**Synthesis of Quinoline and its Derivatives Using Various Name Reactions: An Overview**

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**ABSTRACT**

The quinolines constitute an important class of heterocyclic compounds and constituent of natural alkaloids, that demonstrate a wide range of biological and pharmaceutical activities. Therefore, development of quinoline synthetic methods for efficient synthesis of quinoline and its derivatives has attracted considerable attention of researcher and scientist (over recent years). In this review the progress of quinoline synthesis through various name reactions with reaction mechanism and application of synthesis method for quinolines and its derivatives that provides creative inspiration and expands novel ideas for researchers in this field is summarized.

**GRAPHICAL ABSTRACT**



**Keyword**- Quinoline; Conventional synthesis; Synthesis of quinolines; Name reactions

**I. INTRODUCTION**

Quinoline was first time isolated by Runge in 1834 from coal tar [1]. Coal tar also contains isoquinoline, alkyl quinolines and alkyl isoquinoline.  The quinoline core framework exists in many naturally occurring biologically active entities including quinine, cinchonidine, cinchonine from *Cinchona* alkaloids [2]. Quinoline (Fig. 1) consists of a benzene ring fused to the α and β positions of a pyridine ring hence derives its other name is benzo[b]pyridine, Benzo[b]azine, Benzo[b]azabenzene [3]. The physical and chemical properties of quinoline are shown in Table 1 [4-5].



**Figure 1: Structure of quinoline.**

**Table 1: Physical and Chemical Properties of Quinoline**

|  |  |
| --- | --- |
| Physical Properties | Chemical Properties |
| * Color: Colorless hygroscopic liquid.
* Odour: Characteristics odour.
* Taste: Bitter
* Solubility: Sparingly miscible with cold water, but completely miscible with hot water.
* Bitter in taste
* Melting point: 15°C
* Boiling point: 238°C
* Density: 1.093 g/mol
* Molecular weight: 129.16.
 | * Basic or alkaline in nature and SP2 hybridized ring.
* Electrophilic substitution reaction at C-5 and C-8.
* Nucleophilic substitution reaction at C-2 and followed by C-4.
* Oxidation and Reduction reaction occurs.
* Reaction with alkyl halides.
 |

Quinolines have been synthesized using a wide range of conventional methodologies such as Skraup synthesis (6), Doebner von Miller (7), Conrad-Limpach-Knorr (8), and Combes (9) other alternative ways to synthesize quinoline derivatives are Friedlander (10), Pfitzinger (11), and Niementowski synthesis techniques [12]. That chapter discuss about various name reactions methods related to quinoline scaffolds that would help chemist in the future in organic and medicinal chemistry [13].

**II. NAME REACTIONS METHOD**

A number of preparations have been known since the late 1800s for the synthesis of quinoline and its derivatives (Fig. 2). The structural scaffold of quinoline has been generally synthesized by numerous named reactions such as Skraup, Doebner-von Miller, Friedlander, Pftzinger, Conrad-Limpach, Combes synthesis, Riehm Synthesis, Gould- Jacob’s synthesis, Povarov reaction, Knorr synthesis, Niementowski etc. [14-24].

**1. SKRAUP SYNTHESIS** (Zdenko Hans Skraup, 1880)

In this reaction quinolines is synthesized by the condensation of glycerine with aniline (aromatic amine) in the presence of a strong acid such as conc. H2SO4 and an oxidizing agent nitrobenzene or other [25]. The synthetic reaction involved is shown in Fig. 2.



**Figure 2: General reaction of quinoline synthesis by Skraup Reaction.**

**1.1 Reaction Mechanism:**

The reaction mechanism involved in the synthesis of quinoline is as follows.

**Step-I:** In this stepformation of acrolein by the action of H2SO4 on glycerine by dehydration of glycerine results in the loss of two molecules of water [26].



**Step-II:** In this stepaction of Acrolein on Aniline results in synthesis of the addition product (1,4-addition).



**Step-III:** In this step ring closure and intramolecular electrophilic addition followed by protonation, dehydration and oxidation leads to quinoline formation.



**1.2 Representative of Skraup reaction**

Some examples of Skraup synthesis are mentioned below-

A) The benzoquinoline can be synthesized from α-Naphthylamine with the help of Skraup synthesis [27].



B) The 1,10-Phenanthroline can be synthesized from 8-Aminoquinoline with the help of Skraup synthesis [27].



C) The 1,5-Naphthylidine can be synthesized from 3-Aminopyridine with the help of Skraup synthesis [27].



**1.3 Application of Skraup Reaction**

**A) Intermediate in drug synthesis-**

The 7-methyl-8-nitroquinoline was obtained through a two-step synthesis from *m*-toluidine using Skraup synthesis as a key starting material in the field of medicinal chemistry [28-30].



**B) Green chemistry-**

In green chemistry approach Skraup synthesis can be carried out from Solketal (derived by reaction of acetone with glycerol), a by-product of the biodiesel industry. Solketal is potentially an alternative to glycerol for smaller scale reactions, even if glycerol may eventually turn out to be preferable from a Green Chemistry point of view for larger scale processes [31].



**C) Other reactions-**

Skraup reaction is applied using ionic liquid medium under microwave irradiation condition for synthesis of quinoline derivatives [32].



**2. COMBES SYNTHESIS** (Combes, 1888)

In this reaction quinoline is synthesized by the condensation of primary aromatic amines with acetoacetone or other β-diketones succeeded by cyclization in the presence of sulfuric acid or polyphosphoric acid and this method is providing a rapid access to the 2,4-disubstituted quinoline derivatives [33]. The synthetic reaction involved is shown in Fig. 3.



**Figure 3: General reaction of quinoline preparation by Combes synthesis.**

**2.1 Reaction Mechanism**

The reaction mechanism involved in the synthesis of quinoline is as follows.

**Step-I:** In this step formation of enamine occurs by dehydration [34].



**Step-II:** In this stepprotonation of ketone and cyclisation followed by loss of water resulting in the end product of a substituted [quinoline](https://en.wikipedia.org/wiki/Quinoline).



**2.2 Representative of Combes reaction**

Some examples of Combes synthesis are mentioned below-

A) The 2,4-dimethyl-7-chloroquinoline can be synthesized from *m-*Chloroaniline with the help of Combes synthesis [35].



B) The 3,4-cyclohexano-6-methoxy quinoline can be synthesized from Cyclohexanone-2-aldehyde with the help of Combes synthesis [36].



C) The benzo[g] quinoline derivatives can be synthesized from β-Naphthylamine with the help of Combes synthesis [37].



**2.3 Application of Combes Synthesis**

**A) Intermediate in drug synthesis-** Synthesis of 2-Aryl-4-quinolones from o-Halophenones a base-promoted camps cyclization using as a key starting material in field of medicinal chemistry [38].



**B) Use of gold metal catalyst-** Liu et al. reported gold catalyzed annulations of anthranils with aryloxyethynes or aryl propargyl ethers for the construction of useful benzofuro[2,3-b] quinoline and 6H-chrome no[3,4-b] quinolone scaffolds by combes synthesis [39].



**3. DOEBNER REACTION** (Doebner,1887)

In this reaction [aniline](https://en.wikipedia.org/wiki/Aniline) reacts with [aldehyde](https://en.wikipedia.org/wiki/Aldehyde) in the presence of [pyruvic acid](https://en.wikipedia.org/wiki/Pyruvic_acid) to form [quinoline](https://en.wikipedia.org/wiki/Quinoline)-4-carboxylic acid derivatives [40]. The synthetic reaction involved is shown in Fig. 4.



**Figure 4: General reaction of quinoline synthesis by Doebner reaction.**

**3.1 Mechanism**

The reaction mechanism involved in the synthesis of quinoline is as follows.

This reaction may involve an aldol condensation between the aldehyde and pyruvic acid to afford a β, γ-unsaturated α-keto acid that then undergoes the Michael Addition with aniline. The mechanism can be divided into two steps including reversible formation of imine and later irreversible formation of quinoline in which pyruvic acid assembled to give crystalline and porous framework [41].



**3.2 Representatives of** **Doebner reaction**

Some examples of Doebner reaction are mentioned below-

A) The benzocinchoninic acid (quinoline derivative) can be synthesized from Naphthylamine in the presence of pyruvic acid with the help of Doebner reaction [42].



B) Various quinoline derivatives can be synthesized with the help of aromatic amines and pyruvic acid [ 43].



**3.3 Application of Doebner reaction**

**a) Green Chemistry-** Quinoline derivatives can be synthesized by three-component reaction of ethyl/methyl lactate, anilines and aldehydes through simple iron (III) chloride catalysis without using an additional organic medium or external oxidant by Doebner reaction [43].



**b) Synthesis of drug Intermediate-** The Doebner reaction is the chemical reaction of an aniline with an aldehyde and pyruvic acid to form quinoline-4-carboxylic acids which is intermediate for various drug synthesis [44].



**4. DOEBNER-MILLER REACTION** (Doebner and von Miller, 1881)

In this [organic reaction](https://en.wikipedia.org/wiki/Organic_reaction) [aniline](https://en.wikipedia.org/wiki/Aniline) reacts with [α,β-unsaturated carbonyl compounds](https://en.wikipedia.org/wiki/Alpha-beta_unsaturated_carbonyl_compounds) in the presence of acid to form 2,4-disubstituted quinoline derivatives. It is also known as Skraup-Doebner von miller synthesis [45]. The synthetic reaction involved is shown in Fig. 5.



**Figure 5: General reaction of quinoline synthesis by Doebner-miller reaction.**

**4.1 Mechanism**

The reaction mechanism involved in the synthesis of quinoline is as follows.

The mechanism of Doebner-Miller reaction includes condensation of aniline with a substituted acrolein to yield quinoline. It involves the loss of water as well as two hydrogen atoms. The reaction between a simple aniline and acrolein uses iodine as an oxidizing reagent [46].



**Figure 9: General mechanism of quinoline synthesis by Doebner-miller reaction.**

**4.2 Representative of Doebner-miller reaction**

Some examples of Doebner-miller reaction are mentioned below-

A) The 2-methyl quinoline derivatives can be synthesized using water as a solvent with the aniline and crotonaldehyde by Doebner-miller reaction [47].



B) The quinoline can be synthesized using aniline and acrolein in the presence of HCl and toluene using Doebner-miller reaction [48].



**4.3 Application of Doebner-miller reaction**

**a) Cross-over reaction-** The mechanism of the formation of substituted quinolines from anilines and unsaturated ketones have been studied by the use of 13C-labeled ketones in cross-over experiments using Doebner miller reaction [49].



**b) In green production-** Theproduction of quinoline and derivatives is proposed by using sulfuric acid as commercial homogeneous acid catalyst in water in continuous flow chemistry using Doebner-miller synthesis [50].



**5. RIEHM SYNTHESIS** (P. Riehm, 1885)

This reaction involves the preparation of quinoline derivatives by prolonged heating of arylamine hydrochlorides with ketones with or without use of aluminum chloride or phosphorus pentachloride [51]. The synthetic reaction involved is shown in Fig. 6.



**Figure 6:** **General reaction of quinoline preparation by Riehm synthesis.**

**5.1 Mechanism**

The general mechanism of Riehm synthesis involves the thermal condensation of aniline hydrochloride and acetone or mesityl oxide and results in evolution of water, methane and 2,4-dimethylquinoline. This reaction has been modified by addition of iodine to the mixture of aniline and ketone [52].



**5.2 Representative of Riehm synthesis**

Some examples of Riehm synthesis are mentioned below-

A) The 2-methyl-4-ethylquinoline derivatives can be synthesized with the help of aniline and 2-butanone in the presence of iodine using Riehm synthesis [53].



**5.3 Application of Riehm synthesis**

2,4-disubstituted quinolines derivatives can be synthesized from aniline and nitro benzaldehyde and ethynol using Riehm synthesis [54].



**6. FRIEDLANDER SYNTHESIS (**Paul Friedländer, 1882**)**

This is an aldol condensation type reaction in which *o*-amino aryl aldehyde is reacted with a ketone in the presence of potassium hydroxide (KOH) results in quinoline derivative [55]. The synthetic reaction involved is shown in Fig. 7.



**Figure 7:** **General reaction of quinoline synthesis by Friedlander synthesis.**

**6.1 Mechanism**

The reaction mechanism involved in the synthesis of quinoline is as follows.

**Step-I:** In this reaction starting materials for quinoline synthesis are *o*-aminoaryl aldehydes or ketones and a ketone possessing α-methylene group [56].



**Step-II:** The second step is initial amino-ketone condensation, in which the intermediate undergoes base- or acid-catalyzed cyclocondensation like aldol condensation to produce a substituted quinoline derivatives.



**6.2 Representative of Friedlander synthesis**

Some examples of Friedlander synthesis are mentioned below-

A) The poly-substituted quinolines can be synthesized with the help of *ortho*-aminoaryl aldehydes or ketone in the presence of *p*-toluene sulphonic acid using Friedlander synthesis [57].



B) The functionalized quinolines can be synthesized with the help of *ortho*-amino aldehydes or ketone Catalyzed by Neodymium (III) Nitrate Hexahydrate using Friedlander synthesis [58].



C) The synthesis of quinolines with the help of *ortho*-amino aldehydes or ketone and molecular iodine as a highly efficient catalyst by Friedlander synthesis [59].



**6.3 Application of Friedlander synthesis**

**a) Synthesis of metabolite drug-** SN38 is the active metabolite of the drug irinotecan (1998AO845) and both are antineoplastic agents for the treatment of colon and lung cancers can be synthesized by Friedlander reaction [60].



**b) Synthesis of pentacyclic core**

The synthesis is initiated by Friedlander reaction of 2-aminoacetophenone and tert-butyl acetoacetate to afford quinoline as the precursor of the plakinidines core [61].



**7. PFITZINGER REACTION (**Pfitzinger, 1886**)**

In this reaction the  [isatin](https://en.wikipedia.org/wiki/Isatin) react with [carbonyl](https://en.wikipedia.org/wiki/Carbonyl) compound (ketone or aldehyde) in the presence of strong basic media and produce 2,3-substituted [quinoline](https://en.wikipedia.org/wiki/Quinoline)-4-[carboxylic acids](https://en.wikipedia.org/wiki/Carboxylic_acid). Another name of this reaction is Pfitzinger-Borsche reaction [62]. The synthetic reaction involved is shown in Fig. 8.



**Figure 8: General reaction of quinoline synthesis by Pfitzinger-Borsche reaction.**

**7.1 Mechanism**

The reaction mechanism involved in the synthesis of quinoline is as follows.

**Step-I:** The ring is opened in the presence of a strong base such as KOH [63].

**Step-II:** In this step formation of a Schiff s base through the condensation of -NH2 group with the carbonyl group.

**Step-III:** In this step Claisen condensation occurs between benzylic carbonyl and active α-methylene group of the amine.

**Step-IV:** In this final step cyclization reaction occurs and substituted quinoline forms.



**7.2 Representative of Pfitzinger reaction**

Some examples of Pfitzinger reaction are mentioned below-

A) The 2,6-dimethyl-3-phenoxy-quinoline-4-carboxylic acid can be synthesized with the help of 5-Methylisatin with phenoxy acetone in the presence of potassium hydroxide using Pfitzinger reaction [64].



B) The quinoline derivative can be synthesized with the help of Isatin with large carbon ring ketones using Pfitzinger reaction [65].



C) The 5,6-dimethoxy indano [2,3-b]-6-chloro-4-quinolinic acid is synthesized with the help of 5-Chloroisatin with 5,6-dimethoxy indanone in the presence of basic as well as acidic medium using Pfitzinger reaction [66].



**7.3 Application of Pfitzinger reaction**

**a) Microwave irradiation-** Zhu and coworkers’ synthesized quinoline-4-carboxylic acid, unsubstituted in the 2-position using microwave irradiation by Pfitzinger reaction [67].



**b) Green chemistry-** Many researchers reported an improved [Pfitzinger reaction](https://www.sciencedirect.com/topics/chemistry/pfitzinger-synthesis) for the synthesis of highly functionalized quinaldines from 1,3-dicarbonyl compounds, isatins and alcohols mediated by TMSCl through the approaches of green chemistry [68].



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**8. KNORR QUINOLINE SYNTHESIS** (Ludwig Knorr, 1886)

This  is a [intramolecular](https://en.wikipedia.org/wiki/Intramolecular_reaction) [organic reaction](https://en.wikipedia.org/wiki/Organic_reaction) converting a [β-ketoanilide](https://en.wikipedia.org/wiki/Anilide) to a [2-](https://en.wikipedia.org/wiki/2-hydroxyquinoline)hydroxyquinoline using sulfuric acid. It is also known as Knorr quinoline synthesis reaction [69]. The synthetic reaction involved is shown in Fig. 9.



**Figure 9: General reaction of quinoline synthesis by Knorr synthesis.**

**8.1 Mechanism**

This reaction is a [electrophilic aromatic substitution](https://en.wikipedia.org/wiki/Electrophilic_aromatic_substitution) accompanied by [elimination](https://en.wikipedia.org/wiki/Elimination_reaction) of water. In which altering the reaction conditions can completely alter the regiochemical outcome [70].



**8.2 Representative of Knorr Synthesis**

Some examples of Knorr synthesis are mentioned below-

A)Theamino tetrahydroquinoline can be synthesized with the help of 4-ethyl-1,2,3,4-tetrahydroquinoline and ethyl-4,4,4-trifluoroacetoacetate in presence of ZnCl2 using Knorr synthesis method [71].



B) The quinoline derivatives can be synthesized by 4-amino-6- Bromo veratrole and ethyl acetoacetate with sulfuric acid with the help of Knorr synthesis method [72].



**8.3 Application of Knorr Synthesis**

**a) Other molecule synthesis-** The Knorr synthesis offers a valuable and practical route to a number of [pyrrole carboxylates](https://www.sciencedirect.com/topics/chemistry/pyrrolecarboxylate) synthesis [73].



**9. CONRAD-LIMPACH QUINOLINE SYNTHESIS** (Max Conrad and Leonhard Limpach, 1887)

It is the condensation reaction in which [anilines](https://handwiki.org/wiki/Chemistry%3AAniline) reacts with β-ketoesters to form 4-hydroxy[quinolines](https://handwiki.org/wiki/Chemistry%3AQuinoline) by a [Schiff base](https://handwiki.org/wiki/Chemistry%3ASchiff_base) [74]. The synthetic reaction involved is shown in Fig. 10.



**Figure 10:** **General reaction of quinoline synthesis by Conrad-Limpach Quinoline Synthesis.**

**9.1 Mechanism**

The reaction mechanism involved in the synthesis of quinoline is as follows [75].



**9.2 Representatives of Conrad-Limpach Synthesis**

Some examples of Conrad-Limpach synthesis are mentioned below-

A) The 4-hydroxy-2-methyl-6-nitroquinoline derivatives can be synthesized with the help of nitroaniline and vinyl ether in the presence of sulfuric acid using Conrad-Limpach Quinoline Synthesis [76].



B) The methylquinoline derivatives can be synthesized with the help of *ortho*-nitroaniline and dimethyl acetylene dicarboxylate in the process of reflux using Conrad-Limpach Quinoline Synthesis [77].



**9.3 Application of Conrad-Limpach synthesis**

**a) Field of green chemistry-** TheConrad-Limpach reaction is useful for green synthesis [78].



**10. GOULD- JACOB’S SYNTHESIS** (Gould and Jacobs, 1939)

In this reaction preparation of 4‐hydroxyquinoline derivative from anilines and diethyl ethoxymethylenemalonate involving the condensation reaction [79]. The synthetic reaction involved is shown in Fig. 11.



**Figure 11:** **General reaction of quinoline synthesis by Gould- Jacob’s synthesis.**

**10.1 Mechanism**

The reaction mechanism involved in the synthesis of quinoline is as follows.

The reaction begins from a nucleophilic attack from the amine nitrogen followed by the loss of ethanol to form the condensation product and cyclization reaction with the loss of another ethanol molecule forms a quinoline (ethyl 4-oxo-4,4a-dihydroquinoline-3-carboxylate). The enol form can be represented from the keto form through keto-enol tautomerism [80].



**10.2 Representatives of Gould- Jacob’s synthesis**

A) The quinoline derivatives can be synthesized with the help of aniline and alkoxy methylenemalonic ester by cyclization and decarboxylation [81].



B) The different variety of quinoline derivatives can be synthesized with the help of amino aldehyde and formamide ester by Gould- Jacob’s synthesis [82].



**10.3 Application of Gould- Jacob’s synthesis**

a) In field of medicinal chemistry various antibiotics are synthesized by using gold Jacob’s reaction such as  [rosoxacin](https://en.wikipedia.org/wiki/Rosoxacin), [oxolinic acid](https://en.wikipedia.org/wiki/Oxolinic_acid) etc [83].



**11. POVAROV REACTION** (Povarov and Mikhailov, 1963)

[Aniline](https://en.wikipedia.org/wiki/Aniline) and a [benzaldehyde](https://en.wikipedia.org/wiki/Benzaldehyde) react and forms Schiff base and subsequently involve [cycloaddition](https://en.wikipedia.org/wiki/Cycloaddition) between an [aromatic](https://en.wikipedia.org/wiki/Aromatic) [imine](https://en.wikipedia.org/wiki/Imine) and an [alkene](https://en.wikipedia.org/wiki/Alkene) [84]. The synthetic reaction involved is shown in Fig.12.



**Figure 12: General reaction of quinoline synthesis by Povarov reaction.**

**11.1 Mechanism**

The reaction mechanism involved in the synthesis of quinoline is as follows.

In this mechanism [aniline](https://en.wikipedia.org/wiki/Aniline) and [benzaldehyde](https://en.wikipedia.org/wiki/Benzaldehyde) react and forms [Schiff base](https://en.wikipedia.org/wiki/Schiff_base) by [condensation reaction](https://en.wikipedia.org/wiki/Condensation_reaction) and this reaction requires a [Lewis acid](https://en.wikipedia.org/wiki/Lewis_acid) such as [boron trifluoride](https://en.wikipedia.org/wiki/Boron_trifluoride) to activate the [imine](https://en.wikipedia.org/wiki/Imine) for an [electrophilic addition](https://en.wikipedia.org/wiki/Electrophilic_addition) of the activated [alkene](https://en.wikipedia.org/wiki/Alkene). Then additional [elimination reactions](https://en.wikipedia.org/wiki/Elimination_reaction) create the quinoline ring structure [85].



**11.2 Representative of Povarov reaction**

A) The 2-methylquinoline derivatives can be synthesized from aniline and acetaldehyde using Povarov reaction [86].



B) The 8-phenoxy-4-(pyridin-2-yl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*] quinoline can be synthesized by the three-com­ponent Povarov reaction [87].



**11.3 Application of Povarov reaction**

**a) Multicomponent reaction (MCR) -** The Povarov MCR is especially fruitful for the generation of anti-infective hits molecules [88].



**b) Drug intermediate synthesis-** The Povarov reaction is useful in drug intermediate synthesis such as dienophile, indenonaphthyridine derivatives with antiproliferative activity [89].



**III. CONCLUSION**

In this chapter, the brief history, synthesis and related mechanisms of quinolines is discussed. There are several synthetic routes for the synthesis of quinolines that have been discussed. The multiple-name reaction has been chosen among the various suitable quinoline syntheses in this regard. A variety of quinolone derivatives are produced when aniline and various reagents i.e., glycerol combine in the presence of an acidic or other suitable medium. This book chapter provides creative inspiration and expands innovative ideas by summarizing the advancement of quinoline synthesis through various name reactions, reaction mechanisms, and applications of synthesis methods.

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**V. CONFLICT OF INTEREST**

There are no known financial conflicts of interest, according to the authors.

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