EXTENDED HETEROCYCLIC SYSTEMS

Pervin Unal Civcir

Chem. Eng. (Istanbul Technical University),

M.Sc. (Anadolu University)

A thesis submitted in partial fulfilment of

the requirements for the degree of

Doctor of Philosophy of the University of East Anglia

PREFACE

The research described in this thesis is, to the best of my knowledge, original except where due reference has been made.

Pervin Unal Civcir

To my husband Irfan

ACKNOWLEDGEMENTS

I would like to express my gratitude to a number of people who contributed in some way during the course of my Ph.D..

Firstly, I would like to thank Dr. R. A. Jones for his enthusiasm and guidance during the course of my Ph.D., and for proof-reading the drafts of this thesis.

My thanks go also to the members of the technical and secretarial staff of the School of Chemical Sciences at the University of East Anglia, who were always ready to help and advise. In particular I would like to mention Dr. D.J.R. Massy for providing an efficient NMR service, and Mr. A. W. R. Saunders for performing microanalyses and recording mass spectra.

The financial support of Anadolu University is also gratefully acknowledged. I would also like to thank my colleques in lab. 1.11 and 1.10.

Finally, I would like to thank my parents for their support over the years, and my husband, Irfan for his patience and support throughout the course of my Ph.D..

ABSTRACT

The first chapter of this thesis provides a general introduction to conjugated polymers. The theory underlying the conductive properties of such polymers and their applications are discussed, followed by a brief outline of the aims of the research project.

In Chapter 2 the synthetic approaches to pyridine-thiophene and pyridine-furan systems is discussed. A general review of the synthesis of pyridine, thiophene and furan rings, together with synthetic approaches to 1,4-diketones, is presented.

Chapter 3 describes the synthesis of symmetrical and unsymmetrical three ring oligomeric pyridine- thiophenes and pyridine-furans systems, which use 1,4-diketone intermediates.

In Chapter 4 the synthesis of the polymeric diketones, poly(pyridine-thiophene) and poly(pyridine-furan) is described, together with a discussion of with their spectral data. Chapter 5 gives full details of the experimental procedures.

In Chapter 6 the basicities of the compounds, which have been synthesised in this work, are given together with a general discussion of the data. The Appendix contains the experimental data required for the calculation of the pKa values.

ABBREVIATIONS

a	activity
Ac	acetyl
aq.	aqueous
Ar	aryl
arom.	aromatic
Bu	butyl
conc.	concentrated
d	days (text)
d	doublet (NMR data)
DIBAL-H	diisobutylaluminium hydride
DMF	N,N-dimethylformamide
DMSO	dimethyl sulphoxide
eq.	equivalent
Et	ethyl
f	activity coefficient(s)
h	hour(s)
HMPA	hexamethylphosphoramide
lit.	literature
m	multiplet
Me	methyl
min	minute(s)
OBS.	observations
Ph	phenyl
PPA	polyphosphoric acid
ppm	parts per million

Pr	propyl
Py	pyridine
r.t.	room temperature
s	singlet
s.m.	starting material
symm.	symmetric
T	temperature
THF	tetrahedrofuran
TMS	tetramethylsilane
Ts	*p*-toluenesulphonyl
σ	conductivity

CONTENTS

CHAPTER 1

INTRODUCTION TO POLYMERS

1.1 General Introduction

Strength, elasticity, plasticity, toughness and frictional resistance are properties which are frequently described as typical of metals, but now are also characteristic of many organic polymers. Metals have therefore been replaced by plastics in many areas of application. However, this is not the case with one of the most important properties of metals, which is their electrical conductivity.

Metals conduct electricity because of their structure in the solid state in which there is a crystal lattice of positive ions with the valence electrons free to move as an electron cloud within the solid. Application of an electric field (as a potential difference), causes the electrons to flow through the metal round the circuit and back *via* a second electrode into metal. Overall electrical neutrality within the metal is maintained, although the electrons are said to be delocalized.

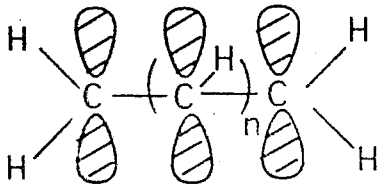
Organic molecules in the solid state are usually electrically neutral with all electrons held strongly in covalent bonds. Since these electrons are not free to move, organic compounds tend to be good electrical insulators. However, solid organic molecules, especially polymers, can house a wide range of desirable mechanical properties, most noticeably flexibility and malleability under mild heating and, perhaps more important, they are cheaper and easier to produce than metals. Hence, if an organic conductor could be produced, it could have great advantages over expensive and more difficult to process metals. Additionally, the density of organic materials tend to be lower that of most metals. Consequently, where weight is an important factor, organic materials, having comparable electrical properties with metals will have a distinct advantage.

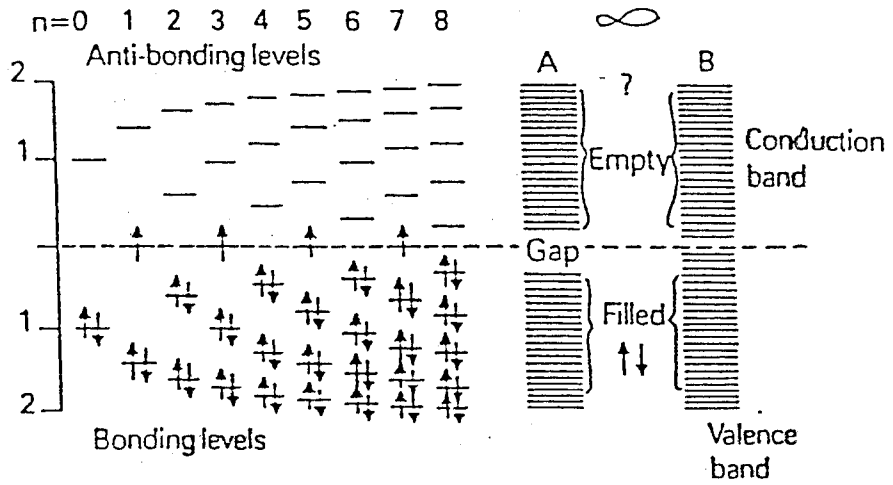
The basic concepts of band theory[1] provide the key to understanding why certain organic molecules might behave like metals. The conduction properties

depend on the electronic structure of the energy levels. In general, organic conductors differ from inorganic materials in one important way; electronic transport in the organic materials is usually anisotropic, i.e. it is associated with a preferred direction by several orders of magnitude. Many organic metals are therefore termed one dimensional metals.

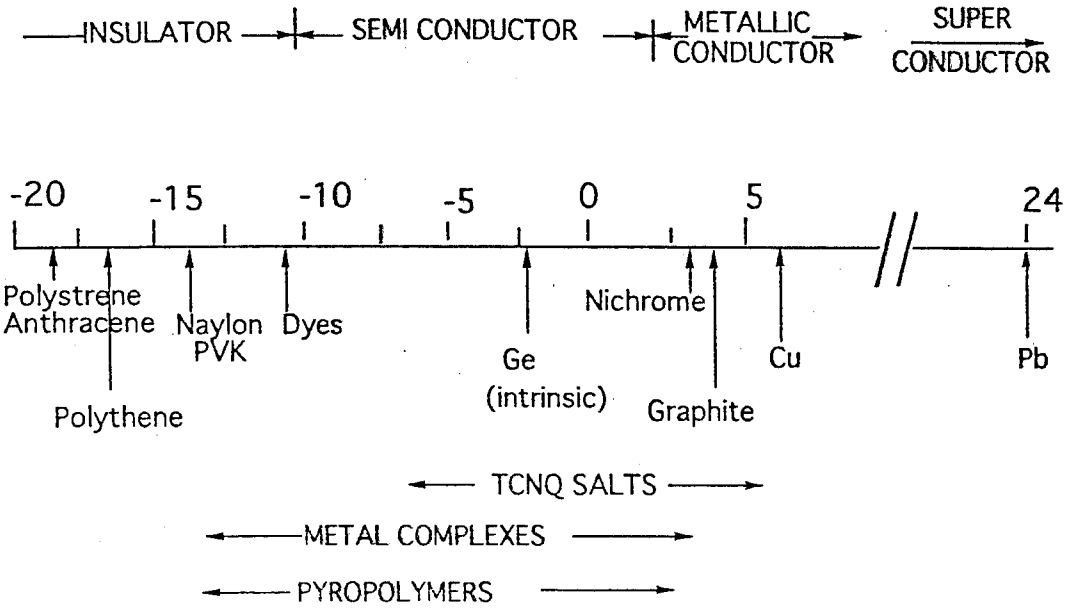
When a large number of atoms or molecules are brought together to form a polymeric chain or a crystalline solid, an energy band will form if there is a sufficient interaction of the constituent atomic or molecular orbitals. Bands may merge together to form a super molecular orbital. However, the interaction of energy bands is not enough in itself to produce metallic properties in the materials. The occupancy of the energy bands is critically important. The highest occupied band, known as the *valence band*, and the lowest unoccupied band, known as the *conduction band*, are separated by an energy gap known as the band gap.[2,3] Using a general polymer with a π-delocalized backbone as a model, we see how sets of π-orbitals interact in a polyene system changes with increased conjugation. The following diagram (Scheme 1.1) shows the effect on the π-orbital energies with an increase in the number of CH units in the polymer.

The conductivities for various organic and inorganic materials at room temperature are given in Scheme 1.2. When the energy gap between the valence band and the conduction band is large, the material is an insulator. As this gap is decreased, thermal excitation of electrons from the valence band into the conduction band is possible and the material becomes a semiconductor. When the gap between the bands becomes vanishingly small, the material behaves as a metal. Metallic behaviour is associated with partly filled bands in which it is possible for a large number of electrons to move easily into infinitesimally



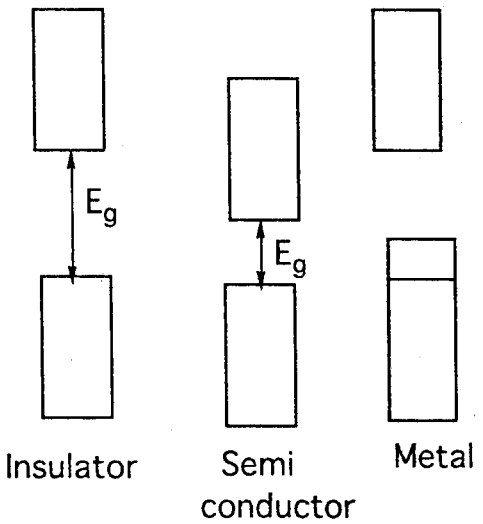


Scheme 1.1



Scheme 1.2 Conductivities of metals and non-metals. The scale gives the log of the conductivity ($ohm^{-1}\ cm^{-1}$)

higher energy states within the band (Scheme 1.3). The shaded areas represent electronic states occupied by electrons (Eg is the energy gap between occupied and empty states). Metals have partly filled bands. Typically, when Eg is over 4 eV the material is an insulator and below 2 eV it is a semiconductor.



Scheme 1.3

According to the band theory, electrons can not move while in a filled band, since movement would result in transition to a filled orbital of similar energy. Entry to an already filled orbital is, of course, forbidden. For this reason, movement of the electrons and therefore conduction needs an electron to enter an empty orbital, the only empty orbitals are the anti bonding orbitals where an electron could move unhindered through the solid, hence, the term *conduction band* for the antibonding orbitals. However, the electron must cross the band gap, which has been shown to exist both theoretically and by experiment and is known to be of the order of a few eV in width in many of the recently synthesised potentially conductive organic polymers. The thermal energy[3] is available to each electron is given by the relationship :

$$E_{thermal} = KT$$

where K is Boltzman's constant, T is the absolute temperature. This energy is about 0.025 eV at room temperature, and therefore most pure polymers have a very poor conductivity at room temperature. The conductivity of the polymer can be improved greatly, however by reducing or oxidising the π-system,[4] either by adding electrons into the conducting band or by their removal from the valence band to leave partially empty orbitals.

Many of the conducting polymers, so far synthesised, have poor physical and mechanical properties.[1] Such properties make organic polymers unattractive as alternatives to metallic electrical conductor. Thus, for example, polyacetylene tends to be an intractable non-malleable substance being both insoluble in most solvents and infusible. The mechanical properties can also be improved by copolymerisation with an insulating polymer of better mechanical properties, e.g. with polystrene or PVC.[5]

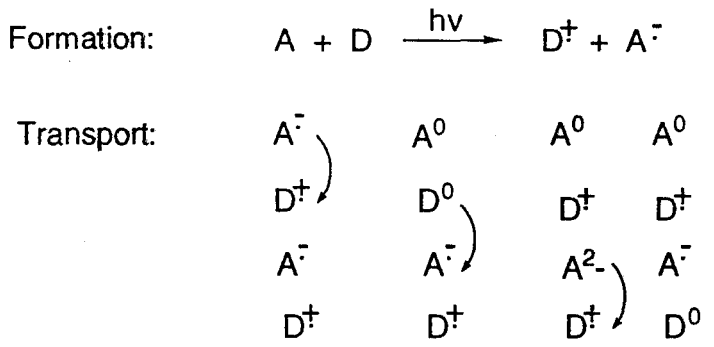
Organic materials can be divided into three classes: Charge transfer complexes and ion radical salts, organometallic species, and conjugated polymers.

1.2 Conducting Materials

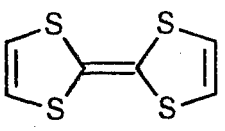
1.2.1 Charge-transfer Complexes

Charge-transfer complexes and ion radical salts are typically crystalline solids comprising a two component system formed by the interaction of electron donor and electron acceptor molecules which have neutral ground states. Radical ion salts are formed from component molecules with ionic ground

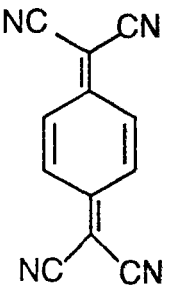
states. The formation of the two-component system is accompanied by partial production of radical ions. Conductivity by these systems is highly anisotropic and occurs by one-electron disproportionation of these radical ions. Schematically, this may be represented as follows:



A 1:1 complex of the donor tetrathiafulvalene (TTF) and the acceptor 7,7,8,8-tetracyano-p-quinodimethane (TCNQ) has a high conductivity of 500 ohm^{-1} cm^{-1} at room temperature,[6] and the conductivity is increased to 10^4 ohm^{-1} cm^{-1} on cooling.



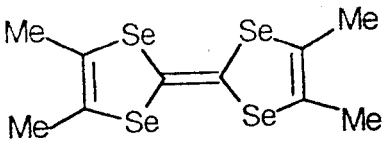
TTF



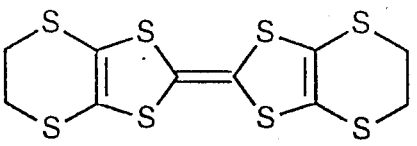
TCNQ

Superconductivity has been observed with many tetramethyltetra-selena-fulvalene (TMTSF) salts, such as $(TMTSF)_2^+PF_6^-$, $(TMTSF)_2^+ClO_4^-$ at 1.5 K under 1 200 Atm pressure.[7] Sulphur-based superconductivity was first reported in 1983 for the bis(ethylenedithiolo)tetrathiafulvalene (BEDT-TTF) salt $(BEDT\text{-}TTF)_2^+ReO_4^-$ at 1.5 K under 7 000 Atm pressure.[8] Currently, the highest

temperature for the onset of superconductivity in an organic material[9] is 10.4 K observed in the copper thiocyanata salt $(BEDT\text{-}TTF)_2\text{-}Cu(SCN)_2$.



TMTSF



BEDT-TTF

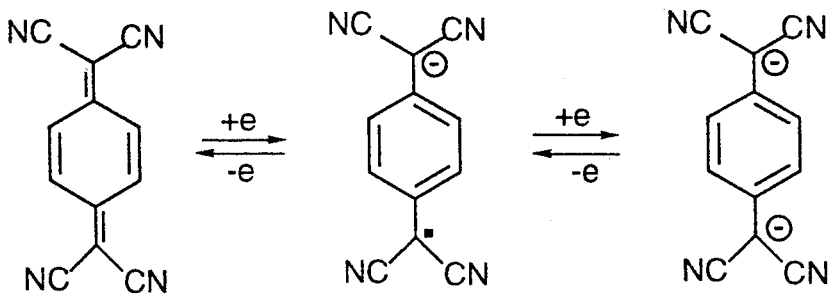
Generally, these charge-transfer complexes are brittle materials. However, they are of value where mechanical properties are not important, as in the case of the poly-(2-vinylpyridine)-iodine complex which is used as cathode in the miniature-Li-I_2 primary cell. The conductivity of the complex is constant at 10^{-3} ohm^{-1} cm^{-1} as the iodine concentration falls from 90 to 75 % on discharging the cell. This solid state cell with the LiI electrolyte formed *in situ* has a very high energy density (120 W h kg^{-1}), compared with the best lead acid battery (30 W h kg^{-1}), and a service life of ten years. It illustrates the use of one commercially valuable conducting polymer.[4]

1.2.2 Radical Ions

Conducting systems of this type are composed of regular stacks of molecules of two types, one of which is a radical ion with suitable counter ion and the other being a *radical acceptor*. The mechanism for electron transfer in such systems can be summarised as follows:

$$A^{\cdot -} + B \longrightarrow A + B^{\cdot -}$$

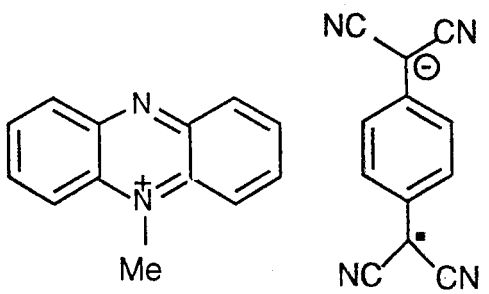
The classical radical ion conductors[10] are based on 1,4-tetracyanoquinodimethane (TCNQ), which forms the redox system shown in Scheme 1.4. Complex salts generally have a higher conductivity than simple salts, but



TCNQ

Scheme 1.4

simple salts can also have high conductivity, if they are associated with a polarizable cation, as with the N-methylphenazinium tetracyanoquinodimethanide system (NMP-TCNQ). The TCNQ species form a homogenous



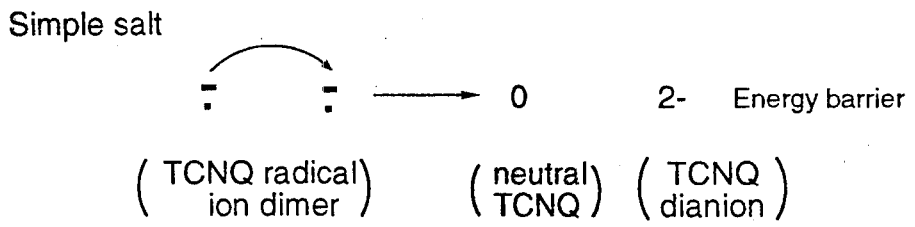
NMP-TCNQ

stack and, in NMP-TCNQ, they are all equally spaced at 0.324 nm, so that the unpaired electrons can delocalize into a conduction band to give metallic conductivity. When the methyl groups of an NMP are replaced by ethyl groups, the conductivity decreases by a factor of 10^{11} (see Table 1.1).[4]

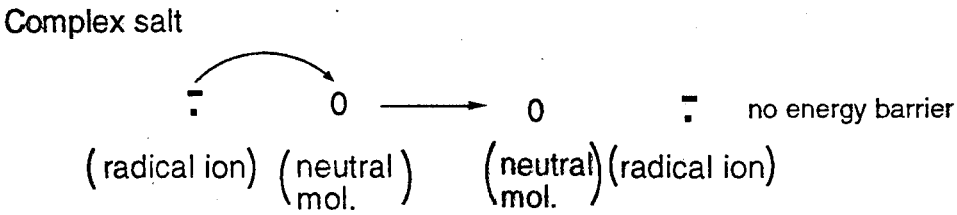
Compound	σ ohm^{-1} cm^{-1}
N-methylphenazinium^{+} TCNQ^{-}	1.4×10^{2}
N-ethylphenazinium^{+} TCNQ^{-}	1×10^{9}
N-methylphenazinium+ $(TCNQ^{-})_2$	7.1×10^{4}

Table 1.1 Conductivities of N-alkylphenazinium tetracyano-quino dimethanide complexes

Schematically, conduction occurs by the following mechanism.



For electrons to move along the stack in the simple salts, coulomb forces have to be overcome in forming the dianion of TCNQ, and so conduction is poor in the simple salts. However, if neutral TCNQ is added forming the complex salt, it is not necessary to form a dianion as electron transfer can take place onto a neutral TCNQ molecule. Conduction then occurs schematically as follows:

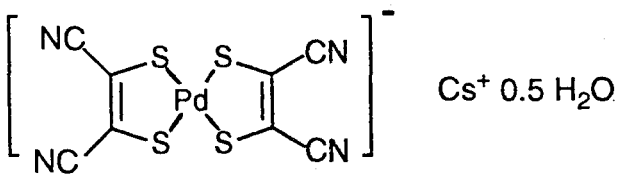


Hence, there is no coulombic energy barrier to overcome for conduction to occur in complex salts, and they therefore tend to have higher conductivities than

simple salts. Sometimes this fails because electron transport from the radical-anion to neutral TCNQ is hindered by the electrostatic attraction of the counter-cation ions. However, this can be avoided by using lower concentrations of neutral TCNQ.

1.2.3 Organometallic Species

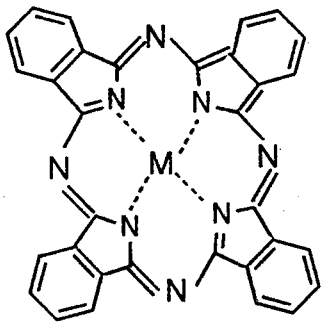
The introduction of metal atoms into a polymer can increase the conductivity. This usually arises from improved intermolecular orbital overlap due to the more diffuse metal d-orbitals and extension of the intramolecular conduction path by conjugation of the d-orbitals with the π-electron system of the polymer so that the electron path passes through the metal atoms. Metal-dithiolene complexes are an important family of organo metallic conductors. For example, complex (1) has a conductivity of 5 ohm^{-1} cm^{-1} at room temperature and is also semiconducting at lower temperatures typical of many organic conductors.[11]



(1)

Metallomacromolecules, e.g. phthalocyanines (2), have been widely studied. They can be co-crystallised with electron acceptors to yield mixed valence, low dimensional conductors.[12] Molecular iodine is a good oxidant because of the stability of polyiodide chains, which are readily accommodated in ion channels within the crystal lattice. For example, nickel phthalocyanine

iodide Ni(Pc)I, (2), is metallic with a conductivity maximum of 5 000 ohm^{-1} cm^{-1} at 25 K. The free phthalocyanine base H_2(Pc)I (3) has a high room temperature conductivity value of 700 ohm^{-1} cm^{-1} indicating that a chelated metal atom is not required for conductivity.



(2) M = Ni

(3) M = 2H

1.2.4 Conjugated Polymers

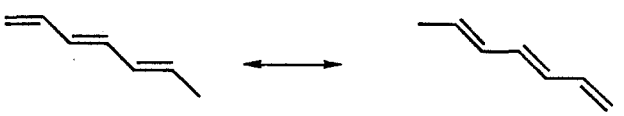
No polymers based on carbon atom backbones are intrinsically conducting; in the virgin state they are generally insulators. However, in a polyene chain $-(CH)_n-$, π-electron delocalization tends to make all the C-C bonds of equal length. As n is increased, the activation energy for carrier formation decreases and conductivity should increase. A value of n typical of a polymer is *ca.* 1000. *Cis*-polyacetylene, which can be prepared at low temperatures, i.e. at room temperature or above, isomerises to the thermodynamically more stable *trans* form. In the pure state, the value of the conductivity[13] of the *trans* isomer is 10^{-7} - 10^{-9} ohm^{-1} cm^{-1}. Which, on adding an oxidising agent or a reducing agent the conductivity increases to *ca.* 1 000 ohm^{-1} cm^{-1}. The conductivity of polymethinimine[14] $-(CH=N)_n-$ is close to the polyacetylene, 1.3 10^{-11} ohm^{-1} cm^{-1}. There are three reasons for the poor

conductivity in polyenes: (i) the large intermolecular barrier; (ii) the bonds are not all equal in length; (iii) rotation of the chain interrupts conjugation particularly where coplanarity of substituents is prevented by steric interaction, as in polyphenylacetylene.

Addition of oxidising agents (e.g. halogens) result in p-type doping, and reducing agents (e.g. an alkali metals) in n-type doping, in which electrons are respectively removed from the filled valence band or added to the vacant conduction band.

The soliton theory is currently the best explanation to account for conductivity in π-conjugated polyene systems and is supported both by theoretical calculations and by experimental results. It has been shown that conduction in polyacetylene is due, not to electronic band conduction but to *soliton* conduction.

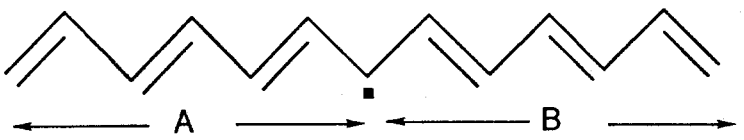
A *soliton* is usually described in polyacetylene as a conformational excited state which interacts with an excited π-electron state. These solitons only arise in *trans* polyacetylene due to the symmetry of the system[15] in which there are two degenerate structures of lowest energy (Scheme 1.5), which are related by interchange of double and single bonds.



Scheme 1.5

Scheme 1.6 shows the soliton defect in a *trans*-polyacetylene chain separating the degenerate phases A and B. However, because of the Peierls instability, a ground state with alternating single and double bonds is favoured over a fully delocalized ground state with a resultant opening of the

semiconductor energy gap. In contrast, solitons, move along the chain under the influence of an electric field. Doped polyacetylene has a very high conductivity



Scheme 1.6

and Schimmel *et al.*[15] have prepared stretch-oriented films, which have the highest room temperature conductivity of any organic material with a conductivity of 80 000 ohm^{-1} cm^{-1} in the aligned direction of the film. For p-doped polyacetylene, the positive soliton which is essentially a delocalized carbocation, increases the conductivity by several orders of magnitude.[16] Highly doped *trans*-polyacetylene has a conductivity 10^{17} times greater than that of the *cis*-isomer.

It is generally accepted that the increase in conductivity originates from a chemical reaction between the polymer and the dopant. All reactions causing a marked increase in conductivity can be classified as redox reactions, and are characterised by charge transfer from the dopant to the polymer. An ionic state of the polymer, delocalized along the backbone is formed, along with a counterion which is derived from the dopant, as shown in the reaction of polyacetylene with silver perchlorate.[17]

$$(CH{=}CH)_n + AgClO_4 \longrightarrow [(CH{=}CH)_n^+ ClO_4^-] + Ag$$

Some typical values for conductivity of doped polyacetylene are given in Table 1.2.

Dopant	Dopant Fraction	σ (ohm^{-1} cm^{-1})
I_2	0.25	360
Br_2	0.10	0.5
AsF_5	0.28	560
SodiumNaphthalite	0.28	80
$(n\text{-}C_4H_9)_4N^+ClO_4^-$*	0.06	970
$AgClO_4$	0.036	3.0

*electrolyte in electrochemical oxidation

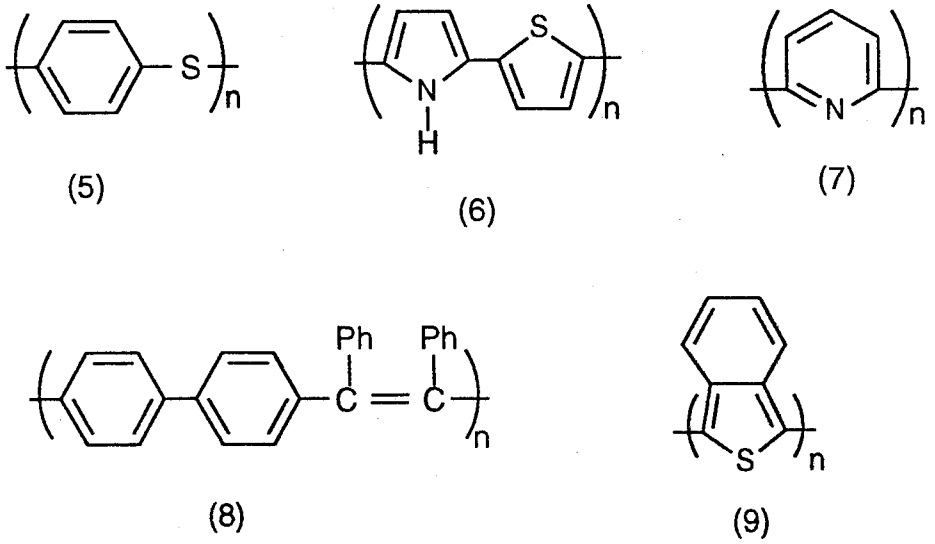
Table 1.2 Conductivities of Doped Polyacetylene

Polyacetylene is an inconvenient material for fabrication; it is insoluble, it can not be melt processed below degradation temperatures and it is oxidised on contact with air. Moreover, the polymer is all too frequently in an impure form being contaminated with residues from the polymerisation catalyst. However, this problem can be overcome by use of soluble precursor polymers which yield *trans*-polyacetylene in high purity.[1] Also, as the mechanical properties of pure polyacetylene are poor, it is frequently copolymerised with other isomers, e.g. 1-propyne and 1-hexyne.[18] However, although the copolymer with 1-hexyne is more malleable and can be readily doped, it is also oxidised easily. There is obviously, therefore, a need to design other semi-conducting organic polymers.

1.2.5 Other Polymers

Numerous other conjugated polymers have been found to be electrically conducting. Typical examples are poly-*p*-phenylene[19-26] (1), polyaniline[27] (2),

polypyrrole[28-39] (3), polythiophene[40-48] (4), poly-*p*-phenylene sulphide[49-50] (5), poly(thienylpyrrole)[51] (6), and polypyridine[52-55] (7), polymer (8)[56], and polyisothianaphthalene[1,4] (9). The search for improved mechanical properties without sacrificing high conductivity has directed studies towards the polyheterocyclic systems, particularly systems (3) and (4). The polymerisation is usually carried out electrochemically and produces the polymer in a doped



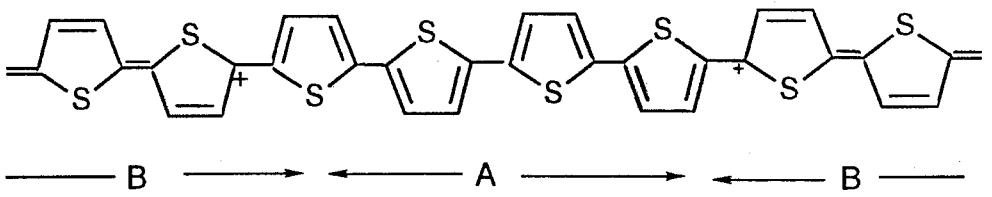
(5) (6) (7)

(8) (9)

Scheme 1.7

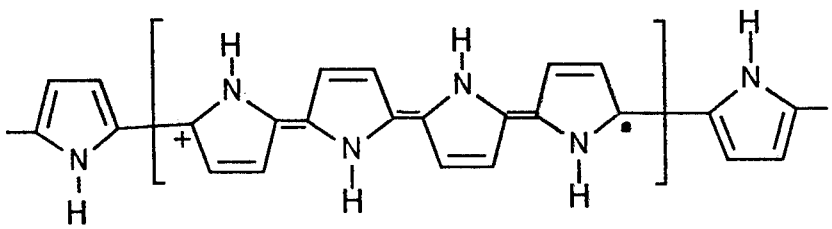
state. Such polymer films are typically very dark in colour and with care, they are characterised as free standings films. Soliton defects in these cyclic systems are not stable, however, as bond alternation is not degenerate. For example, the thiophene units are aromatic in phase A and hence lower in energy than the non-aromatic (quinonoid) units in phase B (Scheme 1.8). Consequently, the semiconductor gap for these types of systems the semiconductor gap is increased relative to that of polyacetylene (3.5 eV for poly-*p*-phenylene, 3.0 eV for polypyrrole, 2.2 eV for polythiophene and 1.5 eV for polyacetylene). For the polymers 1-4, with non-degenerate ground states, the charge carriers produced

by doping are frequently called *polarons* and *bipolarons*. A *polaron* is an isolated charge carrier, whereas a bipolaron is a pair of like charges, with the bipolaron often being favoured energetically over isolated polaron states.



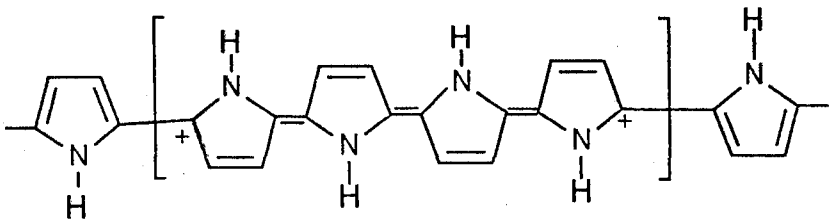
Scheme 1.8

Radicals, radical ions and di-ions are analogous to solitons, polarons, and bipolarons, respectively. In classical terms, the polaron may be depicted as a delocalised radical cation with an associated structural distortion within the polymer chain.[57] One polymer known to be highly conductive in such a states is polypyrrole (Scheme 1.9).



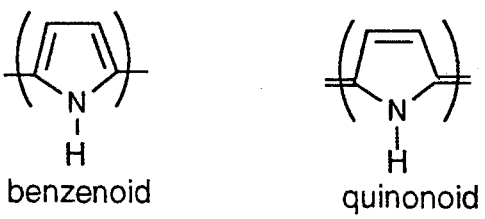
Scheme 1.9

Bipolarons[58] having a double charge arise from substantial doping of the polymers (usually oxidatively) and, in such a case, the classical view is that of a delocalised dication somewhat similar in the structure shown Scheme 1.10. Any charge delocalisation in the polaron is driven partly by the repulsion of like charges, i.e. by electrostatic forces. However, as charge separation causes an



Scheme 1.10

intermediate region of quinonoid character, rather than the normally preferred aromatic structure (Scheme 1.11), the two charges are bound to each other and not individually free.



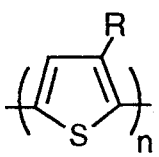
Scheme 1.11

The difference between quinonoid and aromatics rings in total energy terms favours the aromatic form by *ca.* 0.4 eV.[59] However, the quinonoid form has a lower ionisation potential and greater electron affinity. This partly explains the ease of formation of bipolarons and the slightly greater than usual stability of the quinonoid region of the bipolarons. As with solitons and polarons, the bipolarons are best described as a distortion of the chain that increases to a maximum at the bipolaron centre and decays to zero outside the bipolaron zone. The bipolaron width has been estimated by various workers to be about four or five rings.

As indicated earlier, polymers with smaller band gaps are expected to be intrinsically better conductors. Wudl and co-workers[60] have prepared polyisothianaphthalene (9) in which the benzene ring in structure (9) stabilises

the quinonoid contribution to the ground state and so the band gap is lowered to *ca.* 1.0 eV, i.e. half that of polythiophene (4). Polyisothianaphalene also exhibits remarkable properties upon doping, for example, although the films are not highly conducting (σ = 50 ohm^{-1} cm^{-1}), they are transparent to visible light.[60] In no other material are these two properties encountered together.

An important recent development of conducting polymers is the production of polymer films that can be dissolved and then recast into films, which retain conductivity. Solubility in organic solvents has been achieved by attaching flexible, long chain substituents onto, for example, the thiophene ring. Thus, it has been shown that poly(3-alkyl)thiophenes (1) are soluble and have very high conductivities (σ = 1000 ohm^{-1} cm^{-1}).[48,61] The first water soluble derivatives (2) in which the thiophene ring is substituted with a polar alkane sulphonate group have recently been prepared by Patil and co-workers.[62]



(1) R = $(CH_2)_nCH_3$, n = 5-19

(2) R = $(CH_2)_nSO_3H$, n = 2,4

Scheme 1.12

1.3 Applications of Organic Conductors

The replacement of inorganic semiconductors and metals used in the electronic industry by organic materials is frequently referred to as molecular electronics. The main advantages of the organics are their extremely small size, structural diversity, ease of fabrication and potential low cost.

As indicated earlier, a major problem with charge-transfer complexes is the extreme frailty of the crystals of these materials, but powdered samples of semi-conducting TCNQ salts have had limited success in optical recording devices. The recent advent of highly conducting Langmuir Blodgett films of charge transfer complexes offers new possibilities in device technology, e.g. in pyroelectric sensors, where the availability of Langmuir Blodgett film electrodes would be a major step forward.[10]

The recent developments in the processibility of conducting polymers has increased their prospective uses. The most important application of conducting polymers is to be found in batteries where the feasibility of lightweight, rechargeable batteries based on polyacetylene electrodes has been clearly demonstrated.[63] Polymeric organic electrodes should have longer life times than metal electrodes because, for the polymers, the ions involved in delivery and storage of charge are an integral part of the electrodes themselves. This feature reduces the mechanical wear associated with dissolution and redeposition of electrode material in traditional batteries. A rechargeable battery with one polyaniline electrode and one lithium electrode is now commercially available in Japan and is reported to have increased output and shelf life over its nonpolymeric competitors.[63]

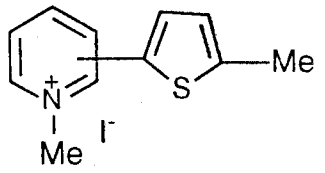
The optical properties of polymers, as well as their electrical properties, are attractive to industry. Research in many laboratories concerns the use of polythiophene and polyaniline electrochromic displays,[64] which exhibit marked colour changes that are reversibly induced in the polymer by applying an electric potential. For example, thin films of polythiophene are red in the doped state and deep blue in the undoped state and they may provide viable alternatives to liquid crystal displays. These optical properties may also be used in fibre optic technology, i.e. in optical computers. Non-linear optical properties

are exhibited by many polymeric and crystalline organic conductors.[65] These properties result from the interactions of electromagnetic fields within the delocalised π-electron systems. Many industrial uses are anticipated, e.g. optical communication, laser scanning and data transmission in the new generation of computers.[66]

More speculative applications of conducting polymers include such diverse areas as solar cells and drug delivery systems for human body. Although conducting polymers can absorb sunlight, conversion efficiencies fall far below those required for effective solar cells. Their potential in drug delivery relies on the redox properties of a polymer implanted in the body. If a drug molecule could function as a dopant ion, the drug would be released on dedoping the polymer by application of a small electric potential. Other possible applications include conductive paints, toners for reprographics and printing, agents for electrostatic dissipation, and as components for aircraft where the combination of light weight, mechanical strength and moderately high conductivity is required.[6]

1.4 Objectives of This Project

The principle objective of this project is the synthesis of alternating π-excessive and π-deficient heterocyclic systems which are expected to be electrically conductive without oxidative or reductive doping. Previous work from this research group has prepared pyridylpyrroles and oligimeric and polymeric alternating pyrrole:pyridine systems.[67] This work is now extended to the synthesis of analogous thiophene:pyridine and furan:pyridine systems 1-8. The preparation of the simple the two-ring systems is described in Chapter 2, the three-ring systems in Chapter 3, and the polymeric compounds in Chapter 4.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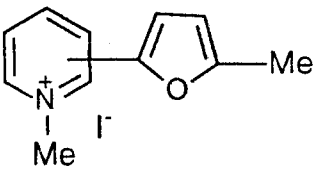
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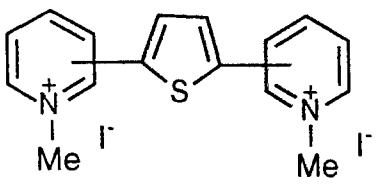
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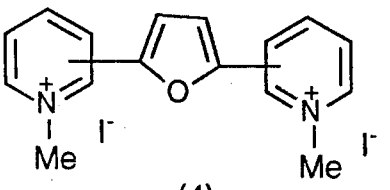
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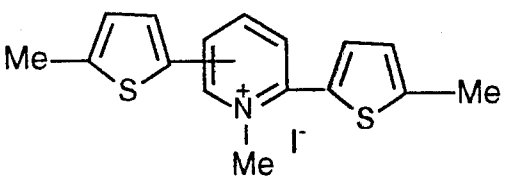
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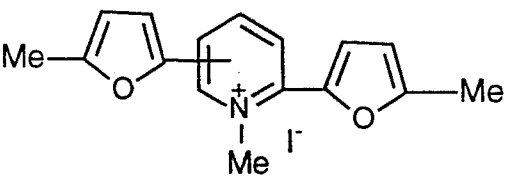
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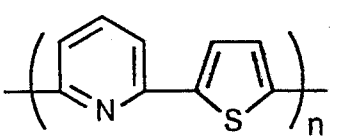
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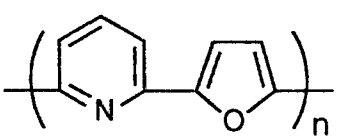
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(8)

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CHAPTER 2

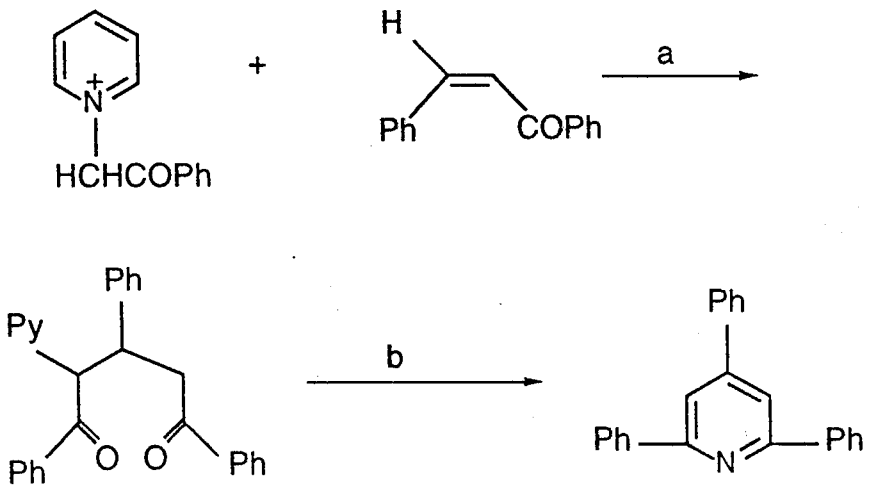
TWO RING SYSTEMS

2.1 General Synthesis of Pyridines

There are many ways of achieving the synthesis of a pyridine ring, but a large number of the methods can be divided into general classes. In one procedure, the pyridine ring is obtained from the other heterocyclic systems and, in the second method, the pyridine ring is obtained from acyclic precursors.

1,5-Dicarbonyl compounds react with ammonia to give unstable 1,4-dihydropyridines which are easily dehydrogenated to pyridines. The method, known as the Krohnke synthesis, involves the conjugate addition of a pyridinium ylide to an α,β-unsaturated carbonyl compound leading to the construction of the 1,5-diketone, which can be converted into the pyridine by reaction with ammonium acetate with elimination of two molecules of water and a molecule of pyridine (Scheme 2.1).[1]

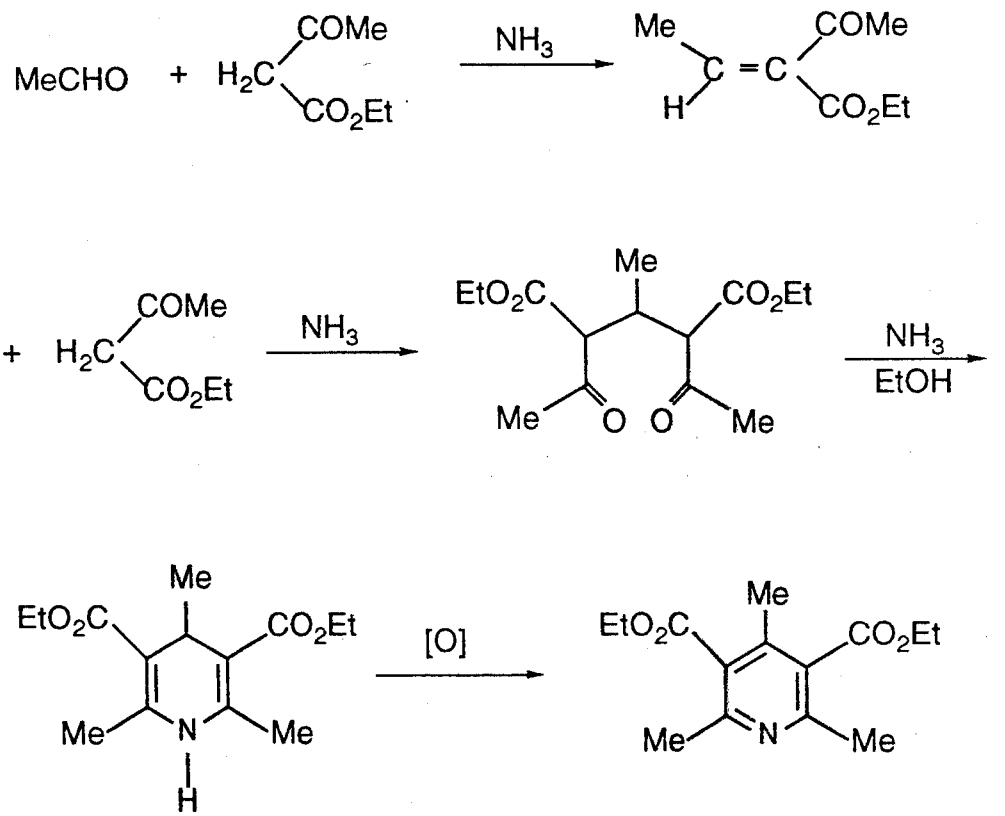
The Hantzsch synthesis of pyridine[2] is the most important and widely used method, in which a β-keto ester, or β-diketone is condensed with an aldehyde in the presence of ammonia. The reaction can be represented as



(a) NaOH (72 %); (b) NH_4OAc (88 %)

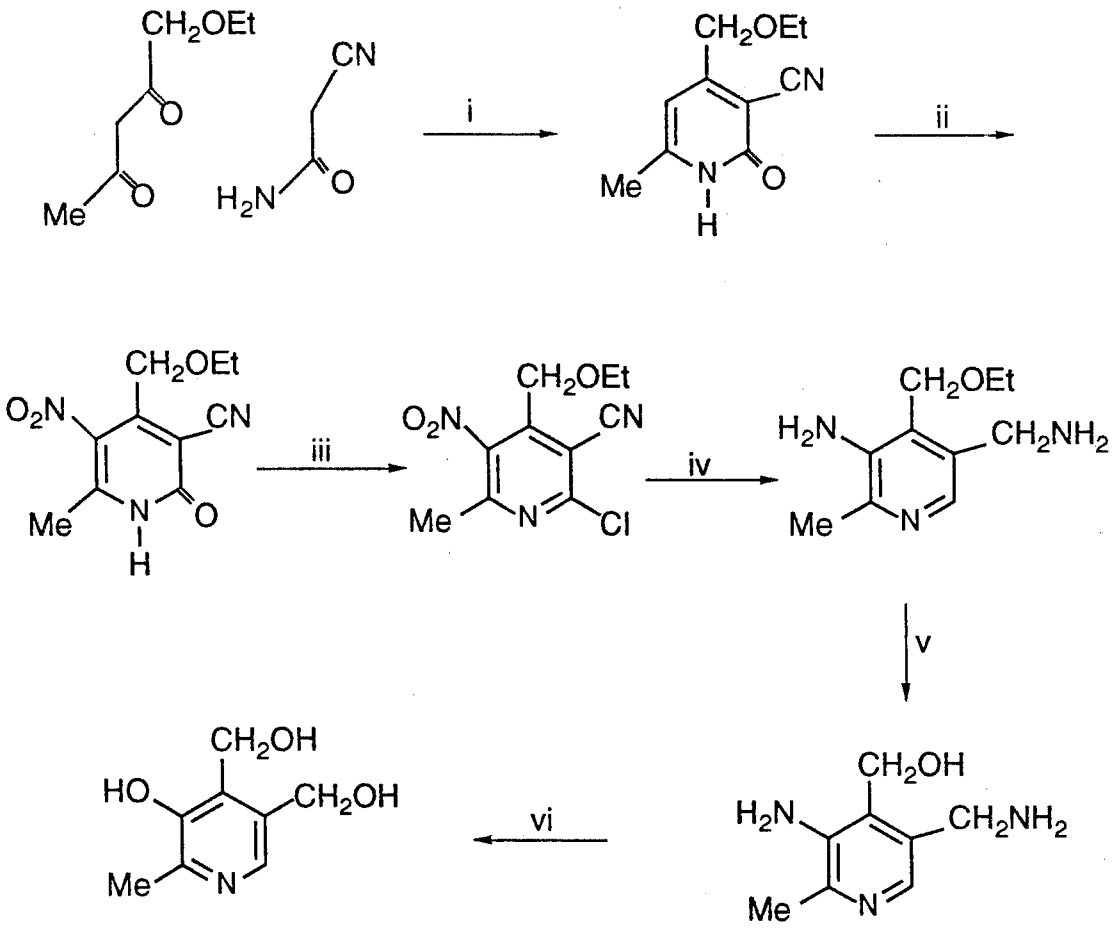
Scheme 2.1

involving the construction of a saturated 1,5-dicarbonyl compound by aldol and conjugate Michael-type addition reactions. Reaction with ammonia leads to ring closure with the formation of a 1,4-dihydropyridine, which is readily oxidised to the aromatic ring system with nitric acid or chromic acid. An example, in which acetaldeyde, ethyl acetoacetate and ammonia are reacted at room temperature, is given in Scheme 2.2.



Scheme 2.2

One of the more important examples for the preparation of pyridines is the Guareschi synthesis, which is especially important for the commercial vitamin B_6 synthesis (1). This approach involves the reaction of cyanoacetamide with a β-dicarbonyl compound under mildly basic conditions to give the pyridines, as shown Scheme 2.3.



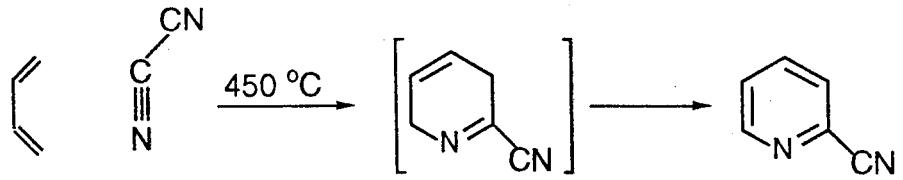
(1) pyridoxine

(i) EtOH, 60 °C, piperidine (65 %); (ii) Ac_2O/HNO_3, 0 °C (75 %); (iii) PCl_5, $POCl_3$, 150 °C (40 %); (iv) H_2-Pd, NaOAc, 3 atm., (54 %); (v) con. HCl, 180 °C (76 %); (vi) $NaNO_2$, 3 N HCl, 90 °C (45 %).

Scheme 2.3

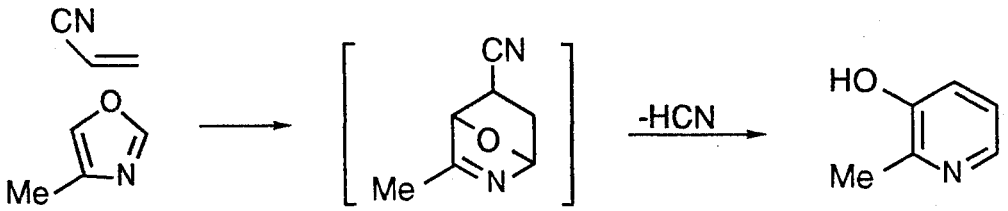
The pyridine ring can also be constructed by [4+2] cycloaddition reaction and this route is particularly useful for the production of partially reduced pyridines. An interesting synthesis of pyridines has been described, which involves the Diels-Alder addition of nitriles to dienes in the gas phase at moderately high temperatures.[3-5] As shown in Scheme 2.4, the reaction of

butadiene and cyanogen at 450 °C provides the dihydro product, which then loses hydrogen at the high temperature used, to yield the pyridine.



Scheme 2.4

An important synthesis involves the cycloaddition of an oxazole, as the diene component, to a dienophile to give an intermediate that can be aromatized either by loss of water, or if the dienophile is maleonitrile or acrylonitrile, by loss of hydrogen cyanide.[6] This reaction has been employed to synthesise vitamin B_6 and analogues.[7,8]

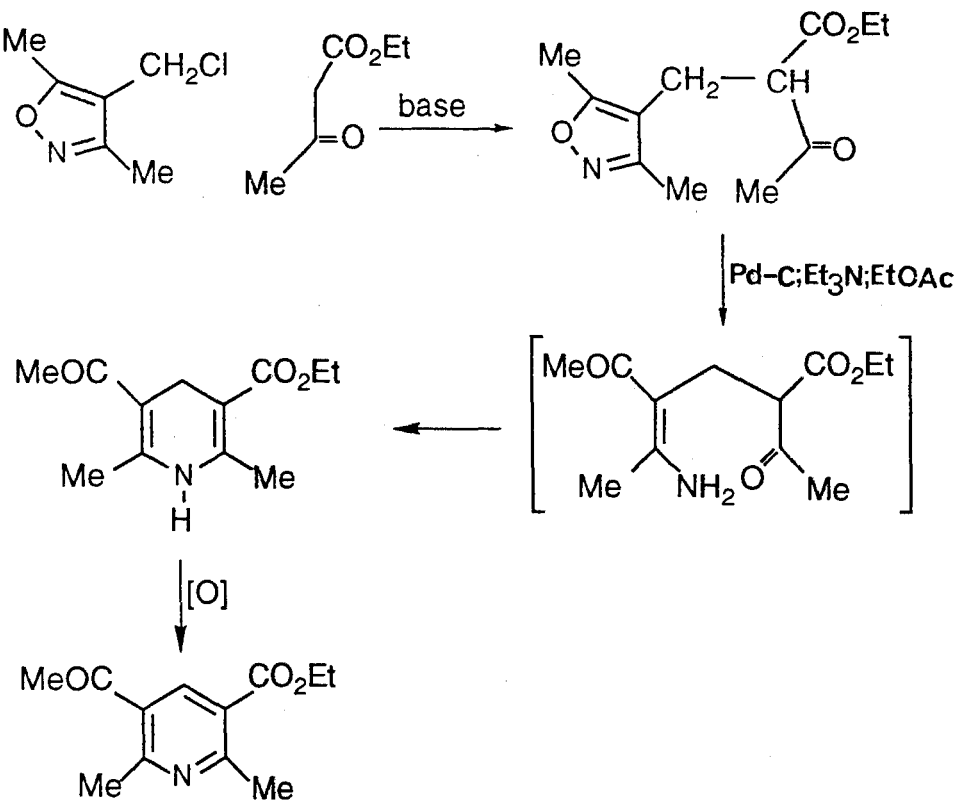


(a) aq. AcOH, 95 °C, 1 d.

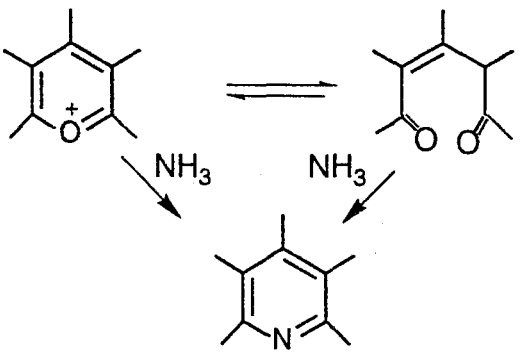
Scheme 2.5

An example of an alternative procedure,[9] which starts from isoxazoles under basic conditions to yield dihydropyridines, is shown in Scheme 2.6.

Pyridines can be obtained from pyrylium salts and ammonia, but the usefulness of this type of synthesis depends on the availability of the starting materials (Scheme 2.7).[10]



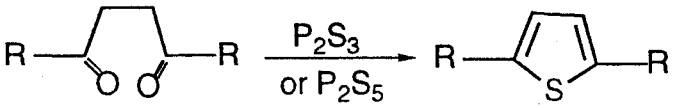
Scheme 2.6



Scheme 2.7

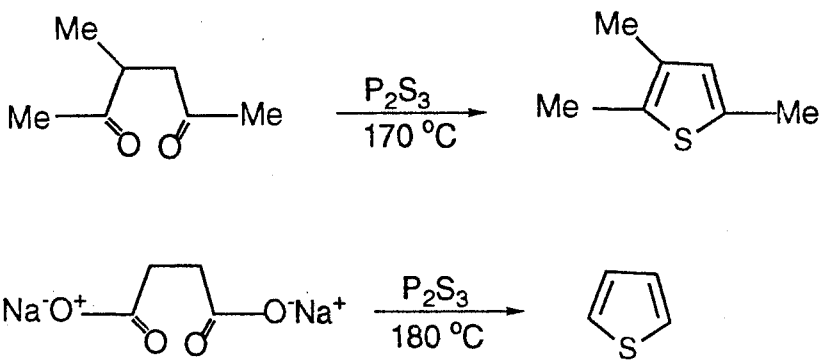
2.2 General Synthesis of Thiophenes

One general synthesis involves the introduction of sulphur into a precursor containing the complete carbon skeleton, as shown Scheme 2.8. The



Scheme 2.8

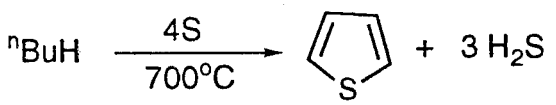
important Paal synthesis utilises the reaction of 1,4-dicarbonyl compounds with phosphorus trisulphide or phosphorus pentasulphide.[11] The dicarbonyl component need not only be 1,4-diketones, 1,4-dialdehydes or δ-keto acids, but can also be compounds such as succinic acids, esters and levulinic acid. The general procedure requires gentle heating of the mixed starting materials. Although the detailed mechanism of the reaction is not known,[12-14] it can be assumed to similar to that for the Paal synthesis of pyrroles.



Scheme 2.9

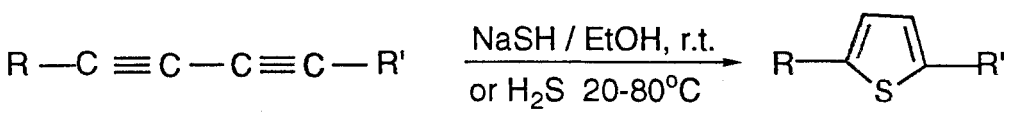
A general and important industrial synthesis of thiophenes involves heating a hydrocarbon such as acetylene, butane, isoprene, or hexane with either sulphur, hydrogen sulphide, or a metal sulphide at high temperatures. This type of reaction takes place *via* prior dehydrogenation of, for example, butane, followed by addition of sulphur to the unsaturated intermediates in the vapour phase (Scheme 2.10). Some cracking and polymerisation also occurs at the high

temperature. The synthesis works well with low molecular weight hydrocarbons.[15]



Scheme 2.10

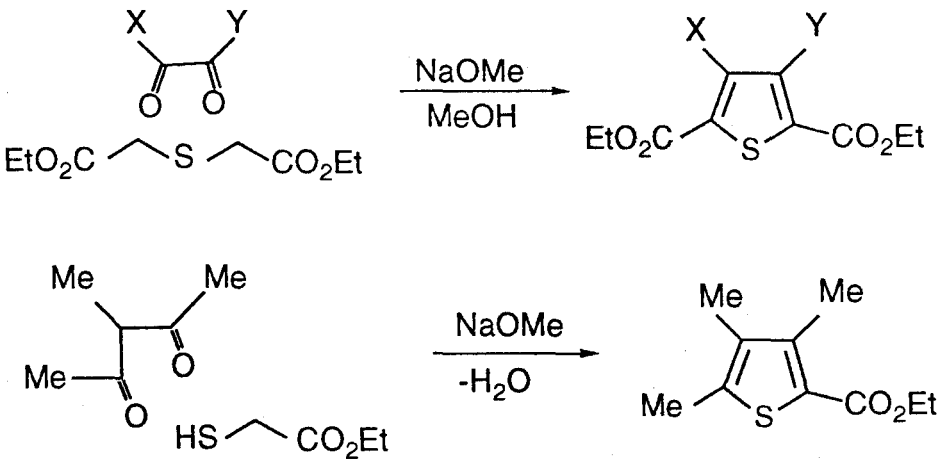
One modification of the Paal approach makes use of the acetylenes, which effectively have the same oxidation level as 1,4-diketones, with hydrosulphide ions or hydrogen sulphide under mild conditions. In Scheme 2.11, R and R' can be hydrogen, alkyl, aryl, or carboxyl.[16]



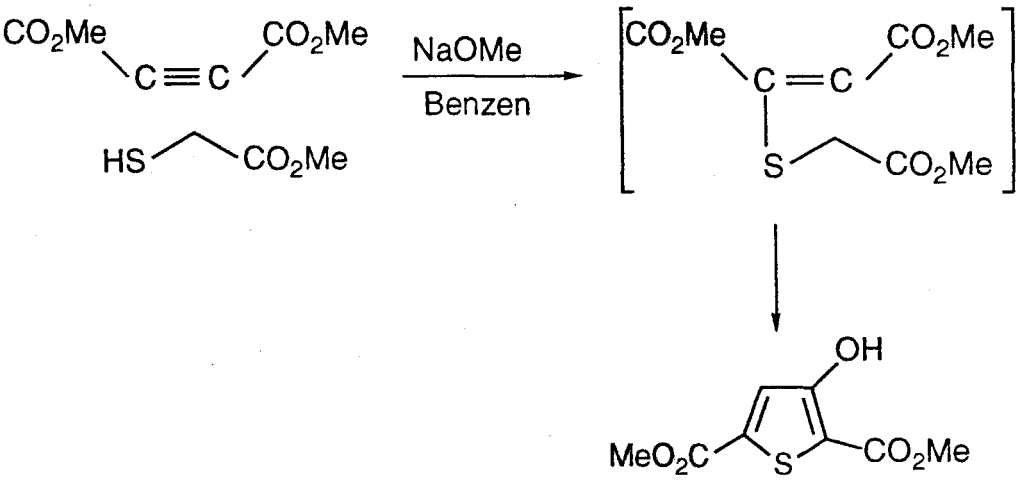
Scheme 2.11

The Hinsberg synthesis of thiophenes comprises two consecutive aldol condensations between either a 1,3-dicarbonyl compound with dimethyl mercaptodiacetate, or a 1,2-dicarbonyl compound with ethyl mercaptoacetate, as shown Scheme 2.12.[17] X and Y can be hydrogen, alkyl, aryl, hydroxyl, methoxyl, or carbonyl.

As shown in Scheme 2.13, mercaptoacetic esters also react with bifunctional compounds, such as conjugated acetylenic esters, ketones or vinyl ketones, or the related β-dialkylamino ketones. The reaction proceeds by nucleophilic addition of the thiolate anion, followed by a Claisen condensation.[18]

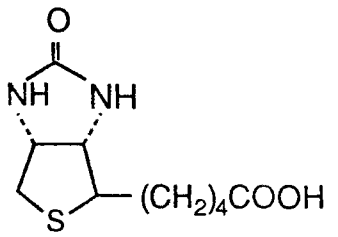


Scheme 2.12

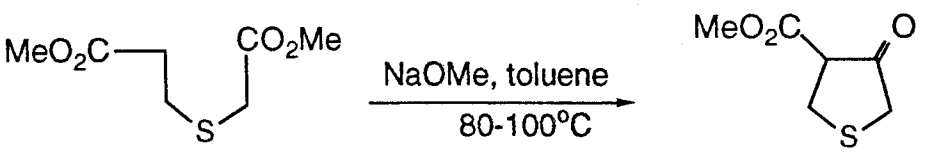


Scheme 2.13

A Dieckmann cyclisation reaction has often been used to obtain oxotetrahydrothiophenes, and is important in one synthesis of vitamin H (biotin).[19]



biotin



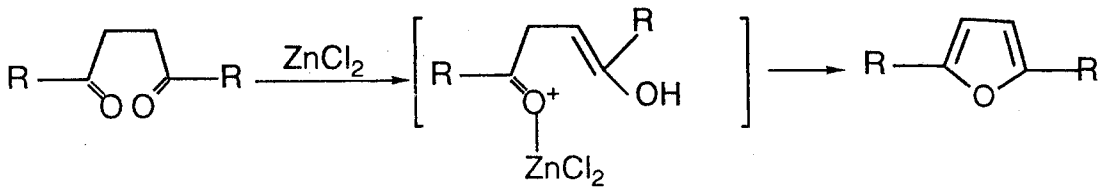
Scheme 2.14

2.3 General Synthesis of Furans

The most widely used methods for the synthesis of furan rings are cyclisation reactions from non-heterocyclic precursors and these are set out schematically below.

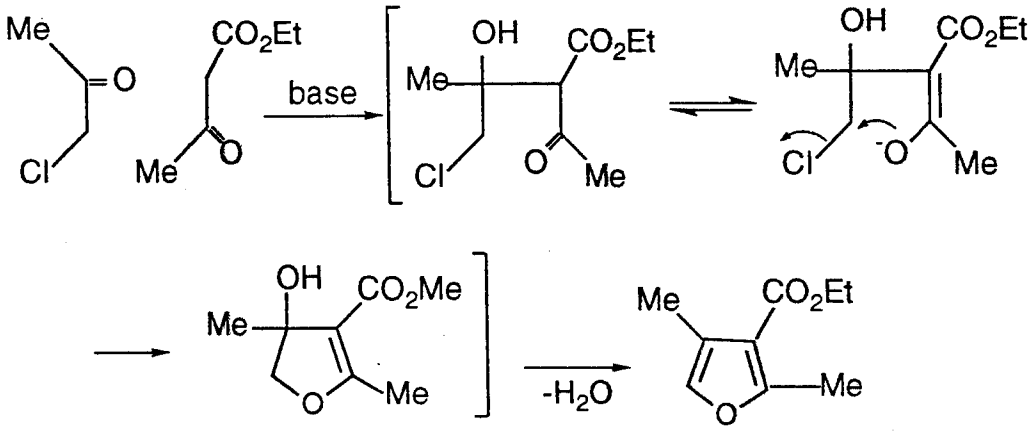
The Paal-Knorr synthesis involves the dehydration of 1,4-dicarbonyl compounds, which can theoretically exist as 1,4-dienols. Such dicarbonyl compounds can be readily prepared in high yields. Usually, non-aqueous acidic conditions are employed to encourage the required loss of water. The mechanism may involve the oxygen of the enol form of one of the carbonyl groups adding to the carbon of the other carbonyl group; elimination of water then completes the process.[20,21]

Cyclisation is effected by heating with sulphuric acid, phosphorus pentoxide, acetic anhydride, zinc chloride, or with some other suitable dehydrating agent. Polyphosphoric acid is particularly effective for system having a pyridine ring. The dehydrating agent probably functions by coordination with the oxygen of carboxyl group, as shown Scheme 2.15.[22-30]



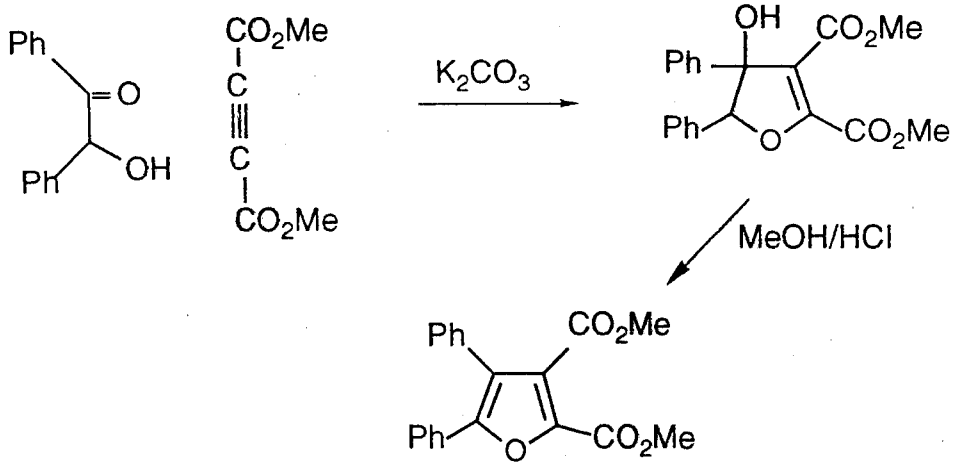
Scheme 2.15

The Feist-Benary synthesis of furans involves the base-catalysed condensation of an α-halo carbonyl compounds with 1,3-dicarbonyl compounds in the presence of a base. Sodium hydroxide, pyridine, or ammonia can be used; the conditions approximate to those of the Hantzch pyrrole synthesis and both furans and pyrroles can be formed.[31,32] The Feist-Benary synthesis is a good method for the preparation of esters of furan 3-carboxylic acids. This synthesis probably involves an aldol condensation with the carbonyl group of the halogen component, followed by formation of the oxygen ring by intramolecular displacement of halide (Scheme 2.16).



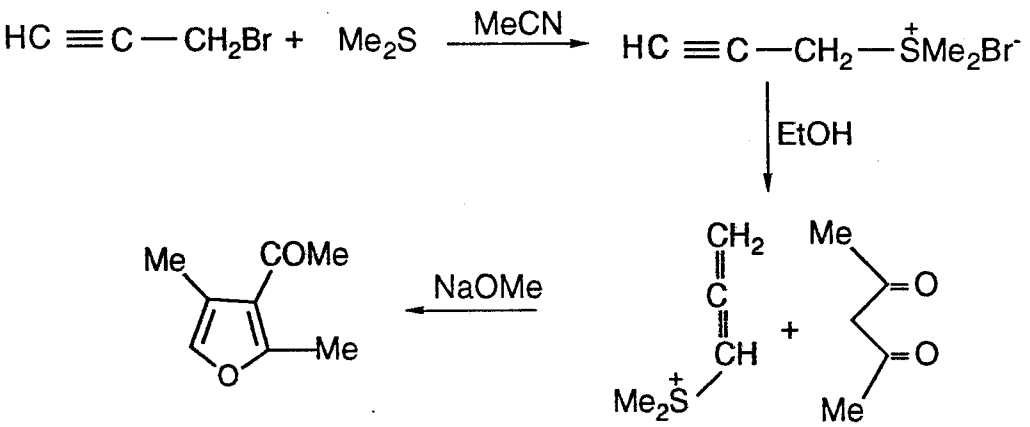
Scheme 2.16

Many other methods have been used for the preparation of the furan rings, for example, α-hydroxyketones react with diacetylenes to give furans (Scheme 2.17).[33]



Scheme 2.17

A similar synthesis of furans makes use of the acetylenic sulphonium salt, which isomerises to an allene and can add to the sodium salt of a 1,3-dicarbonyl compounds, such as a diketone, or β-keto ester (Scheme 2.18). Cyclisation and tautomerism give the furans in 75 % yield.[34]

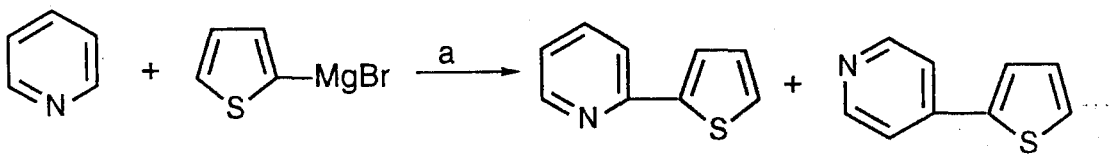


Scheme 2.18

2.4 Synthesis of Thienylpyridines

Several routes have been described in the literature for the preparation of the thienylpyridines. In 1964, Kahmann and co-workers[35] have described the

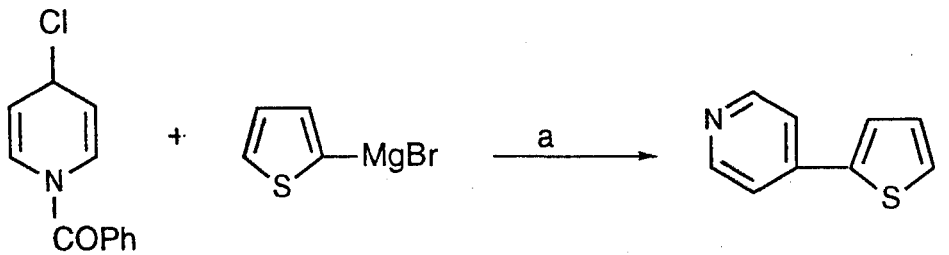
synthesis of thienylpyridines from the Grignard reagent of thiophene in very low yield. The reaction involves the addition of 2-thienylmagnesium bromide to the pyridine and subsequent aromatisation of the dihydro product at 160 °C in an autoclave. In 1969, Wynberg and co-workers[36] also used 2-thienylmagnesium iodide as a Grignard reagent in ether at 130 °C, but they isolated the thienylpyridines in overall yields ranging from 2 to 10 % (Scheme 2.19).



(a) i. ether, ii. xylene, 130 °C

Scheme 2.19

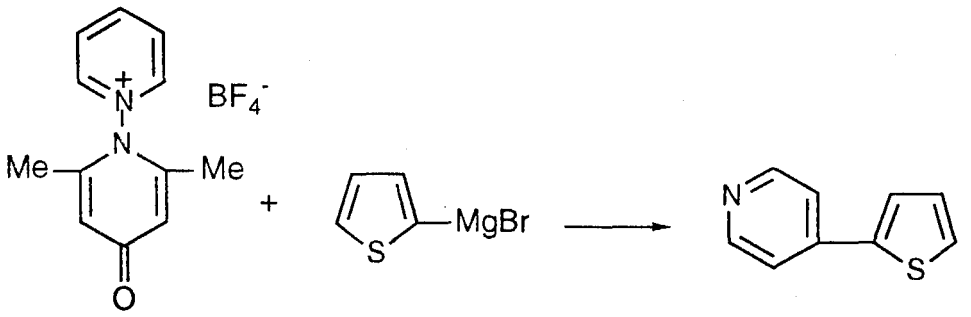
A specific synthesis of 2-(4-pyridyl)thiophene has been accomplished from 2-thienylmagnesium iodide and 1-benzoyl-4-chloro-1,4-dihydro pyridine; the yield was again only 2 % (Scheme 2.20).[37]



(a) i. ether, ii. H_2O

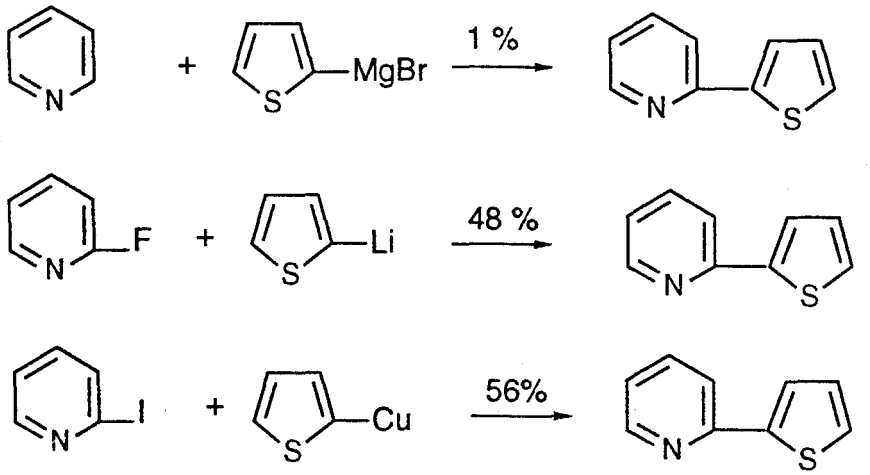
Scheme 2.20

In 1980, Katritzky and co-workers[38] also used the same route to obtain 4-(2-thienyl) pyridine from pyridinium salts and Grignard reagent of thiophene in 35 % yield, as shown Scheme 2.21.



Scheme 2.21

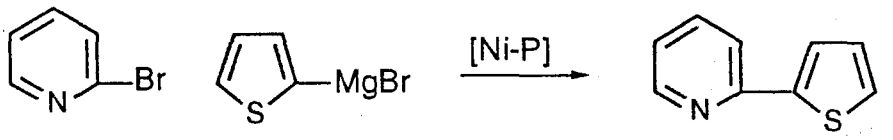
In 1983, Kaufmann co-workers[39,40] prepared the thienylpyridines by the treatment of 2-lithiothiophene with 2-fluoropyridine, as shown in Scheme 2.22. Replacement of the magnesium iodide group by lithium, or copper,[41] as well as the H atom of electrophilic component by halogen, significantly raises the yield.



Scheme 2.22

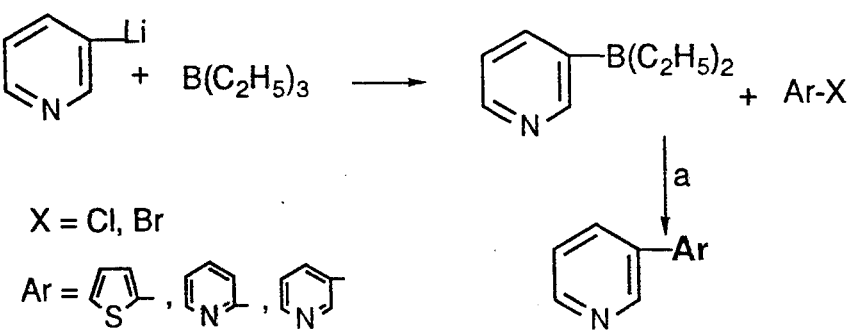
Recently, it has been shown that the heteroarylation of pyridines by palladium or nickel-catalysed cross coupling reaction of the bromopyridines with heteroarylhalides significantly changed the yields. For example, Tamao and co-workers[42] used nickel-phosphine complexes as a catalyst for the cross-

coupling reaction between the Grignard reagent of thiophene and 2-bromopyridine (Scheme 2.23). [$NiCl_2Ph_2P(CH_2)_3PPh_2$] is an effective catalyst for the reaction and yield was 78 %.



Scheme 2.23

Gronowitz and Lawitz[43] have also shown that all six isomeric thienylpyridines are produced in high yields (60-70 %) through the coupling of 2- and 3-thiophene boronic acid with the bromopyridines in the presence of catalytic amounts of $Pd(PPh_3)_4$ in aqueous sodium carbonate and glycoldi-methyl ether mixtures. The same catalyst was also used by Ishikura and Terashima[44] for the synthesis of 3-heteroarylpyridines. The reaction involves the palladium-catalysed-cross-coupling of diethyl-(3-pyridyl)borane with 2-hetero aryl halides in the presence of a base. The borane derivative can be readily obtained from the reaction of 3-lithiopyridine with triethylborane (Scheme 2.24).[45]

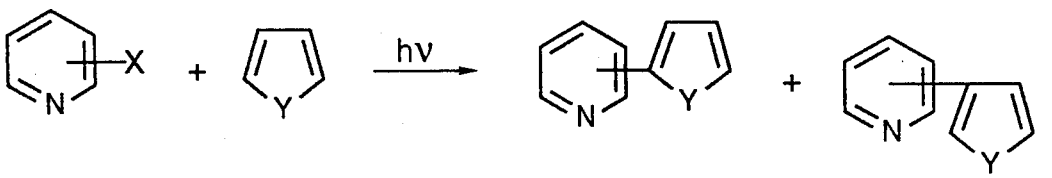


(a) $(Ph_3P)_4Pd$/ KOH/ THF/ $[n\text{-}C_4H_9]_4NBr$

Scheme 2.24

Ishikura and co-workers[46] have also prepared the 4-isomers of pyridine using palladium-catalysed cross-coupling reactions of heteroaryl halides with diethyl borane, which is prepared from diethylmethoxy borane,[47] in 55-70 % yield.

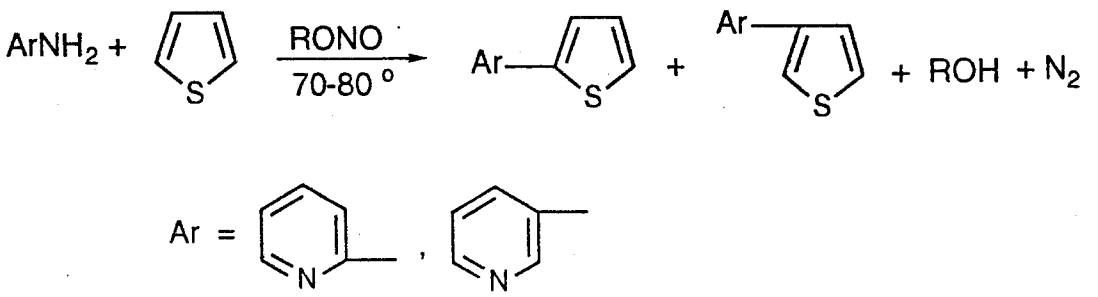
A procedure *via* the photo reaction of 2-, 3-, 4-halopyridines with five-membered heteroaromatics produces the thienylpyridines in more acceptable yields (Scheme 2.25).[48-51]



X : Br, I; Y : O, S, NH, NMe

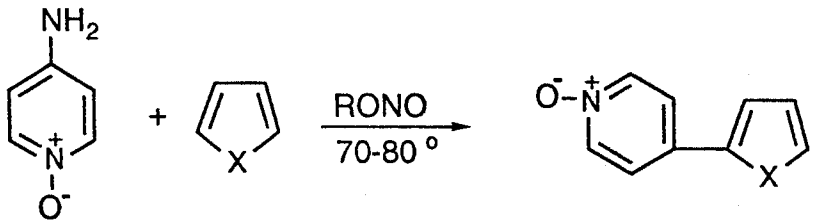
Scheme 2.25

Vernin and Metzger[52] have reported the synthesis of 2- and 3-arylpyridines using a pseudo-Gomberg reaction of heteroaromatic amines. Heteroaryl radicals, which are formed by aprotic diazotization of the corresponding heterocyclic amines in the presence of amyl nitrite, react homolytically with thiophene to produce 2-heteroarylthiophenes, as main reaction products, in overall yields of 20 to 50 % (Scheme 2.26).



Scheme 2.26

Recently, Saeki co-workers[53] have also reported the synthesis of 4-arylpyridines using a modified Gomberg reaction of 4-aminopyridine-1-oxide. The radical, generated from the reaction of 4-aminopyridine-1-oxide with amyl nitrite, reacted smoothly with five-membered heterocycles (i.e. thiophene, furan and pyrrole) to give the arylated products, when acetic acid was used as a solvent (Scheme 2.27). The reaction of the aminopyridine-1-oxide gave a higher yield than that from the corresponding aminopyridine.



X = S (93 %), O (39 %), NSO_2Me (50 %)

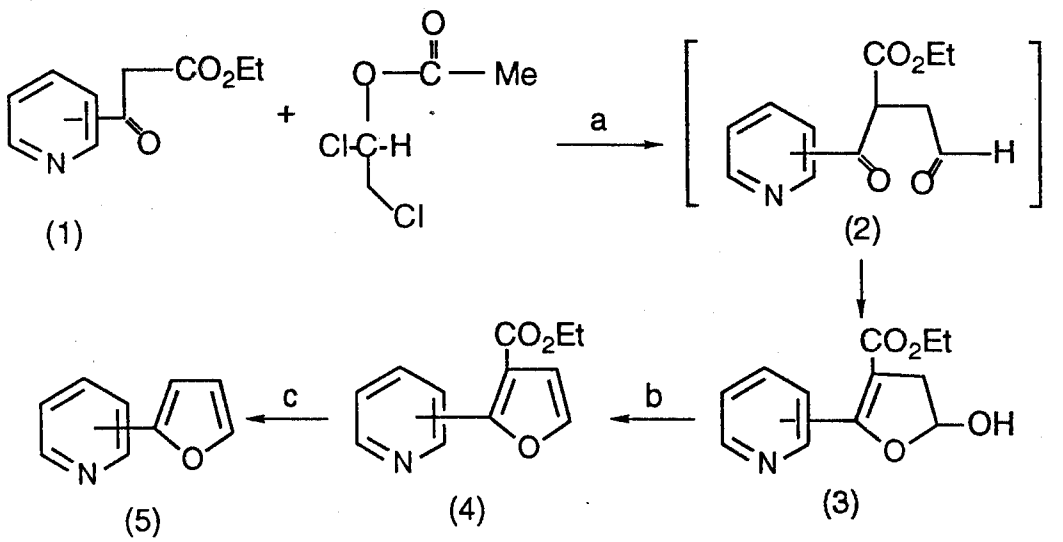
Scheme 2.27

2.5 Synthesis of Furylpyridines

Only a small number of papers dealing with the synthesis and properties of the furylpyridines can be found in the literature. Synthetic methods for these compounds, such as photochemical reactions,[49,50] arylation reactions,[54] and cyclisations[55] are closely related to those for the synthesis of thiophenes, as outlined in Section 2.4, or for pyrroles.

Queguiner and co-workers[56,57] published a reaction which involves the cyclisation of the 1,4-dicarbonyl compounds. The route based on the Paal-Knorr reaction and 1,4-dicarbonyl compounds obtained from a reaction of ethyl pyridoylacetates (1) with 1,2-dichloroethyl acetate and 10 % aqueous ammonia.

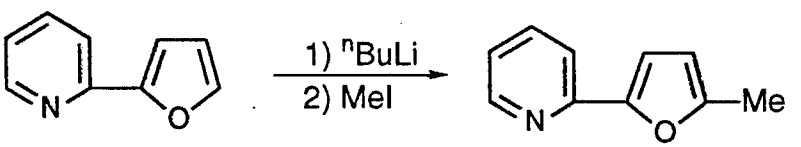
Thermolysis of the first reaction product (3) was necessary to aromatise the compound and decarboxylation of the acid gave the furylpyridines in 80-85 % yield (Scheme 2.28).



(a) aq. NH_4OH; (b) Δ; (c) i. KOH, EtOH, ii. Cu, Δ

Scheme 2.28

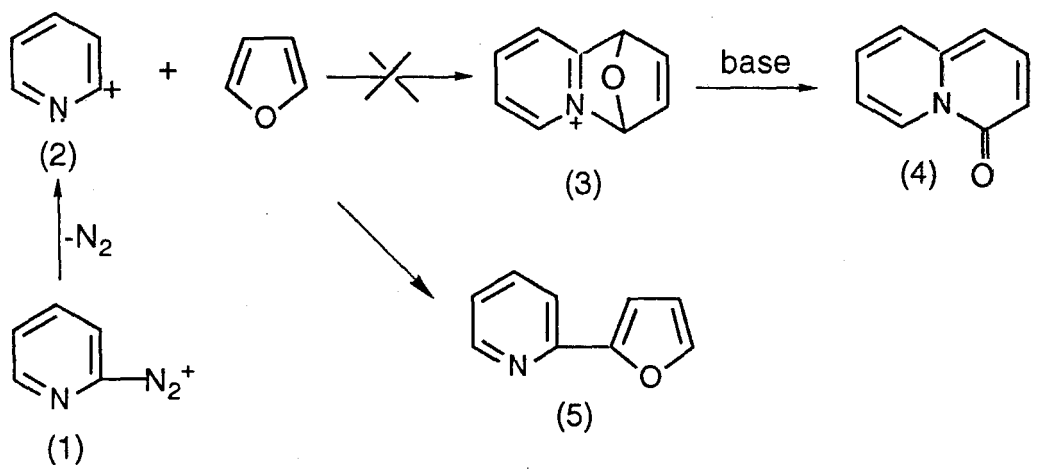
In 1983, Ribereau and Queguiner[58] reported a reaction in which 2-(2-furyl)pyridine is lithiated with *n*-butyllithium in THF at -78 °C and then methylated to give the 2-(5-methyl-2-furyl)pyridine in 19 % yield (Scheme 2.29).



Scheme 2.29

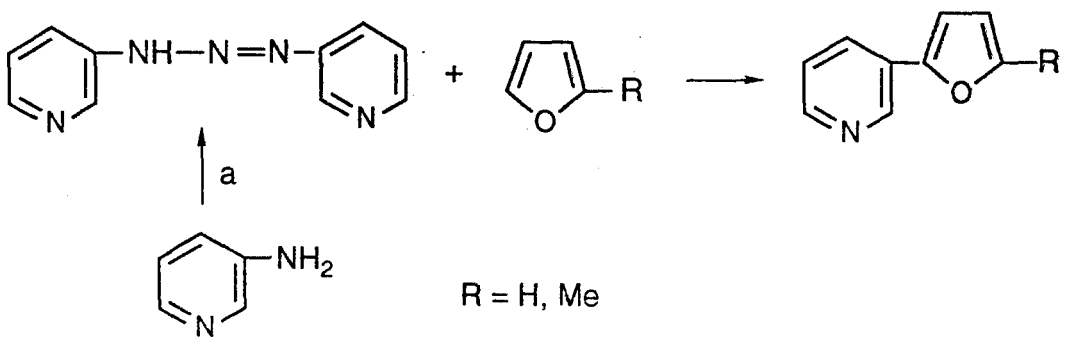
Bunnett and Singh[59] have synthesised 2-(2-thienyl)pyridine in 30 % yield from the reaction of the 2-pyridinediazonium ion (1) and furan at 110 °C. They

expected to obtain a Diels-Alder type product (4), but they isolated furylpyridine (5), as a normal electrophilic substitution product. Compound (2) acts upon furan to form the α-adduct, which then loses a proton (Scheme 2.30).



Scheme 2.30

Fisera and co-workers[60] have reported the synthesis of 2- and 3-aryl pyridines by using a pseudo-Gomberg reaction of heteroaromatic amines. They prepared 3-(2-furyl)pyridine in 28 % yield from the reaction of 3-aminopyridine with isopentyl nitrite in furan at 30 °C. As shown in Scheme (2.31), 1,3-di(3-pyridyl)triazene, which is formed by aprotic diazotization of the 3-amino pyridine in the presence of amyl nitrite, reacts homolytically with furan to

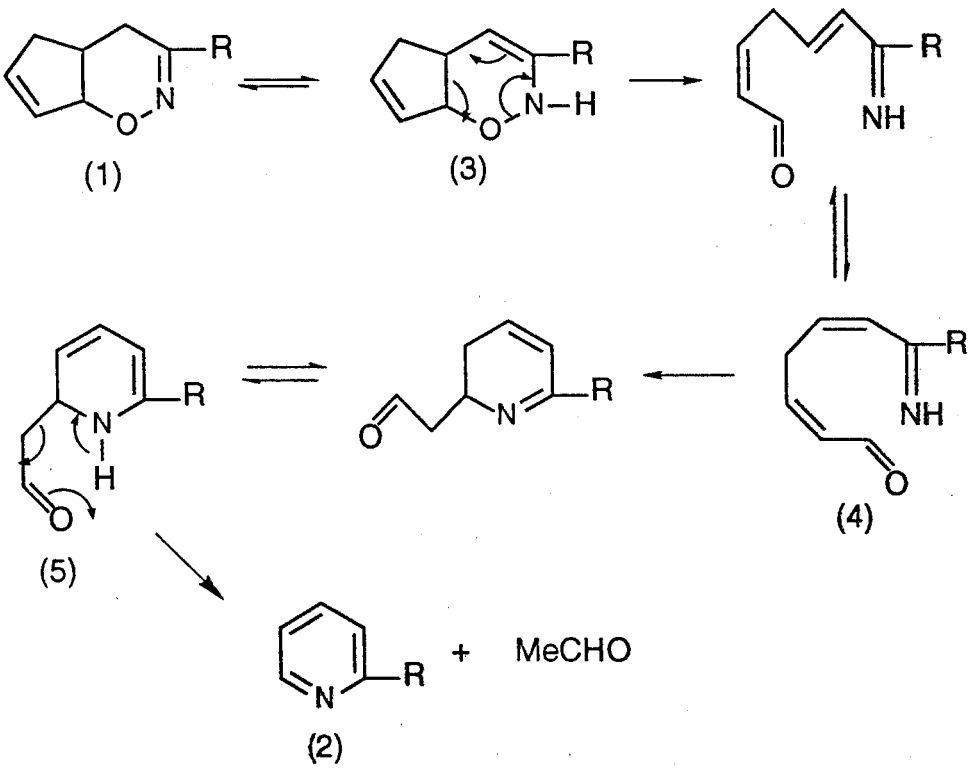


(a) isopentyl nitrite, 30°C

Scheme 2.31

produce 3-(2-furyl)pyridine. Three years later, the same group[61] prepared 3-(5-methyl-2-furyl)pyridine in 17 % yield using an analogous route.

An entirely different approach has been used by Faragher and Gilchrist.[62] When the dihydro-oxazines (1) were heated at 200 °C, were converted into the furylpyridine (2) in 40 % yield. A possible mechanism involves electrocyclic ring opening of the oxazine ring (3) to yield the unsaturated imines (4), which can be cyclised to the dihydropyridines (5) in a retro-ene process (Scheme 2.32).



R = phenyl (80 %), 2-furyl (40 %)

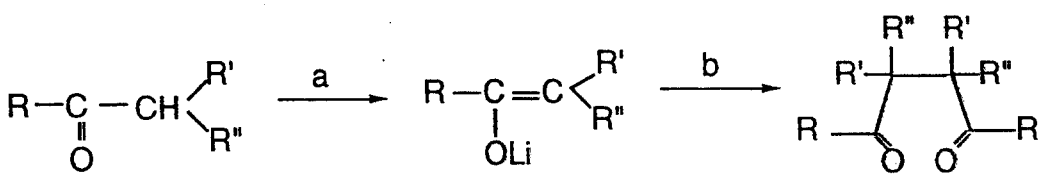
Scheme 2.32

The aim of the present project was to synthesise the mainly unknown furylpyridines and thienylpyridines *via* an alternative route, which would be, if possible, shorter, cheaper and higher yielding than the previous approaches. For the proposes of our work, we decided that the best route to arylpyridines was

via the Paal-Knorr reaction using the pyridylbutan-1,4-dione derivatives with the hope that we can close the ring using any thianation reagent to make thiophene ring, or using any dehydration reagent to make furan ring. The first problem to overcome was the preparation of 1,4-diketones. This can be achieved in a number of ways, as outlined in the next section.

2.6 Synthesis of 1,4-Diketones

Many methods for the synthesis of 1,4-diketones have been briefly reviewed by Ritchie[63] and Rio.[64] Ellison,[65] Ho,[66] and Nimgirawath[67] have reviewed methods for the preparation of purely aliphatic 1,4-diketones. There are several examples of the synthesis of aryl-1,4-diketones, but most of the synthetic methods published are based upon coupling reactions of ketone enolates using a catalyst, such as $CuCl_2$,[68] CuOTf,[69] $Cu(OTf)_2$,[69] $Mn(OAc)_3$,[70] $BF_3.Et_2O$,[71,72] and PbOAc.[73] For example, Ito and co-workers[68] have shown that the oxidative coupling of lithium enolates is accomplished by treating ketone enolates with $CuCl_2$ in DMF. As shown Scheme 2.33, ketone enolates were prepared from a ketone and diisopropylamide in THF at -78 °C and in very high yield.

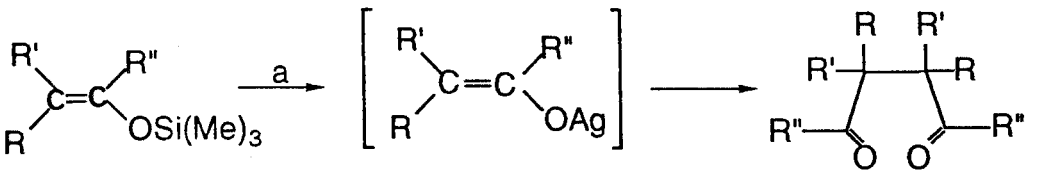


R = Ph (95%), 3-furyl (41%); R', R" = H, Me;

(a) $LiN(^iPr)_2$, THF, -78°C; (b) $CuCl_2$, DMF

Scheme 2.33

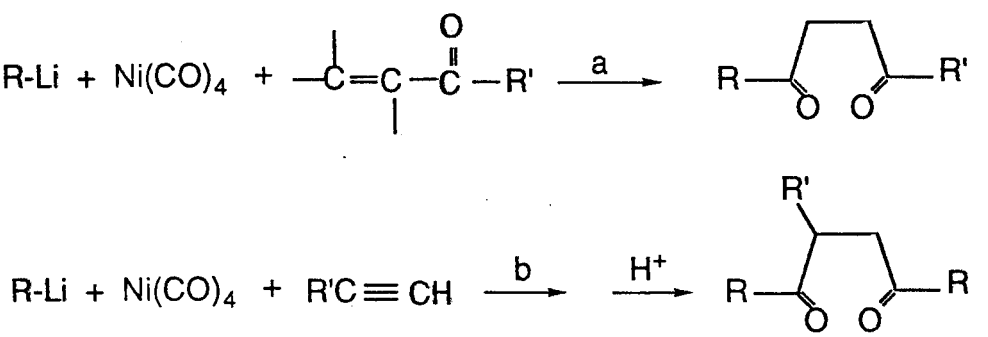
Similarly, Ito and co-workers[74] reported a synthesis of aryl-1,4-diketones by the reaction of silyl enol ethers with silver oxide in DMSO, in which silver enolates are generated regiospecifically, as a reactive intermediate (Scheme 2.34). The reaction takes place under the mild conditions and in quantitative yields.



R, R' = H, or Me; R" = alkyl, or Ph (50 %); (a) Ag_2O, DMSO, 65 °C, 24 h.

Scheme 2.34

Corey and co-workers[75] have prepared aryl-1,4-diketones in quantitative from nickel carbonyl complexes, which are prepared from nickel carbonyl and aryllithium at low temperature (-50 °C), with a variety of α,β-unsaturated carbonyl derivatives. Sawa and co-workers[76] also used the same route to prepare aryl-1,4-diketones in yields of 45-75 %, starting from acetylenes and the nickel carbonyl at -70 °C (Scheme 2.35).

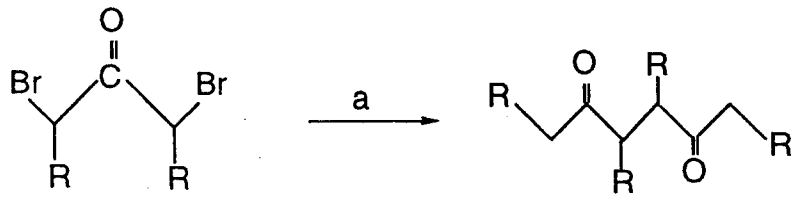


R = Alkyl, Ph or p-$CH_3C_6H_5$; R' = H, Me, or Ph;

(a) ether, -50 °C, 24 h; (b) ether, -70 °C.

Scheme 2.35

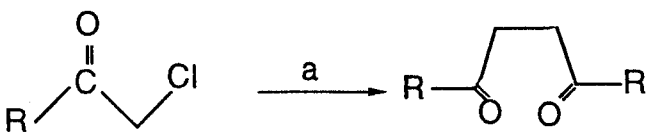
Chassin and co-workers[77] reported that 1,4-diketones can be generated in acceptable yields under mild conditions from α,α'-dihalo ketones using N-methylformamide in combination with a zinc-copper couple at room temperature (Scheme 2.36).



R = H, alkyl, Ph (43 %); (a) Zn-Cu, N-methylformamide, r.t., 12 h.

Scheme 2.36

Iyoda[78] used a similar approach to synthesise 1,4-diphenylbutane-1,4-dione from the nickel-catalysed coupling of a-haloketones. The active nickel complex is generated by reduction of $NiBr_2(PPh_3)_2$ with zinc in the presence of Et_4NI. As shown in Scheme 2.37, the coupling of phenacyl chloride with the active nickel complex proceeded smoothly in THF, DME, and benzene to give 1,4-diphenylbutane-1,4-dione in *ca.* 75 % yield.

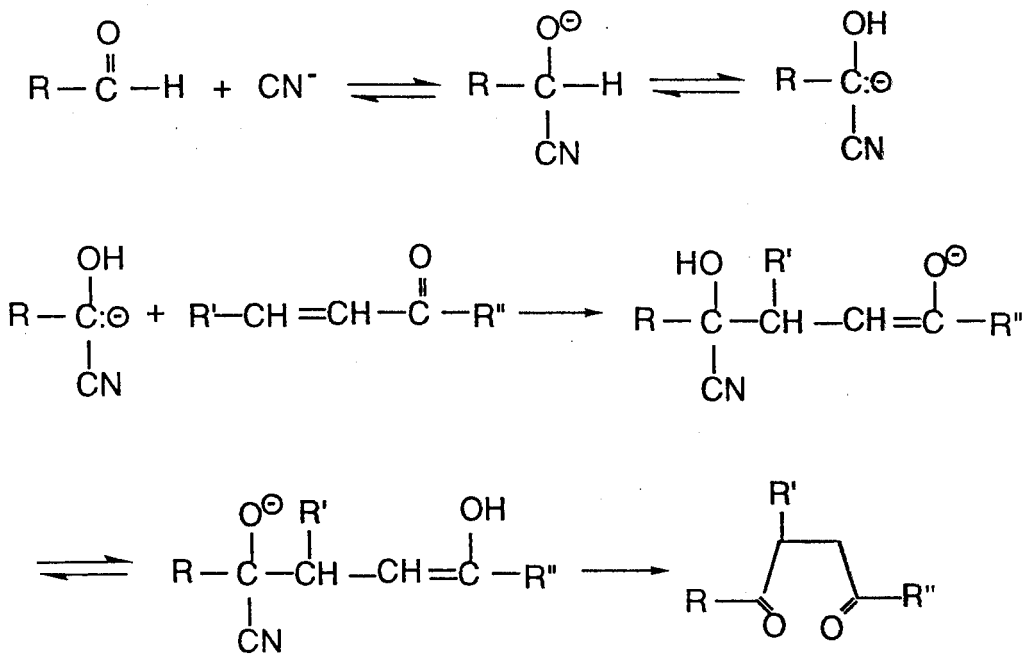


R = Ph, 2-MePh, 2-OMePh; (a) Cat.Ni, Zn, Et_4NI, r.t., 3 h.

Scheme 2.37

Stetter and co-workers,[80-90] have shown that in the presence of a suitable catalyst, such as thiazolium salts or cyanide ions, aromatic and heteroaromatic aldehydes react with α,β-unsaturated carboxylic esters, aldehydes, ketones, nitriles, divinylsulphone, or 3-(N,N-dimethylamino)-1-oxopropyl compounds in

aprotic solvents to form 1,4-diketones, 4-oxocarboxylic esters, and 4-oxonitriles (Scheme 2.38).



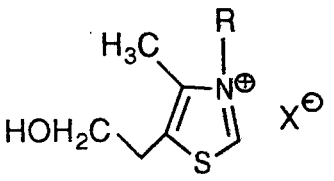
R, R' : alkyl, or aryl;

Scheme 2.38

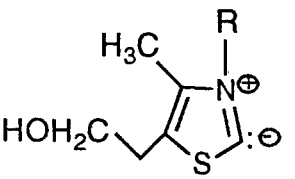
2.7 Results and Discussions

The most satisfactory route for the synthesis of 1-(2-, 3-, or 4-pyridyl) pentan-1,4-diones was found to be the general procedure outlined by Stetter and co-workers,[79-83] which involves the catalysed condensation of the appropriate formylpyridine with but-3-en-2-one in the presence of a thiazolium ion (1). As shown in Scheme 2.39 for the reaction between 2-formylpyridine and but-1-en-3-one, the mechanism of the reaction can be thought to involve a Michael type addition reaction; the reaction also shows many parallels with the benzoin condensation. The reaction can be catalysed either by cyanide ions, or

thiazolium salts which are transformed into the ylide structure (2); the ylide shows a catalytic effect resembling that of the cyanide ion in benzoin condensation. We have successfully employed the thiazolium salt in the presence of triethyl amine, as a base, for the addition of the appropriate formylpyridine to but-3-en-2-one in dioxane and in excess of 60 % yield. The



(1)



(2)

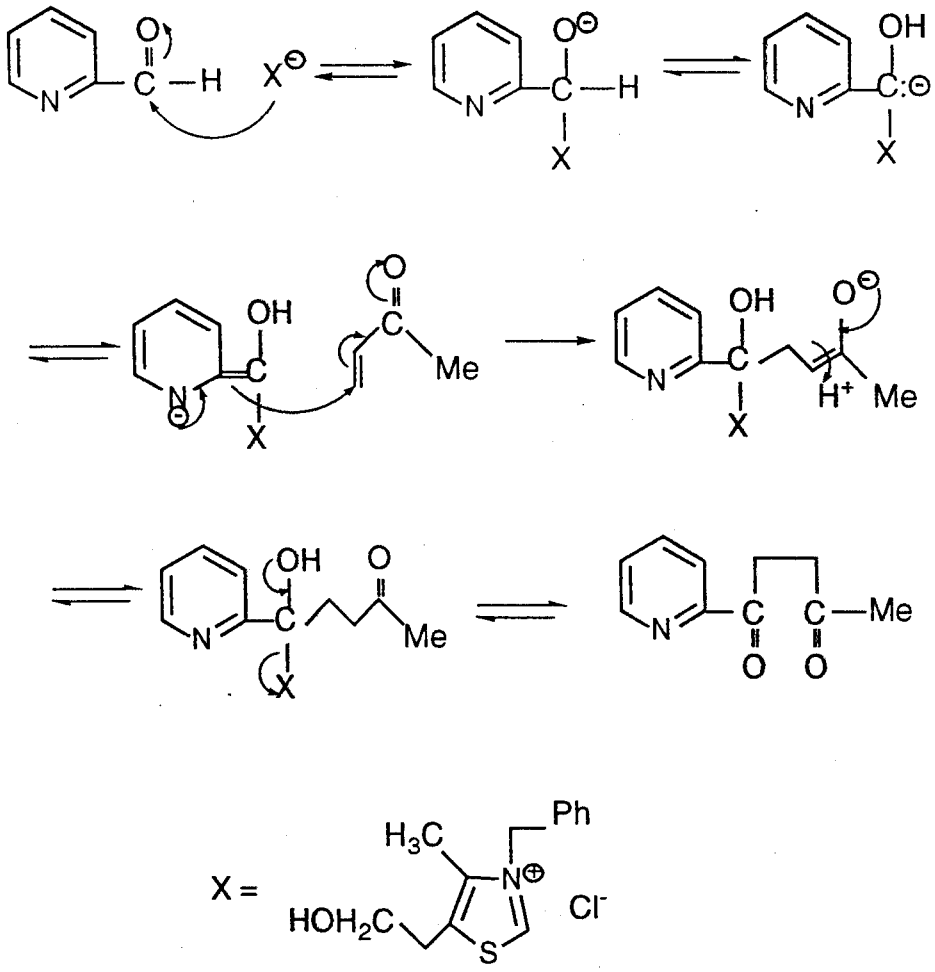
$R = C_6H_5CH_2$, X = Cl

$R = C_2H_5$, X = Br

$R = CH_3$, X = I

pyridyl-1,4-diketones were readily characterised by their IR spectra, which showed two prominent absorptions bands at *ca* 1 690 and 1 715 cm^{-1}, indicating the presence of carbonyl groups. Further evidence for the diketones structures was afforded by ^{13}C NMR spectra, which showed total of ten carbon resonance with signals at 197 and 206 ppm indicating the presence of the two carbonyl groups, and five signals between 120 and 150 ppm attributable to the pyridine carbon atoms. The remaining three signals around 30-40 ppm were assigned to methyl and methylene carbon atoms. The total structures were corroborated by ^1H NMR spectral data, mass spectral and elemental analysis data.

When the diketones were subjected to a Paal-Knorr reaction, as shown in Scheme 2.40, the reaction between the 1,4-diketone and phosphorus penta-sulphide, produced a mixture that turned black and gave a polymerictar after 20min.

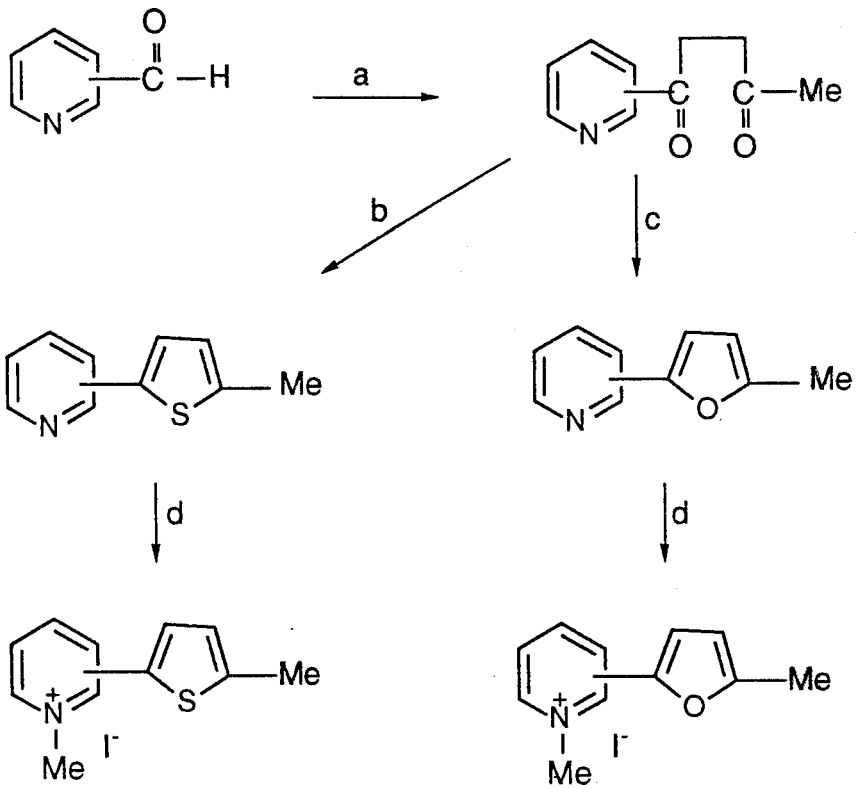


Scheme 2.39

TLC analysis showed the presence of mainly base-line material, which could not be identified. The reaction was repeated using toluene as a solvent; in this case TLC showed some unreacted starting material. At this point, we turned to the literature and found that general thionation reagents, such as O,O-diethyldithiophosphonic acid,[90] boron sulphide,[91] silicon disulphide[92] and elemental sulphur,[93] H_2S in HMPA[94,95] could be used as alternatives to P_2S_5 but, most recently, investigations of the chemistry of 2,4-bis(p-methoxyphenyl)-1,3-dithiadiphosphetane-2,4-di sulphide[96-99] (1) indicate that it is a superior reagent for the conversion of a wide variety of carbonyl into thiocarbonyl compounds

(Scheme 2.41). For example, in 1990, Merril and Goff showed that the cyclisation of 1,4-di(2-pyrrolyl)-1,4-butanedione with Lawesson's reagent to give the thiophene was accomplished in refluxing toluene in 65 % yield.[100] Similarly, closure of the 1,4-di(2-thienyl)-1,4-butanedione gave 90 % yield of the terthienyl compound.[101]

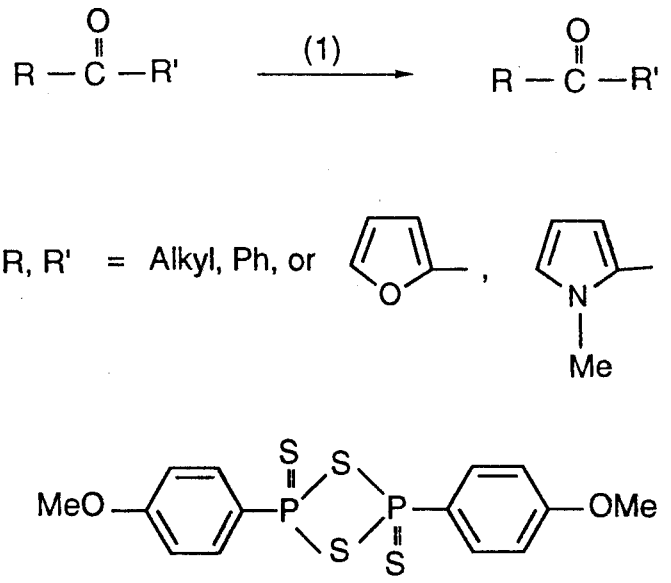
When the Lawesson's reagent in toluene was reacted with the pyridylpentan-1,4-diones, the corresponding thienylpyridines were obtained in 50-70 % yields. The reaction was critically dependent on temperature, reaction time, solvent, and quantity of the reagent. It requires a large excess of reagent, solvent, long reaction times and a stable temperature. The reaction mechanism



(a) CH_2 = CHCOMe in dioxane; (b) Lawesson's reagent in toluene;

(c) Polyphosphoric acid; (d) MeI, EtOH

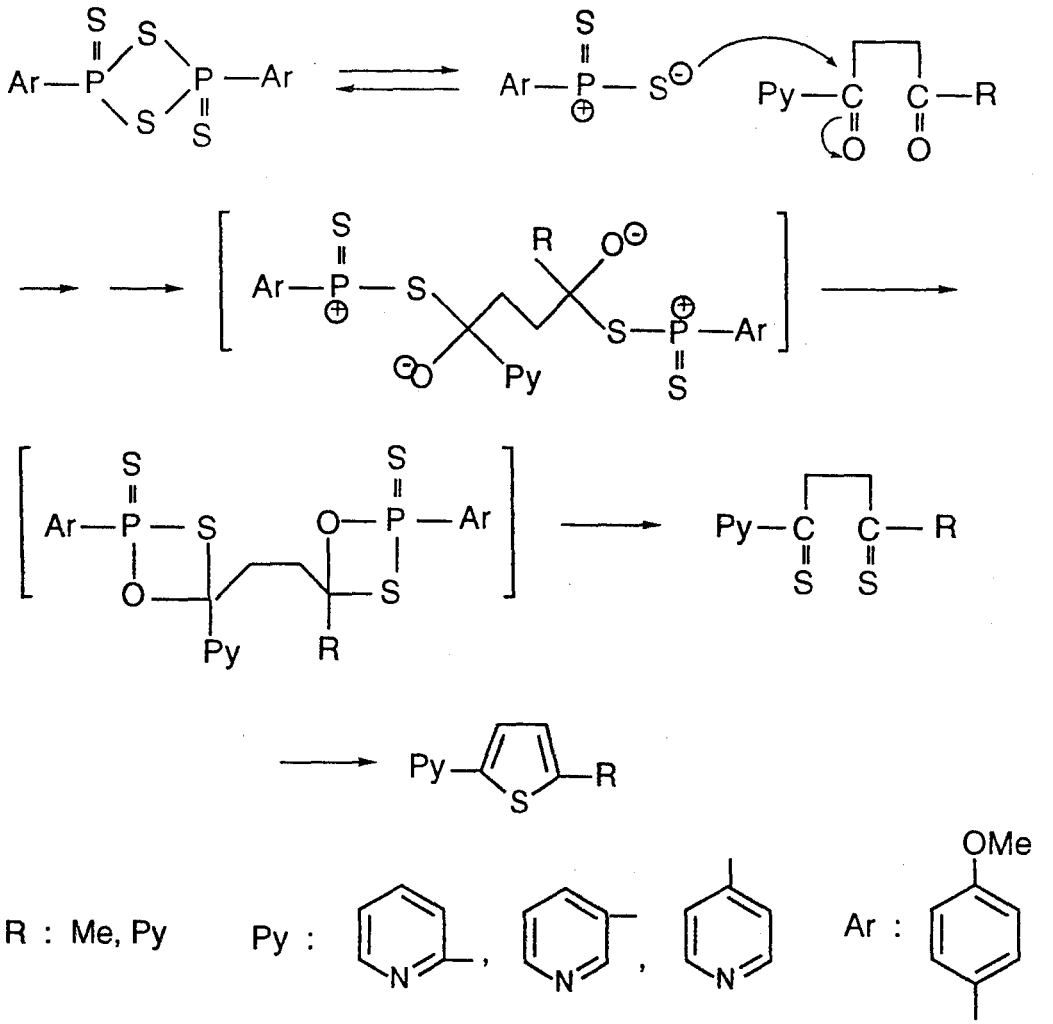
Scheme 2.40



(1) : Lawesson's Reagent

Scheme 2.41

may be considered to involve Wittig-type intermediates, such as the highly reactive dithiophosphine ylide rather than Lawesson's reagent itself, as shown in Scheme 2.42. The ^{1}H NMR spectrum of the previously unknown thienyl pyridines showed a singlet at *ca.* 2.53 ppm, assignable to methyl group. The signals between 6.70 and 8.80 ppm integrated for six aromatic protons, corresponding to the four protons of pyridine and two protons for the thiophene rings. A ^{13}C NMR singlet for the methyl group appeared at *ca.* 15.3 ppm and nine aromatic carbon signals around 118-153 ppm, and $\nu_{C=C}$, $\nu_{C=N}$ bands appeared near 1 575 and 1 595 cm^{-1} in the IR spectrum. The formation of thienylpyridines was also confirmed by their elemental analysis and mass spectra.

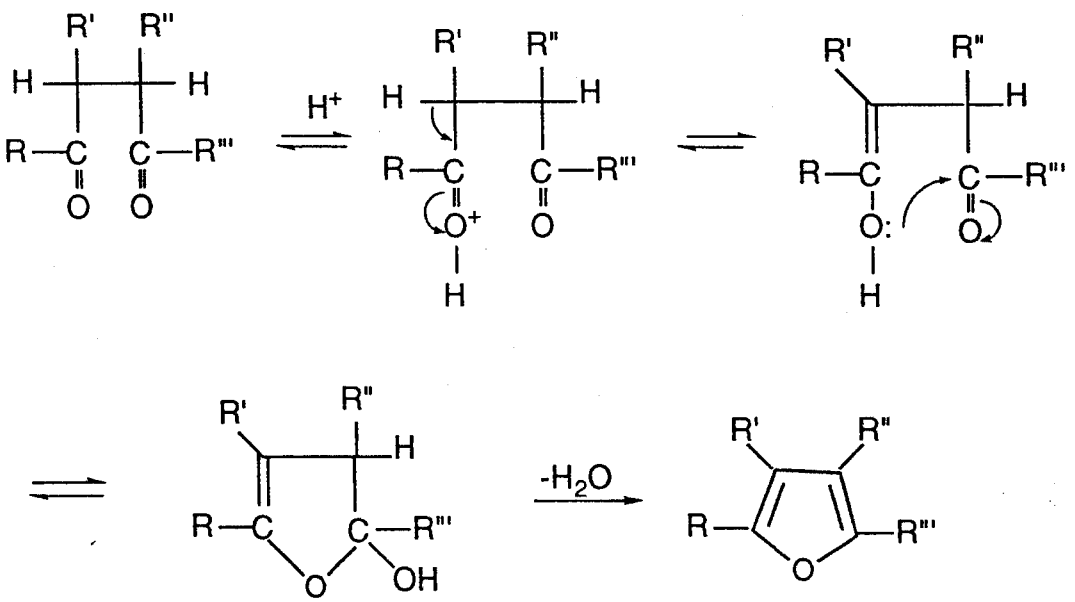


Scheme 2.42

1,4-Dicarbonyl compounds can be cyclised with loss of water, according to the Paal-Knorr procedure in high yields. Usually non-aqueous acidic conditions are employed to encourage the required loss of water (Scheme 2.43). Dehydration reagents, such as sulphuric acid, acetic anhydride, chloric acid, zinc chloride, phosphorus pentoxide and polyphosphoric acid, can be used for the cyclisation reactions.

In order to make the furylpyridines, the appropriate 1,4-diketone was reacted with acetic anhydride in the presence of sulphuric acid at room

temperature, followed by TLC analysis. After 30 h, there was no change in the reaction mixture. The reaction was repeated several times increasing the amount of H_2SO_4 or acetic anhydride, and also heating the mixtures at 50 °C and 140 °C for 24 hours. Each time, there was no success, and each experiment gave the unreacted starting material. The reaction was also repeated with hydrochloric acid at 150 °C and with phosphorus pentoxide in toluene at 110 °C for a day. TLC analysis and the ^1H NMR spectra indicated the presence of only unreacted starting material in each case.

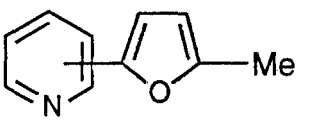


R, R', R", and R"' = alkyl or aryl

Scheme 2.43

At this stage, we used polyphosphoric acid as a dehydration reagent. The mixture was heated for 3 h at 130-140 °C and TLC analysis showed the formation of the required product. Polyphosphoric acid is therefore a superior reagent for the conversion of the pyridyl-1,4-diketones to the corresponding furylpyridines, which were obtained in > 80 % yield. Only the 4-isomer of the

furylpyridines is unknown, but all three isomers were characterised by comparison of the spectral data with those of the starting materials. The infrared absorption at *ca.* 1 535 and 1 585 cm^{-1} for $\nu_{C=C}$, $\nu_{C=N}$ and absence of any typical ν_{CO} absorptions at *ca.* 1 690 and 1 715 cm^{-1}, the ^1H and ^{13}C NMR spectra, together with mass spectra and elemental analysis fully confirmed the structures as (1).



(1)

N-Methylation of the furyl- or thienylpyridines with methyl halides is normally facile and proceeds in high yield. Quaternary ammonium salts of this type are normally crystalline and relatively stable. We found that the N-methylpyridinium salts were readily formed when a reaction was carried out by heating the appropriate furyl- or thienylpyridines with an excess of methyl iodide in ethanol at 60°C. The 3- and 4-isomers of heteroarylpyridines were obtained in greater than 90 % yield, but the yields for 2-isomers were 53 and 76 % for thienyl- and furylpyridines, respectively, because of the steric hindrance. The ^1H NMR spectra of the products showed that methylation had occurred, as judged from the appearance in the spectrum of a methyl singlets at around 4.28-4.64 ppm. The assignment of these signals were made on the basis that the NCH_3 protons are highly deshielded by the inductive effect of the quarternised nitrogen atom. The signal for the remaining methyl group and aromatic protons were assigned by comparison with data for the parent furyl- or thienylpyridines. As expected, the pyridine signals for the protonated system were shifted downfield, compared with those of the free bases. Further evidence for the

successful quarternisation of the furyl- and thienylpyridines was obtained from the IR spectra. In the free base, the aromatic stretching band occurs at *ca.* 1 590 cm^{-1} but, in the pyridinium salts, it shifts to 1 620 cm^{-1}. ^{13}C NMR spectra and elemental analysis data also support the proposed structures, but the mass spectra only showed peaks for the parent heteroarylpyridines, with cleavage of the N-methyl groups.

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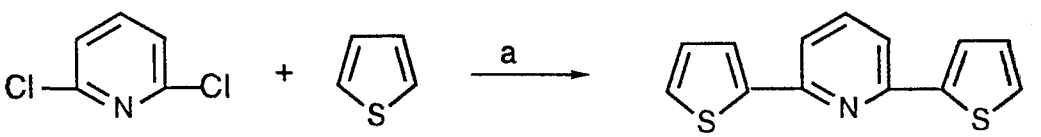
CHAPTER 3

THREE RING SYSTEMS

3.1 Di(heteroaryl)pyridine Systems

3.1.1 2,6-Di(heteroaryl)pyridines

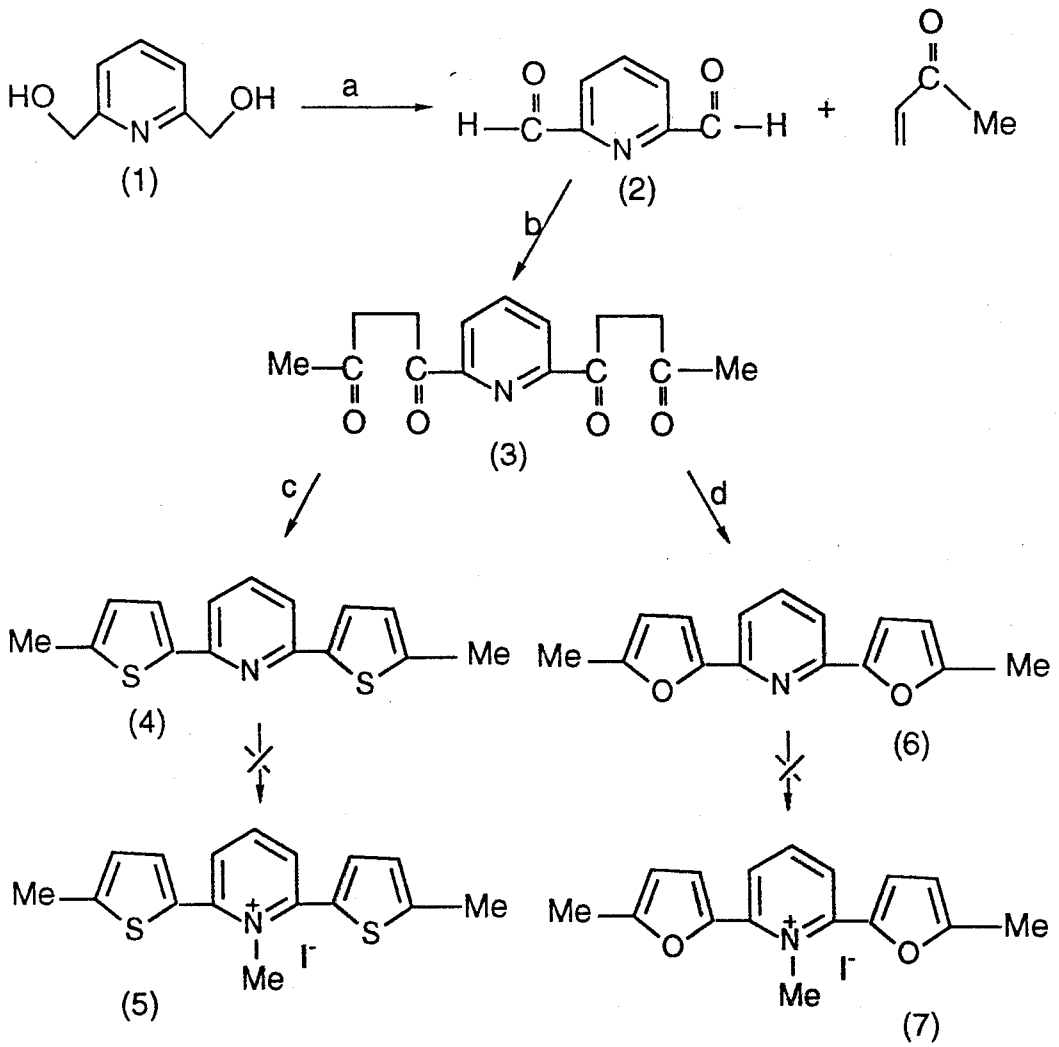
There are no examples in the literature for the synthesis of the 2,6-difurylpyridines, 2,5-difurylpyridines, or 2,5-dithienylpyridines, and there is only one reported synthesis of 2,6-dithienylpyridines. Kauffmann *et al.*[1] have synthesised the 2,6-di(2-thienyl)pyridine in 18 % yield by treating 2,6-dichloro pyridine and 2-lithiothiophene in ether, as shown in Scheme 3.1.



(a) i. ^{n}BuLi, 0 °C, ii. 5 h, 35 °C

Scheme 3.1

In order to make 2,6-di(heteroaryl)pyridines, we decided to follow the Paal-Knorr approach, as described in Chapter 2 for the synthesis of the mono heteroarylpyridines. We adopted the Stetter approach, which we had used for the preparation of pyridyl-1,4-diketones, to obtain 2,6-disubstituted pyridine (3). According to the Stetter approach, it was necessary to start from 2,6-diformylpyridine, which is commercially available, but is also very expensive. In view of the ready availability of 2,6-pyridinemethanol, which is cheaper, we started from this compound for the preparation of the appropriate 1,4-diketones (Scheme 3.2). 2,6-Diformylpyridine was prepared in 54 % yield by oxidation of the dialcohol using activated MnO_2.[2] The dialdehyde was characterised by the absorption at 1 715 and 1 695 cm^{-1} attributed to C=O groups. The appearence of these bands coincided with the disappearance of the ν_{OH} absorption band.



(a) MnO_2, reflux, 5h; (b) thiazolium cat., 110 °C; (c) Lawesson's reagent, reflux, 50h; (d) polyphosphoric acid, 130-140 °C.

Scheme 3.2

Confirmation of the dialdehyde groups was also obtained from ^{1}H NMR singlet at 10.04 ppm, and the ^{13}C NMR signal at 192.3 ppm.

Condensation of the 2,6-diformylpyridine with methyl vinyl ketone in the presence of thiazolium salt and triethylamine in dioxane gave the symmetric 1,4-diketone in 76 % yield, compared with the product form 2-formylpyridine which was obtained in 66 % yield under the same conditions. The previously

unknown diketone was characterised by elemental analysis and mass spectral data. The infrared spectrum showed absorption at 1 695 and 1 645 cm^{-1}, which were assigned to the C=O groups. The ^1H NMR spectrum of the compound showed a two proton singlet at 2.26 ppm, assignable to the methyl groups and two proton triplets at 2.92 and 3.57 ppm attributable to the CH_2 groups. The signals between 7.95 and 8.23 ppm integrated for three hydrogens, corresponding to the three aromatic protons. The ^{13}C spectrum showed only eight carbon resonances, three signals at 29.9, 31.7 and 37.0 ppm, assignable the symmetric methyl and two methylene groups, respectively. The signals at 124.8, 138.0 and 152.2 ppm, corresponding to the symmetric carbons of pyridine and two signals at 199.5 and 206.9 ppm attributable to the symmetric C=O groups.

Cyclization of the diketone with Lawesson's reagent in refluxing toluene for two days, produced 2,6-di(2-thienyl)pyridine in 55 % yield, (cf. 2-(2-thienyl) pyridine was obtained in 69 % yield after refluxing in toluene for a day). Cyclization with polyphosphoric acid gave 2,6-di(2-furyl)pyridine in 74 % yield (under the same conditions, 2-(2-furyl)pyridine was obtained in 82 % yield). The thienylpyridine showed aromatic absorption bands at 1 585 and 1 565 cm^{-1}, and the furylpyridines showed absorption at 1 580 and 1 545 cm^{-1}. The absence of any carbonyl absorption in the spectra confirmed the complete cyclization to the heteroaromatic rings. Similarly, the absence of the typical methylene signals in the ^1H NMR spectrum also support success of the reaction. The ^{13}C NMR spectra, together with the mass spectra and elemental analyses fully confirmed the proposed structures, as (4) and (6).

The next step in our approach involved methylation of pyridine ring. Quarternisation of these compounds failed using standard procedures with methyl iodide, ethyl bromide, methyl *p*-toluenesulfonate and methyl trifluoromethane sulfonate, which are well known for their high reactivity in

nucleophilic substitution reactions.[3-7] Methylation with methyl iodide in a pressure vessel at 100 °C for seven days also gave the unchanged starting material. The results of these reactions are summarised in Table 3.1. Heating the pyridines with methyl iodide in a pressure vessel at 100 °C for 2 weeks did not produce the desired product, as shown by TLC analysis of the reaction product. Reactions of alkyl halides with amines to form quaternary ammonium salts have been extensively investigated in terms of steric effect between reactants and the effects of pressure on the reactions.[8-9] 2,6-Di-t-butyl pyridine does not react with methyl iodide under conventional methods,[10] but Okamoto and Shimagawa[11] have shown that 2,6-di-t-butyl pyridine reacted with methyl iodide under high pressure (~ 5000 atmos.). Another sterically hindered base, 2,4,6-tri-t-butyl-N-methylaniline does not react with methyl iodide under standard methods. Wepster and co-workers[12] have attempted to prepare 2,4,6-tri-t-butyl-N,N-dimethylaniline by nine different methylation procedures, such as with methyl

Reagent	Solvent	Temperature	Time	Result
MeI	EtOH	reflux	24 h	SM
MeI	-	40 °C	12 h	SM
MeI	-	100 °C	7 d	SM
EtBr	toluene	reflux	24 h	SM
EtBr	-	40 °C	24 h	SM
p-$MeC_6H_4SO_3Me$	-	50 °C	4 h	SM
CF_3SO_3Me	toluene	25 °C	12 h	SM
CF_3SO_3Me	-	25 °C	12 h	SM
CF_3SO_3Me	toluene	reflux	12 h	SM

Table 3.1 Quarternisation of diarylpyridines. SM: starting material

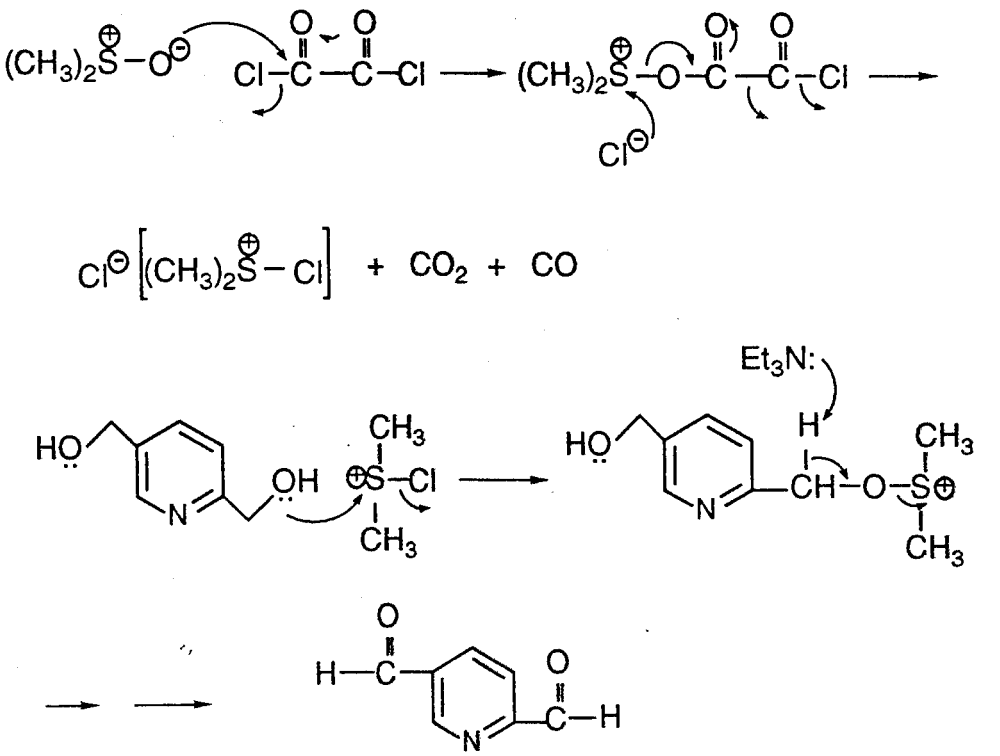
iodide at 200 °C in a sealed tube and dimethyl sulphate at 180 °C, but all attempts failed to produce the desired N-methylated product. However, the aniline has been methylated with methyl iodide under a pressure of 5 000-5 500 atmos. at 100 °C in dioxane or without solvent.[13] We do not have the facilities to methylate the dithienyl- and difurylpyridines under the high pressure, but this may be the only way to effect quarternisation of these compounds in the future.

3.1.2 2,5-Di(heteroaryl)pyridines

Similarly, in order to synthesise the 2,5-dithienylpyridines and 2,5-difurylpyridines according to the Paal-Knorr procedure the precursor is 2,5-diformylpyridine. It is commercially available, but very expensive. In view of the ready availability of pyridine-2,5-dicarboxylic acid, this compound was chosen as the starting material and we adopted the reduction-oxidation procedure. Pyridine-2,5-dicarboxylic acid was esterified to give the dimethyl ester in 81 % yield with BF_3-MeOH complex in MeOH using a procedure described by Hallas[14] for the preparation of methyl benzoate. Esterification with methanol in sulphuric acid gave 67 % yield of methyl ester, while the corresponding reaction with ethanol gave the diethyl ester in same yield as that of dimethyl ester. Both esters were characterised by comparison of melting point and spectral data with those reported in the literature.

2,5-Bis(hydroxymethyl)pyridine was obtained in 9 % yield by reduction of the dimethyl ester with excess $LiAlH_4$, but treatment of the diester with $NaBH_4$ at *ca.* -5 °C with $CaCl_2$ gave the bis(hydroxymethyl) compound in 51 % yield. Oxidation of the 2,5-dicarbinol to the 2,5-dialdehyde using MnO_2 proved a failure, while the 2,6-dicarbinol gave, under same conditions, a 54 % yield. No evidence for the formation of an aldehyde group was obtained.

At this point, it was decided to explore a more efficient preparation of the aldehydes using the Swern oxidation procedure.[15-19] The chlorodimethyl sulphonium chloride, prepared from dimethyl sulphoxide and oxalyl chloride at -60 °C as shown in Scheme 3.3, was allowed to react with the dicarbinol solubilized in dichloromethane and dimethyl sulphoxide at -60 °C in the presence of triethylamine. Analysis by TLC showed the formation of a product, which on analysis by ^{1}H NMR spectroscopy showed a singlet for the aldehyde groups. Repeating the reaction under modified conditions gave two products, the formation of which was monitored by TLC. The ^{1}H NMR spectrum showed the two expected singlets for the 2,5-dialdehyde groups. However, the yield of the product mixture was only 13 % and the two products could not separated. At this point it was apparent to us that the preparation of 2,5-diformylpyridine by oxidation of the dicarbinol was not suitable. We therefore considered the

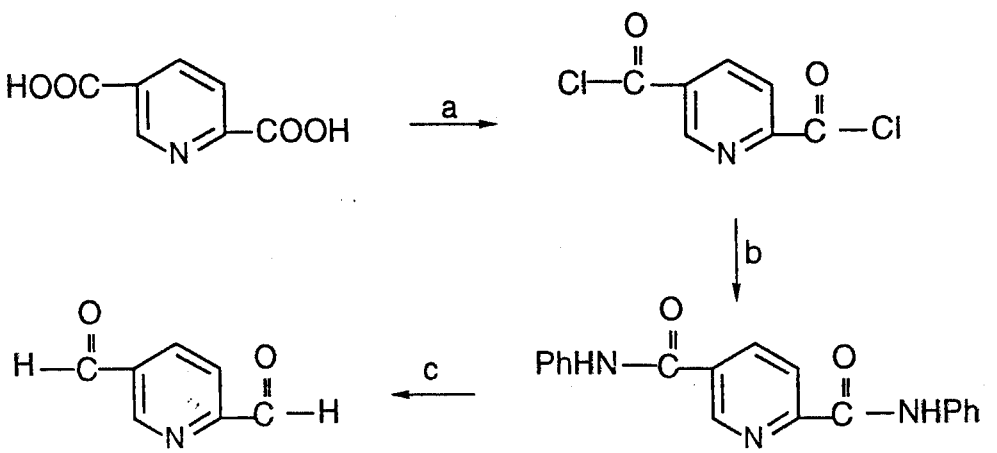


Scheme 3.3

reduction of diamides with $LiAlH_4$ in dioxane to give the dialdehydes (Scheme 3.4). The first problem to overcome was the preparation of the pyridine-2,5-dicarboxamide. Pyridine-2,5-dicarboxylic acid was easily converted into the pyridine-2,5-dicarbonyl chloride (82 %) which, although fully characterised spectroscopically, failed to give satisfactory elemental analytical data owing to hygroscopic nature and sensitivity to air, light and heat.

A reaction of the pyridinedicarbonyl chloride with N-methylaniline in THF was achieved in high yield (91 %) and the anilide was characterised by amide ν_{CO} frequencies at 1 665 and 1 600 cm^{-1}, compared with the carbonyl chloride absorption at 1 775 and 1 745 cm^{-1}. The ^1H NMR showed two singlets at 3.02 and 3.04 ppm, attributed to the N-methyl protons, and signals between 6.80 and 8.16 ppm integrated for thirteen hydrogens, corresponding to the aromatic protons, pyridine and benzene protons.

Reduction of the anilide with excess $LiAlH_4$ at room temperature for five hours failed to produce the dialdehyde. TLC analysis showed some base-line material, starting material, and four other products. The ^1H NMR spectrum showed two singlets for the dialdehyde groups, but attempted purification was

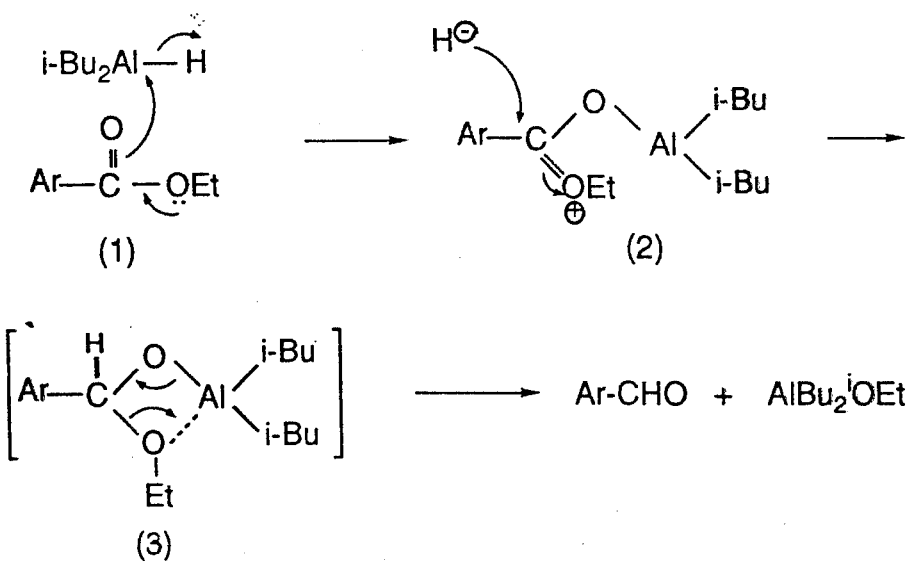


(a)$SOCl_2$, DMF, reflux, 3 h; (b) NHMePh, THF, r.t. 1 h; (c) $LiAlH_4$, THF, 15°C, 5h

Scheme 3.4

unsuccessful. It was therefore decided to apply a direct one-step reduction of esters to aldehydes by use of DIBAL-H,[20,21] as steric effects might be expected to prevent further attack by hydride ion on the chelated complex (3), as seen in Scheme 3.5. Methyl pyridine-2,5-dicarboxylate was reacted with DIBAL-H in THF at -70 °C for 3 hours and produced methyl-2-formylpyridine-5-carboxylate in 31 % yield. The known compound was characterised by comparison of melting point and spectral data with those reported in the literature. When the reaction was repeated under the same conditions for 24 hours, the dialdehyde was obtained and was fully characterised.

The reaction of 2,5-diformylpyridine with but-3-en-2-one in the presence of thiazolium catalyst gave the expected 1,4-diketone in 69 % yield (2,6-diformylpyridine gave a 76 % yield under the same conditions). The conversion into the unknown diketone was confirmed by the absence of aldehyde protons at 10.26 and 10.28 ppm in the ^{1}H NMR spectrum and the appearance a two singlets at 2.24 and 2.25 ppm assignable to the methyl groups. A multiplet



Scheme 3.5

between 2.82 and 3.58 ppm integrating for eight protons is attributed to the methylene protons. ^{13}C NMR spectrum showed fifteen resonance signals; those at 197.1, 199.6, 206.5 and 206.8 ppm are attributable to the four carbonyl groups (cf. the signals at 189.8 and 192.3 ppm for starting dialdehyde).

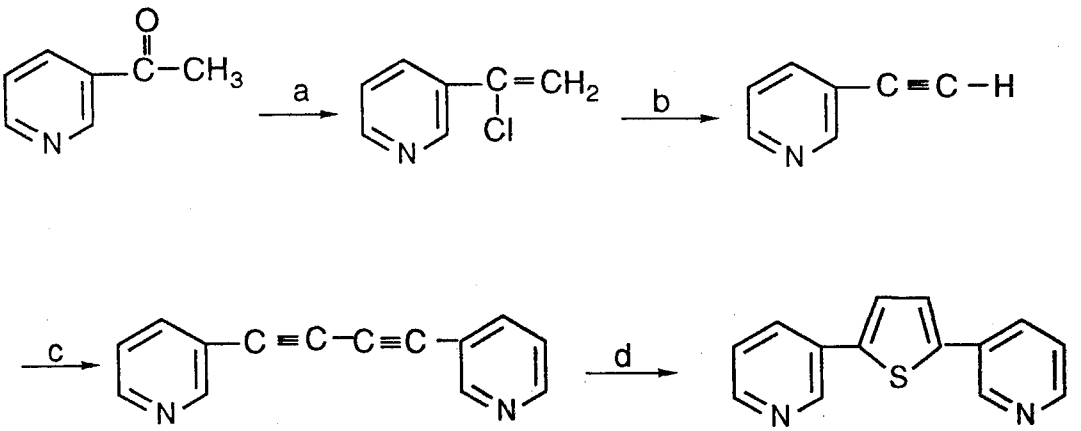
Cyclization of the 1,4-diketone with Lawesson's reagent was achieved in 61 % yield by refluxing in toluene for 50 hours (cf. the corresponding 2,6-di(2-thienyl) pyridine was isolated in 55 % yield). Structural identification of the 2,5-bis(2-methyl-5-thienyl)pyridine was obtained by comparison of spectroscopic data with those of the 1,4-diketone. Attempted methylation of this compound using the standard procedure with methyl iodide in ethanol or in the absence of a solvent was a failure. The reaction was not repeated at high temperature and in a sealed tube, because of the lack of time.

Unexpectively, cyclization of the 1,4-diketone with polyphosphoric acid in the usual way failed. Time and the lack of starting material did not allow further investigations of these compounds.

3.2 Symmetrical Dipyridylaryl Systems

Only two published methods describe the preparation of 2,5-dipyridyl thiophenes and there is no example of the preparation of the 2,5-dipyridylfurans in the literature. In 1963, Schulte and co-workers[22] reported a reaction which starts from 1,4-di(3-pyridyl)buta-1,3-diyne[23] and hydrogen sulfide to give 2,5-di(3-pyridyl)thiophene in 74 % yield, as shown in Scheme 3.6.

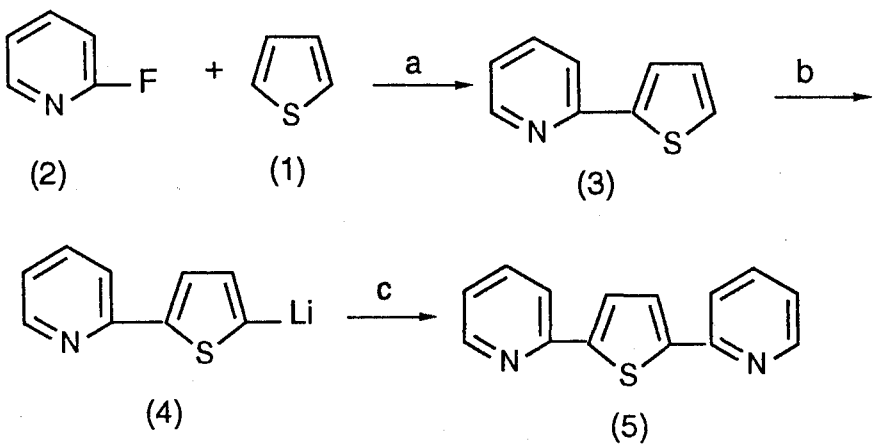
In 1971, Kauffmann *et al.*[24] described a new route to dipyridylthiophenes, but in a yield of only 7 %. The procedure is based on a lithiation reaction between 2-fluoropyridine (2) and lithiated 2-(2-pyridyl)thiophene (4), in anisole at 154 °C, as shown in Scheme 3.7. The 2-(2-pyridyl)thiophene precursor (3) was



(a) PCl_3, 50%; (b) KOH, 42 %, (c) Na, 34 %; (d) H_2S, 74 %

Scheme 3.6

also obtained in 48 % yield from a reaction of 2-fluoropyridine with thiophene (1), which is initially lithiated with *n*-butyllithium in ether at 0 °C.

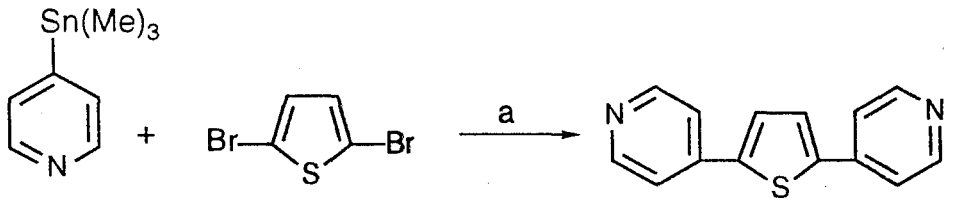


(a) *n*-BuLi, ether, 35 °C, 2 h, 48 %; (b) *t*-BuLi, THF, -60 °C; (c) (2) in anisole, 154°C, 5 h., 7 %.

Scheme 3.7

Subsequent to our experimental work, Takahashi co-workers[25] published another synthetic route to dipyridylthiophenes and furans in 50-60 % yield using a palladium mediated cross-coupling reaction between 4-trimethylstannyl

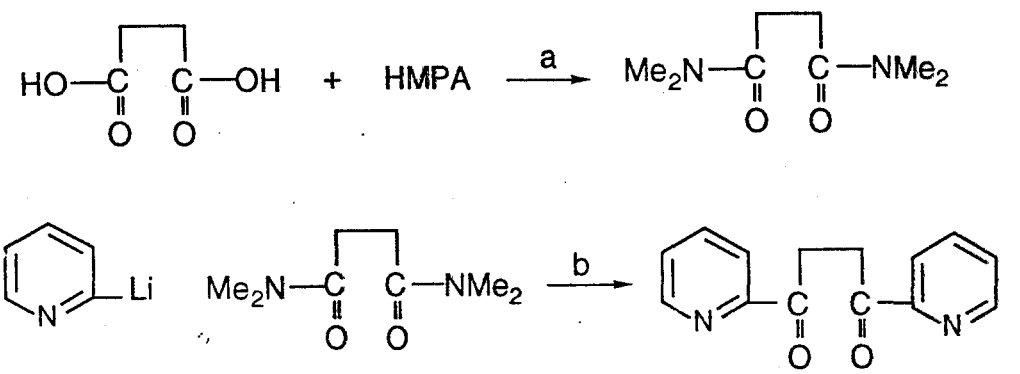
pyridine[26] and corresponding 2,5-dibromothiophene or furan, as outlined in Scheme 3.8.



(a) $Pd[P(Ph)_3]_4$, toluene, reflux.

Scheme 3.8

In our synthesis of the symmetric dipyridylthiophene or furan we adopted the Paal-Knorr approach from symmetric dipyridyldiketones. The key step was the preparation of the symmetrical diketones for which there was a ready one-step reaction available in the literature. Aldehydes and ketones have been prepared from the reaction of N,N-dialkylamides with either Grignard reagents[27,28] or organolithium compounds,[29-33] and it has been reported that diketones are produced in low yield by this reaction. For example, Osley and co-workers[34] described the preparation of 1,4-di(2-pyridyl)butan-1,4-dione in 20 % yield from 2-lithiopyridine and N,N,N',N'-tetramethyl succinamide, at -78 °C, as

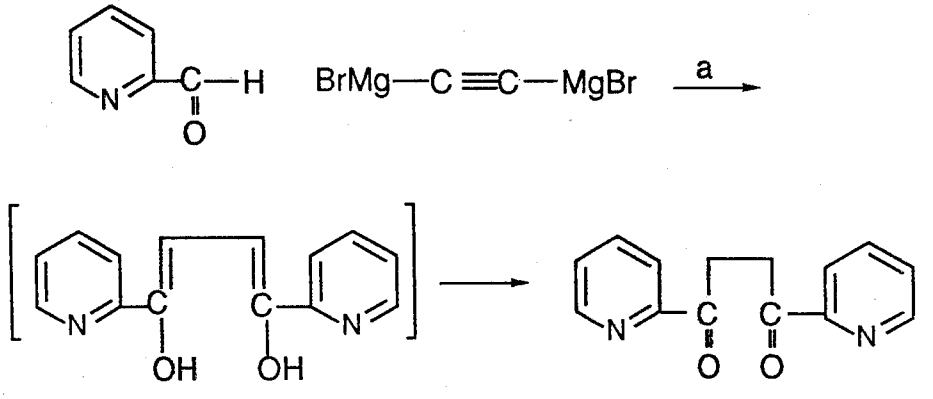


(a) 180-200°C, 2 h; (b) ether, -78 °C, 4 h.

Scheme 3.9

shown in Scheme 3.9. Tetramethyl succinamide[35-38] is readily prepared from a reaction of succinic acid (92 %) or succinic anhydride (32 %) with HMPA.

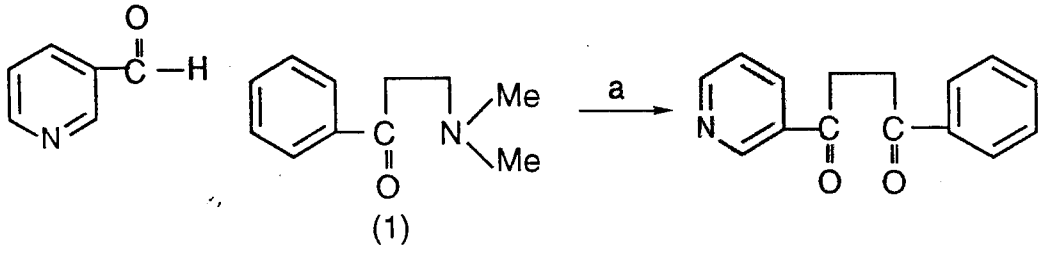
In a different approach, Newcome[39] reacted 2-formylpyridine with the acetylene Grignard reagent to yield 1,4-bis(2-pyridyl)butane-1,4-dione (25 %). The reaction mechanism can be thought to be a double protropic rearrangement of the initially formed 1,4-dihydroxybut-2-yne (Scheme 3.10).



(a) ether, r.t, 3 h.

Scheme 3.10

In 1977, Stetter[40] showed that it is possible to prepare 1,4-diaryl-1,4-diketones *via* the thiazolium salt or cyanide-catalysed addition of arylaldehydes to Mannich bases of saturated or unsaturated arylketones (1). Using this route, Stetter prepared 1-(3-pyridyl)-4-phenylbutan-1,4-dione in 35 % yield (Scheme 3.11).

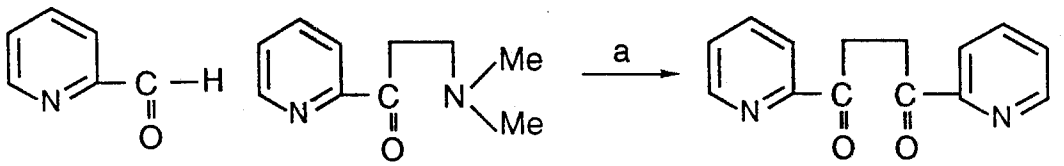


(1)

(a) CN^-, DMF, reflux, 3 h.

Scheme 3.11

Karatza[41] has since used same route to prepare 1,4-di(2-pyridyl)butan-1,4-dione in 36 % yield. In this reaction, 2-formylpyridine is condensed with the Mannich base derived from 2-acetylpyridine in the presence of a catalytic amount of the thiazolium ylide (Scheme 3.12).

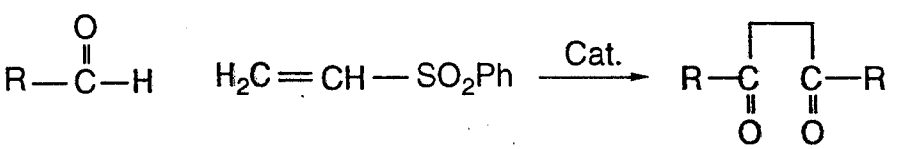


(a) thiazolium salt, DMF, triethylamine, 85 °C.

Scheme 3.12

In a more direct procedure, Stetter and Bender[42,43] obtained the diaryl-1,4-diketones in acceptable yields from the thiazolium ylide catalysed addition of arylaldehydes to divinylsulphone. Their reported yields are 46 and 48 % for the 1,4-diphenyl and 1,4-di(2-thienyl) derivatives, respectively.

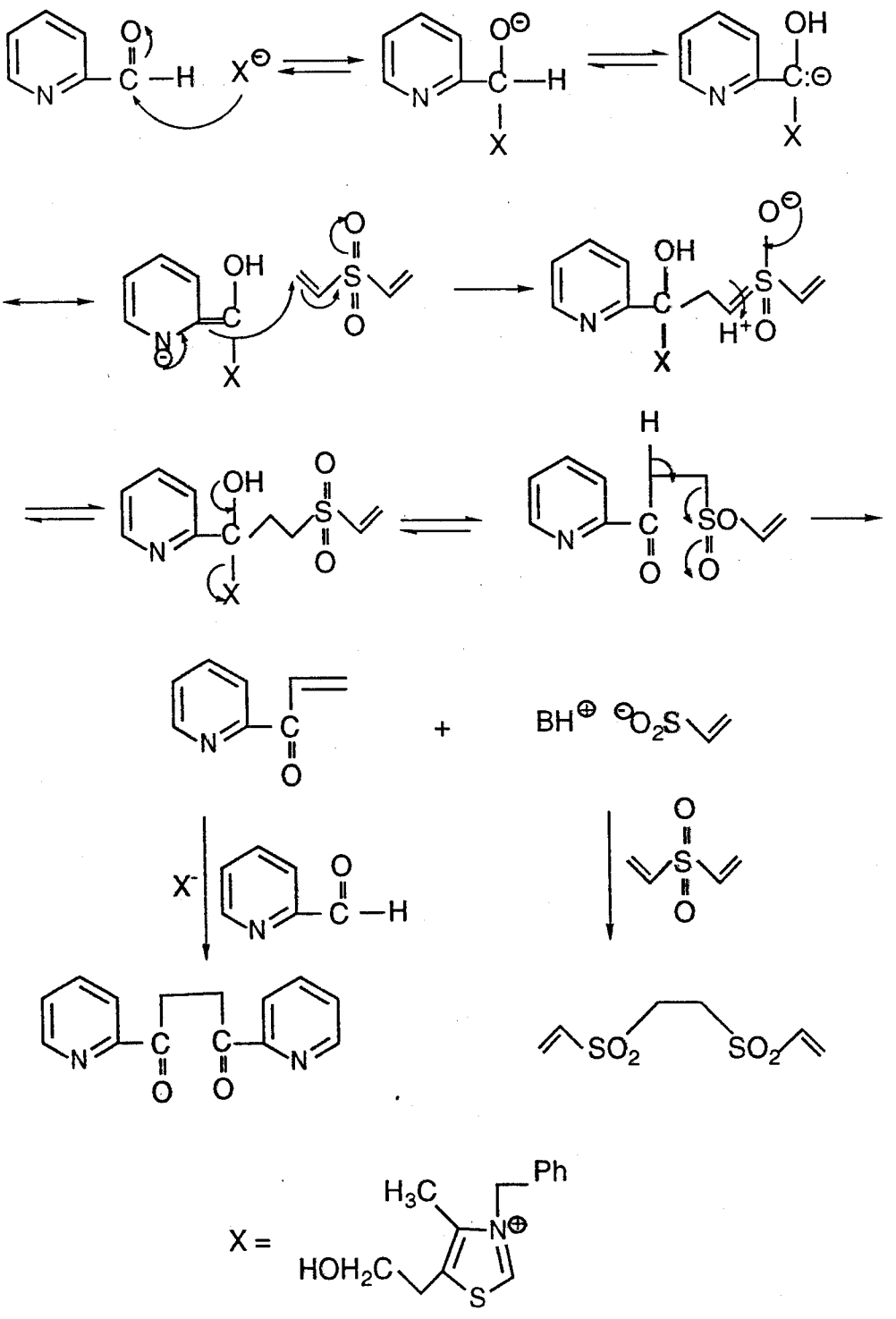
In 1983, El-Hajj and co-workers[44] used same route for the preparation of the 1,4-di(2-furyl) compound in 51 % yield, and more recently, Merril and Goff [45] reported that the high yielding (75 %) reaction of 2-formylpyrrole with phenyl vinylsulphone. We have now exploited this route for the pyridine systems.



R: Ph (46 %), or 2-thienyl (48 %)

Scheme 3.13

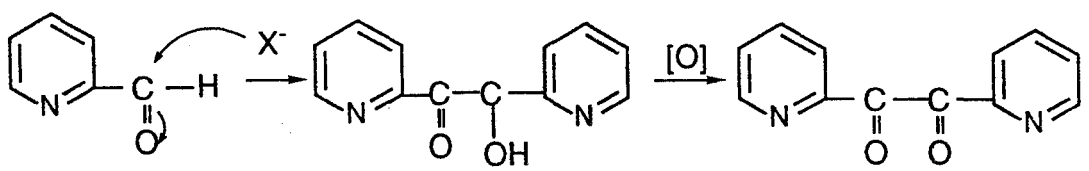
In our extension of this route for the synthesis of three-ring systems, we employed the three-step addition-elimination mechanism reaction of 2- and 3-



Scheme 3.14

formylpyridines with divinylsulphone. However, handling of divinyl-sulphone caused a health problem and the preparation from 4-formyl pyridine was not carried out. The 4-isomer was later prepared by Whitmore[46] in *ca.* 45 % yield, using same procedure. The reaction mechanism leading to the symmetrical dipyridyl-1,4-diketones is outlined in Scheme 3.14 for 2-formylpyridine.

When we used sodium acetate as a base and ethanol as a solvent, yields were 17 and 13 % for 2- and 3-formyl pyridines, respectively, whereas, when we used triethylamine and 1,4-dioxane, the yields were increased to 28 and 39 %. It is interesting to notice that in this procedure, 3-formylpyridine reacts with divinyl sulphone to give only the 1,4-diketone, but in the reaction of 2-formylpyridine the benzoin-type reaction becomes a major pathway and the isolated product is 1,2-di(2-pyridyl)ethan-1,2-dione (2), which is probably formed by air oxidation of the pyridoin (1) in Scheme 3.15.



Scheme 3.15

The structure was consistent with that described by other investigators[47,48] and showed absorption due to the carbonyl groups at 1 690 and 1 710 cm^{-1} in infrared spectrum and the typical signal at 197.0 ppm in ^{13}C NMR spectrum. Characterisation of the compound was accomplished by the elemental analysis, mass spectrum and its ^{1}H NMR spectrum.

Spectral identification of the 1,4-diketones was obtained from the spectroscopic data. In particular, the formation of the 1,4-diketone was

accompained by appearance of the $\nu_{C=O}$ band at 1 695 cm^{-1} in the infrared spectrum and the signal at 200.4 ppm in the ^{13}C NMR sectra. Additionally, the ^{1}H NMR spectra showed a singlet *ca.* 3.5 ppm, attributable to the methylene group.

Cyclization of the 1,4-diketones with Lawesson's reagent in toluene for 50 hours gave the symmetrical 2,5-dipyridylthiophenes in 37-53 % yields. The spectral data for the three isomeric dipyridylthiophenes are in agreement with their structures.

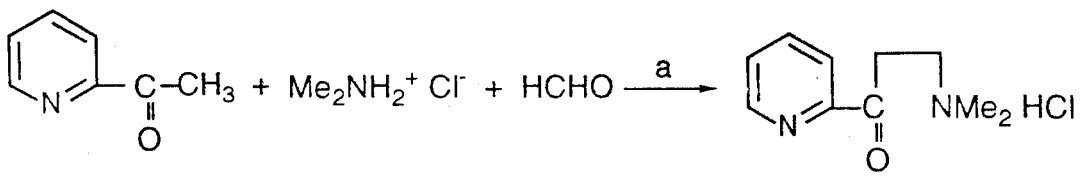
In order to obtain the symmetrical dipyridylfurans, the corresponding 1,4-diketones and polyphosphoric acid were heated at 130-140 °C for 5 hours to produce the 2-, 3-, and 4-isomers in 82, 92, and 55 % yields, respectively. The formation of the previously unknown dipyridylfurans was established by comparison of spectral data with those of the starting materials. The disappearance of the methylene protons at *ca.* 3.5 ppm and the location of all the resonance signals between 6.80 and 8.65 ppm showed of the fully aromatic compounds. The ^{13}C NMR spectra also showed fully aromatic carbons between 108 and 152 ppm.

In contrast with the 3- and 4-isomers, it proved impossible to quarternise the 2,5-(2-pyridyl)thiophene and furan using the standard procedures. The only successful approach required the reaction of the 2-isomers with methyl iodide in the absence of a solvent at 100 °C in a pressure vessel for two weeks. In this way, we obtained the dimethylated products in high yields (> 90 %). Heating with methyl iodide at 100 °C in a pressure vessel for 50 hours gave only the monomethylated product in 92 % yield, whereas heating under the same conditions for a week gave a mixture of the mono- (37 %) and dimethylated (61 %) derivatives. Evidence for the successful quarternisation of the dipyridylfurans and thiophenes was normally obtained by observed shifts to *ca.*

1 630 cm^{-1} in the infrared spectra and appearence in the ^1H NMR spectra of an extra methyl singlet at *ca.* 4.40 ppm and with the aromatic signals for the pyridine ring being shifted downfield by a few ppm. The ^{13}C NMR spectrum and elemental analysis data also support the proposed structures, but again the mass spectra do not give the expected results for the pyridinium salts. The mass spectral data of 3- and 4-isomers showed the main parent structures but with the cleavage of the N-methyl group, while the mass spectrum of 2,5-di(2-pyridyl)thiophene unexpectedly showed a peak corresponding to *m/z* 319, which is 71 a.m.u. greater than that expected for the product and a large number of fragments, with the base peak at *m/z* 142. Similarly, for 2,5-di(2-pyridyl)furan, the highest mass corresponds to *m/z* 280, which is 58 a.m.u. greater than expected, and the base peak is at *m/z* 142 again. No rational explanation can be given for these results.

3.3 Unsymmetrical Systems

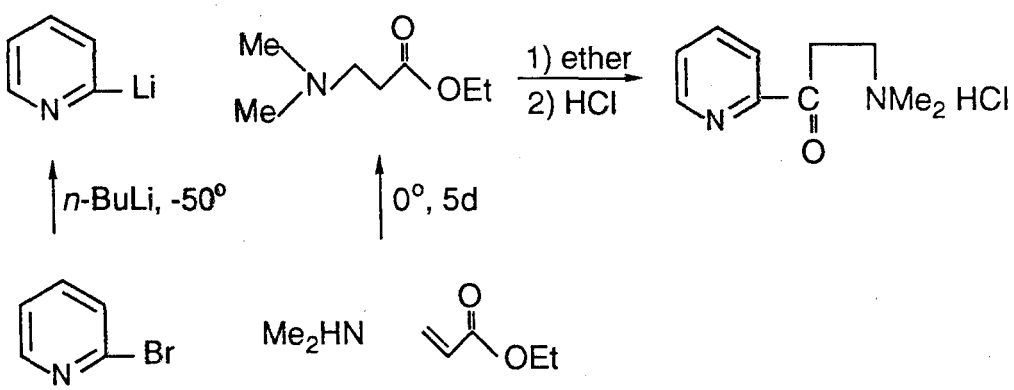
In order to prepare unsymmetrical dipyridylthiophenes or furans by the Stetter approach, the heteroarylaldehydes were condensed with the appropriate Mannich bases of the arylketones in the presence of the thiazolium ylides, or cyanide ions, as described in Section 3.2 for symmetrical systems. The Mannich bases of the pyridine[47-50] were obtained from the reaction of the appropriate acetylpyridine with formaldehyde and dimethylamine, as shown in Scheme 3.16 for the preparation of 3-(N,N-dimethylamino)-1-(2-pyridyl) propane-1-one. The product was obtained in 29 % yield but it was found to be unstable and heating at *ca.* 60 °C resulted in extensive decomposition. We therefore resorted an alternative strategy for the preparation of 3-(N,N-dimethyl-amino)-1-(2-pyridyl)propane-1-one. Ethyl 3-dimethylamino propionate[51] obtained in 87 %



(a) EtOH, reflux, 3 h.

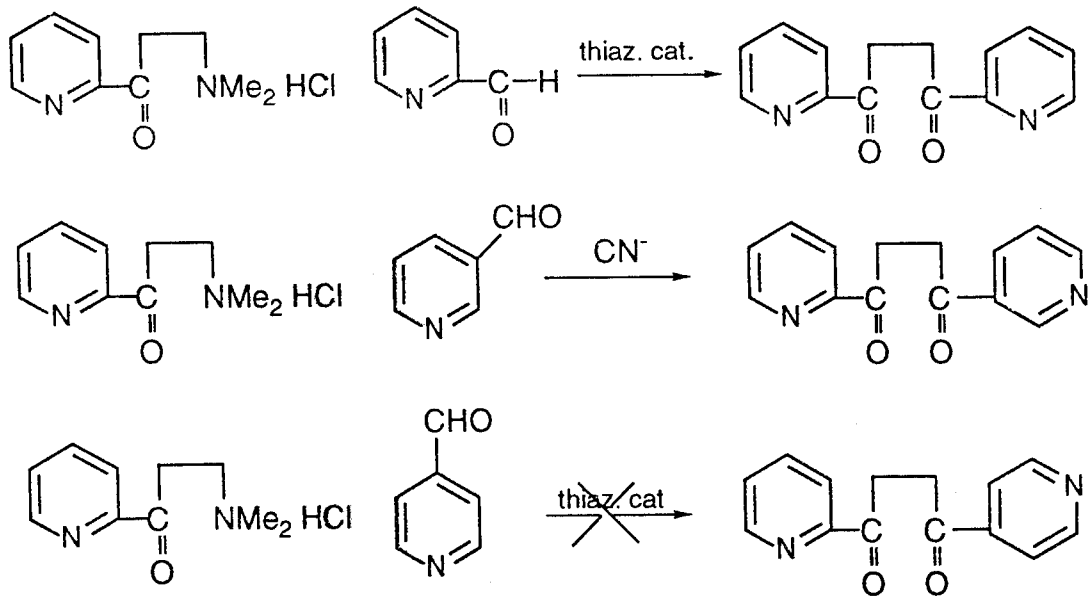
Scheme 3.16

yield from the reaction of anhydrous dimethylamine with ethyl acrylate at 0 °C over a period of 5 days, was allowed to react with 2-pyridyllithium, obtained from 2-bromopyridine and *n*-butyllithium at -50 °C, as shown in Scheme 3.17. The product was used without further purification for the Stetter conversion into the unsymmetrical diketones.



Scheme 3.17

A satisfactory result was obtained for the thiazolium ylide-catalysed condensation of the Mannich base with 2-formylpyridine, but the reaction with 3-formylpyridine only took place with cyanide ions as a catalyst.[41] In our attempt to prepare 1-(2-pyridyl)-4-(4-pyridyl)butane-1,4-dione, we used the thiazolium ylide catalyst, but again the condensation reaction failed (Scheme 3.18). There was insufficient time to investigate this approach further.



Scheme 3.18

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CHAPTER 4

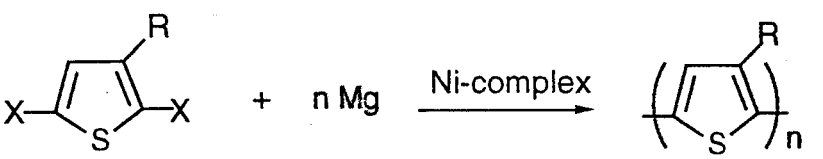
HETEROCYCLIC POLYMERS

4.1 Introduction

As mentioned in Chapter 1, the synthesis and chemical, physical and electrical properties of π-conjugated polymers are subjects of recent interest. For example, all reported syntheses of polythiophenes (1) are based on ring coupling reactions, either electrochemically,[1-4] or by Grignard type reactions of 2,5–dibromothiophene[5-8] using a Ni or Pd complex as a catalyst (Scheme 4.1).

Yamamoto and co-workers[9] prepared polythiophenes and poly(3-alkylthiophenes) (2) from dibromothiophene derivatives. Hotta[10] made same compounds and found that the conductivity of the poly(3-methylthienylene) film is approximately ten times higher than that of a polythienylene film. Later, this result was also supported by Sato.[11,12]

Bryce and co-workers[13] have also reported the electrochemical preparation of poly(3-alkylthiophenes) (3, 4, and 5). Havinga and Horssen[14] have published an electrochemical polymerization of 3-(n-butyl)thiophenes and found that its conductivity in doped state is of the order of 0.1 ohm^{-1} cm^{-1}.



X : Br, I

(1) R : H

(2) R : Me

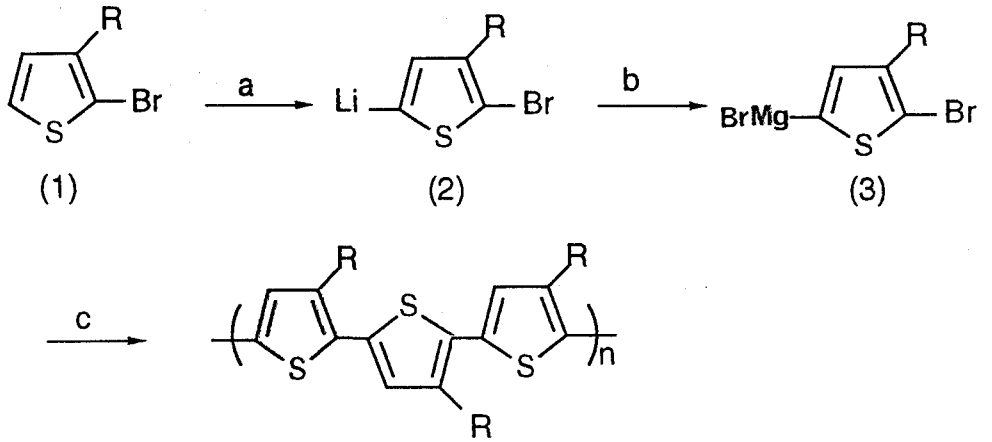
(3) R : $(CH_2)_nMe$ n: 5, to 19

(4) R : $CH_2O(CH_2)_2OMe$

(5) R : $OCH_2NHCO(CH_2)_{10}Me$

Scheme 4.1

Poly(3-alkyl)thiophenes (4) were synthesized from 2-bromo-3-alkyl thiophenes[15] in a one-pot reaction as shown Scheme 4.2. Compound (3) then polymerized through the use of a nickel catalysed cross-coupling reaction to give poly(3-alkyl)thiophenes in 20 to 69 % yield. The oxidation of poly(3-dodecylthiophene) with I_2 exhibit an average conductivity of 600 ohm^{-1} cm^{-1}.



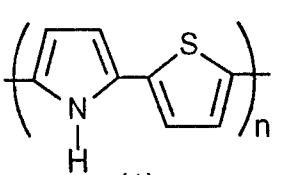
(4)

R : Me, *n*-butyl, *n*-hexyl, *n*-octyl, and *n*-dodecyl

(a)LDA, THF, -40 °C; (b)$MgBr_2$ OEt_2, -60 °C; (c)Ni-1,3-bis(diphenyl phosphino) propane, -5-25 °C.

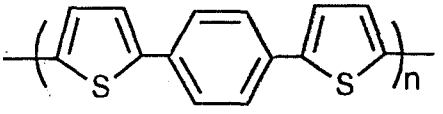
Scheme 4.2

Naitoh[16] have used same procedure to produce a copolymer of thiophene and pyrrole. Poly(thienylpyrrole) (1) has a higher conductivity (up to 3.3 ohm^{-1} cm^{-1}) than the homopolymers.



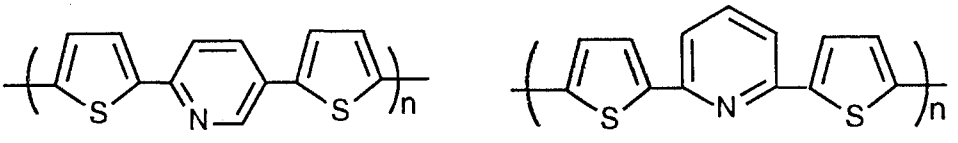
(1)

Danieli and co-workers[17] have shown that electrochemical polymerization of 1,4-di(2-thienyl)benzene leads to a polymer (Scheme 4.3) with an electrical conductivity of $1x10^{-4}$ ohm^{-1} cm^{-1} when doped with ClO_4^- ions. Montheard[18] and Mitsuhara[19] have also obtained same result for this compound.



Scheme 4.3

By following the same procedure on pyridine-thiophene compounds, Tanaka and co-workers[20,21] synthesised the polymers (1) and (2) with the conductivity of about 10^{-2} ohm^{-1} cm^{-1} by iodine doping (Scheme 4.4).

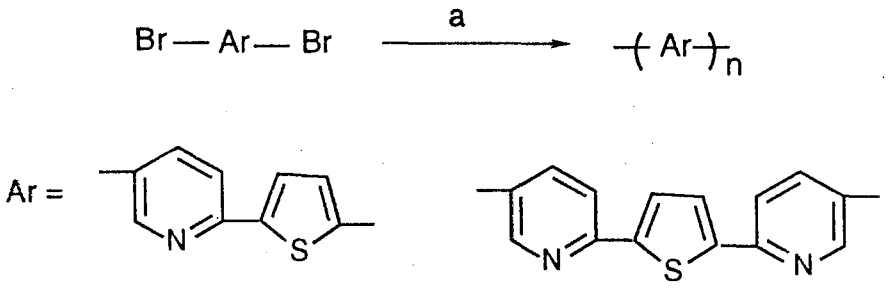


(1) (2)

Scheme 4.4

Subsequent to the completion of our experimental work, Zhou and co-workers[22] published another synthetic route to pyridine-thiophene polymers in 95-100 % yield using a nickel(0) complex based polymerisation, as illustrated in Scheme 4.5.

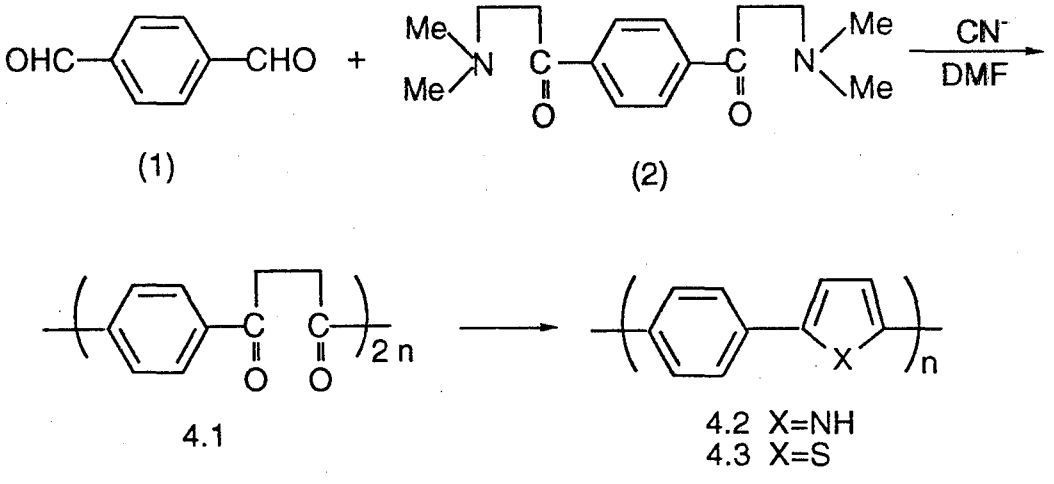
It was not until the work of Wynberg and co-workers[23] and by research in this laboratory[24] that the synthesis of benzene-thiophene, benzene-pyrrole and pyridine-pyrrole polymers from a polymeric precursory, were reported. Thus, poly-(1,4-phenylenebutane-1,4-dione) (4.1) was obtained from the reaction of



(a) $Ni(cod)_2$, DMF, 60-80 °C

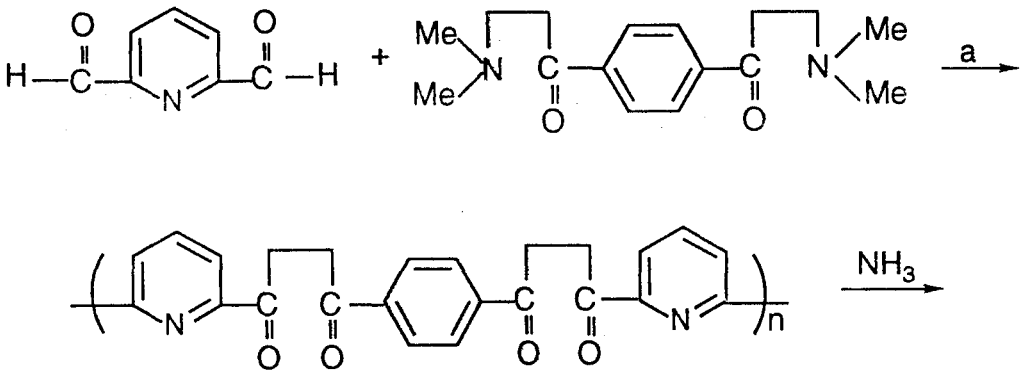
Scheme 4.5

1,4-diformylbenzene (1) and the bis-Mannich base of 1,4-diacetylbenzene (2), using sodium cyanide as a catalyst (Scheme 4.6), and subsequently converted into the thiophene and pyrrole systems (4.2 and (4.3).

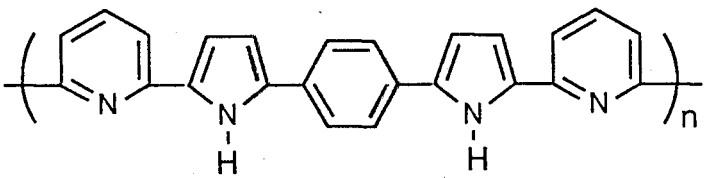


Scheme 4.6

Karatza's synthesis[24] of the polymer (4.2) and analogous polymers (4.5), (4.7), utilized the analogous procedure from the pyridinediketone polymer (4.4), obtained from 2,6-diformylpyridine and the bis-Mannich base of 1,4-diacetylbenzene using a thiazolium ylide catalyst, in the case of polymer (4.5) as illustrated Scheme 4.7 and from the bis-Mannich base of 2,6-diacetylpyridine and 2,6-diformylpyridine, for the preparation of (4.7) (Scheme 4.8).



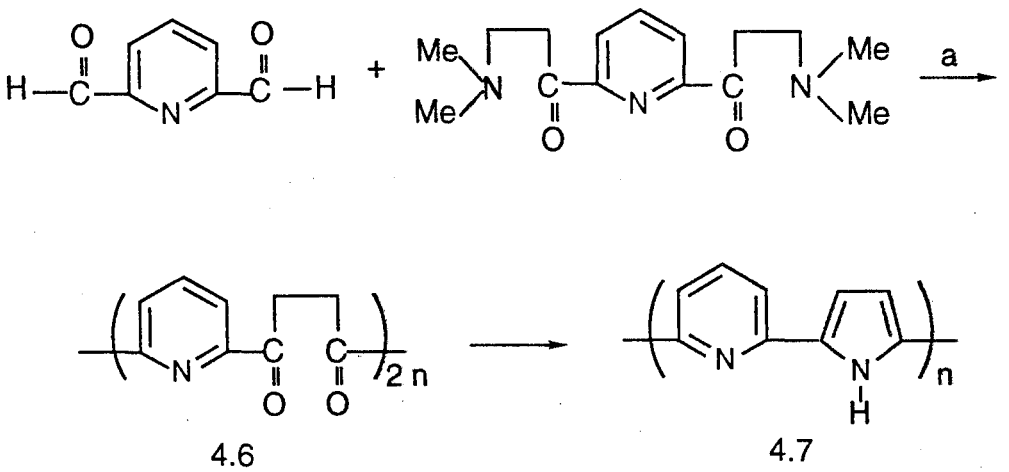
4.4



4.5

(a) thiazolium cat., Et_3N, DMF

Scheme 4.7



4.6 4.7

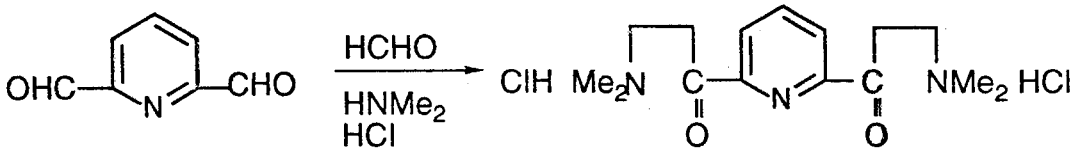
(a) thiazolium cat., Et_3N, DMF

Scheme 4.8

4.2 Results and Discussion

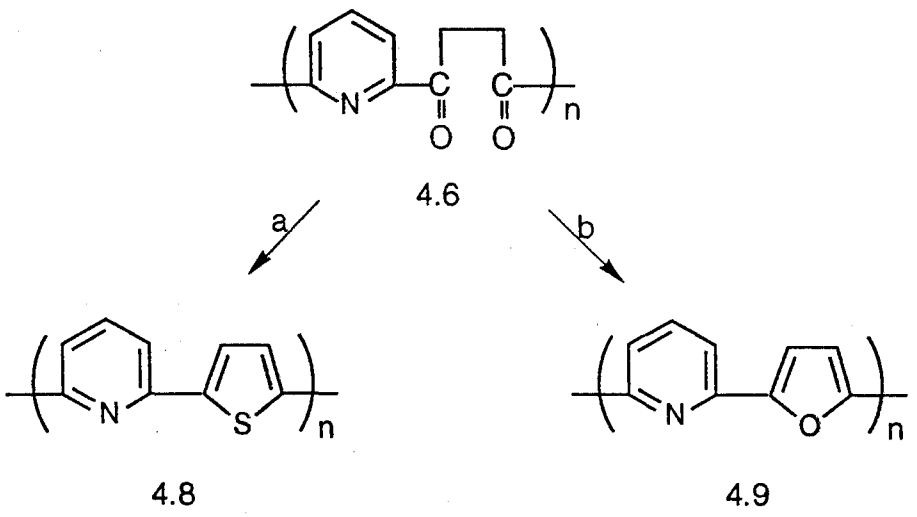
The Stetter reaction,[25-27] as used for the synthesis of the simple 1,4-diketones (Chapter 2), is readily adapted to the synthesis of the polymeric systems from the appropriate diformylarene and Mannich bases.

A key precursor for the preparation of the polymers is the bis-Mannich base of 2,6-diacetylpyridine. However, it was found that there were real problems in the preparation of this Mannich base, in spite of the synthesis of this compound having been described by Khronke,[28] but the synthetic procedure and the spectroscopic data of the compound were not given in detail. Karatza subsequently modified the Khronke synthesis and obtained the product in satisfactory yield. Employing the same method, we synthesised the 2,6-bis(3-N,N-dimethylamino-1-oxopropyl)pyridine dihydrochloride in 45 % yield (Scheme 4.9). However, the product was extremely unstable and all the attempts to obtain a satisfactory ^{1}H NMR spectrum failed. We could not obtain any spectral data for this compound and the product was used without further purification.



Scheme 4.9

In the course of our studies, we have carried out the reaction of 2,6-diformylpyridine and the bis-Mannich base of 2,6-diacetylpyridine in DMF using a catalytic amount of thiazolium ylide as the catalyst. In order to remove low molecular species, the product was washed thoroughly with variety of



4.6

4.8 4.9

(a) Lawesson's reagent, 1,2-dichlorobenzene, 190 °C, 50 h; (b) polyphosphoric acid, 180-190 °C, 12 h.

Scheme 4.10

solvents which let to the isolation of the target polymer (4.6) (Scheme 4.10). The polymer was readily characterised by its IR spectra, which showed a predominant absorption band at 1 690 cm^{-1}, indicating the presence of carbonyl groups. Further evidence for the proposed structure was afforded by the solid state ^{13}C NMR spectra, which showed total of five carbon atom resonances with a signal at 199.7 ppm, indicating the presence of the carbonyl group and three signals at 125.6; 137.8 and 151.4 ppm attributable to the pyridine carbon atoms. The remaining one signal at 34.9 ppm was assigned to the methylene carbon atom.

The solid state ^{13}C NMR spectra of the polymers 4.6, 4.8, and 4.9 correlate very well with the ^{13}C NMR spectral data of the simpler monomeric systems. Table 4.1 summarise the ^{13}C NMR spectral data for the various monomeric systems and Table 4.2 shows the ^{13}C chemical shifts for the polymers with the data from Table 4.1. For polymer 4.6, with the exception of the methylene signal, there is a good match between the data for the polymer and that for the

monomer. Because the system is symmetrical, there are only three signals for the pyridine ring and, in view of the fact that the spectra are measured in different phases, there is a good correlation in the chemical shifts of the carbonyl signals.

The Paal-Knorr ring closure of the diketones to the polymeric thiophene and furan systems required more severe conditions than these used for the formation of the simple monomeric systems. The polymeric diketone was reacted with Lawesson's reagent in 1,2-dichlorobenzene at 190 °C for 50 hours. The pyridine-thiophene polymer (4.8) showed aromatic absorption bands at 1 595, 1 565, 1 500 and 1 445 cm^{-1} in IR spectrum. The absence of the any carbonyl absorption in IR and also ^{13}C NMR spectra confirmed the complete cyclisation to the heteroaromatic rings. The solid state ^{13}C of the polymer (4.8) correlates well with the ^{13}C NMR spectral data for the monomeric system (Table 4.1).

Cyclisation of the polymeric diketone with polyphosphoric at 180-190 °C for 12 hours produced the polymeric pyridine-furan system (4.9). Measurement of the solid state spectrum of the proposal structure (4.9) was less successful. The six signals at 123.2, 136.5, 144.4, and 148.1 ppm correlate with the shifts expected for the pyridine and furan rings, but one signal at around 110.0 ppm for the β-carbon atom of the furan ring was not observed.

Table 4.1 ^{13}C NMR Chemical Shifts for Substituted Pyridines

2-Pyridyl Systems:	Pyridine ring					furan or thiophene ring				CH_2/CH_3		
	α	α	δ	β	β	α	α	β	β			
-$COCH_2CH_2CO$-Me	153.6	148.5	136.6	127.0	121.5	-	-	-	-	36.7	32.5	29.8
-$COCH_2CH_2CO$-2-Py	153.3	148.9	136.8	127.1	121.7	-	-	-	-	32.1	-	-
-(2,5-C_4H_2S)-Me	152.8	149.4	136.4	127.5	124.6	142.3	142.4	121.3	118.2	-	-	15.6
-(2,5-C_4H_2S)-2-Py	152.1	142.5	136.9	126.2	124.6	142.4	-	115.6	-	-	-	-
-(2,5-C_4H_2O)-Me	149.6	149.5	136.4	121.2	118.0	153.4	152.1	109.8	108.3	-	-	13.7
-(2,5-C_4H_2O)-2-Py	149.6	149.0	136.5	122.1	118.7	154.0	-	111.0	-	-	-	-
3-Pyridyl Systems:												
-$COCH_2CH_2CO$-Me	153.4	149.2	135.2	131.8	123.5	-	-	-	-	36.7	32.5	29.8
-$COCH_2CH_2CO$-3-Py	153.7	149.6	135.4	131.9	123.6	-	-	-	-	32.6	-	-
-(2,5-C_4H_2S)-Me	147.8	146.4	137.8	132.4	123.5	140.9	130.7	126.5	124.1	-	-	15.3
-(2,5-C_4H_2S)-3-Py	148.4	146.4	132.8	129.9	123.7	140.6	-	125.4	-	-	-	-
-(2,5-C_4H_2O)-Me	147.5	144.9	130.0	127.1	123.3	152.9	149.2	108.0	107.4	-	-	13.7
-(2,5-C_4H_2O)-3-Py	148.3	145.3	130.6	126.3	123.5	151.2	-	108.6	-			

4-Pyridyl Systems:

-$COCH_2CH_2CO$-Me	150.8	143.5	142.3	120.9	119.7	-	-	-	-	36.7	32.5	29.8
-$COCH_2CH_2CO$-4-Py	-	-	-	-	-	-	-	-	-	-	-	-
-(2,5-C_4H_2S)-Me	150.2	-	141.6	-	126.7	142.4	138.6	125.4	119.4	-	-	15.6
-(2,5-C_4H_2S)-4-Py	150.4	-	140.5	-	126.4	142.4	-	-	119.6	-	-	-
-(2,5-C_4H_2O)-Me	149.6	-	137.6	-	117.2	154.1	150.1	109.8	108.4	-	-	13.7
-(2,5-C_4H_2O)-4-Py	150.2	-	136.0	-	117.6	151.6	-	-	112.1	-	-	-

Disubstituted Pyridyl Systems:

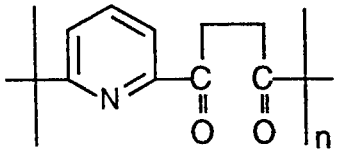
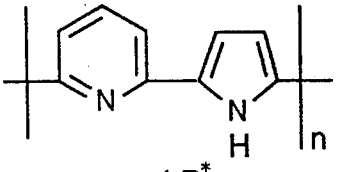
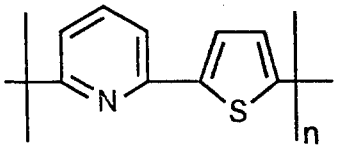
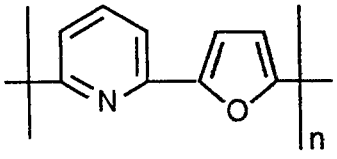
2,6-Substituents

-$COCH_2CH_2CO$-Me	152.2	-	138.0	-	124.8	-	-	-	-	37.0	31.7	29.9
-(2,5-C_4H_2S)-Me	152.1	-	136.9	-	126.4	142.5	142.4	124.6	115.6	-	-	15.6
-(2,5-C_4H_2O)-Me	149.2	-	136.9	-	125.6	153.3	152.2	109.9	108.3	-	-	13.8

2,5-Substituents:

-$COCH_2CH_2CO$-Me	150.8	148.9	138.3	134.2	121.5	-	-	-	-	29.9	32.9	
-(2,5-C_4H_2S)-Me	151.1	146.1	138.2	132.8	121.5	142.4	142.1	124.5	118.6	15.3	15.5	

Table 4.2 Correlations of the Solid State ^{13}C NMR Spectral Data for the Polymers with the Monomeric System.

	Monomer	Polymer	
 4.6	31.7	34.9	CH_2
	124.8	125.6	β-pyridine
	138.0	137.8	δ-pyridine
	152.2	151.4	α-pyridine
	199.5	199.7	C=O
 4.7*	108.5	109.3	α-pyrrole
	126.7	119.9	β-pyridine
	133.2	130.2	β-pyrrole
	132.7	136.5	δ-pyridine
	148.8	148.7	α-pyridine
 4.8	115.6	113.4	β-thiophene
	124.6	123.1	β-pyridine
	136.9	131.6	α-thiophene
	142.4	134.6	δ-pyridine
	152.1	151.0	α-pyridine
 4.9	111.0	?	β-furan
	122.1	123.2	β-pyridine
	136.5	136.5	δ-pyridine
	149.0	144.4	α–pyridine
	154.0	148.1	α-furan

* taken from lit. 24

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CHAPTER 5

EXPERIMENTAL

5.1 General Procedures

Materials available commercially were used without further purification, unless stated otherwise. Benzylchloride, triethylamine, thionyl chloride, and 1,2-dichlorobenzene were distilled prior to use. Light petroleum refers to that boiling in the range 40-60 °C, which was distilled prior to use. Water refers to distilled water. Brine refers to a saturated aqueous solution of sodium chloride. Removal of the solvent means removal of the solvent by distillation under reduced pressure using a rotary evaporator. Solvents which are specified as dry were dried as follows: diethyl ether, tetrahydrofuran, dioxane and toluene were distilled from sodium/benzophenone; benzene was distilled from calcium sulphate; dichloromethane was distilled from calcium chloride; acetonitrile was distilled from phosphorus pentoxide; methanol was predried over molecular sieve and distilled; and chloroform was predried over anhydrous calcium chloride and distilled. *n*-Buthyllithium was titrated prior to use against N-pivaloyl-*o*-benzylaniline, according to the procedure described by Suffert.[1]

Column chromatography was performed at atmospheric pressure using silica gel (Merck 7734). Flash column chromatography was performed according to the procedure described by Still, Kahn and Mitra,[2] on a silica gel (May and Baker Sorpsil C60). Analytical thin layer chromatography (TLC) was performed on aluminium backed silica plates (Merck 5554). Components were visualised by UV irradiation (254 nm).

Melting points were determined on a Kofler hot-stage melting point apparatus and are uncorrected

Microanalyses were performed as a service by Mr. A. W. R. Saunders at the University of East Anglia. ^{1}H NMR spectra were recorded on a Jeol PMX 60 spectrometer (60 MHz), a Jeol EX90 spectrometer (90 MHz), or a Jeol GX 400

spectrometer (400 MHz). ^{13}C NMR spectra were recorded on a Jeol EX90 spectrometer (22.5 MHz), or a Jeol GX400 spectrometer (100 MHz). The ^{13}C spectra of polymers were measured in the solid state using UEA200 spectrometer operating at 50.29 MHz. The spectra recorded on the Jeol GX 400 and Jeol EX90 spectrometers were recorded as a service by Dr. D. J. Massy at the University of East Anglia. For every set of data, the solvent, frequency, and reference are given in that order. Chemical shifts are quoted in parts per million down field from TMS (TMS=0 ppm).

Infra-red spectra were recorded on a Perkin-Elmer 297, 298, or 1720X FT-IR spectrometer.

Low resolution EI mass spectra were recorded as a service by Mr. A. W. R. Saunders at the University of East Anglia on a Kratos MS25 spectrometer.

3.2 Experimental for Chapter 2

3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride.——5-(2-Hydroxy ethyl)-4-methyl-1,3-thiazole (71.6 g, 0.5 mol), freshly distilled benzyl chloride (63.3 g, 0.5 mol) and dry acetonitrile (250 ml) were mixed with stirring. The mixture was heated at reflux for 24 h and then allowed to cool to room temperature. The product was precipitated from the solution on seeding after 12 h. Filtration of the precipitate gave the product, which was washed diethyl ether until colourless, (110.4 g, 82 %), m.p. 141-143 °C (lit.,[3] 140-141 °C).

1-(2-Pyridyl)pentan-1,4-dione.——But-3-en-2-one (35 g, 0.5 mol), 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (16.2 g, 0.06 mol) and dry triethylamine (30.3 g, 0.3 mol) in dry dioxane (40 ml) were heated at 90-100 °C under nitrogen. 2-Formylpyridine (41.73 g, 0.39 mol) in dry dioxane (80 ml) was

added dropwise slowly over a period of 2 h, and the mixture was then stirred at 90-100 °C for further 12 h. The mixture was cooled to room temperature and the solvents were removed under vacuum. Water (300 ml) was added and the aqueous layer was extracted with dichloromethane (3 x 50 ml). The combined organic extracts were washed brine (2 x 25 ml) and dried ($MgSO_4$). Filtration and removal of the solvent gave a crude product, as a dark brown solid and recrystallisation twice from ethanol gave 1-(2-pyridyl) pentan-1,4-dione as a bright brown solid, (45.70 g, 66 %), m.p. 43-44 °C (lit.,[4] 45-46 °C); (Found: C, 67.6; H, 6.0; N, 7.9. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.2; N, 7.9 %); ν_{max} (nujol) 1 730 and 1 710 (C=O), 1 605, 1 590 and 1 575 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 2.22 (3 H, s, CH_3), 2.84 (2 H, t, CH_2), 3.50 (2 H, t, CH_2), 7.20-8.0 (3 H, m, 3-H, 4-H and 5-H), 8.62 (1 H, d, J 4.6 Hz, 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 29.8 (CH_3), 32.5 and 36.7 (CH_2), 121.5, 127.0, 136.6, 148.5 and 153.6 (arom. C), 197.7 and 206.1 (C=O); m/z 177 (M^+, 5 %), 162 (2), 106 (100).

Attempted preparation of 2-methyl-5-(2-pyridyl)thiophene.—(a) 1-(2-Pyridyl)pentan-14-dione (0.35 g, 0.002 mol) and phosphorus pentasulphide (0.44 g, 0.002 mol) were heated at 45 °C, almost and immediately the mixture turned a black polymeric tar, TLC analysis showed mainly dark base-line material and the product could not be identified.

(b) 1-(2-Pyridyl)pentan-14-dione (1.77 g, 0.01 mol) in benzene (50 ml) was added dropwise to a stirred solution of phosphorus pentasulphide (55 g, 0.25 mol) in benzene (100 ml) over a period of about 20 min. The mixture, which turned rapidly from yellow to orange and to dark brown, was refluxed gently for 30 min. Removal of the solvent gave a black polymeric tar, which was analysed by TLC and showed some starting material and some base-line material.

2-Methyl-5-(2-pyridyl)thiophene.——1-(2-Pyridyl)pentan-1,4-dione (1.77 g, 0.010 mol) and Lawesson's reagent (2.42 g, 0.006 mol) in dry toluene (100 ml) were kept under nitrogen at 110 °C until all of the diketone had been consumed (as indicated by TLC analysis). Moisture was strictly excluded, the reaction mixture was then allowed to cool to room temperature and removes of the solvent gave a brown crude product, which was purified by chromatography from silica gel, using dichloromethane : ethyl acetate (5:1) as the eluent. Recrystallisation from ethyl acetate-hexane gave the *pyridylthiophenes*, as almost colourless needles (1.20 g, 69 %), m.p. 78-79 °C; (Found: C, 68.3; H, 5.2; N, 7.9; S, 18.5. $C_{10}H_9NS$ requires C, 68.5; H, 5.2; N, 8.0; S, 18.5 %); ν_{max} (film) 1 605, 1 595, 1 575, 1 500, 1 465, 1 435 cm^{-1} (C=C/C=N); δ_H (90 MHz, $CDCl_3$, TMS) 2.52 (3 H, s, CH_3), 6.76 (1 H, dd, J 1.1, J 2.3 Hz, 4'-H), 7.11 (1 H, m, 5-H), 7.36 (1 H, d, J 3.6 Hz, 3'-H), 7.56 (2 H, m, 3-H and 4-H), 8.50 (1 H, dt, J 1.3, J 4.0, 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 15.6 (CH_3), 118.2, 121.3, 124.6, 127.5, 136.4, 142.3, 142.4, 149.4 and 152.8 (arom. C); m/z 177 (M^+, 5%), 176 (15), 175 (100).

1-Methyl-2-(5-methyl-2-thienyl)pyridinium iodide.——Methyl iodide (11.4 g, 0.08 mol) was added to 2-methyl-5-(2-pyridyl)thiophene (0.52 g, 0.003 mol) in ethanol (10 ml) and the mixture refluxed for 2 h. After cooling, diethyl ether (~10 ml) was added to cause the precipitation of the *methiodide salt*, which was further purified by recrystallisation from ethanol as a light brown crystalline solid, (0.50 g, 53 %), m.p. 125-127 °C; (Found: C, 41.4; H, 3.7; N, 4.2; S, 10.2; I, 40.2. $C_{11}H_{12}NSI$ requires C, 41.7; H, 3.8; N, 4.4; S, 10.1; I, 40.0 %); ν_{max} ($CHCl_3$) 1 620, 1 570, 1 510 and 1 480 cm^{-1} (C=C/C=N); δ_H (90 MHz, DMSO-d_6, TMS) 2.56 (3 H, s, CH_3), 4.36 (3 H, s, NCH_3), 7.04 (1 H, dd, J 1.1 and 3.2 Hz, 4'-H), 7.33 (1 H, m, 5-H), 7.63 (1 H, d, J 3.3 Hz, 3'-H), 7.8-8.80 (2 H, m, 3-H and 4-H), 9.13 (1 H, d J 6.0 Hz, 6-H); δ_C (22.5 MHz, DMSO-d_6, TMS) 15.4 (CH_3), 47.1 (NCH_3),

119.4, 124.6, 125.5, 132.5, 138.6, 141.7, 142.6, 147.1 and 148.2 (arom. C); m/z 177 (M^+, 5%), 176 (15), 175 (100).

Attempted preparation of 2-methyl-5-(2-pyridyl)furan.—(a) 1-(2-Pyridyl)pentan-14-dione (0.88 g, 0.005 mol) and acetic anhydride (4 ml) in the presence of one drop of sulphuric acid were stirred for 30 h at room temperature. The solution was poured into the ice (50 g), neutralized with aqueous sodium carbonate solution, and then extracted with dichloromethane (3 x 20 ml). After drying ($MgSO_4$), evaporation of the extracts gave a solid, which was analysed by TLC and ^1H NMR and proved to be an unreacted starting material.

(b) 1-(2-Pyridyl)pentan-14-dione (0.88 g, 0.005 mol), acetic anhydride (4 ml) and sulphuric acid (5 ml) were stirred for 24 h at room temperature. TLC analysis showed only starting material, and the mixture was heated at 50 °C for 4 h, then left overnight. There was no change again. The mixture was then heated at 130-140 °C for 8 h. The solution was poured into the ice (100 g), neutralized with aqueous sodium carbonate solution, and then extracted with dichloromethane (3 x 20 ml). After drying ($MgSO_4$), evaporation of the extracts produced a solid which was analysed by TLC and ^1H NMR and shown to be exclusively the starting material.

(c) The same experiment as in Section (a) was also repeated using 1-(2-pyridyl)pentan-1,4-dione (0.88 g, 0.005 mol), acetic anhydride (10 ml) and sulphuric acid (5 ml). The mixture was also heated at 50 °C, and then 140 °C for 24 h, the usual work-up afforded the starting material again.

(d) 1-(2-Pyridyl)pentan-1,4-dione (0.88 g, 0.005 mol) was suspended in hydrochloric acid (10 ml) and the mixture was heated at 140-150 °C, after 24 h a white precipitate appeared, but filtration of the reaction mixture gave a solid

which was shown by TLC to be a mixture of starting material and base-line material.

(e) Phosphorus pentoxide (0.85 g, 0.006 mol) and 1-(2-pyridyl)pentan-1,4-dione (1.77 g, 0.01 mol) in toluene (10 ml) were heated at 110 °C for 24 h. The solution was poured into the ice-water (100 g) and extracted with dichloromethane (3 x 50 ml). After drying ($MgSO_4$), evaporation of the extracts gave a white solid, which was analysed by TLC and ^1H NMR and proved to be unreacted starting material as before.

2-Methyl-5-(2-pyridyl)furan.——1-(2-Pyridyl)pentan-1,4-dione (2g, 0.011 mol) and polyphosphoric acid (8-10 g) were stirred and heated for 3 h at 130-140 °C. The solution was poured into the crushed ice (100 g) and neutralized with sodium carbonate solution, extracted with dichloromethane (2 x 100 ml), dried ($MgSO_4$), and evaporated to yield a brown crude product, which was purified by flash column chromatography eluting with ethyl acetate to give light yellow liquid. Bulb to bulb distillation of the product afforded the *pyridylfuran*, as a colourless liquid, (1.48 g, 82 %), b.p. 104-105 °C/7 mm Hg (lit.,[5] 120 °C/14 mm Hg); (Found: C, 75.3; H, 5.8; N, 8.8. Calc. for $C_{10}H_9NO$ C, 75.5; H, 5.7; N, 8.8 %); ν_{max} (film)1 605, 1 585, 1535, 1 465, 1 425 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 2.36 (3 H, s, CH_3), 6.09 (1 H, d, J 1.0 Hz, 4'-H), 7.01 (2 H, m, 3'-H and 5-H), 7.58 (2 H, dd, J 1.0 and 4.5 Hz, 3-H, 4-H), 8.58 (1 H, dd, J 1.2 and 4.5 Hz, 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 13.7 (CH_3), 108.3, 109.8, 118.0, 121.2, 136.4, 149.5, 149.6, 152.1 and 153.4 (arom. C); m/z 160 (M^+, 11 %), 159 (100).

1-Methyl-2-(5-methyl-2-furyl)pyridinium iodide.——Methyl iodide (11.4 g, 0.08 mol) was added to 2-methyl-5-(2-pyridyl)furan (0.48 g, 0.003 mol) in ethanol (10 ml) and the mixture refluxed for 3 h. After cooling, diethyl ether (~5 ml) was

added to cause the precipitation of the *methiodide salt*, which was further purified by recrystallization from ethanol as a brown crystalline solid, (0.69 g, 76%), m.p. 159.5-160 °C (Found: C, 43.9; H, 3.9; N, 4.6; I, 42.0. $C_{11}H_{12}NOI$ requires C, 43.9; H, 4.0; N, 4.7, I, 42.1 %); ν_{max} ($CHCl_3$) 1 627, 1 575, 1 530, 1 445, 1 410 cm^{-1} (C=C/C=N); δ_H (400 MHz, $CDCl_3$, TMS) 2.46 (3 H, s, CH_3), 4.64 (3 H, s, NCH_3), 6.26 (1 H, d, J 3.8 Hz, 4'-H), 7.64 (1 H, d, J 3.6 Hz, 3'-H), 7.93 (1 H, dd, J 1.0 and 7.2 Hz, 5-H), 8.20-8.70 (2 H, m, 3-H and 4-H), 9.35 (1 H, dd, J 1.1 and 5.1, H-6); δ_C (100 MHz, $CDCl_3$, TMS) 14.5 (CH_3), 49.6 (NCH_3), 111.3, 123.4, 124.7, 126.1, 141.1, 141.4, 144.9, 146.6 and 159.6; m/z 175 (M^+, 1 %), 174 (1), 160 (12), 159 (100).

1-(3-Pyridyl)pentan-1,4-dione.——But-3-en-2-one (16.38 g, 0.24 mol), 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (7.65 g, 0.03 mol) and dry triethylamine (14.34 g, 0.14 mol) in dry dioxane (20 ml) were heated at 90-100 °C under nitrogen. 3-Formylpyridine (41.73 g, 0.39 mol) in dry dioxane (80 ml) was added dropwise slowly over a period of 2.5 h, and the mixture was then stirred at 90-100 °C for 16 h, cooled, and the solvent removed under vacuum. Water (300 ml) was added and the aqueous layer was extracted with dichloromethane (3 x 50 ml). The combined organic extracts were washed with brine (2 x 25 ml) and dried ($MgSO_4$). Filtration and removal of the solvent gave a brown syrup, which was chromatographed (silica gel, ethyl acetate : dichloromethane (5:1) to give the title compound as a light brown oil. Bulb to bulb distillation gave the pure product as a colourless oil, (19.74 g, 62 %), b.p. 137-138 °C/1.0 mm Hg (lit.,[6] 112-113 °C/0.25 mm Hg); (Found: C, 67.7; H, 6.0; N, 7.9. Calc. for $C_{10}H_{11}NO_2$ C, 67.8; H, 6.2; N, 7.9 %); ν_{max} (film) 1 710 and 1 690 (C=O), 1 605, 1 585 and 1 570, 1 495, 1 420 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 2.25 (3 H, s, CH_3), 2.98 (2 H, t J 6.0 Hz, 3-CH_2), 3.26 (2 H, t, J 6.0 Hz, 4-

CH_2), 7.39 (1H, dd, J 4.8 and 8.0 Hz, 5-H), 8.26 (1 H, dd, J 1.8 and 8.0 Hz, 4-H), 8.80 (1 H, dd, J 1.2 and 4.8 Hz, 6-H), 9.22 (1 H, d, J 2.0 Hz, 2-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 29.8 (CH_3), 32.5 and 36.7 (CH_2), 123.5, 131.8, 135.2, 149.2 and 153.4 (arom. C), 197.3 and 206.9 (C=O); m/z 178 (M^+, 5 %), 177 (31), 162 (32), 149 (12), 106 (100).

2-Methyl-5-(3-pyridyl)thiophene.——1-(3-Pyridyl)pentan-1,4-dione (1.77 g, 0.01 mol) and Lawesson's reagent (2.42 g, 0.006 mol) in dry toluene (100 ml) were heated at reflux under nitrogen for 36 h. The reaction mixture was then allowed to cool to room temperature and the solvent removed to give a brown oil, which was purified by column chromatography eluting with ethyl acetate to give 2-methyl-5-(3-pyridyl)thiophene as a brown solid. Recrystallisation from ethyl acetate-hexane gave the *pyridylthiophene*, as bright colourless needles, (1.12 g, 64 %), m.p. 67.5-69 °C; (Found: C, 68.3; H, 5.2; N, 7.9; S, 18.5. $C_{10}H_9NS$ requires C, 68.5; H, 5.2; N, 8.0; S, 18.5 %); ν_{max} (film) 1 600, 1 585, 1 570, 1 490, 1 465, 1 425 cm^{-1} (C=C/C=N); δ_H (90 MHz, $CDCl_3$, TMS) 2.48 (3 H, s, CH_3), 6.71(1 H, dd, J 1.1 and 3.5 Hz, 4'-H), 7.17 (2 H, m, 3'-H, 5-H), 7.76 (1 H, m, 4-H), 8.41 (1 H, dd, J 1.0 and 4.8 Hz, 6-H), 8.78 (1 H, d, J 2.4 Hz, 2-H); δ_C (100 MHz, $CDCl_3$, TMS) 15.3 (CH_3), 123.5, 124.1, 126.5, 130.7, 132.4, 137.8, 140.9, 146.4 and 147.8 (arom. C); m/z 177 (M^+, 5%), 176 (15), 175 (100).

1-Methyl-3-(5-methyl-2-thienyl)pyridinium iodide.——Methyl iodide (11.4 g, 80 ml) was added to 2-methyl-5-(3-pyridyl)thiophene (0.52 g, 0.003 mol) in ethanol (10 ml) and the mixture was refluxed for 4 h, cooled, and the solvent removed. The residue was recrystallized from ethanol-diethyl ether to give the *methiodide salt*, as a brown bright solid, (0.75 g, 80 %), m.p. 175-177 °C; (Found: C, 41.9; H, 3.8; N, 4.2; S, 10.1; I, 40.0. $C_{11}H_{12}NSI$ requires C, 41.7; H, 3.8; N, 4.4; S,

10.1; I, 40.0 %); ν_{max} ($CHCl_3$) 1 630, 1 610 and 1 590, 1 510 cm^{-1} (C=C/C=N); δ_H (90 MHz, DMSO-d_6, TMS) 2.54 (3 H, s, CH_3), 4.46 (3 H, s, NCH_3), 7.01 (1 H, dd, J 1.3 and 2.3 Hz, 4'-H), 7.78 (1 H, d, J 3.7 Hz, 3'-H), 8.11 (1 H, t, 5-H), 8.72 (1 H, d, J 8.2 Hz, 4-H), 8.91 (1 H, d, J 5.9 Hz, 6-H), 9.37 (1 H, s, 2-H); δ_C (22.5 MHz, DMSO-d_6, TMS) 15.2, (CH_3), 48.1(NCH_3), 127.5, 127.6, 128.3, 132.7, 133.3, 139.3, 141.0, 142.5 and 143.8 (arom. C); m/z 177 (M^+, 5%), 176 (15), 175 (100).

2-Methyl-5-(3-pyridyl)furan.——1-(3-Pyridyl)pentan-1,4-dione (2 g, 0.011 mol) and polyphosphoric acid (8-10 g) were stirred and heated for 4 h at 130-140 °C. The solution was poured into the crushed ice (100 g), neutralized with sodium carbonate solution, extracted with dichloromethane (2 x 100 ml), dried ($MgSO_4$), and evaporated to yield a brown oil which was purified by flash column chromatography eluting with ethyl acetate to give light brown liquid. The pyridylfuran was further purified by bulb to bulb distillation to yield a colourless oil, (1.51 g, 83%), b.p. 122-125 °C/10 mm Hg (lit.,[7] 72 °C/0.5 mm Hg); (Found: C, 75.4; H, 5.5; N, 8.9. Calc. for $C_{10}H_9NO$ C, 75.5; H, 5.7; N, 8.8 %); ν_{max} (film) 1 570, 1 555, 1 545, 1 465, 1 425 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 2.31 (3 H, s, CH_3), 6.01 (1 H, d, J 3.6 Hz, 4'-H), 6.54 (1 H, d, J 3.6 Hz, 3'-H), 7.18 (1 H, m, 5-H), 7.80 (1 H, m, 4-H), 8.39 (1 H, dd, J 1.8 and 4.8 Hz, 6-H), 8.95 (1 H, d, J 1.6 Hz, 2-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 13.5 (CH_3), 107.4, 108.0, 123.3, 127.1, 130.0, 144.9, 147.5, 149.2 and 152.9 (arom. C); m/z 160 (M^+ 11 %), 159 (100).

1-Methyl-3-(5-methyl-2-furyl)pyridinium iodide.——Methyl iodide (11.40 g, 80 ml) was added to 2-methyl-5-(2-pyridyl)furan (0.48 g, 0.003 mol) in ethanol (10 ml) and the mixture refluxed for 3 h. After cooling, diethyl ether (~ 4 ml) was added to cause the precipitation of the *methiodide salt*, which was further

purified by recrystallization from ethanol as a bright yellow solid, (0.88 g, 97%), m.p. 180-181 °C (Found: C, 43.7; H, 3.9; N, 4.5; I, 41.9. $C_{11}H_{12}NOI$ requires C, 43.9; H, 4.0; N, 4.7; I, 42.1 %); ν_{max} ($CHCl_3$) 1 630, 1 580, 1 545, 1 445, 1 410 cm^{-1} (C=N/C=C); δ_H (90 MHz, $CDCl_3$, TMS) 2.38 (3 H, s, CH_3), 4.68 (3 H, s, NCH_3), 6.14 (1 H, dd, J 1.0 and 3.4 Hz, 4'-H), 7.34 (1 H, d, J 3.6 Hz, 3'-H), 8.02 (1 H, m, 5-H), 8.52 (1 H, m, 4-H), 9.00 (1 H, dd, J 1.8 and 5.2 Hz, H-6), 9.56 (1 H, d, J 1.0 Hz, 2-H); δ_C (22.5 MHz, DMSO-d_6, TMS) 13.5 (CH_3), 48.2 (NCH_3), 10.3, 112.9, 127.7, 129.4, 136.8, 139.5, 142.2, 144.8 and 155.8; m/z 175 (M^+, 1 %), 174 (1). 160 (12), 159 (100).

1-(4-Pyridyl)pentan-1,4-dione.—But-3-en-2-one (8.89 g, 0.13 mol), 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (4.15 g, 0.015 mol) and dry triethylamine (7.78 g, 0.08 mol) in dry dioxane (10 ml) were heated at 90-100 °C under nitrogen for 3 h. 4-Formylpyridine (10.70 g, 0.10 mol) in dry dioxane (40 ml) was added dropwise slowly over 2.5 h at the same temperature with efficient stirring. The mixture was stirred for 18 h at the same temperature, cooled, and the solvent removed under reduced pressure. The dark oil was diluted with water (80 ml) and extracted with dichloromethane (3 x 30 ml). The organic extract was dried ($MgSO_4$) and evaporated to give dark oil which was purified partially by flash column chromatography (silica gel, ethyl acetate) to give the crude product, as a light brown solid. Recrystallisation from dichloromethane gave the *1-(4-pyridyl)-1,4-pentadione* as a colourless solid, (7.32 g, 69 %), b.p. 70.8-73 °C (lit.,[6] 75 °C); (Found: C, 67.7; H, 6.1; N, 7.9. Calc. for $C_{10}H_{11}NO_2$ C, 67.8; H, 6.2; N, 7.9 %); ν_{max} (film) 1 715 and 1 695 (C=O), 1 600, 1 585, 1 560, 1 495, 1 450, 1410 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 2.22 (3 H, s, CH_3), 2.84 (2 H, t, J 5.9 Hz, CH_2), 3.50 (2 H, t, J 5.9 Hz, CH_2), 7.77 (2 H, dd, J 1.7 and 4.5 Hz, 3-H and 5-H), 8.81 (2 H, dd, J 1.5 and 4.5 Hz, 2-H and 6-H);

δ_C (22.5 MHz, $CDCl_3$, TMS) 29.8 (CH_3), 32.5 and 36.7 (CH_2), 119.7, 120.9, 142.3, 143.5 and 150.8 (arom. C), 198.0 and 206.4 (C=O); m/z 178 (M^+, 4 %), 177 (30), 162 (31), 149 (11), 106 (100).

2-Methyl-5-(4-pyridyl)thiophene.——1-(4-Pyridyl)pentan-1,4-dione (1.77 g, 0.01 mol) and Lawesson's reagent (2.42 g, 0.006 mol) in dry toluene (100 ml) were heated to a gentle reflux under nitrogen for 36 h. The brown solution was then allowed to cool to room temperature and the solvent removed to give a brown oil, which was purified partially by column chromatography eluting with ethyl acetate to give the crude product, as a yellow solid, which was further purified by recrystallization twice from dichloromethane-hexane to yield *2-methyl-5-(4-pyridyl)thiphene,* as a pale yellow solid (0.9 g, 51 %), m.p. 139-140 °C; (Found: C, 68.4; H, 5.2; N, 7.9; S, 18.5. $C_{10}H_9NS$ requires C, 68.5; H, 5.2; N, 8.0; S, 18.5 %); ν_{max} (film) 1 600, 1 585, 1 500, 1 480, 1 460, 1 425 cm^{-1} (C=C/C=N); δ_H (400 MHz, $CDCl_3$, TMS) 2.53 (3 H, s, CH_3), 6.78 (1 H, dd, J 1.1 and 4.5 Hz, 4'-H), 7.31 (1 H, dd, J 1.8 and 3.5 Hz, 3'-H), 7.39 (2 H, dd, J 1.8 and 5.0 Hz, 3-H and 5-H), 8.57 (2 H, dd, J 1.8 and 4.6 Hz, 2-H and 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 15.3 (CH_3), 119.4 , 125.4 , 126.7, 138.6, 141.6, 142.4 (d) and 150.2 (d) (arom. C); m/z 177(M^+, 5 %), 176 (15), 175 (100).

1-Methyl-4-(5-methyl-2-thienyl)pyridinium iodide.——Methyl iodide (11.4 g, 0.08 mol) was added to 2-methyl-5-(4-pyridyl)thiophene (0.52 g, 0.003 mol) in ethanol (10 ml) and the mixture refluxed for 4 h, and cooled. The precipitate was collected by filtration, washed with cold ethanol, and recrystallised from ethanol-diethyl ether to give the methiodide salt, as a light brown solid, (0.85 g, 90 %), m.p. 163-165 °C; (Found: C, 41.7; H, 4.0; N, 4.3; S, 10.1; I, 39.9. $C_{11}H_{12}NSI$ requires C, 41.7; H, 3.8; N, 4.4; S, 10.1; I, 40.0 %); ν_{max} ($CHCl_3$) 1 640, 1 600 and

1 535, 1 510, 1 480, 1 470, 1 425 cm^{-1} (C=C/C=N); δ_H (400 MHz, DMSO-d_6, TMS) 2.58 (3 H, s, CH_3), 4.35 (3 H, s, NCH_3), 7.06 (1 H, dd, J 1.0 Hz, J 3.0 Hz, 4'-H), 8.16 (3 H, dd, J 3.9, and J 7.1 Hz, 3'-H), 8.91 (2 H, d, J 8.0 Hz, 5-H); δ_C (22.5 MHz, DMSO-d_6, TMS) 15.6, (CH_3), 46.8 (NCH_3), 121.0, 128.8, 132.4, 134.2, 145.0, 147.2, 148.8 (arom. C); m/z 177 (M^+, 5%), 176 (15), 175 (100).

2-Methyl-5-(4-pyridyl)furan.——1-(4-Pyridyl)pentan-1,4-dione (2 g, 0.011 mol) and polyphosphoric acid (8-10 g) were stirred and heated at 130-140 °C for 4 h. The solution was poured into the crushed ice (100 g), neutralized with sodium carbonate solution, and then extracted with dichloromethane (2 x 100 ml). The extracts were dried ($MgSO_4$), and evaporated to yield a brown oil which was purified by flash column chromatography eluting with ethyl acetate to give a crude product as a yellow solid. Recrystallisation of this material from ethyl acetate-petroleum ether gave the *pyridylfuran*, as a white woolly solid, (1.45 g, 81%), m.p. 63-65 °C; (Found: C, 75.4; H, 5.6; N, 8.8. $C_{10}H_9NO$ requires C, 75.5; H, 5.7; N, 8.8 %); ν_{max} (film) 1 610, 1 585, 1 535, 1 465, 1 425 cm^{-1} (C=C/C=N); δ_H (400 MHz, $CDCl_3$, TMS) 2.34 (3 H, s, CH_3), 6.07 (1 H, dd, J 1.1, J 3.3 Hz, 4'-H), 6.72 (1 H, d, J 3.3 Hz, 3'-H), 7.42 (2 H, dd, J 1.6, J 5.0 Hz, 3-H and 5-H), 8.53 (2 H, dd, J 1.5, J 4.5 Hz, 2-H and 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 13.7 (CH_3), 108.4, 109.8, 117.2, 137.6, 149.6, 150.1, 154.1 (arom. C); m/z 160 (M^+, 11 %), 159 (100).

1-Methyl-4-(5-methyl-2-furyl)pyridinium iodide.——Methyl iodide (11.40 g, 0.08 mol), 2-methyl-5-(4-pyridyl)furan (0.48 g, 0.003 mol) in ethanol (10 ml) was refluxed for 3 h. The precipitate, that formed upon cooling, was collected and recrystallised from ethanol-diethyl ether to yield the *methiodide salt*, as a dark yellow solid, (0.88 g, 97%), m.p. 209-211 °C; (Found: C, 43.9; H, 3.9; N, 4.6; I, 42.1. $C_{11}H_{12}NOI$ requires C, 43.9; H, 4.0; N, 4.7; I, 42.1 %); ν_{max} ($CHCl_3$) 1 640, 1 600,

1 535, 1 475, 1 425 cm^{-1} (C=C/C=N); δ_H (400 MHz, DMSO-d_6, TMS) 2.48 (3 H, s, CH_3), 4.28 (3 H, s, NCH_3), 6.54 (1 H, dd, J 1.0, J 3.1 Hz, 4'-H), 7.76 (1 H, d, J 3.1 Hz, 3'-H), 8.18 (2 H, dd, J 1.2, J 5.0 Hz, 3-H and 5-H), 8.88 (2 H, dd, J 1.8, J 5.0 Hz, 2-H and 6-H); δ_C (22.40 MHz, DMSO-d_6, TMS) 13.7 (CH_3), 46.7 (NCH_3), 110.8 118.7, 118.9, 142.0, 145.1, 146.3 and 158.7; m/z 160 (M^+, 11 %), 159 (100).

3.3 Experimental for Chapter 3

N,N,N',N'-Tetramethylsuccinamide.——(a) Succinic anhydride (1.0 g, 0.01 mol) and hexamethylphosphoramide (HMPA) (5.27 g, 0.03 mol) were stirred and heated gently at around 150 °C until the colour of the reaction mixture changed from white to brown. The solution was evaporated to remove excess of HMPA, and extracted with petroleum ether (5 x 10 ml). Removal of the solvent gave a crude product. Recrystallization from the petroleum ether gave the N-methylated amide, as a white solid, (0.55 g, 32 %), m.p. 79-80 °C (lit.,[8-10] 80-81 °C); (Found: C, 55.6; H, 9.4; N, 16.0. Calc. for $C_8H_{16}N_2O_2$: C, 55.8; H, 9.4; N, 16.3%); ν_{max} ($CHCl_3$) 3 005, 2 935 and 2 860 (N-Me and C-H), 1 645 cm^{-1} ($CONMe_2$); δ_H (60 MHz, $CDCl_3$, TMS) 2.65 (2 H, s, CH_2), 2.93 (3 H, s, NMe), 3.04 (3 H, s, NMe); δ_C (22.5 MHz, $CDCl_3$, TMS) 28.1 (CH_2), 36.7 and 39.1 (NCH_3), 166.4 ($CONMe_2$).

(b) Succinic acid (17.71 g, 0.15 mol) and HMPA (17.9 g, 0.1 mol) were heated at 180-200 °C (bath temperature) for 2 h, cooled and poured into the water (100 ml), and then extracted with dichloromethane (4 x 100 ml). Removal of the solvent gave a pale cream liquid, which rapidly set to a solid. Recrystallization from THF-diethylether gave the pure N,N,N',N'-tetramethyl succinamide, (15.85 g, 92 %).

1,4-Di(2-pyridyl)butan-1,4-dione.——(a) 2-Bromopyridine (6.636 g, 0.042 mol) was dissolved in dry diethyl ether (100 ml) and the mixture was quickly cooled with efficient stirring to -78 °C. *n*-Buthyllithium (26 ml of 1.6 M solution, 0.042 mol) was added in one portion and the solution was stirred a few minutes. N,N,N',N'-tetramethyl succinamide (3.61 g, 0.021 mol) in dry tetrahydrofuran (3 ml) was added dropwise and the mixture was stirred at -78 °C for 4 h, then allowed to warm to room temperature. Water (50 ml) was added and the mixture was extracted with dichloromethane (3 x 50 ml). The combined organic extracts were washed brine (10 ml) and dried (Na_2CO_3). Filtration and removal of the solvent gave an orange/yellow liquid. The crude product was purified by chromatography eluting with ethyl acetate : petroleum ether (1:1), to give a pale yellow solid, which was recrystallized from ethanol to yield a bright white needles, (1.1 g, 22 %), m.p. 141-142 °C (lit.,[11,12] 140-141 °C); ν_{max} ($CHCl_3$) 1 695 (C=O), 1 585, 1 570, 1 465 and 1 440 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 3.70 (2 H, s, CH_2), 7.20-8.20 (3 H, m, 3-H, 4-H and 5-H), 8.65 (1 H, d, J 4.3 Hz, 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 32.1 (CH_2), 121.7, 127.1, 136.8, 148.9 and 153.3 (arom. C), 200.4 (C=O); m/z 241 (M^+, 3 %), 240 (15), 212 (6), 162 (9), 134 (100), 106 (21), 78 (96).

(b) Sodium acetate (0.33 g, 0.004 mol) and 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (0.54 g, 0.002 mol) were added to 2-formyl pyridine (2.14 g, 0.02 mol) in absolute ethanol (20 ml). The mixture was heated under reflux and divinyl sulfone (1.18 g, 0.01 mol) was added dropwise over 30 min and then refluxed for further 12 h. The precipitated product was separated from the orange solution, washed with cold ethanol (10 ml) and diethyl ether (10 ml), and purified by chromatography (silica gel, ethyl acetate: diethyl ether; 1:1) to give 1,4-di(2-pyridyl)butan-1,4-dione (0.40 g, 17 %) and 1,2-di(2-pyridyl) ethan-1,2-dione, as a bright white needles, (0.42 g, 20 %), m.p. 156-157 °C (lit.,[13,14]

154-155 °C); (Found: C, 67.9; H, 3.7; N, 13.2. Calc. for $C_{12}H_8N_2O_2$ C, 67.9; H, 3.8; N, 13.2 %); ν_{max} ($CHCl_3$) 1 710, 1 690 (C=O), 1 582, 1 460 and 1 440 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 7.20-8.20 (3 H, m, 3-H, 4-H and 5-H), 8.52 (1 H, d, J 3.6 Hz, 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 122.6, 127.9, 137.2, 149.4 and 151.7 (arom. C), 197.0 (C=O); m/z 213 (M^+, 4 %), 212 (28), 184 (3), 156 (39), 130 (3), 128 (4), 106 (14), 78 (100). (Note: 2-pyridoin is reported[15,16] to have the m.p. 156 °C).

(c) 2-Formylpyridine (3.54 g, 0.033 mol), 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (1.35 g, 0.005 mol) and dry triethylamine (1.01 g, 0.010 mol) in dry dioxane (70 ml) were heated at 90-100 °C under nitrogen. Divinyl sulfone (1.89 g, 0.016 mol) was added dropwise slowly over a period of 1 h, and the mixture was then stirred at 90-100 °C for 12 h. The mixture was cooled to room temperature and the solvents were removed under vacuum. Water (100 ml) was added to the residue and the aqueous suspension was extracted with dichloromethane (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$). Filtration and removal of the solvent gave the crude product, as a dark brown solid, which was purified by chromatography (silicagel, ethylacetate-petroleumether;1:1). Recrystallisation from ethanol gave two products: 1,4-di(2-pyridyl)butan-1,4-dione (1.10 g, 28 %) and 1,2-di(2-pyridyl) ethan-1,2-dione (0.41 g, 41 %).

2,5-Di(2-pyridyl)thiophene.—1,4-Di(2-pyridyl)butan-1,4-dione (1.92 g, 0.008 mol) and Lawesson's reagent (2.30 g, 0.0055 mol) in dry toluene (100 ml) were kept under nitrogen at 110 °C for 50 h. The reaction mixture was then allowed to cool to room temperature and the solvent removed to give a dark brown liquid, which was purified by flash column chromatography from silica gel, using ethyl acetate : petroleum ether (1:1) as the eluent. Recrystallisation

from dichloromethane-diethyl ether gave the dipyridylthiophene, as a pale cream needles (0.874 g, 46 %), m.p. 161-162 °C (lit.,[17] 162-163 °C); ν_{max} ($CHCl_3$) 1 585, 1 565, 1 535, 1 465, 1 430 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 7.0-7.34 (1 H, m, 5-H), 7.64 (3 H, d, J 4.5 Hz, 3-H, 4-H and 3'-H), 8.56 (1 H, dd, J 1.0, J 4.4 Hz, 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 115.6, 124.6, 126.2, 136.9, 142.4, 142.5 and 152.1 (arom. C); m/z 240 (M^+, 5 %), 239 (18), 238 (100).

Attempted methylation of 2,5-di(2-pyridyl)thiophene.—(a) Methyl iodide (11.4 g, 0.08 mol) was added to 2,5-di(2-pyridyl)thiophene (0.48 g, 0.002 mol) in ethanol (10 ml) and the mixture refluxed for 4 h. After cooling, and diethyl ether (~4 ml) was added to cause the precipitation of the compound, which was dried. TLC and ^1H NMR analysis showed that this product contained only starting material (0.44 g).

(b) 2,5-Di(2-pyridyl)thiophene (0.24 g, 0.001 mol) and methyl iodide (11.4 g, 0.008 mol) were refluxed for 10 h, cooled and the precipitate was collected, washed with cold ethanol (1 ml). Analysis by TLC showed the presence only of starting material.

(c) 2,5-Di(2-pyridyl)thiophene (0.25 g, 0.001 mol) and methyl iodide (11.4 g, 0.008 mol) were heated in a pressure vessel at 100 °C for 2 weeks. The mixture was cooled for 24 h, and the yellow/orange precipitate was collected, washed with cold ethanol (5 ml) and dichloromethane (10 ml), and dried to give the bis methiodide salt of *2,5-di(2-pyridyl)thiophene* as an orange solid, (0.50 g, 91 %), m.p. 256-258 °C (Found: C, 36.6; H, 3.1; N, 5.2; S, 6.1; I, 48.4. $C_{16}H_{16}N_2SI_2$ requires C, 36.8; H, 3.1; N, 5.4; S, 6.1; I, 48.6 %); ν_{max} (nujol) 1 630, 1 580, 1 540 cm^{-1} (C=C/C=N); δ_H (400 MHz, DMSO-d_6, TMS) 4.87 (3 H, s, NMe), 8.43 (1 H, s, 3'-H for thiop.), 8.60-8.90 (2 H, m, 4-H, and 5-H), 9.08-9.17 (1 H, m, 3-H), 9.75 (1 H, dd, J 1.2 and J 6.0 Hz, 6-H); δ_C (22.5 MHz, DMSO-d_6, TMS) 47.6 (NMe), 127.3,

130.6, 133.4, 135.8, 145.3, 147.2, and 147.5 (arom. C); m/z 319 (M^+, 3 %), 310 (2), 309 (2), 305 (1), 268 (1), 238 (35), 237 (5), 205 (7), 156 (11) and 142 (100).

2,5-Di(2-pyridyl)furan.— 1,4-Di(2-pyridyl)butan-1,4-dione (2.0 g, 0.008 mol) and polyphosphoric acid (10-12 g) were stirred and heated for 5 h at 130-140 °C. The reaction mixture was poured into the crushed ice (100 g), neutralized with sodium carbonate solution, and extracted dichloromethane (2 x 100 ml). The extracts were dried ($MgSO_4$), and evaporated to yield a brown solid which was purified by flash column chromatography on a silica gel (Ethyl acetate:petroleum ether; 1:1). The *pyridylfuran* was further purified by recrystallisation from dichloromethane-hexane mixture to give white, woolly crystals, (1.51 g, 82 %), m.p. 123-125 °C; (Found: C, 75.4; H, 4.6; N, 12.6. $C_{14}H_{10}N_2O$ requires C, 75.7; H, 4.5; N, 12.6 %); ν_{max} ($CHCl_3$) 1 610, 1 595, 1580, 1 525, 1 470, 1 425 cm^{-1} (C=C/C=N); δ_H (400 MHz, $CDCl_3$, TMS) 7.0-7.2 (2 H, m, 5-H and 3'-H), 7.50-7.90 (2 H, m, 3-H and 4-H), 8.61 (1 H, dd, J 0.7 and 4.8 Hz, 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 111.0, 118.7, 122.1, 136.5, 149.0, 149.6, 154.0 (arom. C); m/z 224 (M^+, 1 %), 223 (16), 222 (100).

Attempted N-methylation of 2,5-di(2-pyridyl)furan.— (a) Methyl iodide (11.4 g, 0.008 mol) was added to 2,5-di(2-pyridyl)furan (0.66 g, 0.003 mol) in ethanol (10 ml) and the mixture refluxed for 8 h. After cooling, diethyl ether (~10 ml) was added to cause the precipitation of the compound, which was dried. TLC and ^1H NMR analysis showed that this contained only starting material (0.64 g).

(b) 2,5-Di(2-pyridyl)furan (0.40 g, 0.002 mol) and methyl iodide (10 g, 0.007 mol) were refluxed for 50 h, cooled and the precipitate was collected, washed with cold ethanol (5 ml), and analysed by TLC and proved to be a

mixture of starting material and base-line material. 2,5-Di(2-pyridyl)furan is soluble in ethyl acetate and mono and dimethylated compounds are soluble only ethanol or water. The crude product was dissolved in ethyl acetate : dichloromethane and solid phase was separated by filtration. The liquid phase gave the starting material; a solid, which separated by filtration, was washed with cold ethanol (~2 ml) and recrystallised twice from ethanol to give *1-methyl-2-(5-(2-pyridyl)-2-furyl)pyridinium iodide*, as a yellow solid, (0.41 g, 45 %), m.p. 201-202 °C (Found: C, 49.2; H, 3.6; N, 7.5; I, 35.0. $C_{15}H_{13}N_2OI$ requires C, 49.5; H, 3.6; N, 7.7; I, 34.8 %); ν_{max} (nujol) 1 620, 1 600 (C=N-Me), 1 575, 1 530 cm^{-1} (C=C); δ_H (400 MHz, DMSO-d_6, TMS) 4.55 (3 H, s, NMe), 7.52 (2 H, d, J 2.5 Hz, 3''-H and 4''-H for furan), 7.98-8.50 (4 H, m, 4-H, 4'-H and 5-H, 5'-H), 8.66 (3 H, d, J 1.2 Hz, 3-H, 3'-H and 6'-H), 9.10 (1 H, dd, J 1.0 and J 5.5 Hz, 6-H); δ_C (22.5 MHz, DMSO-d_6, TMS) 48.3, 111.8, 120.0, 122.2, 124.1, 125.1, 126.2, 137.4, 143.1, 143.6, 144.4, 146.6, 146.8, 149.9, 156.9; m/z 223 (M^+, 11 %), 222 (64), 221 (10), 194 (3), 193 (8), 192 (2), 156 (5), 145 (1), 144 (14), 143 (1) and 142 (100).

(c) 2,5-Di(2-pyridyl)furan (0.2 g, 0.001 mol) and methyl iodide (22.80 g, 0.16 mol) were kept in a pressure vessel at 100 °C for 50 h, upon cooling, the precipitate was collected and washed with cold ethanol (2 ml) and dried to give the monomethylated product, as a yellow solid, (0.3 g, 92 %), m.p. 201-202 °C

(d) 2,5-Di(2-pyridyl)furan (0.29 g, 0.001 mol) and methyl iodide (~8 ml) were heated in a pressure vessel at 100 °C for 7 d, cooled, and the yellow/orange precipitates were collected, washed with cold ethanol (5 ml) and dichloromethane (10 ml). ^1H NMR analysis identified a mixture of the mono- and dimethylated products (0.40 g). The mixture, which separated by using solubility differences, was extracted with ethanol in a Soxhlet apparatus for 2 d. Every 6 h, the ethanol solution was removed and fresh ethanol was added evaporation of the first fractions gave the mono- methylated product, (0.12 g, 37

0.06 mol) in dry dioxane (30 ml) were heated at 90-100 °C under nitrogen. Divinyl sulfone (0.96 g, 0.008 mol) was added dropwise slowly over a period of 20 min, and the mixture was then stirred at 90-100 °C for 12 h. The mixture was cooled to room temperature and the solvent was removed under vacuum. Water (100 ml) was added to the residue and the aqueous suspension was extracted with dichloromethane (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$). Filtration and removal of the solvent gave the crude product as a yellow solid, which was purified by recrystallization from ethanol to yield 1,4-di(3-pyridyl) butan-1,4-dione, (0.93 g, 39 %)

2,5-Di(3-pyridyl)thiophene.— 1,4-Di(3-pyridyl)butan-1,4-dione (2.88 g, 0.012 mol) and Lawesson's reagent (2.43 g, 0.0058 mol) in dry toluene (100 ml) were heated under nitrogen at 110 °C for 50 h. The reaction mixture was then allowed to cool to room temperature and the solvent removed to give a dark brown liquid, which was purified by flash column chromatography from silica gel, using ethyl acetate : petroleum ether (1:1) as the eluent. Recrystallisation from dichloromethane-diethyl ether gave the dipyridylthiophene, as a pale yellow solid (1.51 g, 53 %), m.p. 94-95.5 °C (lit.,[18,19] 97 °C); (Found: C, 70.3; H, 4.2; N, 11.6; S, 13.3. Calc. for $C_{14}H_{10}N_2S$ C, 70.6; H, 4.2; N, 11.8; S, 13.5 %); ν_{max} ($CHCl_3$) 1 605, 1 585, 1 565, 1 465, 1 410 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 7.30 (2 H, m, 3'-H and 5-H), 7.83 (1 H, dd, J 1.1 and J 5.3 Hz, 4-H), 8.48 (1 H, dd, J 1.0, J 4.3 Hz, 6-H), 8.84 (1 H, d, J 1.9 Hz, 2-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 123.7, 125.4, 129.9, 132.8, 140.6, 146.4 and 148.4 (arom. C); m/z 240 (M^+, 6 %), 239 (17), 238 (100).

N-Methylation of 2,5-di(3-pyridyl)thiophene.—Methyl iodide (9.12 g, 0.064 mol) was added to 2,5-di(3-pyridyl)thiophene (0.54 g, 0.002 mol) in ethanol (10

ml) and the mixture refluxed for 4 h, cooled, and diethyl ether (~4 ml) was added to cause the precipitation of the compound, which was recrystallised from aqueous ethanol and dried to give the *N,N'-dimethylated salt*, as a pale yellow solid, (1.14 g, 96 %), m.p. 274-276 °C (Found: C, 36.5; H, 3.0; N, 5.2; S, 6.1; I, 48.8. $C_{16}H_{16}N_2SI_2$ requires C, 36.8; H, 3.1; N, 5.4; S, 6.1; I, 48.6 %); ν_{max} (nujol) 1 630 (C=N-Me), 1 585, 1 565 cm^{-1} (C=C); δ_H (400 MHz, DMSO-d_6, TMS) 4.43 (3 H, s, NMe), 8.10 (1H, s, 3'-H), 8.22 (1 H, dd, J 6.2 and J 5.2 Hz, 5-H), 8.86 (1 H, d, J 8.4 Hz, 4-H), 8.96 (1 H, d, J 5.9, 6-H), 9.52 (1 H, s, 2-H); δ_C (22.5 MHz, DMSO-d_6, TMS) 48.2 (NMe), 127.9, 129.7, 132.3, 138.2, 142.3, 143.9, 147.5 (arom. C); m/z 254 (M^+ 1 %), 240 (6), 239 (16), 238 (100).

2,5-Di(3-pyridyl)furan.— 1,4-Di(3-pyridyl)butan-1,4-dione (2.0 g, 0.008 mol) and polyphosphoric acid (9-10 g) were stirred and heated for 6 h at 150-160 °C. The reaction mixture was poured into the crushed ice (100 g), neutralized with sodium carbonate solution and extracted dichloromethane (2 x 100 ml). The extracts were dried ($MgSO_4$), and evaporated to yield a brown solid, which was purified by flash column chromatography on a silica gel (ethyl acetate : petroleum ether; 1:1). The *dipyridylfuran* was further purified by recrystallization from dichloromethane-hexane mixture to give a white woolly crystals, (1.71 g, 92 %), m.p. 159-160 °C; (Found: C, 75.4; H, 4.5; N, 12.6. $C_{14}H_{10}N_2O$ requires C, 75.7; H, 4.5; N, 12.6 %); ν_{max} ($CHCl_3$) 1 610, 1 585, 1575, 1 475, 1 430, 1 410 cm^{-1} (C=N/C=C); δ_H (400 MHz, $CDCl_3$, TMS) 6.83 (1H, dd, J 0.7 and J 3.0 Hz, 3'-H), 7.32 (1 H, q, J 4.8 Hz, 5-H), 7.97 (1 H, dd, J 1.5 and 8.0 Hz, 4-H), 8.52 (1 H, dd, J 0.5 and J 4.5 Hz, 6-H), 8.97 (1 H, s, 2-H); δ_C (100 MHz, $CDCl_3$, TMS) 108.6, 123.5, 126.3, 130.6, 145.3, 148.4, 151.2 (arom. C); m/z 224 (M^+, 2 %), 223 (16), 222 (100).

N-Methylation of 2,5-di(3-pyridyl)furan.——Methyl iodide (11.4 g, 0.08 mol) and 2,5-di(3-pyridyl)furan (0.48 g, 0.002 mol) in ethanol (10 ml) were heated under reflux for 4 h, cooled, and diethyl ether (~2 ml) was added to cause the precipitation of the compound, which was recrystallised from aqueous ethanol and dried to give *N,N-dimethylated pyridinium salt*, as a pale cream solid, (1.06 g, 97 %), m.p. > 315 °C (Found: C, 38.0; H, 3.1; N, 5.4; I, 50.1. $C_{16}H_{16}N_2OI_2$ requires C, 38.0; H, 3.2; N, 5.5; I, 50.1 %); ν_{max} (nujol) 1 630, 1605, 1 590 cm^{-1} (C=C/C=N); δ_H (400 MHz, DMSO-d_6, TMS) 4.43 (3 H, s, NMe), 7.70 (1 H, s, 3'-H), 8.27 (1 H, q, J 5.9 Hz, 5-H), 8.97 (1 H, d, J 5.9 Hz, 4-H), 9.09 (1 H, d, J 8.1 Hz, 6-H), 9.70 (1 H, s, 2-H); δ_C (100 MHz, DMSO-d_6, TMS) 48.2 (NMe), 113.9, 127.8, 128.6, 138.4, 141.0, 144.0, 148.6 (arom. C); m/z 224 (M^+, 2 %), 223 (16), 222 (100).

2,5-Di(4-pyridyl)thiophene.——1,4-Di(4-pyridyl)butan-1,4-dione (1.92 g, 0.008 mol) and Lawesson's reagent (2.3 g, 0.005 mol) in dry toluene (100 ml) were heated under nitrogen at 110 °C for 48 h. The reaction mixture was then allowed to cool to room temperature and the solvent removed to give a dark brown solid. The product was washed through Celite with ethanol and dichloromethane, and recrystallisation of the recovered solid from ethanol gave the dipyridylthiophene, as a white plates, (0.71 g, 37 %), m.p. 176.5-180 °C; (Found: C, 70.6; H, 4.1; N, 11.7; S, 13.5. $C_{14}H_{10}N_2S$ requires C, 70.6; H, 4.2; N, 11.8; S, 13.5 %); ν_{max} (nujol) 1 600, 1 585, 1 460, 1 415 cm^{-1} (C=C/C=N); δ_H (90 MHz, $CDCl_3$, TMS) 7.43 (2 H, d, J 1.6 Hz, 3-H and 5-H), 7.48 (1 H, d, 3'-H), 8.64 (2 H, dd, J 1.4, J 5.0 Hz, 2-H and 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 119.6, 126.4, 140.5, 142.4 and 150.4 (arom. C); m/z 240 (M^+, 6 %), 239 (18), 238 (100).

N-Methylation of 2,5-di(4-pyridyl)thiophene.——Methyl iodide (4.56 g, 0.032 mol) and 2,5-di(4-pyridyl)thiophene (0.24 g, 0.001 mol) in ethanol (5 ml) were

heated under reflux for 5 h. After cooling, diethyl ether (~2 ml) was added to cause the precipitation of the compound, which was recrystallized from aqueous ethanol and dried to give N,N-dimethylated salt, as a yellow woolly solid, (0.55 g, 96 %), m.p. 279-281°C (Found: C, 36.8; H, 3.1; N, 5.1; S, 6.3; I, 48.4. $C_{16}H_{16}N_2SI_2$ requires C, 36.8; H, 3.1; N, 5.4; S, 6.1; I, 48.6 %); ν_{max} ($CHCl_3$) 1 635, 1 565, 1 535 cm^{-1} (C=C/C=N); δ_H (90 MHz, DMSO-d_6, TMS) 4.35 (3 H, s, NMe), 8.52 (3 H, d, J 6.4 Hz, 3-H, 5-H and 3'-H), 9.06 (2 H, d, J 6.8 Hz, 2-H and 6-H); δ_C (22.5 MHz, DMSO-d_6, TMS) 47.2 (NCH_3), 122.6, 133.3, 142.2, 145.8, 146.1 (arom. C); m/z 240 (M^+, 3 %), 239 (8), 238 (45), 237 (2), 222 (1), 210 (1), 142 (100).

2,5-Di(4-pyridyl)furan.——1,4-Di(4-pyridyl)butan-1,4-dione (2.0 g, 0.008 mol) and polyphosphoric acid (9-10 g) were stirred and heated for 4 h at 165-170 °C. The reaction mixture was poured into the crushed ice (100 g), neutralized with sodium carbonate solution and extracted dichloromethane (2 x 100 ml). The extracts were dried ($MgSO_4$), and evaporated to yield a brown solid, which was purified by flash column chromatography on a silica gel (ethyl acetate : dichloro methane; 5:1). The *dipyridylfuran* was further purified by recrystallization from ethanol-diethyl ether to give white needles, which are very hygroscopic, (1.01 g, 55 %), m.p. 156.5-158 °C; (Found: C, 72.5; H, 5.01; N, 10.2. $C_{14}H_{10}N_2O$ requires C, 75.7; H, 4.5; N, 12.6 %); ν_{max} ($CHCl_3$) 1 605, 1 585, 1570, 1 470, 1 445, 1 420 cm^{-1} (C=N/C=C); δ_H (90 MHz, $CDCl_3$, TMS) 7.48 (1 H, s, 3'-H), 7.85 (2 H, d, J 4.9 Hz, 3-H and 5-H), 8.65 (2 H, d, J 5 Hz, 2-H and 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 112.1, 117.6, 136.0, 150.2, 151.6 (arom. C); m/z 223 (M^+, 15 %), 222 (100). A satisfactory elemental analysis could not be obtained.

N-Methylation of 2,5-di(4-pyridyl)furan.——Methyl iodide (9.12 g, 0.064 mol) and 2,5-di(4-pyridyl)furan (0.32 g, 0.001 mol) in ethanol (10 ml) were

heated under reflux for 5 h, cooled and diethyl ether (~2 ml) was added to cause the precipitation of the compound, which was recrystallised from ethanol-diethyl ether and dried to give the *N,N'-dimethylated salt*, as a yellow solid, (0.66, 91 %), m.p. 299-300 °C; (Found: C, 37.8; H, 3.2; N, 5.3; I, 50.2. $C_{16}H_{16}N_2OI_2$ requires C, 38.0; H, 3.2; N, 5.5; I, 50.1 %); ν_{max} (nujol) 1 633, (C=N-Me), 1 590, 1 565 cm^{-1} (C=C/C=N); δ_H (90 MHz, DMSO-d_6, TMS) 4.36 (3 H, s, NMe), 8.09 (1 H, s, 3'-H), 8.70 (2 H, d, J 6.4 Hz, 3-H and 5-H), 9.12 (2 H, d, J 5.7 Hz, 2-H and 6-H); δ_C (22.5 MHz, DMSO-d_6, TMS) 47.3 (NCH_3), 119.0, 121.2, 141.3, 145.8, 151.5 (arom. C); m/z 224 (M^+, 2 %), 223 (16), 222 (100).

Pyridine-2,5-dicarbonyl chloride.——Pyridine-2,5-dicarboxylic acid (10 g, 0.06 mol), and thionyl chloride (30 ml, 0.411 mol) in dry DMF (0.02 ml) were refluxed for 3 h; the mixture was cooled and excess of thionyl chloride was removed under the reduced pressure. The residual syrup was extracted with petroleum ether (b.p. 40/60 °C and 100 °C) in a Soxhlet extractor to give a cream coloured solid, which is very hygroscopic and sensitive to the air, light, and heat; the colour changes quickly from white to yellow, purple and dark blue, (9.99 g, 82 %), m.p. 55-56 °C (lit.,[20,21] 57 °C); ν_{max} (film) 1 775, 1 745 (C=O), 1 640, 1 585, 1 565 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 8.08 (1 H, d, 8 Hz, 3-H), 8.43 (1 H, dd, J 2.4 and J 8 Hz, 4-H), 9.36 (1 H, d, J 2.2 Hz, 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 124.8, 132.7, 140.1, 151.6 and 152.7 (arom. C), 166.0, 168.9 (COCl); m/z 205 (M^+, 2 %), 203 (3), 171 (3), 170 (33), 169 (8), 168 (100).

2,5-Bis(N-methylcarboxanilido)pyridine.——Pyridine-2,5-dicarbonyl chloride (5.1 g, 0.025 mol) in THF (20 ml) was added dropwise to a solution of distilled N-methylaniline (10.72 g, 0.1 mol) in THF (30 ml) with stirring for over a period 1 h. An exothermic reaction took place and N-methylaniline hydrochloride

precipitated from the warm solution. The solution was stirred at room temperature for 30 min, filtered under vacuum, and the solid was washed with diethyl ether (50 ml). The combined filtrates were evaporated and the oily residue was diluted with warm diethyl ether (~2 ml) to give a yellow solid, which was recrystallised from toluene as a cream coloured crystals, (15.72 g, 91 %), m.p. 157.5-159.5 °C (lit.,[22] 159 °C); ν_{max} (film) 1 665 (CONMePh), 1 600, 1 505, 1 445 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 3.02 and 3.04 (3 H, s, CH_3), 6.80-7.70 (12 H, m, 3-H, 4-H and Ph-H), 8.16 (1 H, d, J 1.2 Hz, 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 38.0 and 38.3 (CH_3), 122.7, 126.5, 126.6, 126.9, 127.2, 129.0, 129.5, 131.7, 136.5, 143.8, 143.9, 148.2 and 154.51 (arom. C), 167.4, 168.0 (CONMePh); m/z 345 (M^+, 1 %), 212 (1), 166 (1), 165(1), 119 (1), 108 (6), 107 (80), 106 (100).

Attempted preparation of 2,5-diformylpyridine.—Lithium aluminium hydride (0.19 g, 0.005 mol) was added in small portions to a solution of 2,5-bis(N-methylcarboxanilido)pyridine (3.454 g, 0.010 mol) in dry THF (100 ml) at 0 °C with stirring. The mixture was stirred at 15 °C for 5 h, and 2N HCl solution (~10 ml) was then added. The solution was made weakly basic with 2N Na_2CO_3. The precipitate was collected and washed warm dichloromethane (30 ml). The combined extracts were dried over Na_2SO_4 and concentrated. Unchanged diamide was precipitated, when the residue was dissolved in warm diethyl ether. Removal of the solvent gave a brown liquid (1.41 g), ^1H NMR spectrum which showed a proton for aldehyde group. TLC analysis showed some base-line material, some starting material and four other products. Attempted purification by column chromatography using silica gel or neutral alumina eluting with petroleum ether gave four products (each of which was contaminated with traces of at least one of the other products). NMR analysis of

all four mixtures showed the presence of two aldehyde groups. The compound could not purified further.

Dimethyl pyridine-2,5-dicarboxylate.——(a) Pyridine-2,5-dicarboxylic acid (1.67 g, 0.01 mol), boron trifluoride-methanol complex (51 % BF_3; 2 equiv., 4.4 ml) in an excess of dry methanol (22 ml) was heated under reflux for 6 h, After cooling, the mixture was poured into saturated sodium hydrogen carbonate solution and the dimethyl ester was collected as a yellow solid, which was washed several times with cold ethanol. The crude product was purified by recrystallization twice from ethanol to give the dimethyl ester as a pale cream solid, (1.57 g, 81 %), m.p. 163-164 °C (lit.,[23] 164 °C); ν_{max} (nujol) 1 725, 1 710 (C=O), 1 600, 1 570, 1 465 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 3.95 (3 H, s, CH_3), 4.0 (3 H, s, CH_3), 8.11 (1 H, d, 8 Hz, 3-H), 8.44 (1 H, dd, J 2.5 and J 8 Hz, 4-H), 9.26 (1 H, d, J 2.4 Hz, 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 52.2, and 53.2 (CH_3), 124.7, 128.7, 138.3, 150.7 and 150.9 (arom. C), 164.8, 164.9 (COOMe); m/z 195 (M^+, 2 %), 166 (2), 165 (16), 165 (18), 164 (16), 138 (8), 137 (100).

(b) According to the procedure by Tsuda and et al.,[24] concentrated sulphuric acid (10 ml) was added to a suspension of 2,5-pyridinedicarboxylic acid (10 g, 0.06 mol) in methanol (30 ml) over a period of 30 min. The reaction mixture was refluxed for 24 h, and excess methanol was removed. The residue was diluted with ice-water (500 ml), neutralized with solid $NaHCO_3$, and then extracted with diethyl ether. The organic layer was washed with brine, dried (Na_2SO_4), and solvent was removed to yield a yellow solid, which was purified by recrystallization from aqueous ethanol to give the dimethyl ester as a pale cream solid, (8.17 g, 67 %).

Diethyl pyridine-2,5-dicarboxylate.——Concentrated H_2SO_4 (10 ml) was added to a suspension of 2,5-pyridinedicarboxylic acid (10 g, 0.06 mol) in absolute ethanol (30 ml) over a period of 30 min. The brown mixture was refluxed for 16 h and alcohol was removed. The residue was poured onto ice-water (500 ml). Solid $NaHCO_3$ was then added until the mixture was neutralized, and the aqueous solution was extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to yield a yellow solid (9.98 g), which was purified by column chromatography eluting with diethyl ether-hexane (1:3) to give a white solid (9.5 g). Recrystallization from diethyl ether-hexane gave the diethyl ester as a white plates, (9.01 g, 67 %), m.p. 44-46 °C (lit.,[25] 46-47 °C); ν_{max} (film) 1 730, 1 710 (C=O), 1 595, 1 570, 1 535, 1 475 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 1.47 (3 H, t, J 7.5 Hz, CH_3), 1.50 (3 H, t, J 7.5 Hz, CH_3), 4.55 (2 H, q, J 7.5 Hz, CH_2), 4.62 (2 H, q, J 7.5 Hz, CH_2), 8.17 (1 H, d, 8 Hz, 3-H), 8.47 (1 H, dd, J 2.4 and J 8 Hz, 4-H), 9.32 (1 H, d, J 2.4 Hz, 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 14.2, and 14.3 (CH_3), 61.9, and 62.3 (CH_2), 124.5, 128.8, 138.1, 150.8 and 151.2 (arom. C), 164.4, 164.5 (COOEt); m/z 223 (M^+, 1 %), 195 (1), 182 (1), 180 (1), 179 (12), 178 (16), 168 (1), 167 (2), 166 (2), 165 (16), 153 (1), 152 (1), 151 (100).

2,5-Bis(hydroxymethyl)pyridine.——(a) Lithium aluminium hydride (0.76 g, 0.02 mol) in dry diethyl ether (20 ml) was cooled to -5 °C in an ice bath. To the stirred suspension was added a solution of dimethyl pyridine-2,5-dicarboxylate (1.95 g, 0.01 mol) in dry ether (10 ml) over a period of 1 h under a nitrogen atmosphere. When the addition of the dimethyl ester was completed, water (20 ml) was added dropwise to the stirred reaction mixture, which was then filtered. The solid was extracted with methanol (5 x 25 ml) and the methanol extracts were dried (K_2CO_3) and evaporated. Recrystallisation of crude product from

methanol gave the bis(hydroxymethyl)derivative, as a light brown hygroscopic solid, (0.126 g, 9 %), m.p. 155-157 °C (lit.,[26,27] 157 °C); ν_{max} (film) 3 600, 3 100 (OH), 1 575, 1 500, 1 460, 1 400 cm^{-1} (C=C/C=N); δ_H (90 MHz, D_2O, TMS, ^tBuOH) 4.56 and 4.65 (2 H, s, CH_2), 4.71 (2 H, s, OH), 7.47 (1 H, d, 8 Hz, 3-H), 7.83 (1 H, dd, J 2.3 and J 8.2 Hz, 4-H), 8.43 (1 H, d, J 2.2 Hz, 6-H); δ_C (22.5 MHz, D_2O, TMS) 63.6, and 66.4 (CH_2OH), 124.0, 137.7, 139.8, 149.8 and 160.9 (arom. C); m/z 139 (M^+, 1 %), 138 (2), 66 (2), 64 (8), 49 (1), 46 (30), 45 (56), 44 (1), 43 (9), 42 (3), 32 (6), 31 (100).

(b) Diethyl pyridine-2,5-dicarboxylate (1.15 g, 0.005 mol) and $NaBH_4$ (1.14 g, 30 mol) in absolute ethanol (20 ml) was treated dropwise at - 10 °C to - 5 °C with $CaCl_2$ in ethanol (10 ml) over a 30 min period. The mixture was stirred for 2.5 h and then it was neutralized with concentrated H_2SO_4 (~2 ml). The $CaSO_4$, which precipitated, was removed by filtration and washed with ethanol (2 x 10 ml). Removal of the solvent gave 5-carbethoxy-2-hydroxy- methylpyridine, (0.75 g, 80 %), m.p. 67-68 °C (lit.,[28] 67 °C); (Found: C, 59.4; H, 6.2; N, 8.0. Calc. for $C_9H_{11}NO_3$ C, 59.7; H, 6.1; N, 7.7 %); ν_{max} ($CHCl_3$) 3 350 (OH), 1 725 (C=O), 1 595, 1 570 cm^{-1} (C=C/C=N); δ_H (60 MHz,$CDCl_3$, TMS) 1.44 (3 H, t, CH_3), 2.36 (1 H, s, OH), 4.48 (2 H, q, OCH_2), 4.84 (2 H, s, CH_2OH), 7.86 (1 H, d, 8 Hz, 3-H), 8.11 (1 H, dd, J 2.1 and J 8.0 Hz, 4-H), 8.68 (1 H, d, J 2.1 Hz, 6-H); m/z 181 (M^+, 2 %), 180 (3), 165 (2), 152 (3), 136 (4), 78 (4), 59 (2), 43 (11), 32 (19), 31 (100).

(c) To a solution of diethyl pyridine-2,5-dicarboxylate (33.5 g, 0.15 mol) in absolute ethanol (300 ml) was added $NaBH_4$ (11.4 g, 0.3 mol) in several portions over a 30 min period. Anhydrous $CaCl_2$ (33.3 g, 0.3 mol) in ethanol (200 ml) was then added dropwise over a 1 h period and the mixture was stirred at room temperature for 16 h. After neutralization with concentrated H_2SO_4 (~13 ml), the $CaSO_4$, which precipitated, was removed by filtration and washed with ethanol (2 x 5 ml). The combined filtrates were evaporated and the residue was

dissolved in water (10 ml) and purified by column by using Dowex 50W-X8 cation exchange resin (H^+ form). The column was eluted with H_2O until eluate was no longer acidic, and it was then eluted with dilute NH_4OH, to yield the 2,5-bis(hydroxymethyl)pyridine, (10.6 g, 51 %).

Attempted preparation of 5-carbethoxy-2-formylpyridine.——5-Carbethoxy-2-hydroxymethylpyridine (5.25 g, 0.029 mol) was dissolved in dioxane (40 ml) and water (1 ml), and selenium dioxide (2 g, 0.018 mol) was added. The mixture was heated at 100 °C for 4 h, cooled and filtered through Celite and washed with dioxane (30 ml). The filtrate and washings were concentrated and chromatographed on silica gel (ethyl acetate : hexane; 1:1) to give 5-carbethoxy-2-pyridinecarboxylic acid, as a orange solid, which was recrystallised from ethanol to give a orange/yellow crystals, (1.91 g, 34 %), m.p. 183-185 °C (lit.,[21] 185-186.5 °C); (Found: C, 55.2; H, 4.6; N, 7.0. Calc. for $C_9H_9NO_4$ C, 55.4; H, 4.7; N, 7.2 %); ν_{max} ($CHCl_3$) 1 720 (ester, C=O), 1 640 (COOH), 1 610, 1 575, 1 540, 1 450 cm^{-1} (C=C/C=N); δ_H (60 MHz, DMSO-d_6, TMS) 1.41 (3 H, t, CH_3), 4.43 (2 H, q, CH_2), 8.42 (2 H, q, J 8 Hz, 3-H, 4-H), 9.20 (1 H, s, 6-H), 10.59 (1 H, s, COOH); δ_C (22.5 MHz, DMSO-d_6, TMS) 13.9 (CH_3), 61.5 (OCH_2), 124.7, 128.0, 138.1, 149.6 and 151.8 (arom. C), 164.0 (COOEt), 165.4 (COOH); m/z 195 (M^+, 2 %), 152 (10), 151 (100).

Attempted preparation of 2,5-diformylpyridine.——(a) A suspension of freshly prepared manganese dioxide (60 g) in a solution of 2,5-bis (hydroxy methyl)pyridine (5.7 g, 0.041 mol) in dry chloroform (500 ml) was stirred under reflux for 5 h. The mixture was filtered and the solid was washed with diethyl ether (5 x 100 ml). The combined filtrate and washings were evaporated to dryness to give a dark green solid (0.18 g), which on TLC analysis proved to be

mostly base-line material; the ^{1}H NMR spectrum showed a signal for a monoaldehyde, not a dialdehyde. The product could not be purified or identified.

(b) Dimethyl sulfoxide (1.7 ml, 0.022 mol) in dichloromethane (5 ml) was added to the stirred oxalyl chloride (1 ml, 0.011 mol) in dichloromethane (25 ml) at -60 °C in a *ca.* 5 min. The mixture was stirred for 10 min and 2,5-bis(hydroxymethyl)pyridine (1.39 g, 0.01 mol) in dichloromethane (10 ml) was added over *ca.* 5 min, and the stirring was continued for additional 15 min. Triethylamine (7 ml, 0.05 mol) was added with stirring and the mixture was then allowed to warm to room temperature. Water (50 ml) was added and stirring was continued for 15 min. The mixture was extracted with dichloromethane (3 x 50 ml) and the combined extracts were washed with dilute hydrochloric acid, water, aqueous Na_2CO_3 (5 %) and water, then dried ($MgSO_4$). Removal of the solvent gave a brown solid, which was analysed by TLC and ^{1}H NMR spectroscopy and proved to be a mixture of the starting material and a product having an aldehyde group. The mixture could not be separated, because the yield was only 10 % for the mixture.

(c) Dimethyl sulfoxide (3.4 ml, 0.048 mol) in dichloromethane (5 ml) was added with stirring to oxalyl chloride (2 ml, 0.022 mol) in dichloromethane (25 ml) at -60 °C over *ca.* 5 min. The mixture was stirred for a further 10 min and 2,5-bis(hydroxymethyl)pyridine (1.39 g, 0.010 mol) in dichloromethane (10 ml) was added in *ca.* 5 min; the stirring was continued for additional 15 min. Triethylamine (14 ml, 0.1 mol) was added and the mixture was then allowed to warm to room temperature. Water (50 ml) was added and stirring was continued for 15 min. The mixture was extracted with dichloromethane (3 x 50 ml) and the extracts were dried ($MgSO_4$) and evaporated to give a brown liquid, which was analysed by TLC and ^{1}H NMR. Evidence we obtained for some base-

line material and two products. There was again 0.17 g (13 %) of a mixture of the products. The experiment was abondoned at this stage.

(d) Dimethyl pyridine-2,5-dicarboxylate (0.98 g, 0.005 mol) was dissolved in toluene (40 ml), was cooled to -70 °C. Diisobutylaluminum hydride (DIBAL-H, 9 ml of a 1 M solution, 0.009 mol) was added dropwise over a period of 15 min and the mixture was then stirred at -70 °C for 3 h under the nitrogen. A solution of acetic acid (25 ml), water (6 ml), and diethyl ether (50 ml) was added for over a period of 30 min, and the mixture was stirred at room temperature for further 30 min. The mixture was filtered and the different liquid phases were separated; the aqueous layer was extracted with toluene (3 x 5 ml) and the solid was also extracted with toluene (5 x 50 ml). The combined organic extracts were washed with brine (10 ml), dried (Na_2CO_3), and purified by chromatography on a neutral alumina eluting with ethyl acetate-petroleum ether (1:1) to give the starting material (0.46 g) and 5-carbomethoxy-2-formyl pyridine as a white solid, (0.26 g, 31%), m.p. 124-126 °C (lit.,[29] 122-125 °C); ν_{max} ($CHCl_3$) 1 725 (ester, C=O), 1 710 (aldehyde, C=O), 1 570, 1 435 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 4.02 (3 H, s, CH_3), 8.11 (1 H, d, J 8 Hz, 3-H), 8.51 (1 H, dd, J 1.9 and 8 Hz, 4-H), 9.38 (1 H, d, J 2.2 Hz, 6-H), 10.18 (1 H, s, CHO); δ_C (22.5 MHz, $CDCl_3$, TMS) 52.8 (OCH_3), 121.0, 129.2, 138.3, 151.2 and 155.0 (arom. C), 164.8 (COOMe), 192.5 (CHO).

(e) Dimethyl 2,5-pyridinecarboxylate (1.95 g, 0.01 mol) in dry toluene (70 ml) was cooled to -70 °C and DIBAL-H (26 ml of a 1 M solution, 0.026 mol) was added dropwise for over a period of 30 min under a nitrogen atmosphere. The mixture was stirred at -70 °C for 24 h and a solution of acetic acid (25 ml), water (5 ml) and diethyl ether (50 ml) was then added over a period of 30 min. The mixture was allowed to warm to the room temperature and stirred at room temperature for further 1 h. The mixture was filtered and the liquid phases

were separated and the aqueous layer extracted with toluene (5 x 10 ml); the solid was also extracted with toluene (5 x 100 ml) at 70 °C. The combined organic extracts were washed with brine (20 ml), dried (Na_2CO_3), and purified by recrystallization from petroleum ether to give 2,5-diformylpyridine, as a white needles, (0.79 g, 59%), m.p. 65 °C (lit.,[30,31] 65 °C); ν_{max} (film) 1 715, 1 695 (C=O), 1 590, 1 565 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 8.11 (1 H, d, J 8 Hz, 3-H), 8.41 (1 H, dd, J 0.8 and J 1.9 Hz, 4-H), 9.26 (1 H, d, J 0.9 Hz, 6-H), 10.16 and 10.28 (1 H, s, CHO); δ_C (22.5 MHz, $CDCl_3$, TMS) 121.7, 133.6, 137.3, 151.9 and 155.7 (arom. C) 189.8, 192.3 (CHO); m/z 137 (M^+, 1 %), 136 (3), 135 (33), 134 (2), 109 (1), 108 (7), 107 (100).

2,5-Bis(1,4-dioxopent-1-yl)pyridine.—But-3-en-2-one (2.45 g, 0.035 mol), 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (1.13 g, 0.042 mol) and dry triethylamine (2.13 g, 0.021 mol) in dry dioxane (10 ml) were heated at 90-100 °C under nitrogen. 2,5-Diformylpyridine (1.89 g, 0.014 mol) in dry dioxane (20 ml) was added dropwise slowly over a period of 1 h, and the mixture was then stirred at 90-100 °C for further 18 h. The mixture was cooled to room temperature and the solvent were removed under vacuum. Water (50 ml) was added and the aqueous layer was extracted with dichloromethane (3 x 50 ml). The combined organic extracts were washed with brine (5 ml) and dried ($MgSO_4$). Filtration and removal of the solvent gave the crude product as a dark brown liquid, which was purified by flash column chromatography eluting with ethyl acetate : dichloromethane (1:2) and recrystallisation twice from dichloromethane-hexane to give 2,5-bis(1,4-dioxopent-1-yl)pyridine, as a bright white needles, (2.65 g, 69 %), m.p. 80-82.5 °C; (Found: C, 65.1; H, 6.0; N, 5.0. $C_{15}H_{17}NO_4$ requires C, 65.5; H, 6.2; N, 5.1 %); ν_{max} (nujol) 1705 and 1 685 (C=O), 1 585 and 1 565 cm^{-1} (C=C/C=N); δ_H (90 MHz, $CDCl_3$, TMS) 2.24 and 2.25 (3 H,

s, CH_3), 2.82-3.00 (4 H, m, 2 x CH_2), 3.22-3.58 (4 H, m, 2 x CH_2), 8.23 (1 H, dd, J 0.8 and 8.1 Hz, 3-H), 8.35 (1 H, dd, J 2.2 and 8.2 Hz, 4-H), 9.22 (1 H, dd, J 1.0 and 2.4 Hz, 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 29.9 and 32.1 (CH_3), 32.9, 36.9, 37.2, 53.1 (CH_2), 121.5, 134.2, 138.3, 148.9 and 150.8 (arom. C), 197.1, 199.6, 206.5 and 206.8 (C=O); m/z 276 (M^+, 5 %), 275 (29), 258 (5), 232 (100).

2,5-Bis(2-methyl-5-thienyl)pyridine.——2,5-Bis(1,4-dioxopent-1-yl) pyridine (0.8 g, 0.003 mol) and Lawesson's reagent (1.47 g, 0.004 mol) in dry toluene (100 ml) were kept under nitrogen at 110 °C for 50 h. The reaction mixture was then allowed to cool to room temperature and the solvent removed to give a brown solid, which was purified by column chromatography from silica gel, using ethyl acetate : petroleum ether (1:1) as the eluent. Recrystallisation from dichloromethane-hexane gave the *bisthienylpyridine,* compound as a white needles, (0.48 g, 61 %), m.p. 162-165 °C; (Found: C, 66.4; H, 4.8; N, 4.9; S, 23.5. $C_{15}H_{13}NS_2$ requires C, 66.4; H, 4.8; N, 5.2; S, 23.6 %); ν_{max} ($CHCl_3$) 1 585, 1 500, 1 465, 1 435 cm^{-1} (C=C/C=N); δ_H (90 MHz, $CDCl_3$, TMS) 2.01 and 2.49 (3 H, s, CH_3), 6.72 (2 H, dd, J 1.0, J 3.5 Hz, 4'-H), 7.09 (1 H, d, J 3.5 Hz, 3'-H), 7.48 (1 H, dd, J 0.8 and 8.3 Hz, 3'-H), 7.69 (2 H, dd, J 2,2 and 8.4 Hz, 3-H and 4-H), 8.72 (1 H, d, J 1.5 Hz, 6-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 15.3 and 15.5 (CH_3), 118.6, 121.3, 123.6, 124.5, 126.5, 128.4, 132.8, 138.2, 140.4, 142.1, 142.4, 146.1 and 151.1 (arom. C); m/z 274 (M^+, 2 %), 273 (11), 272 (21), 271 (100).

Attempted preparation of 1-methyl-2,5-bis(5-methyl-2-thienyl) pyridinium iodide.——(a) Methyl iodide (3.42 g, 0.024 mol) was added to 2,5-bis(2-methyl-5-thienyl)pyridine (0.15 g, 0.001 mol) in ethanol (5 ml) and the mixture refluxed for 24 h. After cooling, diethyl ether (~2 ml) was added to cause the precipitation

of the product (0.13 g). TLC and ^{1}H NMR analysis showed only starting material (0.13 g).

(b) 2,5-Bis(2-methyl-5-thienyl)pyridine (0.13 g, 0.0005 mol) and methyl iodide (2.5 ml) were refluxed for 12 h; the mixture was cooled and the precipitated solid was collected, washed with cold ethanol (1 ml), and dried. Analysis by TLC and ^{1}H NMR spectroscopy showed only starting material.

Attempted preparation of 2,5-bis(2-methyl-5-furyl)pyridine.——2,5-Bis (1,4-dioxopent-1-yl)pyridine (0.8 g, 0.003 mol) and polyphosphoric acid (7-8 g) were stirred and heated for 4 h at 130-140 °C. The solution was poured into the crushed ice (50 g), neutralized with sodium carbonate solution, and then extracted with dichloromethane (2 x 50 ml). The organic extracts were dried ($MgSO_4$), and evaporated to yield a brown oily solid. Analysis with TLC and ^{1}H NMR spectroscopy showed some base-line material and the starting material.

(b) 2,5-Bis(1,4-dioxopent-1-yl)pyridine (0.23 g, 0.001 mol) and polyphosphoric acid (2 g) was stirred and heated for 8 h at 160-170 °C. The solution was poured into the crushed ice (50 g), neutralized with sodium carbonate solution and then extracted with dichloromethane (2 x 20 ml). Analysis of the product mixture by TLC showed some dark base-line material and mainly starting material. Removal of the solvent gave a viscous brown oil (0.2 g). The experiment was abandoned at this stage.

Activated manganese dioxide.——Following the procedure described by Harfenist, Bavley, and Lazier,[32] manganese dioxide (40 g) was stirred with aqueous nitric acid (15 %, 100ml). The slurry was filtered and the solid washed with distilled water until the washings were about pH 5, and finally the solid

was dried at 220-250 °C. The friable caked black solid was immediately crushed to a powder.

2,6-Diformylpyridine.——A suspension of freshly prepared activated manganese dioxide (60 g) in a solution of 2,6-bis(hydroxymethyl)pyridine (5.7 g, 0.041 mol) in dry chloroform (500 ml) was stirred under reflux for 5 h. The mixture was filtered and the solid was washed with diethyl ether (5 x 100 ml). The combined filtrates and washings were evaporated to dryness to give a pale yellow solid which was recrystallised from petroleum ether to give 2,6-diformylpyridine as a white needles, (3.0 g, 54%), m.p. 123-124 °C (lit.,[33] 122-124 °C); ν_{max} (film) 1 715, 1 695 (C=O), 1 580, 1 560, 1 490, 1 420 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 8.16 (3 H, m, 3-H, 4-H and 5-H), 10.03 and 10.04 (2 H, s, CHO); δ_C (22.5 MHz, $CDCl_3$, TMS) 125.3, 138.4 and 153.0 (arom. C), 192.3 (CHO); m/z 137 (M^+, 3 %), 136 (7), 135 (62), 108 (7), 107 (100).

2,6-Bis(1,4-dioxopent-1-yl)pyridine.——But-3-en-2-one (3.5 g, 0.05 mol), 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (1.62 g, 0.006 mol) and dry triethylamine (3.03 g, 0.003 mol) in dry dioxane (10 ml) were heated at 90-100 °C under nitrogen. 2,6-Diformylpyridine (2.70 g, 0.02 mol) in dry dioxane (20 ml) was added dropwise slowly over a period of 1 h, and the mixture was then stirred at 90-100 °C for further 12 h. The mixture was cooled to room temperature and the solvents were removed under vacuum. Water (30 ml) was added and the aqueous layer was extracted with dichloromethane (3 x 50 ml). The combined organic extracts were washed with brine (5 ml) and dried ($MgSO_4$). Filtration and removal of the solvent gave a crude product, as a dark brown liquid which was filtered through a short column of silica eluting with ethyl acetate. Recrystallisation twice from ethanol gave *2,6-bis(1,4-dioxopent-1-*

yl)pyridine, as a cream coloured plates, (4.18 g, 76 %), m.p. 93-94 °C; (Found: C, 65.3; H, 6.2; N, 5.1. $C_{15}H_{17}NO_4$ requires C, 65.5; H, 6.2; N, 5.1 %); ν_{max} ($CHCl_3$) 1 695 and 1 645 (C=O), 1 590 and 1 545, 1 405 cm^{-1} (C=C/C=N); δ_H (90 MHz, $CDCl_3$, TMS) 2.26 (6 H, s, 2 x CH_3), 2.92 (4 H, t, 2 x CH_2), 3.57 (4 H, t, 2 x CH_2, 7.95-8.23 (3 H, m, 3-H, 4-H, and 5-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 29.9 (CH_3), 31.7 and 37.0 (CH_2), 124.8, 138.0, and 152.2 (arom. C), 199.5, and 206.9 (C=O); m/z 276 (M^+, 5 %), 275 (29), 232 (59), 214 (16), 176 (8), 162 (2), 134 (12), 106 (9), 99 (19), 78 (18), 55 (12), 43 (100).

2,6-Bis(2-methyl-5-thienyl)pyridine.——2,6-Bis(1,4-dioxopent-1-yl)pyridine (1.8 g, 0.007 mol) and Lawesson's reagent (3.80 g, 0.009 mol) in dry toluene (100 ml) were heated at 110 °C for 50 h under N_2. The reaction mixture was then allowed to cool to room temperature and the solvent removed to give a brown oil, which was purified by column chromatography (silica gel, ethyl acetate : petroleum ether; 1:1). Recrystallization from dichloro methane-hexane gave the *bisthienylpyridine*, as a white needles, (0.98 g, 55 %), m.p. 115-117 °C; (Found: C, 66.4; H, 4.9; N, 5.0; S, 23.7. $C_{15}H_{13}NS_2$ requires C, 66.4; H, 4.8; N, 5.2; S, 23.6 %); ν_{max} ($CHCl_3$) 1 585, 1 565, 1 485, 1 440 cm^{-1} (C=C/C=N); δ_H (400 MHz, $CDCl_3$, TMS) 2.55 (6 H, s, 2 x CH_3), 6.74 (2 H, dd, J 1.0, J 3.6 Hz, 2 x 4'-H), 7.39 (4 H, m, 2 x 3-H and 2 x 3'-H) , 7.56 (1 H, dd, J 0.6 and 7.6 Hz, 4-H); δ_C (100 MHz, $CDCl_3$, TMS) 15.6 (CH_3), 115.6, 124.6, 126.2, 136.9, 142.4, 142.5, and 152.1 (arom. C); m/z 273 (M^+, 11 %), 272 (21), 271 (100).

Attempted preparation of 1-methyl-2,6-bis(5-methyl-2-thienyl) pyridinium iodide.——(a) Methyl iodide (3.42 g, 0.024 mol) was added to 2,6-bis(2-methyl-5-thienyl)pyridine (0.15 g, 0.0005 mol) in ethanol (5 ml) and the mixture was refluxed for 24 h. After cooling, diethyl ether (~2 ml) was added to cause the

yl)pyridine, as a cream coloured plates, (4.18 g, 76 %), m.p. 93-94 °C; (Found: C, 65.3; H, 6.2; N, 5.1. $C_{15}H_{17}NO_4$ requires C, 65.5; H, 6.2; N, 5.1 %); ν_{max} ($CHCl_3$) 1 695 and 1 645 (C=O), 1 590 and 1 545, 1 405 cm^{-1} (C=C/C=N); δ_H (90 MHz, $CDCl_3$, TMS) 2.26 (6 H, s, 2 x CH_3), 2.92 (4 H, t, 2 x CH_2), 3.57 (4 H, t, 2 x CH_2, 7.95-8.23 (3 H, m, 3-H, 4-H, and 5-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 29.9 (CH_3), 31.7 and 37.0 (CH_2), 124.8, 138.0, and 152.2 (arom. C), 199.5, and 206.9 (C=O); m/z 276 (M^+, 5 %), 275 (29), 232 (59), 214 (16), 176 (8), 162 (2), 134 (12), 106 (9), 99 (19), 78 (18), 55 (12), 43 (100).

2,6-Bis(2-methyl-5-thienyl)pyridine.——2,6-Bis(1,4-dioxopent-1-yl)pyridine (1.8 g, 0.007 mol) and Lawesson's reagent (3.80 g, 0.009 mol) in dry toluene (100 ml) were heated at 110 °C for 50 h under N_2. The reaction mixture was then allowed to cool to room temperature and the solvent removed to give a brown oil, which was purified by column chromatography (silica gel, ethyl acetate : petroleum ether; 1:1). Recrystallization from dichloro methane-hexane gave the *bisthienylpyridine*, as a white needles, (0.98 g, 55 %), m.p. 115-117 °C; (Found: C, 66.4; H, 4.9; N, 5.0; S, 23.7. $C_{15}H_{13}NS_2$ requires C, 66.4; H, 4.8; N, 5.2; S, 23.6 %); ν_{max} ($CHCl_3$) 1 585, 1 565, 1 485, 1 440 cm^{-1} (C=C/C=N); δ_H (400 MHz, $CDCl_3$, TMS) 2.55 (6 H, s, 2 x CH_3), 6.74 (2 H, dd, J 1.0, J 3.6 Hz, 2 x 4'-H), 7.39 (4 H, m, 2 x 3-H and 2 x 3'-H) , 7.56 (1 H, dd, J 0.6 and 7.6 Hz, 4-H); δ_C (100 MHz, $CDCl_3$, TMS) 15.6 (CH_3), 115.6, 124.6, 126.2, 136.9, 142.4, 142.5, and 152.1 (arom. C); m/z 273 (M^+, 11 %), 272 (21), 271 (100).

Attempted preparation of 1-methyl-2,6-bis(5-methyl-2-thienyl) pyridinium iodide.——(a) Methyl iodide (3.42 g, 0.024 mol) was added to 2,6-bis(2-methyl-5-thienyl)pyridine (0.15 g, 0.0005 mol) in ethanol (5 ml) and the mixture was refluxed for 24 h. After cooling, diethyl ether (~2 ml) was added to cause the

precipitation of the compound. TLC and ^{1}H NMR analysis showed only starting material.

(b) 2,6-Bis(2-methyl-5-thienyl)pyridine (0.13 g, 0.0005mol) and methyl iodide (4 g, 0.028 mol) were refluxed for 12 h. The mixture was cooled and analysed by TLC and proved to be unreacted starting material.

(c) 2,6-Bis(2-methyl-5-thienyl)pyridine (0.11 g, 0.0004 mol) and ethyl bromide (3 ml) were refluxed for 24 h. Usual work-up afforded only the starting material.

(d) 2,6-Bis(2-methyl-5-thienyl)pyridine (0.11 g, 0.0004 mol) and methyl *p*-toluene sulfonate (1 g, 0.005 mol) were kept at reflux for 4 h. The mixture was analysed by TLC and proved to be starting material as before.

(e) Methyl trifluoromethanesulfonate (0.073 g, 0.0005 mol) was added dropwise to a stirred, cooled (ice-bath), solution of 2,6-bis(2-methyl-5-thienyl) pyridine (0.11 g, 0.0004 mol) in toluene (5 ml). The mixture was stirred at room temperature for 12 h. TLC analysis showed only the starting material. The mixture was then heated at reflux for a further 12 h, cooled, and the precipitated solid was collected and dried. TLC analysis showed again starting material.

(f) The experiment in above (section e) was repeated under the same conditions, but without solvent. The result was same.

(g) 2,6-Bis(2-methyl-5-thienyl)pyridine (0.11 g, 0.0004 mol) and methyl iodide (1.0 g, 0.007 mol) was placed in a pressure vessel and heated at 100 °C for 24 h. After allowing it to stand overnight, the tube was opened and the reaction mixture was analysed by TLC and proved the unreacted starting material again.

(h) 2,6-Bis(2-methyl-5-thienyl)pyridine (0.36 g, 0.001 mol) and methyl iodide (3 ml) was heated at 100 °C for 7 d, in a pressure vessel. The usual work up afforded the starting material.

2,6-Bis(2-methyl-5-furyl)pyridine.——2,6-Bis(1,4-dioxopent-1-yl)pyridine (2.0 g, 0.007 mol) and polyphosphoric acid (16-18 g) was stirred and heated for 4 h at 130-140 °C. The solution was poured into the crushed ice (100 g), neutralized with aqueous sodium carbonate, and then extracted with dichloromethane (3 x 100 ml). The organic extracts were dried ($MgSO_4$) and evaporated to yield a brown solid, which was purified by flash column chromatography eluting with ethyl acetate : petroleum ether (1:1) to give the *bisfurylpyridine*, as a pale yellow crystals, (1.28 g, 74 %), m.p. 128-130 °C; (Found: C, 75.0; H, 5.4; N, 5.7. $C_{15}H_{13}NO_2$ requires C, 75.3; H, 5.5; N, 5.9 %); ν_{max} ($CHCl_3$) 1 580, 1 545, 1 470, 1 435 cm^{-1} (C=C/C=N); δ_H (400 MHz, $CDCl_3$, TMS) 2.48 (6 H, s, 2 x CH_3), 6.09 (2 H, d, J 3.3 Hz, 2 x 4'-H), 7.01 (2 H, d, J 2.9 Hz, 2 x 3'-H), 7.2-7.8 (3 H, m, 3-H, 4-H, and 5-H); δ_C (100 MHz, $CDCl_3$, TMS) 13.8 (CH_3), 108.2, 109.9, 115.7, 136.9, 149.2, 152.2, 153.3 (arom. C); m/z 243 (M^+, 1 %), 241 (2), 240 (16), 239 (100).

Attempted preparation of 1-methyl-2,6-bis(5-methyl-2-furyl) pyridinium iodide.——(a) Methyl iodide (4 g, 0.028 mol) was added to 2,6-bis(2-methyl-5-furyl)pyridine (0.36 g, 0.0015 mol) in ethanol (5 ml) and the mixture refluxed for 24 h, cooled, and diethyl ether (~1 ml) was added to cause the precipitation of the product. TLC and ^1H NMR analysis showed only starting material.

(b) 2,6-Bis(2-methyl-5-furyl)pyridine (0.36 g, 0.0015 mol) and methyl iodide (5 g, 0.035 mol) were heated under reflux for 12 h. The mixture was cooled, and the precipitated solid was collected and washed with cold ethanol (3 ml). TLC analysis again showed only starting material.

(c) 2,6-Bis(2-methyl-5-furyl)pyridine (0.36 g, 0.0015 mol) and ethyl bromide (3 ml) was refluxed for 24 h. The mixture was cooled, TLC analysis detected only unreacted starting material.

(d) 2,6-Bis(2-methyl-5-furyl)pyridine (0.1 g, 0.0004 mol) and methyl *p*-toluene sulfonate (1 g, 0.005 mol) were refluxed for 4 h. The mixture was analysed by TLC and proved to be starting material.

(e) Methyl trifluoromethanesulfonate (0.073 g, 0.0005 mol) was added dropwise to a stirred, cooled (ice-bath) solution of 2,6-bis(2-methyl-5-furyl)pyridine (0.1 g, 0.0004 mol) in toluene (5 ml). The mixture was stirred at room temperature for 12 h. TLC analysis showed mostly starting material and some base-line material. The mixture was then heated at reflux for a further 12 h and cooled. The precipitated solid was collected and dried. TLC analysis showed again starting material.

(f) The experiment in above (section e) was repeated under the same conditions, but without solvent. The result was same as above.

(g) 2,5-Bis(2-methyl-5-furyl)pyridine (0.1 g, 0.0004 mol) and methyl iodide (1.0 g, 0.004 mol) were placed in a pressure vessel and heated at 100 °C for 24 h. The pressure vessel was allowed to stand overnight and then opened. Analysis by TLC proved that only unreacted starting material was present.

(h) 2,5-Bis(2-methyl-5-furyl)pyridine (0.36 g, 0.002 mol) and methyl iodide (6 g, 0.042 mol) were heated at 100 °C for 10 d in a pressure vessel. The usual work-up afforded the starting material.

3.4 Experimental for Chapter 4

Diethyl pyridine-2,6-dicarboxylate.——To a suspension of 2,6-pyridine-dicarboxylic acid (10 g, 0.06 mol) in absolute ethanol (30 ml) was added concentrated H_2SO_4 (10 ml) over a period of 30 min. During this time, the solid gradually dissolved. The brown mixture was refluxed for 21 h, and the alcohol was then removed under vacuum. The residue was poured into ice-water (500

ml). Solid $NaHCO_3$ was added until the mixture was neutral, and extracted with ethyl acetate. The organic phase was separated and washed with brine, dried (Na_2SO_4), and concentrated to yield a white solid, which was recrystallized from diethyl ether-hexane to give the diethyl ester as a white needles, (9.77 g, 73 %), m.p. 40-42 °C (lit.,[34] 40-42 °C); (Found: C, 59.0; H, 5.8; N, 6.3. Calc. for $C_{11}H_{13}NO_4$ C, 59.2; H, 5.9; N, 6.3 %); ν_{max} (film) 1 745, 1 725 (C=O), 1 585, 1 480, 1 470, 1 425 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 1.42 (6 H, 2 t, J 7.2 Hz, 2 x CH_3), 4.48 (4 H, 2 q, J 7.2 Hz, 2 x CH_2), 7.84-8.40 (3 H, m, 3-H, 4-H, 5-H); m/z 223 (M^+, 1 %), 208 (1), 180 (1), 179 (10), 178 (9), 153 (1), 152 (10), 151 (100).

2,6-Diacetylpyridine.——Diethyl-2,6-pyridinedicarboxylate (3.35 g, 0.015 mol) in dry ethyl acetate (20 ml) was added dropwise to sodium methoxide (2.04 g, 0.038 mol) with stirring, and then refluxed for 12 h. The mixture was kept at room temperature overnight, and concentrated hydrochloric acid (10 ml) was then added over a period of 30 min and the mixture was heated for 4 h. The residue was poured into water, extracted with diethyl ether (5 x 50 ml), and dried ($MgSO_4$). Removal of the solvent gave the crude product which was purified by column chromatography eluting with ethyl acetate : petroleum ether (1:1) to give 2,6-diacetylpyridine, as a white solid, (0.52 g, 21 %), m.p. 80-82 °C (lit.,[35,36] 78-79 °C); ν_{max} ($CHCl_3$)1 710, 1 700 (C=O), 1 585, 1 565, 1 415 cm^{-1} (C=C/C=N); δ_H (60 MHz, $CDCl_3$, TMS) 2.78 (6 H, s, 2 x CH_3), 7.80-8.30 (3 H, m, 3-H, 4-H, 5-H); δ_C (22.5 MHz, $CDCl_3$, TMS) 25.5 (CH_3), 124.7, 138.0, 152.8 (arom. C), 199.2 (COMe); m/z 164 (M^+, 8 %), 163 (77), 148 (2), 135 (14), 121 (41), 120 (32), 106 (26), 93 (17), 79 (10), 78 (9), 63 (15), 43 (100).

2,6-Bis(3-dimethylamino-1-oxopropyl)pyridine dihydrochloride.——According to Krohnke,[37] 2,6 diacetylpyridine (2.45 g, 0.015 mol), vigorously dried

dimethylammonium chloride (2.45 g, 0.03 mol) and a 6-fold excess of paraformaldehyde (5 g, 0.18 mol) were heated at 60 °C in dry ethanol (25 ml) containing concentrated hydrochloric acid (0.1 ml) under nitrogen for 5 h, with the strict exclusion of moisture. The mixture was allowed to cool and the precipitates were filtered. Removal of about half of the solvent gave an orange/pink coloured solid, which was washed with ice-cold ethanol until the coloration had been removed and dried under vacuum to give the protonated bis-Mannich base, as an unstable white solid, (2.32 g, 45 %), m.p.> 260 °C; ν_{max} (nujol) 3 300 (NH), 1 705 (C=O), 1 585, 1 565, 1 415 cm^{-1} (C=C/C=N). ^1H NMR spectrum could not obtained due to rapid decomposition of the product in D_2O solution.

Polymer (4.6) derived from 2,6-diformylpyridine and 2,6-bis(3-dimethylamino-1-oxopropyl)pyridine.—2,6-Bis(3-dimethylamino-1-oxopropyl)pyridinedihydrochloride (2.0 g, 0.0057 mol) and 3-benzyl-5-(2-hydroxy- ethyl)-4 methyl-1,3-thiazolium chloride (0.32 g, 0.012 mol) in dry DMF (8 ml) were stirred and heated to 85 °C. A solution of triethylamine (2.08 g, 0.013 mol) and 2,6-diformylpyridine (0.77 g, 0.0057 mol) in dry DMF (8 ml) was added dropwise via a gas-tight syringe over a period of 20 min. The mixture was then stirred for further 8 h until it became very viscous and then allowed to stand at room temperature for 15 h. The mixture was well washed with water and the polymer precipitated. In order to remove low molecular species the polymer was thoroughly washed with a variety of solvents (benzene, dichloromethane, ethanol, ethyl acetate and petroleum ether) leading to give the polymer, (1.39 g), m.p.> 300 °C (lit.,[38] m.p.> 300 °C); (Found: C, 64.4; H, 4.9; N, 8.2. Calc. for $C_9H_7NO_2$ C, 67.1; H, 4.4; N, 8.7 %); ν_{max} (KBr) 1 690 (C=O), 1 590 and 1 545,

1 405 cm^{-1} (C=C/C=N); δ_C (50.29 MHz, solid state) 34.9 (CH_2), 125.6, 137.8, 151.4 (arom. C), 199.7 (C=O).

Thiophene polymer (4.8) obtained from the poly-1,4-diketone (4.6).——The polymeric diketone (4.6) (0.81 g) and Lawesson's reagent (1.69 g, 0.004 mol) in dry 1,2-dichlorobenzene (65 ml) were heated at 190 °C for 50 h under N_2. The reaction mixture was then allowed to cool to room temperature and the solvent was removed. The brown residue was collected and washed with water and a variety of solvents (dichloromethane, ethanol, ethyl acetate and petroleum ether) to give the polymer (2), (0.61 g), m.p. > 300 °C; (Found: C, 59.7 H, 4.0; N, 5.4; S, 14.8. C_9H_5NS requires C, 67.9; H, 3.2; N, 8.8; S, 20.1 %); ν_{max} (KBr) 1 595, 1 565, 1 500, 1 445 cm^{-1} (C=C/C=N); δ_C (50.29 MHz, solis state) 113.4, 123.1, 131.6, 134.6, 151.0 (arom. C).

Furan polymer (4.9) obtained from the poly-1,4-diketone (4.6).——The polymeric diketone (4.6) (0.5 g) and polyphosphoric acid (9.5-10 g) was stirred and heated for 12 h at 180-190 °C. The brown oil was poured into the crushed ice (100 g) and the polymer was then collected. Low molecular species were removed by washing with a variety of solvents (dichloromethane, ethanol, ethyl acetate and petroleum ether) to yield the polymer (4.9), (0.31 g), m.p.> 300 °C; (Found: C, 64.4; H, 2.2; N, 8.2. C_9H_5NO requires C, 75.5; H, 3.5; N, 9.8 %); ν_{max} (KBr) 1 580 and 1 545, 1 450 cm^{-1} (C=C/C=N); δ_C (50.29 MHz, solid state) 123.2, 136.5, 144.4, and 148.1 (arom. C).

Ethyl 3-dimethylaminopropionate.——Anhydrous dimethylamine (4.5 g, 0.1 mol) was cooled to 0 °C and added to ethyl acrylate (10.0 g, 0.1 mol). The mixture was left for 5 d at 4 °C, and the reaction mixture was then distilled to

give the aminopropionate, as a colourless liquid, (12.60 g, 87 %), b.p. 70-71 °C/21 mm Hg (lit.,[39] 56-57 °C/12 mm Hg); (Found: C, 58.0; H, 10.6; N, 9.6; Calc. for $C_7H_{15}NO_2$ C, 57.9; H, 10.4; N, 9.6 %); ν_{max} (film) 3 415, 2 940, 2 820, 1 735 cm^{-1} (C=O); δ_H (60 MHz, $CDCl_3$, TMS) 1.21 (3 H, t, J 7.2 Hz, CH_3), 2.02 (6 H, 2 s, NMe_2), 2.58 (4 H, t, J 4.8 Hz, NCH_2-CH_2), 4.08 (2 H, 2 q, J 7.2 Hz, OCH_2); δ_C (22.5 MHz, $CDCl_3$, TMS) 14.2 (CH_3), 33.0 ($COCH_2$), 45.2 and 45.3 (NMe), 54.8 (NCH_2), 60.2 (OCH_2), 172.4 (COOEt); m/z 145 (M^+, 5 %), 100 (2), 71 (1), 69 (1), 59 (1), 58 (100).

3-Dimethylamino-1-(2-pyridyl)propane-1-one.——(a) According to the procedure by Adamson and Billinghurst,[40] *n*-butyllithium (27 ml, 1.24 M, 0.033 mol) was added to a solution of 2-bromopyridine (5 g, 0.032 mol) in anhydrous ether (10 ml) at -50 °C over 15 min, and the mixture was stirred for 6 m. Ethyl 3-dimethylaminopropionate (4.0 g, 0.028 mol) in ether (20 ml) was then added dropwise during 20 min, and stirred for 30 min. The reaction mixture was poured on crushed ice (50 g) and glacial acetic acid was added until the solution was acid to litmus. The aqueous layer was separated and washed ether. Aqueous ammonia was added and the base was extracted with dichloromethane (3 x 100 ml). The organic extracts were washed with water (2 x 100 ml), dried (Na_2SO_4) and evaporated to yield the pyridine derivative as a viscous solid (1.78 g, 32 %), m.p. 150-152 °C (lit.,[40] 154-156 °C); δ_H (60 MHz, D_2O, TMS) 3.05 (6 H, s, 2 x CH_3), 3.75 (4 H, m, CH_2-CH_2), 8.1-9.1 (4 H, m, 3-,4-,5-, and 6-H).

(b) 2-Acetylpyridine (4.04 g, 0.03 mol) and paraformaldehyde (1.5 g, 0.05 mol) were added to a solution of dimethylamine hydrochloride (2.72 g, 0.033 mol) in absolute ethanol (15 ml) containing concantrated HCl (0.5 ml). The mixture was heated under reflux for 3 h and the hot black solution was then filtered, allowed to cool slowly, and then chilled overnight in the refrigerator.

White crystals were collected and washed with cold ethanol and dried under the vacuum for 2 h to give the unstable Mannich base, (6.23 g, 29 %), m.p. 150-152 °C (lit.,[40] 154-156 °C); δ_H (60 MHz, D_2O, TMS) 3.05 (6 H, s, 2 x CH_3), 3.75 (4 H, m, CH_2-CH_2), 8.1-9.1 (4 H, m, 3-,4-,5-, and 6-H). Recrystallization from ethanol resulted in decomposition of the compound.

Attempted synthesis of 1-(2-pyridyl)-4-(4-pyridyl)butan-1,4-dione.—3-Dimethyl amino-1-(2-pyridyl)propan-1-one (2.15 g, 0.01 mol) and 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (0.54 g, 0.002 mol) in dry DMF (8 ml) were stirred and heated to 85 °C. A solution of triethylamine (0.81 g, 0.008 mol) and 4-formylpyridine (1.07 g, 0.01 mol) in dry DMF (2 ml) was added dropwise over a period of 20 min *via* a gas-tight syringe. The mixture was then stirred until the starting material had disappeared (monitored by TLC) and was then poured into the water (25 ml), acidified with 5 % HCl, extracted with dichloromethane (3 x 50 ml), and dried ($MgSO_4$). Filtration and evaporation of the solvent gave a brown/black oil. TLC analysis showed that product was mostly base-line material. Attempted purification by column chromatography eluting with ethyl acetate gave 0.2 g of a product, which could not be identified.

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CHAPTER 6

BASICITY MEASUREMENTS

6.1 Acidity Function Theory

6.1.1 Determination of pK_a for monocations

The acidity function theory has been extensively discussed and reviewed in the literature.[1-5] Therefore only the basic theory and calculations involved will be reported here. For acids, the equilibrium process (4.1) may be expressed as

$$HA \underset{}{\overset{Ka}{\rightleftharpoons}} H^+ + A^- \qquad (4.1)$$

The equilibrium constant for this reaction is given by equation (4.2). For

$$K_a = \frac{a_{H^+}\, a_{A^-}}{a_{HA}} \qquad (4.2)$$

bases, the equilibrium is expressed as the ionization of the conjugate acid and

$$BH^+ \underset{}{\overset{Ka}{\rightleftharpoons}} B + H^+ \qquad (4.3)$$

the ionization constant for the mono protonation of a base B, is given by equation (4.4). The pK_a is defined as the negative logarithm of the ionization

$$K_a = \frac{a_B\, a_{H^+}}{a_{BH^+}} \qquad (4.4)$$

constant. For bases, the pK_a is

$$pK_a = -\log K_a = \log \frac{a_{BH^+}}{a_B\, a_{H^+}} = \log \frac{a_{BH^+}}{a_B} - \log a_{H^+} \qquad (4.5)$$

At given temperature, the ionization constant expressed by equation (4.2) or (4.4) are thermodynamic quantities and all terms involved in these equations are expressed as activities. The activities take into consideration the interaction between the species involved in the equilibrium, whereas stoichiometric molar concentrations do not. The activity is given in terms of concentration and activity coefficient (equation 4.6) and as the interaction becomes less at low

$$\text{activity} = \text{concentration} \times \text{activity coefficient} \qquad (4.6)$$

concentration, the activity coefficient can generally be neglected. Thus, if the solvent is water and the concentration of the compound is not high, then the activity coefficients will be unity in all cases and the equation (4.5) can be written as

$$pK_a = pH + \log \frac{[BH^+]}{[B]} = pH + \log I \qquad (4.7)$$

In dilute solutions, the activity of the non-ionized species (a_B) is approximately equal to the concentrations, i.e. the activity coefficient of non-ionized species will be unity. The activity of the ionized species and the pK_a are given equation (4.8) and (4.9)

$$a_{BH^+} = [BH^+] \times f_{BH^+} \qquad (4.8)$$

$$pK_a = pH + \log\frac{[BH^+]}{[B]} \times f_{BH^+} \qquad (4.9)$$

where f_{BH^+}, known as the activity coefficient of the ionized species, is usually less than one. Therefore, if the pK_a is measured in dilute solutions, the activity of neutral molecule does not differ appreciably from its concentration at any dilution. Thus, the pH is nearer to hydrogen ion activity than to hydrogen concentration, although two values do not differ greatly between pH 2 and 10. Equation (4.7) can therefore be used when pK_a values are determined in solutions of concentration not stronger than 0.01 M and refers to a standard state of water at 25 °C. Equation (4.9) can be used when the concentration lies between 0.1 and 0.01 M.[6]

When the pK_a is measured for concentrated solutions, the activity coefficient of the molecule will no longer be unity. For example, at high acid concentrations there will be insufficient water to solvate every proton completely as the H_3O^+ ion and as the acidity is increased, the activity of proton will increase, due to the loss of the stabilizing solvation.The activity of ionized species will also vary as a result of changes in the environment. Under such circumstances, the pH will no longer be a valid concept, since the ability of an acid solution to donate a proton will be greater than that indicated by the stoichiometric concentration. For this reason, the acidity (H_o) scale was defined by Hammet.[7-8] Equation (4.4) can be written for highly acidic solutions as

$$pK_a = \log\frac{a_{H^+} f_B}{f_{BH^+}} \times \frac{[B]}{[BH^+]} \qquad (4.10)$$

The pK_a is then given by equation (4.11) for highly acid solutions. H_o can be

$$pK_a = H_o + \log\frac{[BH^+]}{[B]} \qquad (4.11)$$

applied to ideal Hammet bases, such as aromatic primary amines. The acidity function, H_o is a measure of the acidity of highly acid solutions, and when the

$$H_o = - \log \left[\frac{a_{H^+} f_B}{f_{BH^+}} \right] \qquad (4.12)$$

activity coefficients equal one, this reduces to pH. Many solutions of known H_o are available,[9] and revision of the scale below H_o -4 has since made by Jorgenson and Hartter[10] and then by Johnson, Katritzky and Shapiro.[11]

Other non-ideal acidity functions, such as H_R, H_R', H_E, H_c, H_A and H_o''' apply to bases for which the activity coefficient ratio of the ionized species (f_B/f_{BH^+}) varies from that of the ideal Hammet bases where the ratio (f_B/f_{BH^+}) is constant.Thus for a series of structurally similar bases, like triarylmethanols,[12,13] aryl olefins and other molecules whose conjugate acids are stable carbocations that do not form hydrogen bonds with the solvent,[14,15] bases that protonate on carbon,[16] aliphatic esters,[17] unsubstituted amides,[18-22] and tertiary aromatic amines[23] the individual acidity functions, are defined respectively as H_R, H_R', H_E, H_c, H_A and H_o''', which have linear relationship to H_o.

The pK_a of any protonating species can be calculated from equation (4.11). However, not all bases follow H_o, and a refinement is consequently necessary. When H_o in equation (4.11) is replaced by H_x, the acidity function of the base, this can be used to calculate the pK_a directly. This method has been used by Yates[24] and can be used in all subsequent calculations. If a base follows an acidity function H_x, then it will have a linear dependence upon H_o when

plotted over a range of acidity, (equation 4.13), where similar compounds have similar values of m.

$$H_x = m \times H_o \qquad (4.13)$$

Replacement of H_x in equation (4.11) gives equation (4.14) and a plot of log I

$$pK_a = mH_o + \log I \qquad (4.14)$$

against H_o gives a gradient m. The differences in m values for different acidity functions arise from differences of the activity coefficient ratio between various indicator series, particularly due to different degrees of solvation the cations. From equation (4.14), it is possible to calculate the pK_a, if logI=0, $pK_a=mH_o^{1/2}$. This calculated value of pK_a represents an accurate quantity which is found to correlate well with many parameters, not necessarily dependent upon acidity function theory. Generally, bases with m values lying between 0.85 and 1.15 are called "*Hammet bases*", and is taken unity. Therefore, it is important to measure m as well as $H_o^{1/2}$ for each basicity measurements.

6.1.2 Determination of pK_a for Dications

Although equations (4.7) or (4.11) can be used for monoacidic bases, it is necessary to use different equations for the compounds which have two ionizing groups, such as diacidic bases and dibasic acids. For these types of compounds, the equilibria is given as

$$H_2A \overset{K_2}{\rightleftharpoons} H^+ + HA^- \qquad \text{for acids} \qquad (4.15a)$$

$$HA^- \overset{K_1}{\rightleftharpoons} H^+ + A^- \qquad (4.15b)$$

and

$$H_2B^{2+} \overset{K_2}{\rightleftharpoons} H^+ + BH^+ \qquad \text{for bases} \qquad (4.16a)$$

$$HA^- \overset{K_1}{\rightleftharpoons} H^+ + A^- \qquad (4.16b)$$

The calculation for the first ionization can be made in exactly the same way as described in Section 4.1.1 for monoacidic bases and monobasic acids. The calculations for the second ionization equilibria expressed by equations (4.15a) and (4.16a), are complicated by the activity coefficients being much smaller than those for the first ionization process expressed equations (4.1) and (4.3). The ionic strength term is also different than for the first equilibrium process. The equilibrium constants for the second ionizations are expressed as

$$K_2 = \frac{a_{H^+}\, a_{HA^-}}{a_{H2A}} = a_{H^+} \frac{[HA^-]}{[H_2A]} \frac{f_{HA^-}}{f_{H2A}} \qquad \text{for acids} \qquad (4.17)$$

and

$$K_2 = \frac{a_{H^+}\, a_{BH^+}}{a_{H2B^{2+}}} = a_{H^+} \frac{[BH^+]}{[H_2B^{2+}]} \frac{f_{BH^+}}{f_{H2B^{2+}}} \qquad \text{for bases} \qquad (4.18)$$

in which the terms f_{HA^-}, f_{H2A}, f_{BH^+} and $f_{H2B^{2+}}$ are the activity coefficients. It is possible to explain the relationship between the concentration of an ion C_i and its activity coefficient f_i, in terms of the ionic strength (I) (equation 4.19)[25,26]

$$I = 0.5 \sum C_i z^2 \qquad (4.19)$$

where C_i is the molecular concentration of an ion and z is its valency. The activity coefficient f_i of an ion of valency z is related to the ionic strength by

$$- \log f_i = \frac{A z^2 \sqrt{I}}{1 + B a_i \sqrt{I}} \tag{4.20}$$

Where the terms A and B are constant and vary with the dielectric constant and temperature of solvent. The values of A are 0.5070 and 0.5115 $mole^{-1/2}\ l^{1/2}$ at 20° and 25 °C, respectively, and values of B are 0.3282 and 0.3291 x 10^8 $cm^{-1}\ mole^{1/2}\ l^{1/2}$ at 20° and 25 °C The term a_i, which is the ionic size parameter, can be taken $5x10^{-8}$ cm as an average value.[27] At 20 °C and 25 °C, the value of -log f_i is

$$\frac{0.507 \sqrt{I}}{1 + 1.6 \sqrt{I}} \quad \text{and} \quad \frac{0.512 \sqrt{I}}{1 + 1.6 \sqrt{I}} \tag{4.21}$$

respectively. The activity coefficients expressed in exponential form, by defining a function (FS) of ionic strength, leads to

$$FS = \frac{\sqrt{I}}{1 + 1.6 \sqrt{I}} \tag{4.22}$$

whereupon

$$f_i = \frac{1}{10^{(0.507\ FS)}} \quad \text{and} \quad \frac{1}{10^{(0.512\ FS)}} \tag{4.23}$$

at 20 °C and 25 °C. Therefore, the activity coefficient terms of equation (4.18) can be expressed as equation (4.24) at 25 °C

$$f_{BH^+} = \frac{1}{10^{(0.512FS)}} \quad \text{and} \quad f_{H2B^{2+}} = \frac{1}{10^{(0.512FS)}} \tag{4.24}$$

and equation (4.18) can be written as

$$K_2 = a_{H^+} \frac{[BH^+]}{[H_2B^{2+}]} \, 10^{(1.5345\ FS)} \tag{4.25}$$

In this equation, the activity of hydrogen ion should be expressed as concentration where $\{H^+\}$ is calculated from the measured pH. The pK_a of the

$$[H^+] = \{H^+\} \times 10^{(0.5115\ FS)} \tag{4.26}$$

diacidic bases is given by

$$pK_2 = pH + \log \frac{[H_2B^{2+}]}{[BH^+]} - \frac{1.5345\sqrt{I}}{1 + 1.6\sqrt{I}} \tag{4.27}$$

The equation (4.27) can be used the calculation of the pK_2 of all diacidic bases. However, when the pK_2 values calculated from equation (4.27) are of poor precision, the two ionization process overlap and the two pK values will be found to be separated by less than 2.7 units of pK. When this occurs, equation (4.27) can not be used to calculate the pK_2. Speakman derived an equation (4.28), which allows these pK values to be calculated.[28]

$$\frac{1}{K_1} \frac{\{H^+\}^2 \, F}{(2-F)} \frac{1}{10^{(0.5115FS)}} - K_2 \, 10^{(1.5345)} = \{H^+\} \frac{(1-F)}{(2-F)} \tag{4.28}$$

where

$$F = \frac{C_A + \{H^+\} - \{OH^-\}}{C_t} \qquad (4.29)$$

In order to calculate the pK of mono or diacidic bases, the relative amounts of B, BH^+ or H_2B^{+2} are required to be known at different acidities. Such data can be measured by various techniques, such as potentiometric titration, U.V. and NMR spectroscopy, or conductimetry, but only potentiometric titration and U.V. spectroscopy, which have been used for determination of the pK values in this thesis, will be considered here.

4.2 Physical Methods

6.2.1 Potentiometric Titration

This procedure, which is by far the most convenient method for the determination of ionization constant, requires the measurement of pH using an electrolitic a cell composed of two half cells. One electrode responds reversibly to hydrogen ions, in that its potential changes as the hydrogen ion concentration is changed. The other half cell, termed the referance electrode, has a known and invariant potential. The potential difference between two electrodes is a measure of the hydrogen ion concentration in solution between the electrodes.

The potentiometric titration is based on the measurement of the pH during the stepwise titration of a known weight of compound against an accurately standardized solution of hydrochloric acid or potassium hydroxide. The mole ratio of the acid-base conjugated pairs is calculated from the amount of the titrant added. Precision results can be obteined for compounds, which are

expected to have the basicity values between 2 and 11, when titrated at 0.1 - 0.01 M concentrations in water against 0.1N hydrochloric acid and 0.1 N potassium hydroxide at given temperature under nitrogen. When the compound is titrated at 0.01 M concentration, the activity effects are small and the equation (4.7) can be used for the measurement of pK_a values which fall the range of 4-10. However, when the pK_a of the compound falls outside of these limits, the pK_a value needs to be corrected for either the hydrogen ion or the hydroxide ion concentrations. For example, equation (4.7) is modified to give equation (4.30) at low pH values (below pH 4)

$$pK_a = pH + \log \frac{[BH^+] - [H^+]}{[B] + [H^+]} \qquad (4.30)$$

and at high pH values (above pH 11)

$$pK_a = pH + \log \frac{[BH^+] - [OH^-]}{[B] + [OH^-]} \qquad (4.31)$$

If the solution being titrated is more dilute than 0.01 M, because of poor solubility, the pH must remain between narrower values. In the case of diprotonation, equation (4.27) can be used for the second protonation of a diacidic base, which is titrated at a concentration greater than 0.0025 M.

6.2.2 U.V. Spectroscopic Technique

The determination of ionization constants by U.V. or visible spectroscopy is an ideal method when the compound is too insoluble for potentiometry or when its pK_a value is particularly low or high (less than 2 or more than 11).

Under suitable conditions, it is the most accurate method, as all measurements being taken in very dilute solutions. The spectroscopic technique is based on the fact that, for solutions containing only the fully protonated or the totally non-protonated species, there will be an absorption due to both the free base (neutral molecule) and conjugate acid. An analytical wavelength is chosen where there is the greatest difference between the absorbances of the two species (neutral and ionized) and the analytical procedures depends upon the direct determination of the ratio of neutral molecule to ionized species in a series of non-absorbing buffer solutions of known pH. Measurement of the absorbance at the chosen wavelength for solution over a range of pH values gives the ratio of neutral to ionized species and the pK_a of the compound can then be calculated. Similarly, the pK_2 values for diprotonation can be calculated from measurements of the spectra over pH range using the observed ratio between the concentrations of the mono- and the dications.

For the calculations of the ratio of the two species present at any pH, it is assumed that Beer's law is obeyed for both species. Thus, the absorbance, A, at the analytical wavelength will be equal to the sum of the absorbances of the free base, A_B, and conjugate acid A_{BH^+}.

$$A = A_B + A_{BH^+} \tag{4.32}$$

From equation (4.7)

$$I = \frac{[BH^+]}{[B]} = \frac{[BH^+]}{C_t - [BH^+]} \tag{4.33}$$

where C_t is total concentration. Multiply both sides of the equation by $\varepsilon_B - \varepsilon_{BH^+}$

$$I = \frac{[BH^+]\,\varepsilon_B - [BH^+]\,\varepsilon_{BH^+}}{C\,\varepsilon_B - C\,\varepsilon_{BH^+} - [BH^+]\,\varepsilon_B + [BH^+]\,\varepsilon_{BH^+}} \tag{4.34}$$

$$I = \frac{C\,\varepsilon_B - (C - [BH^+])\,\varepsilon_B - [BH^+]\,\varepsilon_{BH^+}}{(C - [BH^+])\,\varepsilon_B + [BH^+]\,\varepsilon_{BH^+} - C\,\varepsilon_{BH^+}} \tag{4.35}$$

$$I = \frac{C\,\varepsilon_B - [B]\varepsilon_B - [BH^+]\,\varepsilon_{BH^+}}{[B]\,\varepsilon_B + [BH^+]\,\varepsilon_{BH^+} - C\,\varepsilon_{BH^+}} \tag{4.36}$$

By using Beer Lambert's law:

$$A = \varepsilon \times C \times l \tag{4.37}$$

where ε=extinction coefficient, C=concentration, and l=optical path length of the cell. Equation (4.38) analogous to equation (4.7) can be used to determine the pK_a of the compound.

$$pK_a = pH + \log \frac{A_B - A}{A - A_{BH^+}} \tag{4.38}$$

Thus, from a knowledge of the absorbance of the base and its conjugate acid and by measuring the variation of the absorbance of the solution with its acidity, the pK_a can be calculated using equation (4.38). As the acidity is increased the solution changes from 100% free base to 100% conjugate acid giving a sigmoidal curve for the absorbance as a function of pH (or H_o) (Fig. 4.1). All log I should be between $\pm$ 1.0, since outside of this region one of the concentrations will be vary small and the logarithm of the ratio will have a large experimental error. Special care should be taken in the measurement of A_B and A_{BH^+} if the sigmoidal curve has sloping rather than horizontal arms. This is

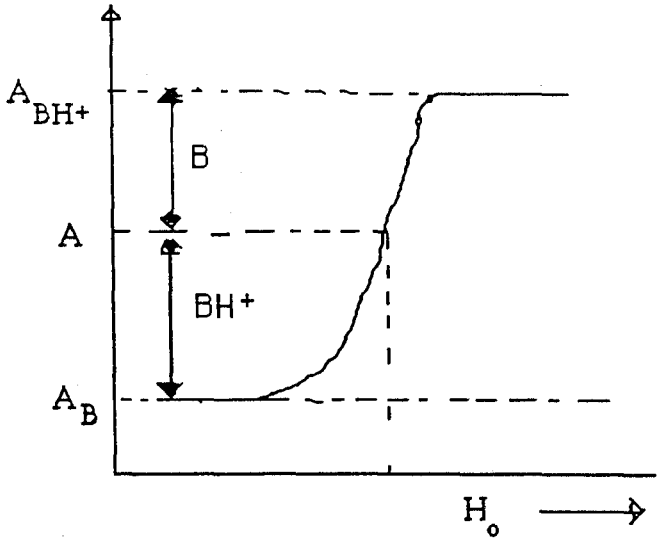


Figure 4.1 For a maximum conjugate acid absorption

due to a medium effect of acid solution. In an ideal case, the spectra of a set of solutions, in which free base and conjugate acid are present in different amounts, show a common point of intersection known as the isobestic point.

6.3 Experimental

6.3.1 Materials Used

The pK_1 (monocation formation) values of the compounds were determined by the spectrometric procedure using SP500 U.V. spectrometer and Spectrocil 1cm U.V. cells. All the pK_2 (dication formation) values were determined by potentiometric titration using a Pye 290 pH-meter. The pH of the buffer solutions were measured using a Direct Reading pH-meter.

Commercial Analar grade samples of sulphuric acid, hydrochloric acid and sodium hydroxide were not purified further. Acid solutions were standardized by titration against 1N standard sodium hydroxide. The buffer

solutions for U.V. technique were prepared using 1N sulphuric acid, sodium acetate, sodium dihyrogen phosphate and disodium hydrogenphosphate (Table 4.1. and 4.2).[29]

$NaAc / H_2SO_4$		NaH_2PO_4 / H_2SO_4	
ml. N H_2SO_4	pH	ml. N H_2SO_4	pH
25	5.32	12.5	2.98
35	5.15	20	2.80
45	5.08	25	2.70
60	4.91	30	2.61
80	4.82	40	2.50
90	4.70	50	2.40
100	4.60	75	2.24
110	4.50	90	2.10
120	4.38	100	1.90
150	4.10	150	1.71
175	3.90	175	1.59
200	3.60	200	1.50

Table 4.1 pH values of the buffer solutions.

For the sodium acetate- sulphuric acid system, 200ml. of a normal solution of sodium acetate was used in each buffer, whilst for the sodium dihydrogen phosphate-sulphuric acid system, 250ml. of a normal solution of the phosphate was used in each buffer (Table 4.1 and 4.2). All buffers were calibrated on a pH-meter.

ml.N $NaHPO_4$	ml.N NaH_2PO_4	pH
100	30	7.00
90	40	6.82
80	50	6.63
70	60	6.50
60	70	6.40
50	80	6.25
40	90	6.11
30	100	6.05

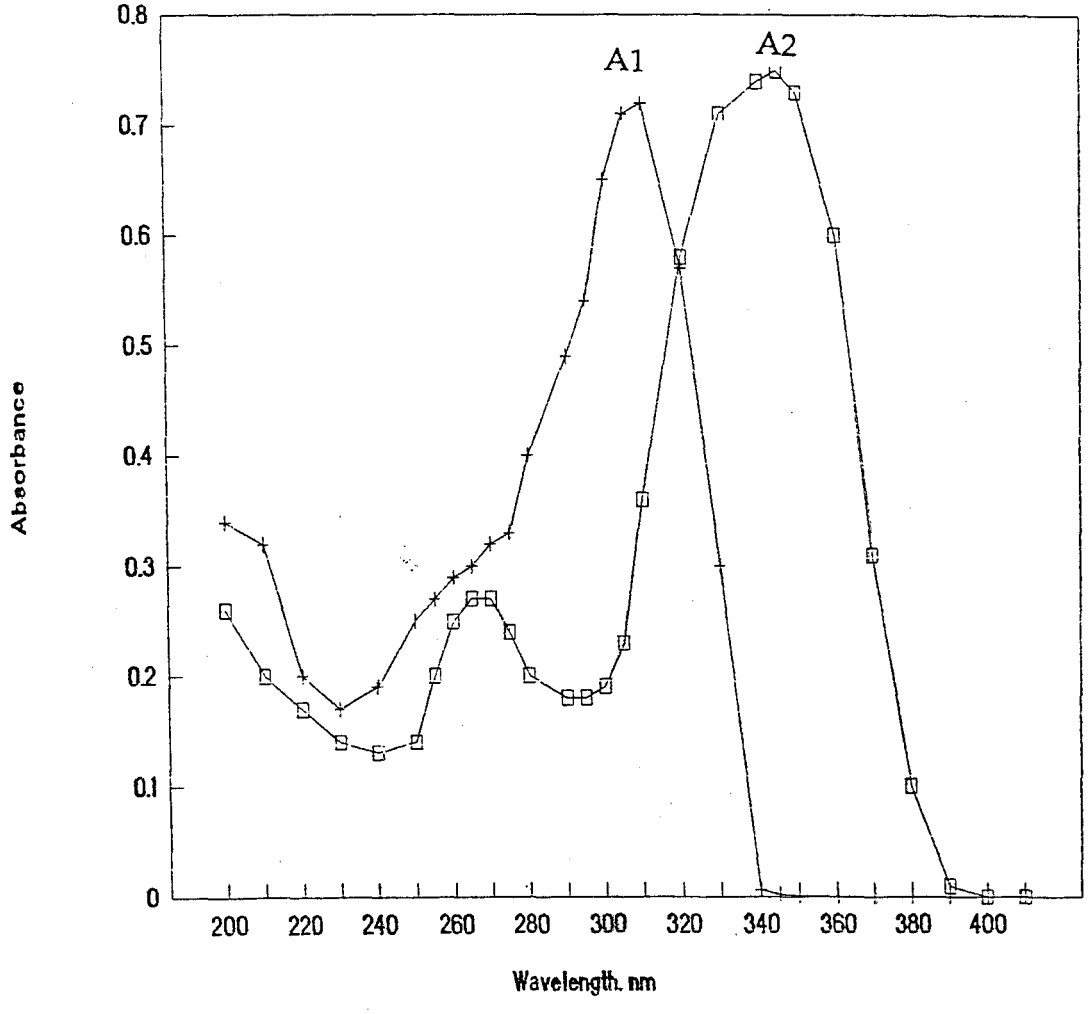
Table 4.2 pH values of the phosphate buffer

6.3.2 Basicity Measurements

The pK_a values for monocation formation were determined by the spectrometric procedure described by Albert and Sergeant.[24] The U.V. spectrum of the base was measured dissolving in U.V. ethanol. The general procedure applied was as follows: A stock solution studied was prepared by dissolving an accurately weighted sample of the compound (*ca.* 10-20 mg) in U.V. ethanol. A 1 ml. of this solution was diluted to 100 ml. with the buffer solutions of different pH. The pH of the buffered solutions was measured before and after addition of the compound. The optical density of each solution was then measured in a 1 cm. cells, against the solvent blanks at 25 °C.

Measurements of the absorbance were made at a number of frequencies, some at the absorption maxima of the species involved where the absorbance of one species is very high and the absorbance of the other is fairly low. Other frequencies were also chosen, for example on the side peak where there was a

shoulder, where possible the absorbance region measured lay between 0.2 and 0.8, since this is the most accurate region of the instrument. Typical U.V. spectrum for 2-(5-methyl-2-thienyl)pyridine is shown in Figure 4.2. A sigmoidal curve of optical density against pH at the analytical wavelength (A_λ), (see Figure 4.3) was obtained to get the values of A_{fb} and A_{ca}. The optical densities of fully



A1, at pH 7.0; A2, in 1N H_2SO_4

Figure 4.2 U.V. spectra for 2-(5-methyl-2-thienyl)pyridine and monoprotonated form.

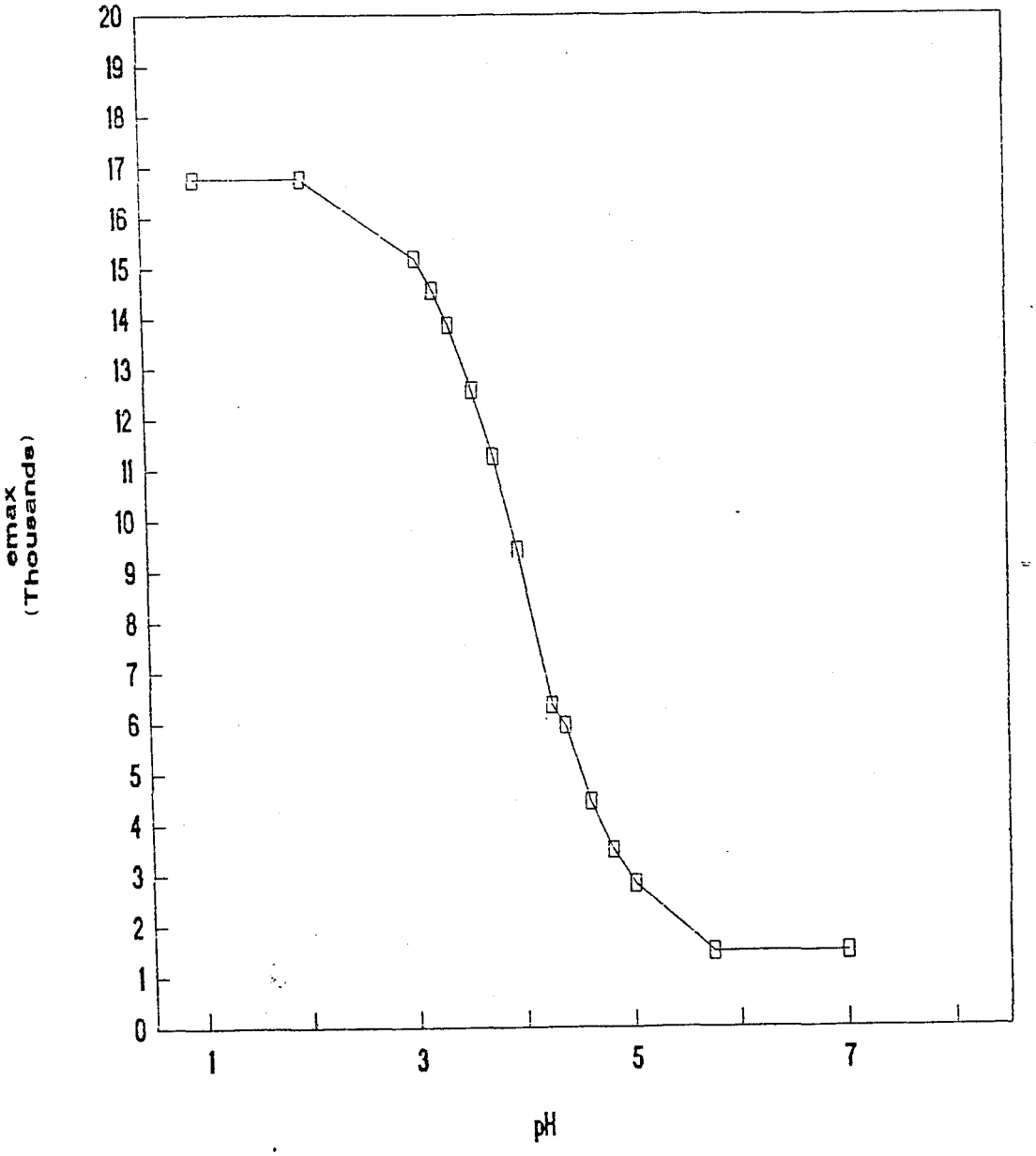


Figure 4.3 U.V. spectra of 2-(5-methyl-2-thienyl)pyridine at 347nm

protonated molecule (A_{ca}) and the pure free base (A_{fb}) at pH which the compound is partially protonated, where then calculated by linear extrapolation of the arms of the curve. ε_{ca} and ε_{fb} were calculated by using Beer Lambert's law. The ionization ratio is given by equation (4.39), where the ε_{obs} is the measurement of extinction coefficient of the solution at the analytical wavelength;

$$I = \frac{[BH^+]}{[B]} = \frac{\varepsilon_{obs} - \varepsilon_{fb}}{\varepsilon_{ca} - \varepsilon_{obs}} \qquad (4.39)$$

An approximate value of the pKa of the compound was first obtained using equation (4.40), and a set of buffer solution were then made up at pH values equal to this pKa + 0.2, 0.4, 0.6, -0.2, -0.4, -0.6. The pKa values, obtained from measurements of the spectra in these solutions where $-1.0 < \log I < +1.0$ gave an exact values of pKa with its the standard deviation.

$$pK_a = pH + \log I \qquad (4.40)$$

The pKa values of compounds which were expected to have basicity values between 2 and 11, were obtained by potentiometric titration of 0.001 to 0.008 M solutions in 50 % ethanol against 0.1 N hydrochloric acid at 25 °C under nitrogen. The titrant was added in ten equal volumes and the pH of the solution was measured after each addition of solution using a Pye 290 pH-meter, which had previously been calibrated at pH 7.0 and at pH 4.0. As the activity coefficients are small at the concentrations used, the simple equation 4.7 was used for compounds having pKa values which fall within the range 4-10 pH. However, when the pKa value of the compound fell outside these pH limits, the pKa value was corrected for either the hydrogen ion or the hydroxide ion concentration. For example, equation 4.30 was used at low pH values.

The investigated compounds which have two ionizing group were titrated sequentially with two equivalents of titrant. The result from the first equivalent was calculated by the standard procedure described above and for the second ionization process, a set of the pK_2 values were calculated from equation (4.41).

$$pK_2 = pH + \log \left\{ \frac{[Cl^-] - C_t - [H^+]}{2C_t - [Cl^-] + [H^+]} \right\} - \frac{1.5345\sqrt{I}}{1 + 1.6\sqrt{I}} \quad (4.41)$$

where

$$I = 2[Cl^-] - [H^+] - C_t \quad (4.42)$$

6.4 Results and Discussion

Absorbance values obtained for the various compounds under investigation are listed in Appendix 1 and 2. The pKa values calculated as shown in Section 6.3 are given in Table 4.3. The basicity of some thienyl pyridines,[30-35] furylpyridines,[30-36] phenylpyridines[37-41] and bipyridyls[42-53] using U.V. and potentiometric techniques have been determined and reported in the literature. The pKa values are subject to simultaneous base-weakening electron-withdrawing inductive effects and mesomeric the base-strengthening electron donating effects of the aryl groups and will, therefore, depend upon whether the substituent is α-, β-, or δ- to the nitrogen ring atom.

3-Arylpyridines (pKa: 4.56, 4.68 and 4.80 for 3-(2-methyl-5-thienyl) pyridine, 3-(2-methyl-5-furyl)pyridine and 3-phenylpyridine respectively) are slightly weaker bases than pyridine (pKa: 5.14).[30] This can be explained by the lack of conjugative interaction for the 3-substitutuent with the pyridine ring and by the inductive electron withdrawing effect of the aryl groups.

4-Arylpyridines (pKa: 5.68, 5.70 and 5.55 for 4-(2-methyl-5-thienyl) pyridine, 4-(2-methyl-5-furyl)pyridine and 4-phenylpyridine respectively) have similar pKa values and they are stronger bases than pyridine. The electron density on the nitrogen atoms of 4-aryl pyridines are affected by the mesomeric effect of the substituent as well as its inductive effect, such that the resonance

No.	Compounds	Method	C[a]	λ[b],nm	pKa	σ[c]
1	2-phenylpyridine	S	0.3	300	4.48[d]	0.030
2	3-phenylpyidine	S	0.6	245	4.80[d]	0.060
3	4-phenylpyidine	S	0.3	285	5.55[d]	0.030
4	2-(2-thienyl)pyridine	S	-	-	3.79[e]	0.012
5	3-(2-thienyl)pyridine	P	-	-	4.51[e]	0.006
6	4-(2-thienyl)pyridine	P	-	-	5.59[e]	0.003
7	2-(2-furyl)pyridine	S	-	303	4.18[f]	0.050
8	3-(2-furyl)pyridine	S	-	283	4.62[f]	0.060
9	4-(2-furyl)pyridine	S	-	294	5.60[f]	0.080
10	2-(2-methyl-5-thienyl)pyridine	S	0.44	347	3.99	0.006
11	3-(2-methyl-5-thienyl)pyridine	S	0.58	328	4.56	0.003
12	4-(2-methyl-5-thienyl)pyridine	S	0.37	349	5.68	0.004
13	2-(2-methyl-5-furyl)pyridine	S	0.49	349	4.24	0.005
14	3-(2-methyl-5-furyl)pyridine	S	0.32	345	4.67	0.004
		S	1.0	345	4.63[g]	0.015
15	4-(2-methyl-5-furyl)pyridine	S	0.49	350	5.70	0.005
16	2,5-bis(2-methyl-5-thienyl)pyridine	P	10.0	-	2.87	0.008
17	2,6-bis(2-methyl-5-thienyl)pyridine	P	20.0	-	2.67	0.012
		S	0.43	330	2.685	0.003
18	2,6-bis(2-methyl-5-furyl)pyridine	P	30.0	-	3.245	0.006

[a] concentration, Mx10^4 [b] analytical wavelength [c] standard deviations [d] data taken from reference [34] [e] data taken from reference [29] [f] data taken from reference[30] [g] data taken from reference [33] [P] potentiometric titration [S] U.V.spectroscopic method.

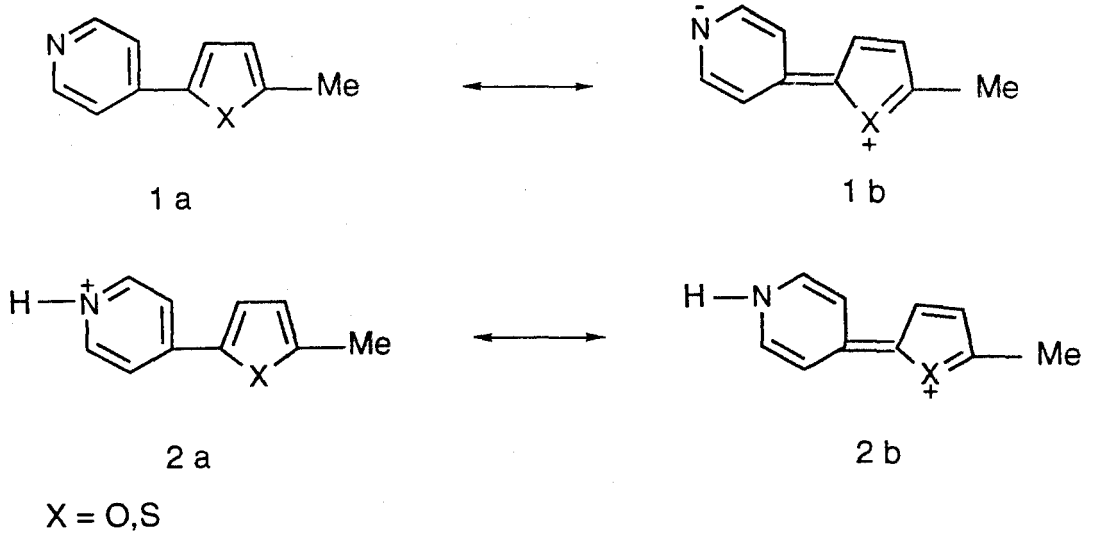
Table 4.3 Basicity and U.V. spectra of the mono protonated compounds.

No.	Compounds	Method	C[a]	pK_1	σ [b]	pK_2	σ [b]
19	2,5-di(2-pyridyl)thiophene	P	60	2.59	0.015	2.92	0.010
		O.P	60	-	-	2.97	0.700
20	2,5-di(3-pyridyl)thiophene	P	80	3.06	0.006	3.50	0.015
21	2,5-di(4-pyridyl)thiophene	P	60	4.49	0.015	2.98	0.005
22	2,5-di(2-pyridyl)furan	P	70	3.41	0.006	3.20	0.040
		O.P	70	-	-	3.24	0.800
23	2,5-di(3-pyridyl)furan	P	60	3.66	0.007	2.32	0.010
24	2,5-di(4-pyridyl)furan	P	60	4.51	0.006	2.39	0.015
25	2,2'-dipyridyl	S	0.3	4.44[c]	-	-	-
26	3,3'-dipyridyl	S	0.3	4.60[c]	-	3.03	-
27	4,4'-dipyridyl	S	0.3	4.82[c]	-	3.16	-
28	2,6-di(2-pyridyl)pyridine	P	-	4.33[d]	-	2.64	-

[a] concentration, $Mx10^4$ [b] standard deviations [c] taken from reference [38] [d] taken from reference [28]] [P] potentiometric titration [S] U.V.spectroscopic method [O.P] overlapping process.

Table 4.4 Basicity of the diprotonated compounds.

between the forms (1a) and (1b) would result in the formation of the unfavourable charged form (1b) (Scheme 4.1). In the case of the protonated forms (2a⟷2b) the resonance is of more importance than it is in the free base (1). The basicity of 4-arylpyridines are similar, this result suggests that the mesomeric effect (+M) for all furyl, thienyl and phenyl groups is of the same order of magnitude.



Scheme 4.1

The basicity of 2-arylpyridines (pKa : 3.99, 4.24 and 4.48 for 2-(2-methyl-5-thienyl)pyridine, 2-(2-methyl-5-furyl)pyridine and 2-phenyl pyridine, respectively) is weaker than that of pyridine. This effect can be related to a reduction in the mesomeric effect (+M) of the aryl groups, as a result of greater steric hindrance, and also by the increased importance of the inductive effect of the aryl groups. The pKa values of 2-arylpyridines are, however, similar, indicating that the steric hindrance of the aryl groups is about same, because the mesomeric and the inductive effects are of the same order magnitude.

On the other hand, a comparison of the pKa values of furyl or thienyl pyridines (compounds 4 to 9) with substituted furyl- or thienylpyridines (compounds 10 to 15) shows that the presence of a methyl group on the furan or thiophene ring increases the basicity of pyridine rings by 0.01-0.2 pH (Table 4.3). The effect of methyl group on the thiophene or furan rings is very small and only weakly increases the basicity of the compounds due to the inductive effect (+ I) of methyl groups.

Examination of the pKa values of 2,5- and 2,6-disubsititued compounds (16 to 18) indicates that the introduction of a second aryl group on the pyridine

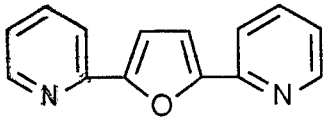
ring results in a further decrease in the pK_a value due to an increase in the inductive effect of the aryl group and greater steric effect. From the comparison of the pK_a values of 2,6-bis(2-methyl-5-thienyl)pyridine is 2.67 with that of 2,5-bis(2-methyl-5-thienyl)pyridine is 2.87, it can be seen that 2,5-disubstitued pyridine is more basic than 2,6-disubsititued pyridine. The inductive effect of second thiophene ring is greater when the thiophene ring is ortho to the pyridine nitrogen, than when the pyridine ring is meta substituted. This is mainly due to the fact that the inductive effect falls with distance.

In the case of the diprotonated compounds, the pK_1 values calculated by using equation (4.7) been described in Section 4.1.2, yielded sufficient and expected results, but the pK_2 values could not be calculated with sufficient accuracy using equation (4.27). This could be attributed to the several factors; the first reason is probable that the low solubility of dipyridylaryl compounds in aqueous ethanol permiting only a rough determination of pK_2 values. Due to the lower solubility of the dipyridylaryl, it was used 0.005 to 0.008 M of concentrations in aqueous ethanol (50 %) for titration. The second reason may be that the end point of the first equivalent is indefinite because the protonation of second pyridine ring has begun before protonation of the first ring complete. In order to overcome this problem, it was decided to use the equation (4.28) described in Section 4.1.2. A computer program (Appendix 3), which calculates the pK_a values from raw data and repeats the process until a constant pK is obtained, was adapted to solve this equation. This computer program was only used to calculate the pK values for 2,5-di(2-pyridyl)thiophene and 2,5-di(2-pyridyl)furan compounds and it was observed that the pK values are of poor precision, it could be not used the calculation the pK values for the other diprotonated componds. A satisfactory result for pK_1 could not be obtained using the computer program, the pK_2 values given Table 4.4 are about same

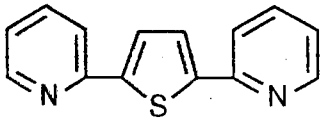
order of magnitude as those obtained by the first method using equation 4.27. On the other hand, the pK_1 and pK_2 values of the 2,5-dipyridylaryl compounds calculated equation 4.27 are close to each other. It can be considered that, if the compound is symmetrical, the dissociation constants K_1 and K_2 are identical in any two successive stages, so that pK_1 is equal to pK_2. The methylation of these compounds also supports this hypothesis as dimethylated products were obtained except 2,5-di(2-pyridyl)furan and thiophene, i.e. kinetic rates of the investigated symmetrical compounds for methylation are equal.

However, a comparison of the pK_a values, the symmetrical 2,2'-, 3,3'- or 4,4'-dipyridyl compounds (pK_a : 4.44, 4.60 and 4.82, respectively) with that of 2,5-di(2-, 3- or 4-pyridyl)furans and thiophenes (pK_a: 3.41, 3.66, 4.51 for the furan derivatives and 2.59, 3.06, 4.49 for the thiophene derivatives, respectively) shows that 4,4'-disubstituted pyridines are the strongest bases and 2,2'-disubstituted isomers are the weakest due the inductive electron withdrawing effect of pyridine ring. Although one might expect the mesomeric effect to be more important for 2,2'- and 4,4'-dipyridyl compounds, the cross-conjugative effect of the system renders the effect less significant (Scheme 4.2).

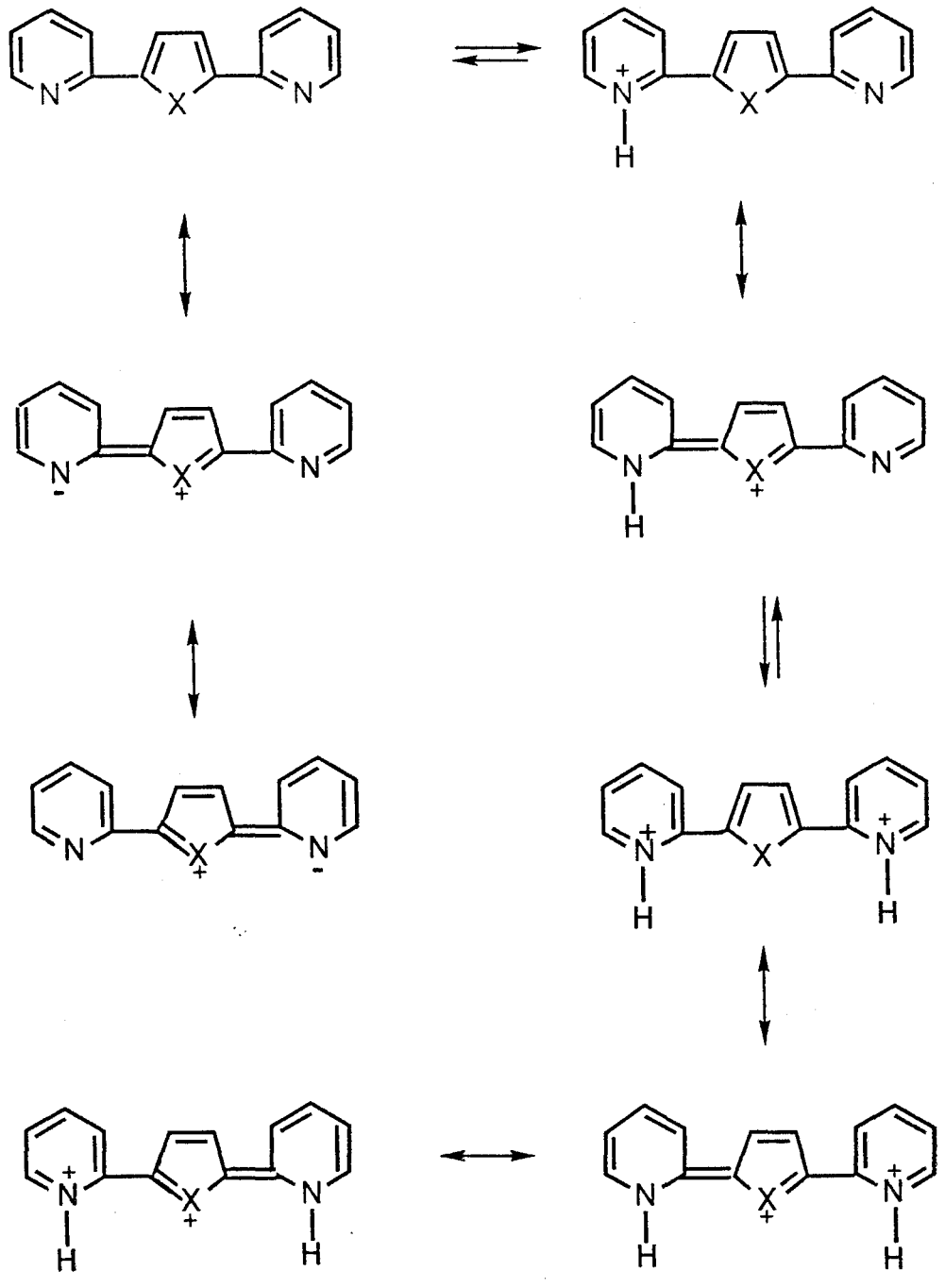
2,5-Di(2-pyridyl)furan (1) is a stronger base than 2,5-di(2pyridyl) thiophene (2), The -I effect which is presumed to be more important for the furan ring than for the thiphene ring, would make 1 a weakest base than 2, it is postulated, therefore, that the coordination of the proton by the oxygen atom of the furan derivatives increase the stability of the diprotonated form .



(1)



(2)



X = O,S

Scheme 4.2

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APPENDIX

Appendix 1. Absorbance values obtained for the monoprotonation of the compounds under investigation are listed with their calculated pKa values by using equation (4.7) and (4.39) in Table 1 to 11.

OBS.	pH	A_{obs}	ε_{max}	logI	pKa
1	.06600	7.0000	1490.2	-	-
2	.06600	5.7400	1490.2	-	-
3	.12500	5.0100	2822.3	-1.0202	3.9898
4	.15500	4.8100	3499.7	-.82000	3.9900
5	.19700	4.6100	4448.0	-.61993	3.9901
6	.26400	4.3800	5960.7	-.38368	3.9963
7	.30400	4.2600	6863.9	-.26589	3.9941
8	.41800	3.9600	9437.8	.03465	3.9947
9	.49900	3.7500	11266.7	.24910	3.9991
10	.55700	3.5700	12576.2	.42157	3.9916
11	.61500	3.3600	13885.8	.63237	3.9924
12	.64500	3.2200	14563.1	.93810	3.9981
13	.67300	3.0600	15195.3	-	-
14	.74300	2.0000	16775.8	-	-
15	.74300	1.0000	16775.8	-	-

Table 4.1 Determination of the pKa of 2-(5-methyl-2-thienyl)pyridine.

OBS.	pH	A_{obs}	ε_{max}	logI	pKa
1	7.0000	.12100	2075.5	-	-
2	6.8300	.12100	2075.5	-	-
3	5.5100	.15500	2658.7	-.94422	4.5658
4	5.3100	.17200	2950.3	-.74270	4.5673
5	5.1000	.19600	361.9	-.53657	4.5634
6	4.9100	.22400	3842.2	-.34890	4.5611
7	4.7600	.25000	4288.2	-.19905	4.5610
8	4.5500	.29000	4974.3	.01304	4.5630
9	4.3900	.32000	5488.9	.17175	4.5617
10	4.1800	.35700	6123.5	.38614	4.5661
11	3.9900	.38400	6586.6	.57486	4.5649
12	3.7500	.41000	7032.6	.81746	4.5675
13	2.0000	.45400	7787.3	-	-
14	1.0000	.45400	7787.3	-	-

Table 4.2 Protonation of 3-(2-methyl-5-thienyl)pyridine

OBS.	pH	A_{obs}	ε_{max}	logI	pKa
1	7.0000	.07000	1914.1	-	-
2	6.3800	.13400	3664.2	-	-
3	6.1900	.27800	7601.9	-.51189	5.6781
4	6.0000	.35300	9652.7	-.32709	5.6729
5	5.8800	.40900	11184.0	-.20620	5.6738
6	5.7700	.46500	12715.3	-.092713	5.6773
7	5.5800	.56100	15340.4	.096690	5.6767
8	5.4000	.64900	17746.8	.27838	5.6784
9	5.1900	.73700	20153.1	.48767	5.6777
10	4.9500	.81400	22258.7	.72545	5.6754
11	4.8700	.83500	22832.9	.80812	5.6781
12	3.2200	.95100	26004.9	-	-
13	1.0000	.95400	26087.0	-	-

Table 4.3 Protonation of 4-(2-methyl-5-thienyl)pyridine

OBS.	pH	A_{obs}	ε_{max}	logI	pKa
1	7.0000	0.00	0.00	-	-
2	5.5600	.0380	781.1	-	-
3	5.2000	.0830	1706.1	-.95715	4.2428
4	4.9800	.13000	2672.1	-.73425	4.2457
5	4.6900	.22200	4563.2	-.44111	4.2489
6	4.5400	.27900	5734.8	-.29947	4.2405
7	4.3100	.38500	7913.7	-.067752	4.2422
8	4.1300	.47200	9702.0	.11404	4.2440
9	3.9600	.54800	11264.1	.28090	4.2409
10	3.8500	.59500	12230.2	.39431	4.2443
11	3.6500	.66600	13689.6	.59560	4.2456
12	3.5000	.070700	14532.4	.74222	4.2422
13	3.3100	.74800	15375.1	.93440	4.2444
14	2.5400	.80600	16567.3	-	-
15	1.0000	.83500	17163.4	-	-

Table 4.4 Protonation of 2-(2-methyl-5-furyl)pyridine

OBS.	pH	A_{obs}	ε_{max}	logI	pKa
1	7.0000	.04900	759.69	-	-
2	6.0200	.04900	759.69	-	-
3	5.4800	.07000	1085.3	-.80531	4.6747
4	5.2600	.08100	1255.8	-.58504	4.6750
5	5.0500	.09500	1472.9	-.37486	4.6751
6	4.9000	.10700	1658.9	-.22350	4.6765
7	4.6700	.12700	1969.0	.00549	4.6755
8	4.4400	.14700	2279.1	.23526	4.6753
9	4.2700	.16000	2480.6	.40179	4.6718
10	4.0000	.17700	2744.2	.67578	4.6758
11	3.7700	.18700	2899.2	.90936	4.6794
12	2.5200	.20400	3162.8	-	-
13	1.0000	.20400	3162.8	-	-

Table 4.5 Protonation of 3-(2-methyl-5-furyl)pyridine

OBS.	pH	A_{obs}	ε_{max}	logI	pKa
1	7.0000	.27300	8680.4	-	-
2	6.8400	.27300	8680.4	-	-
3	6.4400	.34000	10810.8	-.74563	5.6944
4	6.2700	.36500	11605.7	-.57779	5.6922
5	6.1300	.39100	12432.4	-.43597	5.6940
6	5.8400	.45700	14531.0	-.14342	5.6966
7	5.6300	.50900	16184.4	.06328	5.6933
8	5.4000	.56600	17996.8	.29956	5.6996
9	5.2200	.60300	19173.3	.47713	5.6971
10	5.0500	.63200	20095.4	.64662	5.6966
11	4.8800	.65400	20794.9	.81009	5.6901
12	4.7300	.67000	21303.7	.96534	5.6953
13	4.4700	.68800	21876.0	-	-
14	2.7800	.71300	2670.9	-	-
15	1.0000	.71300	22670.9	-	-

Table 4.6 Protonation of 4-(2-methyl-5-furyl)pyridine

OBS.	V_t	pH	C_t	$[BH^+]$	$[H^+]$	[B]	pK_a
1	0.00	7.9000	-	-	-	-	-
2	.03000	4.3000	.0014008	.9990E-4	.5012E-4	.0013009	2.8664
3	.06000	3.9900	.0013994	.1996E-3	.1023E-3	.0011998	2.8633
4	.09000	3.8100	.0013980	.2991E-3	.1549E-3	.0010989	2.8708
5	.12000	3.6800	.0013966	.3984E-3	.2089E-3	.9982E-3	2.8758
6	.15000	3.5700	.0013952	.4975E-3	.2692E-3	.8977E-3	2.8616
7	.18000	3.4900	.0013939	.5964E-3	.3236E-3	.7974E-3	2.8763
8	.21000	3.4100	.0013925	.6951E-3	.3890E-3	.6973E-3	2.8599
9	.24000	3.3500	.0013911	.7937E-3	.4467E-3	.5974E-3	2.8715
10	.27000	3.2900	.0013897	.8920E-3	.5129E-3	.4977E-3	2.8642
11	.30000	3.2400	-	-	-	-	-

Table 4.7 Protonation of 2,5-bis(2-methyl-5-thienyl)pyridine

OBS.	pH	A_{obs}	ε_{max}	logI	pKa
1	7.0000	.14600	3330.5	-	-
2	5.8900	.14600	3330.5	-	-
3	3.8200	.16100	3672.7	-1.1335	2.6865
4	3.4700	.17700	4037.7	-.78279	2.6872
5	3.3100	.18800	4288.6	-.62472	2.6853
6	3.1300	.20400	4653.6	-.44340	2.6866
7	3.0300	.21400	4881.7	-.34647	2.6835
8	2.8900	.23000	5246.7	-.20605	2.6839
9	2.8000	.24100	5497.6	-.11570	2.6843
10	2.6800	.25600	5839.8	.00396	2.6840
11	2.5800	.26900	6136.4	.10764	2.6876
12	2.3500	.29600	6752.3	.33725	2.6872
13	2.2000	.31100	7094.5	.48510	2.6851
14	2.0600	.32300	7368.2	.62473	2.6847
15	1.8500	.33700	7687.6	.83389	2.6839
16	1.0000	.36500	8326.3	-	-

Table 4.8 Protonation of 2,6-bis(2-methyl-5-thienyl)pyridine

OBS.	V_t	pH	C_t	$[BH^+]$	$[H^+]$	[B]	pK_a
1	0.00	7.4700	-	-	-	-	-
2	.05000	4.3600	.0016257	.7570E-4	.4365E-4	.0015500	2.6634
3	.15000	3.8800	.0016233	.2268E-3	.1318E-3	.0013965	2.6732
4	.25000	3.6500	.0016208	.3774E-3	.2239E-3	.0012435	2.6695
5	.35000	3.5000	.0016184	.5275E-3	.3162E-3	.0010909	2.6765
6	.45000	3.3800	.0016160	.6772E-3	.4169E-3	.9388E-3	2.6634
7	.55000	3.2900	.0016135	.8264E-3	.5129E-3	.7871E-3	2.6724
8	.65000	3.2100	.0016111	.9752E-3	.6166E-3	.6359E-3	2.6669
9	.75000	3.1400	.0016087	.0011236	.7244E-3	.4851E-3	2.6585
10	.85000	3.0800	.0016063	.0012715	.8318E-3	.3348E-3	2.6563
11	.95000	3.0300	.0016039	.0014190	.9333E-3	.1849E-3	2.6679
12	1.1000	2.9600	.0016003	.001639	.0010965	-	-

Table 4.9 Protonation of 2,6-bis(2-methyl-5-thienyl)pyridine

OBS.	pH	A_{obs}	ε_{max}	log I	pKa
1	7.0000	0.00	0.00	-	-
2	5.8900	.00700	0.00	-	-
3	4.2100	.06600	1622.8	-.94984	3.2602
4	4.0600	.09000	2212.9	-.79705	3.2630
5	3.8700	.13000	3196.5	-.60539	3.2646
6	3.7300	.16600	4081.6	-.46832	3.2617
7	3.5000	.24200	5950.3	-.23108	3.2689
8	3.3200	.30600	7524.0	-.05585	3.2641
9	3.1800	.35800	8802.6	.08259	3.2626
10	3.0400	.41100	10105.7	.22824	3.2682
11	2.7900	.49100	12072.8	.47891	3.2689
12	2.6600	.52400	12884.2	.60540	3.2654
13	2.5200	.55400	13621.8	.74353	3.2635
14	2.3600	.58100	14285.7	.90088	3.2609
15	2.2800	.59200	14556.2	.97996	3.2600
16	1.5000	.65400	16080.6	-	-
17	1.0000	.65400	16080.6	-	-

Table 4.10 Protonation of 2,6-bis(2-methyl-5-furyl)pyridine

OBS.	V_t	pH	$[BH^+]$	$[H^+]$	[B]	pKa
1	0.00	5.7800	-	-	-	-
2	.050000	4.4600	.1721E-3	.3467E-4	.0028279	3.2443
3	.10000	4.1300	.3436E-3	.7413E-4	.0026564	3.2418
4	.15000	3.9300	.5146E-3	.1175E-3	.0024854	3.2460
5	.20000	3.7700	.6849E-3	.1698E-3	.0024854	3.2460
6	.25000	3.6400	.8547E-3	.2291E-3	.0023151	3.2411
7	.30000	3.5300	.0010239	.2951E-3	.0021453	3.2403
8	.35000	3.4300	.0011925	.3715E-3	.0019761	3.2444
9	.40000	3.3300	.0013605	.4677E-3	.0018075	3.2494
10	.45000	3.2300	.0015280	.5888E-3	.0016395	3.2490
11	.50000	3.1300	.0016949	.7413E-3	.0014720	3.2462
12	.55000	3.0300	.0018613	.9333E-3	.0013051	3.2435
13	.60000	2.9300	.0020270	.0011749	.9730E-3	3.2488
14	.70000	2.8400	-	-	-	-

Table 4.11 Protonation of 2,6-bis(2-methyl-5-furyl)pyridine

Appendix 2. In this section, pK_1 and pK_2 values calculated from equations (4.7) and (4.27) are shown in Table 4.12 to 4.17.

OBS.	V_t	pH	C_t	C_A	$[H^+]$	pK_1	pK_2
1	0.00	5.7900	-	-	-	-	-
2	.20000	3.8900	.0057038	.3984E-3	.1288E-3	2.5855	-
3	.40000	3.5800	.0056812	.7937E-3	.2630E-3	2.5929	-
4	.60000	3.3900	.0056587	.0011858	.4074E-3	2.5927	-
5	.80000	3.2500	.0056364	.0015748	.5623E-3	2.5904	-
6	1.0000	3.1400	.0056143	.0019608	.7244E-3	2.5909	-
7	1.2000	3.0500	.0055924	.0023437	.8913E-3	2.5951	-
8	1.4000	2.9700	.0055707	.0027237	.0010715	2.5949	-
9	1.6000	2.9000	.0055491	.0031008	.0012589	2.5962	-
10	1.8000	2.8300	.0055276	.0034749	.0014791	2.5821	-
11	2.0000	2.7800	.0055064	.0038462	.0016596	2.5986	-
12	2.5000	2.6500	.0054539	.0047619	.0022387	2.5850	-
13	3.4000	2.5000	.0053581	.0063670	.0031623	-	2.9218
14	3.6000	2.4800	.0053381	.0067164	.0033113	-	2.9214
15	3.8000	2.4600	.0053182	.0070632	.0034674	-	2.9230
16	4.0000	2.4400	.0052986	.0074074	.0036308	-	2.9264
17	4.2000	2.4200	.0052790	.0077491	.0038019	-	2.9316
18	4.4000	2.4000	.0052596	.0080882	.0039811	-	2.9383
19	4.6000	2.3700	.0052403	.0084249	.0042658	-	2.9121
20	4.8000	2.3500	.0052212	.0087591	.0044668	-	2.9169
21	5.0000	2.3300	.0052022	.0090909	.0046774	-	2.9214

Table 4.12 Protonation of 2,5-di(2-pyridyl)thiophene

OBS.	V_t	pH	C_t	C_A	$[H^+]$	pK_1	pK_2
1	0.00	4.2500	-	-	-	-	-
2	.40000	4.0700	.0080910	.7937E-3	.8511E-4	3.0521	-
3	.80000	3.7300	.0080273	.0015748	.1862E-3	3.0505	-
4	1.2000	3.5200	.0079646	.0023437	.3020E-3	3.0575	-
5	1.4000	3.4300	.0079336	.0027237	.3715E-3	3.0547	-
6	1.6000	3.3500	.0079028	.0031008	.4467E-3	3.0539	-
7	1.8000	3.2800	.0078723	.0034749	.5248E-3	3.0577	-
8	2.0000	3.2100	.0078420	.0038462	.6166E-3	3.0552	-
9	2.4000	3.0900	.0077822	.0045802	.8128E-3	3.0624	-
10	2.8000	2.9700	.0077232	.0053030	.0010715	3.0535	-
11	3.2000	2.8700	.0076652	.0060150	.0013490	3.0620	-
12	3.6000	2.7700	.0076080	.0067164	.0016982	3.0573	-
13	4.0000	2.6800	.0075516	.0074074	.0020893	3.0568	-
14	4.4000	2.7700	.0074961	.0080882	.0016982	-	3.4988
15	4.6000	2.7300	.0074686	.0084249	.0018621	-	3.5115
16	4.8000	2.6800	.0074414	.0087591	.0020893	-	3.4969
17	5.0000	2.6400	.0074143	.0090909	.0022909	-	3.5087
18	5.4000	2.5600	.0073608	.0097473	.0027542	-	3.5199
19	5.6000	2.5200	.0073343	.010072	.0030200	-	3.5090
20	6.0000	2.4500	.0072819	.010714	.0035481	-	3.5024
21	6.4000	2.3900	.0072303	.011348	.0040738	-	3.5122
22	7.0000	2.3100	.0071541	.012281	.0048978	-	3.4954

Table 4.13 Protonation of 2,5-di(3-pyridyl)thiophene

OBS.	V_t	pH	C_t	C_A	$[H^+]$	pK_1	pK_2
1	0.00	6.5700	-	-	-	-	-
2	.10000	5.6100	.0057795	.4149E-3	.2455E-5	4.4957	-
3	.20000	5.2700	.0057556	.8264E-3	.5370E-5	4.4911	-
4	.30000	5.0500	.0057319	.0012346	.8913E-5	4.4845	-
5	.40000	4.8900	.0057084	.0016393	.1288E-4	4.4904	-
6	.50000	4.7500	.0056851	.0020408	.1778E-4	4.4923	-
7	.60000	4.6200	.0056620	.0024390	.2399E-4	4.4914	-
8	.70000	4.5000	.0056391	.0028340	.3162E-4	4.4947	-
9	.80000	4.3800	.0056163	.0032258	.4169E-4	4.4970	-
10	.90000	4.2500	.0055938	.0036145	.5623E-4	4.4926	-
11	1.0000	4.1200	.0055714	.0040000	.7586E-4	4.4970	-
12	1.1000	3.9700	.0055492	.0043825	.1072E-3	4.4958	-
13	1.2000	3.8100	.0055272	.0047619	.1549E-3	4.5096	-
14	1.6000	3.7800	-	-	-	-	-
15	1.7000	3.7500	.0054197	.0066148	.1778E-3	-	2.9873
16	1.8000	3.6000	.0053986	.0069767	.2512E-3	-	2.9802
17	1.9000	3.4800	.0053778	.0073359	.3311E-3	-	2.9881
18	2.0000	3.3800	.0053571	.0076923	.4169E-3	-	2.9810
19	2.1000	3.2900	.0053366	.0080460	.5129E-3	-	2.9824
20	2.2000	3.2100	.0053162	.0083969	.6166E-3	-	2.9869
21	2.3000	3.1300	.0052960	.0087452	.7413E-3	-	2.9818
22	2.4000	3.0600	.0052760	.0090909	.8710E-3	-	2.9844

Table 4.14 Protonation of 2,5-di(4-pyridyl)thiophene

OBS.	V_t	pH	C_t	C_A	$[H^+]$	pK_1	pK_2
1	0.00	6.8700	-	-	-	-	
2	.40000	4.6900	.0058542	.5168E-3	.2042E-4	3.6568	-
3	.80000	4.3500	.0058241	.0010283	.4467E-4	3.6579	-
4	1.2000	4.1300	.0057943	.0015345	.7413E-4	3.6576	-
5	1.6000	3.9600	.0057648	.0020356	.1096E-3	3.6604	-
6	2.0000	3.8100	.0057356	.0025316	.1549E-3	3.6598	-
7	2.4000	3.6700	.0057067	.0030227	.2138E-3	3.6565	-
8	2.8000	3.5400	.0056781	.0035088	.2884E-3	3.6574	-
9	3.2000	3.4100	.0056498	.0039900	.3890E-3	3.6549	-
10	3.6000	3.2800	.0056218	.0044665	.5248E-3	3.6504	-
11	4.0000	3.1600	.0055940	.0049383	.6918E-3	3.6585	-
12	4.4000	3.0400	.0055665	.0054054	.9120E-3	3.6604	-
13	6.0000	3.1200	.0054592	.0072289	.7586E-3	-	2.3147
14	6.4000	3.0100	.0054330	.0076739	.9772E-3	-	2.3198
15	6.8000	2.9200	.0054071	.0081146	.0012023	-	2.3244
16	7.2000	2.8400	.0053814	.0085511	.0014454	-	2.3201
17	7.6000	2.7700	.0053560	.0089835	.0016982	-	2.3151
18	8.0000	2.7100	.0053308	.0094118	.0019498	-	2.3158
19	8.4000	2.6600	.0053058	.0098361	.0021878	-	2.3279
20	8.8000	2.6100	.0052810	.010256	.0024547	-	2.3262
21	9.2000	2.0800	-	-	-	-	-

Table 4.16 Protonation of 2,5-di(3-pyridyl)furan

OBS.	V_t	pH	C_t	C_A	$[H^+]$	pK_1	pK_2
1	5.6500	0.00	-	-	-	-	-
2	5.4800	.050000	.0046829	.4525E-3	.3311E-5	4.5057	-
3	5.1300	.10000	.0046618	.9009E-3	.7413E-5	4.5049	-
4	4.9000	.15000	.0046409	.0013453	.1259E-4	4.5051	-
5	4.7100	.20000	.0046202	.0017857	.1950E-4	4.5016	-
6	4.5500	.25000	.0045996	.0022222	.2818E-4	4.5100	-
7	4.3800	.30000	.0045793	.0026549	.4169E-4	4.5036	-
8	4.2100	.35000	.0045591	.0030837	.6166E-4	4.5036	-
9	4.0200	.40000	.0045391	.0035088	.9550E-4	4.5017	-
10	3.8000	.45000	.0045193	.0039301	.1585E-3	4.5028	-
11	3.5400	.50000	.0044996	.0043478	.2884E-3	4.5048	-
12	3.5200	.60000	.0044609	.0051724	.3020E-3	-	2.3927
13	3.3100	.65000	.0044417	.0055794	.4898E-3	-	2.4009
14	3.1600	.70000	.0044227	.0059829	.6918E-3	-	2.3960
15	3.0400	.75000	.0044039	.0063830	.9120E-3	-	2.3814
16	2.9500	.80000	.0043852	.0067797	.0011220	-	2.3874
17	2.8700	.85000	.0043667	.0071730	.0013490	-	2.3838
18	2.8100	.90000	.0043484	.0075630	.0015488	-	2.4065
19	2.7400	.95000	.0043302	.0079498	.0018197	-	2.3804
20	2.6900	1.0000	.0043122	.0083333	.0020417	-	2.3938

Table 4.17 Protonation of 2,5-di(4-pyridyl)furan

Appendix 3. The computer programs used in this study are shown in Appendix 3.1-3.4.

A.3. 1. This program shows the calculation of the pK_a by U.V. technique. The program calculates the basicity of the compounds according to equation (4.39) and (4.40).

```
$ pKaol.bat
E=A/c
X=E-Efb
Y=Eca-E
l=0.4343*log(X/Y)
pKa=pH+I
M=Sum(10^pKa)/n
pKa,ave=0.4343*log(M)
Dev=pKa-pKa,ave
$ end of program
```

A.3. 2. This program presents the calculation of the pK_1 by potentiometric titration by using equation (4.7).

```
$ pk1ol.bat
Ct=w*1000/(M*(V+Vt))
Ca=Vt*NHCl/(Vt+V)
H=10^(-pH)
B=Ct-Ca
X=Ca-H
Y=B+H
pK1=pH+0.4343*log(X/Y)
M=Sum(10^pK1)/n
pK1ave=0.4343*log(M)
Dev=pK1-pK1ave
$ end of program
```

A3. 3. Calculation of the pK_2 using equation (4.27)

```
$ pK2ol.bat
Ct=m*1000 / (W*(V+VT))
Ca=Vt*NHCl/(Vt+V)
H=10^(-pH)
I=2*Ca-H-Ct
FS=Sqrt(I)/(1+1.6*Sqrt(I))
H1=H*10^(0.5115*FS)
X=Ca-Ct-H1
Y=2*Ct-Ca+H1
```

```
pK2=pH+0.4343*log(X/Y)-1.5345*FS
M=Sum(10^pK2)/n
pK2,ave=0.4343*log(M)
Dev=pK2-pK2,ave
$ end of  program
```

A.3. 4. Calculation of the pK_1 and pK_2 by overlapping process according to the equation (4.28). This process is repeated, until a constant value is obtained.

```
$  overlop.bat

Ca=(Vt *NHCl) / (V+Vt)
Ct=w*1000/(M*(V + Vt))
H= 10^(-pH)
F=(Ca+H)/Ct
x=H^2*F/(2-F)
y=H*(1-F)/(2-F)
tx=sum(x)
ty=sum(y)
txy=sum(x*y)
tx2=sum(x^2)
de=(n*tx2)-tx2^2
m=(n*txy-tx*ty)/de
C=(tx2*ty-tx*txy)/DE
K1=1/m
K2=Abs(c)

$ 2 th overlop.bat

d=H^2 + K1 * H + K1*K2
HA=(K1*H/d)*Ct
H2A=(H^2/d)*Ct
I=0.5*(Cl+Ca + 4*H2A +HA + 3*H)
FS=Sqrt(I)/(1+1.6 * Sqrt(I))
H1=H*10^(0.5115 *FS)
F1=(Ca + H1) / Ct
a=H1^2*F1/(2-F1)
b=H1*(1-F1)/(2-F1)
x0=a/10^(2.046*FS)
y0=b/10^(0.5115*FS)
tx0=sum(x0)
ty0=sum(y0)
tx0y0=sum(X0*y0)
tx02=sum(x0^2)
ta=sum(a)
tb=sum(b)
ta2=sum(a^2)
tab=sum(A*B)
de1=n*tx02-(tx0)^2
de2=n*ta2-(ta)^2
m1=(n*tx0y0-tx0*ty0)/de1
```

```
m2=(n*tab-ta*tb)/de2
cK1=1/m2
tk1=1/m1
c1=(tX02*ty0-tx0*tx0y0)/de1
c2=(ta2*tb-ta*tab)/de2
tK2=Abs(c1)
cK2=Abs(c2)

$ 3 th overlop.bat

d1=H1^2 +cK1 * H1+ cK1*cK2
HA1=(cK1*H1/d1)*Ct
H2A1=(H1^2/d1)*Ct
I1=0.5*(Cl+Ca + 4*H2A1 +HA1 + 3*H1)
H2=H1*10^(0.5115 * FS1)
F2=(Ca + H2) / Ct
a1=H2^2*F2 / (2-F2)
1=H2*(1-F2)/(2-F2)
x1=a1/10^(2.046*FS1)
y1=b1/10^(0.5115*FS1)
t1=sum(x1)
ty1=sum(y1)
tx1y1=sum(x1*y1)
tx12=sum(x1^2)
ta1=sum(a1)
t=sum(b1)
ta1b1=sum(a1*b1)
ta12=sum(a1^2)
de11=n*tx12-tx1^2
de21=n*ta12-ta1^2
m11=(n*tx1y1-tx1*ty1)/de11
cK11=1/m21
tk11=1/m11
c1=(tx12*ty1-tx1*tx1y1)/de11
c=(ta12*tb1-ta1*ta1b1)/de21
tK21=Abs(c11)
cK21=Abs(c21)

$ end of program
```