QUINOLINE: A VERSATILE HETEROCYCLIC

ParminderKaur, Paramveer Singh

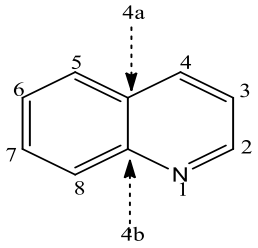
University Institute of Pharma Sciences, Chandigarh University

Introduction

Heterocyclic are abundant in nature and are of great significance to life because theirstructural subunits exist in many natural products such as vitamins, hormones, antibiotics and alkaloids, as well as in pharmaceuticals, herbicides, dyes, and many more compounds.[1]These heterocyclic have great importance in drug discovery as theheteroatoms present in them make hydrogen bonds with the receptors present in thebody and thus giving their significant pharmacological actions. Out of severalheterocyclic compounds, those with Nitrogen atom in their structure give promisingpharmacological activities. According to the literature quinoline and piperazine derivatives are one of the emerging drugs of therapeutic importance showing a widespectrum of biological activities which are discussed here in this chapter.

Nucleus Profile

Structure: Quinoline ring structure is obtained by *o*-condensation of benzene ringwith pyridine. It is also known as 2,3-benzopyridine, 1-azanaphthalene, 1-benzazine,leucoline. In quinoline, the nitrogen atom is one atom away from the position at whichthe rings are fused. The numbering in quinoline commences from the nitrogen atomwhich is assigned position C_1.



The bond lengths of quinolines, which are irregular, support the resonancedescription; thus, the 1,2-, 5,6- and 7,8-linkages are shorter than that of the carbon bond in benzene (more double bond character). There is also a dipole of 2.9 Ddirected towards the nitrogen atom.[2]

Physical Properties

Molecular formula- C_9H_7N

Molar Mass- 129.16 g/mol

Appearance- Yellowish oily liquid

Density- 1.093 g/ml

Boiling point- 237 °C

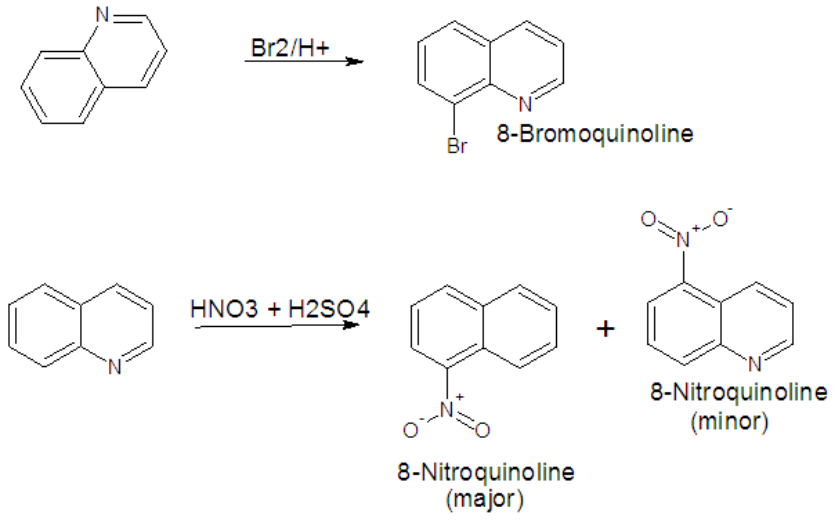
Melting point- 15 °C

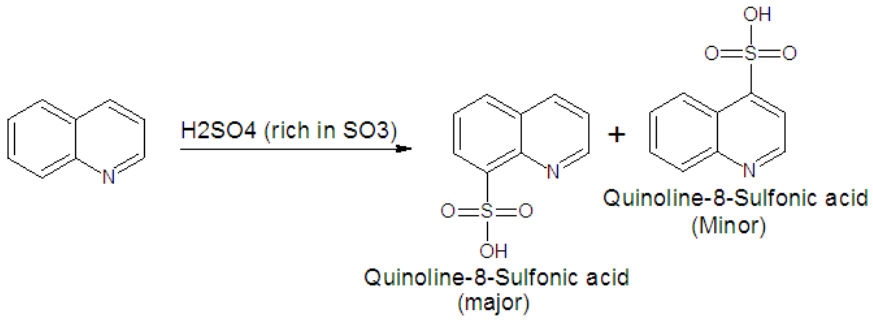
Solubility Slightly soluble in water, soluble in alcohol, ether and CS_2

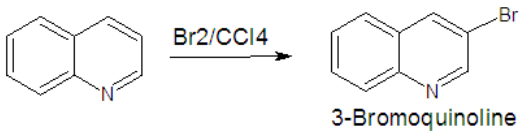
Reactivity

a. **Basicity**: Quinoline is a basic molecule and it forms quaternary salts with acids and haloalkanes. Since it is a fused molecule containing two nucleus *i.e.* benzene and pyridine, so it resembles in reactions with them. The presence of electron donating groups at 2 and 4 positions of quinoline increases the basicity. The pyridine ring in quinoline is electron deficient.

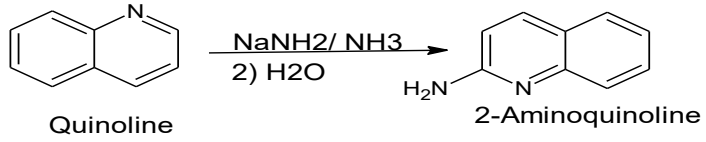
b. **Electrophillic Aromatic substitution reactions**: Electrophillic substitution reactions occur on the benzene ring as pyridine ring is electron deficient as compared to benzene. So in fused ring system electrophile attacks preferably on electron rich benzene ring. These reactions occur at 8- and 5-positions and are summarized here as follows:

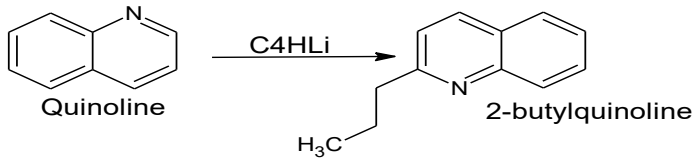


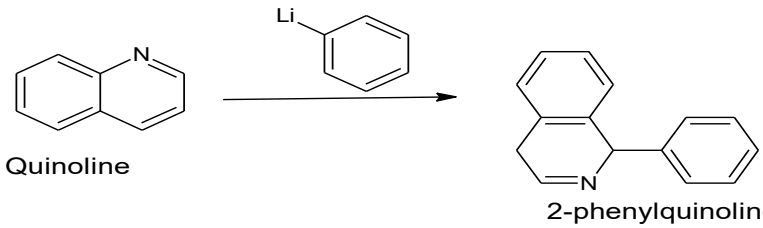




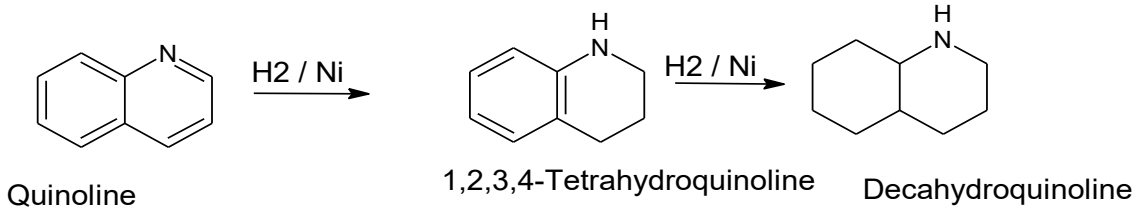
c. Nucleophillic aromatic substitution reactions: Nucleophillic reactions undergo attack at position 2- and 4, *i.e.* to the electron deficient pyridine ring. The reactions are summarized as follows:



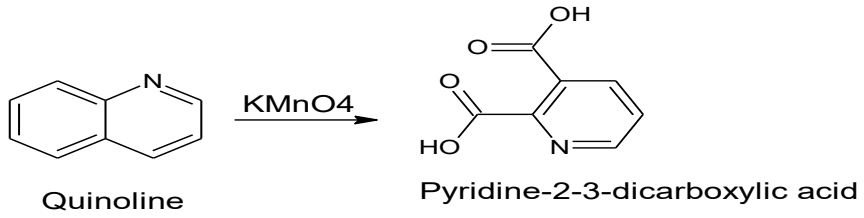




d. Reduction: 1,2,3,4-tetrahydroquinoline is formed by catalytic hydrogenation of quinoline in the presence of nickel. Further reduction results in the formation of decahydroquinoline *via* reduction of benzene ring.



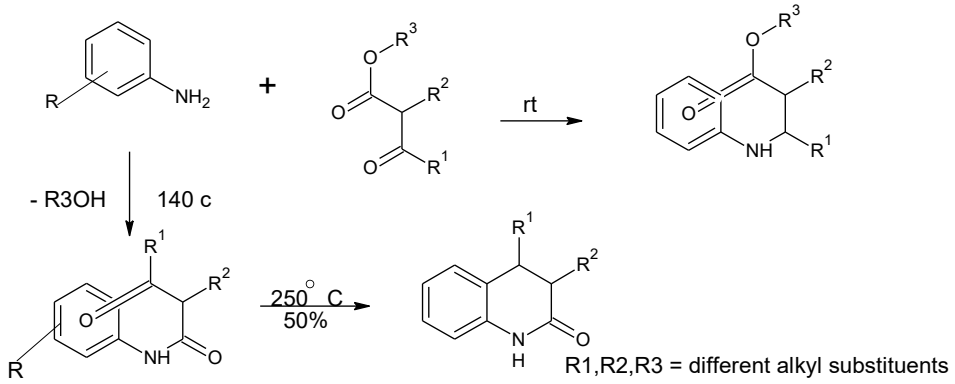
e. Oxidation: Oxidation of quinoline results in the formation of pyridine 2,3-dicarboxylic acid in the presence of potassium permanganate.[3]



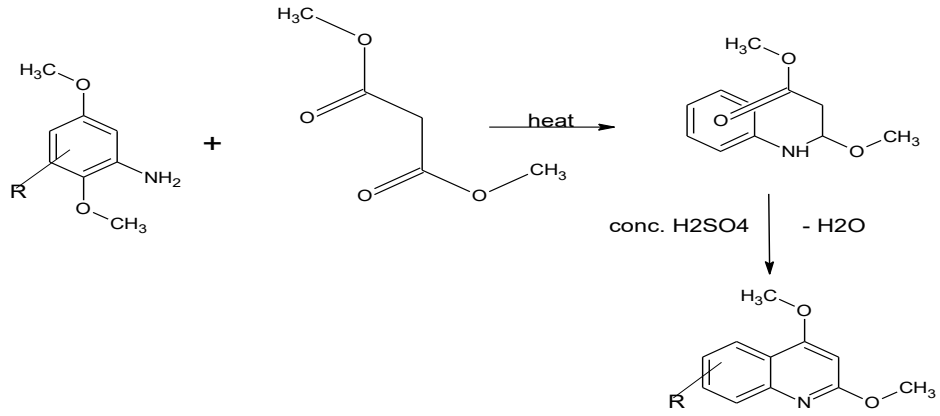
General methods of synthesis

I) Quinolines from arylamine and 1,3-dicarbonyl compounds

a. The Conard-Limpach-Knorr synthesis: It uses anilines and *β*-keto esters that can react at low temperature to give *β*-aminoacrylate which on cyclization gives 4-quinolone. At higher temperature, *β*-keto ester anilides are formed and their cyclization leads to form 2-quinolones. *β*-Aminoacrylates can also be prepared *via* the addition of anilines to acetyllinic esters.[4]

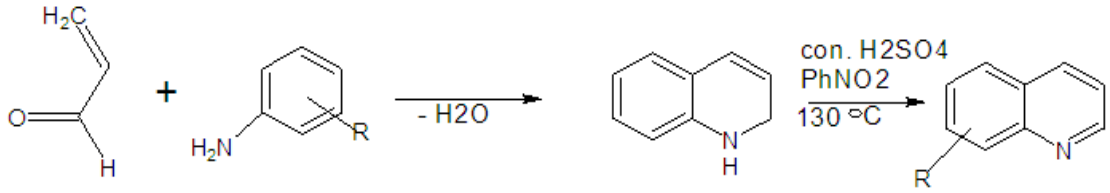


b. The Combes synthesis: It involves the condensation of 1,3-dicarbonyl compound with an aryl amine resulting in formation of *β*-amino-enone which is further cyclized by concentrated acid. It is followed by loss of water molecule to give quinoline.[5]



II) Quinolines from aryl amine and α,β-unsaturated carbonyl compounds :

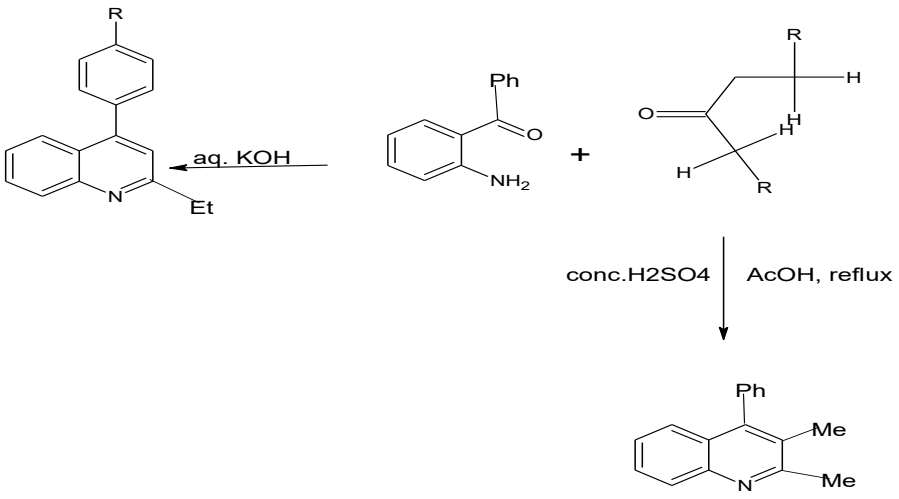
a. The Skraup synthesis: When aniline, concentrated sulphuric acid, glycerol and mild oxidizing agent are heated together, quinoline is produced as an extraordinary reaction. Reaction proceeds *via* dehydration of glycerol to acrolein. The Skraup synthesis is the best for ring synthesis of quinolones un-substituted on the hetero-ring.[6]



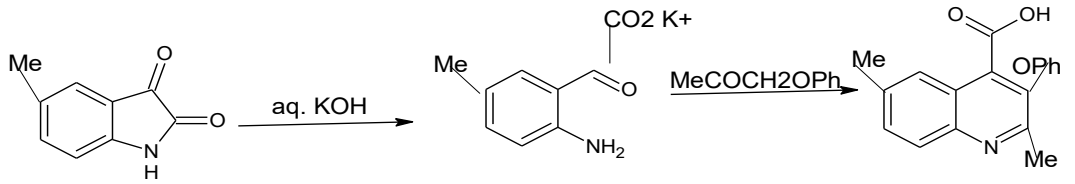
III) Quinolines from ortho-acylarylamines and carbonyl compounds:

a. The Friedlander synthesis: Friedlander synthesis involves condensation followed by cyclo dehydration between an aromatic 2-aminoaldehyde or ketone with an α-methylene functionality. Friedlander reaction can occur under base, Bronsted acids, Lewis acid, inorganic salt or ionic liquid-catalyzed conditions. Better yields observed with acid catalysed reaction.

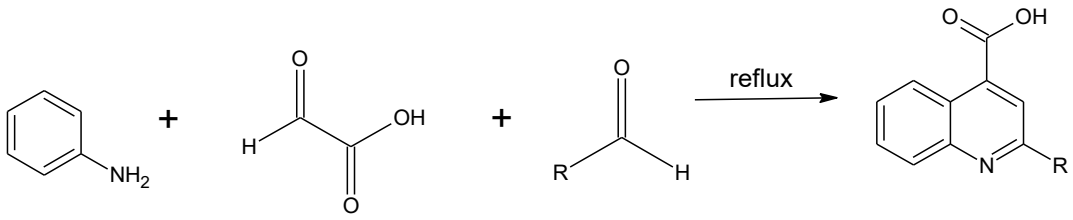
Recently, Yao and co-workers reported an easy and efficient synthesis of 3-nitroquinoline derivatives from *o*-aminobenzaldehyde and *β*-nitrostyrenes in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) and silica gel[7].This one-potreaction represents an interesting variation in the Friedlander type quinoline synthesis.[8]



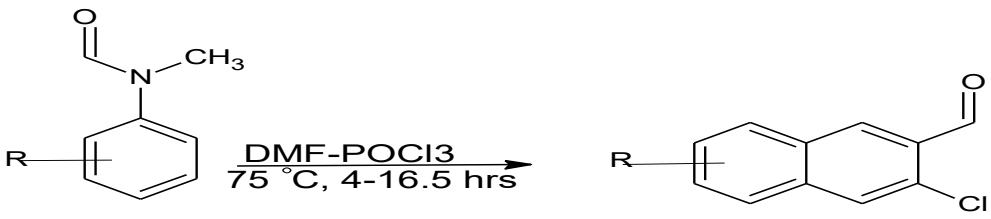
b. The Pfitzinger synthesis: In 1886 Pfitzinger reported a formal extension of theknown Friedlander protocol for the synthesis of quinolic acid which is known as Pfitzinger synthesis (also known as the **Pfitzinger-Borsche reaction**). *o*-Aminoaraldehydes are sometimes difficult to access. In this modification, isatins, which are easy to synthesise, are hydrolysed to *o*-aminoarylglyoxalates, which react with ketones affording quinoline-4-carboxylic acids.[9]



c. Doebner reaction: The Doebner reaction is the one pot chemical reaction ofaniline with an aldehyde and pyruvic acid to form quinoline-4-carboxylic acids.[10]



d. Vilsmeier-Haack synthesis: In 1978, the group of Meth-Cohn demonstrated apractically simple procedure in which acetanilide was efficiently converted into 2-chloro-3-quinolinecarboxaldehyde in 68% yield[11].This type of quinoline synthesis was termed as **"Vilsmeier Approach"** by Meth-Cohn.[12]



Spectral Data

IR spectra: The IR spectra of quinoline is characterized by the bonds at 1690-1640cm^{-1} (C=N), 1600-1475 cm^{-1} (C=C), 2920.12 cm^{-1}(C-H).

NMR spectra: The position of quinoline in^{1}H NMR (δ)is 7.26-8.81 (7H, Ar-H) and in ^{13}C NMR is 121.5-150.1 (7C, -CH), 128.5 & 148.9 (C).

Mass spectra: Mass spectra of quinoline showed moleclular ion peak M^{+}at value of130.06 for molecular weight (129.06).

References

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