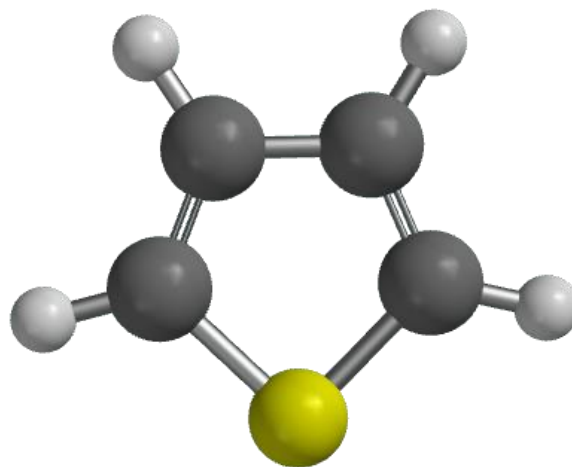


2302687 – Heterocyclic Compounds – Part I

Lecture 5-4

Reactions of Furan Thiophene Pyrrole Part 2



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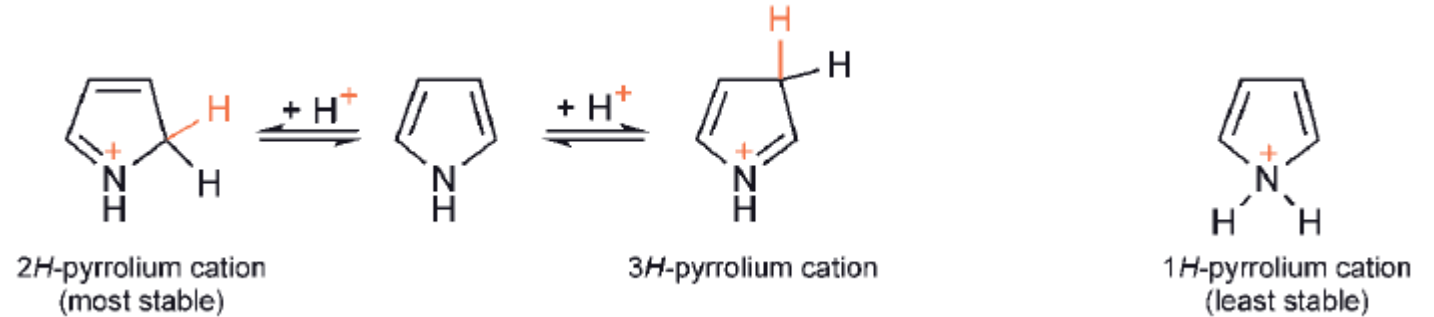
Recommended Textbook:

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

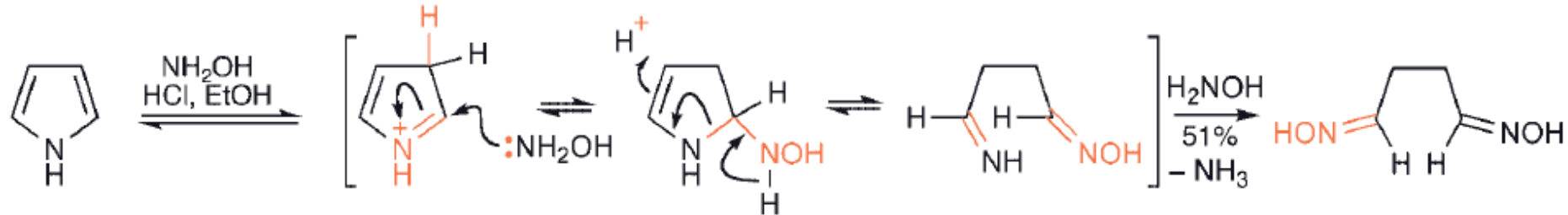
1) Substitution at Carbon - Examples

1.1) Protonation :

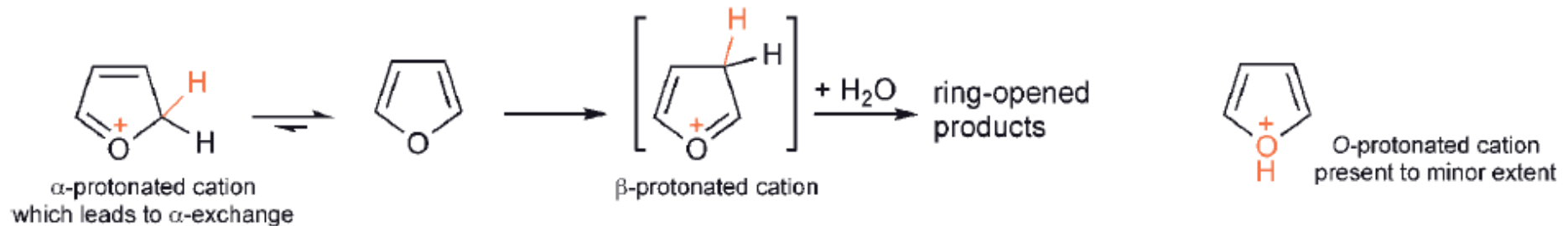
- reversible proton addition occurs at all positions of **pyrrole**



The 2H- and 3H- pyrrolium cations are essentially iminium ions and are **electrophilic**



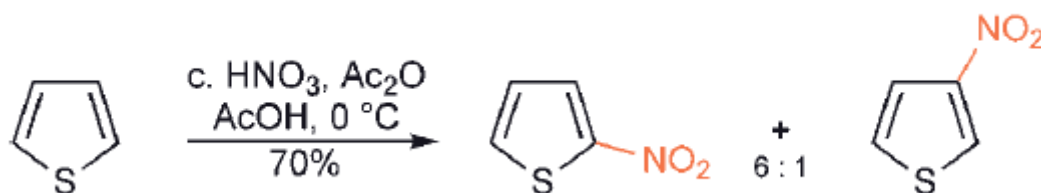
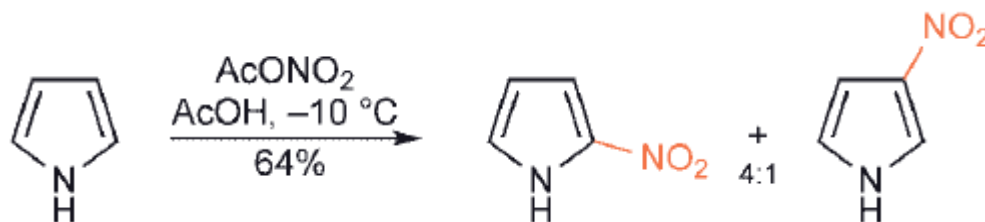
- Hot, dilute aqueous mineral acids cause hydrolytic ring opening of **furan**



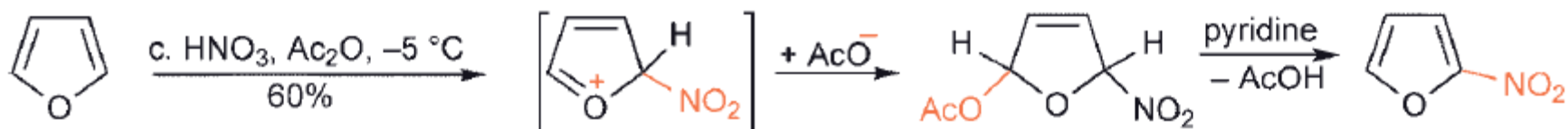
- Thiophene** is stable to all but very strongly acidic conditions

1) Substitution at Carbon - Examples

1.2) Nitration : Nitrating mixtures suitable for benzenoid compounds cause complete **decomposition of pyrrole and thiophene**, but reaction occurs smoothly with **acetyl nitrate** (*from fuming nitric acid with acetic anhydride*) at low temperature

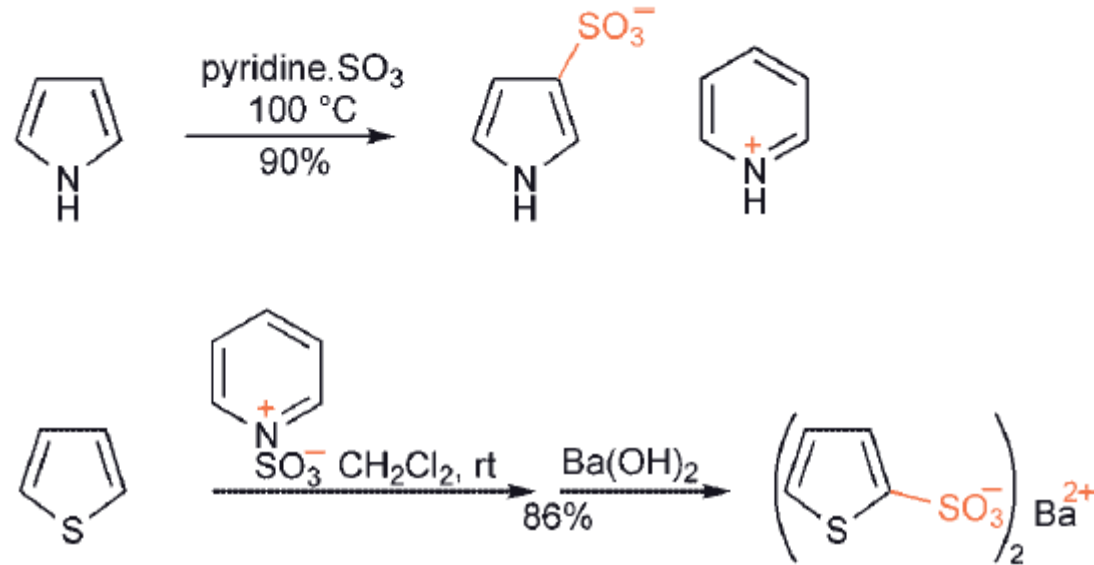


Reaction of **furan** with acetyl nitrate produces **non-aromatic adducts**. Aromatisation is induced by treatment with a weak base, like pyridine

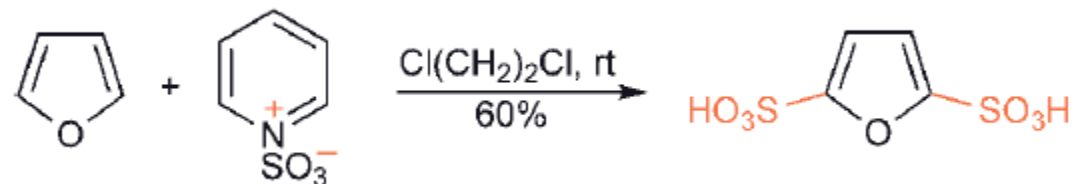


1) Substitution at Carbon - Examples

1.3) Sulfonation : a mild reagent of low acidity must be used: the **pyridine-sulfur trioxide** compound smoothly converts pyrrole into pyrrole-3-sulfonic acid (this isomer results from reversibility of the sulfonation)

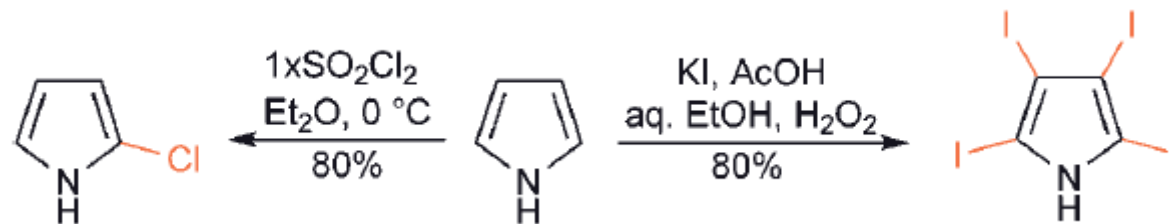


Disubstitution of furan occurring even at room temperature



1) Substitution at Carbon - Examples

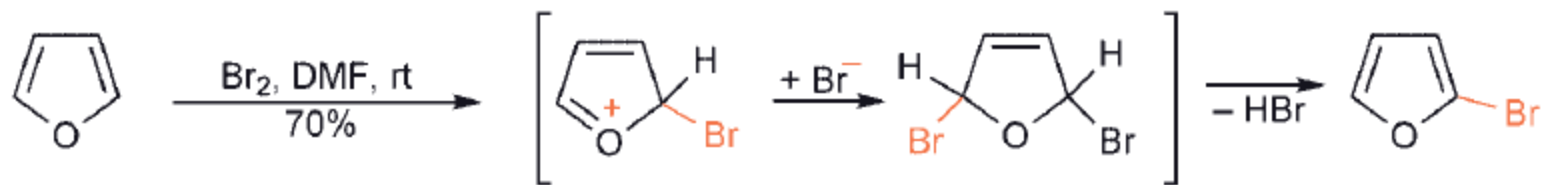
1.4) Halogenation : Pyrrole reacts with halogens so readily that unless controlled conditions are used, **tetrahalo-pyrroles** are the only isolable products



The rate of halogenation of **thiophene** at 25 °C is about 10^8 times that of benzene

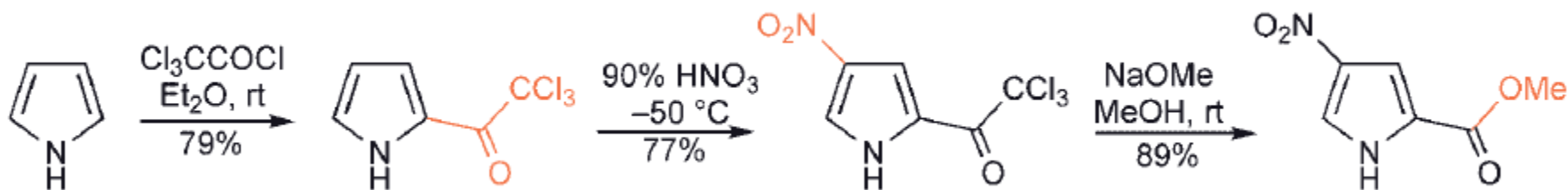


Furan reacts vigorously with chlorine and bromine at room temperature to give polyhalogenated products, but does not react at all with iodine

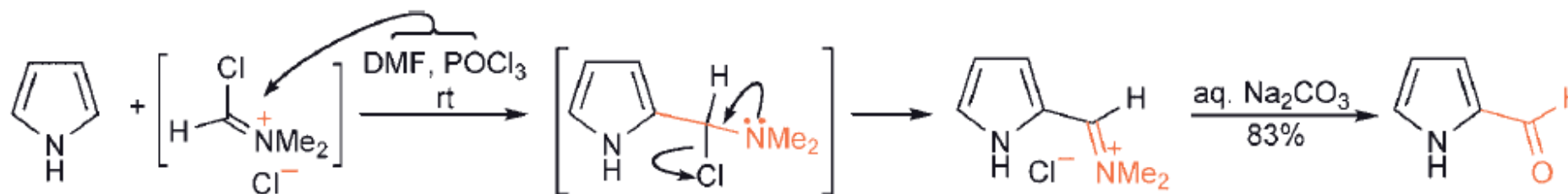


1) Substitution at Carbon - Examples

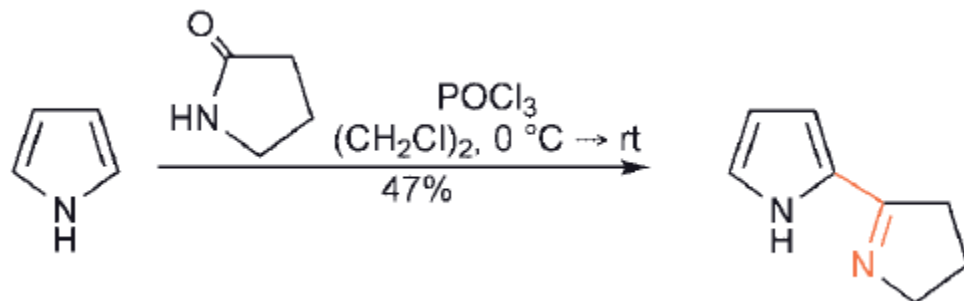
1.5) Acylation : Direct acylation of pyrrole with **acid anhydride** or **acid chloride** leads to 2-acylated pyrrole as main product



Vilsmeier acylation of pyrroles, formylation with dimethylformamide/phosphoryl chloride in particular, is a generally applicable process

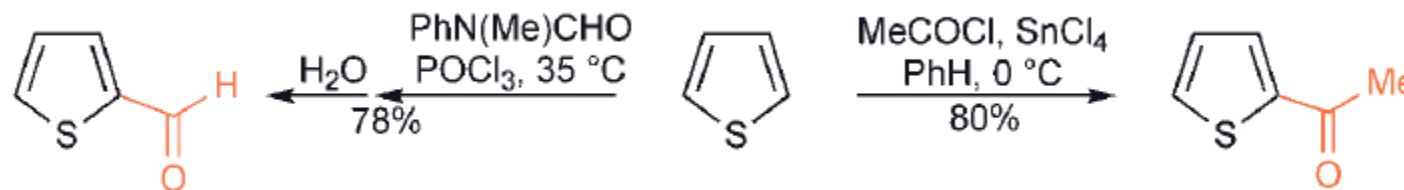


The Vilsmeier reaction



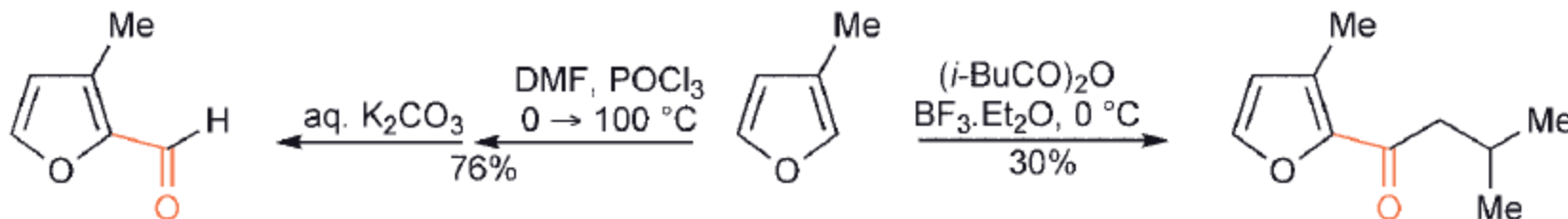
1) Substitution at Carbon - Examples

1.5) Acylation : The Friedel–Crafts acylation of thiophenes is a much-used reaction and generally gives good yields (*despite the fact that aluminium chloride reacts with thiophene to generate tars; this problem can be avoided by using tin tetrachloride*)



Vilmseier formylation of thiophene leads efficiently to 2-formylthiophene

Carboxylic acid anhydrides or halides normally require the presence of a **Lewis acid** (often boron trifluoride) for Friedel–Crafts acylation of furans

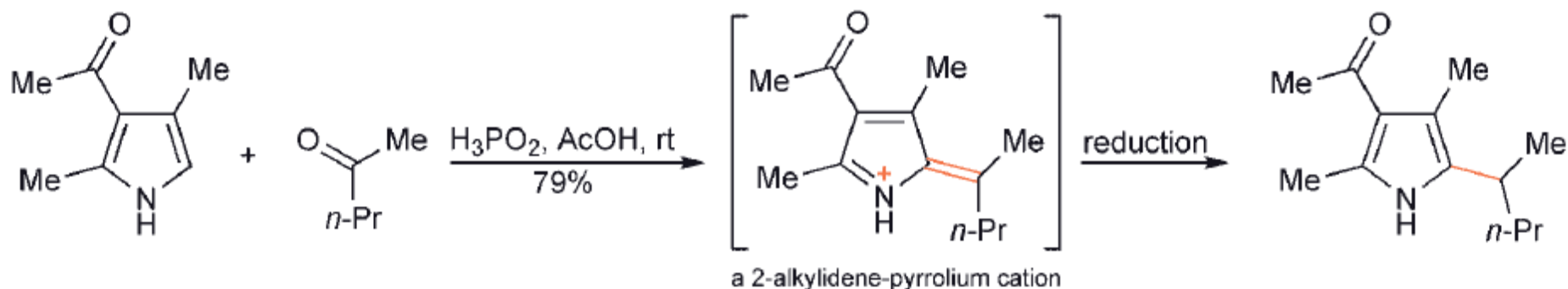


Vilsmeier formylation of furans is a good route to α -formyl-furans

1) Substitution at Carbon - Examples

1.6) Alkylation : Traditional Friedel–Crafts alkylation is not generally practicable for furans, thiophenes and pyrroles, partly because of catalyst - induced **polymerisation** and because of **polyalkylation**

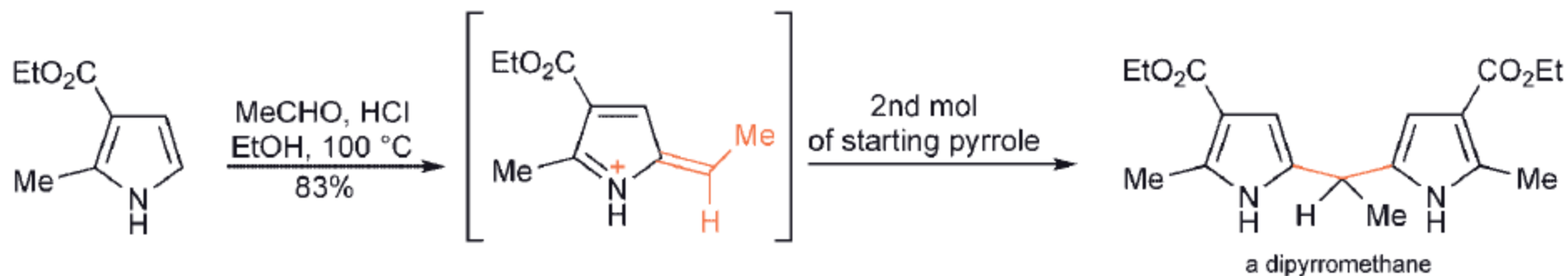
1.7) Condensation with Aldehydes and Ketones : Condensations of pyrroles with aldehydes and ketones occur easily by acid catalysis, but the resulting pyrrolyl-carbinols cannot usually be isolated (**Polymerise !**); **Reductive trapping** of these cationic intermediates, producing alkylated pyrroles



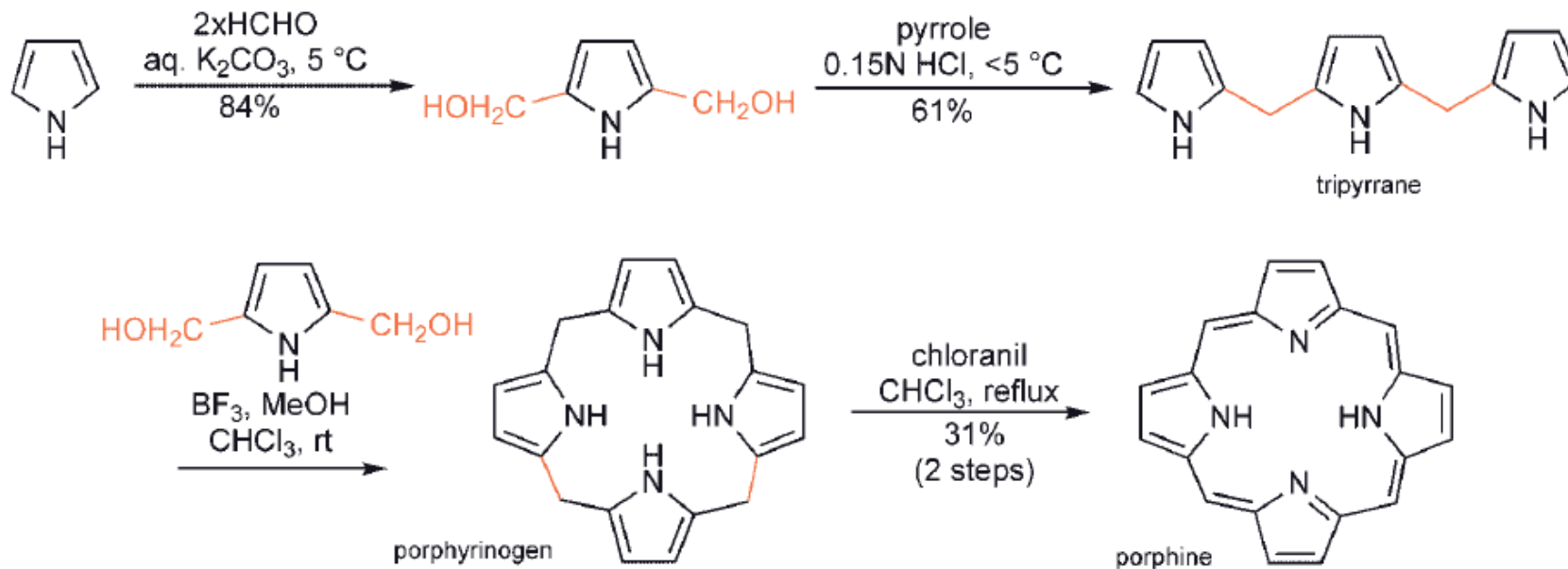
1) Substitution at Carbon - Examples

1.7) Condensation with Aldehydes and Ketones :

Dipyrromethane results from attack by the second mole equivalent of the pyrrole



Porphyrin can be synthesised via this route



1) Substitution at Carbon - Examples

1.7) Condensation with Imines and Iminium Ions :

The Mannich reaction of pyrrole produces; the iminium electrophile being generated in situ from formaldehyde, dialkylamine and acetic acid

