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Preparation new carbon- carbon band by using Aldol condensation

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الشكر والعرفان

بِسۡمِ ٱللَّهِ ٱلرَّحۡمَٰنِ ٱلرَّحِيمِ

﴿وَمَابِكُم مِّن نِّعْمَةٍ فَمِنَ اللَّهِ ثُمَّ إِذَامَسَّكُمُ الضُّرُّفَإِلَيْهِ تَجْأَرُونَ﴾

[سورة النحل: 53]

نحمد الله رب العالمين ...والصلاة والسلام على سيد الخلق أجمعين رسولنا محمد الأكرم وآله وصحبه الطيبين الطاهرين

لا شيء أجمل من كلمة شكر تنبع من القلب وتحمل اعترافًا بالامتنان. ومن لا يشكر الناس لا يشكر الله

بالبدء نتقدم بالشكر الجزيل والامتنان إلى الأستاذ الفاضل الدكتـــــور

"زغدي سعد" الذي أشرف على هذه المذكرة ورافقنا في جميع الأوقات و لم يبخل

علينا بنصائحه القيمة كلما واجهنا مشاكل أو صعوبات كما لا ننسى شكرا للجنة المناقشة

المكونة من الدكتور مختار السعيدي والدكتور محمد حجاج على قبولهم مناقشة هاته المذكرة واشكر كذلك جامعة حمه لخضر الوادي التي اجرينا عندها التحاليل وكذلك جميع

أساتذتنا ومعلمينا الذين رافقونا من بداية مشورنا إلى آخره

شكرا جزيلا لكم معلمينا لكم منا كل التقدير والامتنان

الإهداء

أهدي هذا العمل المتواضع إلى كل من كان له الفضل علينا بعد الله

وأخص بالذكر الوالدين الكريمين رحمهم الله

الذين حرصوا على تنشئتنا وتعليمنا وسهروا الليالي من أجلنا

كما اهديها إلى كل إخوتي وأخواتي وإلى كل الأصدقاء وزملاء الدراسة

وكما لا أنسى الأساتذة الكرام الذين ينيرون الدروب للأجيال بشعلة

العلم

وإلى كل من ساهم في هذا العمل

عليات عبد الصمد

من قال انا لها "نالها "

لم تكن الرحلة قصيرة ولا ينبغي لها أن تكون

لم يكن الحلم قريبا ولا الطريق كان محفوفا بالتسهيلات

لكنيي فعلتها ونلتها

الحمد حبا وشكرا وامتنانا , الذي فضله ها أنا اليوم أنظرو الى حلم طال

انتضاره وقد اصبح واقعاً أفتخره به

الى ملاكي الطاهر وقوتي بعد الله داعمتي الاولى والأبدية "امي "

اهديك هذا الانجاز الذي لولا تضحياتك لما كان له وجود ممتنة لأن الله اصطفاك

لي من البشر

اما ياخير سند وعوض الى من دعمني بلا حدود واعطاني بلا مقابل

"ابي"

الى من قيل فيهم :

{سنشد عضدك بأخيك}

الى من مد يده دون كلل ولا ملل وقت ضعفي "اخي" أدامك الله ضلعا ثابتا لي

إلى من آمنت بقدراتي وامان ايامي "نوسم"

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Dedication:

I dedicate this humble work to all those who have had a positive influence on us, after God, particularly mentioning our kind parents, may God have mercy on them, who were keen on raising and educating us and sacrificed their nights for our sake.

I also dedicate it to all my brothers, sisters, friends, and schoolmates. And I must not forget the honorable teachers who illuminate the paths for generations with the torch of knowledge.

This work is also dedicated to all those who contributed to this endeavor.

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The journey wasn't short and it shouldn't have been the dream wasn't near and the road wasn't paved with ease but I did it and achieved it Praise be to God

With love, thanks, and gratitude, for His favor here I am today, looking at a dream long awaited and now realized,

Proud of it to my pure angel and my strength after God, my eternal supporter, "my mother" I dedicate to you this achievement, which wouldn’t have been possible without your sacrifices? Grateful because God chose you for me from among humans

And to the best support and substitute, to the one who supported me endlessly and gave me without expectation, "my father"

To those whom it was said about them: "We will strengthen your arm with your brother's"

To the one who extended his hand tirelessly and relentlessly in my weakness, "Houcine" may God keep you a steadfast rib for me

To the one who believed in my abilities and the safety of my days, "Nawssem"

To the one who reminds me of my strength and stands behind me like my shadow, my little sister "Malak"

Bouzazel Amani farah

List of abbreviations:

C: Carbone atom

O: Oxygene atom

Nu: Neutralnucleophile

OH: Hydroxyl group

C=O: Carbonyl group

RX: Haloalkanes

X_2: Molecular halogens

Nu^-: Negative nucleophile

: $^-$C-C=O: Enolate ion

C $^-$: Carbanion

R'C (=O) R": Carbonyl compounds

MVK: Methyl vinyl ketone

H_2O: Water

NaOH: Sodium hydroxide

IR: Infra-red

UV: Ultra-violet

NMR: Nuclear magnetic resonance

***K*:** The equilibrium constant

KJ: Kilo joul

D_2O: Deuterium oxide

CH_3CHO: Acetaldehyde

E1cB: Elimination Unimolecular conjugate Base.

$^-OCH_3$: Methoxy

LDA: Lithium diisopropylamide

$NaNH_2$: Sodium amide

KOH: Potassium hydroxide

$^\circ$C: The degree Celsius

M: Molare

HCl: Chlorure d'hydrogène

R: The substitu

Ba (OH) $_2$: Barium hydroxide

EtONa: Ethanoate sodium

PKa: Acidity constant

RCH_2CO_2Et: Substituted acetates

(EtO) $_2$**CO:** Diethyle carbonate

g: Gramme

***i.e.*:** Id est (that is)

ppm: Part-per-million

J: Coupling constant

Hz: Hertz

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General Introduction

General Introduction

The carbonyl group, present in aldehydes, ketones, amides, acids, and their derivatives, as well as numerous other compounds, is central to organic chemistry. Reactions involving nucleophiles and carbonyl groups are pivotal, serving as key tools in synthesizing carbon-carbon (C-C) bonds. These reactions are foundational in bioorganic processes involving carbohydrates, proteins, and lipids. Nucleophiles, whether neutral (Nu:) or negatively charged (Nu:-), target the positively polarized carbon atoms of carbonyl groups (C=O) in a variety of reactions. This polarity, arising from the differing electronegativities of carbon (C) and oxygen (O), enables carbonyl groups to interact with both positively and negatively charged reactants. Additionally, the polar nature of the carbonyl group activates adjacent atoms for various chemical transformations, notably inducing acidity in protons bonded to adjacent carbons in carboxylic acids and carbonyl compounds **[1].**

Our investigation delves into the chemistry of the α position in carbonyl compounds, offering insights that enhance our understanding of complex reactions and facilitate the synthesis of intricate molecules. While much of the forthcoming chemistry builds upon established reactions, we encounter applications in more intricate scenarios. For instance, the addition of nucleophiles to carbon-oxygen double bonds manifests in reactions where enolates add to carbonyl groups, yielding products of greater complexity.

A classic example is the aldol addition, wherein ketones or aldehydes undergo acid- or base-catalyzed dimerization. Under specific conditions, dehydration leads to the formation of α,β-unsaturated aldehydes or ketones, termed aldol condensation. The base-catalyzed mechanism involves the formation of the enolate ion, which subsequently adds to the carbonyl group. These reactions predominantly occur in dilute basic solutions at or below room temperature, with more vigorous conditions inducing elimination steps **[2].**

The term "enolate ion" originally referred to the anion formed by deprotonation at the α position of a carbonyl compound. However, it now encompasses various anions

with a carbanion center attached to functional groups other than the carbonyl group. Enolate ions engage in reactions with different substrates, with significant reactions involving molecular halogens, haloalkanes, and carbonyl compounds.

In these addition reactions, a new carbon-carbon σ bond is formed at the expense of the carbonyl group's π bond. Carbonyl compounds can act as either electrophiles or nucleophiles depending on the reaction conditions and other reagents present. Correspondingly, similarities exist between addition reactions involving carbon-oxygen (C=O) and carbon-carbon (C=C) double bonds, although the presence of oxygen introduces additional complexity.

Our focus lies on unsaturated α,β-acyclic ketones, which have proven valuable in synthesizing nitrogen heterocycles and other compounds with diverse pharmacological activities. These compounds serve as precursors for anti-cancer agents, cardiovascular drugs, anti-anxiety medications, and other bioactive substances, highlighting their versatility and significance in organic synthesis **[3].**

Chapter I: Enols and enolates

Enols and enolates constitute a pivotal chapter in the landscape of organic chemistry, offering a dynamic perspective on the structural transformations of carbonyl compounds. Enols, arising from the intriguing process of tautomerization, showcase a distinctive combination of a carbon-carbon double bond and an adjacent hydroxyl group. This equilibrium-driven phenomenon leads to the coexistence of multiple molecular forms. Enolates, on the other hand, emerge as anionic species through the deprotonation of enols, demonstrating pronounced nucleophilic tendencies. Their significance lies in their active participation in a spectrum of organic reactions, influencing the synthesis of compounds through pathways like aldol condensation and Michael additions. The interplay between enols and enolates opens avenues for understanding and controlling reaction mechanisms, making this chapter indispensable for organic chemists navigating the intricacies of molecular transformations. [3]

I -2- The Acidity of The αHydrogens of Carbonyl Compounds:

I -2-1-enolate anions

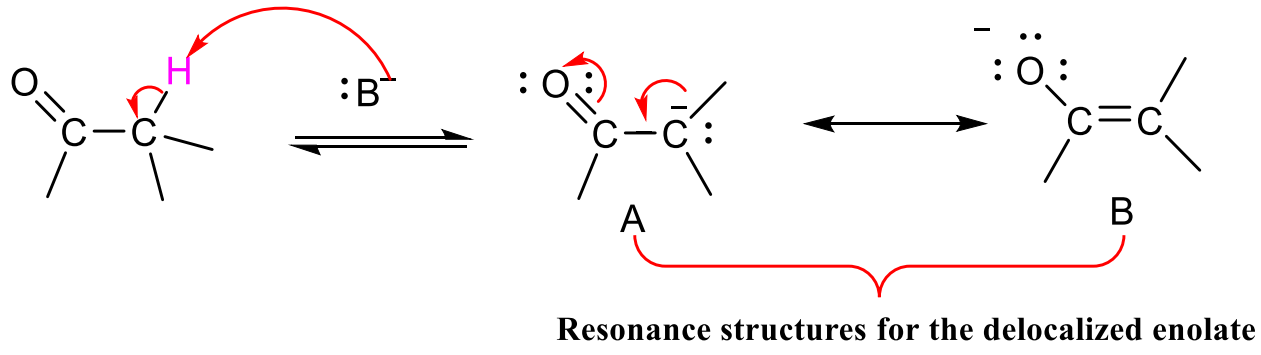
When we say that the *α* hydrogens of carbonyl compounds are acidic.

- The p*K*a values for the *α*hydrogens of most simple aldehydes or ketones are of the order of 19–20.

This means that they are more acidic than hydrogen atoms of ethyne, p*K*a =25, and are far more acidic than the hydrogens of ethene (p*K*a = 44) or of ethane(p*K*a=50).

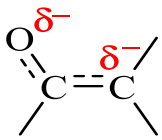
The reasons for the unusual acidity of the *α*hydrogens of carbonyl compounds are straightforward.

- The carbonyl group is strongly electron with drawing, and when a carbonyl compound loses an *α*proton, the anion that is produced, called an enolate, is stabilized by delocalization [4]



Scheme 01: Stabilization of Enolates through Delocalization

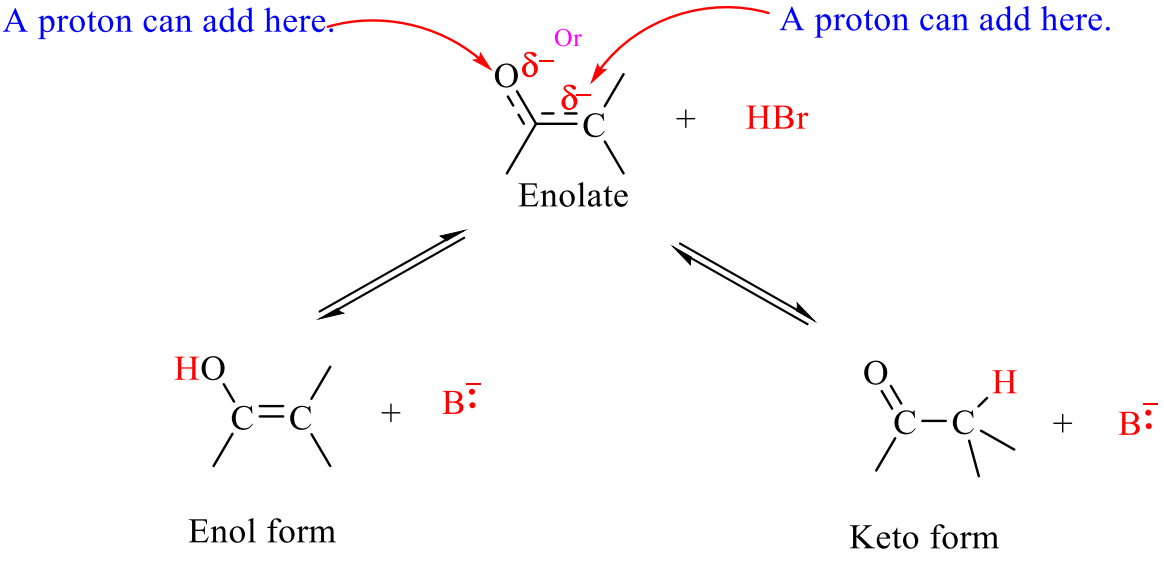
Two resonance structures, (A) and (B), can be written for the enolate. In structure (A) the negative charge is on carbon, and in structure (B) the negative charge is on oxygen. Both structures contribute to the hybrid. Although structure (A) is favored by the strength of its carbon–oxygen πbond relative to the weaker carbon–carbon πbond of (B), structure (B) makes a greater contribution to the hybrid because oxygen being highly electronegative, is better able to accommodate the negative charge. We can depict the enolate hybrid in the following way [4].



Scheme 02: Hybrid resonance structurefor an enolate

When this resonance-stabilized enolate accepts a proton, it can do so in either of two ways: it can accept the proton at carbon to form the original carbonyl compound in what is called the keto form or it may accept the proton at oxygen to form an enol (alkene alcohol).

- The enolate is the conjugate base of both the enol and keto forms.

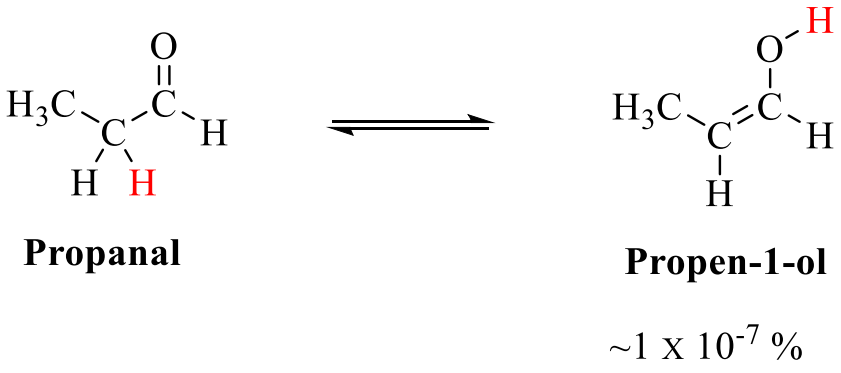


Scheme 03:Enolate as Conjugate Base of Enol and Keto Forms

I-3-Keto-enol Tautomerization

Because of the acidity of α-hydrogens, many carbonyl containing compounds undergo a proton-transfer equilibrium called tautomerism. Tautomers are readily interconverted constitutional isomers, usually distinguished by a different location for an atom or a group. Because tautomers involve the rearrangement of atoms, they are distinctly different than resonance forms, which only differ in the position of bonds and lone pair electrons. This discussion focuses on carbonyl groups with α-hydrogens, which undergo keto-enol tautomerism. Keto implies that the tautomer contains a carbonyl bond while enol implies the presence of a double bond and a hydroxyl group

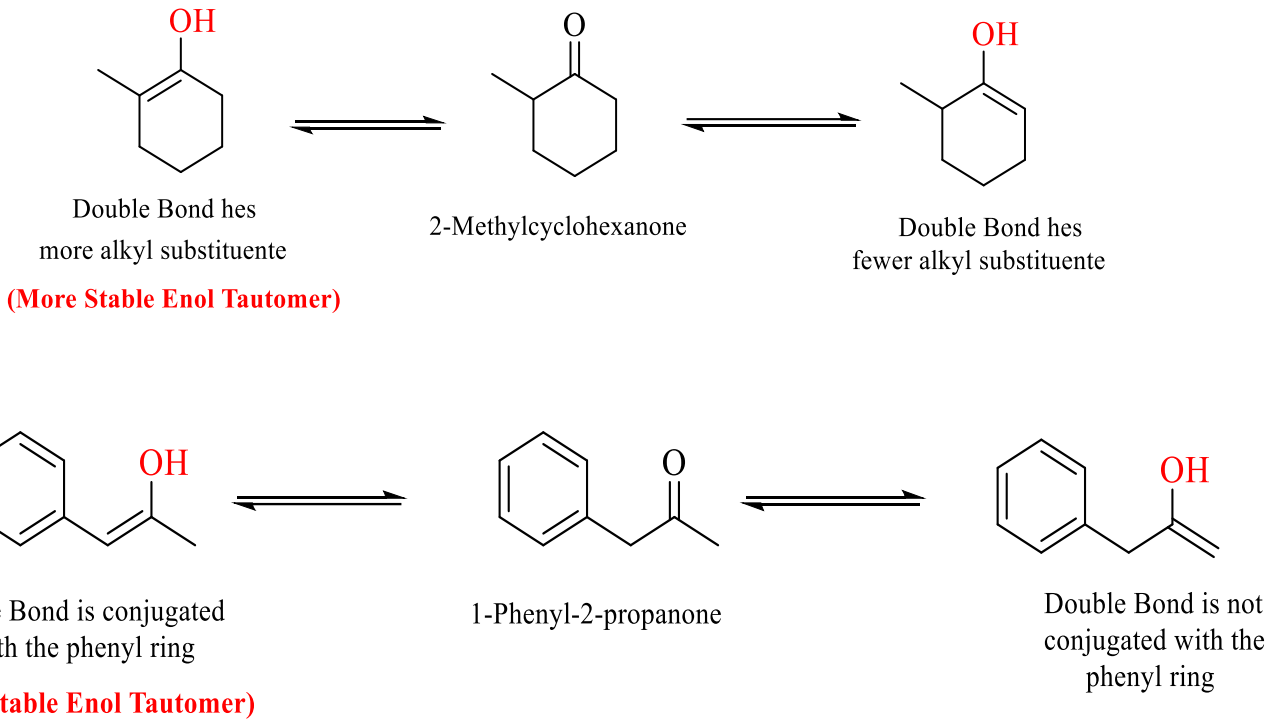
The keto-enol tautomerization equilibrium is dependent on stabilization factors of both the keto tautomer and the enol tautomer. For simple carbonyl compounds under normal conditions,the equilibrium usually strongly favors the keto tautomer (acetone, for example, is >99.999% keto tautomer). The keto tautomer is preferred because it is usually more stable than the enol tautomer by about 45–60 kJ/mol, which is mainly due to the C=O double bond (-749 kJ/mol) being stronger than the C=C double bond (-611 kJ/mol). Because ketones have two alky groups donating electron density into the carbonyl carbon, they tend to be more stable and therefore less apt to form the enol tautomer than aldehydes. For example, propanal is 1000 times more likely to be in its enol tautomer than acetone. With carboxylic acid derivatives, the leaving group tends to stabilize the carbonyl through electron donation which makes the formation of the enol tautomer much less likely. In general, ketones are over 100,000,000 times more likely to be in an enol tautomer form than esters[5].



Scheme 04: Understanding Keto-Enol Tautomerization

Aldehydes and symmetrical ketones typically only have one possible enol tautomer while asymmetrical ketones can have two or more. The preferred enol tautomer formed can be often be predicted by considering effects which can stabilize alkenes, such as conjugation and alkyl group substitution.

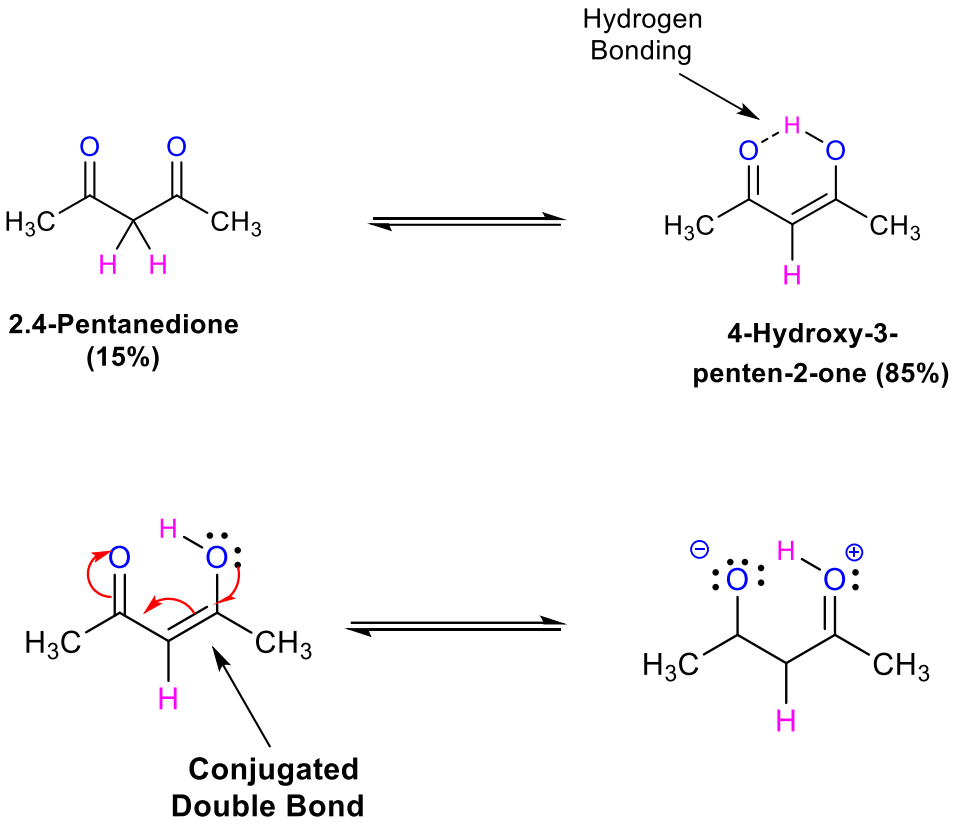
The asymmetrical ketone,2-methylcyclohexanone has two possible enol tautomers. Of the two tautomers, 2-methyl-1-cyclohexen-1-ol, is the more stable and therefore preferred due to the presence of an additional alkyl substituent. Likewise, 1-phenyl-1-propen-2-ol is the more stable enol tautomer of 1-phenyl-2-propanone due to conjugation with the phenyl ring[6].



Scheme 05: Predicting Preferred Enol Tautomers: Effects of Conjugation and Substitution in Ketones

I-4-Thermodynamically stable enols: 1,3-dicarbonyl compounds

In certain cases additional stabilizing effects allow the enol tautomer to be preferred in the tautomerization equilibrium. In particular, the 1,3 arrangement of two carbonyl groups can work synergistically to stabilize the enol tautomer, increasing the amount present at equilibrium. The diketone, 24-pentanedione, is in its enol form 85% of the time under normal conditions. The positioning of the carbonyl groups allows for the formation of a stabilizing intramolecular hydrogen bond between the hydroxyl group of the enol and the carbonyl oxygen. The alkene group of the enol tautomer is also conjugated with the carbonyl double bond which provides additional stabilization. Both of these stabilizing effects are not possible in the keto tautomer.[6]



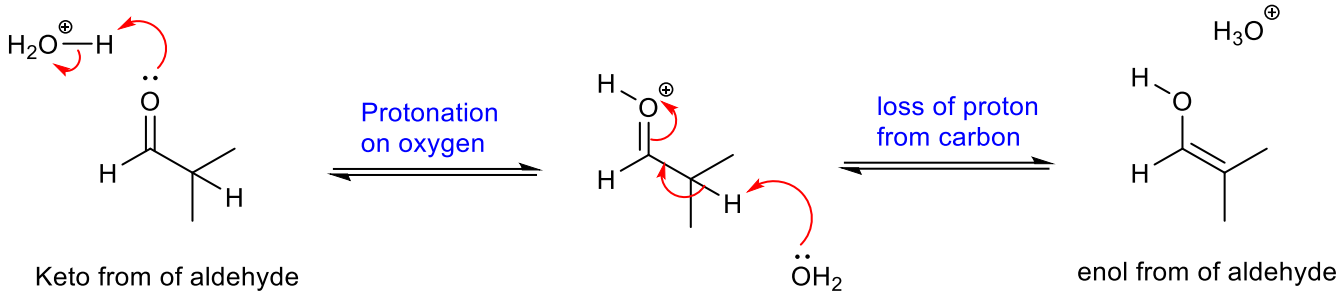
Scheme 06: The Dynamic Interplay Between Enol and Keto Tautomers

Another effect which can stabile an enol tautomer is aromaticity. When considering the molecule 2,4-cyclohexadienone, the enol tautomer is the aromatic molecule phenol. The stabilization gained by forming an aromatic ring is sufficient to make phenol the exclusive tautomer present in the equilibrium.[6]

Scheme 07: Stabilization of Enol Tautomers through Aromaticity

I-4-Enolization is catalysed by acids and bases

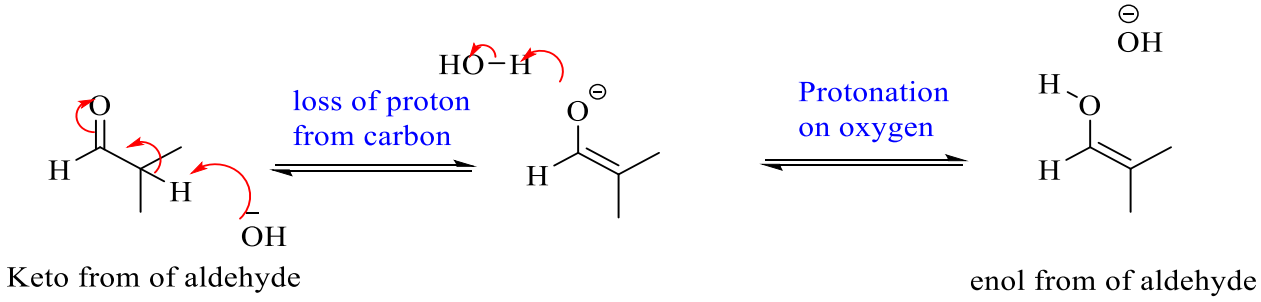
Enolization is, in fact, quite a slow process in neutral solution, even in D2O (the exchange described above might take place over a period of hours to days at room temperature), and we would catalyse it with acid or base if we really wanted it to happen fast. In the acid-catalysed reaction, the molecule is first protonated on oxygen and then loses a proton from Carbon in a second step. We shall use a different example here to show that aldehydes form enols too, but acid or base will catalyse enolization of any carbonyl compound in the same way [7].



Scheme 08: acid-catalyzed enolization of an aldehyde

This is a more detailed mechanism for enolization than those we have been drawing because it shows that something (here a water molecule) must actually be removing the proton from carbon. Although this reaction will occur faster than the uncatalysed enolization, the equilibrium is not changed and we still cannot detect the enol spectroscopically.

In the base-catalysed reaction the C–H proton is removed first by the base, say a hydroxide ion, and the proton added to the oxygen atom in a second step.



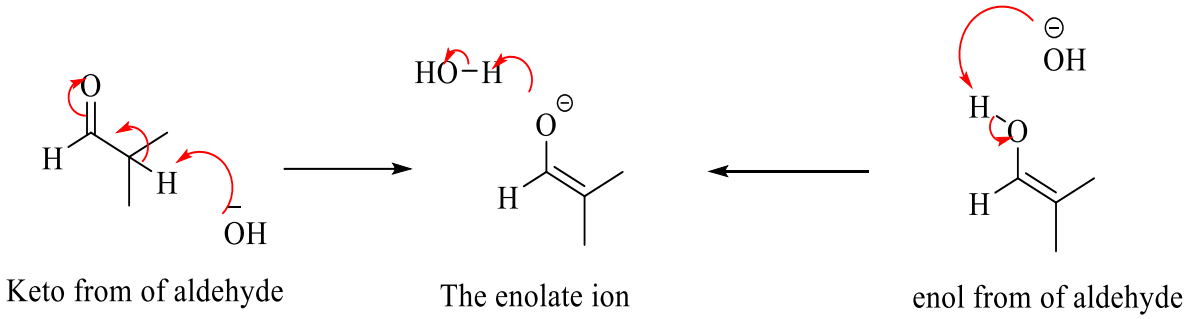
Scheme 09: Base- catalyzed enolization of an aldehyde

This is a good mechanism too because it shows that something must remove the proton from carbon and something (here a water molecule we don't, of course, have protons available in basic solution) must put the proton on the oxygen atom.

Notice that both of these reactions are genuinely catalytic. You get the proton back again (in the form of H_3O^+) at the end of the acid-catalysed mechanism, and you get the hydroxide ion back again at the end of the base-catalysed mechanism

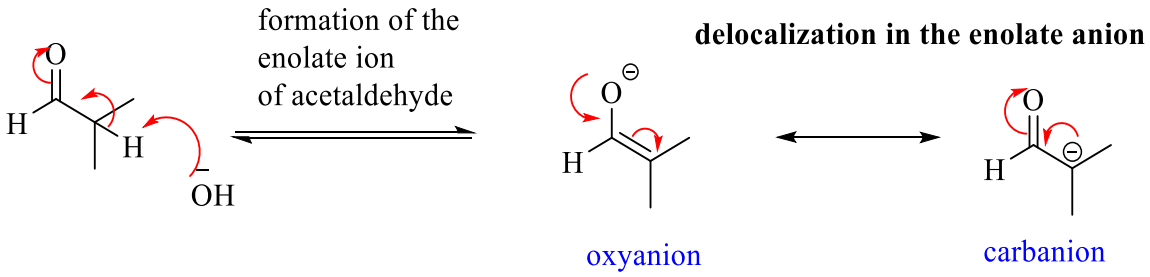
I-5- The intermediate in the base-catalysed reaction is an enolate ion

There are some more insights to be gained from the base-catalysed reaction. The intermediate anion is called the enolate ion. It is the conjugate base of the enol and can be formed either directly from the carbonyl compound by the loss of a C–H proton or from the enol by loss of the O–H proton.



Scheme 10: the enolate ion of an aldehyde

The enolate ion is one of those three-atom four-electron systems related to the allyl anion. The negative charge is mainly on oxygen, the most electronegative atom. We can show this with curly arrows using the simplest enolate possible (from MeCHO).



Scheme 11: formation of the enolate ion of an acetaldehyde

The enolate is a delocalized system, with negative charge carried on both C and O—we use a double-headed conjugation arrow to connect these two representations because the oxyanion and carbanion structures are just two different ways to represent the same thing. We shall usually prefer the oxyanion structure as it is more realistic[7].

Chapter II: The aldol condensation

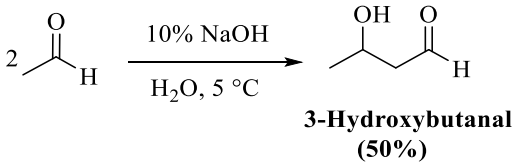
The aldol reaction is one of the most useful tools for the construction of carbon-carbon bonds, creating the β-hydroxy carbonyl derivatives. It provides an atom-economic approach to β-hydroxy carbonyls, which make up a large family of intermediates for the synthesis of biologically active substances and natural products. It is extensively applied in the synthesis of carbohydrates, amino sugars, steroids, and other valuable organic compounds. However, the most classical and conventional aldol reaction which involves the mixed aldol reaction between a ketone containing α-hydrogen with an aldehyde in the presence of base or acid has not been well exploited due to the following reasons side reactions such as self-condensation of the ketone or/and dimerization of the aldehyde can be a problem the harsh reaction conditions employed which usually require a strong acid or base make it unattractive for the complex molecule synthesis which contains acid or base sensitive functional groups the desired aldol product is usually accompanied by dehydrated products, dimmers, and polymers low regioselectivity is observed in most of the cases.Therefore, mild reaction conditions are much sought after to overcome some, if not all, the above problems **[7].**

II-2-Aldol Reactions:

II-2-1-Addition of Enolate and Enols to Aldehydes or Ketones

Aldol reaction and aldol condensations together represent an important class of C-C bond-forming reactions.

Always aldol reaction begins with addition of an enolate or enol to the carbonyl group of an aldehyde or ketone, leading to a *β*-hydroxy aldehyde or ketone as the initial product. A simple example is shown Scheme 10. Where two molecules of acetaldehyde (ethanal) react to form 3-hydroxybutanal.3-Hydroxybutanal is an “aldol” because it contains both an aldehyde and an alcohol functional group. Reactions of this general type are known as aldol reactions (aldol addition).



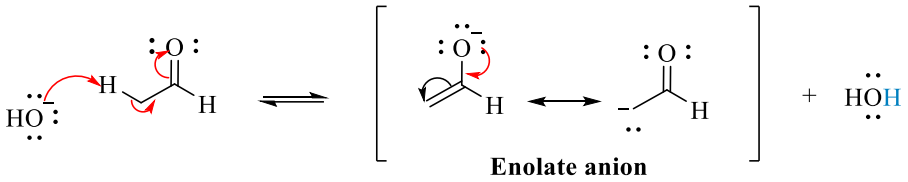
Scheme 12: treatment of acetaldehyde with strong base produces aldol compound.

As we shall see, the initial aldol addition product often dehydrates to form an*α*, *β*-unsaturated aldehyde or ketone. When this is the result, the overall reaction is an aldol reaction.

II-2-2- mechanism of aldol reaction

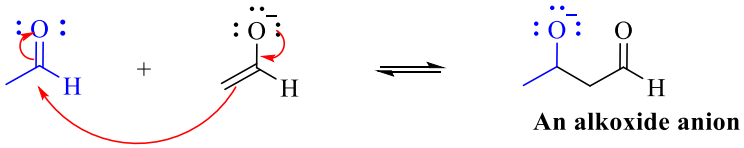
An aldol addition is an equilibrium reaction when it is conducted in a protic solvent with a base such as hydroxide or an alkoxide. The mechanism for an aldol reaction involving an aldehyde is shownScheme 13.

Step 1 Enolate formation



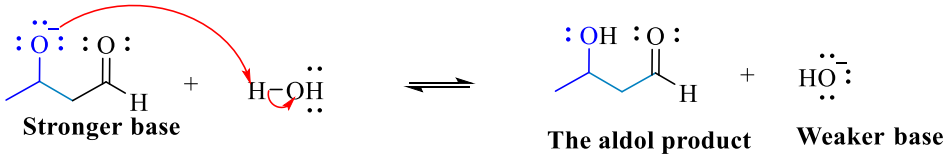
In this step the base (a hydroxide ion) removes a proton from the a carbon of one molecule of acetaldehyde to give a resonance-stabilized enolate

Step 2 Addition of the enolate



The enolate then acts as a nucleophile and attacks the carbonyl carbon of a second molecule of acetaldehyde, producing an alkoxide anion.

Step 3 Protonation of the alkoxide



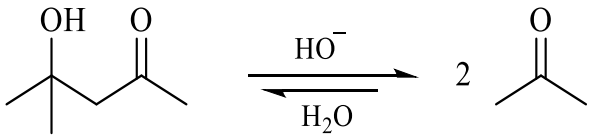
The alkoxide anion now removes a proton from a molecule of water to form the aldol product

Scheme 13: The mechanism for an aldol addition

With ketones, the addition step leading to the aldol is unfavorable due to steric hindrance, and the equilibrium favors the aldol precursors rather than the addition product. However, as we shall see in, dehydration of the aldol addition product can draw the equilibrium toward completion, whether the reactant is an aldehyde or a ketone. Enolate additions to both aldehydes and ketones are also feasible when a stronger base such as Lithium Diisopropylamide (LDA) is used in an aprotic solvent **[8].**

II-2-3-The Retro-Aldol Reaction

Because the steps in an aldol reaction mechanism are readily reversible, a retro-aldolreactioncan occur that converts a *β*-hydroxy aldehyde or ketone back to the precursors of an aldol reaction. For example, when 4-hydroxy-4-methyl-2-pentanone is heated with hydroxide in water, the final equilibrium mixture consists primarily of acetone, the retro-aldol product.

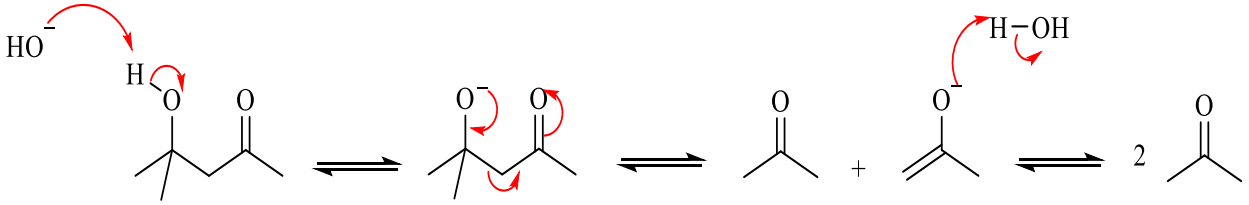


Scheme 14: The retro-aldol product.

This result is not surprising, because we know that the equilibrium for an aldol addition (the reverse of the reaction above) is not favorable when the enolate adds to a ketone. But, as mentioned earlier, dehydration of an aldol addition product can draw the equilibrium forward.

II-2-3-A- Mechanism of retro aldol reactions

Base removes the proton from the *β*-hydroxyl group, setting the stage for reversal of the aldol addition. As the alkoxide reverts to the carbonyl group, a C-C bond breaks with expulsion of the enolate as a leaving group. This liberates one of the original carbonyl molecules. Protonation of the enolate forms the other**[8].**

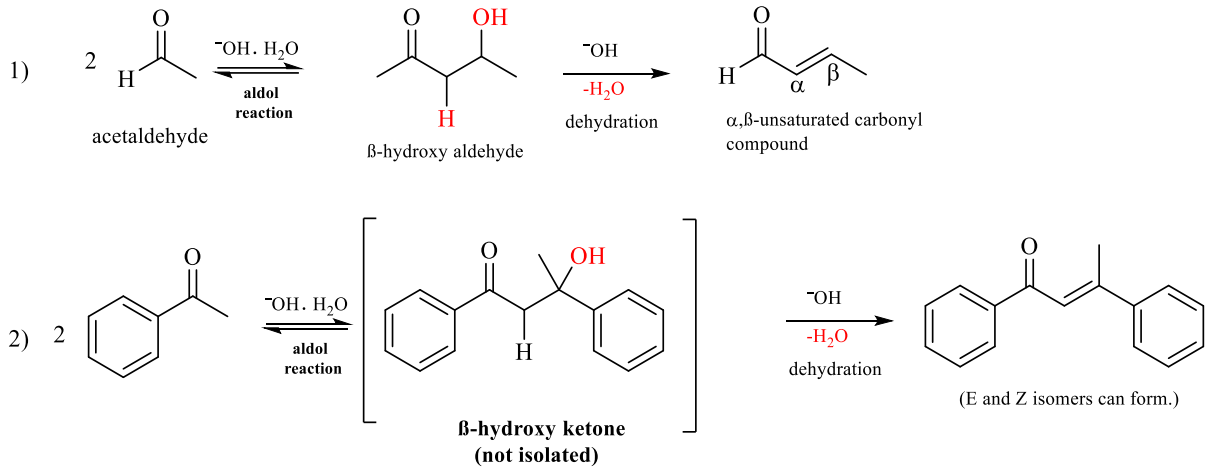


Scheme 15: Retro aldol reaction mechanism

II-3-Aldol Condensation Reactions:

II-3-1-Dehydration of The Aldol Addition Product

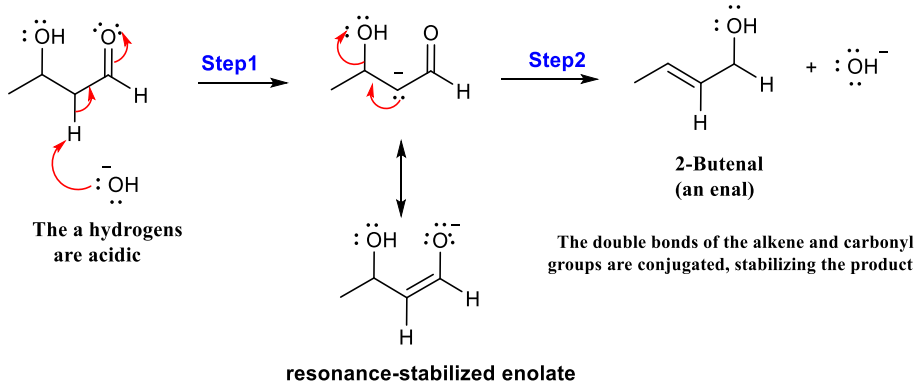
The β-hydroxy carbonyl compounds formed in the aldol reaction dehydrate more readily than other alcohols. In fact, under the basic reaction conditions, the initial aldol product is often not isolated. Instead, it loses the elements of H_2O from the α and β carbons to form an α,β-unsaturated carbonyl compound, a conjugated product.



Scheme 16:Aldol Products: Dehydration and Conjugation

It may or may not be possible to isolate the β-hydroxy carbonyl compound under the conditions of the aldol reaction. When the α,β-unsaturated carbonyl compound is further conjugated with a carbon–carbon double bond or a benzene ring, as in the case of reaction (2), elimination of H_2O is spontaneous and the β-hydroxy carbonyl compound cannot be isolated **[9].**

The mechanism of dehydration consists of two steps: deprotonation followed by loss of –OH, as shown Scheme 16:



Step 1 The base removes a proton on the α carbon to form a resonance-stabilized enolate

Step 2 –OH is eliminated as the electron pair of the enolate forms the new π bond.

Scheme 17: A Mechanism for Aldol Addition Product dehydration

This elimination mechanism, called the E1cB mechanism**,** differs from the two more general mechanisms of elimination, E1 and E2. The E1cB mechanism involves two steps, and proceeds by way of an anionic intermediate.

Regular alcohols dehydrate only in the presence of acid but not base, because hydroxide is a poor leaving group. When the hydroxy group is β to a carbonyl group, however, loss of H and OH from the α and β carbons forms a conjugated double bond,and the stability of the conjugated system makes up for having such a poor leaving group.

Dehydration of the initial β-hydroxy carbonyl compound drives the equilibrium of an aldol reaction to the right, thus favoring product formation. Once the conjugated α,β-unsaturated carbonyl compound forms, it is *not* re-converted to the β-hydroxy carbonyl compound **[9].**

II-3-2-The Base used in aldol reactions:

In aldol condensation reactions, a base is typically used to remove protons from the carbonyl compound and generate the enolate ion, which acts as the nucleophile in the reaction. The choice of base can greatly affect reaction rate, selectivity and efficiency. Some rules commonly used in aldol reactions are summarized in the following table 01.

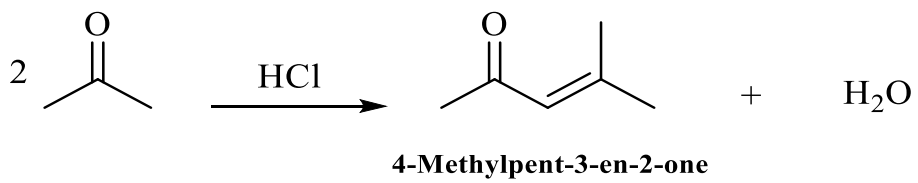
Base	Formula	Type	Comments
Hydroxide ion	OH^-	Strong base	Commonly used in aqueous aldol condensation reactions.
Alkoxide ions	RO^-	Strong base	Generated from alcohols and strong bases; used in non-aqueous aldol condensation reactions.
Lithium Diisopropylamide (LDA)	$LiN(i\text{-}Pr)_2$	Non-nucleophilic	Particularly useful for controlling regioselectivity and stereoselectivity in aldol reactions.
Sodium Hydroxide (NaOH)	NaOH	Strong base	Effective in promoting deprotonation in aqueous aldol condensation reactions.
Potassium Hydroxide (KOH)	KOH	Strong base	Similar to NaOH, commonly used in aqueous aldol condensation reactions
Sodium Hydride (NaH)	NaH	Strong base	Used in non-aqueous aldol condensation reactions, especially with water-sensitive substrates.
Potassium Hydride (KH)	KH	Strong base	Similar to NaH, used in non-aqueousaldol condensation reactions.

Table 01: Commonly Used Bases in Aldol Condensation Reactions

Each base listed above has specific characteristics and applications in aldol condensation reactions. The choice of base depends on factors such as the nature of the substrate, the solvent used, and the desired outcome of the reaction.

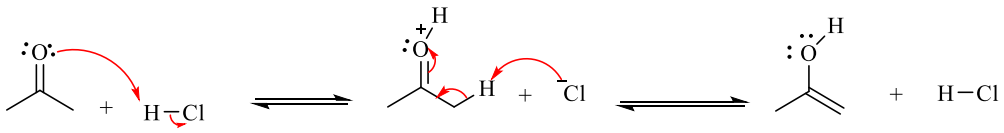
II-3-3- Acid-catalyzed Aldol condensations:

Aldol condensations can occur under acid catalysis, in which case the reaction generally leads to the *α*,*β*-unsaturated product by direct dehydration of the *β*-hydroxy aldol intermediate. This is one way by which ketones can successfully be utilized in an aldol reaction. The following is an example in which acetone forms its aldol condensation product, 4-methylpent-3-en-2-one, on treatment with hydrogen chloride**[10].**

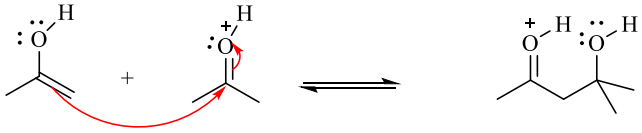


4-Methylpent-3-en-2-one

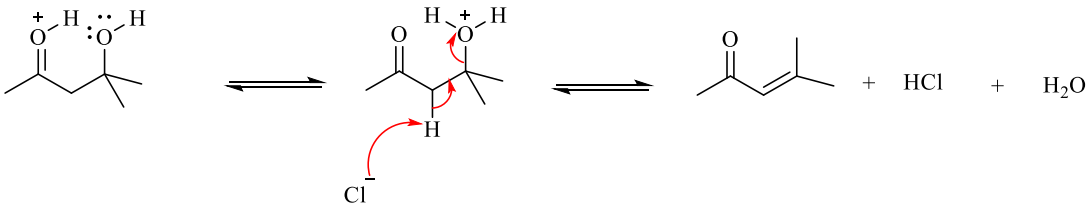
Scheme 18: The Reaction an Acid-Catalyzed Aldol Condensation



The mechanism begins with the acid-catalyzed formation of the enol



The enol then adds to the protonated carbonyl group of another molecule of acetone.



Proton transfers and dehydration lead to the product

Scheme 19: A Mechanism for The Reaction an Acid-Catalyzed Aldol Condensation

Acid catalysis can promote further reactions after the aldol condensation. An example is given in Practice Problem 19.8. Generally, it is more common in synthesis for an aldol reaction to be conducted under basic rather than acidic conditions.

II-4-Crossed Aldol condensations

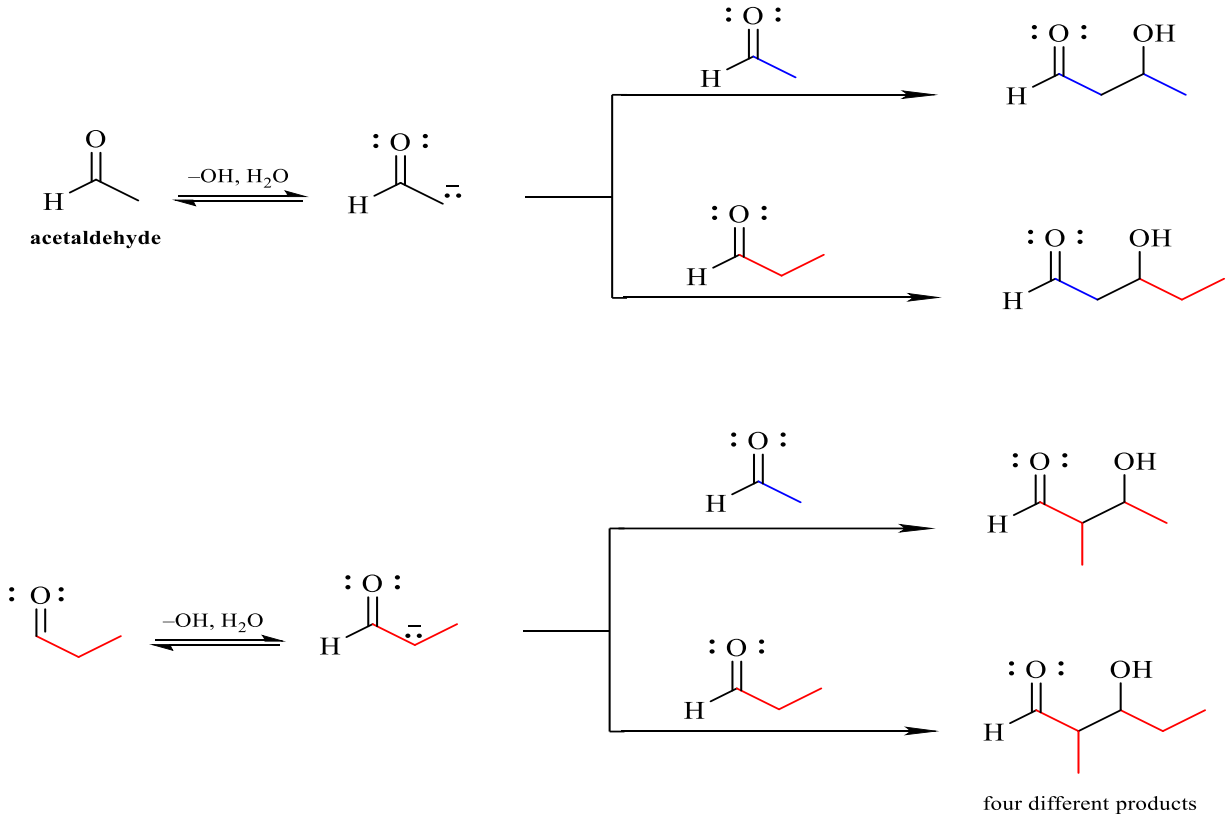
In all of the aldol condensations discussed so far, the electrophilic carbonyl and the nucleophilic enolate have originated from the same aldehyde or ketone. Sometimes, though, it is possible to carry out an aldol reaction between two different carbonyl compounds.An aldol reaction between two different carbonyl compounds is called a crossed aldol or mixed aldol reaction**.**

II-4-1-A Crossed Aldol condensations with Two Different Aldehydes

Both Having αH Atoms

When two different aldehydes, both having αH atoms, are combined in an aldol reaction, four different β-hydroxy carbonyl compounds are formed. Four products form, not one, because both aldehydes can lose an acidic α hydrogen atom and form an

enolate in the presence of base. Both enolates can then react with *both* carbonyl compounds, as shown for acetaldehyde and propanal in the following reaction scheme 19 **[11].**



Scheme 20: The Reaction of Acetaldehyde and Propanal

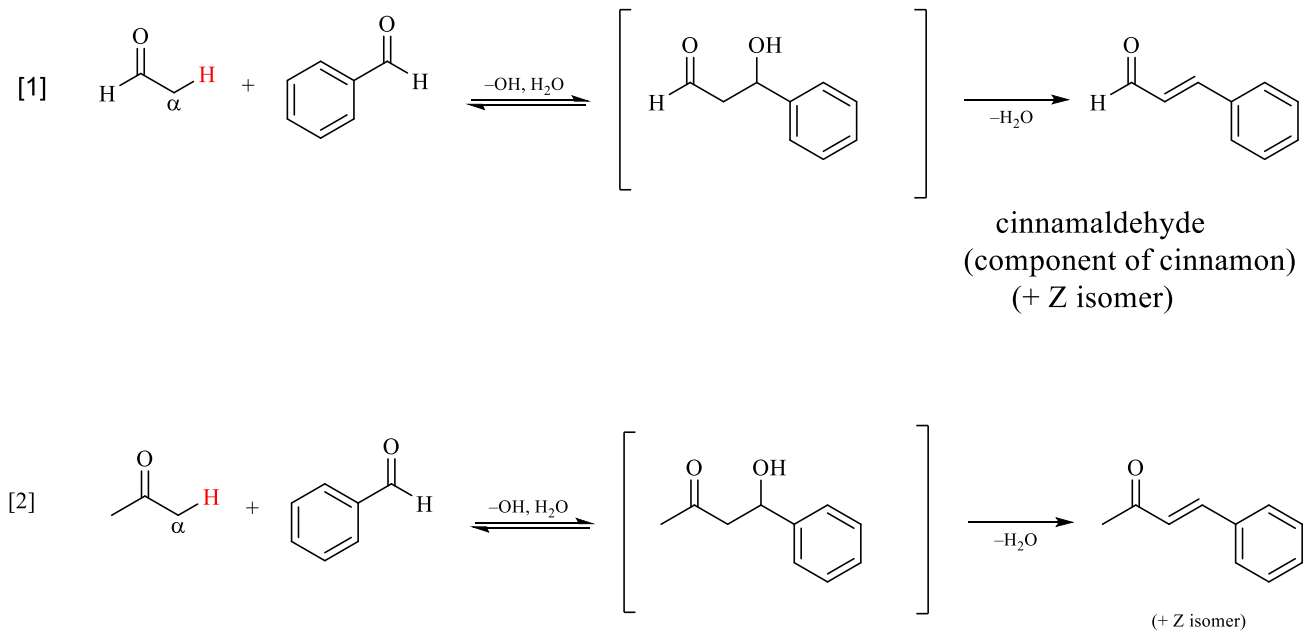
II-4-2-Synthetically Useful Crossed Aldol Condensations

Crossed aldols are synthetically useful in two different situations

A crossed aldol occurs when only one carbonyl compound has α H atoms.

When one carbonyl compound has no α hydrogens, a crossed aldol condensations often leads to one product. Two common carbonyl compounds with no α hydrogens used for this purpose are formaldehyde (CH_2=O) and benzaldehyde (C_6H_5CHO).

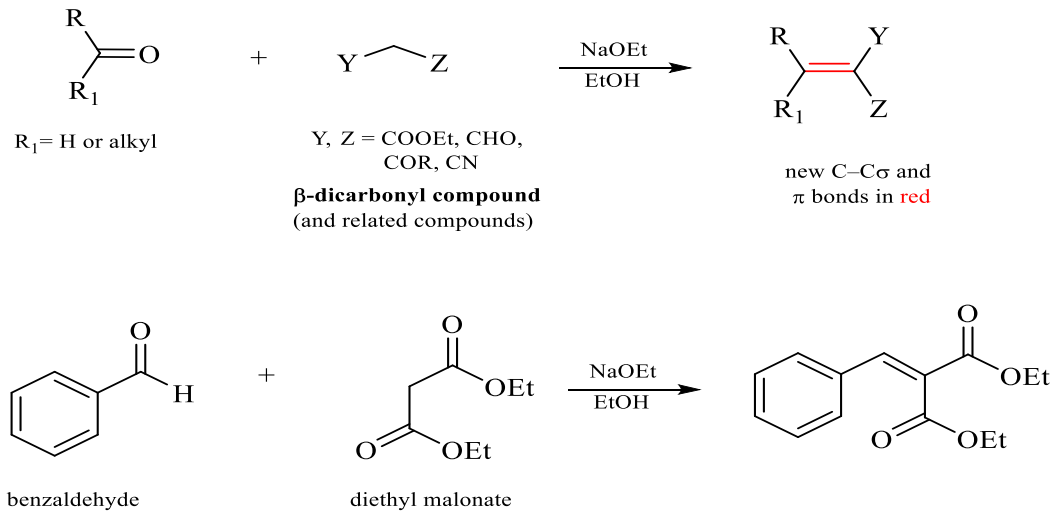
For example, reaction of C_6H_5CHO (as the electrophile) with either acetaldehyde (CH_3CHO) or acetone [$(CH_3)_2C$=O] in the presence of base forms a single α,βunsaturated carbonyl compound after dehydration give us cinnamaldehyde component us shown in scheme 19.



Scheme21:α,β-Unsaturated Compound Formation from Benzaldehyde and Aldehydes/Ketones

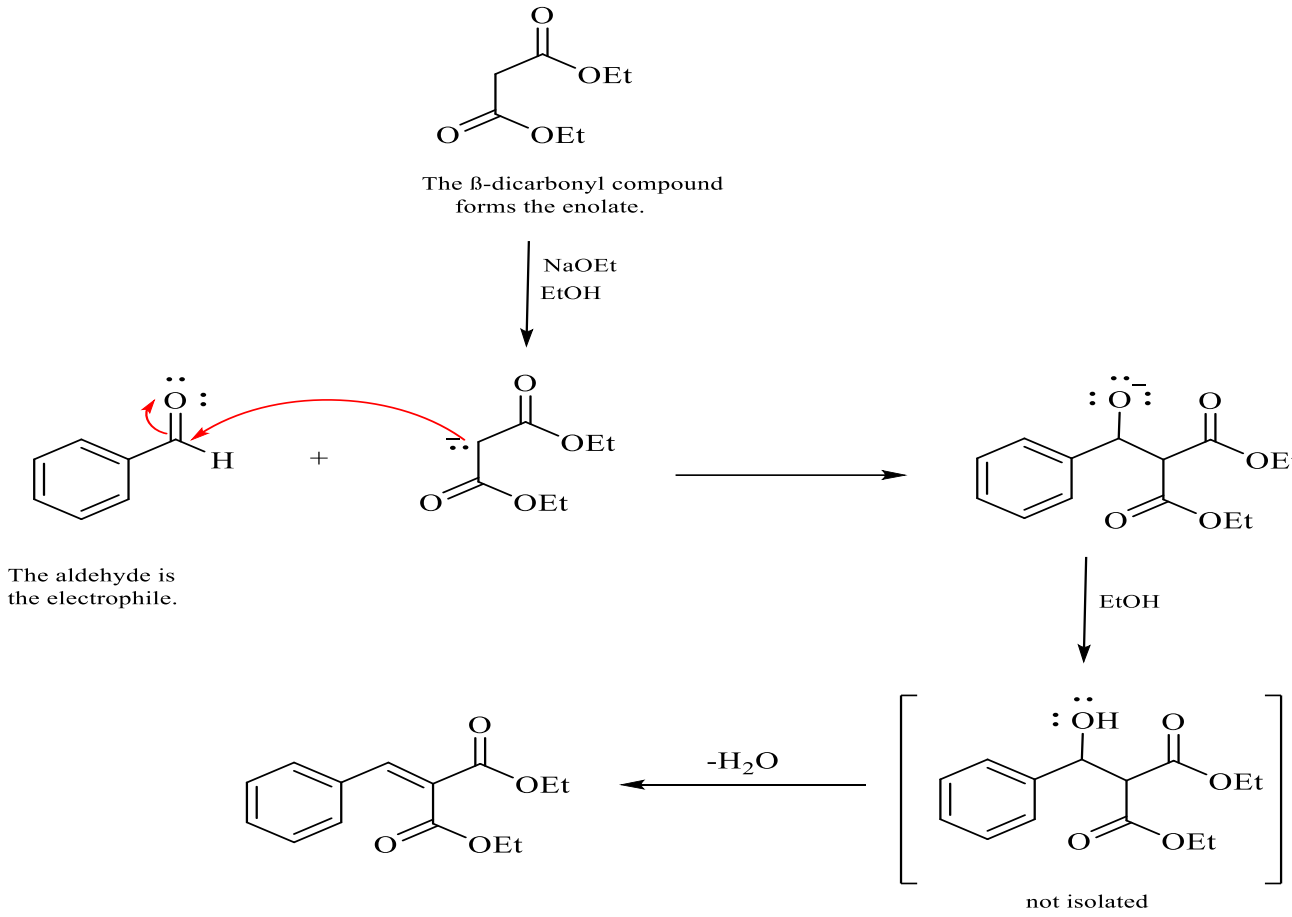
The yield of a single crossed aldol product is increased further if the electrophilic carbonyl component is relatively unhindered (as is the case with most aldehydes), and if it is used in excess..

A useful crossed aldol reaction takes place between an aldehyde or ketone and a β-dicarbonyl (or similar) compound.



Scheme 22: Increasing Yield through Unhindered Electrophiles and Surplus Reactants

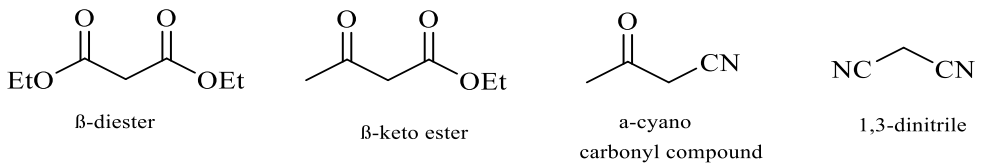
the α hydrogens between two carbonyl groups are especially acidic, and so they are more readily removed than other α H atoms. As a result, the β-dicarbonyl.



Scheme23: Crossed aldol condensations between benzaldehyde and CH2(COOEt)2

compound always becomes the enolate component of the aldol reaction. scheme shows 21 the steps for the crossed aldol reaction between diethyl malonate and benzaldehyde. In this type of crossed aldol reaction, the initial β-hydroxy carbonyl compound always loses water to form the highly conjugated product.

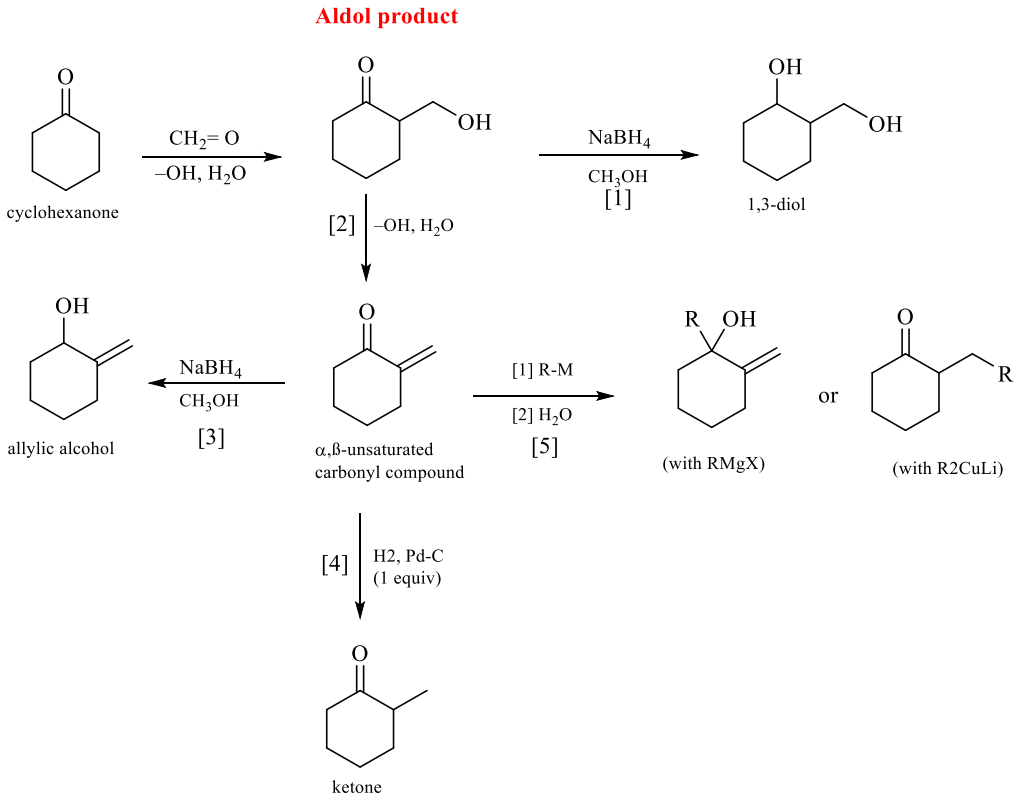
β-dicarbonyl compounds are sometimes called active methylene compounds because they are more reactive towards base than other carbonyl compounds. 1,3-Dinitriles and α-cyano carbonyl compounds are also active methylene compounds **[11].**



Scheme 24: Reactivity of β-Dicarbonyls in Crossed Aldol with Malonate-Benzaldehyde

II-4-3-Useful Transformations of Aldol Products

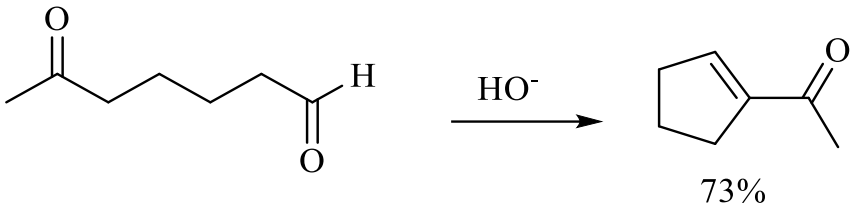
The aldol condensations are synthetically useful because it forms new carbon–carbon bonds, generating products with two functional groups. Moreover, the β-hydroxy carbonyl compounds formed in aldol reactions are readily transformed into a variety of other compounds. scheme 22 illustrates how the crossed aldol product obtained from cyclohexanone and formaldehyde (CH_2=O) can be converted to other compounds by reactions.



Scheme 25: Conversion of a β-hydroxy carbonyl compound into other compounds

II-5-Intramolecular Aldol condensations

The aldol condensation also offers a convenient way to synthesize molecules with fiveand six-membered rings (and sometimes even larger rings). This can be done by an intramolecular aldol condensation using a dialdehyde, a keto aldehyde, or a diketone as the substrate. For example, the following keto aldehyde cyclizes to yield1-cyclopentenyl methyl ketone us shown in scheme 23.



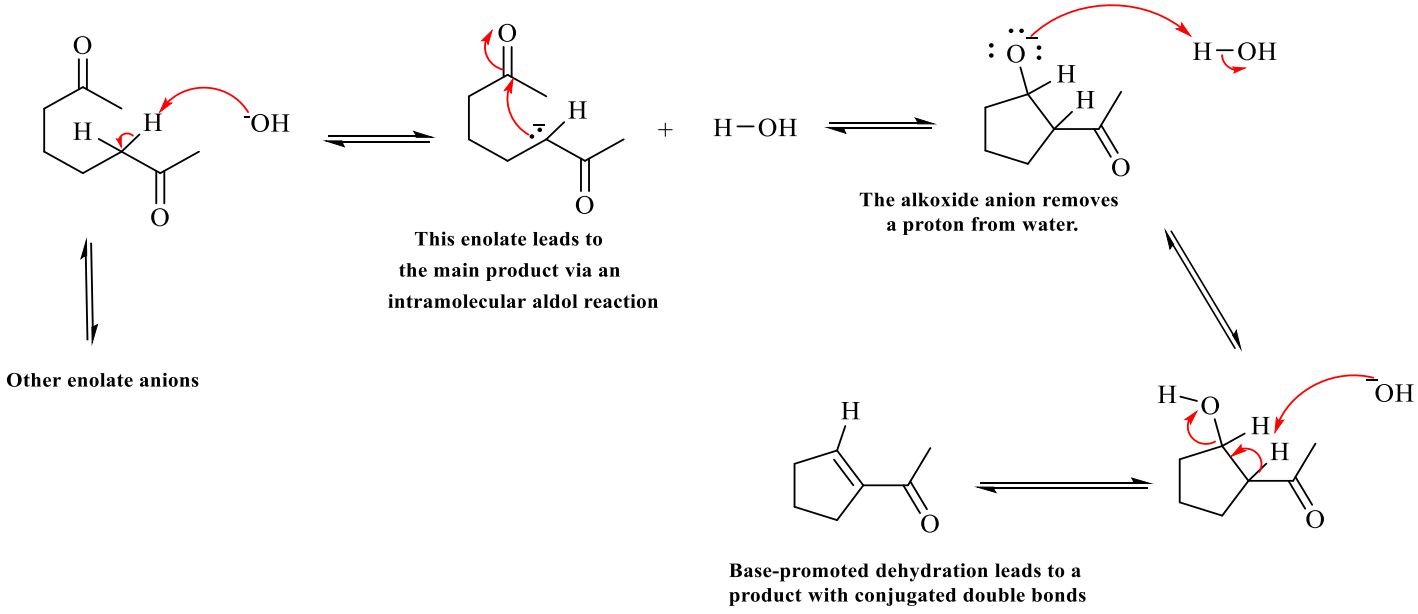
Scheme 26: Ketoaldehyde Cyclization: Synthesis of 1-Cyclopentenyl Methyl Ketone

This reaction almost certainly involves the formation of at least three different enolates. However, it is the thermodynamic enolate from the ketone side of the molecule that adds to the aldehyde group leading to the product.

The reason the aldehyde group undergoes addition preferentially may arise from the greater reactivity of aldehydes toward nucleophilic addition generally. The carbonyl carbon atom of a ketone is less positive (and therefore less reactive toward a nucleophile) because it bears two electron-releasing alkyl groups; it is also more sterically hindered.

Scheme 27: Reactivity and Nucleophilic Addition Preference: Aldehydes vs. Ketones

In reactions of this type, five-membered rings form far more readily than seven-membered rings, and six-membered rings are more favorable than four- or eight-membered rings, when possible **[11]**.



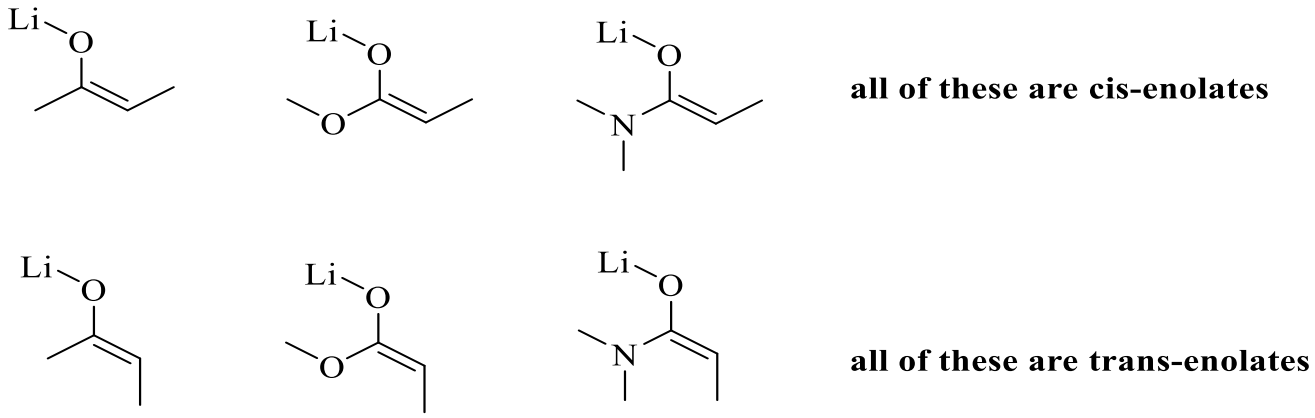
Scheme 28: Mechanism The Intramolecular Aldol Reaction

Chapter III: Stereochemistry of Aldol Condensation

Aldol condensation are pivotal in organic synthesis due to their versatility, particularly in crafting complex molecules with varied functionalities.Essential to their understanding is the intricate stereochemistry involved, dictating the configuration of products and guiding synthetic strategies. This overview provides a comprehensive exploration of aldol condensation stereochemistry, delving into mechanistic insights, factors influencing stereoselectivity, and advanced techniques for controlling stereochemical outcomes. By elucidating these principles, we empower researchers to navigate aldol synthesis with precision, ultimately advancing the field of organic chemistry.

III-1- Stereoselective Enolate Formation - Control of cis/trans Enolate Geometry

(*Z*) and (*E*) descriptors are usually used to assign the configuration of double bonds. Under normal circumstances this is more desirable than using the *cis* and *trans* nomenclature. However, confusion can arise when assigning the configuration of enolates. Some examples will illustrate the point：



Scheme 29: Challenges with Z and E Descriptors for Enolates

the geometry of a substituted enolate (cis or trans) can be very important in determining the stereochemical outcome of aldol condensation. In many cases the aldol reaction is stereospecific; thus if we can access either enolate geometry at will, it should be possible to control the stereochemistry in the aldol products. This Is crucial when preparing polypropionate Natural produs.

In the crossed aldol reaction, the enolate of one carbonyl group reacts with the carbonyl group (usually an aldehyde) of another. To avoid selfcondensation, the enolate component is invariably formed beforehand **[12].**

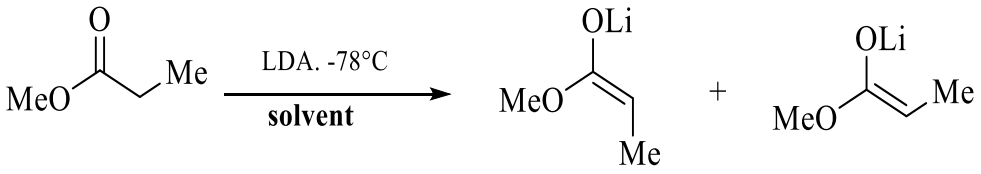
We will consider the reaction of three types of enolate.

- lithium enolates
- boron enolates
- silyl enol ethers

III-1-1-Lithium Enolates in the Aldol Condensation

Lithium- enolates play a pivotal role in the Aldol Condensation. They serve as versatile nucleophiles, enabling the formation of carbon-carbon bonds through the addition of an enolate to a carbonyl compound. This process is highly dependent on the reaction conditions and the specific substrate involved. By carefully controlling factors such as temperature, solvent, and the nature of the enolate, chemists can achieve high levels of selectivity in terms of both regio- and stereochemistry. Additionally, the use of lithium enolates offers advantages such as enhanced reactivity and the ability to access a wide range of complex molecular architectures. As a result, they are widely employed in the synthesis of natural products, pharmaceuticals, and other valuable organic molecules **[13].**

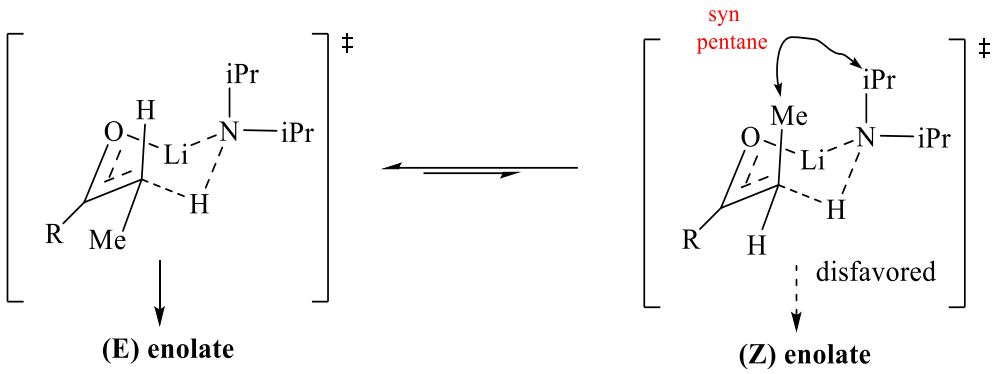
III-1-1-1- Lithium Enolates (and Polar Additives) [14]



THF	94	06
23% **HMPA**-THF	15	85
45% **DMPU**-THF	07	93

Scheme 30: Lithium Enolates and Their Interaction with Polar Additives

• The Ireland Model



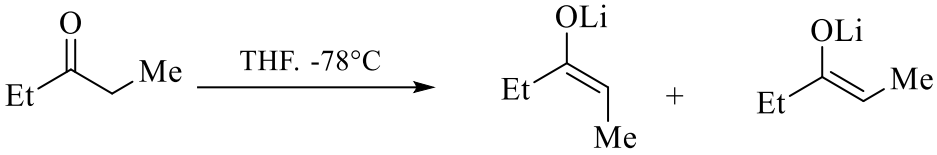
Scheme 31:The Ireland Model

-steric interactions minimized in pericyclic chair-like transition state

-poor orbital overlap suggests this model may not be realistic

-model does not account for Z-selective enolization methods. **[15]**

III-1-1-2-Lithium Enolates (and LiX Additives) [16]



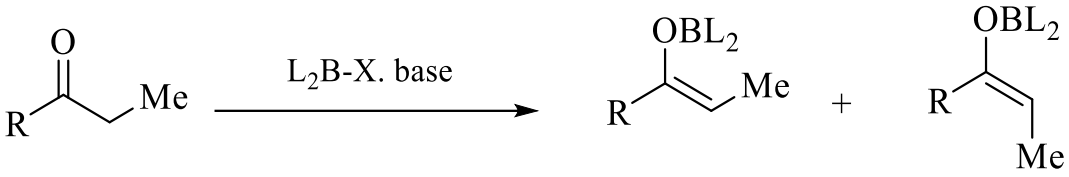
conditions	(E) enolate	(Z) enolate
LDA	77	23
LiTMP	86	14
LiTMP. 10% LiBr	98	02

Scheme 32:Utilizing Lithium Enolates and LiX Additives

III-1-2-Boron Enolates in Aldol Condensation

Synthesis of highly selective enol in return governs the selectivity of the product obtained in aldol synthesis as was observed in the case of directed Aldol Synthesis chapter. Preparation of boron enolates offers an advantage of obtaining highly selective enolate to control aldol condensation.

Boron enolate may be formed by reacting the carbonyl compound (containing α-hydrogens) with the triflic salt of the dialkyl boron compound in the presence of base such as diisopropyl ethyl amine **[17].**



R	conclitions	(E) enolate	(Z) enolate
Et	BuBOTf, iPr_2NEt	<03	**>97**
	9-BBN, Et_3N	<03	**>97**
	Cy_2BCl, Et_3N	**79**	21
iPr	Cy_2BCl, Et_3N	**>97**	<03

Scheme 33: Controlled Aldol Synthesis Through Boron Enolates: A Directed Approach

-L2BOTf reagents favor the formation of (Z) enolates

-L2BCI reagents favor the formation of (E) enolates

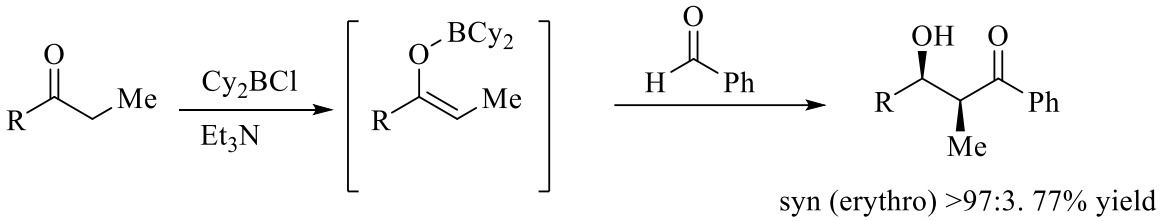
he formation of the enolate is more selective in case of Boron as compared to Lithium salts due to two reasons **[18].**

1 The boron-oxygen bonds are shorter, therefore the cyclic transition state formed is more compact and rigid thus allowing the substituents to play a greater part in the stereo control **[18]**.

2 The substituents on the boron atom (R) can be made very bulky in order to control selectivity for the enolate formed **[18]**.

Therefore, the stereochemistry of enolization is influenced by:

1. The alkyl groups on the boron atom and their bulkiness.
2. The leaving group on the boron (in the case above it is triflate).
3. The base involved in the reaction.



Scheme 34: Stereoselective Aldol Condensation Using Boron Enolate

III-1-2-3The Paterson Model for Stereoselective Enolization

This model helps explain why certain reactions occur the way they do when ketones are turned into enols, a process called ketone enolization. It looks at two main factors:

1) How the Lewis acid interacts with the ketone: Different chemicals can bind to the ketone molecule in different ways. For example, in the case of using L2BCI

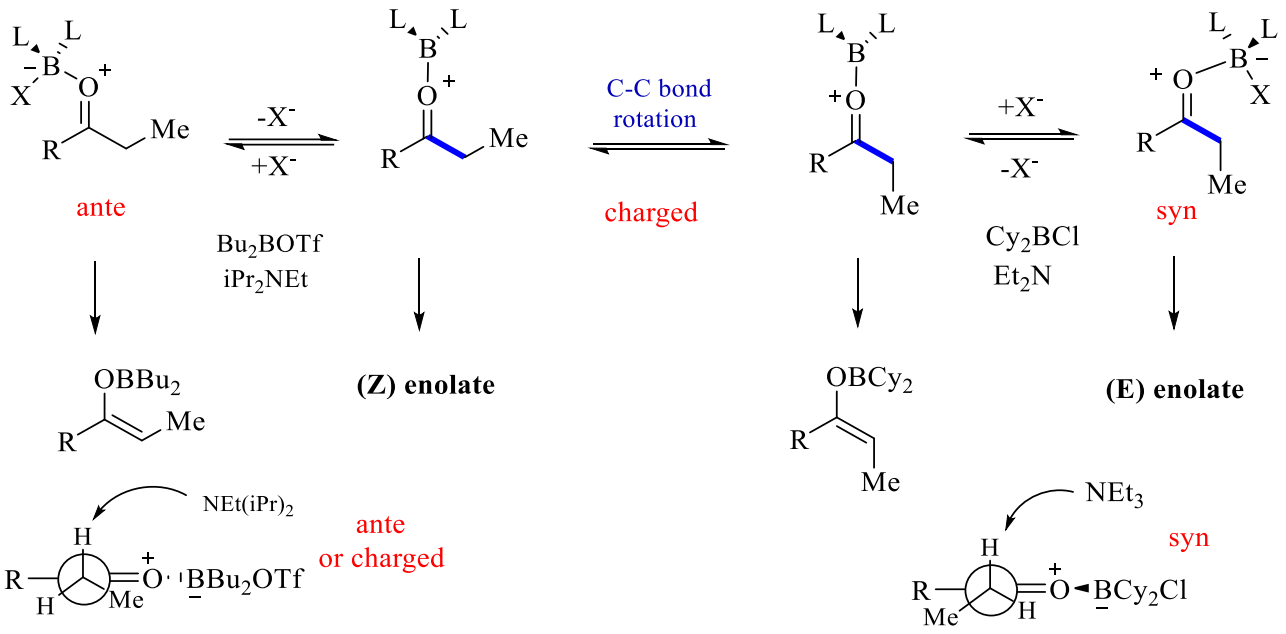
(L = Hex, Ipc) and Et3N with butanone, the chloride part of the reagent attaches to the side of the ketone that has fewer other groups attached to it (less substituted side). This attachment makes that side more likely to react.

2) How easy it is to remove a hydrogen from the adjacent carbon atoms: A certain type of amine base, like Et3N, can easily remove a hydrogen from the carbon atoms next to the ketone. This depends on the structure of the ketone and the surrounding molecules.

For example, when using L2BCI and Et3N with butanone, the chloride part attaches to the less crowded side of the ketone, making it easier for the amine to remove a hydrogen from the adjacent carbon on that side. This results in the formation of the enol predominantly on that side.

Similarly, using different combinations of reagents and ketones can lead to different outcomes. For instance, with certain ketones, the presence of bulky groups can interfere with the reaction, leading to different products.

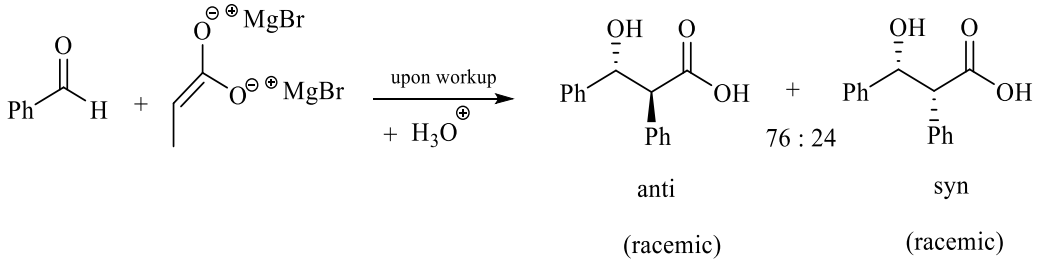
Overall, this model helps predict which products will form in ketone enolization reactions based on the structure of the ketone and the reagents used **[19].**



Scheme 35: The Paterson Model for Stereoselective Enolization

III-2 - Ivanov reaction

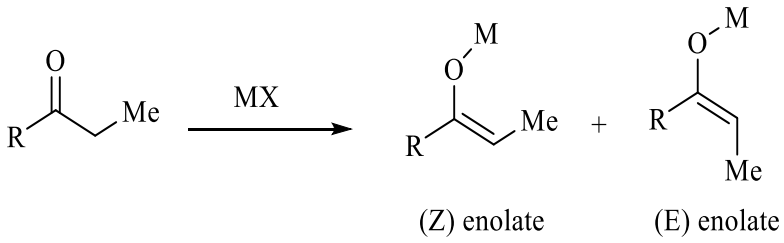
The simple diastereoselectivity of aldol condensation was first studied in detail for the Ivanov reaction (scheme 24). The Ivanov reaction consists of the addition of a carboxylate enolate to an aldehyde. In the example of scheme 24, the diastereomer of the b-hydroxycarboxylic acid product that is referred to as the *anti*-diastereomer is formed in a threefold excess in comparison to the *syn*-diastereoisomer **[20]**.

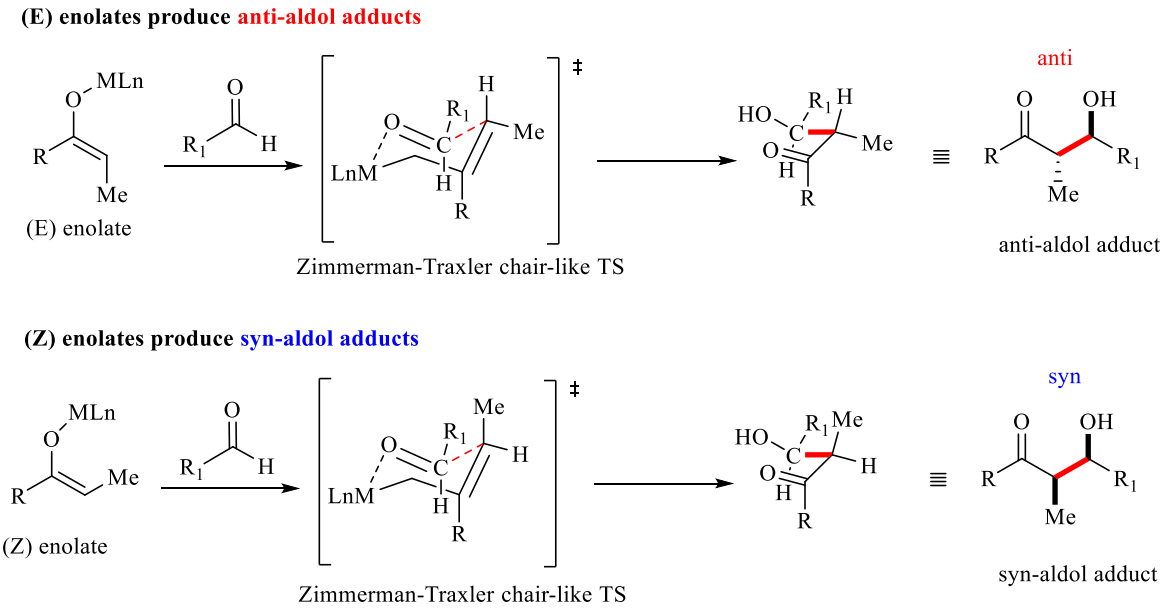


Scheme 36: The Ivanov reaction

II-3-Zimmerman–Traxler model

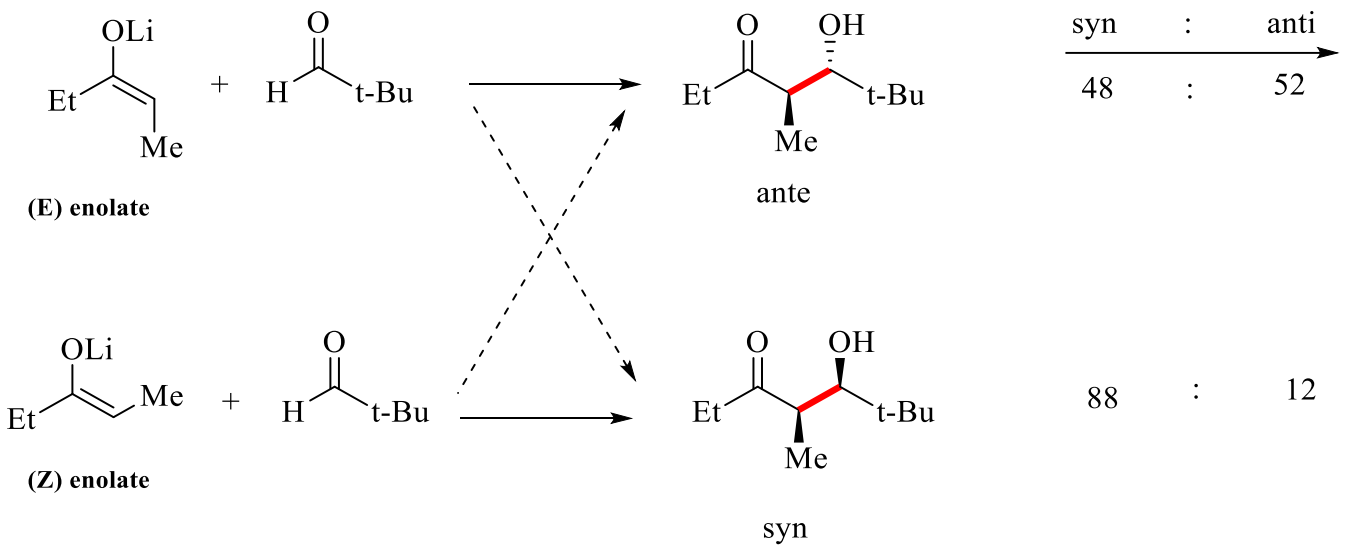
More refined forms of the mechanism are known. In 1957, Zimmerman and Traxler proposed that some aldol reactions have "six-membered transition states having a chair conformation." This is now known as the Zimmerman-Traxler model. E-enolates give rise to anti products, whereas Z-enolates give rise to syn products. The factors which control selectivity are the preference for placing substituents equatorially in six-membered transition states and the avoidance of syn-pentane interactions, respectively. E and Z refer to the cis-trans stereochemical relationship between the enolate oxygen bearing the positive counterion and the highest priority group on the alpha carbon. In reality, only some metals such as lithium and boron reliably follow the Zimmerman-Traxler model.Thus, in some cases, the stereochemical outcome of the reaction may be unpredictable **[21]**.





Scheme 37: Zimmerman–Traxler model

Dubois found in 1975 that there is an approximate relationship between the geometry of enolates and the stereochemistry of the product of the aldol condensation **[22].**



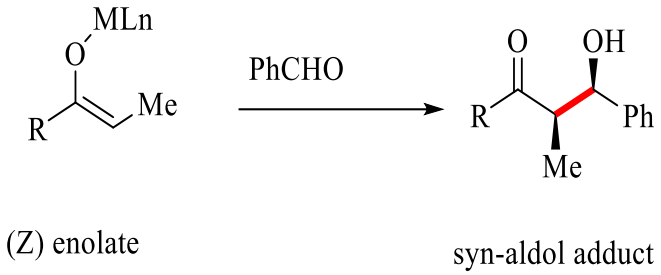
Scheme 38: The relationship between enolate geometry and product stereochemistry in aldol reactions

II-3-1-Effect of Enolate Size

- diastereoselectivity results from the minimization of developing syn pentane

(1, 3-diaxial) interactions in each chair-like transition state (~3.7 kcal/mol)

- as axially- oriented enolate substituent (above: Et) enlargens, the reaction diastereoselectivity often improves regardless of metal identity **[23].**



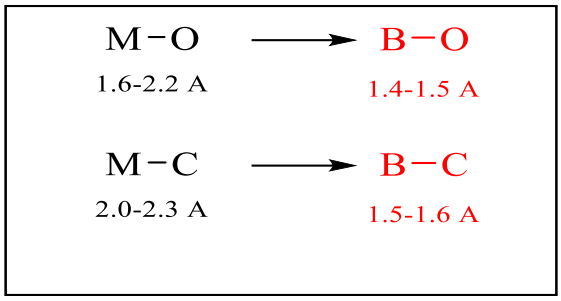
R	MLn	syn:anti
Et	Li	80:20
t-Bu	Li	>98:2
	MgBr	>95:5
	BBu_2	>97:3

Scheme 39: Diastereoselectivity: Syn Pentane, Enolate Size Impact.

II-3-2-Effect of Metal Identity

diastereoselectivity can be highly metal dependent, with boron often providing the highest levels of stereocontrol

Boron tightens transition states by virtue of the short bonds it forms: **[24]**



	R	ML_n	syn:anti
	Et	Li	80:20
		BBu_2	>97:03
	Ph	Li	80:20
		BBu_2	>97:03
		9-BBN	98:02
vis(E) enolate →	Ph	BCy_2	05;90

Scheme 40: Metal-Dependent Diastereoselectivity: Boron's Superior Stereocontrol

III-3-Mukaiyama aldol addition (Silyl Enol Ethers in Aldo Condensation)

The Mukaiyama aldol Condensation is the nucleophilic addition of silyl enol ethers to aldehydes catalyzed by a Lewis acid such as boron trifluoride or titanium tetrachloride. The Mukaiyama aldol reaction does not follow the Zimmerman-Traxler mothod. It gives high levels of enantioselectivity and wide substrate scope.

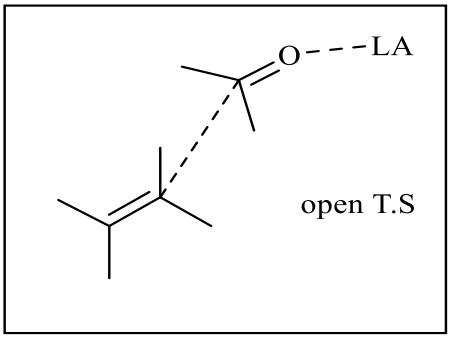
.The method works on unbranched aliphatic aldehydes, which are often poor electrophiles for catalytic, asymmetric processes. This may be due to poor electronic and steric differentiation between their enantiofaces.

-TMS enol ethers are much less nucleophilic than boron or lithium enolates and do not reactdirectly with aldehydes.

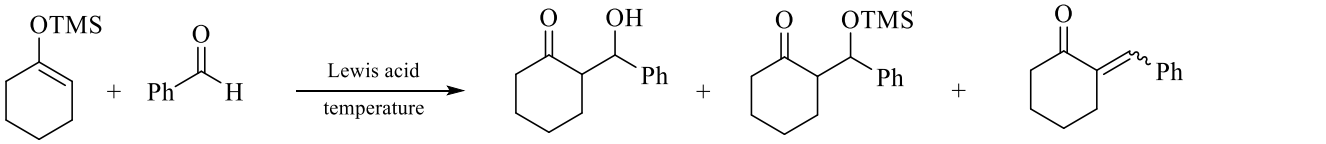
- Lewis acid complexation increases the electrophilicity of aldehydes and this is sufficient toallow reaction.

- The reaction mechanism is quite different to that of lithium or boron enolates described above.Internal coordination and reaction through a 6-membered T.S. is not possible with siliconsince the silicon atom is not Lewis acidic.

- Reaction proceeds through an open T.S.



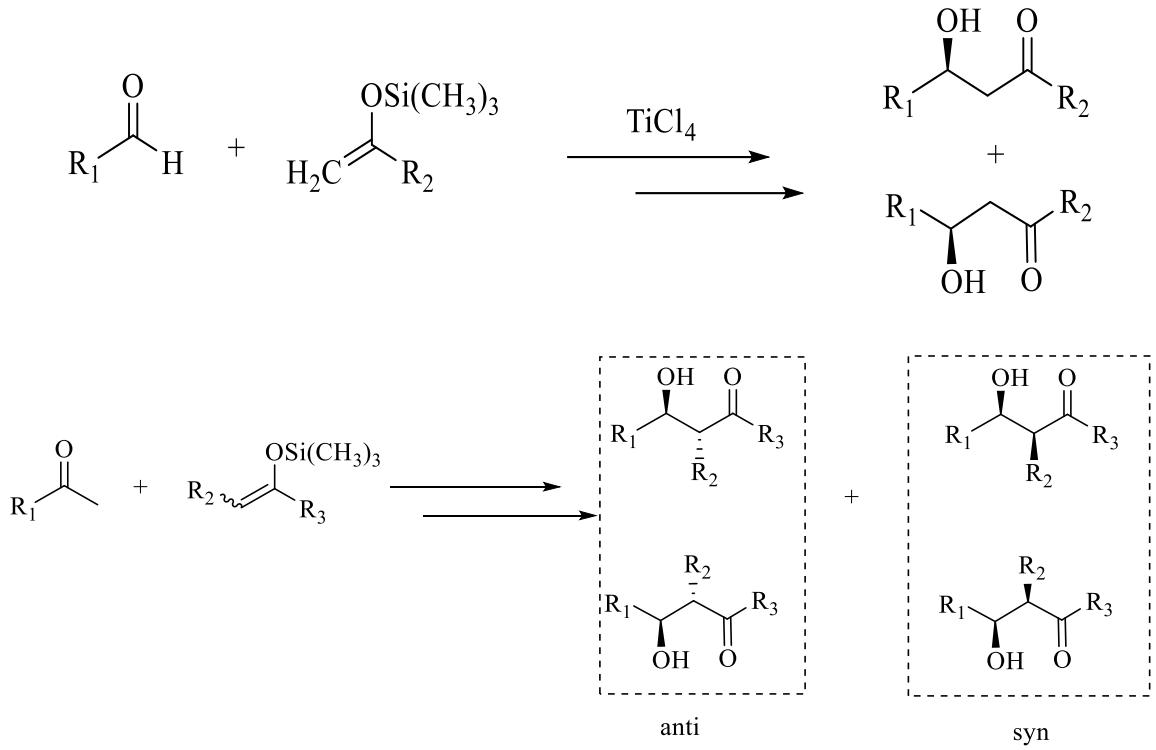
-stereoselectivity of the reaction is usually low (this can be attributed to there being several low energy T.S.s through which reaction can proceed **[25]**



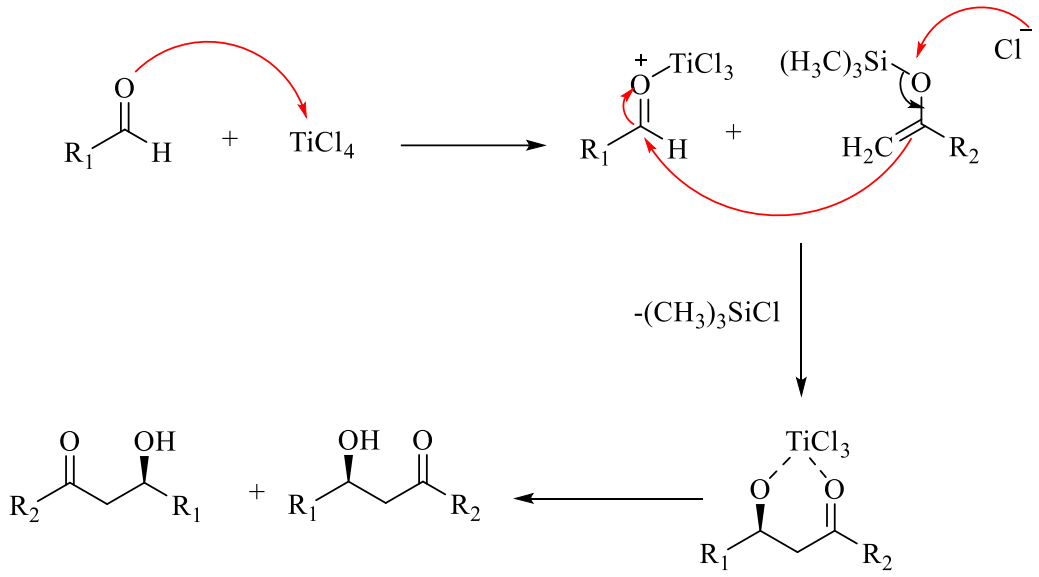
dehydration is a common side-reaction in aldol reactions

$TiCl_4$, -78°C	92%	0%	0%
$SnCl_4$, -78 °C	83%	trace	trace
$BF_3{\cdot}OEt_2$, -78 °C	80%	12%	0%

Scheme 41: Distinct Reactivity: Silicon Enolates vs. Lithium and Boron Enolates



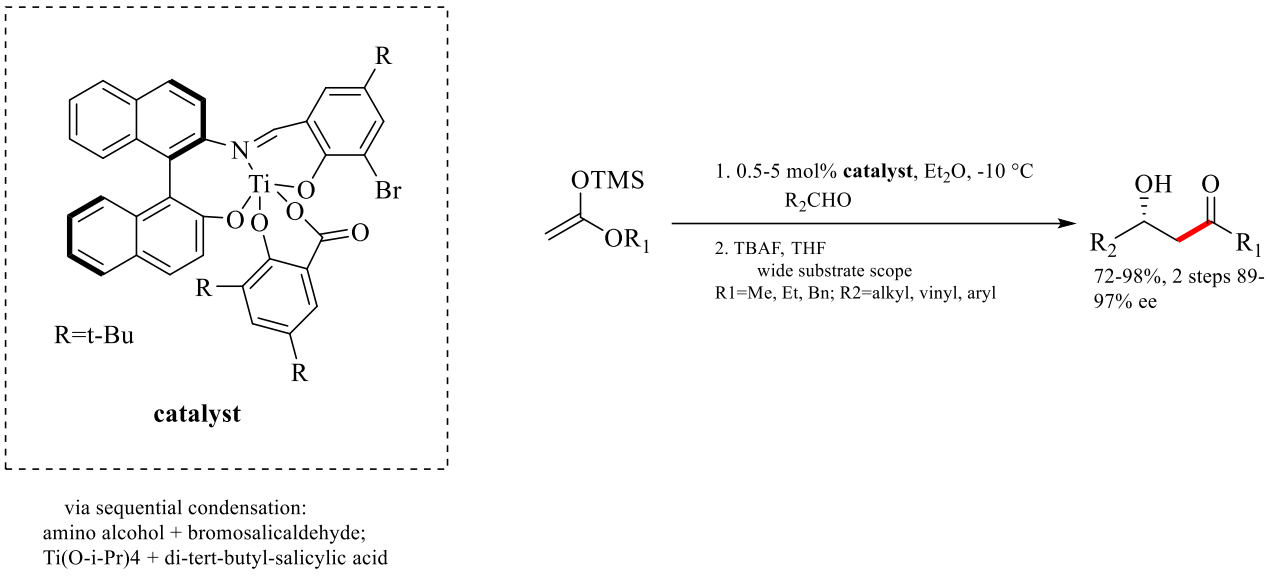
Scheme 42: Transition-state for *syn*-selective transformations



Scheme 43: Mechanism of the Mukaiyama Aldol Addition

The use of chiral Lewis acids in sub-stoichiometric quantities provides one important method for controlling the stereoselectivity of this reaction and is rapidly becoming a

very useful method. One example developed by Carreira will serve to illustrate the idea **[26].**



Scheme 44: Enhancing Stereoselectivity with Chiral Lewis Acids

III-4-Diastereofacial Selectivity

So far we have discussed three types of enolate which sometimes give high levels of simple diastereoselectivity (syn or anti product) in the aldol reaction. In most cases, relative stereocontrol is determined by the geometry of the enolate (cyclic T.S. with boron or lithium enolates).

To control the absolute stereochemistry of the reaction requires π-facial selectivity. There are three methods for tackling this problem:

1-Substrate control in which stereochemical information in the substrate(s) directs the stereochemical outcome of the reaction.

2-Auxiliary control involves the use of a temporary directing group usually attached to the enolate.

3-Reagent control in which chiral ligands on the metal enolate or a chiral Lewis acid provide the stereocontrol.

We will consider each in turn.

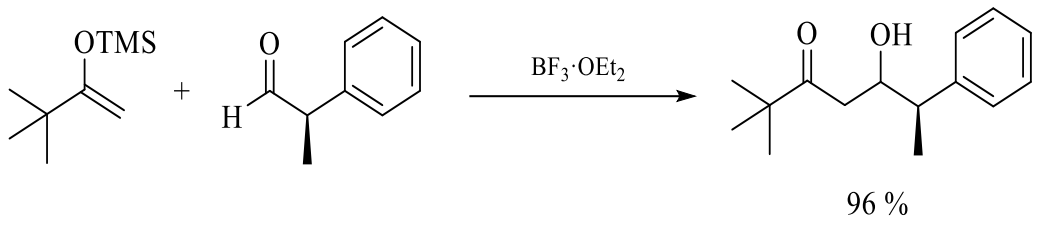
III-4-1-Substrate Control

Chiral Aldehyde and Achiral Enolate

-Aldehydes which possess an α -stereogenic centre often react with high levels of

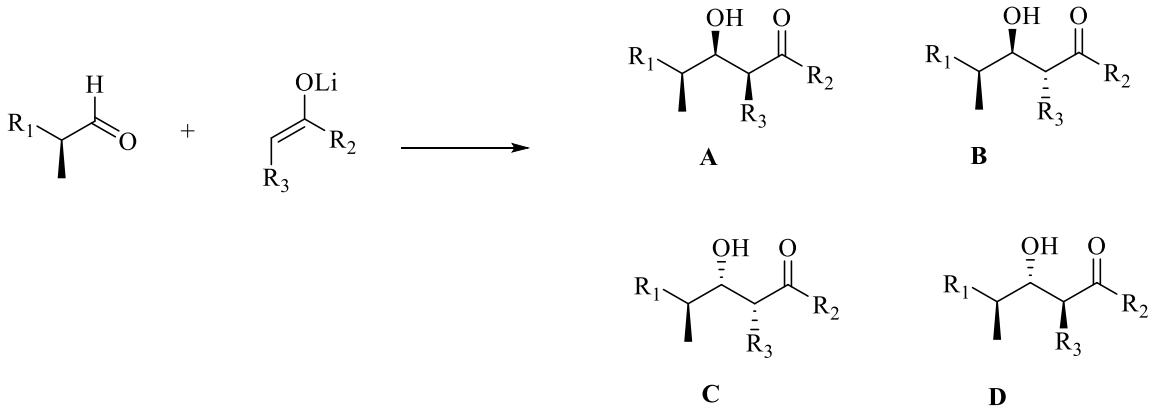
Stereocontrol.

- The nature of the groups attached to the stereogenic centre as well as the precise reaction conditions will determine which type of T.S. is adopted.



Scheme 45: Reactions of Chiral Aldehydes with Achiral Enolates

In the case of substituted enolates, relative and absolute stereocontrol must be considered. Use the enolate geometry to control the relative stereochemistry and the stereogenic centre in the aldehyde to control the π-facial (i.e. absolute) stereochemistry

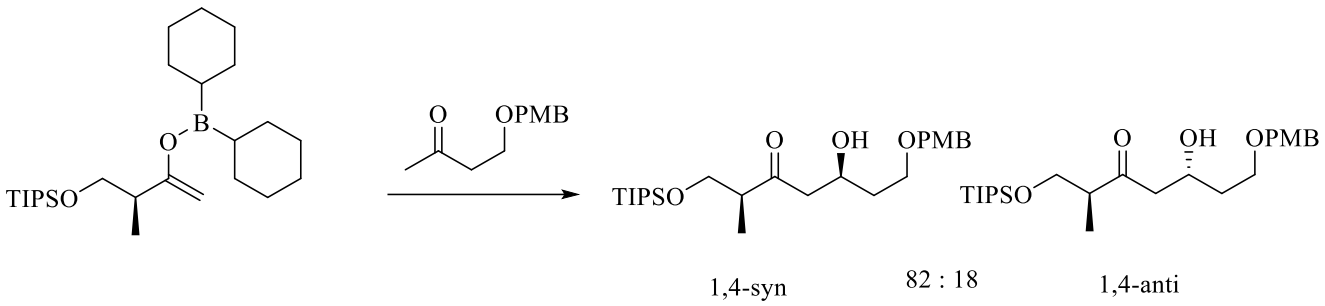


Scheme 46: Stereocontrol Strategies: Enolate Geometry and Aldehyde Centers

The trans-enolate should provide the anti aldol product (cyclic T.S.) i.e. B and D. The α−stereogenic centre in the aldehyde favours product B (Felkin-Anh T.S.)

Chiral Enolate and Achiral Aldehyde

The presence of a stereogenic centre α-to the enolate can sometimes provide a good method for controlling diastereofacial selectivity.



Scheme 47: Diastereofacial Selectivity: Chiral Enolate and Achiral Aldehyde Interactions

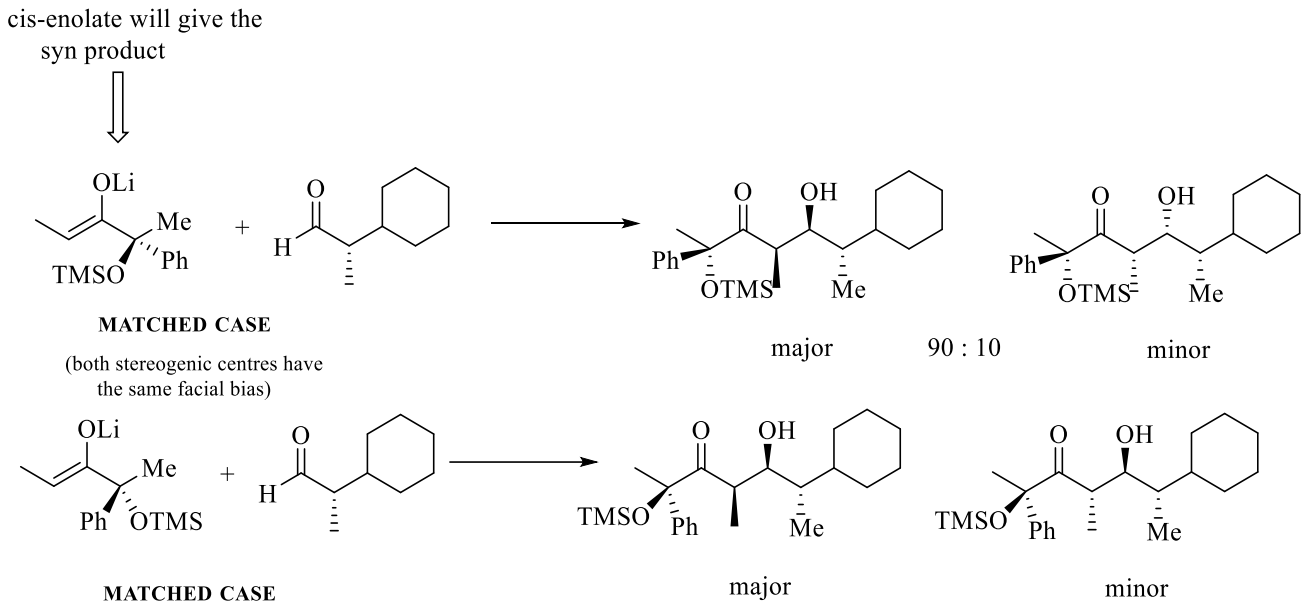
The problem is complicated when both aldehyde and enolate substrates are chiral and possess controlling stereogenic centres (usually α)

This is a common problem in complex natural product synthesis.

In this case each substrate has an inherent facial bias. When both substrates have the same bias, they reinforce the facial selectivity leading to improved stereoselectivity (reinforced stereoselection). Matched case.

When the inherent facial bias in one substrate opposes that in the other, stereoselectivity is reduced. Mismatched case.

One substrate usually exerts a stronger facial bias than the other and on occasion can completely override the inherent facial preference of its partner. In this case one substrate controls the stereochemical outcome entirely. This can be desirable.

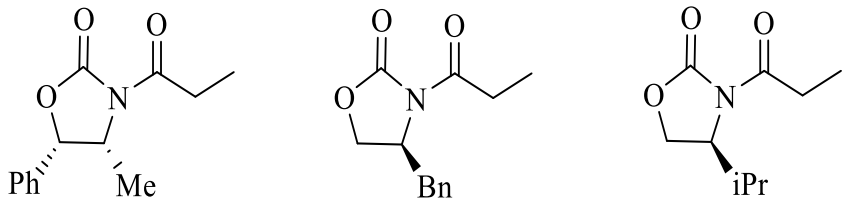


Scheme 48: Facial Bias Dynamics in Stereoselective Reactions: Matched and Mismatched Cases

III-4-2-Auxiliary Control

-many successful chiral auxiliaries have been developed for controlling the stereochemical outcome of the aldol reaction.

-only one example will be discussed here - chiral oxazolidinones developed by Evans.



Scheme 49: Chiral Adjuvants in Aldol Reaction Stereochemistry Control

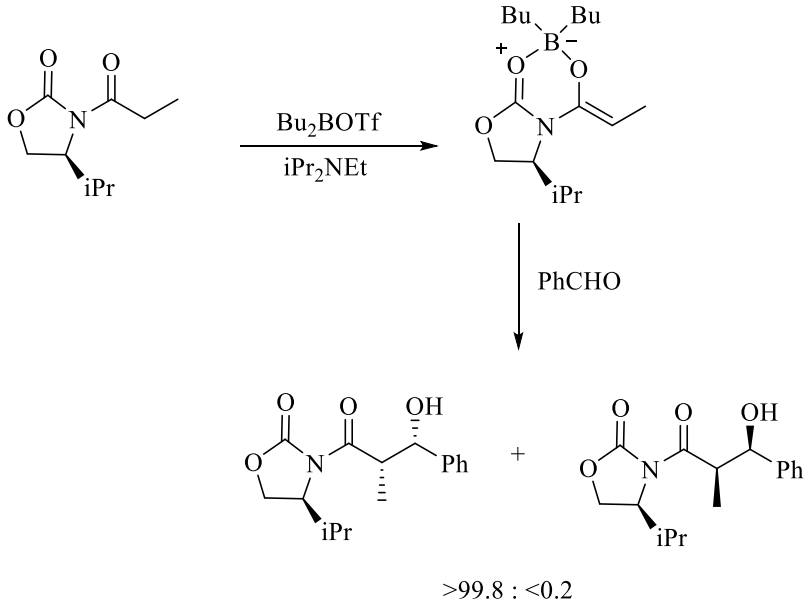
- Lithium enolates derived from these species give poor stereoselectivity

- Boron (and titanium) enolates however give excellent levels of stereocontrol

- Cis-enolates are invariably formed and reaction proceeds through a cyclic T.S. to provide the syn products (almost exclusively)

-The substituent(s) on the oxazolidinone controls the facial selectivity. The norephedrinederived auxiliary provides one product and the phenylalanine- and valine-derived auxiliaries exert the opposite facial selectivity.

-These auxiliaries are so powerful in their facial directing ability that they often override the inherent facial bias of chiral aldehydes - (i.e. even the mismatched pair can provide high levels of stereoselectivity)



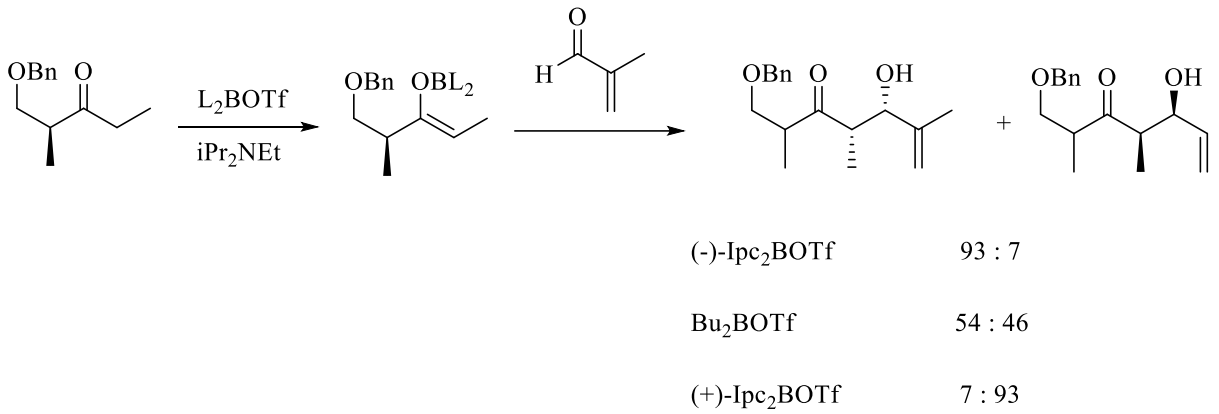
Scheme 50: Influencing Oxazolidinone Chemistry with Selective Auxiliaries

III-4-3-Reagent Control

- Use of chiral ligands at the metal centre provides an alternative and powerful approach tocontrolling the stereochemical outcome of reactions.

- The most widely used system is to prepare the boron enolate from (bisisopinocampheyl) boron triflate or chloride.

- This system is usually used to reinforce or overturn the inherent stereochemical bias of a chiral ketone or aldehyde and is particularly useful at later stages of synthes **[27]**.



Scheme 51: Stereochemical Control: Chiral Ligands and Boron Enolates in Reaction Engineering

Enolates are one of the most important classes of Carbon nucleophiles; their most important application is in the formation of β-hydroxy ketones in the crossed aldol reaction. This versatile functional motif is readily manipulated in a wide variety of stereoselective ways and finds particular application in the preparation of natural products derived from the polyketide biosynthetic pathway.

Before employing an aldol reaction as a key step in a synthesis all the usual issues of selectivity need to be considered and addressed. In the specific case of enolates the following factors are particularly important:

1) which base to form the enolate

2) is the thermodynamic or kinetic enolate required?

3) in the case of B-enolates the ligands on boron and the tertiary amine are important.

Zimmerman-Traxler chair-like T.S.s are very useful for determining the stereochemical outcome of the reaction of Li- and B-enolates with aldehydes (simple diastereoselection).

In the case of silyl enol ethers, these nucleophiles react with aldehydes and acetals under Lewis acid activation (Mukaiyama aldol reaction) through an open T.S. As a result, these reactions are often less stereoselective than those which can react through a closed T.S. Chiral Lewis acids however can be useful in imparting very high levels of stereoselectivity.

The chair T.S. is useful for evaluating simple diastereoselectivity. Other features however need to be considered when trying to account for the absolute stereochemical outcome of the reaction. In particular, proximal stereogenic centres in the form of:

1) chiral auxiliaries

2) chiral Lewis acids

3) chiral ligands on the metal

4) other stereochemical information in either substrate, especially α-stereogenic

centres.

When all things are considered the aldol reaction becomes a very powerful method for stereoselective C−C bond formation; the aldol disconnection is very often a strategic bond disconnection in a retrosynthesis.

.

Chapter IV: The experimental part

IV-1-1- The target of this study:

The aim of this experiment is to explore facets of carbonyl chemistry and the formation of carbon-carbon bonds through the widely studied aldol condensation reaction. The resulting products will be predominantly analyzed using IR spectroscopy, UV-Vis spectrometry.

IV-1-2-Used tools and materials:

The tools	The materials
Conical flask Beaker Thermometer Burette Graduated cylinder Magnetic flea Magnetic stirrer Vacuum filtration Ice water bath	Acetone Benzaldehyde Vanillin p-anisaldehyde potassium hydroxide Sodium hydroxide Water Ethanol

Table 02: Used tools and chemicals materials

IV-2- Synthesis of dibenzalacetone

Synthesis of 4-Phenyl-3-buten-2-one (product A):

The preparation method involves conducting a meticulous synthesis with in a 100 ml flask equipped with a stirrer and thermometer. Initially, 10 ml of benzaldehyde and 20ml of acetone are combined, with excess acetone to minimize the formation of undesired by products. The reaction mixture is kept in a cold water bath, and 2.5 ml of 10% sodium hydroxide solution is slowly added drop by drop while stirring, ensuring the temperature remains below 30°C. After 2 hours of stirring at room temperature, the reaction mixture is neutralized cool the solution in an ice water bath. Filter the resulting yellow solid by Vacuum filtration and recrystallize by Ethanol.

When measuring the products weight, we obtained 3.6 grams, and its melting point is at 39°C, with a yield reaching up to 74%.

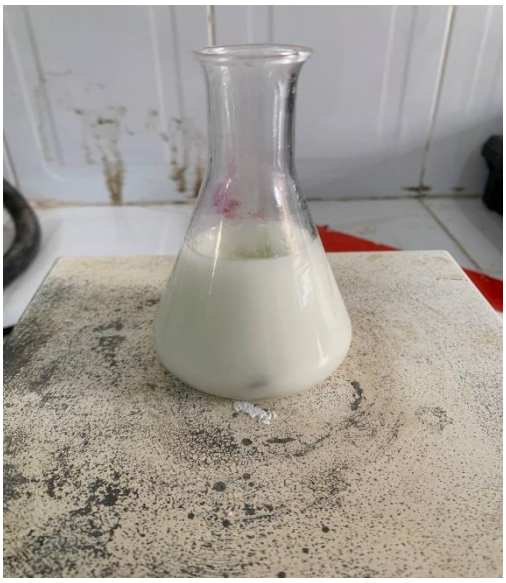


Figure 01: the resulting product 4- phenylbut- 3- en- 2- one

Synthesis of Dibenzalacetone (product B):

Transfer 15mL of ethanol into a 125-mL Erlenmeyer flask and add 20mL of 10% NaOH to it. Using a thermometer, cool the solution to 20ºC.

In a medium size tube, mix 2mL of benzaldehyde with 15 drops of acetone, and leave it at room temperature for 5 minutes. Then, add the mixture to the ethanol-NaOH solution in small portions and stir with magnetic stirrer (if available) for 30 minutes. Chill the solution in an ice-water bath. Collect the yellow crystals by suction filtration and hand-dry them by pressing them between dry paper towels.

When measuring the product's weight, we obtained 3.6 grams, and its melting point is 39°C, with a yield reaching up to 74%.

Figure 02: to prepare 1, 5- diphenylpenta- 1, 4- dien- 3- one

Figure 03: the resulting product 1,5-diphenylpenta-1,4-diene-3-one

Potassium hydroxide instead of sodu hydroxide

In a conical flask, prepare a solution of 4-phenylbut-3-en -2-one (0,6g) and benzaldehyde (0.61 mL) in ethanol (15 mL). In another beaker, prepare a solution of Potassium hydroxide (0.8 g) in water (20 mL) and add slowly (over 2 minutes) to the mixture in the conical flask

while stirring. Stir the solution for 30 minutes. Recover the resulting yellow solid by vacuum filtration and recrystallize from ethanol When measuring the product's weight, we obtained 4.2 grams, and its melting point is at 121°C, with a yield reaching up to 76%.

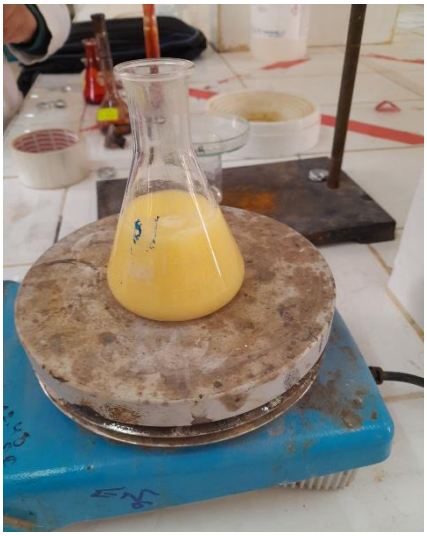


Figure 04: The resulting produc 1, 5 diphenylpent 1, 4-diene-3one using KOH base

IV-3-Vanillin Acetone Aldol Condensation

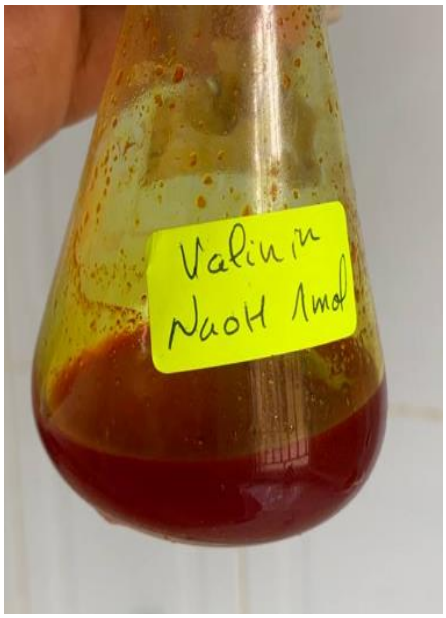
Synthesis of (*E*) - 4- (4- hydroxyl- 3- methoxyphenyl) but- 3- en-2- one (product C):

0.02 mol NaOH was solved in 10 mL water, cooled with ice bath and 0.01 mol vanillin was slowly added under stirring until completely solved. 0.03 mol acetone was slowly dropped to the solution. The temperature was kept on room temperature during 3Hours stirring or until precipitant was produced. Afterward, 3 mL of water was added beforefiltered and washed with water until pH below 7 was reached. The purified product was conducted using recrystallization method.

The physical properties were determined based on its colour, weight and melting point.

This procedure was repeated by substituted the solvent with ethanol-water and methanol and also replace the entering reagent method in to the reaction systemto obtain the optimal result.

When measuring the product's weight, we obtained 4 grams, and its melting point is at 81°C, with a yield reaching up to 81%.



Magnetic stirring

startAfter 3 days

Figure 05: the resulting (*E*)- 4- (4- 47ydroxyl- 3- methoxyphenyl) but- 3- en-2- one using potassium hydroxide.

Synthesis of (1E, 4E) - 1, 5- bis (4- hydroxy- 3- methoxyphenyl) Penta- 1, 4- dien- 3- one (product D):

In a beaker, 0.5g of vanillin was added to 2 mL of (E)-4-(4-hydroxy-3-methoxyphenyl) but-3-en-2-one. In another beaker, 0.8g of NaOH was dissolved in 20 mL of water.

Slowly the NaOH solution was added to the mixture in the conical flask over a period of 2 minutes while stirring. the solution was stired for 30 minutes.

When measuring the product's weight, we obtained 3.6 grams, and its melting point is at 39°C, with a yield reaching up to 74%.

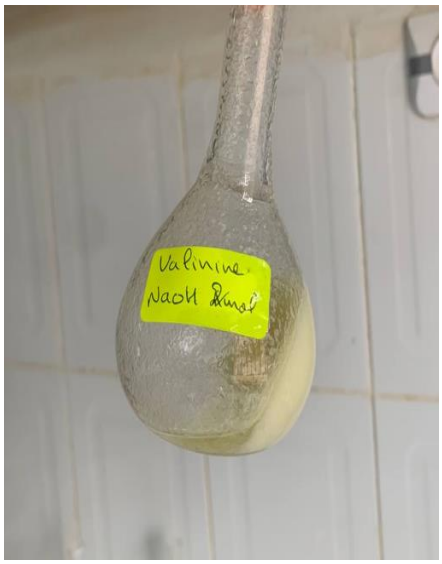


Figure 06: the resulting (*E*) - 4- (4- hydroxy- 3- methoxyphenyl) Penta- 1, 4- dien-3- one using sodium hydroxide.

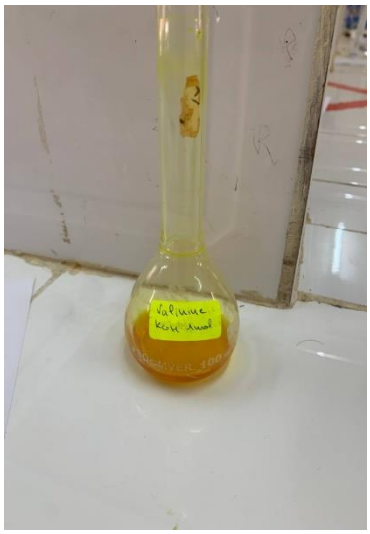
Note: Recrystallization is possible to obtain a purer compound.

When using potassium hydroxide we tried to repeat the same protocol with vanillin.

In a 250 mL conical flask (Erlenmeyer flask) 2g of vanillin was added in 20 drops of acetone and was leaved at room temperature for 5 minutes. In a separate beaker, 15 mL of ethanol was added in 20mL of potassium hydroxide (10%).

The mixture was added to the ethanol-potassium hydroxide solution in small portions and stir with a magnetic stirrer for 30 minutes. The solution was coolded in an ice water bath.

When measuring the product's weight, we obtained 3grams, and its melting point is at 238°C, with a yield reaching up to 70%.



Magnetic stirring start

after 3 days

Figure 07: the resulting (1*E*, 4*E*)- 1, 5-bis (4- 49ydroxyl-3- methoxyphenyl) penta- 1, 4- dien- 3- one .

Alkene Detection Tests

There are several chemical tests used to detect alkenes, and we will discuss several experiments that detect the presence of alkenes in previous experiments

Experiment 1:

In a test tube, we place 0.1 g of the 1,5-diphenylpenta-1,4-diene-3-one compound if it is solid, or 5 drops if it is liquid. Then, we add 2% potassium permanganate into the same tube.

The purple color of the permanganate will turn brown due to the appearance of manganese oxide precipitate within 2-3 minutes. The appearance of the brown color during this period indicates the presence of the alkene.

Figure 07: Detection of Alkenes Using Potassium Permanganate

Experiment 2:

In a test tube, we add a small amount of the1,5-diphenylpenta-1,4-diene-3-one compound, followed by adding a few drops of concentrated sulfuric acid into the same test tube.

We observe the dissolution of the unknown compound and a rise in temperature. These observations confirm the presence of an alkene.

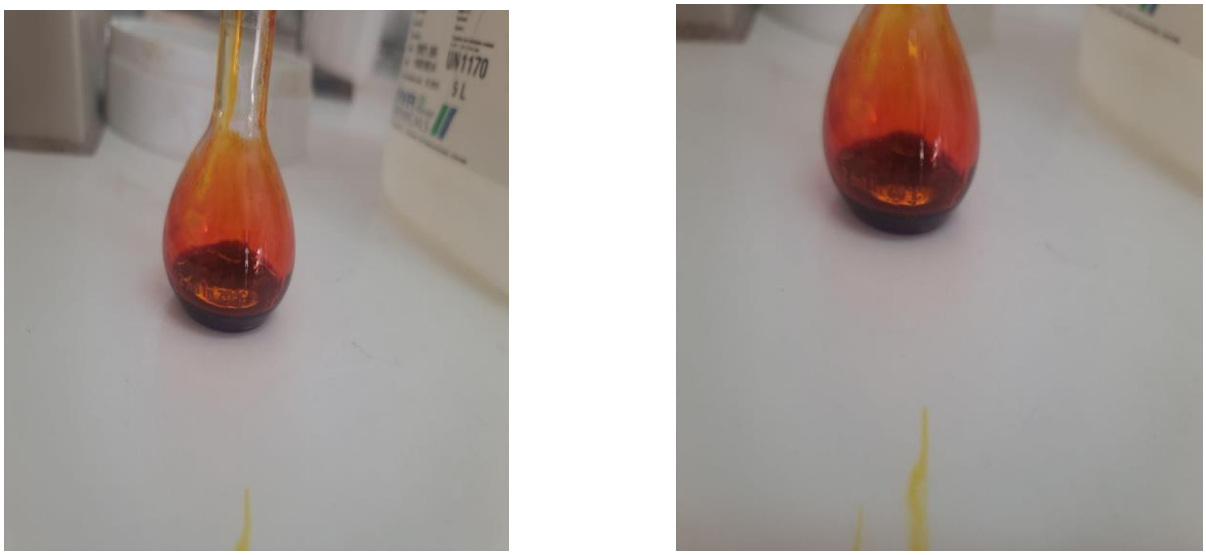


Figure 07: Detection of alkenes using concentrated sulfuric acid

Note: These experiments were repeated with the remaining alkenes. (4- phenylbut- 3- en- 2- one ,(*E*) - 4- (4- hydroxy- 3- methoxyphenyl) but- 3- en-2- one,

(*E*) - 4- (4- hydroxy- 3- methoxyphenyl) Penta- 1, 4- dien-3- one)

ChapterV: Results and discussion

Melting point of all compounds obtained

After the resulting products were purified, we measured the melting point of each compound using the device shown in the picture

Figure 11: Gallenkamp melting point apparatus.

The results were as follows:

The resulting	Melting point
4-phenylbut-3-en-2-one	39°C
1,5-diphenylpenta-1,4-dien-3-one	121°C
4-(4-hydroxy- 3-methoxyphenyl) but- 3- en-2- one	81°C
(1E,4E)-1,5-bis (4-hydroxy-3-methoxyphenyl) penta-1,4-dien-3-one	238°C

Table 05: Properties of Ultraviolet spectrophotometer used in the physicochemical analysis

V-2-1- UV spectrum of 4-phenylbut-3-en-2-one (product A):

In the UV spectrum, product “C” displays a prominent absorption band in ethanol at 404 nm, signaling the presence of a conjugated π-bond system. This observation strongly suggests the existence of resonance within our compound, affirming its structural characteristics.

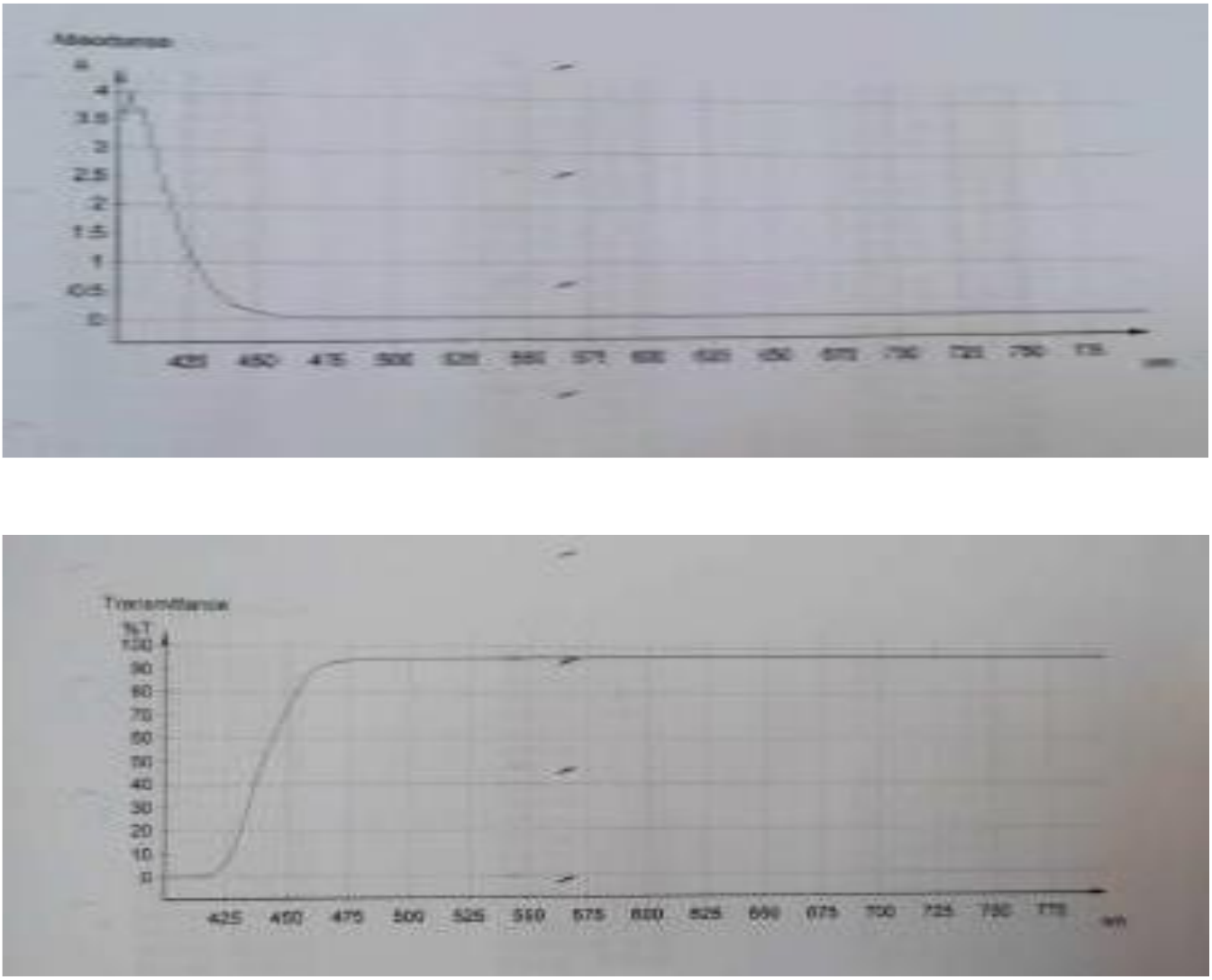


Figure 12: UV spectrum of 4- phenylbut- 3- en- 2- one (product A).

V-2-2- IR spectrum of 4-phenylbut-3-en-2-one

The absorption spectrum of 4-phenylbut-3-en-2-one, as depicted in Figure 13, reveals several distinct bands indicating the molecular structure. Notably, a prominent band spanning 3000-3100 cm-1 signifies the presence of Csp2-H bonds, while a band at 1650 cm-1 indicates the C=O ketone functionality, which is slightly shifted due to conjugation. The stretching vibrations of C=C bonds manifest as absorption bands

around 1600 cm-1. Medium-intensity absorption bands between 1450-1600 cm^{-1} confirm the presence of C=C aromatic bonds. Sharp and strong bands at 692.31 cm^{-1} and 795.81 cm^{-1} indicate the presence of aromatic C-H bonds, specifically monosubstituted benzene, while another band at 976.66 cm^{-1} suggests C-C bond vibrations. Additionally, weak overlapping bands in the range of 1700 cm-1 to 2000 cm^{-1} further support the presence of an aromatic ring within the molecule.

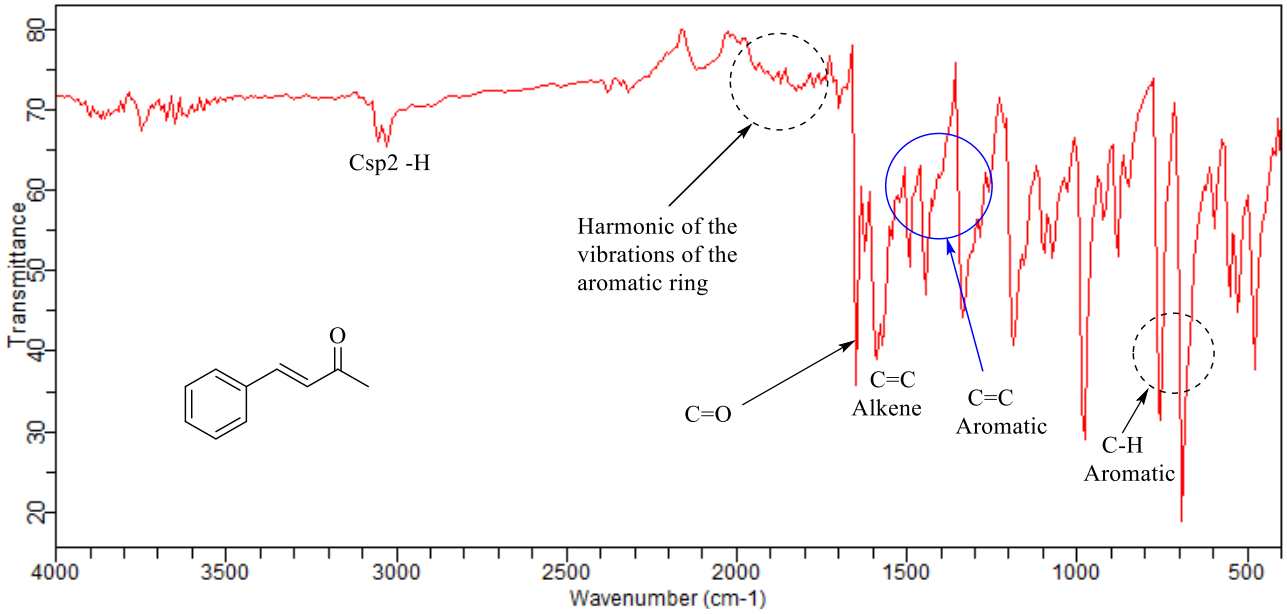


Figure 13: IR spectrum of 4- phenylbut- 3- en- 2- one (product A).

V- 3- 1- UV spectrum of 1,5-diphenylpenta-1, 4-dien- 3- one (product B):

In Figure 14, the UV spectrum of 1,5-diphenylpenta-1,4-dien-3-one (referred to as product D) is presented. The spectrum demonstrates a notable peak at 407 nm, indicating the maximum absorption wavelength. This absorption peak serves as evidence of resonance within the molecular structure of the compound.

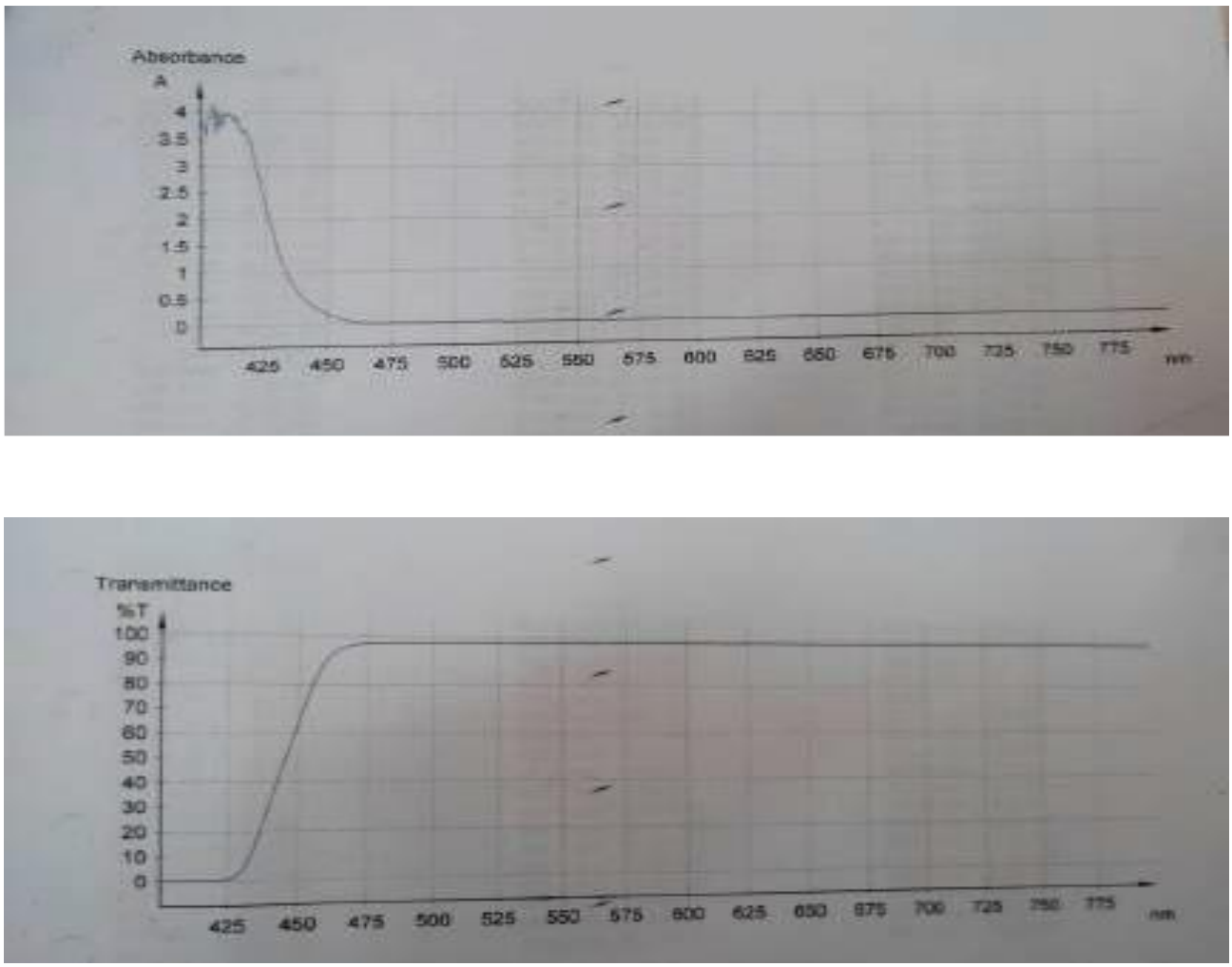


Figure 14: UV spectrum of 1, 6- diphenylhexa- 1, 5- dien- 3- one (Product B).

V- 3- 2- IR spectrum of 1,5-diphenylpenta-1, 4- dien-3-one (product B):

Figure 15 presents the FTIR absorption spectrum of 1,6-diphenylhexa-1,5-dien-3-one (product D). Notably, the spectrum closely resembles that of product C, indicating their structural similarity since compound D is a condensation product of compound C. Both compounds exhibit similar functional groups. A prominent band in the range of 3000-3100 cm^{-1} signifies the presence of Csp2-H bonds of the alkene group, while a band at 1650 cm^{-1} indicates the presence of C=O functionality. The stretching vibrations of C=C (alkene) bonds manifest as an absorption band around 1600 cm^{-1}. Additionally, medium-intensity absorption bands between 1450-1600 cm^{-1} confirm the presence of C=C aromatic bonds. Sharp and strong bands at 692.31 cm^{-1} and 795.81 cm^{-1} indicate the presence of aromatic C-H bonds, particularly monosubstituted benzene, while

another band at 976.66 cm^{-1} suggests C-C bond vibrations. Weak overlapping bands in the range of 1700 cm^{-1} to 2000 cm^{-1} further support the presence of an aromatic ring within the molecule.

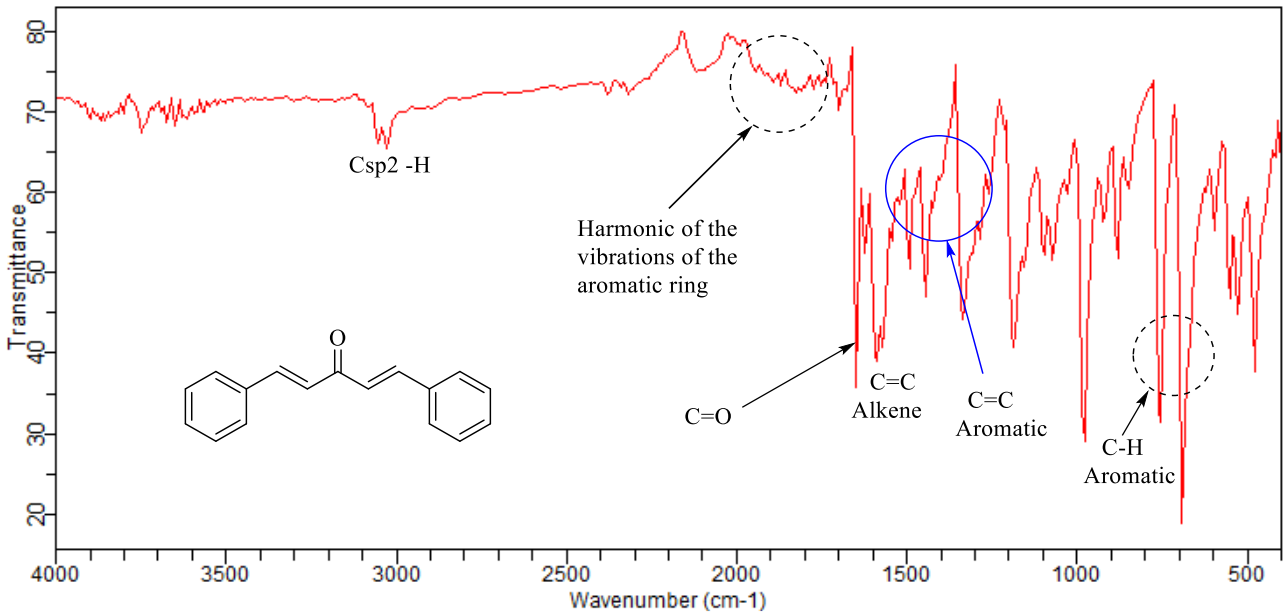


Figure 15: IR spectrum of 1, 6- diphenylhexa- 1, 5- dien- 3- one (product B).

Results of the vanillinacetone experiment

The results of the experiment after changing the solvents in each case showed the following results, shown in the table

No	Solvent	Synthesis sequence	Colour of Resulting Material	yield %
1	H_2O	NaOH, acetone, vanillin	Dark yellow	13.06
2	H_2O	**NaOH, vanillin, acetone**	**Dark yellow**	**73.86**
3	EtOH- H_2O 1:1	NaOH, acetone, vanillin	yellow	94.3
4	EtOH- H_2O 2:3	NaOH, vanillin, acetone	yellow	76.70
5	MeOH	NaOH, acetone, vanillin	Light yello	90.2

The result of the synthesis using water have darker colour than ethanol-water and the lighter yellow was provided by methanol solvent. All resulting material was recrystallized using ethanol-water pr ovided yellow gradated colour to dark brown for Target compound number 1, 3, 4 and 5. It could be occurred due to the uncompleted Reactions which reverse to result the reactant again, which confirm from TLC that showed those four materials were still vanillin. Compound no 2 was then analyzed by Spectroscopy IR and NMR.

IR spectrum of (*E*) - 4- (4- hydroxyl- 3-methoxyphenyl) but- 3- en- 2- one

The FTIR data of (E)- 4- (4-hydroxy- 3-methoxyphenyl) but- 3-en- 2-oneby structure modification showed sharp peak at 1620.21 cm-1 (C-O carbonyl), shoulder on 3300 cm-1 which indicated hydroxyl group. Methyl group was existed at 1327 cm-1 and C-O-C appeared around 1000-1100 cm-1. Characteristic absorption of aromatic appeared at 3055 cm-1 was supported by sharp peak at 1573.91 cm-1. C-H aldehyde characteristic at 2800 and 2700 cm-1 was already disappearing. It could be hold up that the synthesis resulting (E)-4- (4-hydroxy- 3-methoxyphenyl) but- 3-en- 2- one compound.

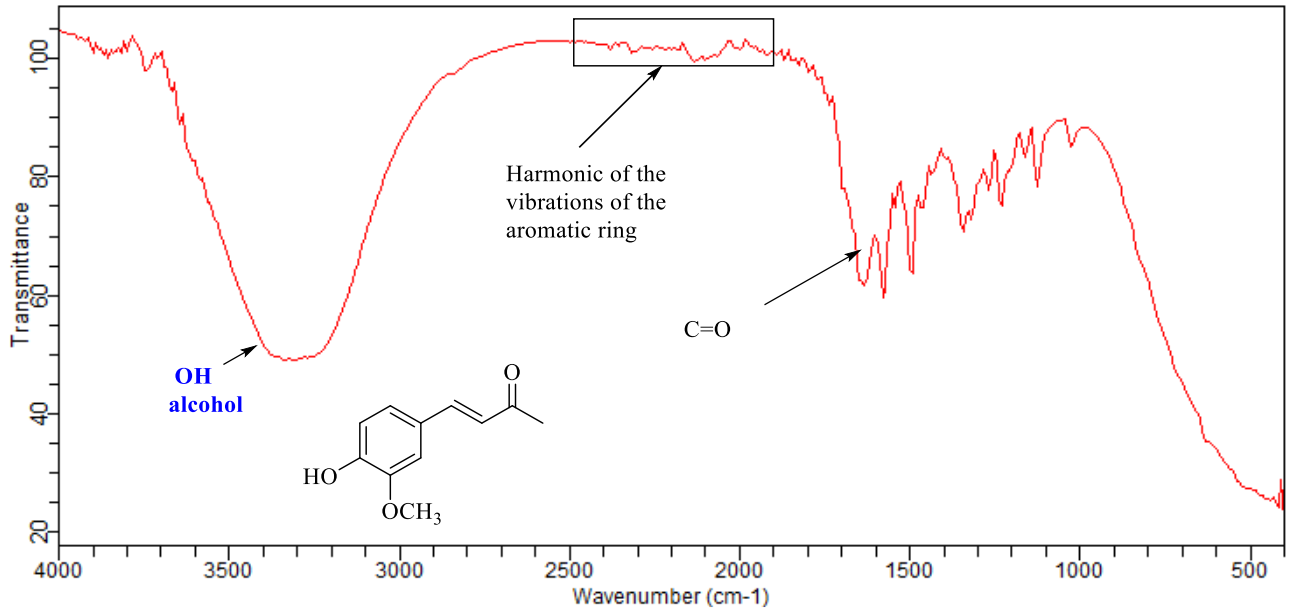


Figure 16: IR spectrum of (*E*)- 4- (4- hydroxyl 3- methoxyphenyl) but- 3- en-2 –one (product C) produced by base- catalyzed reaction using NaOH as base.

V-5- 1-UV spectrum of (1E, 4E)-1,5-bis (4-hydroxy-3-methoxyphenyl) penta-1,4-dien-3- one

In Figure 20, the UV spectrum of (1E, 4E)-1,5-bis(4-hydroxy-3-methoxyphenyl) penta-1,4-dien-3-one (referred to as product F) is depicted, showcasing its absorbance and transmittance characteristics. The prominent feature observed is the maximum absorbance band (λ Max) occurring around 400 nm. This finding leads us to conclude that the compound acts as a chromophore, indicating the presence of a resonance phenomenon within product F.

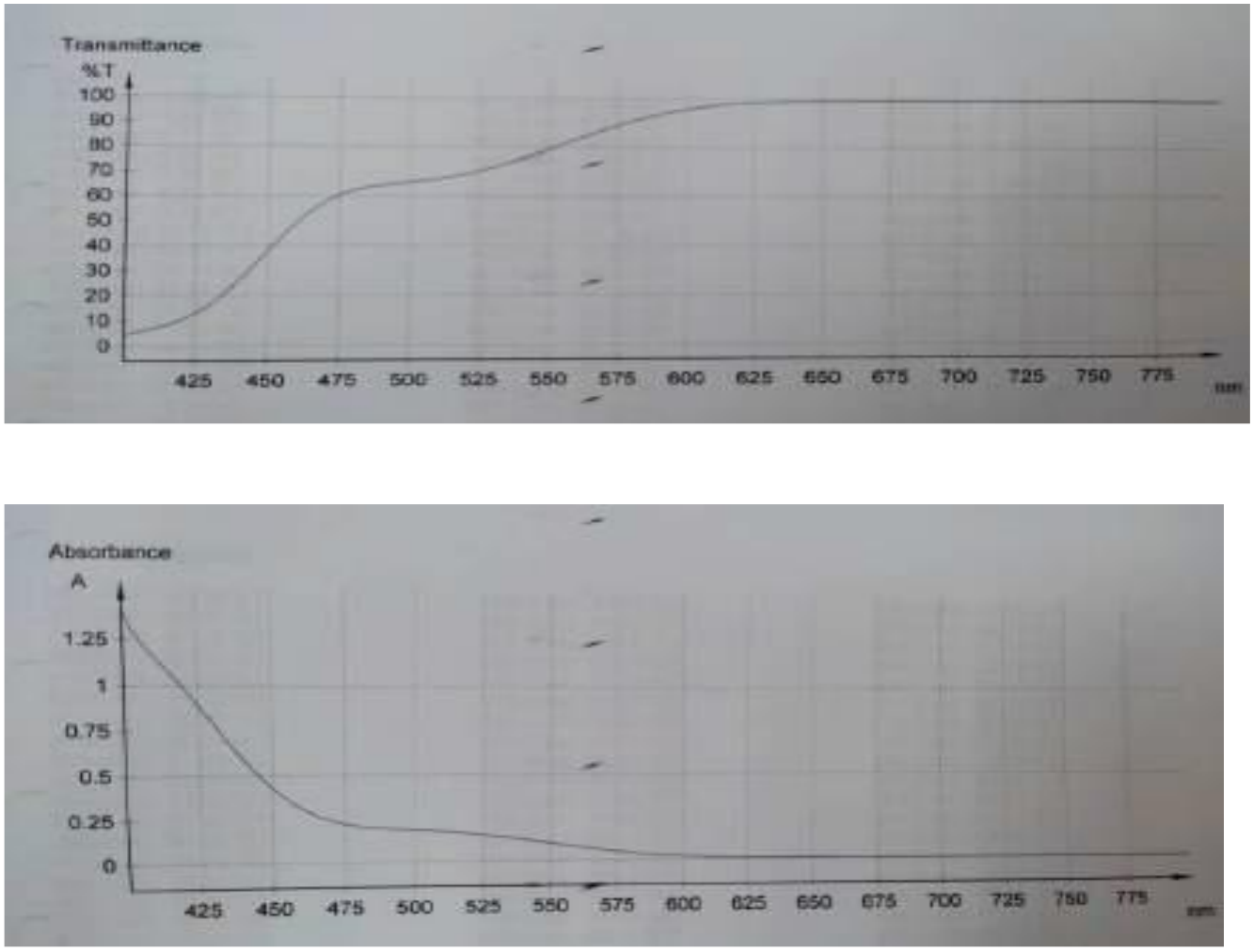


Figure 18: UV spectrum of (1*E*, 4*E*) – 1, 5-bis (4-hydroxy- 3-methoxyphenyl) penta-1, 4-dien-3-one (product D).

V- 5-2- IR spectrum of (1E, 4E)-1, 5-bis (4-hydroxy- 3-methoxyphenyl) Penta-1, 4-dien- 3- one (product F):

The infrared (IR) spectrum analysis reveals key functional groups within the compound. The broad O-H band is observed between 3200-3400 cm^{-1}, while the Csp2-H stretching vibrations appear between 2900-3000 cm^{-1}. Furthermore, the presence of the C=O ketone group is indicated by a band at 1730 cm^{-1}, and the C-O-C group is signaled at 1050 cm^{-1}. A distinctive band at 1450 cm^{-1} signifies the presence of C=C aromatic bonds, while the C-C bond vibrations are represented by a band at 1250 cm-1. Notably, two bands are observed: one strong at 678.82 cm^{-1} and the other medium at 815.74 cm^{-1}, indicating the presence of tri-substituted aromatic C-H bonds.

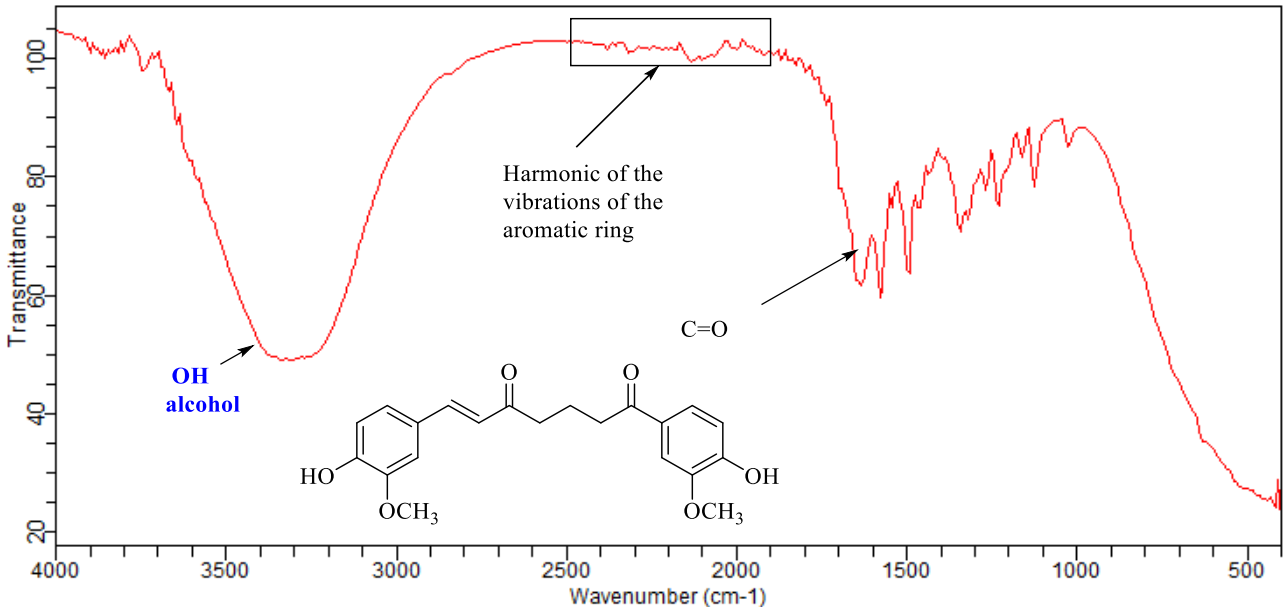


Figure 19: IR spectrum of (1*E*, 4*E*)-1, 5-bis (4- 59ydroxyl-3 – methoxyphenyl) penta- 1, 4-dien- 3-One (product D).

IV-7-1-Discussion of the results of Product A, B, C, D"

The 1H NMR spectrum of recrystallized. Notably a singlet peak at 2.35 ppm with an integral of 2.50 confirms the presence of a methyl group. Additionally, a prominent singlet peak at 3.83 ppm with an integral of 3.00 indicates the presence of the methoxy group attached to the aromatic ring. The remaining resonances observed between 6.37–7.69 ppm accounts for the six protons distributed among four distinct chemical environments. These include the alkene protons and two sets of aromatic proton.

Conclusion

Considerable efforts have been directed towards developing novel synthetic methodologies that prioritize efficiency and cost-effectiveness, aiming to facilitate the production and application of monocarbonyl analogues of curcumin and raspberry ketone methyl ether. The synthesis of curcumin analogues relies on aldol condensation and the creation of fresh C-C bonds, a technique pioneered by numerous researchers.

Our investigations have led to the discovery of several pathways for synthesizing α, β unsaturated ketones and subsequently condensing them to yield curcumin analogues. For instance, we successfully synthesized 4-(4-methoxyphenyl)-3-buten-2-one (Product A) with good yield through aldol condensation of p-anisaldehyde and acetone at room temperature under basic conditions, resulting in a yellow solid product. This one-pot synthesis encompasses both dehydrogenation and aldol condensation processes, with the base acting as a catalyst for dehydrogenation and C-C coupling.

Following this, we replicated the procedure using Product A as the ketone source to generate the bis-addition product 1,5-bis(4'-methoxyphenyl)-1,4-pentadien-3-one (Product B). Similar steps were applied to benzaldehyde with acetone and vanillin with acetone under basic conditions, yielding compounds such as 4-phenylbut-3-en-2-one (Product C) in good yield , 1,6-diphenylhexa-1,5-dien-3-one (Product D), (E)-4-(4-hydroxy-3-methoxyphenyl)but-3-en-2-one (Product E), and (1E,4E)-1,5-bis(4-hydroxy-3-methoxyphenyl)penta-1,4-dien-3-one (Product F).

To characterize these products, we used utilized IR spectroscopy and UV spectrometry techniques.

Summary

In the synthesis and analysis of pivotal compounds achieved through aldol condensation reactions, we delineate the process. Dibenzalacetone, (E)-4-(4-hydroxyl-3-methoxyphenyl) but-3-en-2-one, and 1E,4E) -1,5-bis(4-hydroxy-3-methoxyphenyl) penta-1,4-dien-3-one were synthesized under specified conditions and characterized using spectroscopic and chemical methods. Spectroscopic techniques, encompassing UV-Vis, IR spectroscopy, were employed to elucidate molecular structures, while chemical methods authenticated compound identities and purity. This research advances organic synthesis, spotlighting the application of fundamental principles in practical laboratory settings**.**

KEYWORDS : Aldol condensation, base catalyze, α, β- unsaturated compounds, α, hydrogen

الملخص

في هذا العمل، قمنا بتخليق وتحليل المركبات الرئيسية الناتجة عن تفاعلات تكاثف الألدول: دبينزالأسيتون، بيس(4-هيدروكسي-3-ميثوكسي -1,5-(1E,4E)هيدروكسي-3-ميثوكسي فينيل) بوت-3-ين-2-ون، و-4)-4-(E) فينيل) بينتا-1,4-دين-3-ون. تم تحديد العملية تحت ظروف محددة وتم تشخيص المركبات باستخدام الطرق الطيفية والكيميائية. استخدمنا التقنيات الطيفية، بما في ذلك التحليل الطيفي للأشعة فوق البنفسجية والأشعة تحت الحمراء لتوضيح البنية الجزيئية، بينما أثبتت الطرق الكيميائية هوية المركبات ونقاوتها. يهدف هذا العمل إلى تطوير التخليق العضوي وتسليط الضوء على تطبيق المبادئ الأساسية في البيئات المختبرية العملية.

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Recomedation

This experimental and theoretical work, spanning a full year, is characterized by diligent and continuous effort towards establishing a database for future years to serve as a foundation in organic synthesis at the university. Based on this foundation, we excelled in synthesizing a series of organic compounds featuring the presence of the alkyne functional group, which will serve as the cornerstone for building monomers to form polymers. Moreover, the existence of these compounds containing the alkyne group can be the basis for preparing epoxides, which can be opened in basic or acidic medium through hydrolysis to serve as a fundamental material in cosmetic formulation.