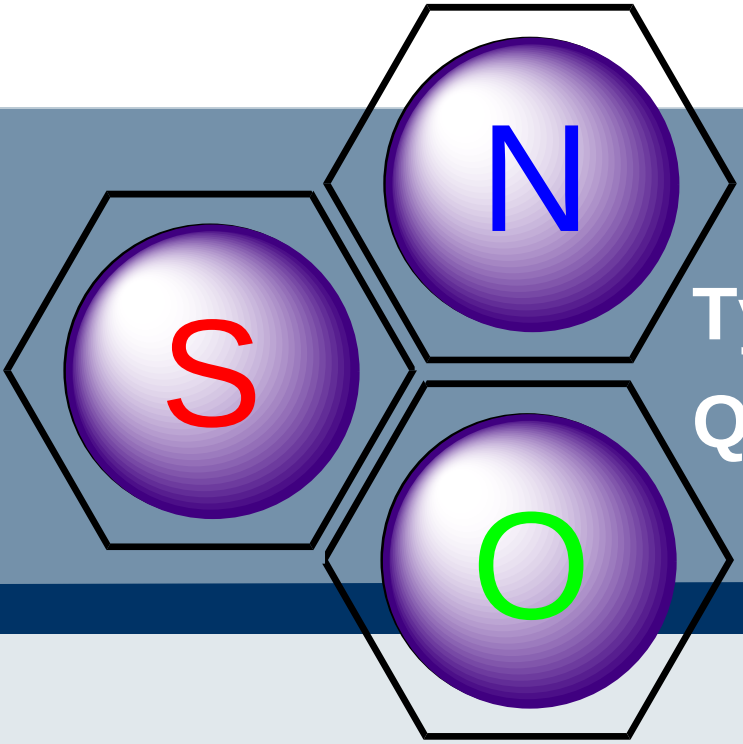
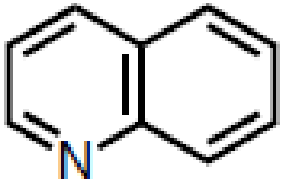
Chapter 5

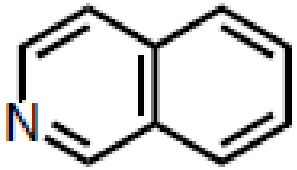


Typical Reactivity of Pyridines, Quinolines and Isoquinolines

Pyridine

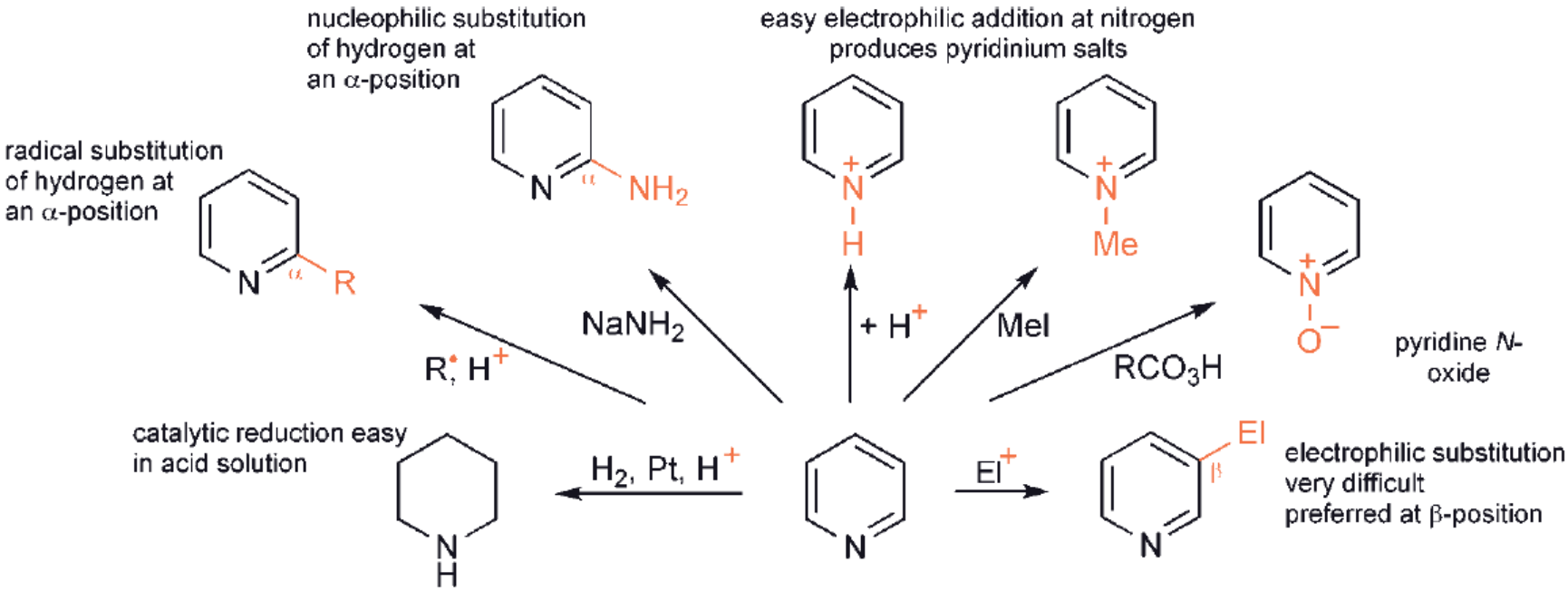


Quinoline



Isoquinoline

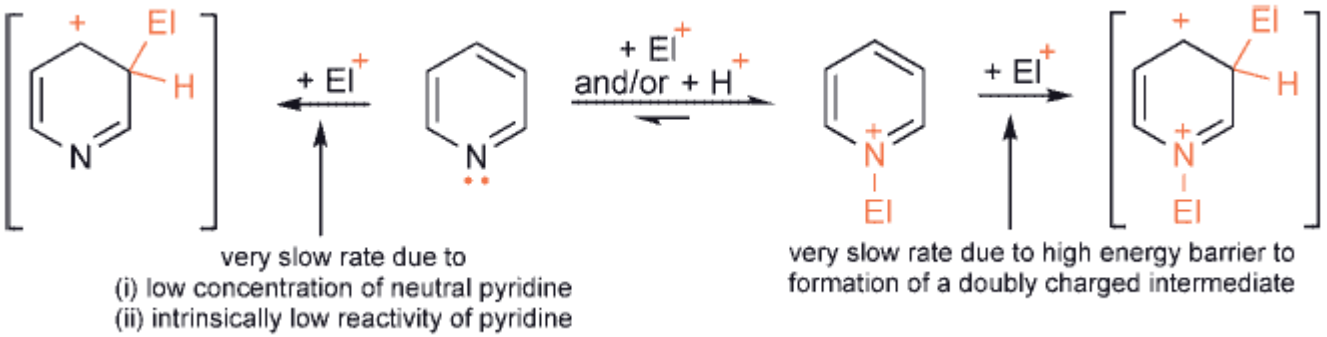
Typical Reactivity of Pyridines



Typical reactions of pyridine

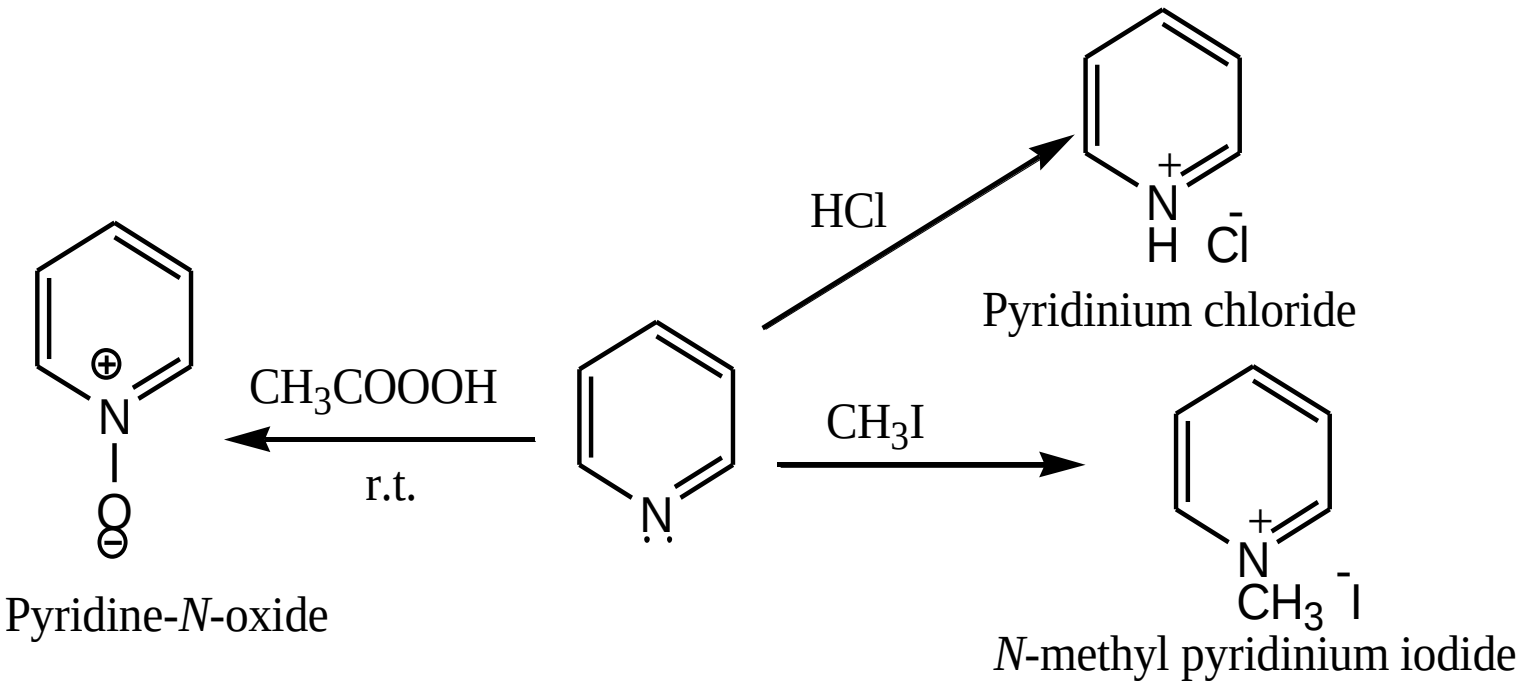
pyridines are much less susceptible to electrophilic substitution than benzene and much more susceptible to nucleophilic attack.

Electrophilic substitution at carbon, in simple pyridines at least, is very difficult, in contrast to the reactions of benzene – Friedel–Crafts acylations, for example, do not occur at all with pyridines. This unreactivity can be traced to two factors:



Pyridine as a nucleophile (reactions on N atom)

- **Nitrogen in pyridine acts as a tertiary amine and has nucleophilic properties, thus it reacts with electrophiles:**

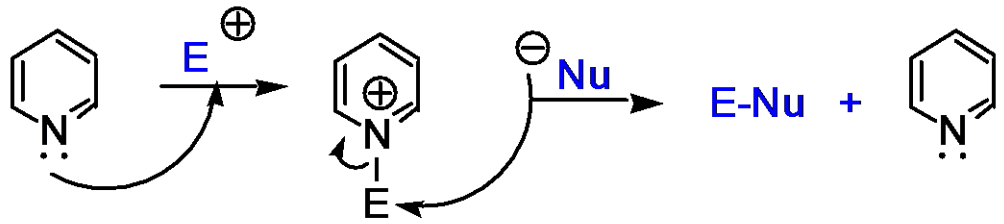


Pyridine as a nucleophile (reactions on N atom)

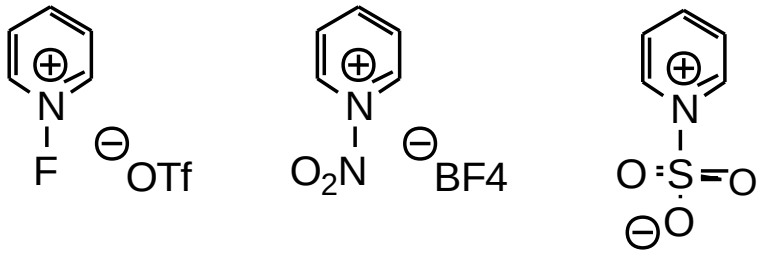
Exposure of a pyridine to a medium containing electrophilic species immediately converts the heterocycle into a pyridinium cation, with the electrophile (or a proton from the medium) attached to the nitrogen.

Reaction with electrophiles - react. on N:

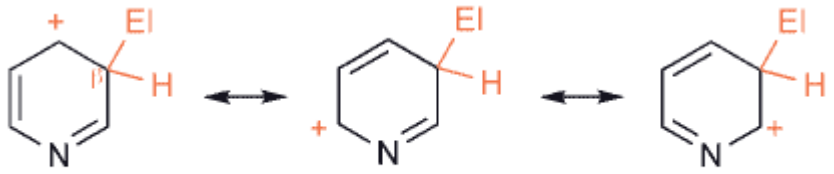
- Protonation
- Nitration
- Sulfonation
- Amination
- Halogenation
- Alkylation
- Acylation



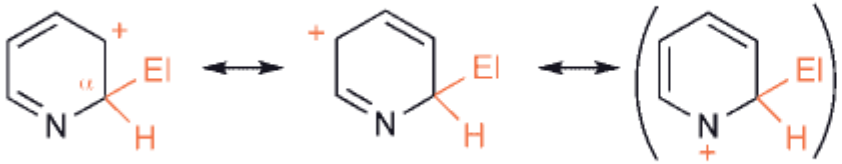
Mild, not acidic electrophile



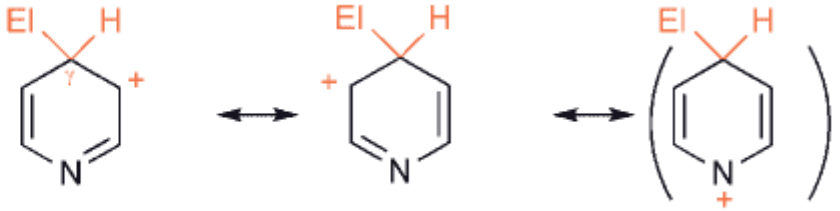
- The carbons of a pyridine are, in any case, electron-poor, particularly at the α- and γ-positions: formation of a σ-complex between a pyridine and an electrophile is intrinsically disfavoured. The least disfavoured, i.e. best option, is attack at a β-position – resonance contributors to the cation thus produced do not include one with the particularly unfavourable sextet, positively-charged nitrogen situation (shown in parentheses for the α- and γ-intermediates). The situation has a direct counterpart in benzene chemistry, where a consideration of possible intermediates for electrophilic substitution of nitrobenzene provides a rationalisation of the observed *meta*-selectivity.



intermediate for β-attack by El^+



intermediate for α-attack by El^+



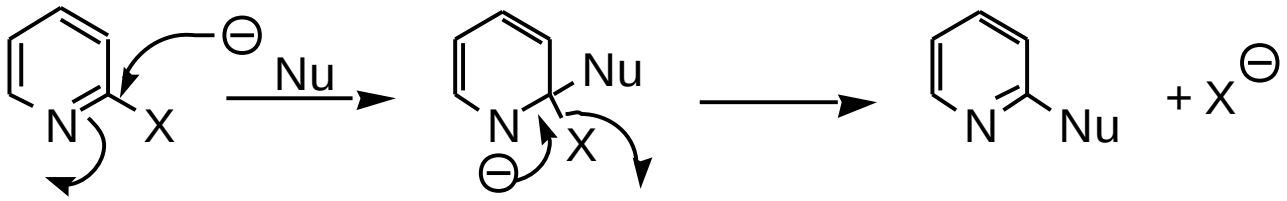
intermediate for γ-attack by El^+

Reaction with Nucleophiles

The electron-deficiency of the carbons in pyridines, particularly α- and γ-carbons, makes nucleophilic addition and, especially nucleophilic displacement of halide (and other good leaving groups), a very important feature of pyridine chemistry.

Nucleophilic displacement of pyridine α- and γ-leaving groups, e.g. halide, is easy

Reaction with Nucleophiles



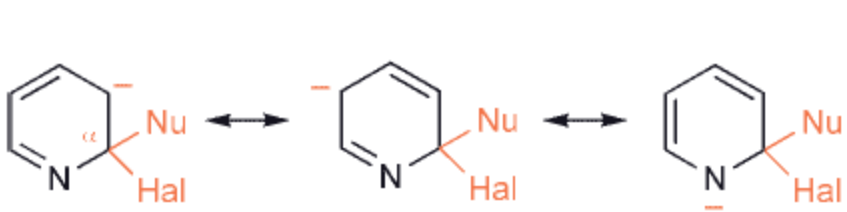
a) X=H, Substitution with "hydride" transfer

Nu: $NaNH_2$ - amination - Chichibabin reaction
Nu: BuLi, PhLi etc - alkylation / arylation
Nu: NaOH - "hydroxylation" - High temp

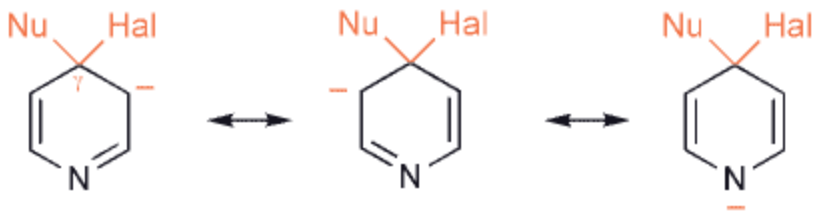
Attack in the 2-pos (not 4-pos)

b) X=LG, Displacement of good leaving group
X: Halogen (F>>Cl,>Br,>I), $-OSO_2R$, $-NO_2$, -OR

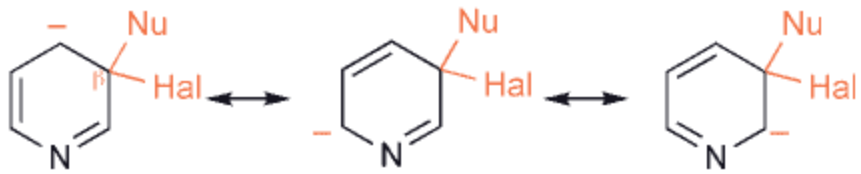
Such substitutions follow the same mechanistic route as the displacement of halide from 2- and 4-halonitrobenzenes, i.e. the nucleophile first adds and then the halide departs. By analogy with the benzenoid situation, the addition is facilitated by: (i) the electron- deficiency at α- and γ-carbons, further increased by the halogen substituent, and (ii) the ability of the heteroatom to accommodate negative charge in the intermediate thus produced. A comparison of the three possible intermediates makes it immediately plain that this latter is not available for attack at a β-position, and thus β-nucleophilic displacements are very much slower.



intermediate for α-attack by Nu^-



intermediate for γ-attack by Nu^-

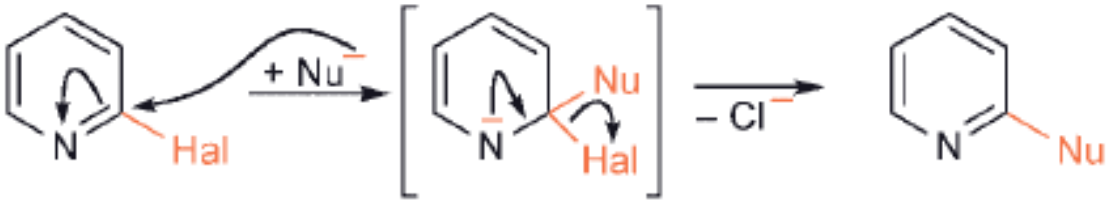


intermediate for β-attack by Nu^-

Intermediates explain selectivity of nucleophilic attack on halopyridines

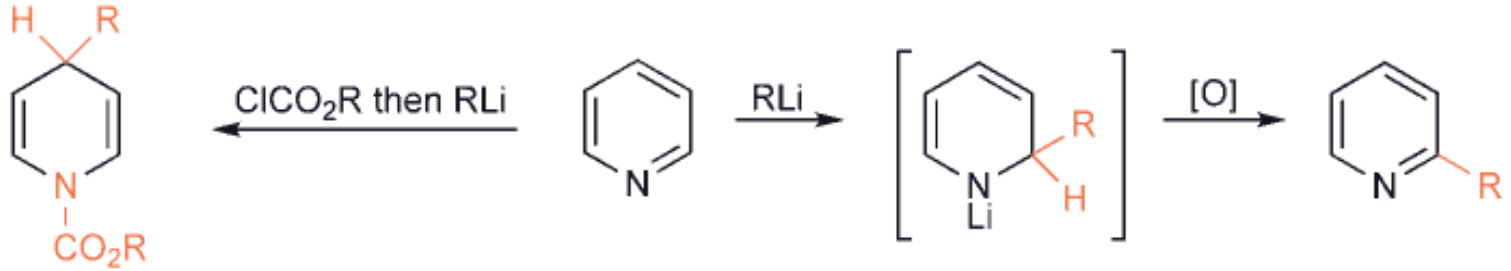
Comparison of the reactivity of an α-halopyridine with an acid chloride

It is useful to compare the reactivity of α- and γ- halopyridines with the reaction of acid halides and β-halo –α,β-unsaturated ketones, respectively, both of which also interact easily with nucleophiles and also by an addition/elimination sequence resulting in overall displacement of the halide by the nucleophile.



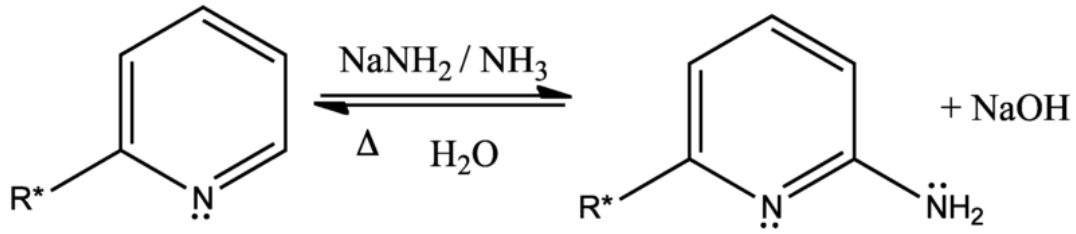
compare

In the absence of an α- or γ-halogen, pyridines are less reactive and, of course, do not have a substituent suitable for leaving as an anion to complete a nucleophilic substitution. Nucleophilic additions do however take place, but the resultant dihydropyridine adduct requires removal of 'hydride' in some way, to complete an overall substitution. Such reactions, for example with sodium amide or with organometallic reagents, are selective for an α-position, possibly because the nucleophile is delivered *via* a complex involving interaction of the ring nitrogen with the metal cation associated with the nucleophile. The addition of organometallic or hydride reagents to N^+-acylpyridinium salts is an extremely useful process: the products, 1,2- or 1,4-dihydropyridines, are stable because the nitrogen electron pair is involved with resonance in the carbamate unit.

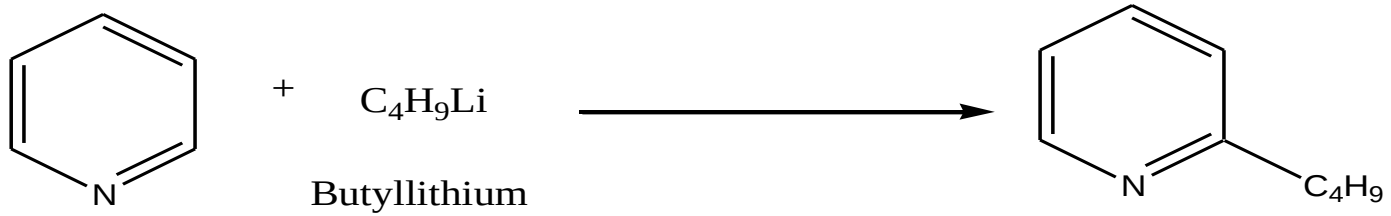


with sodium amide or with organometallic reagents

i) The Chichibabin reaction

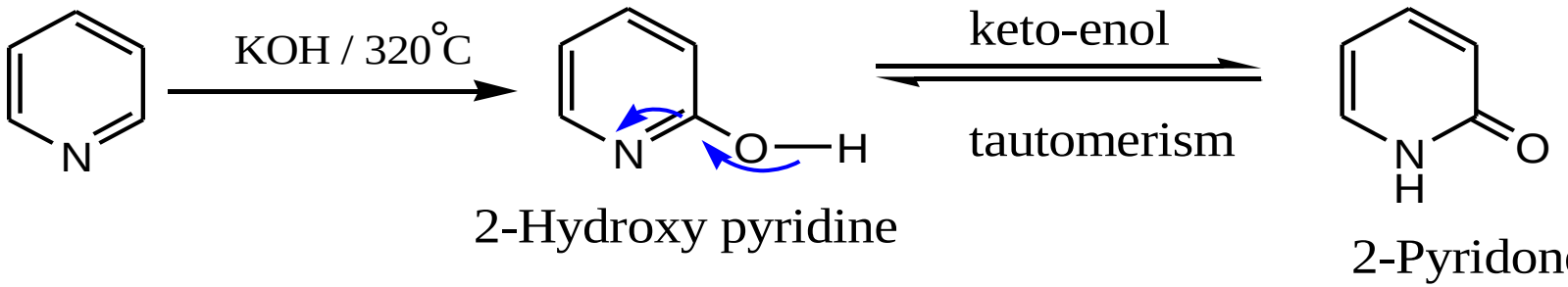


ii) Reaction with organometallic compounds: lithium reagents



2-Butylpyridine

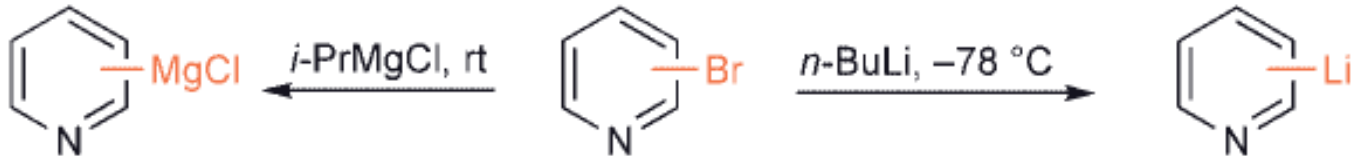
iii) Reaction with potassium hydroxide



2-Hydroxy pyridine

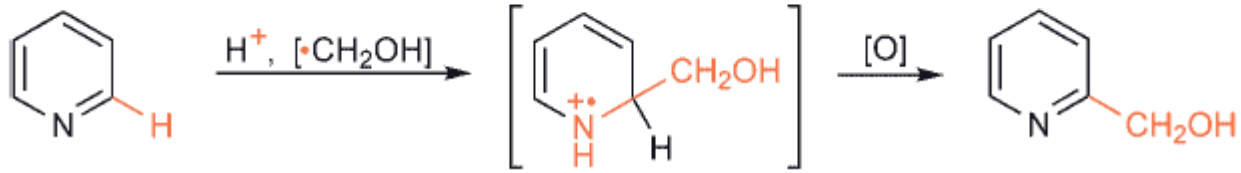
2-Pyridone

The generation and use of metallated aromatics has become extremely important for the introduction of substituents, especially carbon substituents, by subsequent reaction with an electrophile. Despite the ease of nucleophilic addition and substitution discussed above, iodine and bromine at all positions of a pyridine undergo metal/halogen exchange, at low temperature, *without* nucleophilic displacement or addition, thus forming the corresponding pyridyllithiums. Low-temperature direct lithiation of pyridines at an α-position, or elsewhere *via* directed *ortho*-metallation, is also possible. Similarly, useful pyridyl Grignard reagents are available by reaction of bromopyridines with *iso*-propylmagnesium chloride *at room temperature*.

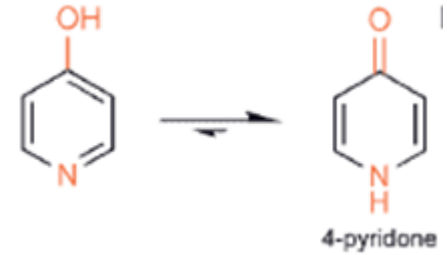


Formation of pyridyllithiums and pyridyl Grignard reagents

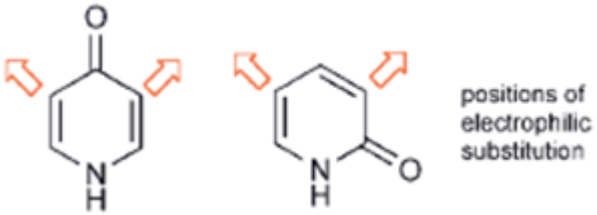
Radical substitution of pyridines, in acid solution, is a preparatively useful process. For efficient reaction, the radicals must be 'nucleophilic', like $^{\bullet}CH_2OH$, alkyl$^{\bullet}$, and acyl$^{\bullet}$. A hydroxymethylation provides the example shown.



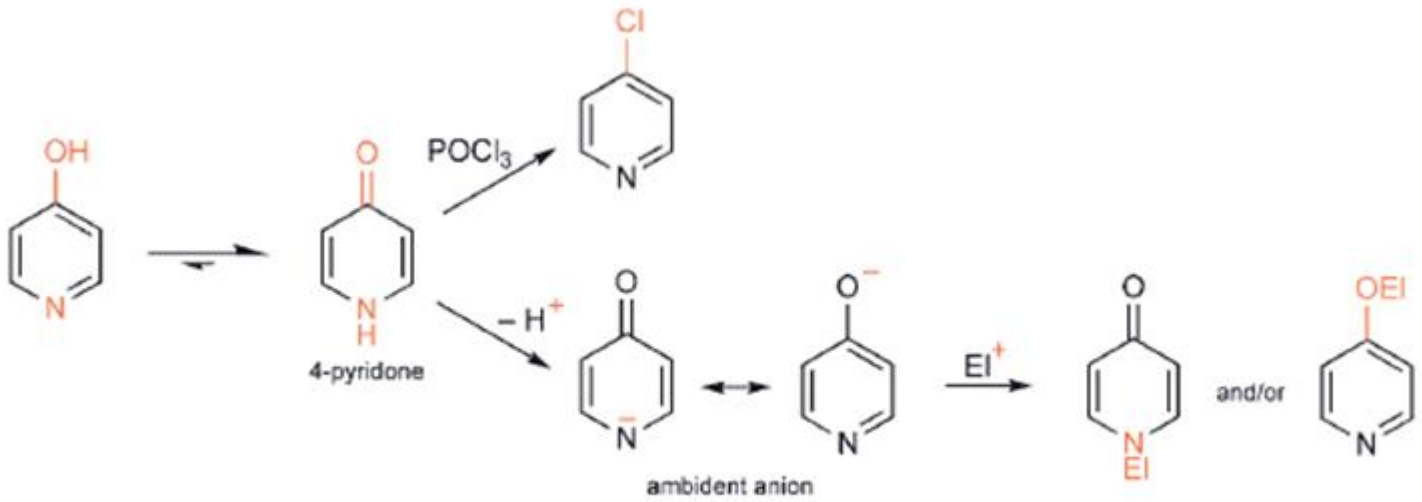
Pyridines carrying oxygen at an α- or γ- position exist as tautomers having carbonyl groups – pyridones. Nonetheless, there is considerable parallelism between their reactions and those of phenols: pyridones are activated towards electrophilic substitution, attack taking place *ortho and para to the oxygen.*



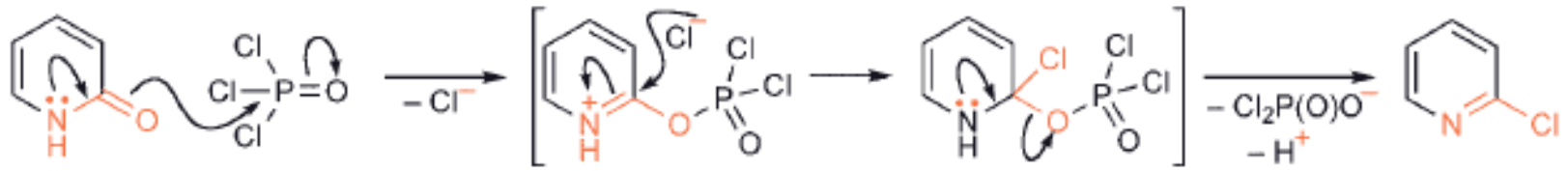
4-pyridone



positions of electrophilic substitution

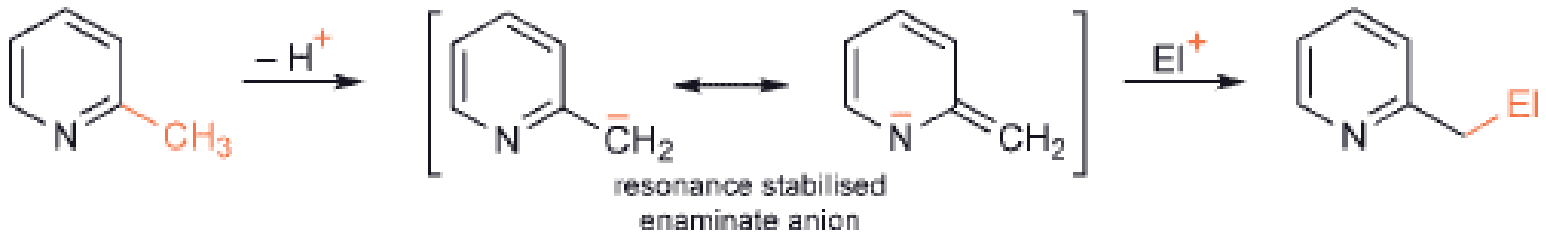


Typical reactions of pyridones, illustrated for 4-pyridone



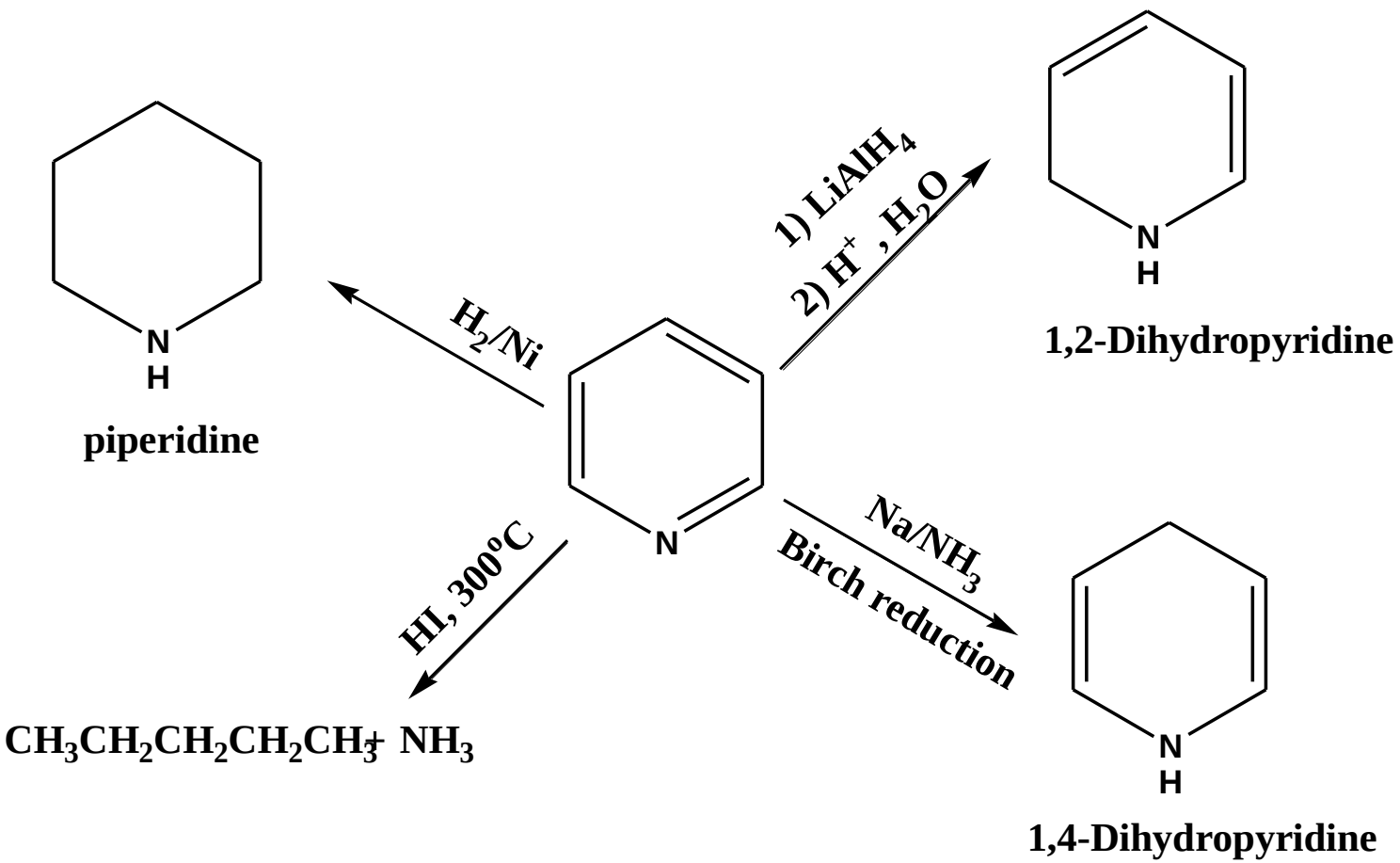
Mechanism of reaction of pyridones with phosphoryl chloride, illustrated for 2-pyridone

The special properties associated with pyridine α- and γ-positions are evident again in the reactions of alkyl-pyridines: protons on alkyl groups at those positions are particularly acidified because the 'enaminate' anions formed by side-chain deprotonation are delocalised. The ability to form side-chain anions provides a useful means for the manipulation of α- and γ-side-chains.

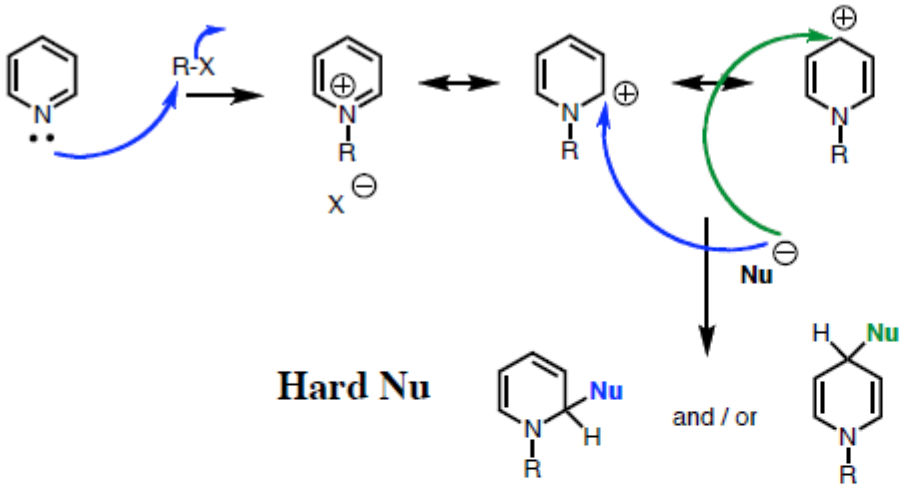


Deprotonation of α- and γ-alkyl groups is relatively easy

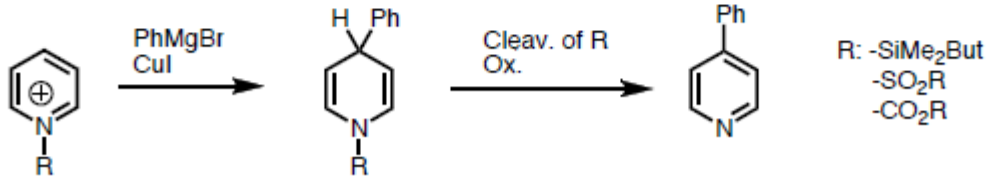
Reduction Reactions



Quartenary pyridinium salts

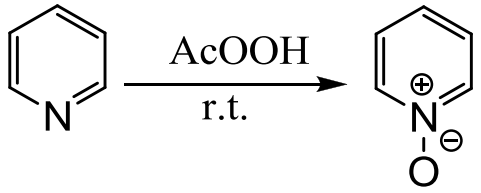


Add of: -hydrides
-dithionite
-organometallics
-stab. carbanions
etc. etc.



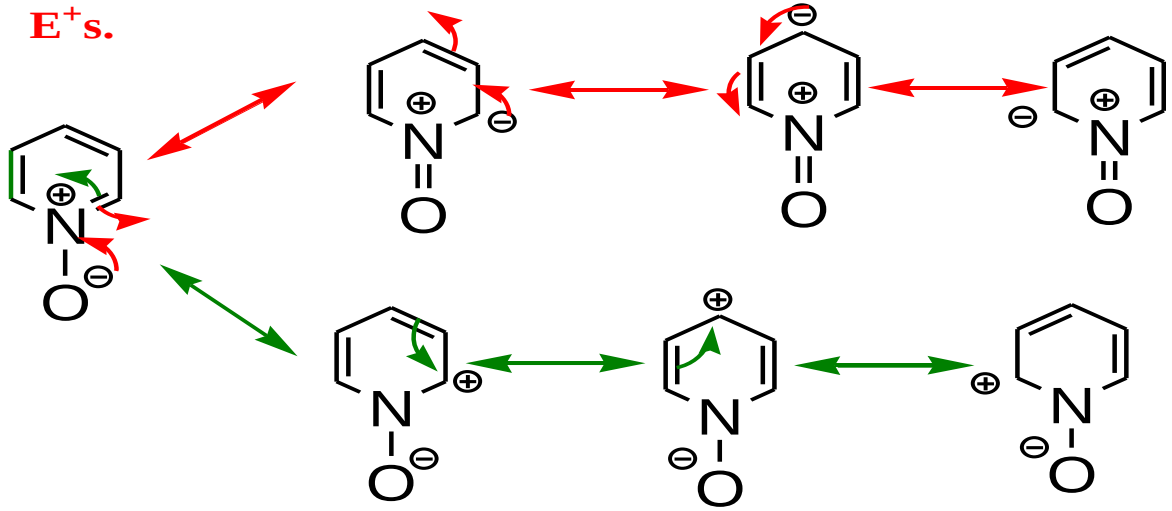
Derivative of pyridine: pyridine N-oxide

- Pyridine can be oxidized easily to pyridine N-oxide by peracids.



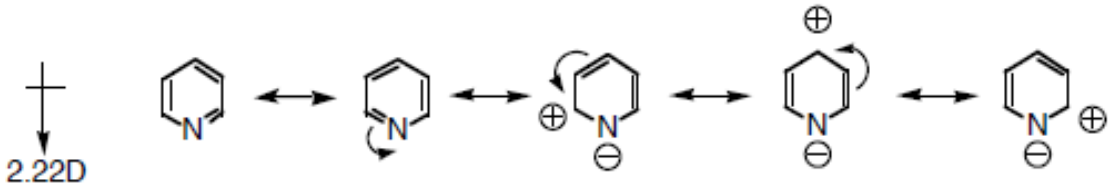
- On the basis of dipole moment studies, N-oxide pyridine is considered as a resonance hybrid of the following structures

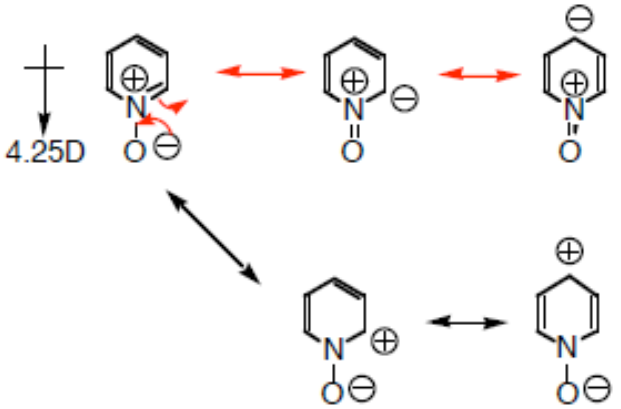
The -ve. charges appear at positions 2, 4 thus active towards E^+s.



The +ve. charges appear at positions 2, 4 thus active towards nucleophiles

Pyridine *N-oxides*

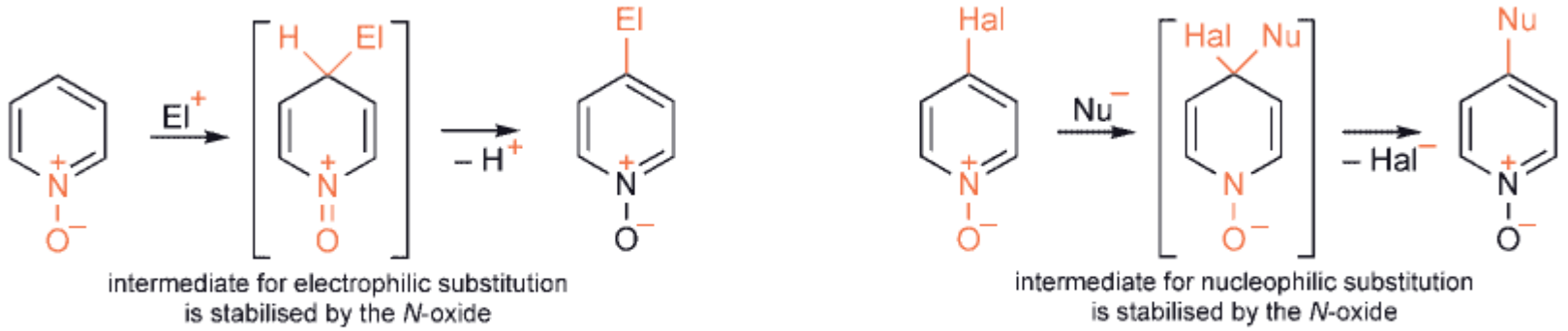




Neg. charge i α,γ pos.

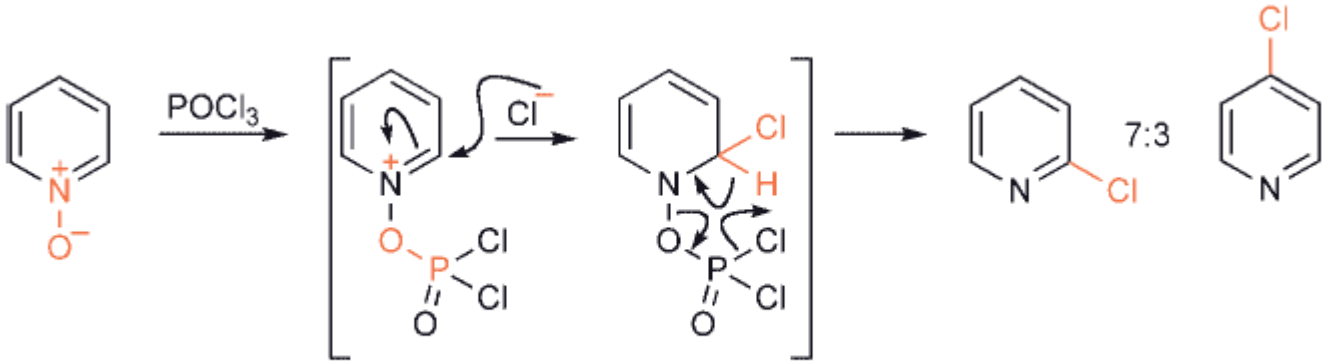
More activated for electrophilic and nucleophilic attack

N-oxide chemistry, which self-evidently has no parallel in benzenoid chemistry, is an extremely important and useful aspect of the chemistry of azines. The structure of *N*-oxides means that they are both more susceptible to electrophilic substitution *and* react more easily with nucleophiles – an extraordinary concept when first encountered. On the one hand, the formally negatively charged oxygen can release electrons to stabilise an intermediate for electrophilic attack and, on the other, the positively charged ring nitrogen can act as an electron sink to encourage nucleophilic addition.



The *N*-oxide group facilitates both electrophilic *and* nucleophilic substitutions

There are a number of very useful processes in which the *N*-oxide function allows the introduction of substituents, usually at an α position, and in the process the oxide function is removed; reaction with phosphoryl chloride is an example.



Conversion of pyridine *N*-oxide into halopyridines (mechanism shown for α-substitution)

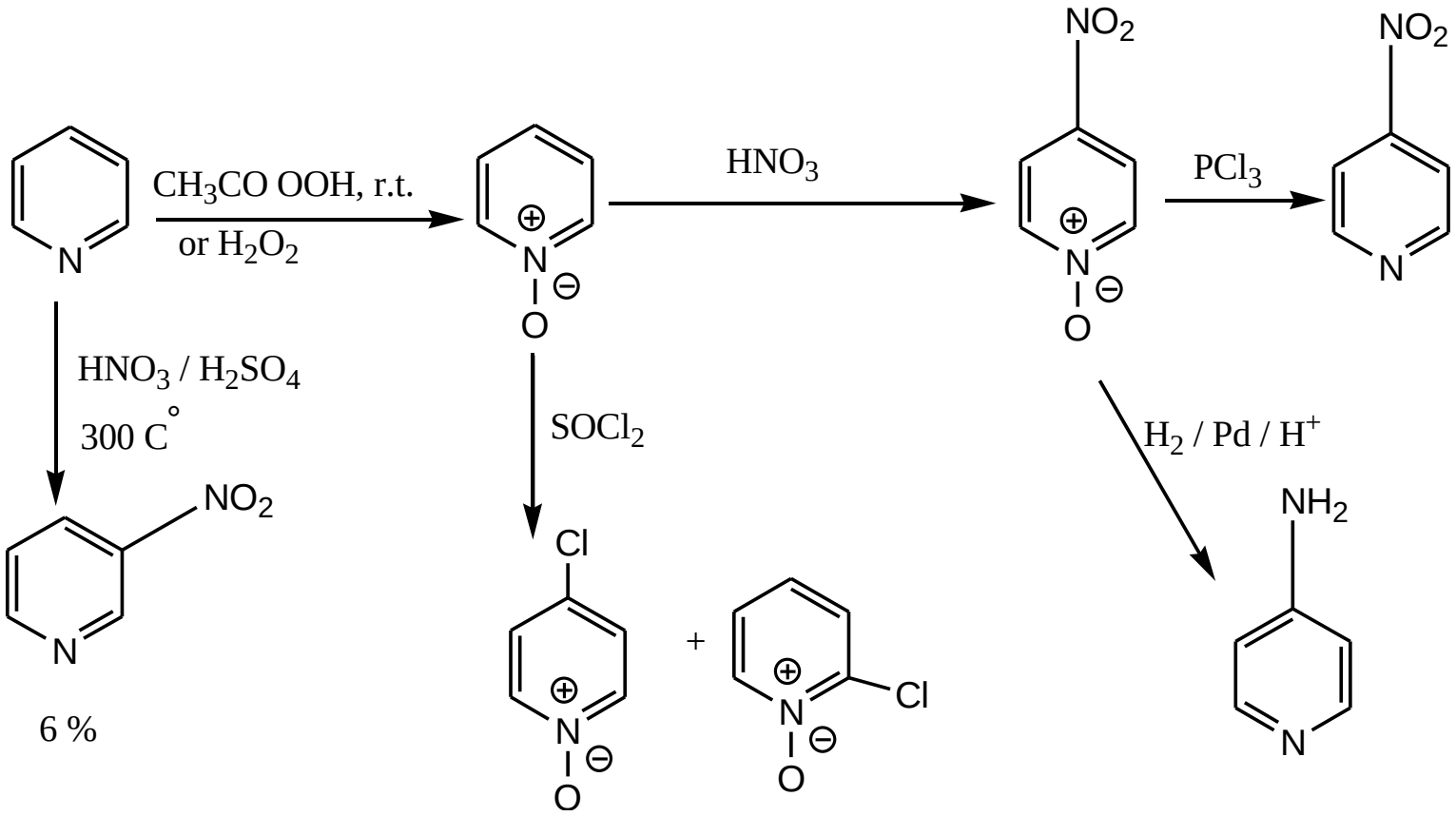
N-oxide pyridine

- As appears from the previous canonical forms , there are positive and negative charges at positions 2 and 4 thus N-oxide pyridine is more activated for electrophilic and nucleophilic attack at these positions than pyridine itself.

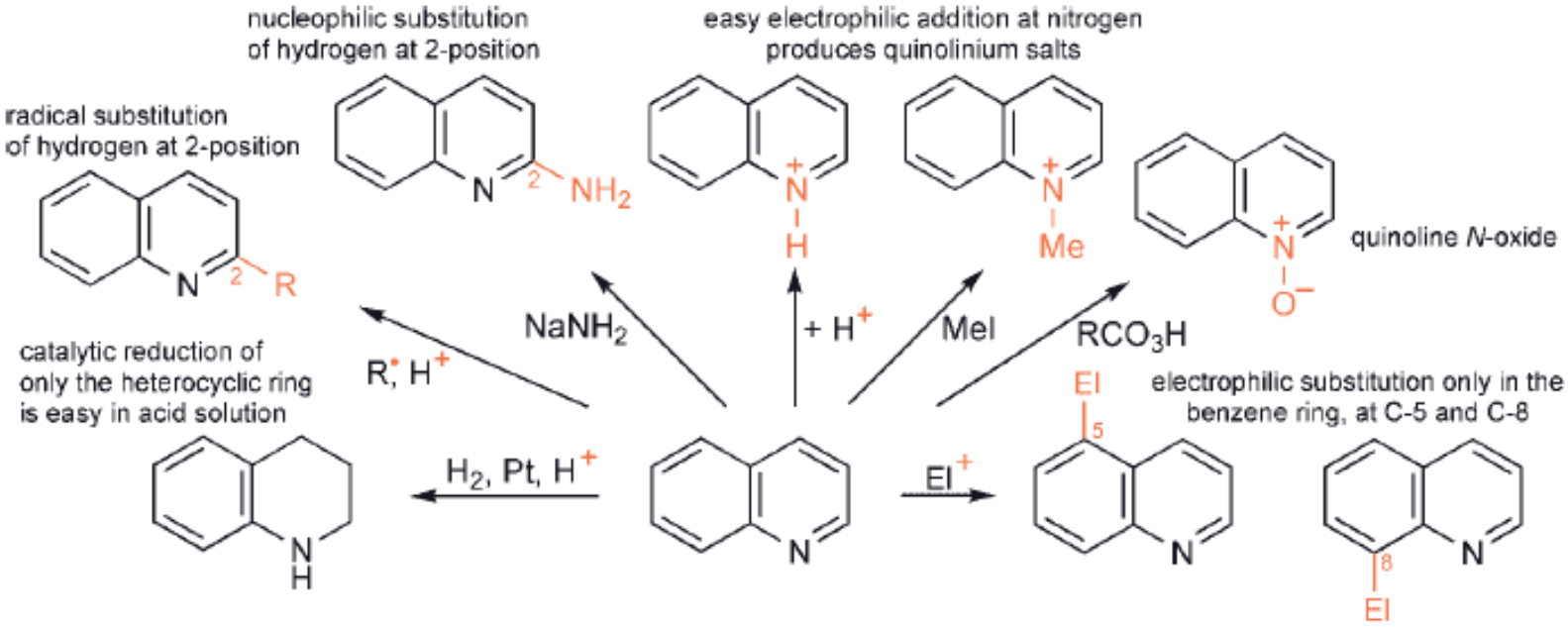
- N-oxide pyridines are very important intermediates for preparing pyridine derivatives that are difficult to prepare due to the easiness of removal of oxygen atom by reduction.

- For instance, nitration of pyridine is very difficult and low yielding reaction and it occurs at position 3, however using N-oxide pyridine will direct the nitration to position 4 and then the oxygen can be easily removed by reduction as shown in the following scheme.

Reactions of N-oxide pyridine

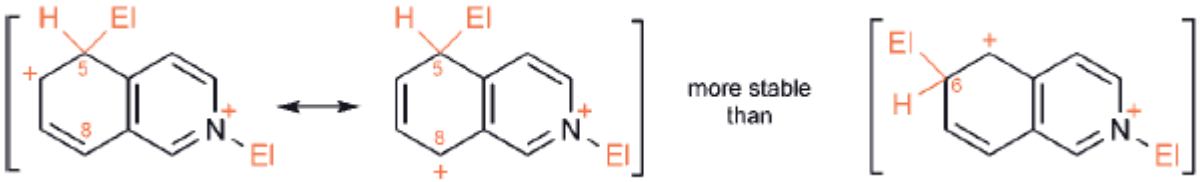


Typical reactions of quinoline (isoquinoline is very similar)

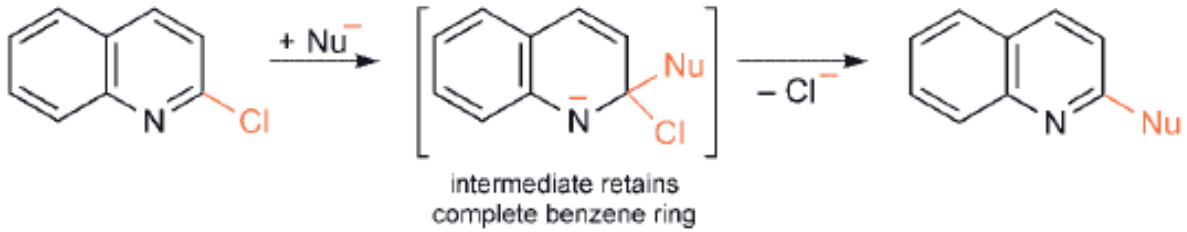


Electrophilic substitution favours the benzenoid ring, rather than the pyridine ring. Regioselectivity, which in naphthalene favours an α-position, is mirrored in quinoline/isoquinoline chemistry by preferred substitution at the 5 - and 8 - positions. It should be noted that such substitutions usually involve attack on the species formed by electrophilic addition (often protonation) at the nitrogen, which has the effect of further discouraging (preventing) attack on the heterocyclic ring.

Just as for naphthalene, the regiochemistry of attack is readily interpreted by looking at the possible intermediates: those for attack at C - 5/8 allow delocalisation of charge, while an intermediate for attack at C - 6/7 would have a localised charge.



Just as quinoline and isoquinoline are reactive towards electrophiles in their benzene rings, so they are reactive to nucleophiles in the pyridine ring, especially (see above) at the positions α and γ to the nitrogen and, further, are more reactive in this sense than pyridines.
This is consistent with the structures of the intermediates for, in these, a full and complete aromatic benzene ring is retained. Since the resonance stabilisation of the bicyclic aromatic is considerably less than twice that of either benzene or pyridine, the loss in resonance stabilisation in proceeding from the bicyclic system to the intermediate is considerably less than in going from pyridine to an intermediate adduct. There is an obvious analogy: the rate of electrophilic substitution of naphthalene is greater than that of benzene for, in forming a σ-complex from the former, less resonance energy is sacrifi ed.



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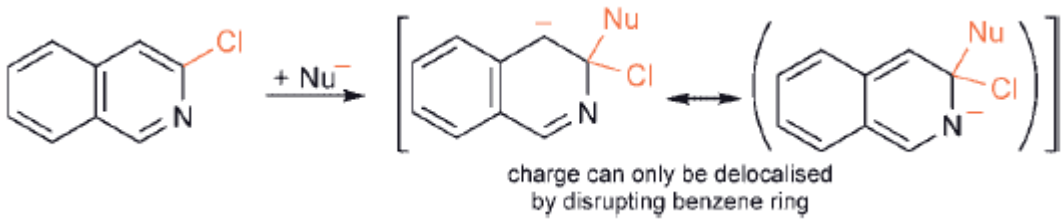
Q: Why 3 - Haloisoquinolines do not undergo easy nucleophilic substitution?



Ans: Because 3-halo-isoquinoline cannot achieve delocalisation of negative charge onto the nitrogen unless the aromaticity of the benzene ring is disrupted. Therefore, such intermediates are considerably less stabilised and reactivity considerably tempered.