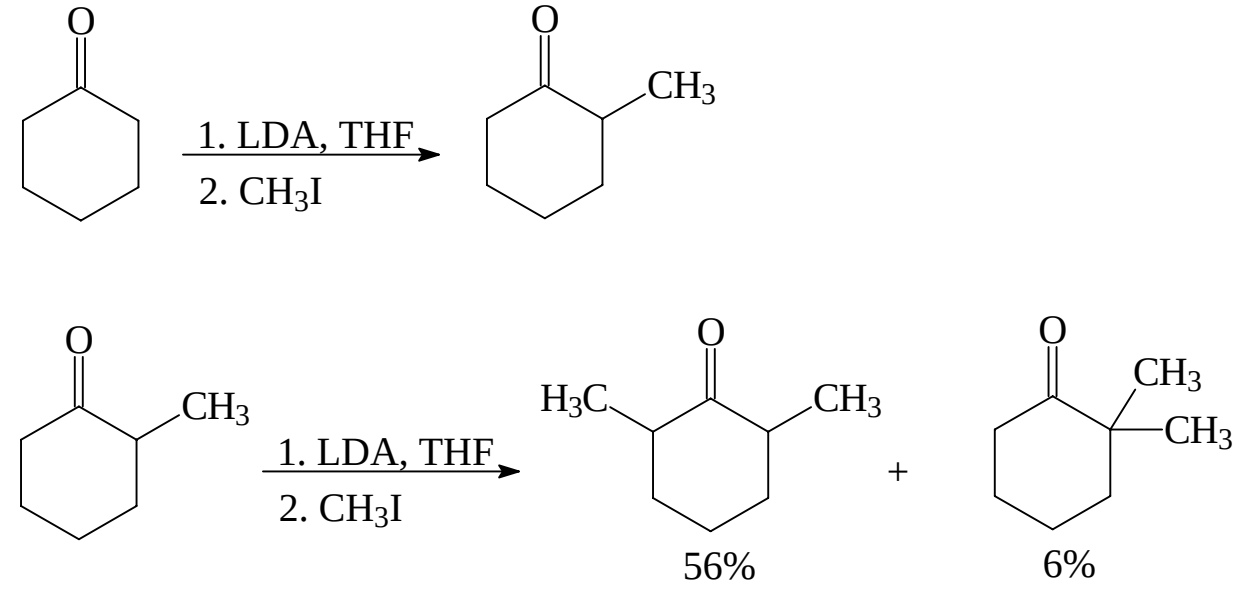


Selenylation of Enolate Ions: *Enone* Synthesis —

A ketone, ester or nitrile is converted to an enolate, then a phenylseleno intermediate, and this is oxidized to an enone.



Alkylation of Enolate Ions —

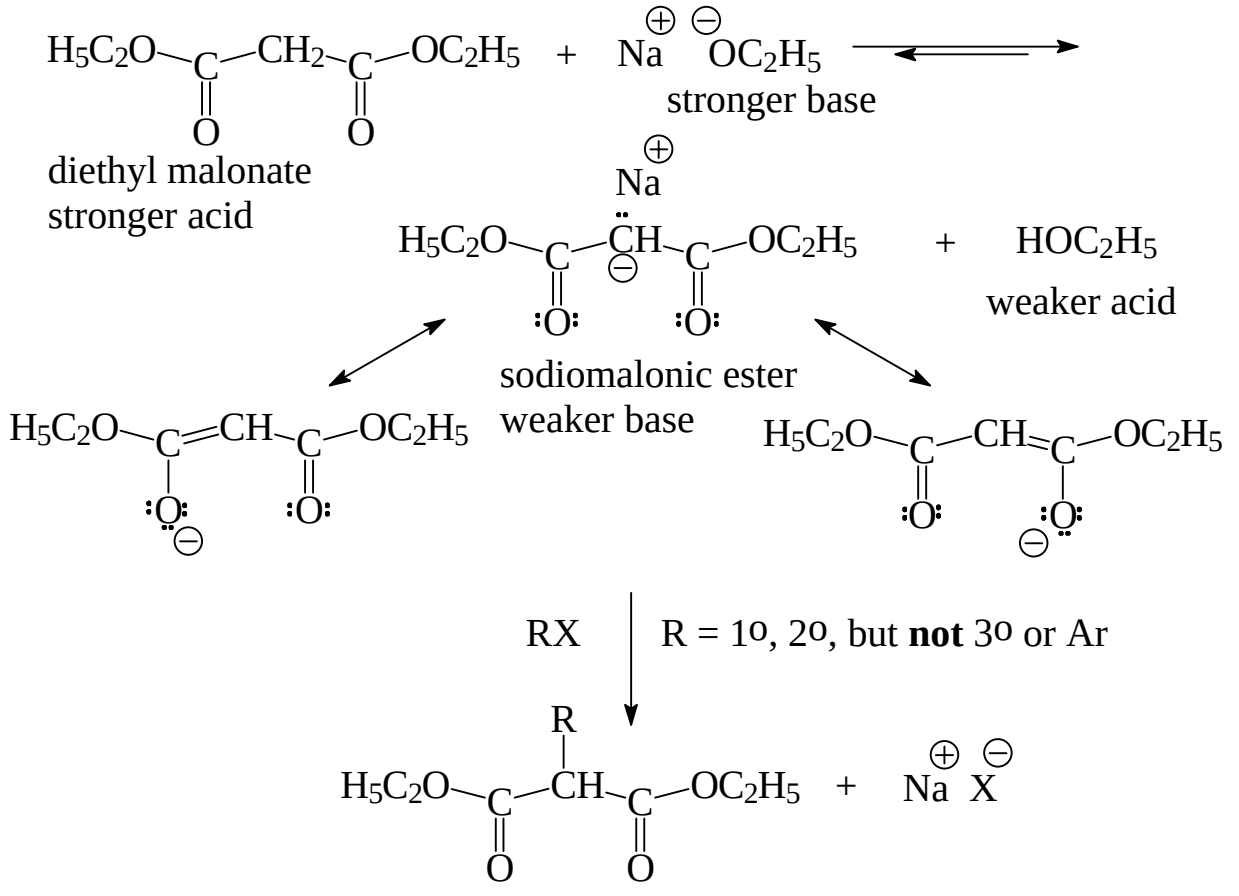


Special examples of the alkylation of enolate ions are involved in the *Malonic Ester Synthesis* and the *Acetoacetic Ester Synthesis.* In these cases, the carbon being alkylated is flanked by two carbonyl groups; hydrogens on such carbons are relatively acidic and the resulting enolates are relatively stable.

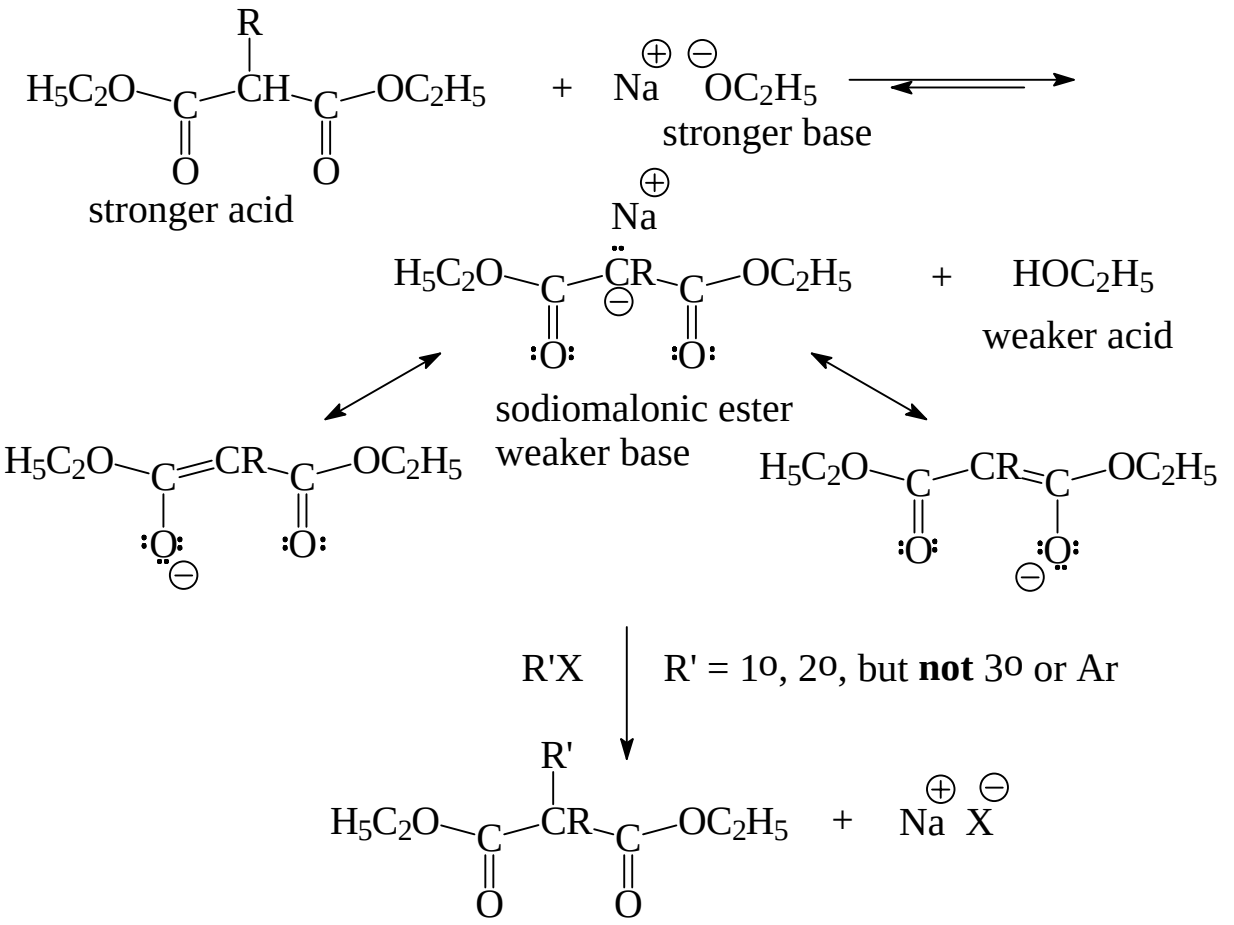
Malonic Ester Synthesis —

For preparation of R-CH_2COOH and RR'CHCOOH.

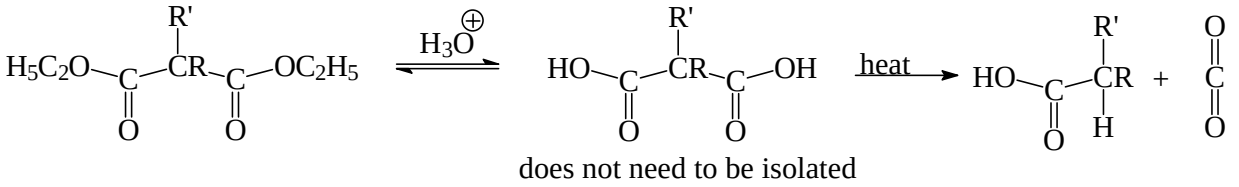
Formation of Alkyl Malonic Ester:



An alkyl malonic ester may be converted to a dialkyl malonic ester —



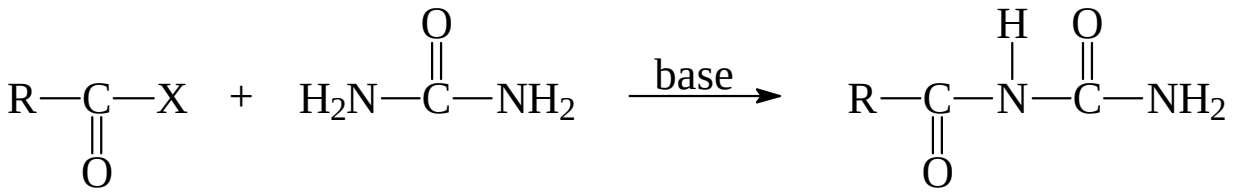
The alkyl or dialkyl malonic ester is then hydrolyzed and decarboxylated —



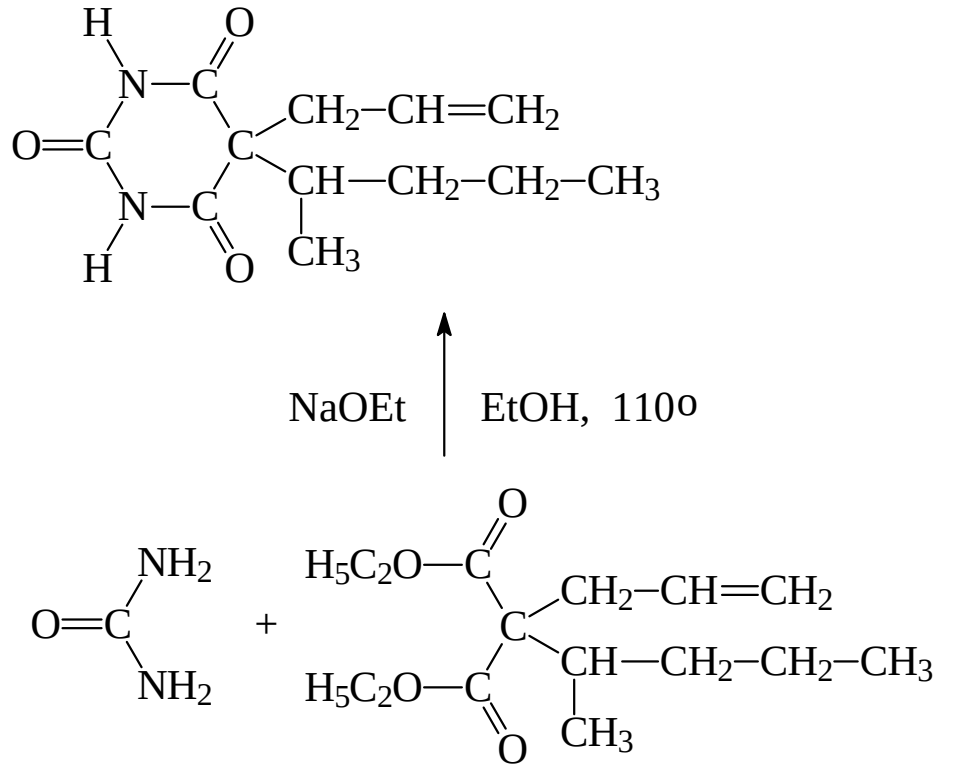
These reactions will also occur under mildly basic conditions, giving the acid salt and carbonate.

Synthesis of Barbiturates Starting with Malonic Ester —

Acid chlorides, anhydrides, and esters react with urea to produce ureides —



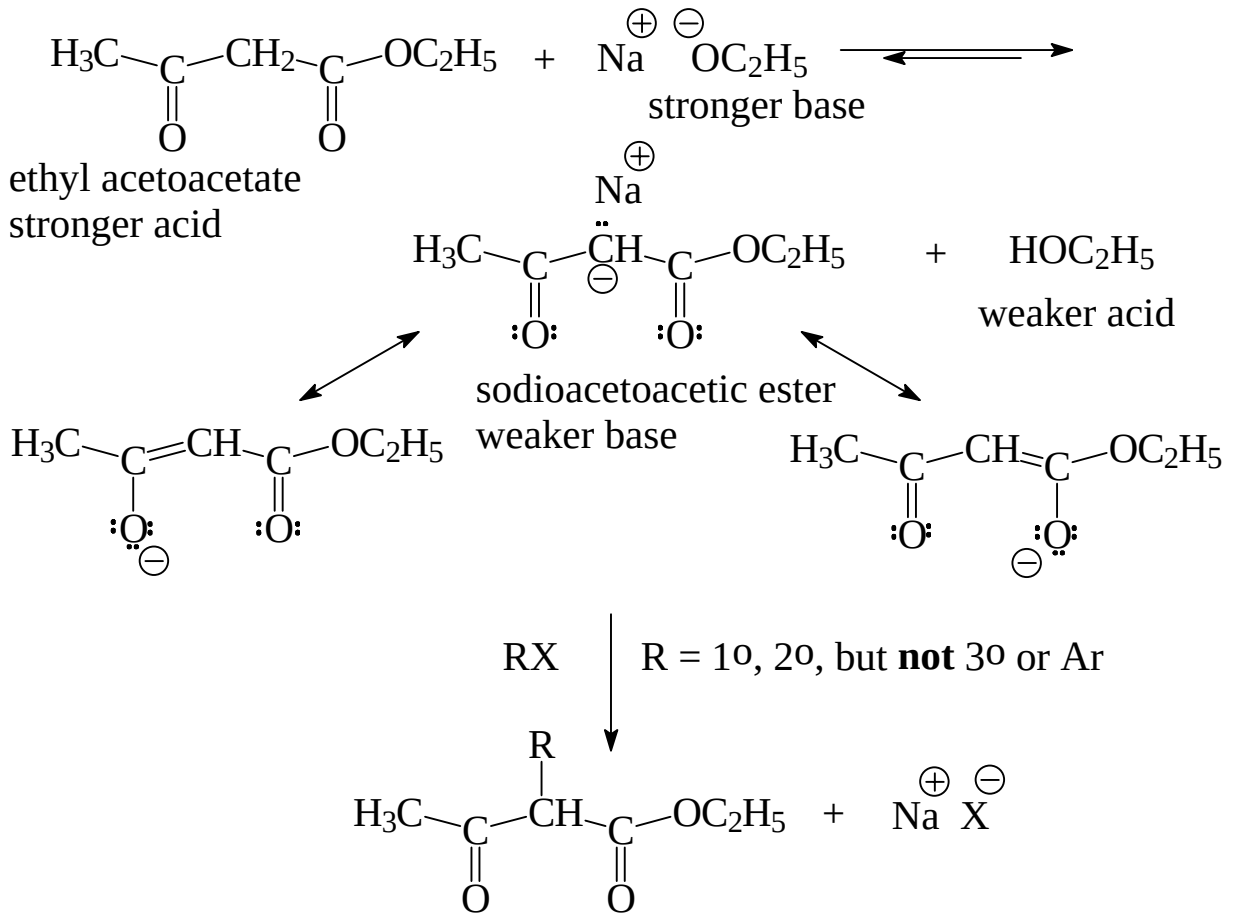
Starting with malonic ester, synthesize seconal.



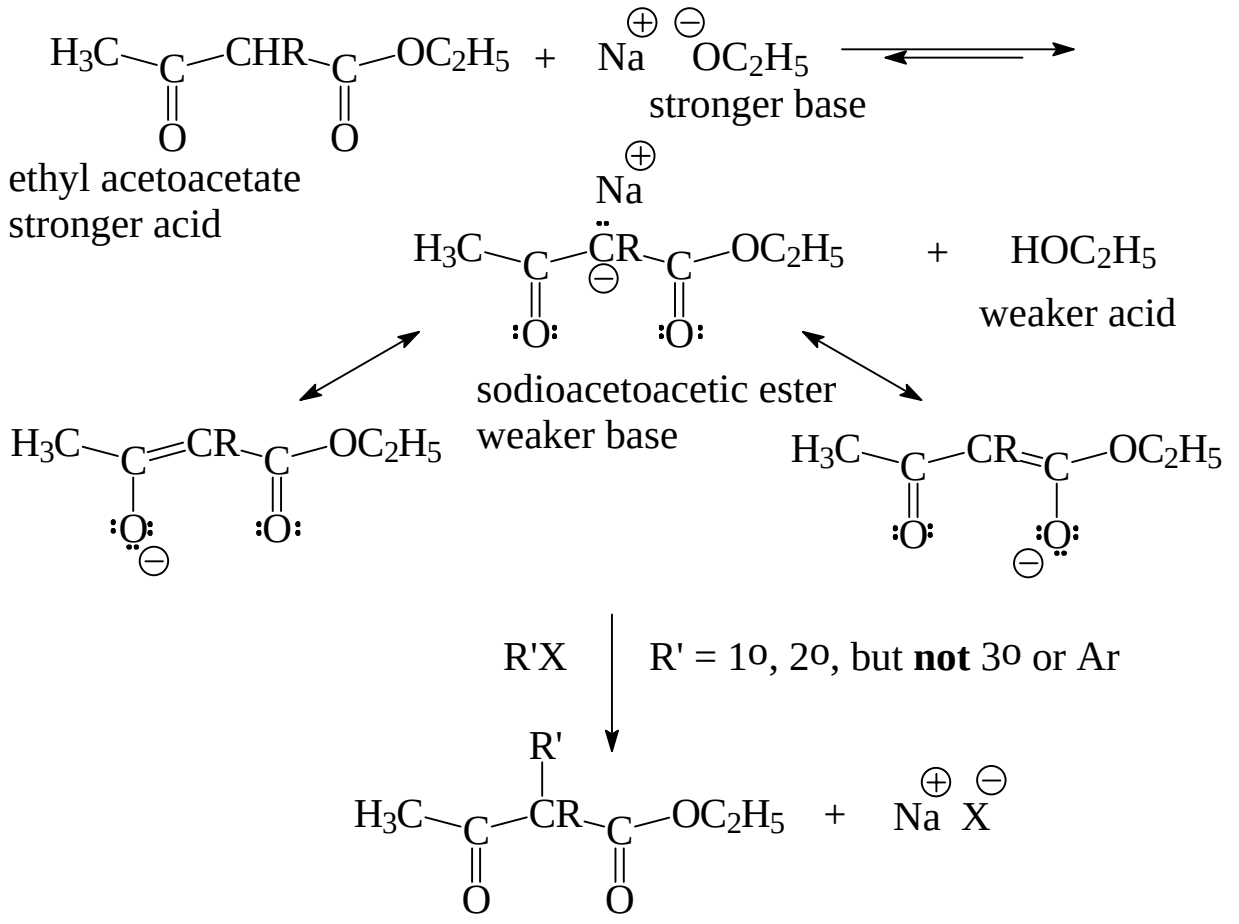
At this point the problem reduces to the synthesis of a disubstituted malonic ester.

Acetoacetic Ester Synthesis —

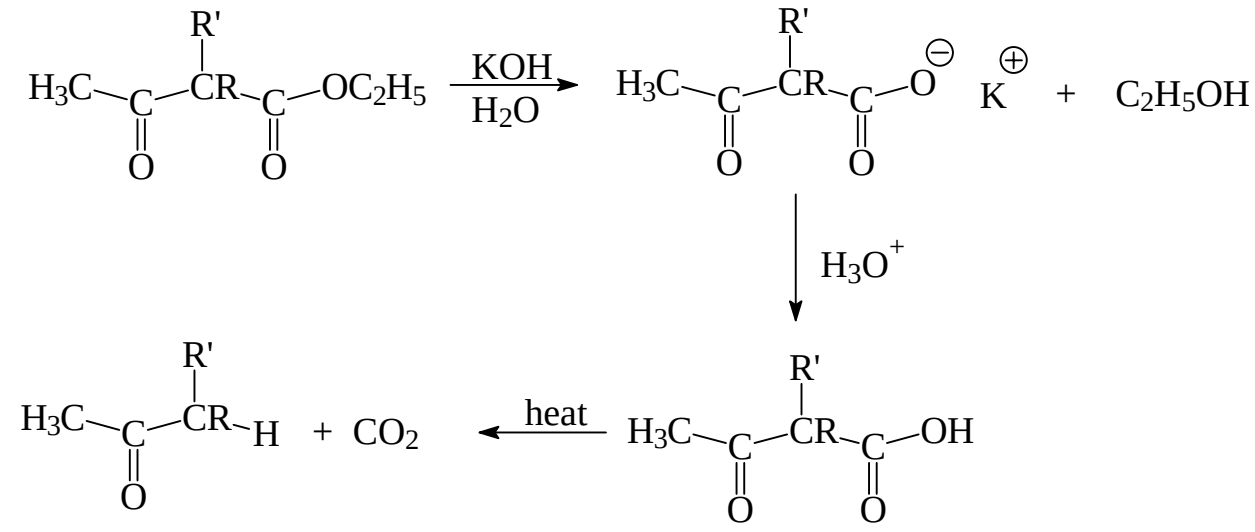
Used to prepare substituted acetones: RR'CH-CO-CH_3, where R' may be H.



An alkyl acetoacetic ester may be converted to a dialkyl acetoacetic ester —



The alkyl or dialkyl acetoacetic ester is then hydrolyzed and decarboxylated —



The decarboxylation of the β-keto acid occurs *via* a cyclic transition state —