SYNTHESIS OF *α*-oxo-*β*,*γ*- UNSATURATED ESTERS AND THEIR REACTIONS WITH PYRROLES

α-oxo-*β*,*γ*- DOYMAMIŞ ESTERLERİN SENTEZİ VE PİROL BİLEŞİKLERİYLE TEPKİMELERİ

SERTAN AYTAÇ

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2006

This study has been certified as a THESIS of MASTER of SCIENCE in CHEMISTRY by our Examining Committee.

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To My Family

SYNTHESIS OF *α*-OXO-*β*,*γ* UNSATURATED ESTERS AND THEIR REACTIONS WITH PYRROLES

Sertan AYTAÇ

ABSTRACT

Pyrrole derivatives are important compounds in organic chemistry because of their biological activites in anticancer, antiviral and immunoregulatory applications and their magnificent role in the natural products, non-linear optics and supramolecular chemistry. Substituted pyrrole derivatives have been used as synthon for the synthesis of natural products and alkoloids containing pyrrolizine, pyrrolizidine and indolizine structures.

In the first part of this study, *α*-oxo-*β*,*γ* unsaturated esters, which have been employed in the synthesis of biological important compounds and natural products, were synthesized to use in 1,4-addition reactions.

In the second part of the study, alkylation reactions of pyrrole were performed with *α*-oxo-*β*,*γ* unsaturated esters *via* Micheal reaction by using metal triflate catalyst. Novel 2-substituted pyrroles were obtained regioselectively and characterized by ^{1}H NMR and ^{13}C NMR techniques. Effect of solvent, substituents on phenyl ring, different metal triflates and temperature on the Michael addition reaction of pyrrole with *α*-oxo-*β*-*γ* unsaturated esters were investigated.

In the last part of the study, potentially biologically active novel pyrrolizine derivatives were synthesized through intramolecular cyclization reaction of methyl 2-oxo-4-phenyl-4-(1*H*-pyrrol-2-yl)butanoate derivatives. Diastereoisomers of novel pyrrolizine compounds were separated and characterized by ^{1}H NMR and ^{13}C NMR techniques.

KEYWORDS: Pyrroles, metal triflates, cyclisation reactions, pyrrolizine, 1,4-addition reaction.

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α-OXO-β,γ DOYMAMIŞ ESTERLERİN SENTEZİ VE PİROL BİLEŞİKLERİYLE TEPKİMELERİ

Sertan AYTAÇ

ÖZ

Pirol türevleri, biyolojik aktiviteleri nedeniyle antikanser, antiviral ve immunoregulator uygulamaları ve doğal ürünler, non-linear optik ve supramoleküler kimyadaki rolleriyle, organik kimyadaki önemli bileşiklerdir. Substitüye pirol türevleri doğal ürünlerin ve yapısında pirolizin, pirolizidin ve indolizin yapıları içeren alkoloidlerin sentezi için kullanılırlar.

Çalışmanın birinci bölümünde, biyolojk öneme sahip moleküllerin ve doğal ürünlerin sentezinde kullanılan α-oxo-β,γ doymamış esterler 1,4- katılma tepkimerinde kullanılmak için sentezlendi.

Çalışmanın ikinci bölümünde, pirolün alkillendirilmesi tepkimeleri α-oxo-β-γ doymamış ester bileşiklerinin Michael tepkimesiyle metal triflatın katalizör olarak kullanılmasıyla yapıldı. Yeni 2- substitüye piroller yerseçimli olarak elde edildi ve ^{1}H NMR ve ^{13}C NMR teKnikleriyle karakterize edildi. Pirolün α-oxo-β,γ doymamış esterlere Michael katılma tepkimesinde, çözücünün, fenil halkasındaki substitüentin, değişik metal triflatların ve sıcaklığın etkisi araştırıldı.

Çalışmanın son bölümde, biyolojik olarak aktif olabilecek yeni pirolizin türevleri, metil 2-oxo-4-fenil-4-(*1H*-pirol-2-yl)butanoat türevlerinin molekül içi halkalaşma tepkimesiyle sentezlendi. Yeni pirolizin bileşiklerinin diastereoizomerleri ayrıldı ve ^{1}H NMR ve ^{13}C NMR teknikleriyle karekterize edildi.

ANAHTAR KELİMELER: Piroller, metal triflatlar, halkalaşma tepkimeleri, pirolizin, 1,4-katılma tepkimesi.

DANIŞMAN: Prof.Dr.Canan Ünaleroğlu, Hacettepe Üniversitesi, Kimya Bölümü Organik Kimya Anabilim Dalı

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ABBREVIATIONS

[bmim][SbF6]: 1-*n*-Butyl-3-methylimidazolium hexafluoroantimonate

CNS: Central nervous system

DIBAH: Diisobutylaluminium hydride

DMA: *N,N*-Dimethyl-acetamide

DMAD: Dimethylacetylenedicarboxylate

DMF: Dimethylformamide

FVP: Flash vacuum pyrolysis

$M(OTf)_x$: Metal triflate

MS4A: Moleculer Sieve 4A

1. INTRODUCTION

Pyrrole is one of the most prominent heterocycle, having been known for then 150 years, and it is structural skeleton of several natural products, synthetic pharmaceuticals and electrically conducting materials (Taddei et al., 2004). Nitrogen containing heterocycles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity. They have found applications in medicine, agriculture and non-linear optics materials (Barluenga et al., 1996, Stetinova et al., 2005). Pyrrole containing groups can be used for the synthesis of naturally occurring compounds, such as pyrrolizine and dihydropyrrolizine derivatives.

Pyrrolizine derivatives have attracted considerable attention since they are used for antiinflammation, and analgesia, as aromatase and tumor inhibitors (Sobenina, et al., 2005). A very large family of natural products such as alkaloids containing pyrrolizine systems which are isolated from plants, insects, animals, marine organisms and microbes having biological activities occupy an important place in the realm of natural and synthetic organic chemistry (Kalantari et al., 2006).

Formation of C-C bond is an important field in the synthesis of heterocyclic compounds. Michael reaction is an important carbon-carbon bond forming process in organic synthesis. Alkylated pyrrole derivatives have interesting activities as anticancer, antiviral, antiretroviral and immunoregulatory. *α*-oxo-*β,γ* unsaturated esters and their derivatives have been used as starting materials for the synthesis of biological important compounds. In the past decade *α*-oxo-*β,γ* unsaturated esters have been emerged as novel useful synthons, especially in Diels-Alder reactions as heterodiene or dienophiles (Dujardin et al., 2001).

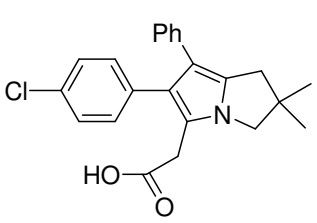
In this study, novel pyrrole derivatives were obtained efficiently from the reaction of pyrrole and *α*-oxo-*β,γ* unsaturated esters *via* Michael reaction in the presence of metal trifluoromethane sulfonate as the catalyst. Alkylated pyrrole derivatives were used in the synthesis of pyrrolizine derivatives.

2. GENERAL INFORMATION

2.1. Synthesis of Pyrrolizine and Dihydropyrrolizine Derivatives

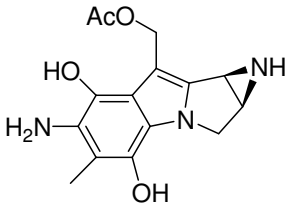
The pyrrolizine and indolizine alkaloids constitue a very large family of natural products having a wide range of biological activities and are isolated from a wide variety of plants, insects, animals, marine organisms and microbes (Sobenina et al.,2005). The construction of nitrogen containing heterocycles is an important goal in organic synthesis because of their abundance in natural and pharmaceutical products.

Licofelon (**1**), active mitomycin C derivative (**2**) and 5-HT_2 type indolizine (**3**) are generally associated with pharmaceutical activities such as anti-inflammatory, anti-tumour agents or even CNS activities (Scheme 2.1), (Bashiardes et al., 2004).



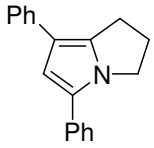
Licofelon

1



Active mitomycin C derivative

2

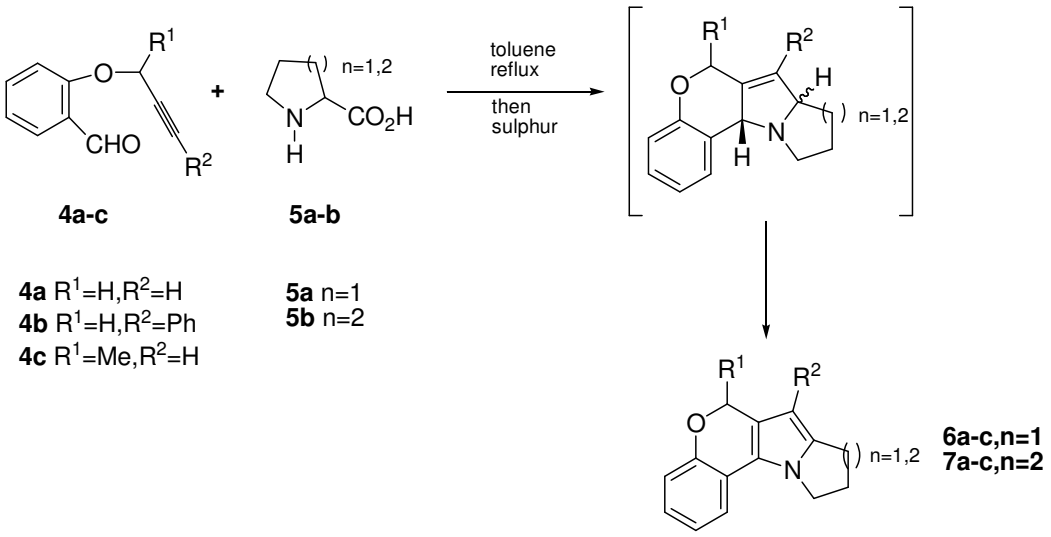


5-HT_2 -candidate

3

Scheme 2.1. Pyrrolizines and indolizines with potential biological activity.

Many methods have been reported for the synthesis of pyrrolizine and indolizine derivatives in the literature. One of them is an intramolecular [3+2] dipolar cycloaddition reaction. The condensation and intramolecular cycloaddition of salicylaldehyde derivatives **4a-c** with *α*-amino acids **5a,b** have given expected pyrrolizines **6a-c** and **7a-c** (Bashiardes et al., 2004), (Scheme2.2.).



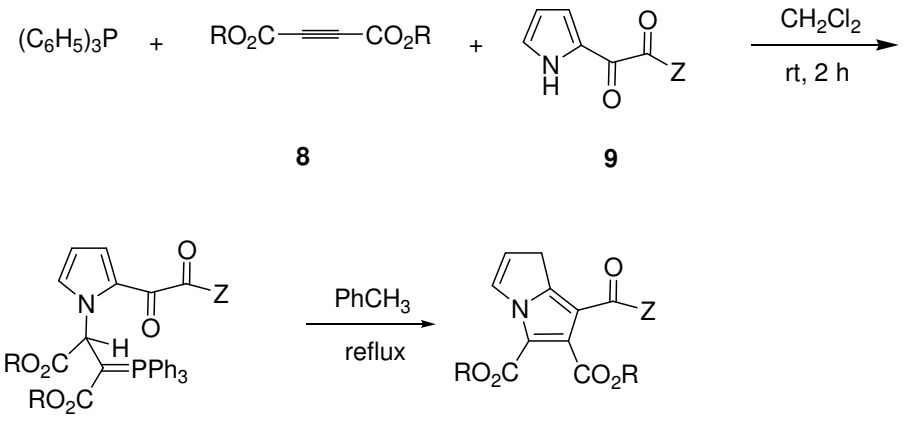
4a-c **5a-b**

4a R^1=H,R^2=H
4b R^1=H,R^2=Ph
4c R^1=Me,R^2=H

5a n=1
5b n=2

Scheme 2.2. Cycloaddition with *α*-amino acids-one-pot synthesis of dihydropyrrolizines.

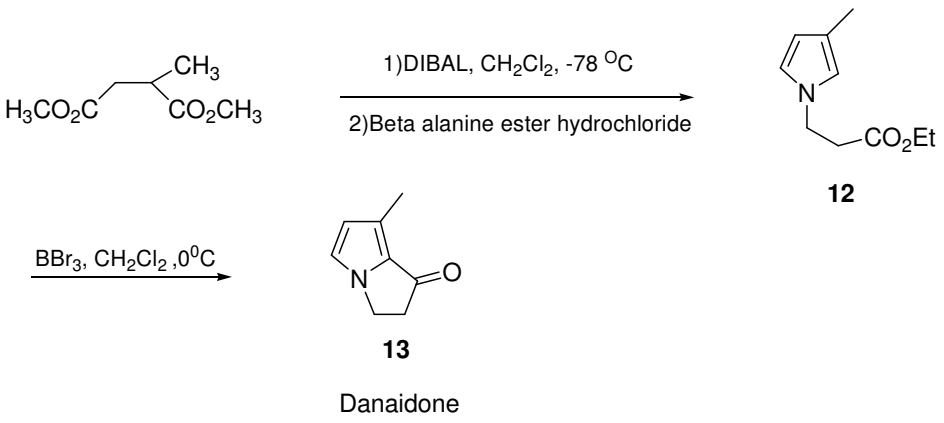
Another method is an intramolecular Witting reaction which was studied by Yavari and Adib in 2001 to obtain pyrrolizine derivatives. **9a, b** undergoes reaction with acetylenedicarboxylates (**8a-c**) and triphenylphosphine to produce **10** and reflux of **10** in toluen affords **11** (Scheme 2.3).



8a: R= -Me, Z=OEt, **8b**: R= -Et**,** Z=OEt, **8c**: R= -iPr, Z=OEt,
9a: Z= -OEt, **9b**: Z= **-**$NHCH_2Ph$

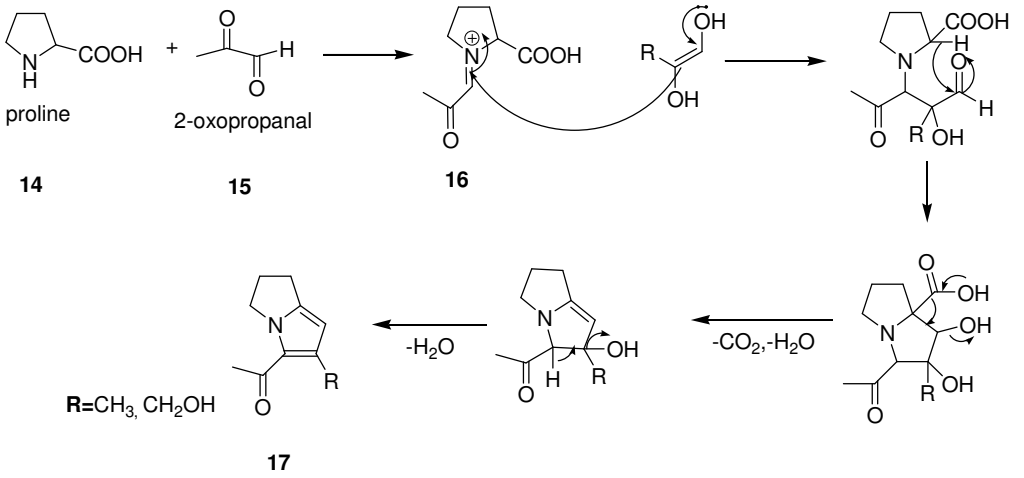
Scheme 2.3. Witting reaction of phosphous ylides with pyrrole derivatives.

In 2002, Jimenez and Rajamaran have been reported the synthesis of dihydropyrrolizine derivatives as a precursors of biofunctional alkylating agent. Pyrrole based alkylating agent have the ability as a antitumor agent. In this method, BBr_3 has been used as a Lewis acid for the cyclization of pyrrole ester **12** to form danaidone (**13**) (Scheme 2.4).



Scheme 2.4. Synthesis of danaidone.

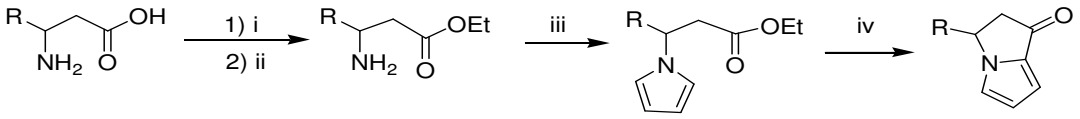
Another method was reported by Adams et al. in 2004. This reaction involves the formation of an iminium ion **16** which is formed from the reaction of proline (**14**) and 2-oxopropanal (**15**). This iminium ion undergoes either an aldol condensation



Scheme 2 .5. Formation of 5-acetyl-6-hydroxymethyl-2,3-dihydro-1*H*-pyrrolizine.

with an *α*-hydroxy carbonyl compound or a nucleophilic attack by an *α*-hydroxy carbonyl compound. Proposed mechanism for the formation of **17** is given in Scheme 2.5.

Another synthetic pathway involves the Clauson-Kaas reaction which is developed by Sonnet et al., in 2000. In this reaction *β*-amino acids (**18a-e**) were used as a starting materials. After esterification of carboxylic acid group (**18a-e**) to obtain **19**, Clauson-Kaas reaction led to arylpyrrolypropionates (**20a-e**), then aryl substituted pyrrolizine derivatives **21a-e** was obtained *via* intramolecular ring closure method (Scheme 2.6).



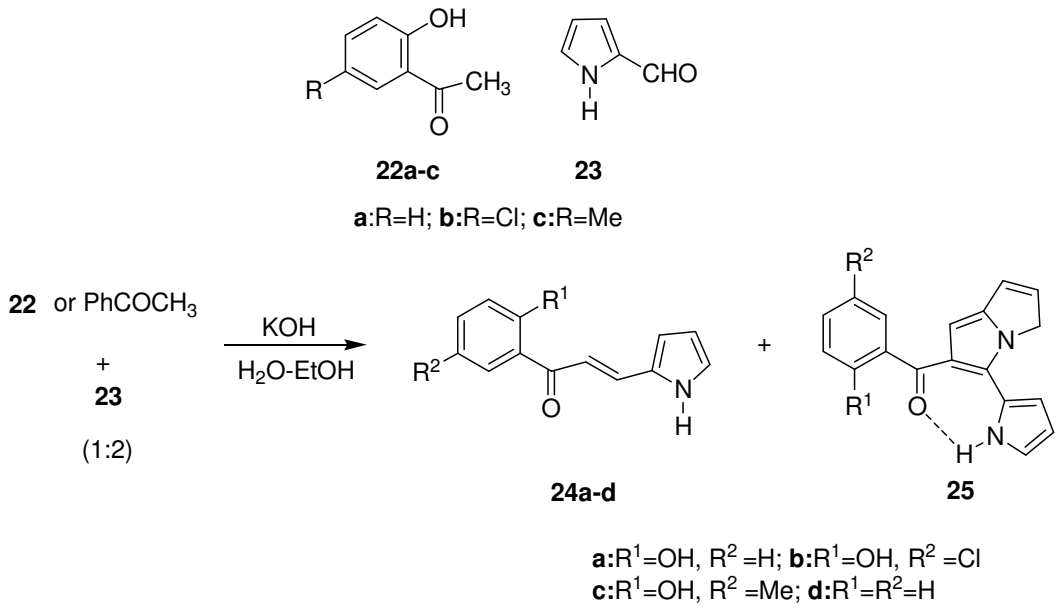
18a-e **19** **20a-e** **21a-e**

i)$SOCl_2$,EtOH; ii) NH_3 gas, Et_2O; iii) 2,5-diOMeTHF, AcOH; iv) BBr_3, $CHCl_3$

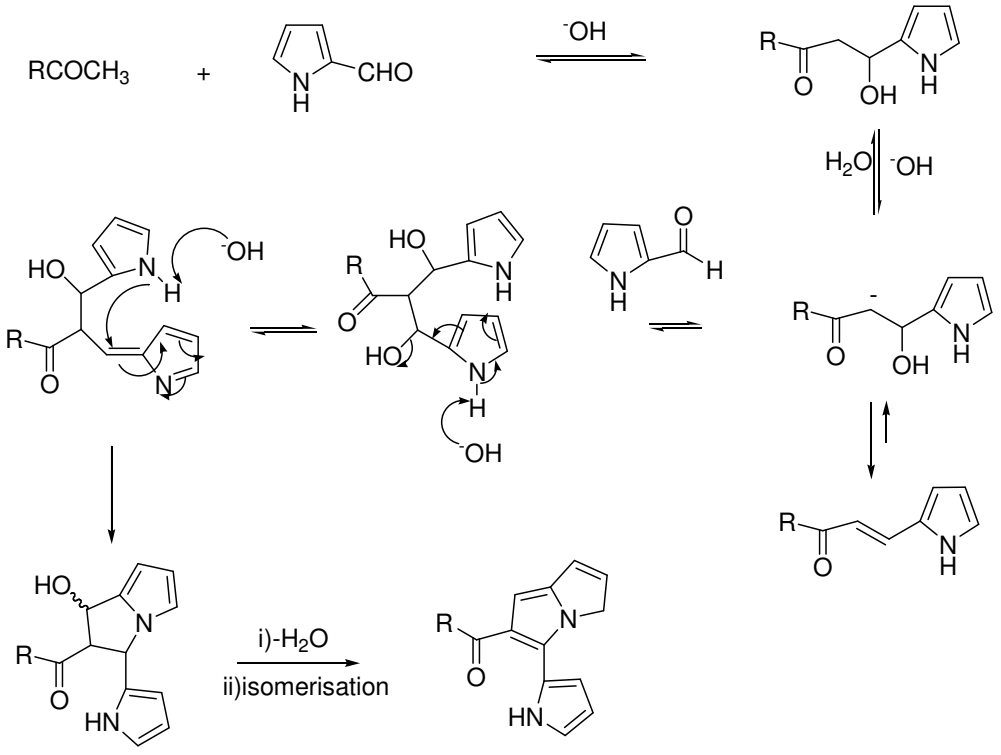
a= C_6H_5-, **b**= o-Cl-C_6H_4-, **c**= p-CN-C_6H_4-, **d**=p-CF_3O-C_6H_4-, **e**= 

Scheme 2.6. Synthesis of aryl substituted pyrrolizine derivatives.

Base catalysed simple condensation reaction of methyl ketones **22a-c** with pyrrole-2-aldehydes (**23**) to synthesise pyrrolizine derivatives was studied by Mallik et al. in 2002. Condensation product **24a-d** and pyrrolizine derivative **25a-d** were obtained from the reaction of **22** or acteophenone with **23** when metylketones were allowed to undergo condensation with 2 molar equivalents of pyrrole-2-aldehyde in ethanolic KOH (Scheme 2.7). The proposed reaction mechanism for the formation of **24** and **25** is given in Scheme2.8

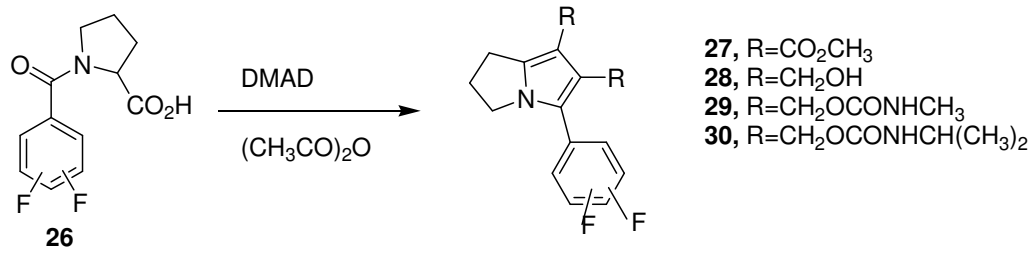


Scheme 2.7. Condensation of methyl ketone with pyrrole-2-aldehyde.



Scheme 2.8. Suggested mechanism for the formation of pyrrolizine derivative.

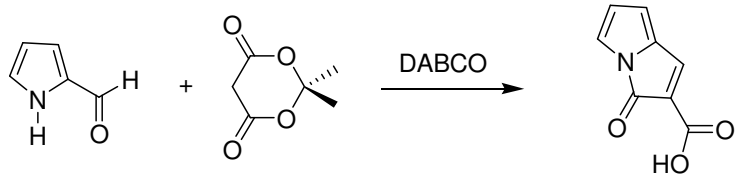
Another method is the 1,3-dipolar cycloaddition reaction of α-amino acids with acetic anhydride-dimethylacetylenedicarboxylate (DMAD) (Andersen and Mc Pherson, 1982). Target compounds **27**-**30** were prepared from the *α*-amino acid **26** (Scheme 2.9).



26

Scheme 2.9. Cyclization reaction of α-amino acid.

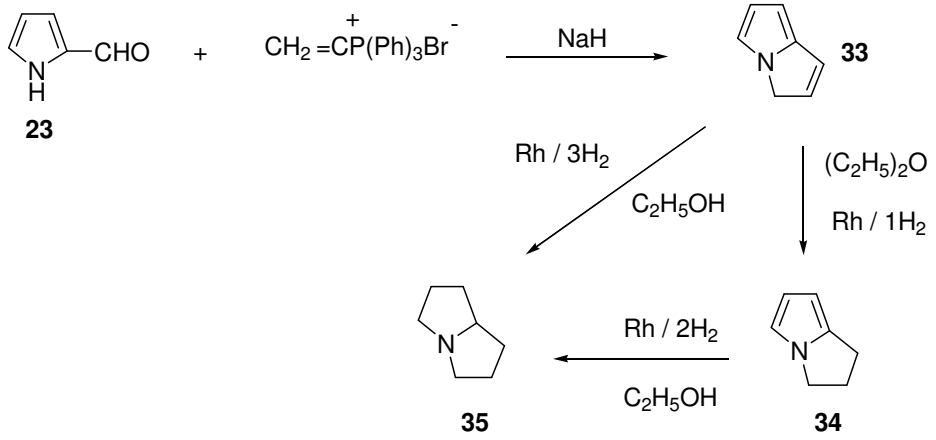
Knoevenegal reaction of pyrrole-2-carbaldehyde (**23**) and meldrum's acid (**31**) in the precence of DABCO (1,4-diazabicyclo [2.2.2] octane) as catalyst to give pyrrolizine derivative **32** (Hekmatshoar, 2005), (Scheme 2.10).



23 **31** **32**

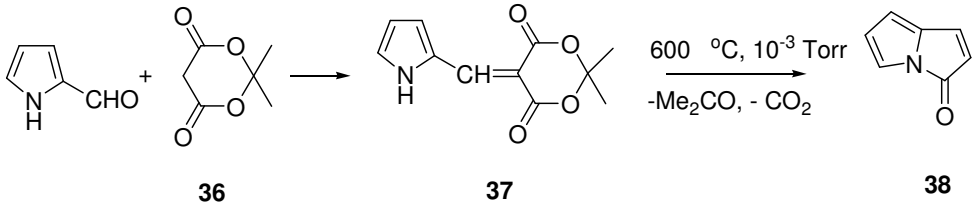
Scheme 2.10. Synthesis of 3-oxo-3H-pyrrolizine-2-carboxylic acid.

The first synthesis of the parent 3*H*-pyrrolizine (**33**) and its reduction to 1,2-dihydro-3*H*-pyrrolizine (**34**) and the fully saturated pyrrolizidine (**35**) was reported by Schweizer and Light in 1964 by using 2-pyrrole-aldehyde and phosphorus compounds in high yield (Scheme 2.11).



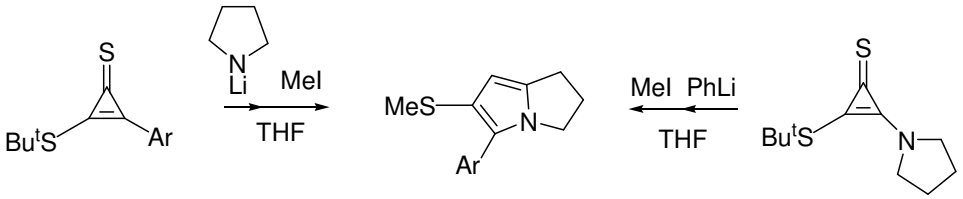
Scheme 2.11. Synthesis of 3*H*-pyrrolizine and 1,2-dihydro-3*H*-pyrrolizine.

Synthesis of pyrrolizine derivatives *via* flash vacuum pyrolysis reaction has been reported by McNab in 1981. Reaction of pyrrole-2-carboxaldehyde with Meldrum's acid (**36**) at room temperature gives the condensation product **37**. Flash vacuum pyrolysis of **37** at 500 °C (Scheme 2.12) generates acetone solution and pyrrolizine-3-one (**38**).



Scheme 2.12. Synthesis of pyrrolizine-3-one via FVP.

One-pot synthesis of *N*-heterocyclic compounds from cyclopropenethione derivatives were reported by Matsumura et al., in 2000. The reaction of 2-tert-butylthio-3-phenylcyclopropenethione (**39a**) and its 3-(2-thienyl) derivative **39b** with lithium pyrrolidinide, followed by methylation with methyl iodide, gives 6-methylthio-5-phenyl-2,3-dihydro-1*H*-pyrrolizine (**40a**) and its 5-(2-thienyl) derivative **40b** (Scheme 2.13). The reaction of 2-tert-buthylthio-3-(pyrrolidin-1-yl) cyclopropenethione (**39c**) with phenyllithium gives also **40a**.



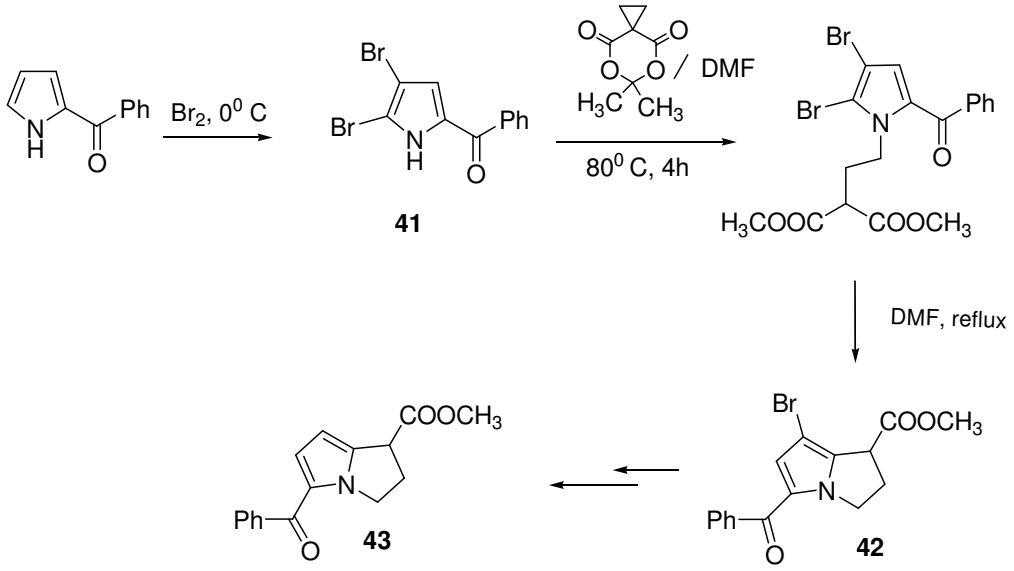
39a: Ar=Ph
39b: Ar=2-Thienyl

40a: Ar=Ph
40b: Ar=2-Thienyl

39c

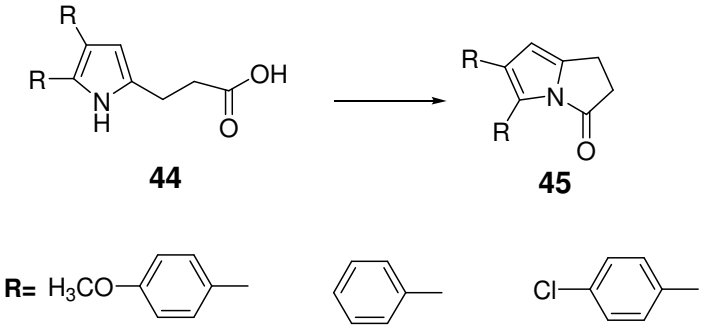
Scheme 2.13. Synthesis of 6-methylthio-5-phenyl-2,3-dihydro-1*H*-pyrrolizine and its 5-(2-thienyl) derivative.

1,2-disubstituted pyrrole derivatives are also important for the synthesis of the pyrrolizine derivatives, which are the intermediates of many biologically active compounds. Intramolecular displacement of suitable 1,2-disubstituted pyrrole derivatives obtained from **41** gave the pyrrolizine derivatives (Scheme 2.14) such as **42** and **43** (Sugden et al., 1987).



Scheme 2.14. Synthesis of pyrrolizine derivatives via intramolecular displacement.

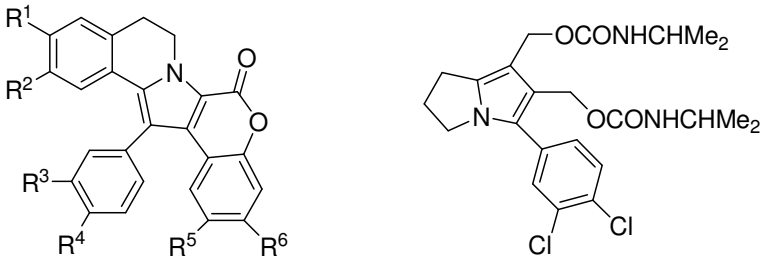
Dehydration of **44** with acetic acid/acetic anhydride mixture or thermally gave **45** (Scheme 2.15), (Sugden et al.,1987).



Scheme 2.15. Synthesis of **45**.

2.2. Synthesis of Substituted Pyrroles

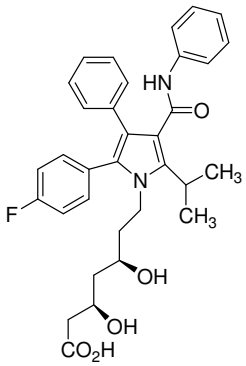
Pyrroles are heterocyles of great importance because of their presence in numerous natural products like heme, chlorophyll, vitamin B_{12} and various cytrochrome enzymes. Functionalizased pyrroles are interesting subunits for both material science and natural product synthesis (Settanbolo et al., 2003). Polysubstituted pyrroles are common pharmacophores for numerous natural compounds which include alkaloids (Katritzky et al, 2000). The unique structural array and the unusual biologically activity displayed by many pyrrole containing natural products such as **46** and **47** have made them attractive synthestic targets (Asoken and Mathew, 2006; Denny et al., 1998), (Scheme2.16).



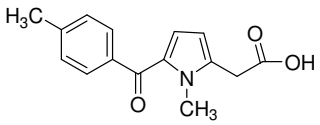
46 **47**

Scheme 2.16. Pyrrole containing biologically active compounds.

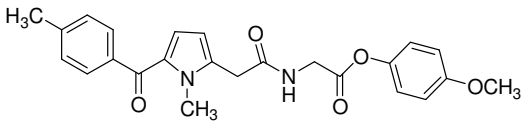
Many of the substituted pyrrole compounds also show appreciable antibacterial and antitumor activity. Representative pyrrole-containing drugs are given in Scheme 2.17.



Lipitor



Tolmetin



Amtolmetin

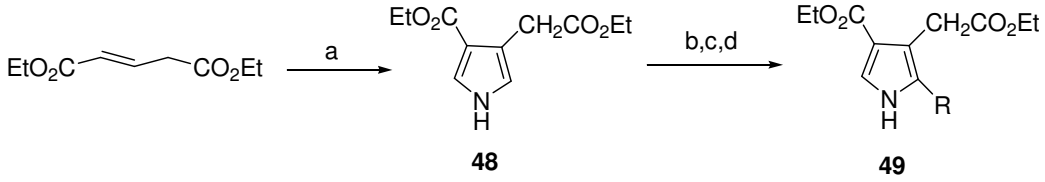
Scheme 2.17. Representative pyrrole-containing drugs.

Substituted pyrroles can be prepared *via* the construction of pyrrole ring starting from suitable materials or functionalization of pyrrole compounds.

2.2.1. Construction of Substituted Pyrrole Rings

The synthesis of pyrrole rings have attracted much research interest for over a century because a number of pyrrole containing compounds are widely distributed in nature. Pyrroles have traditionally been prepared *via* the condensation of 1,4-dicarbonyl compounds with ammonia or primary amines, a reaction known as Paal-Knorr pyrrole synthesis (Knorr, 1884). Since then, many of the methods have been developed for the synthesis of substituted pyrroles.

The synthesis of polysubstituted pyrroles **48** obtained from diethyl glutaconate has been reported by Ganem and Leon in 1996. Vilsmeier-Haack formylation and subsequent reactions of **48** give polysubstituted pyrrole **49** (Scheme 2.18).

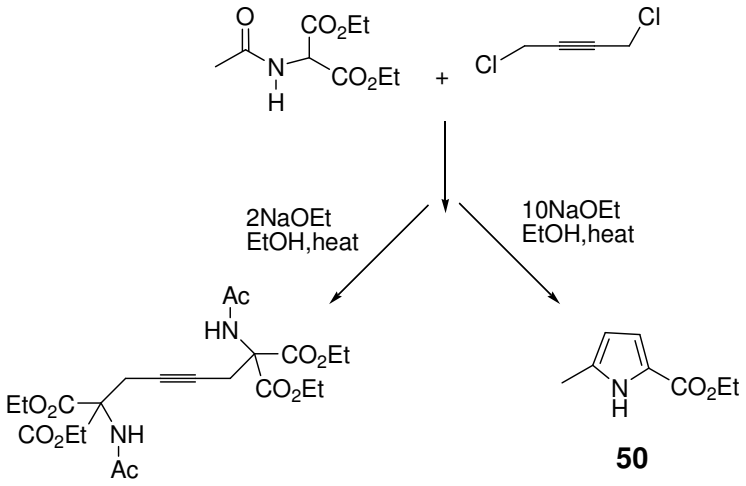


R**:** -CHO, -CHNOH, $-CH_2NH_2$

a)TsCH(Li)N=C **;** b) $POCl_3$,DMF ; c)NH_2OH-EtOH ; d)H_2,$Pd(OH)_2$,HCl,EtOH

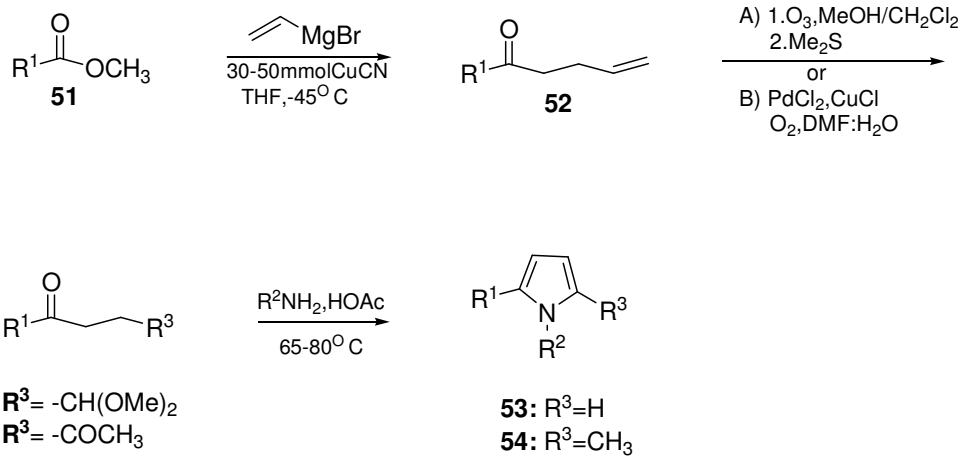
Scheme 2.18. Synthesis of polysubstituted pyrroles.

Curran and Keany (1996) reported one-pot synthesis of the ethyl-5-methyl pyrrole-2- carboxylate (**50**) from the reaction of diethylacetamido malonate and 1,4-dichloro-2-butyne (Scheme 2.19).



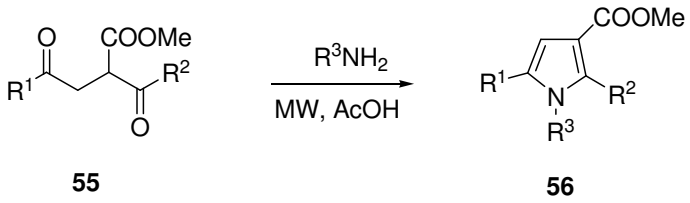
Scheme 2.19. Synthesis of the ethyl-5-methyl pyrrole-2- carboxylate (**50**).

Recently in 2004, Hasford et al. described a three-step-pathway for the synthesis of homoallylic ketones **52** *via* copper-catalyzed addition of vinyl Grignard reagent to carboxylic esters **51**. Preparation of the homoallylic ketones is necessary to form pyrrole ring. Under Paal-Knorr conditions substituted pyrrole compounds **53** and **54** can be obtained (Scheme 2.20).



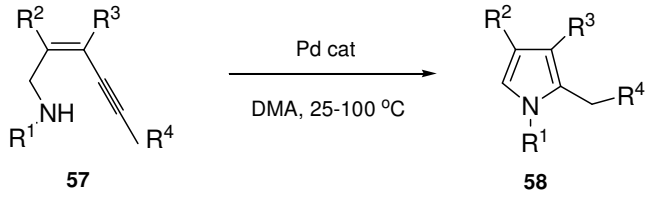
Scheme 2.20. Synthesis of polysubstituted pyrrole derivatives from carboxylic esters.

Recently, in 2005, Taddei et al. reported that regiocontrolled synthesis of polysubstituted pyrroles under microwave assisted Paal-Knorr reaction conditions (Scheme 2.21). Microwaves have been used to increase the yield, reduce the reaction time and provide mild conditions. Diketones **55** were subjected to microwave-assisted reactions in acetic acid in the precence of different amines to give corresponding pyrroles **56**. Reactions were yielded in 65-88%.



Scheme 2.21. Microwave-assisted synthesis of polysubstituted pyrroles.

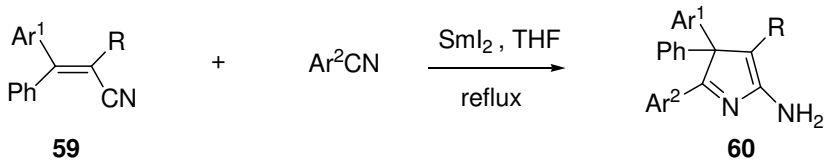
Another new method for the preparation of substituted pyrrole derivatives **58** was performed by Gabriele et al. in 2001 (Scheme 2.22). Pyrrole derivatives were obtained via palladium-catalyzed cycloisomerization of amines **57**. Reaction was performed in anhydrous *N,N*-dimethyl-acetamide (DMA) in the presence of $PdCl_2$ to synthesize pyrroles by cycloisomerization of (Z)-(2-en-4-ynyl)amines.



57 **58**

Scheme 2.22. Palladium-catalyzed cycloisomerization of amines to form pyrrole derivatives.

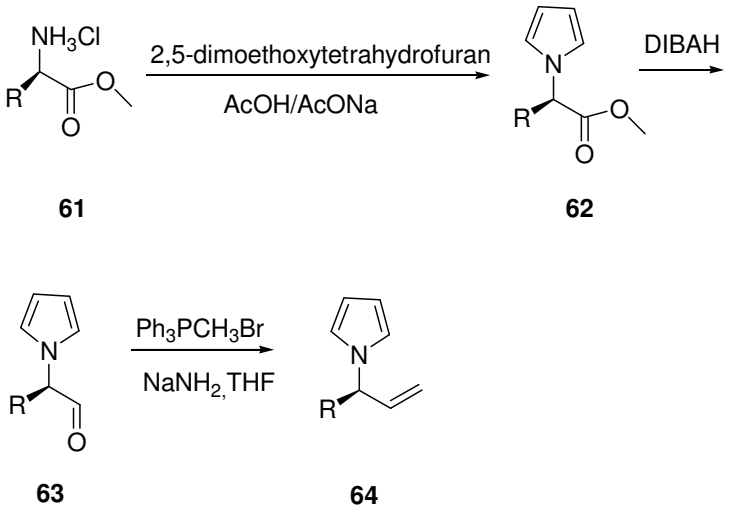
A convenient preparation of the polysubstituted pyrrole derivatives **60** was reported in 2001 by Zhang et al. Intramolecular reductive coupling of 1,1-diaryl-2,2-dicyanoethylenes or 1,1-diaryl-2-cyano-2-ethoxycarbonylethylenes **59** with aromatic nitriles was induced by SmI_2 in THF. Polysubstituted 3*H*-pyrroles were obtained in good yield (71-91%) under mild conditions (Scheme 2.23).



59 **60**

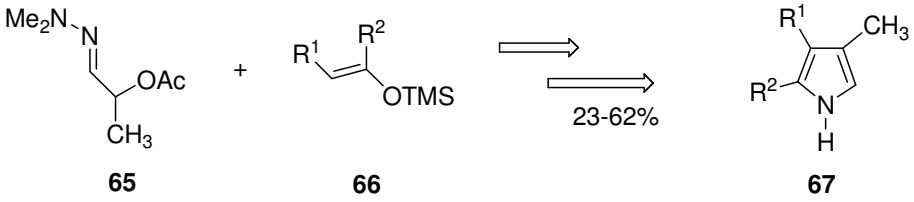
Scheme 2.23. Preparation polysubstituted 3*H*-pyrroles.

Recently a new class of optically active pyrrole derivatives were studied by Settamblo et al. in 2003 (Scheme 2.24). D-α-amino acid methyl ester hydrochloride **61** was chosen as a starting material and its pyrrolation product **62** was performed with 2,5-dimethoxytetrahydrofuran, then reduction of obtained product **62** with DIBAH and subsequent Witting olefination of **63** to give pyrrolylolefines **64**.



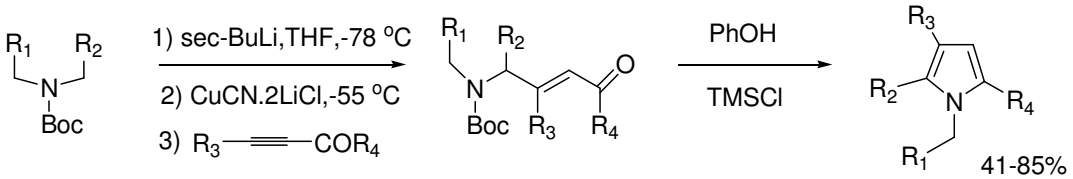
Scheme 2.24. Optically active new pyrrole derivative.

Enders et al. reported a new efficient and flexible method for the synthesis of polysubstituted pyrroles **67** from 2-acetoxypropanal-*N,N*-dimethylhydrazone **65** and various silyl enol ethers **66** in 1995 (Scheme 2.25).



Scheme 2.25. Synthesis of polysubstituted pyrroles from 2-acetoxypropanal-*N,N*-dimethylhydrazone.

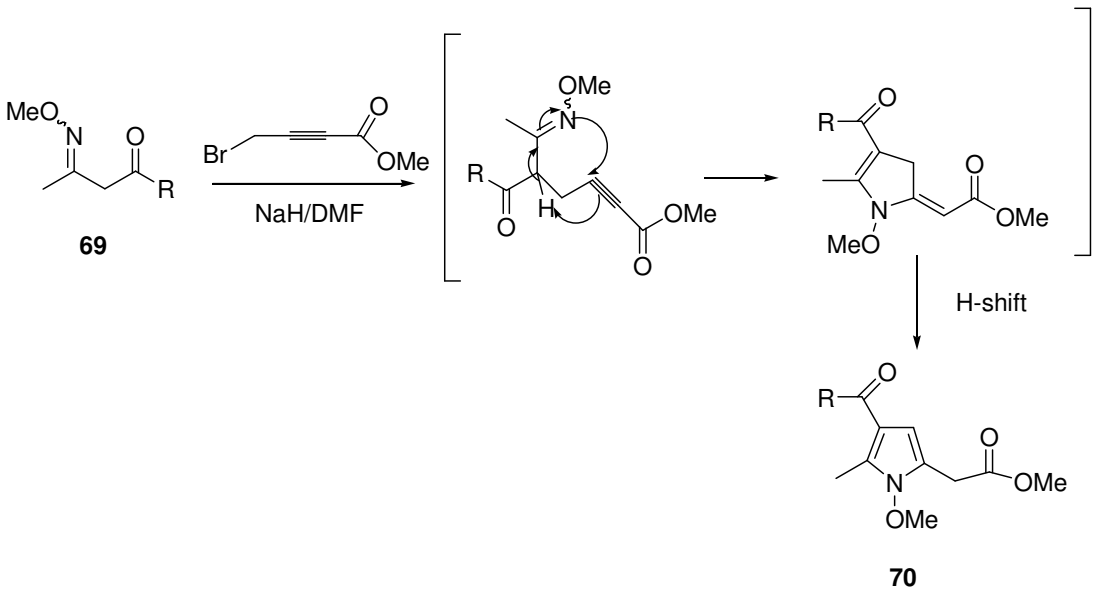
A facile synthesis of polysubstituted pyrrole derivatives were reported in 2000 by Dieter and Yu. They have synthesized corresponding compounds **68** *via* conjugate addition of α-amino-alkylcuprates to alkynyl ketones followed by amine deprotection and cyclization which provides a potential synthetic route to polysubstituted pyrroles (Scheme 2.26).



68

Scheme 2.26. Two-step synthesis of substituted pyrroles *via* conjugate addition of α- amino-alkylcuprates to alkynyl ketones.

Recently, Song et al. (2004) reported a new method for the synthesis of polysubstituted pyrroles **70** starting with the readily avaible *β*-carbonyl *O*-methyloximes **69** (Scheme 2.27).

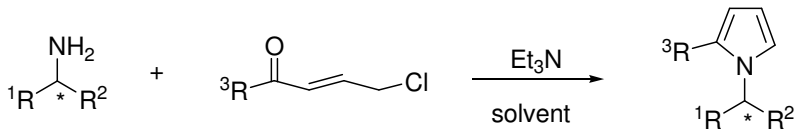


69

70

Scheme 2.27. Synthesis of polysubstituted dihydropyrroles from *β*-carbonyl *O*-methyloximes.

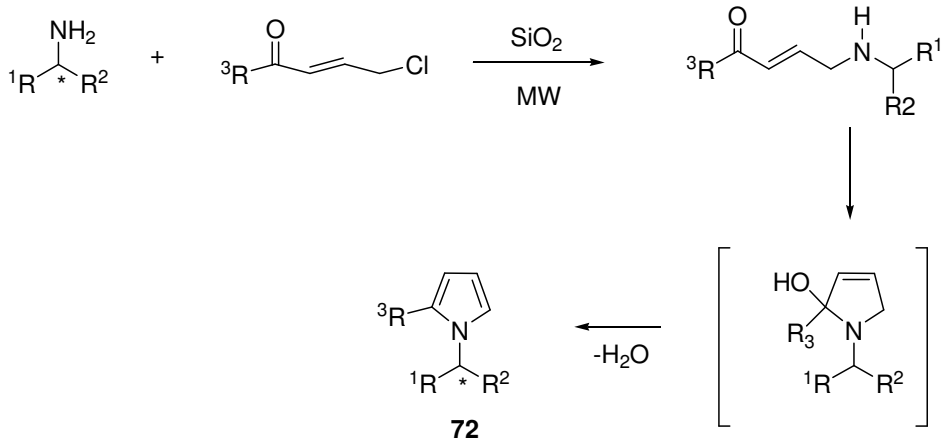
Demir et al., in 1997 have developed a convenient method for the construction of different substituted pyrrole rings **71** from amines, amino alcohols and amino acids with chloroenones prepared from acid chlorides and allylchlorides in the presence of $AlCl_3$ (Scheme 2.28).



71

Scheme 2.28. Construction of substituted pyrrole rings from amines, amino alcohols and amino acids.

Aydoğan and Demir (2005) reported an efficient microwave-assisted one pot synthesis of pyrroles **72** by coupling chloroenones and amine compounds onto the surface of silica gel (Scheme 2.29). Compound **72** was obtained with 68-87% yield.



72

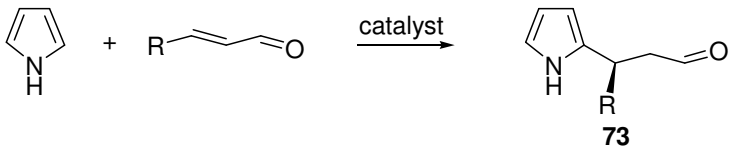
Scheme 2.29. Microwave-assisted one pot synthesis of pyrroles.

2.2.2 Alkylation of Pyrroles

Alkylation of pyrrole is important for the synthesis of the intermediates of the pyrrole containing compounds such as pyrrolizines and indolizines. Generally C-alkyl pyrroles are synthesised by Vilsmeier-Haack formylation followed by Wolf-Kishner reduction. The other approach involves the isomerisation of *N*-alkyl pyrrole by thermal rearrangement at a very high temperature. Alternatively, C-alkyl pyrroles are prepared using pyrrolyl magnesium halides. The other method is the direct alkylation of pyrroles by using Lewis acids as catalyst.

Metal catalyzed addition of aromatic substrates to electron deficient σ-and π-systems, commonly known as Friedel-Crafts alkylation has long been established as a powerful strategy for C-C bond formation (MacMillan and Paras, 2001).

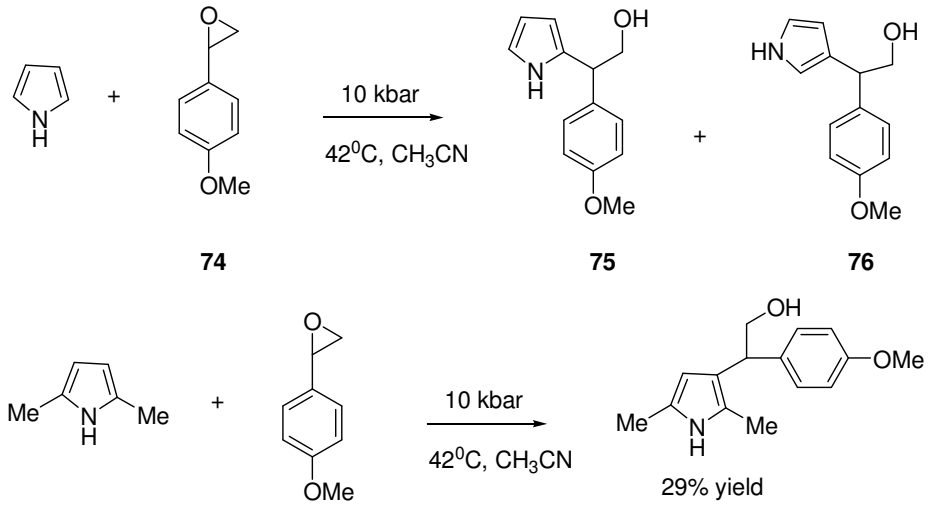
MacMillan and Paras demonstrated in 2001 that organocatalytic strategy is also amenable to the enantioselective Friedel-Crafts alkylation of pyrroles with α,β-unsaturated aldehydes to form **73** (Scheme 2.30).



73

Scheme 2.30. Friedel-Crafts alkylation of pyrroles with organocatalyst.

In 1990, Kotsuki et al. reported a novel neutral alkylation of pyrroles with vinyl epoxides at high pressure. In this study he has described an essential non-catalyzed carbon–carbon bond formation of pyrrole with epoxides **74**. Compounds **75** and **76** were obtained in low yields. He has also demonstrated the utility of high-pressure reaction for the possibile alkylation reactions. Similarly treatmant of 2,5 dimethylpyrrole with p-methoxystyrene oxide provided the sole product **77** in 29% yield (Scheme 2.31).

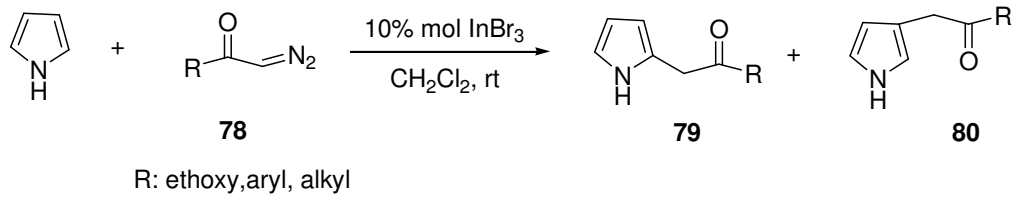


74 **75** **76**

77

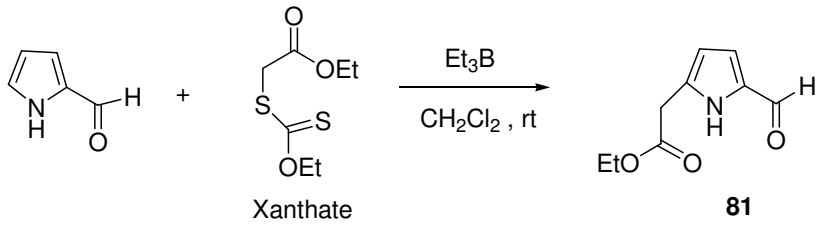
Scheme 2.31. Alkylation of pyrroles with vinyl epoxides at high pressure.

Yadav et al. reported a simple and straightforward method in 2003 for the alkylation of pyrroles with α-diazocarbonyl compounds (**78**) using $InBr_3$ as the catalyst. Treatment of pyrrole with ethyl diazoacetate in the presence of 10% mol of $InBr_3$ afforded C-alkylated pyrroles as a mixture of **79** and **80** in 60 and 25% yield, respectively (Scheme 2.32).



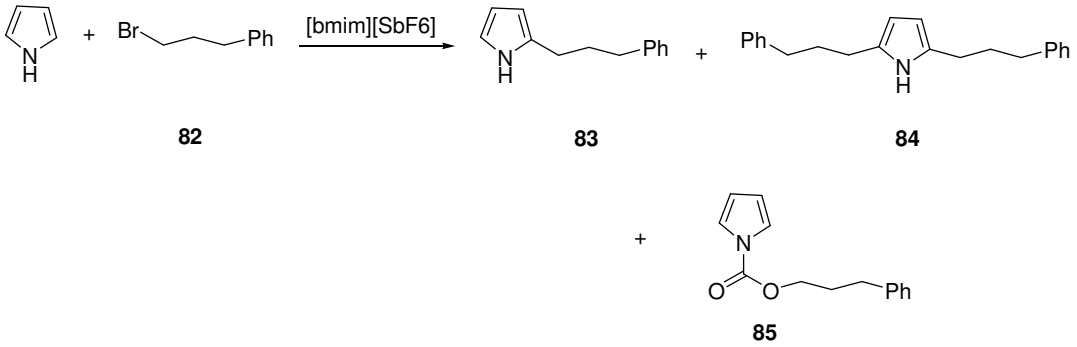
Scheme 2.32. Alkylation of pyrroles with α-diazocarbonyl compounds.

In 2006, Miranda and Guerrero reported the alkylation reaction of pyrroles using xantates as the radical source and Et_3B as initiator at room temperature. Using xanthate as the radical source, Et_3B air as initiator and pyrrole-2-carboxaldehyde generated the expected product **81** (Scheme 2.33).



Scheme 2.33. Radicalic alkylation of the pyrroles.

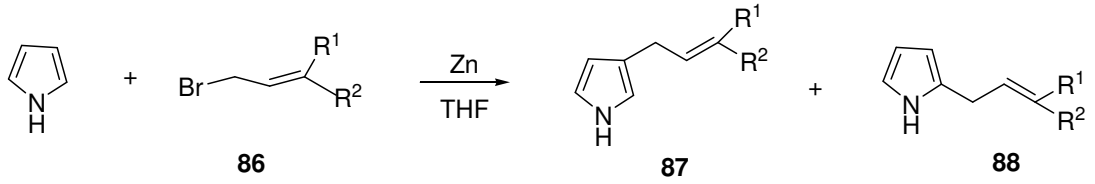
In 2005, Chi et al. reported that by employing an ionic liquides as a solvent significant rate enhancement of the *C*-alkylation of pyrrole at the C-2 position can be accomplished from alkyl halides or alkyl mesylates. In scheme 2.34 **83**, **84** and **85** were obtained from reaction of 1-bromo-3-phenylpropane (**82**) and pyrrole in the presence of K_2CO_3 and [bmim][SbF_6].



82 **83** **84** **85**

Scheme 2.34. C-alkylation of pyrrole employing an ionic as a solvent.

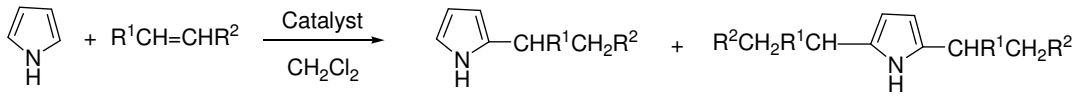
J.S.Yadav et al. reported that a new method for the alkylation of pyrrole in 2002. A novel and efficient method for the preparation of 3- and 2-alkyl pyrrole through the zinc mediated Barbier reaction of pyrrole. Treatment of pyrrole with zinc metal and allyl bromide (**86**) in THF resulted in the formation 3- and 2-allyl pyrrole derivatives **87** and **88** in good yield (Scheme 2.35).



86 **87** **88**

Scheme 2.35. Zinc mediated Barbier reaction of pyrrole with allyl bromide.

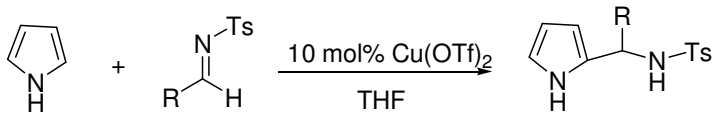
In 2006, Zang et al. have first used Lewis acid Cr^{+3}-Catsan and $ZnCl_2$ as catalysts for Micheal addition of pyrrole to conjugated alkene **89**. 2-alkyl **90** and 2,5-dialkyl pyrrole 91 have been obtained as addition products (Scheme 2.36).



89 **90** **91**

Scheme 2.36. Lewis acid catalysed Micheal addition of pyrrole to conjugated alkenes.

Unaleroglu and Temelli described the regioselective copper triflate catalysed addition reaction of pyrrole to *N*-tosyl imines **92** in 2005. Reaction yielded product **93** (Scheme 2.37).



92 **93**

Scheme 2.37. Regioselective addition reaction of pyrrole to *N*-tosyl imines.

2.3. Metal Triflates in Organic Synthesis

Lewis-acid catalyzed carbon-carbon bond forming reactions are of great current interest in organic synthesis because of the their reactivities and selectivities that can be achieved as well as for the mild conditions. Traditional Lewis acids such as $AlCl_3$, BF_3, $SnCl_4$ etc, are widely used for a variety of reactions, however they represent some undesirable problems. The presence of even a small amount of water stops the reaction because most Lewis acids immediately react with water rather than the substrates and decomposes (Kobayashi and Manabe, 2000). In addition they can not be recovered after the reaction. These have limited the utilization of Lewis acids in organic synthesis.

Nevertheless, the advantages of using water as solvent for organic reactions are numerous. An aqueous media is both economical and avoids usage of inflammable organic solvents. Protection-deprotection processes, product isolation, and catalyst recycling are simplified. This process is regarded as green chemistry (Wang et al., 2005).

In 1991, the first report on water-compatible Lewis acids, lanthanide triflates [Ln(OTf)3], appeared in the literature. Lanthanide triflates were literature-known compounds at that time, but their use in organic synthesis had been limited. The most characteristic feature of $Ln(OTf)_3$ is that they are stable and work as Lewis acids in water. These rare-earth metal triflates [$Ln(OTf)_3$] have been regarded as new types of Lewis acids (Kobayashi et al., 2002).

Rare-earth metal triflates are available not only in aqueous media but also in many organic solvents. The triflates are still active in the coexistence of many Lewis bases containing nitrogen, oxygen, phosphorus, and sulfur atoms. In almost all cases, catalytic use, recovery and reuse of the triflates are possible (Kobayashi et al., 2002).

After 1991, metal triflates have been used as a catalyst in Aldol, Mannich, Micheal, Diels-Alder, Friedel-Crafts type reactions in both organic solvent and aqueous media.

2.4. Synthesis of Metal Triflates

Metal triflates are synthezised by heating the metal oxides or metal chlorides in aqueous media with trifluoromethanesulfonic acid (TfOH) solution. Generally they include water molecule in their structure. Anhydrous compounds of this metal triflates are obtained by heating under high pressure. Synthesis of $Sc(OTf)_3$ was given in equation as an example.

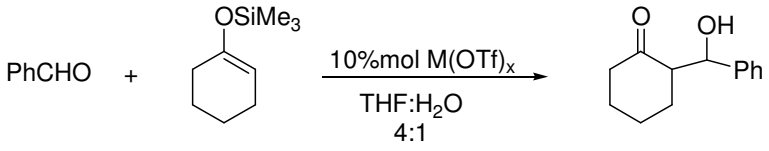
$$Sc_2O_3 + 6TfOH \xrightarrow{(50\%\ TfOH:H_2O)} 2Sc(OTf)_3 + 3H_2O$$

2.5. Metal Triflate Catalyzed Reactions

Many useful reactions such as Aldol, Mannich, Micheal, Diels-Alder and Friedel-Crafts are catalyzed by metal triflate in organic solvent or aqueous media. Only catalytic amounts of the metal triflates are enough to complete the reactions in most cases.

2.5.1. Aldol Reactions

[$Ln(OTf)_3$] catalysed Aldol reaction of aldehydes with enolates to form **94** was performed by Kobayashi and Hachiya in 1992. Investigation of the different $M(OTf)_x$ catalysed reactions showed that metal type also effects the yield ratio (Table 2.1, Scheme 2.38).



94

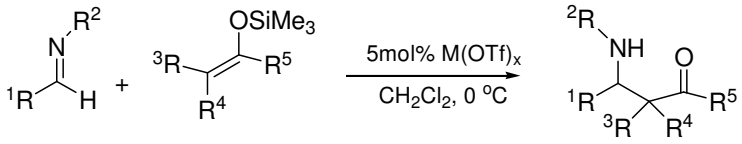
Scheme 2.38. Aldol reaction via $M(OTf)_x$ catalyst.

Table 2.1. Metal Triflate catalysed aldol reaction and the effects of the metal triflates on Aldol reaction.

$M(OTf)_x$	Yield (%)	$M(OTf)_x$	Yield (%)
Sc	81	Gd	89
Y	-	Dy	73
La	8	Ho	47
Pr	28	Er	52
Nd	83	Tm	20
Sm	46	Yb	91
Eu	34	Lu	88

2.5.2. Mannich Reaction

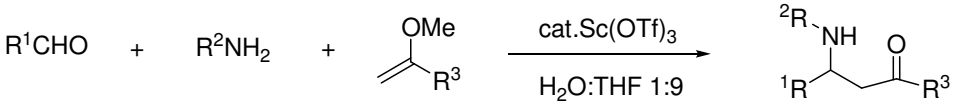
Mannich reaction of imines with silyl enol ethers have been performed with traditional Lewis acid catalyst in 1977 and the same reaction was performed in the presence of the 5% mol metal triflate giving **95** with a high yield (97%) by Kobayashi in 1995, (Scheme 2.39).



95

Scheme 2.39. Metal triflate catalysed Mannich reaction.

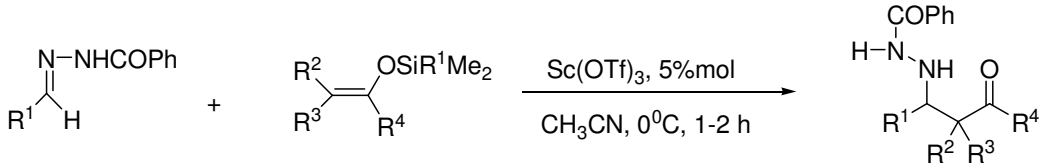
Mannich-type reaction of aldehydes, amines and vinyl ethers proceeded smoothly in the presence of a catalytic amount of $Sc(OTf)_3$ in aqueous media (Kobayashi, 1999) (Scheme 2.40). Compound **96** was obtained as product.



96

Scheme 2.40. Mannich-type reaction of aldehydes, amines and vinyl ethers in aqueous media.

Mannich reaction using hydrozones can also be performed by using $M(OTf)_x$. In the presence of a catalytic amount of $Sc(OTf)_3$, benzoylhydrozones reacted with silyl enolate to afford the corresponding adducts *β-N'*-benzoylhydrozino esters (**97**) in high yields (Scheme 2.41). On the other hand, the catalytic activation of benzoylhydrozones using a typical Lewis acids such as a $TiCl_4$, $SnCl_4$ etc., was not effective in this reaction (Kobayashi, 1999).



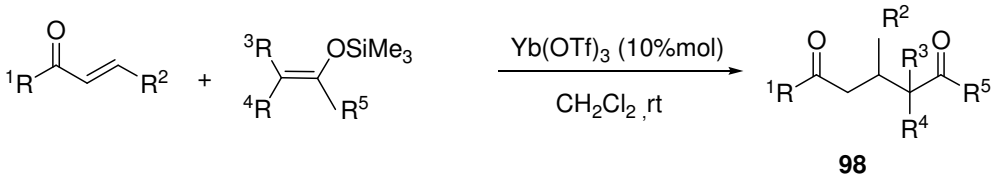
97

Scheme 2.41. Mannich type reaction using hydrozones in the presence of a catalytic amount of Sc(OTf).

2.5.3. Micheal Reaction

Micheal reaction of silyl enol ethers or ketene silyl acetals with α-β-unsaturated carbonyl compounds is the most important carbon-carbon bond forming process in organic synthesis.

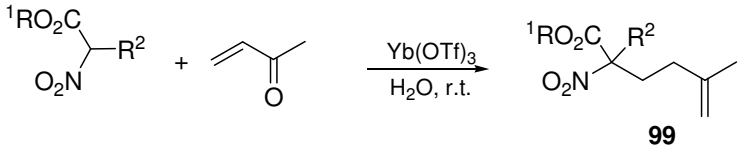
Kobayashi et al., in 1993 showed that lanthanide triflates act quite well as catalyst in the Micheal reaction of silyl enolates with α-β-unsaturated ketones in the presence of catalytic amount of a $Sc(OTf)_3$ under mild conditions to give the corresponding 1,5 dicarbonyl compounds **98** in high yield (Scheme 2.42).



98

Scheme 2.42. Micheal reaction of silyl enolates with α-β-unsaturated ketones in the presence of catalytic amount of a $Yb(OTf)_3$.

In 1997, Feringa and Keller succesfully conducted the Micheal reaction in water at room temparature. Addition reaction of α-nitroesters to α-β-unsaturated compounds gave **99** in high yield by using catalytic amount of $Yb(OTf)_3$ (Scheme 2.43).



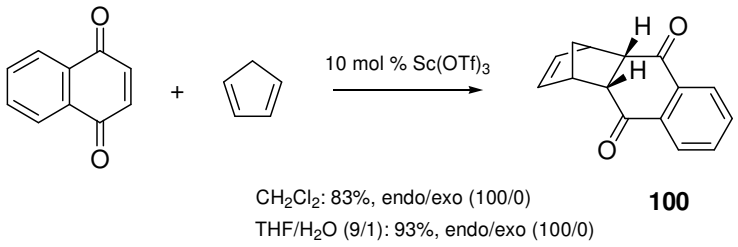
99

Scheme 2.43. Micheal reaction of α-nitroesters with α-β-unsaturated compounds.

2.5.4. Diels-Alder Reactions

The Diels-Alder reaction is one of the most usefull synthetic conversion used to form cyclic structures. Lanthanide triflates are also efficient catalysts in some Diels-Alder reactions. Scheme 2.44 shows an example of $Sc(OTf)_3$ –catalysed

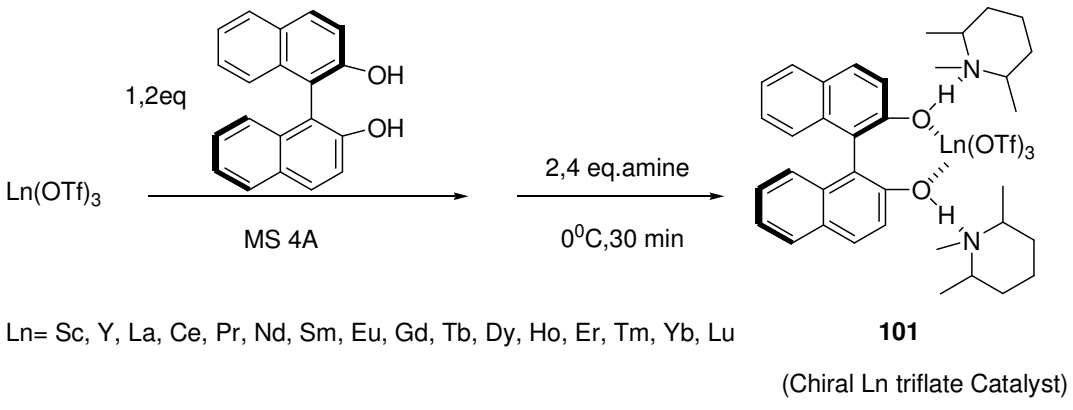
Diels-Alder reaction of naphthoquinone with cyclopentadiene in aquoeus THF solution at room temperature to give coresponding adduct **100** in high yields with endo selectivities (Wang et al., 2005).



Scheme 2.44. $Sc(OTf)_3$ catalysed enantioselective Diels-Alder reaction.

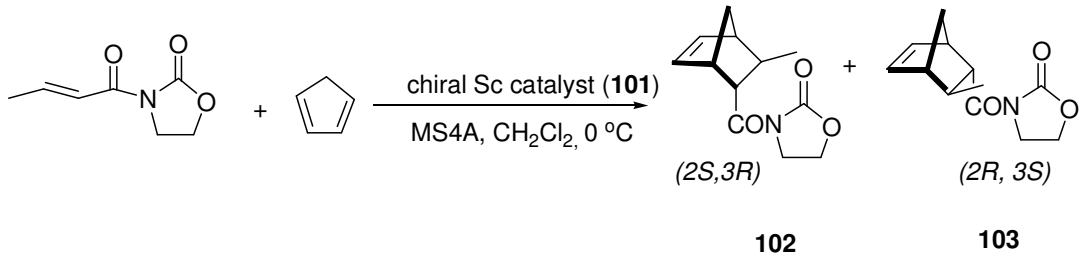
2.5.4.1. Asymmetric Diels-Alder Reaction

Although some efficient asymmetric Diels-Alder reactions had been catalysed by chiral Lewis acids, only a few asymmetric reactions have been catalysed by chiral rare earth metal triflates. Chiral rare earth triflate catalyst can be synthesis from metal triflates. Scheme 2.45 shows the synthesis of chiral triflate catalyst (Kobayashi, 1998).



Scheme 2.45. Synthesis of chiral Lanthanium catalyst.

It was found that a chiral catalyst **101** was quite effective in enantioselective Diels-Alder reactions. Catalytic amount of catalyst is sufficient to complete of reaction yielding the products **102** and **103** in Scheme 2.46 (Kobayashi, 1994).

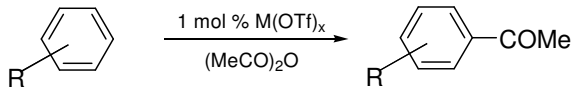


Scheme 2.46. Chiral Sc(OTf) $_3$ catalysed Diels-Alder reaction.

2.5.5. Friedel-Crafts Reactions

The Friedel-Crafts reactions are a fundemental reaction for organic synthesis and important reaction widely used in industrial process. $AlCl_3$ is generally used as Lewis acid in this type reactions. Stochiometric amount of $AlCl_3$ is required to complete the reaction (Ishikawa, 2000). However, use of the $Ln(OTf)_3$, $Sc(OTf)_3$ and $Hf(OTf)_3$ as Lewis catalyst permits Friedel-Crafts reactions to occur with a catalytic amount.

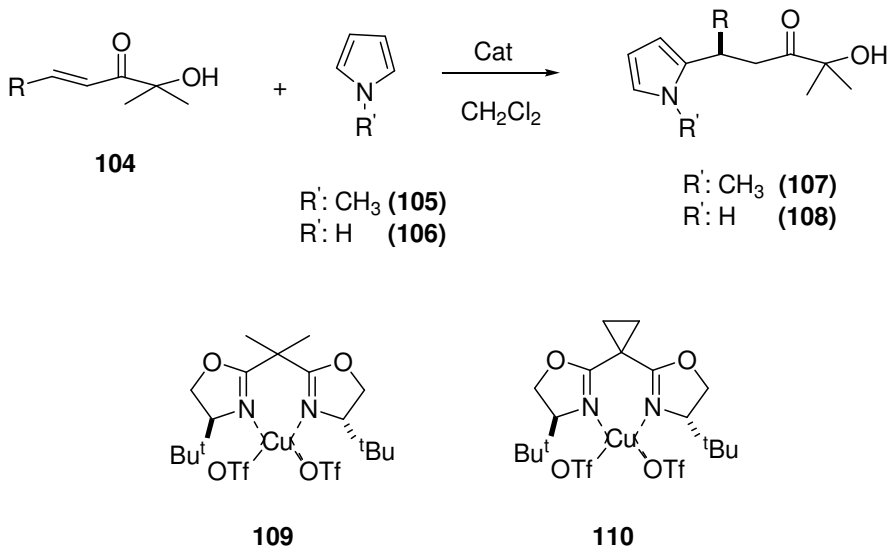
Catalytic amount of $M(OTf)_x$ catalysed Friedel-Crafts reaction was performed in anhydride yielded benzene derivatives with 25-99% yields (Kawada et al., 1994), (Scheme 2.47).



Scheme 2.47. $M(OTf)_x$ catalysed Friedel-Crafts reaction.

Enantioselective Friedel-Crafts alkylation of pyrroles with α'-hydroxy enones under Cu(II)-simple bis(oxazoline) catalysis has been reported by Palamo et al. in 2005. Reaction carried out (Scheme 2.48) with enone **104** and *N*-methyl pyrrole (**105**) or

pyrrole (**106**) in the presence of 10 mol % of chiral bis(oxazoline)-metal complexes **109** and **110**. Friedel-Crafts adducts **107** and **108** were formed by using these catalyst.



Scheme 2.48. Asymmetric catalytic Friedel-Crafts alkylation of pyrrole with Cu(II) bis(oxazoline) catalysis.

3. THE AIM OF THE WORK

Synthesis of pyrrole derivatives is an important goal in organic synthesis because of their magnificent role in the natural products, non-linear optics and supramolecular chemistry. Substituted pyrrole compounds also have biological activity in anticancer, antiviral and immunoreguatory applications.

The pyrrolizines constitute a very large family of natural products having a wide range of biological activities. Therefore, the synthesis of pyrrolizine is an important area of heterocyclic chemistry.

The aim of this work is the synthesis of novel 2-alkylated pyrrole derivatives and study their cyclization reactions. For this purpose, in the first part of the study, novel 2-alkylated pyrrole derivatives were synthesized from *α*-oxo-*β*,*γ*-unsaturated ester and pyrrole *via* Micheal reaction and the effects of the different catalysts, solvents, different substituents and temperature on the reaction were investigated.

In the second part of the reaction, novel pyrrolizine derivatives were synthesized through intramolecular cyclization reaction of synthesized 2-alkylated pyrrole derivatives.

4. EXPERIMENTAL PART

4.1. General Procedures

All chemicals were purchased from Aldrich, Sigma and Merck. Solvents were either reagents or tecnical grade and when necessary were purified by distillation and dried using appropriate desiccants. Organic extracts were dried over anyhdrous Mg_2SO_4 or $CaCl_2$. Solvents were evaporated using rotatory evaporator under reduce pressure. Reactions were monitored by thin layer chromatography plates (Kieselgel 60, F254, E.Merck) and visualized with UV-light or phosphomolybdic acid in methanol or solution of anisaldehyde in methanol and sulphyric acid. Flash column chromatography was employed bu silica gel (0.05-0.63 nm. 230-400 mesh ASTM, Merck) to purify the products.

^{1}H NMR and ^{13}C NMR spectra were performed by Bruker DPX-400, ultra shied, 400 MHz high performance digital FT-NMR spectrometer using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standart. Spin multiplicities are mentioned as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet).

Infrared spectra were performed by 2000 Perkin-Elmer Spectrometer. Melting points were performed by Gallenkamp capillary melting point apparatus. Elementel analysis were performed by LECO CHNS system.

4.2. General Procedure for the Synthesis of (*E*)-2-oxo-4-phenylbut-3-enoic acids and its Phenyl Substituted Derivatives.

Stynthesis of (E)- 2-oxo-4-phenylbut-3-enoic acid and its derivatives have been successfully performed according to the literature (Reimer, 1938; Stecher, 1952). Pyruvic acid (34 mmol, 2.99 g) and benzaldehyde (34 mmol, 3.61 g) was mixed at room temperature and then solution of KOH (50 mmol, 2.8 g) in 25% MeOH was added drop wise. Reaction system was cooled in an ice bath to keep temperature at 5-10 ^{o}C. After the addition of KOH solution, colour changed from light yellow to dark yellow and reaction mixture was stirred for additional 5 hours and kept over

night at 4 °C. Potassium salt of acid washed with MeOH (2x2 ml) and ether (3 ml) respectively. Saturated solution of the potassium salt at 40 °C was acidified with 1N HCl, precipitate filtered and dried.

4.3. General Procedure for the Synthesis of (*E*)-2-Oxo-4-phenylbut-3-enoic acid ester and its Phenyl Substituted Ester Derivatives.

Acid compounds were dissolved in methyl alcohol and HCl gas was passed through the solution for 1 hour. Ester compound was purified using flash column chromotography (EtOAc: Hex 1:3).

(*E*)-Methyl 2-oxo-4-phenylbut-3-enoate (111): Yellow solid. Yield: 55%. Mp: 64-65 °C. R_f: 0.74 (EtOAc:Hex, 1:3). IR(KBr)($\bar{\upsilon}_{max}$/cm^{-1}): 3065, 3016, 2956, 1734, 1681, 1599, 1441, 1258, 1086. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (s, 3H, OC*H*$_3$), 7.37 (d, *J*=16.0, 1H, C*H*), 7.44-7.46 (m, 3H, Ar-*H*), 7.65-7.67 (m, 2H, Ar-*H*), 7.87 (d, *J*=16.4, 1H, C*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.84, 120.66, 129.10, 129.14, 131.61, 134.21, 148.32, 162.50, 181.98.

(*E*)-Methyl 2-oxo-4-*p*-tolylbut-3-enoate (112): Yellow solid. Yield: 55%. Mp: 79-80°C. R_f: 0.53 (EtOAc:hexane, 1:3). IR(KBr)($\bar{\upsilon}_{max}$/cm^{-1}): 3007, 2949, 2848, 1725, 1679, 1594, 1440, 1258, 1085. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2,30 (s, 3H, C*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 7.11 (d, *J*=6.7, 2H, Ar-*H*), 7.17 (d, *J*=16.0, 1H, C*H*), 7.41 (d, *J*=6.0, 2H, Ar-*H*), 7.69 (d, *J*=16.1, 1H, C*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.32, 52.36, 119.38, 128.47, 129.32, 130.88, 141.80, 147.91, 162.30, 181.76.

(*E*)-Methyl 4-(4-methoxyphenyl)-2-oxobut-3-enoate(113): Yellow solid. Yield: 53%. Mp: 106-107°C. R_f: 0.46 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3025, 2957, 2836, 1729, 1682, 1591, 1551, 1501, 1416, 1255, 1161, 1091, 1009. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H, OC*H*$_3$), 3.94 (s, 3H, OC*H*$_3$), 6.93 (d, *J*=8.8, 2H, Ar-*H*), 7.24 (d, *J*=16.0, 1H, C*H*), 7.61 (d, *J*=8.8, 2H, Ar-*H*), 7.83 (d, *J*=16.0, 1H, C*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.75, 55.35, 114.64, 118.30, 127.02, 131.07, 148.20, 162.65, 162.79, 181.84.

(*E*)-Methyl 4-(2-methoxyphenyl)-2-oxobut-3-enoate(114): Yellow solid. Yield: 60%. Mp: 35-36°C. R_f: 0.56 (EtOAc:hexane, 1:3). IR(KBr)($\bar{\upsilon}_{max}$ /cm^{-1}): 2951, 2843, 1734, 1684, 1594, 1452, 1247, 1081, 1025. ^{1}H NMR(400 MHz, $CDCl_3$): δ 3.76 (s, 3H, OC*H*$_3$), 3.82 (s, 3H, OC*H*$_3$), 6.81-6.89 (m, 2H, Ar-*H*), 7.24-7.32 (m, 2H, CH, Ar-*H*), 7.51 (d, *J*=7.6, 1H, Ar-*H*), 8.06 (d, *J*=16.0, 1H, C*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.41, 55.18, 110.15, 111.00, 120.77, 123.72, 129.15, 132.66, 143.33, 158.88, 162.53, 182.39.

(*E*)-Methyl 4-(4-flourophenyl)-2-oxobut-3-enoate (115): Yellow solid. Yield: 65%. Mp: 84-85°C. R_f: 0.58 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$ /cm^{-1}): 3034, 2953, 1728, 1689, 1598, 1507, 1443, 1239, 1068. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H, OC*H*$_3$), 7.04 (d, *J*=8.6, 2H, Ar-*H*), 7.20 (d, *J*=16.1, 1H, C*H*), 7.56-7.59 (m, 2H, Ar-*H*), 7.72 (d, *J*=16.1, 1H, C*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.59, 116.10(d J_{CF}=22.0 Hz), 120.17, 130.24, 130.91 (d, J_{CF}= 8.6 Hz), 146.51, 162. 21, 164.48(d, J_{CF}=252.5 Hz), 181.58.

(*E*)-Methyl 4-(4-chlorophenyl)-2-oxobut-3-enoate (116): Yellow solid. Yield: 60%. Mp: 115-116°C. R_f: 0.54 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3025, 2958, 1727, 1686, 1600, 1485, 1320, 1273, 1083. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (s, 3H, OC*H*$_3$), 7.36 (d, *J*=16.0, 1H, C*H*), 7.43 (d, *J*=8.6, 2H, Ar-*H*), 7.60 (d, *J*=8.4, 2H, Ar-*H*), 7.82 (d, *J*=16.0, 1H, C*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.79, 120.92, 129.43, 130.05, 132.57, 137.72, 146.48, 162. 22, 181.54.

(*E*)-Methyl 4-(4-bromophenyl)-2-oxobut-3-enoate (117): Yellow solid. Yield: 55%. Mp: 121-122°C. R_f: 0.87 (EtOAc:hexane, 1:3). IR(KBr)($\bar{\upsilon}_{max}$/cm^{-1}): 3105, 2646, 1728, 1600, 1481, 1266, 1195, 1081, 1000. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 3H, OC*H*$_3$), 7.37 (d, *J*=16.0, 1H, C*H*), 7.51 (d, *J*=8.4, 2H, Ar-*H*), 7.58 (d, *J*=8.8, 2H, Ar-*H*), 7.79 (d, *J*=16.0, 1H, C*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.91, 121.07, 126.24, 130.31, 132.49, 133.06, 146.68, 162.30, 181.66.

4.4. Synthesis of (*E*)-methyl 4-(4-nitrophenyl)-2-oxobut-3-enoate.

Synthesis of (E)-methyl 4-(4-nitrophenyl)-2-oxobut-3-enoate was performed according to the literature (G.Dujardin et al., 2001). 4-nitrobenzaldehyde(9.92 mmol, 1.5 g) and methylpyruvate (14.88 mmol, 1.52 g) and $Cu(OTf)_2$ (0.992 mmol, 0.316g) was refluxed in dichloromethane for 75 hours at 65 ^{0}C. Reaction was monitored by TLC. After the reaction crude product was extracted with EtOAc and then prufication with flash column chromotograpy (EtOAc:hexane 1:2)

(*E*)-Methyl 4-(4-nitrophenyl)-2-oxobut-3-enoate (118): Yellow solid. Yield: %55. Mp: 183°C. R_f: 0.59 (EtOAc:hexane, 1:1). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3086, 2949, 1728, 1692, 1596, 1516, 1450, 1346, 1263, 1074. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 3H, OC*H*$_3$), 7.02 (d, *J*= 12.8, 1H, C*H*), 7.24 (d, *J*=12.6, 1H, C*H*), 7.79 (d, *J*=8.6, 2H, Ar-*H*), 8.24 (d, J=8.8, 2H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.95, 123.69, 125.49, 129.73, 130.75, 140.34, 144.56, 161.78, 181.80.

4.5. General Procedure for the 1,4 -addition Reaction of Pyrrole

(*E*)-Methyl 2-oxo-4-phenylbut-3-enoate (**111**) (1 mmol, 0.190 g) and $Cu(OTf)_2$ (0.1 mmol, 0.032 g) in the 5 mL of THF was stirred for 30 min at room temperature. Pyrrole (2 mmol, 0.134 g) was added drop wise into the reaction mixture. Colour of mixture turned over to black and reaction was monitored by TLC. After the consumption of reactants, 2 mL of water was added to the reaction media. Product was extracted with ether (2 x 10 mL) and organic layer was dried with anhydrous $CaCl_2$. Solvent was evaporated with rotatory evaporator. Purification of crude product was performed by flash column chromatography.

Methyl 2-oxo-4-phenyl-4-(1*H*-pyrrole-2-yl)butanoate (119): Light brown solid. Yield: 83%. Mp: 76-77°C. R_f: 0.44 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3426, 2978, 2865, 1636, 1360, 1125. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.45 (dd, *J*=18.4, *J*=6.8, 1H, C(*H*)H), 3.67 (dd, *J*=18.4, *J*=8.0, 1H, C(*H*)H), 3.84 (s, 3H, OC*H*$_3$), 4.62 (t, *J*=7.2, 1H, C*H*), 5.94 (bs, 1H, C(3)*H*), 6.08 (dd, *J*=6.0, *J*=2.8, 1H, C(4)*H*), 6.61(bs, 1H, C(5)*H*), 7.24-7.34 (m, 5H, Ar-*H*), 7.95 (bs, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.06, 45.56, 52.81, 105.78, 108.33, 117.41, 127.12, 127.95,

128.80, 133.02, 142.15, 161.10, 192.21. Anal. Calcd. for $C_{15}H_{15}NO_3$: %C 70.02 , %H 5.88, %N 5.44, Found: %C 69.87, %H 5.83, %N 5.43.

Methyl 2-oxo-4-(1*H*-pyrrol-2-yl)-4-*p*-tolylbutanoate (120): Orange viscous oil. Yield: 65%. R_f: 0.32 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3421, 3098, 3022, 2954, 2923, 1730, 1563, 1513, 1438, 1272, 1076, 1041. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H, C*H*$_3$), 3.44 (dd, *J*=18.0, *J*=6.8, 1H, C(*H*)H), 3.65 (dd, *J*=18.0, *J*=7.6, 1H, C(*H*)H), 3.84 (s, 3H, OC*H*$_3$), 4.58 (t, *J*=7.2, 1H, C*H*), 5.94 (bs, 1H, C(3)*H*), 6.08 (dd, *J*=5.6, *J*=2.8, 1H, C(4)*H*), 6.60 (bs, 1H, C(5)*H*), 7.11-7.21 (m, 4H, Ar-*H*), 7.95 (bs, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.07, 38.65, 45.56, 52.76, 105.58, 108.25, 117.27, 127.82, 129.43, 133.24, 136.49, 139.10, 161.10, 192.25. Anal. Calcd. for $C_{16}H_{17}NO_3$: %C 70.83 , %H 6.32, %N 5.16, Found: %C 70.67, %H 6.18, %N 4.77.

Methyl 4-(4-methoxyphenyl)-2-oxo-4-(1*H*-pyrrol-2-yl)butanoate (121): Light brown viscous oil. Yield: 65%. R_f: 0.43 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3442, 2977, 2863, 1636, 1505, 1451, 1381, 1250, 1123, 1012. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.43 (dd, *J*=18.0, *J*=7.2, 1H, C(*H*)H), 3.62 (dd, *J*=18.0, *J*=7.6, 1H, C(*H*)H), 3.80 (s, 3H, OC*H*$_3$), 3.82 (s, 3H, OC*H*$_3$), 4.56 (t, J=7.3, 1H, C*H*), 5.93 (bs, 1H, C(3)*H*), 6.08 (bs, 1H, C(4)*H*), 6.60 (bs, 1H, C(5)*H*), 6.82-6.87 (m, 2H, Ar-*H*), 7.14-7.16 (m, 2H, Ar-*H*), 7.96 (bs, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.28, 45.68, 52.77, 55.08, 105.53, 108.26, 114.05, 117.28, 128.60, 133.41, 134.13, 158.62, 161.12, 192.30. Anal. Calcd. for $C_{16}H_{17}NO_4$: %C 66.89 , %H 5.96, %N 4.88, Found: %C 66.59 , %H 5.83, %N 4.71.

Methyl-4-(2-methoxyphenyl)-2-oxo-4-(1*H*-pyrrol-2-yl)butanoate (122): White solid. Yield: 45%. Mp:119-120°C. R_f: 0.38 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3426, 2980, 2865, 1634, 1382, 1127, 1046. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38 (dd, *J*=17.2, *J*=6.4, 1H, C(*H*)H), 3.73 (dd, *J*=17.2, *J*=8.4, 1H, C(*H*)H), 3.85 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 5.00 (t, *J*=7.2, 1H, C*H*), 5.97 (bs, 1H, C(3)*H*), 6.09 (bs, 1H, C(4)*H*), 6.64 (bs, 1H, C(5)*H*), 6.89-6.93 (m, 2H, Ar-*H*), 7.09 (d, *J*=7.6, 1H, Ar-*H*), 7.20-7.24 (m, 1H, Ar-*H*), 8.25 (bs, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.23, 44.12, 52.83, 55.33, 105.40, 108.08, 111.03, 117.00, 121.16, 128.13,

128.58, 130.52, 133.05, 156.44, 161.25, 192.41. Anal. Calcd. for $C_{16}H_{17}NO_4$: %C 66.89 , %H 5.96, %N 4.88, Found: %C 66.61, %H 5.93, %N 4.52.

Methyl 4-(4-flourophenyl)-2-oxo-4-(1*H*-pyrrol-2-yl)butanoate (123): Light yellow viscous oil. Yield: 58%. R_f: 0.37 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3452, 2976, 2862, 1636, 1504, 1446, 1379, 1121, 991. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.43 (dd, *J*=18.0, *J*=6.8, 1H, C(*H*)H), 3.65 (dd, *J*=18.0, *J*=7.6, 1H, C(*H*)H), 3.87 (s, 3H, OC*H*$_3$), 4.60 (t, *J*=7.2, 1H, C*H*), 5.92 (bs, 1H, C(3)*H*), 6.08 (bs, 1H, C(4)*H*), 6.63 (bs, 1H, C(5)*H*), 6.98-7.03 (m, 2H, Ar-*H*), 7.20-7.24 (m, 2H, Ar-*H*), 7.95 (bs, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.34, 45.66, 52.89, 105.88, 108.45, 115.67(d, J_{CF}=21.3 Hz), 117.59, 129.49(d, J_{CF}=7.9 Hz), 132.84, 137.88, 161.07, 161.90(d, J_{CF}=245.0 Hz), 192.07. Anal. Calcd. for $C_{15}H_{14}FNO_3$: %C 65.45 , %H 5.13, %N 5.09, Found: %C 65.22 , %H 5.18, % N5.12.

Methyl 4-(4-chlorolphenyl)-2-oxo-4-(1*H*-pyrrol-2-yl)butanoate (124): Light brown viscous oil. Yield: 49%. R_f: 0.35 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3403, 2965, 2929, 2862, 1729, 1644, 1487, 1443, 1257, 1091. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.42 (dd, *J*=18.4, *J*=6.8, 1H, C(*H*)H), 3.64 (dd, *J*=18.0, *J*=7.6, 1H, C(*H*)H), 3.84 (s, 3H, OC*H*$_3$), 4.58 (t, *J*=7.2, 1H, C*H*), 5.94 (bs, 1H, C(3)*H*), 6.09 (bs, 1H, C(4)*H*), 6.60 (bs, 1H, C(5)*H*), 7.18 (d, *J*=8.4, 2H, Ar-*H*), 7.27-7.30 (m, 2H, Ar-*H*), 8.03 (bs, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.38, 45.39, 52.88, 105.87, 108.38, 117.64, 128.74, 128.88, 132.45, 132.93, 140.71, 160.95, 191.94. Anal. Calcd. for $C_{15}H_{14}ClNO_3$: %C 61.76 , %H 4.84, %N 4.80, Found: %C 61.93 , %H 4.83, %N 4.65.

Methyl 4-(4-bromophenyl)-2-oxo-4-(1*H*-pyrrol-2-yl)butanoate (125): Light brown solid. Yield: 63%. Mp: 126°C. R_f: 0.46 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$ /cm^{-1}): 3424, 2976, 2863, 1636, 1379, 1261, 1122. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.43 (dd, *J*=18.0, *J*=6.8, 1H, C(*H*)H), 3.65 (dd, *J*=18.0, *J*=7.6, 1H, C(*H*)H), 3.86 (s, 3H, OC*H*$_3$), 4.58 (t, *J*=7.2, 1H, C*H*), 5.93 (bs, 1H, C(3)*H*), 6.08 (dd, *J*=6.0, *J*=2.8, 1H, C(4)*H*), 6.63 (bs, 1H, C(5)*H*), 7.13 (d, *J*=8.4, 2H, Ar-*H*), 7.44 (d, *J*=8.4, 2H, Ar-*H*), 7.94 (bs, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.53, 45.40, 52.94, 106.03, 108.52, 117.70, 121.14, 129.70, 131.95, 132.41, 141.19, 161.02, 191.94.

Anal. Calcd. for $C_{15}H_{14}BrNO_3$: %C 53.59 , %H 4.20, %N 4.17, Found.: %C 54.08, %H 3.99, %N4.06.

Methyl 4-(4-nitrophenyl)-2-oxo-4-(1H-pyrrol-2-yl)butanoate (126): Brown viscous oil. Yield: 70%. R_f: 0.33 (EtOAc:hexane, 1:2). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3401, 2956, 2866, 1733, 1605, 1519, 1438, 1348, 1277, 1076. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.47 (dd, *J*= 18.6, *J*=7.1, 1H, C(*H*)H), 3.69 (dd, *J*=18.6, *J*=7.3, 1H, C(*H*)H), 3.82 (s, 3H, OCH_3), 4.70 (t, *J*=7.2, 1H, C*H*), 5.95 (bs, 1H, C(3)*H*), 6.06 (d, *J*=3.1, 1H, C(4)*H*), 6.62 (bs, 1H, C(5)*H*), 7.36 (d, *J*= 8.7, 2H, Ar-*H*), 8.03 (d, *J*=8.7, 2H, Ar-*H*), 8.46 (bs, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.57, 44.86, 52.90, 105.93, 108.34, 118.04, 123.66, 128.63, 131.24, 146.62, 149.95, 160.67, 191.48. Anal. Calcd. for $C_{15}H_{14}N_2O_5$: %C 59.60 , %H 4.67, %N 9.27, Found: %C 59.27 , %H 4.97, %N 9.12.

4.6. General Procedure for the Cyclisation Reactions

Synthesized novel pyrrole derivatives were refluxed in CCl_4 for 6 hours at 75 ^{o}C and the reaction was monitored by TLC. Diastreoisomers were isolated by flash column chromotograpy (EtOAc:Hex, 1:4).

Methyl 3-hydroxy-1-phenyl-2,3-dihydro-1 *H*-pyrrolizine-3-carboxylate (127):

1st diastreoisomer (127a): Light brown solid. Mp: 64°C. R_f: 0.33 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3455, 3030, 2955, 2871, 1740, 1659, 1495, 1453, 1270, 1146, 1068. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.64 (dd, *J*=13.6, *J*=7.7, 1H, C(*H*)H), 3.39 (dd, *J*=13.6, *J*=8.4, 1H, C(*H*)H), 3.88 (s, 3H, OCH_3), 4.48 (t, *J*=8.0, 1H, C*H*), 4.64 (bs, 1H, O*H*), 5,75 (bs, 1H, Py-*H*), 6.31 (bs, 1H, Py-*H*), 6.62 (bs, 1H, Py-*H*), 7.24-7.37 (m, 5H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.08, 50.14, 53.73, 87.18, 101.20, 110.70, 115.00, 126.93, 127.65, 128.65, 139.16, 142.72, 172.02. Anal. Calcd. for $C_{15}H_{15}NO_3$: %C 70.02 , %H 5.88, %N 5.44, Found: %C 69.72, %H 5.86, % N 5.44.

2nd diastreoisomer (127b): Light brown solid. Mp: 96-97°C. R_f: 0.27 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3460, 3100, 3024, 2955, 2911, 1733, 1493, 1275, 1202, 1115, 1069, 1041. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.00-3.08 (m, 2H, C*H*$_2$), 3.89 (s, 3H, OC*H*$_3$), 4.32 (bs, 1H, O*H*), 4.65 (t, *J*=8.1, 1H, C*H*), 5,78 (bs, 1H, Py-*H*), 6.31 (bs, 1H, Py-*H*), 6.59 (bs, 1H, Py-*H*), 7.24-7.34 (m, 5H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.60, 50.82, 53.68, 86.93, 101.58, 110.99, 115.04, 126.94, 127.71, 128.62, 139.81, 142.46, 171.39.

Methyl 3-hydroxy-1-*p*-tolyl-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (128):

1st diastreoisomer (128a): Light brown solid. Mp: 111-111.5°C. R_f: 0.49 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3446, 3004, 2953, 2923, 1738, 1513, 1454, 1268, 1180, 1146, 1103, 1069. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H, C*H*$_3$), 2.59 (dd, *J*=13.6, *J*=8.0, 1H, C(*H*)H), 3.33 (dd, *J*=13.6, *J*=8.4, 1H, C(*H*)H), 3.88 (s, 3H, OC*H*$_3$), 4.42 (t, *J*=8.0, 1H, C*H*), 4.49 (bs, 1H, O*H*), 5.71 (bs, 1H, Py-*H*), 6.29 (bs, 1H, Py-*H*), 6.58 (bs, 1H, Py-*H*), 7.12 (d, *J*=8.0, 2H, Ar-*H*), 7.23 (d, *J*=8.0, 2H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.10, 42.68, 50.16, 53.70, 87.04, 101.03, 110.49, 114.90, 127.49, 129.27, 136.22, 139.34, 139.64, 172.07. Anal. Calcd. for $C_{16}H_{17}NO_3$: %C 70.83 , %H 6.32, %N 5.16, Found: %C 70.48, %H6.03, %N 4.76.

2nd diastreoisomer (128b): Light brown viscous oil. R_f: 0.41 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3455, 2977, 2917, 2869, 1740, 1658, 1513, 1455, 1262, 1206, 1098, 1073. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H, C*H*$_3$), 2.97-3.03 (m, 2H, C*H*$_2$), 3.88 (s, 3H, OC*H*$_3$), 4.21 (bs, 1H, O*H*), 4.60 (t, *J*=8.1, 1H, C*H*), 5.75 (bs, 1H, Py-*H*), 6.29 (bs, 1H, Py-*H*), 6.56 (bs, 1H, Py-*H*), 7.13 (d, *J*=7.9, 2H, Ar-*H*), 7.22 (d, *J*=8.0, 2H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.10, 41.16, 50.81, 53.62, 86.82, 101.35, 110.77, 114.92, 127.51, 129.21, 136.21, 139.33, 140.02, 171.37.

Methyl-3-hydroxy-1-(4-methoxyphenyl)-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (129):

1st diastreoisomer (129a): Light brown solid. Mp: 116.5-117.5°C. R_f: 0.33 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3479, 3008, 2954, 2841, 1738, 1615, 1513, 1455, 1251, 1190, 1109, 1035. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (dd, *J*=13.6, *J*=7,6, 1H, C(*H*)H), 3.34 (dd, *J*=13.6, *J*=8.4, 1H, C(*H*)H), 3.82 (s, 3H, OC*H*$_3$), 3.88 (s, 3H, OC*H*$_3$), 4.42 (t, *J*=8.0, 1H, C*H*), 4.52 (bs, 1H, O*H*), 5.71 (bs, 1H, Py-*H*), 6.29 (bs, 1H, Py-*H*), 6.59 (bs, 1H, Py-*H*), 6.85 (d, *J*=8.6, 2H, Ar-*H*), 7.26 (d, *J*=8.6, 2H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.39, 50.35, 53.57, 55.11, 87.14, 101.04, 110.60, 114.08, 114.96, 128.62, 134.77, 139.58, 158.66, 172.10. Anal. Calcd. for $C_{16}H_{17}NO_4$: %C 66.89 , %H 5.96, %N 4.88, Found: %C 67.12 , %H 6.39, %N 4.56.

2nd diastreoisomer (129b): Light brown viscous. R_f: 0.28 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3441, 2977, 2866, 1743, 1613, 1512, 1447, 1383, 1252, 1179, 1118, 1036, 939. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.98-3.01 (m, 2H, C*H*$_2$), 3.81 (s, 3H, OC*H*$_3$), 3.84 (s, 3H, OC*H*$_3$), 4.23 (bs, 1H, O*H*), 4.59 (t, *J*=8.4, 1H, C*H*), 5.74 (bs, 1H, Py-*H*), 6.29 (bs, 1H, Py-H), 6.56 (bs, 1H, Py-*H*), 6.85 (d, *J*=8.4, 2H, Ar-*H*), 7.23-7.28 (m, 2H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.90, 51.02, 53.73, 55.16, 86.92, 101.41, 110.89, 114.06, 115.00, 128.67, 134.44, 140.27,158.70, 171.47.

Methyl-3-hydroxy-1-(2-methoxyphenyl)-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (130):

1st diastreoisomer (130a): Light brown solid. Mp: 111-111.5°C. R_f: 0.49 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}**):** 3470, 2954, 2872, 1740, 1625, 1492, 1459, 1385, 1289, 1245, 1146, 1108, 1049. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.21 (dd, *J*=12.8, *J*=9.1, 1H, C(*H*)H), 3.48 (dd, *J*=13.8, *J*=8.7, 1H, C(*H*)H), 3.89 (bs, 6H, OC*H*$_3$), 4.45 (s, 1H, O*H*), 4.77 (t, *J*=7.7, 1H, C*H*), 5.78 (bs, 1H, Py-*H*), 6.32 (bs, 1H, Py-*H*), 6.61 (bs, 1H, Py-*H*), 6.87-6.91 (m, 2H, Ar-*H*), 7.22-7.36 (m, 1H, Ar-*H*), 7.34 (d, *J*=7.5, 1H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.73, 48.63, 53.65,

55.35, 87.26, 101.16, 110.32, 110.73, 114.81, 120.89, 127.84, 128.01, 131.18, 138.50, 156.92, 172.05. Anal. Calcd. for $C_{16}H_{17}NO_4$: %C 66.89 , %H 5.96, %N 4.88, Found: %C 66.45, %H 5.72, %N 4.94.

2nd diastreoisomer (130b): Light brown viscous oil. R_f: 0.41 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3442, 2955, 2869, 1739, 1599, 1492, 1459, 1439, 1245, 1107, 1050, 1027. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.84 (dd, *J*=13.5, *J*=7.2, 1H, C(*H*)H), 3.17 (dd, *J*=13.6, *J*=8.3, 1H, C(*H*)H), 3.80 (s, 3H, OC*H*$_3$), 3.90 (s, 3H, OC*H*$_3$), 4.21 (bs, 1H, O*H*), 4.95 (t, *J*=7.7, 1H, C*H*), 5.82 (bs, 1H, Py-*H*), 6.33 (bs, 1H, Py-*H*), 6.60 (bs, 1H, Py-*H*), 6.87-6.91 (m, 2H, Ar-*H*), 7.19-7.24 (m, 1H, Ar-*H*), 7.32 (d, *J*=7.6, 1H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.73, 48.63, 53.65, 55.35, 87.26, 101.70, 110.07, 110.84, 114.96, 120.58, 127.77, 127.84, 130.83, 138.88, 157.35, 171.75.

Methyl-1-(4-flourophenyl)-3-hydroxy-2,3-dihydro-1*H*-pyrrolizine-3 carboxylate (131):

1st diastreoisomer (131a): Light brown solid. Mp: 121-122°C. R_f: 0.45 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3447, 2978, 2871, 2361 1741, 1604, 1510, 1456, 1270, 1223, 1148, 1100, 1067, 1013. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.57 (dd, *J*=13.6, *J*=6.2, 1H, C(*H*)H), 3.39 (dd, *J*=13.6, *J*=8.4, 1H, C(*H*)H), 3.88 (s, 3H, OC*H*$_3$), 4.45 (t, *J*=7.9, 1H, C*H*), 4.60 (bs, 1H, O*H*), 5.72(bs, 1H, Py-*H*), 6.30 (bs, 1H, Py-*H*), 6.60 (bs, 1H, Py-*H*), 6.99-7.04 (m, 2H, Ar-*H*), 7.30-7.34 (m, 2H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.39, 50.20, 53.85, 87.11, 101.23, 110.80, 115.14, 115.52(d, J_{CF}=21.3 Hz), 129.15(d, J_{CF}=7.9 Hz), 138.51, 139.06, 161.86(d, J_{CF}=244.1 Hz), 171.97. Anal. Calcd. for $C_{15}H_{14}FNO_3$: %C 65.45 , %H 5.13, %N 5.09, Found: %C 65.10 , %H 5.23, % N 5.29.

2nd diastreoisomer (131b): Light brown solid. Mp: 78-79°C. R_f: 0.38 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):3400, 2977, 2871, 1743, 1663, 1510, 1263, 1223, 1121, 1074, 1014. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.98 (dd, *J*=13.4, *J*=8.0, 1H, C(*H*)H), 3.05 (dd, *J*=13.4, *J*=8.0, 1H, C(*H*)H), 3.88 (s, 3H, OC*H*$_3$), 4.29 (bs, 1H, O*H*), 4.62 (t, *J*=8.0, 1H, C*H*), 5.75 (bs, 1H, Py-*H*), 6.30 (bs, 1H, Py-*H*),

6.57 (bs, 1H, Py-*H*), 6.99-7.04 (m, 2H, Ar-*H*), 7.28-7.32 (m, 2H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.80, 50.81, 53.67, 86.78, 101.47, 111.01, 115.27, 115.38(d, J_{CF}=21.1 Hz), 129.06(d, J_{CF}=7.7 Hz), 138.07, 139.54, 161.85(d, J_{CF}=244.4 Hz), 171.18.

Methyl-1-(4-chlorophenyl)-3-hydroxy-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (132):

1st diastreoisomer (132a): Light brown viscous oil. R_f: 0.39 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3459, 3100, 2977, 2955, 2873, 1741, 1659, 1491, 1456, 1410, 1266, 1203, 1148, 1092, 1014. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.57 (dd, *J*=13.7, *J*=7,4, 1H, C(*H*)H), 3.39 (dd, *J*=13.6, *J*=8.4, 1H, C(*H*)H), 3.87 (s, 3H, OCH_3), 4.45 (t, *J*=7.9, 1H, C*H*), 4.71 (bs, 1H, O*H*), 5.73 (bs, 1H, Py-*H*), 6.31 (bs, 1H, Py-*H*), 6.62 (bs, 1H, Py-*H*), 7.27-7.30 (m, 4H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.42, 50.70, 53.78, 87.10, 101.23, 110.88, 115.08, 128.42, 128.98, 132.77, 138.67, 141.26, 171.80. Anal. Calcd. for $C_{15}H_{14}ClNO_3$: %C 61.76 , %H 4.84, %N 4.80, Found: %C 61.34 , %H 4.75, %N 4.72.

2nd diastreoisomer (132b): Light brown viscous oil. R_f: 0.34 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3443, 2978, 2872, 1743, 1657, 1491, 1455, 1409, 1263, 1208, 1121, 1092, 1014. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.97 (dd, *J*=13.4, *J*=8.0, 1H, C(*H*)H), 3.05 (dd, *J*=13.4, *J*=8.1, 1H, C(*H*)H), 3.88 (s, 3H, OCH_3), 4.29 (bs, 1H, O*H*), 4.61 (t, *J*=8.0, 1H, C*H*), 5.75 (bs, 1H, Py-*H*), 6.30 (bs, 1H, Py-*H*), 6.57 (bs, 1H, Py-*H*), 7.26-7.30 (m, 4H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.03, 50.77, 53.82, 86.89, 101.67, 111.19, 115.20, 128.83, 129.18, 132.89, 139.29, 141.03, 171.26.

Methyl-1-(4-bromophenyl)-3-hydroxy-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (133):

1st diastreoisomer (133a): Light brown solid. Mp: 80-81°C. R_f: 0.49 (EtOAc:hexane, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3474, 2949, 1721, 1458, 1284, 1200, 1147, 1098, 1054. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (dd, *J*=13.6, *J*=8.4, 1H,

C(*H*)H), 3.41 (dd, *J*=13.6, *J*=8.4, 1H, C(*H*)H), 3.88 (s, 3H, OC*H*$_3$), 4.46 (t, *J*=8.0, 1H, C*H*), 4.57 (bs, 1H, O*H*), 5.76 (bs, 1H, Py-*H*), 6.35 (bs, 1H, Py-*H*), 6.65 (bs, 1H, Py-*H*), 7.25 (d, *J*=8.8, 2H, Ar-*H*), 7.46 (d, *J*=8.4, 2H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.46, 49.91, 53.90, 87.03, 101.21, 110.85, 115.05, 120.83, 129.33, 131.74, 138.63, 141.74, 171.86. Anal. Calcd. for $C_{15}H_{14}BrNO_3$: %C 53.59 , %H 4.20, %N 4.17, Found: %C 53.32, %H 4.07, %N 4.15.

2nd diastreoisomer (133b): Light brown viscous oil. R_f: 0.44 (EtOAc:hekzan, 1:3). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3497, 2949, 1738, 1476, 1265, 1085, 1023. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.99 (dd, *J*=13.6, *J*=8.0, 1H, C(*H*)H), 3.07 (dd, *J*=13.6, *J*=8.0, 1H, C(*H*)H), 3.87 (s, 3H, OC*H*$_3$), 4.39 (bs, 1H, O*H*), 4.62 (t, *J*=8.0, 1H, C*H*), 5.79 (bs, 1H, Py-H), 6.35 (bs, 1H, Py-*H*), 6.64 (bs, 1H, Py-*H*), 7.22 (d, *J*=8.4, 2H, Ar-*H*), 7.47 (d, *J*=8.4, 2H, Ar-*H*). ^{13}C NMR(100 MHz, $CDCl_3$): δ 40.97, 50.63, 53.80, 86.84, 101.53, 111.18, 115.03, 120.78, 129.36, 131.74, 139.19, 141.45, 171.17.

Methyl-1-(4-nitrophenyl)-3-hydroxy-2,3-dihydro-1H-pyrrolizine-3-carboxylate(134)

1st diastreoisomer (134a): Light brown solid. Mp:111.5-112.5°C. R_f: 0.36 (EtOAc:hexane, 1:2). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3448, 2978, 2869, 1736, 1648, 1518, 1456, 1348, 1267, 1109, 1072, 1014. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (dd, *J*=14.0, *J*=7.2, 1H, C(*H*)H,), 3.47 (dd, *J*=13.6, *J*=8.4, 1H, C(H)H), 3.90 (s, 3H, OCH_3), 4.57 (t, *J*=7.6, 1H, CH), 4.66 (bs, 1H, OH), 5.74 (bs, 1H, Py-H), 6.32 (t, *J*=2.8, 1H, Py-H), 6.63 (bs, 1H, Py-H), 7.52 (d, *J*=8.7, 2H, Ar-H), 8.19 (d, *J*=9.1, 2H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.74, 49.60, 54.01, 87.11, 101.65, 111.33, 115.41, 124.00, 128.53, 137.71, 147.20, 150.38, 171.55. Anal. Calcd. for $C_{15}H_{14}N_2O_5$: %C 59.60 , %H 4.67, %N 9.27, Found: %C 59.14, %H 4.81, %N 8.90.

2nd diastreoisomer (134b): Light brown solid. R_f: 0.31(EtOAc:hexane, 1:2). IR(KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3394, 2900, 1743, 1637, 1518, 1473, 1348, 1263, 1121. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.02 (dd, *J*=13.6, *J*=7.6, 1H, C(*H*)H), 3.13 (dd, *J*=13.6,*J*=8.4, 1H, C(*H*)H), 3.90 (s, 3H, OCH_3), 4.36 (bs, 1H, OH), 5.78 (bs, 1H,

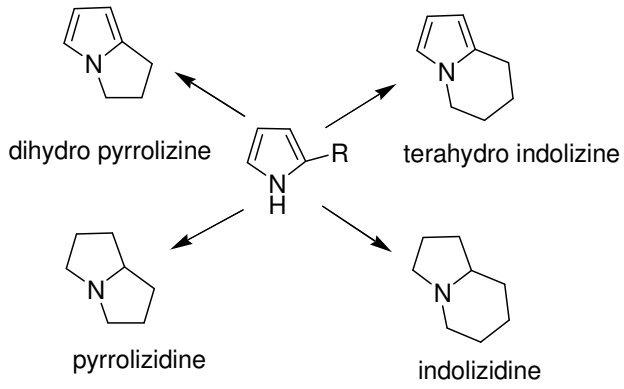
Py-H), 6.33 (bs, 1H, Py-H), 6.61 (bs, 1H, Py-H), 7.51 (d, *J*=8,7, 2H, Ar-H), 8.21(d, *J*=8,7, 2H, Ar-H). ^{13}C NMR(100 MHz, $CDCl_3$): δ 41.37, 51.41, 53.95, 86.88, 101.99, 111.59, 115.46, 123.96, 128.56, 138.15, 147.28, 150.13, 170.96.

5. EXPERIMENTAL RESULTS AND DISCUSSION

5.1. Pyrrole Derivatives as a Precursors of the Biological Active Compounds

Simple nitrogen-containing heterocyles receive a considerable attention in the literature, as a consequence of their exciting biological properties and their role as pharmacophores of historical importance (Yavari et al., 2005). Pyrrole and its derivatives are ubiquitous among naturally occurring organic compounds. They are commonly found as structural motifs in bio-active molecules such as porphyrins, alkaloids and co-enzymes (Rao and Jothilingam, 2001). Therefore, many synthetic methods for the preparation of pyrrole derivatives have been reported in the literature (Yadav et al., 2004).

Highly substituted pyrrole derivatives show remarkable bioactivity. Especially 2-substituted pyrroles also have been used as a synthon for the synthesis of natural products and alkaloids containing pyrrolizine, pyrrolidizine, indolizidine and indolizine structures (Scheme 5.1)



Scheme 5.1. Structure of nitrogen containing heterocyles.

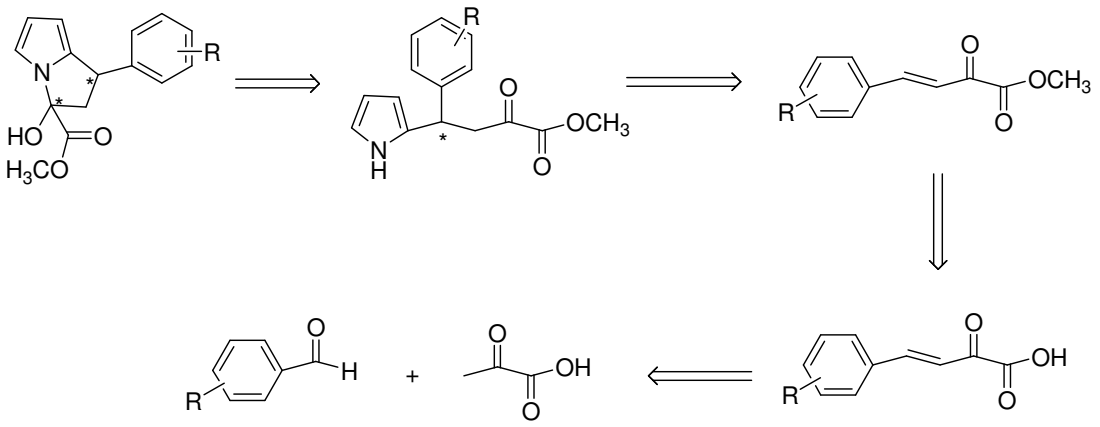
Nitrogen including heterocyles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity (Yavari and Adib, 2001). There has been continuously concern for the synthesis of pyrrolizine derivatives. Access to structural analogues of pyrrolizines and classes of pyrrolizine compounds by methods allowing the synthesis of

diversely substituted derivatives is an important target for research in medicinal chemistry .

Because of the above mentioned importance of the pyrrole and pyrrolizine derivatives it was aimed to synthesize new 2-substituted pyrrole and pyrrolizine derivatives in the study. Synthesis of new pyrrolizine derivatives consist of three steps,

- Synthesis of β,γ-unsaturated α-keto ester derivatives,
- 1,4-addition reaction of pyrrole to β,γ-unsaturated α-keto ester,
- Cyclisation reaction.

Retrosynthetic method has been given in scheme 5.2.



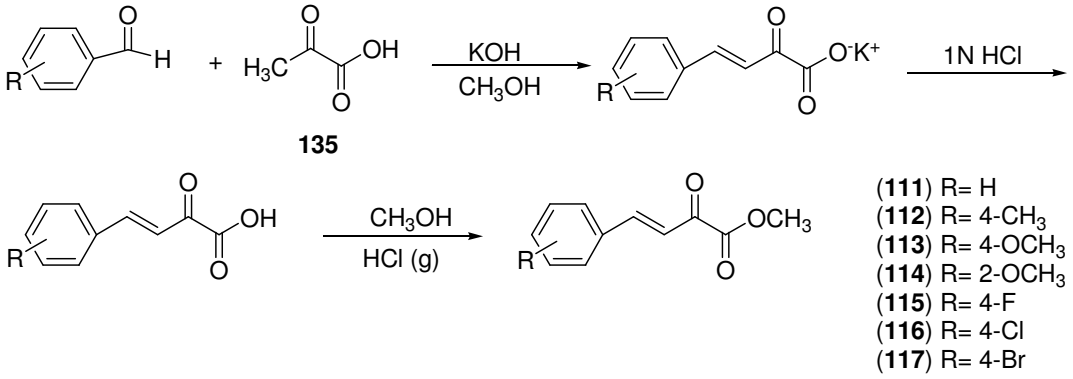
Scheme 5.2. Retrosynthetic pathway for the synthesis of pyrrolizines.

5.2. Synthesis of the β,γ-unsaturated α-keto Ester Derivatives

β,γ-unsaturated α-keto esters are valuable starting materials which provide carbon units for the construction of nitrogen including heterocycles (Temelli, 2002). There has been considerable interst in α-oxo-β,γ-unsaturated esters as intermediates for

the syntheses of substituted dihydropyranes, dihydrothiazines and lactones (Sugimura and Youshida, 1992, Jorgensen et al., 2000,).

At the first step of this study, compounds **111-117** were synthesized as β,γ-unsaturated α-keto ester derivatives (Scheme 5.3). Firstly, condensation reaction of benzaldehyde or substituted benzaldehydes with pyruvic acid (**135**) were performed in alkali solution. Synthesized acid compounds were used without purification in the esterification reactions. After the purification of ester compounds **111-117**, their structures were determined by ^{1}H NMR and ^{13}C NMR and IR tecniques.



Scheme 5.3. Synthesis of *(E)*-Methyl-2-oxo-4-phenylbut-3-enoate derivatives.

Characterization of *(E)*-Methyl-2-oxo-4-phenylbut-3-enoate derivatives were carried out by ^{1}H NMR, ^{13}C NMR techniques and their physical properties were compared with the published data in the litrature. Therefore their recorded NMR data are summarized below without giving the figures.

(E)-Methyl-2-oxo-4-phenylbut-3-enoate (**111**) was obtained in 55% yield as a yellow solid. The signal at 3.96 ppm belongs to methoxy protons. Doublets at 7.37 ppm and 7.87 ppm shows the alkene protons. Multiplets at 7.44-7.46 ppm and 7.65-7.67 belong to phenyl ring protons. The ^{13}C NMR is also in agreement with the structure. The signal at 52.84 belong to methoxy carbon. The signals at 120.66 and 148.32 belong to alkene carbons. The signals of carbonyl carbons appear at

162.50 and 181.98 ppm. Structure is in agreement with the known structure in the literarure (Jorgensen et al., 2000).

(*E*)-Methyl 2-oxo-4-*p*-tolylbut-3-enoate (**112**) was obtained in 55% yield as a yellow solid. Its melting point was determined as 79-80°C. The singlets at 2.30 and 3.83 ppm belong to methyl and methoxy protons, respectively. Doublet at 7.11 ppm is for two phenyl hydrogens. Doublet at 7.17 belongs to alkene proton. For two phenyl hydrogens, a doublet appears at 7.41 ppm. Doublet at 7.69 ppm belong to alkene proton. In the ^{13}C NMR specturm of the compound **112,** methyl and methoxy carbons appear at 21.32 and 52.36 ppm respectively. The signals at 119.38 and 147.91 ppm belong to alkene carbons. The signals of carbonyl carbons appear at 162.30 and 181.76 ppm. Physical properties are in agreement with the known structure in the literarure (Stecher and Ryder, 1952).

(*E*)-Methyl 4-(4-methoxyphenyl)-2-oxobut-3-enoate (**113**) obtained in 53% yield as a yellow solid and its melting point was determined as 106-107 ^{0}C. In the ^{1}H NMR spectrum of the **113**, the singlets at 3.88 and 3.94 ppm belong to the protons of methoxy groups. Doublets at 6.93 and 7.61 ppm belong to aromatic ring hydrogens. Doublets at 7.24 and 7.83 ppm belong to CH protons. In the ^{13}C NMR specturm of the compound **113**, the signal at 52.75 and 55.35 ppm belong to two methoxy carbons. The signals of carbonyl carbons appear at 162.79 and 181.84 ppm. Physical properties are in agreement with the known structure in the literarure (Stecher and Ryder, 1952).

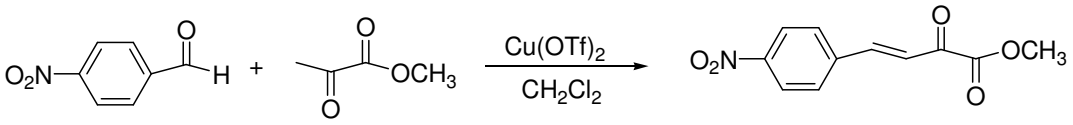
(*E*)-Methyl 4-(2-methoxyphenyl)-2-oxobut-3-enoate (**114**) obtained in 60% yield as yellow solid and its melting point was determined as 35-36 $^{\circ}C$. In the ^{1}H NMR spectrum of the **114**, the singlets at 3.76 and 3.82 ppm belong to the protons of methoxy groups. Phenyl protons appear at 6.81-6.89 and 7.24-7.32 ppm as multiplet. Doublets at 7.51 and 8.06 ppm belong to the protons of –CH=CH- group. In the ^{13}C NMR specturm of the compound **113**, the signals at 52.41 and 55.18 ppm belong to methoxy carbons. The signals at 162.53 and 182.39 ppm belong to carbonyl carbons. The structure is in agreement with known structure of **113** in the literature (Keum et al, 2005).

(*E*)-Methyl 4-(4-flourophenyl)-2-oxobut-3-enoate (**115**) obtained in 65% yield as yellow solid. Its melting point was determined as 84-85 °C. In ^{1}H NMR spectrum of **115**, the singlet at 3.86 ppm belongs to the protons of methoxy groups. Doublet at 7.04 and multiplet at 7.56-7.59 ppm belong to phenyl hydrogens. Doubles at 7.20 and 7.72 ppm show the alkene protons. In the ^{13}C NMR spectrum of the **115**, methoxy carbon appears at 52.59 ppm. The signals of CH carbons appear at 120.17 and 146.51 ppm. Signals at 162. 21 and 181.58 ppm belong to carbonyl carbons.

(*E*)-Methyl 4-(4-chlorophenyl)-2-oxobut-3-enoate (**116**) was obtained in 60% yield as a yellow solid. Its melting point was determined as 115-116 °C. In ^{1}H NMR spectrum of the **116**, the singlet at 3.96 ppm belong to methoxy protons. The protons of alkene (-CH=CH-) appear at 7.36 and 7.82 ppm as doublet. Phenyl protons appear at 7.43 and 7.60 ppm as doublet. In the ^{13}C NMR spectrum of the **116**, methoxy carbon appears at 52.79 ppm. The signal at 120.92 and 146.48 ppm belong to alkene carbons. The signal at 162.22 and 181.54 ppm belong to carbonyl carbons. Physical properties are in agreement with known structure of **113** in the literature (Stecher et al, 1973).

(*E*)-Methyl 4-(4-bromophenyl)-2-oxobut-3-enoate (**117**) was obtained as a yellow solid in 55% yield. Its melting point was determined as 121-122 °C. In ^{1}H NMR spectrum of the **117**, methoxy protons appear at 3.95 ppm as singlet. The protons of alkene appear at 7.37 and 7.79 ppm as doublet. Doublet signal at 7.51 and 7.85 ppm belong to phenyl protons. In the ^{13}C NMR spectrum of the **117**, the signal at 52.91 ppm belong to methoxy carbon. The signals at 121.07 and 146.68 ppm belong to CH carbons. Carbonyl carbons appear at 162.30 and 181.66 ppm. Physical properties are in agreement with known structure of **113** in the literature (Stecher and Ryder, 1952).

As given in Scheme 5.4, compound **118** has been synthesised from the reaction of p-nitrobenzaldehyde and methyl ester of pyruvic acid according to the literature (Dujardin et al., 2001).



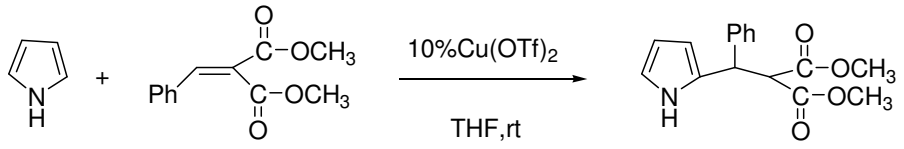
118

Scheme 5.4. Synthesis (*E*)-methyl 4-(4-nitrophenyl)-2-oxobut-3-enoate (**118**)

(*E*)-Methyl 4-(4-nitrophenyl)-2-oxobut-3-enoate (**118**) was obtained in 55% yield as yellow solid. Its melting point is 183°C. Singlet at 3.84 ppm belongs to methoxy protons. Doublets at 7.02 and 7.24 ppm belong to the protons of alkene. Doublets at 7.79 and 8.24 ppm belong to phenyl hydrogens. In ^{13}C NMR spectrum, the signals at 52.95, 161.78 and 181.80 ppm belong to methoxy carbon and carbonyl carbons, respectively. The signals of -CH=CH- carbons appear at 123.69 and 144.56 ppm. The structure is in agreement with the known structure of **118** in the literarure (Dujardin et al, 2001).

5.3. Micheal Reaction of Pyrrole With β,γ-unsaturated α-keto Ester Derivatives

Micheal reactions are fundamental carbon-carbon bond formation reactions in organic synthesis (Nakajimi et al., 2003). Micheal reaction of pyrrole with dimethylbenzylidenemalonate (**136**) was performed to obtain dimethyl 2-(phenyl(1*H*-pyrrol-2-yl)methyl)malonate (**137**) by Yazıcı in 2005 (Scheme 5.5).

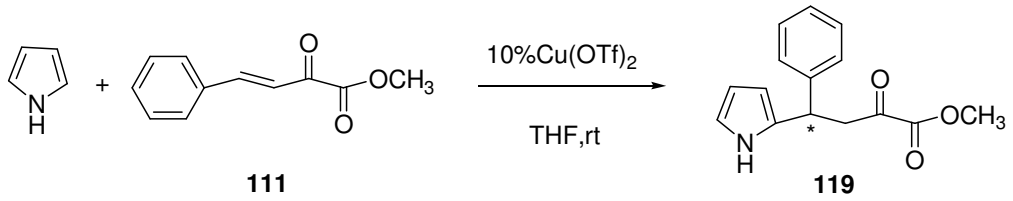


136 **137**

Scheme 5.5. Synthesis of dimethyl 2-(phenyl(1*H*-pyrrol-2-yl)methyl)malonate

In the second part of the study, Micheal reaction of pyrrole with synthesized *(E)*-Methyl-2-oxo-4-phenylbut-3-enoate (**111**) using $Cu(OTf)_2$ was performed (Scheme

5.6). Synthesized pyrrole derivative *via* Micheal reaction is an important key intermediate for the synthesis of pyrrolizine derivative.



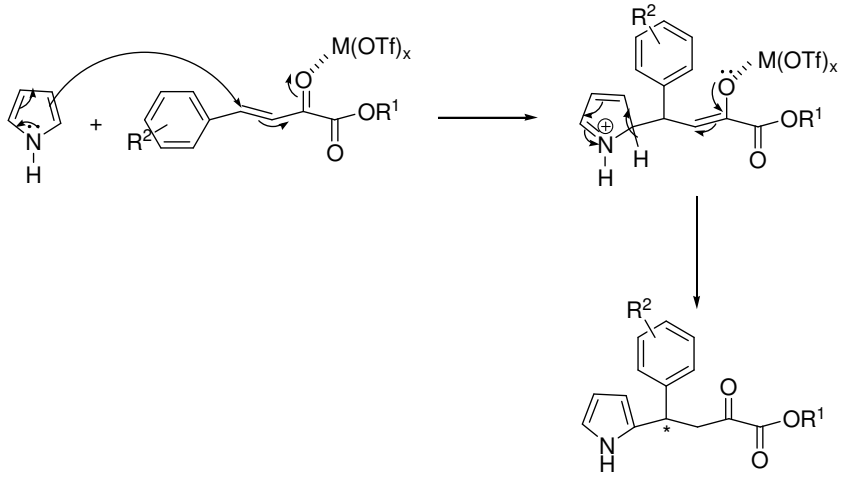
111 **119**

Scheme 5.6. Synthesis of methyl 2-oxo-4-phenyl-4-(1*H*-pyrrol-2-yl)butanoate

(*E*)-methyl 2-oxo-4-phenylbut-3-enoate (**111**) was chosen as a suitable polyfuctional 5 membered ring equivalent subtituent to obtain pyrrolizine structure.

5.3.1. Investigation of the 1,4-Addition Reaction of Pyrrole to β,γ-Unsaturated α-keto Ester Derivatives.

The addition reaction of pyrrole to (*E*)-Methyl 2-oxo-4-phenylbut-3-enoate (**111**) was performed in THF using $Cu(OTf)_2$ as catalyst. Methyl 2-oxo-4-phenyl-4-(1*H*-pyrrole-2-yl)butanoate (**119**) was obtained in 83% yield and characterized by ^1H NMR and ^{13}C NMR tecniques. Proposed mechanism of the Micheal reaction was given in Scheme 5.7.



Scheme 5.7. Suggesed mechanism of the Micheal addition reaction

Figure 5.1 (Page 66) shows the ^{1}H NMR spectrum of methyl 2-oxo-4-phenyl-4-(1*H*-pyrrol-2-yl)butanoate (**119**)**.** Doublet of doublet signals at 3.45 ppm (*J*=18.4 Hz, *J*=6.8 Hz) and 3.67 ppm (*J*=18.4 Hz, *J*=8.0 Hz) belong to CH_2 protons. Methoxy proton gives the signal at 3.84 ppm as singlet. CH proton appears at 4.62 ppm (*J*=7.2 Hz) as triplet. Broad singlet at 5.94 ppm belongs to pyrrole C(3)H proton. Doublet of doublet at 6.08 ppm belongs to pyrrole C(4)H. Broad singlet at 6.61 ppm belongs to pyrrole C(5)H. Phenyl protons appear at 7.24-7.34 ppm as multiplet. NH proton gives the signal at 7.95 ppm. The ^{13}C NMR spectrum (Figure 5.2),(Page 66) is in agreement with structure. Methyl 2-oxo-4-phenyl-4-(1*H*-pyrrol-2-yl)butanoate (**119**) gives the signals at 39.06 ppm, 45.56 ppm and 52.81 ppm for the CH_2, CH and OCH_3 carbon atoms, respectively. The signals at 127.12, 127.95, 128.80 and 142.15 ppm belong to phenyl ring carbons. Pyrrole carbons give signals at 105.78, 108.33, 117.41 and 133.02 ppm. The carbonyl carbons appear at 161.10 and 192.21 ppm.

After performing the addition reaction, optimum reaction conditions have been investigated for solvent, temperature and metal triflate. Results have been given in Table 5.1 for the different solvents.

Table 5.1. The effect of solvent on the reaction at rt.

R	$M(OTf)_x$	Solvent	Yield(%)[a]
Me	$Cu(OTf)_2$	THF	83
Me	$Cu(OTf)_2$	CH_2Cl_2	36
Me	$Cu(OTf)_2$	Toluen	30
Me	$Cu(OTf)_2$	Et_2O	28
Me	$Cu(OTf)_2$	Aseton	20
Me	$Cu(OTf)_2$	CH_3CN	15
Me	$Cu(OTf)_2$	THF:H_2O (1:1)	30

[a] isolated yield after purification.

As shown in the Table 5.1, the highest yield (83%) was obtained in THF. In the other solvents, addition product formed in lower yield.

According to the literature, yield of the addition reactions which have been performed in the presence of metal triflates, are affected by the metal triflate type (Kobayashi and Hachiya, 1992). Because of these reason, reactions were carried out to investigate the effect of the metal triflate . Results have been given in Table 5.2 .

Table 5.2. Addition reaction of (*E*)-methyl 2-oxo-4-phenylbut-3-enoate **(111)** with pyrrole using different $M(OTf)_x$ as catalyst at rt.

R	$M(OTf)_x$	Solvent	Yield(%)[a]
Me	$Cu(OTf)_2$	THF	83
Me	$Y(OTf)_3$	THF	67
Me	$Yb(OTf)_3$	THF	65
Me	$Gd(OTf)_3$	THF	60
Me	$Zn(OTf)_2$	THF	50
Me	$La(OTf)_3$	THF	58
Me	$Nd(OTf)_3$	THF	56

[a] isolated yield after purification

The effect of the different metal triflates on the reaction yield have been investigated by the addition of pyrrole to (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (**111**). The used metal triflates gave the product between 56% and 83% yield. The best yield (83%) was obtained with $Cu(OTf)_2$ (Table 5.2).

Reactions have been performed at different temperatures to investigate the effect of temperature on the reaction. Polimerisation of the pyrrole in the reaction media is one of the most important factor on reaction yield. For this reason, addition reaction of pyrrole to (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (**111**) was performed at diffferent temperatures. As shown in Table 5.3, the best chemical yield was obtained at rt.

Table 5.3. Addition reaction of pyrrole to the (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (**111**) at different temperatures.

R	$M(OTf)_x$	Solvent	Temperature °C	Yield (%)[a]	Time(hour)[b]
-Me	$Cu(OTf)_2$	THF	-20	20	12
-Me	$Cu(OTf)_2$	THF	0	50	12
-Me	$Cu(OTf)_2$	THF	rt	83	0.25

[a] isolated yield after purification

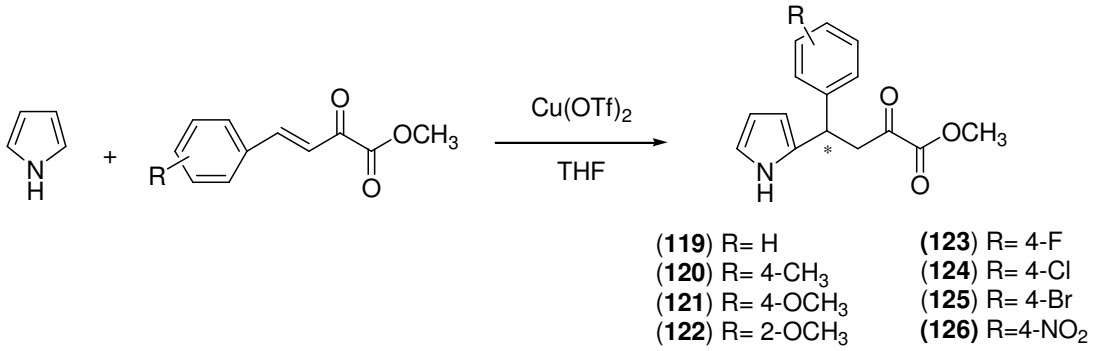
[b] all reactions were monitored by TLC

When the reaction was performed at 0 °C, the yield decreased to 50 % from 83%. At a lower temperature (-20 ^{0}C), the product formed only with 20% yield. Lowering the reaction temperature increased the reaction time thus causing the polymerisation of pyrrole.

Results indicated that the best solvent is THF (Table 5.1), the best catalyst is $Cu(OTf)_2$ (Table 5.2) and the best temperature is rt (Table 5.3) for the addition reaction of pyrrole to the (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (**111**).

5.3.2. The effect of Substituent on the 1,4-Addition Reaction of Pyrrole to β,γ-Unsaturated α-Keto Ester Derivatives.

1,4-addition reaction of pyrrole to enone compounds (**112-118**) have been performed under the optimized reaction conditions to investigate the effect of substituent (Scheme 5.8). The structures of addition products **120-126** have been determined by ^{1}H NMR, ^{13}C NMR and IR techniques.



(**119**) R= H
(**120**) R= 4-CH_3
(**121**) R= 4-OCH_3
(**122**) R= 2-OCH_3
(123) R= 4-F
(**124**) R= 4-Cl
(**125**) R= 4-Br
(126) R=4-NO_2

Scheme 5.8. Investigation of 1,4 addition reaction of pyrrole to substituted β,γ-unsaturated α-keto esters.

The yields are tabulated in Table 5.4. The best yield is obtained with hydrogen substituent. Electron donating and withdrawing substituents on phenyl decreased the yield.

Table 5.4. Addition of the pyrrole to the substituted enones in the presence of $Cu(OTf)_2$ in THF at rt.

R	**Yield(%)[a]**
H	83
4-CH_3	65
4-OCH_3	65
2-OCH_3	45
4-F	58
4-Cl	49
4-Br	63
4-NO_2	70

[a] isolated yield after purification

Figure 5.3 (Page 67) shows the ^{1}H NMR spectrum of the methyl 2-oxo-4-(1*H*-pyrrol-2-yl)-4-*p*-tolylbutanoate (**120**). The signal at 2.36 ppm belongs to CH_3 protons. CH_2 protons give the doublet of doublet signals at 3.44 ppm (J=18.0 Hz, J=6.8 Hz), and at 3.65 ppm (J=18.0 Hz, J=7.6 Hz). Methoxy proton appears at

3.84 ppm as singlet. Triplet at the 4.58 ppm belongs to CH (*J*=7.2 Hz) proton. Pyrrole protons give the broad singlet at 5.94 ppm for C(3)H, doublet of doublet at 6.08 ppm for C(4)H (*J*=5.6 Hz, *J*=2.8 Hz), broad singlet at 6.60 ppm for C(5)H. The multiplet at 7.11-7.21 ppm refers to phenyl ring protons. NH proton gives a broad singlet at 7.95 ppm. Figure 5.4 (Page 67) shows the ^{13}C NMR spectrum of the compound **120**. The signals at 21.07, 38.65, 45.56 and 52.76 ppm belong to the carbon atoms of CH_3, CH_2, CH and OCH_3, respectively. Pyrrole carbons appear at 105.58, 108.25 117.27 and 133.24 ppm. The signals at 127.82, 129.43, 136.49 and 139.10 ppm belongs to phenyl ring carbon atoms. The signals at 161.10 ppm and 192.25 ppm show the carbonyl carbons.

^1H NMR spectrum of methyl 4-(4-methoxyphenyl)-2-oxo-4-(1*H*-pyrrol-2-yl) butanoate (**121**) are given in Figure 5.5 (Page 68). The signals at 3.43 ppm(*J*=18.0 Hz, *J*=7.2 Hz) and 3.62 ppm (*J*=18.0 Hz, *J*=7.6 Hz) as doublet of doublet belong to CH_2 protons. The protons of methoxy groups give the singlet at 3.80 ppm and 3.82 ppm. CH proton appears at 4.56 ppm (*J*=7.3 Hz) as triplet. Pyrrole protons appear at 5.93 ppm (bs, C(3)H), 6.08 ppm (bs, C(4)H), 6.61 ppm (bs, C(5)H). Multiplets at 6.82-6.87 ppm and 7.14-7.16 ppm refer to the phenyl ring hydrogens. NH proton give the signal at 7.96 ppm. ^{13}C NMR spectrum of **121** (Figure 5.6, Page 68) is in agreement with the structure. The signals at 38.28, 45.68, 52.77 and 55.08 ppm belong to the carbon atoms of CH_2, CH, OCH_3 and p-OCH_3, respectively. The signals at 105.53, 108.26 ,117.28 ppm and 133.41 belong pyrrole carbons. Phenyl carbons appear at 114.05, 128.60, 134.13 and 158.62 ppm. The signals at 161.12 ppm and 192.30 ppm show the carbonyl carbons.

Figure 5.7 (Page 69) shows the ^1H NMR spectrum of methyl 4-(2-methoxyphenyl)-2-oxo-4-(1*H*-pyrrol-2-yl)butanoate (**122**). Doublet of doublet signals at 3.38 ppm (*J*=17.2 Hz, *J*=6.4 Hz) and 3.73 ppm (*J*=17.2 Hz, *J*=8.4 Hz) belong to CH_2 protons. The protons of methoxy groups give the singlet at 3.85 ppm and 3.89 ppm. Triplet at 5.00 ppm (*J*=7.2 Hz) belongs to CH proton. Pyrrole protons appear at 5.97 ppm (bs, C(3)H), 6.09 ppm (bs, C(4)H), and 6.64 ppm (bs, C(5)H). The signals at 6.89-6.93 ppm as multiplet and 7.09 ppm as doublet and 7.20-7.24 ppm as multiplet belong to phenyl protons. NH proton gives the broad signal at 8.25 ppm. ^{13}C NMR spectrum of **122** (Figure 5.8, Page 69) is in agreement with

structure. The signals at 33.23 ppm shows the CH carbon. CH_2 carbon appears at 44.12 ppm. Methohxy carbons give the signals at 52.83 ppm for OCH_3 and 55.33 ppm for o-OCH_3. The signals at 105.40, 108.08 ,117.00 ppm and 133.05 belong pyrrole carbons. Phenyl carbons appear at 111.03, 121.16, 128.13, 128.58, 130.52 and 156.44 ppm. The signals at 161.25 ppm and 192.41 ppm show the carbonyl carbons.

Figure 5.9 (Page 70) shows the ^{1}H NMR spectrum of Methyl 4-(4-flourophenyl)-2-oxo-4-(1*H*-pyrrol-2-yl)butanoate (**123**). The signals at 3.43 ppm (*J*=18.0 Hz, *J*=6.8 Hz) and 3.65 ppm (*J*=18.0 Hz, *J*=7.6 Hz) as doublet of doublet show the CH_2 protons. Methoxy protons appear at 3.87 ppm. CH proton gives the triplet signal at 4.60 ppm (*J*=7.2 Hz). The signals at the 5.92 ppm (C(3)H), 6.08 ppm (C(4)H) and 6.63 ppm (C(5)H) belong to pyrrole ring. Phenyl hydrogens appear at 6.98-7.03 ppm and 7.20-7.24 ppm as multiplet. The signals at 7.95 ppm belongs to NH proton. ^{13}C NMR spectrum of **123** (Figure 5.10, Page 70) is in agreement with structure. The signals at 38.34, 45.66 and 52.89 ppm belong to the carbon atoms of CH_2, CH and OCH_3, respectively. Pyrrole carbons give the signals at 105.88 ,108.45 and 117.59 and 132.84 ppm. Phenyl carbons appear at 115.67(J_{CF}=21.3 Hz), 129.49(J_{CF}=7.9 Hz), 137.88 and 161.90 ppm(J_{CF}=245.0 Hz). Carbonyl carbons appear at 161.07 ppm and 192.07 ppm.

Figure 5.11 (Page 71) shows the ^{1}H-NMR spectrum of the methyl 4-(4-chlorolphenyl)-2-oxo-4-(1*H*-pyrrol-2-yl)butanoate (**124**). Doublet of doublet signals at 3.42 ppm (*J*=18.4 Hz, *J*=6.8 Hz), and 3.64 ppm (*J*=18.0 Hz, *J*=7.6 Hz) belong to the CH_2 protons. The signal at 3.84 ppm refers to the methoxy proton. The signal at 4.58 ppm(*J*=7.2 Hz) as triplet shows the CH proton. Pyrrole protons appear at 5.94 ppm (bs, C(3)H), 6.09 ppm (bs, C(4)H) and 6.60 ppm (bs, C(5)H). Phenyl protons appear at 7.18 ppm (*J*=8.4) as a doublet and at 7.27-7.30 ppm as multiplet. NH proton gives the signal at 8.03 ppm as a broad singlet. ^{13}C NMR spectrum of the compound **124** is given in Figure 5.12 (Page 71). The carbon atoms of CH_2, CH and CH_3 appear at 38.38, 45.39 and 52.88 ppm respectively. Pyrrole carbons appear at 105.87, 108.38 ,117.64 and 132.93 ppm. The signals at 128.74, 128.88, 132.45 and 140.71 belong to pheny carbons. Carbonyl carbons appear at 160.95 ppm and 191.94 ppm.

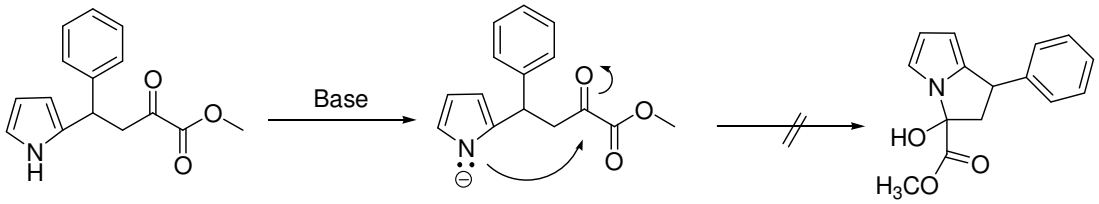
Figure 5.13 (Page 72) shows the ^{1}H NMR spectrum of the methyl 4-(4-bromophenyl)-2-oxo-4-(1*H*-pyrrol-2-yl)butanoate (**125**). Doublet of doublet at the 3.43 ppm (*J*=18.0 Hz, *J*=6.8 Hz) and 3.65 ppm (*J*=18.0 Hz, *J*=7.6 Hz) show the CH_2 protons. The singlet at the 3.86 ppm belongs to the methoxy protons. CH proton gives the triplet at 4.58 ppm (*J*=7.2 Hz). Pyrrole protons appear at 5.93 ppm for C(3)H, 6.08 ppm for C(4)H and 6.63 ppm for C(5)H. Doublet at 7.13 ppm (*J*=8.4) and at 7.44 ppm (*J*=8.4 Hz) belong to phenyl ring protons. NH proton gives the signal at 7.94 ppm as broad singlet. Figure 5.14 (Page 72) shows the ^{13}C NMR spectrum of the methyl 4-(4-bromophenyl)-2-oxo-4-(1*H*-pyrrol-2-yl)butanoate (**125**). The signals at 38.53, 45.40 and 52.94 ppm refers to the carbon atoms of CH_2 , CH and OCH_3, respectively. Pyrrole carbon atoms appear at 106.03, 108.52, 117.70 and 132.41 ppm. Phenyl carbons appeared at 121.14, 129.70, 131.95 and 141.19 ppm. Typical signal of the carbonyl carbons appear at 161.02 ppm and 191.94 ppm.

Figure 5.15 (Page 73) shows the ^{1}H NMR spectrum of the methyl 4-(4-nitrophenyl)-2-oxo-4-(1H-pyrrol-2-yl)butanoate (**126**). CH_2 protons give the doublet of doublet signals at t 3.47 ppm (*J*= 18.6 Hz, *J*=7.1 Hz) and 3.69 ppm (*J*=18.6 Hz, *J*=7.3 Hz). The singlet at 3.82 ppm refers to the methoxy protons. CH proton appears at 4.70 ppm (*J*=7.2 Hz) as triplet. Pyrrole protons appear at 5.95 ppm for C(3)H), 6.06 ppm for C(4)H and 6.62 ppm for C(5)H. Phenyl protons gave the signal at 7.36 ppm (*J*= 8.7 Hz) and 8.03 ppm (*J*=8.7 Hz) as doublet. The signal at 8.46 ppm belongs to the NH proton. ^{13}C NMR spectrum of the methyl 4-(4-nitrophenyl)-2-oxo-4-(1H-pyrrol-2-yl)butanoate (**126**) shows the signal at 38.57 ppm for CH, 44.86 ppm for CH and 52.90 ppm for CH_3 carbon atoms. Pyrrole carbon atoms appear at 105.93 108.34, 118.04 and 131.24 ppm. The signals at 123.66, 128.63, 146.62 and 149.95 ppm belong to phenyl carbon atoms. The signals at 160.67 ppm and 191.48 ppm show the carbonyl carbons (Figure 5.16), (Page 73).

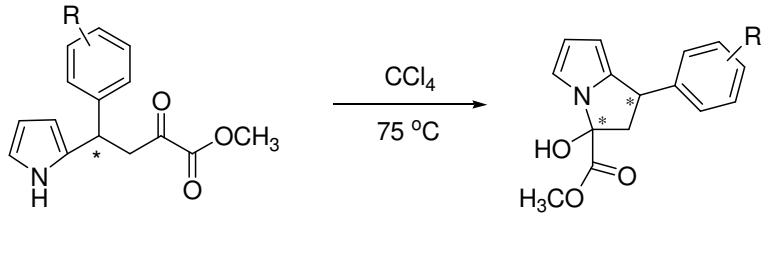
5.4. Synthesis of Novel Pyrrolizine Derivatives

Novel pyrrole derivatives **127-134** have been used for the synthesis of novel pyrrolizine derivatives. For this purpose, different bases such as, NaOH, Na_2CO_3,

NaH or acids such as, p-toluenesulphonic acid and metal triflates have been used under different reaction conditions, but no product was observed.

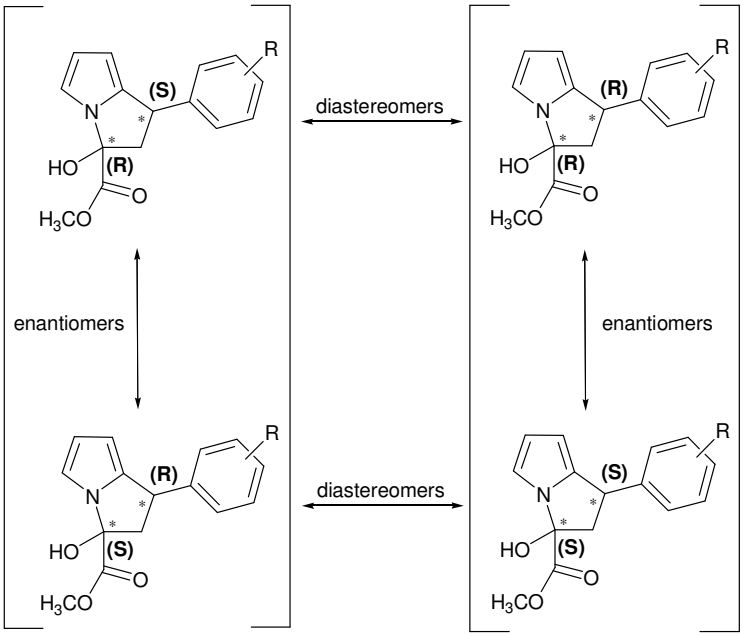


After this examination, we carried out the reaction in CCl_4, by heating. When the addition product **119** was refluxed in CCl_4 at 75 °C, formation of cyclisation product was observed. The reaction was monitored by TLC and novel pyrrole derivative converted to novel pyrrolizine derivative **127** with 100% yield in 6 hours. The same method was applied to obtain novel pyrrolizine derivatives **128-134** (Scheme 5.9) . The structures of **127-134** were determined by ^{1}H NMR and ^{13}C NMR tecniques.



Scheme 5.9. Synthesis of the novel pyrrolizine derivatives.

It can be seen that synthesized new type pyrrolizine derivatives have two asymmetric carbon atoms resulting in four stereoisomers. Relationships among the stereoisomers have been given in Scheme 5.10.



Scheme 5.10. Relationship among the stereoisomers of synthesized novel pyrrolizine derivatives.

These diatereoisomers were separated from each other by column chromatography and identified with ^{1}H NMR and ^{13}C NMR techniques. Diastereomers are assigned as a and b. Diastereomer a refers to the bigger R_f value and diastereomer b refers to the smaller R_f value.

Methyl 3-hydroxy-1-phenyl-2,3-dihydro-1 *H*-pyrrolizine-3-carboxylate (127)

Figure 5.17 (Page 74) shows the ^{1}H NMR spectrum of **127a**. CH_2 protons give the doublet of doublet signals at 2.64 ppm (J=13.6 Hz, J=7.7 Hz) and 3.39 ppm (J=13.6 Hz, J=8.4 Hz). The singlet at 3.88 ppm belongs to methoxy protons. The triplet at 4.48 ppm (J=8.0 Hz) belongs to CH proton. The broad singlet at 4.64 ppm refers to OH proton. Pyrrole protons appear at 5,75, 6.31 and 6.62 ppm as broad singlets. Phenyl protons appear at 7.24-7.37 ppm as multiplet. The ^{13}C NMR spectrum of the compound **127a** is given in Figure 5.18 (Page 74). The signals of the carbon atoms of CH, CH_2 and OCH_3 appear at 42.08, 50.14 and 53.73 ppm, respectively. The signal at 87.18 ppm belongs to the carbon atom of C-OH. Pyrrole carbon atoms appear at 101.20, 110.70 ppm, 115.00 and 139.16 ppm.

Phenyl carbons appear at 126.93, 127.65, 128.65 and 142.72. Characteristic signal of the carbonyl carbon appears at 172.02 ppm.

Figure 19 (Page 75)shows the COSY spectrum of **127a**. Pyrrole protons at 5,75 and 6.31ppm correlate with each other. Pyyrole proton at 6.31 ppm also correlates with pyrrole proton at 6.62 ppm. These correlations show that pyrrole proton at 6.31ppm is neighbour to the other pyrrole protons. These interactions confim the suggested structure of the product.

Figure 5.20 (Page 76) shows the ^{1}H NMR spectrum of **127b**. The signals of the CH_2 protons appear at 3.00-3.08 ppm as multiplet. The singlet at 3.89 ppm shows the methoxy protons. OH proton appears at 4.32 ppm as broad singlet. The triplet at 4.65 ppm (*J*=8.1 Hz) belongs to the CH proton. Pyrrole protons appear at 5.78 ppm for the C(3)H, 6.31 ppm C(4)H and 6.59 ppm for C(5)H. Multiplet at 7.24-7.34 ppm belongs to the phenyl protons. Figure 5.21 (Page 76) shows the ^{13}C NMR spectrum of compound **127b** . The signals at 41.60, 50.82, 53.68 and 86.93 ppm belong to the carbon atoms of CH, CH_2, OCH_3 and C-OH, respectively. Pyrrole carbons appear at 101.58, 110.99, 115.04 and 139.81 ppm. Phenyl carbons show the signals at 126.94, 127.71, 128.62 and 142.46 ppm. The signal at 171.39 ppm shows the carbonyl carbon.

Methyl 3-hydroxy-1-*p*-tolyl-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (128)

Figure 5.22 (Page 77) shows the ^{1}H-NMR spectrum of the compound **128a**. The singlet at 2.37 ppm belongs to methyl protons. The doublet of doublet signals at 2.59 (*J*=13.6 Hz, *J*=8.0 Hz) and 3.33 ppm (*J*=13.6 Hz, *J*=8.4 Hz) belong to CH_2 protons. Methoxy protons appear at 3.88 ppm as singlet. Triplet at 4.42 ppm (*J*=8.0 Hz) refers to the CH proton. Broad singlet at 4.49 ppm belongs to OH. Pyrrole protons appear at 5.71, 6.29 and 6.58 ppm as broad singlet. Doublets at 7.12 ppm (*J*=8.0 Hz) and 7.23 ppm (*J*=8.0 Hz) belong to phenyl protons. Figure 5.23 (Page 77) shows the ^{13}C NMR spectrum of the compound **128a**. The signals at 21.10, 42.68, 50.16, 53.70 and 87.04 ppm belong to the carbon atoms of CH_3, CH, CH_2, OCH_3 and C-OH, respectively. Pyrrole carbons appear at 101.03, 110.49, 114.90 and 139.34 ppm. The signals at 127.49, 129.27, 136.22 and

139.64 ppm belong to phenyl carbon atoms. The signal at 172.07 ppm shows the carbonyl carbon atoms.

Figure 5.24 (Page 78) shows the ^{1}H NMR spectrum of the compound **128b**. Methyl protons give the singlet at 2.38 ppm. Multiplet at 2.97-3.03 ppm belong to CH_2 protons. Methoxy protons appear at 3.88 ppm as singlet. Broad singlet at 4.21 ppm belongs to OH proton. Triplet at the 4.60 ppm (*J*=8.1 Hz) belong to CH proton. Pyrrole protons appear at 5.75 ppm for C(3)H, 6.29 ppm for C(4)H and 6.56 ppm for C(5)H. Doublets at 7.13 ppm (*J*=7.9 Hz) and 7.22 ppm (*J*=8.0 Hz) belong to phenyl protons. Figure 5.25 (Page 78) shows the ^{13}C NMR spectrum of the compound **128b**. The signals at 21.10, 41.16, 50.81, 53.62 and 86.82 ppm belong to the carbon atoms of CH_3, CH, CH_2, OCH_3 and C-OH, respectively. Pyrrole carbon atoms appear at 101.35, 110.77, 114.92 and 139.33 ppm. The signals at 127.51, 129.21, 136.21 and 140.02 ppm show the phenyl carbons. Carbonyl carbon appears at 171.49 ppm.

Methyl-3-hydroxy-1-(4-methoxyphenyl)-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (129):

Figure 5.26 (Page 79) shows the ^{1}H NMR spectrum of **129a.** Doublet of doublet signals at 2.58 ppm (*J*=13.6 Hz, *J*=7,6 Hz) and 3.34 ppm (*J*=13.6 Hz, *J*=8.4 Hz) belong to CH_2 protons. The singlets at 3.82 and 3.88 ppm show the protons of the methoxy groups. The triplet at 4.42 ppm (*J*=8.0 Hz) shows the CH proton. OH proton appears at 4.57 ppm as broad singlet. Pyrrole protons appear at 5.71, 6.29, and 6.59 ppm as broad singlet. Phenyl protons give the signals at 6.85 ppm (*J*=8.6 Hz) and 7.26 ppm (*J*=8.6 Hz) as doublet. Figure 5.27 (Page 79) shows the ^{13}C NMR spectrum of the compound **129a**. The signals at 41.39, 50.35, 53.57, 55.11 and 87.14 ppm belong to the carbon atoms of CH, CH_2, OCH_3, p-OCH_3 and C-OH, respectively. Pyrrole carbons appear at 101.04, 110.60, 114.08 and 139.58. Phenyl carbon atoms appear at 114.96, 128.62, 134.77 and 158.66 ppm. The signal at 172.10 ppm belongs to carbonyl carbon.

Figure 5.28 (Page 80) shows the ^{1}H NMR spectrum of **129b.** Multiplet at 2.98-3.01 ppm belong to CH_2 protons. Singlets at 3.81 ppm and 3.84 ppm refer to the

protons of the methoxy groups. OH proton appears at 4.23 ppm as broad singlet. CH proton appears at 4.59 ppm (*J*=8.1 Hz) as triplet. The signals of pyrrole protons appear at 5.74 ppm for C(3)H, 6.29 ppm for C(4)H and 6.56 ppm for C(5)H. Doublet at 6.85 ppm (*J*=8.4 Hz) and the multiplet at the 7.23-7.28 ppm belong to the phenyl protons. Figure 5.29 (Page 81) shows the ^{13}C NMR spectrum of **129b**. The carbon atoms of CH, CH_2, OCH_3, p-OCH_3 and C-OH appear at 40.90, 51.02, 53.73, 55.16 and 86.92 ppm, respectively. Pyrrole carbon atoms give the signals at 101.41, 110.89, 114.06 and 140.27 ppm. Phenyl carbons give the signal at 115.00, 128.67, 134.44 and 158.70 ppm. Characteristic signal of the carbonyl carbon appears at 171.47 ppm.

Methyl-3-hydroxy-1-(2-methoxyphenyl)-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (130):

Figure 5.30 (Page 81) shows the ^{1}H NMR spectrum of the **130a**. Doublet of doublet signals at 2.21 ppm (*J*=12.8 Hz, *J*=9.1 Hz) and 3.84 ppm (J=13.8 Hz, J=8.7 Hz) belong to CH_2 protons. Broad singlet at 3.89 ppm shows the methoxy protons. The signal at 4.45 ppm shows the OH proton. Triplet at 4.77 ppm (*J*=7.7 Hz) refers to the CH proton. Pyrrole protons appear at 5.78 ppm for C(3)H, 6.32 ppm for C(4)H and 6.61 ppm for C(5)H as broad singlet. Multiplet signals at the 6.87-6.91 and 7.22-7.36 ppm and the doublet at 7.34 ppm (*J*=7.5 Hz) belong to the phenyl protons. Figure 5.31 (Page 81) shows the ^{13}C NMR spectrum of the compound **130a**. The carbon atoms of CH, CH_2, OCH_3, o-OCH_3 and C-OH appear at 35.73, 48.63, 53.65, 55.35 and 87.26, respectively. Pyrrole carbons appear at 101.16, 110.32, 114.81 and 138.50 ppm. The signals at 110.73, 120.89, 127.84, 128.01, 131.18 and 156.92 ppm belong to the phenyl carbons. Carbonyl carbon appears at 172.05 ppm.

Figure 5.32 (Page 82) shows the ^{1}H NMR spectrum of methyl-3-hydroxy-1-(2-methoxyphenyl)-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (**130b**). Doublet of doublet signals at 2.84 ppm (*J*=13.5 Hz, *J*=7.2 Hz) and 3.17 ppm (*J*=13.6 Hz, *J*=8.3 Hz) belong to CH_2 protons. Singlets at 3.80 ppm and 3.90 ppm refer to the protons of methoxy groups. Proton signal of OH appears at 4.21 ppm. CH proton appears at 4.95 ppm (*J*=7.7 Hz) as triplet signal. Broad singlets at 5.82, 6.33 and

6.60 ppm belong to pyrrole C(3)H, C(4)H and C(5)H, respectively. Multiplet signals at 6.87-6.91 and 7.19-7.24 ppm and doublet at 7.32 ppm (J=7.6 Hz) belong to phenyl protons. Figure 5.33 (Page 82) shows the ^{13}C NMR spectrum of the methyl-3-hydroxy-1-(2-methoxyphenyl)-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (**130b**). The signals at 35.73, 48.63, 53.65, 55.35 and 87.26 ppm belong to carbon atoms of the CH, CH_2, OCH_3, o-OCH_3 and C-OH, respectively. Pyrrole carbon atoms appear at 101.70, 110.07, 114.96, 138.88 ppm. The signals at 110.84, 120.58, 127.77, 127.84, 130.83 and 157.35ppm show the phenyl carbon atoms. The signal at 171.75 ppm refers to the carbonyl carbon.

Methyl-1-(4-fluorophenyl)-3-hydroxy-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (131):

Figure 5.34 (Page 83) shows the ^{1}H NMR spectrum of **131a**. The signals of the CH_2 protons appear at 2.57 ppm (J=13.6, J=6.2 Hz) and 3.39 ppm (J=13.6 Hz, J=8.4 Hz) as doublet of doublet. Methoxy protons gives the signal at 3.88 ppm as singlet. CH proton appears at 4.45 ppm (J=7.9 Hz) as triplet. The signal at 4.60 ppm belongs to the OH proton. The signals of pyrrole protons appear at 5.72 ppm for C(3)H, 6.30 ppm for C(4)H and 6.60 ppm C(5)H. Multiplet signals at 6.99-7.04 and 7.30-7.34 ppm belong to phenyl protons. Figure 5.35 (Page 83) shows the ^{13}C NMR spectrum of **131a**. The signal at 41.39 ppm shows the CH carbon. The signal at 50.20 ppm shows the CH_2 carbon. The signal at 53.85 ppm belongs the OCH_3 carbon. The signal at 87.11 ppm shows the C-OH carbon atom. Pyrrole carbon atoms appear at 101.23, 110.80, 115.14 and 139.06 ppm. Phenyl carbon atoms appear at 115.52 (d, J_{CF}=21.3 Hz), 129.15 (d, J_{CF}=7.9 Hz), 138.51 and 161.86 ppm (d, J_{CF}=244.1 Hz). Carbonyl carbon atom gives the signal at 171.97 ppm.

Figure 5.36 (Page 84) shows the ^{1}H NMR spectrum of the **131b**. Doublet of doublet signals at 2.98 ppm (J=13.4 Hz, J=8.0 Hz) and 3.05 ppm (J=13.4 Hz, J=8.0 Hz) refers to the CH_2 protons. Methoxy protons give the singlet at 3.88 ppm. Signal at the 4.29 ppm belongs to OH proton. CH proton gives the signal 4.62 ppm (J=8.0 Hz) as triplet. Broad singlets at 5.75, 6.30 and 6.57 ppm belong the pyrrole C(3)H, C(4)H and C(5)H protons, respectively. Multiplet signals at 6.99-7.04 ppm and 7.28-7.32 ppm refer to the phenyl protons. Figure 5.37 (Page 84) shows the

^{13}C NMR spectrum of the compound **131b.** The signals at the 40.80, 50.81, 53.67 and 86.78 ppm show the carbon atoms of the CH, CH_2, OCH_3 and C-OH, respectively. The signals at 101.47, 111.01, 115.27 and 139.54 ppm belong to pyrrole carbon atoms. Phenyl carbons appear at 115.38 (d, J_{CF}=21.1 Hz), 129.06 (d, J_{CF}=7.7 Hz), 138.07 and 161.85 (d, J_{CF}=244.4 Hz). Signal at 171.18 ppm belong to carbonyl carbon.

Methyl-1-(4-chlorophenyl)-3-hydroxy-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (132):

Figure 5.38 (Page 85) shows the ^1H NMR spectrum of the **132a**. Doublet of doublet signals at 2.57 and 3.39 ppm refer to the CH_2 protons. Singlet at the 3.87 ppm belongs to methoxy protons. Triplet at 4.45 ppm (J=7.9 Hz) shows the CH proton. Broad singlet at 4.71 ppm shows the OH proton. The signals of pyrrole protons appear at 5.73 ppm for the C(3)H, 6.31 ppm for the C(4)H and 6.62 ppm for C(5)H. Multiplet at 7.27-7.30 ppm shows the phenyl protons. Figure 5.39 (Page 85) shows the ^{13}C NMR spectrum of **132a**. The signals at 41.42, 50.70, 53.78 and 87.10 ppm show the carbon atoms of the CH, CH_2, OCH_3 and C-OH, respectively. The signals of the pyrrole carbon atoms appear at 101.23 ppm , 110.88, 115.08 and 138.67 ppm. Phenyl carbons give the signal at 128.42, 128.98, 132.77 and 141.26 ppm. Signal at 171.80 ppm shows the carbonyl carbon.

Figure 5.40 (Page 86) shows the ^1H NMR spectrum of compound **132b**. Doublet of doublet signals at 2.97 ppm (J=13.4 Hz, J=8.0 Hz) and 3.05 ppm (J=13.4 Hz, J=8.1 Hz) refer to the CH_2 protons. Methoxy protons give the singlet at 3.88 ppm. The signal at 4.29 ppm refers to OH proton. The signals at 4.61 ppm shows the CH proton. The signals of pyrrole protons appear at 5.75 ppm for the C(3)H, 6.30 ppm for the C(4)H and 6.57 ppm for C(5)H. The multiplet at 7.26-7.30 ppm belongs to the phenyl protons. Figure 5.41 (Page 86) shows the ^{13}C NMR spectum of the **132b**. The signals at 41.03, 50.77, 53.82 and 86.89 ppm show the carbon atoms of the CH, CH_2 OCH_3 and C-OH, respectively. The signals at 101.67, 111.19, 115.20 and 139.89 ppm belong to the pyrrole carbon atoms. Phenyl carbons appear at 128.83, 129.18, 132.89 and 141.03 ppm. The signal at 171.26 ppm shows the carbonyl carbon.

Methyl-1-(4-bromophenyl)-3-hydroxy-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (133):

Figure 5.42 (Page 87) shows the ^{1}H NMR spectrum of compound **133a**. Doublet of doublet signals at 2.58 ppm (*J*=13.6 Hz, *J*=8.4 Hz) and 3.41 ppm (*J*=13.6 Hz, *J*=8.4 Hz) belongs to CH_2 protons. Methoxy protons give the singlet at 3.88 ppm. Triplet at 4.46 ppm (*J*=8.0 Hz) refers to the CH proton. OH proton gives signal at 4.57 ppm as broad singlet. The signals at the 5.76, 6.35 and 6.65 ppm show the pyrrole C(3)H, C(4)H and C(5)H protons, respectively. Doublets at 7.25 ppm (*J*=8.8 Hz) and 7.46 ppm (*J*=8.4 Hz) belong to phenyl protons. Figure 5.43 (Page 87) shows the ^{13}C NMR spectrum of **133a**. Carbon atoms of the CH, CH_2, CH_3 and C-OH appear at 41.46 ppm, 49.91 ppm, 53.90 ppm and 87.03 ppm, respectively. The signals at 101.21, 110.85, 120.83 and 138.63 ppm belong to the pyrrole carbon atoms. Phenyl carbon atoms appear 115.05, 129.33, 131.74 and 141.74 ppm. Carbonyl carbon gives the signal at 171.86 ppm.

Figure 5.44 (Page 88) shows the ^{1}H NMR spectrum of **133b**. Doublet of doublet signals at 2.99 ppm (*J*=13.6 Hz, *J*=8.0 Hz) and 3.07 ppm (*J*=13.6 Hz, *J*=8.0 Hz) refer to the CH_2 protons. Methoxy protons give the singlet at 3.91 ppm. OH proton gives the broad singlet at 4.39 ppm. Triplet signal at the 4.62 ppm (*J*=8.0 Hz) belongs to CH. Pyrrole protons appear at 5.79 ppm for C(3)H, 6.35 ppm for C(4)H and 6.64 ppm for C(5)H. Doublet signals at 7.22 ppm (*J*=8.4 Hz) and 7.47 ppm(*J*=8.4 Hz) show the phenyl protons. Figure 5.45 (Page 88) shows the ^{13}C NMR spectrum of the compound **133b**. The signals at 40.97, 50.63, 53.80 and 86.84 ppm show the carbon atoms of CH, CH_2, CH_3 and C-OH, respectively. The signals at 101.53, 111.18, 120.78 and 139.19 ppm belong to pyrrole carbons. Phenyl carbons appear at 115.03, 129.36, 131.74 and 141.45 ppm. The signal at 171.17 ppm shows the carbonyl carbon.

Methyl-1-(4-nitrophenyl)-3-hydroxy-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate(134)

Figure 5.46 (Page 89) shows the ^{1}H NMR spectrum of **134a**. Doublet of doublet signals at 2.59 ppm (*J*=14.0 Hz, *J*=7.2 Hz) and 3.47 ppm (*J*=13.6 Hz, *J*=8.4 Hz)

belong to CH_2 protons. The signal at 3.90 ppm belongs to methoxy potons. Triplet at 4.57 ppm (J=7.6 Hz) shows the CH proton. OH proton gives the broad singlet at 4.66 ppm. Pyrrole protons appear at 5.74 for the C(3)H, 6.32 for C(4)H and 6.63 ppm for C(5)H. Doublet signals at 7.52 ppm (J=8.7 Hz) and 8.19 ppm (J= 9.1 Hz) belong to phenyl protons. Figure 5.47 (Page 89) shows the ^{13}C NMR spectrum of the **134a**. The signals at 41.74, 49.60, 54.01 and 87.11 ppm show the carbon atoms of CH, CH_2, OCH_3 and C-OH, respectively. Pyrrole carbon atoms appear at 101.65, 111.33, 115.41, and 137.71 ppm for the C(3), C(4), C(5) and C(2), respectively. The signals at 124.00, 128.53, 147.20 and 150.38 ppm belong to phenyl carbons. The signal of carbonyl carbon appears at 171.55 ppm.

Figure 5.48 (Page 90) shows the ^1H NMR spectrum of methyl-1-(4-nitrophenyl)-3-hydroxy-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (**134b**). Doublet of doublet signals at 3.02 ppm (J=13.6 Hz, J=7.6 Hz) and 3.13 ppm (J=13.6 Hz, J=8.4 Hz) belong to CH_2 protons. The signal at 3.90 ppm belongs to methoxy protons. Broad singlet at 4.36 ppm belongs to OH proton. Pyrrole ring protons give signals at 5.78 ppm for C(3)H, 6.33 ppm for C(4)H and 6.61 ppm for C(5)H. Doublets at 7.51ppm (J=4.8 Hz) and 8.21 ppm (J=6.88 Hz) belong to phenyl hydrogens. Figure 5.49 (Page 90) shows the ^{13}C NMR spectrum of **134b**. The signals at 41.37, 51.41, 53.95 and 86.88 ppm belong to the carbon atoms of CH, CH_2, OCH_3 and C-OH, respectively. Pyrrole carbons appear at 101.99, 111.59, 115.46 and 138.15 ppm for the C(3), C(4(, C(5) and C(2), respectively. The signal at 123.96, 128.56, 147.28, and 150.13 ppm belong to phenyl carbons. Carbonyl carbon appears at 170.96 ppm.

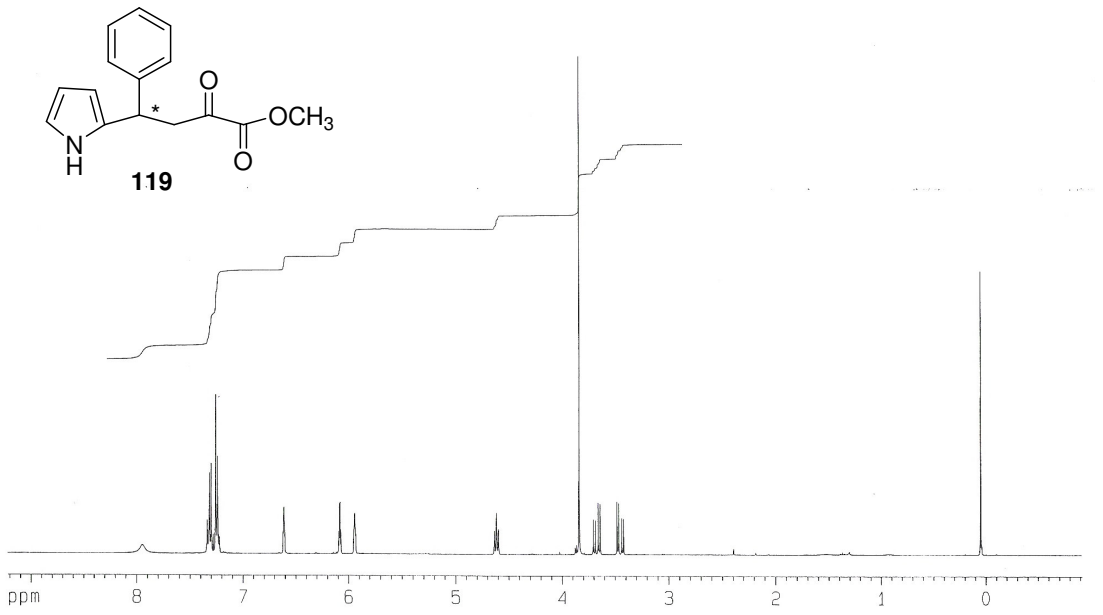


Figure 5.1. ^{1}H-NMR spectrum of the compound 119

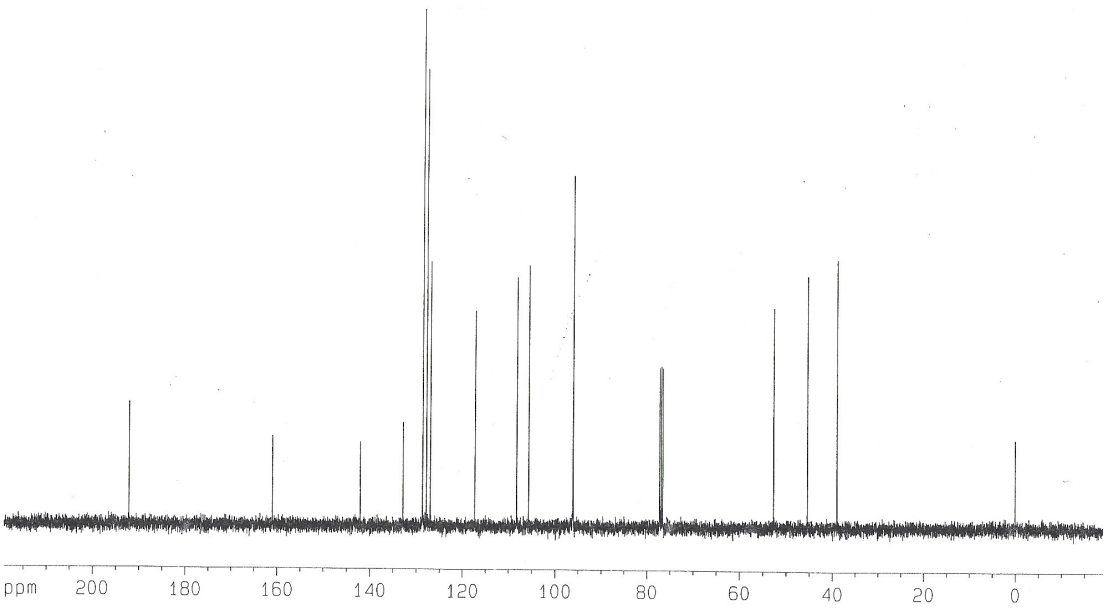


Figure 5.2. ^{13}C-NMR spectrum of the compound 119

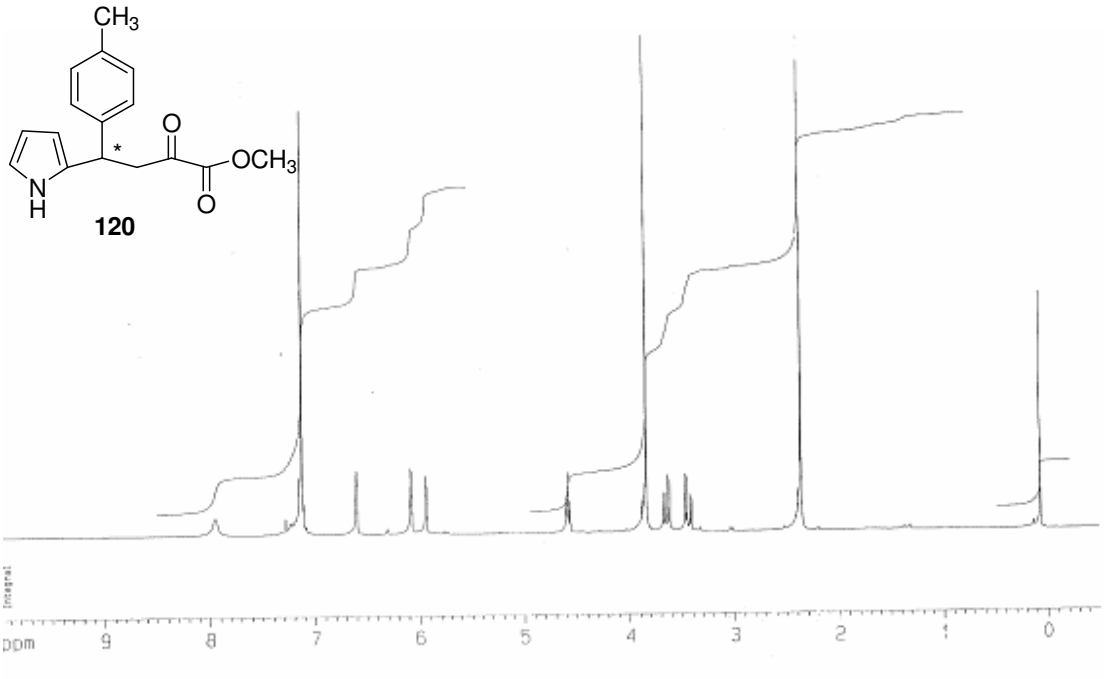


Figure 5.3. ^{1}H-NMR spectrum of the compound 120

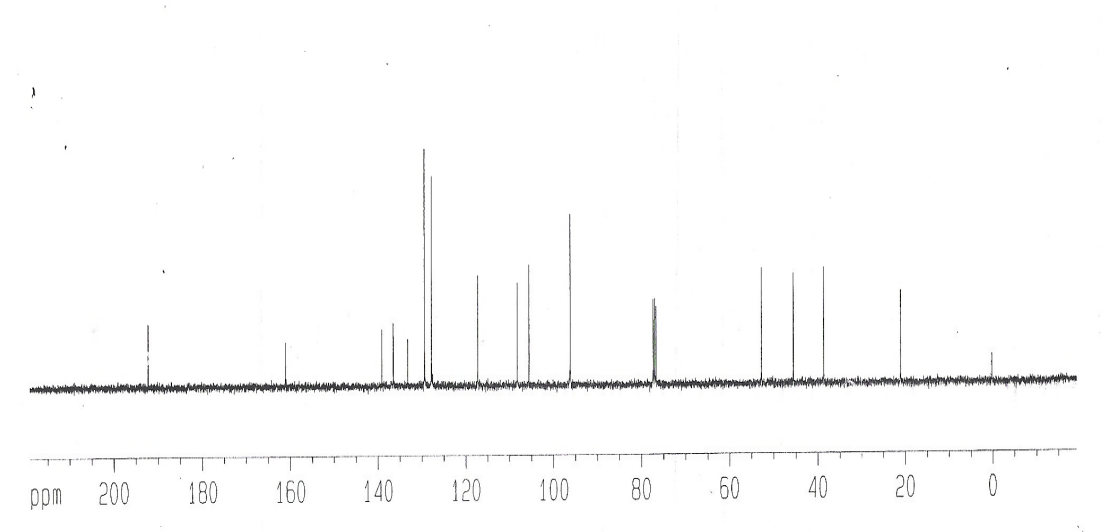


Figure 5.4. ^{13}C-NMR spectrum of the compound 120

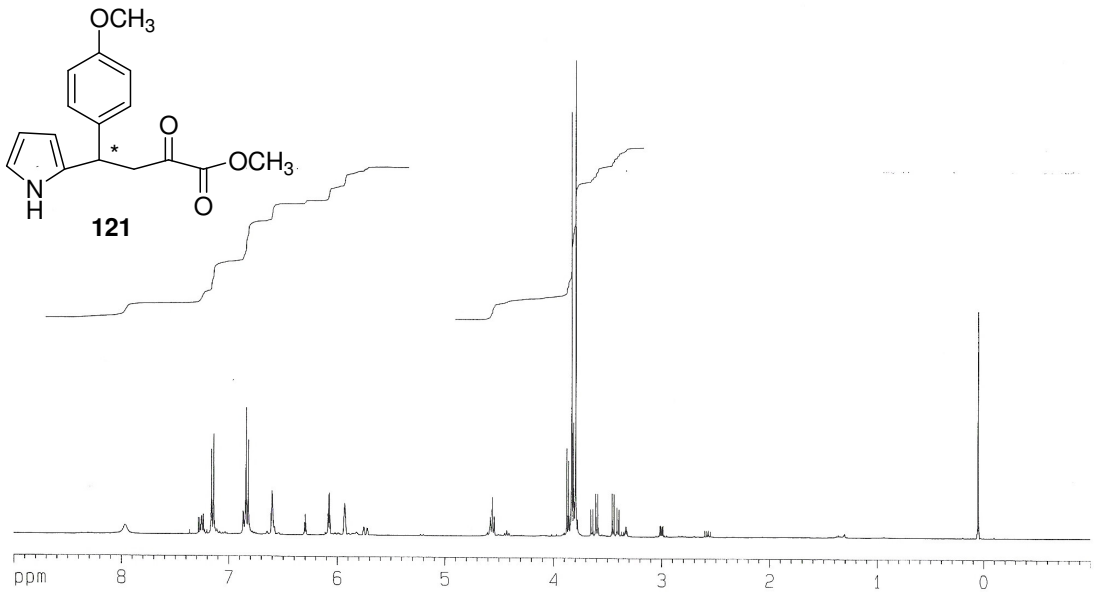


Figure 5.5. ^{1}H-NMR spectrum of the compound 121

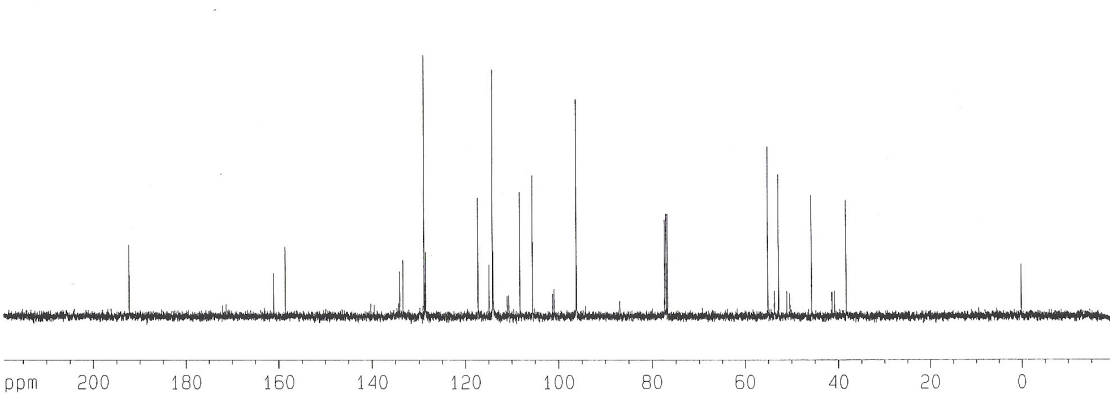


Figure 5.6. ^{13}C-NMR spectrum of the compound 121

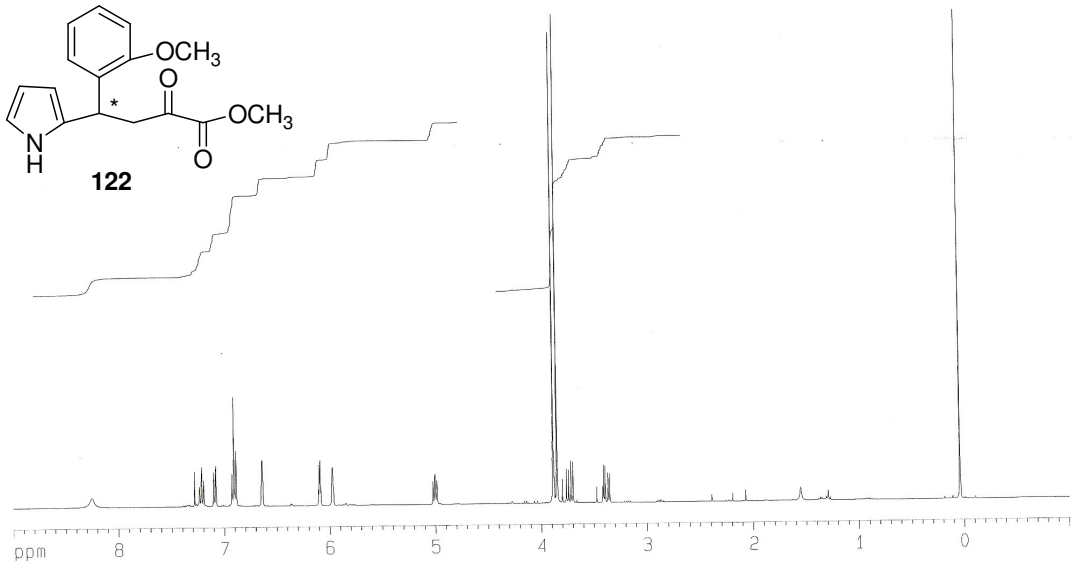


Figure 5.7. ^{1}H-NMR spectrum of the compound 122

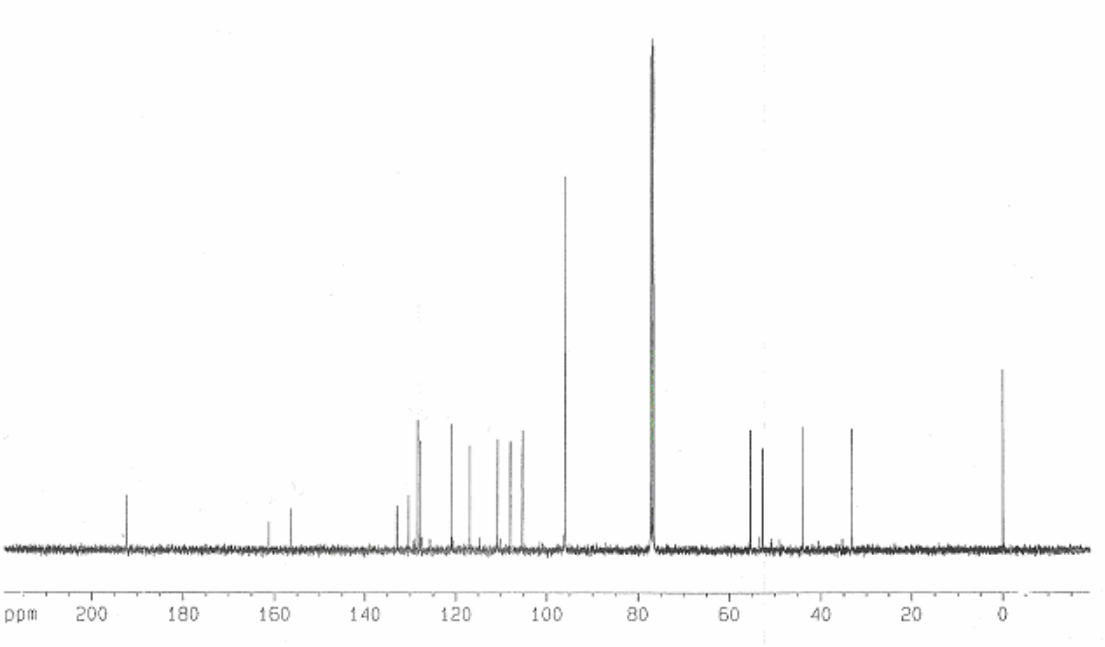


Figure 5.8. ^{13}C-NMR spectrum of the compound 122

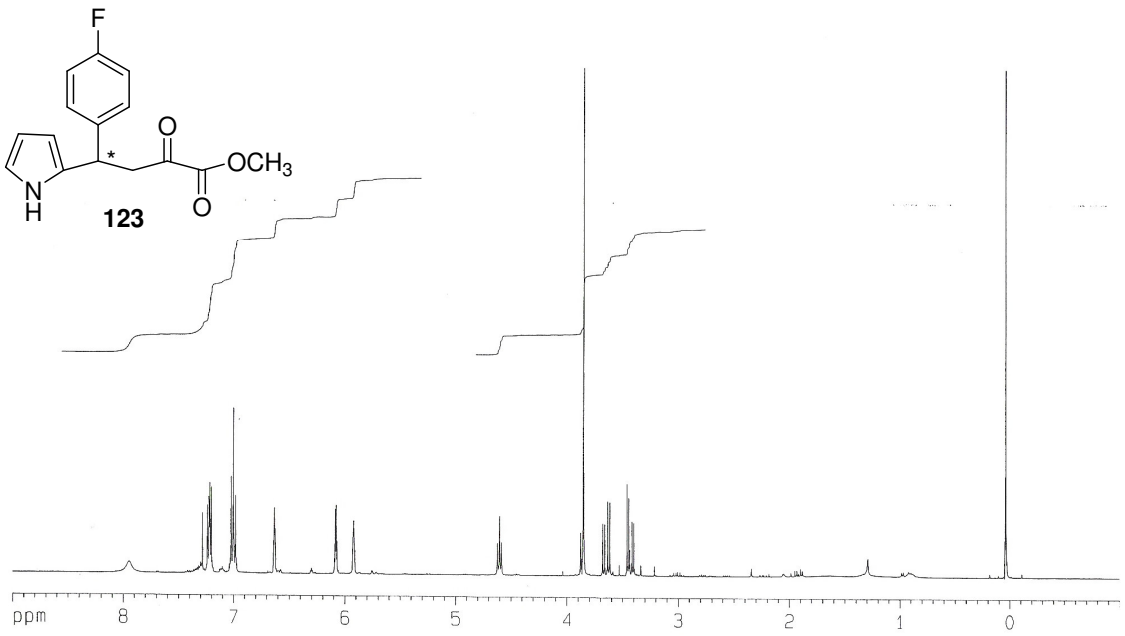


Figure 5.9. ^{1}H-NMR spectrum of the compound 123

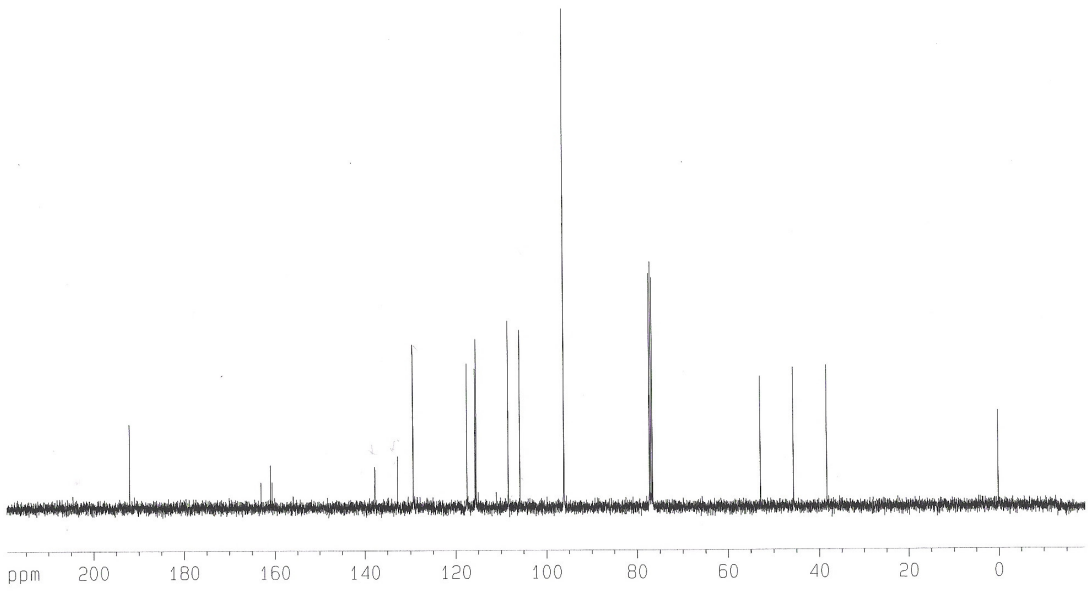


Figure 5.10. ^{13}C-NMR spectrum of the compound 123

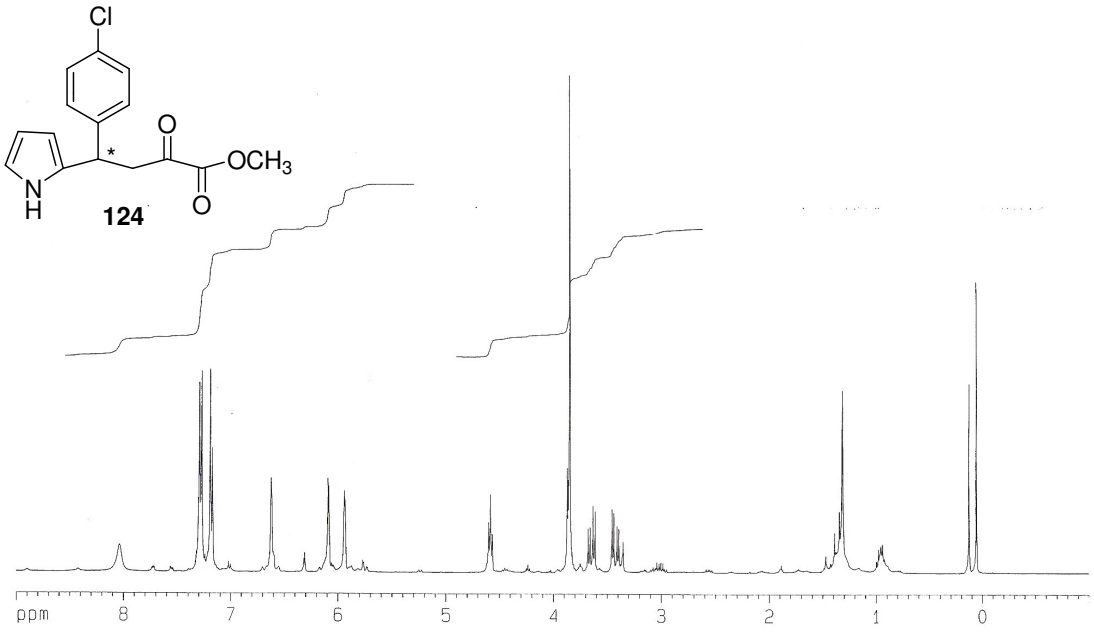


Figure 5.11. ^{1}H-NMR spectrum of the compound 124

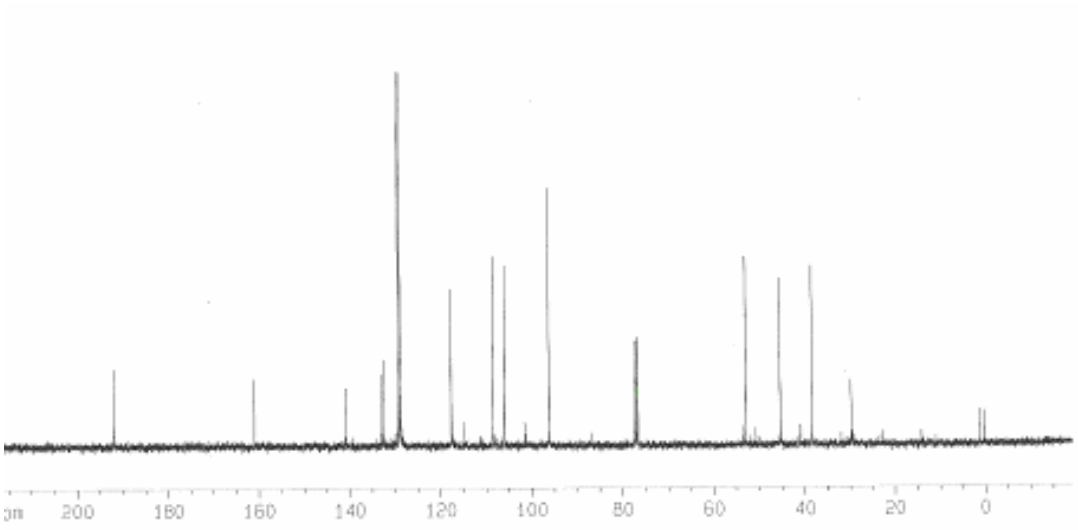


Figure 5.12. ^{13}C-NMR spectrum of the compound 124

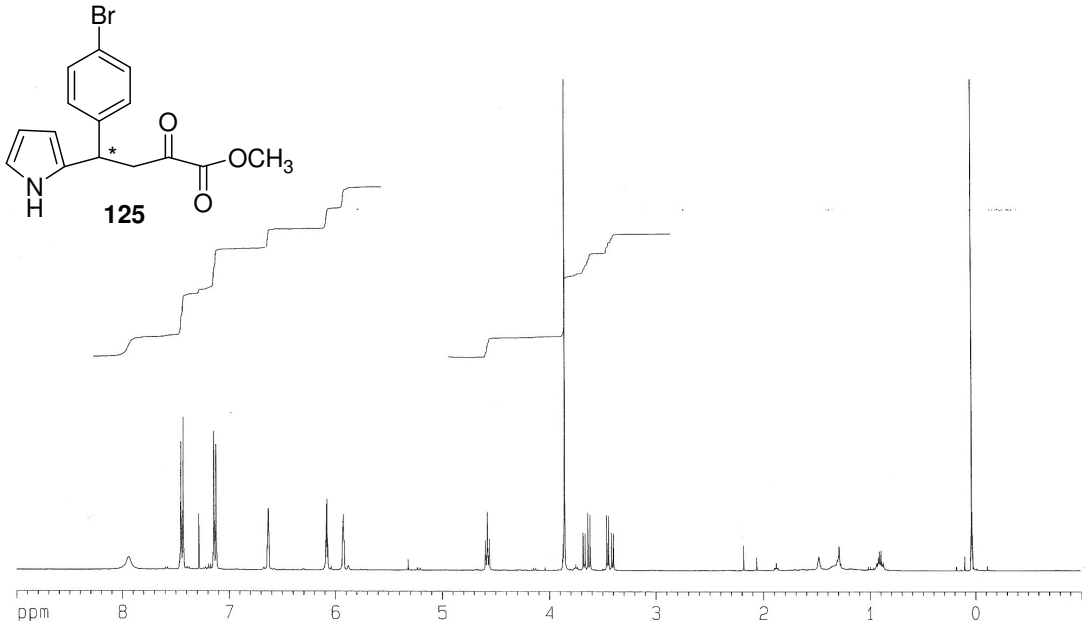


Figure 5.13. ^{1}H-NMR spectrum of the compound 125

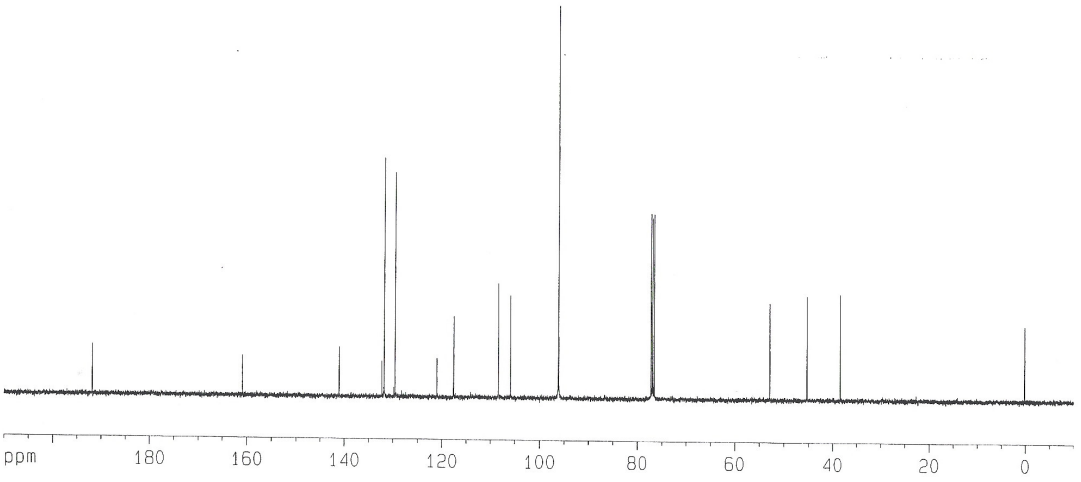


Figure 5.14. ^{13}C-NMR spectrum of the compound 125

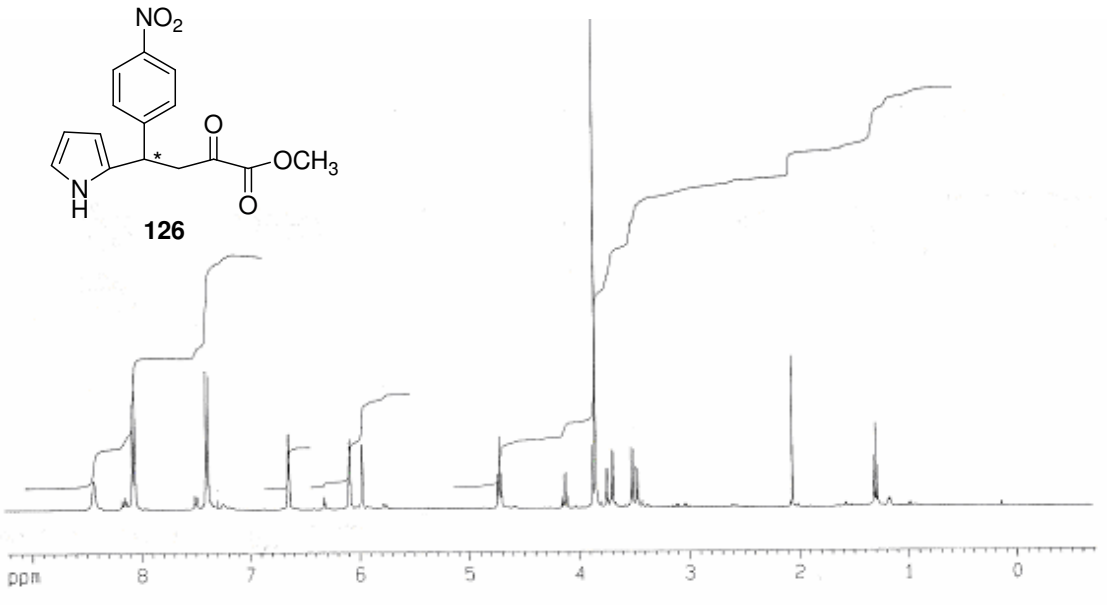


Figure 5.15. ^{1}H-NMR spectrum of the compound 126

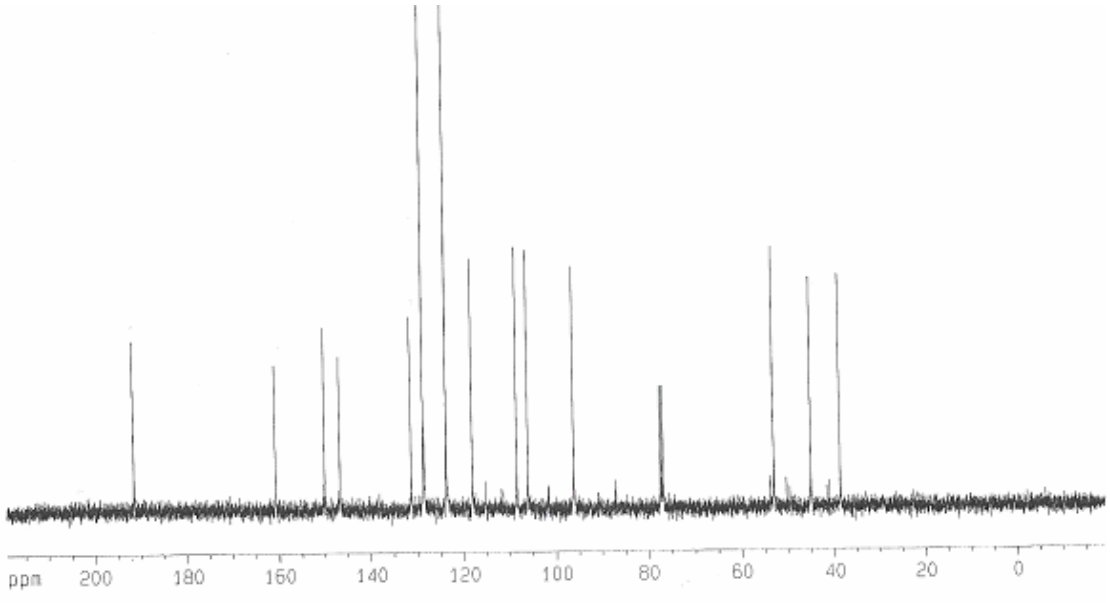


Figure 5.16. ^{13}C-NMR spectrum of the compound 126

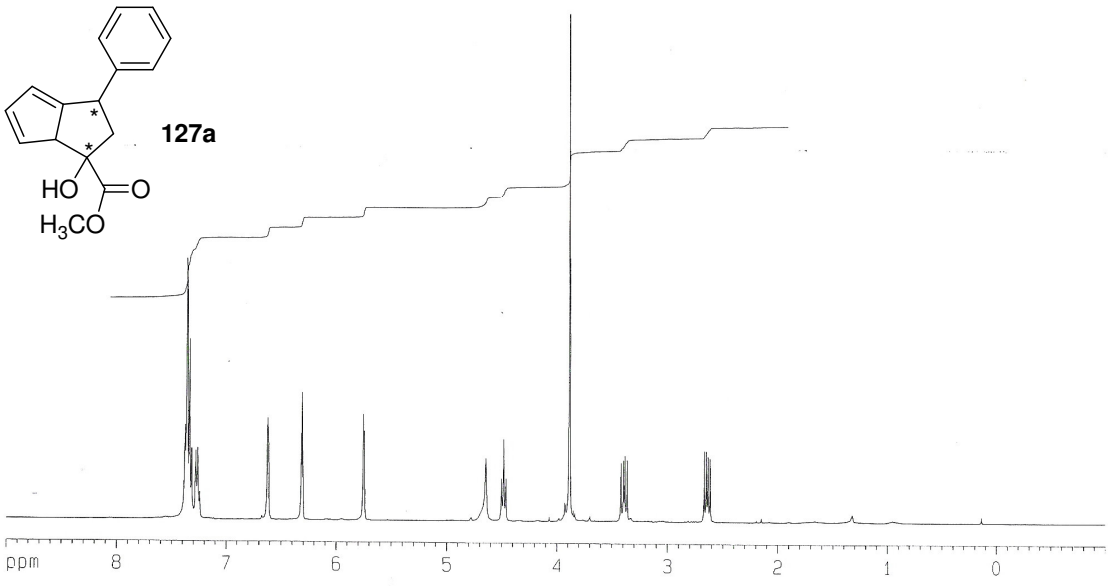


Figure 5.17. ^{1}H-NMR spectrum of the compound 127a

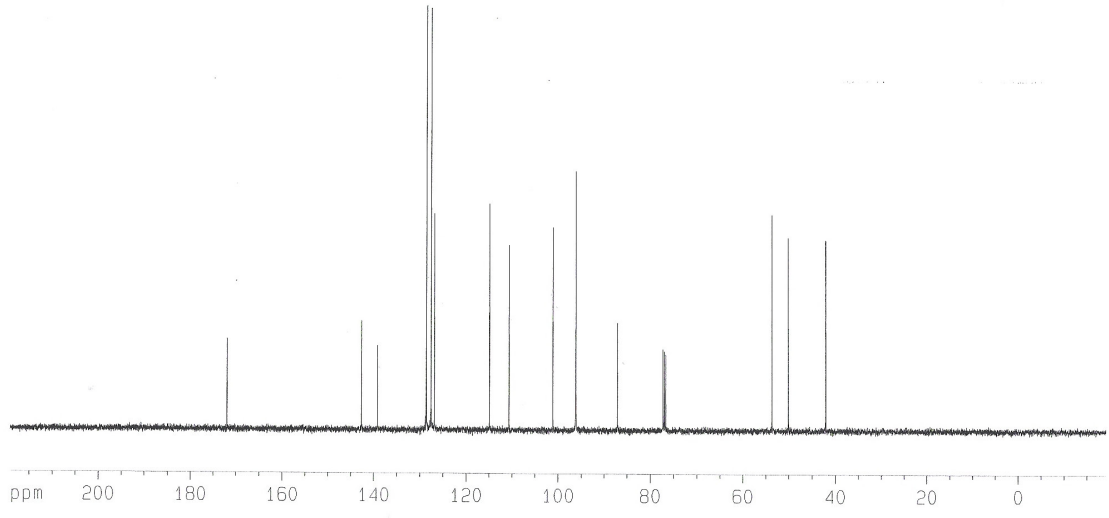


Figure 5.18. ^{13}C-NMR spectrum of the compound 127a

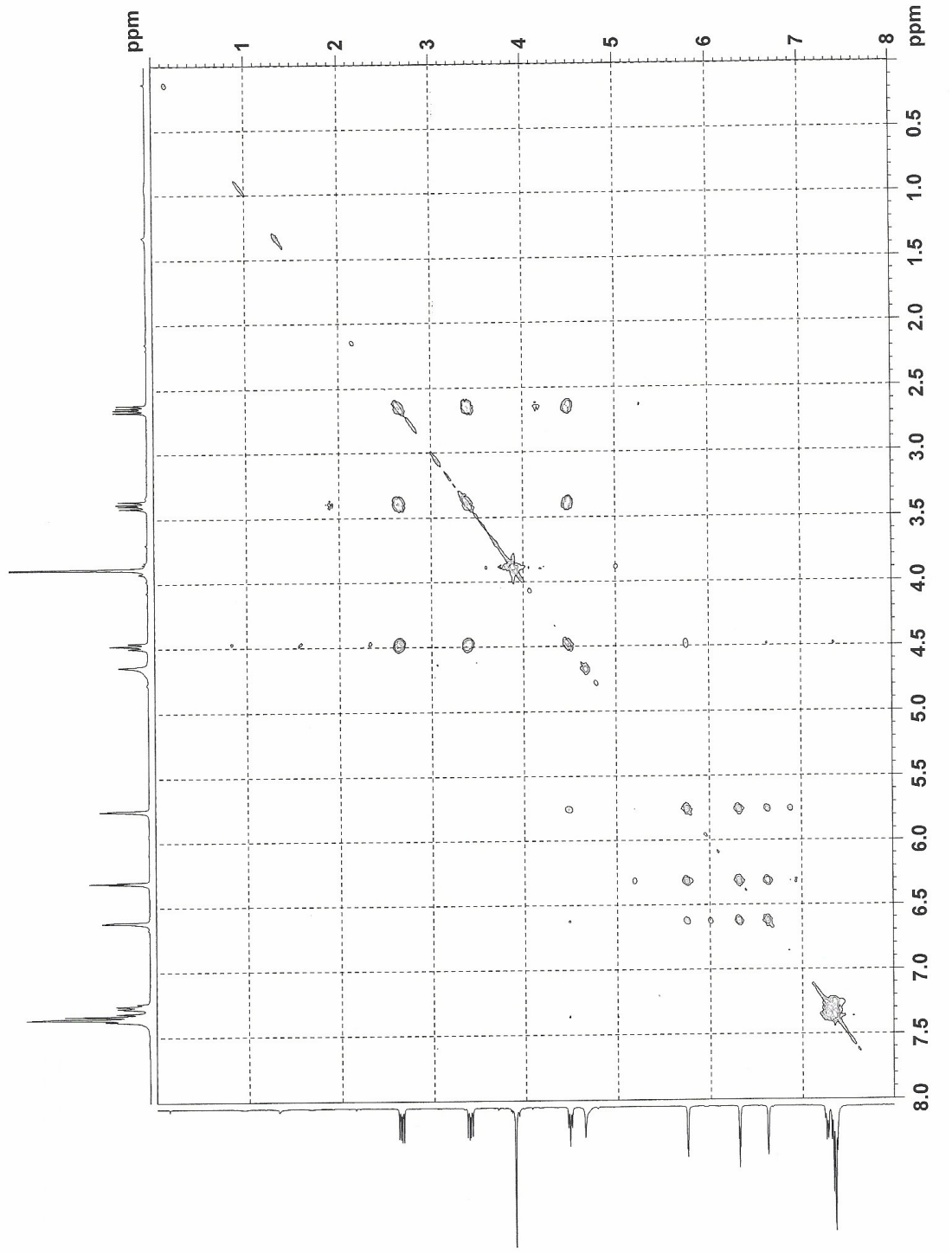


Figure 5.19. COSY spectrum of compound 127a

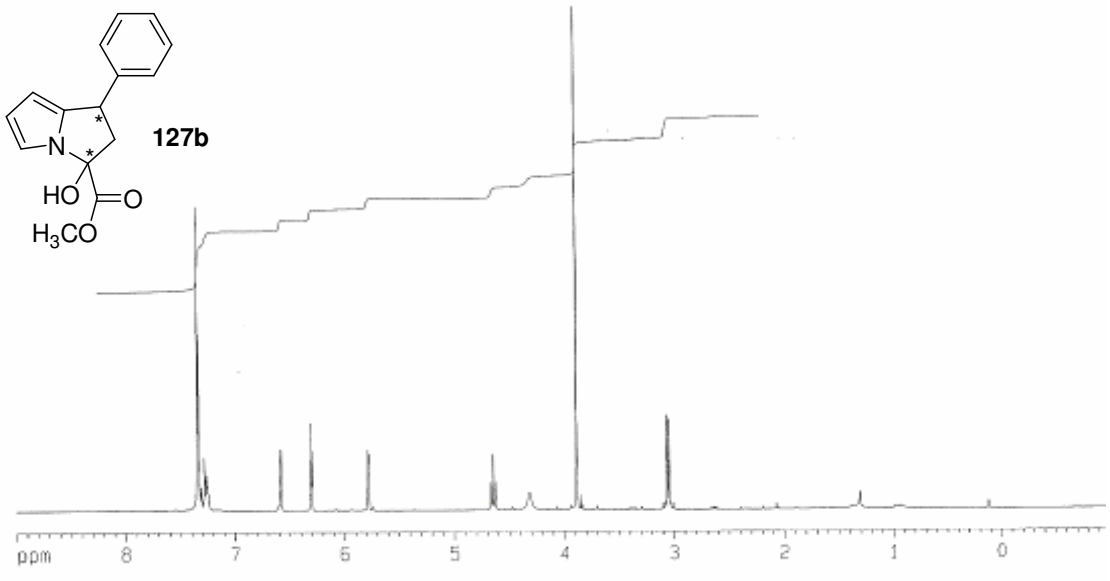


Figure 5.20. ^{1}H-NMR spectrum of the compound 127b

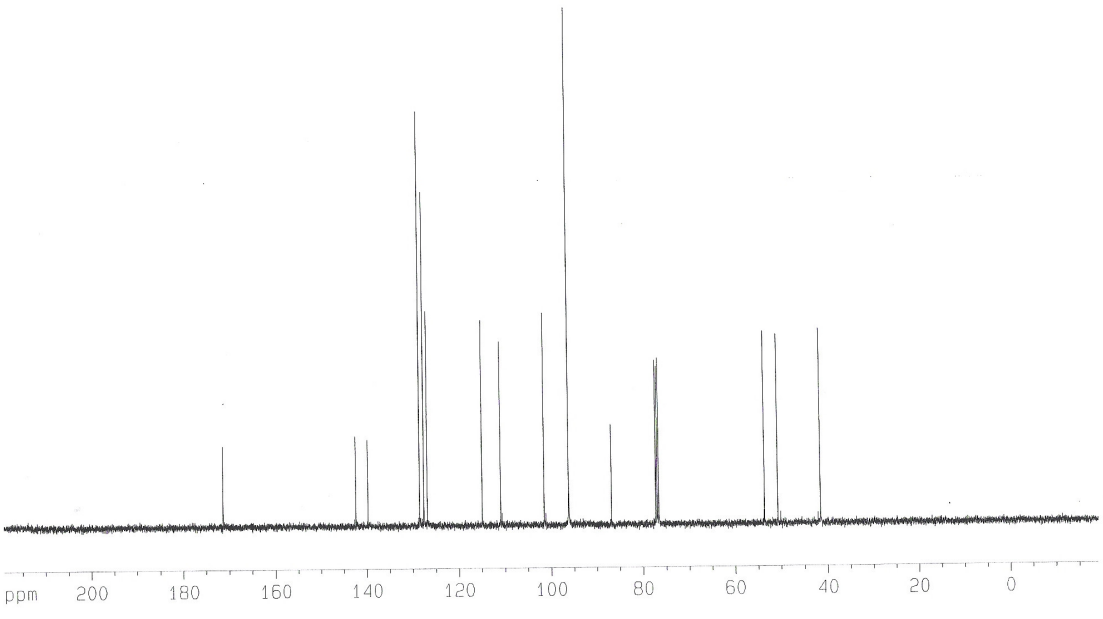


Figure 5.21. ^{13}C-NMR spectrum of the compound 127b

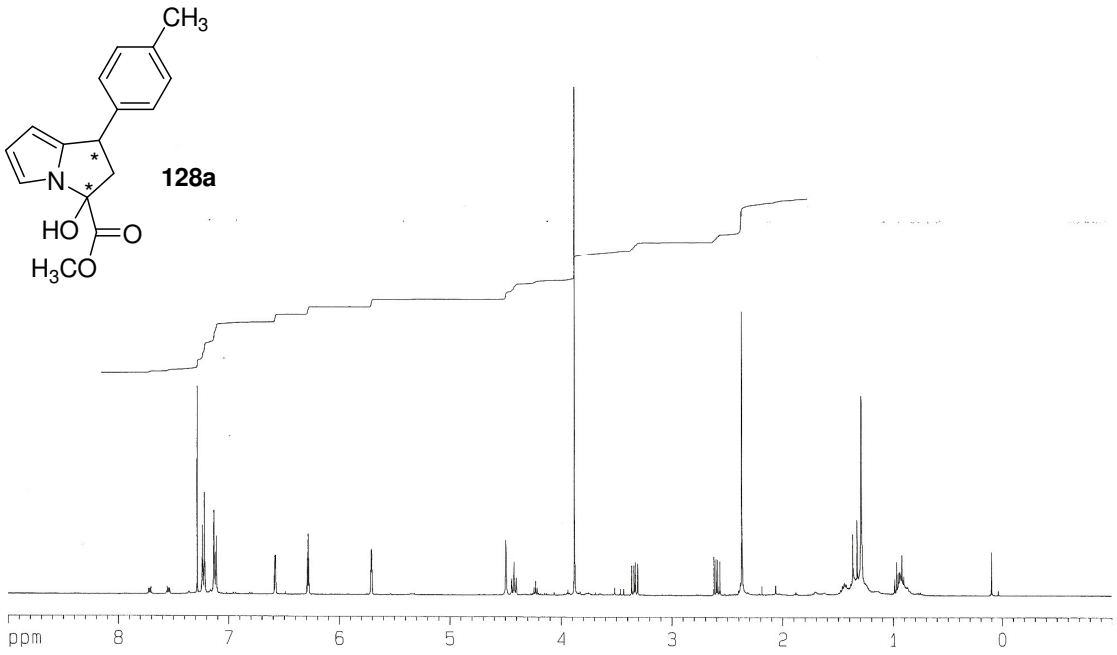


Figure 5.22. ^{1}H-NMR spectrum of the compound 128a

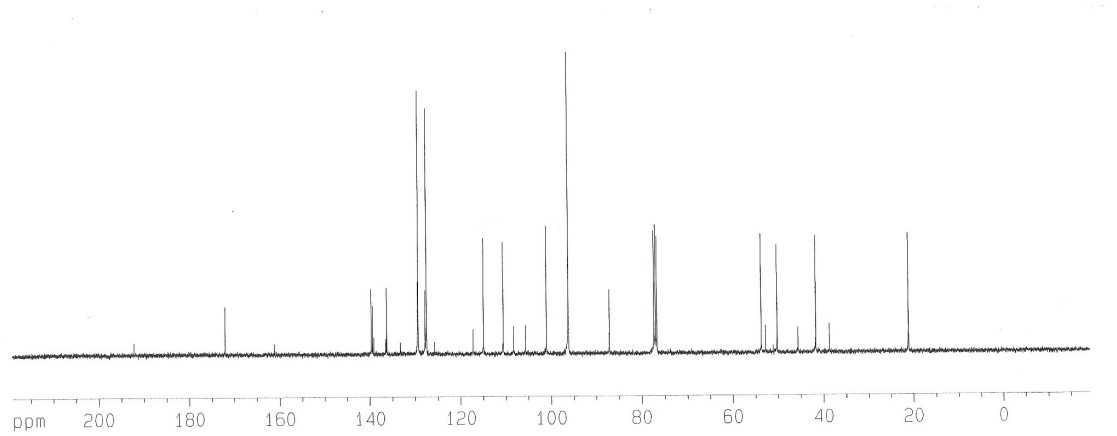


Figure 5.23. ^{13}C-NMR spectrum of the compound 128a

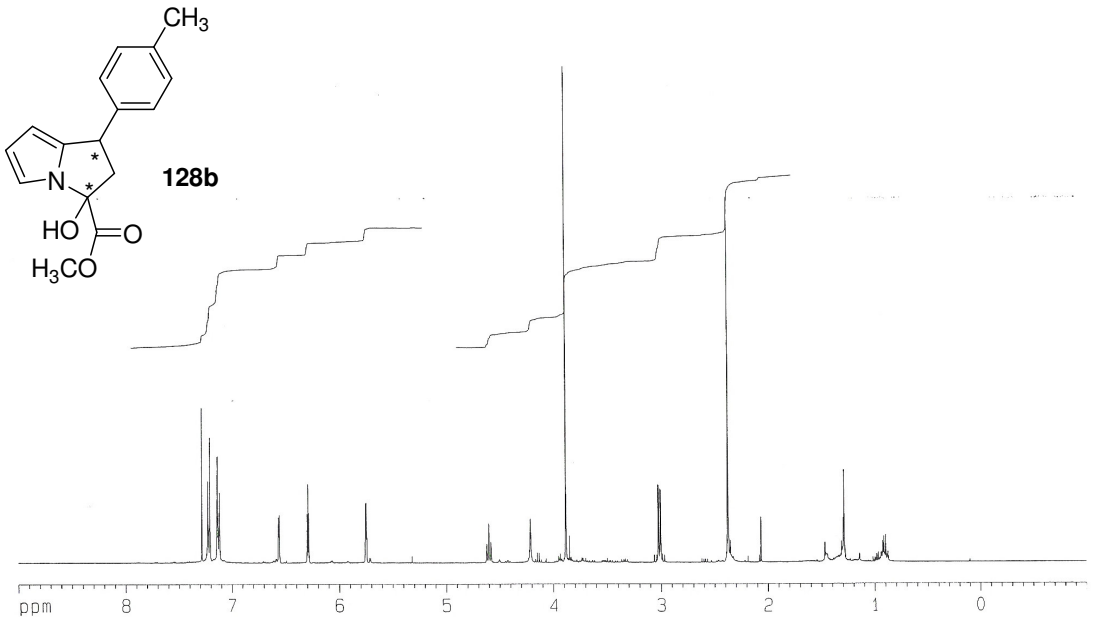


Figure 5.24. ^{1}H-NMR spectrum of the compound 128b

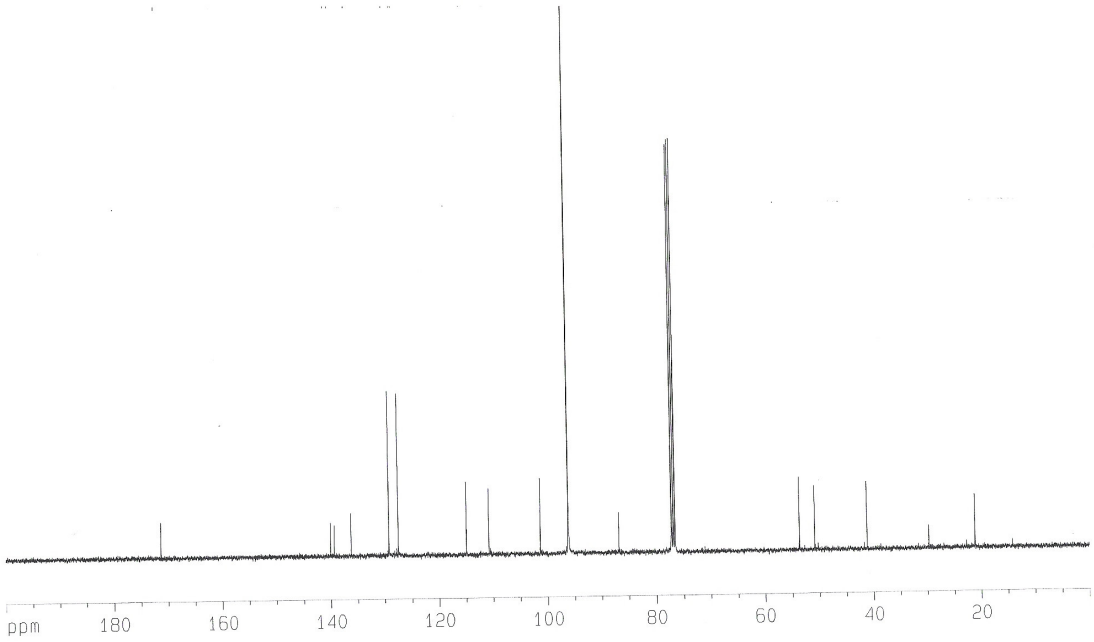


Figure 5.25. ^{13}C-NMR spectrum of the compound 128b

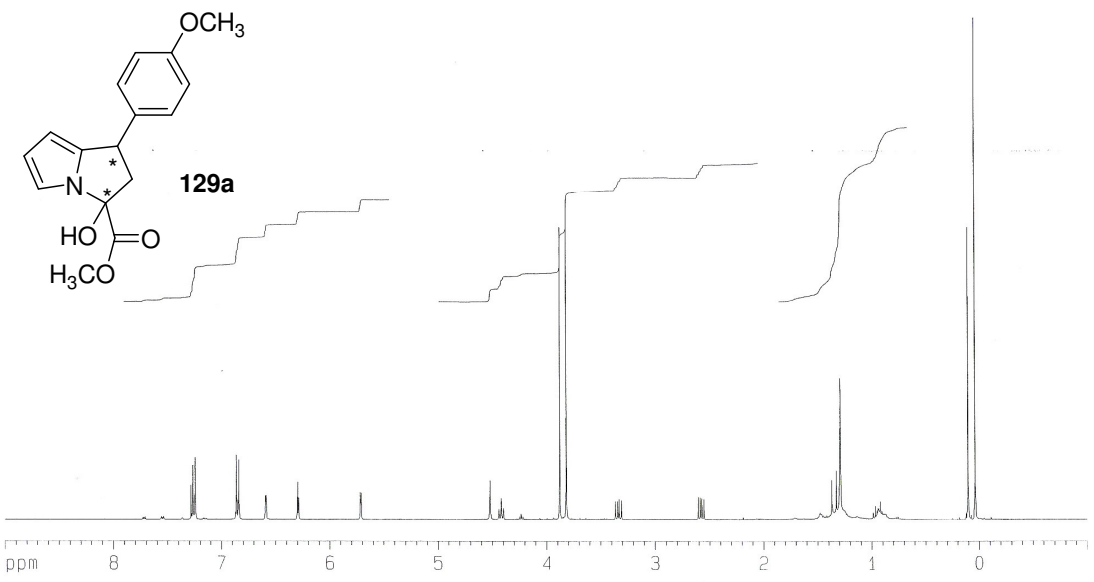


Figure 5.26. ^{1}H-NMR spectrum of the compound 129a

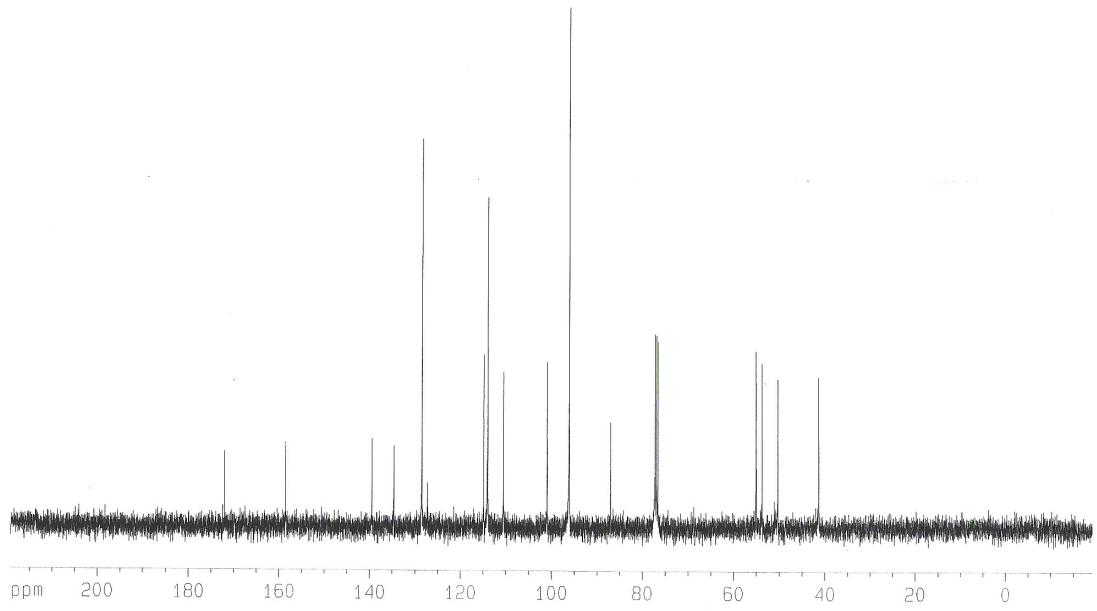


Figure 5.27. ^{13}C-NMR spectrum of the compound 129a

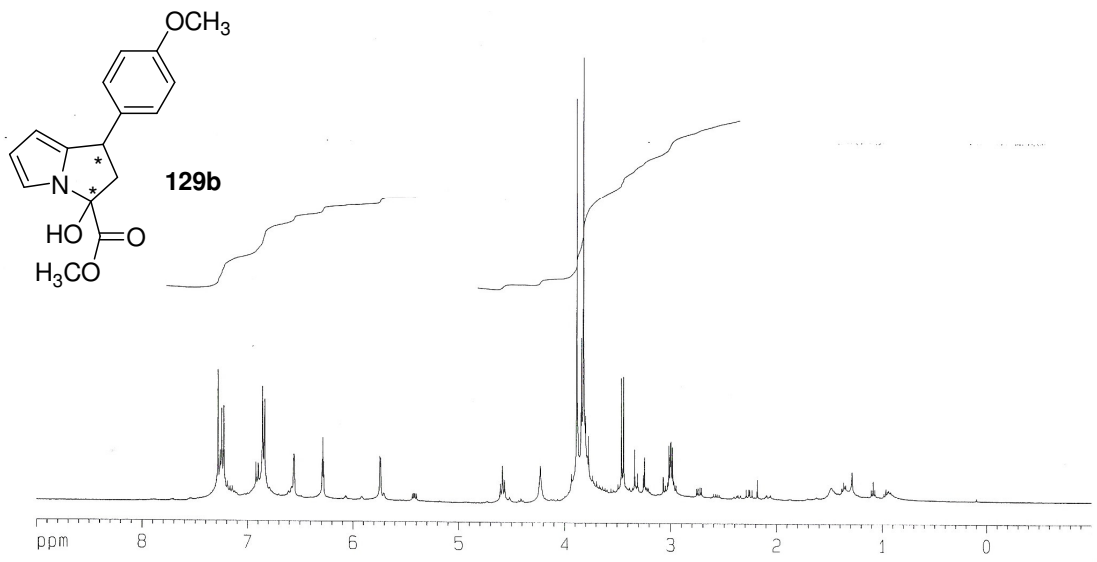


Figure 5.28. ^{1}H-NMR spectrum of the compound 129b

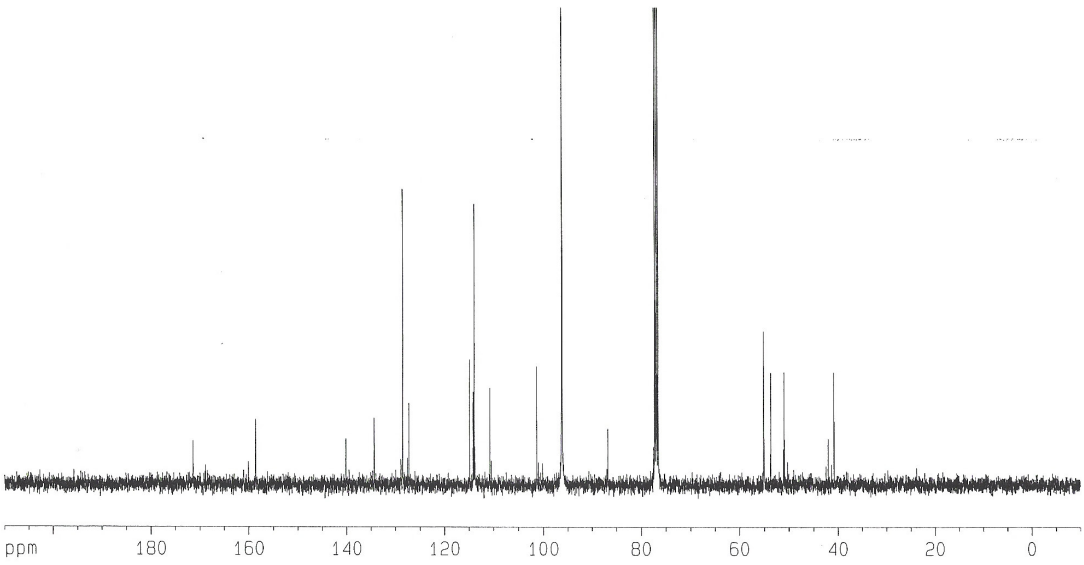


Figure 5.29. ^{13}C-NMR spectrum of the compound 129b

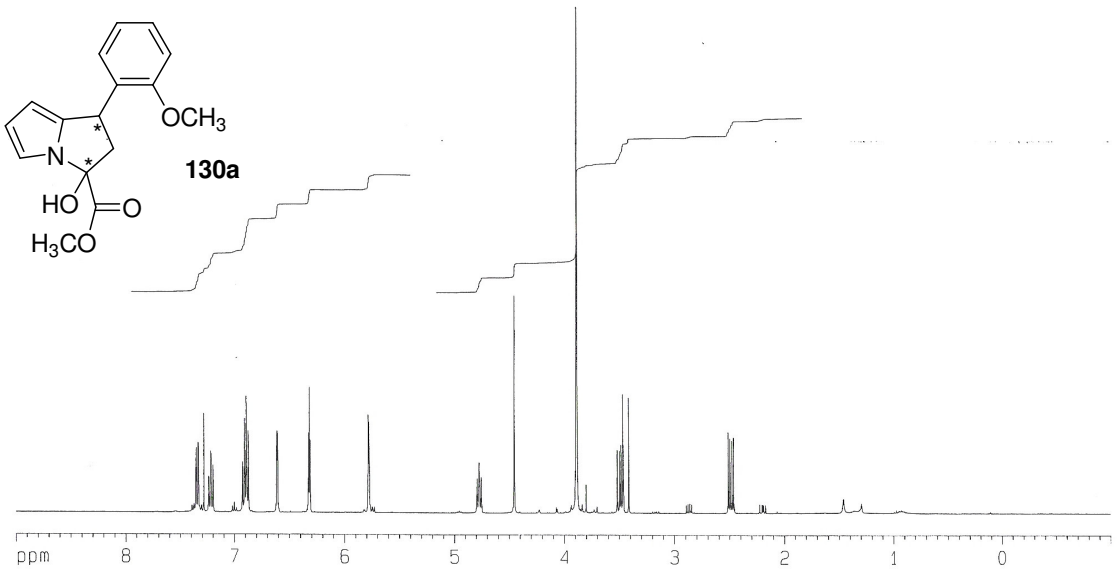


Figure 5.30. ^{1}H-NMR spectrum of the compound 130a

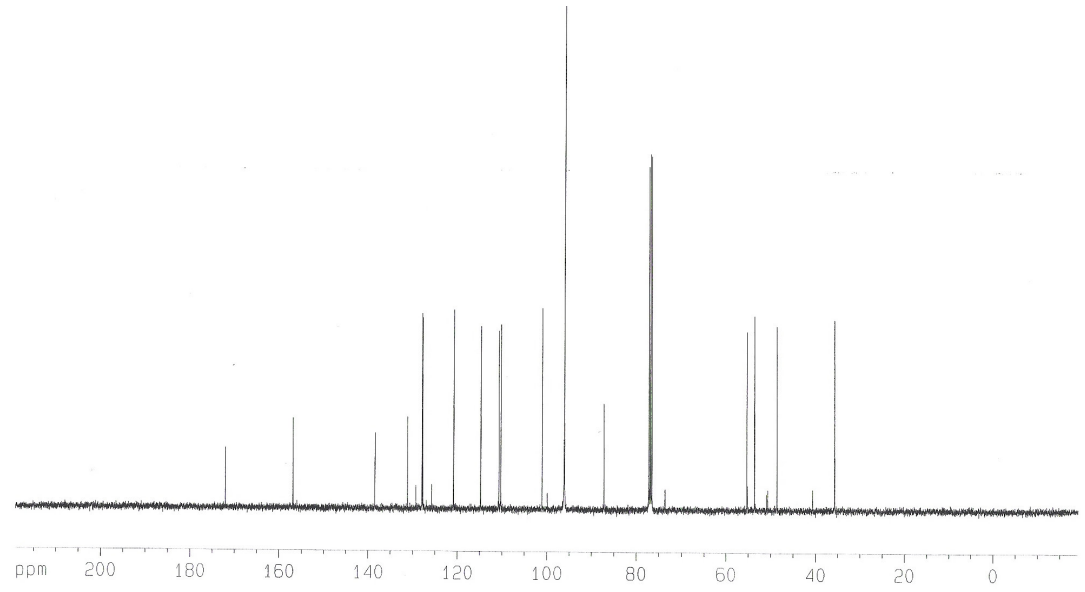


Figure 5.31. ^{13}C-NMR spectrum of the compound 130a

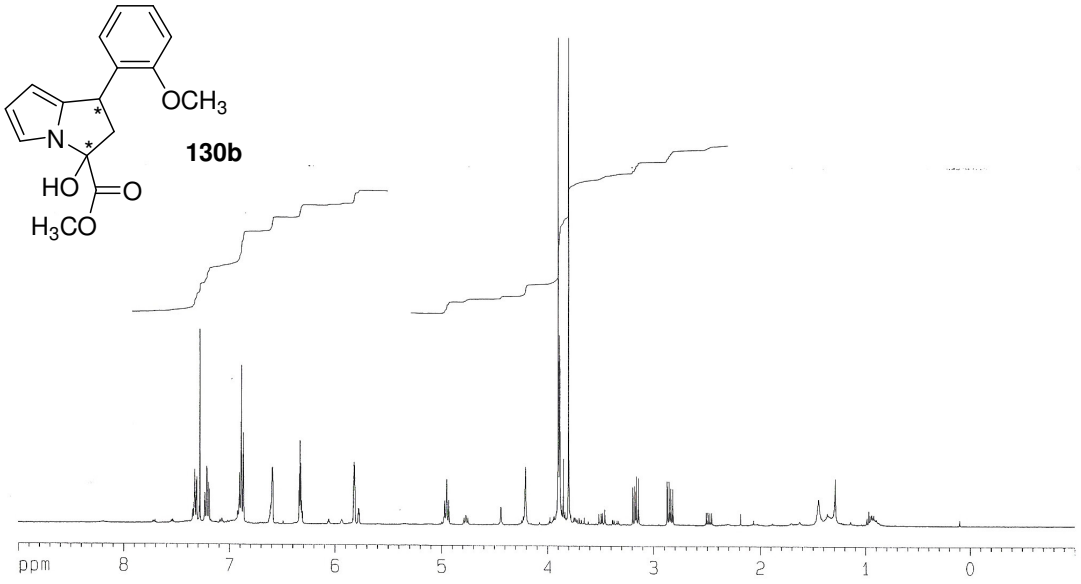


Figure 5.32. ^{1}H-NMR spectrum of the compound 130b

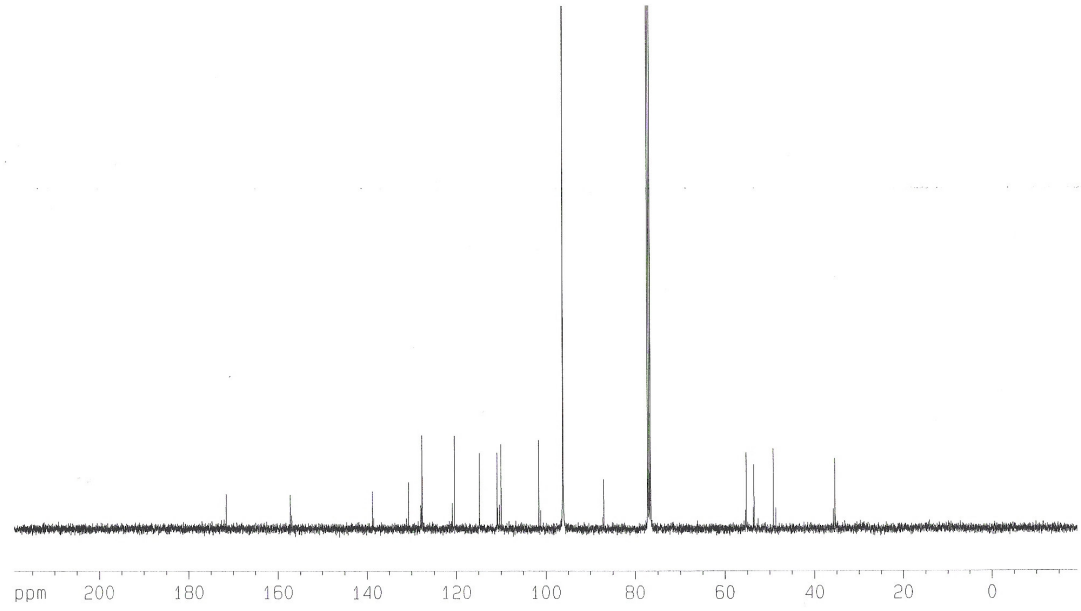


Figure 5.33. ^{13}C-NMR spectrum of the compound 130b

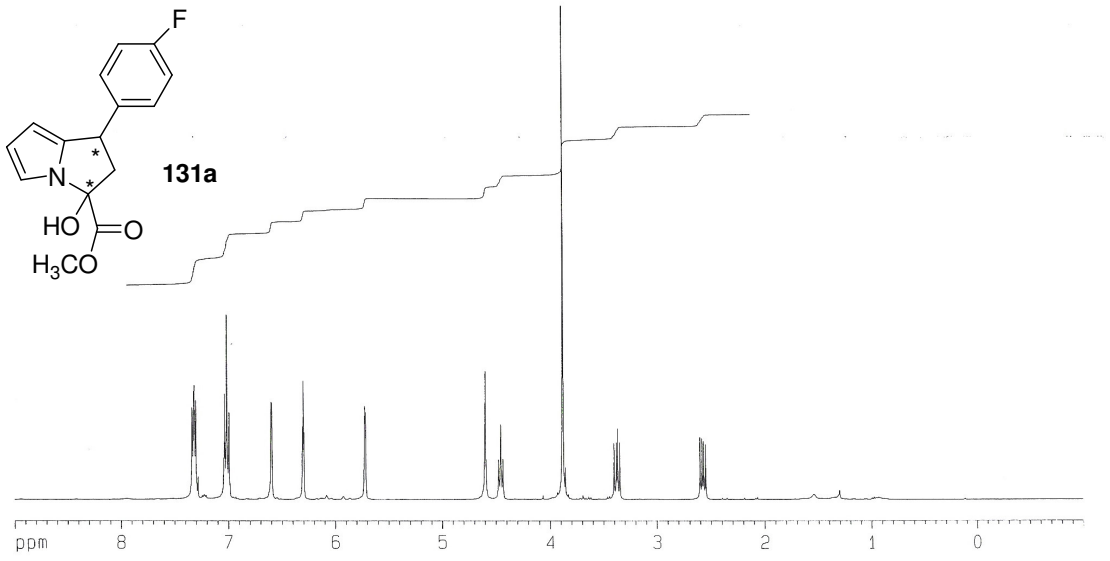


Figure 5.34. ^{1}H-NMR spectrum of the compound 131a

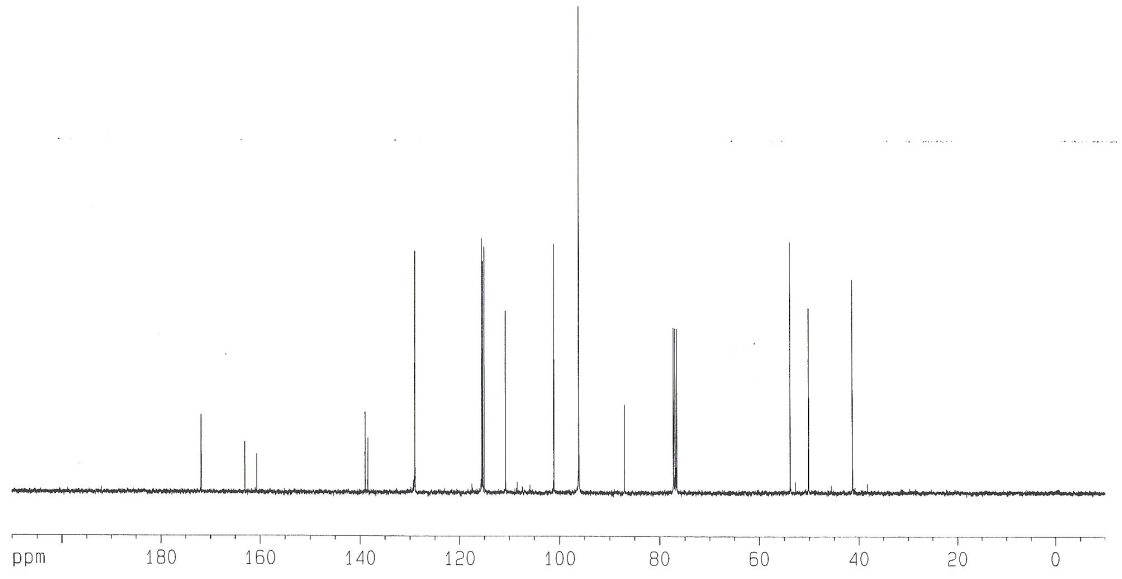


Figure 5.35. ^{13}C-NMR spectrum of the compound 131a

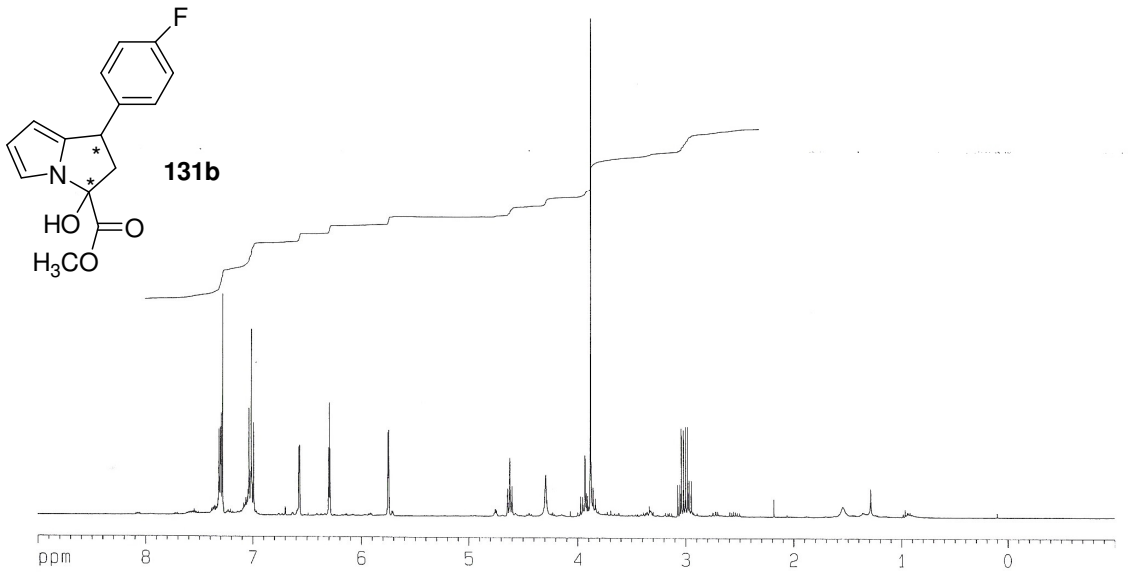


Figure 5.36. ^{1}H-NMR spectrum of the compound 131b

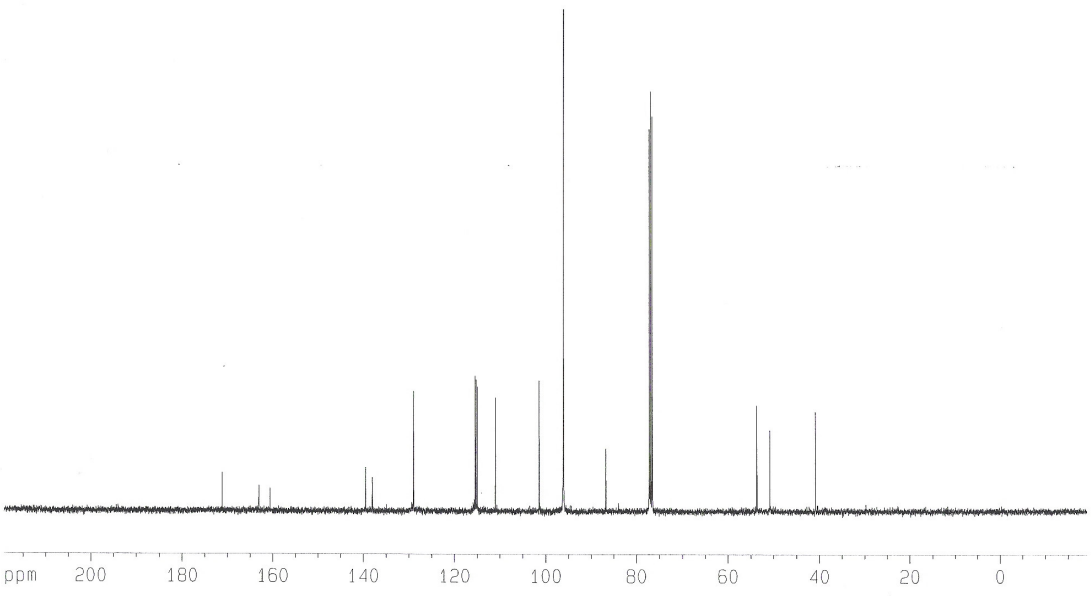


Figure 5.37. ^{13}C-NMR spectrum of the compound 131b

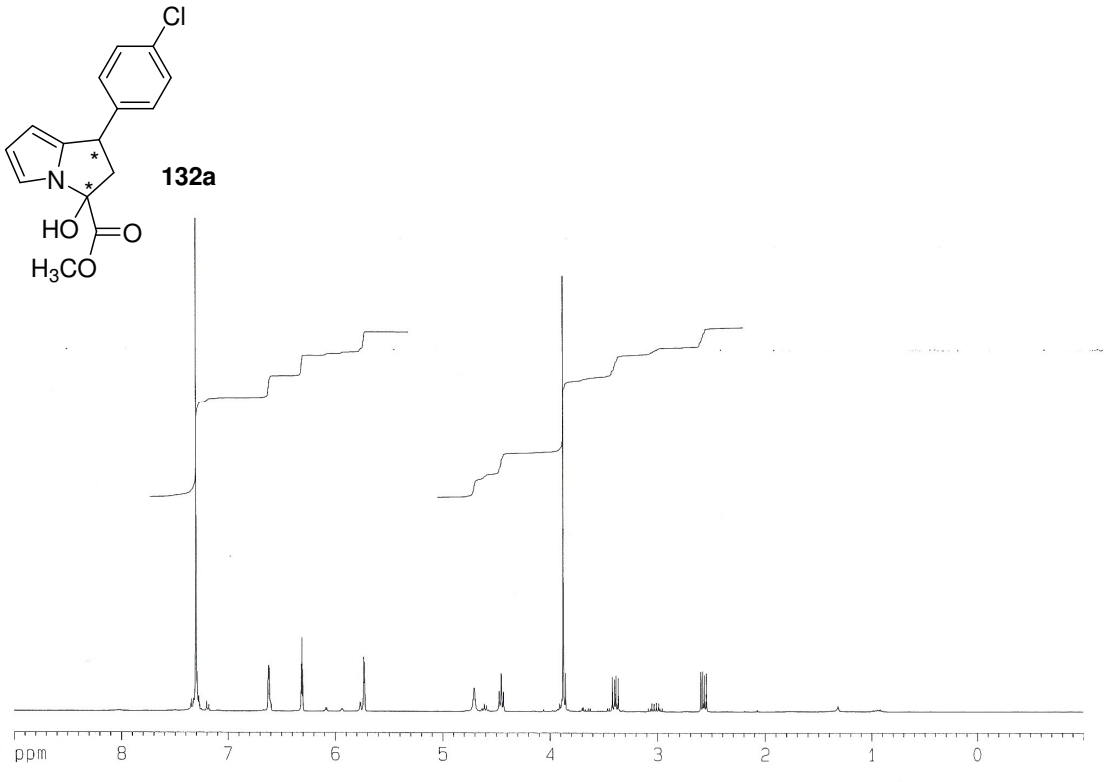


Figure 5.38. ^{1}H-NMR spectrum of the compound 132a

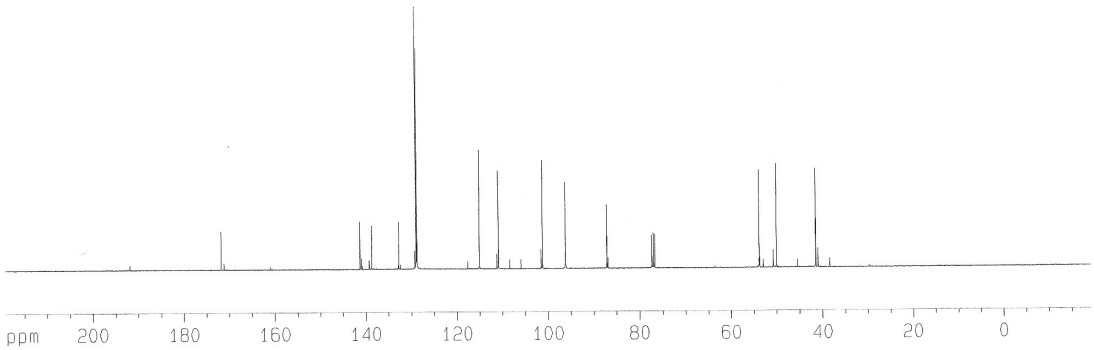


Figure 5.39. ^{13}C-NMR spectrum of the compound 132a

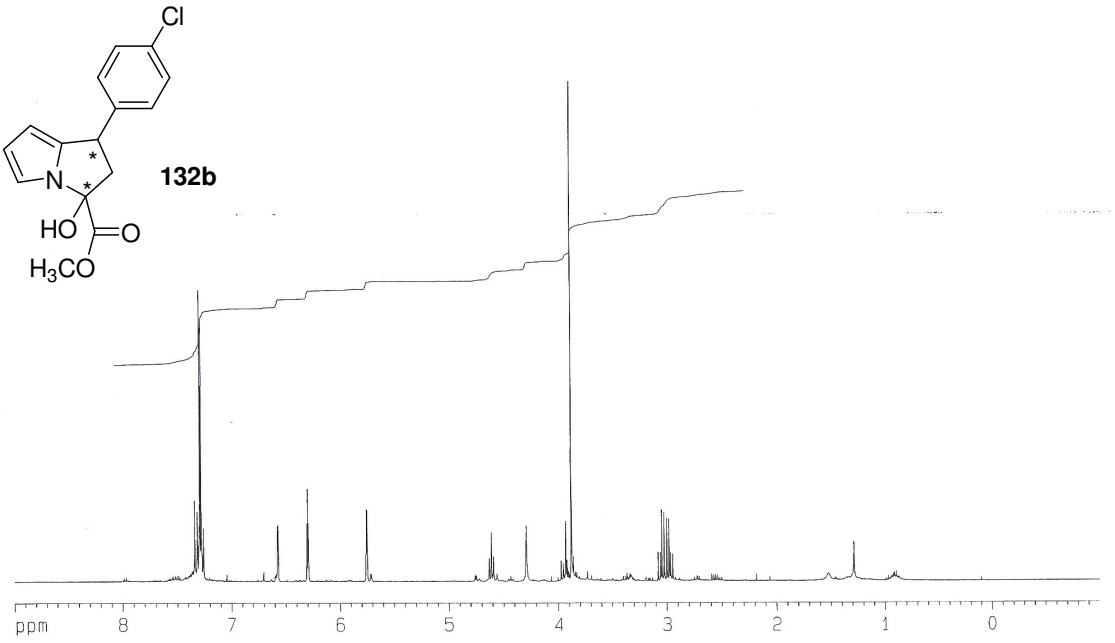


Figure 5.40. ^{1}H-NMR spectrum of the compound 132b

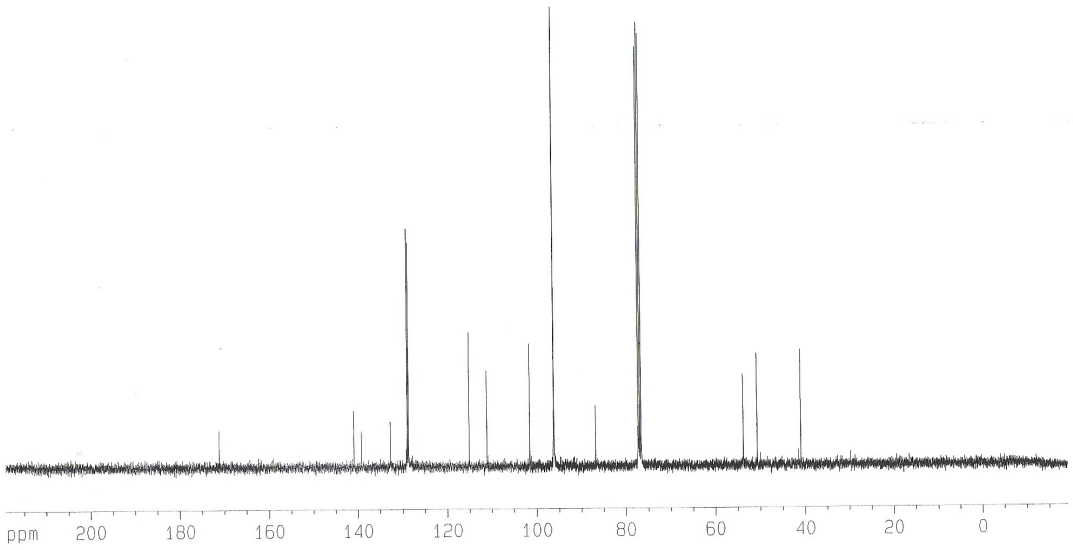


Figure 5.41. ^{13}C-NMR spectrum of the compound 132b

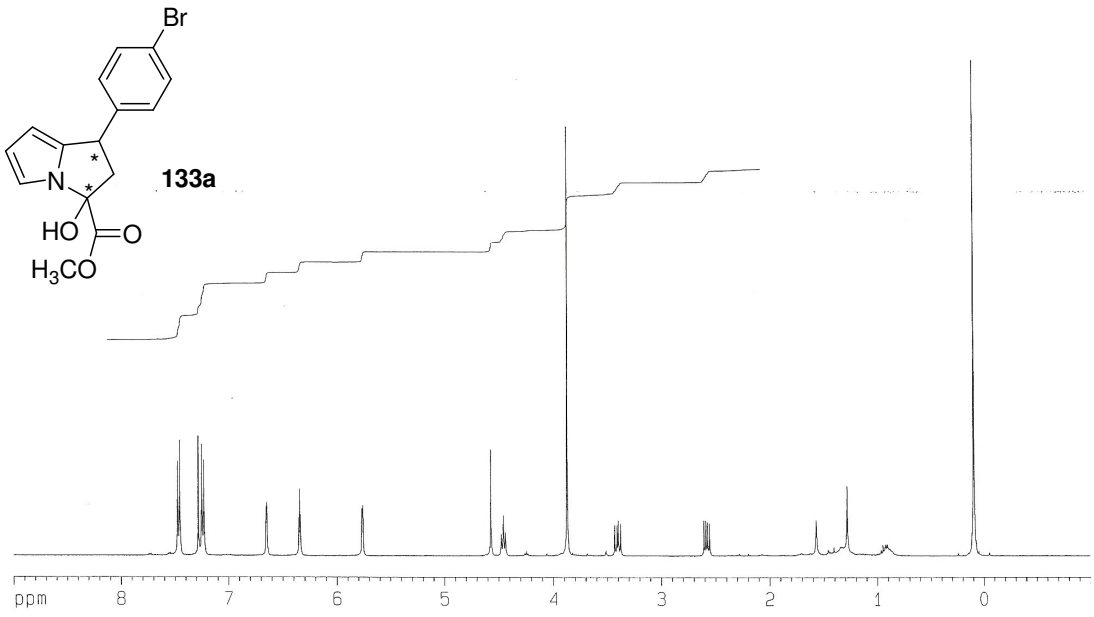


Figure 5.42. ^{1}H-NMR spectrum of the compound 133a

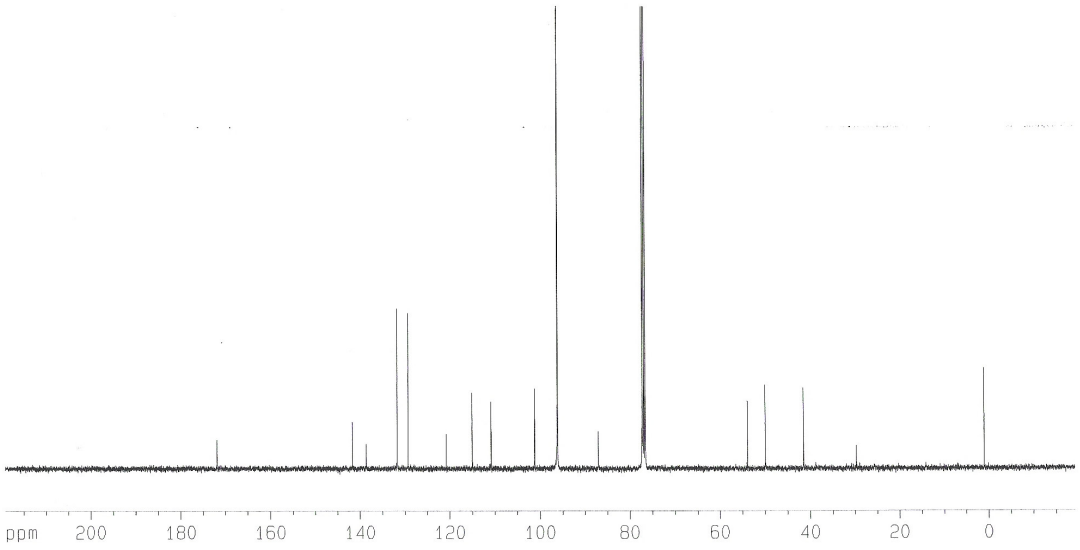


Figure 5.43. ^{13}C-NMR spectrum of the compound 133a

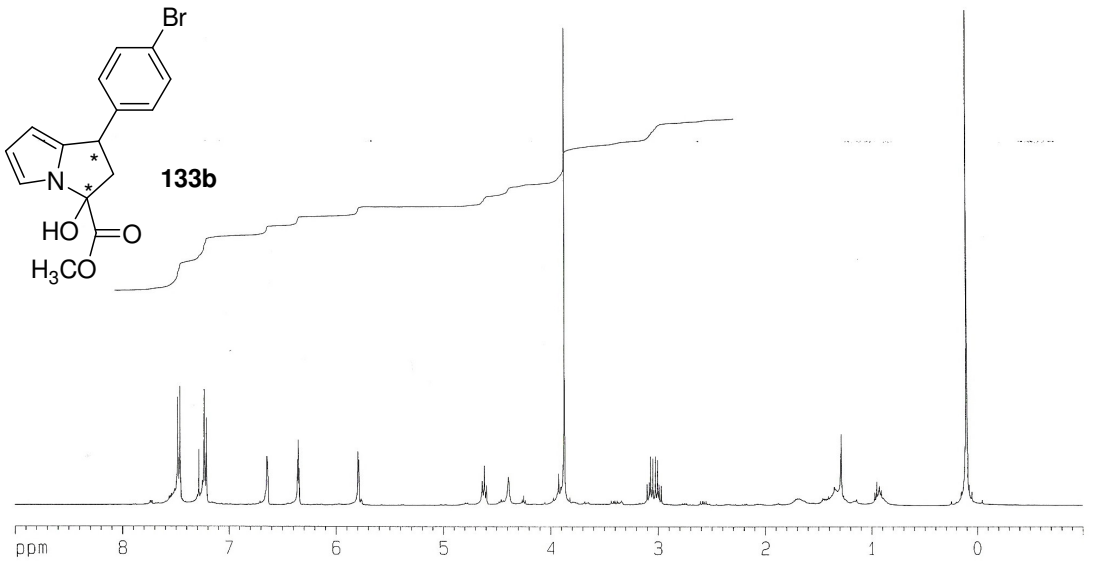


Figure 5.44. ^{1}H-NMR spectrum of the compound 133b

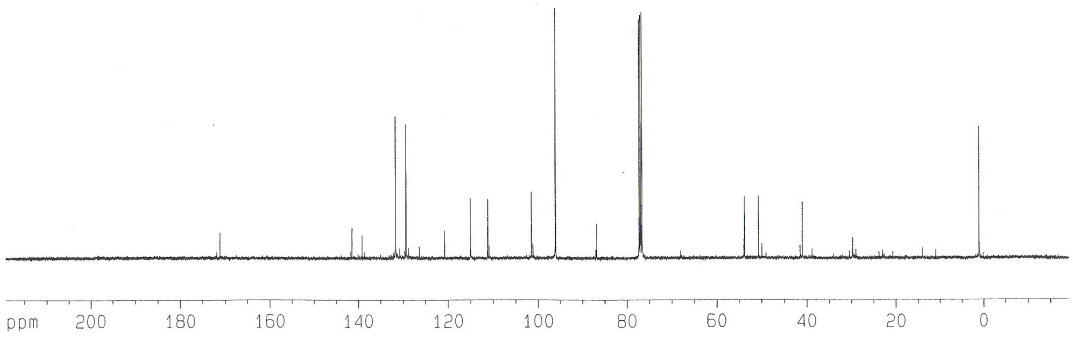


Figure 5.45. ^{13}C-NMR spectrum of the compound 133b

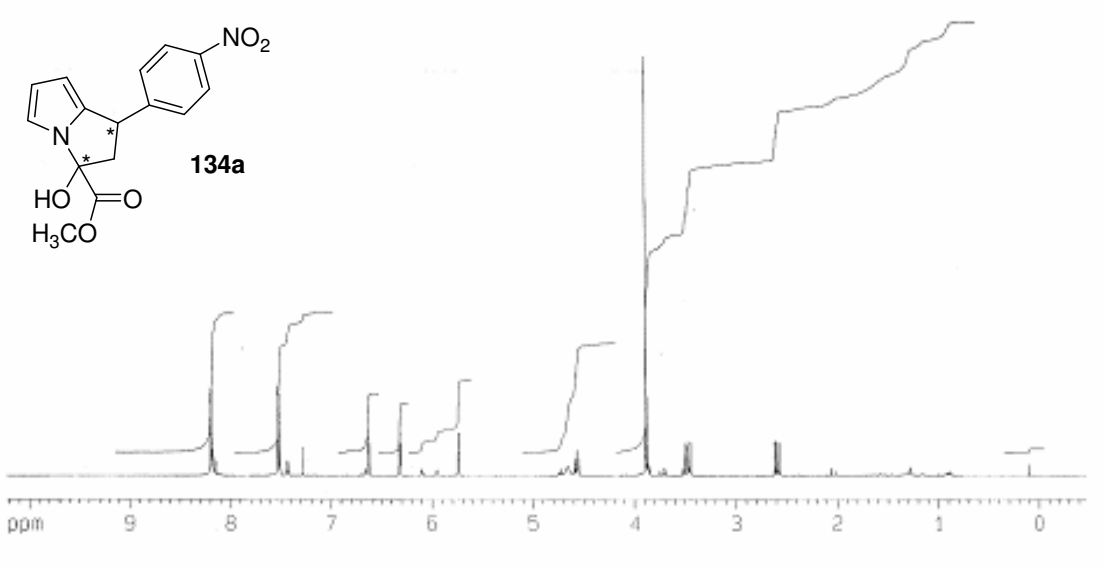


Figure 5.46. ^{1}H-NMR spectrum of the compound 134a

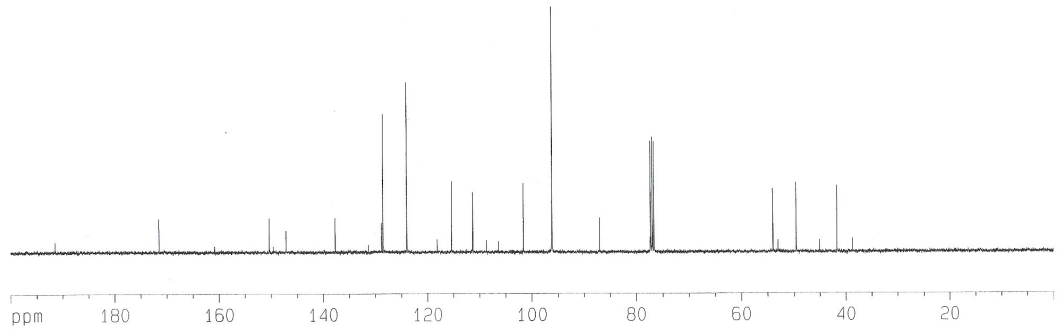


Figure 5.47. ^{13}C-NMR spectrum of the compound 134a

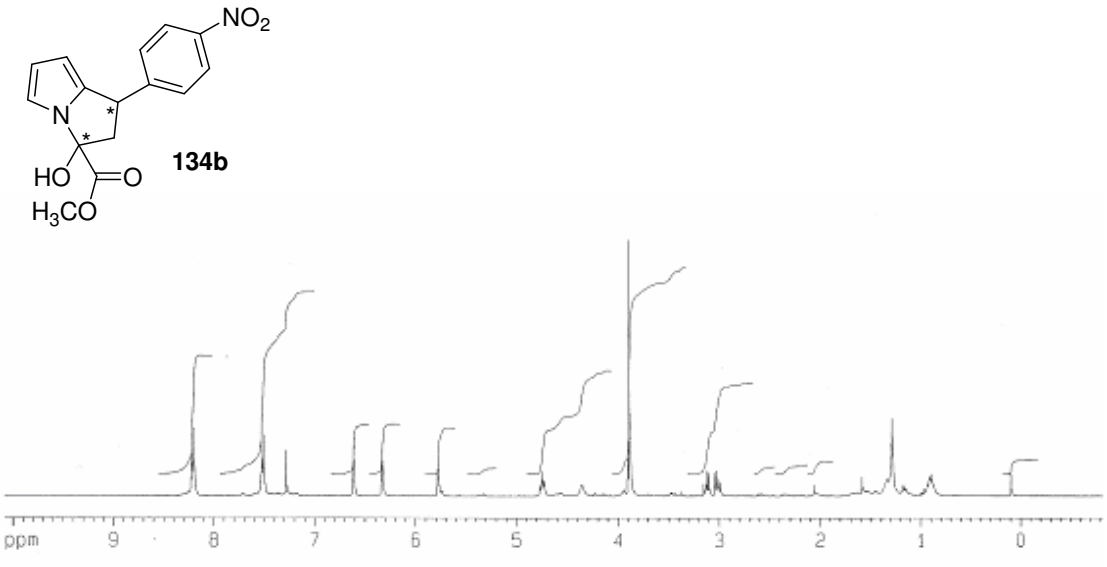


Figure 5.48. ^{1}H-NMR spectrum of the compound 134b

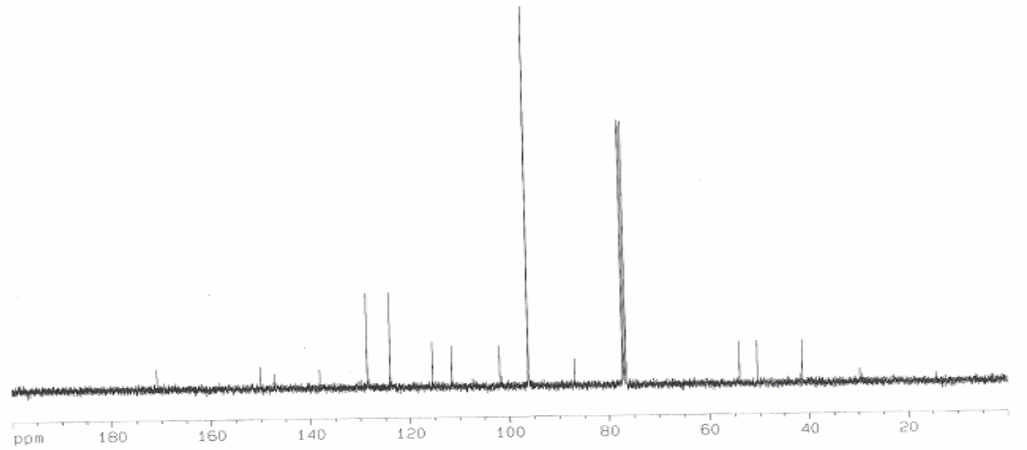


Figure 5.49. ^{13}C-NMR spectrum of the compound 134b

6.CONCLUSIONS

(*E*)-2-Oxo-4-phenylbut-3-enoic acid and derivatives were synthesized by the reaction of pyruvic acid and substituted benzaldehydes and then their methyl ester derivatives were obtained. The synthesized enone compounds and yields are:

(*E*)-Methyl 2-oxo-4-phenylbut-3-enoate (**111**): Yield: 55%.
(*E*)-Methyl 2-oxo-4-*p*-tolylbut-3-enoate **(112**): Yield: 55%.
(*E*)-Methyl 4-(4-methoxyphenyl)-2-oxobut-3-enoate(1**13**): Yield: 53%.
(*E*)-Methyl 4-(2-methoxyphenyl)-2-oxobut-3-enoate(**114**): Yield: 60%.
(*E*)-Methyl 4-(4-flourophenyl)-2-oxobut-3-enoate (**115**): Yield: 65%.
(*E*)-Methyl 4-(4-chlorophenyl)-2-oxobut-3-enoate (**116**): Yield: 60%.
(*E*)-Methyl 4-(4-bromophenyl)-2-oxobut-3-enoate (**117**): Yield: 55%
(*E*)-Methyl 4-(4-nitrophenyl)-2-oxobut-3-enoate (**118**): Yield: %55.

Novel 2-substituted pyrrole derivatives were successfully performed *via* regioselective Micheal Reaction of pyrrole with enone derivatives by using $M(OTf)_x$. The synthesized novel pyrrole compounds and yields are:

Methyl 2-oxo-4-phenyl-4-(1*H*-pyrrole-2-yl)butanoate (**119**): Yield: 83%.
Methyl 2-oxo-4-(1*H*-pyrrol-2-yl)-4-*p*-tolylbutanoate(**120**): Yield: 65%.
Methyl 4-(4-methoxyphenyl)-2-oxo-4-(1*H*-pyrrol-2-yl)butanoate (**121**): Yield: 65%.
Methyl-4-(2-methoxyphenyl)-2-oxo-4-(1*H*-pyrrol-2-yl)butanoate (**122**): Yield: 45%
Methyl 4-(4-flourophenyl)-2-oxo-4-(1*H*-pyrrol-2-yl)butanoate (**123**):Yield: 58%.
Methyl 4-(4-chlorolphenyl)-2-oxo-4-(1*H*-pyrrol-2-yl)butanoate (**124**): Yield: 49%.
Methyl 4-(4-bromophenyl)-2-oxo-4-(1*H*-pyrrol-2-yl)butanoate (**125**): Yield: 63%.
Methyl 4-(4-nitrophenyl)-2-oxo-4-(1H-pyrrol-2-yl)butanoate (**126**): Yield: 70%.

The effect of solvent, metal triflate and temperature were examined in synthesis of Methyl 2-oxo-4-phenyl-4-(1*H*-pyrrole-2-yl)butanoate (**119)**

The optimum reaction conditions are:

-THF is determined as a suitable solvent for this reaction

-The best metal trifilate is $Cu(OTf)_2$

-The optimum reaction temperature is rt.

Synthesized novel pyrrole derivatives were used to synthesize novel pyrrolizine derivatives. Novel pyrrolizine derivatives were obtained successfully in highest yield through the intramolecular cyclizations of methyl 2-oxo-4-phenyl-4-(1*H*-pyrrole-2-yl)butanoate derivatives. Diastereoisomers of the cyclization products were seperated and characterised by spectroscopic tecniques. Synthesized novel pyrrolizine derivatives are:

Methy 3-hydroxy-1-phenyl-2,3-dihydro-1 *H*-pyrrolizine-3-carboxylate (**127a,b**)
Methy 3-hydroxy-1-*p*-tolyl-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (**128a,b**)
Methyl-3-hydroxy-1-(4-methoxyphenyl)-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (**129a,b**)
Methyl-3-hydroxy-1-(2-methoxyphenyl)-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (**130a,b**)
Methyl-1-(4-flourophenyl)-3-hydroxy-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (**131a,b**)
Methyl-1-(4-chlorophenyl)-3-hydroxy-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (**132a,b**)
Methyl-1-(4-bromophenyl)-3-hydroxy-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate (**133a,b**)
Methyl-1-(4-nitrophenyl)-3-hydroxy-2,3-dihydro-1H-pyrrolizine-3-carboxylate(**134a,b)**

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