Heterocyclic compounds

Structure, synthesis and reactivity
Heterocyclic compounds

They classification is based on the ring size, the quality and number of heteroatoms. They can be unsaturated, partially or completely saturated.

By the ring size:

By the quality of heteroatoms:

By the number of the heteroatoms:

By the level of saturation of the ring:

Common names, Hantzsch–Widman nomenclature and/or replacement nomenclature are used. The Hantzsch-Widman nomenclature is based on the type of the heteroatom; the ring size and nature of the ring, whether it is saturated or unsaturated. This system of nomenclature applies to monocyclic three-to-ten-membered ring heterocycles.
**Hantzsch–Widman nomenclature**

The type of heteroatom is indicated by a **prefix** as shown below. The heteroatoms are listed in a specific order, with position numbers before the name if necessary. In the case of monocyclic compounds, the numbering is starting from the highest ranking heteroatom (O>S>N) so that the heteroatoms are given the lowest possible positions number.

<table>
<thead>
<tr>
<th>prefix</th>
<th>Oxygene</th>
<th>Sulphur</th>
<th>Nitrogene</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>oxa-</td>
<td>thia-</td>
<td>aza-</td>
</tr>
</tbody>
</table>

The ring size is indicated by a **suffix** according to table below. Some of the syllables are derived from Latin numerals, namely **ir** from tri, **ete** from tetra, **ep** from hepta, **oc** from octa, **on** from nona, **ec** from deca. The **endings** indicate the size and degree of unsaturation of the ring.

<table>
<thead>
<tr>
<th>Ring size</th>
<th>Unsaturated</th>
<th>Saturated</th>
<th>Ring size</th>
<th>Unsaturated</th>
<th>Saturated</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>-irine</td>
<td>-irane*</td>
<td>7</td>
<td>-epine</td>
<td>-epane</td>
</tr>
<tr>
<td>4</td>
<td>-ete</td>
<td>-etane*</td>
<td>8</td>
<td>-ocine</td>
<td>-ocane</td>
</tr>
<tr>
<td>5</td>
<td>-ole</td>
<td>-olane*</td>
<td>9</td>
<td>-onine</td>
<td>-onane</td>
</tr>
<tr>
<td>6</td>
<td>-ine</td>
<td>-ane</td>
<td>10</td>
<td>-ecine</td>
<td>-ecane</td>
</tr>
</tbody>
</table>

* In the case of the nitrigene containing saturated system the endings of the name is **idine**!
3-Membered heterocyclic compounds

3-Membered unsaturated heterocyclic compounds with one heteroatom (oxirine, 1H-azirine and 2H-azirine) are highly unstable compounds.

Oxirane, aziridine and thirane are the basic compounds of the three membered, saturated heterocyclic compounds.

The derivatives of the saturated 3-membered heterocyclic compounds with two heteroatoms are known. The structure of the basic compounds are shown below (dioxirane, az oxaziridine and diaziridine).
4-Membered heterocyclic compounds

Generally, the unsubstituted, unsaturated derivatives cannot be prepared, or only under special conditions, due to their increased degradability. However, some of their derivatives are stable compounds.

The basic compounds of 4-membered saturated heterocyclic compounds are stable compounds (oxetane, azetidine and thietane). These compounds exist in different ratios of non-flat conformers.
Synthesis of 3-membered heterocyclic compounds with one heteroatom.

The unsaturated derivatives are highly unstable, it cannot be synthesized, by the formation of these type of intermediate can be supposed in several reactions (e.g. Neber rearrangement of oximes):

![Chemical structure](image)

**Synthesis of oxirane derivatives**

It can be synthesized from alkenes in one or two-step procedure. The former one is known as epoxidation. Circumstances: 1. peroxycacid in CHCl₃ or CH₂Cl₂. m-Chloroperoxybenzoic acid (mCPBA) is widely used because it is stable and commercialy available. H₂O₂/NaOH/H₂O or DMDO/acetone (dimethyl dioxirane) also are used as oxidizing agent. DMDO is prepared from acetone under neutral condition.
Synthesis of DMDO

Epoxidation with DMDO can be performed under mild condition. The advantage of this reagent, that the side product of the reaction is acetone, which is easy to remove/separate. This is one of the best reagents for epoxidation, because it can be used under neutral condition. The disadvantage of DMDO, that it is a volatile peroxide and should be treated carefully. It must be prepared freshly from acetone, but it can be stored in a fridge in a solution of acetone for some days. The preparation and all reactions of the dioxirane should be carried out in a hood.

Two-step synthesis of epoxides.

Addition of hypohalogenic acids to alkenes gives halohydrins, which are cyclized into epoxides under basic conditions by intramolecular nucleophilic substitution.
Synthesis of epoxides from oxo compounds

a) Johnson–Corey–Chaykovsky reaction

\[ \text{H}_3\text{C-S-CH}_3 + \text{CH}_3\text{I} \xrightarrow{\text{K}_2\text{CO}_3} \text{H}_3\text{C-S-CH}_3 + \text{CH}_3\text{I}^- \xrightarrow{\text{NaH}, \text{DMSO}} \text{H}_3\text{C-S-CH}_3 \]

- Using other alkyl halide (instead of methyl halide), the epoxide ring will be substituted at both carbon atoms.
- Using imine as starting compounds give aziridines as products!

b) Darzens reaction

\[ \text{R}_1\text{R}_2\text{C}=\text{O} + \text{R}_3\text{X} \xrightarrow{\text{B}} \text{R}_1\text{R}_2\text{X} \]

- Using imine as starting compounds give aziridines as products!

\[ \text{X: Br, Cl} \]
\[ \text{EWG: COOR, CN, NO}_2 \]
Synthesis of aziridines and tiiranes

a) Johnson–Corey–Chaykovsky reaction

\[ \text{NR}_3 \text{R}_2 + \text{H}_3\text{C}-\text{SCH}_3 \rightarrow \text{N}^\ominus \text{R}_2^\oplus \text{S} \rightarrow \text{R}_1 \text{N}^\ominus \text{R}_2^\oplus \]

b) Aza-Darzen reaction

\[ \text{NR}_3 \text{R}_2 + \text{X} \text{EWG} \rightarrow \text{R}_1 \text{N}^\ominus \text{R}_2^\oplus \text{EWG} \rightarrow \text{R}_1 \text{N} \text{EWG} \]

X: Br, Cl
EWG: COOR

C) With intramolecular cyclazation and aziridination of alkenes.

\[ \text{OH} \text{R}_3 \text{N} \text{R}_2 \text{R}_1 \rightarrow \text{R}_2^\ominus \text{OTs} \rightarrow \text{R}_1 \text{N}^\ominus \text{R}_2^\oplus \]

R \rightarrow \text{N}^\ominus \text{S}^\ominus \text{R}^\oplus \rightarrow \text{R}_1 \text{N} \text{S} \text{R} \text{R}_2 \text{R}_3
Although oxiranes (epoxides) are stable compounds but can be easily reacted due to the strained ring system.

- With nucleophiles, the epoxide ring is opened by a backside attack (SN$_2$ mechanism) and the nucleophiles attack on the sterically less hindered carbon.

- Under acid-catalyzed conditions, SN$_1$ character is dominate, usually with opposite regioselectivity.
Reactivity of aziridines

- Aziridines can be easily reacted due to the strained ring system.
- Those transformations in which other heterocyclic compounds can be prepared are most important.
Synthesis of four membered heterocycles

- General synthetic methods of these compounds are based on the nucleophilic substitution, but in the case of substituted derivatives, special circumstances must be applied.
Reactivity of four membered heterocycles

- Their reactivity is similar to that of oxiranes because of their strained ring system.
- They can ring system be opened with nucleophiles.

- The azetidines are more important than oxetanes and tetetanes! It can react as a secondary amines: alkylation, acylation.

\[
\begin{align*}
\text{BnO} & \quad \text{BH}_{3}CN, \text{THF, MeOH} & \quad 4 \ ^{\circ}\text{C} & \quad \text{R-CHO} \\
\text{+} & \quad & \quad & \quad \\
\text{COOEt} & \quad \text{NaBH}_{3}CN, \text{THF, MeOH} & \quad & \quad \\
\text{COOEt} & \quad \text{DMAP, Et}_{3}N, \text{rt} & \quad & \quad \\
\text{O=COEt}_{2} & \quad & \quad & \quad \\
\text{BnO} & \quad \text{O=C(OEt)}_{2} & \quad & \quad \\
\end{align*}
\]
**β-Lactam antibiotics**

**Mode of action:** The β-lactam antibiotics mimics the D-Ala-D-Ala peptide terminus that serves as the natural substrate for transpeptidase activity during cell wall synthesis. Binding of these drugs to the transpeptidase active site inhibits cell wall synthesis, resulting in a weakened cell wall that is susceptible to lysis during periods of cell growth. One of the major driving forces of cell lysis is the very high internal osmotic pressure present in bacteria, which is caused by the presence of a high concentration of proteins and other molecules that growing bacteria need to survive.
**β-lactam mechanism of action**

**ABX-free Cell Wall Synthesis**

D-Ala-D-Ala structural mimics:

- Pen
- Ceph
- Mono
- Carba

**β-lactams** bind to transpeptidase active site

Block of transpeptidase activity interrupts cross-linking & cell wall synthesis

Block of transglycosylase subunit

Terminal D-Ala

http://tmedweb.tulane.edu/pharmwiki/doku.php/betalactam_pharm
Researchers observed that the addition of carboxylic acids to the fermentation medium of *Penicillium chrysogenum* can influence the direction and yield of biosynthesis. These materials (so called precursors) are not degraded by fungi but incorporated without modification. However, it has been mentioned that only carboxylic acids containing an apolar side chain can be used as precursors.

- The resistance of bacteria against antibiotics is a serious problem. While in 1946 less than 1% of Staphylococcus strains were penicillin resistant today it is ~90%.
- Another problem of the penicillins was the *narrow-spectra* of their effect, they act just against Gram-positive bacteria.
- The allergic effect was a serious problem too, which could not be eliminated with antihistamines.
- Solution: new semi synthetic penicillins are necessary.
Semi-synthetic penicillins

6- Aminopenicillanic acid is prepared by fermentation (usually from G-penicillin by enzymatic hydrolysis with PA enzyme) and than it has been acylated with different carboxylic acid derivatives under synthetic laboratory condition.

Against resistant staphylococcus strains
Against Gram negative strains, but it can be used against Gram positive strains too. But it is ineffective against *Acinetobacter* strains and *Pseudomonas aeruginosa*.
Penicillin resistance

In the last decades, several ampicilline, amoxacilline sensitive Gram-negative bacteria (*H. influenzae*, *E. coli*, *Shigella*, *Salmonella streins*) have become resistant against these antibiotics. They can be produced β-lactamase enzyme, which inhibits these molecules.

Penicilins can be protected by using β-lactamase inhibitors, which block this enzyme, and the drug molecules still will be active against those bacteria, which produces β-lactamase enzyme. These drugs have broad spectra.
5 membered heterocycles with one heteroatom

The most important, five-membered heterocyclic compounds are pyrrole, furan, thiophene (aromatic), tetrahydrofuran, pyrrolidine, tetrahydrothiophene (saturated), dibenzofuran, indole and carbazole (benzo-fused derivatives).
5 membered heterocycles with two or three heteroatoms

1,2-oxazole
isoxazole

1,3-oxazole
oxazole

1,2-thiazole
isotiazole

1,3-thiazole
thiazole

1,2-diazole
pirazole

1,3-diazole
imidazole

X = O: oxadiazole
X = S: thiadiazole
Structure of five-membered heterocycles I.

Five membered heterocycles with one heteroatom

First case:

1 heteroatom (O,N,S), with nonbonding electron pair:

The heteroatoms (sp2 hybrid state) participate with one nonbonding electron pair in the formation of $\pi^6$ electron system.

Non-symmetrical electron delocalization: reduced aromaticity – decreased electron density on heteroatoms, and increased on carbons

Electron densities:

Without considering of EN

$-0.2 \quad -0.2$

$-0.2 \quad -0.2$

$+0.8$

$EN_X > EN_C$

The electron density of C atom is decreased!

„electron rich” heteroaromatic system

Illustration with resonance forms
The least aromatic system!

Incorporation of further heteroatoms into the ring: aromaticity can only be kept with "pyridine-type" nitrogens!

Nitrogene: two-type sp\(^2\) hybrid state

„pyrrole-type“: \(h_1^1h_2^1h_3^1p_z^2\)

„pyridine-type“: \(h_1^1h_2^1h_3^2p_z^1\)

Imidazole is an electron rich heteroaromatic system, but the second nitrogen in the ring decreased the \(\pi\)-electron density of the ring. Reactivity is similar to the five-membered heteroaromatic system with one heteroatom.
Synthesis of five-membered heterocyclic compounds I.

Five-membered heterocyclic compounds with one heteroatom can be synthesized by 3+2 cyclization, which can be performed by condensation between an 1,2-dioxo compounds and 1,3-dinucleophile possessing one heteroatom.

Another possibility is a cyclization of 1,4-diketones in the presence of dehydrating agent like P_2O_5 or P_2S_5, gave furanes or thiophene. Using dehydrating agents and ammonia or amines pyrrole derivatives will be obtained.
Synthesis of five-membered heterocycles with more than one heteroatoms I.

Cyclization of binucleophiles with bielectrophiles gave heterocycles with two heteroatoms.

1,2- bielectrophiles

1,3- bielectrophiles

1,3- binucleophiles

1,2- binucleophiles

Syntheseis of imidazole derivatives

\[
\text{EtO} \overset{\text{NH}}{\text{NH}} \cdot \text{HCl} + \text{Ph} \overset{\text{Br}}{\text{CH}} \rightarrow \overset{\text{O}}{\overset{\text{EtO}}{\text{N}}} \overset{\text{NH}}{\text{N}} \overset{\text{H}}{\text{N}} \overset{\text{N}}{\text{N}} \overset{\text{O}}{\text{Et}} \overset{\text{NH}}{\text{NH}} \cdot \text{HCl} + \overset{\text{O}}{\overset{\text{EtO}}{\text{N}}} \overset{\text{NH}}{\text{N}} \overset{\text{H}}{\text{N}} \overset{\text{N}}{\text{N}} \overset{\text{O}}{\text{Et}} \overset{\text{NH}}{\text{NH}} \cdot \text{HCl}
\]
Synthesis of five-membered heterocycles with more than one heteroatoms II.

- **Synthesis of 1,3-azoles**
  - Reaction of ArCOCl with ArH$_2$N-R$_X$ (where X: O = amide, X: S = tioamide, X: NH = amidine)
  - Result: 1,3-oxazole, 1,3-thiazole, 1,3-imidazole

- **Synthesis of 1,2-diazoles**
  - Reaction of ArCONH$_2$ with ArCl-R$_X$ (where X: O, S)
  - Result: 1,2-diazole

- **Additional Synthesis**
  - Reaction of RCONCOR' with R'NHNH$_2$
  - Result:
  - Reaction of H$_3$CO-CO-CH$_3$ with PhNHNH$_2$
  - Result: [Product structure]
Reactivity of five-membered heterocycles I.

1. Acid-base reactions

1.1. Basicity

Nonbonding electron pair of azoles can be protonated if it is not a member of $\pi^6$ aromatic system!

„Pyrrole like” nitrogen $\Rightarrow$ weak base

Losing the aromatic character!

Furane

$pK_b \sim 13.5$

Diene and enol ether character! Sensitivity against acids, polymerization in SE reaction!

1.2. Acidity

Weak acidity in the presence of „pyrrole-like” nitrogen!

$pK_a \sim 15$
2. Electrophilic substitution ($S_{E\text{Ar}}$)

2.1. Heterocycles with one heteroatom.

High electron density at the carbons, lower aromaticity than in the case of benzene ⇒ higher reactivity

Reactivity order: pyrrole > furan > thiophene > benzene

Because of the higher reactivity, milder circumstances are necessary than in the case of the benzene. Substitution at the C-2 and C-5 positions.


Pyrrole and thiophene

Furan can react as diene or dienol ether!

Electron density without $E_N$

$\begin{array}{cc}
-0.2 & -0.2 \\
-0.2 & +0.8 \\
\end{array}$

$EN_X > EN_C$,
But still higher electron density on the carbon!

$\begin{array}{c}
\delta^- \\
\delta^- \\
\delta^- \\
\delta^- \\
\delta^+ \\
\end{array}$
Reactivity of five-membered heterocycles III.

2.1.2. Sulfonation: SO$_3$ complex (py x SO$_3$) instead of oleum (SO$_3$/cc H$_2$SO$_4$).

2.1.3. Friedel-Crafts acylation: Furan and pyrrole are unstable in the presence of strong Lewis-sav catalysts (e.g.: AlCl$_3$) but BF$_3$•Et$_2$O, TiCl$_4$, SnCl$_4$ are usable.

Explanation of regioselectivity: in the case of competitive reactions, the more stable intermediate has lower activation energy → faster reaction: kinetic control

more resonance form, higher stability
Reactivity of five-membered heterocycles IV.

### 2.1.4. Chlorination: under mild conditions at C-2 position

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reagent</th>
<th>Y</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>X = NH, pyrrole</td>
<td>SO$_2$Cl$_2$</td>
<td>Cl</td>
<td>0 °C</td>
</tr>
<tr>
<td>X = O, furan</td>
<td>Cl$_2$</td>
<td>Cl</td>
<td>-40 °C</td>
</tr>
<tr>
<td>X = S, thiophene</td>
<td>CH$_3$CONHCl</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 2.1.5. Reactions with bases: it can be deprotonated with alkyl-lithium (e.g.: BuLi) on the C-2 and this carbanion react with electrophiles to form new C-C bond.

X = NR, O, S  \hspace{1cm} E: HC$_3$I, CO$_2$  \hspace{1cm} Y: CH$_3$, CO$_2$H
2.1.4. Reactions with bases: The unprotected pyrroles can be substituted on C-2 carbon by different ways.

2.1.5. Addition reactions: by catalytic hydrogenation, they can be converted into their partially or fully saturated derivatives.

2.1.5. Addition reactions: the [4 + 2] cycloaddition reactions with dienophiles (e.g., alkynes) indicate the diene nature of these compounds.
2.2. Imidazole

It’s chemical properties are defined by pyrrole- and pyridine-type nitrogen.

2.2.1. Acid-base properties

Amphoteric compound due to the two "types" of nitrogen:
- Moderately strong base
- Weak acid

\[
\begin{align*}
\text{imidazole} & \quad \text{imidazole} + \text{H}^+ & \quad \text{imidazole} - \text{H}^- \\
pK_a = 6.95 & \quad pK_a = 14.2
\end{align*}
\]

~2000 times stronger acid than pyrrole

Reason: resonance stabilization

Virtual tautomerism

4-substituted or 5-substituted

Equilibrium mixture with inseparable virtual tautomers.

1,4-disubstituted vs. 1,5-disubstituted

N-substituted derivatives are separable
Reactivity of five-membered heterocycles VII.

\[ \text{SEAr reactions} \]

\[
\begin{align*}
\text{Br}_2/\text{AcOH} & \quad \text{NaOAc} \\
\text{cc.HNO}_3/\text{H}_2\text{SO}_4 & \quad 90\% \\
\text{Na}_2\text{SO}_3/\text{H}_2\text{O} & \quad \text{H}_2\text{SO}_4 \quad \text{160 }^\circ\text{C} \\
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \quad \text{Na}_2\text{SO}_3/\text{H}_2\text{O} \quad \text{melegítés} \\
\text{HO}_3\text{S} & \quad \text{Et}_3\text{N} \\
\end{align*}
\]

\[
\begin{align*}
\text{SO}_3\text{H} & \quad \text{PhCOCl} \\
\\text{1. KOH} & \quad \text{2. Mel} \\
\end{align*}
\]

\[
\begin{align*}
\text{Regioselectivity} \\
1,2- \text{ and } 1,3-\text{ azoles}
\end{align*}
\]
Six-membered heterocycles are \( \pi \) electron poor compounds. The nitrogen containing derivative (pyridine) is neutral aromatic molecule, but in the case of oxygen and sulphur, the aromatic derivatives have positive charge. If these molecules are neutral, they are not aromatic systems.
2.2. Structure of six-membered heterocycles

Low $\pi$-electron density on carbons, but similar resonance energy ($117 \text{ kJ/mol vs. } 149 \text{ kJ/mol}$) as in the case of benzene ⇒ Low reactivity

Further problem: the non-bonding electron pair of nitrogen: Lewis base ⇒ $\pi$ elektron cloud and non-bonding electron pair compete for electrophile, reagent and non-bonding electron pair compete for catalyst ⇒ poor reactivity

Pyridine: analogue structure with benzene, a nitrogen add only one $p_z$ electron into the $\pi^6$ aromatic system.

But: $E_N^N > E_N^C$ ⇒ distorted electron density: increased on the nitrogen and decreased on the carbons. Electron poor heteroaromatic system!
Similar molecular orbitals as in the case of benzene. Highly stabilized aromatic system! Resonance energy: 117 kJ/mol

Molecular orbitals of benzene and pyridine

Rezonance structures:
Synthesis of pyridine derivatives with *Hantzsch* synthesis

**A route**

\[ R^1 \text{CO, COOR} \]
\[ R^2, R^3 = \text{alkyl, aryl, H} \]

**B route**

\[ R^2 = \text{alkyl, aryl, H} \]
Chemical properties of pyridine I.

Competitive reactions

Brönsted-base

$\text{pK}_b = 8.8$

N-alkylation

Highly limited $S_E$ reactions, characterized with „brutal” reaction conditions and very low yield

RCOCl or (RCO)$_2$O/AlCl$_3$

no reaction

Substitution on C-3!
Explanation of regioselectivity: in competitive reactions, lower activation energy belong to the more stable the intermediate → the faster the reaction: kinetic control.

In the case of the C-2 and/or C-4 substitution, the nitrogen possess only six electrons – unstable system.
Chemical properties of pyridine III.

Reactivity of pyridine-N-oxide

Nucleophilic substitutions
The pyridine reacts „easily” with nucleophilic reagents in the \( S_{NAr} \) reaction.

Mechanism: \( Ad + E \)
Chemical properties of pyridine IV.

2-Alkyl pyridines can react with bases (KOH/EtOH; NaNH₂, vagy RLi) to give nucleophiles.
Six-membered heterocycles with two or more heteroatoms

The skeletons of six-membered heterocyclic compounds containing two or more heteroatoms show high diversity due to the variability of the heteroatoms (N, O, S), their positions and the possibilities of saturation and unsaturation of the molecules.
Synthesis of diazines I.

Synthesis of 1,2-diazines

\[
\begin{align*}
&\text{R} \quad \text{RCOO} \quad \xrightarrow{\text{N}_2\text{H}_4} \quad \text{RCO} \quad \xrightarrow{\text{ox.}} \quad \text{N} \quad \text{R} \\
&\text{R} \quad \text{RCOO} \quad \xrightarrow{\text{N}_2\text{H}_4} \quad \text{R} \quad \text{N} \quad \xrightarrow{\text{ox.}} \quad \text{N} \quad \text{R}
\end{align*}
\]

Synthesis of 1,4-diazines

\[
\begin{align*}
&\text{R}^4 \quad \text{RCOO} \quad + \quad \text{H}_2\text{N} \quad \text{R}_1 \quad \xrightarrow{\text{N}_2\text{H}_4} \quad \text{R}^3 \quad \text{N} \quad \text{R}_1 \quad \xrightarrow{\text{ox.}} \quad \text{N} \quad \text{R}_1 \\
&\text{R}^4 \quad \text{RCOO} \quad + \quad \text{H}_2\text{N} \quad \text{R}_1 \quad \xrightarrow{\text{N}_2\text{H}_4} \quad \text{R}^3 \quad \text{N} \quad \text{R}_1 \quad \xrightarrow{\text{ox.}} \quad \text{N} \quad \text{R}_1 \\
&\text{R}^4 \quad \text{RCO} \quad \text{NH}_2 \quad + \quad \text{H}_2\text{N} \quad \text{R}_1 \quad \xrightarrow{\text{N}_2\text{H}_4} \quad \text{R}^3 \quad \text{N} \quad \text{R}_1 \quad \xrightarrow{\text{ox.}} \quad \text{N} \quad \text{R}_1
\end{align*}
\]
Synthesis of 1,3-diazines

\[ \text{urea (X: O)} \]
\[ \text{thiourea (X: O)} \]
\[ \text{guanidine (X: NH)} \]

X: O, S, NH

amidines

pyrimidine-4(3H)-on derivatives

barbiturates

X: O, S, NH
Reactions of pyrimidine I.

The π-electron deficiency of six-membered heteroaromatic compounds with two or more heteroatoms determine their reactivity. They are less reactive in SEAr, but more reactive in SNAr reactions than benzene.

Acid – base properties

These compounds are basic. Their basicity can be characterized by the acidity (pKa) of the conjugated acid. In the order of 1.2 > 1.3 > 1.4 diazines, the basicity of the compounds decreases, thus the acidity of the conjugated acid are increased, pKa = pyridazine: 2.33; pyrimidine: 1.30; pyrazine: 0.65.

S_N reactions

It can be attacked with nucleophiles on the C-2, C-4 and C-6-positions!

It react faster on C-4/C-6 than on C-2!
Reactions of pyrimidine II.

$S_{E}Ar$ reactions

Their reactivity are similar to 1,3-dinitrobenzene or 3-nitropyridine: highly deactivated molecules!

BUT!

In the presence of activating substituents their reactivity are increased:

2 electron donating groups: $\sim$ similar reactivity as the benzene
3 electron donating groups: $\sim$ similar reactivity as the phenol

Nitration, nitrosation, azocoupling on C-5 position!

\[
\begin{align*}
\text{OH} & \quad \text{HNO}_3/\text{AcOH} \quad 20 ^\circ \text{C} \\ 
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\text{C} & \quad \text{O}_2\text{N} \\
\text{N} & \quad \text{OH} \\
\text{N} & \quad \text{OH}
\end{align*}
\]