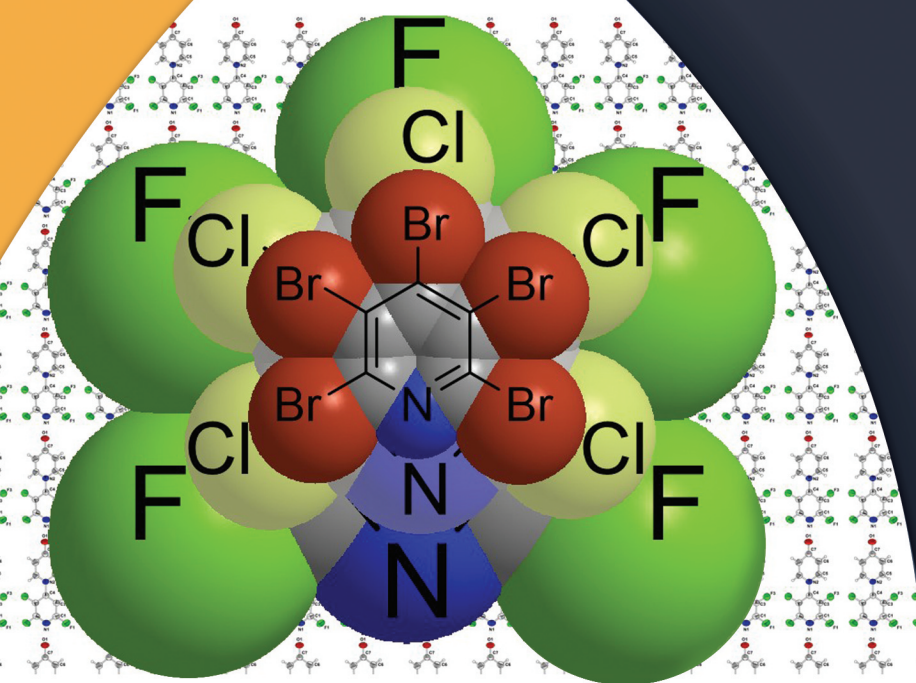


PERHALOPYRIDINES: SYNTHESIS AND SYNTHETIC UTILITY



Reza Ranjbar-Karimi
Alireza Poorfreidoni

Bentham Books

Perhalopyridines: Synthesis and Synthetic Utility

Authored by

Reza Ranjbar-Karimi

&

Alireza Poorfreidoni

*Department of Chemistry, Faculty of Science
Vali-e-Asr University of Rafsanjan
Islamic Republic of Iran*

Rgt j cmr { tlf lpgu'U{ pyj gulu'cpf 'U{ pyj gyle'Wlrlw{

Authors: Reza Ranjbar-Karimi and Alireza Poorfreidoni

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

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

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

© 2020, Bentham Books imprint.

Published by Bentham Science Publishers Pte. Ltd. Singapore. All Rights Reserved.

BENTHAM SCIENCE PUBLISHERS LTD.

End User License Agreement (for non-institutional, personal use)

This is an agreement between you and Bentham Science Publishers Ltd. Please read this License Agreement carefully before using the ebook/echapter/ejournal (“**Work**”). Your use of the Work constitutes your agreement to the terms and conditions set forth in this License Agreement. If you do not agree to these terms and conditions then you should not use the Work.

Bentham Science Publishers agrees to grant you a non-exclusive, non-transferable limited license to use the Work subject to and in accordance with the following terms and conditions. This License Agreement is for non-library, personal use only. For a library / institutional / multi user license in respect of the Work, please contact: permission@benthamscience.net.

Usage Rules:

1. All rights reserved: The Work is the subject of copyright and Bentham Science Publishers either owns the Work (and the copyright in it) or is licensed to distribute the Work. You shall not copy, reproduce, modify, remove, delete, augment, add to, publish, transmit, sell, resell, create derivative works from, or in any way exploit the Work or make the Work available for others to do any of the same, in any form or by any means, in whole or in part, in each case without the prior written permission of Bentham Science Publishers, unless stated otherwise in this License Agreement.
2. You may download a copy of the Work on one occasion to one personal computer (including tablet, laptop, desktop, or other such devices). You may make one back-up copy of the Work to avoid losing it.
3. The unauthorised use or distribution of copyrighted or other proprietary content is illegal and could subject you to liability for substantial money damages. You will be liable for any damage resulting from your misuse of the Work or any violation of this License Agreement, including any infringement by you of copyrights or proprietary rights.

Disclaimer:

Bentham Science Publishers does not guarantee that the information in the Work is error-free, or warrant that it will meet your requirements or that access to the Work will be uninterrupted or error-free. The Work is provided "as is" without warranty of any kind, either express or implied or statutory, including, without limitation, implied warranties of merchantability and fitness for a particular purpose. The entire risk as to the results and performance of the Work is assumed by you. No responsibility is assumed by Bentham Science Publishers, its staff, editors and/or authors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products instruction, advertisements or ideas contained in the Work.

Limitation of Liability:

In no event will Bentham Science Publishers, its staff, editors and/or authors, be liable for any damages, including, without limitation, special, incidental and/or consequential damages and/or damages for lost data and/or profits arising out of (whether directly or indirectly) the use or inability to use the Work. The entire liability of Bentham Science Publishers shall be limited to the amount actually paid by you for the Work.

General:

1. Any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims) will be governed by and construed in accordance with the laws of Singapore. Each party agrees that the courts of the state of Singapore shall have exclusive jurisdiction to settle any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims).
2. Your rights under this License Agreement will automatically terminate without notice and without the

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Pte. Ltd.

80 Robinson Road #02-00

Singapore 068898

Singapore

Email: subscriptions@benthamscience.net



CONTENTS

PREFACE	i
CONSENT FOR PUBLICATION	i
CONFLICT OF INTEREST	i
ACKNOWLEDGEMENTS	i
FOREWORD	ii
ABBREVIATIONS	iii
CHAPTER 1 PROPERTIES OF PERHALOPYRIDINES	1
1. PHYSICAL AND CHEMICAL PROPERTIES	1
2. SPECTROSCOPY	2
3. REACTIONS	3
REFERENCES	5
CHAPTER 2 PERFLUOROPYRIDINES	8
1. INTRODUCTION	8
2. SYNTHESIS OF PENTAFLUOROPYRIDINE	9
3. REACTION MECHANISM	10
4. REACTION OF PENTAFLUOROPYRIDINE WITH VARIOUS MONO DENTATE NUCLEOPHILES	12
4.1. Reaction of S-centered Nucleophile with Pentafluoropyridine	12
4.2. Reaction of O-centered Nucleophile with Pentafluoropyridine	17
4.3. Reaction of C-centered Nucleophile with Pentafluoropyridine	22
4.4. Reaction of N-centered Nucleophile with Pentafluoropyridine	32
4.5. Reaction of Pentafluoropyridine 3 with Halogenating Reagents (Cl, Br, I)	51
4.6. Reduction of Perfluorinated Pyridines	56
5. REACTION OF PERFLUOROPYRIDINES WITH VARIOUS MULTIDENTATE NUCLEOPHILES	59
5.1. Synthesis of Perfluorinated Heterocycles	59
5.2. Synthesis of Fluorinated Ring-fused Heterocycles	76
6. ORGANOMETALLIC COMPOUNDS OF PERFLUORO- HETEROAROMATICS	94
7. PHOTOCHEMICAL REACTIONS OF FLUORINATED PYRIDINES	109
8. COPOLYMERIZATION OF PENTAFLUOROPYRIDINE	121
9. THE PENTAFLUOROPYRIDINE CATION C ₅ F ₅ N ⁺	122
10. SALTS OF PERFLUOROPYRIDINE	122
11. SYNTHESIS OF MACROCYCLIC COMPOUNDS FROM POLYFLUOROPYRIDINES	123
12. PENTAFLUOROPYRIDINE IN MEDICINAL CHEMISTRY AND BIOCHEMISTRY	129
REFERENCES	135
CHAPTER 3 PERCHLOROPYRIDINES	152
1. INTRODUCTION	152
2. SYNTHESIS OF PENTACHLOROPYRIDINE	153
2.1. By Straight Chlorination	153
2.2. By Ring-closing Method	154
2.3. Synthesis of Pentachloropyridine-1-15N-2,6-13C ₂	154
3. NUCLEOPHILIC REACTIONS OF PERCHLOROPYRIDINES	155
3.1. Reaction of Pentachloropyridine with Various Mono Dentate Nucleophiles	155
3.1.1. Reaction of N-centered Nucleophile with Pentachloropyridine	156
3.1.2. Reaction of S-centered Nucleophile with Pentachloropyridine	172
3.1.3. Reaction of C-centered Nucleophile with Perchloropyridines	184

3.2. Reaction of Perchloropyridines with Bidentate Nucleophiles	184
4. CROSS-COUPLED REACTIONS OF PERCHLOROPYRIDINES	192
5. BROMINATION OF PENTACHLOROPYRIDINE	195
6. OXIDATION OF POLYCHLOROPYRIDINES	196
7. REDUCTION OF POLYCHLOROPYRIDINES	200
8. ALKYLATION OF POLYCHLOROPYRIDINES	201
9. PHOTOCHEMICAL REACTIONS OF POLYCHLOROPYRIDINES	203
10. ORGANOMETALLIC REAGENTS OF PERCHLOROPYRIDINE	205
REFERENCES	210
CHAPTER 4 PERBROMOPYRIDINES	219
1. SYNTHESIS OF PENTABROMOPYRIDINE	219
2. NUCLEOPHILIC REACTIONS OF PENTABROMOPYRIDINE	220
2.1. Reaction of O-centered Nucleophile with Pentabromopyridine	220
2.2. Reaction of N-centered Nucleophile with Pentabromopyridine	221
2.3. Reaction of S-centered Nucleophile with Pentabromopyridine	225
3. ORGANOMETALLIC REAGENT OF POLYBROMOPYRIDINES	228
4. SALTS OF PENTABROMOPYRIDINE	229
5. OXIDATION OF PENTABROMOPYRIDINE	229
6. PHOTOCHEMICAL REACTIONS OF PENTABROMOPYRIDINE	229
7. SYNTHESIS AND REACTIONS OF 2,4,6-TRIBROMO-3,5-DIFLUOROPYRIDINE	230
8. SYNTHESIS AND REACTIONS OF 3,5-DIBROMO-2,6-DICHLOROPYRIDINE	233
REFERENCES	234
SUBJECT INDEX	236

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.

Reza Ranjbar-Karimi
Department of Chemistry, Faculty of Science
Vali-e-Asr University of Rafsanjan
Islamic Republic of Iran

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.

Mohammad Ali Zolfigol
Bu-Ali Sina University
Hamadan
Iran

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-Dichloroethane
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 Perfluorocarbonyl
S_{RN}1 Unimolecular Radical Nucleophilic Substitution
TBHS Tetrabutylammonium hydrogen sulfate
TFA Trifluoroacetic Acid

iv

TFAA Trifluoroacetic Anhydride THF: Tetrahydrofuran

TMG 1,1,3,3-Tetramethylguanidine

TMSCl Trimethylsilyl chloride

Vis/NIR Visible/Near Infra-Red

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 led to increasing intramolecular forces and basicity of system, thus pentachloropyridine has more intermolecular forces and basicity in comparison with pentafluoropyridine [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].

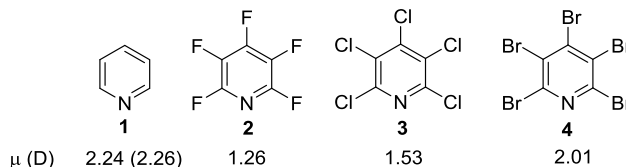


Fig. (1-1). Dipole moment values of pyridine and pentahalopyridines.

2. SPECTROSCOPY

Aromatic character of pentafluoropyridine has been shown by its spectroscopy properties. IR and Raman analysis confirmed planning 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 $256 \mu\text{m}$ [3]. In ^{19}F -NMR spectrum of pentafluoropyridine, the resonances of the *ortho*, *meta* and *para* fluorines located at $\delta = -86.72$, -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, $\text{C}_{(3,5)}$, $\text{C}_{(2,6)}$ and $\text{C}_{(4)}$ appeared at $\delta = 134.3$, 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].

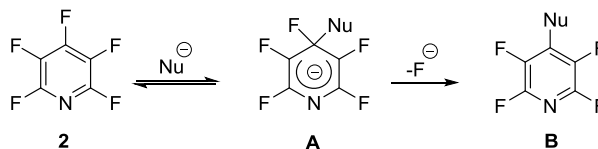
Table 1-1. Spectroscopic properties of pentahalopyridines.

¹³ C-NMR	C _{2,6}	C _{3,5}	C ₄
C ₅ F ₅ N ^a	144.8	134.3	150.3
C ₅ Cl ₅ N ^a	146.8 ^a	129.9	144.9
C ₅ Br ₅ N ^b	141.2	127 ^b	140.4 ^b

^a 22.635 MHz, CDCl₃^b 75 MHz, DMSO-d₆

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

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, Macrocyclic, Medicinal Chemistry, Meisenheimer Intermediate, Monodentate Nucleophile, *N*-Methylated Pyridinium, Nucleophilic Substitution, Organometallic Perfluoroheteroaromatics, Pentafluoropyridine, Pentafluoropyridine Cation, Photochemical Reaction, Polyheterocycles, Radical Addition, Regioselectivity, Ring-Fused, Tetrafluoropyridine.

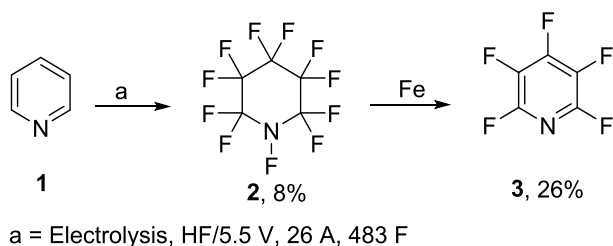
1. INTRODUCTION

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

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].

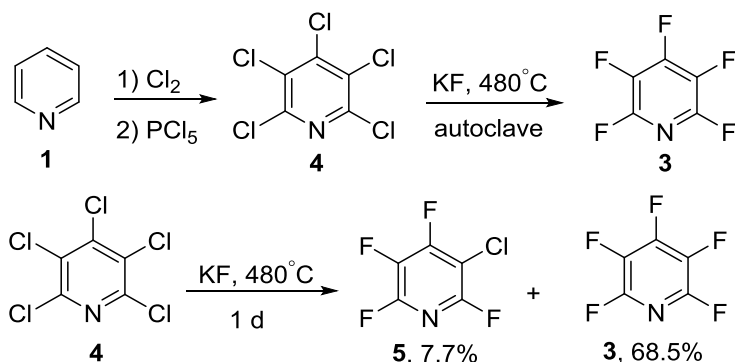
2. SYNTHESIS OF PENTAFLUOROPYRIDINE

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].



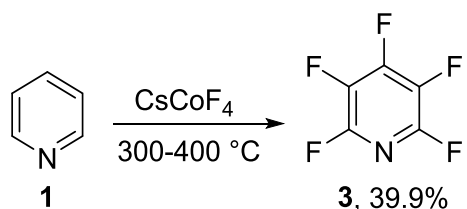
Scheme 2-1. Synthesis of pentafluoropyridine **3** by electrochemical methods.

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.

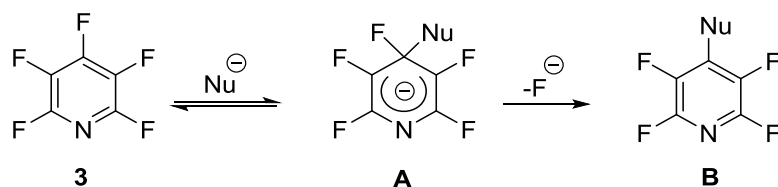
Fluorination of pyridine over caesium tetrafluorocobaltate (III) at 300-400°C gave pentafluoropyridine **3** and a mixture of other products (Scheme 2-3) [4].



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 expected to follow order reactivity $4 > 2 \gg 3$ 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**.

Polyhaloheterocycles are more active systems than corresponding benzoic compounds toward aromatic nucleophilic substitution. Activating effect of an aza group is similar to nitro group effect in aromatic systems and active *ortho* and *para* positions [9, 11]. Halogen substitution acts 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 is affected by reaction with nucleophile species due to presence of electronegative atoms of fluorine that activate the ring toward

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 pentachloropyridine in reaction with various electrophiles produced corresponding substituted products.

Keywords: Biological Activities, Heteronium Salts, *N*-ethylpentachloropyridinium 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].

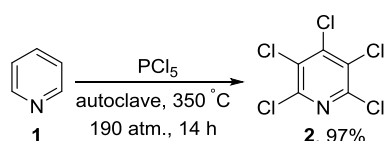
Polychloroheteroaromatic compounds have a great interest in the industry and showed a wide range of biological activities such as herbicides and pesticides [6]. Tetrachloro-4-sulfanylpuridine, 2,3,5-trichloro-4,6-bis-sulfanylpuridines and 3,5-dichloro-2,4,6-tris-sulfanylpuridines have found interest 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-trichloro-2,6-dicyanopyridine and 4-pyridine-2,3,5,6-tetrachlorosulfonylacetic acid ethyl ester have been found as a fungicide for treatment against *Peronospora* 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].

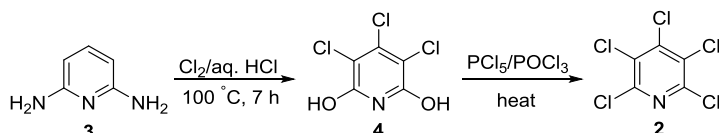
2. SYNTHESIS OF PENTACHLOROPYRIDINE

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].



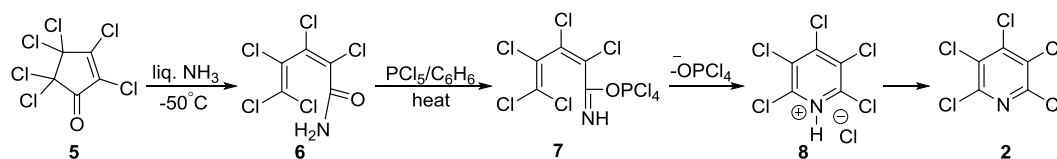
Scheme 3-1. Preparation of pentachloropyridine **2** from pyridine **1**.



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

2.2. By Ring-closing Method

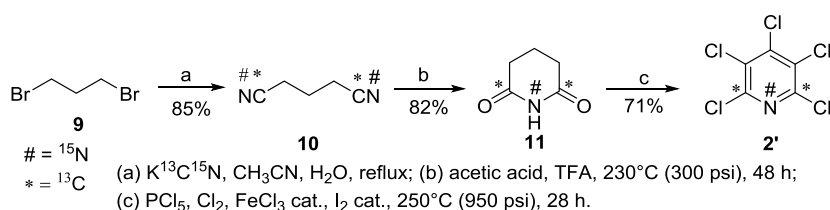
Reaction of perchlorocyclopentene-3-one with ammonia and the subsequent reaction with phosphorus pentachloride produced pentachloropyridine as major product (Scheme 3-3) [15]. Also, tetrachloro-*N*-methyl-2-pyridone on reaction with a mixture of phosphorus pentachloride and phosphoryl chloride converted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



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

2.3. Synthesis of Pentachloropyridine-1-¹⁵N-2,6-¹³C₂

Pentachloropyridine-1-¹⁵N-2,6-¹³C₂ has been synthesized from glutarimide-1-¹⁵N-2,6-¹³C₂ which obtained from reaction of 1,3-dibromopropane with K¹³C¹⁵N followed by acetic acid and trifluoroacetic acid (Scheme 3-4) [17].



Scheme 3-4. Synthesis of pentachloropyridine-1-¹⁵N-2,6-¹³C₂ **2'**.

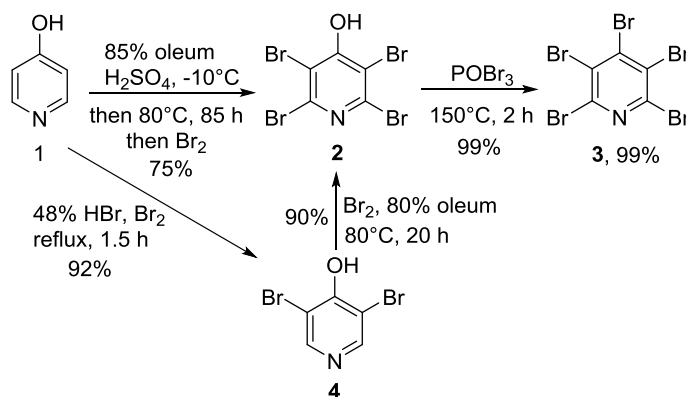
Perbromopyridines

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.

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(triethoxyphosphazanyl)-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-sulfonyl 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).

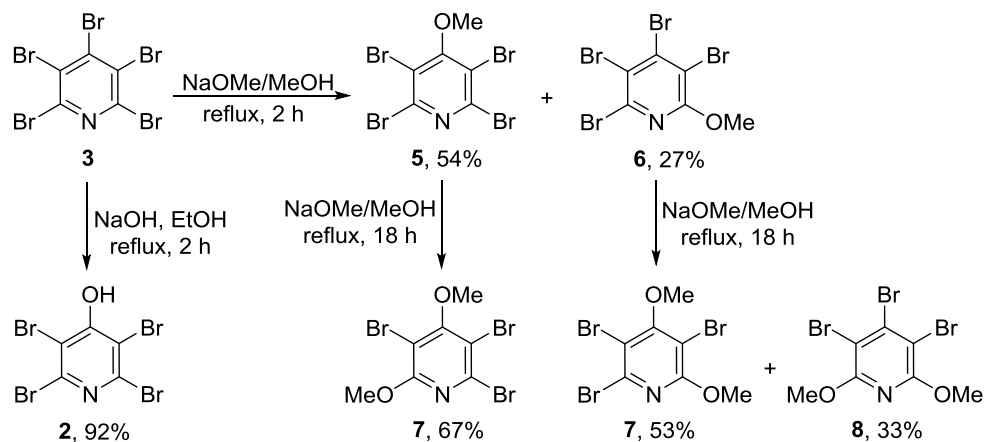


Scheme 4-1. Preparation of pentabromopyridine 3.

2. NUCLEOPHILIC REACTIONS OF PENTABROMOPYRIDINE

2.1. Reaction of O-centered Nucleophile with Pentabromopyridine

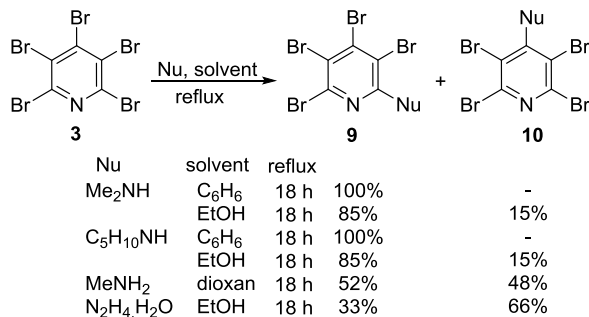
Pentabromopyridine **3** invariably gives a lower proportion of the 4-substituted product with larger nucleophiles [2]. This is due to steric deflection from the 4-position by the larger bromine atoms to the less hindered 2-position, whereas small nucleophiles give 4-substituted products as the major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



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

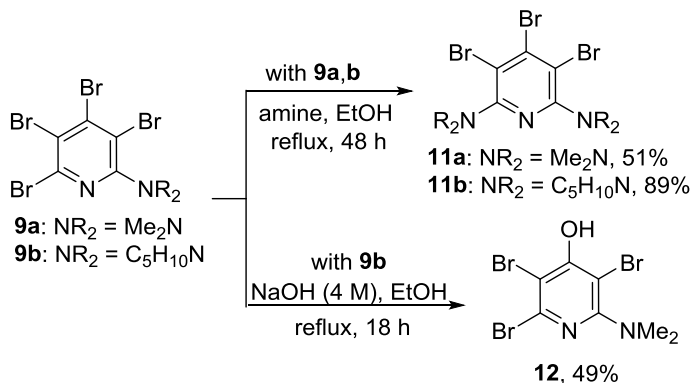
2.2. Reaction of N-centered Nucleophile with Pentabromopyridine

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].



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-alkylaminotetrabromopyridines **9** with various nucleophiles.

SUBJECT INDEX

A

- Absorption 2, 45
 - narrow 45
 - band 2
- Acetamidine 89, 91, 92
 - hydrochloride 91, 92
- Acetic anhydride 86
- Acetic acid 2, 153, 154, 177, 196, 198
 - glacial 177
- Acetone 19, 61, 181, 199, 227
 - oxime 19
- Acetylation 85, 86
- Acetylcholinesterase 22
- Acetylenes 22, 233
 - substituted 233
- Acid 2, 23, 32, 38, 44, 98, 107, 154, 177, 183, 188, 190, 196, 198, 205, 206, 219, 222, 228, 229
 - 3,4,5,6-tetrachloro-2-pyridylacetic 190
 - 4-amino-2,5,6-trifluoronicotinic 98
 - 4-amino-3,5,6-trichloropicolinic 183
 - 4-amino-3,6-dichloropicolinic 183
 - concentrated sulphuric 2, 196, 229
 - formic 222
 - hydrobromic 219
 - hydrofluoric 38
 - hydrolysis 188
 - peroxytrifluoroacetic 32
 - phenylboronic 107
 - polyphosphoric 198
 - tetrabromopyridine-4-carboxylic 228
 - thioacetic 44
 - trifluoroacetic 154, 196, 229
 - ylacetic 190
- Acrylonitrile 153
- Activating effect 1, 3, 11, 82
 - high 3, 11
- Acyclic products 92
- Addition 1, 17, 43, 54, 55, 63, 77, 89, 91, 100, 114, 115, 121, 124, 194
 - elimination mechanism 1
 - nucleophilic 63, 124
 - oxidative 194
 - smooth 55
- Agrochemical compounds 8
- Alkylating ability 31
- Alkylation reaction 118
- Alkynes 131, 193
 - isomeric aryl-tetrafluoropyridyl 31
- Allylmagnesium halides 94
- Aluminium 28, 170
 - tribromide 28
 - hydride 170
- Alzheimer therapy 132
- Amines 34, 35, 40, 63, 72, 81, 111, 156, 165, 178, 181, 221, 222, 224
 - aliphatic 156
 - alkyl 34, 35
 - benzyl 34, 35
 - diallyl 178
 - diethyl 165
 - primary 81, 224
 - secondary 81, 181
 - substituent 222
- Amino 21, 134
 - functionalized quinolines 134
 - oxylating agents 21
- Amino acid derivatives 60, 61
 - non-natural fluorinated 60
- Ammonia 1, 32, 34, 35, 36, 154, 162, 197, 227, 230
 - aqueous 230
 - gas 227
- Ammonium 57, 99, 178, 200
 - chloride 99, 200
 - formate 57
 - hydroxide 178
- Anion 16, 19, 22, 24, 59, 64, 182
 - alkylthiolate 182
 - nucleophilic attack oximate 19
 - perfluorinated 24
 - thiolate 182
 - thiophenolate 182
- Antibacterial 131, 134
 - agents 131
 - effects 134
- Antimalarial activity 134

Apoptotic activities 134
Arbuzov reaction on reaction 165
Aromatic 35, 39, 40, 64, 156, 157, 179, 185, 195
 aldehyde 163
 amines 35, 39, 40, 156, 157, 179, 195
 azides 169, 224
 boronic acids 232
 character of pentafluoropyridine 2
 N-centered nucleophiles 34
 nucleophilic substitution process 11
 systems 10
Arylboronic acids 192
Atom, nucleophilic 74

B

Basicity 1, 103, 122, 201
 low 1, 122, 201
 reduced 1
Benzoic compounds 10
Biological 8, 123, 152, 153, 185
 activities 8, 152, 153, 185
 properties 123
Bispyridine produced 25
Bispyridine systems 25
 multifunctional 25
Bis-silane derivatives 125
Bond activation 30, 100, 102, 117
 products 102

C

Carbanions, produced 22
Carbanion stability 11
Carbonate 1, 66
 potassium 66
Catalysts 3, 8, 32, 57, 94, 96, 101, 102, 123, 132
 cobalt 102
 cross-coupling 96
 metallic 3
 nickel 57
 transfer hydrogenation 101
Catalytic 101, 102, 105, 107, 108
 cross-coupling reactions 107, 108
 formation 105
 hydrodefluorination 101, 102
 reaction 105

Catalyzed coupling reaction 96
Chemical 1, 2, 45
 shifts 1, 2
 stability 45
Chemistry 8, 10, 15, 41, 48, 123, 129, 133, 152
 medicinal 8, 48, 129, 133
 metal 99
 organic 8, 41, 123
Competition 155, 176
 hydrogen bonding 155
Complexes 29, 103, 105, 106, 107, 108
 cationic 103
 nickel tetrafluoropyridyl 108
 produced 106
Complex VII/TF factor inhibitors 130
Compounds 13, 15, 22, 52, 53, 56, 57, 58, 69, 71, 73, 84, 85, 94, 116, 117, 119, 129, 133, 152, 153, 157, 191, 193, 207, 224, 228
 3,5-difluoro-triaryloxypyridine 129
 3,5-difluoro-triaryloxypyridine 129
 bioactive 133
 cyclohexene 191
 decacationic 157
 electrophilic 207
 host 153
 organomagnesium 184
 organometallic 94, 152, 228
 phosphazeny 224
 produced 116
 tetraalkenylpyridine 193
Computed transition state 105
Copolymerization 121
Copolymers 8, 121
 novel 121
Copper 33, 95, 152, 168, 196, 207, 208
 tetrachloro-4-pyridyl 152, 207, 208
 powder 33
 reagent 95
 sulfate 168
Cross-coupling reactions 53, 54, 107, 152, 192, 193, 194, 219
 catalysed 194
 palladium-catalyzed 193
 selective 192
Curtius reaction on treatment 98
Cyclic products 80
Cyclization 46, 61, 119, 169, 177, 186, 204
 intermolecular 186

photochemical 119
radical ipso 46
reactions 169
Cycloaddition reactions 114

D

Decarboxylation 61, 63
thermal 61
Decomposition 122, 176
of salt 122
Density 1, 2, 10, 11
heron electron 11
Drugs 8, 111, 130
anti-clotting 130
total commercial 8

E

Effect 1, 2, 11, 31, 129
dominant 11
inactivating 11
induced withdrawing 11
medium inhibitory 129
protecting 31
shielding 1, 2
Electrochemical reduction 183
Electrophilic 36, 37, 108
fluorinating agent 37
site-selective 36
Electroreduction 15

F

Fluorinated 8, 9, 22, 76
medicinal 8
pyridine aldoximes 22
ring-fused heterocycles 76
synthetic blocks 9
Fluorinated compounds 8, 42
produced 42
Formation 14, 47, 48, 57, 58, 65, 66, 67, 70,
118, 119, 120, 156, 163, 169, 186, 190
bromotetrachloropyridines 169
photochemical 118
Functionalization of 3-chlorotrifluoropyridine
112
Functionalized fluorinated organic compounds
96

G

Grignard reagent 34, 95, 205
Guanidine 69

H

Haloacetic acids 174
Halogenating reagents 51
Halogen 1, 3, 8, 9, 10, 122, 123
atoms 1, 3, 8, 122, 123
exchange 9
substitution act 10
Heating 177, 184, 190
mixture 184
of acid 177
of ester 190
Herbicides 153, 183
plant growth regulator 183
Heteroarenium 157, 159
molecules 157
salt 159
Heterocyclic compounds 8, 157, 185
fluorinated 8
multifunctional 157
novel 185
Heterocyclic systems 8, 123, 191
fluorinated 8
ring-fused 191
Human melanoma cell growth, inhibited 31
Hydrazine 58, 59, 197
hydrate 197
monohydrate 58, 59
Hydrodefluorination 8, 57, 101, 102, 110, 111
catalytic homogeneous 57
selective 102
reactions 101
Hydrogen fluoride (HF) 64
Hydrolysis 63, 115, 116, 188, 224, 225, 228
acidic 225

I

Imidazopyridine, produced 89
Iminothionyl chlorides 162
Inhibitory 129, 130, 133
activity 133
property 130
Irradiation 67, 68, 116

Subject Index

ultrasonic 67, 68

L

Lithium 52, 53, 55, 85, 94, 95
diethylamide 85
exchange 55
organometallic compounds 94
reagents 52, 53, 95

M

Macrocycles 8, 123, 124, 125, 126, 127, 128, 133
synthesis of 123, 124, 125, 126, 127, 128, 133
Macrocyclic 8, 123, 125, 127, 128
compounds 8, 123
systems 123, 127
produced 125, 128
Mechanism 3, 10, 20, 44, 47, 48, 65, 70, 73, 89, 91, 118, 119, 120, 173, 179, 182, 185, 190, 224
addition nucleophile 10
amidation 44, 190
bimolecular addition-elimination 3, 10
elimination-addition 10
free-radical 120
irradiation of pentafluoropyridine 120
of photocycloaddition 118, 119
plausible 48
postulated 70, 89, 91, 118
steps addition-elimination 3
suggested radical 182
Meldrum's acid 63
Metal-halogen exchange 206, 219, 228
reaction 206
Methanethiolate 14, 15
sodium 14
Method 25, 40, 9
electrochemical 9
halogen exchange 9
selective 40
synthetic 25
Methyl ester 71, 73, 200
ammonium methylphosphonic acid 200
mono-protected L-threonine 73
perfluorinated dehydrobutyrine 73
Microreactor technology 40

Perhalopyridines: Synthesis and Synthetic Utility 25;

Miyaura cross-coupling 152, 192
Molecules 44, 70, 74, 111, 114, 176, 225
asymmetric 111
form amide 44
heteroaromatic 114
multiagent 74
Multifunctional pyridines, produced 161
Multisubstituted 25, 77
bicyclic N-heterocycles 77
heteroaromatics 25

N

Nature 1, 3, 8, 64, 88, 152, 185
electron-withdrawing 1
withdrawing 8
Nucleophiles 12
Nickel compounds 108
Nitrogen 44, 64, 67, 68, 171, 185, 221, 224
bidentate nucleophiles 67
gas 44
losing 224
Nitrogen nucleophiles 68, 221
monodentate 171
Nitro products 222
Nucleophiles 3, 4, 10, 11, 25, 52, 59, 66, 68, 76, 82, 88, 152, 155, 156, 161, 180, 181, 220, 221, 230
ambident 68, 188
attacking 88
hard 59
heteroaromatic 161
hindrance 152
less-hindered 172
multidentate 59, 76
nature 230
primary 181
Nucleophilic 3, 8, 10, 11, 60, 63, 64, 65, 123, 185, 186, 188, 191, 219, 222
addition-elimination reactions 123
attack 3, 8, 10, 11, 60, 63, 64, 123, 185, 186, 188, 191, 219, 222
Nucleophilic reactions 19, 25, 26, 40, 74, 152, 155, 162, 165, 179, 180, 209, 219, 220
of bi-perfluoropyridine 26
of pentabromopyridine 220
of pentachloropyridine 155
of perchloropyridines 155
Nucleophilic substitution 1, 8, 11, 12, 108, 122, 123, 185, 195, 198, 202, 229

- of 4-bromotetrachloropyridine 195
- of sodium dimethyldithiocarbamate 198
- of sodium dimethyldithiocarbamate on pentachloropyridine-N-oxide 198
- intramolecular 185
- Nucleophilic substitution reactions 1, 3, 10, 82, 84, 88, 152, 155, 208, 226
- in *N*-heterocyclic systems 10
- Nucleophilicity, high 76

O

- One-step synthesis of pentaalkynylpyridines 193
- Organic 3, 29, 48, 96
 - oxidants 157
 - solar cells 29
 - synthesis 3, 48, 96
- Organofluorine compounds 36
- Organometallic 8, 228
 - reagent of polybromopyridines 228
 - reactions 8
- Organophosphorus nerve-agent poisoning 22
- Oxazolone enolates 60
- Oxidation 14, 152, 167, 168, 169, 175, 176, 196, 198, 219, 222, 223, 229
 - and methylation of pentabromopyridine 219
 - of 4-aryl and 4-alkylthio tetrachloropyridine derivatives 175
 - of pentabromopyridine 229
 - of pentachloropyridine 152, 196
 - of polychloropyridines 196
 - of tetrabromo-6-methylaminopyridine 223
 - of tetrabromo-4-piperidinopyridine 222
 - of tetrachloro-4-dimethylaminopyridine 167, 168
 - of tetrachloro-2-hydrazinopyridine 169
 - of tetrachloro-4-hydrazinopyridine 168, 169
 - of tetrachloro-4-methoxypyridine 198
 - of tetrachloro-4-methoxypyridine 198
 - of tetrachloropyridine-4-thiol 176
 - reaction 222
 - reduction process 14

P

Pentaalkynylpyridine

- Pentachloropyridine 1, 2, 3, 5, 152, 153, 154, 155, 156, 157, 166, 167, 168, 172, 173, 180, 182, 183, 184, 185, 187, 195, 201, 205, 208, 229
 - optimum reaction condition 180
 - persulfuration of 182
 - preparation of 152, 153, 154, 208
 - produced 153, 154
 - reactions 5, 229
 - reduced 201
 - synthesis of 153, 154
- Pentafluoropyridine 1, 2, 8, 9, 10, 12, 15, 17, 18, 19, 20, 32, 40, 64, 66, 88, 89, 100, 101, 102, 103, 104, 106, 111, 115, 116, 122, 124
 - bond of 100, 101, 102, 104, 111
 - cation 8
 - protonate 1
 - leades 106
 - salt 122
- Pentakis 15, 16, 30
 - produced 16, 30
- Perfluorinated
 - dehydrobutyrine-containing amino acids 24, 56, 59, 73, 123
 - heteroaromatics 24
 - heterocycles 123
 - Heterocycles 59
 - Pyridines 56
- Perfluoroalkylation 13, 25, 124, 176
 - of perchloropyridine-4-thiols 176
- Perfluoroheteroaromatics 8, 94
 - organometallic 8, 94
- Perfluoropyridyl 75, 104, 105
 - boronate ester 104, 105
 - ether 75
- Perhalogenated heteroaromatic compounds 41
- Perhalogenated heterocycles 123
- Peronosporu fungi 153
- Persulfurated pyridine derivatives 15
- Phosphorimidate, produced 225
- Phosphorus 153, 154, 162, 197, 219
 - oxybromid 219
 - pentachloride 153, 154, 162
 - pentasulfide 197
 - trichloride 197
- Photocatalytic 109, 110, 111, 112, 113, 114
 - alkylation 110
 - arylation 111
 - coupling 111

Subject Index

E-alkenylation 114
hydrodefluorination 112
Z-alkenylation 113, 114
Photochemical 114, 115, 116, 119, 120
 addition 114, 115, 116
 products 120
 transformations 114, 119
Photochemical reactions 8, 109, 117, 118,
 152, 153, 203, 229
 self-condensing 153
 of pentabromopyridine 229
Photocycloaddition 116, 118, 119
 of m-amido isomer 118
 of o-amido isomer 118
 of p-amido isomer 118
Photoinduced electron transfer (PET) 119
Photolysis 102, 169, 203, 204, 205, 230
 of 2-aryloxy and
 arylaminotetrachloropyridines 205
 of 4-aryl and
 heteroarylthiotetrachloropyridines 204
 of 4-aryloxy and
 arylaminotetrachloropyridines 204
 of 4-bromotetrachloropyridine 203
 of pentabromopyridine 230
 of pentachloropyridine 203
 of tetrachloropyridines 203
 of tetrachloro-2-iodopyridine 203
 of tetrachloro-3-iodopyridine 204
 of tetrachloro-4-iodopyridine 203
Polychlorinated heterocycles 153
Polychloroheteroaromatic compounds 153
Polyethylene glycol 123
Polyfluorinated heteroaromatic compounds 25
Polyfluoroaromatic compounds 10, 18
Polyfunctional 30, 77, 86, 192
 analogues 77
 pyridines 192
Polyhalogenated 122, 194
 pyridines 122
 substrates 194
Polymeric material 69
Preparation 122, 200, 220
 of pentabromopyridine 220
 of pentafluoropyridine salt 122
 problem 200
Primary 117, 179
 aliphatic amines 179
 hydroxy alkane solutions 117
Produced 26, 38, 127

Perhalopyridines: Synthesis and Synthetic Utility 263

4-alkoxytetrafluoropyridine derivatives 127
multisubstituted perfluoropyridine
 derivatives 26
perfluorinated azoxy-compounds 38
Pyridine 1, 2, 3, 8, 10, 11, 15, 16, 30, 39, 59,
 77, 82, 106, 109, 117, 153, 157, 179,
 180, 184, 188, 194, 221, 233
 bond 30
 fluorinated 109, 117
 polyfluorinated 59
 polysubstituted 157
 tetraalkynylated 194, 233
Pyridine derivatives 25, 41, 67, 123, 134
 fluorinated 134
 multifunctional 67
 produced multisubstituted 41
Pyrolysis 38, 169
Pyrrolic squaraine dye 45

Q

Quinazolines 152
Quinoline nucleus 134
Quinoxaline scaffolds 89

R

Radical Addition 8, 48, 51
 initiated 48
Raman analysis 1, 2
Reaction 14, 26, 34, 35, 43, 44, 45, 59, 67, 71,
 79, 87, 90, 128, 155, 156, 157, 159, 162,
 163, 167, 168, 169, 181, 172, 173, 181,
 182, 184, 185, 189, 191, 195, 196, 197,
 199, 200, 208, 220, 221, 223, 229
4-phenylsulphonyltetrafluoropyridine 87
 of 2-aminotetrachloropyridine 163
 of 4-aminotetrachloropyridine 163
 of 4-bromotetrachloropyridine 195, 196
 of 4-bromotetrafluoropyridine 35
 of 4-phenylsulfonyl-tetrachloropyridine
 181
 of 4-phenylsulphonyltetrafluoropyridine 85
 of 4-phenylsulphonyl tetrafluoropyridine
 90
 of aromatic N-centered nucleophiles 34
 of excess sodium azide 223
 of heteroarenium salt 159
 of morpholine and piperidine 159

- of nitrogen bidentate nucleophiles 67
- of pentabromopyridine 220, 221, 223
- of pentachloropyridine 128, 155, 156, 157, 162, 167, 168, 169, 172, 173, 181, 182, 184, 185, 189
- of pentachloropyridine *N*-oxide 199
- of pentacloropyridine 208
- of pentafluoropyridine 71
- of perfluorinated compounds 59
- of piperidine 223
- of sodium salt 173
- of tetrachloro-4-cyanopyridine 171, 182, 191
- of tetrafluoro-4-isopropyl pyridine 26
- of 4-azidotetrafluoropyridine 43, 44, 45
- of 4-thioalkyltetrafluoropyridines 14
- of bromofluoropyridine 52
- of grignard reagent of 4-bromotetrafluoropyridine 34
- of imidazopyridines 79
- of *N*-methyl bromopyridinium fluorosulphonate 229
- of pentachloropyridine-*N*-oxide 197, 200
- Reagents 8, 75, 95, 100, 103, 155, 156, 205
 - nucleophilic 103
 - organolithium 205
 - organometallic 8, 205
 - perfluoroarylcopper 95
 - preferred organometallic 205
- Reduction 30, 36, 56, 57, 58, 157, 200, 201, 224, 230
 - of 3-chlorotetrafluoropyridine 57
 - of azide 224
 - of nitroamines 36
 - of pentachloropyridine by lithium aluminum hydride 201
 - of pentachloropyridine by lithium borohydride 201
 - of pentafluoropyridine 56, 58
 - of Perfluorinated Pyridines 56
 - of polychloropyridines 200
- Refluxing 103, 199
 - mixture 103
- Reflux temperature 166
- Ring-fused 76, 204
 - heterocycles 76
 - products 204
- Ring-fused systems 8, 77, 79, 80, 81, 86, 91, 152, 204
 - fluorinated 77
- Route 77, 95, 124, 128
 - synthetic 77
- S**
- Salts 11, 17, 36, 41, 42, 62, 63, 73, 81, 122, 152, 157, 158, 159, 160, 161, 162, 178, 200, 202, 229
 - ammonium enolate 63
 - bisheteroaromatic 161, 162
 - formate 101
 - heteronium 152, 157, 158, 161
 - keto-oxime 11
 - monosodium 36
 - of pentabromopyridine 229
 - of perfluoropyridine 122
 - produced 178, 200
 - produced ammonium enolate 62
 - produced pyridinium 41
 - pyridinium 41, 42
 - reaction of 157, 159, 160
 - sulfonate 17
 - tricationic pyridinium 159
- Selective electrophilic fluorinating agents 36
- Selective reduction 112, 113
 - of 4-acetamidotetrafluoropyridines 112
 - of 4-arylamino-tetrafluoropyridines 112
- Singlet oxygen scavengers 31
- Sites 3, 29, 59, 62, 64, 68, 76, 81, 85, 186, 187, 188, 192
 - activated 3
 - carbon 81
 - nucleophilic 68
 - oxygen 59, 68
- SNAr reactions 71, 72
- Sodium 1, 19, 28, 34, 35, 36, 54, 88, 157, 172, 176, 177, 180, 183, 188, 195, 197, 198, 199, 220, 221
 - acetate 197
 - benzenesulphinatate 88, 180
 - borohydride 157
 - bromide 195
 - cation 19
 - cyanide 172
 - dimethyldithiocarbamate 198, 199
 - formate 102
 - hydrogensulfide 176
 - hydrohite 172
 - hydroxide 1, 34, 35, 172, 177, 183, 188, 197, 221

Subject Index

iodide 54
methoxide 28, 36, 172, 220
Sodium nitrite 38, 180
phenylsulfate 180
Solution 64, 77, 173
aqueous sodium bicarbonate 173
concentrated acetonitrile 64
diluted acetonitrile 77
Solvents 45, 94, 155, 199, 206
etheric 94
hydrocarbon 206
low polarity 45
protic 155
Spectrum of pentafluoropyridine 2
Stabilizing 3, 11, 41, 157
influence 3
properties 41
Stable perfluoropyridyl carbanion 24
Staphylococcus aureus 134
Staudinger reaction 43, 224
Steric 1, 4, 100
deflection 220
factors 1, 4
Steric hindrance 180
cases 180
nucleophiles 180
Stoichiometric coupling reaction 105
Substituents 25, 31, 64, 86, 88, 89, 103, 119, 152, 157, 185, 192
amidine 89
electron-withdrawing tetrafluoropyridine 119
high chlorine 152
hydrogen 86
lysine 31
ring 64, 185
Substituted 30, 31, 62, 64, 92
acetylene amino acid conjugates 30, 31
imidamide systems 64
imidazopyridines 92
Meldrum's acids 62
Substitution 4, 10, 11, 16, 20, 28, 56, 60, 71, 77, 88, 117, 180, 182
active aromatic electrophilic 10
nucleophilic aromatic 60, 71
regiospecific 117
Substitution reactions 3, 24, 55, 68, 82, 123, 155, 208
aromatic nucleophilic 3, 123
nucleophilic aromatic 82

Perhalopyridines: Synthesis and Synthetic Utility 265

of perfluorinated heteroaromatics 24
susceptible nucleophilic 208
Sulfuric acid 153, 189, 196, 198
concentrated 198
concerted 153
Sulfur nucleophiles 12, 13
Suzuki 219, 232
Cross-coupling Reaction 219, 232
reactions 232
Synthesis 15, 23, 24, 33, 38, 41, 43, 46, 59, 67, 68, 76, 86, 117, 123, 157, 186, 192, 195, 197, 200, 219, 227, 234
and reactions of salt 200
efficient 86
heterocyclic compounds 186
of 2-alkoxy-4-aminotrifluoropyridine derivatives 41
of 2-alkoxy-4-dialkylamino trifluoropyridine derivatives 41
of 4-amino-tetrabromopyridine 227
of 4-aminotetrafluoropyridine 33
of 4-azidotetrafluoropyridine 43
of 4-bromotetrachloropyridine 195
of 4-substitued tetrafluoropyridines 67
of bis-perfluoropyridines 68
of fluorinated ring-fused heterocycles 76
of macrocycles by aromatic nucleophilic substitutions 123
of pentabromopyridine 219
of pentachloropyridine-n-oxide 197
of perfluoropyridinium salts 41
of perfluorinated azo dyes 38
of perfluorinated heterocycles 59
of perfluoropyridine-pyrrolic squaraine dye 46
of persulfurated pyridine derivatives 15
of polyfunctional pyridines 192
of tetrafluoropyridine-2-aldoxime 23
of tetrafluoropyridine-4-aldoxime 23
of tetrafluoropyridine-4-carboxylic acid 24
of unsymmetrical tetraalkynylpyridines 234
regiospecific 117
selective 157, 192
Systems 1, 2, 3, 9, 25, 40, 64, 76, 77, 84, 88, 89, 94, 116, 123, 124, 129, 157, 186
activated 3
bis-perfluoropyridyl 76
bis-perfluoropyridylimidamide 64
bridged bispyridyl 88
chelating 81

continuous flow reactor 40
efficient perfluorinated structural 25
fluorinated 9
fused ring 77
macrocycls 129
macrocylic 124
multifunctional heteroaromatic 25
perchlorinated 9
perfluoropyridineimidamide 64
polycationic 157
polysubstituted 25
pyrazine 84, 88
pyridooxadiazine 77
quinazoline 186
triazine 94
tricyclic 89, 116

T

Tetrachloropyridine sulfonamides 178
TFA salt 71
Therapeutic agents 131
Thermal 95, 102, 224, 228
 decomposition 224
 elimination 228
 reaction 102
 stability 95
Thermolysis 224
Treatment 2, 8, 21, 22, 23, 98, 103, 106, 107,
 108, 152, 153, 169, 177, 188, 189, 195,
 219, 224
 acetic anhydride 177
 of azide 224
 of tetrachlorohydrazinopyridine 169
 medical 8
 seed 153
Triethyl phosphite 38, 165, 225
 electron-rich 225
Trifluorobenzo, produced 88
Trifluoroperoxyacetic acid 167

U

Ultrasonic irradiation conditions 81
UV-Vis Spectrum 1, 2

W

Well-documented photoconducting
 capabilities 45

X

Xanthates 45, 47, 48, 156, 182
 DMF 156
 potassium 182
Xenone 176
 bisperfluoroalkane carboxylate 176
 difluoride 176

Z

Zinc 28, 29, 94, 95, 200
 acetate 29
 complexes 29
 perfluoroheteroaromatics 94
 powder 94, 95, 200
Z-isomer 73, 113
 single elimination product 73



REZA RANJBAR-KARIMI

Reza Ranjbar-Karimi is a Professor of organic chemistry at the Vali-e-Asr University of Rafsanjan (IRAN). After studying chemistry in the faculty of chemistry at Isfahan University, he obtained his PhD in 2006 with Professor Majid Mirmohammad-Sadeghi and Professor Hossein Loghmani-Khuzani. After a research course stay with Professor Graham Sandford at Durham University (UK), he started his independent research obtaining a permanent position first as assistant professor and associated professor (2010) and obtaining full professorship in 2015. His main interests of research concern the synthesis of halogenated heterocyclic compounds via perhalogenated pyridines.



ALIREZA POORFREIDONI

Dr. Alireza Poorfreidoni obtained his PhD in 2015 with Professor Reza Ranjbar-Karimi at the Vali-e-Asr University of Rafsanjan (IRAN). His main interests of research concern the synthesis of polynitrogen heterocyclic compounds and halogenated heterocyclic compounds.