# STUDY ON THE DEOXYDATIVE SUBSTITUTION REACTION OF PYRIDINE 1-OXIDES WITH THIONE NUCLEOPHILES

AN ABSTRACT

BY

WARAPHORN SINSIRI

Presented in partial fulfillment of the requirements

for the Master of Education Degree in Chemistry

Srinakharinwirot University

May 2004

Waraphorn Sinsiri. (2004). *Study on the Deoxydative Substitution Reaction of Pyridine 1-Oxides with Thione Nucleophiles*. Master thesis, M.Ed. (Chemistry). Bangkok : Graduate school ; Srinakharinwirot University. Advisor Committee : Assoc. Prof. Dr. Supaluk Prachayasittikul, Prof. Dr. Somsak Ruchirawat

In this study, we have investigated the deoxydative substitution reaction of 3-and 4-substituted pyridine 1-oxides with thione nucleophiles (2-thiouracil and thiourea) in phosphorus oxychloride containing triethylamine. It was found that nicotinamide 1-oxide and 3-cyanopyridine 1-oxide reacted with thione nucleophiles to produce 2-and 6-chloro-3-cyanopyridines. Treatment of 3-phenylpyridine 1-oxide under the similar condition afforded only 2-chloro-3-phenylpyridine. The product from the reaction of nicotinic acid 1-oxide with 2-thiouracil was tentatively assigned to be [1,3]oxathiino[4,5-*b*]pyridine-2,4-dione. When nicotinic acid 1-oxide was treated with thiourea, methyl nicotinate 1-oxide was obtained. In addition, substitution of 4-cyanopyridine 1-oxide with 2-thiouracil afforded 3-chloro-4-cyanopyridine. In the other hand, 4-cyanopyridine 1-oxide yielded 2-chloro-4-cyanopyridine when reacted with thiourea. Treatment of 4-phenylpyridine 1-oxide with 2-thiouracil or thiourea furnished only 2-chloro-4-phenylpyridine. However, the isolated 2-chloro-3-cyanopyridine reacted with thiourea in methanol under reflux to afford 3-cyano-2(1*H*)-pyridinethione.

# การศึกษาปฏิกิริยา DEOXYDATIVE SUBSTITUTION ของ PYRIDINE 1-OXIDES กับ ไทโอนนิวคลีโอไฟล์

บทคัดย่อ

ของ

วราภรณ์ สินศิริ

เสนอต่อบัณฑิตวิทยาลัย มหาวิทยาลัยศรีนครินทรวิโรฒเพื่อเป็นส่วนหนึ่งของการศึกษา
ตามหลักสูตรปริญญาการศึกษามหาบัณฑิต สาขาวิชาเคมี
พฤษภาคม 2547

วราภรณ์ สินศิริ (2004). *การศึกษาปฏิกิริยา Deoxydative Substitution ของ Pyridine 1-Oxides กับไทโอนนิวคลีโอไฟล์*. ปริญญานิพนธ์ กศ.ม.(เคมี). กรุงเทพฯ : บัณฑิตวิทยาลัย มหาวิทยาลัยศรีนครินทรวิโรฒ คณะกรรมการควบคุม : รองศาสตราจารย์ ดร.สุภาลักษณ์ ปรัชชญาสิทธิกุล, ศาสตราจารย์ ดร.สมศักดิ์ รุจิรวัฒน์

ในการศึกษานี้เราได้ศึกษาปฏิกิริยา deoxydative substitution ของ 3-และ 4-substituted pyridine 1-oxides กับไทโอนนิวคลีโอไฟล์ (2-thiouracil และ thiourea) ในฟอสฟอรัสออกซีคลอไรด์และไตรเอททิลลามีน จากผลการศึกษาพบว่า nicotinamide 1-oxide และ 3-cyanopyridine 1-oxide ทำปฏิกิริยากับไทโอนนิวคลีโอไฟล์ ได้ผลิตภัณฑ์ 2-และ 6-chloro-3-cyanopyridines ส่วน 3-phenylpyridine 1-oxide พบว่าจะให้ 2-chloro-3-phenylpyridine เท่านั้น สำหรับ nicotinic acid 1-oxide เมื่อทำปฏิกิริยากับ 2-thiouracil คาดว่าได้ [1,3]oxathiino[4,5-*b*]pyridine-2,4-dione แต่เมื่อทำปฏิกิริยากับ thiourea พบว่าจะได้ผลิตภัณฑ์เป็น methyl nicotinate 1-oxide นอกจากนี้ปฏิกิริยา deoxydative substitution ของ 4-cyanopyridine 1-oxide กับ 2-thiouracil พบว่าจะให้ 3-chloro-4-cyanopyridine แต่เมื่อให้ 4-cyanopyridine 1-oxide ทำปฏิกิริยากับ thiourea จะได้ 2-chloro-4-cyanopyridine ส่วน 4-phenylpyridine 1-oxide เมื่อทำปฏิกิริยากับ 2-thiouracil หรือ thiourea จะได้ผลิตภัณฑ์ 2-chloro-4-phenylpyridine เท่านั้น อย่างไรก็ตามเมื่อนำ 2-chloro-3-cyanopyridine ทำปฏิกิริยากับ thiourea ในเมทานอลซึ่งให้ความร้อนแบบ reflux พบว่าได้ผลิตภัณฑ์ 3-cyano-2(1*H*)-pyridinethione

# STUDY ON THE DEOXYDATIVE SUBSTITUTION REACTION OF PYRIDINE 1-OXIDES WITH THIONE NUCLEOPHILES

WARAPHORN SINSIRI

**Presented in partial fulfillment of the requirements**

**for the Master of Education Degree in Chemistry**

**Srinakharinwirot University**

**May 2004**

Thesis

Entitled

# STUDY ON THE DEOXYDATIVE SUBSTITUTION REACTION OF PYRIDINE 1-OXIDES WITH THIONE NUCLEOPHILES

by

**MISS WARAPHORN SINSIRI**

was submitted to Graduate School, Srinakharinwirot University

for the Degree of Master of Education in Chemistry

.....  Dean of Graduate School

(Assoc. Prof. Dr. Napaporn Havanon)

May, 2004

Advisor Committee

.....  Chairman

(Assoc. Prof. Dr. Supaluk Prachayasittikul)

.....  Co-advisor

(Prof. Dr. Somsak Ruchirawat)

.....  Member

(Asst. Prof. Dr. Sunan Chainakul)

.....  Member

( Dr. Apinya Chaivisutthangkul)

# ACKNOWLEDGEMENT

To my advisor, Associate Professor Dr. Supaluk Prachayasittikul, I would like to express my sincere gratitude and great appreciation for her kindness, meaningful guidance, invaluable suggestions and encouragement throughout my study. Everything will always be in my mind. Special thanks are expressed to my co-advisor, Professor Dr. Somsak Ruchirawat, for his warmly helpful guidance, suggestion and correction of this thesis. My deep appreciations are due to Assistance Professor Dr. Sunan Chainakul and Dr. Apinya chaivisuthangkure, for their valuable suggestions and comments.

I would like to express my appreciation to academic staffs of the Department of Chemistry, Faculty of Science, Srinakharinwirot University including the research facilities. Thanks are also due to the supporting staffs in providing NMR spectral data and assistance throughout my work.

Unforgettable, I would also like to express my gratitude to Chulabhorn Research Institute for providing chemicals and the facility of mass spectrometer.

I thank the Benchamaratrungsarit School for allowing me to make a study leave.

Thanks are also extended to the Graduate School, Srinakharinwirot University for providing partial support.

Finally, I wish to express my infinite to my family and my friends for their love and continuous support throughout my life.

All of these are deep seated in my mind forever.

Waraphorn Sinsiri

# TABLE OF CONTENTS

# LIST OF TABLES

# LIST OF FIGURES

## LIST OF FIGURES(continued)

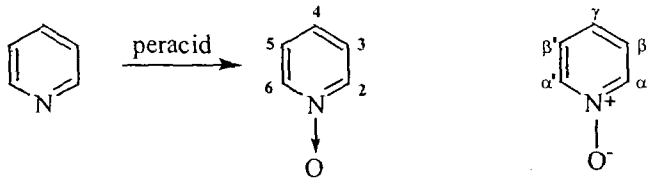
# Chapter I

# Introduction

## Background

Pyridine and its derivatives are stable and relatively unreactive substances with strong and unpleasant odor. They are used as solvent and base[1].

Pyridine possesses a tertiary amine character reacting with peracid to form an amine oxide or pyridine 1-oxide **I**. The new N-O bond is represented as an arrow or dipolar representation **II**[2].




**I** **II**

Resonance structures of pyridine 1-oxide are shown in **Figure 1**.

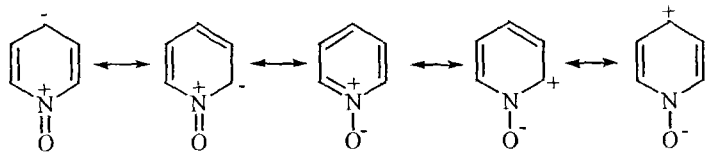


**Figure 1** Resonance structures of pyridine 1-oxide

The 1-oxide group in pyridine 1-oxide has both electron-withdrawing and electron-donating effects. Consequently, pyridine 1-oxide reacts with both electrophiles and nucleophiles, resulting in a more versatile reactivity of the pyridine ring compared to pyridine itselt.

The well-established substitutions of pyridine 1-oxide **1** leading to a variety of pyridine **2** with the simultaneous loss of the 1-oxide function are summarized in **Figure 2**.

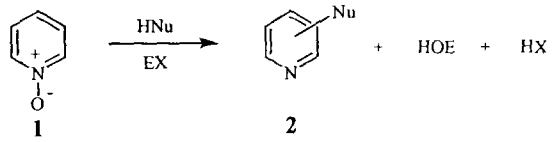



**Figure 2** Substitution of pyridine 1-oxide leading to a variety of pyridines

Such substitutions usually require an auxiliary reagent, such as an alkylating or acylating agent, represented here by EX, where E is an electrophilic atom and X becomes a nucleofuge. The process begins after **1** is quaternized to form the salt **3**. Attack by a nucleophile, Nu:, at an $\alpha$- or $\gamma$-ring position of **3** forms the neutral dihydropyridine, **4** or **5** , while $\beta$-attack would generate the dipolar ion, **6**. Aromatization is completed by the elimination of HOE to form one of the pyridine, **7**, **8**, or **9**. Since one of the steps involves nucleophilic attack followed by the loss of the N-oxy function, these reactions are classified as **deoxydative nucleophilic substitution** shown in **Figure 3**. Form these considerations, $\alpha$- and $\gamma$-attack should predominate. This holds for many reactions but frequently a considerable quantity of a $\beta$-substituted pyridine is isolated also.

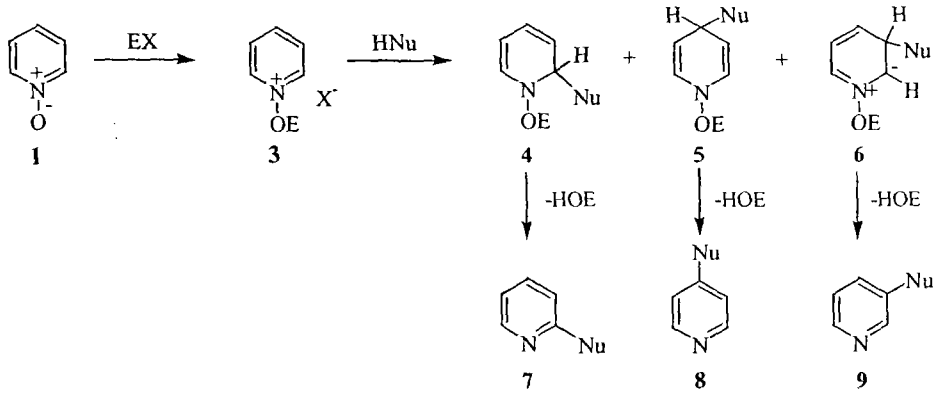



**Figure 3** The deoxydative nucleophilic substitution reaction

Attacking nucleophiles for these substitutions can be a halide ion or oxygen, sulfur, carbon, nitrogen and phosphorus bearing nucleophiles[3]. Many ways to introduce an oxy function into the pyridine ring, for example, reaction of pyridine 1-oxides with acetic anhydride afford pyridyl acetates, which are readily hydrolyzed to either pyridones or pyridinols[4]. Pyridine 1-oxides reacted with chlorinating agents such as sulfuryl chloride, phosphorus oxychloride and phosphorus pentachloride to yield essentially 2-and 4-chloro-substituted pyridines[5]. In addition, the reaction of pyridine 1-oxides with thiols in acetic anhydride furnished pyridyl sulfides[3].

The deoxydative substitutions of pyridine 1-oxides by a variety of nucleophiles were reported, but for thione nucleophile has not yet been studied. Thus, this attracts our attention to investigate the deoxydative substitution of some pyridine 1-oxides with thione nucleophiles.

## Objectives

1. To study the deoxydative substitution of pyridine 1-oxides by thione nucleophiles (2-thiouracil and thiourea) in phosphorus oxychloride containing triethylamine

2. To elucidate the structure of products by using spectroscopic methods

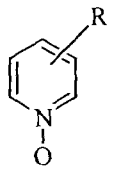
## Benefits

1. To obtain pure compounds from the reaction of pyridine 1-oxides and thiones in phosphorus oxychloride containing triethylamine

2. The obtained compounds will be further evaluated for biological activities and toxicity.

## Scopes

1. Pyridine 1-oxides used for this study are 3-and 4-substituted pyridine 1-oxides as shown.




R = 3-COOH, 3-$CONH_2$, 3-CN, 3-$C_6H_5$

R = 4-COOH, 4-$CONH_2$, 4-CN, 4-$C_6H_5$

2. Thiones used are 2-thiouracil and thiourea.

3. Isolation and purification of the products was performed by chromatographic techniques and recrystallization.

4. Structure elucidation of the obtained compounds was carried out using infrared spectroscopy, nuclear magnetic resonance spectroscopy and mass spectrometry.

# Chapter II

# Literature Review

In this chapter, the deoxyadative substitution of pyridine 1-oxides by chlorinating agents, thiols, and some related reactions of thiones will be reviewed, including the bioactivity of some pyridine derivatives.

## 1. Deoxydative Substitution of Pyridine 1-oxides by Chlorinating Agents

Generally, pyridine 1-oxides reacted with phosphorus pentachloride, phosphorus oxychloride and sulfuryl chloride to give a mixture of 2-and 4-chloropyridines. Presumably the pyridinium salt **10** was formed first, which was attacked by chloride ion to give intermediates **11** and **12**. Further loss of phosphoryl chloride ($POCl_3$) and hydrogen chloride afforded 2-and 4-chloropyridines **13** and **14** as shown in **Figure 4**.

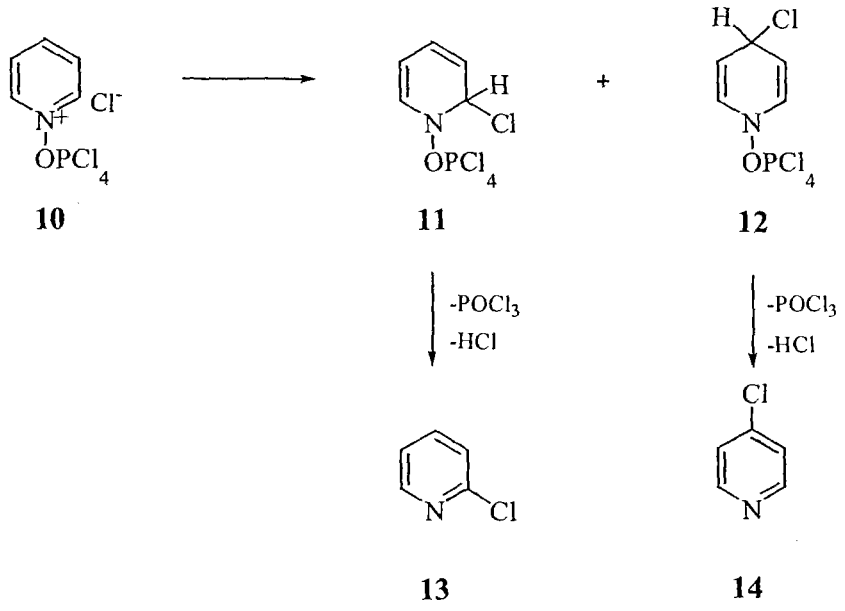



**Figure 4** The reaction of pyridine 1-oxide with phosphorus pentachloride

Some other reactions are outlined in **Figure 5**. Treatment with phosphorus oxychloride, 2-chloropyridine 1-oxide **15** gave 2,6-dichloropyridine[6] **16**. However, 2-picoline 1-oxide **17** reacted with the same reagent to produce only 4-chloro-2-picoline **18**[7]. 3-Picoline 1-oxide **19** furnished a mixture of 2-, 4- and 6-chloro-3-picolines[8]. Furthermore, the reaction of 4-substituted pyridine 1-oxides (R= $CH_3$ ,$CONH_2$ , $COOC_2H_5$) with a mixture of $POCl_3$ and $PCl_5$ only gave 2-chloropyridine derivatives[5, 2, 8]. The product isolated from the reaction of isonicotinamide 1-oxide (**23**, R = $CONH_2$) was 2-chloro-4-pyridinecarbonitrile (**24**, R = CN) as a result of dehydration of the amide group[5]. Some typical reactions of pyridine 1-oxides with $PCl_5$ and $POCl_3$ are summarized in **Table1**.

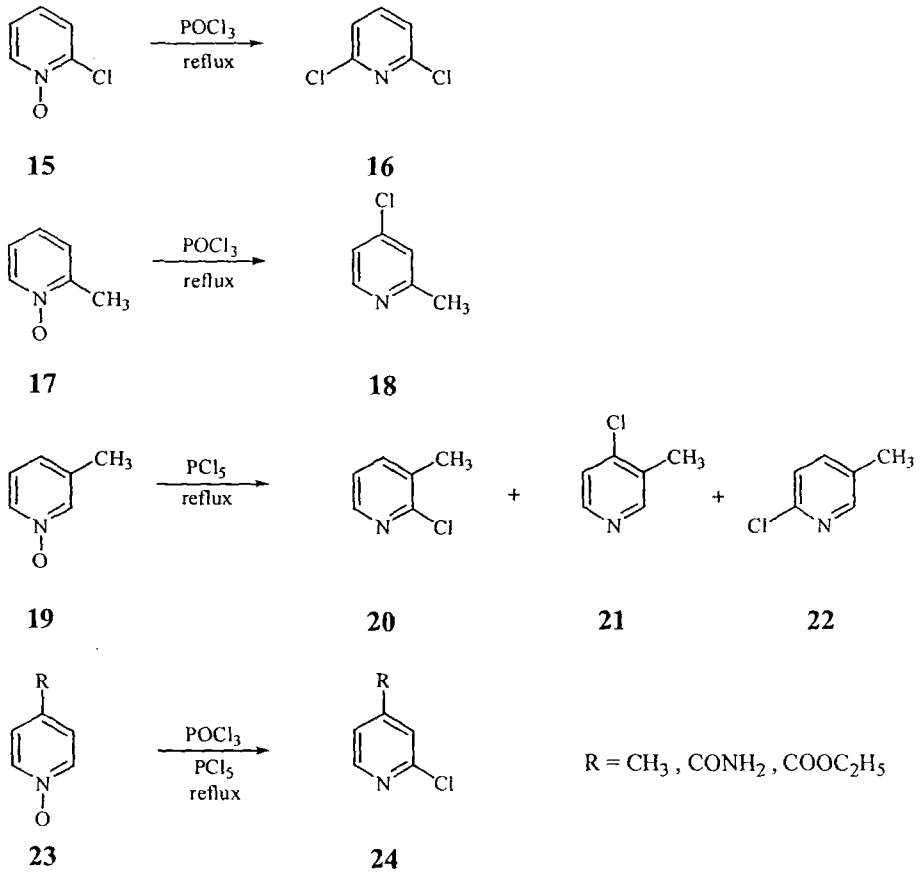
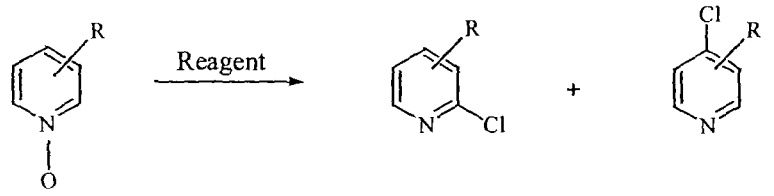



**Figure 5** Some typical reactions of pyridine 1-oxides with phosphorus oxychloride and phosphorus pentachloride

**Table 1** Reaction of pyridine 1-oxides with $PCl_5$ or $POCl_3$




| R | Reagent | Distribution of Isomers | | | Yield, % | References |
|---|---|---|---|---|---|---|
| | | 2 or 6 | 4 | 3 | | |
| H | $PCl_5$ | 42 | 58 | - | 13 | 6, 8 |
| H | $POCl_3$ | 68 | 32 | - | 62 | 6, 8 |
| 2-Cl | $POCl_3$ | 100 | - | - | 91 | 6, 8 |
| 2-$CH_3$ | $POCl_3$ | - | 100 | - | - | 7 |
| 3-$CH_3$ | $PCl_5$ | 48[a] | 52 | - | 30 | 6, 8 |
| 3-$CH_3$ | $POCl_3$ | 56[b] | 44 | - | 97 | 6, 8 |
| 3-COOH | $PCl_5$ or $POCl_3$ | 100 | - | - | - | 9 |
| 3-$NO_2$ | $POCl_3/PCl_5$ | 100 | - | - | 45 | 10 |
| 4-$CH_3$ | $POCl_3$ | 100 | - | - | 34 | 6, 8 |
| 4-$CONH_2$ | $PCl_5/POCl_3$ | 100 | - | - | 50-60 | 5 |
| 4-$COOC_2H_5$ | $POCl_3$ | 100 | - | - | 70 | 6, 8 |
| 4-CN | $POCl_3/PCl_5$ | - | - | 100 | 73 | 5 |

[a]Ratio of substitution at C-2 and C-6 was 28:20.

[b]Ratio of substitution at C-2 and C-6 was 31:25.

In 1978, Rokach and co-worker reported unexpected result from the reaction of 4-cyanopyridine 1-oxide **25** with phosphorus oxychloride containing phosphorus pentachloride. The product from such reaction was 3-chloro-4-cyanopyridine **26** in good yield[5]. A mechanistic interpretation of the result was proposed *via* a chloride attack at the 4-position of pyridinium salt **25a** as the main feature shown in **Figure 6**.

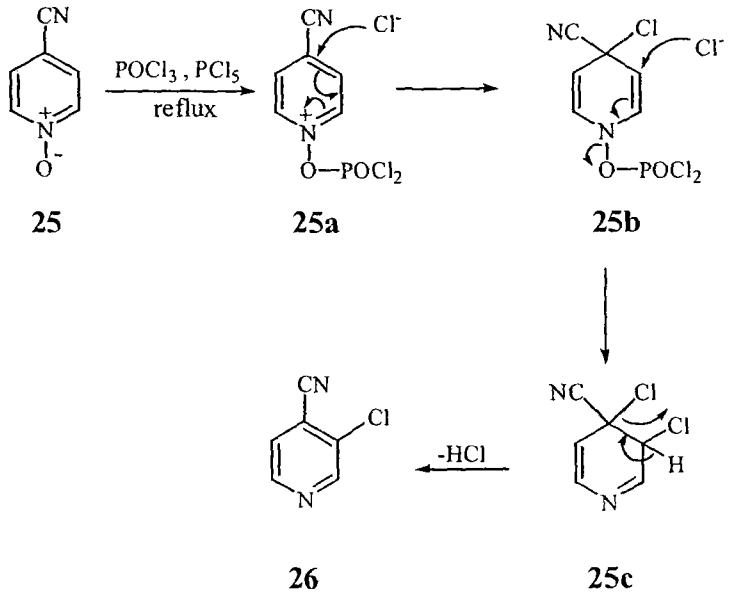



**Figure 6** The reaction of 4-cyanopyridine 1-oxide with phosphorus oxychloride and phosphorus pentachloride

In 1986, Moran and co-worker reported the deoxydative substitution reaction of bipyridine 1-oxides. It was found that 3,3′-bipyridine 1-oxide[11] **28** reacted with phosphorus oxychloride to provide a mixture of 2-chloro-3,3′-bipyridine **29** (50%) and 6-chloro-3,3′-bipyridine **30** (50%). Similarly, the reaction of 2,2′-bipyridine 1-oxide **32** afforded a 1 :1 mixture of 6-chloro-2,2′-bipyridine **33** and 4-chloro-2,2′-bipyridine **34** as shown in **Figure 7**. The starting 1-oxides **27** and **31** were prepared by general procedure using $H_2O_2$ oxidation.

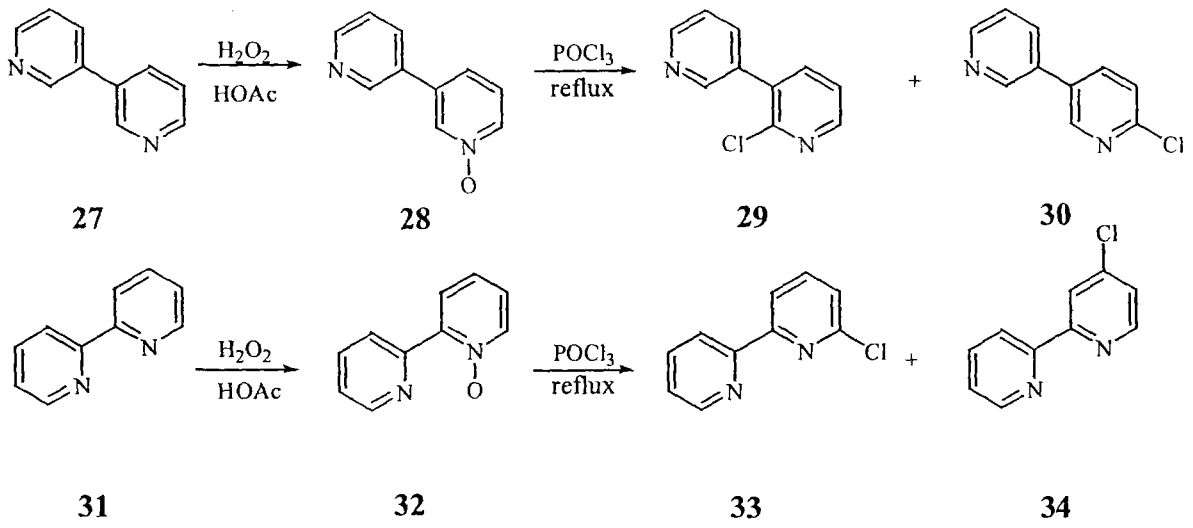



**Figure 7** The deoxydative substitution reaction of bipyridine 1-oxides

In 1990, Singh and co-workers reported that phosphorus oxychloride reacted with 2,6-dimethylpyridine 1-oxide hydrochloride **35** to yield a mixture of 2-(chloromethyl)-6-methylpyridine **36** and 4-chloro-2,6-dimethylpyridine **37**[12]. Treatment of this mixture with triethylamine, **35** was converted to quaternary salt **38** which was separated by water extraction as shown in **Figure 8**.

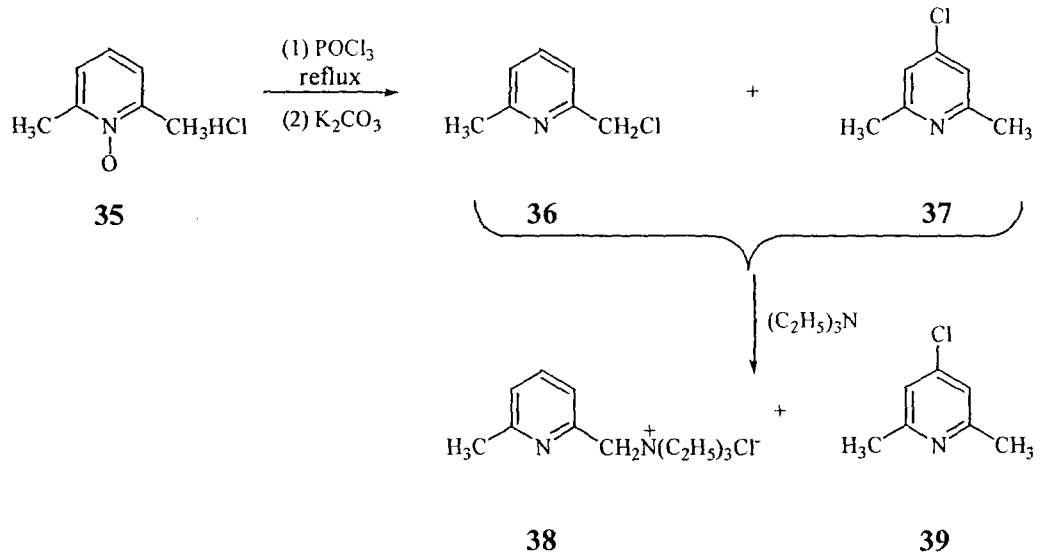



**Figure 8** The reaction of 2,6-dimethylpyridine 1-oxide hydrochloride with phosphorus oxychloride

In 2001, Jung and co-worker reported the selective 2-chlorination of pyridine 1-oxide **1**. It was found that **1** reacted with phosphorus oxychloride in the presence of a stoichiometric amount of triethylamine[13] to furnish 2-chloropyridine **13** as shown in **Figure 9**. Other chlorinating agents such as sulfuryl chloride, *p*-toluenesulfonyl chloride, trichloroacetyl chloride, benzenesulfonyl chloride and methanesulfonyl chloride also produced 2-chloropyridine, albeit in moderate yield.

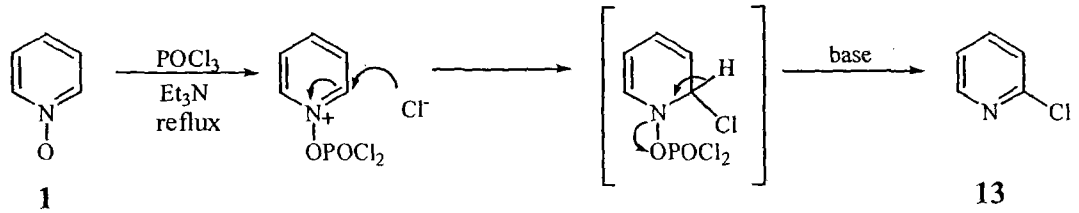


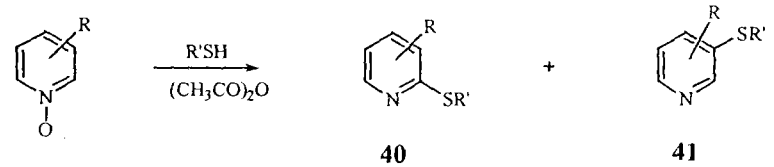

**Figure 9** Preparation of 2-chloropyridine

## 2. Deoxydative Substitution of Pyridine 1-oxides by Thiols

This section reviews the reaction of pyridine 1-oxides with thiols in the presence of various acylating agents. The deoxydative substutution of pyridine 1-oxides by thiols were studied extensively by Bauer et al.[14-18] The major products were found to be pyridyl sulfides. The acylating agents or quaternizing agents can be acid chlorides, such as acetyl, benzoyl, diethylcarbamyl chlorides, and acid anhydride[17].

It was discovered that acetic anhydride was a convenient solvent and reagent for these reactions[19]. The majority of the reaction of pyridine 1-oxides with thiols in acetic anhydride gave a mixture of 2-and 3-pyridyl sulfides, **40** and **41**, respectively. The results are summarized in **Table 2**. Besides these sulfides, some tetrahydropyridyl sulfides were also isolated in selected reactions.

**Table 2** Substitutions of pyridine 1-oxides with thiols in acetic anhydride, with or without triethylamine




**40** **41**

| R | R' | Addition of $N(C_2H_5)_3$ | Distribution of isomers at α-carbons | | Distribution of isomers at β-carbons | | Ratio attack α:β | Yield, % | References |
|---|---|---|---|---|---|---|---|---|---|
| | | | C-2 | C-6 | C-3 | C-5 | | | |
| H | $CH_3$ | - | 52 | - | 48 | - | 52:48 | 38 | 19 |
| H | n-$C_3H_7$ | - | 76 | - | 24 | - | 76:24 | 46 | 19 |
| H | n-$C_4H_9$ | - | 61 | - | 39 | - | 61:39 | 67 | 19 |
| H | t-$C_4H_9$ | - | 70 | - | 30 | - | 70:30 | 62 | 19 |
| H | 1-Adm | - | 68 | - | 32 | - | 68:32 | 44 | 22 |
| 2-$CH_3$ | t-$C_4H_9$ | - | - | 84 | - | 16 | 84:16 | 32[a] | 19 |
| 3-$CH_3$ | t-$C_4H_9$ | - | 45 | 19 | - | 36 | 64:39 | 66 | 19, 21 |
| 3-$CH_3$ | t-$C_4H_9$ | yes | 61 | 34 | - | 5 | 95:5 | 20 | 19, 21 |
| 4-$CH_3$ | t-$C_4H_9$ | - | 71 | - | 29 | - | 71:29 | 41[b] | 19, 21 |
| 4-$CH_3$ | t-$C_4H_9$ | yes | 82 | - | 18 | - | 82:18 | 33 | 19, 21 |
| 4-$C_2H_5$ | t-$C_4H_9$ | - | 67 | - | 33 | - | 67:33 | 49 | 21 |
| 4-$C_2H_5$ | t-$C_4H_9$ | yes | 87 | - | 13 | - | 87:13 | 32 | 21 |
| 4-i-$C_3H_7$ | t-$C_4H_9$ | - | 62 | - | 38 | - | 62:38 | 61 | 21 |
| 4-i-$C_3H_7$ | t-$C_4H_9$ | yes | 80 | - | 20 | - | 80:20 | 39 | 21 |
| 4-t-$C_4H_9$ | t-$C_4H_9$ | - | 83 | - | 17 | - | 83:17 | 48 | 19, 20 |
| 4-t-$C_4H_9$ | t-$C_4H_9$ | yes | 96 | - | 4 | - | 96:4 | 48 | 19, 20 |
| 4-t-$C_4H_9$ | 1-Adm | - | 98 | - | 2 | - | 98:2 | 48 | 19, 20 |
| 4-C6H5 | t-$C_4H_9$ | - | 44 | - | 56 | - | 44:56 | 18 | 19 |
| 2,6-(CH3)2 | t-$C_4H_9$ | - | - | - | - | - | - | 0[c] | 19 |
| 3,4-(CH3)2 | t-$C_4H_9$ | - | 48 | 23 | - | 29 | 71:29 | 35[d] | 19 |
| 3,5-(CH3)2 | t-$C_4H_9$ | - | 100 | - | - | - | 100:0 | 66 | 19 |

[a]The yield of an accompanying active methylene substituted sulfides was 10%

[b]The yield of an accompanying active methylene substituted sulfides was 3%

[c]The yield of an accompanying active methylene substituted sulfides was 1%

[d]The yield of an accompanying active methylene substituted sulfides was 1%

The substitution was postulated to proceed *via* the mechanisms outlined in **Figure 10**. After formation of 1-acetoxypyridinium acetate **42**, attack of the thiol at C-2 gave rise to the 1,2-dihydropyridine intermediate **43**. Ultimately, the loss of the acetic acid from **43** led to either 2- or 3-pyridyl sulfides, **40** or **41**. It was suggested that **43** separated into an ion pair **44**. Loss of a proton from **44** furnished 2-pyridyl sulfides **40**.

Neighboring group participitation of the intermediate **44c** led to episulfonium ion **45**. Subsequent migration of the sulfide moiety to C-3 position produced **46**. Finally loss of acetic acid from **46** provided 3-pyridyl sulfides **41**.

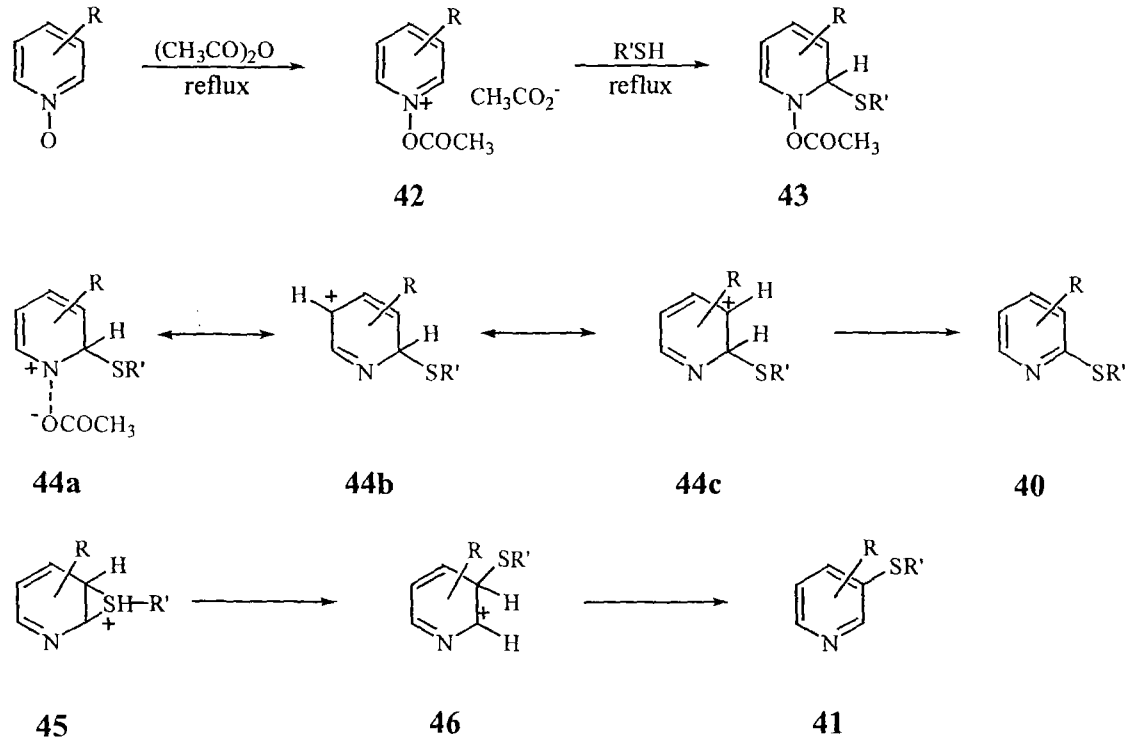



**Figure 10** Synthesis of 2- and 3-pyridyl sulfides

In 1985, Prachayasittikul and co-workers reported that the reaction of nicotinamide 1-oxide **47** with 1-adamantanethiol(1-AdmSH) in acetic anhydride afforded a mixture of 2-and 6-(1-adamantylthio)nicotinamides **48** and **49** (49%, in the ratio of 24:1) and 2-, 5-, and 6-(1-adamantylthio)nicotinonitriles **50, 51** and **52** (18%, in the ratio of 79:1:20)[23]. Similarly, the reaction of nicotinic acid 1-oxide **53** with 1-adamantanethiol , there was isolated 2-(1-adamantylthio)nicotinic acid **54** as the only sulfide in 23% yield as shown in **Figure 11**.

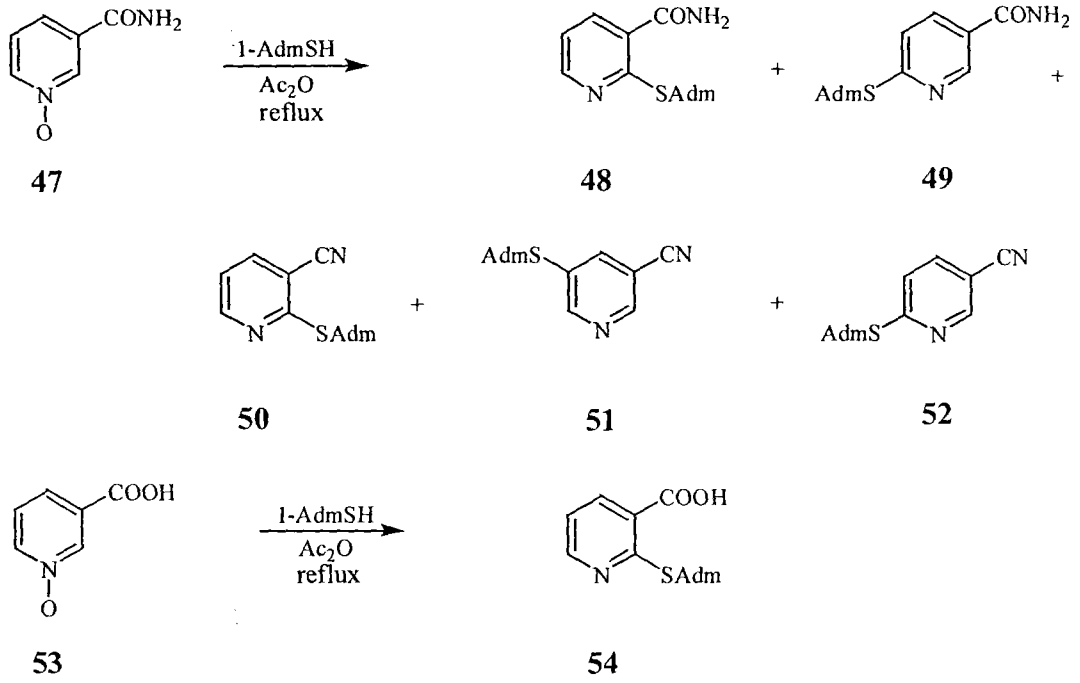



**Figure 11** The deoxydative substitution reaction of nicotinamide and nicotinic acid 1-oxides with 1-adamantanethiol in acetic anhydride

In 1991, Prachayasittikul and co-workers reported that substitutions of 2-, 3- and 4-substituted pyridine 1-oxides by 1-adamantanethiol in acetic anhydride took place at available $\alpha$-, to a lesser degree at $\beta$- , and rarely at $\gamma$-ring carbons[24]. It was found that 2-phenylpyridine 1-oxide **55** produced a mixture of 5- and 6-(1-adamantylthio)-2-phenylpyridines **56** and **57**. Similarly, the reaction of

4-phenylpyridine 1-oxide **60** afforded a mixture of 2- and 3-isomeric sulfides **61** and **62** .

Substitution of the 1-oxide of 3-phenyl **63** by 1-adamantanethiol in acetic anhydride led to a mixture consisting predominantly of 2- and 6-sulfides **64** and **65**, and to a lesser extent, the 5-sulfide **66** as depicted in **Figure 12.** When triethylamine was present in otherwise identical reaction mixture, the ratio of $\alpha$ to $\beta$-sulfides increase.

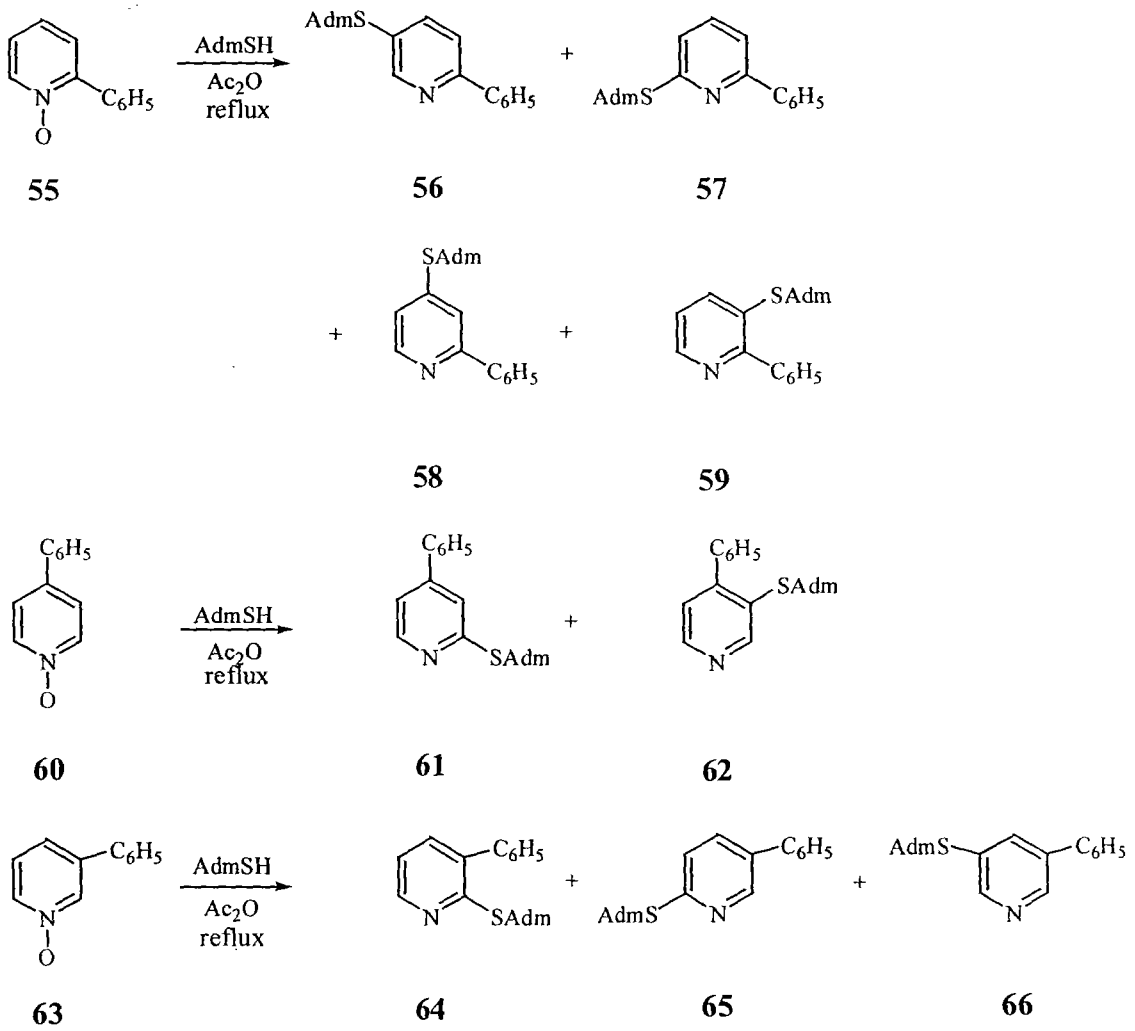
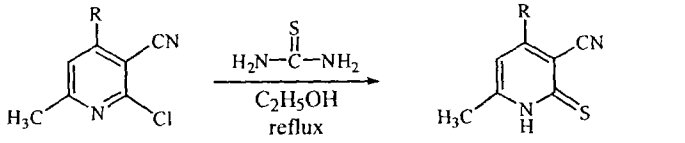



**Figure 12** The deoxydative substitution reaction of 2, 3, and 4-phenylpyridine 1-oxides with 1-adamantanethiol in acetic anhydride

## 3. Substitution of Halopyridines by Thiones and Related Reactions

In 1995, Ho and Wang reported that 2-chloropyridines **67** reacted with thiourea in refluxing ethanol[25] to provide the corresponding 2-pyridothiones **68** as depicted in **Figure 13**.

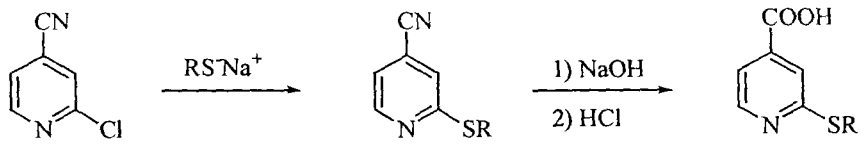



**67a**, R=H **67b**, R=$CH_3$ **68a**, R=H **68b**, R=$CH_3$

**Figure 13** The reaction of 2-chloropyridines with thiourea in refluxing ethanol

It is well known that the reaction of 2- and 4- halopyridines with alkyl sulfide ion affords the corresponding pyridyl sulfides.

In 2001, Miroslav and co-workers reported that 2-chloro-4-cyanopyridine **69** reacted with sulfide ion to yield 2-alkylthio-4-cyanopyridine **70**. Treatment of the sulfide **70** with ethanolic sodium hydroxide solution afforded the 2-alkylthio-4-pyridinecarboxylic acid[26] **71** as shown in **Figure 14**.



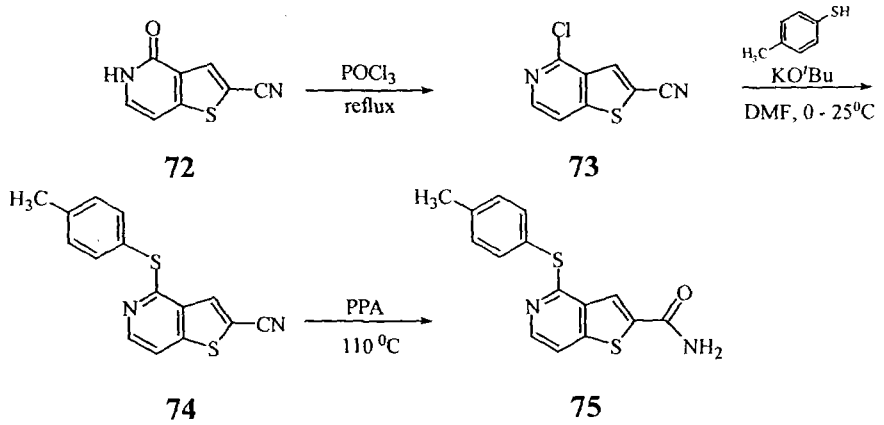

**69** **70** **71**

R = $C_3H_7$, $iC_4H_9$, $C_5H_{11}$, $CH_2C_6H_6$

**Figure 14** Synthesis of 2-alkylthio-4-pyridinecarboxylic acid

Similarly, nucleophilic displacement of chlorothienopyridine by thiol was reported, in 2001 by Stewart and co-workers. For example, 4-chlorothieno[3,2-*c*] pyridine **73** was substituted by 4-methylthiophenol, using potassium *tert*-butoxide as base, to provide sulfide[27] **74** in 97%. The final partial hydrolysis was carried out using polyphosphoric acid at 110 °C for 3 h to give amide **75** in 75% yield as shown in

**Figure 15.** The chloro compound **73** was prepared in **73%** by treatment of thieno [2,3-*b*]pyridin-4-one **72** with phosphorus oxychloride .

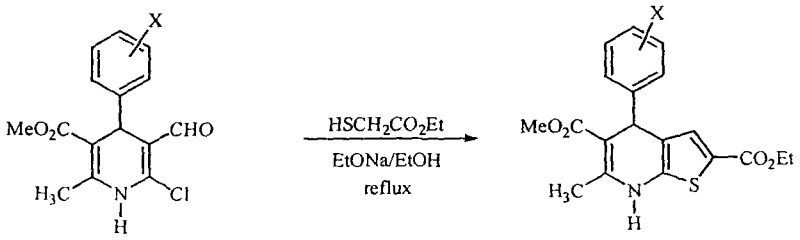



**72** **73**

**74** **75**

**Figure 15** Nucleophilic displacement of chlorothienopyridine by thiol

Morever, nucleophilic displacement of 1,4- dihydropyridine by thiol was reported by Suarez and co-workers in 1997. It was found that *o*-chloroformyl substituted 1,4-dihydropyridine **76** reacted with an equimolecular amount of ethyl mercaptoacetate in the presence of sodium ethoxide and dry ethanol under reflux to afford the novel 4,7-thieno[2,3-*b*]pyridines[28] **77a-d**. The reaction took place by nucleophilic attack of the thiolate ion, generated in the alkaline medium, at the carbon bearing the chlorine atom. Subsequent, *5-exo-trig* cyclization and dehydration afforded the compounds **77a-d** as shown in **Figure 16.**



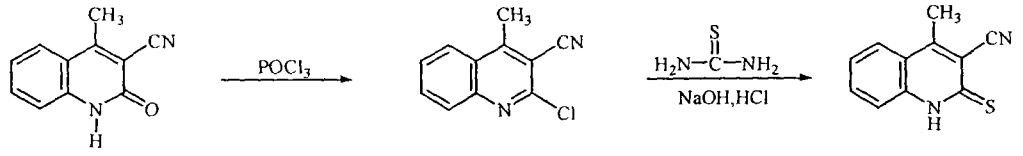

**76** **77**

a: X=H b: X=*o*-Cl

c: X=*m*-$NO_2$ d: X=*p*-$CO_2Me$

**Figure 16** Nucleophilic displacement of 1,4-dihydropyridine by thiol

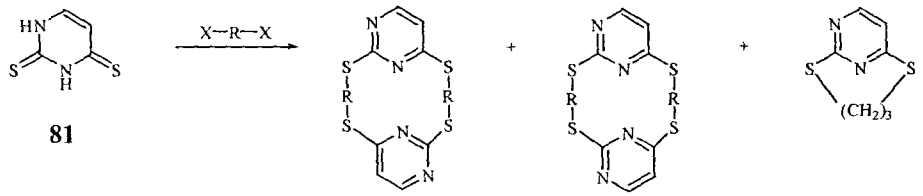
Similarly, the reaction of 2- chloroquinoline with thiourea was reported by Hafez and co-workers in 1996. For example, treatment of 2-chloroquinoline derivative **79** with thiourea in boiling ethanol gave the 3-cyano-4-methylquinolin-2(1*H*)-thione[29] **80**. The starting 2-chloroquinoline **79** was prepared from the reaction of 3-cyano-4-methylquinolin-2(1*H*)-one **78** with phosphorus oxychloride as shown in **Figure 17**.




**78** **79** **80**

**Figure 17** Synthesis of 3-cyano-4-methylquinolin-2(1*H*)-thione

In 1997, Itahara reported that treatment of 2,4-dithiouracil **81**with diiodomethane or dibromomethane in the presence of sodium hydride in *N*,*N*-dimethylformamide gave a mixture of the thiapyrimidinophanes[30] **82a** and **83a**. However, it was not an easy way to isolate both compounds in the pure state. When the mixture was subjected to HPLC, compound **82a** was isolated. Attempts were made to isolate **83a** by HPLC, but found unsuccessful. Under the similar conditions, the reaction of 2,4-dithiouracil with 1,3-diiodopropane afforded **84** and a mixture of **82b** and **83b**. Further separation of the mixture by HPLC resulted in the isolation of **83b** as depicted in **Figure 18**.




**81** **82** **83** **84**

**82a**, R=$CH_2$ **83a**, R=$CH_2$

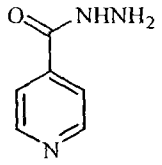
**82b**, R=$(CH_2)_3$ **83b**, R=$(CH_2)_3$

**Figure 18** Preparation of thiapyrimidinophanes from 2,4-dithiouracil

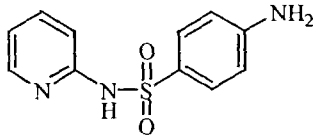
## 4. Bioactivity of Pyridine Derivatives and Related Compounds

This section briefly reviews some of the bioactivities of pyridine derivatives and related compounds.

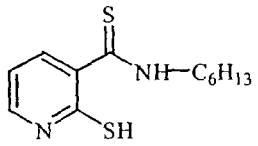
Many synthetic pyridine derivatives and some 1-oxides are important as therapeutic agents, for example, isoniazide **85** is an antituberculosis agent, sulphapyridine **86** is one of the sulfonamide antibacterials[1] and *N*-hexyl-1,2-dihydro-2-thioxo-3-pyridinecarbothioamide[31] **87** also exhibited antibacterial activity. Chloroquine[32] **88** is the drug for treatment of acute malaria. A number of 2-thioxopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **89** displayed antiinflammatory activity[33].



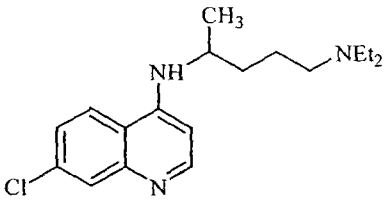
**85**



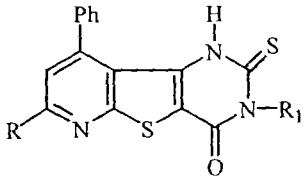
**86**



**87**



**88**



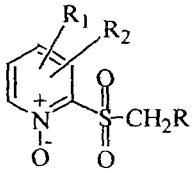
**89**

R = 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$

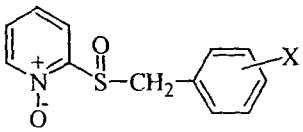
$R_1$ = *n*-$C_4H_9$ , $C_6H_5$

Furthermore, pyridine 1-oxide and sulfoxide or sulfone derivatives have proved to be herbicides[34]. Representative structures are sulfones **90** (R is alkyl or aryl , and $R_1$, $R_2$ are $C_1$ to $C_4$ alkyl groups), including sulfoxides **91** (X is alkyl, aryl or nitro) and **92** (R is alkyl). Some fungicides such as davicil **93** is also pyridine derivative.[1]

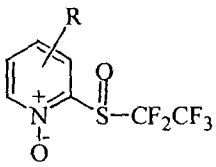
In addition, 2,6-diamino-4-methyl-3-pyridinecarbonitrile **94** and 3-cyano-4,6-dimethyl-2(1*H*)-pyridinethione **95** have found application in the dyeing[35,36].



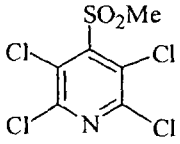
**90**



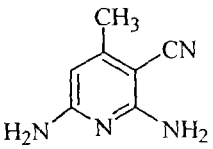
**91**



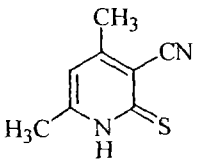
**92**



**93**



**94**



**95**

# Chapter III

# Experimental

## Chemicals

- nicotinamide 1-oxide
- nicotinic acid 1-oxide
- 3-cyanopyridine
- 3-phenylpyridine
- 4-cyanopyridine 1-oxide
- 4-phenylpyridine 1-oxide
- isonicotinic acid 1-oxide
- isonicotinamide
- 2-thiouracil
- thiourea
- phosphorus oxychloride
- triethylamine
- anhydrous sodium sulfate
- anhydrous sodium carbonate
- hexane, chloroform, dichloromethane, acetone, ethyl acetate and methanol (commercial grade , all solvents were distilled prior to use)
- silica gel for column chromatography

  silica gel (0.063-0.200 mm Merck 1.07734.2500)
- silica gel for thin layer chromatography

  silica gel $60GF_{254}$ (Merck 7730.1000)

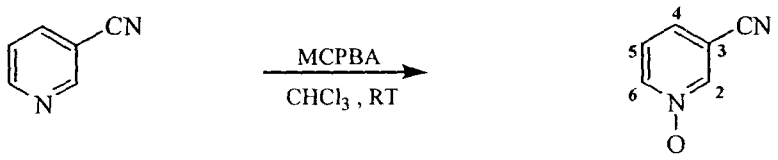
## Instruments

Melting points were determined on electrothermal melting point apparatus (Electrothermal 9100) and reported without correction.

$^{1}$H-Nuclear magnetic resonance ($^{1}$H NMR) spectra were recorded on a Bruker Advance-300 (300 MHz) using deuterochloroform and dimethylsulfoxide $d_6$ as solvents with tetramethylsilane as an internal standard. $^{13}$C-Nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on a Bruker Advance-300 (75 MHz) using deuterochloroform and dimethylsulfoxide $d_6$ as solvents with tetramethylsilane as an internal standard. Infrared spectra (IR) were obtained on a Perkin Elmer FT- IR Spectrum BX and JASCO A-302 spectrometers. Mass spectra were determined using a Finnigan INCOS.50, MAT.90 and Thermofinnigan Polaris Q instruments.

## Methods

### Preparation of 3-cyanopyridine 1-oxide[37]




**96** **97**

A solution of 3-cyanopyridine **96** 10.1196 g (0.0972 mol) and *m*-chloroperbenzoic acid 16.7877 g (0.0972 mol) was stirred in chloroform (100 mL) at room temperature until the starting material disappeared on thin layer chromatography plate. The solution was poured into water (50 mL) and made basic with solid sodium carbonate. The solution was extracted with chloroform(3×100 mL), and the extracts were combined, dried over anhydrous sodium sulfate and evaporated *in vacuo* to dryness to give crude product (9.477 g) .The crude product was purified by silica gel column using methanol:chloroform(1:9) as an eluting solvent to give a white solid (9.185 g) which was recrystallized from hexane to provide 3-cyanopyridine 1-oxide **97** (8.874 g , 76.00%).

m.p.(Hexane) : 170-173 $^{0}$C [lit(38); 174-175 $^{0}$C]

IR(KBr) : $\nu_{max}$ 2236, 1581, 1547, 1457, 1373, 1110, 936, 858, 798 cm$^{-1}$

$^{1}$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

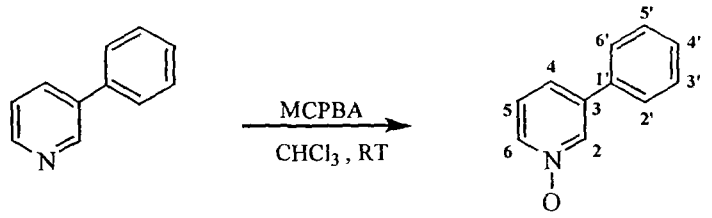
7.59 (dd, 1H, J = 7.9, 6.4 Hz, H-5)

7.82 (d, 1H, J = 7.9 Hz, H-4)

8.46 (d, 1H, J = 6.4 Hz, H-6)

8.81 (s, 1H, H-2)

**Preparation of 3-phenylpyridine 1-oxide**[37]




**98** **63**

A solution of 3-phenylpyridine **98** 7.4 mL (0.0516 mol) and *m*-chloroperbenzoic acid 8.9046 g (0.0516 mol) in chloroform (100 mL) was stirred at room temperature until the starting material disappeared on thin layer chromatography plate. The solution was poured into water (50 mL) and made basic with solid sodium carbonate. The solution was extracted with chloroform(3×100 mL) and the combined extract was dried over anhydrous sodium sulfate, then evaporated *in vacuo* to dryness to give crude product (7.843 g). The crude product was purified by silica gel column using methanol:dichloromethane(1:9) as an eluent to give a solid (7.058 g). The product was recrystallized from hexane to give 3-phenylpyridine 1-oxide **63** (6.943 g, 78.61%).

m.p.(Hexane) : 117-118 $^0$C [lit(39); 119 -120 $^0$C]

IR(KBr) : $\nu_{max}$ 1581, 1555, 1457, 1362, 1234, 1147, 1106, 1004 cm$^{-1}$

$^1$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

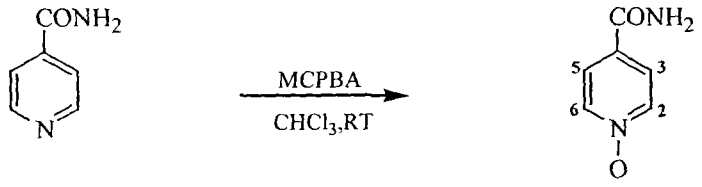
7.41-7.60 (m, 6H, ArH, H-5)

7.86 (d, 1H, J = 8.1 Hz, H-4)

8.20 (d, 1H, J = 6.2 Hz, H-6)

8.43 (s, 1H, H-2)

**Preparation of isonicotinamide 1-oxide**[37]




**99** **23**

A solution of isonicotinamide **99** 10.2510 (0.0839 mol) and *m*-chloroperbenzoic acid 14.4882 g (0.0839 mol) in chloroform (100 mL) was stirred at room temperature until the starting material disappeared on thin layer chromatography plate. The solution was poured into water (50 mL) and made basic with solid sodium carbonate. The solution was extracted with chloroform(3×100 mL) and the combined extract was dried over anhydrous sodium sulfate, then evaporated *in vacuo* to dryness to give crude product (9.432 g). The crude product was purified by silica gel column using methanol:dichloromethane (1:9) as an eluent to give a solid (8.235 g). The product was recrystallized from water to give isonicotinamide 1-oxide **23** (7.428. g, 64.07%).

m.p.(Water) : 300-303 $^{0}$C [lit(40); 305-307]

IR(KBr) : $\nu_{max}$ 3480, 1680, 1630, 1320 cm$^{-1}$

$^{1}$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

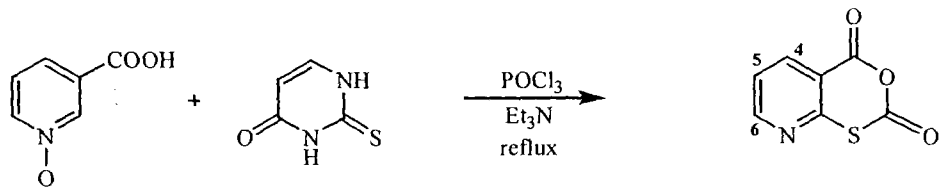
8.30 (d, 2H, J = 7.0 Hz, H-2, H-6)

8.18 (br s, 1H, NH)

7.83 (d, 2H, J = 7.0 Hz, H-3, H-5)

7.66 (br s, 1H, NH)

**Reaction of nicotinic acid 1 - oxide with 2 - thiouracil in phosphorus oxychloride containing triethylamine**




**53** **100**

The reaction of nicotinic acid 1-oxide **53** 2.0351g (14.629 mmol) with 2-thiouracil 2.249 g (17.5548 mmol) in phosphorus oxychloride (10 mL) containing triethylamine (15.1 mL) was heated under reflux for 8 h, then phosphorus oxychloride was evaporated *in vacuo*. The residue was neutralized with 10% sodium carbonate. The solution was extracted with choroform (3 × 50 mL). The combined chloroform extracts were washed with water (2×50 mL), dried over anhydrous sodium sulfate and evaporated *in vacuo* to dryness. The residue (0.2401 g) was chromatographed on silica gel 45 g, elution with chloroform : hexane(18:82) to produced 0.1120 g of **100**. Recrystallization from hexane afforded orange crystals of product **100** (0.1079 g, 4.07%)

m.p.(Hexane) : 171-172 $^{0}$C

IR(KBr) : $\nu_{max}$ 1564, 1542, 1385, 1291, 1230, 1018, 799 cm$^{-1}$

$^{1}$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

7.40 (dd, 1H, J = 4.5 Hz, 8.1 Hz, H-5)

8.42 (d, 1H, J = 8.1 Hz, H-4)

8.83 (d, 1H, J = 3.6 Hz, H-6)

$^{13}$C NMR (75 MHz, $CDCl_3$) : $\delta$ (ppm)

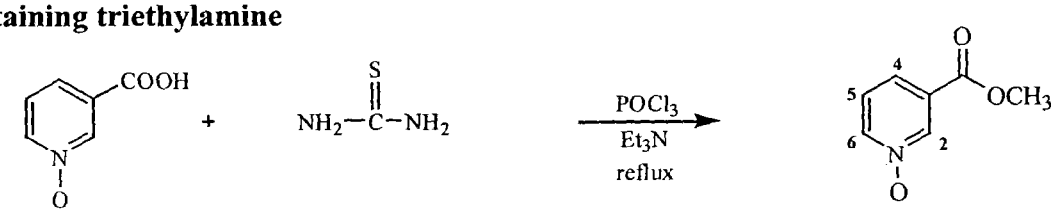
120.35(C-5), 134.16(C-3), 136.32(C-4), 154.11(C-6), 172.29(C-2),

214.28(C=O)

Mass Spectrum : m/z (% relative intensity)

157($M^+$, 9.46), 156(79.87), 155(100.00), 154(80.06)

**Reaction of nicotinic acid 1-oxide with thiourea in phosphorus oxychloride containing triethylamine**




**53** **101**

A mixture of nicotinic acid 1-oxide **53** 2.0041 g (14.406 mmol) and thiourea 1.3260 g (17.422 mmol) in phosphorus oxychloride (10 mL) containing triethylamine (15.1 mL) was heated under reflux for 8 h, then phosphorus oxychloride was evaporated *in vacuo*. The residue was neutralized with 10% sodium carbonate . The solution was extracted with chloroform (3 ×50 mL). The combined extracts were washed with water (2×50 mL ) and dried (anh.$Na_2SO_4$). The solvent was evaporated *in vacuo* to dryness to give crude product (0.9852 g). Purification by silica gel (50 g) column, elution with methanol : dichloromethane(1:9) gave product **101** which was further recrystallized from hexane to give as white crystals(153.2 mg , 6.94 %) of **101**.

m.p.(Hexane) : 100-102 $^0$C

IR(KBr) : $\nu_{max}$ 1735, 1603, 1429, 1306, 1237, 1111, 1014, 801, 753 cm$^{-1}$

$^1$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

3.59 (s, 3H, $OCH_3$)

7.35 (t, 1H, J = 7.2 Hz, H-5)

7.84 (d, 1H, J = 7.9 Hz, H-4)

8.32 (d, 1H, J = 6.3 Hz, H-6)

8.75 (s, 1H, H-2)

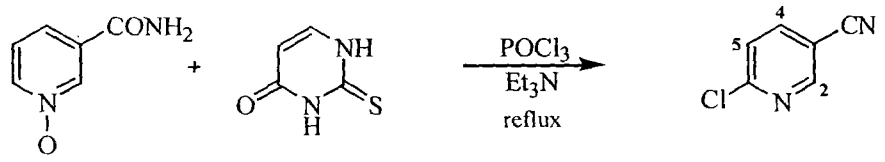
$^{13}$C NMR (75 MHz, $CDCl_3$) : $\delta$ (ppm)

53.06($OCH_3$), 125.78(C-5), 126.10(C-4), 129.92(C-3), 140.29(C-2), 142.47(C-6), 164.00(C=O)

Mass Spectrum : m/z (% relative intensity)

153($M^+$,100.00), 123(26.62), 122(22.76), 94(22.06), 61(25.13)

**Reaction of nicotinamide 1 - oxide with 2 - thiouracil in phosphorus oxychloride containnig triethylamine**




**47** **102**

A mixture of nicotinamide 1-oxide **47** 0.9522 g ( 6.895 mmol) and 2- thiouracil 1.0603 g (8.274 mmol) in phosphorus oxychloride (10 mL) containing triethylamine (15.1 mL) was refluxed for 8 h, then phosphorus oxychloride was evaporated *in vacuo* to give crude product. The residue was neutralized with 10% sodium carbonate. The solution was extracted with dichloromethane(3 ×50 mL). The combined dichloromethane extracts were washed with water (2 ×50 mL), dried over anhydrous sodium sulfate and evaporated *in vacuo* to dryness. The crude product was purified by silica gel(25 g) column. Elution with ethyl acetate : hexane(1:9) provide crude product which was further recrystrallized form hexane to give 6-chloro-3-cyanopyridine **102** as white needles (28.9 mg , 3.02 %).

m.p.(Hexane) : 115-116 $^0$C [lit(41); 115-116$^0$C]

IR (KBr) : $\nu_{max}$ 2236, 1581, 1547, 1457, 1373, 1110, 936, 858, 798 cm$^{-1}$

$^1$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

7.47 (d, 1H, J = 8.3 Hz, H-5)

7.90 (dd, 1H, J = 2.2, 8.3 Hz, H-4)

8.67 (d, 1H, J = 2.2 Hz, H-2)

$^{13}$C NMR (75 MHz, $CDCl_3$) : $\delta$ (ppm)

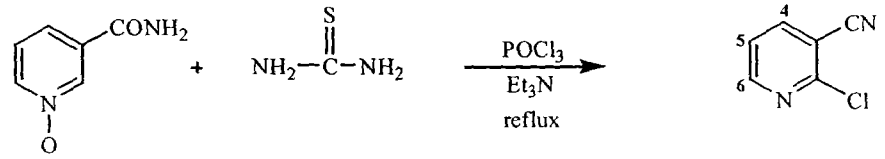
113.95 (CN), 125.00 (C-5), 141.60 (C-4), 153.00 (C-2)

Mass Spectrum : m/z (% relative intensity)

141($M^+$+ 2, 31.41), 139($M^+$, 100.00), 138(50.26), 103(59.68),

76(83.23), 75(38.24)

**Reaction of nicotinamide 1-oxide with thiourea in phosphorus oxychloride containing triethylamine**




**47** **103**

A mixture of nicotinamide 1-oxide **47** 1.0005 g ( 7.244 mmol) with thiourea 0.6704 g (8.808 mmol) in phosphorus oxychloride (10 mL) containing triethylamine (15.1 mL) was refluxed for 8 h, then phosphorus oxychloride was evaporated *in vacuo* to give crude product (0.8872 g). The residue was neutralized carefully with 10% sodium carbonate and extracted with dichloromethane (3 ×50 mL). The dichloromethane extracts were washed with water (2 ×50 mL) and dried over anhydrous sodium sulfate. Evaporation to dryness under reduced pressure provided crude product (115 mg) which was purified by silica gel(25 g) column. Elution with 50% dichloromethane in hexane gave product which was recrystrallized from hexane to yield 2-chloro-3-cyanopyridine **103** as white needles(38 mg, 3.78%).

m.p.(Hexane) : 109-110 $^{0}$C [lit(42); 105 $^{0}$C]

IR (KBr) : $\nu_{max}$2234, 1578, 1443, 1146, 1080, 809, 736, 674 cm$^{-1}$

$^{1}$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

7.38 (dd, 1H, J = 4.9, 7.7 Hz, H-5)

8.00 (dd, 1H, J = 1.4, 7.7 Hz, H-4)

8.59 (dd, 1H, J = 1.4, 4.9 Hz, H-6)

$^{13}$C NMR (75 MHz, $CDCl_3$) : $\delta$ (ppm)

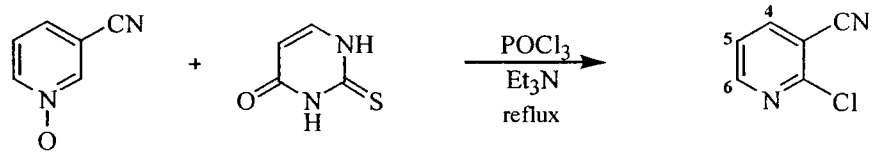
110.95 (C-3), 114.56 (CN), 122.17 (C-5), 142.58 (C-4), 152.90 (C-6)

Mass Spectrum : m/z (% relative intensity)

141($M^+$ + 2, 32.58), 139($M^+$, 100.00), 138(45.96), 103(39.08),

76(61.21), 75(28.47)

**Reaction of 3-cyanopyridine 1-oxide with 2-thiouracil in phosphorus oxychloride containing triethylamine**




**97** **103**

A solution of 3-cyanopyridine 1-oxide **97** 2.0447 g (17.024 mmol), 2-thiouracil 2.5962 g (20.259 mmol) in phosphorus oxychloride (10 mL) was added triethylamine (15.1 mL) . The mixture was heated at 110-120 $^0$C for 8 h, cooled down and phosphorus oxychloride was evaporated *in vacuo* to afford crude product (1.847 g). The residue was neutralized carefully with 10% sodium carbonate, and extracted with dichloromethane(3 ×50 mL). The combined organic extracts were washed with water (2 ×50 mL), dried (anh. $Na_2SO_4$) and evaporated under reduced pressure to dryness. Purification of the residue by using silica gel (45 g) column. Elution with ethyl acetate : hexane (15:85) provided crude product which was recrystrallized from hexane to give 2-chloro-3-cyanopyridine **103** as white needles(83.5 mg, 3.54 %).

m.p.(Hexane) : 109 –110 $^0$C [lit(42); 105 $^0$C]

IR(KBr) : $\nu_{max}$ 2237, 1578, 1555, 1446, 1146, 1080, 809, 737 cm$^{-1}$

$^1$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

7.38 (dd, 1H, J = 4.9, 7.7 Hz, H-5)

8.00 (dd, 1H, J = 1.4, 7.7 Hz, H-4)

8.59 (dd, 1H, J = 1.4, 4.9 Hz, H-6)

$^{13}$C NMR (75 MHz, $CDCl_3$) : $\delta$ (ppm)

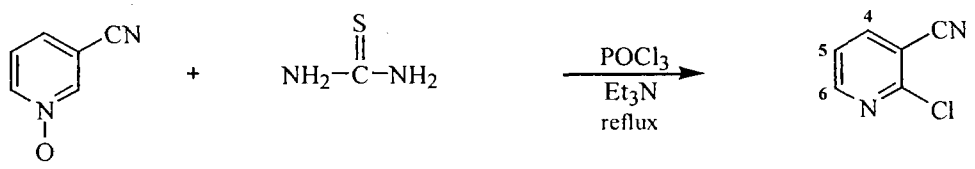
110.95(C-3), 114.55 (CN), 122.17(C-5), 142.55(C-4), 152.83(C-6)

Mass Spectrum : m/z (% relative intensity)

141($M^+$+ 2, 30.58), 139($M^+$, 100.00), 138(46.75), 103(39.08),

76(60.43), 75(26.23)

**Reaction of 3-cyanopyridine 1-oxide with thiourea in phosphorus oxychloride containing triethylamine**




**97** **103**

A mixture of 3-cyanopyridine 1-oxide **97** 2.0055 g (16.697 mmol) with thiourea 1.5299 g (20.1011 mmol) in phosphorus oxychloride (10 mL) containing triethylamine (15.1 mL) was refluxed for 8 h. The solution was cooled down and phosphorus oxychloride was evaporated under reduced pressure, and the residue was neutralized with 10% sodium carbonate. The solution was extracted with dichloromethane(3 ×50 mL). The combined dichloromethane extracts were washed with water(2 ×50 mL), dried over anhydrous sodium sulfate and evaporated *in vacuo* to dryness. The residue was chromatographed on silica gel(45 g) column using acetone:hexane(1:9) as an eluting solvent to provide a solid. The obtained solid was recrystallized from hexane to give 2-chloro-3-cyanopyridine **103** as white needles (123.9 mg , 5.35 %).

m.p.(Hexane) : 109 –110 $^{0}$C [lit(42); 105 $^{0}$C]

IR(KBr) : $\nu_{max}$ 2236, 1578, 1554, 1445, 1146, 1080, 809, 737 cm$^{-1}$

$^{1}$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

7.38 (dd, 1H, J = 4.9, 7.7 Hz, H-5)

8.00 (dd, 1H, J = 1.8, 7.7 Hz, H-4)

8.60 (dd, 1H, J = 1.8, 4.9 Hz, H-6)

$^{13}$C NMR (75 MHz, $CDCl_3$) : $\delta$ (ppm)

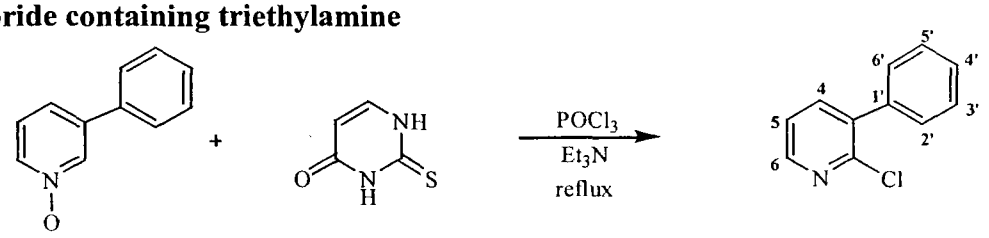
111.38 (C-3), 114.56 (CN), 122.18(C-5), 142.56(C-4), 152.83(C-6)

Mass Spectrum : m/z (% relative intensity)

141($M^+$+ 2, 32.54), 139($M^+$, 100.00), 138(48.96), 103(41.08),

76(62.21), 75(29.27)

**Reaction of 3-phenylpyridine 1-oxide with 2-thiouracil in phosphorus oxychloride containing triethylamine**




**63** **104**

A mixture of 3-phenylpyridine 1-oxide **63** 1.5211 g (8.8849 mmol) and 2-thiouracil 1.370 g (10.698 mmol) in phosphorus oxychloride (10 mL) was added triethylamine (15.1 mL). The solution was refluxed for 8 h, then cooled down and phosphorus oxychloride was evaporated under reduced pressure to give crude product (1.248 g). The residue was neutralized carefully with 10% sodium carbonate in an ice bath, and extracted with dichloromethane(3 ×50 mL). The organic layer was separated and combined, then washed with water (2 ×50 mL) and dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The resulting orange residue was purified by using silica gel (40 g) column. Elution with ethyl acetate : dichloromethane(3:7) gave 2-chloro-3-phenylpyridine **104** (25.3 mg, 1.50 %) which was further recrystallized from ethyl acetate.

m.p.(Ethyl acetate) : 56-57 $^{0}$C [lit(43); 52-56 $^{0}$C]

IR(KBr) : $\nu_{max}$ 1580, 1555, 1457, 1361, 1106, 842, 763, 698, cm$^{-1}$

$^{1}$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

7.35-7.55 (m, 6H, ArH, H-5)

7.82 (dd, 1H, J = 2.3, 8.2 Hz, H-4)

8.58 (d, 1H, J = 2.1 Hz, H-6)

$^{13}$C NMR (75 MHz, $CDCl_3$) : $\delta$ (ppm)

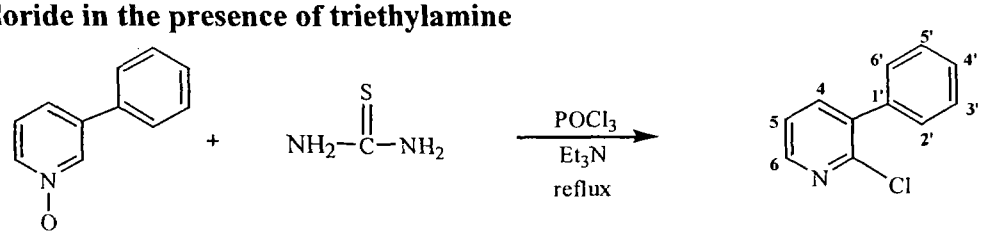
124.22(C-5), 127.07(C-3′, C-5′), 128.48(C-4′), 129.23(C-2′, C-6′), 135.67(C-1′), 136.52(C-3), 137.19(C-4), 148.02(C-6), 150.34(C-2)

Mass Spectrum : m/z (% relative intensity)

191($M^+$+ 2, 35.08), 189($M^+$, 100.00), 154(33.01), 127(21.19),

126(21.88)

**Reaction of 3-phenylpyridine 1-oxide with thiourea in phosphorus oxychloride in the presence of triethylamine**




**63** **104**

A solution of 3-phenylpyridine 1-oxide **63** 1.0357 g (6.049 mmol), thiourea 0.5539 g (7.277 mmol) in phosphorus oxychloride (10 mL) was added triethylamine (15.1 mL). The reaction mixture was heated under reflux for 8 h, then phosphorus oxychloride was removed under reduced pressure to give a residue which was neutralized with 10% sodium carbonate in an ice bath. The solution was extracted with methylene chloride(3 ×50 mL). The combined organic extracts were washed with water(2 ×50 mL) and dried over anhydrous sodium sulfate. After removal of solvent, the residue (0.452 g) was chromatographed on silica gel (25 g) column using dichloromethane:hexane(2:8) as an eluent to provide 2-chloro-3-phenylpyridine **104** which was recrystallized from hexane to give white solids(34.5 mg, 3.01%).

m.p.(Ethyl acetate) : 56-57 $^{0}$C [lit(43); 52-56 $^{0}$C]

IR(KBr) : $\nu_{max}$ 1585, 1560, 1540, 1457, 1345, 1020, 765, 694 cm$^{-1}$

$^{1}$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

7.35-7.55 (m, 6H, ArH, H-5)

7.82 (dd, 1H, J = 2.3, 8.2 Hz, H-4)

8.59 (d, 1H, J = 2.1 Hz, H-6)

$^{13}$C NMR (75 MHz, $CDCl_3$) : $\delta$ (ppm)

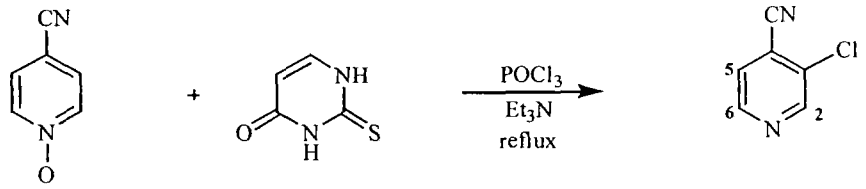
124.22(C-5), 127.07(C-3′, C-5′), 128.48(C-4′), 129.23(C-2′, C-6′), 135.67(C-1′), 136.52(C-3), 137.19(C-4), 148.02(C-6), 150.34(C-2)

Mass Spectrum : m/z (% relative intensity)

191($M^+$+ 2, 35.10), 189($M^+$, 100.00), 154(33.15), 127(22.49),

126(23.88)

**Reaction of 4 - cyanopyridine 1 - oxide with 2-thiouracil in phosphorus oxychloride in the presence of triethylamine**




**25** **26**

Triethylamine 15.1 mL was added to a solution of 4-cyanopyridine 1-oxide **25** 2.000 g (16.65 mmol) and 2-thiouracil 2.5594 g (19.97 mmol) in phosphorus oxychloride(10 mL). The solution was refluxed for 8 h, then phosphorus oxychloride was evaporated *in vacuo*. The residue was neutralized by addition of 10% sodium carbonate and then extracted with dichloromethane (3×50 mL). The combined dichloromethane extracts were washed with water(20 mL), dried over anhydrous sodium sulfate and evaporated to dryness to give crude product. The crude product was purified by silica gel (25 g) column using acetone:hexane(1:9) as an eluent to provide 3-chloro-4-cyanopyridine **26** which was recrystallized from hexane to give white solids (532.3 mg, 23.06%).

m.p.(Hexane) : 69 –70 $^{0}$C [lit(5); 71-72$^{0}$C]

IR(KBr) : $\nu_{max}$ 2239, 1588, 1460, 1374, 1284, 1117, 888, 851 cm$^{-1}$

$^{1}$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

7.45 (d, 1H, J = 5.0 Hz, H-5)

7.58 (s, 1H, H-2)

8.58 (d, 1H, J = 5.0 Hz, H-6)

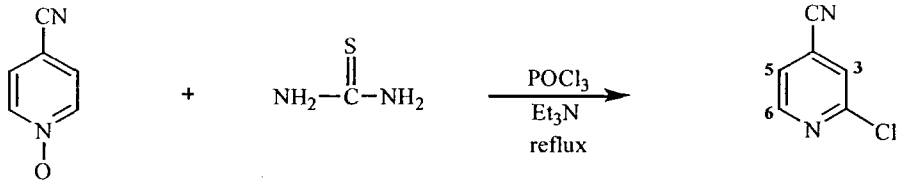
$^{13}$C NMR (75 MHz, $CDCl_3$) : $\delta$ (ppm)

115.14 (CN), 121.98(C-3), 122.95(C-4), 123.72(C-5), 126.29(C-2), 150.86(C-6)

Mass Spectrum : m/z (% relative intensity)

141($M^{+}$+ 2, 8.34), 139($M^{+}$, 26.86), 103(57.31), 76(100.00)

**Reaction of 4-cyanopyridine 1 - oxide with thiourea in phosphorus oxychloride in the presence of triethylamine**




**25** **73**

A solution of 4-cyanopyridine 1-oxide **25** 2.0043 g (16.7 mmol) and thiourea 1.5288 g (20.0 mmol) in phosphorus oxychloride (10 mL) was added triethylamine (15.1 mL). The reaction mixture was refluxed for 8 h, then phosphorus oxychloride was removed under reduced pressure to give a residue which was neutralized with 10% sodium carbonate in an ice bath. The solution was extracted with dichloromethane (3×50 mL). The combined organic extracts were washed with water (20 mL) and dried over anhydrous sodium sulfate. After removal of solvent, the residue was chromatographed on silica gel(45 g) column using acetone : hexane(1:9) as an eluent to provide 2-chloro-4-cyanopyridine **73** which was recrystallized from hexane to give white solids(267.6 mg , 11.57 %)

m.p.(Hexane) : 72 –74 $^{0}$C [lit(5); 69.5-71.5 $^{0}$C]

IR(KBr) : $\nu_{max}$ 2248, 1588, 1461, 1374, 1284, 1212, 888, 852 cm$^{-1}$

$^{1}$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

7.46 (dd, 1H, J = 1.2, 5.1 Hz, H-5)

7.57 (br.s, 1H, H-3)

8.57 (d, 1H, J = 5.1 Hz, H-6)

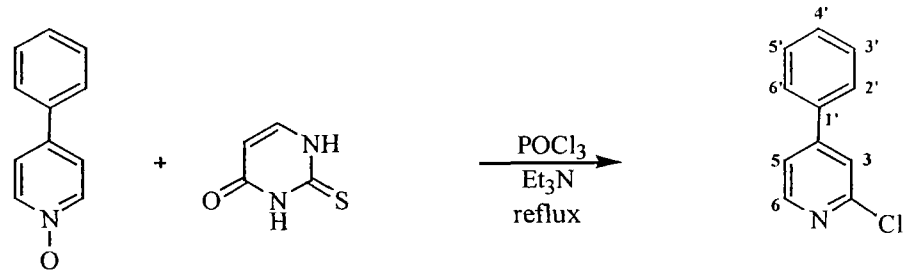
$^{13}$C NMR (75 MHz, $CDCl_3$) : $\delta$ (ppm)

115.15 (CN), 121.95(C-4), 123.74(C-5), 126.30(C-3), 150.87(C-6), 152.73(C-2)

Mass Spectrum : m/z (% relative intensity)

141($M^+$+ 2, 8.34), 139($M^+$, 26.86), 103(57.31), 76(100.00)

**Reaction of 4-phenylpyridine 1-oxide with 2-thiouracil in phosphorus oxychloride containing triethylamine**




**60** **105**

A mixture of 4-phenylpyridine 1-oxide **60** 2.0332 g (11.876 mmol) with 2-thiouracil 1.8303 g (14.282 mmol) in phosphorus oxychloride (10 mL) containing triethylamine (15.1 mL) was refluxed for 8 h, then phosphorus oxychloride was evaporated *in vacuo* to give crude product. The residue was neutralized carefully with 10% sodium carbonate in an ice bath and extracted with methylene chloride (3×50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was purified by silica gel (40 g) column using ethyl acetate : hexane(1:9) as an eluent affording 2-chloro-4-phenylpyridine **105** (48 mg). The product was recrystallized from hexane to give white solids of **105** (35.1 mg , 1.56%).

m.p.(Hexane) : 75 –77 $^{0}$C

IR(KBr) : $\nu_{max}$ 1590, 1534, 1458, 1376, 1090, 860, 756, 690 cm$^{-1}$

$^{1}$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

7.39-7.51 (m, 6H, H-3, ArH)

7.63 (br.d, 1H, J = 6.7 Hz, H-5)

8.65 (d, 1H, J = 5.9 Hz, H-6)

$^{13}$C NMR (75 MHz, $CDCl_3$) : $\delta$ (ppm)

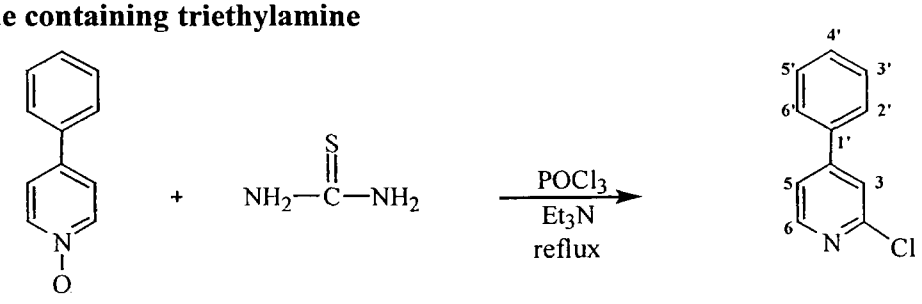
121.63(C-5), 126.93(C-3), 129.10($C_6H_5$), 138.69(C-4),

148.59(C-2), 150.25(C-6)

Mass Spectrum : m/z (% relative intensity)

156(79.87), 155(100.00), 154(80.06), 127(28.91), 126(17.73)

**Reaction of 4-phenylpyridine 1-oxide with thiourea in phosphorus oxychloride containing triethylamine**




**60** **105**

A solution of 4-phenylpyridine 1-oxide **60** 2.0041 g (11.706 mmol) and thiourea 1.0731 g (14.099 mol) in phosphorus oxychloride (10 mL) was added triethylamine (15.1 mL). The mixture was refluxed for 8 h, then cooled down and phosphorus oxychloride was evaporated under reduced pressure to give crude product. The residue was neutralized carefully with 10% sodium carbonate in an ice bath, and extracted with dichloromethane (3×50 mL). The organic layer was separated and washed again with water (20 mL), dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The residue was purified by silica gel (45 g) column. Elution with 5% ethyl acetate : hexane gave 2-chloro-4-phenylpyridine **105** (487.3 mg , 21.94%) which was further recrystallized from hexane.

m.p.(Hexane) : 75 –77 $^{0}$C

IR(KBr) : $\nu_{max}$ 1588, 1544, 1483, 1410, 1233, 1042, 830, 762, 688 cm$^{-1}$

$^{1}$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

7.39-7.51 (m, 6H, H-3, ArH)

7.63 (d, 1H, J = 6.7 Hz, H-5)

8.65 (d, 1H, J = 5.9 Hz, H-6)

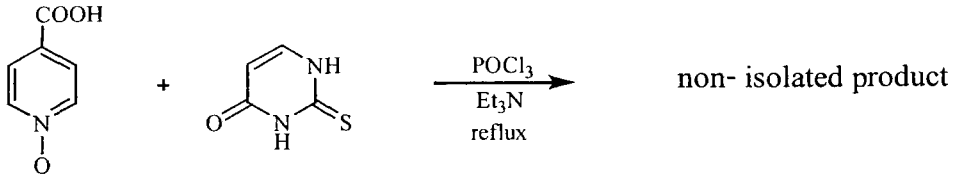
$^{13}$C NMR (75 MHz, $CDCl_3$) : $\delta$ (ppm)

121.63(C-5), 126.93(C-3), 129.10($C_6H_5$), 138.69(C-4), 148.59(C-2), 150.25(C-6)

Mass Spectrum : m/z (% relative intensity)

156(80.57), 155(100.00), 154(81.42), 127(29.05), 126(19.12)

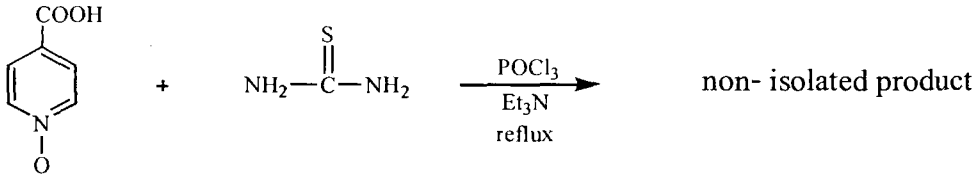
**Reaction of isonicotinic acid 1-oxide with 2-thiouracil in phosphorus oxychloride containing triethylamine**




**106**

A solution of isonicotinic acid 1-oxide **106** 2.0274 g (14.57 mmol) and 2-thiouracil 2.2461 g (17.52 mmol) in phosphorus oxychloride (10 mL) was added triethylamine (15.1 mL). The mixture was heated under reflux for 12 h, then cooled down and phosphorus oxychloride was evaporated under reduced pressure to give crude product. The residue was neutralized carefully with 10% sodium carbonate in an ice bath, and extracted with dichloromethane (3×50 mL). The organic layer was separated and washed again with water (20 mL), dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The residue was purified by silica gel (45 g) column and led to non-isolated product.

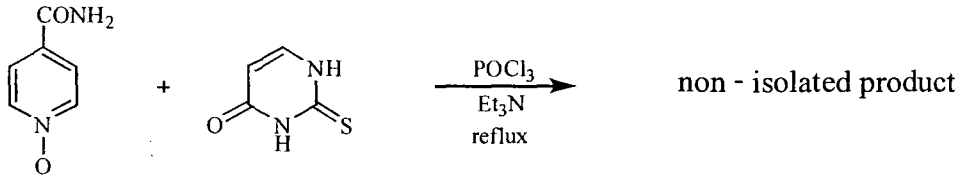
**Reaction of isonicotinic 1- oxide with thiourea in phosphorus oxychloride containing triethylamine**




**106**

A solution of isonicotinic acid 1-oxide **106** 3.000 g (21.57 mmol) and thiourea 1.9906 g (26.15 mmol) in phosphorus oxychloride (10 mL) was added triethylamine (15.1 mL). The mixture was heated under reflux for 12 h, then cooled down and phosphorus oxychloride was evaporated under reduced pressure to give crude product. The residue was neutralized carefully with 10% sodium carbonate in an ice bath, and extracted with dichloromethane (3×50 mL). The organic layer was separated and washed again with water (20 mL), dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The residue was purified by silica gel (45 g) column and led to non-isolated product.

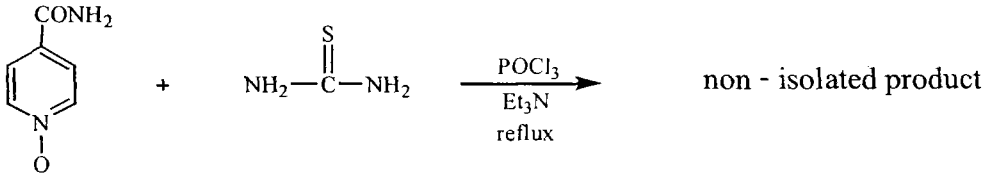
**Reaction of isonicotinamide 1-oxide with 2-thiouracil in phosphorus oxychloride containing triethylamine**




**23**

A solution of isonicotinamide 1-oxide **23** 1.0128 g (7.333 mmol) and 2-thiouracil 1.1210 g (8.747 mmol) in phosphorus oxychloride (10 mL) was added triethylamine (15.1 mL). The mixture was heated under reflux for 12 h, then cooled down and phosphorus oxychloride was evaporated under reduced pressure to give crude product. The residue was neutralized carefully with 10% sodium carbonate in an ice bath, and extracted with dichloromethane (3×50 mL). The organic layer was separated and washed again with water (20 mL), dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The residue was purified by silica gel (45 g) column and led to non-isolated product.

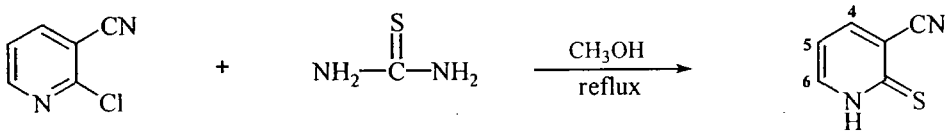
**Reaction of isonicotinamide 1-oxide with thiourea in phosphorus oxychloride containing triethylamine**




**23**

A solution of isonicotinamide 1-oxide **23** 1.0066 g (7.289 mmol) and thiourea 0.6793g (8.9252 mmol) in phosphorus oxychloride (10 mL) was added triethylamine (15.1 mL). The mixture was heated under reflux for 12 h, then cooled down and phosphorus oxychloride was evaporated under reduced pressure to give crude product. The residue was neutralized carefully with 10% sodium carbonate in an ice bath, and extracted with dichloromethane (3×50 mL). The organic layer was separated and washed again with water (20 mL), dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The residue was purified by silica gel (45 g) column and led to non-isolated product.

**Reaction of 2-chloro-3-cyanopyridine with thiourea in methanol**




**103** **107**

To a solution of 2-chloro-3-cyanopyridine **103** 51.7 mg (0.373 mmol) and thiourea 0.056 g (0.746 mmol) in methanol (5 mL) was refluxed for 5 h. After cooling, the precipitate was filtered and recrystallized from dichloromethane to obtain 3-cyano-2(1*H*)-pyridinethione **107** (20.0 mg, 39.4%)

m.p.(Dichloromethane) : 227-230 $^{0}$C [lit(44); 228-230 $^{0}$C]

IR(KBr) : $\nu_{max}$ 2228, 1589, 1492, 1441, 1238, 1176, 1161, 860 cm$^{-1}$

$^{1}$H NMR (300 MHz, $CDCl_3$) : $\delta$ (ppm)

6.81 (t, 1H, J = 6.8 Hz, H-5)

7.90 (dd, 1H, J = 1.4, 6.1 Hz, H-6)

8.06 (dd, 1H, J = 1.4, 7.4 Hz, H-4)

14.18 (br s, 1H, NH)

$^{13}$C NMR (75 MHz, $CDCl_3$) : $\delta$ (ppm)

112.80(C-5), 117.40(CN), 143.38(C-6), 145.84(C-4), 177.88(C-2)

Mass Spectrum : m/z (% relative intensity)

136($M^+$, 48.12), 93(7.33), 92(100.00), 82(12.42), 76(18.71), 75(20.26)

# Chapter IV

# Results and Discussion

Generally, pyridine 1-oxides reacted with a variety of nucleophiles in the presence of quaternizing agents such as phosphorus pentachloride to furnish mainly 2-and4-chloropyridines[6,8] as described in the introduction. In addition, 2-chloropyridines reacted with thiourea in refluxing condition to give the corresponding 2-pyridenethiones.[25] In our study, the results from one pot reactions of 3- and 4-substituted pyridine 1-oxides with 2-thiouracil or thiourea in phosphorus oxychloride containing triethylamine are discussed.

## 1. Deoxydative substitution reaction of 3-substituted pyridine 1-oxides with thione nucleophiles

### 1.1 Deoxydative substitution reaction of nicotinic acid 1-oxide with 2-thiouracil

The reaction of nicotinic acid 1-oxide **53** with 2-thiouracil in phosphorus oxychloride containing triethylamine was carried out under reflux for 8 h. After work up, then separation by silica gel column and recrystallization from hexane afforded compound **100**. The structure of compound **100** was elucidate by spectroscopic methods.

The IR spectrum of compound **100** exhibited absorption band at 1564, 1542, 1385, 1291, 1230, and 1018 $cm^{-1}$.

The $^1H$ NMR spectrum showed a doublet of H-4 at $\delta$ 8.42 with coupling constant of 8.1 Hz and another doublet of H-6 at $\delta$ 8.83 with coupling constant of 3.6 Hz. In addition, H-5 appeared as a doublet of doublet at $\delta$ 7.40 with coupling constant of 4.5 and 8.1 Hz.

Mass spectral data showed a molecular ion at m/z 157 and a base peak at m/z 155.

According to the $^{1}H$ NMR and $^{13}C$ NMR spectral data, the structure of **100** is tentatively assigned to be [1,3]oxathiino[4,5-*b*]pyridine-2,4-dione. The formation of compound **100** is postulated as shown in **Figure 19**.

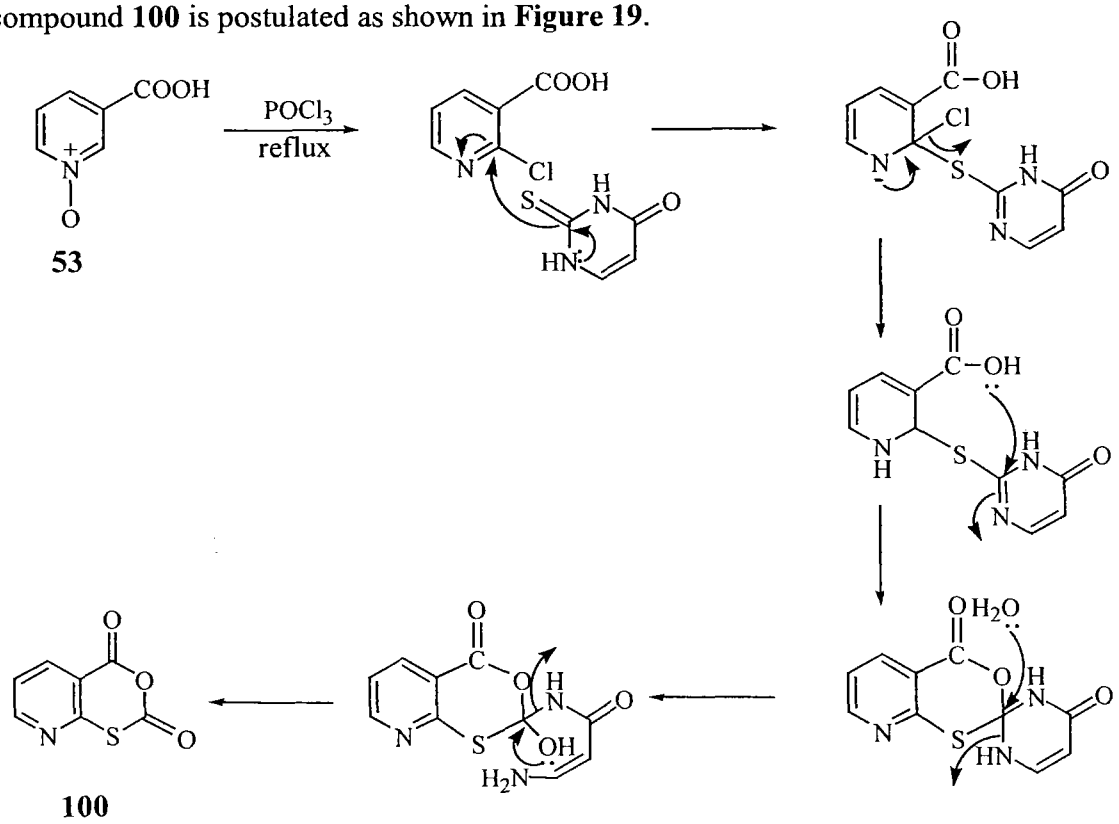
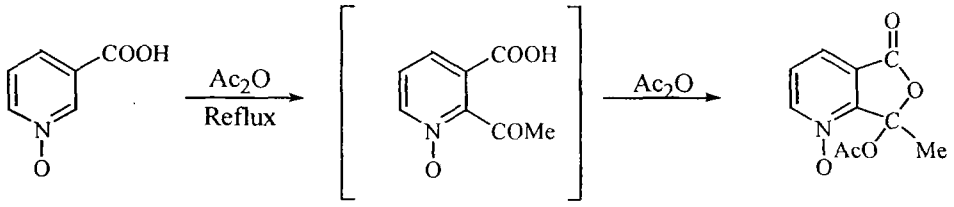



**Figure 19** The formation of [1,3]oxathiino[4,5-*b*]pyridine-2,4-dione

Previously, it was reported that nicotinic acid 1-oxide **53** was substituted by 1-adamantanethiol in acetic anhydride under reflux to give 2-(1-adamantylthio)nicotinic acid **54** as mentioned in **Figure 11**[23]. Furthermore, treatment of nicotinic acid 1-oxide **53** with boiling acetic anhydride furnished 3-acetoxy-4-aza-3-methyl-1(3*H*)-isobenzofuranone 4-oxide **109**. It was proposed that nicotinic acid 1-oxide **53** underwent electrophilic substitution to give 2-acetylnicotinic acid 1-oxide **108**. Further cyclization took place *via* attack of the carboxylic group to keto function, thus formed the 3-acetoxy-4-aza-3-methyl-1(3*H*)-isobenzofuranone 4-oxide[45] **109** as shown in **Figure 20**.




**53** **108** **109**

**Figure 20** The reaction of nicotinic acid 1-oxide with acetic anhydride

1.2 Deoxydative substitution reaction of nicotinic acid 1-oxide with thiourea

Treatment of nicotinic acid 1-oxide **53** with thiourea in phosphorus oxychloride containing triethylamine under reflux for 8 h gave methyl nicotinate 1-oxide **101** in 6.94% yield after recrystallization from hexane. The structure methyl nicotinate 1-oxide **101** was elucidated by spectral data analysis.

The IR spectrum of 1-oxide of nicotinic acid methyl ester **101** showed the absorption band at 1735 $cm^{-1}$ (C=O) and 1111, 1237 $cm^{-1}$ indicating C-O stretching. The $^1H$ NMR spectrum of methyl nicotinate 1-oxide exhibited a singlet at $\delta$ 3.59 resulting from three protons of methoxy group. Another singlet of H-2 appeared at $\delta$ 8.75. Additionally, the spectrum showed a doublet of H-4 at $\delta$ 7.84 with coupling constant of 7.9 Hz, and a doublet of H-6 at $\delta$ 8.32 with coupling constant of 6.3 Hz. Therefore, the remaining triplet at $\delta$ 7.35 (J = 7.2 Hz) was assigned for H-5.

Its mass spectrum showed a molecular ion and base peak at m/z 153 corresponding to $C_7H_7NO_3$.

Obviously, the product methyl nicotinate 1-oxide **101** did not form *via* nucleophilic or electrophilic substitution of the 1-oxide function of **53**. However, the reaction took place at the carboxylic group to form the methyl nicotinate 1-oxide **101**. It is presumably that the esterification occurred during silica gel column using methanol : dichloromethane as an eluent.

1.3 Deoxydative substitution reaction of nicotinamide 1-oxide with 2-thiouracil

The reaction of nicotinamide 1-oxide **47** with 2-thiouracil in phosphorus oxychloride containing triethylamine was carried out under reflux for 8 h to give 6-chloro-3-cyanopyridine **102** in 3.02% yield after recrystallization from hexane. Structure of 6-chloro-3-cyanopyridine **102** was verified by spectroscopic methods.

The IR spectrum of 6-chloro-3-cyanopyridine **102** exhibited characteristic absorption of nitrile group at 2236 $cm^{-1}$ resulting from dehydration of the amide group.

The $^1H$ NMR spectrum showed a doublet of H-5 at $\delta$ 7.47 with coupling constant of 8.3 Hz, and H-4 displayed at $\delta$ 7.90 as a doublet of doublet with coupling constant of 2.2 and 8.3 Hz. In addition, H-2 appeared as a doublet at $\delta$ 8.67 with coupling constant of 2.2 Hz.

The mass spectrum showed a molecular ion at m/z 139 corresponding to $C_6H_3N_2Cl$.

1.4 Deoxydative substitution reaction of nicotinamide 1-oxide with thiourea

In this part, it was found that treatment of the nicotinamide 1-oxide **47** with thiourea in phosphorus oxychloride containing triethylamine under refluxing temperature afforded 2-chloro-3-cyanopyridine **103** in 3.78% yield after recrystallization from hexane. Structure of 2-chloro-3-cyanopyridine **103** was determined by spectral data analysis.

The IR spectrum of 2-chloro-3-cyanopyridine **103** showed the absorption band of nitrile group at 2234 $cm^{-1}$ indicating the dehydration of amide moiety.

The $^1H$ NMR spectrum of 2-chloro-3-cyanopyridine **103** exhibited a doublet of doublet of H-5 at $\delta$ 7.38 with coupling constant of 4.9 and 7.7 Hz, and a doublet of doublet of H-4 at $\delta$ 8.00 with coupling constant of 1.4 and 7.7 Hz. In addition, H-6 appeared as a doublet of doublet at $\delta$ 8.59 with coupling constant of 1.4 and 4.9 Hz.

The mass spectrum showed a molecular ion at m/z 139 corresponding to $C_6H_3N_2Cl$.

1.5 Deoxydative substitution reaction of 3-cyanopyridine 1-oxide with 2-thiouracil

Treatment of 3-cyanopyridine 1-oxide **97** with 2-thiouracil in phosphorus oxychloride containing triethylamine under reflux for 8 h furnished 2-chloro-3-cyanopyridine **103** in 3.54% yield after recrystallization from hexane. Structure of 2-chloro-3-cyanopyridine **103** was elucidated by spectroscopic methods.

The IR spectrum of 2-chloro-3-cyanopyridine **103** exhibited characteristic absorption of nitrile group at 2237 $cm^{-1}$.

The $^1H$ NMR spectrum of 2-chloro-3-cyanopyridine **103** exhibited three doublets of doublets of three ring protons of H-5 at $\delta$ 7.38 with coupling constant of 4.9 and 7.7 Hz, H-4 at $\delta$ 8.00 with coupling constant of 1.4 and 7.7 Hz, and H-6 appeared at $\delta$ 8.59 with coupling constant of 1.4 and 4.9 Hz.

Its mass spectrum showed a molecular ion at m/z 139 corresponding to $C_6H_3N_2Cl$.

1.6 Deoxydative substitution reaction of 3-cyanopyridine 1-oxide with thiourea

It was found that treatment of 3-cyanopyridine 1-oxide **97** with thiourea in phosphorus oxychloride containing triethylamine under refluxing temperature gave 2-chloro-3-cyanopyridine **103** in 5.35% yield after recrystallization from hexane. Structure of 2-chloro-3-cyanopyridine was determined by spectral data analysis.

The IR spectrum of 2-chloro-3-cyanopyridine **103** showed the absorption band of nitrile group at 2236 $cm^{-1}$

Its $^1H$ NMR spectrum exhibited identical pattern of three aromatic ring protons, H-4, H-5, and H-6 as described in **1.5** for compound **103** obtained from 3-cyanopyridine 1-oxide with 2-thiouracil.

1.7 Deoxydative substitution reaction of 3-phenylpyridine 1-oxide with 2-thiouracil

The reaction of 3-phenylpyridine 1-oxide **63** with 2-thiouracil in phosphorus oxychloride containing triethylamine was carried out under reflux for 8 h to give 2-chloro-3-phenylpyridine **104** in 1.50% yield after recrystallization from ethyl acetate. Structure of 2-chloro-3-phenylpyridine **104** was elucidated by spectroscopic methods.

The IR spectrum of 2-chloro-3-phenylpyridine **104** showed the absorption band at 1580 and 1457 $cm^{-1}$(C=C stretching of aromatic ring)

The $^{1}H$ NMR spectrum of 2-chloro-3-phenylpyridine **104** exhibited the resonance of H-4 as a doublet of doublet at $\delta$ 7.82 with coupling constant of 2.3 and 8.2 Hz, and a doublet of H-6 at $\delta$ 8.58 with coupling constant of 2.1 Hz. In addition, five phenyl protons and H-5 appeared as a multiplet at $\delta$ 7.35-7.55.

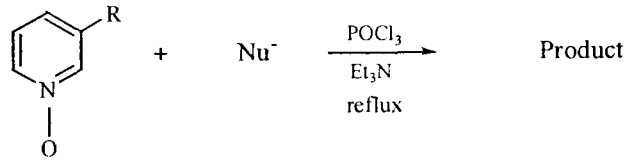
The mass spectrum data showed a molecular ion at m/z 189 corresponding to $C_{11}H_8NCl$.

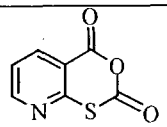
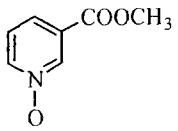
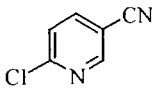
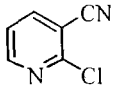
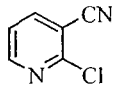
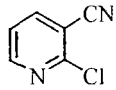
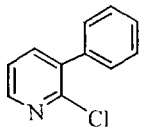
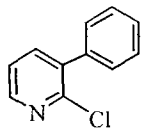
1.8 Deoxydative substitution reaction of 3-phenylpyridine 1-oxide with thiourea

Similarly, 3-phenylpyridine 1-oxide **63** reacted with thiourea in phosphorus oxychloride containing triethylamine under reflux for 8 h to produce 2-chloro-3-phenylpyridine **104** in 3.01% yield after recrystallization from ethyl acetate. The structure of 2-chloro-3-phenylpyridine **104** was elucidated by spectral data analysis, and are identical to the compound **104** obtained from the reaction with 2-thiouracil in **1.7**.

The results from the reaction of 3-substituted 1-oxides are summarized in **Table 3**.

**Table 3** Deoxydative substitution reaction of 3-substituted pyridine 1-oxides with thione nucleophiles




| R | Nu⁻ | % Yield | Product |
|---|---|---|---|
| COOH | 2-thiouracil | 4.07 |  |
| COOH | thiourea | 6.94 |  |
| $CONH_2$ | 2-thiouracil | 3.02 |  |
| $CONH_2$ | thiourea | 3.78 |  |
| CN | 2-thiouracil | 3.54 |  |
| CN | thiourea | 5.35 |  |
| $C_6H_5$ | 2-thiouracil | 1.50 |  |
| $C_6H_5$ | thiourea | 3.01 |  |

## 2. Deoxydative substitution reaction of 4-substituted pyridine 1-oxides with thione nucleophiles

2.1 Deoxydative substitution reaction of 4-cyanopyridine 1-oxide with 2-thiouracil

The reaction of 4-cyanopyridine 1-oxide **25** with 2-thiouracil in phosphorus oxychloride containing triethylamine was heated under reflux for 8 h to form 3-chloro-4-cyanopyridine **26** in 23.06% yield after recrystallization from hexane. The structure of 3-chloro-4-cyanopyridine **26** was elucidated by spectroscopic methods.

The IR spectrum of 3-chloro-4-cyanopyridine **26** exhibited characteristic absorption of nitrile group at 2239 $cm^{-1}$.

The $^1H$ NMR spectrum of 3-chloro-4-cyanopyridine **26** showed two doublets of H-5 at $\delta$ 7.45 with coupling constant of 5.0 Hz, and H-6 at $\delta$ 8.58 with the same coupling constant of 5.0 Hz. In addition, H-2 appeared as a singlet at $\delta$ 7.58.

Its mass spectrum showed a molecular ion at m/z 139 and a base peak at m/z 76 corresponding to $C_6H_3N_2Cl$.

The formation of 3-chloro-4-cyanopyridine **26** occurred *via* the attack of chloride ion at the C-4 position of the **25a** to give **25b** which was further attacked of the chloride ion at C-3 position to form **25c**. Finally, loss of hydrogen chloride produced 3-chloro-4-cyanopyridine **26**[5] as shown in **Figure 6.**

2.2 Deoxydative substitution reaction of 4-cyanopyridine 1-oxide **25** with thiourea

In the other hand, it was found that treatment of 4-cyanopyridine 1-oxide **25** with thiourea in phosphorus oxychloride containing triethylamine under refluxing temperature gave 2-chloro-4-cyanopyridine **73** in 11.57% yield after recrystallization from hexane. Structure of 2-chloro-4-cyanopyridine **73** was determined by spectral data analysis.

Its IR spectrum showed the absorption band of nitrile group at 2248 $cm^{-1}$

The $^1$H NMR spectrum of 2-chloro-4-cyanopyridine exhibited a doublet of doublet of H-5 at $\delta$ 7.46 with coupling constant of 1.2 and 5.1 Hz, and a doublet of H-6 at $\delta$ 8.57 with coupling constant of 5.1 Hz. In addition, H-3 appeared as a broad singlet at $\delta$ 7.57.

The mass spectrum showed a molecular ion at m/z 139 and a base peak at m/z 76 corresponding to $C_6H_3N_2Cl$.

2.3 Deoxydative substitution reaction of 4-phenylpyridine 1-oxide with 2-thiouracil

4-Phenylpyridine 1-oxide **60** reacted with 2-thiouracil in phosphorus oxychloride containing triethylamine under reflux for 8 h to give 2-chloro-4-phenylpyridine **105** in 1.56% yield after recrystallization from hexane. Structure of 2-chloro-4-phenylpyridine **105** was elucidated by spectral data analysis.

The IR spectrum of 2-chloro-4-phenylpyridine showed the absorption band at 1590 and 1458 $cm^{-1}$ (C=C stretching of aromatic ring)

The $^1$H NMR spectrum of 2-chloro-4-phenylpyridine exhibited a broad doublet of H-5 at $\delta$ 7.63 with coupling constant of 6.7 Hz, and doublet of H-6 at $\delta$ 8.65 with coupling constant of 5.9 Hz. In addition, H-3 and phenyl ring protons showed a multiplet at 7.39-7.51 Hz.

Its mass spectral data showed a base peak at m/z 155, a molecular ion was not observed corresponding to a molecular formula of $C_{11}H_8NCl$.

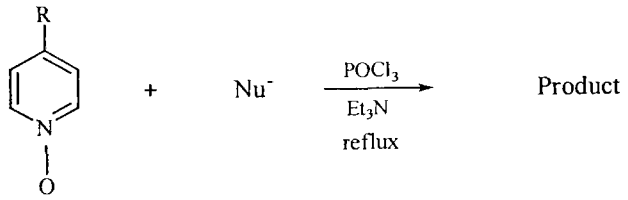
2.4 Deoxydative substitution reaction of 4-phenylpyridine 1-oxide with thiourea

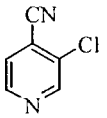
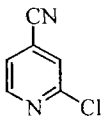
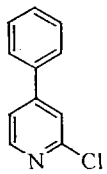
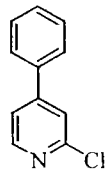
Similarly, when 4-phenylpyridine 1-oxide **60** reacted with thiourea in phosphorus oxychloride containing triethylamine under reflux for 8 h, 2-chloro-4-phenylpyridine **105** was obtained in 21.94% yield after recrystallization from hexane. Structure of 2-chloro-4-phenylpyridine was elucidated by spectroscopic methods. Its IR, $^1$H and $^{13}$C NMR and MS are identical to the compound **105** from the reaction in **2.3**.

However, it was found that the reaction of isonicotinic acid 1-oxide **106** and isonicotinamide 1-oxide **23** with either 2-thiouracil or thiourea under the similar conditions as discussed above led to the non-isolated products.

The results from the reaction of 4-substituted pyridine 1-oxides are showed in **Table 4**.

**Table 4** Deoxydative substitution reaction of 4-substituted pyridine 1-oxides with thione nucleophiles




| R | Nu⁻ | % Yield | Product |
|---|---|---|---|
| COOH | 2-thiouracil | - | - |
| COOH | thiourea | - | - |
| $CONH_2$ | 2-thiouracil | - | - |
| $CONH_2$ | thiourea | - | - |
| CN | 2-thiouracil | 23.06 |  |
| CN | thiourea | 11.57 |  |
| $C_6H_5$ | 2-thiouracil | 1.56 |  |
| $C_6H_5$ | thiourea | 21.94 |  |

The results from the reactions of 3- and 4-substituted 1-oxides with 2-thiouracil or thiourea in phosphorus oxychloride containing triethylamine produced mainly 2-chlorosubstituted pyridines. The products from these reactions arose from the nucleophilic attack of chloride ion, generated from phosphorus oxychloride, instead of thione functions. The transformation of these reactions is believed to take place *via* deoxydative substituted as described in the chapter II, Figure 4.

In conclusion, in our study it was found that nicotinamide 1-oxide and 3-cyanopyridine 1-oxide with thione nucleophiles produced 2-or 6-chloro-3-cyanopyridine, and 3-phenylpyridine 1-oxide afforded only 2-chloro-3-phenylpyridine. The product of nicotinic acid 1-oxide with 2-thiouracil is tentatively assigned to be [1,3] oxathiino[4,5-*b*]pyridine-2,4-dione. However, treatment of nicotinic acid 1-oxide with thiourea gave methyl nicotinate 1-oxide. In addition, substitution of the 1-oxide of 4-cyanopyridine afforded 2-or 3-chloro-4-cyanopyridine based on the use of thione nucleophiles. In addition, 4-phenylpyridine 1-oxide reacted with either thione to give only 2-chloro-4-phenylpyridine. Furthermore, the isolated 2-chloro-3-cyanopyridine reacted with thiourea in boiling methanol to afford 3-cyano-2(1*H*)-pyridinethione. Unfortunately, 3- and 4-substituted pyridine 1-oxides with thiones in phosphorus oxychloride containing triethylamine in one pot reaction did not afford the expected pyridinethiones. This perhaps due to the acidic condition, thus decreasing the nucleophilicity of the thiones.

# BIBLIOGRAPHY

# Bibliography


1. Joule, J.A. & Mills, K. (2000). ***Heterocyclic chemistry***. 4th ed. Oxford : Malden.
2. Klingsberg, E. (1961). ***Heterocyclic compounds pyridine and derivatives***. New Jersey : American cyanamid.
3. Bauer, L. & Prachayasittikul, S. (1986). "Deoxydative Substitution of Pyridine 1- Oxide by Thiols," ***Heterocycles***. (24) : 161-179.
4. Ochiai, E. (1967). ***Aromatic Amine Oxides***. Amsterdam : Elsevier Scientific Plublishing.
5. Rokach, J. & Cirard, Y. (1978). "An Unexpected and Efficient Synthesis of 3-Chloro-4-cyanopyridine," ***J. Heterocycl. Chem***. (15) : 683-684.
6. Katritzky, A.R. & Lagowski, J.M. (1971). ***Chemistry of the Heterocyclic N-Oxides***. New York : Academic Press.
7. Endo, M. & Nakashima, T. (1960). "Synthesis of 4-Substituted Compounds of Picolic Acid and 5-Ethoxypicolinic acid," ***J. Pharm. Soc. Japan***. (80) : 875-879.
8. Abramovitch, R.A. & Smith, E.M. (1974). ***Pyridine and its Derivatives***. 2th ed. New York : John Wiley and Sons.
9. Euler, H.V., Hasselquist, H. & Heidenberger, O. (1959). "Zur kenntnis der N-Oxyde," ***Chem. Ber***. (92) : 2266-2270.
10. Ochiai, E. & Kameko, C. (1960). "Polarisation der Heterozyklischen Ring mit Aromatischen Charakter. CXXXVII. Bemerking zur Nitrierung des Pyridin-1-Oxydes Mittels Acylnitrates und uber 3,5-Dinitropyridin-1-oxyde," ***Chem. Pharm. Bull***. (8) : 28-32.
11. Moran, D.B., Morton, G.O., & Albright, J.D. (1986). "Synthesis of (Pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridines," ***J. Heterocycl. Chem***. (23) : 1071-1077.

12. Singh, B., Lesher, G.Y., & Pennock, P.O. (1990). "A Convenient Large Scale Synthesis of 2,6-Dimethyl-4-(trimethylstannyl)pyridine," ***J. Heterocycl. Chem.*** (27) : 1841-1842.

13. Jung, J.C., Jung, Y.J. & Park, O.S. (2001). "Preparation of 2-Chloropyridine," ***Synthetic Communication.*** 31(16) : 2507-2511.

14. Bauer, L. & Gardella, L.A. (1963). "Nucleophilic Substitution of 1-Alkoxypyridinium Salts by Mercaptide Ions," ***J. Org. Chem.*** (28) : 1320-1323.

15. Bauer, L. & Gardella, L.A. (1963). "The Reaction of 1-Alkoxypicolinium Salts with Mercaptide and Thiophenoxide Ions," ***J. Org. Chem.*** (28) : 1323-1327.

16. Bauer, L. & Dickerhofe, T.E. (1964). "Substitution of 1-Alkoxy, 1-Acyloxy, and 1-Sulfonyloxypyridinium Salts by Mercaptans," ***J. Org. Chem.*** (29) : 2183-2187.

17. Bauer, L., Dickerhofe, T.E. & Tserng, K.Y. (1975). "The Deoxydative Substitution of Pyridine 1-Oxide by Mercaptans in the Presence of Carbamoyl, Carbonyl, and Sulfamyl Chlorides," ***J. Heterocycl. Chem.*** (12) : 797-799.

18. Bauer, L. & Hirsch, A.L. (1966). "Ring Substitution of Picoline and Methylpyrazine N-Oxides by Mercaptans," ***J. Org. Chem.*** (31) : 1210-1214.

19. Herchenson, F.M. & Bauer, L. (1969). "Steric and Electronic Effects Influencing the Deoxydative Substitution of Pyridine N-Oxides by Mercaptans in Acetic Anhydride," ***J. Org. Chem.*** (34) : 655-660.

20. Kokosa, J.M., Chu, I. & Bauer, L. (1976). "Tetrahydropyridines and Furans from the Reaction of 4-*t*-Butylpyridine 1-Oxide with *t*-Butyl and 1-Adamantyl Mercaptan," ***J. Heterocycl. Chem.*** (13) : 861-868.

21. Mikruth, B.A., et al. (1971). "The Effect of Triethylamine on the Deoxydative Substitution of Pyridine N-Oxides by Mercaptan," ***J. Org. Chem.*** (36) : 3749-3754.

22. Mikruth, B.A., et al. (1974). "(1-Adamantanethio)pyridines and Tetrahydropyridines from the Reaction of 1-Adamantanethiol with Pyridine 1-Oxide in Acetic Anhydride," ***J. Heterocycl. Chem.*** (11) : 713-717.

23. Prachayasittikul, S. & Bauer, L. (1985). "Deoxydative Substitution Reaction of Nicotinamide and Nicotinic Acid *N*-Oxides by 1-Adamantanethiol in Acetic Anhydride," ***J. Heterocycl. Chem.*** (22) : 771-775.

24. Prachayasittikul, S., Doss, G., & Bauer, L. (1991). "Deoxydative Substitution of Pyridine 1-Oxides by Thiol. Part XX. Reaction of (2-,3-, and 4-Phenyl)-, 3-Acetamido-, 3-Bromo-, 3-Acetoxy-,3-Ethoxypyridine 1-Oxides with 1-Adamantanethiol in Acetic Anhydride," ***J. Heterocycl. Chem.*** (28) : 1051-1060.

25. Ho, Y.W. & Wang, I.J. (1995). "Studies on the Synthesis of Some Styryl-3-cyano-2(1*H*)-pyridinethiones and Polyfunctionally Substituted 3-Aminothieno[2,3-*b*]-pyridine Derivatives," ***J. Heterocycl. Chem.*** (32) : 819-825.

26. Miletin, M. et al. (2001). "Some Anilides of 2-Alkylthio- and 2-Chloro-6-Alkylthio-4-Pyridinecarboxylic Acids: Synthesis and Photosynthesis-Inhibiting Activity," ***Molecules.*** (6) : 603-613.

27. Stewart, A.O. et al. (2001). "Discovery of Inhibitors of Cell Adhesion Molecule Expression in Human Endothelial Cell. 1. Selective Inhibition of ICAM-1 and E-selection Expression," ***J. Med. Chem.*** (44) : 998-1002.

28. Suarez, M. et al. (1997). "Synthesis and Structural Characterization of Substituted Thieno[2,3-*b*]pyridine from *o*-Chloroformyl-1,4-dihydropyridines," ***J. Heterocycl. Chem.*** (34) : 931-935.

29. Hafez, A.A.A. et al. (1996). "Synthesis of Some Pyrimido[4′,5′:4,5]thieno [2,3-*b*]quinolines and Related Heterocycles," ***J. Heterocycl. Chem.*** (33) : 431-438.

30. Itahara, T. (1997). "Preparation of Thiapyrimidinophanes from 2,4-Dithiouracil," ***J. Heterocycl. Chem.*** (34) : 687-688.

31. Pagani, G. et al. (2000). "Synthesis and in Vitro Anti-*Mycobacterium* Activity of *N*-Alkyl-1,2-dihydro-2-thioxo-3-pyridinecarbothioamide. Preliminary Toxicity and Pharmacokinetic Evaluation," ***J. Med.Chem.*** (43) : 199-204.

32. De, D., Byers, L.D. & Krogstad, D.J. (1997). "Antimalarials : Synthesis of 4-Aminoquinolines that Circumvent Drug Resistance in Malaria Parasite," ***J. Heterocycl. Chem.*** (34) : 315-320.

33. Dave, C.G., Shah, A.B. & Shah, H.C. (1997). "Synthesis and *S*-Methylation of 2-Thioxopyrido[3′,2′ :4,5]thieno[3,2-*d*]-pyrimidin-4(3*H*)-ones With and Without a Phase Transfer Catalyst,"***J. Heterocycl. Chem.*** (34) : 937-940.

34. Bauer, L. & Prachayasittikul, S. (1987). "Review of Some Recent Syntheses, Reactions and Bioactivities of Pyridyl Sulfides," ***Sulfur Report.*** 7(4) : 275-309.

35. Katritzky, A.R. & Rachwal, S. (1995). "Synthesis and Reactivity of 2,6-Diamino-4-methyl-3-pyridinecarbonitrile," ***J. Heterocycl. Chem.*** (32) : 979-984.

37. Lyle, R.E. et al. (1973). "The Synthesis of an Analog of Camptothecin by a General Method," ***J. Org. Chem.*** 19(38) : 3268-3271.

38. Prasad, R. et al. (2000). "An Efficient Synthesis of Heterocyclic N-Oxide Over Molecular Sieve Catalysts," ***Chemical Communications(Cambridge).*** (17) : 1577-1578.

39. Nobuhiro, S. & Eiichi, N. (1993). "Deoxydative Thiation of 3-Substituted Pyridine N-Oxide with 4-Methoxytoluene-$\alpha$-thiol : a divergent route to pyridinethiols," ***J. Heterocycl. Chem.*** 30(3) : 691-697.

40. Yoshinobu, T., Hideo, T. & Yoshinobu, G. (1992). "Elucidation of the Reaction Path for the Nitrosation of 2- and 4-Methylpyridine 1-Oxides with Alkylnitrile in Liquid Ammonia," ***Heterocycles.*** 33(1) : 327-336.

41. Forrest, H.S. & James, W. (1948). "Chemotherapeutic Agents of the Sulfone Type. V.2,5-Disubstituted Derivatives of Pyridine," ***J. Chem. Soc.*** Abstracts : 1939-1945.

42. Tsuyoshi, T. & Mayumi, N. (2003). "Palladium Charcoal-Catalyzed Suzuki-Miyaura Coupling to Obtain Arylpyridines and Arylquinolines," ***J. Org. Chem.*** 68(24) : 9412-9415.

43. New, J.S. et al. (1988). "Atypical Antipsychotic Agents: Patterns of Activity in a Series of 3-Substituted 2-Pyridinyl-1-piperazine Derivatives," ***J. Med. Chem.*** (31) : 618-624.

44. Tadeusz, Z. & Wieslaw, M. (1987). "Hydrolysis of Various 6-Substituted 2-amino-3,5-dicyanopyridines," ***Acta Poloniae Pharmaceutica.*** 44(1) : 32-41.

45. Prachayasittikul, S., Abdel-Sayed,A.N. & Bauer, L. (1987). "Reinvestigation of the Reaction of Nicotinic Acid 1-Oxide with Acetic Anhydride," ***Heterocycles.*** 5(26) : 1263-1270.

# GLOSSARY

# GLOSSARY

| | |
|---|---|
| s | singlet |
| d | doublet |
| dd | doublet of doublet |
| t | triplet |
| m | multiplet |
| J | coupling constant |
| EIMS | electron impact mass spectra |
| IR | infrared spectrum |
| *m/z* | a value of mass divided by charge |
| $^{0}C$ | degree celcius |
| g | gram |
| mg | milligram |
| mL | millilitre |
| h | hour |
| % | percent |
| m.p. | melting point |
| $cm^{-1}$ | wave number |
| Hz | hertz |
| Lit | literature |
| $\nu_{max}$ | maximum absorption frequencies |
| $^{1}H$ MNR | proton nuclear magnetic resonance |
| $^{13}C$ NMR | carbon nuclear magnetic resonance |

# VITA

# VITA

| | |
|---|---|
| NAME | Miss Waraphorn Sinsiri |
| DATE OF BIRTH | 30 July 1975 |
| PLACE OF BIRTH | Bangkok, Thailand |
| ADDRESS | 639 Rama 9 Road, Bangkapi, Huaykwang, Bangkok 10320 |
| INSTITUTION ATTENDED | |
| 1993 | Aranyaprathet School, Certificate |
| 1997 | Burapha University, Bachelor of Education (B.Ed.) (Chemistry) |
| 2004 | Srinakharinwirot University, Master of Education (M.Ed.) (Chemistry) |
| POSITION & OFFICE | 1997-present, Teacher Benchamaratrungsarit School, Chachoengsao, Thailand |