Chapter

The Chemistry of Benzo and Carbocyclic Derivatives of Pyridine

Adebimpe D. Adesina

Abstract

The chemistry of pyridine and its derivatives is of considerable importance in the synthesis of intermediates leading to biologically active compounds and novel materials. Generally, derivatives of pyridine are stable and relatively unreactive but can be attacked by electrophiles at ring nitrogen and certain carbon atoms. Pyridines undergo radical substitution reactions preferentially at the 2-position. Simple pyridines and their benzo derivatives are weak bases that form salts with strong acids. Various Lewis acids form complexes with pyridine and its benzo derivatives. The quaternization of pyridine and its benzo derivatives using alkyl and acyl halides have been used as versatile synthetic intermediates to biologically active compounds as final products. Precursors to cyanine dyes have been prepared by means of the 1,4-addition of pyridines and quinolines to acrylamide. *N*-oxides, obtained by the oxidation of pyridine and its benzo analogues, are versatile intermediates in organic synthesis.

Keywords: benzo derivatives, pyridine, quinoline, isoquinoline, synthetic intermediates, electrophilic substitution, nucleophilic substitution

1. Introduction

Pyridine was first isolated in a pure state from bone oil by Anderson [1] who had earlier obtained picoline from coal tar. He established the molecular formula of pyridine and showed it to be a tertiary base, capable of forming quaternary salts. A Kekule-type structure was proposed for pyridine **1** by Korner (**Figure 1**) [2]. The proposed structure was confirmed by the reduction of pyridine to piperidine, by the reverse oxidation and by the synthesis of piperidine.

In addition to being attacked by electrophiles, strong nucleophiles can also react, at the α- or γ- ring carbon atoms of the pyridine ring [3, 4].

Quinoline **2** and isoquinoline **3** are the two possible structures in which a benzene ring is annelated to a pyridine ring. The effect that the benzene ring has on the reactivity of the pyridine ring, and *vice versa* should be considered. Electrophilic substitution favors the benzenoid ring, rather than the pyridine ring with preferred substitution at the 5- (**Figure 2**) and 8- positions.

The electron-deficiency of the carbons in pyridines, particularly the α- and γ-carbons, and the ability of the heteroatom to accommodate negative charge in the

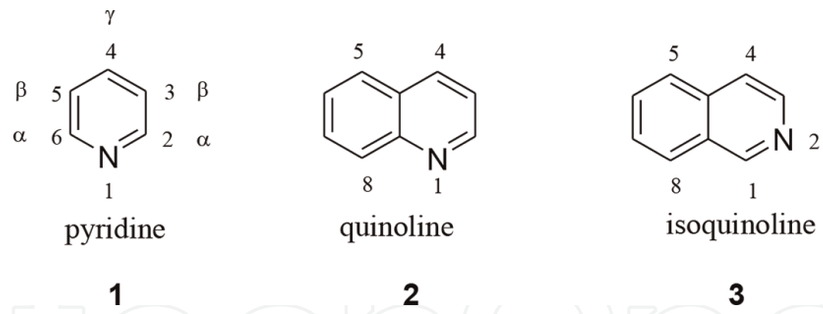


Figure 1.
Structure of pyridine and its benzo-fused analogues.

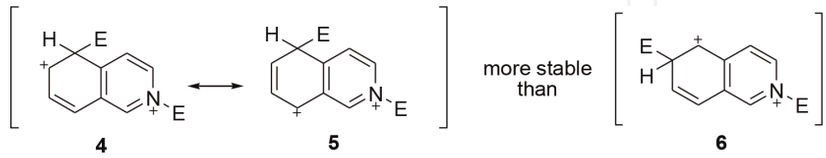


Figure 2.
Electrophilic substitution of isoquinoline.

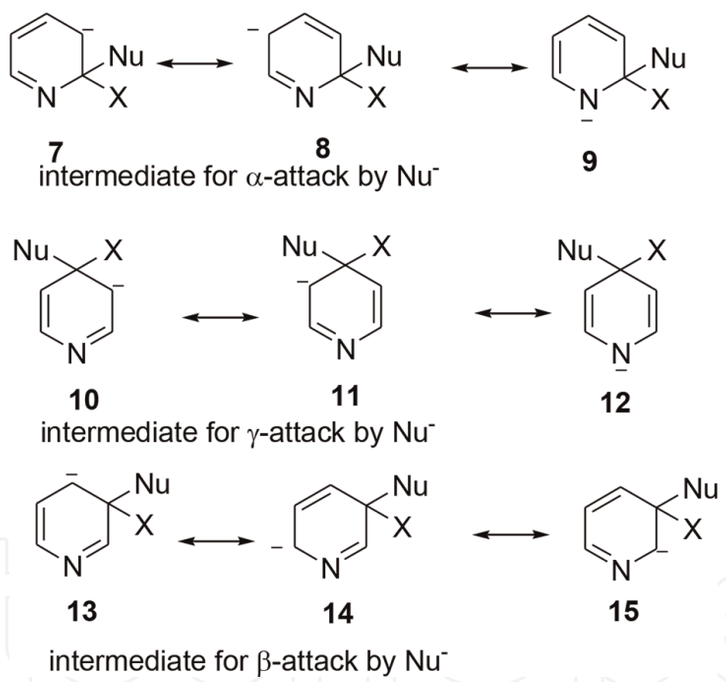


Figure 3.
Selectivity of nucleophilic attack on halopyridines.

intermediate thus produced, makes nucleophilic addition and, especially nucleophilic displacement of halide (and other good leaving groups), a very important feature of pyridine chemistry (**Figure 3**) [5]. Quinoline and isoquinoline are reactive to nucleophiles in the pyridine ring, especially at the positions α and γ to the nitrogen and, further, are more reactive in this sense than pyridines.

2. Synthesis

The synthesis of a pyridine ring can be achieved in many ways. Some of these will be described and exemplified.

2.1 Condensation reactions

One of the methods for constructing the pyridine nucleus is by way of condensation reactions. This is done by the combination of an amino group with two carbonyl groups followed by the loss of two or more equivalents of water. A final oxidation step was often necessary to obtain the aromatic ring system. Most condensations leading to a pyridine derivative **17** proceed through an intermediate which can be related to a 1,5-dicarbonyl compound **16** (**Figure 4**).

The Chichibabin pyridine synthesis is an example of the condensation method for synthesizing pyridine rings. The reaction involves the condensation of aldehydes, ketones, α, β-unsaturated carbonyl compounds, or any combination of these, with ammonia.

Frank and Seven [6] have reported the modified synthesis of pyridine by heating the carbonyl compounds or derivatives with aqueous ammonia and catalytic amounts of ammonium acetate to produce good yields of single products. But-2-enal was reacted with ammonia to form 5-ethyl2-methylpyridine (**Figure 5**). However, the use of a steel autoclave at high temperatures and pressures was a drawback in this process.

An improved Chichibabin synthesis was also investigated by Weiss [7] and a mechanism was proposed for the formation of the pyridine ring. The mechanism of the reaction of benzaldehyde **20** with acetophenone **21** involved an aldol condensation to form **22**, followed by a Michael-type reaction to give a 1,5-dicarbonyl **23,** which then condenses with ammonia to form a dihydropyridine **24**, which, in turn, is dehydrogenated to a pyridine **25** (**Figure 6**).

2.2 Cycloaddition reactions

Some 6π cycloadditions have been used to form pyridines. The first to be reported was the addition of a dienophile **28** to an oxazole **27** [8, 9]. When acrylonitrile was used, hydrogen cyanide was lost to aromatise and the oxazole oxygen retained to give 3-hydroxypyridines, while with the use of acrylic acid, the oxygen was lost as water (**Figure 7**).

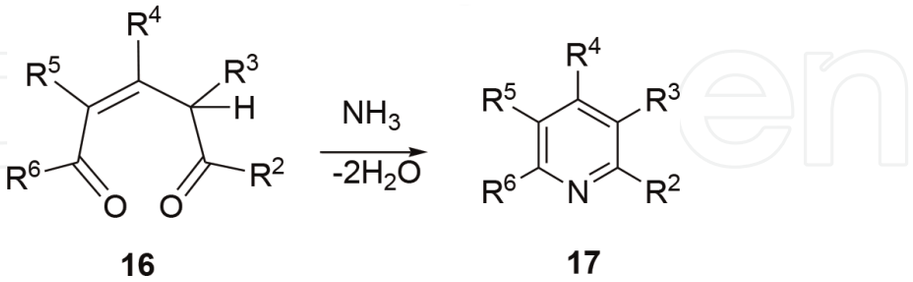


Figure 4.
Typical pyridine ring synthesis.

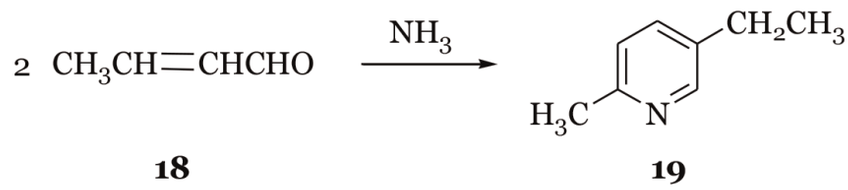


Figure 5.
An example of the Chichibabin synthesis.

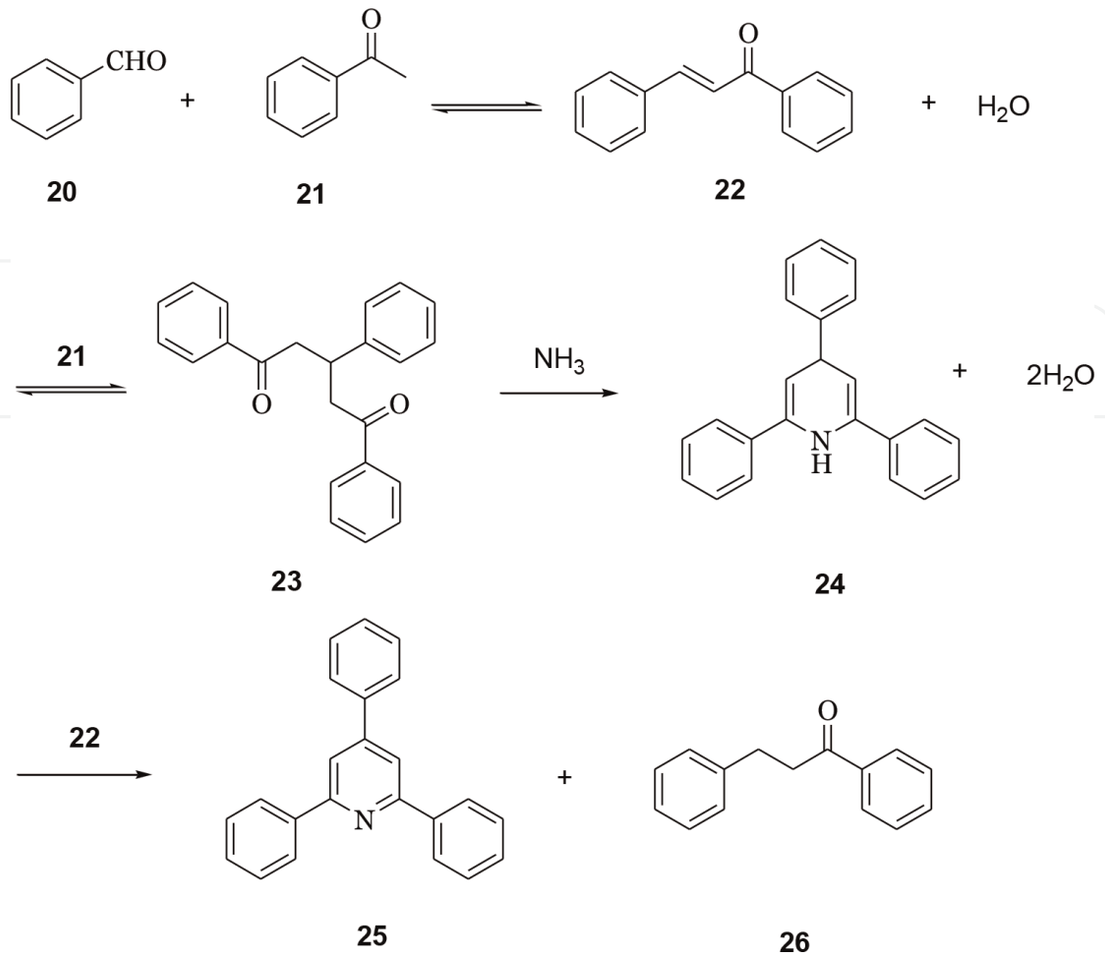


Figure 6.
An improved Chichibabin synthesis of pyridine.

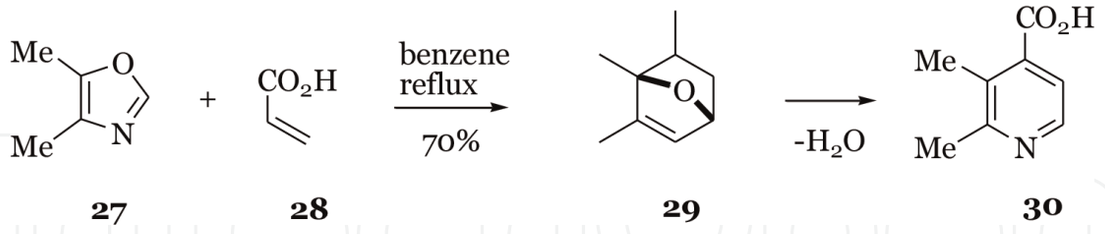


Figure 7.
Synthesis of pyridines via cycloadditions.

The interaction of propargylamine **32** with a cyclic ketone **31**, produced an enamine **33**, followed by a ring closure which when effected with a gold catalyst, gave a carbocyclic pyridine derivative **34** (**Figure 8**) [10].

2.3 Cyclization reactions

Pyridines can be formed by the cyclization of nitriles at either carbon or nitrogen. Cyclizations at nitrogen were more common and incorporated the nitrogen into the pyridine ring.

Methyl-substituted pyridine derivatives have been synthesized from the cyclization of cyclic precursors **36** which were prepared from the treatment of β-ketoesters

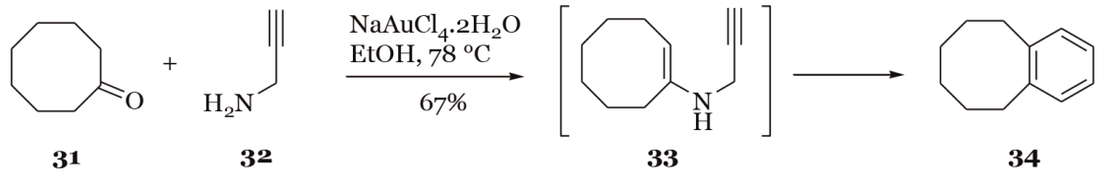


Figure 8.
Synthesis of a carbocyclic pyridine derivative.

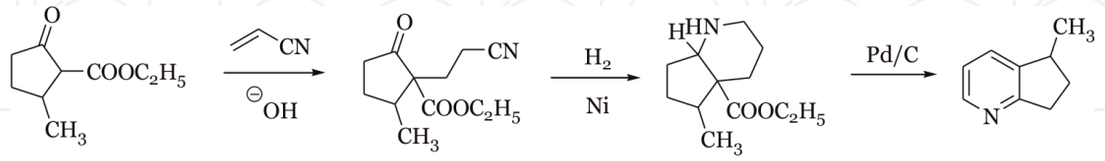


Figure 9.
Synthesis of pyridine from nitrile cyclization.

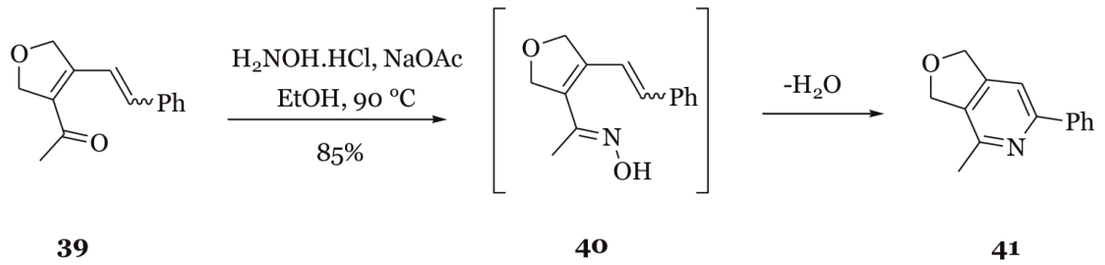


Figure 10.
Azatriene cyclizations to form pyridines.

35 with acrylonitrile (**Figure 9**) [11]. The dehydrogenation of the piperidine ring in the final step also resulted in the loss of the ester group.

The fusion of pyridines to other ring systems has been investigated via thermal electrocyclization [12]. The pyridines were formed from the oxidation of dihydropyridines which were generated from the electrocyclization of aza-1,3,5-trienes. However, the use of an oxime or hydrazine derivative, followed by the elimination of water or an amine *in situ* gave the pyridine directly (**Figure 10**).

3. Reaction with electrophilic reagents

3.1 Addition to nitrogen

3.1.1 Protonation and salt formation

Pyridines behave like tertiary aliphatic or aromatic amines in reactions that involves bond formation using the lone pair of electrons on the ring nitrogen. Simple pyridines and their benzo derivatives are weak bases that form crystalline, frequently hygroscopic, salts with most protic acids [3, 4].

Chromium salts of pyridine have become important reagents in organic synthesis because of their mild oxidizing capability. Pyridinium chlorochromate (Corey's

reagent), pyridinium dichromate, and $(Py)_2CrO_3$ (Collins' reagent) are the most widely used.

3.1.2 Alkylation

Alkyl halides and sulfates react readily with pyridine and its benzo derivatives at room temperature, giving quartenary *N*-substituted pyridinium salts, which have been used as versatile synthetic intermediates to biologically active compounds or as final products [13–15]. Quaternization of pyridine with alkyl halides or related compounds is an example of Menschutkin reaction (**Figure 11**).

A review on quartenary salts of pyridines and related compounds describing their synthesis, physicochemical properties, possible applications, and their biological activities has been published [16].

3.1.3 Acylation

Acylation of pyridines can be achieved at temperatures as low as −78°C. Acid halides react readily with pyridines to generate *N*-acylpyridinium salts in solution, and in some cases, as crystalline, non-hygroscopic solids (**Figure 12**) [17]. *N*-Acylpyridinium salts have been found to be more reactive than their *N*-alkyl counterparts and are susceptible to attack by nucleophiles.

3.1.4 Halogenation

Pyridines and their benzo derivatives react with halogens to give *N*-halogenopyridinium salts. The complexes of pyridine with chlorine have been well studied [18]. Pyridine iodo compounds can be prepared by treating $TiI_3[AsF_6]$ with pyridines, from which the pyridinium salt $[C_5H_5NI]^+[AsF_6]^-$ has been isolated and characterized [19]. Several syntheses of *N*-fluoropyridinium salts have been reported.

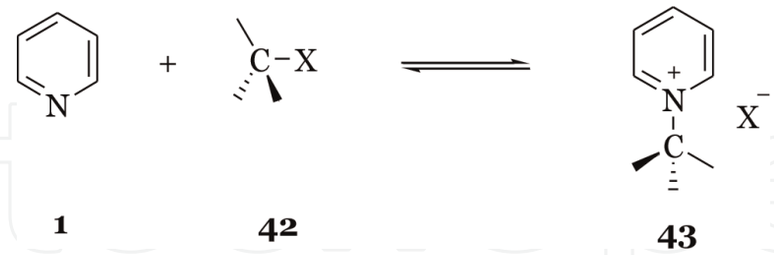


Figure 11.
Alkylation of pyridine.

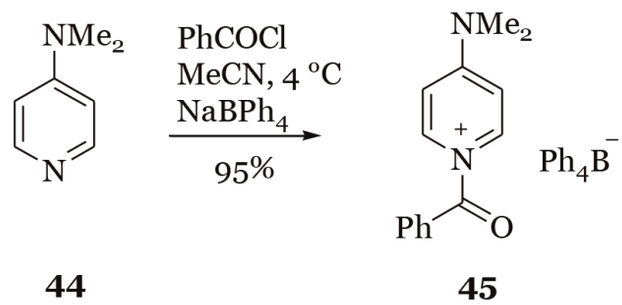


Figure 12.
Acylation at nitrogen of 4-dimethylaminopyridine (DMAP).

These compounds have received growing interest because of their use as fluorinating agents [20].

N′, *N′*-Difluoro-2,2′-bipyridinium bis(tetrafluoroborate) **47,** prepared in one pot by introducing BF3 gas into 2,2′-bipyridine **46** at 0°C followed by fluorine gas diluted with nitrogen, has been shown to be a highly reactive electrophilic fluorinating agent (**Figure 13**) [21].

3.1.5 N-*oxidation*

N-Oxides, obtained from the oxidation of pyridine and its benzo analogues, are versatile intermediates in organic synthesis [22–24]. Reagents used for the *N*-oxide formation include peracids, [3] H2O2/AcOH, dioxiranes, [25] organic hydrotrioxides, [26] Caro's acid, oxaziridines [27] and oxygen with ruthenium trichloride as catalyst [28].

Similarly, there are many ways to deoxygenate pyridine *N*-oxides: samarium iodide, chromous chloride, stannous chloride with low-valent titanium, ammonium formate with palladium and catalytic hydrogenation at room temperature can be used [29–33]. The most frequently used methods have involved oxygen transfer to trivalent phosphorus [34] or divalent sulfur [35] (**Figure 14**).

3.2 Electrophilic attack at carbon

In most cases, electrophilic substitution of pyridines occurs very much less readily than for the correspondingly substituted benzene. This is because the electrophilic reagent, or a proton in the reaction medium, adds first to the pyridine nitrogen, generating a pyridinium cation, which is naturally very resistant to attack by an electrophile.

The electron-withdrawing effect of nitrogen in pyridine is profound at the 2- and 4-positions and diminished at the 3-position. When electrophilic attack does occur, it is generally at the 3-position.

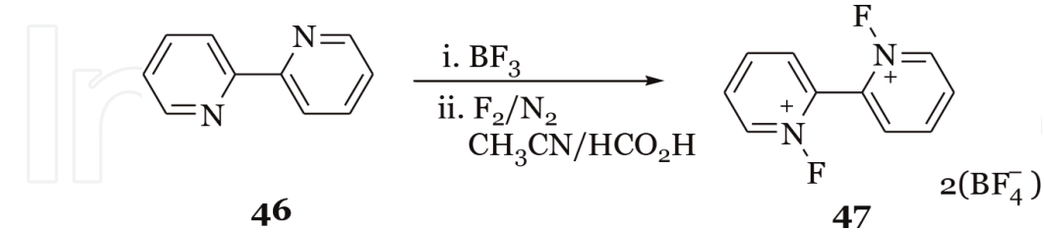


Figure 13.
Fluorination of pyridine compounds at nitrogen.

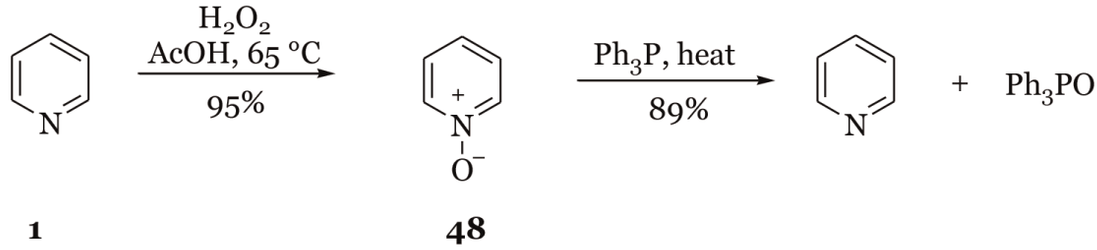


Figure 14.
Oxidation of pyridine at nitrogen.

3.2.1 Nitration

The electron-deficient nature of pyridine makes its direct nitration difficult even under rigorous conditions, whereas pyridine *N*-oxide, pyridines and pyridinamines can be nitrated more easily [36].

Initial reaction of pyridines with dinitrogen pentoxide in sulfur dioxide proceeds by addition at 2-position forming a 1,2-dihydropyridine intermediate. Transfer of the nitro group to a β-position, via a [1,5]-sigmatropic migration, is then followed by elimination of the nucleophile, regenerating the aromatic system to give 3-nitropyridines **49** (**Figure 15**) [37].

3.2.2 Halogenation

The halogenation of pyridines can be achieved using a variety of reagents which are not always mild and compatible with other functionalities in the molecule. Due to the electron-deficiency of the pyridine ring, electrophilic halogenations are mostly difficult.

The reaction of bromine with pyridine in oleum has produced 3-bromopyridine **51** in good yield [38]. The reactive species in the process involves pyridinium-1-sulfonate. Similarly, 3-chloropyridine **50** has been produced by chlorination at 200°C, or at 100°C in the presence of aluminum chloride, although in low yield (**Figure 16**) [39].

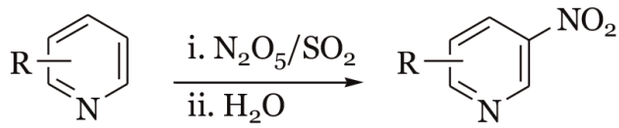
3.2.3 Sulfonation

The reaction of pyridine with concentrated sulfuric acid only gave low yields of 3-sulfonic acid after prolonged reaction time at 320°C. However, a higher yield was achieved with the addition of mercuric sulfate in catalytic quantities at a somewhat lower temperature (**Figure 17**) [40].

The sulfonation of quinoline has been achieved under conditions of 30% oleum at 90°C, occurring at the 8-position to give **53** in good yield, whereas isoquinoline gave the 5-acid. At higher temperatures, under thermodynamic control, other isomers are produced, for example quinoline-8-sulfonic acid is isomerised to the 6-acid **54** (**Figure 18**) [41, 42].

3.2.4 Oxidation

Pyridines require vigorous conditions to be oxidized as they are generally resistant to oxidizing agents. Pyridines have been converted into 2-pyridones **55** using copper sulfate (**Figure 19**) [43]. A similar conversion using zinc sulfate heptahydrate or



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R = H, 2-Me, 3-Me, 4-Me, 4-Ph, 3-Ac,
4-Ac, 3-Cl, 4-CN, Quinoline, Isoquinoline

Figure 15.
Nitration of pyridine and substituted pyridine.

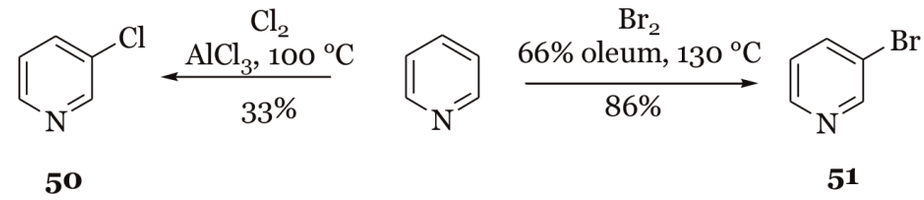


Figure 16.
Chlorination and bromination of pyridine.

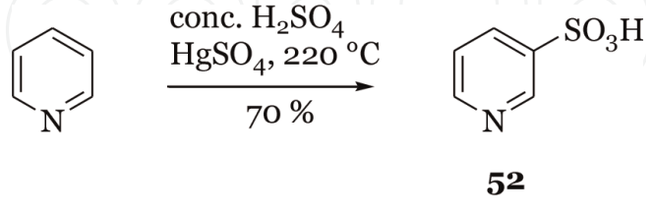


Figure 17.
Sulfonation of pyridine.

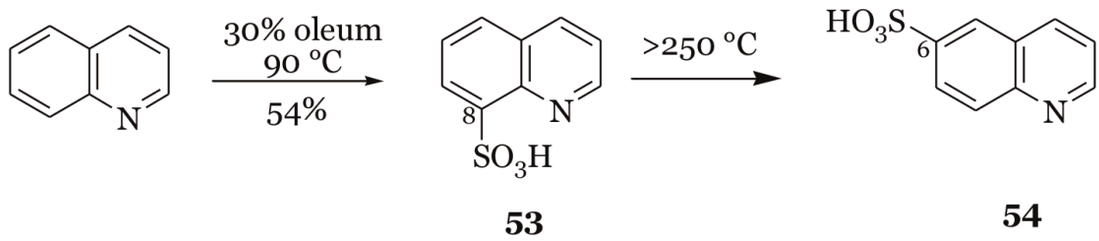


Figure 18.
Sulfonation of quinoline.

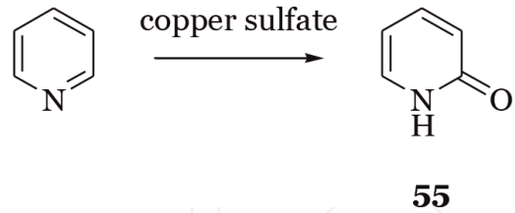


Figure 19.
Oxidation of pyridine.

tricadmium sulfate octahydrate and oxygen has also been reported, although with low yield [44].

When quinoline was oxidized under ozonolysis conditions, it gave pyridine-2,3-biscarboxaldehyde. The oxidation of quinoline or isoquinoline with permanganate can occur in either the benzene or pyridine ring, depending on the conditions. Electron-withdrawing or donating groups can direct the oxidation to either the benzene or pyridine ring. The oxidation of 5-aminoisoquinoline occurred in the benzene ring; however, 5-nitroquinoline gave the product of pyridine ring oxidation [4].

4. Reaction with nucleophilic reagents

Nucleophilic substitution reactions are characteristic of pyridines just as electrophilic substitution reactions are characteristic of benzene and electron-rich

heteroaromatic compounds such as pyrrole and furan. The nucleophilic substitution of hydrogen usually involves a hydride transfer in the last step [5].

4.1 Nucleophilic attack at carbon

Although many nucleophiles react with halogenated pyridines effecting the displacement of halogen, only strong nucleophiles react with simple pyridine. However, pyridine *N*-oxide and certain pyridines readily undergo nucleophilic substitution [4].

Nitro group has been introduced into the position 1 of isoquinoline using a mixture of potassium nitrite, dimethylsulfoxide and acetic anhydride [45]. The mechanism is shown in the quaternisation reaction of a complex of dimethylsulfoxide and the anhydride at nitrogen followed by the key step, the nucleophilic addition of nitrite to the heterocycle (**Figure 20**).

4.1.1 Alkylation and arylation

Reaction with alkyl- or aryl-lithiums proceeds in two discrete steps: addition to give a dihydro-pyridine *N*-lithio-salt which can then be converted into the substituted aromatic pyridine by oxidation, disproportionation or elimination of lithium hydride (**Figure 21**) [46]. The *N*-lithio salts can be observed spectroscopically and, in some cases, isolated as solids [47].

4.1.2 Amination

Amination of pyridines and related heterocycles, generally at a position α to the nitrogen, is called the Chichibabin reaction, [48–50] the pyridine reacting with sodamide in toluene, xylene or dimethylaniline with the evolution of hydrogen. The 'hydride' transfer and production of hydrogen probably involve interaction of amino-pyridine product, acting as an acid, with the anionic intermediate. Vicarious

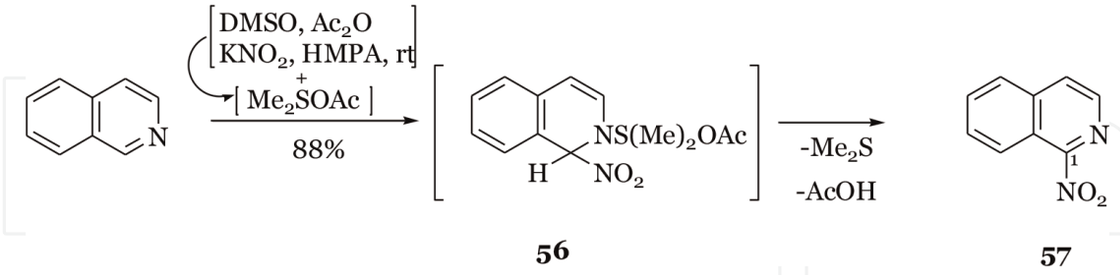


Figure 20.
An example of nucleophilic attack at carbon of isoquinoline.

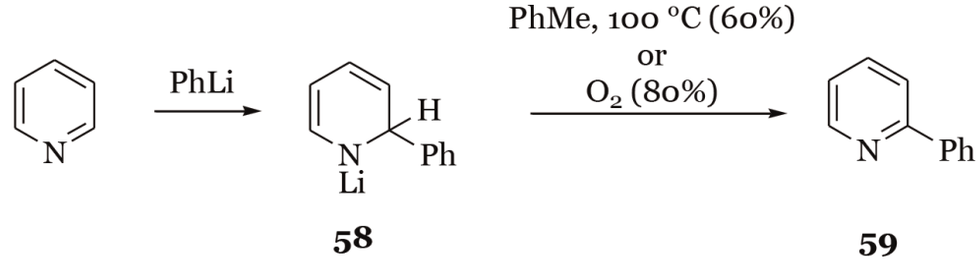


Figure 21.
Arylation of pyridine.

nucleophilic substitution permits the introduction of amino groups *para* (or *ortho* if *para* blocked) to nitro groups by reaction with 1-amino-1,2,4-triazole **61** (**Figure 22**).

The amination of quinoline with potassium amide in liquid ammonia can, depending on conditions, give 2- or 4-aminoquinoline. The quinoline-2-aduct rearranges to the more stable 4-aminated adduct at higher temperatures (**Figure 23**) [51]. Isoquinoline, however, reacts with potassium amide in liquid ammonia at room temperature to give 1-aminoisoquinoline [52, 53].

4.1.3 Silylation

The reaction of pyridine with trimethylsiliconide anion has afforded 4-trimethylsilylpyridine efficiently. This process probably proceeds via a 1,4-dihydro-adduct (which can be trapped as its *N*-CO2Et derivative by addition of ethyl chloroformate), to give the fully aromatic product via hydride shift to silicon (**Figure 24**) [54, 55].

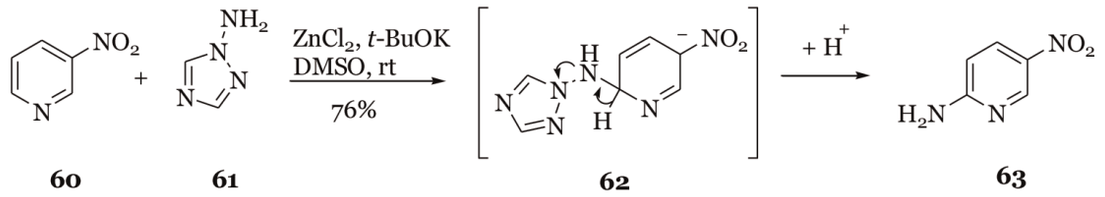


Figure 22.
Amination of pyridine.

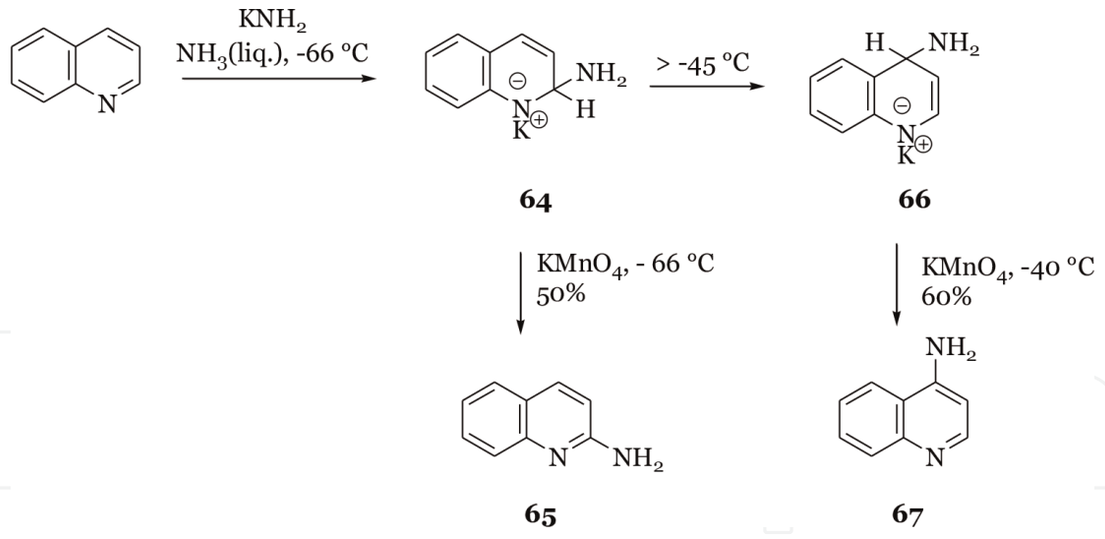


Figure 23.
Amination of quinoline.

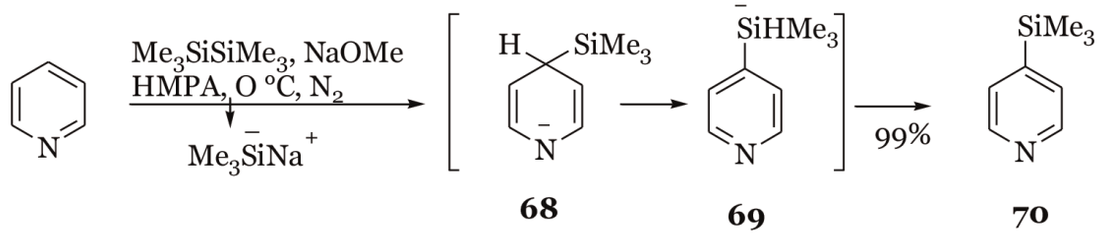
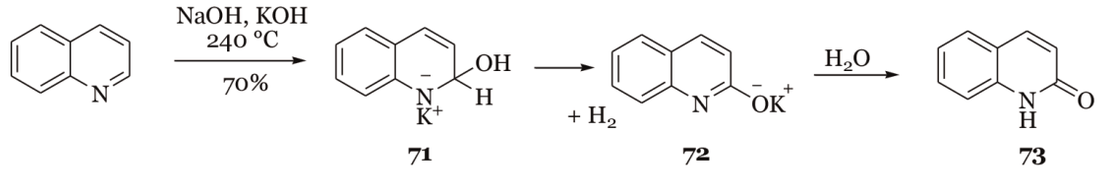


Figure 24.
Silylation of pyridine.



71 72 73

Figure 25.
Hydroxylation of quinoline.

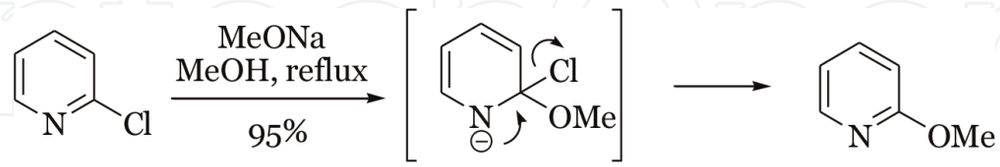


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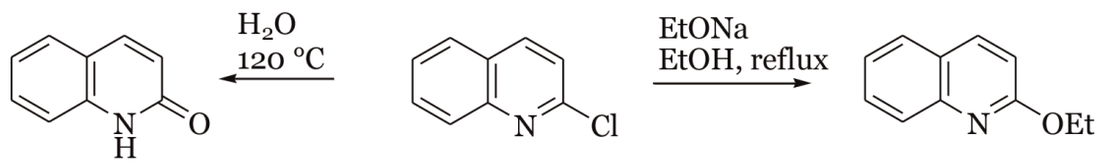
Figure 26.
Nucleophilic substitution of pyridine.



77 78 79

Figure 27.
Nucleophilic substitution of quinoline.

4.1.4 Hydroxylation

Hydroxide ion attacks pyridine only at very high temperatures to produce 2-pyridone in low yield. This can be usefully contrasted with the much more efficient reaction of hydroxide with quinoline and isoquinoline and with pyridinium salts [56].

Quinoline and isoquinoline can be directly hydroxylated with potassium hydroxide at high temperature with the evolution of hydrogen to give 2-Quinolone and 1-isoquinolone as the isolated products (**Figure 25**).

4.2 Nucleophilic substitution with displacement of good leaving groups

Halogen, and some other good leaving groups such as nitro, alkoxysulfonyloxy and methoxy at α- or γ- positions of the pyridine ring are easily displaced by nucleophiles via an addition-elimination mechanism. The nucleophilic substitution of halopyridine and haloquinoline are shown in the **Figures 26** and **27** respectively.

5. Metallation and reactions of *C*-Metallated pyridines, quinolines and isoquinolines

5.1 Direct ring C-H metalation

The heating of pyridine in MeONa-MeOD at 165°C causes an H-D exchange at all positions via small concentrations of deprotonated species. An example of the use of

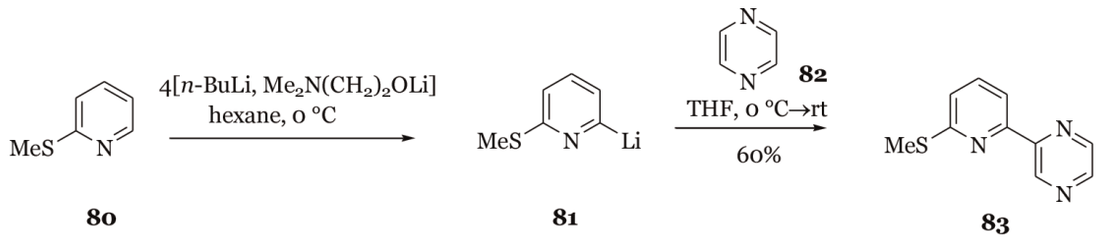


Figure 28.
Lithiation of pyridines.

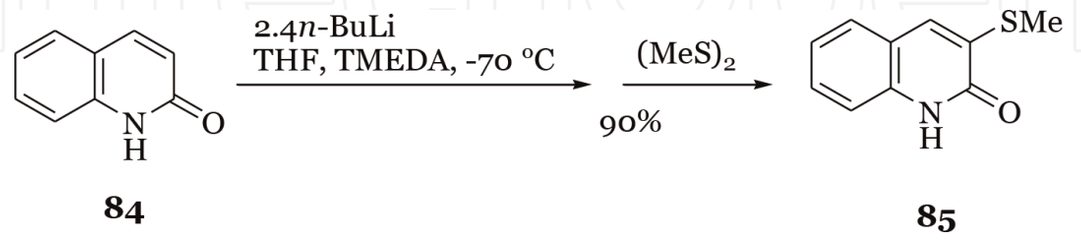


Figure 29.
Lithiation of quinolone.

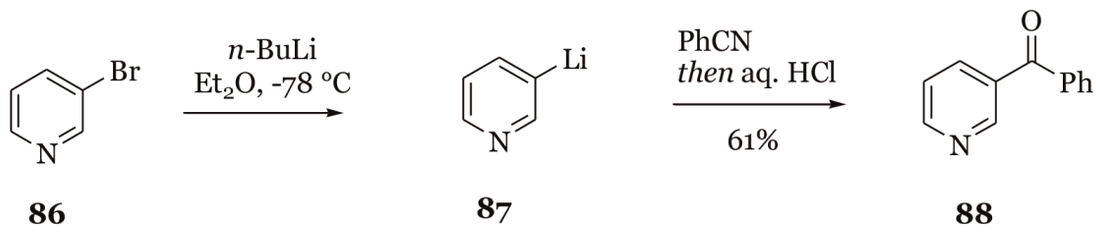


Figure 30.
Metal-halogen exchange of pyridine.

lithiated pyridines, is their nucleophilic addition to azines **82**, to produce bihetaryls **83** on oxidation during work-up (**Figure 28**) [57].

2-Lithiation of 1-substituted 4-quinolones and 3-lithiation of 2-quinolone provides derivatives with the usual nucleophilic propensity (**Figure 29**) [5].

5.2 Metal-halogen exchange

Lithio-pyridines behave as typical organometallic nucleophiles, as in the reaction of 3-bromopyridine with n-butyllithium in ether at −78°C (**Figure 30**) [5].

Nucleophilic addition is a competing reaction in the preparation of lithio-quinolines and isoquinolines via metal-halogen exchange, however the use of low temperatures allow metal-halogen exchange at both pyridine [58] and benzene ring positions [59] in quinolines, and the isoquinoline-1-[60] and 4-positions, [61] subsequent reaction with electrophiles generating *C*-substituted products (**Figure 31**).

6. Photochemical reactions

The ultraviolet irradiation of pyridines can produce highly strained species that can lead to isomerised pyridines or can be trapped. When *N*-methyl-2-pyridone **92** was

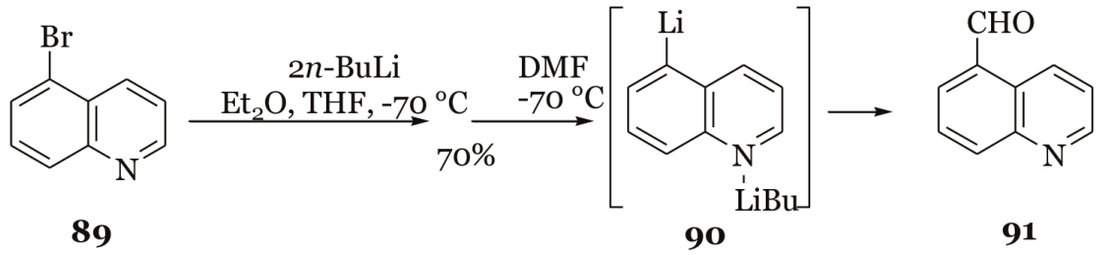


Figure 31.
Metal-halogen exchange of quinoline.

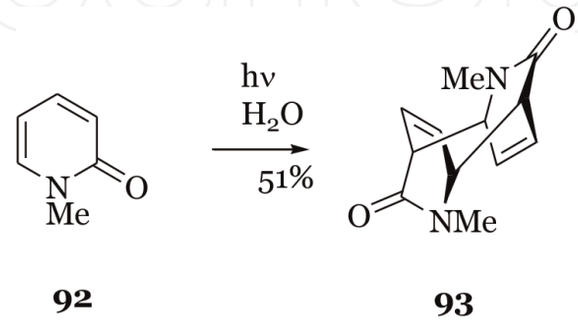


Figure 32.
Ultraviolet irradiation of pyridone.

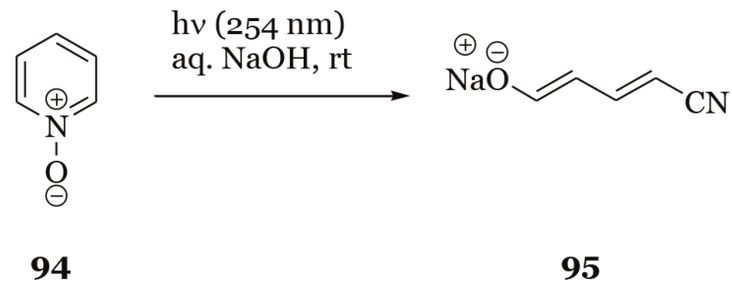


Figure 33.
*Photolysis of pyridine-*N*-oxide.*

irradiated in aqueous solution, a mixture of regio- and stereoisomeric 4π plus 4π photo-dimers **93** were produced (**Figure 32**).

The photolysis of pyridine *N*-oxides in alkaline solution induced ring opening to cyano-dienolates (**Figure 33**) [62].

2-Quinolones undergo 2 + 2 photo dimerization involving the C-3-C-4 double bond [63].

7. Conclusion

The synthesis and reactions of pyridine and its benzo derivatives have been extensively discussed. The Chichibabin synthesis is a notable example of the condensation method of preparing pyridines. Electrophilic substitution reactions occur less readily than the nucleophilic reactions. These reactions have been used for the preparation of versatile intermediates and precursors for biologically active compounds.

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Author details

Adebimpe D. Adesina
Federal University of Agriculture, Abeokuta, Ogun State, Nigeria

*Address all correspondence to: adesinaad@funaab.edu.ng

References

[1] Anderson T. Transactions of the Royal Society Edinburgh. 1849;**16**(123): 463

[2] Korner GG. Science National Economic Palermo. 1869:5. reprinted in Calm, A. and Buchka, K. v. Die Chemie des Pyridins und seiner Derivate, Braunschweig, 1889-1891, which contains an excellent account of the early history of these bases

[3] Scriven EFV. In: Katritzky AR, Rees CW, editors. Comprehensive Heterocyclic Chemistry I. Oxford: Pergamon; 1984. 2, 165, 216, 220

[4] Comins DL, Joseph SP. In: Katritsky AR, Rees CW, Scriven EFV, editors. Comprehensive Heterocyclic Chemistry II. Elsevier, Oxford; 1996. 5, 37, 41, 68, 76, 78, 80, 82, 98

[5] Joule JA, Mills K. Heterocyclic Chemistry. 5th ed. West Sussex: Blackwell; 2010

[6] Frank RL, Seven RP. Pyridines. IV. A study of the Chichibabin synthesis. Journal of the American Chemical Society. 1949;**71**:2629-2635

[7] Weiss M. Acetic acid-ammonium acetate reactions. An improved Chichibabin pyridine synthesis. Journal of the American Chemical Society. 1952; **74**:200-202

[8] Naito T, Yoshikawa T, Ishikawa F, Isoda S, Omura Y, Takamura I. Synthesis of 3-pyridinols. I. Reaction of 5-unsubstituted oxazoles with acrylonitrile. Chemical & Pharmaceutical Bulletin. 1965;**13**:869

[9] Ya Kondrat'eva G, Huan C-H. Doklady Akademii Nauk SSSR. 1965;**164**: 816. (Chem. Abstr., 1966, 64, 2079)

[10] Abbiati G, Arcadi A, Bianchi G, Giuseppe SD, Marinelli F, Rossi E. Sequential amination/annulation/ aromatization reaction of carbonyl compounds and propargylamine: A new one-pot approach to functionalized pyridines. The Journal of Organic Chemistry. 2003;**68**:6959

[11] Lochte HL, Pittman AG. Notes - The nitrogen compounds of petroleum distillates. XXIX. Identification of 5-methyl-6,7-dihydro-1,5-pyridine. The Journal of Organic Chemistry. 1960;**25**: 1462

[12] Trost BM, Gutierrez AC. Ruthenium-catalyzed cycloisomerization-6pi-cyclization: A novel route to pyridines. Organic Letters. 2007;**9**:1473

[13] Donohoe TJ, Johnson DJ, Mace LH, Thomas RE, Chiu JYK, Rodrigues JS, et al. The ammonia-free partial reduction of substituted pyridinium salts. Organic & Biomolecular Chemistry. 2006;**4**:1071

[14] Baudoux J, Judestein P, Cahard D, Plaquevent J-C. Design and synthesis of novel ionic liquid/liquid crystals (IL2Cs) with axial chirality. Tetrahedron Letters. 2005;**46**:1137

[15] Borisov AB, Belsky VK, Goncharova TV, Borisova GN, Osmanov VK, Matsulevich ZV, et al. Sulfenyl halides in the synthesis of heterocycles. 2. Cyclization in reactions of hetarenesulfenyl chlorides with 3,3-dimethyl-1-butene. Chemistry of Heterocyclic Compounds. (English Translation). 2005;**41**:771

[16] Sliwa W. Quaternary salts of pyridines and related compounds. Current Organic Chemistry. 2003;**7**:995

[17] King JA, Bryant GL. Preparation and characterization of crystalline N-acylammonium salts. The Journal of Organic Chemistry. 1992;**57**:5136

[18] Breslow R, Brandl M, Hunger J, Turro N, Cassidy K, Krogh-Jespersen K, et al. Pyridine complexes of chlorine atoms. Journal of the American Chemical Society. 1987;**109**:7204

[19] Tornieporth-Oetting I, Klapoetke T, Passmore J, Anorg Z. The reactivity of the I3+ cations to ammonia, nitriles and pyridine. Allgemeine Chemistry. 1990; **586**:93 (Chem. Abstr., 1991, 114, 16 578)

[20] Silvester MJ. Fluoroheterocyclic compounds: Synthesis, reactions, and commercial applications. Aldrichimica Acta. 1991;**24**:31

[21] Adachi K, Ohira Y, Tomizawa G, Ishihara S, Oishi S. Electrophilic fluorination with N,N'-difluoro-2,2'-bipyridinium salt and elemental fluorine. Journal of Fluorine Chemistry. 2003;**120**:173

[22] Marchais-Oberwinkler S, Nowicki B, Pike VW, Halldin C, Sandell J, Chou Y-H, et al. N-Oxide analogs of WAY-100635: New high affinity 5-HT1A receptor antagonists. Bioorganic & Medicinal Chemistry. 2005;**13**:883

[23] Krebs FC. Functionalisation of the hinge region in receptor molecules for explosive detection. Tetrahedron Letters. 2003;**44**:6643

[24] Razus AC, Birzan L, Nae S, Cristian L, Chiraleu F, Cimpeanu V. Azulene-1-azopyridine 1'-oxides. Dyes and Pigments. 2003;**57**:223

[25] Murray RW, Singh M, Jeyaraman R. Dioxiranes. 20. Preparation and properties of some new dioxiranes. Journal of the American Chemical Society. 1992;**114**:1346

[26] Shereshovets VV, Bachanova LA, Komissarov VD, Vostrikov NS, Tolstikov GA. Izvestiya Akademi Nauk SSSr, Seriya Khimicheskaya. 1982:1922. (Chem. Abstr., 1983, 98, 4465)

[27] Youssif S. Recent trends in the chemistry of pyridine N-oxides. ARKIVOC. 2001;**2001**:242

[28] Jain SL, Sain B. Ruthenium catalyzed oxidation of tertiary nitrogen compounds with molecular oxygen: An easy access to N-oxides under mild conditions. Chemical Communications. 2002;(10):1040

[29] Zhang Y, Lin R. Some deoxygenation and reduction reactions with samarium diiodide. Synthetic Communications. 1987;**17**:329

[30] Akita Y, Misu K, Watanabe T, Ohto A. Deoxygenation of heterocyclic N-oxides by chromium (II) chloride. Chemical & Pharmaceutical Bulletin. 1976;**24**:1839

[31] Malinowski M, Kaczmarek L. Titanium (0) reagents; 2. A selective and efficient deoxygenation of halogen containing heteroaromatic N-oxides. Synthesis. 1987;(11):1013

[32] Balicki R, Kaczmarek L, Malinowski M. Selective reduction of the N–O bond in heteroaromatic N-oxides by TiCl4/SnCl2. Synthetic Communications. 1989;**19**:897

[33] Balicki R. Efficient deoxygenation of heteroaromatic N-oxides with ammonium formate as a catalytic hydrogen transfer agent. Synthesis. 1989;(8):645

[34] Katritzky AR, Lam JN. Heterocyclic N-oxides and N-imides. Heterocycles. 1992;**33**:1011

[35] Olah GA, Arvanaghi M, Vankar YD. Synthetic methods and reactions. 87. Deoxygenation of pyridine N-oxides with sodium iodide-trimethyl(ethyl) amine-/sulfur dioxide complexes. Synthesis. 1980;(8):660

[36] Katritzky AR, Fan W-Q. Mechanisms and rates of the electrophilic substitution reactions of heterocycles. Heterocycles. 1992;**34**:2179

[37] Bakke JM. Nitropyridines, their synthesis and reactions. Journal of Heterocyclic Chemistry. 2005;**42**:463

[38] den Hertog HJ, den Does LV, Laandheer CA. Recueil des Travaux Chimiques des Pays-Bas. 1962;**91**:864

[39] Pearson DE, Hargreave WW, Chow JKT, Suthers BR. The swamping catalyst effect. III. The halogenation of pyridine and picolines. The Journal of Organic Chemistry. 1961;**26**:789

[40] McElvain SM, Goese MA. The sulfonation of pyridine and the picolines. Journal of the American Chemical Society. 1943;**65**:2233

[41] Beisler JA. A short synthesis of several gambir alkaloids. Tetrahedron. 1970;**26**: 1961

[42] McCasland GE. The preparation of 8-quinolinesulfonic acid. The Journal of Organic Chemistry. 1946;**11**:277

[43] Tomasik P, Woszczyk A, Abramovitch RA. Oxidation of pyridines with copper sulfate. Journal of Heterocyclic Chemistry. 1979;**16**:1283

[44] Gillard RD, Hall DPJ. Simple oxidations of pyridines: Zinc sulphates or natural sand as remarkably specific catalysts. Journal of the Chemical Society, Chemical Communications. 1988;(17):1163

[45] Baik W, Yun S, Rhee JU, Russell GA. DMSO-Ac2O promoted nitration of isoquinolines. One step synthesis of 1-nitroisoquinolines under mild conditions. Journal of Chemical Society, Perkin Transactions. 1996;(15):1777

[46] Evans JCW, Allen CFH. Organic Synthesis, Collection, II. 1943:517

[47] Illuminati G, Stegel F. The formation of anionic σ-adducts from heteroaromatic compounds: Structures, rates and equilibria. Advances in Heterocyclic Chemistry. 1983;**34**:305

[48] Leffler MT. Organic Reactions. 1942; **1**:91

[49] McGill CK, Rappa A. Advances in the Chichibabin reaction. Advances in Heterocyclic Chemistry. 1988;**44**:2

[50] Vorbruggen H. Advances in amination of nitrogen heterocycles. Advances in Heterocyclic Chemistry. 1990;**49**:117

[51] Zoltewicz J, Helmick LS, Oestreich TM, King RW, Kandetzki PE. Addition of amide ion to isoquinoline and quinoline in liquid ammonia. Nuclear magnetic resonance spectra of anionic sigma complexes. The Journal of Organic Chemistry. 1973;**38**:1947

[52] Berstrom FW. Justus Liebigs Annalen der Chemie. 1935;**515**:34

[53] Ewing GW, Steck EA. Absorption spectra of heterocyclic compounds. I. Quinolinols and isoquinolinols. Journal of the American Chemical Society. 1946;**68**: 2181

[54] Postigo A, Rossi RA. A novel type of nucleophilic substitution reactions on nonactivated aromatic compounds and benzene itself with trimethylsiliconide anions. Organic Letters. 2001;**3**:1197

[55] Postigo A, Vaillard SE, Rossi RA. Reactions of trimethylstannide and trimethylsiliconide anions with aromatic and heteroaromatic substrates. Journal of Physical Organic Chemistry. 2002;**15**:889

[56] Chichibabin AE. Chemische Berichte. 1879;**1923**:56

[57] Gros P, Fort Y. Direct synthesis of unsymmetrical bis-heterocycles from 2-heterosubstituted 6-lithiopyridines. Journal of Chemical Society, Perkin Transactions. 1998;**1**:3515

[58] Gilman H, Soddy TS. Carbonation of lithium derivatives of certain quinolines and isoquinolines. The Journal of Organic Chemistry. 1957;**22**:565

[59] Wommack JB, Barbee TG, Thoennes DJ, McDonald MA, Pearson DE. Synthesis of quinoline- and isoquinolinecarboxaldehydes. Journal of Heterocyclic Chemistry. 1969; **6**:243

[60] Fernandez M, de la Cuesta E, Avendano C. Metallation of 2 (1H)-quinoline: Synthesis of 3-substituted compounds. Synthesis. 1995;(11):1362

[61] Baradarani MM, Dalton L, Heatley F, Joule JA. Cyclising nucleophilic addition to azinium systems. Part 1. Reaction of 3-indol-2-ylpyridine, 3-indol-2-ylquinoline, 4-indol-2-ylisoquinoline and pyrido [3, 4-a]carbazoles with acetic anhydride. Journal of Chemical Society, Perkin Transactions. 1985;**1**:1503

[62] Buchardt O, Christensen JJ, Nielsen PE, Koganty RR, Finsen L, Lohse C, et al. Photochemical studies. XXII. Photochemical ring-opening of pyridine N-Oxide to 5-Oxo-2-pentenenitrile and/or 5-Oxo-3-pentenenitrile. A reassignment of structure. Acta Chemica Scandinavica, Series B. 1980;**34**:31

[63] Woodward RB, Doering WE. The total synthesis of quinine. Journal of the American Chemical Society. 1945;**67**:860