Substituted Effects on Electrophilic Substitution

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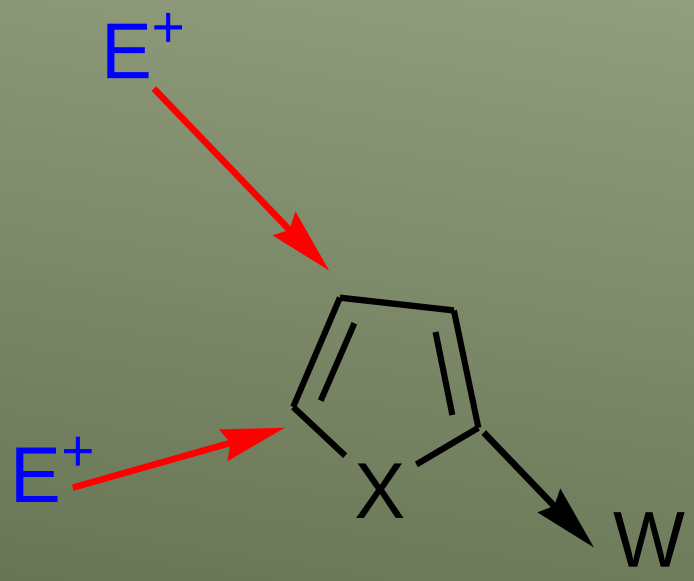
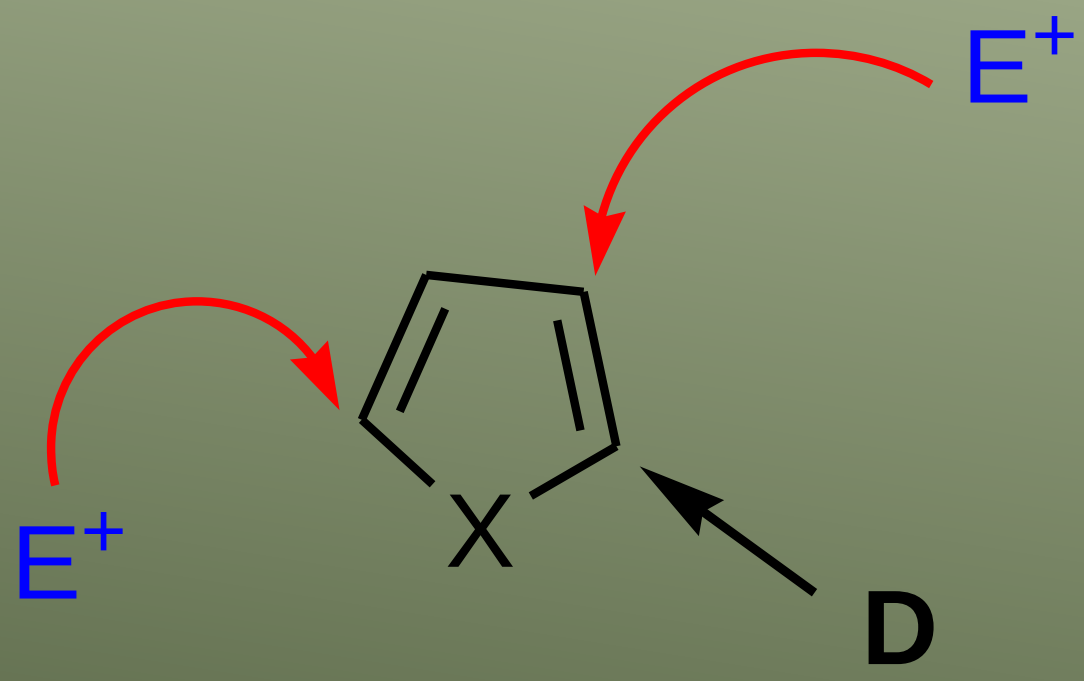
Ph.D. of Organic Chemistry
"Synthesis of Hetero Cyclic"

College of Pharmacy-2020

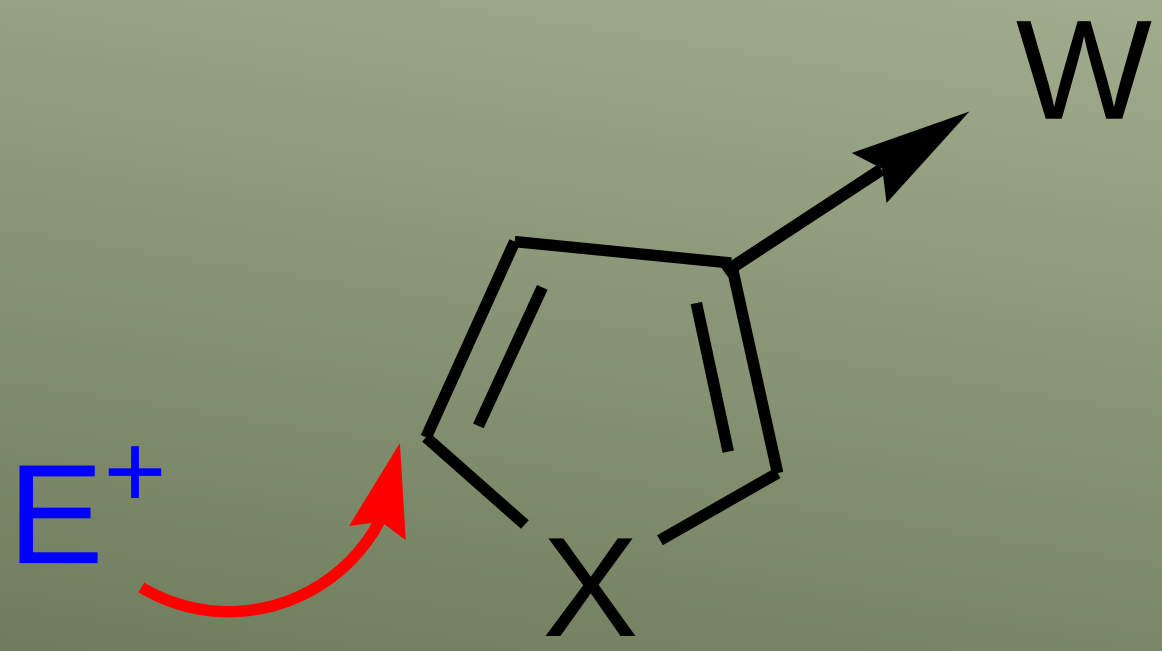
1- **Electron-withdrawing** substituents (**W**) at the position "α" to the heteroatom generally cause substitution at the **4**- and / or **5**-position.



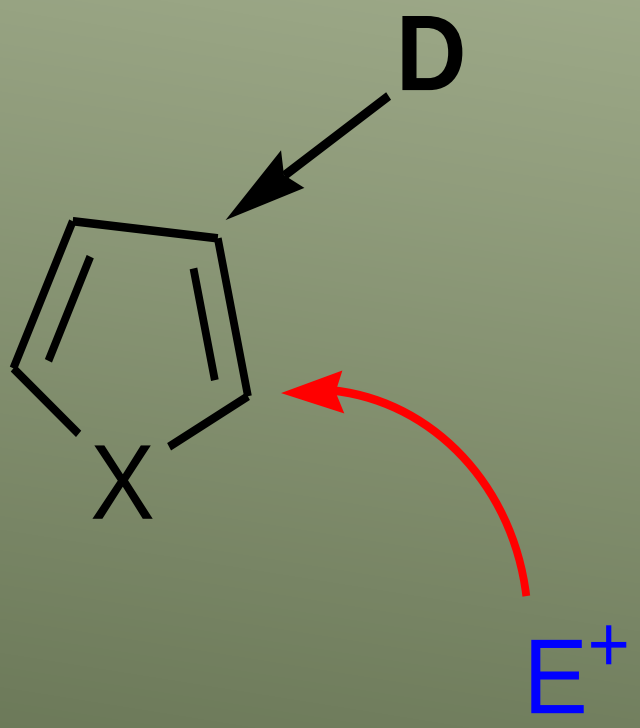
2- **Electron-donating** substituents (**D**) at the position "α" to the heteroatom tend to cause substitution at both the remaining "α" position (C-5) and at the (3-position).



3- **Electron-withdrawing** substituents (W) at the position "β" to the heteroatom facilitate substitution at position 5.

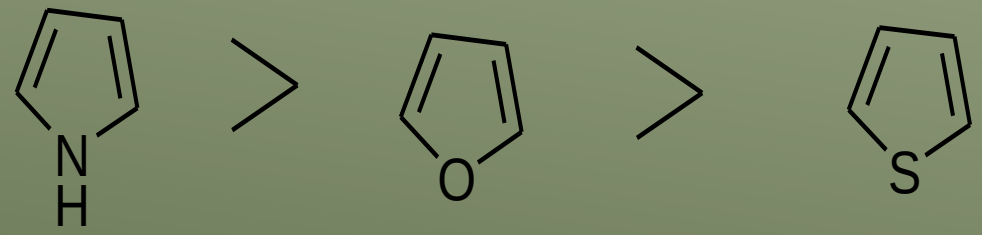


4- **Electron-donating** substituents (**D**) at the position "β" to the heteroatom generally cause substitution to take place at the 2-position.

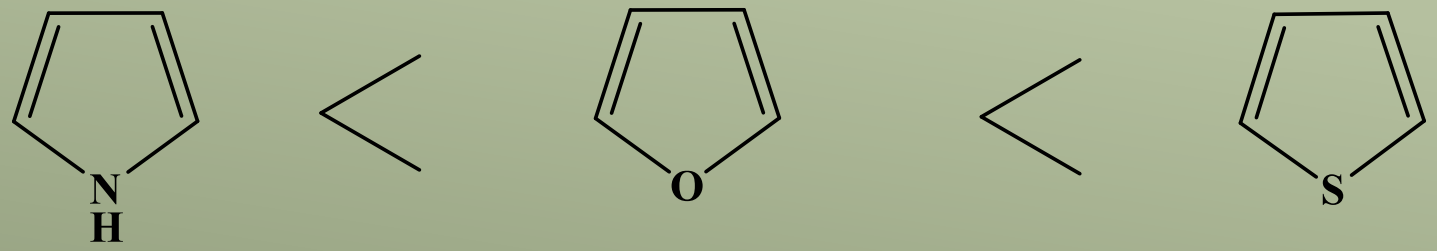


Nucleophilic Substitutions in Pyrrole, Furan and Thiophene

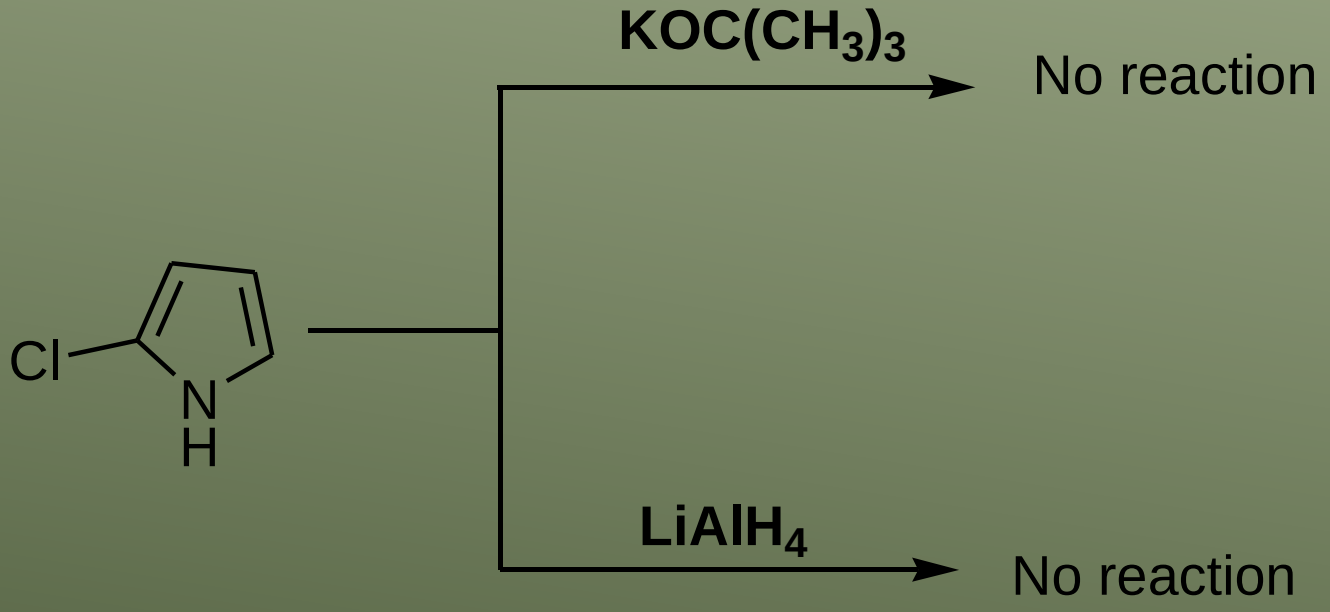
We have seen that the reactivity of pyrrole, furan and thiophene towards electrophilic substitution is in the following order



The reactivity of these rings towards nucleophilic substitution is in the opposite order

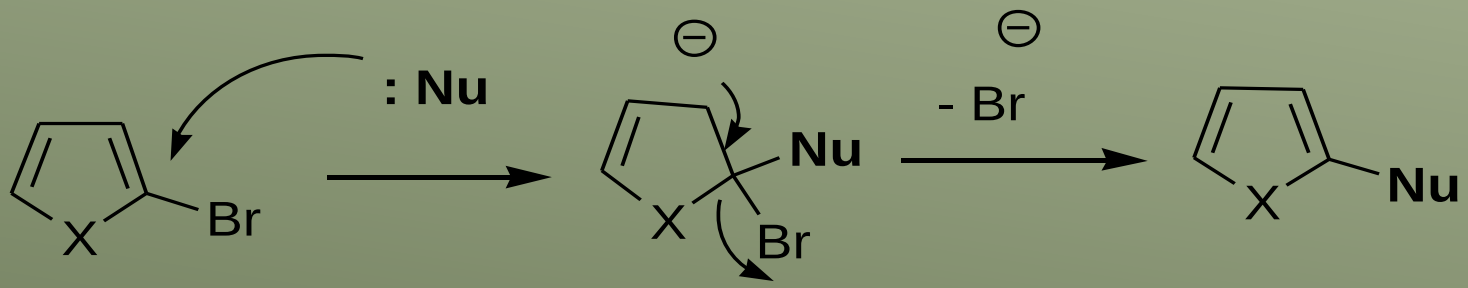


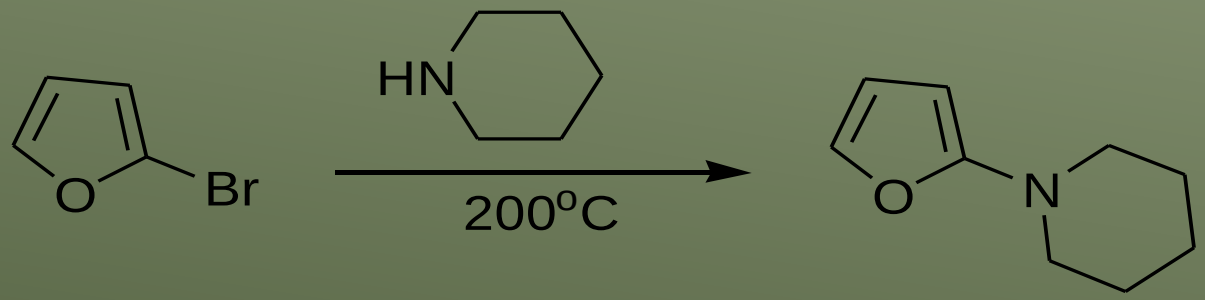
Pyrroles: the pyrrole ring is the least reactive and both 2-halo- and 3-halopyrroles behave like-aryl halides in nucleophilic displacement. Thus, 2-chloropyrrole does not react with potassium tert-butoxide or with lithium aluminum hydride



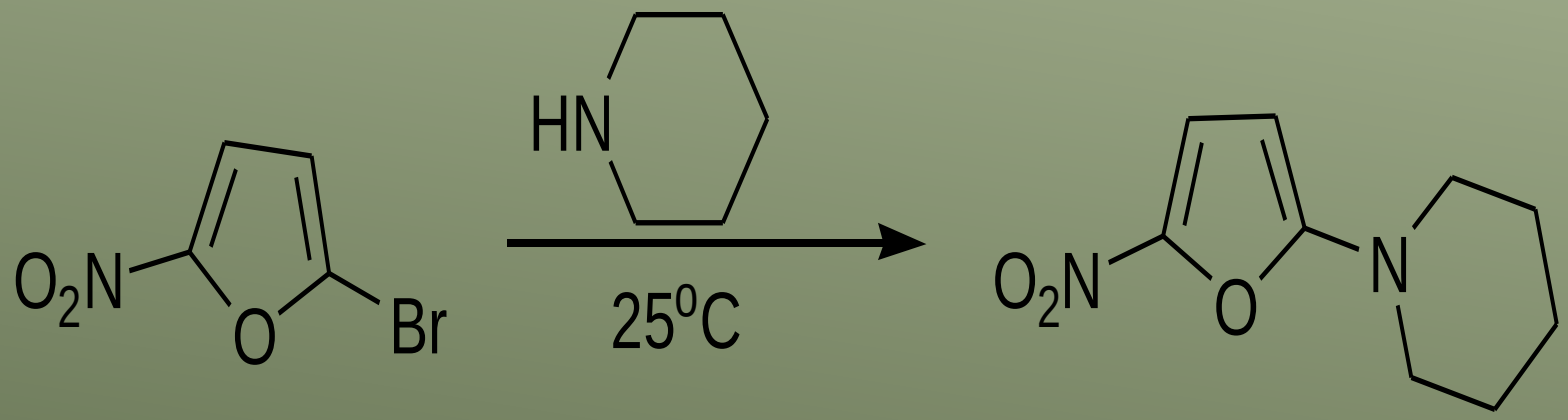
FURANS

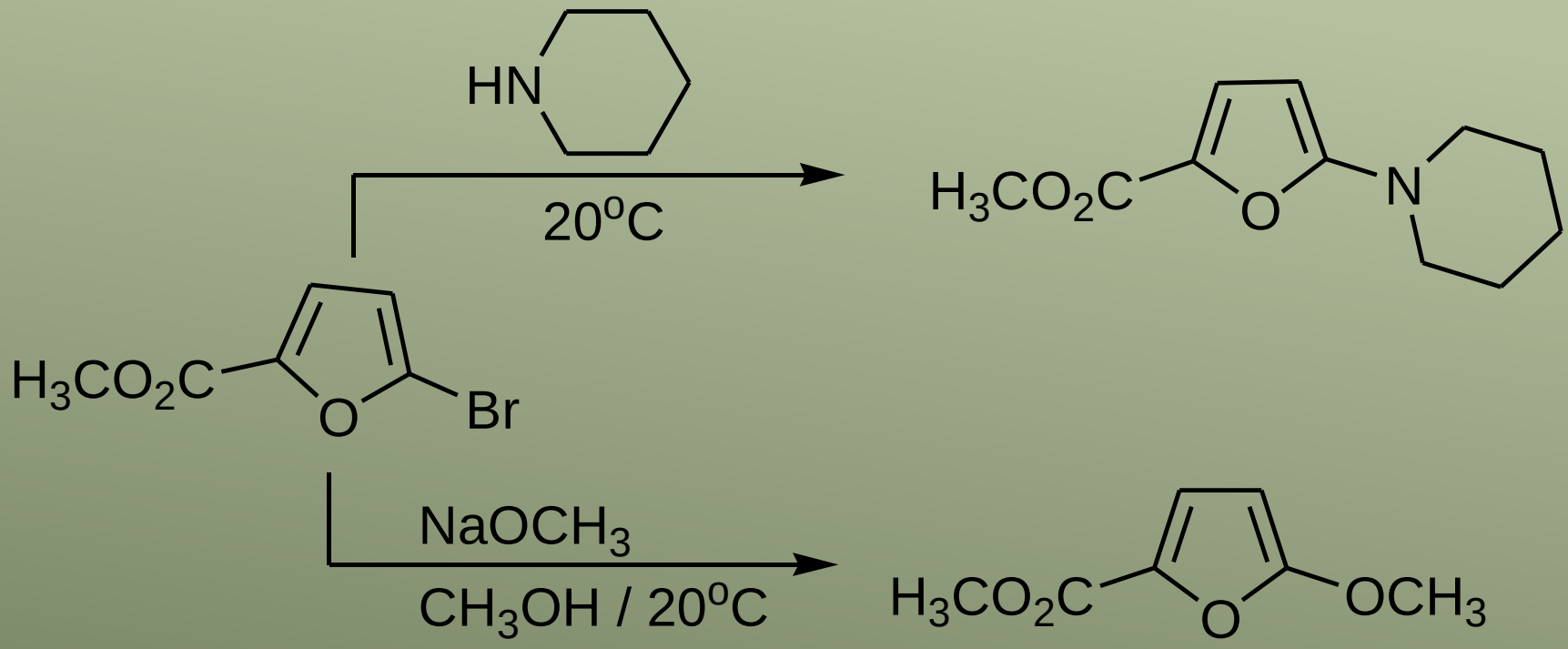
Furns are more reactive towards nucleophilic displacement than pyrrole. 2-bromo- and 2-chloro react with piperidine at 200°C as follows:





The presence of electron-withdrawing groups on the furan ring facilitates nucleophilic displacement. Thus, 2-bromo-5-nitrofuran and methyl 2-bromo-5-carboxylate react readily with nucleophiles



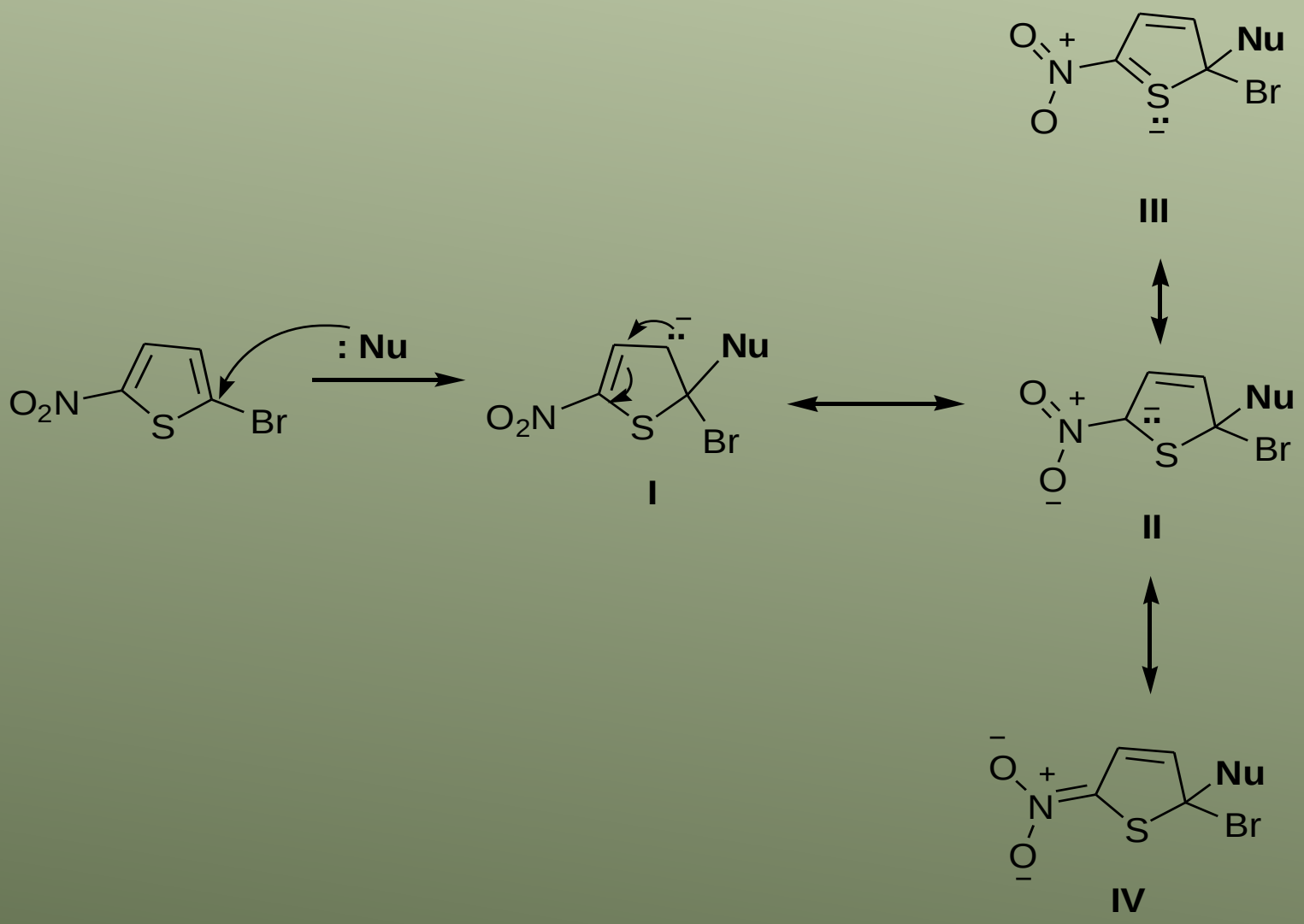


- **It is of considerable interest that in these reactions the furans react about 10 times faster than the corresponding benzene analogues. This strong behavior has also been observed in theiophene series**

Thiophenes

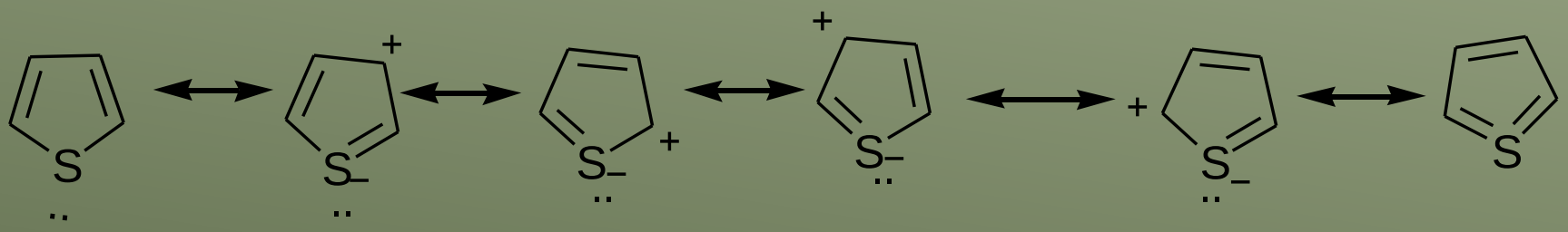
Nucleophilic substitution occurs much more readily within the thiophene series than it does for the corresponding benzene compounds. The thiophenes are at least 1000 times more reactive than corresponding benzene analogues **(This increased reactivity has also been noticed in the electrophilic substitution of thiophenes compared to the corresponding benzene analogues).**

The increased reactivity of thiophene ring nucleophilic substitution can be explained by *Wheland* intermediates involved in nucleophilic substitution of bromine in 2-bromo-5-nitrothiophene.

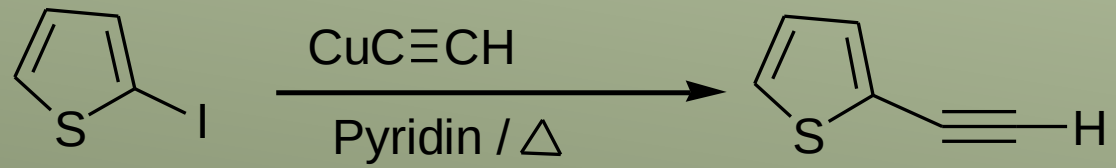


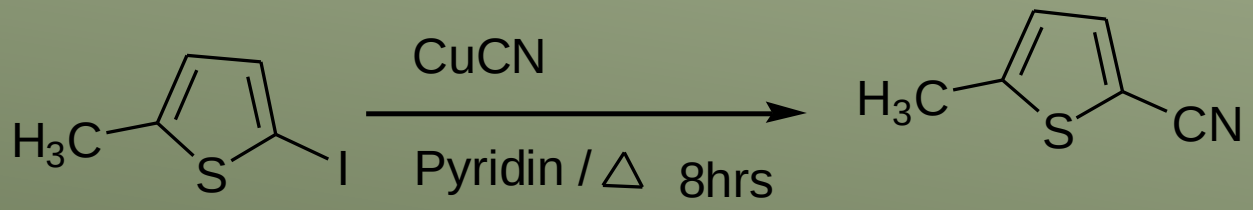
It is suggested that the sulfur atom causes additional stabilization by involvement of its d-orbitals "Structure III"

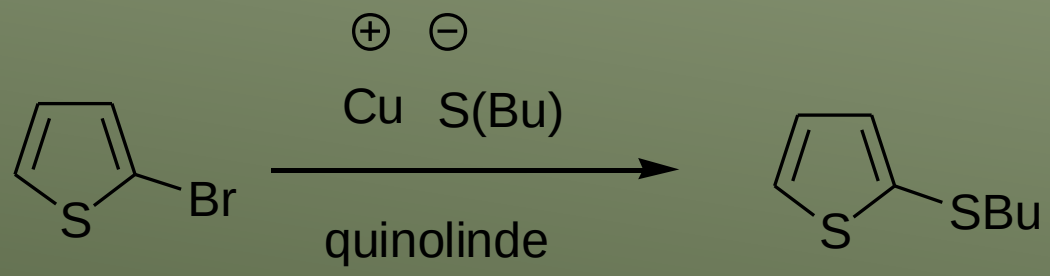
It must be noted that the lone pair of the sulphur atom also enters into resonance with the π electrons. X-ray studies indicate that the valency angle of C-S-C in thiophene is nearly 91^{o} and not 105^{o} as expected. This can be explained by assuming that the 3d orbital of sulphur are also used in resonance and following additional contributing structures may be written.



Copper-meditated nucleophilic substitutions of halo thiophenes are also of great synthetic utility. Examples of some transformation follow

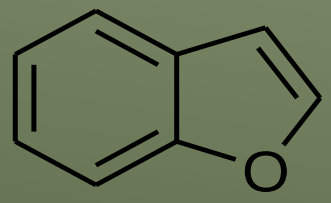




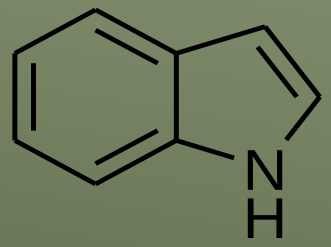


Condensed Five-Membered Heterocycles

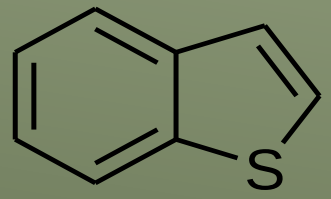
Fusing benzene ring with 2,3-positions of furan, pyrrole and thiophene leading to benzo[*b*]furan, indole and benzo[*b*]thiophene, respectively.



benzo[*b*]furan



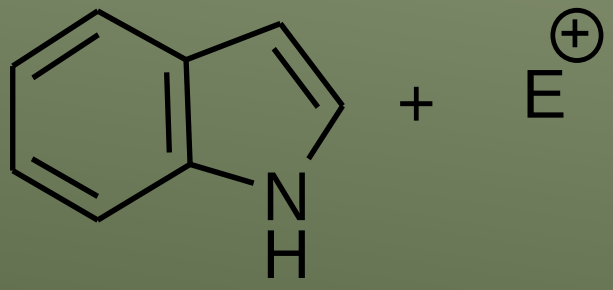
indole



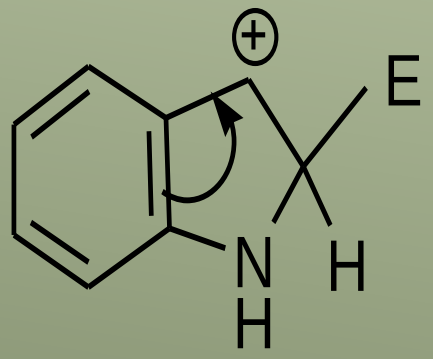
benzo[b]thiophene

The molecular orbital description of benzofused heterocycles with one heteroatom is very similar to that furan, pyrrole and thiophene, the only added feature being distribution of π- electrons. The reactivity of these fused heterocycles is lower than that of the parent heterocycle but still higher than that of benzene.

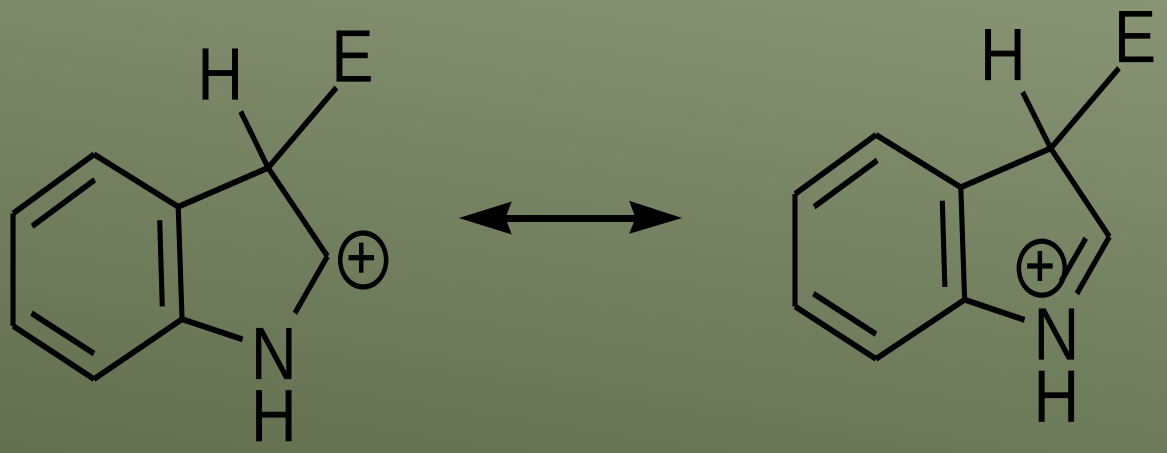
Position 3- is preferred position for electrophilic attack in indole, since it results in two more stable resonance structures in the aromatic sixtet of the benzene ring is preserved, which attack at position 2-yield one structure only in which the aromatic sixtet is preserved.

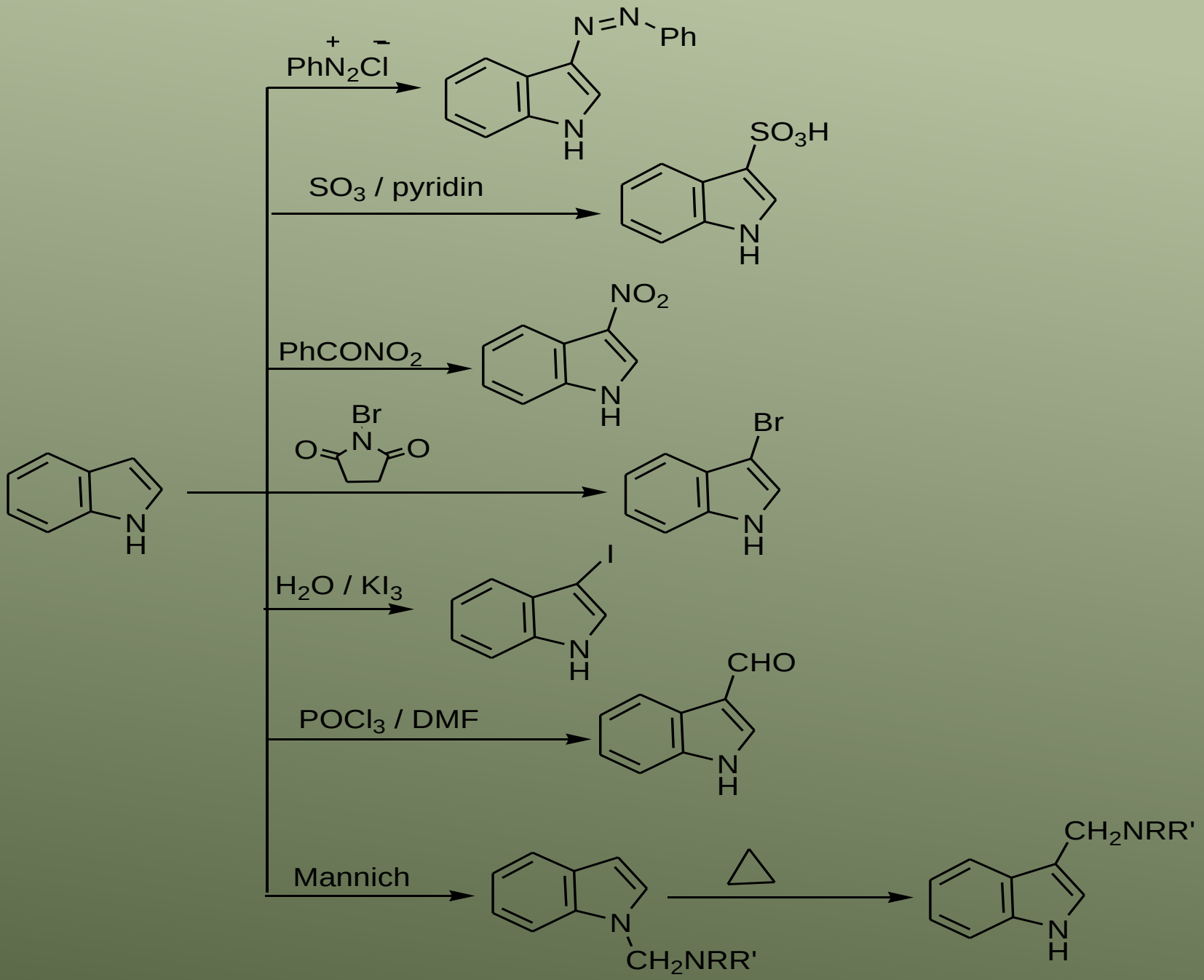


Attack at position 2-



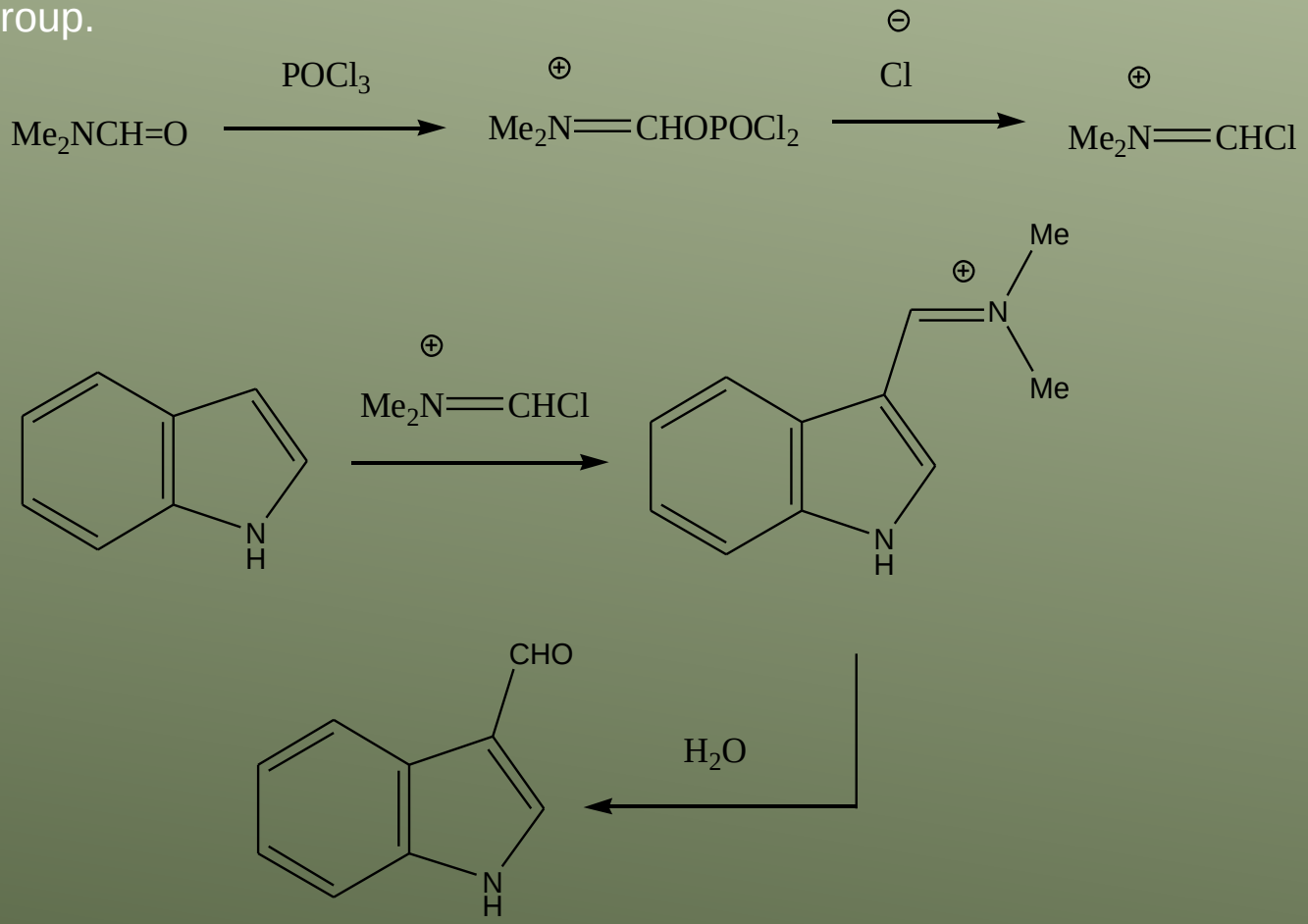
Attack at position 3-



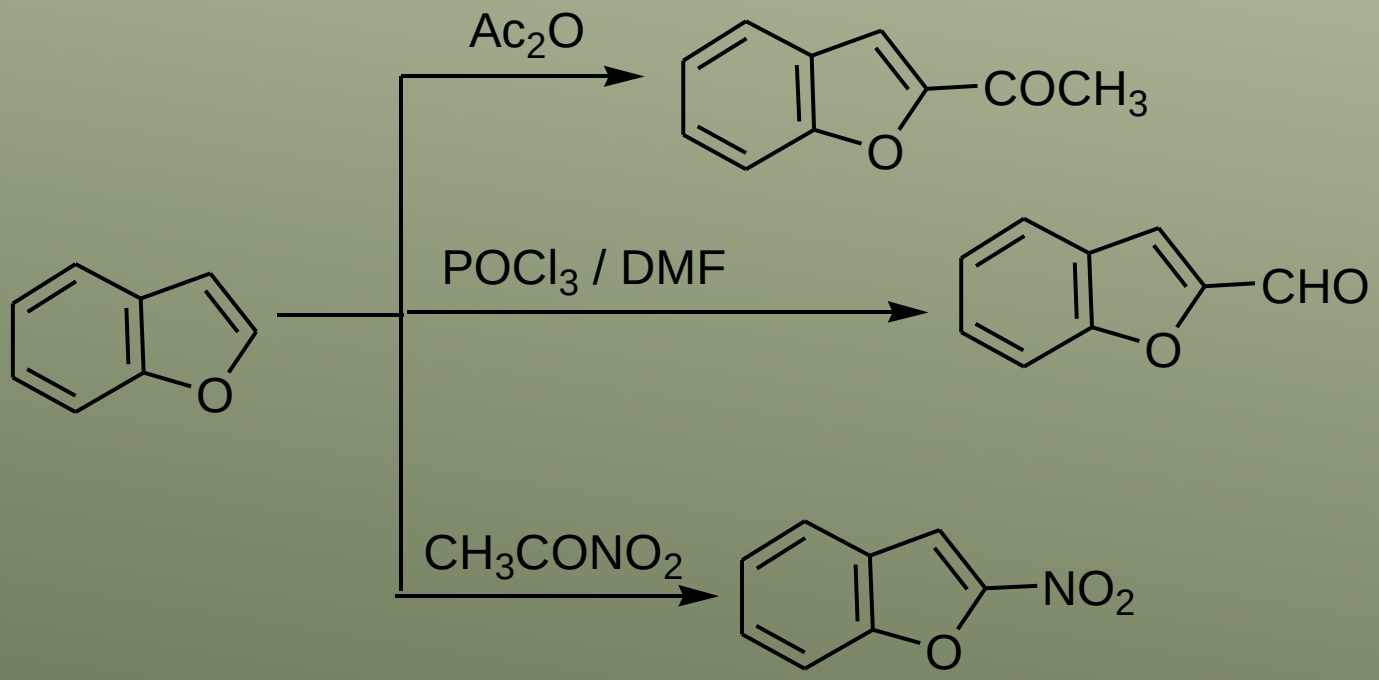

PhN2Cl
N=N
Ph
N
H
SO3H
SO3 / pyridin
NO2
PhCONO2
Br
O
N
O
Br
H2O / KI3
I
CHO
POCl3 / DMF
Mannich
CH2NRR'
CH2NRR'

Vilsmeier–Haack Formylation with N,N-Dimethylformamide.

The mechanism of the reaction involves first the phosphorylation of the carbonyl oxygen of the formamide with $POCl_3$ to form a dichlorophosphate. Chloride ion then displaces the phosphate group, which forms the electrophilic species that attacks the ring. Hydrolysis of the imino group restores the carbonyl group.



Electrophilic substitution in benzo[*b*]furan occurs mainly at C-2.



Both C-2 and C-3 of benzo[*b*]thiophene are involved as the intermediates are of comparable stability.