بسم الله الرحمن الرحيم

A PRIMER TO

Heterocyclic Chemistry

Heterocyclic Chemistry

Prepared by:

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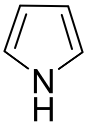
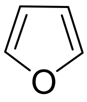
Nomenclature of heterocyclic:

Examples of heterocycles with ‘recognized’ trivial names.



Pyrrole



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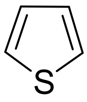
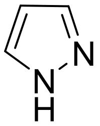
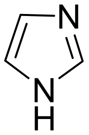


Thiophene



Pyrazole



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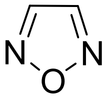
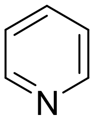
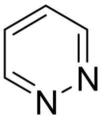


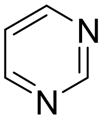
Furazan



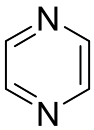
Pyridine



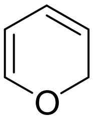
Pyridazine



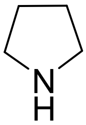
Pyrimidine



Pyrazine



Pyran



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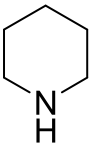
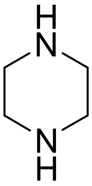


Piperidine



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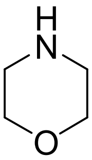
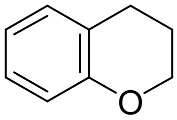
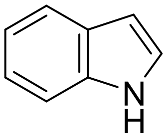


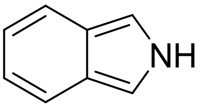
Morpholine



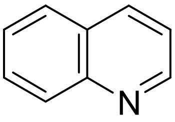
Chroman



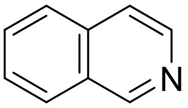
Indole



Isoindole



Quinoline



Isoquinoline

- rules to nomenclature heterocycles-

According to Hantzsch-Widman system-follow this steps (for one ring system):-

1-consider priority starting the numbering in this order Oxa(O) then Thia(S) then Aza(Z).
2-tend the numbering direction to nearest heteroatom .
3-follow the nearest saturated atom.
4-write suitable prefixes and stems.

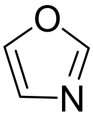
Hantzsch -Widman system :common prefixes

Element	Valence	Prefix
Oxygen	II	Oxa
Sulphur	II	Thia
Selenium	II	Selena
Tellurium	II	Tellura
Nitrogen	III	Aza
Phosphorus	III	Phospha
Arsenic	III	Arsa
Silicon	IV	Sila
Germanium	IV	Germa
Boron	III	Bora

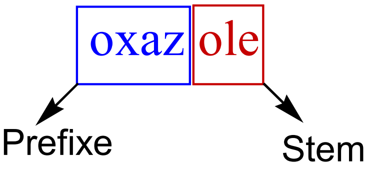
the final ‘a’ in the prefix is dropped when is followed by a vowel.

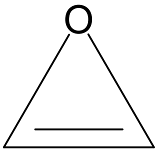
Stems for the Hantzsch-Widman system:

Ring size	**Unsaturated ring**	**Saturated ring**	**Saturated have (N)**
3	**irine**	**irane**	**iridine**
4	**ete**	**etan**	**etidine**
5	**ole**	**olane**	**olidine**
6	**ine**	**inane**	
7	**epine**	**epane**	
8	**ocine**	**ocane**	
9	**onine**	**onane**	
10	**ecine**	**ecane**	

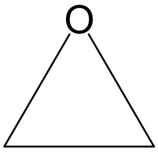


oxazole

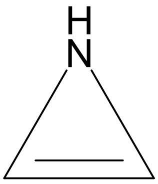




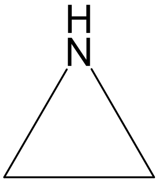
oxirene



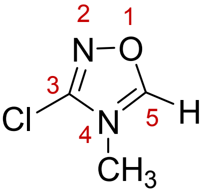
oxirane



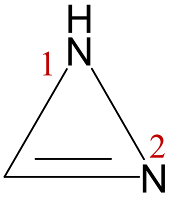
1*H*-azirine



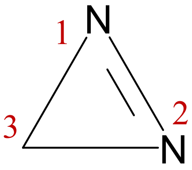
aziridine



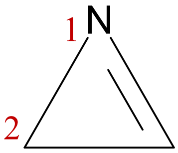
3-chloro-4-methyl-1,2,4-oxadiazole



1*H*-diazirine

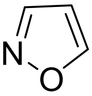


3*H*-diazirine

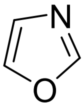


2*H*-azirine

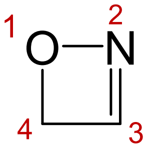
H refer to saturated atom



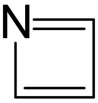
1,2-oxazole
common as isoxazole



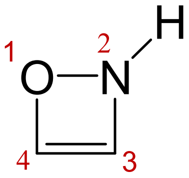
1,3-oxazole
common as oxazole



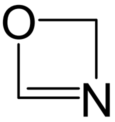
4*H*-1,2-oxazete



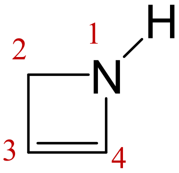
azete



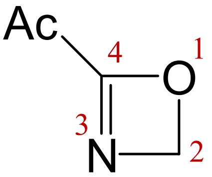
2*H*-1,2-oxazete



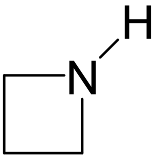
2*H*-1,3-oxazete



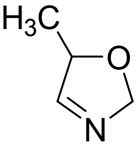
1,2-dihydroazete



4-acetyl-2H-1,3-oxazete

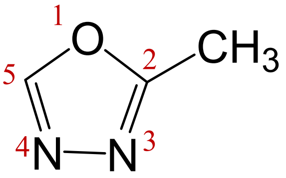


azetidine

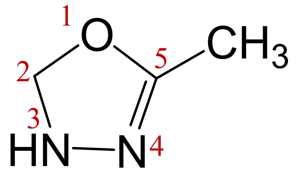


2,5-dihydro-5-methyloxazole

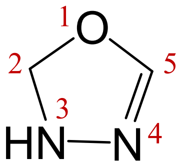
1 saturated	1H	4 saturated	Tetrahydro
2 saturated	Dihydro	5 saturated	1H+tetrahydro
3 saturated	1H+dihydro		



2-methyl-1,3,4-oxadiazole



2,3-dihydro-5-methyl-1,3,4-oxadiazole

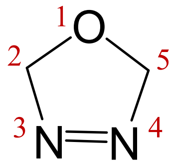


naming 1 2,3-dihydro-1,3,4-oxadiazole

naming 2 Δ^2-oxadiazoline

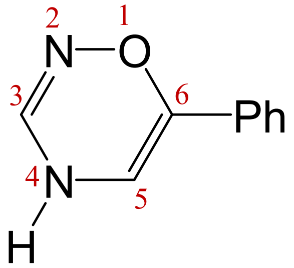
priority to double bond

oline=half saturation

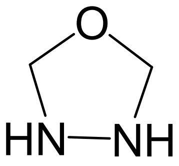


naming 1 2,5-dihydro-1,3,4-oxadiazole

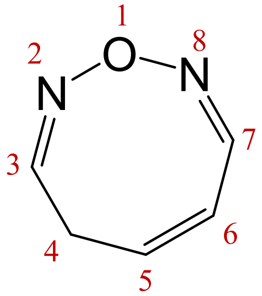
naming 2 Δ^3-oxadiazoline



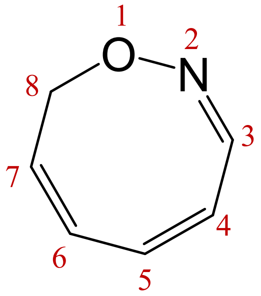
6-phenyl-4*H*-1,2,4-oxadiazine



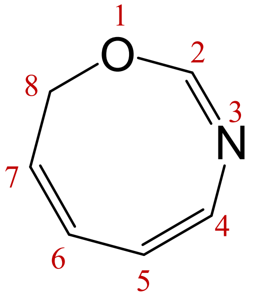
1,3,4-oxadiazolidine



4*H*-1,2,8-oxadiazocine

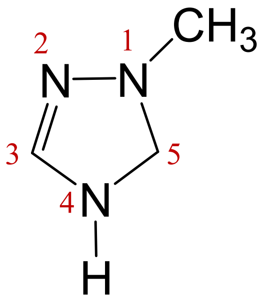


8*H*-1,2-oxazocine



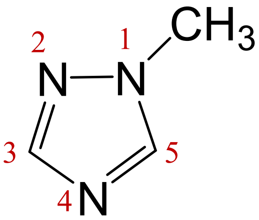
8*H*-1,3-oxazocine

When structure of heteroatoms have only one types of atoms start numbering with saturated heteroatom nearest to another heteroatom,,as followed…

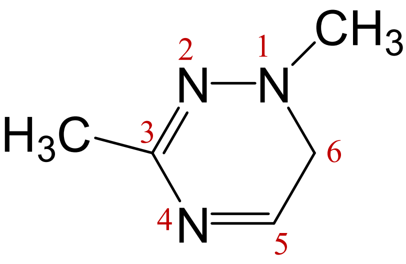


4,5-dihydro-1-methyl-1*H*-1,2,4-triazole

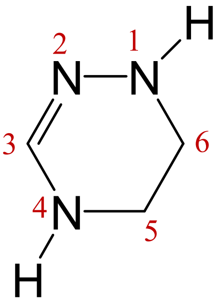
or Δ^2-1,2,4-triazole



1-methyl-1*H*-1,2,4-triazole



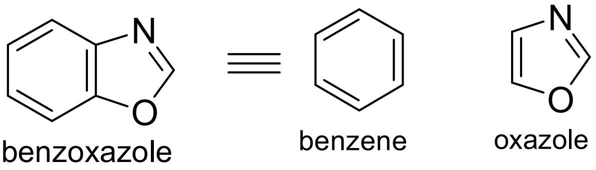
1,6-dihydro-1,3-dimethyl-1,2,4-triazine

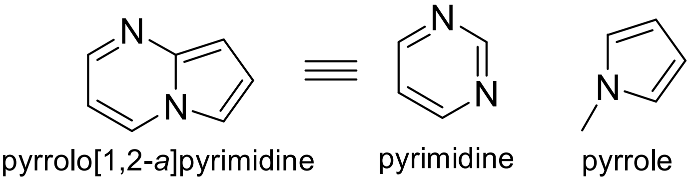


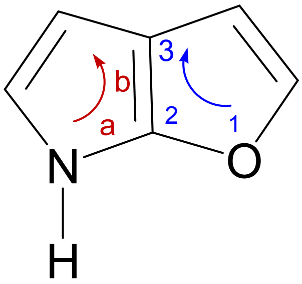
1,4,5,6-tetrahydro-1,2,4-triazine

The naming of fused ring systems:

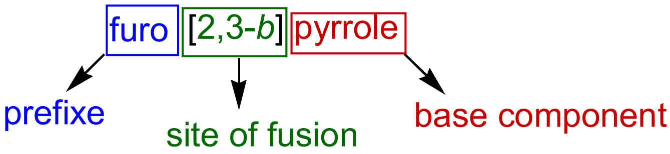
A very large heterocycles contain two or more fused rings. Some of these have recognized trivial names,but the vast majority have not. The systematic names of fused ring systems are derived by regarding common atoms as belonging to both ring systems. The name is then constructed by combining the names of the individual rings.







furo[2,3-*b*]pyrrole



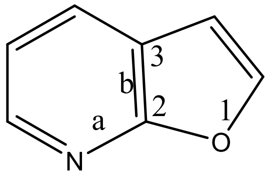
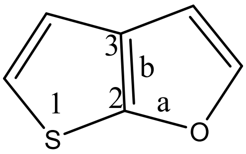
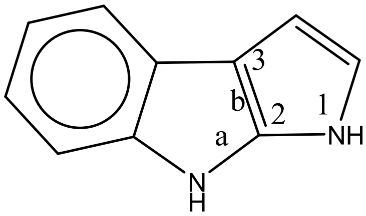
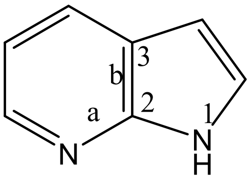
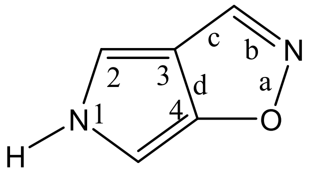
Base component are labeled a,b,c,..,etc ,, atoms forming the ring system of the second component are numbered in normal way 1,2,3,..
Considering in both numbering and labelling toward the nearest heteroatom then to fusion site.

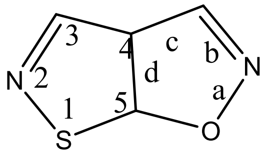
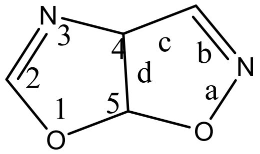
Non-standard prefixes in fusion names.

Heterocycles	Name as prefix
Furan	Furo
Imidazole	Imidazo
Isoquinoline	Isoquino
Pyridine	Pyrido
Quinoline	Quino
Thiophene	Thieno

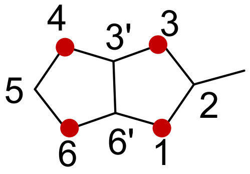
-Some rules to choose base component-

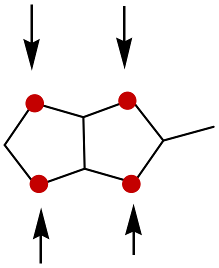
Follow this steps:

1) choose the ring have N	 furo[2,3-*b*]pyridine
2) No Nitrogen, choose oxa rather than thia	 thieno[2,3-*b*]furan
3) choose more than one ring	 pyrrolo[2,3-*b*]indole
4) choose the larger ring	 pyrrolo[2,3-*b*]pyridine
5) choose larger number of heteroatoms	 pyrrolo[3,4-*d*]isoxazole

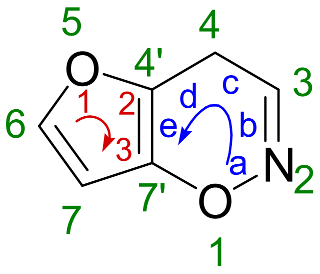
6) choose oxaza rather than thiaza	 isothiazolo[4,5-*d*]isoxazole
7) choose 1,2heteroatoms rather than 1,3heteroatoms	 oxazolo[4,5-*d*]isoxazole

*Numbering the fused ring system:





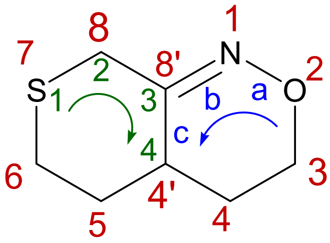
-start the numbering from this positions
-Consider gives the heteroatoms the lowest combined numbers.
-opt the direction the nearest to fusion

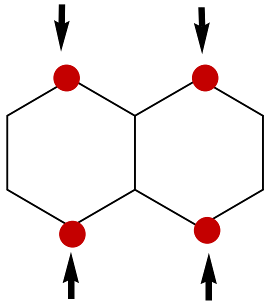


4*H*-furo[2,3-e][1,2]oxazine

Numbering in this direction gives the three heteroatoms the lowest combined numbers, (1,2,and 5)

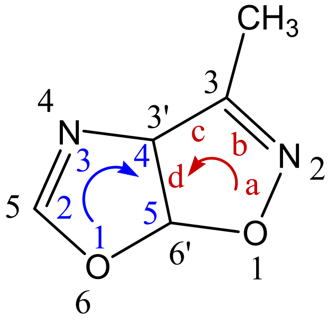
the contrary direction gives the three heteroatoms the unpreferable combined numbers (3,6,and 7)



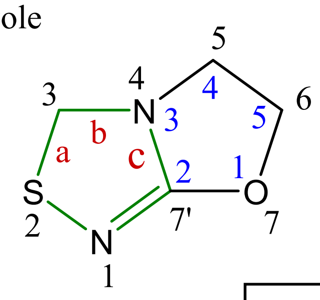


3,4,4',5,6,8-hexahydrothiopyrano[3,4-*c*] [1,2]oxazine

individial name of the base component

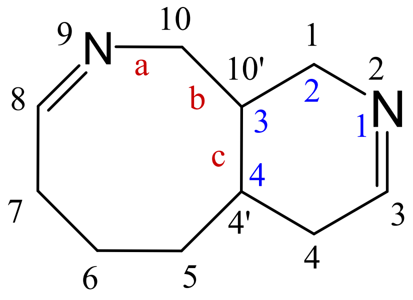


3',6'-dihydro-3-methyl-oxazolo[4,5-*d*]isoxazole



5,6-dihydro-3*H*-oxazolo[2,3-*c*] [1,2,4]thiadiazole

individual name to the base component



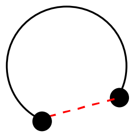
1,4,4',5,6,7,10,10'-octahydropyrido[3,4-*c*]azocine

Ring Synthesis

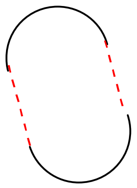
The types of ring-forming reaction available can be divided into two broad groups:

-Reaction in which a single bond is formed in the ring-closure process are called ***cyclization reaction***

-Reaction in which two ring bonds are formed, and no small molecules are eliminated in the process , are called ***cycloaddition reaction***



One bond formation



Two new σ-bonds

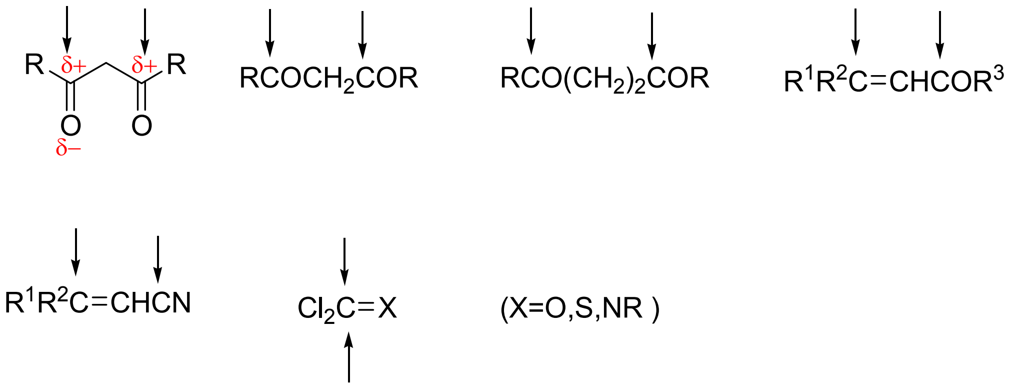
1-Cyclization reactions

Cyclization reaction can involve any intramolecular version of the common σ-bond –forming processes ,by far the most common are those in which a nucleophilic atom interacts with an electrophile. The predominant reaction types are:-

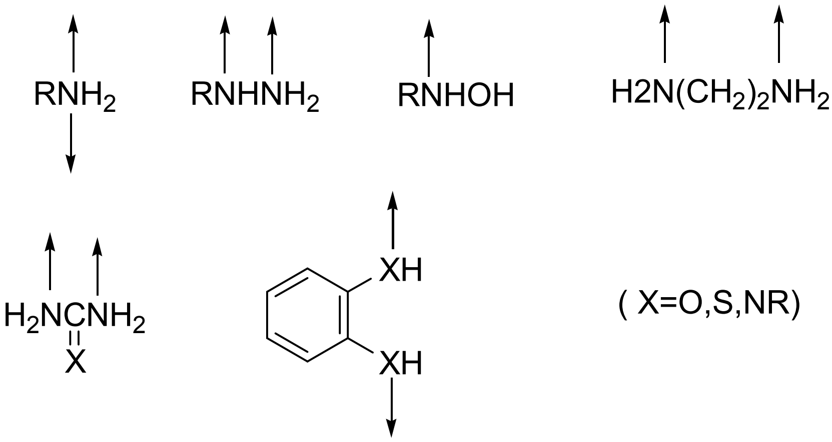
-nucleophilic displacement at a saturated carbon atom.
-nucleophilic addition to unsaturated carbon .
Nucleophilic addition elimination .

Heterocyclic rings can also be constructed by intramolecular **radical**, **carbene**, and **nitrene reaction**, and **by electrocyclic ring closure of conjugated π-electron systems**.

Doubly electrophilic reagents

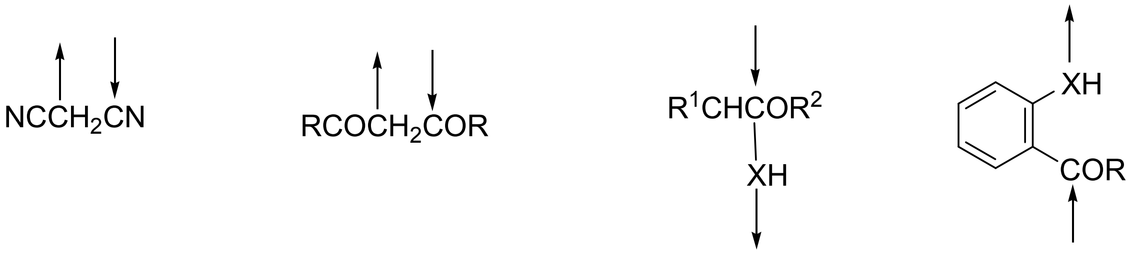


Doubly nucleophilic reagents



(X=O,S,NR)

Reagents with electrophilic and nucleophilic centres

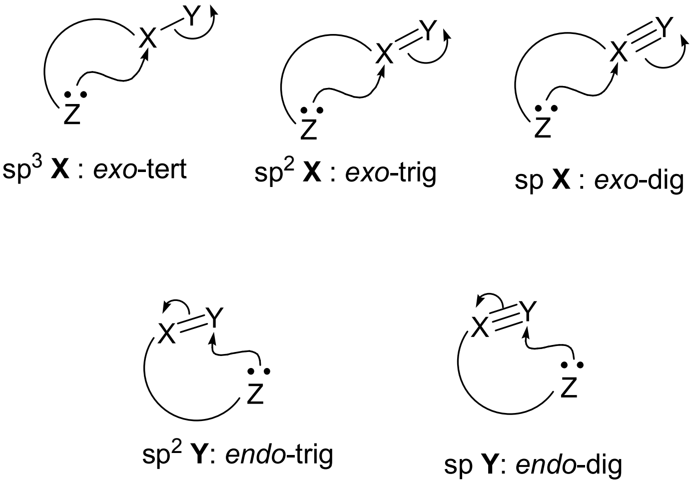


(X=O,S,NR)

Types of nucleophilic-electrophilic cyclization

This is based on the state of hybridization of the atom attacked by nucleophile and on whether the shift of electrons away from that atom in the cyclization reaction is within (*endo*-) or outside (*exo*-) the ring being formed.

Intramolecular displacement at a saturated carbon atom is an example of an *exo-tert* process, and nucleophilic addition and addition-elemination reaction of carbonyl compounds are *exo-trig* process.



sp^3 **X** : *exo*-tert

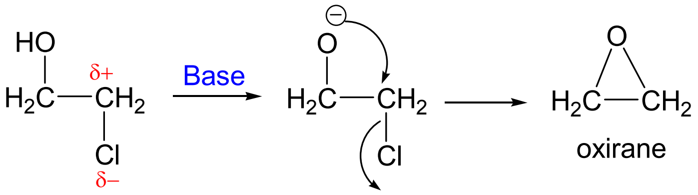
sp^2 **X** : *exo*-trig

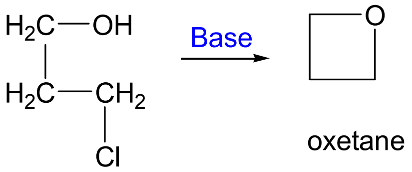
sp **X** : *exo*-dig

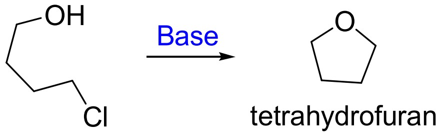
sp^2 **Y**: *endo*-trig

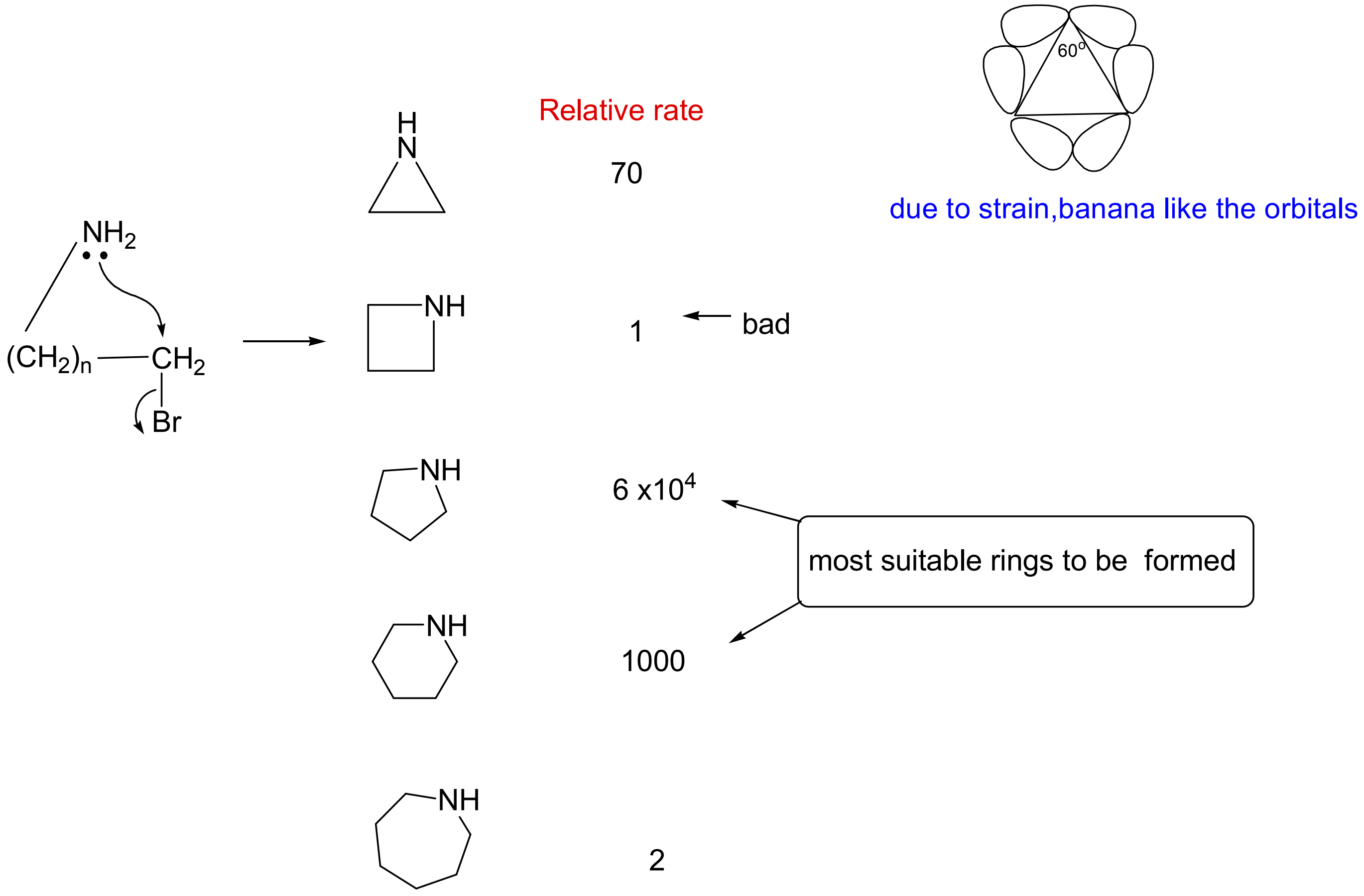
sp **Y**: *endo*-dig

1.1 -nucleophilic displacement at a saturated carbon atom (substitution) .





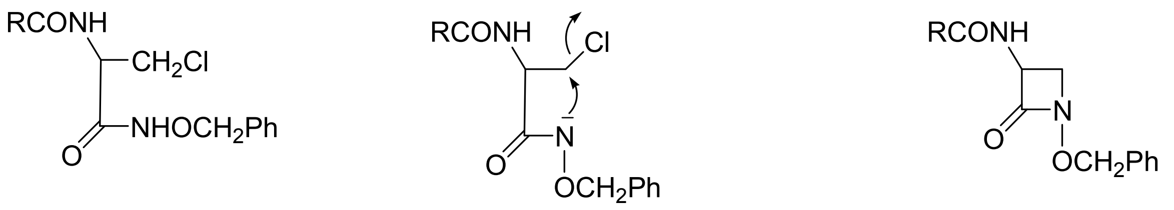




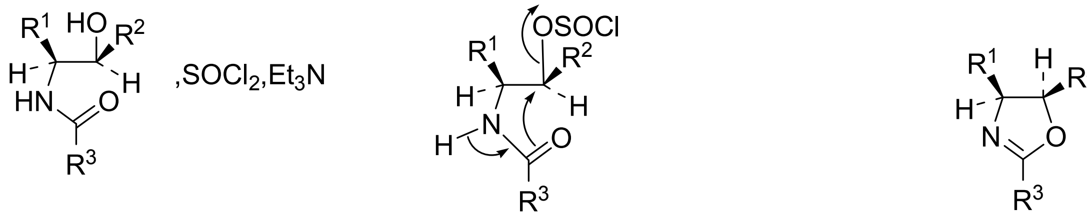
Examples of cyclization by Nucleophilic displacement at saturated carbon

Reagents	likely cyclization intermediates	Products

(i)

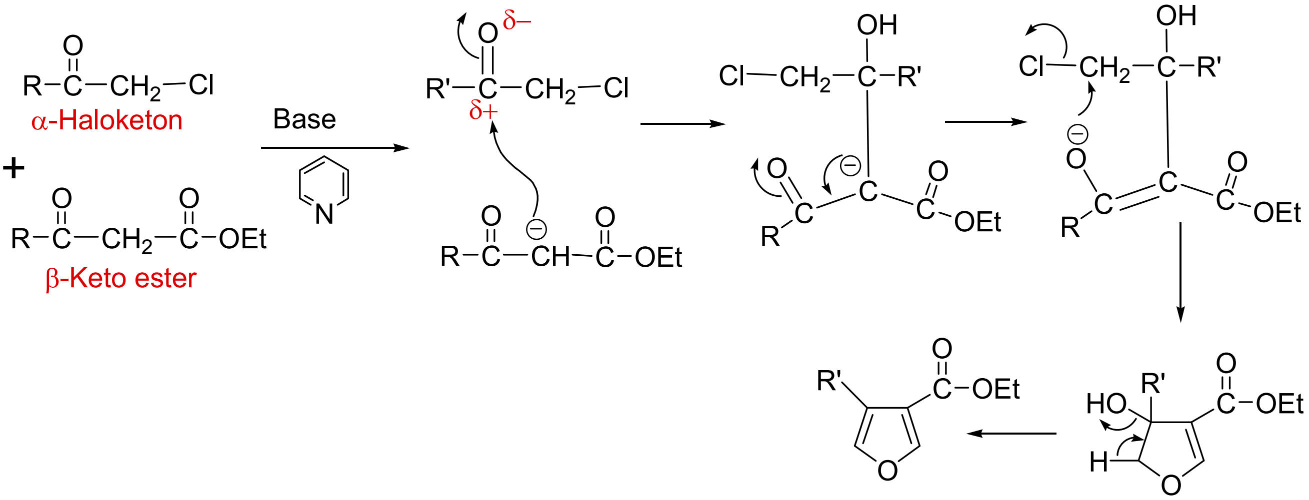


(ii)

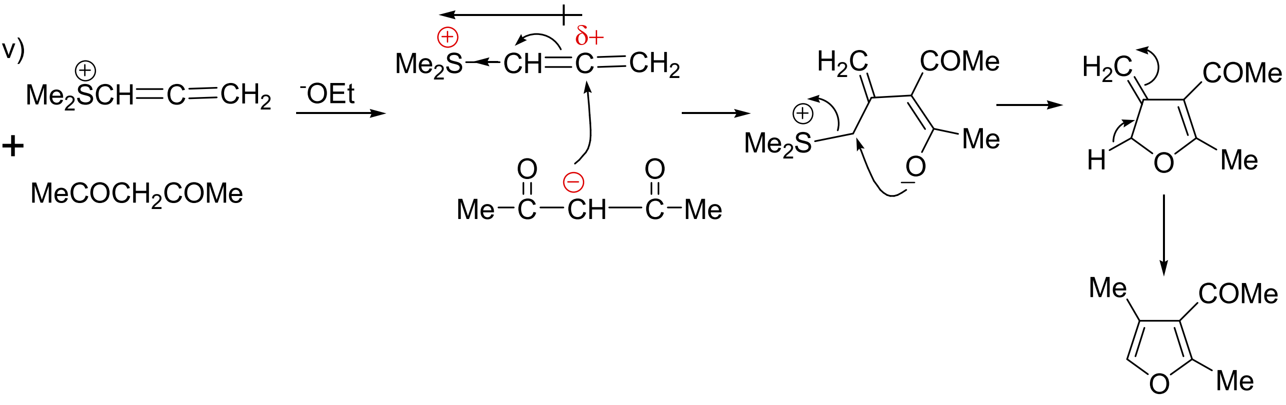


(iii)

Feist-Benary Furane synthesis



(iv)



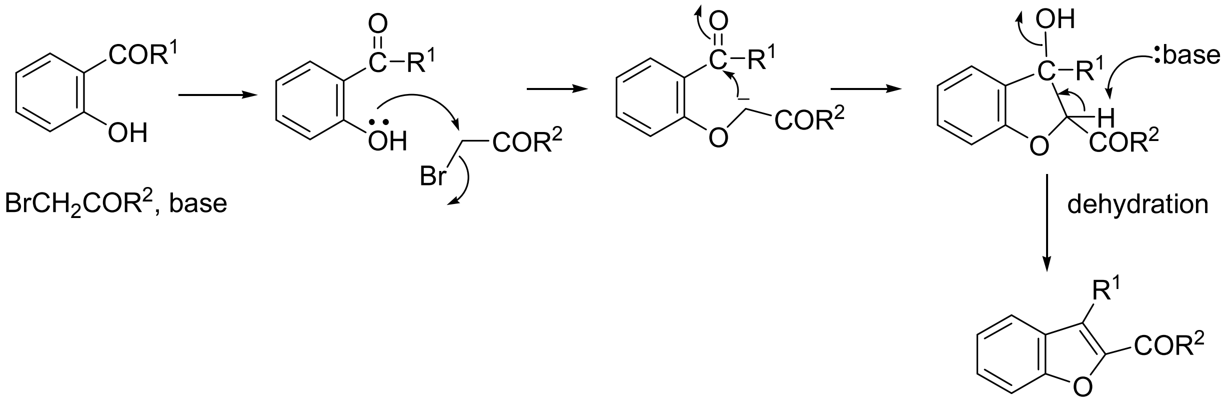
1.2-Intramolecular nucleophilic addition to carbonyl groups

This type of process is the most common cyclization reaction in heterocyclic synthesis . Internal nucleophilic attack at the carbonyl group of esters, acid chlorides.etc. is followed by displacement of a leaving group, and the carbonyl function is retained in the cyclic product. Attack by a nucleophile on an aldehydic or ketonic carbonyl group is often followed by dehydration of the intermediate, especially when it lead to the formation of a heteroaromatic ring system. Such cyclization may be acid-catalyzed when the nucleophile is a weak one, and the attack is then probably on the protonated carbonyl function.

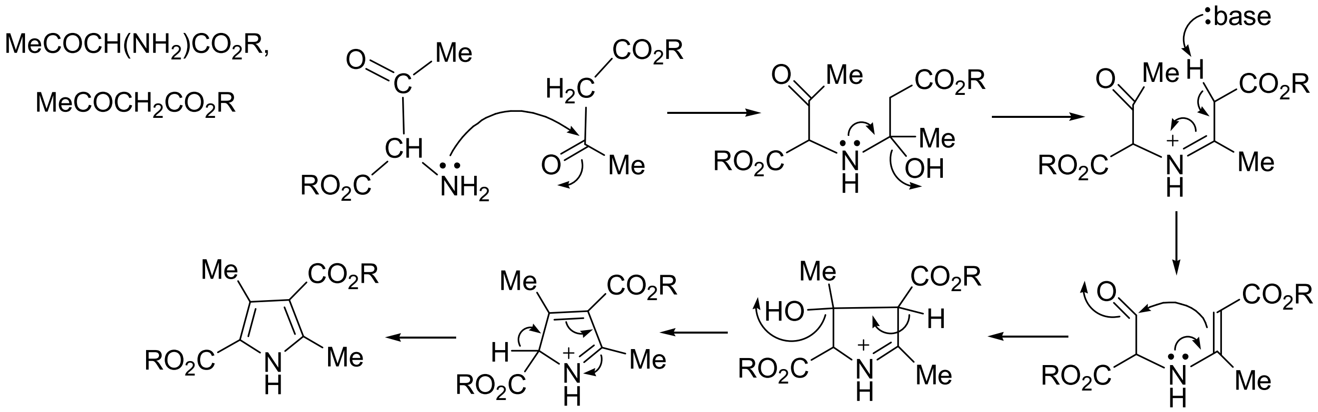
Three types of intramolecular cyclization on to aldehydic and ketonic carbonyl groups,and examples of heterocyclic ring synthesis involving cycization by nucleophilic attack on carbonyl group are illustrated ,**below**.

(a)Aldol-type cycliation

(i)

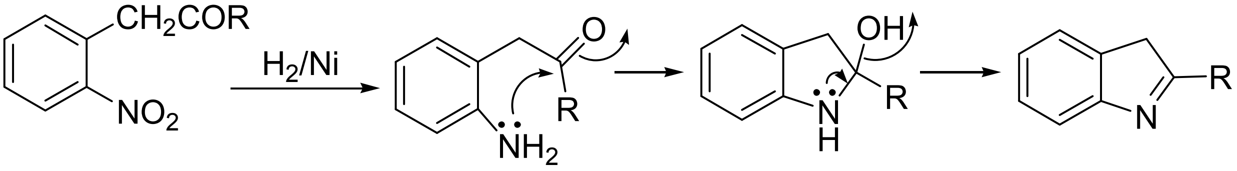


(ii)

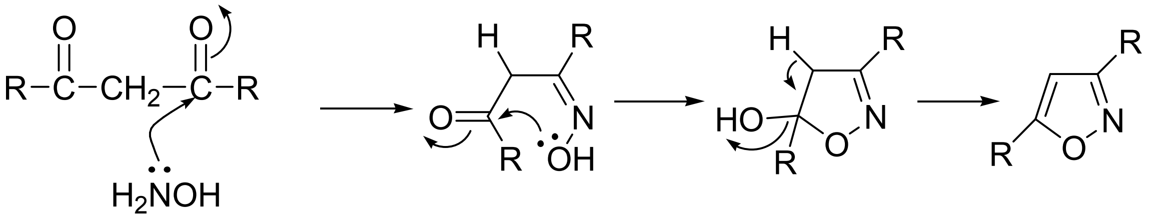


(b) Cyclization through nucleophilic heteroatoms

(iii)

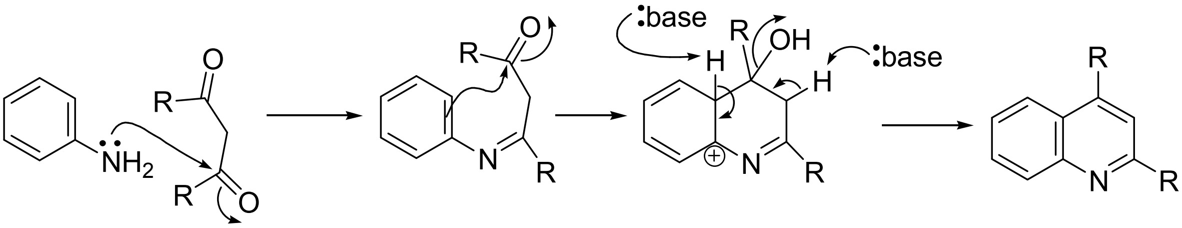


(iv)



(c) Cyclization onto an ortho position of a benzene ring

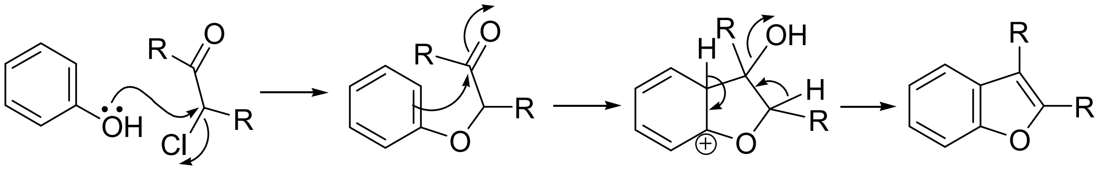
(v)



(vi) RCOCH(Cl)R,

PhOH, base,

then $ZnCl_2$



1.3-Intramolecular addition of nucleophiles to other double bonds

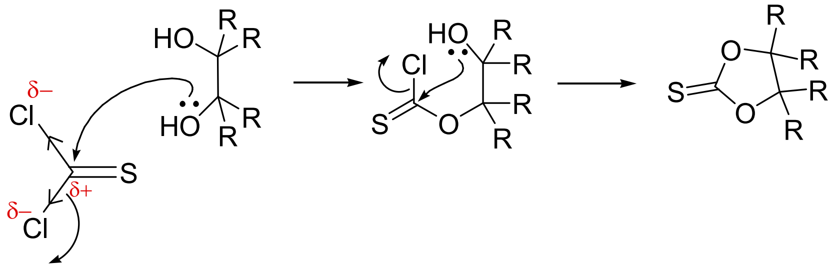
Cyclization by nucleophilic addition to double bonds other than carbonyl groups is illustrated below,

Activated C=S bond can act as the electrophiles, as in example (i) .In example (ii) the electrophile is activated C=C bond to which an internal conjugate addition reaction can take place, it is worth that in example (ii), the kinetically favored 4-*exo-trig* reaction is taking place , rather than the feasible alternative, a 5-*endo-trig* addition.

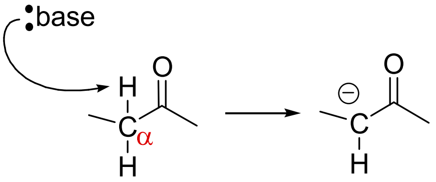
The great majority of cyclization take place by reaction at an electrophilic carbon centre, but ther are a few heterocyclic synthesis which involve cyclization onto electrophilic nitrogen. One such reaction, in which a nitro group act as electrophile ,is shown in example (iii).

(i) $R_2C(OH)C(OH)R_2$

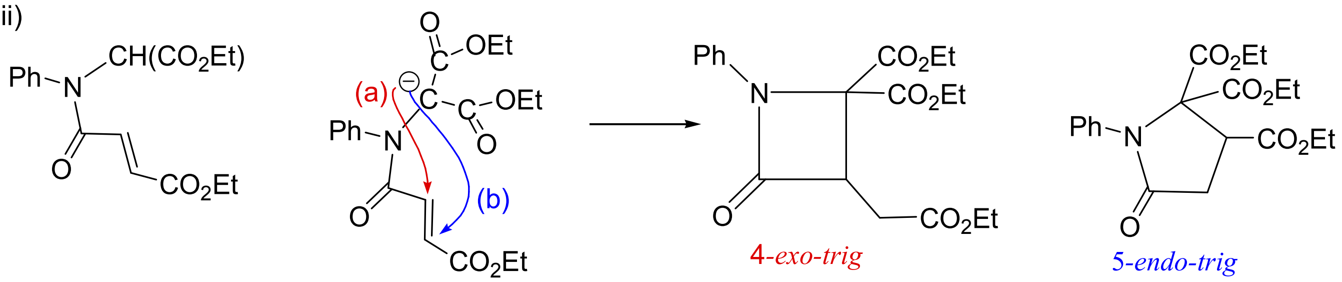
$Cl_2C=S$



α-carbon toward [carbonyl,withdrawal group],it's hydrogen is acidic removed easyly by base ,leave carbon very active Nu⁻ .



(ii)



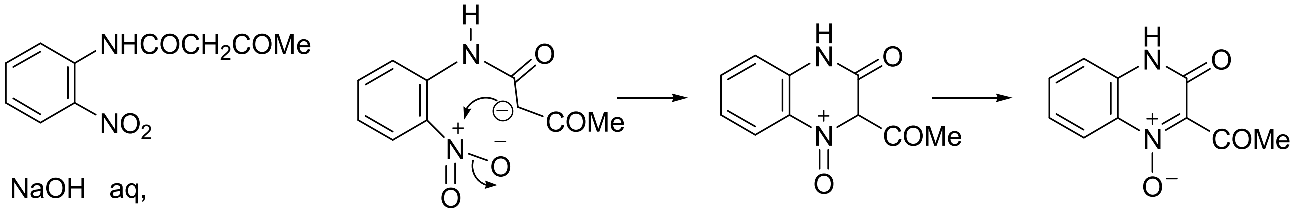
(a) 4-*exo-trig*

(b) 5-*endo-trig*

4-*exo-trig*
Actual product
[Kinetic product]
the fastest product formed

5-*endo-trig*
thermodynamic product
the stable product

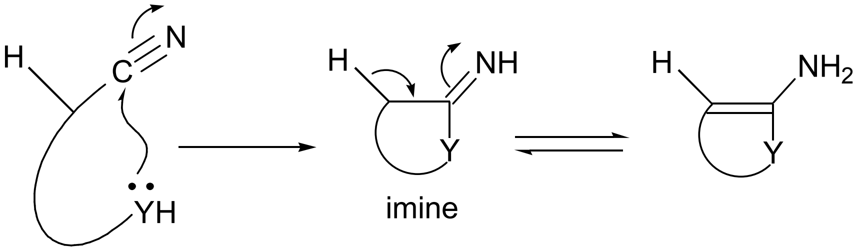
(iii)



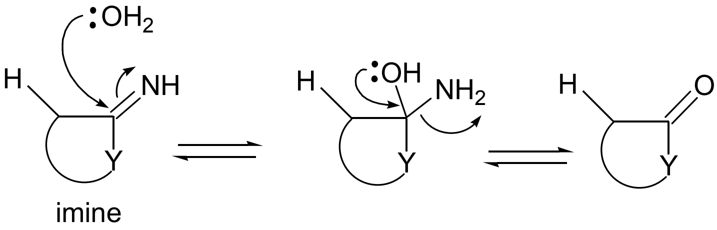
1.4-Cyclization onto triple bonds

1.4.a-Cyclization onto Nitriles

Nucleophilic addition to cyano groups provides an important method of synthesis of C-amino-substituted heterocycles,
In these reaction the initial product of cyclization is an imine, as shown below, Proton shift then take place to convert this initial product into a mor stable ,aromatic, C-amino compound. *If such poton shift cannot occur the imino group is often hydrolysed to carbonyl group during workup.*



C-Amino compouds by cyclization of nitriles

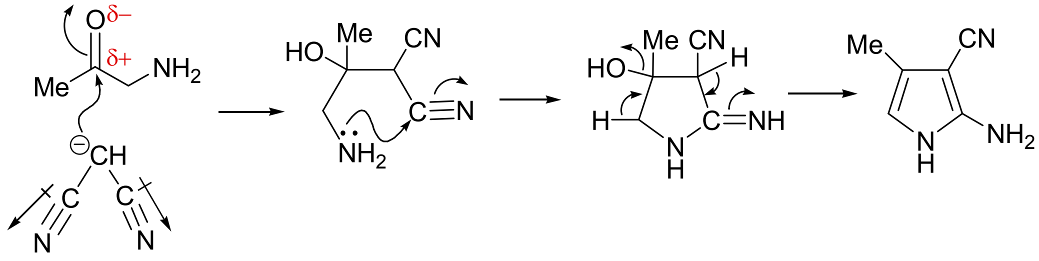


hydrolysis of imino group to carbonyl group

Some Cyclization involving *exo* addition to nitriles

(i)

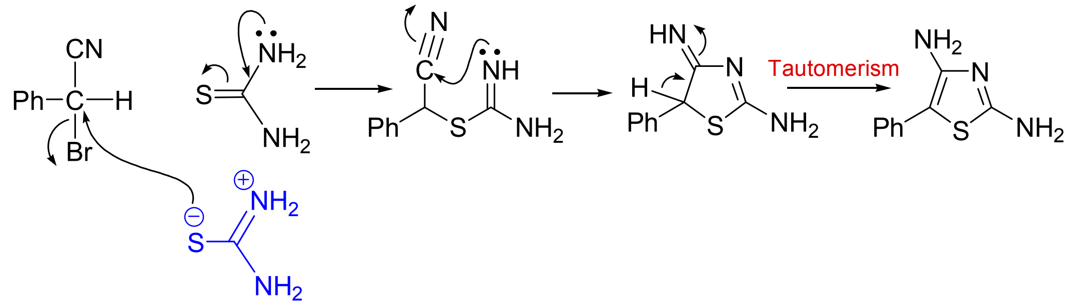
$MeCOCH_2NH_2$,
$CH_2(CN)_2$



(ii)

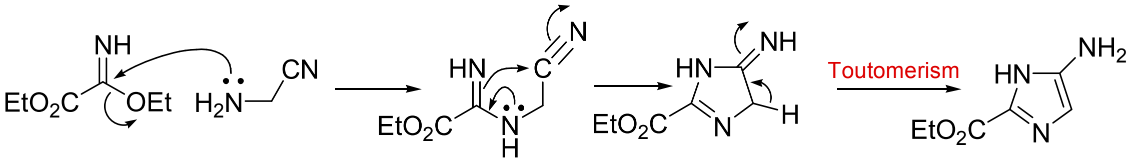
$(H_2N)_2CS$

$PhCHBrCN$



(iii)

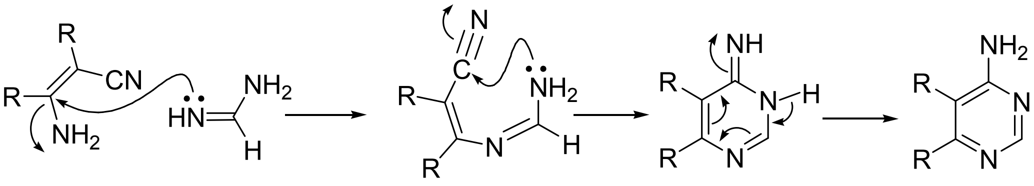
$EtO_2CC{=}NH.OEt$,
H_2NCH_2CN



(iv)

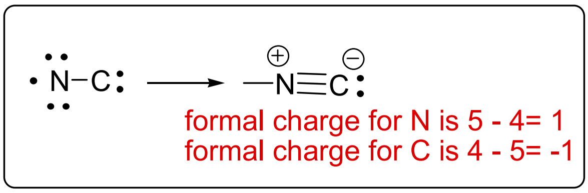
$H_2NCR{=}CRCN$

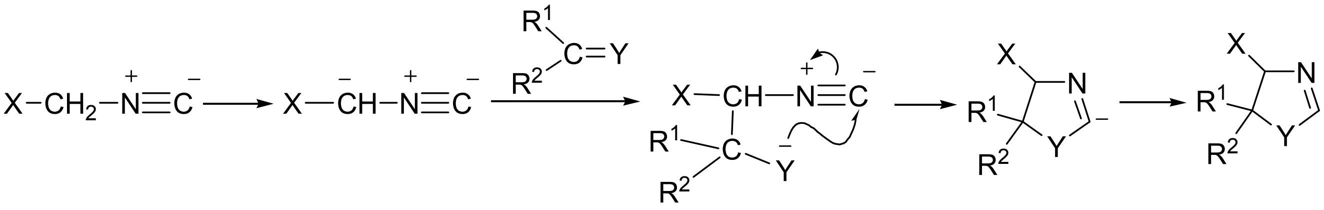
$H_2NCH{=}NH$



1.4.b-Cyclization onto Isonitriles

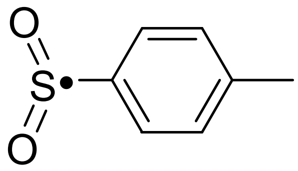
<u>Isonitriles undergo *endo* cyclization</u> reaction readily, and these reaction provide useful methods for the preparation of several five-membered heterocycles containing nitrogen.
The Isonitrile cyclizations often give heterocycles with substitution patterns which are not easily available by other methods of ring synthesis.
The most common reaction sequence using isonitriles is, A simple isonitrile XCH_2NC is deprotonated by a base, and the anion is then made made to react with an unsaturated electrophile.The intermediate so generated can cyclize in a 5-*endo-dig* process to give the heterocycle which is unsubstituted at the 2-position.



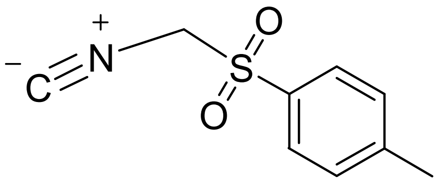


Construction of five-membered heterocycles through isonitriles

Tosylmethyl isocyanide (TOSMIC) has found the widest use because of the mild conditions required for its reaction and because the tosyl substituent is often lost in an aromatization step , after cyclization.



tosyl (Ts)



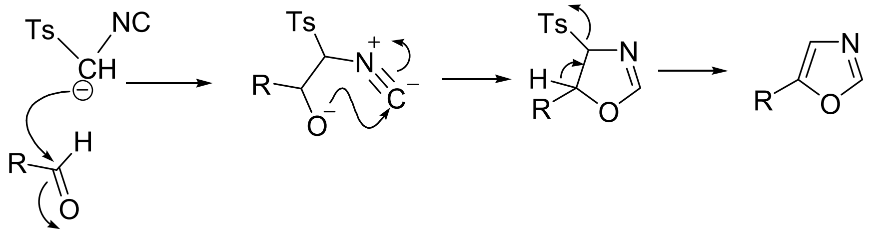
Tosylmethyl isocyanide

Cyclizations of isonitriles

(i)

$TsCH_2NC$, K_2CO_3,

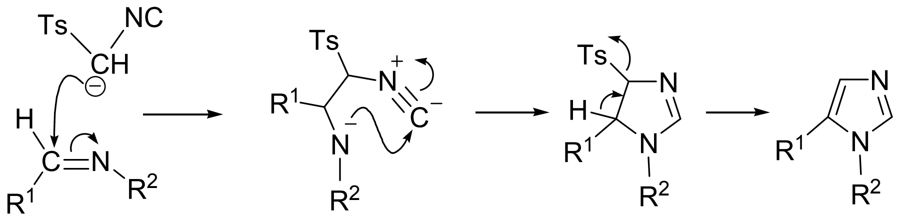
RCHO



(ii)

$TsCH_2NC$, K_2CO_3,

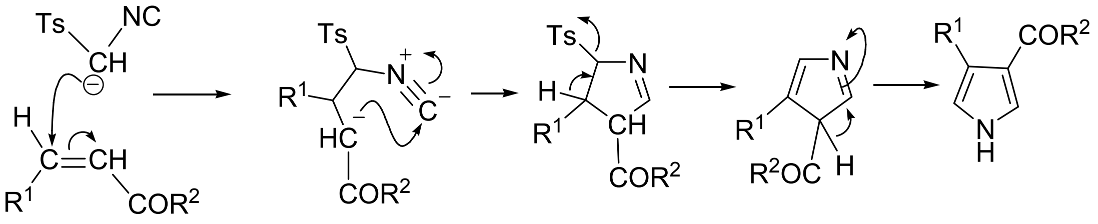
$R^1CH{=}NR^2$



(iii)

$TsCH_2NC$, NaH,

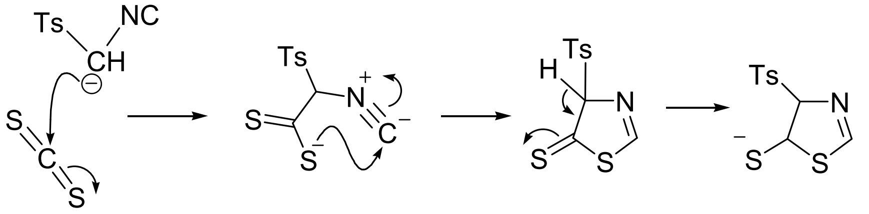
$R^1CH{=}CHCOR^2$



(iv)

$TsCH_2NC$, R_4NOH,

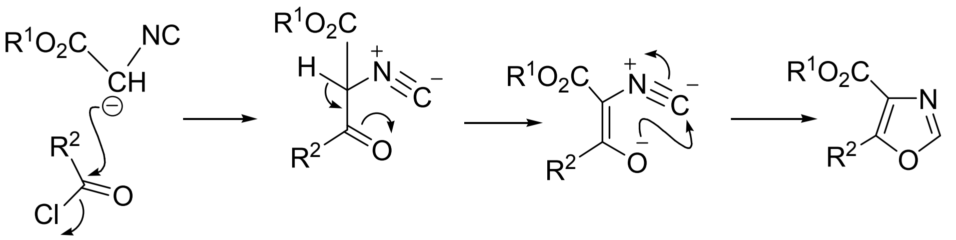
CS_2



(v)

$R^1O_2CCH_2NC$,NaH,

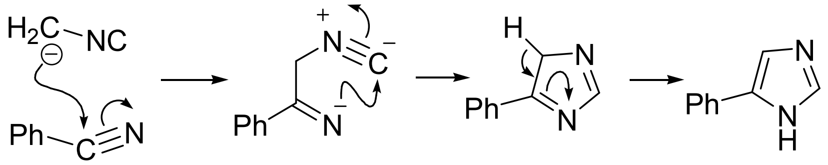
R^2COCl



(vi)

MeNC, BuLi,

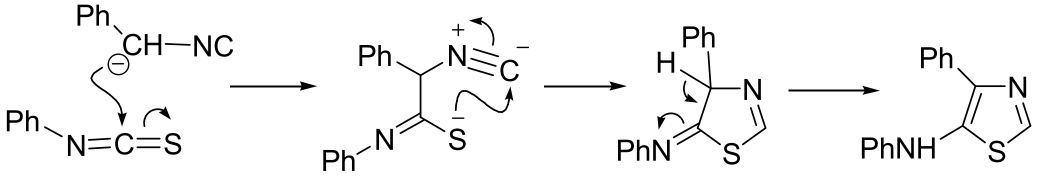
PhCN



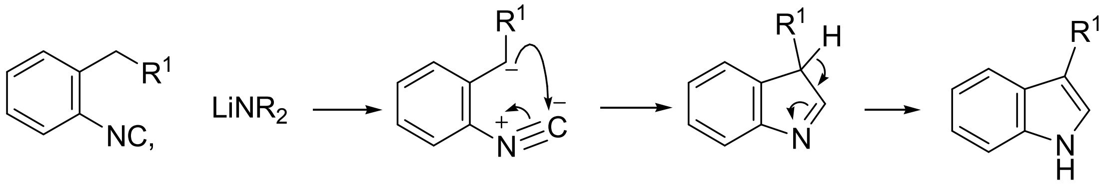
(vii)

$PhCH_2NC$, BuLi,

PhNCS



(viii)



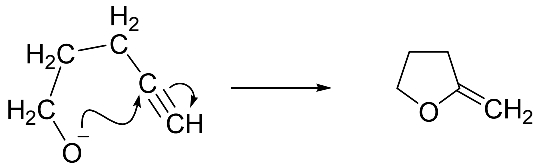
1.4.c-Cyclization onto alkynes

The *exo* addition to carabon-carbon triple bonds **is not so common** , but it has been used to synthesize some five- and six-membered heterocycles, as shown below in examples (i) and (ii) .

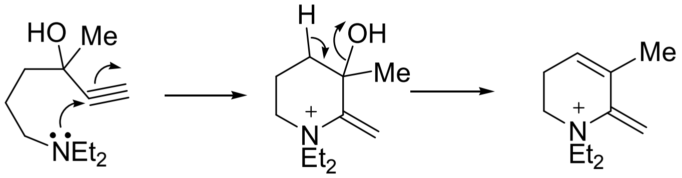
The reactive intermediate benzyne (1,2-didehydrobenzene) can be regard as a cyclic acetylene, and intramolecular nucleophilic additions to arynes are useful for the synthesis of some benzo-fused heterocycles, an example of this type of cyclization is shown below in (iii)

Some Cyclization involving *exo* addition to alkynes.

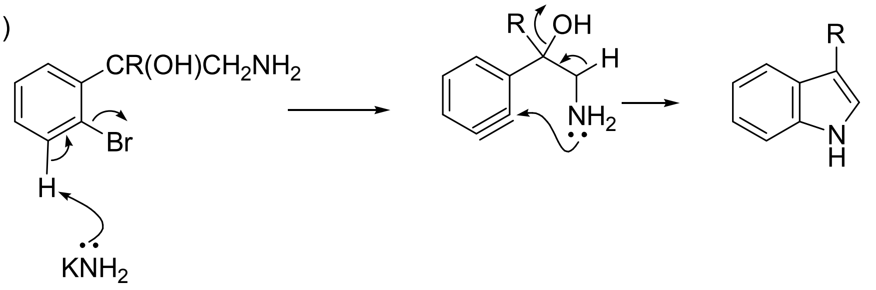
(i) $HC\equiv C(CH_2)_3OH$, $NaNH_2$



(ii) $HC\equiv CCMeOH(CH_2)_3NEt_2$, Base



(iii)



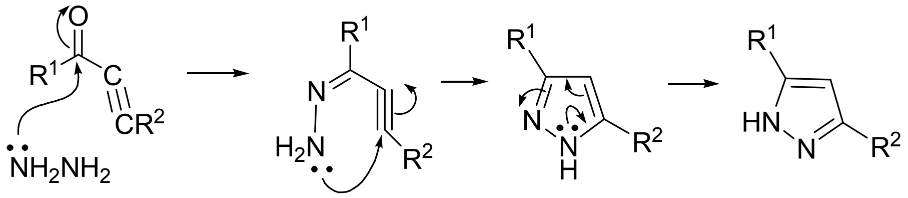
There are significant number of examples of heterocyclic synthesis which involve ***endo*** **cyclization on to a triple bond**. Although such reactions appear to be sterically unfavourable because of the linear nature of the triple bond, it is easily to distort the triple bond to achieve the required transition state geometry.

Examples of ring formation by *endo* attack on carbon-carbon triple bonds

(i)

$R^1COC\equiv CR^2$

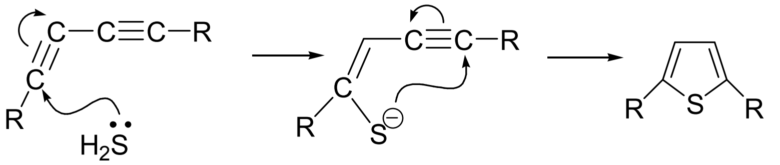
NH_2NH_2



(ii)

$RC\equiv CC\equiv CR$,

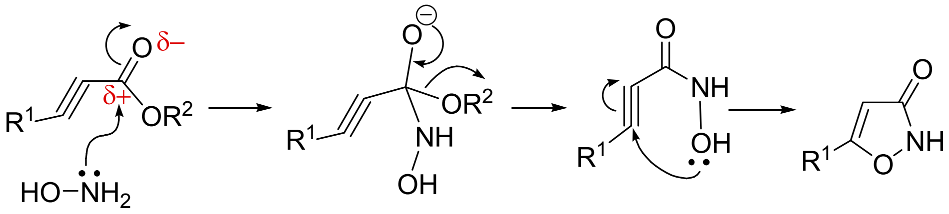
$H_2S,Ba(OH)$



(iii)

$R^1C\equiv CCO_2R^2$,

H_2NOH



1.5-Radical cyclization

The intramolecular addition of a radical to a π bonds lead to the formation of a new ring system. Most of the ring system produced by radical cyclization are five- or six-membered, and either partly or fully saturated . **The method usually lead to the formation of heterocycles by a process in which a carbon-center radicals becomes bonded to the carbon atom of a π bond.** This π bond may be a carbon-carbon double or triple bond, or it may be part of an aromatic ring; there are also a few examples of cyclization onto π bonds containing heteroatoms. A heterocycle is formed if there is a heteroatom present in the linking chain. Less commonly one of the atoms. Unless the radicals are highly stabilized the intramolecular addition step is irreversible. Such reactions are thus kinetically controlled. Five- and six-membered rings are most commonly formed by preferential *exo* cyclization.

The final product isolated from these cyclization depend on the method used to generate the radicals. One of the most common methods of carrying out these reactions is illustrated by example shown in below,,

The reaction is a reductive cyclization brought about by **tributyltin hydride**. A radical initiator, here **azobis(isobutyronitrile),** decomposes to produce radical initiator (step 1) which abstract a hydrogen atom from tributyltin hydride, breaking the weak tin-hydrogen bond (step 2). The tributyltin radical so formed abstract bromine from **the substrate** (step 3). The carbon radical then cyclizes to produce a new alkyl radical (step 4) which abstract hydrogen from tributyltin hydride(step 5) ,steps 3-5 are then continued, as a radical chain reaction.

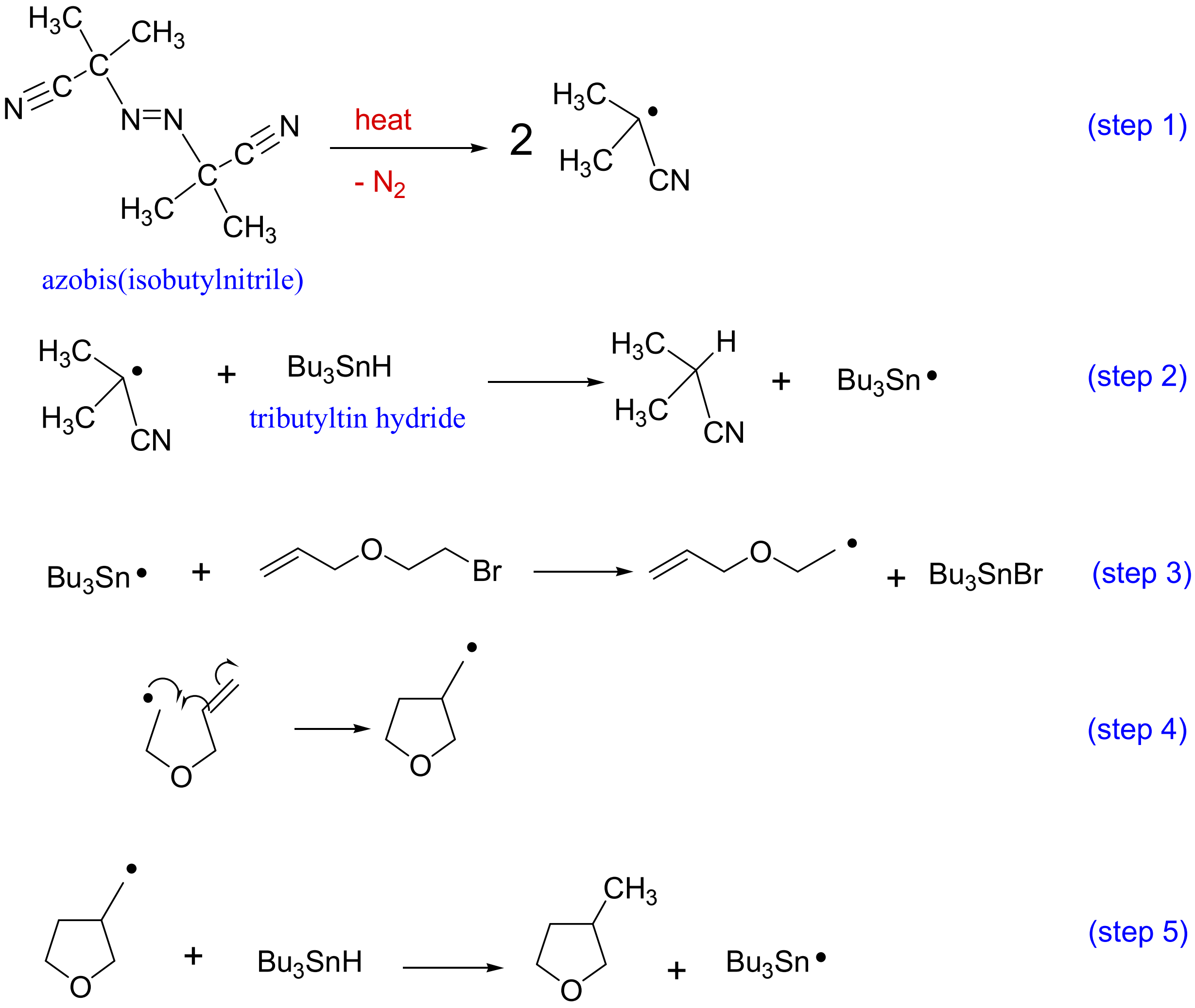


Fig. A radical cyclization using tributyltin hydride.

Two mor examples of cyclization using tributyltin hydride are shown in the following examples.

In example (i) an iminyl radical is generated by cleavage of an N-S bond.

Example (ii) illustrate the great power of this method in that two successive cyclization take place, the product being formed in high yield.

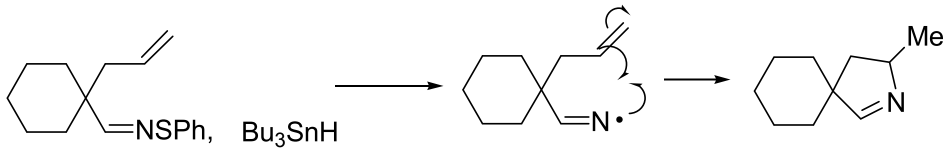
Other methods of reductive generation of radicals are illustrated in the remaining examples.

In example (iii) samarium iodide(SmI_2) is acting as a one-electron reducing agent. This cyclization gives better yields if carried out in the presence of one equivalent of an acid, indicating that the protonated aminoalkyl radical is more electrophilic than the neutral species. Similarly, nitrogen-centered radicals tend to be mor electrophilic when protonated ; that is, as aminium radical cations. Example (iv) shows the cyclization of a radical of this type .

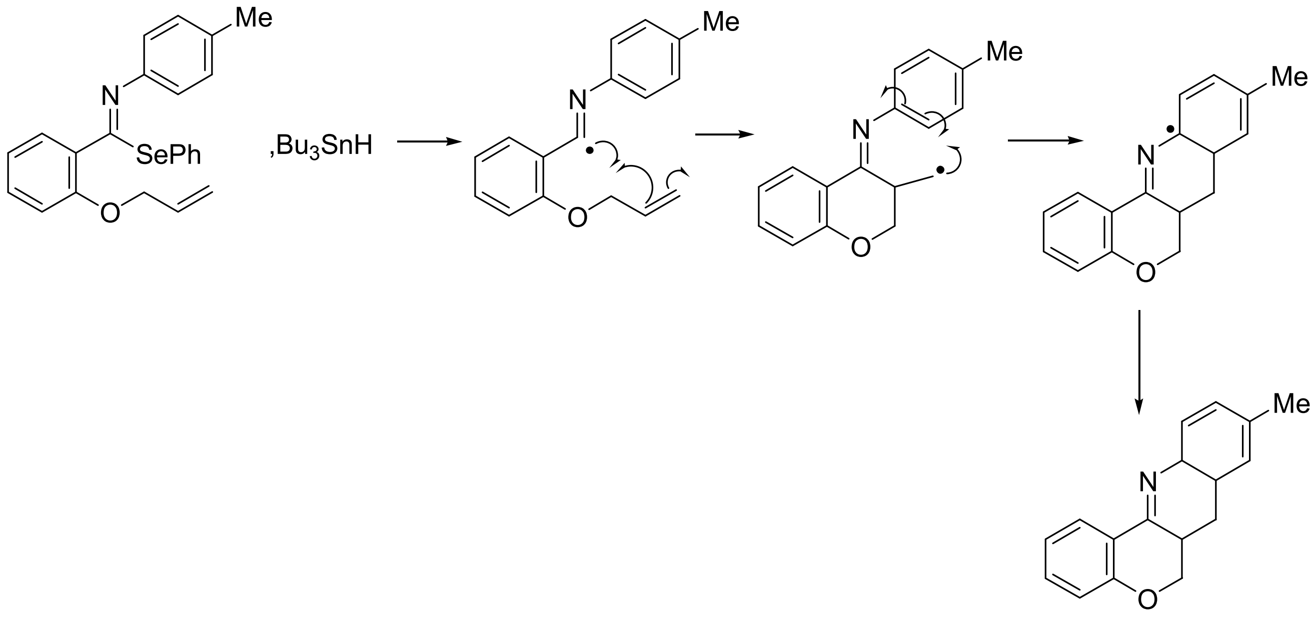
The cyclization shown in example (v) is typical of many based on aromatic diazonium salts, these being converted into aryl radicals by one-electron reduction followed by loss of nitrogen.

Examples of radical cyclization.

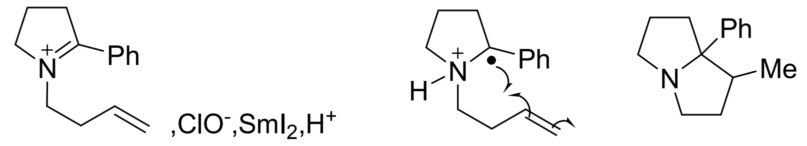
(i)



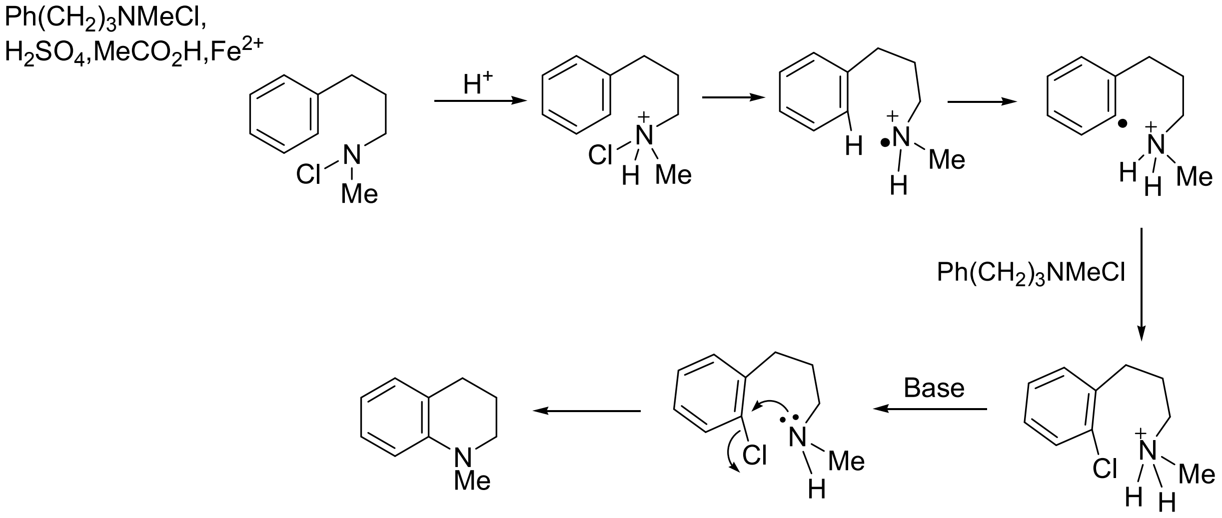
(ii)



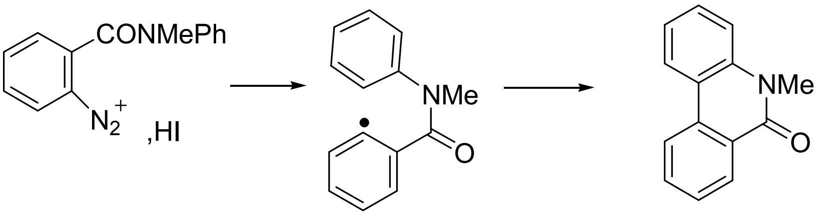
(iii)



(iv)



(v)



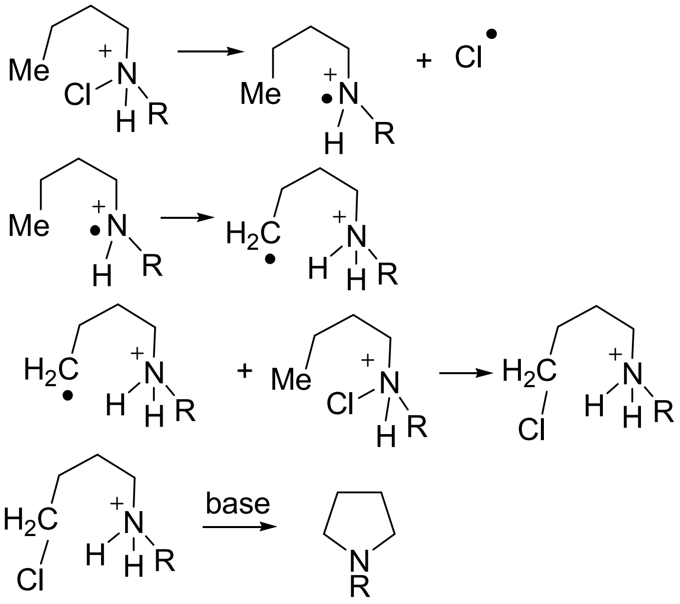
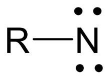
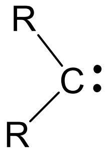


Figure Formation of pyrrolidines by the Hofman-Loffler raction.

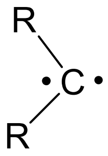
1.6-Carbene and nitrene cyclization



Nitrene



Singlet carbene

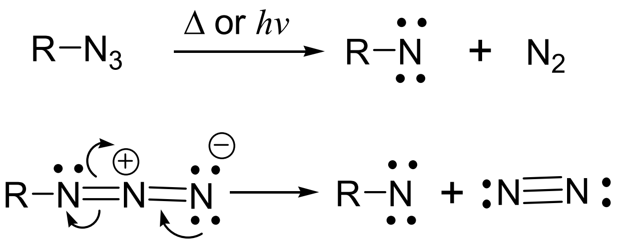


triplet carbene

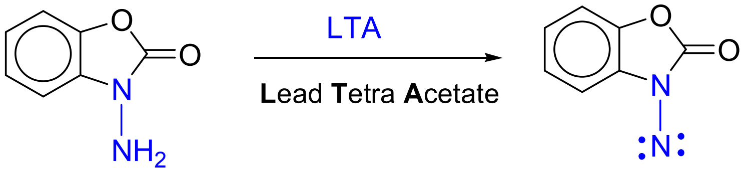
consider as biradical

Formation of nitrenes

1- the most method of forming nitrenes is photolytic or thermal decomposition of azide

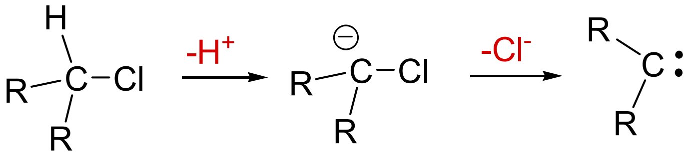


2-

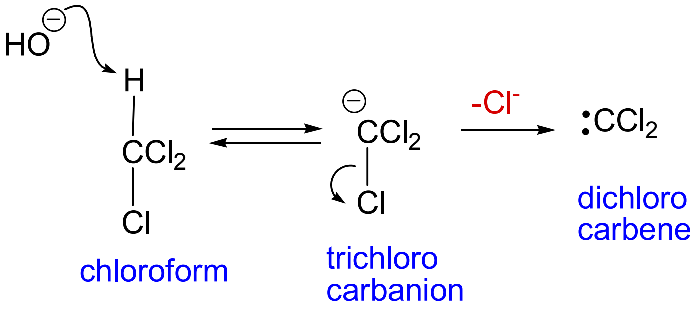


Formation of carbenes

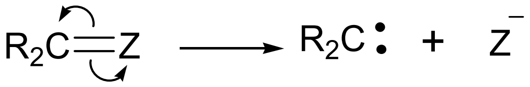
1-In **α-elimination** ,a carbon loses a group without its electron pair, usually a proton, and then a group with its electron pair, usually halide ion:



The most common example is formation of dichlorocarbene by treatment of chloroform with a base.

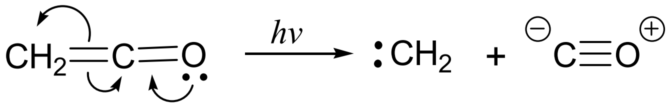


2-Disintegration of compounds containing certain types of double bonds:

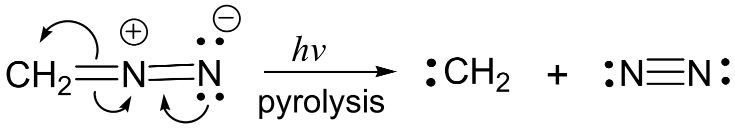


The two most important ways of forming :CH_2 are examples:

-the photolysis of ketene.



-the isoelectronic decomposition of diazomethane.



Monovalent nitrogen intermediates (nitrenes) and divalent carbon intermediates (carbenes) are highly reactive species which can undergo addition reactions with multiple bonds and can insert into unactivated carbon-hydrogen bonds.

Some examples of intramolecular versions of these reactions, leading to heterocycles, are shown in the following figure ,

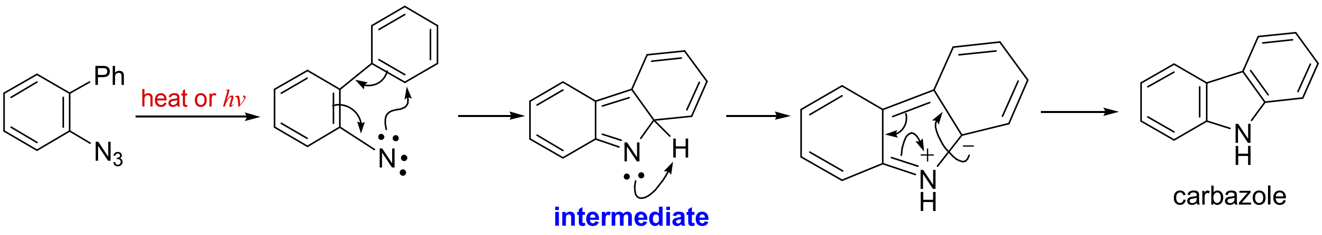
In **example (i)** the thermal or photochemical decomposition of 2-azidobiphenyl, is an important route to carbazole.
It has been shown to go by way of the singlet (spin-paired) nitrene, which cyclize onto the ortho position of attached phenyl substituent to give an **intermediate**, this intermediate can then aromatize to give carbazole by hydrogen shift to nitrogen. It is reasonable to assume that similar modes of cyclization are involved in related process such as those in examples (ii) and (iii).

In **example (iv)** the photodecomposition of vinyl azides to give azirines, can be regarded as an intramolecular nitrene addition to a double bond.

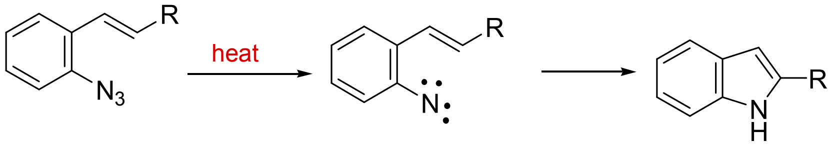
In **examples (v) to (vii)** the ability of singlet carbene and nitrene to insert into unactivated CH bonds is a valuable characteristic of intermediates .

Examples of formation of heterocycles by carbene and nitrene cyclization.

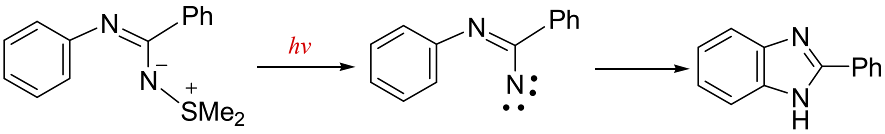
(i)



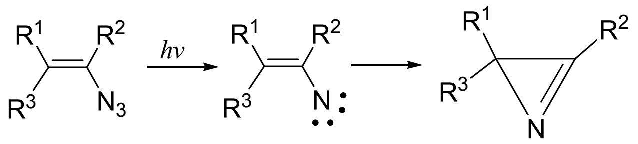
(ii)



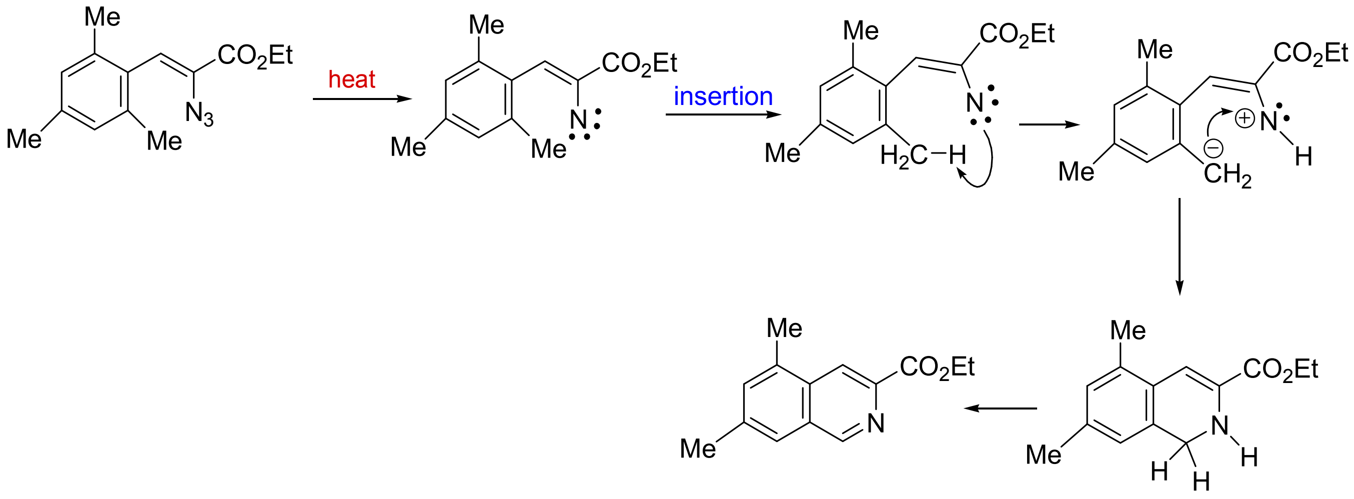
(iii)



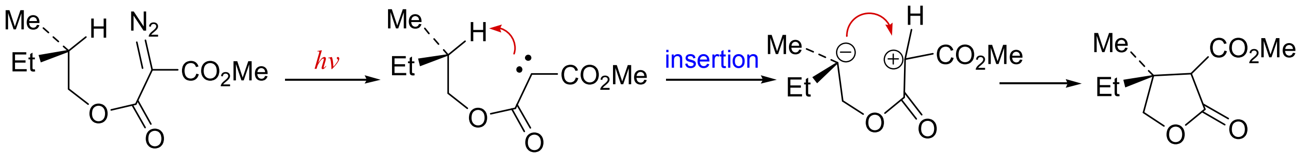
(iv)


R1
R2
R3
N3
hv
N

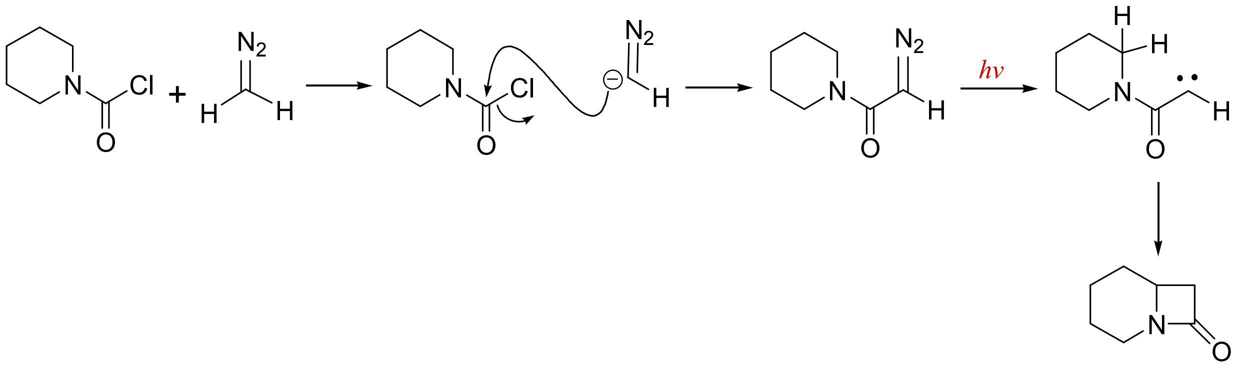
(v)


Me
CO2Et
N3
heat
insertion
H2C−H
CH2
N
H

(vi)


Me
Et
H
N2
CO2Me
O
hv
insertion

(vii)


N
Cl
O
+
N2
H
hv

1.7-Electrocyclic reactions.

The cyclization reactions that we have considered so far are all intramolecular versions of well-known σ-forming-processes.

Electrocyclic reaction are different, in that they have no direct intermolecular counterpart.

The-open chain reagent used in an electrocyclic ring closure must be a fully conjugated π-electron system .

Electrocyclic ring closure is the reaction in which a σ-bond is formed at the termini of the π system .

The reactions are normally brought about by input of energey in the form of heat or light and without any addition reagent.

An equilibrium is set up between the acyclic and cyclic isomers. In many cases the acyclic isomer predominates, so that the electrocyclic reaction may be a ring opening rather than a ring formation.

The most important types of electrocyclic reaction found in heterocyclic chemistry are illustrated schematically in the following figure.

Reactions (a) and (b) involve the use of open-chain reagents containing four π-electrons, (a) in a 1,3-dipolar species ,or (b) in a heterodiene .

Reaction (c) and (d) are the six-π-electrons analogues of (a) and (b).

The open-chain species can thus be precursors of saturated or partially saturated heterocycles containing from three to six atoms .

Higher-order electrocyclic reaction of system with more than six π-elecrons are also feasible ,but they are not so commonly encountered.

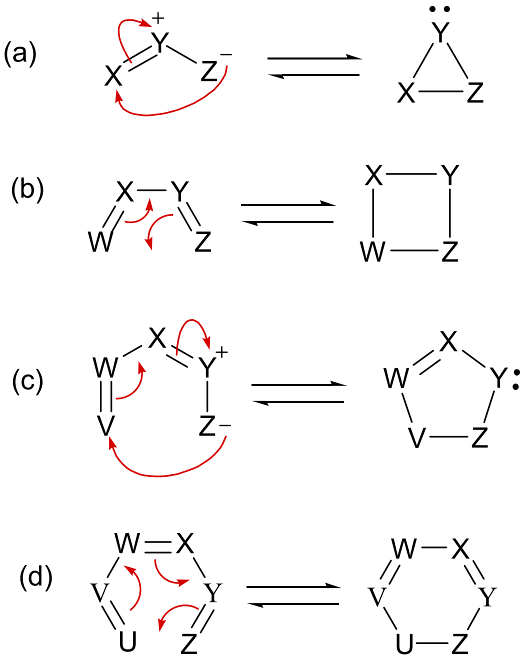
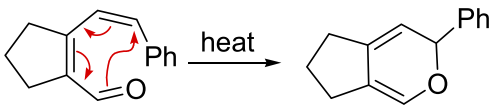


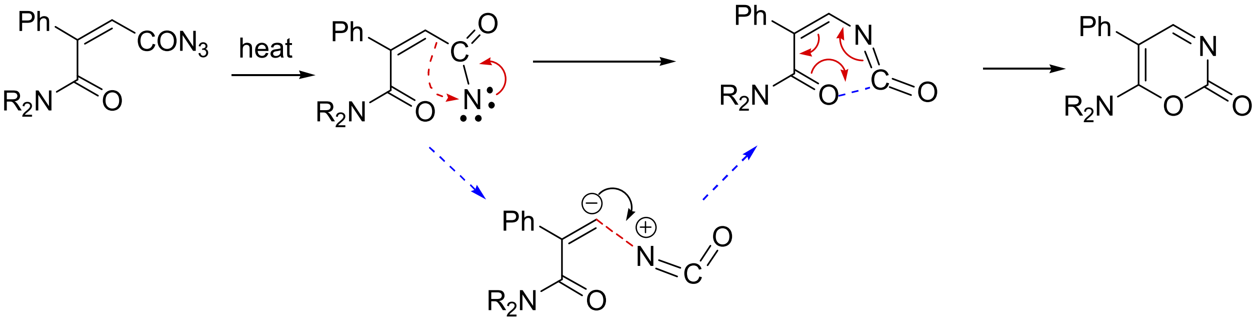
Fig. Electrocyclic reaction involving open-chain isomers containing four or six π- electrons

Examples of formation of six-membered heterocycles by electrocyclic ring closure

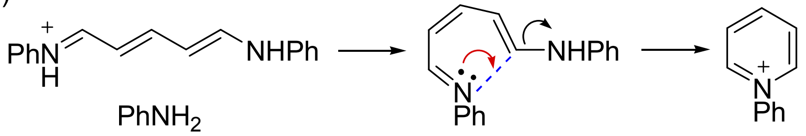
(i)



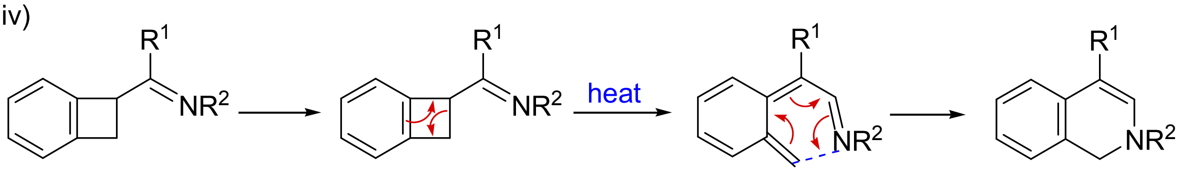
(ii)



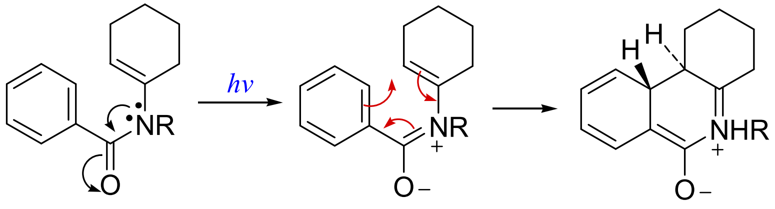
(iii)



(iv)



(v)



Ring opening and cyclization reactions involving three-membered heterocycles

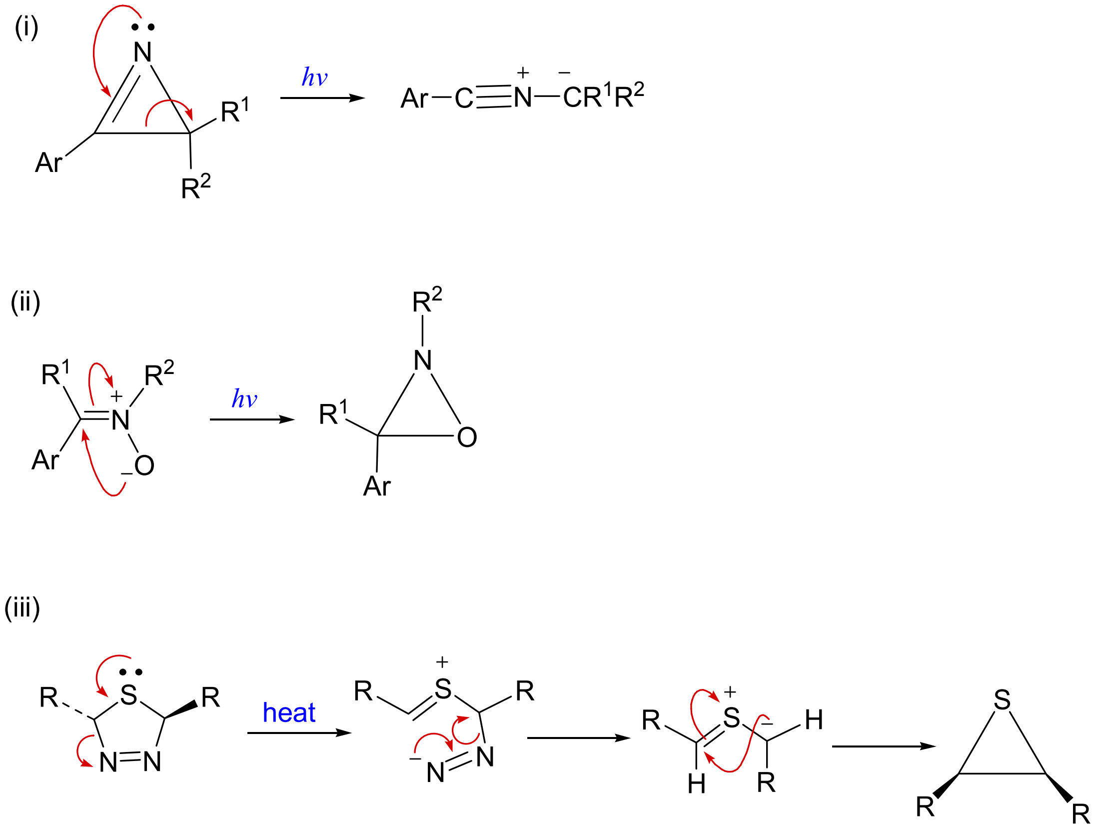
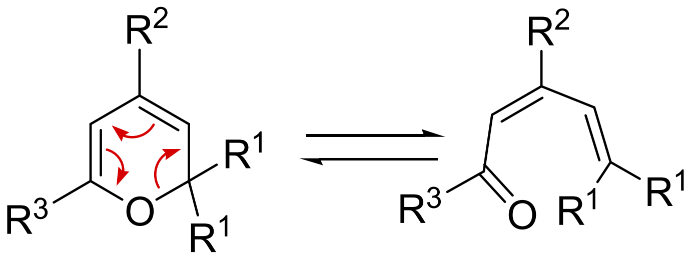
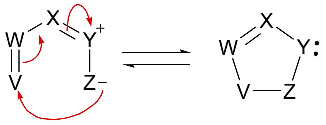


Fig. Ring opening and cyclization reactions involving three-membered heterocycles

The reverse of cyclization, (ring-opening) reactions also occur and are sometimes more useful from a preparative point of view.
Example is the revesible ring opening of 2H-Pyrans.



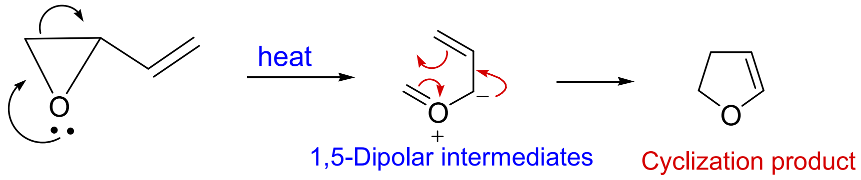
Six π-electrons cyclization of type  are much more common and have been given the general description of 1,5-*dipolar cyclization* , *cyclize* thermally to the five-membered heterocycles.

The cyclic isomers can also be removed from the equilibria by irreversible *tautomerization* to a more stable (often aromatic) structure.

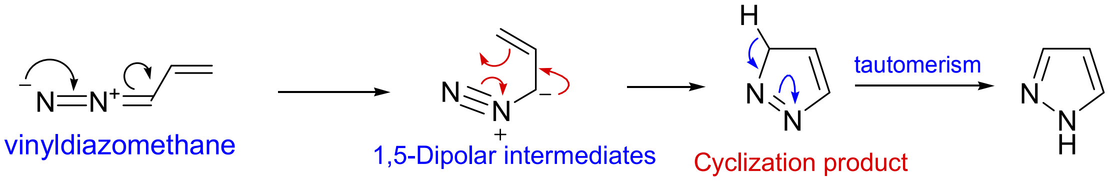
Examples of 1,5-dipolar cyclization are shown in the following Figure.
In examples (ii) and (iii) the primary cyclization products tautomerize to aromatic system and so displace the equilibria in favour of the cyclic forms.
In examples (iv) and (v) aromatic heterocycles are formed directly in cyclization.

Examples of 1,5-dipolar cyclization

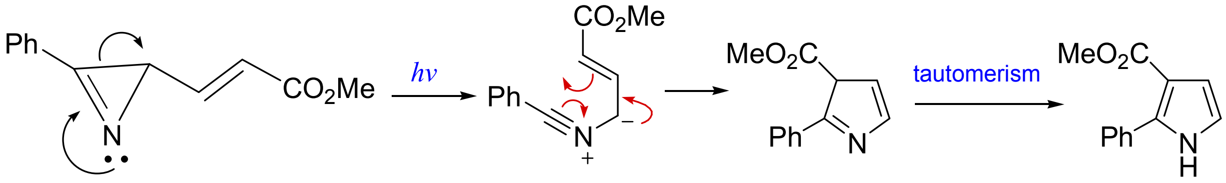
(i)



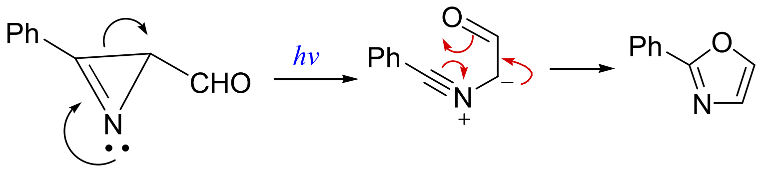
(ii)



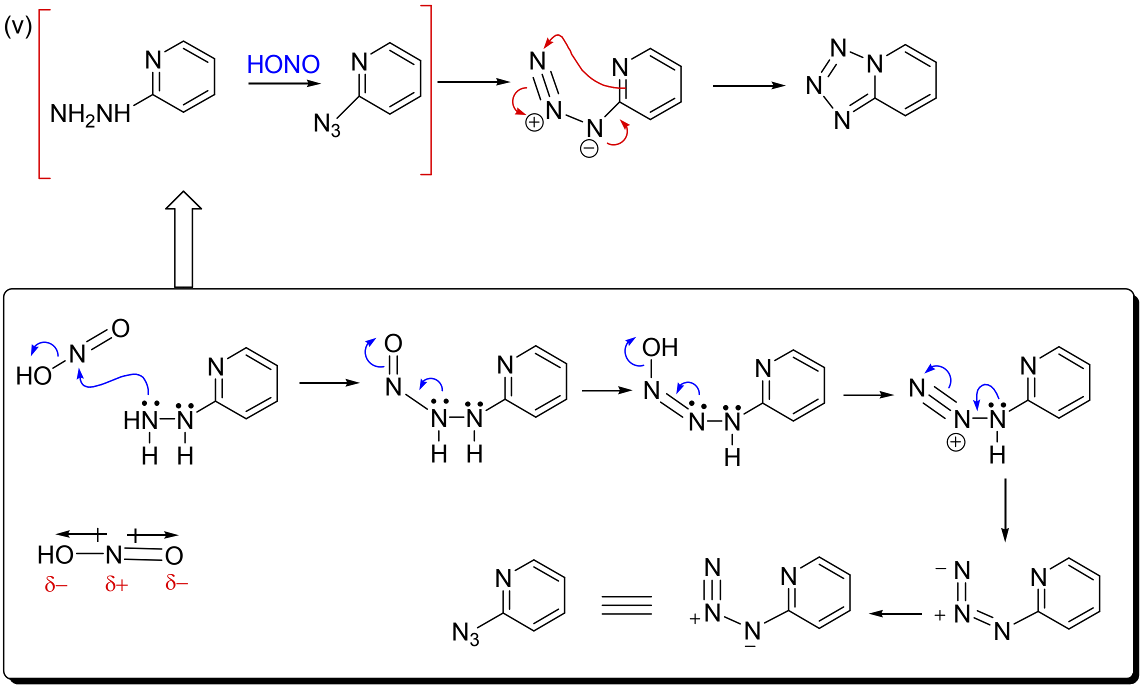
(iii)



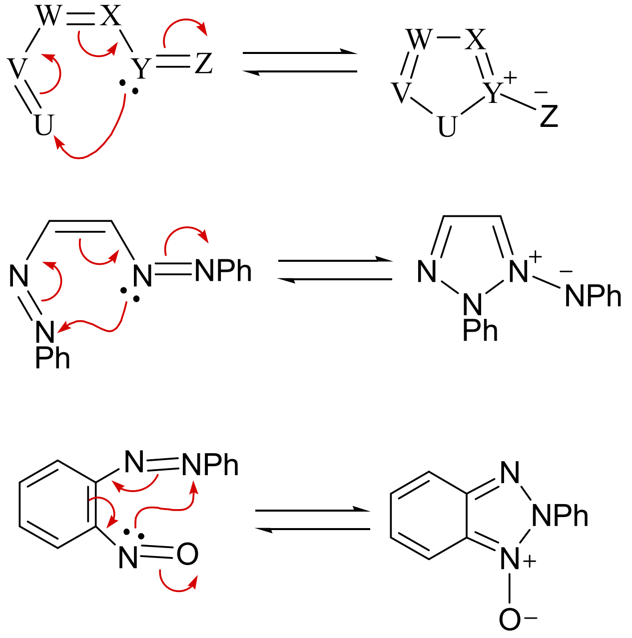
(iv)



(v)



A different type of electrocyclization of heterotrienes, leading to the formation of Five-membered rings, sometimes takes precedence over the usual type of ring closure. The general form of this reaction is shown in the following figure,



Fig, Alternative mode of cyclization of heterotrienes

2-Cycloaddition reactions

Reaction in which two ring bonds are formed, and no small molecules are eliminated in the process , are called ***cycloaddition reaction***

Cycloaddition reaction provide useful synthetic routes to a wide range of heterocycles, especially those containing four, five, or six atoms in the ring

The most important types of cycloaddition reaction are:-

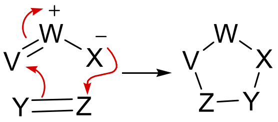
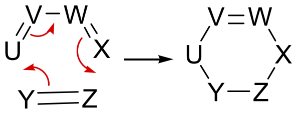
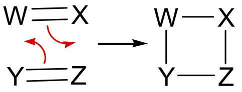
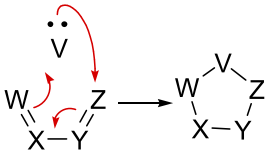
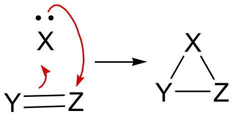
	Type name	**example**	**geometry**	**π-electrons**
a	1,3-dipolar cycloaddition		3+2⟶ 5	4+2 π
b	Diels-Alder reaction		4+2⟶ 6	4+2 π
c	[2+2] cycloaddition		2+2⟶ 4	2+2 π
d	cheletropic	(i)  (ii) 	4+1⟶ 5 2+1⟶ 3	4+2 π 2+2 π

Figure 2.1 the major types of cycloaddition process used in heterocyclic synthesis

2.a- 1,3-Dipolar Cycloaddition

A 1,3-dipole is a three-atom π-electron system with four π-electrons delocalized over the three atoms.
1,3-Dipolar species contain a heteroatom as the central atom. This can be formally sp- or sp^2-hybridized, depending upon whether or not there is a double bond orthogonal to the delocalized π-system.

The two types of 1,3-dipole are :

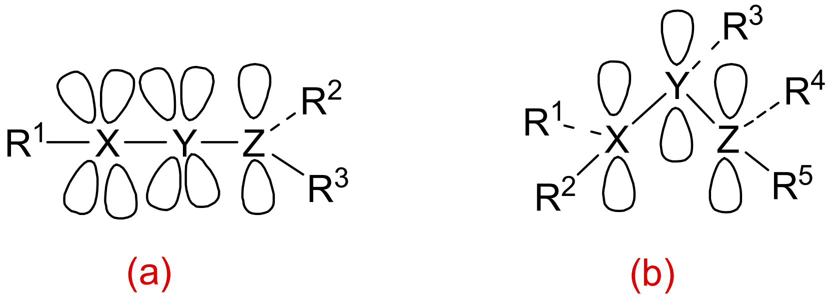
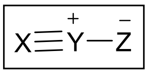
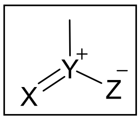
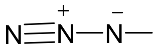
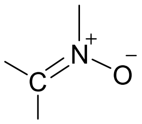
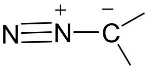
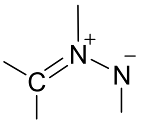
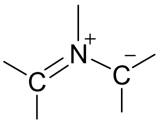
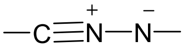
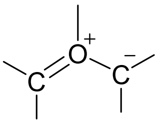
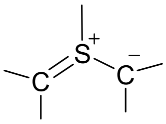
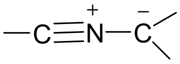


Fig 2.2 Types of 1,3-dipole:(a)with,and(b)without an orthogonal double bond. R^1-R^5 can be substituents or lone pairs.

1,3-dipoles which undergo cycloaddition reactions readily are listed in the table 2.1 .
The first six species listed are dipoles of type (a),which formally have a central sp-hybridized atom, but the species are easily bent to permit cycloaddition reactions at the termini.

Compounds which can react with these species in cycloadditon reactions are commonly called **dipolarophiles**. These contain unsaturated functional groups such as C≡C, C=C, C≡N, C=N, C=O, and C=S.

Table 2.1

 $X\equiv\overset{+}{Y}-\overset{-}{Z}$			
 $N\equiv\overset{+}{N}-\overset{-}{N}-$	azide		nitrones
	diazo compounds		azomethine imides
 $-C\equiv\overset{+}{N}-\overset{-}{O}$	nitrile oxides		azomethine ylides
 $-C\equiv\overset{+}{N}-\overset{-}{N}-$	nitrile imides		carbonyl ylides
 $-C\equiv\overset{+}{N}-\overset{-}{S}$	nitrile sulphides		thiocarbonyl ylides
	nitrile ylides		

In considering the viability of 1,3-dipolar cycloaddition as a route to a particular heterocycle, it is desirable to be able to estimate (i) the *reactivity* of the components under a given set of conditions and (ii) the *selectivity* of the reaction in giving a single isomer where more than one might be formed.

QUICK REVISION

HOMO-LUMO Interactions

As long as the molecules whose interaction we want to consider are far apart, each has its own set of molecular orbitals undisturbed by the other. These MO's form the unperturbed basis from which the interaction is to be evaluated. As the molecules approach sufficiently closely that overlap between their orbitals becomes significant, the new interaction constitutes a perturbation that will mix orbitals of each molecule into those of the other. The strongest interactions will be between those orbitals that are close to each other in energy, but interaction between two filled levels will cause little change in the total energy because one orbital moves down nearly as much as the other moves up. The significant interactions are therefore between filled orbitals of one molecule and empty orbitals of the other; furthermore, since the interaction is strongest for orbital pairs that lie closest in energy, **the most important interactions are between the highest occupied molecular orbital (HOMO) of one molecule and the lowest unoccupied molecular orbital (LUMO) of the other.**

These orbitals are sometimes referred to as the ***frontier orbitals.***

If HOMO-LUMO interaction cannot occur, for example because the orbitals are of different symmetry types, this stabilizing interaction is absent, the small energy increase arising from the filled level interactions will dominate, and no reaction will occur.

It is instructive also to look at an example in which the HOMO levels of the two molecules are of different energies. In the following Figure, the HOMO and LUMO levels are indicated for molecules ***D*** and ***A***, ***D*** having its highest filled level substantially higher than that of ***A***. **This is a donor-acceptor situation**, with ***D*** the donor and ***A*** the acceptor. Note that the HOMO of ***D*** is much closer in energy to the LUMO of ***A*** ,but the ***A*** HOMO is much farther from the ***D*** LUMO. Hence the ***A*** HOMO will be relatively little affected, and most of the stabilization will occur by lowering the ***D*** HOMO. As it is lowered, it will mix in substantial amounts of the ***A*** LUMO; charge is thereby transferred from ***D*** to ***A*.** Note that charge transfer occurs primarily to the lowest antibonding acceptor orbital.

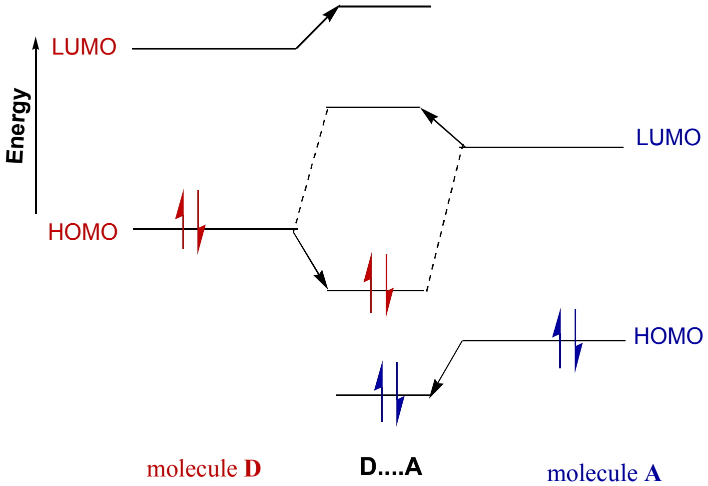
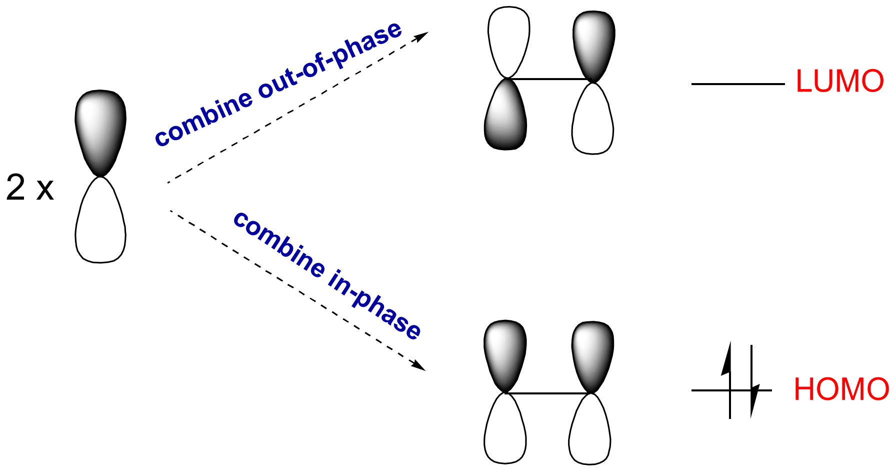
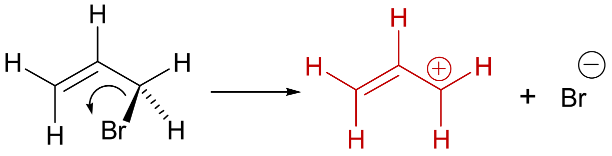


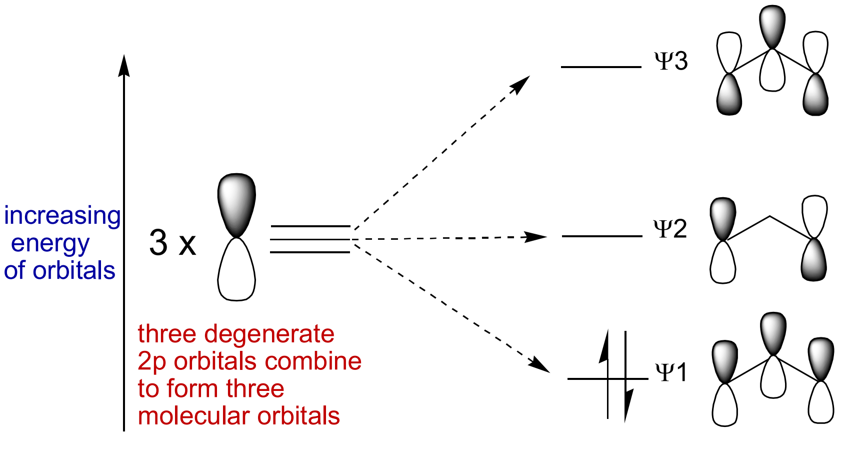
Figure: HOMO-LUMO interaction of a donor **D** with an acceptor **A**.



The allyl system

the allyl cation





antibonding
molecular orbital
higher in energy
than a p orbital

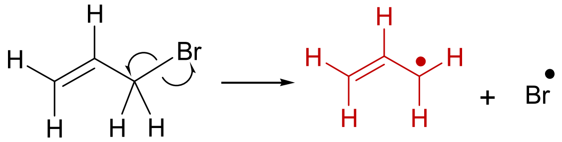
nonbonding
molecular orbital
Same energy
as a p orbital

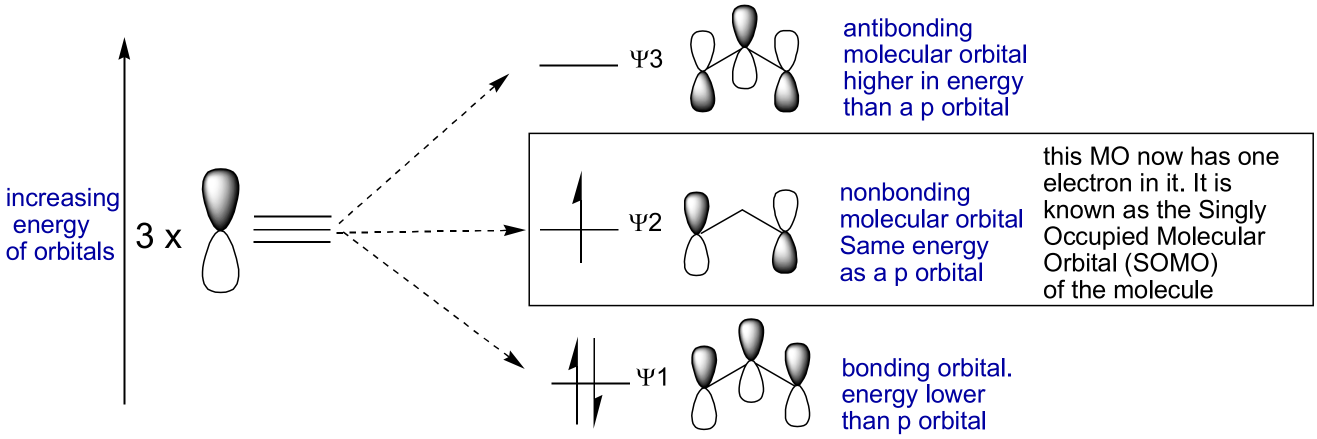
this is the
Lowest Unoccupied
Molecular Orbital
(LUMO)

bonding orbital.
energy lower
than p orbital

this is the
Highest Occupied
Molecular Orbital
(HOMO)

The allyl radical





increasing energy of orbitals

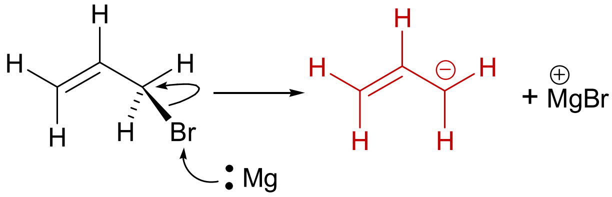
antibonding molecular orbital higher in energy than a p orbital

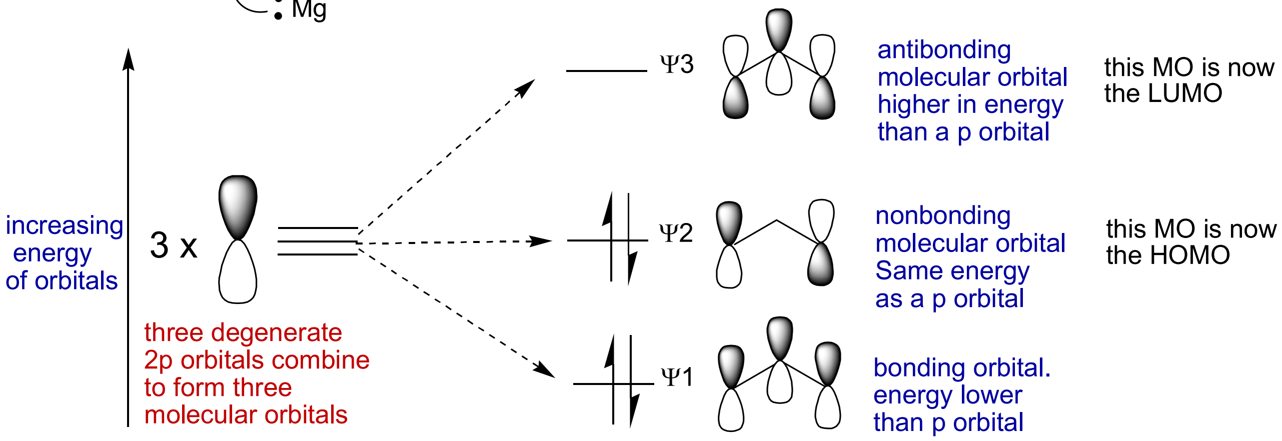
nonbonding molecular orbital Same energy as a p orbital

this MO now has one electron in it. It is known as the Singly Occupied Molecular Orbital (SOMO) of the molecule

bonding orbital. energy lower than p orbital

The allyl anion





increasing energy of orbitals

three degenerate 2p orbitals combine to form three molecular orbitals

antibonding molecular orbital higher in energy than a p orbital

this MO is now the LUMO

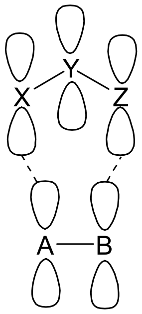
nonbonding molecular orbital Same energy as a p orbital

this MO is now the HOMO

bonding orbital. energy lower than p orbital

The Reactivity:

the currently most widely accepted view of the mechanisms of 1,3-dipolar cycloadditions is that they are **concerted processes** (that is , with no distinct reaction intermediates).



Transition state

The reactivity of 1,3-dipoles towards different dipolarophiles often varies considerably. Frontier orbital theory proposes that reaction through transition state is favoured if there is a favourable interaction between a filled π-orbital of one reactant and an empty π^*-orbital of the other. The orbital must be of the correct phase to interact, the interaction must be sterically feasible, and interaction will be stronger , the closer in energy the orbitals are. These interactions are therefore dominated by the highest occupied π – orbitals (HOMO) and the lowest unoccupied π^*–orbitals (LUMO) of the two reactants. The relative energies of these so-called frontier orbitals can vary as shown in Fig 2.3

Concerted mechanism : formation two bonds at same time without rotation

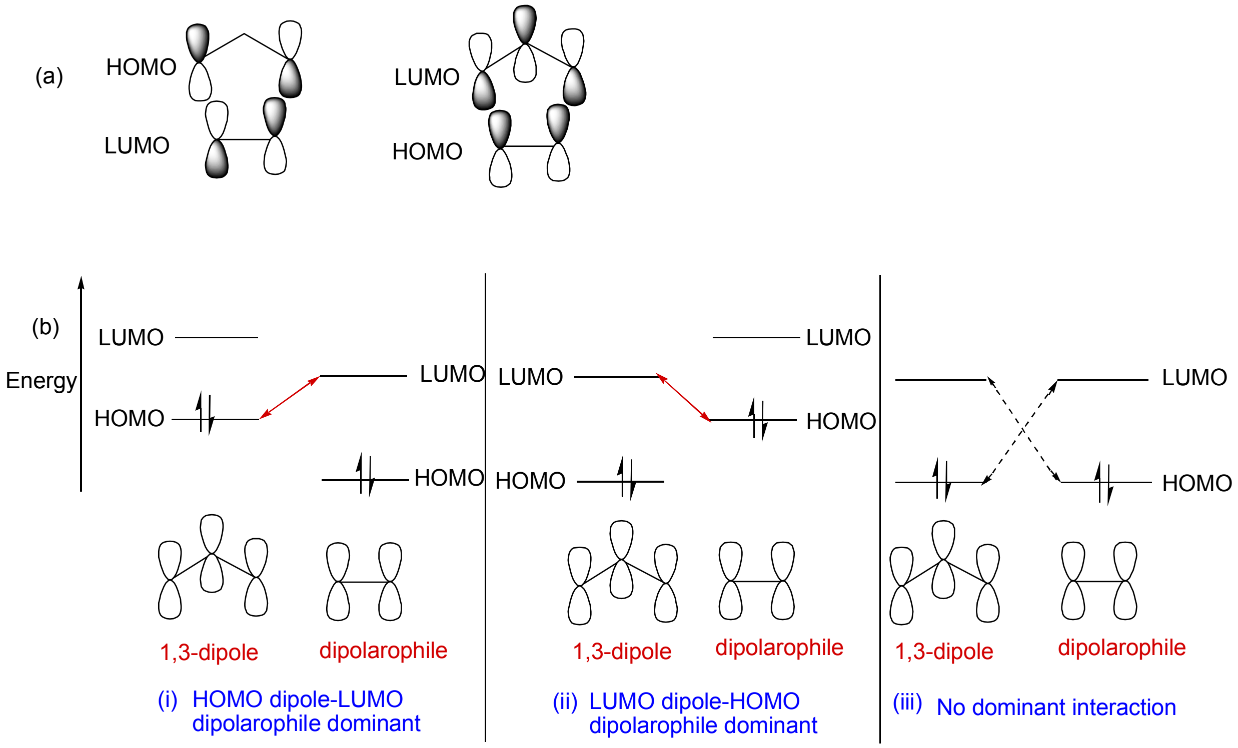


Fig 2.2 (a) Frontier orbital combination in 1,3-dipolar cycloaddition.
(b) Types of frontier orbital interaction.

Reactions are therefore favoured if one component is strongly "nucleophilic" and the other strongly "electrophilic". The orbital energies are determined both by the nature of the skeletal atoms in the two components and by their substituents. Estimated HOMO and LUMO energies for different types of carbon dipolarophiles **are given in Table 2.2**

The more electrophilic dipolarophiles have lower energy LUMO values, whereas the more nucleophilic species have higher energy HOMO values.

Thus for a given 1,3-dipole, the dominant interaction is mor likely to be of type (i) (fig.2.2) For dipolarophiles with conjugative electron-withdrawing groups,
But of type (ii) for enol ethers, enamines, and other electron-rich dipolarophiles.

It's found practice the reactivity of 1,3-dipoles towards these various types of dipolarophiles varies widely. For example,
Ozone reacts preferentially with electron rich dipolarophiles,
But the rates of reaction of diazoalkanes are greater for electron-deficient dipolarophiles.

Table 2.2 Estimate frontier orbital energies of carbon dipolarophiles

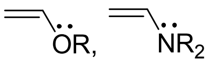
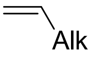
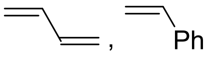
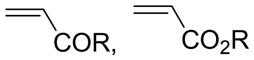
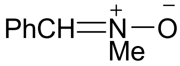
	Dipolarophile	HOMO (eV)	LUMO (eV)
(i)		-8	+3
(ii)		-9	+2
(iii)	≡—Alk	-10	+2
(iv)		-9	+1
(v)	$H_2C{=}CH_2$	-10.5	+1.5
(vi)		-11	0
(vii)	≡—CO_2R	-11	0

Table 2.3 Frontier orbital energies of some 1,3-dipoles

1,3-Dipole	HOMO (eV)	LUMO (eV)
(i) $PhC{\equiv}\overset{+}{N}{-}\overset{-}{N}Ph$	-7.5	-0.5
(ii)  $PhCH{=}\underset{Me}{\overset{+}{N}}{-}\overset{-}{O}$	-8	-0.4
(iii) $N{\equiv}\overset{+}{N}{-}\overset{-}{C}H_2$	-9	+1.8
(iv) $N{\equiv}\overset{+}{N}{-}\overset{-}{N}Ph$	-9.5	-0.2
(v) $PhC{\equiv}\overset{+}{N}{-}\overset{-}{O}$	-10	-1
(vi) $O{=}\overset{+}{O}{-}\overset{-}{O}$ ozone	-13.5	-2.2

Azides, nitrile oxides, and several other types of 1,3-dipole react faster both with electron-rich and with electron-deficient species than they do with simple olefins. These differences can be understood if the frontier orbital energies of the 1.3-dipoles are compared (Table 2.3).

It is clear that the HOMO of ozone is so low in energy that is unlikely to interact strongly with the LUMO of any dipolarophiles in table 2.2 .
The reaction of ozone will therefore be dominated by interaction of type (ii) in Fig 2.2 and the electron-rich dipolarophiles will react most rapidly (since the energy gap is smallest, and the interaction strongest).
In contrast, diazomethane has a high energy LUMO and so it's reaction with dipolarophiles are dominated by interactions of the HOMO with the LUMO of dipolarophile, of type (i) in Fig 2.2,
Dipolarophiles with low energy LUMO values thus react most rapidly.with a dipole such as azidobenzezne, interaction either of type (i) or of (ii) may be dominant, depending upon the nature of the dipolarophile .
Addition to ethylene is slow because neither interaction is strong [type (iii) in Fig 2.2].
The reactivity of the 1,3-dipoles are, of course modified by functional groups. For example , the HOMO and LUMO energies of diazoketones and diazoesters are lower than those of simple diazoalkanes, and their reactivity are modified accordingly.

the selectivity:

many 1,3-dipolar cycloadditions can, in principle, give mixtures of isomers. Fortunately, most such reactions show considerable selectivity in that they give predominantly or exclusively one of the possible products. The formation of possible regioisomers is shown in Fig. 2.4 (a) and possible stereoisomers are shown in (b) and (c).

The first of the two products shown in each of (b) and (c) have retained the stereochemistry of the original reagents.

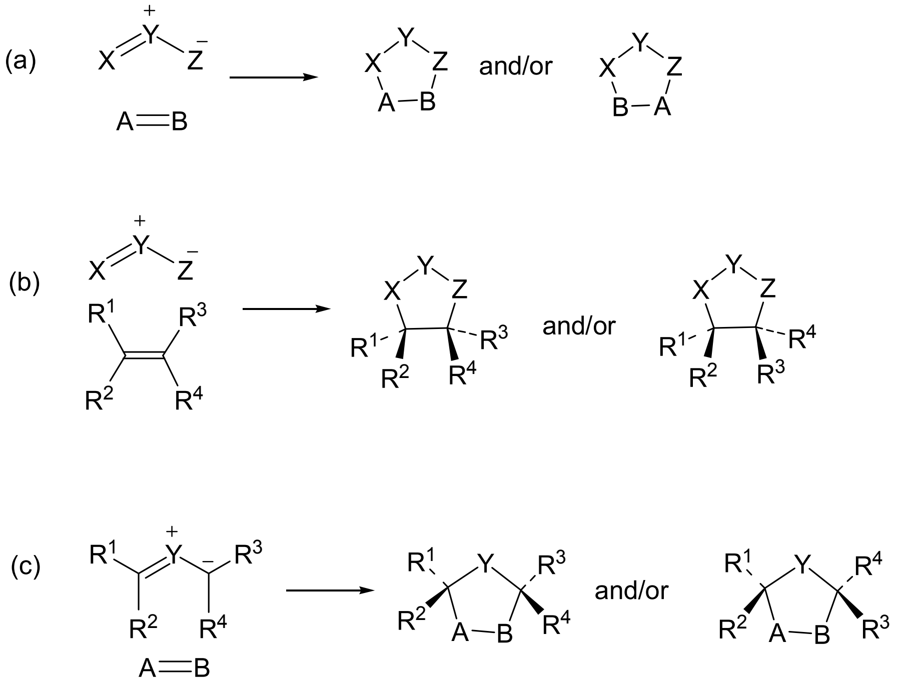


Fig. 2.4 Possibilities for isomer formation in 1,3-dipolar cycloaddition

Any reaction in which only one of a set of stereoisomers is formed exclusively or predominantly is called a *stereoselective* synthesis. The same term is used when a mixture of two or more stereoisomers is exclusively or predominantly formed at the expense of other stereoisomers.

In a *stereospecific* reaction, a given isomer leads to one product while another stereoisomer leads to the opposite product. All stereospecific reactions are necessarily stereoselective, but the converse is not true.

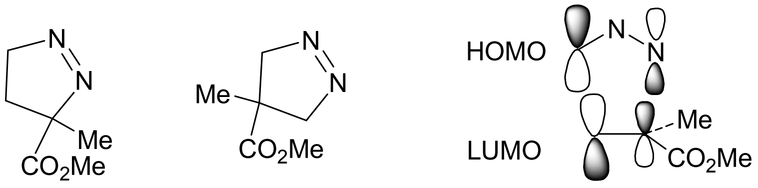
Viz , *stereoselective* reaction that yield predominantly one stereoisomer (or one pair of enantiomers) of several possible diastereomers.

stereospecific reaction, certain reactant give certain product.

When a reaction can potentially give rise to two or more structural isomers , but actually produces only one, the reaction is said to be *regioselective.*

(Mostly regioselective always a stereoselective)

The interaction of the dipole with the dipolarophile is usually dominated by one of two possible frontier orbital combinations. Consider, as an example, the addition of diazomethane to methyl methacrylate, which is dominated by the interaction of the HOMO of the dipole with the LUMO of the dipolarophile. Two regioisomers (i) and (ii) could be formed, but only the first is isolated. This can be explained by the fact that in the dominant HOMO-LUMO combination shown in Fig. 2.5 the interaction leading to product (i) is much stronger than that leading to it's isomer (ii), because the coefficients on the termini of the reaction partners are not equal.



(i) (ii)

Fig. 2.4 HOMO-LUMO interaction leading to the formation of regioisomer (i). the more favourable direction of combination is that in which the two terminal atoms with the large orbital coefficients interact

The initial products of 1,3-dipolar addition of diazo compounds to multiple bonds are not aromatic and they incorporate an azo group in the new ring system. Many of these products are thermally unstable and are not isolated. They react further either by loss of nitrogen or by **tautomerization**. *Example (ii) in table 2.4 and (iii) in Table 2.5* , show reactions in which the isolated products result from proton shifts in the initial 1,3-dipolar products.

Table 2.4 Examples of 1,3-dipolar addition to carbon-carbon double bonds.

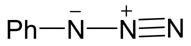
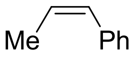
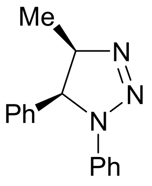
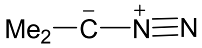
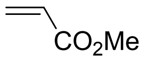
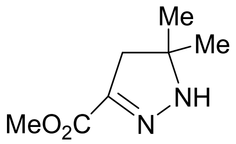
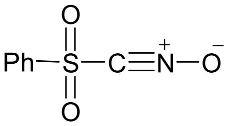
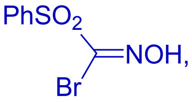
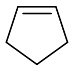
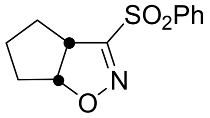
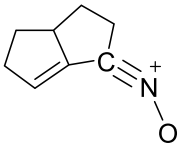
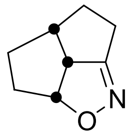
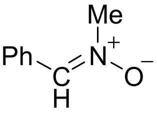
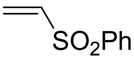
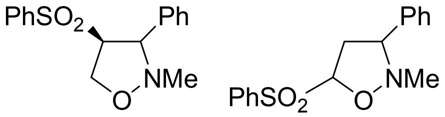
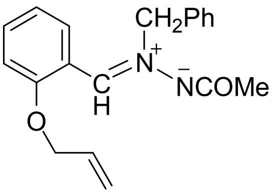
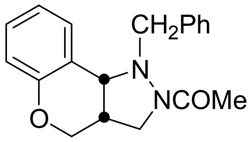
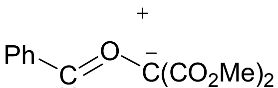
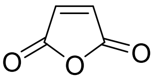
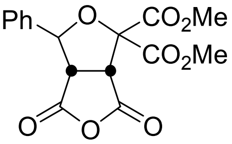
	dipole (conditions)	Dipolarophile	Products
(i)	 $Ph-\overset{-}{N}-\overset{+}{N}\equiv N$ (80°C, 7h)		
(ii)	 $Me_2-\overset{-}{C}-\overset{+}{N}\equiv N$ (0°C, 7h)		
(iii)	 ( Na_2CO_3, r.t)		
(iv)	 (RCH_2NO_2, PhNCO, 80°C)	internal	
(v)	 (80°C)		 [non regioselectivity, because give two possible isomer]
(vi)	 (ArCHO, $PhCH_2NHNHCOMe$,110°C)	internal	
(vii)	 (PhCHO, $N_2C(CO_2Me)_2$, Cu, 125°C)		

Table 2.5 Examples of 1,3-dipolar addition to carbon-carbon trible bonds.

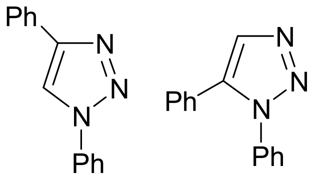
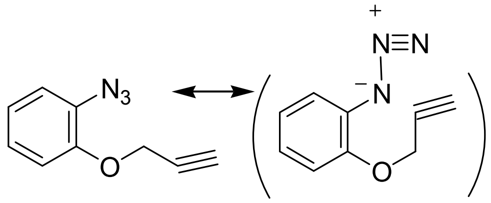
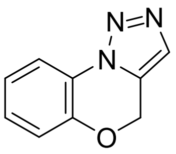
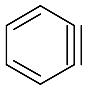
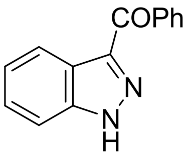
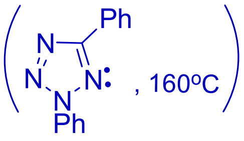
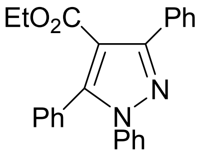
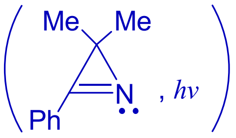
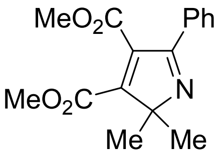
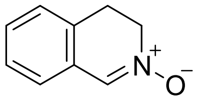
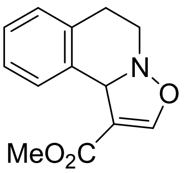
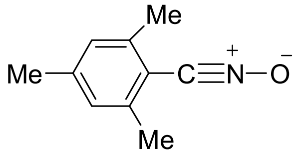
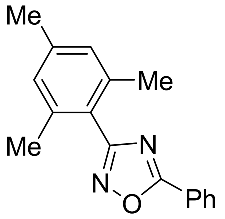
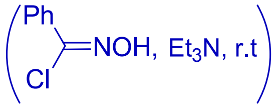
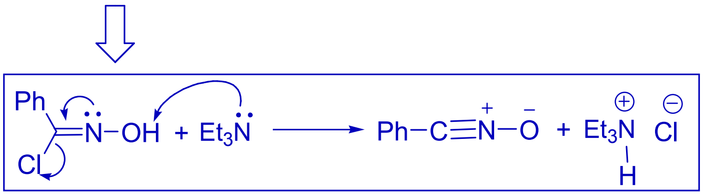
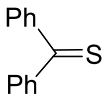
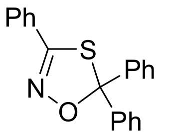
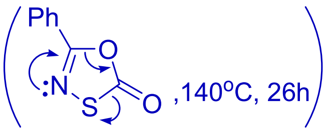
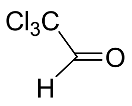
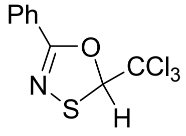
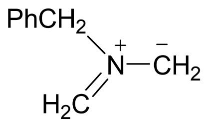
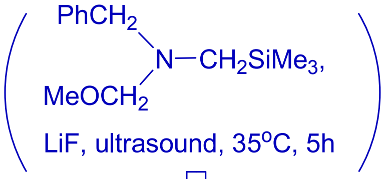
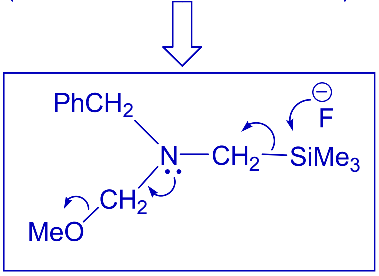
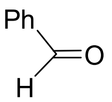
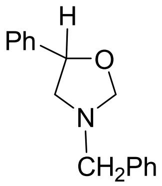
dipole (conditions)	Dipolarophile	Products
(i) $Ph-\overset{-}{N}-\overset{+}{N}\equiv N$ (110°C, 18h)	$PhC\equiv CH$	 [non regioselective, because give two possibe isomer]
(ii)  (140°C, 2h)	internal	
(iii) $PhCO\overset{-}{C}H-\overset{+}{N}\equiv N$ (40°C)		
(iv) $Ph-C\equiv\overset{+}{N}-\overset{-}{N}Ph$ 	$PhC\equiv CCO_2Et$	
(v) $Ph-C\equiv\overset{+}{N}-\overset{-}{C}Me_2$ 	$MeO_2CC\equiv CCO_2Me$	
(vi)  (r.t.)	$HC\equiv CCO_2Me$	

Table 2.6 Examples of 1,3-dipolar addition to multiple bonds containing hetero-atoms .

	dipole (conditions)	Dipolarophile	Products
(i)	 (50°C, 10 days)	$PhC\equiv N$	
(ii)	$Ph-C\equiv\overset{+}{N}-\overset{-}{O}$  		
(iii)	$Ph-C\equiv\overset{+}{N}-\overset{-}{S}$ 		
(iv)	  		

2.b- Hetero-Diels-Alder reactions

The cycloaddition of conjugated dienes to activated olefins and acetylenes commonly known as the *Diels-Alder reaction* ,used for the construction of six-membered carbocyclic compounds. It is preparative value lies in the high stereo- and regioselectivity with which the adduct are formed, and in the range of substituents which the reaction partners can bear. The selectivity of the reaction can be accounted for, as with 1,3-dipolar addition , by means of *frontier orbital theory*.

the majority of all-carbon Diels-Alder reactions involve the interaction of a nucleophilic diene with an electrophilic dienophile. In terms of frontier orbitals, the dominant interaction is that between the HOMO of the diene and the LUMO of dienophile.
The reactions show high selectivity, with products arising from *endo* transition states being kinetically favoured.

The Diels alder reaction is, in general, facilitated by the presence of electron-donating substituents, e.g. alkyl groups, in the diene, and by the presence of electrone-withdrawing groups in the alkene (the dienophile), e.g. the C=O groups.

Table 2.7 Some compounds that act as hetero-dienophiles in the Diels-Alder reaction.

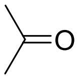
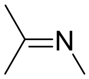
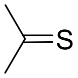
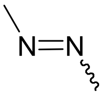
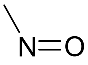
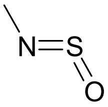
	Aldehydes; ketones
	Imines
$-C\equiv N$	Nitriles
	Thioaldehydes; thioketones; thioesters; thiophosgene
	Azocarbonyl compounds
	Nitroso compounds
	Sulphinylamines

Table 2.8 Some compounds that act as hetero-dienes in the Diels-Alder reaction.

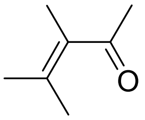
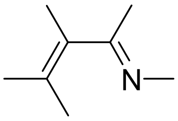
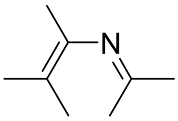
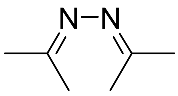
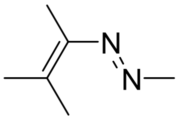
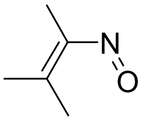
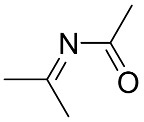
	α,β–unsaturated carbonyl compounds;quinon methides
	α,β–unsaturated imines and dimethylhydrazones
	*N*-Vinyl-and *N*-arylimines; oxazoles; 1,2,4-triazines
	1,2,4,5-Tetrazines
	Azoalkenes
	Nitrosoalkenes
	*N*-Acylimines

Table 2.9 Examples of Diels-Alder cycloadditon with hetero-dienophiles

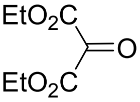
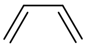
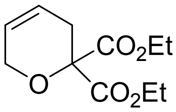
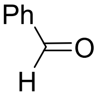
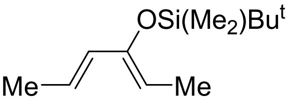
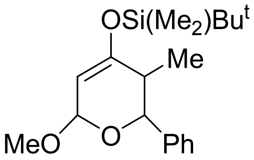
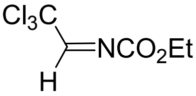
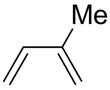
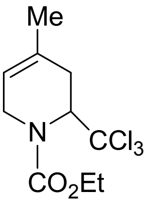
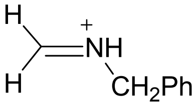
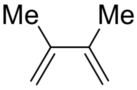
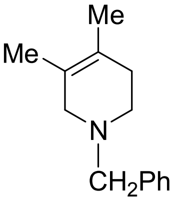
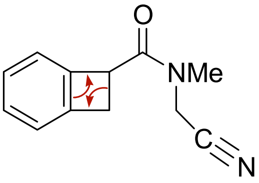
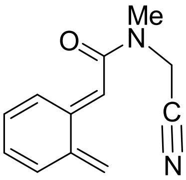
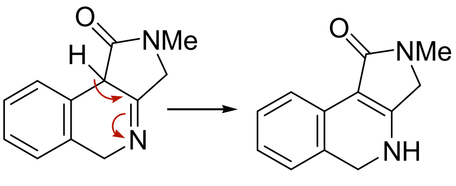
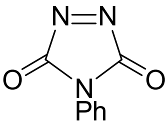
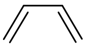
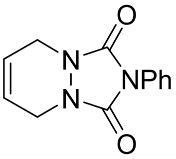
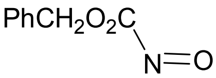
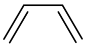
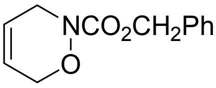
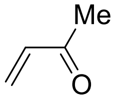
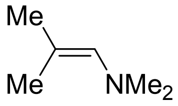
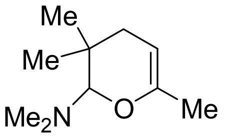
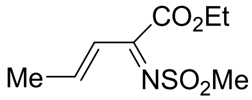
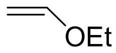
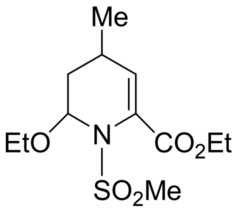
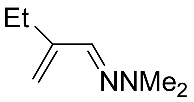
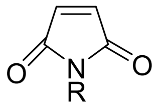
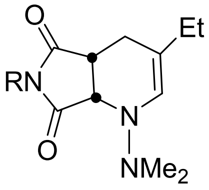
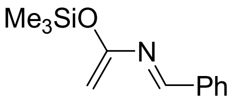
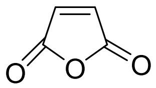
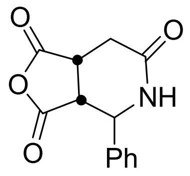
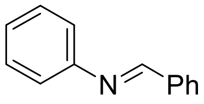
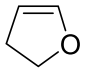
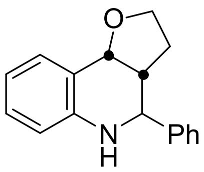
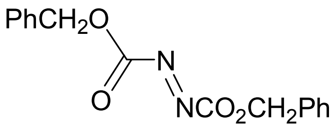
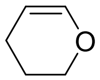
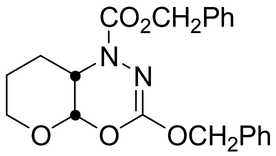
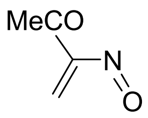
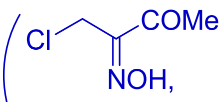
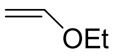
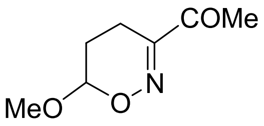
	Hetero-dienophile (conditions)	Diene	Product
(i)	 (130°C, 4h)		
(ii)	 (ZnCl$_2$, r.t.)		
(iii)	 (100°C, 80h)		
(iv)			
(v)	 (180°C, 16h)		
(vi)	 (-50°C, 30min)		
(vii)	 (PhCH$_2$O$_2$CNHOH, Et$_4$N$^+$IO$_4^-$, -10°C)		

Table 2.10 Examples of Diels-Alder cycloadditon with hetero-dienes.

	Hetero-diene (conditions)	Dienophile	Product
(i)	 (r.t., 12h)		
(ii)	 (25^{o}C, 17-26h)		
(iii)	 (55^{o}C, 3h)	 [R=C(Me)(CN)CHMe$_2$]	
(iv)	 (20^{o}C, MeOH)		
(v)	 (r.t., 4h, $BF_3.OEt_2$)		
(vi)	 (35^{o}C, 4 days, $h\nu$/350nm)		
(vii)	  Na_2CO_3, CH_2Cl_2, r.t., 24h		

2.c- [2+2] Cycloaddition

Several four-membered heterocycles can be prepared by [2+2] cycloaddition reaction but most of the reactions are not general. The range of substituents which can be incorporated is limited, and the inherent instability of many four-membered heterocycles means that side reactions often compete or predominate. The most important of these are cycloreversion and expansion to give six-membered rings (Fig. 2.5)

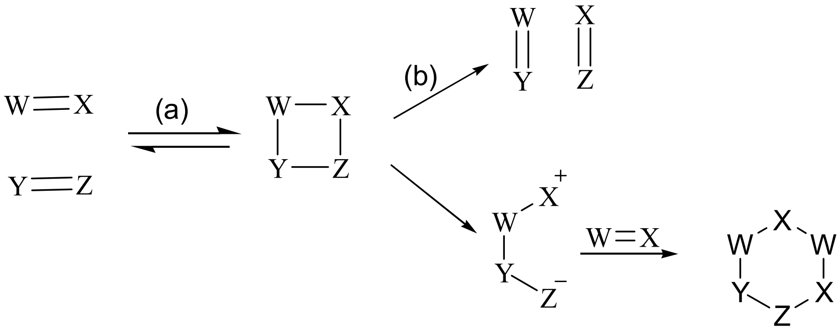


Fig. 2.5 Competing reactions in [2+2] additions. (a) Cycloaddition to starting materials; (b) cycloadition with dismutation.

Some of the heterocycles which can be prepared in good yields are listed in **Table 2.11,** Chlorosulphonyl isocyanate [example (i)] is a particulary good reagent for the formation of β-lactams because it adds to a wide range of nucleophilic olefins, and because the chlorosulphonyl group is readily removed from the cycloadducts by hydrolysis. Addition to olefins are generally highly stereoselective, but the reaction rates are much greater in polar than in nonpolar solvents. The most likely mechanism for addition is stepwise one, in which a dipole intermediate is formed but which rapidly collapses to give the azetidinone (Fig. 2.6)

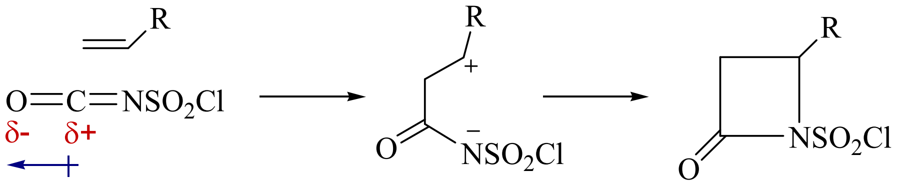
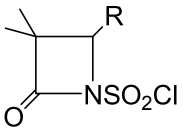
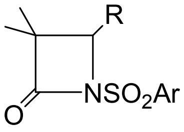
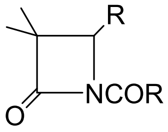
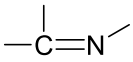
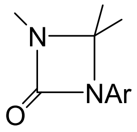
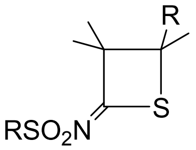
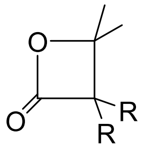
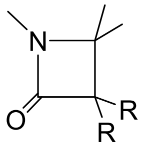
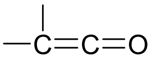
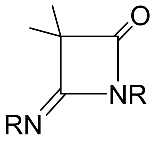
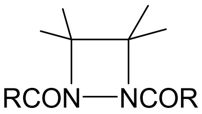


Fig. 2.6 Stepwise mechanism for chlorosulphonyl isocyanate addition.

Table 2.11 Reagents for the synthesis of four-membered heterocycles by [2+2] addition.

Reagent	Typical reaction partners	Products
(i) $ClSO_2N{=}\underset{\delta+}{C}{=}\underset{\delta-}{O}$	alkenes, dienes, enol ethers	
(ii) $ArSO_2N{=}C{=}O$	enamines, enol ethers	
(iii) $RCON{=}C{=}O$	enamines, enol ethers	
(iv) $ArN{=}C{=}O$	 imines	
(v) $RSO_2N{=}C{=}S$	enamines	
(vi) $R_2C{=}C{=}O$	activated carbonyl compounds	
$R_2C{=}C{=}O$	imines	
(vii) $RN{=}C{=}NR$	 Ketenes	
(viii) $RCON{=}NCOR$	cyclic alkenes, enol ethers	

It also possible to form four-membered rings by photochemical [2+2] addition. The most important such process in heterocyclic chemistry is the Paterno-Buchi reaction, which is the photoaddition of olefins to aldehydes or ketones. Oxetanes are formed by the addition of the excited-state carbonyl compound to olefins. An example is shown in Fig 2.7; the products in this case can be rationalized as being formed through diradical intermediates, with that from the mor stable diradical predominating.

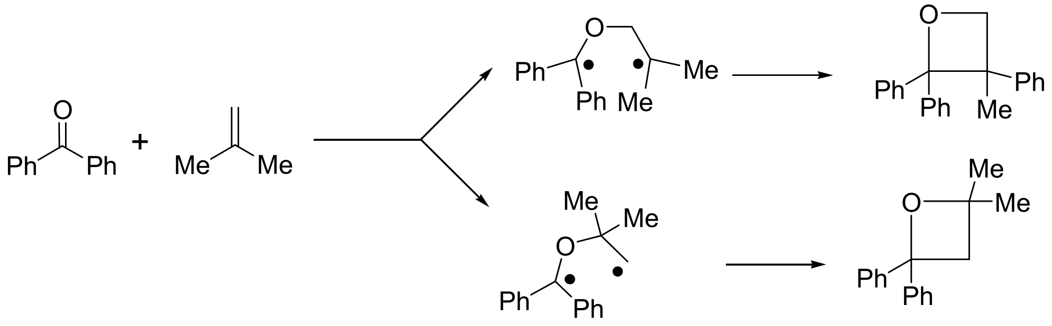
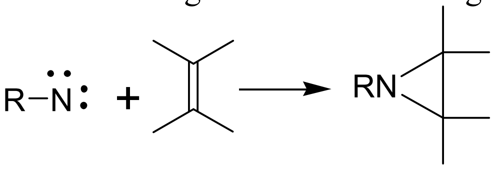


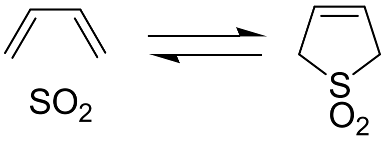
Fig. 2.7 The Paterno-Buchi reaction.

2.d- Cheletropic reactions

Reaction (d) of Figure 2.1 represent types of cycloaddition process in which both new σ-bonds are made to the same atom. These so-called cheletropic reactions have a limited utility as method of heterocyclic synthesis. Reaction of type [d-(i)] in figure 2.1 are represented by the cycloaddition of carbenes and nitrenes to double bonds. Many types of carbene add to olefins to give cyclopropanes but their addition to multiple bonds containing heteroatoms is not general reaction.

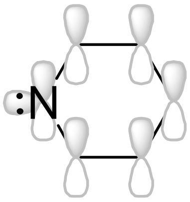


Cheletropic reaction of type [d-(ii)] in Figure 2.1 are exemplified by the addition of sulphur dioxide to butadiene to give 2,5-dihydrothiophene-1,1-dioxide. The reaction is reversed at high temperatures and compounds can used to generate butadiene.

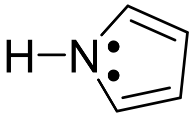


Heterocyclic synthesis

Pyridin



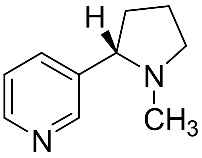
Pyridine



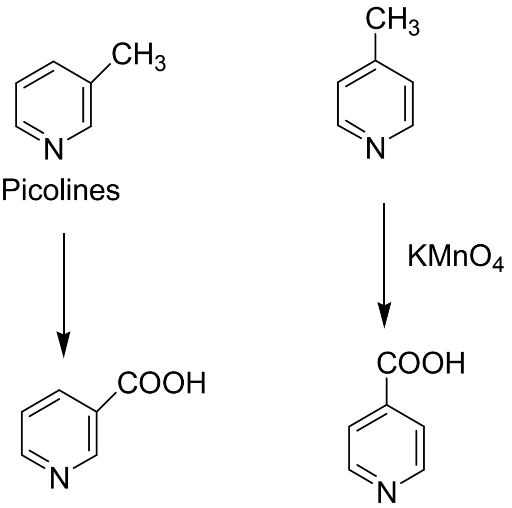
Pyrrole

-Pyridine is a water-miscible liquid,b.p.115^{O}C with an unpleasant odour
An Excellent polar solvent
A base (pka=5.23)

-Pyrrole is less basic than pyridine because the lone pair of electrons in pyrrole is part of the aromatic ring ,while that in pyridine is free .



Tobacco alkaloid (nicotine)
Alkaloide (alkali like)



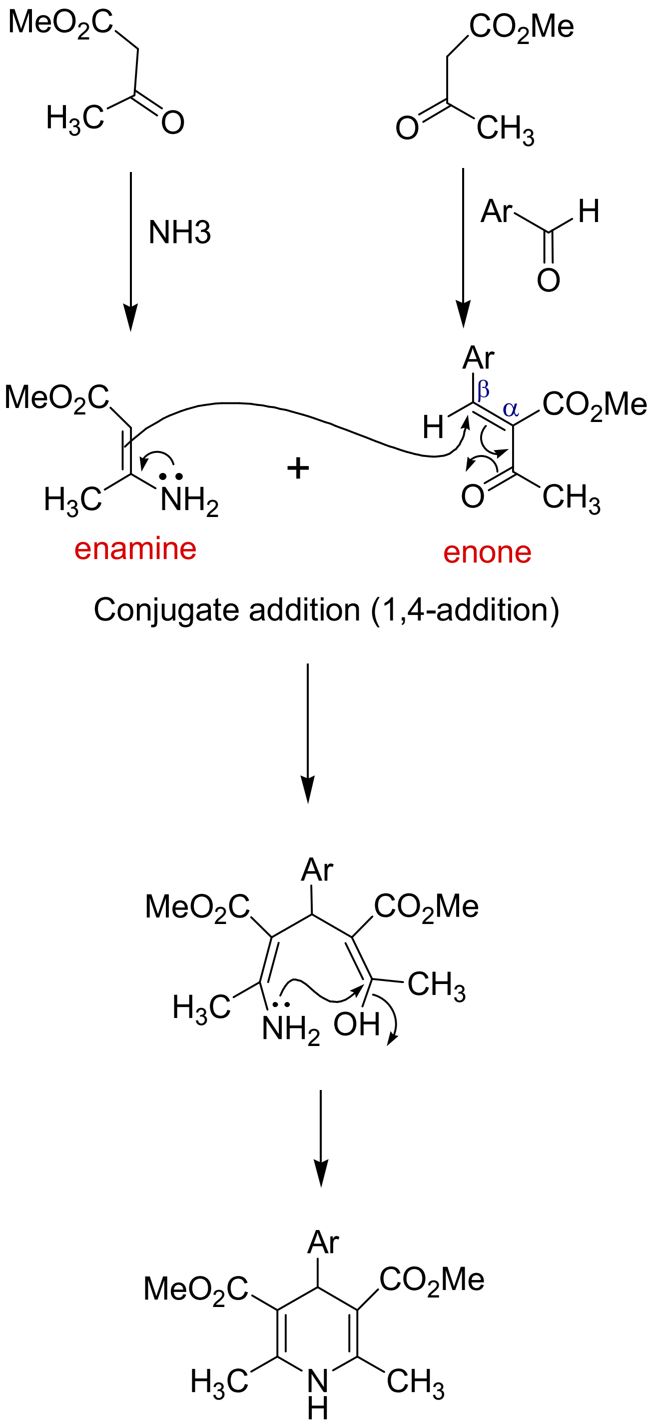
nicotinic acid

isonicotinic acid

-Pyridine ring synthesis:

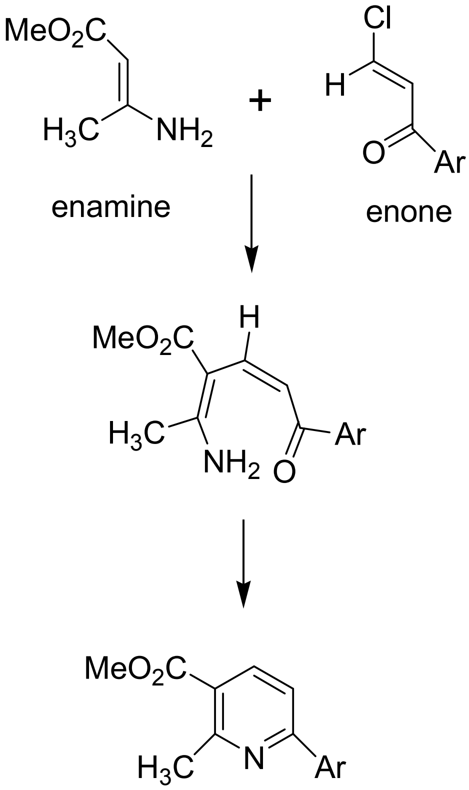
1) The Hantzsch synthesis

1,3-dicabonyl compound + ammonia +aldehyde

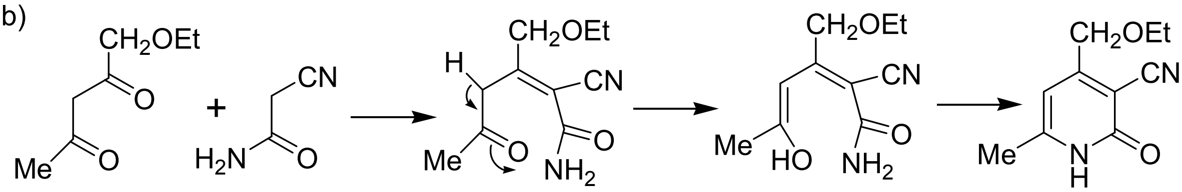


Unsymmetrical pyridine can be prepared from different enamines and enones

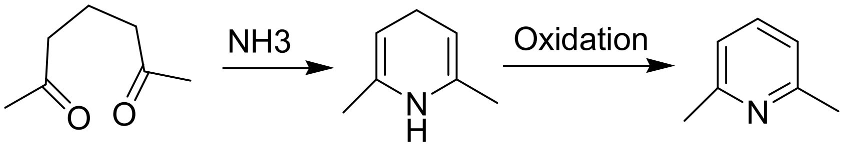
a)

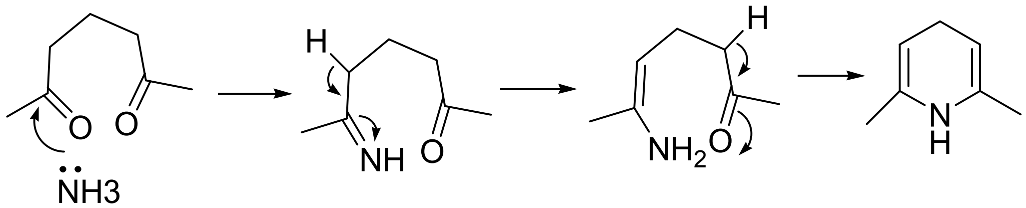


b)

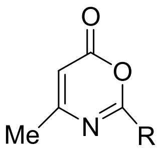
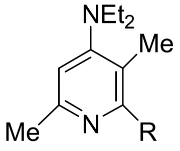
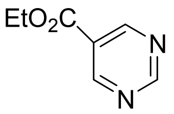
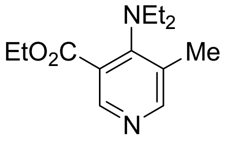
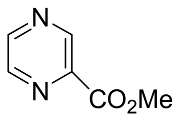
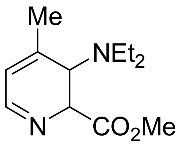
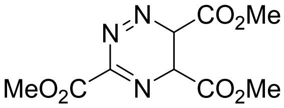
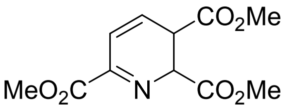


2) Reaction of ammonia + 1,5-diketone



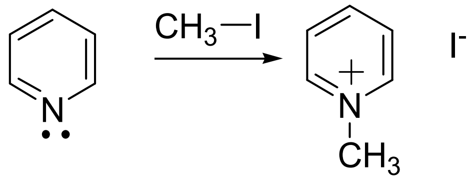


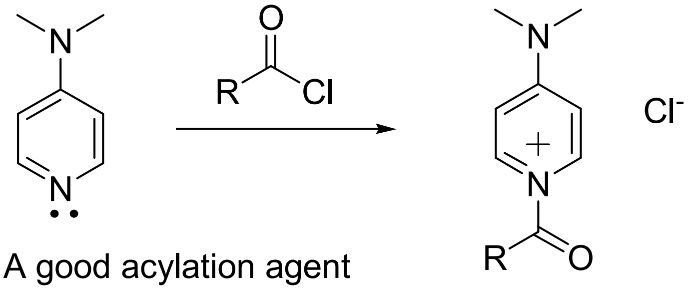
Examples of Pyridine synthesis by cycloaddition of alkenes and alkynes to heterocycic dienes

Diene	Dienophile	Conditions	Product
	$Et_2N-C\equiv C-Me$	Et_2O , 20C°	
	$Et_2N-C\equiv C-Me$	MeCN , 80C°	
	$Et_2N-C\equiv C-Me$	$CHCl_3$, 25C°	
	$H_2C=CHOAc$	dioxane , 100C°	

Chemistry of Pyridine

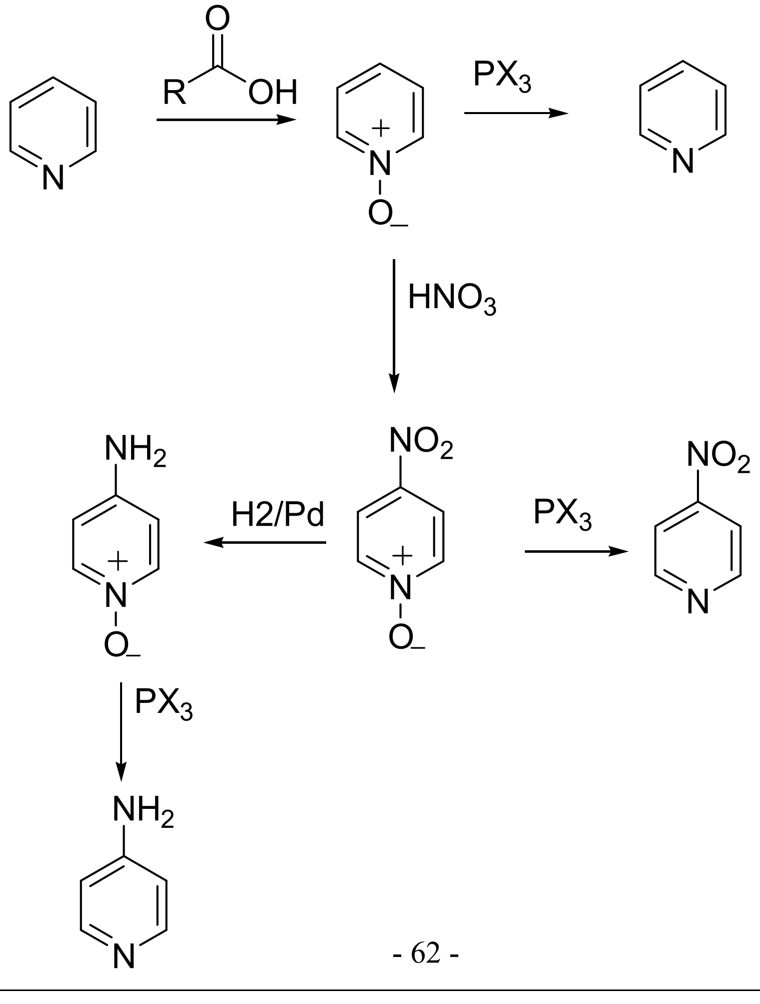
a) Reaction at nitrogen





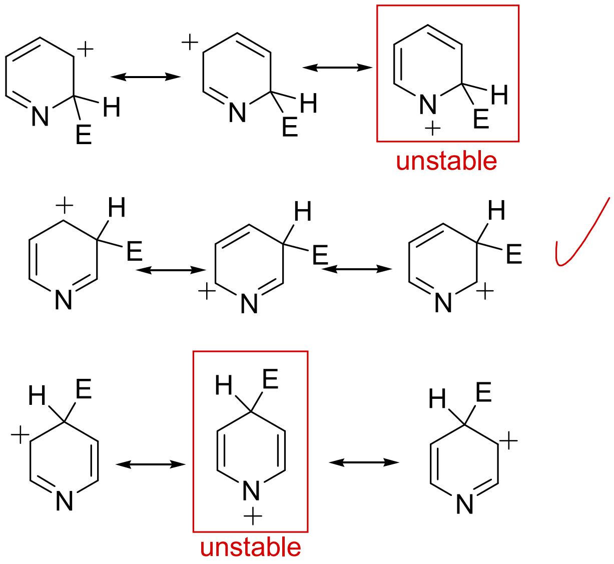
A good acylation agent

Use of N-Oxides



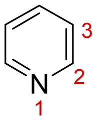
Electrophilic substitution

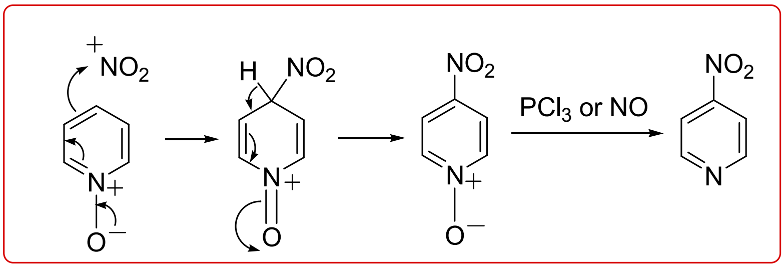
Pyridine is million times less reactive than benzene
Nitration (less than 5% ,Chlorination in moderate yield, bromination in a good yield)
3-position is usually attacked preferably



Internediates in the electrophilic substitustion of pyridine

the prefable electrophilic attack on pyridine on position 3

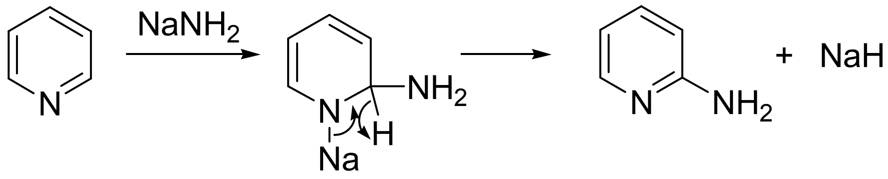




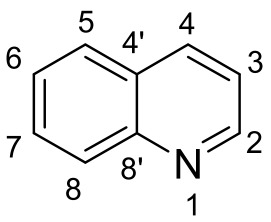
Nitration of pyridine N-oxide,preferable on position4

ChiChibabin Reaction:

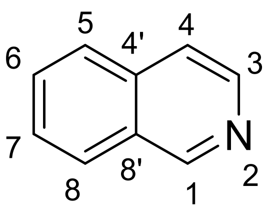
Amination of pyridine and related heterocycles at 2-position by sodamide



Quinoline and Isoquinoline



Quinoline

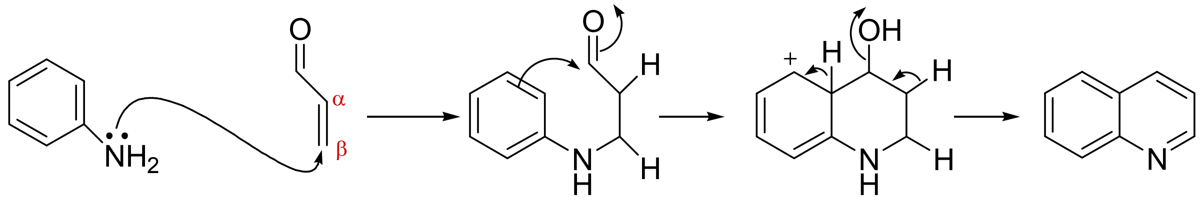


Isoquinoline

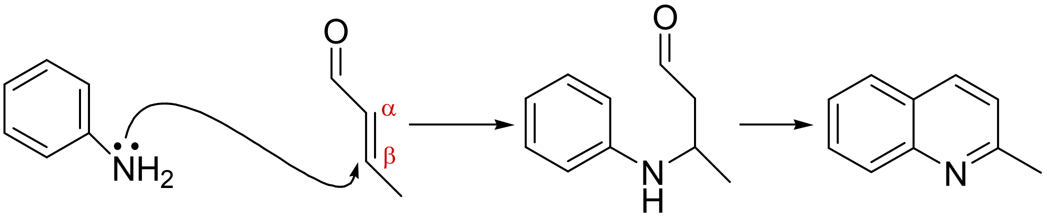
a)Quinoline synthesis

- Quinoline Skraup Synthesis

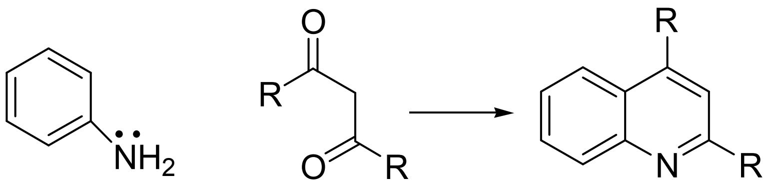
Aniline + [Glecerol + H_2SO_4] $\longrightarrow$ Quinoline



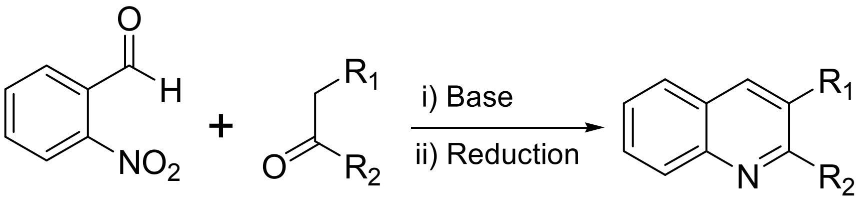
- Doebner-von Millar



- Combes Synthesis

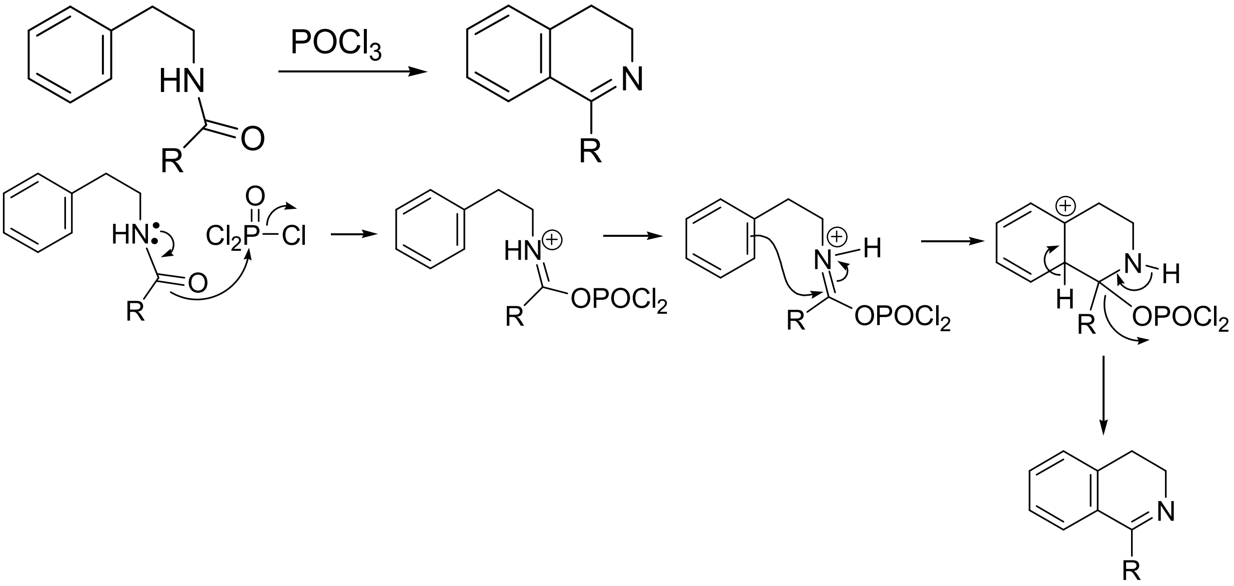


- Friedlaender Synthesis

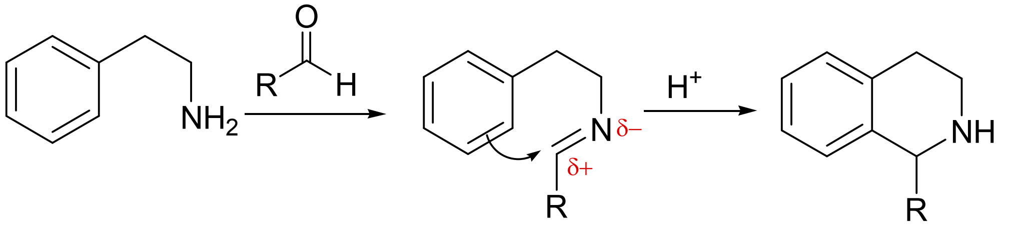


b) Isoquinoline Synthesis

-Bischler-Napierlaski

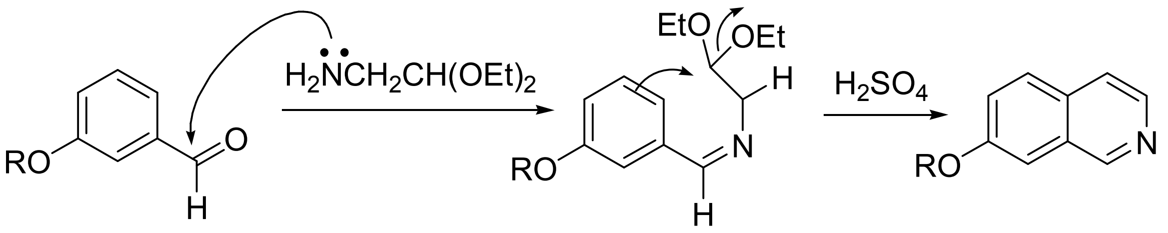


-Pictet -Spengler Synthesis



tetrahydroisoquinoline

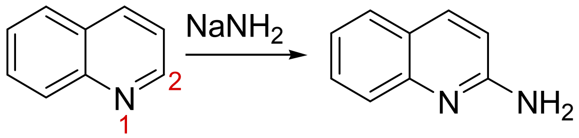
-Pomeranz-Fritsch Synthesis

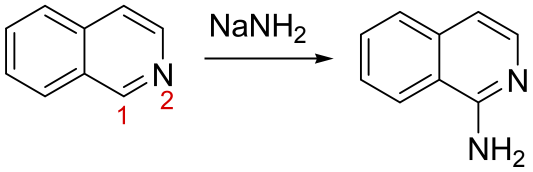


Chemistry of Quinoline and Isoquinoline

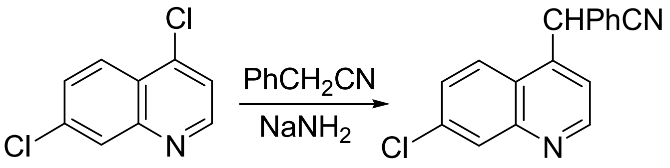
Nucleophilic Substitution

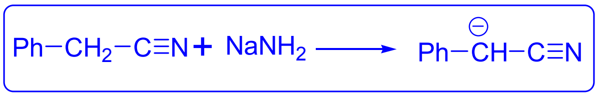
-(ChiChibabin reation)



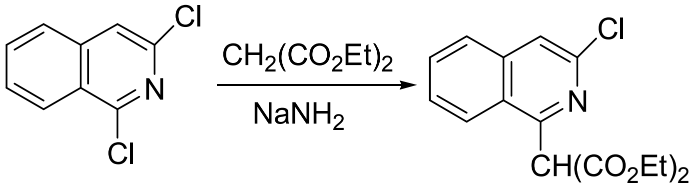


The displacement of chloride from the 2- and 4-positions of quinoline and from the 1-position of isoquinoline by nucleophilic such as alkoxides , thiophenoxide , and secondary amines take place readily by an addition-elimenation mechanism. Two examples of selective displacement of chloride by carbanions are shown in below, it is possible to displacement of chloride from the 3-position of isoquinoline under more vigorous conditions.



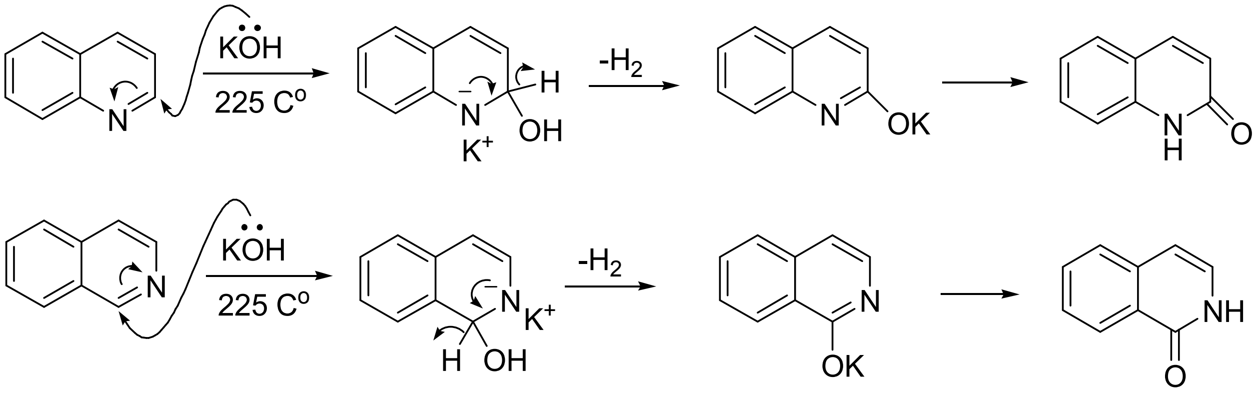


$$Ph{-}CH_2{-}C{\equiv}N + NaNH_2 \longrightarrow Ph{-}\overset{\ominus}{C}H{-}C{\equiv}N$$



selective displacement of chloride.

Quinoline and Isoquinoline can be hydroxylated by heating wit dry potassium hydroxide.



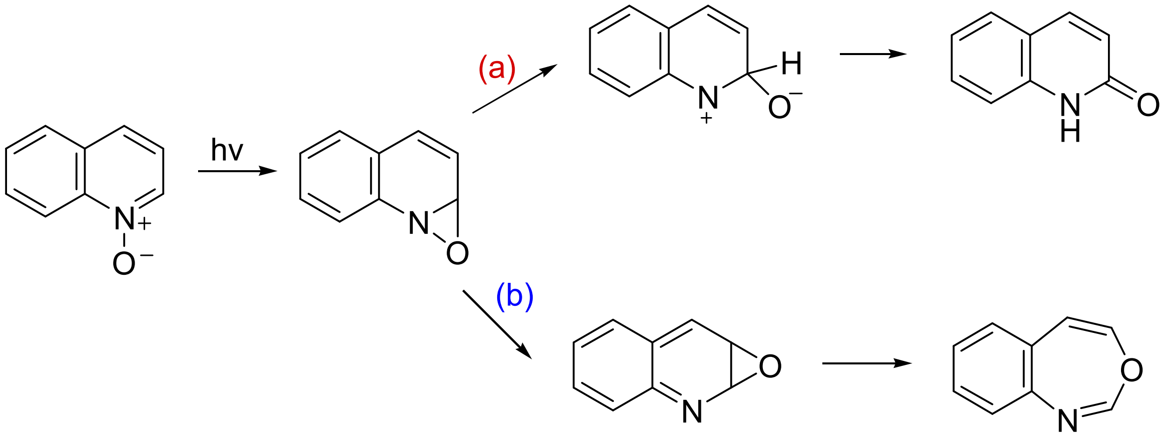
Electrophilic substitution

Occurs at 5- or 8- positions, or both.

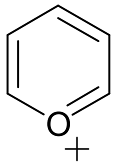
Electrophilic substitution of quinoline and isoquinoline

Electrophile	Reagents and Conditions	Major products
Quinoline		
D+	70% D_2SO_4 , 150°C	8-
NO_2^+	H_2SO_4 , HNO_3 , 0°C	5- and 8- (1:1)
Br^+	Br_2 , $AlCl_3$,80°C	5-
SO_3H^+	H_2SO_4 , SO_3 ,90°C	8-
Isoquinoline		
D+	90% D_2SO_4 , 180°C	5-
NO_2^+	H_2SO_4 , HNO_3 , 0°C	5- and 8- (9:1)
Br^+	Br_2 , $AlCl_3$,75°C	5-

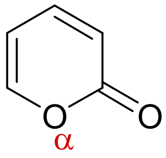
Quinoline N-Oxides can be nitrated at the 4-position or photoisomerize as follows:



Ring systems containing oxygen

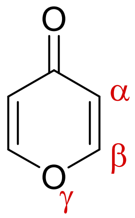


Pyrylium salta



2*H*-pyran-2-one

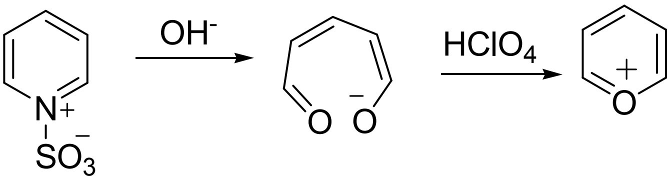
α-pyrone



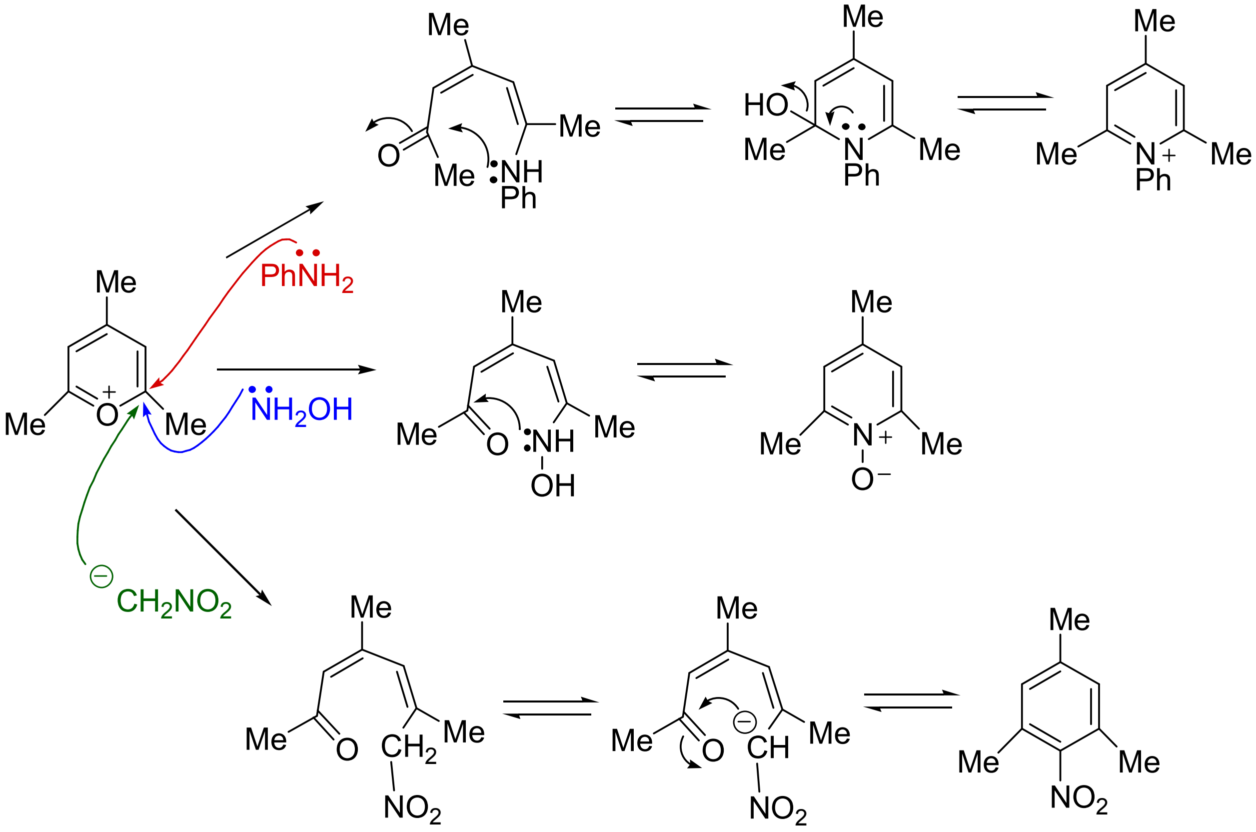
4*H*-pyran-4-one

γ-pyrone

Preparation of Pyrylium salts



Reactions of Pyrylium salts.

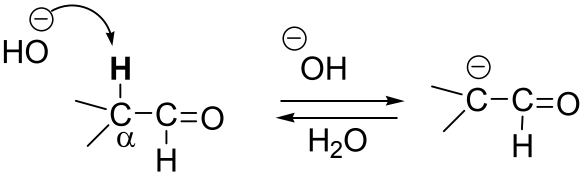


Reminder:

the $\overset{O}{\overset{||}{C}}$ group is attached to a carbon atom that has at least one H substituent

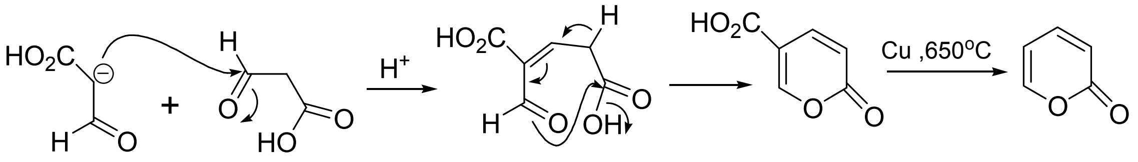
(e.g.-C**H**CHO,-C**H**COR, -C**H**CO_2Et),then electron-withdrawal by the $\overset{O}{\overset{||}{C}}$ group

results in such **H** atom being acidic,removed easyly as H^+, leaving carbon as Nu^-

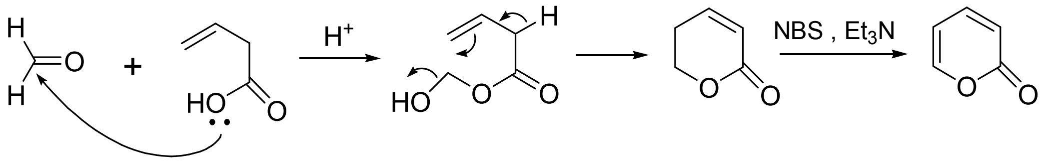


Synthesis of α-Pyrones .

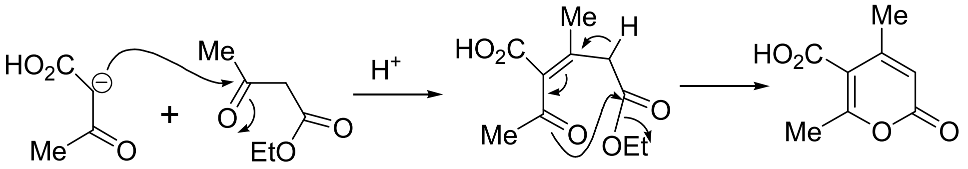
(a) $HO_2CCH_2CHOHCO_2H \xrightarrow{H_2SO_4\ ,\ SO_3} HO_2CCH_2CHO$



(b)



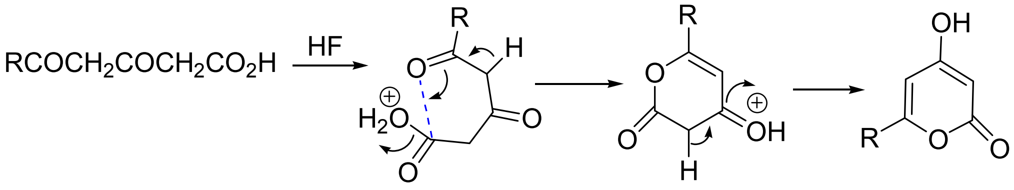
(c)



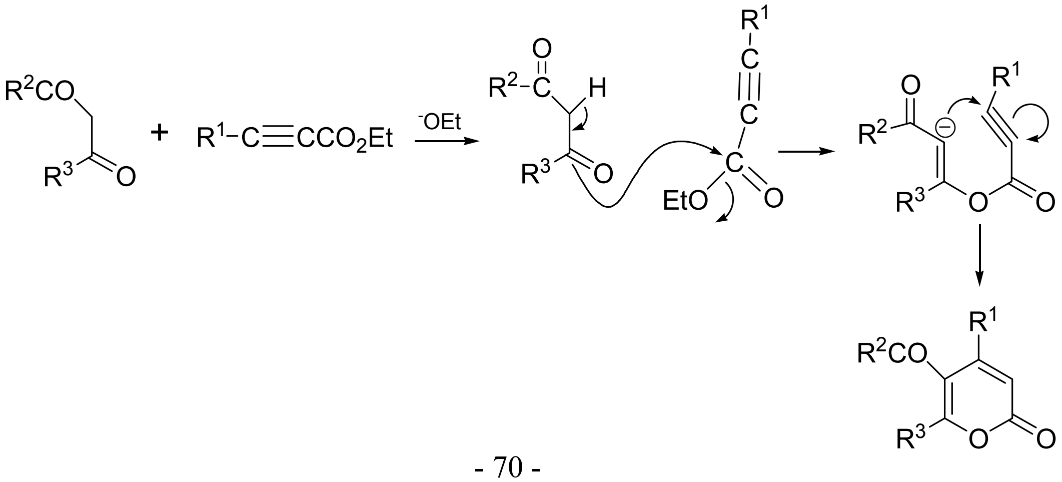
(d)

$RCOCH_2COMe \xrightarrow{2\overset{-}{N}H_2} RCO\overset{-}{C}HCO\overset{-}{C}H_2$

$RCO\overset{-}{C}HCO\overset{-}{C}H_2 \xrightarrow{CO_2} RCOCH_2COCH_2CO_2H$

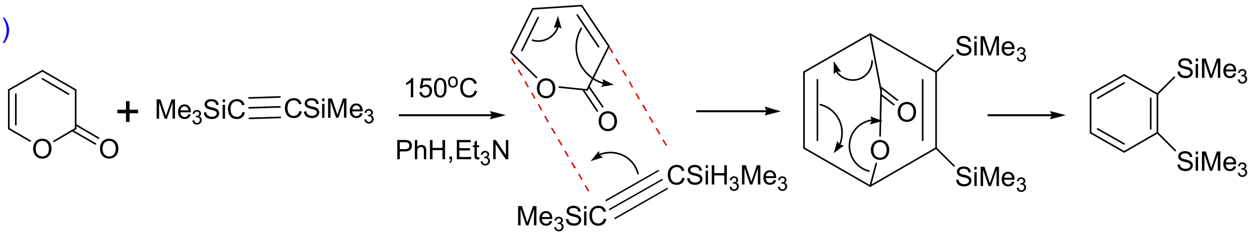


(e)

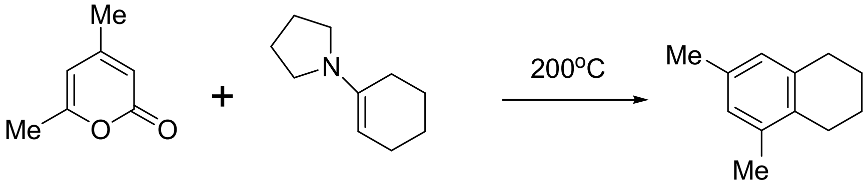


Diels-Alder reactions of α-Pyrones.

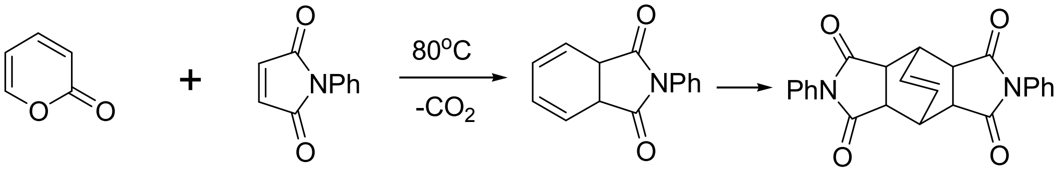
(a)



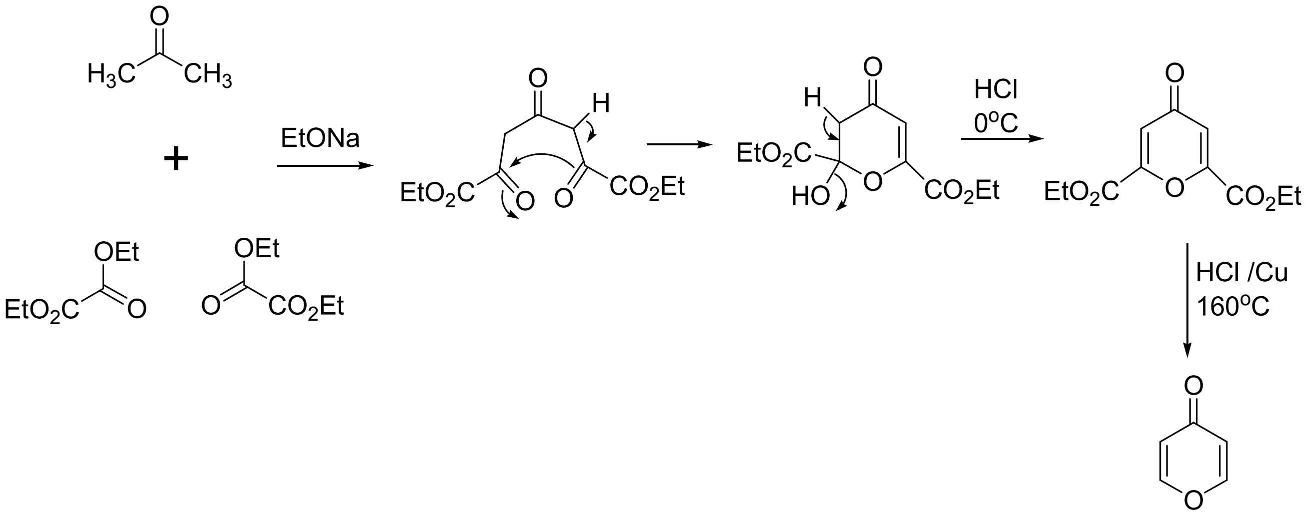
(b)



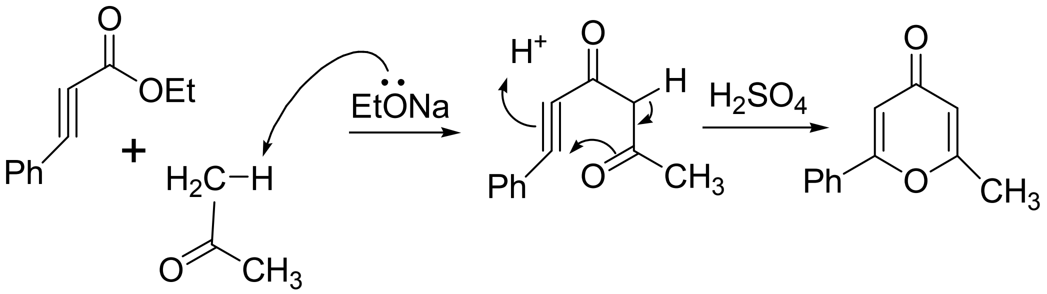
(c)



γ-Pyrone



Cliasen Condensation of Ethylpropiolate with acetone:



References:-

[1] T.L Gilchrist;Ch4&Ch5.*Heterocyclic Chemistry*,2nd edition;Longman:Malaysia,1993;pp59-179
[2] Jie-Jack Li; E. J. Corey; *Name Reactions in Heterocyclic Chemistry:* WILEY;2005