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Ministry of Higher Education and Scientific Research
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Faculty of Sciences

Department of Chemistry

Field: Material Sciences
Sector: Organic Chemistry

Course Handout

Heterocyclic Systems: From Nomenclature to Various Organic Synthesis Methods

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This handout is intended for students enrolled in Master M2 Specialty of organic chemistry

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Forword

This course has been specifically designed for second-year Master's students in organic chemistry, covering the official curriculum of the subject titled "Heterocyclic Chemistry." The knowledge gained in this course can also serve as a solid foundation for better understanding for students in other disciplines such as chemistry, biology, pharmacy, medicine, etc.

The content has been simplified to facilitate students' understanding and enable them to master the fundamental principles of heterocyclic compound nomenclature as well as various synthesis methods. This document is divided into three main parts. The first part addresses the rules of nomenclature for heterocyclic compounds, whether monocyclic, polycyclic, or spirocyclic heterocycles. The second part focuses on the different synthesis methods of heterocycles, including substitution reactions, cyclizations involving double or triple bonds, reactions involving nitriles and isonitriles, carbene and nitrene reactions, as well as electrocyclic and cycloaddition reactions. This part is illustrated through several examples to enhance understanding of the different reactions. Finally, the last part explores the applications of heterocycles in medicinal chemistry and everyday life.

Additionally, a list of references is provided at the end of the course for readers wishing to further explore the various aspects of heterocyclic chemistry.

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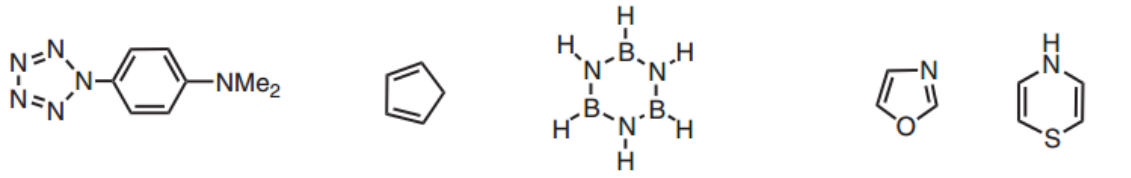
Introduction

The classification of chemical systems is based on the different types and numbers of atoms and bonds that constitute them. Generally, they can be found either in aliphatic structures if the arrangement of atoms is linear (acyclic) or in cyclic structures where the atoms form a ring. Cyclic systems whose ring is composed of atoms of a single chemical element are called isocyclic compounds (see example 1). An isocyclic system is referred to as a carbocyclic system when the chemical element constituting the ring is carbon (see example 2). Cyclic systems with at least two different atoms in the ring are called heterocyclic systems. Heterocyclic systems can be divided into two types: inorganic heterocyclic systems, if the cycle does not contain any carbon atoms (see example 3), and organic heterocyclic systems if the cycle contains at least one carbon atom (see examples 4 and 5). In this case, the atoms in the cycle that are not carbon are called heteroatoms.



1 (4-dimethylaminophenyl)-pentazole

2 cyclopenta-1,3-diene

3 borazine

4 oxazole

5 4*H*-1,4-thiazine

The smallest heterocycle consists of three members. The most important heterocycles contain five and six members. In the literature, there is no size limit for a heterocycle, and there are heterocycles with larger rings of seven, eight, nine, and more members.

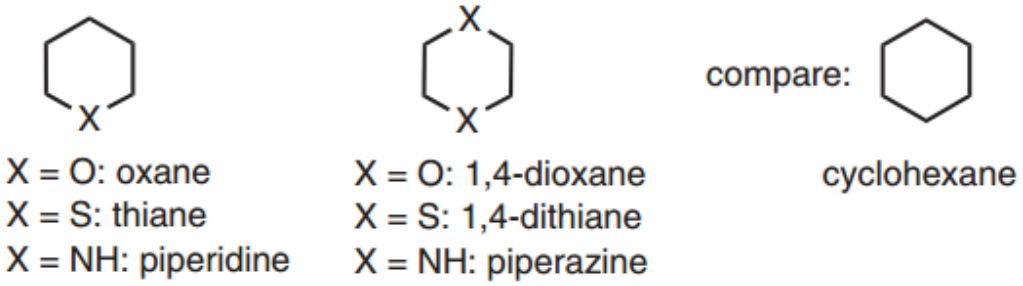
In principle, all elements, except alkali metals, can act as ring atoms. For the organic heterocycles covered in this course, nitrogen (N) is the most common heteroatom, followed by oxygen (O) and sulfur (S). Heterocycles with atoms like Se, Te, P, As, Sb, Bi, Si, Ge, Sn, Pb, or B are less common. To determine the stability and reactivity of

heterocyclic systems, it is useful to compare them to their carbocyclic analogs containing carbon (carbocyclics). In principle, it is possible to derive each heterocycle from a carbocyclic compound by replacing appropriate CH2 or CH groups with heteroatoms. If we limit ourselves to monocyclic systems, we can distinguish four types of heterocycles as follows:

Saturated Heterocycles (Heterocycloalkanes)

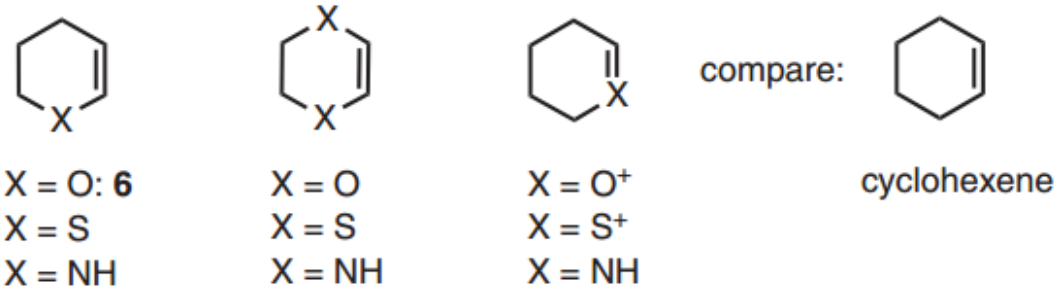
For this type of heterocycles, there are no multiple bonds between the atoms in the ring. All the atoms are saturated. These saturated cyclic systems react similarly to their aliphatic counterparts. For example:

- Oxane (tetrahydropyran) and dioxane behave like dialkyl ethers.
- Thiane and 1,4-dithiane behave like dialkyl sulfides.
- Piperidine and piperazine behave like secondary aliphatic amines.



Partially Unsaturated Systems (Heterocycloalkenes)

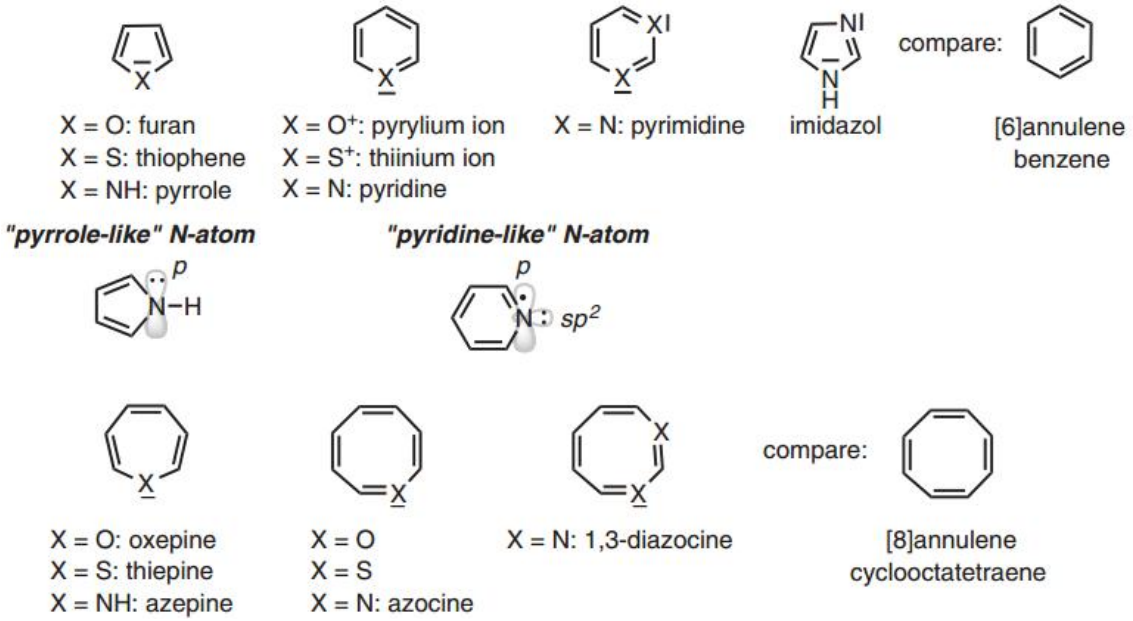
If the double or triple bonds are between two carbon atoms ($_6$C) in the ring, as in the case of 3,4-dihydro-2H-pyran (6), then these systems essentially react like alkenes or alkynes, enol ethers, enamines, etc. The heteroatom can also be part of a double bond. In the case of X=O+, the compounds behave like oxenium salts; for X=S+, they behave like sulfenium salts, and for X=N, they behave like imines (azomethines).



Systems with the Maximum Number of Non-Cumulated Double Bonds (Heteroannulenes)

Formally, two types of heterocycles can be derived for this type of systems:

1. Systems of the same ring size, where CH is replaced by X.
2. Systems of one ring size smaller, where HC=CH is replaced by X.



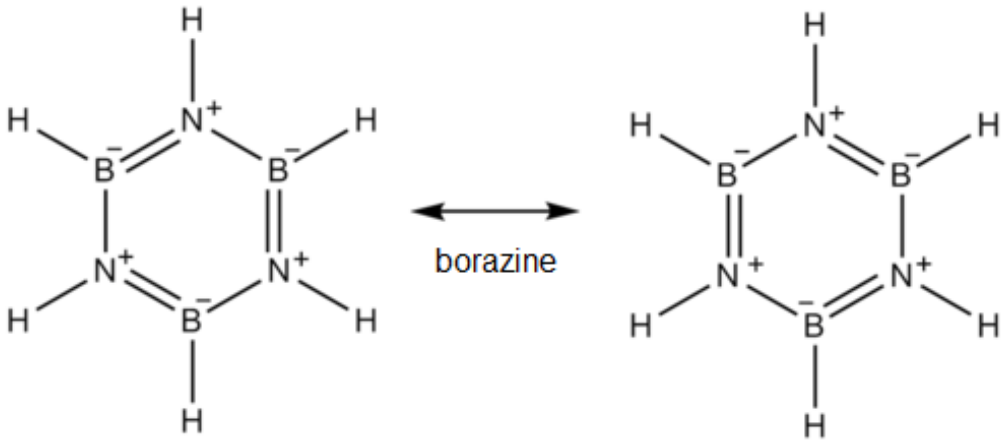
In both cases, the resulting heterocycles are iso-electronic with the corresponding annulenes, meaning that the number of π electrons in the ring is the same. Indeed, in pyrylium and thiinium salts, as well as in pyridine, pyrimidine, azocine, and 1,3-diazocine, each heteroatom contributes one electron to the conjugated system, and its non-bonding electron pair does not contribute to the π system. However, with furan, thiophene, pyrrole, oxepine, thiepine, and azepine, the non-bonding electron pair of the heteroatom is incorporated into the conjugated

system (π electron delocalization).

When the heteroatom is X=N (Nitrogen), two types of nitrogen can be distinguished: Pyridine-type nitrogen or Pyrrole-type nitrogen (see example). In imidazole, both types can be observed simultaneously.

Heteroaromatic Systems

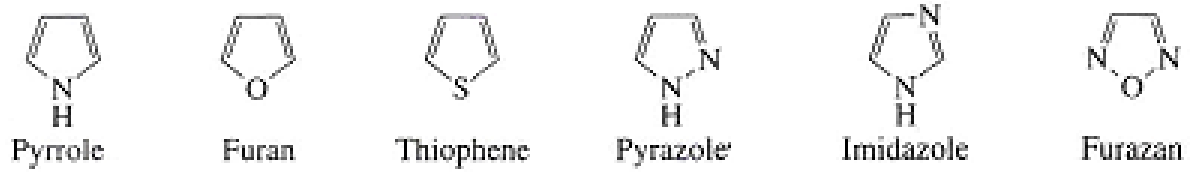
This concerns heteroannulenes that adhere to Hückel's rule, meaning they possess a number of π electrons equal to (4n + 2) delocalized on the ring. The most important systems among these compounds are derived from benzene ([6]annulene). They are known as heteroarenes, for example, furan, thiophene, pyrrole, pyridine, and pyrylium and thiinium ions. In terms of stability and reactivity, they can be compared to their corresponding benzene-like compounds. On the other hand, anti-aromatic systems, meaning systems with a number of π electrons equal to 4n delocalized on the ring, such as oxepine, azepine, thiepine, azocine, and 1,3-diazocine, as well as their corresponding annulenes, are much less stable and highly reactive. The classification of heterocycles into heterocycloalkanes, heterocycloalkenes, heteroannulenes, and heteroaromatics allows for an estimation of their stability and reactivity. In some cases, this can also be applied to inorganic heterocycles. For instance, borazine (3), a colorless liquid with a boiling point of 55°C, is classified as a heteroaromatic system.

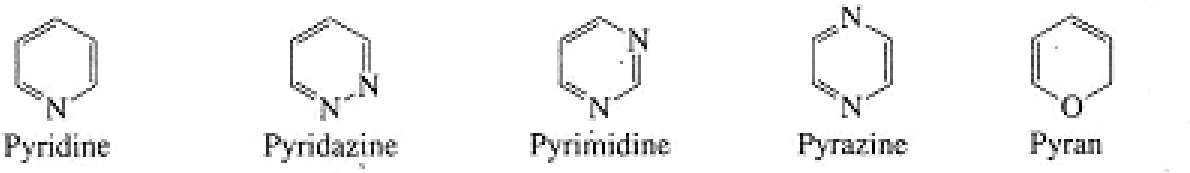


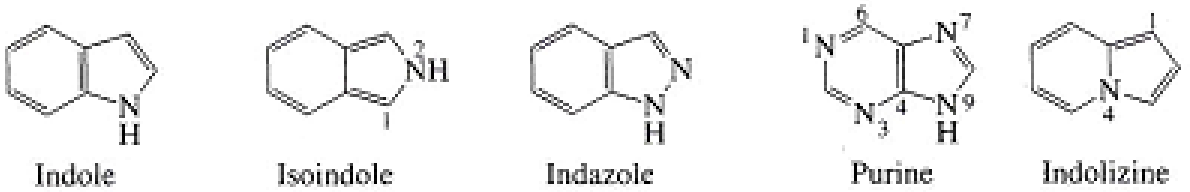
Systematic nomenclature of heterocyclic compounds

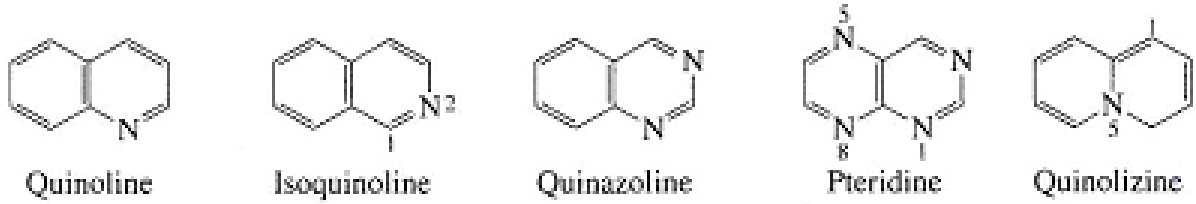
The systematic derivation of the name of a heterocyclic compound is based on its structure. Nomenclature rules have been established by the IUPAC Commission. These rules generally allow for two nomenclatures. The Hantzsch-Widman nomenclature is recommended for heterocycles with 3 to 10 members. For larger heterocycles, a replacement nomenclature must be used. Many heterocyclic systems have a trivial name. This typically arises from the compound's occurrence, its first preparation, or its specific properties. It should be noted that in some cases, such as pyridine, the trivial name must be used as the systematic name.

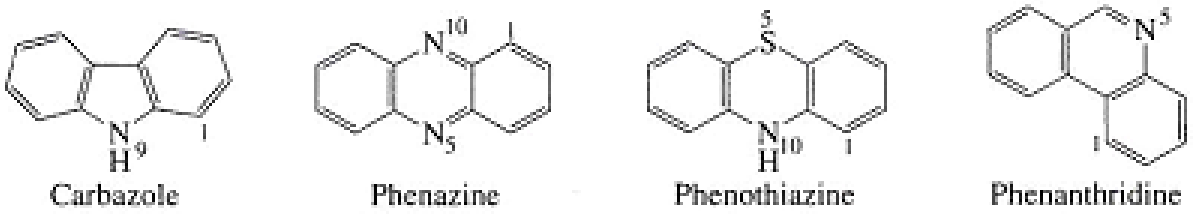
Heterocycles with recognized trivial names

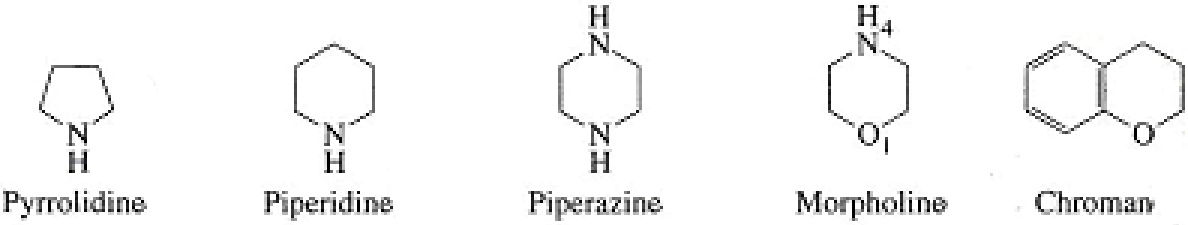

Pyrrole
Furan
Thiophene
Pyrazole
Imidazole
Furazan


Pyridine
Pyridazine
Pyrimidine
Pyrazine
Pyran


Indole
Isoindole
Indazole
Purine
Indolizine

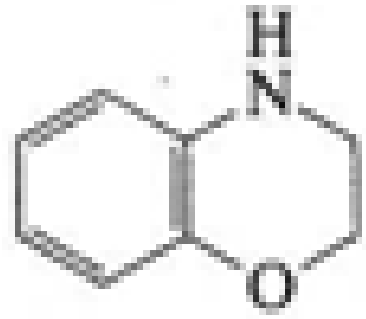

Quinoline
Isoquinoline
Quinazoline
Pteridine
Quinolizine


Carbazole
Phenazine
Phenothiazine
Phenanthridine


Pyrrolidine
Piperidine
Piperazine
Morpholine
Chroman

Note:

Names of the saturated heterocyclic compound showed above are not used in fusion names, for example, compound X is 3,4-dihydro-2H-1,4-benzoxazine, not benzomorpholine.



X

Hantzsch-Widman Nomenclature

Nomenclature of Monocycles

The systematic name for monocycles is formed by combining a prefix and a suffix. The prefix includes information about the type of heteroatoms, the number of heteroatoms, and their positions, while the suffix provides information about the size of the heterocycle and its degree of unsaturation

The prefix generally describes the type, number, and position of heteroatoms. The sequence in Table 2.1 indicates the decreasing order of priority for prefixes. If two vowels are adjacent, elision is performed (omitting the vowel at the end of the prefix in this case) before the vowel starting the next word. For example, in the case of a heterocycle containing both N and O atoms, you would write "Oxaza" instead of "Oxaaza."

The suffix describes both the number of ring members (cycle size) and the degree of unsaturation of the heterocycle (See Table 2.2).

Table 2.1. Prefixes to indicate heteroatoms

Element	Prefix	Element	Prefix
O	oxa	**Bi**	bisma
S	thia	**Si**	sila
Se	selena	**Ge**	germa
Te	tellura	**Sn**	stanna
N	aza	**Pb**	plumba
P	phospha	**B**	bora
As	arsa	**Hg**	mercura
Sb	stiba		

Table 2.2. Stems to indicate the ring size of heterocycles.

Ring size	Unsaturated	Saturated
3	irene[a]	irane[b]
4	ete	etane[b]
5	ole	olane[b]
6A[c]	ine	ane
6B[c]	ine	inane
6C[c]	inine	inane
7	epine	epane
8	ocine	ocane
9	onine	onane
10	ecine	ecane

[a]The stem ‘‘irine’’ may be used for rings containing only N.

[b]The traditional stems ‘‘iridine’’, ‘‘etidine’’, and ‘‘olidine’’ are preferred for N-containing rings and are used for saturated heteromonocycles having three, four, or five ring members, respectively.

[c]The stem for six-membered rings depends on the least preferred heteroatom in the ring: that immediately preceding the stem. To determine the correct stem for a structure, the set below containing this least-preferred heteroatom is selected.

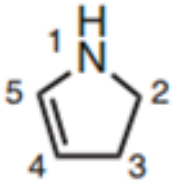
6A : O, S, Se, Te, Bi, Hg.

6B : N, Si, Ge, Pb.

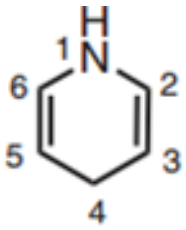
6C : B, P, As, Sb

Indication of Saturated Positions

Partially or fully saturated heterocycles are designated by suffixes as per Table 2.2. If no termination is specified, the following prefixes indicating saturated positions should be used: 1 position (H), 2 positions (dihydro), 3 positions (dihydro + H), 4 positions (tetrahydro), 5 positions (tetrahydro + H). It should be noted that these saturated positions should be assigned the smallest possible numbering (see example below)



2,3-dihydro-1H-pyrrole



1,4-dihydropyridine

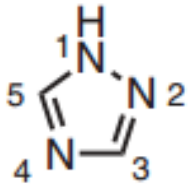
Numbering

Monocyclic Systems with One Heteroatom

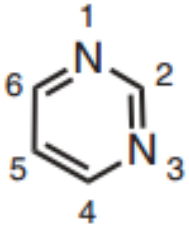
The numbering of such systems starts with the heteroatom.

Monocyclic Systems with Two or More Identical Heteroatoms

The prefixes di-, tri-, tetra-, etc., are used for two or more heteroatoms of the same type. When indicating the relative positions of heteroatoms, the numbering of the system should be done in a way that the position indices of all heteroatoms receive the smallest possible sum.



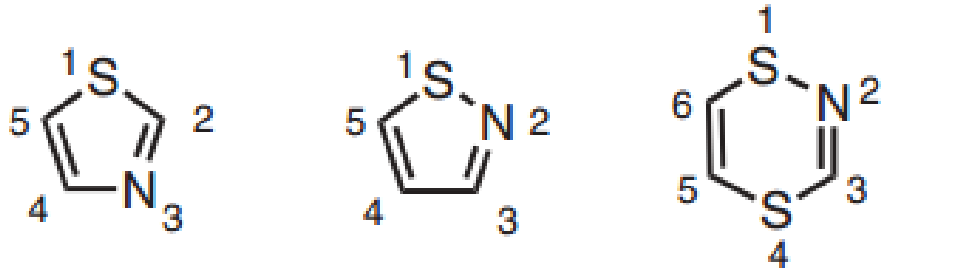
1,2,4-triazole
(not 1,3,5-triazole)



pyrimidine
(1,3-diazine, not
1,5-diazine)

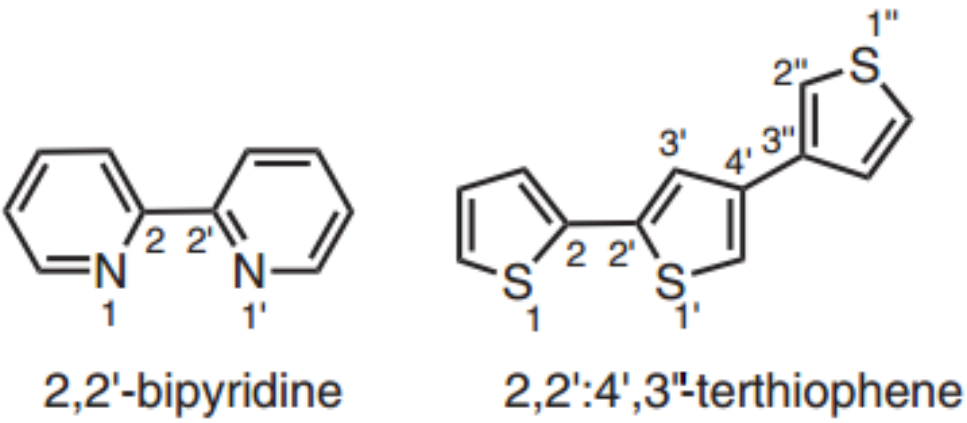
Monocyclic Systems with Two or More Different Heteroatoms

The prefixes are used according to the order in which they appear in Table 2.1, for example, thiazole and not azathiole; dithiazine and not azadithiine. The highest-priority heteroatom in Table 2.1 is assigned position 1 in the heterocycle. The remaining heteroatoms will have lower rank in the order of heteroatom precedence:



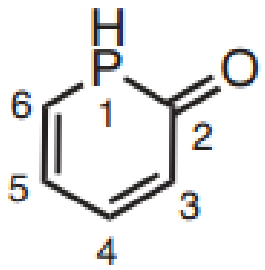
Monocyclic Identical Systems Connected by a Single Bond

This type of system is defined by prefixes bi-, ter-, quater-, etc., depending on the number of cycles comprising the system, and the linkage is indicated as follows:

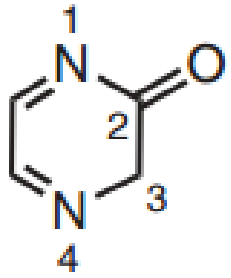


Monocyclic Systems Containing the Exocyclic C=O and C=S Bond

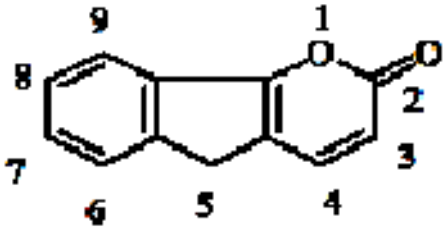
Heterocyclic compounds in which a carbon atom ($_6$C) in the ring is part of a carbonyl group are named using the indicated hydrogen as follows:



phosphinin-2-(1*H*)-one



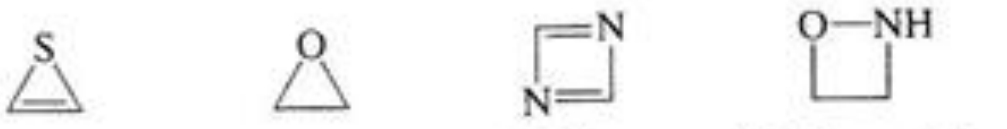
pyrazin-2-(3*H*)-one



indeno[1,2-b]pyran-2-(5H)-one

In the case of the C=S bond, the termination "thione" is used instead of "one."

Examples of Applications: Completely Saturated and Unsaturated Monocycles



Thiirene Oxirane 1,3-Diazete 1,2-Oxazetidine

1,3-Dioxolane 1,2,4-Triazine Thiepane Azocine

Examples of Applications: Partially Unsaturated Monocycles

azirine

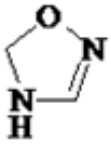
2H-azirine

1,2 oxazete

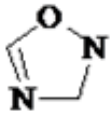
4H-1,2 oxazete

1,4-dihydro-1,2 diazete

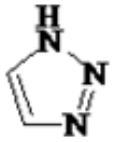
3,4-dihydro-1,2 diazete



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

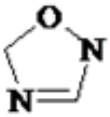


2,3-dihydro-1,2,4 oxadiazole

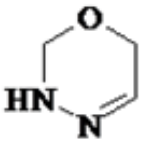


1,2,3 triazole

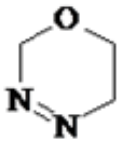
4H-1,2,3 triazole



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



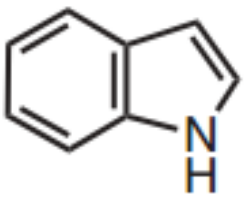
3,6-dihydro-2H-1,3,4 oxadiazine



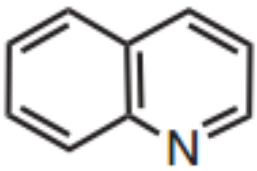
5,6-dihydro-2H-1,3,4 oxadiazine

Nomenclature of Bicyclic Systems with One Benzene Ring

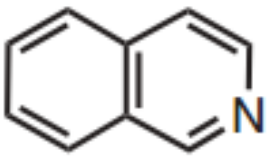
Systems in which at least two neighboring atoms are common to two or more rings are called fused systems (fused). Most bicyclic systems with one benzene ring have trivial names, for example:



indole



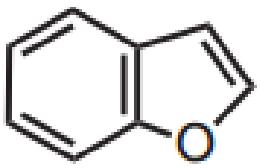
quinoline



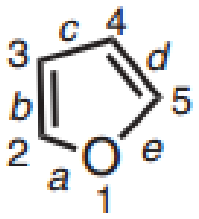
isoquinoline

The systematic name for these types of systems consists of three parts in the following format: benzo[letter]heterocycle. To name them, here are the steps to follow:

1. The name of the heterocycle is preceded by the prefix -benzo (with elision of the "o" in the prefix -benzo before the vowel of the heterocycle).
2. A letter enclosed in brackets follows the prefix -benzo [a, b, c, ...], indicating the common linkage between the two cycles defined from the heterocycle.
3. For a system containing only one heteroatom, each bond in the heterocycle is then designated by a letter starting from "a" for the heteroatom-carbon bond closest to the common linkage with the benzene ring.
4. For a bicyclic system containing a heterocycle with multiple heteroatoms, the direction of rotation around this heterocycle is determined by considering the precedence of the heteroatoms; the bonds in the heterocycle a, b, c, ... are deduced accordingly.



benzo[*b*]furan



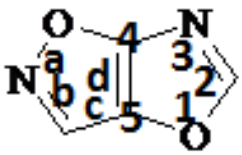
furan

Nomenclature of Bicyclic Systems Formed from Two Heterocycles

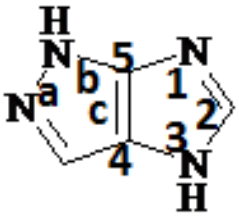
The systematic name for these types of systems follows the following format: prefix[numbers, letter]base component. To name them, here are the steps to follow:

1. It is necessary to determine which cycle will be considered as the base component (base component).
2. This base component will be preceded by the prefix that designates the secondary heterocycle (see Table 2.3).
3. Describe the common linkage between the fused cycles: To describe the fusion or common linkage between the two fused

rings, first, the bonds between the atoms of the base component (suffix) should be designated by letters a, b, c,..., etc., and the bonds between the atoms of the secondary cycle (prefix) should be designated by numbers 1, 2, 3,..., etc. Atoms common to both cycles are described by numbers and letters enclosed in brackets as previously described, prefix[numbers, letter]base component, where the sequence of numbers should correspond to the direction of lettering in the base component (it should follow the same direction as the succession of letters in the base component, see the example below).



oxazolo[5,4-d]isoxazole



imidazo[5,4-c]pyrrazole

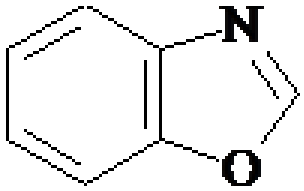
Table. 2.3. prefixes of the secondary heterocycle

Heterocycle	Prefix
Pyrrol	Pyrrolo
Furan	Furo
Thiophene	Thieno
Imidazol	Imidazo
Pyridine	Pyrido
Quinoleine	Quino
Isoquinoleine	Isoquino

How to Choose the base component (?)

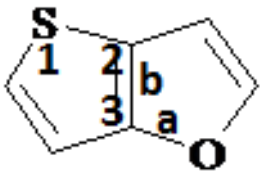
To choose the base constituent among the two heterocycles, one must apply these seven rules in the sequential order presented below:

1. If the system has a single cycle containing nitrogen, choose it



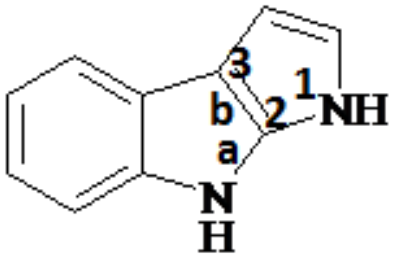
benzoxazole

2. If the system does not contain nitrogen, follow the order of priority: oxa > thia > aza



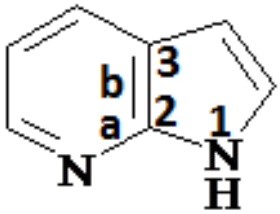
thieno[3,2-b]furane

3. If the system contains a part consisting of two or more cycles, choose it



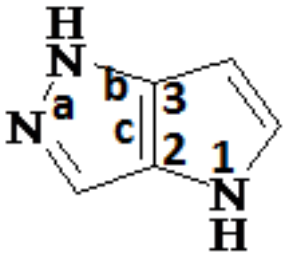
pyrrolo[2,3-b] indole

4. If the system contains two cycles of different sizes, choose the larger cycle



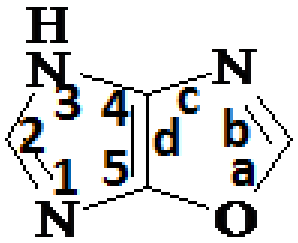
pyrrolo[2,3-b]pyridine

5. Choose the cycle that contains a higher number of heteroatoms



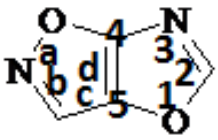
pyrrolo[3,2-c]pyrrazole

6. If both cycles contain the same number of heteroatoms, follow the priority order: oxa > thia > aza

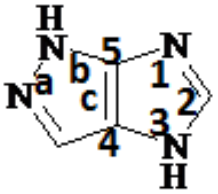


imidazo[4,5-d]oxazole

7. If both cycles contain the same number of heteroatoms and follow the same priority order oxa > thia > aza, choose the one with the smallest numbering of heteroatoms

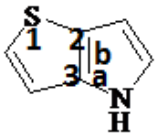


oxazolo[5,4-d]isoxazole

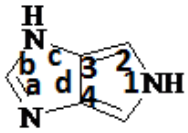


imidazo[5,4-c]pyrrazole

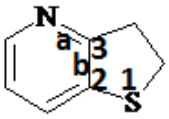
Examples of Applications: Bicyclic Systems



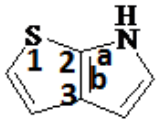
thieno[3,2-b]pyrrole



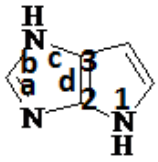
pyrrolo[3,4-d]imidazole



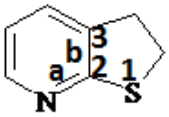
thieno[3,2-b]pyridine



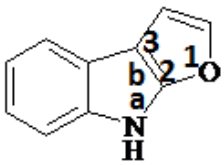
thieno[2,3-b]pyrrole



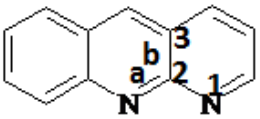
pyrrolo[3,2-d]imidazole



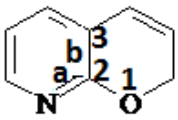
thieno[2,3-b]pyridine



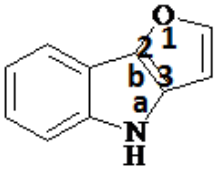
furo[2,3-b]indole



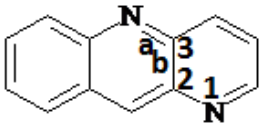
pyrido[2,3-b]quinoleine



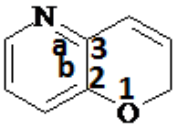
pyrano[2,3-b]pyridine



furo[3,2-b]indole

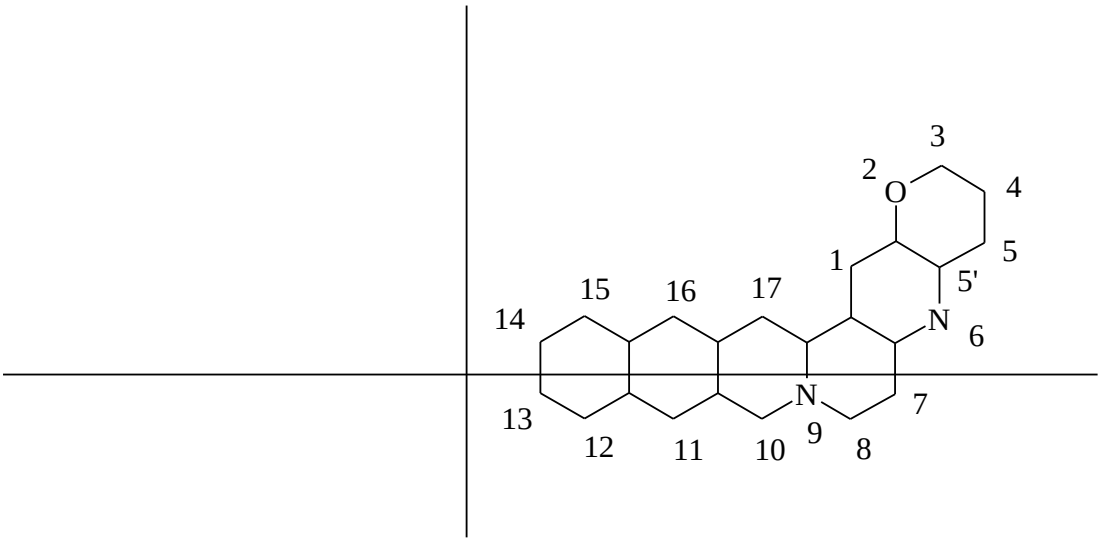


pyrido[3,2-b]quinoleine



pyrano[3,2-b]pyridine

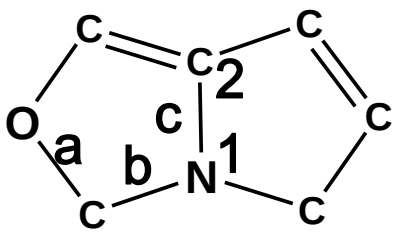
Describe the position of substituents throughout the polycyclic system



It is generally accepted that the numbering of the entire system in the case of bi- and polycyclic compounds should be done independently of the numbering of its two components (prefix and base component), and this is done as follows:

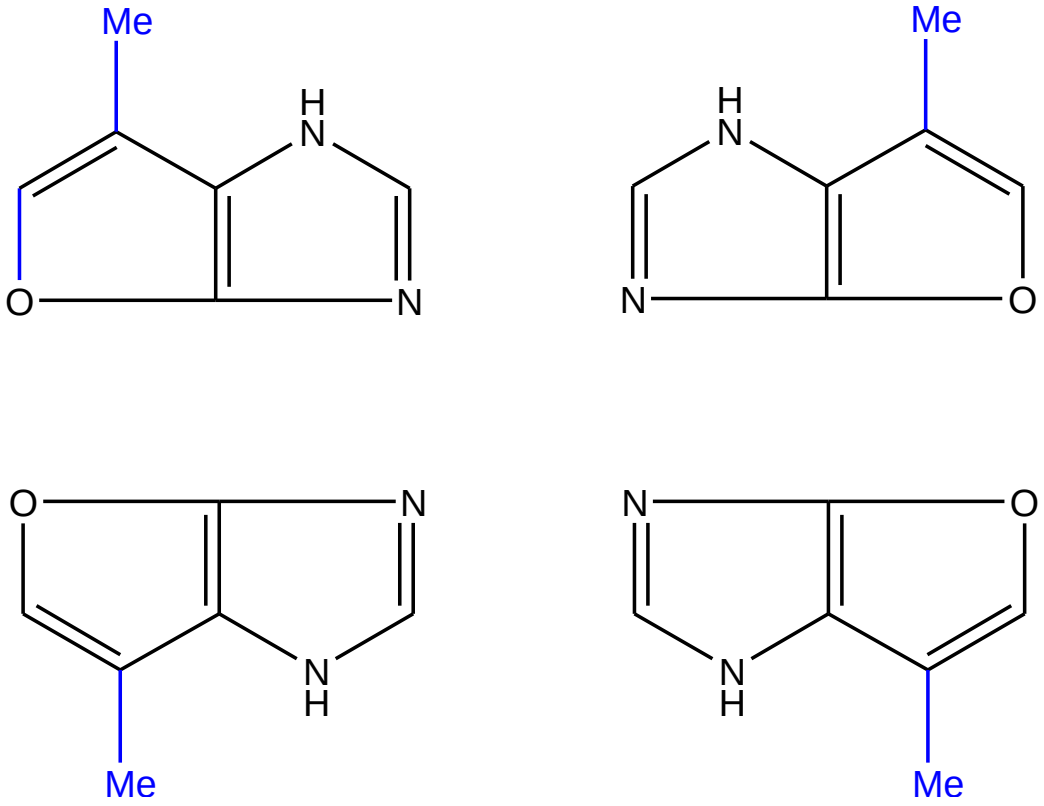
1. Use rectangular coordinate axes to project the entire polycyclic system.
2. Place as many cycles as possible along the horizontal coordinate axis.
3. Place the maximum number of cycles in the upper right quadrant.
4. The system is numbered clockwise, starting from the atom that is not involved in the fusion of the two cycles and is the leftmost atom in the upper cycle or the rightmost atom in the upper row.

Note: Carbon atoms ($_6$C) that belong to more than one cycle are omitted. However, heteroatoms in such positions are included (see example):

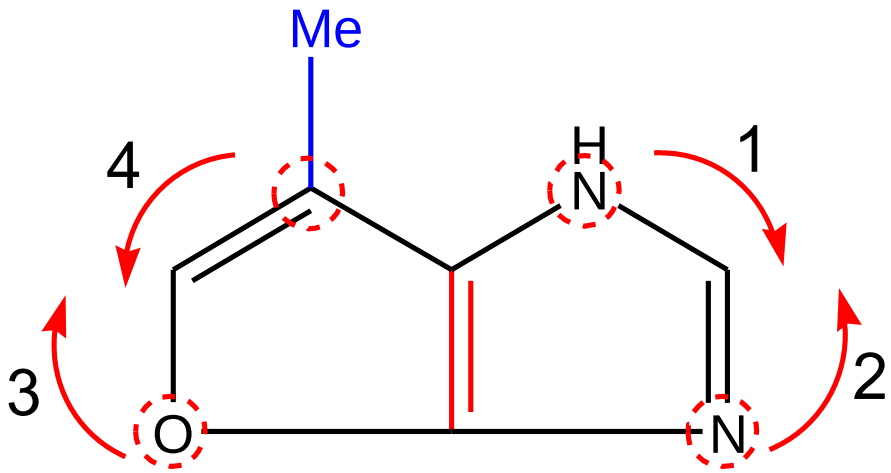


pyrrolo[1,2-c]oxazole

For a bicyclic system, there are four (4) possible orientations of the molecule along the coordinate axis (XZ). In this case, it is crucial to establish a rule that provides the same numbering for the substituent in all 4 molecular orientations:

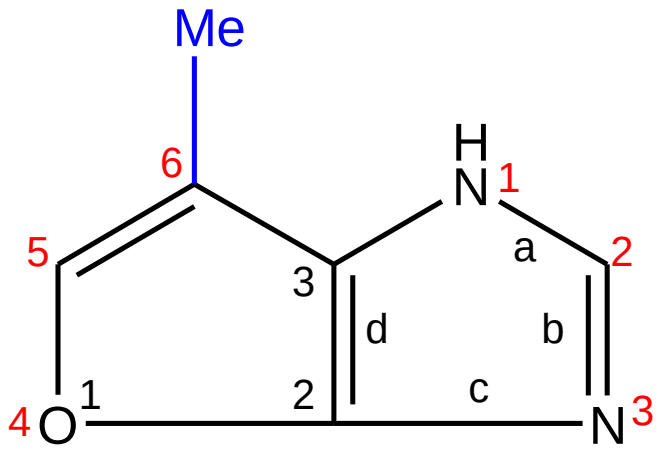


In this case, there are 4 possible numbering options, always starting with the atom that is not involved in the fusion of the two cycles, which is the rightmost atom in the upper row (see diagram below)



Order of preference among different numbering systems

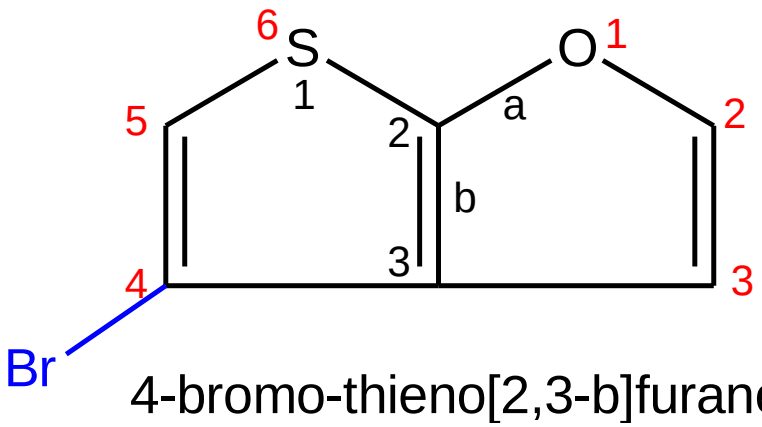
Rule 1. The sum of the positions of heteroatoms should be minimal.



6-methyl-furo[2,3-d]imidazole

In this example, we have 4 orientations of the system, meaning we have 4 starting points to number the system. In this case, it is necessary to provide numbering in such a way that the sum of the heteroatoms positions is minimal. Therefore, 1,3,4 is preferred over 1,3,6; 1,4,6; and 3,4,6.

Rule 2. The sum of the positions of heteroatoms is equal.



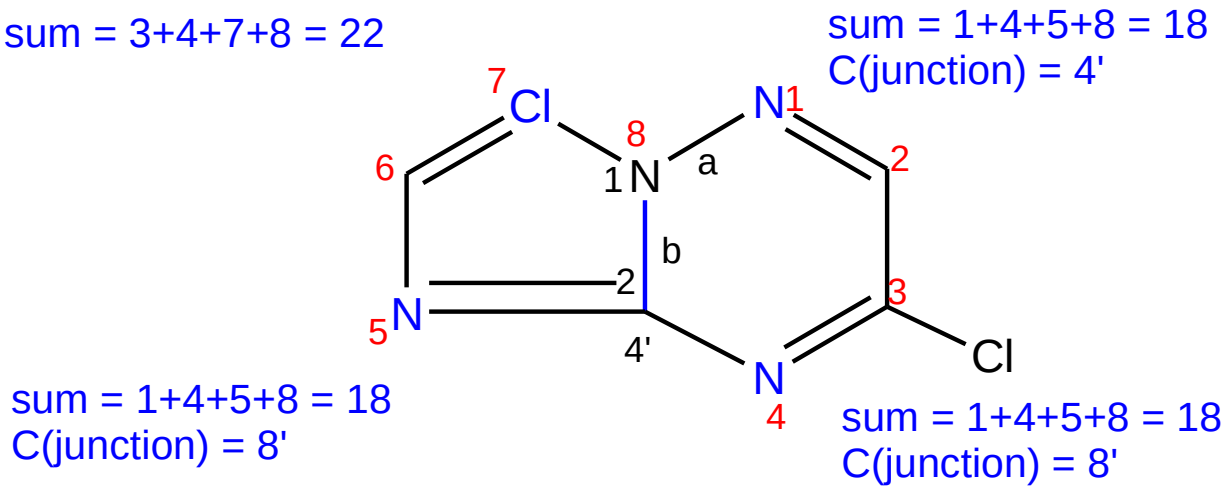
4-bromo-thieno[2,3-b]furane

Option 1: O(1), S(6) sum = 7

Option 2: S(1), O(6) sum = 7

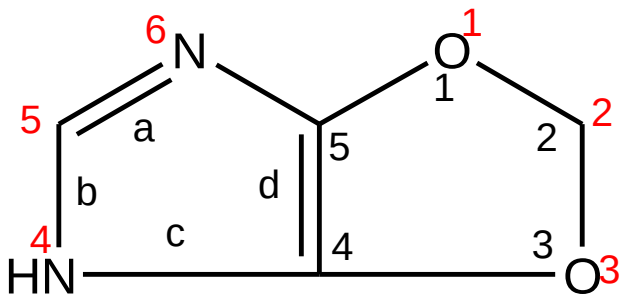
In this case, start numbering from the highest-priority heteroatom in the precedence table Oxa(O) > Thia(S) > Aza(N), so option 1 is preferred.

Rule 3. Assign the smallest number to the carbon at the junction.



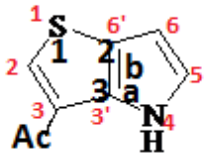
3-chloro-imidazo[1,2-b]triazine

Rule 4. Assign the smallest number to saturated atoms.

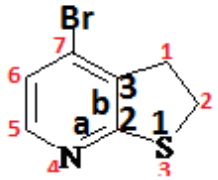


2H,4H-[1,3]dioxolo[4,5-d]imidazole
not : 2H,6H-[1,3]dioxolo[4,5-d]imidazole

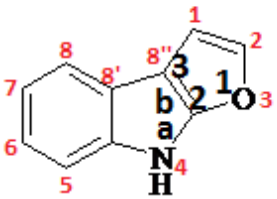
Examples of Applications: Substituted Bicyclic Systems



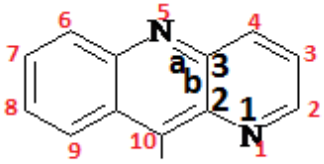
3-acetyle-4H-thieno[3,2-b]pyrrole



7-bromo-1,2-dihydro thieno[2,3-b]pyridine



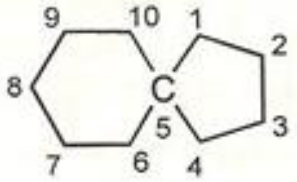
4H- furo[2,3-b]indole



10-methyl- pyrido[3,2-b]quinoleine

Nomenclature of Spiro Heterocycles

By definition, spiro heterocyclic compounds are bicyclic molecules in which the two cycles are connected by a single atom. The connecting atom is typically tetrahedral and called the spiro atom, most often a carbon atom. All spiro compounds are named with the prefix 'spiro' followed by two numbers in brackets separated by a dot in the following format: spiro[x.y]alkane. The two numbers x and y represent the length of the two cycles in ascending order, not counting the spiro atom. The number of atoms in the spiro skeleton determines the name of the compound, identical to that of the corresponding linear alkane. Heteroatoms must be indicated with their positions as prefixes.



Spiro hydrocarbon

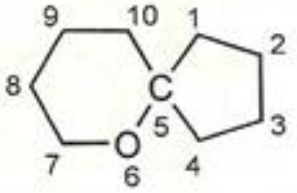
Spiro[x.y]alkane

x = number of atoms other than spiro atom in smaller ring.

y = number of atoms other than spiro atom in larger ring

↓

Spiro[4.5]decane



Spiro heterocycle

Spiro[x.y]alkane

x = four atoms
(spiro atom is not included)

y = five atoms
(spiro atom is not included)

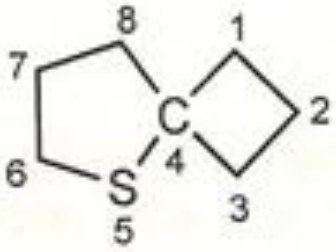
alkane : total number of atoms (including heteroatom) are = 10 : decane

Prefix for heteroatom : oxa

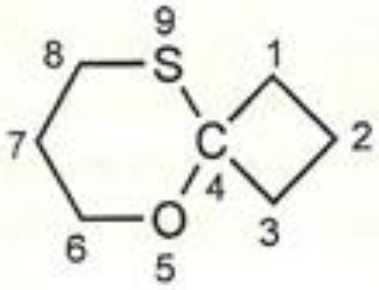
↓

6-Oxaspiro[4.5]decane

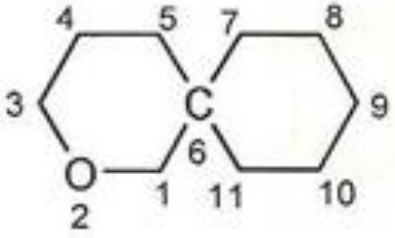
Examples of Applications :



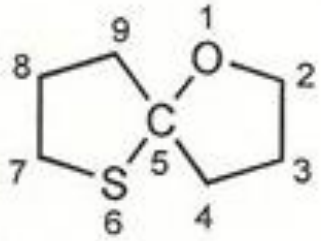
5-Thiaspiro[3.4]octane



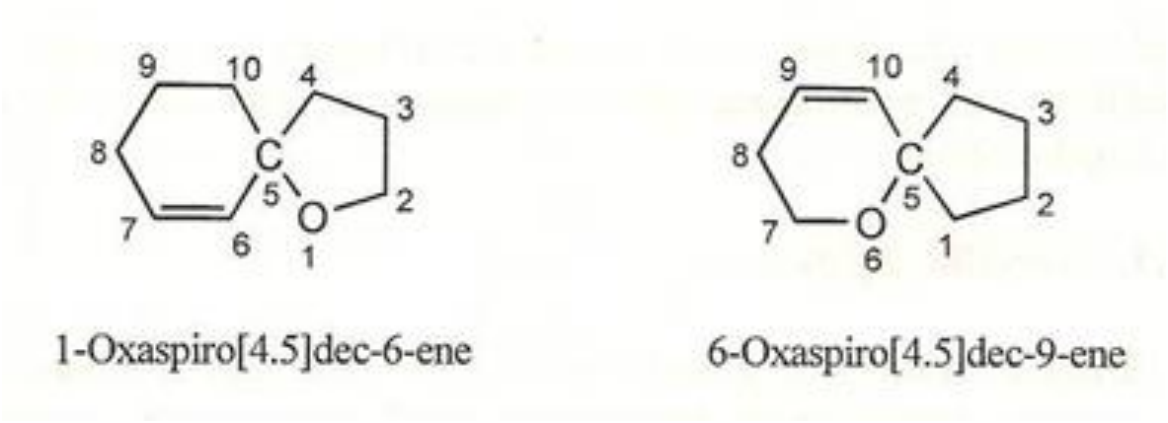
5-Oxa-9-thiaspiro[3.5]nonane



2-Oxaspiro[5.5]undecane



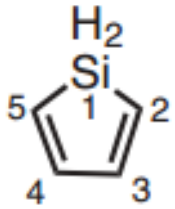
1-Oxa-6-thiaspiro[4.4]nonane



Replacement Nomenclature or 'a' Nomenclature

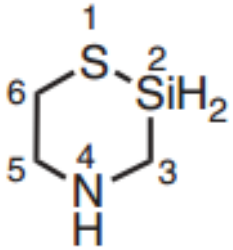
Monocyclic systems

Since all the prefixes end with the letter 'a,' replacement nomenclature is also known as 'a' nomenclature. In this nomenclature, the heterocyclic system is transformed into a carbon cycle, i.e., by replacing each heteroatom with a carbon atom, and then the corresponding carbocycle is named. The name of the carbocycle is preceded by a prefix indicating the type and position of the heteroatom, presented according to their precedence as indicated in Table 2.1 (see the example below). The two compounds chosen as examples could also be named according to Hantzsch-Widman nomenclature.



silacyclopenta-2,4-diene

cyclopentadiene

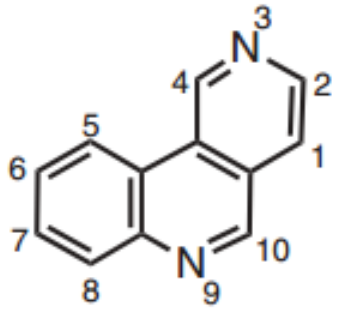


1-thia-4-aza-2-silacyclohexane

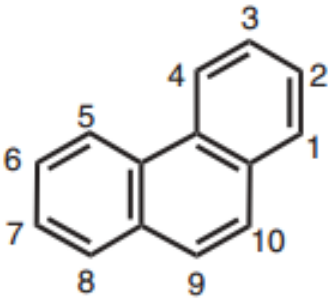
cyclohexane

polycyclic systems

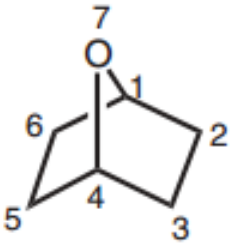
Once more, the position and prefix are placed before the name of the corresponding hydrocarbon, while retaining the numbering of the hydrocarbon.



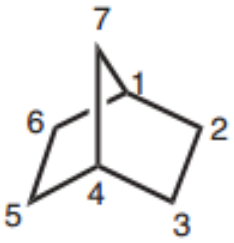
3,9-diazaphenanthrene



phenanthrene

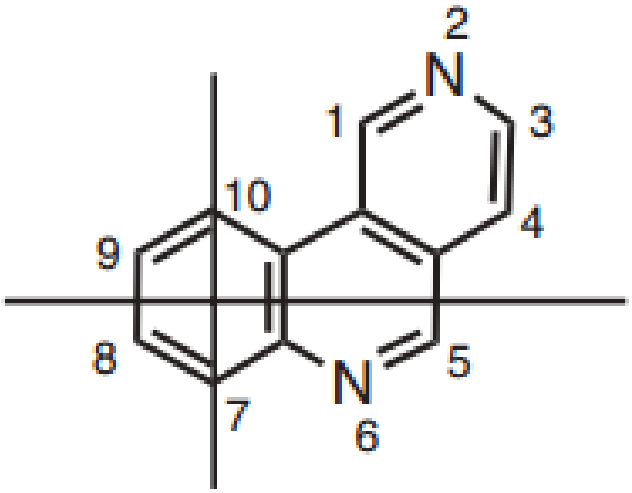


7-oxabicyclo[2.2.1]heptane



bicyclo[2.2.1]heptane

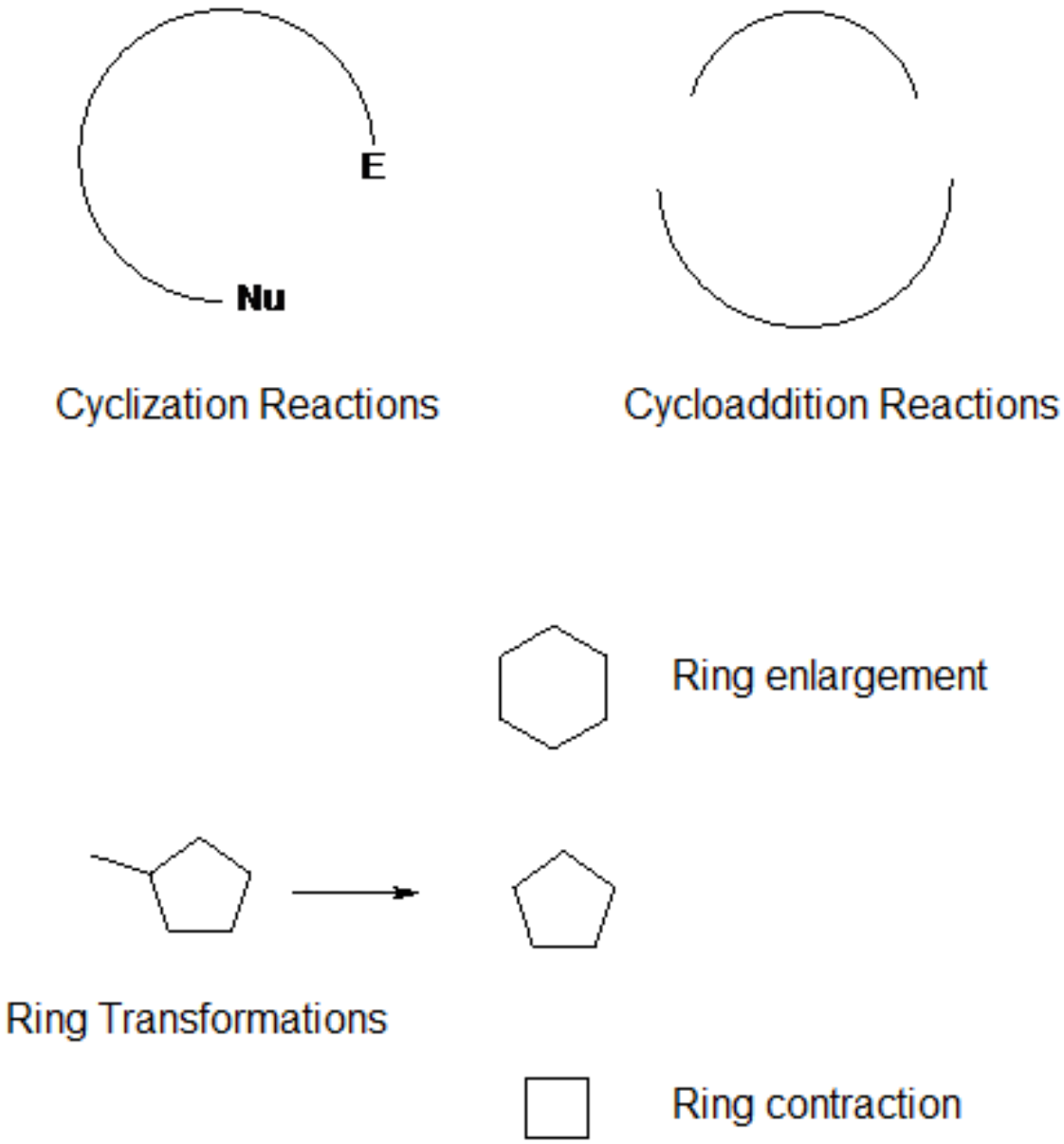
Hantzsch-Widman nomenclature is applied only to the first example, leading to different numbering.



pyrido[4,3-*c*]quinoline

The General Methods for the Synthesis of Heterocycles

In general, there are three methods outlined in the diagram below for the synthesis and preparation of heterocycles.



Scheme: General Methods for Heterocycle Synthesis

Cyclization Reactions

This type of reactions leads to the transformation of a linear organic molecule into a cyclic molecule. During cyclization (or chain closure), a single chemical bond is formed.

Cycloaddition Reactions

This type of reactions involves two linear molecules that combine to form a single cyclic molecule. During cyclization, two chemical bonds are formed.

Cyclic Rearrangement Reactions (Cycle Transformation)

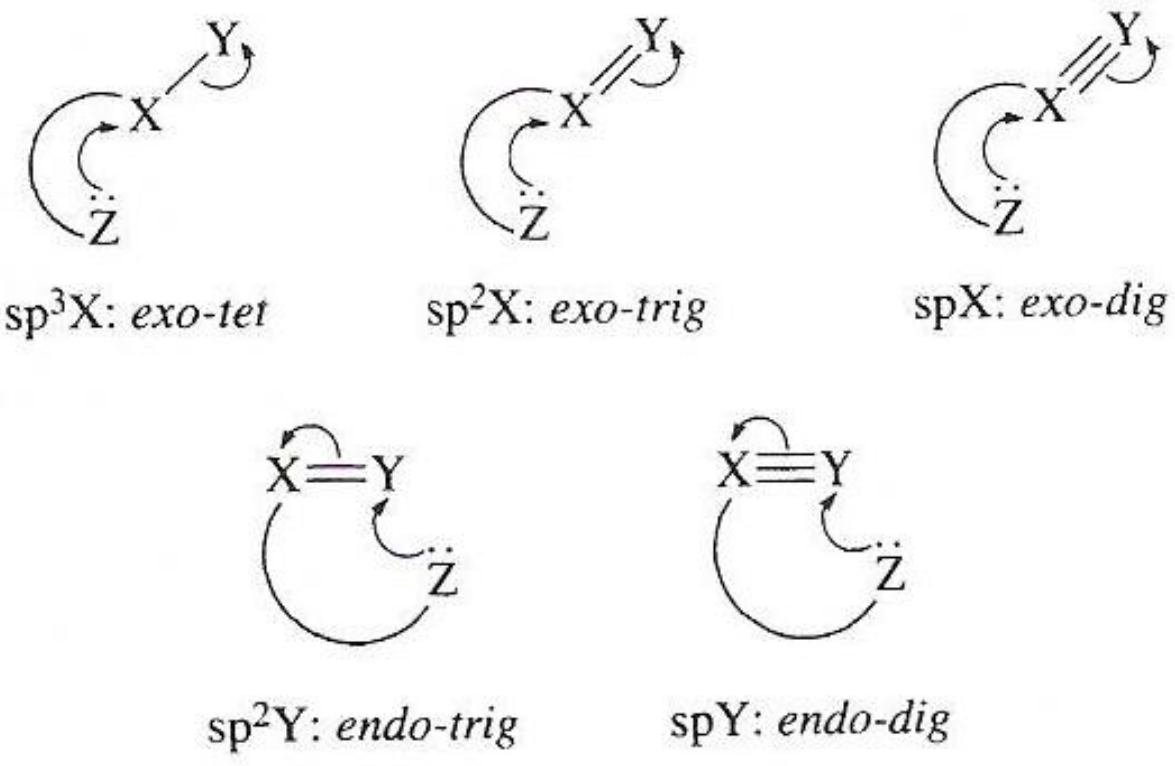
In this type of reactions, there isn't a well-defined method for achieving this transformation. The contraction or expansion of the cycle happens spontaneously during organic synthesis.

Cyclization Reactions

Jack Baldwin's Rules

Jack Baldwin's rules, proposed in 1976, offer a predictive guide for the type of cyclization that may occur in alicyclic compounds during a chemical reaction. To name the cyclization, one must follow the following order:

Size of the formed cycle: Exo or Endo-Geometry of the substituted atom

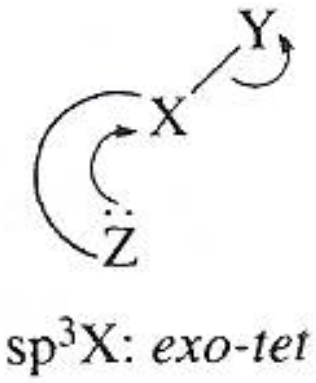


Scheme: Types of nucleophile-electrophile cyclization

Looking at the diagram above, each time the attack is carried out by the

nucleophile (symbolized by Z) on the most electrophilic atom (X).

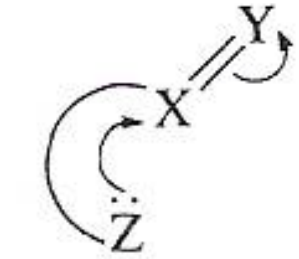
The 1st type:



sp^3X: *exo-tet*

Case of a single bond (X-Y): the nucleophile Z attacks the most electrophilic atom X with tetrahedral geometry (tet) and removes the leaving group Y => substitution reaction => the bond moves outward => exo

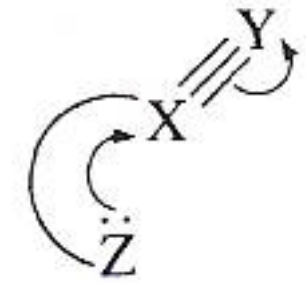
The 2nd type:



sp^2X: *exo-trig*

Case of a double bond (X=Y), the nucleophile Z attacks the most electrophilic atom X with trigonal geometry (trig). The bond moves outward, exhibiting an exo configuration

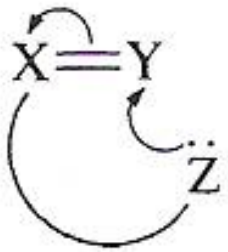
The 3rd type:



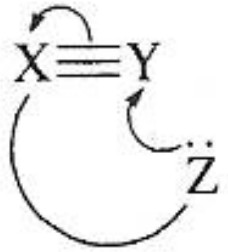
spX: *exo-dig*

Case of a triple bond (X≡Y), the nucleophile Z attacks the most electrophilic atom X with digonal geometry (dig). The bond moves outward, exhibiting an exo configuration.

The 4th and 5th types :



sp^2Y: *endo-trig*

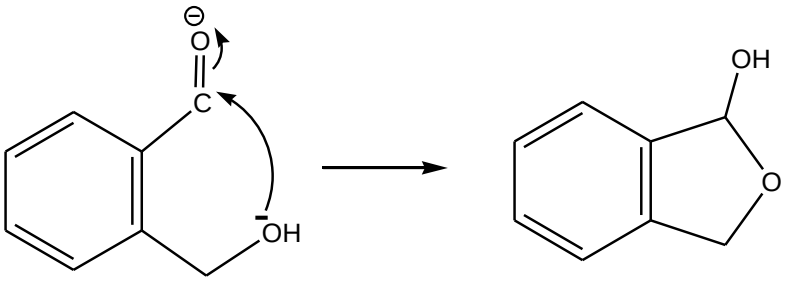


spY: *endo-dig*

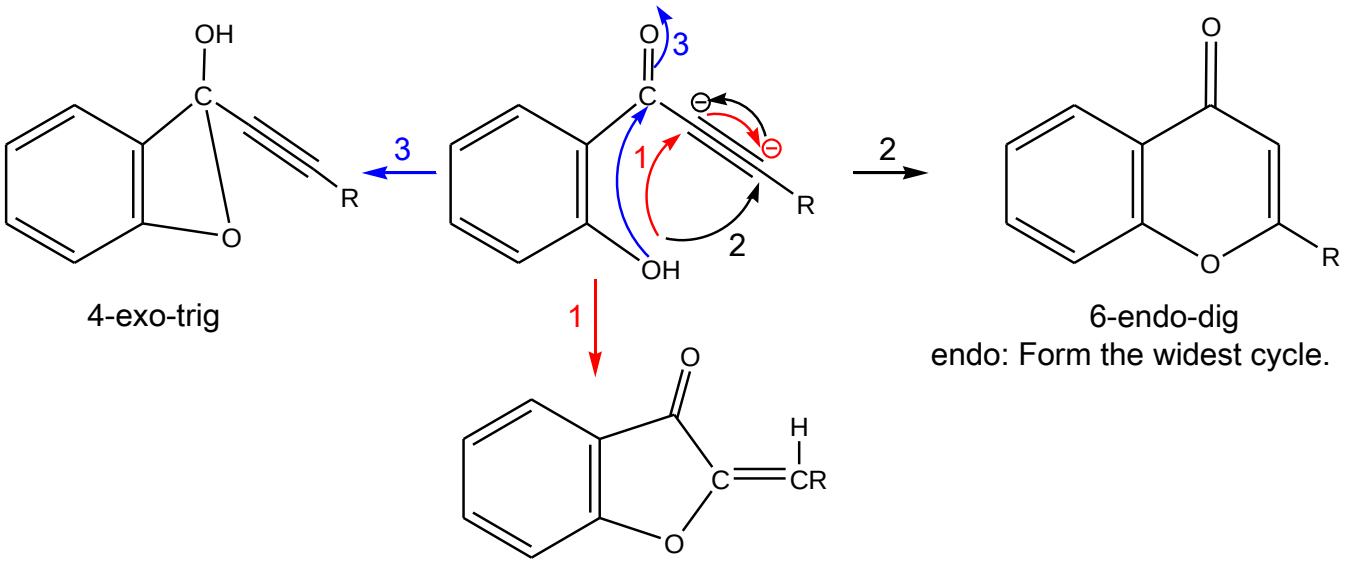
For double bonds (X=Y) and triple bonds (X≡Y), where the attack can occur on both sides of the bond, for example, the case of (C=C) and (C≡C): in this situation, we may observe cyclizations of endo-trig and endo-dig types, respectively, where the bond moves inward (endo), resulting in the formation of the widest cycle.

Examples of applications

Classify each of the following cyclizations using Baldwin's nomenclature:



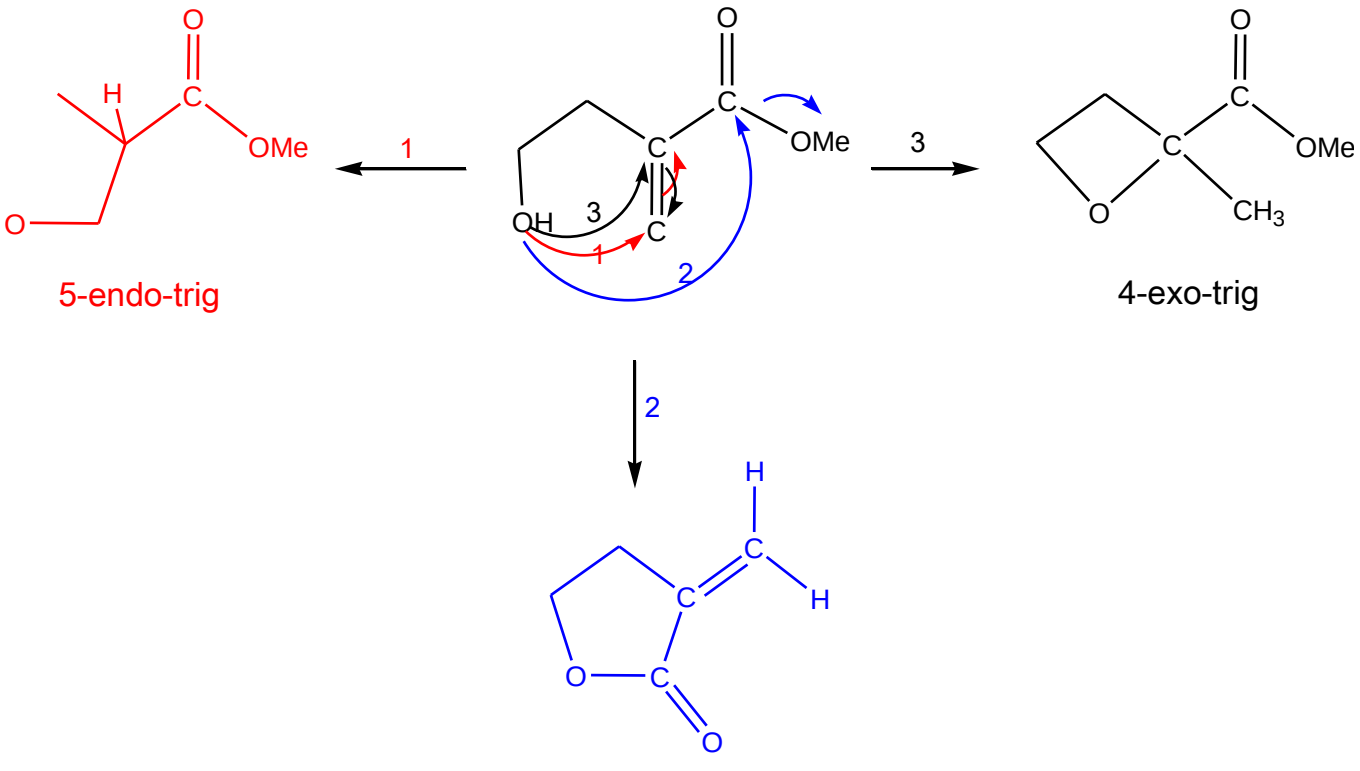
5-exo-trig



4-exo-trig

6-endo-dig
endo: Form the widest cycle.

5-exo-dig
exo: Form the smallest cycle.



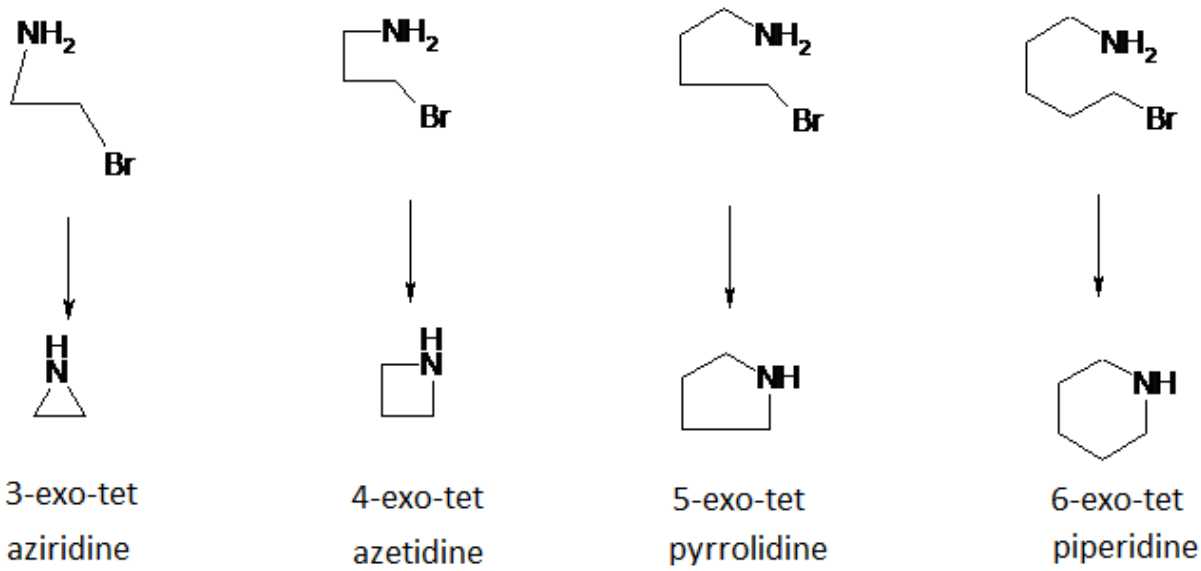
5-endo-trig

4-exo-trig

5-exo-trig

Cyclization on the single bond (Substitution reactions): Attack on the sp^3 carbon (tetragonal)

All these heterocycles containing 3, 4, 5, and 6 members as shown in the diagram below can be prepared using the same synthesis method, which is the substitution reaction.



3-exo-tet aziridine

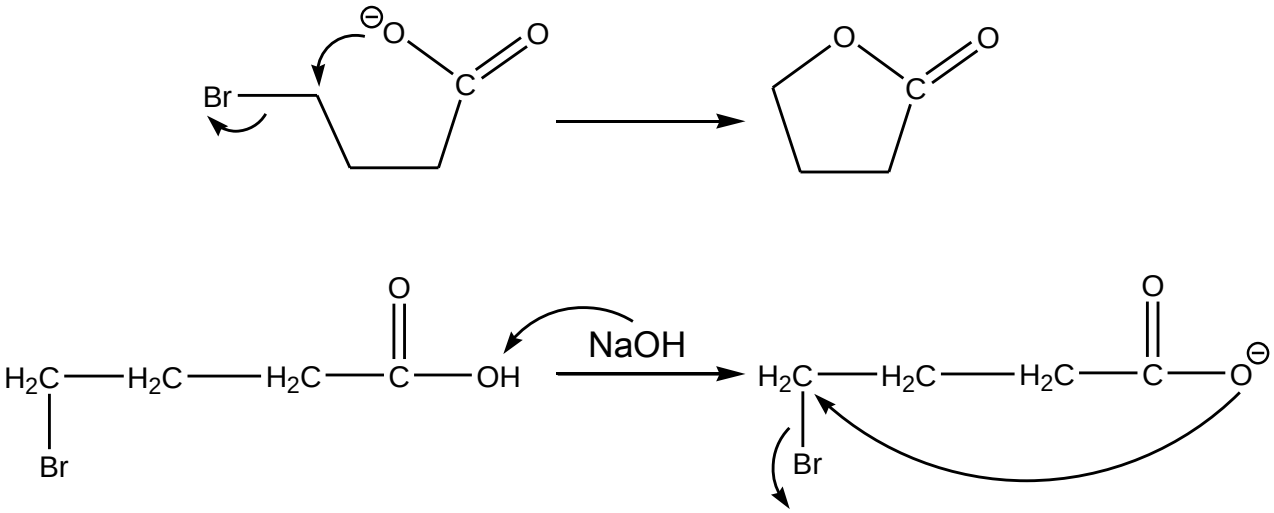
4-exo-tet azetidine

5-exo-tet pyrrolidine

6-exo-tet piperidine

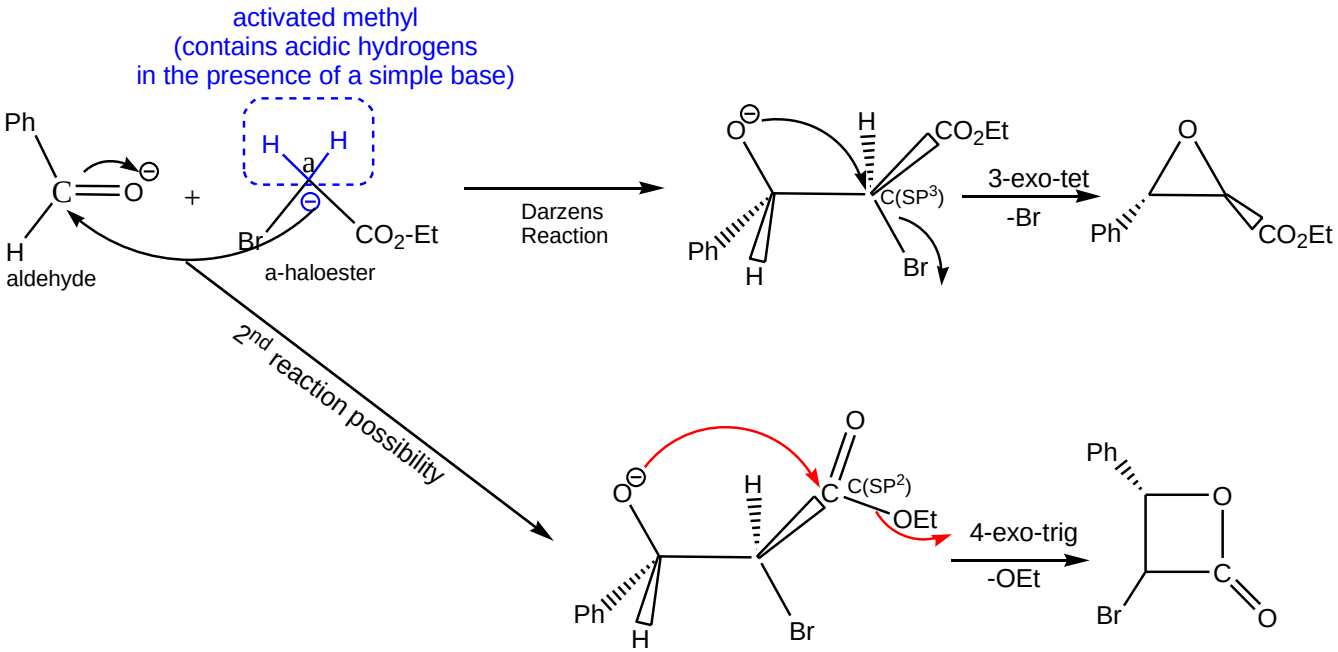
Note: When the nucleophile is next to the electrophile, the cyclization reaction is straightforward and can be easily observed. The challenge arises when the nucleophile is not clearly defined and is far from the electrophile. In this case, one must envision the reaction in the presence of other reactants to obtain the nucleophile that will attack the electrophile, and then predict the type of cyclization that may occur (see example).

Ion carboxylate is next to the electrophile C(tet)

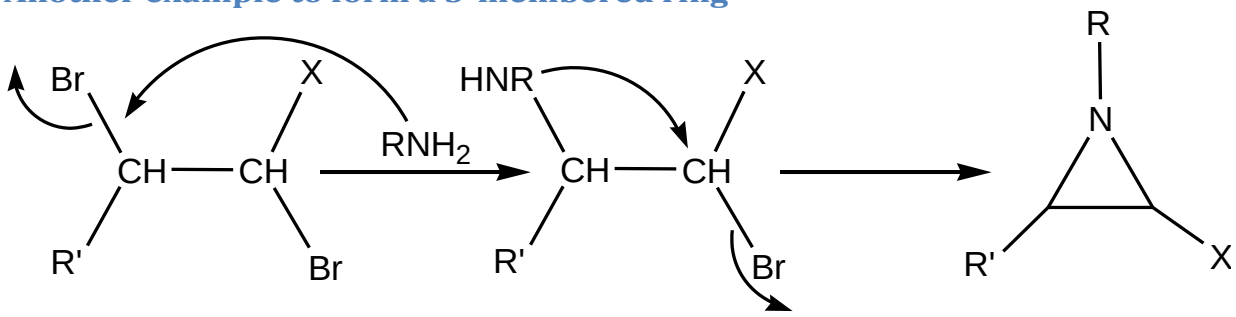


Darzens reactions to prepare epoxides

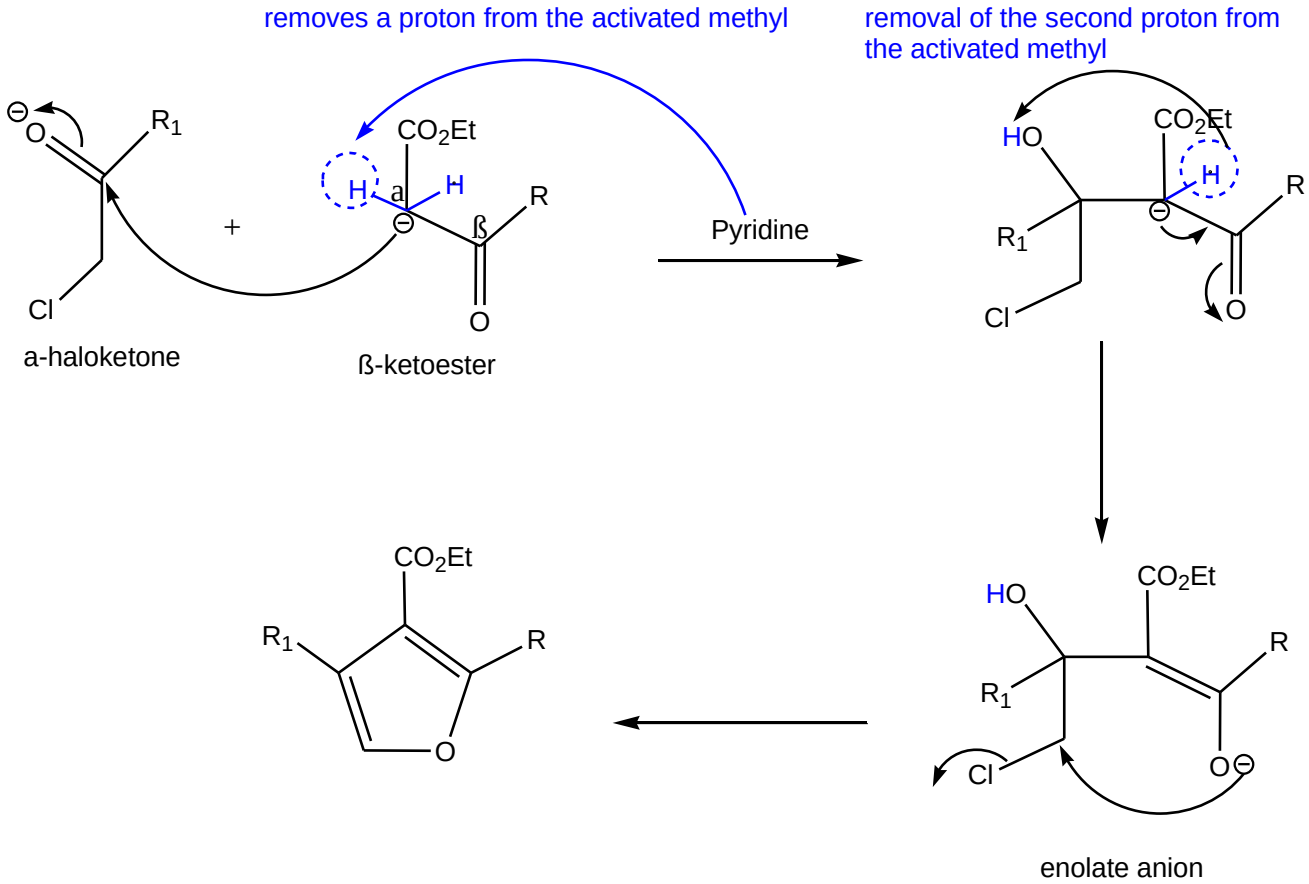
The Darzens reaction (Darzens condensation) is a chemical reaction between a ketone or an aldehyde and an α-halogenoester in the presence of a base to form α,β-epoxy ether (3-membered ring epoxides). This reaction was discovered by Auguste George Darzens in 1904.



Another example to form a 3-membered ring



Feist-Benary synthesis to prepare furan



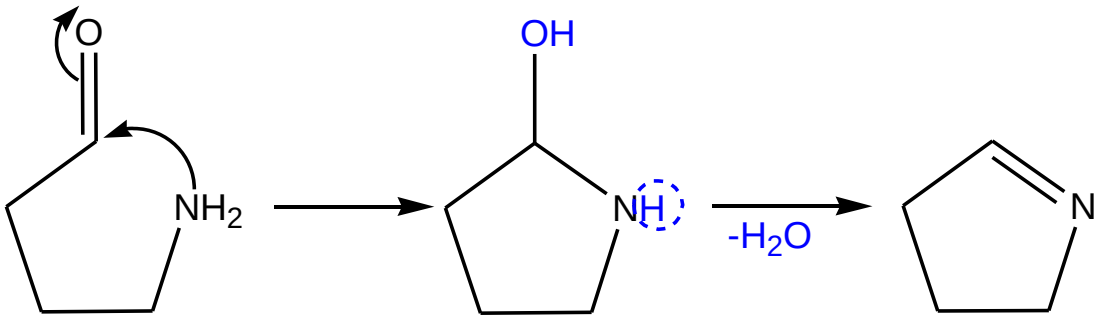
Cyclization on the double bond: attack on the sp² carbon (trigonal)

As we mentioned earlier for cyclization on the single bond type (C-X), there is no such thing as "endo-cyclization." The nucleophile's attack on the tetrahedral carbon (sp^3) always leads to "exo-cyclization." In the case where the nucleophile attacks a hybridized carbon (sp^2) belonging to a double bond,

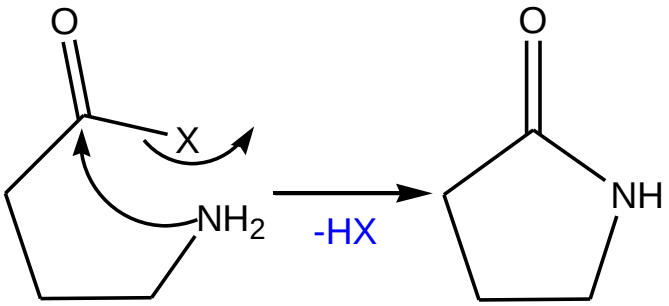
we have two types of cyclization: either "exo-cyclization," which results in a simple addition reaction, or "endo-cyclization," where the double bond moves inside the cycle. The most well-known double bonds of type (C=X) that participate in "exo-cyclization" are C=O, C=N, C=S, all having a difference in electronegativity between the two atoms constituting the double bond. The carbon atom has a partial positive charge, so the nucleophile in this case attacks the carbon atom, causing the double bond to move outward, resulting in "exo-cyclization." However, in the case of the double bond (C=C), during a chemical reaction, we may expect to have two products resulting from both "exo and endo" cyclizations because it is not clear which of the two atoms constituting the double bond is more electropositive; it strongly depends on the substituent environment of each atom.

Reactions of carbonyl compounds (C=O)

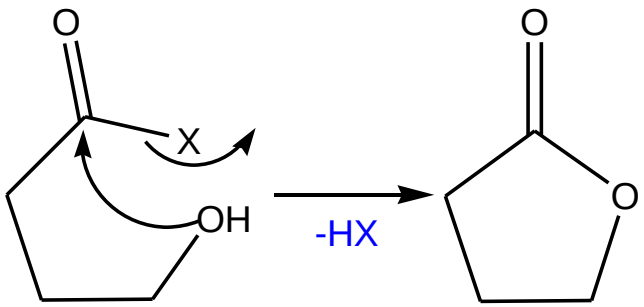
It is well-established in the literature that organic compounds containing the carbonyl group (C=O) are classified into two main categories. The first category involves aldehydes and ketones, which undergo addition reactions. The second category is represented by acids and their derivatives (halogenated esters, anhydrides (CO-O-CO), amides, etc.), which undergo substitution reactions. In this case, it is crucial to pay attention to the type of reaction being conducted, whether it is a substitution or addition reaction.



ketone, aldehyde



acide, ester,... cyclic amide (lactam)



acide, ester,... cyclic ester (lactone)

Carbon nucleophile

In organic chemistry, nucleophiles come in various types, with the most common often containing elements where electron density is potentially high, such as oxygen, nitrogen, or sulfur. In some cases, carbon can act as a nucleophile with the help of neighboring atoms. Carbon typically doesn't have free electron pairs, except in cases like activated methyl, where it loses protons and becomes highly labile in the presence of a carbonyl group, for example: (CH_3-CO). This activation increases if the methyl is between two carbonyl groups (CO-CH_2-CO), where it loses (H^+) to form the carbon

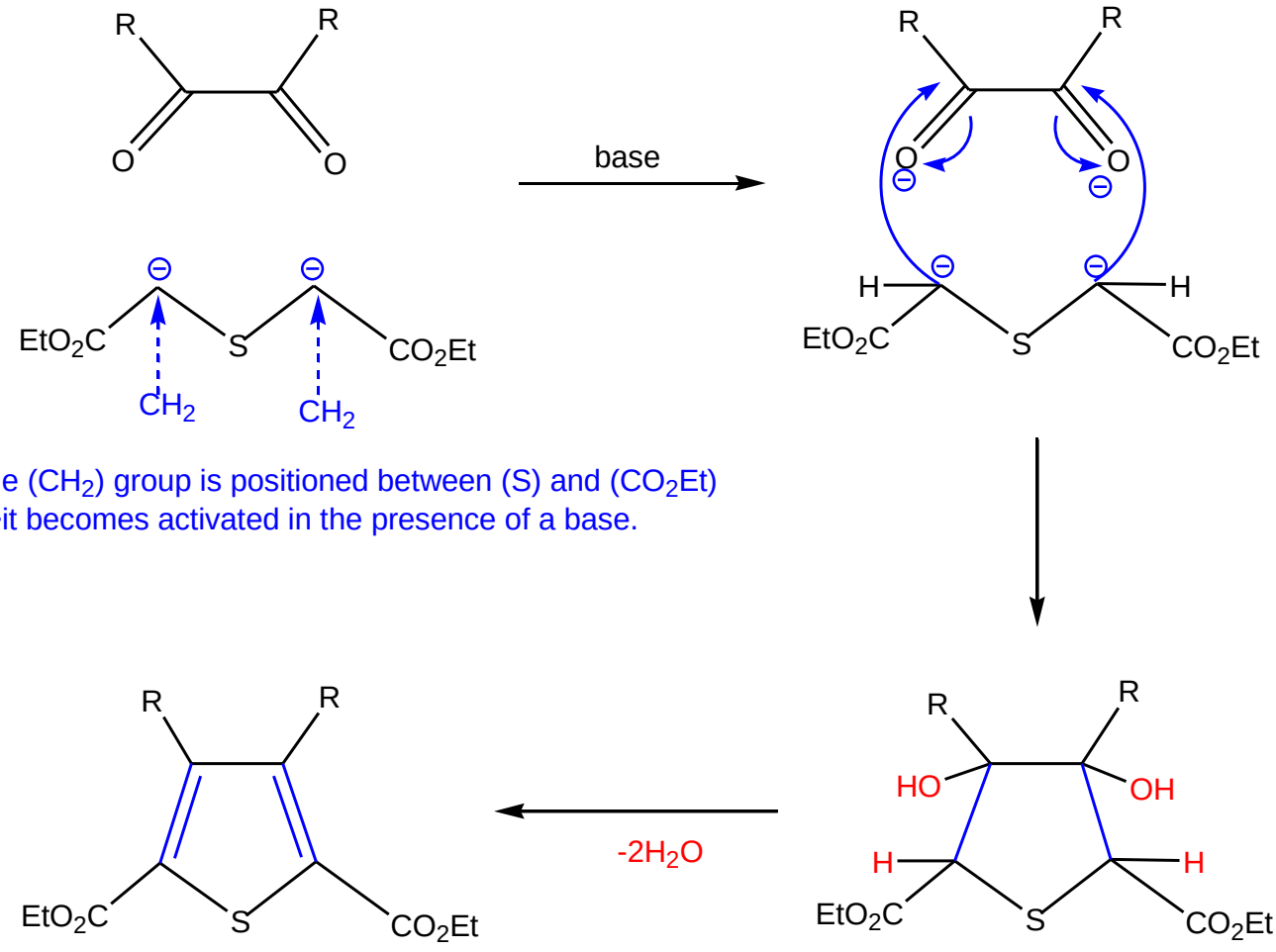
nucleophile (CO-CH:CO). It has also been observed that groups like (NC), S, Ph, halogens (Br, Cl, etc.) aid in the activation of methyl.

The second example where carbon acts as a nucleophile is the Grignard reagent (R-MgX, R-LiX, ...).

The third example is acetylide (R-C≡C-H), which can lose its proton under the influence of a strong base.

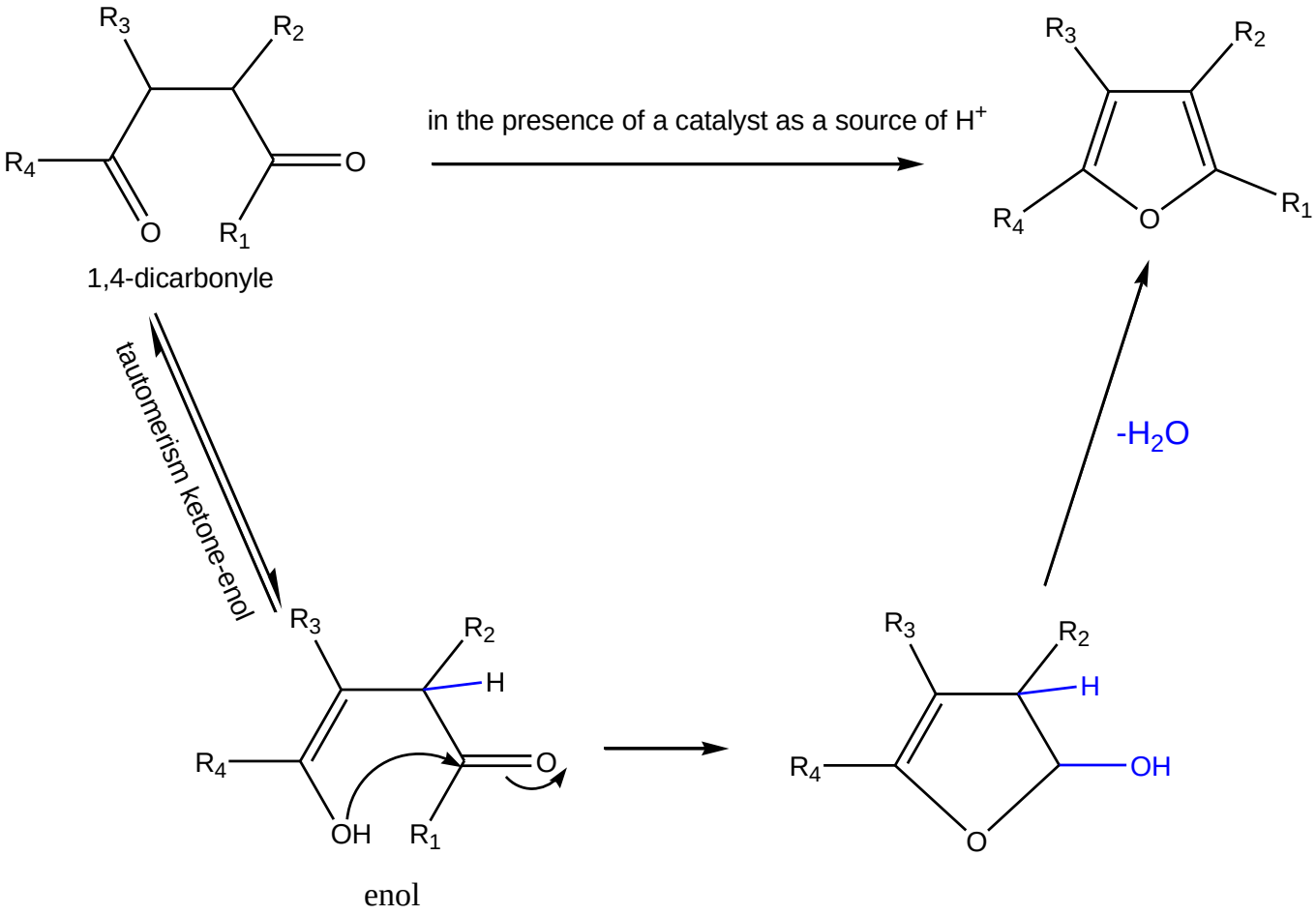
How carbon can act as a nucleophile in various organic reactions ?

Intramolecular Nucleophilic Addition to the Carbonyl Group (Hinsberg Synthesis of Thiophene)

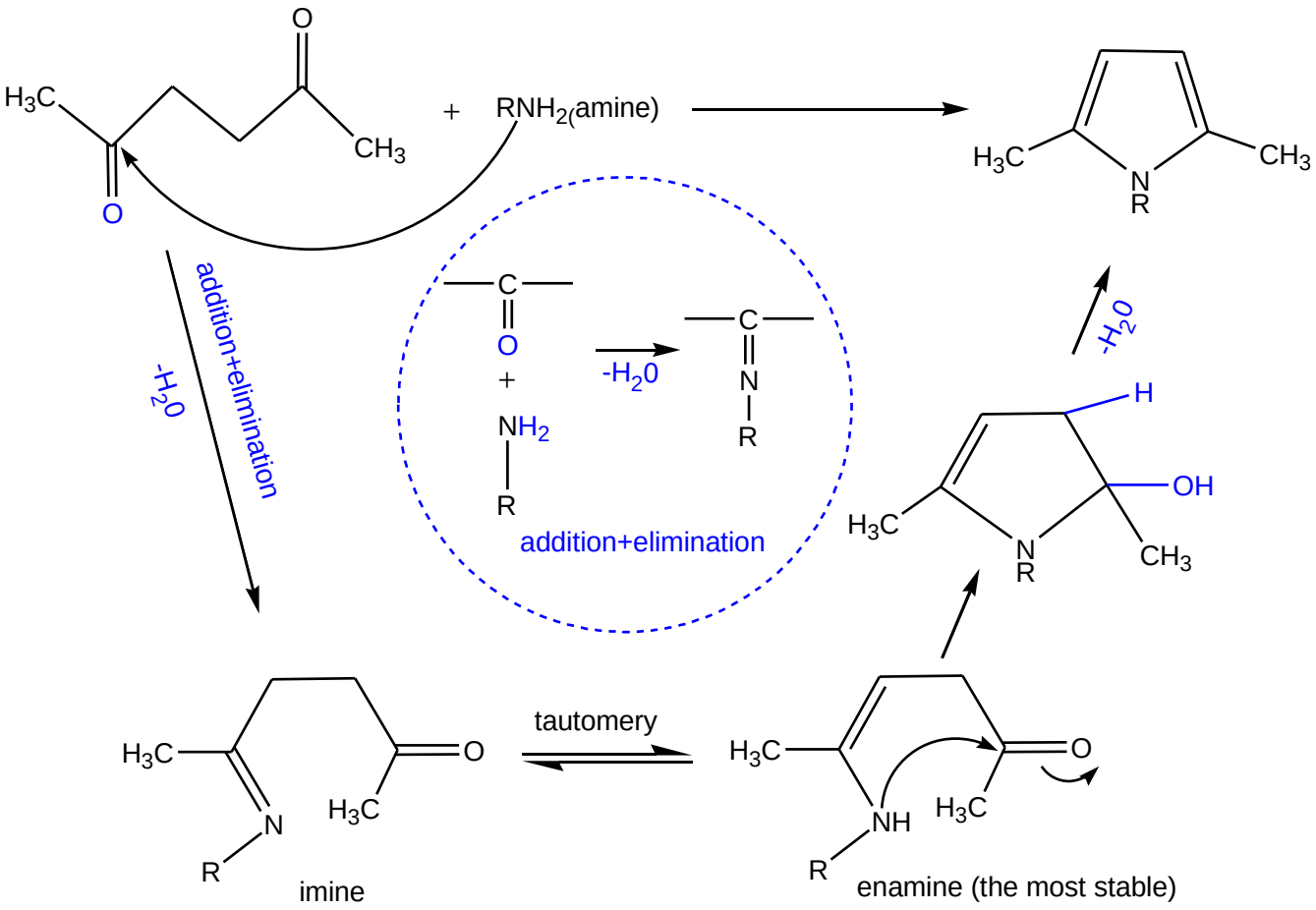


The (CH_2) group is positioned between (S) and (CO_2Et)
=>it becomes activated in the presence of a base.

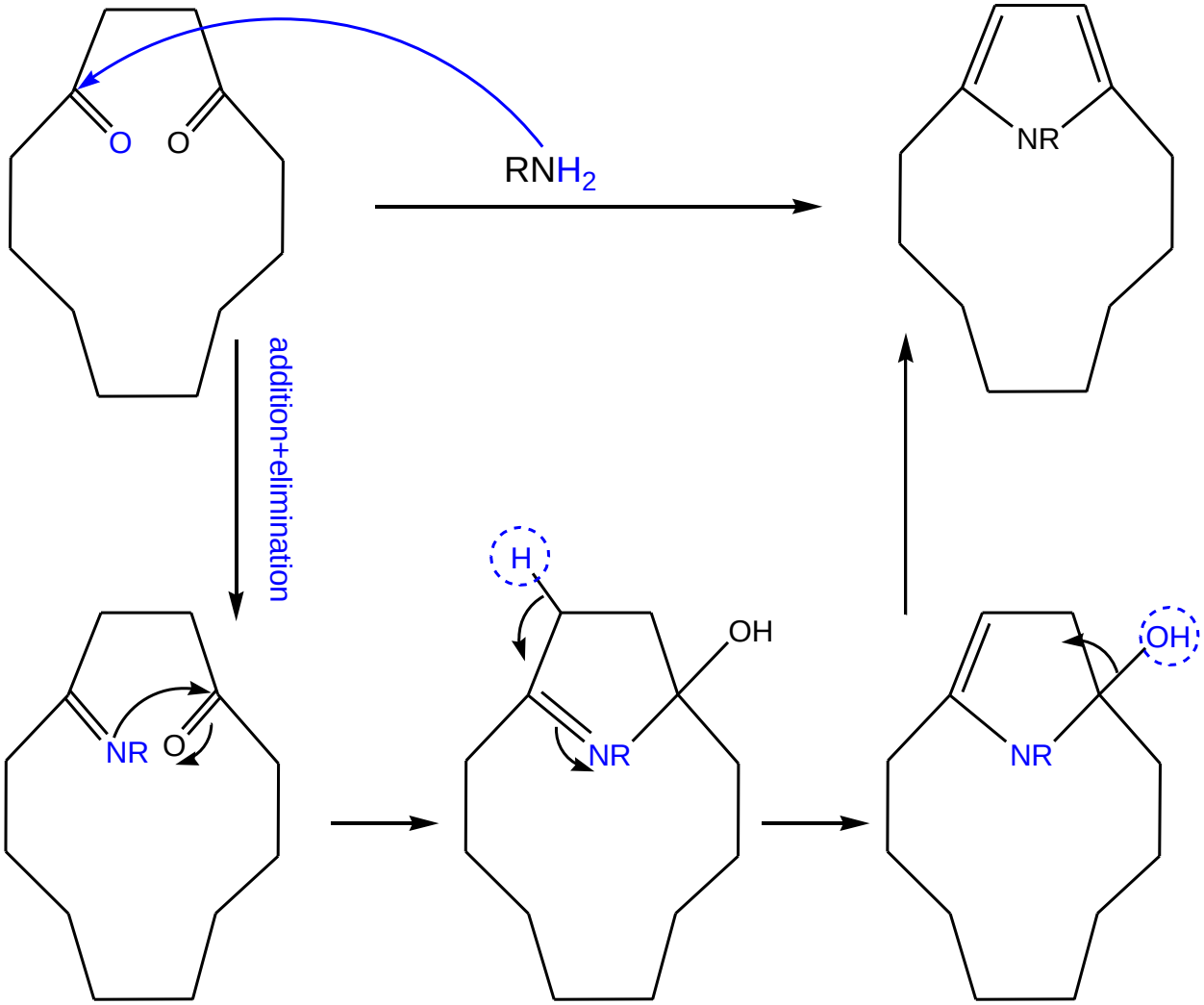
Pall-Knorr Synthesis of Furan



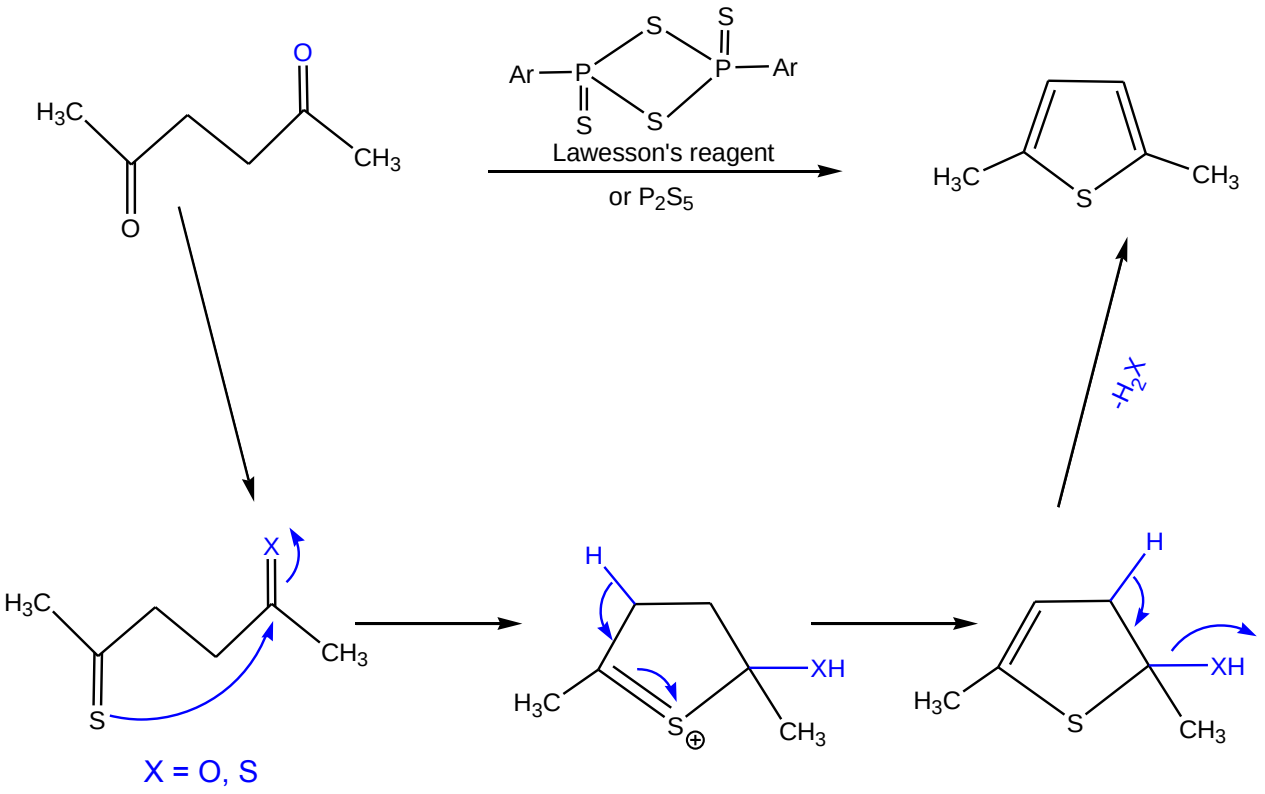
Pall-Knorr Synthesis of Pyrrole



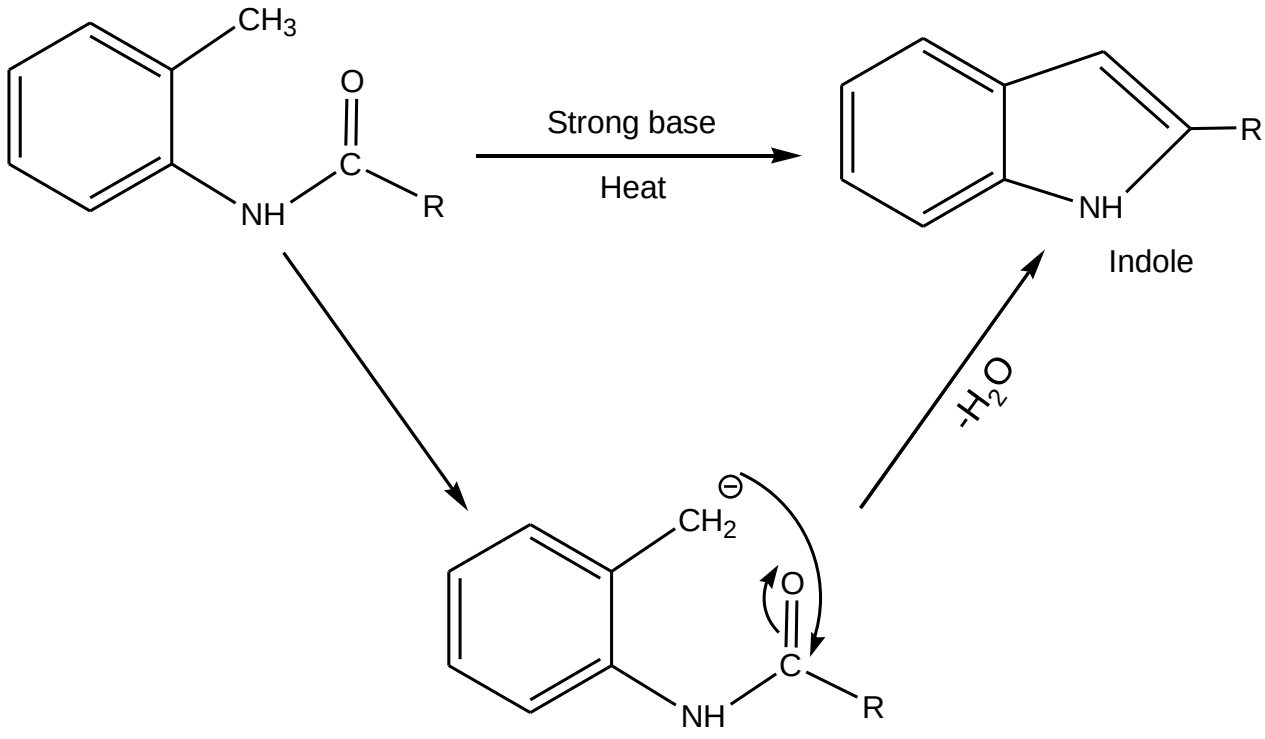
Another example of the synthesis of Pyrrole.



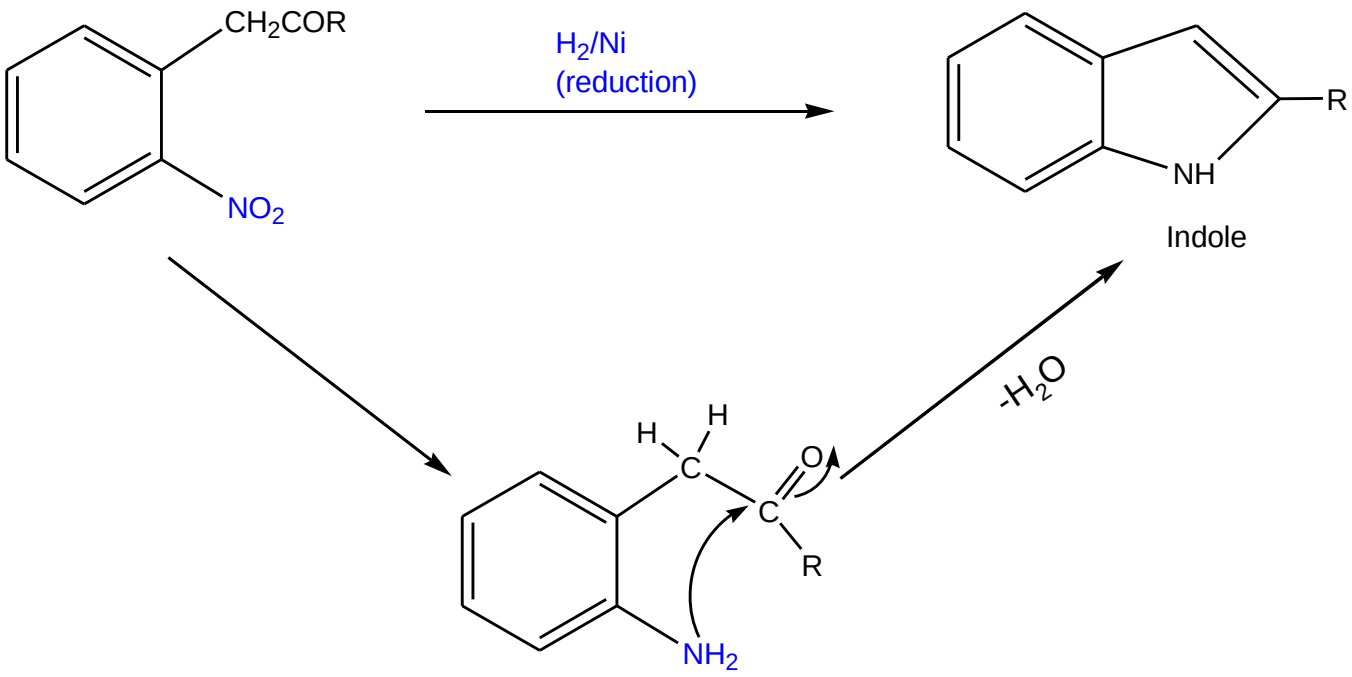
Pall-Knorr Synthesis of Thiophene



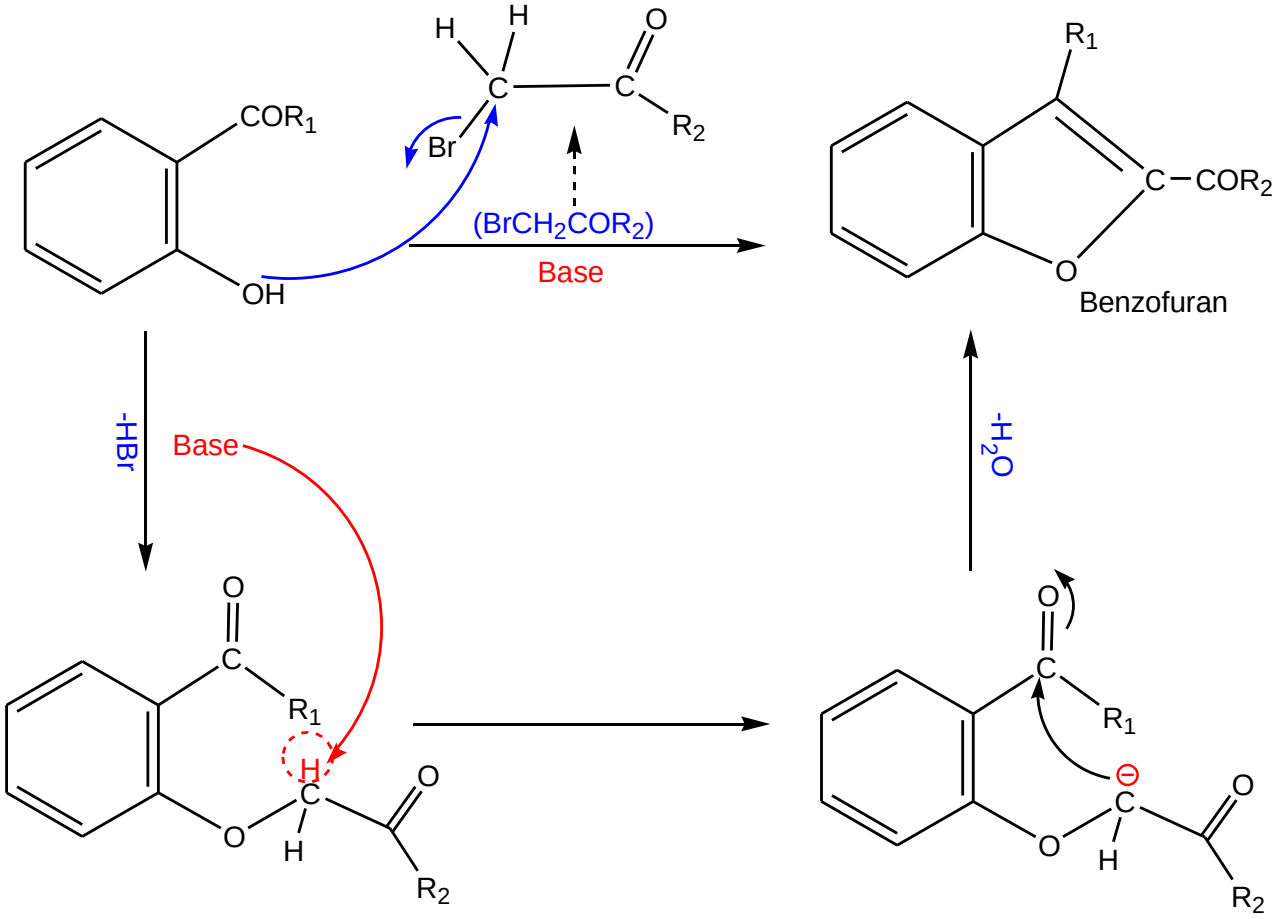
Synthesis of Indole



Another example of Indole synthesis

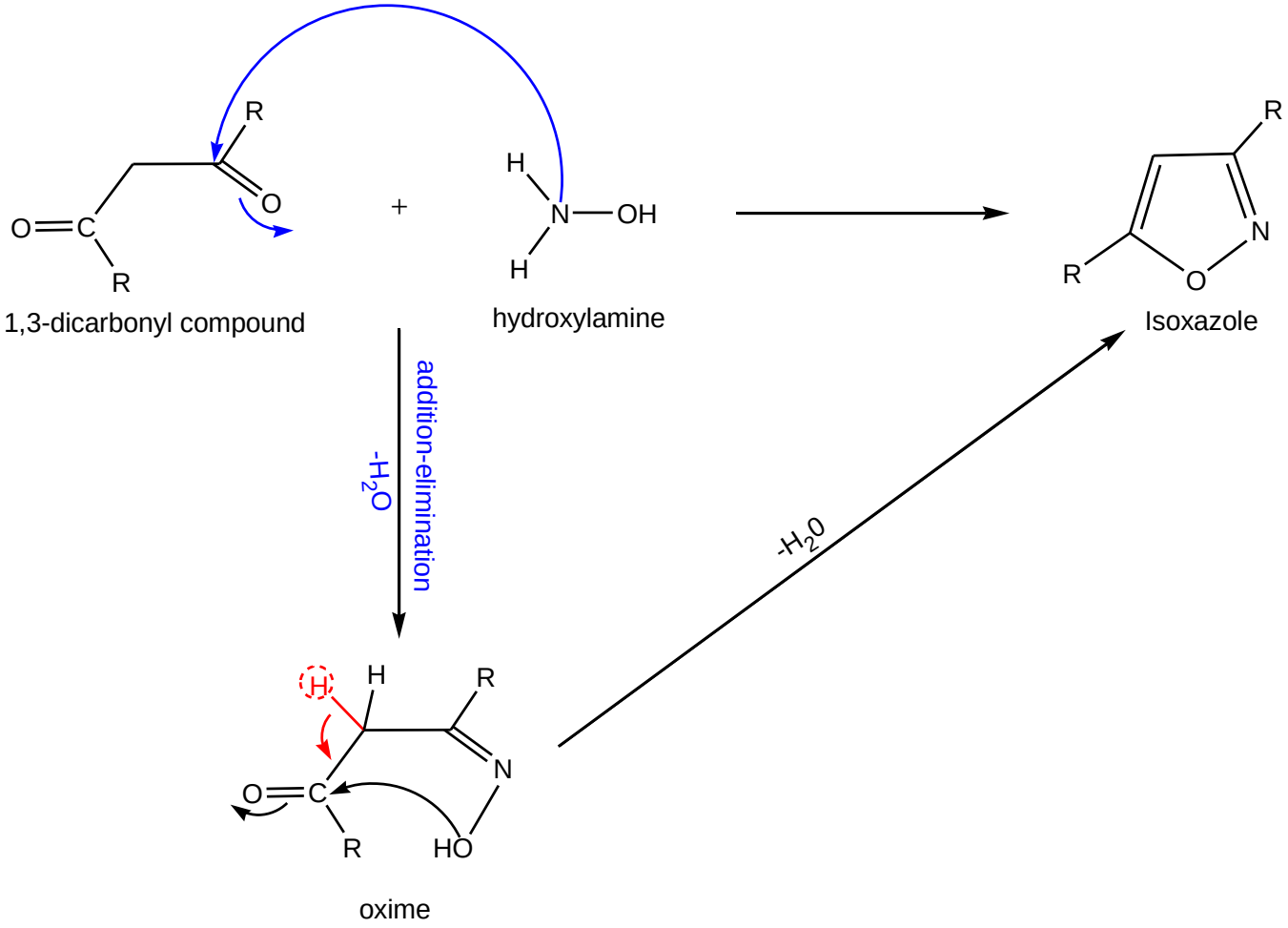


Synthesis of Benzofuran



Synthesis of Isoxazole

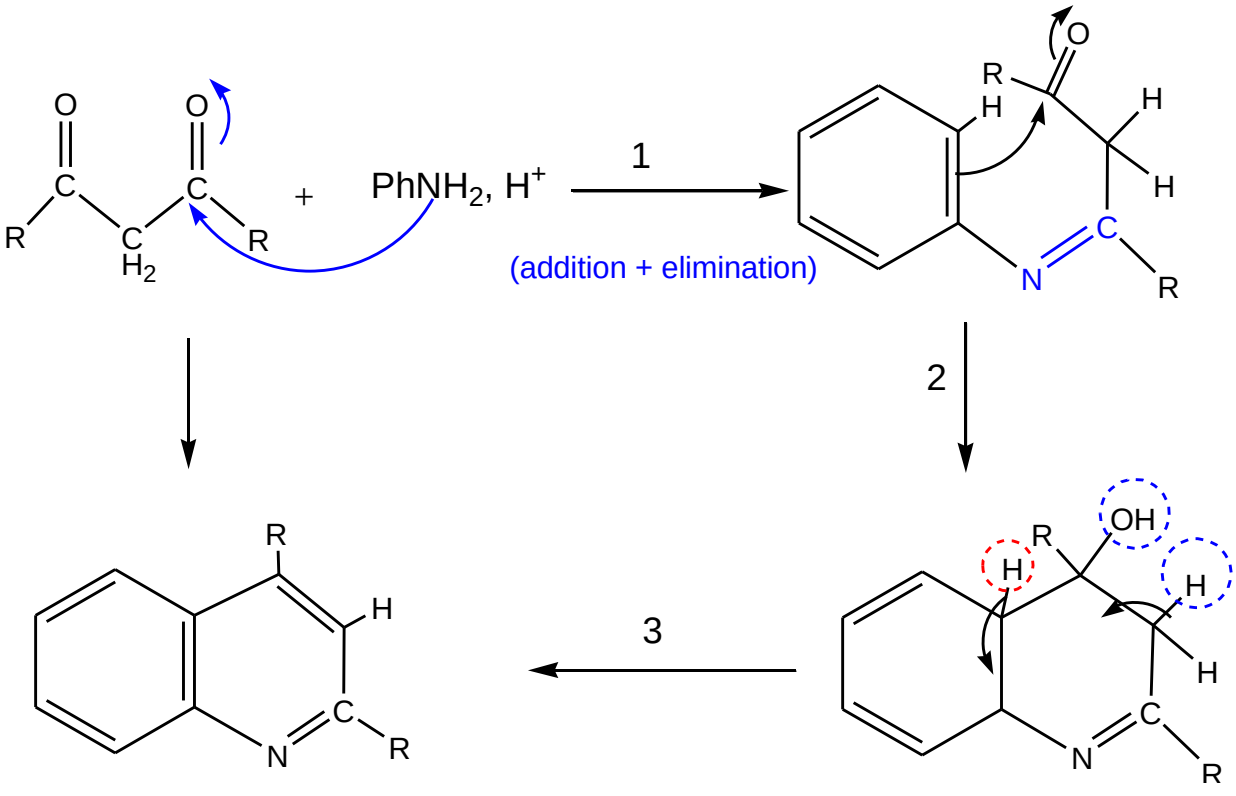
The synthesis of isoxazole from a 1,3-dicarbonyl compound and a hydroxylamine involves the reaction of the two compounds to form an oxime intermediate. Subsequently, cyclization and dehydration steps lead to the formation of the isoxazole ring.



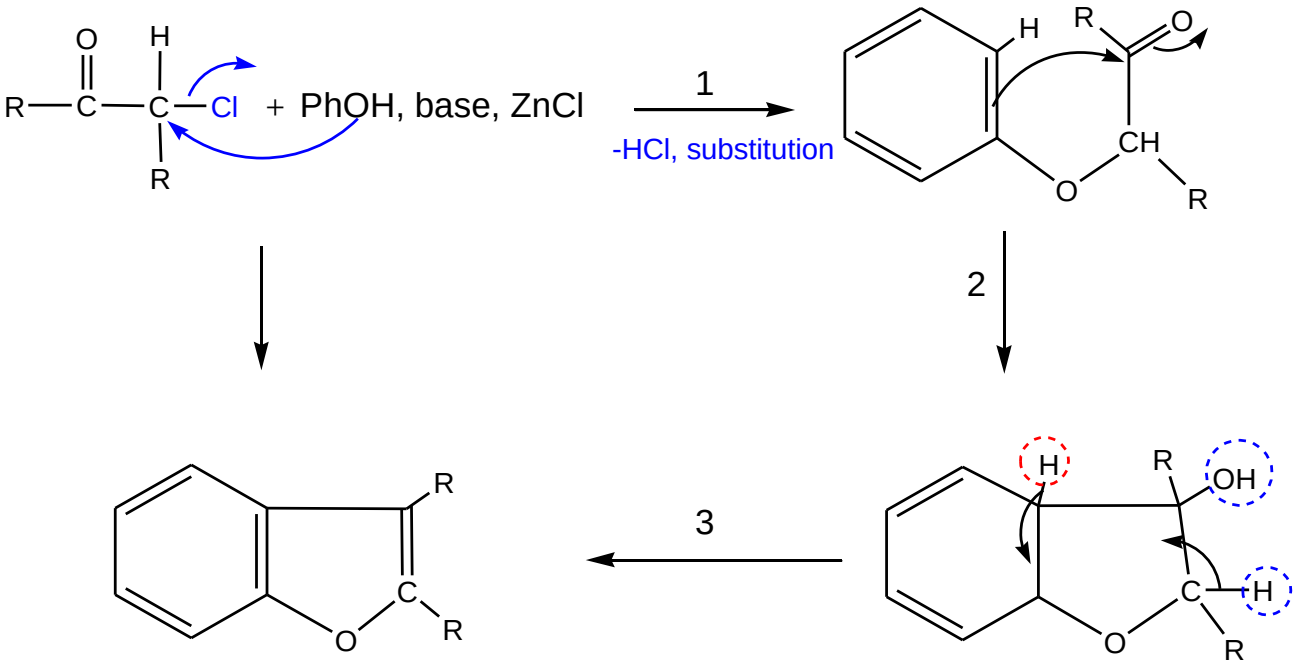
Ortho cyclization of benzene

Another type of cyclization, known as Ortho cyclization of benzene, leads to the formation of fused heterocyclic rings, where the ortho position of benzene acts as a nucleophile. The ortho cyclization of benzene can be achieved through different methods, and the choice of reaction conditions and reagents depends on the specific substrates and desired products.

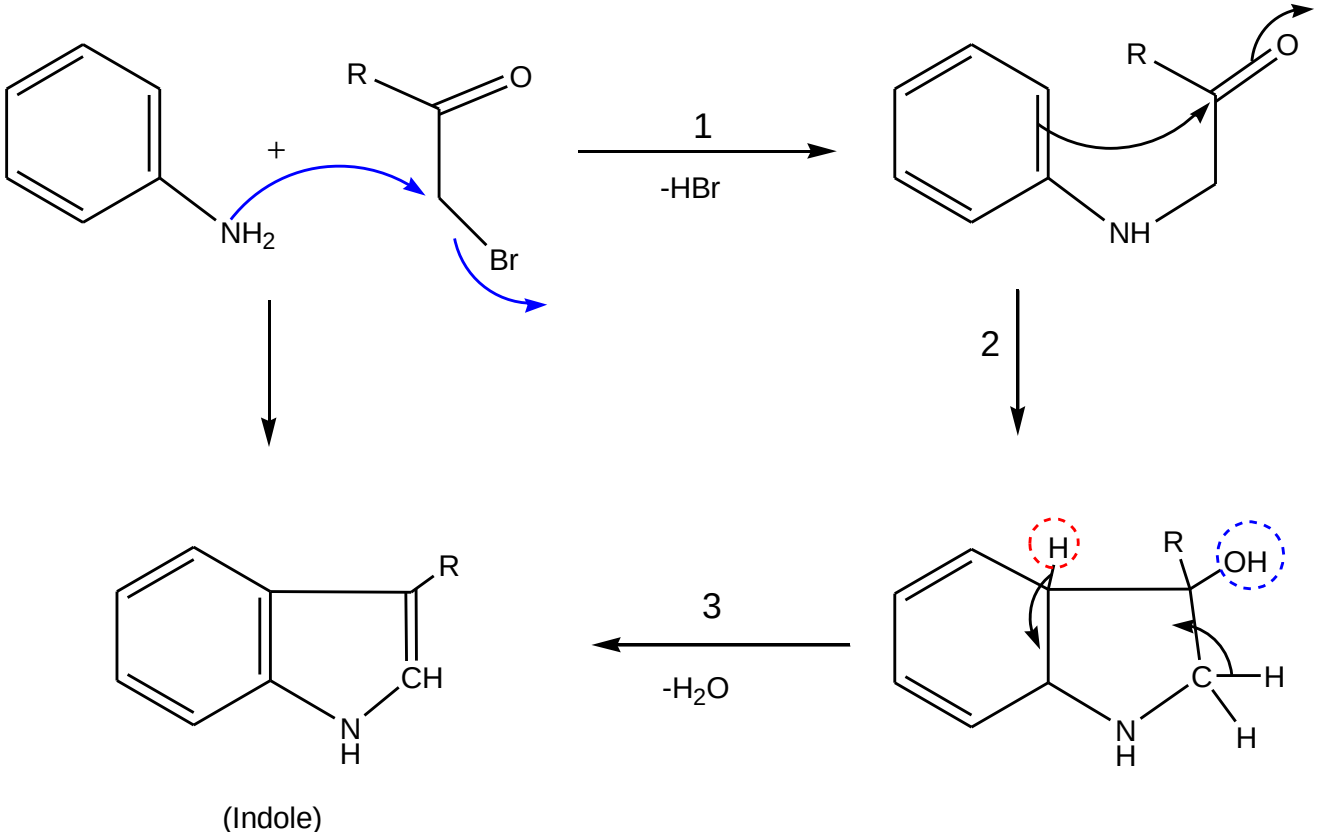
Example 1



Example 2

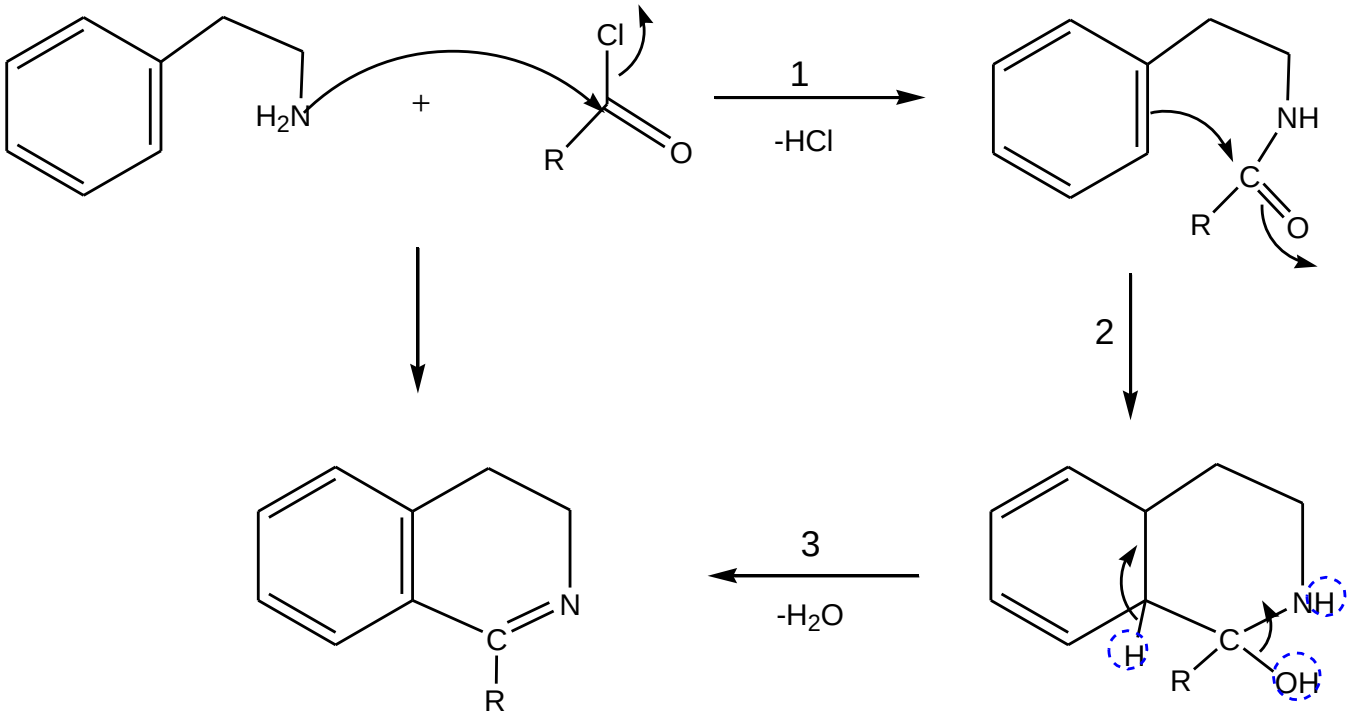


Example 3. Preparation of indole

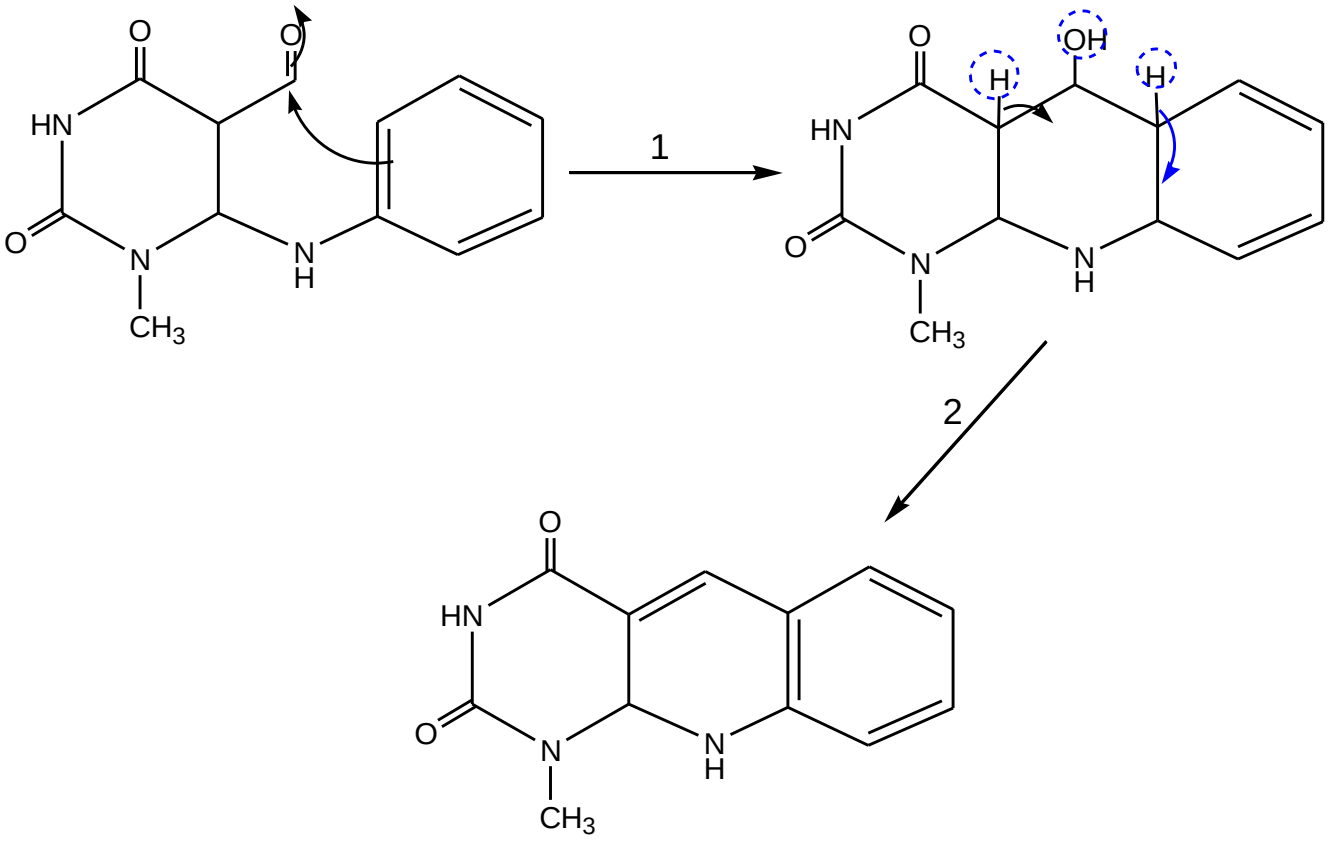


(Indole)

Example 4

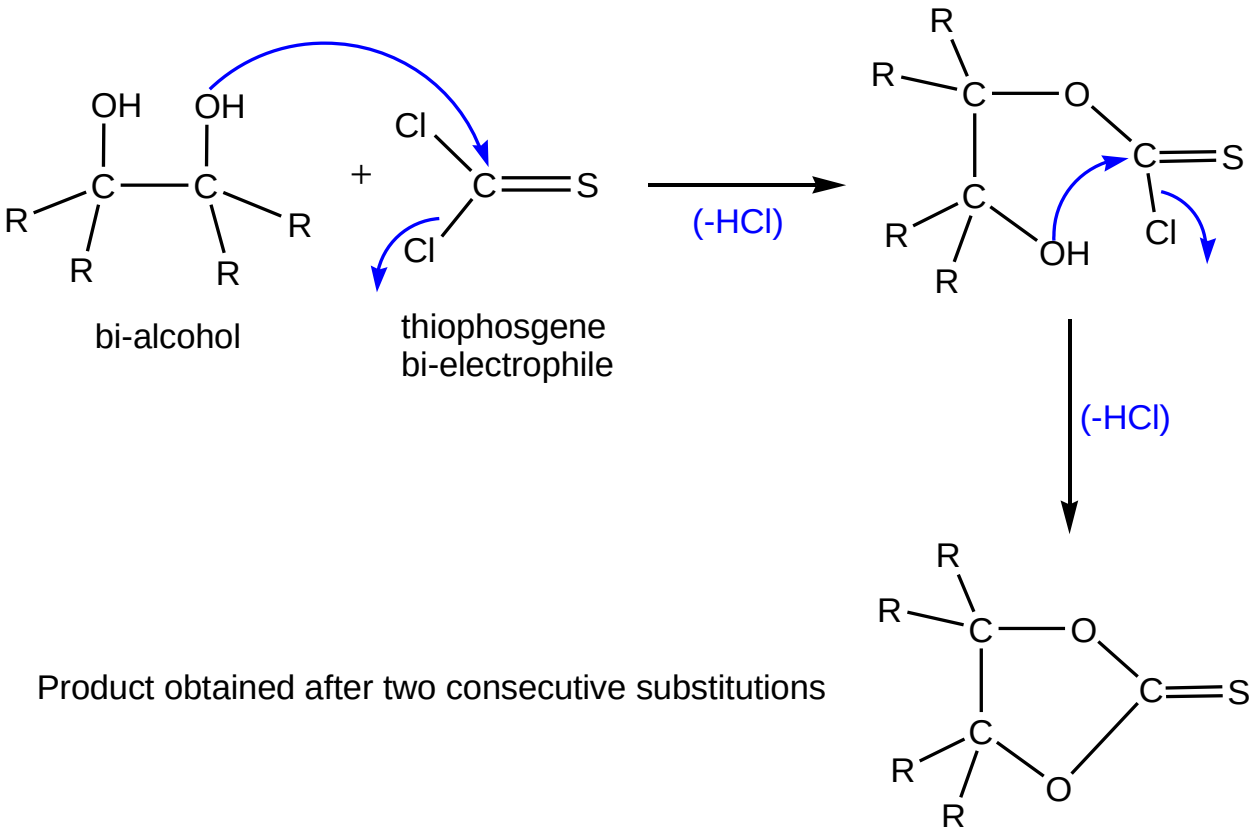


Example 5

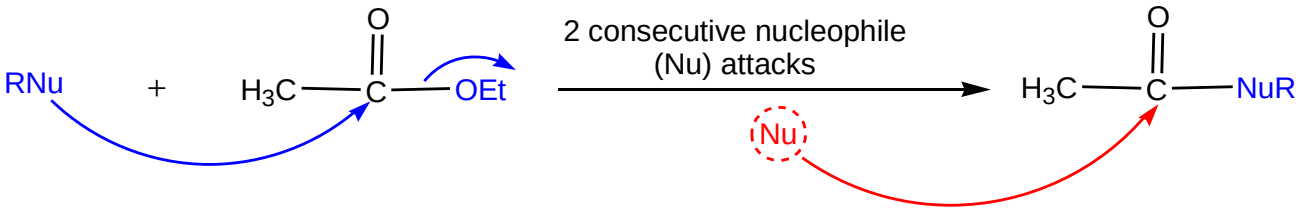


Cyclization with other double bonds (C=S, C=N, C=C)

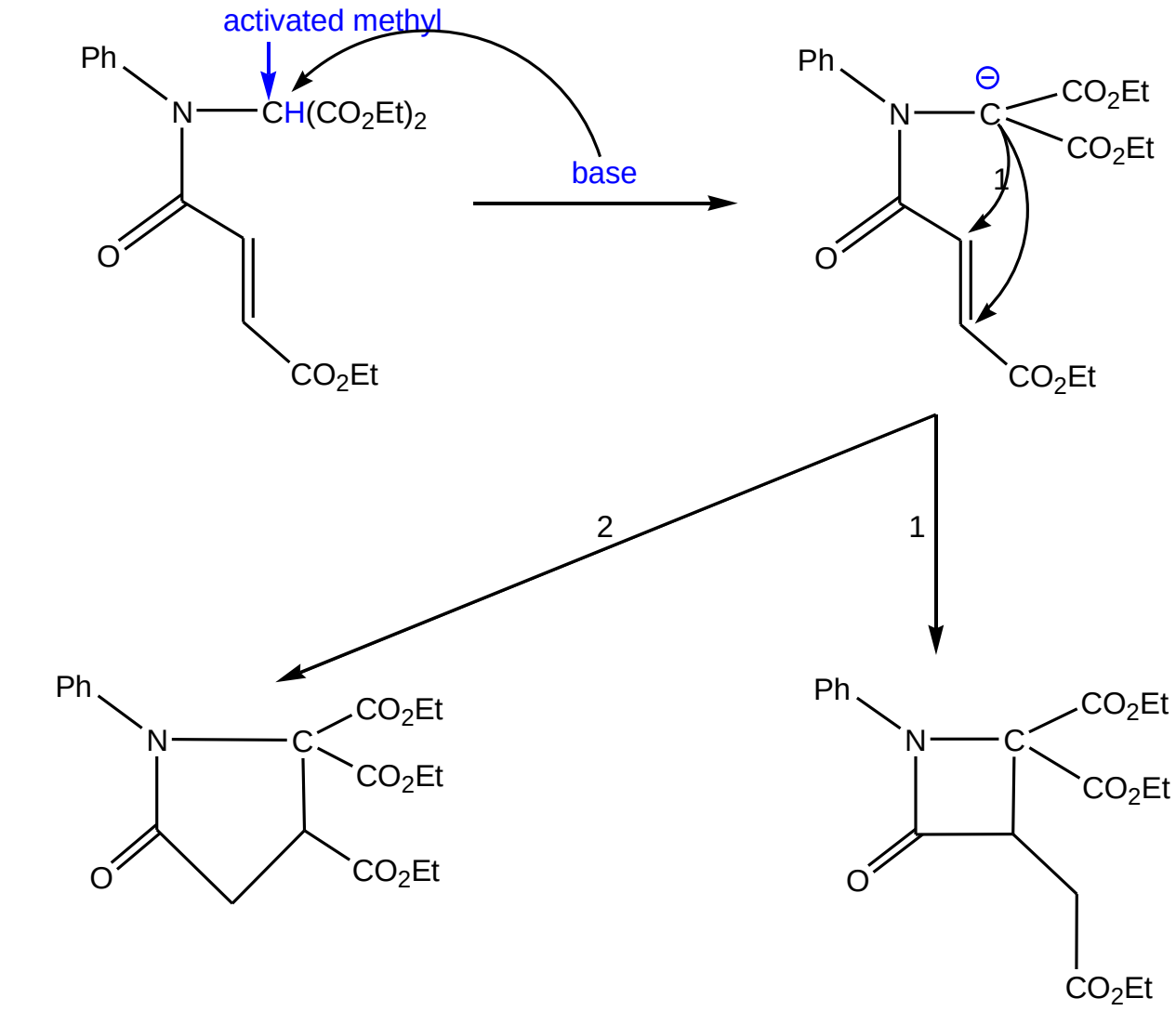
Cyclization on the (C=S) bond



This example illustrates a cyclization reaction between a bi-alcohol compound and thio-phosgene '$Cl_2C=S$,' which resembles phosgene '$Cl_2C=O$,' a highly toxic gas used in chemical warfare. Phosgene and thio-phosgene are considered bi-electrophiles. Aldehydes, ketones, esters, and other compounds can also be used as bi-electrophiles.



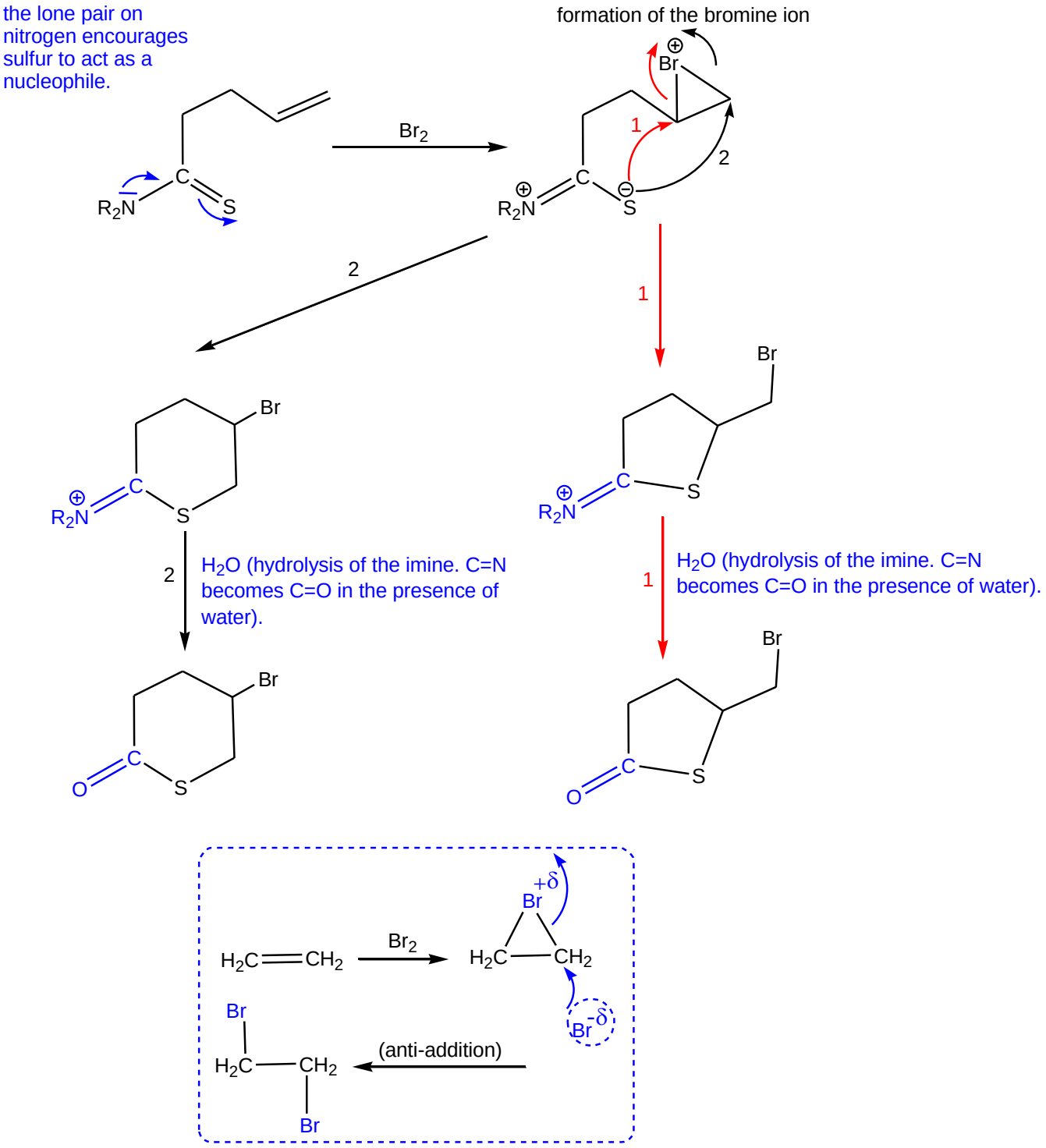
Cyclization on the (C=C) bond



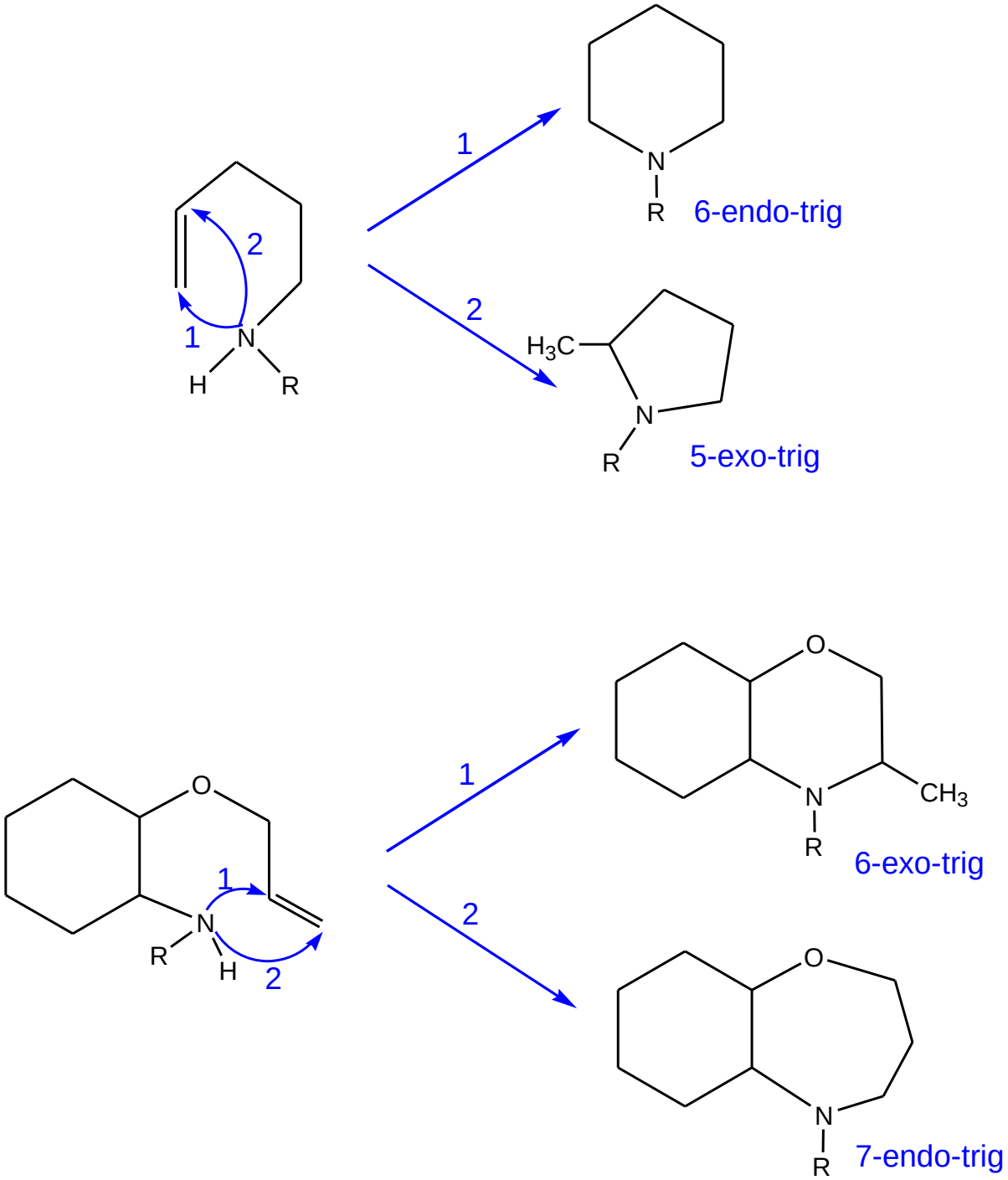
endo-cyclization
thermodynamic product (the most stable)

exo-cyclization
kinetic product

Cyclization on the (C=C) bond in the presence of Br_2



Cyclization on the (C=C) bond



Experimentally, to verify which of the two compounds, 6-exo-trig or 7-endo-trig, has been formed, one must conduct analyses such as proton NMR or infrared spectroscopy (IR). If 6-exo-trig is obtained, the IR spectrum should show a characteristic vibration at around 1380 cm-1 indicative of the CH_3 group.

Cyclization on the triple Bond: Attack on the sp Carbon (digonal)

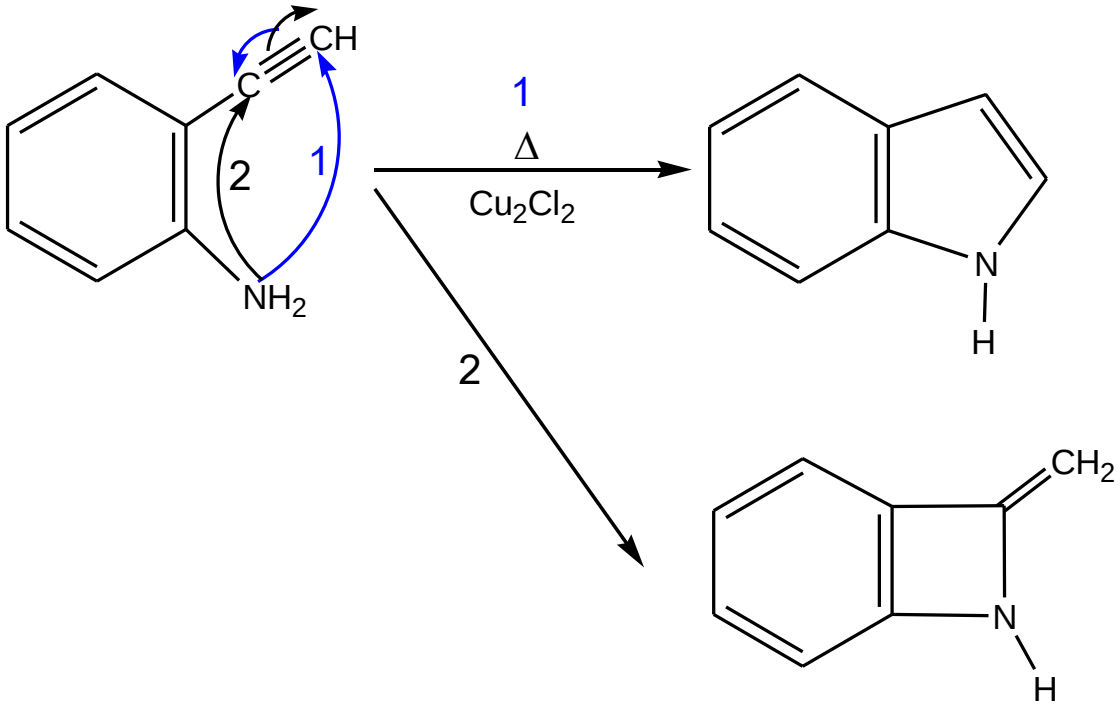
Cyclization on the triple bond occurs in two types: endo and exo. The most well-known triple bonds in the literature are:

1. Nitrile (R-C≡N): In this case, the nucleophile attacks the carbon of the nitrile, leading to an "exo" cyclization.
2. Isocyanide (R-$N^{\delta+}$≡$C^{\delta-}$): In this case, the nucleophile attacks the carbon of the isocyanide, leading to an "endo" cyclization.
3. Acetylide (R-C≡C): In this case, the nucleophile attacks both carbons of the triple bond, leading to both "exo" and "endo" cyclizations.

Cyclization on the triple bond (C≡C)

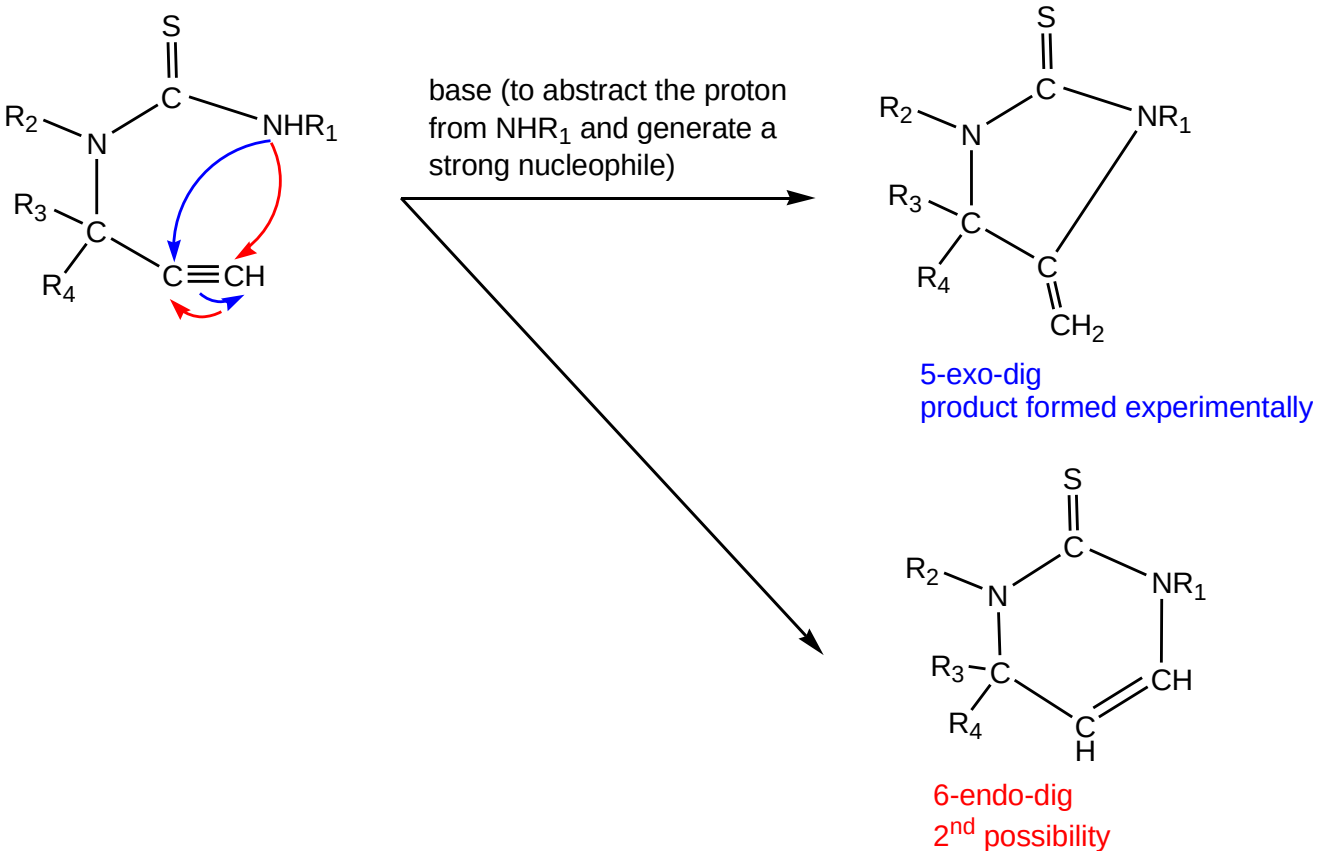
Example 1

In this example, the experimentally obtained product is icndeed indole. However, theoretically, one would expect two products based on the two possible nucleophilic attack positions on the triple bond, as mentioned below.

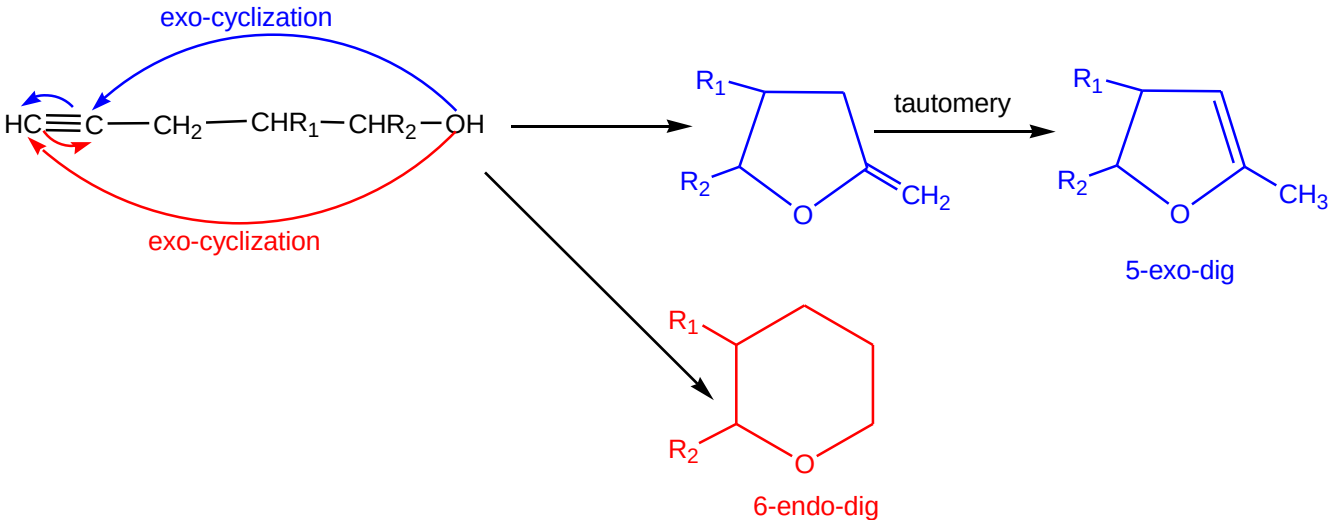


Example 2

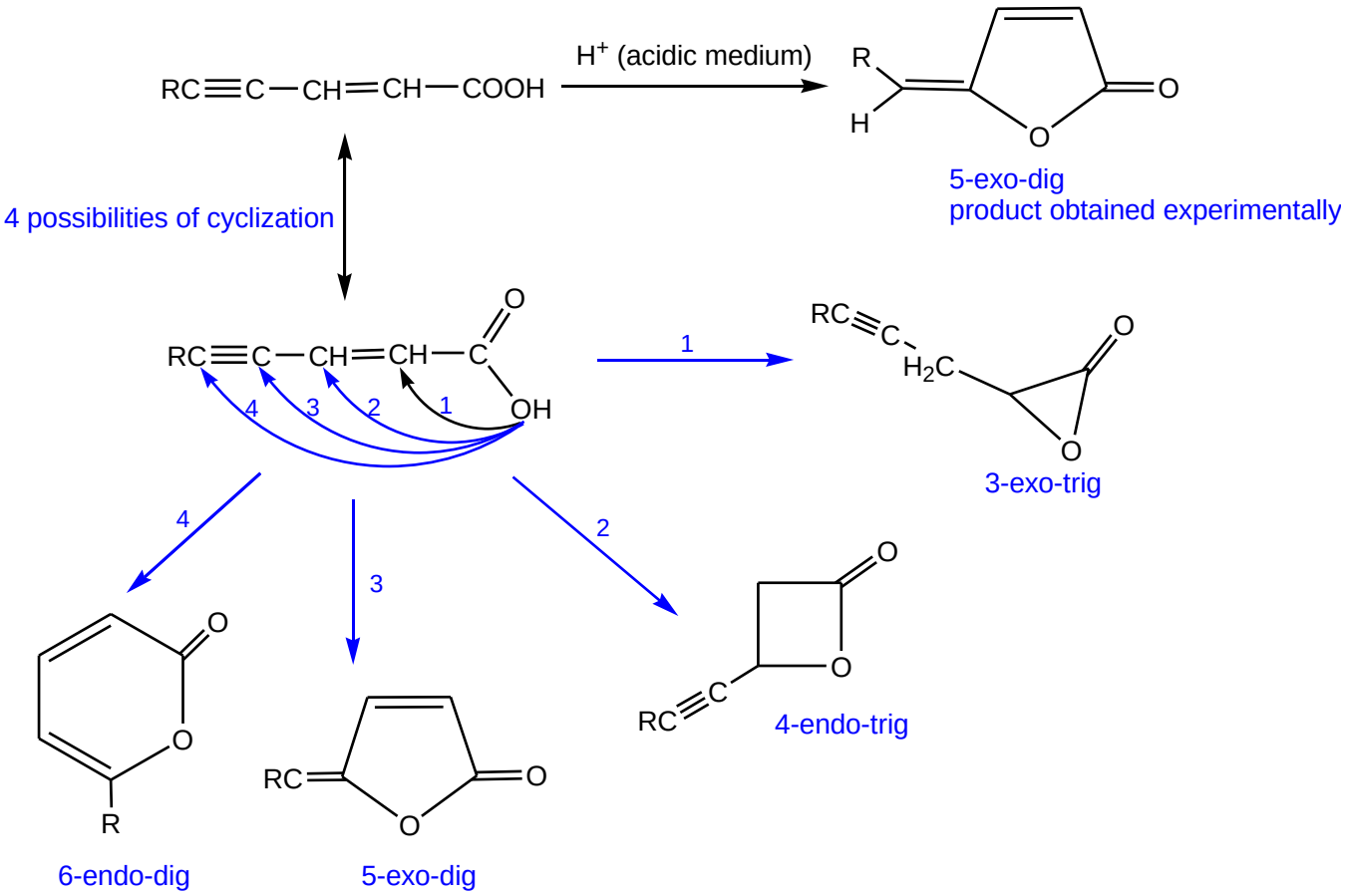
In this example, the experimentally formed product is a 5-membered ring resulting from an "exo" cyclization. It's worth noting that before the experiment, one would anticipate the formation of two products, "exo" and "endo," as illustrated in the diagram below.



Example 3



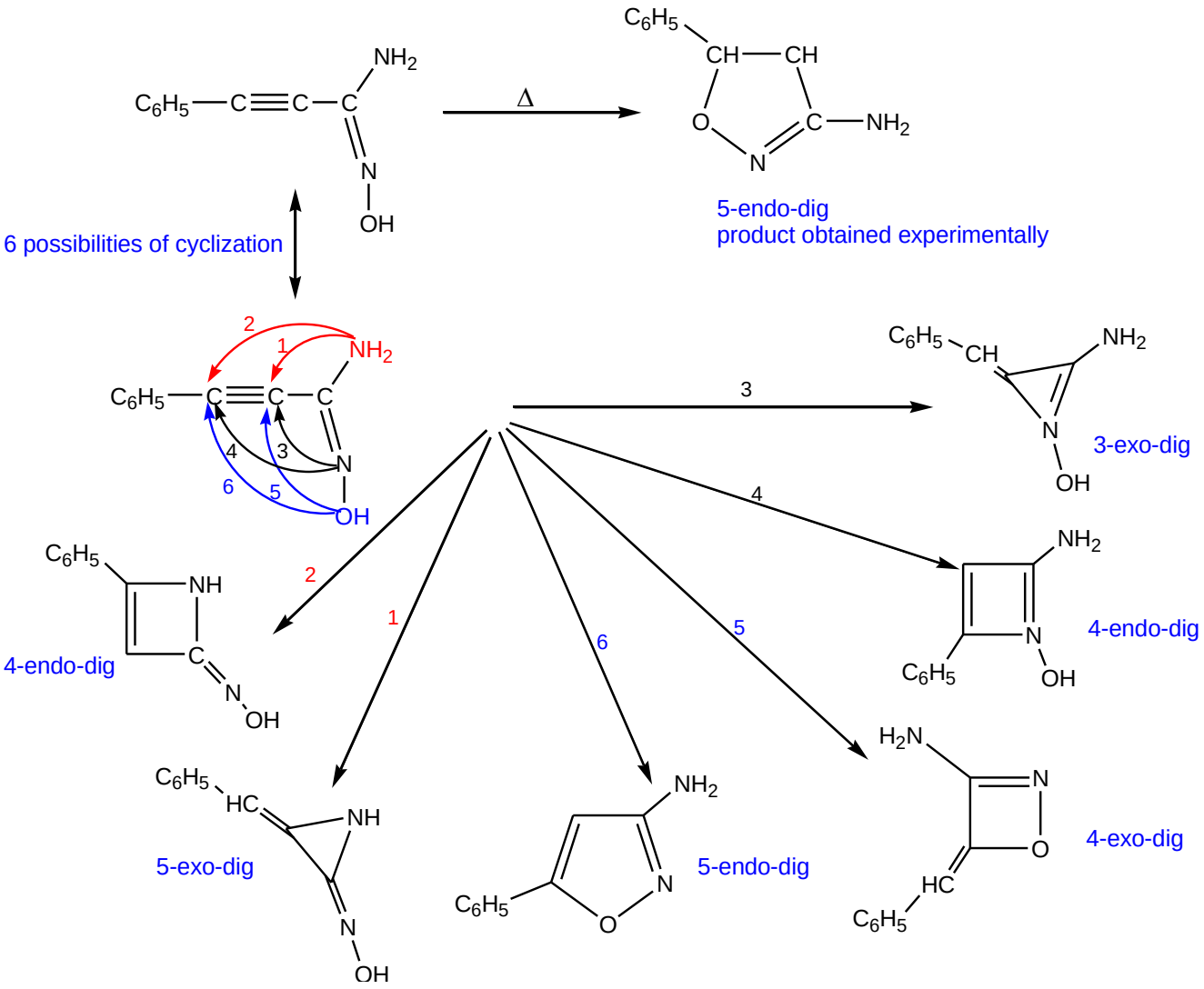
Example 4



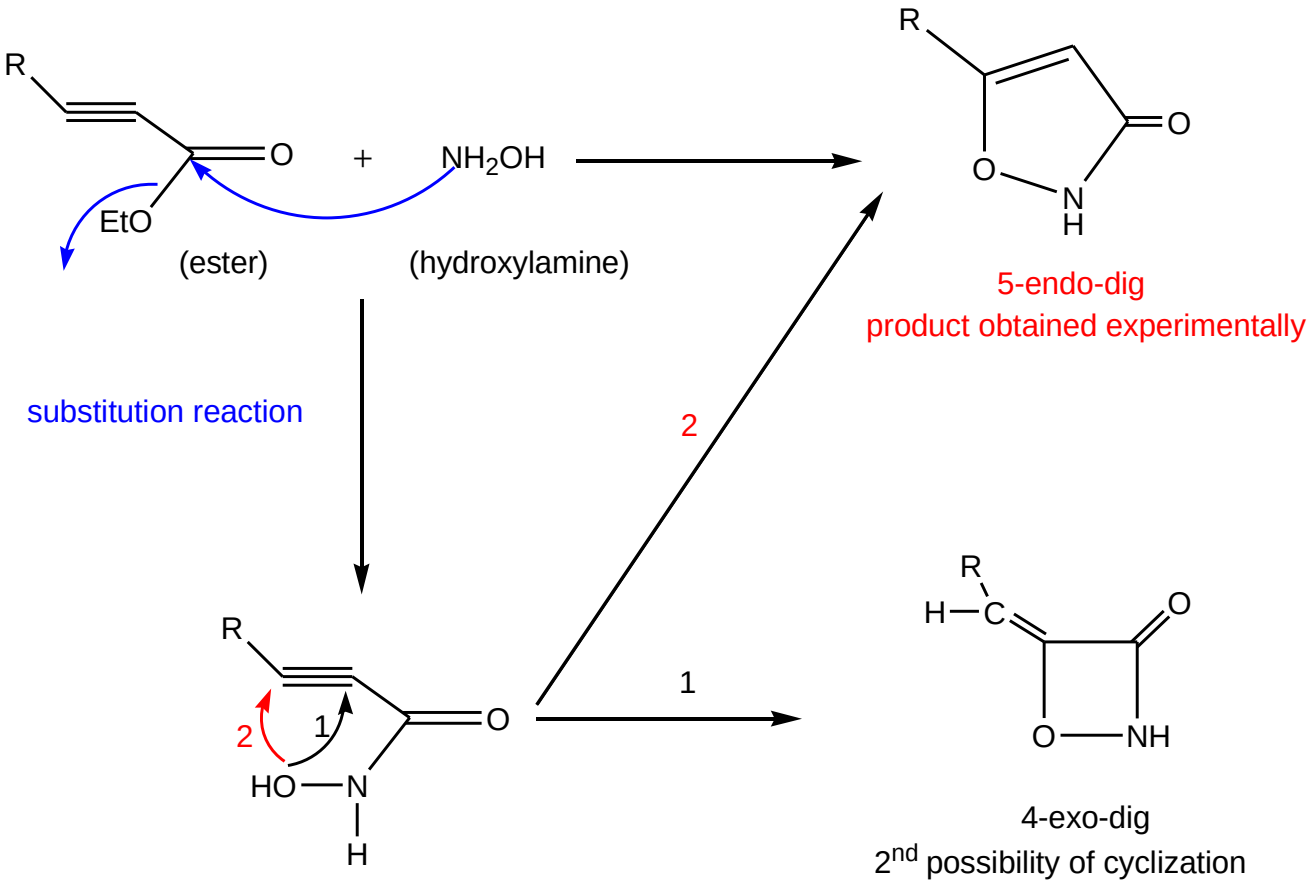
Example 5

In this example, we have several nucleophiles (NR, NH_2, and OH), leading to multiple cyclization possibilities. NH is a stronger nucleophile than NH_2, and NH2 is stronger than NR, suggesting that cyclization through the attack

of the nucleophile NR (reactions 3 and 4) is less favored than the cyclization through the attack of OH (reactions 5 and 6) or NH_2 (reactions 1 and 2).

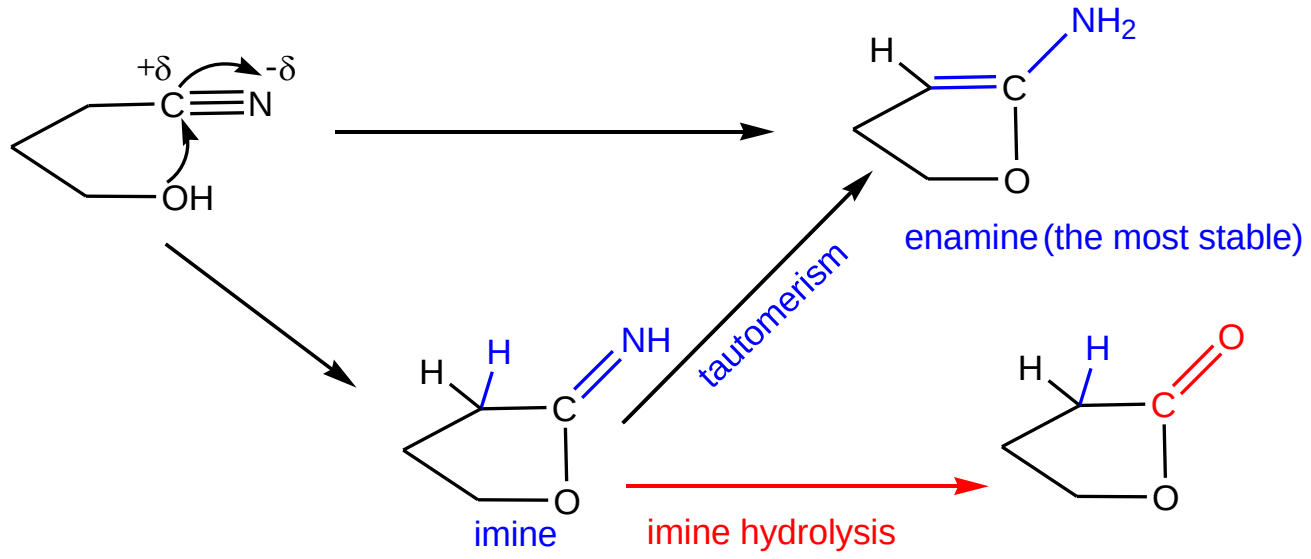


Example 6



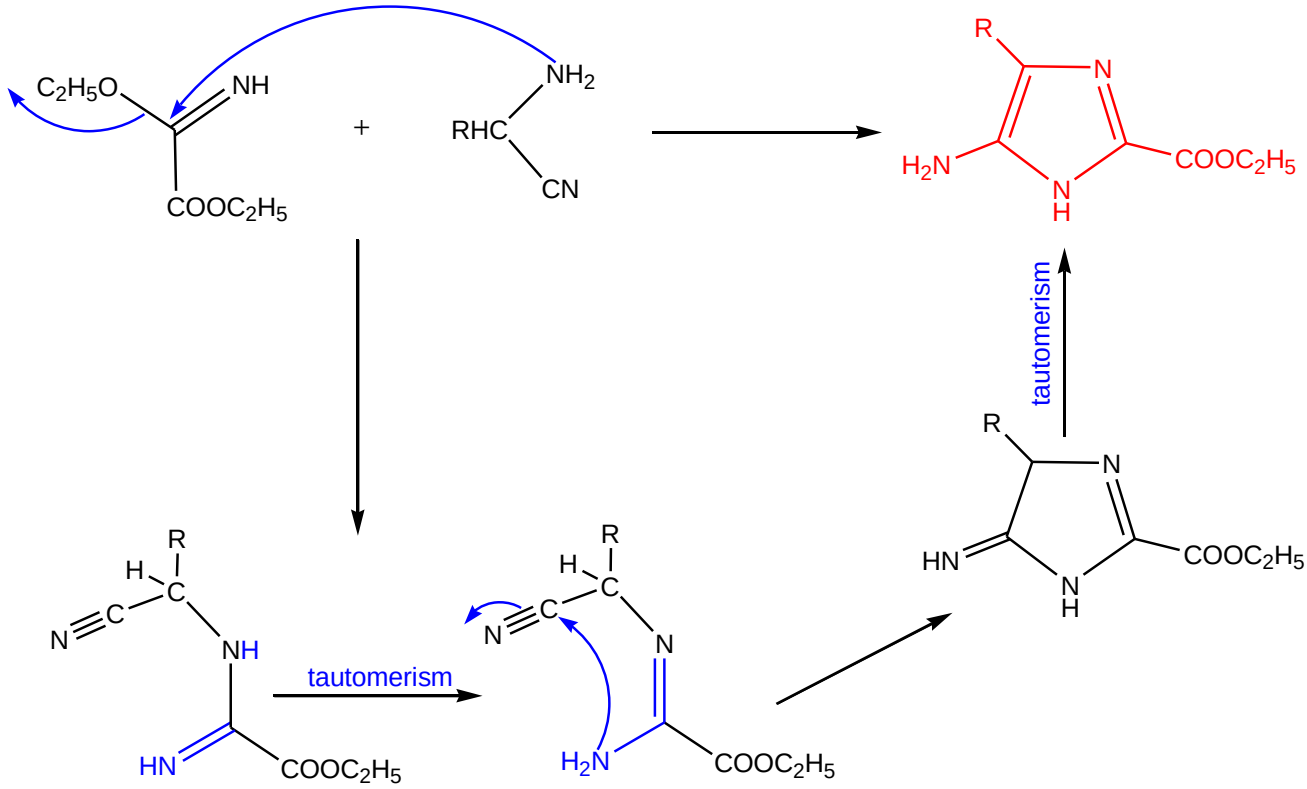
Cyclization on the nitrile (C≡N) bond

Example 1

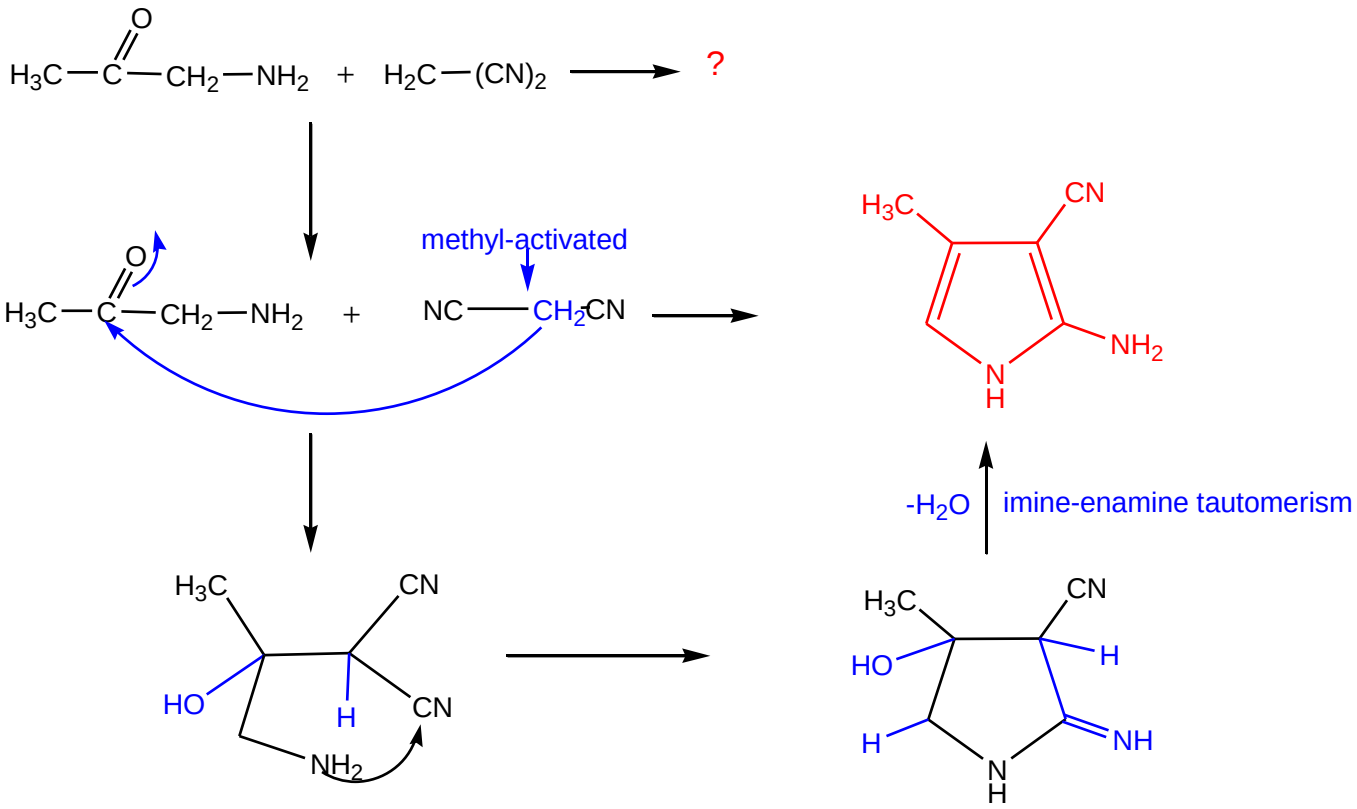


In this example, the carbon of the (C≡N) bond is more electropositive compared to nitrogen, so the nucleophile attacks the more electrophilic center (carbon), resulting in an exo-cyclization, forming the enamine (the most stable form of imine, unlike the keto-enol tautomerism where the keto form is the most stable), as shown in the diagram below. It is noteworthy that in some cases, the reaction stops at the imine (no tautomerism). In such cases, the C=NH group is converted to C=O through imine hydrolysis.

Example 2

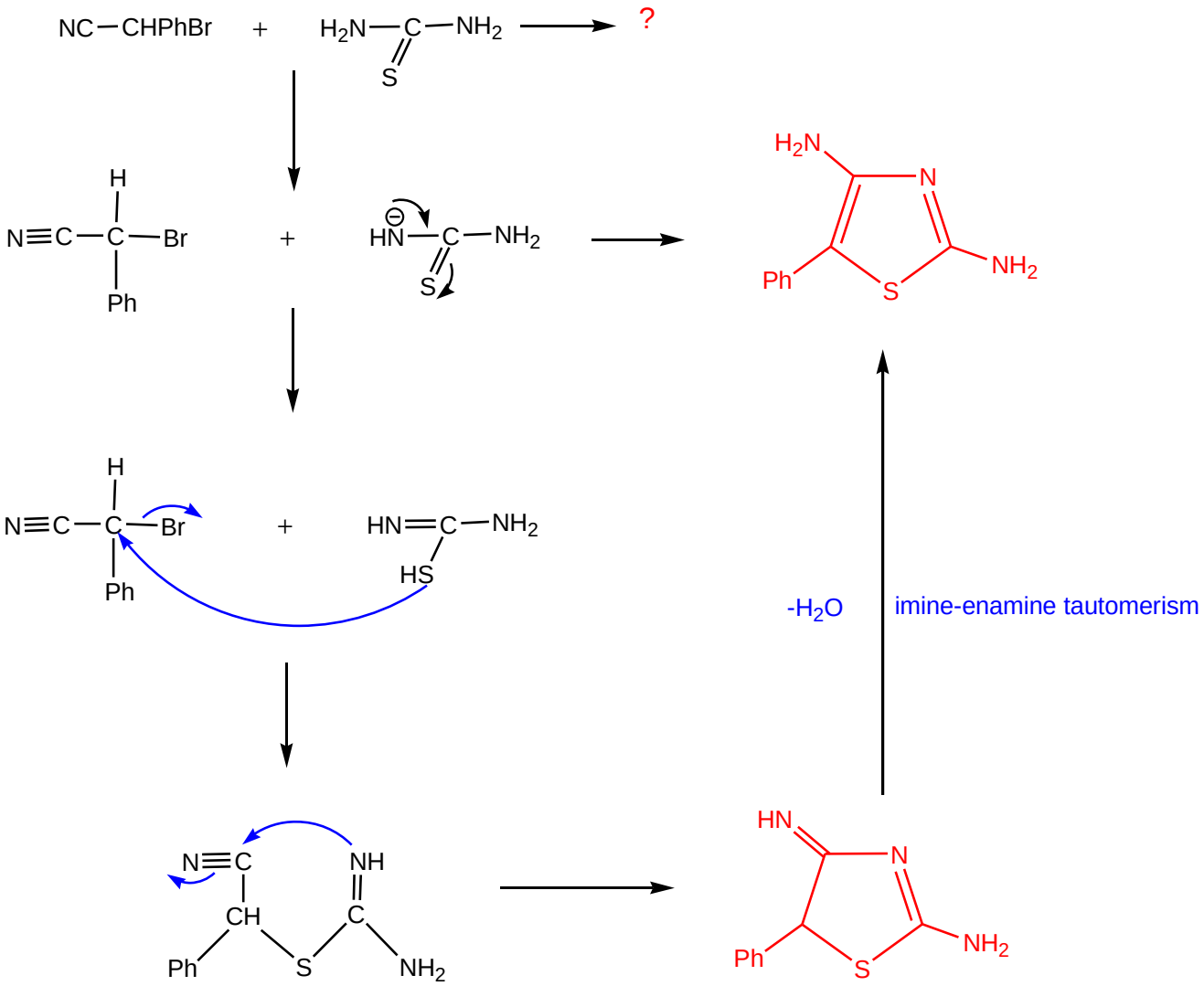


Example 3

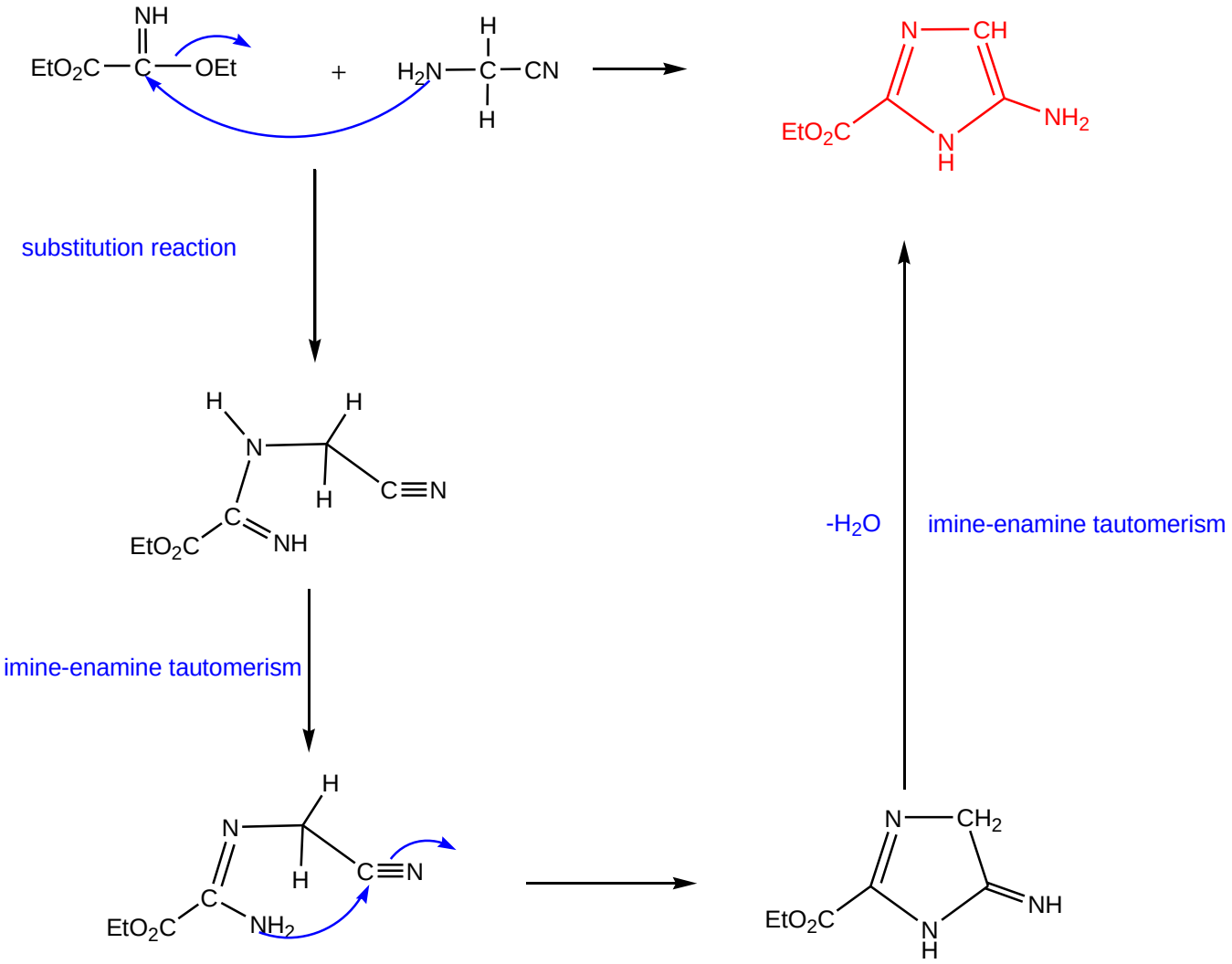


Example 4

In this example, nitrogen acts as a nucleophile, and sulfur is a stronger nucleophile than nitrogen due to its larger size and greater polarizability, enhancing its nucleophilic character. Therefore, sulfur tends to be the attacking species when both sulfur and nitrogen are present simultaneously particularly in reactions with soft electrophiles.


NC—CHPhBr
+
H2N—C—NH2
S
?
H
N≡C—C—Br
Ph
+
HN—C—NH2
S
H2N
N
Ph
S
NH2
H
N≡C—C—Br
Ph
+
HN=C—NH2
HS
-H2O
imine-enamine tautomerism
N≡C
NH
CH
C
Ph
S
NH2
HN
N
Ph
S
NH2

Example 5



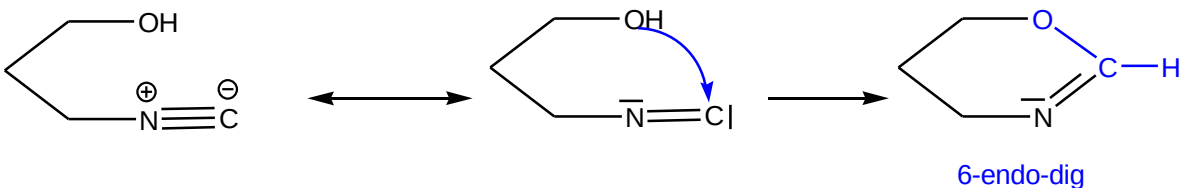
Cyclization on the isonitrile bond (R-N≡C)

The two resonance structures of the isonitrile bond are:

Cyclization on the isonitrile bond always occurs on the carbon, leading the reaction to endo-cyclization.

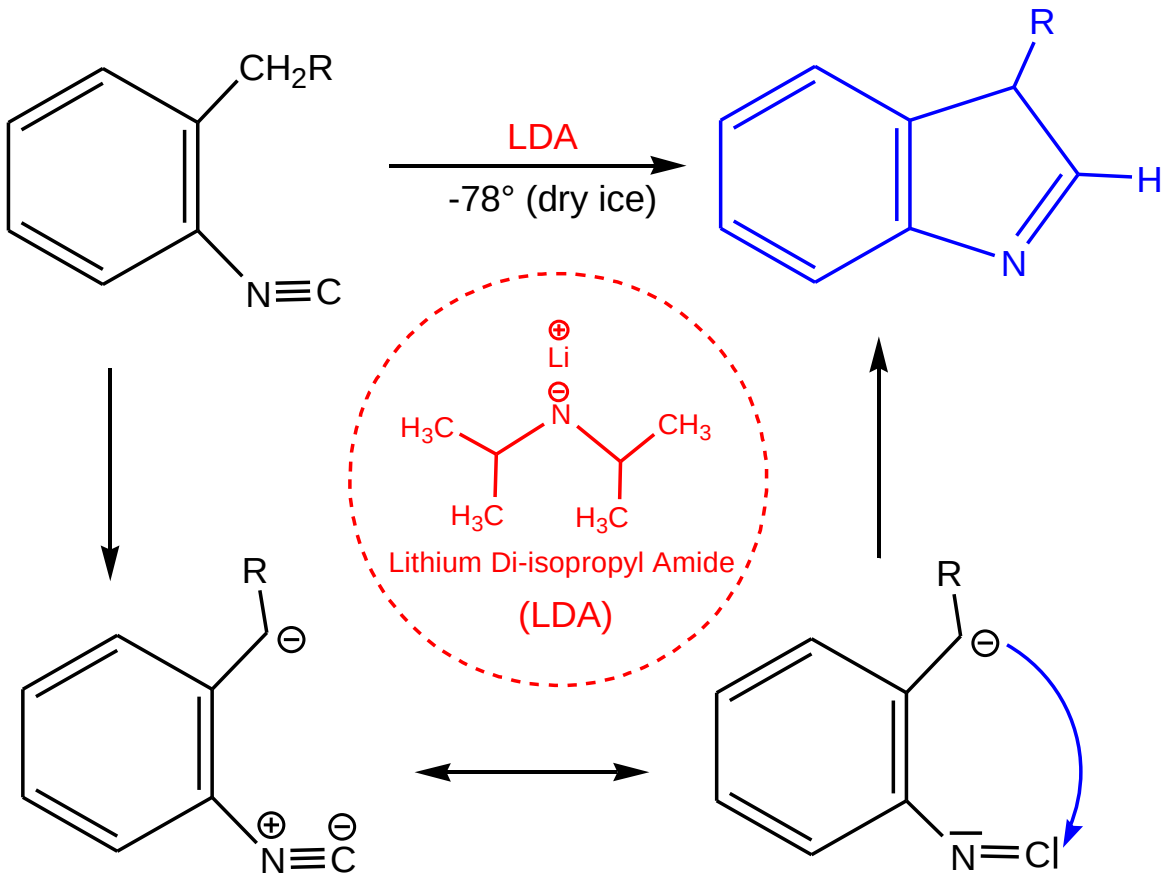
Example 1

In this example, the nucleophile (OH) attacks the carbon to form the 6-endo dig heterocycle. The lone pair of the carbon captures the proton from the nucleophile (OH) and forms the C-H bond (see diagram below).

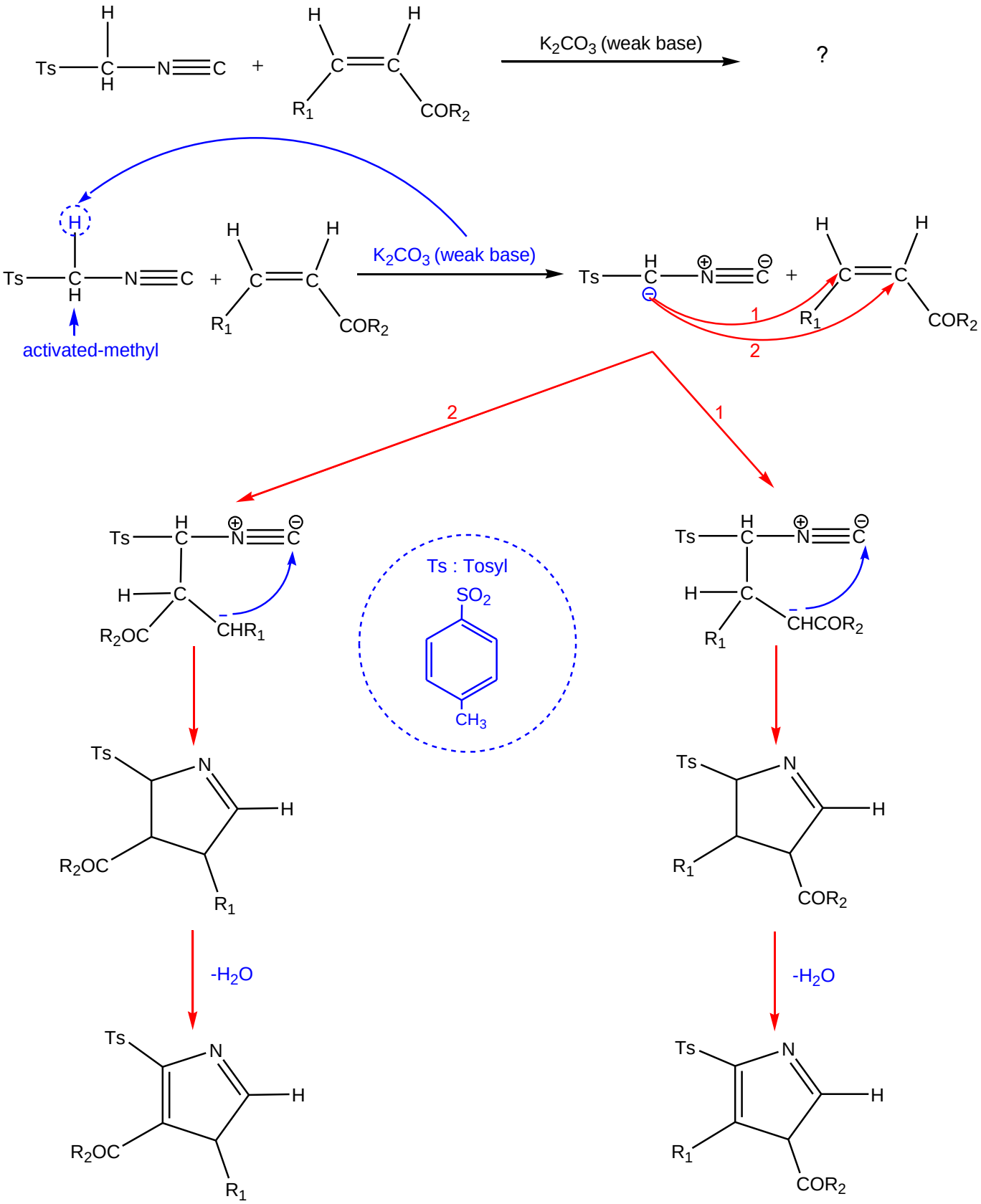


Example 2

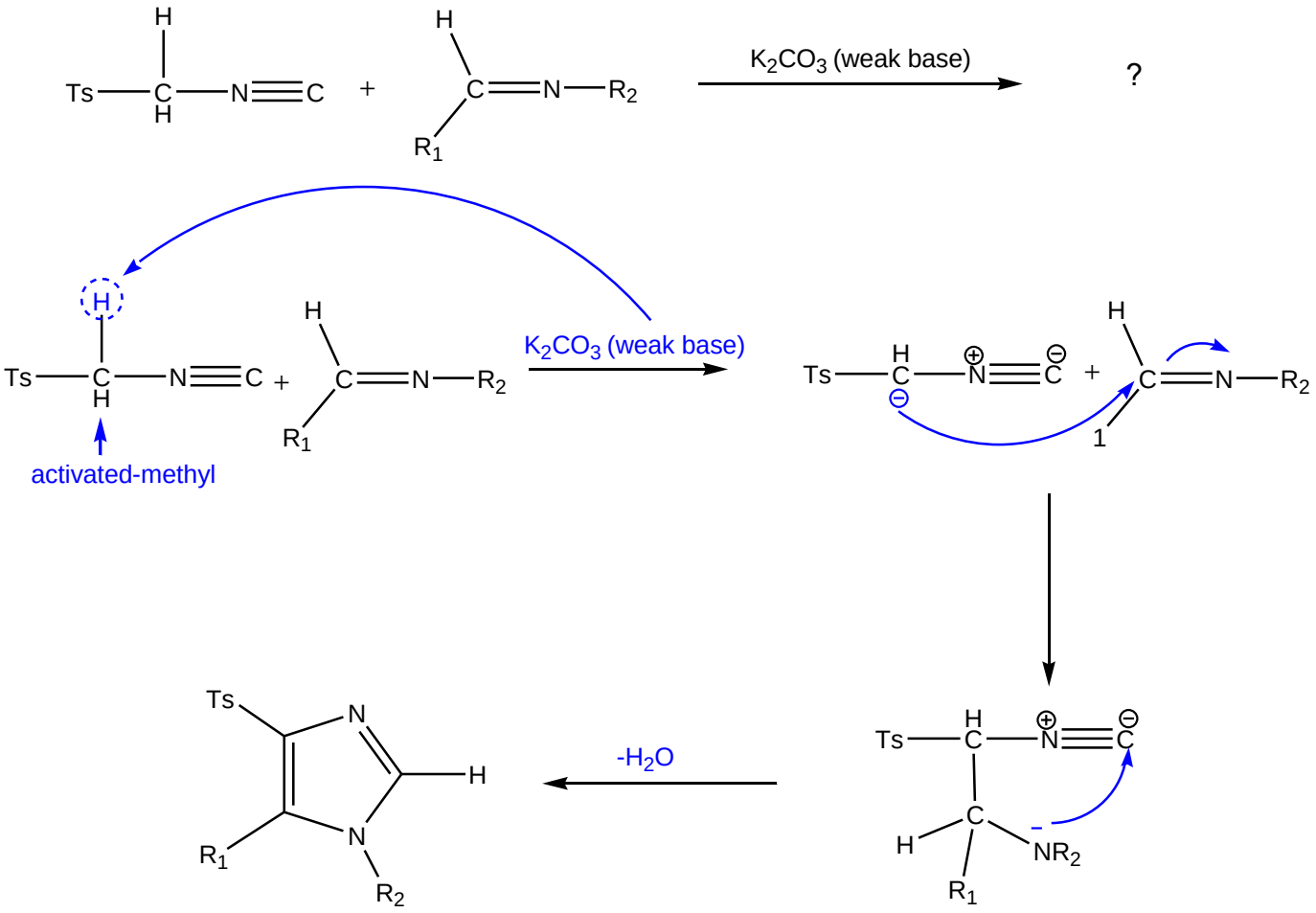
In this example, the methyl group is not very well activated, which is why a strong base (LDA) was used.



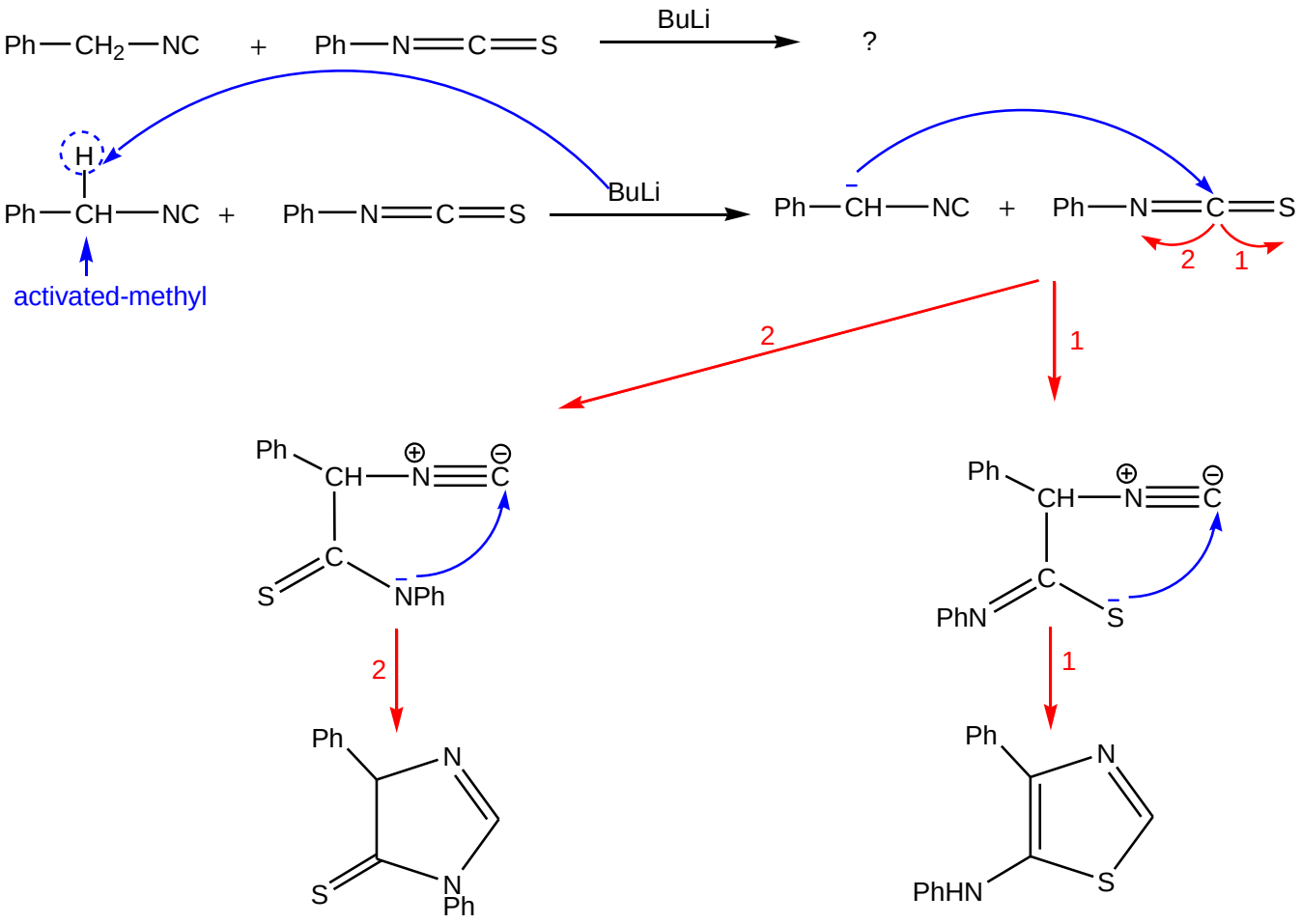
Example 3


K2CO3 (weak base)
?
activated-methyl
K2CO3 (weak base)
1
2
2
1
Ts : Tosyl
-H2O
-H2O

Example 4


Ts
C
H
N
C
+
C
N
R2
R1
K2CO3 (weak base)
?
activated-methyl
K2CO3 (weak base)
1
-H2O
NR2

Example 5

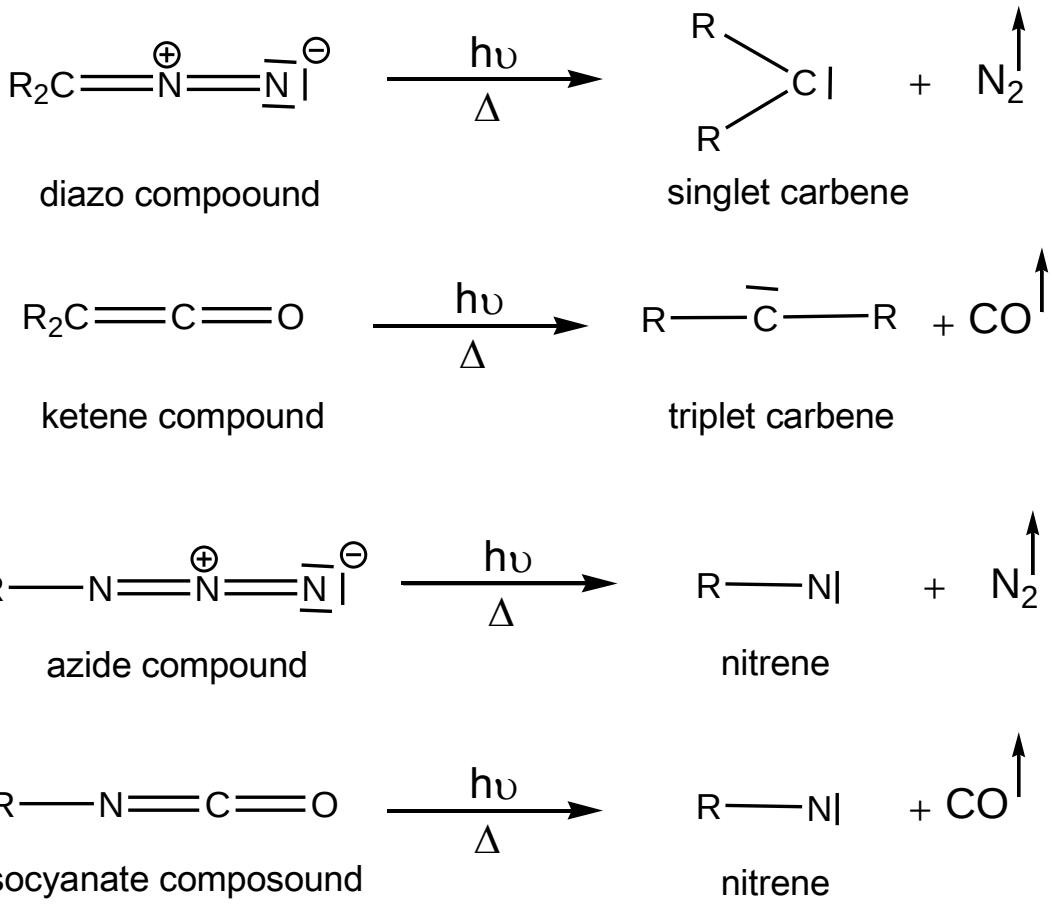


Cyclisation of carbenes and nitrenes

By definition, carbenes are non-charged molecular species with electron deficiency that contain a divalent carbon atom (2 substituents, CR1R2) surrounded by six electrons. Nitrenes are non-charged molecular species with electron deficiency that contain a monovalent nitrogen atom (1 substituent, NR) surrounded by six electrons.

The main reactions for the formation of carbene and nitrene

The two reactive intermediates are formed through thermolysis or photolysis reactions (see the reactions below).



Orbital structure of the carbene

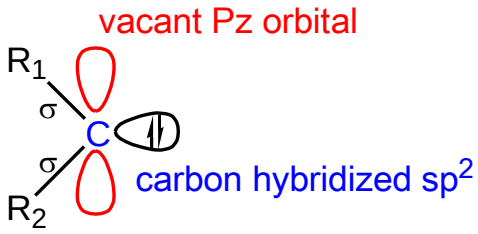
There are two types of carbenes:

Singlet carbene :

The two electrons are paired and occupy the same orbital, giving the singlet carbene a diamagnetic nature. Carbon is sp^2 hybridized, and the geometry is trigonal planar (see scheme below).

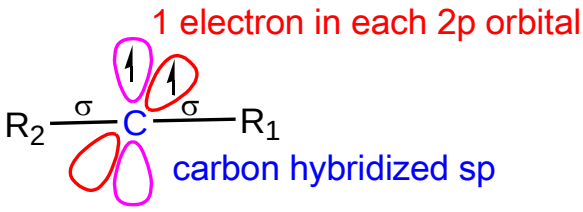
Triplet carbene :

The two electrons are in different orbitals, giving the triplet carbene a paramagnetic nature. Carbon is *sp* hybridized, and the geometry is linear (see the diagram below). Regarding the spin multiplicity (S=2s+1, where s represents the number of unpaired electrons), we have S=1 for the singlet carbene, meaning only one quantum state is possible in the ground state where all electrons are paired. For the triplet carbene, S=3.



singlet carbene

bond angle HCH = 103° (R is H atom)
less stable, highly reactive
spin multiplicity S=1
diamagnetic



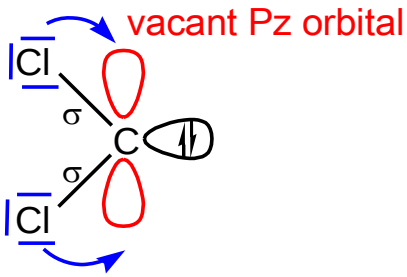
triplet carbene

bond angle HCH = 180° (R is H atom)
more stable, less réactif
spin multiplicity S=3
paramagnetic

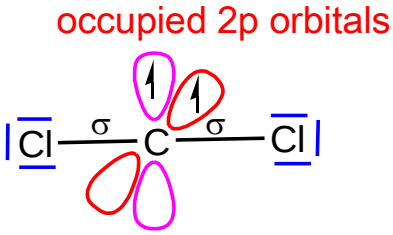
Note

The singlet CH_2 carbene is less stable than the triplet CH_2 carbene, whereas the singlet CCl_2 carbene is more stable than its triplet counterpart. Why?

Looking at the orbital structure of the two carbenes, singlet CCl_2 is more stable than triplet CCl_2 due to the back-donation of the halogen (Cl) lone pairs to the vacant carbon (2p) orbital. Whereas in triplet CCl_2, there is no back-donation because there are no vacant 2p orbitals; they are all occupied. It should be noted that back-donation is proportional to the size of the halogen, so the stability order is: $CF_2 > CCl_2 > CBr_2 > CI_2$



singlet carbene



triplet carbene

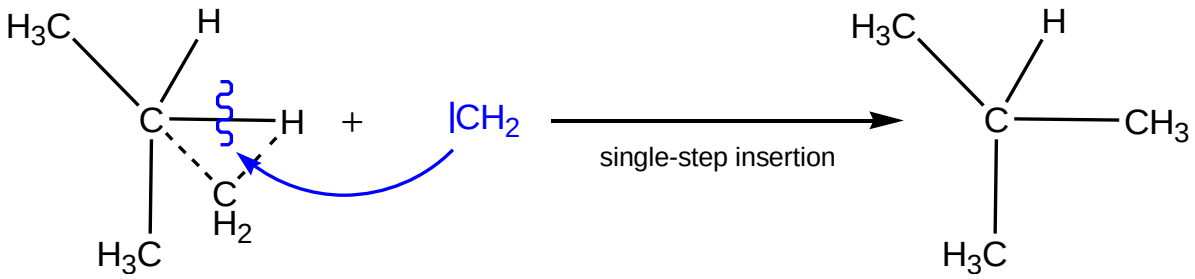
The main reaction of the carbene (and nitrane) is cyclo-addition to the double bond. In cases where the carbene is without the double bond, it will undergo another reaction called insertion reaction. In this reaction, the reaction intermediate inserts itself into the bond formed between carbon and

hydrogen.

Intermolecular insertion of the carbene between the carbon and hydrogen

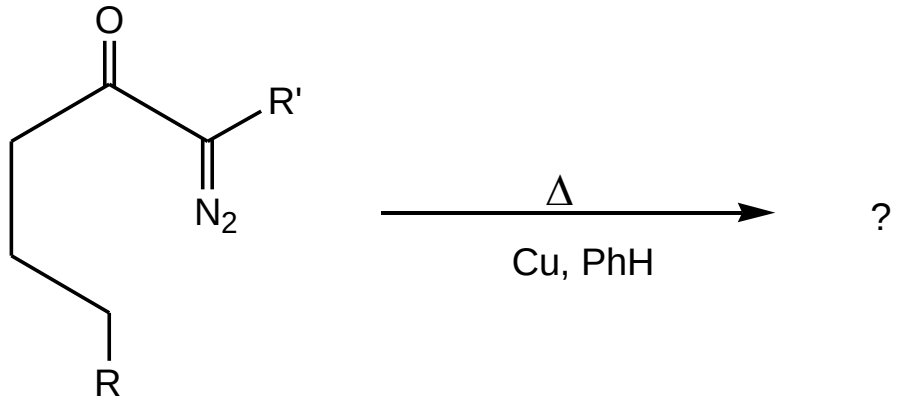
This intramolecular reaction typically occurs within a 3-membered ring. The carbene forms a 3-membered ring with the C-H bond, and then this bond breaks, leaving the CH_3 group resulting from the CH_2+H groups (see the diagram below). Generally, experimental evidence has shown that carbene insertion favors tertiary carbon over secondary and primary carbons (see the diagram below). Additionally, it has been found that the most favorable cycles formed are those with 5 and 6 members.

Example 1



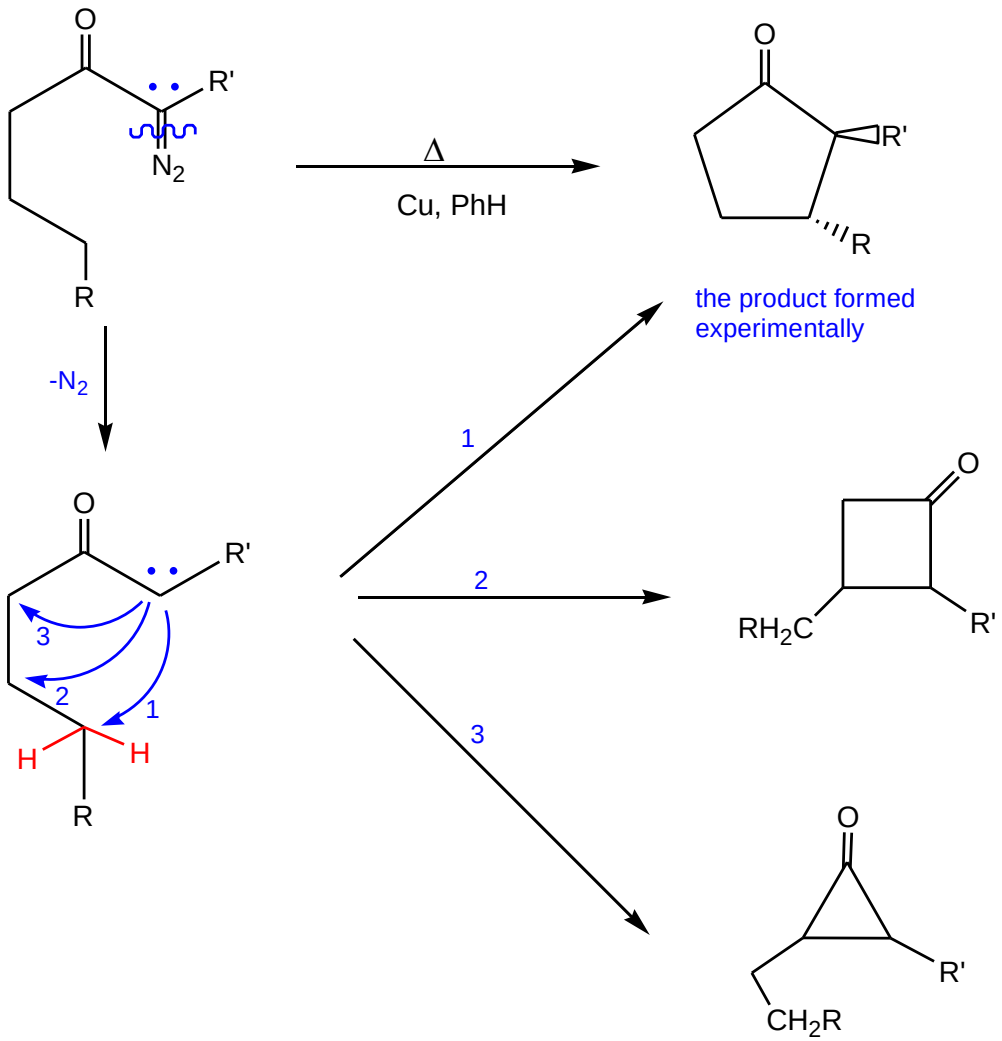
Example 2

Give all the possible insertion possibilities for this reaction:



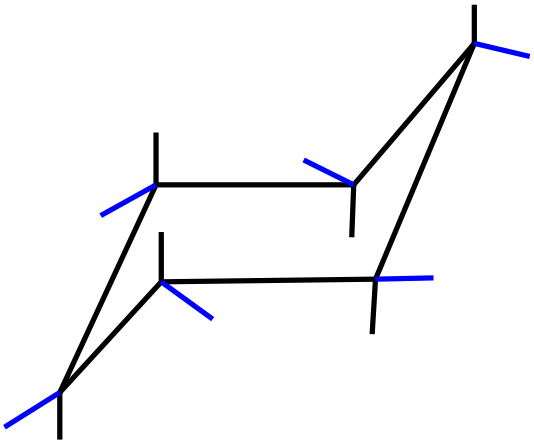
In this example, the $C=N_2$ bond breaks, and the carbene is formed. All three carbons present are secondary carbons, so we have three possibilities of intramolecular insertion leading to the formation of 3-, 4-, and 5-membered cycles. Experimentally, the obtained product is a 5-membered cycle

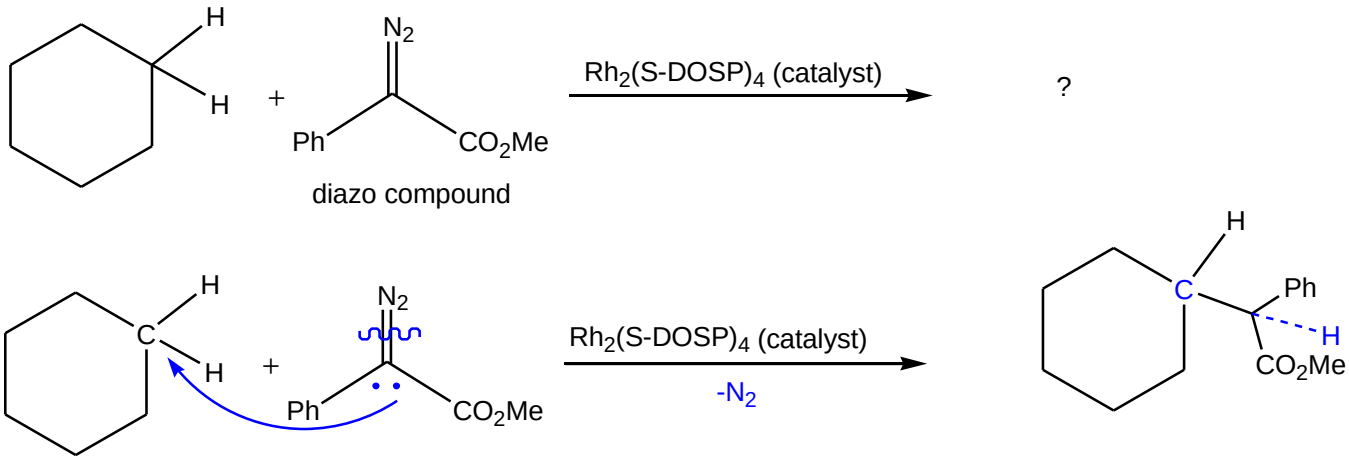
(thermodynamically favored product).



Example 3

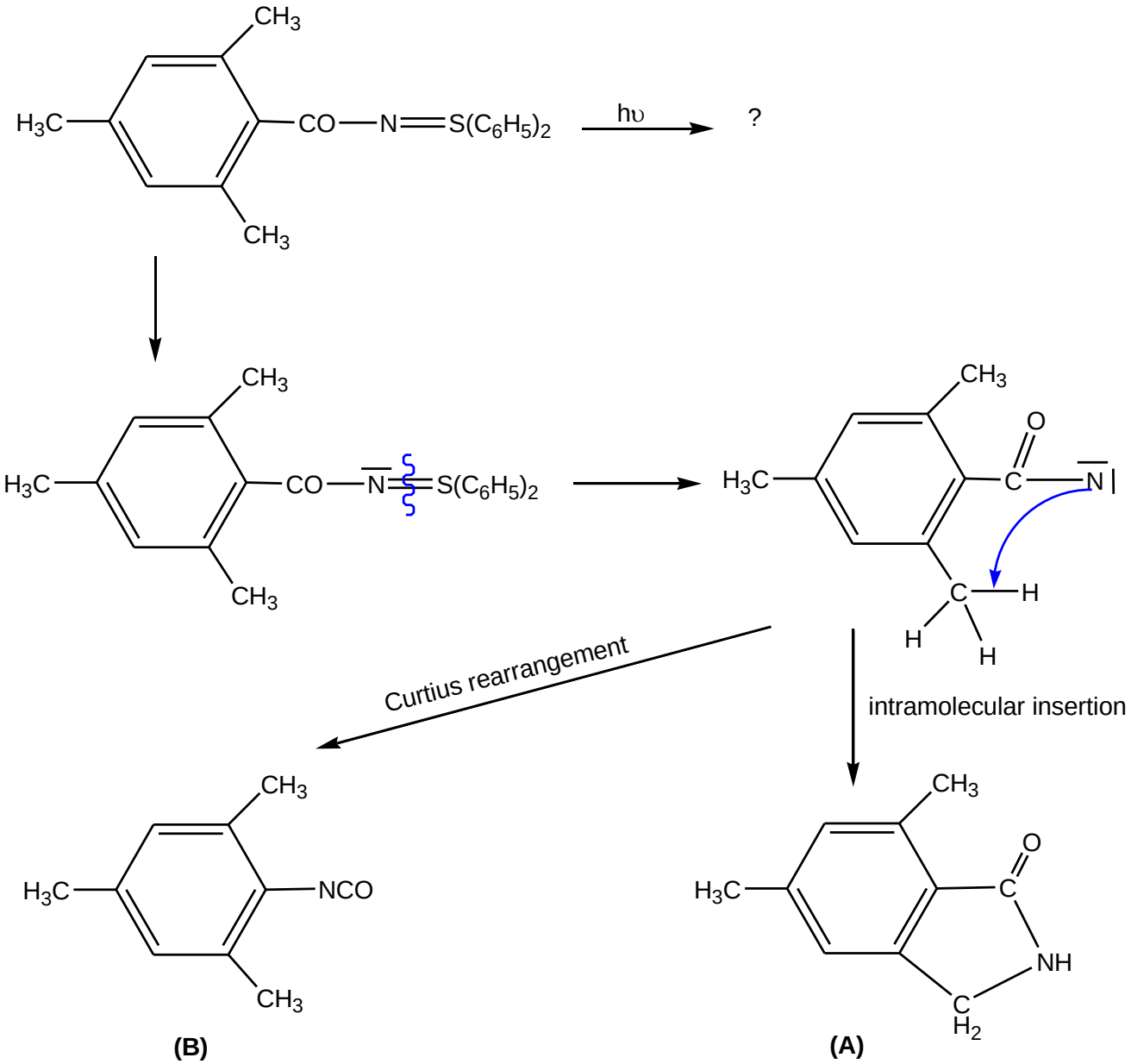
In this example, the C=N_2 bond breaks, and the carbene is formed. The cyclohexane has two conformations, chair and boat, with the chair conformation being the most stable. The hydrogens in cyclohexane are of two types based on their axial and equatorial positions. At room temperature, the hydrogens in cyclohexane are all of the same type because at this temperature, the movement of hydrogens (flipping) is very fast, so only one type of hydrogen is observed, either all axial or all equatorial. When the temperature is lower than room temperature, the two types of hydrogens can be distinguished (see scheme below).



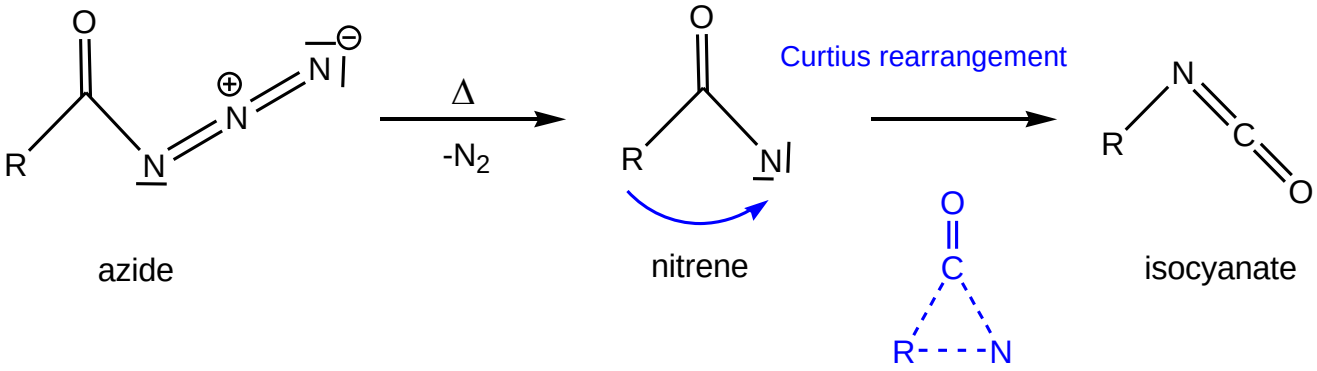


Example 4

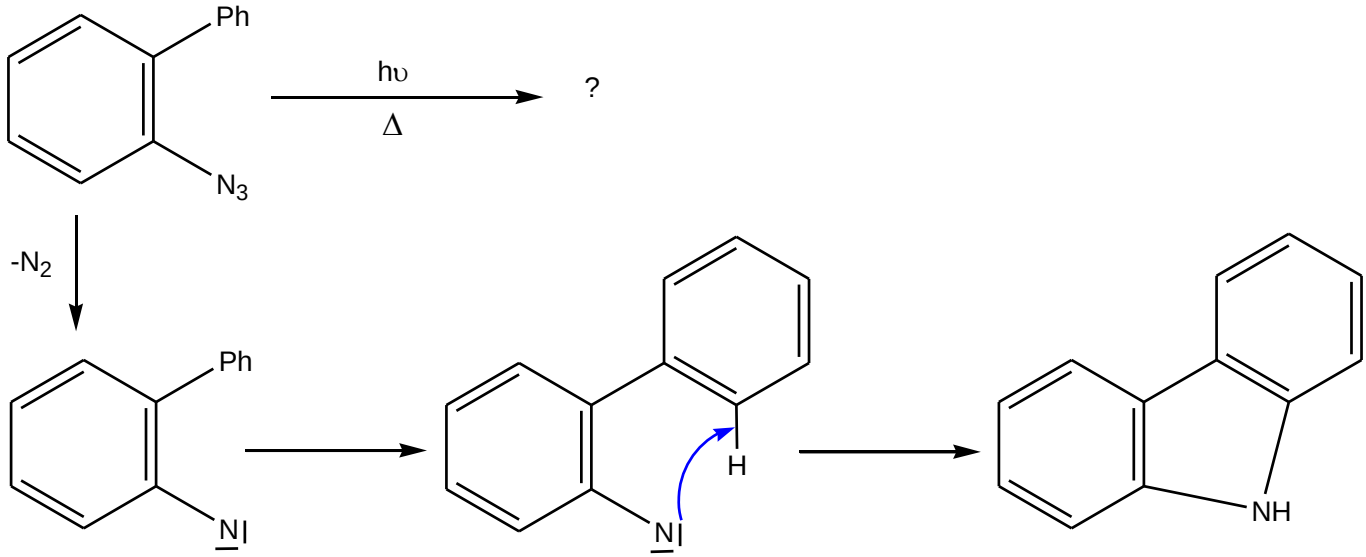
In this example, two products, A and B, can be obtained. Product A results from the intramolecular insertion of the nitrene into the (C-H) bond. In product B, the (R-C(N)=O) bond transforms into an isocyanate (R-N=C=O) through a well-known rearrangement called the "Curtius rearrangement." This rearrangement is one of the most commonly used methods for the preparation of isocyanates.



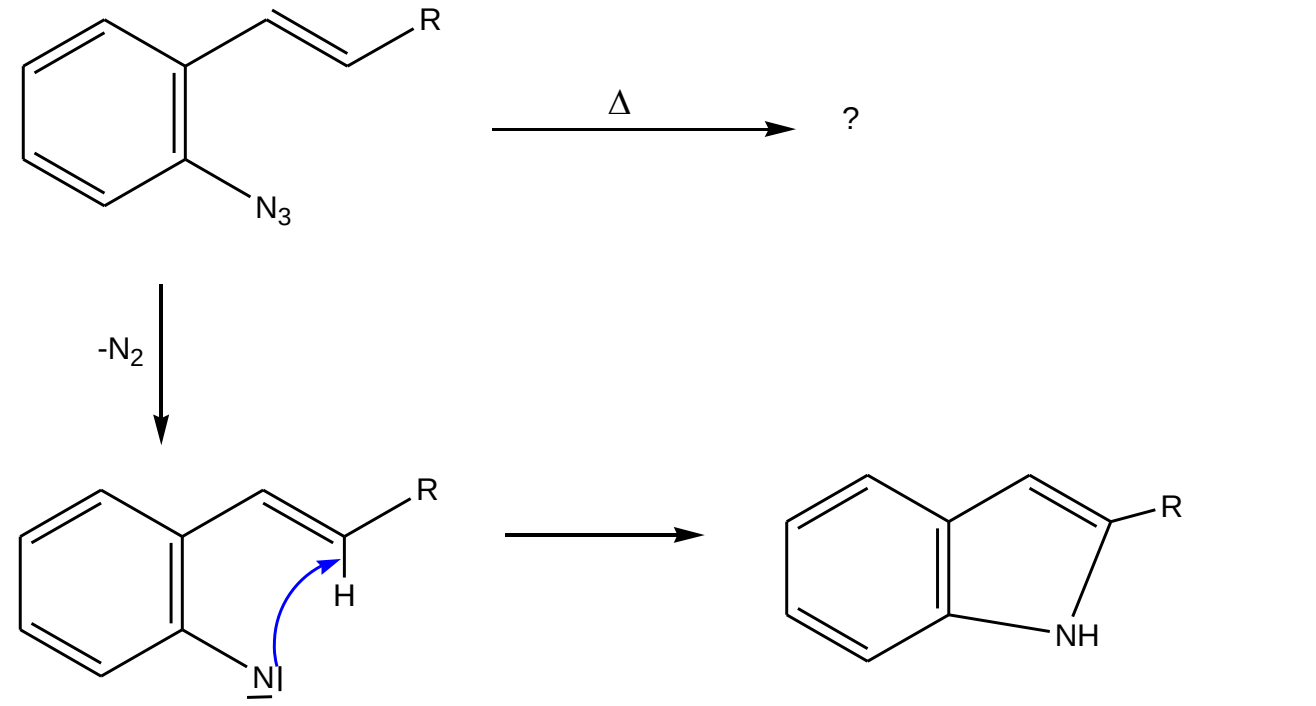
Curtius rearrangement:



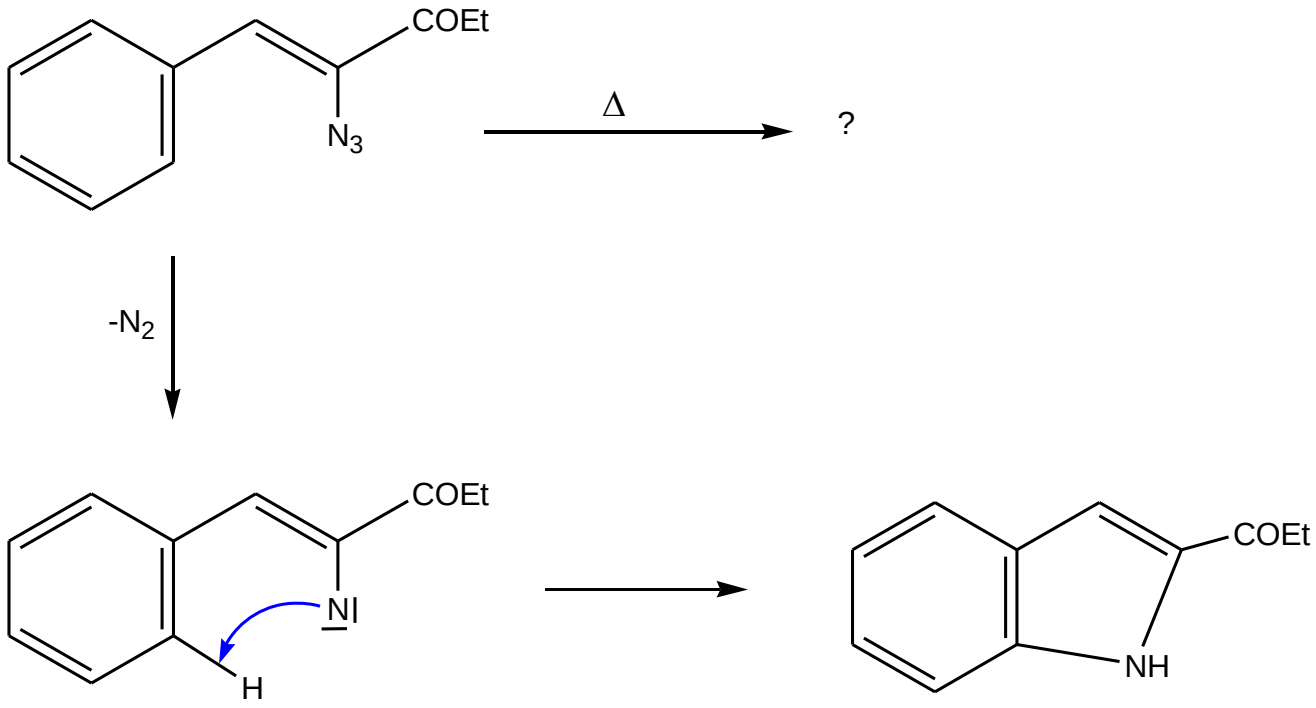
Example 5



Example 6

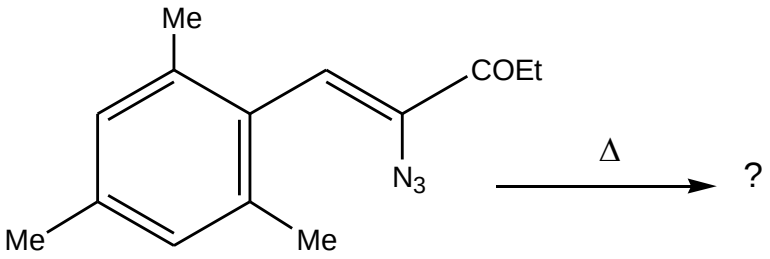


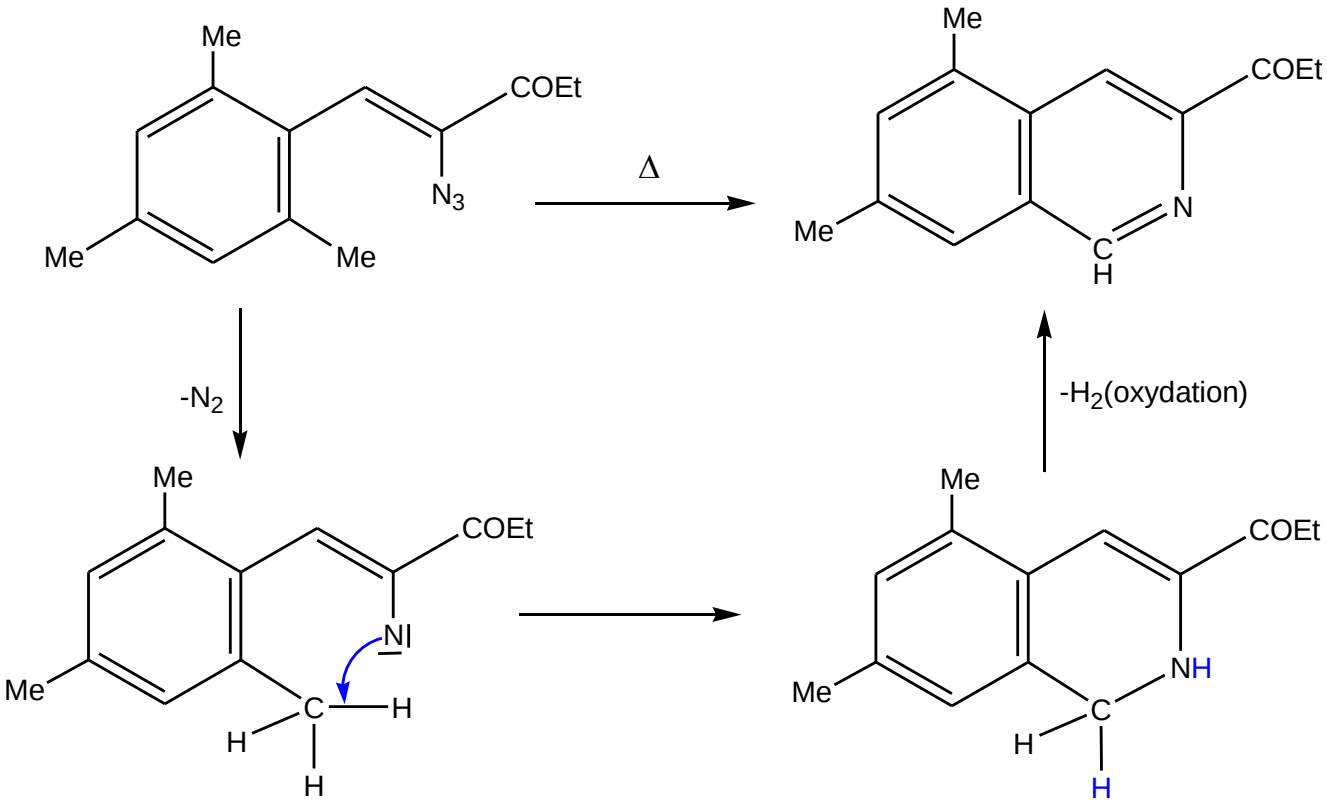
Example 7



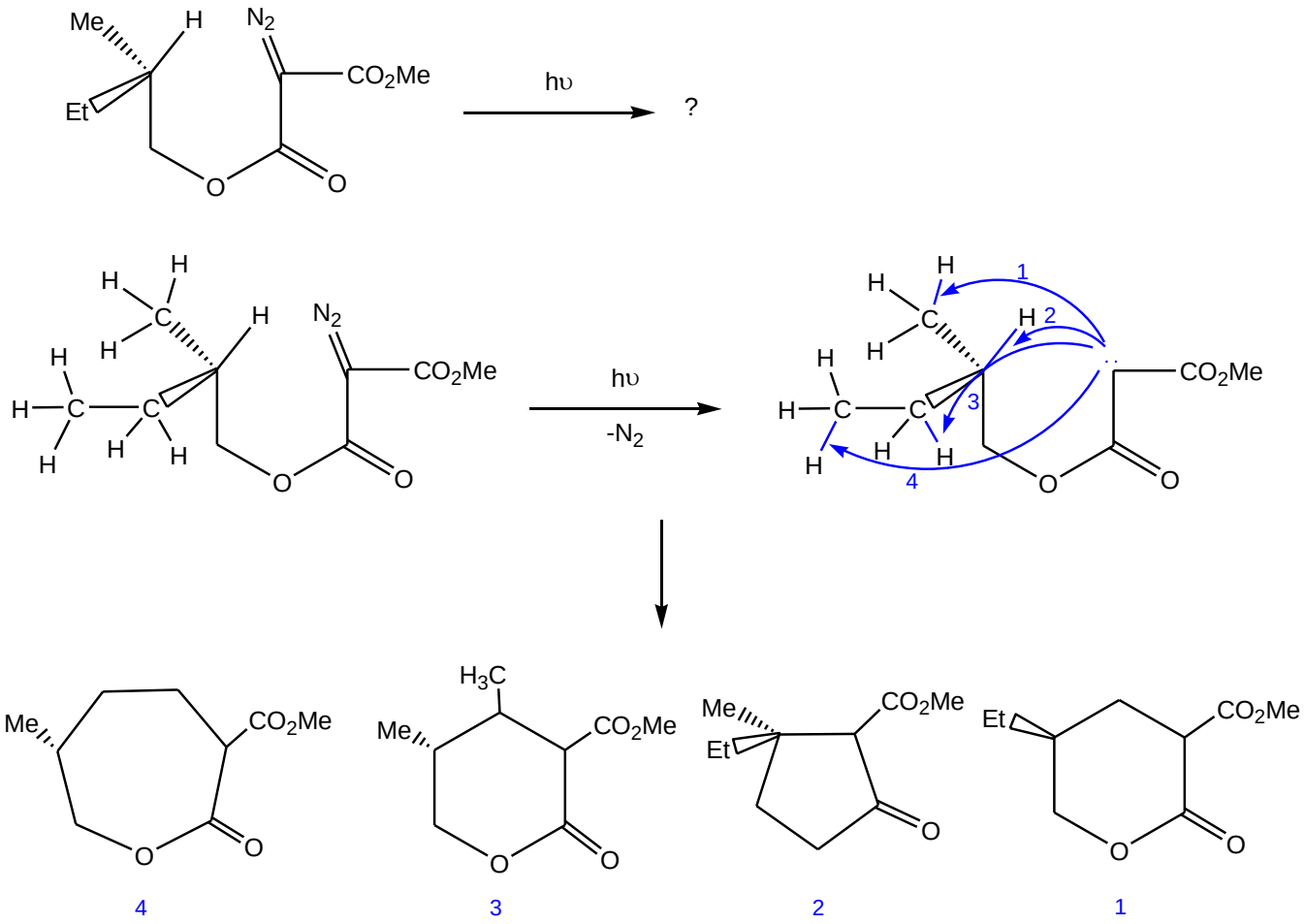
Example 8

In this example, there is an insertion of the nitrene into the C-H bond of the methyl group, followed by elimination of hydrogen (2H) to form the aromatic system 4n+2 (=10 e in this case).

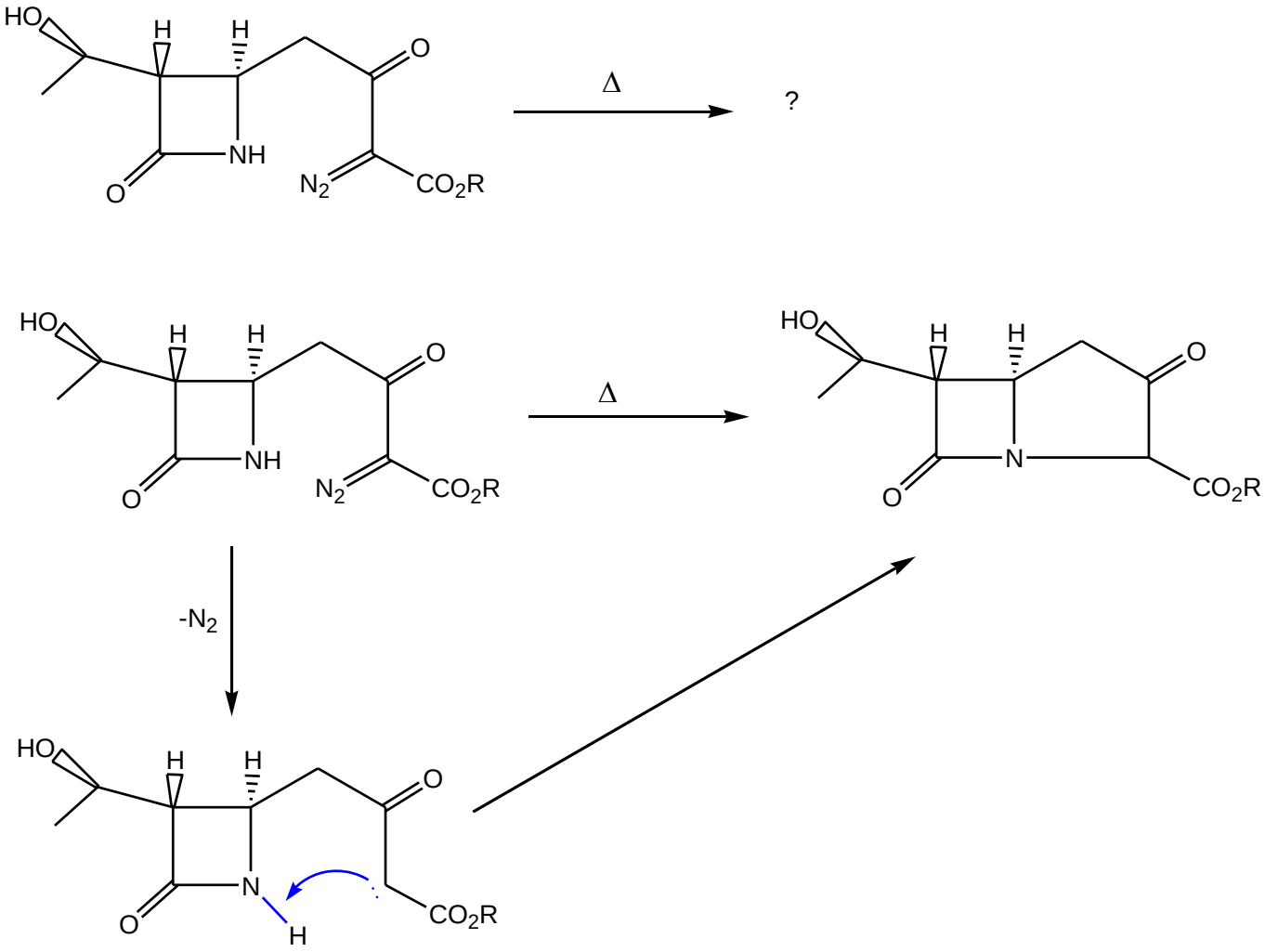

Me
COEt
N3
Δ
?
Me
Me


Me
COEt
N3
Δ
Me
Me
Me
COEt
N
C
H
-N2
-H2(oxydation)
Me
COEt
NI
Me
C
H
H
H
Me
COEt
NH
Me
C
H
H

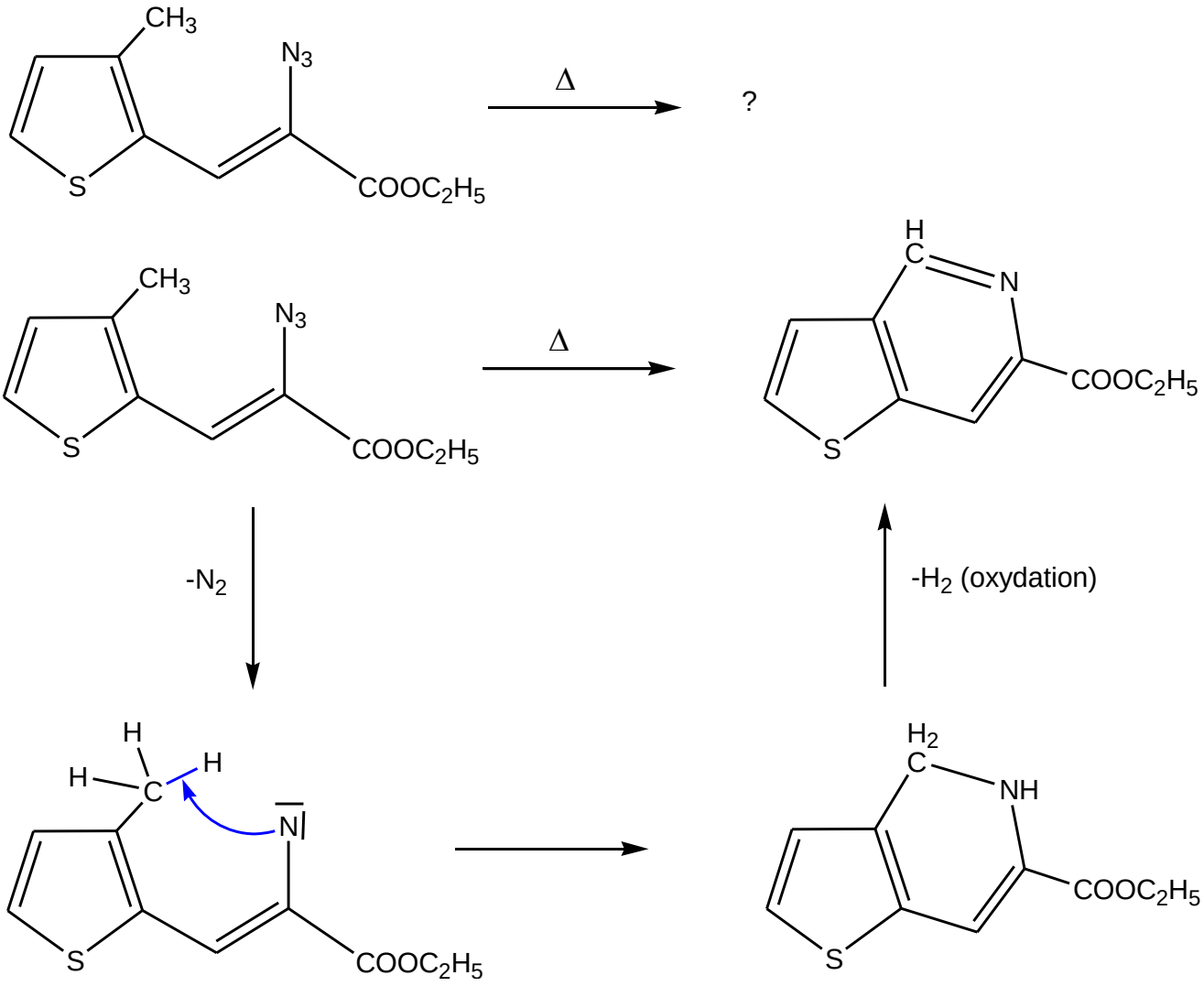
Example 9


Me
H
N2
CO2Me
Et
O
O
hυ
?
H
C
H
H
H
C
C
H
H
H
H
N2
CO2Me
O
O
hυ
-N2
1
2
3
4
4
3
2
1
H3C
Me
Et

Example 10


HO
H
H
O
NH
O
N2
CO2R
Δ
?
HO
H
H
O
NH
O
N2
CO2R
Δ
HO
H
H
O
N
O
CO2R
-N2
HO
H
H
O
N
H
O
CO2R

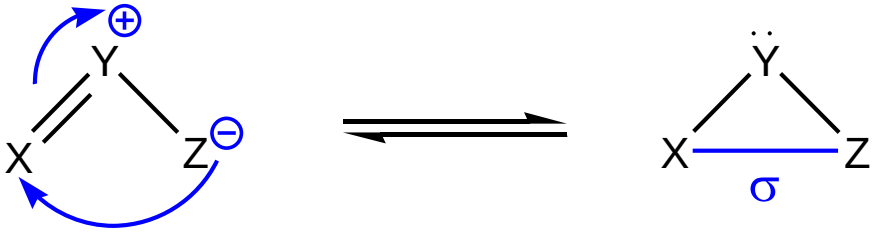
Example 11

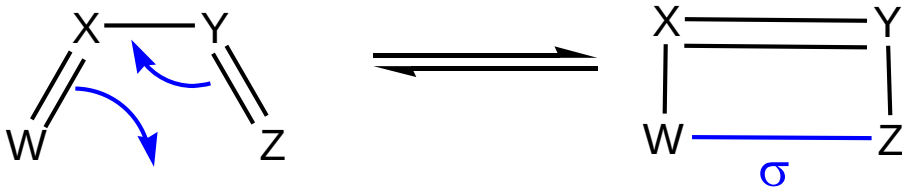


Electrocyclic Reactions

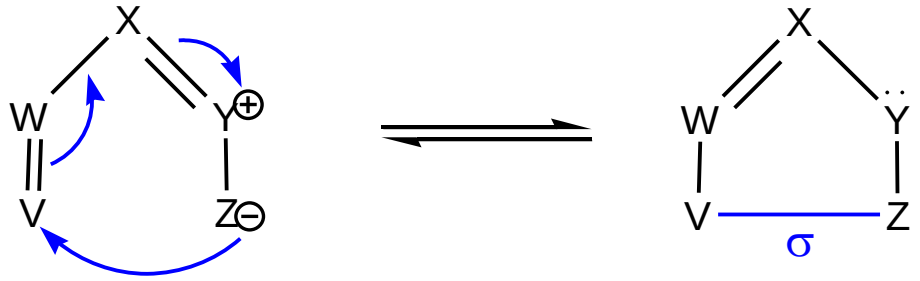
By definition, these are reactions that involve the formation of the sigma (σ) bond in the termination of a fully conjugated π system with the help of heat or light. These reactions come in two types:

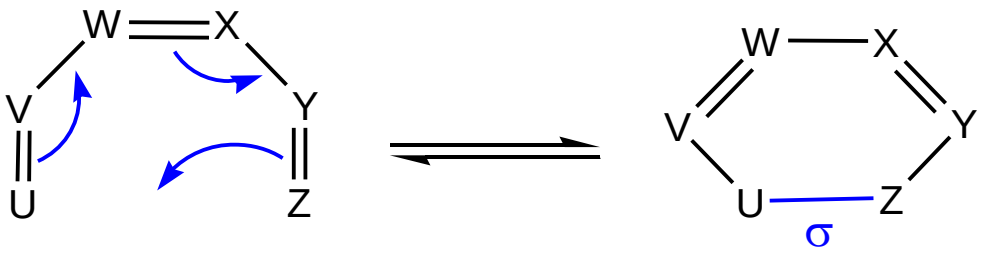
4π electrons :





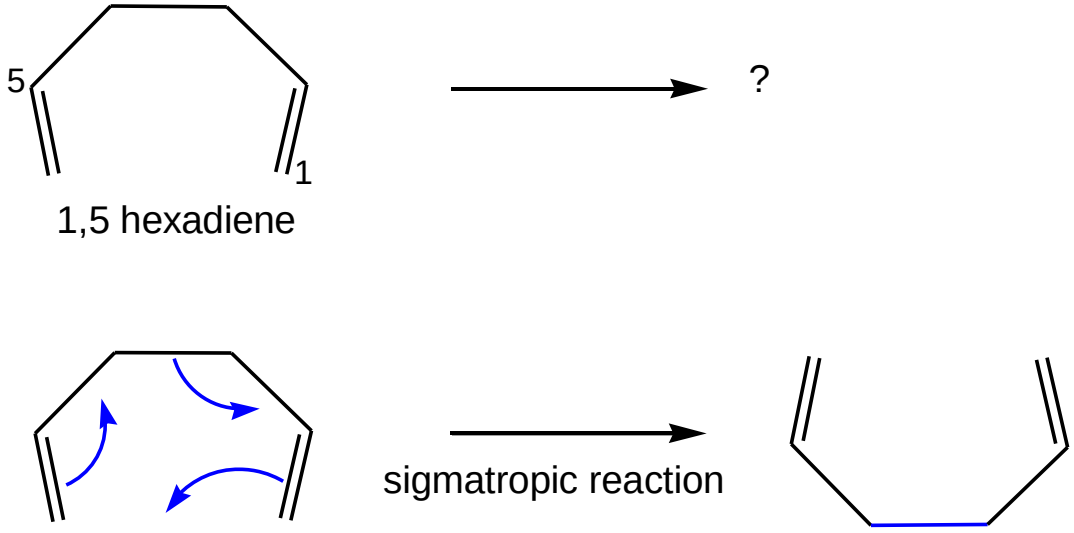
6π electrons :





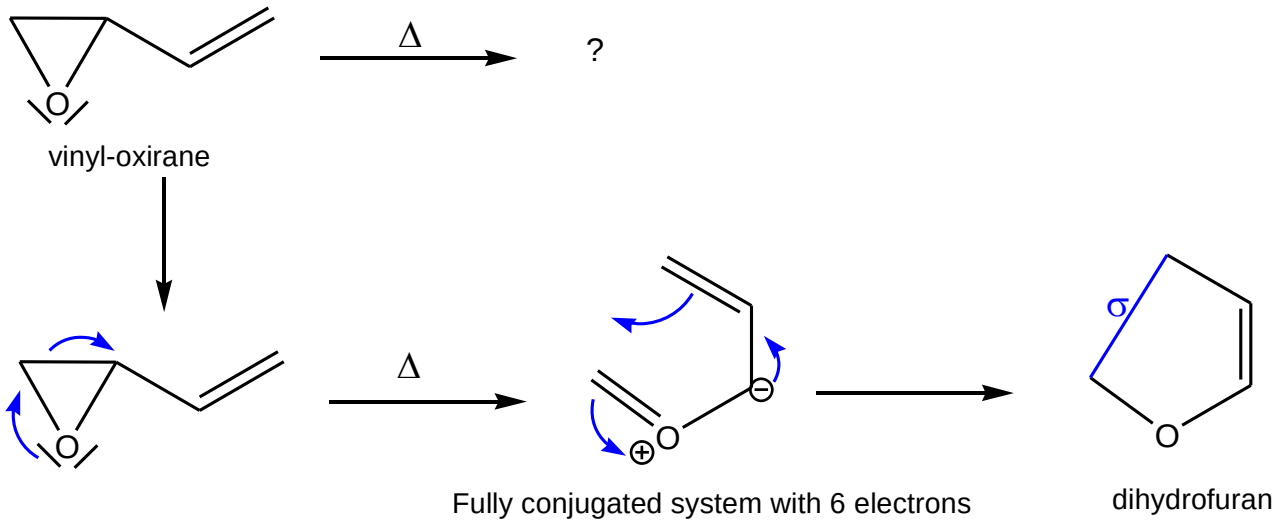
Note

Looking at this system (1,5-hexadiene), it is close but not completely conjugated. The reaction that occurs is not an electrocyclic reaction but rather a sigmatropic reaction.

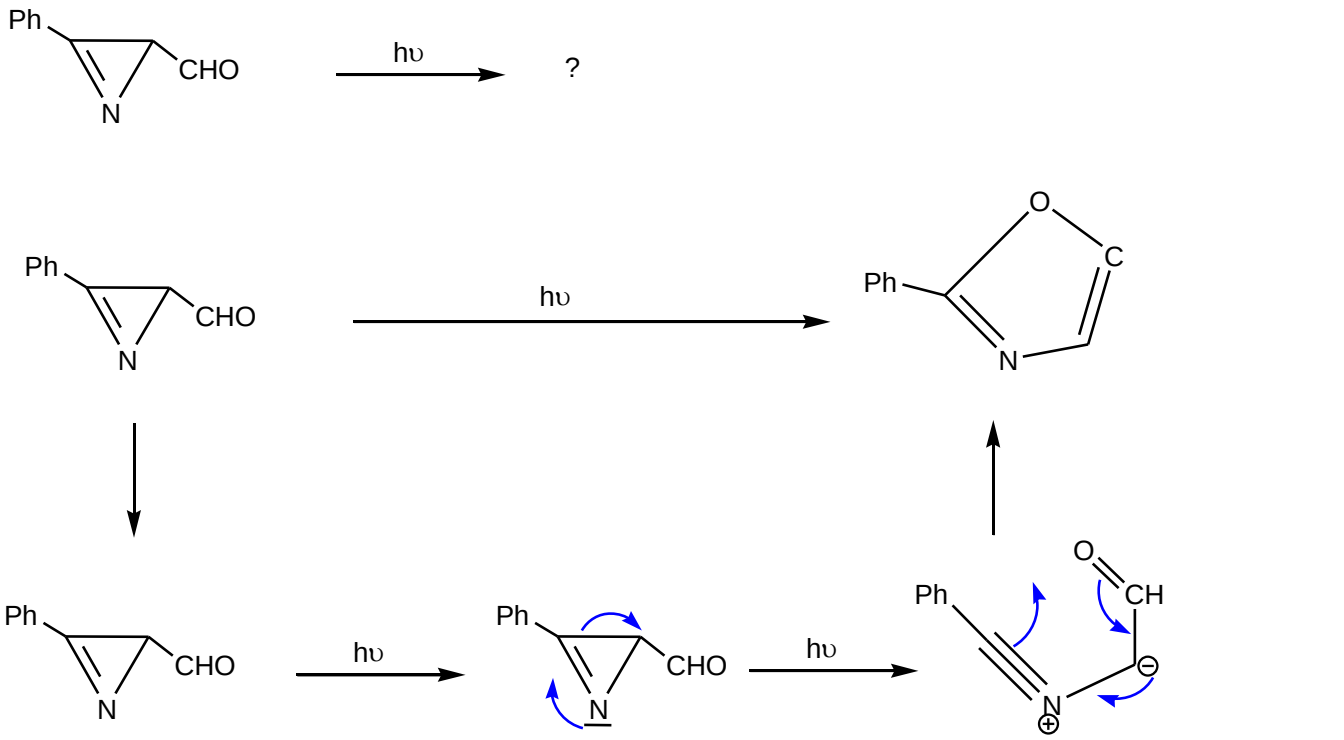


Example 1

In most cases, the fully conjugated system is prepared. Looking at what happens, for example, with vinyl-oxirane, first, the ring-opening occurs under the influence of heat, then the electrocyclic reaction takes place.

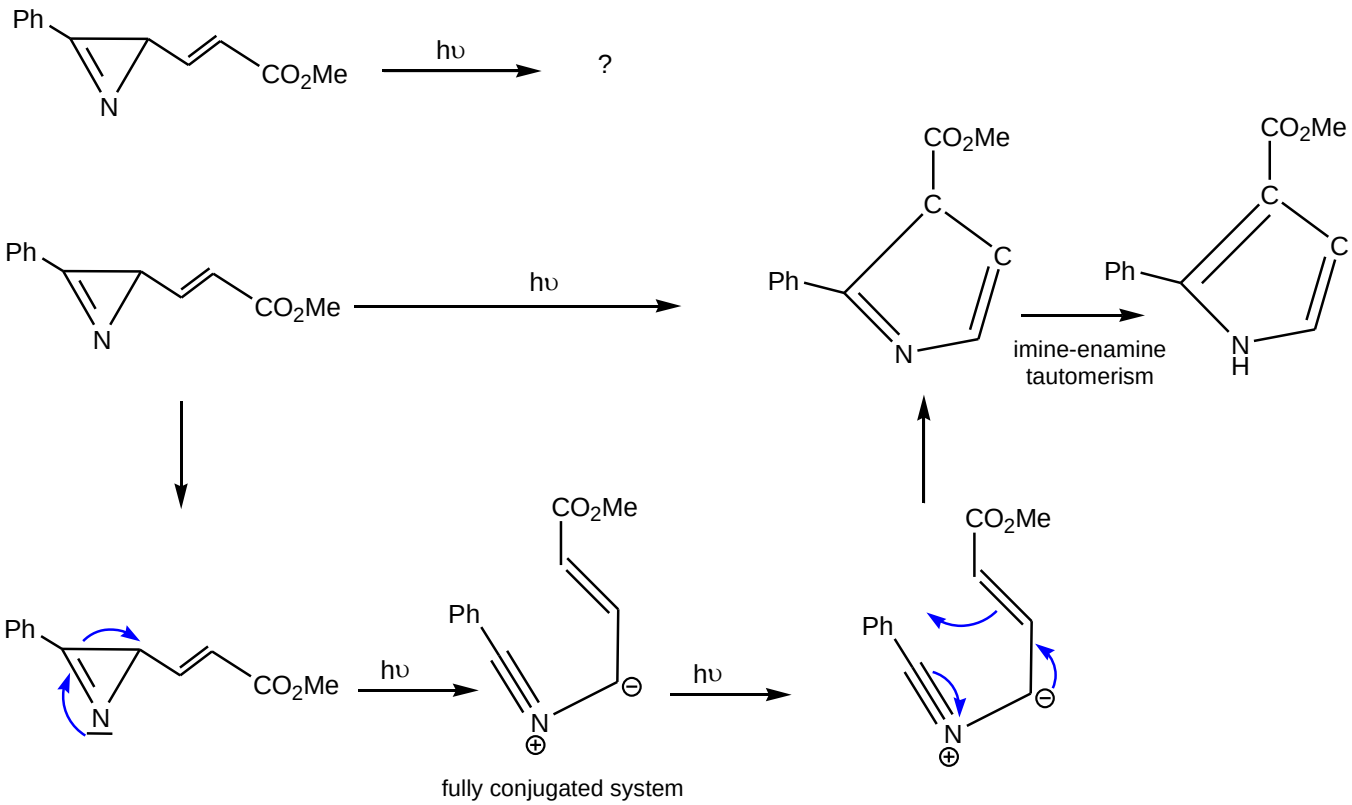


Example 2



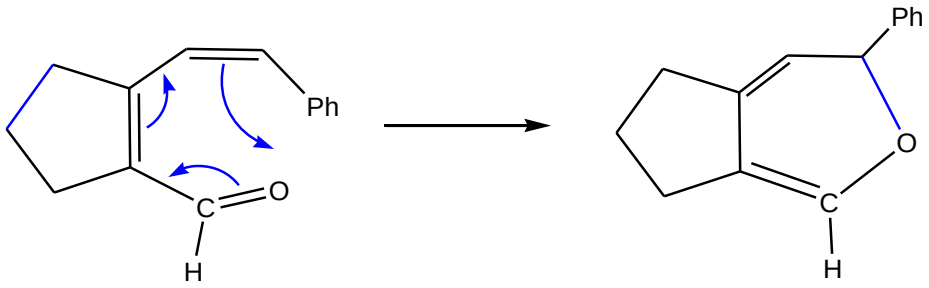
fully conjugated system with 6 electrons

Example 3

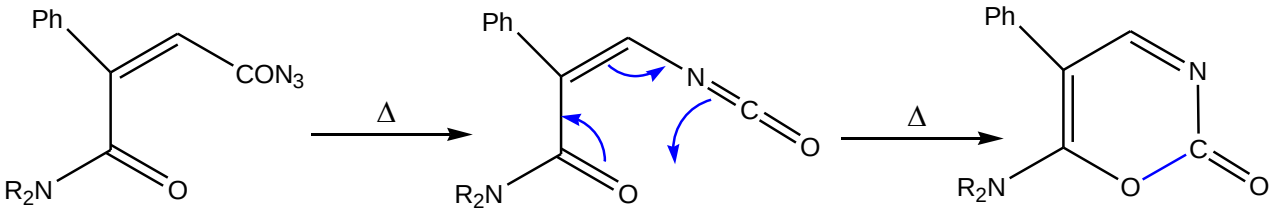


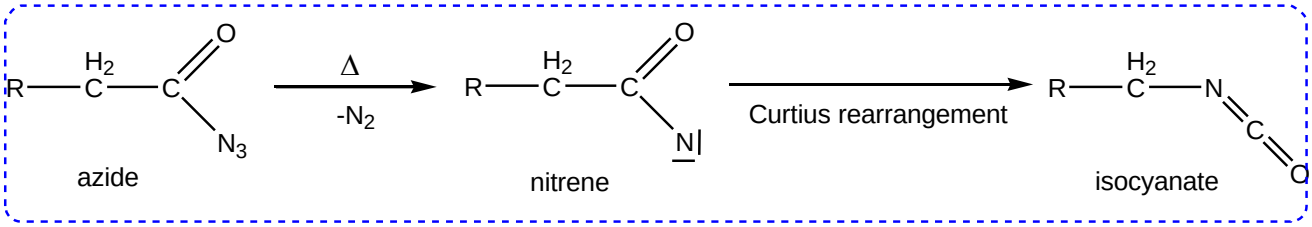
fully conjugated system

Example 4

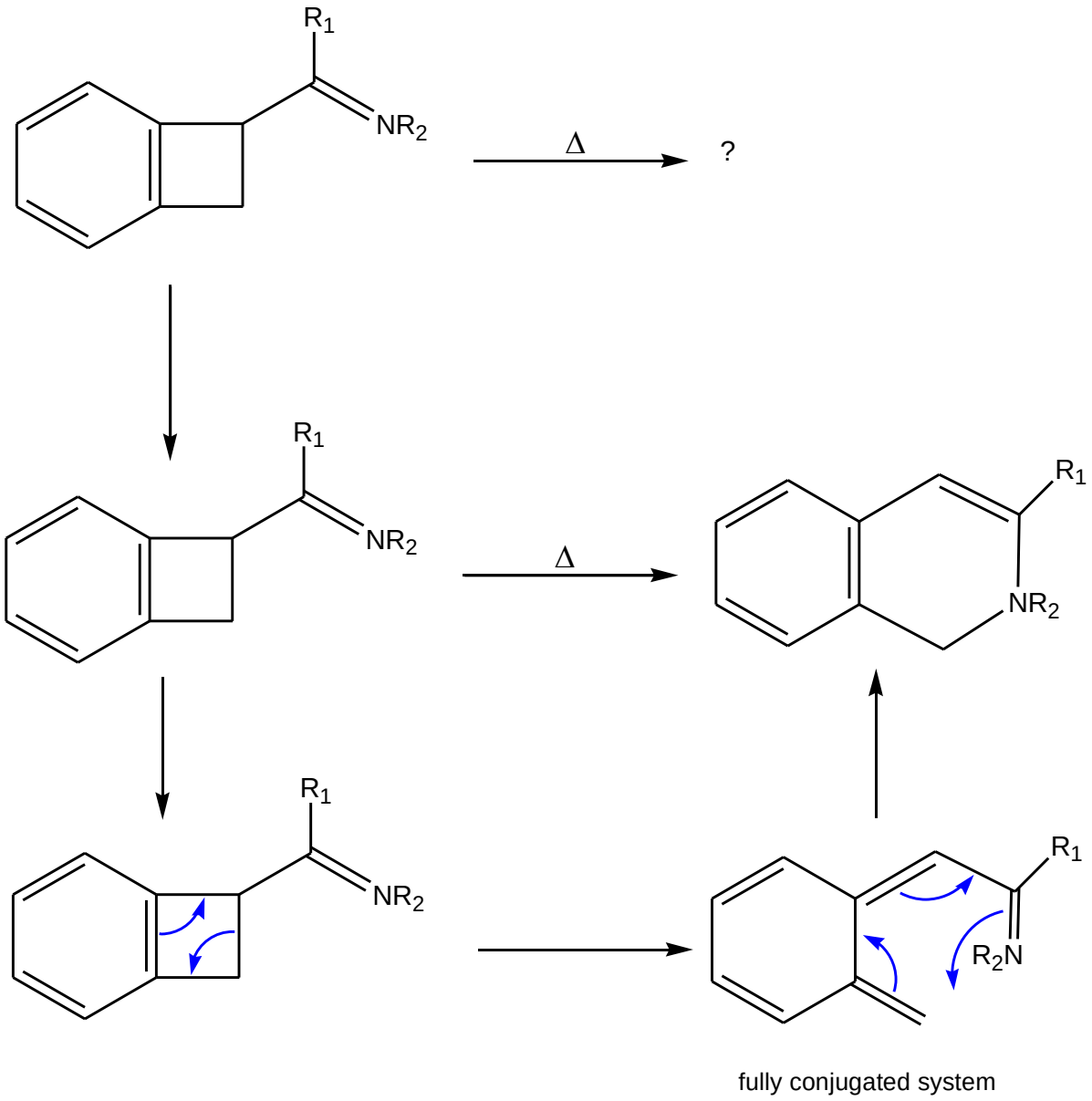


Example 5

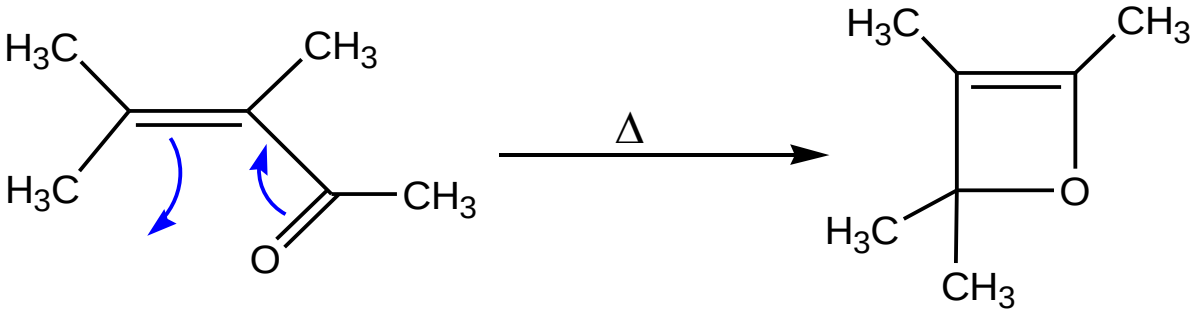




Example 6



Example 7



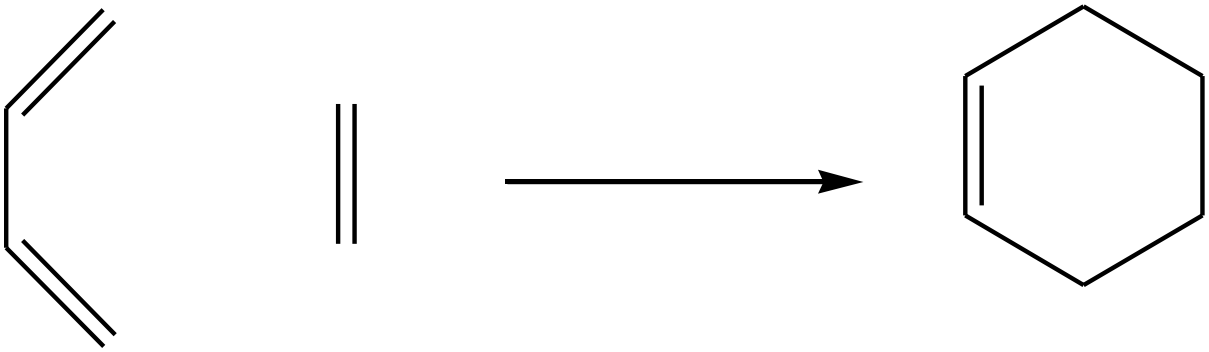
Cycloaddition Reactions

By definition, the cycloaddition reaction is a chemical reaction to form

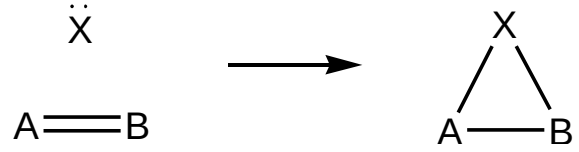
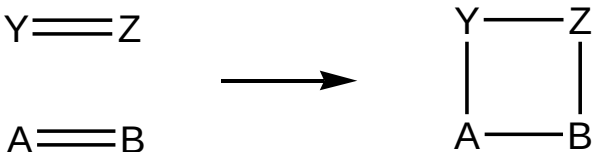
cycles in which two parts of 2 molecules (or the same molecule) combine to form the cycle in which there is a reduction in the multiplicity of the bond (reduction of double bonds).

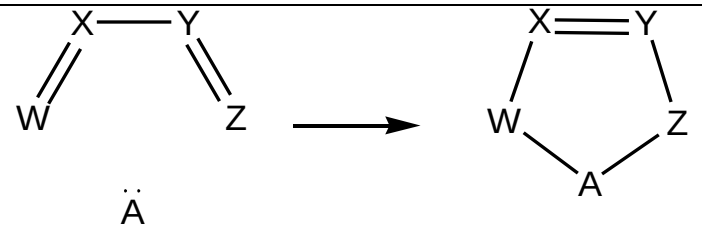
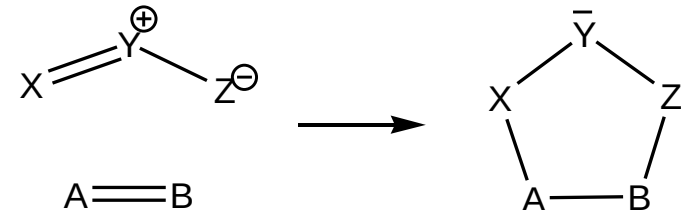
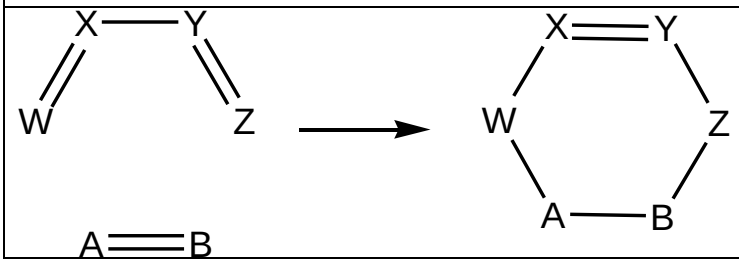
Diels-Alder Reaction

In this example, a 6-membered ring is formed with a reduction of two double bonds (π) that have transformed into single bonds (σ).



Cycloaddition reactions can be classified into several types, either based on their geometry (the number of atoms involved in the reaction and the size of the formed cycle) or by the number of π bonds involved in each reacting part, as shown in the table below.

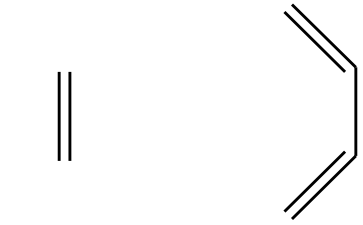
Cycloaddition Reactions	Geometry	Electrons (π)
	Chelotropic 1+2=3	2+2
	2+2 Cycloaddition 2+2=4	2+2

	Chelotropic 1+4=5	2+4
	1,3 dipolar 2+3=5	2+4
	Diels Alder 2+4	2+4

By definition, a chelotropic reaction is a pericyclic reaction in which two sigma (σ) bonds form on the same atom. This is similar to what we discussed earlier with the cycloaddition of nitrenes and carbenes.

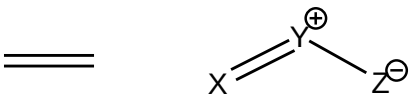
In heterocyclic chemistry, one of the most prominent reactions is the 1,3-dipolar cycloaddition, also known as the Huisgen cycloaddition. Rolf Huisgen, a distinguished scientist, extensively documented information on the 1,3-dipolar cycloaddition in 1963. In contrast, in carbon chemistry, the Diels-Alder reaction holds significant recognition, and when an atom other than carbon is involved, it is referred to as "hetero-Diels-Alder.

Diels-Alder



dienophile diene

1,3-dipolar



dipolarophile dipole

Notes

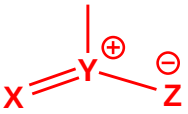
The diene is known for its structure containing the two double bonds. For C=N, for example, how can we determine if it is a dienophile or a dipolarophile?

The answer is simple:

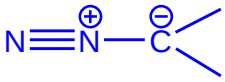
If it reacts with a diene => dienophile

If it reacts with a dipole => dipolarophile

The most well-known dipoles are two forms: propargyl and allyl (see below). The most commonly used dipoles in the literature are ranked in priority order, in blue, in the scheme below from 1 to 4.

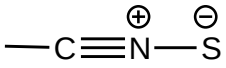


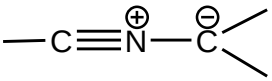
3  azides

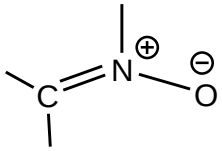
4  diazo compounds

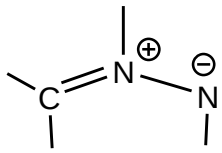
2  nitrile oxides

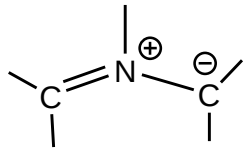
1  nitrile amides (nitrile amines)

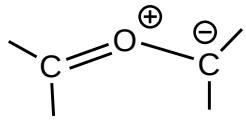
 nitrile sulfides

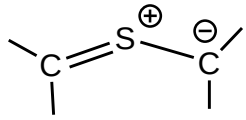
 nitrile ylides

 nitrones

 azomethine imides

 azomethine ylides

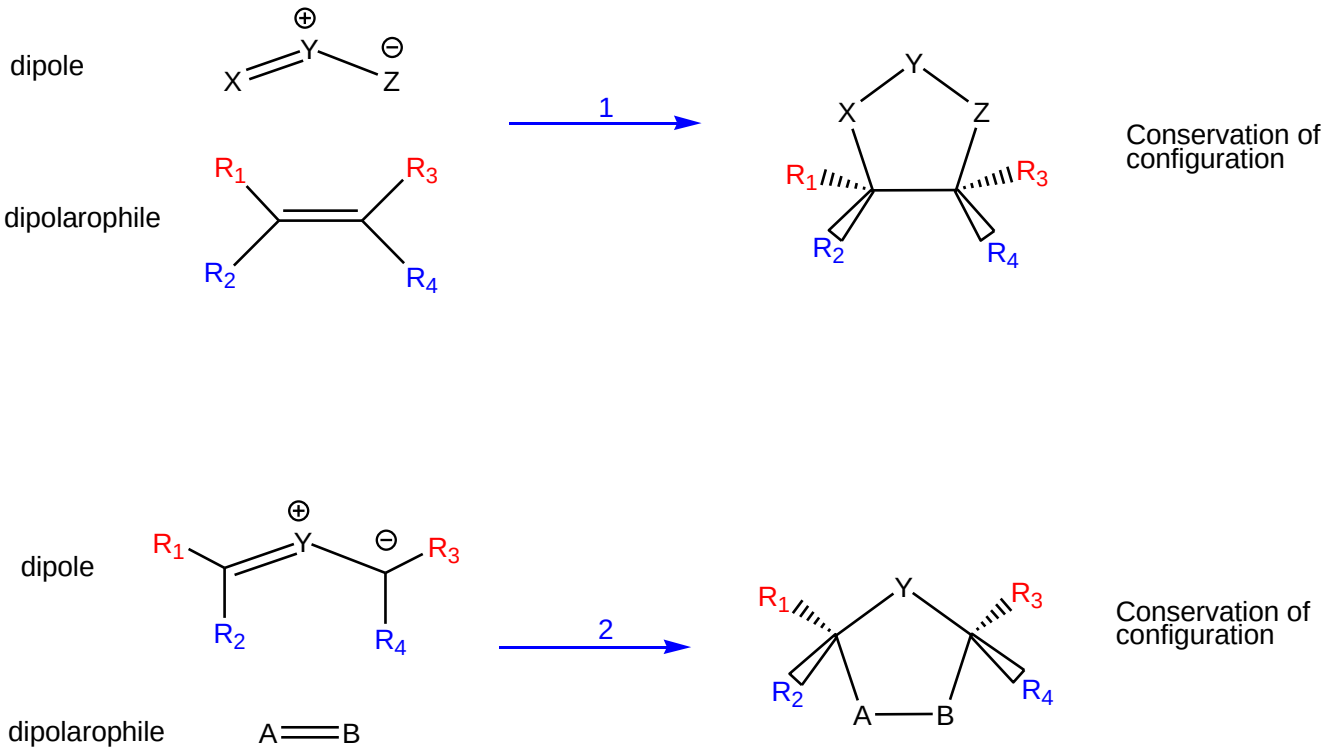
 carbonyl ylides

 thiocarbonyl ylides

What is the mechanism of the 1,3 dipolar cycloaddition reaction?

By definition, a mechanism serves as the explanatory framework for a phenomenon observed through experimentation. In simpler terms, when we have a product, our aim is to comprehend the process that led to its formation, rather than vice versa. For instance, the 1,3-dipolar cycloaddition reaction is experimentally noted for its stereoselectivity, as illustrated by the preservation of configuration (as seen in the example below). The proposed mechanism for this reaction must account for this stereoselectivity. Moreover, experimental observations reveal that most 1,3-dipolar cycloaddition reactions exhibit regioselectivity, yielding only one product. However, there are instances where this regioselectivity is absent, resulting in the formation of a mixture of two products (structural isomers, as depicted in the example below). The proposed mechanism should elucidate the factors contributing to the regioselectivity observed in some cases and its absence in others.

Stereoselectivity

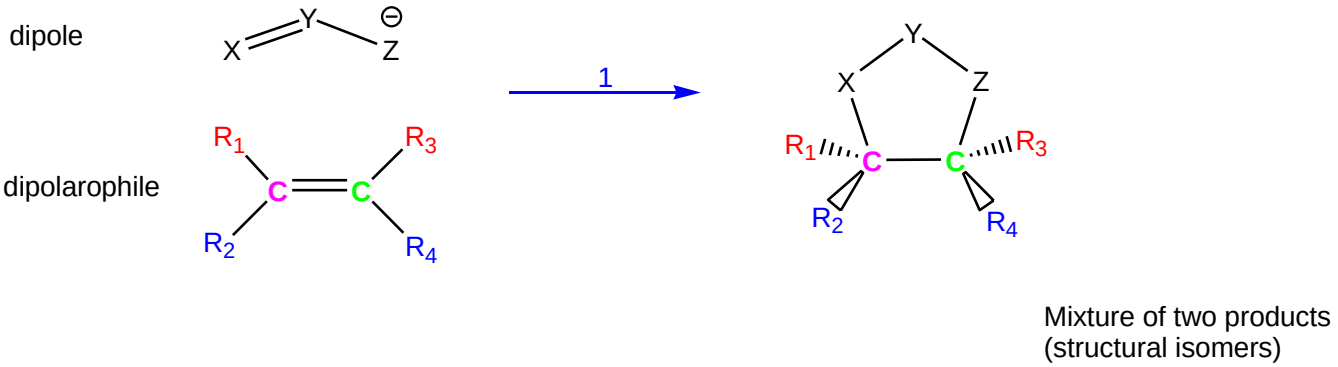


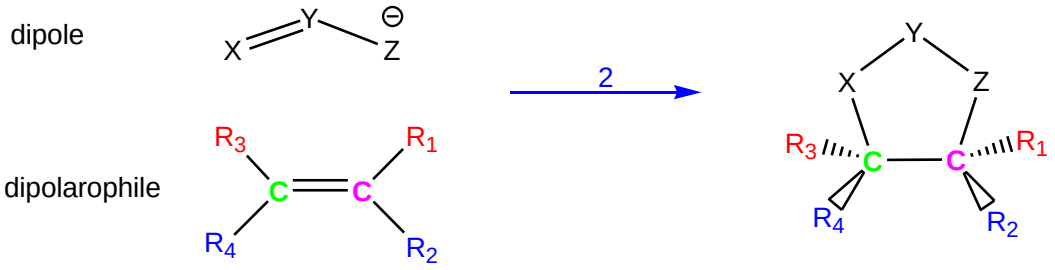
At reaction 1: R_1, R_3 and R_2, R_4 are on the same side of the dipolarophile.

At reaction 2: R_1, R_3 and R_2, R_4 are on the same side of the dipole.

After the 1,3 dipolar cycloaddition reaction => conservation of configuration (stereoselectivity)

Regioselectivity





Generally, the proposed mechanisms fall into two types: either they occur in a single step or in two steps:

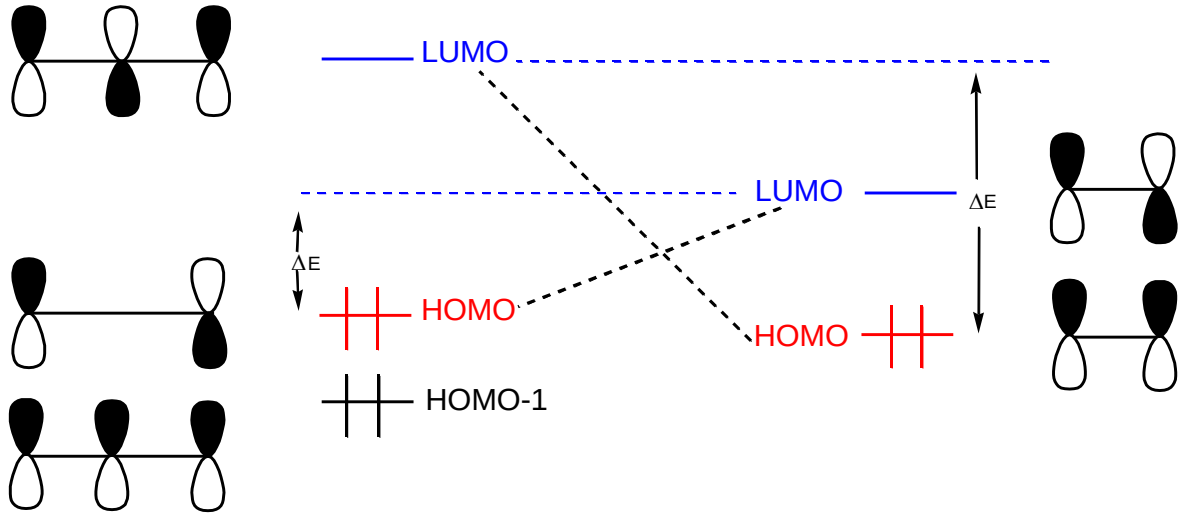
A. The concerted mechanism (one-step mechanism)

B. The biradical mechanism (stepwise mechanism)

The concerted mechanism (one-step mechanism)

Explain the Stereoselectivity

This mechanism, proposed by R. Huisgen, involves the simultaneous formation of two bonds. To gain a better understanding of this mechanism, let's examine the interaction of frontier orbitals (refer to the diagram below).



dipole (3 atoms) 4eπ

dipolarophile (2 atoms) 2eπ

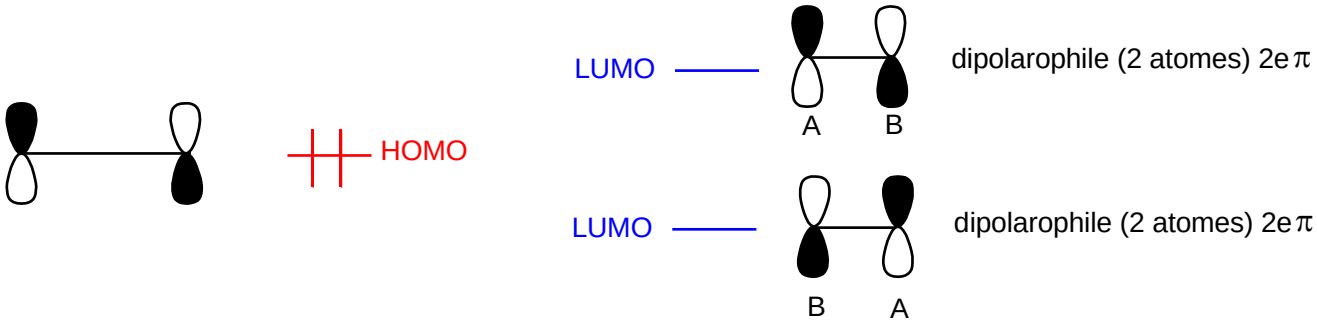
Examining the phases of the molecular orbitals of both fragments (dipole and dipolarophile), we observe that there can be overlap between orbitals with the same phase. Specifically, the orbital interaction occurs between the Highest Occupied Molecular Orbital (HOMO) of one component (dipole or dipolarophile) and the Lowest Unoccupied Molecular Orbital (LUMO) of the other component (dipolarophile or dipole). The reaction tends to occur between HOMO-LUMO orbitals that are energetically similar (exhibiting the smallest energy difference ΔE between them).

The dipolarophile typically comprises a substituted A=B motif, where rotation of substituents around the double bond is prohibited. As the HOMO of the dipole approaches the LUMO of the dipolarophile, they converge and transform from a double bond (where rotation is forbidden) to a cyclic structure (single bond, where rotation remains prohibited), thereby elucidating the stereoselectivity of the reaction.

Explain the Regioselectivity

If we envision that the HOMO of the dipole remains stationary and we aim for it to interact with the LUMO of the dipolarophile (A=B) (as illustrated in the example below), theoretically, the overlap between the HOMO (dipole)

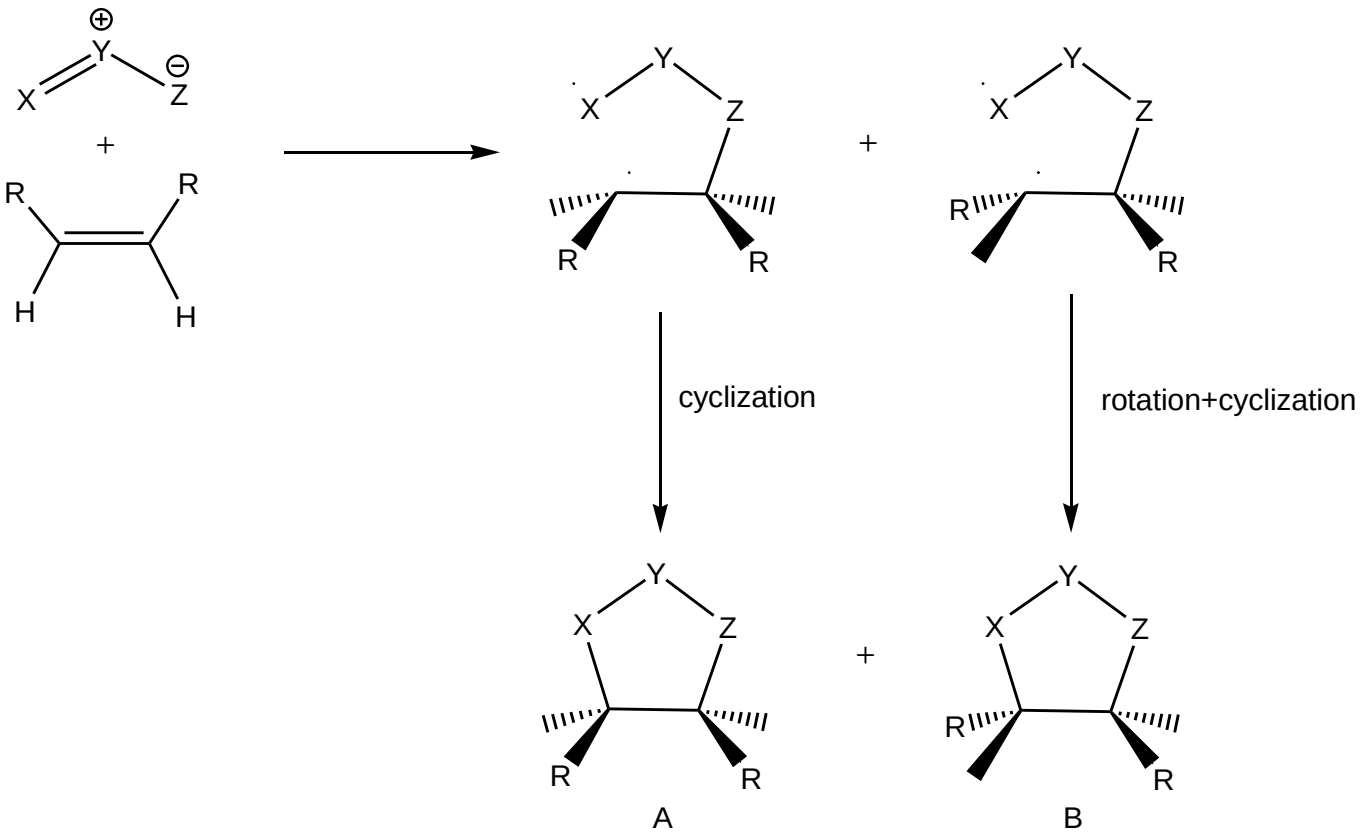
and the LUMO (dipolarophile, A=B or B=A) is feasible in both scenarios. This could lead to a non-regioselective reaction, where two products (two structural isomers) are possible at the end of the reaction. We will later explore the explanation behind what is termed a regioselective reaction.



The biradical mechanism (stepwise mechanism)

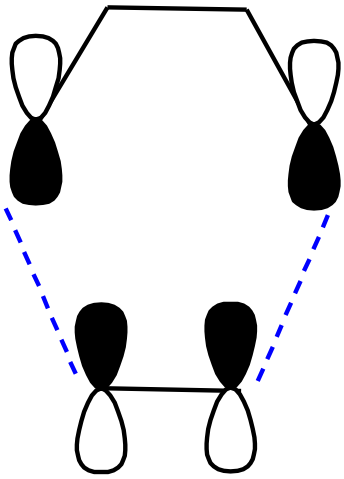
Explain the Stereoselectivity

The mechanism proposed by Firestone:

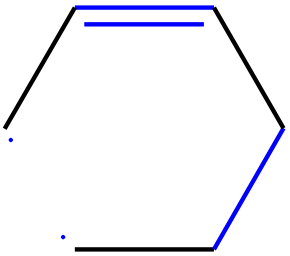


Experimentally, it has been demonstrated that the reaction exhibits stereoselectivity, yielding only product A. Firestone proposed an explanation: when the biradical forms, two possibilities arise—either it undergoes direct cyclization, producing product A, or it undergoes rotation (since the double bond is no longer present, rotation becomes feasible), followed by cyclization, resulting in the formation of both products A and B. Firestone suggests that the time required for cyclization is considerably shorter than the time needed for rotation and subsequent cyclization, as determined by physical calculation methods.

Now, with two explanations for stereoselectivity (Huisgen and Firestone), which one aligns more closely with reality? Presently, various instruments, such as Electron Spin Resonance (ESR), can measure the presence of free radicals in a sample. Approximately 95% of 1,3-dipolar reactions occur via a concerted mechanism (Huisgen). However, there are instances where free radicals have been detected (biradical mechanism, Firestone). Similar mechanisms (concerted or biradical) apply to Diels-Alder reactions. In some instances, the reaction is elucidated by a concerted mechanism, while in others, a biradical mechanism is proposed. There isn't a single mechanism that universally applies to all reactions. Nevertheless, the occurrence of free radicals in Diels-Alder reactions is more prevalent than in 1,3-dipolar reactions.



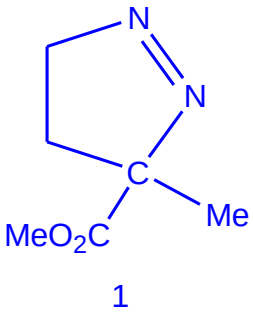
concerted mecanism



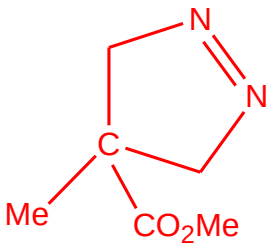
biradical mecanism

Explain the Regioselectivity

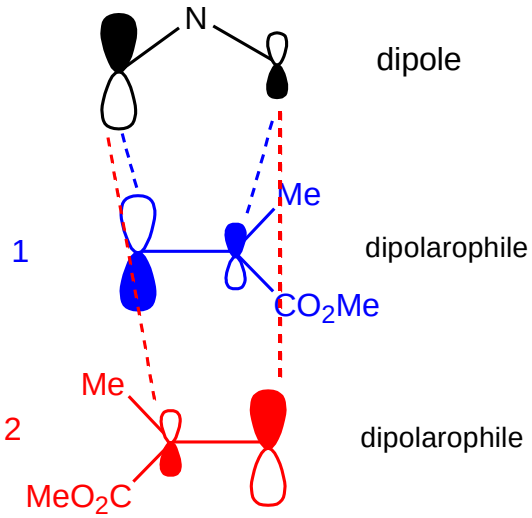
Examining the diagram below, concerning the phases of the molecular orbitals of the dipole and dipolarophile, overlap is feasible in both scenarios. However, following the "hard-hard-soft-soft" principle, product 1 is favored due to the more favorable interaction between orbitals of similar size. Consequently, while both products 1 and 2 are plausible, product 1 is preferred. Therefore, the mechanistic explanation for the regioselectivity of the reaction lies in the disparity in the sizes of the orbitals of the dipole and dipolarophile. A mixture of isomers arises when there is interaction between orbitals of similar sizes.



1



2



Application of heterocycles in medicinal chemistry and in everyday life

Heterocycles, or compounds containing cycles with at least one atom other than carbon, play a significant role in various aspects of everyday life and medicine. Here are some of their implications:

Everyday Life

Dyes and Pigments

Some heterocyclic compounds are used in the production of dyes and pigments that provide color to clothing, food, and other everyday products.

Examples

Indigo (found in blue jeans)

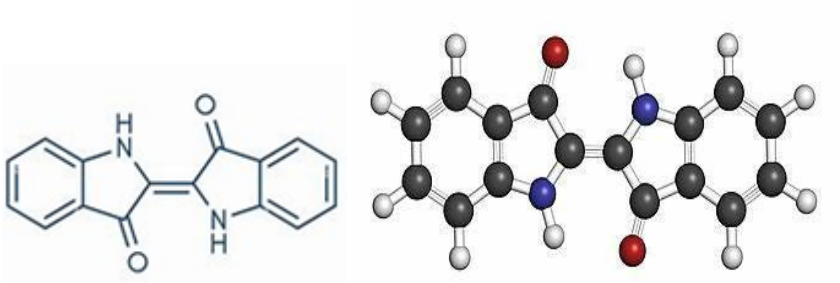


Figure a. Structure of indigo

Rhodamine (fluorescent dye)

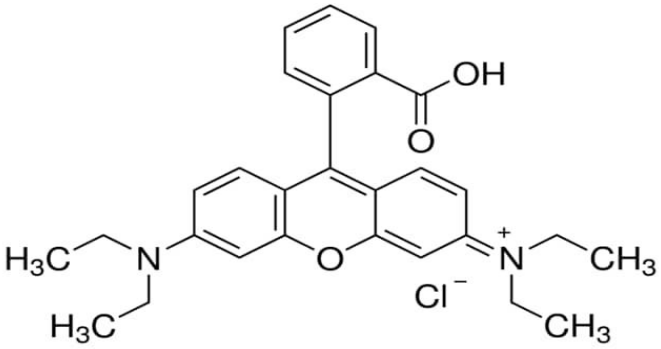
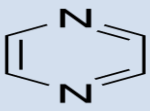
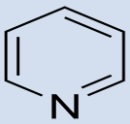
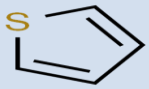
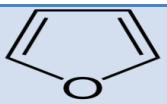
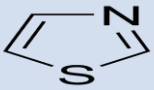


Figure b. Structure of Rhodamine

Flavors and Fragrances

Certain heterocyclic compounds are present in flavors and fragrances used in personal care products, cleaning products, and perfumes.

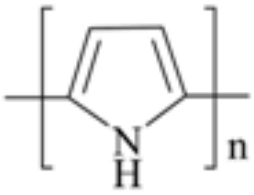
Examples

compound name	**Pyrazine**	**Pyridine**	**Thiophene**	**Furane**	**Thiazole**
compound structure					
Flavors or Fragrances	grilled or roasted, coffee, chocolate	tobacco flavors	garlic, onion	sweet and caramelized	hazelnut, ripe fruit and hay

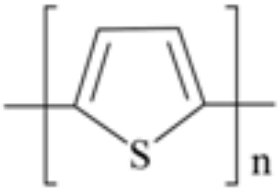
Polymers

Some heterocycles are used in the synthesis of polymers, which are widely used in the manufacturing of various products, including packaging, textiles, and construction materials.

Examples



Polypyrrol



Polythiophene

Medicinal Chemistry

Medications

Many drugs contain heterocycles in their structure. For example, antibiotics, antivirals, antidepressants, and many other types of drugs fall into this category.

Antibiotics

Examples

Penicillin :

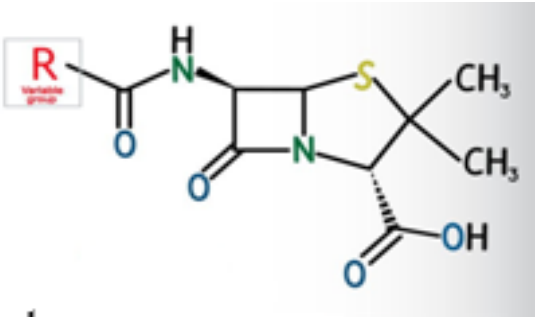


Figure a. Structure of Penicillin.

Ciprofloxacin :

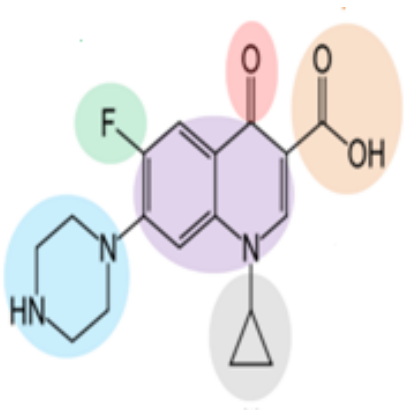


Figure b. Structure of Ciprofloxacin.

Antivirals

Zidovudine :

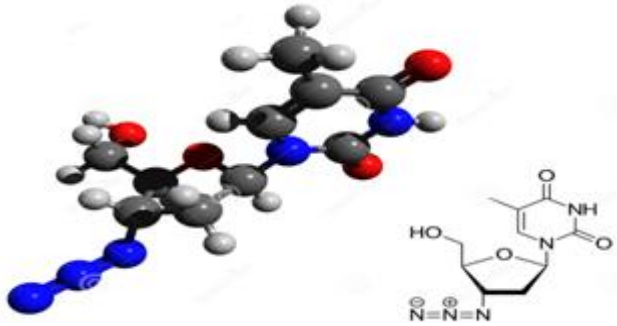


Figure a. Structure of Zidovudine.

Acyclovir :

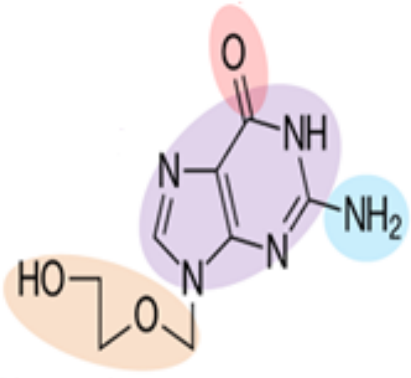


Figure b. Structure of Acyclovir.

Anti-depressants

Imipramine :

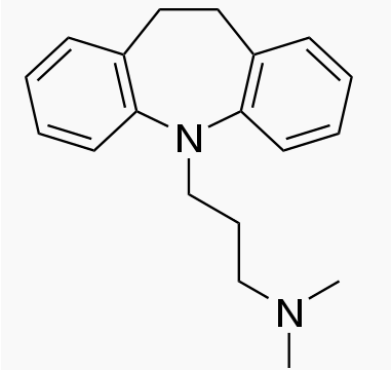


Figure a. Structure of Imipramine.

Anticancer Agents

Some heterocycles are used in the design of anticancer agents. Compounds such as quinolines and indole derivatives have shown anticancer properties.

Examples

Paclitaxel :

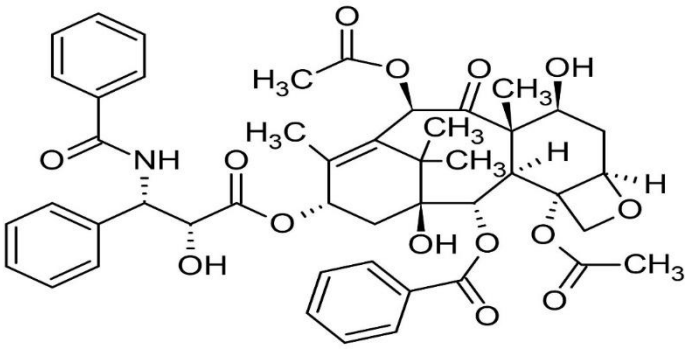


Figure a. Structure of Paclitaxel.

Imatinib :

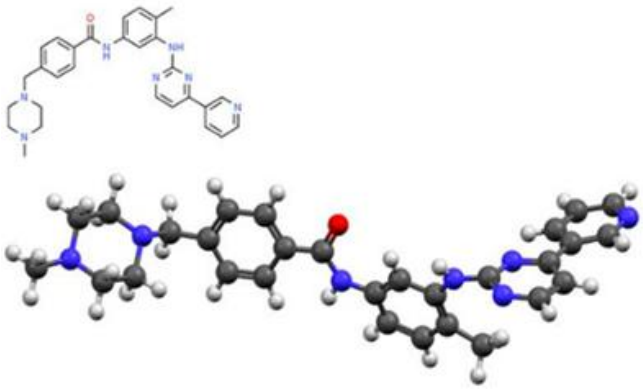


Figure b. Structure of Imatinib.

Diagnostic Reagents

Certain heterocycles are used in the synthesis of diagnostic reagents used in medical imaging, blood analysis, and other areas of diagnostic medicine.

Examples

Fluorescein (fluorescent tracer) :

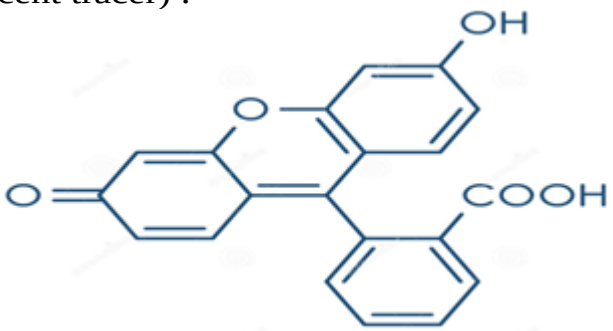


Figure a. Structure of Fluorescein.

Antimalarials

Antimalarial drugs like quinine, derived from quinoline, are used to treat malaria.

Examples

Chloroquine :

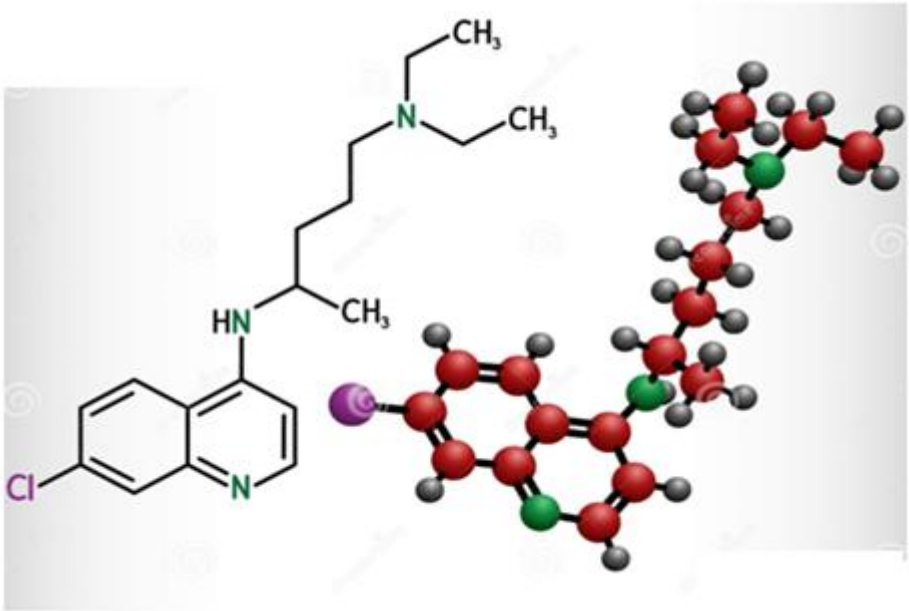


Figure a. Structure of Chloroquine.

Mefloquine :

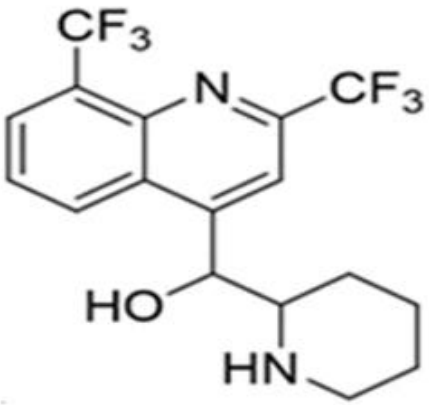


Figure b. Structure of Mefloquine.

Analgesics

Some heterocycles are present in analgesics, helping to alleviate pain.

Examples

Morphine :

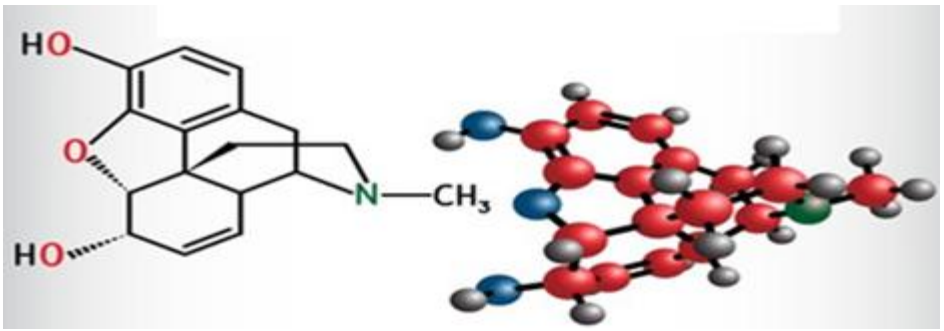


Figure a. Structure of Morphine.

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4. Comprehensive heterocyclic chemistry, edited by; A. R. Katritzky and C. W. Rees
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