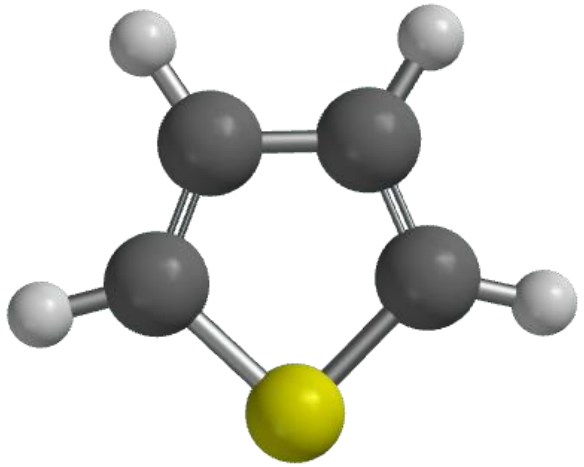
2302687 – Heterocyclic Compounds – Part I

Lecture 5-1

Ring Synthesis of Furan and Thiophene



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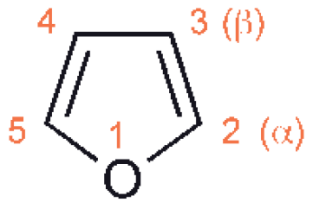
Recommended Textbook:

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

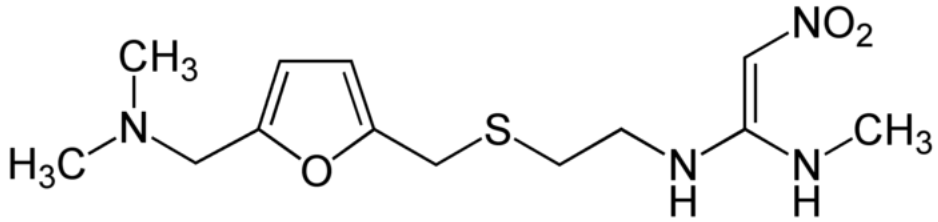
Furan

- Volatile, fairly stable compounds with pleasant odours
- Slightly soluble in water
- Precursor of the widely used solvent tetrahydrofuran (THF)
- Produced by the gas-phase decarbonylation of furfural

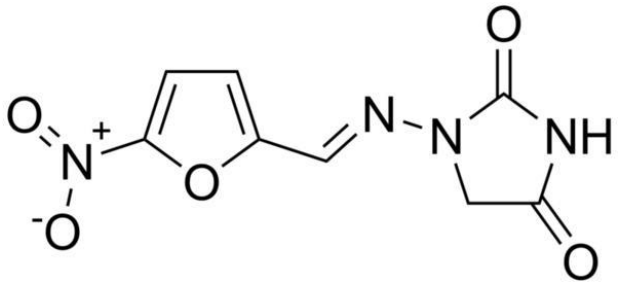


furan

Drugs & Bioactive Furans



Ranitidine is one of the biggest selling drugs in history; it is used to treat and prevent ulcers in the stomach and intestines



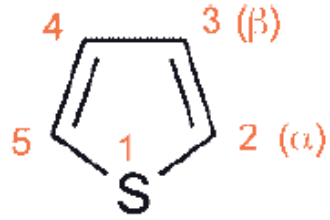
Name: **Nitrofurantoin**

2008 Sales: $164 million

Disease: Antibiotic for urinary tract infections

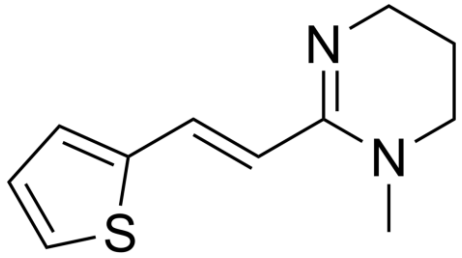
Thiophene

- Stable liquids that closely resemble the corresponding benzene compounds in boiling points and even in smell
- Occur in coal-tar distillates
- Thiophene is named after **theion** (the Greek word for sulfur) and **phaino** (the Greek word for shining)

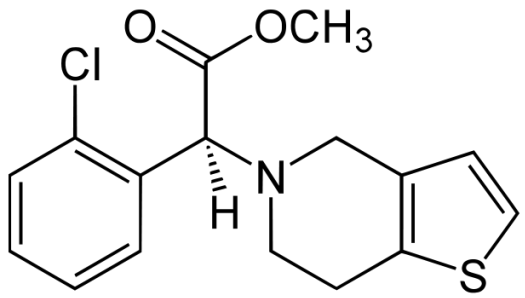


thiophene

Drugs & Bioactive Thiophenes



Pyrantel is an antiparasitic drug that is widely used to treat worm in livestock



Name: **Plavix**

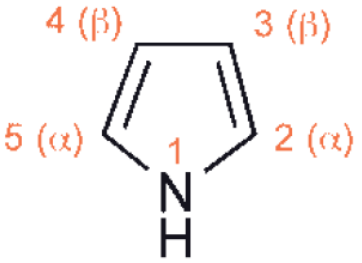
2008 Sales: $3.8 billion

Company: Bristol-Myers Squibb

Disease: Stroke and heart attack

Pyrrole

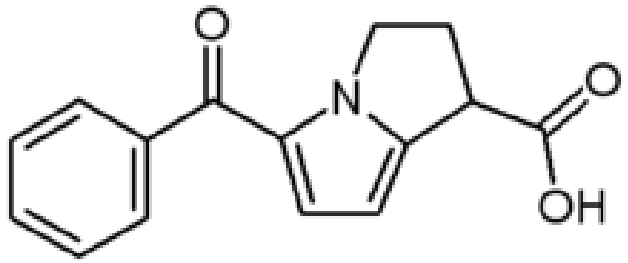
- Colourless liquids, with relatively weak odours rather like that of aniline, which, also like the anilines, darken by autoxidation
- Manufactured by alumina-catalysed gas-phase interaction of furan and ammonia



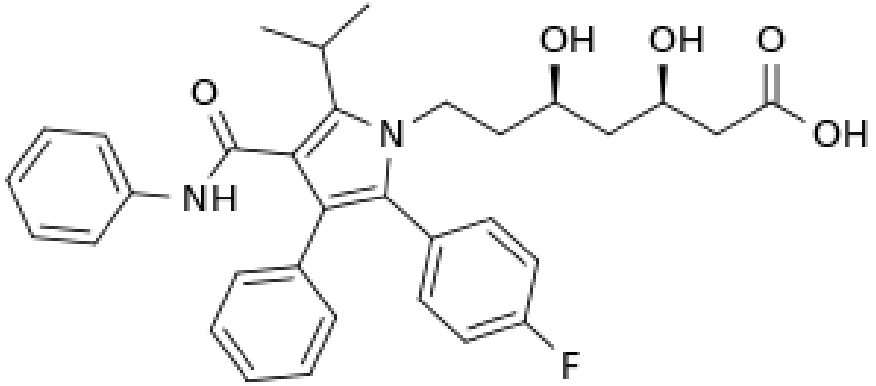
pyrrole
1*H*-pyrrole

- First isolated from coal tar in 1834 and then in 1857 from the pyrolysate of bone

Drugs & Bioactive Pyrrole



Ketorolac is a pain relief and anti-inflammatory drug



Name: **Lipitor**

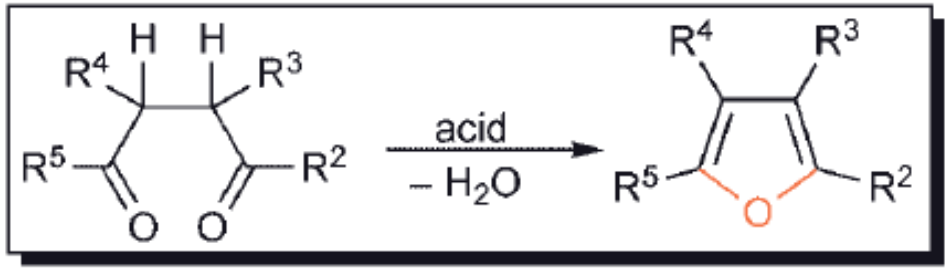
2008 Sales: $5.88 billion (Top-selling)

Company: Pfizer

Disease: Lowers LDL levels

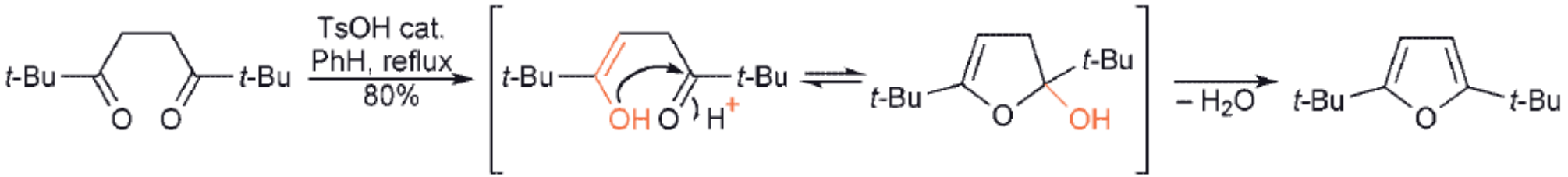
Ring Synthesis of Furan

1) From 1,4-Dicarbonyl Compounds



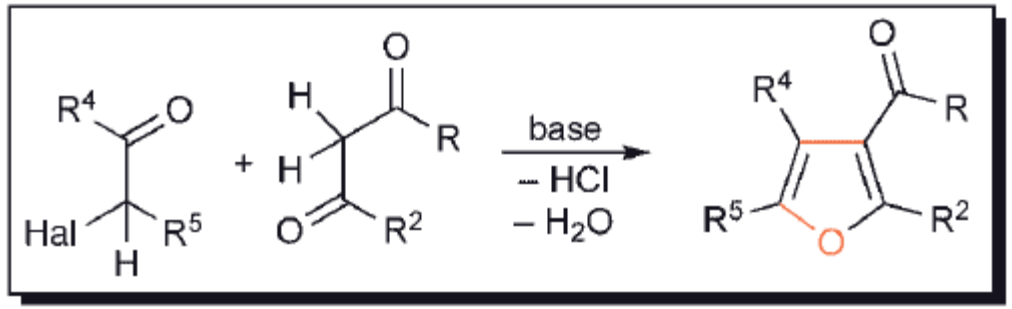
The Paal – Knorr Synthesis

- The most widely used approach to furans
- Usually, non-aqueous acidic conditions are employed to encourage the loss of water



Ring Synthesis of Furan

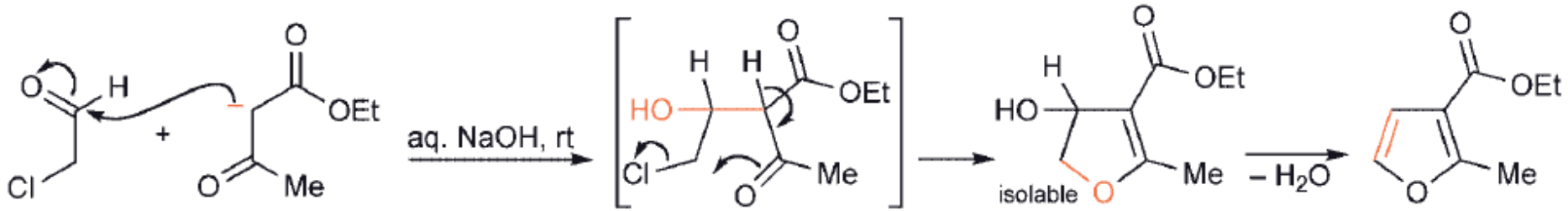
2) From α-Halo-Carbonyl and 1,3-Dicarbonyl Compounds



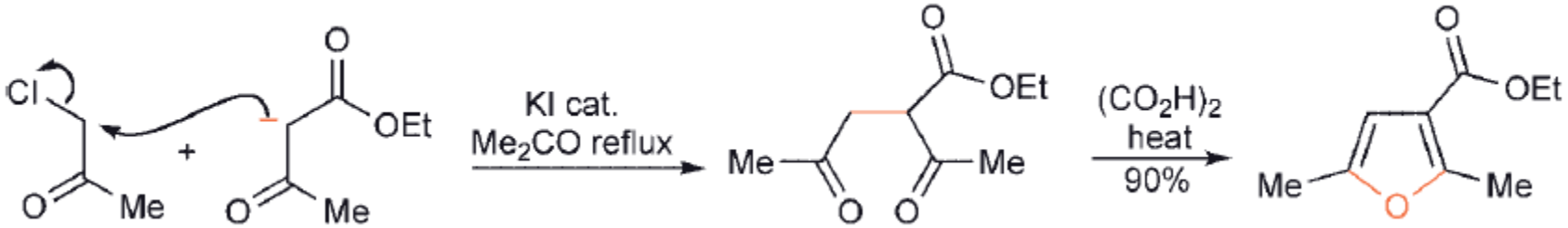
The Feist–Benary Synthesis

- Initial aldol condensation at the carbonyl carbon of a 2-halo-carbonyl then ring closure is achieved via intramolecular displacement of halide by enolate oxygen

Aldehyde:

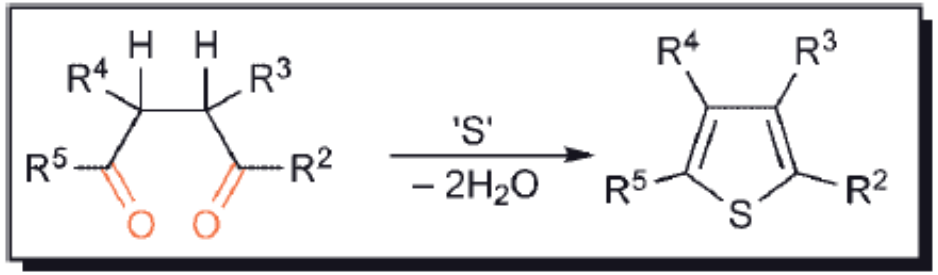


Ketone:

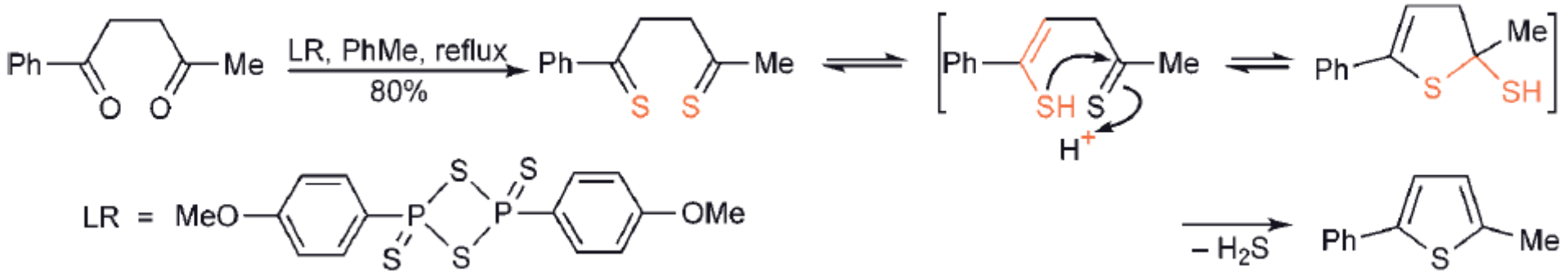


Ring Synthesis of Thiophene

1) From 1,4-Dicarbonyl Compounds and a Source of Sulphide

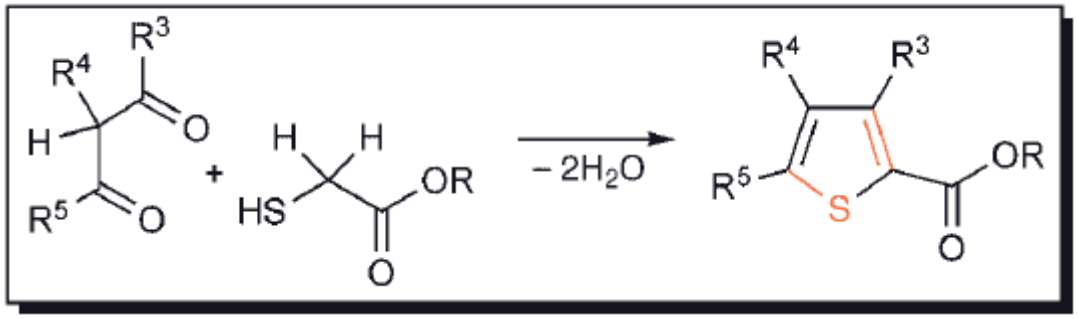


Sources of sulphide such as phosphorus sulphides, Lawesson's reagent (LR)

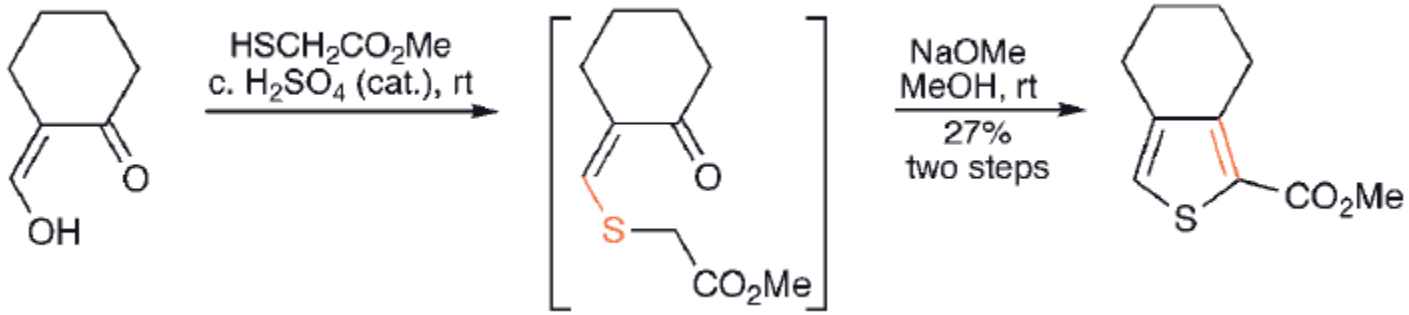


Ring Synthesis of Thiophene

2) From Thioglycolates and 1,3-Dicarbonyl Compounds

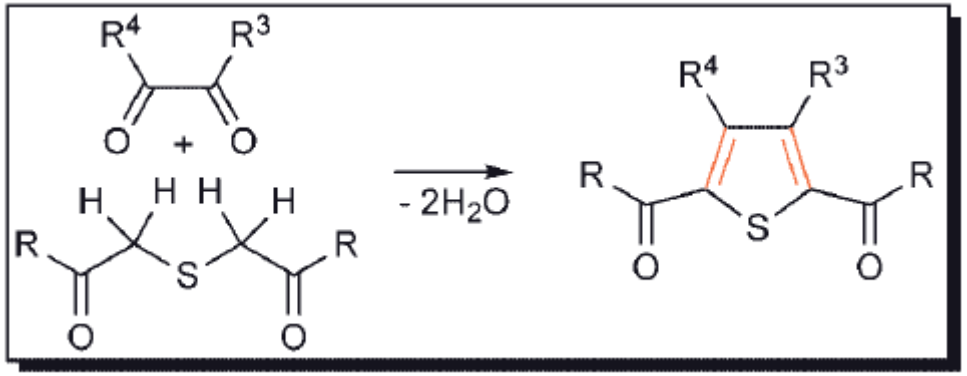


In most of the examples of this approach, thioglycolates, as donors of an S–C unit, have been reacted with 1,3-keto-aldehydes, to give intermediates that can be ring closed to give thiophenes



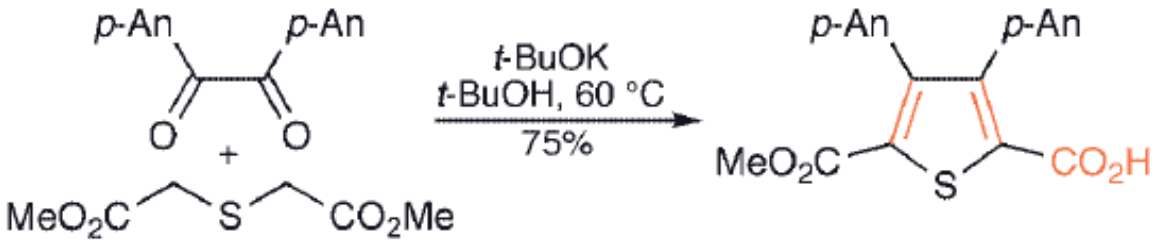
Ring Synthesis of Thiophene

3) From Thiodiacetates and 1,2-Dicarbonyl Compounds



The Hinsberg Synthesis

- Two consecutive aldol condensations between a 1,2-dicarbonyl compound and diethyl thiodiacetates give thiophenes. The immediate product is an ester-acid.



The Hinsberg Synthesis