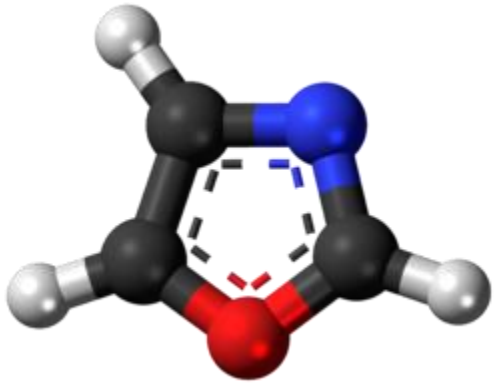
2302687 – Heterocyclic Compounds – Part I

Lecture 6-3

Reactivities of 1,2 and 1,3-Azoles Part 1



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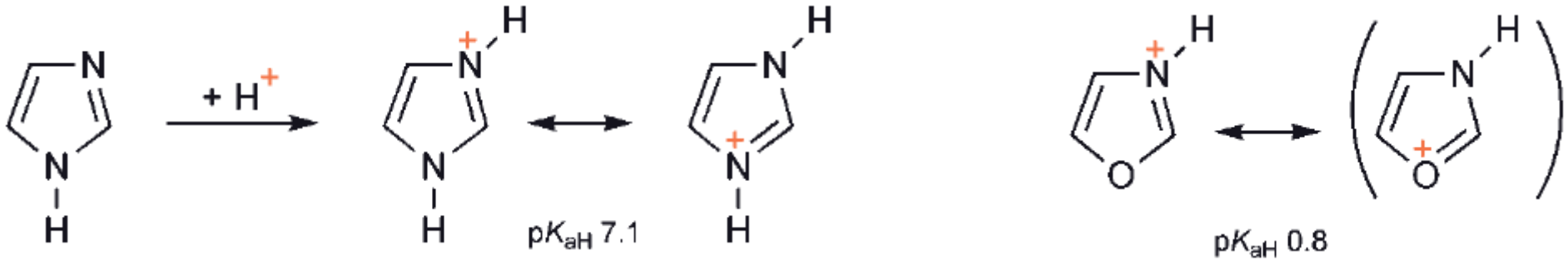
Recommended Textbook:

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

1) Addition at Nitrogen: 1.1) Protonation

1,3-Azoles

Imidazole, thiazole and alkyl-oxazoles 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 **pK_{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

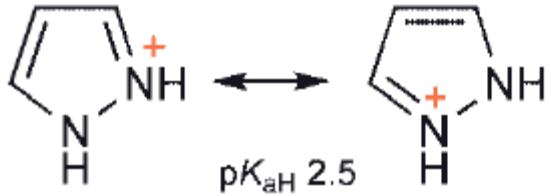
The particularly low basicity of **oxazole** can be understood as a combination of inductive withdrawal by the oxygen and weaker mesomeric electron release from it

1) Addition at Nitrogen: 1.1) Protonation

1,2-Azoles

Direct linking of two heteroatoms has a very marked base - weakening effect, as one can see by comparing ammonia with hydrazine and hydroxylamine (pK_{aH}: **NH_3, 9.3**; **H_2NNH_2, 7.9**; **$HONH_2$, 5.8**)

This is mirrored in the 1,2-azoles: pyrazole with a pK_{aH} of 2.5 is 4.5 pK_a units weaker than imidazole; isothiazole (−0.5) and isoxazole (−3.0) are three pK_a units weaker than their 1,3-isomers



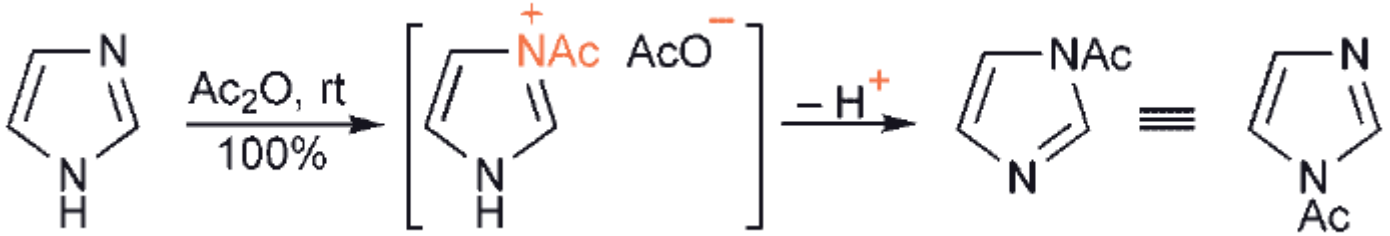
The higher basicity of pyrazole reflects the symmetry of the cation, with its two equivalent contributing resonance structures

Clearly, again, oxygen has a larger electron - withdrawing effect than sulfur

1) Addition at Nitrogen: 1.2) Acylation at Nitrogen

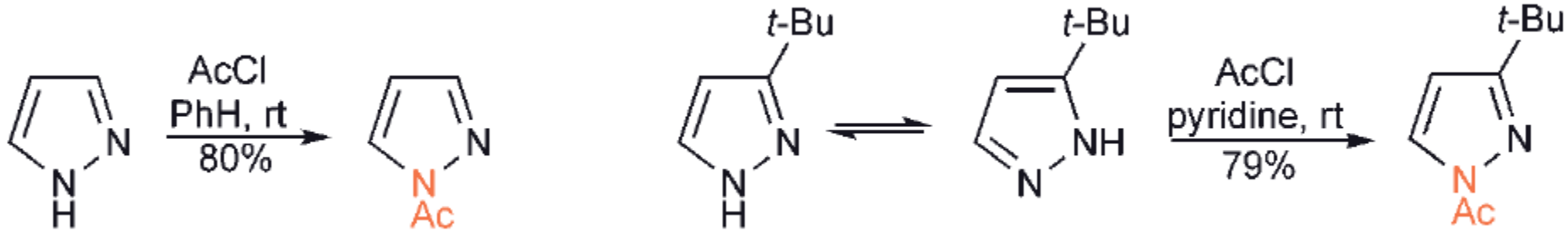
1,3-Azoles

Acylation of imidazole produces *N*-acylimidazoles via loss of proton from the initially-formed *N*-3–acylimidazolium salt



1,2-Azoles

The introduction of an acyl or phenylsulfonyl group onto a pyrazole nitrogen is usually achieved in the presence of a **weak base**, such as pyridine; such processes proceed via imine *N*-2 acylation, then *N*-1^{+}–H deprotonation. Since acylation, unlike alkylation, is reversible, the more stable product is obtained

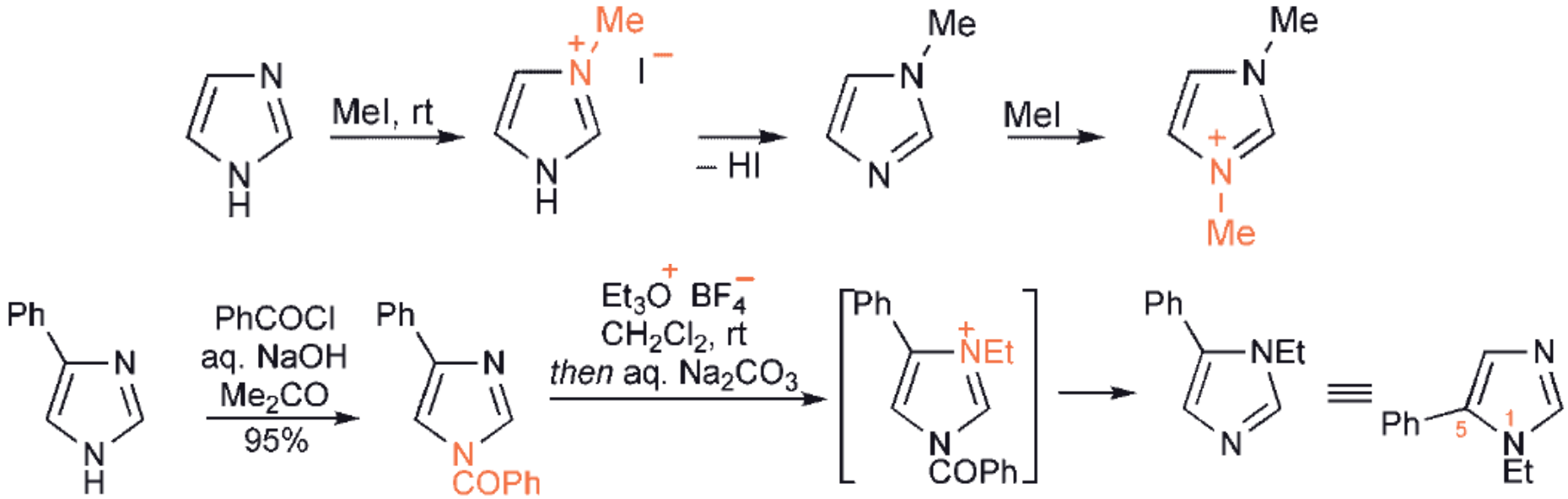


1) Addition at Nitrogen: 1.3) Alkylation at Nitrogen

1,3-Azoles

The 1,3-azoles are quaternised easily at the imine nitrogen with alkyl halides; the relative rates are: **1–methylimidazole:thiazole:oxazole, 900 : 15 : 1**

In the case of imidazoles that have an *N*-hydrogen, the product can react a second time, giving **mixtures** of imidazolium, 1-alkyl-imidazolium and 1,3-dialkyl-imidazolium salts



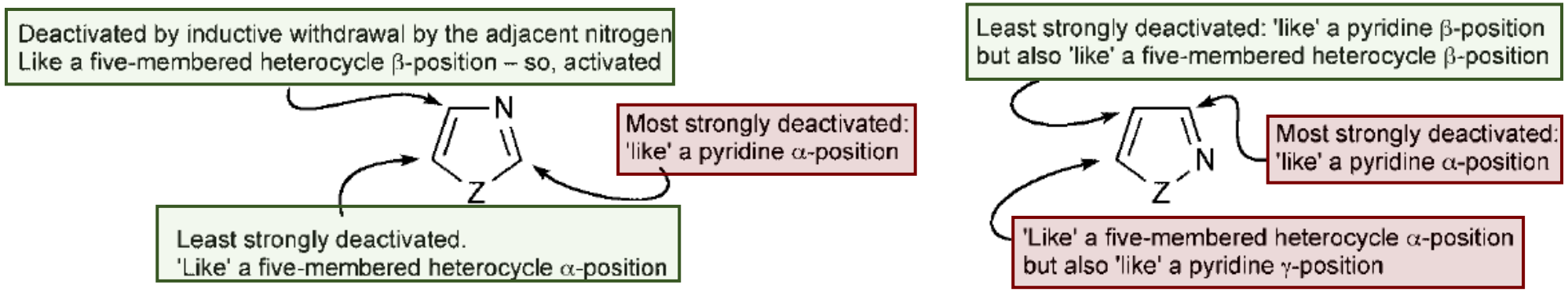
1,2-Azoles

The 1,2-azoles are more difficult to quaternise than their 1,3-analogues; they require more reactive reagents such as benzyl halides or Meerwein salts

2) Electrophilic Substitution at Carbon

Electrophilic substitution in the azoles is **intermediate** in facility between pyridine on the one hand and pyrroles, thiophenes and furans on the other

The regiochemistry of electrophilic attack can be rationalised nicely by comparing the 'character' of the various ring positions – those that are activated in being five-membered in character and those that are deactivated by their similarity to *α*-and *γ*-positions in pyridine



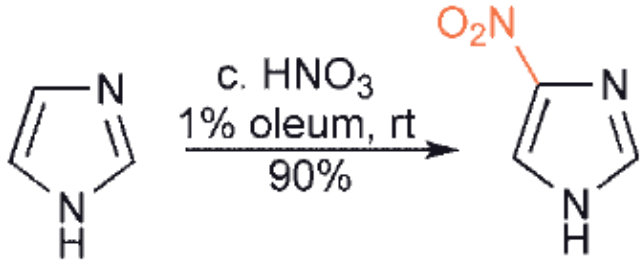
Influences on the positional reactivities of 1,3- and 1,2-azoles towards electrophilic substitution

The order of reactivity – **pyrrole > furan > thiophene** – is echoed in the azoles, though the presence of the basic nitrogen complicates such comparisons

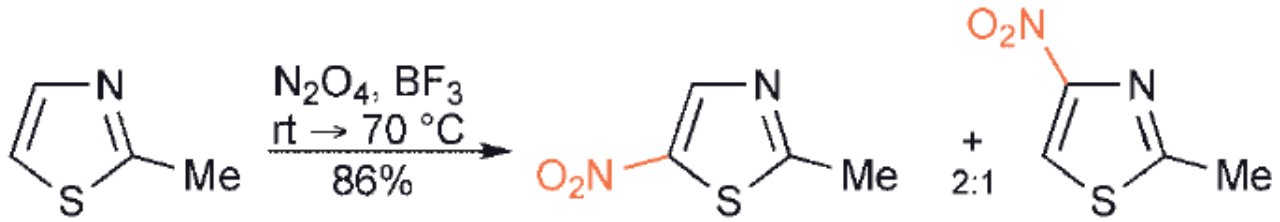
2.1) Nitration

1,3-Azoles

Imidazole is much more reactive towards nitration than thiazole, substitution taking place via the salt

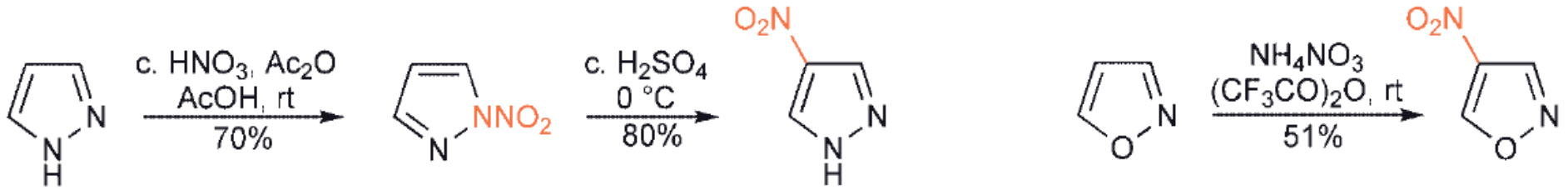


Methyl-thiazoles are sufficiently activated to undergo substitution, the typical regioselectivity being for formation of more 5-nitro than 4-nitro derivatives



The much less reactive **oxazoles** do not undergo nitration

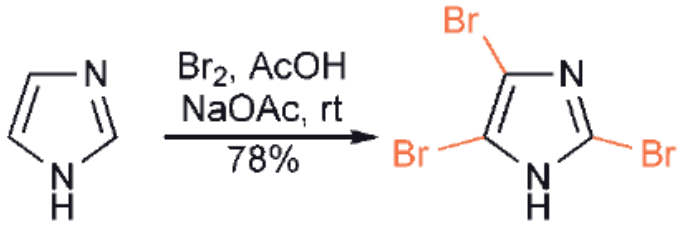
1,2-Azoles: Pyrazole, isothiazole and isoxazole undergo straightforward nitration, at C-4

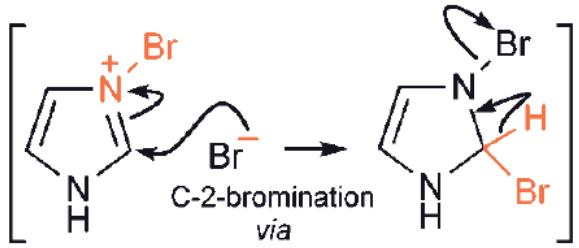


2.2) Halogenation

1,3-Azoles

Imidazole are brominated with remarkable ease at all free nuclear positions

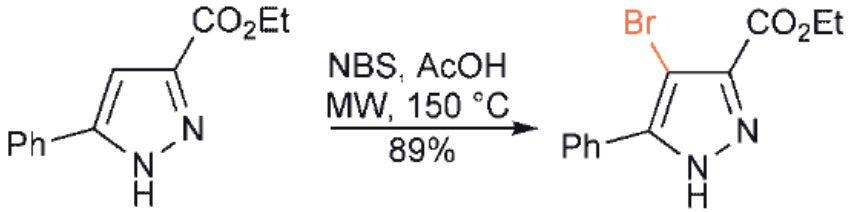


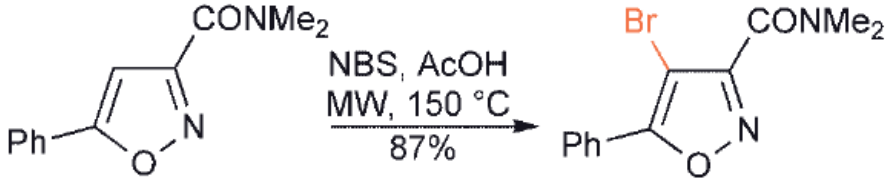


Thiazole does not brominate easily, though 2-methylthiazole brominates at C-5

1,2-Azoles

Halogenation of pyrazole gives 4-monohalo-pyrazoles





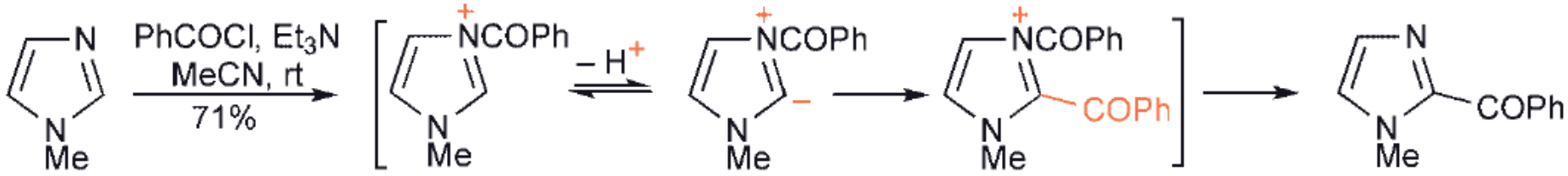
Poor yields are obtained on reaction of isothiazole and isoxazole with bromine, again with attack at C-4, but with stabilising groups present, halogenation proceeds better

2.3) Acylation

1,3-Azoles

Friedel–Crafts acylations are unknown for the azoles, clearly because of interaction between the **basic nitrogen and the Lewis-acid catalyst**

It is, however, possible to 2-aroylate by reaction with the acid chloride in the presence of triethylamine, the substitution proceeding via an N-acyl-imidazolium ylide



1,2-Azoles

Only for pyrazole, of the trio, have any useful electrophilic substitutions involving carbon electrophiles and, even here, only *N*-substituted pyrazoles react well