TRANSFORMATION OF CYCLOHEXANONE DERIVATIVES TO BICYCLIC FURAN AND PYRROLE DERIVATIVES

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ABSTRACT

TRANSFORMATION OF CYCLOHEXANONE DERIVATIVES TO BICYCLIC FURAN AND PYRROLE DERIVATIVES

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Tetrahydrobenzofurans and tetrahydroindoles are two very valuable classes of substances which have wide usage area; either as starting materials for drug substances or many other compounds which have fused heterocyclic rings in their structures and pharmacophore for many complex natural products; syntheses of derivatives of these compounds with different substitution patterns, is an exciting challenge for many scientists. Benzofuran and tetrahydroindole derivatives, which are potent bioactive substances, are synthesized from various cyclohexanone derivatives that are allylated by Stork-enamine or $Mn(OAc)_3$ mediated allylation methods. Allylated ketones are later transformed to benzofuran derivatives upon treatment with base or tetrahydroindole derivatives upon treatment with primary amines.

Keywords: Benzofuran, tetrahydrobenzofuran, tetrahydroindole, natural product

ÖZ

SİKLOHEKZANON TÜREVLERİNİN ÇİFT HALKALI FURAN VE PİROL TÜREVLERİNE DÖNÜŞTÜRÜLMESİ

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Tetrahidrobenzofuranlar ve tetrahidroindoller, gerek ilaç maddelerinin başlangıç maddesi olarak, gerekse yapısında heterohalkalı bileşik grupları bulunan çeşitli bileşiklerin ve doğal ürünlerin başlangıç maddesi olarak kullanılabilecek oldukça değerli iki bileşik sınıfıdır ve bu çeşit bileşiklerin değişik türevlerinin sentezi halen sentetik organik kimyanın önemli başlıklarından birisidir. Bu çalışmada biyoaktif özelliğe sahip olabilecek benzofuran ve tetrahidroindol türevleri, Stork-enamini veya $Mn(OAc)_3$ alilasyonu yöntemiyle alillenmiş siklohekzanon türevlerinden sentezlenmiştir. Alillenmiş ketonlar daha sonra baz ile tepkime verdirilerek benzofuran türevlerine ya da primer aminlerle tepkime verdirilerek tetrahidroindol türevlerine dönüştürülmüştür.

Anahtar kelimeler: Benzofuran, tetrahidrobenzofuran, tetrahidroindol, doğal ürün

To my family

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LIST OF ABBREVIATIONS

DAMP: Diazomethylphosphonate

DDQ: 2,3-Dichloro-5,6-dicyano-benzoquinone

DIBAL-H: Diisobutylaluminum hydride

DMF: *N*,*N*-Dimethyl formamide

DMSO: Dimethyl sulfoxide

DPPF: Diphenylphosphinoferrocene

IMD: 2-Iodomethyl-1,3-dioxalane

LDA: Lithium diisopropylamide

m-CPBA: *m*-Chloroperbenzoic acid

NMP: *N*-Methyl -2- pyrrolidone

PTSA: *p*-Toluenesulfonic acid

TEA: Triethylamine

THF: Tetrahydrofuran

TMSCl: Trimethylsillyl chloride

CHAPTER 1

INTRODUCTION

1.1 Indoles

History of indole **1** chemistry dates back to birth of organic chemistry as a science (Figure 1) by use of indigo. It is recorded that the mummy cloths of the ancient Egyptians were colored with indigo; the early writings in Sanskrit explain its use by oriental nations; Romans used it as a highly prized dye.

Erdmann and Laurent used nitric acid for oxidation of indigo at 1841. Baeyer and Knop reduced isatin to dioxindole and oxindole in 1866, and later in the same year Baeyer accomplished realizing the last step in the degradation of the blue dye to the parent substance, indole, by pyrrolytic reduction of oxindole with zinc dust. Baeyer had earlier proposed the existence of this parent substance and named it accordingly.

From 1866 up through the first decade of the twentieth century, indole chemistry was a major research subject in numerous laboratories. As other dyestuffs were developed, the interest in indole chemistry diminished in intensity. In fact up to early 1930's, indole was unavailable commercially in America. The researches in 1930's which showed that a large number of alkaloids contain the indole nucleus, the recognition of the importance trytophan in animal and human nutrition, and the discovery of the plant hormones served to bring about a renaissance in indole chemistry that has been most fruitful. Together with synthetic indole, *dl*-tryptophan and several other indole derivatives are readily available today in quantity, but the study of practical methods for their preparation has greatly enriched organic chemistry.

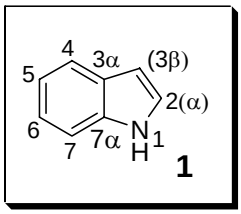
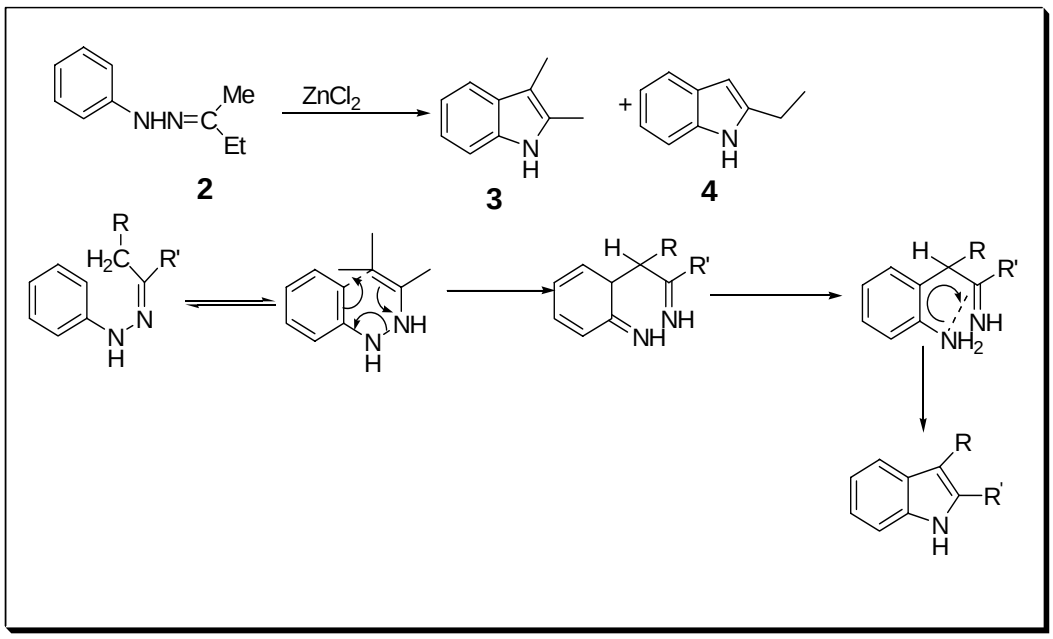


Figure 1

Indole **1** (in Figure1) is the trivial name of a benzopyrrole in which the 2- and 3- carbon atoms of the nitrogen ring (pyrrole) are members of a benzenoid nucleus. The systematic name for this compound is 1-benzo[*b*] pyrrole. Two different systems have been usually employed in nomenclature of indole compounds. In the more predominant, and more recent of the two systems,the atoms are numbered consecutively, beginning from nitrogen , counterclockwise around the two fused rings with the bridgehead carbons being denoted by 3α and 7α (Figure 1). According to the older and more limited system, the two open carbons of the pyrrole ring as designated α-, and β-, and the substituted indoles are prefixed with N-, α-, or β-, depending on the site of the attachment of the substituent. In this treatment the former and more recent system is employed. In both systems the radical names are formed in customary fashion, e.g., 3-indolyl-, β-indolyl-. Fischer, in 1866, proposed another system of nomenclature, which is used for a short time. In this system the nitrogen ring was labeled Pr and the atoms numbered 1 to 3 beginning with nitrogen, and the benzenoid ring was labeled B and the atoms numbered 1 to 4 beginning with the open carbon atom next to the bridgehead carbon adjacent to nitrogen. Many substituted indoles have got trivial names, such as skatole, methylketole, gramine, and trytophane, which have become firmly used in literature.

Through the years certain methods have been developed for obtaining indole and its derivatives. Indole occurs to some extent in coal tar, jasmine flowers, and orange-blossom oil, synthetic methods for its preparation have proved to be more useful when compared with the isolation from the natural sources. Indole and certain of its homologs have been synthesized from oxygenated indole derivatives. The conversion of these derivatives together with their synthesis constitute feasible means have assumed commercial significance for the manufacture of indole itself. In 1866, Baeyer discovered that when oxindole was heated with zinc dust, it transformed into the parent substance, indoles. This method has been applied to various substituted indoles.[1] The cyclization of arylhydrazones to indoles, widely known as the Fischer indole synthesis (depicted in scheme 1), remains the most versatile and widely applied reaction for the construction of the indole ring. The conversion of the phenylhydrazone of ethyl methyl ketone **2** to 2,3-dimethylindole **3** and small amounts of 1-ethyl indole **4** can serve as an example for discussion. The mechanism of this cyclization has been the subject of considerable investigation and the mechanism originally proposed by Robinson and Robinson as reformulated by Carlin and Fisher has obtained wide acceptance.[2]



Scheme 1: Reaction mechanism for Fischer indole synthesis

Crystallinity of substances are dependent upon, among other factors, shape, symmetry, and polarity. Indole is flat and relatively polar (dipole moment of 2.38 D), but it has got a low order of symmetry. It has a melting point of 52°-54° C, which is lower than that of the more symmetrical, but less polar naphtalene (80-81°), but higher than that of the less polar, unsymmetrical indene (-5 to -3°). Substitution of indole with small substituents which do not significantly change the polarity or introduce intermolecular hydrogen bonding does not greatly increase the melting point. For instance, 2-methylindole melts at 58-60°C, 5-methoxyindole at 56-58°C , and 5-chloroindole at 69-71°C . In contrast, groups that engage in strong intermolecular hydrogen bonding afford much higher melting points. Because of the fact, indole 3- carboxaldehyde and indole-3-carboxylic acid melt at 198-199° C and 235-236° C respectively.

The low melting point and moderate polarity of indole provides good solubility in a wide range of solvents, including petroleum ether, benzene,

chloroform and alcohol. It is slightly soluble in water at 20° C (1 part in 540), but quite soluble in boiling water.

Indoles may be transferred to both their conjugate acids and conjugate bases. Aqueous solutions of appropriate strong acids or bases in high concentration generally affect these conversions. A high concentration of hydrogen ion is necessary to provide protonation of indoles. Abstraction of hydrogen from the N-H bond of indoles occurs in the presence of concentrated aqueous alkali systems containing stronger bases.

1.2 4,5,6,7-Tetrahydroindoles and their derivatives

4,5,6,7-tetrahydroindole **5** constitute core of an interesting class of bicyclic pyrrole compounds where the pyrrole ring is fused on a cyclohexane ring (Figure 2). They are found in the structure of many biologically active natural products which have important pharmacological properties or used as (η^5) metal-coordinating ligands.[4-7] Because of their properties, synthesis of 4,5,6,7-tetrahydroindoles and their derivatives with different substitution patterns, is an exciting challenge for many scientists.

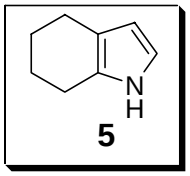
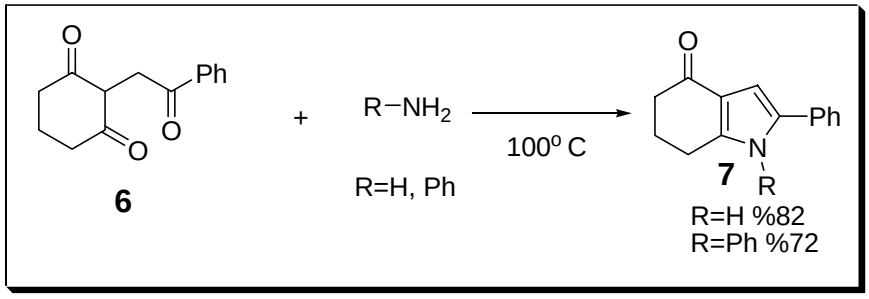


Figure 2

Early studies in synthesis of 4,5,6,7-tetrahydroindole derivatives includes information on development of new synthetic procedures for cyclization reactions and reports on interesting reduction products of indoles. The earliest example available for the synthesis of 4,5,6,7-tetrahydroindole derivatives dates back to 1955 by Stetter and Sienhold[8] by a condensation reaction of **6** yielding 4-

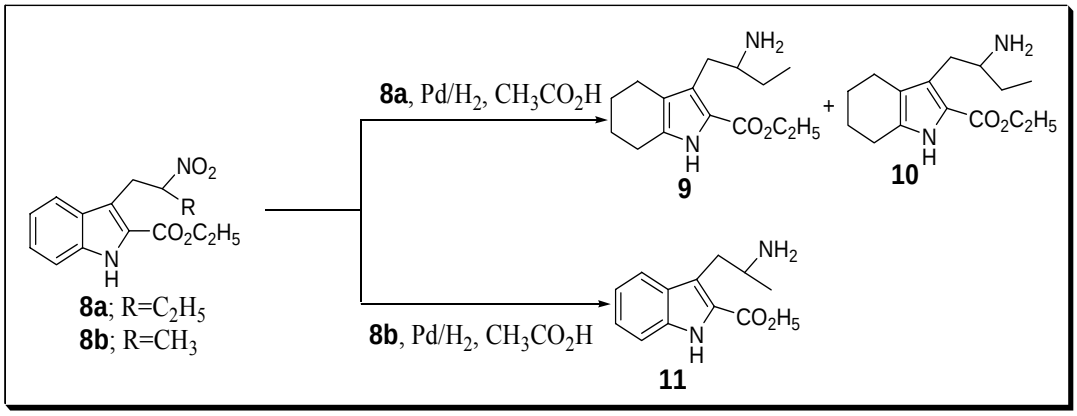
oxo-2-phenyl- and 4-oxo-1,2-diphenyl-4,5,6,7-tetrahydroindoles **7** with 82 and 72 % yields, respectively (Scheme 2).



Scheme 2

Dissolving metal reductions of indoles were investigated by O'Brien and Smith[9] in 1960. It was observed that in the absence of protons an added source of a lithium-ammonia solution reduces indole to a small extent and a proton source must be added to reduce the indole to a varying extent. It is reported that the most effective proton source is methanol and when a large excess of lithium and methanol in ammonia is being used, reduction gives a product free from indole and consisting of 4,7-dihydroindole and 4,5,6,7-tetrahydroindole. It is claimed that salt formation in pyrrole nitrogen protects pyrrole from reduction.

In 1961 Young and Snyder[10] reported that 1-(α-carbethoxy-β-indolyl)-2-nitrobutane **8a** is reduced in glacial acetic acid on %30 Pd/C yields 1-(α-carbethoxy-β-4,5,6,7-tetrahydroindolyl)-2-aminobutane **9** with 48% yield. In this reaction a selective hydrogenation of benzene ring occurs in a compound which also contains a nitro group, selectivity resulting from a combination of steric and electronic factors that protect the nitro group and facilitate attack on the aromatic ring system (Scheme 3). It is reported that in **8a** rate of hydrogenation of nitro group is much faster when compared with **8b**.

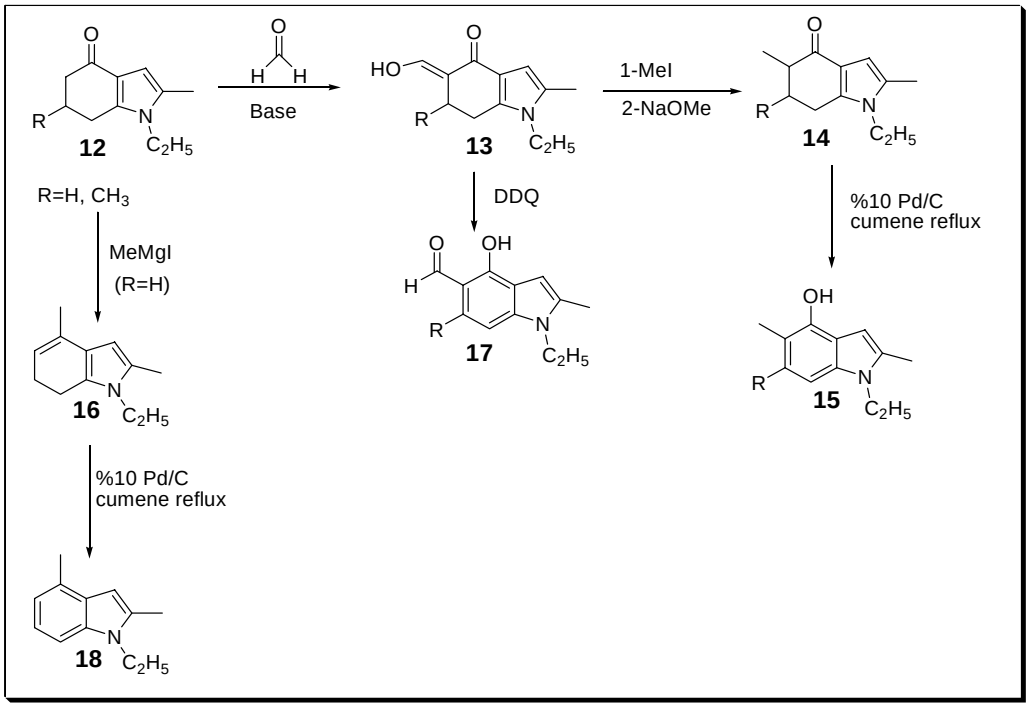


Scheme 3

The explanation of the difference in hydrogenation rates of nitro groups (and also hydrogenation products) is the presence of an extra methylene unit in (5*E*)-methyl-5-((*Z*)-but-2-enylidene)-4,5-dihydro-3-(2-nitropropyl)-1*H*-pyrrole-2-carboxylate **8a,** which hinders contact between nitro group and catalyst surface, prevents rapid hydrogenation of nitro group and directs hydrogenation through benzene ring yielding **9** and **10**. It is also observed that hydrogenation of the ring in **8a** occurs when the nitro function is isolated from the catalyst surface which also suggests that electron attraction by the nitro group facilitates hydrogenation of benzene ring.

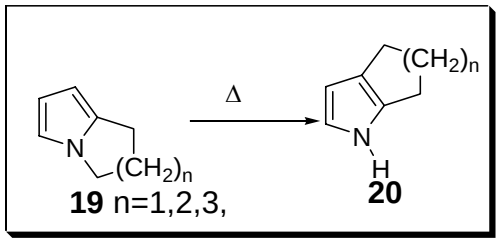
In 1965 Remers and Weiss[4] accomplished synthesis of various substitued indoles from 4,5,6,7-tetrahydroindole derivatives (Scheme 4). This work was a part of study on synthesis of mitomycin antibiotics. This compound belongs to a class of compounds called cytotoxic (anticancer) antibiotics. Mitomycin works by inserting itself into the strands of genetic material (DNA) inside the cell and binding them together. This stops the cell from making genetic material (DNA and RNA) and proteins. All this prevents the cell from growing and therefore it dies.The oxotetrahydroindoles **12** used in this reaction were obtained by a condensation reaction of appropriate 2-acetonyl-1,3-cyclohexanedione and ethylamine.

This approach presents an versatile synthesis of indoles with substituents including hydrogen, alkyl, or aryl at the 1,2, and 6 positions, and a variety of substituents at the 3, 4, and 5 positions. **15**, **17** and **18** are some examples (Scheme 4).



Scheme 4

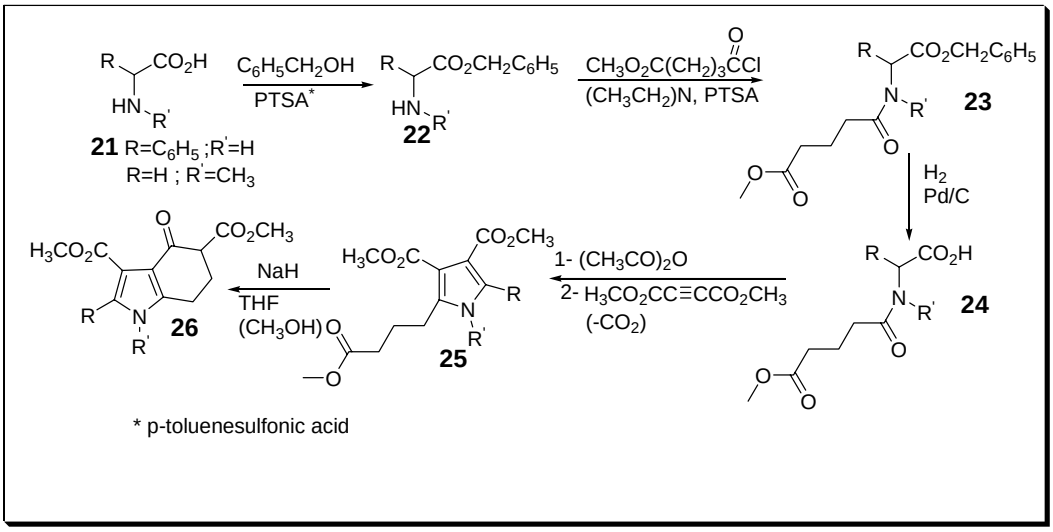
In 1967 Patterson and Soedigdo[11] investigated pyrolysis products of cycloalkano[a]pyrroles **19**. The pyrolysis of N-substituted pyrroles, where the substituent is alkyl, benzyl, and phenyl leads to the production of a mixture of isomers. In this study cycloalkano[a]pyrroles **19** were pyrolyzed at several temperatures (between 550°-650° C) and the rearrangement products which were characterized by H-NMR and IR spectroscopy were found to be cycloalkano[b]pyrroles **20** as expected. 4,5,6,7-tetrahydroindoles are one of the product classes where n=2 in scheme 5. Trace amount of indole is also reported to be found in some products.



Scheme 5

Another work on 1968 by Pleninger and Klinga[12] also describes synthesis of 4-hydroxyindoles from 4-oxo-4,5,6,7-tetrahydroindoles by Pd/C dehydrogenation method.

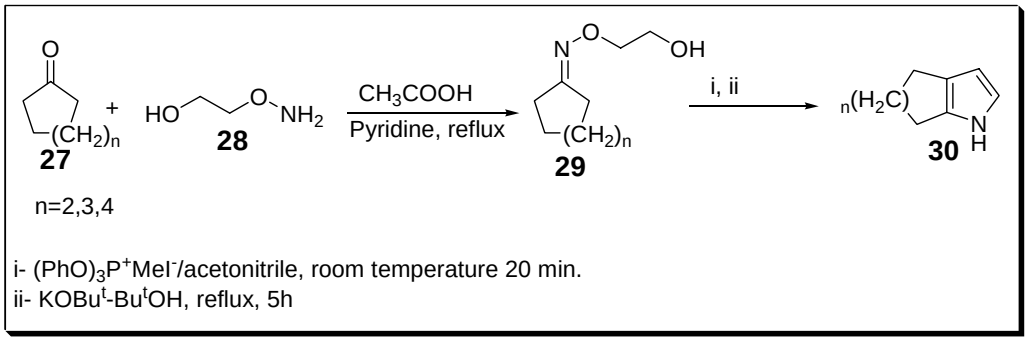
In 1975 Hershenson[13] described synthesis of 4-keto-4,5,6,7-tetrahydroindoles **26** from munchnone intermediates which are mesionic oxazolium 5-oxides. The synthetic procedure involves conversion of different amino acids **21** into their *N*-(4-carbomethoxybutyroyl) **24** derivatives by first preparing the benzyl ester with methyl (4-chloroformyl)butyrate in the presence of triethylamine, and finally removing the benzyl ester by hydrogenolysis. Later **24** is converted into pyrrole derivative **25** by first dissolving in acetic anhydride (which generates munchnone intermediate) and later treating with dimethylacetylenedicarboxylate. Later by a Dieckmann condensation using sodium hydride in tetrahydrofuran containing a trace of methanol target compound **26** is obtained (Scheme 6).



Scheme 6

In a study about reduction of acyl pyrroles to N-unsubstituted alkyl pyrroles by $NaBH_4$ in refluxing 2-propanol in 1985 by Greenhouse and Ramirez[14], it is reported that 4-oxo-4,5,6,7-tetrahydroindoles can be reduced to 4,5,6,7-tetrahydroindoles with 45% yield.

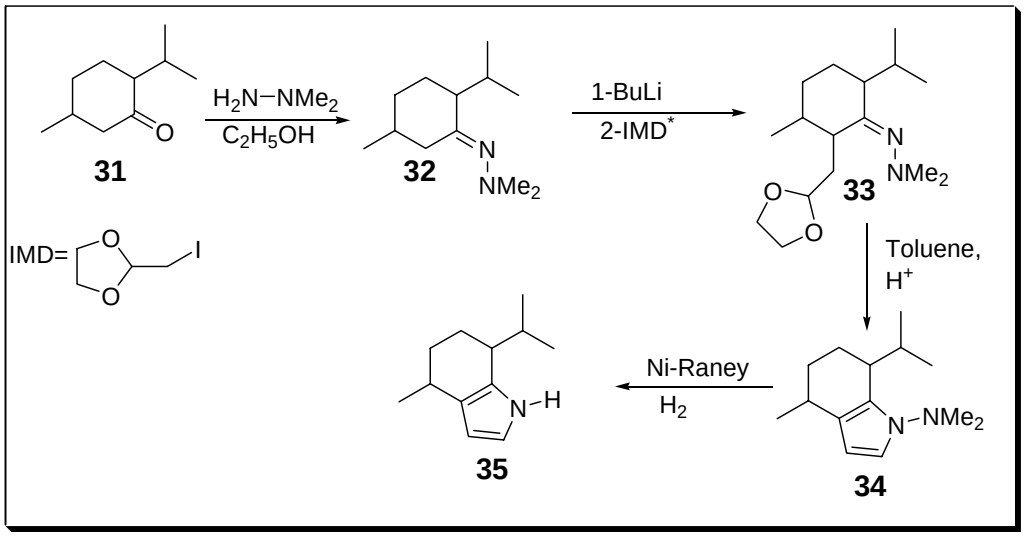
Reese[15] *et. al.* described a different procedure for the synthesis of 4,5,6,7-tetrahydroindole together with other bicylic pyrroles in 1986 in a work for synthesis of pyrrole derivatives from *O*-(2-hydroxyethyl)-ketoximes **29** in satisfactory overall yields. In this study various cyclic **27** and acyclic ketones were converted to their to *O*-(2-hydroxyethyl)-ketoxime **29** derivatives with *O*-(2-hydroxyethyl)-hydroxylamine. Later a slight excess of methyltriphenoxyphosphonium iodide in dry acetonitrile yielded *O*-(2-iodoethyl)-ketoxime, which is finally converted to corresponding pyrrole **30** with potassium *tert*-butoxide in refluxing *tert*-butanol (Scheme 7).



Scheme 7

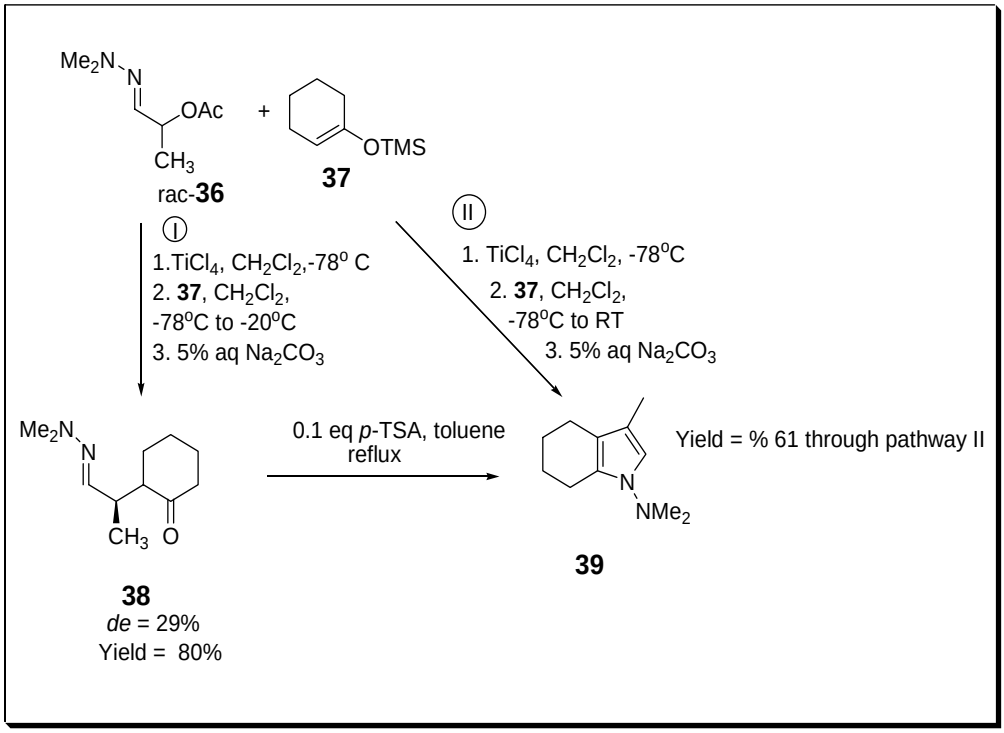
Another work in 1988 by Chelucci and Marchetti[16] describes synthesis of substituted pyrroles prepared from ketones through a four step reaction sequence based on the regiospecific alkylation of *N*,*N*-dimethylhydrazones with 2-iodomethyl-1,3-dioxalane.

Scheme 8 describes the synthetic route followed for optically active menthone **31** as the ketone. General procedure is, after preparation of dimethylhydrazone **32** of corresponding ketone, obtained hydrazone is alkylated with 2-iodomethyl-1,3-dioxolane (referred as IMD in figure 10) to yield **33**, followed by acid catalyzed cyclization of the iminoacetal derivatives **34** and finally hydrogenolysis of the N-N bond **35** is obtained.



Scheme 8

Due to recent indications on the biological activity of pyrrole derivatives in last two decades, development of more synthetic pathways together with determination of biological activity of tetrahydroindoles has attracted considerable attention and this resulted in increase in the number of reports in literature. In a study on synthesis of polysubstituted pyrroles by Enders[17] et. al. in 1995, [3+2] cyclization of C_2N and a C_2 fragment forming the N-C(2) and C(3)-C(4) bonds which is a common method for pyrrole synthesis (best known and most variable example being Knorr pyrrole synthesis) has been modified so that simple silyl enol ethers **37** serve as C_2 fragment and **36** dimethylhydrazone serve as C_2N unit bearing a leaving group (Scheme 9).



Scheme 9

As seen from Scheme 9, 2-acetoxypropanal-*N*,*N*-dimethylhydrazone **36** and various open chain and cyclic silyl enol ethers (in this specific example **37**) are reacted to obtain polysubstituted pyrrole derivatives. Most important step of this protocol is the Lewis acid mediated nucleophilic attack of the silyl enol ethers at the position 2 of the hydrazone rac-**36** (rac- indicating racemic mixture). Thus *N*-(dimethylamino)-pyrroles **39** can be obtained either in two steps via 4-oxoaldehyde-*N*,*N*-dimethylhydrazone **38** (reaction pathway I) or directly in an one pot synthesis (reaction pathway II). For synthesis of *N*-dimethylamino derivative of tetrahydroindole **39** pathway II is used. For N-N bond cleavage in some derivatives reduction with sodium in liquid ammonia at room temperature under 8 - 10 bar pressure is used.

In 1996 Ravina and Masaguer[5] reported a new route for synthesis of 6-aminomethyl-4-oxo-4,5,6,7-tetrahydroindoles. In figure 3 we see some target compounds. Among these compounds moleindole posses tetrahydroindole moiety. Haloperidol **40** is a prototype of butyrophenone derivatives with potent antipsychotic activity, and among them spiperone **41** and fluanisone **42**, which are 4-amino-*p*-fluorobutyrophenone derivatives with most potent neuroleptic (antipsychotic) activity. In a previous study by the same group they have prepared and studied several 5-aminoethyl-1,2,3,-tetrahydroindole-4-ones as butyrophenone homologues of molindole **43**.

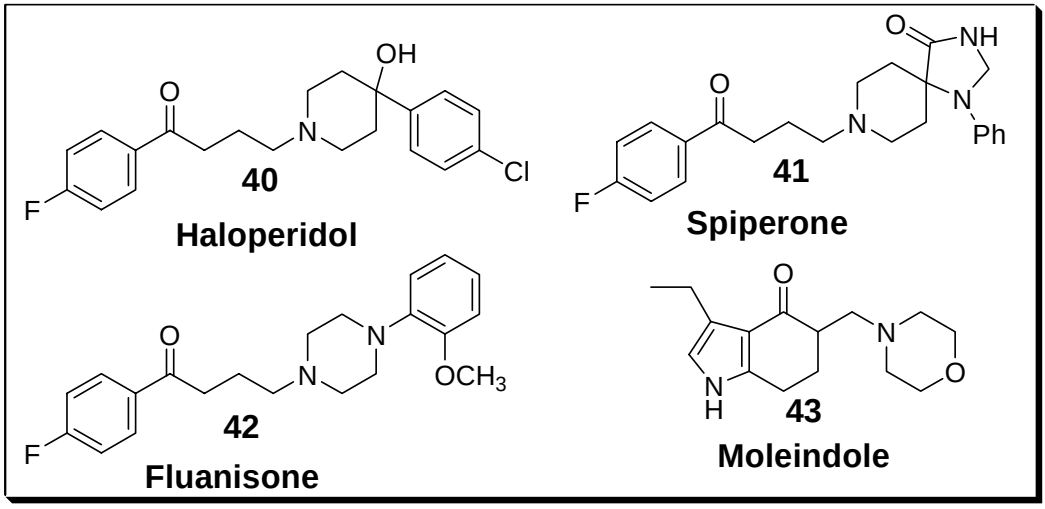
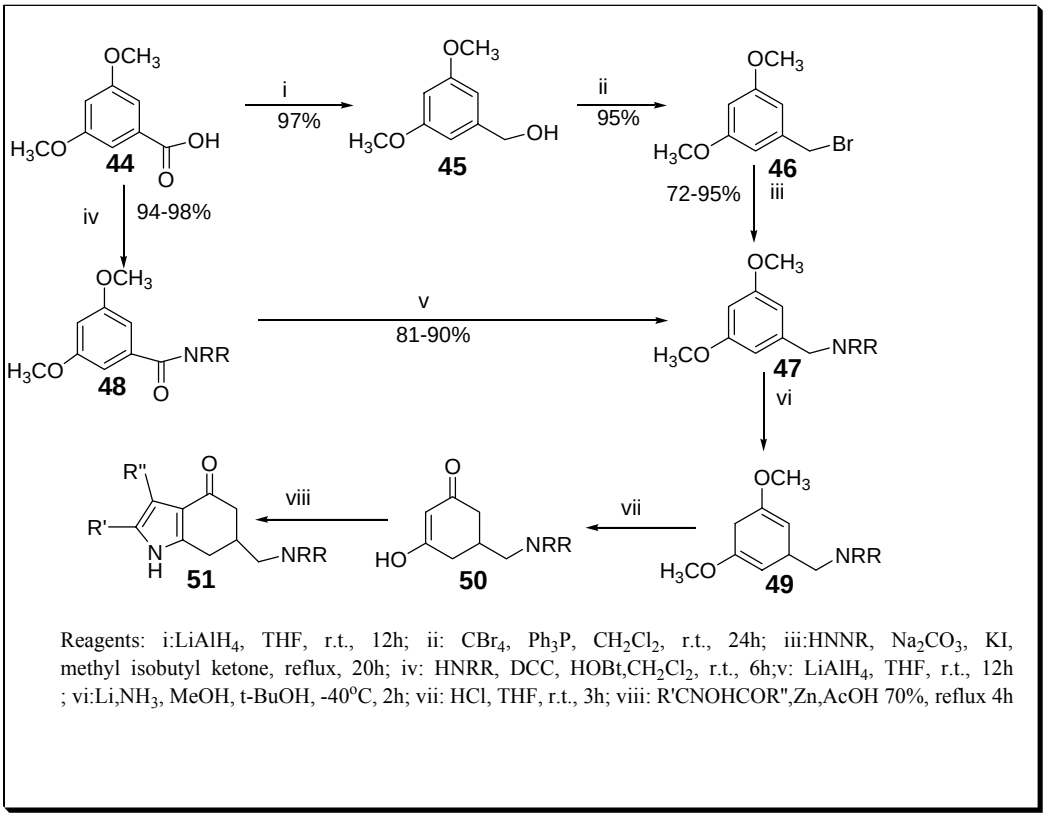


Figure 3: Some butyrophenone derivatives with very potent antipsychotic activity

The synthetic strategy that they describe for synthesis of 6-aminomethyl-4-oxo-4,5,6,7-tetrahydroindoles **51** as cyclic butyrophenone derivatives is depicted in scheme 10. **44** is reduced with lithium aluminum hydride ($LiAlH_4$) in THF to obtain alcohol **45** which was treated with carbon tetrabromide-triphenylphosphine in dichloromethane to obtain **46** in quantitative yield.

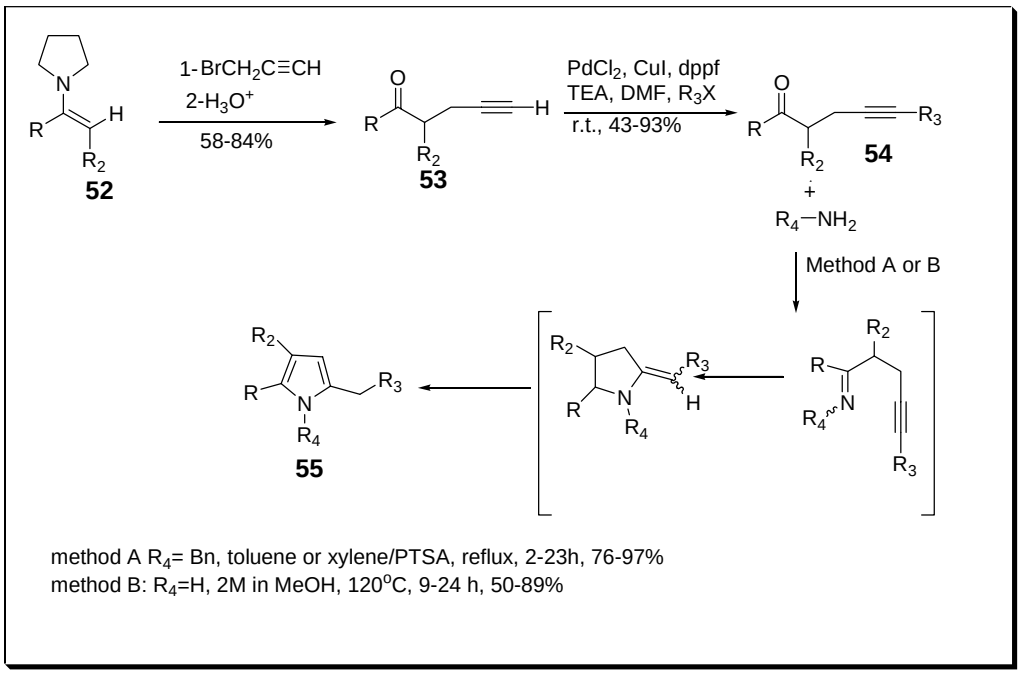
There are two alternative methods for synthesis of **47**, one employs nucleophilic displacement of bromine atom in **46** in methyl isobutyl ketone in the presence of potassium carbonate and catalytic amounts of potassium iodide, and other uses coupling with dicycloheylcarbodiimide (DCC) in presence of 1-hydroxybenzotriazole in DMF at room temperature which gives amides **48** and later treatment with $LiAlH_4$ again gives **47**. Reduction of **47** with lithium-ammonia in methanol containing *tert*-butyl alcohol afforded bis-enol ethers **49** in quantitative yields. Acid hydrolysis of **49** with hydrochloric acid in THF at room temperature gave 1-aminomethyl-3,5-dimethoxy-2,5-cyclohexadienes **50** again in quantitative yields. And at last step pyrrole ring was obtained by Knorr reaction with isonitroketones in 70% acetic acid in the presence of Zn powder at reflux to give tetrahydroindoles **51** in yields between 37-60 %.



Reagents: i:$LiAlH_4$, THF, r.t., 12h; ii: CBr_4, Ph_3P, CH_2Cl_2, r.t., 24h; iii:HNNR, Na_2CO_3, KI, methyl isobutyl ketone, reflux, 20h; iv: HNRR, DCC, HOBt,CH_2Cl_2, r.t., 6h;v: $LiAlH_4$, THF, r.t., 12h ; vi:Li,NH_3, MeOH, t-BuOH, -40^{o}C, 2h; vii: HCl, THF, r.t., 3h; viii: R'CNOHCOR",Zn,AcOH 70%, reflux 4h

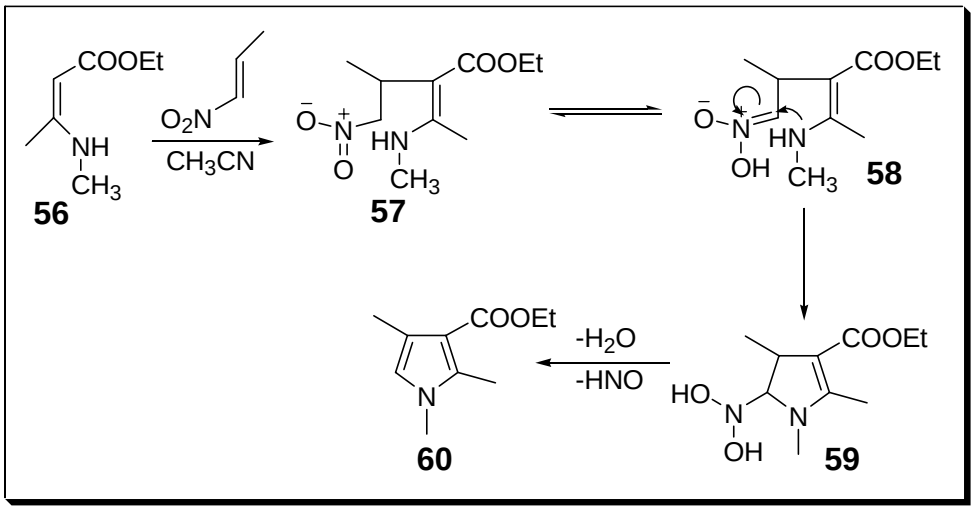
Scheme 10

In 1998 Arcadi and Rossi[6] described synthesis of functionalised furans and pyrroles from annulation reactions of 4-pentynones together with preparation of various steroids which are modulators of androgen biosynthesis and potential agents for the treatment of prostatic cancer and hypertension. In scheme 11 we see synthesis of polysubstituted pyrrole compounds. Starting building blocks, 2-propynyl ketones **53** are obtained by the reaction of Stork enamine **52** with propargyl bromide. Later a palladium-catalysed coupling reaction of **53** with aryl iodides or vinyl triflates at room temperature , in the presence of $PdCl_2$/dppf/CuI catalytic system are used in order to obtain functionalized 4-pentynones **54** in moderate to high yields. The synthesis of functionalised pyrrole **55** is carried out in good to high yields by the reaction of **54** derivatives with benzylamine and ammonia with either method A or method B. The reaction mechanism is assumed to involve the formation of an imine that undergoes a 5-*exo*-*dig* cyclization followed by isomerization give pyrroles **55**. 2-methyl-4,5,6,7-tetrahydroindole and *N*-benzyl derivative is synthesized with this methodology in 69 and 97% yields respectively.



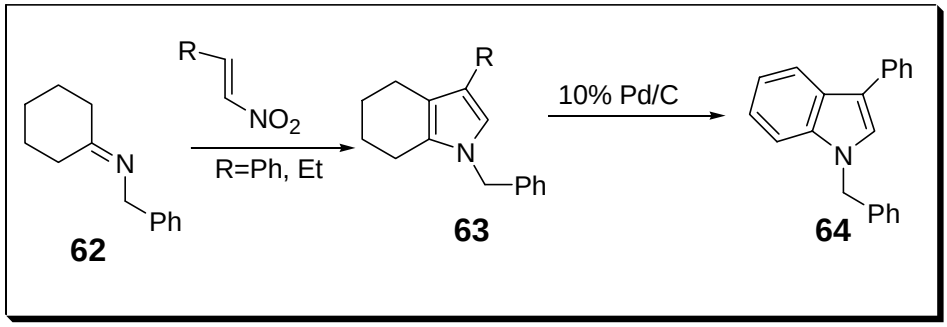
Scheme 11

A different methodology for the synthesis of pyrroles involves the addition of secondary enaminoesters to 1-nitropropene folowed by an intramolecular displacement of the nitro group by the amino group as shown in scheme 12.[20]



Scheme 12

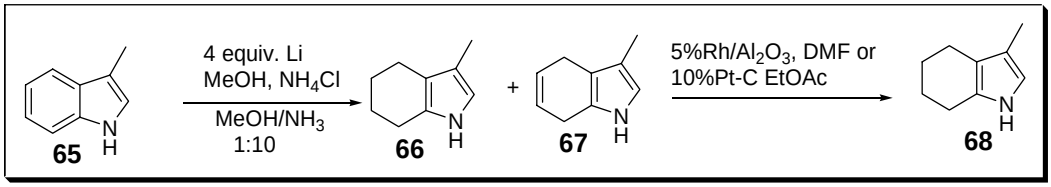
In 1999 Revial[19a] et. al. extended this methodology for the synthesis of various indole and tetrahydroindole **64** derivatives. They thought that, as imines are known to react through their secondary enamine form in Michael type addition reactions, reaction above could be extended to simple imines and utilized to obtain tetrahydroindoles and indoles. When imine **62** (scheme 13) was reacted with one equivalent of trans-β-nitrostyrene in toluene at the tetrahydroindole **63** was obtained in 70% yield for benzyl derivative. Its structure was confirmed by the dehydrogenation reaction of **63** by Pd/C in xylene at 140 ^{o}C yielding indole **64.**



Scheme 13

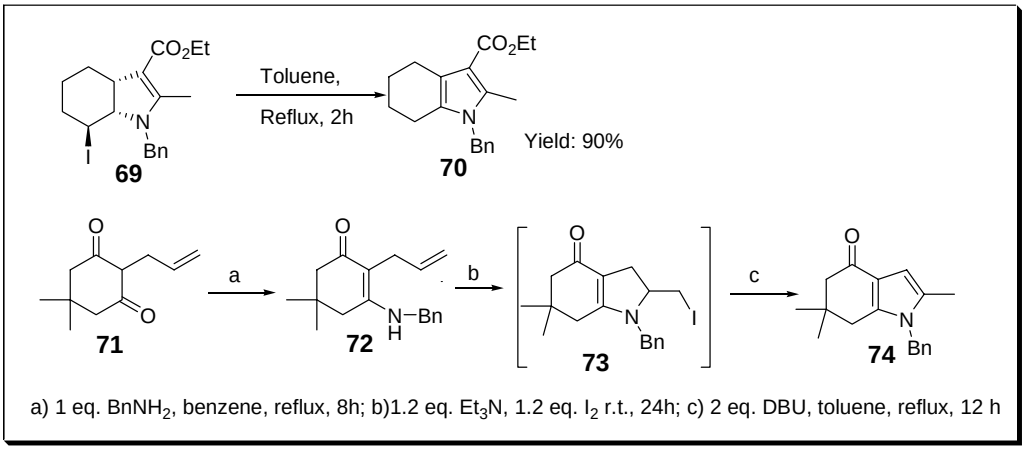
Another work in 1999 is made by Van Vranken and McComas[7] for the synthesis of tetrahydroindoles by a two step procedure which involves reduction of indoles to the corresponding 4,5,6,7-tetrahydroindoles (Scheme 14). In this report it is told that tetrahydroindoles are interesting ligands for transition metals because they are isoelectronic with tetrahydroindenyl ligands. (η^5) coordination of indenyl ligands are told to make them easy to hydrogenate , (η^5) coordination of indolyl ligands is difficult to achieve relative to (η^1) coordination with the indole nitrogen. They thought 4,5,6,7-tetrahydroindoles must be synthesized prior to (η^5) coordination. They applied a regioselective Birch reduction followed by catalytic hydrogenation to accomplish transformation of indoles to tetrahydroindoles as seen scheme 14 . There were two challenges, the first being complete conversion of starting material after Birch reduction because of hard separation of indoles from tetrahydroindoles, and second being the complete the reduction of 4,7-dihydroindole by hydrogenation of product mixture. For the reduction of skatole **65** (3-methylindole) it is observed that addition of increasing proportions of methanol failed in the complete consumption of starting material. In order to reduce the basicity of the reaction medium they have added 5 equiv. of ammonium chloride and under tihs condition starting material is completely comsumed. Catalytic hydrogenation of dihydroskatole **67** is observed to be complicated by its propensity to re-aromatize , especially when Pd-C is used as the catalyst under atmospheric pressure. In order to overcome this problem they also used 1,4-cyclohexadiene as proton source but this approach has also failed.

They obtained better results when rhodium and platinum based catalysts were used under 50 psi hydrogen. It is reported that while Rh/Al_2O_3 gave good results with 2,3-disubstituted indoles , Wilkinson's catalyst (Pt-C) gave better results with 2,3-disubstituted indoles. Yields are told to be in the range of 40-50%.



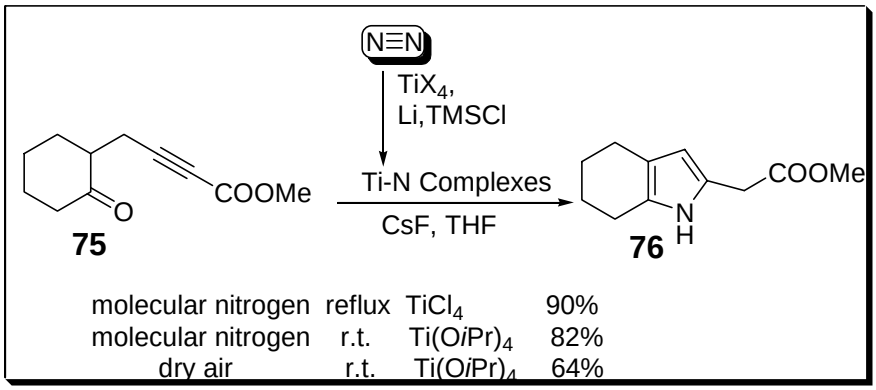
Scheme 14

Again in 1999, in a work by Ferraz[19b] et. al. synthesis of *N*-substituted pyrrole and tetrahydroindoles from alkenyl β-dicarbonyl compounds is reported. In a previous work of same group[20] iodocyclization reactions of a series of alkenyl substituted β-enamino esters and ketones are used preparation of mono and bicyclic heterocycle derivatives like **69** dehydroiodination of which gives tetrahydroindole **70** (Scheme 15). Also starting from the β-allyldimedone **71** they prepared indolone (4-oxotetrahydroindole) **74.** The iodo-β-enamino ketone **73** is proved to be very unstable, and was treated with DBU (1,5-diazabicycloundecene), affording **74** in 87% overall yield from **72**.



Scheme 15

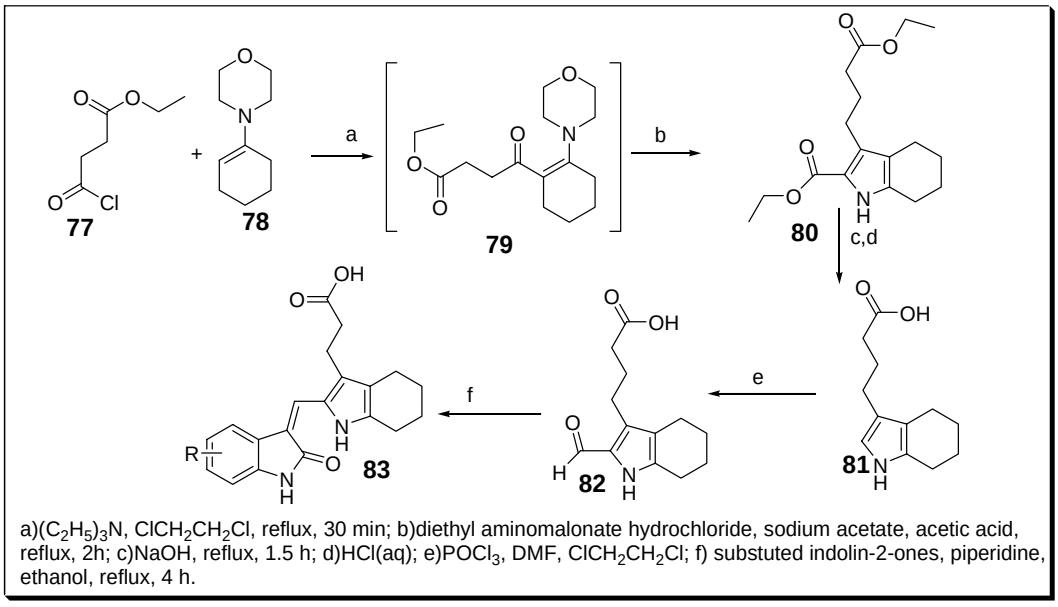
Mori[21] et. al. studied synthesis of tetrahydroindole derivatives from keto-alkynes using titanium-nitrogen complexes generated from Ti(O*i*Pr)$_4$, Li, and TMSCl (trimethyl silyl chloride). The process that they use is called "nitrogen fixation " , and has a simple procedure; a THF (tetrahydrofuran) solution of TiX_4 (X= -O*i*Pr or Cl) and TMSCl in the presence of Li is being stirred under nitrogen (1 atm) at room temperature for 12-24 h. The method also worked when dry air used instead of nitrogen but the yields were lowered. In scheme 16 we see the reaction scheme. **75** is converted to **76** using standard nitrogen fixation procedure. The reaction yields are higher for α,β-unsaturated ester moiety carrying ketones when compared with α,β-unsaturated amides, aliphatic or aromatic group carrying alkynes.



Scheme 16: Nitrogen fixation for building heterocycles.

Sun et. al. synthesized and investigated biological activity of 3-[(4,5,6,7-tetrahydro-1*H*-indol-2-yl)methylene]-1,3-dihydroindol-2-ones which are growth factor receptor tyrosine kinase inhibitors.[22] Derivatives of these compounds are planned to inhibit growth of solid tumors by inhibiting tumor angiogenesis and become a means to develop new cancer treatment methods. In this work two classes of substituted indolin-2-ones **83** (Scheme 17) containing a tetrahydroindole moiety at the C-3- position of the indolin-2-one core were told to be designed and evaluated for their potential to inhibit kinase activities because in a previous work by the same group it was shown that 3-substituted indolin-2-ones as antiangiogenic agents.

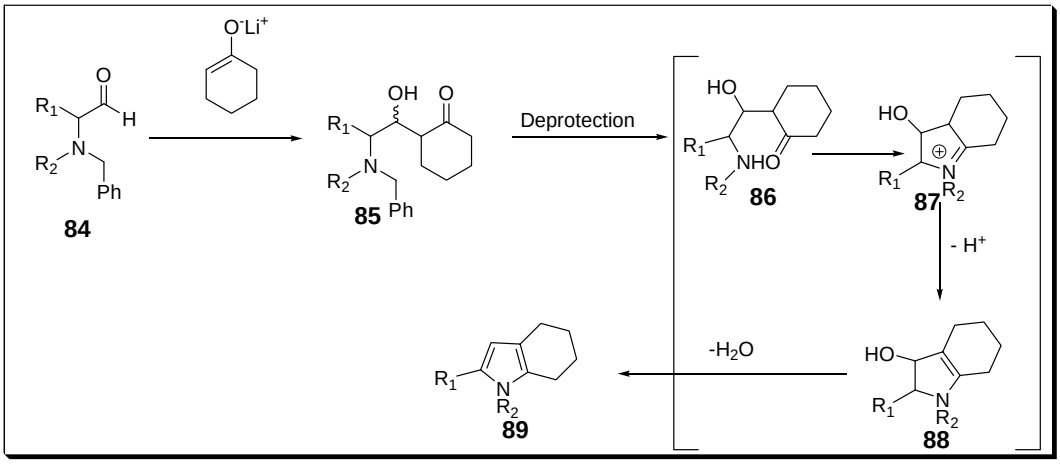
In scheme 17 we see the synthetic pathway followed. 4-cyclohex-1-enylmorpholine **78** was acylated with 3-chlorocarbonylpropionic acid ethyl ester **77** to give **79**, which was later condensed with diethyl aminomalonate hydrochloride to give 3-(2-ethoxycarbonylethyl)-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylic acid ethyl ester **80**. Hydrolysis of **80** followed by decarboxylation resulted in compound **81** and formylation gave **82**. **83** derivatives were synthesized by condensing indolin-2-ones with **82**. Later derivatives of **83** are tested for biological activity.



a)$(C_2H_5)_3N$, $ClCH_2CH_2Cl$, reflux, 30 min; b)diethyl aminomalonate hydrochloride, sodium acetate, acetic acid, reflux, 2h; c)NaOH, reflux, 1.5 h; d)HCl(aq); e)$POCl_3$, DMF, $ClCH_2CH_2Cl$; f) substuted indolin-2-ones, piperidine, ethanol, reflux, 4 h.

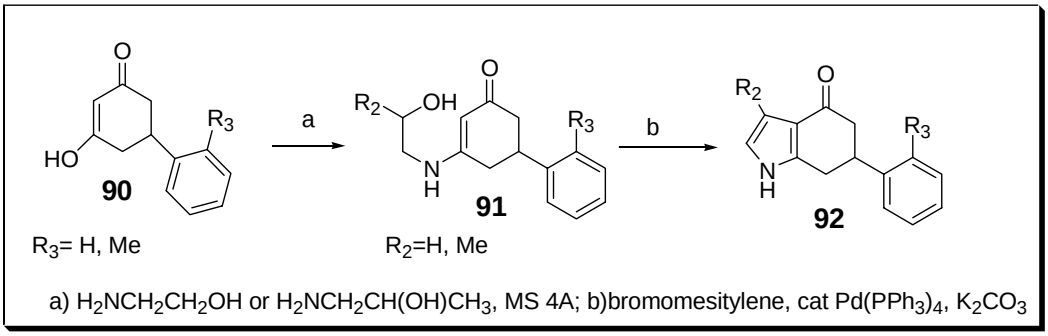
Scheme 17

Lagu[23] et. al. , used aldol products formed from the reaction of α-(*N*-benzyl or *N*-Cbz)aminoaldehydes and lithium enolates of various ketones to obtain polysubstituted pyrroles in 2001. They were trying to obtain pyrrole compounds bearing electron withdrawing groups. In a similar work Cushman[24] and co-workers reported synthesis of polysubstituted pyrroles from aldol products of (*N*-Boc)-α-amino aldehydes and ketones. The yields of this reaction is told to be between 5-40% and it is claimed by Lagu that a rapid polymerization of the resulting pyrroles under the acidic conditions employed to remove *N*-Boc (*tert*-butoxy carbonyl) might be the reason. To overcome this problem they used benzyl protecting group which may be removed under relatively neutral conditions. In scheme 18 we see the reaction scheme for a tetrahydroindole derivative obtained by this methodology, using cyclohexanone as the ketone. On α-amino aldehyde **84** lithium enolate of cyclohexanone is added and aldol product **85** is obtained, when **85** is subjected to hydrogenation by H_2 and Pd-black, deprotection of benzyl group to yield **86** followed by the iminium ion **87** formation which is deprotonated to give the enamine **88**. After dehydration, the enamine yielded **89**, (R_2 = benzyl group , R_1 = methyl) in 52 % yield.



Scheme 18

Fukumoto[25] et. al. investigated synthesis and pharmacology of 5-tetrahydroquinolinylidene aminoguanidine derivatives as non-acylguanidine-type Na^+/H^+ exchanger inhibitors at 2002. These compounds are planned to regulate ionic concentration of Ca^{2+} and Na^+ during some injuries; overload of these two ions during injuries is told to cause detrimental effects. For this purpose they have synthesized cyclohexylidene aminoguanidine derivatives with various fused heterocycles which are reported to have inhibitory activities. In scheme 19 we see tetrahydroindole derivatives **92** synthesized for further investigation. First **90** is converted to its enamino alcohol derivatives **91** with amino alcohols and molecular sieves. Later **91** ia converted to **92** by palladium-catalyzed oxidation. [26]



Scheme 19: Synthesis of tetrahydroindoles by Pd complex catalyst

1.3 Benzofurans

Benzofuran is composed of a ring system where a benzene nucleus is fused on the furan ring **93**. The older name for benzofuran is coumarone, but this name of compound is not used any longer, for it is easily confused with coumarin **94 (**Figure 4).[27] Other names are also used (but very rarely) in literature. Among these names there are coumaranone, 2,3-benzofuran and benzo(b)furan.

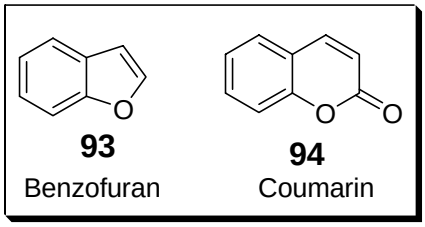


Figure 4

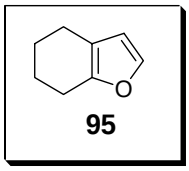
Benzofuran nucleus can be seen on the structure of many natural products. These products have complicated structures, and the furan ring is usually found in a somewhat changed form, for instance, in morphine, lignin (which are largely composed of benzofuran residues), and some alkaloids derived from isobenzofuran but not benzofuran. Benzofurans resembles naphtalenes much less than they resemble thionaphtalenes. They behave similar to condensed aromatic systems. Benzofuran (and its homologs) are present in certain fractions of coal tar, lignite tar, and tar from beechwood. It is considerably stable toward alkali, but polymerizes easily by action of concentrated sulphuric acid., and because of this behaviour it has technical importance for production of cheap, chemically relatively inert resins.

Benzofuran may be obtained by passing ethylene through phenol at 170^{o} to180^{o}, and then over Fe_2O_3 –Al_2O_3 catalyst at 650^{o} . The vapor-phase catalytic dehydrocyclization of 2-ethylphenol to yield benzofuran in the presence of cobalt sulfide or hydrogen sulfide and a catalyst. , such as magnesium oxide and

aluminum oxide, gives yields of 85 and 75% with selectivites of 99 and 98% respectively.[27] It is proposed that dehydrogenation of the ethyl group to a vinyl group, followed by ring closure to dihydrobezofuran takes place first, and later dehydrogenation of the latter to the benzofuran **93**. Catalytic dehydrocycliztion of *o*-alkylphenols in presence of various catalysts has been extensively studied resulting in formation of alkyl substituted benzofurans.[28,29]

1.4 4,5,6,7-Tetrahydrobenzofurans and their derivatives

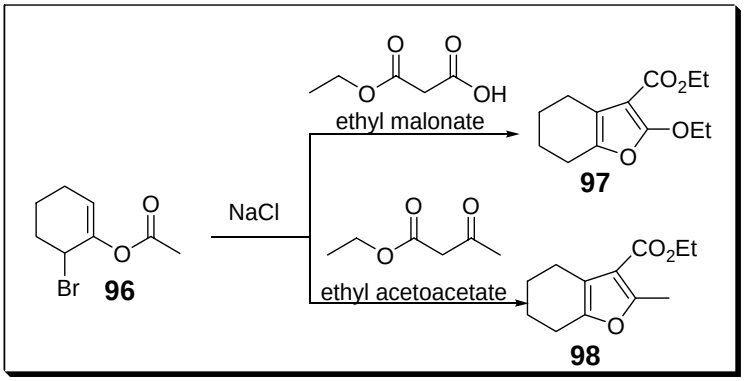
Like 4,5,6,7-tetrahydroindoles, 4,5,6,7-tetrahydrobenzofuran **95** is an important pharmacophore and is found in the structure of many bioactive natural products. There is a huge number of reports in literature which tells about constitution of ring system; either alone or in structure of a natural product, and investigating biological activity of its various derivatives.[32-42]



95

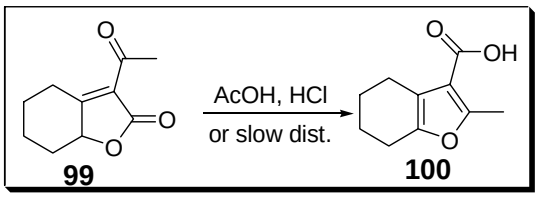
Figure 5

The early studies are about construction of tetrahydrobenzofuran ring system, rather than testing its biological activity. The earliest report on the subject dates back to 1929, in this study 3-bromo-2-acetoxy-1-cyclohexene with ethyl acetoacetate in presence of sodium chloride yields 2-methyl-3-carbethoxy-4,5,6,7-tetrahydrobenzofuran **97** (scheme 20), another study at 1956 repeated the work this time using ethyl malonate which afforded 2-ethoxy-3-carbethoxy-4,5,6,7-tetrahydrobenzofuran **98**.[27]



Scheme 20

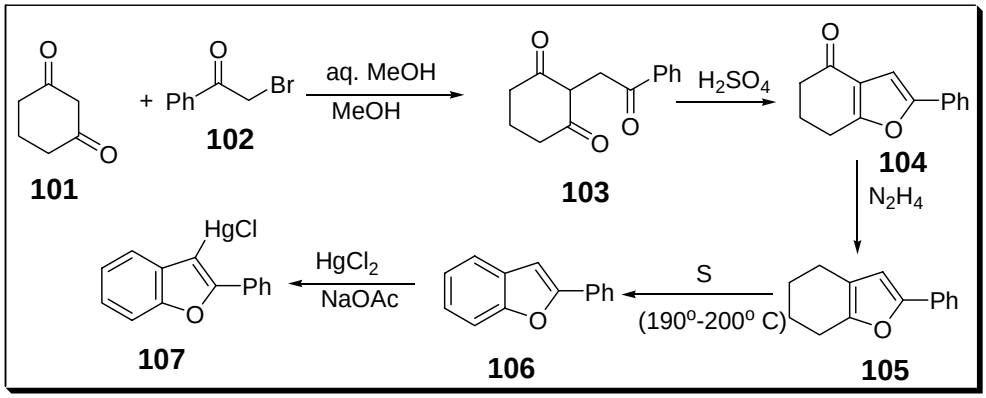
In 1954 Lacey[30] ,while investigating acid catalysed rearrangement of lactones, found out that when 3-acetyl-2,4,5,6,7,7-α-hexahydrobenzofuran-2-one **99**, is treated with hydrochloric-acetic acid mixture or distilled slowly, reaarranges to 4,5,6,7-tetrahydro-2-methyl-3-benzofurancarboxylicacid **100** (Scheme 21).



Scheme 21

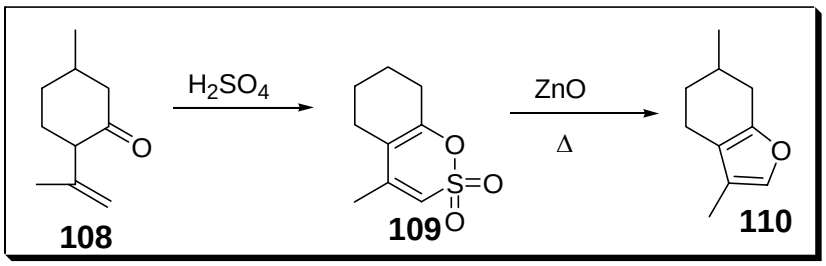
In a study in 1955, Stetter and Sienhold[31] synthesized tetrahydrobenzofurans by first reacting phenacyl bromide **102** (Scheme 22) and 1,3-cyclohexanedione **101** in the presence of KOH in methanol to obtain 1,3-dioxo-2-phenacylcyclohexanone **103** which is later treated with sulfuric acid and yielded 5,6,7-trihydro-4-oxo-2-phenylbenzofuran **104**.

With Wolff-Kishner reduction is reduced to 4,5,6,7-tetrahydro-2-phenylbenzofuran **105**, dehydrogenated with sulfur to 2-phenylbenzofuran **106** and treated with mercuric chloride, sodium acetate, and ethanol to obtain mercuri compound **107**. In 1962 Stetter and Lauterbach[32] converted derivatives of **104** to 4-oxotrihydroindoles by using primary amines.



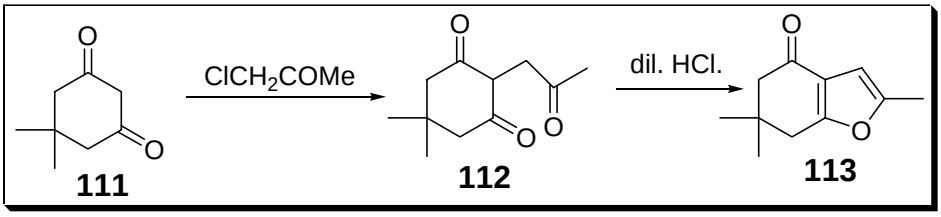
Scheme 22

In 1937 Triebs[33] showed that *d*-sultone **109** obtained from menthone **108**, affords menthofuran **110** when heated with zinc oxide (Scheme 23).



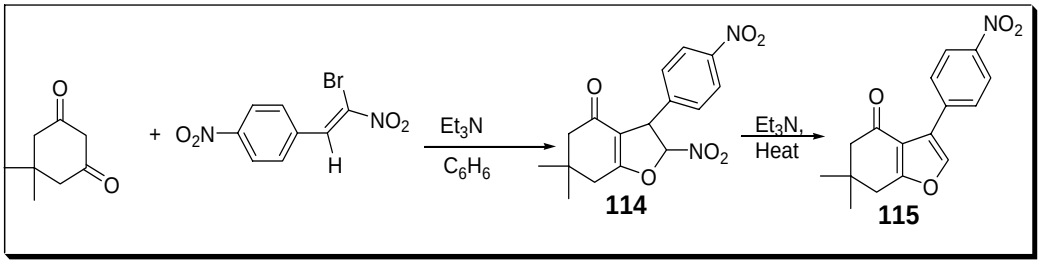
Scheme 23

In a work in 1962 by Schaeffer and Vince,[34] it is shown that condensation of chloroacetone with dimedone (5,5,-dimethyl-1,3-cyclohexanedione) **111** and later treatment of product **112** with dilute hydrochloric acid solution gives oxotetrahydrobenzofuran **113** as shown in scheme 24.



Scheme 24: Oxotetrahydrobenzofuran as a condensation product

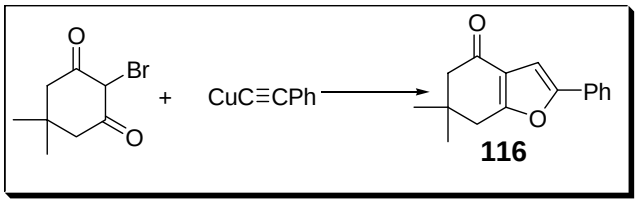
A similar condensation studied by Sopova[27] et. al. and reported in 1964 investigates reaction of dimedone **111** with α-(*p*-nitrophenyl)-β-nitro-β-bromoethylene to yield 2-nitro-3-(*p*-nitrophenyl)-4-oxo-6,6,-dimethyl-2,3,4,5,6,7-hexahydrobenzofuran **114** when refluxed with triethylamine, it affords 3-(*p*-nitrophenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydrobenzofuran **115** (Scheme 25).



Scheme 25

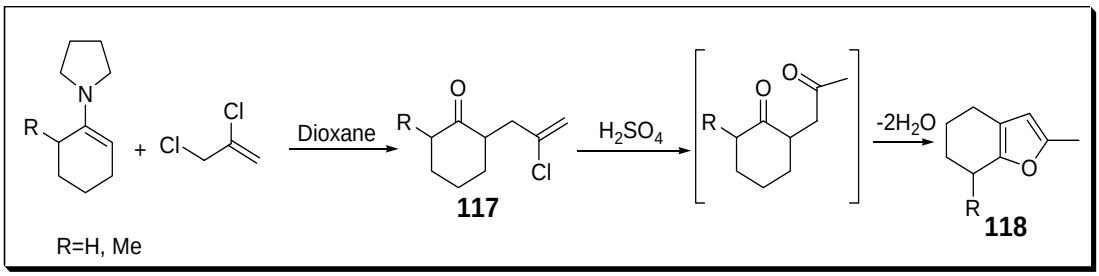
In 1966 Castro[35] et. al. developed a method for preparation of benzofurans by transformation of α-haloketones upon reflux with cuprous acetylides.

Later Castro[36] applied the same methodology in 1967 to synthesis of tetrahydrobenzofurans **113** from 1,3-cyclic diketones (α-bromodimedone in this example) (scheme 26). Cyclization is proposed to be proceeding through copper-coordinated enol formation.



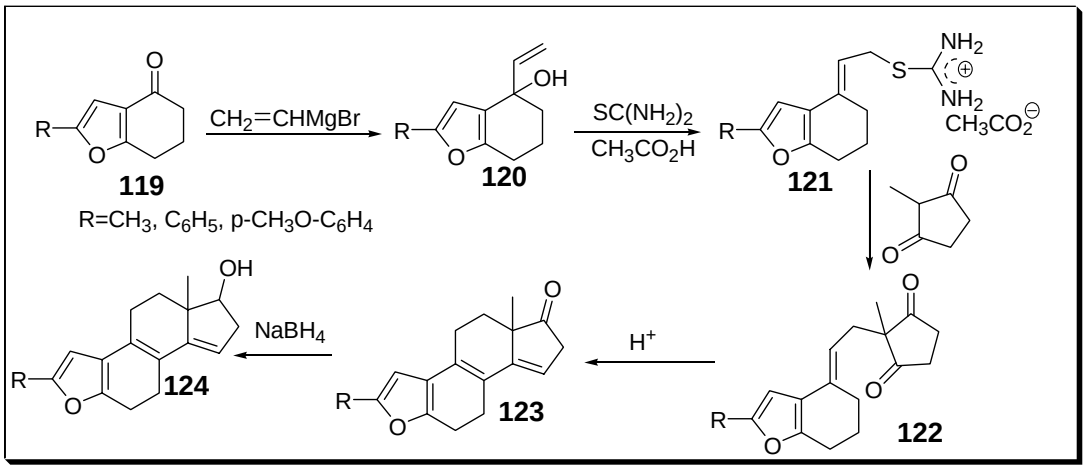
Scheme 26

Another work on 1967 by Nienhouse[37] et al. used β-chloroallylketones **116** in scheme 27 obtained by reaction of Stork enamines of cyclohexanone and 2,3-dichloropropene for synthesis of tetrahydrobenzofuran derivatives. Later treatment of **117** with H_2SO_4 affords **118** through a dicarbonyl intermediate. Here β-chloroallyl group serves as a "masked" carbonyl group. Among the tetrahydrobenzofuran derivatives obtained by this methodology, 3,6-dimethyltetrahydro-4,5,6,7-benzofuran possesses certain physiological action on fruit flies and other insects. Other derivatives potent drug substances in treatment of infectious diseases in urology.



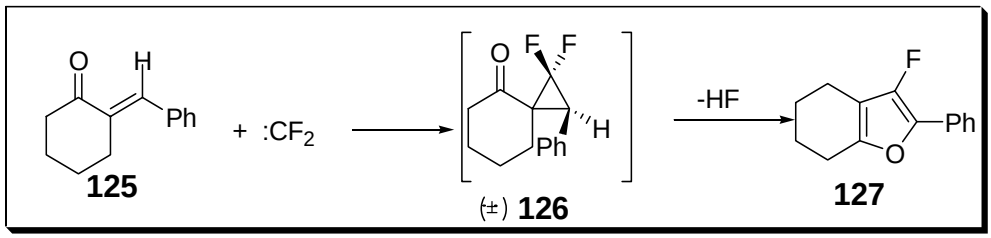
Scheme 27

In 1969 Lehmann and Lücke[38] accomplished synthesis of A-nor-3-oxaestrane derivatives **124** by Grignard reaction of 4-oxo-5,6,7-trihydrobenzofurans **119** with vinyl magnesium bromide and subsequent condensation with 1,3-dioxo-2-methylcyclopentane as shown in scheme 28.



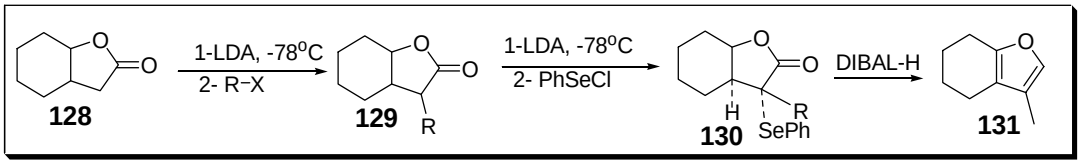
Scheme 28

In 1971, Hodge and Derenberg[27] synthesized 2-Phenyl-3-fluoro-4,5,6,7-tetrahydrobenzofuran **127** from reaction of 2-benzylidenecyclohexanone **125** with difluorocarbene, which adds to the double bond by 1,2 addition and the adduct obtained in this manner **126** (in racemic form) rearranges with elimination of hydrogen fluoride (Scheme 29) to yield **127**.



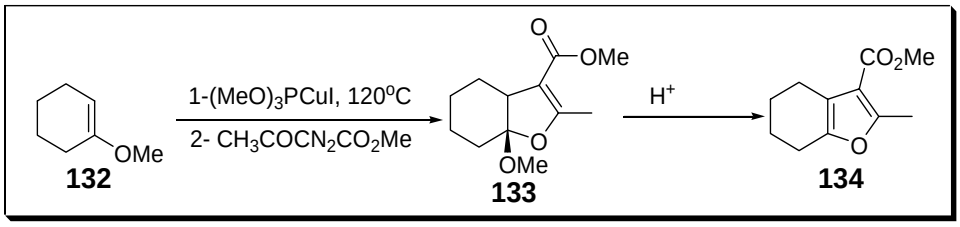
Scheme 29

Grieco[39] et al. showed transformation of various γ-lactones (in Scheme 30) we see **128** as one of the derivatives) to corresponding 2,4- and 2,3,4-substituted furans in 1975. For this purpose they first prepared α-selenenylated- γ-lactones **130** either by direct alkylation of lactone enolates or by conjugate addition of an organocopper reagent to an α-alkylated- γ-lactone. Later elimination with diisobutylaluminum hydride gave the corresponding furan **131** compound in high yields. Also some exocyclic olefin formation is observed as minor product.



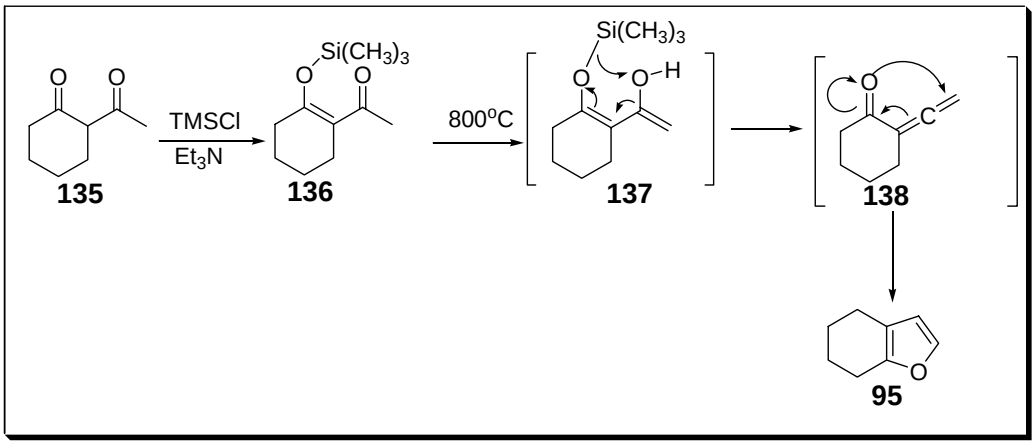
Scheme 30

In 1977, Wenkert[40] et al. reported synthesis of various substituted furans by copper-catalyzed thermolysis reactions of α-diazo-β-dicarbonyl compounds in the presence of enol ethers of an aldehyde and a ketone in a study directed towards synthesis of terpenoid products. In scheme 31 we see synthesis of methyl 2-methyl-4,5,6,7-tetrahydrobenzofuran-3-carboxylate **134** as an example. 1-methoxy-1-cyclohexene **132** is heated on trimethoxyphosphinecopper(I)iodide and later diazoacetoacetic ester was added to yield methyl 2-ethoxy-5-methyl-3,3-pentamethylene-2,3-dihydrofuran-4-carboxylate **133**. Later treatment of **133** on a cation exchange resin gave **134**.



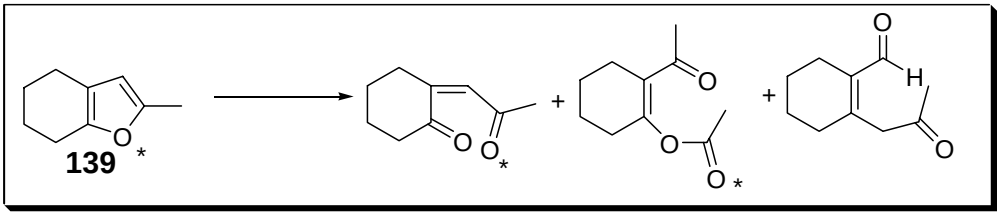
Scheme 31

In 1982, Pechine[41] et al. reported investigation on thermolytic rearrangement of β-keto-trimethylsillyl-enol-ethers like **136** to substituted furans above 800° C under vacuum. In previous studies by the same group they observed that above 750° C at low pressures a series of β-diketones yield furans about 5% yield. This reaction is proposed to be proceeding through enol form of β-diketone so they converted one of the carbonyl groups of the diketone to sillyl-enol-ether, and examined the thermal reactivity by flash vacuum thermolysis. In scheme 32 we see mechanism of 4,5,6,7-tetrahydrobenzofuran **95** synthesis; first 2-acyl-1-cyclohexanone **135** is converted to its enol-ether **136** and subsequent flash vacuum thermolysis which gave the product through intermediates **137** and **138** . Yield is 12,5 %.



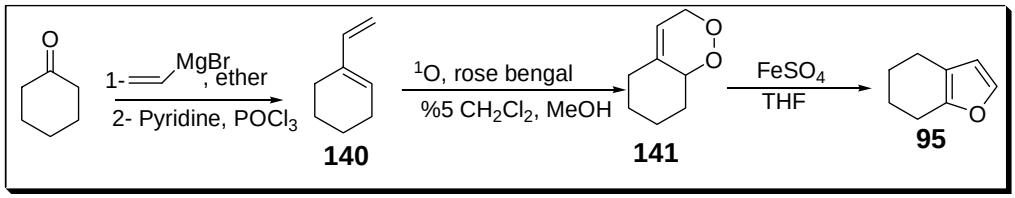
Scheme 32

In a report in 1983, *m*-chloroperbenzoic acid oxidation of 2-methyl-4,5,6,7-tetrahydrobenzofuran **139** is investigated by Jennings and Gingerich[42]. The reaction products are depicted in scheme 33. Reaction mechanism is suggested to start by epoxidation of the more substituted double bond and evidence is provided by ^{18}O labeling experiment.



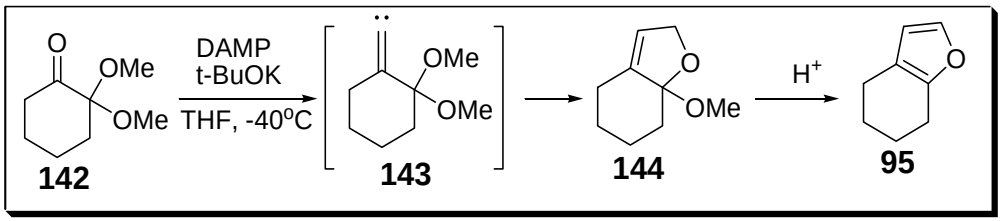
Scheme 33

In a study reported at 1985 by Hernz and Huo[43,] photooxygenation of 1-vinylcycloalkanes and their rearrangement to furans by $FeSO_4$ is examined as a part of the work done. In scheme 34 we see synthesis of 4,5,6,7-tetrahydrobenzofuran **95** as a specific example. Cyclohexanone is converted to 1-vinyl-1-cylohexene **140** by first reacting with vinylmagnesium bromide and treatment with $POCl_3$ at 0-5^oC in pyridine, later photooxygenation with singlet oxygen affords **141** at 0^oC and finally treatment with $FeSO_4$ yields **95** with 75% yield.



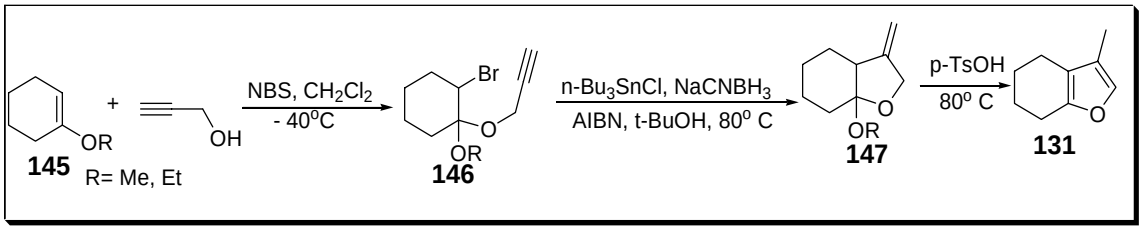
Scheme 34

Skattebøl[44] et al. performed synthesis of furans by carbene insertion method and reported at 1987. In scheme 35 we see synthetic procedure applied. α,α-dimethoxycyclohexanone **142** is reacted with diazomethylphosphonate (DAMP) for generation of carbene intermediate **143**. Later **143** rearranges to afford bicyclic dihydrofuran derivative **144**, which in the presence of acid is converted to 4,5,6,7-tetrahydrobenzofuran **95**.



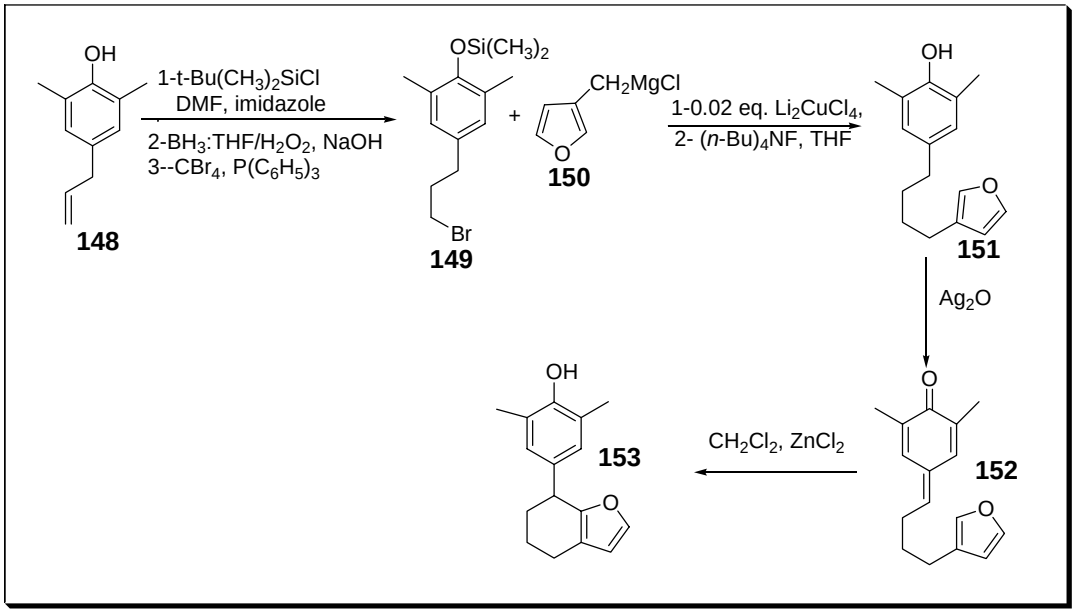
Scheme 35

In another at 1987, Sriksihna and Pullaiah[45] reported a three step 4-methyl furan annulation sequence via radical cyclisation reaction. Reaction scheme can be seen in scheme 36; 1-alkoxy1-cyclohexene **145** is reacted with propargyl alcohol in dichloromethane in presence of N-bromosuccinimide to obtain radical precursor **146**. Later tri n-butyltinhydride (TBTH) in benzene is used as radical forming reagent in the presence of azabisisobutyronitrile or more conveniently sodium cyanaoborohydride and tertiary butanol and converted to bicyclic product **147**, which is finally converted to 3-methyl-4,5,6,7-tetrahydrobenzofuran derivatives **131** by para-toluenesulfonic acid in benzene at room temperature with about 40% yield.



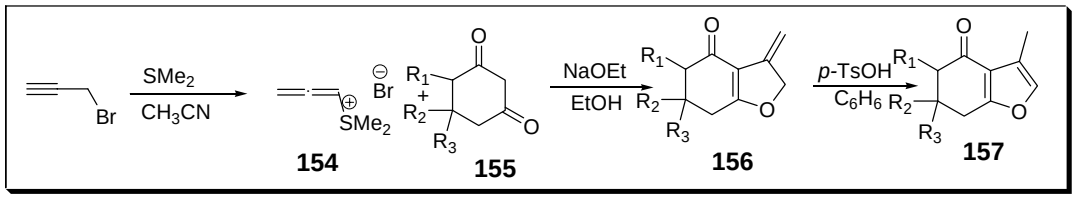
Scheme 36

In 1989, Angle[46] et al. reported a work on synthesis and characterization of *p*-quinone methides as cyclization initiators and later cyclization of these compounds using furan, pyrrole and monosubstituted benzene rings as so called "cyclization terminators". In scheme 37 we see the synthetic pathway followed. Protection of 2,6-dimethyl-4-(2-propenyl)-phenol **148** is protected with *tert*-butyldimethylsillyl chloride to yield **149** which is reacted with Grignard reagent prepared from 3-chloromethyl furan **150** to obtain phenol **151** after cleavage of the protecting group. **151** is later oxidized with Ag_2O to obtain quinone methide **152**, and finally cyclized to afford **153**. It is reported that among the three derivatives studied pyrrole compounds has highest reaction rate and mono alkyl substituted benzene has lowest reaction rate.



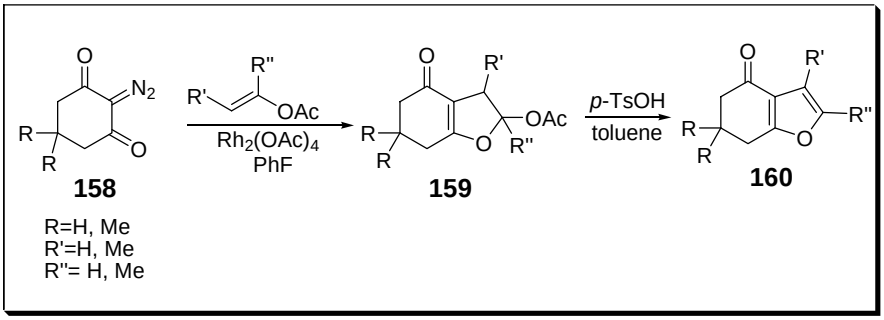
Scheme 37

In a study directed towards synthesis of marine terpenoids, Kenematsu[47] et. al. synthesized various oxodihydrobenzofurans by reaction of diketones **155** (scheme 38) and allenic sulfonium salts **154**, which are prepared by reaction of propargyl bromide and dimethyl sulfide. Formed bicyclic product with an exocyclic double bond **156**, is later treated with *p*-toluenesulfonic acid to obtain oxodihydrobenzofurans **157**.



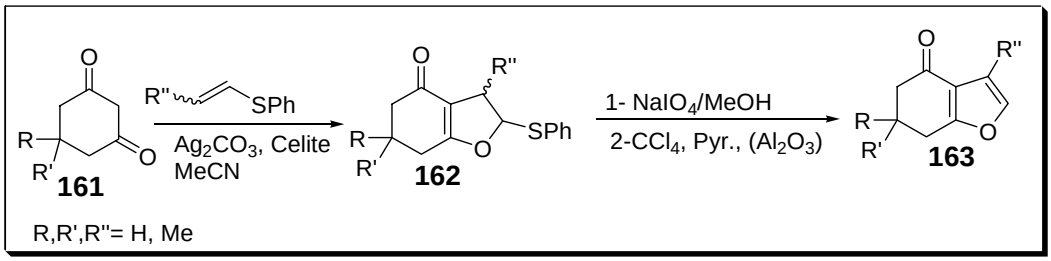
Scheme 38

At 1995 Lee[48] reported synthesis of oxodihydrobenzofurans in a study aiming synthesis of angular furanocoumarins; angelicin, oroselone and oroselol. These compounds are told to have photosensitizer activity in human skin and are potent drug substances in skin diseases. In scheme 39 we see synthetic pathway followed; cyclic diazoketones **158** are reacted with vinyl acetates in presence of catalytic amount of $Rh_2(OAc)_4$ and converted to oxotetrahydrobenzofuran compounds **159** which are finally transformed to oxodihydrobenzofurans **160** with catalytic amount of *p*-toluenesulfonic acid with 69% overall yield. The same methodology is applied before by Pirrung[49] et. al. using electrone deficient or electron rich acetylenes instead of vinyl acetates.



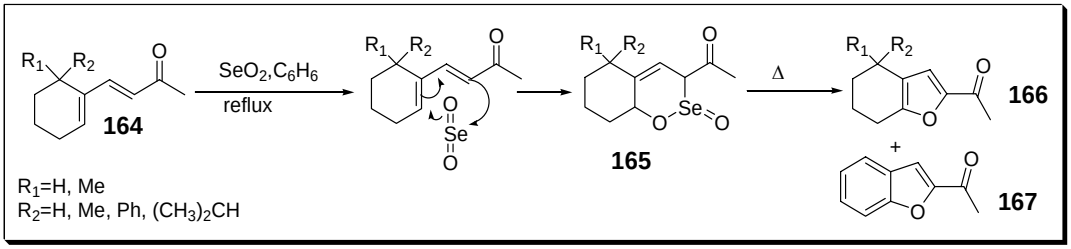
Scheme 39

Another work reported by Lee[50] at 1997, oxodihydrobenzofuran synthesis is again studied with another methodology en route to synthesis of α-clausenan. This methodology employs silver(I)-celite mediated addition of cis-trans isomer mixture of vinyl sulfides to 1,3-dicarbonyl compounds **161** which are later converted to corresponding oxodihydrobenzofurans **163** by treatment of formed dihydrofuran **162** derivatives with sodium periodate at aqueous methanol at room temperature for 24 and subsequent reflux with CCl_4/pyridine mixture, with around 50% overall yield for different derivatives (Scheme 40).



Scheme 40

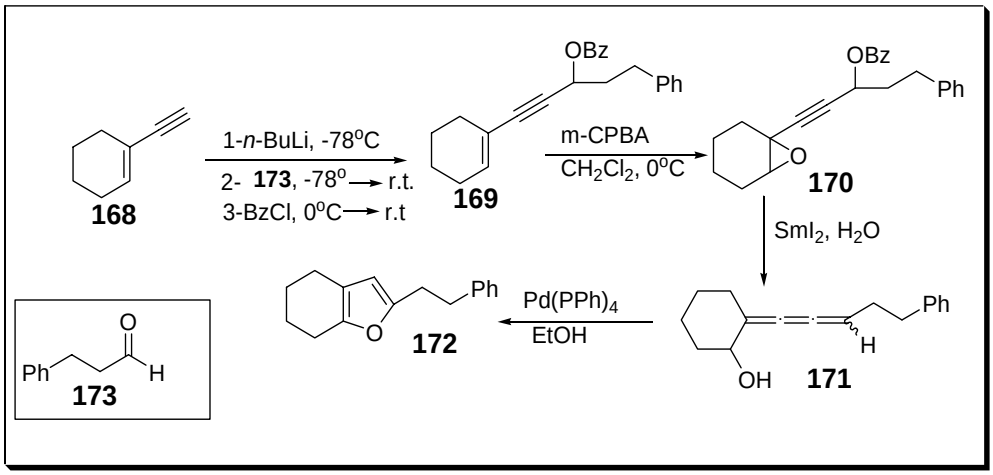
In 1998, No[51] et al. reported SeO_2 oxidation of dienones to 2-acetylfurans. Reaction scheme is depicted in scheme 41; various dienes **164** are treated with SeO_2 in dry, refluxing benzene. 2-acetyl-4,5,6,7-tetrahydrobenzofuran derivatives **165** are obtained with low (5%-32%) yields through formed selenophenes **166**, together with some 2-acetylbenzofuran product **167**.



Scheme 41

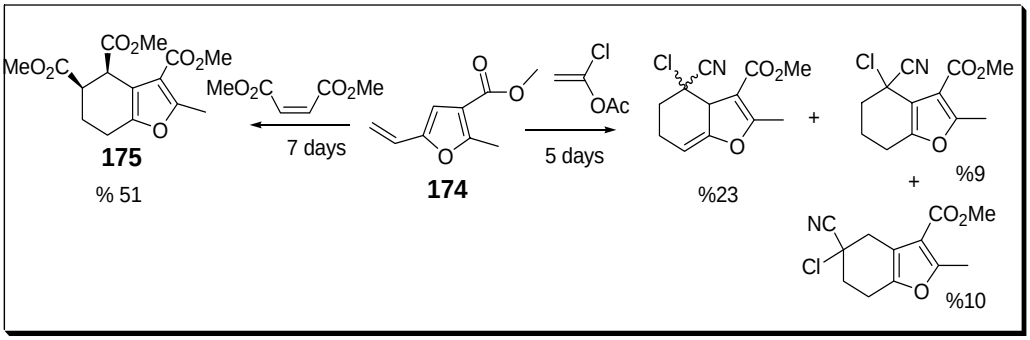
In 2001, Arrecoechea[52] et al. announced synthesis of trisubstituted furans from epoxypropargyl esters by SmI_2-promoted reduction-elimination and Pd(II) catalyzed cycloisomerization process. In scheme 42 we see the general procedure applied. The substrate ; 4,5-epoxy-2-cyclohexynyl ester **170** is prepared from treatment of enyne **168** with *n*-BuLi, reaction of formed enolate with carbonyl compound and subsequent protection of formed alcohol with benzyl chloride to afford **169** which is later oxidized with *m*-chloroperbenzoic

acid (*m*-CPBA) to obtain **170**. At this stage **170** is treated with SmI_2 which reduces **170** to an organosamarium species by donating electrons, later elimination of SmI_2 gives triene **171**. Here two procedures are applied; treatment of **171** by either potassium tertiary butoxide in tertiary butanol which gives furan compound **172** in %7 yield or $Pd(PPh_3)$ catalyzed cyclization in an alcohol as a proton source which has overall yield 50%.



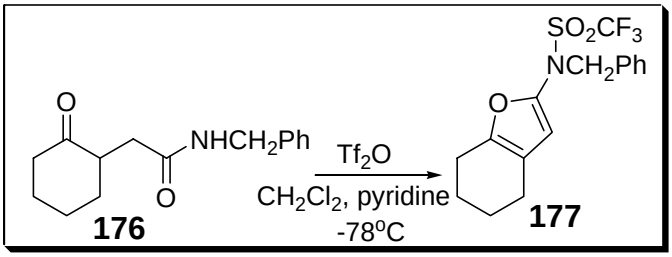
Scheme 42

At 2002 Drew[53] et. al. reported the results of an study on Diels-Alder reactions of 2-methyl-5-vinyl-3-furoate ester **174** with different dienophiles. It is told that for this type of Diels-Alder adducts like **175** may form through intra-annular cycloaddition as well as extra-annular cycloaddition reactions. In order to reduce the intra-annular pathway, they used a furan ring with an ester group so that electron density in furan ring would be reduced. In scheme 43 we see various products formed for different dienophiles. The reaction yields are generally varies depending on dienophile, and high pressure conditions together with extended reaction times (like 7 days) are also applied in some derivatives.



Scheme 43

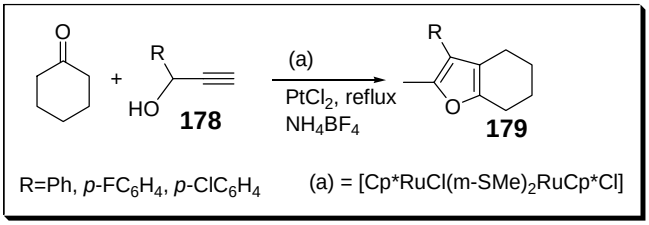
In another work in 2002, Padwa[54] et al. reported synthesis of 2-amino substituted furans which are planned to be used as dienes in Diels-Alder reactions. The amido compounds are obtained through one of isocyanide, copper catalyzed amidation, or cyclic carbinol amide-triflic anhydride approaches. In figure 48 we see the product formed by last approach. Cyclic ketoamide **176** is reacted with triflic anhydride-pyridine in dichloromethane at -78^{o} C to afford α-trifluoromethylsulfonamido furan **177** (Scheme 44).



Scheme 44: Construction of pyrrole ring by triflic acid approach

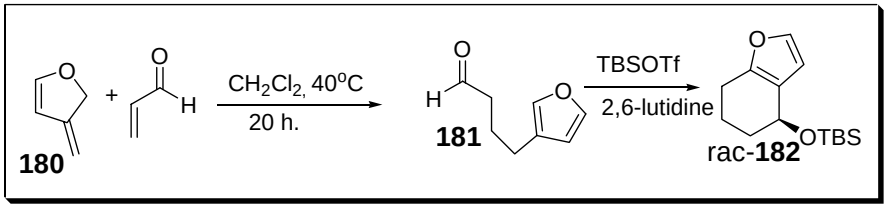
In a report by Hidai[55] et. al. at 2003, ruthenium and platinum complex catalysts are used together in synthesis of tri- and tetra- substituted furans and pyrroles from propargylic alcohols and ketones. In scheme 45 we see synthesis of substituted tetrahydrobenzofuran compounds. Cyclohexanone is reacted with

propargylic alcohol derivatives **178** to yield **179**. The reactions have 69%-75% yields for three different derivatives depicted in scheme 45.



Scheme 45

In another work by Miles and Connell[56], published in 2003, tetrahydrobenzofuran analogue has been synthesized en route to construction of A ring of vitamin D, which has a wide range of biological activity. 3-methylene-2,3-dihydrofuran **180** (scheme 46) is reacted with acrolein to obtain furanyl aldehyde **181**, which is cyclized with TBSOTf to give the TBS protected racemic alcohol **182**.

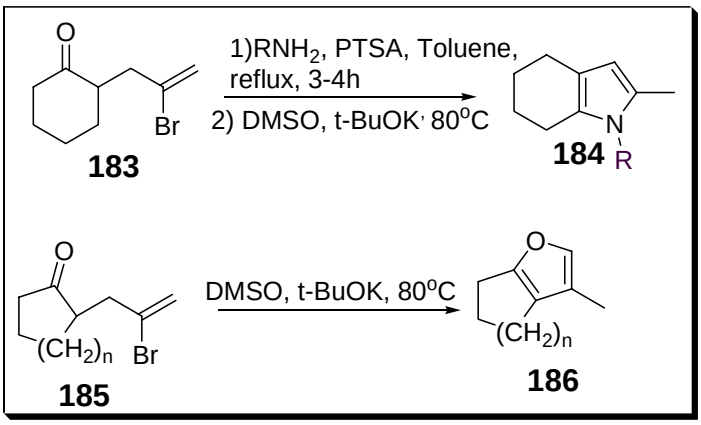


Scheme 46

1.4 The aim of the work

From the literature survey made so far, it can readily be seen that both tetrahydrobenzofurans and tetrahydroindoles are two very valuable classes of substances which have wide usage area; either as starting materials for drug substances or many other compounds which have fused heterocyclic rings in their structures and pharmacophore for many complex natural products.[57-59] Some derivatives of these compounds are potent drug substances themselves.[60] It has been observed that challenge for development of shorter, cheaper and more versatile synthetic pathways for these two substance classes has been a subject of great challenge for many chemists around the world, beginning from the early decades of last century and still today many reports about the subject can be seen since there is a huge number of natural products reported to have one or both of these bicyclic systems in their structures.

The factors outlined above directed our efforts towards development of new and shorter synthetic procedures for synthesis of derivatives of these two substance classes. The methodology that will be used is depicted in scheme 47. 2-(2-bromoallyl)cyclohexanone **183** is planned to react with primary amines and later treated with a strong base to afford *N*-substituted 2-methyltetrahydroindoles **184** through a one-pot sequence. Similarly bromoallylated cyclic ketones **185** are planned to be prepared and treated with potassium tertiary butoxide to obtain bicyclic furans **186** (including different tetrahydrobenzofuran derivatives).



Scheme 47

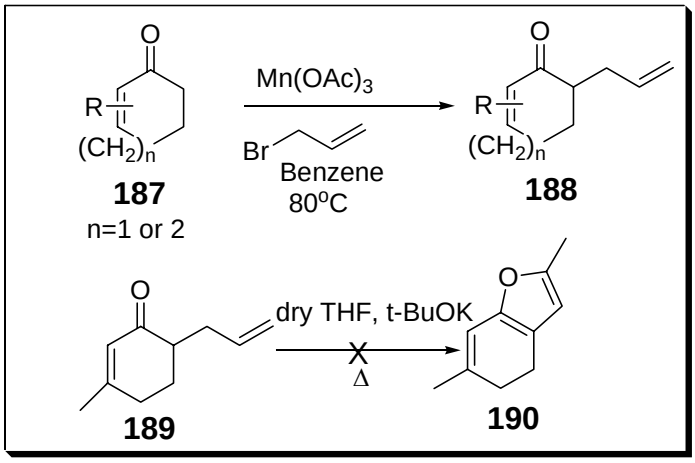
Here we represent the retrosynthetic plan for synthesis of both tetrahydrobenzofurans and tetrahydroindoles. Common starting material for syntheses of two substance classes is 2-(2-bromoallyl)cyclohexanone; treatment of 2-(2-bromoallyl)-cyclohexanone with primary amines will yield tetrahydroindoles, and treatment with a strong base will yield tetrahydrobenzofuran. 2-(2-bromoallyl)cyclohexanone is planned to be synthesized from cyclohexanone and 2,3-dibromopropene by either Stork enamine or direct alkylation with lithium diisopropylamine.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis benzofuran derivatives

In a study in 2002 by Tanyeli and Özdemirhan[61], $Mn(OAc)_3$ mediated regioselective α′-allylation of α,β-unsaturated cyclic ketones were presented (Scheme 48). A number of 5 or 6 membered α,β-unsaturated cyclic ketones **187** were treated with $Mn(OAc)_3$ and allyl bromide in refluxing benzene and α′-allylated products **188** were obtained in high yields. We tried to extend this chemistry, by searching whether it is possible to obtain a dihydrobenzofuran compound by treating allylated product with a suitable base.[62] For this purpose α'-allyl-3-methylcyclohex-2-en-1-one **189** obtained by the $Mn(OAc)_3$ mediated allylation methodology from 3-methyl-cyclohex-2-en-1-one was chosen as the model compound which would be used as starting material and the 2,5-dimethyl-4,5-dihydrobenzofuran **190** was the target compound that was planned to be afforded. Unfortunately treatment of **189** with potassium *tert*-butoxide in refluxing dry tetrahydrofuran under argon atmosphere did not afford any product at the end of 8 hours.



Scheme 48

2.1.1 Characterization of 6-allyl-3-methylcyclohex-2-en-1-one (189)

One equivalent of 3-methylcyclohex-2-en-1-one is mixed with 2 equivalent of allyl bromide and 2 equivalent of manganese(III)acetate in dry benzene at 80°C for 8 hours by using a Dean-Stark trap. After workup and chromatography yield was 73% percent.

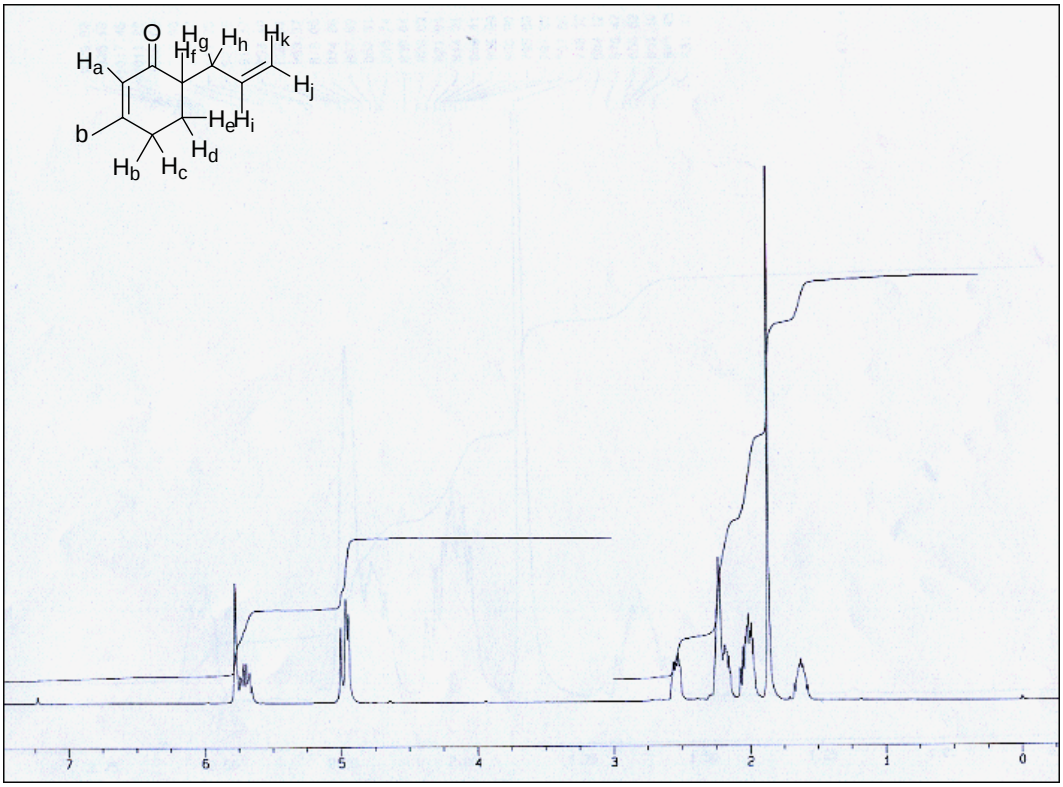


Figure 6: ^{1}H-NMR spectrum of 6-allyl-3-methylcyclohex-2-en-1-one

In figure 6 we see ^{1}H-NMR spectrum of 6-allyl-3-methylcyclohex-2-en-1-one. Proton H_e exhibits a multiplet peak between 1.58-1.68 ppm due to interaction with H_d, H_b, H_c and H_f. Methyl group (b) protons give a singlet peak at 1.87 ppm. There are three multiplets at aliphatic region; H_g, H_d peaks overlap to give a multiplet between 1.97-2.07 ppm, H_b,H_c and H_h signals overlap to give a multiplet between 2.15-2.23 ppm and H_f gives a multiplet between 2.52-2.58 ppm. Terminal olefinic protons H_k and H_j multiplet between 4.95-5.00 ppm.Olefinic proton H_i give a mutiplet between 5.66-5.76 ppm due to interaction with H_k, H_j, H_g, H_h protons. Finally olefinic H_a peak appears as a singlet at 5.78 ppm.

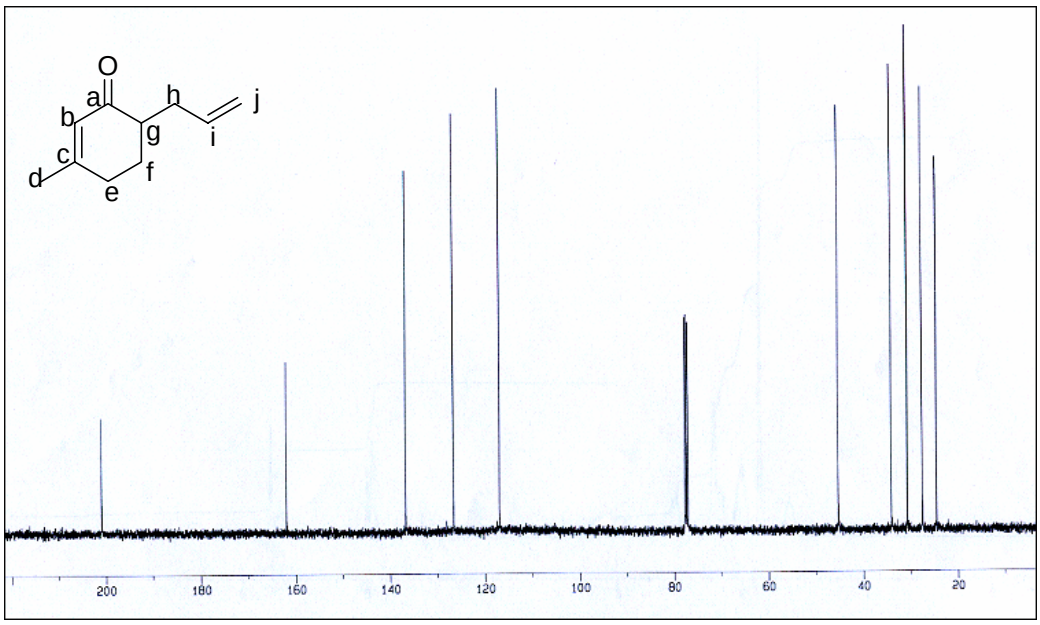
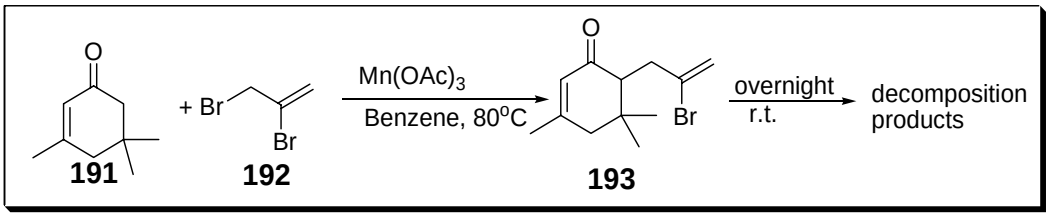


Figure 7: ^{13}C-NMR spectrum of 6-allyl-3-methylcyclohex-2-en-1-one

In figure 7 we see ^{13}C-NMR spectrum of 6-allyl-3-methylcyclohex-2-en-1-one. There are ten peaks in spectrum which confirm the proposed structure.

After this result we thought that a modification in the starting compound may be required, so we tried to introduce a 2-bromopropenyl (bromoallyl) group instead of allyl group in our α,β-unsaturated cyclic ketone. We thought that as the halogen in the allyl group would behave like a leaving group, the cyclization might proceed easier.

For this purpose we reacted 3,5,5-trimethylcyclohex-2-en-1-one (isophorone) **191** (scheme 49) with 2,3-dibromopropene **192** by using $Mn(OAc)_3$ methodology[61] and we obtained 6-(2-bromopropenyl)-3,5,5-trimethylcyclohex-2-en-1-one **193**. When this compound was left overnight at room temperature it decomposed to give a mixture of products.



Scheme 49

2.1.2 Characterization of 6-(2-bromoallyl)-3,5,5-trimethylcyclohex-2-en-1-one (193)

One equivalent of 3,5,5-trimethylcyclohex-2-en-1-one is mixed with of 2,3-dibromopropene and manganese(III)acetate in dry benzene by using a Dean-Stark trap. After workup and chromatography yield was 59% percent.

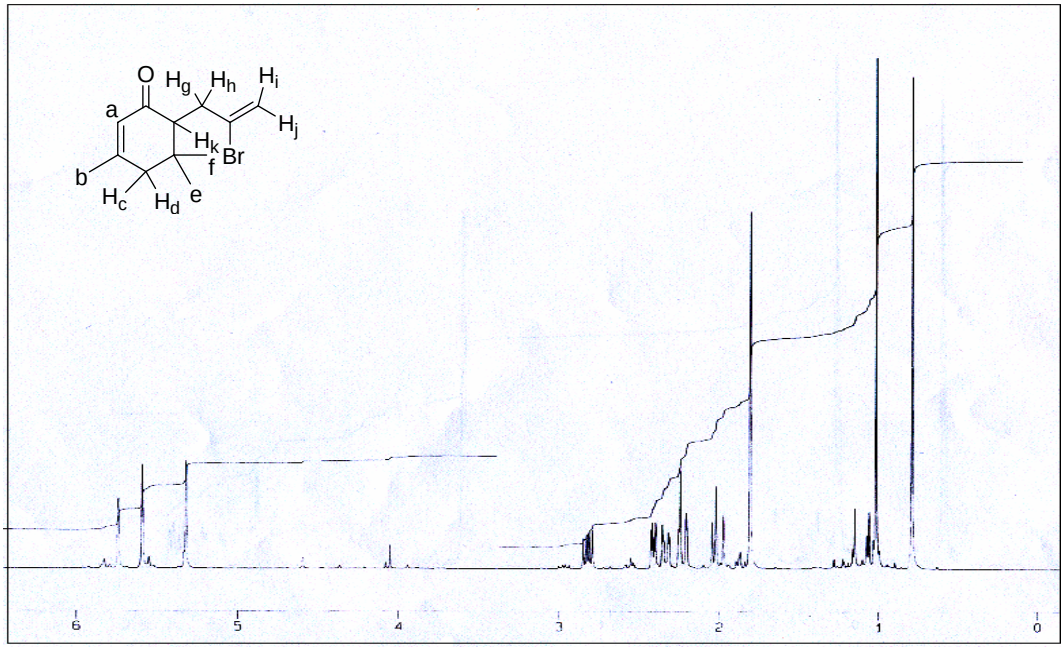


Figure 8: ^{1}H-NMR spectrum of 6-(2-bromoallyl)-3,5,5-trimethylcyclohex-2-en-1-one

In figure 8 we see ^{1}H-NMR spectrum of 6-(2-bromoallyl)-3,5,5-trimethylcyclohex-2-en-1-one. Protons on methyl groups (e), (f) give two singlet peaks at 0.79 ppm and 1.02 ppm. Protons on methyl group on C-3 (b), exhibit a singlet peak 1.81 ppm. H_c and H_d appear as two doublets at 1.96 ppm and 2.20 ppm as they interact with each other. H_g and H_h peaks are seen as two separate doublet of doublets at 2.34 ppm and 2.41 ppm due to interaction with each other and (k) proton. Proton on carbon (k) gives a doublet of doublet at 2.82 ppm. Terminal olefinic protons H_i, H_j and C-2 olefinic proton (a) gives three singlets at 5.32 5.59, and 5.74 ppm.

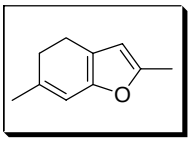
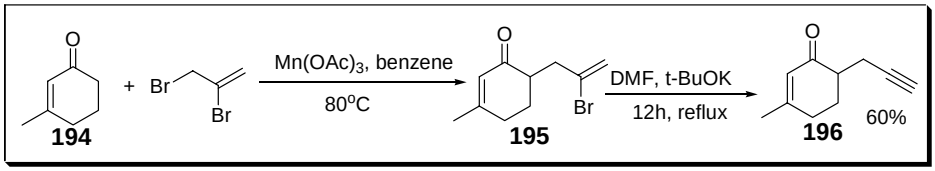


Figure 9

We reacted 2,3-dibromopropene with 3-methyl-cyclohex-2-ene-1-one **194** using $Mn(OAc)_3$ in refluxing benzene and obtained bromoallylated ketone **195** (Scheme 50). Later **195** was treated with 2 equivalent of potassium *tert*-butoxide in refluxing *N,N*-dimethylformamide (DMF) for 12h. After workup and chromatography we noticed that instead of cyclization which would yield a product as in figure 9, an elimination reaction occured and bromoallyl group was converted to propargyl group and yielded **196** in 60% yield. This may be a useful result, since introduction of a propargyl group to α′ position of an α,β-unsaturated ketone is not an easy task to perform. Another trial with **196**, this time using potassium carbonate in dimethyl sulfoxide at 110 ^{o}C for 8 hours did not give the target bicyclic furan compound.



Scheme 50

2.1.3 Characterization of 6-(2-bromoallyl)-3-methylcyclohex-2-en-1-one (195)

One equivalent of 3-methylcyclohex-2-en-1-one is mixed with 2 equivalent of 2,3-dibromopropene and 2 equivalent of manganic acetate in dry benzene at 80°C for 8 hours by using a Dean-Stark trap. After workup and chromatography yield was 50% percent.

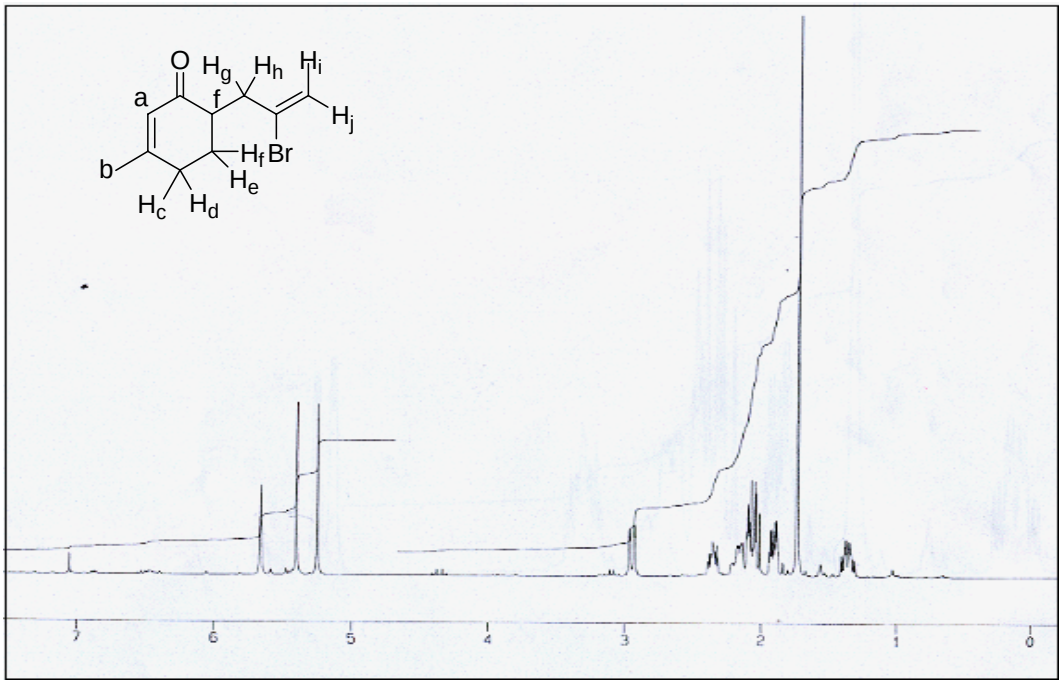


Figure 10: ^{1}H-NMR spectrum of 6-(2-bromoallyl)-3-methylcyclohex-2-en-1-one

In figure 10 we see the ^{1}H-NMR of 6-(2-bromoallyl)-3-methylcyclohex-2-en-1-one. H_e proton exhibits a multiplet peak between 1.34-1.38 ppm. The singlet at 1.74 ppm is singlet of protons on methyl group (b). Multiplet between 1.90-1.93 ppm is due to H_f. Allyllic methylene protons H_g and H_h and one of the diastereotopic methylene protons at the C-4, H_c, exhibit a multiplet between

2.04-2.11 ppm and H_d gives another multiplet between 2.14-2.18 ppm.Methine proton on C-6 (f) gives a doublet of doublet at 2.95 ppm. Terminal olefinic protons H_i and H_j give two singlets at 5.25 and 5.40 ppm. Olefinic (a) proton appears at 5.66 ppm.

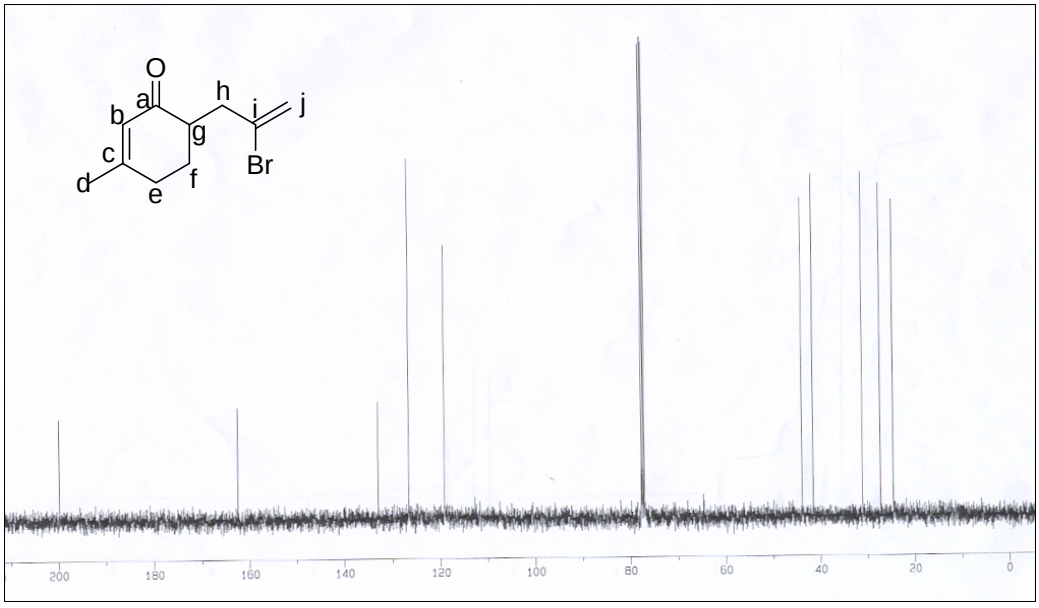


Figure 11: ^{13}C-NMR spectrum of 6-(2-bromoallyl)-3-methylcyclohex-2-en-1-one

In figure 11 we see ^{13}C-NMR spectrum of 6-(2-bromoallyl)-3-methylcyclohex-2-en-1-one. There are ten peaks in spectrum which are in accordance with the structure.

2.1.4 Characterization of 6-propargyl-3-methylcyclohex-2-en-1-one (196)

6-(2-bromoallyl)-3-methylcyclohex-2-en-1-one was treated with 2 equivalent of potassium tertiary butoxide in dry *N*,*N*-dimethyl formamide for 14 hours at reflux temperature. After workup and chromatography yield was 60%.

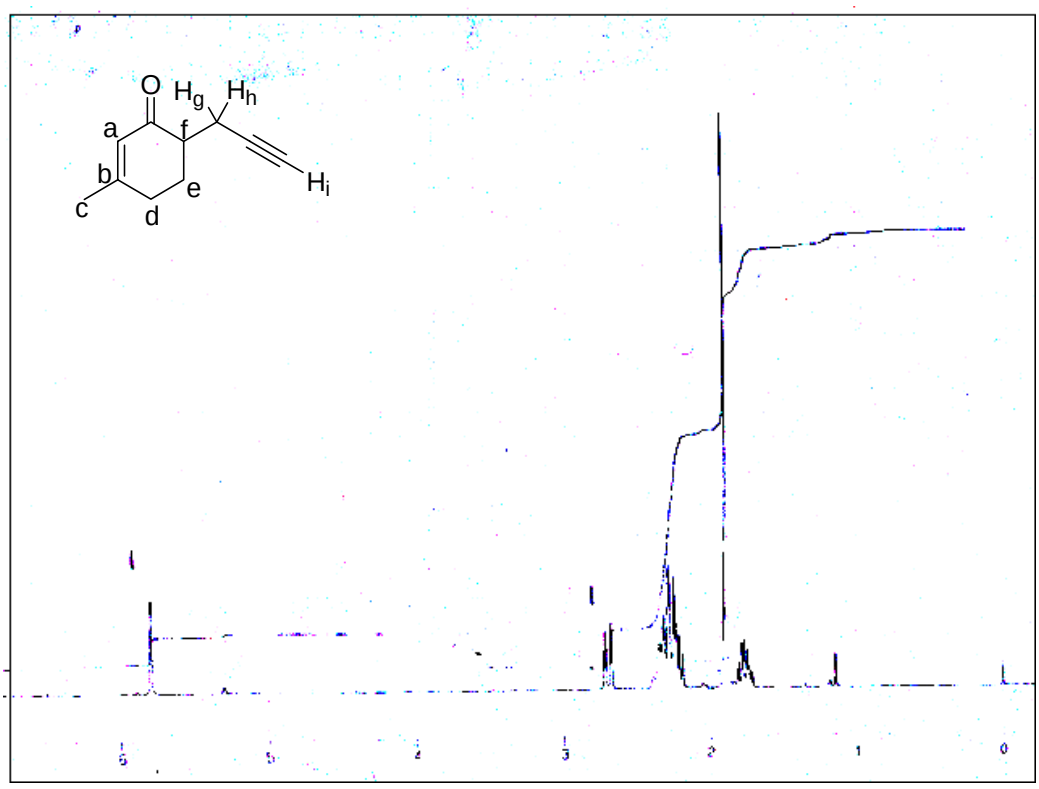


Figure 12: ^{1}H-NMR spectrum of 6-propargyl-3-methylcyclohex-2-en-1-one

In figure 12 we see ^{1}H-NMR spectrum of 6-propargyl-3-methylcyclohex-2-en-1-one. Between 1.71-1.81 ppm there is a multiplet peak of one of the methylene protons of propargyl group (H_g). Methyl group (c) protons and acetylenic proton H_i overlap to give a singlet at 1.89 ppm. Other methylene proton peaks of (d) and (e) and proton H_g overlap to give a multiplet between 2.19-2.39 ppm. The peak of proton on stereogenic center (f) appears as a

multiplet between 2.67-2.73 ppm. Olefinic proton (a) appear at 5.58 ppm as a singlet.

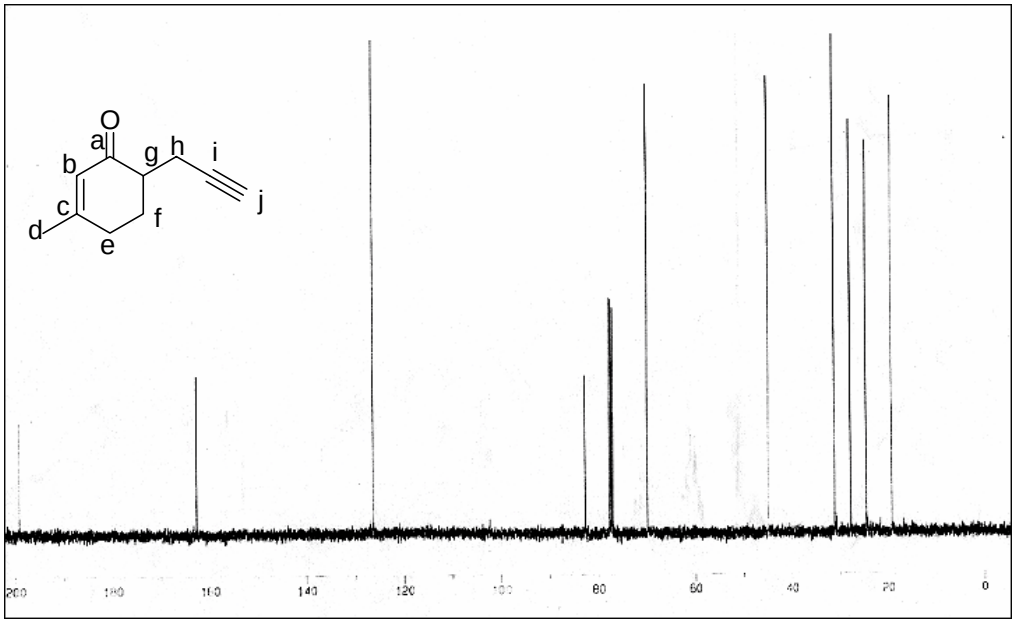
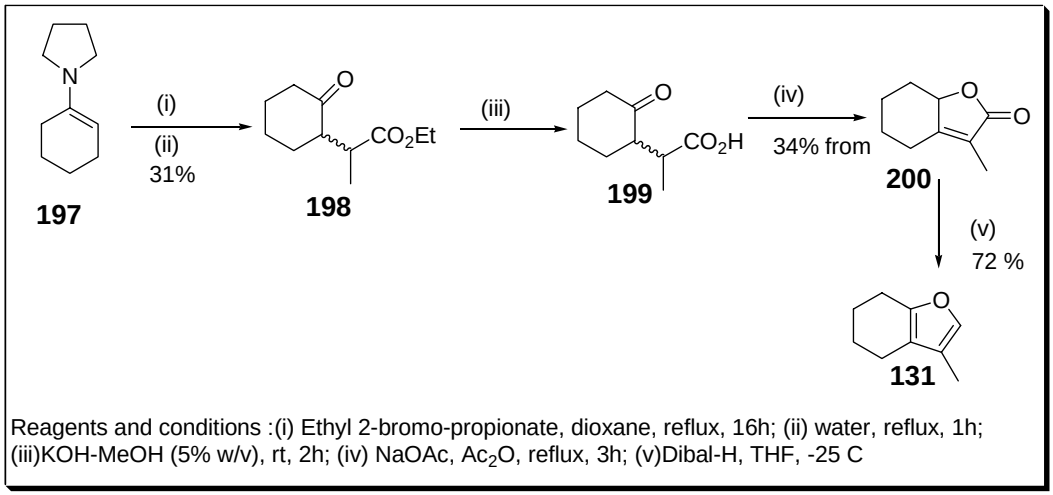


Figure 13: ^{13}C-NMR spectrum of 6-propargyl-3-methylcyclohex-2-en-1-one.

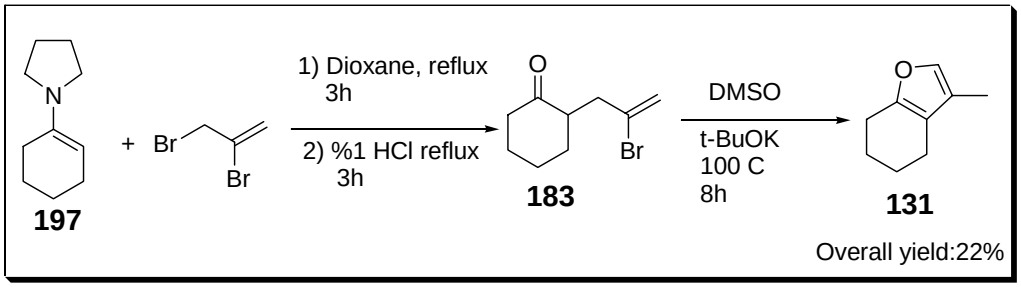
In figure 13 we see ^{13}C-NMR spectrum of 6-propargyl-3-methylcyclohex-2-en-1-one. There are nine peaks which confirm the proposed structure.

In a report published in 2003 by Baldwin[63] et al., synthesis of a tetrahydrobenzofuran derivative in five steps is described. Synthesized compound, 3-methyl-4,5,6,7-tetrahydrobenzofuran **131** in scheme 51 is later converted in several steps to bisesquiterpene lactones. Overall yield for the formation of **131** from **197** is 7 %. The method involves formation of lactone **200** from acid **199** by a condensation reaction and subsequent reduction of **200** by diisobutyl aluminum hydride.



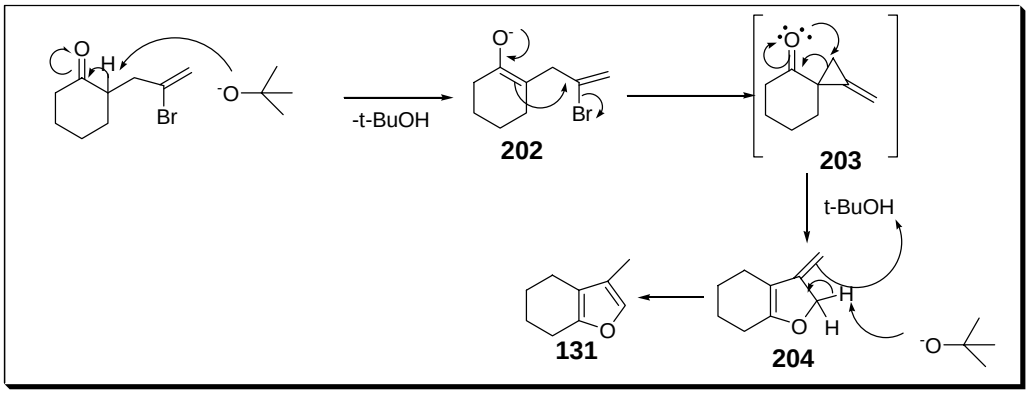
Scheme 51

We synthesized the same compound with an easier and shorter procedure as depicted on scheme 52. 1-pyrrolidinyl-1-cyclohexene **197** is reacted with 2,3-dibromopropene and later hydrolyzed to obtain 2-(2-bromopropenyl)cyclohexan-1-one . Later **183** is treated with potassium tertiary butoxide in dry dimethyl sulfoxide and **131** is afforded with 22% overall yield from **197**. The interesting point is that the methyl substituent appears regiospecifically at 3- position of the furan ring instead of the expected 2- position.



Scheme 52

This interesting result is explained by Zefirov's mechanism which is proposed by N.S. Zefirov[64] et al. in 1984. According to this mechanism as seen in scheme 53, first base abstracts the relatively acidic proton to form the enolate **202** which later rearranges by attack of negatively charged C-2 on cyclohexane ring to halogenated carbon on allyl group, to give spiro intermediate **203**. This intermediate is proposed to be quickly rearranged to dihydrofuran compound with an exocyclic double bond **204**. Finally **204** reaarranges to **131**.



Scheme 53

2.1.5 Characterization of 2-(2-bromoallyl)cyclohexanone (183)

1-pyrrolidinyl-1-cyclohexene is mixed with 1 equivalent of 2,3-dibromopropene in refluxing dry dioxane for 3 hours and later hydrolized with 1% HCl solution and refluxed for another 3h. After workup mixture is purified by vacuum distillation. Yield is 40%.

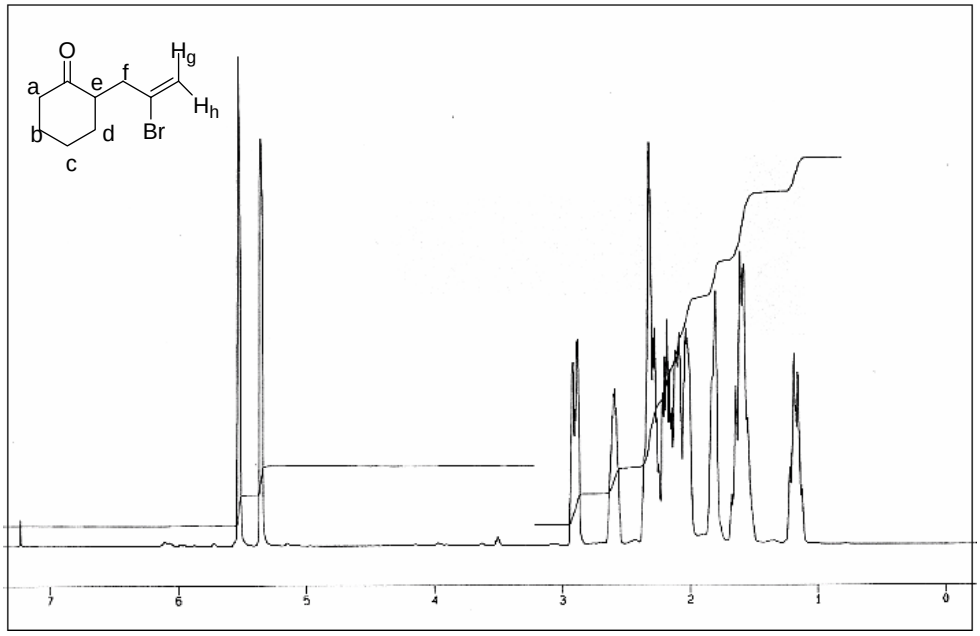


Figure 14: ^{1}H-NMR spectrum of 2-(2-bromoallyl)cyclohexanone

In figure 14 we see ^{1}H-NMR spectrum of 2-(2-bromoallyl)cyclohexanone. Between 1.13-2.93 ppm we see a series of multiplets due to aliphatic carbon hydrogens (a), (b), (c), (d), (e), (f). Terminal olefinic protons H_g and H_h give two singlets at 5.36 ppm. 5.53 ppm. Characterization is confirmed by literature[69].

2.1.6 Characterization of 3-methyl-4,5,6,7-tetrahydrobenzofuran (131)

1 equivalent of 2-(2-bromoallyl)cyclohexan-1-one was mixed with 1.5 equivalent of potassium *tert*-butoxide in dry dimethyl sulfoxide, under argon atmosphere at 100 ^{o}C for 8 hours.After workup and chromatography, % 40 percent.

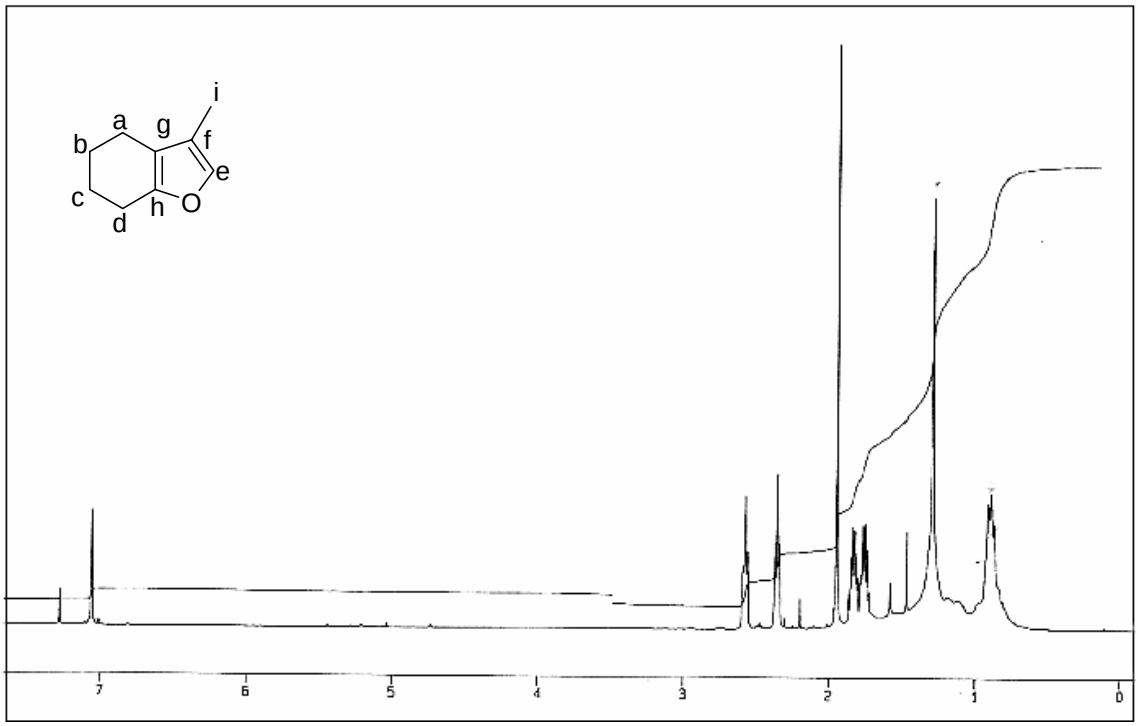


Figure 15: ^{1}H-NMR spectrum of 3-methyl-4,5,6,7-tetrahydrobenzofuran.

In figure 15 we see the ^{1}H-NMR spectrum of 3-methyl-4,5,6,7-tetrahydrobenzofuran. Protons on C-5 (c) and C-4 (b) carbons give two multiplet peaks between 1.73-1.78 ppm and 1.81-1.87 ppm due to interacting with each other an (a) and (d) protons. Methyl carbon (i) gives a singlet peak at 1.97 ppm. C-7 (d), C-4 (a) protons give two multiplet peaks between 2.34-2.38 ppm and 2.56-2.59 ppm respectively. Furan C-2 peak proton (e) appears as a singlet at 7.07 ppm.

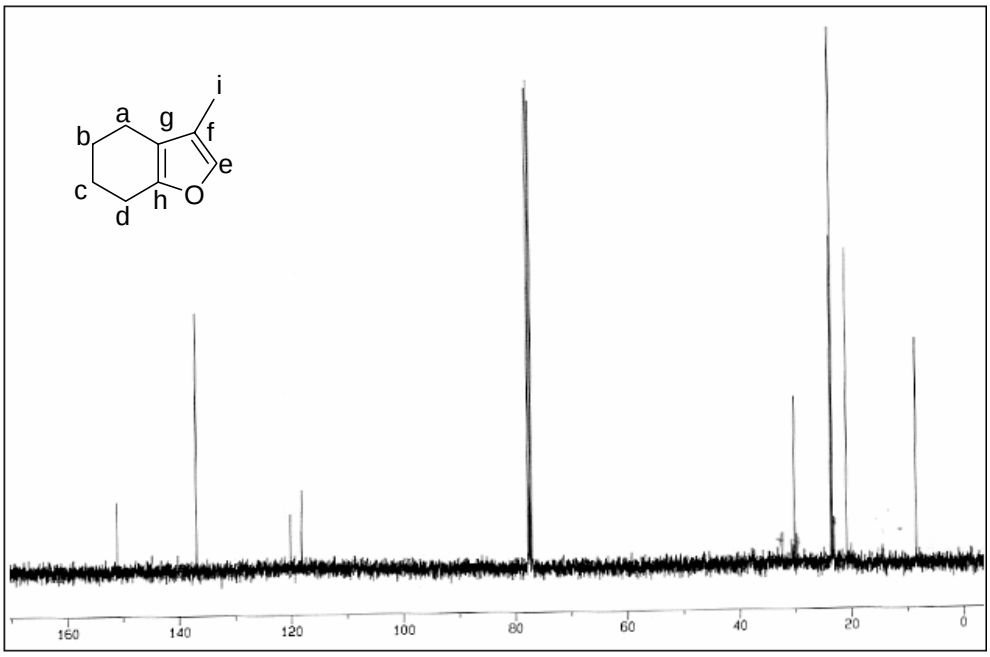
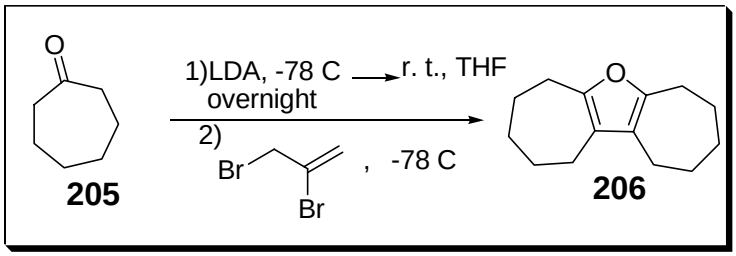


Figure 16: ^{13}C-NMR spectrum of 3-methyl-4,5,6,7-tetrahydrobenzofuran.

In figure 16 we see ^{13}C-NMR spectrum of 3-methyl-4,5,6,7-tetrahydrobenzofuran.There are nine peaks in accordance with the proposed structure.[63]

In order to obtain other bicyclic furan derivatives we tried to introduce bromoallyl group to α- position of cyclic ketones. For this purpose we tried to synthesize 2-(2-bromopropenyl)cycloheptan-1-one by first preparing the lithium enolate of cycloheptanone **205** (scheme 54) with lithium diisopropylamide (LDA) treatment in dry THF and added 2,3-dibromopropene onto formed enolate at –78^{o}C. Instead of bromoallylated product we obtained tricyclic furan product **206**. Probably formed enolate gave condensation reaction with itself while standing overnight to reach room temperature from –78^{o}C which it was initially prepared, to afford **206** and not reacted with 2,3-dibromopropene. Behaviour of other cyclic ketones under same conditions will be explored. There is another report on literature about synthesis of this compound.[65]



Scheme 54

2.1.7 Characterization of a symmetric tricyclic furan (206)

Lithium enolate of cycloheptanone is prepared by treating cycloheptanone with lithium diisopropylamide (LDA) in dry THF at -78^{o}C and in order to ensure formation of enolate mixture is gradually warmed to room temperature. Later the mixture is cooled back to -78^{o}C and 2,3-dibromopropene is added onto formed enolate at this temperature. After workup and chromatography yield was 82%. We believe 2,3-dibromopropene has no role in formation of product.

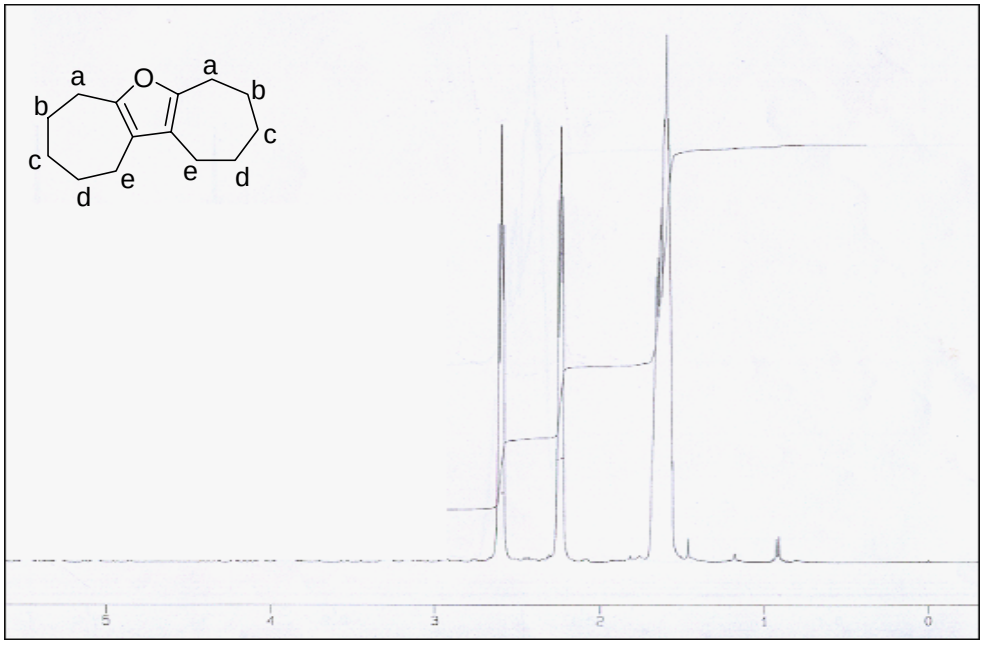
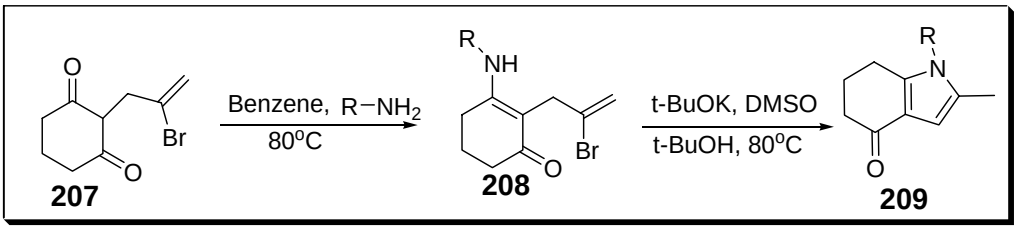


Figure 17: ^{1}H-NMR spectrum of symmetric tricyclic furan product **206**

In figure 17 we see ^{1}H-NMR spectrum of tricyclic furan product **206**. The protons on carbons (b), (c) and (d) overlap to give a multiplet peak between 1.56-1.67 ppm. Protons on carbons (e) and (a) give two triplet signals at 2.26 ppm and 2.61 ppm respectively. There is also literature data about the compound.[65] Melts between 59-62 ^{o}C.

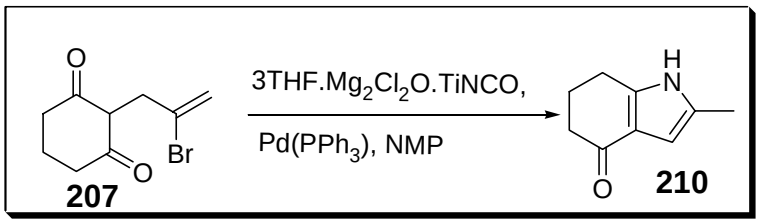
2.2 Synthesis of *N*-substituted 4,5,6,7-tetrahydroindole derivatives

In a study reported by Demir, Akhmedov and Şeşenoğlu[66] in 2002, syntheses of 1,2,3,5 substituted pyrrole derivatives are described. In this study, first a diketone is reacted with the 2,3-dibromopropene regioselectively to obtain a bromoallylated diketone like **207** (scheme 55). Later afforded diketone is reacted with a primary amine to form an enamine **208** and subsequently treated with a base to form the substituted pyrrole product, **209**.



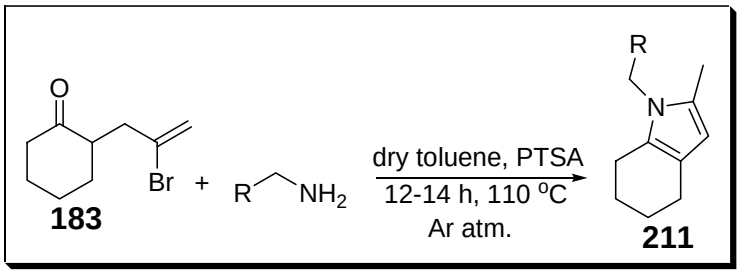
Scheme 55

In another work by Mori[67] et. al., transition metals are used for 2,3,5 substituted pyrrole derivatives **210** from same kind of starting materials as shown in scheme 56.



Scheme 56

Our first strategy for obtaining enamine was mixing the bromoallylated cyclohexanone **183**, 1.5 equivalent of primary amine (with respect to **183) ,** and a drying agent in dry toluene under argon atmosphere at room temperature (Scheme 57). The purpose for using drying agent was; it could absorb the water which will be a product of the condensation reaction between primary amine and ketone and prevent possible hydrolysis of formed enamine (or imine) which would lower the yield of reaction. As drying agent we used $MgSO_4$ which was dried under the vacuum at 200 ^oC. Unfortunately this drying agent did not afford any condensation product after overnight mixing at room temprature in toluene. The best procedure for obtaining condensation product is, mixing primary amine (again 1.5 equivalent w.r.t **183**), bromoallylated ketone **183** and a few cystals of *p*-toluene sulfonic acid (PTSA) which would protonate the carbonyl oxygen of ketone making it more susceptible to nucleophilic attack in refluxing dry toluene under argon atmosphere, using a Dean-Stark trap which would provide azeotropic removal of eliminated water from reaction medium. Using this procedure we were able to obtain the *N*-substituted 2-methyl-4,5,6,7-tetrahydroindole **211** derivatives directly. The yields are about 30-50% for different derivatives. Using more than a few crystals of PTSA results in para-toluene sulfonate salt of amine formation.

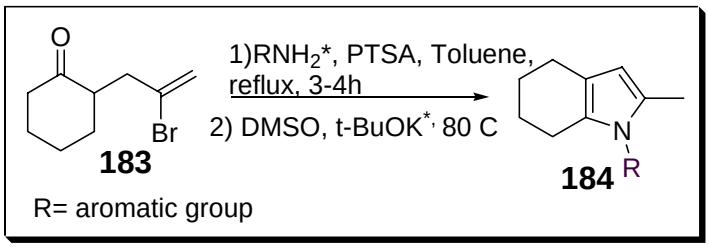


Scheme 57

L-alanine ethyl ester's hydrochloride salt is also used as a primary amine with the same procedure described above. But no pyrrole formation is observed. The

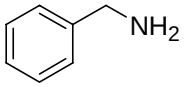
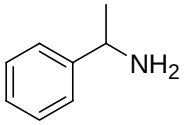
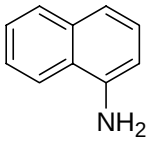
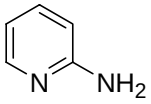
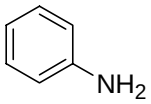
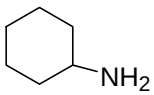
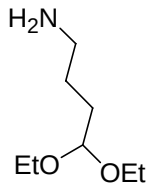
possible reason for failure may be prolonged heating at reflux temperature which results in amide linkage formation and which yields peptides.

For aromatic primary amines we followed a different route, as procedure described above yields only enamine formation with the primary aromatic amines. For conversion of the enamines to corresponding pyrrole compounds, we first mixed bromoallylated ketone **183**, with 1.5 equivalent of primary amine (w.r.t. **183**) in dry toluene, under argon atmosphere with a few crystals of para-toluene sulfonic acid (PTSA), using a Dean-Satrk trap for 3-4 hours. Without making any further purification we just evaporated solvent *in vacuo*, and added dry dimethyl sulfoxide together with 1.5 equivalent of potassium tertiary butoxide (w.r.t. **183** weighed at the beginning of the reaction) at 80 ^{o}C. After mixing under argon atmosphere for another 3-4 hours, and purification, we obtained pyrrole compounds with yields between 75-90%.



Scheme 58

Table 1- Yields with different amines

RNH_2	Yield	Entry
	50%	**211a**
	42%	**211b**
	74%	**211c**
	72%	**211d**
	92%	**211e**
	%31	**211f**
	%22	**211g**

In table 1, we see yields of tetrahydroindole derivatives for different primary amines. It is seen that aliphatic amines have lower yields for tetrahydroindole formation. Characterization of the products were made by ^{1}H-NMR and ^{13}C-NMR spectra. Mass spectra is also available for benzylamine product. All tetrahydroindole derivatives obtained have the methyl group at the C-2 position on the pyrrole ring regiospecifically. Tetrahydroindole compounds obtained from aliphatic amines are sensitive to silica gel, so flash chromatography through a short and wide column shall be preferred.

2.2.1 Characterization of *N*-benzyl-2-methyl-4,5,6,7-tetrahydroindole (211a)

2-(2-bromoallyl)cyclohexan-1-one was mixed with 1.5 equivalent of benzylamine in dry toluene, under argon atmosphere and refluxed for 12 hours by using a Dean-Stark trap. After evaporation of solvent and chromatography yield was 50%.

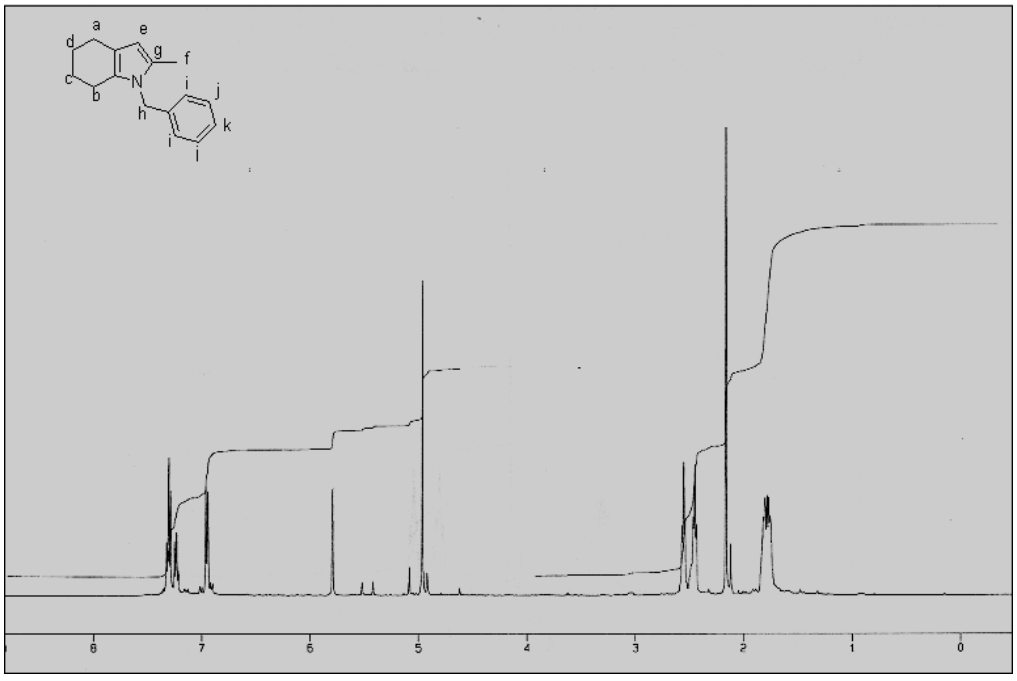


Figure 18: ^{1}H-NMR spectrum of *N*-benzyl-2-methyl-4,5,6,7-tetrahydroindole

In figure 18 we see ^{1}H-NMR spectrum of *N*-benzyl-2-methyl-4,5,6,7-tetrahydroindole. ^{1}H-NMR spectrum of *N*-benzyl-2-methyl-4,5,6,7-tetrahydroindole exhibits a multiplet for protons on methylene groups (c) and (d) between 1.61-1.79 ppm which are interacting with each other and (a) and (b) protons . Methyl group on pyrrole ring (f) shows a singlet at 2.17 ppm. There is a triplet of (a) protons which are interacting with (d) protons at 2.44 ppm and a triplet of (b) protons which are interacting with (c) protons at 2.50 ppm. A singlet of (h) protons of the methylene group bonded to phenyl ring appears at 4.97 ppm. Another singlet of the (e) proton on the pyrrole ring appears at 5.80 ppm. Aromatic protons at (i) carbons show a doublet at 7.10 ppm. Other aromatic protons at (j) and (k) appears as a multiplet between 7.22-7.33 ppm.

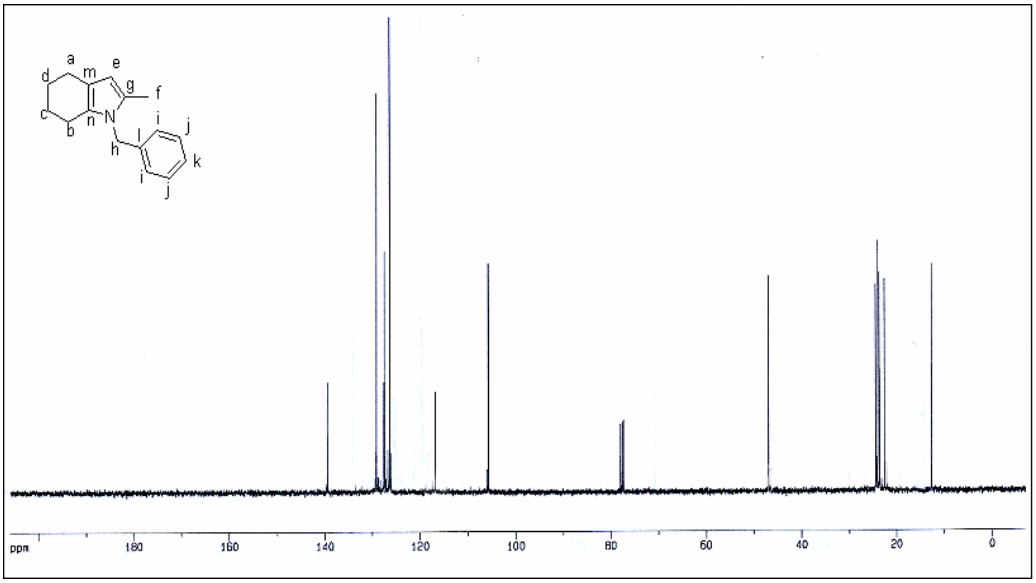


Figure 19: ^{13}C-NMR spectrum of *N*-benzyl-2-methyl-4,5,6,7-tetrahydroindole

In figure 19 we see ^{13}C-NMR spectrum of *N*-benzyl-2-methyl-4,5,6,7-tetrahydroindole. There are fourteen peaks in spectrum in accordance with the proposed structure.

Mass analysis gives the closed formula $C_{16}H_{20}N$ for the compound.

2.2.2 Characterization of *N*-((*S*)-methylbenzyl)-2-methyl-4,5,6,7-tetrahydroindole (211b)

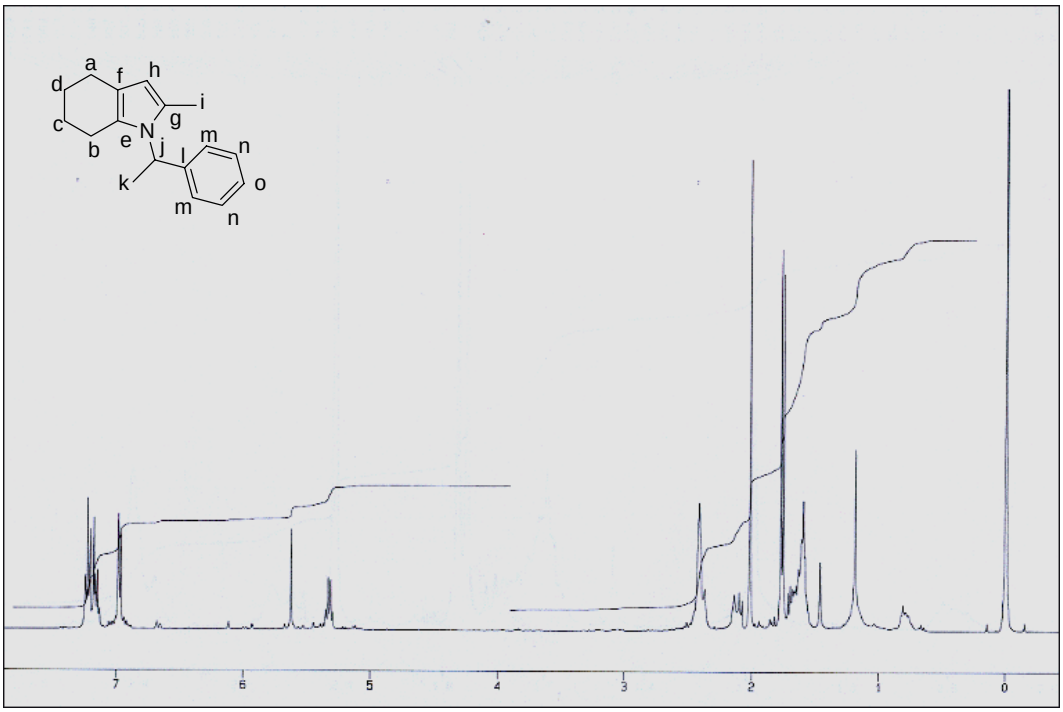


Figure 20: ^{1}H-NMR of *N*-((*S*)-methylbenzyl)-2-methyl-4,5,6,7-tetrahydroindole

^{1}H-NMR spectrum of *N*-((*S*)-methylbenzyl)-2-methyl-4,5,6,7-tetrahydroindole is presented in figure 20. Protons on C-5 (c), and C-6 (d) overlap to give multiplet between 1.57-1.63 ppm. Protons on methyl group (k) appear as a doublet at 1.76 ppm, and protons methyl group on pyrrole ring (i) are seen as a singlet at 2.02 ppm. C-4 (a) and C-7(b) protons exhibit a broad singlet 2.41 ppm. Benzylic proton (j) appears as a quartet due to interaction with methyl hydrogens (k), at 5.35 ppm. Characteristic C-3 pyrrole proton is seen at 5.63 ppm. Protons (m) on phenyl ring appear as a doublet at 6.96 ppm, other aromatic protons (n) and (o) appear as a multiplet between 7.14-7.25 ppm due to overlap. Other peaks are due to impurities.

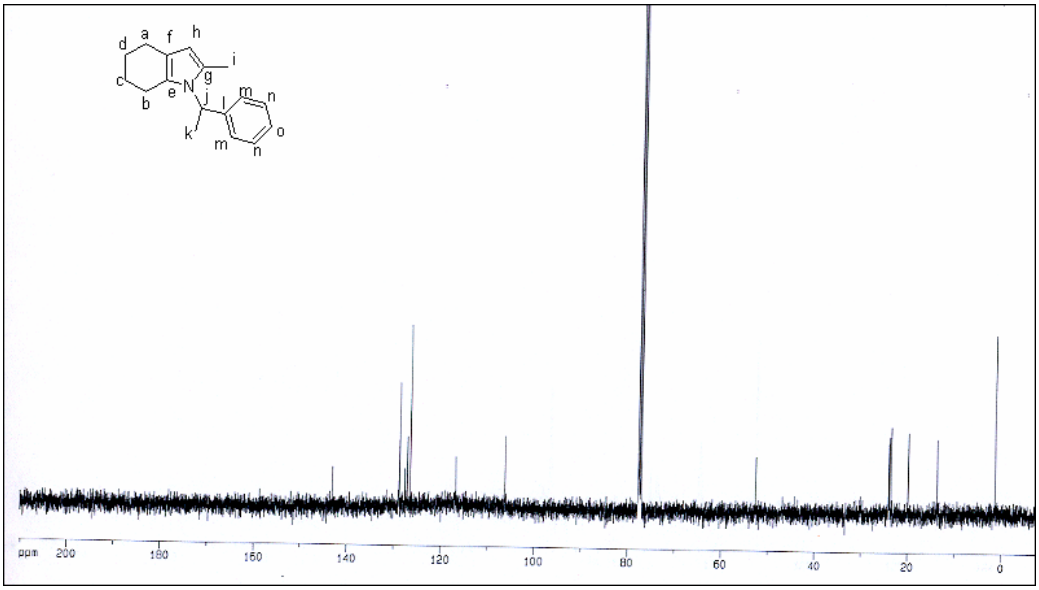


Figure 21: ^{13}C-NMR spectrum of *N*-((*S*)-methylbenzyl)-2-methyl-4,5,6,7-tetrahydroindole

We see ^{13}C-NMR spectrum of *N*-((*S*)-methylbenzyl)-2-methyl-4,5,6,7-tetrahydroindole in figure 21. There are fifteen peaks which are in accordance with the proposed structure.

Mass analysis of the compund gave the closed formula $C_{17}H_{22}N$.

2.2.3 Characterization of *N*-(1-naphthyl)-2-methyl-4,5,6,7-tetrahydroindole (211c)

2-(2-bromoallyl)cyclohexan-1-one was mixed with 1.5 equivalent of 1-naphtylamine in dry toluene, under argon atmosphere and refluxed for 3 hours by using a Dean-Stark trap. After evaporation of solvent, without any further purfication, dry dimethyl sulfoxide and 1.5 equivalent (with respect to 2-(2-bromoallyl)cyclohexan-1-one) potassium *tert*-butoxide is added to reaction medium and mixture is kept at 80^{o}C by using a magnetic stirrer for another 3h. After chromatography yield is 74%.

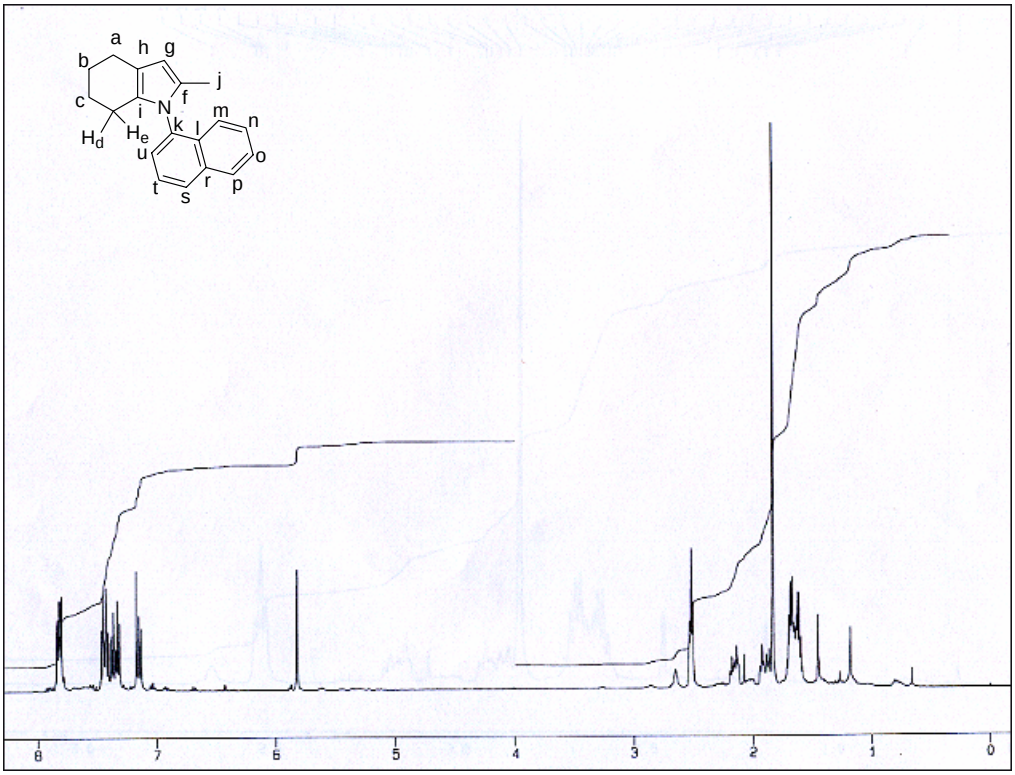


Figure 22: ^{1}H-NMR spectrum of *N*-(1-naphthyl)-2-methyl-4,5,6,7-tetrahydroindole

In figure 22 we see the ^{1}H-NMR spectrum of *N*-(1-naphthyl)-2-methyl-4,5,6,7-tetrahydroindole. Peaks of protons on C-5 and C-6 (b), (c) methylenes overlap to give a multiplet between 1.57- 1.72 ppm. Protons on methyl group on pyrrole ring (j) appear as a singlet peak at 1.84 ppm. Due to effect of naphtyl ring current signal H_d and H_e appears as two separate multiplets between 1.87-1.92 ppm and 2.13-2.20 ppm. C-4 (a) protons give a triplet signal at 2.53 ppm due to interaction with C-5 (b) protons. Characteristic pyrrole C-3 (g) hydrogen peak appears at 5.83 ppm. Aromatic naphtalene protons appear as a series of multiplets between 7.14-7.84 ppm.

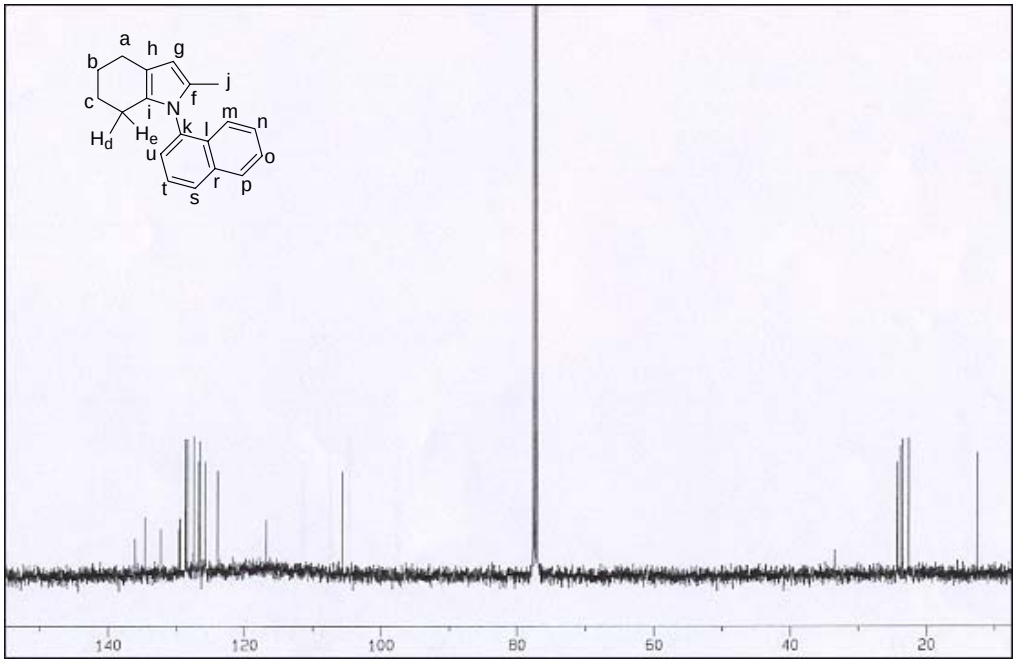


Figure 23: ^{13}C-NMR spectrum of *N*-(1-naphthyl)-2-methyl-4,5,6,7-tetrahydroindole.

In figure 23 we see the ^{13}C-NMR spectrum of *N*-(1-naphthyl)-2-methyl-4,5,6,7-tetrahydroindole. There are ninteeen peaks in spectrum which are in accordance with the proposed structure.

2.2.4 Characterizatin of *N*-(2-pyridinyl)-2-methyl-4,5,6,7-tetrahydroindole (211d)

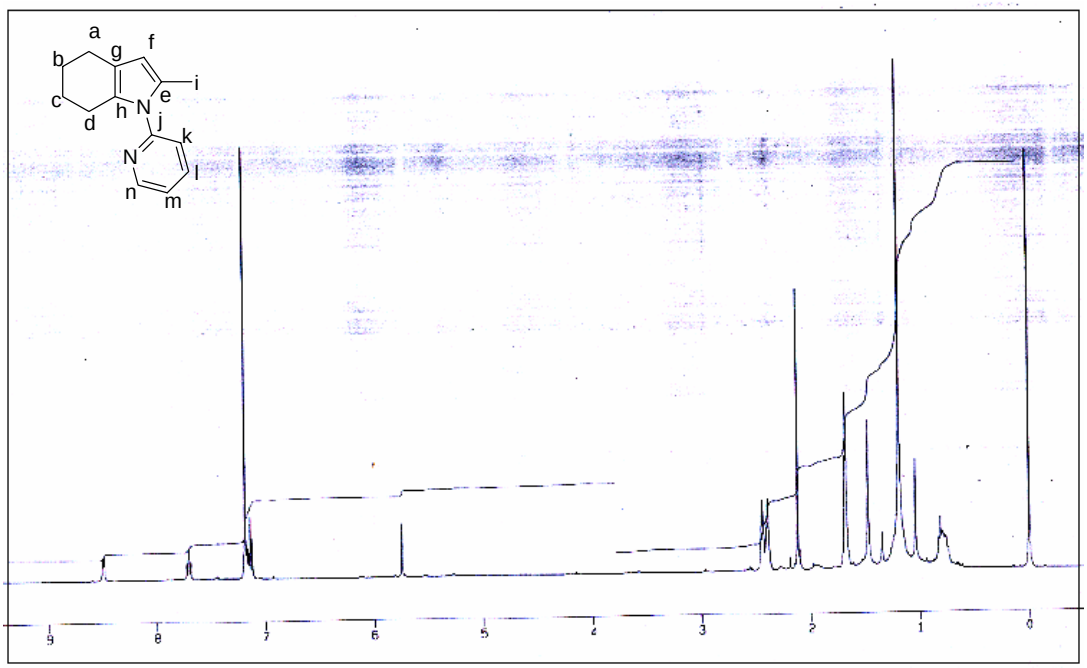


Figure 24: ^{1}H-NMR spectrum of *N*-(2-pyridinyl)-2-methyl-4,5,6,7-tetrahydroindole

In figure 24 we see ^{1}H-NMR spectrum of *N*-(2-pyridinyl)-2-methyl-4,5,6,7-tetrahydroindole. Protons on C-4 (b) and C-5 (c) overlap to exhibit a triplet at 1.68 ppm. Protons of methyl group on pyrrole ring (i) appear as a singlet at 2.12 ppm. C-4 protons (a) and C-7 protons (d) are seen as two broad singlets at 2.40 ppm and 2.45 ppm respectively. Characteristic C-3 pyrrole hydrogen (f) appears at 5.75 ppm. Among aromatic protons on pyridine ring; peaks of protons (m) and (k) overlap to give a multiplet between 7.13-7.18 ppm. Proton (l) signal appears as a doublet of triplet at 7.71 ppm due to interaction with (m), (k) and (n) protons. Proton (n) signal appears as a doublet of doublet at 8.50 ppm due to interaction with (m) and (l) protons.

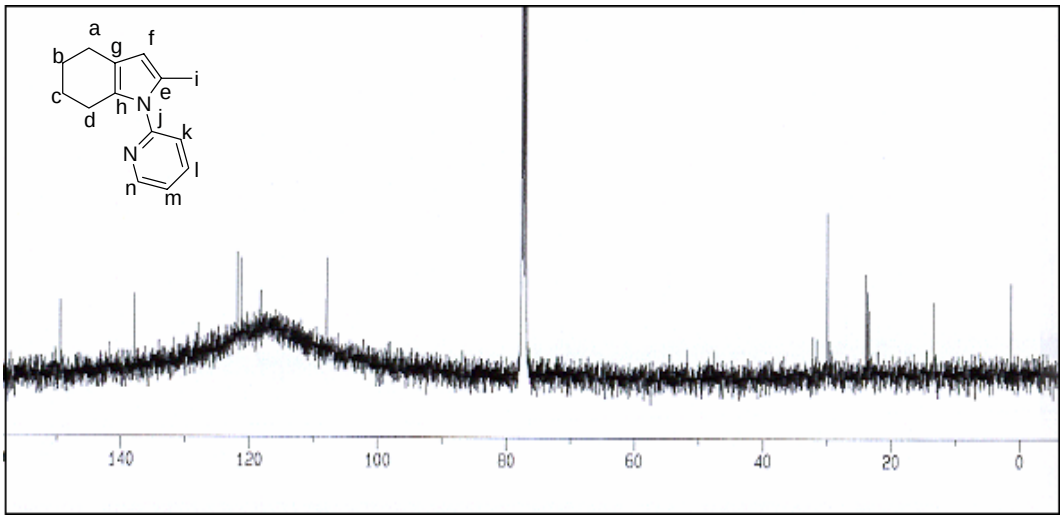


Figure 25: ^{13}C-NMR spectrum of *N*-(2-pyridinyl)-2-methyl-4,5,6,7-tetrahydroindole

In figure 25 ^{13}C-NMR spectrum of *N*-(2-pyridinyl)-2-methyl-4,5,6,7-tetrahydroindole is presented. There are fourteen peaks in accordance with proposed structure in spectrum.

2.2.5 Characterization of *N*-phenyl-2-methyl-4,5,6,7-tetrahydroindole (211e)

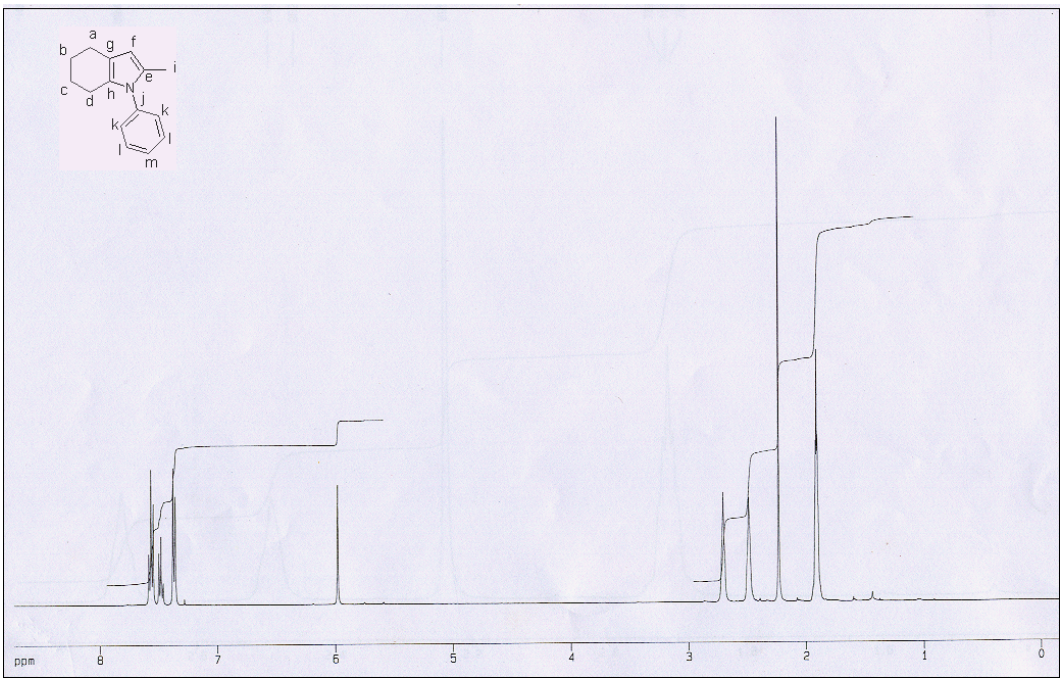


Figure 26: ^{1}H-NMR spectrum of *N*-phenyl-2-methyl-4,5,6,7-tetrahydroindole

In figure 26 we see ^{1}H-NMR spectrum of *N*-phenyl-2-methyl-4,5,6,7-tetrahydroindole. Protons on C-4 (b) and C-5 (c) overlap to exhibit a triplet at 1.91 ppm. Protons on methyl on pyrrole ring (i) appear as a singlet at 2.24 ppm. C-4 protons (a) and C-7 protons (d) are seen as two broad singlets at 2.49 ppm and 2.62 ppm respectively. Characteristic C-3 pyrrole hydrogen (f) appears at 5.99 ppm. Among aromatic protons on phenyl ring; equivalent (k) protons appear as a doublet at 7.37 ppm, (m) proton appear as a triplet at 7.49 ppm and equivalent (l) protons appear as a triplet at 7.57 ppm.

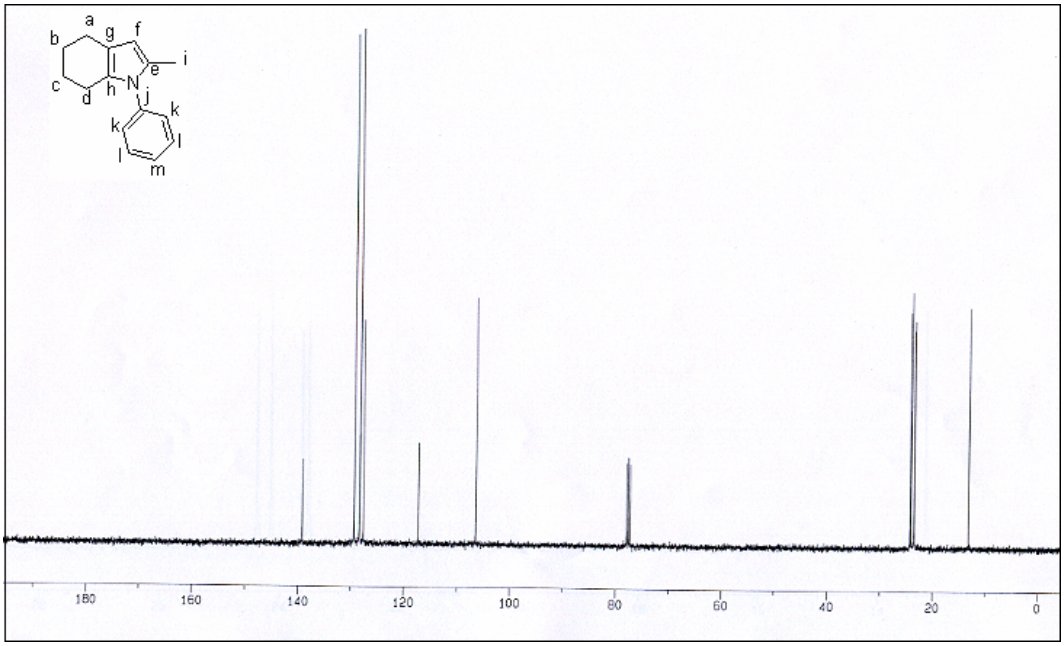


Figure 27: ^{13}C-NMR spectrum of *N*-phenyl-2-methyl-4,5,6,7-tetrahydroindole

In figure 27 ^{13}C-NMR spectrum of *N*-phenyl-2-methyl-4,5,6,7-tetrahydroindole is presented. Methyl carbon on pyrrole ring (i) peak appears at 13.20 ppm. Aliphatic C-4, C-5, C-6, C-7 carbons (a), (b), (c), (d) give peaks at 23.51, 23.62, 24.13, 24.37 ppm. Pyrrole C-3 carbon (f) signal is seen at 106.49 ppm and (g) signal is seen at 117.31 ppm. Carbons on the phenyl ring (j), (k),(l), (m) and pyrrole carbon (e) give peaks at 127.67, 128.34, 128.45, 129.44 ppm, altough there should be five distinct peaks, two of them overlap to give a single peak (probably (l) and (m) carbon peaks). Aromatic (h) carbon on pyrrole ring gives a signal at 139.29 ppm.

2.2.6 Characterization of *N*-(cyclohexyl)-2-methyl-4,5,6,7-tetrahydroindole (211f)

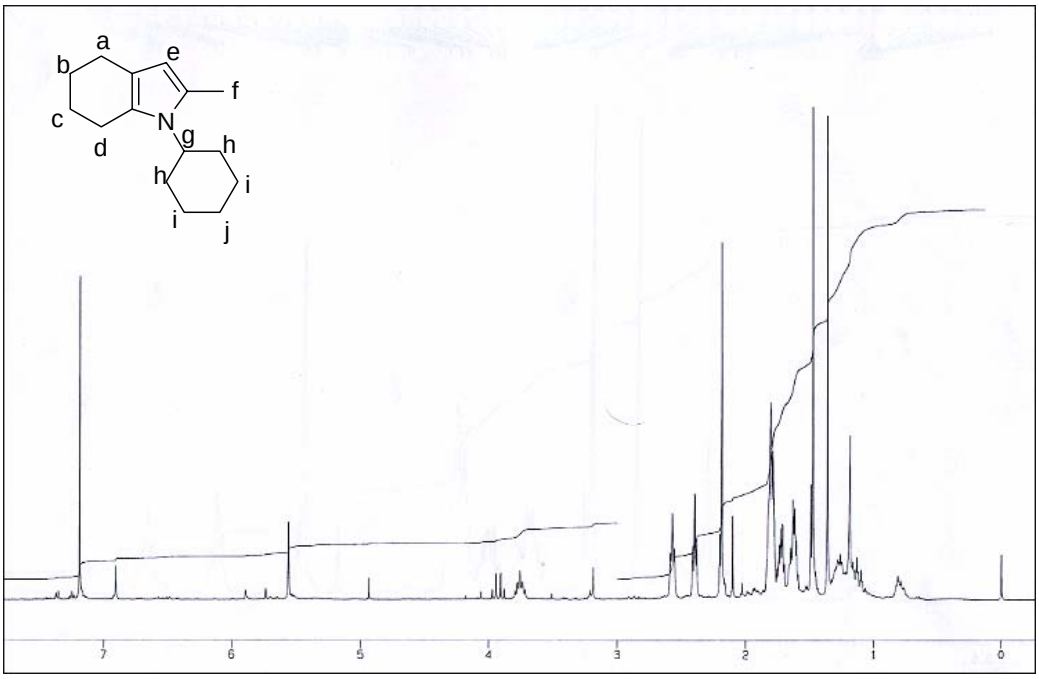


Figure 28: ^{1}H-NMR spectrum of *N*-(cyclohexyl)-2-methyl-4,5,6,7-tetrahydroindole

In figure 28 we see ^{1}H-NMR spectrum of *N*-(cyclohexyl)-2-methyl-4,5,6,7-tetrahydroindole. Between 1.10-1.84 ppm ring methylenes (b), (c), (h), (i), and (j) give a series of multiplets. Methyl protons on (f) give a singlet peak at 2.20 ppm. Allylic methylene protons on (a) and (d) give two triplet peaks at 2.39 ppm and 2.57 ppm. Proton on methine group (g) appears as a pentet at 3.76 ppm. Characteristic pyrrole peak appears at 5.55 ppm. Characterization of the product was confirmed by literature.[72]

2.2.7 Synthesis of *N*-(4,4-diethoxybutyl)-2-methyl-4,5,6,7-tetrahydroindole (211g)

2-(2-bromoallyl)cyclohexan-1-one was mixed with 1.5 equivalent of 4-aminobutyraldehyde diethylacetal in dry toluene, under argon atmosphere and refluxed for 3 hours by using a Dean-Stark trap. After evaporation of solvent, without any further purfication, dry dimethyl sulfoxide and 1.5 equivalent (with respect to 2-(2-bromoallyl)cyclohexan-1-one) potassium *tert*-butoxide is added to reaction medium and mixture is kept at 80°C by using a magnetic stirrer for another 3h. After chromatography yield is 21%.

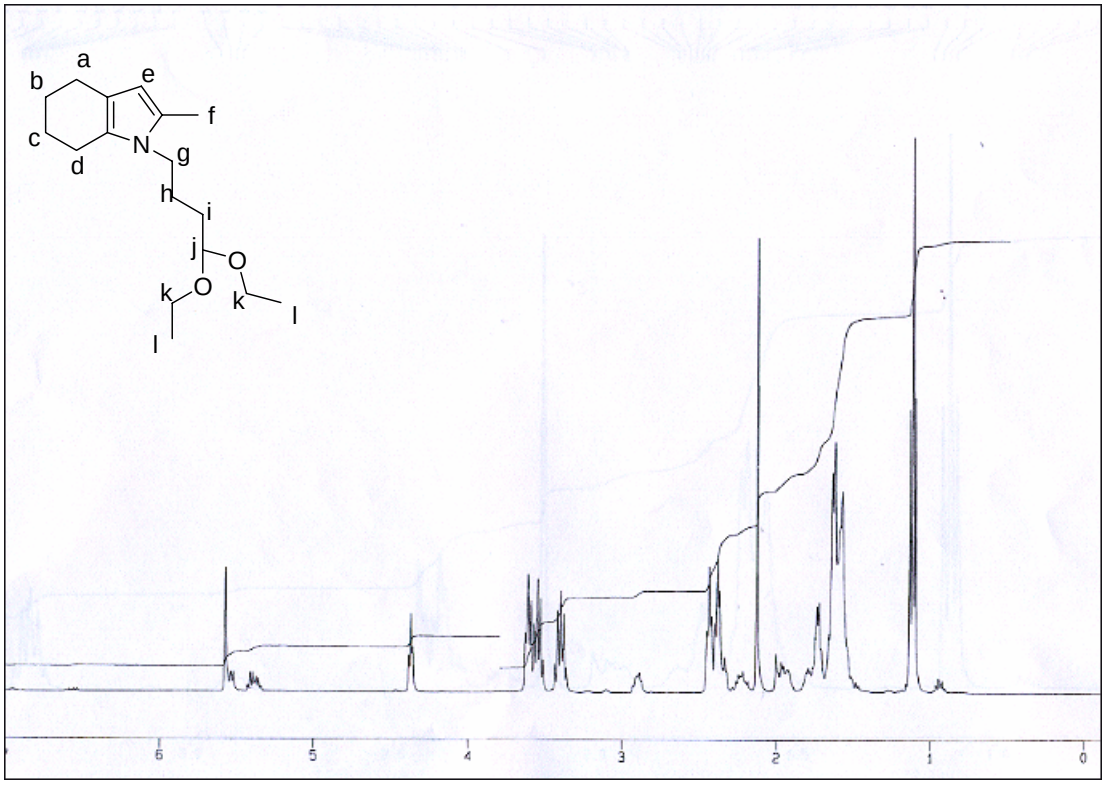
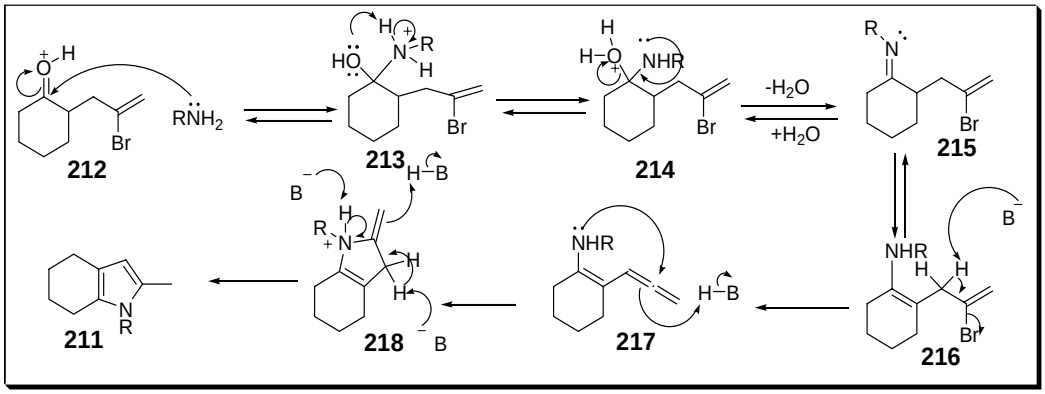


Figure 29: ^{1}H-NMR spectrum of *N*-(4,4-diethoxybutyl)-2-methyl-4,5,6,7-tetrahydroindole

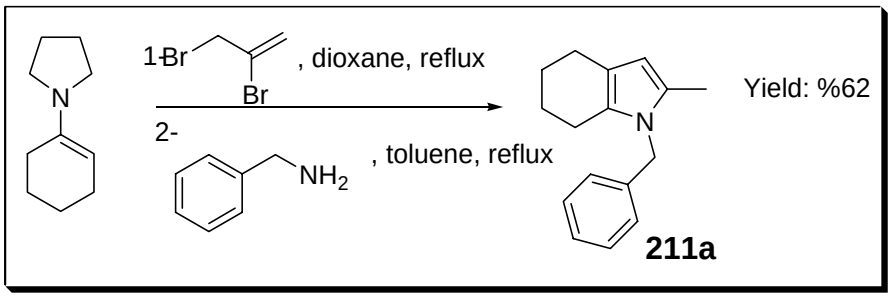
In figure 29 we see ^{1}H-NMR spectrum of *N*-(4,4-diethoxybutyl)-2-methyl-4,5,6,7-tetrahydroindole.Methyl carbons (l) give a single triplet peak at 1.12. Aliphatic carbons on (b), (c), (h), (i) give multiplets between 1.49-2.22 ppm. Methyl (f) protons give a singlet at 2.13 ppm. Allylic (a) and (d) protons give triplet peaks at 2.37 ppm and 2.44 ppm. Protons on methylenes (k), (g) bonded to heteroatoms give a series of multiplets between 3.36-3.63 ppm. Proton on stereogenic center (j) give triplet peak at 4.38 ppm. Characteristic pyrrole hydrogen on C-2 carbon (e) is observed at 5.58 ppm.

In scheme 59, we see the propoposed mechanism for the reaction. The reaction starts with the attack of amine to the carbonyl group of the ketone **211** of which oxygen is protonated by the *p*-toluene sulfonic acid. Elimination of the water yields the imine **215** through the tetrahedral intermediates **213** and **214** that are formed by the attack of amine. Imine **215** is thought to be in equilibrium with the enamine **216**. At this step base abstracts the proton on nitrogen the yield allene **217**. In syntheses of aromatic tetrahydroindoles this base is potassium tertiary butoxide itself, in aliphatic amines case, no base is added to reaction medium so any anion in reaction medium (or maybe the amine itself) may react as the base. Attack of nitrogen on allene substituent affords the dihydropyrrole compound with an exocyclic double bond **218**, which rearranges to give the *N*-substituted 2-methyl-4,5,6,7-tetrahydroindole compound **211**.



Scheme 59

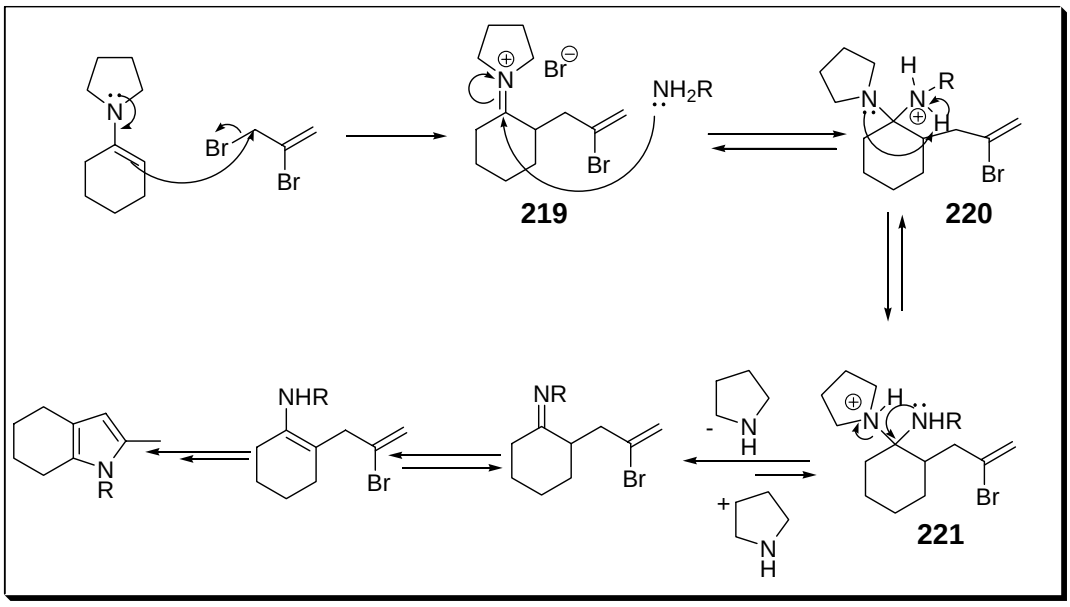
In order to increase the yield for the tetrahydroindole formation from aliphatic amines we tried to develop a transamination procedure. Before hydrolysis, the reaction between freshly distilled 1-pyrrolidinyl-1-cyclohexene with 2,3-dibromopropene in dioxane yields a white waxy solid (if 1-pyrrolidinyl-1-cyclohexene is not freshly distilled you afford a blackish-brown viscous liquid) which is thought to be a bromide salt formed from the reaction. Later this solid is reacted with 1.5 eq. of benzylamine as the primary aliphatic amine using the same procedure applied for aliphatic amines. Here the pyrrolidine group is planned to behave as a better leaving group than protonated oxygen and be more susceptible to nucleophilic attack. There was a 12% increase in the yield when compared with the reaction between bromoallylated ketone and benzylamine to afford tetrahydroindole derivative **211a** (scheme 60).



Scheme 60

Proposed reaction mechanism for transamination is presented in scheme 60. The mechanism is quite similar to one which is presented at scheme 59. The reaction starts with attack of Stork enamine to 2,3-dibromopropene to yield the iminium salt **219**. Due to permanent positive charge on nitrogen, iminium carbon should be more susceptible to nucleophilic attack. After the attack of the amine, tetrahedral intermediate **220** which is in equilibrium with **221** may be formed. After elimination of the pyrrolidine from the molecule, the reaction proceeds through the imine which is in equilibrium with the enamine and after similar

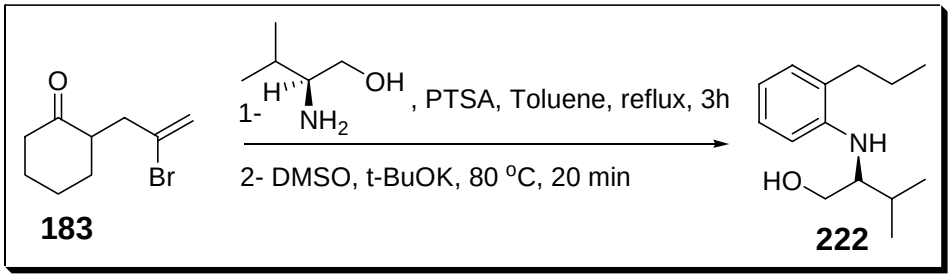
steps to those in scheme 60, tetrahydroindole derivative is afforded. We believe that after some adjustment in the reaction parameters, (like solvent, temperature etc.) transamination may be a better procedure for one-pot synthesis of tetrahydroindole derivatives from aliphatic amines so research for development of a better procedure will continue.



Scheme 61

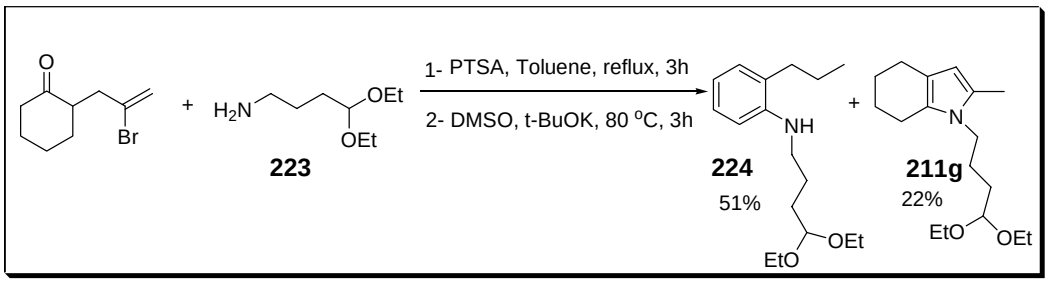
In order to obtain a chiral tetrahydroindole derivative we used (*S*)-valinol as our primary amine and applied the procedure used in syntheses of tetrahydroindole derivatives from aromatic amines. First bromoallylated ketone was refluxed with 1.5 eq. of (*S*)-valinol in dry toluene with a few crystals of PTSA using a Dean-Stark trap. At the end of three hours complete conversion of starting material to a product is observed by checking with thin layer chromatography. All the reactions were carried under argon atmosphere.Without making any purification and characterization, we evaporated solvent, added dimethyl sulfoxide and 1.5 eq. of potassium *tert*-butoxide (w.r.t bromoallylated ketone). It is observed that all of the product afforded from the last reaction was transformed completely with 20 minutes to some other product.

The result was quite surprising that instead of having tetrahyroindole derivative we obtained a substituted benzene ring **222** as depicted in scheme 62. Characterization of **222** was made by full NMR analysis.



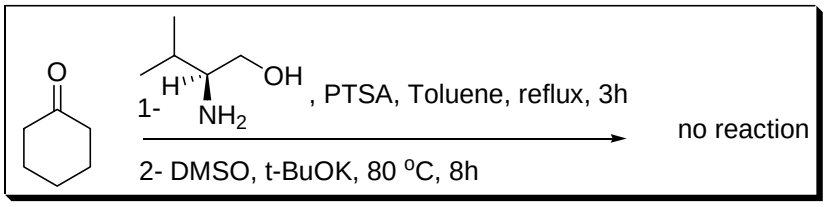
Scheme 62

The same result was obtained when 4-aminobutyraldehyde diethylacetal **223** (scheme 63) was used as the starting material and procedure above was applied. The difference is that, conversion at base treatment step took 3 hours to be completed and some tetrahydroindole **224** formation together with the aromatization product **211g** is also observed.



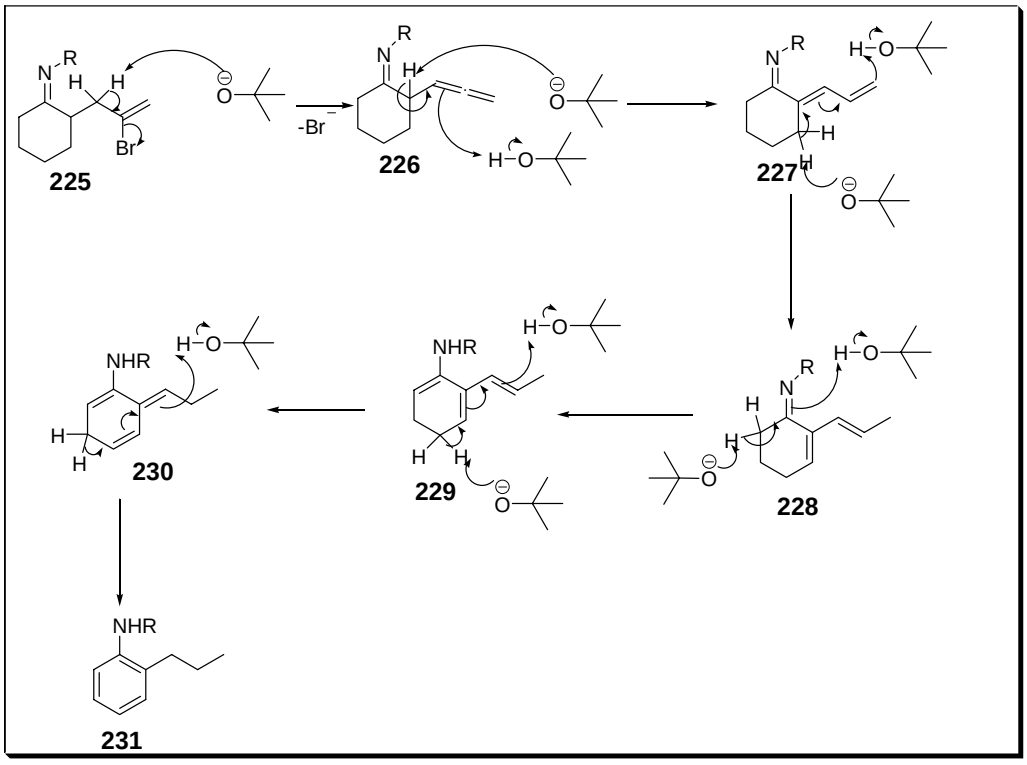
Scheme 63

In order to investigate whether presence of bromoallyl group is essential for aromatization, we repeated the same experimental procedure by using cyclohexanone and (*S*)-valinol (scheme 64). We observed that at the end of 8 hours in base treatment in dimethyl sulfoxide step no aromatization product could be obtained by this methodology so we arrived to conclusion that for aromatization bromoallyl group must be present in the cyclohexanone ring.



Scheme 64

Proposed reaction mechanism for aromatization is depicted in Scheme 65.



Scheme 65

Reaction is proposed to be started by reaction of imine (which is formed at the first step of the reaction, where the amine is refluxed with the bromoallylated ketone) with potassium *tert*-butoxide to yield allene substituted ketone **226**. This compound rearranges to **227** where the double bonds are conjugated affording the more stable intermediate. Later the exocylic double bond becomes endocyclic by the help of the base to yield **228.** The imine **228** is transformed to enamine **229** by reacting with base (this imine formation step may be earlier depending on the relative acidity of the protons on the molecule in each step, position of the enamine formation step in the whole sequence will not affect the formation of final product). Rearrangement of **229** yields **230** where the double bond on the propene group moves between to α position of cyclohexane ring. At the last step **231** aromatizes and **232** is formed as the product. The base used (potassium *tert*-butoxide) behaves both like reagent and catalyst throughout the reaction. This mechanism explains why the presence of the bromoallyl group is essential because the unsaturation in the allyl group is, in a way, "moved" into cyclohexane ring, without bromoallyl group there will be no source for unsaturation.

2.2.8 Characterization of 2-(2-propylphenylamino)-3-methylbutan-1-ol (223)

2-(2-bromoallyl)cyclohexan-1-one was mixed with 1.5 equivalent of (*S*)-valinol in dry toluene, under argon atmosphere and refluxed for 3 hours by using a Dean-Stark trap. After evaporation of solvent, without any further purfication, dry dimethyl sulfoxide and 1.5 equivalent (with respect to 2-(2-bromopropenyl)cyclohexan-1-one) potassium *tert*-butoxide is added to reaction medium and mixture is kept at 80^{o}C by using a magnetic stirrer for another 30 min. After chromatography yield is quantitative.

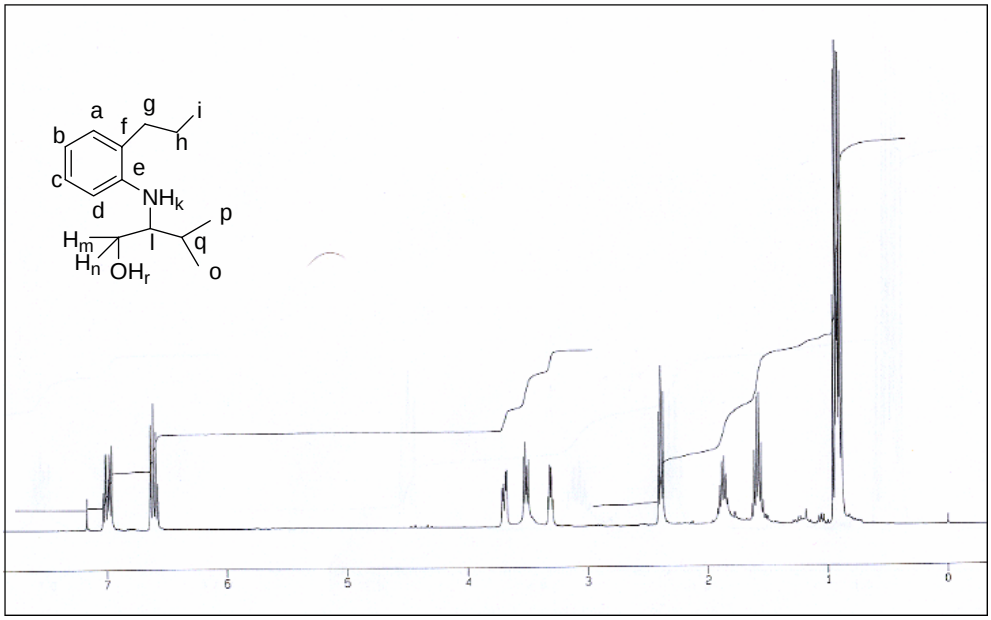


Figure 30: ^{1}H-NMR of 2-(2-propylphenylamino)-3-methylbutan-1-ol

By using full NMR analysis technique we tried to prove proposed structure for the product. Structure is seen on figure 30. In figure 30 we also see ^{1}H-NMR of *o*-propyl-*N*-(2-(3-methyl-1-propanol))aniline. Methyl group protons on (i), (o), (p) overlap to give multiplet peak between 0.83-0.96 ppm. Methylene protons on (h) give a sextet at 1.59 ppm due to interaction with (i) and (g) protons. Proton on methine carbon (q) and H_r peaks overlap and give a multiplet between 1.78-1.92 ppm. We believe that hydroxy proton H_r is at this range because upon shaking with deuterated water intensity of this peak changes. Protons on methylene carbon (g) exhibit a triplet peak at 2.40 ppm. Proton at stereogenic center (l) gives a quartet at 3.32 ppm. H_m and H_k overlap to exhibit a multiplet peak between 3.50-3.54 ppm. H_n gives a doublet of doublet at 3.70 ppm. Aromatic protons on (b) and (d) give a multiplet peak between 6.58-6.64 ppm and protons on (a) and (c) give another multiplet between 6.97-7.04 ppm.

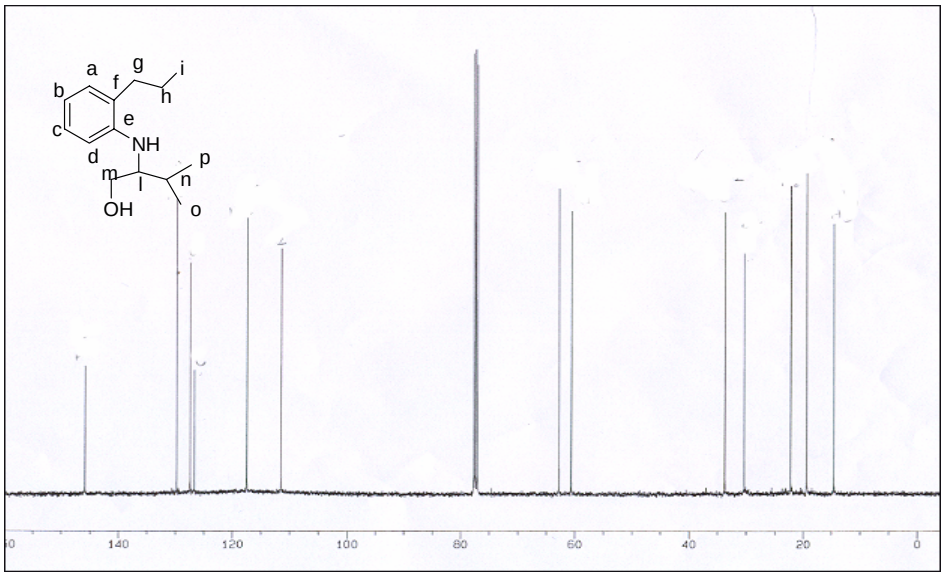


Figure 31 : ^{13}C-NMR spectrum of 2-(2-propylphenylamino)-3-methylbutan-1-ol

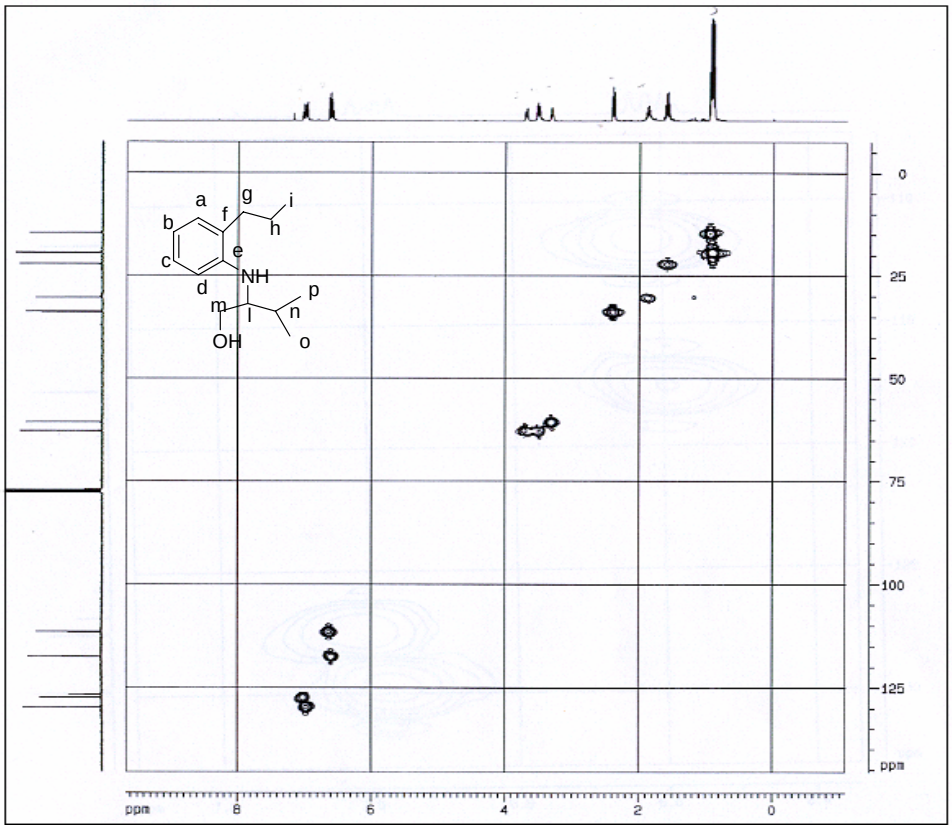


Figure 32: HMQC spectrum of 2-(2-propylphenylamino)-3-methylbutan-1-ol

In figure 31 we see ^{13}C-NMR spectrum of 2-(2-propylphenylamino)-3-methylbutan-1-ol. By DEPT-90^{o} and 135^{o} techniques we were able to determine the number of protons on each carbon. In figure 32 we see HMQC spectra for 2-(2-propylphenylamino)-3-methylbutan-1-ol. So we can determine which carbon is bonded to which proton and confirm our structure. There are three methyl groups which have carbon peaks at 14.49, 14.67, 18.52 ppm these are (i), (p) and (o) carbons as seen in HMQC spectra. We have a methylene group peak 22.23 ppm which must belong to (h) carbon because it is in interaction with (h) protons as seen in HMQC . At 30.39 ppm methine carbon (n) is seen. At 37.08 ppm we have a methylene carbon which must be (g) due to interaction with (g) protons. At 60. 71 we observe methine carbon peak which is peak exhibited by (l) carbon. At 62.86 ppm we have another methylene which is interaction with H_m and H_n in H-NMR spectra in figure 89. So this carbon must be (m) carbon. There are two methine carbon peaks at 111.55 and 117.51 ppm which interacts with protons on (b) and (d) so these two peaks must be carbons (b) and (d). There is a quarternary carbon peak at 126.76 ppm which does not interact with any hydrogen so it may be carbon (f). Two other methine carbon peaks are observed at 129.52 and 129.81 which are carbons (a) and (c). And finally there is another quarternary carbon peak at 145.94 which may be carbon (e). As it comes more downfield than the other quarternary carbon, it must be bonded to a heteroatom.

2.2.9 Characterization of *o*-*N*-(4,4-diethoxybutyl)propylaniline (225)

N-(4,4-diethoxybutyl)-2-propylbenzenamine was another product of same experiment of with .Yield %52.

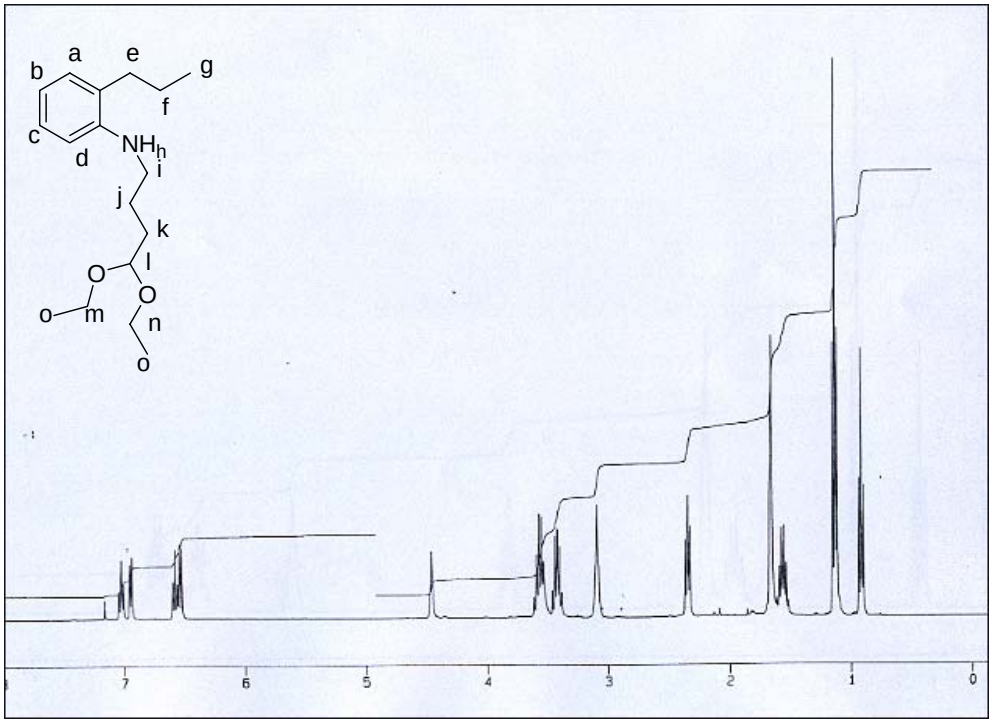


Figure 33: ^{1}H-NMR spectrum of *o*-*N*-(4,4-diethoxybutyl)propylaniline

In figure 34 we see the ^{1}H-NMR spectrum of *o*-*N*-(4,4-diethoxybutyl)propylaniline. Protons on methyl carbon (g) give a triplet peak at 0.92 ppm. Other methyl protons (o) give another triplet at 1.12 ppm. Methylene group (f) protons exhibit a sextet at 1.57 ppm; protons of methylenes (j) and (k) exhibit a broad singlet 1.66 ppm, and on carbon (e) exhibit a triplet at 2.35 ppm. Methylene proton on carbon (i) gives a broad singlet at 3.10 ppm. Methylene protons on (m) and (n) exhibit two multiplets between 3.39-3.47 ppm and 3.55-3.62 ppm. Methine proton (l) peak appears at 4.47 ppm as a broad singlet. Among aromatic protons (a) give a doublet peak at 6.10 ppm, (b) gives a triplet

peak at 6.59 ppm, (d) gives a doublet peak 6.96 ppm, and (c) gives a triplet peak at 7.04 ppm.

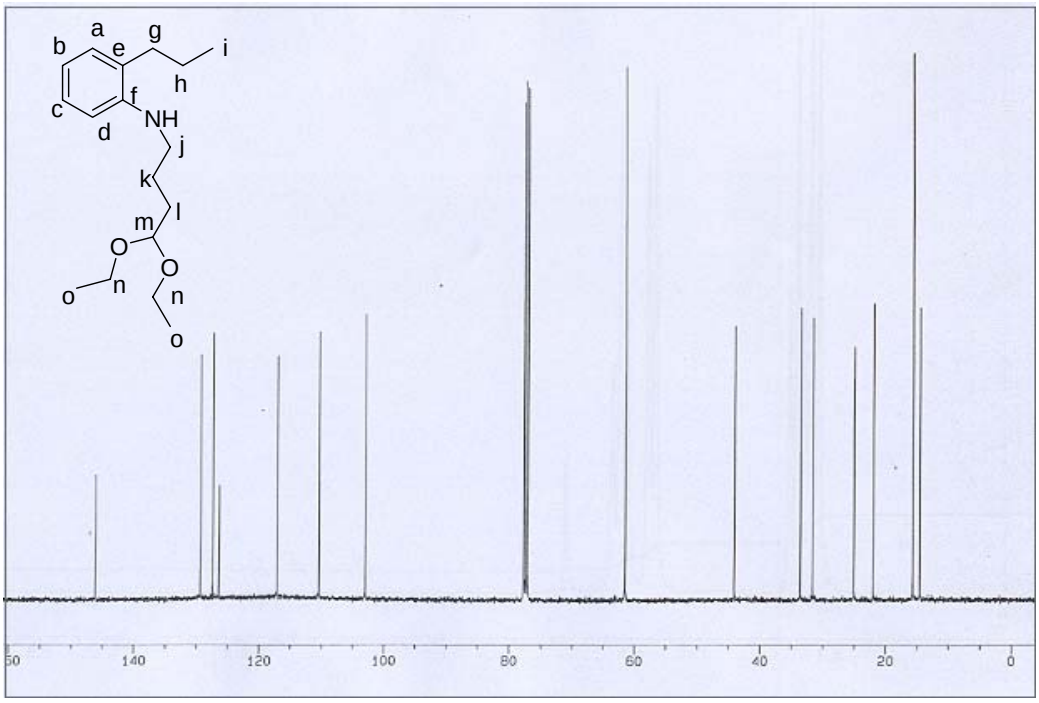


Figure 34: ^{13}C-NMR spectrum of *o*-*N*-(4,4-diethoxybutyl)propylaniline

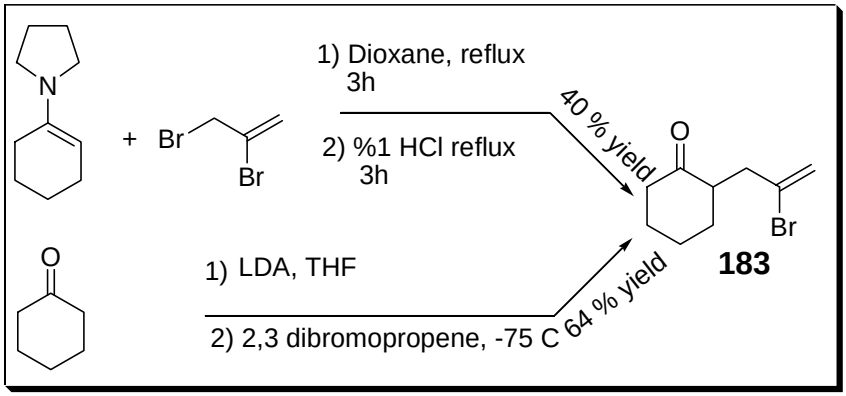
In figure 35 we see ^{13}C-NMR spectrum of *N*-(4,4-diethoxybutyl)-2-propylaniline. There are fifteen peaks in spectrum which are in accordance with the proposed structure.

We also investigated whether we could be able to develop a room temperature procedure for imine formation from bromoallylated ketone and primary amine by using Lewis acids. Such a procedure is needed to work with amino acids or amino acid esters, because they tend to peptidize on high temperature conditions. For this purpose we used $TiCl_4$ as our Lewis acid, using experimental method described in the literature.[68] According to this procedure, to a solution of bromoallylated cyclohexanone, primary amine (benzylamine was chosen as the amine) in dry toluene, 0.5 equivalent of $TiCl_4$ in toluene (w.r.t ketone) was added at room temperaure. As soon as the $TiCl_4$ was added, it was

observed that a solid cake settled down. With thin layer chromatography (TLC) control it was observed that starting material remains in the solution without formation of a new product after two hours mixing. As a control experiment benzylamine was mixed with $TiCl_4$ and again precipitation of a solid cake is observed, most probably $TiCl_4$ forms a stable complex with benzylamine, preventing it to react with carbonyl group of the ketone. In another first cyclohexanone was mixed with $TiCl_4$ is mixed for complex formation, and later benzylamine was added. At TLC check immediate formation of a new spot is noticed probably due to formation of an imine product. This procedure is applied to reaction of benzylamine and bromoallylated cyclohexanone for imine formation; first ketone was mixed with $TiCl_4$ at 0^oC and brought slowly to room temperature, subsequently benzylamine in dry toluene is added to reaction mixture. All reaction is carried out under argon atmosphere. Unfortunately no product formation could be observed on TLC check. Other Lewis acids (Al_2O_3, BF_3:THF, etc.) are being planned to be employed for development of a room temperature procedure with Lewis acids.

2.3 Synthesis of starting material 2-(2-bromoallyl)cyclohexanone

For synthesis of common starting material for both tetrahydroindole and tetrahydrobenzofuran synthesis which is 2-(2-bromoallyl)cyclohexanone there are two methods available in literature. In scheme 66 we see two different procedures for synthesis from literature.[69,70] In first method 1-pyrrolidinyl-1-cyclohexene is refluxed with 2,3-dibromopropene in dry dioxane for three hours, later 1% HCl solution is added for hydrolysis and purification after workup and distillation under vacuum gives 40% yield.[69] This procedure is applied and the same yield is obtained. In another method first lithium enolate of cyclohexanone is prepared and later 2,3-dibromopropene is added onto formed enolate at -78^oC and mixture is gradually warmed to room temperature.[70] We also tried this procedure but yields we obtained were lower than reported. So we used Stork-enamine procedure throughout the work.


N
+ Br
Br
1) Dioxane, reflux
3h
2) %1 HCl reflux
3h
40 % yield
O
Br
183
O
1) LDA, THF
2) 2,3 dibromopropene, -75 C
64 % yield

Scheme 66

CHAPTER 3

EXPERIMENTAL

In this study structure characterizations of the compounds were done with the instruments as written.

^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ on Bruker Spectrospin Avance DPX 400 spectrometer. Chemical shifts are given in ppm from tetramethylsilane. Spin multiplicities are mentioned as: s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet), dt (doublet of triplet), t (triplet), p (pentet), sxt (sextet), m (multiplet).

Flash column chromatography was performed by using thick-walled glass columns with a flash grade (Merck Silica Gel 60). Reactions were monitored by thin layer chromatography using precoated silica gel plates (Merck Silica Gel PF-254), visualized by UV-light and polymolybden phosphoric acid, in ethanol as appropriate.

All extracts were dried over anhydrous magnesium sulphate and solutions were concentrated under vacuum by using rotary evaporator.

3.1 Synthesis of 6-allyl-3-methylcyclohex-2-en-1-one (189)

$Mn(OAc)_3.2H_2O$ (5.35 g. 18 mmol) was refluxed in benzene (50 mL) using a Dean-Stak trap for 2 hours. Later 3-methylcyclohex-2-en-1-one (1.1 g, 9.02 mmol) and allyl bromide (1.72 mL, 18 mmol) was added and reaction mixture was refluxed for 8 hours. For workup; mixture is extracted with 1N HCl (50 mL), organic phase was neutralized by $NaHCO_3$. Aqueous phase is extracted with EtOAc (2x100 mL), and again organic phase is neutralized with $NaHCO_3$. Combined extracts were washed with saturated brine, dried over $MgSO_4$ and concentrated *in vacuo*. Mixture was purified with flash chromatography, using 1:10 EtOAc-hexane as eluent. Yellow oil (yield: 1.51 g. 73%)

^{1}H-NMR ($CDCl_3$)

δ (ppm): 1.58-1.68 (m, 1H)
1.87 (s, 1H)
1.97-2.07 (m, 2H)
2.15-2.23 (m, 3H)
2.52-2.58 (m, 1H)
4.95-5.00 (m, 2H)
5.66-5.76 (m, 1H)
5.78 (s, 1H)

^{13}C-NMR ($CDCl_3$)

δ (ppm) 201.0, 162.0, 136.7, 126.7, 116.9, 45.3, 34.1, 30.7, 27.6, 24.5

3.2 Synthesis of 6-(2-bromoallyl)-3,5,5-trimethylcyclohex-2-en-1-one (193)

$Mn(OAc)_3.2H_2O$ (3.88 g. 14.5 mmol) was refluxed in benzene (50 mL) using a Dean-Stak trap for 2 hours. Later 3,5,5-trimethylcyclohex-2-en-1-one (1.0 g, 7.24 mmol) and 2,3-dibromopropene (1.5 mL, 14.5 mmol) was added and reaction mixture was refluxed for 8 hours. For workup; mixture is extracted with 1N HCl (50 mL), organic phase was neutralized by $NaHCO_3$. Aqueous phase is extracted with EtOAc (2x100 mL), and again organic phase is neutralized with

$NaHCO_3$. Combined extracts were washed with saturated brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Mixture was purified with flash chromatography, using 1:4 EtOAc-hexane as eluent. Yellow oil (yield: 1.10 g. 59%).

^{1}H-NMR ($CDCl_3$)

δ (ppm): 0.79 (s, 3H)
1.02 (s, 3H)
1.81 (s, 3H)
1.96 (d, *J*=10.8 Hz, 1H)
2.20 (d, *J*=10.7 Hz, 1H)
2.34 (dd, *J*=3.3, 11.3 Hz, 1H)
2.41 (dd, *J*=3.5, 4.6 Hz, 1H)
2.82 (dd, *J*=8.1, 6.5 Hz, 1H)
5.32 (s, 1H)
5.59 (s, 1H)
5.74 (s, 1H)

3.3 Synthesis of 6-(2-bromoallyl)-3-methylcyclohex-2-en-1-one (196)

$Mn(OAc)_3.2H_2O$ (4.90 g. 18.3 mmol) was refluxed in benzene (50 mL) using a Dean-Stak trap for 2 hours. Later 2-(2-bromoallyl)-3-methylcyclohex-2-en-1-one (1.2 g, 7.90 mmol) and 2,3-dibromopropene (1.5 mL, 14.5 mmol) was added and reaction mixture was refluxed for 8 hours. For workup; mixture is extracted with 1N HCl (50 mL), organic phase was neutralized by $NaHCO_3$. Aqueous phase is extracted with EtOAc (2x100 mL), and again organic phase is neutralized with $NaHCO_3$. Combined extracts were washed with saturated brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Mixture was purified with flash chromatography, using 1:3 EtOAc-hexane as eluent. Yellow oil (yield: 1.15 g. 50%).

^{1}H-NMR ($CDCl_3$)

δ (ppm): 1.34-1.38 (m, 1H)
1.74 (s, 3H)
1.90-1.93 (m, 1H)
2.04-2.11 (m, 3H)
2.11-2.18 (m, 1H)
2.95 (dd, *J*=3.7, 14.7 Hz, 1H)
5.25 (s, 1H)
5.40 (s, 1H)
5.66 (s, 1H)

^{13}C-NMR ($CDCl_3$)

δ (ppm): 199.9, 163.5, 132.9, 126.6, 119.2, 44.0, 41.6, 31.1, 27.6, 24.6

3.3.1 Synthesis of 6-propargyl-3-methylcyclohex-2-en-1-one (197)

2-(2-bromoallyl)-3-methylcyclohex-2-en-1-one (0.24 g., 1.21 mmol) was treated with 2 equivalent of potassium *tert*-butoxide (0.27 g 2.41 mmol) in dry *N*,*N*-dimethyl formamide (6 mL) for 14 hours at reflux temperature. For workup; mixture is extracted with 1N HCl (6 mL), neutralized by $NaHCO_3$, extracted with ether (2x100 mL). Combined extracts were washed with saturated brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Mixture is purified with flash chromatography using 1:8 EtOAc-hexane as the eluent. Yellow oil (Yield: 0.11 g, 60%).

^{1}H-NMR ($CDCl_3$)

δ (ppm): 1.71-1.79 (m, 1H)
1.89 (s, 4H)
2.19-2.39 (m, 5H)
2.67-2.73 (m, 1H)
5.58 (s, 1H)

^{13}C-NMR ($CDCl_3$)

δ (ppm): 199.18, 162.76, 126.45, 82.74, 69.67, 44.87, 31.18, 27.88, 24.58, 19.27

3.4 Synthesis of 2-(2-bromoallyl)cyclohexan-1-one (183)

To a solution of 1-pyrrolidinyl-1-cyclohexene (5 g, 33 mmol) in anhydrous dioxane (20mL), was added a solution of 2,3-dibromopropene (6,7 g., 33 mmol) in anhydrous dioxane (10 mL) under an atmosphere of argon at 0 ^{o}C. After being refluxed for three hours, %1 solution of HCl (11 mL) is added to reaction mixture and then refluxed for three hours. Mixture is concentrated under vacuum and extracted with ether (3x60 mL). After evaporation of ether under vacuum, vacuum distillation at 3 mm Hg at 92-96 ^{o}C yields the product. Colorless oil (2.86 g 40% yield).

^{1}H-NMR ($CDCl_3$)

δ (ppm): 1.13-2.92 (m, 11H)
5.36 (s, 1H)
5.53 (s, 1H)

3.4.1 Synthesis of 3-methyl-4,5,6,7-tetrahydrobenzofuran (131)

2-(2-bromoallyl)cyclohexan-1-one (0.43 g, 1.98 mmol) was mixed with potassium *tert*-butoxide (0.44 g, 3.96 mmol) in dimethyl sulfoxide (5 mL) at 104 ^{o}C for 14 h under argon atmosphere. For workup; 10 ml of water is added, mixture is extracted with ether (3x50 ml), organic phase is washed with saturated brine (150 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Mixture is purified with flash chromatography (in order to visualize substance in TLC, phosphomolybdic acid must be used; it can hardly be seen under UV light even at high concentrations) using 1:15 EtOAc-hexane as eluent. (Yield: 0.11 g % 55 yield)

^{1}H-NMR ($CDCl_3$)

δ (ppm): 1.73-1.78 (m, 2H)
1.81-1.87 (m, 2H)
1.97 (s, 3H)
2.34-2.38 (m, 2H)
2.56-2.59 (m, 2H)
7.07 (s, 1H)

^{13}C-NMR ($CDCl_3$)

δ (ppm): 151.1, 136.9, 120.8, 118.2, 30.1, 23.7, 23.4, 20.8, 8.4

3.5 Synthesis of symmetric tricyclic furan (206)

Lithium enolate of cycloheptanone is prepared by treating cycloheptanone (1.5 g. 12 mmol) with lithium diisopropylamide (LDA) which is prepared by treating diisopropyl amide (1.87 mL, 13mmol) with butyl lithium (5.59 mL, 2.5 M in hexane) in dry THF (50 mL) at -78^{o}C and in order to ensure formation of enolate mixture is gradually warmed to room temperature. Later the mixture is cooled back to -78^{o}C and 2,3-dibromopropene (2.54 g, 13mmol) is added onto formed enolate at –78^{o}C. 5 mL of water is added, and reaction mixture is extracted with ether (2x50 mL). Organic phase is dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Mixture is purified with flash chromatography. White crystal compound is obtained (2.12 g, 80% yield).

^{1}H-NMR ($CDCl_3$)

δ (ppm): 1.56-1.57 (m, 12H)
2.26 (t, *J*=5.7 Hz, 6H)
2.61 (t, *J*=6.0 Hz, 6H)

3.6 Synthesis of *N*-benzyl-2-methyl-4,5,6,7-tetrahydroindole (211a)

2-(2-bromoallyl)cyclohexan-1-one (2.1 g, 9.7 mmol) was mixed with 1.5 equivalent of benzylamine (1.56 g, 15mmol) in dry toluene (40 mL), with a few crystals of *p*-toluenesulfonic acid under argon atmosphere and refluxed for 12 hours by using a Dean-Stark trap. After evaporation of solvent *in vacuo* and flash chromatography, yellow oil substance was obtained (1.02 g., 50% yield).

^{1}H-NMR ($CDCl_3$)

δ (ppm): 1.61-1.79 (m, 4H)
2.17 (s, 3H)
2.44 (t, *J*=6.1 Hz, 2H)
2.50 (t, *J*=5.3 Hz, 2H)
4.97 (s, 2H)
5.80 (s, 1H)
7.10 (d, *J*=7.4 Hz, 2H)
7.22-7.33 (m, 3H)

^{13}C-NMR ($CDCl_3$)

δ (ppm): 139.4, 128.8, 127.6, 127.5, 126.7, 126.4, 115.3, 105.8, 46.3, 24.5, 24.1, 24.0, 22.4, 12.7

3.7 Synthesis of *N*-((*S*)-methylbenzyl)-2-methyl-4,5,6,7-tetrahydroindole (211b)

2-(2-bromoallyl)cyclohexan-1-one (0.6 g, 2.8 mmol) was mixed with 2 eq equivalent of (*S*)-methylbenzylamine (0.57 mL, 5.6 mmol) in dry toluene (40 mL), with a few crystals of *p*-toluenesulfonic acid under argon atmosphere and refluxed for 12 hours by using a Dean-Stark trap. After evaporation of solvent *in vacuo* and flash chromatography, yellow-brown oil substance was obtained (0.27 g., 42% yield).

^{1}H-NMR ($CDCl_3$)

δ (ppm): 1.57-1.63 (m, 4H)

1.76 (d, *J*=7.2 Hz, 3H)

2.02 (s, 3H)

2.41 (br s, 4H)

5.35 (q, *J*=7.1 Hz, 1H)

5.62 (s, 1H)

6.96 (d, *J*=8.4 Hz, 2H)

7.14-7.25 (m, 3H)

^{13}C-NMR ($CDCl_3$)

δ (ppm): 143.1, 128.8, 127.7, 127.6, 127.2, 126.5, 116.8, 106.3, 52.8, 24.2, 24.1, 23.6, 20.0, 13.8, 1.4

3.8 Synthesis of *N*-(1-naphtyl)-2-methyl-4,5,6,7-tetrahydroindole (211c)

2-(2-bromoallyl)cyclohexan-1-one (0.32 g, 1.49 mmol) was mixed with 1.1 eq equivalent of 1-naphtylamine (0.23 g, 1.64 mmol) in dry toluene (20 mL), with a few crystals of *p*-toluenesulfonic acid under argon atmosphere and refluxed for 4 hours by using a Dean-Stark trap. After evaporation of solvent *in vacuo,*dimethyl sulfoxide (3 mL) is added together with potassium *tert*-butoxide (0.30 g, 1.79 mmol) and reaction mixture is kept at 80^{o}C for 4h. Later reaction mixture is brought to room temperature and purified with flash chromatography without any workup step. Yellow oil substance (0.35 g, 74% yield).

^{1}H-NMR ($CDCl_3$)

δ (ppm): 1.57-1.72 (m, 4H)

1.84 (s, 3H)

1.87-1.92 (m, 1H)

2.13-2.20 (m, 1H)

2.53 (t, *J*=6.1 Hz, 2H)

7.14-7.84 (m, 7H)

^{13}C-NMR ($CDCl_3$)

δ (ppm): 136.1, 134.6, 132.3, 129.7, 129.5, 128.7, 128.4, 127.4, 126.8, 126.5, 125.8, 124.0, 116.8, 105.7, 24.3, 23.9, 23.5, 22.7, 12.6

3.9 Synthesis of *N*-(2-pyridinyl)-2-methyl-4,5,6,7-tetrahydroindole (211d)

2-(2-bromoallyl)cyclohexan-1-one (0.7 g, 3.22 mmol) was mixed with 2 eq equivalent of 2-aminopyridine (0.91 g, 6.44 mmol) in dry toluene (30 mL), with a few crystals of *p*-toluenesulfonic acid under argon atmosphere and refluxed for 4 hours by using a Dean-Stark trap. After evaporation of solvent *in vacuo,*dimethyl sulfoxide (4 mL) is added together with potassium *tert*-butoxide (0.54 g, 4.83 mmol) and reaction mixture is kept at 80^{o}C for 4h. Later reaction mixture is brought to room temperature and purified with flash chromatography without any workup step. Yellow oil substance (0.68 g, 72% yield).

^{1}H-NMR ($CDCl_3$)

δ (ppm): 1.68 (t, *J*= 2.8 Hz, 4H)
2.12 (s, 3H)
2.40 (br s, 2H)
2.45 (br s, 2H)
5.75 (s, 1H)
7.13-7.18 (m, 2H)
7.71 (dt, *J*=1.9, 5.9 Hz, 1H)
8.50 (dd, *J*=1.2, 3.5 Hz, 1H)

^{13}C-NMR ($CDCl_3$)

δ (ppm): 149.6, 138.0, 129.8, 128.0, 126.0, 121.9, 121.3, 118.3, 108.1, 30.1, 24.0, 23.7, 23.5, 13.5

3.10 Synthesis of *N*-phenyl-2-methyl-4,5,6,7-tetrahydroindole (211e)

2-(2-bromoallyl)cyclohexan-1-one (0.31 g, 1.43 mmol) was mixed with 1.1 eq equivalent of aniline (0.15 g, 1.57 mmol) in dry toluene (30 mL), with a few crystals of *p*-toluenesulfonic acid under argon atmosphere and refluxed for 3 hours by using a Dean-Stark trap. After evaporation of solvent *in vacuo,* dimethyl sulfoxide (3 mL) is added together with potassium *tert*-butoxide (0.28 g, 2.46 mmol) and reaction mixture is kept at 80^{o}C for 4h. Later reaction mixture is brought to room temperature and purified with flash chromatography without any workup step. Yellow oil substance (0.27 g, 92% yield).

^{1}H-NMR ($CDCl_3$)

δ (ppm): 1.91 (t, *J*=2.9 Hz, 4H)
2.24 (s, 3H)
2.49 (br s, 2H)
2.62 (br s, 2H)
5.99 (s, 1H)
7.37 (d, *J*=7.3 Hz, 2H)
7.49 (t, *J*=7.4 Hz, 1H)
7.57 (t, *J*=7.3Hz, 2H)

^{13}C-NMR ($CDCl_3$)

δ (ppm): 139.3, 129.4, 128.5, 128.3, 127.7, 117.3, 106.3, 24.4, 24.1, 23.6, 23.5, 13.2

3.11 Synthesis of *N*-(cyclohexyl)-2-methyl-4,5,6,7-tetrahydroindole (211f)

2-(2-bromoallyl)cyclohexan-1-one (0.50 g, 2.3 mmol) was mixed with 1.5 equivalent of benzylamine (0.34 g, 3.45 mmol) in dry toluene (25 mL), with a few crystals of *p*-toluenesulfonic acid under argon atmosphere and refluxed for 12 hours by using a Dean-Stark trap. After evaporation of solvent *in vacuo* and flash chromatography, yellow oil substance was obtained (0.21 g., 31% yield).

^{1}H-NMR ($CDCl_3$)

δ (ppm): 1.10-1.84 (m, 14H)
2.20 (s, 3H)
2.39 (t, *J*=5.9 Hz, 2H)
2.57 (t, *J*=6.0 Hz, 2H)
3.76 (p, *J*=8.0 Hz, 1H)
5.55 (s, 1H)

3.12 Synthesis of 2-(2-propylphenylamino)-3-methylbutan-1-ol (211g)

2-(2-bromoallyl)cyclohexan-1-one (0.31 g, 1.43 mmol) was mixed with 1.1 eq equivalent of (*S*)-valinol (0.16 g, 1.58 mmol) in dry toluene (30 mL), with a few crystals of *p*-toluenesulfonic acid under argon atmosphere and refluxed for 12 hours by using a Dean-Stark trap. After evaporation of solvent *in vacuo,* dimethyl sulfoxide (5 mL) is added together with potassium *tert*-butoxide (0.28 g, 2.46 mmol) and reaction mixture is kept at 80^{o}C for 30 min. Later reaction mixture is brought to room temperature and purified with flash chromatography without any workup step. Yellow oil substance (0.30 g, 95% yield).

^{1}H-NMR ($CDCl_3$)

δ (ppm): 0.83-0.96 (m, 9H)
1.59 (sxt, *J*=7.3, 2H)
1.78-1.92 (m, 2H)
2.40 (t, *J*=7.9 Hz, 2H)
3.32 (t, *J*=6.2 Hz, 1H)
3.50-3.54 (m, 2H)
3.70 (dd, *J*=4.2, 6.7 Hz, 1H)
6.58-6.64 (m, 2H)
6.97-7.04 (m, 2H)

^{13}C-NMR ($CDCl_3$)

δ (ppm): 154.9, 145.9, 129.8, 129.5, 126.8, 117.5, 111.6, 62.9, 60.7, 37.1, 30.4, 22.2, 18.5, 14.7, 14.5

3.13 Synthesis of *o*-*N*-(4,4-diethoxybutyl)propylaniline (222)

2-(2-bromoallyl)cyclohexan-1-one (0.69 g, 3.18 mmol) was mixed with 1.5 eq equivalent of 4-aminobutyraldehyde diethylacetal (0.77 g, 4.77 mmol) in dry toluene (40 mL), with a few crystals of *p*-toluenesulfonic acid under argon atmosphere and refluxed for 6 hours by using a Dean-Stark trap. After evaporation of solvent *in vacuo,* dimethyl sulfoxide (5 mL) is added together with potassium *tert*-butoxide (0.28 g, 2.46 mmol) and reaction mixture is kept at 80^{o}C for 3 hours. Later reaction mixture is brought to room temperature and purified with flash chromatography without any workup step. Blackish-brown oil substance (0.44 g, 52% yield).

^{1}H-NMR ($CDCl_3$)

δ (ppm): 0.92 (t, *J*=7.3, 3H)
1.12 (t, *J*=8.5 Hz, 6H)
1.57 (sxt, *J*=7.6 Hz, 2H)
1.66 (br s, 4H)
2.35 (t, *J*=7.73 Hz, 2H)
3.10 (br s, 2H)
3.39-3.47 (m, 2H)
3.55-3.62 (m, 2H)
4.47 (br s, 1H)
6.10 (d, *J*=8.0, 1H)
6.59 (t, *J*=7.4, 1H)
6.96 (d, *J*=7.3, 1H)
7.04 (t, *J*=7.6, 1H)

^{13}C-NMR ($CDCl_3$)

δ (ppm): 146.2, 129.4, 126.5, 117.1, 110.5, 103.1, 61.6, 44.2, 33.7, 31.7, 25.2, 20.0, 15.8, 14.7

3.13.1 Synthesis of *N*-(4,4-diethoxybutyl)-2-methyl-4,5,6,7-tetrahydroindole (224)

This compound is another product of same experiment. Dark brown oil substance. (0.2 g, %22 yield)

^{1}H-NMR ($CDCl_3$)

δ (ppm): 1.12 (t, *J*=7.01, 6H)
1.49-2.22 (m, 8H)
2.13 (s, 3H)
2.37 (t, *J*=6.10, 2H)
2.44 (t, *J*=5.59, 2H)
3.36-3.63 (m, 6H)
4.38 (t, *J*=5.0, 1H)
5.58 (s, 1H)

CHAPTER 4

CONCLUSION

In this study synthesis and characterization of tetrahydrobenzofuran and dihydrobenzofuran derivatives **131**, **194** are synthesized from various allylated or bromoallylated, saturated or α,β-unsaturated cyclic ketones in 55% and 10% yields. Allylation of ketones were performed by either $Mn(OAc)_3$ mediated allylation or Stork-Enamine reaction with allyl halides. An interesting tricyclic furan compound **206** was obtained via reaction of cycloheptanone with lithium diisopropylamide in 80% yield. We also observed that treatment of 6-(2-bromoallyl)-3-methylcyclohex-2-en-1-one **196** with base at high temperatures results in formation of 6-propargyl-3-methylcyclohex-2-en-1-one **197** with 60% yield.

Also various 2-methyl-4,5,6,7-tetrahydroindole derivatives were obtained by reacting primary amines with 2-(2-bromoallyl)cyclohexan-1-one **183** in moderate to excellent yields. Two different methodologies were followed in synhtesis; direct treatment of amine and ketone for aliphatic amines, or treatment of formed imine with base for aromatic amines. In base treatment methods interesting aromatization products **222** and **224** were also isolated.

Synthesized compounds are potent biologically active substances or valuable precursors in synthesis of complex natural products.

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