Quinolines and Isoquinolines: Reactions and Synthesis

للحفظ 📌

Quinoline = Benzo[b]pyridine

أما:

Isoquinoline = Benzo[c]pyridine

Q19. Quinoline is also known as:

A. Benzo[c]pyridine
B. Benzo[b]pyridine
C. Benzo[d]pyridine
D. Dibenzopyridine

- 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.
- 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

The IUPAC systematic name for quinoline is benzo[b]pyridine.

A) True
B) False

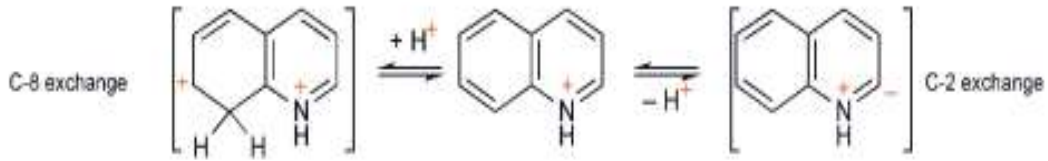
Correct Answer: A) True

Quinoline is only a synthetic heterocyclic compound.

A) True
B) False

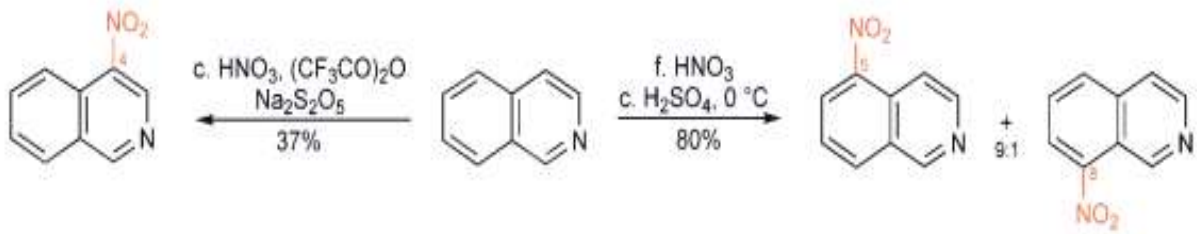
Correct Answer: B) False

- 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 p KaH 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.



- 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

- Nitration
- 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



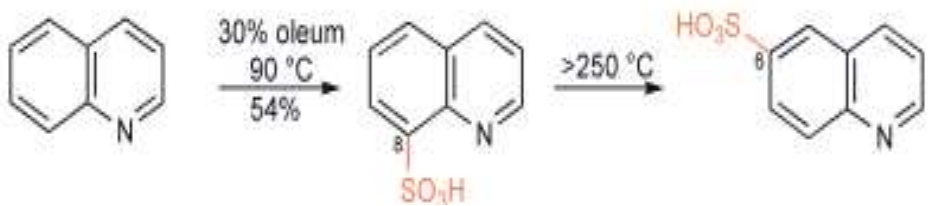
Sulfonation

Upon reaction, nitration of isoquinoline yields the 5-nitro isomer, while sulfonation of quinoline gives largely the 8-sulfonic acid.

A) True
B) False

Correct Answer: A) True

- 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

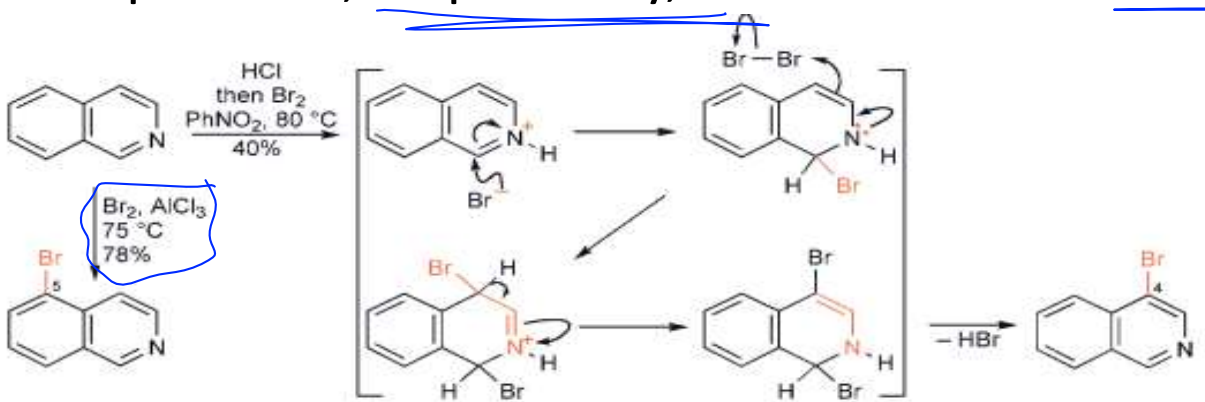


- Acylation and Alkylation There are no generally useful processes for the introduction of carbon substituents by electrophilic substitution of quinolines or isoquinolines.

Halogenation

- 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

- 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



Q23. In hydride transfer reactions, nucleophilic substitution occurs at _____ in quinoline.

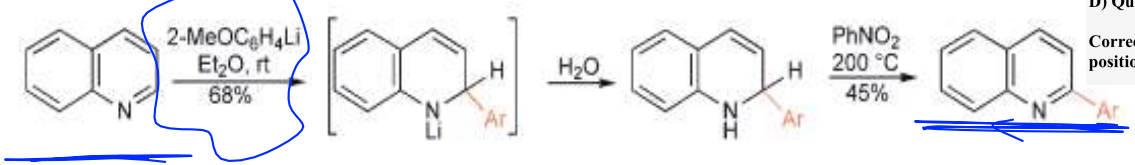
A. C-1
B. C-2
C. C-4
D. C-8

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

الخلاصة النهائية

- C-2 = بداية التفاعل
- C-4 = نتيجة الاستبدال بعد hydride transfer



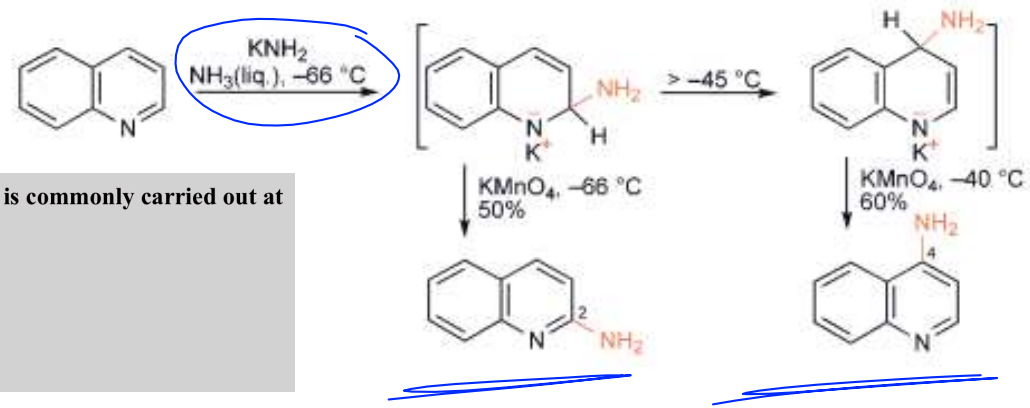
Which statement is correct for nucleophilic substitution?

A) Quinoline reacts at position 4; Isoquinoline reacts at position 2.
B) Quinoline reacts at position 3; Isoquinoline reacts at position 3.
C) Quinoline reacts at position 2; Isoquinoline reacts at position 1.
D) Quinoline reacts at position 2; Isoquinoline reacts at position 4.

Correct Answer: C) Quinoline reacts at position 2; Isoquinoline reacts at position 1.

Amination and Nitration

- 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



Q31. Amination of quinoline is commonly carried out at approximately:

A. 0°C
B. -20°C
C. -40°C
D. -100°C

Isoquinoline

Amination

$NH_2^- \rightarrow$ C-1

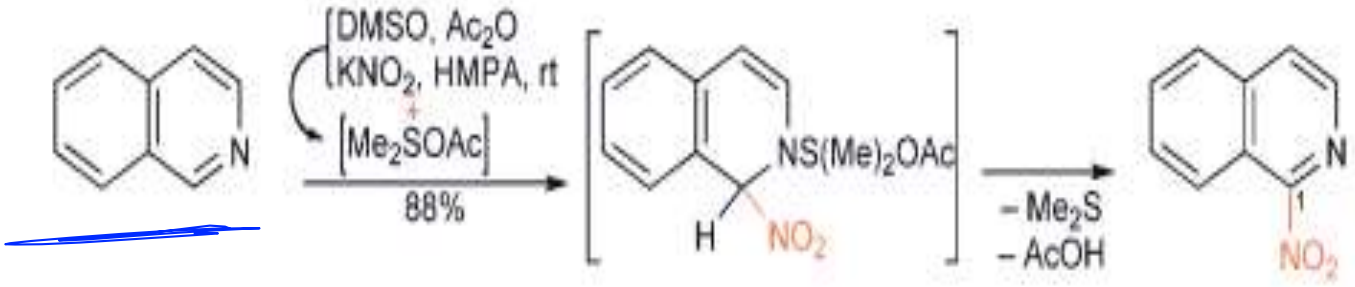
Nitration (بهذه الطريقة الخاصة)

$NO_2^- \rightarrow$ C-1

يعني:

C-1 هو أهم موقع للهجوم النيوكليوفيلي في isoquinoline

- 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



Quinoline

✅ KOH + حرارة عالية

✅ الناتج:

2-Quinolone (Carbostyril)

✅ الموقع:

C-2

Isoquinoline

✅ KOH + حرارة عالية

✅ الناتج:

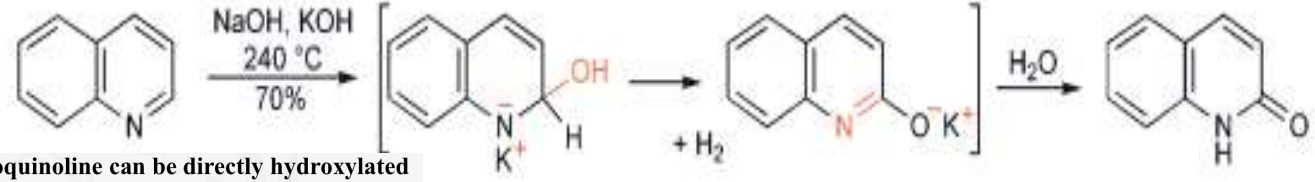
1-Isoquinolone (Isocarbostyril)

✅ الموقع:

C-1

- Hydroxylation

- Both quinoline and isoquinoline can be directly hydroxylated with potassium hydroxide at high temperature with the evolution of hydrogen. 2 - Quinolone (‘ carbostyril ’) and 1 - isoquinolone (‘ isocarbostyril ’) are the isolated products



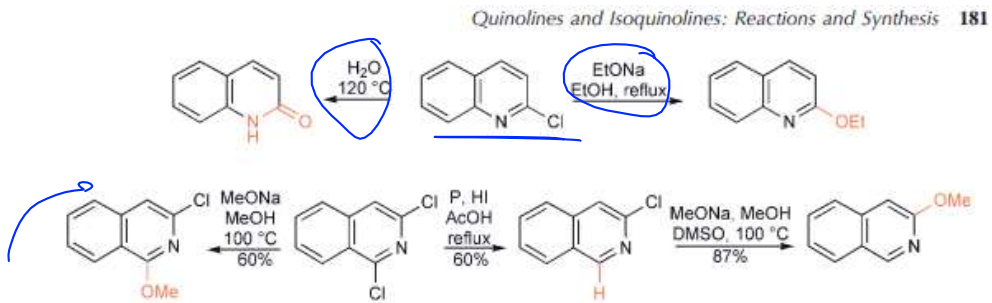
Both quinoline and isoquinoline can be directly hydroxylated with potassium hydroxide at high temperature with the evolution of hydrogen.

A) True
B) False

Correct Answer: A) True

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



Synthesis : ch. 2 and 3