PURINES - kap 24

9H purine  \rightleftharpoons  7H purine  \rightleftharpoons  \begin{array}{c}
\text{1H purine} \\
\text{3H purine}
\end{array}

two 6\pi electron aromatic ring

Reaction with electrophiles at N - Protonation

\begin{array}{c}
pK_a 2.5 \\
\text{major protonated form}
\end{array}
Reaction with electrophiles at N - Alkylation

Selectivity depends on substituents and conditions

Complete selectivity

Base
N7/N9: - Sterical factors (Large 6-subst)
Termodyn. control (reversible react.)

<table>
<thead>
<tr>
<th>X</th>
<th>Time</th>
<th>N9 / N7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>1h</td>
<td>4.3 : 1</td>
</tr>
<tr>
<td>Cl</td>
<td>24h</td>
<td>19 : 1</td>
</tr>
<tr>
<td>Cl</td>
<td>24h</td>
<td>200 : 1</td>
</tr>
<tr>
<td>OMe</td>
<td>1h</td>
<td>1 : 1</td>
</tr>
<tr>
<td>OMe</td>
<td>14 days</td>
<td>Still mixt.</td>
</tr>
</tbody>
</table>

Electrophiles - cancer
**Reaction with electrophiles at N - Acylation / Sulfonation**

- Acylation products generally unstable
- Sulfonation - Stable prod., selective N9

![Chemical structures and reactions](image)

**Reaction with electrophiles at N - oxidation**

- ROOH
- X=NH₂, Y=H
- X=OH, Y=NH₂
- X=CN, Y=H

![Chemical structures and reactions](image)
Reaction with electrophiles at C

Electron rich pyrole like

Pyridine like

More benzene like
**Reaction with electrophiles at C**

E-fil Ar subst, generally not working

Mechanism?

**Reaction with nucleophiles**

Reactivity towards Nu

Most probably react. on

activated for Nu attack
Nu.Ar.Subst: Reactivity F>Cl>Br>I

Other leaving groups

from DABCO
Deprotonation at N

\[ \text{pKa 8.9} \]

\[ \text{pKa 14.2} \quad \text{pKa 12.3} \]
**Deprotonation at C / C-metallation**

**c.f. H-2 in imidazoles**

**Heteromines**

**X, Y: NH₂, "OH" ; Excess base**
Org. Lett, 2003, 4289
Nolsøe et al., Synth Commun 1998, 4303

JOC 1997, 6833

Rf = 2,3,5-tris-O-TBDMS-β-D-ribofuranosyl
-Oxo forms

Oxy purines

Hypoxanthine

Xanthine

Uric acid

Alkylation, acylation etc

N-alkylation

O-Silylation

O-Sulfonation

O-Acylation

Isolated yields

not detected
Replacement of $O$ with other hetero atoms

Amino purines

Amino form
Alkylation, acylation etc

Diazotation etc.

Alkylation, acylation etc

Diazotation etc.
Synthesis of Purines

Carbonyl condensations

*Strategy A - Traube synth. etc*

\[
\text{CH(OEt)}_3 / \text{HCONH}_2 \quad \text{H}^+ \quad \text{Ac}_2\text{O} \quad \text{NH}_2\text{R} \quad \text{Zn/H}^+ \quad \text{NH}_3 \quad \text{HNO}_3 / \text{H}_2\text{SO}_4 \quad \text{CH(OEt)}_3 / \text{HCONH}_2
\]
Carbonyl condensations

*Strategy B*

\[
\text{Ph-N=C=S} \quad \xrightarrow{\text{EtO}} \quad \text{N} \quad \text{N} \quad \text{CO}_2\text{Et}
\]

\[
\text{EtO}_2\text{C} \quad \text{N} \quad \text{N} \quad \text{CO}_2\text{Et}
\]

**Cycloadditions**

\[
\text{Diels Alder} \quad \xrightarrow{\text{EtO}} \quad \text{EtO}_2\text{CCN}
\]

\[
\text{EtO}_2\text{C} \quad \text{N} \quad \text{N} \quad \text{CO}_2\text{Et}
\]

\[
\text{EtO}_2\text{C} \quad \text{N} \quad \text{N} \quad \text{CO}_2\text{Et}
\]
Bioactive Purines

DNA / RNA bases

- Adenine
- Guanine

Anticancer / antiviral drugs

- 6-MP
- Fludarabine
- ddI
- Acyclovir
- Abacavir
Adenosine and adenosine receptor ligands

At least 4 sub-types. $A_1$, $A_{2A}$, $A_{2B}$, $A_3$

No drugs (yet)...

Parkinson's and selective $A_{2A}$ antag. ??

Cytokinin - Plant growth hormones

Heteromines

• Isolated from *Heterostemma brownii*

• Treatment of tumors in Taiwanese folk medicine
Purine-Containing Marine Natural Products

From marine algae, sponges, gorgonians (sea fans), ascidians (tunicates) etc., etc.

Saxitoxin
(red tide)

Microxine

Aplidiamine

Spongosome

J Nat Prod 2005, 68, 1288
Purine-Containing Marine Natural Products

Agelasines

Agelasimines

Asmarines

Agelarine A

Agelasimine A

Asmarine A
Reversine