MAIN SYNTHETICAL METHODS FOR THE PREPARATION OF HETARENES

- **1. Ring Synthesis Strategy**
  - **1.1. Hydrolytic disconnection**
  - **1.2. Redox disconnection**
  - **1.3. The mains precursors**
  - **1.3.1. Precursors as nucleophiles**
  - **1.3.2. Precursors as electrophiles**
  - **1.3.3. Precursors as both electrophiles and nucleophiles**

- **2. Substituent modification**

- **3. Nomenclature: I.U.P.A.C., general rules**

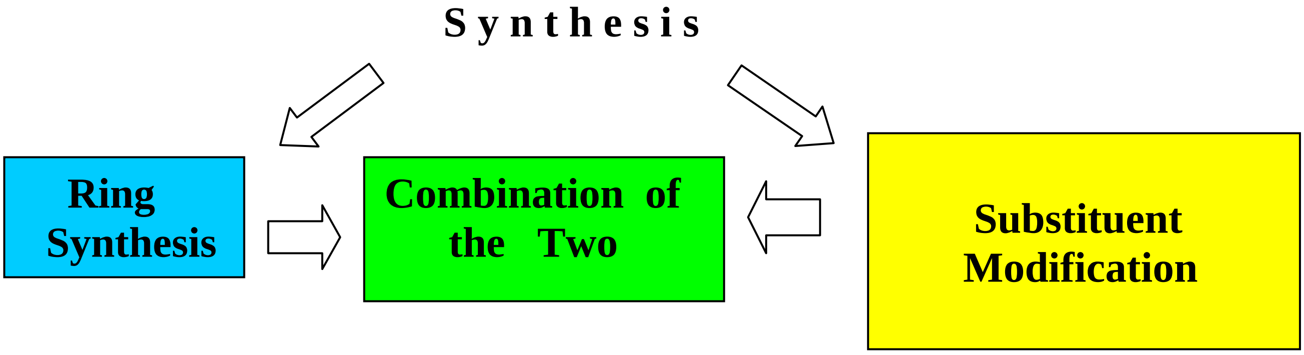
References:

1. Alan R. Katritzky, A. F. Pozharskii *Handbook of Heterocyclic Chemistry* 2nd Edition, Pergamon **2000**
2. Alan R. Katritzky *Short Course in Heterocyclic Chemistry for Ph. D. Students*, University of Florida **1996/1997**
3. David T. Davis *Chimie des Hétérocycles Aromatiques* De Boeck Université **1997**, Oxford University Press **1992**
4. René Milcent *Chimie Organique Hétérocyclique* EDP Sciences **2003**, www.edpsciences.org
5. Jonathan Clayden, Nick Greeves, Stuart Warren, Peter Wothers *Organic Chemistry*, De Boeck Diffusion s.a., **2003**, Oxford University Press **2001**, www.deboeck.com

Modifications (improvements, additions, corrections, up to dates *etc.*) are subjected to no notice.

MAIN SYNTHETICAL METHODS FOR THE PREPARATION OF HETARENES

Definition: the term ***hetarenes*** designes all heterocyclic compounds possessing aromatic character according to Hückel rule.



Synthesis

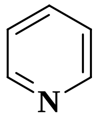
Ring Synthesis

Combination of the Two

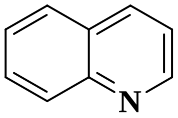
Substituent Modification

1. Ring Synthesis Strategy : the following *three* factors *increase the importance* of the ring synthesis

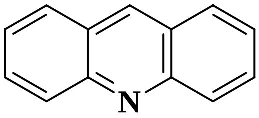
a) **Fused** Ring *vs.* **Mono** cyclic
b) **Five** *vs.* **Six** memebered Ring
c) **More Hetero** atoms



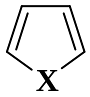
pyridine



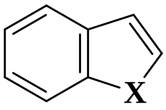
quinoline



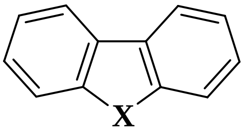
acridine



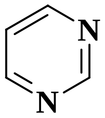
pyrrole X=NH
thiophene X=S
furane X=O



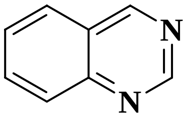
indole
benzothiophene
benzofurane



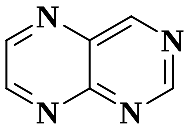
carbazole
dibenzothiophene
dibenzofurane



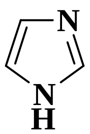
pyrimidine



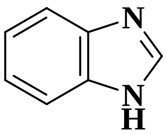
quinazoline



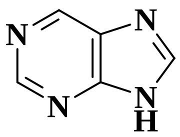
pteridine



imidazole



benzimidazole



purine

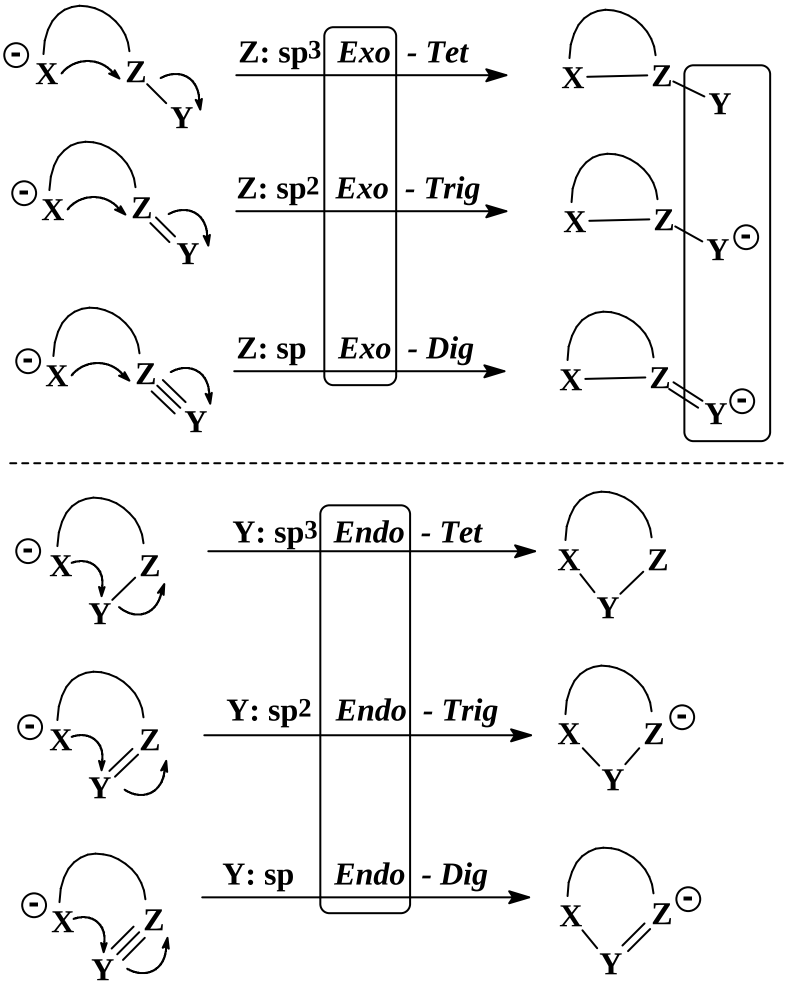
Ii it is **easier** to synthesise **a second ring** onto **a first one than** to synhtesise **a monocyclic compound.**

The **more heteroatoms** one has in the **ring,** the **more methods** of synthesis they are.

Substitution reactions tend to be **easier** on the whole when one has **fewer heteroatoms** in the ring.

Baldwin's Rules for 3 to 7 Membered Ring Closure

J. E. Baldwin *J. Chem. Soc., Chem. Commun.* **1976**, 734



Exo-Tet: **From 3 to 7 membered rings**
☞ **FAVOURED**

Exo-Trig: **From 3 to 7 membered rings**
☞ **FAVOURED**

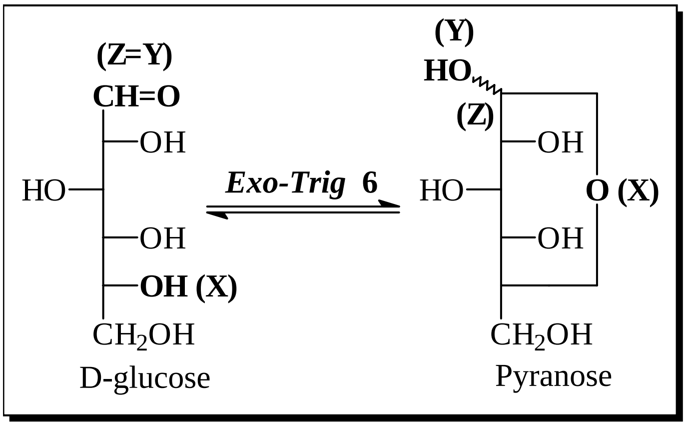
Exo-Dig: **From 3 to 4 membered rings**
☞ **DISFAVOURED**
Exo-Dig: **From 5 to 7 membered rings**
☞ **FAVOURED**

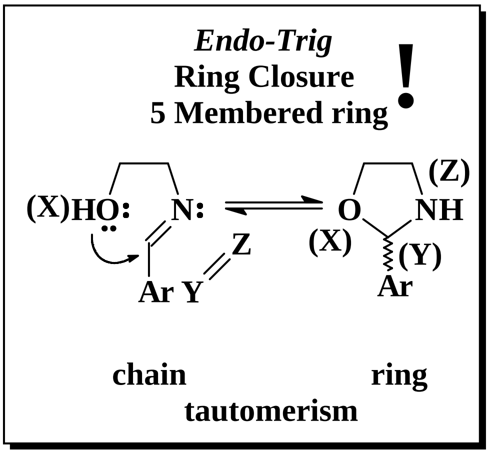
Endo-Tet: **From 5 to 6 membered rings**
☞ **FAVOURED**

Endo-Trig: **From 3 to 5 membered rings**
☞ **DISFAVOURED**
Endo-Trig: **From 6 to 7 membered rings**
☞ **FAVOURED**

Endo-Dig: **From 3 to 7 membered rings**
☞ **FAVOURED**

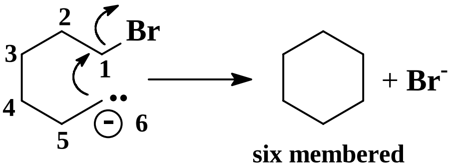
- i) all the above rules have **empirical support** only.
- ii) **disfavoured** does not mean **impossible** but **more difficult** to realise.
- iii) the **basic support** of the above rules is **stereochemical** (bond lenghts and bond angles).
- iv) a lot of cases (**before** and **after 1976** are in **substantial accord** with these rules).

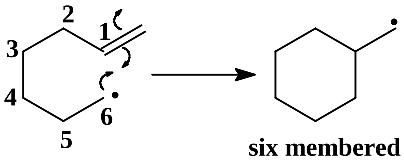


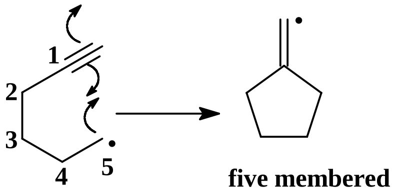


D. E. Bergmann, *Chem. Rev.* **1953**, *53*, 309-353
L. Lázár, F. Fülöp, *Eur. J. Org. Chem.* **2003**, 3025-3042

Examples : *exo*-cyclisations according to stereoelectronic requirements in the transition state



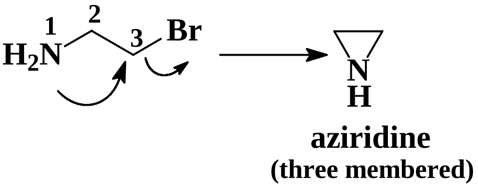


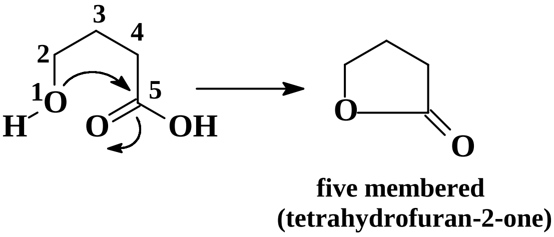


<u>6-*exo*-tet</u> cyclisation
(Intramolecular SN_2)
FAVOURED
Stereoelectronically

<u>6-*exo*-trig</u> cyclisation
(Intramolecular RA)
FAVOURED
Stereoelectronically

<u>5-*exo*-dig</u> cyclisation
(Intramolecular RA)
FAVOURED
Stereoelectronically

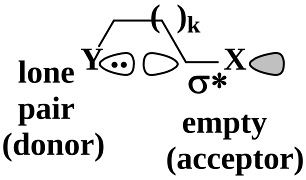


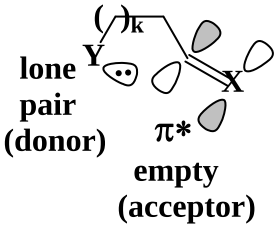


<u>3-*exo*-tet</u> cyclisation
(Intramolecular SN_2)
FAVOURED
Stereoelectronically

<u>5-*exo*-trig</u> cyclisation
(Intramolecular SN_2)
FAVOURED
Stereoelectronically

Generalisation:





<u>n-*exo*-tet</u> cyclisation
k = 0 - 4
FAVOURED
Stereoelectronically

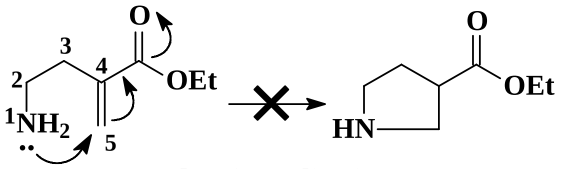
<u>n-*exo*-trig</u> cyclisation
k = 0 – 4
FAVOURED
Stereoelectronically

***exo*-dig** cyclisations are favoured for **five** to **seven** membered rings

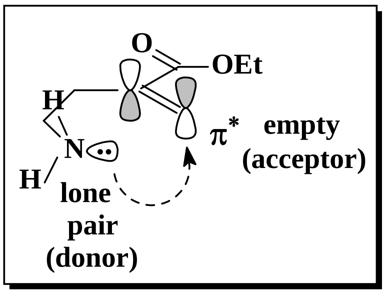
Examples: *endo*-cyclisations according to stereoelectronic requirements in the transition state

NOTE: only 6- and 7-*endo*-tet cyclisation are favoured
all 3 – 7-*endo*-dig cyclisations are favoured
almost all 3 – 7-*endo*-tet cyclisations are less favoured

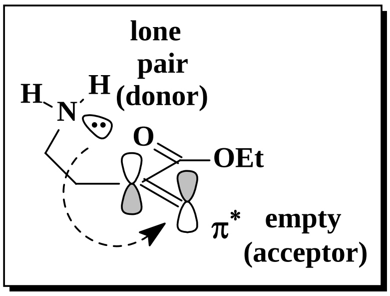
Plausible but…



5-*endo*-trig cyclisation
DISFAVOURED
(Intramolecular 1,4-addition)

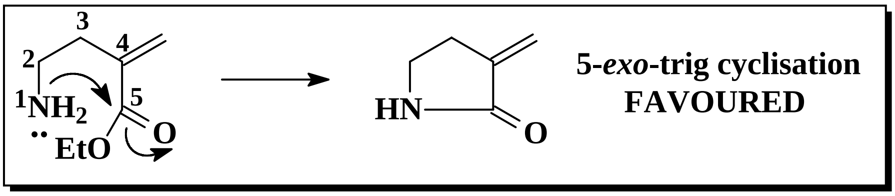


Inappropriate orientation



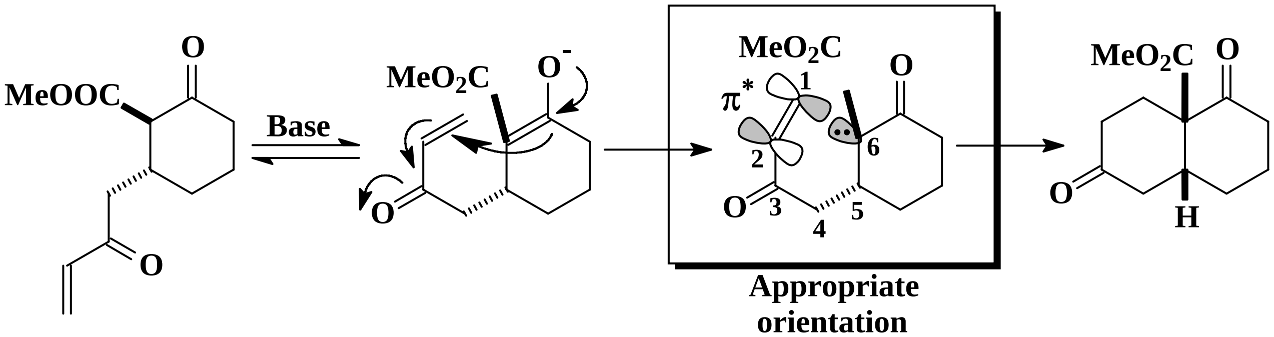
Too far...

This is the real:



5-*exo*-trig cyclisation
FAVOURED

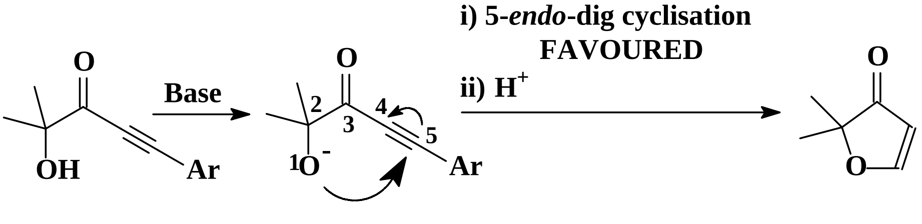
A 6-*endo*-trig cyclisation: **favoured, occuring in 89 % yield**

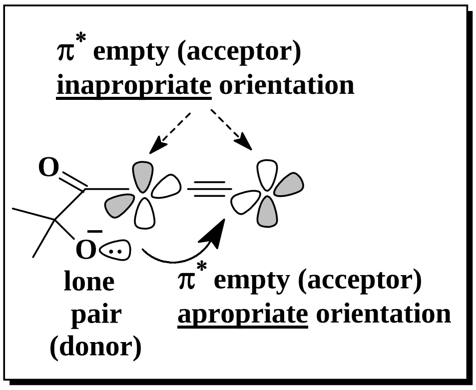


Appropriate orientation

***trans* stereochemistry with respect to cyclanone ring**

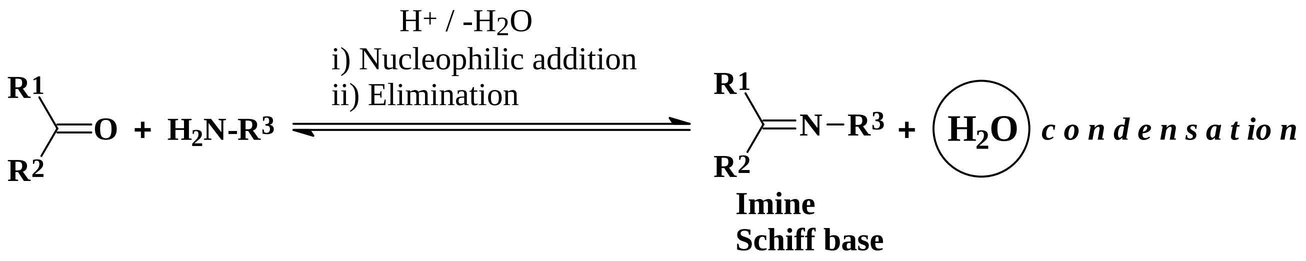
A 5-*endo*-dig cyclisation: **favoured**



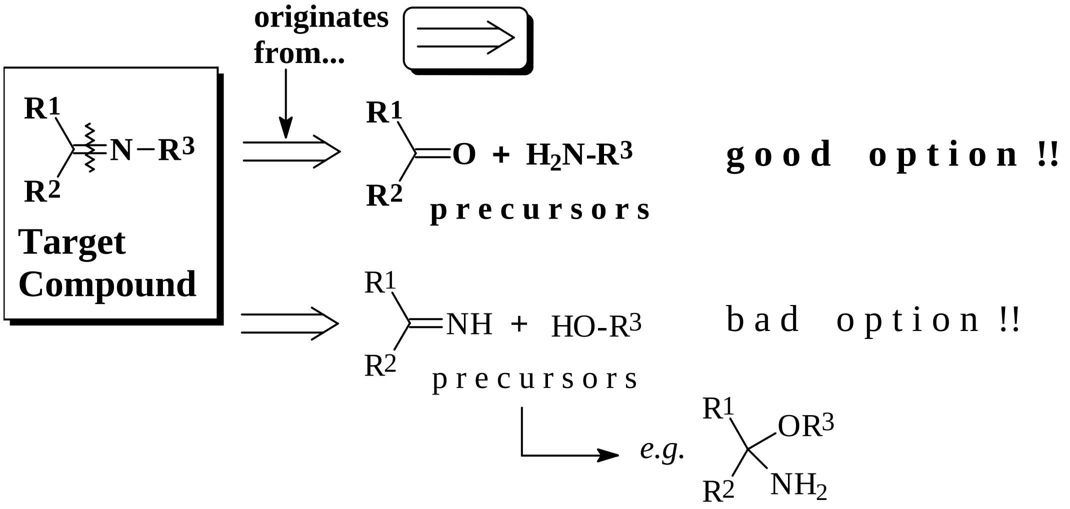


1.1. Hydrolytic disconnection

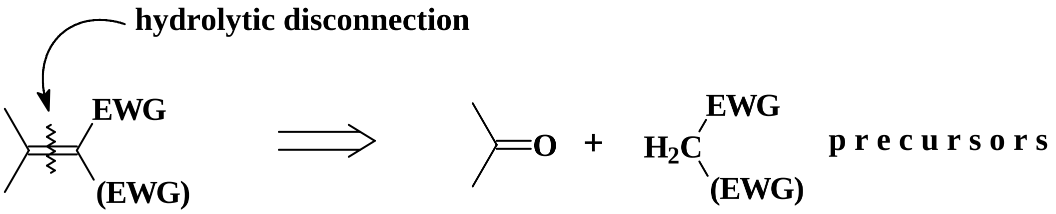
- **hydrolytic disconnections** of the **double bonds** are very useful since **most of the ring closures** to afford heterocyclic systems are **simple condensation**



Example 1:

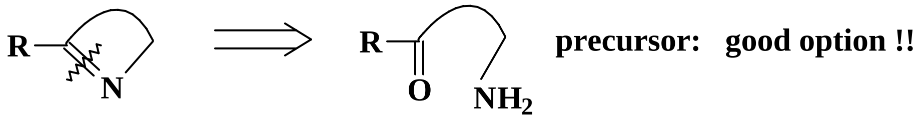


Example 2:

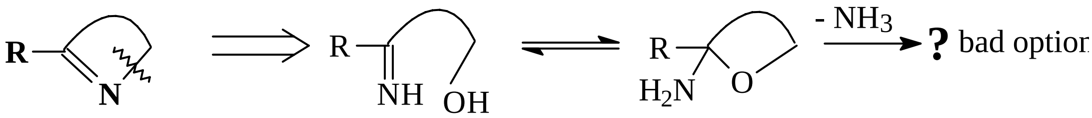


EWG: **E**lectro(no) **W**ithdrawing **G**roup
CO, COOR, CN, etc.

Example 3:



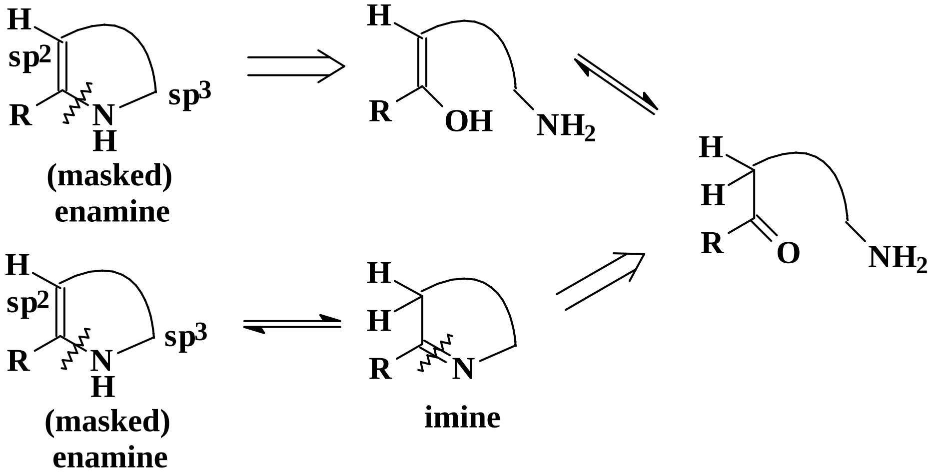
heterocyclic compound
seen as a **cyclic imine**



heterocyclic compound
seen as a cyclic amine

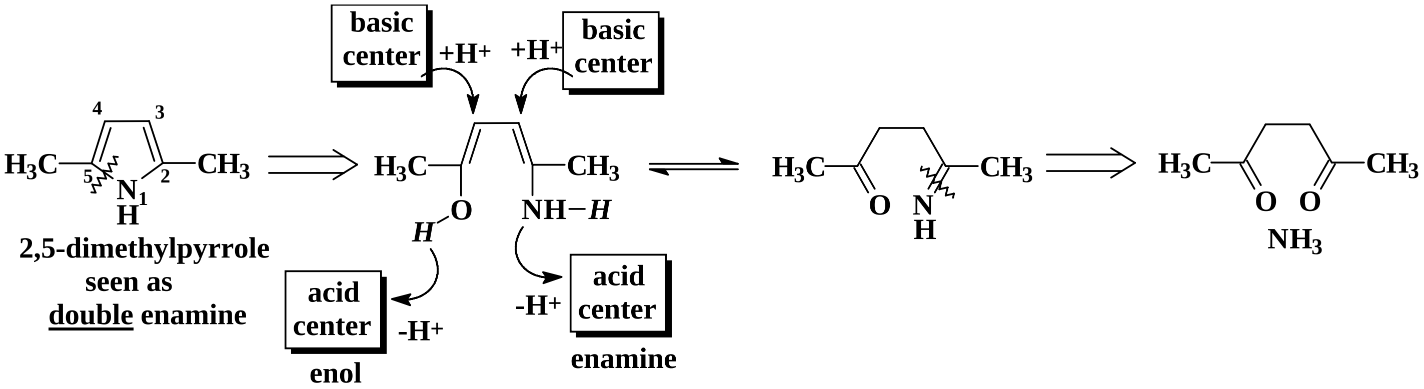
Example 4:

Imine or enamine ? **It doesn't matter…**



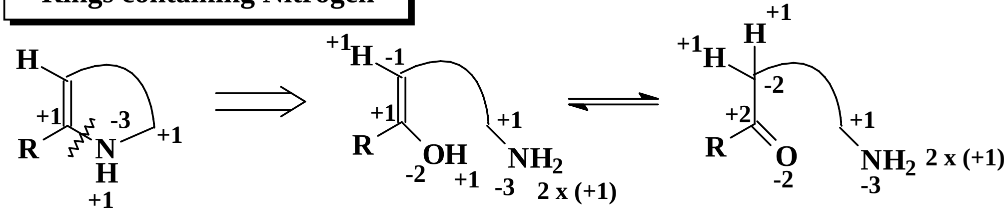
Example 5:

Retrosynthesis of pyrroles seen as hydrolytic disconnection:

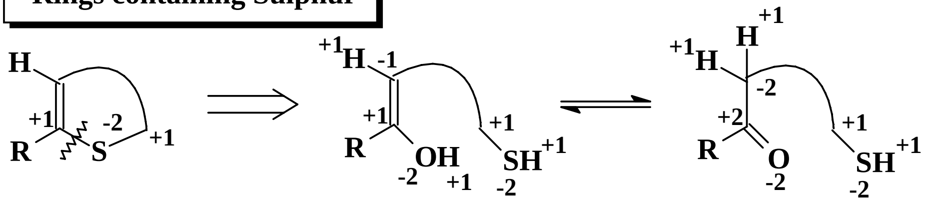


Example 6: the importance of the formal charges

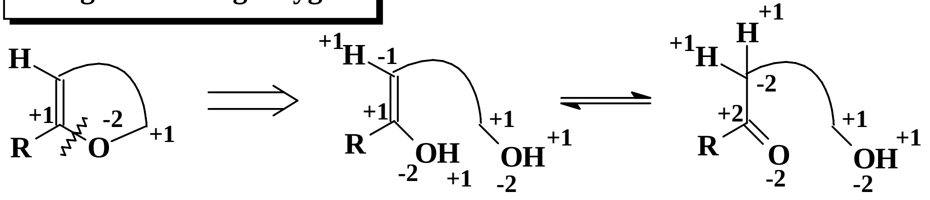
Rings containing Nitrogen



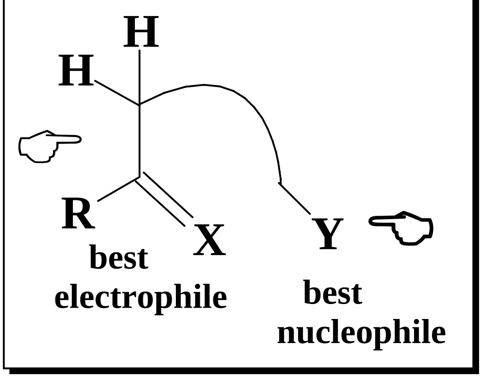
Rings containing Sulphur



Rings containing Oxygen



the best precursor



To be kept in mind:

1. If a hydrolytic disconnection appears suitable, the best pair nucleophile-electrophile sould be considered

2. All cyclisations (or cyclocondensations) involve classic tautomerism: keto-enolic, imino-enamine, etc.

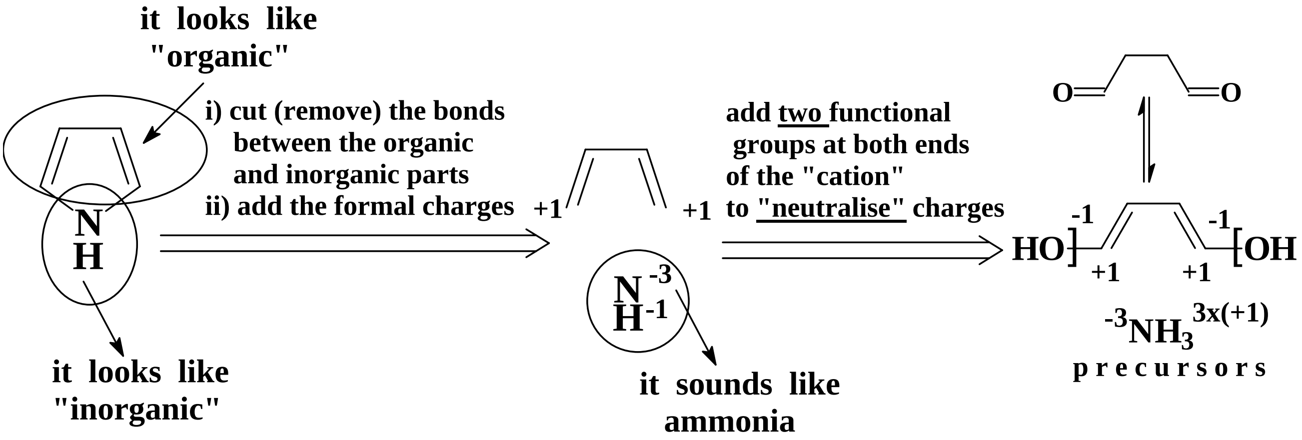
3. During cyclocondensation (or retrosynthetic hydrolytic disconnection) <u>no global redox process</u>, involving <u>the whole molecule</u> occurs.

<u>1.2. Redox disconnection</u>

-this methodology provides information about the general strategy to be used to access the target compound: <u>is there any redox step</u> ?

<u>Example 1:</u>

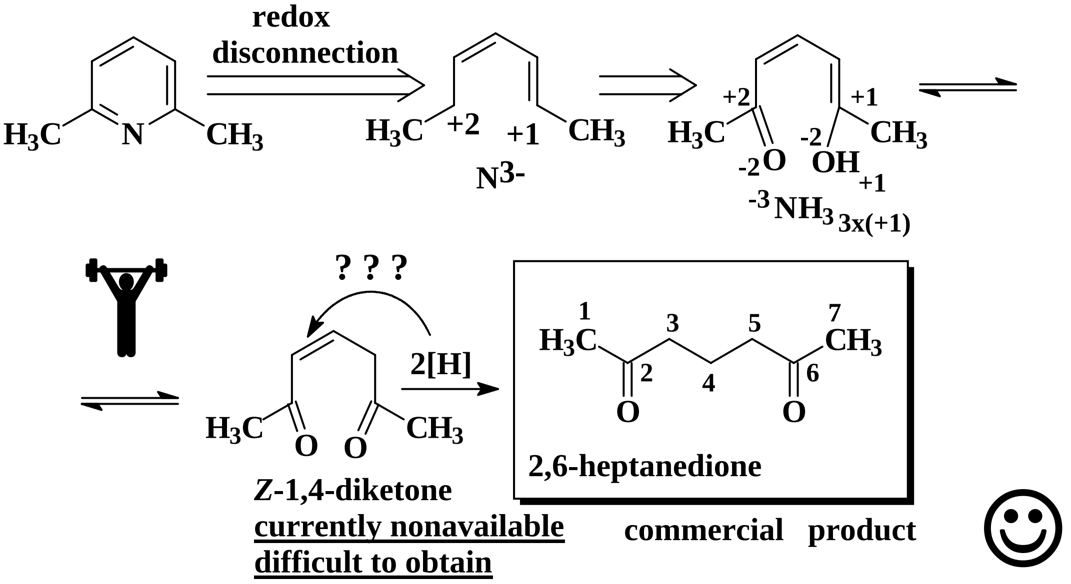
- a **five membered** hetarene:



Obs: the structure of the target compound (bond connection and aromaticity) is automatically issued by preserving the formal charges of each of the involved (hetero)atoms: **no redox step in the synthesis**

<u>Example 2:</u>

- a **six membered** hetarene



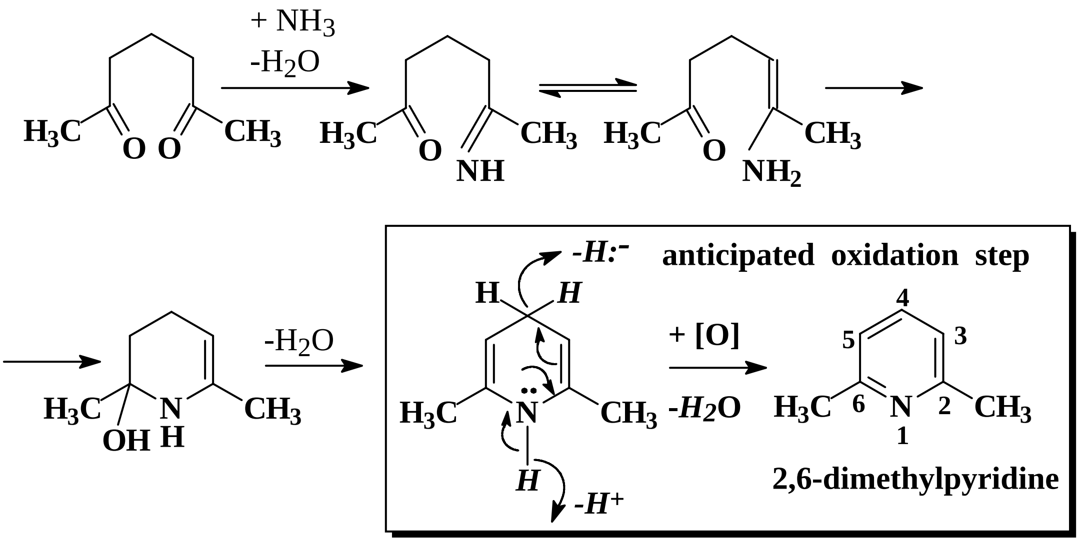
is the above disconnection useful for a chemist ? Why ?

a) Because it provides rapidly the type of precursors

b) Because it provides rapidly the most convenient precursors.

c) Because it infers that if, **for reason of availability**, a **redox step is revealed** (*e.g. reduction*) by the **redox disconnection**, in the **synthesis** of the target molecule **a redox step must be accomplished**: *e.g. oxidation.*

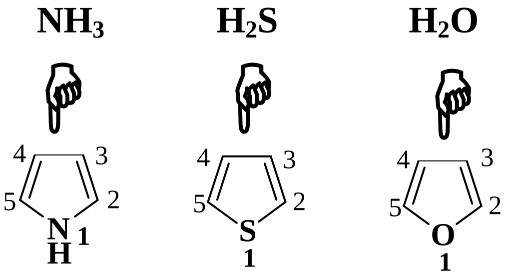
The direct synthesis:



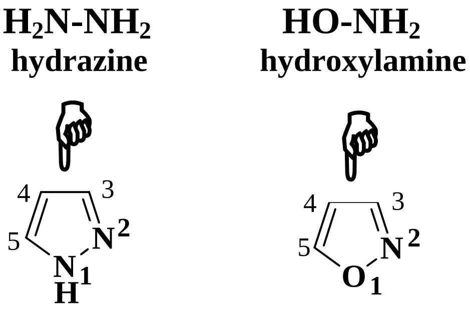
1.3. The main precursors

1.3.1. Precursors as Nucleophiles: this is **the traditional route** to bring **heteroatoms** (**N, S, O**) in the target compound

Example 1: bringing **one heteroatom** in the target compound:

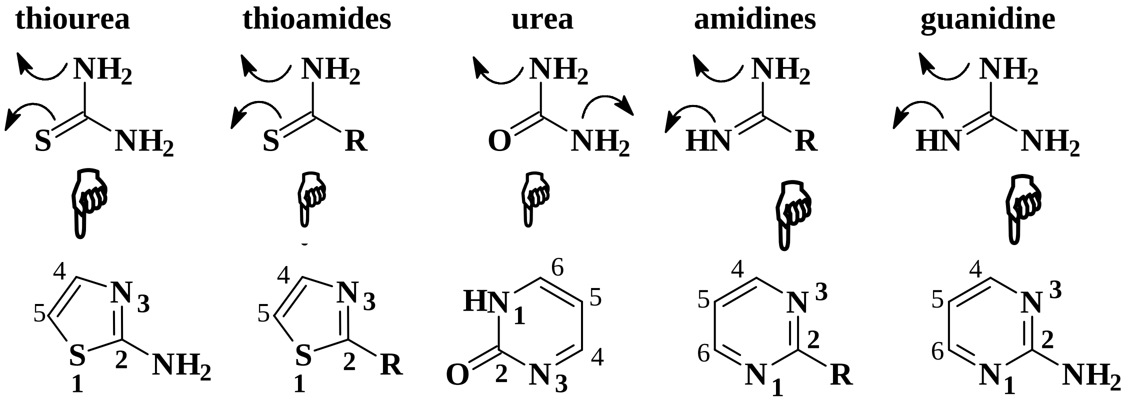


Example 2: bringing **two heteroatoms** in the target compound:



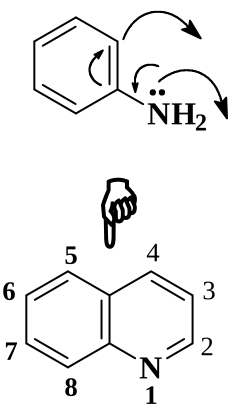
pyrazole isoxazole

Example 3: bringing **three atoms** in the target compound:

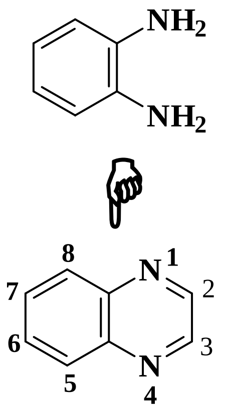


2-substituted thiazoles **2-pyrimidone** **2-substituted pyrimidines**

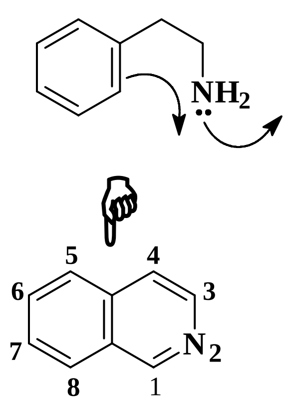
Example 4: bringing **three**, **four** and **five atoms** in the target compound: **benzoderivatives**



Quinoline



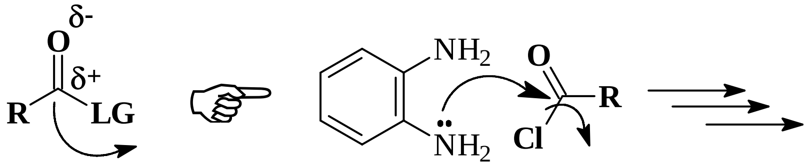
Quinoxaline

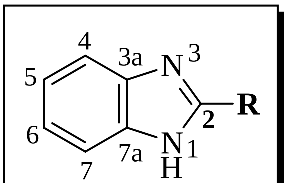


Isoquinoline

1.3.2. Precursors as Electrophiles:

Example 1: bringing **one atom**:

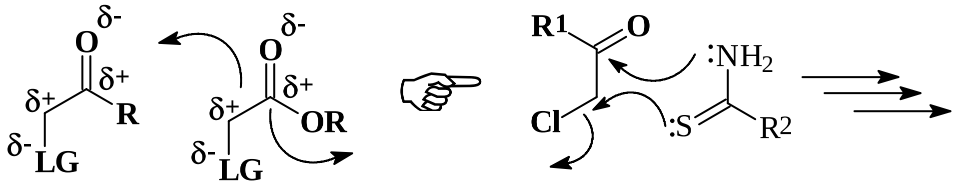


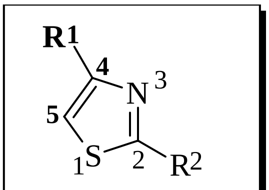


2-substituted benzimidazoles

LG: *leaving group as* **LG:⁻**
e.g. **Cl** as **Cl⁻**; **R'O** as **R'OH** etc.

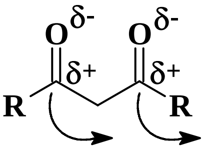
Example 2: bringing **two atoms**:



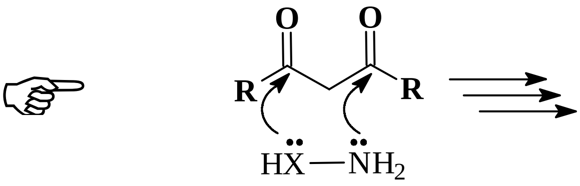


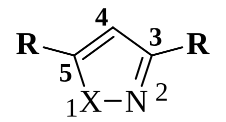
2,4-disubstituted thiazoles

Example 3: bringing **three atoms**:

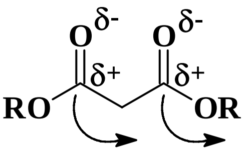


1,3-dicarbonylic compounds

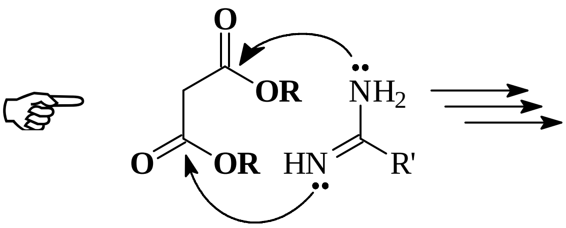


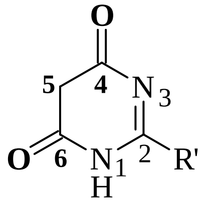


3,5-disubstituted
X = NH pyrazoles
X = O isoxazoles

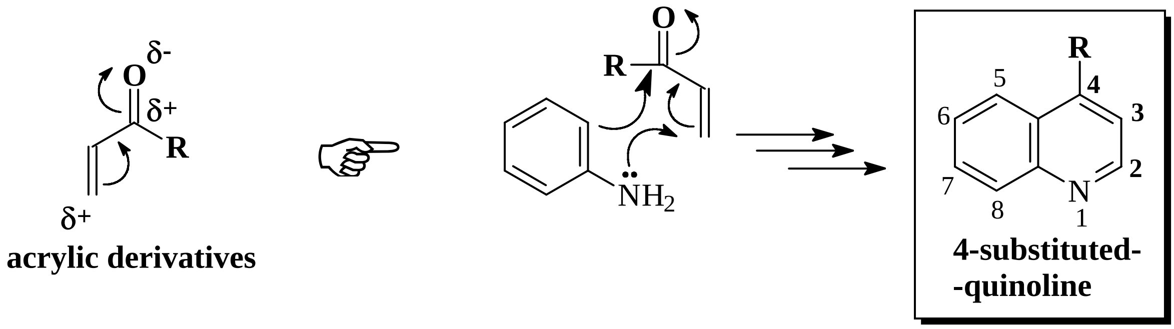


malonic esters





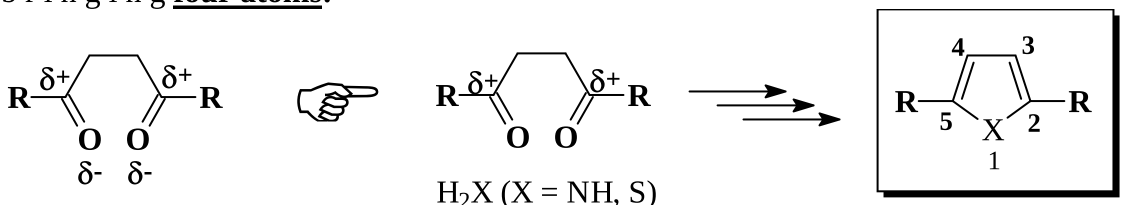
2-substituted-pyrimidin-
-4,6-dione



acrylic derivatives

4-substituted--quinoline

Example 4: bringing **four atoms**:



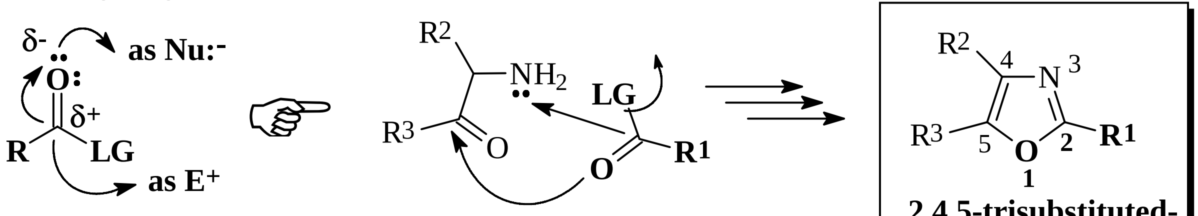
H_2X (X = NH, S)

1,4-diketones

Note: electrophilic fragments usually **do not bring heteroatoms** in the target compound

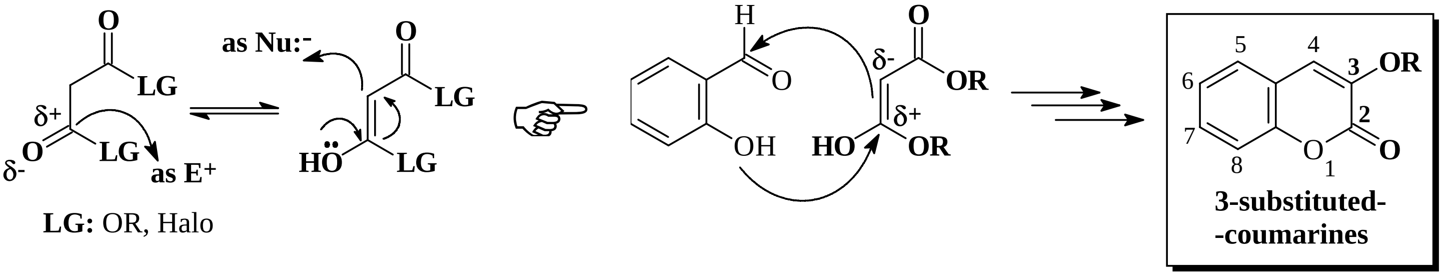
1.3.3. Precursors as *both* Electrophiles and Nucleophiles:

Example 1: bringing **two atoms:**



2,4,5-trisubstituted--oxazoles

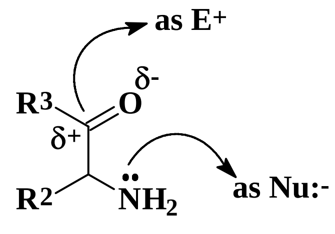
LG: *leaving group as* **LG:-**
e.g. **Cl** as **Cl-**



LG: OR, Halo

3-substituted--coumarines

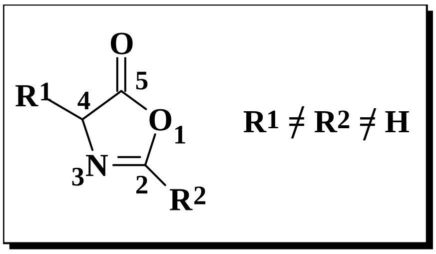
Example 2: bringing **three atoms**, see **Example 1**



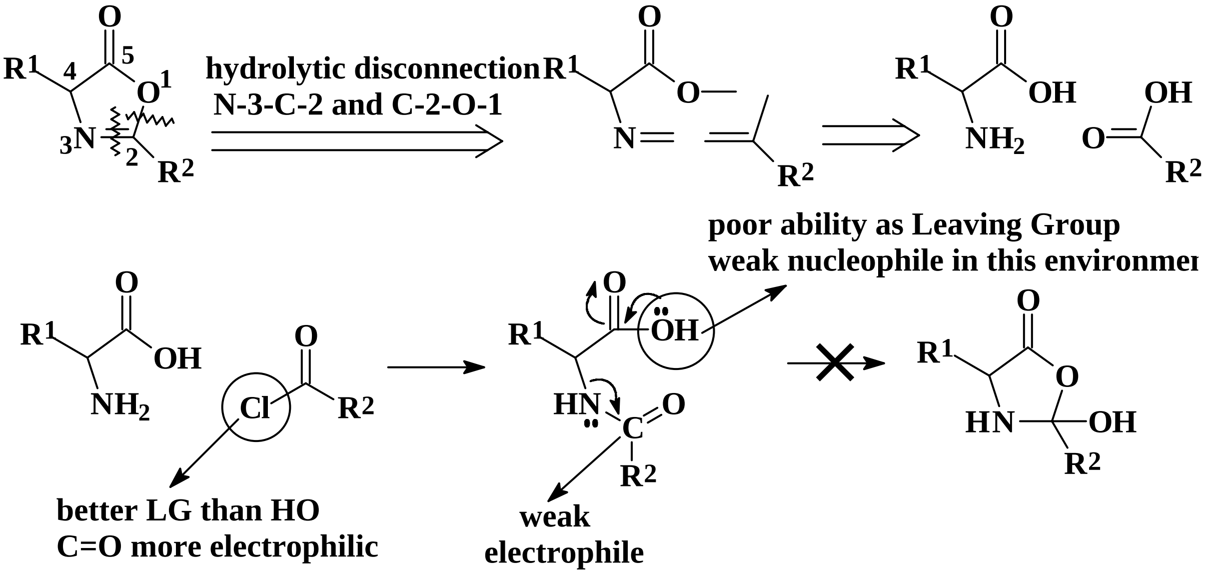
an α-aminoketone

<u>Example 3:</u> acid chlorides **as good <u>electrophiles</u>** to generate **good <u>nucleophiles.</u>**

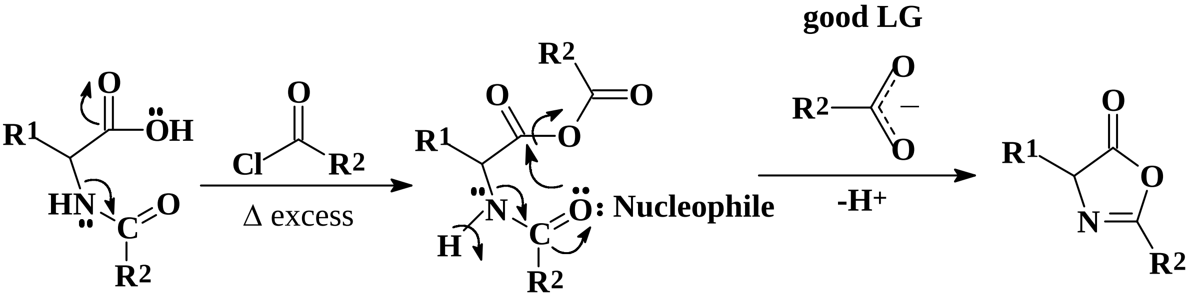
The target compound:



Retrosynthetic analysis:



Solution of the problem:

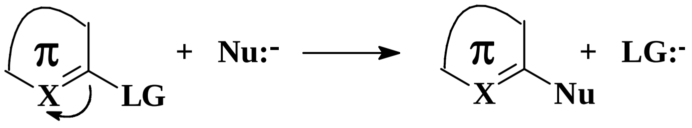


Note: obsolete cyclisation of α-aminoacids as double protected *N*-, *C*OO- form (oxazoline)

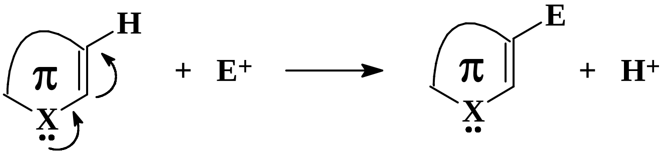
2. Substituent modification

- the below **three main** types of substituent modification are of general interest

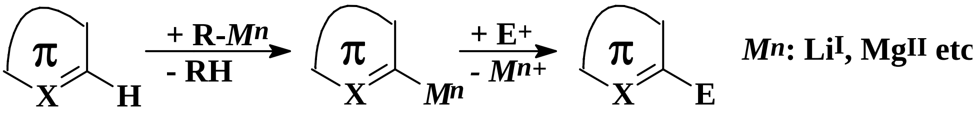
i) nucleophilic displacement:



ii) electrophilic displacement:



iii) electrophilic displacement *via* metallation:



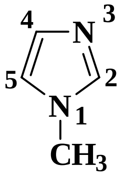
3. Nomenclature: IUPAC general rules

- important **trivial names** are given at the beginning of each chapter: *e.g. **pyridine*** instead of ***azabenzene***
- the **type of heteroatom** present in the ring is indicated by **the** below **prefixes**, in **decreasing order of citation** (nomenclature as **a**):

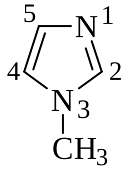
O oxa > S thia > Se selena > N aza > P phospha > As arsa > Si sila > B bora etc.

Note: the final **a** is however elided before a vowel *e.g.* **az**a**ole** → **azole**

- **two** or **more identical heteroatoms** are indicated by **dioxa**, **triaza**, etc.
- If **different,** the **prefixes** should be **combined** according to the above order: ***e.g.* thi**a-**az**a-**ole** → **thiazole**; ***e.g.* oxa-diaz**a-ole → **oxadiazole**; ***e.g.* oxa-thi**a-**ane** → **oxathiane.**
- **numbering of the positions starts at an oxygen, sulphur or nitrogen** (in decreasing order of preference) and **continues** in such way that the **heteroatoms** are assigned **the lowest possible numbers.**
- other things being equal, **numbering starts** at a **substituted** rather than at **a multiply bonded nitrogen** atom.



1-methyl-1,3-diazole
1-methylimidazole



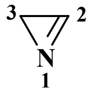
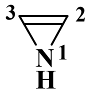
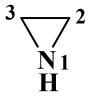
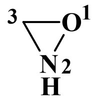
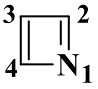
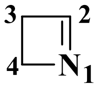
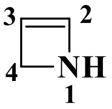
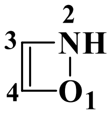
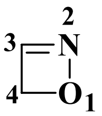
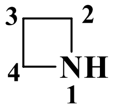
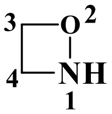
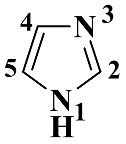
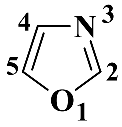
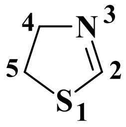
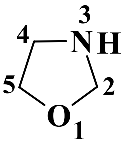
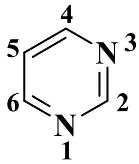
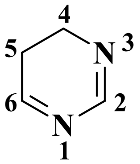
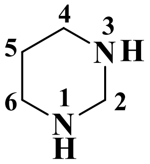
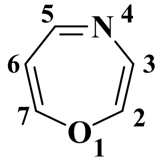
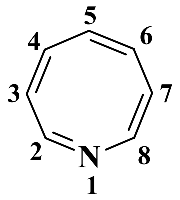
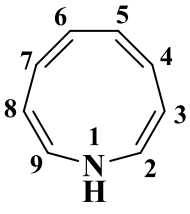
3-methyl-1,3-diazole
3-methylimidazole

MAXIMUM UNSATURATION is defined as THE MAXIMUM POSSIBLE NON CUMULATIVE DOUBLE BONDS BY CONSIDERING:

O- two valencies
S – two valencies
N – three valencies

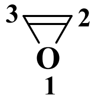
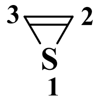
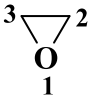
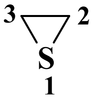
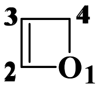
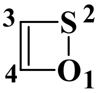
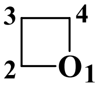
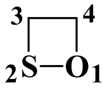
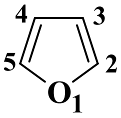
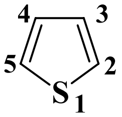
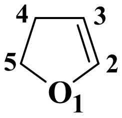
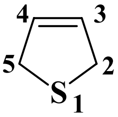
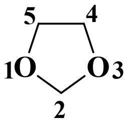
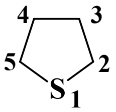
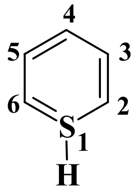
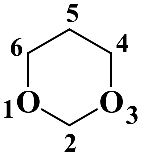
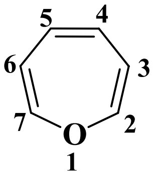
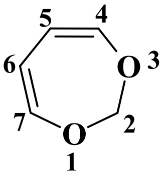
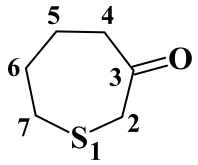
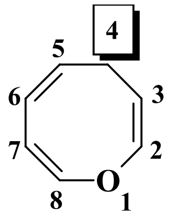
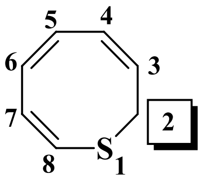
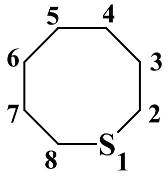
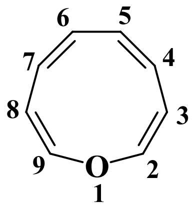
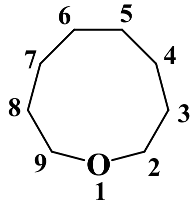
The Hantzsch-Widman Nomenclature for Heterocyclic Compounds

Rings with Nitrogen

Ring Size	Maximum Unsaturation		One Double Bond		Saturated	
3	***Eng.*** ***-irine*** **Rom.** **-irină**	 1-az*irine*  2-az*irine*	**-**	**-**	***Eng.*** ***-iridine*** **Rom.** **-iridină**	 az*iridine*  oxaz*iridine*
4	***Eng.*** ***-ete*** **Rom.** **-etă**	 az*ete*	***Eng.*** ***-etine*** **Rom.** **-etină**	 1-az*etine*  2-az*etine*   2*H*-1,2-oxaz*etine* 4*H*-1,2-oxaz*etine*	***Eng.*** ***-etidine*** **Rom.** **-etidină**	 az*etidine*  1,2-oxaz*etidine*
5	***Eng.*** ***-ole*** **Rom.** **-ol**	 1,3-diaz*ole* imidazole  1,3-oxaz*ole*	**Eng.** ***-oline*** **Rom.** **-olină**	 Δ^2-thiaz*oline*	***Eng.*** ***-olidine*** **Rom.** **-olidină**	 1,3-oxaz*olidine*
6	***Eng.*** ***-ine*** **Rom.** **-ină**	 1,3-diaz*ine* pyrimidine	-	 4,5-*dihydro*pyrimidine	Nomenclature is made by using the prefix ***perhydro*** (*total hydrogenated*) which precedes the name of the corresponding non saturated structure  *perhydro*-1,3-diaz*ine*	
7	***Eng.*** ***-epine*** ***Rom.*** **-epină**	 1,4-oxaz*epine*	-	-		
8	***Eng.*** ***-ocine*** **Rom.** **-ocină**	 az*ocine*	-	-		
9	***Eng.*** ***-onine*** **Rom.** **onină**	 1*H*-az*onine*	-	-		

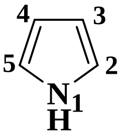
The Hantzsch-Widman Nomenclature for Heterocyclic Compounds

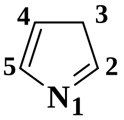
Rings without Nitrogen

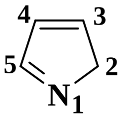
Ring Size	Maximum Unsaturation		One Double Bond		Saturated	
3	***Eng.*** ***-irene*** ***Rom.*** **irenă**	 oxi*rene*  thii*rene*	-	-	***Eng.*** ***-irane*** **Rom.** **-iran**	 oxi*rane*  thii*rane*
4	***Eng.*** ***-ete*** **Rom.** **-etă**	 ox*ete*  1,2-oxathi*ete*	***Eng.*** ***-etene*** **Rom.** **-etenă**	-	***Eng.*** ***-etane*** **Rom.** **-etan**	 ox*etane*  1,2-oxathi*etane*
5	***Eng.*** ***-ole*** **Rom.** **-ol**	 ox*ole* furane  thi*ole* thiophene	***Eng.*** ***-olene*** **Rom.** **-olen**	 Δ^2-ox*olene*  Δ^3-thi*olene*	***Eng.*** ***-olane*** **Rom.** **-olan**	 1,3-diox*olane*  thi*olane*
6	***Eng.*** ***-in*** **Rom.** **-ină**	 thii*n*	-		***Eng.*** ***-ane*** **Rom.** **-an**	 1,3-diox*ane*
7	***Eng.*** ***-epin*** **Rom.** **epină**	 ox*epin*  1,3-diox*epin*	-		***Eng.*** ***-epane*** **Rom.** **-epan**	 thi*epane*-3-one
8	***Eng.*** ***-ocin*** **Rom.** **ocină**	 4*H*-oxo*cin*  2*H*-thio*cin*	-		***Eng.*** ***-ocane*** **Rom.** **-ocan**	 thi*ocane*
9	***Eng.*** ***-onin*** **Rom.** **onină**	 ox*onin*	-		***Eng.*** ***-onane*** **Rom.** **-onan**	 ox*onane*

- **indicated hydrogen:** ***H*** in compounds possessing **maximum unsaturation**, if the *double bonds* can be **arranged** **<u>in more than one way</u>**, their positions are defined by **indicating the nitrogen or carbon** atoms **<u>which are not multiply bonded</u>** and consequently carry an **"extra" hydrogen atom**: 1*H*, 2*H*, etc.
- in **partially saturated compounds, the position of the hydrogen atoms** can be indicated by the prefixes **dihydro if convenient suffix is not available**
- in **partially saturated compounds**, the position of the double bond can be indicated by the symbol $\Delta^{a,b}$ which indicates that the double bond is between the atoms numbered **"a"** and **"b"**

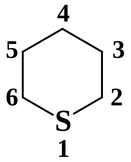
Example 1:

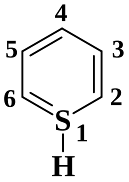

1*H*-pyrrole

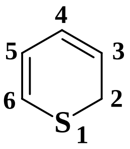

3*H*-pyrrole

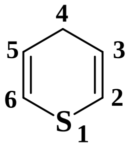

2*H*-pyrrol

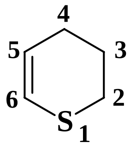
Example 2:

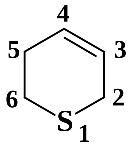

thiane (I.U.P.A.C.)
3,4,5,6-tetrahydro-2*H*-thiin


1*H*-thiin


2*H*-thiin


4*H*-thiin


3,4-dihydro-2*H*-thiin
2,3-dihydro-4*H*-thiin

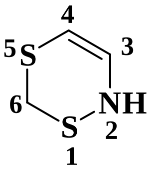

5,6-dihydro-2*H*-thiin

with suffix according to IUPAC: *in*

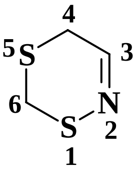
no suffix available according to IUPAC

Note: the **number** of the **indicated hydrogen is the lowest** possible

Example 3:

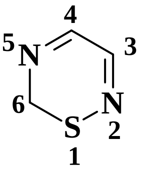


2*H*,6*H*-1,2,5-dithiazine → max. unsaturation possible is **1 double bond**: suffix **ine**
→ order of citation: **S, S > N**
→ supplementary hydrogen at **N-2** and **C-6**: **2*H*,6*H***

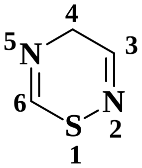


4*H*,6*H*-1,2,5-dithiazine → max. unsaturation possible is **1 double bond**: suffix **ine**
→ order of citation: **S, S > N**
→ supplementary hydrogen at **C-4** and **C-6**: **4*H*,6*H***

Example 4:



6*H*-1,2,5-thiadiazine → max. unsaturation possible is **2 double bonds**: suffix **ine**
→ order of citation: **S > N, N**
→ supplementary hydrogen at **C-6**: **6*H***



4*H*-1,2,5-thiadiazine → max. unsaturation possible is **2 double bonds**: suffix **ine**
→ order of citation: **S > N, N**
→ supplementary hydrogen at **C-4**: **4*H***