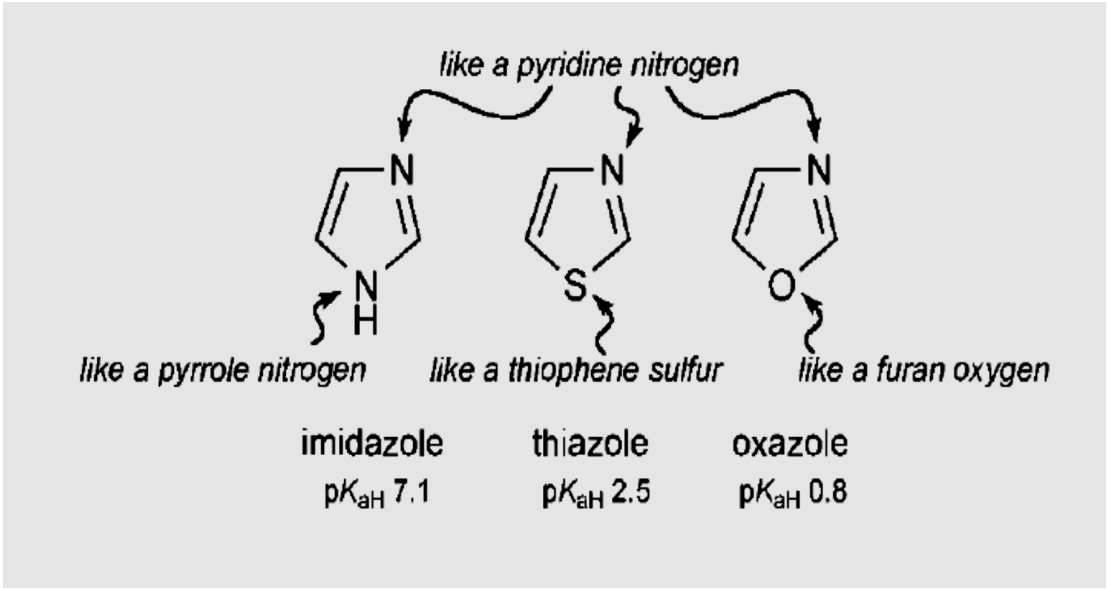
1,3-Azoles

Prof. Dr. Ayad Kareem
Department of Pharmaceutical Chemistry,
Collage of Pharmacy, Mustansiriyah University, (2024-2025).

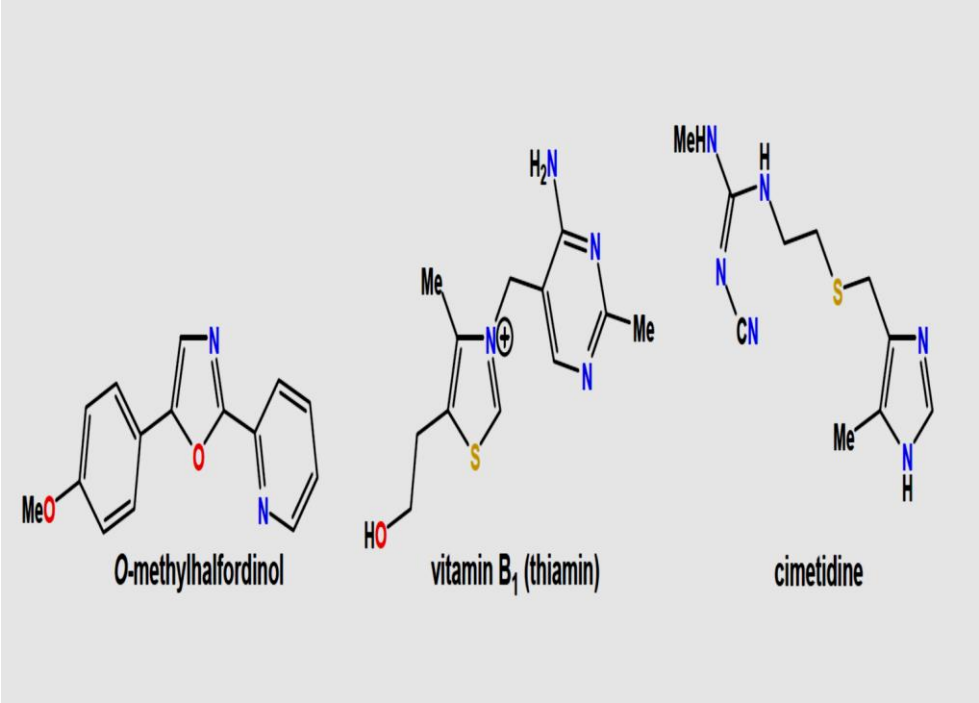
Introduction:

- The 1,3-azoles contain a nitrogen in an environment analogous to that in pyridine, that is, an imine nitrogen with a lone pair of electrons in a sp^2 orbital in the plane of the ring and not involved in the aromatic sextet.
- Also has another heteroatom in the environment of the nitrogen in pyrrole, the sulfur in thiophene, or the oxygen in furan, with a pair of electrons in a p orbital orthogonal to the ring and part of the aromatic sextet.
- Consequently, the chemical reactions of the azoles present a combination and mutual interaction of the types of reactivity typical of pyridine on the one hand and of pyrrole, thiophene and furan on the other.



Bioactive 1,3-Azoles

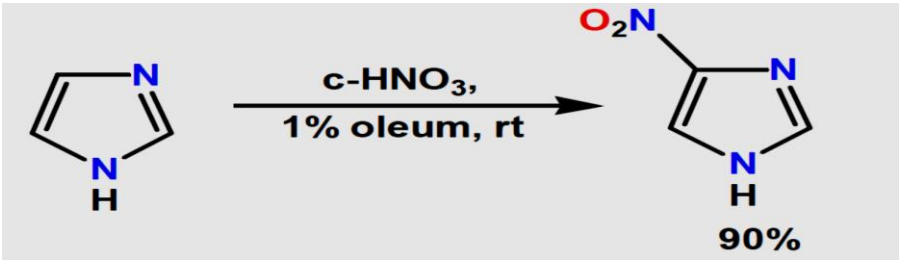
- *O*-Methylhalfordinol is a plant-derived alkaloid.
- Vitamin B1 (thiamin) is essential for carbohydrate metabolism. Deficiency leads to beriberi, a disease which is characterized by nerve, heart, and brain abnormalities.
- Cimetidine is an H2-receptor antagonist which reduces acid secretion in the stomach and is used to treat peptic ulcers and heartburn.

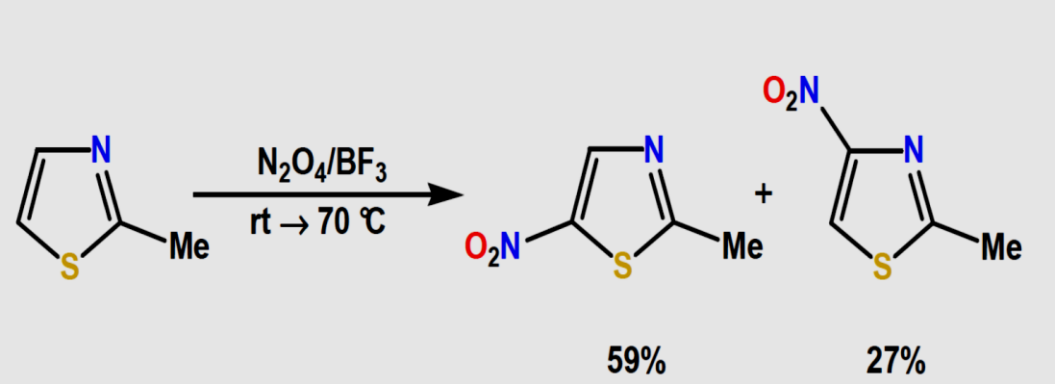


1,3-Azoles – Electrophilic Substitution

Nitration:

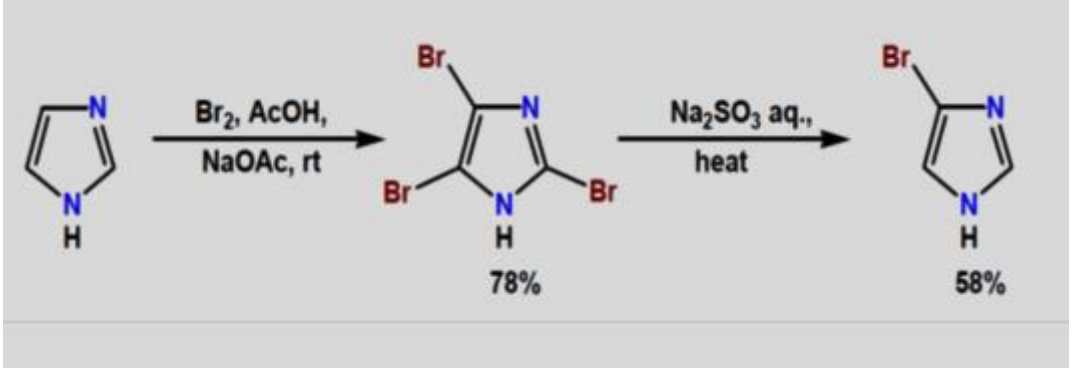
- Imidazoles are much more reactive to nitration than thiazoles (activation helps).
- Oxazoles do not generally undergo nitration.
- Imidazoles usually nitrate at the 4-position and thiazoles tend to react at the 5-position.





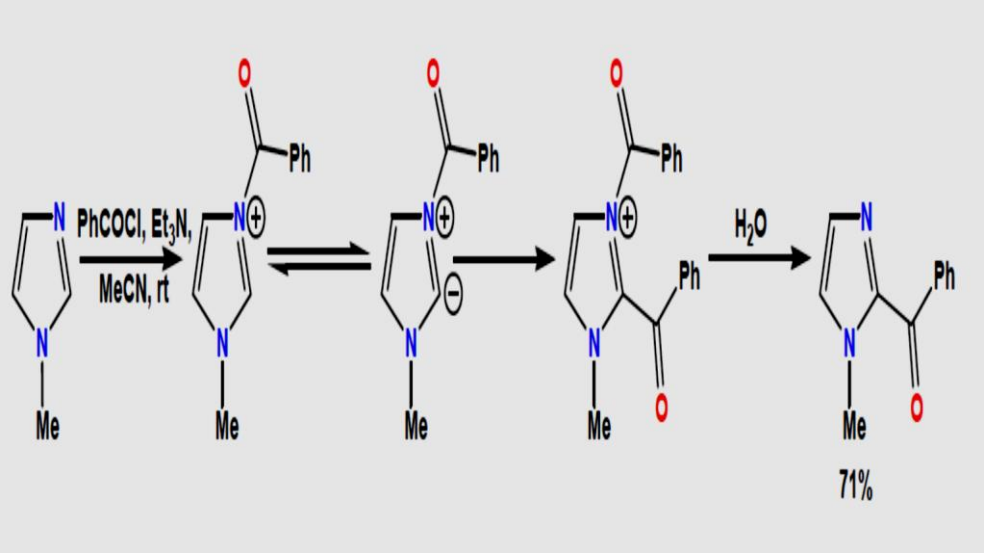
Halogenation:

- Imidazoles are brominated easily and bromination at multiple positions can occur.
- Thiazole does not brominate easily but 2-alkylthiazoles brominate at the 5-position.



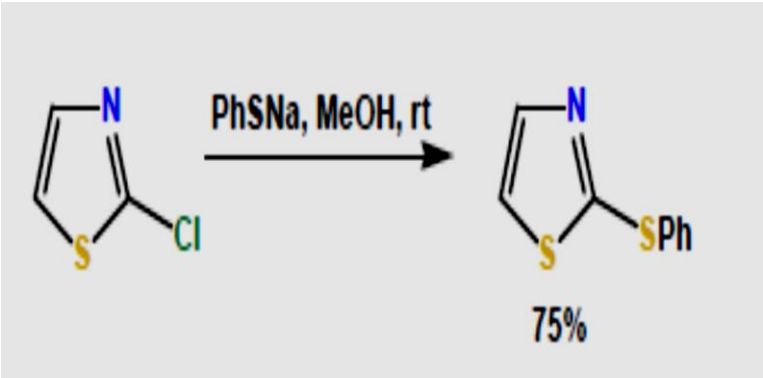
Acylation:

- 1,3-Azoles do not undergo Friedel-Crafts acylation because complexation between the Lewis acidic catalyst and *N* deactivates the ring.
- Acylation can be accomplished under mild conditions *via* the *N*-acyl imidazolium ylide.

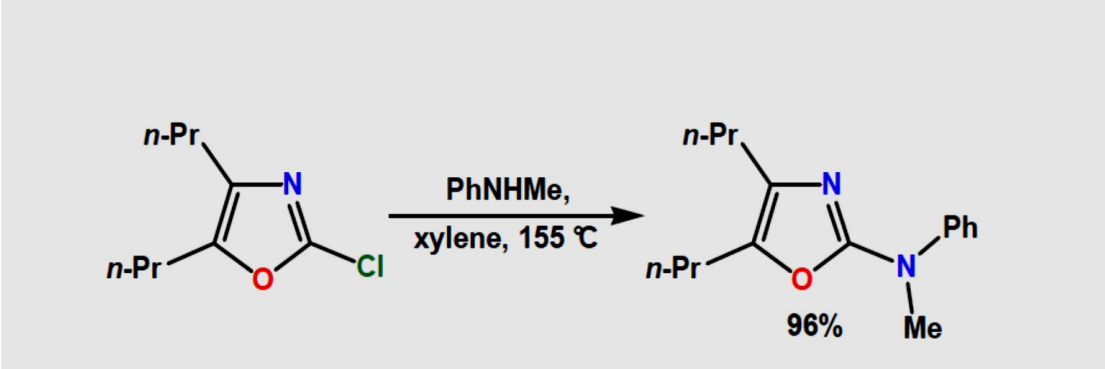


1,3-Azoles – Nucleophilic Substitution

- Displacement of Halogen
- There are many examples of displacement of halogen at the 2-position.
- 2-Halothiazoles react rapidly with sulfur nucleophiles, and are even more reactive than 2-halopyridines



- 2-Halo-1-alkylimidazoles and 2-halooxazoles will react with nitrogen nucleophiles.



Metal-Halogen Exchange

- Metallation at the 4-position can be accomplished by metal-halogen exchange.
- In the case of imidazoles without substitution at the 1-position, two equivalents of base are required.