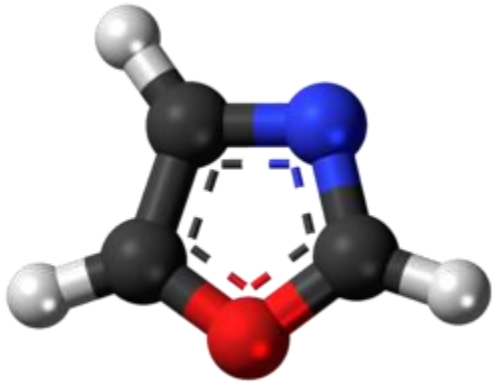
2302687 – Heterocyclic Compounds – Part I

Lecture 6-2

Ring Synthesis of 1,2-Azoles



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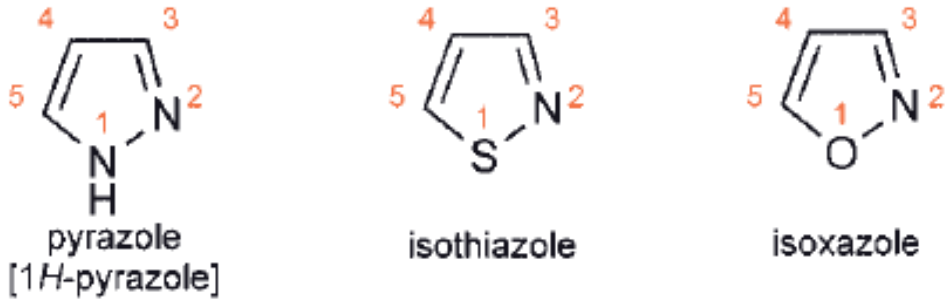
Recommended Textbook:

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

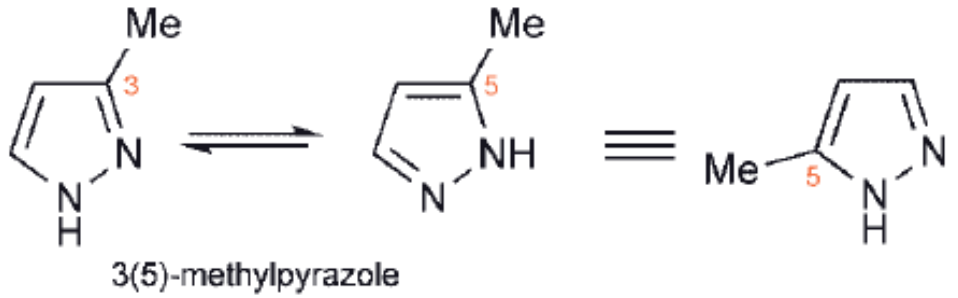
1,2-Azoles: Imidazoles, Thiazoles and Oxazoles



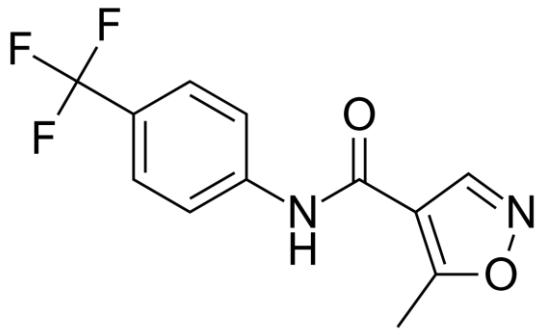
- Pyrazole has a much higher boiling point (187 °C) than isothiazole or isoxazole (114 °C and 95 °C), again reflecting the **intermolecular hydrogen bonding available only to pyrazole**

- Each 1,2-azole has a pyridine-like odour, but is only partially soluble in water

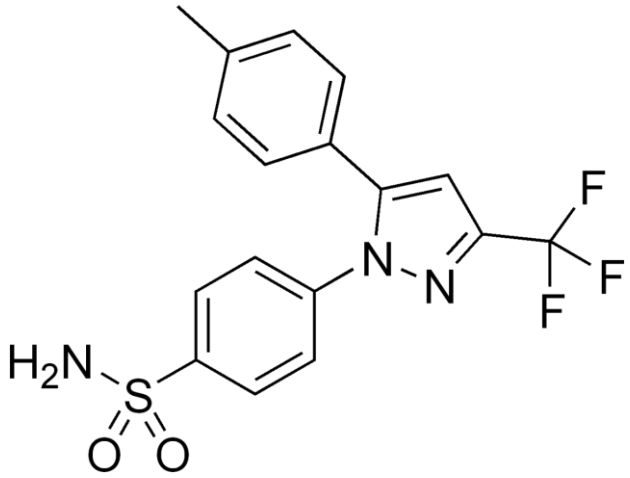
- Rapid **tautomerism**, involving switching of hydrogen from one nitrogen to the other, as in imidazoles, means that substituted pyrazoles are inevitably mixtures



Bioactive and Drugs Containing 1,2-Azoles



Lefluonomide (Arava®, Sanofi-aventis) inhibits pyrimidine synthesis in the body and used for the treatment of rheumatoid arthritis and psoriatic arthritis

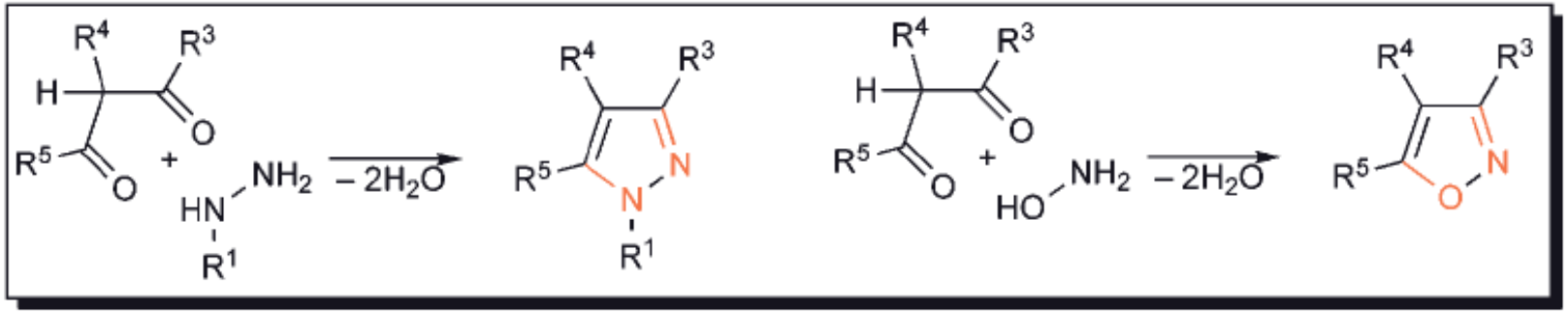


Celecoxib (Celebrex®, Pfizer) is a non-steroidal anti-inflammatory (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms

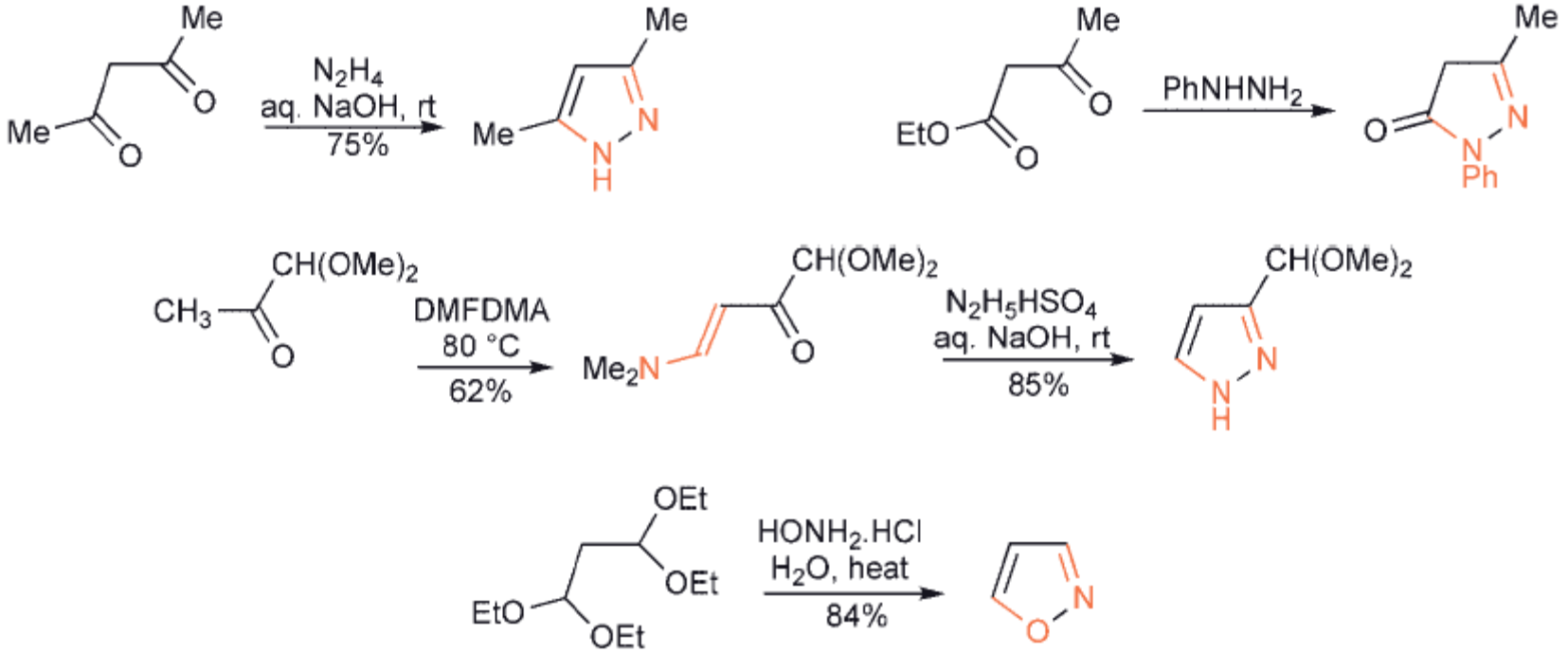
Celecoxib is a COX-2 inhibitor, blocking the cyclooxygenase-2 enzyme responsible for the production of prostaglandins. It is supposed to avoid gastrointestinal problems associated with other NSAIDS, bud side effects (heart attack, stroke) have emerged

Ring Synthesis of 1,2-Azoles

1) From 1,3-Dicarbonyl Compounds and Hydrazines or Hydroxylamine



Examples

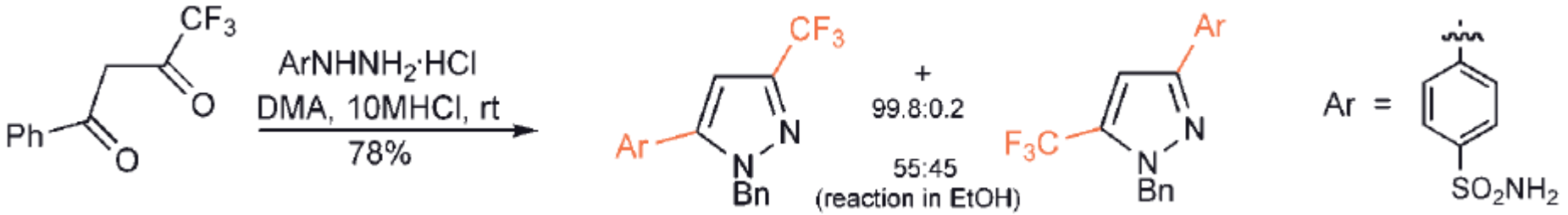


Ring Synthesis of 1,2-Azoles

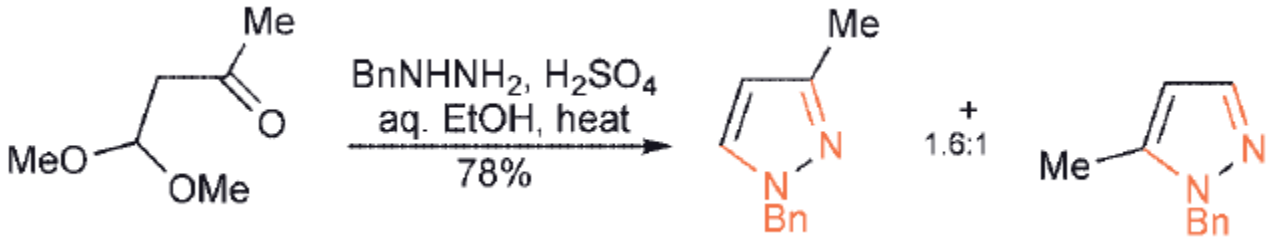
1) From 1,3-Dicarbonyl Compounds and Hydrazines or Hydroxylamine

Unsymmetrical 1,3-dicarbonyl components produce mixtures of 1,2-azole products

- The regioselective can sometimes be achieved by careful choice of reaction conditions and solvent



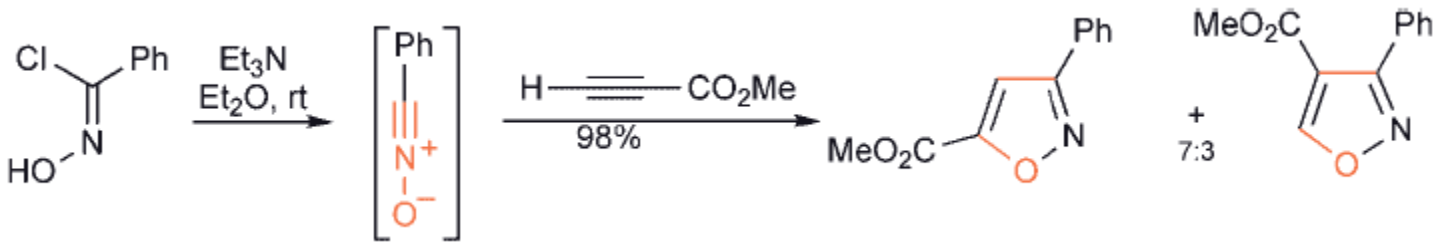
- Formation of **Hydrazone** or **oxime** first by reaction at the carbonyl group, and then cyclised in a separate, second step

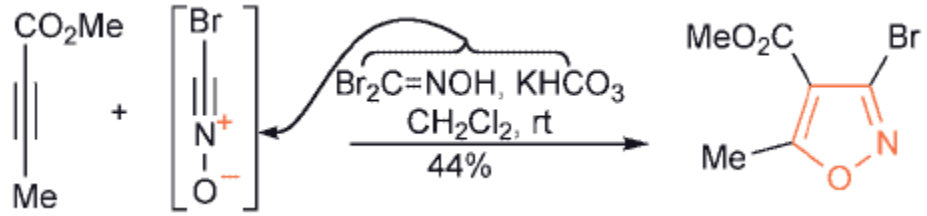


Ring Synthesis of 1,2-Azoles

2) Dipolar Cycloadditions of Nitrile Oxides and Nitrile Imines

Nitrile oxides (R–C≡N⁺–O⁻), which can be generated by base-catalysed elimination of hydrogen halide from halo-oximes (RC(Hal)=NOH), readily add to **alkyne** generates an aromatic **isoxazole** directly

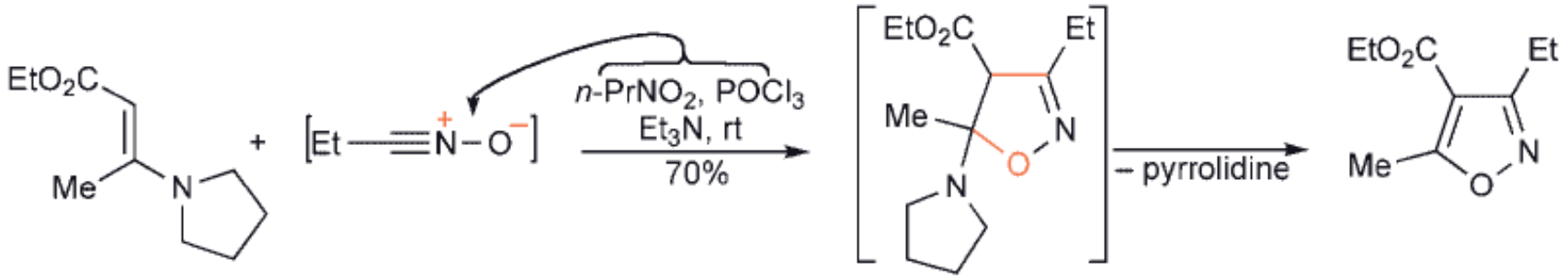




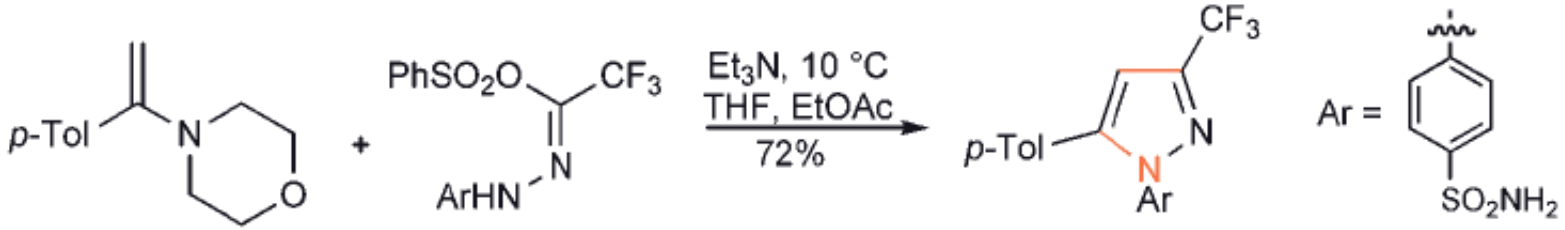
Ring Synthesis of 1,2-Azoles

2) Dipolar Cycloadditions of Nitrile Oxides and Nitrile Imines

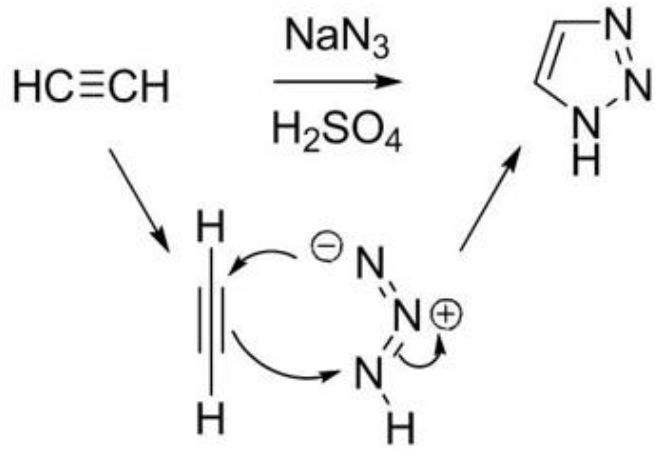
Addition to an **alkene** produces an **isoxazoline**, unless the alkene also incorporates a group capable of being eliminated in a step after the cycloaddition, generating the **isoazole** in the process



Nitrile imines can be generated in a similar way: the dehydrohalogenation of hydrazonyl halides (from *N*-halosuccinimide and a hydrazone), or, as in the sequence below, elimination of benzenesulfonate



Ring Synthesis of triazole



Ring Synthesis of tetrazole