DIAZINES

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3.2. Two aza-atoms in positions 1, 3
3.2.1. Monocyclic rings: pyrimidines
3.2.2. Fused rings: quinazolines

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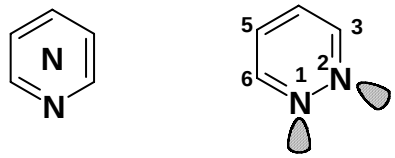
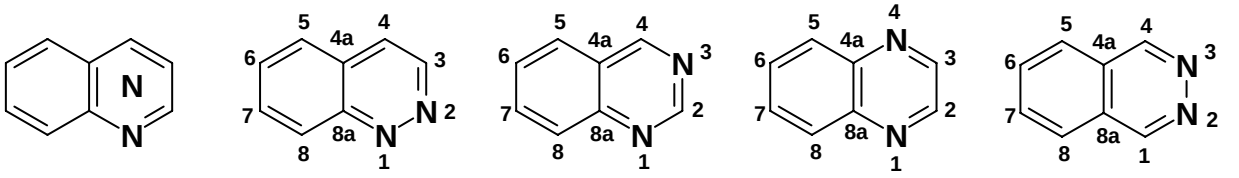
Modifications (improvements, additions, corrections, up to dates *etc.*) are subjected to no notice.

D I A Z I N E S

1. Typical representatives and symbols:



symbol **pyridazine** **pyrimidine** **pyrazi**

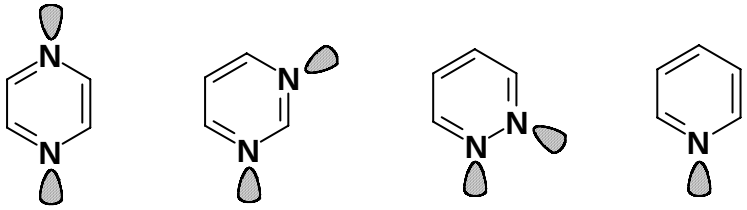


symbol **cinnoline** **quinazoline** **quinoxaline** **phthalazin**

benzo[*c*]pyridazine **benzo[*d*]pyrimidine** **benzo[*b*]pyrazine** **benzo[*d*]pyridazine**

2. Structure:

2.1. Basicity:



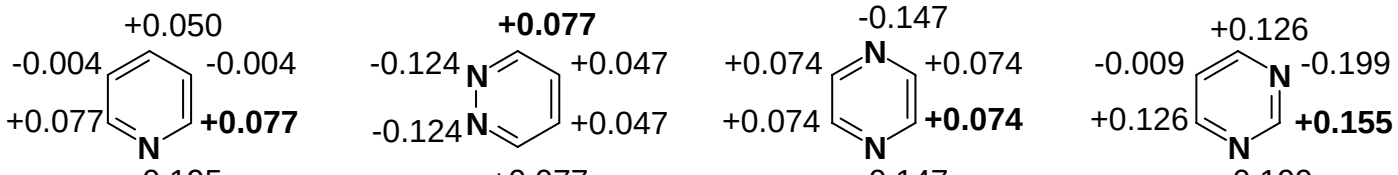
pKb **13.49** **12.77** **10.76** **8.7**

- **additional pyridine-like nitrogen strongly decreases basicity (protonation is less tolerated by the previous *N*-atom**); more stabilization of the protonated form is plausible for pyridazine in order to avoid adjacent lone-pair *vs.* lone pair repulsion in the neutral form.

2.2. Aromaticity:

- they all are **π-deficient** systems as indicated by the **Atomic π-charges**:

Total π - deficiency



i) The order is different if relative local **π-deficiency** (the **largest positive charge** on any carbon atom in a molecule) is considered.

ii) The **π-acceptor action** of heteroatoms in azines is **most effective** when they are ***meta*-position** each other (pyrimidine).

iii) The ***ortho-para* disposition** subjects each carbon atom **to two contradicroty** forces: **a)** the strong electron acceptor influence of an *ortho-para*-nitrogen; **b)** the weak electron donor influence of a *meta*-nitrogen.

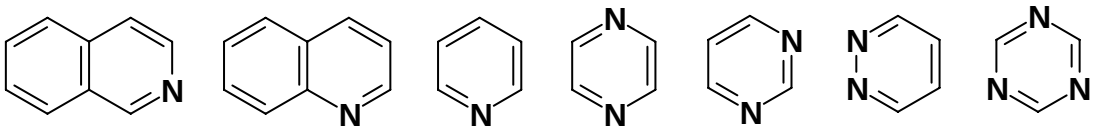
Important notes:

1. The resonance energy (**ER**) decreases as the number of pyridine like nitrogen increases, according to all methods used to evaluate them (calculation, estimation).

Benzene > Pyridine > Pyrimidine > Pyrazine > Pyridazine

ER (kj/mol)	**151**	**142**	**138**	**134**	**109**

2. As the number of pyridine like nitrogen atoms increases, the heterocycle becomes more **π-acceptor** and **less π-donor** as revealed by the HMO Energies of Frontier (both **decreasing** β-values)



E_{LUMO} (β<0)	- 0.576	- 0.527	- 0.841	- 0.686	- 0.871	- 0.727	- 0.78
E_{HOMO} (β<0)	+ 0.646	+ 0.703	+ 1.000	+1.000	+ 1.077	+ 1.101	+ 1.28

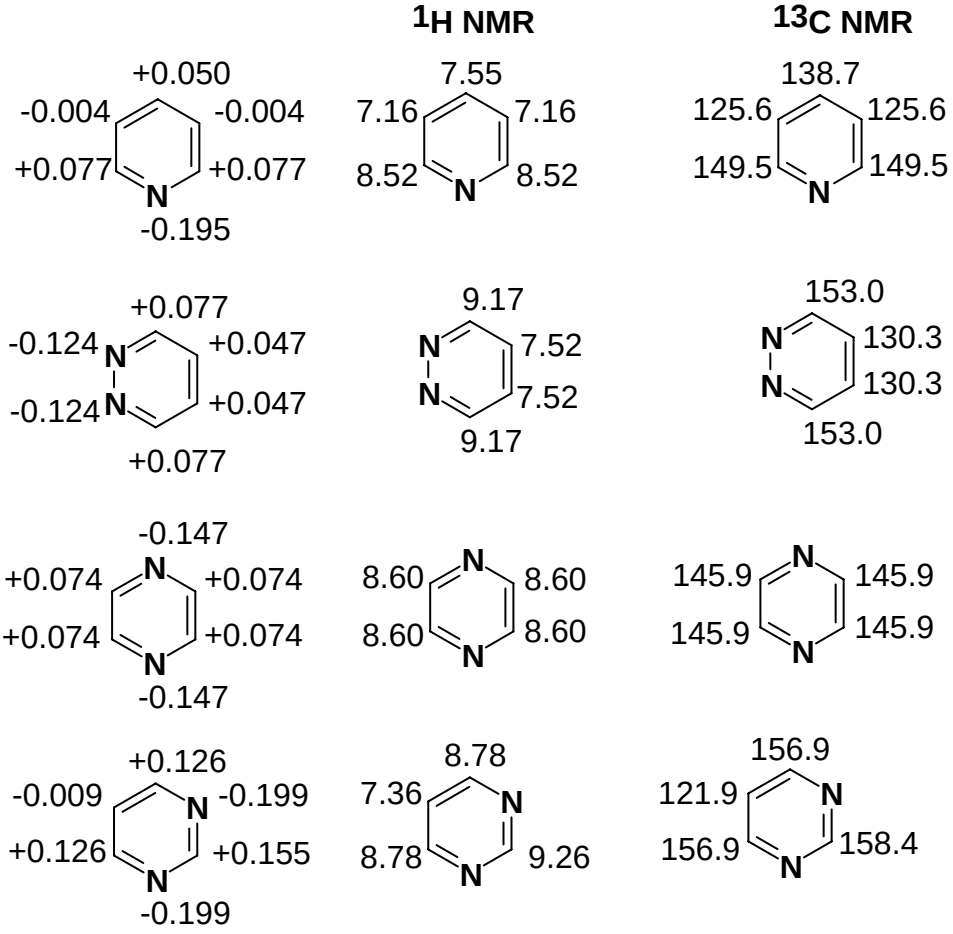
i) **electrophilic substitution** become successively **more difficult** as **E_{HOMO} decreases** both at nitrogen (weakened basicity) and on ring carbon atoms: no reaction at all without activating substituents.

ii) **nucleophilic substitution** becomes successively **easier** as **E_{LUMO} decreases**

iii) successive introduction of nitrogen atoms causes a **gradual reduction in aromatic stabilisation** in both **nucleophilic** and **electrophilic** substitution

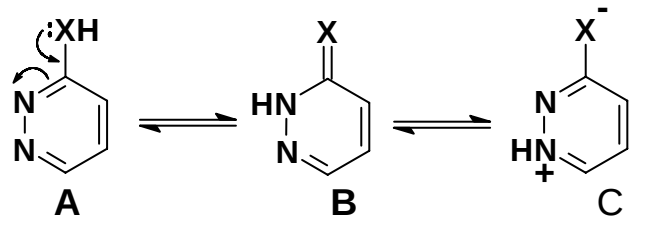
2.3. NMR data:

- they are in **agreement** with the **Atomic π-charges:**

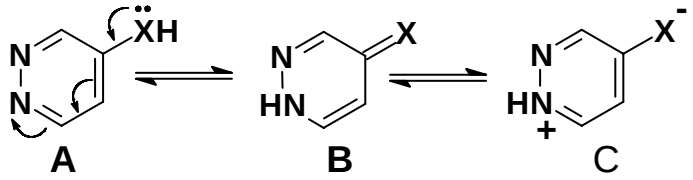


2.4. Prototropic tautomerism:

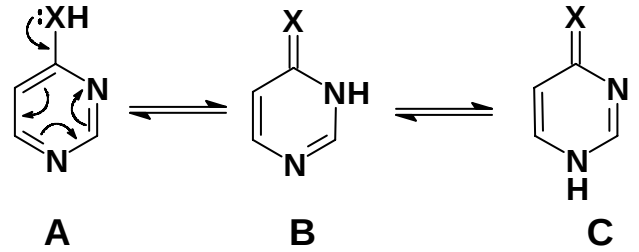
- relevance is found in **hydroxy-, mercapto**- and **amino**-derivatives (in aq. solution, at r.t.):



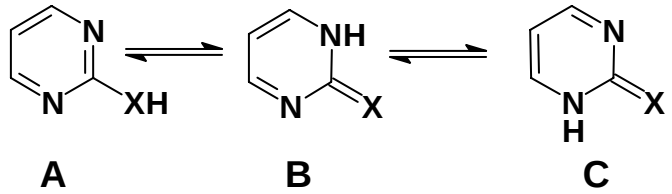
X = O : dominant **B** (minor **A**)
X = S : exclusive **B**
X = NH : exclusive **A**



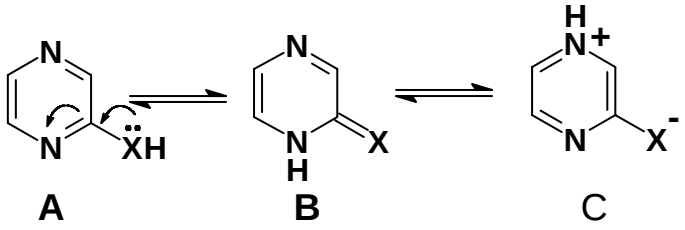
X = O : dominant **B** (minor **A**)
X = S : exclusive **B**
X = NH : major **A** (minor **B**)



X = O : dominant **B** *vs.* **C**
X = S : exclusive **B**
X = NH : **A** major (minor **B**+**C**)



X = O : exclusive **B** identical with **C**
X = S : exclusive **B** identical with **C**
X = NH : **A** major (minor **B**+**C**)



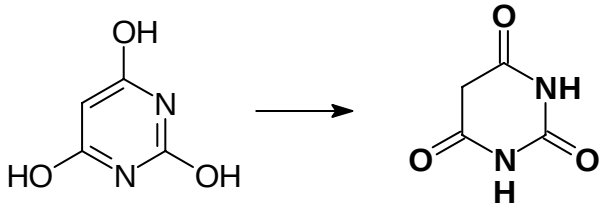
X = O : exclusive **B**
X = S : exclusive **B**
X = NH : exclusive **A**

Notes:

i) for **amino derivatives**, aromatic tautomeric forms are favored

ii) tautomerism involving proton transfer to a ring **carbon** atom is **not known** if **but one XH** group is present

iii) tautomerism involving proton transfer to a ring **carbon** atom is important if **more than two XH** group are present



2,4,6-trihydroxypyrimidine

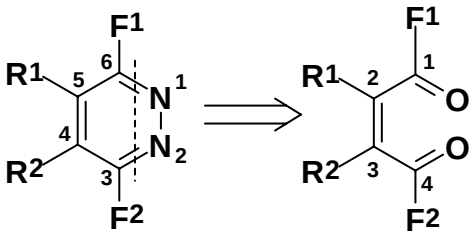
pyrimidyn "trione
Barbituric acid

3. Synthesis:

3.1. Two aza-atoms in positions 1,2

3.1.1. Monocyclic rings: pyridazines

- **retrosynthesis:** simple hydrolytic disconnection N-1-C-6 and N-2-C-3

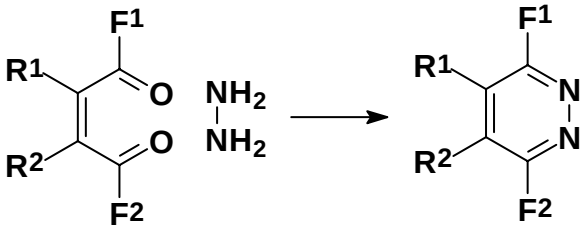


NH_2
NH_2
hydrazine

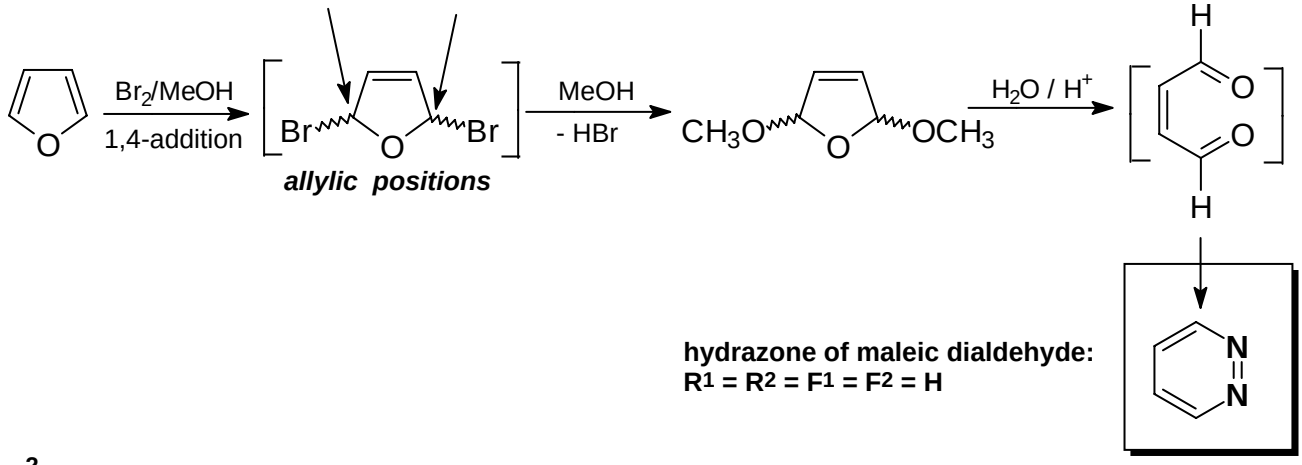
F1, F2: functionality (optional **H**
R1, R2: H, groups

2,3-non saturated 1,4-dicarbonyl compound

- **C-1, -4** functionality as ***H***, ***OH*** in the starting compound **is crucial** for the functionality of the subsequent **pyridazine** system:

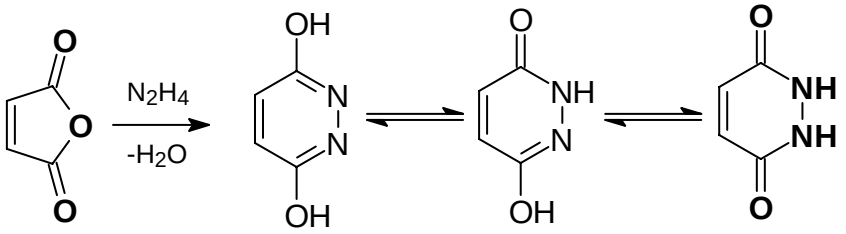


i) F^1, F^2 functionality as *H*:



hydrazone of maleic dialdehyde:
$R^1 = R^2 = F^1 = F^2 = H$

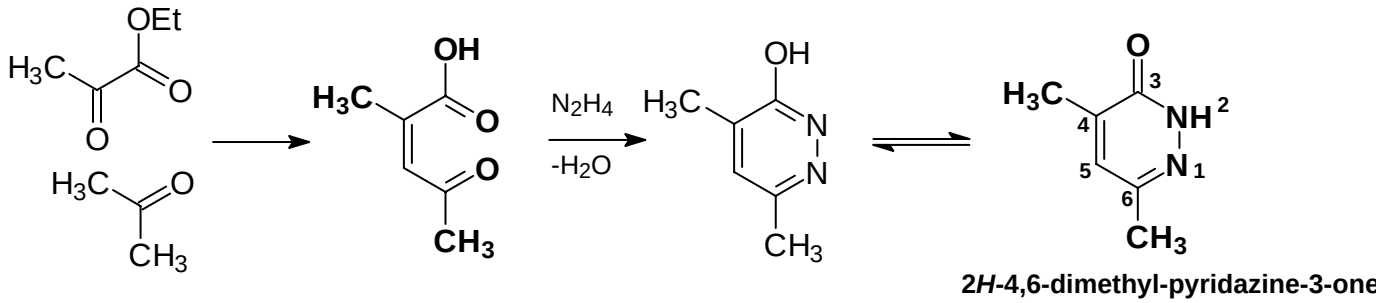
ii) F^1, F^2 functionality as *OH*:



3,6-dihydroxypyrazine

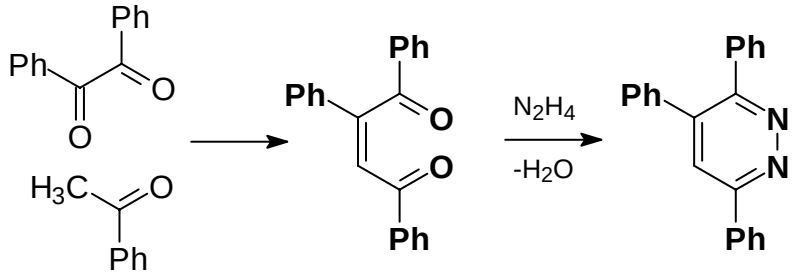
hydrazide of maleic acid:
$R^1 = R^2 = H$ $F^1 = F^2 = OH$

iii) F^1, F^2 functionality as *OH and group*:

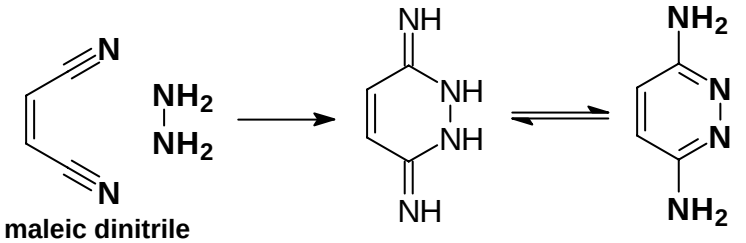


2*H*-4,6-dimethyl-pyridazine-3-one

iv) F^1, F^2 functionality as *groups*:



v) F^1, F^2 functionality as *amino groups*:



maleic dinitrile

Notes:

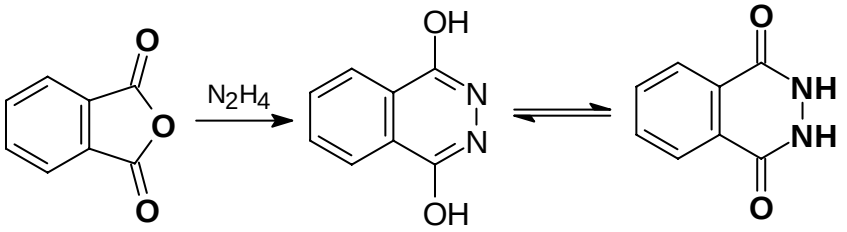
- the appropriate *cis* (*Z*) disposal of the 1,4-dicarbonyl-2,3-non saturated precursor is ensured (and originates) by the stereochemistry of the (masked) maleic anhydride
- other appropriate precursors of are not *E-Z* stereoisomers

3.1.2. Fused rings: phthalazines

- the appropriate disposal of the carbonyl groups is ensured by their *ortho* linkage at the benzene ring:

(masked) maleic anhydride → pyridazines

(masked) phthalic anhydride → phthalazines

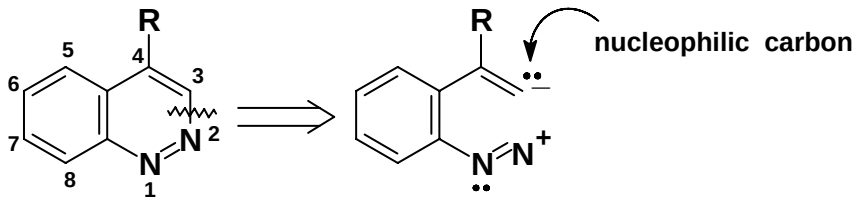


1,4-dihydroxyphthalazine ***phthalhydrazide***

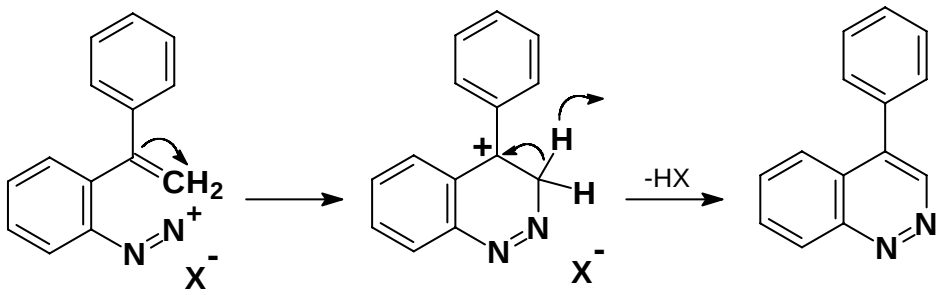
2,3-dihydrophthalazine-1,4-dione

3.1.3. Fused rings: cinnolines

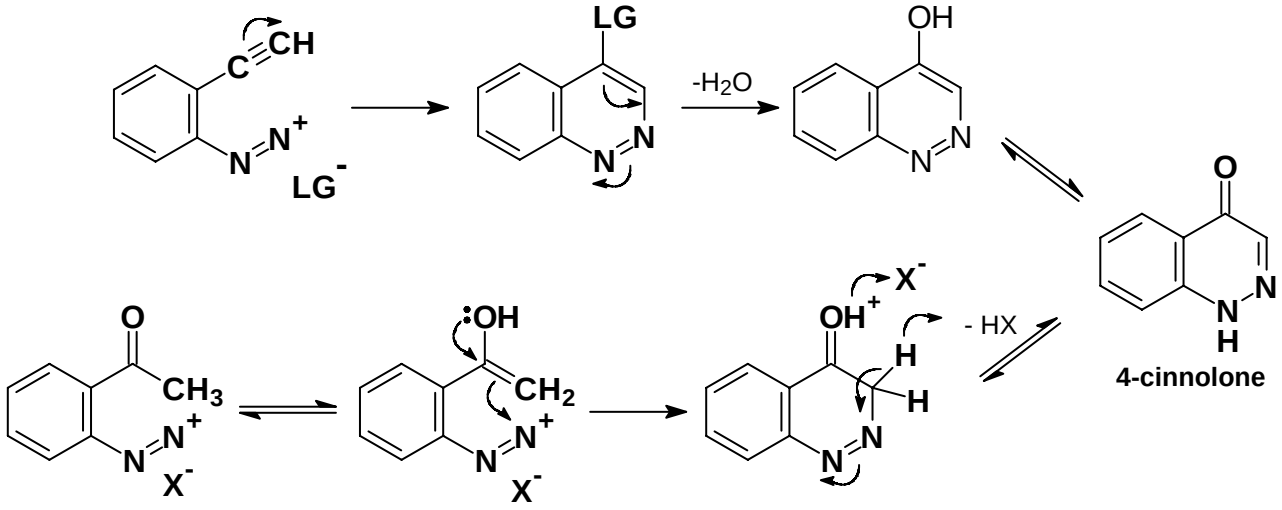
A) From *o*-substituted diazonium salts: retrosynthetic disconnection as N-2-C-3



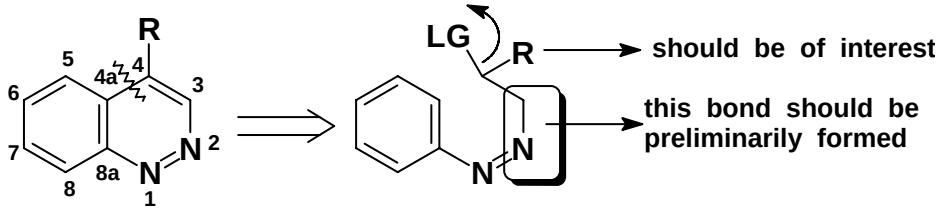
Example 1: methodology based on diarylmethane motif to stabilize carbocations of type benzyl

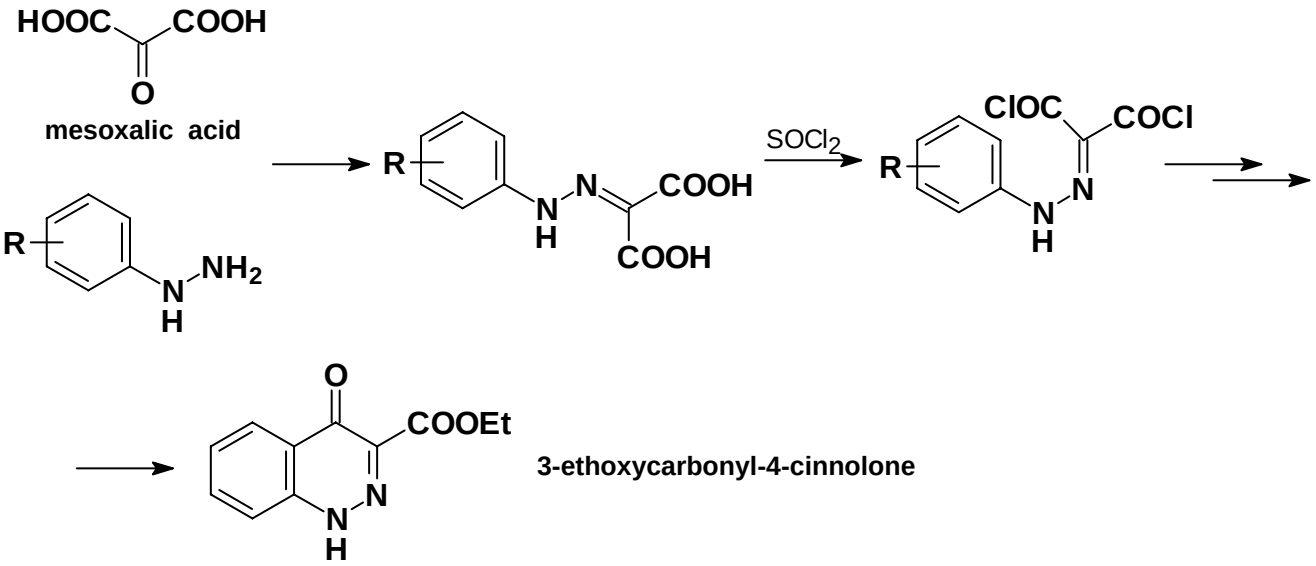


Example 2: methodology based on nucleophilicity of the termini carbon in a phenylacetylene fragment and synthetic equivalents

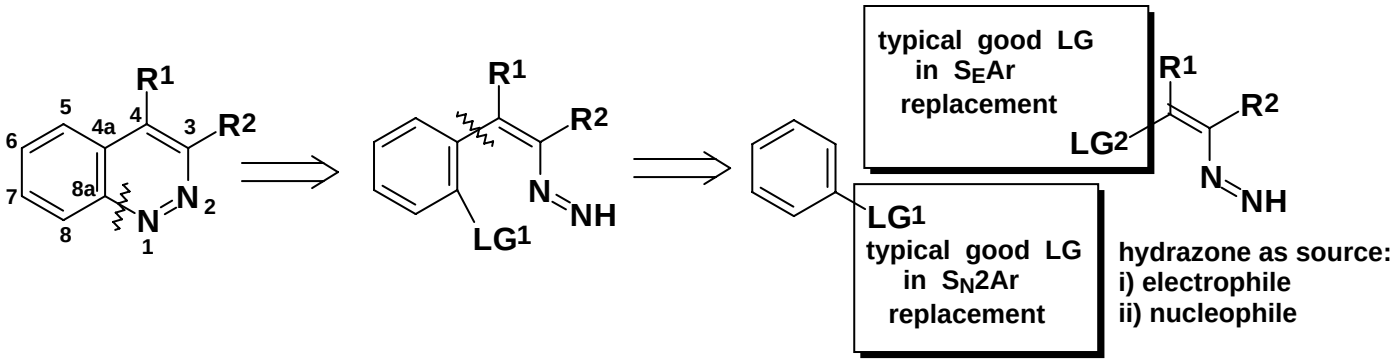


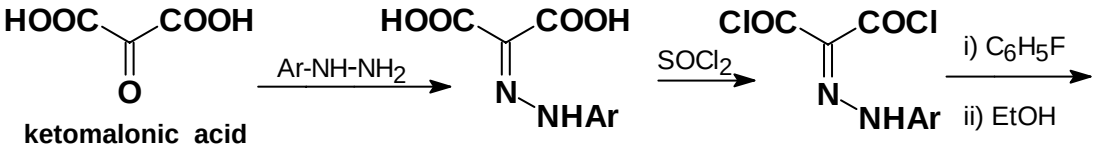
B) Friedel-Crafts methodology: retrosynthetic disconnection as C-4-C-4a

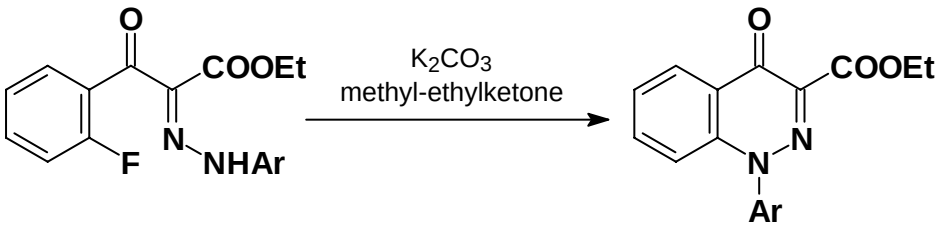




C) Intramolecular S_N2Ar nucleophilic substitution: retrosynthetic disconnection as C-8a-N-1



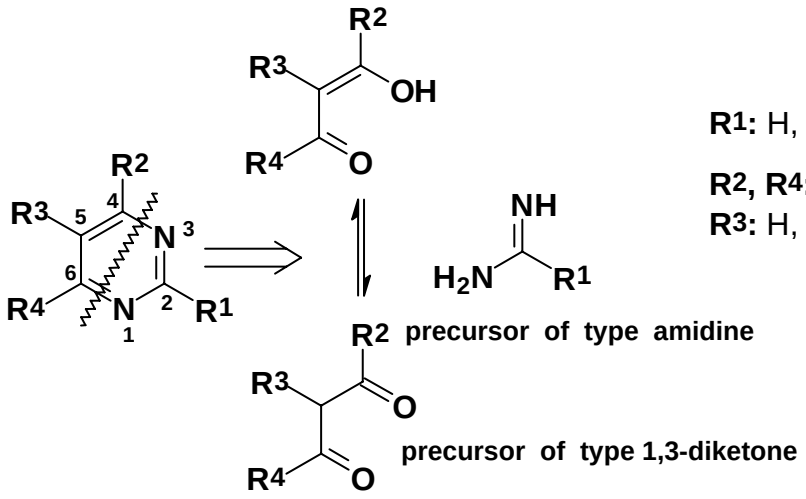




3.2. Two aza-atoms in positions 1,3

3.2.1. Monocyclic rings: pyrimidines

- general retrosynthesis: double hydrolytic disconnection as N-3-C-4 and N-1-C-6 is the most useful.

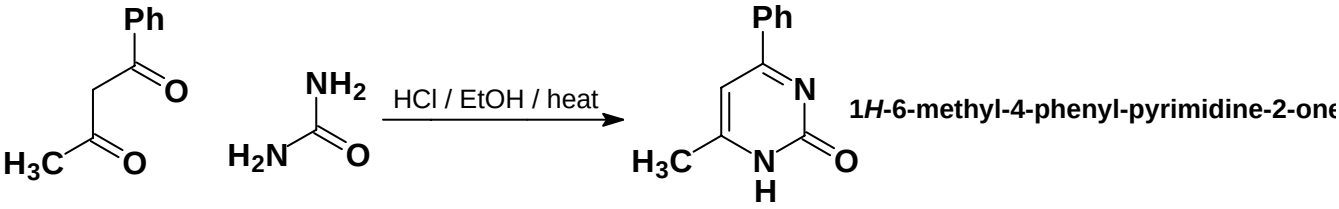


R1: H, Me, Ph, OMe, **OH**, SMe, **SH, NH2**

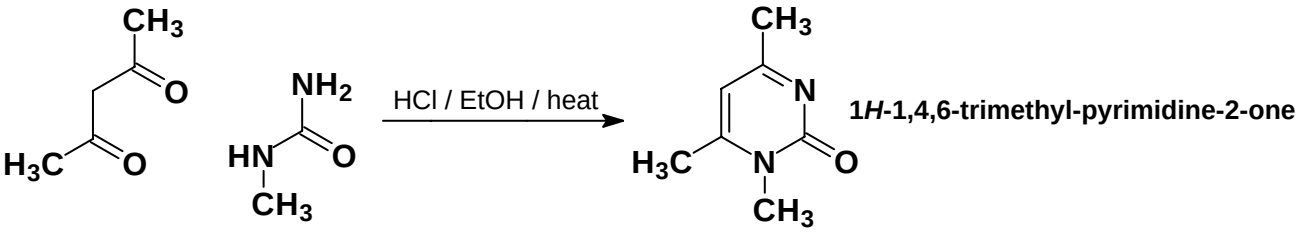
R2, R4: H, Me, Ph, **OEt**

R3: H, Me, Ph, Br, NO, NO_2

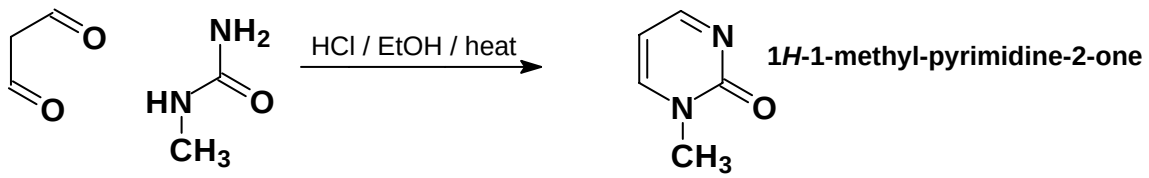
- **in bold:** groups which afford tautomeric **(thi)one-** or **imine** forms
- general conditions: **basic (NaOH, EtONa)** → to activate amidine precursor
  acidic conditions are also used → to activate 1,3-diketone precursor.



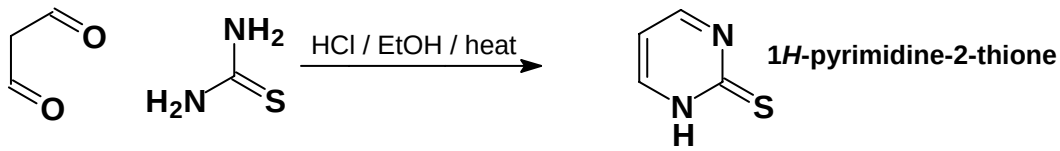
1*H*-6-methyl-4-phenyl-pyrimidine-2-one



1*H*-1,4,6-trimethyl-pyrimidine-2-one

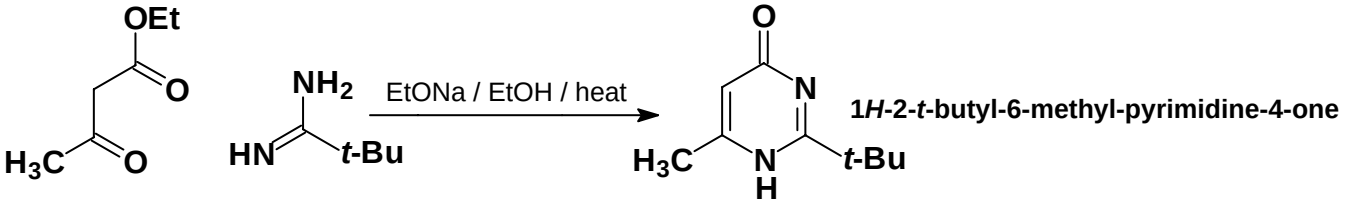


1*H*-1-methyl-pyrimidine-2-one

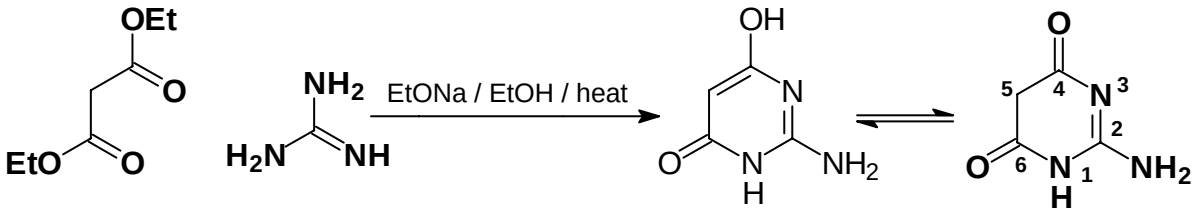


1*H*-pyrimidine-2-thione

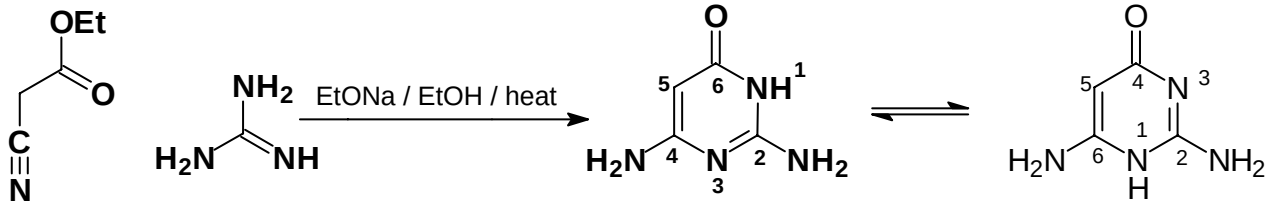
Obs.: acid catalysis is used to activate **>C=O** of type **carbonyl** as **$>C=OH^+ \leftrightarrow >C^+-OH$**



1*H*-2-*t*-butyl-6-methyl-pyrimidine-4-one



1*H*,5*H*-2-amino-pyrimidine-4,6-dione

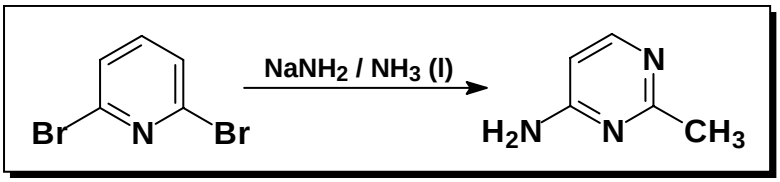


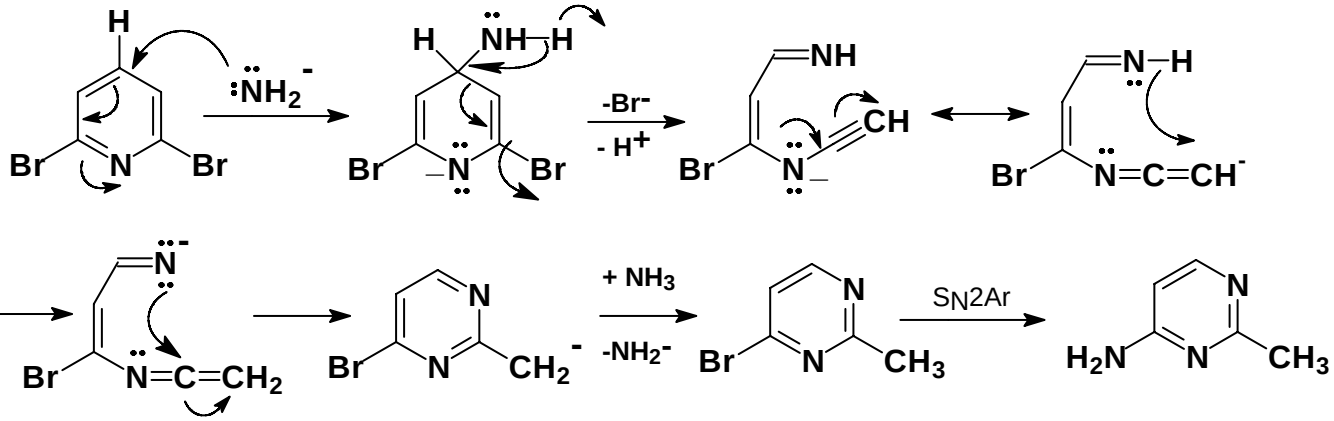
1*H*-2,4-diamino-pyrimidine-6-one 1*H*-2,6-diamino-pyrimidine-4-on

Obs.: in basic conditions **NH_2 is activated** against carbonyl groups of type **ester** and **nitrile**. Equilibrium might occur. EtOH should be continuously removed from the reaction mixture.

Synthesis *via* the A N R O R C mechanism

Definition: the **ANRORC** (**A**ddition of **N**ucleophile, **R**ing **O**pening, **R**ing **C**losure) reaction involves the initial addition of a nucleophile to a ring carbon **not carrying a halogen atom**, followed by electrocyclic ring opening when the halogen atom is removed.

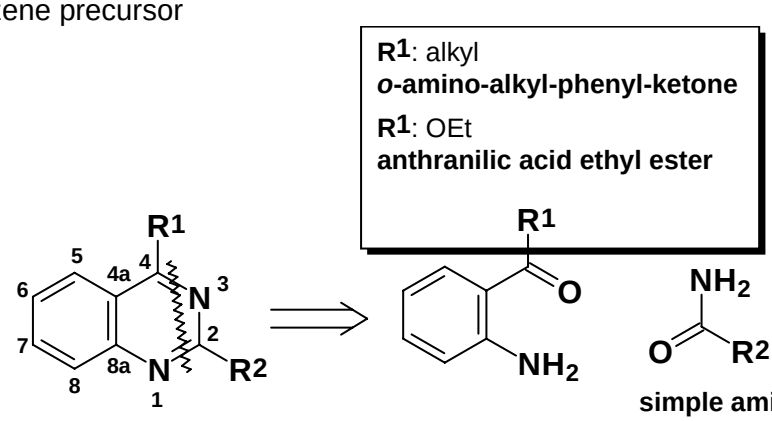


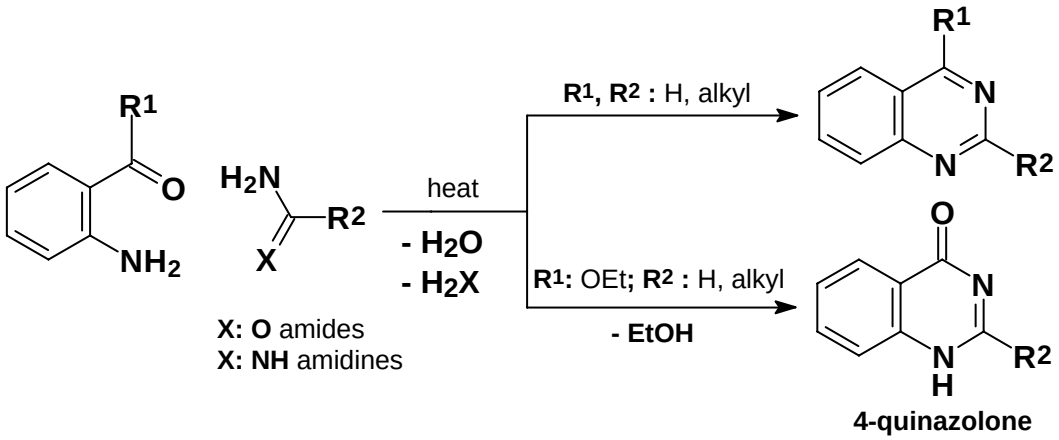


- the method is general and of synthetic interest
- halogen should be a good **LG**.
- note **conditions** for the nucleophilic displacement of **the second** bromine atom

3.2.2. Fused rings: quinazolines

- **retrosynthetic disconnection: hydrolytic** (N1-C-2 and N-3-C-4) because of the availability of the *o*-disubstituted benzene precursor



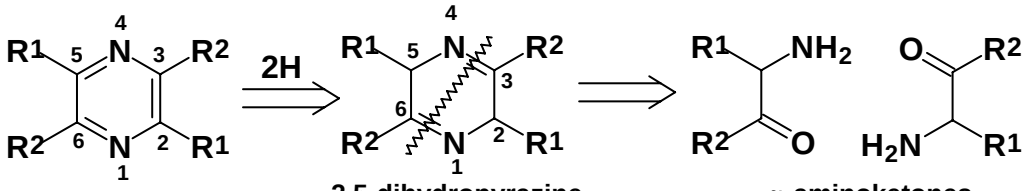


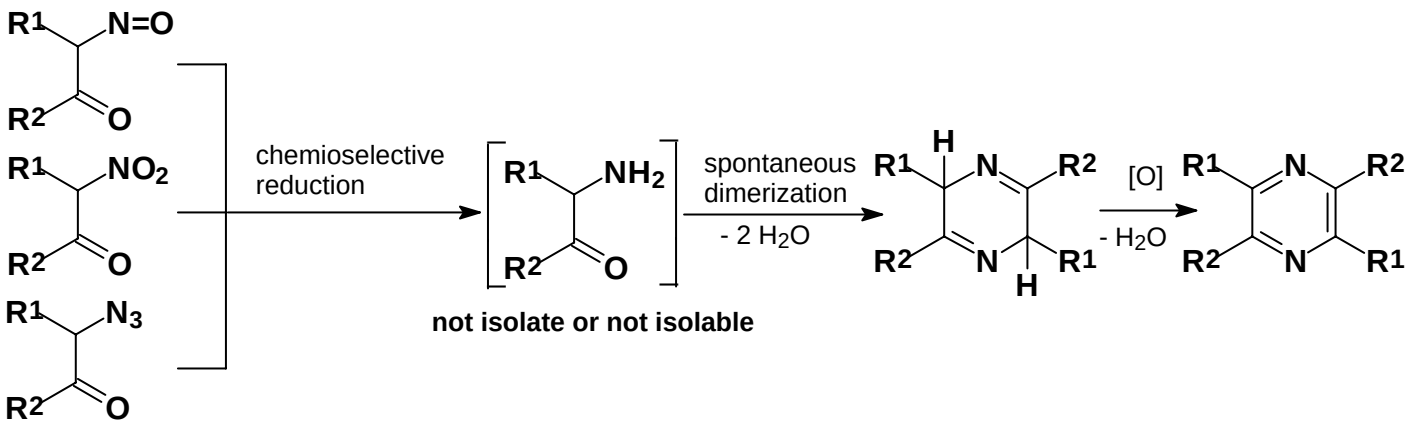
Obs.: note the similitude with pyrimidines / pyrimidinones synthesis

3.3. Two aza-atoms in positions 1,4

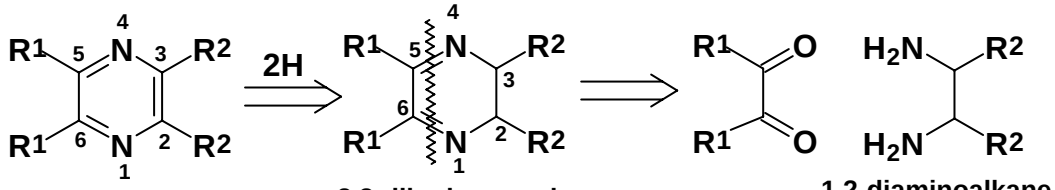
3.3.1. Monocyclic rings: pyrazines

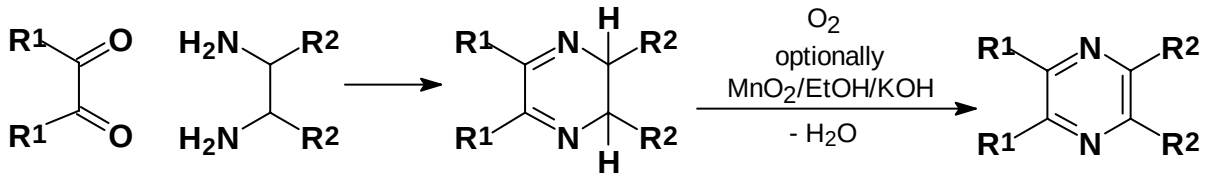
A) retrosynthetic disconnection: hydrolytic as N-1-C-2 and N-4-C-5 in the reduced form:





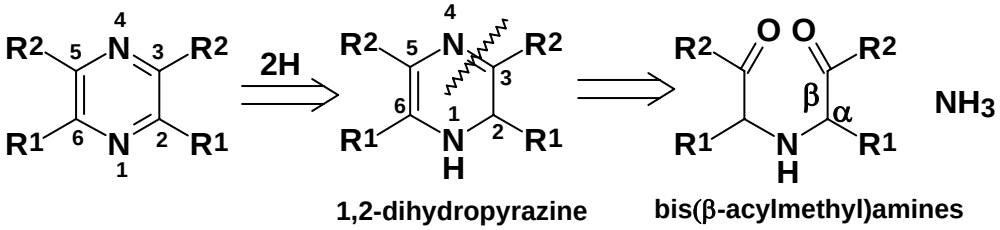
B) retrosynthetic disconnection: hydrolytic as N-1-C-6 and N-4-C-5 in the reduced form:

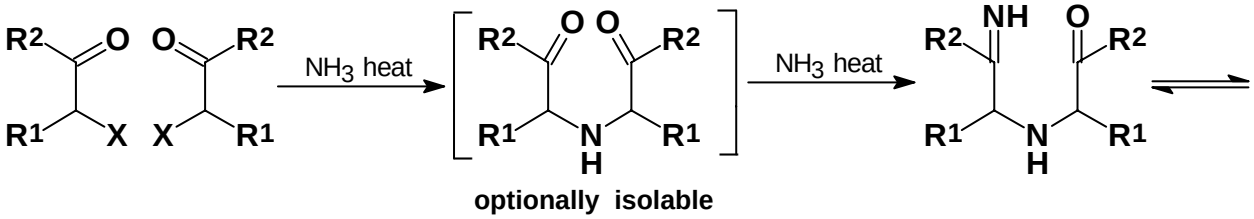


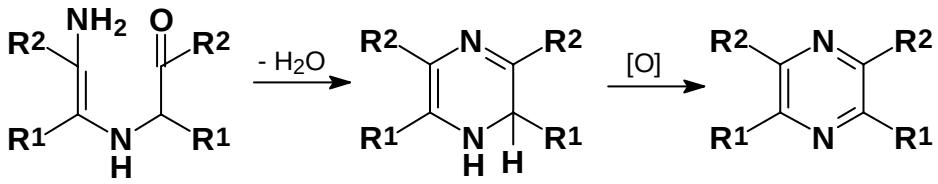


Note: if $R^1 = R^2 = H$, pyrazine itself is prepared

C) retrosynthetic disconnection: hydrolytic as N-4-C-3 (or N-4-C-5) in the reduced form:



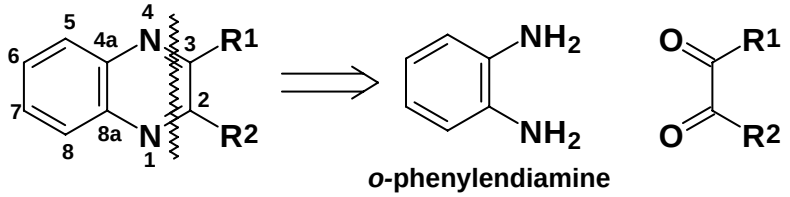




Notes: the methodology is also known **for acetals** of the starting α-cloro carbonylic compounds

3.3.2. Fused rings: quinoxalines

retrosynthetic disconnection: hydrolytic as double hydrazone (N-1-C-2 and N-4-C-3)



***o*-phenylendiamine**

α-diketones ⟶ **2,3-disubstituted quinoxalines**
glyoxal ⟶ **quinoxaline**

4. Reactivity:

4.1. Electrophilic substitution:

i) almost **non reactive unless** resonance donors substituents are present in the molecule
ii) almost all substituents linked *a priori* in the precursors are **resonance donors**

4.1.1. At ring nitrogen

- less important, according to lower basicity, in comparison with pyridines; significance is given to substituted pyridazines (the more basic).

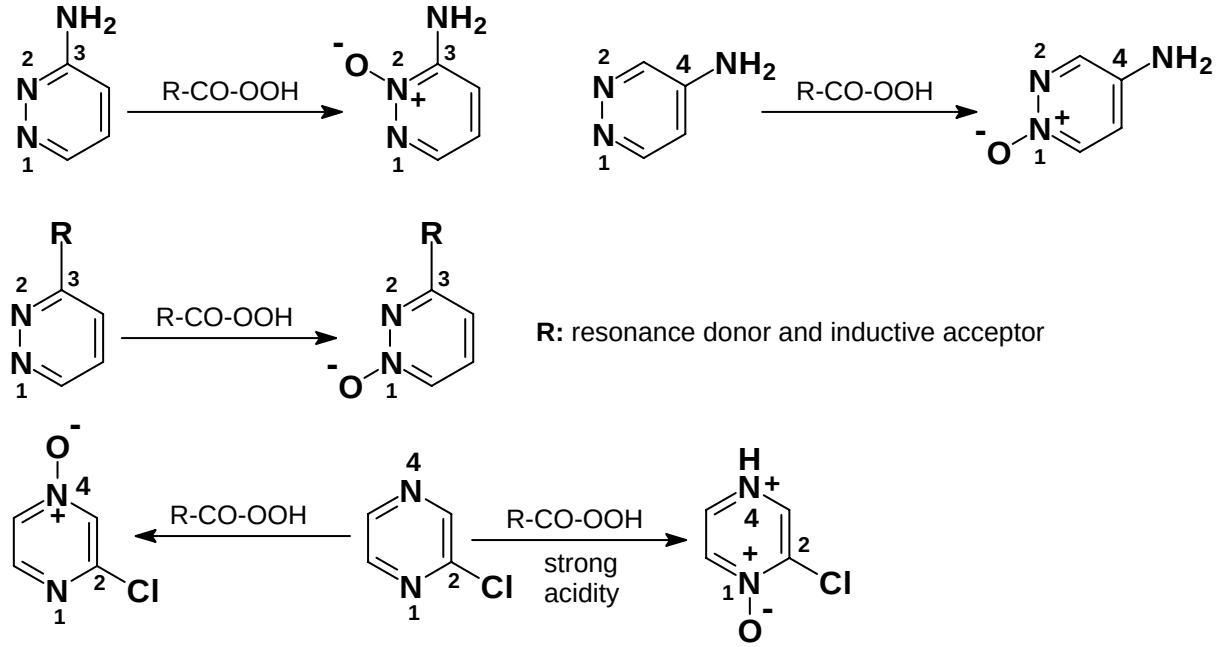
- rules:

1. strongly withdrawing substituents (NO_2, COR, Cl) are very effective in **α-position** *vs.* nitrogen ring atom since the effect is largely **inductive**

2. strongly electron donating substituents (NH_2, OR) operate by **mesomeric effects** and is strongest from the **γ-position**

3. from the **α-position**, **inductive effects** possessed by the **same groups** can partially or wholly **cancel** the increase of reactivity

Example: ***N*-oxidation**



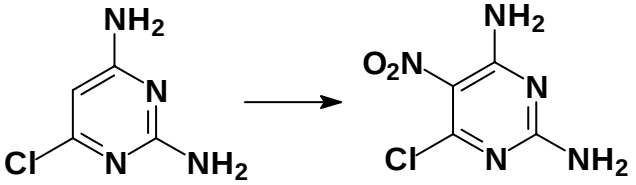
Note: similar reactivity is found for ***N*-alkylation**, especially with MeI to afford quaternary salts

4.1.2. At carbon ring

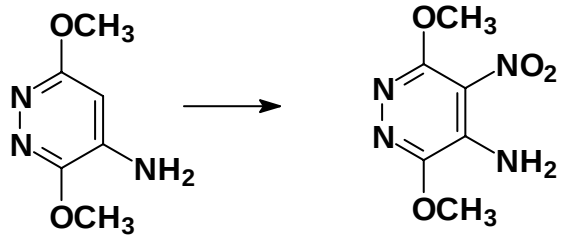
General: ***reactivity can be predicted from a knowledge of benzene chemistry.***

1. The **poor reactivity** of diazines is **exacerbated** by the protonation at ring nitrogen in strong acidic media (however, this protonation, including other electrophilic substitution, is often **reversible**).
2. Diazines **without strongly activating** substituents (NH_2, OR)**, do not react**.
3. Diazines with **a single strongly activating substituent** and **diazinones** undergo nitration and sulfonation with difficulty (*ca.* ***m*-dinitrobenzene**).
4. Diazines with **two strongly activating substituents** readily undergo nitration, sulfonation and halogenation (*ca.* **benzene**).
5. Diazines with **three strongly activating substituents** are very reactive towards electrophilic substitution.
6. **Alkyl groups** and **halogen atoms** behave normally, as **weakly activating** and **deactivating substituents** respectively.

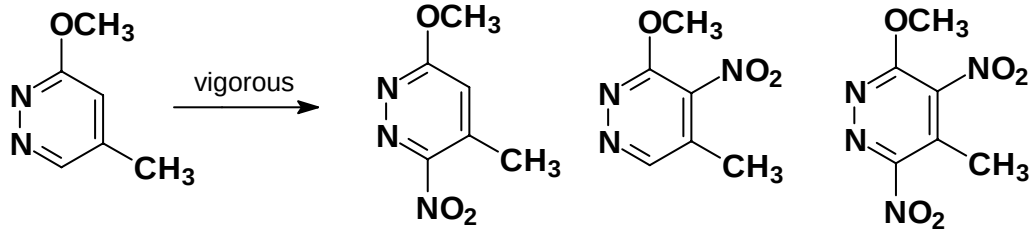
Nitration:

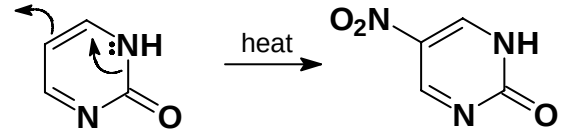


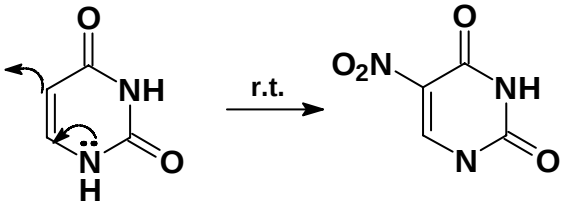
2,4-diamino-6-chloro-5-nitro-pyrimidine



4-amino-3,6-dimethoxy-5-nitro-pyridazine

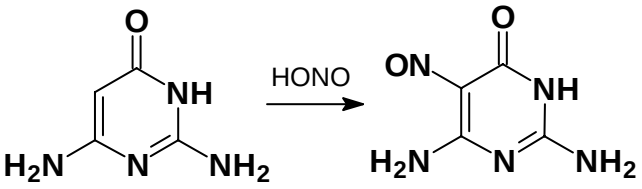






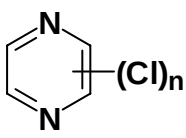
5-nitro uracil

Nitrosation:

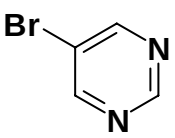


r.t., quantitative yield

Halogenation:



n = 1 - 4, (400^{o}C)



***ca.* 200^{o}C (62 - 88% yield**

Note: for synthetic interest**, nucleophilic chlorination is preferred**

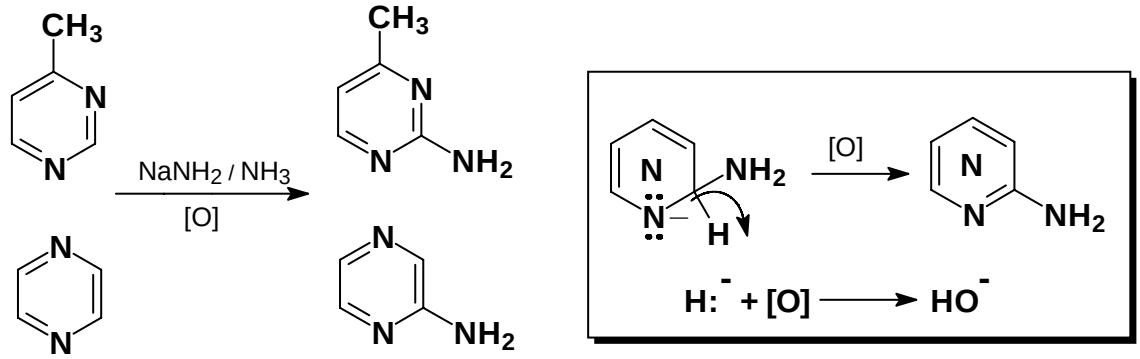
4.2. Nucleophilic substitution:

General:

- crucial to **enlarge functionality** of diazines.
- of particular importance: **H** (Chichibabin methodology) and **halogens**
- **much more facilitated than in pyridine series because of the additional ring nitrogen (*e.g.* the LUMO level, as acceptor, decreases).**

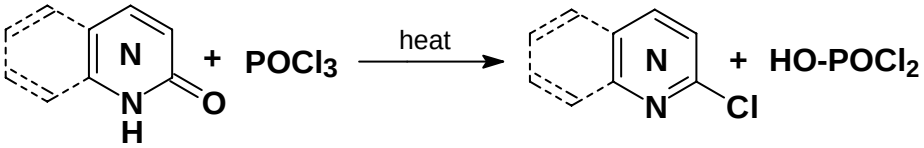
4.2.1. Hydride ion as leaving group

- reaction is made in **liquid ammonia** with **sodamide** as nucleophile because of the **increased π-deficiency** of diazines; accordingly, the σ-complex, as intermediate, has less tendency for re-aromatization; combined with the poor ability of hydride ion to be a good **LG**, an oxidant is needed to push the reaction (KNO_3, $KMnO_4$), even **ammonia itself**.



4.2.2. Halogen as leaving group

- the *most useful*: **chlorine** since it is easier to introduce in a **classic variant:**



(benzo)diazinone

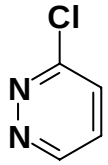
- the general decreasing order of reactivity, **according to halogen (exceptions make the rule !!):**

F > I > Br > Cl in agreement with a S_N2Ar (S_{AE}) mechanism

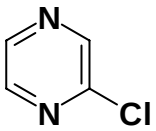
- nucleophilic reagents, as **general** decreasing of reactivity:

Nucleophile	Conditions	Product
HO^- hydroxy	NaOH / H_2O, 150°C	*Diazin**ones***
RO^- alcoxy	RONa / ROH / 65°C	Alcoxydiazines
PhO^- phenoxy	PHONa / EtOH	Phenoxydiazines
HS^- mercapto	KSH / propylene glycol	*Diazinthi**ones***
MeS^- methylmercapto	NaSMe / MeOH, 65°C	Methylmercaptodiazines
NH_3 (amino), **Me_2NH** (dimethylamino), **N_2H_4** (hydrazine)	NH_3/H_2O etc.100 – 200°C	Amino-, methylamino-hydrazinodiazines
HSO_3^-	$NaHSO_3$ / H_2O	Diazine sulfonic acids
I_2	HI	Iododiazines
F^-	KF, HF (heat)	Fluorodiazines

- typical examples for the nucleophiles listed in **Table:**

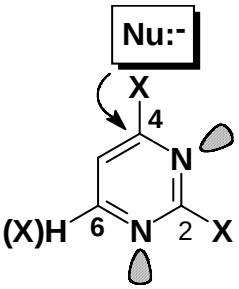


3-chloropyridazine



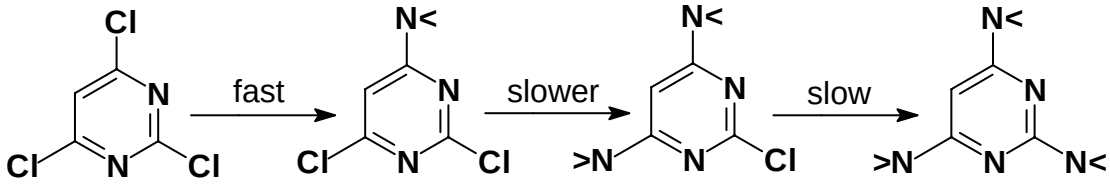
2-chloropyrazine

Selective nucleophilic substitution – general rules and conditions:



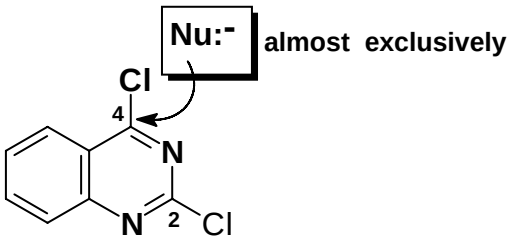
X: halogen
Aminolysis: F 60 - 200 times faster than Cl, Br, I
Positions 4 (6): up to **10 times** more reactive than

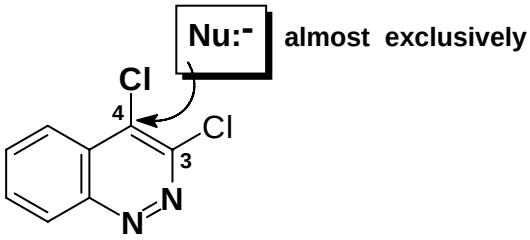
- as in **benzene chemistry**: **electron donating** substituents (Me, Ph, OMe, NH_2, NMe_2, etc.) **decrease** the rate of nucleophilic substitution, whereas **electron-withdrawing** substituents (Cl, CF_3, NO_2, etc.) have **opposite** effect



- comparison of (poly)chloro-derivatives of diazine type as masked imidoyl chlorides is **more pertinent** than in **pyridine** series.

- **in benzodiazine series:**



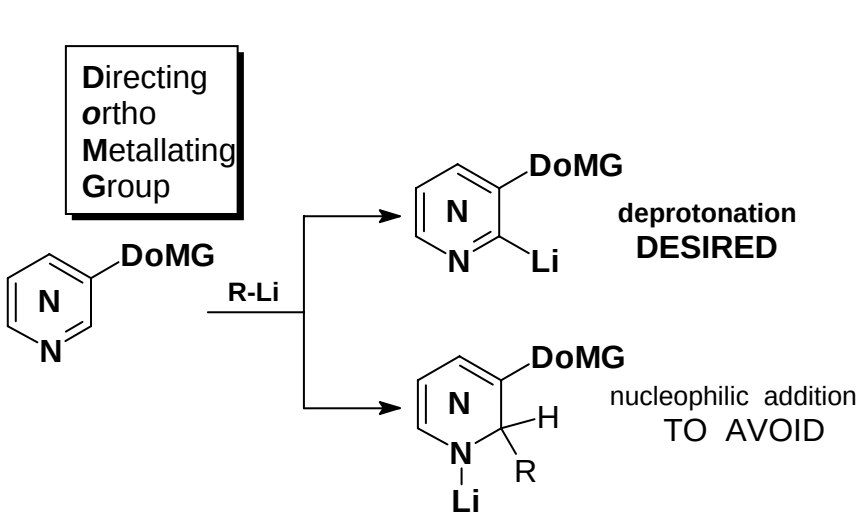


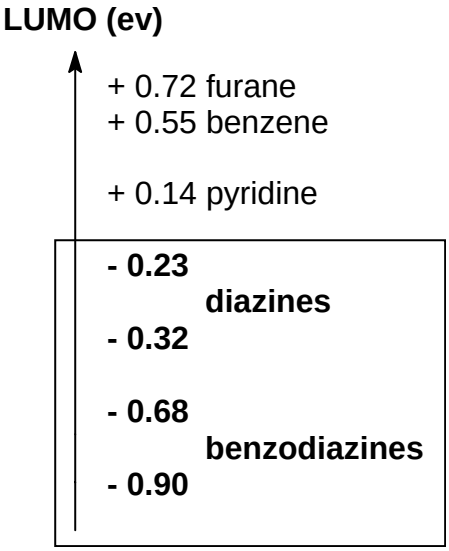
- the better regioselectivity in the above dichloro-benzodiazines series might be explained by **the more aromatic character** of the intermediate **σ-complex** following the attack at **C-4** than at C-2 (-3).

4.3. Advanced functionalization *via* metallation:

Overview:

- diazines, possessing **two nitrogen atoms**, are very sensitive to nucleophilic additions at the carbon ring.
- the **LUMO (diazines)** << **LUMO (pyridines)**
- **hydrogen atoms** linked to the ring are **more acidic** than in the pyridine series.





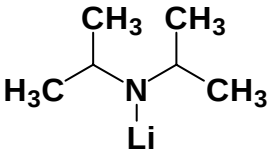
Remarks:

- the metallating reagent should be less nucleophilic (*e.g.* by **intrinsic steric hindrance**)
- the metallating reagent can be **less basic** (since diazines are **more acidic**)
- **alkyllithium reagenats** (e.g. *n*-BuLi) should **be avoided** in diazine series.

R-Li

R: *n*-Bu, *sec*-Bu, *t*-Bu

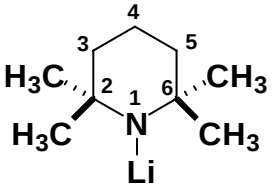
pKa: 45 - 50



LDA

lithium **d**iisopropyl **a**mide

pKa: 35.7



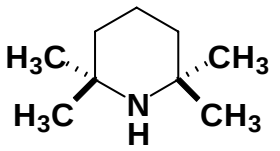
LTMP

lithium 2,2,6,6-**t**etra**m**ethyl-**p**yperidyl amid

pKa: 37.3

Generation *in situ*:

$(i\text{-Pr})_2NH$ → (*n*-BuLi, 0°C, min. quantitative yield) → **LDA**



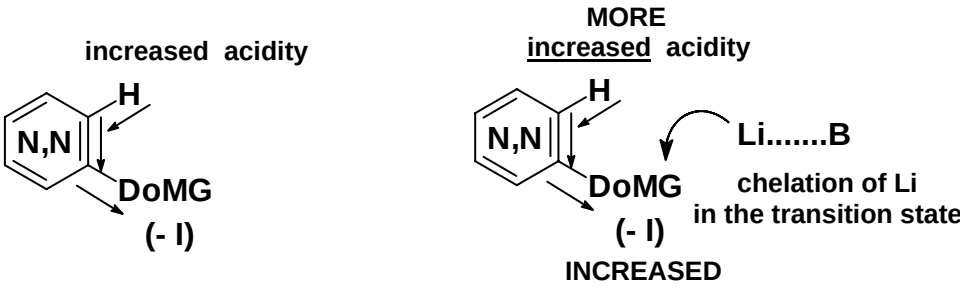
LTMP

DoMG Directing *ortho*-Metallating Group, structural unit with crucial role**:**

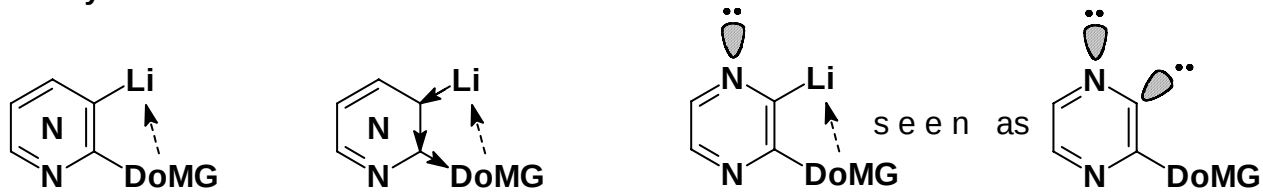
- **kinetic** and **thermodynamic**
- useful structure to develop **multi step synthesis**
- **it should be not Methyl group, in order to avoid the deprotonation at this site.**

DoMG Directing *ortho*-Metallating Group, structural unit with **crucial role:**

i) kinetic role:



ii) thermodynamic role:



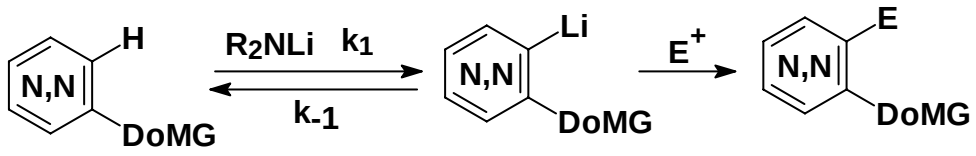
stabilisation as complexed carbanion

stabilisation by the (-I) of DoMG

stabilisation against vicinal repulsion

Note: the DoMG **must** be **simple enough**, **easily to introduce** in the diazine motif or, even better, **present before** the ring closure.

General mechanism:



a) $k_1 >>> k_{-1}$: trivial case; deutherated species detectable
b) $k_1 <<< k_{-1}$: metallation in equilibirum; **"trapping *in situ*"** methodology;
no deutherated species detectable
no reaction between R_2NLi and E^+

Directing *ortho*-Metallating Groups

Halogens: F, Cl, Br, I

Oxygenated Groups: OCH_3, OCH_2OCH_3 $OCONEt_2$ etc.

Carbonyl: CONH-*t*-Bu, $CONEt_2$, CF_3 etc.

Nitrogen: NH-CO-*t*-Bu, NH-COO-*t*-Bu

Sulfur: SCH_3, SOR, SO_2R, SO_3R, SO_2NHR

Functionalisations as:

Halogen: F, Cl, Br, I

Carbonated: $C(OH)R_1R_2$, COOH, COR, CHO, CH_3, $CONR_2$ etc.

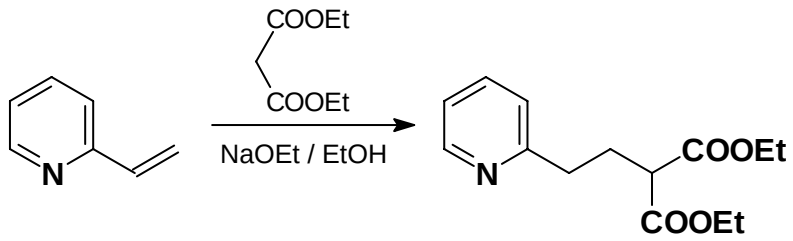
Nitrogen: NH_2 (*via* N_3)

Others: SiR_3, SnR_3 etc.

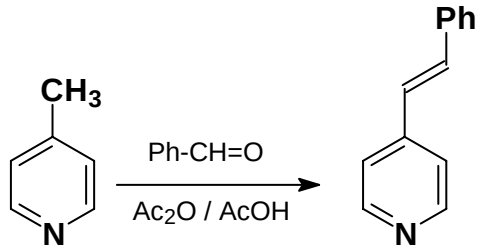
Note: in the absence of **DoMG**, yields and regioselectivities much decrease: **no synthetic importance**

P – 6

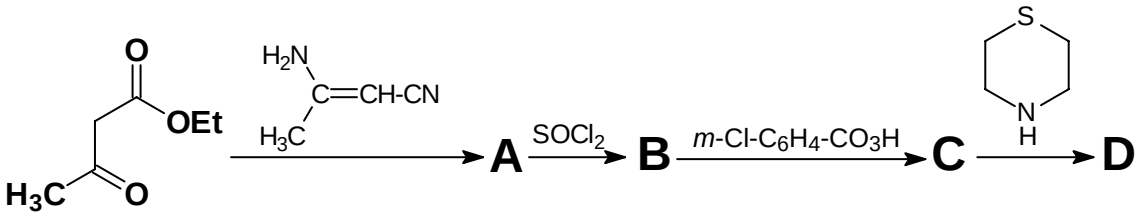
1. Propuneti un mecanism de reactie pentru transformarea de mai jos :



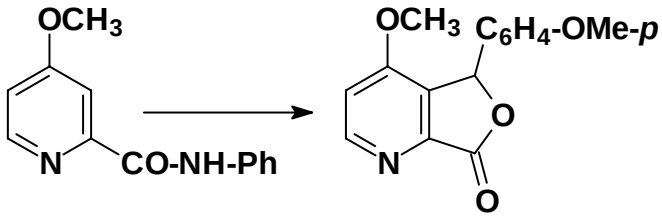
2. Propuneti un mecanism de reactie pentru transformarea de mai jos :



3. Identificati compusii **A**, **B**, **C**, **D** din schema de mai jos :



4. Realizati transformarea :



5. Identificati compusii **A – E** din schema de obtinere a alcaloidului de mai jos :