DIAZINES

1. Typical representatives and symbols

2. Structure
   2.1. Basicity
   2.2. Aromaticity
   2.3. NMR data
   2.4. Prototropic tautomerism

3. Syntheses
   3.1. Two aza-atoms in positions 1, 2
      3.1.1. Monocyclic rings: pyridazines
      3.1.2. Fused rings: phthalazines
      3.1.3. Fused rings: cinnolines
         a) From o-substituted diazonium salts
         b) Friedel & Crafts methodology
         c) Intramolecular \textit{S}N2\textit{Ar} nucleophilic substitution
   3.2. Two aza-atoms in positions 1, 3
      3.2.1. Monocyclic rings: pyrimidines
      3.2.2. Fused rings: quinazolines
   3.3. Two aza-atoms in positions 1, 4
      3.3.1. Monocyclic rings: pyrazines
      3.3.2. Fused rings: quinoxalines

4. Reactivity
   4.1. Electrophilic substitution
      4.1.1. At ring nitrogen
      4.1.2. At ring carbon
   4.2. Nucleophilic substitution
      4.2.1. Hydride ion as leaving group
      4.2.2. Halogen as leaving group
   4.3. Advanced functionalisation \textit{via} metallation

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

1. Typical representatives and symbols:

![Symbols of diazines]

2. Structure:

2.1. Basicity:

- 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:

<table>
<thead>
<tr>
<th>Symbol</th>
<th>π-deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Cinnoline symbol]</td>
<td>+0.050</td>
</tr>
<tr>
<td>![Quinazoline symbol]</td>
<td>+0.077</td>
</tr>
<tr>
<td>![Quinoxaline symbol]</td>
<td>+0.147</td>
</tr>
<tr>
<td>![Phthalazine symbol]</td>
<td>+0.126</td>
</tr>
</tbody>
</table>

- The order is different if relative local π-deficiency (the largest positive charge on any carbon atom in a molecule) is considered.
- The π-acceptor action of heteroatoms in azines is most effective when they are meta-position each other (pyrimidine).
- 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).

\[
\text{Benzene} > \text{Pyridine} > \text{Pyrimidine} > \text{Pyrazine} > \text{Pyridazine}
\]

<table>
<thead>
<tr>
<th>ER (kJ/mol)</th>
<th>151</th>
<th>142</th>
<th>138</th>
<th>134</th>
<th>109</th>
</tr>
</thead>
</table>

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

\[
\begin{align*}
\text{ELUMO (}\beta<0\text{ )} & \quad -0.576 \quad -0.527 \quad -0.841 \quad -0.686 \quad -0.871 \quad -0.727 \quad -0.781 \\
\text{EHOMO (}\beta<0\text{ )} & \quad +0.646 \quad +0.703 \quad +1.000 \quad +1.000 \quad +1.077 \quad +1.101 \quad +1.281
\end{align*}
\]

i) electrophilic substitution become successively more difficult as \(E_{\text{HOMO}}\) 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 \(E_{\text{LUMO}}\) 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 \(\pi\)-charges:

\[
\begin{align*}
\text{\(^1\text{H NMR}\)} & \quad 7.16 \quad 7.55 \quad 8.52 \quad 8.52 \\
\text{\(^{13}\text{C NMR}\)} & \quad 125.6 \quad 138.7 \quad 149.5 \quad 153.0 \\
\end{align*}
\]
2.4. Prototropic tautomerism:
- relevance is found in hydroxy-, mercapto- and amino-derivatives (in aq. solution, at r.t.):

\[
\begin{align*}
\text{A} & \quad \text{X = O} : \text{dominant B (minor A)} \\
\text{X = S} : \text{exclusive B} \\
\text{X = NH} : \text{exclusive A}
\end{align*}
\]

\[
\begin{align*}
\text{A} & \quad \text{X = O} : \text{dominant B (minor A)} \\
\text{X = S} : \text{exclusive B} \\
\text{X = NH} : \text{major A (minor B)}
\end{align*}
\]

\[
\begin{align*}
\text{A} & \quad \text{X = O} : \text{dominant B vs. C} \\
\text{X = S} : \text{exclusive B} \\
\text{X = NH} : \text{A major (minor B+C)}
\end{align*}
\]

\[
\begin{align*}
\text{A} & \quad \text{X = O} : \text{exclusive B identical with C} \\
\text{X = S} : \text{exclusive B identical with C} \\
\text{X = NH} : \text{A major (minor B+C)}
\end{align*}
\]

\[
\begin{align*}
\text{A} & \quad \text{X = O} : \text{exclusive B} \\
\text{X = S} : \text{exclusive B} \\
\text{X = NH} : \text{exclusive A}
\end{align*}
\]

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

![Chemical structure of pyridazines](image)

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:

![Chemical structure of pyridazines](image)

i) F₁, F₂ functionality as H:

![Chemical structure of pyridazines](image)

hydrazone of maleic dialdehyde:
R₁ = R₂ = F₁ = F₂ = H

ii) F₁, F₂ functionality as OH:

![Chemical structure of pyridazines](image)

3,6-dihydroxypyrazine

hydrazide of maleic acid:
R₁ = R₂ = H F₁ = F₂ = OH
iii) $F_1, F_2$ functionality as $OH$ and group:

\[
\begin{align*}
\text{H}_3\text{C}-\text{COO} & \rightarrow \text{H}_3\text{C}-\text{COOH} & \text{N}_2\text{H}_4 & \rightarrow \text{H}_3\text{C}-\text{C} & \text{H}_3 \\
\text{H}_3\text{C}-\text{CO} & \rightarrow \text{H}_3\text{C}-\text{COOH} & \text{N}_2\text{H}_4 & \rightarrow \text{H}_3\text{C}-\text{C} & \text{H}_3 \\
\end{align*}
\]

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

iv) $F_1, F_2$ functionality as groups:

\[
\begin{align*}
\text{Ph} \text{C} & \rightarrow \text{Ph} \text{C} & \text{N}_2\text{H}_4 & \rightarrow \text{Ph} \text{C} & \text{Ph} \\
\text{Ph} \text{C} & \rightarrow \text{Ph} \text{C} & \text{N}_2\text{H}_4 & \rightarrow \text{Ph} \text{C} & \text{Ph} \\
\end{align*}
\]

v) $F_1, F_2$ functionality as amino groups:

\[
\begin{align*}
\text{N} & \text{H}_2 & \text{N} & \text{NH}_2 & \text{N} & \text{NH}_2 \\
\text{maleic dinitrile} & \rightarrow & \text{maleic dinitrile} & \rightarrow & \text{maleic dinitrile} \\
\end{align*}
\]

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:

\[
\begin{align*}
\text{masked maleic anhydride} & \rightarrow \text{pyridazines} \\
\text{masked phthalic anhydride} & \rightarrow \text{phthalazines} \\
\end{align*}
\]

\[
\begin{align*}
\text{N}_2\text{H}_4 & \rightarrow \text{N}_2\text{H}_4 \\
\text{1,4-dihydroxyphthalazine} & \rightarrow \text{phthalhydrazide} \\
\end{align*}
\]

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\textsubscript{N}2Ar nucleophilic substitution:** retrosynthetic disconnection as C-8a-N-1

- **Electrophile:**
  1. C\textsubscript{6}H\textsubscript{5}F
  2. EtOH

- **Nucleophile:**
  1. K\textsubscript{2}CO\textsubscript{3}
  2. Methyl-ethylketone
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.

\[
\begin{align*}
\text{R1: } & \text{H, Me, Ph, OMe, OH, SMe, SH, NH}_2 \\
\text{R2, R4: } & \text{H, Me, Ph, OEt} \\
\text{R3: } & \text{H, Me, Ph, Br, NO, NO}_2
\end{align*}
\]

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

\[
\begin{align*}
\text{Ph} & \quad \text{H}_3\text{C} \\
\text{O} & \quad \text{NH}_2 \\
\text{H}_3\text{C} & \quad \text{O} \\
\text{HCl / EtOH / heat} & \quad \text{N} \\
\text{Ph} & \quad \text{H}_3\text{C} \\
\text{1H-6-methyl-4-phenyl-pyrimidine-2-one} & \quad \text{1H-1,4,6-trimethyl-pyrimidine-2-one} \\
\text{CH}_3 & \quad \text{O} \\
\text{NH}_2 & \quad \text{H}_3\text{C} \quad \text{O} \\
\text{HCl / EtOH / heat} & \quad \text{N} \\
\text{CH}_3 & \quad \text{O} \\
\text{1H-1-methyl-pyrimidine-2-one} & \quad \text{1H-pyrimidine-2-thione}
\end{align*}
\]

Obs.: acid catalysis is used to activate \(>\text{C}=\text{O}\) of type carbonyl as \(>\text{C}=\text{OH}^+ \leftrightarrow >\text{C}^+\cdot\text{OH}\)
Obs.: in basic conditions NH₂ 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 ANRORC mechanism**

**Definition:** the ANRORC (Addition of Nucleophile, Ring Opening, Ring Closure) 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.
3.2.2. Fused rings: quinazolines

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

\[
\begin{align*}
R^1 & : \text{alkyl} \\
\alpha\text{-amino-alkyl-phenyl-ketone} \\
R^1 & : \text{OEt} \\
\text{anthranilic acid ethyl ester}
\end{align*}
\]

\[
\begin{align*}
\text{simple amide}
\end{align*}
\]

\[
\begin{align*}
\text{Obs.: note the similitude with pyrimidines / pyrimidinones synthesis}
\end{align*}
\]

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:

\[
\begin{align*}
\text{chemioselective reduction} \\
\text{spontaneous dimerization} \\
\text{not isolate or not isolable}
\end{align*}
\]

\[
\begin{align*}
\text{[O]} \\
\text{[O]}
\end{align*}
\]
B) **retrosynthetic disconnection**: hydrolytic as N-1-C-6 and N-4-C-5 in the reduced form:

![Chemical structure diagram]

**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:

![Chemical structure diagram]

**Notes**: the methodology is also known for acetics of the starting \( \alpha \)-chloro carbonylic compounds

### 3.3.2. Fused rings: quinoxalines

**retrosynthetic disconnection**: hydrolytic as double hydrazone (N-1-C-2 and N-4-C-3)
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\textsubscript{2}, COR, Cl) are very effective in $\alpha$-position vs. nitrogen ring atom since the effect is largely inductive
  2. strongly electron donating substituents (NH\textsubscript{2}, OR) operate by mesomeric effects and is strongest from the $\gamma$-position
  3. from the $\alpha$-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\textsubscript{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:

\[
\begin{align*}
\text{2,4-diamino-6-chloro-5-nitro-pyrimidine} & \quad \text{Nitrosation:} \\
\text{4-amino-3,6-dimethoxy-5-nitro-pyridazine} & \\
\text{5-nitro uracil} & \\
\text{Halogenation:} \\
\text{Note: for synthetic interest, nucleophilic chlorination is preferred}
\end{align*}
\]
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 (KNO₃, KMnO₄), even ammonia itself.

![Reaction Scheme]

4.2.2. Halogen as leaving group

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

![Reaction Scheme]

- 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:

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO⁻ hydroxy</td>
<td>NaOH / H₂O, 150°C</td>
<td>Diazinones</td>
</tr>
<tr>
<td>RO⁻ alkoxy</td>
<td>RONa / ROH / 65°C</td>
<td>Alcoxydiazines</td>
</tr>
<tr>
<td>PhO⁻ phenoxy</td>
<td>PHONa / EtOH</td>
<td>Phenoxydiazines</td>
</tr>
<tr>
<td>HS⁻ mercapto</td>
<td>KSH / propylene glycol</td>
<td>Diazinthiones</td>
</tr>
<tr>
<td>MeS⁻ methylmercapto</td>
<td>NaSMe / MeOH, 65°C</td>
<td>Methylmercaptopdiazines</td>
</tr>
<tr>
<td>NH₃ (amino), Me₂NH (dimethylamino), N₂H₄ (hydrazine)</td>
<td>NH₃/H₂O etc. 100 – 200°C</td>
<td>Amino-, methylamino-hydrazinodiazines</td>
</tr>
<tr>
<td>HSO₃⁻</td>
<td>NaHSO₃ / H₂O</td>
<td>Diazine sulfonic acids</td>
</tr>
<tr>
<td>I₂</td>
<td>HI</td>
<td>Iododiazines</td>
</tr>
<tr>
<td>F⁻</td>
<td>KF, HF (heat)</td>
<td>Fluorodiazines</td>
</tr>
</tbody>
</table>
- typical examples for the nucleophiles listed in Table:

3-chloropyridazine  2-chloropyrazine

Selective nucleophilic substitution – general rules and conditions:

Nu: -  

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, NH₂, NMe₂, etc.) decrease the rate of nucleophilic substitution, whereas electron-withdrawing substituents (Cl, CF₃, NO₂, 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.

LUMO (ev)
+ 0.72 furane
+ 0.55 benzene
+ 0.14 pyridine
- 0.23 diazines
- 0.32
- 0.68 benzodiazines
- 0.90

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 reagents (e.g. n-BuLi) should be avoided in diazine series.

R-Li
R: n-Bu, sec-Bu, t-Bu
pKa: 45 - 50

LDA
lithium disopropyl amide
pKa: 35.7

LTMP
lithium 2,2,6,6-tetramethyl-pyperidyl amid
pKa: 37.3

Generation in situ:

\[(i-Pr)_{2}NH\] + n-BuLi \rightarrow \text{LDA} \text{ (0°C, min. quantitative yield)} \rightarrow \text{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:

![Chemical structure](image1)

**Increased acidity**

![Chemical structure](image2)

**MORE increased acidity**

**Li........B** chelation of Li in the transition state

**INCREASED**

ii) thermodynamic role:

![Chemical structure](image3)

**Stabilisation as complexed carbanion**

![Chemical structure](image4)

**Stabilisation by the (-I) of DoMG**

![Chemical structure](image5)

**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:**

![Chemical structure](image6)

a) $k_1 >>> k_{-1}$: trivial case; deuterated species detectable

b) $k_1 <<< k_{-1}$: metallation in equilibrium; "trapping in situ" methodology; no deuterated species detectable

no reaction between $R_2NLi$ and $E^+$

---

**Directing ortho-Metallating Groups**

**Halogens:** F, Cl, Br, I

**Oxygenated Groups:** OCH$_3$, OCH$_2$OCH$_3$, 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$_2$R, SO$_3$R, SO$_2$NHR

**Functionalisations as:**

**Halogen:** F, Cl, Br, I

**Carbonated:** C(OH)R$_1$R$_2$, 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 :

\[
\text{COOEt} \quad \text{COOEt} \quad \text{NaOEt / EtOH} \quad \text{COOEt} \quad \text{COOEt}
\]

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

\[
\text{CH}_3 \quad \text{Ph-CH=O} \quad \text{Ac}_2\text{O / AcOH} \quad \text{Ph}
\]

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

\[
\text{Et} \quad \text{H}_3\text{C} \quad \text{A} \quad \text{SOCl}_2 \quad \text{m-Cl-C}_6\text{H}_4\text{-CO}_2\text{H} \quad \text{C} \quad \text{D}
\]

4. Realizati transformarea :

\[
\text{COOEt} \quad \text{H}_3\text{C} \quad \text{OCH}_3 \quad \text{CH}=\text{O} \quad \text{CO-NH-Ph} \quad \text{OCH}_3 \quad \text{C}_6\text{H}_4\text{-OMe-}p
\]

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

\[
\text{H}_3\text{CO} \quad \text{CH}=\text{O} \quad \text{A} \quad \text{B} \quad \text{C} \quad \text{D} \quad \text{E}
\]