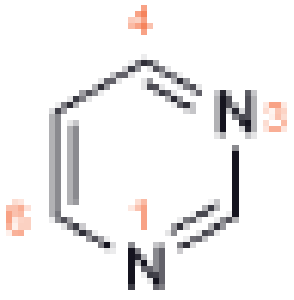
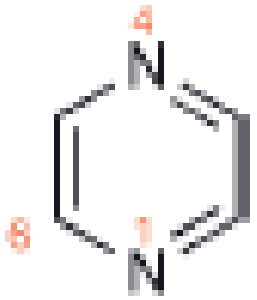
Typical Reactivity of the Diazines: Pyridazine, Pyrimidine and Pyrazine

pyridazine



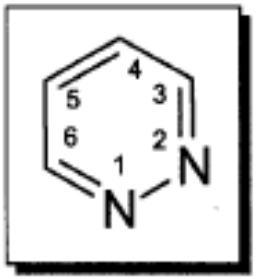
pyrimidine



pyrazine

Pyridazine

The structurally isomeric diazines pyridazine (1,2-diazine), pyrimidine (1,3-diazine) and pyrazine (1,4- diazine) are derived from pyridine by appropriate substitution of a CH group by nitrogen.

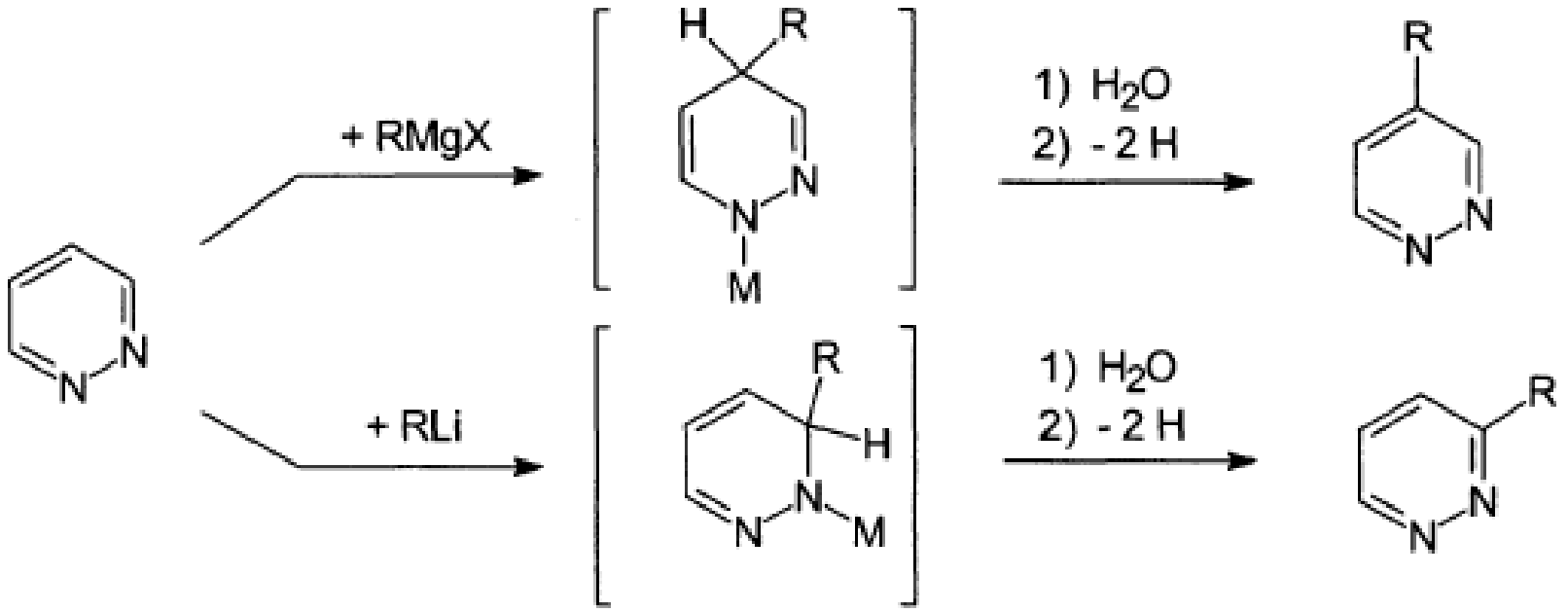


The N-N bond has single bond character. Therefore, pyridazine can be described as a resonance hybrid with limiting structures a and b, the canonical form a making the major contribution

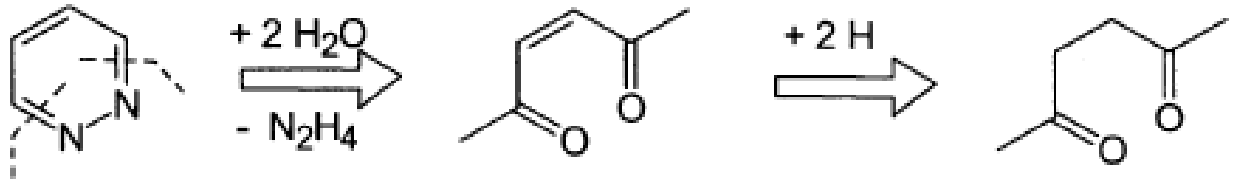
The diazines – pyridazine, pyrimidine and pyrazine – contain two imine nitrogen atoms, so the lessons learnt with regard to pyridine are, in these heterocycles, exaggerated. Two heteroatoms withdraw electron density from the ring carbons even more than one in pyridine, so unsubstituted diazines are even more resistant to electrophilic substitution than is pyridine. A corollary is that this same increased electron deficiency at carbon makes the diazines more easily attacked by nucleophiles than pyridine.

The availability of nitrogen lone pair(s) is also reduced: each of the diazines is appreciably less basic than pyridine, refl ecting the destabilising infl uence of the second nitrogen on the *N* - protocation. Nevertheless, diazines will form salts and will react with alkyl halides and with peracids to give *N* - alkyl quaternary salts and *N* - oxides, respectively. Generally speaking, such electrophilic additions take place at one nitrogen only, because the presence of the positive charge in the products renders the second nitrogen extremely unreactive towards a second electrophilic addition.

Reactions of pyridazine also show analogies to pyridine. Electrophiles attack the ring Natoms, for instance in protonation, alkylation or TV-oxidation. SEAr reactions at the ring C-atoms are difficult to carry out, even in the presence of activating substituents due to the deactivation by the additional N-atom. However, TV-oxidation facilitates the substitution in some cases. Reactions with nucleophiles occur at ring position C-4 (e.g. with GRIGNARD reagents), or at C-3 (with organolithium compounds). They are preparatively not as important as the CHICHIBABIN or ZIEGLER reaction in pyridine.


+ RMgX
+ RLi
H
R
N
N
M
1) H2O
2) - 2 H
R
N
N
R
H
N
N
M
1) H2O
2) - 2 H
R
N
N
(M = Li or MgX)

The synthesis of pyridazines



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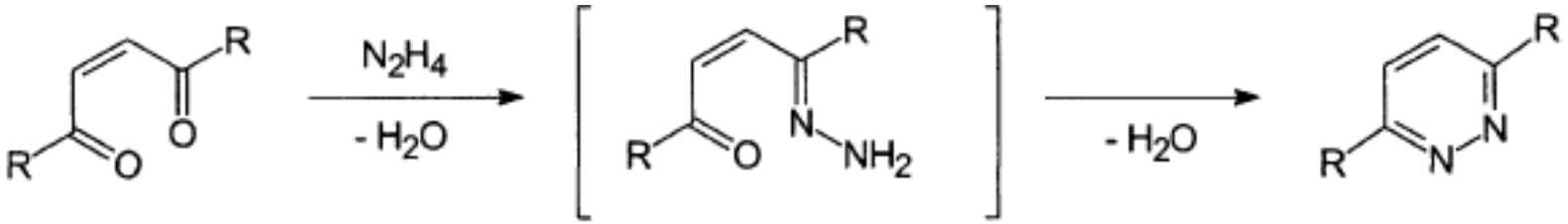

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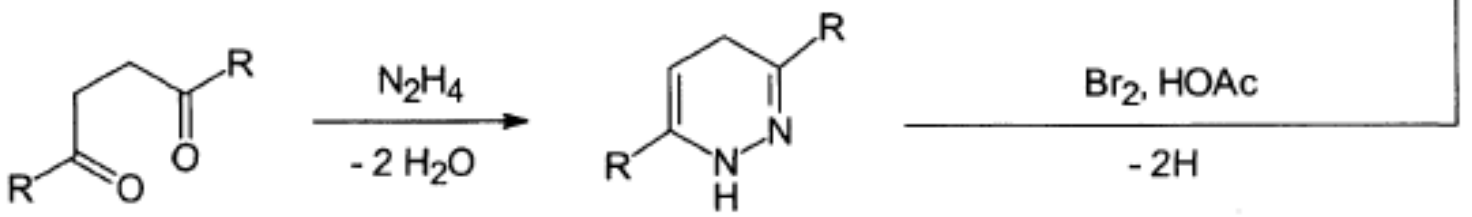
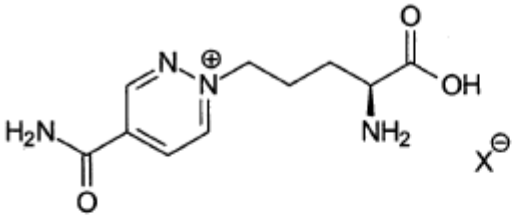


Pyridazine, mp -8°C, bp 208°C, is a colourless liquid, soluble in water and alcohols but insoluble in hydrocarbons (H-bridges, due to acceptor function of the N-atoms). Of the diazines, pyridazine has the highest basicity *(pKa* = 2.3, pyrimidine = 1.3, pyrazine = 0.4), but in common with all diazines, it is much less basic than pyridine *(pKa* = 5.2). Its dipole moment (μ = 3.95 D) is higher than that of pyrimidine (μ = 2.10 D). Pyrazine has no dipole moment

Relatively few pyridazine derivatives occur in nature, e.g. the quaternary salt pyridazinomycin 20. Some pyridazine derivatives show biological activity and are applied as herbicides and anthelmintics, e.g. maleic hydrazide 18 and the chlorinated pyridazinones 21 (pyrazon)/22 (pyridaben). The tetrahydropyridazinone derivative levosimendan 23 is an innovative myofilament calcium sensitizer applied as cardiotonic in treatment of heart failure.



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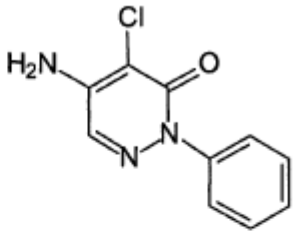

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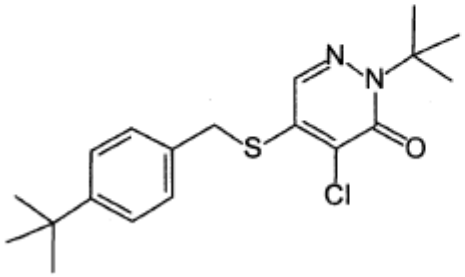

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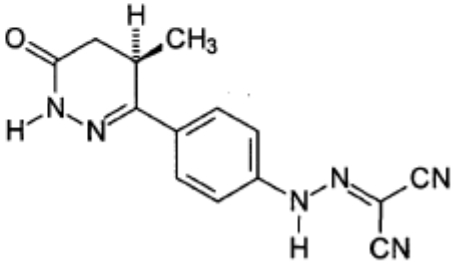

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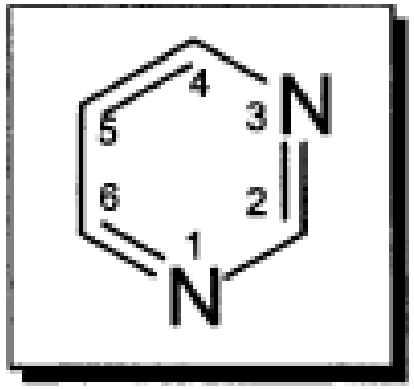
1,3 - Azoles: Imidazoles, Thiazoles and Oxazoles: Reactions and Synthesis

Imidazole
[1*H*-imidazole]

thiazole

oxazole

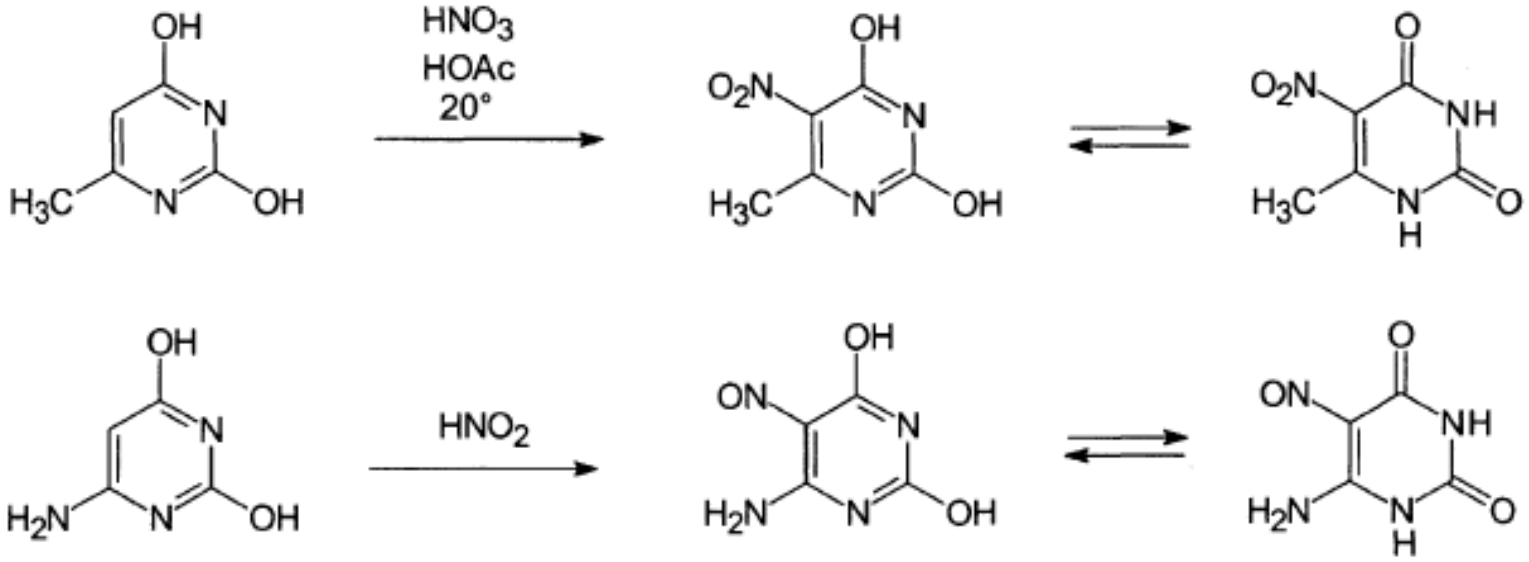


1,3 - Azoles: Imidazoles, Thiazoles and Oxazoles: Reactions and Synthesis

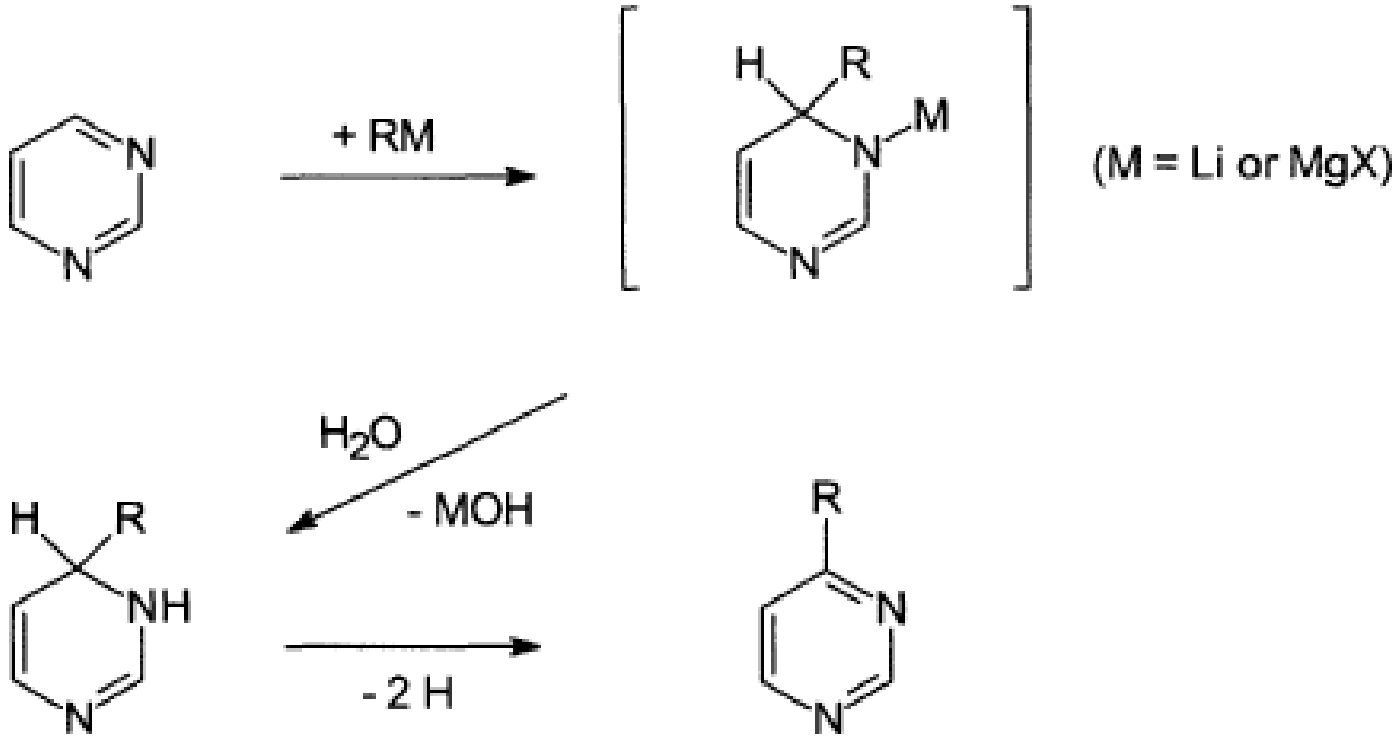
Imidazole, thiazole and alkyl - oxazoles, though not oxazole itself, form stable crystalline salts with strong acids, by protonation of the imine nitrogen, N - 3, known as imidazolium, thiazolium and oxazolium salts.

Imidazole, with a p *K* aH of 7.1, is a very much stronger base than thiazole (2.5) or oxazole (0.8). That it is also stronger than pyridine (5.2) is due to the amidine - like resonance that allows both nitrogens to participate equally in carrying the charge. The particularly low basicity of oxazole can be understood as a
combination of inductive withdrawal by the oxygen and weaker mesomeric electron release from it. The 1,3 - azoles are stable in hot, strong aqueous acid.

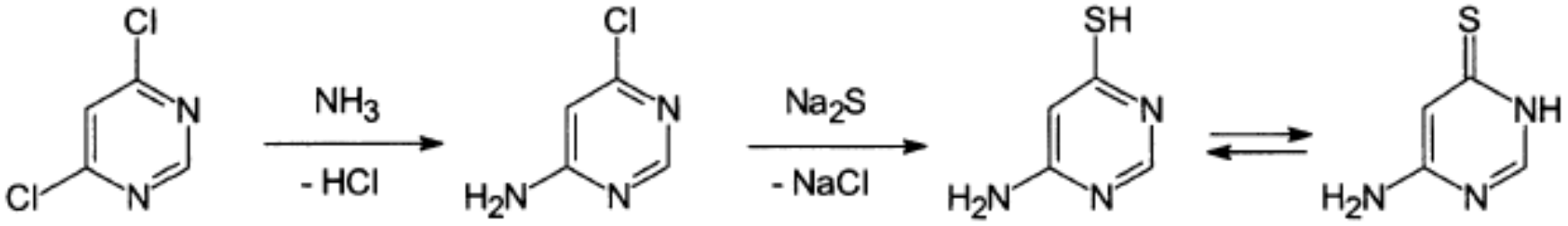
In its reactions, pyrimidine behaves as a deactivated heteroarene. Its reactivity is comparable to that of 1,3-dinitrobenzene or 3-nitropyridine. Electrophiles attack on nitrogen in protonating and alkylating reactions. Electrophilic substitutions at carbon are not observed in the parent compound. Electron-donating substituents (OH, NH2) increase the SEAr reactivity in the pyridmidine system (two substituents give a reactivity corresponding to benzene, three to that of phenol) and enable nitration, nitrosation, aminomethylation and azo-coupling to take place at the 5-position, e.g.:



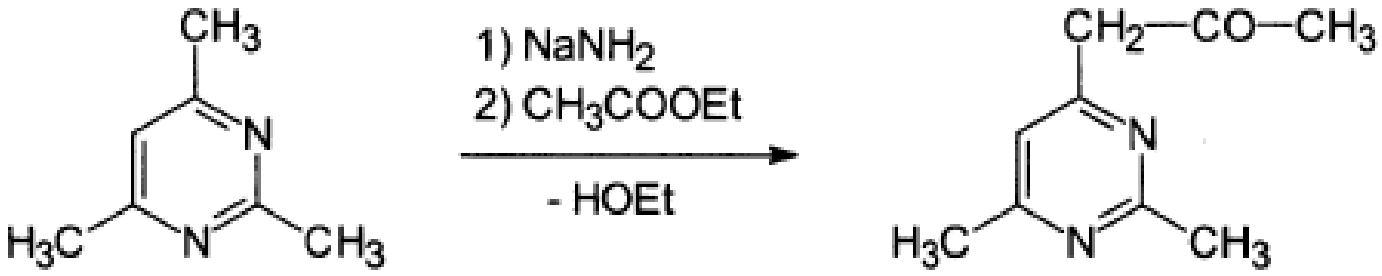
Nucleophilic attack occurs at the 2-, 4- and 6-positions. Only a few examples are known for pyrimidine itself, e.g. addition of some organometallic compounds to 3,4-dihydropyrimidines that can then be dehydrogenated to give pyrimidines



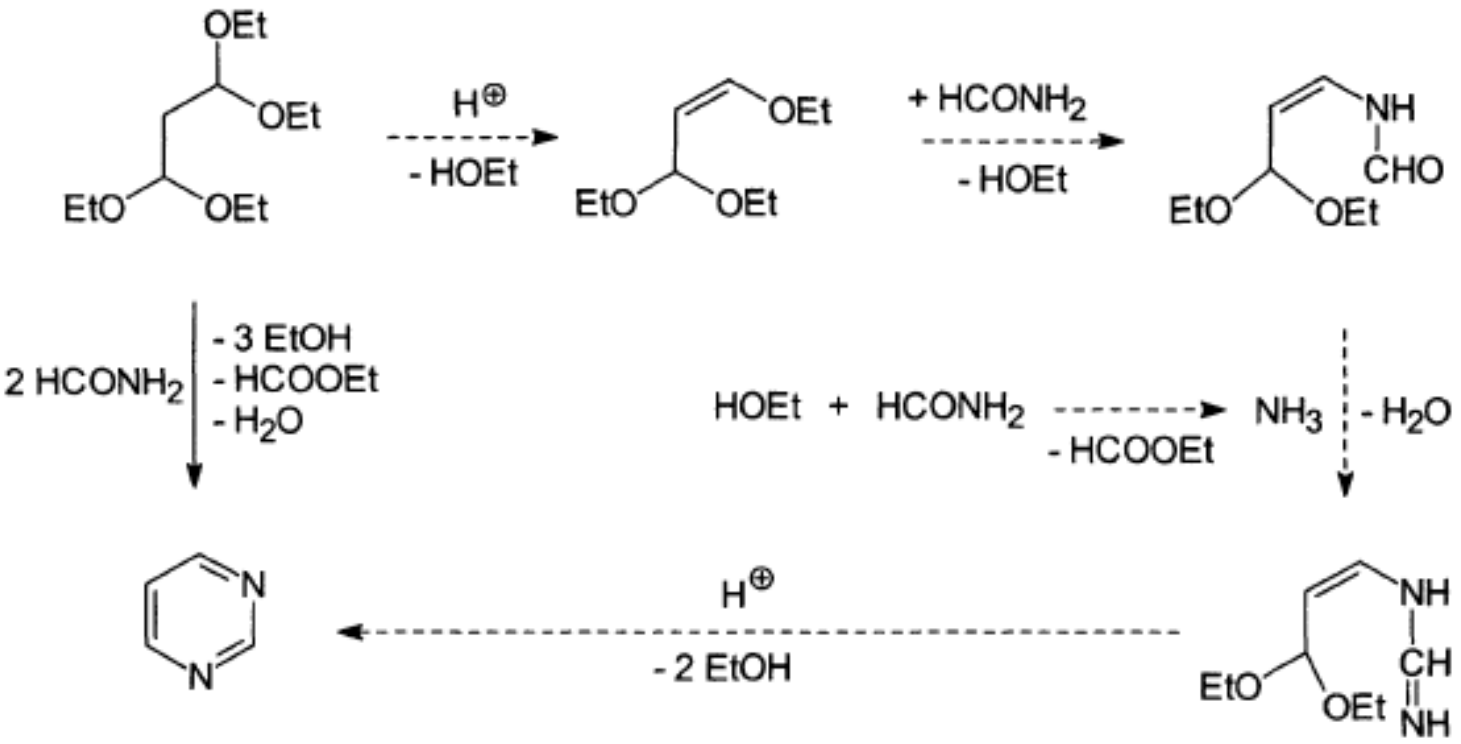
Nucleophilic substitutions (e.g. with amides, amines, alcoholates, sulfides) in 2-, 4- or 6-halosubstituted pyrimidines are widely applied for the preparation of functionalized pyrimidines, e.g.:



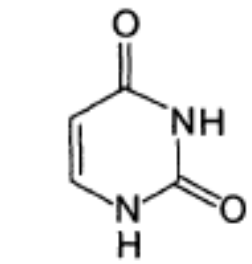
The pyrimidine system shows side-chain reactivity typical of azines. CH3 groups at the 2-, 4- or 6- position undergo aldol condensations (with aldehydes in the presence of LEWIS acids) or CLAISEN condensations (with esters in the presence of strong bases) with marked preference at C-4, e.g.:



Pyrimidine, mp 22,5°C, bp 124°C, is a water-soluble, weak base that forms a sparingly soluble complex with $HgCl_2$. Pyrimidine is prepared by condensation of 1,1,3,3-tetraethoxypropane with formamide over montmorillonite *(Bredereck synthesis)* at 210°C in the gas phase



Uracil 22, thymine 23, cytosine 24, barbituric acid 25 and orotic acid 26 are important pyrimidine derivatives.



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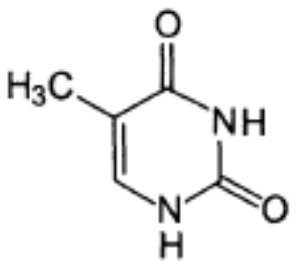

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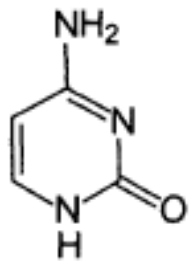

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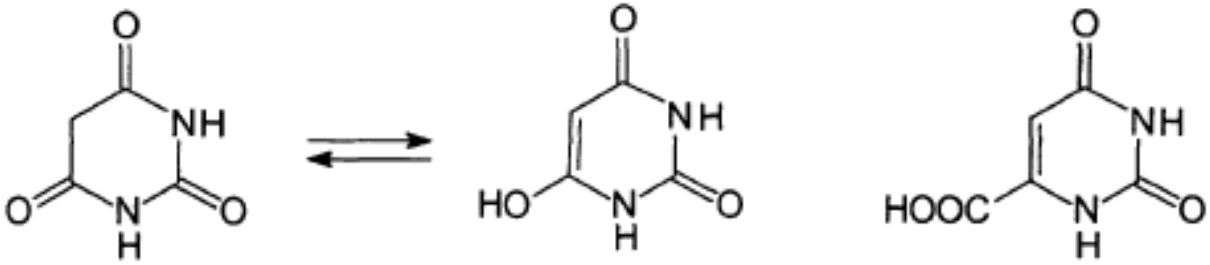

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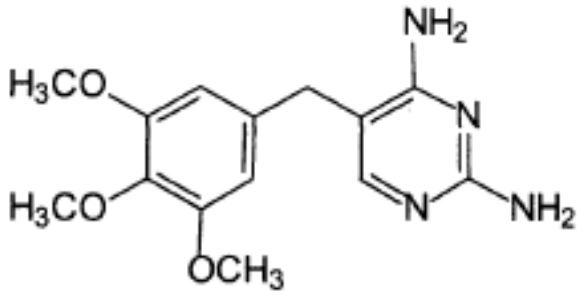
The pyrimidine ring is a constituent of many pharmaceuticals, such as the chemotherapeutics trimethoprim 32 and sulfadiazine 33, the dihydrofolate reductase inhibitor pyrimethamine 34 and hexetidine 35 derived from hexahydropyrimidine and used as an oral antiseptic.



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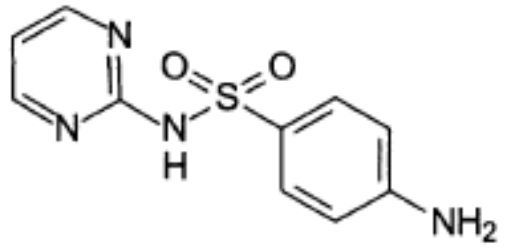

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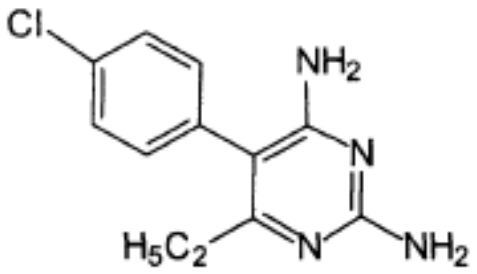

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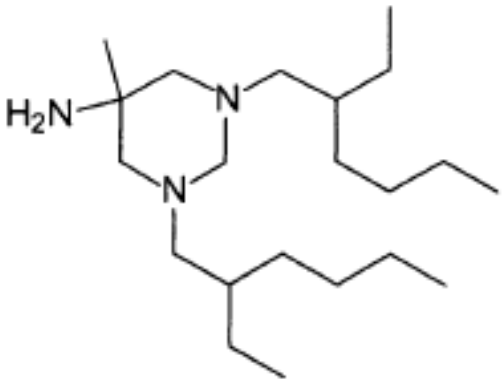

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