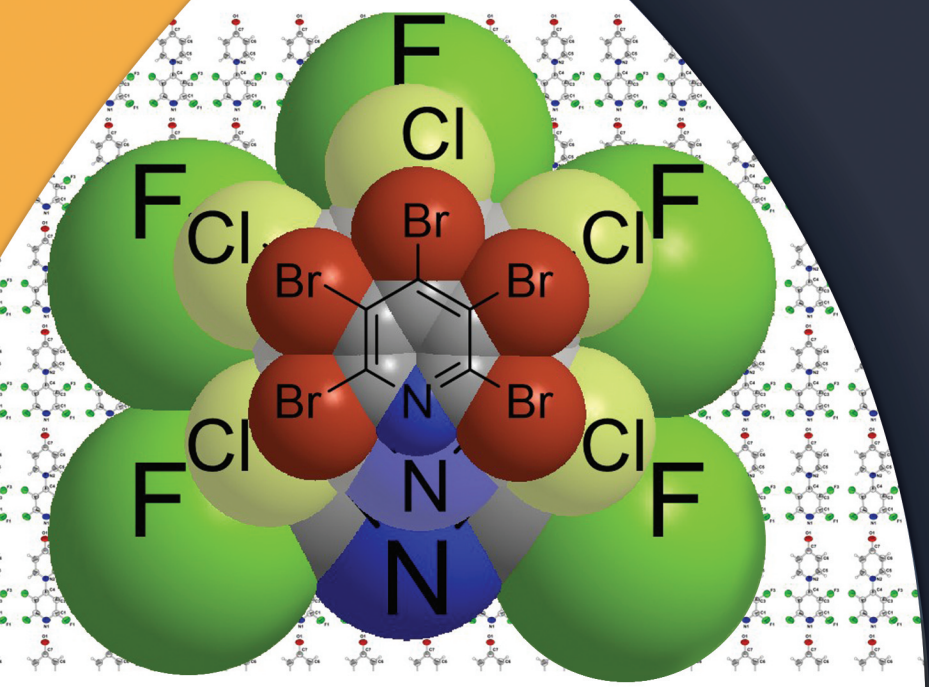
PERHALOPYRIDINES:

SYNTHESIS AND SYNTHETIC UTILITY



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Perhalopyridines: Synthesis and Synthetic Utility

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ISBN (Online): 978-981-14-7379-1

ISBN (Print): 978-981-14-7377-7

ISBN (Paperback): 978-981-14-7378-4

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PREFACE

The heterocyclic ring is found in half of known compounds and most of these compounds have possessed an aromatic heterocyclic ring. Heteroaromatic compounds were found in a great number of metabolism products, pest-controlling agents, dyeing agents, flavors and commercial synthetic compounds such as drugs. Heterocyclic systems have broad applications especially in pharmaceutical chemistry and this accelerated the discovery and development of the chemistry of heterocycles. Heteroaromatic compounds have broad chemistry and numerous investigations have been carried out for synthetic methods of heteroaromatic derivatives to continuous development and applications of these systems. Perhalogenated pyridines are an attractive group of heteroaromatics that play an important role in organic chemistry, biochemistry, and pharmaceutical chemistry. These compounds have great interesting chemistry because of their reactivity toward nucleophilic attack. Therefore, they have become unique scaffolds for the construction of other heterocyclic and macrocyclic compounds. So far, there has been extensive research on perhalopyridine compounds. Some of the books published in the heterocyclic chemistry area have been cited for the synthesis, their reactions and their applications. For example, in "Fluorinated heterocyclic compounds: synthesis, chemistry, and applications" (Edited by Petrov, Viacheslav A. 2009), a brief summary of perfluoropyridine has been gathered or in "Pyridine and Its Derivatives" (Edited by R. A. Abramovitch 2009), some aspect about pentafluoro- and pentachloropyridine are briefly mentioned. Recently, we published a review article concerning "Utility of pentachloropyridine in organic synthesis" in the journal of the Iranian chemical society. In this book, we tried to focus on perhalopyridine including perfluoropyridine, perchloropyridine, perbromopyridine, so that readers can easily get to know the chemistry of these compounds. I would like to thank my coworker, Dr. Alireza Poorfreidoni, who helped me complete this book. I wish to thank those that reviewed the book and provided helpful suggestions. Finally, I have to thank my wife, Fatemeh SayyedBagheri, and my children, Javad, Mohadeseh, Ali, and Zahra, for putting up with me during manuscript preparation. I would also like to thank Bentham Science for the opportunity to publish this book. I have no conflicts of interest in relation to this book.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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FOREWORD

This book highlights all aspects of the synthetic reactions and various applications of perhalopyridines. Halogenated pyridines can be used as interesting starting materials in a wide range of organic synthesis and/or synthetic organic methodologies. Substituted pyridine compounds are used generally as starting materials in the nucleophilic substitution reactions. Also, they have important features of various medicinal agents. Due to synthetic difficulties in the synthesis of the highly substituted pyridine derivatives from pyridine itself, perhalopyridines have special importance in this regard. The author, Prof. Reza Ranjbar-Karimi, has attracted many outstanding contributions to emphasize regio- and chemoselectivity of perhalopyridines toward various nucleophiles. I think that this book will be a very valuable source of information for every chemist in the area of heterocyclic chemistry and a useful document in the area of synthetic/medicinal chemistry.

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Abbreviations

1,4-CHD 1,4-Cyclohexadiene

AChE Acetylcholinesterase

AE Addition-Elimination

ANRORC Addition of the Nucleophile, Ring Opening, and Ring Closure

BDC Benzodichalcogenophene

BINOL 1,1′-Binaphthyl-2,2′-diol

COD 1,5-Cyclooctadiene

Cp Cyclopentadienyl

DBU 1,8-Diazabicyclo[5.4. 0]undec-7-ene

DCE 1,2-Dichlroethane

DIBAL Diisobutylaluminium Hydride

DIPEA Diisopropylethylamine

DLP Lauroyl Peroxide

DMAD Dimethyl Acetylenedicarboxylate

DMEU 1,3-dimethyl-2-imidazolidinone

DMF N,N-Dimethylformamide

DMI 1,3-dimethylimidazolidin-2-one

DMSO Dimethyl Sulfoxide

DNA Deoxyribonucleic Acid

DPPA Diphenyl Phosphorazidate

EA Elimination-Addition

HDF Hydrodefluorination

HOMO Highest Occupied Molecular Orbital

LDA Lithium diisopropylamide

MAs Meldrum's Acids

NHCs N-heterocyclic Carbenes

OLEDs Organic Light-Emitting Diodes

PET Photoinduced Electron Transfer

PFC Perfluorocarbone

$S_{RN}1$ Unimolecular Radical Nucleophilic Substitution

TBHS Tetrabutylammonium hydrogen sulfate

TFA Trifluoroacetic Acid

TFAA Trifluoroacetic Anhydride THF: Tetrahydrofuran

TMG 1,1,3,3-Tetramethylguanidine

TMSCl Trimethylsilyl chloride

Vis/NIR Visible/Near Infra-Red

CHAPTER 1

Properties of Perhalopyridines

Abstract: The introduction of halogen atoms on the pyridine ring causes significant changes in its properties. Halogens reduced basicity of pyridine ring as well as dipole moment. The presence of dense halogen atoms renders a higher density of perhalopyridines than pyridine. Fluorine atoms cause a low-field shift of pyridine carbons than chlorine and bromine atoms. Perhalopyridines are mainly involved in nucleophilic substitution reactions due to the electron-withdrawing nature of halogens while perfluoropyridines are more active than others.

Keywords: ^{13}C-NMR spectrum, ^{19}F-NMR spectrum, Activating Effect, Addition-Elimination Mechanism, Basicity, Chemical Shifts, Density, Dipole Moment, Intermolecular Forces, IR spectrum, Meisenheimer Intermediate, Nucleophilic Substitution, Pentabromopyridine, Pentachloropyridine, Pentafluoropyridine, Raman Analysis, Shielding Effect, Spectroscopy, Steric Factors, UV-Vis Spectrum.

1. PHYSICAL AND CHEMICAL PROPERTIES

Pentafluoropyridine is a colorless, mobile and almost odorless liquid with boiling point 83-84 °C. Replacement of a C-F group by N in fluorocarbons has little effect on the boiling point (C_6F_6 has b. p. 81 °C) [1]. The boiling point pentafluoropyridine is lower than the corresponding hydrocarbon (pyridine; bp 115 °C), and this attributed to the much lower intermolecular forces and the very low basicity of pentafluoropyridine. Fluorine atoms ortho to ring nitrogen have a major influence on low basicity of the system and superacids are required to protonate pentafluoropyridine [1, 2]. Its reaction with hydrogen chloride not converted to hydrochloride form, but react with hot aqueous solution of sodium hydroxide and formed 2,3,5,6-tetrafluoro-4-hydroxypyridine in 58% yield. 40% aqueous solution of sodium hydroxide converted completely pentafluoropyridine to ammonia, carbonate, fluoride ions and 3,5,6-trifluoro-2,4-dihydroxypyridine (20% yield) in 12 h [3]. Replacement of C-F groups by C-Cl in leaded to increasing intramolecular forces and basicity of system, thus pentachloropyridine has more intermolecular forces and basicity in comparison with pentafluoro-pyridine [4, 5]. It is methylated by methyl fluorosulphonate and give the

corresponding *N*-methylpyridinium fluorosulphonate [6]. Also, it converted to tetrachloro-2-hydroxypyridine on treatment with a mixture of acetic acid and concentrated sulphuric acid [6]. Similar to pentachloropyridine, pentabromopyridine methylated on treatment with methyl fluorosulphonate [7].

The dipole moment (μ) of pentafluoropyridine is 1.26 D [8, 9], which is lower than pyridine (2.24 D [8], 2.26 D [9]). Fluorine atoms on pyridine ring (especially para fluorine) have major effect on decreasing dipole moment of pyridine. Also, it has lower dipole moment than pentachloropyridine (1.53 D) and pentabromopyridine (2.01 D) due to lower electron affinity of Cl and Br atoms than F atom [8]. Presence of five dense fluorine atoms on pentafluoropyridine render more density of system (1.540 g/cm^3) than pyridine (0.987 g/cm^3) (Fig. **1-1**) [9].

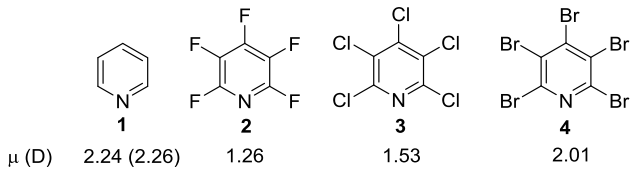


Fig. (1-1). Dipole moment values of pyridine and pentahalpoyridines.

2. SPECTROSCOPY

Aromatic character of pentafluoropyridine has been shown by its spectroscopy properties. IR and Raman analysis confirmed plannering of pentafluoropyridine. IR spectrum of pentafluoropyridine has been shown strong bands at 980, 1075 and 1081 cm^{-1} attributed to stretching vibrations of C-F bonds and three strong bands at 1497, 1529, 1645 cm^{-1} for pyridine ring. UV-Vis spectrum of pentafluoropyridine has been shown a type B absorption band at 256 μm [3]. In ^{19}F-NMR spectrum of pentafluoropyridine, the resonances of the *ortho*, *meta* and *para* fluorines located at δ = -86.72, -160.1 and -132.82 ppm, respectively [10]. In ^{13}C-NMR spectroscopy, carbons of pentafluoropyridine appear to multiplets because of the presence of fluorine atoms. In ^{13}C-NMR spectrum ($CDCl_3$, 22.635 MHz) of pentafluoropyridine, $C_{(3,5)}$, $C_{(2,6)}$ and $C_{(4)}$ appeared at δ = 134.3, 144.8 and 150.3 ppm, respectively [10]. A comparison of chemical shifts of pentachloropyridine carbons with that for pentafluoropyridine indicates that the chlorine atom at 2-position lead to a low-field shift, while at 3- and 4-positions has a shielding effect (Table **1-1**) [10]. In contrast with chlorine atom, bromine atom at 2-position has shielding effect as well as 3- and 4-positions in comparison between pentabromopyridine and pentafluoropyridine (Table **1-1**) [11].

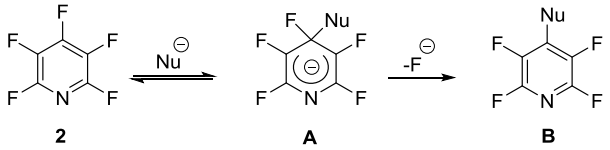
Table 1-1. Spectroscopic properties of pentahalopyridines.

^{13}C-NMR	$C_{2,6}$	$C_{3,5}$	C_4
C_5F_5N[a]	144.8	134.3	150.3
C_5Cl_5N[a]	146.8[a]	129.9	144.9
C_5Br_5N[b]	141.2	127[b]	140.4[b]

[a] 22.635 MHz, $CDCl_3$
[b] 75 MHz, DMSO-d_6

3. REACTIONS

Pentahalopyridines and their derivatives are very active toward aromatic nucleophilic substitution reactions due to presence of halogen atoms on pyridine ring and their nucleophilic substitution reactions have been used widely in organic synthesis. Substitution reactions carried out *via* various mechanisms. Aromatic nucleophilic substitution reactions proceed frequently *via* two steps addition-elimination mechanism (AE mechanism) [12 - 14]; but, EA [15 - 17], SN (ANRORC) [18], $S_{RN}1$ [19 - 21] mechanisms are also observed. 3-position of pyridine ring is inert toward nucleophilic attack, unless, elimination-addition mechanism acts by amide ions or metallic catalysts [22]. In general, 2- and 4-positions of pyridine ring are most activated sites toward nucleophilic attack due to the stabilizing influence of the ring nitrogen atom in the transition state [23 - 25]. Nucleophilic substitution reactions in these systems followed from bimolecular addition-elimination mechanism *via* meisenheimer intermediate (Scheme **1-1**) [26, 27].



Scheme 1-1. Meisenheimer intermediate in pentafluoropyridine **2**.

A comparison between these compounds, pentafluoropyridine **2** is more activated system than pentachloropyridine **3** and pentabromopyridine **4** in nucleophilic substitution reactions because of high activating effect of fluorine atom than chlorine and bromine atoms. Furthermore, order reactivity toward nucleophilic attack in pentafluoropyridine is 4 > 2 >> 3 (Scheme **1-2**) [28 - 30], while it for pentachloropyridine is changed depending on nature of solvent and nucleophile

CHAPTER 2

Perfluoropyridines

Abstract: Fluorine atom has unique properties and has a great interest in organic chemistry and pharmaceuticals. Insertion of fluorine atoms on pyridines induces significant properties to the pyridine ring. The introduction of fluorine atoms on pyridine is carried out by the fluorination of pyridine or pentachloropyridine. The withdrawing nature of these atoms is mainly responsible for the high reactivity of perfluoropyridines toward nucleophilic attack. Therefore, perfluoropyridines are a significant starting material for the synthesis of other substituted pyridines, ring-fused systems as well as macrocyclic compounds *via* reaction with various monodentate and bidentate nucleophiles, whereas the nature of nucleophile, reaction condition, and solvent have a basic role in the regiochemistry of the reactions. Furthermore, these compounds could participate in organometallic reactions by the reaction of halogen atom with metals and organometallic reagents. Additionally, they underwent hydrodefluorination in photochemical reactions in the presence of catalysts.

Keywords: Bidentate Nucleophile, Continuous Flow Processes, Copolymers, Hard–Hard Interaction Principle, Hydrodefluorination, Macrocycle, Medicinal Chemistry, Meisenheimer Intermediate, Monodentate Nucleophile, *N*-Methylated Pyridinium, Nucleophilic Substitution, Organometallic Perfluoroheteroaromatics, Pentafluoropyridine, Pentafluoropyridine Cation, Photochemical Reaction, Polyhaloheterocyls, Radical Addition, Regioselectivity, Ring-Fused, Tetrafluoropyridine.

1. INTRODUCTION

Chemistry of fluorinated heterocyclic compounds is rapidly progressing. In the last decade, checking of fluorine chemistry international conferences has shown close to 40 percent of presented papers containing heterocyclic compounds due to high and diverse biological activity of fluorinated heterocyclic compounds. Also, fluorinated heterocyclic systems used in dielectrics, liquid crystals, High temperature lubricants, complexones and extragents. About 10% of the total commercial drugs currently used for the medical treatment are containing fluorine atom. Over 50 years, large number fluorinated medicinal and agrochemical compounds have been discovered and attracted considerable interest toward development of fluorinated compounds have been existed. The strong interest to

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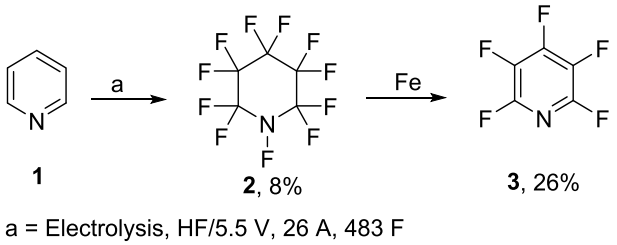
fluorinated systems arose from unique biological properties of fluorine. Also, development fluorine chemistry fluorination technology accelerated due to availability of the fluorinated synthetic blocks, the broadly reliable fluorination technology, the effective fluorinating reagents [1].

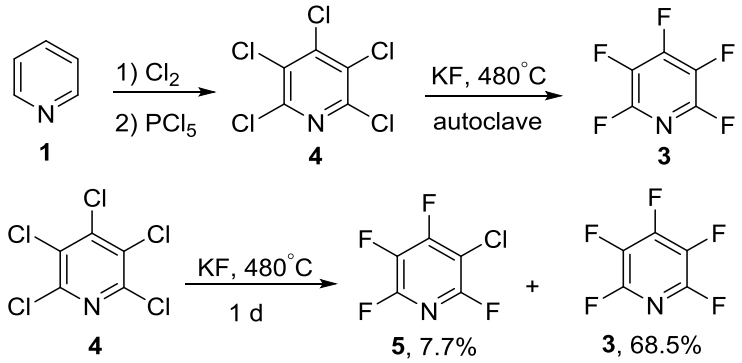
2. SYNTHESIS OF PENTAFLUOROPYRIDINE

For first time, pentafluoropyridine **3** was prepared in low yield from electrochemical fluorination of pyridine **1** and following elimination of fluorine (Scheme **2-1**) [2].



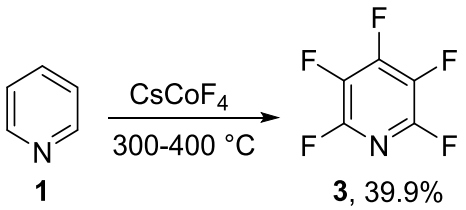
Scheme 2-1. Synthesis of pentafluoropyridine **3** by electrochemical methods.

Standard method for synthesis of pentafluoropyridine **3** is halogen exchange of perchlorinated systems with KF in autoclave at high temperature (Scheme **2-2**) [3].



Scheme 2-2. Synthesis of pentafluoropyridine **3** by halogen exchange method.

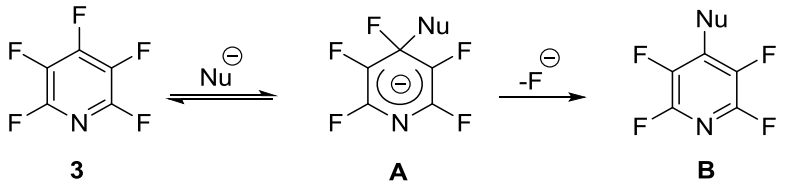
Fluorination of pyridine over caesium tetrafluorocobaltate (III) at 300-400°C gave pentafluoropyridine **3** and a mixture of other products (Scheme **2-3**) [4].



Scheme 2-3. Synthesis of pentafluoropyridine **3** by direct fluorination of pyridine.

3. REACTION MECHANISM

Pyridine is not very active aromatic electrophilic substitution, but active toward nucleophilic attack [5]. Density of electronic cloud in pyridine follows the sequence 4 > 2 > 3; therefore, it is expect to follow order reactivity 4 > 2 >> 3 toward nucleophilic attack [6]. Nucleophilic substitution reactions in *N*-heterocyclic systems followed from bimolecular addition-elimination mechanism *via* meisenheimer intermediate (Scheme **2-4**) [7, 8]. Nevertheless, some reactions carried out *via* elimination-addition mechanism when starting materials are inactive and nucleophile is very basic [9, 10].



Scheme 2-4. Addition nucleophile mechanism to pentafluoropyridine **3**.

Polyhaloheterocyls are more active systems than corresponding benzoied compounds toward aromatic nucleophilic substitution. Activating effect of aza group is similar to nitro group effect in aromatic systems and active *ortho* and *para* positions [9, 11]. Halogen substitution act as a good activating group because of the effect of electron induced withdrawing as well as a good leaving group. Polychloro- and polyfluoroaromatic compounds become easily undergo nucleophilic substitution reactions toward various nucleophiles [12 - 14].

Chemistry of pentafluoropyridine affected by reaction with nucleophile species due to presence of electronegative atoms of fluorine that activate the ring toward

CHAPTER 3

Perchloropyridines

Abstract: Preparation of pentachloropyridine is carried out by chlorination of pyridine ring or it is obtained from perchlorocyclopentene-3-one *via* several steps. Perchloropyridines are mainly involved in nucleophilic reactions and produce various substituted perchloropyridines, whereas the nature of solvent and nucleophile hindrance affect the regiochemistry of the reactions. Furthermore, these compounds participated in cross-coupling reactions and produced arylated and alkenylpyridines pyridines. Additionally, they are involved in photochemical reactions and produce ring-fused systems. Oxidation of pentachloropyridine gave pentachloropyridine-*N*-oxide, which is active toward nucleophiles at *ortho* positions. The reaction of perchloropyridines with methyl fluorosulphonate produced corresponding *N*-methylated compounds, which are active toward nucleophilic attack. Organometallic compounds obtained from pentachloropyridined in reaction with various electrophiles produced corresponding substituted products.

Keywords: Biological Activities, Heteronium Salts, *N*-ethylpentachloropyri-dinium Fluoroborate, Nucleophilic Substitution Reactions, Pentaalkynylpyridines, Pentachloropyridine, Pentachloropyridine-*N*-oxide, Sonogashira Cross-Coupling, Steric Hindrance, Suzuki–Miyaura Cross-Coupling, Tetraalkenylpyridines, Tetraalkynylpyridines, Tetrachloro-4-pyridyl Copper, Tetrachloro-4-pyridyl-lithium, Tetrachloro-4-pyridylmagnesium Chloride, Tetrachloropyridines, Tetrahydro-5H-pyrido[3,2-*b*]indoles, Tetrahydro-9H-pyridi[2,3-*b*]indoles, Thiazolo[2,3-*b*] quinazolines, Trichloro-thiazolo[3,2-*a*]pyrimidines.

1. INTRODUCTION

Pentachloropyridine is commercially available and its chemistry has been investigated in some detail. The first synthesized compound is attributed to Sell and Dooston [1], but there is a possibility that the first time was synthesized by Kekule [2]. The base strength of polychloropyridines decreased by increasing the chlorine atoms. Therefore, pyridines with high chlorine substituents are resistant toward the formation of their salts. Nevertheless, pentachloropyridine, tetrachloro-2-fluoropyridine and 3,5-dichlorotrifluoropyridine have been methylated by methyl fluorosulfonate [3, 4]. Pentachloropyridine on treatment

with a mixture of acetic acid and concerted sulfuric acid converted to tetrachloro-2-hydroxypyridine *via* protonation of pyridine nitrogen [5].

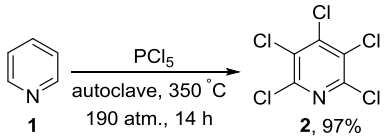
Polychloroheteroaromatic compounds have a great interest in the industry and showed a wide range of biological activities such as herbicides and pesticides [6]. Tetrachloro-4-sulfanylpyridine, 2,3,5-trichloro-4,6-bis-sulfanylpyridines and 3,5-dichloro-2,4,6-tris-sulfanylpyridines have found interest as bactericides, as pesticides for controlling bacteria, insects, crustaceans, nematodes, fungi and weeds, and as host compounds [7, 8]. Also, 2,6-dichloro-4-phenylpyridine-3,5-dicarbonitrile, 3,4,5-trichioro-2,6-dicyanopyridine and 4-pyridine-2,3,5-6-tetrachlorosulfonylacetic acid ethyl ester have been found as a fungicide for treatment against Peronosporu fungi, against soil fungi in cereals and cotton, and for seed treatment, respectively [9].

Polychlorinated heterocycles played an important role in the synthesis of the corresponding perfluoro compounds [10]. For example, pentachloropyridine is used as intermediates for the synthesis of other useful material such as pentafluoropyridine [11].

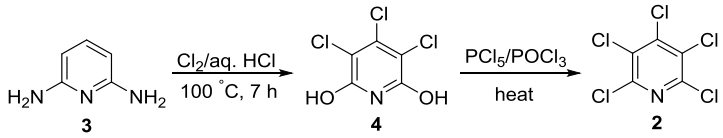
2. SYNTHESIS OF PENTACHLOROPYRIDINE

2.1. By Straight Chlorination

Vapor phase chlorination of pyridine by chlorine at 250˚C produced a small amount of pentachloropyridine [12]. In a similar method, 2-chloropyridine and α-picoline produced pentachloropyridine [6]. Chlorination of pyridine in excess phosphorus pentachloride at 210-220˚C for 15-20 h produced a mixture of products [1, 2]. Higher yield of pentachloropyridine is obtained at higher temperatures and reaction time and using nickel-lined autoclave [11, 13]. When a mixture of pyridine and phosphorus pentachloride in mole ratio 1:12 heated at 350˚C for 14 h, pentachloropyridine obtained in 97% yield (Scheme **3-1**) [13]. A laboratorial method for synthesis of pentachloropyridine is included reaction of 2,6-diaminopyridine with chlorine at the presence of HCl and the subsequent reaction with phosphorus pentachloride and phosphoryl chloride (Scheme **3-2**) [14]. In addition, chlorination of piperidine with chlorine at the presence of carbon tetrachloride has been produced pentachloropyridine along with other products [6]. An unusual method for preparation of pentachloropyridine included self-condensing photochemical reaction of acrylonitrile and the subsequent reaction with chlorine. Pentachloropyridine produced mainly if valeronitrile to be used [6].



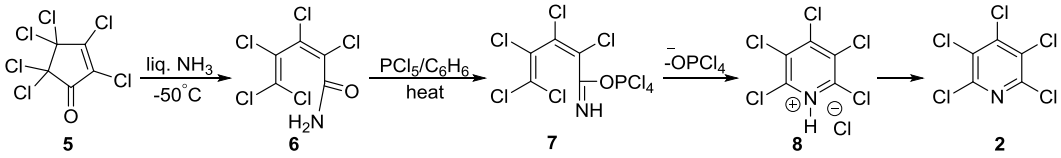
Scheme 3-1. Preparation of pentachloropyridine **2** from pyridine **1**.



Scheme 3-2. Preparation of pentachloropyridine **2** from 2,6-diaminopyridine **3**.

2.2. By Ring-closing Method

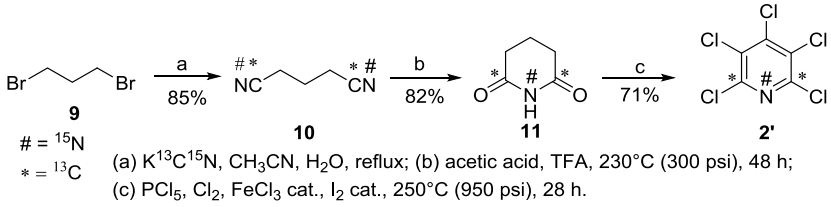
Reaction of perchlorocyclopentene-3-one with ammonia and the subsequent reaction with phosphorus pentachloride produced pentachloropyridine as major product (Scheme **3-3**) [15]. Also, tetrachloro-*N*-methyl-2-pyridone on reaction with a mixture of phosphorus pentachloride and phosphoryl chloride converted to pentachloropyridine [16].



Scheme 3-3. Synthesis of pentachloropyridine **2** from perchlorocyclopentene-3-one **5**.

2.3. Synthesis of Pentachloropyridine-1-^{15}N-2,6-$^{13}C_2$

Pentachloropyridine-1-^{15}N-2,6-$^{13}C_2$ has been synthesized from glutarimide-1-^{15}*N*-2,6-$^{13}C_2$ which obtained from reaction of 1,3-dibromopropane with K^{13}C^{15}N followed by acetic acid and trifluoroacetic acid (Scheme **3-4**) [17].



Scheme 3-4. Synthesis of pentachloropyridine-1-^{15}N-2,6-$^{13}C_2$**2′**.

CHAPTER 4

Perbromopyridines

Abstract: Pentabromopyridine is prepared from 4-hydroxypyridine *via* two pathways. Pentabromopyridine is less active than pentachloro- and pentafluoropyridine toward nucleophilic attack. Its nucleophilic reaction is affected by the hindrance of the bromine atom. Oxidation and methylation of pentabromopyridine give pentabromopyridine-*N*-oxide and *N*-methylbromopyridinium salt. Metal-halogen exchange between pentabromopyridine and *n*-butyl-lithium or magnesium give tetrabromo-4-pyridyl-lithium and tetrabromo-4-pyridylmagnesium bromide. 2,4,6-tribromo-3,5-difluoropyridine is obtained from the bromination of pentafluoropyridine in the reaction with nucleophiles at the C-F bond. Cross-coupling reactions of 2,4,6-tribromo-3,5-difluoropyridine and 3,5-dibromo-2,6-dichloropyridine produced arylated and alkenylpyridines pyridines.

Keywords: 2,3,5,6-Tetrabromo-4-pyridylamidophosphate Esters, 2,3,5,6-Tetrabromo-4-pyridylmethylsulfoxide, 2,4,6-Triazido-3,5-dibromopyridine, 2,4,6-Tribromo-3,5-difluoropyridine, 2,4,6-Tris(triethoxyphosphazenyl)-3,5-dibromopyridine, 2,6-dichloro-3,5-dialkynyl-substituted Pyridines, 2-*N*,N-dialkylaminotetrabromopyridines, 3,5-Dibromo-2,6-dichloropyridine, 3,5-Dibromo-2,6-dichloropyridine, Lithium–bromine Exchange, Nitrotetrabromopyridines, *N*-Methylbromopyridinium Fluorosulphonate, Pentabromopyridine, Pentabromopyridine-*N*-oxide, Suzuki Cross-coupling Reaction, Tetraalkynylpyridines, Tetrabromo-4-pyridyl-lithium, Tetrabromo-4-pyridylmagnesium Bromide, Tetrabromopyridine-4-sulfenyl Chloride, Tetrabromopyridine-4-thiol.

1. SYNTHESIS OF PENTABROMOPYRIDINE

Pentabromopyridine **3** was prepared *via* a two steps method from 4-hydroxypyridine **1** [1]. The reaction of 4-hydroxypyridine with bromine in 80% oleum gives 2,3,5,6-tetrabromo-4-hydroxypyridine **2**, while it converted to pentabromopyridine **3** on treatment with phosphorus oxybromid (Scheme **4-1**). Also, 2,3,5,6-tetrabromo-4-hydroxypyridine was obtained from the reaction of 4-hydroxypyridine with 48% hydrobromic acid, and followed by treatment with bromine in 80% oleum (Scheme **4-1**).

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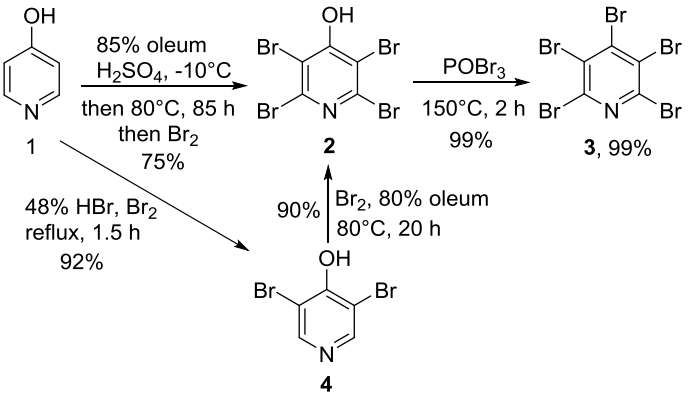
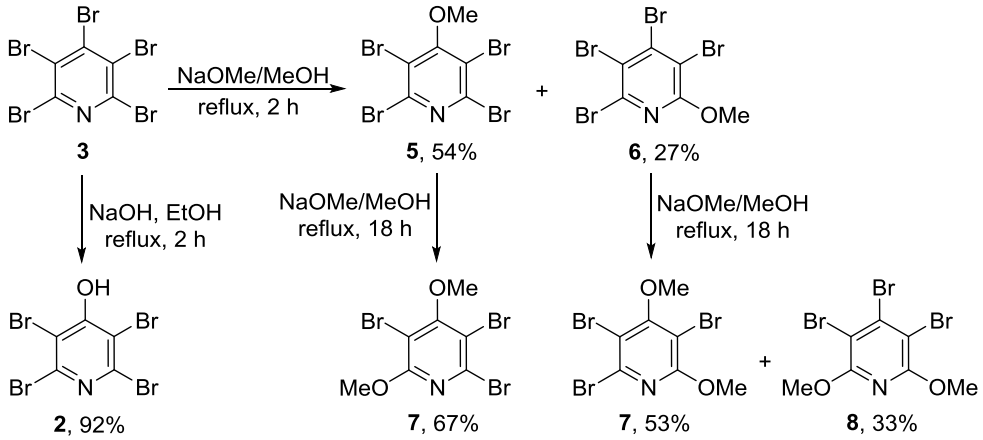


Scheme 4-1. Preparation of pentabromopyridine **3**.

2. NUCLEOPHILIC REACTIONS OF PENTABROMOPYRIDINE

2.1. Reaction of O-centered Nucleophile with Pentabromopyridine

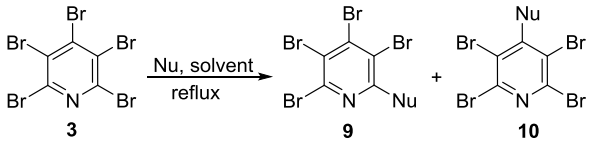
Pentabromopyridine **3** invariably gives a lower proportion of the 4-substituted product with larger nucleophiles [2]. This is due to steric deflection from the 4-position by the larger bromine atoms to the less hindered 2-position, whereas small nucleophiles give 4-substituted products as the major product and 2-substituted products (Scheme **4-2**).



Scheme 4-2. Reaction of pentabromopyridine **3** with sodium methoxide.

2.2. Reaction of N-centered Nucleophile with Pentabromopyridine

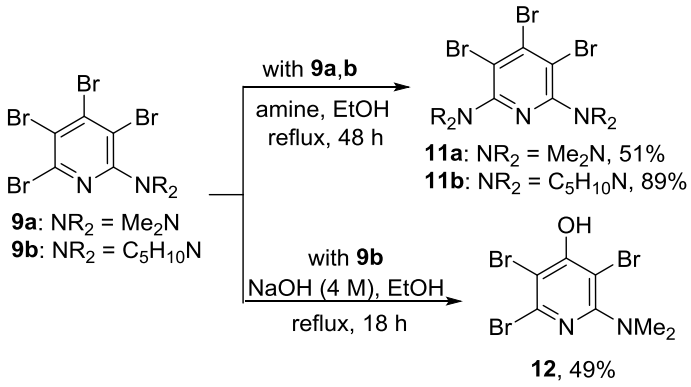
Reaction of pentabromopyridine **3** with nitrogen nucleophiles has been carried out at both 2- and 4-positions of pyridine ring depend on the steric hindrance of the nucleophile (Scheme **4-3**) [2].



Nu	solvent	reflux		
Me_2NH	C_6H_6	18 h	100%	-
	EtOH	18 h	85%	15%
$C_5H_{10}NH$	C_6H_6	18 h	100%	-
	EtOH	18 h	85%	15%
$MeNH_2$	dioxan	18 h	52%	48%
$N_2H_4.H_2O$	EtOH	18 h	33%	66%

Scheme 4-3. Reaction of pentabromopyridine **3** with various nucleophiles.

The 2-*N*,*N*-dialkylaminotetrabromopyridines **9** upon reaction with amines produced the 2,6-bis-(*N*,*N*-dialkylamino)tribromopyridine **11** as the only product. Whilst sodium hydroxide in reaction with tetrabromo-6-dimethylaminopyridine **9a** was replaced at the 4-position of pyridine ring (Scheme **4-4**) [2]. Piperidine on reaction with tetrabromo-4-methoxy- and 4-piperidinopyridines produced tribromo-4-methoxy-6-piperidinopyridine **13a** and tribromo-4,6-dipiperidinopyridine **13b** *via* replacing at the 2-position of pyridine ring (Scheme **4-5**) [2].



Scheme 4-4. Reaction of 2-alkylaminotetrabromoyridines **9** with various nucleophiles.

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