Alpha Carbon Chemistry
1 – Keto Enols and Substitution Reactions

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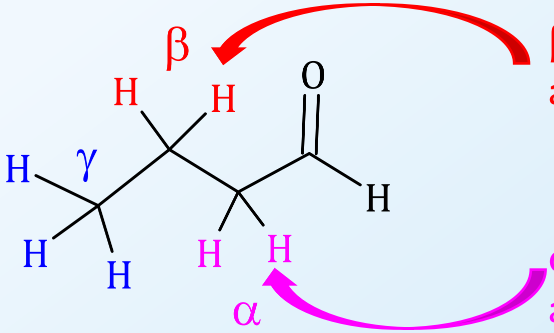
The α Carbon Proton

Alpha (α) carbon is the one next to carbonyl carbon. Due to polarity of carbonly group the protons on alpha carbon are slightly acidic.

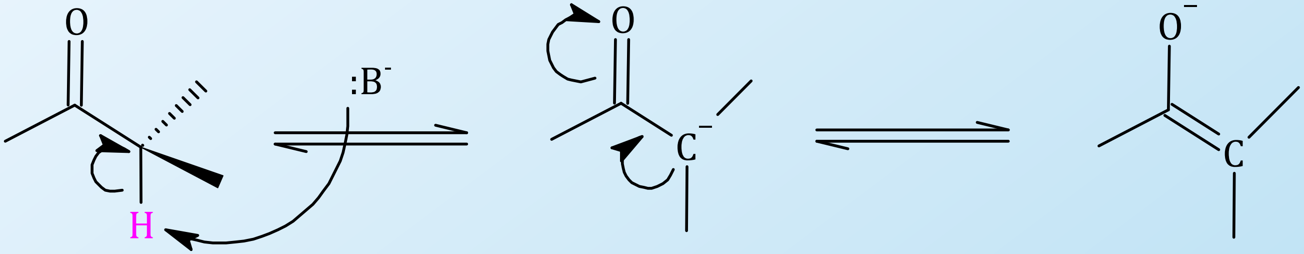


β hydrogens are not that acidic. pKa ~ 40-50

α hydrogens most acidic. pKa ~ 19-20

After abstraction of the α proton by a strong base, the resulting ion is resonance stabilized, however, both structures can be isolated hence they are not really resonance structures but isomers – called tautomers.

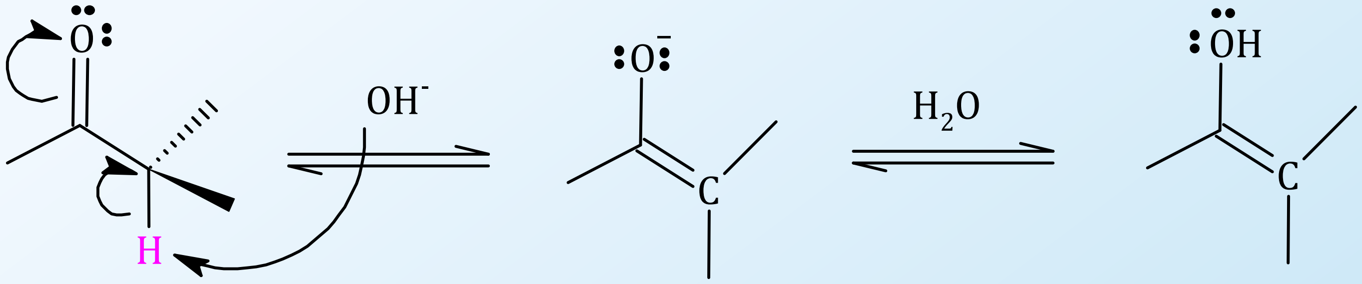
Keto tautomer **enol tautomer**



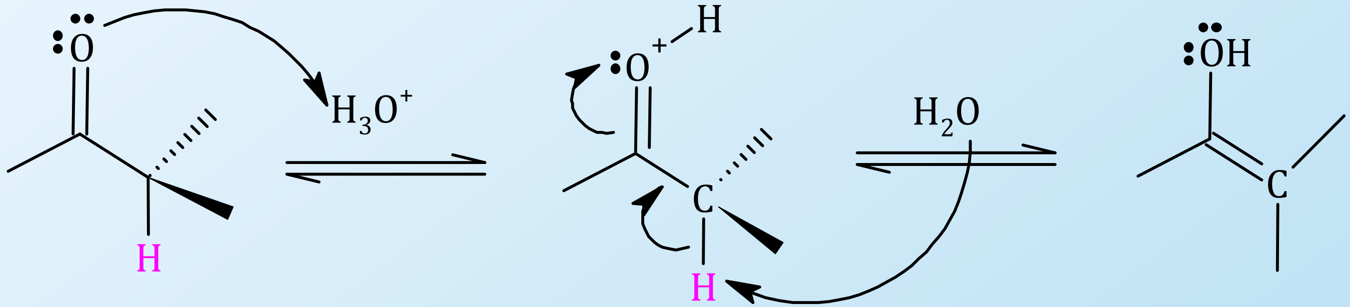
Keto-Enol Formation in Acids/Bases

Carbonyl compounds can be converted to keto-enols in both acidic and basic conditions, and the keto-enol are interconvertible to carbonyls.

Basic Conditions

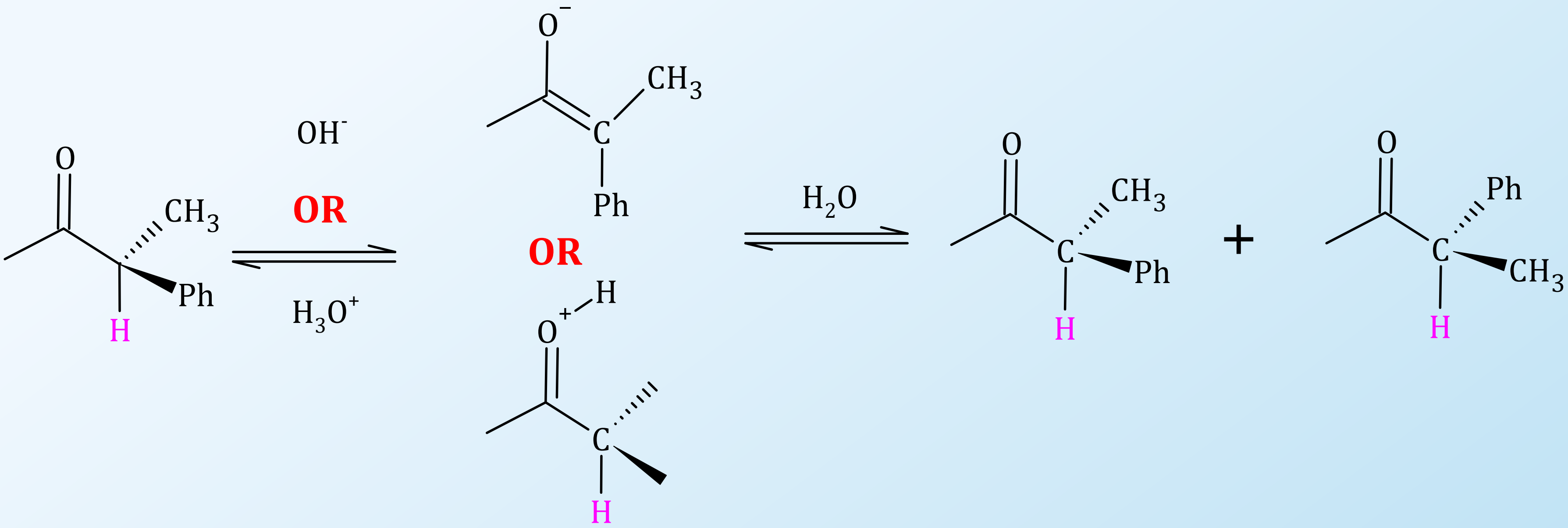


Acidic Conditions

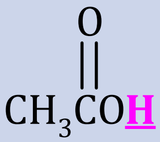
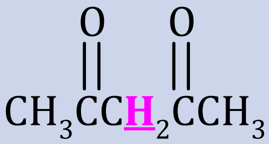
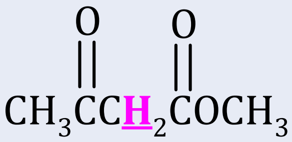
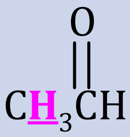
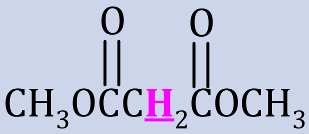
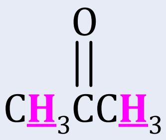
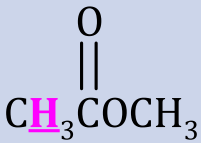


Keto-Enol Tautomers for Chiral Compounds

If a carbon is chiral then chirality is lost during the abstraction of the α proton and tautomerism.



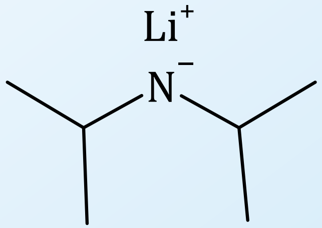
pKa for Some Carbonyl Compounds

Functional group	Structure	pK_a	Functional group	Structure	pK_a
Carboxylic acid	 $CH_3\overset{\overset{O}{\|}}{C}O\underline{H}$	5	1,3-Diketone	 $CH_3\overset{\overset{O}{\|}}{C}C\underline{H}_2\overset{\overset{O}{\|}}{C}CH_3$	9
Alcohol	$CH_3CH_2O\underline{H}$	16	2-Keto ester	 $CH_3\overset{\overset{O}{\|}}{C}C\underline{H}_2\overset{\overset{O}{\|}}{C}OCH_3$	11
Aldehyde	 $C\underline{H}_3\overset{\overset{O}{\|}}{C}H$	17	1,3-Diester	 $CH_3O\overset{\overset{O}{\|}}{C}C\underline{H}_2\overset{\overset{O}{\|}}{C}OCH_3$	13
Ketone	 $C\underline{H}_3\overset{\overset{O}{\|}}{C}C\underline{H}_3$	19	Nitrile	$C\underline{H}_3CN$	25
Ester	 $C\underline{H}_3\overset{\overset{O}{\|}}{C}OCH_3$	25			

Bases Used for Making Keto-Enols

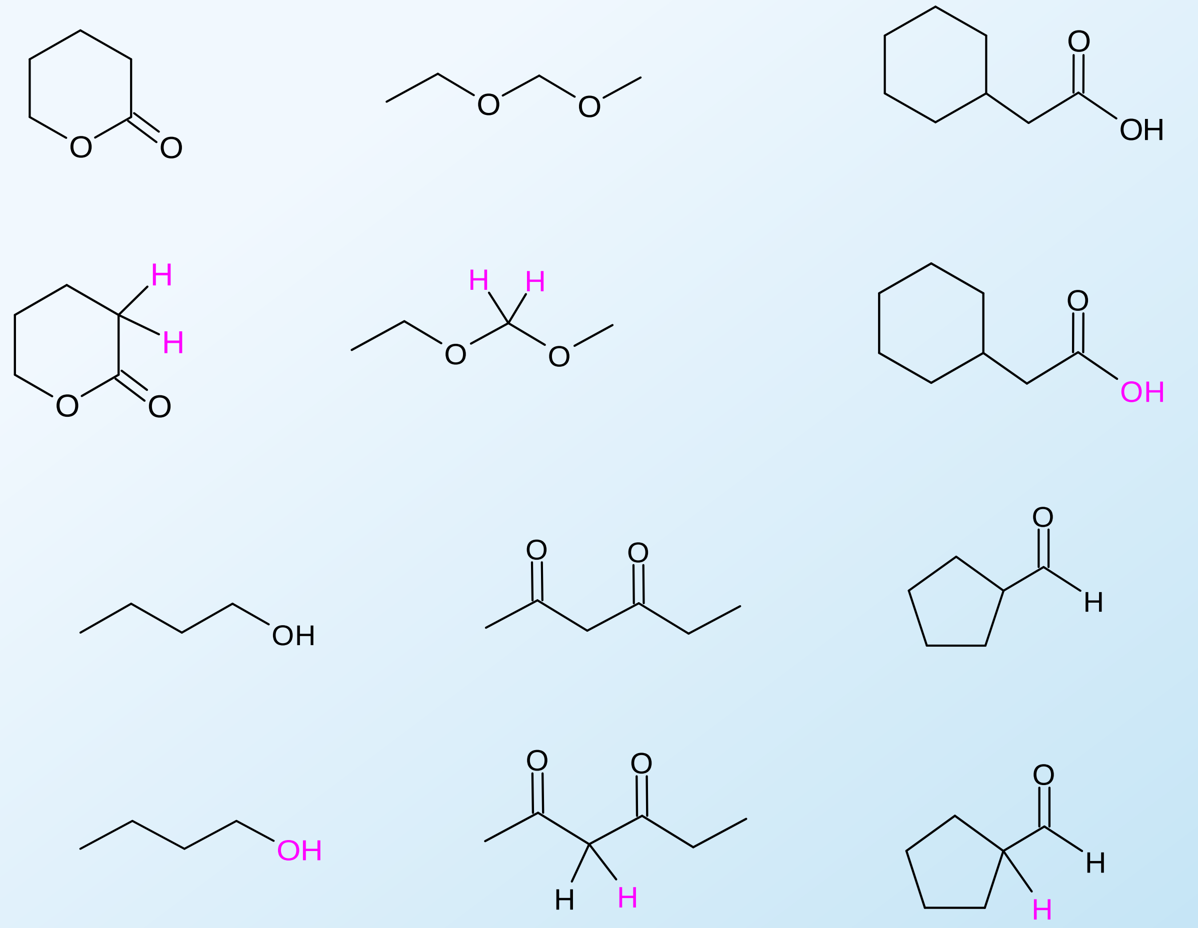
The bases used for abstracting the acidic protons are strong bases – but not good nucleophiles or they will carry out nucleophilic addition on the carbonyl carbon.

Good bases are Lithium diisopropyl amide (LDA), MeO^-, EtO^-, and NaOH.



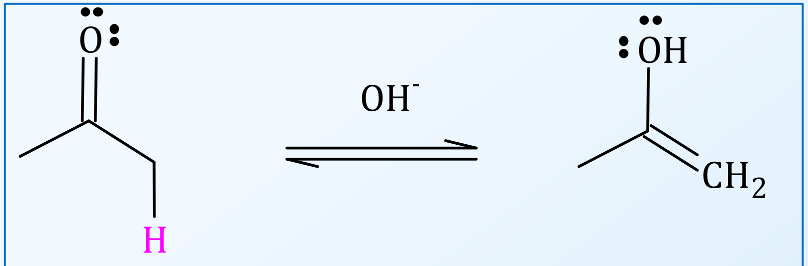
Lithium **D**iisopropyl **A**mide

Worked Example: Identify the most acidic protons in the following compounds.

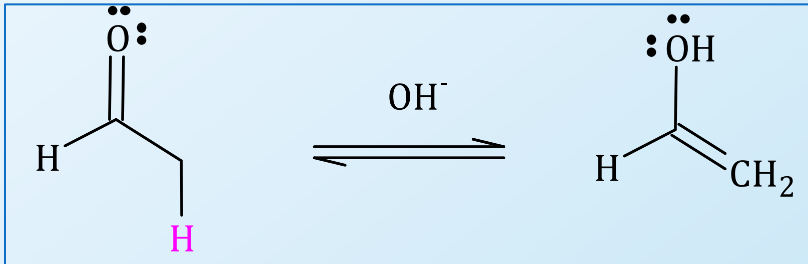


Stability of Keto-Enol Tautomers

Some tautomers are more stable than others. For example, the keto form of acetaldehyde and acetone are more stable than the enol form.

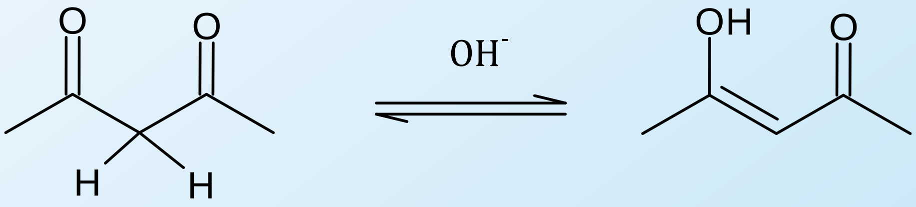


acetone: keto tautomer is major > 99%

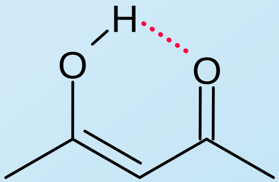


acetaldehyde: keto tautomer is major > 99%

In the compound below the enol is more stable because it is stabilized by hydrogen bond.



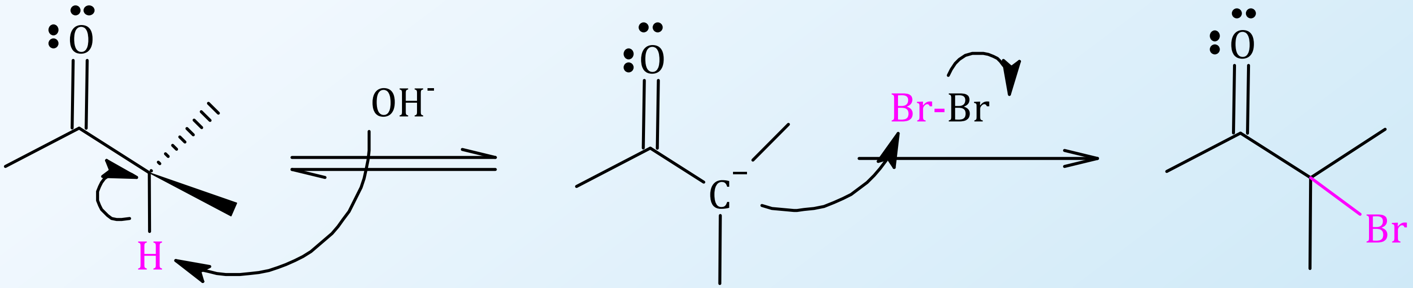
Pentane-2,4-dione: enol is major > 75%



enol is stabilized by H-bond

Reactions: α-Halogenation

Once the α proton is abstracted, a nucleophile is generated which can now carry out substitution reactions with electrophiles.

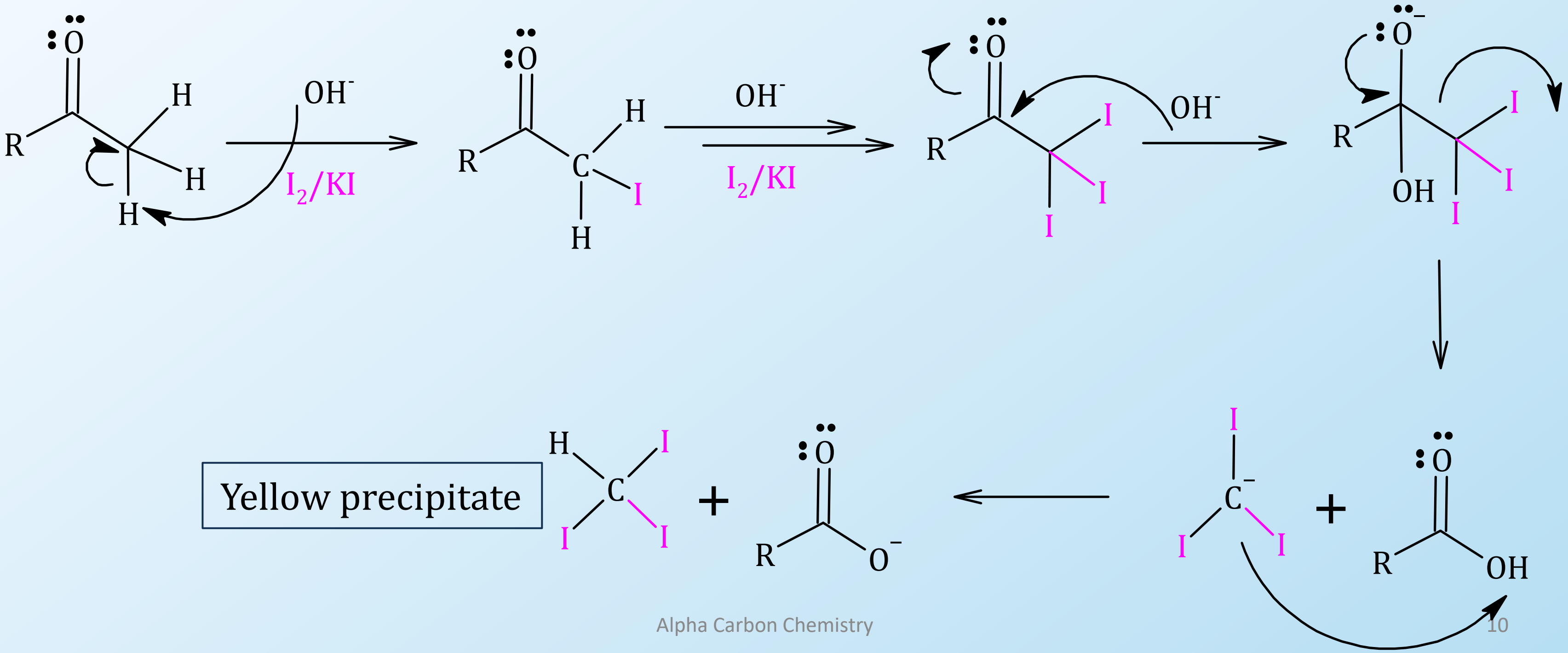


Bromination on the alpha position opens up the substrate for all substitution and/or elimination reactions can be performed. (*This is the basis of iodoform test of methyl ketones – next slide*)

Reactions: α-Halogenation - Iodoform Test

In iodoform test, a methyl ketone can be identified by the formation of a yellow precipitate in the presence of an aqueous solution of iodine in presence of a strong base (NaOH or KOH).

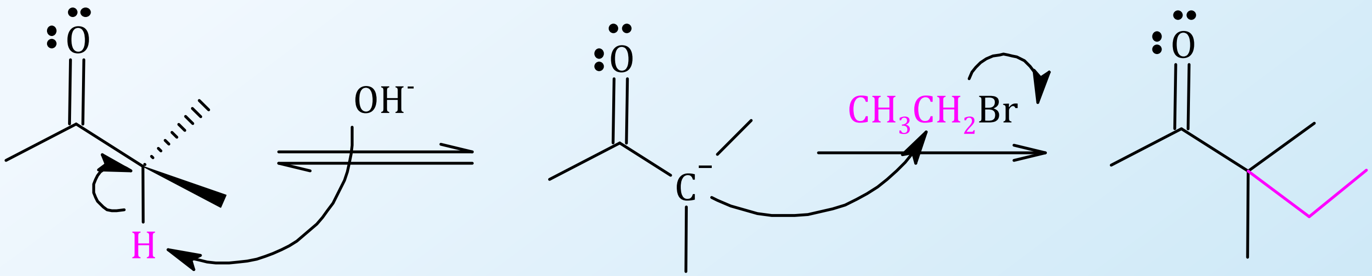
The reaction involves the acidic protons abstracted using a strong base, one by one, and substituted with iodide. Eventually in the last step, CHI_3, iodoform, cleaves giving a yellow precipitate while the ketone is oxidized to a carboxylic acid. (**NOTE**: R should not be CH_3.)



Yellow precipitate

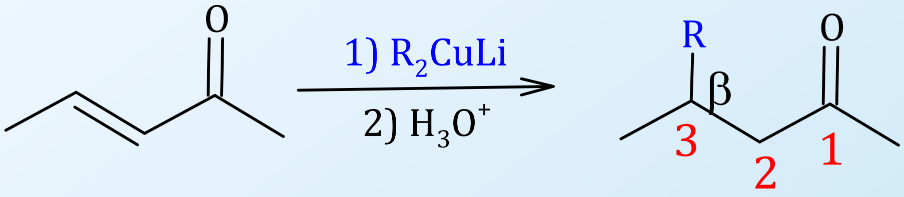
Reactions: α-Alkylation

Alkylation is a great way of forming a C-C bond and extending the carbon chain with just hydrocarbons. Again, once the alpha proton is abstracted, the nucleophile generated will react with any alkyl halide in a S_N2 mechanism.

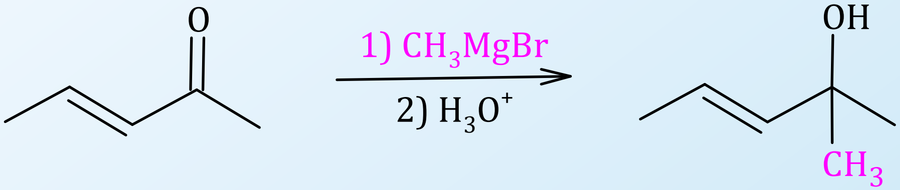


Reactions: Conjugate Addition/Michael Addition

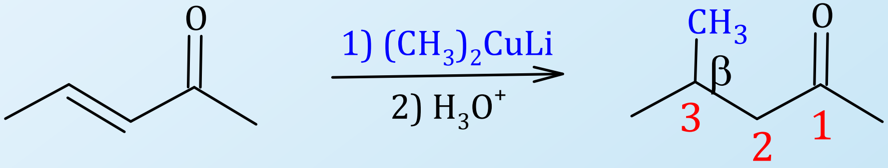
This is a very specific reaction that adds an alkyl group on the beta carbon (3rd carbon from carbonyl).



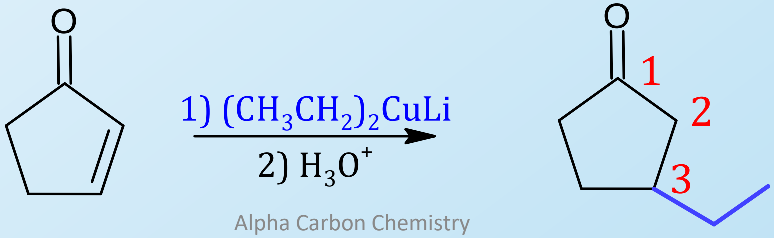
In a normal organometallic reaction, as in Grignard reaction, the alkyl group adds to carbonyl to give an alcohol as shown below.



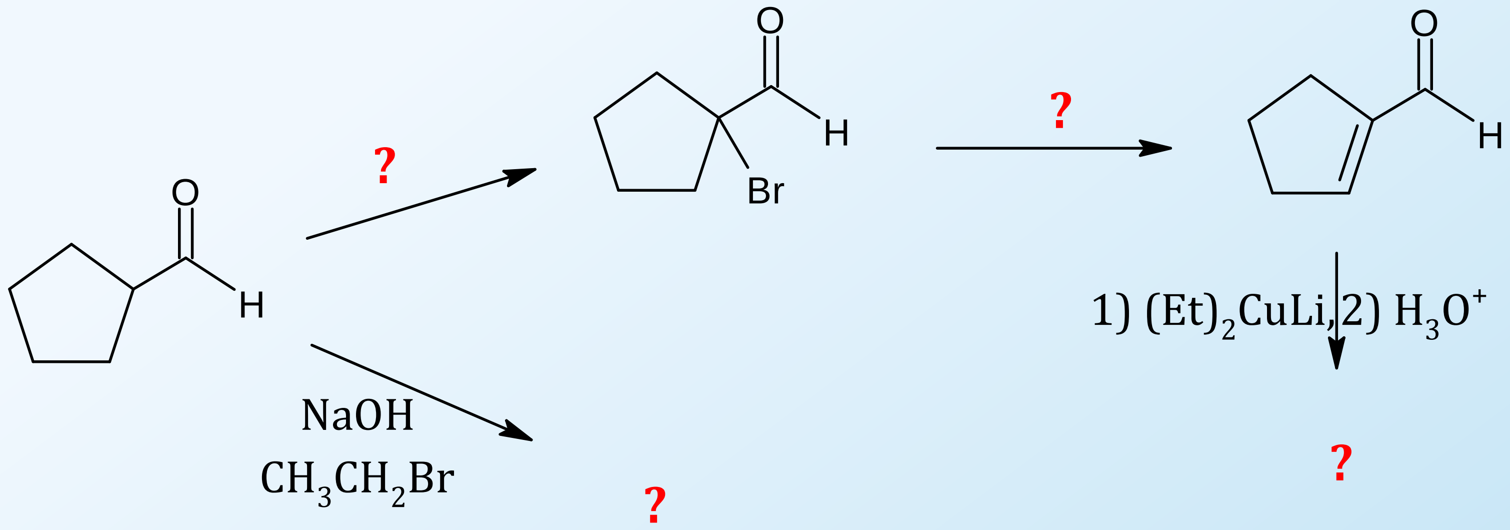
However, when there is a double bond conjugated with the carbonyl, there is addition on beta (β) carbon with a weakly nucleophilic dialkyl cuperate reagent.



Another example:

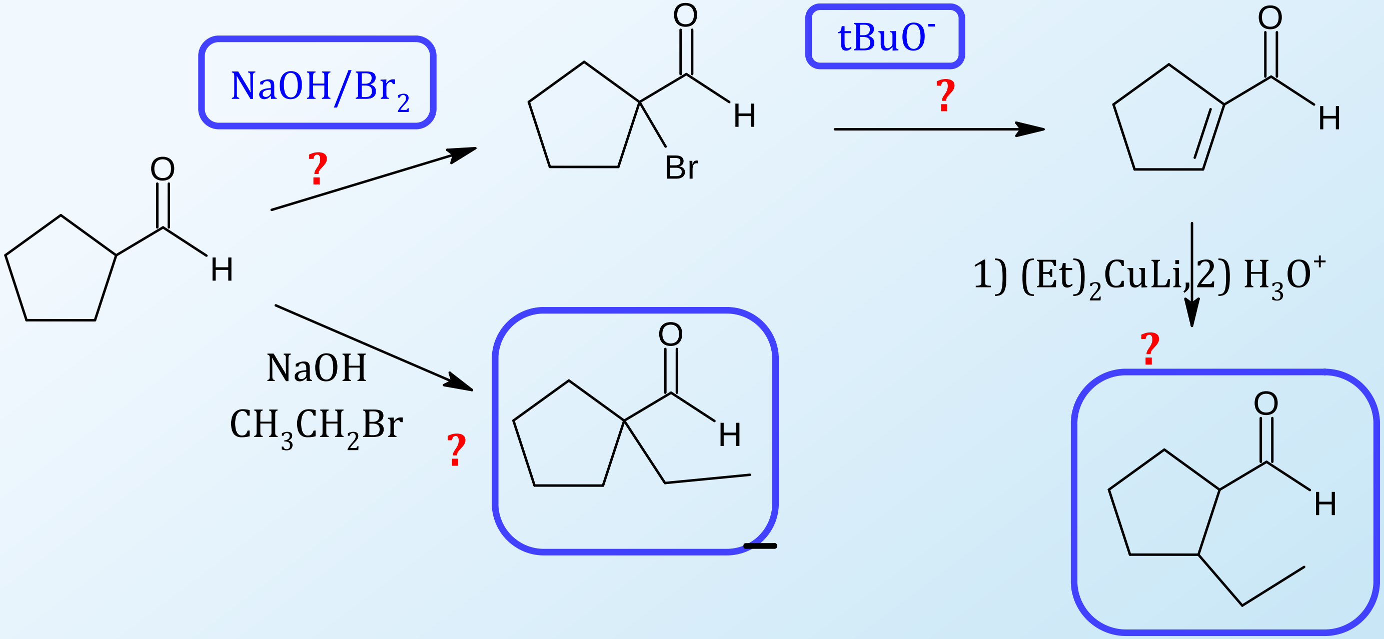


Worked Example: Complete the following reactions with the appropriate product, reagent or substrate.



Worked Example: Complete the following reactions with the appropriate product, reagent or substrate.

Answers



Key Concepts

- α protons
- Keto enol tautomerism
- Halogenation at α carbon
- Iodoform reaction
- Substitution reaction at α carbon
- Michael addition