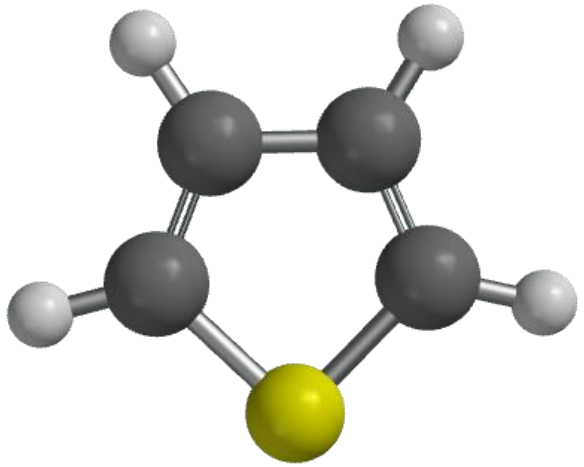
2302687 – Heterocyclic Compounds – Part I

Lecture 5-5

Reactions of Furan Thiophene Pyrrole vs Indole



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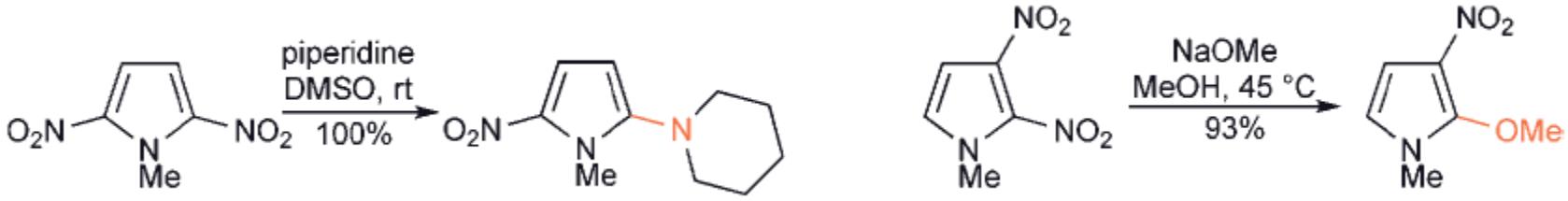
Recommended Textbook:

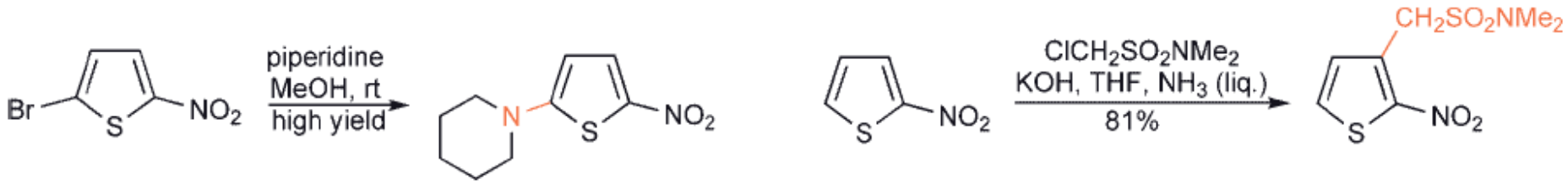
Heterocyclic Chemistry, 5th Edition, J. A. Joule, K. Mills, **2010**, Wiley

2) Reactions with Nucleophiles

Pyrroles and Furans do not react with nucleophilic reagents by addition or by substitution, except in the same type of situation that allows nucleophilic substitution in benzene chemistry, i.e. where the **leaving group is *ortho* or *para* to an electron-withdrawing group**



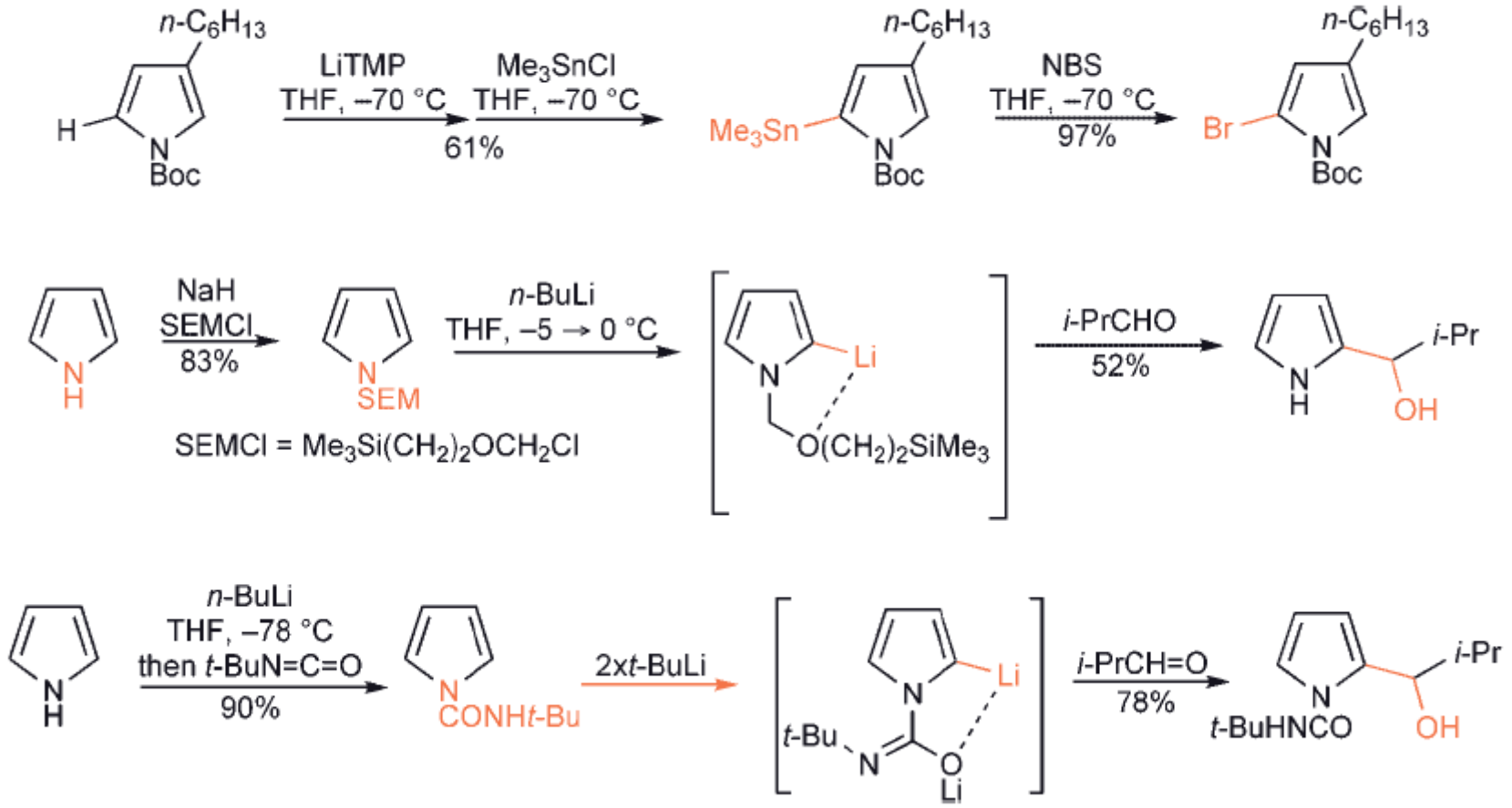
Nucleophilic displacements of thiophenes proceed at least 10^2 times faster than for benzenoid counterparts (**Vicarious Nucleophilic Substitution also possible**)



3) Metallation

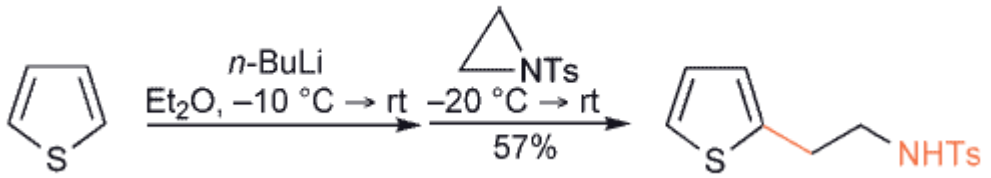
3.1) Direct Ring C–H Metallation

- The *C*-lithiation of pyrroles requires the absence of the acidic *N*-hydrogen, i.e. the presence of an *N*-substituent; ***metallation proceeds at the α-position***

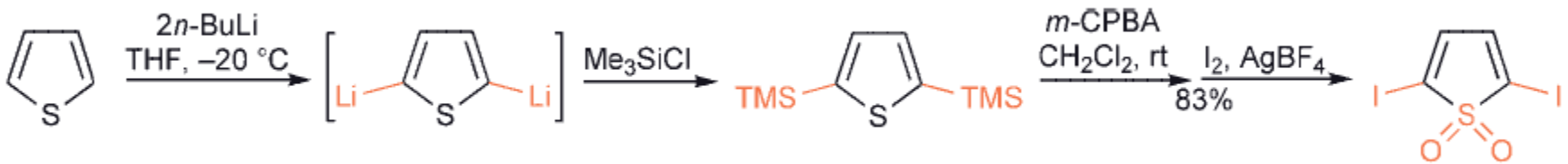


3.1) Direct Ring C–H Metallation

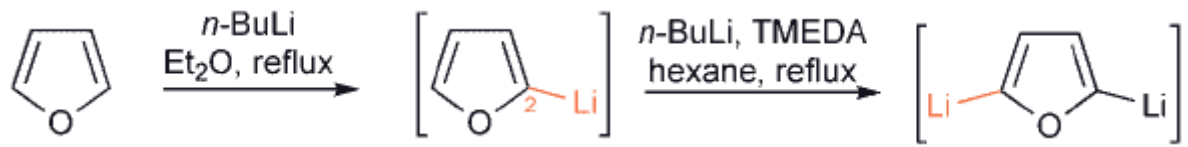
- Monolithiation of thiophene takes place at C-2

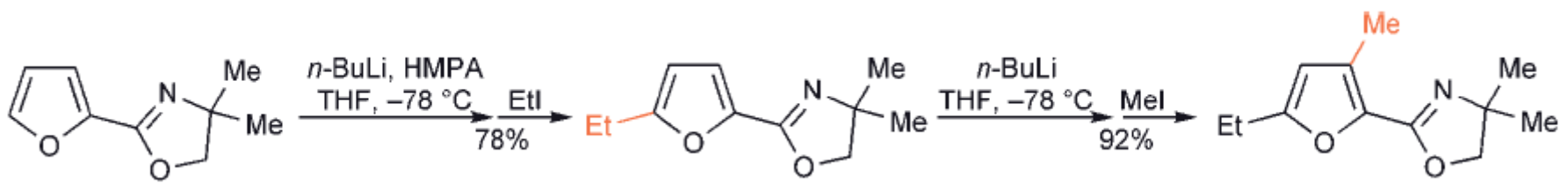


- Two mole equivalents of lithiating agent easily produces 2,5-dilithiothiophene



- Furan has a similar reactivity

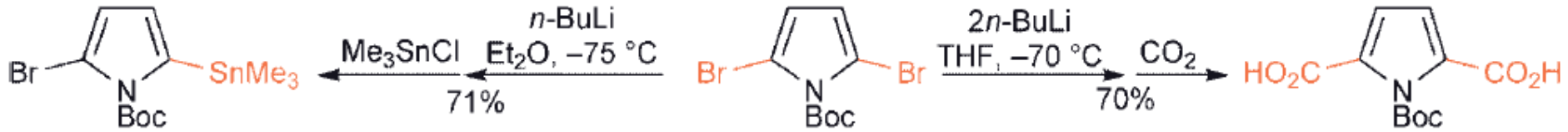


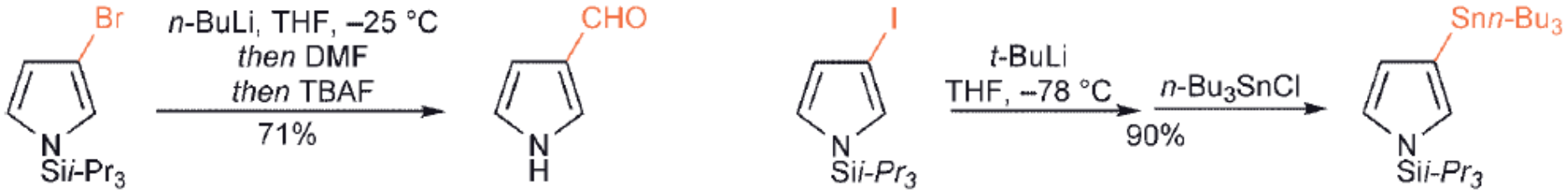


3) Metallation

3.2) Metal–Halogen Exchange

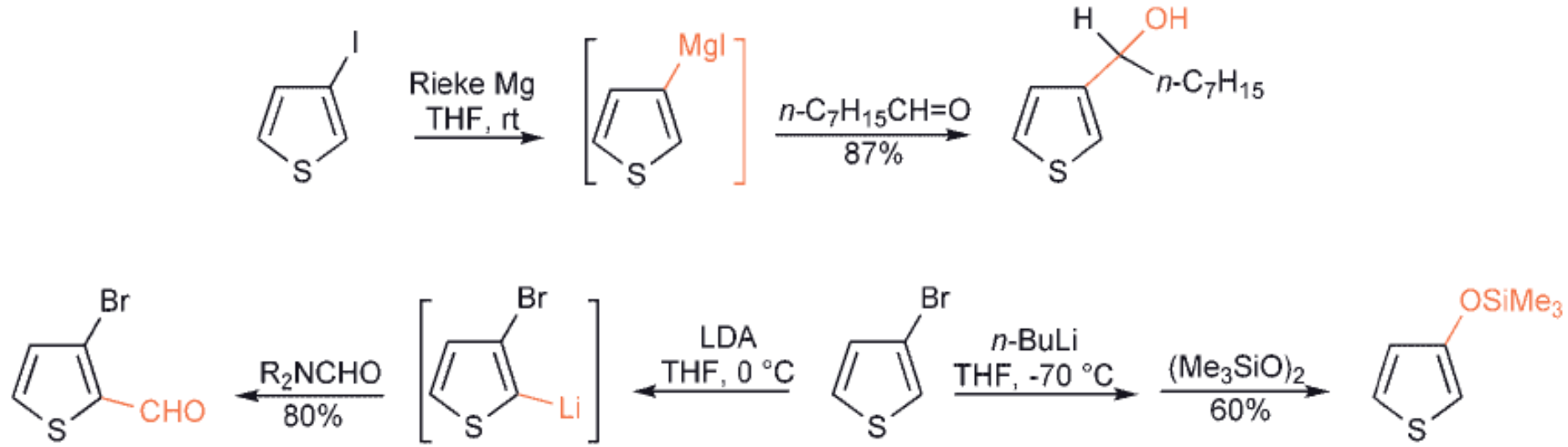
- Metal–halogen exchange on *N*-protected-pyrroles can provide access to either 2- or 3-lithio-pyrroles



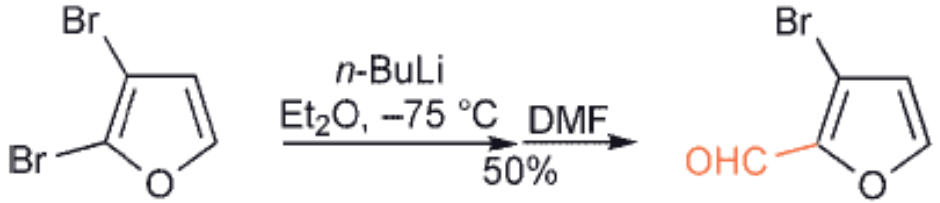


3.2) Metal–Halogen Exchange

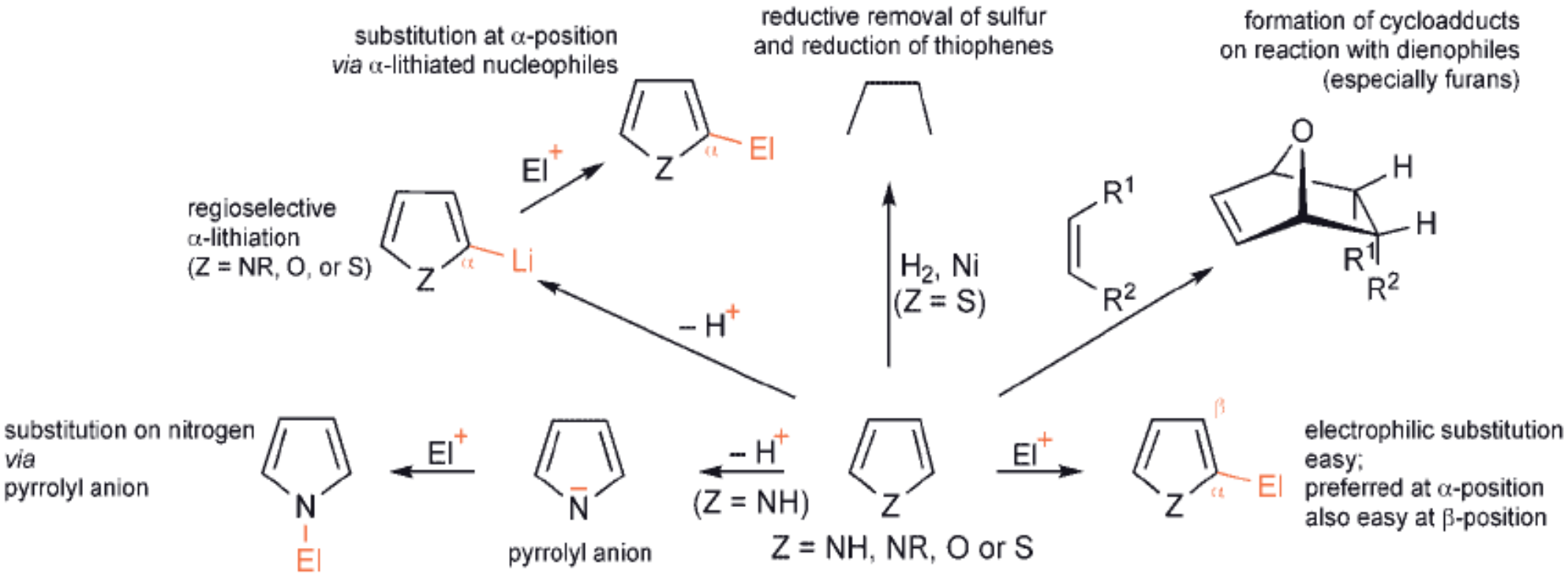
- Thiophenes and furans have similar reactivity



- The greater stability of a carbanion at an *α*-position shows up again in a mono-exchange of 2,3-dibromofuran with selective replacement of the *α*-bromine

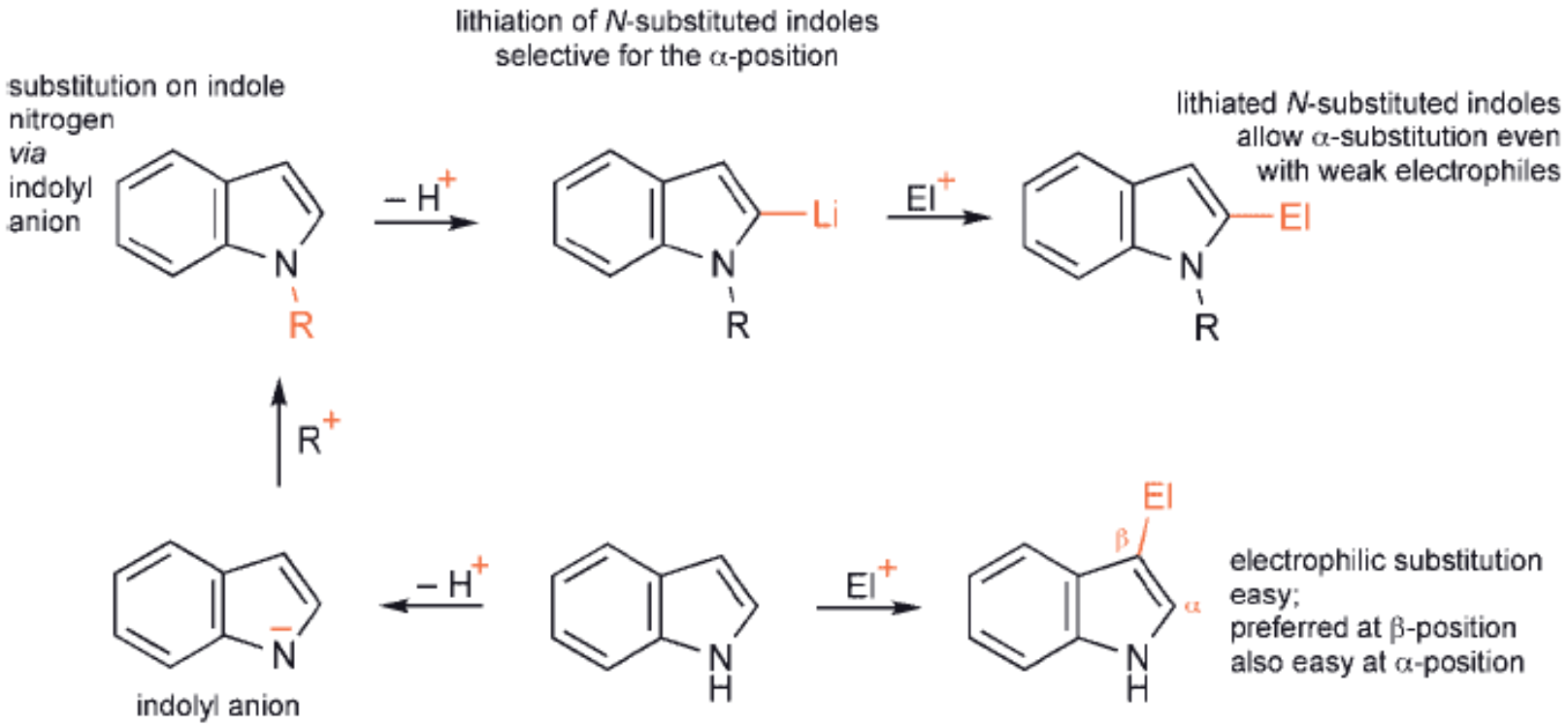


Typical reactions of Pyrroles, Furans and Thiophenes



Typical reactions of pyrroles, furans and thiophenes

Typical reactions of Indoles

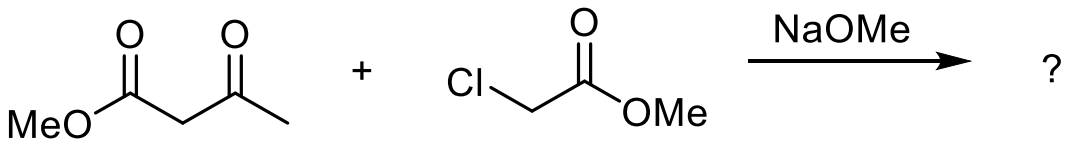


Typical reactions of indole

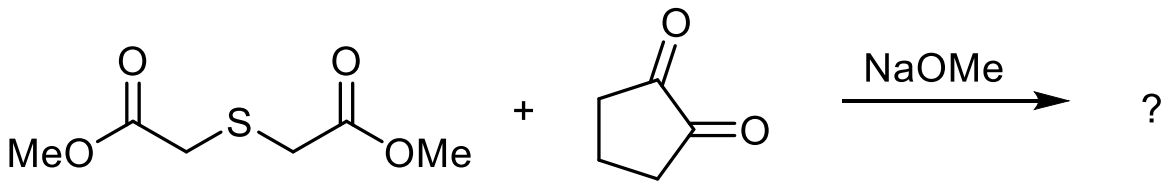
Homework #1

Give the mechanism and the structure of products resulting from the following reagent combinations:

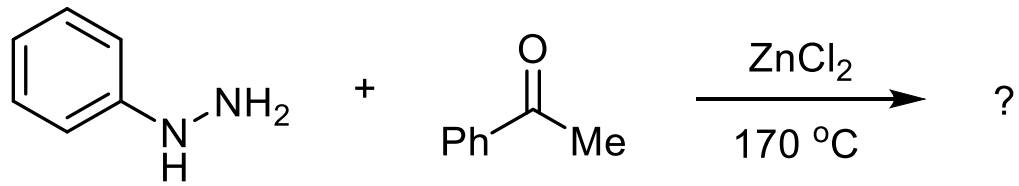
1.1)



1.2)



1.3)



Homework #2

2.1) Deduce structures for the products formed at each stage by treating pyrrole successively with: (i) $Me_2NH/HCHO/AcOH$, (ii) CH_3I, (iii) piperidine in hot EtOH → $C_{10}H_{16}N_2$

2.2) Deduce structures for the products formed at each stage by treating pyrrole successively with: (i) Cl_3CCOCl, (ii) Br_2 , (iii) $MeONa/MeOH$ → $C_6H_6BrNO_2$

2.3) Deduce structures for the products formed at each stage by treating pyrrole successively with: (i) $DMF/POCl_3$, (ii) NaH then MeCOCl

Homework #3

3.1) Suggest structures for the major and minor isomeric products, $C_5H_5NO_3S$, from 2–methoxythiophene with HNO_3/AcOH at −20 °C

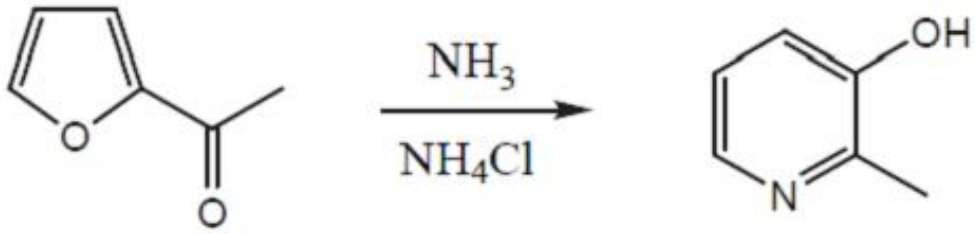
3.2) Deduce structures for the compounds, C_4HBr_3S and $C_4H_2Br_2S$, produced successively by treating 2,3,4,5-tetrabromothiophene with Mg then H_2O and then the product again with Mg then H_2O

3.3) Deduce structures for the formed at each stage by treating furan successively with (i) *n*-BuLi, reflux , (ii) cyclohexanone

3.4) Indole reacts with a mixture of *N*-methyl-2-piperidone and $POCl_3$, followed by NaOH work-up to give $C_{14}H_{18}N_2O$. What is its structure?

Homework #4

Give mechanisms for the following transformations.



Homework #5

Suggest a method for the synthesis of the following compound