

**ADDITION REACTIONS OF AROMATIC COMPOUNDS
TO MULTIPLE BONDS IN THE PRESENCE OF
METAL TRIFLUOROMETHANESULFONATES**

**AROMATİK BİLEŞİKLERİN ÇOKLU BAĞLARA
METAL TRİFLORMETANSÜLFONATLAR VARLIĞINDA
KATILMA TEPKİMELERİ**

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AROMATİK BİLEŞİKLERİN ÇOKLU BAĞLARA METAL TRİFLORMETANSÜLFONATLAR VARLIĞINDA KATILMA TEPKİMELERİ

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ÖZET

Doktora tezi olarak sunulan bu çalışmanın ilk kısmında çeşitli *N*-tosil imin bileşikleri sentezlenmiş ve metal triflormetansulfonatlar (triflatlar) katalizörlüğünde pirol'e katılma tepkimelerinde kullanılmışlardır. Katılma tepkimesi üzerine çözücü, sıcaklık, katalizör türü ve substitüent etkileri araştırılmış ve optimum tepkime koşulları saptanmıştır. Yeni pirol bileşikleri olan 2-pirol sülfonamitler yer seçimli olarak yüksek verimde elde edilmiştir.

Çalışmanın ikinci kısmı porfirin ve birçok makrohalkalı yapının önemli ara ürünü olan 5-substitüye dipirolmetan bileşikleri için yeni bir sentez yönteminin geliştirilmesini içermektedir. Elektron verici ve çekici gruplar içeren dipirolmetan bileşikleri *N*-tosil iminlerin fazla miktarda pirol ile metal triflatların katalizör olarak kullanılması sonucu yüksek verimle elde edilmiştir.

Çalışmanın son kısmında 5,10,15,20-tetrafenilporfirin (TPP) gibi *meso*-substitüye aril porfirin bileşiklerinin sentezi için yeni bir metod sunulmuştur. Bu metal triflat katalizli, tek tepkime kabında, iki adımlı yöntem *N*-tosil iminlerin dipirolmetanlarla tepkimesi sonucu porfirinojenlerin sentezini ve bu porfirinojenlerin 2,3-dikloro-5,6-disiyano kinon (DDQ) ile porfirinlere yükseltgenmesini içermektedir. Bu tezde ayrıca porfirinlerin verimini etkileyen faktörlerin incelenmesi de sunulmuştur.

Sentezlenen bileşikler kromatografik yöntemlerle veya kristallendirme ile saflaştırılmış, yapıları ¹H NMR, ¹³C NMR, FTIR ve UV spektroskopik teknikleriyle aydınlatılmıştır.

Anahtar Kelimeler: Porfirinler, Dipirolmetanlar, Piyol, Piyol trevleri, Metal triflatlar, *N*-tosil iminler.

Danışman: Prof. Dr. Canan naleroęlu, Hacettepe niversitesi, Fen Fakltesi, Kimya Blm, Organik Kimya Anabilim Dalı.

ADDITION REACTIONS OF AROMATIC COMPOUNDS TO MULTIPLE BONDS IN THE PRESENCE OF METAL TRIFLUOROMETHANESULFONATES

Bariş Temelli

ABSTRACT

In the first part of the study presented as a PhD thesis, various *N*-tosyl imine compounds were synthesized and used in the addition reactions of pyrrole in the presence of metal trifluoromethanesulfonates (triflates) as catalysts. The effects of solvent, temperature, catalyst type and substituents on the addition reactions were investigated and optimum reaction conditions were determined. New pyrrole addition products, 2-pyrrole sulfonamides, were obtained regioselectively in high yields.

The second part of the study consists of the development of a new method for the synthesis of 5-substituted dipyrromethanes, which are important intermediates for the synthesis of porphyrins and many macrocyclic compounds. Dipyrromethanes containing electron donating and withdrawing groups were synthesized in high yields from the reactions of *N*-tosyl imines with excess pyrrole by using metal triflates as catalyst.

In the last part of the study, a new method for the synthesis of *meso*-substituted aryl porphyrins, such as 5, 10, 15, 20-tetraphenylporphyrin (TPP), is presented. This metal triflate catalysed, one flask, two-step method involves the synthesis of *meso*-substituted porphyrinogens by the reaction of dipyrromethanes with *N*-tosyl imines and oxidizing porphyrinogens to porphyrins by 2,3-dichloro-5,6-dicyano quinone (DDQ). The examination of many factors that influence the yield of porphyrin formation is also presented in this thesis.

Synthesized compounds were purified by chromatographic methods and their structures were identified by ¹H NMR, ¹³C NMR, FTIR and UV spectroscopic techniques.

Keywords: Porphyrins, Dipyrromethanes, Pyrrole, Pyrrole derivatives, Metal triflates, *N*-tosyl imines.

Advisor: Prof. Dr. Canan Unaleroglu, Hacettepe University, Faculty of Science, Department of Chemistry, Organic Chemistry Division.

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ABREVIATIONS

bmim	: 1-Butyl-3-methylimidazole
BNCT	: Boron neutron capture therapy
BPA	: L-4-dihydroxyborylphenylalanine
BPD-MA	: Benzoporphyrin derivative monoacid
br	: Broad
BSH	: Mercapto-closo-dodecarborate
d	: Doublet
DCM	: Dichloromethane
dd	: Doublet of doublet
DDQ	: 2,3-Dichloro-5,6-dicyanoquinone
DMF	: Dimethylformamide
DNA	: Deoxyribonucleic acid
FDA	: Food and Drug Administration
FT-IR	: Fourier Transform Infrared
Hp	: Haematoporphyrin
HVD	: Hydroxyethylvinyldeuteroporphyrin
ISC	: Intersystem crossing
IUPAC	: International union of pure and applied chemistry
Kh	: Hydrolysis constants
LDA	: Lithium diisopropylamide
m	: Multiplet
MACE	: Mono-L-aspartyl chlorin e6
N-Boc	: <i>t</i> -Butoxycarbonyl
NMR	: Nuclear magnetic resonance

NSAID	: Nonstereoidal antiinflammatory drug
<i>o</i> -Chloranil	: Tetrachloro <i>o</i> -benzoquinone
OEP	: β -Octaethylporphyrin
Tf	: Trifluoromethanesulfonate
PA-Sc-TAD	: Polyallyl scandium triflamide ditriflate
<i>p</i> -Chloranil	: 2,3,5,6-Tetrachloroquinone
PDT	: Photodynamic therapy
Pp	: Protoporphyrin
Rf	: Retardation Factor
q	: Quartet
s	: Singlet
t	: Triplet
TBDMS	: <i>tert</i> -Butyldimethylsilyl
TFA	: Trifluoroacetic acid
TfOH	: Trifluoromethanesulfonic acid
THF	: Tetrahydrofuran
TLC	: Thin layer chromatography
TMSCI	: Trimethylchlorosilane
Tol-BINAP	: 2,2'-Bis(di- <i>p</i> -tolylphosphino)-1,1'-binaphthyl
Tosyl	: Toluenesulfonyl
TPP	: <i>meso</i> -Tetraphenylporphyrin
Triflate	: Trifluoromethanesulfonate
UV	: Ultraviolet
WERC	: Water exchange rate constants

1. INTRODUCTION

Porphyrins and related molecules play a very important role in biological systems. The main function of porphyrins and porphyrin-like compounds in nature is to bind to metal atoms, which act as centers for significant biochemical events. For example; heme group is iron protoporphyrin and in many organisms O₂ transport and storage mediated by heme proteins. Chlorophyll consists of a chlorin, a reduced porphyrin, which captures sunlight for photosynthesis. The active site of another important molecule Vitamin B₁₂ also contains corrin structure. Due to their biological importance and their physical and chemical properties, porphyrin chemistry has been an important research area since the early 1800s.

A large number of naturally occurring and synthetic porphyrin derivatives are currently being used in a wide variety of applications, including molecular electronic devices, catalysis, energy conversion, photodynamic cancer therapy and boron neutron capture therapy.

A variety of synthetic methods have been developed for the synthesis of non-natural porphyrins, especially for the *meso* tetra-substituted porphyrins. In general, porphyrins can be synthesized using four principal pathways; i) synthesis from monopyrrole tetramerization, ii) synthesis using tripyrrolic intermediates (3+1 methodology), iii) synthesis from linear tetrapyrrolic precursors and iv) synthesis from dipyrrolic intermediates (2+2 methodology).

5-substituted dipyrromethanes are the most commonly used dipyrrolic intermediates for '2+2' porphyrin synthesis. 5-Substituted dipyrromethanes are also important precursors for the synthesis of expanded porphyrins and porphyrin analogues. Several methods have been reported for the synthesis of 5-substituted dipyrromethanes by the condensation of an aldehyde and pyrrole using various combinations of solvents and acids such as BF₃·etherate, trifluoroacetic acid (TFA), propionic acid, etc. All these reports claim moderate yields of *meso*-substituted dipyrromethanes with side products such as azafulvenes and *N*-confused dipyrromethanes and oligomeric products. The yields are reduced due to

the formation of oligomers and stringent purification methods are needed to remove the by-products.

In connection with the chemistry of porphyrins and 5-substituted dipyrromethanes, the development of new synthetic methodologies for the synthesis of these compounds is also important. In this thesis, three new methods were developed for the synthesis of i) 2-substituted pyrrolesulfonamides, ii) 5-substituted dipyrromethanes and iii) *meso*-tetraarylporphyrins by using metal trifluoromethanesulfonates (triflates) as catalyst. The optimization of these novel methods was carried out by changing different reaction parameters such as solvent, temperature, concentration of reactants, reactant ratio and catalyst type. The products were obtained generally in high yields with catalytic amounts of metal triflates, although various kinds of Lewis acids have been applied in stoichiometric amounts in the literature for the synthesis of porphyrins and 5-substituted dipyrromethanes.

2. GENERAL INFORMATION

2.1. Porphyrins and Their Properties

The word porphyrin was derived from the greek word porphura, which pertains to the characteristic purple color of porphyrins (Milgrom, 1997). Porphyrins are aromatic macrocycles containing 22 conjugated π -electrons with 18 π -electrons participating in the delocalization pathway. This conforms with the $[4n+2]$ rule for aromaticity. The unsubstituted macrocycle is called porphin (**1**) (Figure 2.1.), whereas the substituted macrocycle is referred to as porphyrin. Peripheral pyrrolic positions are called β -positions. The bridge carbon atoms are called the meso position. The two major classes of substituted porphyrins are the *meso*-substituted and the β -octasubstituted porphyrins, examples of which are *meso*-tetraphenylporphyrin (TPP) (**2**) and, β -octaethylporphyrin (OEP) (**3**) respectively (Figure 2.1).

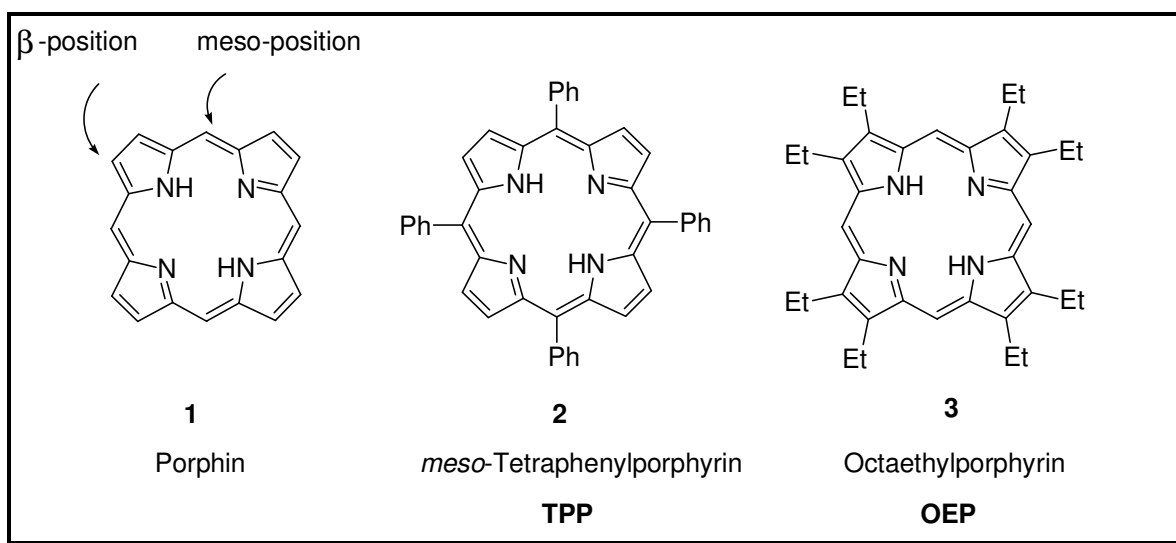


Figure 2.1. Porphin and its derivatives

The first system of naming porphyrins was established by Fisher (Fisher and Orth, 1934; 1937). The nomenclature was based on porphyrins side chains at β position. For example;

- URO- porphyrin has an acetate and a proprionate side chain.
- COPRO- porphyrin has a methyl and a proprionate side chain.
- PROTO- porphyrin has two pyrrole rings with a methyl and proprionate side chain and two pyrrole rings with a methyl and vinyl side chain.

A more formal and consistent system was developed by the IUPAC in 1979 and finalized in 1989. The IUPAC nomenclature numbers all of the atoms in the porphyrin. The numbers of nomenclature system is given in Figure 2.2.

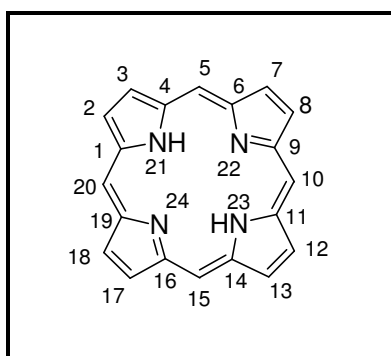


Figure 2.2. IUPAC recommended numbering scheme for porphyrins.

The porphyrin macrocycle is an aromatic system consisting of four pyrrole units linked by four sp^2 hybridized *meso* carbons. The aromaticity of porphyrins has been well established both by its chemical and physical properties. These tetrapyrrolic systems have a closed loop of edgewise overlapping p orbitals which interact favorably to stabilize the olefins; the 22 π electrons in porphyrins make up six different 18 e-delocalization pathways, (Figure 2.3) which follow Huckel's $4n + 2$ rule for aromaticity.

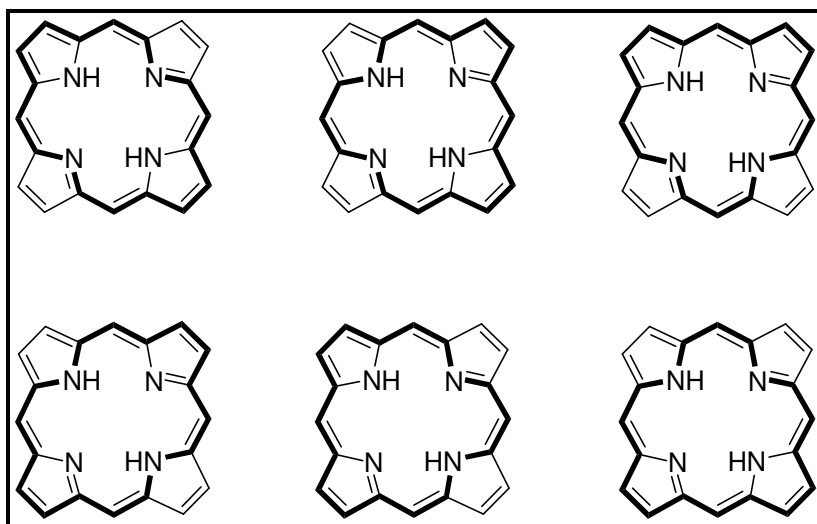


Figure 2.3. 18 pi-electron pathways which make up the aromatic character of the porphin ring system

Porphyrins belong to a large family of tetrapyrrolic macrocyclic compounds. Some members of the family include chlorin (reduced at one pyrrole ring), bacteriochlorin and isobacteriochlorin (reduced at two pyrrole rings), phlorin (reduced at one of the *meso*-positions), and porphyrinogen (reduced at all four *meso*-positions) (Figure 2.4).

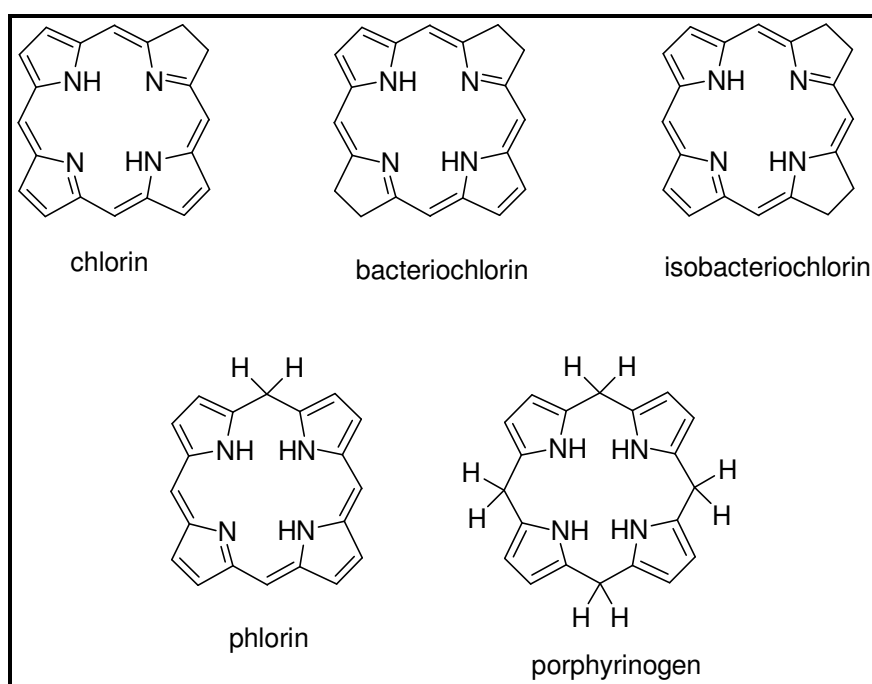


Figure 2.4. Hydroporphyrins

Porphyrins that occur naturally play a major role in the life sustaining biochemical reactions. The most important porphyrins for life are iron hemes (**4**) (Figure 2.5). The heme group is found in the hemoglobin-myoglobin and cytochrome families. In many organisms, O₂ transport and storage are frequently mediated by heme proteins. In mammals, oxygen is transported by the hemoglobin and stored by myoglobin (Scheer, 1978). Vitamin B₁₂ and chlorophyll are also essential porphyrin containing molecules in the nature. The active site of vitamin B₁₂ molecule is a corrin, which plays an important role in biological systems. Chlorophyll (**5**) consists a chlorin, a reduced porphyrin, which captures sunlight for photosynthesis (Figure 2.5). This process is the important light-harvesting phenomenon that converts solar energy to support the whole ecosystem in the planet.

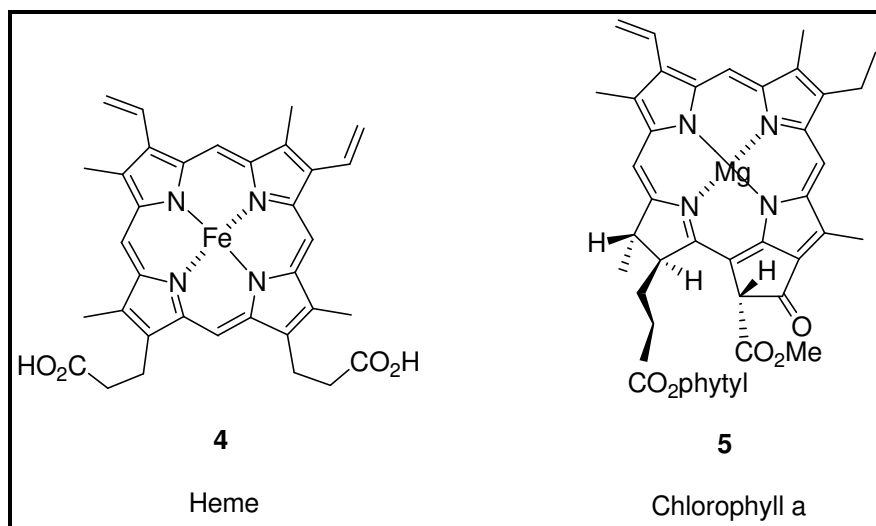


Figure 2.5. Two important naturally-occurring porphyrin complexes

2.2. Applications of Porphyrins

There are a lot of interesting applications of porphyrins and other tetrapyrroles (chlorins and bacteriochlorins) in chemical and biomedical research (Kadish et al., 2000). For example:

- Photodynamic therapy (PDT)
- Boron neutron capture therapy (BNCT)
- Modellsystems of photochemical reaction centres

- Biomimetic models of several enzymes
- Catalysis (especially with Mn, Fe and Pd metalloporphyrins)
- Sensors and biosensors

2.2.1. Photodynamic therapy (PDT)

One of the most important biological application of porphyrin is photodynamic therapy. Photodynamic therapy (PDT) is a special form of phototherapy, a term which includes all treatments which use light to induce reactions in the body which are of benefit to patients. PDT is a developing technique which can potentially destroy unwanted tissue, while sparing normal tissue. First, a drug called a photosensitiser is administered to the patient, usually by injection. The photosensitiser alone is harmless and has no effect on either healthy or abnormal tissue. However, when light (often from a laser) is directed onto tissue containing the drug, the drug becomes activated and the tissue is rapidly destroyed, but only precisely where the light has been directed. Thus, by careful application of the light beam, the technique can be targeted selectively to the abnormal tissue.

Photosensitisers are molecules which have the special property of absorbing light energy and using this energy to carry out chemical reactions in cells and body tissues. The activation of the photosensitizer by irradiation of the tumor with red light generates cytotoxic species that cause irreversible destruction of the tumor issue. Activation of the porphyrin nucleus causes an excitation of an electron from the ground state (^0P) to an excited state ($^1P^*$) as shown Figure 2.6. The singlet excited porphyrin can either decay to the ground state with emission of light (fluorescence) or can change its spin *via* intersystem crossing (ISC) to give the triplet state ($^3P^*$).

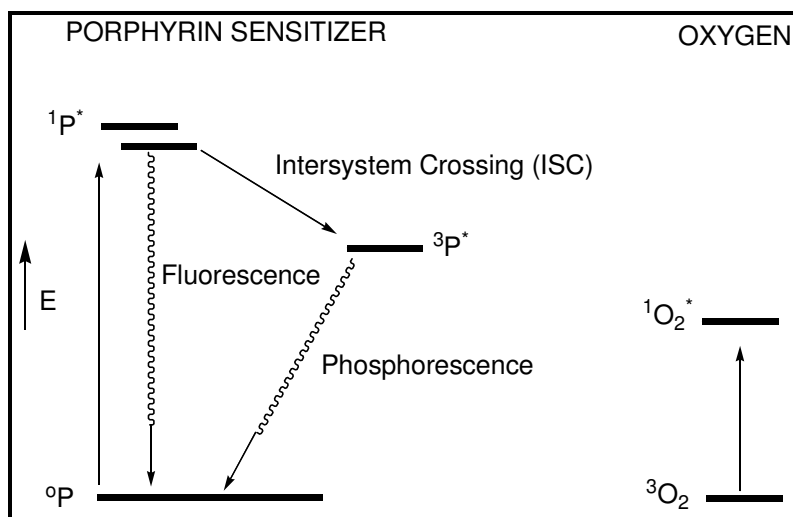


Figure 2.6. Mechanism of PDT

According to the spectroscopic selection rules, the transition state porphyrin sensitizer has time to react with its chemical environment. Two possible reaction mechanisms have been proposed: in the first mechanism, the excitation energy is transferred to molecular oxygen in its ground state ($^3\text{O}_2$) to produce the highly toxic singlet oxygen ($^1\text{O}_2$) as shown in Figure 2.6. In the second mechanism, the excited triplet state of sensitizer reacts with biological substrate molecules by transfer processes to form radical anions (equation 2.1). These radicals can subsequently react with oxygen to produce a variety of oxidized products such as peroxides and superoxide ion, which are mortal to cells.



The profile of an ideal PDT photosensitizer is that the drug should have good pharmacokinetic properties, fluorescent with increased absorbance in the red region of the optical spectrum, high quantum yield of triplet formation, good cytotoxic oxygen species generation, increased selectivity for malignant tissue over normal tissue and exhibiting low dark toxicity.

Porphyrins are the most explored sensitizer / tumoractive compounds because i) they absorb strongly in the visible region of the optical spectrum, ii) are non-toxic

in the dark, iii) are chemically stable, iv) are fluorescent and v) form stable complexes with a variety of metals while retaining their *in vivo* tumor localization properties. Numerous porphyrin type chromophores have been shown to be effective as photosensitizers for PDT of cancers (Kaye et al., 1988).

The first sensitiser used in clinical PDT was haematoporphyrin derivative and its purified fraction, Photofrin[®]. HpD was first described by Lipson et al. in 1961 and was prepared by acetylation of haematoporphyrin (Hp) (**6**) (Figure 2.7), followed by neutralisation prior to alkaline hydrolysis. The resulting mixture is known to contain haematoporphyrin, hydroxyethylvinyldeuteroporphyrin (HVD) and protoporphyrin (Pp), as well as a complex dimeric and oligomeric fraction containing ester, ether and carbon-carbon linkages of haematoporphyrin. HpD is typically 45% monomeric/dimeric porphyrins and 55% oligomeric material, the latter being accountable for the tumour localising activity of HpD *in vivo*. Photofrin[®] was approved by the Food and Drug Administration (FDA) in the US and in eleven European countries and has been used successfully over the last two decades in the treatment of patients with melanoma, early and advanced stages of cancer of the lung, digestive tract and genitourinary tract (Dougherty, 1983).

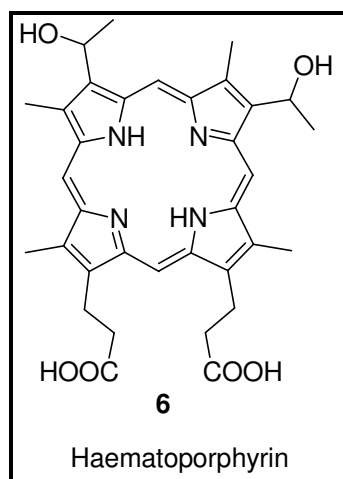


Figure 2.7. The structure of Haematoporphyrin

Following the success of PDT, "second generation" photosensitisers have been developed. Chlorins, bacteriochlorins, benzoporphyrins, phthalocyanines, and texaphyrins (tripyrrole expanded macro cycles) are long wavelength absorbers

and are the most studied porphyrin-type photosensitizing drugs. Compounds that absorb in the 650-750 nm spectral window are preferred, because light of this wavelength penetrates deeper through tissue with minimal light scattering.

Mono-L-aspartyl chlorin e6 (MACE) (**7**) obtained from chlorophyll and benzoporphyrin derivative mono-carboxylic acid (BPD-MA, Visudyne™) (**8**) (Figure 2.8) are examples of naturally derived second generation photosensitizers currently undergoing human clinical trials for treatment of various cancers using PDT (Kessel, 1997). The FDA and the Canadian Therapeutic Products Health Program approved Visudyne™ for the treatment of age-related macular degeneration (Richter et al., 1994).

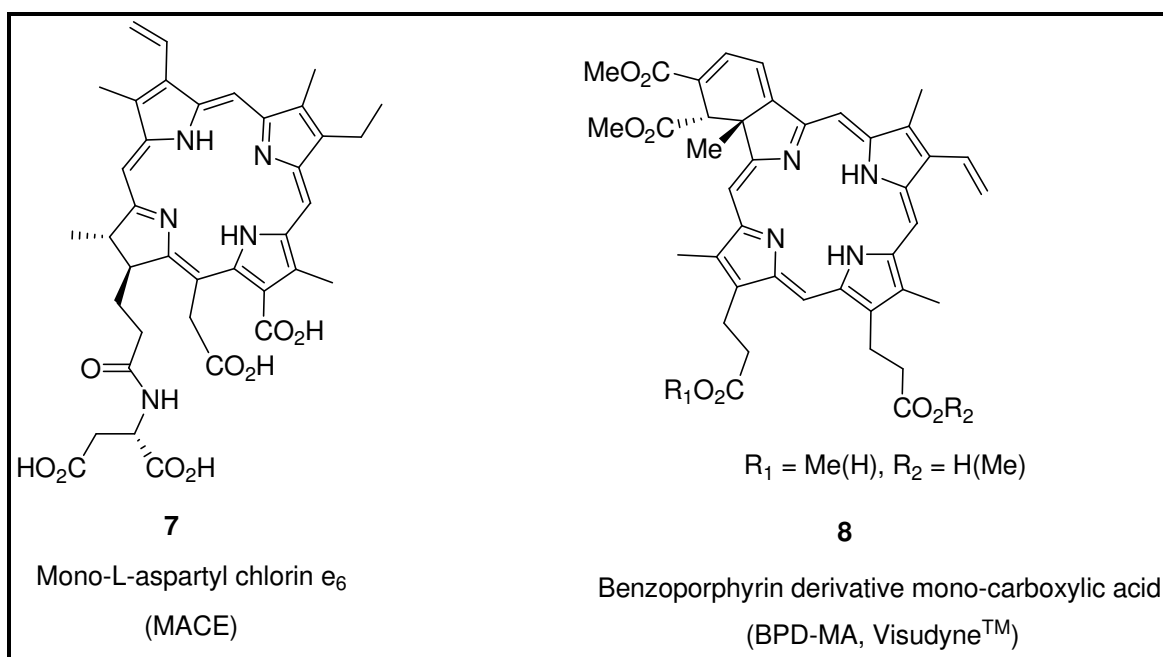
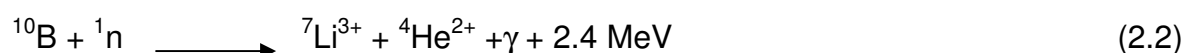


Figure 2.8. Some examples of porphyrin drugs

2.2.2. Boron neutron capture therapy (BNCT)

Boron neutron capture therapy (BNCT) of cancer is a binary radiation therapy that entails the capture of thermal neutrons by boron-10 (^{10}B) nuclei, which have been selectively delivered to tumor cells. BNCT is a new developing cancer therapy that destroys the diseased tissue while protecting normal tissue. The first component is a stable isotope of boron (^{10}B) that can be concentrated in tumor cells by attaching

it to a tumorseeking compound. The second component is a beam of low energy neutrons. After capturing a neutron, the ^{10}B disintegrates and the high-energy charged particles are produced. These particles destroy the cells in close proximity, primarily killing the cancer cells while leaving the adjacent normal cells largely unaffected (Barth et al., 1990). BNCT is based on a nuclear reaction that occurs when a stable isotope of ^{10}B that has a relatively high neutron capture crosssection value ($\sigma = 3838$), is irradiated with low energy / thermal neutrons to yield highly energetic helium -4 ($^4\text{He}^{2+}$) nuclei/ alpha particles and recoiling Lithium -7 ($^7\text{Li}^{3+}$) ions and releasing about 2.4 MeV of kinetic energy (equation 2.2).



A number of porphyrins have been boronated and are under evaluation as boron delivery agents for use in BNCT. The source of boron in porphyrins is usually the hydrophobic o-carborane cage or its amphiphilic *nido*-carborane, containing ten and nine boron atoms, respectively (Figure 2.9).

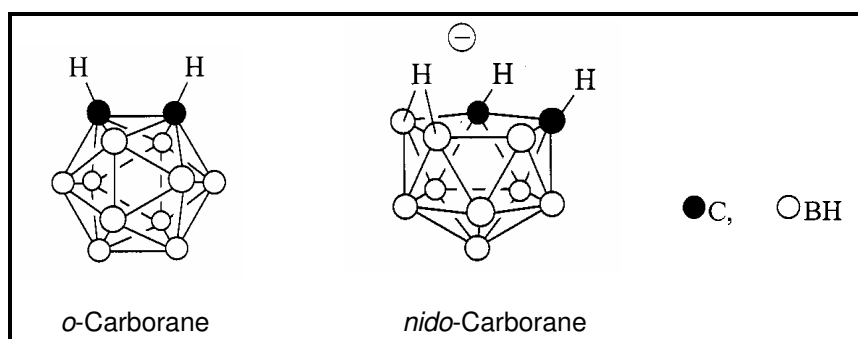


Figure 2.9. The boron structures in porphyrins

Today, only two boron containing drugs, L-4-dihydroxyborylphenylalanine (BPA) (**9**) and mercapto-closo-dodecarborate (BSH) (**10**), (Figure 2.10) clinically have been approved for use Boron Neutron Capture Therapy. However, several boron containing porphyrins derivatives have been synthesized and have been shown to have much higher tumor targeting ability and longer retention times in tumors compared with (BPA) and (BSH) .

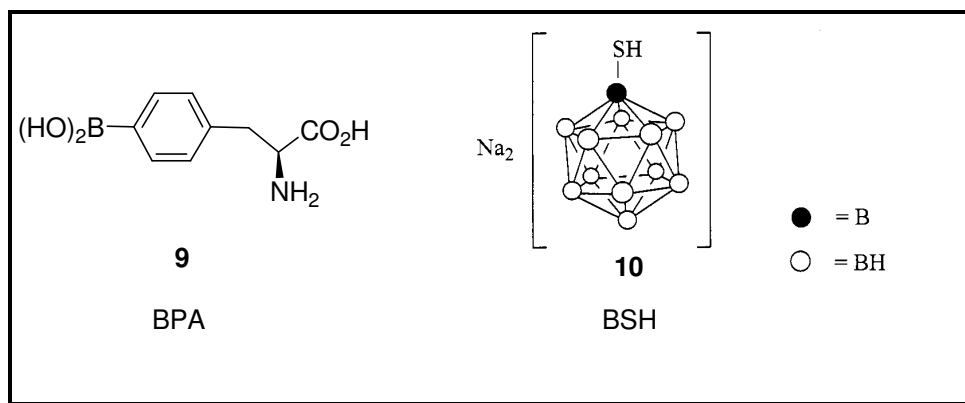


Figure 2.10. Chemical structures of BPA and BSH.

Boronated protoporphyrin-IX derivative porphyrin **11** (Kahl and Koo, 1990), nido-carboranylporphyrin derivative **12** (Miura et al., 1990), carborane-containing *meso*-tetraphenylporphyrin derivative **13** (Haushalter et al., 1981) and tetra(nido-carboranyl)porphyrin derivative **14** (Lauceri et al., 2001) are some of porphyrin macrocycles containing boron clusters reported in literature (Figure 2.11).

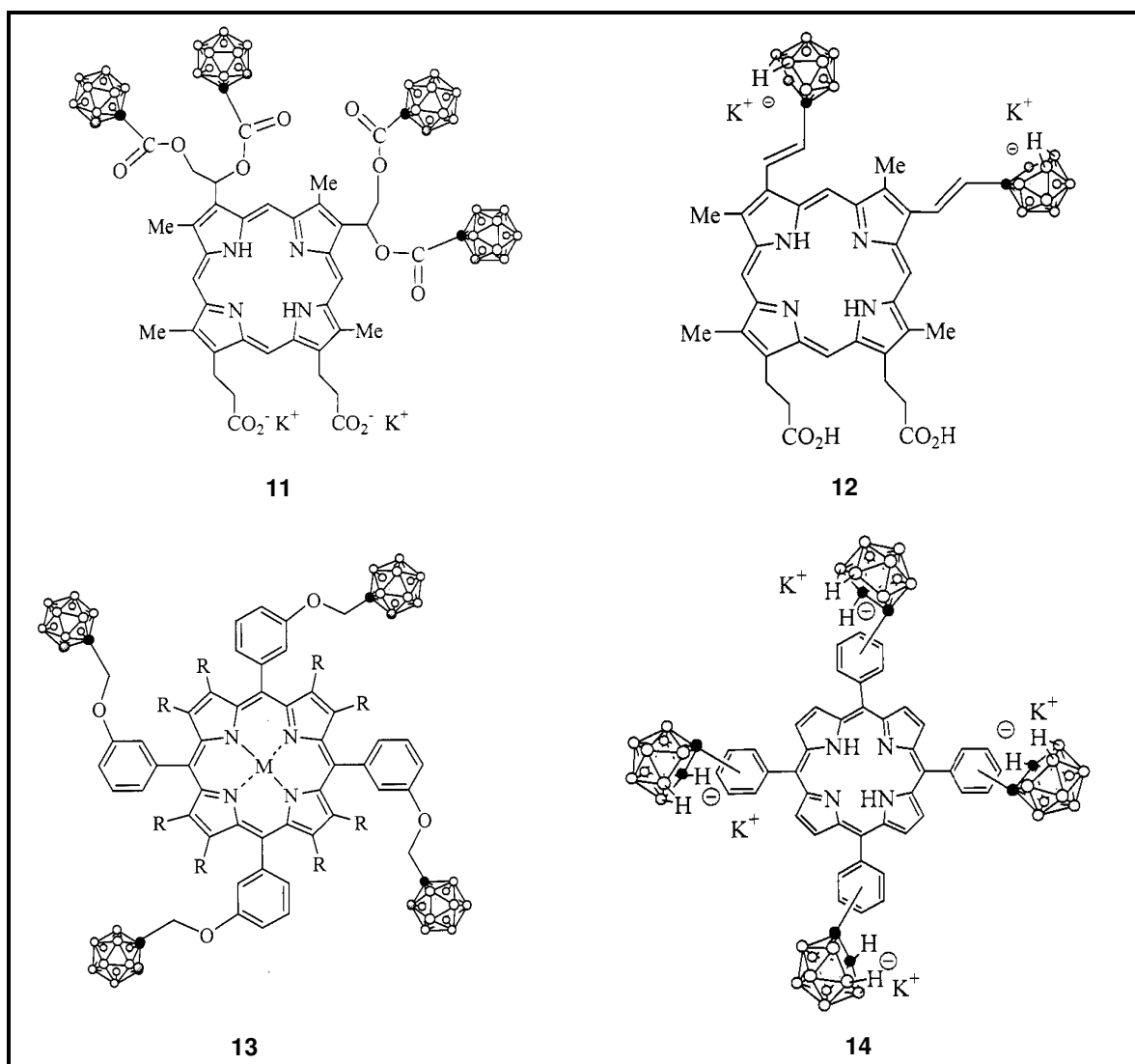


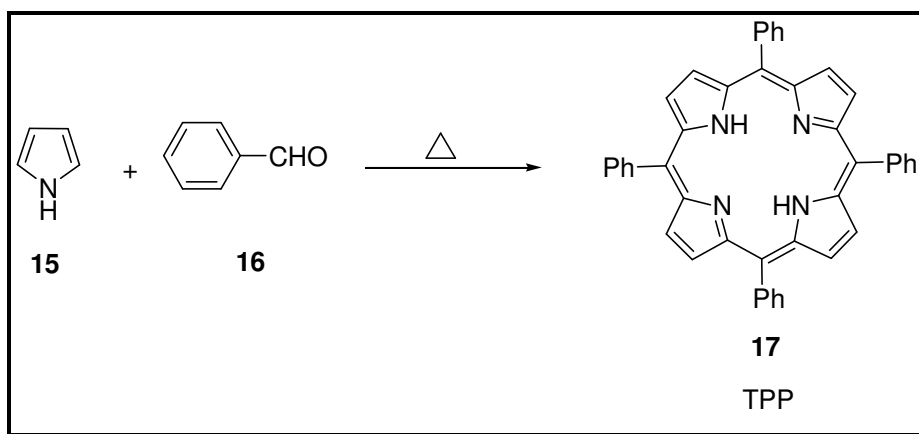
Figure 2.11. Examples of boron containing porphyrins used for BNCT.

2.3. Synthesis of Porphyrins

The porphyrin field began with the synthesis of a large class of pyrroles. Most of this early work was accomplished by Fischer and was followed by the synthesis of a variety of porphyrins. Hans Fischer is known as the grandfather of porphyrin chemistry and he has inspired a large number of research groups throughout the world to improve upon his methodologies. In general, there are several routes that can be followed to afford porphyrins.

2.3.1. Rothemund method

The first synthetic tetraphenylporphyrin (TPP) (**17**) was synthesized by Rothemund in 1936. The reaction was carried out in a sealed tube at 150 °C for 24 hours in the absence of an oxidant. Only limited number of aromatic aldehydes could be used with this method in harsh reaction conditions. The reaction afforded porphyrins with the ~5% yield (Scheme 2.1).



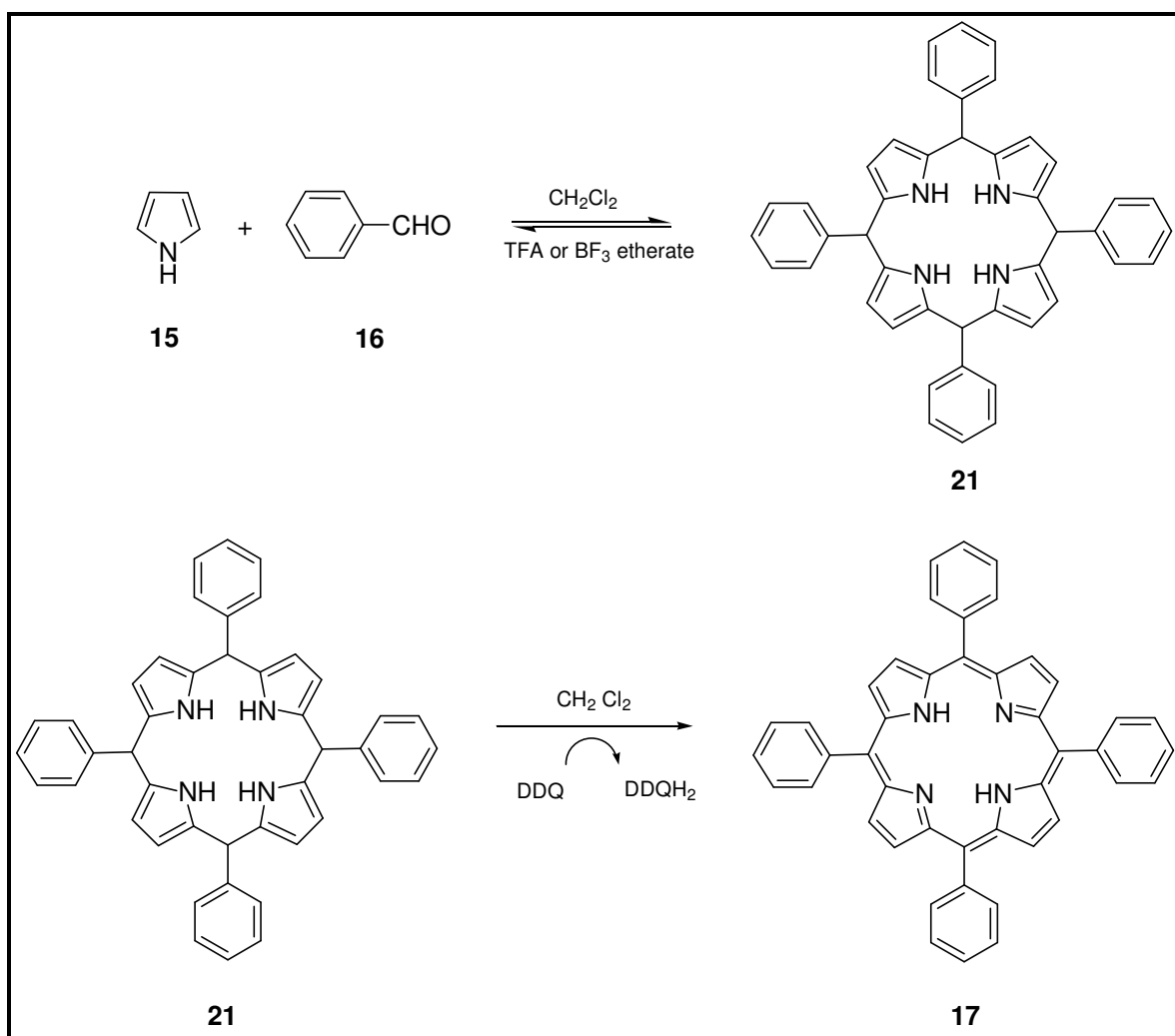
Scheme 2.1. Synthesis of TPP by Rothemund method

2.3.2. Adler - Longo method

Adler and Longo made some improvements to Rothemund method in 1967 (Adler et al., 1967). They refluxed 0.27 M of pyrrole (**15**) and benzaldehyde (**16**) in propionic acid for 30 min in open reaction vessel (Scheme 2.2). The TPP (**17**) was obtained after cooling of the reaction mixture. Using these conditions, a variety of substituted benzaldehydes were converted into the 5,10,15,20-tetraphenylporphyrins in yields ranged from 10% to 30%. The advantage of the method is that it can be scaled up to give multi-gram quantities of porphyrin. This method is still used widely when large quantities of porphyrin are needed.

2.3.3. Lindsey method

Another major contribution to the synthesis of porphyrins was achieved by Lindsey et al. (1987). The methodology of Lindsey overcame the problems associated with the harsh conditions of Adler-Longo method. The Lindsey method is a two steps reaction. The first step consists of the reaction of pyrrole and benzaldehyde at room temperature in CH_2Cl_2 by using trifluoroacetic acid (TFA) or BF_3 etherate as a catalyst. The second step is the oxidation of the porphyrinogen **21** to TPP (**17**) by using 2,3-dichloro-5,6-dicyanoquinone (DDQ) or 2,3,5,6-tetrachloroquinone (p-chloranil). The advantage of this method is that it allows the formation of porphyrins from sensitive aldehydes, in higher yields than Adler method (35-40%), using in mild reaction conditions. A major problem of the Lindsey method is that the high dilution conditions (generally 10^{-2} M) make difficult to prepare porphyrins in large scales. The dilute conditions are important to optimise formation of the porphyrinogen in high yields in the reaction medium. After the equilibrium was established, an oxidant is added which irreversibly converts porphyrinogen **21** to the corresponding porphyrin **17** (Scheme 2.4).

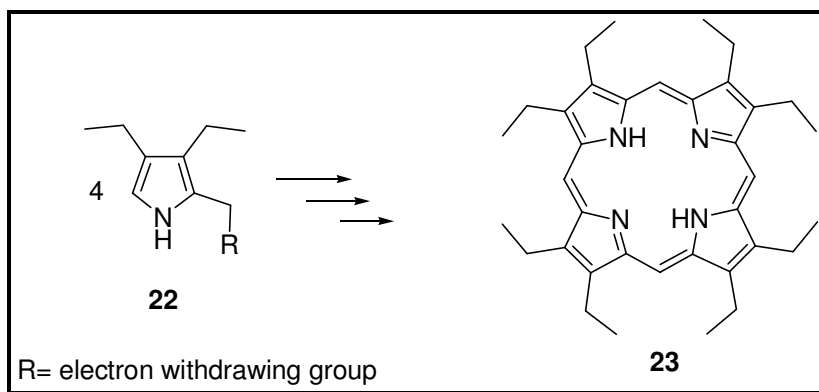


Scheme 2.4. The synthesis of porphyrins by Lindsey method

Lindsey method conditions were later modified by i) using ethanol as a co-catalyst (Groves and Nemo, 1983), ii) the addition of salts (such as NaCl) (Li et al., 1997), iii) using clays (Onaka et al., 1993), iv) using transition metals (Gradillas et al., 1995).

2.3.4. Porphyrins from tetramerisation of 2-substituted pyrroles

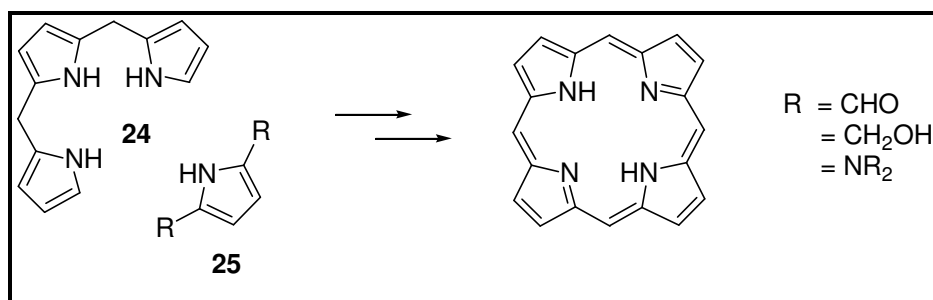
Octa- β substituted porphyrins **23** were synthesized *via* self-condensation of pyrroles **22** in the presence of base. Monopyrrole tetramerization works best for pyrroles with identical 3- and 4 substituents. Since if the substituents on the monopyrrole are not identical, acid catalyzed pyrrole ring scrambling reaction occurs.



Scheme 2.5. Synthesis of porphyrins by tetramerization of 2-substituted pyrroles.

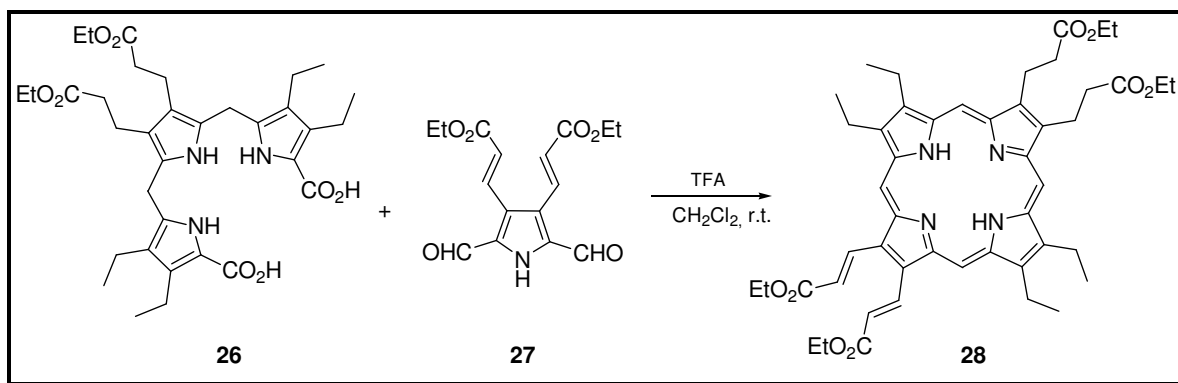
2.3.5. Synthesis of porphyrins from tripyrrolic intermediates: '3+1' route

Condensation of a linear tripyrrolic intermediate (in most cases a tripyrrane **24**) with a 2,5-disubstituted monopyrrolic intermediate **25** is referred as the '3+1' methodology (Scheme 2.6).



Scheme 2.6. Synthesis of porphyrins by 3+1 route

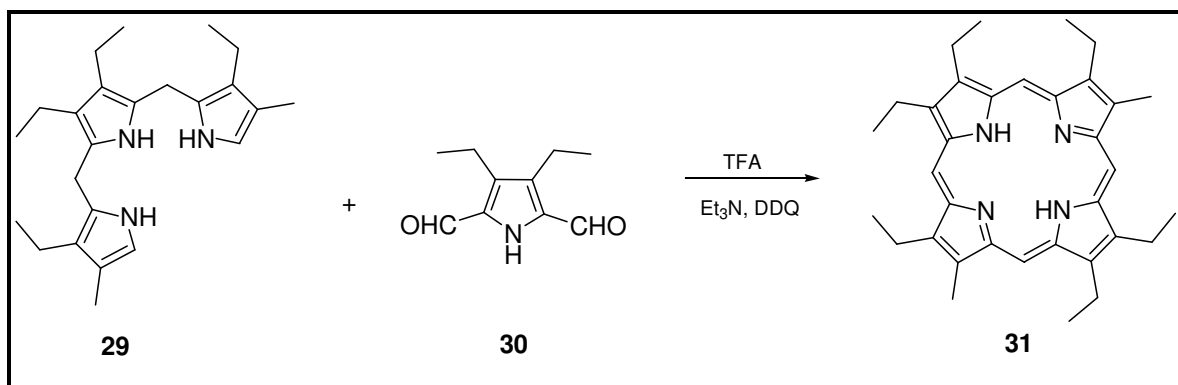
This method was first used by Johnson and coworkers (Broadhurst et al., 1971). Later Boudif and Momenteau (1994; 1996) used tripyrrane **26** and a 2,5-diformylated pyrrole **27** to prepare the porphyrin **28** in 33% yield containing two acrylic acid units on the same pyrrole as shown in Scheme 2.7.



Scheme 2.7. The reaction of 2,5-diformylpyrrole and tripyrane

Alternatively, 2,5-bis(hydroxymethyl)pyrrole (Taniguchi et al., 2001) or 2,5-bis(*N,N*-dimethylaminomethyl)pyrrole (Nguyen et al., 1994; 1996) was used as the monopyrrolic intermediate in the place of diformylpyrrole.

Lash (1997) has used tripyrrane **29** and pyrrole dialdehyde **30** to prepare the octaalkylporphyrin **31** (60% yield). The porphyrinogen was formed with acid catalysis and then oxidized to porphyrin **31** by using DDQ (Scheme 2.8).



Scheme 2.8. Synthesis of octaalkylporphyrin.

This method was also used to prepare a wide variety of 5,10-disubstituted porphyrins (Hatscher and Senge, 2002) and *N*-confused porphyrin (Furuta et al., 2003).

2.3.6. Synthesis of porphyrin from linear tetrapyrroles

This methodology favors the synthesis of totally unsymmetrical porphyrins from tetrapyrrolic intermediates. Bilanes, *a*-oxobilanes, *b*-oxobilanes, *a*-bilenes, *b*-bilenes, and *a,c*-biladiens are tetrapyrrolic intermediates for the synthesis of substituted porphyrins (Figure 2.12). Limitations of this methodology are the accessibility of the building blocks and the limited stability of tetrapyrroles. Thus, this method is not widely used in the syntheses of symmetrical porphyrins.

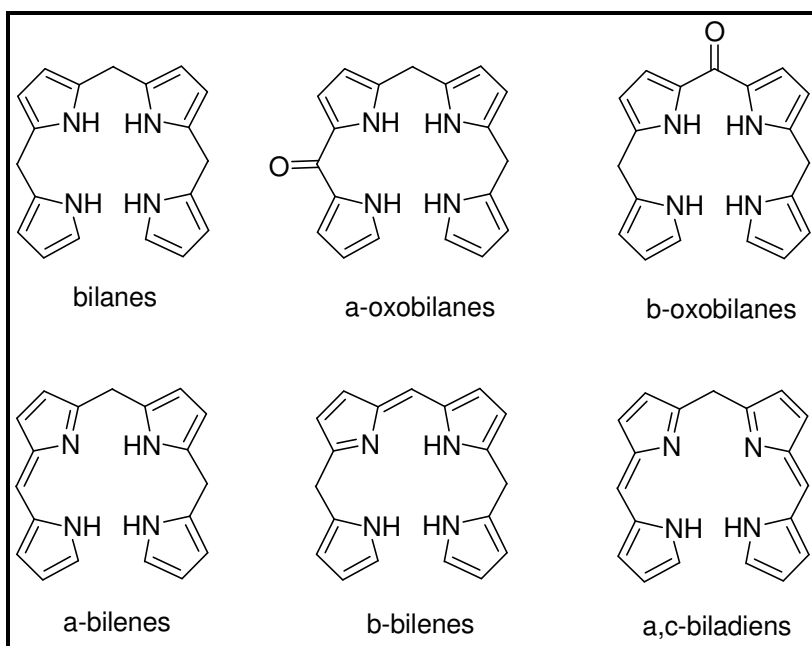
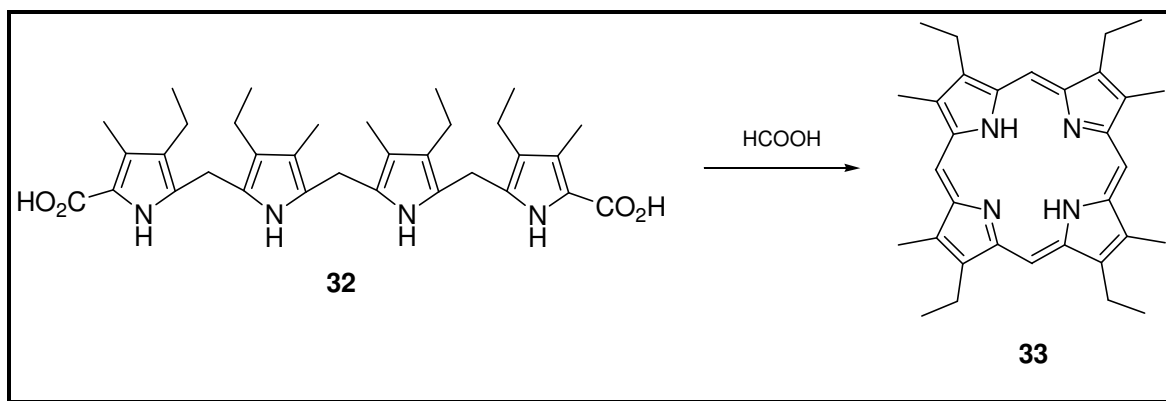


Figure 2.12. Tetrapyrrolic intermediates

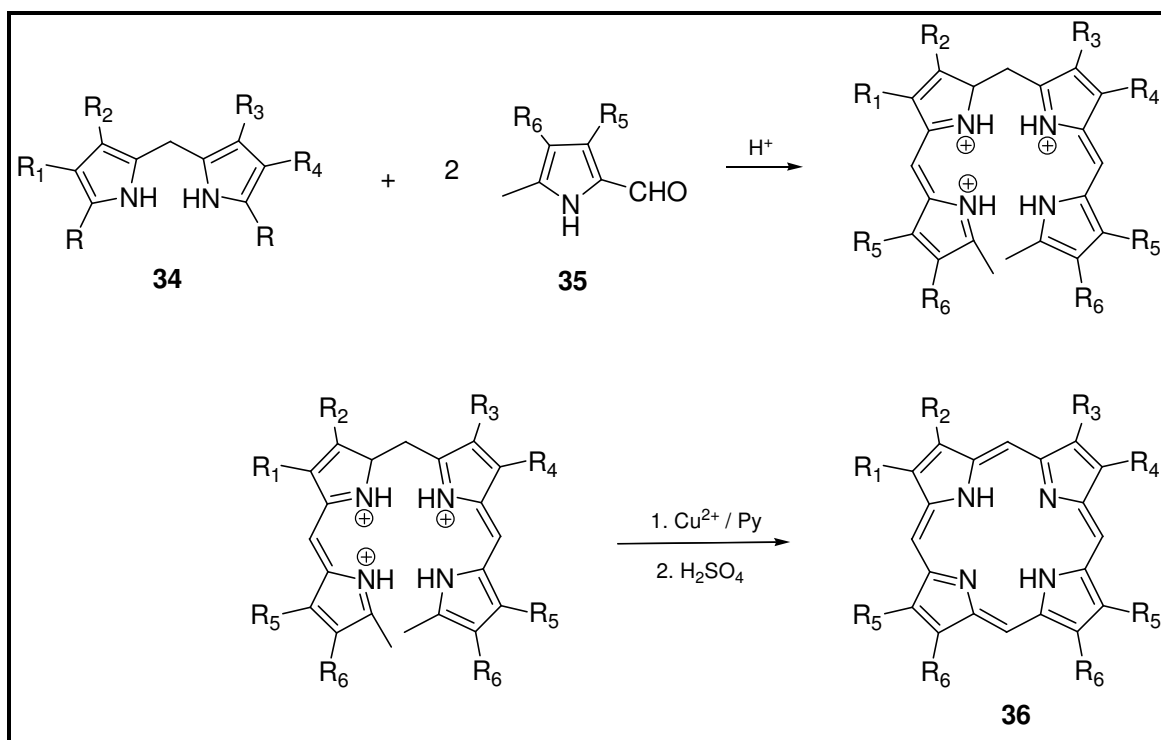
Corwin and Coolidge (1952) used the bilane **32** to synthesize etioporphyrinporphyrin II (**33**) (Scheme 2.9). However, this route was not very successful because it afforded a mixture of inseparable isomers due to the instability of bilanes that resulted in redistribution.



Scheme 2.9. Synthesis of porphyrin by cyclization of bilane.

Jackson et al. (1968) used a method by introducing an electron withdrawing group (oxobilane) to prevent pyrrole redistribution. In this method, *b*-oxobilanes are more successful than *a*-oxobilanes. In *a*-oxobilanes, electron withdrawing effect of oxo function stabilize the pyrrole ring and stabilized pyrrole ring is reluctant to the substitution reaction. The major drawbacks of the *b*-oxobilane route was that the method was lengthy and required a large number of steps.

The most common tetrapyrroles used for porphyrin synthesis are *a,c*-biladienes. The symmetrical *a,c*-biladienes can be easily prepared by treating a 1,9-diacid or *meso*-unsubstituted dipyrromethane **34** with formylatedpyrrole **35** as shown in Scheme 2.10 (Smith, 1975). Cyclization of the *a,c*-biladiene using Copper (II) salts in DMF affords the Cu(II) complex porphyrin, high yields of the metal-free porphyrin **36** are usually obtained after removal of chelating copper atom with H_2SO_4 (Landau, 1970) (Scheme 2.10).



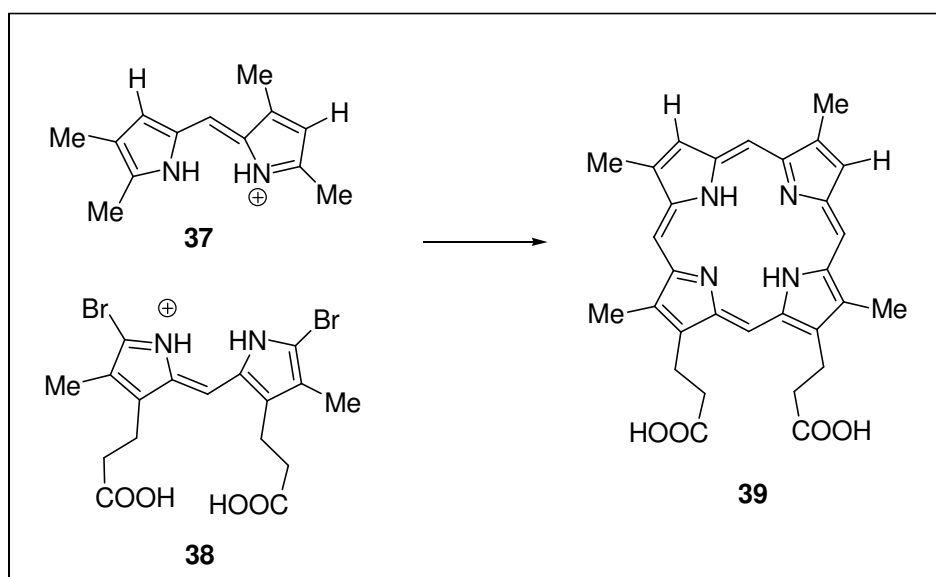
Scheme 2.10. Synthesis of porphyrin by cyclization of *a,c*-biladiene.

2.3.7. Synthesis of porphyrins from dipyrrolic intermediates: ‘2+2’ route

The 2+2 method is constructed by condensation of two dipyrrolic units to form the porphyrin. The most commonly used dipyrrolic intermediates in the synthesis of porphyrins are dipyrromethenes and dipyrromethanes.

2.3.7.1. Porphyrins from condensation of dipyrromethenes

The method for the synthesis of porphyrins from dipyrromethenes is rarely used because dipyrromethenes are difficult to prepare and purify. The first synthesis of porphyrins by using dipyrromethenes procedure was developed by Fisher and Klarer (1929). This method consists of the condensation of 1,9-dimethyl substituted dipyrromethene **37** and 1,9-dibromo substituted dipyrromethene **38**. The condensation reaction affords porphyrin **39**, which is the intermediate in the synthesis of Hemin (Scheme 2.11).



Scheme 2.11. Synthesis of porphyrins by dipyrromethene condensation

The condensation reaction of dipyrromethene was accomplished in organic acid melts such as tartaric or succinic acid at high temperatures (200 °C). Very harsh thermal conditions is main synthetic restriction of this method.

2.3.7.2. Porphyrins from condensation of dipyrromethanes

5- Substituted dipyrromethanes are key building blocks in the synthesis of linear porphyrin arrays. These are important precursors for the synthesis of *meso*-substituted porphyrins, corroles, expanded and reduced porphyrins and related compounds such as dipyrins, calixpyrroles and chlorins (Figure 2.13).

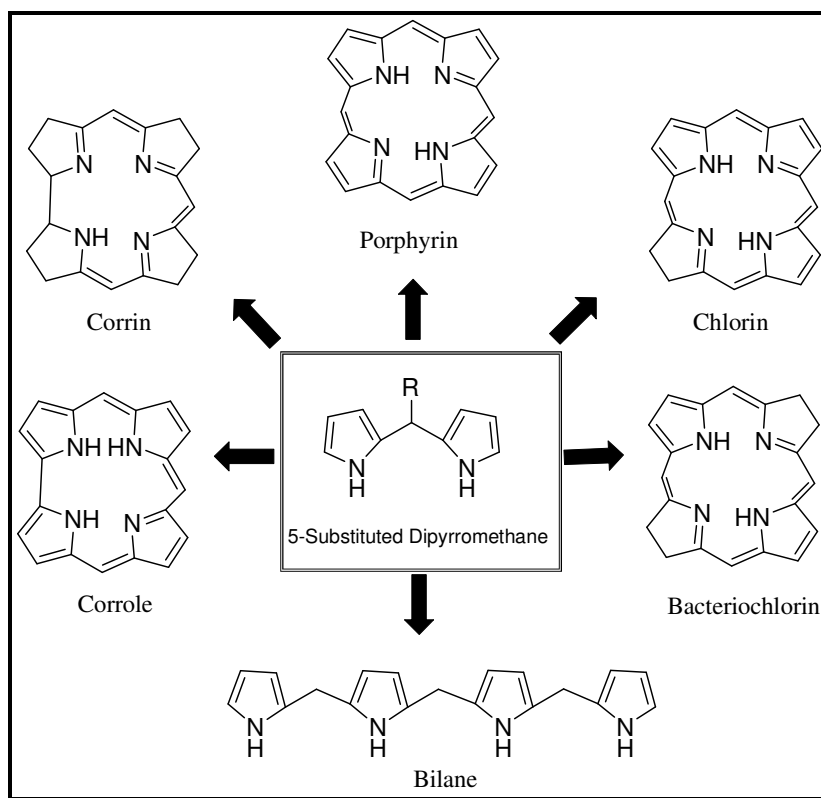
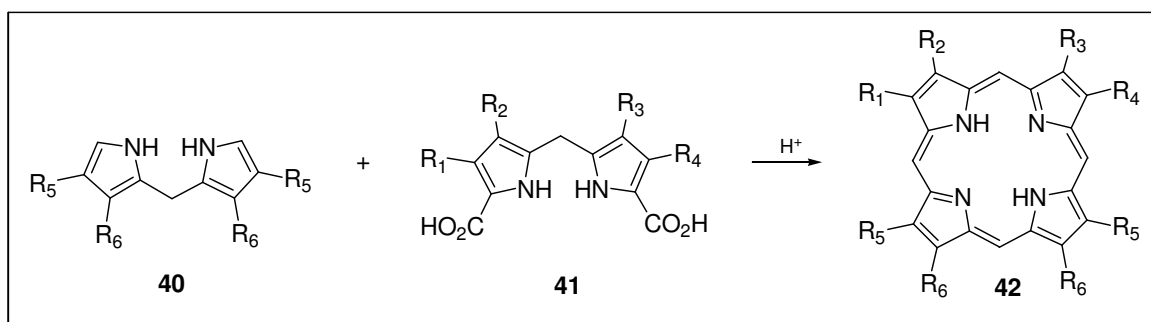


Figure 2.13. Compounds synthesized from 5-(*meso*) substituted dipyrromethanes.

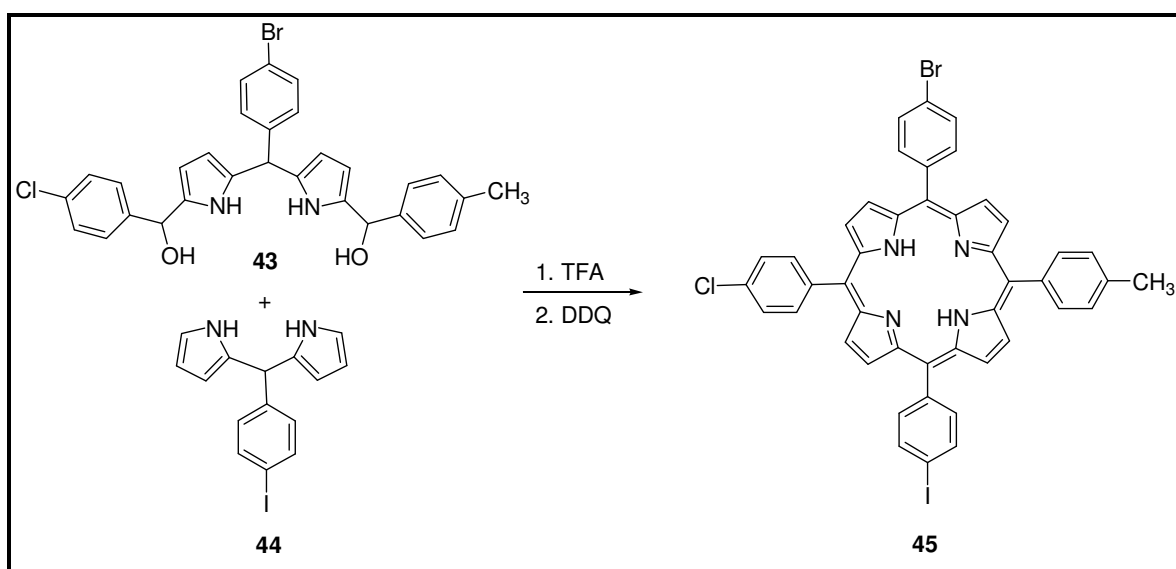
The use of dipyrromethanes in the porphyrin synthesis was highlighted by MacDonald's work in 1960 (Arsenault et al., 1960). MacDonald and coworkers discovered that 1,9-dicarboxylic acid **41** can be condensed with 1,9-diunsubstituted dipyrromethane derivative **40** in the presence of an acid catalyst to give the corresponding porphyrins **42** in yields up to 60% (Scheme 2.12).



Scheme 2.12. Synthesis of porphyrin by the condensation of dipyrromethanes.

There is obvious scope for the preparation of a large variety of functionalized porphyrins using this method and a greater degree of regioselectivity can be

attained relative to the Adler and Lindsey methods. The β -positions can be differentially functionilized and the bridging carbon in the dipyrromethane can also be substituted. The 2+2 methodology allows a step-wise synthesis of porphyrins bearing four different *meso* aryl substituents. Introduction of different acyl substituents at the 1- and 9-positions of *meso* substituted dipyrromethane and reduction of this structure to more reactive carbinol groups supply dipyyrolic intermediate carrying three different aryl groups **43**. Oxidation of the condensation product of dicarbinol **43** and dipyrromethane **44** gave unsymmetrical *meso*-tetraarylporphyrin **45**. Lindsey et al. have synthesized porphyrins **45** containing different halogen substituted phenyl groups at *meso* position in 14% yield (Scheme 2.13) (Lee et al., 1995).



Scheme 2.13. Synthesis of four different *meso* aryl group containing porphyrin.

2.4. Synthesis of Dipyrromethanes

Dipyrromethanes occupy a central place in porphyrin chemistry. The dipyrromethane structures have been employed in the synthesis of naturally occurring porphyrins bearing substituents at the β -positions and lack any substituents at *meso* position (Figure 2.14).

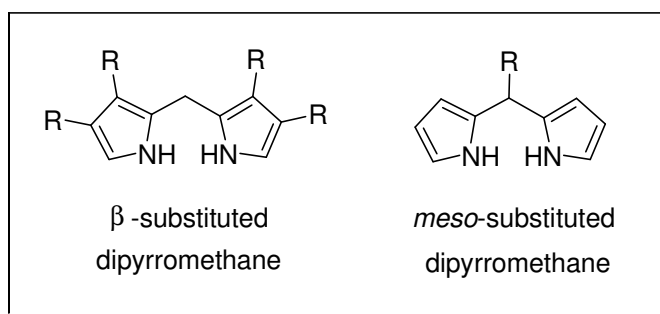
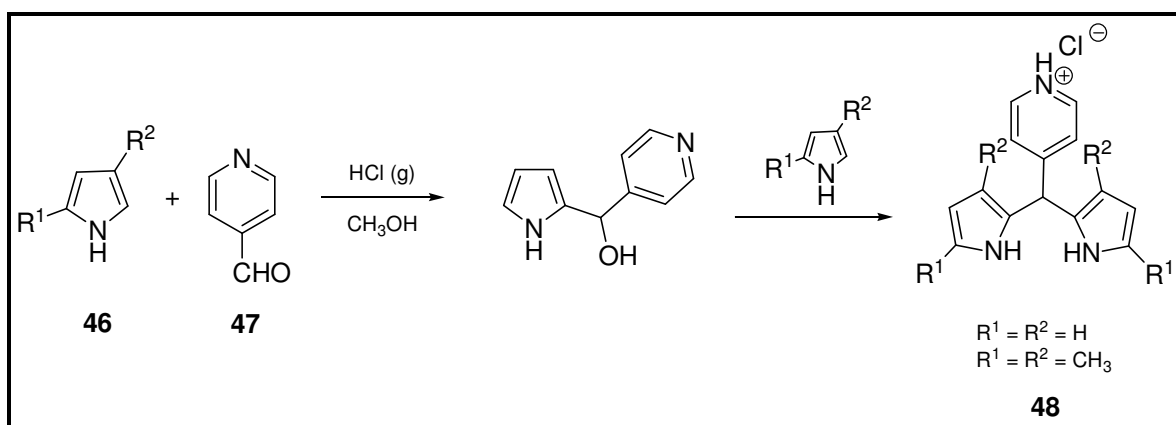


Figure 2.14. Structures of β and *meso* substituted dipyrromethanes.

In the past decade, dipyrromethanes without β -substituents but substituted at the *meso*-position (the 5-position) have come to play a valuable role in the preparation of synthetic porphyrins and related compounds. A number of stepwise syntheses of dipyrromethanes lacking β -substituents have been developed, while more direct routes have employed one-flask condensation of pyrrole and the desired aldehyde.

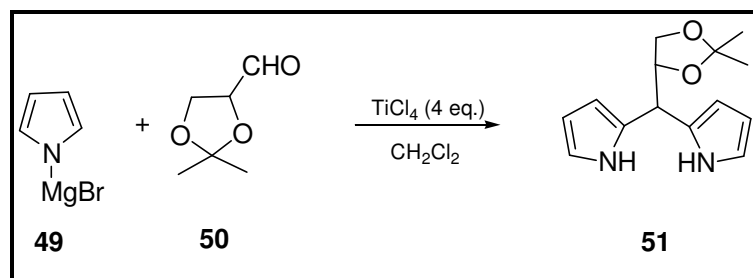
The first a one flask synthesis of *meso*-substituted dipyrromethanes was reported by Nagarkatti and Ashley (1974). They reacted 4-pyridine carboxaldehyde (**47**) with 2.1 mol equiv.of pyrrole **46** in methanol acidified with gaseous HCl and 5-(4-pyridyl)dipyrromethane **48** precipitated as the hydrochloride salt (Scheme 2.14).



Scheme 2.14. HCl (g) catalyzed synthesis of *meso*-substituted dipyrromethanes.

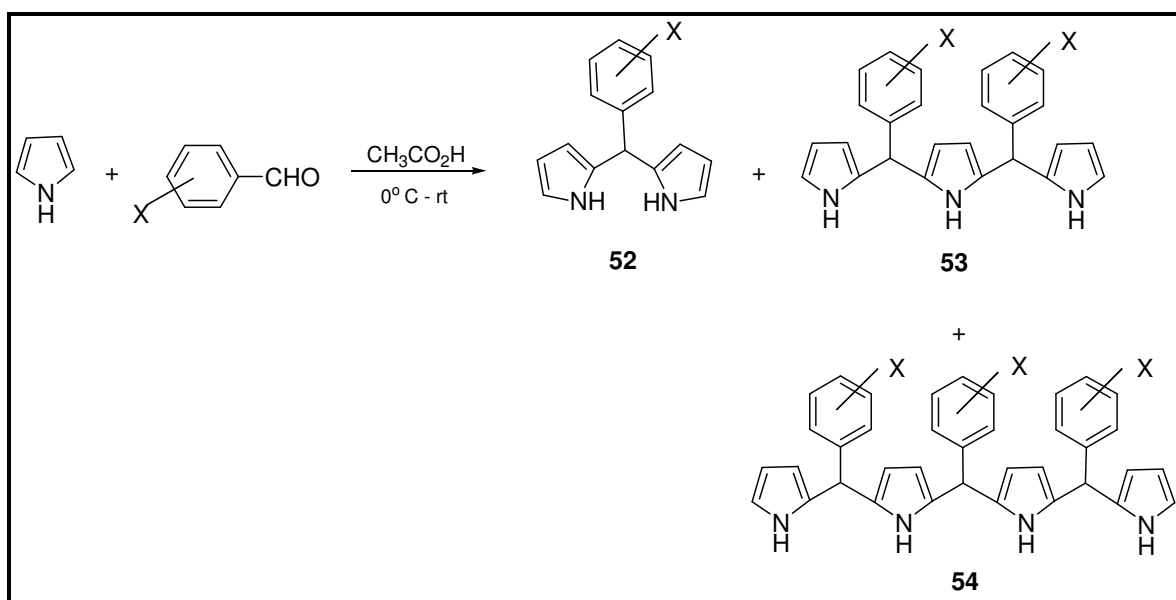
After this report a number of methods were described in the early-mid 1990s, where aldehyde was treated with excess pyrrole (2.1 - 40 eq.) in an acidified organic solvent. One of them is the reactions of 4 equivalents of Grignard reagent

PyMgBr (**49**) with aldehyde (**50**) in the presence of 4 eq of TiCl_4 in CH_2Cl_2 (Casiraghi et al., 1992). The reaction gave dipyrromethane **51** with 60% isolated yield (Scheme 2.15).



Scheme 2.15. TiCl_4 catalyzed synthesis of *meso*-substituted dipyrromethanes.

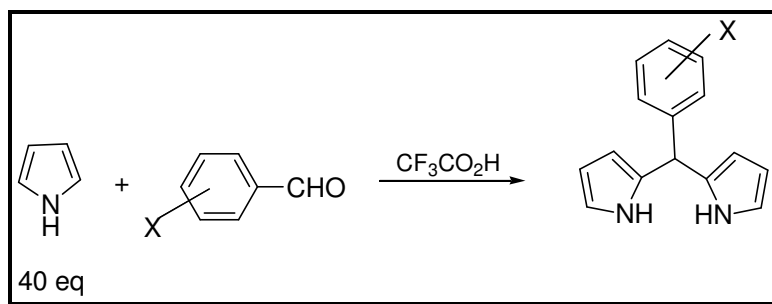
Direct synthesis of aryl dipyrromethanes was reported in 1994 by Vigmond et al. The reaction of 2 equivalents of pyrrole with substituted benzaldehydes was carried out in the presence of acetic acid. Chemical yields of dipyrromethanes **52** are between 20% and 35% depending on the substituents. Another drawback of this method is the formation of oligomers **53** and **54** as byproducts (Scheme 2.16).



Scheme 2.16. Acetic acid catalyzed synthesis of *meso*-substituted dipyrromethanes.

The first one-flask solventless synthesis of *meso*-substituted dipyrromethanes was reported by Lee and Lindsey (1994). Lindsey reported that, when equimolar

concentrations of aldehyde and pyrrole were used, the condensation reaction yields oligomers and the cyclic porphyrinogen. In order to achieve a direct synthesis of dipyrromethanes without oligomerization, they have performed the pyrrole – aldehyde condensation in the presence of a large excess of pyrrole (40 eq.). Excess pyrrole served as the reactant and the solvent in the reaction. The dipyrromethanes were obtained in 49% - 86% yields (Scheme 2.17).



Scheme 2.17. One-flask solventless synthesis of *meso*-substituted dipyrromethanes.

meso-Alkyl substituted dipyrromethanes were synthesized by the condensation of furanosyl and pyranosyl aldoses with pyrrole (1:5 molar ratio) at room temperature (Casiraghi et al., 1994). SnCl_4 was used as a catalyst in a stoichiometric ratio and yields were ranging between 30% and 40% (Figure 2.15).

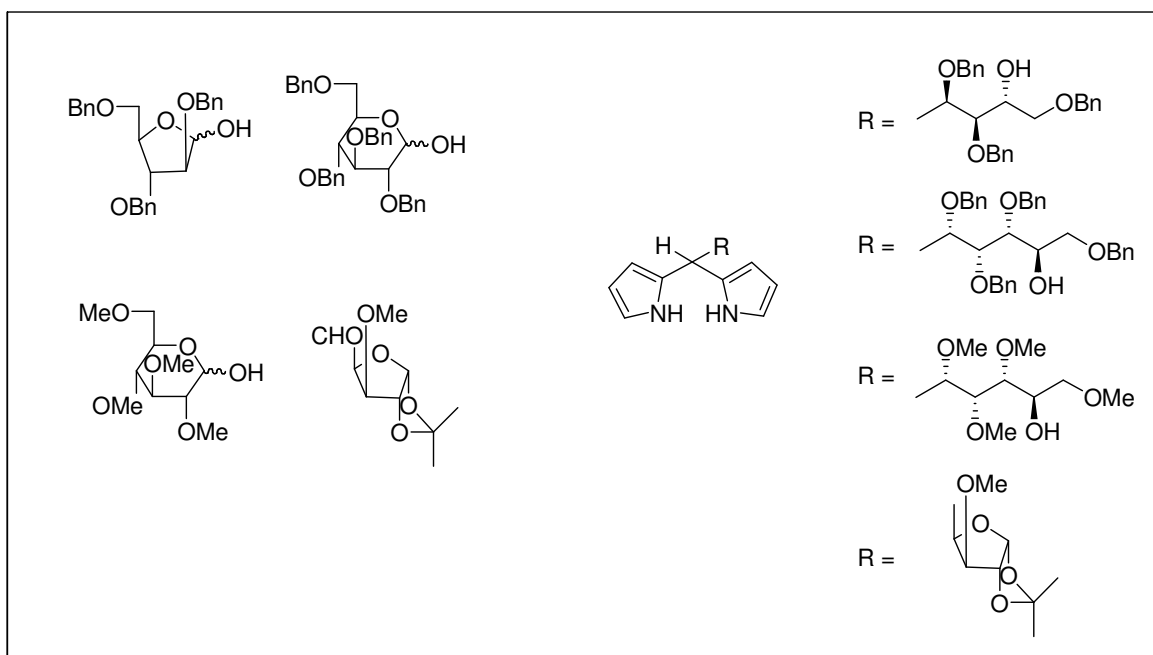
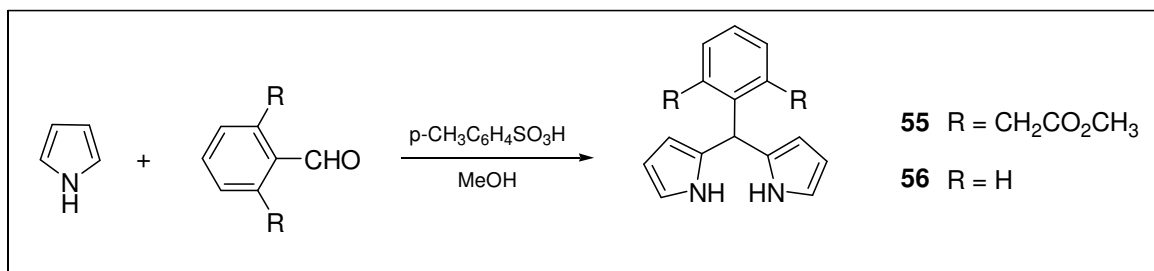


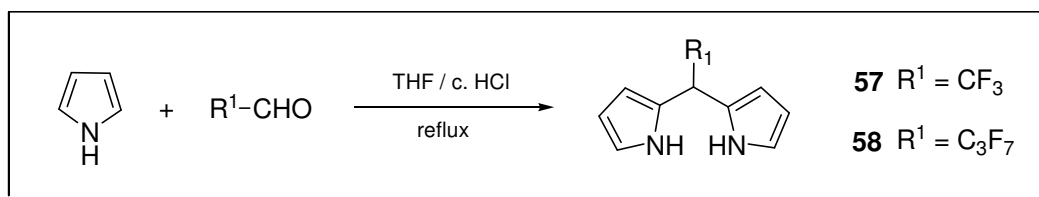
Figure 2.15. The structures of furanosyl and pyranosyl aldoses used for the synthesis of *meso*-alkyl dipyrromethanes in the presence of SnCl_4 catalyst.

p-Toluenesulfonic acid is another catalyst used in the synthesis of *meso*-substituted dipyrromethanes (Mizutani et al., 1994). *ortho*-Substituted benzaldehydes were subjected to the condensation with excess pyrrole (40 eq.) in the presence of stoichiometric amounts of *p*-toluenesulfonic acid in methanol. *meso*-Substituted dipyrromethanes were obtained with 68% for **55** and 36.5% for **56** (Scheme 2.18).



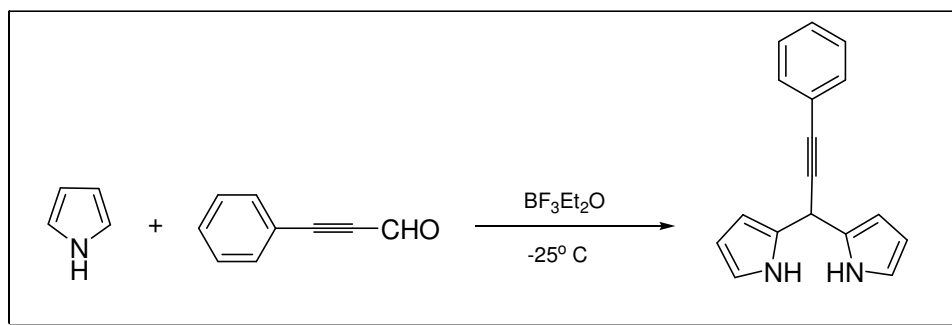
Scheme 2.18. *p*-Toluenesulfonic acid catalyzed synthesis of *meso*-dipyrromethanes.

Wijesekona was reported in 1996 the concentrated HCl catalyzed reaction of pyrrole with the fluorinated aliphatic aldehydes in THF under reflux. Two mono-substituted diyrromethanes **57** and **58** were obtained in 50% and 35% yields respectively (Scheme 2.19).



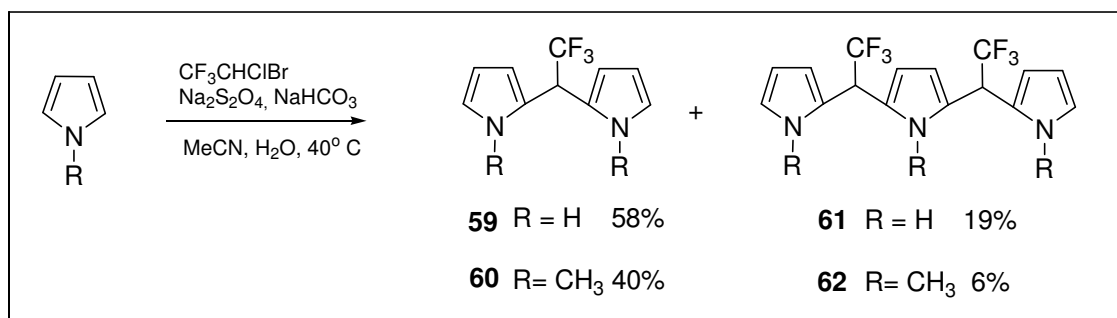
Scheme 2.19. Concentrated HCl catalyzed synthesis of *meso*-dipyrromethanes.

Borontrifluoride etherate complex was also used in the synthesis of *meso*-alkyl substituted dipyrromethanes (Milgrom and Yahioğlu, 1996). The synthesis involves the reaction of phenylpropargyl aldehyde with a large excess of pyrrole at -25° C. 3 Equivalents of catalyst was used in the reaction and desired dipyrromethane product was obtained in high yield (80%) (Scheme 2.20).



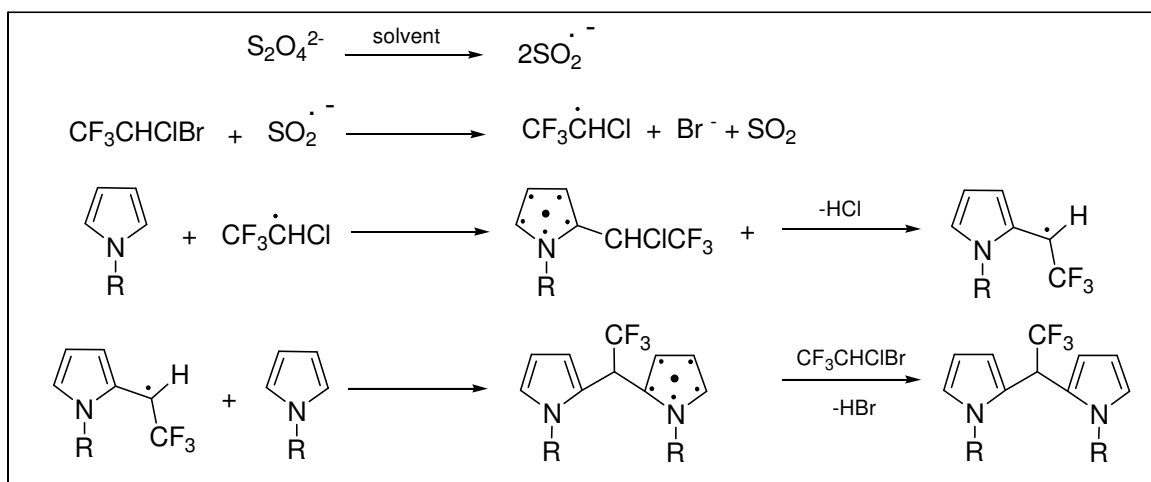
Scheme 2.20. $\text{BF}_3\cdot\text{OEt}_2$ catalyzed synthesis of *meso*-substituted dipyrromethanes.

Sodium dithiolate initiated reaction of 1-bromo-1-chloro-2,2,2-trifluoroethane with pyrrole for the synthesis of 5-trifluoromethyl dipyrromethanes **59** and **60** (Scheme 2.21) was reported by Dmonski et al. (2003).



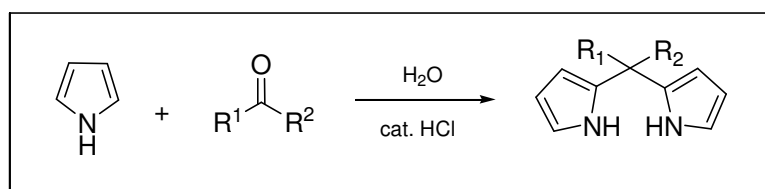
Scheme 2.21. Synthesis of 5-trifluoromethyl dipyrromethanes.

Tripyrranes **61** and **62** were isolated as side products. It was reported that; the amounts of side products depends on the ratio of pyrroles to CF_3CHClBr . The mechanism of the reaction was given in Scheme 2.22.



Scheme 2.22. The mechanism of radicalic reaction of pyrrole with CF_3CHClBr .

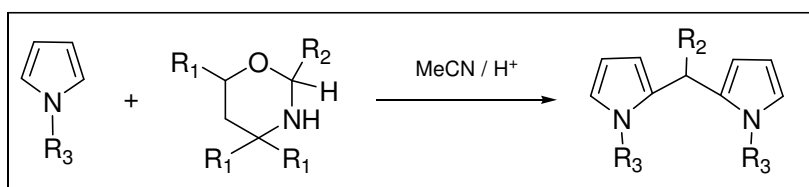
The synthesis of β -free, *meso*-substituted dipyrromethanes in water in the presence of catalytic amounts of HCl was developed in 2003 by Sobral et al. (Scheme 2.23). The method affords very pure products from moderate to high yields (25%-90%). The main advantage of this method is the use of a cheap, non-toxic and environment friendly solvent and need of little or no work up procedures.



Scheme 2.23. The synthesis of *meso*-substituted dipyrromethanes in water.

Naik et al. (2003) has been used cation exchange resins as heterogeneous solid acid catalysts to produce dipyrromethanes in good yields. The reaction of substituted aldehydes with pyrrole was catalyzed by different cation exchange resins and afforded the corresponding *meso*-substituted dipyrromethanes in yields ranging between 61% and 80%.

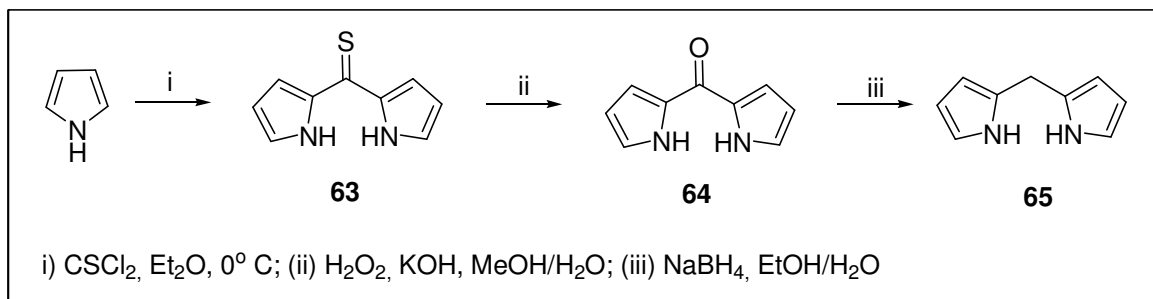
Singh et al. (2005) used various oxazinanes and oxazolidines in the synthesis of a number of 5-substituted dipyrromethanes. Oxazinanes reacted with pyrrole under acid catalysed (TFA) reaction conditions. Relatively lower stoichiometric amounts of pyrrole (4 eq.) compared to the other reported methods, were used for this reaction and the products were formed from low to moderate yields (25% - 65%). Tripyrrane side products were obtained in some cases in low yields (13% - 15%) (Scheme 2.24).



Scheme 2.24. The synthesis of *meso*-substituted dipyrromethanes by the reaction of pyrrole with oxazinanes.

The 5-unsubstituted dipyrromethane, has been prepared from pyrrole in three steps (Plater et al., 2002). In the first step, thione **63** was prepared by uncatalysed

reaction of pyrrole and thiophosgene. Second step is the synthesis of dipyrnylketone (**64**) by the oxidation reaction of **63**. In the last step, the 5-unsubstituted dipyrromethane **65** was obtained from the reduction of compound **64** (Scheme 2.25).



Scheme 2.25. The synthesis of *meso*-unsubstituted dipyrromethane.

2.5. The Importance of the Pyrrole

The first isolation of pyrrole has been achieved at the end of the nineteenth century and since then the physical and chemical properties of the pyrrole heterocycles have been the subject of intensive research in all of the fields of chemistry and biology. Pyrroles can serve as intermediates for the synthesis of drugs, pigments and pharmaceuticals (Katritzky et al., 1996; Di Santo et al., 1998). They can also be used as synthons for the synthesis of many natural and unnatural compounds. For example Lipitor is an anal drug that lowers the level of cholesterol in the blood. Another pyrrole containing drug is tolmetin, which is a nonsteroidal antiinflammatory drug (NSAID). It reduces hormones that cause inflammation and pain in the body. Amtolmetin has also similar NSAID properties like tolmetin with additional analgesic, antipyrotic and gastro protective properties (Figure 2.16) .

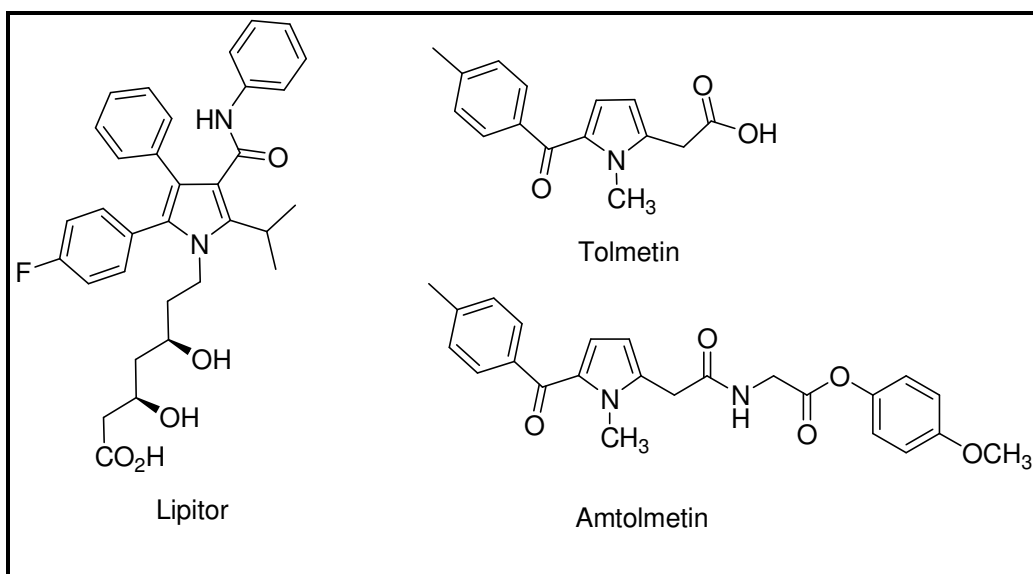


Figure 2.16. Some examples of pyrrole containing drugs.

2.6. Alkylation of Pyrroles

2-alkyl or 2-acyl pyrroles are also versatile intermediates for the synthesis of a wide range of pyrrole derivatives.

Several indirect methods leading to C-alkyl pyrroles have been established:

- 1) Wolff-Kishner reduction of 2-formyl or 2-acetyl pyrroles (Schumacher and Hall, 2000).
- 2) The isomerisation of *N*-alkyl pyrroles by thermal rearrangement at high temperature (Patterson and Soedigdo, 1968).
- 3) Preparation of 2- and 3- alkyl pyrroles from pyrrolyl magnesium halides (Martinez and Grieco, 1981).

These indirect methods share the drawbacks of multistep reactions and they tend to polymerize under most reaction conditions. The direct method to synthesize alkylated pyrroles is the alkylation of pyrroles by using Lewis acids.

2.6.1. Catalytic alkylation of pyrroles

Friedel-Crafts alkylation processes are rightfully placed among the fundamental cornerstones of organic synthesis. Traditionally, conventional Lewis acids such as AlCl_3 , TiCl_4 , BF_3 and SnCl_4 have been used in the Friedel-Crafts reactions. However, poor regioselectivity, large amount of Lewis acids, undesired intramolecular rearrangements and environmental problems are some of the most relevant disadvantages of the classic Friedel-Crafts alkylation reactions (Figure 2.17).

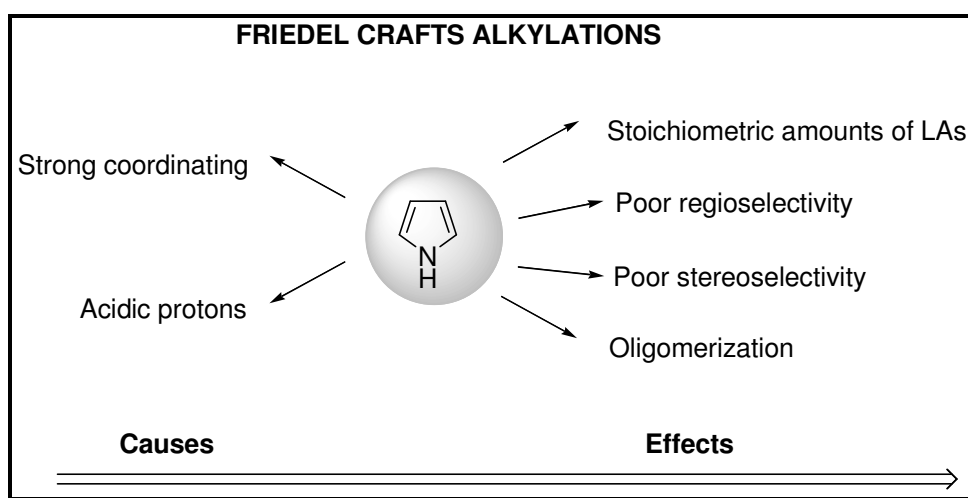


Figure 2.17. Problems that affect the Friedel-Crafts alkylation of pyrroles.

There are many different ways for the alkylation of pyrrole compounds. 1,2-addition of pyrrole to carbonyl compounds ($\text{C}=\text{O}$, $\text{C}=\text{NR}$), Michael-type reaction between pyrrole and electron-deficient $\text{C}=\text{C}$ bonds, ring opening of tensioned heterosubstituted cycles (epoxides, aziridines) and electrophilic substitution reactions represent some of the most useful and reliable approaches (Figure 2.18).

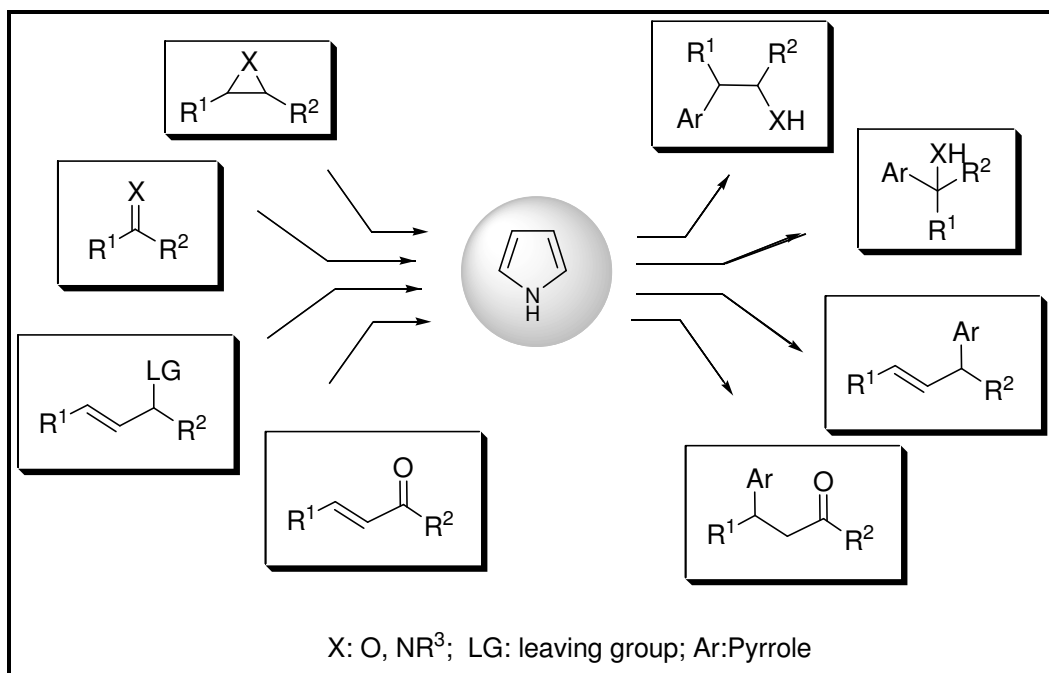
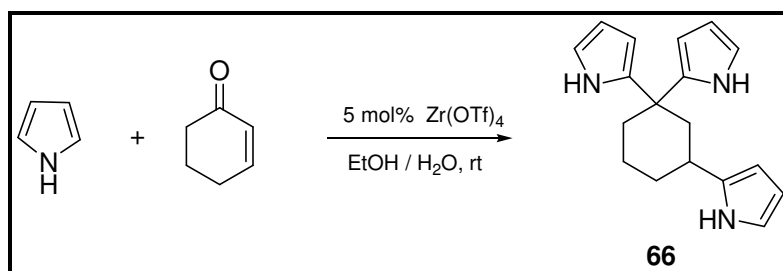


Figure 2.18. Different approaches for the Friedel-Crafts alkylation of pyrroles.

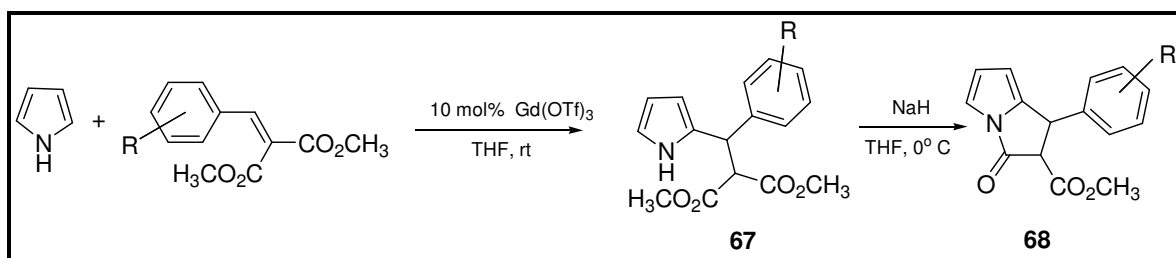
2.6.1.1. Synthesis of pyrrole derivatives by Michael reaction

The Michael addition is one of the most important C-C bond forming reaction in organic chemistry. The direct synthesis of pyrrole derivatives *via* Michael addition reactions with α,β -unsaturated compounds remains a challenge due to the sensitivity of pyrroles to air and acids. Some catalysis were used in literature for this reaction type. One of them is zirconium triflate. Shi et al. (2004) reported $\text{Zr}(\text{OTf})_4$ catalysed reactions of pyrrole with α,β -unsaturated cyclic ketones. The expected product of the reaction was 1,4 addition product. But the reaction can not be controlled and both of 1,2-addition and 1,4-addition reaction occurred at the same time. Tripyrrolylcyclohexane (**66**) was obtained in 40% yield (Scheme 2.26).



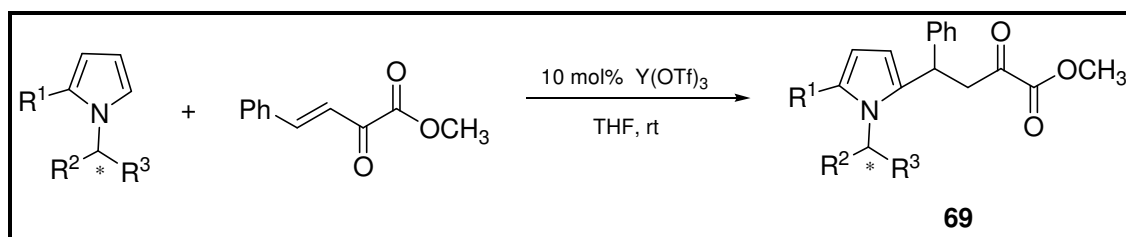
Scheme 2.26. $\text{Zr}(\text{OTf})_4$ catalysed alkylation of pyrrole.

Unaleroglu and Yazici (2007) also used another metal triflate catalyst, $\text{Gd}(\text{OTf})_3$, for the synthesis of alkylated pyrroles. The reaction of 2-benzylidenemalonate with pyrrole was investigated by using different metal triflates and different substituents on the phenyl ring. 2-Substituted pyrroles **67** were obtained between 37-92% yields. Obtained pyrrole derivatives were used for the intramolecular cyclization reactions to obtain pyrrolizine compounds **68** (Scheme 2.27).



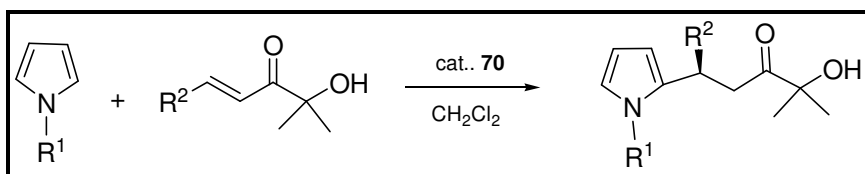
Scheme 2.27. $\text{Gd}(\text{OTf})_3$ catalysed alkylation of pyrrole and synthesis of pyrrolizines.

Another rare earth metal triflate $\text{Yb}(\text{OTf})_3$ used for conjugate addition reactions of homochiral pyrroles to $\alpha,\text{oxo}-\beta,\gamma$ -unsaturated esters (Unaleroglu et al., 2004). 2-substituted homochiral pyrroles **69** were synthesized in good to high yields (50-84%) (Scheme 2.28).



Scheme 2.28. $\text{Y}(\text{OTf})_3$ catalysed alkylation of homochiral pyrroles.

$\text{Cu}(\text{OTf})_2$ catalysed enantioselective Friedel-Crafts alkylation of pyrroles were reported by Palomo et al. (2005). They reacted pyrrole with α' -hydroxy enones in the presence of $\text{Cu}(\text{OTf})_2$ -bis(oxazoline) catalysis (**70**) (Scheme 2.29).



Scheme 2.29. Enantioselective Friedel-Crafts alkylation of pyrroles.

The structure of asymmetric catalyst **70** and stereochemical model for substrate – catalyst complex are given in Figure 2.19. The reactions were carried out with a series of enones and high yields and enantioselective products were obtained.

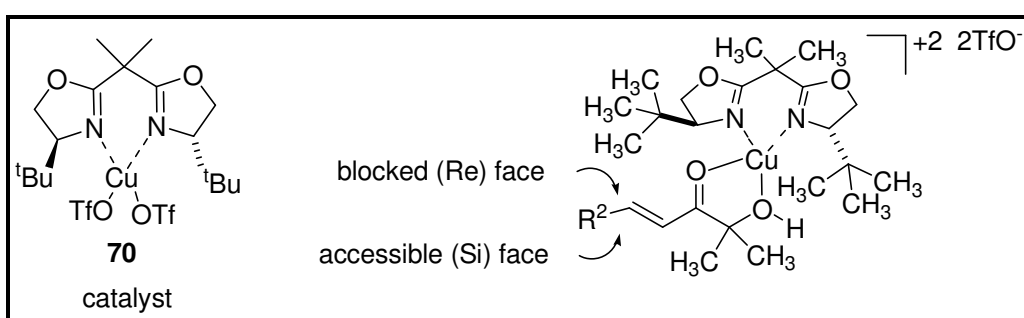
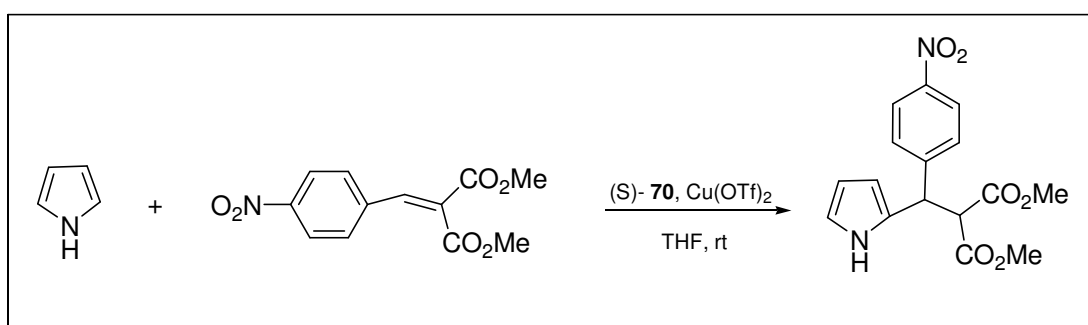


Figure 2.19. Asymmetric catalyst and substrate – catalyst complex.

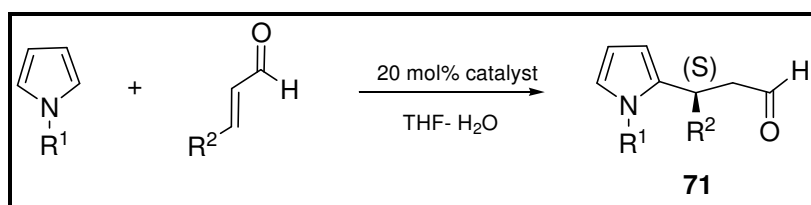
Another application of asymmetric alkylation of pyrrole is the addition of pyrrole to p-nitro benzylidene malonate catalysed by the same oxazoline ligand in excellent yield (99%) but low enantioselectivity (28 %) (Zhuang et al.,2001) (Scheme 2.30).



Scheme 2.30. Asymmetric alkylation of pyrrole by using oxazoline ligand.

Paras and MacMillan (2001) made a major contribution to asymmetric Friedel-Crafts alkylation of pyrroles by developing organocatalytic enantioselective method. It has been documented that α,β -unsaturated aldehydes are poor electrophiles for pyrrole conjugate addition due to the capacity of electron-rich

aromatics to undergo acid catalysed 1,2-carbonyl addition. They have proposed the preparation of chiral iminium ions **73** in the reaction medium and the addition of pyrrole to this iminium ions enantioselectively. As illustrated with the model (Figure 2.20), α,β -unsaturated iminium ions formed from chiral amine were expected to be unreactive to 1,2-addition (Figure 2.20, pathway a) because of the steric hinderance of the structure. It was assumed that; catalyst **73** might selectively partition heteroatomic nucleophiles toward a nonconventional and less sterically demanding 1,4-addition manifold (Figure 2.20, pathway b). So chiral pyrrole derivatives **71** were prepared in high yields (68-87 %) and high enantioselectivity (89-97 %) (Scheme 2.31).



Scheme 2.31. Organocatalytic enantioselective alkylation of pyrrole.

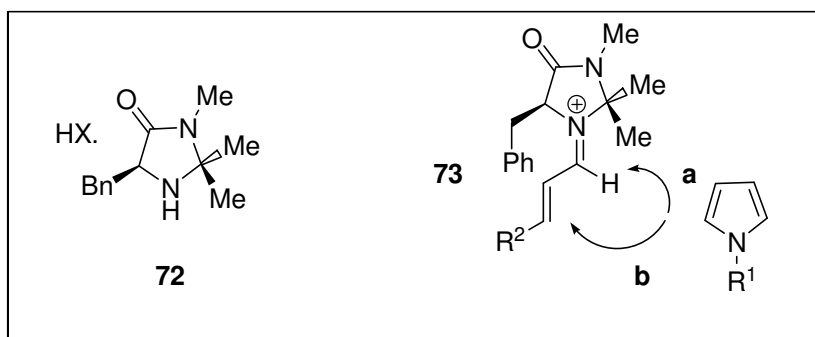


Figure 2.20. The structure of organocatalyst and reaction pathways.

Other alkylation methods of pyrroles with unsaturated compounds are; a) I_2 catalysed Michael addition of pyrrole to nitro olefins (Lin et al., 2005), b) Microwave-assisted addition of pyrroles to electron deficient olefins (Zhan et al., 2005), c) Bismuth trichloride catalysed allylation of pyrroles (Zhan et al., 2006), d) addition of pyrroles to electron deficient olefins by using $InCl_3$ (Yadav et al., 2001) and e) Michael addition of pyrrole to conjugated alkenes catalysed by Cr^{3+} Catsan (Cr^{3+} exchanged commercially available montmorillonite clay) and $ZnCl_2$ (Zhang et al. 2006) (Figure 2.21).

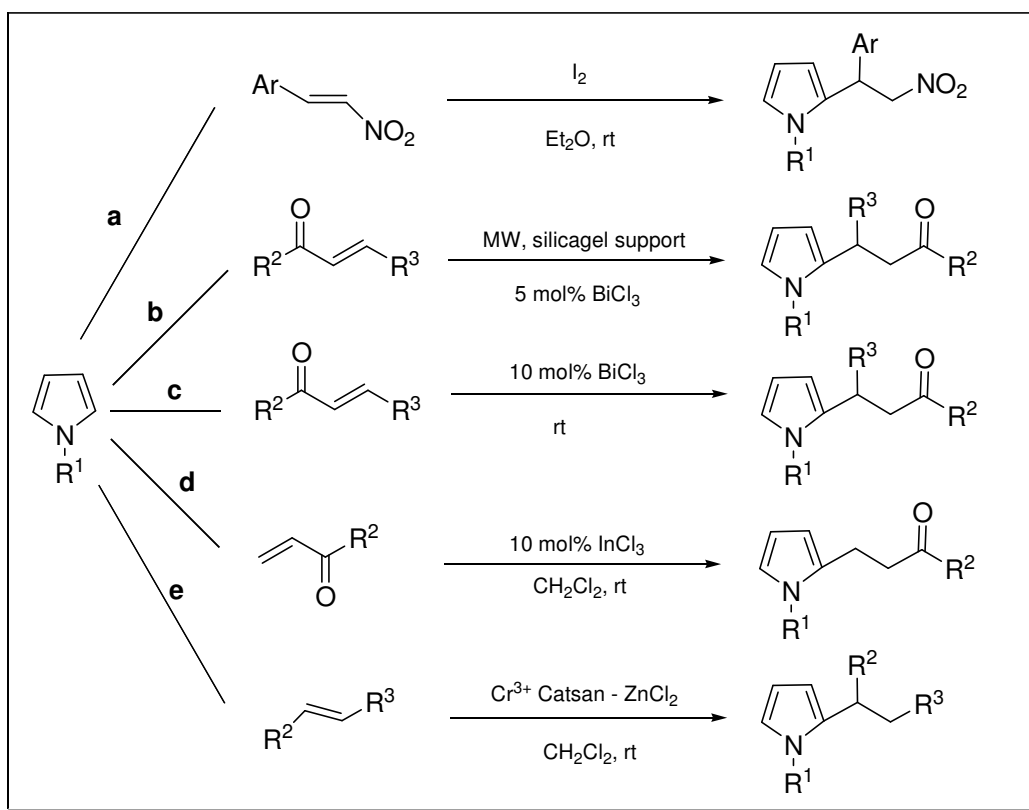


Figure 2.21. Other alkylation methods of pyrrole in the literature.

2.6.1.2. Synthesis of pyrrole derivatives by ring opening reactions

Among the several types of electrophilic routinely encountered organic synthesis, strained three membered epoxide and aziridine rings play a central role. This family of compounds allow to synthesize complex and polyfunctionalized organic molecules. Reaction of pyrrole systems with carbonyls (C=O) generally give unstable initial addition product and undesired side products obtaining in most cases. These problems make epoxides and aziridines a valid alternative to carbonyls for accessing important building blocks for complex molecules (Figure 2.22 pathway a). But there are side reaction problems in Friedel – Crafts alkylation of pyrrole with enantiomerically pure epoxides;

- epoxide transposition via β -H migration consequent pyrrole oligomerisation (Figure 2.22, pathway b)
- partial racemization of the starting oxirane due to the oxygen – Lewis acid coordination (Figure 2.22, pathway c).

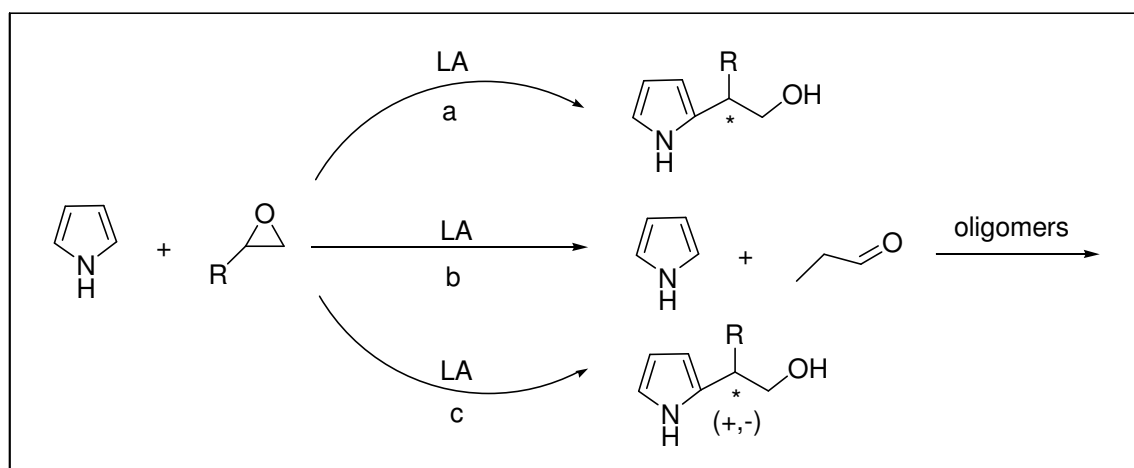
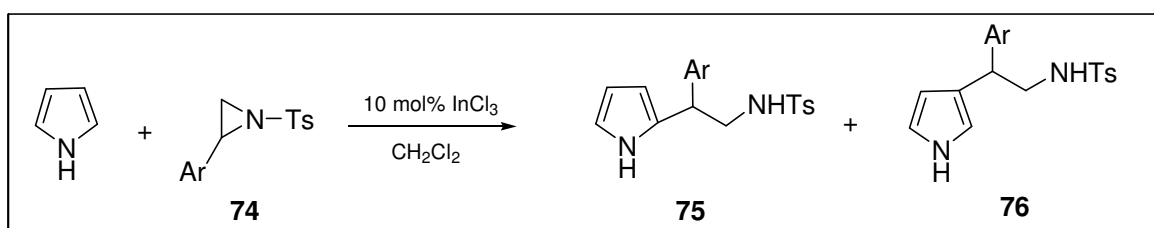


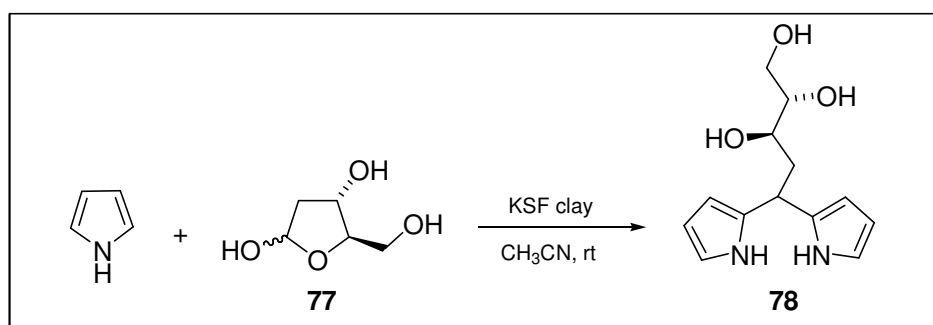
Figure 2.22. Synthetic routes in the ring opening reaction of epoxides with pyrrole.

Yadav et al. (2002) reported InCl_3 catalysed ring opening of aziridines with pyrroles. *N*-tosyl aziridines **74** were converted to 2- and 3- alkylated pyrrole derivatives **75**, **76** in high yields and moderate regioselectivities (Scheme 2.32).



Scheme 2.32. InCl_3 catalysed ring opening of aziridines with pyrroles.

The other report in the literature on the ring opening reactions is the montmorillonite clay catalysed alkylation of pyrroles with cyclic hemiacetals (Yadav et al., 2004). Pyrroles reacted with 2-deoxyribose (**77**) in the presence of montmorillonite KSF clays to give bis pyrrolyl alkanols **78** in good yield (58-62%) (Scheme 2.33).



Scheme 2.33. Montmorillonite clay catalysed alkylation of pyrrole.

The mechanism of the ring opening reaction is given in Figure 2.23. The reaction probably proceed through the formation of a 2-tetrahydro-2-furanyl-1*H*-pyrrole (**79**) followed by cleavage of the tetrahydrofuran ring and subsequent addition of another molecule of pyrrole leading to the dipyrrolyl alkanols.

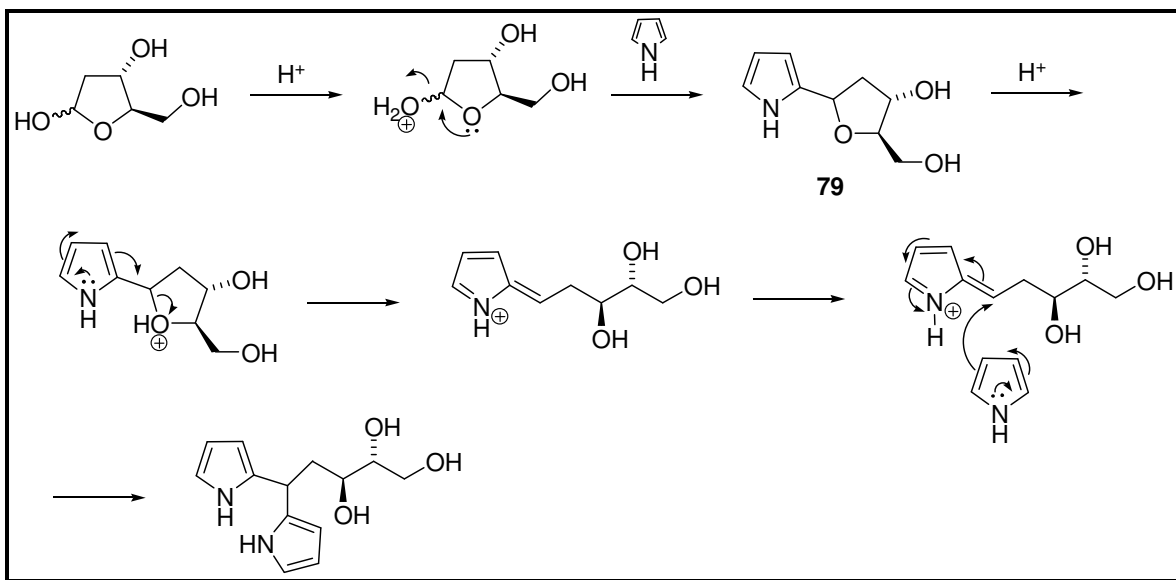
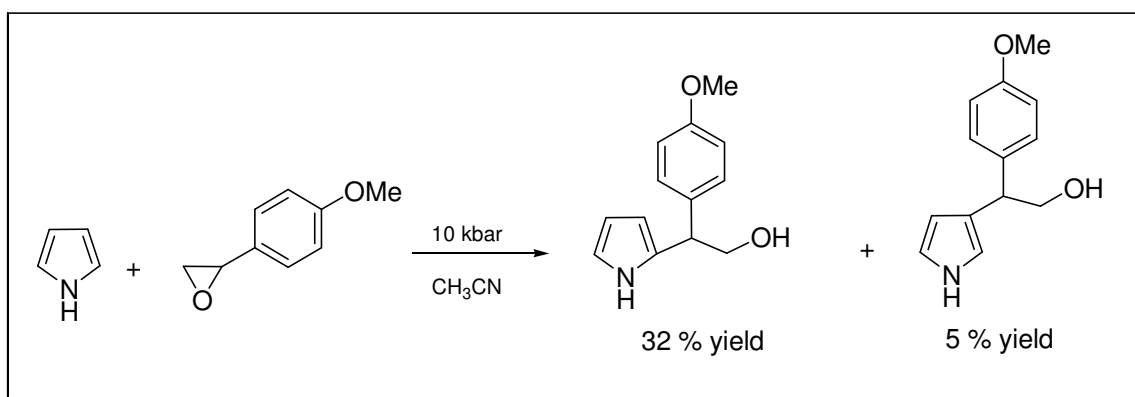


Figure 2.23. The mechanism of Montmorillonite clay catalysed ring opening reaction.

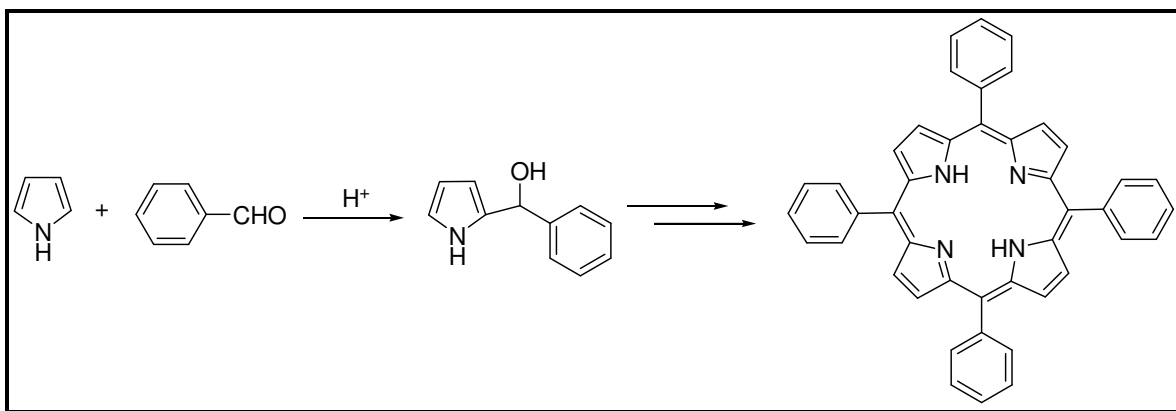
Pyrroles can also be alkylated with epoxides under high pressure. 10 kbar pressure was used in 42° C for alkylation of pyrroles but the products were obtained in low yields (Kotsuki et al., 1990) (Scheme 2.34). Adducts are very unstable and storage even under nitrogen atmosphere is very hard.



Scheme 2.34. Alkylation of pyrrole with epoxides by using high pressure.

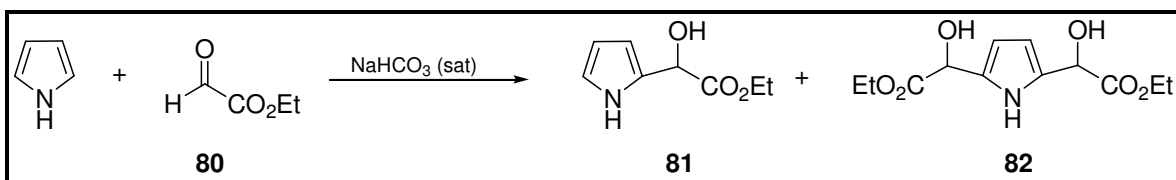
2.6.1.3. Alkylation of pyrroles by 1,2-addition reactions

The Lewis acid catalysed addition of pyrroles to aldehydes, ketones and imines is a synthetically outstanding C-C bond forming process that leads to functionalized alcohols and amines in a completely atom-economical way. Friedel-Crafts alkylation of pyrroles with carbonyl compounds is limited in the literature due to the unstability of the adducts and side reaction problems such as oligomerisation. As mentioned in Section 2.3.2, the 1,2-addition of pyrroles to aldehydes generally give the unstable α -hydroxypyrrole derivatives which are used as a intermediate for the synthesis of porphyrines (Scheme 2.35).



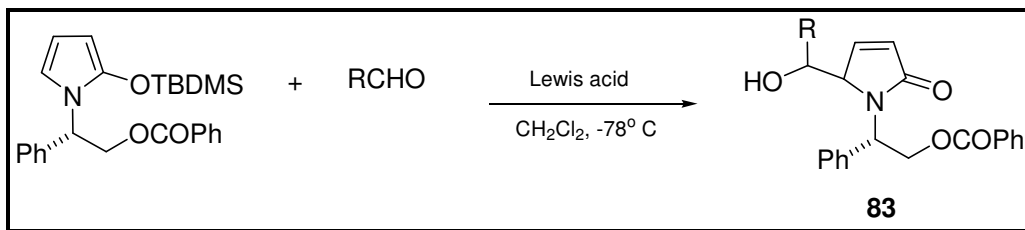
Scheme 2.35. Acid catalysed 1,2-addition of pyrroles to aldehydes

Because of the sensitivity of pyrrole derivatives to acids and air, some 1,2-addition reaction of pyrrole to C=O bonds have been reported in the literature without using traditional Lewis acid catalysis. For example, the reaction of pyrrole with ethyl glyoxylate (**80**) in NaHCO₃ solutions resulted both 2-alkylated **81** and 2,5-dialkylated **82** products (Zhuang and Jorgensen, 2002) (Scheme 2.36).



Scheme 2.36. The reaction of pyrrole with ethyl glyoxylate in aqueous solution.

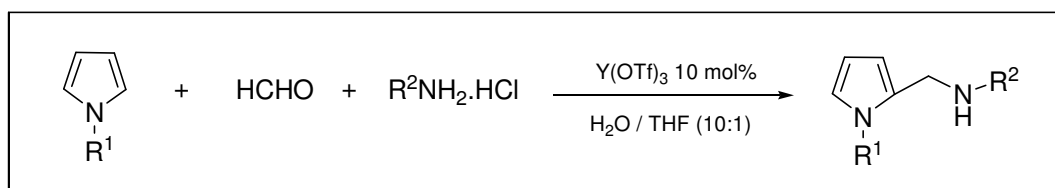
Lewis acid - catalysed Aldol type reaction of silyloxypyrroles with aldehydes has been reported by Dudot and Chiaroni (2000) in CH_2Cl_2 at -78°C . This reaction allowed access to chiral lactams **83** (Scheme 2.37).



Scheme 2.37. Aldol reaction of silyloxypyrroles with aldehydes.

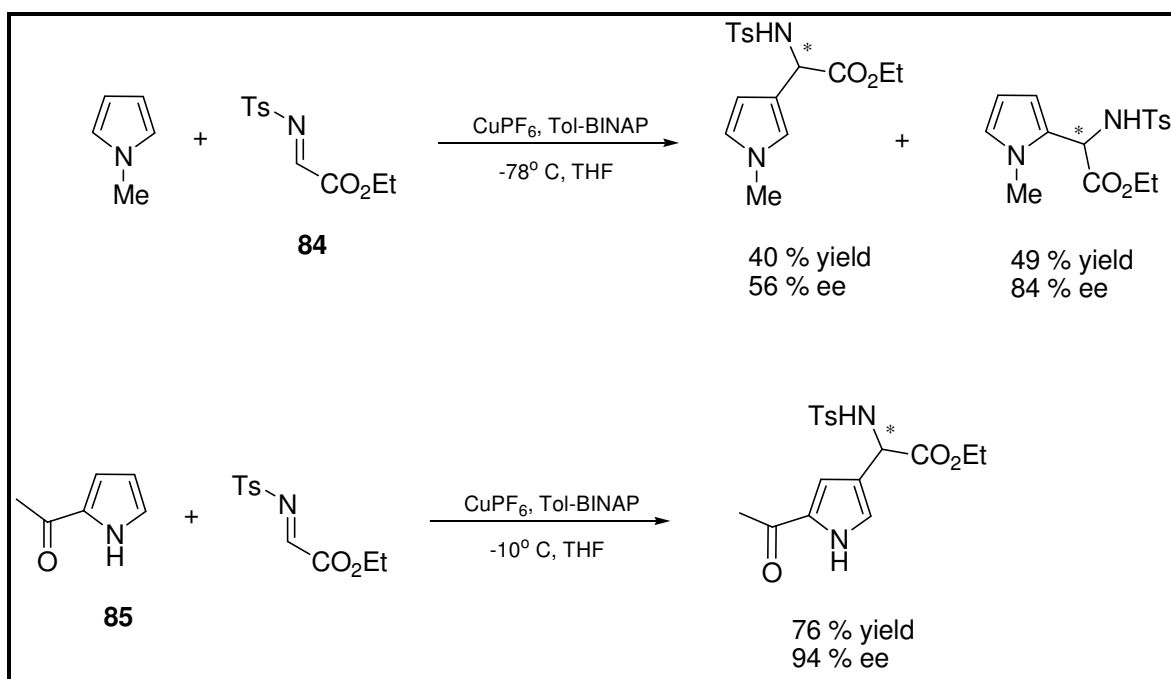
Mannich reactions are also reported in the literature for the alkylation of pyrroles. It has been reported that Mannich reactions of pyrrole compounds with primary amine hydrochlorides gave lower yields than secondary amine hydrochlorides. Heaney et al. (1988; 1988; 1997) found chlorosilane sulfurdioxide was able to be catalyze the Mannich reaction with amins or amino ethers. However, only *N*-substituted pyrroles were investigated by using this method.

The $\text{Y}(\text{OTf})_3$ catalysed Mannich reaction of *N*-alkoxycarbonyl pyrroles, formaldehyde and primary aminehydrochloride was reported by Zhang et al. (2001). However, no reaction was observed when formaldehyde was replaced by acetaldehyde or benzaldehyde (Scheme 2.38).



Scheme 2.38. $\text{Y}(\text{OTf})_3$ catalysed Mannich reaction of pyrroles.

Enantioselective addition of pyrroles to activated *N*-tosyl imino esters **84** was performed by Johannsen (1999). *N*-methyl and the deactivated 2-acethyl pyrrole reacted primarily at the 4-position of pyrrole in the presence of $\text{Cu}(\text{OTf})_2$ and Tol-BINAP. The chemical yields and enantiomeric excesses are higher for 2-acethyl pyrrole **85** than *N*-methyl pyrrole (Scheme 2.39).



Scheme 2.39. Enantioselective addition of pyrroles to activated *N*-tosyl imino esters.

2.6.1.4. Synthesis of pyrrole derivatives by substitution reactions

The reaction of pyrrolyl Grignard reagents with alkylating agents is well known process to produce a mixture, consisting mainly 2-alkyl, 3-alkyl and *N*-alkyl pyrroles. It has been reported that the product ratio of monosubstituted pyrrole isomers was affected by the nature of the medium and the metal ion (Hobbs et al., 1962). Two mechanistic pathways were suggested for the homogenous alkylation of salts of pyrrole with alkyl halides (Figure 2.24).

The first mechanism (**a**) involves the reaction of the pyrrol ion-metal coordinated complex **86** and produces 2-alkylated product. In the second mechanism (**b**) proceeds through the reaction of alkyl halide with dissociated pyrrol ion to give 1-alkylated product.

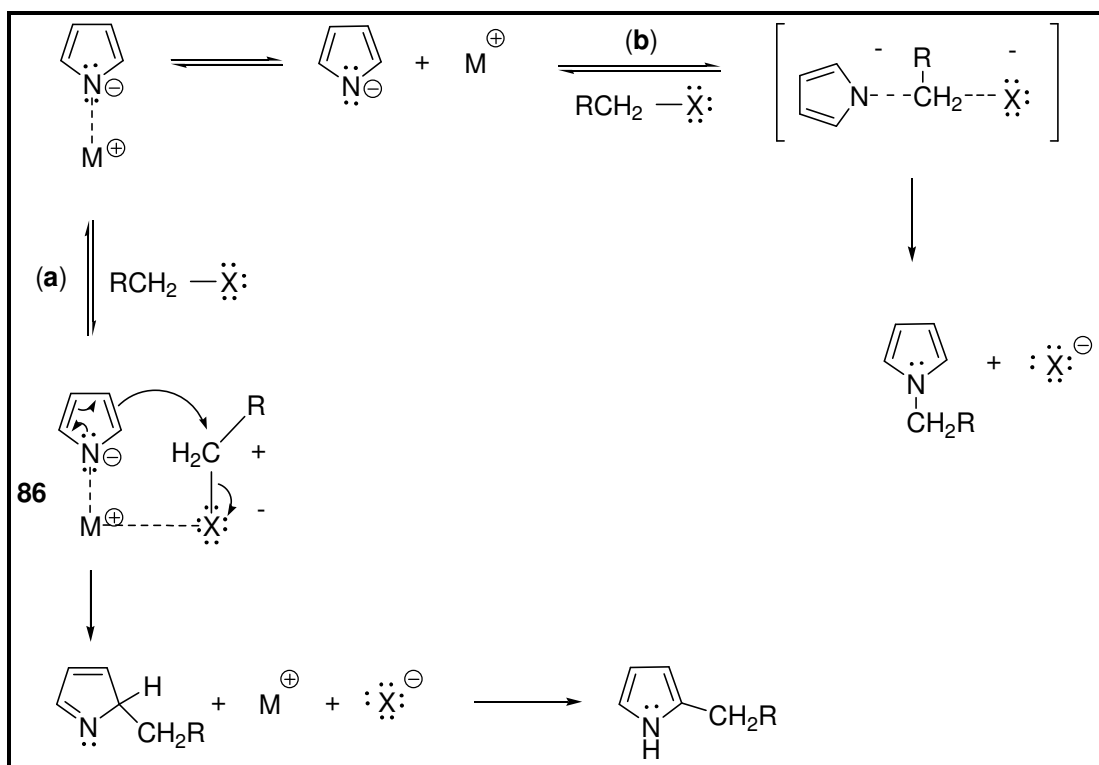
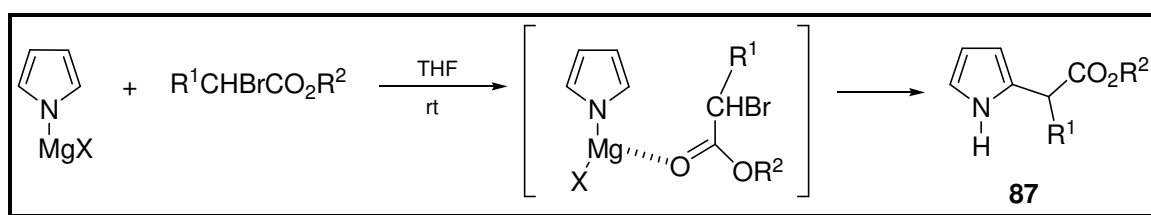


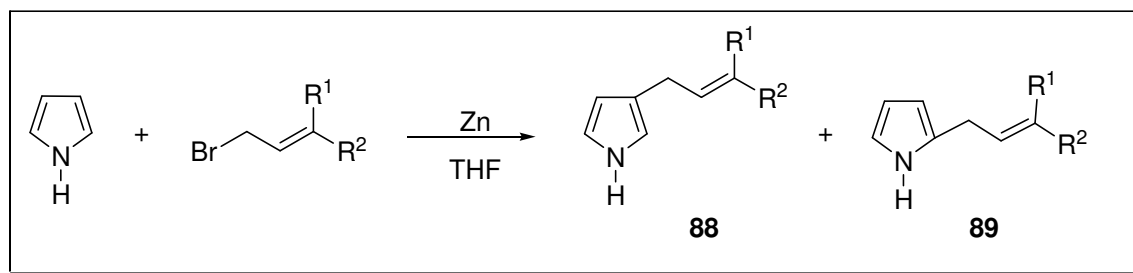
Figure 2.24. The mechanism of alkylation of pyrrole with Grignard reaction.

Grignard reaction was used by Schloemer (1994) for the synthesis of 2-alkylated pyrroles **87** (Scheme 2.40). Although the reaction gave high regioselective pyrrole products, the chemical yields were low.



Scheme 2.40. C2-alkylation of pyrroles with Grignard reaction.

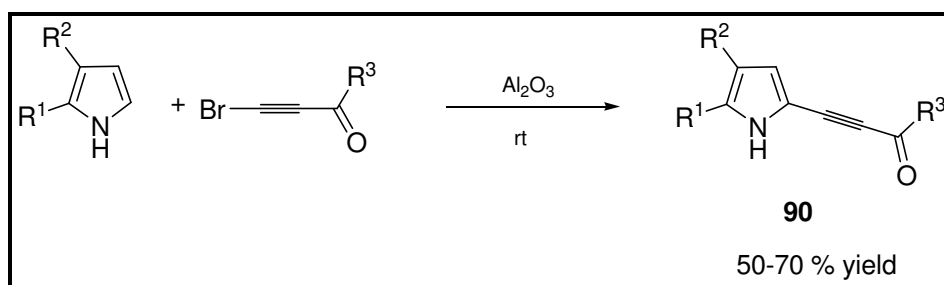
Another organometallic reaction for the synthesis of pyrrole derivatives was reported by Yadav et al. (2002). The method consists of the preparation of 3- and 2-alkyl pyrroles **88**, **89** through the zinc-mediated Barbier reaction of pyrrole. Treatment of pyrrole with zinc metal and allyl bromide in THF resulted the formation of pyrrole derivatives in good yields (Scheme 2.41).



Scheme 2.41. Alkylation of pyrrole with zinc-mediated Barbier reaction.

However, the method is only suitable for the allylation of *N*-unprotected pyrroles. The reaction of *N*-methyl pyrrole, *N*-benzyl pyrrole, *N*-Boc protected pyrrole with allylic bromides did not yield any product under the reaction conditions.

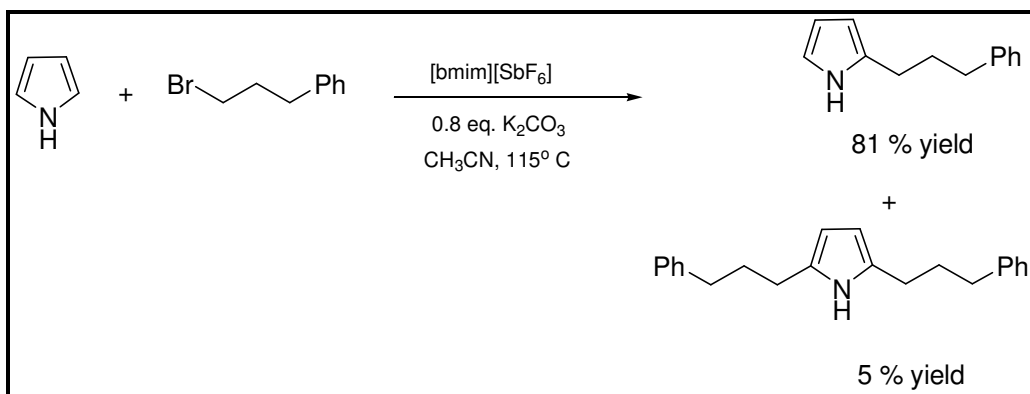
Another method has been developed by Trofimov et al. (2004) for the synthesis of 2-acylethynylpyrroles **90** from pyrroles and 1-acyl-2-bromoacetylenes (Scheme 2.42). The reaction was carried out at room temperature with a 10-fold mass excess of Al_2O_3 under solvent-free conditions. The reaction is regioselective and no isomeric 1- or 3-(acylethynyl)pyrroles were observed.



Scheme 2.42. The synthesis of 2-acylethynylpyrroles from pyrroles and 1-acyl-2-bromoacetylenes.

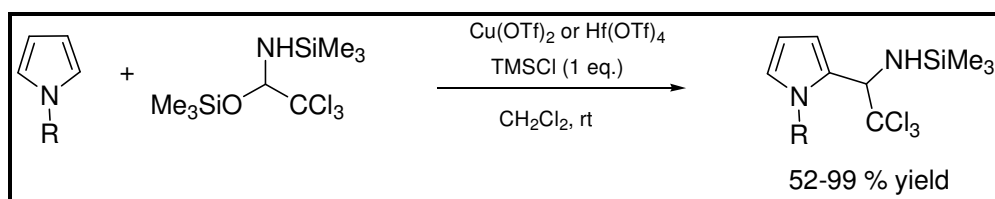
Regioselective alkylation of pyrrole with reactive halides in ionic liquids as a solvent has been reported by Jorapur et al. (2005). Recently, room temperature ionic liquids have increasingly attracted attention as the green, high-tech reaction media of the future. Nucleophilic substitution reactions in ionic liquids are very efficient way for the development of practical methodology. The alkylation of pyrrole at C2 position was achieved with simple alkyl halides in good yields with minimal byproducts under mild reaction conditions. A mixture of ionic liquid, $[\text{bmim}][\text{SbF}_6]$, and CH_3CN were used as a solvent system (Scheme 2.43). The

main advantage of the method is that; Lewis acid or base does not required in the reaction.



Scheme 2.43. Ionic liquid mediated alkylation of pyrrole.

In the past decade, metal trifluoromethanesulfonates (triflates) have found attractive use as Lewis acid catalysts in the alkylation of pyrrole compounds. Their high coordination numbers, large atomic radius, fast coordination-dissociation ability and high water-tolerant properties make these Lewis acids favourable for Friedel-Crafts reactions. For example; $\text{Cu}(\text{OTf})_2$ and $\text{Hf}(\text{OTf})_4$ are used by Sakai et al. (2003) for C2 aminoalkylation of pyrroles with *N*-silyl-*N,O*-acetals containing trichloromethyl groups (Scheme 2.44).



Scheme 2.44. $\text{Cu}(\text{OTf})_2$ and $\text{Hf}(\text{OTf})_4$ catalysed aminoalkylation of pyrrole.

A plausible mechanism for the metal triflate-TMSCl-catalyzed aminomethylation of pyrrole is given in Figure 2.25. First, the coordination of metal triflate to an oxygen atom of acetal **91** forms a cationic complex **92**, where cleavage of the C-O bond occurs and gives the *N*-silylimine **93**, $\text{M}(\text{OTf})_{n-1}\text{OSiMe}_3$ and TfOH . An equilibrium would generate a silanol and the imine complex **94**, composed by the imine and

metal triflate. Pyrrole would be expected to attack the intermediate **94** to produce the corresponding amine **95** with the regenerated catalyst metal triflate.

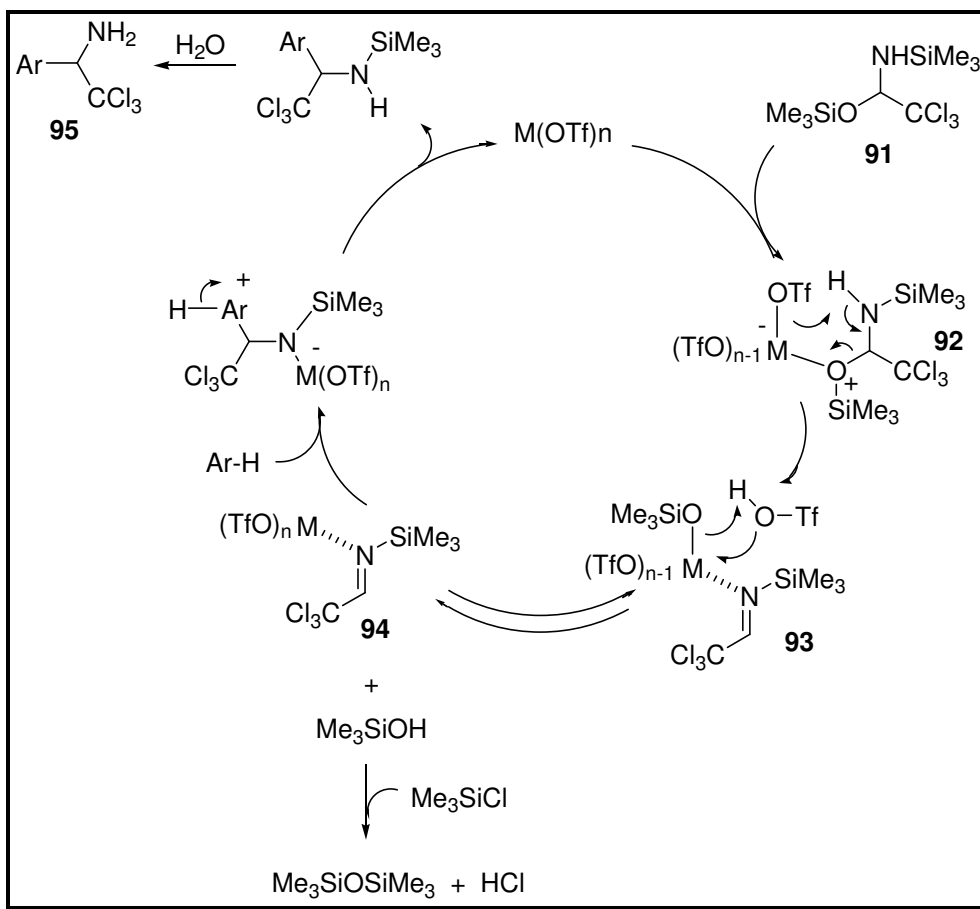


Figure 2.25. The mechanism of metal triflate catalysed aminoalkylation of pyrrole.

2.7. Metal triflates in Organic Synthesis

Lewis-acid catalysed reactions are of great interest because of their unique reactivities, selectivities and mild reaction conditions. Although various kinds of Lewis acids have been applied in organic synthesis, and many of them are successfully utilized in industry, most of the reactions were carried out under strictly anhydrous condition and in many cases, stoichiometric amount of catalyst was needed. In the presence of even a small amount of water, the Lewis acid was immediately decomposed and deactivated. Furthermore, these Lewis acids can not be recovered and reused after the reactions were completed. These are the limits of the utilization of Lewis acid in organic synthesis (Kobayashi et al., 2002).

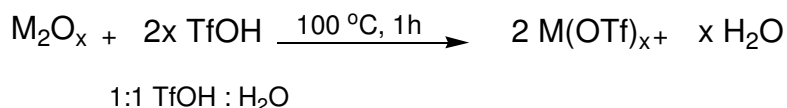
The most characteristic feature of metal triflates is that they are stable and work as Lewis acids in water. Many useful reactions are catalyzed by metal triflates in aqueous media. Only catalytic amounts of the triflates are enough to complete the reactions in most cases. Furthermore, they can be recovered easily after reactions and reused without loss of activity (Kobayashi, 1994; Kobayashi et al., 2002; Luo et al., 2005).

Metal triflates have the following advantages compared with the traditional Lewis acids:

- Metal triflates are prepared in aqueous media, and are air- and water-stable, can be used in pure water system or protic media (mixture of water with organic solvents or alcohols)
- Metal triflates have strong Lewis acidity due to the electron-withdrawing trifluoromethanesulfonyl group and can effectively activate carbonyl and imine functionalities.
- Metal triflates can activate carbonyl, imine, sulfur and phosphorous functionalities.
- Metal triflates are more soluble in water than in organic solvents, and easily recovered and reused.
- Metal triflates are stable thermally and less toxic.

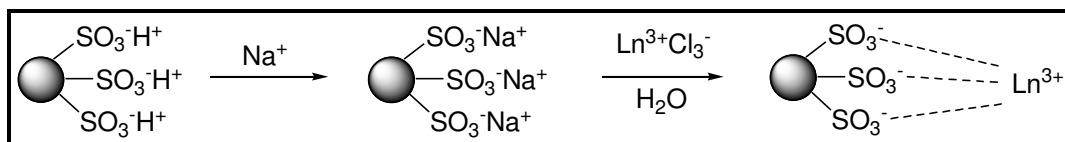
2.7.1. Preparation of metal triflates

Metal triflates are readily obtained by heating the corresponding metal oxides or chlorides in an aqueous trifluoromethanesulfonic acid (TfOH) solution. They are also prepared by the reaction of aqueous solutions of the corresponding metal halides with silver triflate. Typically, metal triflates contain eight or nine molecules of water after removal of water at room temperature. Anhydrous samples are obtained after drying at elevated temperature under high vacuum.



An inherent limitations of metal triflates, especially lanthanide triflates, are that they are rare in nature, thus may be expensive for large scale synthesis. In order to expand the application of metal triflates, various immobilization techniques have been developed to further modify the catalyst for a greener and more economic catalytic procedure.

The first effort toward this aim is solid-supported lanthanide. Yu et al. (1997) developed a series of polymersupported lanthanides catalysts based on cation exchange resins. The catalysts were introduced employing an ion-exchange process (Scheme 2.45).

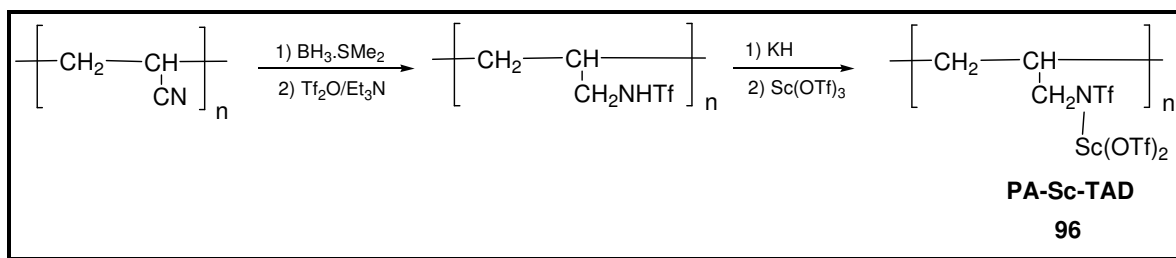


Scheme 2.45. The synthesis of polymer supported metal triflates.

In order to evaluate the efficiency of Ln-resins catalysts, a series of organic reactions were carried out including acetalization, Aldol, allylation, aza Diels-Alder, glycosylation and epoxide ring opening reactions. In most cases, the Ln-resins demonstrated good to excellent catalytic effect.

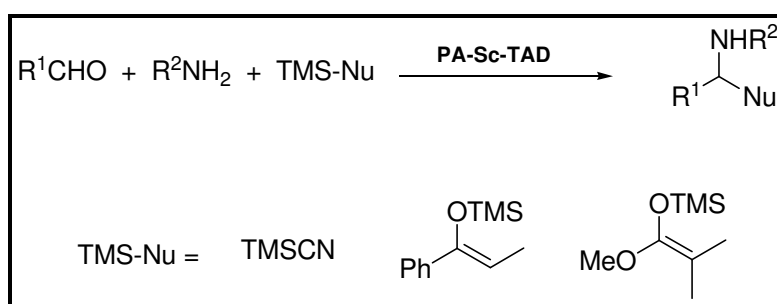
Similarly to Ln-resin, Kobayashi and Nagayama (1996) developed a Nafion-Sc catalyst. Nafion-Sc was prepared by treatment of three equivalents of Nafion with $\text{ScCl}_3 \cdot \text{H}_2\text{O}$ in refluxing acetonitrile. Nafion-Sc was shown to be an effective Lewis acid catalyst in the Allylation, Diels-Alder, Friedel-Crafts acylation, and aza Diels-Alder reaction.

Kobayashi and Nagayama (1996) developed a new strategy for the construction of quinoline library using polyacrylonitrile supported scandium catalyst, polyallyl scandium triflylamide ditriflate (PA-Sc-TAD) (**96**). PA-Sc-TAD was prepared as given in Scheme 2.46 and was partially soluble in the DCM- CH_3CN (2:1) solvent system.



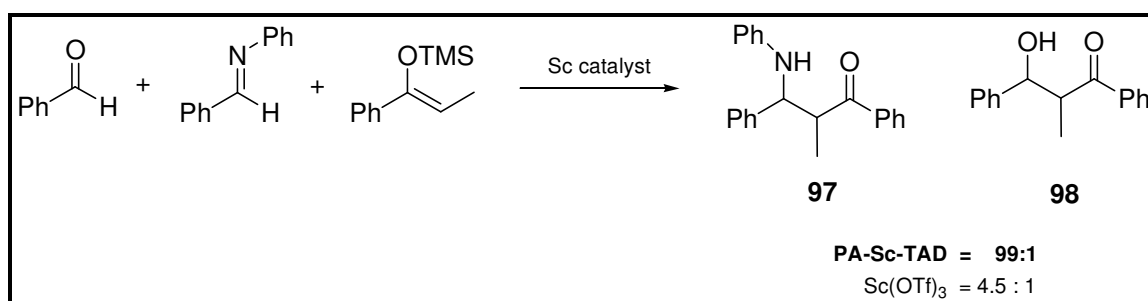
Scheme 2.46. The synthesis of polyacrylonitrile supported scandium triflate.

The same catalyst was also applied in the nucleophilic addition to *in situ* generated imines with silylated nucleophiles (Kobayashi et al., 1996) (Scheme 2.47).



Scheme 2.47. PA-Sc-TAD catalysed addition reactions to imines.

Moreover, PA-Sc-TAD was found to preferentially activate imines in the coexistence of aldehydes (Kobayashi and Nagayama, 1997). Thus, treatment of 1:1:1 solution of aldehyde, imine and silyl enol ether in the presence of catalytic amount of PA-Sc-TAD (**96**) afford predominantly β - amino ketones **97** (99/1 selectivity over β -hydroxyl ketones **98**). When the same reaction catalyzed by using $\text{Sc}(\text{OTf})_3$, the selectivity decreased to 4.5/1. (Scheme 2.48).



Scheme 2.48. Activation of imines by Sc catalysis.

Kobayashi and coworkers initially developed microencapsulated scandium triflate (MC-Sc(OTf)₃) (Kobayashi et al., 1999; Nagayama et al., 1998). This MC-Sc(OTf)₃ is easy to prepare and more active than other solid-supported scandium such as Nafion-Sc, PA-Sc-TAD and non-supported Sc(OTf)₃. It's also recoverable and reusable, and effective in catalysis of a variety of carbon-carbon bond forming reaction. Compared with the nonencapsulated catalyst, MC-Sc(OTf)₃ shows remarkable ability to activate aldimine group and can be used to catalyze Mannich, aza Diels-Alder, cyanation, and allylation reaction of aldimines. It's also a carbonyl group activator, catalyzing Friedel-Crafts acylation and alkylation, Michael addition, Aldol, allylation, and cyanation of aldehydes (Kobayashi and Nagayama, 1998).

Nowadays, room temperature ionic liquids now emerging as novel “designer’s solvent”, have drawn more and more attention in biphasic system and served as a promising alternative for water (Welton, 1999; Dupont et al., 2002). Unlike the common volatile solvents (VOLs), ionic liquids have practically no vapor pressure, which makes them more economical and environmentally benign in product separation. Most importantly, ionic liquid can form biphasic system with most of organic substrates and metal triflates have been successfully immobilized in ionic liquids for a number of reactions (Kobayashi et al., 1993). The immobilized M(OTf)_x is easily recycled and reused directly, which offers potential environmental and economic benefits. In most cases, the metal triflate catalysis in ionic liquid demonstrates superior catalytic activity and selectivity than in other media.

2.7.2. Recover and reuse of metal triflates

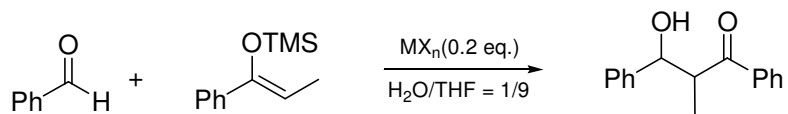
Metal triflates are more soluble in water than in organic solvents such as dichloromethane. Very interestingly, almost 100% of metal triflates was quite easily recovered from the aqueous layer after the reaction completed and it could be reused. The reactions are usually quenched with water and the products are extracted with an organic solvent (for example, dichloromethane). Metal triflate is in aqueous layer and only removal of water gives the catalyst which can be used in the next reaction.

2.7.3. The catalytic effect of metal triflates in water

The most notable feature of $M(OTf)_x$ is their stability in water, which makes them effective Lewis acids in aqueous media. The catalytic effect of Lewis acids in water was systematically investigated by Kobayashi et al. (1998). They found that catalytic effect of Lewis acids in water was correlated to their hydrolysis constants and water exchange rate constants (WERC) for substitution of inner-sphere water ligands. A model reaction of benzaldehyde and (*Z*)-1-phenyl-1-(trimethylsiloxy) propene was chosen to screen various metal salts including $M(OTf)_x$ (Table 2.1). In the cases the yield exceeding 50%, the metal salts have the pKh (Kh= hydrolysis constant) values from 4.3-10.08, and WERC greater than $3.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$. A notable exception is InCl_3 , which was reported to catalyze the reaction in water effectively but with a pKh of 4.00 and WERC of 4.0×10^4 . Obviously, all rare earth metal triflates work well in water with the pKh and WERC values falling in the range. Intrinsically, these two values are closely related to the $(\text{electron})^2 / (\text{ionic radii})$ value. The Lewis acids working well in water are strictly consistent with the requirements of pKh and WERC.

The mechanism of $M(OTf)_x$ catalysis can be deduced by judging from these findings. Upon the addition of $M(OTf)_x$ to water, the dissociation and hydration of the metal center ion occur, the exchange of intermolecular water and intramolecular water gives chances for the substrate to coordinate with the center ion. The substrate is activated and the reaction is readily to occur. After the reaction, the products are extracted and the catalysts remain in the aqueous phase, and could be easily recovered and reused.

Table 2.1. The effect of catalyst on the reaction of benzaldehyde and (Z)-1-phenyl-1-(trimethylsiloxy) propene



MX _n	Yield %	pK _h	WERC	MX _n	Yield %	pK _h	WERC
AlCl ₃	trace	1.14	1.64	Pr(OTf) ₃	83	8.1	3.1x10 ⁸
Co(ClO ₄) ₂	17	9.65	2.0x10 ⁵	Nd(OTf) ₃	78	8.0	3.9x10 ⁸
Ni(ClO ₄) ₂	17	9.86	2.7x10 ⁴	Sm(OTf) ₃	85	7.9	5.9x10 ⁸
InCl ₃	68	4.00	4.0x10 ⁴	Eu(OTf) ₃	88	7.8	6.5x10 ⁸
Zn(ClO ₄) ₂	57 ^a	8.96	5.0x10 ⁸	Gd(OTf) ₃	90	8.0	6.3x10 ⁸
Fe(ClO ₄) ₂	55 ^a	9.5	3.2x10 ⁶	Tb(OTf) ₃	81	7.9	7.8x10 ⁷
Pb(ClO ₄) ₂	65 ^a	7.71	7.5x10 ⁹	Dy(OTf) ₃	85	8.0	6.3x10 ⁷
Cu(ClO ₄) ₂	81 ^a	7.53	2.0x10 ⁸	Ho(OTf) ₃	89	8.0	6.1x10 ⁷
ScCl ₃	78 ^a	4.3	4.8x10 ⁷	Er(OTf) ₃	86	7.9	1.4x10 ⁸
YCl ₃	86 ^a	7.7	1.3x10 ⁷	Tm(OTf) ₃	85	7.7	6.4x10 ⁶
La(OTf) ₃	80	8.5	2.1x10 ⁸	Yb(OTf) ₃	92	7.7	8.0x10 ⁷
Ce(OTf) ₃	81	8.3	2.7x10 ⁸	Lu(OTf) ₃	84	7.6	6.0x10 ⁷

^a Solvent System : H₂O:EtOH:Toluene = 1:7:3

3. THE AIM OF THE WORK

Porphyrins play a very important role in biological systems and used in a wide variety of applications such as photodynamic cancer therapy, boron neutron capture therapy and catalysis. A variety of synthetic methods have been developed for the synthesis of porphyrins. Dipyrromethanes have been used as key building blocks in the synthesis of porphyrin and porphyrin like compounds. 2-alkyl pyrroles are also versatile intermediates for the synthesis porphyrin, dipyrromethanes and many biologically active compounds.

Therefore, it was aimed in this thesis to develop three new methods for the synthesis of 2-substituted pyrrolesulfonamides, 5-substituted dipyrromethanes and *meso*-substituted porphyrins by using metal triflate catalyst.

For this purpose, in the first part of the study, *N*-tosyl imines were synthesized from substituted benzaldehydes and *p*-toluene sulfonamide. The synthesized *N*-tosyl imines were used in the metal triflate catalysed addition reactions of pyrrole in order to obtain novel 2-substituted pyrrolesulfonamides.

In the second part of the work, it was aimed to synthesize 5-substituted dipyrromethanes from the reaction of *N*-tosyl imines with excess pyrrole in the presence of metal triflate catalysts.

The aim of the last part of the work is to synthesize *meso*-substituted porphyrins *via* the metal triflate catalysed reaction of synthesized 5-substituted dipyrromethanes with *N*-tosyl imines.

It was also aimed to examine the mechanisms and the effects of different parameters (solvent, temperature, catalyst type and amount, substituents, concentrations of reactants) on these reactions.

4. EXPERIMENTAL

4.1 General Procedures

All chemicals were purchased from Aldrich, Sigma and E. Merck. Solvents were either reagents or technical grade purified and dried by distillation from appropriate desiccant. Concentrations of solutions after reactions and extractions were achieved using a rotatory evaporator at reduced pressure. Organic extracts were dried over anhydrous magnesium sulphate or calcium chloride.

Reactions were monitored by thin layer chromatography using precoated silica plates (Kieselgel 60, F254, E. Merck), visualized with UV-light or phosphomolybdic acid in methanol. Flash column chromatography employed by silica gel (0.04-0.63 mm, 230-400 mesh ASTM, E. Merck). The relative proportion of solvents are in volume:volume ratio used in column chromatography as eluent.

Melting points were measured with an Gallenkamp melting point apparatus. FT-IR spectra were determined on Unicam Mattson 1000 FT IR spectrometer. Electronic absorption spectra were measured using a Jasco V-530 UV-vis spectrophotometer. Elemental analysis experiments were performed by LECO CHNS.

^1H and ^{13}C NMR spectra were performed on Bruker DPX-400, ultra shield, 400 MHz high performance digital FT-NMR Spectrometer using CDCl_3 as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts are as in parts per million (δ) downfield and upfield from internal standard. Spin multiplicities are mentioned are: s (singlet), br (broad), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet).

4.2. General Procedure for the Synthesis of *N*-Tosyl Imines

Aldehyde (29 mmol), *p*-toluenesulfonamide (23 mmol), *p*-toluenesulfonic acid (0.29 mmol) and 40 mL toluene were placed in a round bottom flask with a Dean-Stark trap and heated at reflux for 10 h. The reaction turned a deep brown color. After 10 h, charcoal was added to the hot solution and the mixture was stirred for 1h and filtered. The solvent was removed under reduced pressure to give *N*-tosyl imine and the product was recrystallized from benzene or petroleum ether.

- ***N*-benzylidene-4-methylbenzenesulfonamide (106).** Rf: 0.35 (1:3 EtOAc: hexane); m.p : 108-109 °C; IR (KBr) 1600, 1569, 1447, 1312, 1156, 1088, 672, 537, 487 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.47 (s, 3H, CH₃), 7.36 (d, *J*= 8.1, 2H, Ar-H), 7.51-7.53 (m, 2H, Ar-H), 7.64 (t, *J*= 8.00, 1H, Ar-H), 7.89-7.96 (m, 4H, Ar-H), 9.04 (s, 1H, CH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.66, 126.54, 128.19, 129.04, 129.56, 129.67, 131.28, 134.65, 144.16, 169.69.
- ***N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide (107).** Rf: 0.24 (1:3 EtOAc: hexane); mp : 127-128 °C; IR (KBr) 1595, 1557, 1313, 1155, 1085, 667, 591, 518 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.45 (s, 3H, CH₃), 3.91 (s, 3H, OCH₃), 6.97 (d, *J*= 8.8, 2H, Ar-H), 7.32-7.35 (m, 2H, Ar-H), 7.87-7.91 (m, 4H, Ar-H), 8.95 (s, 1H, CH); ¹³C NMR (100 MHz) δ: 21.66, 55.49, 114.57, 125.36, 126.54, 128.00, 129.60, 133.66, 143.84, 165.10, 168.83.
- ***N*-(2-methoxybenzylidene)-4-methylbenzenesulfonamide (108).** Rf: 0.35 (1:3 EtOAc: hexane); mp: 91-92 °C ; IR (KBr) 1589, 1476, 1311, 1248, 1152, 1084, 672, 567 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.43 (s, 3H, CH₃), 3.95 (s, 3H, OCH₃) 6.94-7.00 (m, 2H, Ar-H), 7.33 (d, *J*= 8.4, 2H, Ar-H), 7.55-7.57 (m, 1H, Ar-H), 7.81 (d, *J*= 8.0, 2H, Ar-H), 8.06 (d, *J*= 8.0, 1H, Ar-H), 9.52 (s, 1H, CH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.63, 55.48, 55.62, 111.41, 120.87, 126.53, 128.08, 129.44, 129.56, 136.54, 143.79, 161.58, 165.86.

- ***N*-(4-methylbenzylidene)-4-methylbenzenesulfonamide (109).** Rf: 0.47 (1:3 EtOAc: hexane); mp: 110-111 °C; IR (KBr) 1592, 1555, 1310, 1156, 1085, 666, 503, 495 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.47 (s, 6H, 2CH₃), 7.28-7.36 (m, 4H, Ar-H), 7.81-7.90 (m, 4H, Ar-H), 9.00 (s, 1H, CH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.88, 21.99, 126.53, 128.11, 129.82, 130.07, 131.41, 135.82, 143.99, 145.91, 169.53.
- ***N*-(2-hydroxybenzylidene)-4-methylbenzenesulfonamide (110).** Rf: 0.45 (1:3 EtOAc: hexane); mp: 120-121 °C; IR (KBr) 1598, 1492, 1338, 1148, 1088, 680, 542, 471; ¹H NMR (400 MHz, CDCl₃) δ: 2.48 (s, 3H, CH₃), 6.98-7.02 (m, 2H, Ar-H), 7.36 (d, *J* = 8.1, 2H, Ar-H), 7.50-7.53 (m, 2H, Ar-H), 7.86-7.89 (m, 2H, Ar-H), 9.09 (s, 1H, CH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.66, 116.67, 117.98, 120.04, 127.99, 129.91, 135.51, 137.06, 144.63, 162.33, 171.18.
- ***N*-(4-nitrobenzylidene)-4-methylbenzenesulfonamide (111).** Rf: 0.45 (1:3 EtOAc: hexane); mp: 205-206 °C; IR (KBr) 1593, 1520, 1345, 1316, 1150, 1087, 840, 780, 688, 559 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.48 (s, 3H, CH₃), 7.41 (d, *J* = 8.4, 2H, Ar-H), 7.93 (d, *J* = 8.0, 2H, Ar-H), 8.13 (d, *J* = 8.0, 2H, Ar-H), 8.32 (d, *J* = 8.4, 2H, Ar-H), 9.13 (s, 1H, CH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.72, 124.19, 128.41, 130.02, 131.85, 134.19, 137.46, 145.33, 151.20, 167.26.
- ***N*-(4-(trifluoromethyl)benzylidene)-4-methylbenzenesulfonamide (112).** Rf: 0.26 (1:3 EtOAc: hexane); mp: 158-159 °C; IR (KBr) 1613, 1573, 1320, 1164, 1125, 1060, 873, 838, 790, 676, 555 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.49 (s, 3H, CH₃), 7.38 (d, *J* = 8.4, 2H, Ar-H), 7.78 (d, *J* = 8.0, 2H, Ar-H), 7.91 (d, *J* = 8.0, 2H, Ar-H), 8.08 (d, *J* = 8.4, 2H, Ar-H), 9.10 (s, 1H, CH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.66, 123.34 (q, ¹*J*_{C-F} = 271.3), 126.08 (q, ³*J*_{C-F} = 3.6), 128.08, 129.95, 131.35, 134.52, 135.40, 135.59 (q, ²*J*_{C-F} = 32.7), 145.09, 169.05.

- ***N*-(4-fluorobenzylidene)-4-methylbenzenesulfonamide (113).** Rf: 0.39 (1:3 EtOAc: hexane); mp: 115-116 °C ; IR (KBr) 1538, 1300, 1231, 1088, 810, 671 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.47 (s, 3H, CH₃), 7.19 (d, *J*= 8.5, 2H, Ar-H), 7.36 (d, *J*= 8.0, 2H, Ar-H), 7.89 (d, *J*= 8.0, 2H, Ar-H), 7.96-8.00 (m, 2H, Ar-H), 9.00 (s, 1H, CH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.66, 116.55 (d, ²*J*_{C-F}= 22.1), 128.18, 128.95 (d, ⁴*J*_{C-F}= 3.3), 129.70, 133.70 (d, ³*J*_{C-F}= 9.5), 135.50, 144.26, 166.74 (d, ¹*J*_{C-F}= 257.3), 168.06.
- ***N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide (114).** Rf: 0.54 (1:3 EtOAc: hexane); mp: 172-173 °C ; IR (KBr) 3359, 3261, 1916, 1606, 1592, 1486, 1401, 1317, 1304, 1163, 1083, 1011, 870, 825, 800, 787, 707, 694, 658, 567, 556, 498 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.47 (s, 3H, CH₃), 7.37 (d, *J*= 8.0, 2H, Ar-H), 7.49 (d, *J*= 8.5, 2H, Ar-H), 7.87-7.92 (m, 4H, Ar-H), 9.01 (s, 1H, CH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.61, 128.10, 129.56, 129.82, 130.80, 132.31, 134.88, 141.39, 144.74, 168.60.
- ***N*-(4-bromobenzylidene)-4-methylbenzenesulfonamide (115).** Rf: 0.52 (1:3 EtOAc: hexane); mp: 182-183 °C ; IR (KBr) 3358, 3261, 3062, 3040, 2975, 1586, 1558, 1482, 1397, 1303, 1289, 1088, 1018, 1000, 870, 823, 812, 799, 705, 683, 646, 560, 494 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.47 (s, 3H, CH₃), 7.37 (d, *J*= 8.0, 2H, Ar-H), 7.70 (d, *J*= 8.4, 2H, Ar-H), 7.80 (d, *J*= 8.4, 2H, Ar-H), 7.90 (d, *J*= 8.2, 2H, Ar-H), 9.00 (s, 1H, CH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.63, 126.42, 128.12, 129.67, 129.84, 132.36, 132.57, 134.85, 144.78, 168.60.

4.3. General Procedure for the Synthesis of 2-Pyrrole Sulfonamides

N-Tosyl imine (1 mmol) and metal triflate (0.1 mmol) were dissolved in 10 mL solvent. After 30 min., 5 mL solution of pyrrole (1 mmol) in solvent was added dropwise. After 3 hours the reaction mixture was subjected to short flash silica gel chromatography in order to remove the metal triflate. The eluent was removed under reduced pressure and the residue was purified by flash silica gel chromatography.

• **4-Methyl-*N*-(phenyl(1*H*-pyrrol-2-yl)methyl)benzenesulfonamide (118).**

White powder; mp: 132–133 °C; Rf 0.40 (1:3 EtOAc:hexane); IR (KBr): 3458, 2085, 1633, 1390, 1282, 1136, 1080, 1021, 689, 605, 531 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.38 (s, 3H, CH₃), 5.57–5.60 (m, 2H, C3-H, CH), 5.85 (d, *J* = 9.9, 1H, SO₂NH), 5.97 (dd, *J* = 2.8, 6.0, 1H, C4-H), 6.65 (dd, *J* = 2.5, 4.0, 1H, C5-H), 7.09–7.20 (m, 7H, Ar-H), 7.53 (d, *J* = 8.3, 2H, Ar-H), 8.76 (br s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.49, 55.78, 108.20, 118.57, 127.16, 127.38, 127.57, 128.35, 129.05, 129.29, 130.53, 137.47, 138.89, 142.87. Anal. Calcd for C₁₈H₁₈N₂O₂S: C, 66.23; H, 5.56; N, 8.58; S, 9.82. Found: C, 66.12; H, 5.63; N, 8.40; S, 9.73.

• ***N*-((4-Methoxyphenyl)(1*H*-pyrrol-2-yl)methyl)-4-methylbenzene**

sulfonamide (119). Colourless viscous oil; Rf 0.30 (1:3 EtOAc:hexane); IR (KBr): 3516, 2072, 1636, 1507, 1243, 1169, 1027, 762, 715, 556 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.40 (s, 3H, CH₃), 3.77 (s, 3H, OCH₃), 5.50 (d, *J* = 8.1, 1H, CH), 5.57–5.59 (m, 2H, SO₂NH, C3-H), 5.98 (dd, *J* = 2.7, 6.0, 1H, C4-H), 6.67 (br s, 1H, C5-H), 6.70 (d, *J* = 8.7, 2H, Ar-H), 7.02 (d, *J* = 8.7, 2H, Ar-H), 7.14 (d, *J* = 8.2, 2H, Ar-H), 7.55 (d, *J* = 8.3, 2H, Ar-H), 7.84 (d, *J* = 8.4, 2H, Ar-H), 8.72 (br s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.55, 55.09, 55.53, 108.08, 108.19, 113.79, 118.51, 127.25, 128.04, 129.03, 130.90, 131.06, 137.54, 142.88, 159.19. Anal. Calcd for C₁₉H₂₀N₂O₃S: C, 64.02; H, 5.66; N, 7.86; S, 9.00. Found: C, 64.25; H, 5.63; N, 7.88; S, 9.08.

• ***N*-((2-Methoxyphenyl)(1*H*-pyrrol-2-yl)methyl)-4-methylbenzene**

sulfonamide (120). Light brown powder; mp: 132–133 °C; Rf 0.34 (1:3 EtOAc:hexane); IR (KBr): 3440, 2954, 2835, 1638, 1491, 1453, 1328, 1247, 1156, 1092, 1023, 909, 790, 743, 664, 549 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.37 (s, 3H, CH₃), 3.70 (s, 3H, OCH₃), 5.51 (br s, 1H, C3-H), 5.64 (d, *J* = 9.3, 1H, CH), 5.90 (d, *J* = 9.1, 1H, SO₂NH), 5.97 (dd, *J* = 2.8, 5.8, 1H, C4-H), 6.70 (dd, *J* = 2.5, 4.1, 1H, C5-H), 6.73 (d, *J* = 8.3, 1H, Ar-H), 6.81 (t, *J* = 7.4, 1H, Ar-H), 7.00 (dd, *J* = 1.6, 7.5, 1H, Ar-H), 7.09 (d, *J* = 8.2, 2H, Ar-H), 7.16–7.21 (m, 1H, Ar-H), 7.55 (d, *J* = 8.2, 2H, Ar-H), 8.72 (br s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.55, 53.85, 55.45,

107.04, 108.26, 111.21, 118.01, 120.87, 126.82, 127.22, 129.09, 129.60, 130.55, 137.86, 142.55, 156.76. Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66; N, 7.86; S, 9.00. Found: C, 64.11; H, 5.81; N, 7.82; S, 8.75.

• ***N*-((1*H*-Pyrrol-2-yl)(*p*-tolyl)methyl)-4-methylbenzenesulfonamide (121).**

Light brown powder; mp: 96–97 °C; R_f 0.44 (1:3 EtOAc:hexane); IR (KBr): 3426, 2963, 2924, 2866, 2104, 1636, 1509, 1426, 1321, 1262, 1154, 1091, 1026, 910, 790, 722, 663, 563 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ : 2.34 (s, 3H, CH_3), 2.43 (s, 3H, SO_2Ph-CH_3), 5.52 (d, J = 8.2, 1H, CH), 5.58 (br s, 1H, C3-H), 5.62 (d, J = 8.0, 1H, SO_2NH), 5.98 (dd, J = 2.8, 5.7, 1H, C4-H), 6.66 (br s, 1H, C5-H), 7.00–7.02 (m, 4H, Ar-H), 7.13 (d, J = 8.1, 2H, Ar-H), 7.55 (d, J = 8.2, 2H, Ar-H), 8.62 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.15, 21.53, 55.64, 108.13, 108.17, 118.51, 127.24, 127.37, 129.06, 129.31, 130.78, 135.98, 137.27, 137.55, 142.83. Anal. Calcd for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.23; S, 9.42. Found: C, 66.90; H, 5.95; N, 8.20; S, 9.37.

• **4-Methyl-*N*-((4-nitrophenyl)(1*H*-pyrrol-2-yl)-methyl)benzenesulfonamide (122).**

Light brown powder; mp: 153–154 °C; R_f 0.34 (1:3 EtOAc:hexane); IR (KBr): 3419, 1716, 1636, 1512, 1412, 1337, 1255, 1150, 1089, 1014, 909, 791, 741, 688, 549 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ : 2.43 (s, 3H, CH_3), 5.29 (br s, 1H, SO_2NH), 5.52 (br s, 1H, C3-H), 5.70 (br s, 1H, CH), 6.02 (dd, J = 2.8, 6.0, 1H, C4-H), 6.76 (dd, J = 2.6, 4.0, 1H, C5-H), 7.20 (d, J = 8.0, 2H, Ar-H), 7.37 (d, J = 8.6, 2H, Ar-H), 7.60 (d, J = 8.3, 2H, Ar-H), 8.10 (d, J = 8.7, 2H, Ar-H), 8.56 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 20.93, 55.06, 108.69, 119.38, 123.54, 127.15, 128.16, 128.99, 129.56, 134.98, 137.06, 143.78, 145.64. Anal. Calcd for $C_{18}H_{17}N_3O_4S$: C, 58.21; H, 4.61; N, 11.31; S, 8.63. Found: C, 58.00; H, 4.68; N, 11.38; S, 8.51.

• ***N*-((1*H*-Pyrrol-2-yl)(4-(trifluoromethyl)phenyl)-methyl)-4-methylbenzene sulfonamide (123).** White powder; mp: 113–114 °C; R_f 0.38 (1:3 EtOAc:hexane); IR (KBr): 3382, 3272, 3107, 3061, 2926, 2867, 1918, 1802, 1612, 1489, 1422, 1325, 1160, 1125, 1063, 1026, 915, 850, 792, 732, 665, 660, 555 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ : 2.34 (s, 3H, CH_3), 5.55 (br s, 1H, C3-H), 5.69 (d, J = 8.6, 1H,

CH), 6.00–6.03 (m, 2H, C4-H, SO₂NH), 6.69 (br s, 1H, C5-H), 7.07 (d, *J* = 8.1, 2H, Ar-H), 7.24 (d, *J* = 8.1, 2H, Ar-H), 7.39 (d, *J* = 8.2, 2H, Ar-H), 7.47 (d, *J* = 8.2, 2H, Ar-H), 8.86 (br s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.32, 55.66, 108.36, 108.61, 119.15, 125.17 (q, ³*J*_{C-F} 3.6), 127.05, 127.91, 129.39, 129.49, 129.90 (q, ²*J*_{C-F} 32.2), 137.01, 142.49, 143.46. Anal. Calcd for C₁₉H₁₇F₃N₂O₂S: C, 57.86; H, 4.34; N, 7.10; S, 8.13. Found: C, 57.60; H, 4.32; N, 7.13; S, 7.99.

- ***N*-((4-Fluorophenyl)(1*H*-pyrrol-2-yl)methyl)-4-methylbenzenesulfonamide (124).** Colourless viscous oil; Rf 0.37 (1:3 EtOAc:hexane); IR (KBr): 3423, 2978, 2922, 2870, 1640, 1505, 1429, 1322, 1223, 1154, 1092, 1029, 915, 844, 774, 722, 664, 542 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.45 (s, 3H, CH₃), 5.54 (br s, 1H, C3-H), 5.57 (d, *J* = 8.4, 1H, CH), 5.86 (d, *J* = 8.4, 1H, SO₂NH), 5.98 (dd, *J* = 2.7, 5.9, 1H, C4-H), 6.67 (dd, *J* = 2.6, 4.1, 1H, C5-H), 6.84 (t, *J* = 8.6, 2H, Ar-H), 7.07–7.13 (m, 4H, Ar-H), 7.52 (d, *J* = 8.3, 2H, Ar-H), 8.77 (br s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.50, 55.27, 108.25, 115.21 (d, ²*J*_{C-F} 21.4), 118.81, 127.15, 129.10 (d, ³*J*_{C-F} 8.1), 129.37, 130.31, 134.58 (d, ⁴*J*_{C-F} 3.1), 137.35, 143.15, 162.21 (d, ¹*J*_{C-F} 245.7). Anal. Calcd for C₁₈H₁₇FN₂O₂S: C, 62.77; H, 4.98; N, 8.13; S, 9.31. Found: C, 62.40; H, 5.01; N, 8.05; S, 9.19.

- ***N*-((4-Chlorophenyl)(1*H*-pyrrol-2-yl)methyl)-4-methylbenzenesulfonamide (125).** Brown powder; mp: 115–116 °C; Rf 0.43 (1:3 EtOAc:hexane); IR (KBr): 3448, 3405, 2965, 2922, 2863, 1636, 1332, 1155, 1087, 1022, 805, 721, 662, 561 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.40 (s, 3H, CH₃), 5.54–5.57 (m, 2H, C3-H, CH), 5.88 (d, *J* = 8.5, 1H, SO₂NH), 5.98 (dd, *J* = 2.7, 6.0, 1H, C4-H), 6.65–6.66 (m, 1H, C5-H), 7.05 (d, *J* = 8.5, 2H, Ar-H), 7.11–7.13 (m, 4H, Ar-H), 7.49 (d, *J* = 8.3, 2H, Ar-H), 8.79 (br s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.53, 55.34, 108.27, 108.40, 118.91, 127.13, 128.44, 128.89, 129.40, 129.92, 133.60, 137.26, 137.32, 143.23. Anal. Calcd for C₁₈H₁₇ClN₂O₂S: C, 59.91; H, 4.75; N, 7.76; S, 8.89. Found: C, 59.67; H, 4.70; N, 7.82; S, 8.78.

- ***N*-((4-Bromophenyl)(1*H*-pyrrol-2-yl)methyl)-4-methylbenzenesulfonamide (126).** Brown powder; mp: 116–117 °C; R_f 0.42 (1:3 EtOAc:hexane); IR (KBr): 3388, 3275, 2961, 2921, 2862, 2756, 1691, 1596, 1484, 1432, 1323, 1154, 1088, 1025, 807, 663, 559 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.40 (s, 3H, CH₃), 5.55–5.57 (m, 2H, C3-H, CH), 5.97–6.00 (m, 2H, SO₂NH, C4-H), 6.66 (dd, *J* = 2.5, 4.0, 1H, C5-H), 6.98 (d, *J* = 8.4, 2H, Ar-H), 7.10 (d, *J* = 8.1, 2H, Ar-H), 7.26 (d, *J* = 8.4, 2H, Ar-H), 7.47 (d, *J* = 8.3, 2H, Ar-H), 8.83 (br s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ: 21.55, 55.42, 108.27, 108.43, 118.94, 121.70, 127.11, 129.24, 129.41, 129.79, 131.38, 137.20, 137.77, 143.26. Anal. Calcd for C₁₈H₁₇BrN₂O₂S: C, 53.34; H, 4.23; N, 6.91; S, 7.91. Found: C, 53.67; H, 4.31; N, 6.84; S, 7.98.

4.4. General Procedure for the Synthesis of 5-Substituted Dipyrromethanes

N-Tosyl imine (1 mmol) was dissolved in excess pyrrole (40 mmol) and metal triflate (0.1 mmol) was added to the reaction mixture at the temperature indicated in Table 5.12. The reaction was monitored with TLC and completed after 6 h. Metal triflate was removed from the reaction medium by subjecting the mixture to a short flash silica gel chromatography using ethyl acetate as an eluent. The eluent was removed under reduced pressure and the residue was purified by flash silica gel chromatography.

- **5-Phenyldipyrromethane (127).** Pale yellow crystals; mp: 100–101 °C; R_f 0.60 (1:3 EtOAc:hexane); IR (KBr) 3449, 2951, 1630, 1510, 1410, 1293, 1225, 1048, 760, 703, 607 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 5.49 (s, 1H, *meso*H), 5.92 (br s, 2H, 2C3-H), 6.14 (dd, *J* = 2.8, 5.9, 2H, 2C4-H), 6.68 (dd, *J* = 2.6, 4.2, 2H, 2C5-H), 7.22–7.35 (m, 5H, Ar-H), 7.88 (br s, 2H, 2N-H); ¹³C NMR (100 MHz, CDCl₃) δ: 44.10, 107.45, 108.75, 117.12, 127.03, 128.51, 128.68, 132.36, 142.23.
- **5-(4-Methoxyphenyl)dipyrromethane (128).** Pale yellow powder; mp: 98–99 °C; R_f 0.47 (1:3 EtOAc:hexane); IR (KBr) 3405, 2964, 2936, 1616, 1507, 1457, 1299, 1245, 1175, 1103, 1027, 965, 838, 774, 720, 554 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 3.82 (s, 3H, OCH₃), 5.42 (s, 1H, *meso*H), 5.90–5.92 (m, 2H, 2C3-H), 6.14 (dd, *J* = 2.8, 6.0, 2H, 2C4-H), 6.65–6.67 (m, 2H, 2C5-H), 6.85 (d, *J* = 8.6, 2H,

Ar-H), 7.14 (d, J = 8.6, 2H, Ar-H), 7.82 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, CDCl_3) δ : 43.21, 55.15, 107.27, 108.67, 114.03, 117.02, 129.44, 132.76, 134.29, 158.61.

• **5-(2-Methoxyphenyl)dipyrromethane (129).** Pale yellow powder; mp: 114–115 °C; Rf 0.65 (1:3 EtOAc:hexane); IR (KBr) 3425, 1636, 1485, 1242, 1090, 1023, 966, 715, 555 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 3.83 (s, 3H, OCH_3), 5.82 (s, 1H, *meso*H), 5.91 (br s, 2H, 2C3-H), 6.15 (d, J = 2.5, 2H, 2C4-H), 6.63 (d, J = 1.4, 2H, 2C5-H), 6.94–6.97 (m, 2H, Ar-H), 7.12 (d, J = 6.8, 1H, Ar-H), 7.28 (t, J = 7.8, 1H, Ar-H), 7.97 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, CDCl_3) δ : 37.68, 55.74, 107.10, 108.70, 111.24, 116.67, 121.04, 128.07, 129.60, 131.14, 132.47, 156.73.

• **5-(4-Methylphenyl)dipyrromethane (130).** Pale yellow crystals; mp: 110–111 °C; Rf 0.65 (1:3 EtOAc:hexane); IR (KBr) 3417, 2356, 1635, 1508, 1420, 1254, 1089, 1025, 964, 909, 790, 742, 509 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 2.37 (s, 3H, CH_3), 5.44 (s, 1H, *meso*H), 5.91 (br s, 2H, 2C3-H), 6.13 (dd, J = 2.8, 5.9, 2H, 2C4-H), 6.66 (dd, J = 2.6, 4.2, 2H, 2C5-H), 7.10–7.15 (m, 4H, Ar-H), 7.85 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, CDCl_3) δ : 21.18, 43.72, 107.32, 108.74, 116.99, 128.42, 129.38, 132.57, 136.42, 139.25.

• **5-(2-Hydroxyphenyl)dipyrromethane (131).** Light brown oil; Rf 0.32 (1:3 EtOAc:hexane); IR (KBr) 3418, 2072, 1635, 1493, 1451, 1330, 1255, 1085, 1023, 909, 790, 741, 529 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 5.17 (br s, 1H, OH), 5.53 (s, 1H, *meso*H), 6.01 (br s, 2H, 2C3-H), 6.16 (dd, J = 2.8, 5.9, 2H, 2C4-H), 6.70 (dd, J = 2.6, 4.1, 2H, 2C5-H), 6.87–6.95 (m, 2H, Ar-H), 7.08–7.10 (m, 1H, Ar-H), 7.18–7.22 (m, 1H, Ar-H), 8.14 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, CDCl_3) δ : 40.59, 107.22, 108.85, 117.89, 118.00, 121.63, 128.52, 128.81, 130.19, 130.78, 153.87. Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.48; H, 6.03; N, 11.58.

• **5-(4-Nitrophenyl)dipyrromethane (132).** Yellow powder; mp: 159–160 °C; Rf 0.48 (1:3 EtOAc/hexane); IR (KBr) 3394, 3359, 3101, 1595, 1512, 1348, 1114, 1027, 808, 735, 660, 568 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 5.59 (s, 1H,

*meso*H), 5.88 (br s, 2H, 2C3-H), 6.18 (dd, $J = 2.8, 6.0$, 2H, 2C4-H), 6.75 (dd, $J = 2.6, 4.2$, 2H, 2C5-H), 7.39 (d, $J = 8.6$, 2H, Ar-H), 7.98 (br s, 2H, 2N-H), 8.18 (d, $J = 8.8$, 2H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3) δ : 43.87, 107.92, 108.95, 117.94, 123.80, 129.25, 130.76, 147.02, 149.66.

• **5-(4-Trifluoromethylphenyl)dipyrromethane (133).** Yellow oil; R_f 0.47 (1:3 EtOAc:hexane); IR (KBr) 3448, 3401, 2980, 1618, 1416, 1326, 1164, 1124, 1067, 1019, 775, 722 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 5.51 (s, 1H, *meso*H), 5.91 (br s, 2H, 2C3-H), 6.20 (dd, $J = 2.8, 6.0$, 2H, 2C4-H), 6.67–6.69 (m, 2H, 2C5-H), 7.35 (d, $J = 8.3$, 2H, Ar-H), 7.63 (d, $J = 8.1$, 2H, Ar-H), 7.82 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, CDCl_3): δ 43.78, 107.84, 108.82, 117.66, 124.16 (q, $^1J_{\text{C-F}} 270.3$), 125.54 (q, $^3J_{\text{C-F}} 3.7$), 128.75, 129.29 (q, $^2J_{\text{C-F}} 32.2$), 131.50, 146.28. Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{N}_2$: C, 66.20; H, 4.51; N, 9.65. Found: C, 66.07; H, 4.70; N, 9.59.

• **5-(4-Fluorophenyl)dipyrromethane (134).** Light brown crystals; mp: 80–81 $^\circ\text{C}$; R_f 0.53 (1:3 EtOAc:hexane); IR (KBr) 3410, 2928, 1610, 1498, 1451, 1285, 1175, 1103, 960, 764, 554 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 5.45 (s, 1H, *meso*H), 5.89 (br s, 2H, 2C3-H), 6.16 (dd, $J = 2.8, 5.8$, 2H, 2C4-H), 6.66 (br s, 2H, 2C5-H), 7.00–7.05 (m, 2H, Ar-H), 7.16–7.20 (m, 2H, Ar-H), 7.81 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, CDCl_3) δ : 43.28, 107.55, 108.79, 115.42 (d, $^2J_{\text{C-F}} 21.3$), 117.34, 129.92 (d, $^3J_{\text{C-F}} 7.9$), 132.24, 137.96 (d, $^4J_{\text{C-F}} 3.2$), 161.85 (d, $^1J_{\text{C-F}} 244.5$).

• **5-(4-Chlorophenyl)dipyrromethane (135).** Pale yellow powder; mp: 112–113 $^\circ\text{C}$; R_f 0.58 (1:3 EtOAc:hexane); IR (KBr) 3382, 2958, 2923, 2861, 1641, 1485, 1405, 1255, 1087, 1022, 767, 720, 550, 508 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 5.42 (s, 1H, *meso*H), 5.90 (br s, 2H, 2C3-H), 6.17 (dd, $J = 2.8, 5.8$, 2H, 2C4-H), 6.66 (dd, $J = 2.6, 4.2$, 2H, 2C5-H), 7.15 (d, $J = 8.4$, 2H, Ar-H), 7.31 (d, $J = 8.4$, 2H, Ar-H), 7.80 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, CDCl_3) δ : 43.35, 107.61, 108.75, 117.42, 128.70, 129.74, 131.88, 132.81, 140.69.

- **5-(4-Bromophenyl)dipyrromethane (136).** Pale yellow powder; mp: 122–123 °C; Rf 0.59 (1:3 EtOAc/hexane); IR (KBr) 3374, 3098, 2957, 2920, 2861, 1707, 1481, 1400, 1083, 1021, 765, 720, 643, 544, 503 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 5.41 (s, 1H, *meso*H), 5.90 (br s, 2H, 2C3-H), 6.16 (dd, *J* = 2.8, 5.9, 2H, 2C4-H), 6.66 (dd, *J* = 2.6, 4.2, 2H, 2C5-H), 7.10 (d, *J* = 8.4, 2H, Ar-H), 7.46 (d, *J* = 8.4, 2H, Ar-H), 7.80 (br s, 2H, 2N-H); ¹³C NMR (100 MHz, CDCl₃) δ: 43.50, 107.65, 108.83, 117.44, 120.95, 130.17, 131.71, 131.77, 141.27.

4.5. General Procedure for the Synthesis of *meso*-Substituted Porphyrins

A solution of *N*-tosyl imine (1 mmol) and metal triflate (0.1 mmol) in dichloromethane (50 mL) was stirred for 30 min. at room temperature under nitrogen atmosphere. 50 mL solution of dipyrromethane (1 mmol) in dichloromethane was added dropwise into the reaction mixture. After 1.5 hours, DDQ (1.5 mmol) was added and the reaction mixture was further stirred for 2 hours. Water (10 mL) was added to the mixture and aqueous phase was extracted with dichloromethane (3x 10 mL). The combined organic phases were dried over magnesium sulphate and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography with dichloromethane.

- **5, 10, 15, 20-Tetraphenylporphyrin (140).** Purple crystal; mp >300 °C; Rf 0.95 (CH₂Cl₂); UV-vis (λ_{max} / CH₂Cl₂): 416, 514, 548, 590, 646; IR (KBr) 3315, 3052, 3023, 2921, 1594, 1557, 1471, 1440, 1349, 1174, 1070, 1000, 964, 799, 738, 699, 656, 639 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: -2.71 (bs, 2H, NH), 7.78-7.80 (m, 12H, *p*- and *m*-PhH), 8.26 (d, *J* = 5.9, 8H, *o*-PhH), 8.89 (s, 8H, pyr-H); ¹³C NMR (100 MHz, CDCl₃) δ: 120.14, 126.68, 127.70, 133.33 (br s), 134.56, 142.20.

- **5, 10, 15, 20-Tetrakis(4-methoxyphenyl)porphyrin (141).** Purple crystal; mp >300 °C; Rf 0.74 (CH₂Cl₂); UV-vis (λ_{max} / CH₂Cl₂): 416, 512, 546, 588, 648; IR (KBr) 3434, 3312, 3029, 2996, 2929, 2832, 1605, 1508, 1468, 1439, 1349, 1287, 1246, 1174, 1106, 1033, 965, 840, 802, 735, 597, 536 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: -2.72 (bs, 2H, NH), 4.16 (s, 12H, OCH₃), 7.27-7.32 (m, 8H, *m*-PhH), 8.15

(d, $J = 8.6$, 8H, o-PhH), 8.89 (s, 8H, pyrr-H); ^{13}C NMR (100 MHz, CDCl_3) δ : 55.59, 112.20, 119.74, 130.91 (br s), 134.67, 135.60, 159.39.

• **5, 10, 15, 20-Tetrakis(4-methylphenyl)porphyrin (142).** Purple crystal; mp >300 °C; Rf 0.95 (CH_2Cl_2); UV-vis (λ_{max} / CH_2Cl_2): 416, 514, 546, 590, 646; IR (KBr) 3378, 3018, 2942, 1558, 1472, 1403, 1350, 1174, 1068, 964, 782, 734, 672, 524 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : -2.73 (bs, 2H, NH), 2.73 (s, 12H, CH_3), 7.57 (d, $J = 8.0$, 8H, m-PhH), 8.12 (d, $J = 8.0$, 8H, o-PhH), 8.88 (s, 8H, pyrr-H); ^{13}C NMR (100 MHz, CDCl_3) δ : 21.52, 120.07, 127.40, 130.87 (br s), 134.52, 137.30, 139.34.

• **5, 10, 15, 20-Tetrakis(4-trifluoromethylphenyl)porphyrin (143).** Purple crystal; mp >300 °C; Rf 0.95 (CH_2Cl_2); UV-vis (λ_{max} / CH_2Cl_2): 416, 512, 546, 588, 644; IR (KBr) 3312, 3044, 2929, 1614, 1557, 1477, 1405, 1322, 1165, 1125, 1067, 1019, 967, 854, 796, 727, 680, 605 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : -2.70 (bs, 2H, NH), 8.08 (d, $J = 8.2$, 8H, m-PhH), 8.37 (d, $J = 8.0$, 8H, o-PhH), 8.85 (s, 8H, pyrr-H); ^{13}C NMR (100 MHz, CDCl_3) δ : 119.00, 123.80 (q, $^3J_{\text{C-F}} = 3.6$), 124.50 (q, $^1J_{\text{C-F}} = 270.5$), 130.39 (q, $^2J_{\text{C-F}} = 32.5$), 131.34 (br s), 134.58, 145.49.

• **5, 10, 15, 20-Tetrakis(4-fluorophenyl)porphyrin (144).** Purple crystal; mp >300 °C; Rf 0.56 (CH_2Cl_2); UV-vis (λ_{max} / CH_2Cl_2): 416, 514, 548, 590, 646; IR (KBr) 3436, 3309, 2923, 1599, 1504, 1469, 1350, 1223, 1156, 1092, 967, 846, 806, 793, 729, 589, 529 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : -2.75 (bs, 2H, NH), 7.45-7.59 (m, m-PhH), 8.16-8.21 (m, 8H, o-PhH), 8.90 (s, 8H, pyrr-H).

• **5, 10, 15, 20-Tetrakis(4-chlorophenyl)porphyrin (145).** Purple crystal; mp >300 °C; Rf 0.95 (CH_2Cl_2); UV-vis (λ_{max} / CH_2Cl_2): 418, 514, 548, 590, 646; IR (KBr) 3319, 3018, 2987, 1555, 1488, 1471, 1393, 1346, 1212, 1174, 1089, 1015, 964, 844, 799, 785, 728, 490 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : -2.83 (bs, 2H, NH), 7.77 (d, $J = 8.2$, 8H, m-PhH), 8.16 (d, $J = 8.2$, 8H, o-PhH), 8.87 (s, 8H, pyrr-H); ^{13}C NMR (100 MHz, CDCl_3) δ : 118.99, 127.05, 131.16 (br s), 134.42, 135.50, 140.38.

- **5, 10, 15, 20-Tetrakis(4-bromophenyl)porphyrin (146).** Purple crystal; mp >300 °C; Rf 0.95 (CH₂Cl₂); UV-vis (λ_{max} / CH₂Cl₂): 418, 514, 548, 590, 646; IR (KBr) 3430, 3320, 3012, 2986, 1555, 1472, 1390, 1347, 1176, 1068, 1012, 964, 799, 725, 642, 525, 455 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : -2.85 (bs, 2H, NH), 7.93 (d, J = 8.2, 8H, m-PhH), 8.09 (d, J = 8.2, 8H, o-PhH), 8.87 (s, 8H, pyrr-H); ¹³C NMR (100 MHz, CDCl₃) δ : 119.00, 122.66, 130.00, 131.33 (br s), 135.83, 140.85.

4.6. The Synthesis of 4-methyl-*N*-(phenyl(5-(phenyl(1*H*-pyrrol-2-yl)methyl)-1*H*-pyrrol-2-yl)methyl)benzene sulfonamide (147) and 5,5'-(phenylmethylene)bis(2-(phenyl(1*H*-pyrrol-2-yl)methyl)-1*H*-pyrrole) (149)

N-benzylidene-4-methylbenzenesulfonamide (0.5 mmol) and Cu(OTf)₂ (0.05 mmol) were dissolved in THF (10 mL) at 0 °C and 5 mL solution of 5-phenyldipyrromethane (1.5 mmol) in THF was added dropwise after 30 min. The reaction was monitored with TLC and 5 mL of H₂O was added to the reaction when the reaction completed. The aqueous layer was extracted with 2x10 mL of ether. The organic phase was dried with anhydrous MgSO₄. The solvent was then removed under reduced pressure and crude product was purified by flash column chromatography (1:6 EtOAc/hexane).

4-methyl-*N*-(phenyl(5-(phenyl(1*H*-pyrrol-2-yl)methyl)-1*H*-pyrrol-2-yl)methyl)benzene sulfonamide (147). Brown viscous oil; Rf 0.24 (1:3 EtOAc:hexane); IR (KBr) 3429, 2924, 2845, 1720, 1645, 1488, 1452, 1322, 1281, 1156, 1085, 1023, 808, 769, 699, 666, 561 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 2.39 (bs, 3H, CH₃), 5.36 (d, J = 6.68, 1H, SO₂NH), 5.53-5.58 (m, 3H, pyrrole H, 2*meso* H), 5.70 (bs, 1H, pyrrole H), 5.89 (bs, 1H, pyrrole H), 6.13 (bs, 1H, pyrrole H), 6.64 (bs, 1H, pyrrole H), 7.12-7.57 (m, 10 H, Ar-H), 8.03 (bs, 1H, NH), 8.36 (bs, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ : 21.51, 44.05, 55.91, 107.18, 107.28, 108.31, 108.39, 117.28, 126.89, 127.31, 127.75, 128.43, 128.56, 129.47, 130.11, 132.47, 133.84, 137.12, 138.77, 142.10, 143.33. Anal. Calcd. for C₂₉H₂₇N₃O₂S: C, 72.32; H, 5.65; N, 8.72; S, 6.66. Found: C, 71.97; H, 5.72; N, 8.53; S, 6.81.

- **5,5'-(phenylmethylene)bis(2-(phenyl(1*H*-pyrrol-2-yl)methyl)-1*H*-pyrrole) (149).** Brown viscous oil; Rf 0.36 (1:3 EtOAc:hexane); IR (KBr) 3429, 2924, 2857, 1695, 1627, 1488, 1451, 1286, 1158, 1113, 1068, 875, 769, 716, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 5.31 (bs, 1H, *meso* H), 5.38 (bs, 2H, *meso* H), 5.73-5.75 (m, 4H, pyrrole H), 5.88 (bs, 2H, pyrrole H), 6.16 (bs, 2H, pyrrole H), 6.69 (bs, 2H, pyrrole H), 7.17-7.52 (m, 11H, Ar-H), 7.74 (bs, 2H, NH), 7.92 (bs, 2H, NH), 8.11-8.15 (m, 4H, Ar-H); ¹³C NMR (100 MHz, CDCl₃) δ: 44.08, 44.16, 107.31, 107.38, 108.37, 117.16, 126.48, 126.89, 126.93, 128.32, 128.36, 128.48, 128.51, 128.58, 129.44, 129.73, 130.21, 132.24, 132.30, 132.50, 133.70, 142.06.

4.7. The Synthesis of Di Sulfonamidealkylated Dipyrromethane, *N,N'*-(5,5'-(phenylmethylene)bis(1*H*-pyrrole-5,2-diyl)bis(phenylmethylene))bis(4-methylbenzenesulfonamide) (148).

N-benzylidene-4-methylbenzenesulfonamide (1.5 mmol) and Cu(OTf)₂ (0.15 mmol) were dissolved in THF (10 mL) at -20 °C. 5 mL solution of dipyrromethane (0.5 mmol) in THF was added dropwise into the reaction mixture after 30 min. The reaction was monitored with TLC and 5 mL of H₂O was added when the reaction completed. The aqueous layer was extracted with 2x10 mL of ether. Combined organic phase was dried with anhydrous MgSO₄ and the solvent was evaporated under reduced pressure. The product was purified by flash column chromatography (1:4 EtOAc/hexane) and was obtained as a diastereisomeric mixture.

- ***N,N'*-(5,5'-(phenylmethylene)bis(1*H*-pyrrole-5,2-diyl)bis(phenylmethylene))bis(4-methylbenzenesulfonamide) (148).** Brown viscous oil; Rf 0.23 (1:3 EtOAc:hexane); IR (KBr) 3379, 3269, 2922, 2851, 1598, 1493, 1453, 1426, 1323, 1157, 1092, 1026, 909, 809, 731, 699, 664, 563 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 2.24 (s, 6H, CH₃), 2.25 (s, 6H, CH₃), 5.18 (s, 1H), 5.23 (s, 1H), 5.24 (bs, 1H), 5.31 (bs, 1H), 5.35-5.41 (m, 5H), 5.46-5.59 (m, 6H), 5.78 (bs, 1H), 6.37 (d, *J*= 9.6, 1H), 6.44 (d, *J*= 9.6, 1H), 7.00-7.23 (m, 38H, Ar-H), 7.23-7.50 (m, 8H, Ar-H), 8.25 (bs, 2H, 2xNH), 8.42 (bs, 1H, NH), 8.47 (bs, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ: 20.42, 20.45, 43.02, 43.12, 54.89, 54.99, 55.11, 106.15, 106.31, 106.35,

106.71, 107.23, 107.48, 107.58, 107.65, 125.77, 125.86, 125.90, 126.14, 126.16, 126.36, 126.39, 126.69, 126.72, 126.77, 127.28, 127.30, 127.35, 127.38, 127.50, 128.38, 128.45, 128.47, 129.04, 129.24, 129.87, 130.32, 132.27, 132.47, 133.28, 135.92, 135.97, 136.17, 136.26, 136.79, 136.87, 137.56, 137.63, 140.63, 140.79, 140.84, 142.22, 142.30, 142.34. Anal. Calcd. for $C_{43}H_{40}N_4O_4S_2$: C, 69.70; H, 5.44; N, 7.56; S, 8.66. Found: C, 69.45; H, 5.47; N, 7.91; S, 8.37.

4.8. The Synthesis of *meso*-Tetraphenylporphyrin via Self Condensation of 4-methyl-*N*-(phenyl(5-(phenyl(1*H*-pyrrol-2-yl)methyl)-1*H*-pyrrol-2-yl)methyl) benzene sulfonamide (147**)**

$Cu(OTf)_2$ (0.02 mmol) was added to the solution of 4-methyl-*N*-(phenyl(5-(phenyl(1*H*-pyrrol-2-yl)methyl)-1*H*-pyrrol-2-yl)methyl) benzene sulfonamide (**147**) (0.2 mmol) in 20 mL of CH_2Cl_2 under N_2 atmosphere. The mixture stirred for 1.5 hours and the solution of 0.3 mmol DDQ in CH_2Cl_2 was added to the reaction mixture. After 2 hours, the reaction mixture passed through short silica gel column with CH_2Cl_2 eluent to remove the catalyst. After removing solvent under reduced pressure, the crude product was purified by using flash column chromatography (CH_2Cl_2).

4.9. The Synthesis of *meso*-Tetraphenylporphyrin (140**) via Condensation of Di Sulfonamidealkylated Dipyrromethane **148** with 5-Phenyl dipyrromethane (**127**)**

5-Phenyl dipyrromethane (**127**) (0.1 mmol) and $Cu(OTf)_2$ (0.01 mmol) was dissolved in 5 mL of CH_2Cl_2 at room temperature under N_2 atmosphere. The solution of *N,N'*-(5,5'-(phenylmethylene)bis(1*H*-pyrrole-5,2-diyl)bis(phenylmethylene))bis(4-methylbenzenesulfonamide) (**148**) (0.1 mmol) in 5 mL of CH_2Cl_2 was added to the mixture. DDQ was added to this solution after 1.5 hours and the mixture was stirred 2 hours. After 2 hours, the reaction mixture passed through short silica gel column with CH_2Cl_2 eluent to remove the catalyst. After removing solvent under reduced pressure, the crude product was purified by using flash column chromatography (CH_2Cl_2).

5. EXPERIMENTAL RESULTS AND DISCUSSION

5.1. General Overview of Porphyrin Synthesis

Porphyrins are biochemically important, medically useful, and synthetically interesting compounds. Porphyrins that occur naturally play a major role in the life sustaining biochemical reactions. They have many important biological representatives including hemes, chlorophylls, myoglobins, cytochromes etc. (Kadish et al., 2000).

Porphyrins are used in the field of medicine as photosensitizers in photodynamic therapy and boron neutron capture therapy for cancer. These compounds are also being evaluated as probes for early detection of cancer because of their fluorescent properties. Porphyrins have been used in molecular recognition because of their binding properties to DNA. The other specific uses of porphyrins are electrodes for sensors for oxygen and chemicals, stationary phases in liquid chromatography, dyes and electropolymerised film.

meso-Substituted porphyrins are one of the most studied porphyrins because of their various potential applications in medicinal and materials chemistry and biomimetics. There are seven main types of *meso*-substituted porphyrins (Figure 5.1).

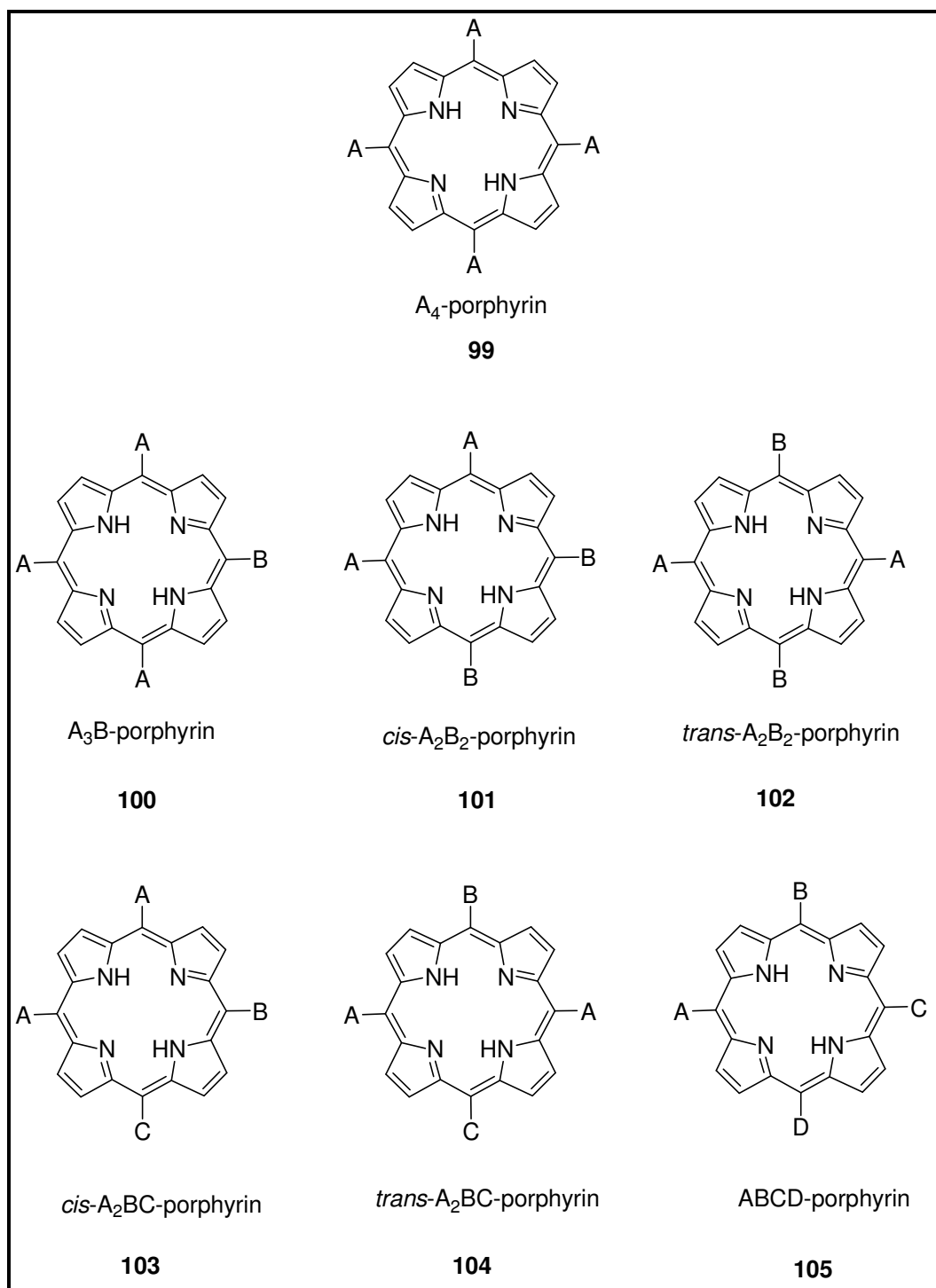
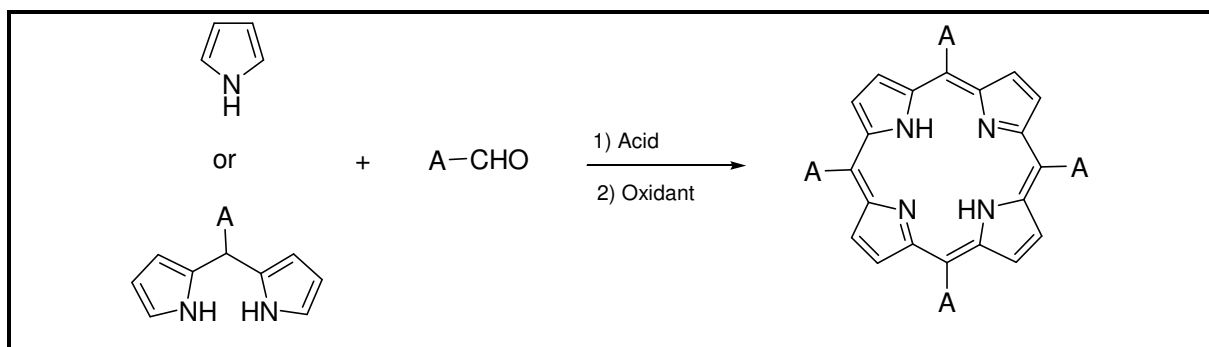


Figure 5.1. Main types of *meso*-substituted porphyrins

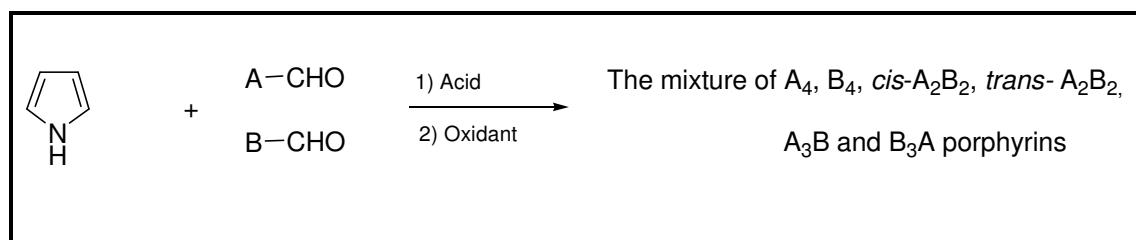
The best methods to prepare each of the seven classes of *meso*-substituted porphyrins (lacking β -substituents) are summarized as follows:

- A₄-porphyrins **99** are synthesized by one-flask reaction of pyrrole or *meso*-substituted dipyrromethane with an aldehyde. (Scheme 5.1) (Lindsey et al., 1994).



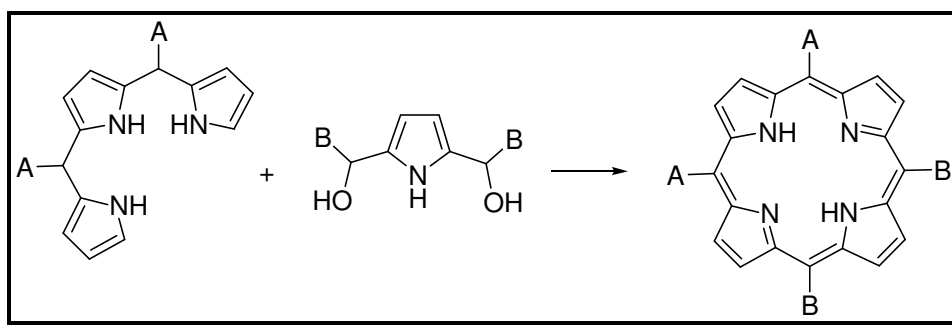
Scheme 5.1. Synthesis of of A₄-porphyrins.

- A₃B-porphyrins **100** have been prepared by the reaction of pyrrole and two aldehydes, affording a mixture of all six substituted products, which were then separated by chromatography (Scheme 5.2). The chromatographic separation was generally lengthy and afforded only small quantities of the desired porphyrin (Little, 1981).



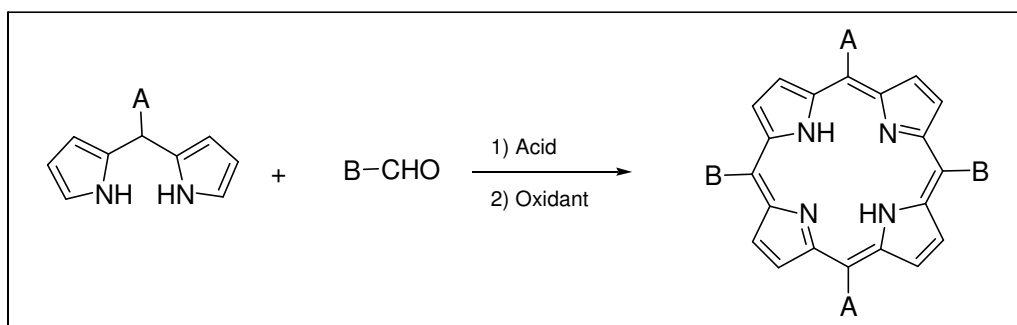
Scheme 5.2. Synthesis of A₃B-porphyrins

- *cis*-A₂B₂ porphyrins **101** have been prepared rationally in milligram quantities by the reaction of a tripyrrane with pyrrole dicarbinol (Scheme 5.3) (Heo and Lee, 1996).



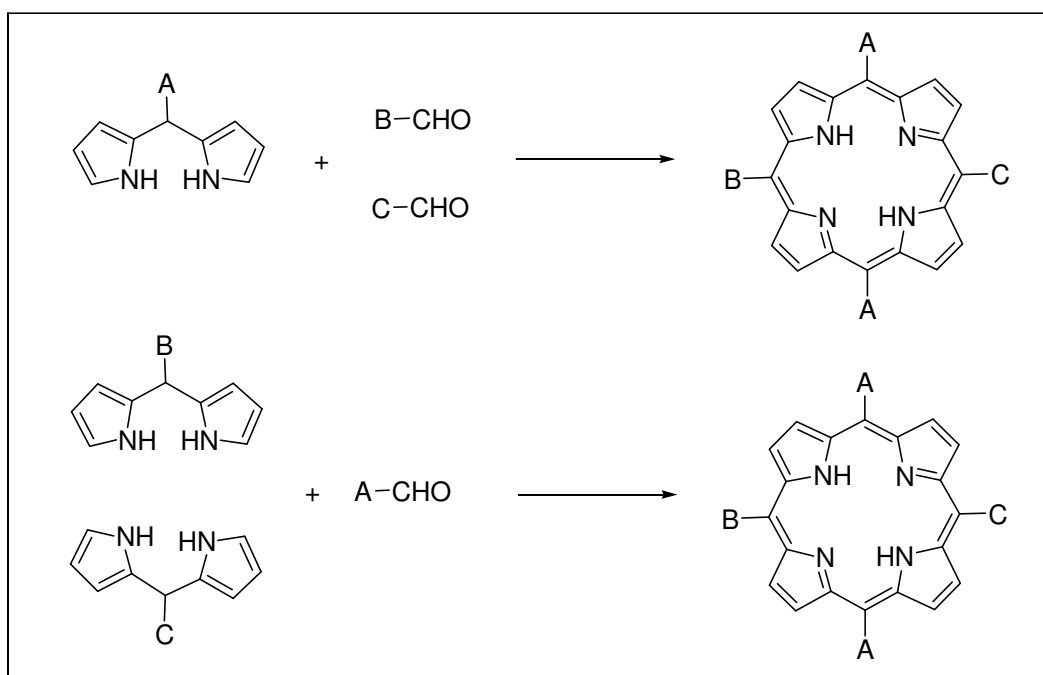
Scheme 5.3. Synthesis of *cis*-A₂B₂ porphyrins

- *trans*-A₂B₂ porphyrins **102** have been prepared by the reaction of an aldehyde with *meso*-substituted dipyrromethane (Scheme 5.4.) (Littler et al., 1999).

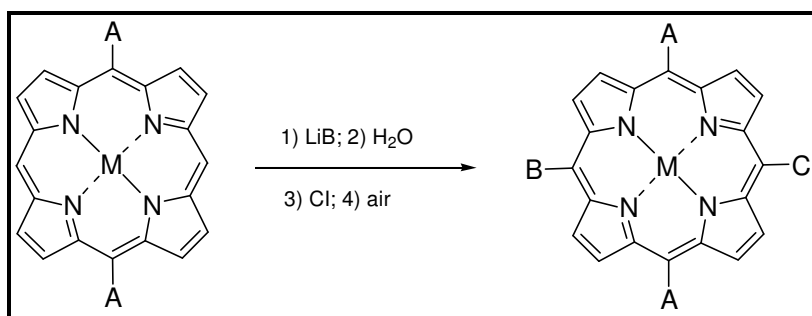


Scheme 5.4. Synthesis of *trans*-A₂B₂ porphyrins

- *cis*-A₂BC porphyrins **103** have not been prepared *via* reasonable routes.
- *trans*-A₂BC porphyrins **104** have been prepared by statistical reaction of a dipyrromethane and two aldehydes, or of two dipyrromethanes and one aldehyde (Scheme 5.5). An alternative route to this class of porphyrins involves treating a 5,15-disubstituted porphyrin with an organolithium reagent, quenching with water, and then treating with an alkyl iodide followed by oxidation (Scheme 5.6) (Lee et al., 1995; Feng and Senge, 2000).

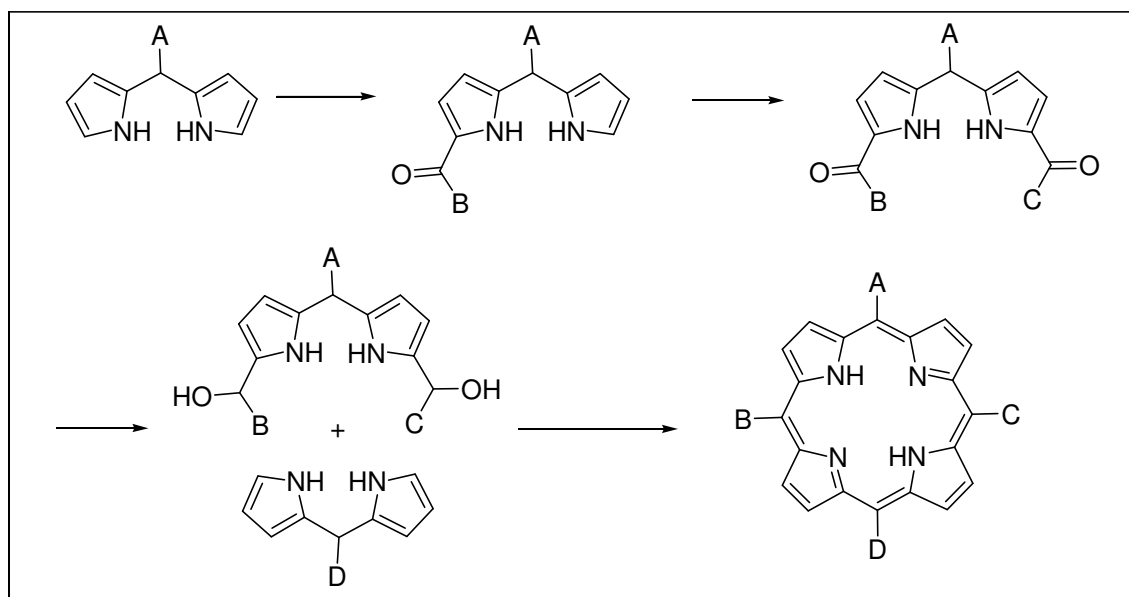


Scheme 5.5. Synthesis of *trans*-A₂BC porphyrins *via* dipyrromethanes



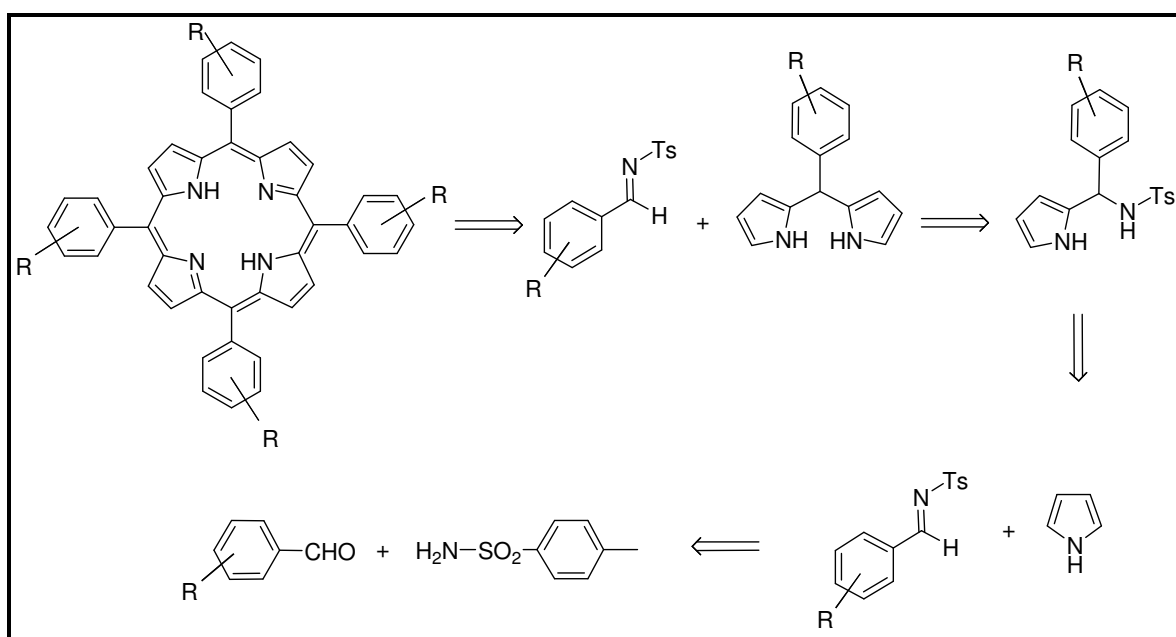
Scheme 5.6. Synthesis of *trans*-A₂BC porphyrins *via* organolithium reagents

- ABCD porphyrins **105** have been prepared in small amounts by a rational approach involving sequential introduction of acyl groups onto the dipyrromethane nucleus, followed by reduction to the dipyrromethane – dicarbinol, and then condensation of the dipyrromethane-dicarbinol with a dipyrromethane (Scheme 5.7) (Lee et al., 1995).



Scheme 5.7. Synthesis of ABCD porphyrins

As outlined above, there are several ways to synthesize *meso*-substituted porphyrins. *meso*-Substituted dipyrromethanes play a central role for the synthesis of these compounds. Because of the importances of dipyrromethanes and porphyrins, it was aimed in this thesis to develop a new metal triflate catalysed method for the synthesis of 2-substituted pyrrolesulfonamides, *meso*-substituted dipyrromethanes and *meso*-substituted porphyrins, as outlined in retrosynthetic pathway (Scheme 5.8).



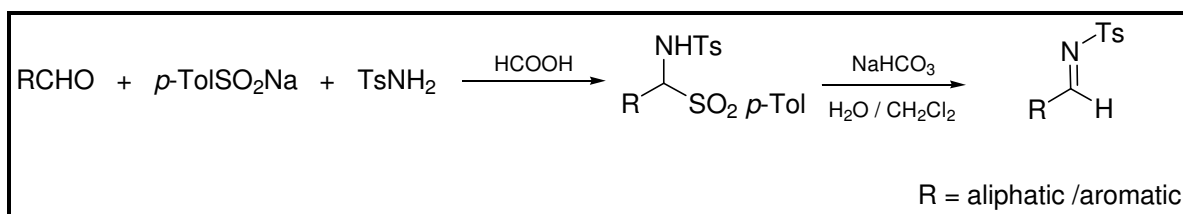
Scheme 5.8. Retrosynthetic pathway

As described in the retrosynthetic pathway, several phenyl substituted *N*-tosyl imines were synthesized to react with pyrrole in the presence of metal triflates catalysts.

5.2. Synthesis of *N*-Tosyl Imines

N-tosyl imines are versatile synthetic intermediates in organic chemistry. They are activated imines and this property supplies an advantage to *N*-tosyl imines in the addition reactions. *N*-Tosyl imines are used in olefination reactions and various C-C bond forming reactions such as aminomethylation of aromatic compounds (Wynne and Stalick, 2002), nitro-Mannich reactions (Qian et al., 2001), asymmetric alkylation reactions (Soeta et al., 2003), [3+2] cycloaddition reactions (Xu and Lu, 1998) and aza Diels-Alder reactions (Mancheno et al., 2004).

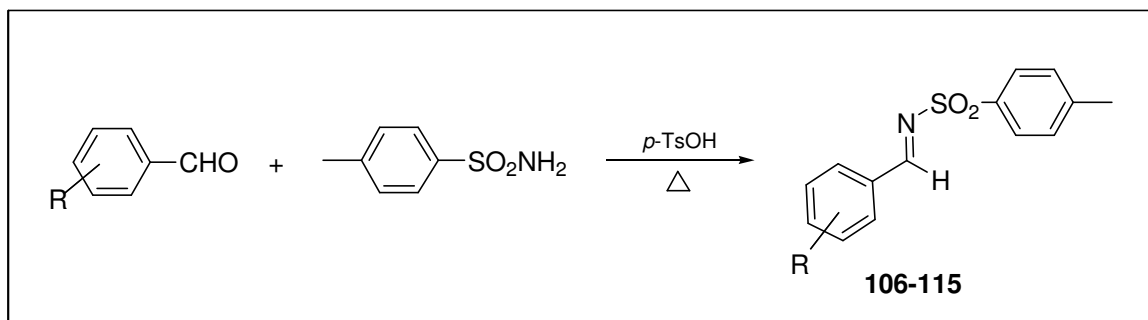
There are many well established methods in the literature to synthesize *N*-sulfonyl imines involving the rearrangement of oxime *O*-sulfinates (Boger and Corbett, 1992), Lewis acid- or solid acid-catalysed reactions (Davis et al., 1980; Jin et al., 2003), use of methyl orthosilicate (Love et al., 1994), halogen mediated conversion of *N*-(trimethylsilyl)imines in the presence of corresponding sulfonyl chloride (Georg et al., 1995). Most useful synthesis of these compounds was reported by Chemla et al. in 2000 for both aliphatic and aromatic group substituted *N*-tosyl imines (Scheme 5.9).



Scheme 5.9. Synthesis of aliphatic and aromatic group substituted *N*-tosyl imines

In the first part of the study the starting compounds, *N*-tosyl imines, were synthesized by the condensation of aromatic aldehydes with *p*-toluenesulfonamide using *p*-TsOH as catalyst as reported in the literature by Padwa et al. (2003). The

reactions were carried out with Dien-Stark trap under reflux for 10 hours (Scheme 5.10). Crude products were crystallized from benzene or petroleum ether and *N*-tosyl imine derivatives **106-115** were obtained in the range of 70 and 90% yield. The highest yield was obtained with strong electron withdrawing trifluoromethyl group as 92% yield.



Scheme 5.10. Synthesis of *N*-tosyl imines

The structures of *N*-tosyl imines were identified by using ^1H NMR, ^{13}C NMR and FTIR techniques. Chemical yields, characteristic ^1H NMR and ^{13}C NMR peak values of synthesized *N*-tosyl imines are given in Table 5.1. The characteristic imine proton appears at ~ 9 ppm in ^1H NMR spectrums and the imine carbons give a signal at ~ 170 ppm. ^1H NMR and ^{13}C NMR spectrums of *N*-tosyl imines **107-115** are given in Figure 5.21 – 5.38 (page 130-138). Structures are in agreement with the known structures of **106-115** in the literature (Chemla et al., 2000).

Table 5.1. Chemical yields and important spectroscopic values of synthesized *N*-tosyl imines

Entry	<i>N</i> -Tosyl imine	R	Yield (%) ^a	^1H NMR values of CH=NR (ppm) ^b	^{13}C NMR values of CH=NR (ppm) ^b
1	106	H	80	9.04	169.69
2	107	p-OCH ₃	84	8.95	168.83
3	108	o-OCH ₃	73	9.52	165.86
4	109	p-CH ₃	81	9.00	169.53
5	110	o-OH	70	9.09	171.18
6	111	p-NO ₂	90	9.13	167.26
7	112	p-CF ₃	92	9.10	167.97
8	113	p-F	75	9.00	168.06
9	114	p-Cl	75	9.01	168.60
10	115	p-Br	72	9.00	168.60

^a Yield refers to pure product after crystallization.

^b NMR solvent is CDCl₃.

N-benzylidene-4-methylbenzenesulfonamide (**106**) was synthesized in 80 % yield. The ^1H NMR and ^{13}C NMR spectra of **106** is given in Figure 5.2 and Figure 5.3. CH_3 protons of tolyl group appear at 2.47 ppm and aromatic protons of the compound give signals between 7.36 and 7.96 ppm. The characteristic imine CH proton gives a singlet signal at 9.04 ppm.

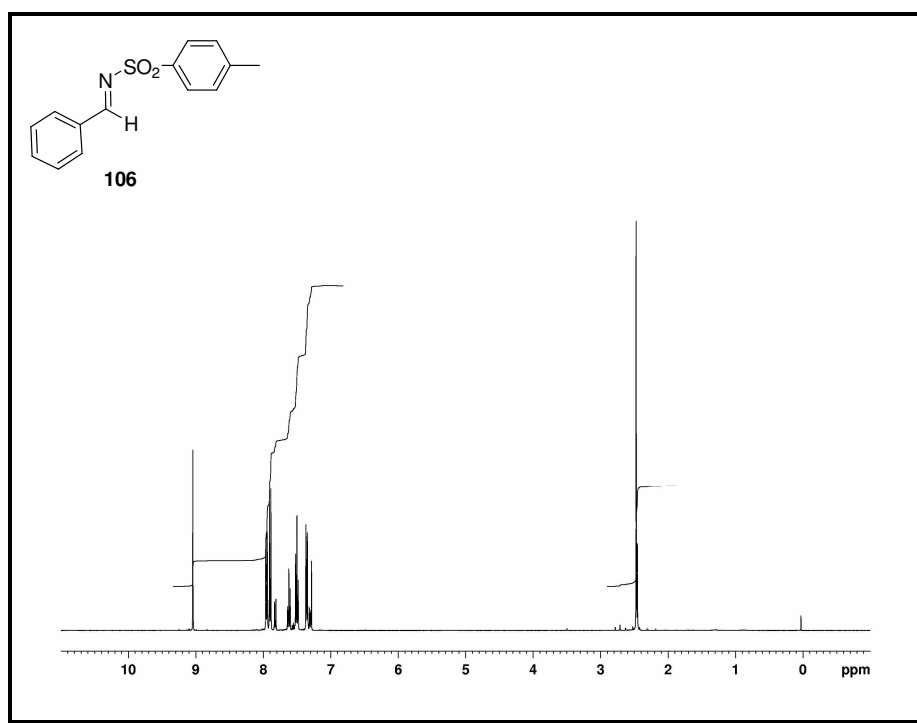


Figure 5.2. ^1H NMR spectrum of **106** in CDCl_3 - CCl_4

^{13}C NMR spectrum of the compound also confirms the related structure (Figure 5.3). Methyl carbon gives a signal at 21.66 ppm and aromatic carbons appear between 126.54 and 144.16 ppm. Imine functional group carbon appears at 169.69 ppm.

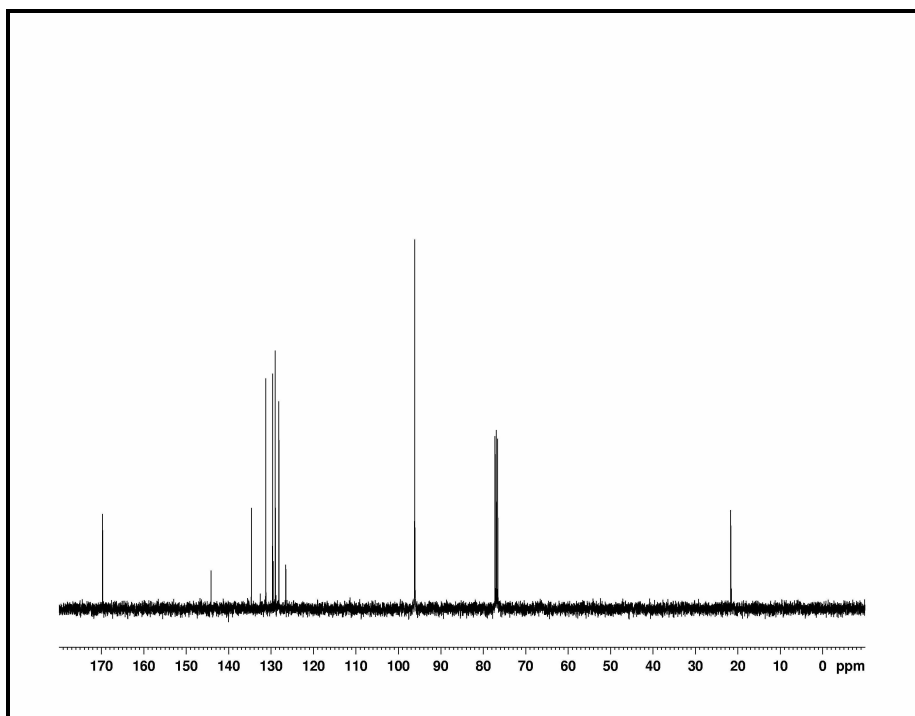


Figure 5.3. ^{13}C NMR spectrum of **106** in $\text{CDCl}_3\text{-CCl}_4$

5.3. Metal triflate catalysed regioselective addition of pyrrole to *N*-tosyl imines

The Lewis acid mediated Friedel-Crafts reaction is one of the most important reactions in organic synthesis. It provides a useful method for the direct introduction of a functional group onto heterocycles or aromatic compounds. Aminoalkylation by Lewis acids is also a quite powerful tool for the synthesis of heterocycles that contain amino group, a structure which is broadly found in a large number of natural products and biologically active substances. Amino alkylated pyrrole derivatives have important usage areas in medicine. For example; pyrrole Mannich base **116** (Thurkauf et al., 1995) used as potential antipsychotic agents and **117** (Biava et al., 2003) shows significant degree of antifungal and antimycobacterial activities (Figure 5.4).

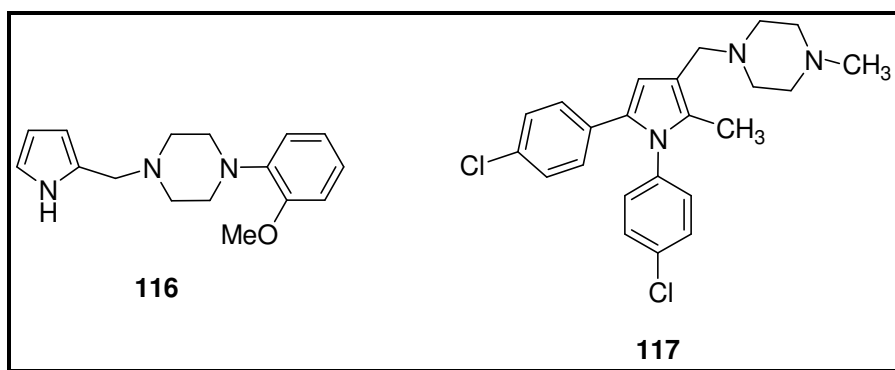


Figure 5.4. Examples of important aminoalkylated pyrroles

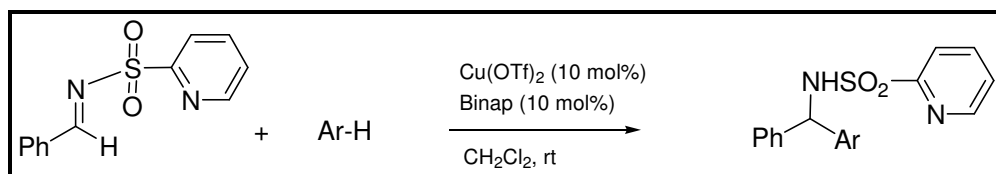
The most common method for *C*-aminoalkylation of pyrroles reported in the literature is the reaction of formaldehyde with an amine hydrochloride, a process known as the Mannich reaction. This method is useful when secondary amines are used but there are some side products and low yield problems with primary amines.

The other method involves the reactions of pyrrole compounds with imines that are activated by protonation using acids or by complexation with Lewis acids. However, acid catalysed reactions of pyrroles are limited because of their sensitivity to acids. The reactions of nitrogen-containing compounds activated with a catalytic amount of conventional Lewis acids are also limited due to their deactivation by strong coordination to the Lewis acid and in many cases stoichiometric amounts of the acid are required.

In the last decade, metal triflate catalyzed organic reactions have attracted great deal of attention. They have been used as waterstable and reuseable Lewis acids in several carbon–carbon bond forming reactions such as Aldol, Michael, Diels–Alder and Friedel–Crafts acylation and alkylations. Metal triflates are also efficient catalysts for the synthesis of nitrogen-containing compounds due to their high activity towards imines and they have several advantages as compared to conventional Lewis acids as stated in Section 2.7.

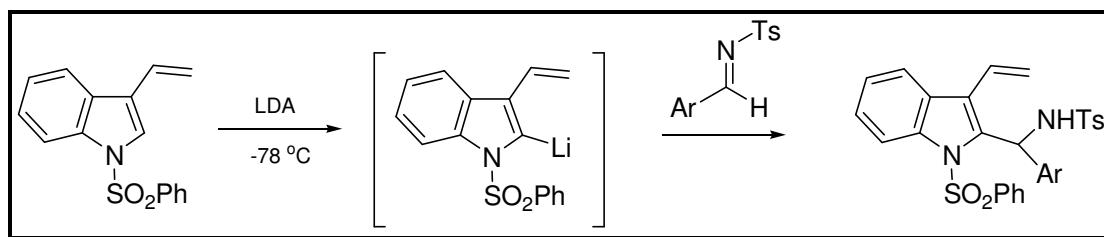
Recent example of metal triflate catalysed addition reaction to imine compounds was reported by Esquivias et al. (2006). The researchers have developed

Cu(OTf)₂-Binap catalysed Friedel-Crafts reaction of *N*-sulfonylimines with aromatic compounds (indole, furan, thiophene, naphthalene and benzene) (Scheme 5.11).



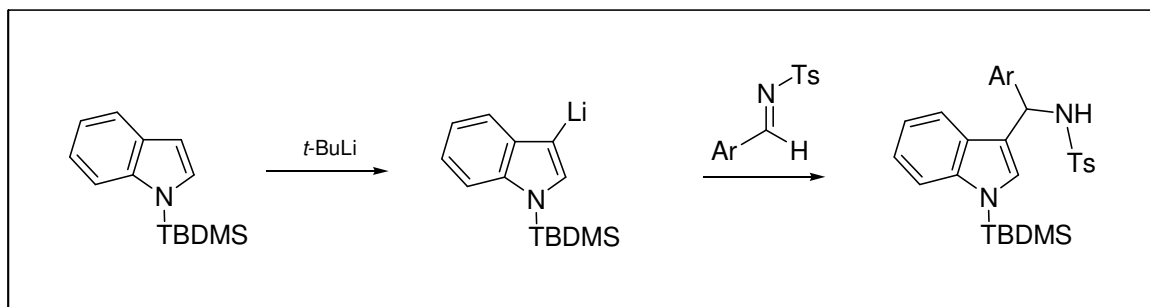
Scheme 5.11. Cu(OTf)₂-binap catalysed Friedel-Crafts reaction of *N*-sulfonylimines

N-tosyl imines were used to attach the amino group to heterocyclic compounds by the addition of indoles to *N*-tosyl imines in the presence of strong bases such as *t*-BuLi or LDA. For example; Love and Raje (1994) obtained 2-substituted indolesulfonamide derivatives in good yields (59-78 %) by treatment of indole with LDA at -78 °C and then reacting with aryl *N*-tosyl imines (Scheme 5.12).



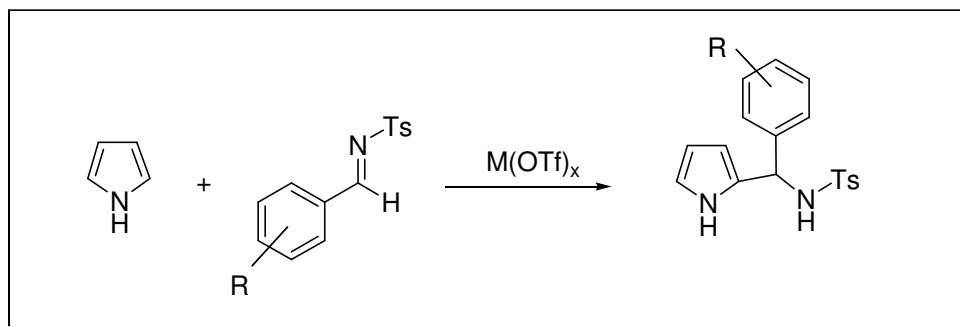
Scheme 5.12. Synthesis 2-substituted indolesulfonamide derivatives with LDA

Wyne and Stalick (2003) were used *t*-BuLi for lithation of indole. Obtained lithium salt of indole was reacted with *N*-tosyl imines to obtain 3-substituted indole derivatives (Scheme 5.13).



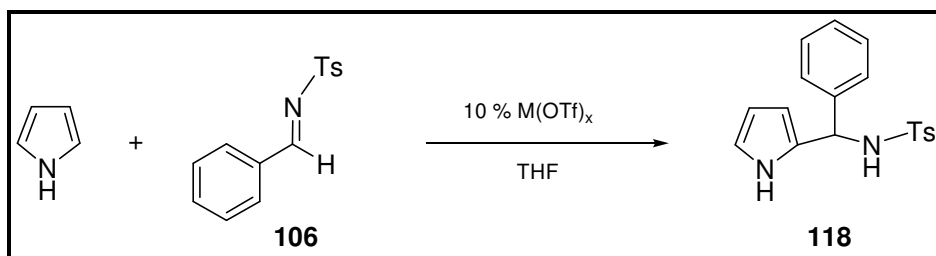
Scheme 5.13. Synthesis of 3-substituted indolesulfonamide derivatives with *t*-BuLi

In the second step of the study, we focused on metal triflates catalysed additions of pyrrole to *N*-tosyl imines in order to obtain 2-aminoalkylated pyrrole derivatives (Scheme 5.14). To our knowledge; there is no example of such a addition reaction of pyrrole to *N*-tosyl imines in the literature.



Scheme 5.14. Metal triflate catalysed addition of pyrrole to *N*-tosyl imines

The addition of pyrrole to *N*-benzylidene-4-methylbenzenesulfonamide (**106**) was chosen as a model reaction (Scheme 5.15) and different metal triflates used at -20 °C, 0 °C, and rt to compare the activity of catalysts on the addition reaction (Table 5.2.).



Scheme 5.15 The model reaction to optimize the conditions of addition reactions.

The addition reaction was carried out by mixing *N*-tosyl imine and metal triflate for 30 minutes in THF for complexation and activation of imines. Then the solution of pyrrole in THF was added dropwise to the mixture. The reaction was monitored with TLC and completed in 6 hours.

The addition product 4-Methyl-*N*-(phenyl(1*H*-pyrrol-2-yl)methyl)-benzenesulfonamide **118** was formed in 47% yield at 0 °C only with Cu(OTf)₂ (Table 5.2). The other metal triflates catalysed the addition reaction at rt but only with low yields (5–40%) and no addition product was observed at -20 °C.

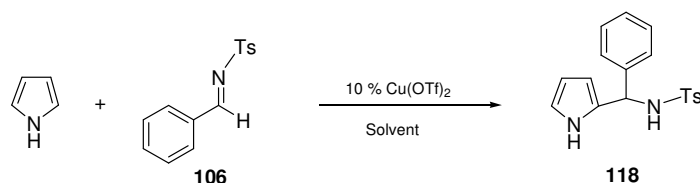
Table 5.2. The effect of different metal triflates on the addition reactions at different temperatures

Entry	M	-20 °C Yield (%) ^a	0 °C Yield (%) ^a	r.t. Yield (%) ^a
1	Cu	-	47	40
2	Zn	-	-	20
3	La	-	-	15
4	Nd	-	-	12
5	Ga	-	-	5
6	Yb	-	-	10
7	Y	-	-	30

^a Yield refers to pure product after column chromatography.

The effect of solvent was investigated on the model addition reaction in the presence of 10 mol % Cu(OTf)₂ at 0 °C. Of various organic solvents, CH₃CN, acetone, THF, Et₂O, DCM and toluene, the best chemical yield (47%) was obtained in THF (Table 5.3.).

Table 5.3. The effect of different solvents on the addition reactions



Solvent	CH ₃ CN	Acetone	THF	Et ₂ O	Toluene	DCM
Yield (%) ^a	-	25	47	30	26	25

^a Yield refers to pure product after column chromatography.

Identification of the compound **118** was achieved by ^1H NMR, ^{13}C NMR, FTIR techniques and elemental analysis. Figure 5.5 shows the ^1H NMR spectrum of **118**. CH_3 protons of tosyl group appear as singlet at 2.38 ppm. CH-NTs proton and pyrrole C3-H give multiplet between 5.57–5.60 ppm. NH proton of sulfonamide group gives doublet at 5.85 ppm ($J=9.9$ Hz). Characteristic pyrrole signals of C4-H and C5-H appear at 5.97 (dd, $J=2.8, 6.0$) and 6.65 (dd, $J=2.5, 4.0$) respectively. Aromatic protons of phenyl groups can be seen as multiplet between 7.09 and 7.53. The broad signal at 8.76 ppm belongs to NH proton of the pyrrole ring.

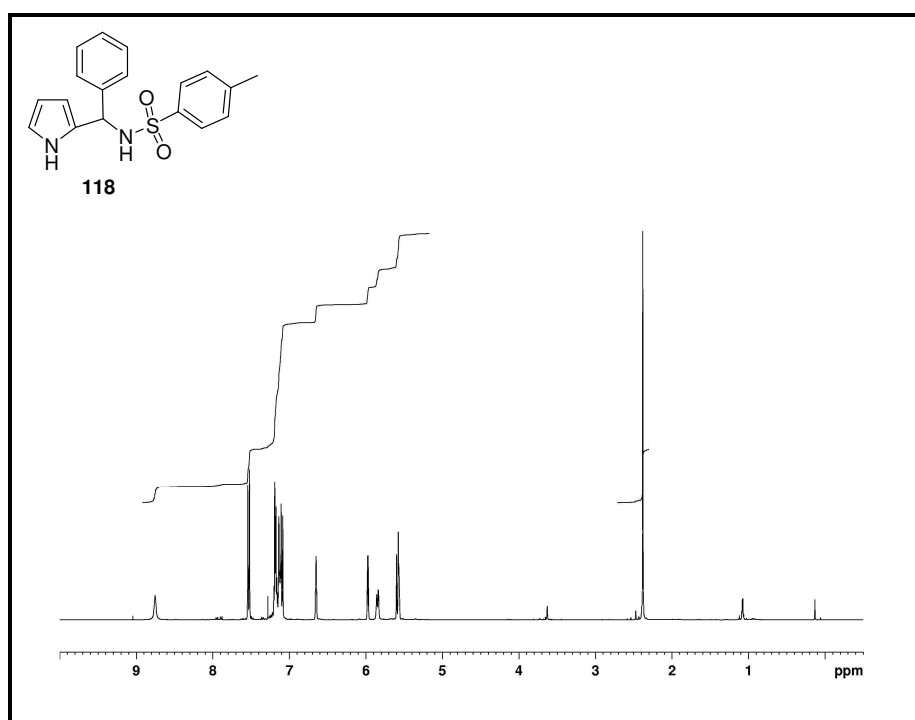


Figure 5.5. ^1H NMR spectrum of **118** in $\text{CDCl}_3\text{-CCl}_4$

^{13}C NMR spectrum of **118** (Figure 5.6) also confirms the suggested structure. Typical signal at 21.49 ppm belongs to methyl carbon. CH-NH carbon gives signal at 55.78 ppm. Signals belongs to pyrrole ring appear at 108.20 ppm, 118.57 ppm, and 130.53.

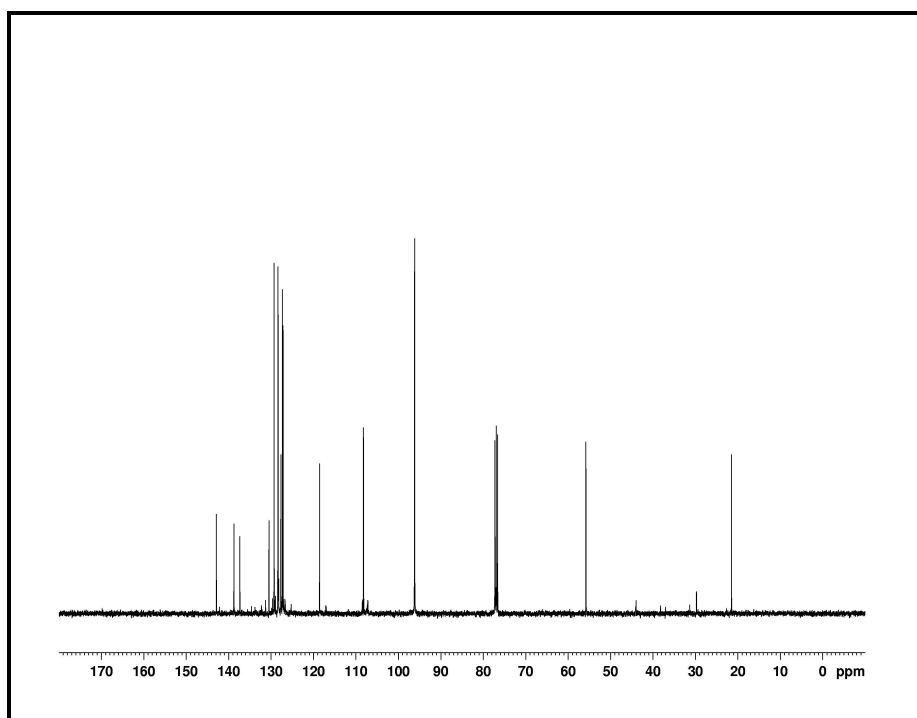
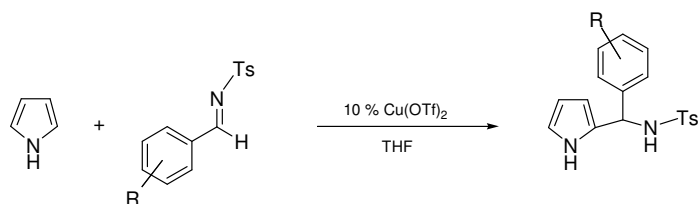


Figure 5.6. ^{13}C NMR spectrum of **118** in $\text{CDCl}_3\text{-CCl}_4$.

After the optimisation of the effect of different metal triflates and solvents on the reaction yield, the reactions of pyrrole with tosyl imines having different substituents in the presence of $\text{Cu}(\text{OTf})_2$ catalysis in THF were carried out at 0 °C and room temperature. The results of these reactions (Table 5.4.) indicate that 0 °C is more suitable temperature for addition reactions in all cases. Tosyl imines bearing electron withdrawing groups (Table 5.4., entry 6 and 7) gave higher yields of addition products than electron donating groups (Table 5.4., entry 1-4). OH substituted pyrrolesulfonamide derivative decomposed after the reaction and could not be isolated by flash column chromatography or crystallization (Table 5.4.-entry 5).

Table 5.4. The effect of substituent on the addition reaction.



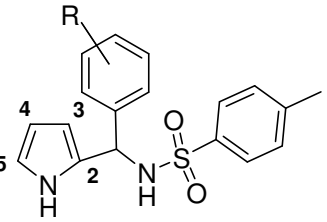
Entry	2-Akylated Pyrrole	R	0 °C, Yield (%) ^a	rt, Yield (%) ^a
1	118	H	47	40
2	119	p-OCH ₃	64	52
3	120	o-OCH ₃	65	65
4	121	p-CH ₃	52	44
5	-	o-OH	- ^b	- ^b
6	122	p-NO ₂	85	72
7	123	p-CF ₃	82	71
8	124	p-F	70	58
9	125	p-Cl	68	61
10	126	p-Br	62	57

^a Yield refers to pure product after column chromatography.

^b Addition product decomposed and could not be isolated by column chromatography.

Structures of novel 2-substituted pyrrole sulfonamides **118-126** are identified by using ¹H NMR, ¹³C NMR, FTIR techniques. ¹H NMR and ¹³C NMR spectra of the synthesized compounds are given in Figure 5.39 – 5.54 (page 139-146). Table 5.5. and Table 5.6. summarize some important ¹H and ¹³C NMR spectrum values of pyrrole derivatives.

Table 5.5. Important ^1H NMR values of synthesized pyrrole sulfonamide derivatives

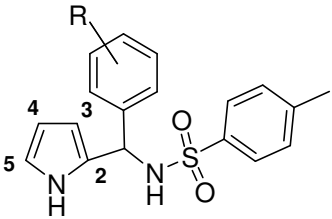
	<u>Pyrrolesulfonamide</u>	<u>R</u>	<u>Pyrrolesulfonamide</u>	<u>R</u>
	118	H	123	4-CF ₃
	119	4-OCH ₃	124	4-F
	120	2-OCH ₃	125	4-Cl
	121	4-CH ₃	126	4-Br
	122	4-NO ₂		

^1H NMR (ppm) ^{a,b}						
Compound	CH-NTs	NHTs	Pyrrole C3-H	Pyrrole C4-H	Pyrrole C5-H	Pyrrole N-H
118	5.57–5.60 (m)	5.85 (d, J = 9.9)	5.57–5.60 (m)	5.97 (dd, J = 2.8, 6.0)	6.65 (dd, J = 2.5, 4.0)	8.76 (br s)
119	5.50 (d, J = 8.1)	5.57–5.59 (m)	5.57–5.59 (m)	5.98 (dd, J = 2.7, 6.0)	6.67 (br s)	8.72 (br s)
120	5.64 (d, J = 9.3)	5.90 (d, J = 9.1)	5.51 (br s)	5.97 (dd, J = 2.8, 5.8)	6.70 (dd, J = 2.5, 4.1)	8.72 (br s)
121	5.52 (d, J = 8.2)	5.62 (d, J = 8.0)	5.58 (br s)	5.98 (dd, J = 2.8, 5.7)	6.66 (br s)	8.62 (br s)
122	5.70 (br s)	5.29 (br s)	5.52 (br s)	6.02 (dd, J = 2.8, 6.0)	6.76 (dd, J = 2.6, 4.0)	8.56 (br s)
123	5.69 (d, J = 8.6)	6.00–6.03 (m)	5.55 (br s)	6.00–6.03 (m)	6.69 (br s)	8.86 (br s)
124	5.57 (d, J = 8.4)	5.86 (d, J = 8.4)	5.54 (br s)	5.98 (dd, J = 2.7, 5.9)	6.67 (dd, J = 2.6, 4.1)	8.77 (br s)
125	5.54–5.57 (m)	5.88 (d, J = 8.5)	5.54–5.57 (m)	5.98 (dd, J = 2.7, 6.0)	6.65–6.66 (m)	8.79 (br s)
126	5.55–5.57 (m)	5.97–6.00 (m)	5.55–5.57 (m)	5.97–6.00 (m)	6.66 (dd, J = 2.5, 4.0)	8.83 (br s)

^a NMR solvent is CDCl₃.

^b Temelli and Unaleroglu, 2005; 2006

Table 5.6. Important ^{13}C NMR values of synthesized pyrrole sulfonamide derivatives

	<u>Pyrrolesulfonamide</u>	<u>R</u>	<u>Pyrrolesulfonamide</u>	<u>R</u>
	118	H	123	4-CF ₃
	119	4-OCH ₃	124	4-F
	120	2-OCH ₃	125	4-Cl
	121	4-CH ₃	126	4-Br
	122	4-NO ₂		

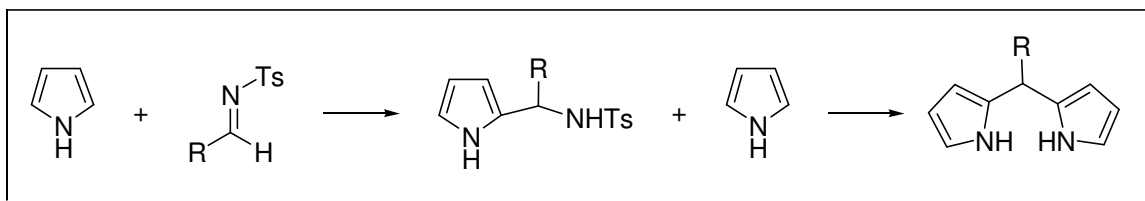
^{13}C NMR (ppm) ^{a,b}					
Compound	CH-NTs	Pyrrole C2	Pyrrole C3	Pyrrole C4	Pyrrole C5
118	55.78	130.53	108.20	108.20	118.57
119	55.09	130.90	108.08	108.19	118.51
120	53.85	129.60	107.04	108.26	118.01
121	55.64	130.78	108.13	108.17	118.51
122	55.06	129.56	108.69	108.69	119.38
123	55.66	129.49	108.36	108.61	119.15
124	55.27	129.37	108.25	108.25	118.81
125	55.34	129.92	108.27	108.40	118.91
126	55.42	129.79	108.27	108.43	118.94

^a NMR solvent is CDCl₃.

^b Temelli and Unaleroglu, 2005; 2006

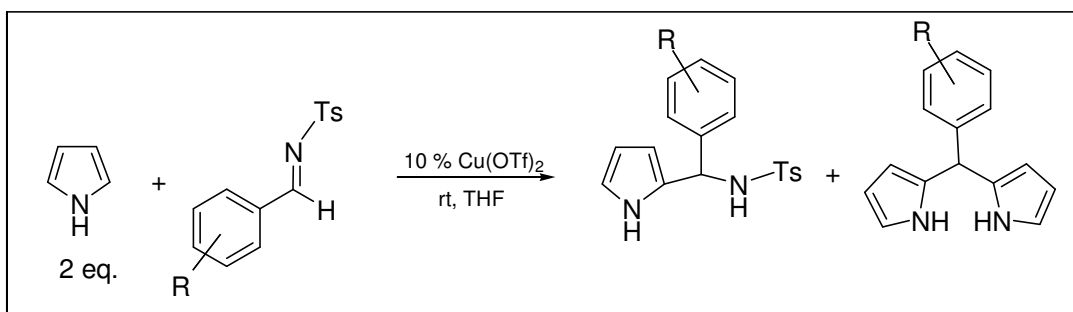
5.4. Synthesis of 5-Substituted Dipyrromethanes

The next step of the study was to synthesize 5-substituted dipyrromethanes from the reaction of *N*-tosyl imines and pyrrole. *N*-tosyl group is known as good leaving group in organic reactions and so we decided to introduce a second pyrrole addition to synthesized 2-alkylated pyrrole derivatives in order to reach the target, 5-substituted dipyrromethanes (Scheme 5.16).



Scheme 5.16. Synthetic plan for the 5-substituted dipyrromethanes

Consequently, the addition reactions of pyrrole with *N*-tosyl imines were repeated by using two equivalents of pyrrole (Scheme 5.17). The reactions were performed at room temperature for 6 hours in THF and 5-substituted dipyrromethanes were obtained in some cases as a minor product (Table 5.7). The distribution of the products depends on the nature of the substituents. While electron donating groups giving dipyrromethanes in yield ranging between 15 and 25%, strong electron withdrawing groups NO₂ and CF₃ and ortho hydroxy substituted tosyl imines didn't give dipyrromethane side products (Table 5.7., entry 3,6,7).



Scheme 5.17. The reaction of *N*-tosyl imines with 2 equivalents of pyrrole.

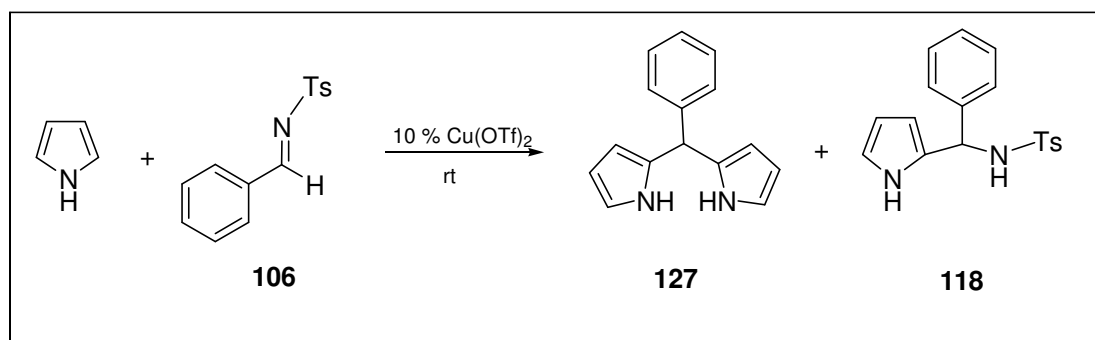
Table 5.7. Yields of the reaction of 2 equivalents of pyrrole with *N*-tosyl imines

Entry	R	2-Alkylated Pyrroles Yield (%) ^a	5-substituted dipyrromethanes Yield (%) ^a
1	H	55	20
2	p-OCH ₃	53	18
3	o-OCH ₃	70	-
4	p-CH ₃	44	25
5	o-OH	- ^b	17
6	p-NO ₂	80	-
7	p-CF ₃	74	-
8	p-F	63	15
9	p-Cl	60	15
10	p-Br	55	20

^a Yield refers to pure product after column chromatography.

^b Addition product decomposed and could not be isolated by column chromatography.

After this examination, we focused on obtaining the 5-substituted dipyrromethane as the major product from the reaction of pyrrole and *N*-benzylidene-4-methylbenzenesulfonamide (**106**). We performed the reaction of pyrrole with **106** by using different pyrrole/*N*-tosyl imine ratios in the presence of copper triflate (10 mol %) at rt (Scheme 5.18, Table 5.8).



Scheme 5.18. The reaction of *N*-benzylidene-4-methylbenzenesulfonamide (**106**) with pyrrole in the presence of Cu(OTf)₂

Reactions with 10 and 20 equiv of pyrrole were carried out in THF, monitored with TLC, completed after 6 h and afforded **127/118** with 34/37 and 40/32% yields, respectively (Table 5.8). When the reaction was performed with 40 equiv of pyrrole

without solvent, dipyrromethane **127** was formed as the major product in 55% yield. Increasing the pyrrole equivalent did not obviously affect the yield of **127**.

Table 5.8. The effect of different pyrrole to *N*-tosyl imine ratio on the yield at rt.

Mole Ratio	Yield (%)^a	
Tosyl Imine : Pyrrole	Dipyrromethane 127 / Addition Product 118	Solvent
1 : 1	- / 40	THF
1 : 2	20 / 55	THF
1 : 10	34 / 37	THF
1 : 20	40 / 32	THF
1 : 40	55 / 16	- ^b
1 : 60	53 / 20	- ^b

^a Yield refers to pure product after column chromatography.

^b Reactions were carried out in excess pyrrole as solvent.

To investigate the effects of metal triflates, the reactions of pyrrole and *N*-benzylidene-4-methylbenzenesulfonamide **106** were carried out in the presence of different metal triflates with excess pyrrole (40 equiv) at rt. Among all the metal triflates tested, Gd(OTf)₃ and Cu(OTf)₂ gave the highest yields of 5-phenyldipyrromethane (**127**), 69 and 55%, respectively (Table 5.9).

Table 5.9. The effect of different metal triflates on the addition of pyrrole to *N*-tosyl imine^a

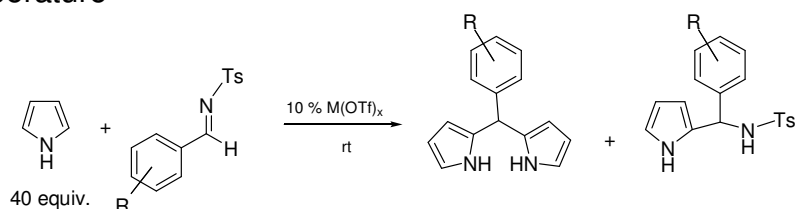
Entry	Catalyst	Yield (%)^b 127/118
1	Cu(OTf) ₂	55/16
2	Gd(OTf) ₃	69/20
3	Yb(OTf) ₃	52/38
4	Y(OTf) ₃	45/43
5	La(OTf) ₃	34/53
6	Zn(OTf) ₂	23/60
7	Nd(OTf) ₃	14/72

^a Reactions were carried out in excess pyrrole (40 equiv) as solvent at rt.

^b Yield refers to pure product after column chromatography

We continued to study the effect of substituents on the phenyl ring of the *N*-tosyl imines using $\text{Cu}(\text{OTf})_2$ and $\text{Gd}(\text{OTf})_3$ on the synthesis of 5-substituted dipyrromethanes. Reactions of *N*-tosyl imines **106-115** and pyrrole with $\text{Gd}(\text{OTf})_3$ catalyst gave 2-alkylated pyrrole sulfonamides **118-126** in 10–85% yields and 5-substituted dipyrromethanes **127-136** in 5–90% yields (Table 5.10.). Similar results were obtained when $\text{Cu}(\text{OTf})_2$ was used as the catalyst at rt; the corresponding pyrrole derivatives were obtained in 7–86% yields and dipyrromethanes in 5–85% yields (Table 5.10.).

Table 5.10. $\text{Gd}(\text{OTf})_3$ and $\text{Cu}(\text{OTf})_2$ catalysed addition of pyrrole to *N*-tosyl imines at room temperature^a



		Yield (%) ^b		Products
		Dipyrromethane / Addition Product		
		Catalyst		
	R	Gd(OTf) ₃	Cu(OTf) ₂	
1	H	69 / 20	55 / 16	127 / 118
2	p-OCH ₃	83 / 10	85 / 8	128 / 119
3	o-OCH ₃	71 / 17	55 / 20	129 / 120
4	p-CH ₃	83 / 10	80 / 7	130 / 121
5	o-OH	90 / - ^c	77 / - ^c	131 / -
6	p-NO ₂	5 / 85	7 / 78	132 / 123
7	p-CF ₃	11 / 82	5 / 86	133 / 123
8	p-F	40 / 50	38 / 45	134 / 124
9	p-Cl	44 / 46	40 / 55	135 / 125
10	p-Br	20 / 71	38 / 53	136 / 126

^a Reactions were carried out in excess pyrrole (40 equiv) as solvent.

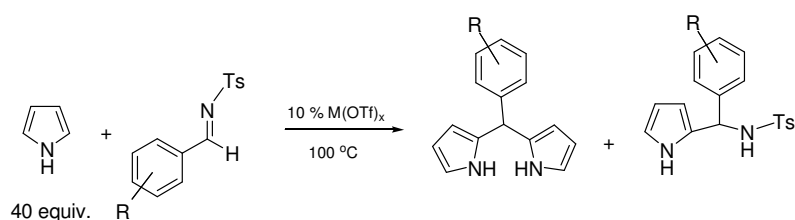
^b Yield refers to pure product after column chromatography.

^c Addition product decomposed and could not be isolated by column chromatography.

For both catalysts, formation of the products is very sensitive to the nature of the substituents on *N*-tosyl imine. When the phenyl ring bears an electron donating substituent such as a methyl, hydroxy or methoxy, dipyrromethane products are obtained in high yields (Table 5.10., entries 2–5). The reactions with electron withdrawing groups such as nitro, trifluoromethyl or halogens on the phenyl ring gave 5-substituted dipyrromethanes in lower yields at rt (Table 5.10., entries 6–10).

To improve the yields of dipyrromethane products having electron withdrawing substituents, reactions were carried out at 100 °C (Table 5.11).

Table 5.11. Gd(OTf)₃ and Cu(OTf)₂ catalysed addition of pyrrole to *N*-tosyl imines at 100 °C^a



Entry	R	Yield (%) ^b		
		Dipyrromethane / Addition Product		
		Gd(OTf) ₃	Cu(OTf) ₂	Products
1	H	65 / 17	48 / 10	127 / 118
2	p-OCH ₃	64 / 15	45 / 19	128 / 119
3	o-OCH ₃	61 / 21	48 / 35	129 / 120
4	p-CH ₃	69 / 9	35 / 11	130 / 121
5	o-OH	44 / - ^c	27 / - ^c	131 / -
6	p-NO ₂	79 / 8	72 / 9	132 / 123
7	p-CF ₃	68 / 13	85 / 6	133 / 123
8	p-F	70 / 14	53 / 32	134 / 124
9	p-Cl	71 / 13	62 / 25	135 / 125
10	p-Br	74 / 12	74 / 14	136 / 126

^a Reactions were carried out in excess pyrrole (40 equiv) as solvent.

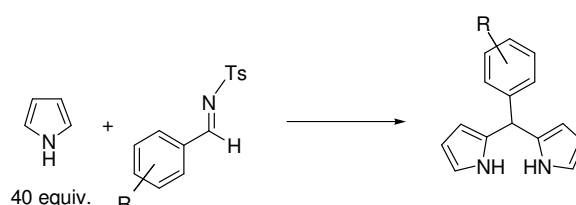
^b Yield refers to pure product after column chromatography.

^c Addition product decomposed and could not be isolated by column chromatography.

It was observed that at high temperatures the yields of dipyrromethane products with electron withdrawing substituents and halogens increase dramatically (Table 5.11., entries 6–10). Dipyrromethanes with strongly electron withdrawing groups (nitro, trifluoromethyl) and halogens were synthesized in 68–79% yields with $\text{Gd}(\text{OTf})_3$ and in 53–85% yields with $\text{Cu}(\text{OTf})_2$. Despite this increase for electron withdrawing groups at 100 °C, yields for electron donating groups are lower.

So, 5-substituted dipyrromethanes with electron donating or withdrawing substituents (**127-136**) can be obtained in high yields (69-90%) selectively only by tuning the reaction temperature and selecting suitable metal triflate as catalyst. The optimum reaction conditions and catalysts are given in Table 5.12.

Table 5.12. Optimum reaction conditions to obtain 5-substituted dipyrromethanes^a



Entry	R	Optimum Reaction Condition	Yield (%) ^b	Products
1	H	$\text{Gd}(\text{OTf})_3$, rt	69	127
2	p- OCH_3	$\text{Cu}(\text{OTf})_2$, rt	85	128
3	o- OCH_3	$\text{Gd}(\text{OTf})_3$, rt	71	129
4	p- CH_3	$\text{Gd}(\text{OTf})_3$, rt	83	130
5	o- OH	$\text{Gd}(\text{OTf})_3$, rt	90	131
6	p- NO_2	$\text{Gd}(\text{OTf})_3$, 100 °C	79	132
7	p- CF_3	$\text{Cu}(\text{OTf})_2$, 100 °C	85	133
8	p-F	$\text{Gd}(\text{OTf})_3$, 100 °C	70	134
9	p-Cl	$\text{Gd}(\text{OTf})_3$, 100 °C	71	135
10	p-Br	$\text{Gd}(\text{OTf})_3$ or $\text{Cu}(\text{OTf})_2$, 100 °C	74	136

^a Reactions were carried out in excess pyrrole (40 equiv) as solvent.

^b Yield refers to pure product after column chromatography.

Identification of dipyrromethanes (**127-136**) were achieved by ^1H NMR, ^{13}C NMR, FTIR techniques and elemental analysis.

Figure 5.7 shows the ^1H NMR spectrum of 5-Phenyldipyrromethane (**127**). *meso*-Hydrogen of the compound gives singlet at 5.49 ppm. Broad singlet peak at 5.92 ppm belongs to C3-H of pyrrole. C4-H and C5-H protons appear as doublet of doublet at 6.14 ($J = 2.8, 5.9$) and 6.68 ($J = 2.6, 4.2$) respectively. Aromatic protons of phenyl groups can be seen as multiplet between 7.22-7.35 ppm. The broad signal at 7.88 ppm belongs to NH proton of the pyrrole ring.

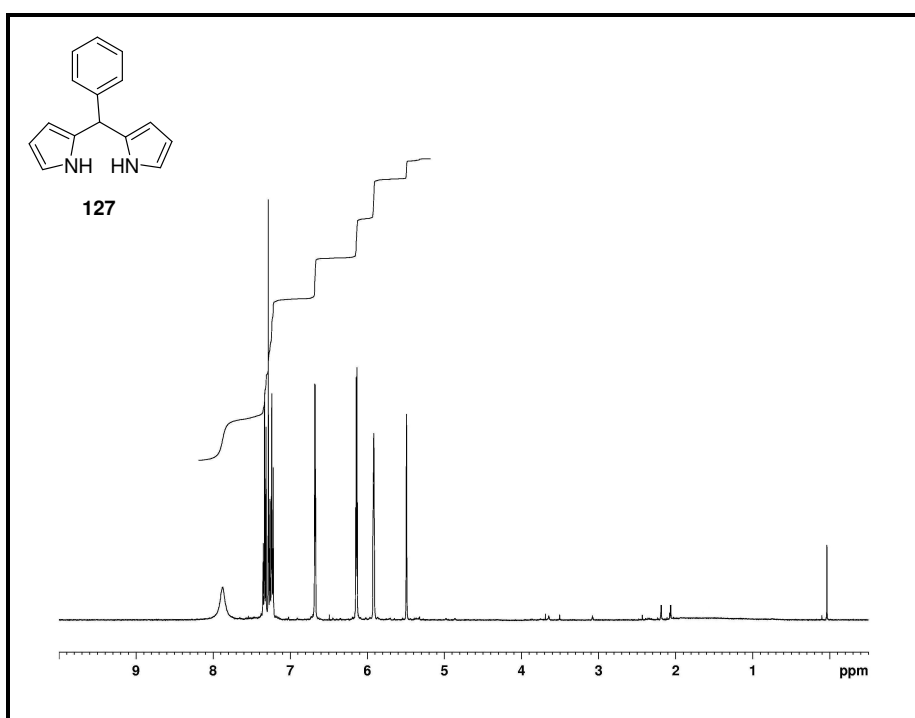


Figure 5.7. ^1H NMR spectrum of **127** in $\text{CDCl}_3\text{-CCl}_4$.

^{13}C NMR spectrum of **127** (Figure 5.8) is also in agreement with the suggested structure. The signal at 44.10 ppm belongs to *meso* carbon. C3, C4 and C5 carbons of pyrrole ring appears at 107.45, 108.75, 117.12 respectively. C2 of pyrrole appears at 132.36 ppm. Other signals belong to phenyl ring of the dipyrromethane structure.

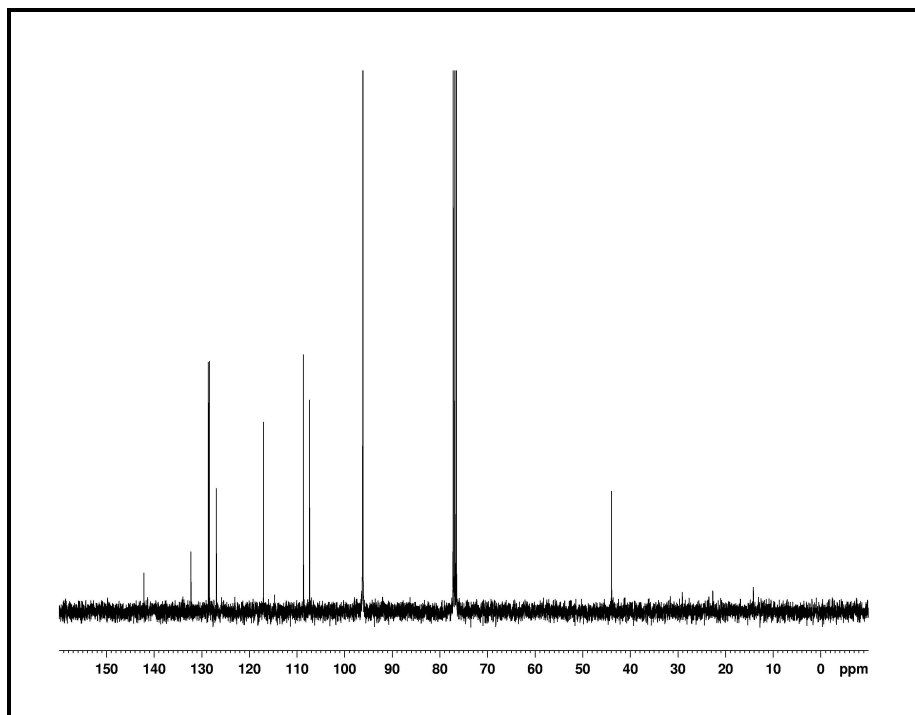
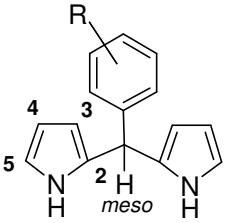


Figure 5.8. ^{13}C NMR spectrum of **127** in $\text{CDCl}_3\text{-CCl}_4$.

^1H NMR and ^{13}C NMR spectra of synthesized dipyrromethanes are given in Figure 5.55 - 5.72, (page 147 - 155). Important ^1H NMR and ^{13}C NMR data for identification of these compounds are given in Table 5.13. and Table 5.14.

Table 5.13. Important ^1H NMR values of synthesized *meso*-substituted dipyrromethane derivatives

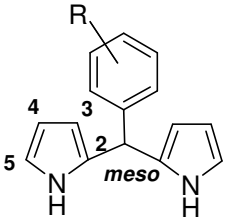
	<u>Dipyrromethane</u>	<u>R</u>	<u>Dipyrromethane</u>	<u>R</u>
	127	H	132	4-NO ₂
	128	4-OCH ₃	133	4-CF ₃
	129	2-OCH ₃	134	4-F
	130	4-CH ₃	135	4-Cl
	131	2-OH	136	4-Br

^1H NMR (ppm) ^a					
Compound	<i>meso</i> -H	Pyrrole C3-H	Pyrrole C4-H	Pyrrole C5-H	Pyrrole N-H
127	5.49 (s)	5.92 (br s)	6.14 (dd, J = 2.8, 5.9)	6.68 (dd, J = 2.6, 4.2)	7.88 (br s)
128	5.42 (s)	5.90–5.92 (m)	6.14 (dd, J = 2.8, 6.0)	6.65–6.67 (m)	7.82 (br s)
129	5.82 (s)	5.91 (br s)	6.15 (d, J = 2.5)	6.63 (d, J = 1.4)	7.97 (br s)
130	5.44 (s)	5.91 (br s)	6.13 (dd, J = 2.8, 5.9)	6.66 (dd, J = 2.6, 4.2)	7.85 (br s)
131	5.53 (s)	6.01 (br s)	6.16 (dd, J = 2.8, 5.9)	6.70 (dd, J = 2.6, 4.1)	8.14 (br s)
132	5.59 (s)	5.88 (br s)	6.18 (dd, J = 2.8, 6.0)	6.75 (dd, J = 2.6, 4.2)	7.98 (br s)
133	5.51 (s)	5.91 (br s)	6.20 (dd, J = 2.8, 6.0)	6.67–6.69 (m)	7.82 (br s)
134	5.45 (s)	5.89 (br s)	6.16 (dd, J = 2.8, 5.8)	6.66 (br s)	7.81 (br s)
135	5.42 (s)	5.90 (br s)	6.17 (dd, J = 2.8, 5.8)	6.66 (dd, J = 2.6, 4.2)	7.80 (br s)
136	5.41 (s)	5.90 (br s)	6.16 (dd, J = 2.8, 5.9)	6.66 (dd, J = 2.6, 4.2)	7.80 (br s)

^a NMR solvent is CDCl₃.

^b Temelli and Unaleroglu, 2005; 2006.

Table 5.14. Important ^{13}C NMR values of synthesized *meso*-substituted dipyrromethane derivatives

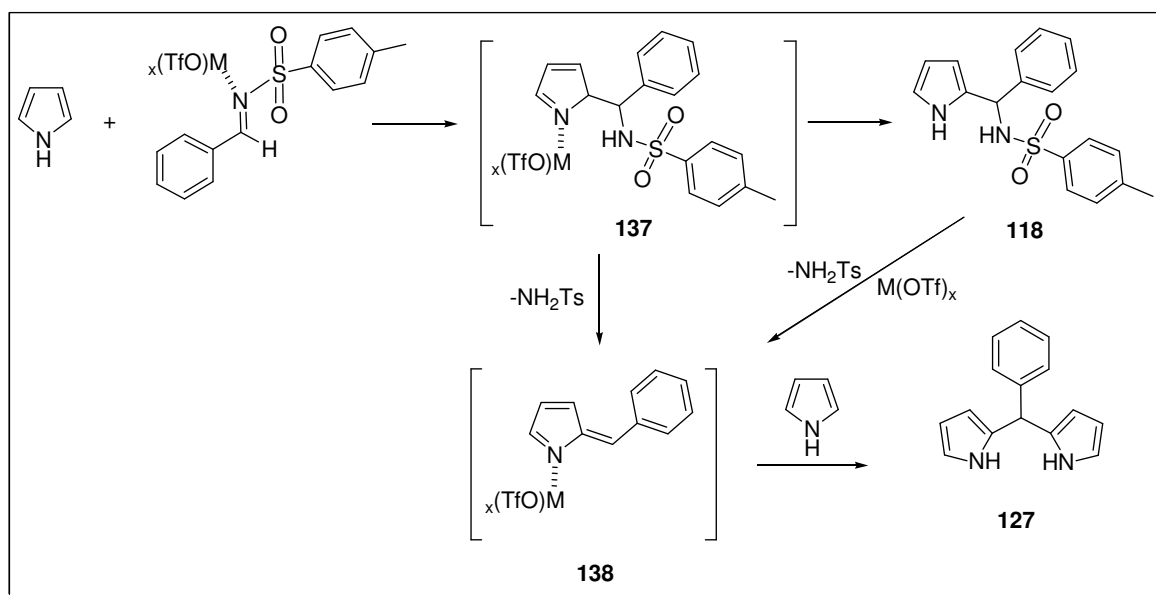
	<u>Dipyrromethane</u>	<u>R</u>	<u>Dipyrromethane</u>	<u>R</u>
	127	H	132	4-NO ₂
	128	4-OCH ₃	133	4-CF ₃
	129	2-OCH ₃	134	4-F
	130	4-CH ₃	135	4-Cl
	131	2-OH	136	4-Br

^{13}C NMR (ppm) ^a					
Compound	<i>meso</i> -C	Pyrrole C2	Pyrrole C3	Pyrrole C4	Pyrrole C5
127	44.10	132.36	107.45	108.75	117.12
128	43.21	132.76	107.27	108.67	117.02
129	37.68	132.47	107.10	108.70	116.67
130	43.72	132.57	107.32	108.74	116.99
131	40.59	130.78	107.22	108.85	117.89
132	43.87	130.76	107.92	108.95	117.94
133	43.78	131.50	107.84	108.82	117.66
134	43.28	132.24	107.55	108.79	117.34
135	43.35	131.88	107.61	108.75	117.42
136	43.50	131.77	107.65	108.83	117.44

^a NMR solvent is CDCl₃.

^b Temelli and Unaleroglu, 2005; 2006.

The proposed reaction mechanism for the metal triflate catalyzed reaction of *N*-tosyl imine with pyrrole is given in Scheme 5.19. In the first step, *N*-tosyl imine is activated by the metal triflate. The addition of pyrrole to the activated imine complex affords structure **118** through the intermediate **137**. Formation of dipyrromethane could be explained by the addition of a second pyrrole to the intermediate **138**, which is generated by the elimination of sulfonamide from intermediate **137** or compound **118**.



Scheme 5.19. The proposed reaction mechanism for the metal triflate catalyzed reaction of *N*-tosyl imine with pyrrole

Intermediate **138** type structures are proposed by other researchers for the reaction of indole with imines (Xie et al., 1999), aldehydes (Chen et al., 1996) and enones (Shi et al., 2004).

To support this proposed mechanism;

- The isolated product **118** was reacted with excess pyrrole in the presence of metal triflate. Dipyrromethane was obtained as the main product after 6 h under the same conditions and leaving group, *p*-toluenesulfonamide, was isolated after the reaction.

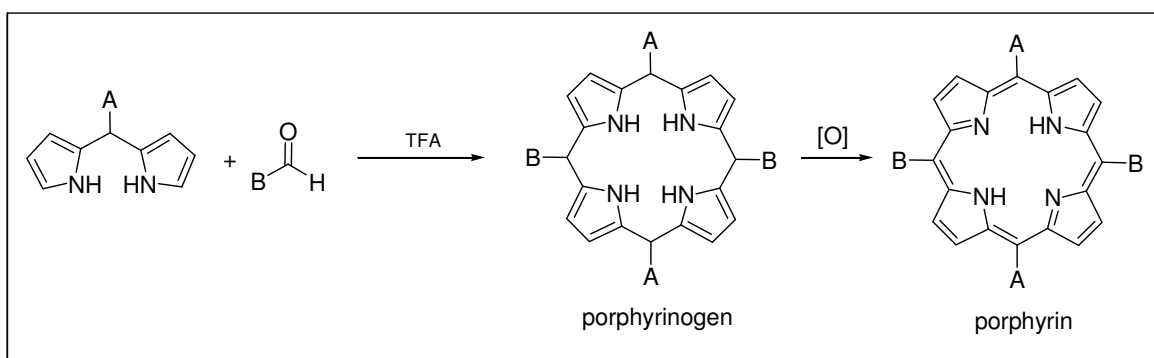
- The same reaction was performed without using the metal triflate and dipyrromethane formation was not observed.

This examination shows that the metal triflate has a crucial role in the formation of dipyrromethane from intermediate **138**.

5.5. Synthesis of *meso*-Substituted Porphyrins

After development of new methods for the synthesis of 2-substituted pyrrole sulfonamides and *meso*-substituted dipyrromethanes, in the next step of the study we focused on the synthesis of *meso*-substituted porphyrins by using *meso*-substituted dipyrromethanes and *N*-tosyl imines in the presence of metal triflates as catalyst.

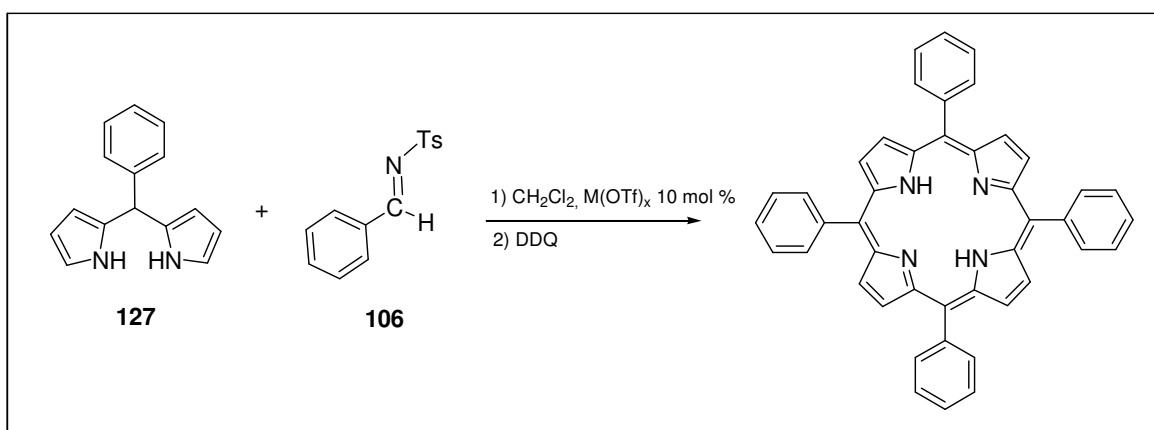
Although there are various methods for the construction of *meso*-tetraaryl substituted porphyrins in the literature, as mentioned in Section 5.1., most of them are based on the condensation of aromatic aldehydes with pyrrole or dipyrromethanes in the presence of conventional acids such as; BF_3 or TFA. The most important method for the synthesis of *meso*-substituted porphyrins by using dipyrromethanes is '2+2 synthesis' known as MacDonald method which is improved by Lindsey later. The first step of the method is the acid catalysed condensation yielding oligomers and porphyrinogen. The second step involves the oxidation of the porphyrinogen to porphyrin (Scheme 5.20). Both of A_4 and *trans*- A_2B_2 type porphyrins can be synthesized by using MacDonald method.



Scheme 5.20. TFA catalysed synthesis of *meso*- substituted porphyrins

The main goal of our study is to develop a new method for the synthesis of porphyrins by using *N*-tosyl imines instead of aldehydes with metal triflates, which are water tolerant and reusable Lewis acids.

As known from literature, it is necessary to select the specific conditions for the generation of the porphyrinogen and oxidation of porphyrinogen to porphyrin. So, we firstly directed the experiments toward the systematic investigation of the best reaction conditions for porphyrin synthesis.



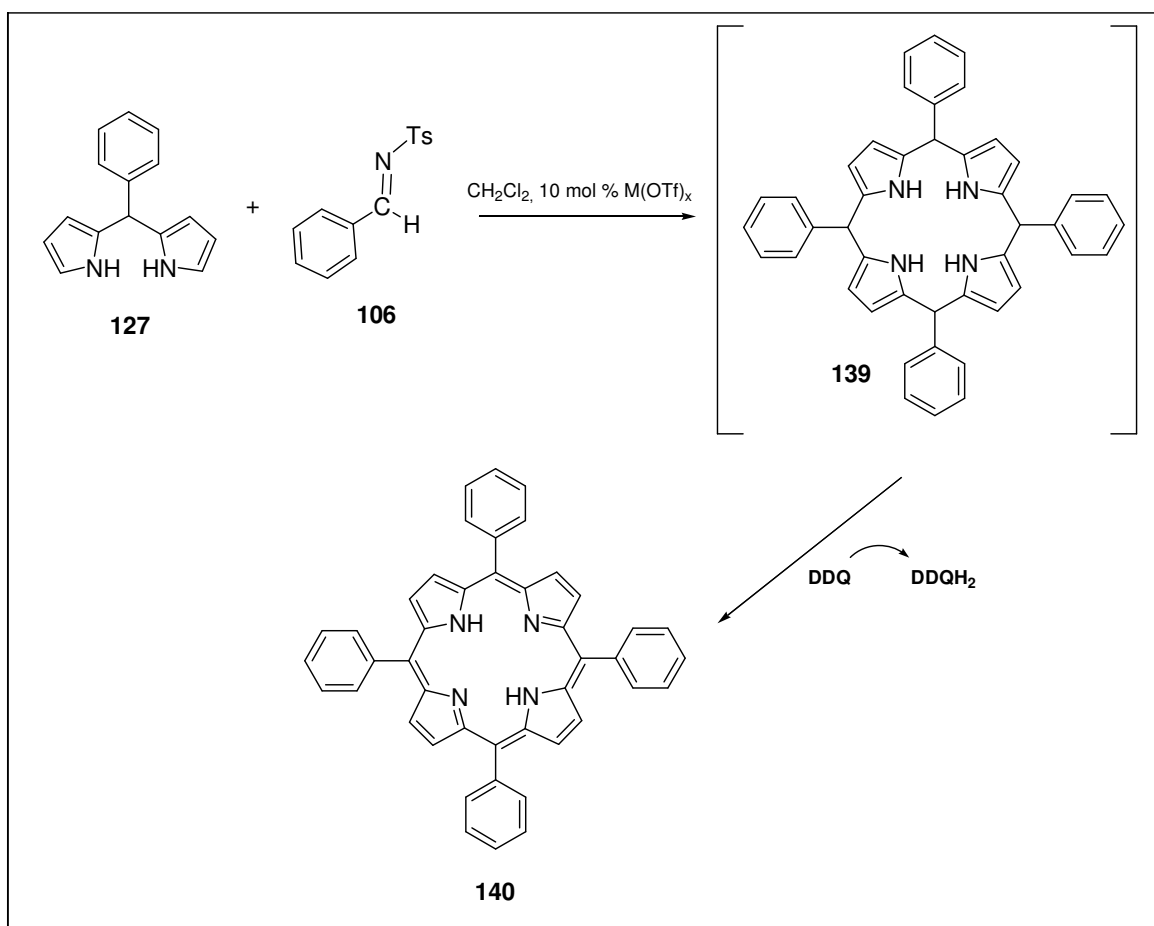
Scheme 5.21. A model reaction for the synthesis of *meso*-substituted porphyrins

The reaction of 5-phenyldipyrromethane (**127**) and *N*-benzylidene-4-methylbenzenesulfonamide (**106**) was chosen as a model reaction (Scheme 5.21). In the first step, different metal triflates were tested to investigate catalytic activities of catalysts in the model reaction. As reported in the literature, the metal type of the metal triflates is very effective on the reaction yield. Kobayashi et al. (2002) reported that the efficiency of metal triflates vary from one reaction to another. The atomic radii of metals and the enone type which is activated by metal triflates are important factors for efficiency.

N-benzylidene-4-methylbenzenesulfonamide (**106**) and metal triflate were stirred in CH₂Cl₂ for 30 minutes under nitrogen atmosphere at room temperature. The solution of 5-phenyldipyrromethane (**127**) in CH₂Cl₂ was added to the mixture in the dark in order to avoid from side products produced by photochemical reactions. Dichloro dicyano quinone (DDQ) was added to the reaction mixture after

2 hours to oxidize porphyrinogen **139** to the porphyrin structure **140** (Scheme 5.22). After 2 hours 10 mL of water was added to the reaction. The aqueous solution was extracted with CH₂Cl₂. Combined organic layers were removed under reduced pressure and the residue was purified by flash silica gel chromatography using CH₂Cl₂ as eluent.

In these reactions, the molarity of the reactants was adjusted to 10⁻² M as reported in the literature by Lindsey et al. (1987). This dilute reaction condition was used in porphyrin synthesis by Lindsey to limit oligomerization reaction and maximize the percentage of the porphyrinogen in the reaction vessel before the oxidation step. CH₂Cl₂ was also proposed by many researchers as most suitable solvent for the condensation reaction of pyrrole or dipyrromethane with aldehydes.



Scheme 5.22. Two step synthesis of *meso*-substituted porphyrins

The model reaction was carried out by using seven different metal triflates which have been used generally in the literature (Table 5.15.). The best chemical yield of tetraphenylporphyrin (TPP) was obtained when Cu(OTf)₂ was used as Lewis acid catalyst in the model reaction (44%).

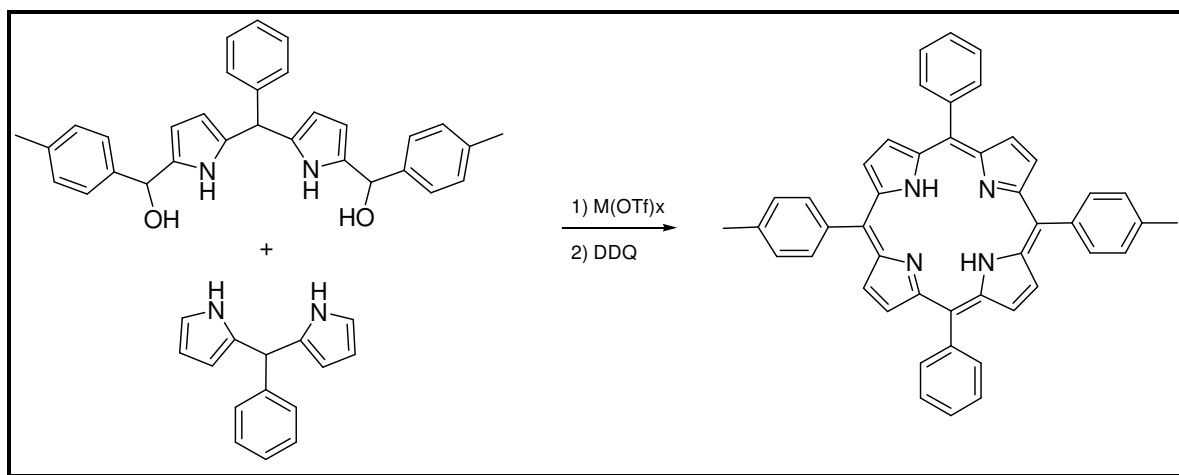
Table 5.15. The effect of different metal triflates on the porphyrin synthesis

Solvent	Molarity [M]	Catalyst 10 % (mol)	Time (h)	Oxidant	Yield (%) ^a of TPP (140)
DCM	10 ⁻²	Gd(OTf) ₃	2	DDQ	-
DCM	10 ⁻²	Cu(OTf) ₂	2	DDQ	44
DCM	10 ⁻²	Yb(OTf) ₃	2	DDQ	-
DCM	10 ⁻²	Y(OTf) ₃	2	DDQ	30
DCM	10 ⁻²	La(OTf) ₃	2	DDQ	2
DCM	10 ⁻²	Zn(OTf) ₂	2	DDQ	-
DCM	10 ⁻²	Nd(OTf) ₃	2	DDQ	4

^a Yield refers to pure product after column chromatography.

There are very few reports on the metal triflate catalysed synthesis of porphyrins using aldehydes. For example Geier III et al. (2000) used Yb(OTf)₃ and Sc(OTf)₃ as Lewis acids in the reaction of pyrrole with benzaldehyde to synthesize TPP. Only 9.5 % yield of TPP was obtained after the reaction.

Zaidi et al. (2006) also reported metal triflate catalysed reaction of 5-phenyl-1,9-di-*p*-tolylidipyrromethane with 5-phenyldipyrromethane (Scheme 5.23). 15 different metal triflates were tested on this reaction and Sc(OTf)₃, Zn(OTf)₂ and Sn(OTf)₂ were selected as suitable catalysts which gave 20-22% yield of porphrin.



Scheme 5.23. Metal triflate catalysed synthesis of porphyrins

The another parameter for the optimization of the reaction condition is the amount of catalyst used in the reaction. Many metal triflates catalysed C-C bond forming reactions were reported in the literature varying between 1% and 20% amounts of catalysts. Also this parameter becomes more important in the reactions of pyrrole compounds because of the sensitivity of these compounds to acidic conditions. So, the model reaction was repeated by $\text{Cu}(\text{OTf})_2$ as catalyst between 2% and 20% mole amounts (Table 5.16).

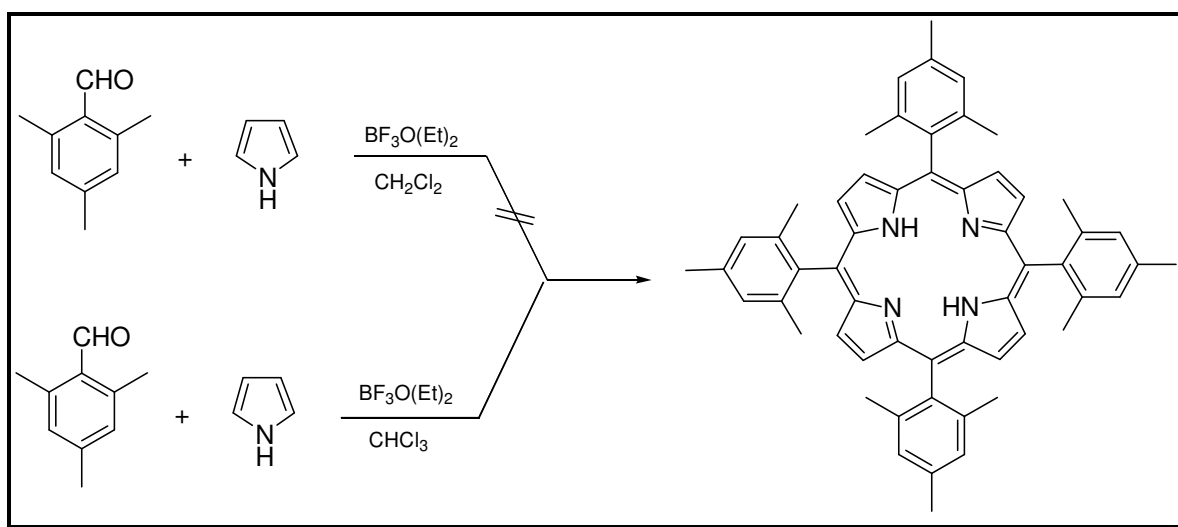
Table 5.16. The effect of the amount of $\text{Cu}(\text{OTf})_2$ on the synthesis of TPP (**140**).

Solvent	Molarity [M]	Catalyst $\text{Cu}(\text{OTf})_2$ mol (%)	Time (h)	Oxidant	Yield (%) ^a of TPP (140)
DCM	10^{-2}	2	2	DDQ	11
DCM	10^{-2}	5	2	DDQ	20
DCM	10^{-2}	10	2	DDQ	44
DCM	10^{-2}	15	2	DDQ	25
DCM	10^{-2}	20	2	DDQ	10

^a Yield refers to pure product after column chromatography.

The chemical yield of the reaction was increased by increasing amount of the catalyst up to 10% mol. The reactions with 15% and 20% amounts of catalyst gave lower yields than the reactions catalysed with 10% mol $\text{Cu}(\text{OTf})_2$.

We continued searching solvent effect on the reaction parameters. Porphyrin syntheses were generally carried out in the literature by using two chlorinated solvents, CH_2Cl_2 and CHCl_3 . The most striking observation on the effect of solvent was found by Lindsey in the comparison of CHCl_3 and CH_2Cl_2 (Scheme 5.24) (Wagner et al., 1987). Lindsey found that the condensation of mesitaldehyde and pyrrole in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in CH_2Cl_2 did not yield porphyrin. However, when the same reaction was performed in CHCl_3 , tetramesitylporphyrin was produced in 31% yield.



Scheme 5.24. Comparison of CHCl_3 and CH_2Cl_2 in $\text{BF}_3 \cdot \text{O}(\text{Et})_2$ catalysed porphyrin synthesis

By employing these two solvents, Lindsey found out that the major difference between the two chlorinated solvents was the presence of 0.75% ethanol as a stabilizer in the commercial CHCl_3 . The addition of 0.75% ethanol to CH_2Cl_2 resulted in a 25% yield of TMP, showing that the solvent effect was due to the presence of ethanol.

According to these informations, we carried out the model reaction by using different solvents. As shown in Table 5.17, chlorinated solvents CHCl_3 and DCM gave higher yields than others in agreement with the literature. DCM was chosen most suitable solvent for the synthesis of porphyrin.

Table 5.17. The effect of the solvent on the synthesis of porphyrin.

Solvent	Molarity [M]	Catalyst 10 % mol	Time (h)	Oxidant	Yield (%) ^a of TPP (140)
CH ₃ CN	10 ⁻²	Cu(OTf) ₂	2	DDQ	15
Acetone	10 ⁻²	Cu(OTf) ₂	2	DDQ	-
THF	10 ⁻²	Cu(OTf) ₂	2	DDQ	-
Et ₂ O	10 ⁻²	Cu(OTf) ₂	2	DDQ	9
Toluene	10 ⁻²	Cu(OTf) ₂	2	DDQ	11
CHCl ₃	10 ⁻²	Cu(OTf) ₂	2	DDQ	29
DCM	10 ⁻²	Cu(OTf) ₂	2	DDQ	44

^a Yield refers to pure product after column chromatography.

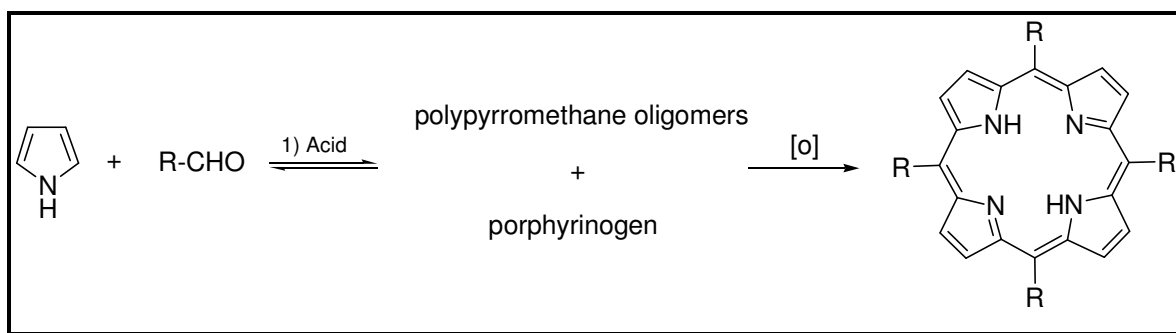
There are three oxidants reported in the literature to oxidize the porphyrinogen to porphyrin. These are dichloro dicyano quinone (DDQ), tetrachloro *p*-benzoquinone (*p*-chloranil) and tetrachloro *o*-benzoquinone (*o*-chloranil). These oxidants were also tested on the model reaction and DDQ was determined as the most suitable oxidant for the reaction (Table 5.18).

Table 5.18. The effect of the oxidant on the synthesis of porphyrin.

Solvent	Molarity [M]	Catalyst 10 mol %	Time (h)	Oxidant	Yield (%) ^a of TPP (140)
DCM	10 ⁻²	Cu(OTf) ₂	2	DDQ	44
DCM	10 ⁻²	Cu(OTf) ₂	2	<i>p</i> -chloranil	34
DCM	10 ⁻²	Cu(OTf) ₂	2	<i>o</i> -chloranil	22

^a Yield refers to pure product after column chromatography.

As reported by Linsey, the yield of the porphyrin is very sensitive to the concentration of reactants. The reaction of pyrrole with aldehyde in the presence of acid affords porphyrinogen as discussed in Section 2.3. An important information obtained from literature is that these reactions gave generally oligomeric by products beside porphyrinogen (Scheme 5.25). Lindsey suggested that decrease of the ratio of oligomeric products should increase the ratio of porphyrinogen and also porphyrin yield. Dilute reaction conditions (generally 10⁻² M) were reported as most suitable condition to obtain maximum porphyrinogen product (Lindsey et al., 1987).



Scheme 5.25. Acid catalysed two step formation of porphyrins

Depending on these informations, the reaction of 5-phenyldipyrromethane (**127**) with *N*-benzylidene-4-methylbenzenesulfonamide (**106**) was carried out with different concentrations of reactants by using 10 mol % Cu(OTf)₂ in CH₂Cl₂ (Table 5.19).

The maximum yield of tetraphenylporphyrin (**140**) was obtained, when the concentration of the reactants are equal to 10⁻² M (44%). The yield of the product decreased when the concentration of reactants decreased or increased. As mentioned before high concentrations should increase the ratio of oligomeric products and lower concentrations than 10⁻² M decrease the porphyrinogen formation.

Table 5.19. The effect of concentrations of reactants on the synthesis of porphyrin.

Solvent	Molarity [M]	Catalyst 10 mol %	Time (h)	Oxidant	Yield (%) ^a of TPP (140)
DCM	10 ⁻¹	Cu(OTf) ₂	2	DDQ	11
DCM	10 ^{-1,5}	Cu(OTf) ₂	2	DDQ	23
DCM	10 ^{-1,75}	Cu(OTf) ₂	2	DDQ	29
DCM	10 ⁻²	Cu(OTf) ₂	2	DDQ	44
DCM	10 ^{-2,25}	Cu(OTf) ₂	2	DDQ	30
DCM	10 ^{-2,5}	Cu(OTf) ₂	2	DDQ	23
DCM	10 ⁻³	Cu(OTf) ₂	2	DDQ	0

^a Yield refers to pure product after column chromatography.

Regarding with the knowledge according to the reaction of pyrrole with aldehydes, the first step of the porphyrin synthesis is the reversible formation of the porphyrinogen. The second step, the oxidation of porphyrinogen to porphyrin is irreversible (Scheme 5.25). So, the amount of porphyrinogen formed in the first step determines the yield of the reaction. In addition, the amounts of oligomeric by products in the first step also depends on the reaction time of the first step. The reaction should be stopped by the addition of the oxidant when the amount of the porphyrinogen is maximum.

For this reason, the first step of the model reaction was repeated with different reaction times and a slight increase was obtained when the reaction was carried out in 1,5 hour (45%) (Table 5.20).

Table 5.20. The effect of the reaction time on the synthesis of porphyrin.

Solvent	Molarity [M]	Catalyst 10 mol %	Time (h)	Oxidant	Yield (%) ^a of TPP (140)
DCM	10 ⁻²	Cu(OTf) ₂	0,5	DDQ	24
DCM	10 ⁻²	Cu(OTf) ₂	1	DDQ	32
DCM	10 ⁻²	Cu(OTf) ₂	1,5	DDQ	45
DCM	10 ⁻²	Cu(OTf) ₂	2	DDQ	44
DCM	10 ⁻²	Cu(OTf) ₂	3	DDQ	26

^a Yield refers to pure product after column chromatography.

After the optimization of the reaction conditions, we also tested some well-known Lewis acids and protonic acids on the model reaction to compare their reactivity with metal triflates. The only broad scope investigation of different acids on the reaction of pyrrole with benzaldehyde to synthesize TPP was reported by Geier et al. (2000). They selected 45 different acids from four general categories; i) acids previously used in porphyrin synthesis, ii) acids commonly used in other organic reactions involving condensation of carbonyl containing compounds (e.g., Aldol condensation, Friedel-Crafts acylation), iii) water soluble metal triflates, iv) novel acids with unknown previous application in organic synthesis. Metal triflates gave ~10% yield of porphyrinogen. The highest yield of TPP (58%) was obtained when BF₃-etherate/NaCl was used.

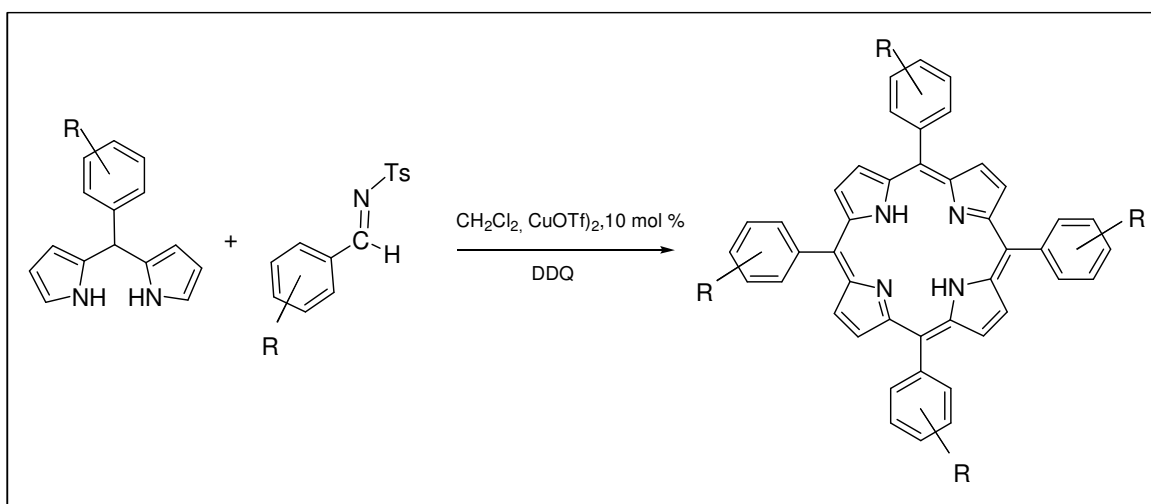
We have used nine different acid catalysts, selected from literature, in our model reaction (Table 5.21). Surprisingly BF_3 -etherate catalyst gave no porphyrin product. The highest yield of the reaction was obtained when $\text{CF}_3\text{SO}_3\text{H}$ was used as acid catalyst (39%).

Table 5.21. The effect of different catalysts on the synthesis of porphyrin from dipyrromethane and *N*-tosyl imine.

Solvent	Molarity [M]	Catalyst 10 mol %	Time (h)	Oxidant	Yield (%) ^a of TPP (140)
DCM	10^{-2}	p-Toluenesulfonic acid	2	DDQ	13
DCM	10^{-2}	CuCl_2	2	DDQ	-
DCM	10^{-2}	AlCl_3	2	DDQ	11
DCM	10^{-2}	HCl	2	DDQ	5
DCM	10^{-2}	$\text{CF}_3\text{SO}_3\text{H}$	2	DDQ	39
DCM	10^{-2}	Cl_3CCOOH	2	DDQ	3
DCM	10^{-2}	SnCl_4	2	DDQ	-
DCM	10^{-2}	TiCl_4	2	DDQ	-
DCM	10^{-2}	$\text{BF}_3\text{O}(\text{C}_2\text{H}_5)_2$	2	DDQ	-

^a Yield refers to pure product after column chromatography.

The optimum conditions of the model reaction were applied to reactions of the substituted 5-substituted dipyrromethanes (**127-136**) with *N*-tosyl imines (**106-115**) to obtain A_4 -type porphyrins (**140-146**) (Scheme 5.26).



Scheme 5.26. Synthesis of A_4 -type meso-aryl substituted porphyrins.

Reactions were carried out in CH₂Cl₂ at room temperature and the concentrations of reactants were adjusted as 10⁻² M. After 1,5 hours the oxidant DDQ was added to the reaction medium and the reaction quenched with water after 2 hours. The aqueous layer was extracted with CH₂Cl₂. The purification of the products were carried out with flash column chromatography by using CH₂Cl₂ as eluent. The results are summarized in Table 5.22.

Table 5.22. The effect of the substituents on the synthesis of porphyrin.

Entry	Compound	R	Yield (%) ^a
1	140	H	45
2	141	p-OCH ₃	44
3		o-OCH ₃	-
4	142	p-CH ₃	35
5		o-OH	-
6		p-NO ₂	-
7	143	p-CF ₃	25
8	144	p-F	13
9	145	p-Cl	31
10	146	p-Br	29

^a Yield refers to pure product after column chromatography.

Structures of the products were identified with ¹H NMR, ¹³C NMR, FTIR and UV spectroscopic techniques. The results were compared with the data published in the literature and all obtained data are in agreement with the literature values (Naik et al., 2003).

The ¹H NMR spectra of porphyrins show anisotropic effects. The NH protons, inside the porphyrin ring system thus shift upfield to as high as -5 ppm. The pyrrolic protons are also deshielded and tend to resonate at 8 to 9, versus ~ 6 ppm in pyrrole. The ¹H NMR spectrum of TPP (**140**) is given in Figure 5.9. A broad singlet at -2.71 ppm belongs to two NH protons of porphyrin inside the ring system. Para and meta substituted hydrogens of phenyl rings give signals between 7.78 and 7.80 ppm as multiplet. The doublet at 8.26 ppm belongs to the ortho substituted hydrogens of phenyl rings. Pyrrole hydrogens give a singlet at 8.89 ppm.

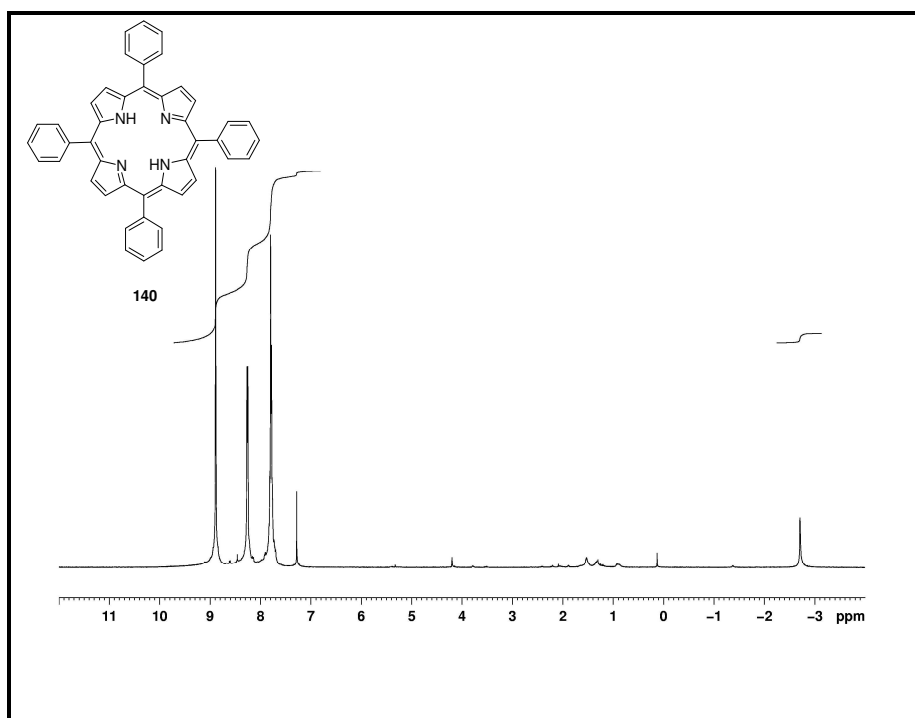


Figure 5.9. ^1H NMR spectrum of **140** in CDCl_3 .

The determination of ^{13}C NMR data is complicated by NH tautomerism (Abraham et al., 1984) which broadens the signal for the α and β carbons and in many cases the α carbons are undetectable (Abraham et al, 1974). ^{13}C NMR spectrum of TPP (**140**) is also in agreement with the structure (Figure 5.10). C-5, 10, 15 and 20 carbons give a signal at 120.14 ppm. Phenyl carbons give signal at 126.68, 127.70, 134.56 and 142.20 ppm. β -Pyrrolic carbons of **140** give a broad signal at 131.33 ppm. α -carbons give too broad resonance peak and can not be detected.

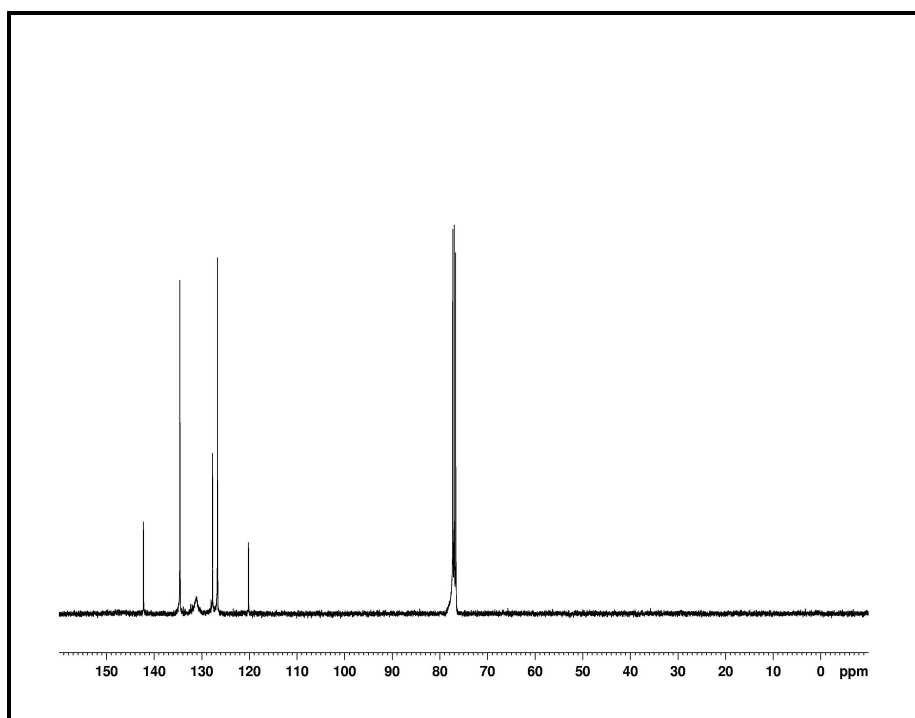
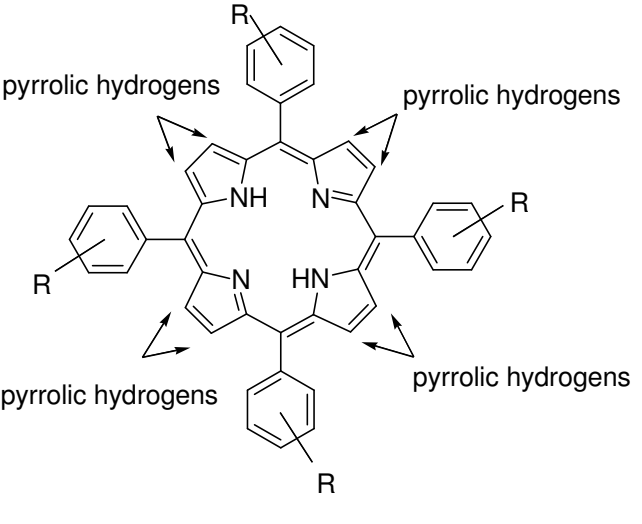


Figure 5.10. ^{13}C NMR spectrum of **140** in CDCl_3 .

^1H NMR and ^{13}C NMR spectra of other synthesized porphyrins are given in Figure 5.73 - 5.83 (page 156 - 161). The important peak values of these compounds are summarized in Table 5.23 and Table 5.24.

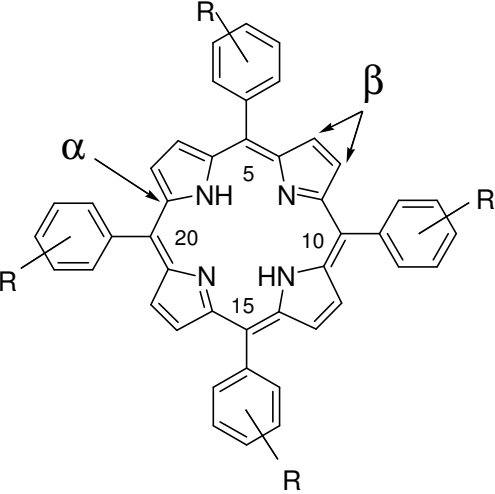
Table 5.23. Important ^1H NMR values of synthesized *meso*-substituted porphyrin derivatives

		Porphyrin	R	Porphyrin	R
		140	H	144	4-F
		141	4-OCH ₃	145	4-Cl
		142	4-CH ₃	146	4-Br
		143	4-CF ₃		

^1H NMR (ppm) ^a					
Compound	NH	Para phenyl-H	Meta phenyl-H	Ortho phenyl-H	Pyrrolic H
140	-2.71 (br s)	7.78-7.80 (m)	7.78-7.80 (m)	8.26 (d, J = 7.6)	8.89 (s)
141	-2.72 (br s)	-	7.27-7.32 (m)	8.15 (d, J = 8.6)	8.89 (s)
142	-2.73 (br s)	-	7.57 (d, J = 8.0)	8.12 (d, J = 8.0)	8.88 (s)
143	-2.70 (br s)	-	8.08 (d, J = 8.2)	8.37 (d, J = 8.0)	8.85 (s)
144	-2.75 (br s)	-	7.45-7.59 (m)	8.16-8.21 (m)	8.90 (s)
145	-2.83 (br s)	-	7.77 (d, J = 8.2)	8.16 (d, J = 8.2)	8.87 (s)
146	-2.85 (br s)	-	7.93 (d, J = 8.2)	8.09 (d, J = 8.2)	8.87 (s)

^a NMR solvent is CDCl₃.

Table 5.24. Important ^{13}C NMR values of synthesized *meso*-substituted porphyrin derivatives

	Porphyrin	R	Porphyrin	R
	140	H	144	4-F
	141	4-OCH ₃	145	4-Cl
	142	4-CH ₃	146	4-Br
	143	4-CF ₃		

^{13}C NMR (ppm) ^{a,b}			
Compound	C (5, 10, 15, 20)	$\beta\text{-C}$	Phenyl - C
140	120.14	131.33 (br s)	126.68, 127.70, 134.56, 142.20
141	119.74	130.91 (br s)	112.20, 134.67, 135.60, 159.39
142	120.07	130.87 (br s)	127.40, 134.52, 137.30, 139.34
143	119.00	131.34 (br s)	123.80 (q), 124.50 (q), 130.39 (q), 134.58, 145.49
144	*	*	*
145	119.00	131.16 (br s)	127.05, 134.42, 135.50, 140.38
146	119.00	131.33 (br s)	122.66, 130.00, 135.83, 140.85

^a NMR solvent is CDCl₃.

^b The resonance peak of α -carbons were too broad to be detected.

* The solubility of compound **144** is very poor to determine ^{13}C NMR data (Fleisher et al.1973).

UV visible absorption spectroscopy is another important tool to identify the structure of porphyrins. The absorption spectra of porphyrins correlate and reflect many of their physicochemical properties. The absorption spectra of porphyrins display an intense band in the region of 400 nm. This absorption is called the Soret or β band, which is characteristic of the macrocyclic conjugation and it has a strong absorption. When the aromatic delocalization pathway is disrupted, the Soret band disappears. This explains why the Soret band is not observed strongly in chlorins and isobacteriochlorins (Figure 5.11, c,e).

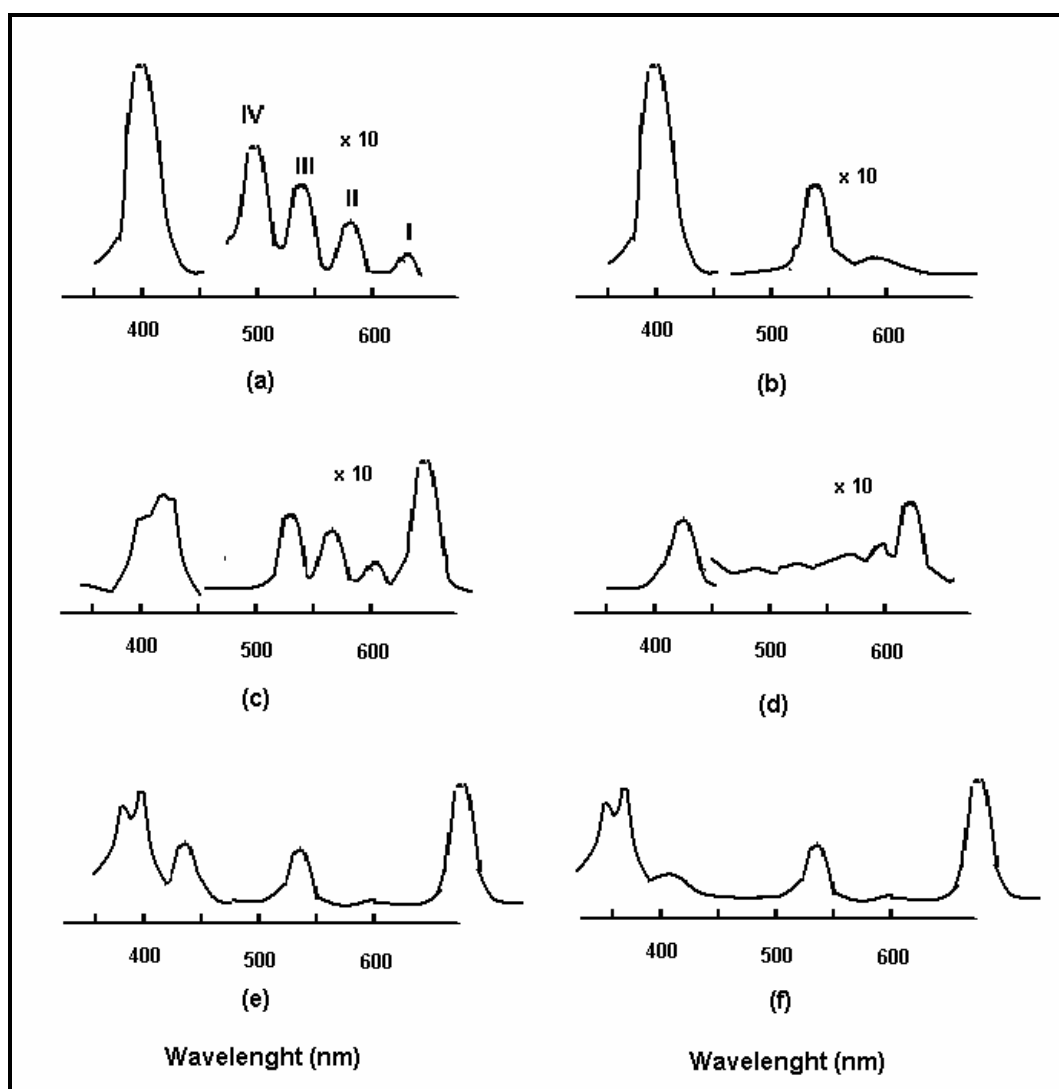


Figure 5.11. Absorption spectra of (a) TPP, (b) metalloporphyrins, (c) chlorins, (d) metallochlorins, (e) isobacteriochlorins and (f) metallobacteriochlorins.

Porphyrins also display four accompanying bands commonly referred to as the Q-bands. These bands have lower intensity between 450-650 nm. The absorption pattern of Q-bands varies, depending upon factors such as the porphyrin is protonated or metalated (Figure 5.11, b,d,f). These four bands denoted I to IV in order of decreasing wavelength $IV > III > II > I$ in TPP (Figure 5.11, a).

The UV-absorption spectrum of synthesized TPP (**140**) is given in Figure 5.12. The Soret band gives absorption at 416 nm. Four Q-bands absorptions appears at 514, 548, 590 and 646 nm as decreasing the intensities of absorptions. The wavenumbers of absorptions and the shape of the Q-bands agree with the spectrum as stated in the literature.

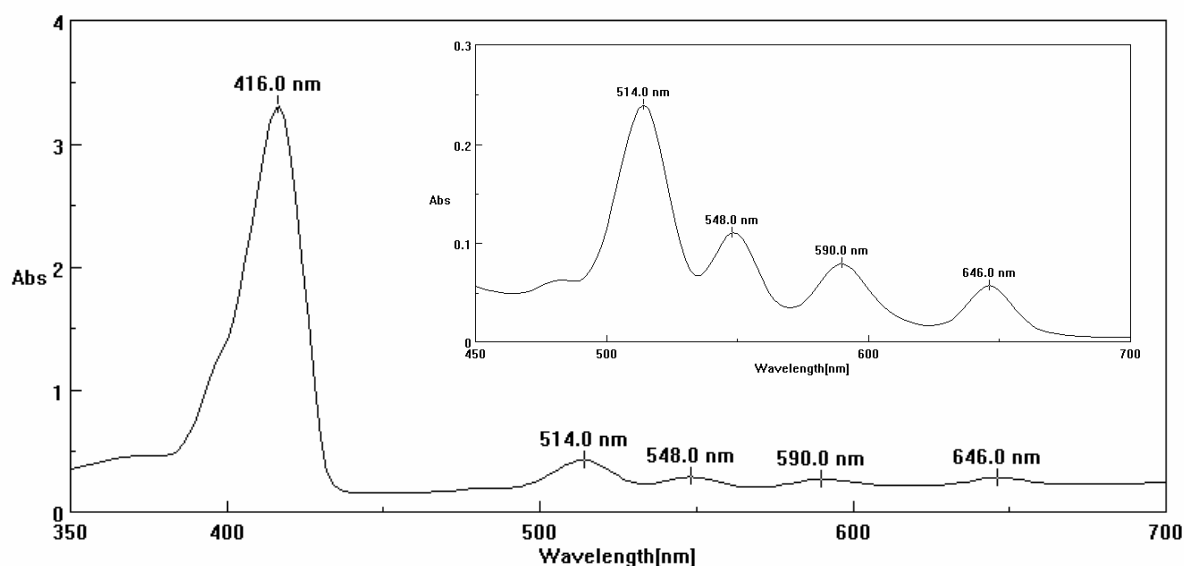
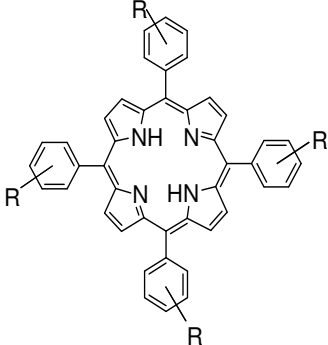


Figure 5.12. UV absorption spectrum of **140**.

UV-absorption spectra data of other synthesized porphyrins are given in Table 5.25.

Table 5.25. Important UV absorption values of synthesized *meso*-substituted porphyrin derivatives

	<u>Porphyrin</u>	<u>R</u>	<u>Porphyrin</u>	<u>R</u>
	140	H	144	4-F
	141	4-OCH ₃	145	4-Cl
	142	4-CH ₃	146	4-Br
	143	4-CF ₃		

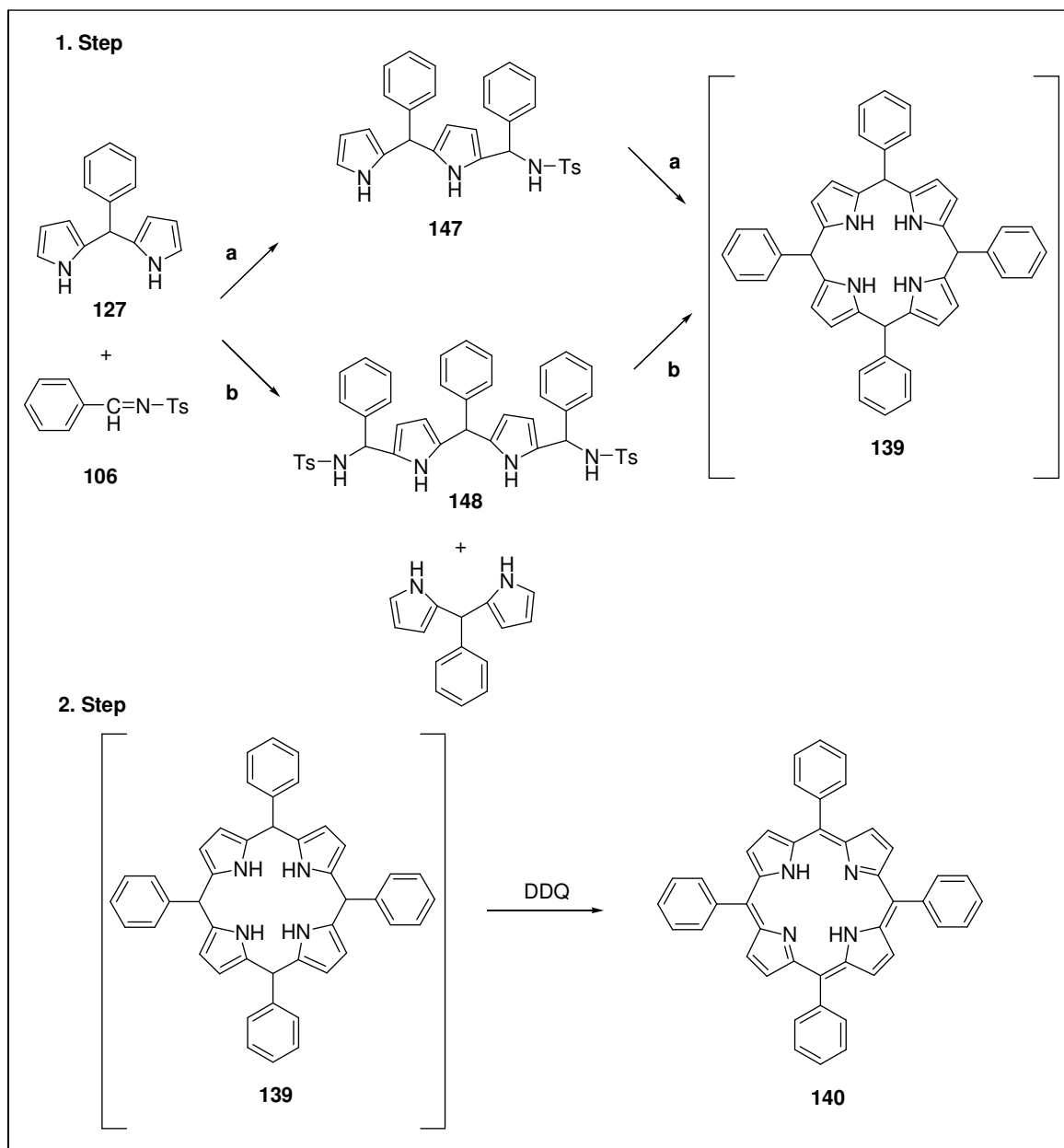
UV Absorption (nm) (CH ₂ Cl ₂)		
Compound	Soret Band	Q Bands
140	416	514, 548, 590, 646
141	416	512, 546, 588, 648
142	416	514, 546, 588, 648
143	416	512, 546, 588, 644
144	416	514, 548, 590, 646
145	418	514, 548, 590, 646
146	418	514, 548, 590, 646

5.5.1. The Investigation of the Mechanism of Porphyrin Formation.

Two possible pathways were suggested for the formation of porphyrin from the reaction of dipyrromethane and *N*-tosyl imine in the presence of metal triflates.

- First pathway (Scheme 5.27, pathway **a**) is the synthesis of porphyrinogen **139** by the self condensation reaction of mono sulfonamidealkylated dipyrromethane product, 4-methyl-*N*-(phenyl(5-(phenyl(1*H*-pyrrol-2-yl)methyl)-1*H*-pyrrol-2-yl)methyl)benzene sulfonamide (**147**).

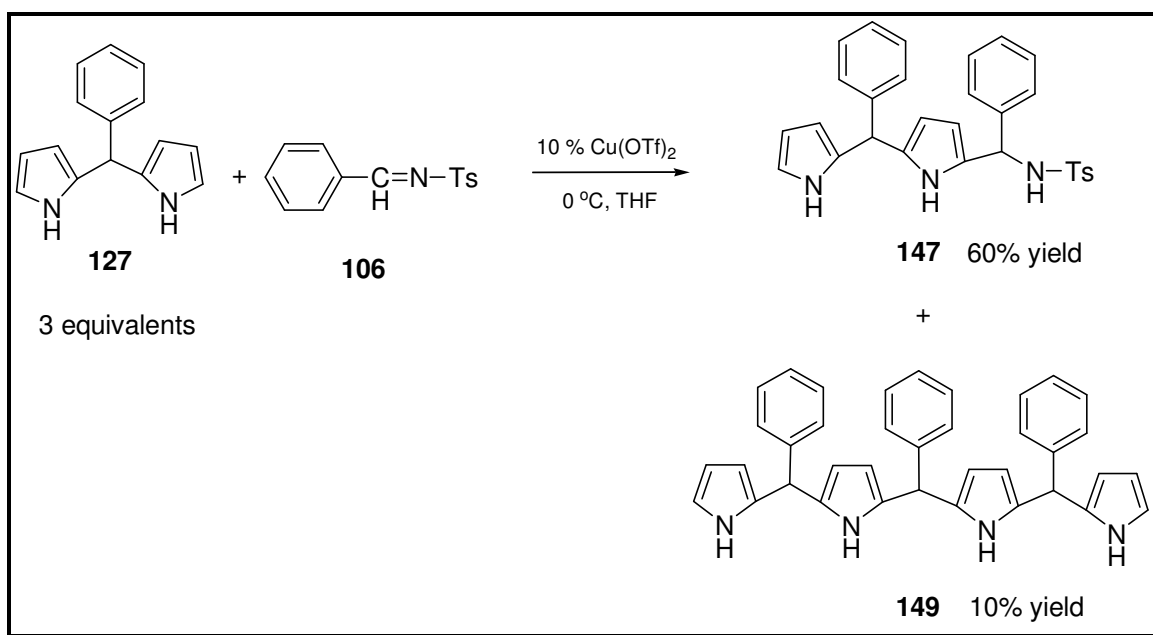
- Second pathway is the condensation reaction of di sulfonamidealkylated dipyrromethane product **148** with 5-phenyl dipyrromethane (**127**) (Scheme 5.27, pathway **b**). For both pathways, the porphyrinogen **139** could be obtained by the oxidation of porphyrinogen **139** to porphyrin **140** with DDQ.



Scheme 5.27. Two possible pathways for the synthesis of porphyrins

With the purpose described above, mono and di sulfonamidealkylated dipyrromethane products, **147** and **148**, were synthesized at low reaction temperatures.

For the synthesis of 4-methyl-*N*-(phenyl(5-(phenyl(1*H*-pyrrol-2-yl)methyl)-1*H*-pyrrol-2-yl)methyl)benzene sulfonamide (**147**), three equivalent of dipyrromethane **127** and *N*-tosyl imine **106** were reacted in the presence of 10% mol Cu(OTf)₂ at 0 °C for 10 hours. The expected addition product **147** was obtained in 60% yield while giving side product *meso*-substituted bilane **149** in 10% yield (Scheme 5.28).



Scheme 5.28. The synthesis of mono sulfonamidealkylated dipyrromethane **147**.

The characterization of compounds **147** and **149** was carried out by using ¹H NMR, ¹³C NMR, COSY and FTIR spectroscopic techniques.

Figure 5.13 shows the ¹H NMR spectrum of addition product **147**. Broad peaks at 8.34 and 8.03 ppm belong to NH protons **6** and **1** respectively. Phenyl protons appear as multiple between 7.15 and 7.57 ppm. Pyrrole protons **2**, **3** and **4** give resonance at 6.64, 6.13 and 5.89 ppm as broad singlets respectively. Pyrrole proton **7** or **8** gives a broad singlet at 5.70 ppm. Two *meso* protons **5**, **9** and one pyrrole proton **7** or **8** appear as multiplet between 5.37 and 5.54 ppm.

¹³C NMR spectrum of **147** is in agreement with the suggested structure (Figure 5.14). CH₃ carbon and two *meso* carbons appear at 21.51, 44.05 and 55.91 ppm. Four carbon atoms of C(3) and C(4) carbons of two pyrrole ring (**3**, **4**, **7** and **8**) appear at 107.18, 107.28, 108.31 and 108.39 ppm. The signal at 117.28 ppm

belongs to tertiary C(5) carbon (**2**) of pyrrole ring. Phenyl carbons and quartarnery C(2) carbons of pyrrole give resonance between 126 and 143 ppm.

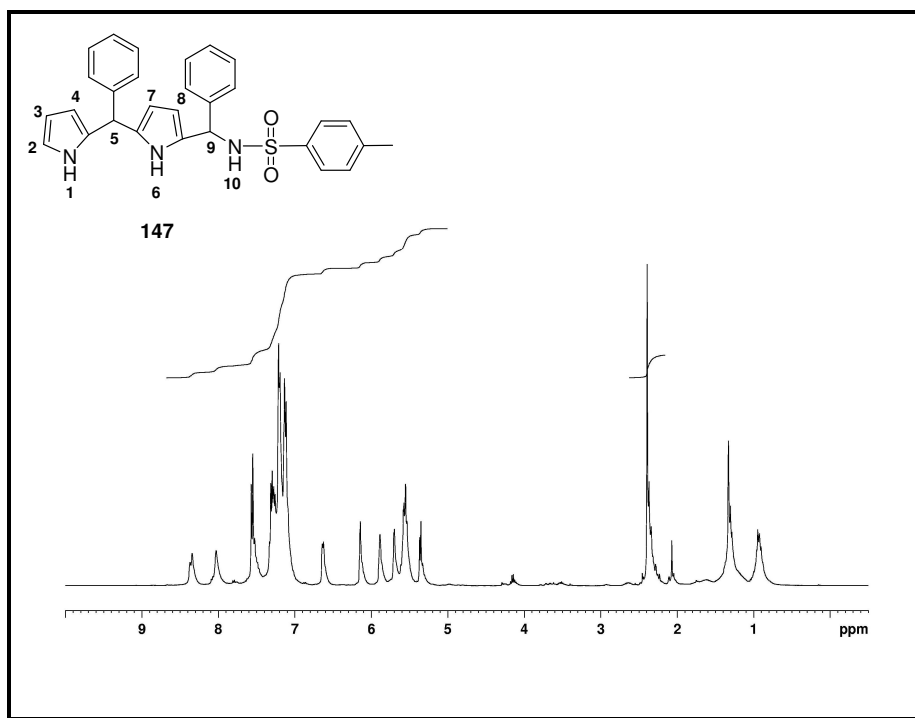


Figure 5.13. ^1H NMR Spectrum of **147** in CDCl_3 .

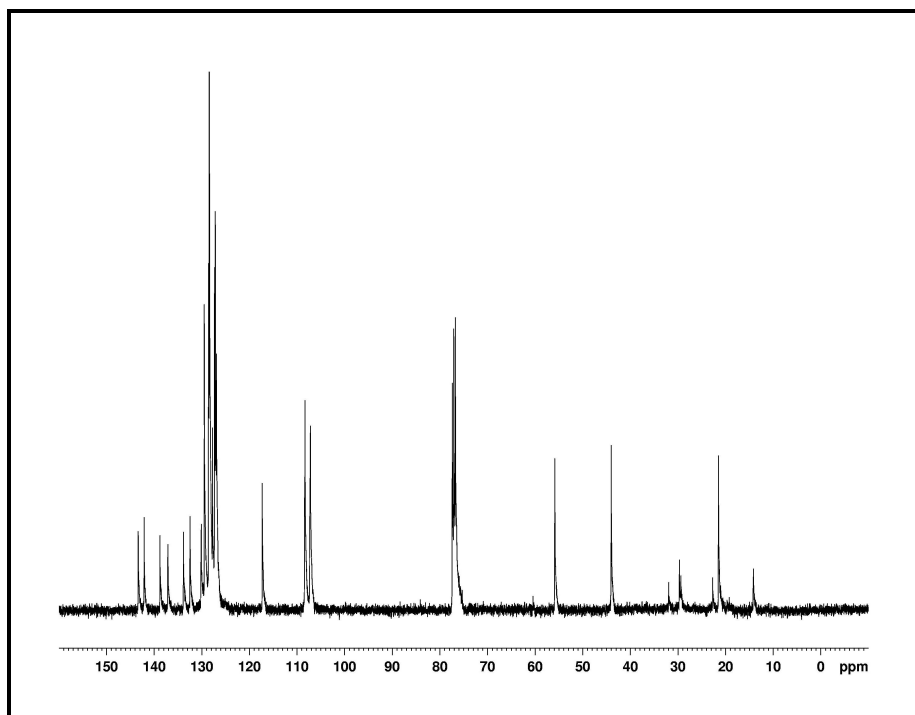


Figure 5.14. ^{13}C NMR Spectrum of **147** in CDCl_3 .

The COSY spectrum of **147** (Figure 5.15) shows that neighbour pyrrole protons **1**, **2**, **3** and **4** correlate with each other. The pyrrole protons (**6**, **7** and **8**) of second pyrrole ring give crosspeak signals with each other.

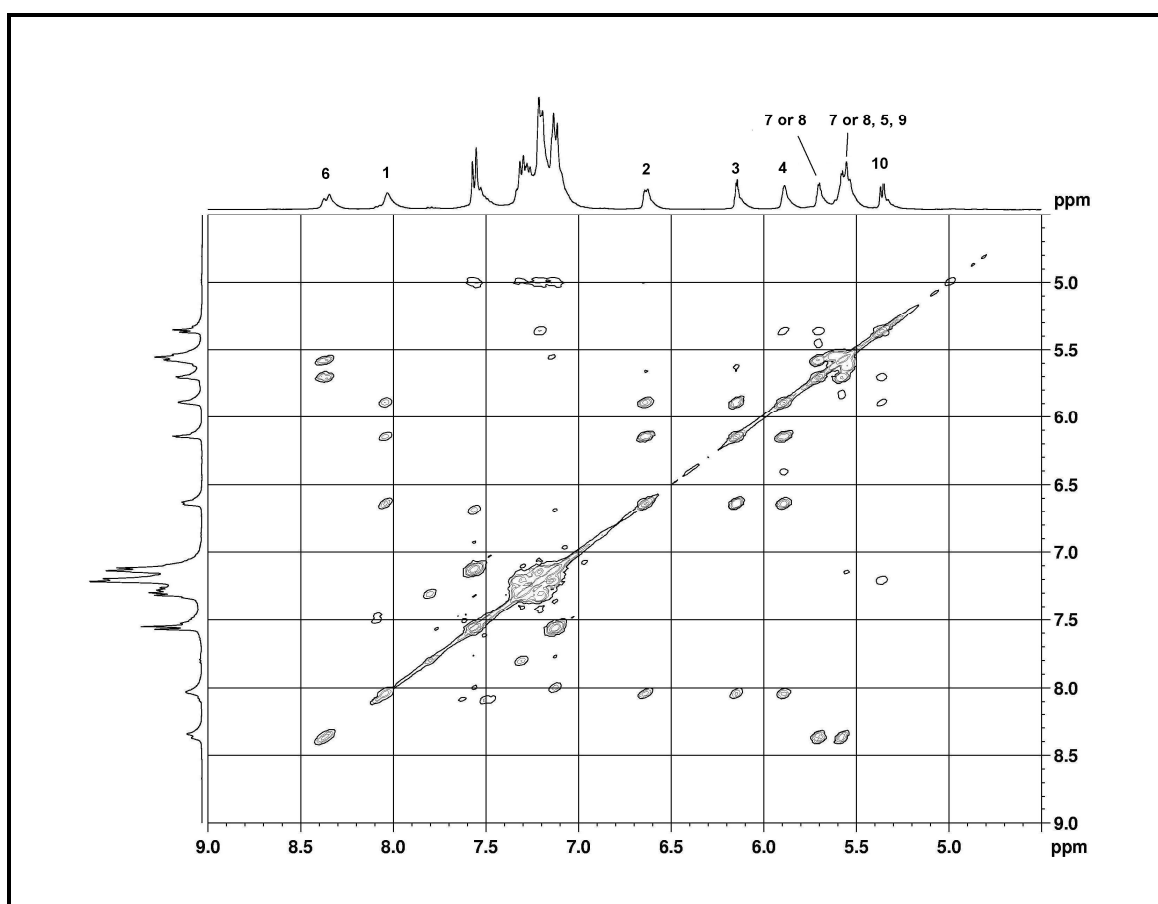
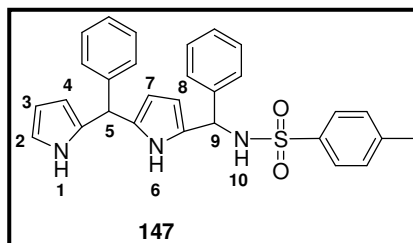


Figure 5.15. COSY spectrum of **147**.

^1H NMR spectrum of side product **149** is given in Figure 5.16. NH protons of pyrrole rings appear at 7.92 and 7.74 ppm as broad peaks. Pyrrole protons (**2**, **3** and **4**) give signals at 6.69, 6.16 and 5.88 ppm respectively. Two pyrrole protons **7** and **8** give multiplet between 5.73 and 5.80 ppm. The broad signal at 5.38 ppm belongs to *meso* protons **5**. Another *meso* proton **9** gives a resonance at 5.31 ppm.

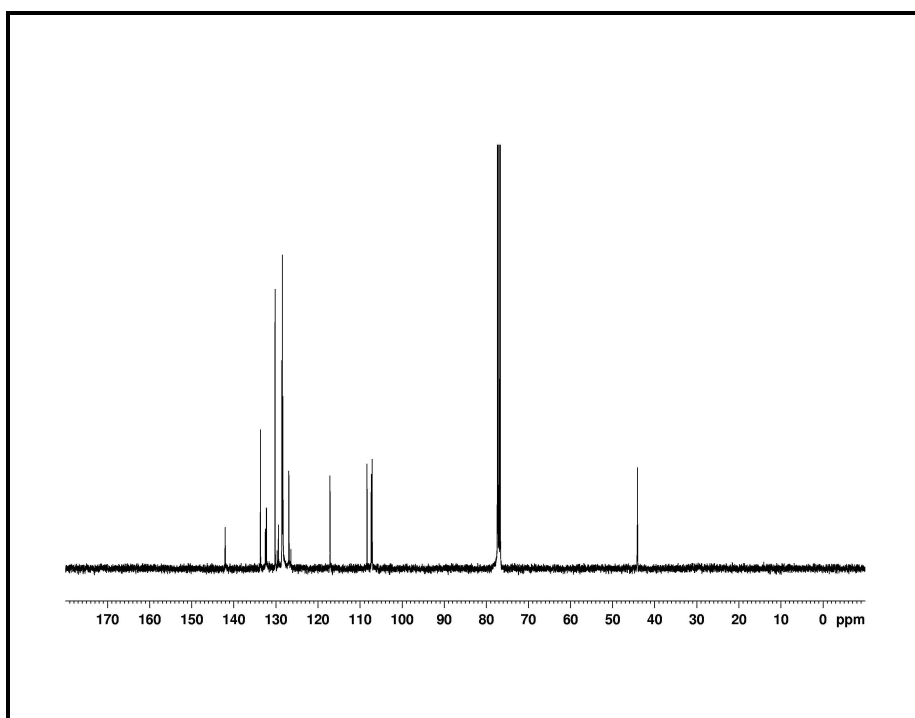


Figure 5.17. ^{13}C NMR spectrum of **149** in CDCl_3 .

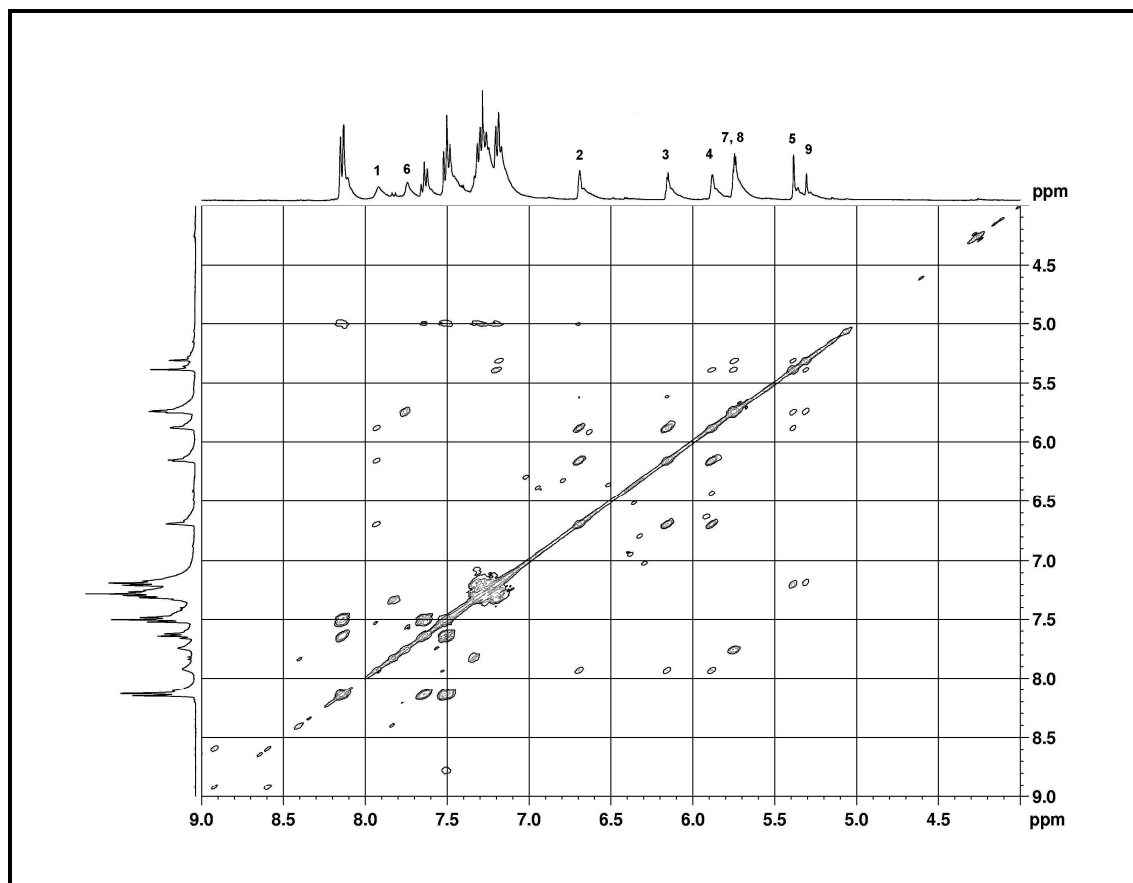
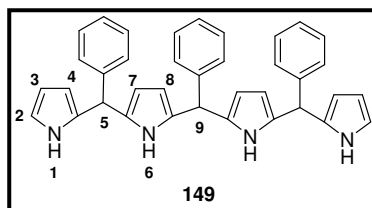
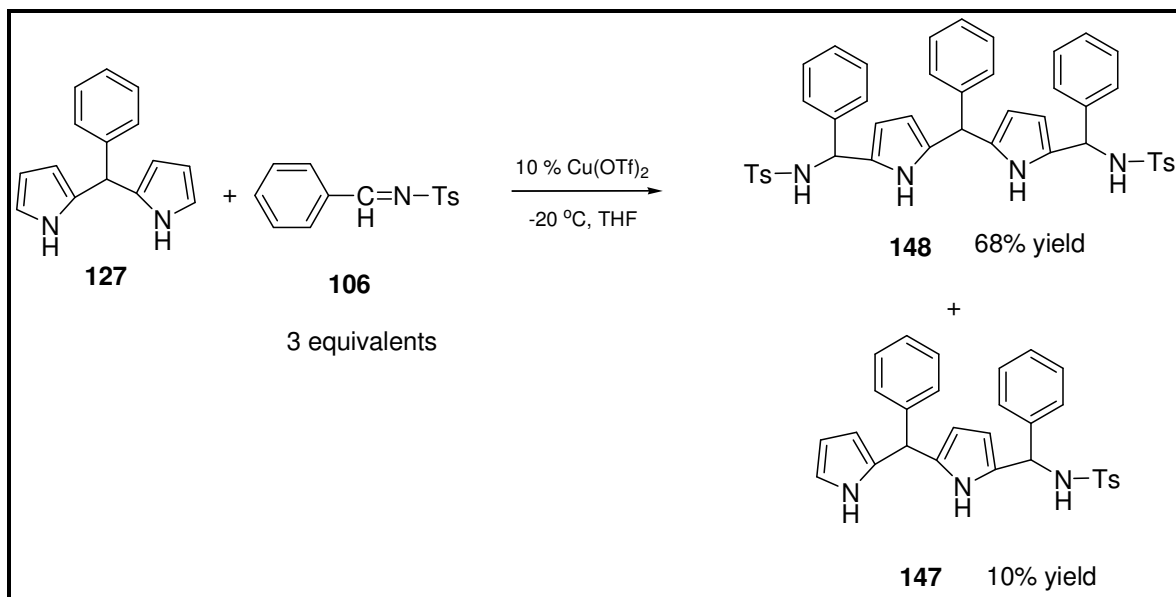


Figure 5.18. COSY spectrum of **149**.

The COSY spectrum of **149** (Figure 5.18) supports the suggested structure. Neighbour protons of two pyrrole rings correlate with each other. *meso* Hydrogen **5** correlates with pyrrolic hydrogens **4** and **7**, while other *meso* carbons **9** correlates with only hydrogen **8**.

After the synthesis of **147**, the synthesis of di sulfonamidealkylated dipyrrromethane product **148** was carried out by the reaction of three equivalents of *N*-tosyl imine with dipyrrromethane in the presence of 10% Cu(OTf)₂ at -20 °C. The expected product isolated after work-up and purification procedures in 68% yield. The mono sulfonamidealkylated dipyrrromethane **147** was also obtained as side product in 10 % yield (Scheme 5.29).



Scheme 5.29. The synthesis of di sulfonamidealkylated dipyrromethane product **148**.

The di sulfonamidealkylated product **148** has two asymmetric centers and one pseudoasymmetric center. Accordingly it was obtained as the mixture of stereoisomers and the ¹H NMR and ¹³C NMR spectra of compound **148** were identified as the mixture of diastereoisomers.

Figure 5.19 shows the ¹H NMR spectrum of compound **148**. Broad signals of NH pyrrole protons **4** appear at 8.25, 8.42 and 8.47 ppm. Aromatic protons of phenyl groups give multiplets between 7.00 - 7.50 ppm. Two NH protons of sulfonamide groups **2** appear as doublet at 6.37 and 6.44 ppm. Signals between 5.18 and 5.78 ppm belong to *meso* CH and pyrrole CH protons (**3**, **5**, **6** and **7**). Methyl protons **1** of tosyl groups give singlet signals at 2.24 and 2.25 ppm.

Figure 5.20 shows the ¹³C NMR spectrum of **148**. Characteristic peaks of C(3) and C(4) carbons (**5** and **6**) of pyrrole rings give signals between 106.15 and 107.65 ppm. CH carbon atoms of **3** give absorbance at 54.89, 54.99 and 55.11 ppm. *meso* CH proton **7** appears at 43.02 and 43.12. Methyl carbons give signals at 20.42 and 20.45.

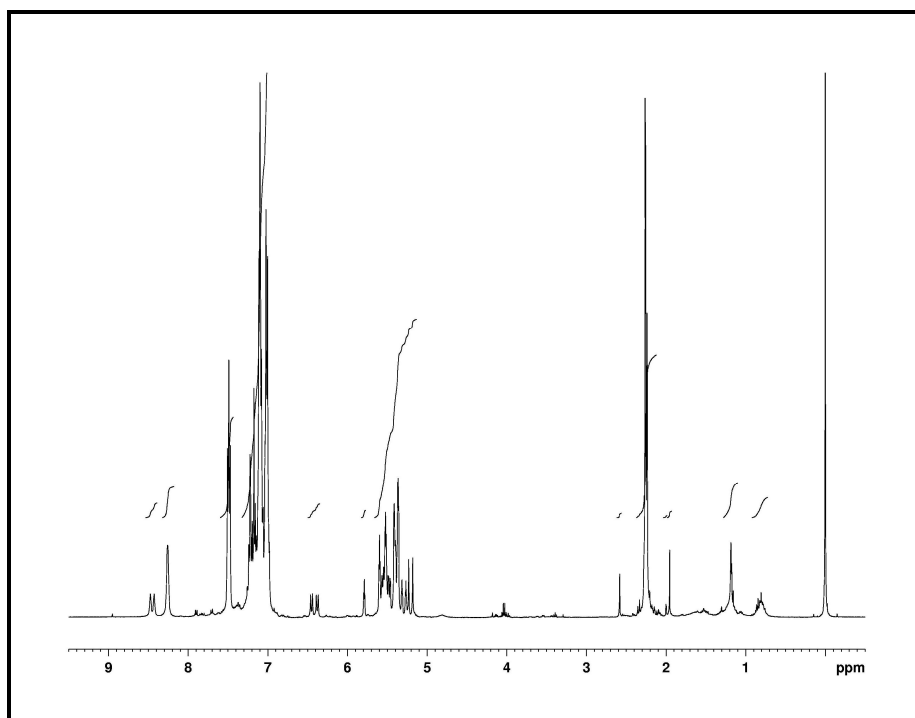
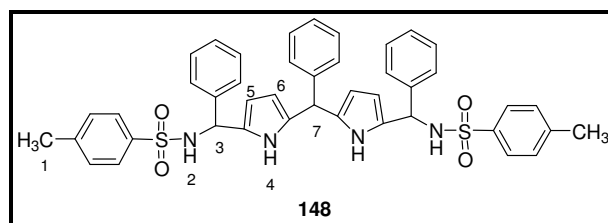


Figure 5.19. ^1H NMR spectrum of **148**.

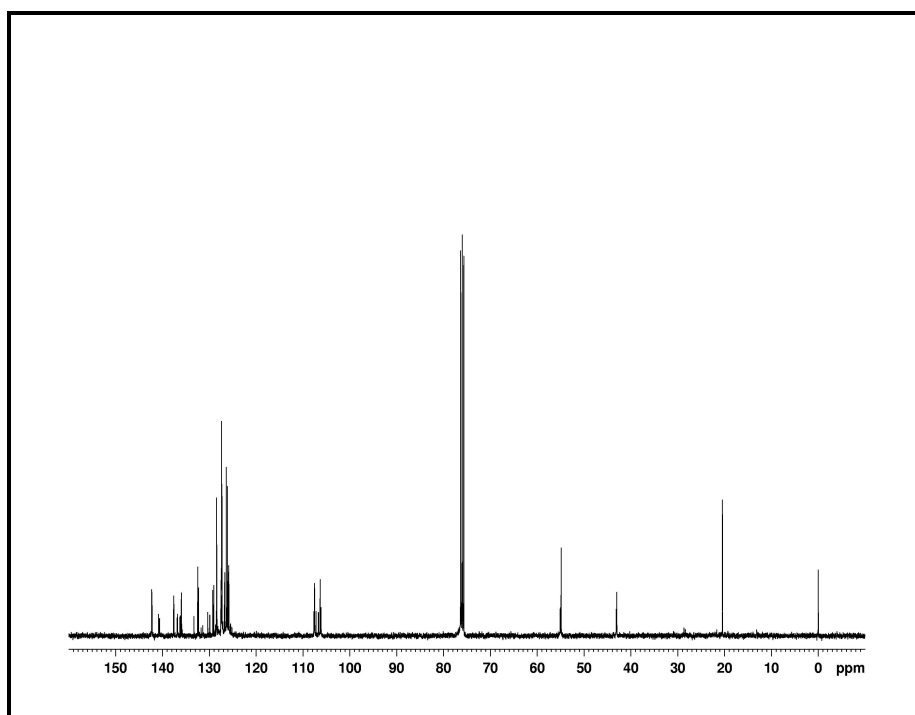
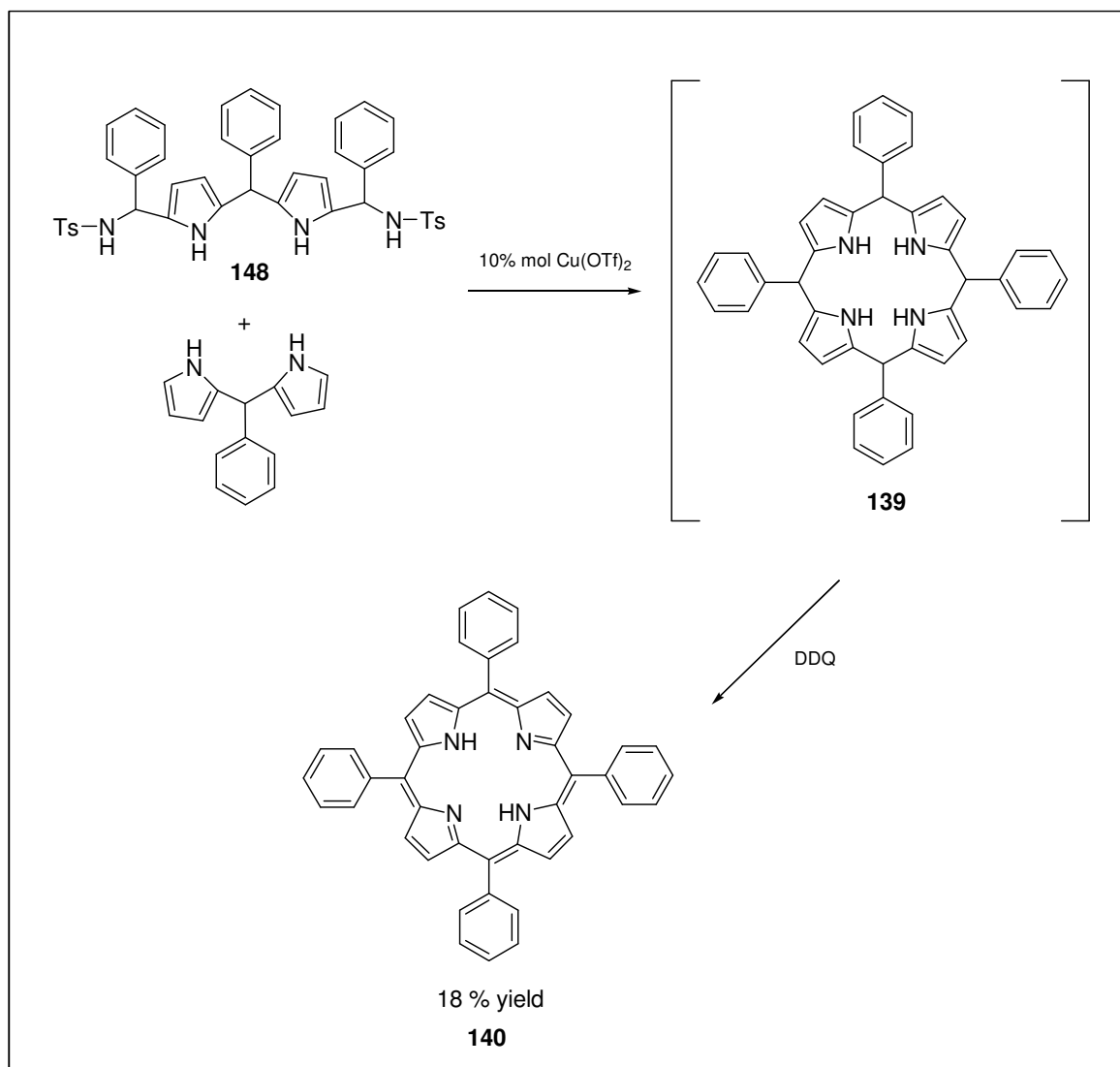


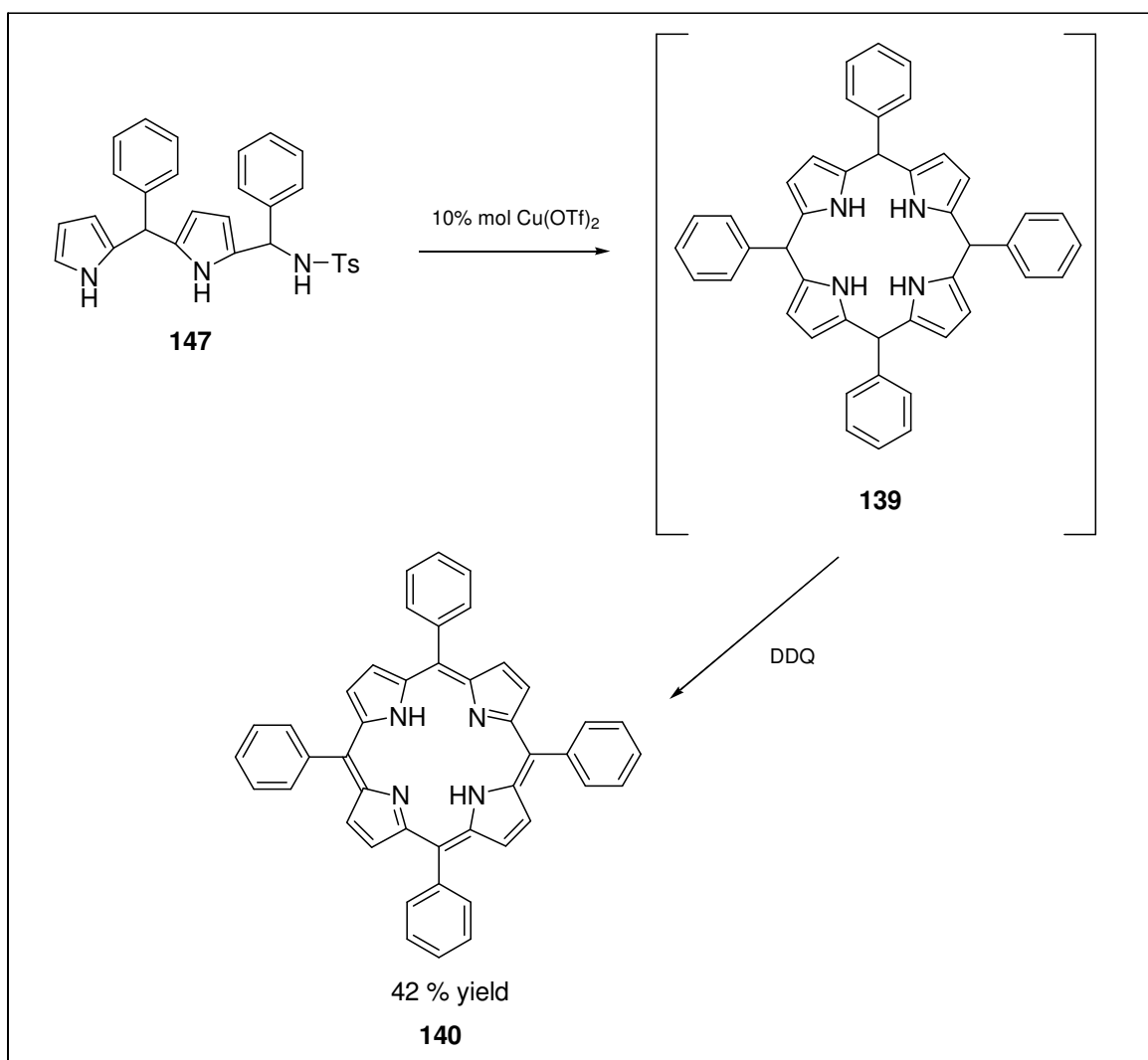
Figure 5.20. ^{13}C NMR spectrum of **148**.

The reaction of di sulfonamidealkylated dipyrromethane product **148** with 5-phenyldipyrromethane (**127**) was carried out in optimized reaction conditions (10^{-2} M of reactants, 10% mol $\text{Cu}(\text{OTf})_2$). The TPP product was isolated only in 18% yield (Scheme 5.30).



Scheme 5.30. The synthesis of porphyrin **140** via condensation of **148** with 5-phenyl dipyrromethane (**127**).

The porphyrin formation reaction through self-condensation reaction of mono sulfonamidealkylated dipyrromethane **147** was carried out in CH_2Cl_2 at room temperature in the presence of $\text{Cu}(\text{OTf})_2$. The concentration of the reactant **147** was adjusted as 10^{-2} M and DDQ was added to the reaction after 1.5 h. The yield of TTP (**140**) was obtained in 42% yield (Scheme 5.31).



Scheme 5.31. The synthesis of porphyrin **140** via self cyclization of **147**.

These results indicate that the formation of porphyrin from the reaction of dipyrromethanes with *N*-tosyl imines goes through mainly the formation of mono sulfonamidealkylated dipyrromethane and self condensation of this product.

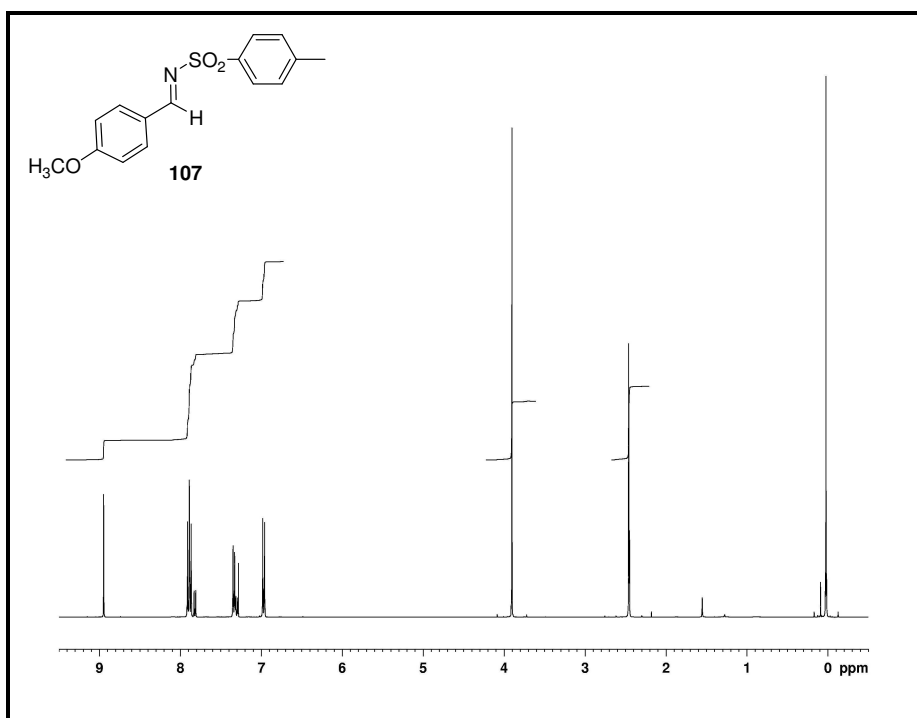


Figure 5.21. ¹H NMR Spectrum of **107** in CDCl₃-CCl₄

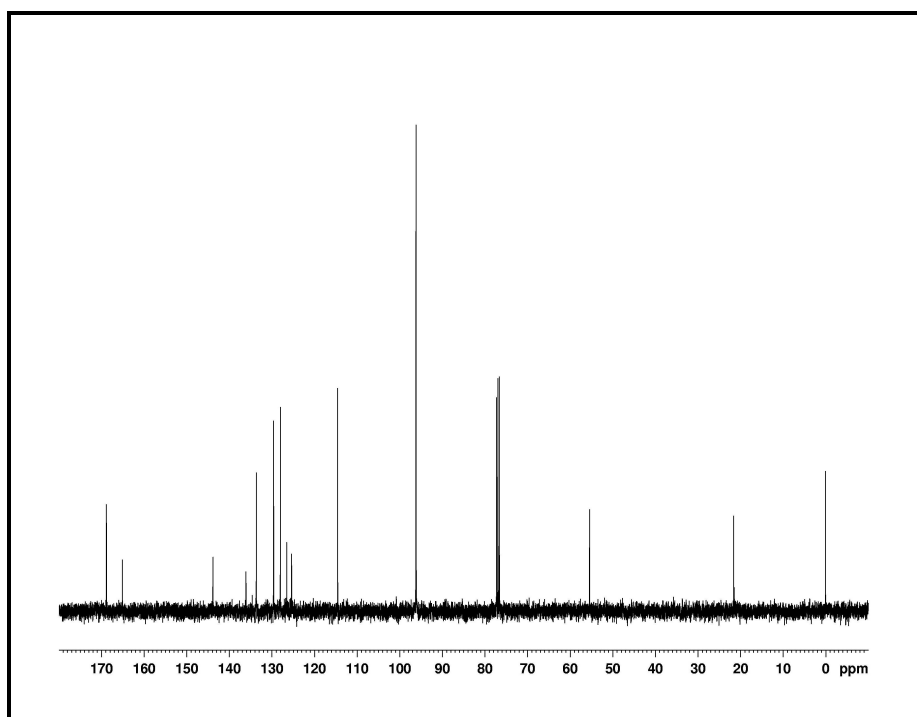


Figure 5.22. ¹³C NMR Spectrum of **107** in CDCl₃-CCl₄

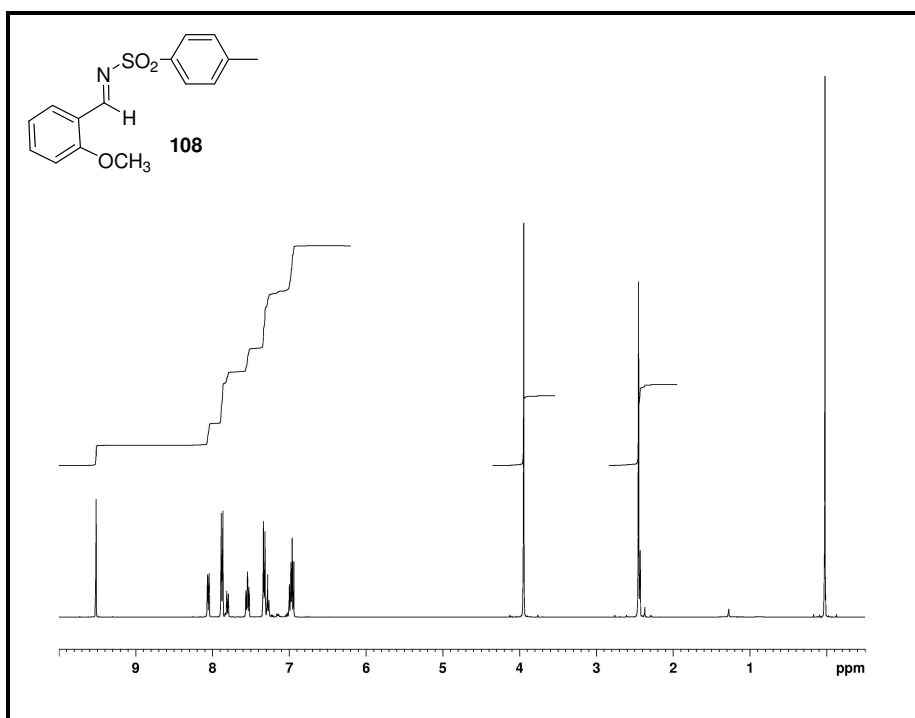


Figure 5.23. ¹H NMR Spectrum of **108** in CDCl₃-CCl₄

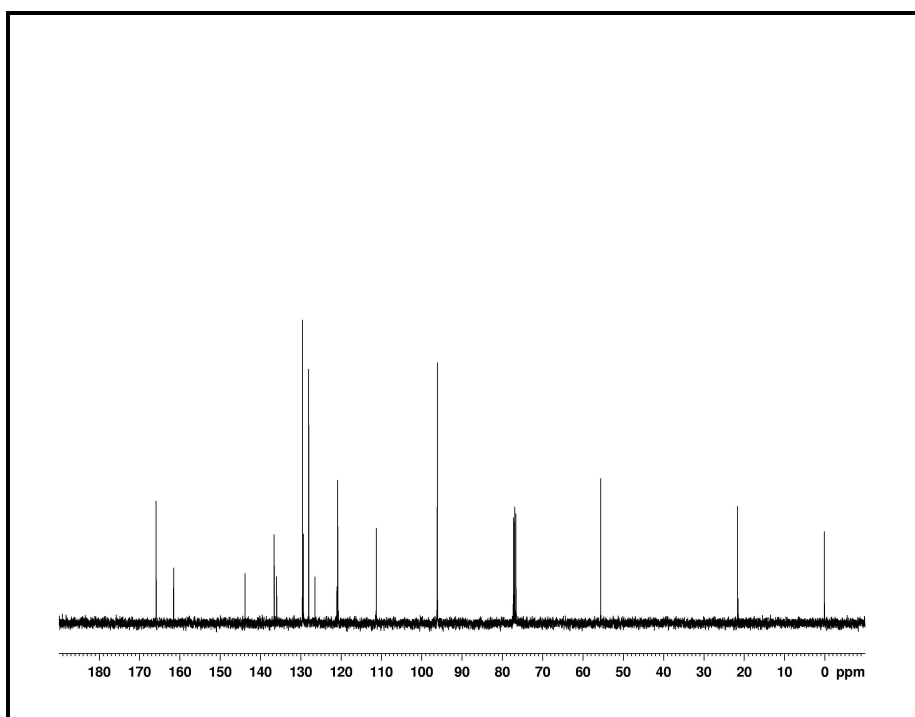


Figure 5.24. ¹³C NMR Spectrum of **108** in CDCl₃-CCl₄

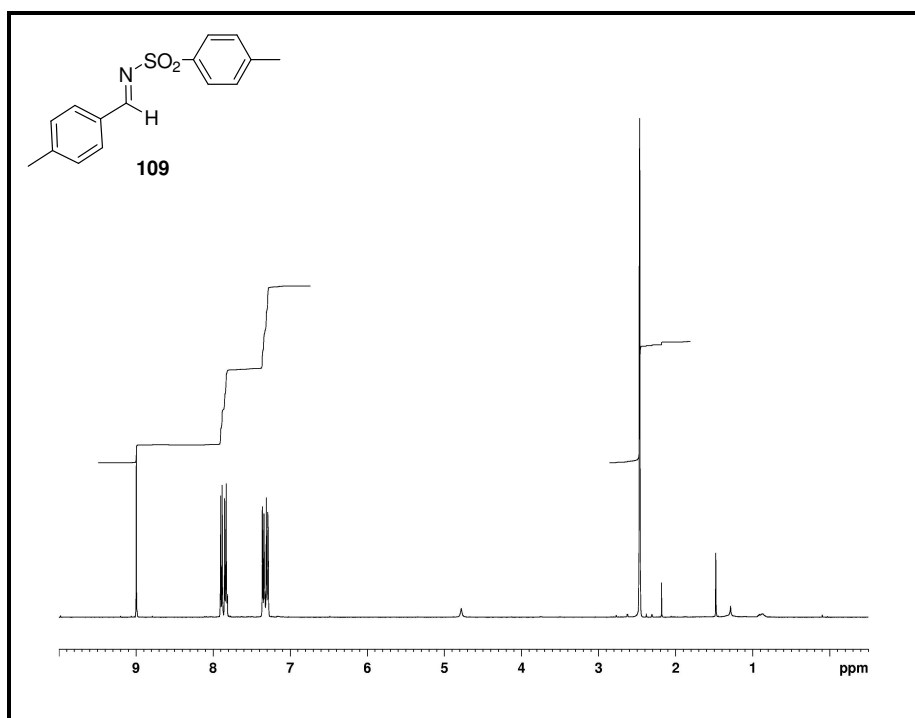


Figure 5.25. ¹H NMR Spectrum of **109** in CDCl₃-CCl₄

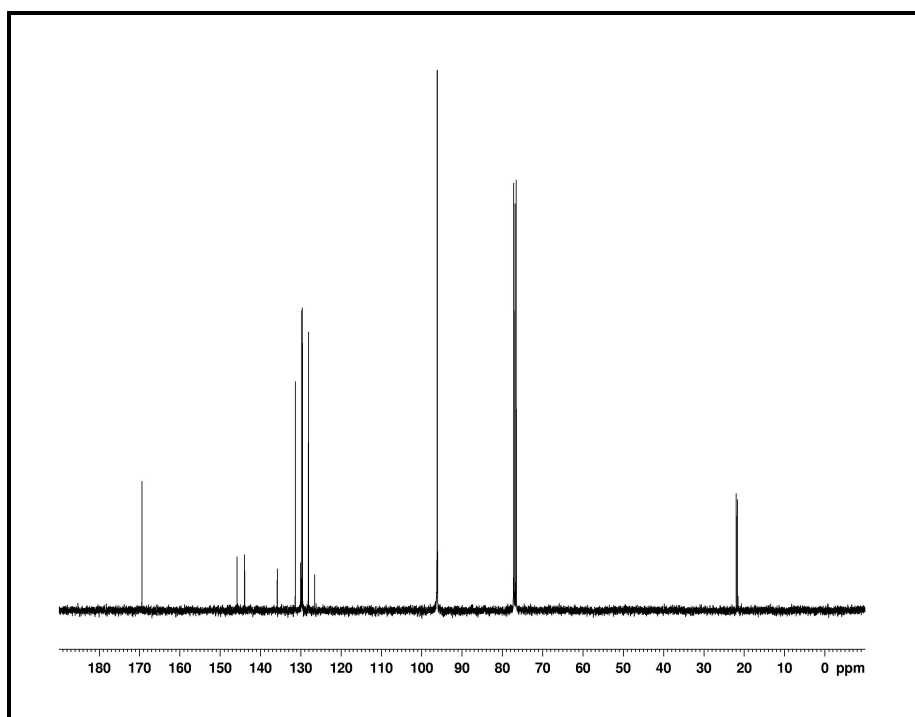


Figure 5.26. ¹³C NMR Spectrum of **109** in CDCl₃-CCl₄

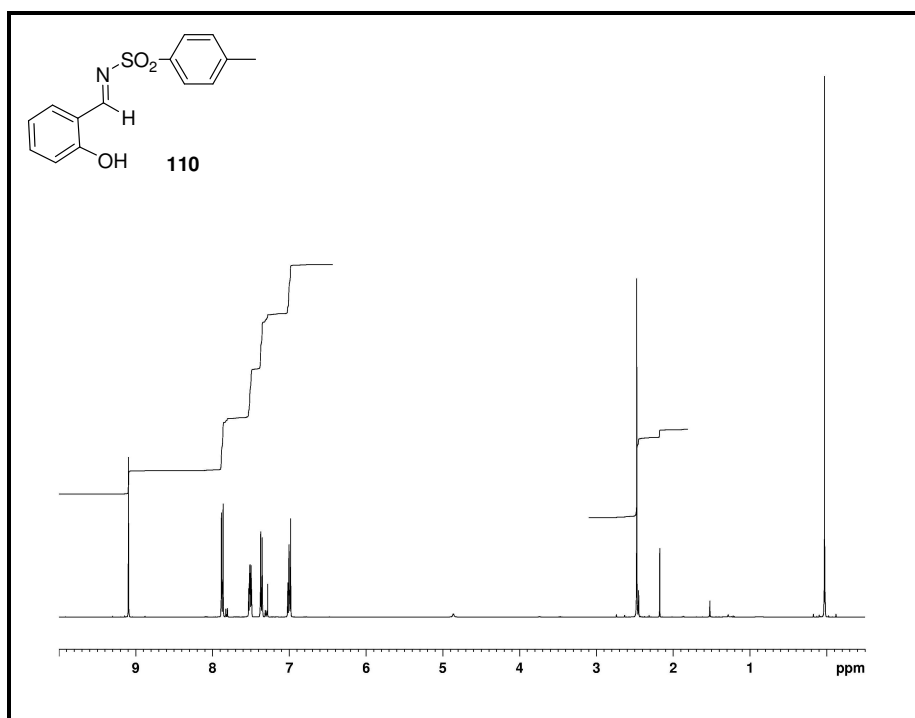


Figure 5.27. ¹H NMR Spectrum of **110** in CDCl₃-CCl₄

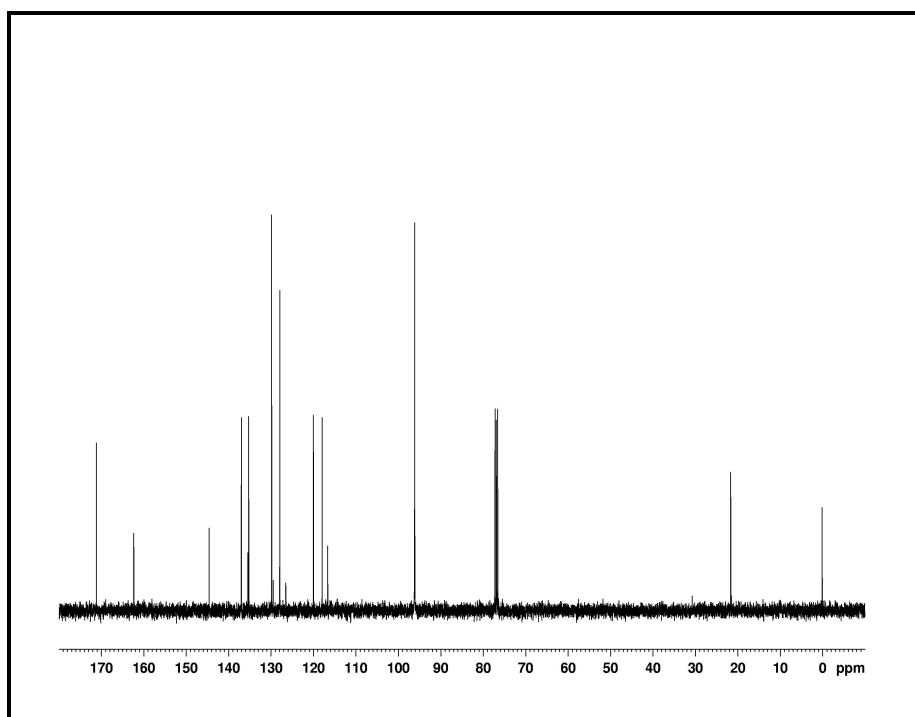


Figure 5.28. ¹³C NMR Spectrum of **110** in CDCl₃-CCl₄

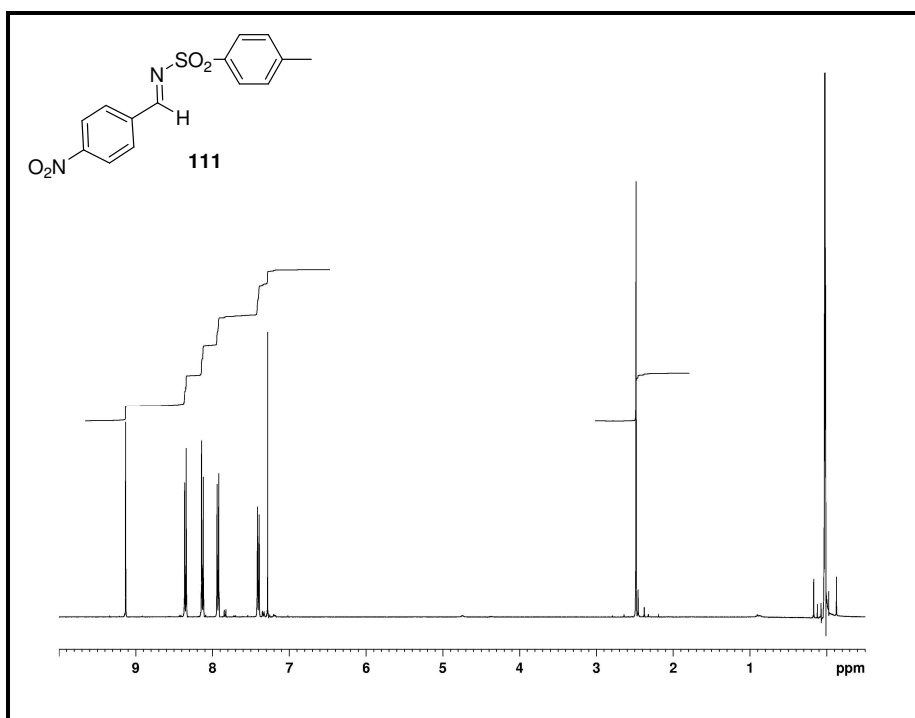


Figure 5.29. ^1H NMR Spectrum of **111** in $\text{CDCl}_3\text{-CCl}_4$

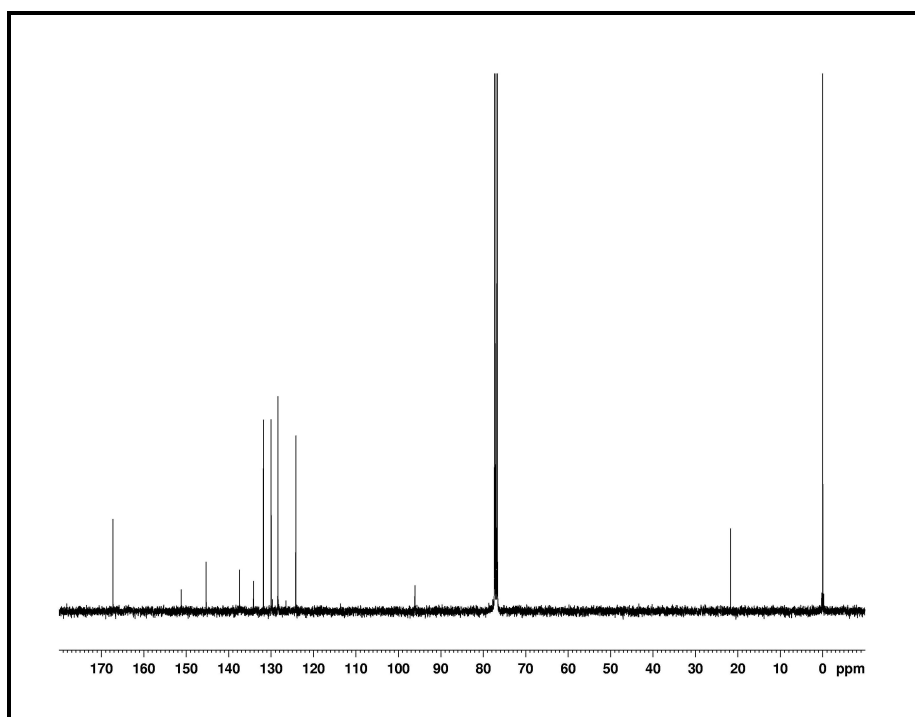


Figure 5.30. ^{13}C NMR Spectrum of **111** in $\text{CDCl}_3\text{-CCl}_4$

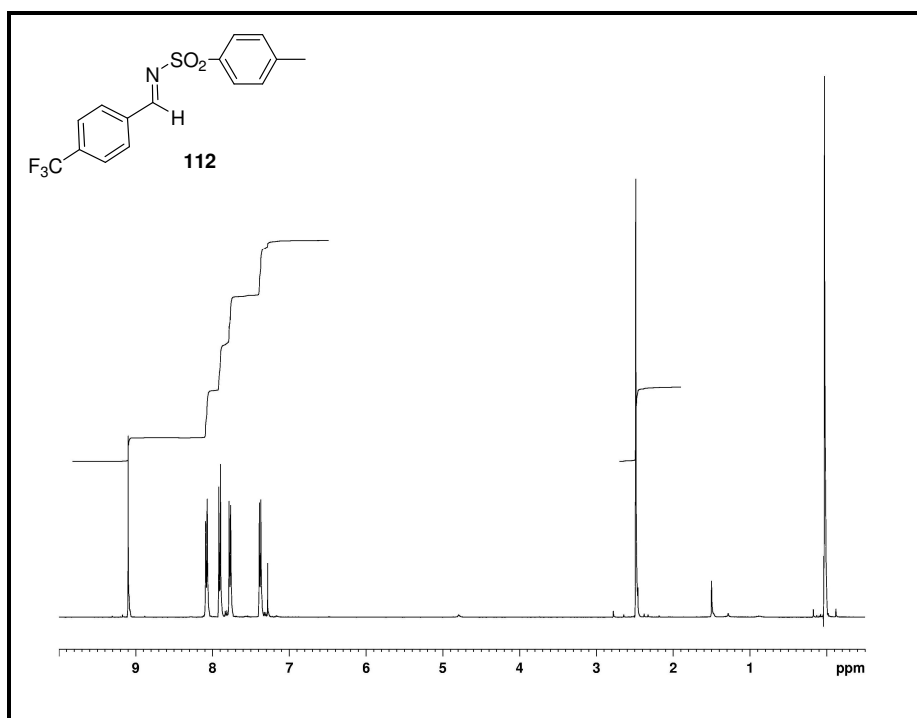


Figure 5.31. ¹H NMR Spectrum of **112** in CDCl₃-CCl₄

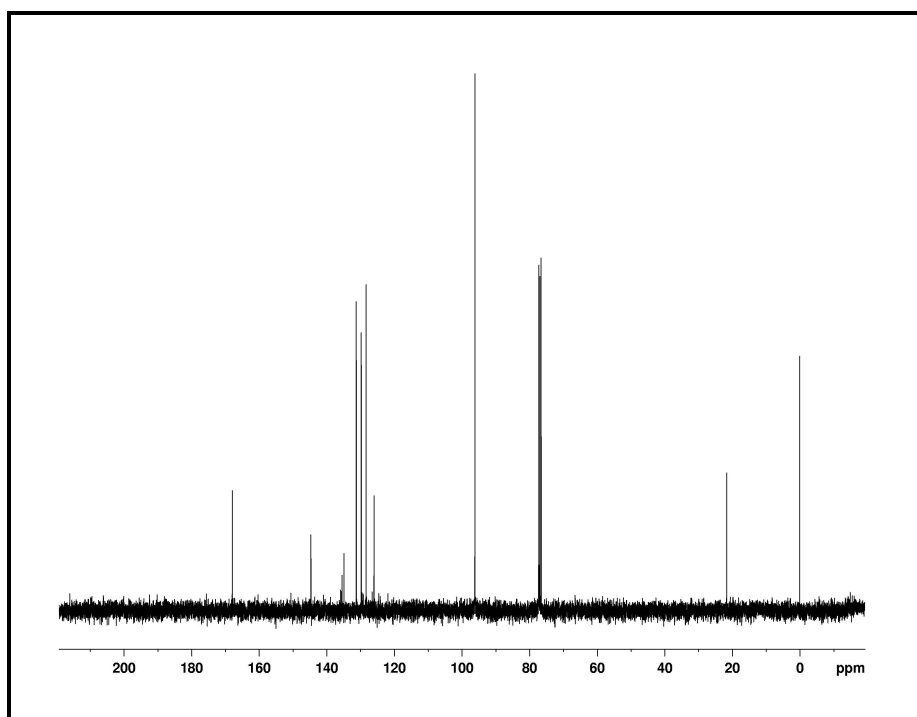


Figure 5.32. ¹³C NMR Spectrum of **112** in CDCl₃-CCl₄

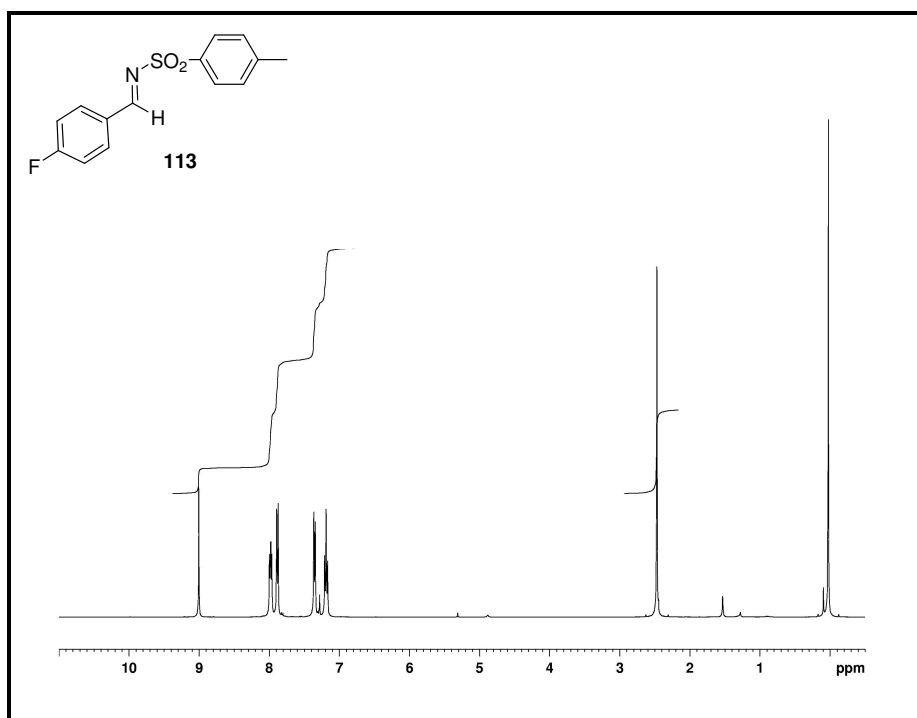


Figure 5.33. ¹H NMR Spectrum of **113** in CDCl₃-CCl₄

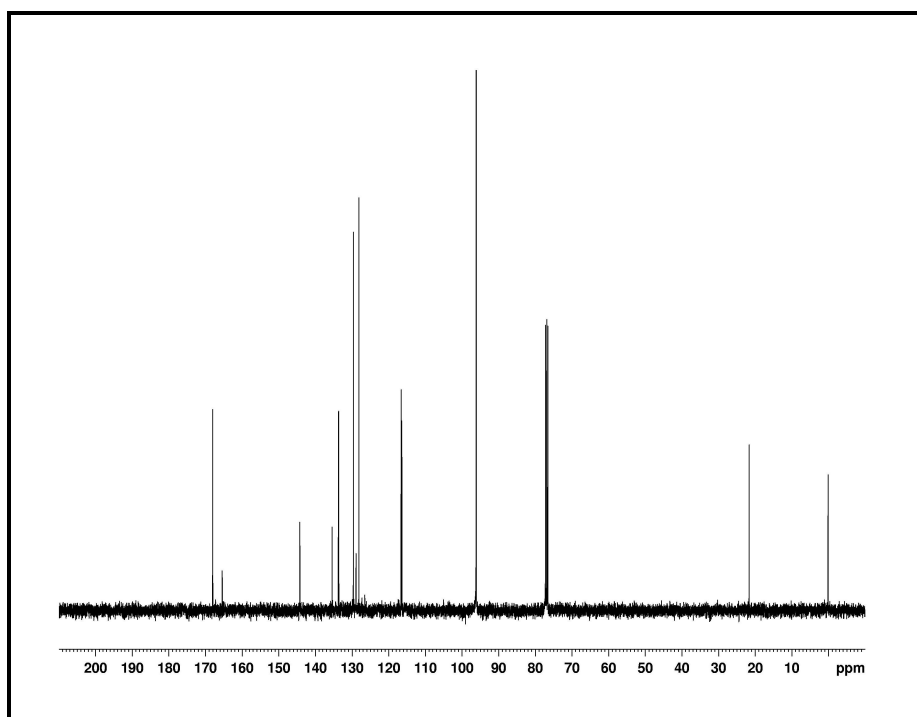


Figure 5.34. ¹³C NMR Spectrum of **113** in CDCl₃-CCl₄

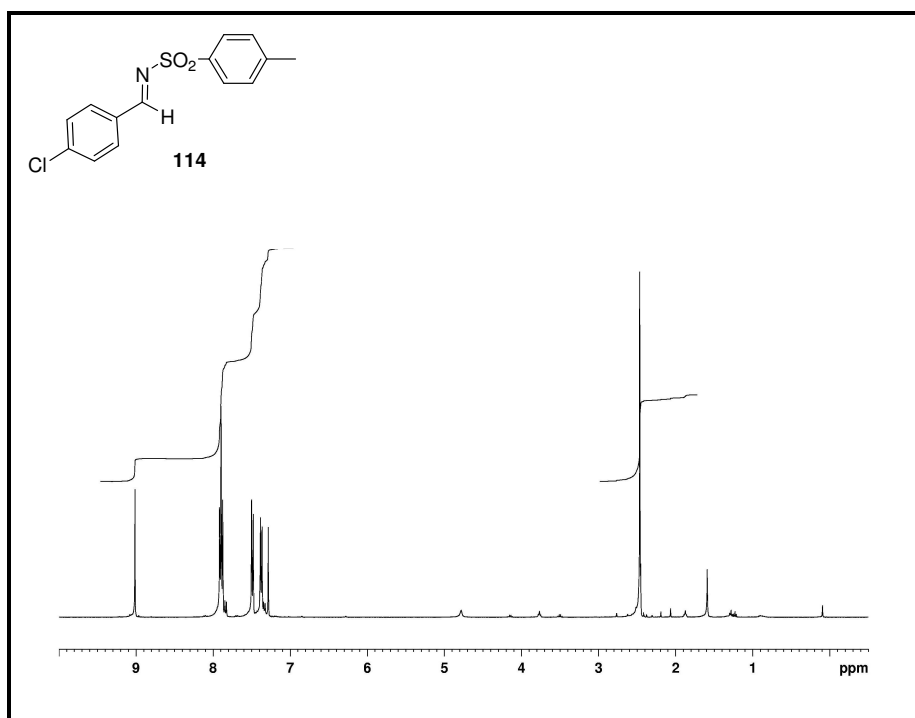


Figure 5.35. ¹H NMR Spectrum of **114** in CDCl₃-CCl₄

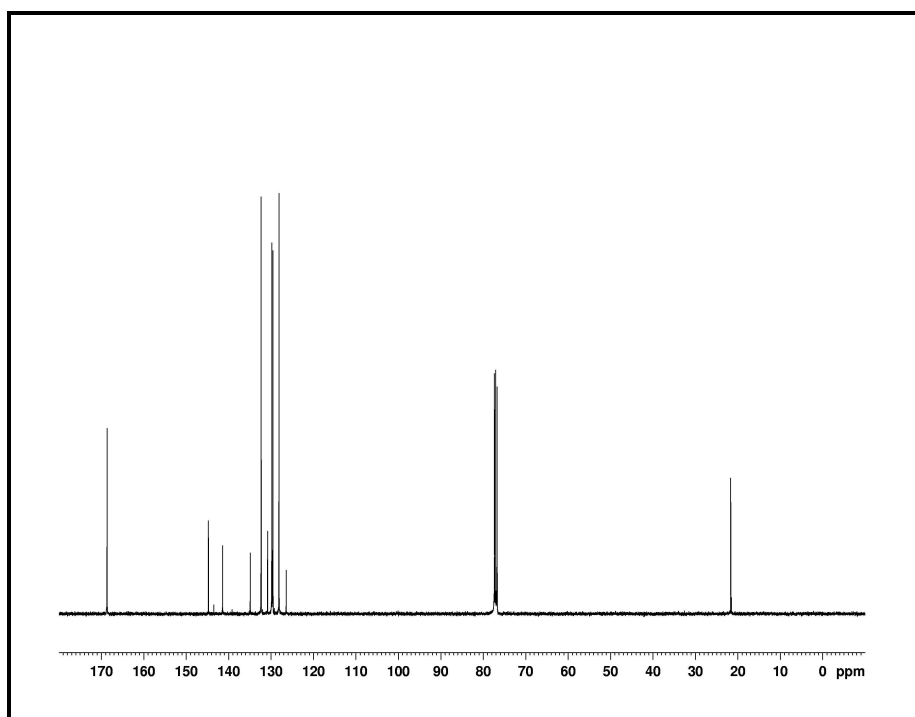


Figure 5.36. ¹³C NMR Spectrum of **114** in CDCl₃-CCl₄

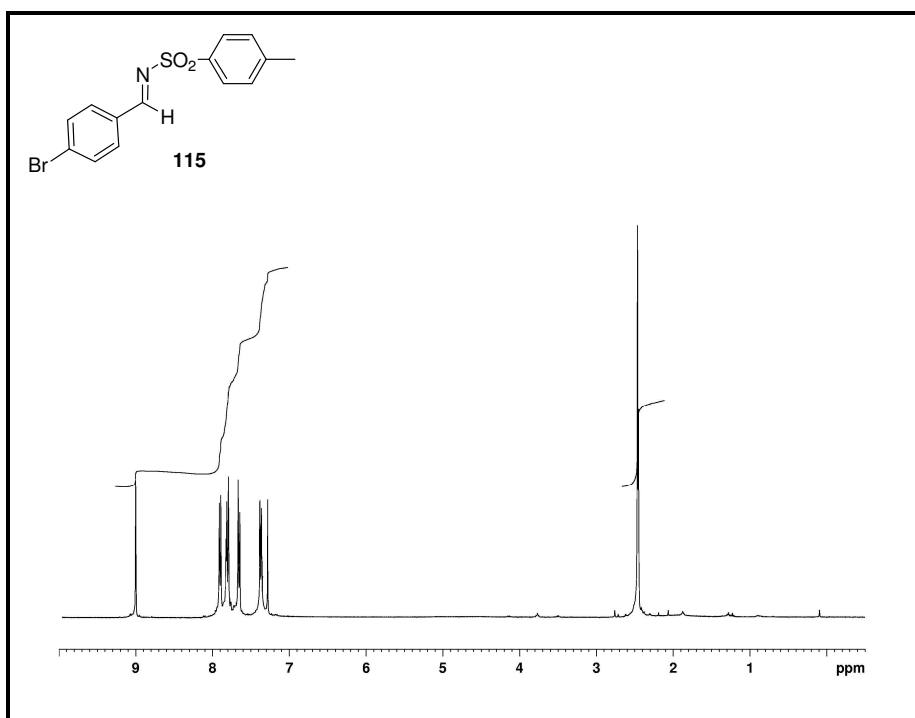


Figure 5.37. ^1H NMR Spectrum of **115** in $\text{CDCl}_3\text{-CCl}_4$

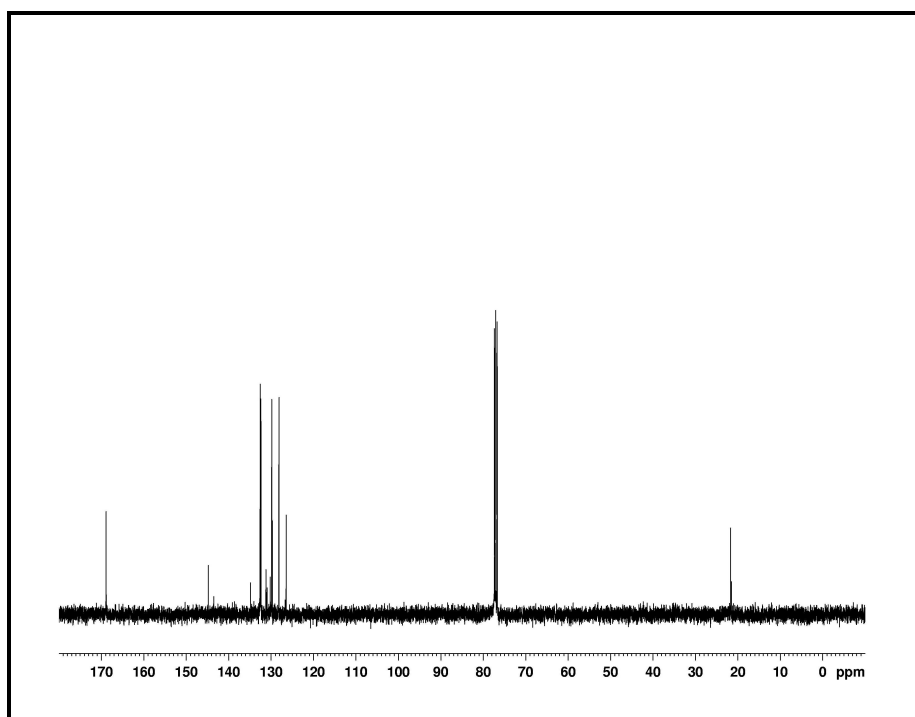


Figure 5.38. ^{13}C NMR Spectrum of **115** in $\text{CDCl}_3\text{-CCl}_4$

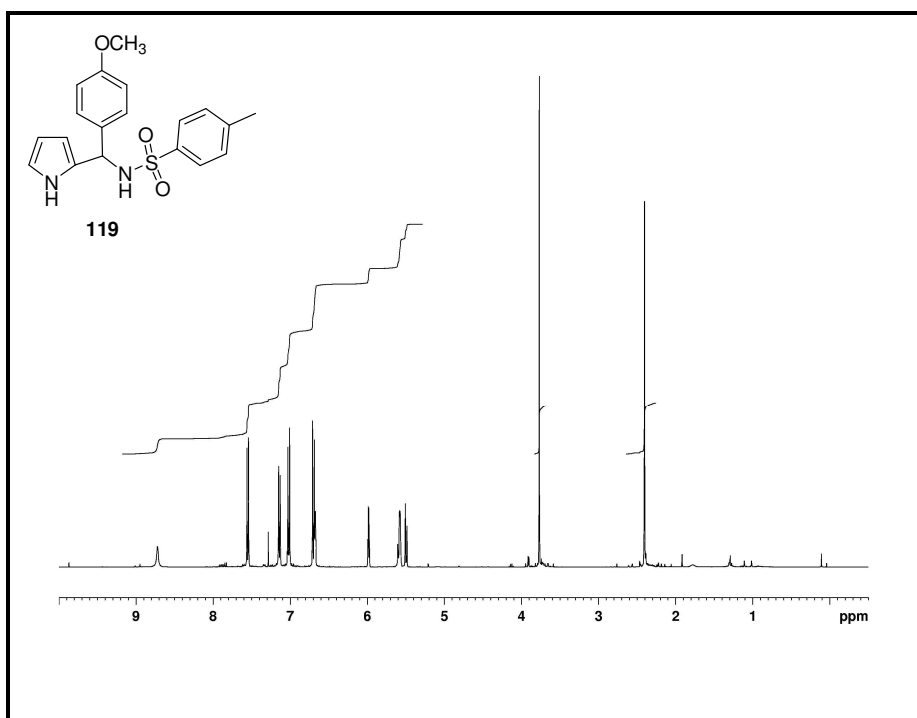


Figure 5.39. ¹H NMR Spectrum of **119** in CDCl₃-CCl₄

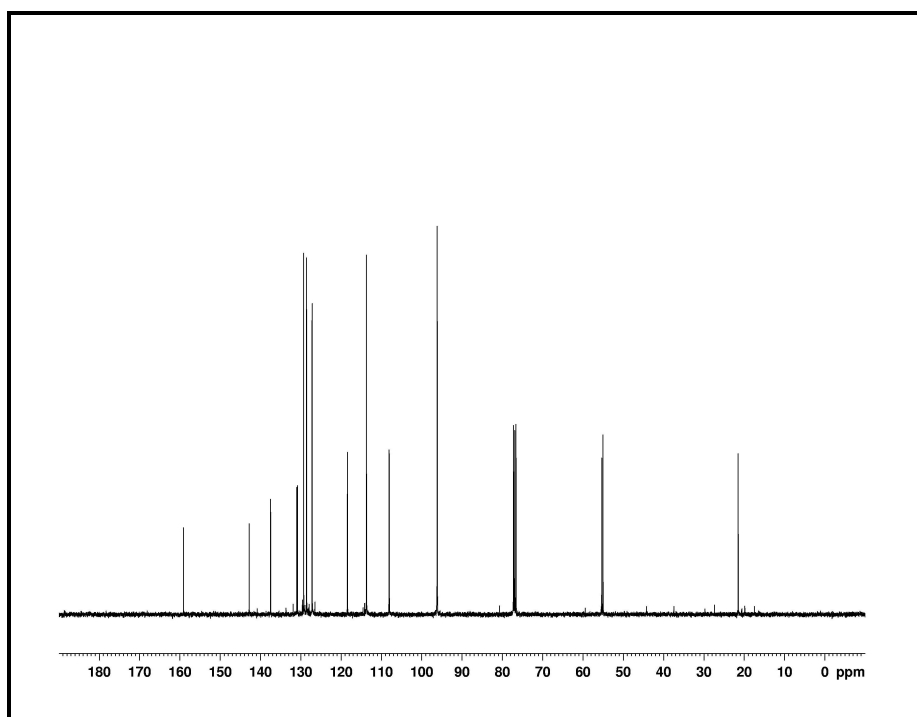


Figure 5.40. ¹³C NMR Spectrum of **119** in CDCl₃-CCl₄

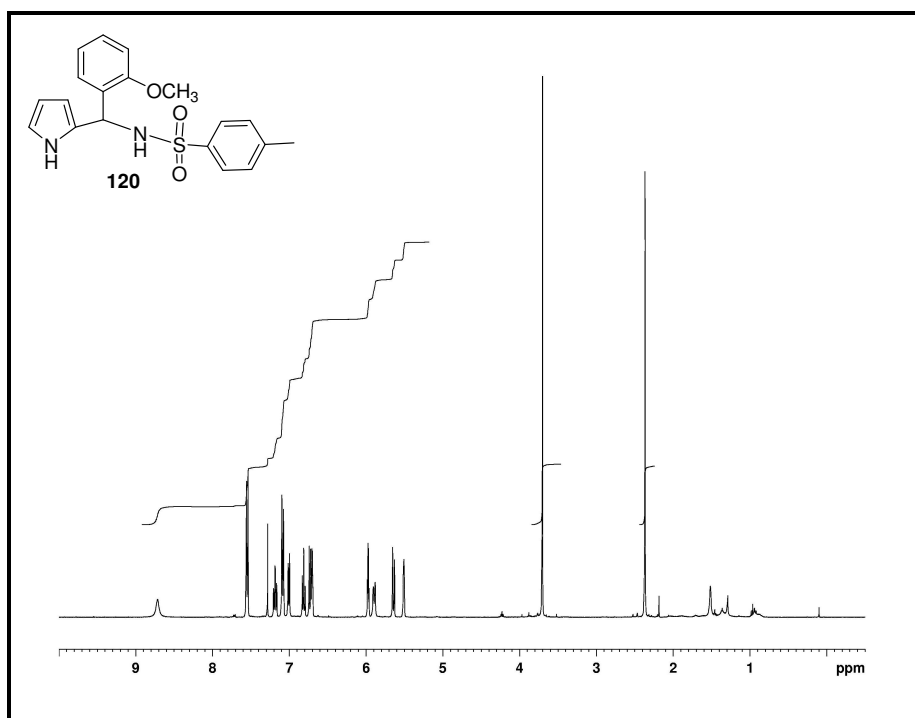


Figure 5.41. ¹H NMR Spectrum of **120** in CDCl₃-CCl₄

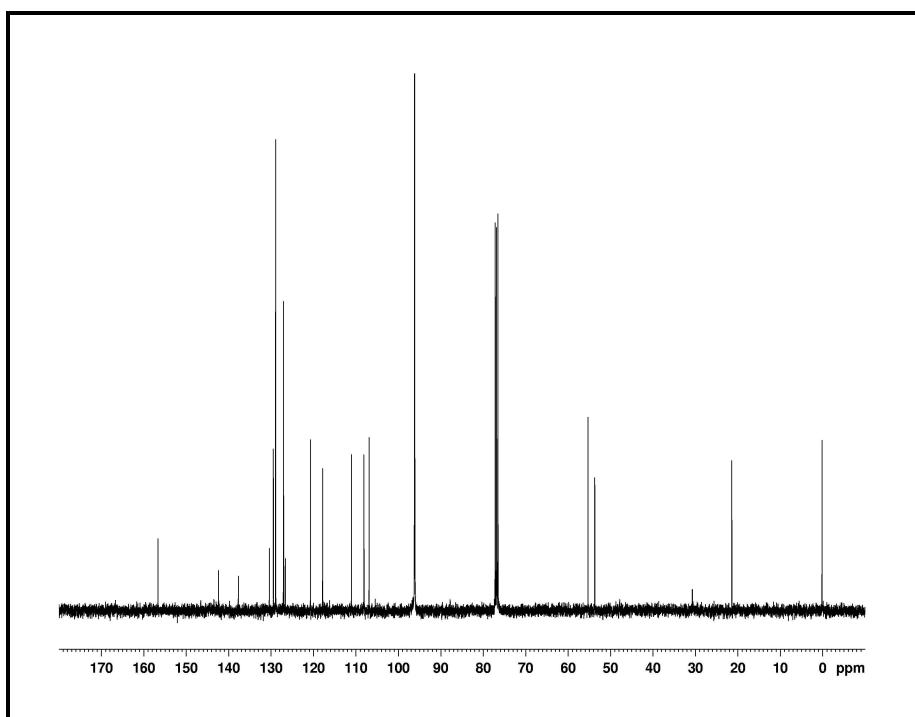


Figure 5.42. ¹³C NMR Spectrum of **120** in CDCl₃-CCl₄

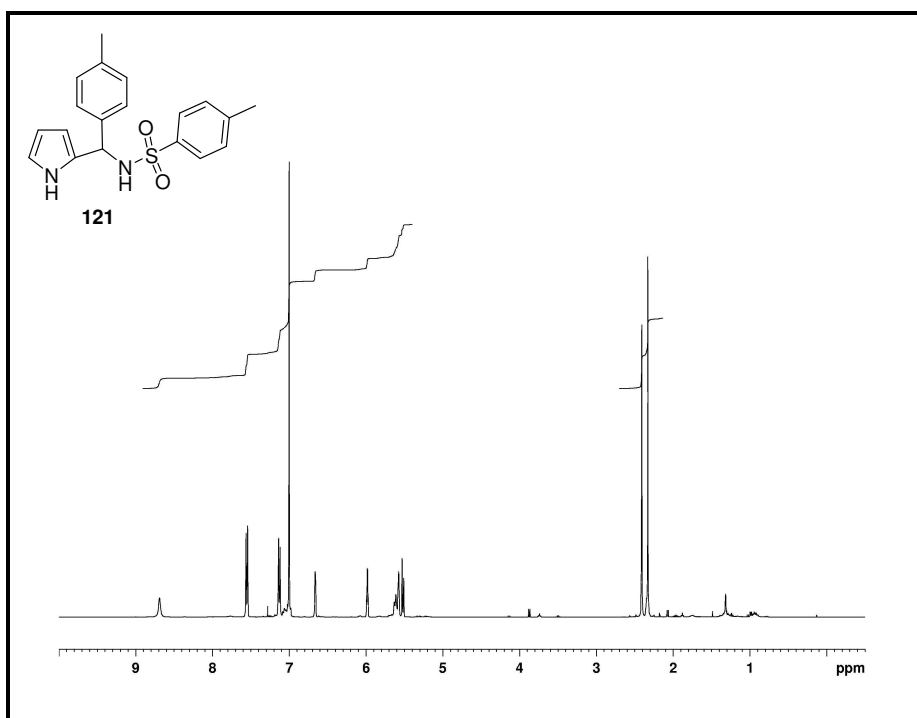


Figure 5.43. ¹H NMR Spectrum of **121** in CDCl₃-CCl₄

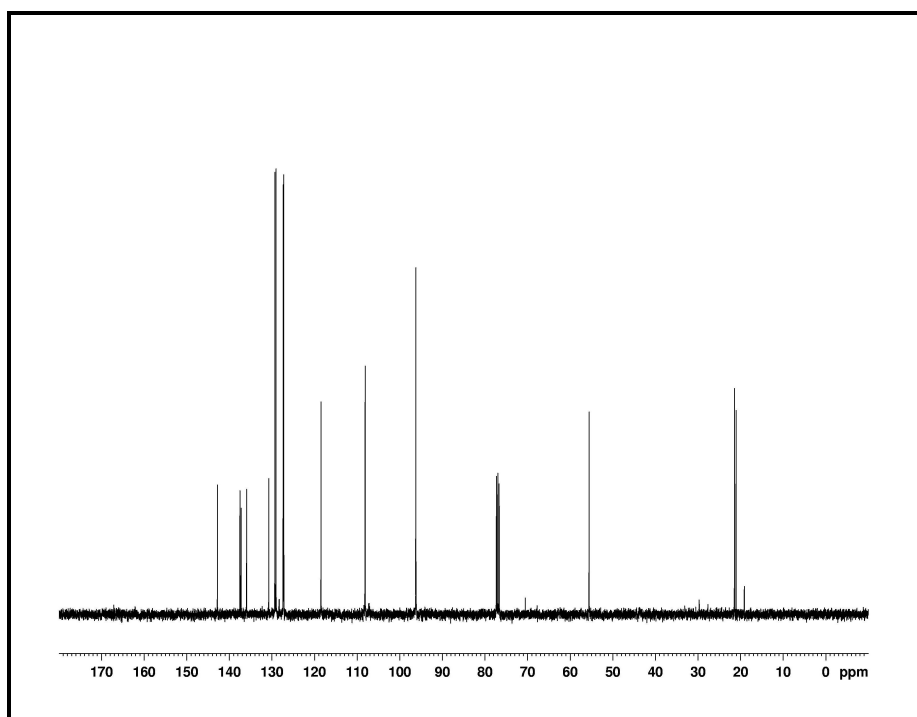


Figure 5.44. ¹³C NMR Spectrum of **121** in CDCl₃-CCl₄

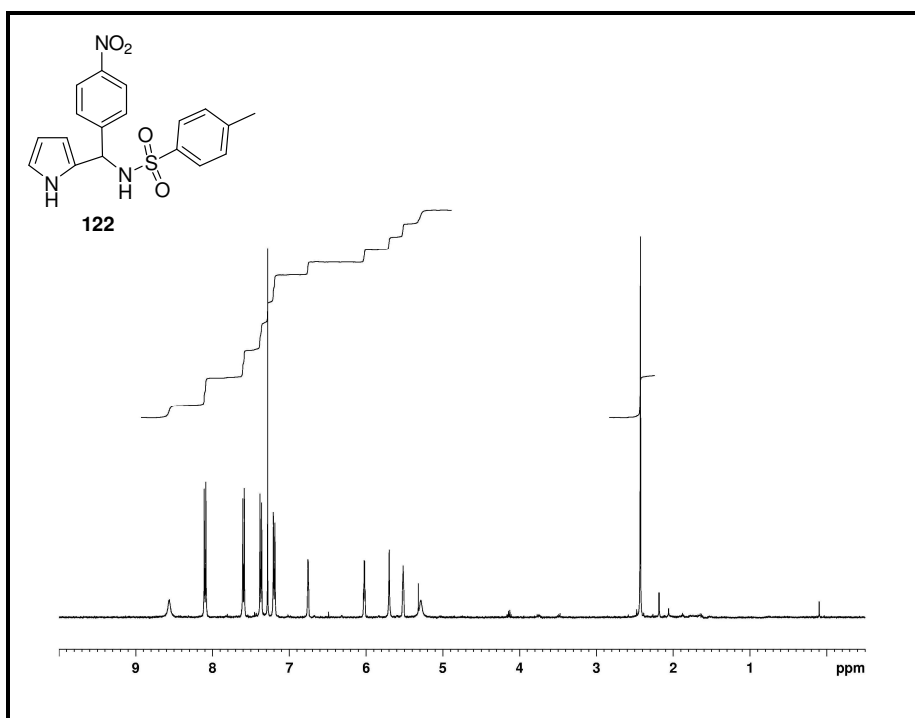


Figure 5.45. ^1H NMR Spectrum of **122** in $\text{CDCl}_3\text{-CCl}_4$

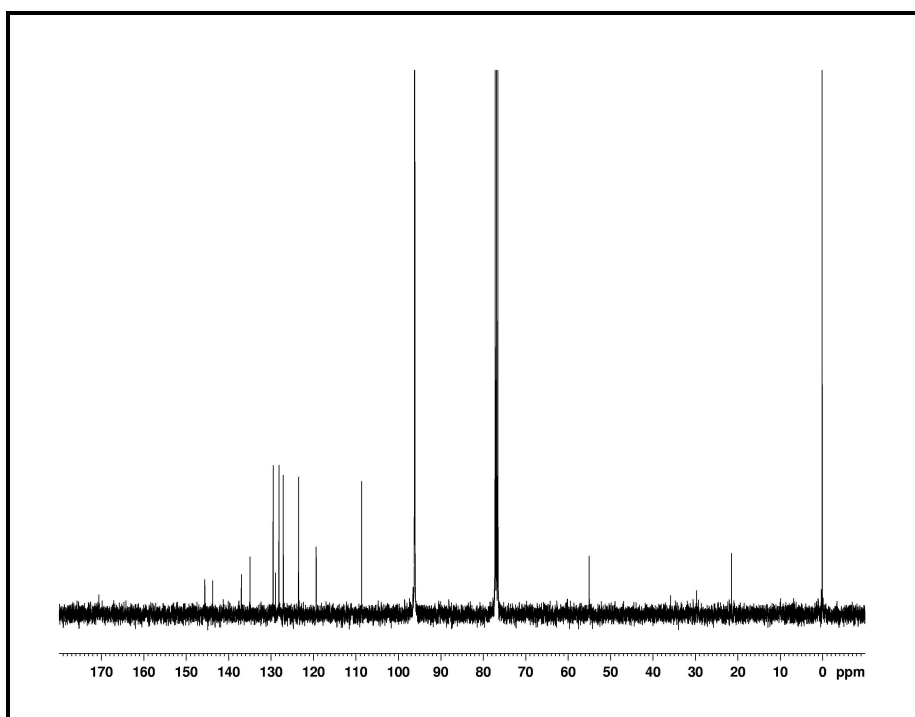


Figure 5.46. ^{13}C NMR Spectrum of **122** in $\text{CDCl}_3\text{-CCl}_4$

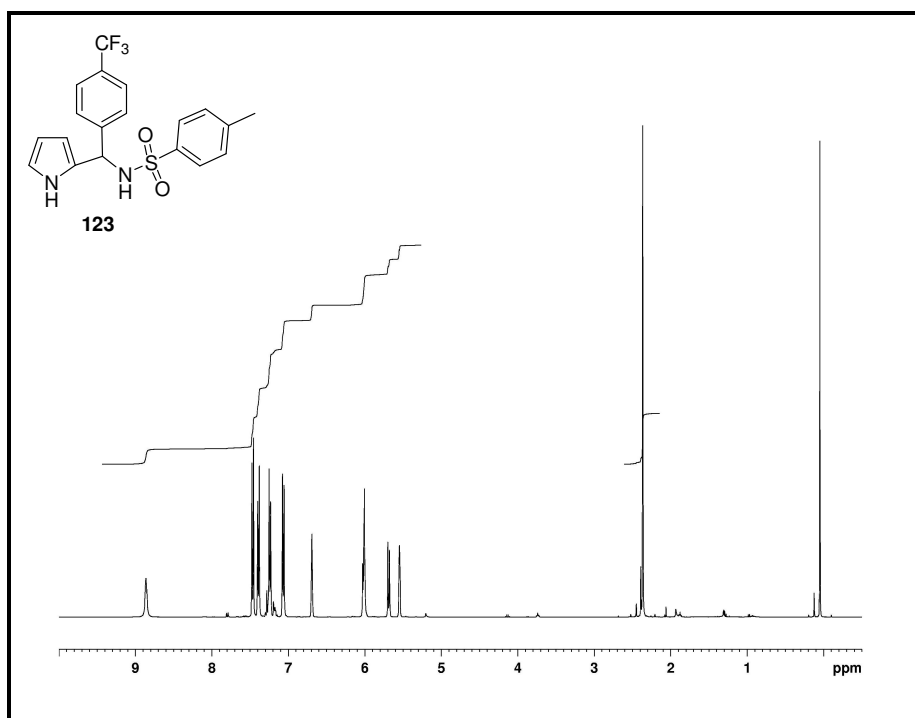


Figure 5.47. ¹H NMR Spectrum of **123** in CDCl₃-CCl₄

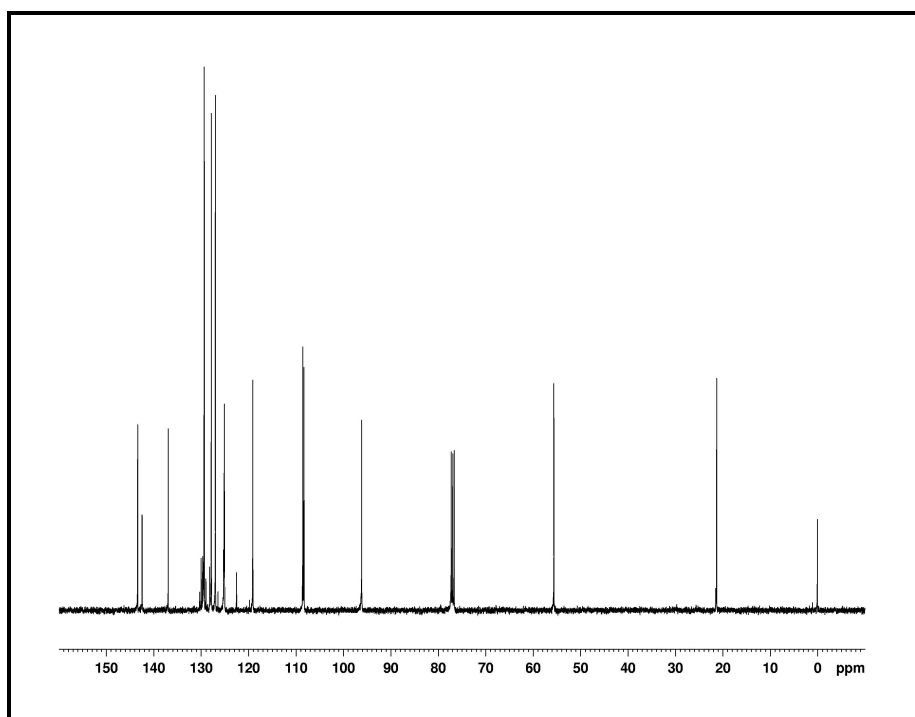


Figure 5.48. ¹³C NMR Spectrum of **123** in CDCl₃-CCl₄

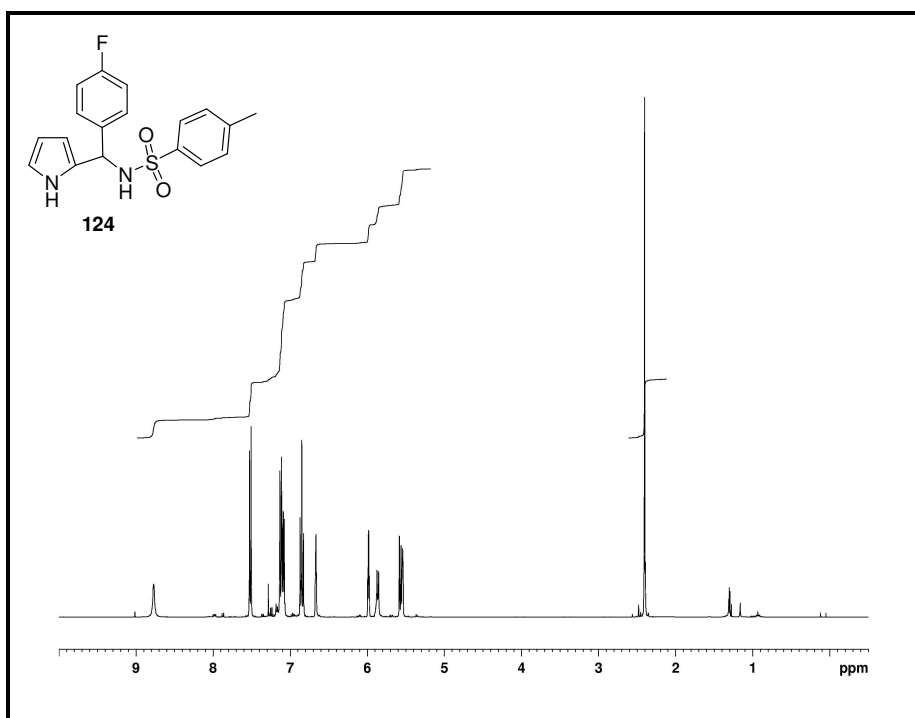


Figure 5.49. ^1H NMR Spectrum of **124** in $\text{CDCl}_3\text{-CCl}_4$

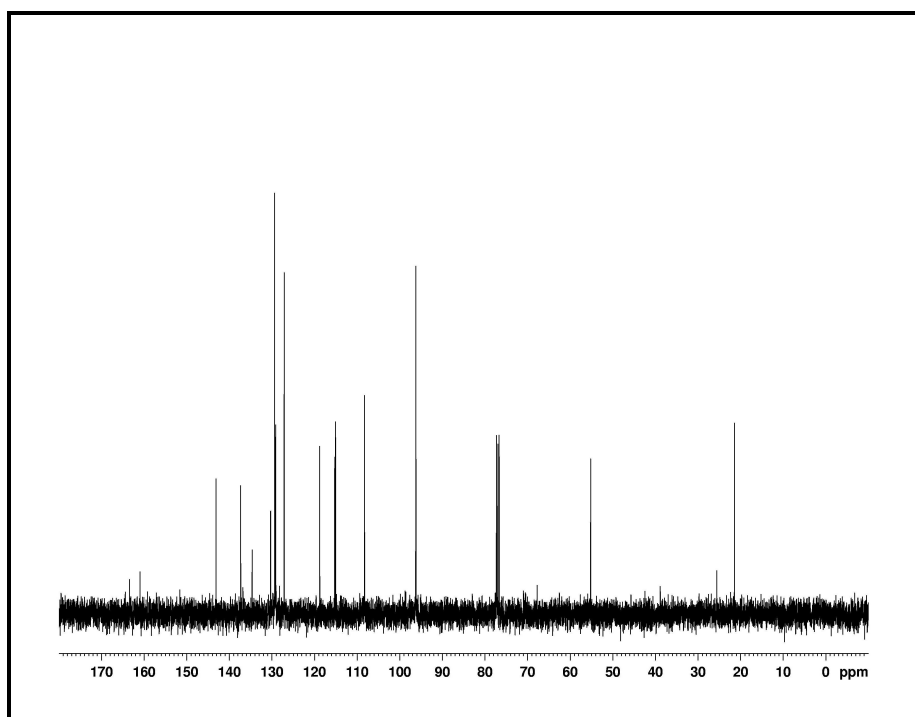


Figure 5.50. ^{13}C NMR Spectrum of **124** in $\text{CDCl}_3\text{-CCl}_4$

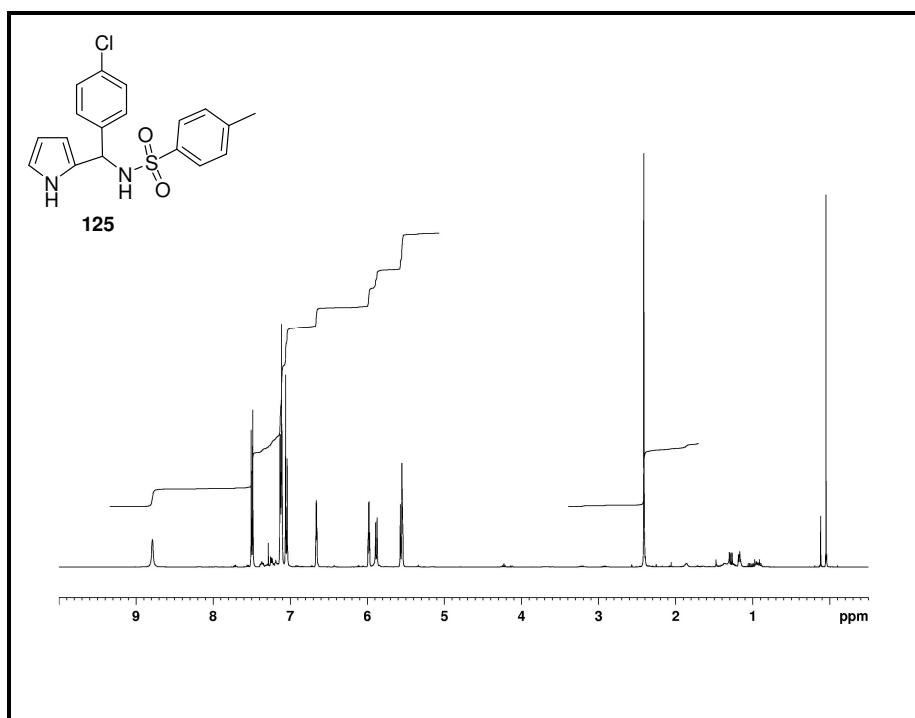


Figure 5.51. ¹H NMR Spectrum of **125** in CDCl₃-CCl₄

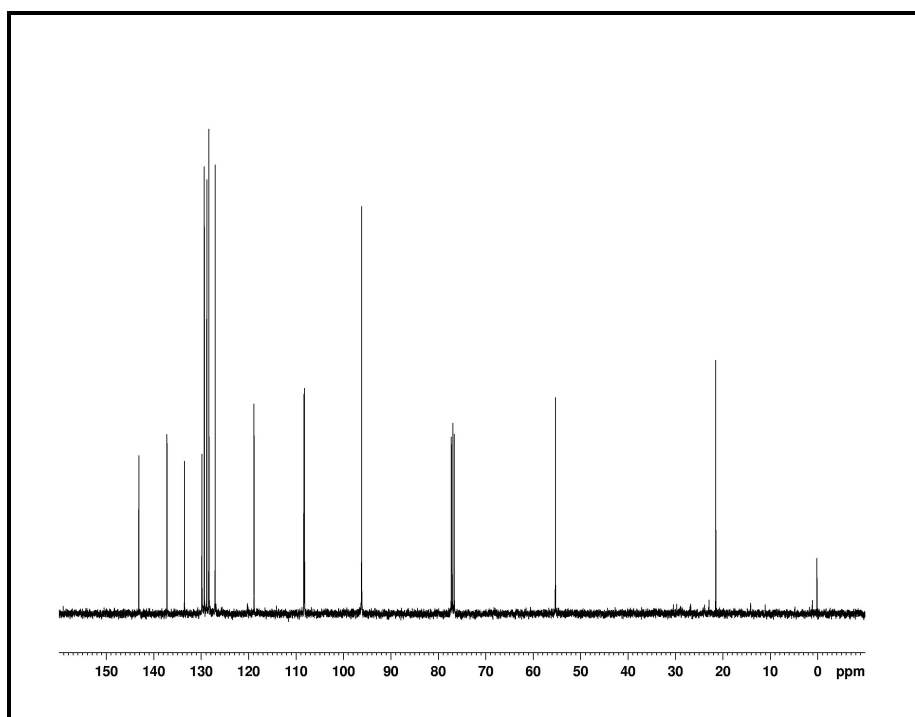


Figure 5.52. ¹³C NMR Spectrum of **125** in CDCl₃-CCl₄

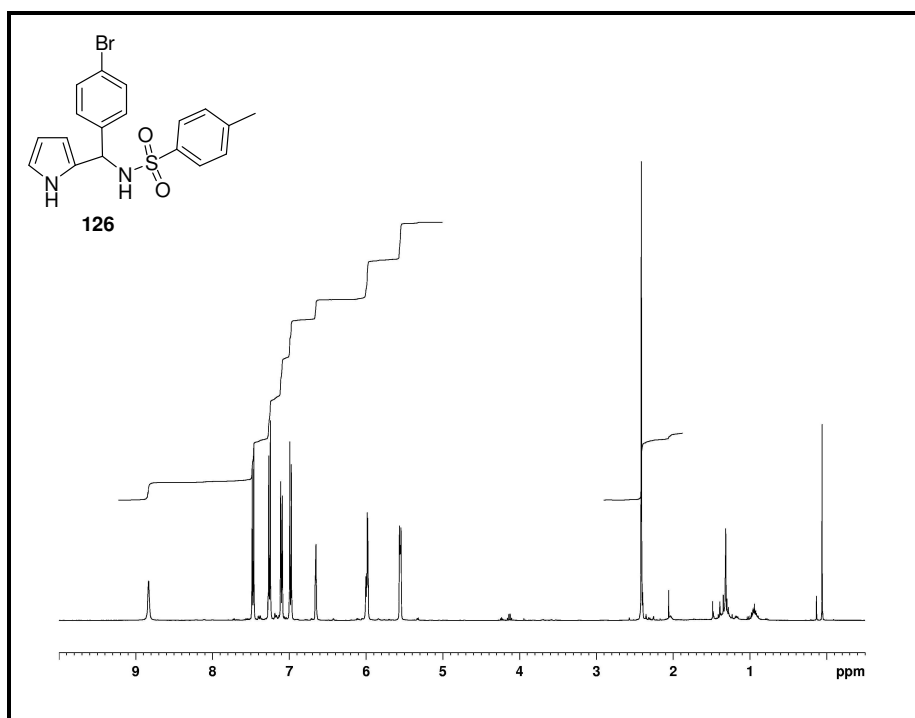


Figure 5.53. ^1H NMR Spectrum of **126** in $\text{CDCl}_3\text{-CCl}_4$

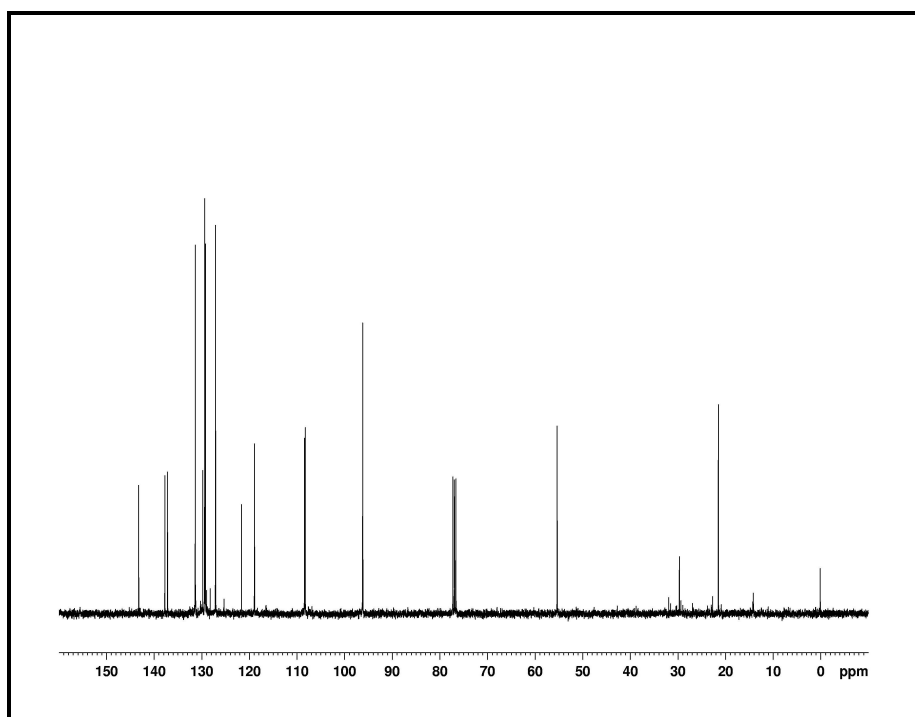


Figure 5.54. ^{13}C NMR Spectrum of **126** in $\text{CDCl}_3\text{-CCl}_4$

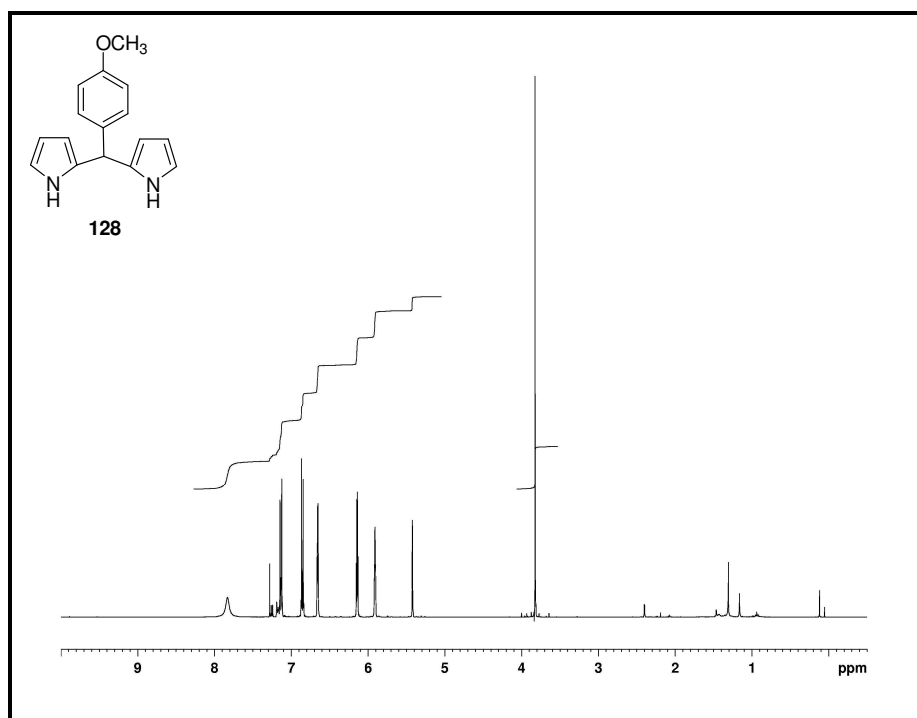


Figure 5.55. ¹H NMR Spectrum of **128** in CDCl₃-CCl₄

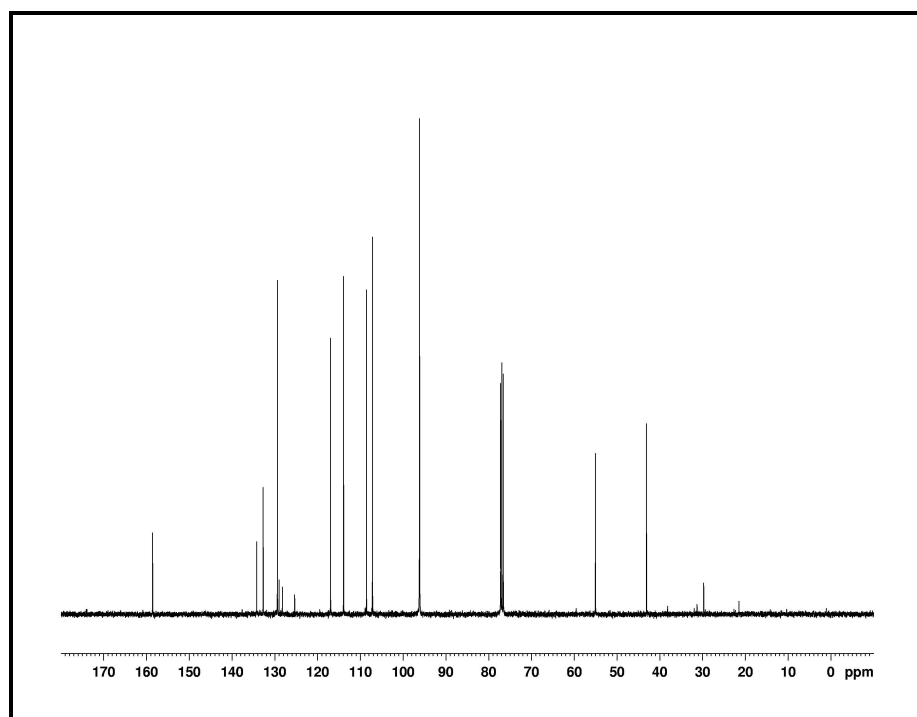


Figure 5.56. ¹³C NMR Spectrum of **128** in CDCl₃-CCl₄

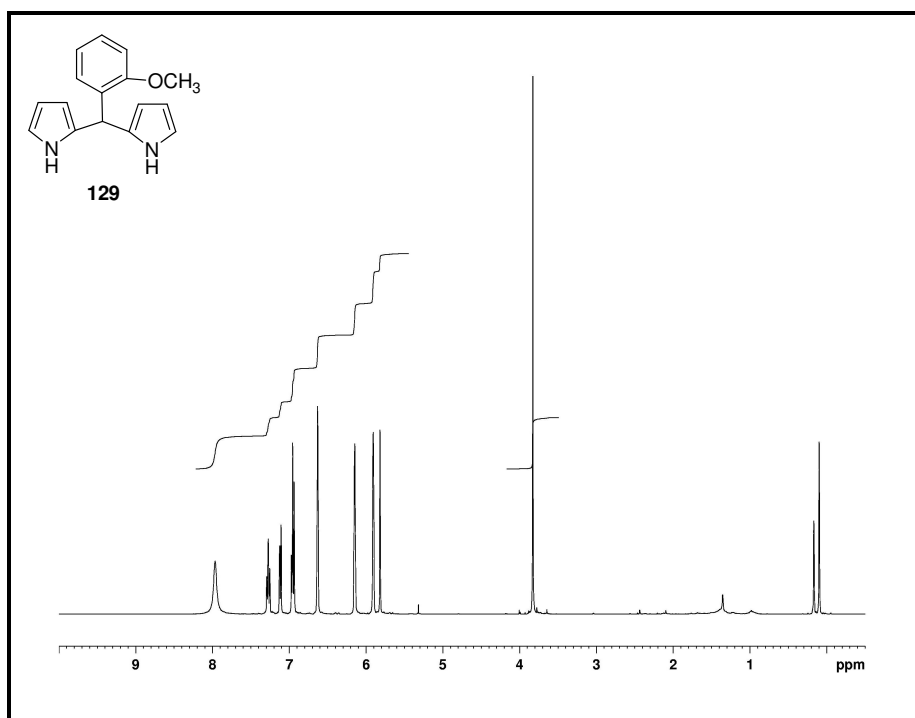


Figure 5.57. ¹H NMR Spectrum of **129** in CDCl₃-CCl₄

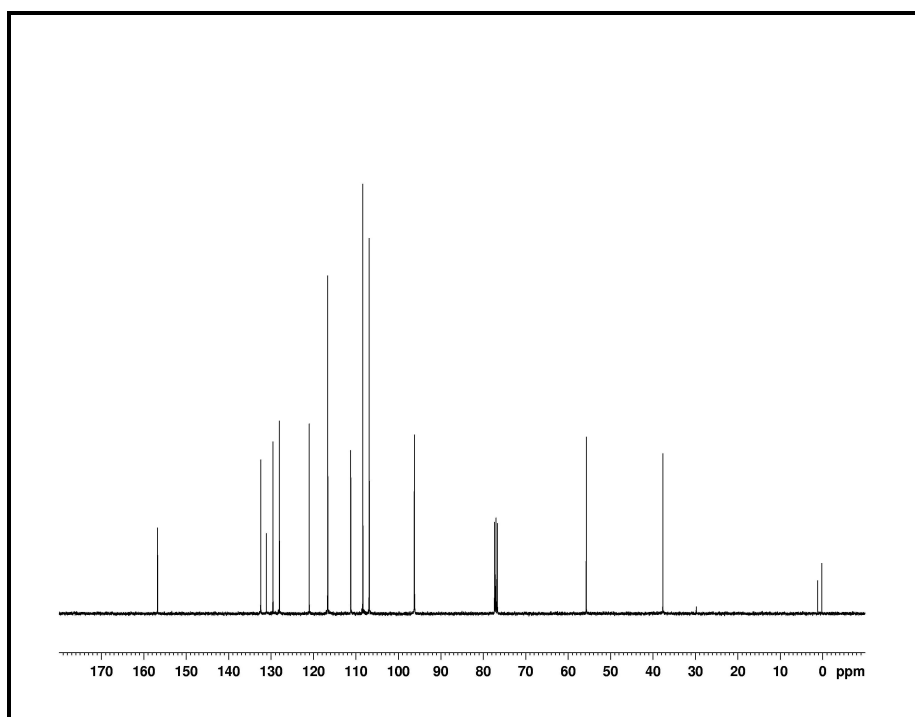


Figure 5.58. ¹³C NMR Spectrum of **129** in CDCl₃-CCl₄

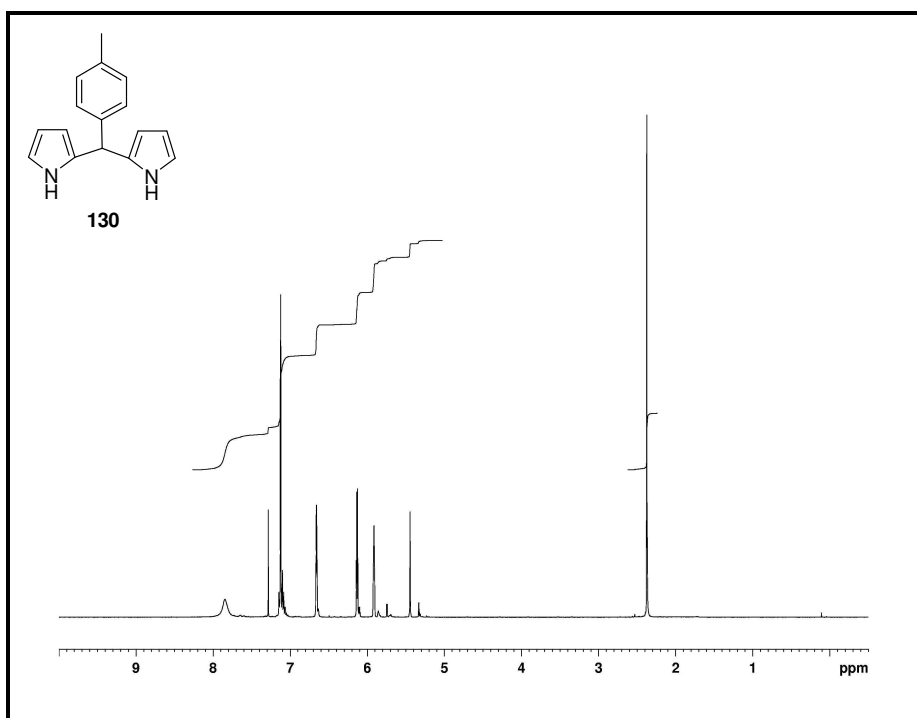


Figure 5.59. ^1H NMR Spectrum of **130** in $\text{CDCl}_3\text{-CCl}_4$

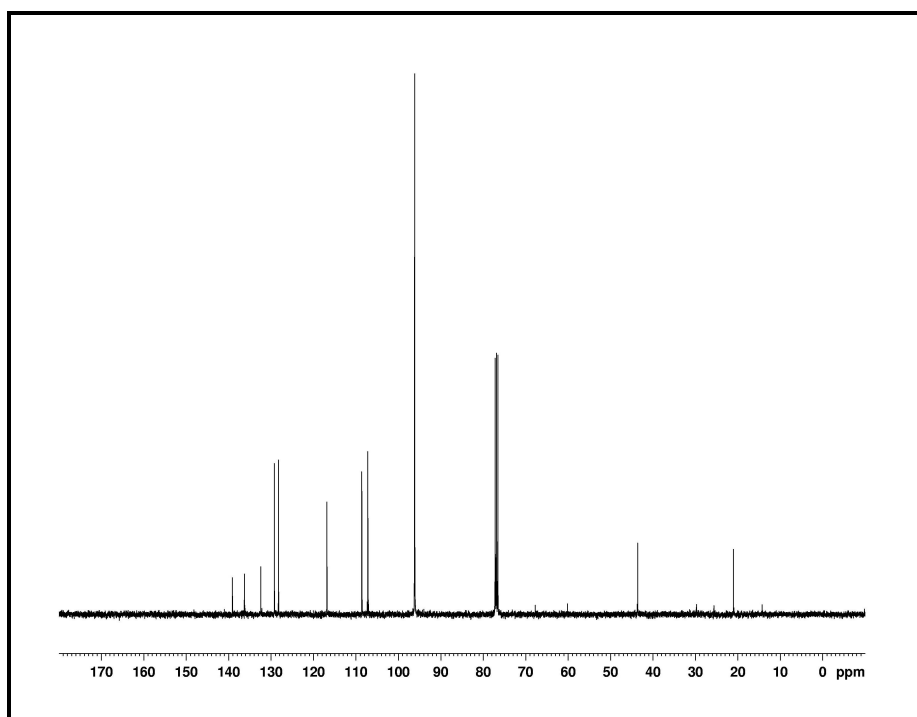


Figure 5.60. ^{13}C NMR Spectrum of **130** in $\text{CDCl}_3\text{-CCl}_4$

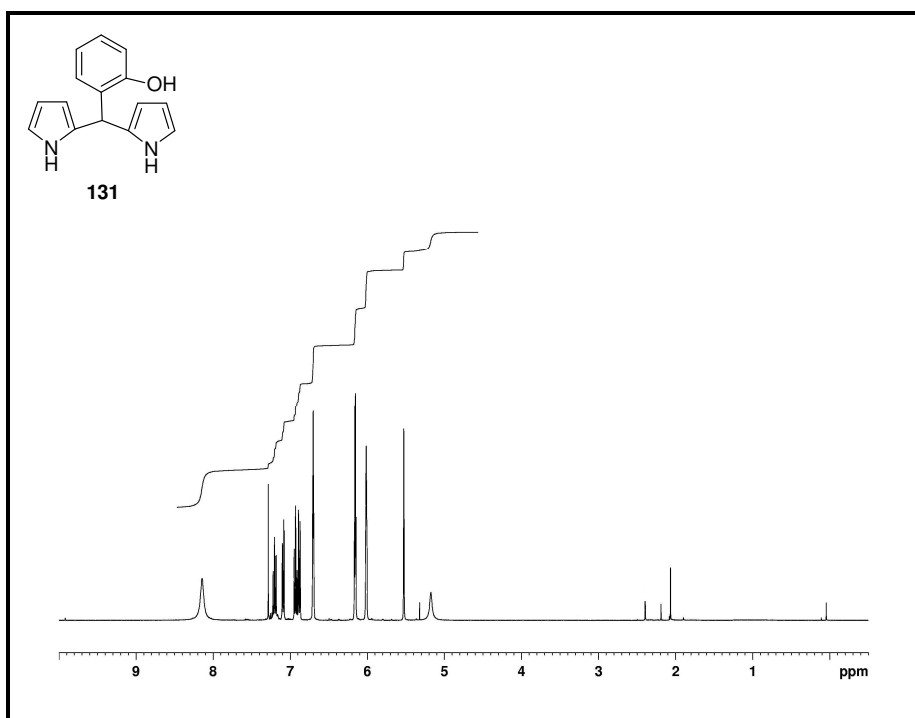


Figure 5.61. ¹H NMR Spectrum of **131** in CDCl₃-CCl₄

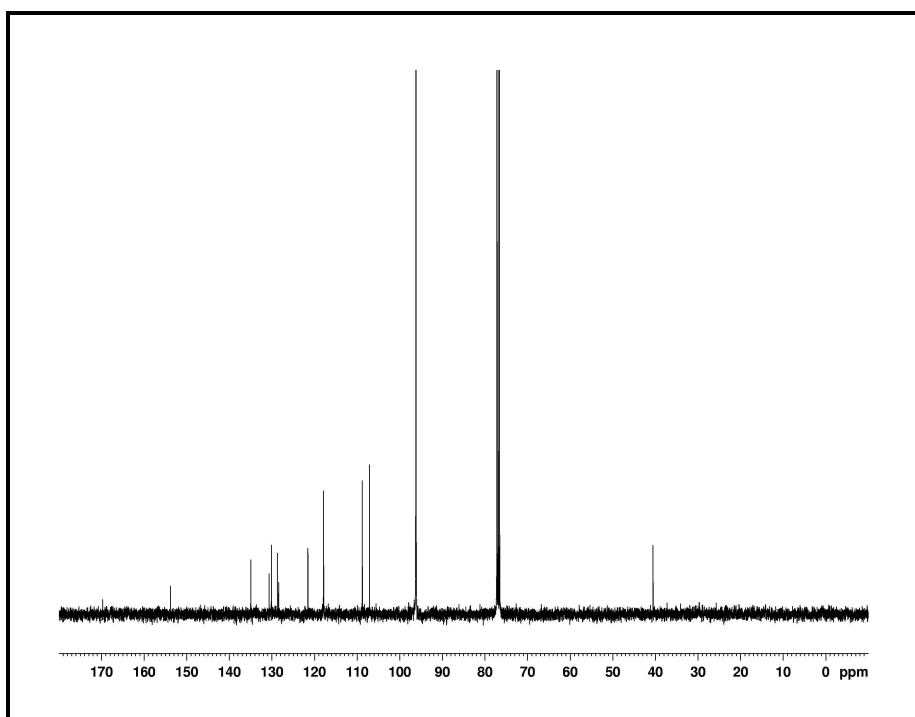


Figure 5.62. ¹³C NMR Spectrum of **131** in CDCl₃-CCl₄

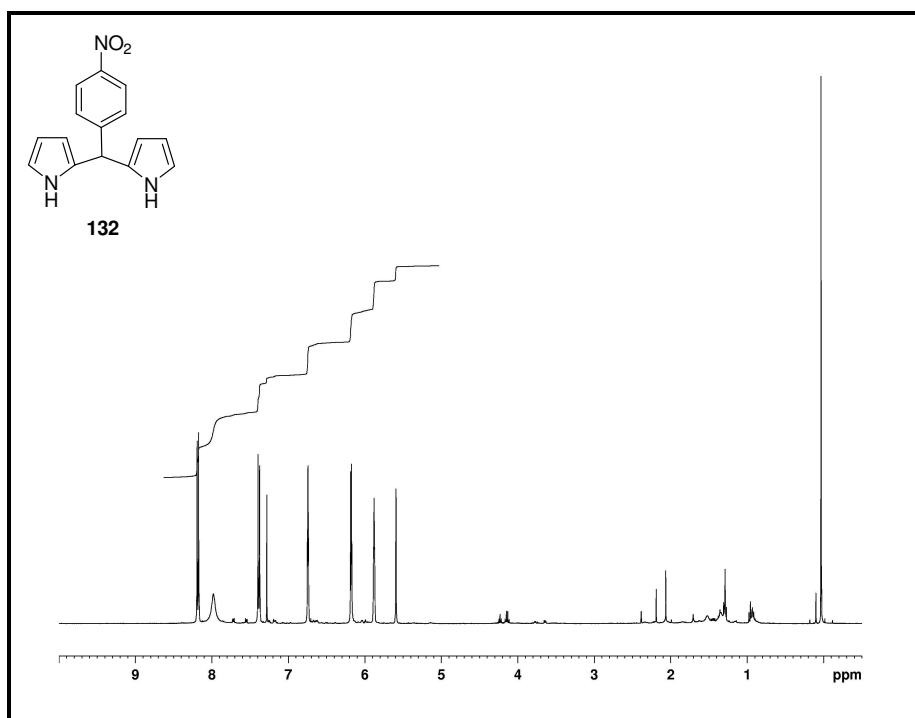


Figure 5.63. ^1H NMR Spectrum of **132** in $\text{CDCl}_3\text{-CCl}_4$

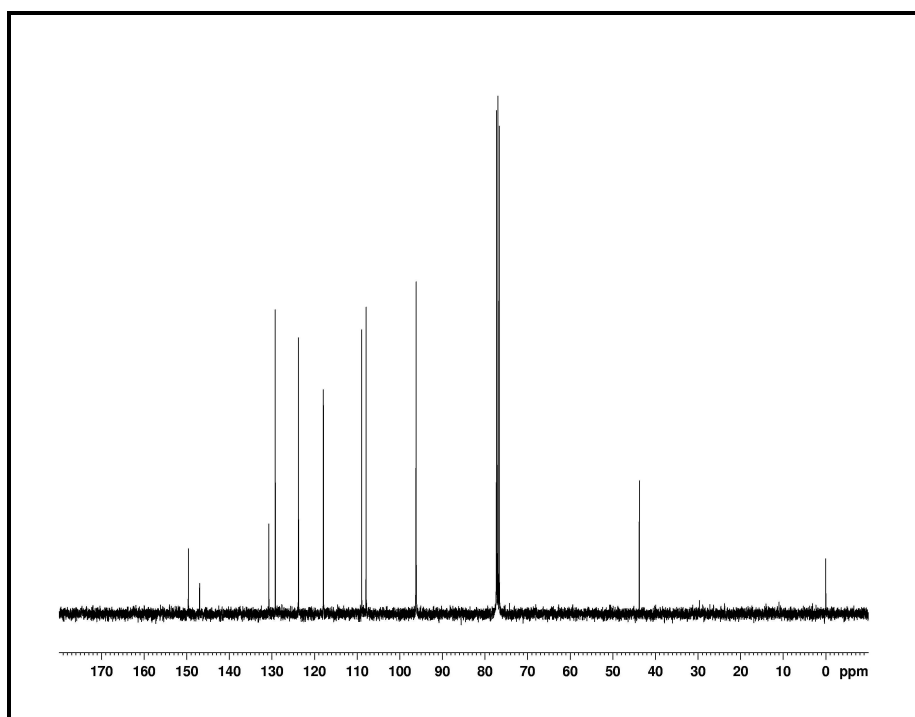


Figure 5.64. ^{13}C NMR Spectrum of **132** in $\text{CDCl}_3\text{-CCl}_4$

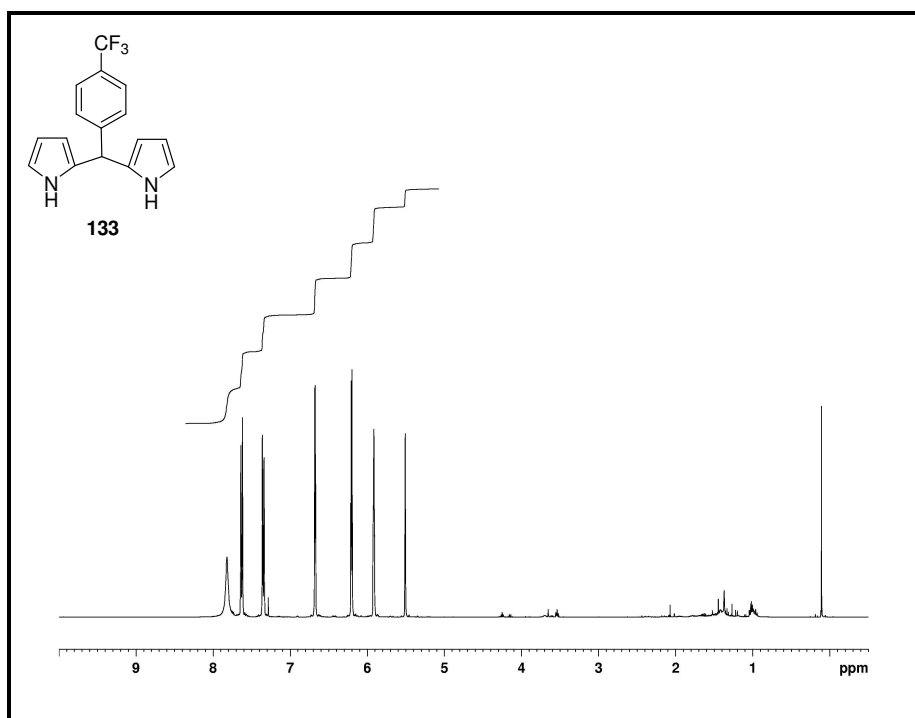


Figure 5.65. ¹H NMR Spectrum of **133** in CDCl₃-CCl₄

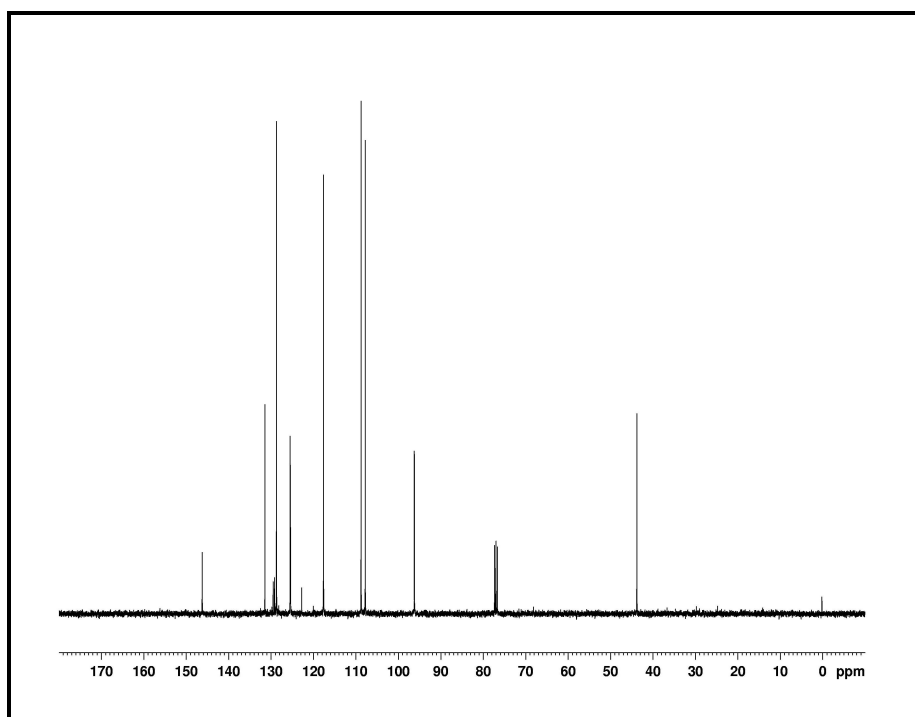


Figure 5.66. ¹³C NMR Spectrum of **133** in CDCl₃-CCl₄

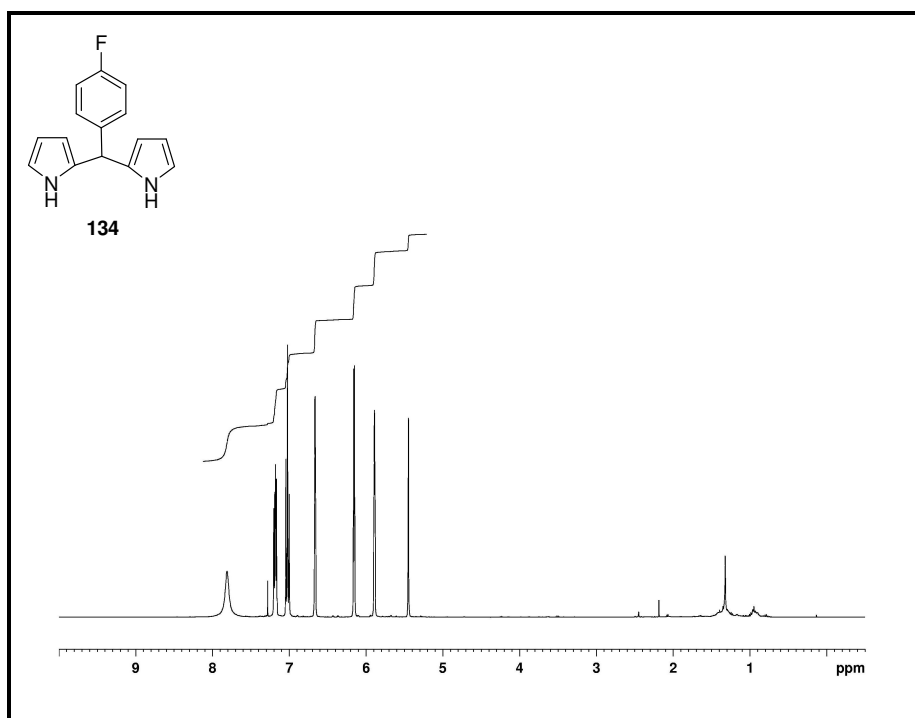


Figure 5.67. ^1H NMR Spectrum of **134** in $\text{CDCl}_3\text{-CCl}_4$

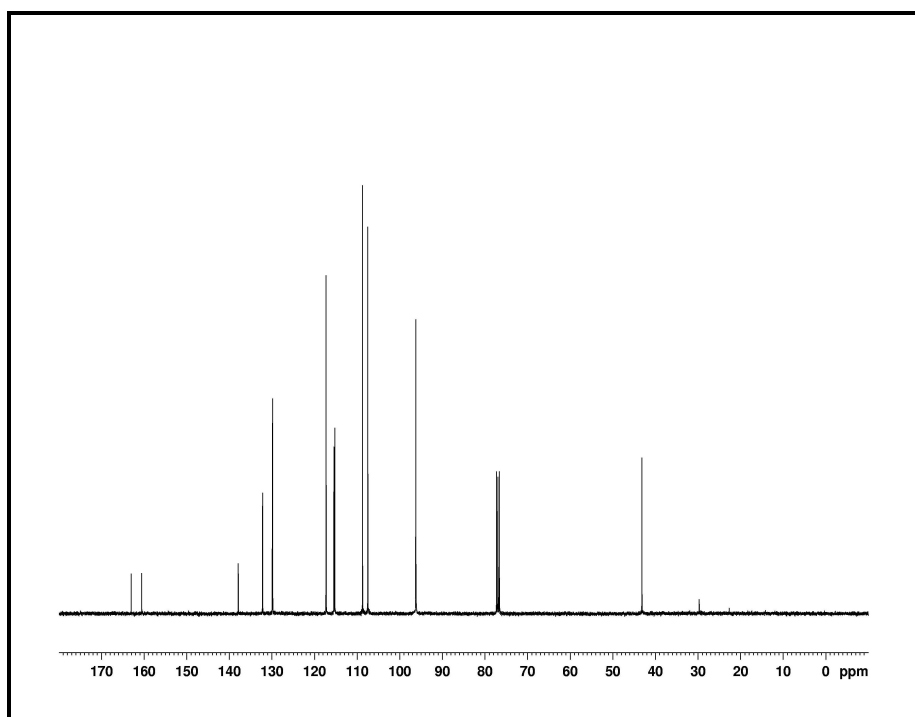


Figure 5.68. ^{13}C NMR Spectrum of **134** in $\text{CDCl}_3\text{-CCl}_4$

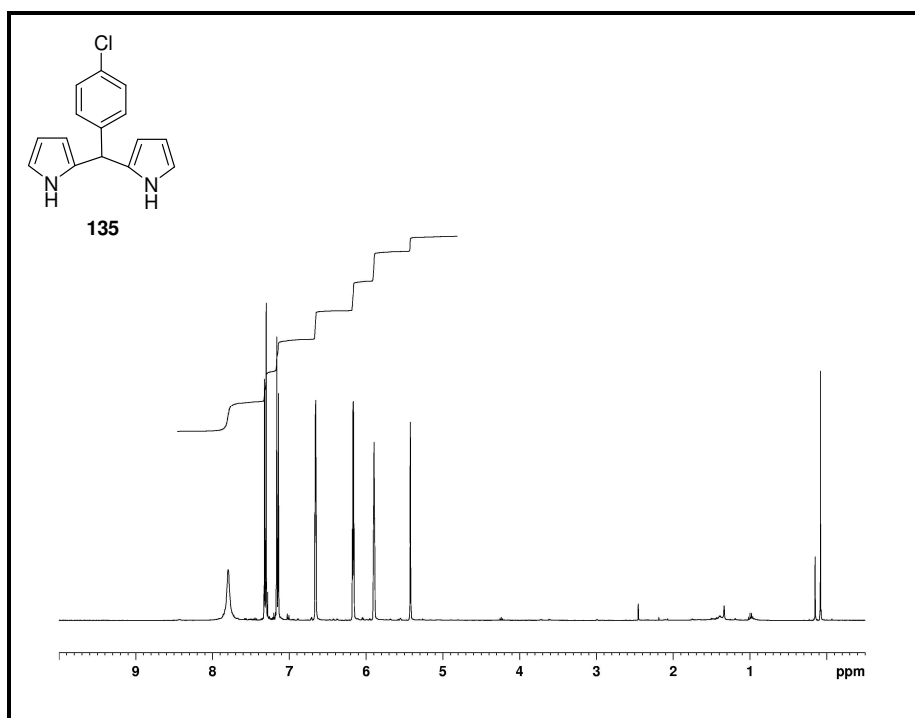


Figure 5.69. ^1H NMR Spectrum of **135** in $\text{CDCl}_3\text{-CCl}_4$

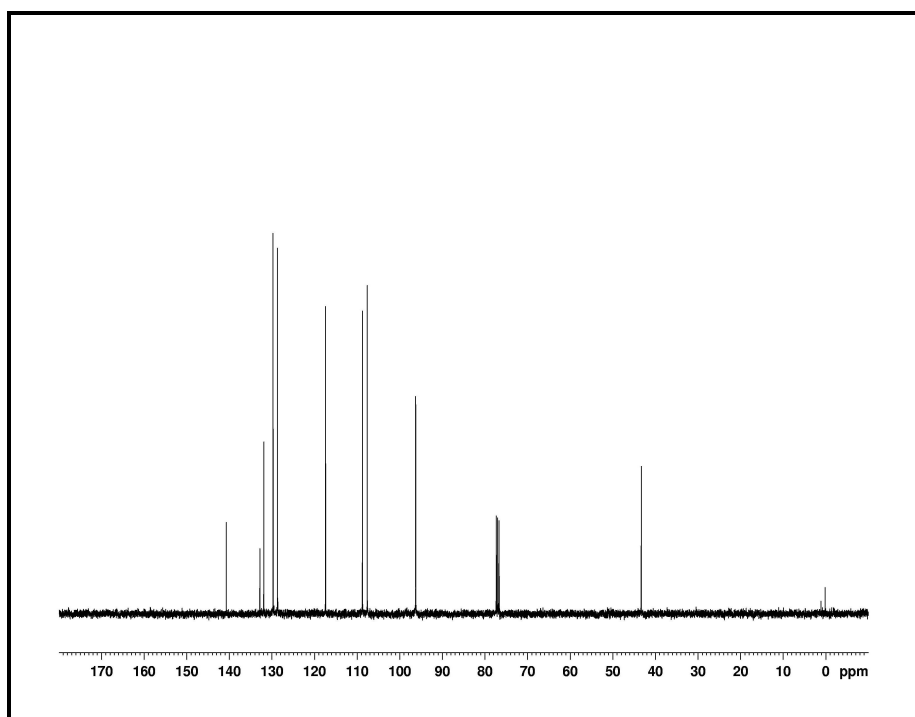
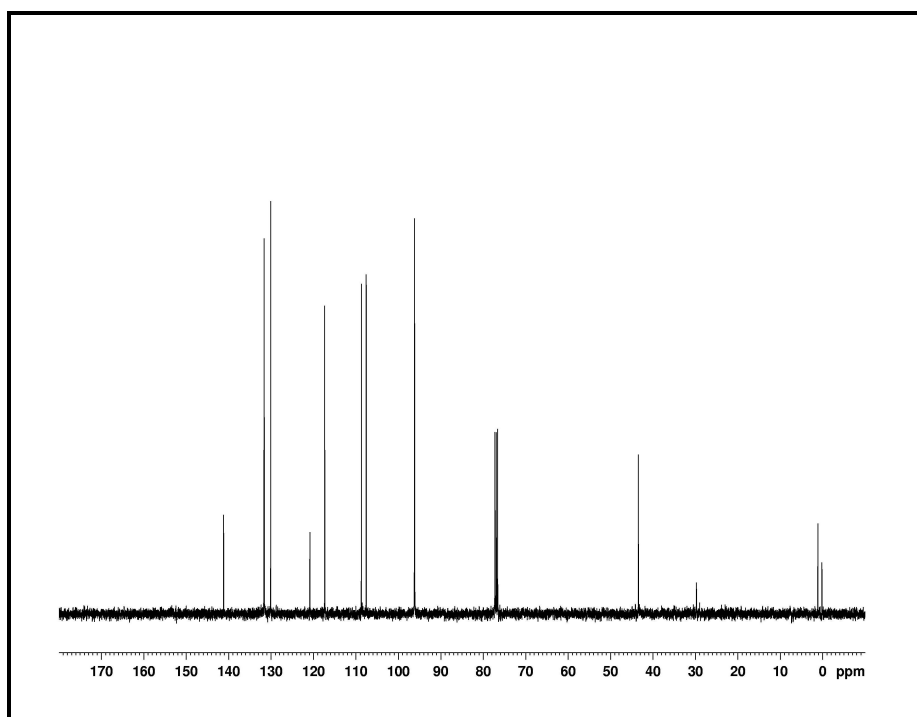
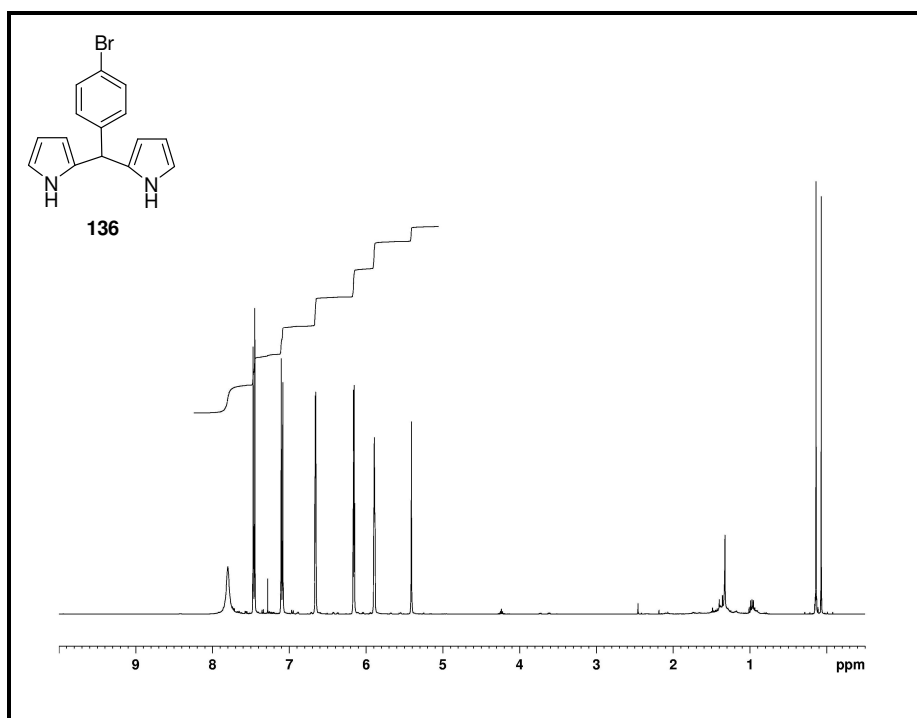


Figure 5.70. ^{13}C NMR Spectrum of **135** in $\text{CDCl}_3\text{-CCl}_4$



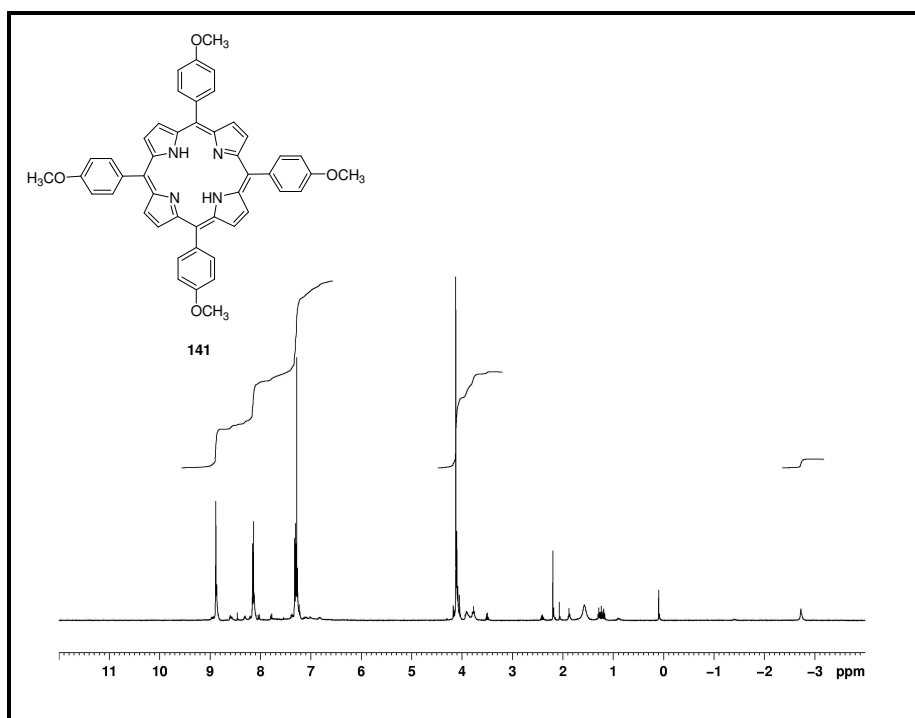


Figure 5.73. ^1H NMR Spectrum of **141** in CDCl_3

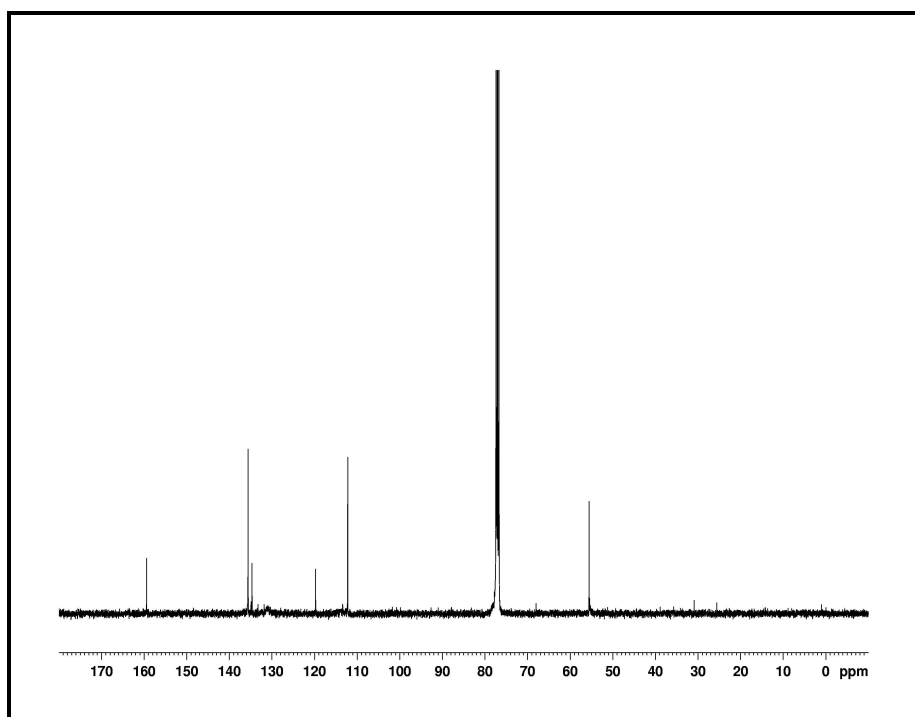


Figure 5.74. ^{13}C NMR Spectrum of **141** in CDCl_3

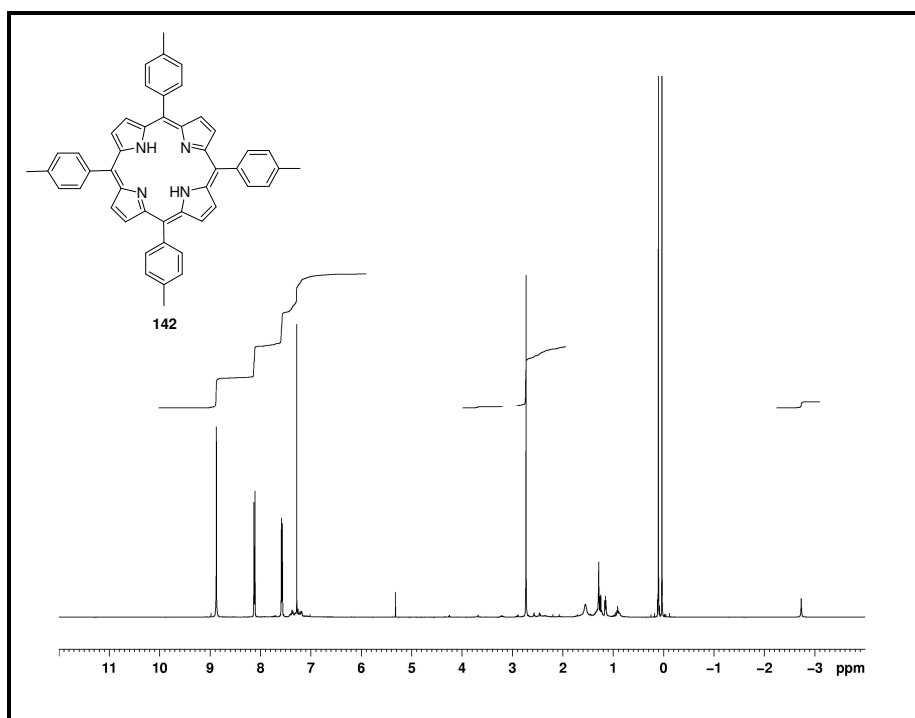


Figure 5.75. ^1H NMR Spectrum of **142** in CDCl_3

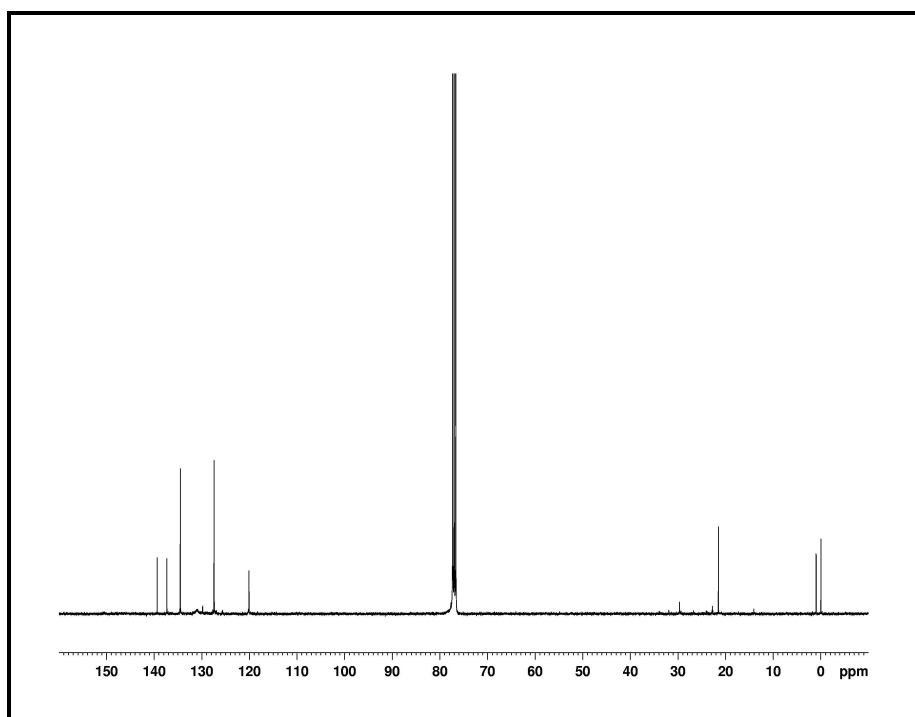


Figure 5.76. ^{13}C NMR Spectrum of **142** in CDCl_3

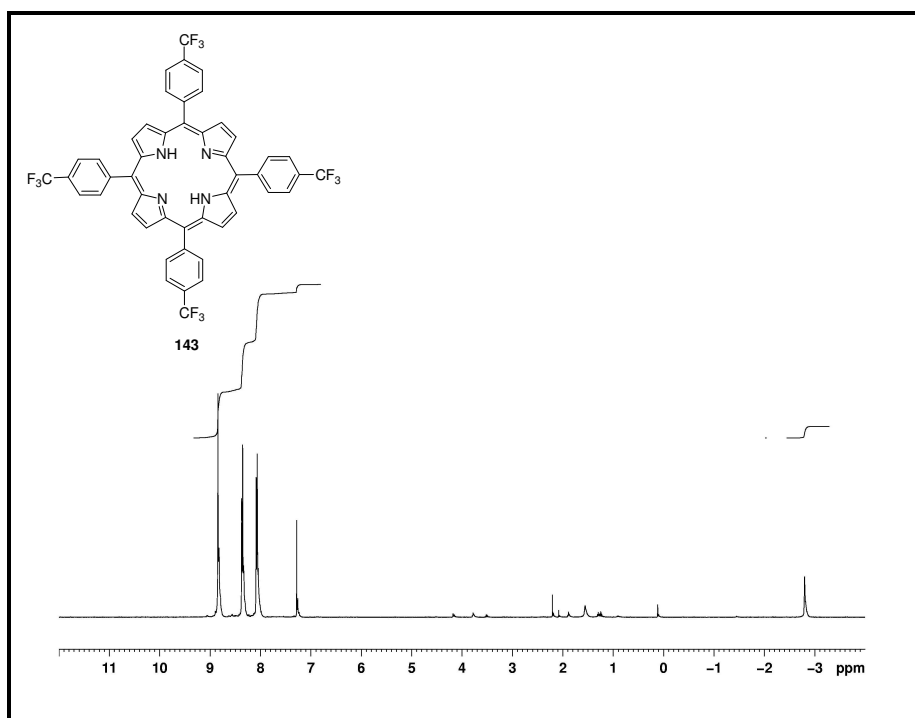


Figure 5.77. ^1H NMR Spectrum of **143** in CDCl₃

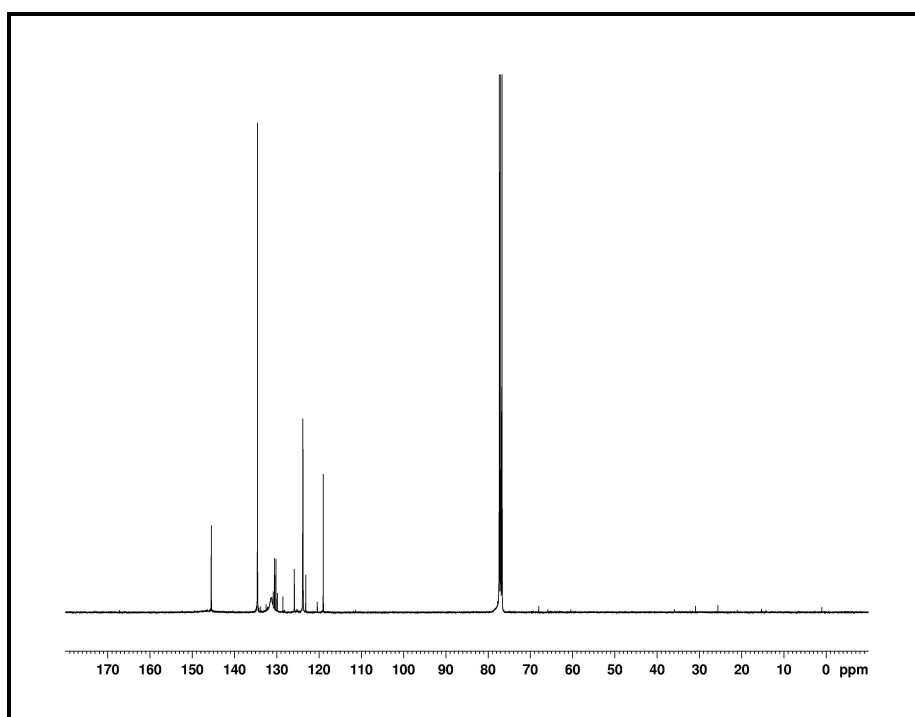


Figure 5.78. ^{13}C NMR Spectrum of **143** in CDCl₃

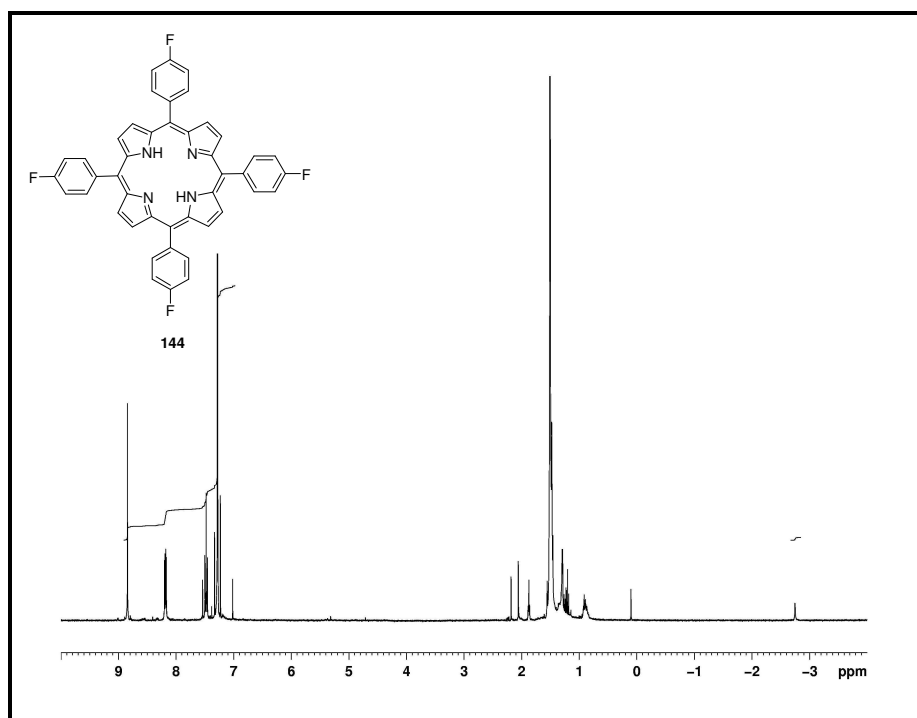


Figure 5.79. ^1H NMR Spectrum of **144** in CDCl_3

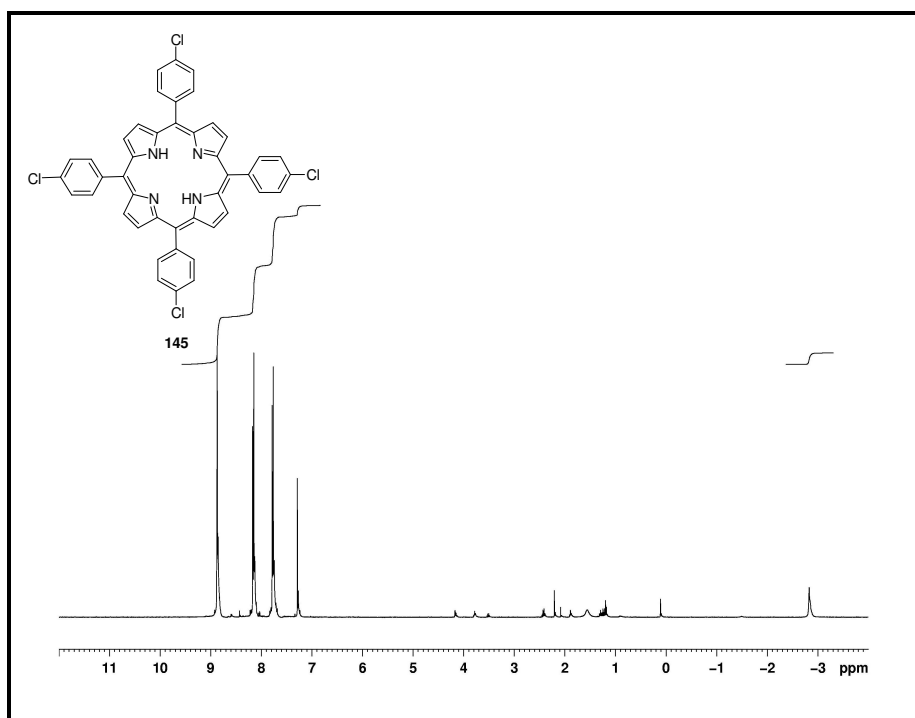


Figure 5.80. ^1H NMR Spectrum of **145** in CDCl_3

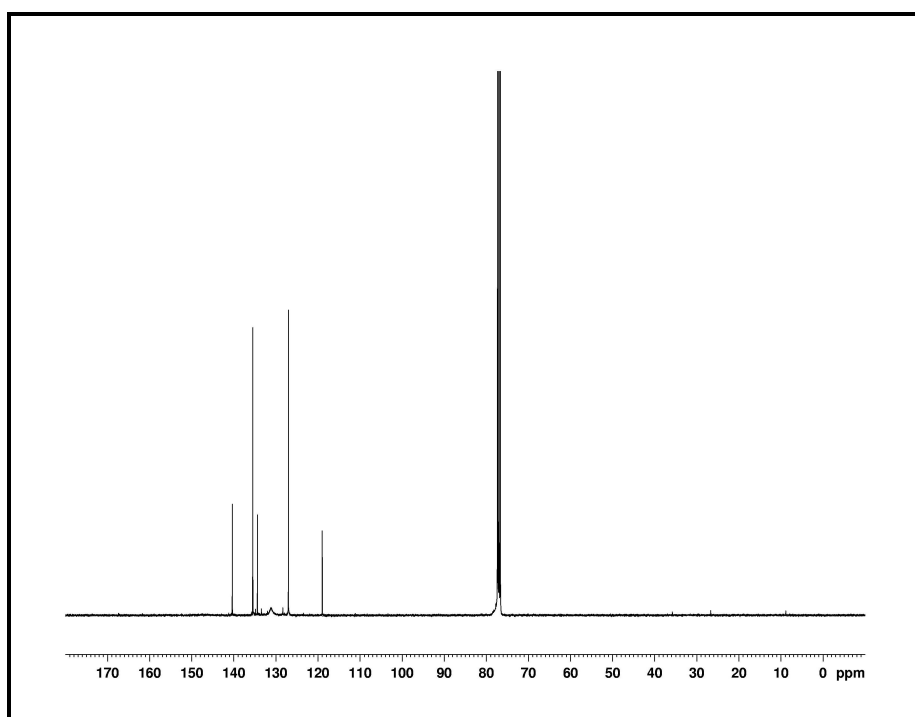


Figure 5.81. ^{13}C NMR Spectrum of **145** in CDCl_3

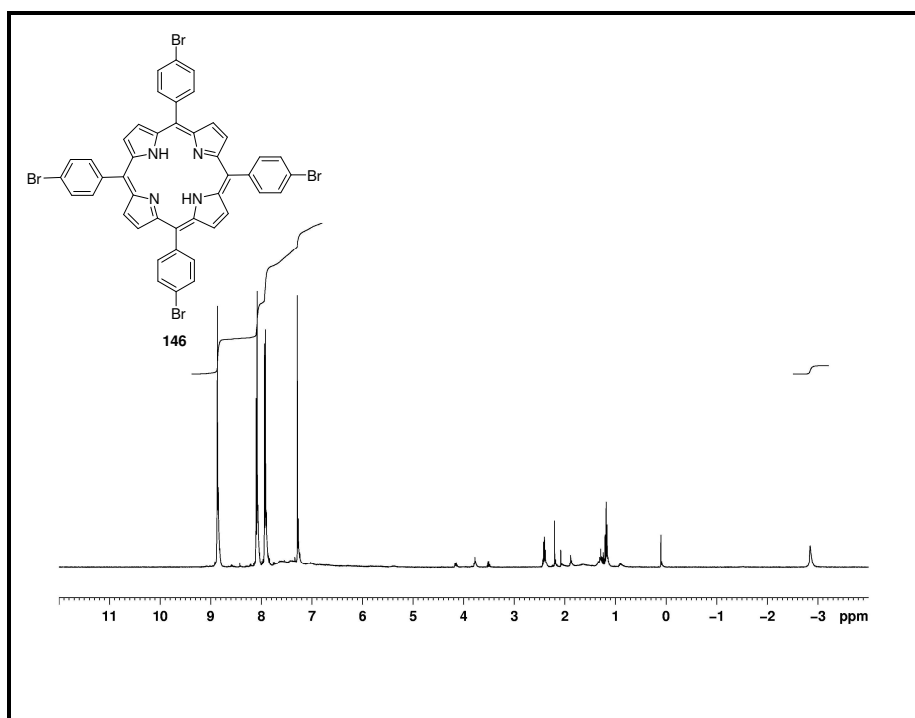


Figure 5.82. ^1H NMR Spectrum of **146** in CDCl_3

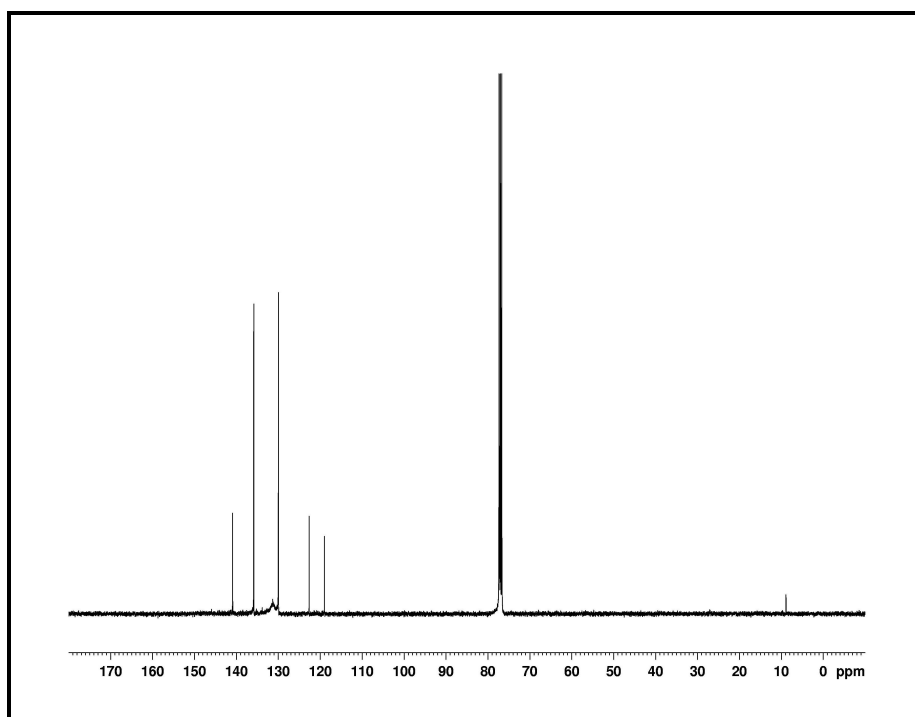
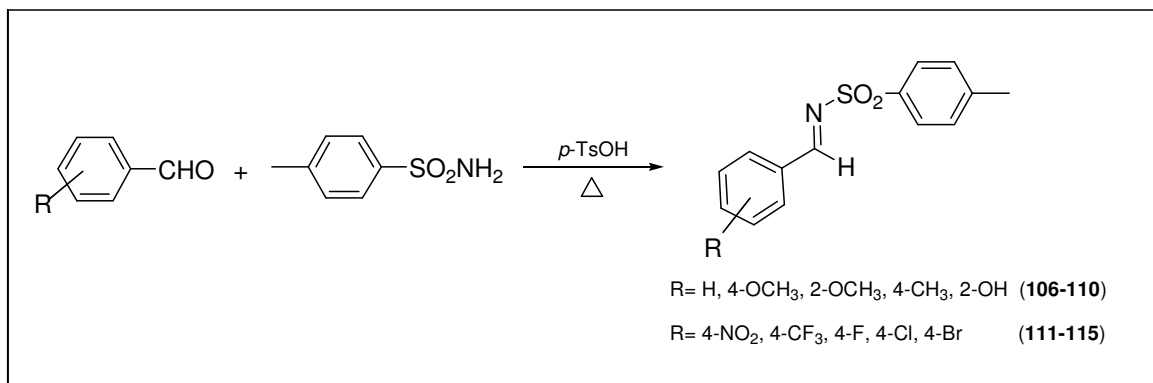


Figure 5.83. ^{13}C NMR Spectrum of **146** in CDCl_3

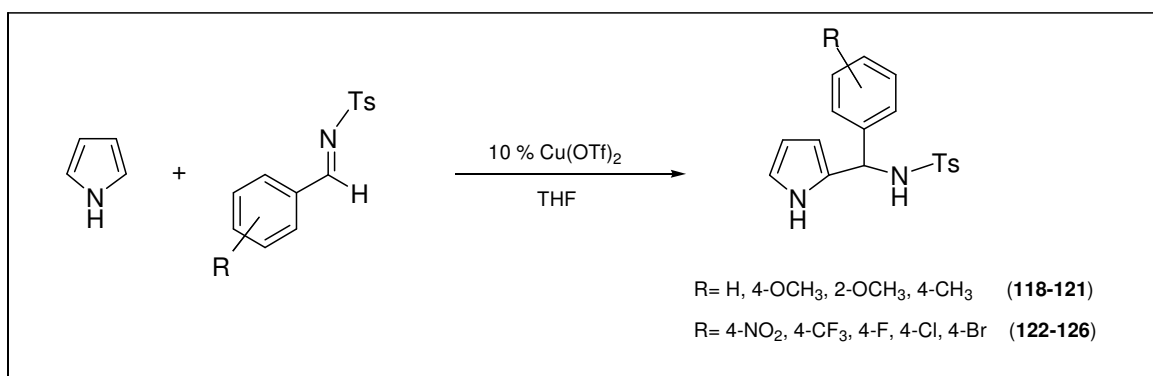
6. CONCLUSIONS

In the first part, a novel and versatile synthetic methodology was developed for the synthesis of 2-substituted pyrrolesulfonamides. *N*-tosyl imines were synthesized by the reaction of *p*-toluenesulfonamide with substituted benzaldehydes in high yields. Synthesized imines and their chemical yields are ;



- *N*-benzylidene-4-methylbenzenesulfonamide (**106**) ; 80%
- *N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide (**107**) ; 84%
- *N*-(2-methoxybenzylidene)-4-methylbenzenesulfonamide (**108**) ; 73%
- *N*-(4-methylbenzylidene)-4-methylbenzenesulfonamide (**109**) ; 81%
- *N*-(2-hydroxybenzylidene)-4-methylbenzenesulfonamide (**110**) ; 70%
- *N*-(4-nitrobenzylidene)-4-methylbenzenesulfonamide (**111**) ; 90%
- *N*-(4-(trifluoromethyl)benzylidene)-4-methylbenzenesulfonamide (**112**) ; 92%
- *N*-(4-fluorobenzylidene)-4-methylbenzenesulfonamide (**113**) ; 75%
- *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide (**114**) ; 75%
- *N*-(4-bromobenzylidene)-4-methylbenzenesulfonamide (**115**) ; 72%

Synthesized *N*-tosyl imines have been used to develop a new method for the metal triflate catalysed regioselective addition reaction of pyrrole to *N*-tosyl imines. The obtained novel 2-substituted pyrrolesulfonamide derivatives and chemical yields are;



- 4-Methyl-*N*-(phenyl(1*H*-pyrrol-2-yl)methyl)- benzenesulfonamide (**118**); 55%
- *N*-((4-Methoxyphenyl)(1*H*-pyrrol-2-yl)methyl)-4-methylbenzene sulfonamide (**119**); 64%
- *N*-((2-Methoxyphenyl)(1*H*-pyrrol-2-yl)methyl)-4-methylbenzene sulfonamide (**120**); 70%
- *N*-((1*H*-Pyrrol-2-yl)(*p*-tolyl)methyl)-4-methylbenzenesulfonamide (**121**); 52%
- 4-Methyl-*N*-((4-nitrophenyl)(1*H*-pyrrol-2-yl)-methyl)benzenesulfonamide (**122**); 85%
- *N*-((1*H*-Pyrrol-2-yl)(4-(trifluoromethyl)phenyl)-methyl)-4-methylbenzene sulfonamide (**123**); 82%
- *N*-((4-Fluorophenyl)(1*H*-pyrrol-2-yl)methyl)-4-methylbenzenesulfonamide (**124**); 70%
- *N*-((4-Chlorophenyl)(1*H*-pyrrol-2-yl)methyl)-4-methylbenzenesulfonamide (**125**); 68%
- *N*-((4-Bromophenyl)(1*H*-pyrrol-2-yl)methyl)-4-methylbenzenesulfonamide (**126**); 62%

The effects of different reaction parameters (temperature, solvent and metal type of catalyst) were investigated and optimum conditions have been determined (0 °C, THF, Cu(OTf)₂).

In the literature the requirement of harsh reaction conditions or stoichiometric amounts of reagents have been reported for the addition of aromatic compounds to imines. In this work, the first addition reaction of pyrrole to *N*-tosyl imines was

achieved easily by using catalytic amounts of metal triflate. The advantages of this new method are;

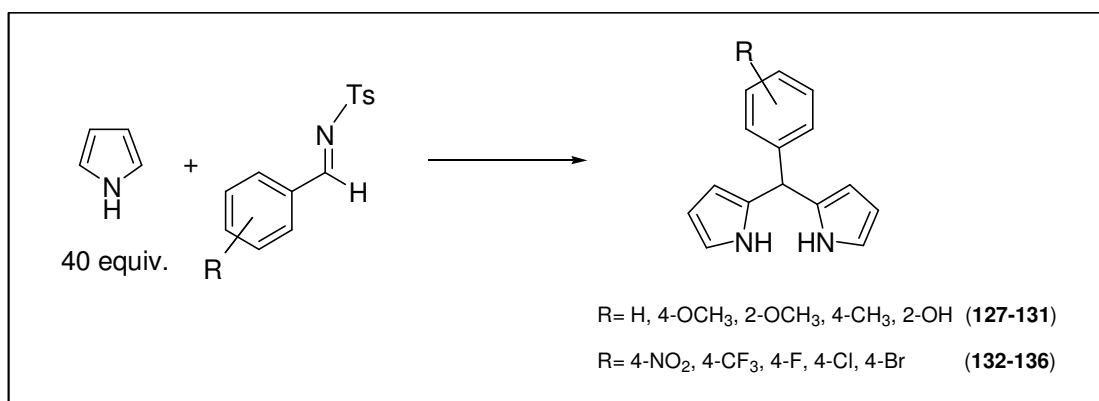
- The reaction procedure is simple.
- Catalytic amounts of metal triflate is enough to complete the reaction.
- The addition reactions of pyrrole to tosyl imines occur regioselectively at C(2) of the pyrrole.
- 3-Substituted or *N*-substituted pyrrole side products were not observed in any of the reactions.
- Anhydrous conditions are not required.

In the second part, a novel and an efficient method was developed for preparing 5-substituted dipyrromethanes from the reaction of *N*-tosyl imines and excess pyrrole by using catalytic amounts of metal triflate. Although there are several methods for the synthesis of these compounds in the literature, the main problem is the formation of side products and oligomers and the separation problems. The low yield of dipyrromethanes depending on the substituent type (electron donating or withdrawing) is another problem.

The advantages of this new method are;

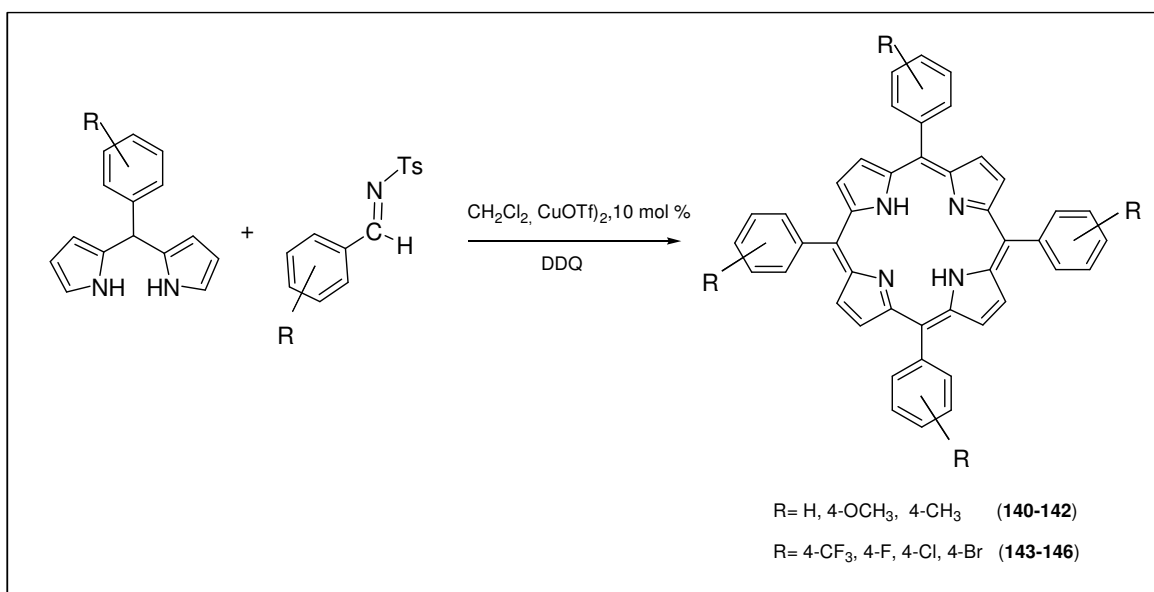
- Tripyrromethane or any other oligomeric side products were not observed.
- Catalytic amounts of metal triflate is enough to complete the reaction.
- The reaction procedure is simple and anhydrous conditions are not required.
- High yields of 5-substituted dipyrromethanes with electron donating or withdrawing substituents can be obtained selectively only by tuning the reaction temperature.

Synthesized 5-substituted dipyrromethanes and chemical yields are;



- 5-Phenyldipyrromethane (**127**); 69%
- 5-(4-Methoxyphenyl)dipyrromethane (**128**); 85%
- 5-(2-Methoxyphenyl)dipyrromethane (**129**); 71%
- 5-(4-Methylphenyl)dipyrromethane (**130**); 83%
- 5-(2-Hydroxyphenyl)dipyrromethane (**131**); 90%
- 5-(4-Nitrophenyl)dipyrromethane (**132**); 79%
- 5-(4-Trifluoromethylphenyl)dipyrromethane (**133**); 85%
- 5-(4-Fluorophenyl)dipyrromethane (**134**); 70%
- 5-(4-Chlorophenyl)dipyrromethane (**135**); 71%
- 5-(4-Bromophenyl)dipyrromethane (**136**); 74%

In the last part of the study, the first synthetic method using the reaction of 5-substituted dipyrromethanes with *N*-tosyl imines in the presence of metal triflate catalyst has been developed for the synthesis of *meso* tetraarylporphyrins. Determination of optimum reaction conditions was carried out by changing several parameters (solvent, catalyst type, the amount of catalyst, the molarity of reactants, reaction time and oxidant type). The maximum yield of the porphyrin was obtained when 10^{-2} M of reactants were reacted in CH₂Cl₂ for 1.5 h in the presence of 10% mole of Cu(OTf)₂ and by using DDQ as oxidant. Synthesized *meso* tetraarylporphyrins and chemical yields are;



- 5, 10, 15, 20-Tetraphenylporphyrin (**140**); 45%
- 5, 10, 15, 20-Tetrakis(4-methoxyphenyl)porphyrin (**141**); 44%
- 5, 10, 15, 20-Tetrakis(4-methylphenyl)porphyrin (**142**); 35%
- 5, 10, 15, 20-Tetrakis(4-trifluoromethylphenyl)porphyrin (**143**); 25%
- 5, 10, 15, 20-Tetrakis(4-fluorophenyl)porphyrin (**144**); 13%
- 5, 10, 15, 20-Tetrakis(4-chlorophenyl)porphyrin (**145**); 31%
- 5, 10, 15, 20-Tetrakis(4-bromophenyl)porphyrin (**146**); 29%

The chemical yields of the porphyrins are higher than those reported with earlier methods and comparable with the recently published methods. Porphyrins with strong electron withdrawing substituents (NO_2) and ortho substituted porphyrins couldn't be synthesized in this reaction condition.

Although various kinds of Lewis acids have been applied for the synthesis of porphyrins, almost all methods need stoichiometric amounts of catalyst. The main advantage of the developed method is that only catalytic amounts of metal triflate catalyst is enough to complete the reaction.

The mechanistic studies on the porphyrin formation showed that the reaction goes through mainly self condensation of mono sulfonamidealkylated dipyrromethane

rather than condensation reaction of dipyrromethane with di sulfonamidealkylated dipyrromethane.

The synthesized and isolated products 4-methyl-*N*-(phenyl(5-(phenyl(1*H*-pyrrol-2-yl)methyl)-1*H*-pyrrol-2-yl)methyl)benzene sulfonamide (**147**) and *N,N'*-(5,5'-(phenylmethylene)bis(1*H*-pyrrole-5,2-diyl)bis(phenylmethylene))bis(4-methyl benzenesulfonamide) (**148**) are important intermediates for the synthesis of different type of porphyrins. So, this study not only supplies a new route for the synthesis of A₄ type porphyrins, but also opens a new window for the synthesis of different types of porphyrins (*cis*-A₂B₂, *trans*-A₂B₂, A₃B, *trans*- A₂BC, *cis*-A₂BC, ABCD).

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