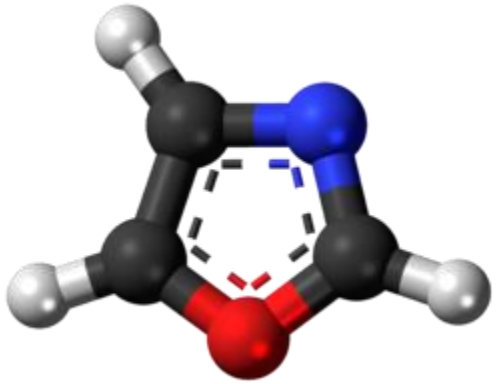
2302687 – Heterocyclic Compounds – Part I

Lecture 6-1

Ring Synthesis of 1,3-Azoles



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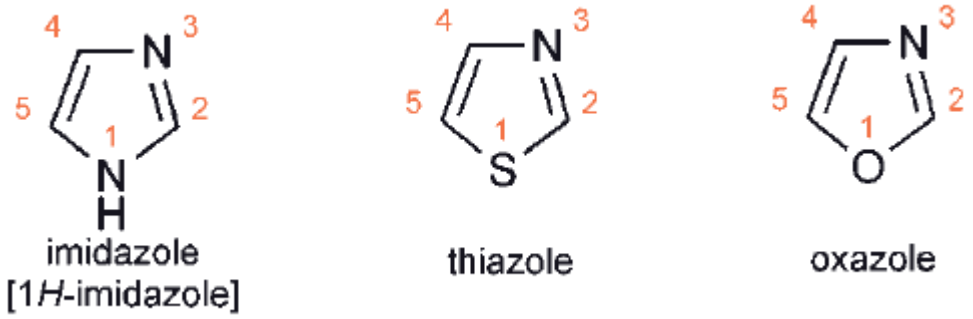
Recommended Textbook:

Heterocyclic Chemistry, 5th Edition, J. A. Joule, K. Mills, **2010**, Wiley

1,3-Azoles: Imidazoles, Thiazoles and Oxazoles



imidazole
[1*H*-imidazole]

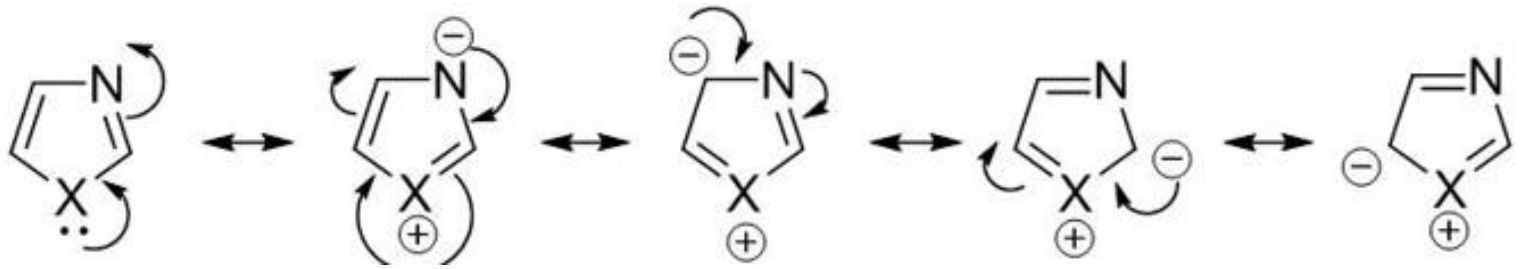
thiazole

oxazole

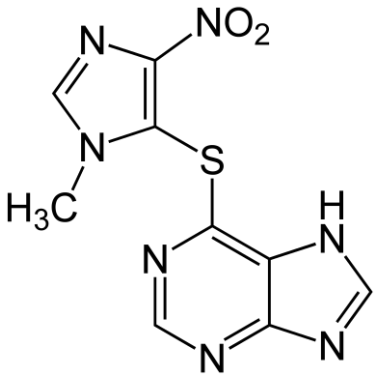
- The three 1,3-azoles, **imidazole**, **thiazole** and **oxazole**, are all very stable compounds that do not autoxidise

- They are the parent structures of the related series of 1,3-azoles containing a nitrogen atom plus second heteroatom in a 5-membered ring

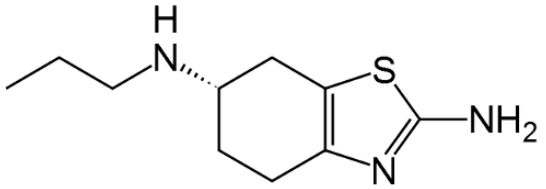
- Their aromaticity derives from delocalization of the lone pair from the second heteroatom



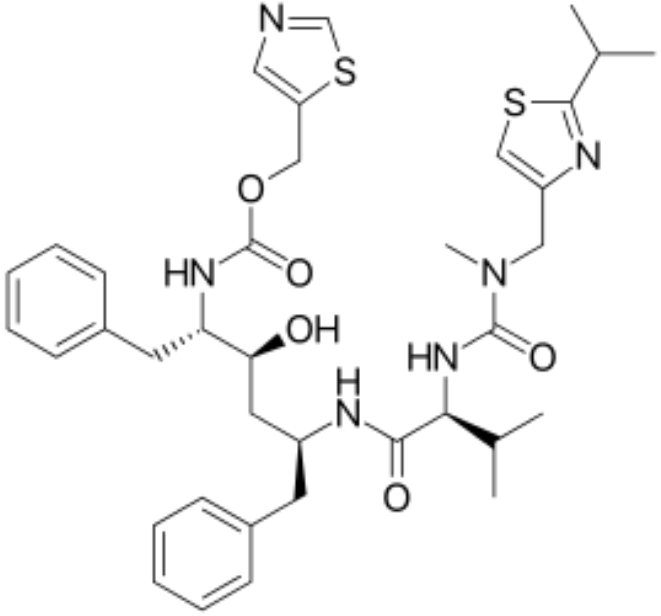
Bioactive and Drugs Containing 1,3-Azoles



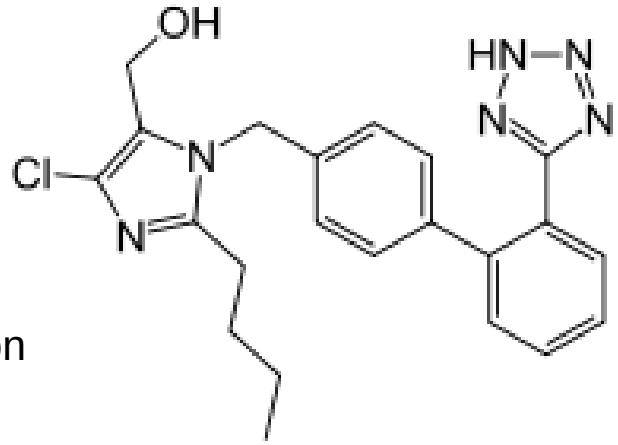
Name: **Azathioprine**
2008 Sales: $53 million
Disease: Kidney transplant rejection



Name: **Mirapex**
2008 Sales: $340 million
Company: Boehringer Ingelheim
Disease: Parkinson's disease



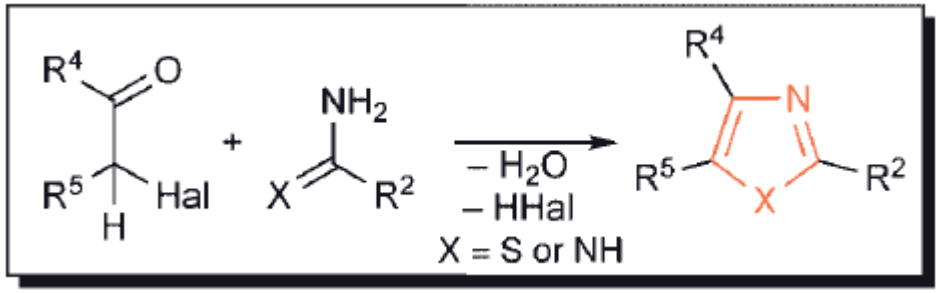
Name: **Norvir**
2008 Sales: $310 million
Company: Abbott
Disease: HIV/AIDS



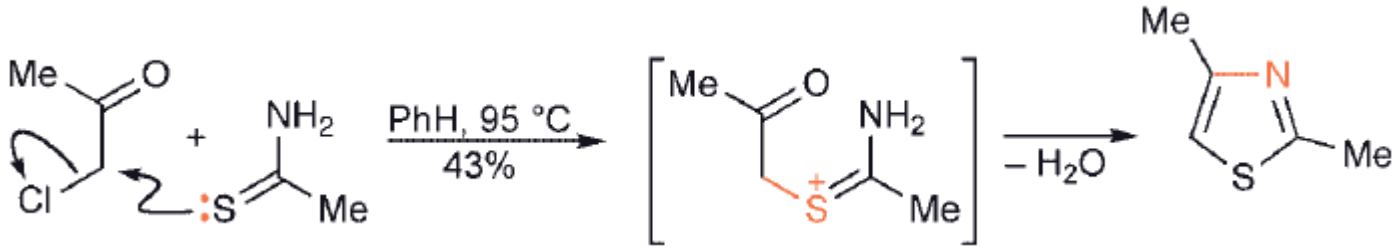
Name: **Cozaar**
2008 Sales: $690 million
Company: Merck
Disease: Hypertension

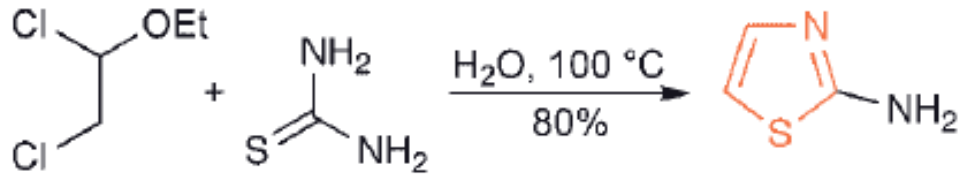
Ring Synthesis of 1,3-Azoles

1) From an ***α*-Halo-Carbonyl**-Component (or an Equivalent) and a **Three-Atom Unit Supplying C-2 and Both of the Heteroatoms**



Thiazoles (Hantzsch synthesis)

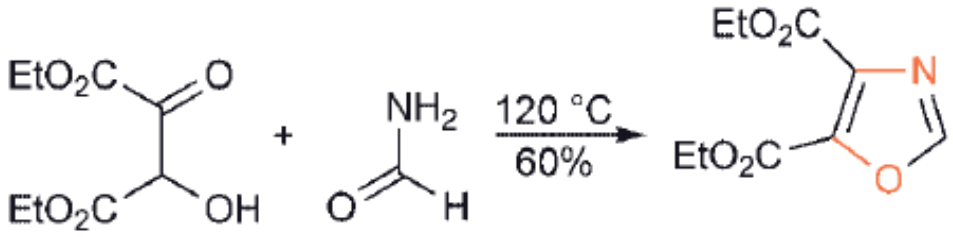




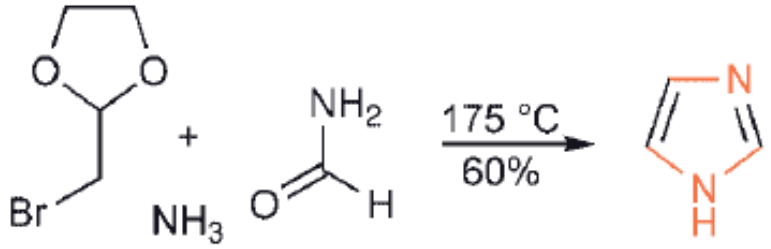
Ring Synthesis of 1,3-Azoles

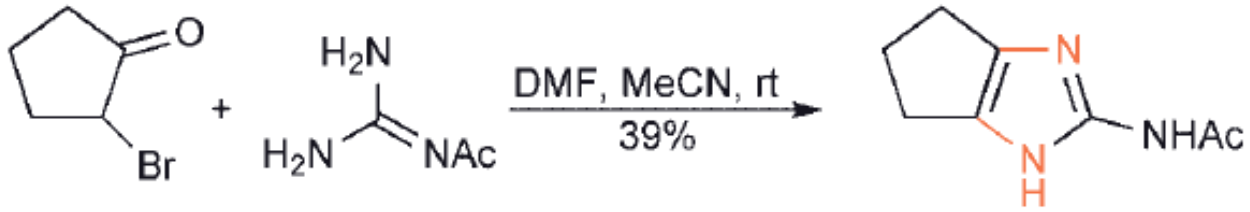
1) From an ***α*-Halo-Carbonyl**-Component (or an Equivalent) and a **Three-Atom Unit Supplying C-2 and Both of the Heteroatoms**

Oxazoles



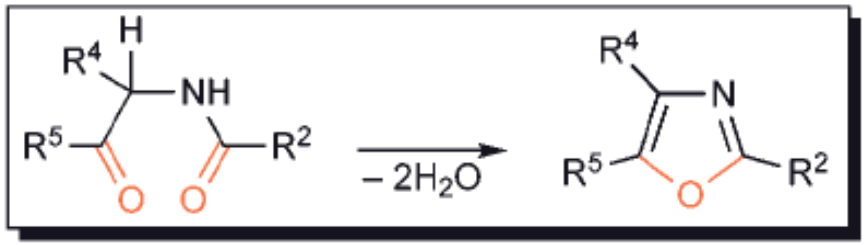
Imidazoles



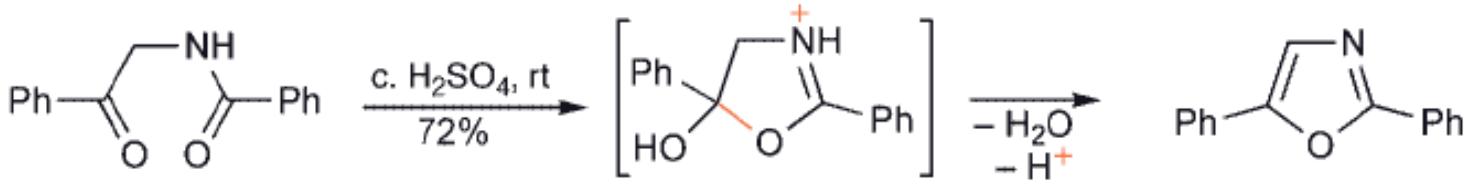


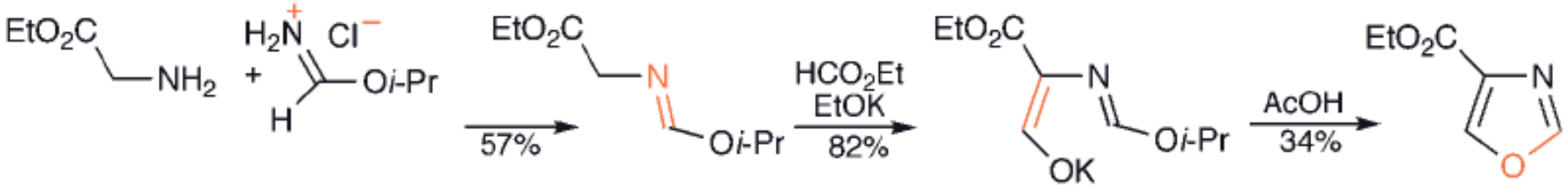
Ring Synthesis of 1,3-Azoles

2) By Cyclising Dehydration of *α*-Acylamino-Carbonyl-Compounds



Oxazoles *(Robinson–Gabriel synthesis)* – analogous to the cyclising dehydration of 1,4-dicarbonyl compounds to furans

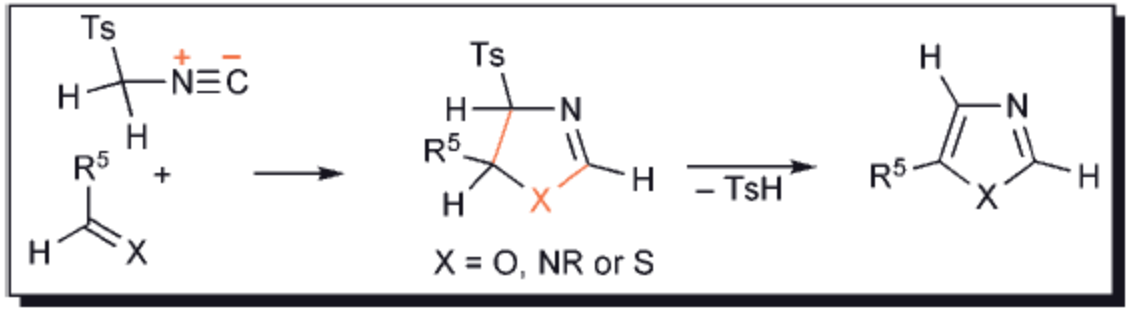


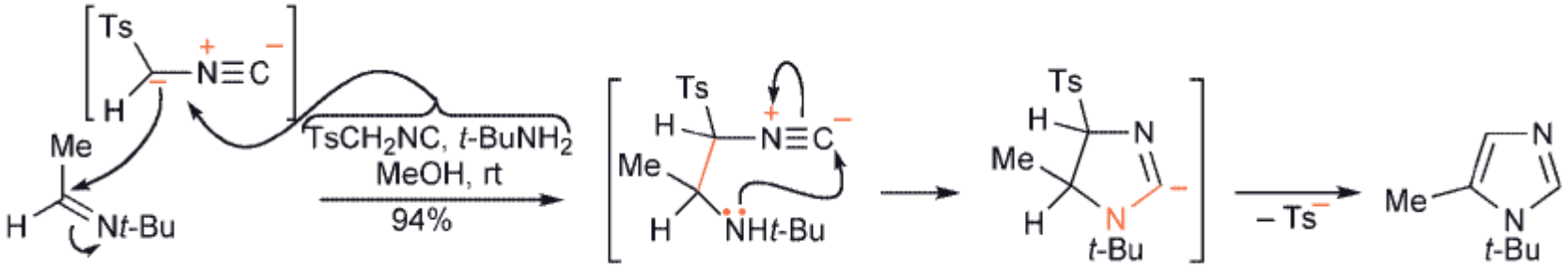


Ring Synthesis of 1,3-Azoles

3) From Isocyanides

Tosylmethylisocyanide (TosMIC), can be used for the synthesis of all three 1,3 - azole types





Anions derived from other isocyanides can be acylated (or thioformylated), the products spontaneously closing to oxazoles (thiazoles)