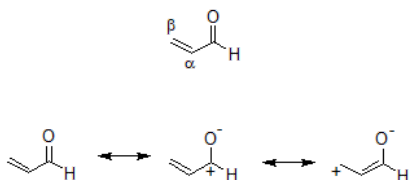


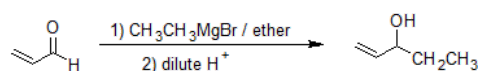
23.10: CONJUGATE ADDITIONS- THE MICHAEL REACTION

1,2 (DIRECT) VERSUS 1,4 (CONJUGATE) ADDITION

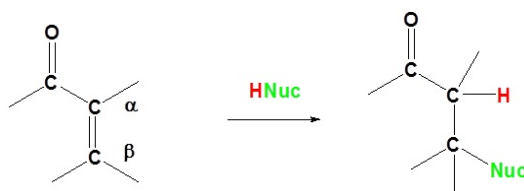
There are two electrophilic sites in alpha,beta-unsaturated carbonyls: the carbonyl carbon and the beta carbon. The second electrophilic site is created through resonance as shown below.



It is the strength of the nucleophile that determines the dominant reaction pathway. Strong nucleophiles like Grignard reagents and hydrides will react directly at the carbonyl carbon following the reactivity previously studied. The strong nucleophile reacts with the carbonyl carbon to produce a tetrahedral intermediate that is protonated to form an alcohol. The 1,2 direct addition reaction of prop-2-enal with a Grignard reagent is shown as an example below.

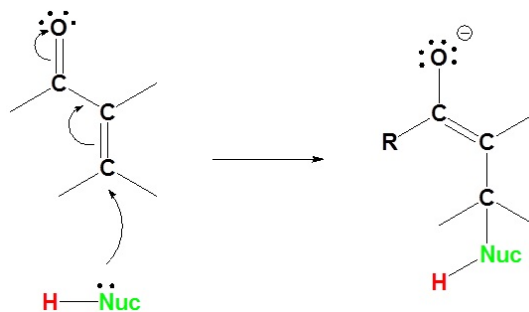


In 1,4 conjugate addition, the nucleophile reacts with the carbon β to the carbonyl driving the formation of an enolate ion that tautomerizes back to the carbonyl upon protonation, while the hydrogen is added to the carbon alpha to the carbonyl.

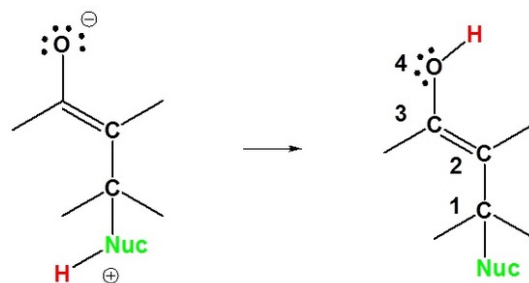


MECHANISM FOR 1,4 CONJUGATE ADDITION

1) Nucleophilic reaction at the carbon β to the carbonyl

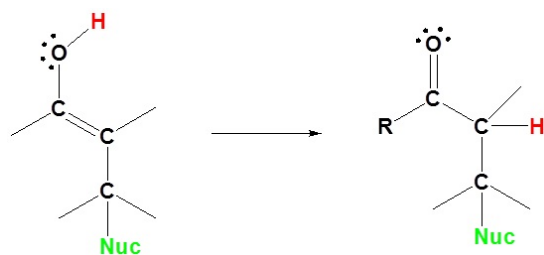


2) Proton Transfer



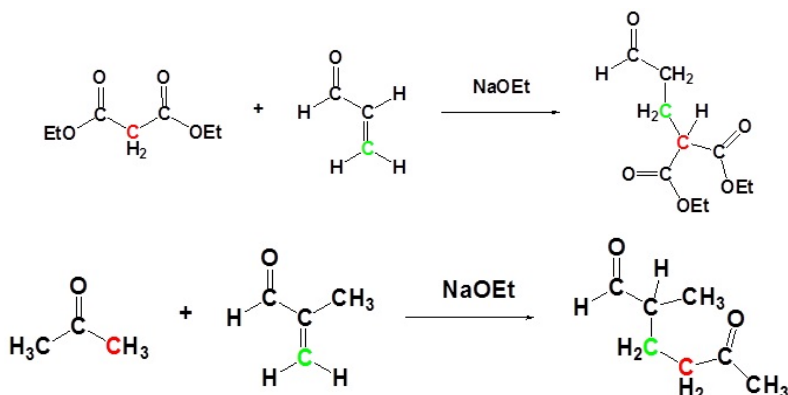
Here we can see why this addition is called 1,4. The nucleophile bonds to the carbon in the one position and the hydrogen adds to the oxygen in the four position.

3) Tautomerization



MICHAEL ADDITIONS

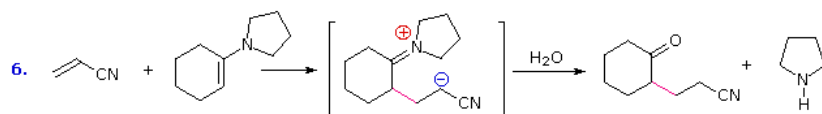
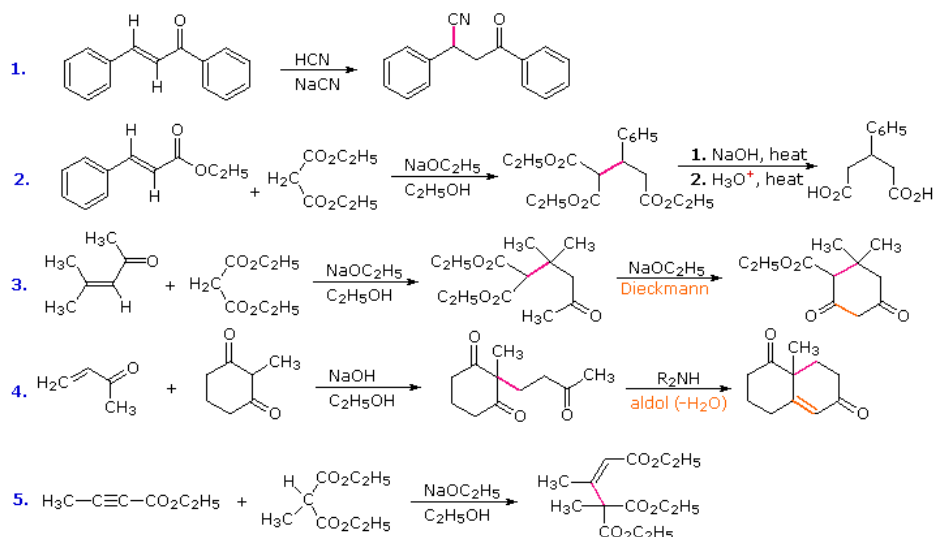
Enolates are weak nucleophiles and undergo 1,4 addition to α, β -unsaturated carbonyl compounds in a process called a Michael addition. The reaction is named after American chemist Arthur Michael (1853-1942). Two examples are shown below.



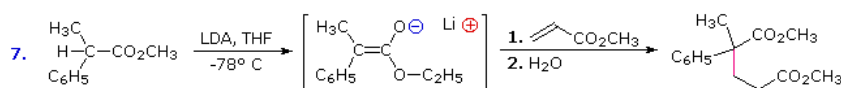
In combination with alkylations and condensations, the Michael reaction may be used to construct a wide variety of complex molecules from relatively simple starting materials. The nucleophile is called the Michael Donor and the electrophile (the α, β -unsaturated carbonyl) is called the Michael Acceptor. The table below shows common reagents used for Michael addition reactions.

Michael Donors (aka nucleophile)	Michael Acceptors (aka electrophile)
R_2CuLi Gilman reagent	$CH_2=CH-CHO$ α, β -unsaturated aldehyde
enamine	$CH_2=CH-C(=O)R$ α, β -unsaturated ketone
$R-C(=O)-CH_2-C(=O)-R$ β -diketone	$CH_2=CH-C(=O)OR$ α, β -unsaturated ester
$R-C(=O)-CH_2-C(=O)OR'$ β -ketoester	$CH_2=CH-C(=O)NH_2$ α, β -unsaturated amide
$R-C(=O)-CH_2-CN$ β -keto nitrile	$CH_2=CH-CN$ α, β -unsaturated nitrile
$R-C(=O)-CH_2-NO_2$ α -nitro ketone	$CH_2=CH-NO_2$ nitroethylene

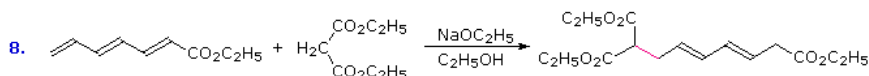
There are several examples shown below including cyanide as another potential Michael donor. These anions are sufficiently stable that their addition reactions may be presumed reversible. If this is so, the thermodynamic argument used for hetero-nucleophile additions would apply here as well, and would indicate preferential formation of 1,4-addition products. Cyanide addition does not always follow this rule, and aldehydes often give 1,2-products (cyanohydrins). In each case the initial reaction is a Michael addition, and the new carbon-carbon bond is colored magenta. Any subsequent bonds that are formed by other reactions are colored orange.



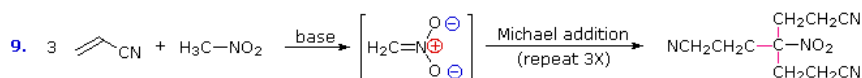
Enamine nucleophiles are good Michael donors. Hydrolysis is necessary to obtain the ketone product.



Weak carbon acids may be converted to their enolate anions prior to addition of the Michael acceptor.



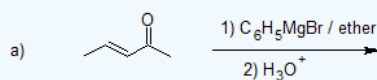
Extended vinylous Michael acceptors have been used. This is a 1,6-addition (1,8 if the enol is counted).



Nitroalkanes have acidic α -hydrogens and make excellent Michael donors.

Exercise2

14. Draw the bond-line structures for the products of the reactions below.



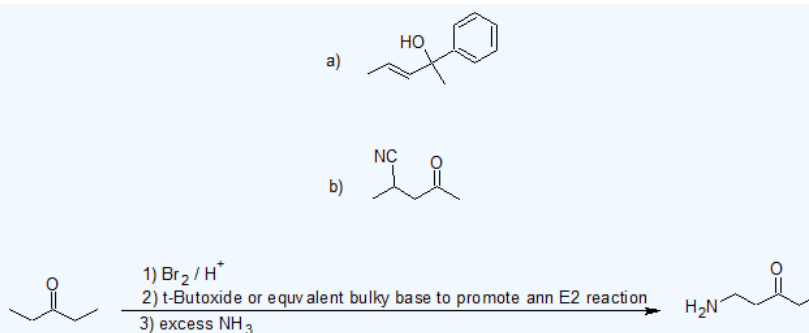
15. Specify the reagents needed to perform the following chemical transformation.



Answers

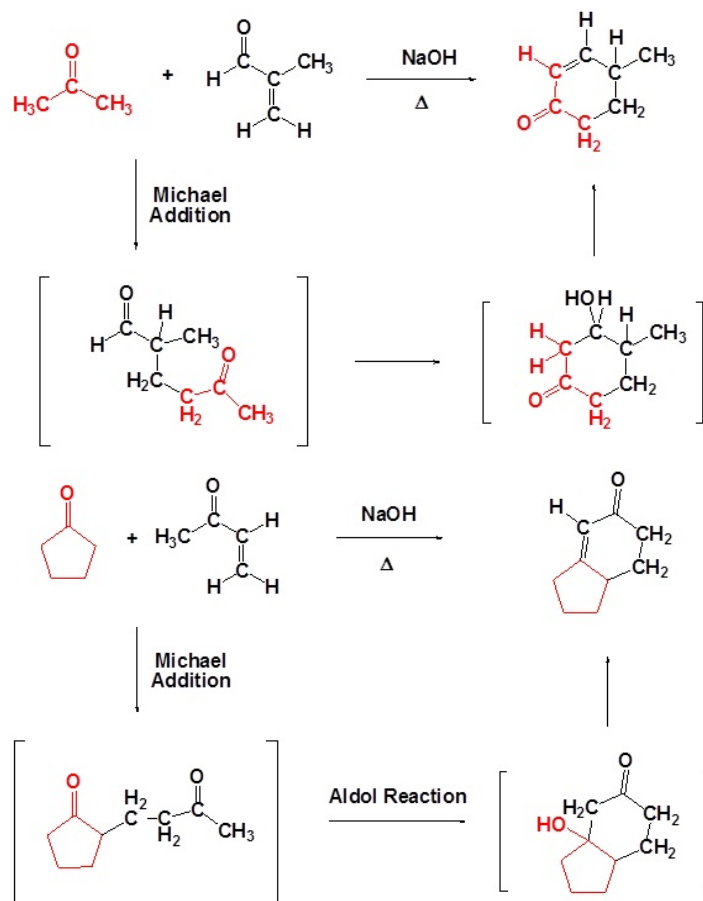
14.

15.



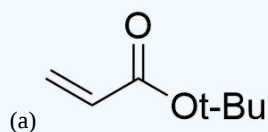
ROBINSON ANNULATIONS

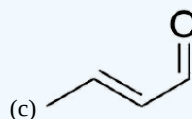
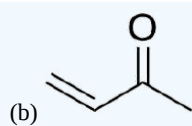
Many times the product of a Michael addition produces a dicarbonyl which can then undergo an intramolecular aldol reaction. These two processes together in one reaction creates two new carbon-carbon bonds and also creates a ring. Ring-forming reactions are called annulations after the Latin word for ring annulus. The reaction is named after English chemist Sir Robert Robinson (1886-1975) who developed it. He received the Nobel prize in chemistry in 1947. Remember that during annulations five and six membered rings are preferred.



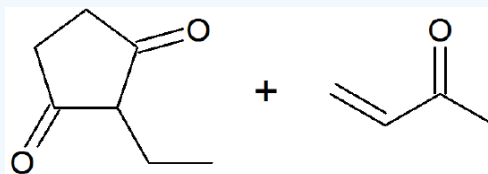
Exercise

16. Draw the product of the reaction with the enamine prepared from cyclopentanone and pyrrolidine, and the following molecules.



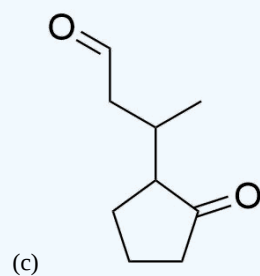
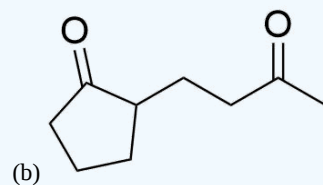
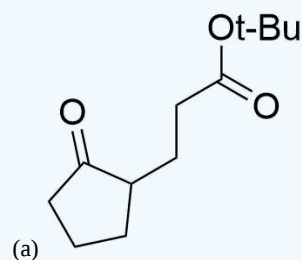


17. Draw the product of the following reaction.

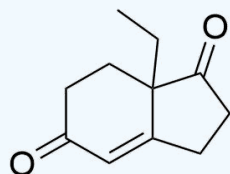


Answer

16.



17.



CONTRIBUTORS AND ATTRIBUTIONS

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- Prof. Steven Farmer ([Sonoma State University](#))
- William Reusch, Professor Emeritus ([Michigan State U.](#)), [Virtual Textbook of Organic Chemistry](#)

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