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Faculty of **S**ciences

Department of **C**hemistry

Course **S**upport for **A**dvanced **C**hemistry **I**: "**R**eaction **M**echanisms and **M**ajor **R**eactions"

Master 1. **P**harmaceutical **C**hemistry and **O**rganic **C**hemistry

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Foreword

The study of organic reaction mechanisms represents one of the most powerful tools for understanding and mastering chemical transformations. Through this course, students will explore how bonds are broken and formed, and how different reaction conditions influence the course and outcome of a reaction.

This document has been prepared as an educational support to accompany lectures and practical sessions. It aims to provide a coherent and comprehensive overview of advanced organic reaction mechanisms, with an emphasis on both conceptual understanding and synthetic application. Each section is structured to help students develop a mechanistic mindset enabling them to analyze, compare, and predict the behavior of organic molecules under various conditions.

This course will prepare students to approach organic synthesis with confidence and creativity, essential qualities for any aspiring researcher or professional chemist.

Preface

This course support entitled "***Reaction Mechanisms and Major Reactions***" has been designed for **Master 1** students in **Pharmaceutical Chemistry** and **Organic Chemistry** at the Faculty of Sciences, Department of Chemistry, Université Badji Mokhtar Annaba. The main objective of this course is to provide students with a detailed understanding of the fundamental principles that govern organic reaction mechanisms and to highlight their applications in modern organic synthesis.

Organic chemistry is a continuously evolving discipline that lies at the heart of molecular science. Mastery of reaction mechanisms enables chemists to predict, design, and optimize synthetic pathways for the preparation of new compounds with potential applications in pharmaceuticals, materials science, and agrochemistry. This course thus emphasizes the correlation between theory and practice, encouraging critical thinking and problem-solving in synthetic design.

The material has been carefully structured to progressively introduce key mechanistic concepts from nucleophilic substitutions and eliminations to radical and organometallic reactions followed by detailed studies of major named reactions frequently used in synthetic organic chemistry. Each chapter combines theoretical explanations, mechanistic schemes, and illustrative examples to facilitate comprehension and to strengthen the link between reaction mechanisms and synthetic strategy.

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6. Addition of hydrides and organometallic compounds to carbonyl compounds.

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*Mannich reaction.

*Michael and aza-Michael reaction.

*Robinson annulation.

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List of abbreviation and symbols

AIBN	Azobisisobutyronitrile	**Me**	Methyl
Ac	Acetyl	**MCR**	Multicomponent reactions
Ar	Aryl	**$NaBH_4$**	Sodium borohydride
Boc	*tert*-butoxycarbonyl	**NBS**	N-bromosuccinimide
Bn	Benzyl	**NCS**	N-chlorosuccinimide
DCC	Dicyclohexylcarbodiimide	**NHR**	Amino group
CCl_4	Carbon tetrachloride	**OH**	Hydroxyl group
$CHCl_3$	Chlorofom	**OR**	Alkoxy group
EAS:	Electrophilic aromatic substitution	**OEt**	Ethoxide
E1	First order elimination	**OMe**	Methoxide
E2	Second order elimination	**Ph**	Phenyl
Et	Ethyl	**r.t**	Room temperature
H^-	Hydride ion	**SN**	Nucleophilic substitution
HX	Hydrogen halide	**THF**	Tetrahydrofuran.
HCN	Hydrogen cyanide	**Tos**	Tosyl (*p*-toluenesulfonyl)
hν	Photochemical	**UV**	Ultra-violet
LDA	Lithium diisopropylamide	**°C**	Degrees centigrade
$LiAlH_4$	Lithium aluminum hydride	**%**	Percentage

1. Definition of organic synthesis

Organic synthesis is a branch of chemistry dedicated to the creation of complex organic compounds from simpler molecules. It involves carefully controlled chemical reactions to form new chemical bonds and structure the desired molecules. These reactions must be optimized based on various criteria, including:

Chemoselectivity: the ability to favor a particular chemical reaction among several competing possibilities.

Regioselectivity: the preference for forming a product at a specific position on a molecule.

Stereoselectivity: the preferential formation of a particular stereoisomer.

Organic synthesis can be carried out using classical approaches, involving well-defined sequential steps, or through multicomponent reactions (MCR), where multiple reactants are combined in a single step to yield a complex final product (**Figure 1**).

This discipline plays a crucial role in numerous fields, including pharmaceutical research, polymer material manufacturing, biological sciences, and agriculture. The objectives of organic synthesis include maximizing yields, minimizing production costs, and enhancing process safety to ensure efficient and environmentally friendly manufacturing [1].

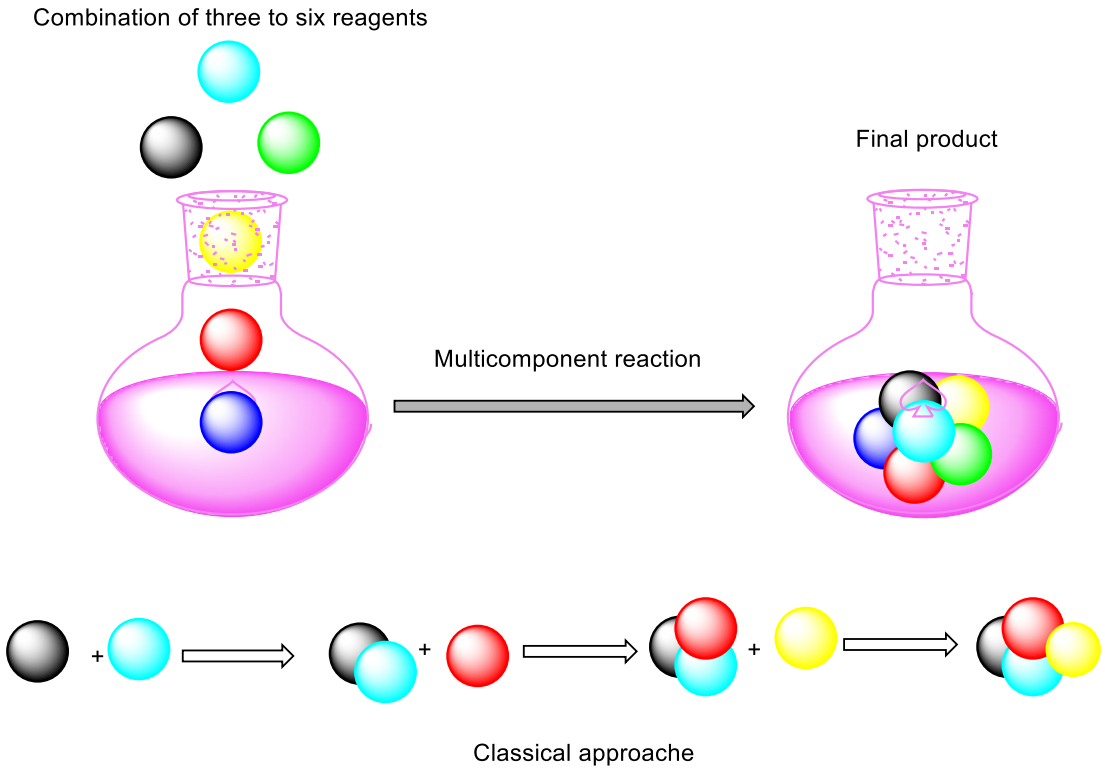


Figure 1. *Classical approaches and multicomponent reactions (MCR).*

1.1. Chemoselectivity

Chemoselectivity refers to the preference for forming a specific product over other possible outcomes in a chemical reaction facilitated by the same reaction mechanism. This selectivity can apply to several scenarios, such as:

Different functional groups within the same molecule: the reaction favors one functional group over others present in the target molecule.

The same functional group in different molecules: the reaction preferentially targets a molecule with a particular functional group when competing molecules are present.

Different possible products from the same functional group: the reaction selectively produces a specific chemical derivative despite multiple transformation possibilities.

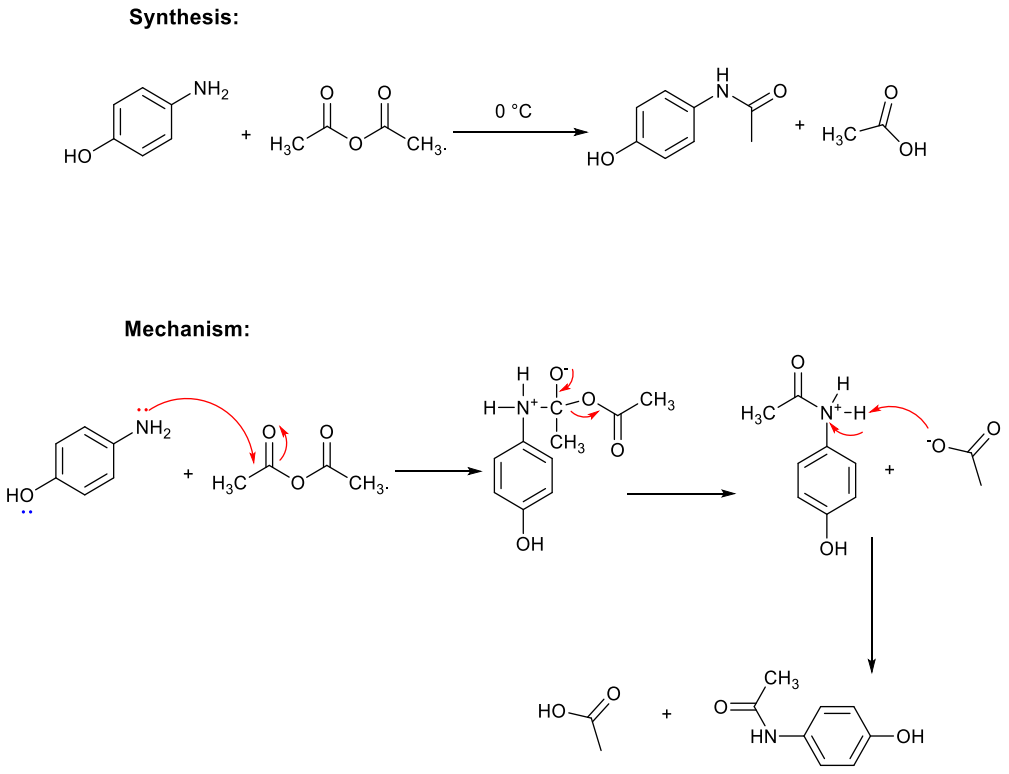
Mastering chemoselectivity is crucial in organic synthesis to avoid undesired side reactions and enhance the efficiency and purity of final products. This control becomes particularly significant in fields requiring precise molecular structures, such as the synthesis of pharmaceuticals, advanced materials, and agrochemicals. Ensuring chemoselectivity can improve product yields, reduce waste, and streamline complex synthesis processes, contributing to more sustainable and cost-effective manufacturing practices.

Example: Paracetamol synthesis.

The synthesis of paracetamol is typically performed in a single primary step where para-aminophenol is acetylated to form paracetamol using acetic anhydride (**Scheme 1**).

In this process, the free lone pair on the nitrogen atom participates in the reaction, while the hydroxyl group's lone pair remains unreactive under these reaction conditions. The selectivity of this reaction demonstrates chemoselectivity by favoring the amine functional group for acylation without affecting the hydroxyl group.

This controlled chemoselective approach ensures the efficient synthesis of paracetamol **3** while minimizing by-products, highlighting the importance of targeted functional group manipulation in synthetic strategies.



Scheme 1. *Synthesis of paracetamol (chemoselective reaction).*

1.2. Regioselectivity

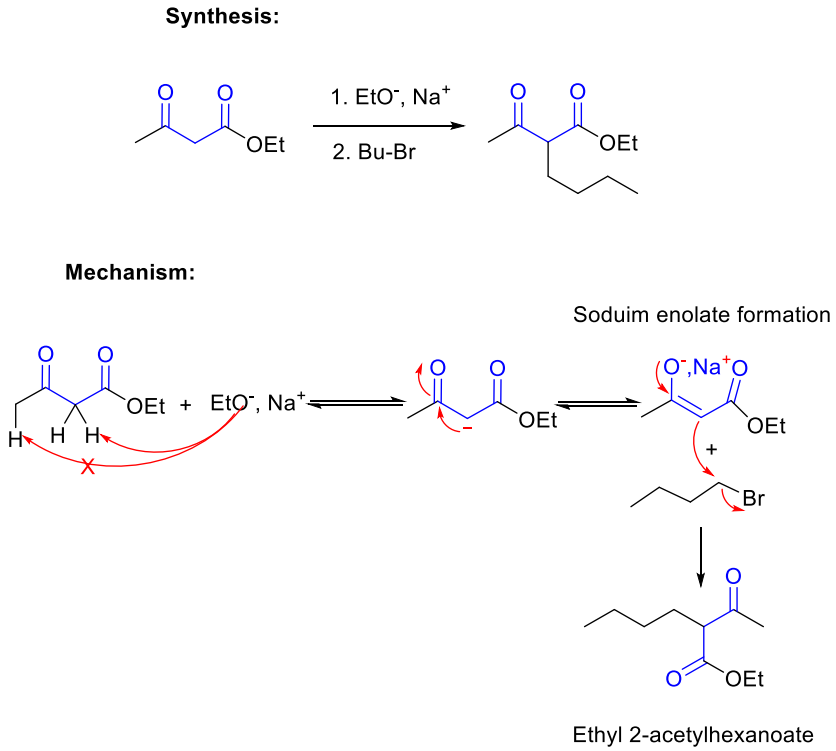
Regioselectivity refers to the preference of a chemical reaction to produce one structural isomer over others when multiple possibilities exist due to the reaction occurring at different locations (or "regions") within a molecule. This phenomenon plays a crucial role in organic synthesis, as it determines the distribution of products in reactions involving unsymmetrical molecules or functional groups. The key principles of regioselectivity are electrophilic addition to alkenes, in the case of unsymmetrical alkenes, electrophilic additions often follow Markovnikov's rule, where the electrophile (usually a proton, H^+) adds to the carbon with the greatest number of hydrogen atoms, and the nucleophile adds to the carbon with fewer hydrogens. This regioselectivity is due to the stability of the carbocation intermediate formed during the reaction. The nucleophilic substitution on aromatic compounds influences also the regioselectivity by directing incoming groups to specific positions (*ortho*, *meta*, or *para*) based on their electron-donating or withdrawing nature.

Electron-donating groups (e.g., -OH, $-NH_2$) typically direct substitutions to *ortho* and *para* positions.

Electron-withdrawing groups (e.g., $-NO_2$, -CN) favor substitution at the meta position.

In reactions involving the formation of enolates, regioselectivity determines whether the kinetic (less substituted) or thermodynamic (more substituted) enolate forms, depending on reaction conditions such as temperature and choice of base.

Example: Ethyl 2-ethylhexanoic synthesis.



Scheme 2. *Synthesis of ethyl 2-acetylhexanoate (regioselective reaction).*

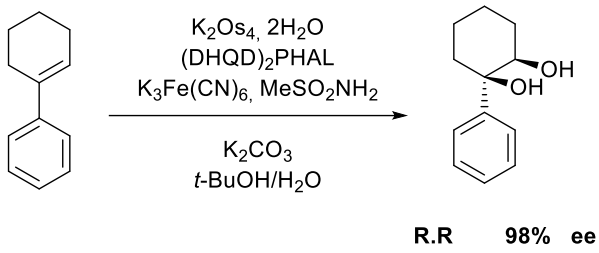
1.3. Stereoselectivity

Stereoselectivity refers to the preference of a chemical reaction to produce one stereoisomer over others when multiple stereoisomers are possible. Stereoisomers are molecules that have the same molecular formula and connectivity of atoms but differ in the spatial arrangement of their atoms or groups. Stereoselectivity can occur when a reaction transforms a specific substrate into a mixture of stereoisomers, with one stereoisomer being favored over the others in unequal amounts. This is crucial in many areas of organic synthesis, particularly in the preparation of compounds where the three-dimensional arrangement of atoms is critical.

Example : Sharpless reaction.

The Sharpless epoxidation is a widely used and highly effective reaction for the synthesis of epoxides from alkenes, and it can be extended to the formation of diols (two hydroxyl groups) via a two-step process. This reaction is particularly significant because it is highly

enantioselective, making it an essential tool for creating chiral diols in a stereoselective manner (**Scheme 3**).



Scheme 3. *Sharpless catalytic dihydroxylations.*

2. Nucleophilic substitution reactions on saturated carbon (SN1 and SN2)

Organic reactions are classified based on their overall reaction equations and mechanisms. The three fundamental types of organic reactions are addition, elimination, and substitution. In this chapter, we will explore nucleophilic substitution reactions of first and second order (SN1 and SN2) [2].

2.1. First order nucleophilic substitution (SN1)

The SN1 reaction occurs in two steps and is typical when the starting molecule is heavily sterically hindered:

Step 1*: heterolytic cleavage of the carbon-leaving group bond (formation of a carbocation).*

A heterolytic cleavage is the breaking of a covalent bond in a neutral molecule, generating an anion and a cation.

In SN1 reactions, the atoms or groups involved, especially around the asymmetric carbon (C*), typically include: bromine atom (Br), methyl group (CH_3), ethyl group (C_2H_5), phenyl group (C_6H_5), and other aromatic functional groups.

These large groups contribute to the steric hindrance of the asymmetric carbon (C*), making the two-step SN1 pathway more favorable.

Factors influencing SN1 reactions

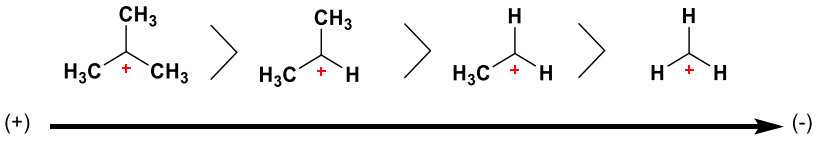
-Weak nucleophile: H_2O

-Good leaving group: $I^- > Br^- > Cl^- > F^-$

-Steric hindrance: favorable for tertiary and bulky secondary alkyl halides (RX)

-Carbocation stability: the reaction is more favorable when the resulting carbocation is stable (tertiary > secondary > primary)

-Understanding these parameters is crucial to optimizing conditions for efficient nucleophilic substitution reactions.



-Polar protic solvents: H_2O, ROH

Step 2: *Nucleophile addition to the carbocation (C^+)*

In the second step of the SN1 reaction, the nucleophile donates a lone pair of electrons to the electrophilic carbon (which is electron-loving and attracted to negative charges). This mechanism

results in racemization the conversion of a pure enantiomer into a racemic mixture (a 50/50 mixture of both enantiomers of a chiral compound).

The nucleophile can attack the planar carbocation (C^+) from either side with equal probability, leading to the formation of two different compounds (**Figure 2**).

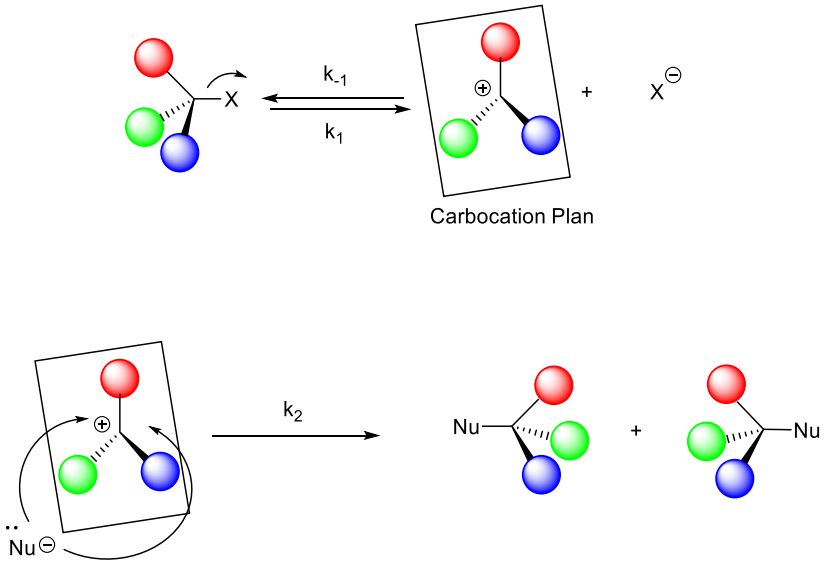


Figure 2. *Mechanism of SN1 nucleophilic substitution.*

2.2. Second order nucleophilic substitution (SN2)

The SN2 reaction occurs in a single step and is favored when the starting molecule is not sterically hindered.

In this mechanism, the nucleophile (a species that is attracted to positive charges and seeks nuclei) attacks the carbon atom from the side opposite the leaving group (nucleofuge), which is a chemical group capable of detaching from the molecule.

This backside attack results in an inversion of configuration at the asymmetric carbon (C*), known as the Walden inversion.

Factors influencing SN2 reactions

-Strong nucleophile: CN^-, OH^-, RO^-, etc.

-Good leaving group: $I^- > Br^- > Cl^- > F^-$

-Less steric hindrance: rrimary alkyl halides (RX) and lightly hindered secondary halides are preferred.

Polar aprotic solvents: examples include DMF and DMSO, which stabilize the nucleophile without forming strong hydrogen bonds.

The efficiency of SN2 reactions is highly dependent on the combination of these parameters to ensure rapid and clean substitution with minimal by-products (**Figure 3**).

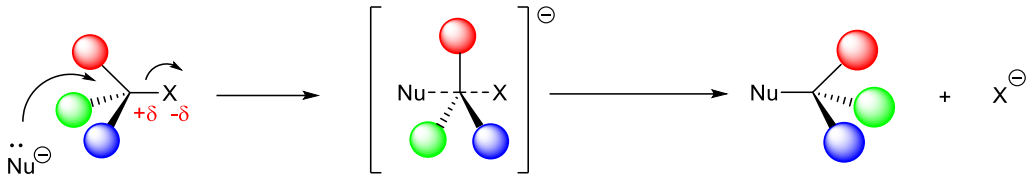
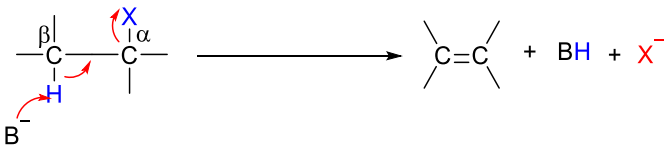


Figure 3. *Mechanism of SN2 nucleophilic substitutions.*

3. β-Elimination (concepts and principles of elimination reactions, β-elimination of H/Hhet, β-elimination of Het1/Het2)

In organic chemistry, an elimination reaction (or β-elimination) is a fundamental process that converts a substituted alkane, such as a haloalkane or alcohol, into an alkene by removing atoms or functional groups from adjacent carbon atoms (α and β positions). This reaction typically involves the simultaneous or sequential loss of a proton (H^+) from the β-carbon and a leaving group (such as a halide or hydroxide derivative) from the α-carbon, leading to the formation of a carbon-carbon double bond (alkene). The overall transformation can be described as replacing two α-bonds with a single β-bond. Elimination reactions play a crucial role in synthetic organic chemistry, particularly for constructing unsaturated compounds such as alkenes and alkynes, which serve as key intermediates in the synthesis of complex molecules in pharmaceuticals, polymers, and agrochemicals (**Scheme 4**) [3].



Scheme 4. *β-elimination reaction.*

These reactions are typically favored by high temperatures and the use of strong bases such as hydroxides (K^+, HO^-) or alkoxides (Na^+, RO^-), that facilitate the removal of protons from the β-carbon. The stereochemistry and regioselectivity of the elimination can be influenced by the reaction conditions and substrate geometry, often leading to the formation of the more thermodynamically stable (Zaitsev) product, though exceptions such as the Hofmann product can occur in sterically hindered systems. Two possible mechanisms are considered:
First order elimination (E1) and second order elimination (E2).

3.1. First order elimination reaction mechanism (E1)

The E1 elimination mechanism is a two-step process where the rate-determining step involves the formation of a carbocation intermediate. The reaction is called "first-order" because the reaction rate depends solely on the concentration of the substrate, not the base. This mechanism typically occurs under conditions of weak bases and polar protic solvents and is favored by tertiary substrates due to carbocation stability.

The reaction occurs in two steps:

Step 1*: departure of the leaving group and formation of a carbocation.*

This is a slow, reversible step and determines the overall reaction rate.

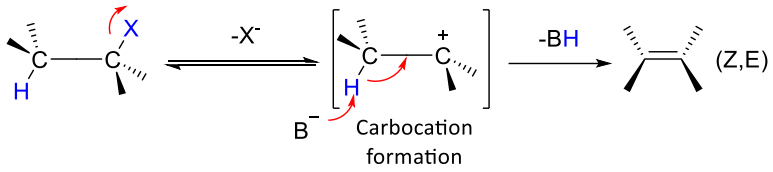
The leaving group (often a halide or sulfonate) detaches from the α-carbon, forming a carbocation.

The stability of the carbocation is crucial; tertiary carbocations are the most stable, followed by secondary, while primary carbocations are rarely formed in E1 reactions due to their instability.

Step 2*: acid-base reaction.*

The base removes a proton, causing the lone pair of electrons to shift to form a double carbon-carbon bond.

Since the single carbon-carbon bond can rotate, two stereoisomers may form. This step is much faster than the previous one and does not influence the overall reaction rate (**Scheme 5**).



Scheme 5. *Mechanism of E1 reaction.*

Factors influencing E1 reactions

-Tertiary substrates are preferred due to carbocation stability.

-Secondary substrates can participate, though less efficiently.

-Primary substrates rarely undergo E1 elimination.

-A good leaving group (such as halides like Br^-, I^-, or tosylates) facilitates the reaction.

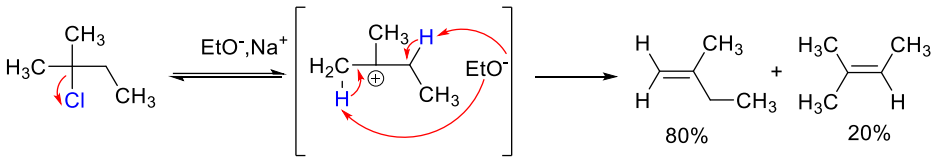
-Weak bases are sufficient since the carbocation formation does not require a strong base.

-Polar protic solvents (e.g., water, alcohols) stabilize the carbocation intermediate through solvation.

Regiochemistry

When several constitutional isomers can form, the most thermodynamically stable alkene is preferentially formed. If there are only alkyl groups, it is the most substituted alkene. If mesomerism can occur, it is the most conjugated alkene that is in the majority. This is called regioselectivity or Zaitsev's rule.

Example : E1 reaction.



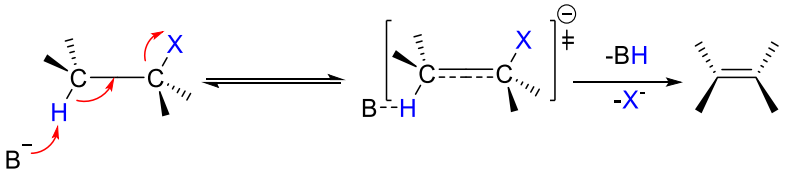
Scheme 6. *Example of regiochemistry E1 elimination reaction mechanism.*

3.2. Second order elimination (E2) reaction mechanism

The E2 mechanism is a one-step, concerted process in which a base abstracts a proton from the β-carbon while the leaving group simultaneously departs from the α-carbon, forming a carbon-carbon double bond (alkene). This reaction is called "second-order" because the rate of the reaction depends on the concentration of both the substrate and the base, meaning the reaction is bimolecular.

The E2 reaction occurs in one concerted step, meaning all bond-breaking and bond-forming processes occur simultaneously. “Simultaneous proton abstraction and departure of leaving group”.

The base (often a strong one, such as hydroxide, alkoxide, or even a negatively charged species like methoxide or ethoxide) abstracts a proton from a β-carbon (a carbon adjacent to the one bearing the leaving group). As the base pulls away the proton, the electrons from the C-H bond form a double bond between the α and β carbons. Simultaneously, the leaving group departs from the α-carbon, completing the elimination and forming an alkene (**Scheme 7**).



Scheme 7. *Mechanism of E2 reaction.*

Factors influencing E1 reactions

-Primary and secondary alkyl halides are commonly involved in E2 reactions. Tertiary substrates are more likely to undergo E1 elimination due to steric hindrance.

-Strong bases (e.g., OH^-, alkoxides like EtO^-, or even bulky bases like tert-butoxide) favor E2, as they can effectively abstract the proton from the β-carbon.

-Aprotic solvents (e.g., DMF, DMSO, acetone) are preferred because they do not solvate the base as protic solvents would. This allows the base to remain reactive, promoting the E2 mechanism.

-Protic solvents (e.g., water or alcohols) can stabilize carbocations and often promote the E1 pathway, so they are less favorable for E2.

-The rate of the reaction is second-order because it depends on the concentration of both the substrate and the base.

-E2 reactions proceed with an anti-periplanar geometry, meaning that the proton being abstracted and the leaving group must be on opposite sides of the molecule, in a trans-diaxial arrangement if the substrate is cyclic (like cyclohexane). This geometry ensures proper overlap of orbitals to form the double bond.

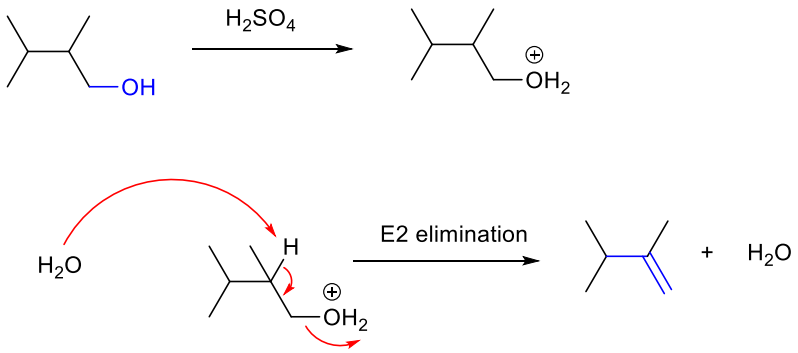
-Stereoselectivity is a key feature of E2: because of the anti-periplanar requirement, the reaction typically produces cis and trans isomers of the alkene, with the trans isomer often being the more stable.

Regiochemistry

The product distribution follows Zaitsev's rule, which states that the more substituted alkene (i.e., the one with more alkyl groups attached to the double-bonded carbons) will be the major product.

However, in some cases, particularly with bulky bases (such as tert-butoxide), the less substituted alkene (Hofmann product) may be favored because the bulky base is less able to abstract protons from the more hindered β-carbon.

Example : E2 reaction.



Scheme 8. *Example of E2 elimination reaction mechanism.*

4. Addition on the C=C olefinic double bond

Addition reactions at the C=C olefinic double bond typically involve converting the double bond to a single bond while attaching new substituents to the formerly double-bonded carbon atoms. These reactions are crucial in organic synthesis and industrial chemistry, as they allow for the functionalization and structural modification of alkenes, enabling the production of a wide range of valuable compounds such as alcohols, halides, and polymers.

Common types of addition reactions include electrophilic, nucleophilic, and radical additions. Electrophilic addition reactions, often driven by the nucleophilic nature of the electron-rich double bond, involve reagents such as hydrogen halides (HX), water in the presence of acid catalysts (hydration), and halogens (halogenation). These reactions typically follow Markovnikov's or anti-Markovnikov's rules depending on reaction conditions and catalysts.

Nucleophilic additions, though less common in simple alkenes, play an important role in conjugated systems and heteroatom-containing compounds. Radical addition reactions occur under specific conditions, often involving peroxide catalysts, leading to anti-Markovnikov products in reactions like the addition of HBr. Additionally, catalytic hydrogenation is a fundamental process where alkenes are converted to alkanes through the addition of hydrogen (H_2) in the presence of metal catalysts such as palladium, platinum, or nickel. Oxidative additions, including epoxidation and dihydroxylation, further expand the chemical versatility of alkenes by introducing oxygen-containing functional groups, paving the way for the synthesis of complex molecules.

The ability to manipulate C=C double bonds through various addition reactions is a cornerstone of organic chemistry, providing pathways to diverse chemical products essential for pharmaceuticals, materials, and fine chemicals.

The electrophilic reaction is generally encountered in the case of alkenes and alkynes where a π bond opens under the action of an E-Nu reagent in which the π bond is broken heterolytically.

In all cases, the electrophile attaches to the carbon with the highest electron density. The electrophilic reaction obeys Markovnikov's rule: "the electrophile attaches to the least substituted (or most hydrogenated) carbon to have the most stable carbocation.

4.1. Addition of H-X on double bond

The addition of hydrogen halides H-X to C=C double bonds is a classic electrophilic addition reaction in organic chemistry. This reaction typically results in the formation of alkyl halides and is governed by regioselectivity based on Markovnikov's or anti-Markovnikov's rules, depending on the reaction conditions.

4.1.1. Mechanism of H-X addition (Markovnikov addition)

Protonation: the π-electrons of the double bond attack the proton (H^+) from the hydrogen halide (H-X, where X is a halogen such as Cl, Br, or I), generating a carbocation on the most stable carbon.

Carbocation formation: the stability of the carbocation follows the trend tertiary > secondary > primary. The proton typically attaches to the carbon with the greatest number of hydrogen substituents (Markovnikov's rule).

Nucleophilic attack: the halide anion (X^-) attacks the carbocation, resulting in the formation of the corresponding alkyl halide.

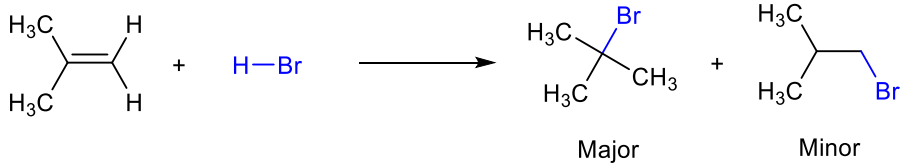
Regioselectivity (Markovnikov vs. Anti-Markovnikov)

Markovnikov's rule: in the absence of peroxides or radical initiators, the hydrogen attaches to the carbon with more hydrogens, and the halogen bonds to the carbon with more alkyl substituents.

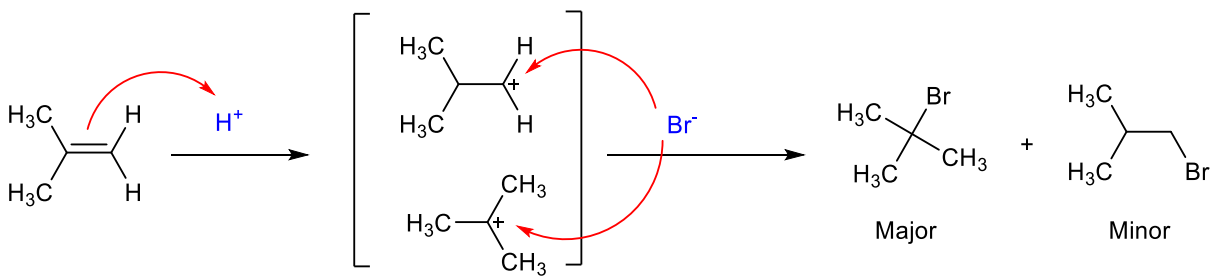
Anti-Markovnikov addition: in the presence of peroxides (ROOR) and under radical conditions, the addition occurs in an anti-Markovnikov fashion, where the hydrogen attaches to the more substituted carbon. This is commonly observed in the addition of HBr but not as readily for HCl or HI [4].

Example reaction:

Reaction:



Mechanism:



Scheme 9. *Mechanism reaction of H-Br addition on double bond.*

4.2. Addition of X_2 on double bond

The addition of diatomic halogens (X_2, where X is typically Cl or Br) to alkenes is a classic electrophilic addition reaction. It leads to the formation of vicinal dihalides (haloalkanes with halogen atoms on adjacent carbon atoms). The reaction is stereospecific, proceeding through an anti-addition mechanism to form trans products when starting with a simple alkene.

General reaction

$$\mathbf{R\text{-}CH{=}CH\text{-}R' + X_2 \rightarrow R\text{-}CHX\text{-}CHX\text{-}R'}$$

4.2.1. Mechanism of X_2 addition

The mechanism involves two key steps: formation of a halonium ion intermediate and nucleophilic attack by a halide.

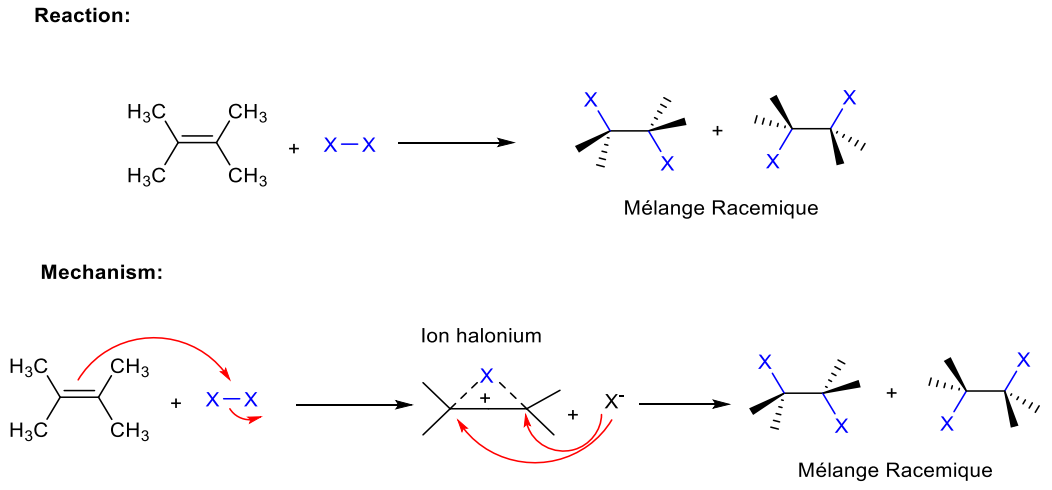
Step 1: electrophilic attack and halonium ion formation.

The π-electrons of the double bond act as a nucleophile, attacking the electrophilic halogen molecule (X_2). This polarization of the halogen molecule (X-X) makes one halogen atom partially positive and susceptible to nucleophilic attack.

A three-membered halonium ion intermediate forms, where the halogen is covalently bonded to both carbons of the original double bond. This stabilizes the positive charge. One halogen atom becomes a halide ion (X^-) after dissociation.

Step 2: nucleophilic attack by the halide ion (x^-)

The halide ion (X^-) attacks one of the carbon atoms in the halonium ion from the opposite side of the halogen bridge (anti-addition). This opens the three-membered ring and forms the vicinal dihalide [5].



Scheme 10. *Mechanism reaction of X_2 addition on double bond.*

Stereochemistry

Anti-addition: the two halogen atoms attach to opposite sides of the former double bond, leading to a stereoselective formation of trans products in cycloalkenes.

In unsymmetrical alkenes, stereochemical outcomes depend on substituent effects, although anti-addition remains dominant.

Reaction in different solvents

In nonpolar solvents (CCl_4): produces pure vicinal dihalides.

In polar solvents (water or alcohols): leads to the formation of halohydrins, where one halogen and one hydroxyl group are added across the double bond.

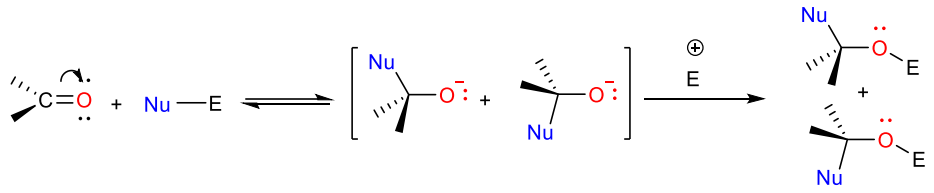
Reaction selectivity: no regioselectivity for simple alkenes but stereoselective due to anti-addition.

Side reactions: in the presence of nucleophilic solvents, halohydrin formation competes with simple dihalide formation.

5. Addition of heteronucleophiles on heterocumulenes and carbonyl compounds, including their subsequent reactions

Heteronucleophiles, such as alcohols, amines, thiols, and water, play a key role in the transformation of heterocumulenes (like isocyanates, carbodiimides, and carbon dioxide) and carbonyl compounds (like aldehydes and ketones) into various functionalized organic products. These addition reactions are fundamental in organic synthesis, biochemistry, and materials science. Like all compounds with multiple bonds, carbonyl compounds can undergo addition reactions. Aldehydes and ketones can undergo nucleophilic additions, thanks to the strong polarization of the double bond which makes the carbon atom very reactive towards nucleophiles. Because of the difference in electronegativity between carbon and oxygen, the C-O bond is highly polarized: carbon has a strongly electrophilic character and the hydrogens fixed on the carbon in a are mobile "acid" character.

In addition, the presence of free doublets on the oxygen atom makes it a privileged site of attack for Lewis acids and electrophiles (**Scheme 11**) [6].



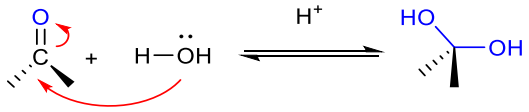
Scheme 11. *General reaction of the addition of heterocumulenes and carbonyl compounds.*

5.1. Reaction with H_2O (Hydration)

The hydration of aldehydes and ketones is a nucleophilic addition reaction in which water adds to the carbonyl group, producing a geminal diol, a compound with two hydroxyl (-OH) groups attached to the same carbon atom. This reaction can occur under either acidic or basic conditions. In acid-catalyzed hydration, the mechanism begins with the protonation of the carbonyl oxygen by an acid increasing the electrophilic character of the carbonyl carbon. Water then acts as a nucleophile and attacks the positively charged carbonyl carbon, forming a protonated intermediate. Finally, deprotonation of these intermediates yields the neutral geminal diol.

In base-catalyzed hydration, the mechanism starts with a nucleophilic attack by a hydroxide ion directly on the carbonyl carbon, generating an alkoxide intermediate. This intermediate is then protonated by water to produce the geminal diol, regenerating the hydroxide ion and completing the catalytic cycle. Aldehydes generally hydrate more readily than ketones due to lower steric hindrance and higher electrophilicity of carbonyl carbon, as aldehydes contain only one electron-

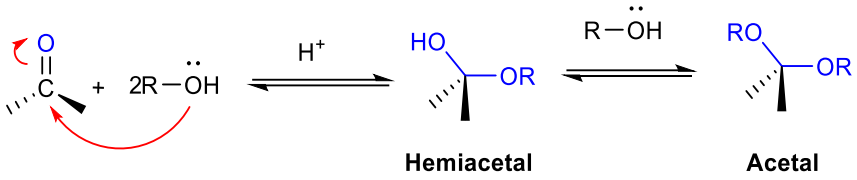
donating alkyl group compared to two in ketones. For highly reactive aldehydes such as formaldehyde, the equilibrium strongly favors the geminal diol form (**Scheme 12**) [7].



Scheme 12. *Hydratation of carbonyle compounds.*

5.2. Reaction with ROH (Acetalization)

The reaction of aldehydes or ketones with alcohols, known as acetalization, is a reversible nucleophilic addition–elimination reaction that occurs in the presence of an acid catalyst, leading to the formation of acetals (or ketals when starting from a ketone). In this process, two molecules of an alcohol react with the carbonyl compound, and water is released as a by-product. The general reaction can be represented as follows (**Scheme 13**):



Scheme 13. *Reaction of acetalization.*

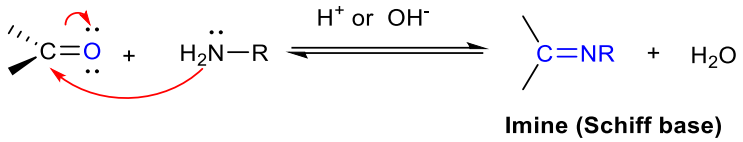
His equilibrium reaction is driven toward acetal formation by using an excess of alcohol or by continuously removing the water formed during the reaction.

The mechanism occurs in two main stages: formation of a hemiacetal, followed by conversion of the hemiacetal to an acetal. In the first stage, the carbonyl oxygen is protonated by the acid catalyst, which increases the electrophilic character of the carbonyl carbon. Then, a molecule of alcohol attacks the carbonyl carbon, producing a protonated intermediate that, upon deprotonation, forms a hemiacetal containing both a hydroxyl (-OH) group and an alkoxy (-OR) group on the same carbon atom.

In the second stage, the hydroxyl group of the hemiacetal is protonated to form a good leaving group, which departs as water, generating a carbocation intermediate. A second molecule of alcohol then attacks this carbocation, forming a protonated acetal. Finally, deprotonation of these intermediate yields the stable acetal [8].

5.3. Imine synthesis

Imine synthesis, also known as **Schiff base** formation, is an important organic reaction in which a carbonyl compound (aldehyde or ketone) reacts with a primary amine (RNH_2) in the presence of a mild acid or basic catalyst to form an imine, a compound characterized by a carbon-nitrogen double bond (C=NR). This reaction plays a vital role in organic chemistry, biochemistry, and industrial synthesis and is reversible, with water produced as a by-product. The general reaction can be represented as follows (**Scheme 14**):



Scheme 14. *General reaction of imine synthesis.*

The equilibrium of this reaction can be shifted toward imine formation by removing water using molecular sieves or azeotropic distillation. Aldehydes usually react more readily than ketones because they are less sterically hindered and have a more electrophilic carbonyl carbon.

The mechanism of imine formation in acidic medium involves four main steps:

Nucleophilic addition, the reaction begins with the protonation of the carbonyl oxygen by the mild acid catalyst, increasing the electrophilic character of the carbonyl carbon. The primary amine then uses its lone pair of electrons to attack the carbonyl carbon, leading to the formation of a tetrahedral intermediate known as a carbinolamine (amino alcohol), which contains both a (-OH) and an amino group (-NHR") attached to the same carbon atom.

Proton transfer, internal proton transfers occur within the carbinolamine to activate the hydroxyl group for removal. The hydroxyl group is protonated, turning it into a good leaving group (water), while the nitrogen may be deprotonated, stabilizing the intermediate and preparing it for the next step.

Elimination of water, the protonated hydroxyl group departs as a molecule of water, producing a positively charged intermediate called an iminium ion ($C=NH^+$-R). Since water is a by-product, its continuous removal drives the reaction toward imine formation.

Deprotonation, the iminium ion undergoes deprotonation, losing a proton from the nitrogen atom to form the neutral imine, regenerating the acid catalyst and completing the reaction cycle.

Several factors affect imine synthesis

Aldehydes are generally more reactive than ketones due to lower steric hindrance and higher electrophilicity of their carbonyl carbon. The amine must be primary, as secondary amines cannot

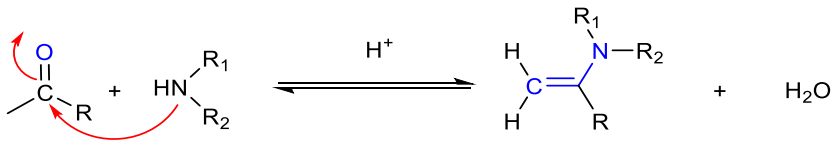
form imines; instead, they produce enamines. A mild acid such as acetic acid is required to activate the carbonyl group without fully protonating the amine. Strong acids should be avoided because they convert the amine into its ammonium salt, which cannot act as a nucleophile. Finally, since the reaction is reversible, removing water is essential to shift the equilibrium toward the imine product.

Imines have significant biological and synthetic importance. In biological systems, they are key intermediates in enzymatic processes, such as amino acid metabolism. For instance, the coenzyme pyridoxal phosphate (PLP) forms imines with amino acids during transamination reactions. In synthetic organic chemistry, imines are crucial intermediates in the preparation of heterocycles, pharmaceuticals, and fine chemicals. They can also undergo reductive amination, where the imine is reduced to form primary, secondary, or tertiary amines. Additionally, imines derived from aldehydes and amines, known as Schiff bases, are widely used as ligands in coordination chemistry, forming stable complexes with metals used in catalysis and material science [9].

5.4. Enamine synthesis

Enamine synthesis is an important organic reaction in which a secondary amine (R_2NH) reacts with a carbonyl compound (aldehyde or ketone) in the presence of a mild acid catalyst, leading to the formation of an enamine. Enamines are compounds characterized by a carbon-carbon double bond (C=C) adjacent to a nitrogen atom (C=C–NR_2). This reaction is conceptually similar to imine formation, but because secondary amines lack a proton on nitrogen needed for the formation of a carbon-nitrogen double bond (C=NR), the reaction proceeds differently, ultimately forming a C=C bond instead. Like imine synthesis, water is released as a by-product, and the reaction is reversible.

The general reaction can be represented as (**Scheme 15**):



Scheme 15. *General reaction of enamine synthesis.*

This equilibrium can be shifted toward enamine formation by removing water during the reaction, often using molecular sieves or azeotropic distillation. Enamines are valuable intermediates in organic synthesis, particularly in reactions such as the Stork enamine alkylation and acylation.

The mechanism occurs through a series of steps involving nucleophilic attack, proton transfers, dehydration, and deprotonation:

Activation of the carbonyl group: the reaction begins with protonation of the carbonyl oxygen by the acid catalyst. This step increases the electrophilicity of the carbonyl carbon, making it more susceptible to nucleophilic attack by the amine.

Nucleophilic attack by the secondary amine (formation of a carbinolamine): the lone pair of electrons on the nitrogen atom of the secondary amine attacks the carbonyl carbon, forming a tetrahedral intermediate called a carbinolamine (amino alcohol), which contains both a hydroxyl (-OH) group and an amino ($-NHR_2$) group on the same carbon.

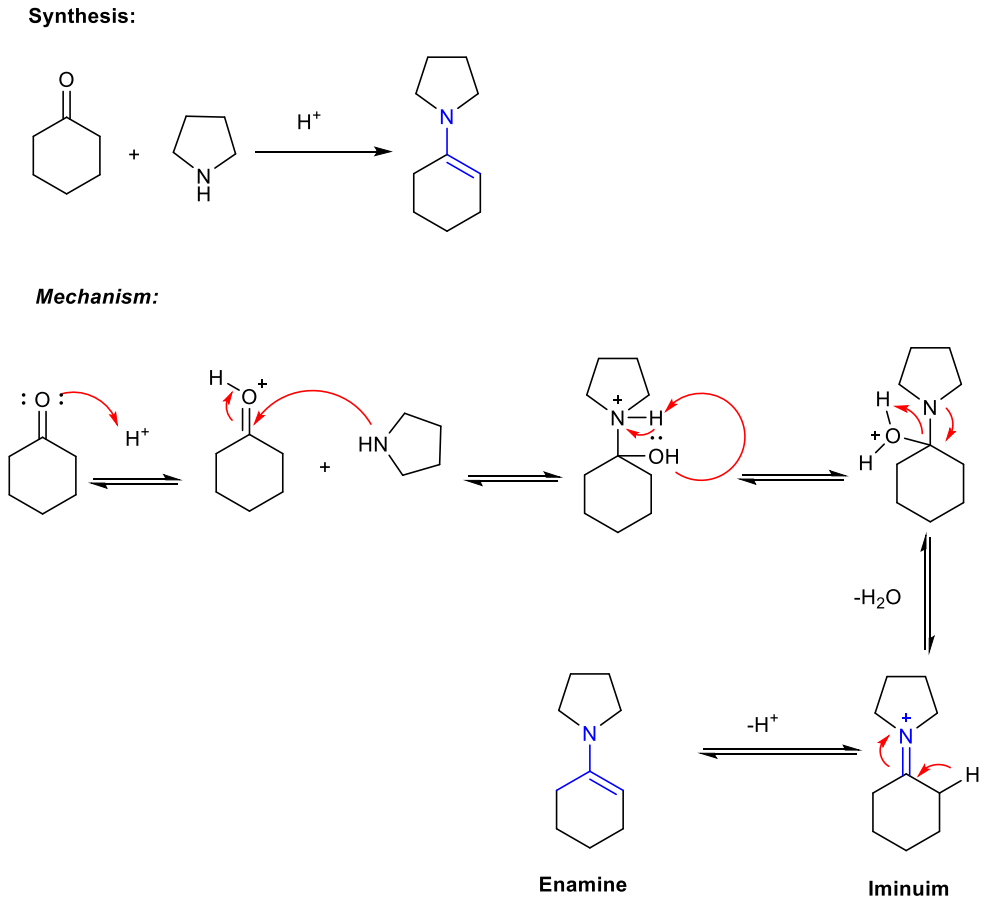
Proton transfer to prepare for water elimination: a proton transfer occurs to convert the hydroxyl group into a better leaving group. The hydroxyl group is protonated, forming a water molecule, while the nitrogen group loses its extra proton to stabilize the intermediate.

Elimination of water and formation of an iminium ion: the protonated hydroxyl group leaves as water, producing an iminium ion (a positively charged species with a $C=N^+$ bond).

At this point, the mechanism resembles imine formation. However, because the nitrogen belongs to a secondary amine and does not have a hydrogen to lose, it cannot form a neutral C=NR double bond. Instead, the reaction proceeds through deprotonation at the α-carbon.

Deprotonation at the α-carbon and enamine formation: a base (often the conjugate base of the acid catalyst or another amine molecule) removes a proton from the α-carbon adjacent to the iminium group. This deprotonation generates a carbon–carbon double bond (C=C) while simultaneously neutralizing the positive charge on nitrogen, forming the stable enamine product [10].

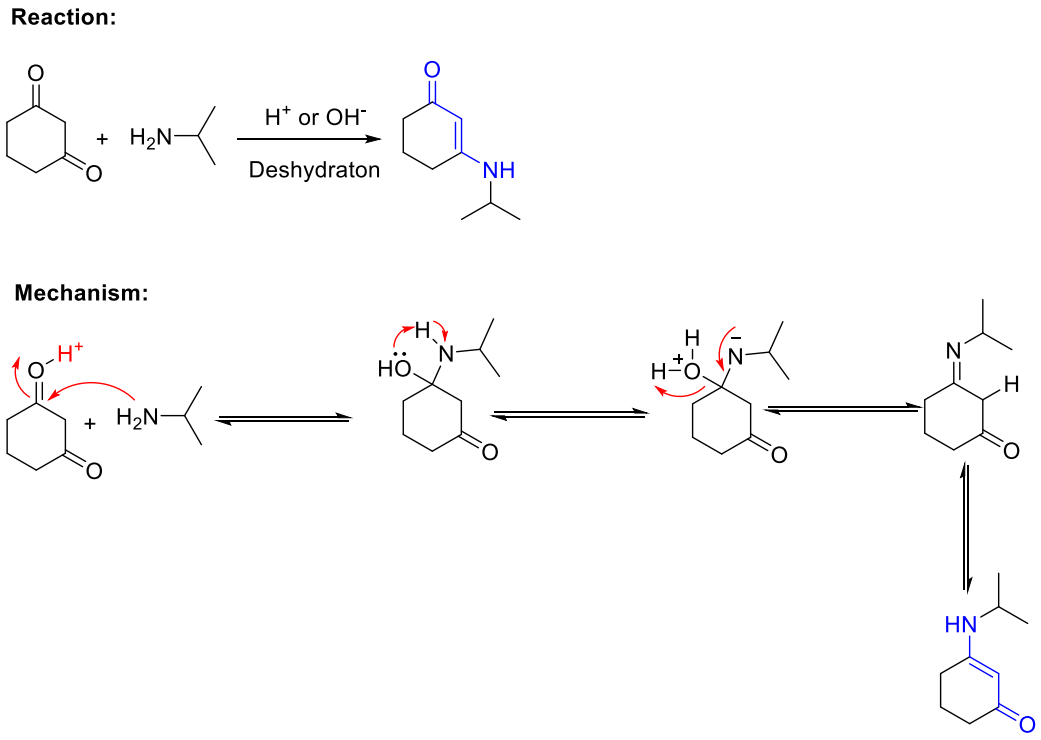
Example:



Scheme 16. *Example of the synthesis of enaminone compound.*

5.5. Enaminone synthesis

Enaminones are versatile organic compounds containing both an enamine group (C=C–NR_2) and a carbonyl group (C=O) within the same molecule. They can be viewed as hybrid structures between enamines and enones. Enaminones are important intermediates in organic synthesis because they are ambident nucleophiles, meaning they can react through either the nitrogen atom or the α-carbon of the enamine moiety. They are also present in biologically active molecules and are widely used for the synthesis of heterocyclic compounds, pharmaceuticals, and natural product analogues. Enaminones are typically synthesized by the reaction of a amine with a β-dicarbonyl compound (such as a β-ketoester or β-diketone) or with an α,β-unsaturated carbonyl compound (like an enone). The process resembles enamine formation, but the starting carbonyl compound has an additional electron-withdrawing group that stabilizes the final product (**Scheme 17**).



Scheme 17*. Example of reaction and the mechanism of enaminone synthesis.*

This reaction is reversible, and the removal of water drives the equilibrium toward enaminone formation. A mild acid catalyst (e.g., acetic acid, *p*-toluenesulfonic acid) is commonly used to activate the carbonyl group without fully protonating the amine. The mechanism is similar to enamine formation but occurs specifically on a β-dicarbonyl system or a conjugated carbonyl compound. The key steps involve nucleophilic attack by the amine, dehydration, and deprotonation to generate the enaminone.

Protonation of the carbonyl group: the reaction begins with protonation of the more electrophilic carbonyl oxygen by the acid catalyst. This increases the electrophilicity of the carbonyl carbon, making it more susceptible to nucleophilic attack.

Nucleophilic attack by the secondary amine: the nitrogen atom of the secondary amine attacks the activated carbonyl carbon. This forms a tetrahedral intermediate (carbinolamine), in which the nitrogen and hydroxyl group are both attached to the same carbon atom.

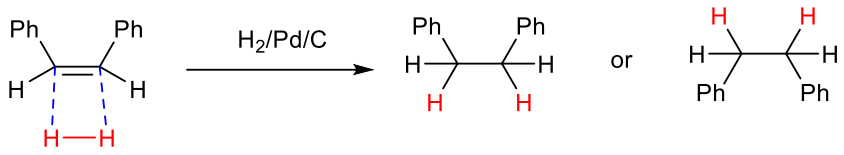
Proton transfer: the hydroxyl group is protonated, making it a good leaving group as water.

The nitrogen simultaneously loses a proton to stabilize itself. The intermediate now has a protonated hydroxyl group ready for elimination: elimination of water formation of an iminium ion: the protonated hydroxyl group leaves as water, generating an iminium ion. This step is analogous to the dehydration stage in enamine formation.

Deprotonation at the α-carbon: instead of deprotonating the nitrogen, a base (often the conjugate base of the acid catalyst or another amine molecule) removes a proton from the α-carbon adjacent to the iminium group. This generates a C=C double bond, neutralizes the nitrogen, and forms the stable enaminone product [11].

5.6. Catalytic H_2 addition

Catalytic hydrogenation (catalytic H_2 addition) is a fundamental reaction in organic chemistry in which molecular hydrogen (H_2) is added across unsaturated bonds, such as carbon–carbon double or triple bonds, or carbon–heteroatom double bonds (C=O, C=N), in the presence of a metal catalyst. This process converts unsaturated compounds into saturated ones and is widely applied in the food industry (e.g., hydrogenation of vegetable oils to make margarine), pharmaceuticals, fuels, and bulk chemicals. Common heterogeneous catalysts include palladium on carbon (Pd/C), platinum (PtO_2, Adams' catalyst), Raney nickel, rhodium, and ruthenium, while homogeneous catalysts such as Wilkinson's catalyst are used for selective hydrogenations. The reaction proceeds via the Horiuti-Polanyi mechanism, which involves four key steps: (1) adsorption of H_2 onto the metal surface, where the H–H bond dissociates into two metal-bound hydrogen atoms, (2) adsorption of the unsaturated substrate, with its π-bond interacting with the metal, (3) syn addition of hydrogen atoms stepwise to the substrate's double bond, forming a saturated intermediate, and (4) desorption of the final saturated product, regenerating the catalyst surface. This mechanism explains the stereospecific syn addition of hydrogen, meaning both hydrogens add to the same face of the molecule. For example, an alkene is reduced to an alkane, an alkyne can be reduced to a cis-alkene using a Lindlar catalyst or fully to an alkane with unpoisoned catalysts, and aldehydes or ketones can be reduced to alcohols. The reaction is influenced by factors such as the type of catalyst, hydrogen pressure, temperature, solvent, and substrate structure. Catalytic hydrogenation is highly atom-efficient, producing no by-products other than the desired saturated compound, making it an environmentally friendly and essential reaction in both industrial and laboratory organic synthesis (**Scheme 18**) [12].



Scheme 18. *Catalytic H_2 addition.*

6. Addition of hydrides and organometallic compounds to carbonyl groups

6.1. Hydride addition

Hydride addition is a fundamental reaction in organic chemistry where a hydride ion (H^-), acting as a nucleophile, is added to an electrophilic carbonyl group such as an aldehyde, ketone, ester, carboxylic acid, or amide, resulting in the reduction of the carbonyl compound to an alcohol, alkane or amine. This reaction is widely used for the preparation of primary, secondary, or tertiary alcohols depending on the type of carbonyl compound reduced. The most common hydride donors used in laboratory synthesis are lithium aluminum hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$), both of which contain polar metal-hydrogen bonds that facilitate hydride transfer.

In both reagents, the polarity of the metal hydrogen bond determines the reducing strength. Aluminum is less electronegative than boron, so the Al–H bond in $LiAlH_4$ is significantly more polarized than the B–H bond in $NaBH_4$, which makes $LiAlH_4$ a much stronger reducing agent. As a result, $LiAlH_4$ can reduce a broad range of compounds, including esters, carboxylic acids, amides, nitriles, and even some epoxides, whereas $NaBH_4$ is milder and generally limited to reducing aldehydes and ketones under standard conditions.

The general reaction mechanism for hydride reduction involves three main steps. First, the hydride ion attacks the electrophilic carbonyl carbon, breaking the π-bond of the C=O and forming a tetrahedral alkoxide intermediate. This step occurs because the carbonyl carbon carries a partial positive charge due to the polarization of the C=O bond, making it highly susceptible to nucleophilic attack. Second, the reaction intermediate remains bound to the metal ion (e.g., Li^+ or Na^+) until protonation. Finally, in a separate work-up step, usually involving water or a dilute acid, the alkoxide is protonated, yielding the corresponding alcohol product. The choice between $LiAlH_4$ and $NaBH_4$ depends on the substrate and reaction conditions. $LiAlH_4$ must be used under strictly anhydrous conditions because it reacts violently with water, releasing hydrogen gas. Typical solvents include dry ethers such as diethyl ether or tetrahydrofuran (THF). On the other hand, $NaBH_4$ is stable in protic solvents like water or alcohol, making it safer and easier to handle, though its reducing power is limited.

6.1.1. Reduction of ester

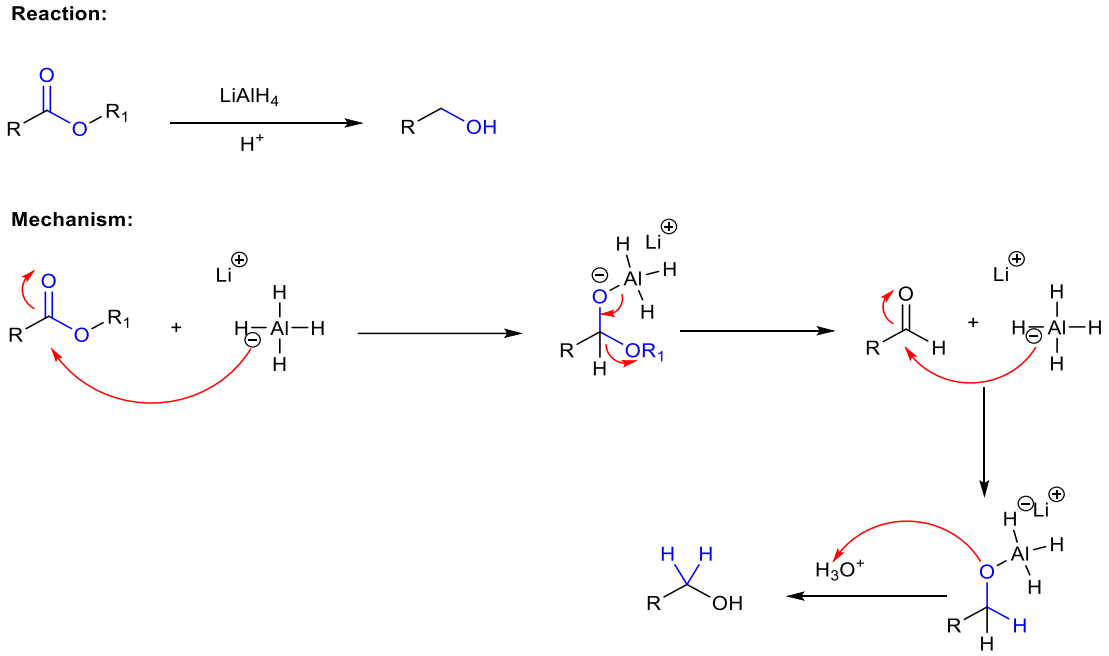
The reduction of esters using $LiAlH_4$ is a key reaction in organic synthesis for converting esters into primary alcohols. This reaction proceeds through the transfer of hydride ions (H^-) from $LiAlH_4$ to the electrophilic carbonyl carbon of the ester, ultimately breaking the ester's C–O bond and replacing it with hydrogen atoms. It is widely used in the synthesis of alcohols from

carboxylic acid derivatives and plays an important role in the preparation of pharmaceuticals, fragrances, and other fine chemicals.

$LiAlH_4$ is a powerful and highly reactive reducing agent because of the strong polarity of its Al–H bonds. Since aluminum is significantly less electronegative than hydrogen, the hydride behaves as a strong nucleophile. Due to its high reactivity, $LiAlH_4$ must be used under strictly anhydrous conditions, typically in dry ether solvents such as diethyl ether or tetrahydrofuran (THF). Any contact with water leads to rapid hydrolysis of $LiAlH_4$, releasing hydrogen gas violently. After the reaction, a careful aqueous work-up is performed to protonate the intermediate alkoxide species and release the final alcohol products.

The mechanism of ester reduction with $LiAlH_4$ proceeds through two consecutive hydride additions, followed by cleavage of the C–O bond:

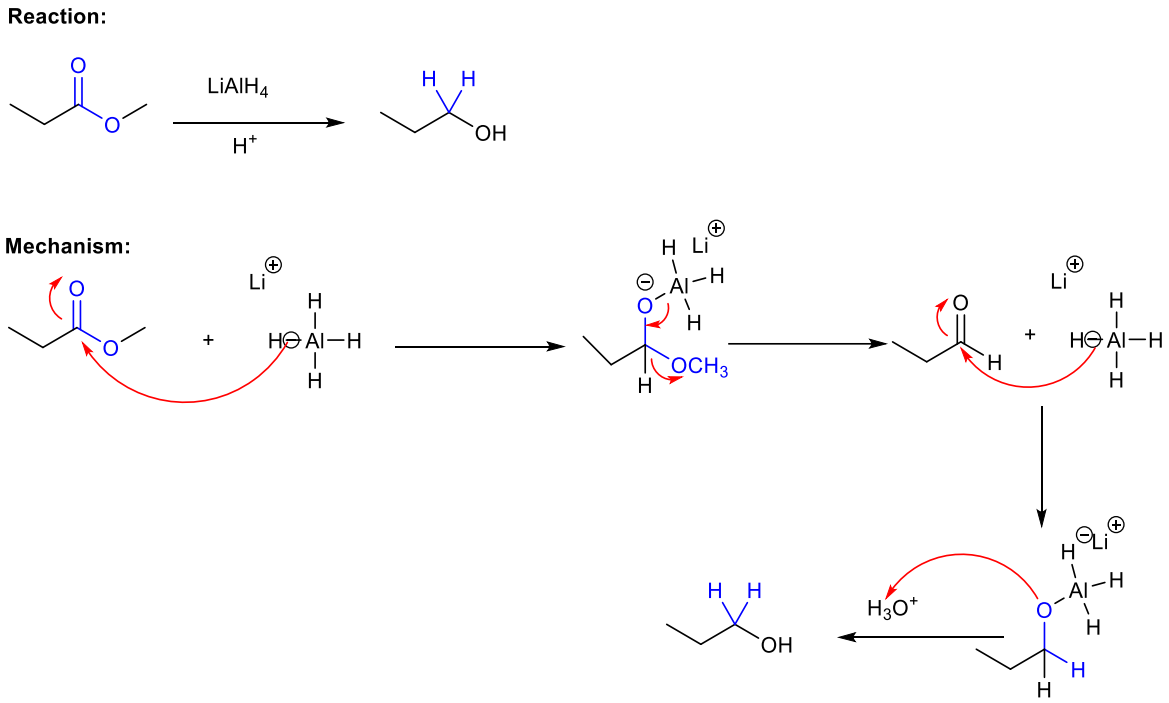
The first step begins with a hydride ion from $LiAlH_4$ attacking the electrophilic carbonyl carbon of the ester. This breaks the π-bond of the C=O and forms a tetrahedral alkoxide intermediate. The negatively charged alkoxide oxygen collapses back to reform the C=O double bond. This expels the alkoxy group (OR') as a leaving group, producing an aldehyde (RCHO) and an alkoxide ion. The newly formed aldehyde is still reactive and undergoes a second hydride attack by $LiAlH_4$. This converts the aldehyde into a primary alkoxide. In the final step, the reaction mixture is carefully treated with water or dilute acid. The alkoxide ions are protonated, yielding the corresponding alcohols (**Scheme 19**) [13].



Scheme 19. *Reduction of ester group using $LiAlH_4$.*

Example:

This reaction occurs through two successive hydride transfers from $LiAlH_4$ and proceeds via a tetrahedral intermediate. After the reduction is complete, a careful work-up with methanol (MeOH) is carried out to quench any remaining $LiAlH_4$ and to protonate the alkoxide intermediates, releasing the final alcohol products in a controlled and safe manner (**Scheme 20**).



***Scheme 20**. Reduction of methyl propanoate using $LiAlH_4$ and MeOH.*

6.1.2. Reduction of amides

The reduction of amides using $LiAlH_4$ is an important reaction that converts amides into amines. This transformation is highly valuable because amides are common functional groups in peptides, pharmaceuticals, and natural products, and their conversion into amines expands their synthetic utility. $LiAlH_4$ is reducing agent due to its strongly polarized Al–H bonds, which allow it to deliver hydride ions to the electrophilic carbonyl carbon of the amide. The reaction proceeds through a multi-step mechanism involving two hydride transfers, cleavage of the C=O bond, and final protonation to yield the corresponding amine.

This reaction is highly selective for the reduction of the C=O bond without breaking the C–N bond, which is why the nitrogen remains attached to the carbon skeleton. It must be carried out under strictly anhydrous conditions, typically using dry ether solvents such as diethyl ether or tetrahydrofuran (THF), because $LiAlH_4$ reacts violently with water, releasing hydrogen gas. After

completion, the reaction mixture is carefully quenched with water or dilute acid to neutralize excess hydride and to protonate the intermediate species, yielding the free amine.

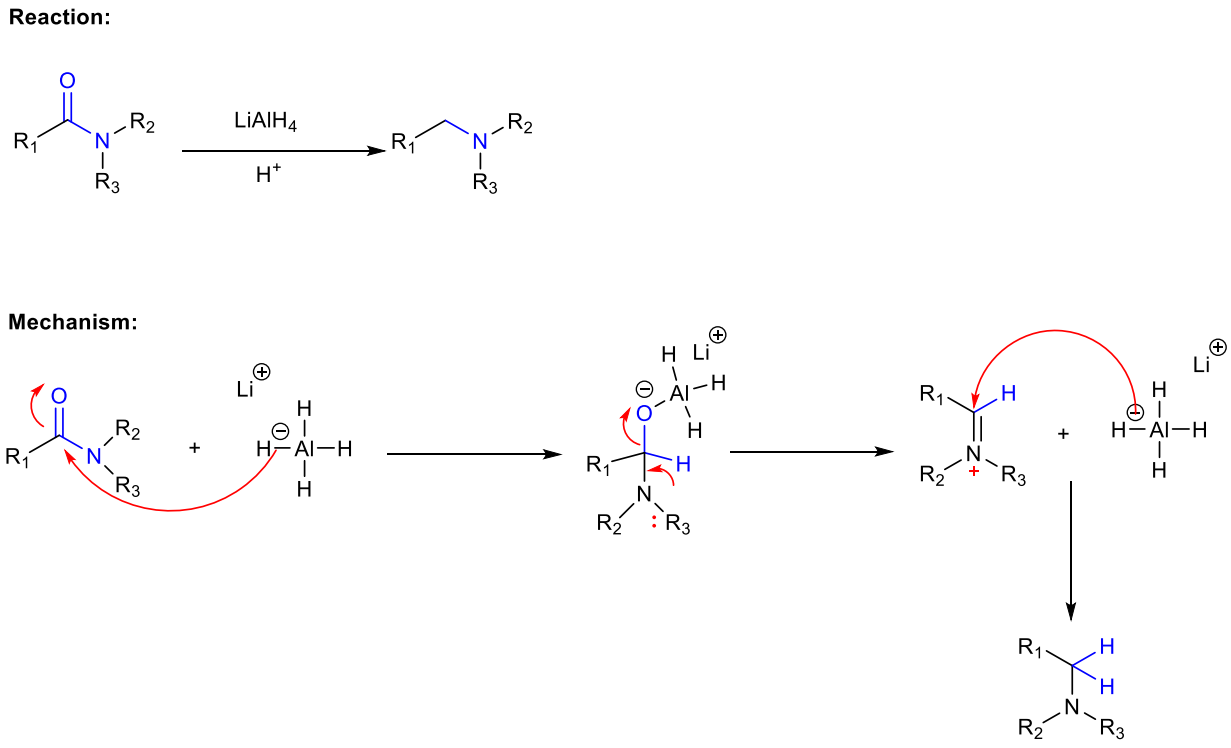
The reduction mechanism of an amide with $LiAlH_4$ involves several distinct steps:

A hydride ion from $LiAlH_4$ attacks the electrophilic carbonyl carbon of the amide, breaking the C=O π-bond. This generates a tetrahedral intermediate, where the oxygen now bears a negative charge and is coordinated to the aluminum center.

The second step is the formation of imino-aluminum complex, the negatively charged oxygen atom collapses back reforming a C=O double bond and displacing the nitrogen's lone pair onto aluminum, producing an iminium-like intermediate ($C=NH^+$). This step essentially transforms the original amide into a positively charged iminium species bound to aluminum.

Reduction of the iminium group: another hydride ion from $LiAlH_4$ attacks the electrophilic carbon of the iminium species, breaking the C=N bond. This step yields a neutral amine anion bound to aluminum.

In the final step, the reaction mixture is carefully treated with water or dilute acid. This protonates the amine anion, releasing the free amine as the final product. Thus, the C=O group of the amide is completely replaced by two hydrogen atoms, converting it into a methylene group while keeping the nitrogen intact (**Scheme 21**) [14].



Scheme 21. *Reduction of amide group using $LiAlH_4$.*

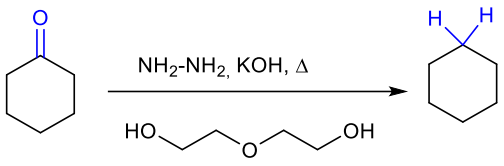
6.1.3. Reduction of Wolff-Kishner

The Wolff Kishner reduction is a classical organic reaction that reduces a carbonyl group (C=O) in aldehydes and ketones to a methylene group (CH_2), ultimately converting the carbonyl compound into a saturated hydrocarbon. This reaction is especially useful when catalytic hydrogenation cannot be performed due to the presence of functional groups that may be sensitive to metal catalysts. The reaction occurs in two main stages: (1) formation of a hydrazone intermediate and (2) its subsequent base-induced decomposition with the evolution of nitrogen gas (N_2).

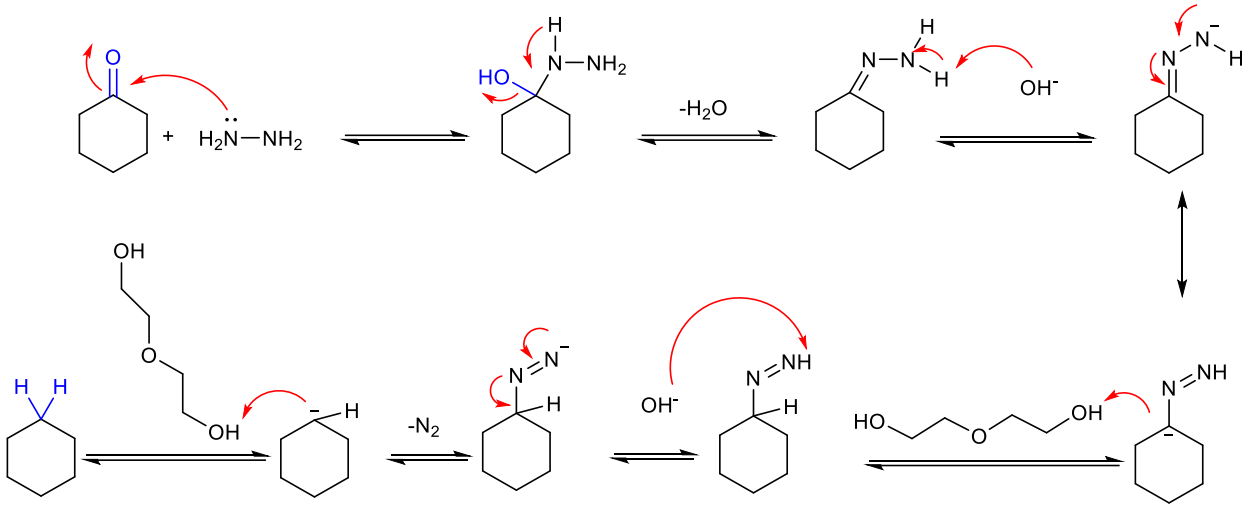
It was independently discovered by Ludwig Wolff and Nikolai Kishner in the early 20th century and remains widely used in modern organic synthesis, especially in the preparation of fully reduced hydrocarbon frameworks from carbonyl precursors.

The mechanism of the Wolff–Kishner reduction begins with the condensation of a carbonyl compound (aldehyde or ketone) with hydrazine (NH_2NH_2) to form a hydrazone intermediate through nucleophilic attack on the carbonyl carbon followed by dehydration. In the second step, under strongly basic conditions (e.g., NaOH or KOH) and high heat, the base deprotonates the terminal $–NH_2$ group of the hydrazone, generating a negatively charged nitrogen species. This anion undergoes electron rearrangement, pushing electrons through the C=N bond, leading to the cleavage of the N–N bond and the release of nitrogen gas (N_2), which is very stable and acts as a driving force for the reaction. The loss of nitrogen forms a carbanion at the former carbonyl position, which is then protonated by water or another proton donor to yield the fully reduced hydrocarbon (alkane). This entire process efficiently converts the carbonyl group into a methylene group without the need for metal catalysts, making it especially useful for compounds sensitive to acidic or catalytic hydrogenation conditions (**Scheme 22**) [15].

Reaction:



Mechanism:



Scheme 22. *Reduction of Wolff-Kishner.*

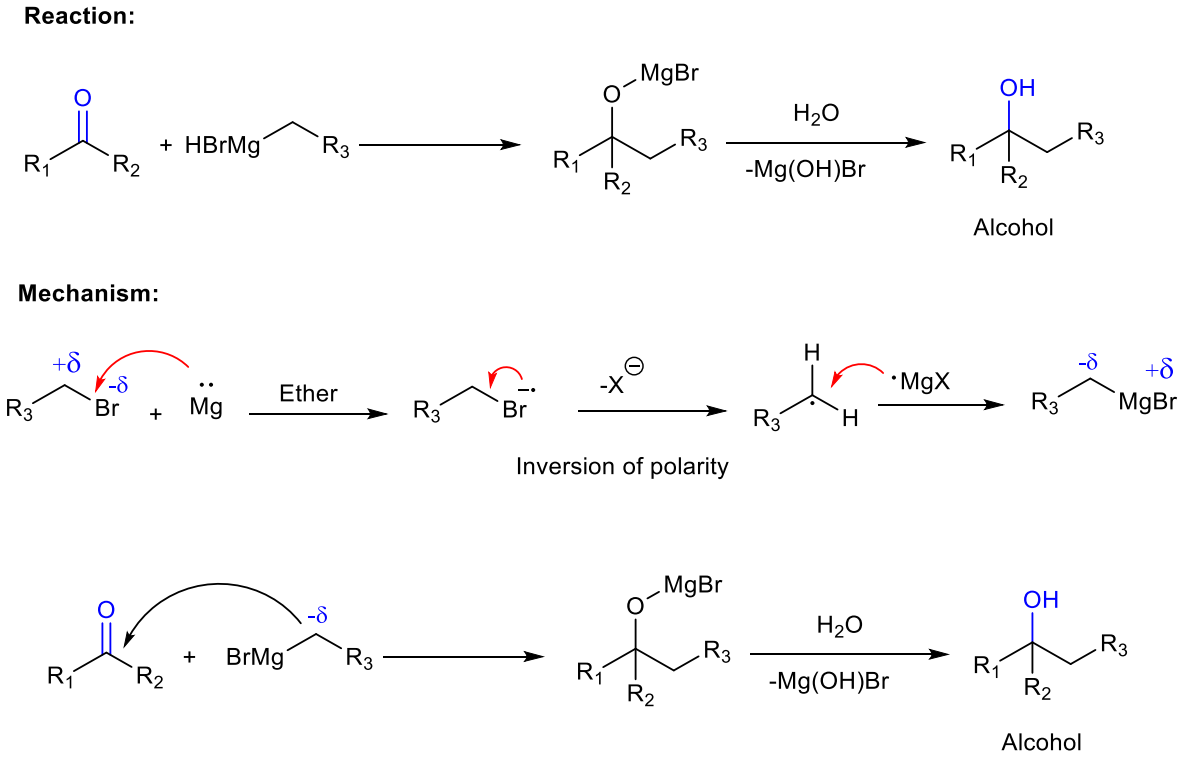
6.2. Addition of an organomagnesium compound

The Grignard reaction is one of the most versatile and widely used methods in organic chemistry for forming carbon–carbon bonds, making it a fundamental tool in synthetic organic synthesis. It involves the reaction of a Grignard reagent (R–MgX), where R represents an alkyl, aryl, or allyl group and X is a halide (typically bromide, chloride, or iodide), with a carbonyl-containing compound, such as an aldehyde or ketone. The reaction proceeds through a highly nucleophilic mechanism because the carbon atom bonded to magnesium carries a significant partial negative charge due to the polar C–Mg bond. This makes the Grignard reagent behave like a carbanion, enabling it to attack the electrophilic carbonyl carbon, which is partially positive because of the electronegativity difference between carbon and oxygen.

The mechanism begins when the nucleophilic R^- group approaches the carbonyl carbon, causing the π electrons of the C=O bond to shift onto the oxygen atom. This step generates a tetrahedral alkoxide intermediate, which is highly reactive and unstable. During the subsequent acidic work-up, usually with dilute acid or water, the alkoxide is protonated to yield the corresponding alcohol. The nature of the final alcohol depends on the starting carbonyl compound: reaction with formaldehyde gives a primary alcohol, reaction with other aldehydes yields secondary alcohols,

and reaction with ketones produces tertiary alcohols. For instance, reacting methylmagnesium bromide (CH_3MgBr) with acetone (CH_3COCH_3) results in the formation of 2-propanol after protonation.

The Grignard reaction requires strictly anhydrous conditions because the Grignard reagent is highly reactive toward water. Even trace amounts of moisture can destroy it by simple acid–base reaction, forming the corresponding hydrocarbon (R–H) and magnesium hydroxide (Mg(OH)X), thus preventing the desired nucleophilic addition. For this reason, reactions are carried out in dry, aprotic solvents such as diethyl ether or tetrahydrofuran (THF), which can also coordinate with the magnesium atom and help stabilize the reagent. Additionally, the glassware must be completely dry and free of water or alcohol residues (**Scheme 23**) [16].



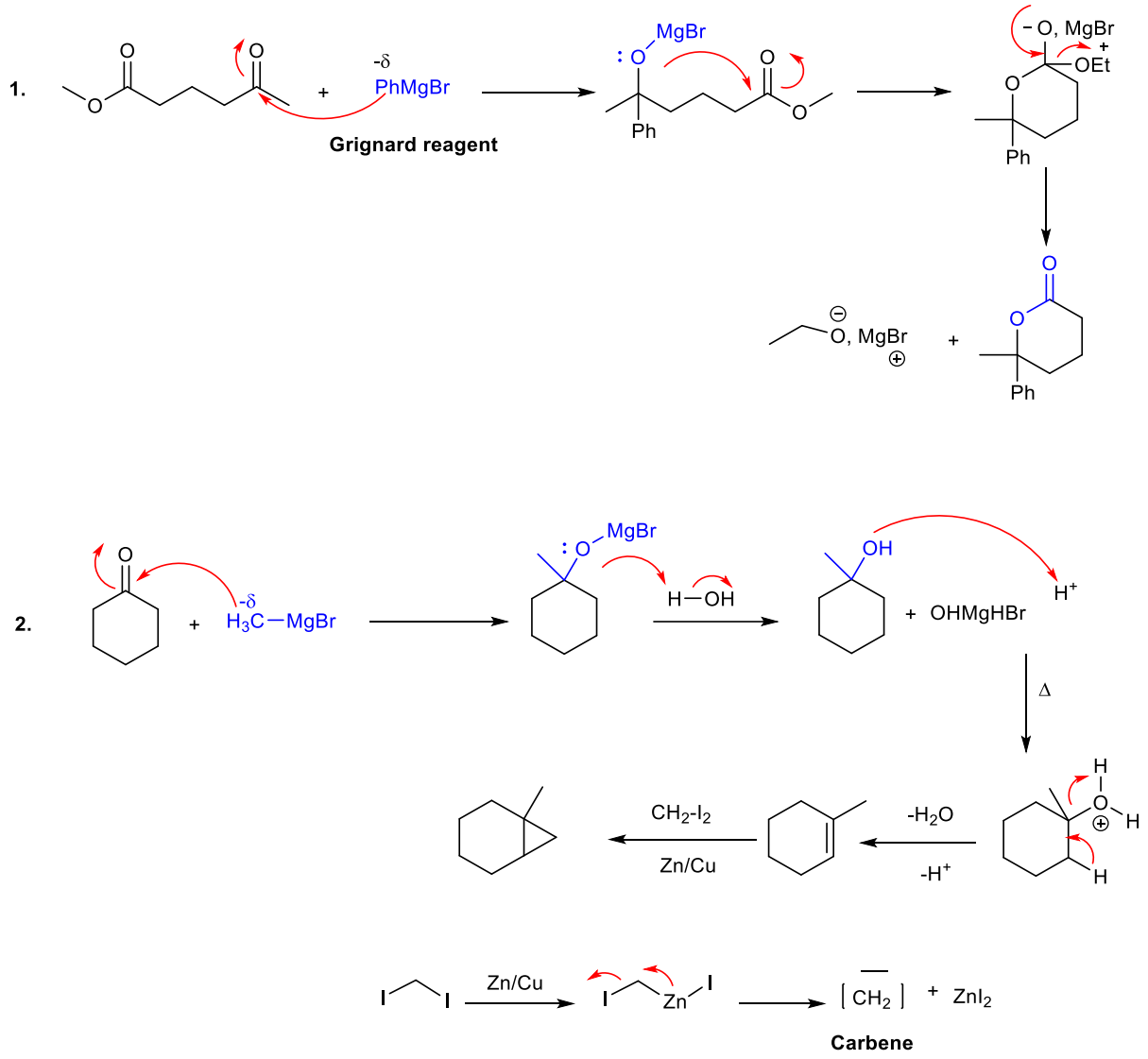
Scheme 23. *Addition of an organomagnesium to a carbonyl compound.*

This reaction is especially valuable in organic synthesis because it not only enables the formation of alcohols with various substitution patterns but also allows the introduction of diverse carbon chains, thus expanding molecular complexity. By carefully selecting the type of Grignard reagent and carbonyl compound, chemists can design a wide range of products, making it essential for the synthesis of bioactive compounds.

However, Grignard reactions are sensitive to functional groups within the molecule. Since the Grignard reagent is a strong base as well as a nucleophile, it will react with acidic protons such

as those in alcohols, amines, or carboxylic acids before it can attack the carbonyl carbon. Therefore, protecting groups are often employed to temporarily mask reactive sites during synthesis.

Example:



Scheme 24. *Examples of compounds synthesis via an organomagnesium reaction.*

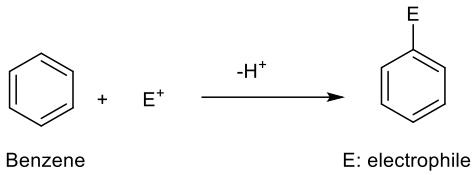
7. Electrophilic aromatic substitution (EAS)

EAS is one of the most important classes of reactions in organic chemistry because it enables the direct functionalization of aromatic compounds while retaining their highly stable aromatic system. Aromatic compounds, such as benzene and its derivatives, possess a delocalized π-electron cloud distributed over a cyclic conjugated structure, which gives them exceptional stability known as aromatic stabilization energy. Due to this stability, aromatic rings generally do not undergo simple addition reactions like alkenes because such reactions would disrupt the aromaticity, leading to a significant loss of stability. Instead, they react through substitution processes where a hydrogen atom or another substituent on the ring is replaced by an electrophile (E^+) without destroying the aromatic system.

In an EAS reaction, the aromatic ring acts as a nucleophile because its π-electrons are rich in electron density and can attack a strongly electron-deficient species, the electrophile. The reaction occurs in three main stages: generation of the electrophile, formation of a sigma complex, and deprotonation to restore aromaticity. Initially, the electrophile is generated by activation of a reagent, often in the presence of a catalyst such as a Lewis acid (e.g., $AlCl_3$, $FeCl_3$) or a strong acid (e.g., H_2SO_4). This step is crucial because only a sufficiently strong electrophile can overcome the stability of the aromatic ring and initiate the reaction.

Once formed, the electrophile reacts with the aromatic ring. The π-electrons attack the electrophile, forming a carbocationic intermediate known as the sigma complex or arenium ion. This intermediate is no longer aromatic because one of the ring carbons now has four substituents, disrupting the continuous delocalization of electrons. However, resonance helps stabilize the sigma complex by delocalizing the positive charge over three carbon atoms of the ring. Despite this partial stabilization, the sigma complex is still high in energy and unstable, so it rapidly undergoes the next step to regain aromaticity.

The final step is deprotonation, where a base often the conjugate base of the catalyst abstracts a proton (H^+) from the carbon that initially bonded to the electrophile. The electrons from the broken C–H bond move back into the ring, restoring the fully conjugated π-system and regenerating the aromatic stability. This step also regenerates the catalyst, making the process catalytic and efficient. The overall result is substitution: the electrophile takes the place of the original hydrogen atom, yielding a new substituted aromatic compound (**Scheme 25**) [17].

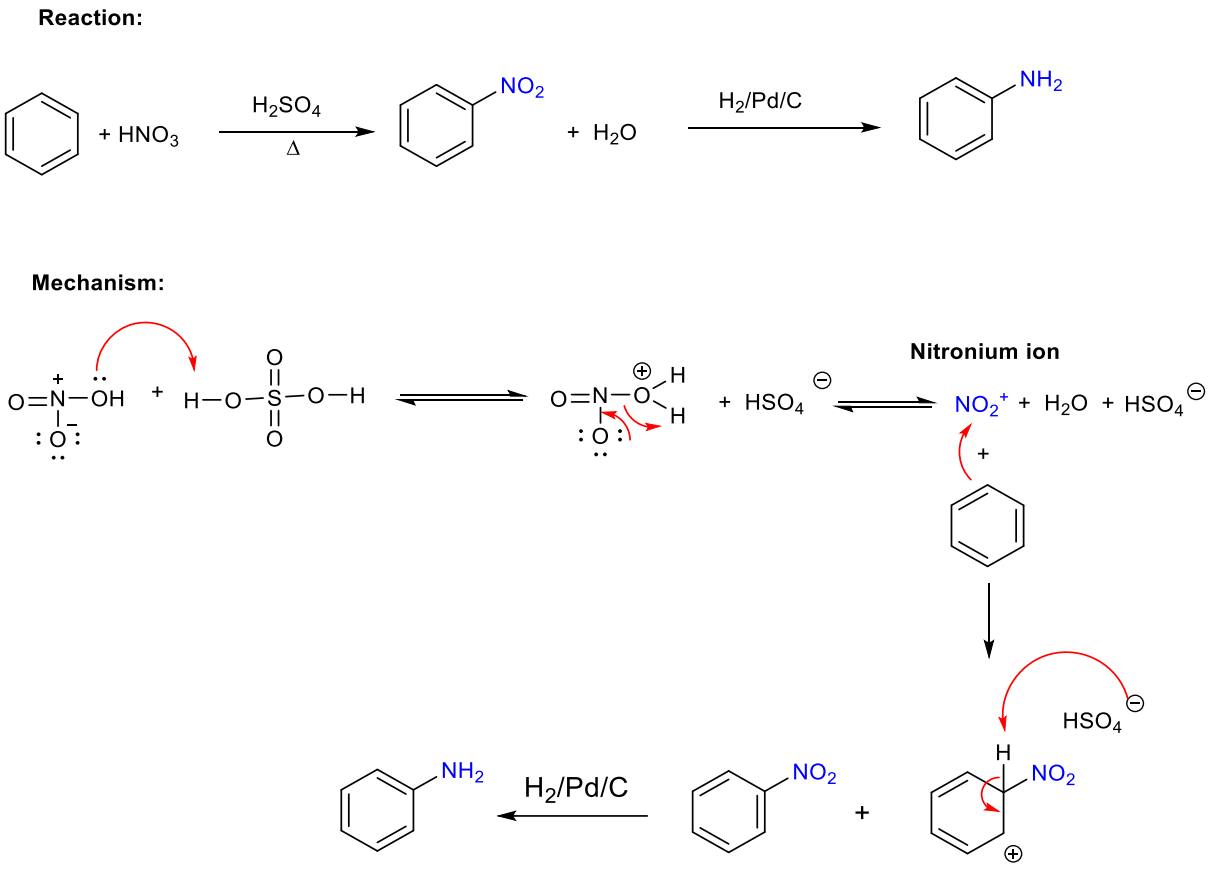


Scheme 25. General reaction electrophilic aromatic substitution.

EAS is incredibly versatile and widely used in both laboratory synthesis and industrial processes. By carefully selecting reagents and reaction conditions, a variety of electrophiles can be introduced into the aromatic ring, enabling the synthesis of compounds with diverse functional groups. Common types of EAS include **nitration**, **sulfonation**, **halogenation**, **Friedel–Crafts alkylation**, and **Friedel–Crafts acylation**.

7.1. Nitration

Aromatic nitration is a reaction in which a hydrogen atom on the aromatic ring is replaced by a nitro group (NO_2) to form nitrobenzene. The reaction begins with the generation of the nitronium ion (NO_2^+), the strong electrophile responsible for the substitution. This occurs when concentrated nitric acid (HNO_3) reacts with concentrated sulfuric acid (H_2SO_4), where sulfuric acid acts as a protonating agent and drives the equilibrium to produce NO_2^+ along with water and bisulfate ion (HSO_4^-) as by-products. Once the nitronium ion is generated, the aromatic ring acts as a nucleophile, and its π-electrons attack the electrophilic NO_2^+ to form a high-energy, non-aromatic intermediate known as the sigma complex or arenium ion. In this intermediate, the positive charge is delocalized across three carbons through resonance, providing partial stabilization. However, because aromaticity is lost, the system quickly proceeds to the next step, deprotonation, where a base such as HSO_4^- abstracts the proton (H^+) from the carbon bonded to the nitro group. The removal of this proton restores the aromaticity of the ring, yielding nitrobenzene ($C_6H_5NO_2$) as the final product and regenerating the catalyst (**Scheme 26**).

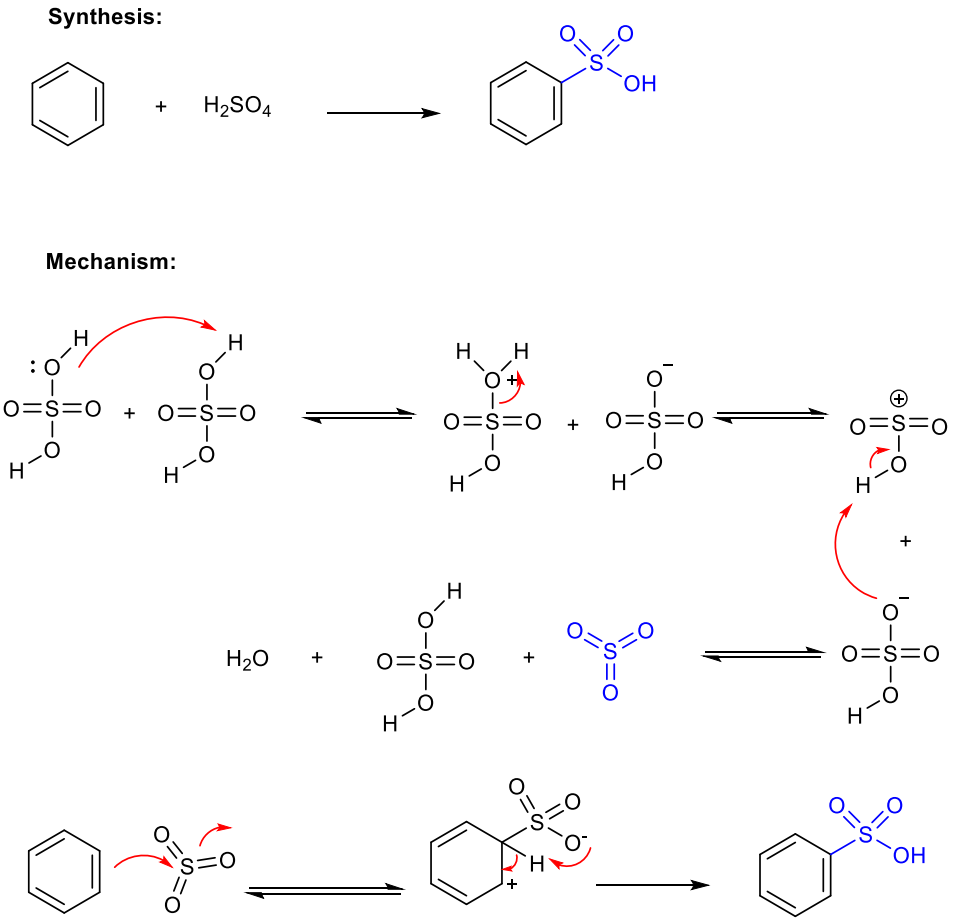


Scheme 26. Aromatic substitution nitration.

7.2. Sulfonation

Aromatic sulfonation is an important reaction in which a hydrogen atom on an aromatic ring is replaced by a sulfonic acid group (SO_3H), producing compounds such as benzenesulfonic acid. This reaction occurs under strongly acidic conditions, typically using concentrated sulfuric acid (H_2SO_4) or oleum, a solution of sulfur trioxide (SO_3) in sulfuric acid, and is widely used in the synthesis of detergents, dyes, pharmaceuticals, and as a reversible protecting strategy for aromatic compounds. The reaction begins with the generation of the electrophile, where sulfur trioxide, already highly electron-deficient due to the presence of three strongly electronegative oxygen atoms, is protonated by sulfuric acid to form SO_3H^+, a very strong electrophile, according to the equilibrium: $SO_3 + H_2SO_4 \rightleftharpoons SO_3H^+ + HSO_4^-$. Once the electrophile is generated, the π-electrons of the aromatic ring attack SO_3H^+, leading to the formation of a high-energy, non-aromatic intermediate called the sigma complex or arenium ion. In this intermediate, the positive charge is delocalized across three carbon atoms of the ring through resonance, partially stabilizing it, but aromaticity is temporarily lost. Because this intermediate is unstable, the reaction quickly proceeds to the deprotonation step, where a base, usually the bisulfate ion (HSO_4^-) formed in the first step, removes a proton (H^+) from the carbon attached to the sulfonic

group. The electrons from the broken C–H bond return to the ring, restoring aromaticity and yielding the final product, benzenesulfonic acid ($C_6H_5SO_3H$), while regenerating sulfuric acid, making the reaction catalytic. A unique characteristic of aromatic sulfonation is its reversibility: at low to moderate temperatures (40–50 °C) and in concentrated sulfuric acid or oleum, the forward reaction is favored, resulting in sulfonation, while heating the sulfonated product with dilute aqueous acid or steam reverses the reaction, removing the sulfonic group and regenerating the original aromatic compound. This reversibility is highly useful in multi-step organic synthesis, where the $–SO_3H$ group can serve as a temporary protecting group to control the position of subsequent substitutions (**Scheme 27**).



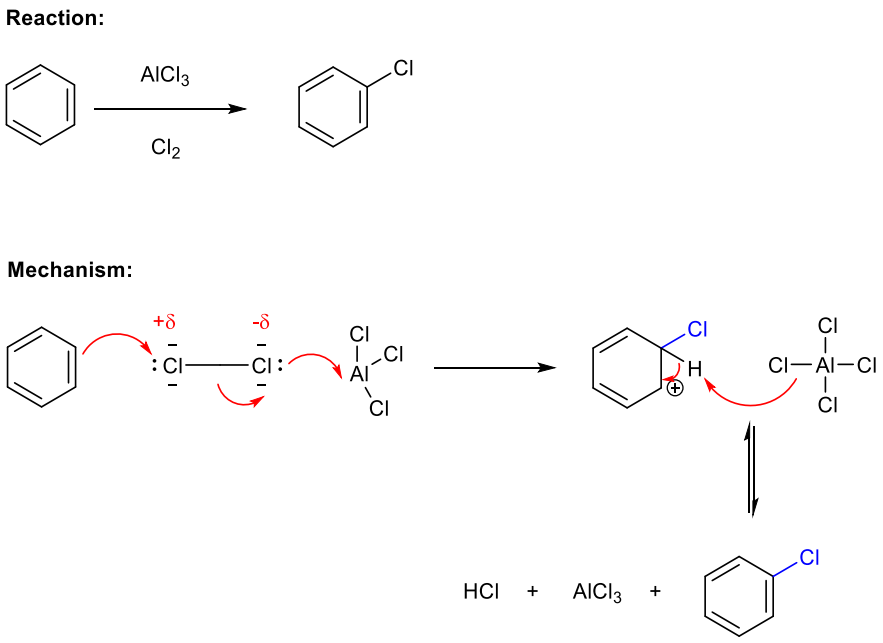
Scheme 27. *Aromatic substitute sulfonation.*

7.3. Halogenation

Aromatic halogenation is a reaction in which a hydrogen atom on an aromatic ring is replaced by a halogen atom such as chlorine (Cl), bromine (Br), or iodine (I), resulting in compounds like chlorobenzene or bromobenzene. This reaction is widely used in chemistry for the synthesis of halogenated aromatic compounds, which serve as important intermediates in the production of

important compounds. Aromatic rings are highly stable due to their delocalized π-electron system, and because halogen molecules (Cl_2 or Br_2) are not strongly electrophilic on their own, a Lewis acid catalyst such as $FeCl_3$, $FeBr_3$, or $AlCl_3$ is required to activate the halogen. The reaction begins with the generation of the electrophile, where the Lewis acid interacts with the halogen molecule to polarize and form a highly reactive halonium ion (Cl^+ or Br^+).

Once the electrophile is generated, the π-electrons of the aromatic ring act as a nucleophile and attack the halonium ion, forming a non-aromatic, high-energy intermediate known as the sigma complex or arenium ion. In this intermediate, the positive charge is delocalized over three carbon atoms through resonance, which provides partial stabilization but still represents a loss of aromaticity. To restore the aromatic stability, a deprotonation step occurs, where the ion (or another base present) removes the proton (H^+) from the carbon that bonded to the halogen. The electrons from the broken C–H bond return to the ring, restoring aromaticity and regenerating the Lewis acid catalyst. The final product is a halogenated aromatic compound such as chlorobenzene or bromobenzene (**Scheme 28**).



Scheme 28. *Aromatic halogenation.*

7.4. Friedel-Crafts alkylation

Friedel–Crafts alkylation is a fundamental EAS reaction in which an alkyl group (R) is introduced into an aromatic ring by replacing a hydrogen atom. Discovered by Charles Friedel and James Crafts in 1877 [18], this reaction is widely applied in organic synthesis to produce alkyl-substituted aromatic compounds such as toluene, ethylbenzene, and cumene. It plays a crucial

role in the synthesis of pharmaceuticals, dyes, fragrances, and polymers because it directly forms carbon–carbon bonds between an aromatic ring and an alkyl group. The general reaction involves an aromatic compound reacting with an alkyl halide (R–Cl, R–Br, or R–I) in the presence of a Lewis acid catalyst like aluminum chloride ($AlCl_3$), ferric chloride ($FeCl_3$), or boron trifluoride (BF_3).

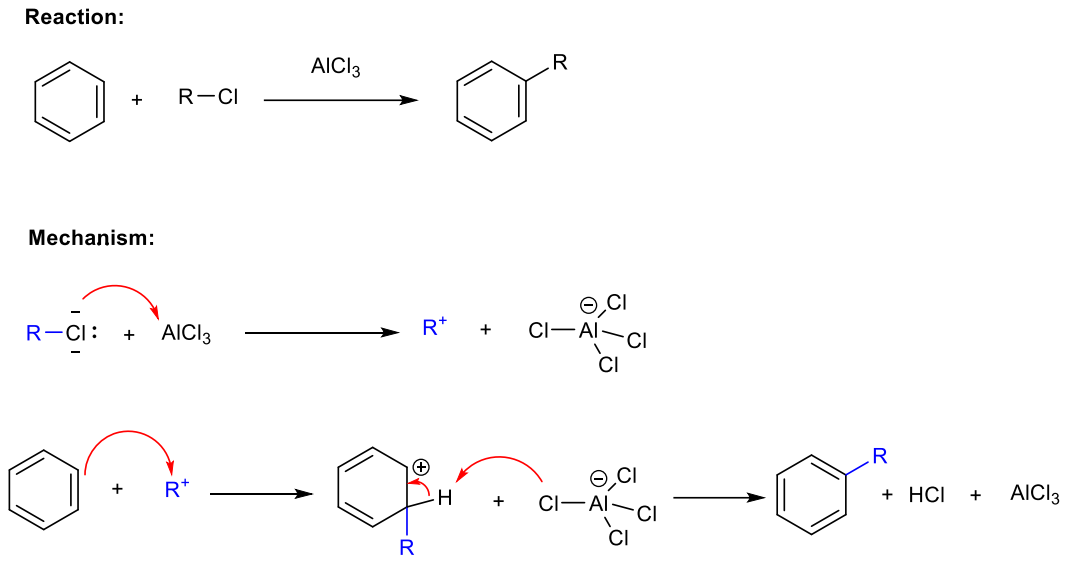
The mechanism proceeds in three main steps.

Step 1: generation of the electrophile (carbocation formation), the Lewis acid activates the alkyl halide by accepting a lone pair of electrons from the halogen, polarizing the carbon–halogen bond and facilitating the departure of the halide as a leaving group. This generates a carbocation (R^+), which acts as the electrophile. Primary carbocations are unstable and may undergo rearrangements to form more stable secondary or tertiary carbocations, often leading to rearranged products.

Step 2: electrophilic attack and formation of the complex; the π-electrons of the aromatic ring act as a nucleophile and attack the carbocation, forming a high-energy, non-aromatic intermediate known as arenium ion.

Step 3: deprotonation and restoration of aromaticity, the ion or another base removes the proton (H^+) from the carbon bonded to the alkyl group. The electrons from the broken C–H bond move back into the ring, restoring aromaticity and regenerating the Lewis acid catalyst. The final products are the alkylated aromatic compound and hydrogen halide, such as HCl.

While Friedel–Crafts alkylation is widely used, it has certain limitations. The newly introduced alkyl group is electron-donating and activates the ring, making it more reactive toward further electrophilic substitution, which can result in polyalkylation unless excess benzene or controlled conditions are used. Additionally, carbocation rearrangements may occur, especially when primary alkyl halides are used, leading to unexpected products. Aromatic compounds bearing strong electron-withdrawing groups like $–NO_2$ or $–CF_3$ are typically unreactive because they deactivate the ring and prevent sigma complex formation. Moreover, the reaction must be carried out under anhydrous conditions because $AlCl_3$ and other Lewis acids are moisture-sensitive (**Scheme 29**).



Scheme 29. *Friedel-Crafts alkylation.*

7.5. Friedel-Crafts acylation

Friedel–Crafts acylation is reaction in which an acyl group (RCO) is introduced into an aromatic ring by replacing a hydrogen atom. Unlike Friedel–Crafts alkylation, the acylation process does not lead to carbocation rearrangements or polyacylation, making it highly selective and controlled. This is due to the stability of the electrophile formed during the reaction the acylium ion (RCO^+) which is resonance-stabilized and, therefore, less reactive than typical carbocations. The general reaction involves an aromatic compound reacting with an acyl halide (RCOCl) or acid anhydride (RCO–O–COR') in the presence of a Lewis acid catalyst such as aluminum chloride ($AlCl_3$). The overall transformation produces an aromatic ketone and a hydrogen halide by-product, typically HCl.

The mechanism of Friedel–Crafts acylation proceeds in three main steps.

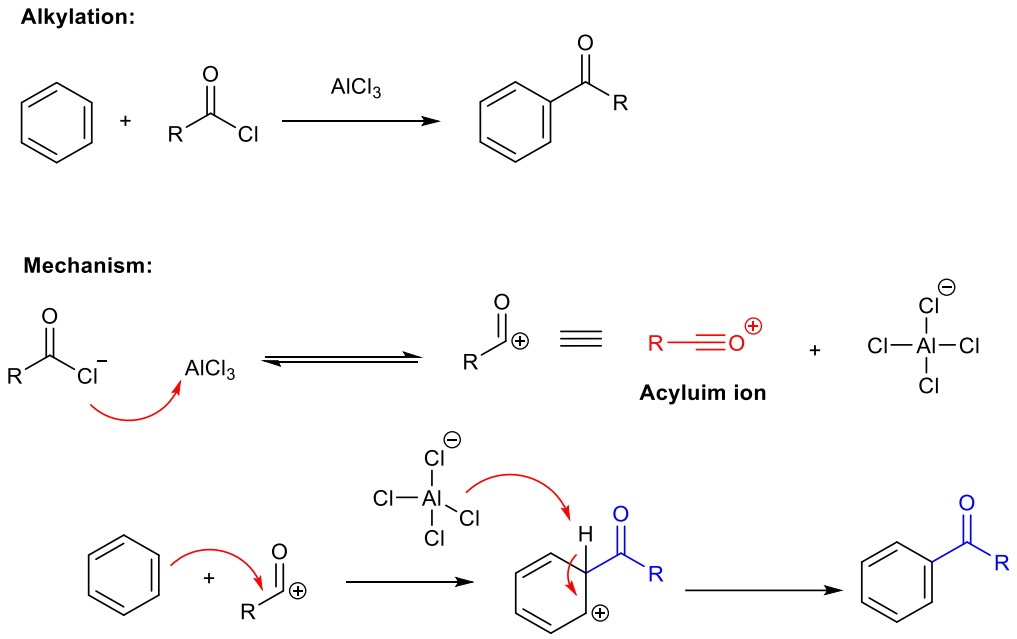
Step 1: generation of the acylium ion. The Lewis acid catalyst coordinates with the halogen atom of the acyl halide, polarizing the carbonyl group and facilitating the departure of the halide ion (Cl^-). This produces the acylium ion (RCO^+), which is stabilized through resonance between two structures: $R–C{\equiv}O^+ \leftrightarrow R–C^+{=}O$. This resonance stabilization prevents rearrangements and makes the acylium ion a strong yet stable electrophile.

Step 2: electrophilic attack by the aromatic ring. The π-electrons of the aromatic ring act as a nucleophile and attack the carbon of the acylium ion.

Step 3: deprotonation and restoration of aromaticity. Finally, the $AlCl_4^-$ ion or another base removes a proton (H^+) from the carbon that bonded to the acyl group. The electrons from the C–

H bond return to the ring, restoring aromaticity and regenerating the $AlCl_3$ catalyst. The final product is an aryl ketone, along with HCl as a by-product.

Friedel–Crafts acylation offers several advantages. The resonance-stabilized acylium ion eliminates the possibility of carbocation rearrangements, providing clean and predictable products. Additionally, the introduced carbonyl group (–COR) is strongly electron-withdrawing and deactivates the aromatic ring, preventing further substitution and thus avoiding polyacylation. However, the reaction must be performed under anhydrous conditions, as $AlCl_3$ reacts violently with water and can be deactivated by moisture (**Scheme 30**).



Scheme 30. *Friedel-Crafts acylation.*

8. Nucleophilic reactions on carboxylic acid

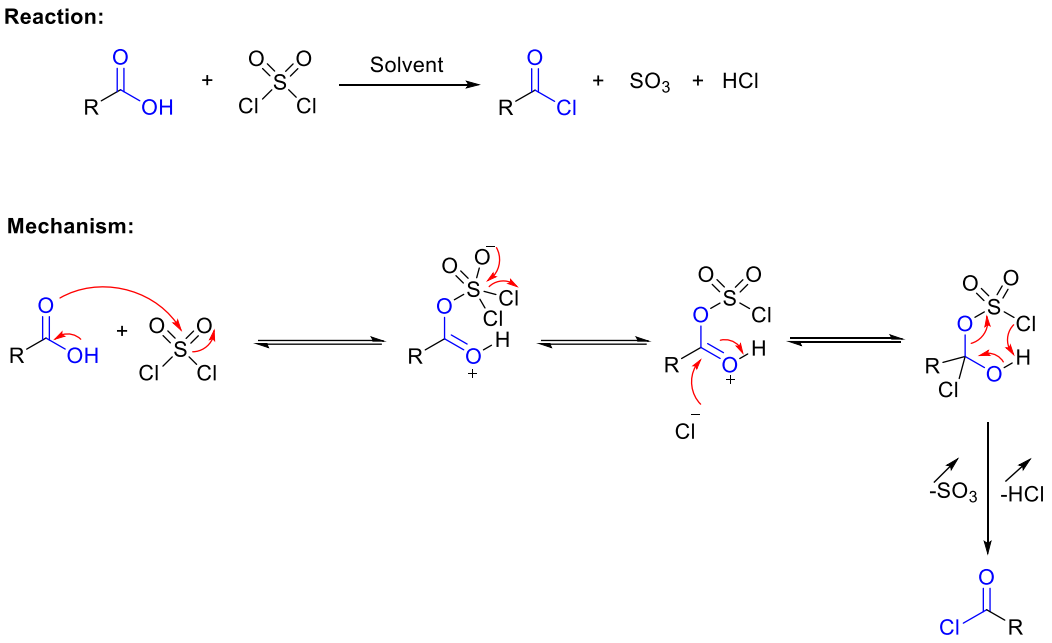
Nucleophilic reactions on carboxylic acids are fundamental processes in organic chemistry in which a nucleophile attacks the electrophilic carbon of the carbonyl group (C=O) in a carboxylic acid or its derivatives. Carboxylic acids, with the general formula R–COOH, are highly reactive due to the presence of both a polar carbonyl group and a hydroxyl group (OH). The carbonyl carbon carries a partial positive charge because of the electronegative oxygen, making it susceptible to nucleophilic attack. However, the direct nucleophilic substitution of carboxylic acids is often difficult because the hydroxyl group (OH) is a poor leaving group. For this reason, many nucleophilic reactions of carboxylic acids first involve converting the OH group into a better leaving group, such as by forming an acid chloride, anhydride, or ester.

Carboxylic acids and their derivatives typically undergo nucleophilic acyl substitution, a two-step mechanism involving addition of the nucleophile to the carbonyl carbon, followed by elimination of a leaving group. This is different from aldehydes and ketones, which usually undergo nucleophilic addition without elimination. The general pathway starts when the nucleophile attacks the electrophilic carbonyl carbon, forming a tetrahedral intermediate. In the second step, these intermediate collapses, expelling the leaving group and regenerating the carbonyl bond, resulting in the substituted product [19].

8.1. Formation of acid chlorides (acyl chlorides)

Formation of acid chlorides is an essential transformation where a carboxylic acid (RCOOH) is converted into an acid chloride (RCOCl), a highly reactive derivative of carboxylic acids. Acid chlorides are key intermediates in the synthesis of various functional groups, including esters, amides, and anhydrides, through nucleophilic acyl substitution reactions. This conversion is widely applied in laboratory, because acid chlorides serve as excellent acylating agents due to the strong leaving ability of the chloride ion (Cl^-). The hydroxyl group in carboxylic acids is a poor leaving group, making direct nucleophilic substitution difficult. To overcome this, specific reagents are used to activate the carboxylic acid, replacing the OH group with a chlorine atom (**Scheme 31**). Common reagents for this conversion include sulfuryl chloride (SO_2Cl_2), phosphorus trichloride (PCl_3), and phosphorus pentachloride (PCl_5), with thionyl chloride being the most widely preferred because its by-products are gases (SO_2 and HCl), which easily escape, driving the reaction to completion and simplifying product purification [20].

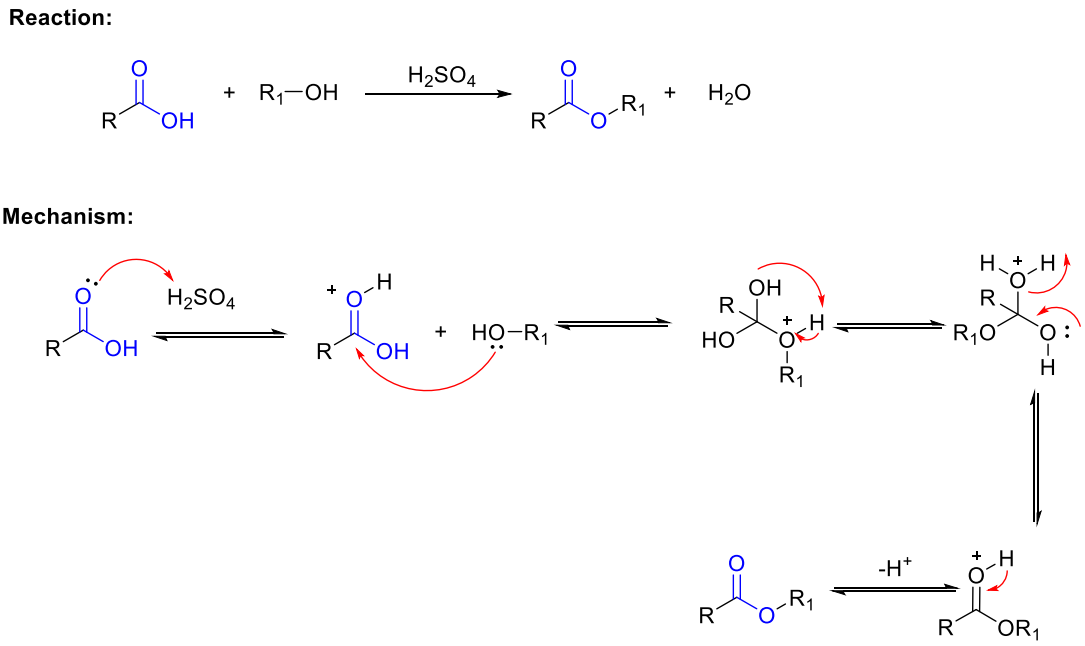
The general reaction using sulfuryl chloride is:



Scheme 32. *Formation of acid chloride via the condensation of carboxylic acids with sulfuryl chloride.*

8.2. Fischer esterification

Fischer esterification is a fundamental organic reaction in which a carboxylic acid (RCOOH) reacts with an alcohol (R_1OH) in the presence of an acid catalyst, typically concentrated sulfuric acid (H_2SO_4), to form an ester ($RCOOR_1$) and water (H_2O). This reaction is a reversible condensation reaction, meaning that two molecules combine with the elimination of a small molecule, in this case, water. Fischer esterification is highly significant in both laboratory and industrial chemistry because esters are important compounds used in perfumes, flavorings, solvents, pharmaceuticals, and as intermediates in polymer production, such as polyesters. The overall reaction can be summarized as (**Scheme 33**):



Scheme 33. *Fischer esterification of carboxylic acid.*

This process is equilibrium-controlled, and to drive it toward ester formation, one of the products, usually water, is continuously removed, or an excess of alcohol is used. Sulfuric acid plays a dual role as both a catalyst and a dehydrating agent, promoting the reaction and shifting the equilibrium toward ester formation.

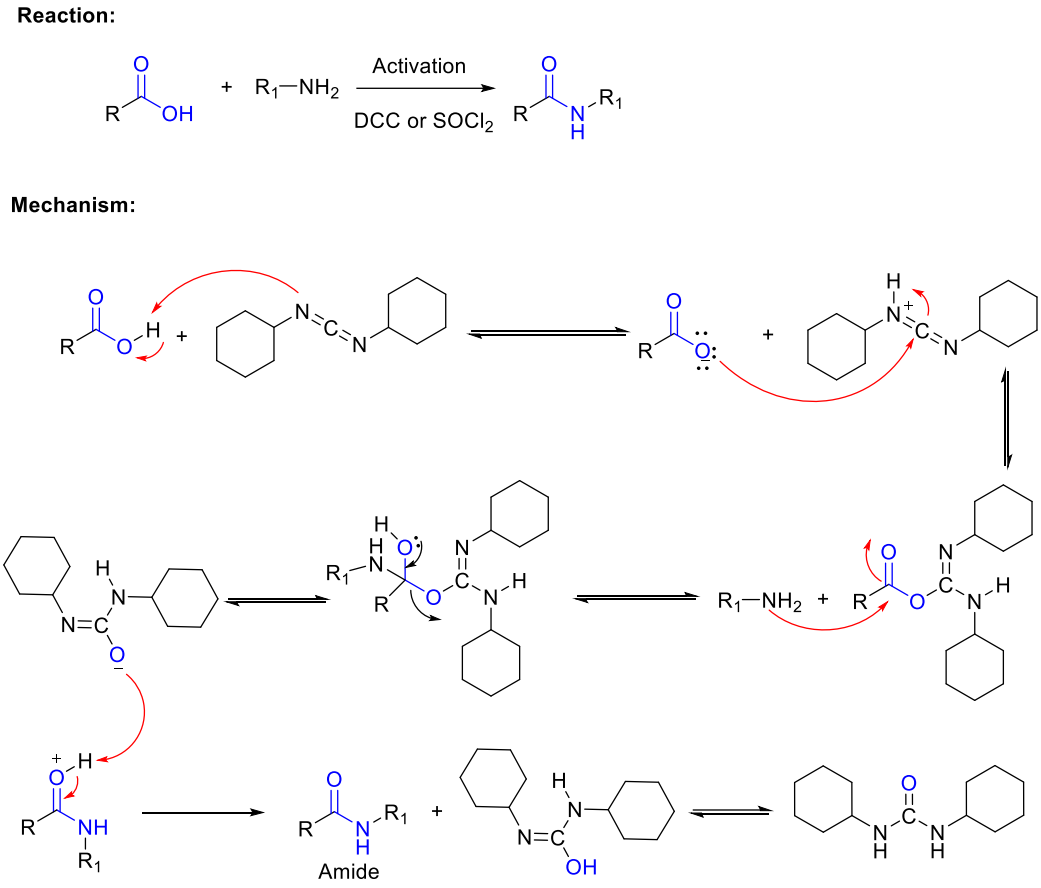
The mechanism of Fischer esterification proceeds through a nucleophilic acyl substitution pathway involving several key steps. In ***step 1***, the carbonyl oxygen of the carboxylic acid is protonated by the acid catalyst, increasing the electrophilicity of the carbonyl carbon and making it more susceptible to nucleophilic attack. In ***step 2***, the alcohol acts as a nucleophile and attacks the carbonyl carbon, breaking the π bond of the carbonyl group and forming a tetrahedral intermediate containing both the original OH group from the acid and the OR′ group from the alcohol. In ***step 3***, proton transfers occur within the intermediate to stabilize the molecule and convert the OH group into a good leaving group by protonating it. In ***step 4***, the protonated OH group is eliminated as water (H_2O), producing a protonated ester. Finally, in ***step 5***, deprotonation of the ester occurs, regenerating the acid catalyst and yielding the neutral ester product [21].

8.3. Formation of amides

Amidation from carboxylic acids is a fundamental organic reaction in which a carboxylic acid (RCOOH) reacts with an amine (R_1–NH_2, R_2–NH, or R_3–N) to produce an amide (R–CONH) and water. This process is of great importance in both biological and industrial chemistry because amides are essential structural motifs found in proteins, peptides, pharmaceuticals, polymers, and

many bioactive molecules. Amides are characterized by the peptide bond (–CONH–), which links amino acids together in proteins. However, the direct formation of an amide from a carboxylic acid and an amine is often challenging because carboxylic acids are relatively unreactive, and amines are basic, leading to acid-base neutralization rather than nucleophilic attack. Therefore, activation of the carboxylic acid or the use of condensing agents is typically required to facilitate the reaction.

The general reaction can be summarized as follows (**Scheme 34**):



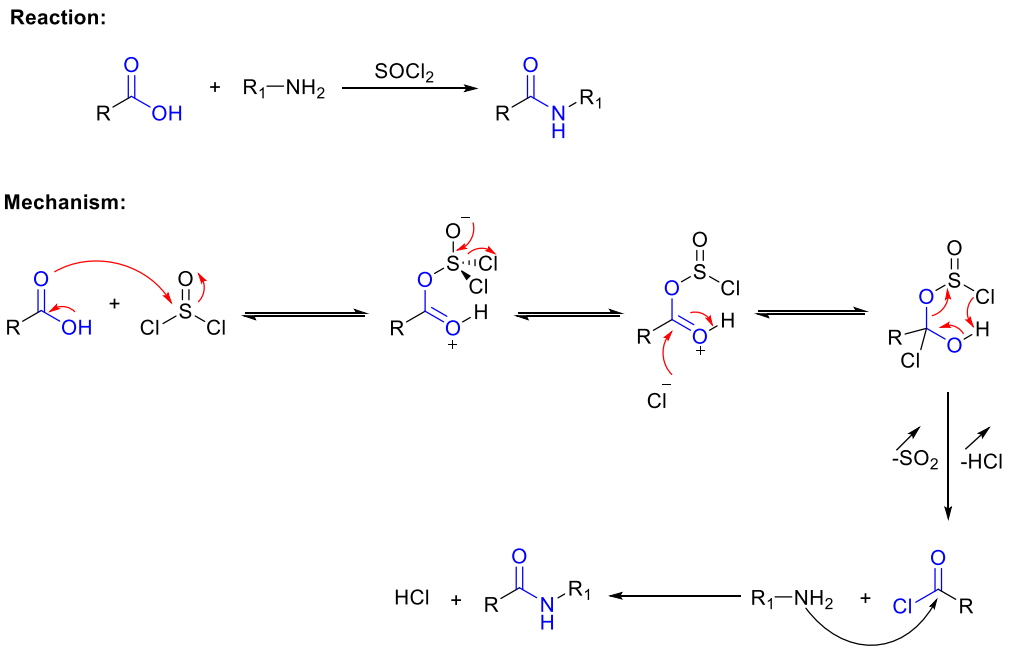
Scheme 34. *Amidation of carboxylic acids using DCC as an activator.*

Amidation mechanism proceeds through a nucleophilic acyl substitution pathway, typically requiring activation of the carboxylic acid because the hydroxyl group (–OH) of the acid is a poor leaving group. In the first step, the carboxylic acid is activated by a coupling reagent such as DCC (dicyclohexylcarbodiimide), thionyl chloride ($SOCl_2$), or by conversion into a more reactive intermediate like an acid chloride or anhydride. Activation increases the electrophilicity of the carbonyl carbon, making it more susceptible to nucleophilic attack. Next, the amine nucleophile attacks the carbonyl carbon, breaking the C=O bond and forming a tetrahedral intermediate. Within this intermediate, proton transfers occur to stabilize charges: the nitrogen

becomes neutralized while the leaving group, introduced during activation, is protonated. Following this, the leaving group is eliminated, restoring the carbonyl double bond and resulting in the formation of the amide product. Finally, any remaining proton transfers regenerate the catalyst or neutralize by-products [22].

Example:

For example, when using thionyl chloride, the carboxylic acid first reacts with $SOCl_2$ to form an acid chloride. The amine then attacks the carbonyl carbon of the acid chloride, producing another tetrahedral intermediate. This intermediate undergoes elimination of chloride ion (Cl^-) and proton transfer to yield the amide (R–CONH–R′) and hydrogen chloride (HCl) as a by-product. The overall mechanism involves activation of the acid, nucleophilic attack by the amine, formation of a tetrahedral intermediate, proton transfers, and loss of a leaving group, making the process efficient for synthesizing stable amide bonds (**Scheme 35**).



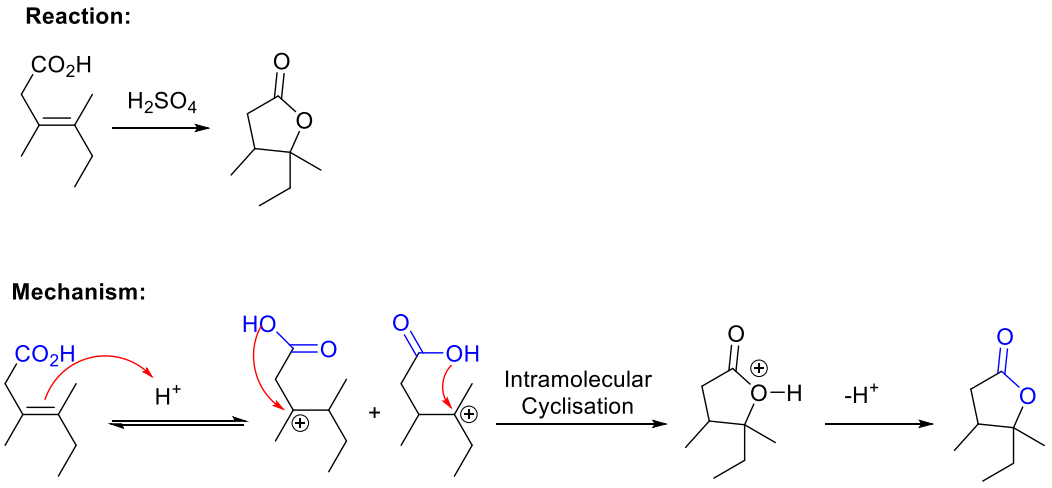
Scheme 35. *Amidation of carboxylic acids using $SOCl_2$ as an activator.*

8.4. Intramolecular cyclisation of carboxylic acid

Intramolecular cyclisation of carboxylic acids involves the formation of cyclic compounds through the reaction with another reactive functional group present within the same molecule. This process occurs via an intramolecular nucleophilic substitution mechanism, where the nucleophile and electrophile are part of the same molecule, resulting in ring closure. Such cyclisation reactions are widely observed in the synthesis of lactones (cyclic esters) and lactams (cyclic amides).

The general reaction occurs when a molecule contains both a carboxylic acid group and a reactive functional group, such as a hydroxyl group, an amino group, or an electrophilic site like a double bond, allowing for intramolecular attack. Under appropriate conditions, such as heating, the presence of an acidic catalyst, or the use of a dehydrating agent, the nucleophilic and electrophilic sites within the same molecule can react with each other, leading to ring closure. In some cases, the carboxylic acid group can act as the nucleophile, while in other cases, it may serve as the electrophile, depending on the nature of the reacting group.

When a double bond is present in the molecule alongside the carboxylic acid, a strong acid catalyst, such as concentrated sulfuric acid (H_2SO_4), is required to protonate the double bond and generate a carbocation. This carbocation is then attacked by the hydroxyl group of the carboxylic acid, resulting in the formation of a cyclic ester (lactone) or related cyclic compound. The stability and size of the ring formed depend on the number of atoms between the two reacting groups, with five- and six-membered rings being the most favorable due to minimal ring strain (**Scheme 36**) [23].

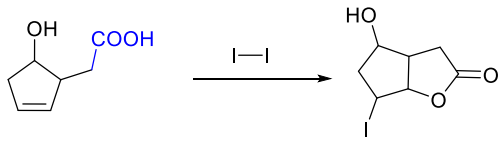


Scheme 36. *Intramolecular cyclisation of carboxylic acid compound.*

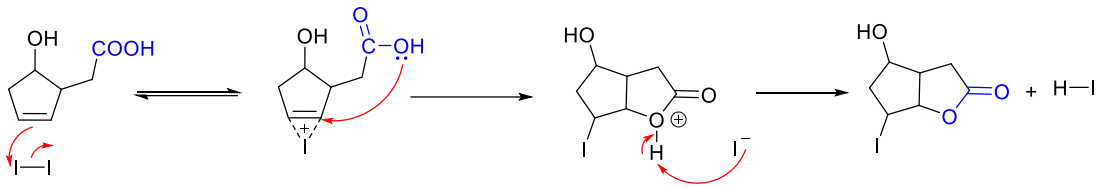
Example:

In this example, the carboxylic acid reacts with a halonium ion generated by the addition of I_2 to the double bond. This intramolecular reaction leads predominantly to the formation of a five-membered ring, accompanied by the elimination of a molecule of hydrogen iodide (HI) (**Scheme 37**).

Reaction:



Mechanism:



Scheme 37. *carboxylic acid reacts with a halonium ion.*

9. Organic synthesis – reactivity of carbonyl compounds

Carbonyl compounds (aldehydes, ketones, carboxylic acid derivatives, etc.) are highly reactive due to the polarized carbonyl group (C=O). The carbonyl carbon is electrophilic (δ^+) and the oxygen is nucleophilic (δ^-), which makes them susceptible to a wide range of chemical reactions. Their reactivity depends on both electronic effects and steric effects.

The result of carbonyl bond polarization, however it is depicted, is straightforward to predict. The carbon, because it is electron-poor, is an electrophile: it is a great target for attack by an electron-rich nucleophilic group. Because the oxygen end of the carbonyl double bond bears a partial negative charge, anything that can help to stabilize this charge by accepting some of the electron density will increase the bond's polarity and make the carbon more electrophilic (**Figure 4)**. Very often a general acid group serves this purpose, donating a proton to carbonyl oxygen, the same effect can also be achieved if a Lewis acid, such as a magnesium ion, is located near the carbonyl oxygen.

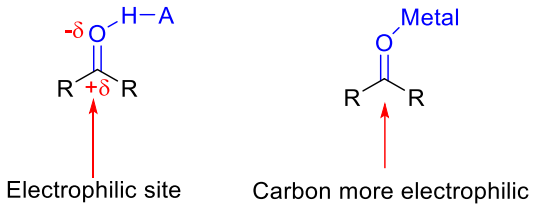


Figure 4. *General structure of carbonyl compounds linked to an acid and metal.*

Their chemistry is dominated by nucleophilic addition (aldehydes/ketones), nucleophilic acyl substitution (acid derivatives), and α-hydrogen reactivity (enolate chemistry).

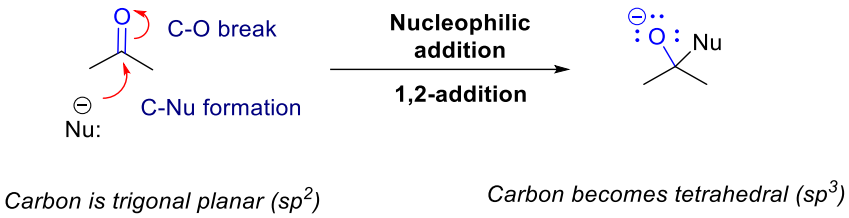
Tableau 1. *Reactivity of carbonyls compounds.*

Compound type	Dominant reaction	Relative reactivity
Aldehydes	Nucleophilic addition	Very reactive
Ketones	Nucleophilic addition	Moderate
Acid chlorides	Nucleophilic acyl substitution	Very high
Anhydrides	Nucleophilic acyl substitution	High
Esters/Carboxylic acids	Nucleophilic acyl substitution	Moderate–low
Amides	Nucleophilic acyl substitution	Low

9.1. Nucleophilic addition to carbonyls

The most important reaction of the carbonyl group is the nucleophilic addition to the carbonyl carbon, commonly referred to as "1,2-addition." This reaction takes place because the C=O bond is polarized: the carbonyl carbon carries a partial positive charge and acts as an electrophilic center, while the oxygen atom carries a partial negative charge and can accommodate extra electron density. During nucleophilic attack, the carbonyl carbon undergoes a change in hybridization from sp^2 to sp^3, and its geometry changes from trigonal planar to tetrahedral, producing a tetrahedral alkoxide intermediate that is subsequently protonated to give the final addition product. Depending on the strength and basicity of the nucleophile, the addition may be either irreversible or reversible. Strong nucleophiles such as hydride donors or organometallic reagents react irreversibly, usually yielding alcohols after protonation, while weaker nucleophiles such as hydroxide ions, alcohols, or cyanide ions undergo reversible additions, leading to important transformations such as cyanohydrin formation or hemiacetal and acetal equilibria. The reverse of nucleophilic addition is elimination, often referred to as "1,2-elimination," where the tetrahedral intermediate collapses and ejects a leaving group, regenerating the carbonyl; this is the fundamental principle underlying nucleophilic acyl substitution in carboxylic acid derivatives (**Scheme 38**).

The rate and outcome of nucleophilic addition are influenced by several factors. Electron-withdrawing groups adjacent to the carbonyl increase the electrophilicity of the carbonyl carbon and accelerate the reaction, while electron-donating groups reduce electrophilicity and slow the reaction. Steric hindrance also plays an important role: aldehydes, which are less sterically hindered and have only one electron-donating substituent, are generally more reactive than ketones, which bear two alkyl groups. The nature of the nucleophile further determines whether the reaction is fast and irreversible, as in the case of strong bases, or reversible, as with weaker nucleophiles. Reaction conditions also matter: under acidic conditions, protonation of the carbonyl oxygen enhances the electrophilicity of the carbon, making it more susceptible to attack, whereas under basic conditions stronger nucleophiles such as alkoxides or enolates can form and drive the reaction. Classic examples of nucleophilic addition include the reduction of aldehydes to primary alcohols and ketones to secondary alcohols by hydride reagents, the reversible addition of HCN to form cyanohydrins, and the acid-catalyzed addition of alcohols to aldehydes and ketones to form hemiacetals and acetals [24].



Scheme 38. *1,2-addition to carbonyls.*

9.2. Nucleophilic substitution of RC=OY (Y = Leaving Group)

Carbonyl compounds that contain a leaving group, generally referred to as carboxylic acid derivatives, undergo reactions that resemble the nucleophilic addition observed in aldehydes and ketones, but with an important distinction: the presence of an electronegative substituent (Y) bonded to the carbonyl carbon. This substituent can function as a leaving group, which allows the overall process to proceed through nucleophilic acyl substitution rather than simple nucleophilic addition (**Figure 5**).

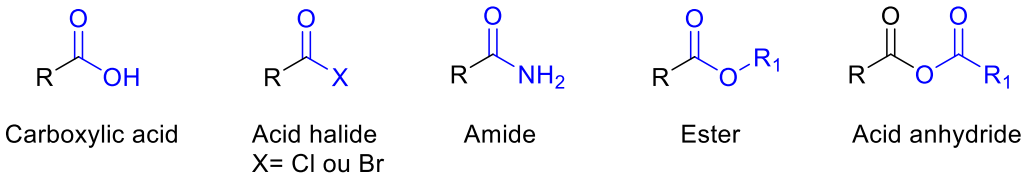
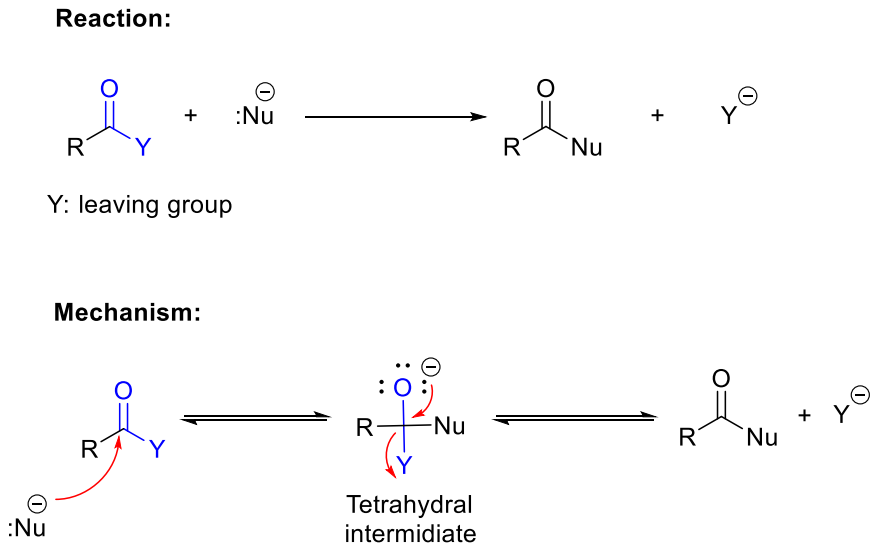


Figure 5. *Chemical structures of some carbonyl compounds.*

The general mechanism involves three stages: first, the nucleophile attacks the electrophilic carbonyl carbon, breaking the π-bond and producing a tetrahedral intermediate; second, the negatively charged oxygen reforms the carbonyl double bond; and third, the leaving group Y^- is expelled, restoring the C=O functionality with a new substituent attached. Thus, unlike aldehydes and ketones that retain the addition product, carboxylic acid derivatives are characterized by their ability to undergo substitution at the acyl carbon.

The efficiency of this reaction depends strongly on the nature of the leaving group Y and the extent of resonance stabilization of the derivative. Four common classes of carboxylic acid derivatives acid halides, acid anhydrides, esters, and amides illustrate the range of reactivity. Acid halides (R-C=O-Cl or R-C=O-Br) are the most reactive, because the halide ion is a very good leaving group and the C=O bond in acid halides is only weakly stabilized by resonance. They readily undergo nucleophilic substitution with water (to form carboxylic acids), with alcohols (to form esters), or with ammonia and amines (to form amides). Acid anhydrides are also highly reactive, as they contain two acyl groups bonded to the same oxygen; nucleophilic attack on one carbonyl releases a carboxylate ion, which is a relatively stable leaving group.

Esters, by contrast, are less reactive, because the alkoxide ion (RO^-) is a poorer leaving group compared to halides or carboxylates, and resonance donation from the alkoxy oxygen stabilizes the carbonyl carbon, making it less electrophilic. Esters can nevertheless be converted into carboxylic acids, other esters (via transesterification), or amides under appropriate conditions, especially when catalyzed by acid or base. Finally, amides are the least reactive of the four. This is because the NH_2 group is a very poor leaving group and, more importantly, because the nitrogen lone pair is strongly delocalized into the carbonyl, giving the C–N bond partial double bond character and greatly stabilizing the structure. As a result, amides resist nucleophilic substitution unless subjected to strong heating or activation, but when they do react, they can yield carboxylic acids (via hydrolysis) or undergo transformations under more forcing conditions (**Scheme 39**) [25].

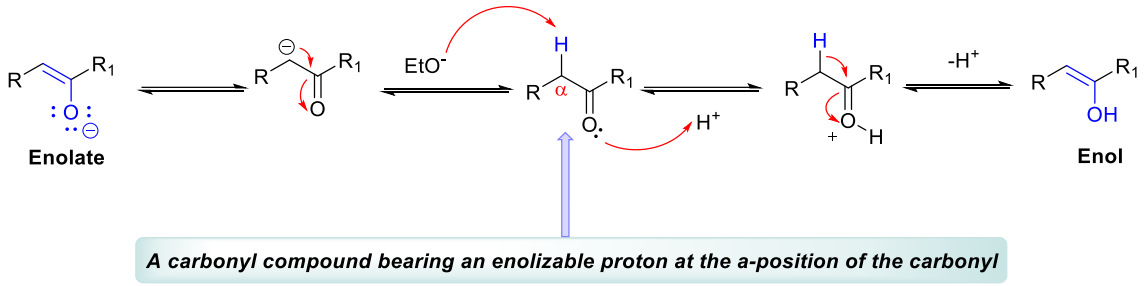


Scheme 39. *General mechanism of nucleophilic substitution.*

The overall reactivity order of these derivatives is: acid halides > acid anhydrides > esters > amides. This trend reflects both the relative ability of the substituent to serve as a leaving group (Cl^- > $RCOO^-$ > RO^- > NH_2^-) and the extent of resonance stabilization that reduces the electrophilicity of the carbonyl carbon.

10. Aldol condensation and crotonisation

The aldol condensation is a fundamental carbon–carbon bond forming reaction that involves the reaction of enolate ions (generated from aldehydes or ketones) or enol (**Scheme 40**) with the carbonyl group of another molecule to form β-hydroxy aldehydes or β-hydroxy ketones, known as aldols. Upon heating or under acidic/basic conditions, these aldols undergo dehydration (elimination of water) to produce α,β-unsaturated carbonyl compounds, a process known as crotonisation. The term "aldol" comes from the combination of aldehyde and alcohol, as the initial product contains both a carbonyl group and a hydroxyl group. The reaction can occur under basic or acidic conditions, but the base-catalyzed pathway is most common [25].

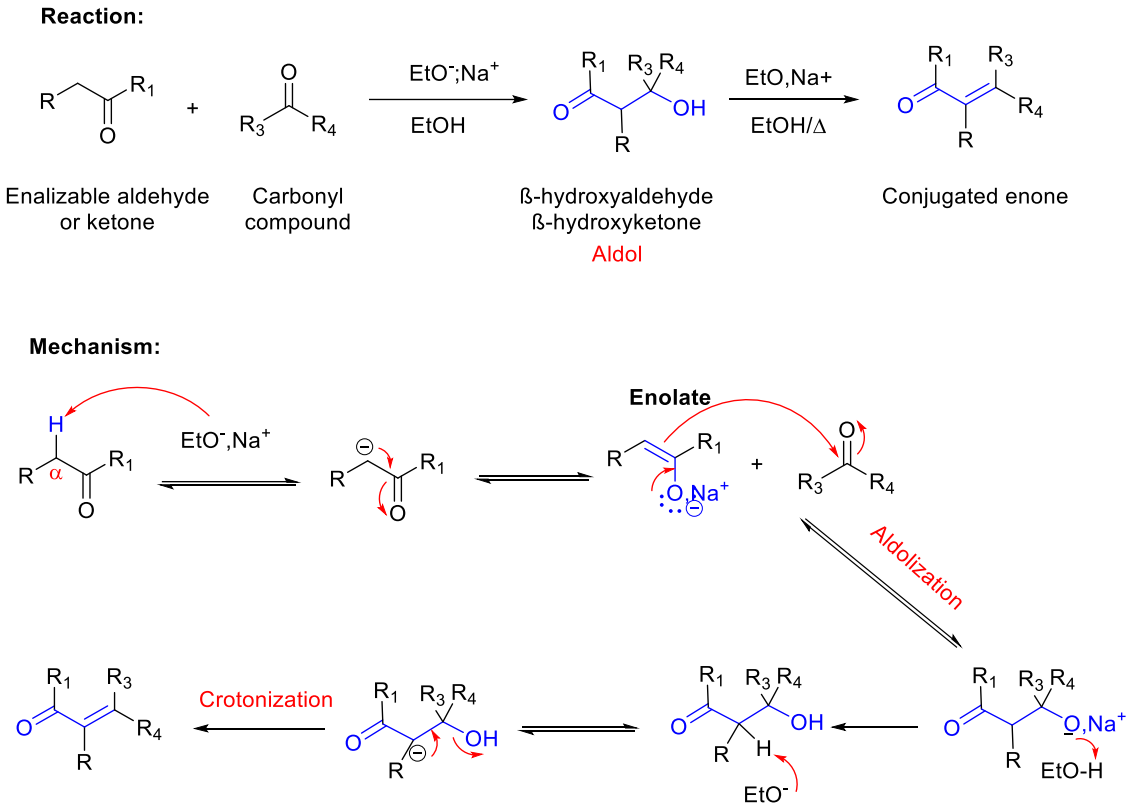


Scheme 40. *Formation of enolate and enol using a carbonyl compound enolizable.*

In the aldol condensation, a carbonyl compound such as an aldehyde or a ketone containing at least one α-hydrogen undergoes a base-catalyzed reaction to form a β-hydroxy carbonyl compound, which then may dehydrate in a process known as crotonisation to yield an α,β-unsaturated carbonyl compound. The mechanism begins when a base such as hydroxide ion abstracts an α-hydrogen from the carbonyl compound. This deprotonation generates a resonance-stabilized enolate ion in which the negative charge is delocalized between the α-carbon and the carbonyl oxygen. The enolate then acts as a nucleophile and attacks the electrophilic carbonyl carbon of another molecule of the aldehyde or ketone, forming a new carbon–carbon bond and giving rise to an alkoxide intermediate. The alkoxide ion is subsequently protonated by water or solvent such as MeOH and EtOH to produce the β-hydroxy aldehyde or β-hydroxy ketone, known as the "aldol" product.

Under heating or continued base (or acid) catalysis, this aldol undergoes dehydration in the crotonisation step. Here, the base again abstracts an α-hydrogen, forming another enolate, and the negative charge facilitates elimination of the adjacent hydroxide group. In an acid-catalyzed pathway, the hydroxyl group is first protonated to form a good leaving group (water), which then departs as the double bond forms. In either case, the result is the loss of water and the formation of a conjugated α,β-unsaturated carbonyl compound, which is thermodynamically favored due

to extended conjugation and resonance stabilization. Thus, the overall transformation of the aldol condensation followed by crotonisation converts two molecules of a carbonyl compound into a single molecule containing a new carbon–carbon bond and a conjugated enone or enal system [26] (**Scheme 41**).



Scheme 41. *Aldol condensation and crotonisation mechanism and general reaction.*

The protons located at the α-position of a carbonyl group are relatively acidic compared to normal C–H bonds because the resulting conjugate base, known as an enolate ion, is stabilized by resonance between the α-carbon and the carbonyl oxygen. The exact acidity of these α-protons depends on the nature of the carbonyl compound, and therefore their pKa values differ; for example, the α-protons of aldehydes and ketones typically have pKa values around 19–20, those of esters and nitriles are slightly less acidic with pKa values around 25, while the α-protons of β-diketones or β-keto esters are much more acidic, with pKa values in the range of 9–13, due to additional resonance stabilization. Because of this enhanced acidity, these protons can be readily abstracted by bases to generate enolates, which are key reactive intermediates in many carbon–carbon bond-forming reactions such as aldol condensation, Claisen condensation, and Michael addition [27] (**Figure 6**).

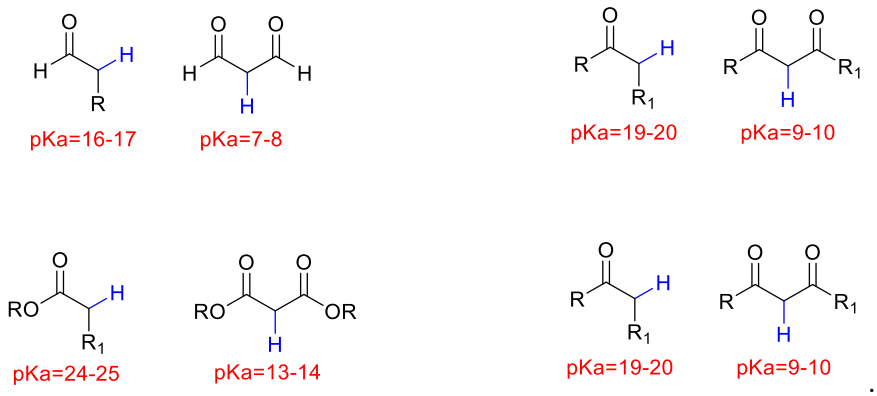
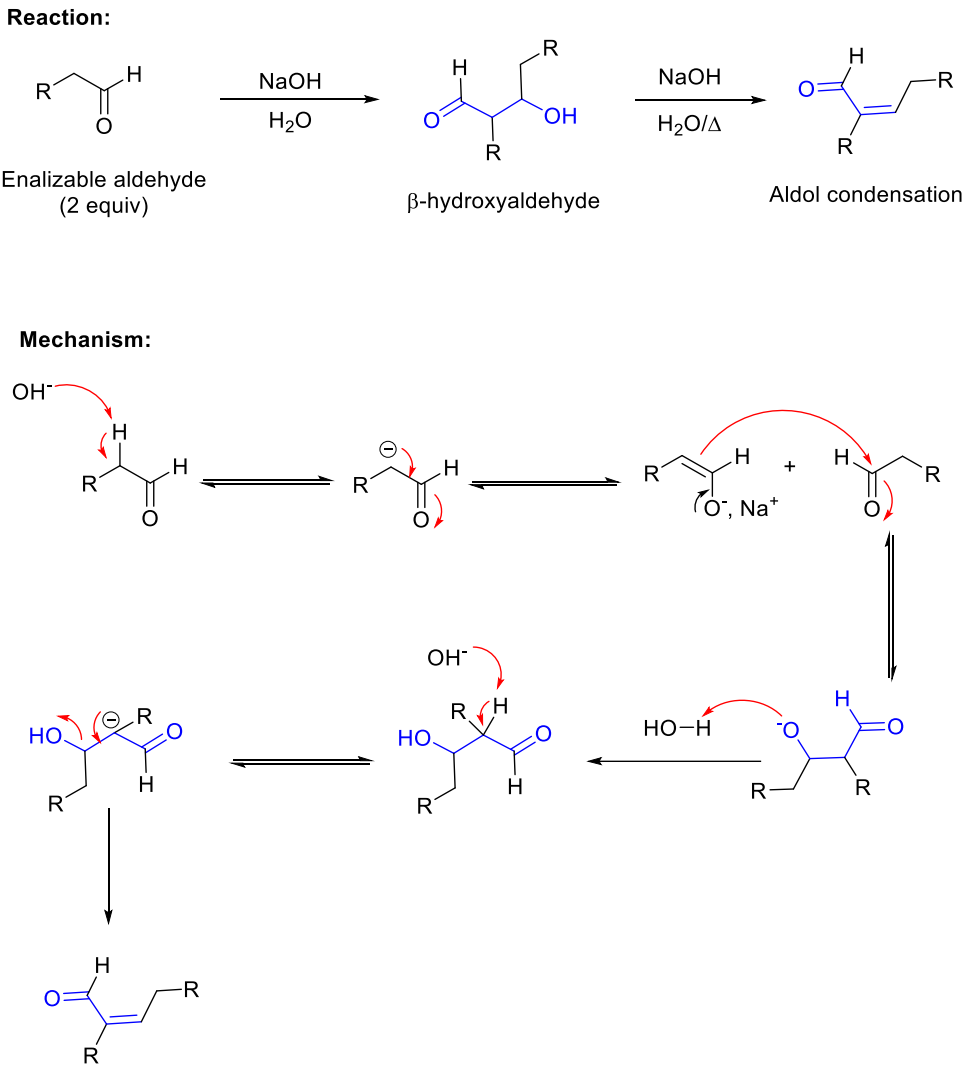


Figure 6. *Acidity of the protons in the α position of the different carbonyl derivatives.*

10.1. Auto-condensation reaction

The auto-condensation reaction of an enolizable aldehyde, commonly referred to as self-aldol condensation, is an important C–C bond-forming reaction that occurs when two molecules of the same aldehyde participate in an aldol addition followed by dehydration. The reaction requires that the aldehyde possess at least one α-hydrogen, which is sufficiently acidic due to the electron-withdrawing effect of the adjacent carbonyl group. In the presence of a base catalyst such as hydroxide ion or alkoxide, the reaction begins with the abstraction of an α-hydrogen from the aldehyde, leading to the formation of a resonance-stabilized enolate ion. This enolate has two resonance contributors: one with a negative charge localized on the α-carbon, making it nucleophilic, and another with a negative charge on the oxygen atom. The carbon-centered resonance form is the reactive species that attacks the electrophilic carbonyl carbon of another aldehyde molecule. This nucleophilic addition forms a new carbon–carbon bond and gives rise to an alkoxide intermediate. Proton transfer from the solvent then converts this alkoxide into a neutral β-hydroxyaldehyde, which is the characteristic product of the aldol addition step.

However, β-hydroxyaldehydes are often unstable under the reaction conditions, and upon heating or under continuous basic or acidic catalysis, they undergo a dehydration reaction known as aldol condensation or crotonization. This elimination occurs *via* an E1cB mechanism in basic medium: the base removes another α-hydrogen, generating a carbanion that expels the hydroxide group, or via protonation of the hydroxyl group followed by water loss under acidic conditions. In both cases, the result is the formation of an α,β-unsaturated aldehyde, a conjugated system that is stabilized by resonance between the carbon–carbon double bond and the carbonyl group [28] (**Scheme 42**).



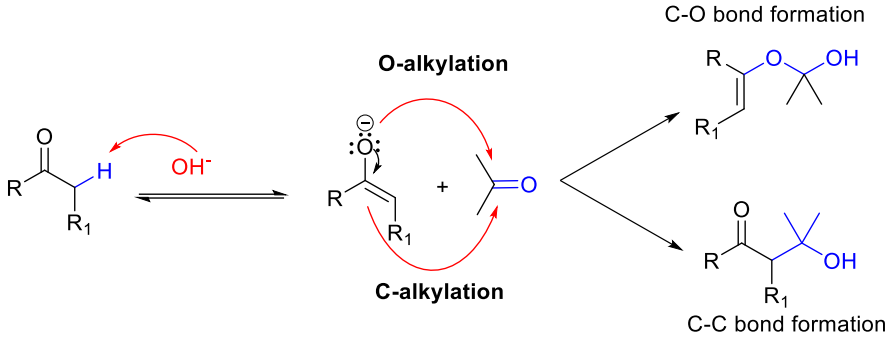
Scheme 42. *General reaction and mechanism reaction of auto-condensation reaction.*

10.2. Regioselectivity of enolate formation

An enolate ion is generated when a base abstracts an acidic α-hydrogen (a hydrogen atom adjacent to the carbonyl group) of a carbonyl compound. Due to resonance, the resulting negative charge can be delocalized between the α-carbon and the oxygen atom of the carbonyl group. This delocalization greatly stabilizes the enolate anion compared to a typical carbanion.

Enolates can be formed from aldehydes and ketones, as well as from esters, amides, nitriles, and many other carbonyl-containing compounds. When an additional electron-withdrawing group is present on the α-carbon, the acidity of the α-hydrogen increases, making enolate formation significantly easier. This delocalization makes enolates ambident nucleophiles, meaning they can attack through either the carbon (C-enolate, common in aldol reactions) or oxygen (O-enolate, common in silyl enol ethers or alkylation)

Enolates are strong nucleophiles and participate in a wide range of reactions with electrophiles. Common examples include reactions with protons (H^+), halogens, and simple electrophiles, which form the basis for many important transformations in organic synthesis [29] (**Scheme 43**).



Scheme 43. *O-alkylation versus C-alkylation of condensation of enolate with carbonyl group.*

When the carbonyl compound has different sets of α-hydrogens, different enolates are possible. The distribution depends on regioselectivity and reaction conditions, leading to two major types: kinetic enolate and thermodynamic enolate.

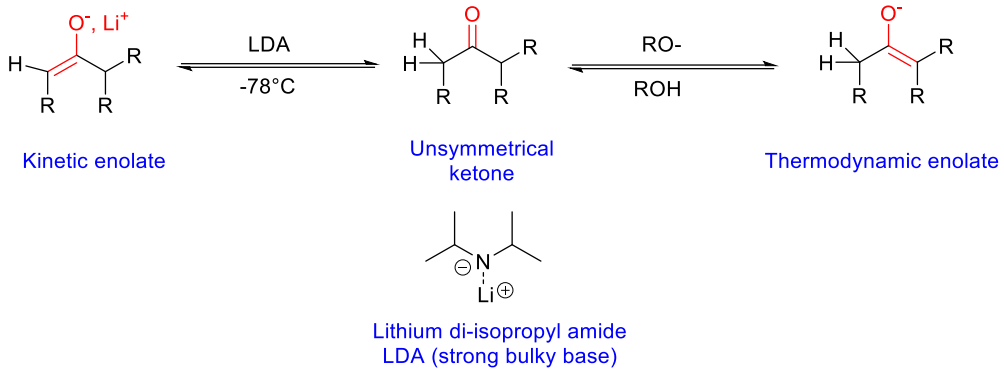
10.2.1. Kinetic versus thermodynamic enolates

Enolates share many features with alkenes. They are planar species with a delocalized C–C π bond. According to Zaitsev's rule, the stability of alkenes increases with the number of carbon substituents attached to the double bond; in other words, the more substituted the alkene, the more stable it is. By analogy, more substituted enolates are also more stable. When enolates are generated using small, strong, non-bulky bases (e.g., NaOH or $NaOCH_3$), equilibrium conditions favor formation of the more substituted, thermodynamically stable enolate. Consequently, when such an enolate reacts with an electrophile, substitution occurs preferentially at the more substituted α-carbon.

However, this inherent preference can be altered. The use of a strong, bulky, non-nucleophilic base such as LDA (lithium diisopropylamide) under kinetic conditions allows selective abstraction of the less hindered, more accessible α-proton. This pathway leads to the less substituted enolate, known as the kinetic enolate. The kinetic enolate forms rapidly and irreversibly, and although it is less stable than its thermodynamic counterpart, it can be selectively obtained under appropriate conditions.

In general, the kinetic enolate is formed by deprotonation at the least hindered α-position and predominates under conditions of strong bulky base, low temperature (around -78 °C), aprotic solvents such as THF or ether, and short reaction times that prevent equilibration. By contrast, the thermodynamic enolate results from deprotonation at the more substituted α-position,

producing a resonance-stabilized enolate favored by hyperconjugation and alkyl substitution. This enolate forms more slowly but dominates under equilibrium conditions, typically promoted by small bases such as sodium ethoxide, sodium hydroxide, or sodium hydride, at higher temperatures (room temperature or above), in protic or equilibrating solvents, and with longer reaction times [30] (**Scheme 44**).



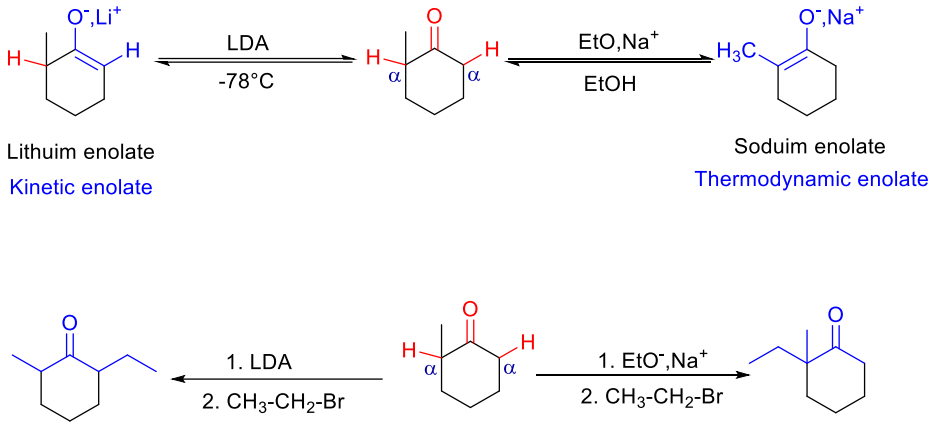
Scheme 44. *Kinetic versus thermodynamic enolate formation.*

Example :

A classical and widely cited example illustrating the distinction between kinetic and thermodynamic enolate formation is 2-methylcyclohexanone, a ketone that contains two different sets of α-hydrogens. One set is located on the methyl substituent at the C-2 position, which represents the less substituted and sterically accessible site, while the other set is located on the ring α-carbon, which is more substituted and leads to a more stable enolate. When 2-methylcyclohexanone is treated with a strong, bulky, non-nucleophilic base such as LDA (lithium diisopropylamide) at low temperature (-78 °C), the base rapidly and irreversibly abstracts the proton from the less hindered methyl side. This process occurs because steric accessibility governs the rate of proton removal under kinetic control, resulting in the preferential formation of the kinetic enolate, which is less substituted and therefore less stable. In contrast, when the same ketone is treated with a smaller base such as sodium ethoxide under equilibrium conditions at room temperature, the base is able to reversibly deprotonate different α-sites, and over time the system equilibrates to favor the formation of the thermodynamic enolate. This enolate arises from deprotonation at the more substituted α-carbon on the ring side, producing the more stable resonance-stabilized species due to greater alkyl substitution and hyperconjugation effects.

The contrast between these two outcomes highlights the profound influence of reaction conditions on enolate regioselectivity. The kinetic enolate is characterized by rapid formation, irreversibility, and dominance under conditions involving bulky bases, low temperatures, and aprotic solvents, which restrict equilibration and lock in the initial, less substituted product. Conversely, the thermodynamic enolate forms more slowly but predominates under reversible conditions, where smaller bases, higher temperatures, protic or equilibrating solvents, and longer reaction times allow proton transfers to occur until the most stable enolate is achieved. Thus, the regioselectivity of enolate formation is not an inherent property of the substrate alone but a tunable outcome determined by the experimental parameters.

This example of 2-methylcyclohexanone clearly demonstrates how chemists can deliberately manipulate base strength, steric hindrance, solvent, temperature, and reaction time to exert precise control over whether the kinetic or thermodynamic enolate dominates. Such control is of great synthetic value, since different enolates often lead to distinct products in aldol reactions, Michael additions, and other enolate-based transformations. By mastering the interplay between kinetic and thermodynamic conditions, organic chemists can selectively channel reactivity toward the desired regioisomer, thereby improving yields, selectivity, and efficiency in complex molecule synthesis (**Scheme 45**).



***Scheme 45**. Kinetic and thermodynamic enolate formation of 2-methylcyclohexanone.*

11. Major reactions in organic synthesis

11.1. Claisen condensation

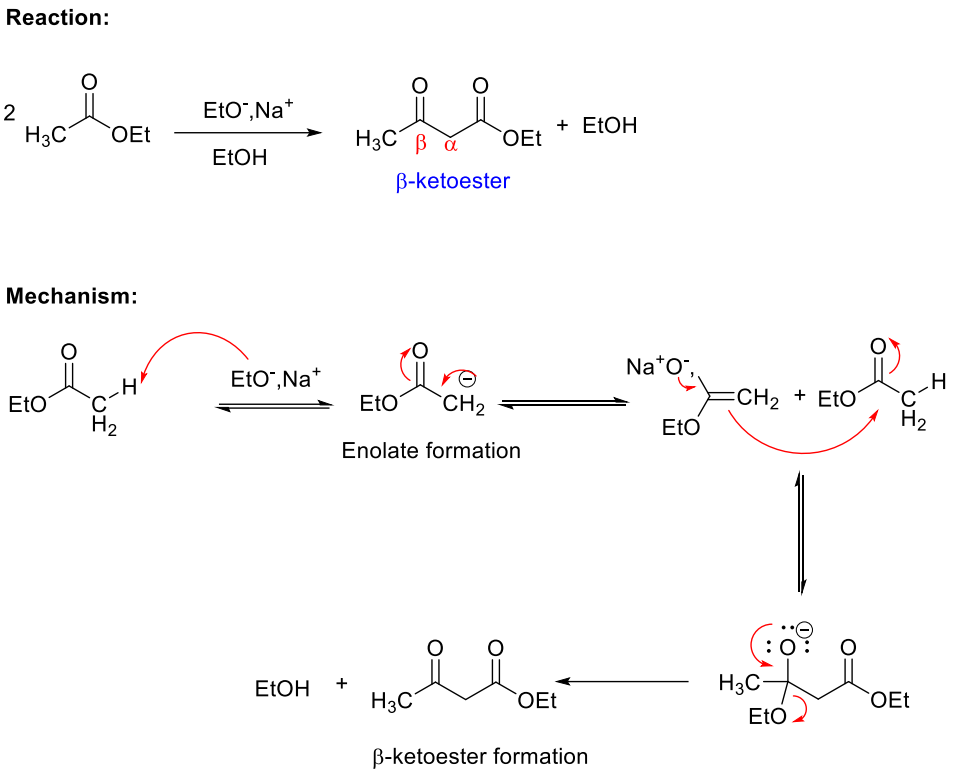
The Claisen condensation is an important C-C bond-forming reaction in which an ester reacts with another ester, or with a carbonyl compound such as a ketone, in the presence of a strong base (EtO^-,Na^+) to give a β-keto ester or a β-diketone. The key feature of this reaction is the

generation of an enolate ion from an ester or ketone, which then acts as a nucleophile and attacks the carbonyl carbon of another ester molecule, leading to the formation of a new C–C bond.

The mechanism proceeds in several steps. First, a strong base, typically an alkoxide ion such as ethoxide (OEt) or methoxide (OMe), deprotonates the α-hydrogen of the ester or ketone, generating a resonance-stabilized enolate ion. This enolate then performs a nucleophilic attack on the carbonyl carbon of another ester molecule, forming a tetrahedral intermediate. Next, the tetrahedral intermediate collapses with the expulsion of an alkoxide leaving group, regenerating the base used and producing a β-keto ester (if two esters react) or a β-diketone (if an ester reacts with a ketone). In the final step, because the β-keto ester product contains acidic α-hydrogens between the two carbonyl groups, the base deprotonates the product, shifting the equilibrium toward product formation. Upon acidic work-up, the neutral β-keto ester or β-diketone is obtained.

Several important features govern the Claisen condensation. The base used must match the alkoxy group of the ester in order to avoid unwanted transesterification side reactions; for example, sodium ethoxide is typically used with ethyl esters. The starting ester must have at least one α-hydrogen to allow for enolate formation. The reaction is driven by the stabilization of the β-keto ester or β-diketone product, which benefits from resonance and the acidity of its central methylene group (**Scheme 46**).

There are several variations of the Claisen condensation. The classic Claisen condensation involves the self-condensation of an ester. The crossed Claisen condensation occurs between two different esters or between an ester and a ketone; this reaction can be selective when one reactant lacks α-hydrogens and therefore cannot form an enolate, ensuring only one enolate donor is available [31].

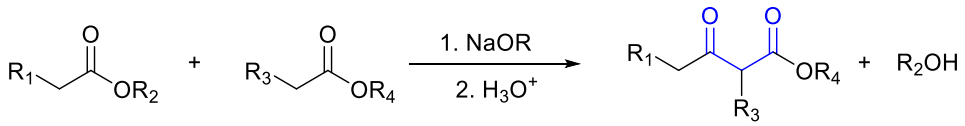


***Scheme 46**. Claisen condensation.*

The **mixed Claisen condensation** is a variation of the Claisen condensation in which an enolizable ketone reacts with an ester in the presence of a strong base to yield a β-diketone. This reaction differs from the classic Claisen condensation between two esters because it involves two different types of carbonyl compounds, and it is designed in such a way that only one partner provides the enolate donor while the other acts exclusively as the electrophile. For this reason, the ester used is typically non-enolizable, meaning it lacks α-hydrogens and cannot form its own enolate, which avoids unwanted self-condensation.

The reaction begins with the deprotonation of the ketone at its α-position by a strong base such as sodium ethoxide or LDA. Since the α-hydrogens of a ketone are significantly more acidic (pKa ≈ 19-20) than those of an ester (pKa ≈ 25), the ketone is preferentially deprotonated to form the corresponding enolate ion. This enolate is resonance-stabilized and serves as the nucleophile in the subsequent step. The enolate then performs a nucleophilic attack on the carbonyl carbon of the ester, forming a tetrahedral alkoxide intermediate. This intermediate collapses with elimination of the alkoxide leaving group (OR), regenerating the base and forming a β-diketone product, which features two carbonyl groups separated by one carbon atom.

One additional important mechanistic feature is the final deprotonation step. The β-diketone formed contains very acidic α-hydrogens located between the two carbonyl groups (pKa ≈ 9-11), much more acidic than the starting ketone. As a result, the base readily deprotonates the product, shifting the equilibrium strongly toward product formation. To recover the neutral β-diketone, an acidic work-up is performed at the end of the reaction (**Scheme 47**).



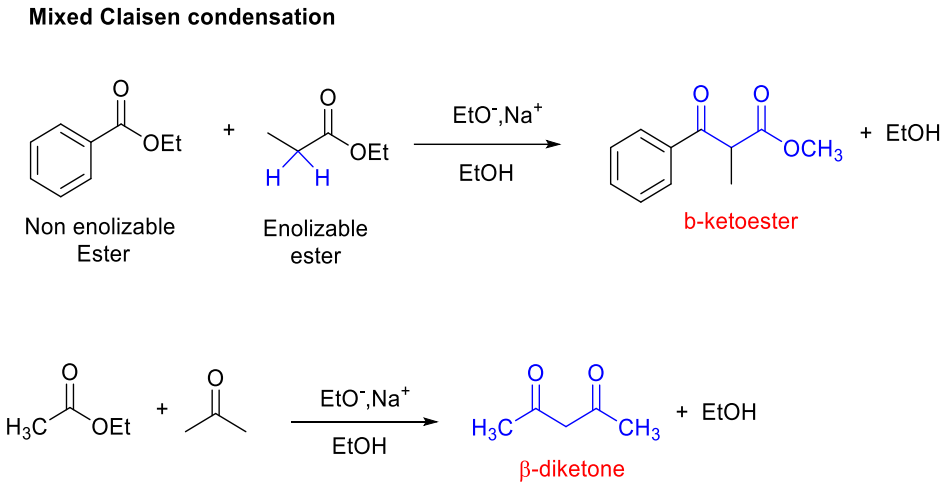
Scheme 47. *Mixed Claisen condensation.*

Example :

Claisen condensations involving two different esters are referred to as crossed Claisen condensations. In such reactions, both reactants have the potential to act as Claisen donors (enolate sources) and as Claisen acceptors (electrophiles), which often leads to the formation of complex mixtures that are difficult to separate. To avoid these complications, successful crossed Claisen condensations generally require that one of the two esters lacks α-hydrogens. In this case, the ester that contains α-hydrogens is deprotonated to form the enolate and serves as the Claisen donor, while the ester without α-hydrogens cannot form an enolate and therefore functions exclusively as the Claisen acceptor. Even under these conditions, the ester with α-hydrogens can still undergo self-condensation to form an undesired byproduct. This side reaction is typically minimized by using a large excess of the ester lacking α-hydrogens, ensuring that cross-condensation is favored.

A second important variation is the crossed Claisen condensation between a ketone and an ester. In this case, it is not necessary to use a non-enolizable ester because the ketone is much more reactive. The α-hydrogens of ketones (pKa ≈ 20) are significantly more acidic than those of esters (pKa ≈ 25), and thus the ketone is preferentially deprotonated to generate the enolate. This ketone enolate then serves as the Claisen donor, while the ester acts as the electrophilic acceptor. The ester is often employed in excess to suppress side reactions. A potential competing pathway is the aldol condensation of the ketone with itself, but this reaction is generally disfavored under Claisen conditions. Moreover, even if a small amount of aldol product forms, it is reversible because the product lacks a sufficiently acidic α-hydrogen to drive the reaction forward. By contrast, the desired β-diketone Claisen product is strongly stabilized: its central methylene group, positioned between two carbonyls, is highly acidic and can be irreversibly deprotonated.

This drives the equilibrium toward the β-diketone, making it the predominant product of the reaction [32] (**Scheme 48**).



Scheme 48. *Example of mixed Claisen condensation.*

11.2. Dickmann reaction (Intramolecular Claisen)

The Dieckmann reaction is an intramolecular Claisen condensation in which a diester containing two ester groups within the same molecule undergoes cyclization in the presence of a strong base to yield a cyclic β-keto ester. It is essentially the intramolecular counterpart of the Claisen condensation and is favored when the cyclization leads to the formation of a 5-membered or 6-membered ring, which are the most stable ring sizes due to minimal ring strain.

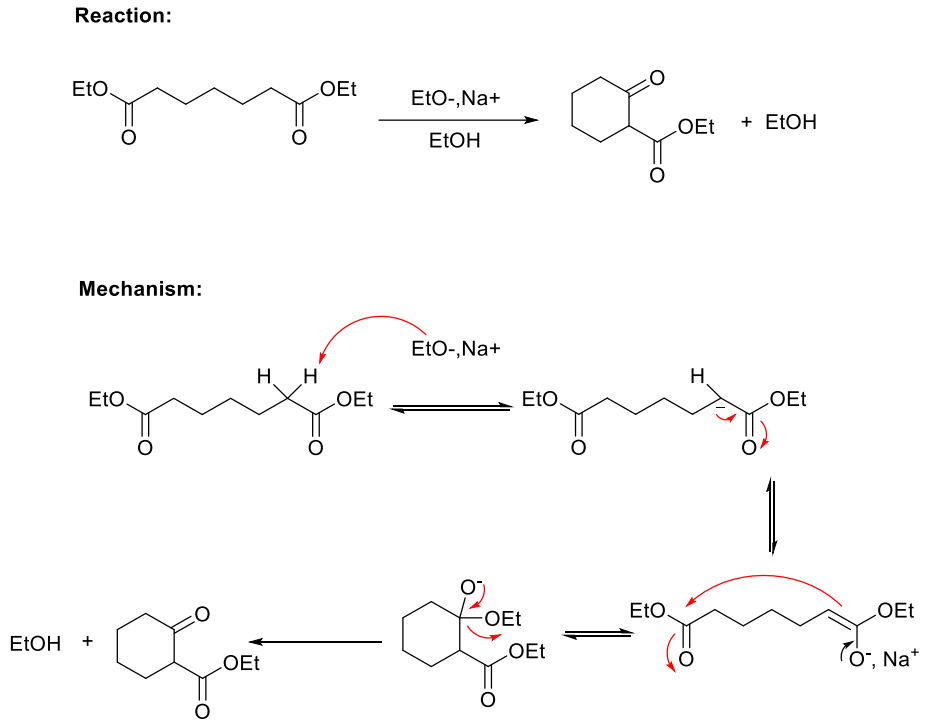
For example, when diethyl heptanedioate is treated with sodium ethoxide (a base that matches the ester alkoxy group), it undergoes an intramolecular attack to form ethyl 2-oxocyclohexanecarboxylate, a six-membered cyclic β-keto ester.

The mechanism proceeds step by step as follows:

Enolate formation: the base (ethoxide ion) deprotonates the methylene group located between one of the ester groups and the central carbon chain. This generates a resonance-stabilized enolate ion. After that, an intramolecular nucleophilic attack, the enolate ion then attacks the carbonyl carbon of the second ester group within the same molecule. This intramolecular reaction is favored if the attack leads to the formation of a 5- or 6-membered ring. A tetrahedral alkoxide intermediate is formed. The tetrahedral intermediate collapses, eliminating an ethoxide ion (OEt), and producing a cyclic β-keto ester. Because the β-keto ester product has very acidic α-hydrogens located between the two carbonyl groups, the base present in the reaction mixture deprotonates it, driving the equilibrium toward product formation.

Acidic work-up: To obtain the neutral product, an acidic work-up is performed, regenerating the protonated form of the cyclic β-keto ester.

Thus, the Dieckmann reaction is highly useful for the synthesis of cyclic β-keto esters, which are versatile intermediates in organic synthesis and can undergo further transformations such as decarboxylation, alkylation, and cyclization toward natural products and pharmaceuticals [33] (**Scheme 49**).

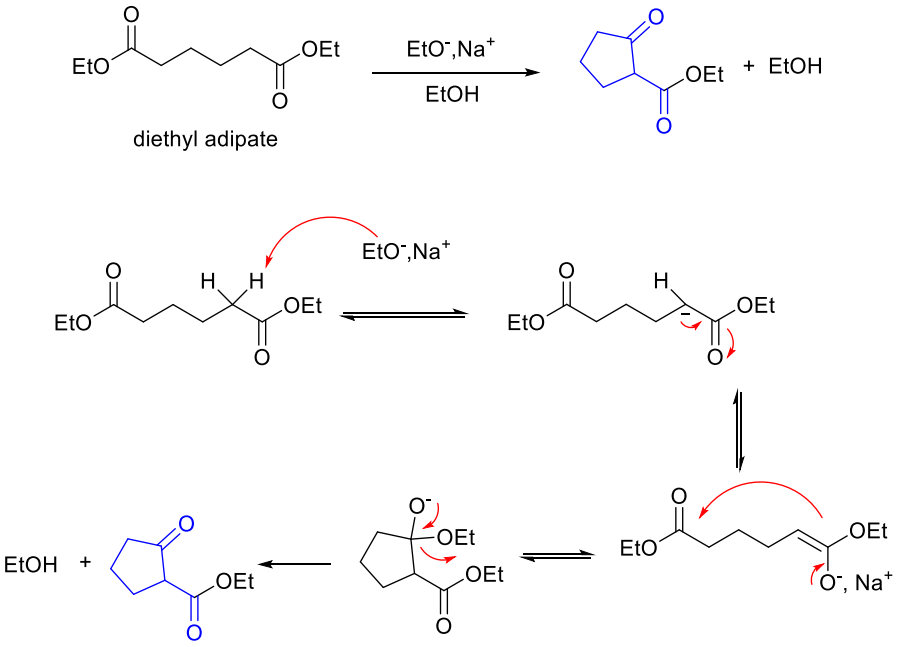


Scheme 49. *Dickmann reaction and mechanism.*

Example:

A clear example is the reaction of diethyl adipate (diethyl hexanedioate) with sodium ethoxide. In this process, the base abstracts an α-hydrogen from one of the methylene groups adjacent to an ester function, generating a resonance-stabilized enolate ion. This enolate then attacks the carbonyl carbon of the second ester group within the same molecule in an intramolecular nucleophilic substitution. Because the two ester groups are connected by a four-carbon chain, this attack leads to the formation of a five-membered ring, giving a tetrahedral intermediate. The intermediate collapses with the elimination of an ethoxide ion, producing a cyclic β-keto ester. The product is initially formed in its deprotonated form because the methylene group between the two carbonyl groups in the β-keto ester is highly acidic, which strongly drives the equilibrium toward product formation. Upon acidic work-up, the neutral compound ethyl 2-

oxocyclopentanecarboxylate is obtained. This reaction demonstrates how the Dieckmann condensation efficiently forms five- and six-membered cyclic β-keto esters, which are key intermediates in organic synthesis (**Scheme 50**).



Scheme 50. *Formation of a five-membered ring compound via Dieckmann reaction.*

11.3. Michael and aza-Michael reaction

The Michael addition is one of the most important C–C bond-forming reactions in organic chemistry, classified as a conjugate (1,4) addition reaction. It involves the addition of a stabilized nucleophile to the β-carbon of an α,β-unsaturated carbonyl compound, resulting in the formation of a new C–C bond and producing a 1,5-dicarbonyl compound or related structure. This reaction was first described by Arthur Michael in 1887 and remains a cornerstone transformation in both laboratory synthesis and biosynthetic pathways [34].

The general principle of the reaction is that a nucleophile derived from a compound with an active methylene group (such as malonates, β-keto esters, β-diketones, cyanoacetates, or nitroalkanes) is generated under basic conditions. The base removes an α-proton, forming a resonance-stabilized enolate ion, which acts as the Michael donor. The electrophilic partner, known as the Michael acceptor, is typically an α,β-unsaturated carbonyl compound (such as enones, enals, acrylates, or α,β-unsaturated esters). The enolate undergoes nucleophilic attack specifically at the β-carbon of the conjugated system, not at the carbonyl carbon, because conjugate addition yields a more stable product. After protonation of the resulting enolate intermediate, a stable 1,5-difunctionalized compound is obtained (**Scheme 51**).

During the is reaction the C=C pi bond of the α, β-unsaturated carbonyl is broken. An C-H bond is formed on the carbon in the α-position from the carbonyl. An acidic hydrogen is removed from the nucleophile and then it is used to form a C-C bond with the carbon in the beta position from the carbonyl. During a Michael reaction the enolate acts as a nucleophilic donor and the α, β-unsaturated carbonyl acts as the electrophilic acceptor.

Mechanistically, the process can be viewed as a combination of α-deprotonation of the donor (to generate an enolate) and conjugate addition to the acceptor. Unlike the Claisen condensation, the Michael reaction does not require irreversible deprotonation of the product to drive the equilibrium; the reaction is thermodynamically favorable because the newly formed C–C σ bond is stronger and more stable than the C=C π bond being replaced. As a result, only a catalytic amount of base is usually required.

Step 1: enolate formation

A base (commonly an alkoxide) removes an acidic α-hydrogen from the donor compound, producing a resonance-stabilized enolate nucleophile.

Step 2: nucleophilic conjugate attack

The enolate nucleophile attacks the electrophilic β-carbon of the α,β-unsaturated carbonyl. This breaks the π bond of the alkene, pushing electrons onto the carbonyl oxygen, and generates a new enolate intermediate.

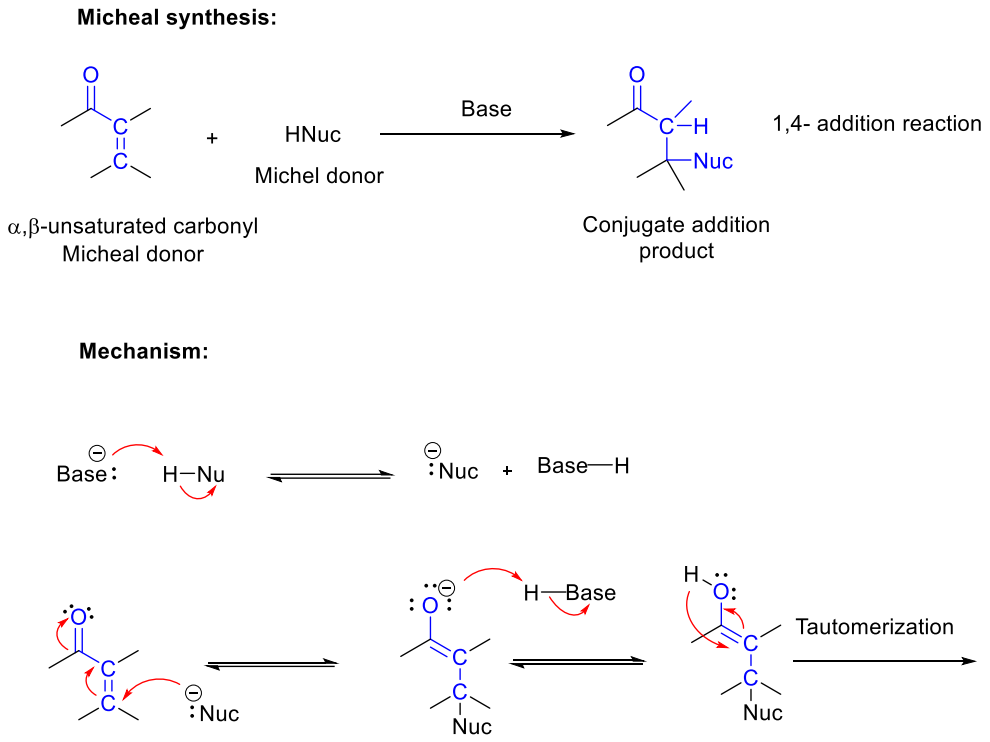
Step 3: protonation

The enolate intermediate is protonated by the solvent or conjugate acid, yielding an enol form of the product.

Step 4: tautomerization

The enol tautomerizes back to the more stable keto form, giving the final conjugate addition product (**Scheme 51**).

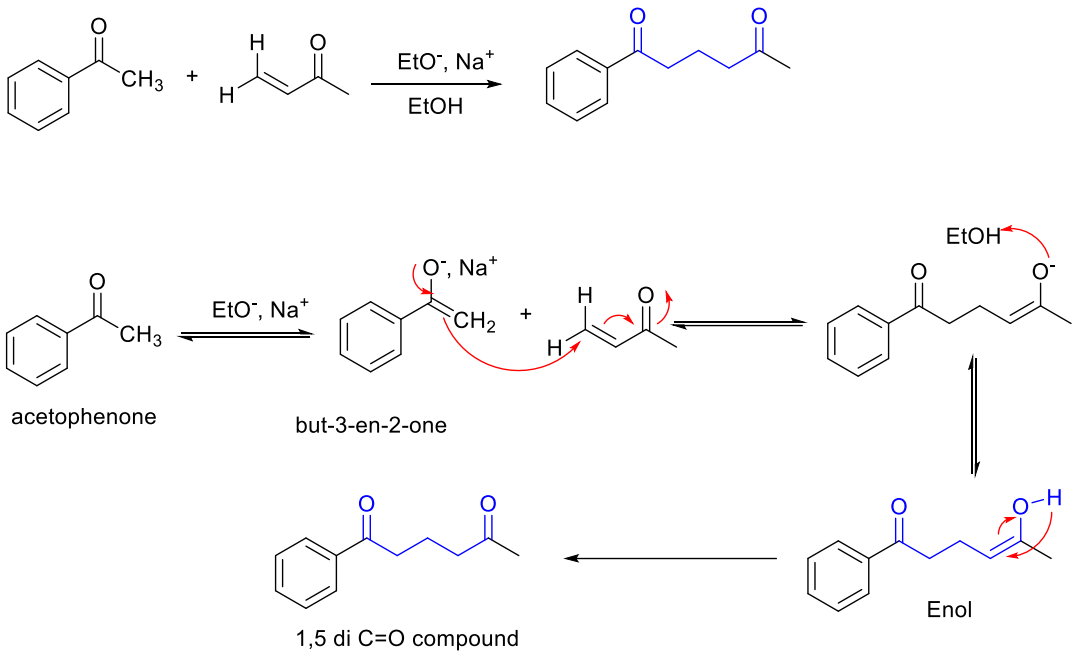
The scope of the Michael reaction is broad. Michael acceptors include α,β-unsaturated ketones, aldehydes, esters, amides, and even nitroalkenes. Michael donors are compounds with acidic α-hydrogens, such as β-diketones, β-keto esters, malonic esters, β-keto nitriles, α-nitro ketones, and nitroalkanes. This versatility makes the reaction a powerful method for constructing C–C bonds and synthesizing 1,5-difunctionalized products, which can undergo further transformations in complex molecule synthesis.



Scheme 51. *General reaction and mechanism of the Michael reaction.*

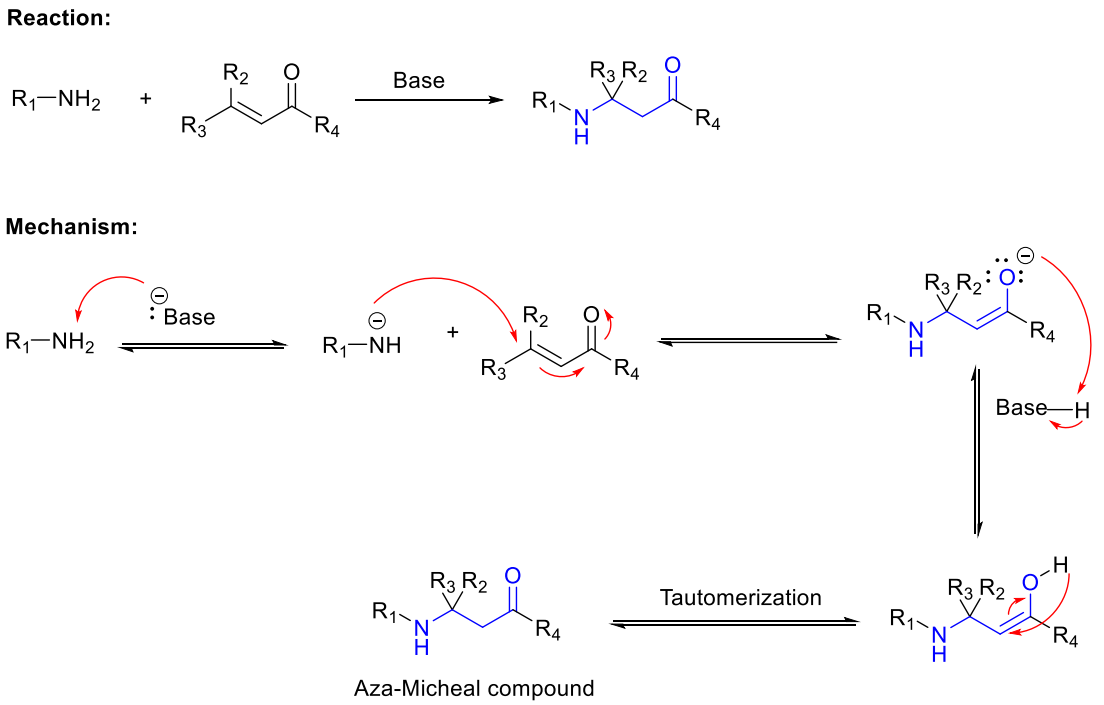
Example :

In this case, acetophenone acts as the Michael donor, and but-3-en-2-one also known as methyl vinyl ketone acts as the Michael acceptor. The base used is sodium ethoxide (NaOEt), which deprotonates the acetophenone at its α-position to form the enolate nucleophile. abstracts the acidic α-hydrogen of acetophenone, generating a resonance-stabilized enolate ion. This enolate serves as the nucleophile. The enolate attacks the electrophilic β-carbon of but-3-en-2-one. This step breaks the C=C π bond of the enone, pushing electrons onto the carbonyl oxygen, and forming a new C–C bond between the α-carbon of acetophenone and the β-carbon of the enone. The result is an enolate intermediate. The negatively charged oxygen of the enolate is protonated by ethanol, forming an enol intermediate. The enol tautomerizes back to the more stable keto form, yielding the final Michael adduct (**Scheme 52**).



Scheme 52. *Example of Michael reaction.*

The **Aza-Michael reaction** is a conjugate addition reaction in which a nitrogen nucleophile, such as a primary or secondary amine, adds across the β-carbon of an α,β-unsaturated carbonyl compound, providing an efficient method to form C–N bonds. The reaction is analogous to the classical Michael addition, except that instead of an enolate donor, the amine donates its lone pair of electrons to attack the electrophilic β-carbon of the conjugated system. In the mechanism, the amine nucleophile attacks the β-carbon of the α,β-unsaturated carbonyl, breaking the C=C π bond and generating a resonance-stabilized carbanion intermediate, which is then protonated by solvent or the conjugate acid of the amine to give a neutral product. The final product is a β-amino carbonyl compound, which can be a β-amino ketone, β-amino ester, or β-amino amide depending on the Michael acceptor. The Aza-Michael reaction is widely applied in organic synthesis because it provides straightforward access to β-amino carbonyl compounds, which are important building blocks in pharmaceuticals, natural products, and heterocyclic synthesis. It also finds applications in polymer chemistry, where multifunctional amines react with acrylates to generate functionalized polymers. Due to its efficiency, mild conditions, and atom economy, the Aza-Michael reaction is also considered an important transformation in green chemistry (**Scheme 53**) [35].



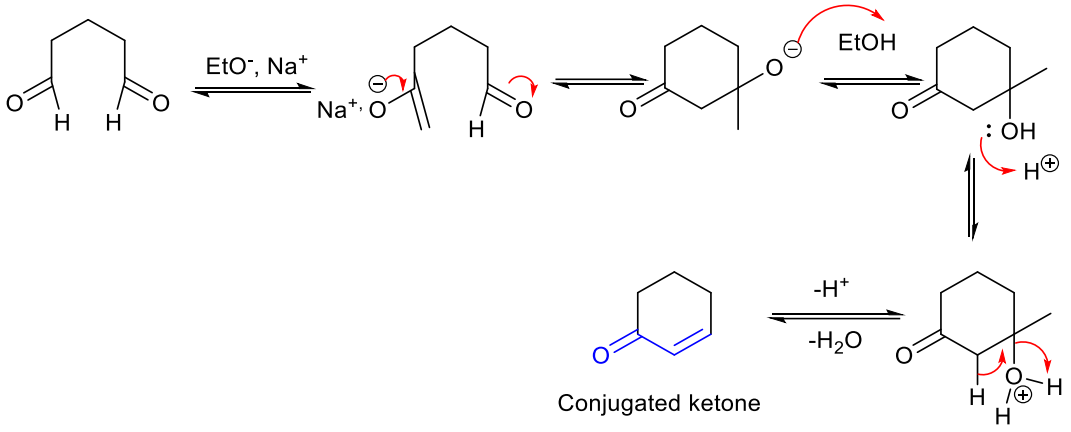
Scheme 53. *General reaction and mechanism of aza-Michael addition.*

11.4. The Robinson annulation

The building of an alicyclic compound from acyclic starting materials can present an interesting challenge to the synthetic organic chemist. One route by which such a synthesis can be achieved is through the use of the Robinson annulation reaction. This reaction, which may at first look very complex, can be readily understood once you realize that it simply involves a Michael reaction followed by an intramolecular aldol condensation. Both of these steps involve attack by enolate anions. The Robinson annulation is a powerful carbon–carbon bond-forming, leading to the construction of six-membered rings fused to another ring or substituent. It is widely used in the synthesis of steroids, terpenes, and other natural products because it efficiently builds complex cyclic structures from relatively simple starting materials.

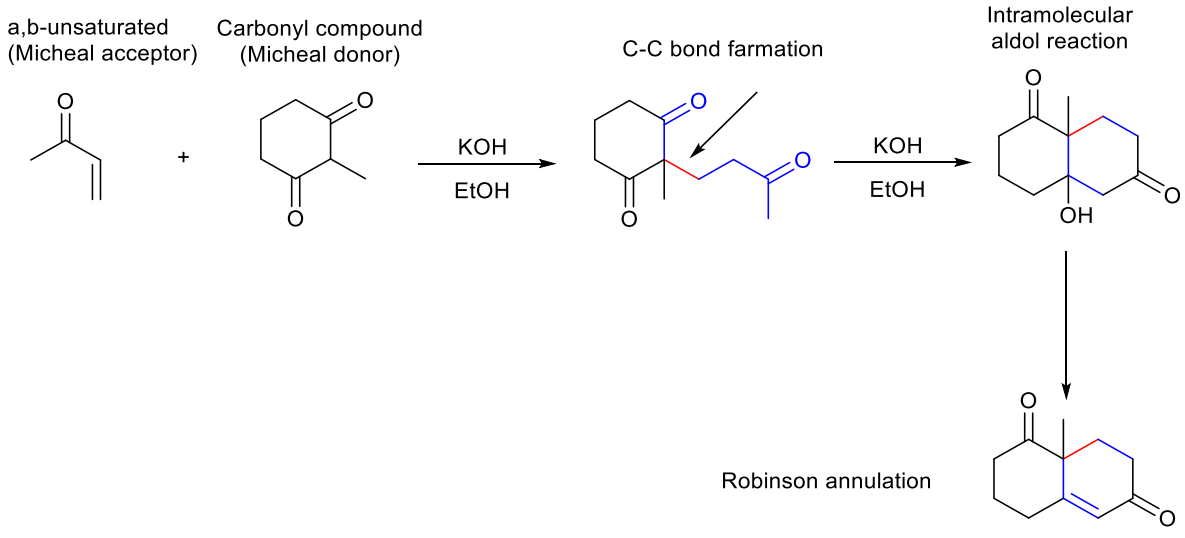
The reaction proceeds under basic conditions, often using sodium hydroxide, potassium hydroxide, or an alkoxide base, sometimes in ethanol or aqueous medium. Many times the product of a Michael addition produces a dicarbonyl which can then undergo an intramolecular aldol reaction. These two processes together in one reaction creates two new carbon-carbon bonds and also creates a ring. Ring-forming reactions are called annulations after the Latin work for ring annulus. The reaction is named after English chemist Sir Robert Robinson who developed it. He received the Nobel prize in chemistry in 1947. Remember that during annulations five and six membered rings are preferred.

The nucleophilic enolate donor is typically an enolate ion or enamine of a cyclic ketone, β-keto ester or β-diketone. The electrophilic acceptor is usually an α, β-unsaturated ketone (**Scheme 54**) [36].



Scheme 54. *Robinson annulation reaction.*

In the example below, 2-methyl-1,3-cyclohexanedione is deprotonated to form an enolate which affects a Michael reaction addition on 3-buten-2-one forming a C-C bond. The product contains a 1,5-diketone fragment which can undergo an intramolecular aldol condensation. This occurs through creation of a new enolate at the methyl ketone which undergoes an intramolecular aldol reaction. A new C-C bond is formed to one of the ring carbonyls, creating a new six-membered ring. In the last step, the resulting alcohol is eliminated to form a α, β-unsaturated ketone as the final Robinson annulation product. Because the Robinson Annulation involves an aldol reaction, a full equivalent of base is required (**Scheme 55**).



Scheme 55. *Application of the Robinson annulation reaction.*

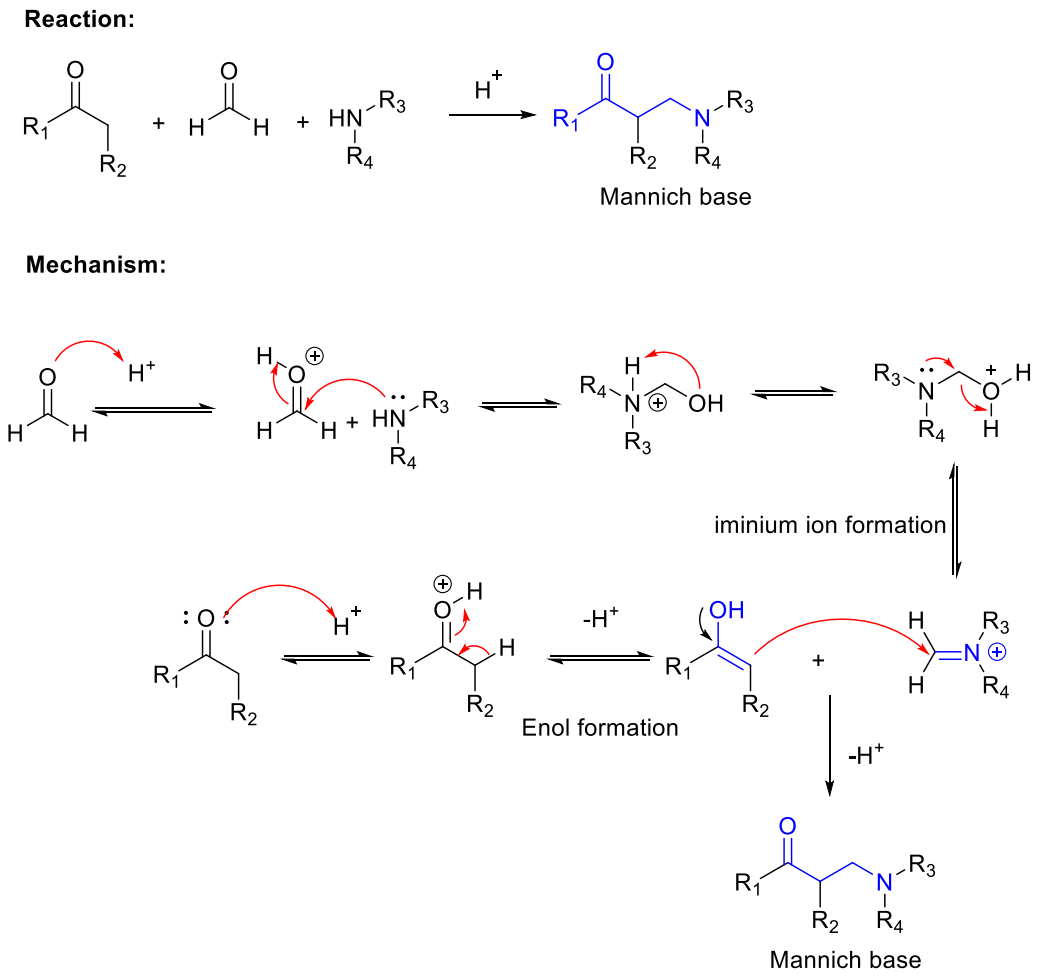
11.5. Mannich reaction

The Mannich reaction is a classical and widely used method for the preparation of β-aminoketones and β-aminoaldehydes, compounds that are commonly referred to as Mannich bases. These compounds are important intermediates in organic synthesis and serve as building blocks in the preparation of natural products, pharmaceuticals, and fine chemicals. The reaction typically involves three components: an enolizable carbonyl compound (such as acetone, acetophenone, or aldehydes with α-hydrogens), formaldehyde (as a reactive methylene source), and a secondary amine (such as dimethylamine, morpholine, or piperidine). The reaction is usually carried out in the presence of an acid catalyst such as aqueous hydrochloric acid, which promotes the formation of the reactive iminium ion intermediate.

The mechanism of the Mannich reaction proceeds through several key steps. First, the secondary amine reacts with formaldehyde under acidic conditions to form an iminium ion ($R_2N^+=CH_2$), which serves as the electrophile in the reaction. At the same time, the enolizable aldehyde or ketone undergoes acid-catalyzed enolization, generating the enol or its corresponding enolate form. In the nucleophilic step, the enol attacks the electrophilic iminium carbon, forming a new C–C bond at the β-position relative to the carbonyl group. This leads to the formation of a β-amino carbonyl intermediate, which upon proton transfers yields the stable Mannich base.

The overall transformation therefore installs an aminomethyl group ($-CH_2NR_2$) at the β-position of a carbonyl compound, providing access to β-aminoketones and β-aminoaldehydes.

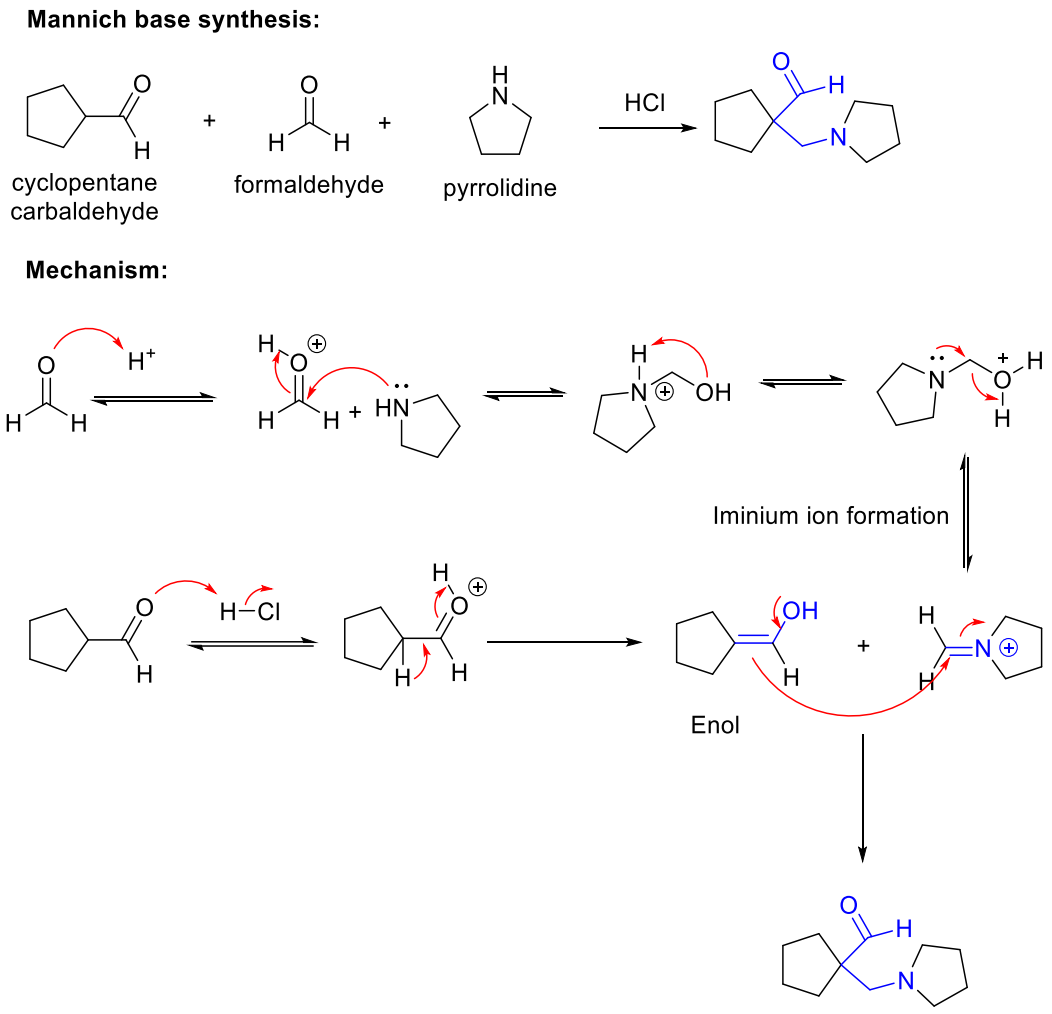
The Mannich reaction is significant because Mannich bases are versatile intermediates that can undergo further transformations such as cyclizations, reductions, or eliminations to yield heterocycles and other valuable molecules. It is also considered one of the earliest examples of a multicomponent reaction (MCR) in organic chemistry, as it combines three simple starting materials in a single operation to yield complex functionalized products (**Scheme 56**) [37].



Scheme 56. *General reaction and mechanism of Mannich reaction.*

Example: Mannich base synthesis.

In this example, cyclopentanecarbaldehyde (an aldehyde with α-hydrogens) serves as the enolizable carbonyl compound, pyrrolidine acts as the secondary amine, and formaldehyde provides the methylene unit. The catalyst is aqueous HCl, which promotes both the formation of the iminium ion and the enolization of the aldehyde. Under acidic conditions, formaldehyde reacts with pyrrolidine to form a protonated iminium ion (pyrrolidinium methylene cation, $R_2N^+{=}CH_2$), which functions as the key electrophilic intermediate. Meanwhile, cyclopentanecarbaldehyde undergoes partial enolization: the α-hydrogen adjacent to the carbonyl group is sufficiently acidic to be removed transiently, giving the nucleophilic enol form. The enol then attacks the electrophilic carbon of the iminium ion, forming a new C–C bond at the β-position relative to the carbonyl group. After subsequent proton transfers and stabilization of intermediates, the final product is a Mannich base, in which a $–CH_2–$N(pyrrolidine) substituent is introduced at the α-position of the carbonyl compound (**Scheme 57**).

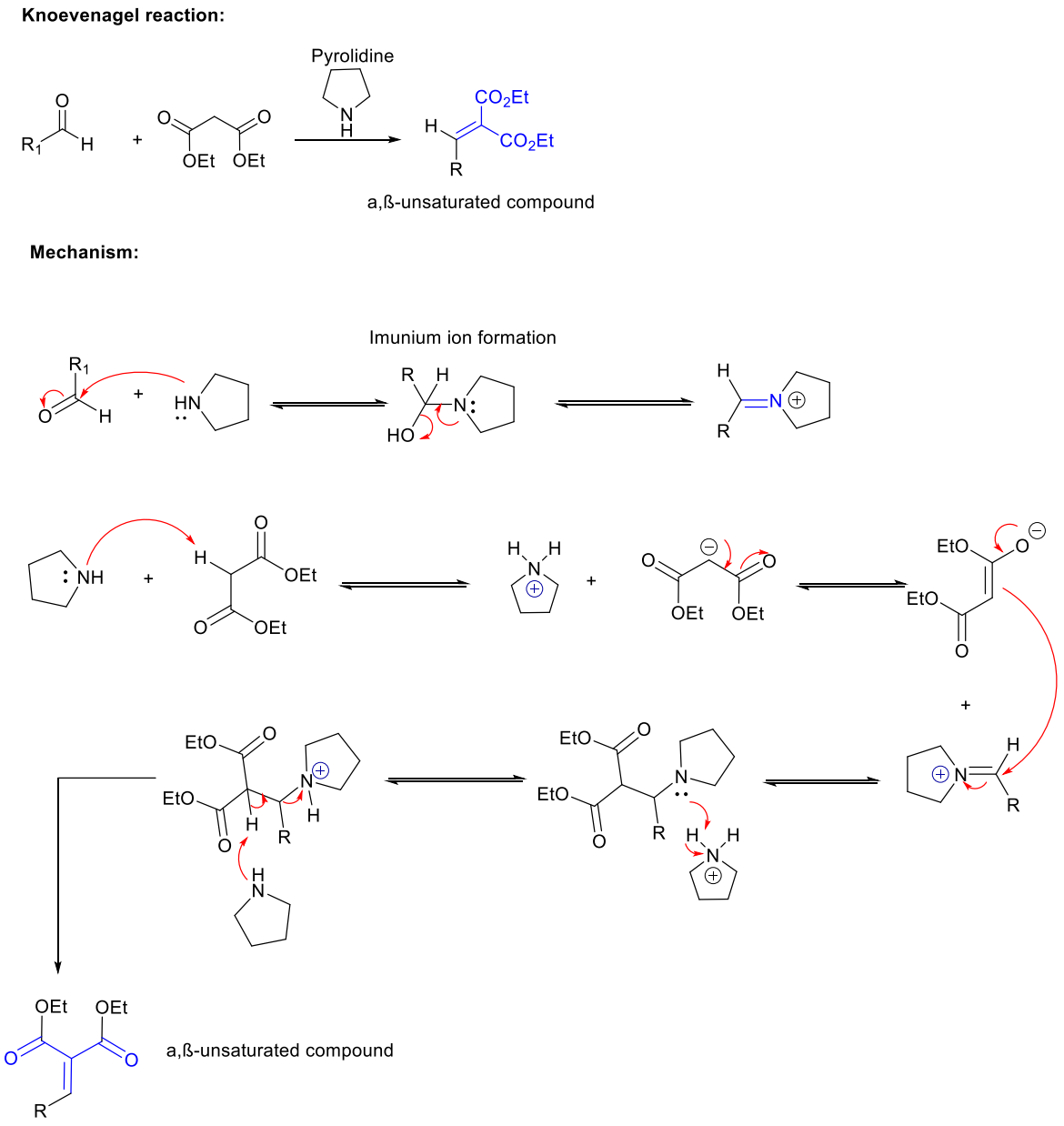


Scheme 57. *Example of Mannich reaction*

11.6. Knoevenagel reaction

The Knoevenagel condensation is an important C–C bond-forming reaction widely applied in organic synthesis for the preparation of α,β-unsaturated carbonyl and related compounds. It involves the condensation of an aldehyde or ketone with an active methylene compound such as malononitrile, ethyl cyanoacetate, diethyl malonate, or β-keto esters, in the presence of a weak base catalyst like piperidine, pyridine, or ammonium salts. The mechanism begins with the deprotonation of the acidic methylene group by the base, generating a resonance-stabilized enolate or carbanion intermediate, which is nucleophilic enough to attack the formed electrophilic iminium ion from the carbonyl carbon of the aldehyde or ketone, forming a β-hydroxy intermediate. Proton transfer steps regenerate the catalyst, and finally, elimination of water occurs through an E1cb mechanism to yield the conjugated α,β-unsaturated product. This transformation is highly useful because it provides access to extended π-conjugated systems, which serve as precursors for heterocycle formation, natural product synthesis, pharmaceuticals,

and advanced functional materials. Moreover, aldehydes generally react more readily than ketones due to their greater electrophilicity and lower steric hindrance, while the reaction efficiency strongly depends on the presence of electron-withdrawing groups on the active methylene compound, which enhance the acidity of the α-protons and stabilize the carbanion compound (**Scheme 58**) [38].

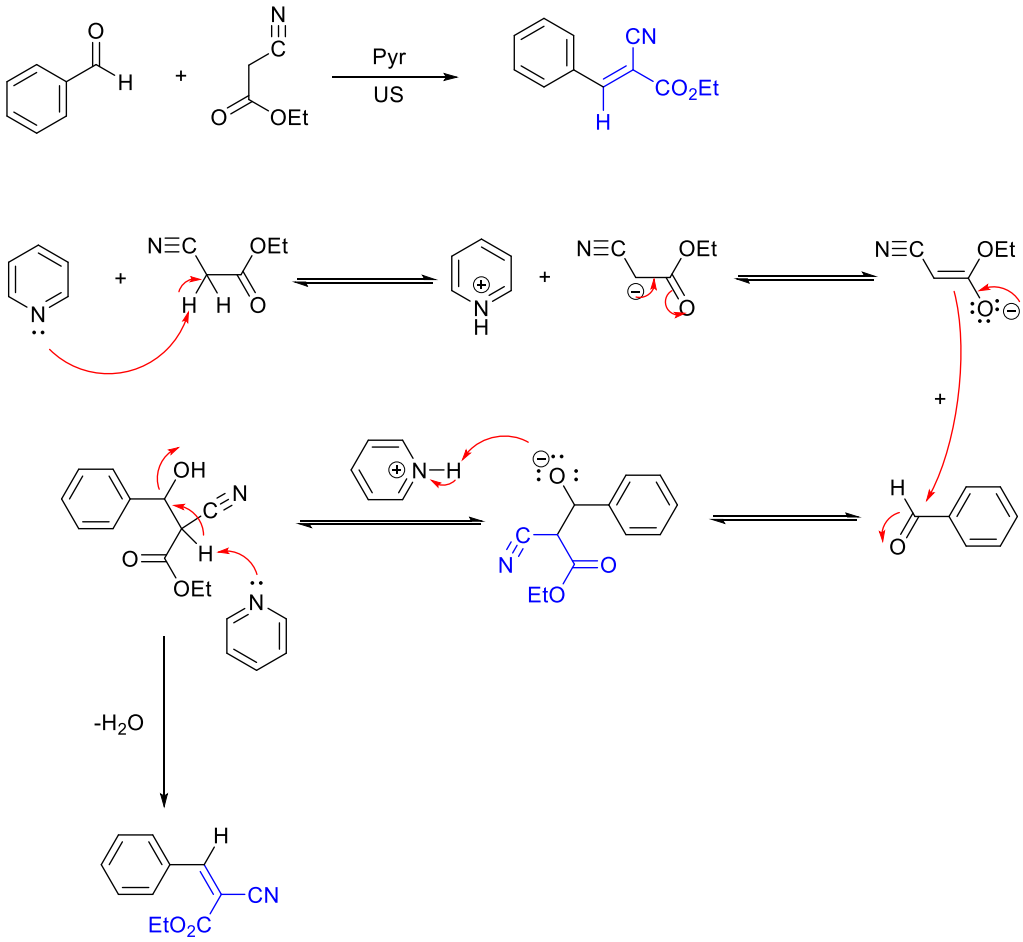


Scheme 58. *General reaction and mechanism of Knoevenagel condensation.*

Example :

The Knoevenagel condensation of ethyl 2-cyanoacetate with benzaldehyde under pyridine catalysis and ultrasonic irradiation proceeds smoothly to give the conjugated product (E)-ethyl 2-cyano-3-phenylacrylate. Mechanistically, pyridine acts as a mild base and general base

catalyst: it deprotonates the acidic methylene of ethyl 2-cyanoacetate to generate a resonance-stabilized enolate (stabilized by both the cyano and ester groups). This nucleophilic species attacks the electrophilic carbonyl carbon of benzaldehyde to form a tetrahedral alkoxide intermediate, which is then protonated by pyridinium to give a β-hydroxy intermediate. Under the reaction conditions the β-hydroxy intermediate undergoes base-promoted dehydration (typically via an E1cb-type step: deprotonation to an anionic species followed by loss of water) to afford the conjugated α,β-unsaturated nitrile-ester product; conjugation and steric factors favor the E (trans) alkene. Ultrasonic irradiation accelerates the transformation by cavitation-induced local heating, enhanced mass transfer and mixing, and improved contact between reagents and catalyst, often allowing lower bulk temperatures, shorter reaction times, higher yields. Typical practical conditions are catalytic pyridine (a few mol %), solvent-free medium, and sonication at room temperature (**Scheme 59**).



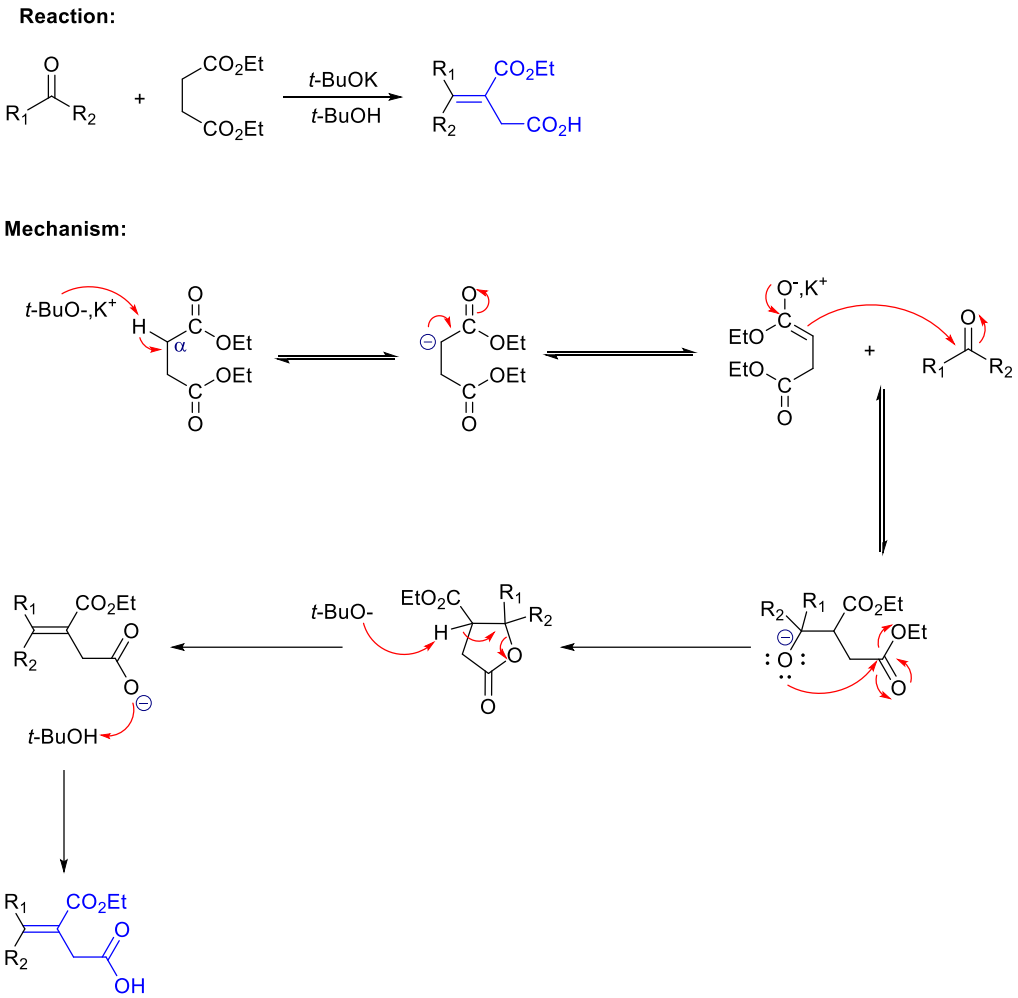
Scheme 59. *Knoevenagel condensation of ethyl 2-cyanoacetate with benzaldehyde under pyridine catalysis and ultrasonic irradiation.*

11.7. Stobbe condensation

The Stobbe condensation is an important reaction between a diethyl ester of succinic acid (or a substituted succinate ester) and an aromatic aldehyde or ketone in the presence of a strong base, typically sodium ethoxide, potassium *tert*-butoxide, or metallic sodium in an alcohol solvent. The reaction provides substituted succinic acid half-esters, which are versatile intermediates in organic synthesis.

Mechanistically, the base first deprotonates one of the methylene hydrogens of the succinate ester to form a resonance-stabilized enolate ion. This nucleophilic enolate then attacks the electrophilic carbonyl carbon of the aldehyde or ketone, forming a tetrahedral alkoxide intermediate. Protonation of these intermediate yields a β-hydroxy succinate derivative. Under the strongly basic conditions, the β-hydroxy compound undergoes intramolecular elimination of ethanol (or the corresponding alcohol) through an E1cb-type mechanism, generating an α,β-unsaturated succinate half-ester. Importantly, the reaction tends to stop at the half-ester stage due to the acidic nature of the remaining ester group, which can undergo deprotonation and stabilize the intermediate. After acidic hydrolysis or neutralization, the final isolated product is usually a γ-substituted succinic acid half-ester ($HOOC–CH_2–CH(CR=CHAr)–CO_2R$).

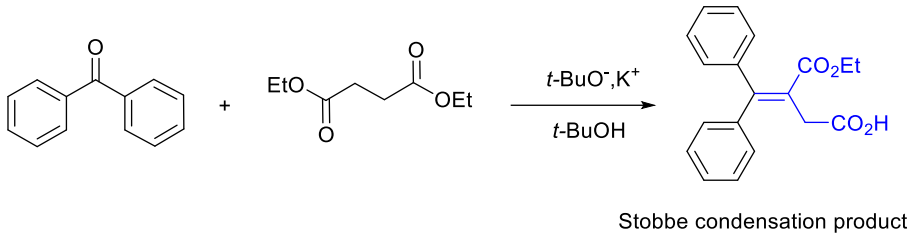
The Stobbe condensation has wide utility because the products unsaturated succinic acid derivatives can be further transformed into cyclic anhydrides, substituted aromatic systems, or heterocycles. It is widely applied in the synthesis of organic intermediates, agrochemicals, natural product derivatives, and dye precursors. For example, condensation of diethyl succinate with benzaldehyde yields a benzylidene-succinic acid half-ester, which can be cyclized to form phthalic derivatives. A key advantage of the Stobbe condensation is its regioselectivity: the succinate ester always acts as the enolate donor, while the aldehyde or ketone acts as the acceptor (**Scheme 60**) [39].



Scheme 60. *General reaction and mechanism of Stobbe condensation.*

In the case of acetophenone and diethyl succinate using potassium *t*-butoxide in *t*-butanol, the reaction proceeds as follows: the strong, non-nucleophilic base *t*-BuOK first deprotonates the methylene group situated between the two ester groups of diethyl succinate, generating a resonance-stabilized succinate enolate. This enolate acts as the nucleophilic partner and attacks the carbonyl carbon of acetophenone, producing a new C–C bond and forming a tetrahedral alkoxide intermediate. Proton transfer from the solvent converts this alkoxide into a neutral β-hydroxy succinate derivative, analogous to an aldol-type adduct. Under the strongly basic conditions, the β-hydroxy intermediate undergoes deprotonation at the position adjacent to the hydroxyl group, followed by elimination of ethoxide, which collapses to give a conjugated alkylidene succinate product. The resulting anionic half-ester is stabilized by conjugation and resonance. Upon acidic workup, the final isolated compound is a γ-substituted succinic half-ester, specifically a monoester/monoacid derivative in which the acetophenone fragment is introduced at the γ-position relative to the succinate framework. This outcome reflects the hallmark of the Stobbe condensation: selective formation of a half-ester product rather than a diester, driven by

the ease of deprotonation and the irreversible stabilization of the half-ester anion. Thus, the reaction of acetophenone with diethyl succinate under *t*-BuOK/*t*-BuOH conditions provides a γ-substituted succinic monoester through a sequence of enolate generation, nucleophilic addition, β-hydroxy elimination, and acidic workup (**Scheme 61**).



Scheme 61. *Stobbe condensation of acetophenone with diethylsuccinate.*

11.8. Darezens reaction

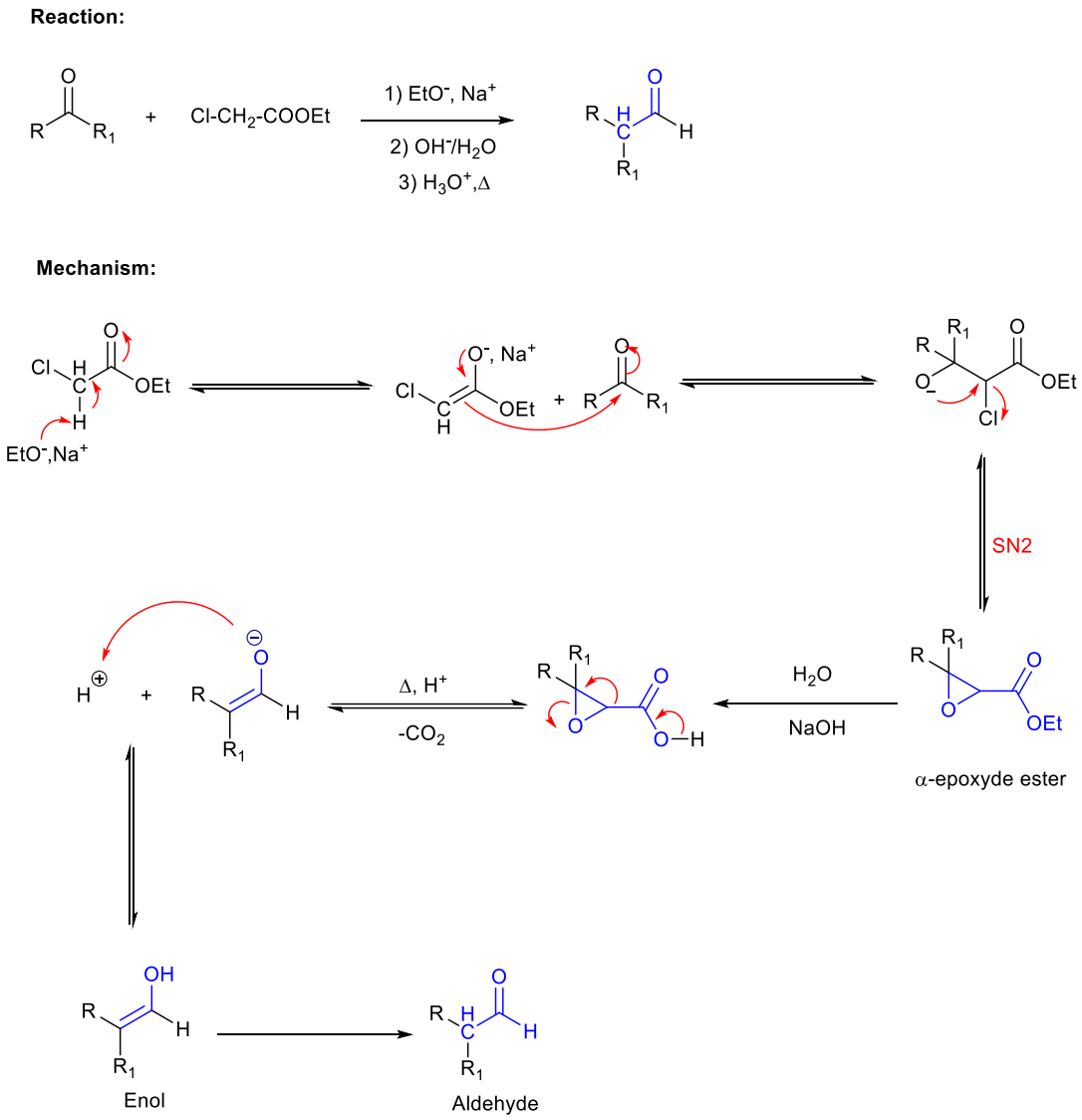
The Darzens reaction (also called the Darzens condensation or glycidic ester condensation) is a powerful method in organic synthesis that allows the conversion of ketones or aldehydes into α,β-epoxy esters (glycidic esters), which upon hydrolysis and decarboxylation yield aldehydes or ketones extended by one carbon atom. The overall transformation is particularly valuable because it enables homologation of a carbonyl compound, i.e., the introduction of an extra carbon atom adjacent to the carbonyl group, a transformation that is otherwise difficult to achieve directly.

Mechanistically, the Darzens reaction begins with the generation of an enolate from an ester (most often an α-haloester) under basic conditions such as sodium alkoxide. For example, the α-haloester is treated with base, which abstracts the acidic α-hydrogen, producing an ester enolate stabilized by resonance. This enolate then undergoes nucleophilic attack on the carbonyl carbon of a ketone or aldehyde, forming a tetrahedral alkoxide intermediate. Intramolecular cyclization subsequently occurs when the alkoxide displaces the halide substituent intramolecularly, closing the three-membered epoxide ring and producing the glycidic ester. The product at this stage is an α,β-epoxy ester, which is a versatile intermediate because the strained epoxide ring and the adjacent ester group make it reactive towards further transformations.

Upon treatment with aqueous base (e.g., sodium hydroxide, “soda”), the glycidic ester undergoes hydrolysis to the corresponding acid, followed by decarboxylation. At the same time, cleavage of the epoxide and rearrangement yield an aldehyde containing one more carbon atom than the starting ketone. This sequence illustrates the importance of the Darzens reaction: a ketone or

aldehyde can be extended to a homologated aldehyde through a predictable and efficient pathway.

A key discussion point is the synthetic utility of the Darzens reaction. The glycidic ester intermediate is not only a stepping stone to aldehydes but can also be used in further transformations, such as nucleophilic ring opening, reductive cleavage, or rearrangement to yield β-hydroxy carbonyl compounds or α,β-unsaturated systems. The reaction is also stereoselective in some cases, as the formation of the epoxide can generate cis- or trans-glycidic esters depending on the geometry of the enolate addition. Furthermore, the choice of base, solvent, and α-haloester strongly influences the yield and selectivity of the reaction (**Scheme 61**) [40].



Scheme 61. *Darzens condensation.*

11.9. Reformatsky reaction

The Reformatsky reaction is a classical reaction that provides an efficient route to β-hydroxy esters (hydroxyesters) through the condensation of an α-haloester with an aldehyde or ketone in the presence of metallic zinc. It is an important transformation in organic synthesis because it allows the construction of β-hydroxy esters under relatively mild and controlled conditions, avoiding the harsh reactivity and poor selectivity often associated with Grignard or organolithium reagents. The key feature of the Reformatsky reaction lies in the generation of a zinc enolate intermediate, which behaves as a nucleophilic species that can add to the carbonyl carbon of aldehydes or ketones.

Mechanistically, the reaction proceeds through several well-defined steps. First, activation of zinc occurs when metallic zinc reacts with the α-haloester (such as ethyl bromoacetate or ethyl chloroacetate), inserting into the C–H bond via a single-electron transfer process. This oxidative addition produces a zinc enolate complex ($EtO_2C–CHZnX$), in which the carbon adjacent to the carbonyl becomes nucleophilic. The zinc enolate is resonance-stabilized by the carbonyl group and remains relatively mild compared to Grignard reagents because the C–Zn bond is more covalent and less polar than a C–Mn bond. This makes it compatible with a broader range of functional groups and reduces the likelihood of overreaction or polymerization.

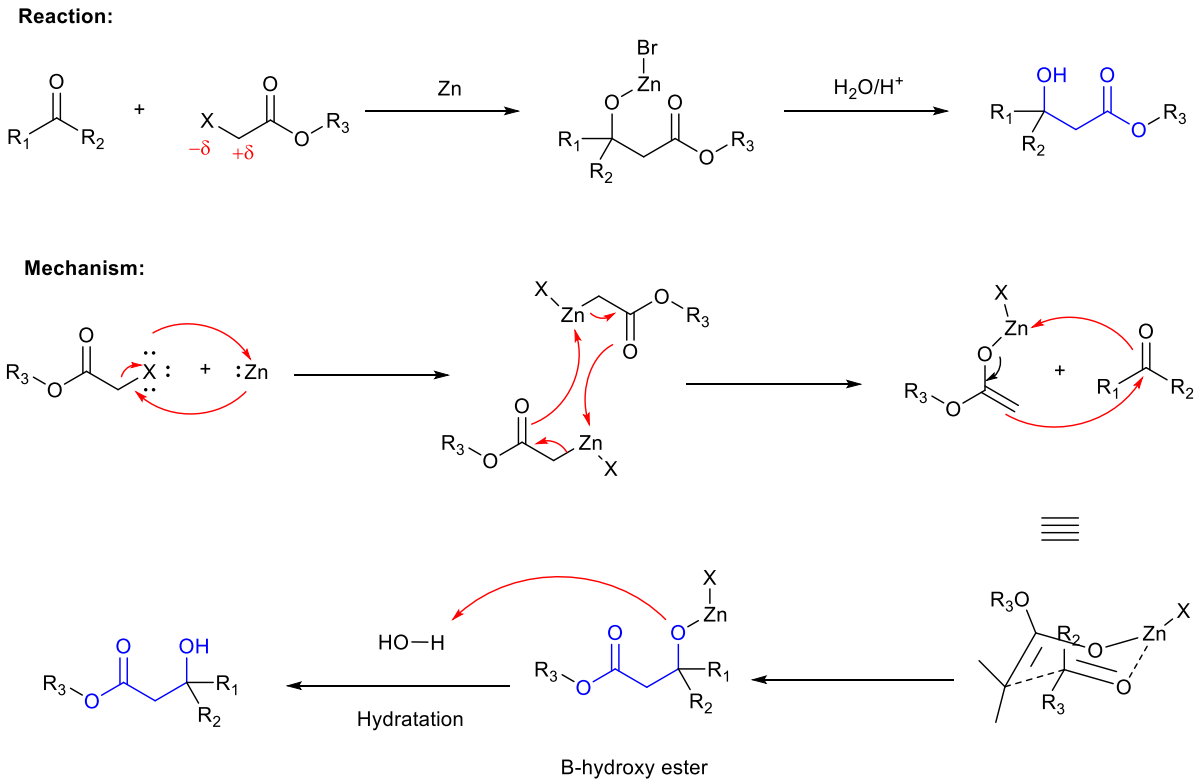
In the second step, the nucleophilic addition takes place. The carbon center of the zinc enolate attacks the electrophilic carbonyl carbon of an aldehyde or ketone, forming a new C–C bond and generating a zinc alkoxide intermediate. The transition state of this step often involves a six-membered cyclic structure stabilized by coordination of zinc with both oxygen atoms (from the ester and the carbonyl), which explains the reaction's relatively high diastereoselectivity in certain cases. After the C–C bond formation, the intermediate rearranges to a stable zinc alkoxide complex.

Finally, during acidic or aqueous workup, the zinc alkoxide intermediate is protonated to yield the desired β-hydroxy ester. The product features a hydroxyl group at the β-position relative to the ester function, a pattern characteristic of the Reformatsky reaction. If desired, subsequent dehydration of the β-hydroxy ester under acidic conditions can lead to α,β-unsaturated esters, providing further synthetic versatility.

The reaction conditions play an essential role in determining the outcome. Solvents such as benzene, toluene, or diethyl ether are commonly used to maintain the reactivity of the organozinc species, while activation of zinc (e.g., by iodine, acid washing, or ultrasonic agitation) ensures

efficient insertion into the α-haloester. Aldehydes typically react faster than ketones because of their greater electrophilicity and lower steric hindrance.

The Reformatsky reaction exemplifies a mild, selective, and reliable method for forming β-hydroxy esters via the addition of a zinc enolate to a carbonyl compound. It represents an elegant balance between reactivity and control: the zinc enolate is reactive enough to form new carbon–carbon bonds but sufficiently stable to allow chemoselective addition to carbonyl groups without unwanted side reactions. This reaction remains an indispensable tool in synthetic organic chemistry for the preparation of key intermediates in natural product synthesis, pharmaceuticals, and fine chemicals [41] (**Scheme 62**).



Scheme 62. *General synthesis of β-hydroxy esters via Reformatsky reaction.*

Example:

Below is a concrete example of the Reformatsky reaction of propionaldehyde with ethyl 2-bromoacetate, presented as two practical variants; a classical (thermal / Zn-activated) procedure and an ultrasound-assisted procedure together with the mechanistic outline, expected product identity, and practical notes. The net transformation installs the –CH_2CO_2Et fragment on the aldehyde to give the β-hydroxy ester ethyl 3-hydroxybutanoate, normally obtained as a racemic mixture at the newly formed stereocenter.

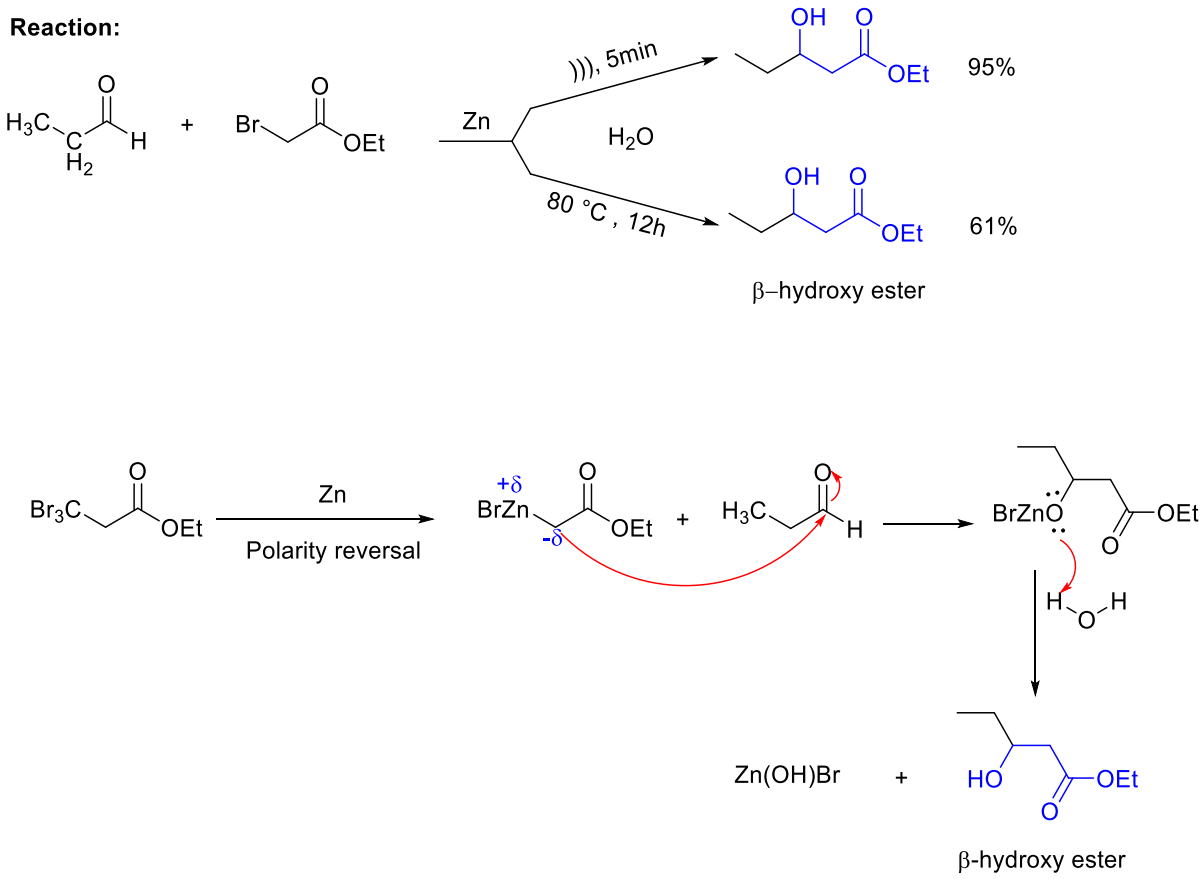
Classical (thermal, Zn-mediated) procedure: in a dry three-neck flask under N_2, add Zn dust activated by brief washing with dilute HCl, rinsing, and drying and anhydrous THF. Charge with ethyl 2-bromoacetate and stir at 0 °C room temperature for 30–60 min to allow oxidative insertion of Zn into the C–Br bond and generation of the zinc enolate. Cool to 0 °C and add a solution of propionaldehyde in THF; allow the mixture to warm to 0 °C–rt and stir 1–3 h. After consumption of the aldehyde, quench carefully with saturated NH_4Cl and then add water; extract with ethyl acetate, wash organic layers with brine, dry over Na_2SO_4, filter and concentrate. isolate ethyl 3-hydroxybutanoate. Mechanistically the key events are: Zn insertion into $BrCH_2CO_2Et$ to give the zinc enolate, after a nucleophilic attack of the enolate carbon at the aldehyde carbonyl (often via a Zn-coordinated six-membered transition state), forming a zinc alkoxide, and (3) aqueous workup to protonate the alkoxide to the β-hydroxy ester.

Ultrasound-assisted variant: sonication often accelerates Reformatsky reactions by improving contact between zinc and substrate and by activating zinc surface without harsh chemical activation. In a suitable sonication vessel (probe or bath), combine Zn dust and ethyl 2-bromoacetate in THF. Sonicate the suspension for 10–30 min at rt to promote Zn insertion and enolate formation; then add propionaldehyde and continue sonication for an additional 10–60 min. After completion, quench with saturated NH_4Cl, extract with ethyl acetate, wash, dry, concentrate and purify as above. Sonochemical conditions typically shorten reaction times and may eliminate the need for chemical activation of zinc, yielding the β-hydroxy ester in comparable or sometimes improved yield and cleaner crude mixtures. Practical tips: avoid prolonged high-power sonication that causes solvent heating or foaming; use appropriate vessel and cooling; scale-up with sonication requires care and validation.

Mechanistic summary (applies to both methods): (1) Zn inserts into the C–Br bond of ethyl 2-bromoacetate to form a zinc enolate ($EtO_2C–CH_2–ZnBr$), a nucleophilic species stabilized by the ester group; (2) the carbon of the zinc enolate attacks the electrophilic carbonyl carbon of propionaldehyde, often through a Zn-chelating transition state that orients both oxygens, giving a zinc alkoxide complex; (3) aqueous acidic workup protonates the alkoxide, releasing the β-hydroxy ester, ethyl 3-hydroxybutanoate (**Scheme 63**).

The Reformatsky reaction with simple aldehydes typically gives moderate to good yields of the β-hydroxy ester when zinc is fresh/activated and moisture/oxygen are minimized; ultrasound often reduces reaction time and may improve zinc activation and reproducibility. Side reactions can include aldol condensation of the aldehyde (minimized by low temperature and rapid

addition), over-reduction of aldehyde by zinc (rare with properly activated Zn), and formation of small amounts of diester/oligomeric byproducts. Workup and purification (aqueous quench, extraction, silica gel chromatography) typically provide the product as a clear oil or crystalline solid depending on scale and purity [42].



Scheme 63. *Synthesis of β-hydroxy esters via Reformatsky reaction using ultrasound irradiation.*

11.10. Wittig reaction

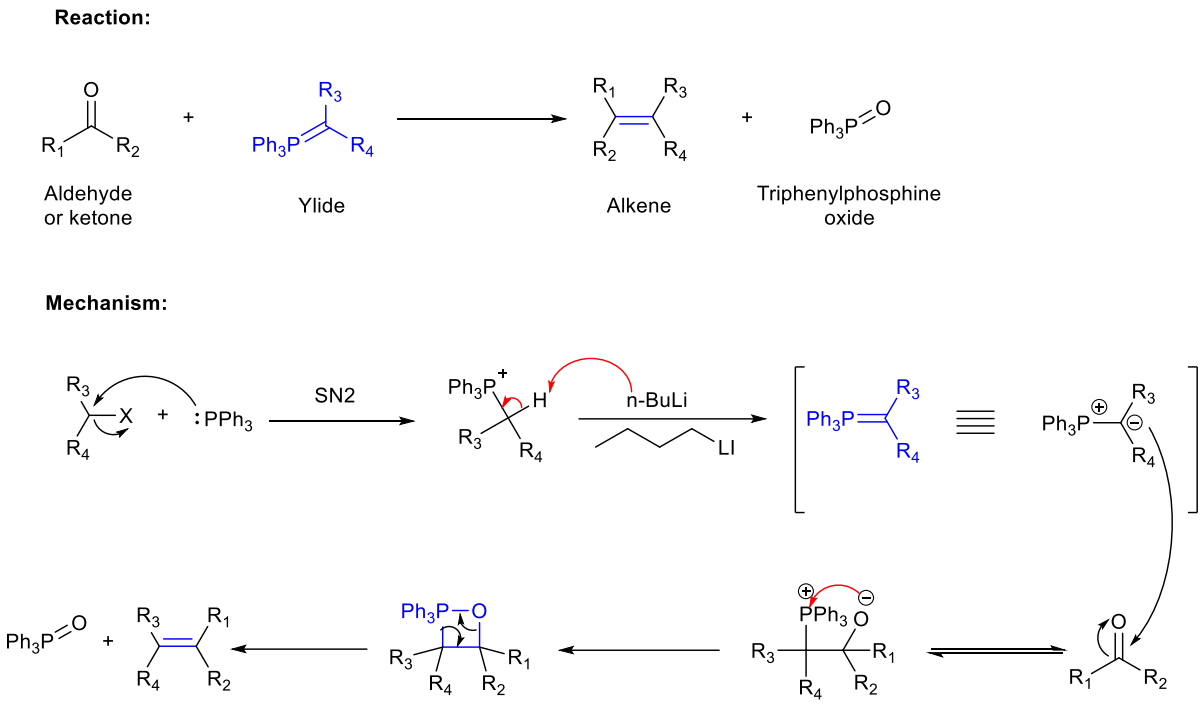
The Wittig reaction is one of the most powerful and versatile methods for the formation of carbon–carbon double bonds (alkenes) in organic synthesis. It involves the reaction between an organophosphorus ylide (also called a Wittig reagent) and a carbonyl compound (aldehyde or ketone) to yield a substituted alkene and triphenylphosphine oxide as a byproduct. This reaction, discovered by Georg Wittig in 1954, earned him the Nobel Prize in Chemistry in 1979 for his pioneering contribution to synthetic organic chemistry. A key advantage of the Wittig reaction is that it allows precise control over the position of the double bond, in contrast to the often unpredictable mixtures obtained through dehydration of alcohols.

The Wittig reaction is based on the unique reactivity of phosphonium ylides, which are dipolar organophosphorus compounds containing adjacent atoms bearing opposite charges but complete octets. Phosphorus stabilizes the carbanionic center of the ylide through p–d orbital overlap (π-character), enabling resonance structures such as $Ph_3P^+–CH^-$ ↔ $Ph_3P=CH_2$. This stabilization increases the acidity of the α-hydrogen (pKa ≈ 35), making it possible to generate ylides using very strong bases like n-butyllithium or sodium hydride. Because these ylides are highly basic and moisture-sensitive, they must be handled under anhydrous, inert conditions. Water or alcohols decompose phosphonium ylides to hydrocarbons and phosphine oxides.

Ylides are typically prepared from alkyl halides and triphenylphosphine via an SN2 reaction, producing a phosphonium salt, which is subsequently deprotonated by a strong base to yield the ylide. The reaction is most efficient with methyl and primary alkyl halides, while secondary halides often give lower yields due to steric hindrance. Once formed, the ylide acts as a nucleophile, capable of attacking the electrophilic carbonyl carbon of aldehydes or ketones to form a new carbon–carbon bond.

Mechanistically, the Wittig reaction proceeds through four fundamental steps. First, the phosphonium ylide is generated by reacting triphenylphosphine with an alkyl halide, followed by deprotonation with a strong base. In the second step, the nucleophilic carbon of the ylide attacks the electrophilic carbonyl carbon, producing a betaine intermediate a charge separated species bearing both negatively charged oxygen and positively charged phosphorus centers. The third step involves cyclization of this betaine to form a four-membered oxaphosphetane intermediate, in which the phosphorus atom is bonded to the oxygen of the original carbonyl group. Finally, in the fourth step, the oxaphosphetane decomposes, yielding the desired alkene and triphenylphosphine oxide ($Ph_3P=O$). This last step is exothermic and irreversible, driven by the strong thermodynamic stability of the P=O bond.

Two intermediates betaine and oxaphosphetane are generally observed in this reaction, depending on the nature of the substrates and reaction conditions. The formation of the alkene is stereospecific: stabilized ylides (bearing electron-withdrawing groups) often give E-alkenes, while unstabilized ylides tend to produce Z-alkenes. Overall, the Wittig reaction provides an elegant and predictable method for alkene synthesis, with exceptional control over regio- and stereochemistry, making it an indispensable transformation in the construction of complex organic molecules (**Scheme 64**) [43].



Scheme 64. *General synthesis and mechanism of Wittig reaction.*

11.11. Nef reaction

The Nef reaction is a classic organic transformation that converts a nitro compound specifically the salt of a nitroalkane anion into a carbonyl compound (either an aldehyde or a ketone) under acidic conditions. This reaction was first discovered by John Ulric Nef in 1894, and it represents one of the most important methods for transforming nitroalkanes into carbonyl derivatives. The general process involves the hydrolysis of a nitronate salt, typically formed by deprotonating a primary or secondary nitroalkane with a base, followed by acidic workup that leads to cleavage of the C–N bond and formation of the carbonyl group. The overall transformation is thus a redox-neutral conversion of $RCH_2NO_2 \rightarrow RCHO$ and $R_2CHNO_2 \rightarrow R_2C{=}O$, depending on whether the nitro compound is primary or secondary.

Mechanistically, the Nef reaction proceeds in several key stages. First, the formation of the nitronate anion occurs when a primary or secondary nitroalkane is treated with a strong base such as sodium ethoxide or sodium hydroxide. The base abstracts an acidic α-hydrogen adjacent to the nitro group, generating a resonance-stabilized nitronate ion ($RCH{=}NO_2^- \leftrightarrow R{-}C(=NO_2^-){-}H$). The nitronate can be isolated as a salt (e.g., sodium or potassium nitronate) under basic conditions.

In the second step, upon acidic hydrolysis (using concentrated sulfuric acid, hydrochloric acid, or other strong acids), the nitronate anion is protonated at oxygen, forming a nitronic acid

intermediate (RCH(OH)NO). This unstable species rapidly undergoes tautomerization to the aci-nitro form, which features a C=N–OH structure. Protonation and rearrangement steps lead to the cleavage of the N–O bond, generating a nitrosyl cation (NO^+) and a carbocationic intermediate at the carbon previously bearing the nitro group.

In the third step, water acts as a nucleophile, attacking the carbocation to form a geminal diol intermediate ($RCH(OH)_2$). Subsequent loss of water from this intermediate leads to the formation of the final carbonyl compound an aldehyde if the starting nitroalkane was primary, or a ketone if the nitroalkane was secondary. Tertiary nitroalkanes do not undergo the Nef reaction because they lack an α-hydrogen necessary for nitronate formation.

A simplified overall sequence for a primary nitro compound (e.g., nitroethane → acetaldehyde) is as follows:

Deprotonation: $CH_3CH_2NO_2 + NaOH \rightarrow CH_3CHNO_2^- Na^+ + H_2O$

Acidic protonation: $CH_3CHNO_2^- + H^+ \rightarrow CH_3CH(OH)NO$ (nitronic acid)

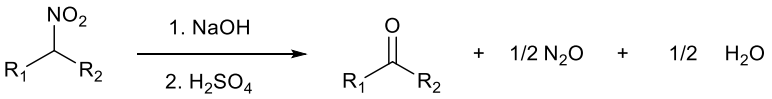
Rearrangement and cleavage: $CH_3CH(OH)NO \rightarrow CH_3CHO + HNO$

Product formation: acetaldehyde and nitrous oxide (or related nitrogen oxide species) form as final products.

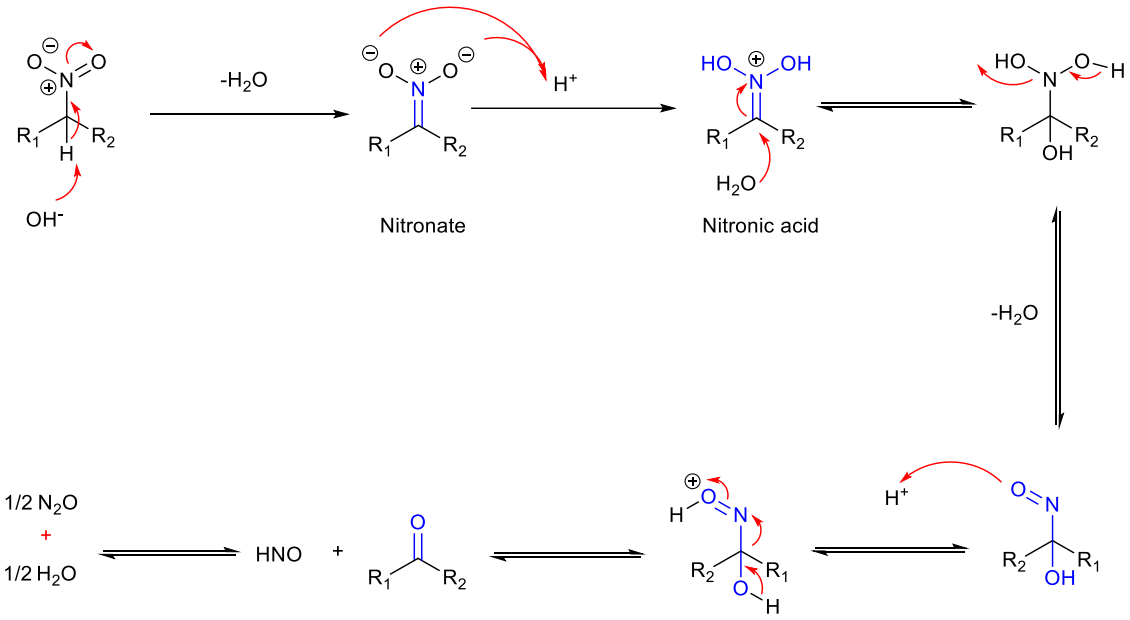
The Nef reaction is particularly valuable in multistep synthesis because it allows nitro compounds which are readily accessible from alkanes via nitration or from halides via substitution to act as synthetic equivalents of acyl anions. In effect, the nitro group serves as a “masked carbonyl” that can later be unveiled under controlled conditions.

In modern practice, the reaction can be carried out under either classical acidic conditions (H_2SO_4, HCl) or milder oxidative conditions, using reagents such as ozone, peracids, or metal oxidants, which enable the transformation of nitronate salts to carbonyl compounds without harsh acid treatment. Ultrasound or microwave irradiation has also been reported to enhance the rate and yield of the reaction by improving mass transfer and activation (**Scheme 65**) [44].

Reaction:



Mechanism:



Scheme 65. *General synthesis and mechanism of Nef reaction.*

12. Radical substitution reactions on saturated carbon

Radical substitution reactions on saturated carbon atoms are a fundamental class of organic reactions in which a hydrogen atom on an alkane or saturated hydrocarbon is replaced by another atom or group through a free-radical mechanism. These reactions typically occur under the influence of heat, light (UV radiation), or radical initiators such as peroxides, which generate highly reactive radical species.

12.1. Halogenation of alkanes

The most well-known example of this process is the **halogenation of alkanes** (**Scheme 66**), where halogen atoms (Cl, Br) substitute for hydrogen atoms on saturated carbons, forming alkyl halides.

The mechanism of radical substitution proceeds through three main stages: initiation, propagation, and termination.

Initiation: in this first step, homolytic cleavage of a covalent bond occurs to generate free radicals. For example, when chlorine gas is exposed to ultraviolet light, the Cl–Cl bond breaks to produce two chlorine radicals:

$Cl_2 \rightarrow 2Cl\bullet$

These chlorine atoms are highly reactive and serve as the initiating species for the substitution process.

Propagation: the chain reaction begins when the chlorine radical abstracts a hydrogen atom from an alkane (RH), forming hydrogen chloride and an alkyl radical (R•):

$Cl\bullet + RH \rightarrow HCl + R\bullet$

The newly formed alkyl radical is also highly reactive and reacts with another molecule of chlorine to form the alkyl halide (RCl) and regenerate a new chlorine radical:

$R\bullet + Cl_2 \rightarrow RCl + Cl\bullet$

These two propagation steps create a self-sustaining chain reaction in which the radicals are continuously regenerated.

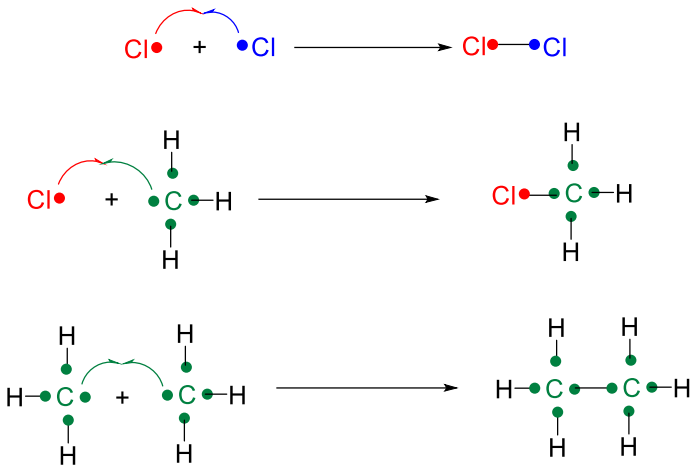
Termination: the reaction is terminated when two radicals combine to form a stable molecule, effectively removing radicals from the system. Typical termination steps include:

$R\bullet + R\bullet \rightarrow R–R$

$R\bullet + Cl\bullet \rightarrow RCl$

$Cl\bullet + Cl\bullet \rightarrow Cl_2$

In the final step, free radicals combine and form new molecules. In this case, either two chlorine-free radicals combine to give dichlorine, a chlorine-free radical combines with an alkyl radical, or two alkyl radicals combine to form a higher alkane [45].



Scheme 66. *Halogenation mechanism of alkanes.*

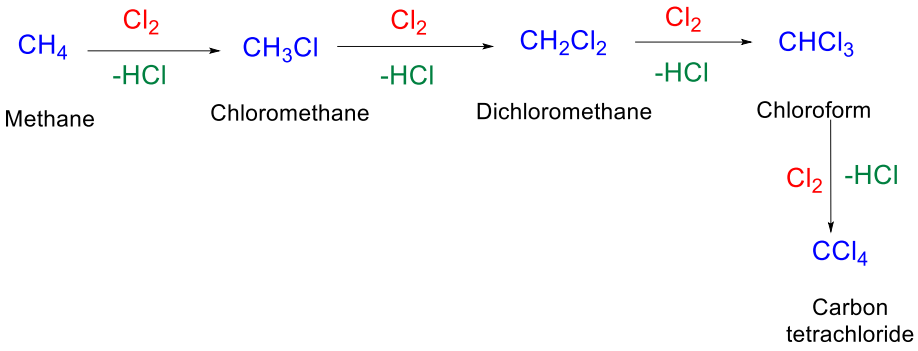
The overall result of these steps is the replacement of a hydrogen atom in an alkane by a halogen atom, with the formation of hydrogen halide as a byproduct. The reaction is exothermic but requires initiation energy (e.g., UV light or heat) to start the radical chain process.

Radical substitution is non-selective for small alkanes but becomes more selective with bromine than with chlorine due to the difference in bond dissociation energies and radical stabilities. For instance, bromination is more controlled and favors substitution at the more substituted (tertiary or secondary) carbon because bromine radicals are less reactive and more selective. In contrast, chlorination is faster but less selective, often producing a mixture of mono-, di-, and poly-halogenated products.

12.1.1. Control of free radical halogenation

Free radical halogenation of alkanes is a chain reaction that, if not carefully controlled, can lead to multiple substitutions rather than a single halogen substitution. This occurs because the halogenated product formed in the first step can still contain hydrogen atoms that are susceptible to further halogenation. For example, when methane undergoes chlorination, the initial product is chloromethane (CH_3Cl). However, this chloromethane can undergo additional substitution reactions to form dichloromethane (CH_2Cl_2), which in turn can be further chlorinated to produce chloroform ($CHCl_3$), and finally carbon tetrachloride (CCl_4). To control the extent of halogenation and obtain mainly monosubstituted products, conditions such as limiting the concentration of the halogen, controlling reaction temperature, or using an excess of the

hydrocarbon are employed. These measures reduce the probability of secondary reactions and help in achieving selective substitution (**Scheme 67**).



Scheme 67. *Control of free radical halogenation.*

12.1.2. Relative reactivity and selectivity of halogens

Although both bromine and chlorine undergo free radical halogenation, they do not behave in the same way and give different yields for the same products. This differentiation is related to the relative selectivity of each halogen. For instance, methane reacts with bromine in a similar way to chlorine and produces bromomethane, methylene bromide, bromoform, and carbon tetrabromide.

However, in contrast to chlorination, bromination is a slower reaction due to the stability of free radical bromine, which is maintained by the bromine polarizability. As a result, more energy must be provided to bromine to surpass the activation energy barrier and generate bromine free radicals. The diagrams below illustrate the difference between chlorination and bromination of methane. The activation energy of chlorination is smaller than the activation energy of bromination. In addition, chlorination of alkanes is an exothermic reaction where the products are more stable than the starting material. In contrast, bromination is an endothermic reaction that requires more energy to proceed (**Figure 7**).

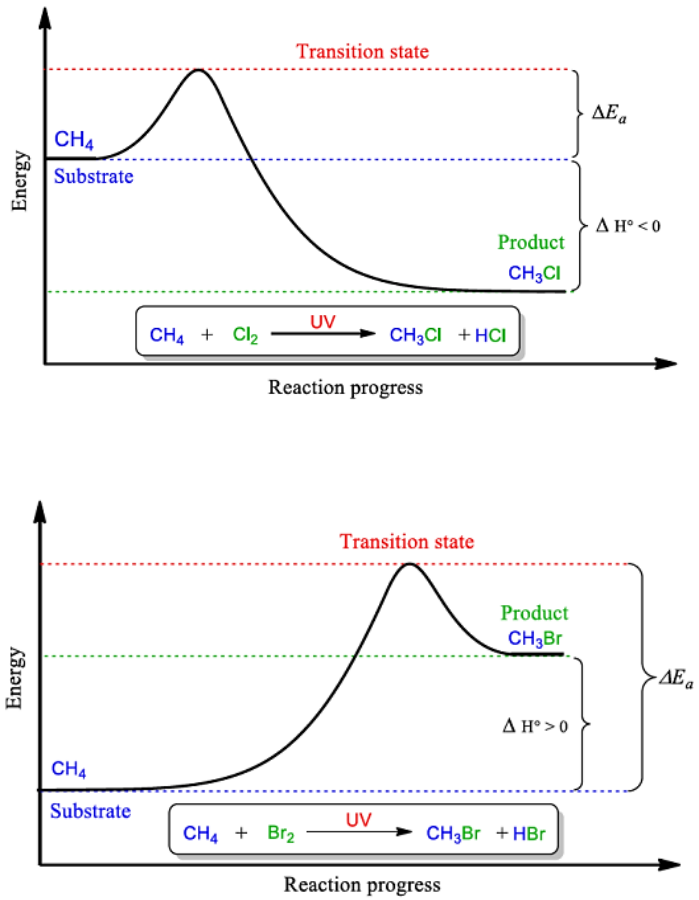


Figure 7. *Reactivity and selectivity of halogens.*

Unlike bromine and chlorine, fluorine reacts vigorously with methane so even in the dark and at room temperature, fluorination must be carefully controlled. The reason behind this is that fluorine has a higher reactivity than all the other halogens due to its higher electronegativity and small size. Iodine, on the other hand, does not react with methane because of its higher stability

12.2. Allylic and benzylic halogenation

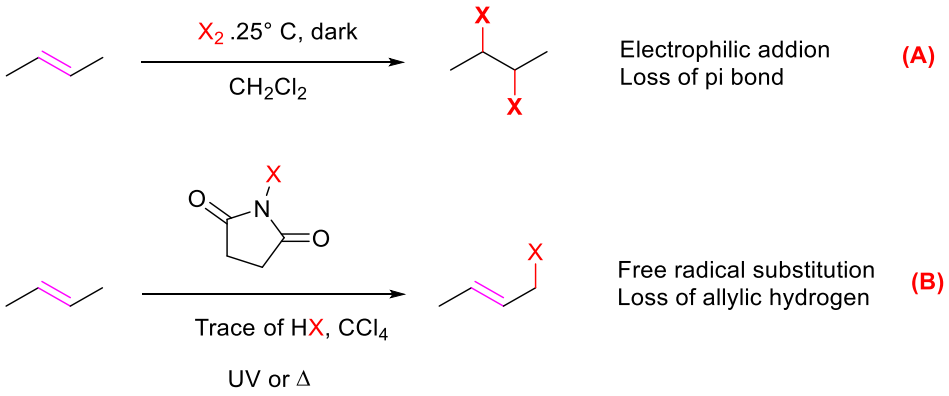
Unlike saturated hydrocarbons, allylic compounds may follow different pathways depending on reaction conditions. At high concentrations of halogens, allylic compounds undergo electrophilic addition rather than a free radical substitution reaction. However, when the concentration of halogens is controlled and kept low, a free radical substitution reaction takes place whereby the allylic hydrogen atom gets replaced by the halogen.



Figure 8. *Allylic and benzylic position of halogenation reaction.*

The addition of X_2 to an alkene under dark conditions proceeds through an electrophilic addition mechanism rather than a radical pathway. In the absence of light, no free radicals are formed, and the reaction involves polarization of the halogen molecule by the electron-rich double bond. The π electrons of the alkene attack the polarized halogen molecule leading to the formation of a three-membered cyclic halonium ion intermediate and a halide anion. The halide ion then attacks the more substituted carbon of the halonium ion from the opposite side (anti-addition), opening the ring and giving a vicinal dihalide as the final product.

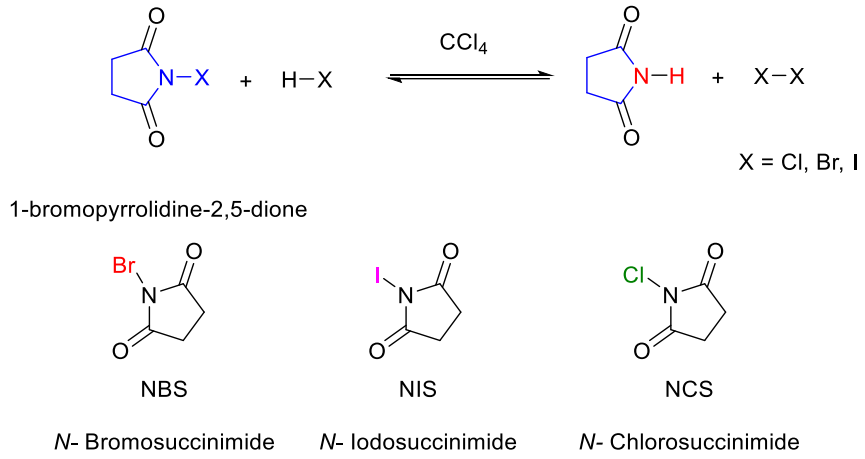
Thus, under dark conditions, the addition of halogens to alkenes occurs via electrophilic addition, forming vicinal dihalides through an anti-addition mechanism (**Scheme 68**).



Scheme 68. *Electrophilic addition of X_2 to alkene and free radical substitution.*

N-halosuccinimides (*N*-halo derivatives of succinimide such as *N*-chlorosuccinimide, *N*-bromosuccinimide, and *N*-iodosuccinimide abbreviated as NCS, NBS, and NIS respectively) are commonly used reagents for allylic and benzylic halogenation reactions. These reagents act as controlled sources of halogen and are used to achieve selective free radical substitution at allylic or benzylic positions while avoiding unwanted electrophilic addition to double bonds. In these reactions, a stoichiometric amount of *N*-halosuccinimide is used along with a small quantity of the corresponding hydrogen halide (HX), which helps maintain a low but continuous concentration of molecular halogen (X_2) in the reaction mixture. This limited concentration of X_2 prevents its electrophilic addition to carbon–carbon double bonds and instead favors radical

substitution. The reaction proceeds via a free radical mechanism initiated by light, heat, or a radical initiator such as benzoyl peroxide or AIBN, which generates halogen radicals (X•) from *N*-halosuccinimide. These radicals abstract an allylic or benzylic hydrogen atom from the substrate, forming a resonance-stabilized carbon radical that subsequently reacts with another molecule of *N*-halosuccinimide to produce the allylic or benzylic halide and regenerate a halogen radical, thus propagating the chain reaction. The process continues until termination occurs through the combination of two radicals. This mechanism allows selective halogenation at the allylic or benzylic position under mild conditions (**Scheme 69**) [46].



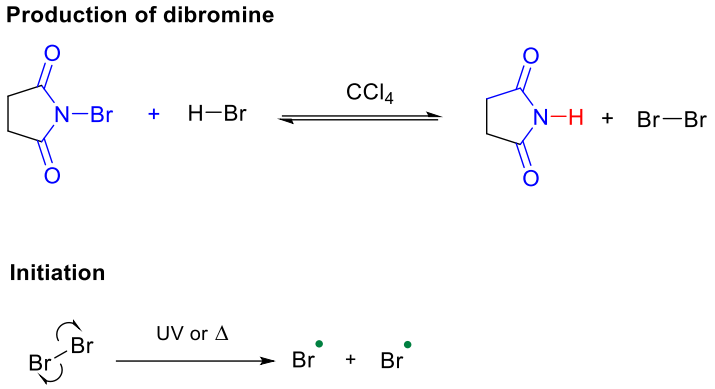
Scheme 69. *N-halo succinimides are halogen source reagents reactions for electrophilic addition.*

The allylic bromination reaction, also known as the **Wohl Ziegler** reaction [47], is an important organic transformation used to convert olefins (alkenes) into their corresponding allylic bromides. This reaction proceeds through a free radical chain mechanism and is particularly valuable because it selectively introduces a bromine atom at the allylic position (the carbon atom adjacent to a double bond) without adding bromine across the double bond.

In this reaction, NBS serves as the bromine source. Unlike molecular bromine, which can easily add electrophilically to the carbon–carbon double bond, NBS maintains a low, steady concentration of bromine in the reaction mixture. This controlled release of bromine allows the reaction to proceed through radical substitution rather than electrophilic addition. A small amount of hydrogen bromide (HBr) is usually present or generated during the reaction, and it reacts with NBS to produce a limited quantity of bromine, which in turn forms bromine radicals under the reaction conditions.

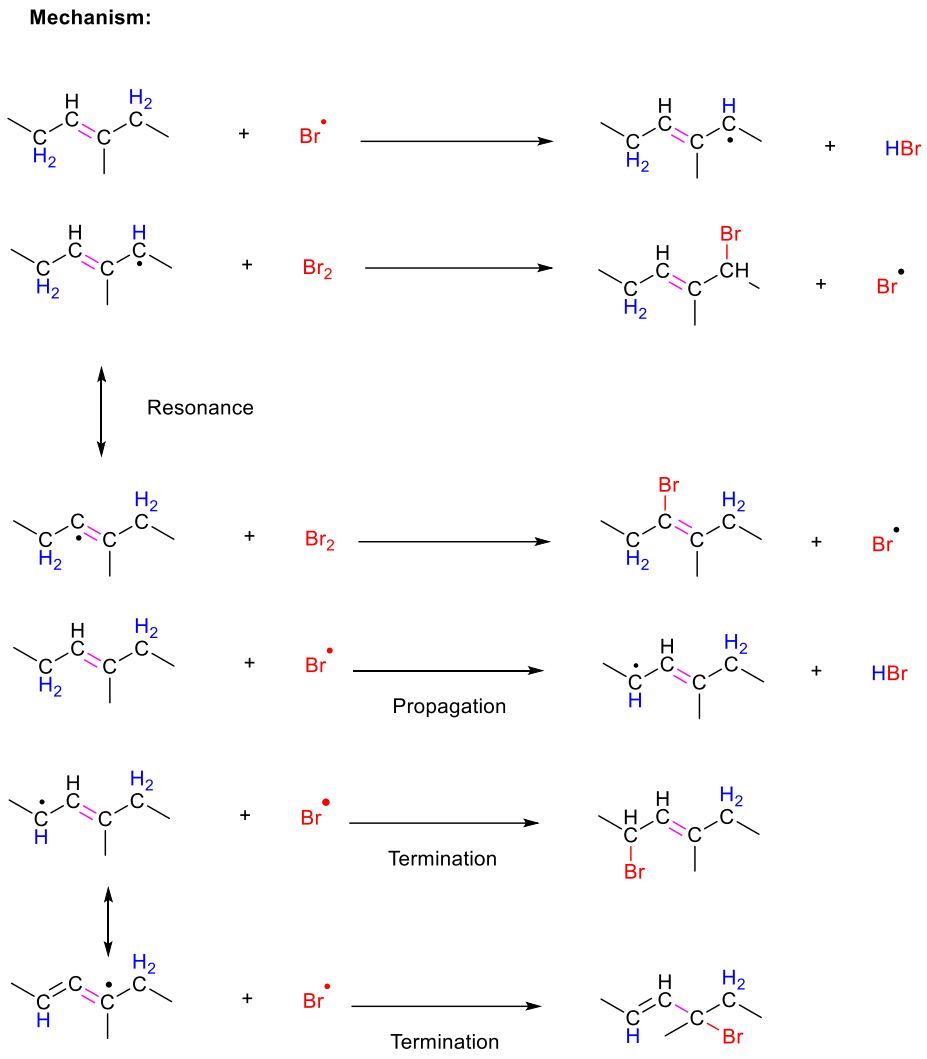
The reaction is typically initiated by heat, light (hν), or a radical initiator such as benzoyl peroxide or AIBN. The **mechanism** proceeds as follows:

Production of dibromine: this is a reversible reaction where NBS reacts with HBr to produce dibromine and succinimide. This process is repeated whenever a new HBr is available. ***Initiation:*** under UV light or at high temperature, the dibromine formed would give two bromine free radicals upon homolytic fission of the covalent bond (**Scheme 70**).



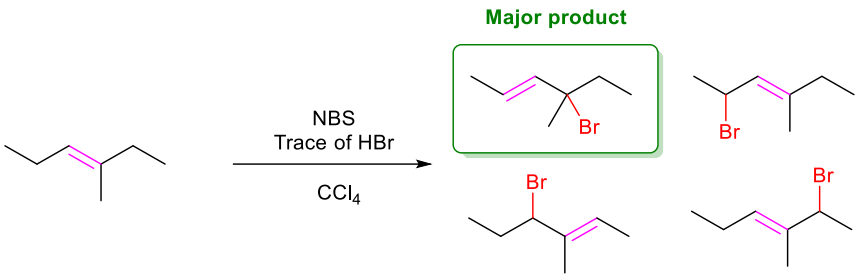
Scheme 70. *Production of dibromine and initiation of Wohl Ziegler reaction.*

Propagation and termination: during the propagation stage, when a bromine radical abstracts an allylic hydrogen atom from an alkene, a resonance-stabilized allylic radical is formed. This radical is unique because the unpaired electron is delocalized over two carbon atoms through resonance, meaning the radical center can shift between the two allylic carbons. As a result, bromine can add to either of these resonance forms, leading to the formation of one or more allylic brominated products depending on which site the bromine radical attacks. The propagation continues as the allylic radical reacts with molecular bromine, yielding the allylic bromide product and regenerating a bromine radical to sustain the chain reaction. The process ends during the termination stage when two radicals combine to form stable, non-radical products, such as when two bromine radicals form Br_2, or when a bromine radical and an allylic radical combine to form the final allylic bromide. The resonance stabilization of the allylic radical thus explains both the high selectivity of the reaction and the possibility of multiple brominated products (**Scheme 71**).



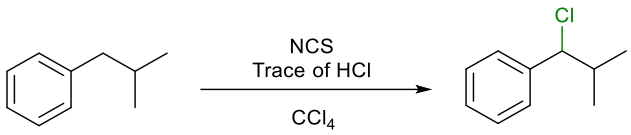
Scheme 71. *Propagation and termination of Wohl Ziegler reaction.*

Moreover, although the allylic bromination reaction can theoretically produce up to four different brominated products due to the resonance stabilization of the allylic radical and the possibility of bromine addition at different positions, in practice, only one product predominates. This selectivity arises because bromine preferentially adds to the most substituted and therefore most stable allylic radical. The stability of the intermediate radical plays a crucial role in determining the major product, as more substituted radicals are better stabilized by hyperconjugation and electron-donating effects. Consequently, the reaction proceeds mainly through the pathway leading to the formation of the most substituted allylic bromide, while other possible products are formed in much smaller amounts (**Scheme 72**).



Scheme 72. *different brominated products obtained from allylic reaction.*

Under UV radiation, at elevated temperature, or in the presence of radical initiators, benzylic compounds undergo free radical substitution reactions at the benzylic position when treated with NCS and a small amount of HCl in CCl_4 as solvent. In this reaction, NCS serves as a controlled source of chlorine, maintaining a low concentration of Cl_2 necessary for selective substitution at the benzylic site rather than addition to aromatic rings or other positions. The reaction proceeds through a radical chain mechanism similar to allylic halogenation: chlorine radicals generated by UV light, heat, or a radical initiator abstract a hydrogen atom from the benzylic carbon, forming a resonance-stabilized benzylic radical, which then reacts with molecular chlorine or NCS to produce the benzylic chloride and regenerate a chlorine radical, propagating the chain process. Although NCS and HCl provide a milder and more controlled source of chlorine, the same benzylic chlorination can also occur when Cl_2 is directly used under UV light, which generates chlorine radicals by photochemical cleavage. However, the use of NCS is generally preferred because it minimizes over-chlorination and side reactions by maintaining an optimal, steady-state concentration of reactive chlorine species (**Scheme 73**).

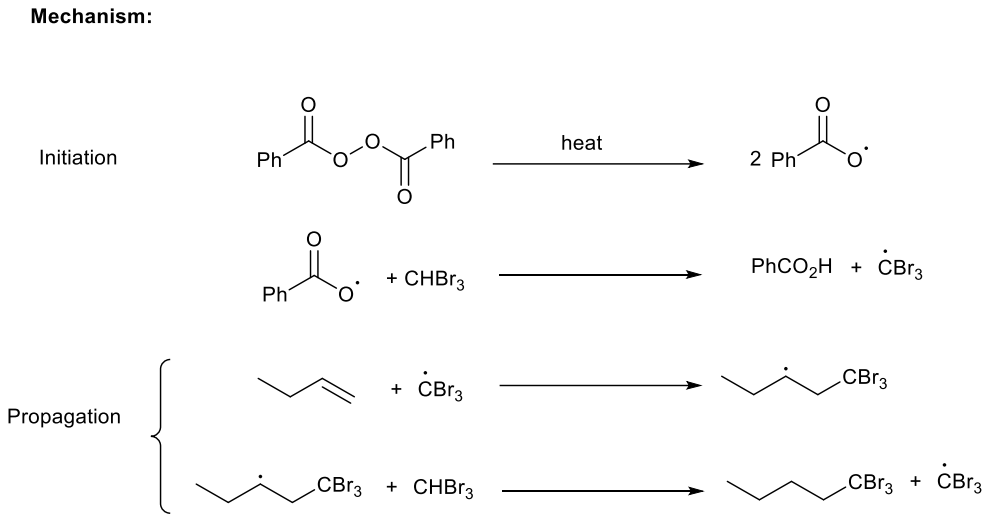


Scheme 73. *Radical substitution reaction treated with NCS and HCl in CCl_4 as solvent.*

12.3. Addition to carbon-carbon double bonds

The addition of aliphatic free radicals to C–C double bonds is an important and widely applied reaction, particularly in chain-growth polymerization and halogenated compound synthesis. This process involves the attack of a free radical on an alkene, leading to the formation of a new C–C or C–X bond.

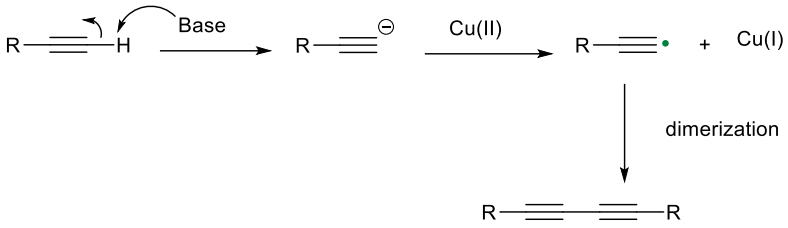
A representative example is the reaction of bromoform ($CHBr_3$) with 1-butene ($CH_2=CH–CH_2–CH_3$). Under suitable conditions such as UV irradiation or the presence of a radical initiator (like peroxides), bromoform undergoes homolytic cleavage to generate a tribromomethyl radical ($•CBr_3$). This highly reactive radical then adds to the C–C double bond of 1-butene, forming a new C–C bond and generating a secondary radical intermediate. The addition follows the Markovnikov or anti-Markovnikov pathway depending on the stability of the resulting radical. The reaction of bromoform with 1-butene is illustrative (**Scheme 74**) [48]:



Scheme 74. *Addition of bromoform to 1-butene.*

12.4. The coupling of alkynes

The coupling of alkynes, often referred to as the Glaser coupling reaction, is a classical method for forming diynes (compounds containing a –C≡C–C≡C– linkage) from terminal alkynes. This reaction is catalyzed by copper(II) salts (such as $CuCl_2$ or $Cu(OAc)_2$) in the presence of a base like pyridine, ammonia, or amines, which helps in generating the reactive acetylide intermediate. The mechanism begins when the terminal alkyne (RC≡CH) reacts with base to form a metal acetylide anion ($RC≡C^-$). This anion then coordinates with the copper(II) ion to form a copper(II) acetylide complex. Subsequently, a one-electron oxidation of the acetylide anion by copper(II) produces an acetylide radical (RC≡C•) along with the reduction of Cu(II) to Cu(I). Two such acetylide radicals then undergo radical coupling (dimerization) to form a new carbon–carbon bond between the two sp-hybridized carbons, resulting in the formation of a 1,3-diyne (RC≡C–C≡CR) (**Scheme 75**) [49].



Scheme 75. *The coupling of alkynes.*

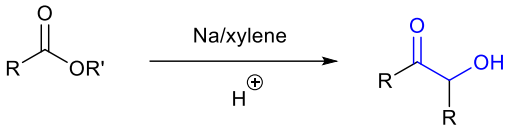
12.5. Acyloin condensation

The acyloin condensation is a valuable reaction for the formation of α-hydroxy ketones (acyloins) from aliphatic esters through reductive coupling. In this reaction, two molecules of an ester react with molten sodium metal in hot xylene or toluene under an inert nitrogen atmosphere to form a disodium intermediate, which upon acidic hydrolysis yields the corresponding acyloin. This transformation provides an efficient method to link two carbonyl groups via a new C-C bond at the α-position, leading to the formation of an α-hydroxy ketone.

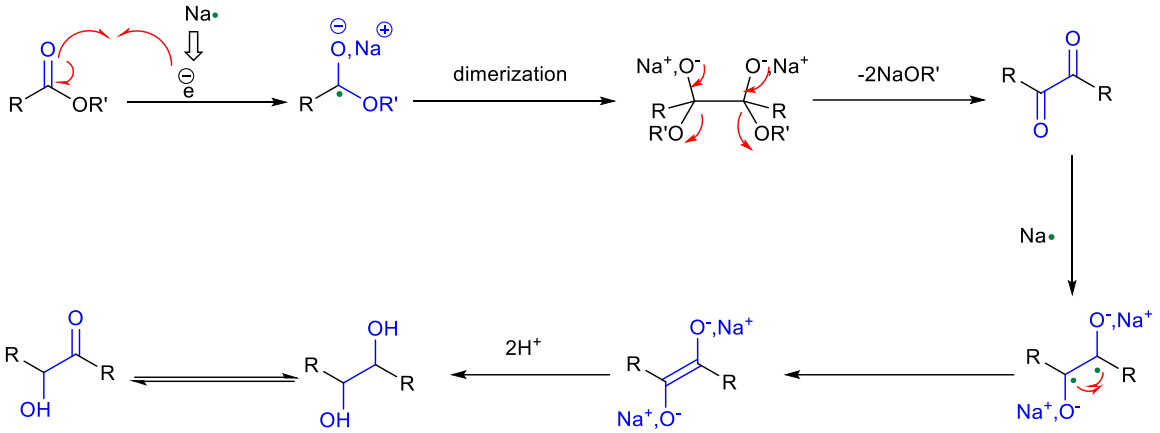
The mechanism begins with the one-electron reduction of the ester by sodium metal, producing a radical anion. Two such radical species then couple to form a 1,2-diol dianion intermediate (the disodium salt of the acyloin). Upon acidic work-up, this dianion is protonated to generate the final acyloin product. The reaction must be carried out under anhydrous and oxygen-free conditions, as both sodium and the acyloin intermediates are highly reactive and prone to oxidation by air.

The reaction is initiated by electron transfer from sodium to the carbonyl group of the ester, generating a carbon-centered radical and an alkoxide ion. These radicals dimerize, leading to the elimination of alkoxide groups and the formation of a diketone intermediate. Further reduction of this diketone by sodium yields the disodium derivative, which, upon treatment with acid, produces the acyloin (**Scheme 76**) [50].

Reaction:



Mechanism:

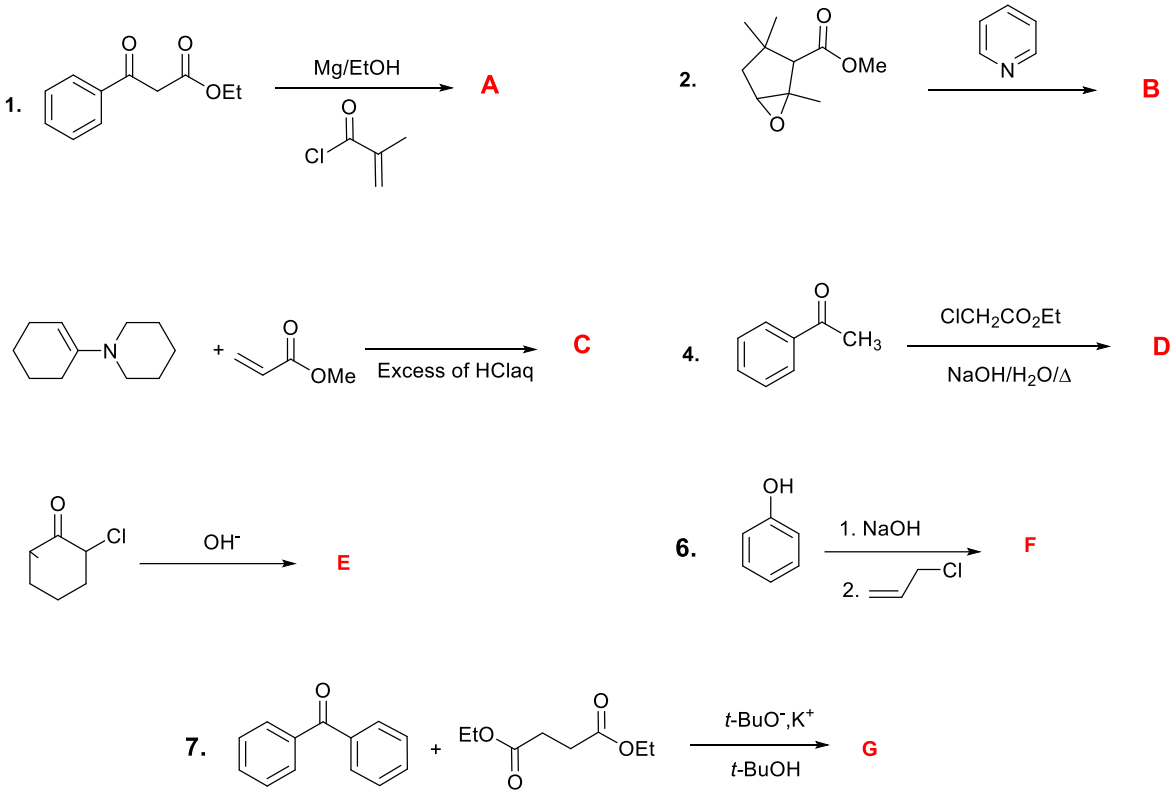


***Scheme 76**. Acyloin condensation.*

Practice problems

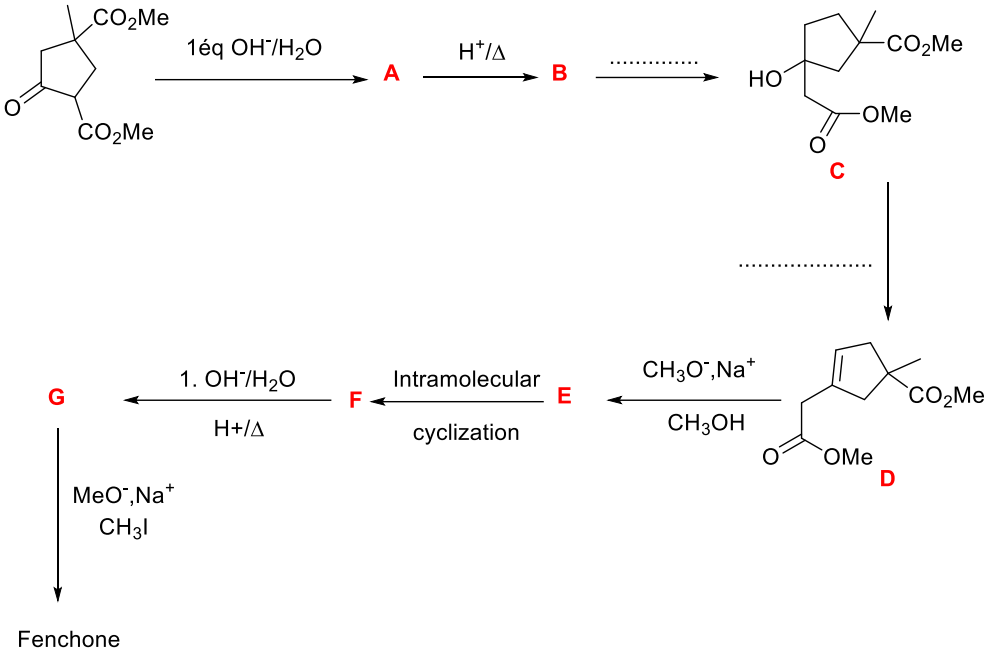
Exercise 01.

Draw the structures of the reactions and name each reaction.



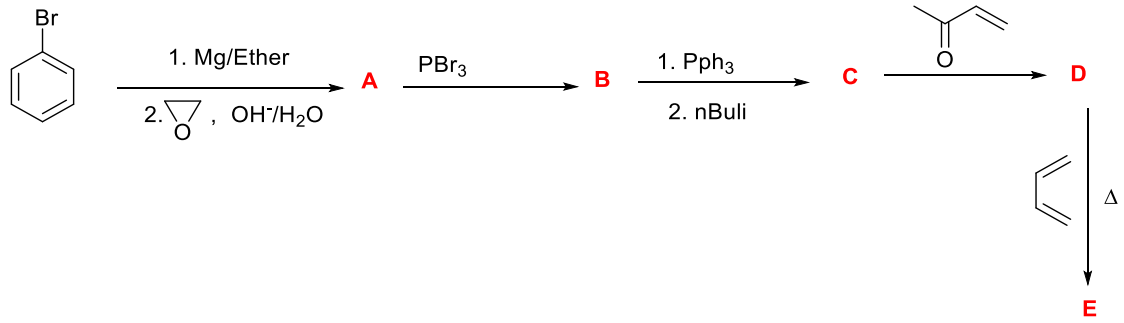
Exercise 02.

Draw the structures of products **A** to **G**. Determine the reagents and the conditions required for the formation of all products, and write the mechanisms for the formation of these products.



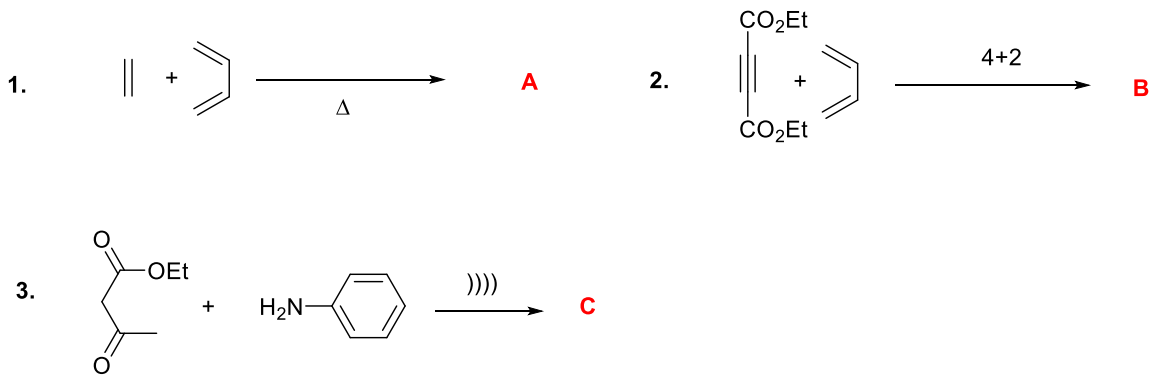
Exercise 3.

Draw the structures of products **A** to **E**. Give the name of each reaction. Write all the mechanisms in as much detail as possible.



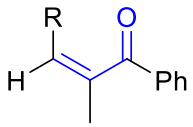
Exercise 4.

Draw the structures of products **A**, **B** and **E**. Give the name and the mechanisms of each reaction.



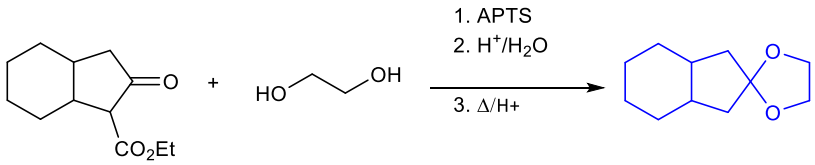
Exercise 5.

Propose two methods of synthesis for the following compound:



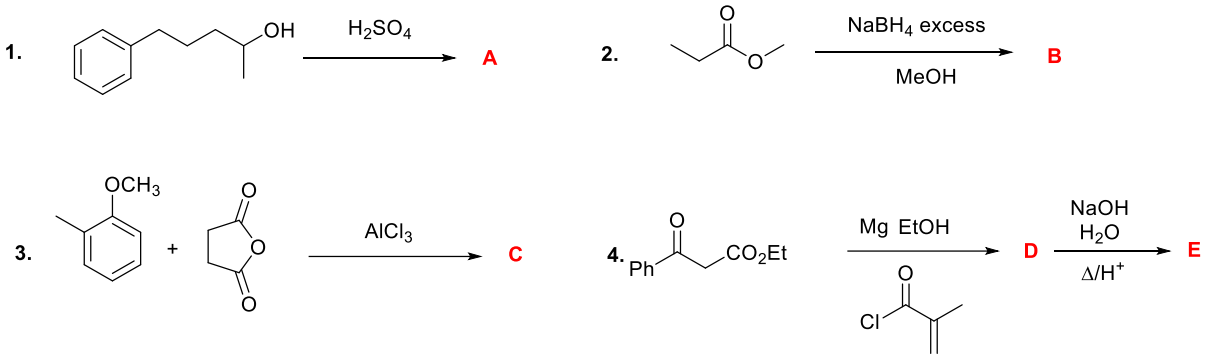
Exercise 6.

Write the detailed reaction mechanism of the following reaction:



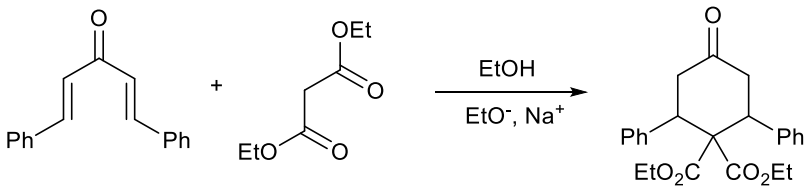
Exercise 7.

Determine the structures of products **A**, **B**, **C**, **D**, and **E**. For each reaction, write the mechanism in as much detail as possible.



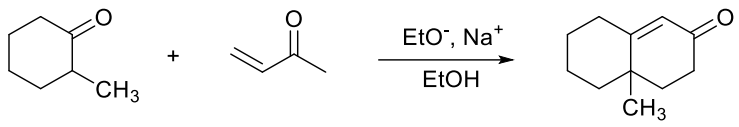
Exercise 8.

Propose a reaction mechanism for the following reaction:



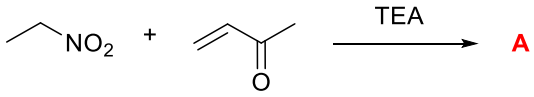
Exercise 9.

Write the reaction mechanism for the formation of the hexahydronaphthalen-2(3H)-one derivative.



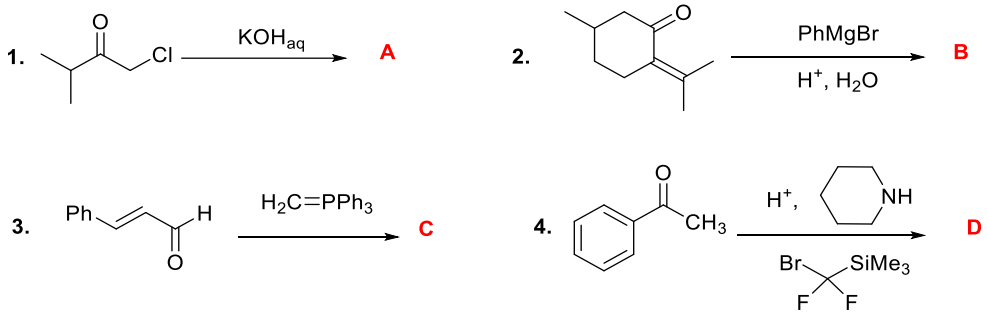
Exercise 10.

Give the structure of compound **A**, and write the mechanism of the formation.



Exercise 11.

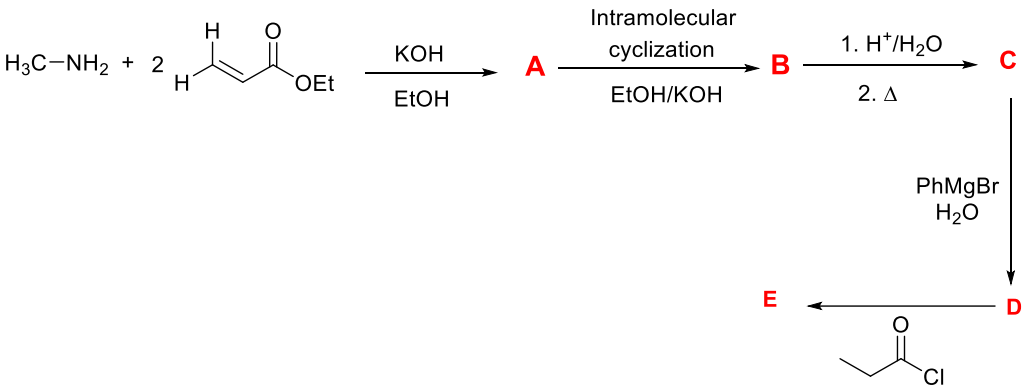
Write the structure of compounds **A**, **B**, **C**, **D**.



Exercise 12.

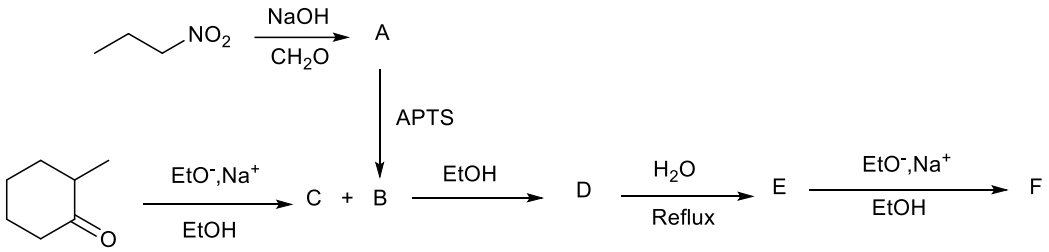
Draw the structures of products A to E. Give the name of each reaction.

Write all possible mechanisms.



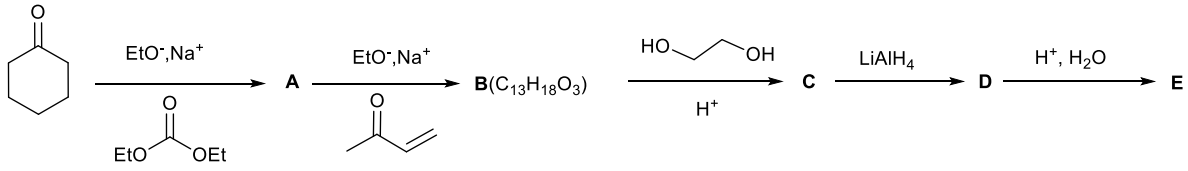
Exercise 13.

- Draw the structures of products **A** to **F**. Give the name of each reaction.
- Write all the mechanisms in as much detail as possible.



Exercise 14.

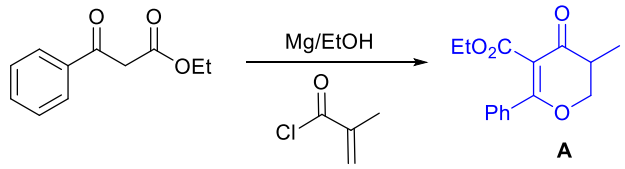
Draw the structures of products **A** to **E**. Give the name of each reaction and write all the mechanisms in as much detail as possible.



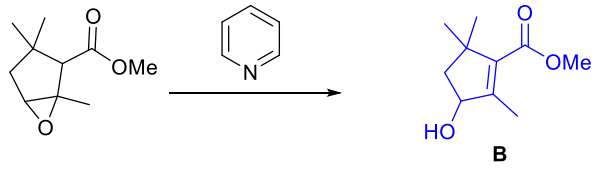
Solutions

Exercise 01.

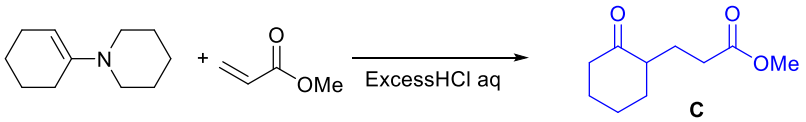
The structure of the products of the reactions with the name of each reaction.

1. 

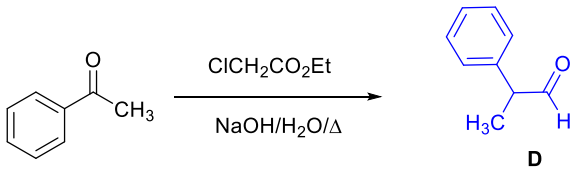
Cyclo-addition

2. 

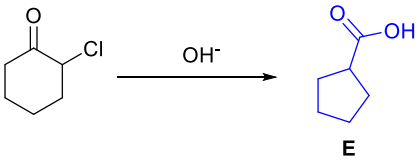
Enolization

3. 

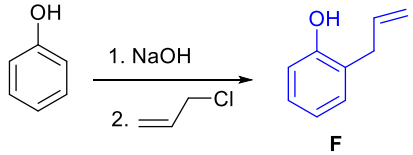
Micheal add-deprotection

4. 

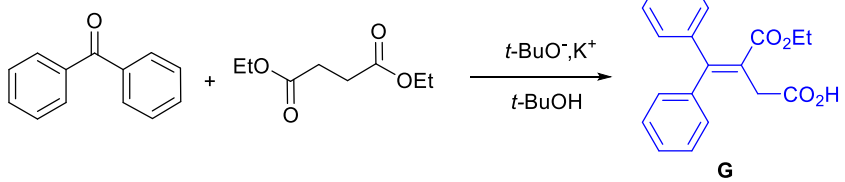
Darzens reaction

5. 

Favorskii rearrangement

6. 

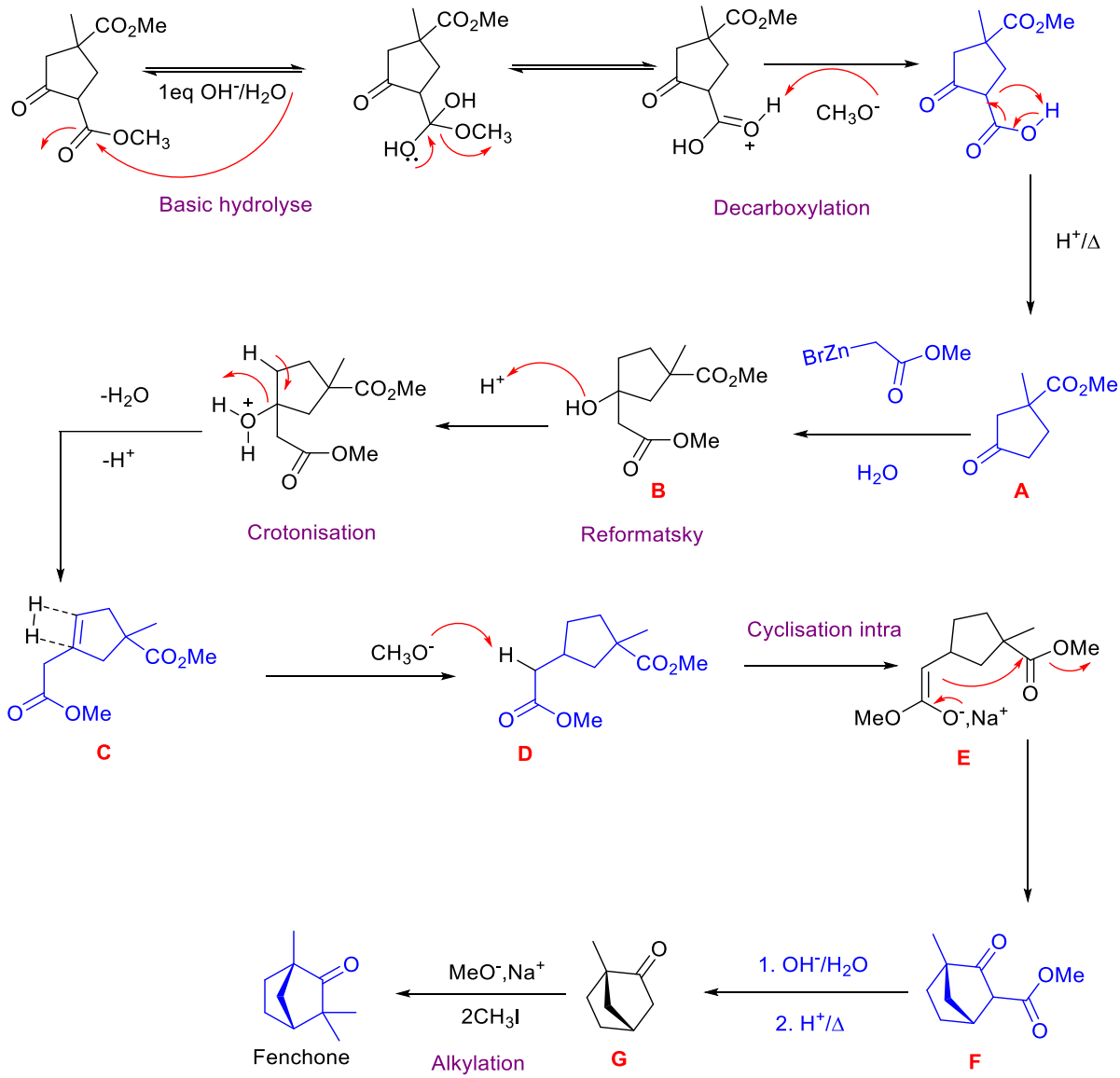
Claisen rearrangement

7. 

Stobbe condensation

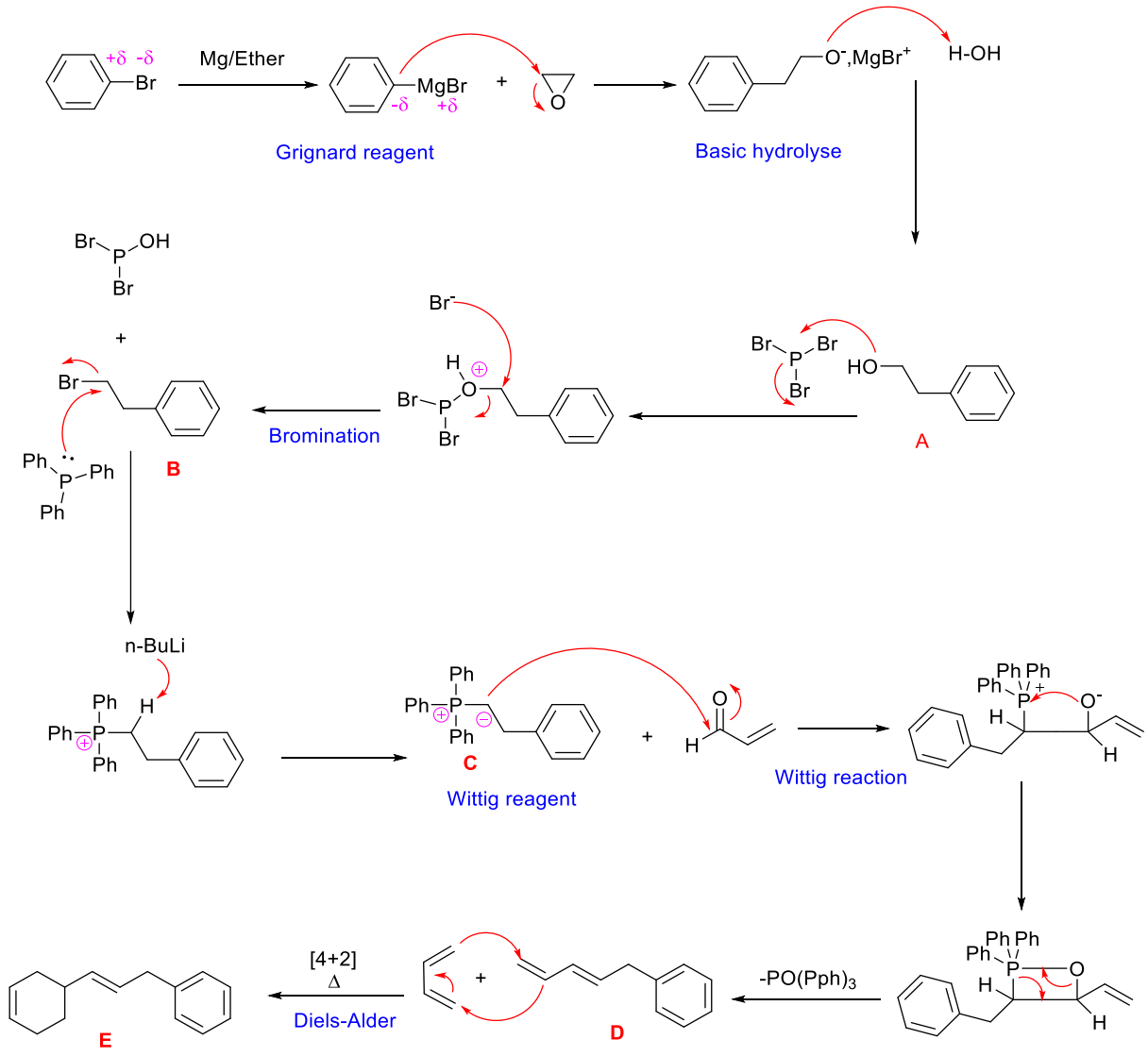
Exercise 02.

The structures of products **A** to **G**; the reagents and the conditions required for the formation of all products is described in the following scheme.



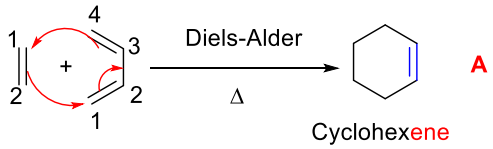
Exercise 03.

The structures of products **A** to **E**; the mechanism and the reactions names for all steps the is described in the following scheme.

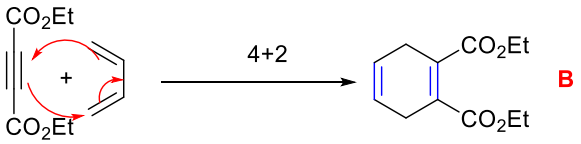


Exercise 04.

1.



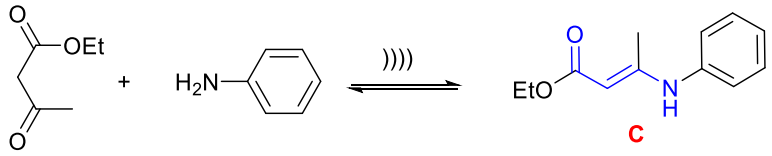
2.



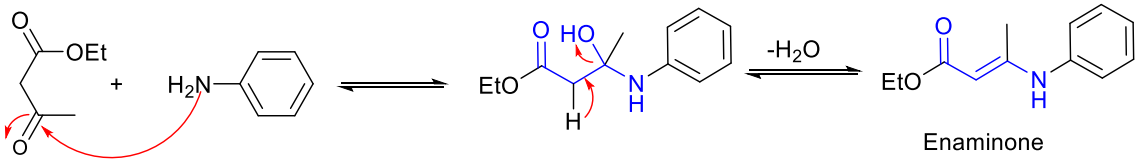
Activated alkyne

Diethyl cyclohexa-1,4-diene
-1,2-dicarboxylate

3.



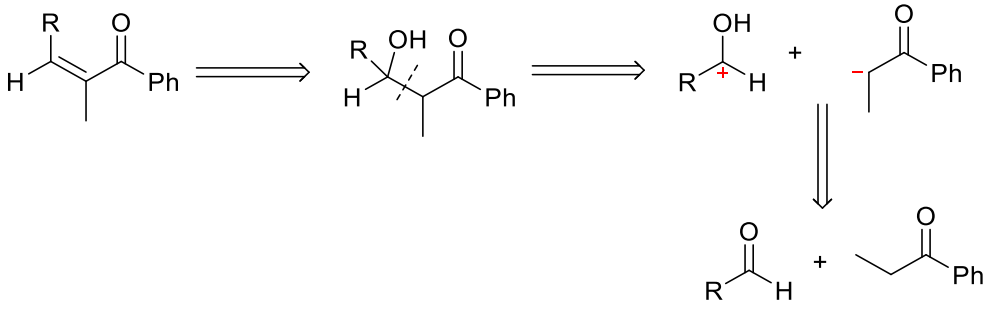
Mécanisme



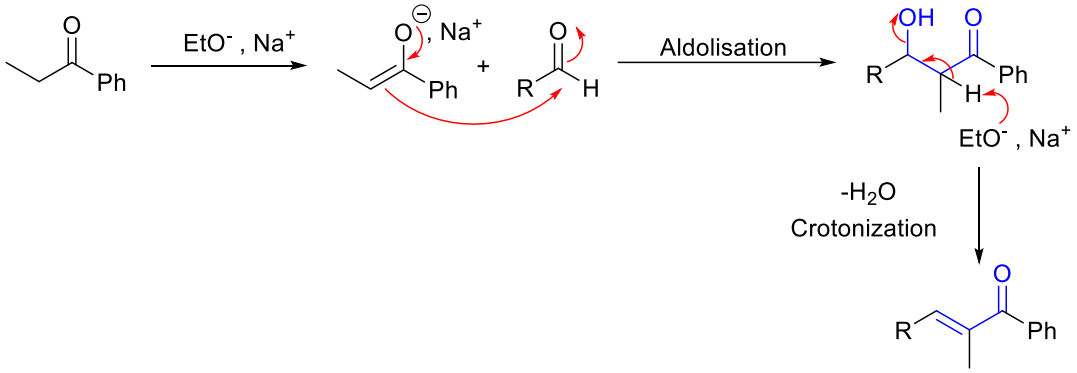
Enaminone

Exercise 05.

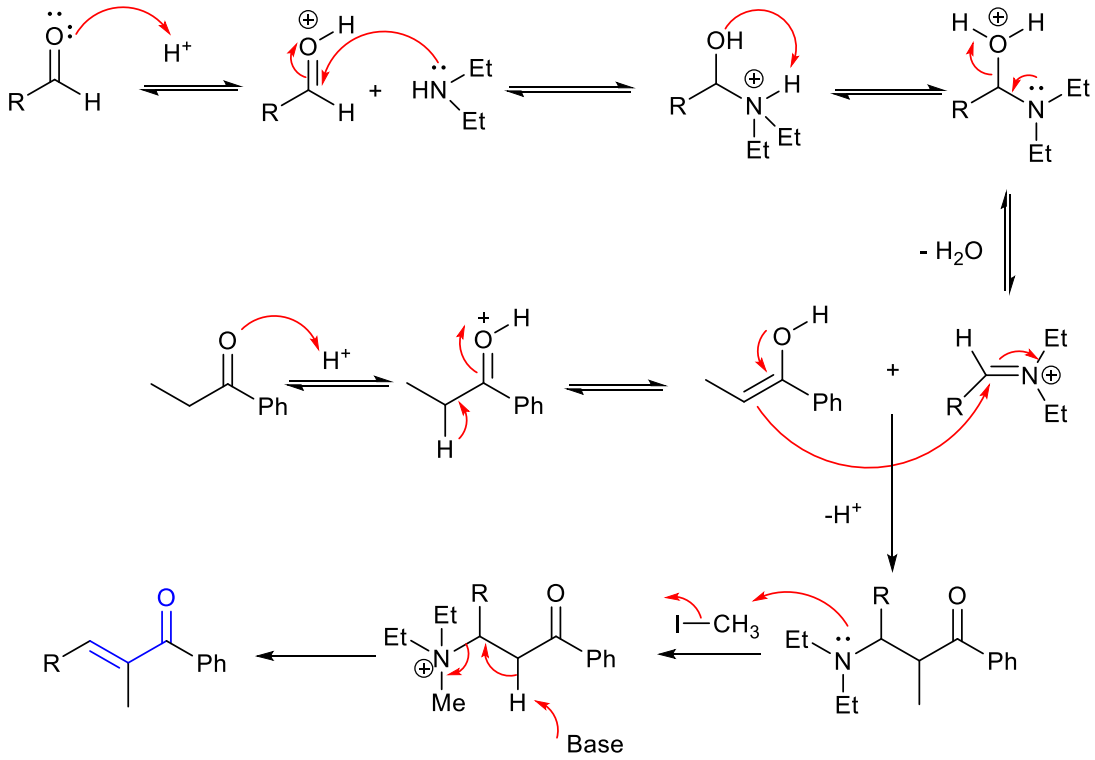
The analysis of the α,β-unsaturated carbonyl compound yielded a non-enolizable aldehyde and an enolizable ketone.



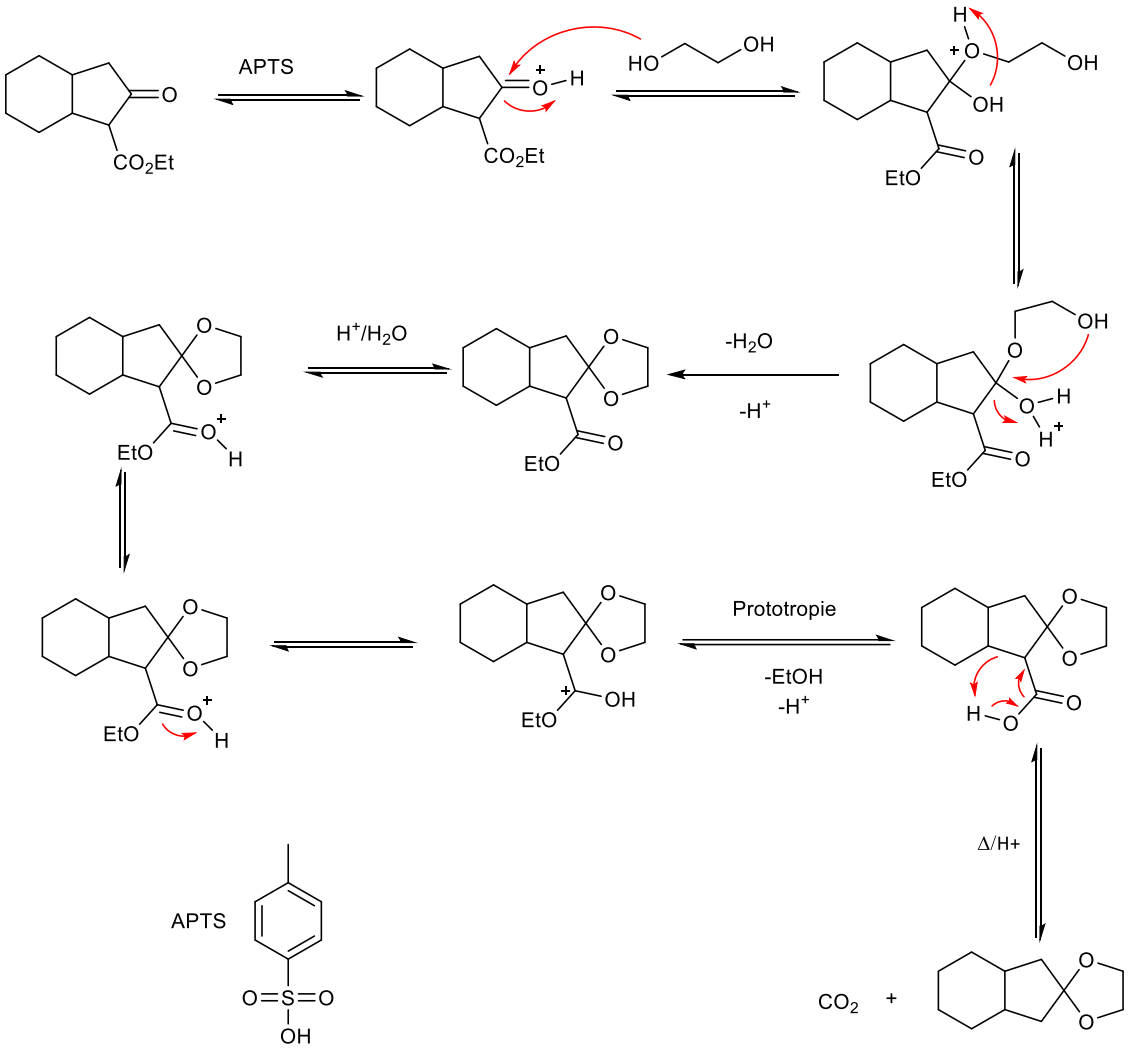
1. Synthesis via the aldol–crotonization reaction



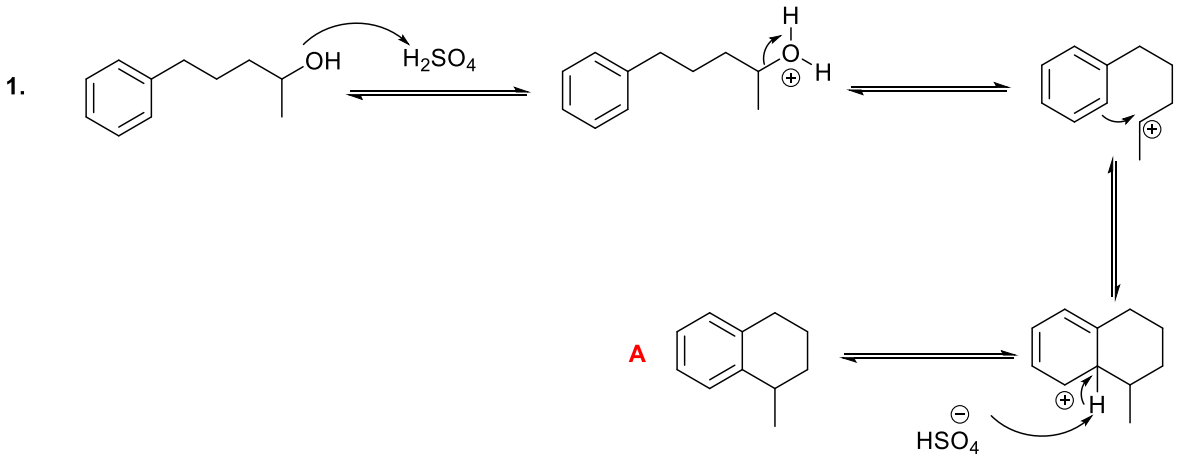
2. Synthesis via Mannich

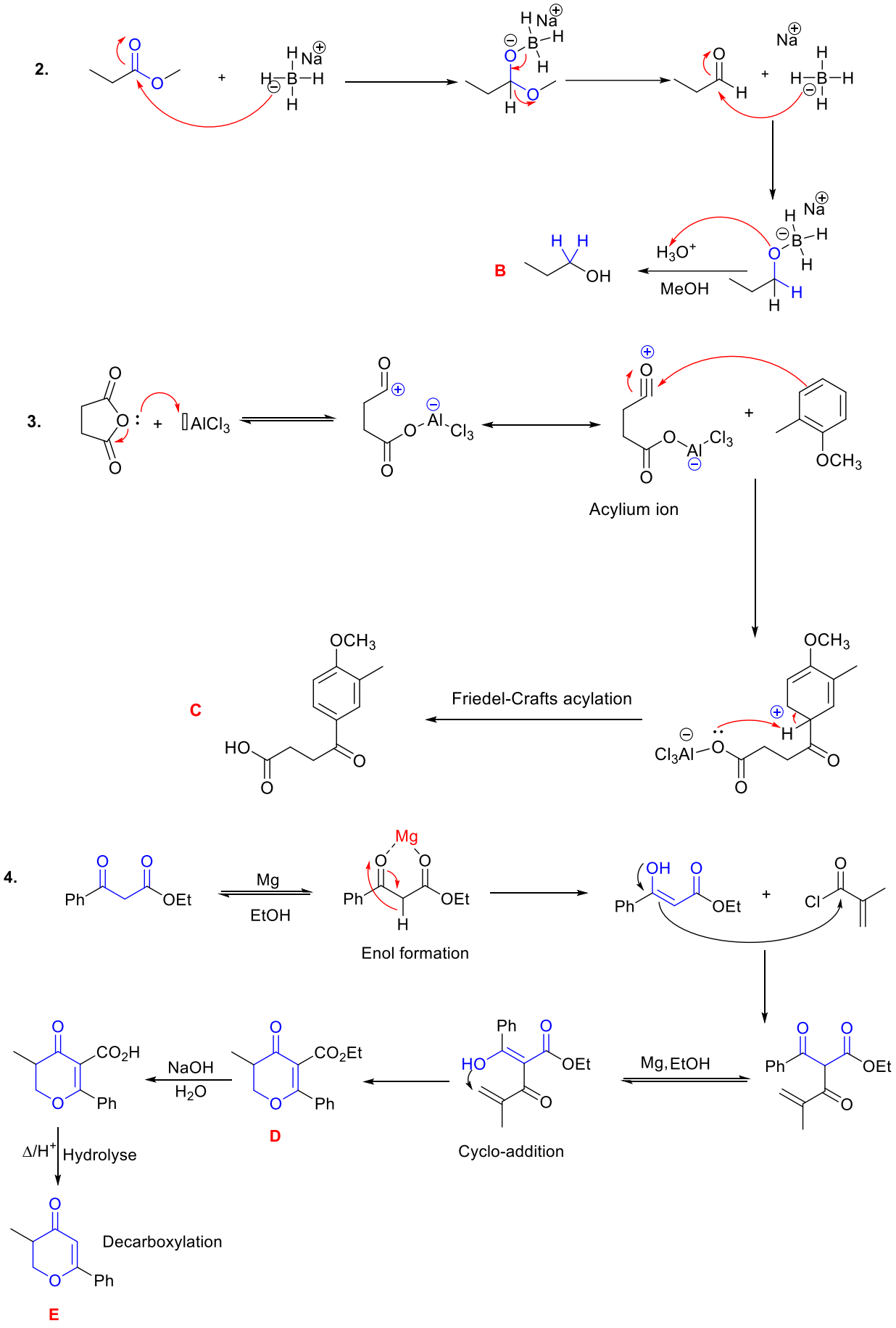


Exercise 06.

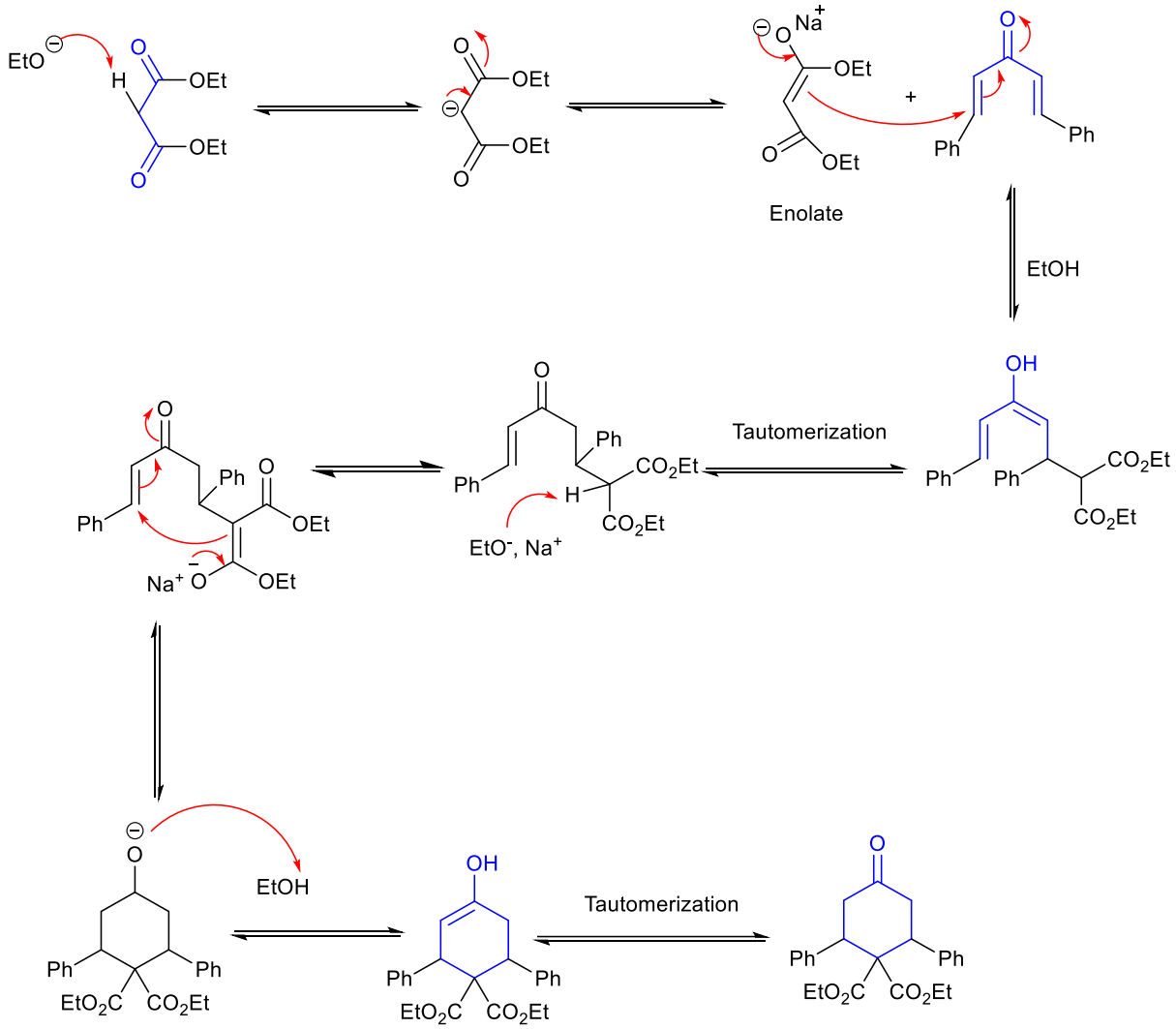


Exercise 07.



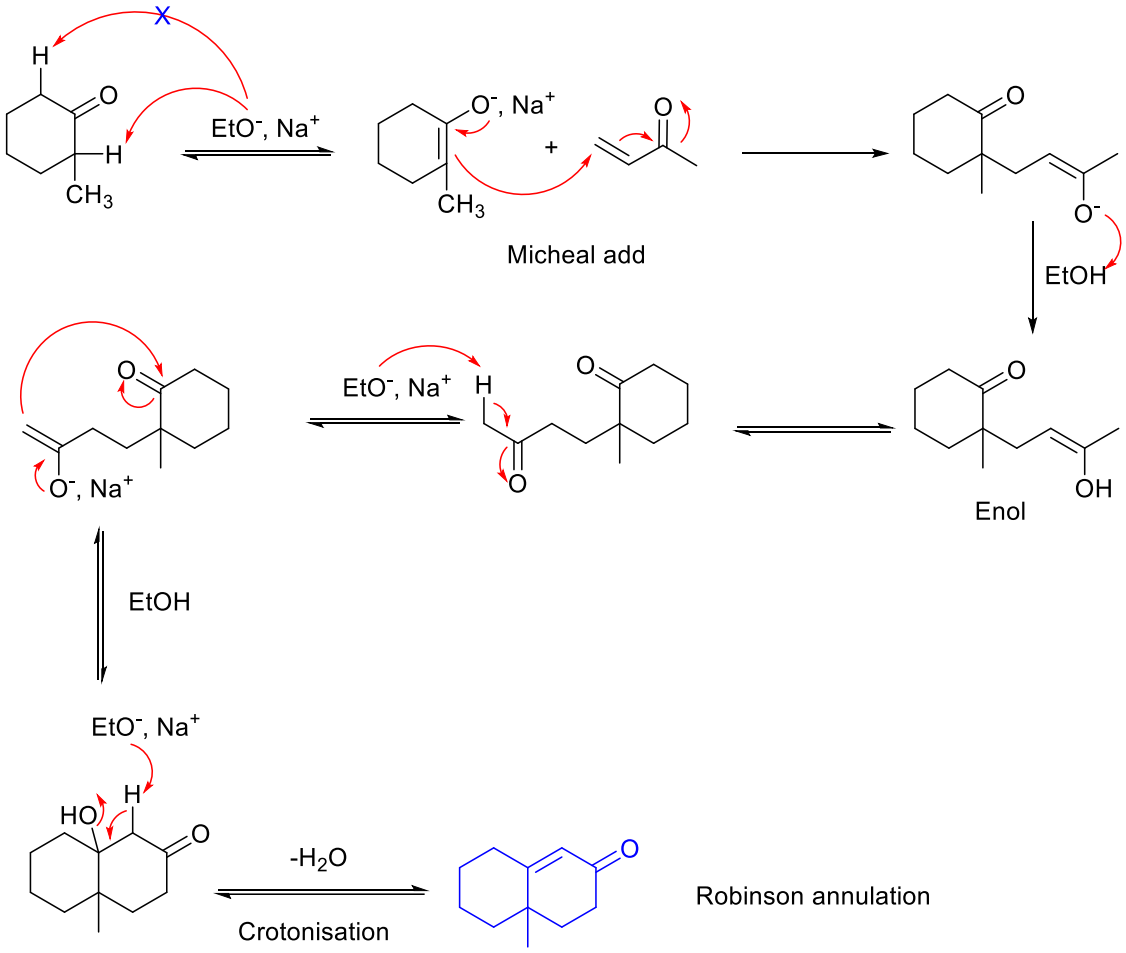

2.
B
MeOH
3.
Acylium ion
C
Friedel-Crafts acylation
4.
Mg
EtOH
Enol formation
Mg, EtOH
Cyclo-addition
D
NaOH
H2O
Δ/H+ Hydrolyse
Decarboxylation
E

Exercise 08.

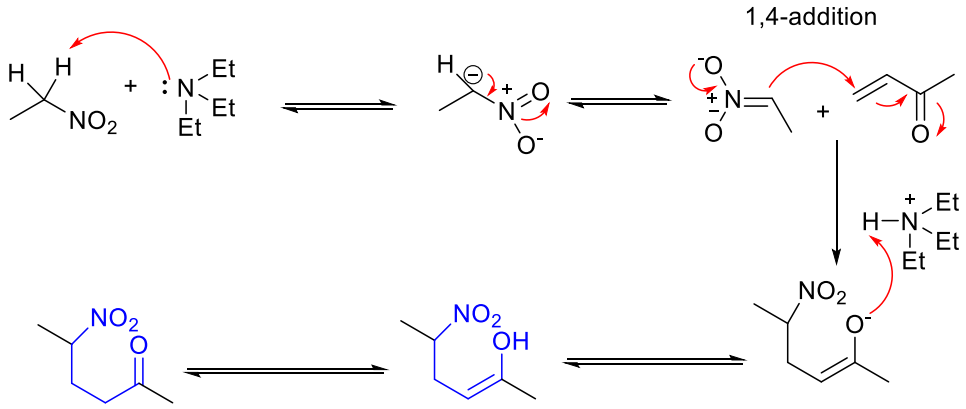


EtO
H
OEt
OEt
Na+
Enolate
Ph
Ph
EtOH
Tautomerization
OH
CO2Et
CO2Et
EtO-, Na+
Na+
EtOH
Tautomerization
EtO2C
CO2Et

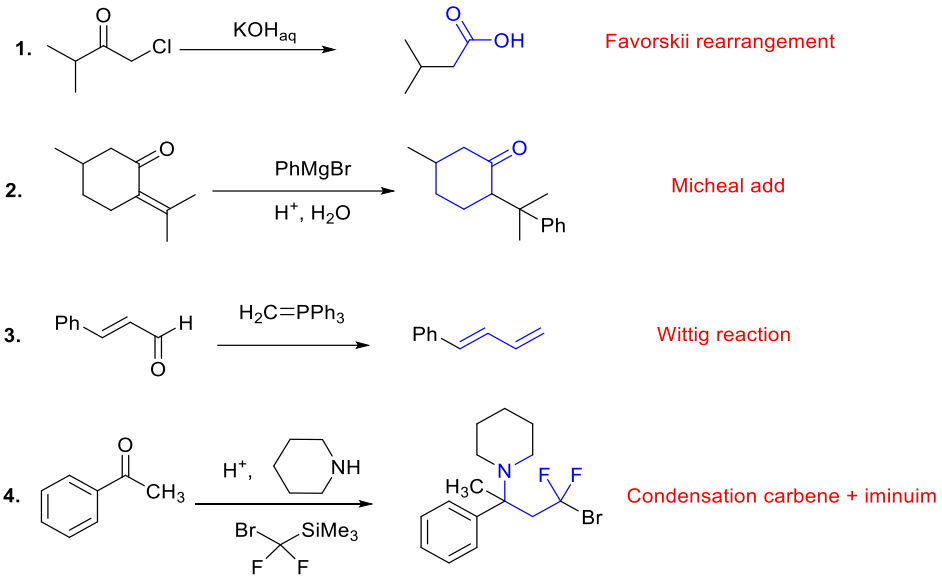
Exercise 9.



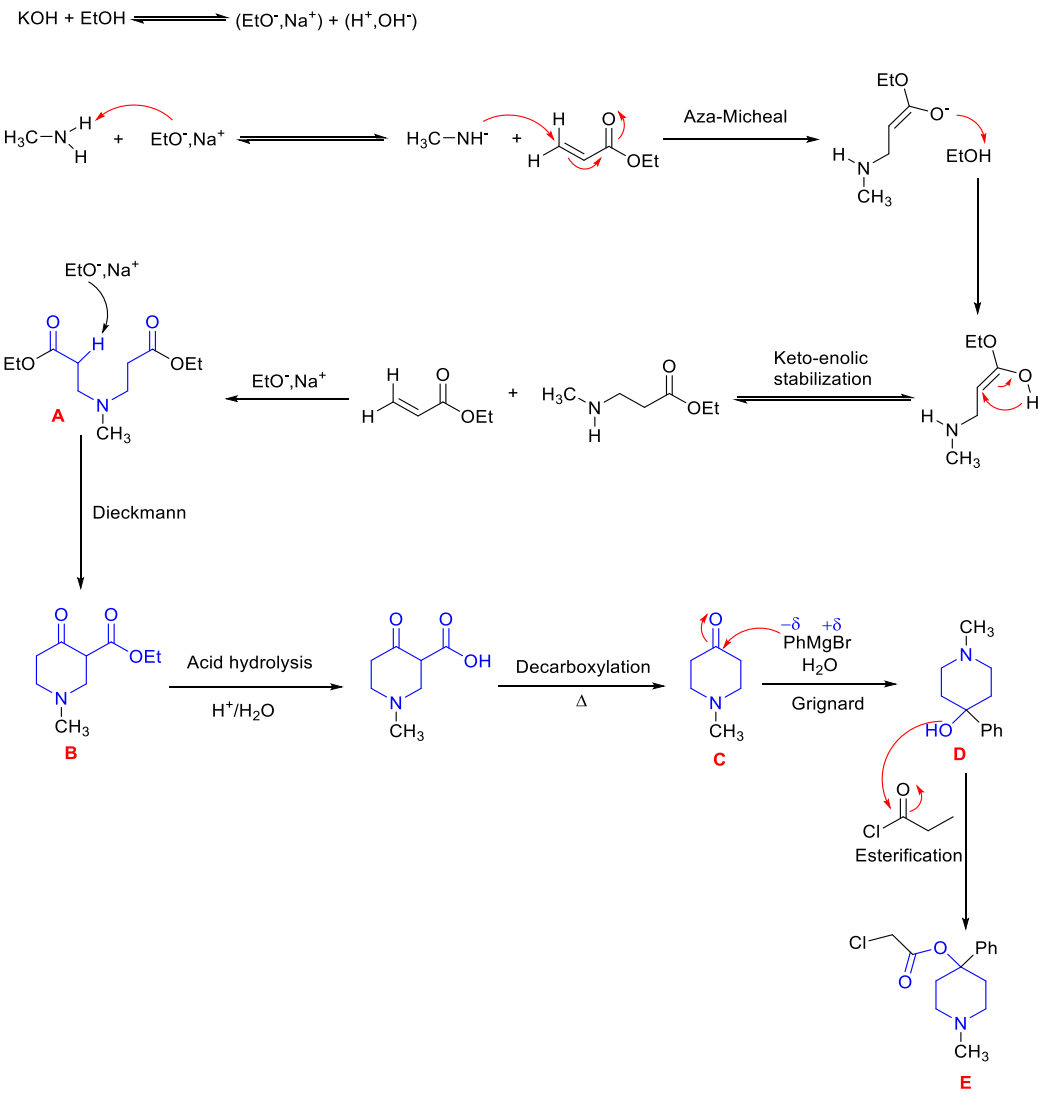
Exercise 10.



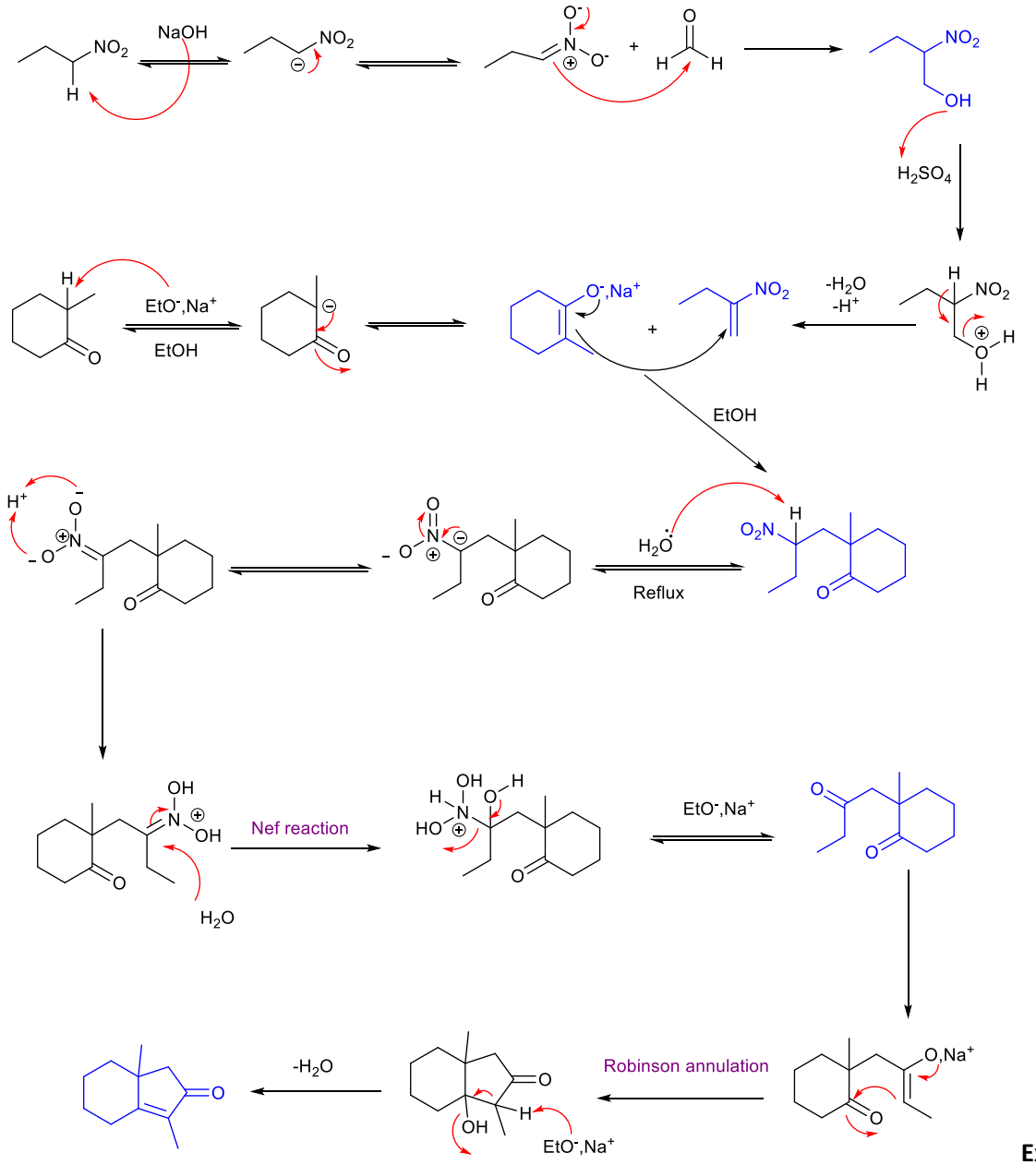
Exercise 11.



Exercise 12.

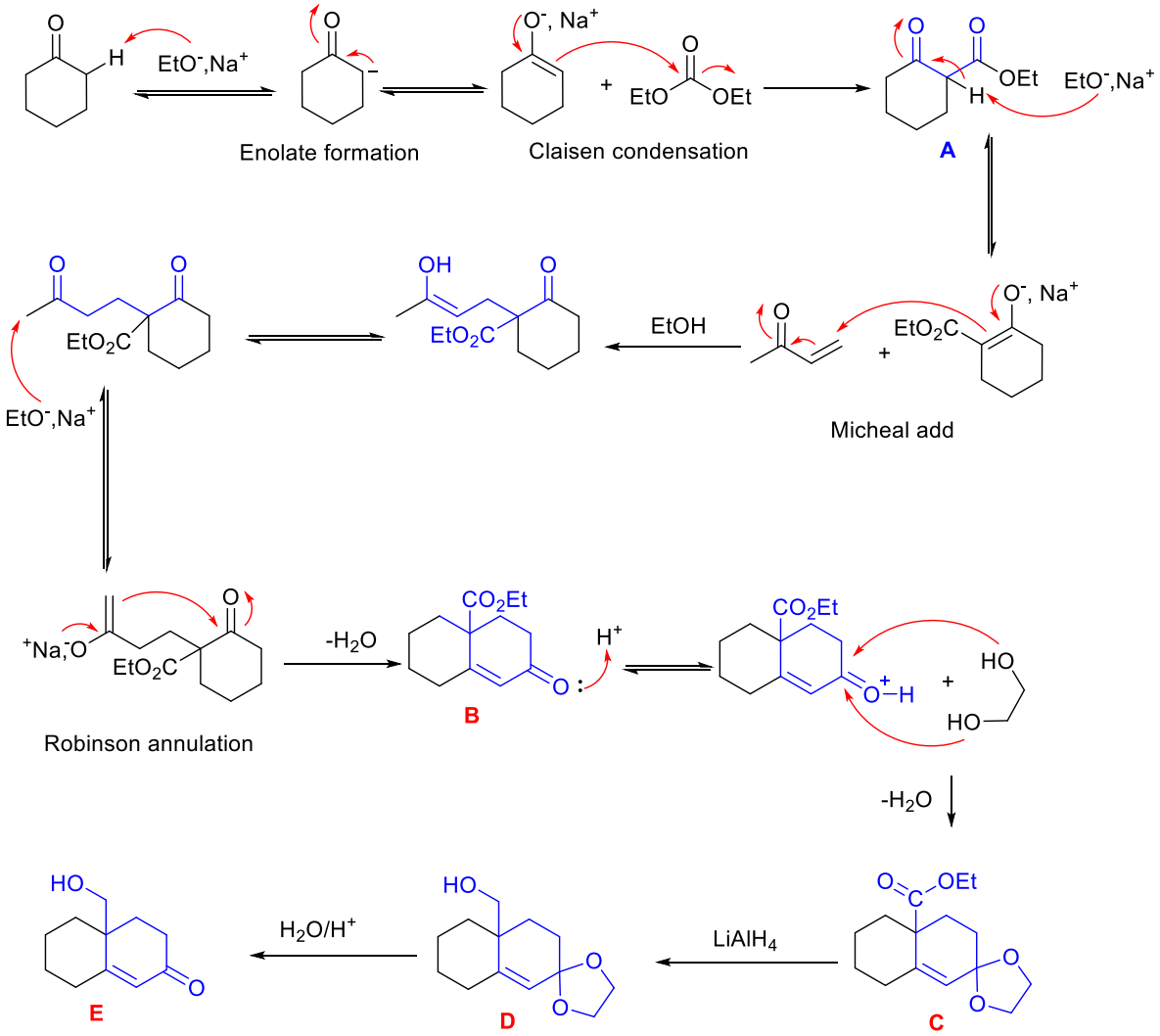


Exercise 13.



Exercice 14 :

Exercise 14.



EtO⁻,Na⁺
Enolate formation
Claisen condensation
A
EtOH
Micheal add
Robinson annulation
-H2O
B
-H2O
LiAlH4
C
D
E
H2O/H+

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