CHAPTER 1: SYNTHESIS AND REACTIVITY OF QUINOLINE

1.0 Introduction of quinoline

Quinoline **(1)** is a heterocyclic compound that gets attention because of their present in nature.[1-3] Quinoline **(1)** consists of a benzene ring and a pyridine ring which are fused through carbon bond as shown in Figure 1.1. It has the molecular formula of C_9H_7N and is a colourless hygroscopic liquid with a strong odour.

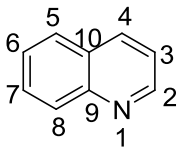

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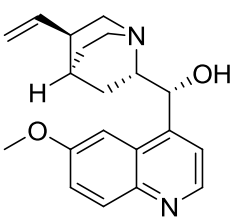
Figure 1.1: **Structure and numbering of quinoline**

It was firstly produced from coal tar in 1834. [4]It has been found that quinoline activity is important in biological activities such as antibacterial,[5] therapeutic antitumor agents,[6-7] anti-tuberculosis agents [8-9] and immunosuppressive activity.[10] Quinoline compounds are also use as antimalarials treatment [11] such as quinine **(2)**, amodiaquine **(3)** and primaquine **(4)**.



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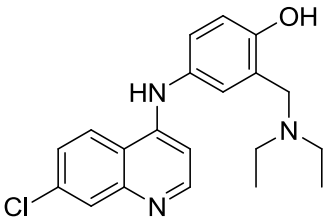

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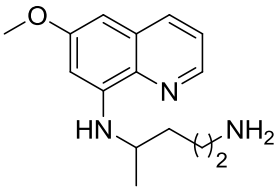

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1.2 Synthesis of Quinoline

Many synthetic methods have been developed to synthesize quinolines and their substituted compounds. Traditional synthesis methods of quinolines such as Skraup,[12] Doebner-von Miller, Combes and Friedländer [13] has been widely used and there is also some modifications of these methods to produce better percentage of yield and conform to recent environmental standards. [14-15]

1.2.1 Skraup synthesis

This reaction is named after the Czech chemist Zdenko Hans Skraup (1850-1910). Quinoline **(1)** was prepared when aniline **(5)** and concentrated sulfuric acid acts as a dehydrating agent, glycerol and a mild oxidizing agent such as nitrobenzene, stannic chloride, ferric salts, oxygen, or arsenic pentoxide were heated together to produce 1, 2-dihydroquinoline **(6).** Dehydrogenation by an oxidizing agent gave quinoline **(1)** as the product as shown in Figure 1.2.

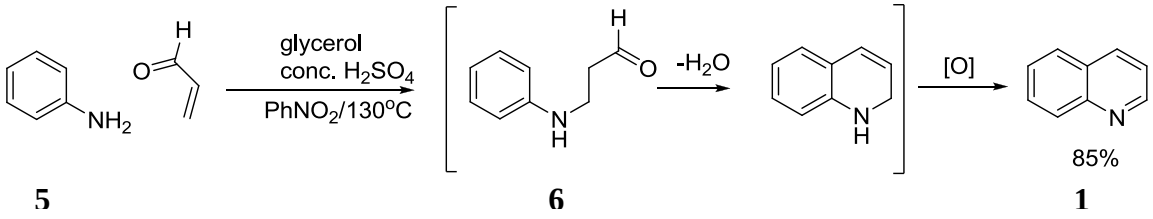
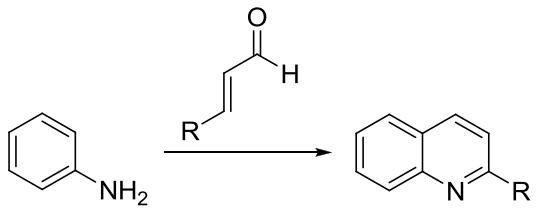


Figure 1.2: Skraup synthesis of quinoline

1.2.2 Doebner-von Miller synthesis

This reaction is name after Germans Oscar Döbner (Doebner) (1850-1907) and Wilhelm von Miller (1848-1899). In this reaction, α,β-unsaturated aldehydes or ketones were used. Hydrochloric acid or zinc chloride was used as a catalyst. Reaction of aniline **(5)** with β-substituted unsaturated aldehyde such as

crotonaldehyde leads to the formation of a 2-substituted quinoline **(7)** [16] as shown in Figure 1.3.

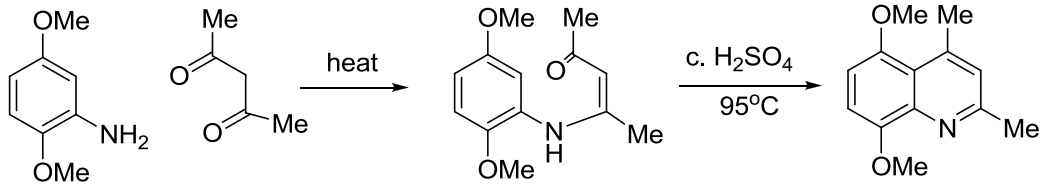


5 **7**

Figure 1.3: Doebner-von Miller synthesis of quinoline

1.2.3 The Combes synthesis

The Combes quinoline is a chemical reaction involving the condensation of 1, 3-dicarbonyl compound **(8)** with an arylamine **(9)** gives a high yield of β-amino-enone **(10)**. Cyclisation in the presence of concentrated acid [17] gives quinoline **(11)** as shown in Figure 1.4.



8 **9** **10** **11**

Figure 1.4: Combes synthesis of quinoline

1.2.4 The Friedländer synthesis

The Friedländer synthesis involves condensation reaction of ortho-acylaniline **(12)** condense with a ketone or aldehyde by base or acid catalysis to yield quinolines. The orientation of condensation depends on the orientation of enolate or enol formation [18] as shown in Figure 1.5.

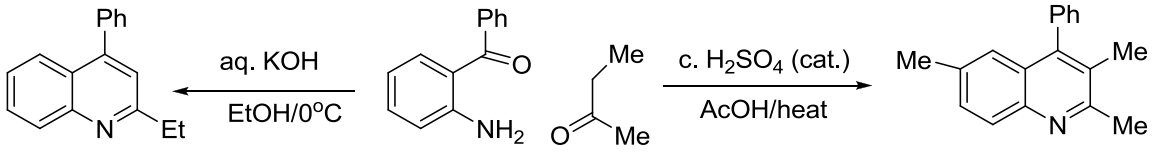


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Figure 1.5: Friedländer synthesis of quinoline

1.3 Reactivity of Quinoline

1.3.1 General features of the chemistry of quinolines

Many of the reactions of quinolines are analogous to pyridine. Protonation and reactions of other electrophiles at nitrogen are similar to pyridine. Quinoline with pKa = 4.94 forms crystalline salts with a wide variety of inorganic and organic acids. They also form complexes with boron trifluoride, sulfur trioxide, and other Lewis acids. Alkylation on nitrogen will produce quaternary salts. The nitrogen atoms also selectively activate positions in the heterocyclic rings to nucleophilic attack, as in pyridine. C-2 and C-4 are the activated positions in quinoline. Amino, alkyl and hydroxyl subtituents at these ‘activated’ positions show properties similar to those in the analogous pyridines, with respect to tautomerism, substitution of hydrogen and displacement.

Electrophilic substitution is greatly easier in quinoline than it is in pyridine. The ring nitrogen atoms, even when protonated, have much less influence on the reactivity of the carbon atoms in the carboxylic rings than on those in pyridine. Consequently, electrophilic substitution is a useful method for introducing substituent into the carboxylic rings of quinoline.

The main distinction between pyridine and quinoline is that quinoline undergoes addition reactions much more readily in the nitrogen-containing ring. The initial coordination of an electrophile at nitrogen is quite frequently followed by addition of a nucleophile at an adjacent carbon atom, as shown in Figure 1.6. Nucleophilic attack on the heterocycle also sometimes results in the formation of addition products rather than substitution products. [19]

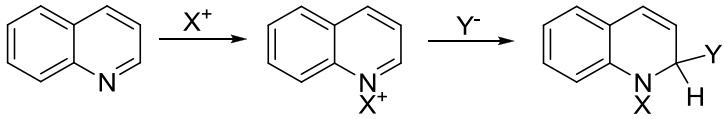

Figure 1.6: Addition reactions initiated by electrophilic attack at nitrogen

1.3.2 Reactions with nucleophilic reagents

1.3.2.1 Nucleophilic substitution with hydride transfer

Alkylation and arylation

The immediate products of addition of alkyl and aryl Grignard reagents and alkyl- and aryllithiums are dihydroquinolines and can be characterized as such, but can be oxidized to afford the C-substituted, rearomatised heterocyles as illustrated below [20] in Figure 1.7.

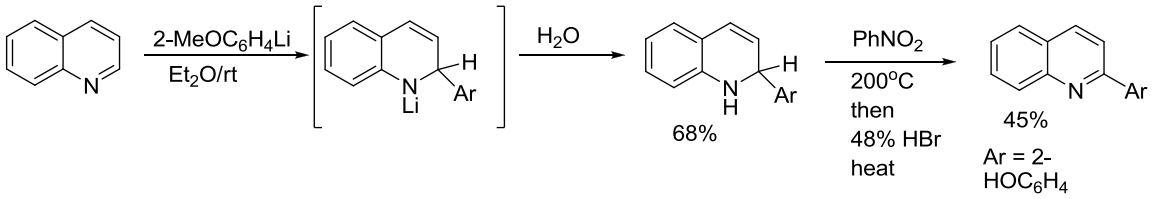

Figure 1.7: Alkylation and arylation of quinoline

Amination

Sodium amide reacts rapidly and completely with quinoline even at -45^{o}C, to give dihydro-adducts with initial amide attack at C-2 and C-4 [21-22] as shown in Figure 1.8.

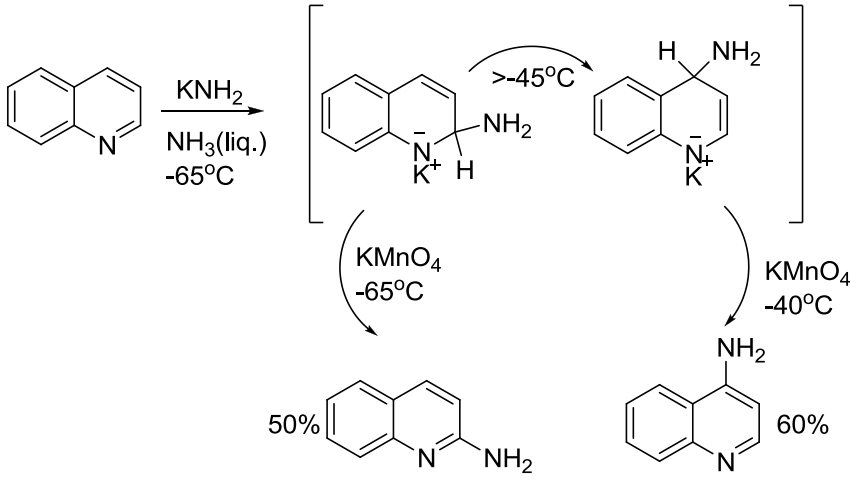

Figure 1.8: Amination of quinoline

1.3.2.2 Nucleophilic substitution with displacement of halide

In this reaction halogen on the homocyclic rings of quinoline and at the quinoline 3-positions behave as halobenzene [4] as shown in Figure 1.9.

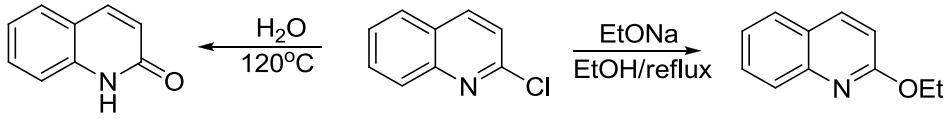

Figure 1.9: Nucleophilic substitution with displacement of halide of quinoline