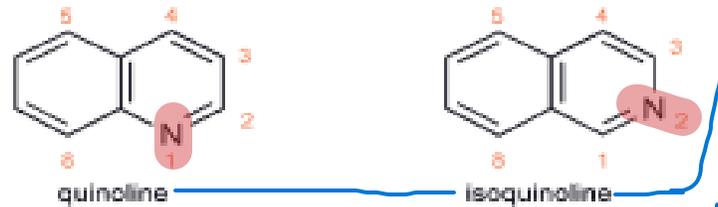


Quinolines and Isoquinolines: Reactions and Synthesis



is liquid

solid

the same composed from pyridine attached to benzene ring and the same reaction just differ in position of N.

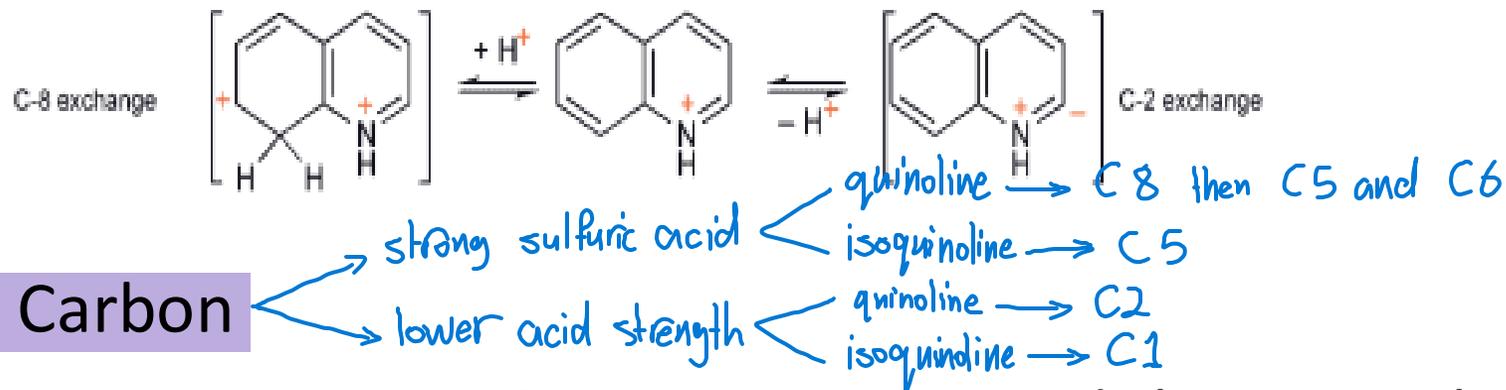
- Quinoline is a high - boiling liquid; isoquinoline is a low - melting solid; each has a sweetish odour.
- Both bases have been known for a long time: quinoline was first isolated from coal tar in 1834, isoquinoline from the same source in 1885.
 - الكوينولين تم اكتشافه قبل
 - لأهم الشجرة التي هي مصدر الكوينولين وايزوكوينولين
- Shortly after the isolation of quinoline from coal tar,
- it was also recognised as a pyrolytic degradation product of cinchonamine, an alkaloid closely related to quinine, from which the name quinoline is derived; the word quinine, in turn, derives from quina, a Spanish version of a local South American name for the bark of quinine - containing Cinchona species

- Reactions with Electrophilic Reagents

- 9.1.1 Addition to Nitrogen

- All the reactions noted in this category for pyridine which involve donation of the nitrogen lone pair to electrophiles, also occur with quinoline and isoquinoline, for example the **respective pKaH values, 4.94 and 5.4, show them to be of similar basicity to pyridine.** Each, like pyridine, **readily forms** an N - oxide and quaternary salts.

← الإضافة تكون على النيتروجين لأن quinoline و isoquinoline سلوكهم نفس سلوك بيريدين الذي على ذرة N
التي فيه lone pair تتفاعل مع مركبات أخرى.



Substitution at Carbon

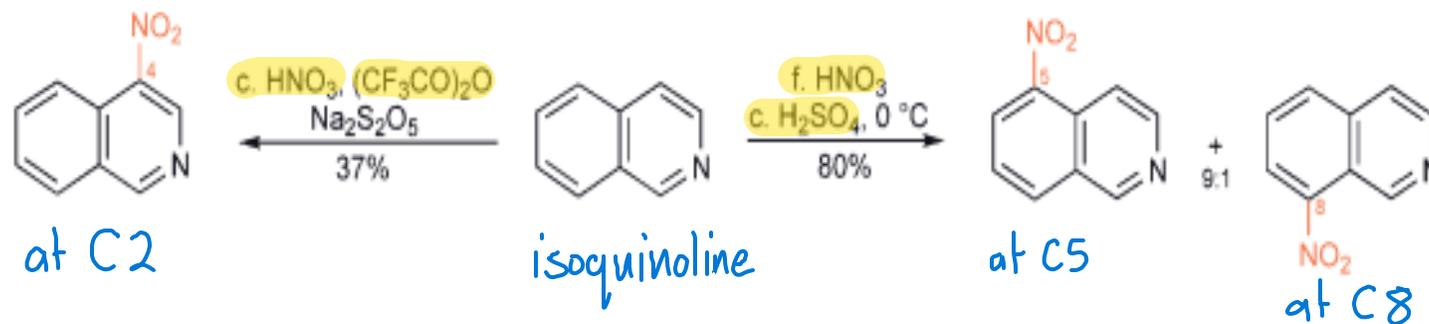
- Proton Exchange Benzene ring C - protonation, and thence exchange, via N - protonated quinoline, requires strong sulfuric acid and occurs fastest at C - 8, then at C - 5 and C - 6; comparable exchange in isoquinoline takes place somewhat faster at C - 5 than at C - 8.
- 1 At lower acid strengths each system undergoes exchange α to nitrogen, at C - 2 for quinoline and C - 1 for isoquinoline.
- These processes involve a zwitterion produced by deprotonation of the N - protonated heterocycle

في تسمية بالبنية ووجودها
بعض

↳ remove proton (H⁺)

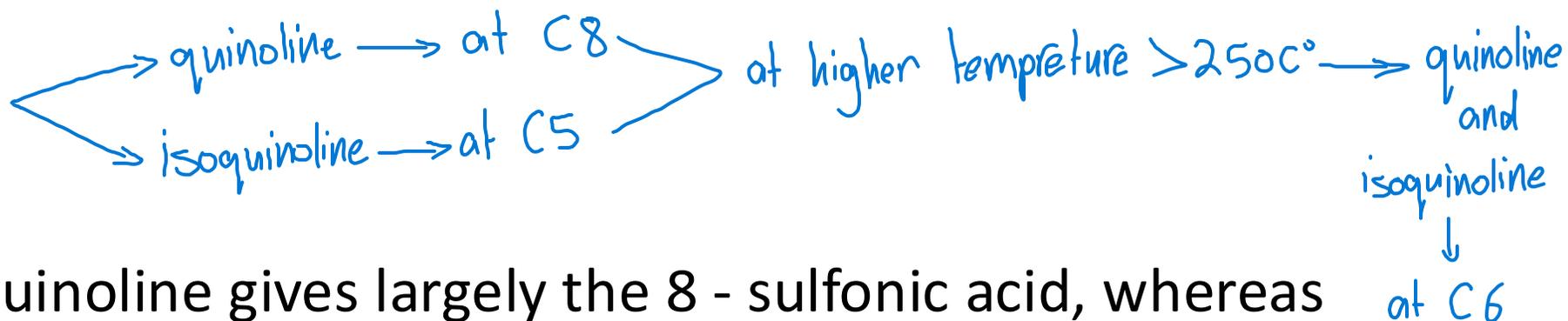
- Nitration
 - quinoline equal amount at position C5 and C8 when nitration
 - isoquinoline at C5

- The positional selectivity for proton exchange is partly mirrored in nitrations, quinoline gives approximately equal amounts of 5 - and 8 - nitro - quinolines, whereas isoquinoline produces almost exclusively the 5 - nitro - isomer

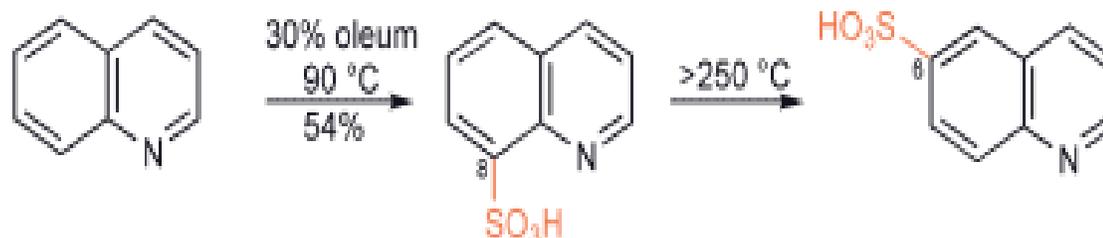


Sulfonation

↳ add sulfur group



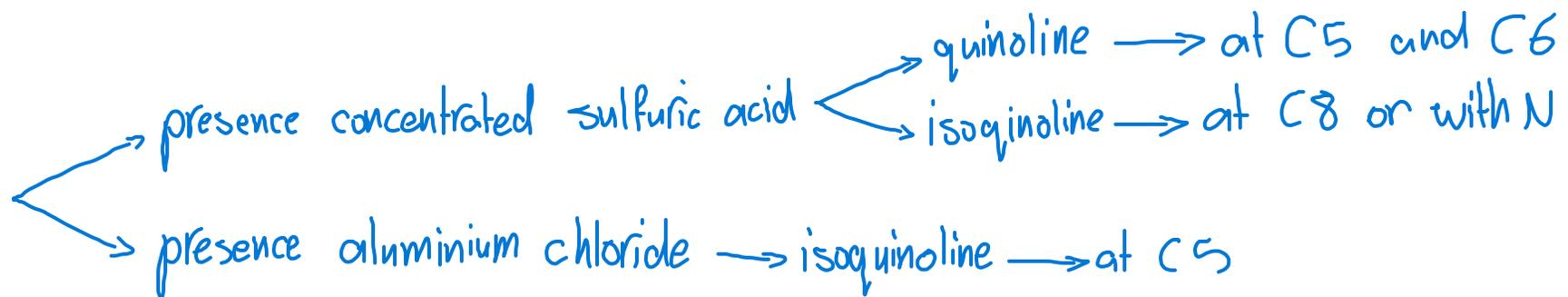
- Sulfonation of quinoline gives largely the 8 - sulfonic acid, whereas isoquinoline affords the 5 - acid.
- Reactions at higher temperatures produce other isomers, under thermodynamic control, for example both quinoline 8 - sulfonic acid and quinoline 5 - sulfonic acid are isomerised to the 6 - acid



- Acylation and Alkylation There are no generally useful processes for the introduction of carbon substituents by electrophilic substitution of quinolines or isoquinolines.

Halogenation

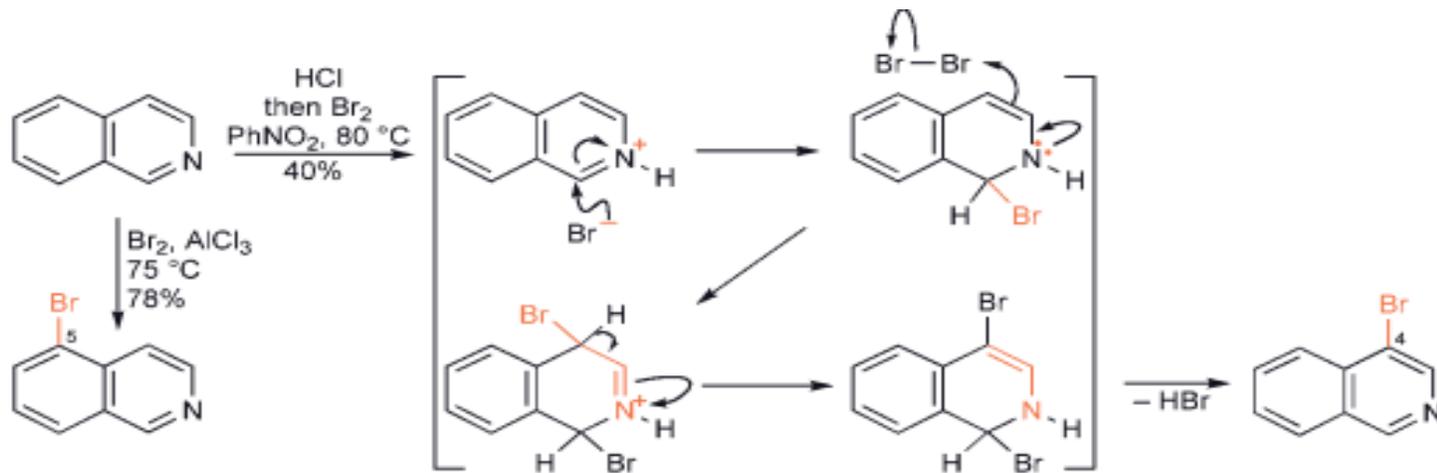
↳ add halogen



- Ring substitution of quinoline and isoquinoline by halogens is rather **complex**, products **depending on the conditions used**.
- In concentrated sulfuric acid, quinoline gives a mixture of 5 - and 8 - bromo derivatives; comparably, isoquinoline is efficiently converted into the 5 - bromo - derivative in the presence of aluminium chloride, 8 or with N - bromosuccinimide in concentrated sulfuric acid

Halide addition to salt initiate \rightarrow quinoline at C3
 \rightarrow isoquinoline at C4

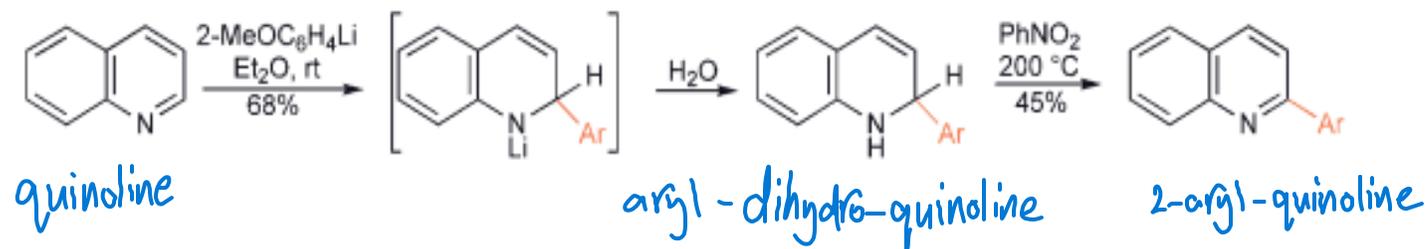
- Introduction of halogen to the hetero - rings occurs under remarkably mild conditions in which halide addition to a salt initiates the sequence. Thus treatment of quinoline or isoquinoline hydrochlorides with bromine produces 3 - bromoquinoline and 4 - bromoisoquinoline, respectively, as illustrated below for the latter



Reactions with Nucleophilic Reagents



- Nucleophilic Substitution with 'Hydride' Transfer Reactions of this type occur fastest at C - 2 in quinoline and at C - 1 in isoquinolines.
- Alkylation and Arylation
- The immediate products of addition of alkyl and aryl Grignard reagents and alkyl - and aryl lithiums are dihydro - quinolines and - isoquinolines and can be characterised as such, but can be oxidised to afford the C - substituted, re - aromatised heterocycles; illustrated below is a 2 - arylation of quinoline



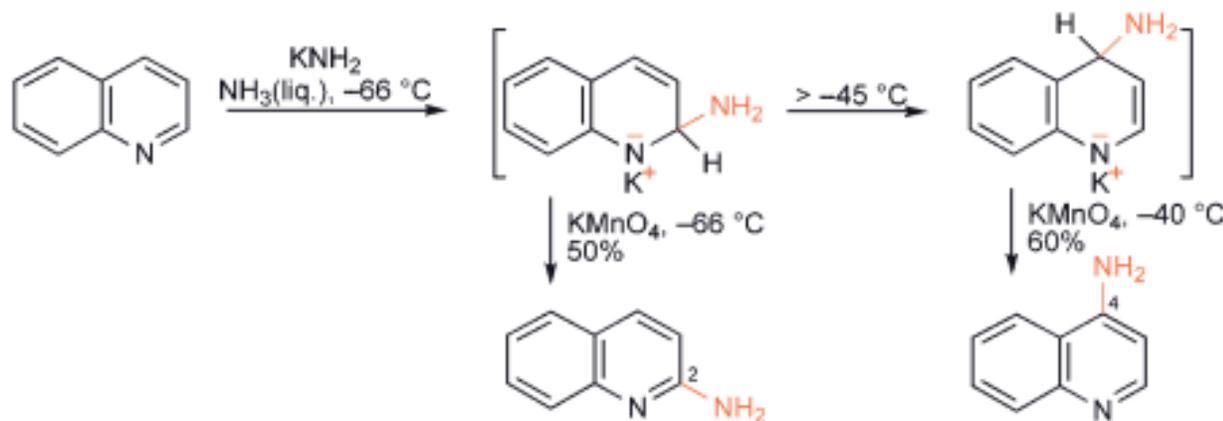
Amination and Nitration

→ quinoline → at C2 (main), C4 (minor)
↳ more stable at high temperature (from C2 to C4)

→ isoquinoline → at C1

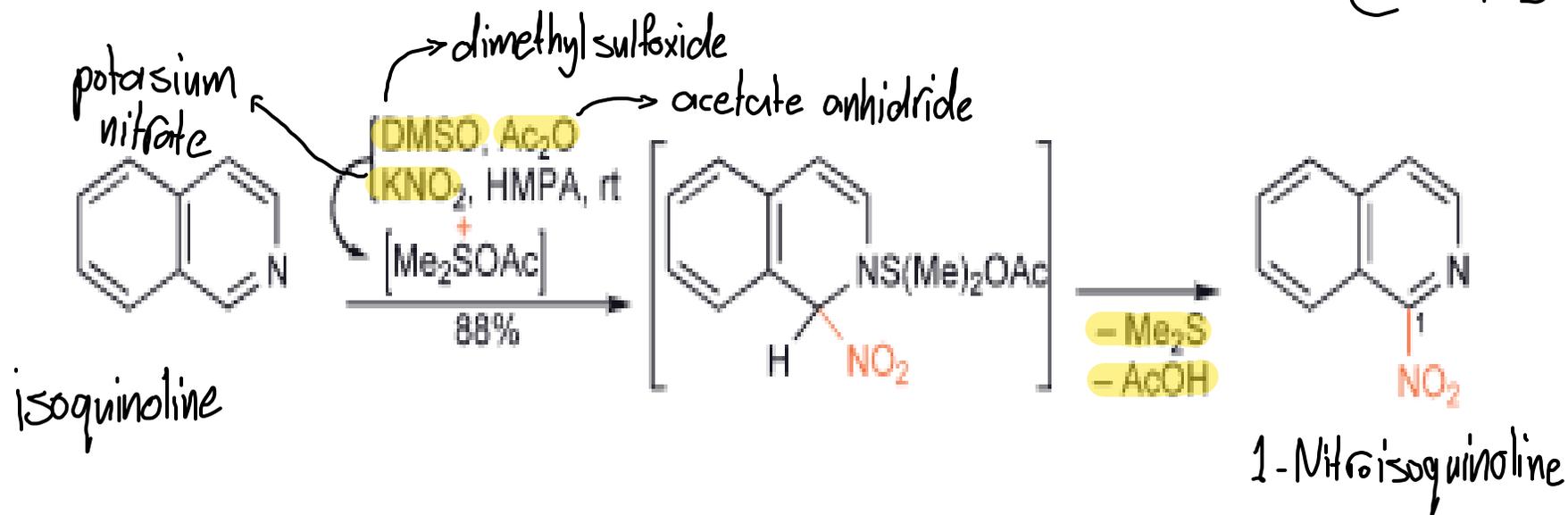
NaNH_2

- Sodium amide reacts rapidly and completely with quinoline and isoquinoline, even at -45°C , to give dihydro-adducts with initial amide attack at C - 2 (main) and C - 4 (minor) in quinoline, and C - 1 in isoquinoline.
- The quinoline 2-adduct rearranges to the more stable 4-aminated adduct at higher temperatures. 21 Oxidative trapping of the quinoline adducts provides 2- or 4-aminoquinoline; isoquinoline reacts with potassium amide in liquid ammonia at room temperature to give 1-aminoisoquinoline



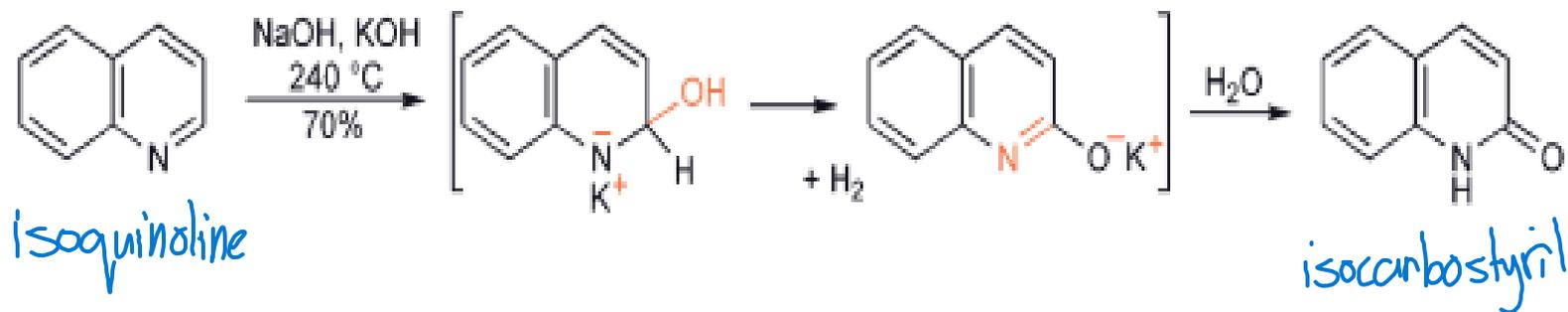
- The introduction of a nitro group at C - 1 in isoquinolines can be achieved using a mixture of potassium nitrite, dimethylsulfoxide and acetic anhydride. The key step is the **nucleophilic addition of nitrite to the heterocycle** previously quaternised by reaction at nitrogen with a **complex of dimethylsulfoxide and the anhydride** →

لما يتفاعل مع هذا المركب يصبح +ve



- Hydroxylation
 - isoquinoline \rightarrow 2-quinoline \rightarrow carbostyryl
 - quinoline \rightarrow 1-isoquinoline \rightarrow isocarbostyryl
 > isolated product
- Both quinoline and isoquinoline can be directly hydroxylated with potassium hydroxide at high temperature with the evolution of hydrogen. 2 - Quinolone (' carbostyryl ') and 1 - isoquinolone (' isocarbostyryl ') are the isolated products

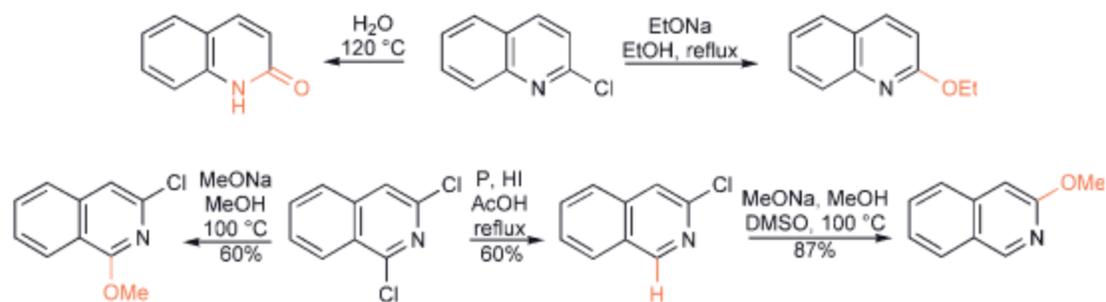
عاز الهيدروجين



Nucleophilic Substitution with Displacement of Good Leaving Groups

- The main principle here is that halogen on the homocyclic rings of quinoline and isoquinoline, and at the quinoline - 3 - and the isoquinoline - 4 positions, behaves as would a halo - benzene. In contrast, 2 - and 4 - halo - quinolines and 1 - halo - isoquinolines have the same susceptibility as α - and γ - halopyridines. 3 - Halo - isoquinolines are intermediate in their reactivity to nucleophiles

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Synthesis : ch. 2 and 3