NOVEL SYNTHETIC APPLICATIONS OF MORITA-BAYLIS-HILLMAN ADDUCTS OF ISATIN

THESIS SUBMITTED TO THE
UNIVERSITY OF KERALA FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN CHEMISTRY UNDER THE FACULTY OF SCIENCE

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Dedicated To

My Beloved Parents, Brother, Sister and Teachers

DECLARATION

I hereby declare that the matter embodied in this thesis entitled "**NOVEL SYNTHETIC APPLICATIONS OF MORITA-BAYLIS-HILLMAN ADDUCTS OF ISATIN**" is a bonafide record of the investigation carried out by me in the Chemical Sciences and Technology Division of National Institute for Interdisciplinary Science and Technology (NIIST), Trivandrum, under the guidance of Dr. P. Shanmugam and no part of this thesis has been submitted elsewhere for the award of any other degree or diploma.

February-2009 **(V. Vaithiyanathan)**

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Certified that the work embodied in this thesis entitled **"NOVEL SYNTHETIC APPLICATIONS OF MORITA-BAYLIS-HILLMAN ADDUCTS OF ISATIN"** is a record of bonafide research carried out by **Mr. V. Vaithiyanathan** under my supervision in fulfillment of the requirements for the degree of **Doctor of Philosophy** in **Chemical Sciences** of University of Kerala and the same has not been submitted elsewhere for any other degree or diploma

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CONTENTS

PREFACE

Reactions involving Carbon-Carbon and Carbon-Heteroatom bond formation occupy a central position in organic synthesis. A number of carbon-carbon bond forming reactions have been discovered and their applications in organic chemistry have also been well developed. Recently, the Morita-Baylis-Hillman reaction, is yet another important reaction, has been added to the list of useful carbon-carbon bond forming reactions. The Morita-Baylis-Hillman reaction has been fascinated by synthetic organic chemists in recent years because of its easy preparation and potential applications in the synthesis of densely functionalized molecules. These adducts have also been subjected to various transformations for the synthesis of important biologically active natural products and related core structures.

The synthetic versatility of isatin has led to the extensive use of this compound in organic synthesis. Many synthetic methodologies have been described for the conversion of isatins to other heterocyclic systems and alkaloid natural products.

The spiro-oxindole ring system is found as a core structure of a number of alkaloids, which display significant biological activities and are interesting, challenging targets for chemical synthesis. Construction of such systems can be appropriate from isatin.

In order to focus novel synthetic transformations of highly functionalized Morita-Baylis-Hillman adduct of isatin derivatives which are less explored in the literature until 2005, we have undertaken a systematic investigation to bring out novel synthetic methods from Morita-Baylis-Hillman adduct of isatin and the results are presented in the thesis entitled **"NOVEL SYNTHETIC APPLICATIONS OF MORITA-BAYLIS-HILLMAN ADDUCTS OF ISATIN"**.

The thesis has been divided into four chapters. Relevant experimental procedures along with characterization data of the products and references are given at the end of each chapter.

Chapter I of thesis embodies a brief general introductory discussion on the genesis, historical development and synthetic application of MBH-reaction. Followed by the origin, development, synthetic transformations and applications in the synthesis of

natural products based on the chemistry of isatin have also been presented. A statement of the present research problem has also been incorporated at the end of this chapter.

The bromo- and methoxy derivatives of isomerised Morita-Baylis-Hillman adduct of isatin have been used as starting materials for the synthesis of 3-spirocyclopropane-2-indolones and 3-Spiro α-methylene-γ-butyrolactone oxindoles, respectively. Further, the Morita-Baylis-Hillman adduct of isatin has been used without any transformation directly for the NC-H bond activation study with CAN/ROH and the synthesis of γ-butyrolactones by reductive cyclization protocol.

Chapter II of the thesis deals with synthesis of functionalized 3-spirocyclopropane-2-indolones from bromo isomerised MBH of isatin. A plausible mechanism has proposed and assignment of stereo- and geometrical isomers of the products has been extensively studied by spectroscopic methods. General information on the experimental procedure and characterization are also given at the end of this chapter.

Chapter III of the thesis deals with activation of the *N*C-H bond of MBH adducts of *N*-substituted isatin with CAN/ROH. We have chosen various MBH adducts with different *N*-alkyl substitutions such as methyl, methylene and methine which in principle generate 1°, 2° and 3° radical cation intermediates during the *N*C-H activation process. Mechanism, reactivity and selectivity reason of the activation reaction study have also been discussed. The preparative methods, characterization of new compounds and experimental procedure have been presented in detail at the end of the chapter III.

The chapter IV has been divided into Part A and Part B. Part A contains the detailed synthesis of 3-spiro-α-methylene-γ-butyrolactone oxindoles from methoxy isomerised MBH adducts of isatin. Part B outlines the synthesis of functionalized γ-butyrolactones from MBH adducts of isatin by reductive cyclization methodology. Characterization of new compounds, mechanism of the reaction and detailed experimental procedure are presented at end of the chapter IV.

It may be noted that each chapters of the thesis is presented as a separate unit and therefore, Figures, Schemes, Tables, Structures and references are numbered accordingly. A summary of the work is given towards the end of the thesis.

ABBRIVIATIONS

CAN	Ceric (IV) ammonium nitrate
DABCO	1.4-diaza bicyclo-[2.2.2] Octane
DBU	Diazabicyclo-[5.0.4]-undecane
DMAP	4-dimethyl aminopyridine
DMSO	Dimethylsulfoxide
HRMS	High Resolution Mass Spectrometer
HCl	Hydrochloric acid
IR	Infrared
J	Coupling Constant
K10 (or) Mont.K10	Montmorillonite K-10
min.	Minute
mg	Milligram
mmol	milli mole
mL	milli liter
MBH	Morita-Baylis-Hillman
µw (or) MW	Microwave
NBS	*N*-bromo succinamide
NHC	Nucleophilic heterocyclic carbene
NHPI	*N*-hydroxyphthalimide
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
PL	Power Level
PPTS	Pyridinium Para Toluene Sulfonate
PTSA	p-Toluene Sulphonic Acid
RCM	Ring Closing Metathesis
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TMSOTf	tetramethyl silyl trifluoroacetate
w/w	Weight per weight

Chapter I

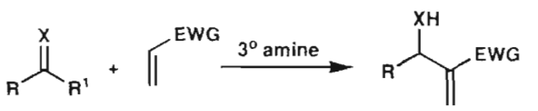
An account on Morita-Baylis-Hillman reaction and chemistry of isatin

1.1. An account on Morita-Baylis-Hillman reaction

Chemists ever show an eager to bring new structural discoveries from the nature in order to benefit human being. Although the fundamental chemistry begins from atom level, there are diverse and complex structural frameworks existing in the nature. To understand them systematically, there are number of chemistry branches created in Science. One among them is Organic Chemistry, with a wide contribution for the welfare of human being has been achieved through organic synthesis. Developing novel synthetic routes for the construction of new organic molecules are ever growing task in synthetic organic chemistry. Syntheses of target molecules and synthetic intermediates are mainly based on novel C-C and C-X bond formation reactions[1-5]. The most fundamental reaction for the construction of molecular frameworks is carbon-carbon bond forming reactions and the functional group transformations[5]. Several carbon-carbon bond forming reactions have been discovered and their applications in organic chemistry have been well documented[3]. A very recent development in organic chemistry have clearly established that the atom economy, selective (chemo-, regio-, and stereo-) transformations and catalytic processes have become primary and most essential requirements for the development of any efficient synthetic reaction[4]. Against this aspect, very recently, the Morita-Baylis-Hillman (MBH) reaction[6], is yet another important reaction, has been added to the list of useful carbon-carbon bond forming reactions. Since the Morita-Baylis-Hillman (MBH) reaction fulfils the two most important requirements, atom economy and generation of functional groups, it qualifies to be in the list of efficient synthetic reactions.

1.1.1. Definition of Morita-Baylis-Hillman reaction

The Morita-Baylis-Hillman reaction[7-10a-c] is essentially a three-component reaction involving the bond formation between α-position of an activated alkene and a carbon electrophile such as aldehydes under the catalytic influence of a tertiary amine (traditionally 1,4-diazobicyclo-[2.2.2] octane, DABCO) providing densely functionalized molecules. The general schematic representation of the MBH reaction is shown in Scheme 1[7].



R=aryl, alkyl, hetero aryl; R^1=H, CO_2R, alkyl; X=O, $NHCO_2R$, N-Ts, $NHSO_2Ph$
EWG=COR, CHO, CN, CO_2R, $PO(OEt)_2$, SO_2Ph, SO_3Ph

Scheme 1

1.1.2. Origin and history of MBH reaction

In 1968, Morita *et al.*[11] described the reaction of an aldehyde with activated alkenes catalyzed by tricyclohexyl phosphine. He named the transformation "Carbinol Addition". However, the yield of the reaction was extremely poor (20%). In 1972, Anthony Baylis and Melville Hillman[6] from Celanese Corporation were granted a German patent for performing the same reaction using a tertiary amine catalyst instead of phosphine catalyst. In the patent, they reported the yields of the reaction are 70-85% and the duration of the reaction time was one week at room temperature. They also reported that DABCO was the most successful catalyst.

In 1982, the reaction was re-discovered and its scope was explored primarily by Drewes and Basavaiah[7,8]. After sixteen years, the transformation was named as Baylis-Hillman reaction. Recently, it is referred and started to call as Morita-Baylis-Hillman (MBH) reaction as the initial work was carried out by Morita *et al.* Earlier this reaction referred as "DABCO reaction", when DABCO was used as catalyst. Drewes *et al.*[12] first made reference to the work of Baylis and Hillman in connection with the synthesis of a necic acid precursor and subsequently a steady stream of papers has appeared on the subject.

In 1964, Oda *et al.*[13] investigated the reaction of acrylonitrile with benzaldehyde and triphenyl phosphine in roughly equimolar proportions. The reaction was carried out under nitrogen atmosphere at an initial temperature of 130 °C which was subsequently raised to

140 °C and maintained for 6 hours. After workup, "witting type" products could be isolated in yields varying between 9 to 45%. Oda suggested a mechanism for the reaction, as shown in Figure 1.

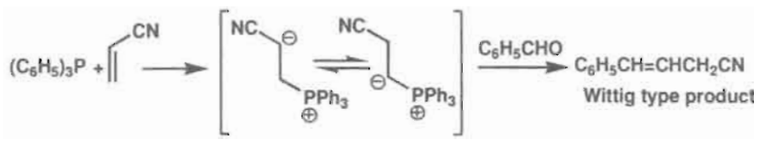


Figure 1

It seems likely that the order of addition (phosphine, aldehyde, acrylic), coupled with the high temperature, lead to the formation of a betaine intermediate rather than vinyl carbanion. Oda also reached a conclusion that the addition of a proton donor (such as an alcohol or carboxylic acid) has no influence on the overall yield of end product and the proton shift from the betaine to the phosphorous ylide occurs without outside intervention.

Later, Morita *et al.*[11] used the same reactants as used by Oda, but employed only a catalytic amount of tricyclohexyl phosphine (instead of triphenyl phosphine) and allowed reaction to proceed for 2 hours at 120-130 °C, reported for the first time, isolation of 2-hydroxyalkyl derivatives of acrylate and related systems. He claimed yields up to 85% but the conversion of α,β-unsaturated reactant remained low (~23%). The mechanism proposed by him was the same as that described for amine catalyzed reaction. While he concedes that the ylide formation and isomerisation as described by Oda is possible only when triphenyl phosphine used as a catalyst, this is not the case when tricyclohexyl phosphine or tributyl phosphine are employed as catalysts. He also considered the cyclic intermediate possibility, as shown in Figure 2.

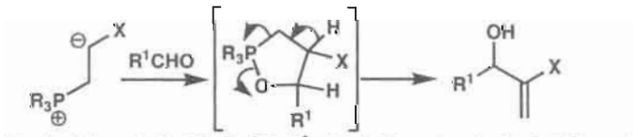


Figure 2

Though, unfortunately this fascinating reaction had missed the attention of organic chemists for almost a decade, in fact, now this reaction has become one of the most useful and popular carbon-carbon bond forming reactions with enormous synthetic utility and

potential. The major reviews[7-10a-c] and large number of research papers on this reaction are the evidence for its exponential growth and importance. Particularly, in the past 10 years a huge number of research publications have appeared in describing various aspects and application of the Morita-Baylis-Hillman chemistry.

1.1.3. Mechanism of the MBH reaction

Mechanism of this reaction is believed to proceed through the Michael initiated addition-elimination sequence. The most generally accepted mechanism of the amine catalyzed reaction is illustrated in Figure 3, considering the reaction between methyl acrylate (as an activated olefin) and benzaldehyde (as an electrophile) under the catalytic influence of DABCO **1**. The 1st step in this catalytic cycle involves the Michael-type nucleophilic addition of the tertiary amine to the activated alkene (methyl acrylate) to produce a zwitter ionic enolate **A**, which makes a nucleophilic attack on to the aldehyde in an aldol fashion to generate zwitterion **B**, subsequent proton migration and release of the catalyst provide the desired multifunctional molecules i.e the adduct.

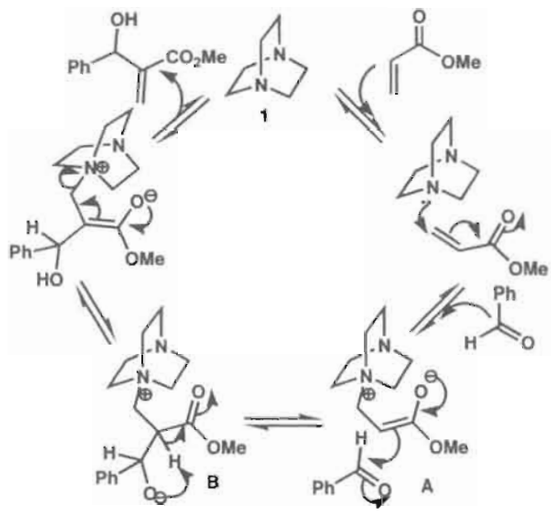
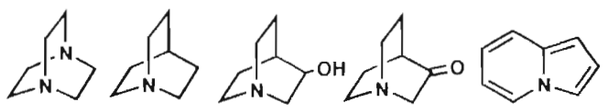


Figure 3

Although DABCO **1** has been the catalyst of choice, various other tertiary amine catalysts such as quinnuclidine **2**, 3-hydroxyquinnuclidone **3**, 3-quinnuclidone **4** and

indolizine **5** have also been employed to perform the MBH reaction in certain cases as depicted in Figure 4.



1 2 3 4 5

Figure 4

1.1.4. Developments on rate of MBH reaction

The MBH reaction has traditionally suffered from low reaction rates and limited substrate scope. Therefore, there has been considerable interest in enhancing reaction rate. Numerous chemical and physical methods have been developed to accelerate MBH reaction. Early efforts to accelerate the MBH reaction relied on physical methods (i.e., high pressure or ultrasound/microwave irradiation).

The rate determining step (RDS) of the MBH reaction is the reaction between the ammonium enolate **A** and the aldehyde (Figure 3). Thus, by chemical method, increasing the amount of the enolate or activation of the aldehyde will result in increased rate. Most methods for promoting the MBH reaction have largely focused on activation of the aldehyde (electrophile).

1.1.4.1. Activation of electrophile

Aggarwal *et al.* [14] demonstrated that the use of lanthanides resulted in modest rate enhancement and further acceleration could be achieved by the addition of alcohol ligands, e.g., Binol and triethanolamine. They believed that the primary source of acceleration in these systems was due to the enhanced acidity of the -OH group of the additive as a result of metal binding which resulted in enhanced hydrogen-bonded activation of the aldehyde. They have also shown that enhanced rates could be achieved by conducting reactions in water or formamide. In these highly polar solvents, it is believed that rate acceleration is achieved by not only hydrogen bonded activation of the aldehyde but also by increasing the amount of the zwitterionic intermediate **A** (Figure 3) by solvation.

1.1.4.2. Role of Zwitterionic intermediate and basicity of nucleophiles

Aggarwal *et al.* have also considered methods for increasing the amount of the ammonium enolate **A** (Figure 3) through stabilization of the ammonium ion. This should provide increased concentrations of the reactive intermediate without having a negative impact on the rate of the subsequent reaction between the enolate and aldehyde as the enolate is not stabilized. They showed that amidines[15] (DBU in particular) and quanidines provided substantial increases in rate, and they believe this occurs by the stabilization of ammonium ion through delocalization as shown in Figure 5.

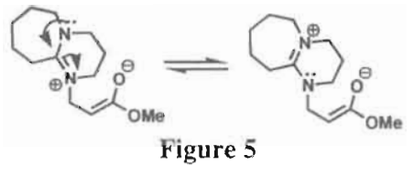


Figure 5

However, while good rates were achieved with DBU, the reaction was limited to non-enolizable aldehydes. In the case of DBU, it has high pK_a but is also sterically hindered that resulted in severely reduced rates. The high rate increase observed with DBU indicates that, in this specific case, the basicity of the amine is more important than steric hindrance.

In 2003, Aggarwal *et al.* [16] tested a broader range of quinnuclidine based catalysts and established a straight forward correlation between the basicity of the base and reactivity. They found that higher the pK_a, faster the rate. This is presumably; the pK_a provides enhanced stabilization of the intermediate ammonium enolate, resulting in its increased concentration without compromising its reactivity, which in turn leads to faster rates.

1.1.4.3. Hydrogen bonding and autocatalysis

The origin of the rate acceleration of 3-hydroxyquiniclidine over DABCO had previously been ascribed to hydrogen bonding (Figure 6), but it is now believed that its higher pK_a is the primary factor for increased rate.

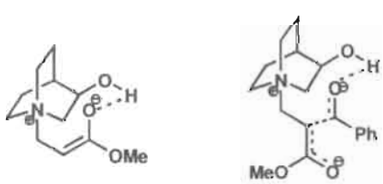


Figure 6

In this analysis[16], the parent compound quinnuclidine, which had the highest pK_a of all the quinuclidines and had previously been reported to be a poor catalyst, was re-evaluated and found to be the best catalyst to date. The reactions of all the quinuclidine based catalysts devoid of hydroxyl groups showed significant autocatalysis (the product of the reaction is enhancing the rate). The origin of the autocatalysis was the hydroxyl group of the MBH product which promoted the reaction through hydrogen bonding. This observation led to the addition of hydrogen bond donors to the reaction for further enhancement of the rate of the reaction. A number of additives were effective (methanol, formamide, triethanolamine and water) and this new combination of quinnuclidine-methanol was found to be most effective and was found to be general for a broad range of substrates.

1.1.4.4. Chalcogenide catalyst

One of the Lewis acids typically used to activate the carbonyl group is $TiCl_4$,[14] used with or without additives (e.g., quaternary ammonium salts, an organic chalcogenide, phosphanes, a diol or a bisoxazoline)[10]. Although the rates of the MBH reactions are improved significantly with the assistance of $TiCl_4$, the yields are generally moderate and limitations are encountered on the structures of the Michael acceptors and the aldehydes which undergo addition frequently producing complex mixtures[10, 17-19].

The first mechanism suggested for MBH reactions mediated by a chalcogenide/metal halide catalyst system involved attack of the sulfur atom from R_2S on the activated alkene[20]. However, it is currently believed that these reactions proceed by attack of a halide ion released from a Lewis acid by R_2S[21]. Supporting evidence for this observation was the unsuccessful use of $BF_3.OEt_2$ as the Lewis acid, from which release of a halide ion is far less likely[17, 20]. The MBH reaction of methyl vinyl ketone (MVK) with aldehydes mediated by tetrahydrothiophene/$BF_3.OEt_2$ was developed which gave moderate product yields, indicating the unambiguous requirement of the sulfide for attack on the activated alkene.[22]

Verkade *et al.*[23] reported that in the presence of proazaphosphatrane **6**, activated compounds such as acrylonitrile react efficiently with aromatic aldehydes to afford MBH adducts as only product. However, when the activated alkenes such as cyclohex-1-en-1-one, vinyl ketones, acrylates were used as substrates in the presence of **6**, the MBH reactions

failed whether with or without the presence of a Lewis acid ($TiCl_4$ or $AlCl_3$). They explained that the proazaphosphatrane sulfide **7** prepared from **6** (Figure 7) facilitates unparalleled speed and selectivity in MBH reactions catalyzed by $TiCl_4$ (screening a variety of such Lewis acids e.g., $MgSO_4$, $BF_3.OEt_2$, BCl_3, $SnCl_4$, $AlCl_3$, Ti $(O_iPr)_4$).

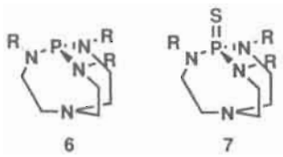


Figure 7

1.1.4.5. Impact of heteroatom within a heterocycle

The fast reacting substrates for MBH reaction are interest since they help to expedite the process of exploring and studying various synthetic and mechanistic aspects of the reaction. Batra and co-workers[24] reported that the substituted isoxazolecarbaldehydes were fast reacting electrophiles for the MBH reaction and the reason explained for the enhanced rate was concerned with the proximity of the formyl group with the heteroatom as shown in Figure 8.

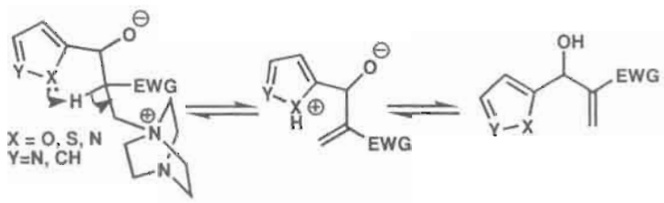


Figure 8

1.1.4.6. Influence of reaction medium

To influence the rate of MBH reaction, the use of aqueous solution as reaction medium has also been the recent research focus. Hu and co-workers[25] demonstrated that the MBH reaction of methyl acrylate and acrylamide could be accelerated simply by conducting the reaction in aqueous dioxane solution. In an earlier report, Auge *et al.*[26] examined the salt effect in aqueous MBH reaction. Aggarwal *et al.* in their report showed that the use of $Yb(OTf)_3$ could produce further acceleration in water or formamide solvent system.[27] Cheng and co-workers[28] reported that the reaction could be greatly accelerated by adjusting the pH

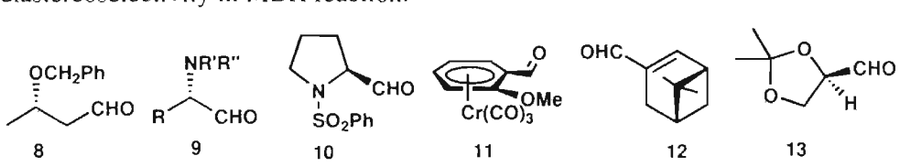
value of the aqueous medium. They also examined with various pH conditions using imidazole as catalyst and selected 1M $NaHCO_3$ (pH = 8.9) gives the best rate and yield. They rationalize the rate increase in basic water solution by considering there may be interaction of imidazole with the medium, *i.e.*, proton transfer between imidazole (pKa = 7.1 in water) and its cation. In alkaline solution, the proton exchange between water and imidazole is depressed, therefore leaving more neutral imidazole to take part in MBH reaction as nucleophiles i.e., the increase of the effective molarity of neutral imidazole, the apparent "enhanced basicity", is most likely responsible for further rate enhancement in alkaline solution. The variations in reaction medium like ionic liquid,[29,30] sulpholane as solvent[31] recoverable hydrogen bonding organocatalyst[32] have been employed to enhance the MBH reaction rate.

1.1.5. Asymmetric MBH reaction

The traditional MBH reaction consists of three components: an electrophile, a π-deficient alkene, and a nucleophilic catalyst. Any one of these component can be used to influence the stereochemistry at the newly formed stereogenic carbon.

1.1.5.1. Chiral electrophile

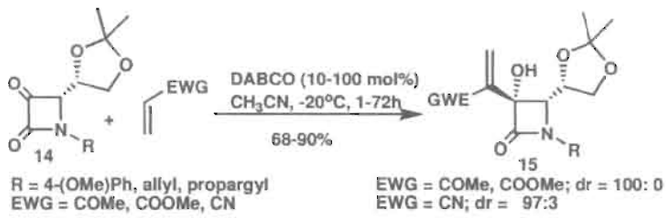
In order to obtain optically active chiral MBH adducts, several efforts have been made using various enantiopure aldehydes. The enantiopure electrophiles such as (S)-3-benzylloxybutyraldehde **8**, α-dialkylamino aldehydes **9**, N-phenylsulfonyl-L-prolinal **10**, enantiopure ortho-substituted benzaldehyde tricarbonylchromium complex **11**, (R)-myrtenal **12**, isopropylidene (R)-glyceraldehyde **13**, etc. (Figure 9), have been studied in achieving high diastereoselectivity in MBH reaction.[10]



8 9 10 11 12 13

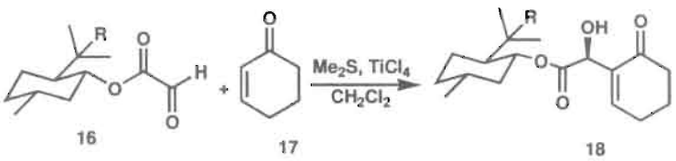
Figure 9

Alcaide and co-workers[33] successfully used enantiopure 3-oxo-2-azetidinones **14** for MBH reaction with activated alkenes to provide **15** in high diastereoselectivity (Scheme 2).



Scheme 2

The most impressive selectivities using an optically active electrophile come from studies carried out by Bauer and Tarasiuk.[34] They used chiral glyoxylates **16** derived from menthol and 8-phenylmenthol (Table 1) and found that the sterically more demanding 8-phenylmenthol not only gave higher yields (78%), but also provided excellent diastereoselctivities (>95%) (Scheme 3).



Scheme 3

Table 1

R	Reactant	% Yield	% de
H	**16a**	45	8.7
Ph	**16b**	78	>95

1.1.5.2. Chiral π-deficient olefins

Considerable progress has been achieved in asymmetric version of this reaction using various chiral acrylate esters[10] (Figure 10) derived from various chiral auxiliaries such as cyclohexanol derivative **19**, (R)-(+)-pentolcatone **20** and camphor sultam derivative **21**.

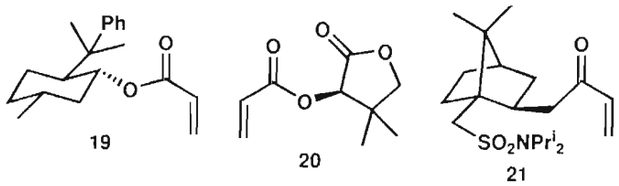
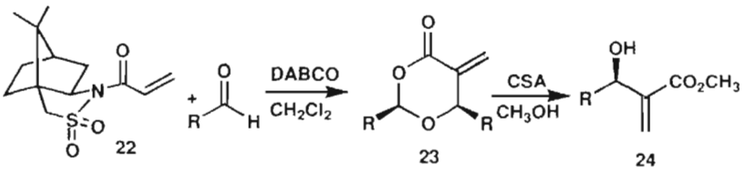


Figure 10

These types of chiral auxiliaries have led to the greatest degree of success in asymmetric MBH reaction. The most prominent example is the use of camphor derived sultam **22** by Leahy[35] as detailed in Scheme 4. By using second equivalent of aldehyde, the chiral auxiliary can be fortuitously cleaved from the product *in situ* to give an optically active dioxanone **23** in good yields and excellent stereoselectivities. This method is effective for unbranched aliphatic aldehydes. However, the α-branched aldehydes give lower yields, while aromatic aldehydes are found to be unreactive. Treatment of mild acid or base, the dioxanone **23** can be converted to the target enantiopure MBH adduct **24**.



Scheme 4

Table 2

R	%Yield	% *ee*
Me	85	>99
Et	98	>99
Ph	0	-

1.1.5.3. Chiral catalyst

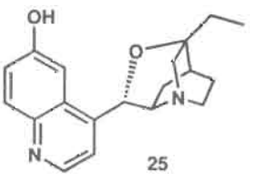
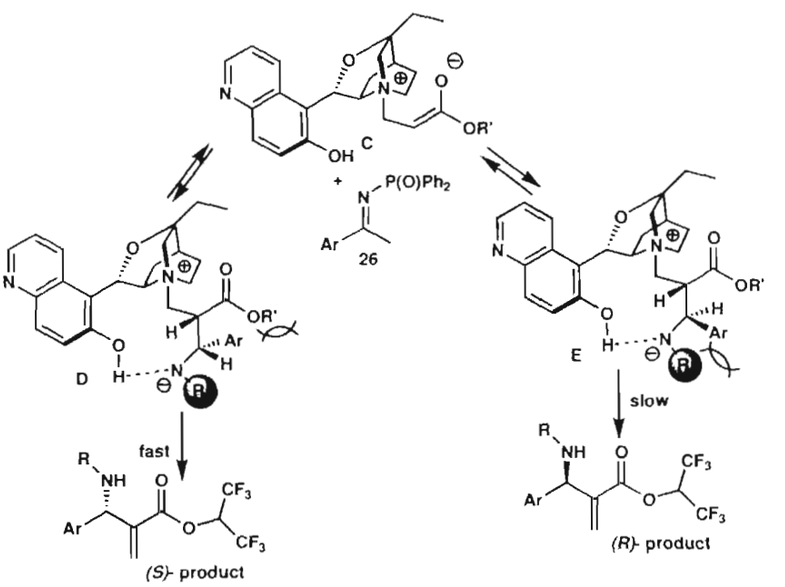


Figure 11

The holy grail of the asymmetric MBH reaction lies in an efficient, general catalyst that can be recovered and reused. Almost all of the chiral catalysts applied to the MBH reaction have been plagued with low yields or low selectivities. Hatakeyama[36] has developed the best catalyst to date. Amine **25** (Figure11) is a derivative of quinidine that gives moderate yields and high selectivities. Unfortunately, this catalyst is still very

substrate dependent. To react with a wide variety of aldehydes in a highly enantioselective manner an activated acrylate such as hexafluoroisopropylacrylate is necessary.

Hatakeyama and co-workers[37] reported the β-isocupreidine **25** catalyzed asymmetric MBH reaction of imine **26** and they showed the imines furnished opposite enantioselectivity in contrast to the corresponding aldehydes. They presented a mechanistic proposal governed by hydrogen bonding (Scheme 5).



Scheme 5

1.1.5.4. Chiral Lewis acid

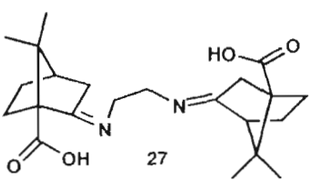
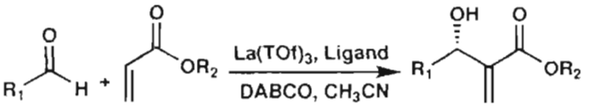


Figure 12

Report from Aggarwal's work showed that it is possible to use chiral Lewis acid catalyst to influence the enantioselectivity of the MBH reaction. Chen and co-workers[38]developed an additive **27** (Figure 12) which improved yields and selectivities when it used in conjunction with DABCO and $La(OTf)_3$ (Scheme 6). This method had the greatest success when α-napthyl acrylate and aromatic aldehydes were used.



Scheme 6

They have explained the enantioselectivity of the MBH reaction based on key structure represented in Figure 13.

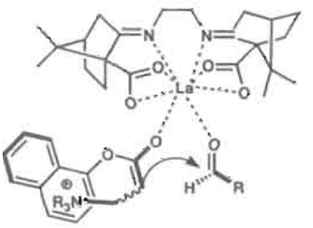


Figure 13

1.1.5.5. Chiral Bronsted acid

McDougal and Schaus[39] reported a highly enantioselective asymmetric MBH reaction of cyclohexenone with aldehydes using a chiral Bronsted acid as the catalyst and trimethyl phosphine as the nucleophilic promoter. The proposed catalytic cycle for the Bronsted-Acid catalyzed MBH reaction is shown in Figure 14.

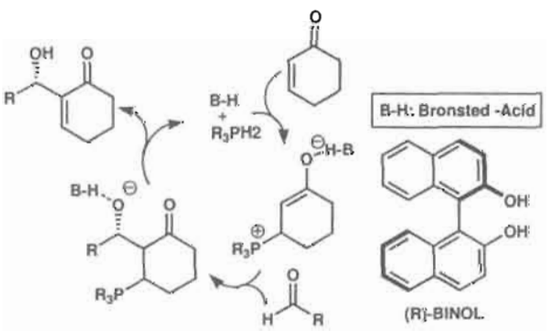
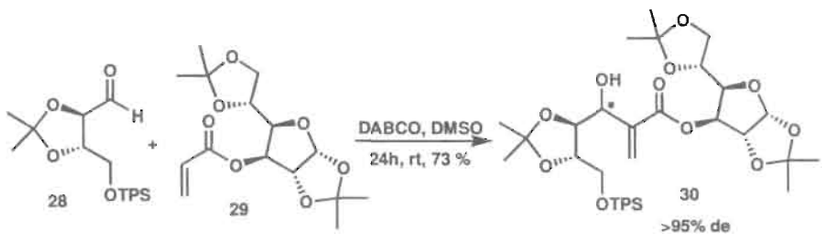


Figure 14

1.1.5.6. Double asymmetric induction

Very recently Krishna *et al.*[40] reported a strategy of double asymmetric induction in MBH reaction for the first time by the use of chiral aldehyde **28** with chiral acrylate **29** (1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose-3-acrylate) to obtain corresponding MBH

adduct **30** with high *syn* diastereoselectivity, as shown in Scheme 7 and selectivity bath way in Figure 15.



Scheme 7

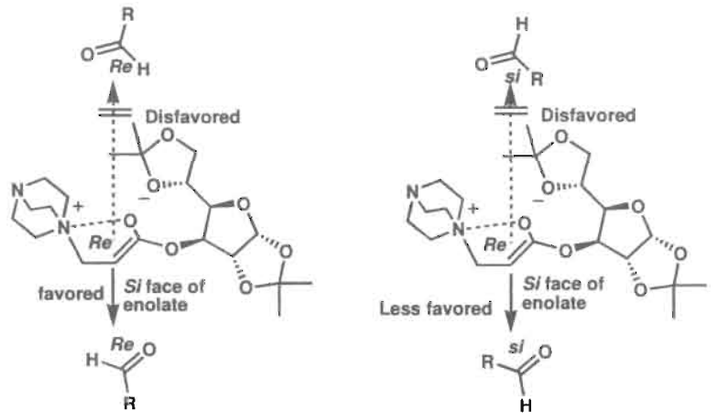
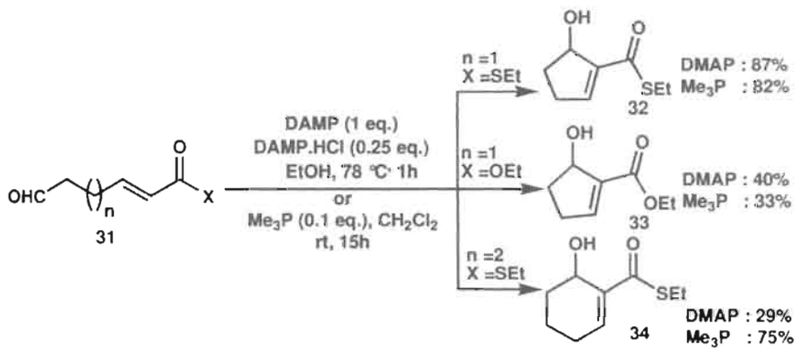


Figure 15

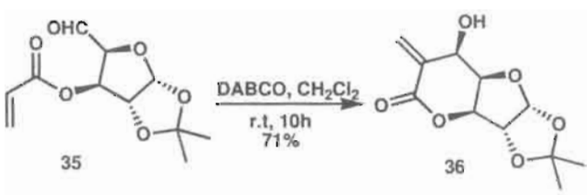
1.1.6. Intramolecular MBH reaction

Although the MBH reaction, in general has been developed largely with respect to all three essential components, the intramolecular version of this reaction is not studied in depth. Keck and Welch[41] examined an intramolecular MBH reaction of α,β-unsaturated ester/thioester **31** containing an enolizable aldehyde group, at various conditions. In the case of thiol esters cyclopentenol product **32** was formed in high yield when DMAP and DMAP.HCl in EtOH or Me_3P were employed as reagent. However, in the case of oxyester, the desired cyclopentenol adduct **33** was obtained in low yield. Cyclohexenol product **33** was obtained in high yield when Me_3P is used as a reagent, whereas DMAP and DMAP.HCl provided **34** in low yield. One representative example for each case is outlined in Scheme 8.



Scheme 8

Krishna *et al.*[42] first demonstrated a diastereoselective intramolecular MBH reaction using chiral substrates. Both aldehydes and activated olefin coexist as substituents in compound **35** to afford α-methylene-β-hydroxylactones **36** in good yield exclusively as single isomers under the standard base catalyzed reaction conditions (Scheme 9).



Scheme 9

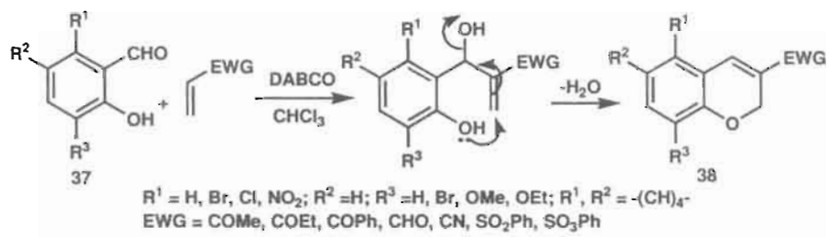
1.1.7. Applications of MBH adducts in organic synthesis

The presence of functional groups in MBH adducts play an important role in bringing latitude to organic synthesis and in the construction of molecular assemblies. The MBH adducts obtained via the reaction between electrophiles and activated vinylic systems contain a minimum of three chemo-specific functional groups, that is, hydroxy (or amino), alkene, and electron-with-drawing groups. Since these functional groups are in close proximity, they should in principle be useful in various stereoselective synthetic transformations through appropriate tuning of these groups either individually or two at a time or collectively. Several efforts have already been meticulously and articulately made in these directions, leading to the development of facile and simple methodologies for a variety of organic transformations involving high degree of stereoselectivities. In fact, some of these strategies/methodologies were also successfully employed in the synthesis of various

biologically active molecules and natural products. Especially, during the last 5 years, applications of MBH chemistry have been extensively investigated and numbers of organic transformation methodologies were developed[10]. The following sections describe some of applications of MBH adduct in organic synthesis.

1.1.7.1. Synthesis of chromene derivatives

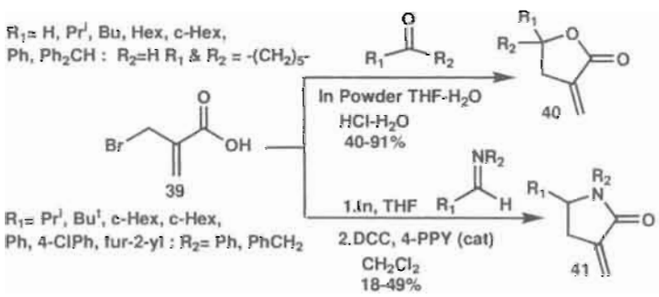
Kaye and Nocanda[43,44]described a simple one-pot methodology for the synthesis of 2H-1-chromenes **38** via the reaction between activated alkenes and o-hydroxybenzaldehes **37** catalyzed by DABCO. (Scheme 10)



Scheme 10

1.1.7.2. Synthesis of lactones

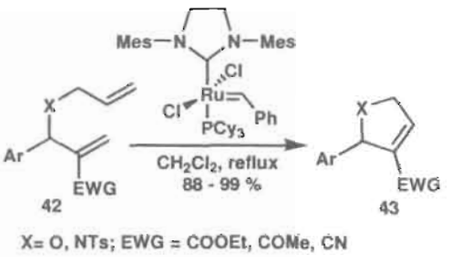
The bromide derivative of MBH adducts has been successfully used by various research groups for the synthesis of α-methylene-γ-butyrolactone independently.[8] Yus and co-workers[45,46]developed indium-promoted synthesis of substituted α-methylene-γ-lactones **40** and α-methylene-γ-butyrolactams **41** via the reaction of 2-(bromomethyl)acrylic acid **39** with carbonyl compounds and aldimines, respectively (Scheme 11).



Scheme 11

1.1.7.3. Synthesis of dihydrofurans and dihydropyrroles

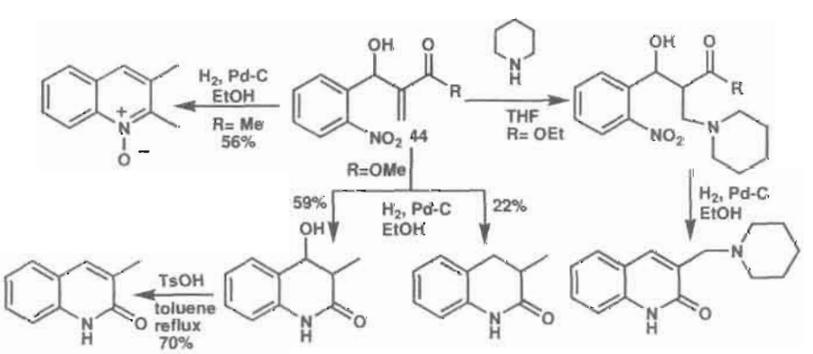
Kim *et al.*[47] reported the synthesis of 2,5-dihyrofurans and 2,5-dihydropyrroles **43** from the *O*-allyl and *N*-allyl derivatives of MBH adducts **42** respectively via Ring Closing Metathesis (RCM) using Grubb's second generation catalyst.



Scheme 12

1.1.7.4. Synthesis of quinolines

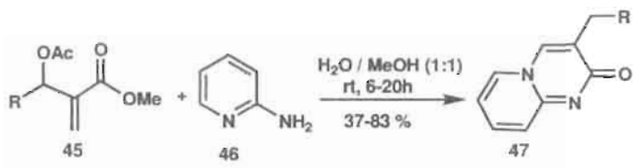
Kaye and co-workers[48] reported the synthesis of quinoline derivatives from MBH adducts **44** derived from *o*-nitrobenzaldehyde and acrylates/alkyl vinyl ketones via catalytic hydrogenation (Scheme 13).



Scheme 13

1.1.7.5. Synthesis of pyramidones

Basavaiah and co-workers[49] have successfully utilized the acetates of MBH adduct **45** for a facile one-pot transformation into fused pyrimidones **47** *via* reaction with 2-aminopyridine **46** in an environment-friendly aqueous medium (Scheme 14).

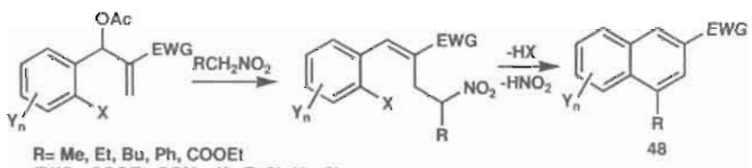


R = Ph, 4-MePh, 4-EtPh, 4-(i-Pr)Ph, 2-ClPh, 4-ClPh, 3-(OMe)Ph, 4-(OMe)Ph

Scheme 14

1.1.7.6. Synthesis of naphthalenes

Kim and co-workers[50] described a facile synthetic methodology for the synthesis of 2-substituted naphthalenes **48** from the acetates of the MBH adducts involving intramolecular tandem S_N2'-S_NAr-elimination chemistry according to Scheme 15.

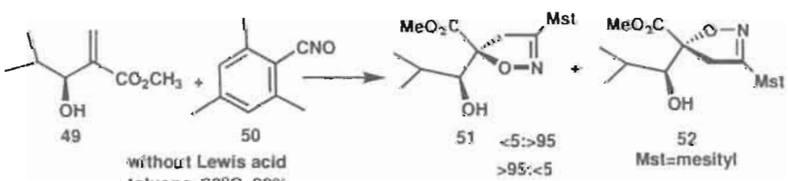


R= Me, Et, Bu, Ph, COOEt
EWG= COOEt, COMe, X= F, Cl; Y_n=Cl

Scheme 15

1.1.7.7. Synthesis of isoxazolines

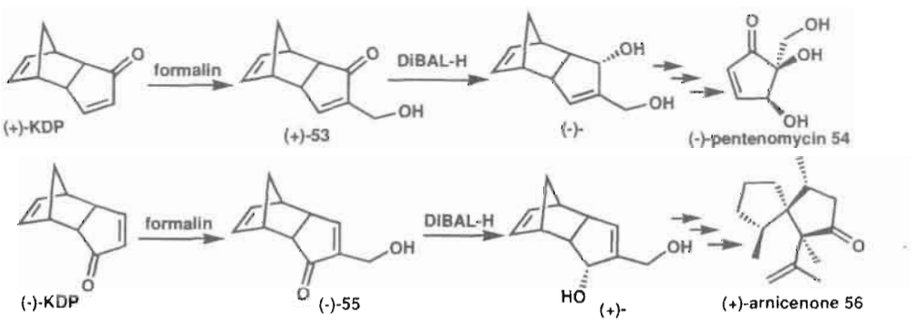
Fisera *et al.*[51] reported the diastereoselective synthesis of isoxazolines **51, 52** from the 1,3-dipolar cycloaddition reaction of mesitonitrile oxide **50** with MBH adduct **49** with high diastereoselectivities. It was also found the addition of Grignard reagent as Lewis acid reverses the diastereoselectivity of the cycloaddition. The reaction rate is strongly accelerated under microwave irradiation with a small change in diastereoselectivities. One representative example is shown in Scheme 16.



Scheme 16

1.1.7.8. Synthesis of natural products

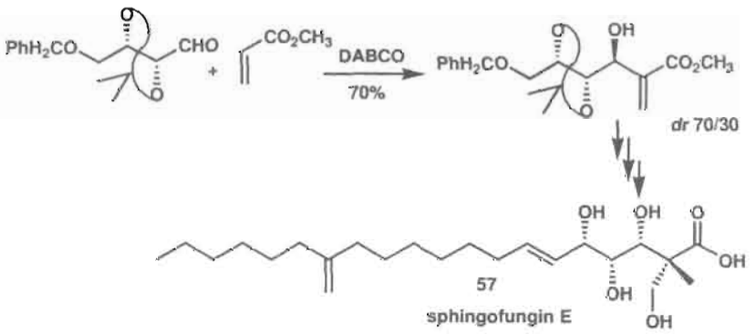
Ogasawara and co-workers[52, 53] have performed the MBH reaction between chiral bicyclic enones (+)-Ketodicyclopentadiene (KDP) and (-)-Ketodicyclopentadiene (KDP) and formalin.



Scheme 17

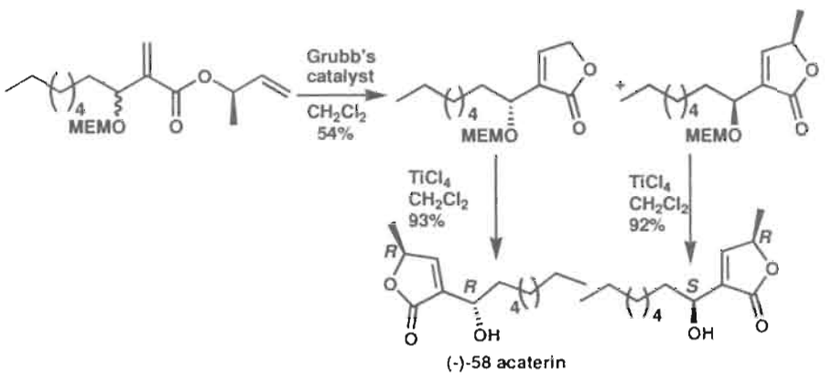
The resulting adducts (+)-**53** and (-)-**55** were transformed into a cyclopentanoid antibiotic (-)-pentenomycin **54** and angular triquinane sesquiterpene (+)-arnicenone **56**, respectively (Scheme 17).

Lin and co-workers[54] successfully described a total synthesis of sphingofungin E **57** using MBH adduct as the key intermediate (Scheme 18).



Scheme 18

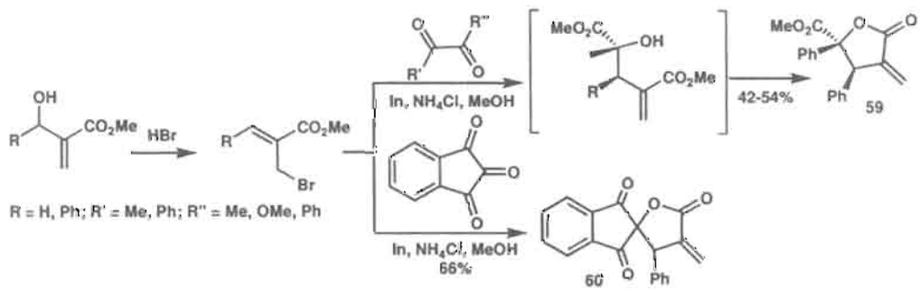
Singh and co-workers[55] outlined a short and efficient synthesis of (-)-acaterin **58**, a biologically important natural product, by elaboration of a MBH adduct obtained from octanal and methyl acrylate (Scheme 19).



Scheme 19

1.1.7.9. Synthesis of α-methylene-γ-butyrolactone

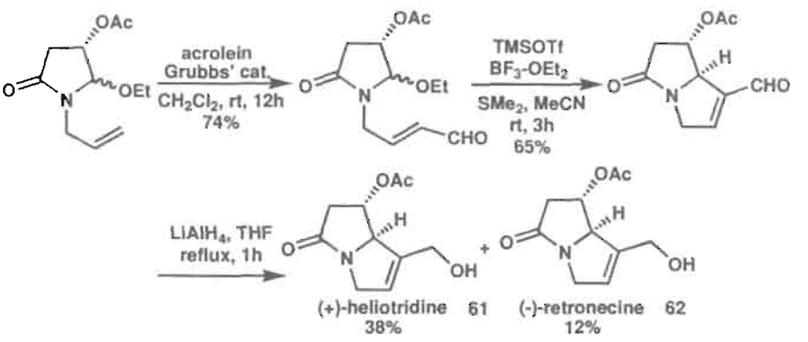
Kim and co-workers have successfully developed the synthesis of α-methylene-γ butyrolactones **59** and **60** via the reaction between allyl bromides and a variety of reactive carbonyl compounds under the influence of indium metal and NH_4Cl, as shown in Scheme 20.[56]



Scheme 20

1.1.7.10. Synthesis of (+)-heliotridine

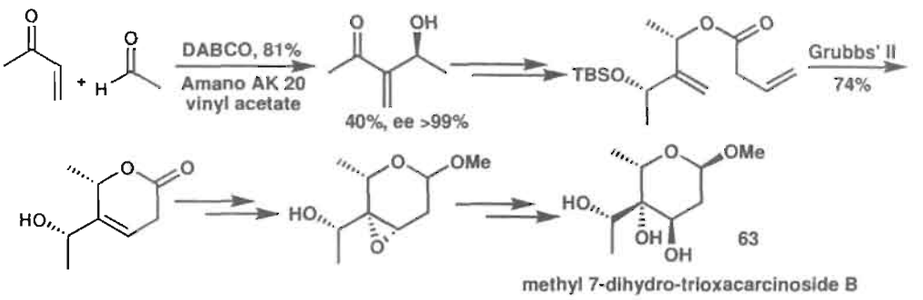
Aggarwal and co-workers reported a novel methodology in which a broad range of Michael acceptors were allowed to couple with the readily available iminium ion in an inter- and intramolecular MBH-type reaction to afford densely functionalized heterocycles.[57] The iminium ions generally present as masked N,O-acetals were generated by TMSOTf, while $BF_3.Et_2O$ in the presence of Me_2S was used to accomplish the reaction. More importantly, the process was highly enantioselective for cyclic enones. By employing this methodology, they reported a short synthesis of (+)-heliotridine, as shown in Scheme 21.



Scheme 21

1.1.7.11. Synthesis of methyl 7-dihydro-trioxacarcinoside B

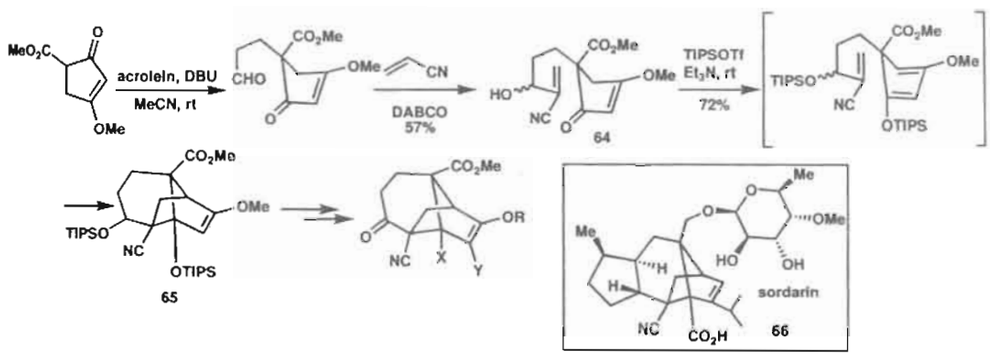
Koert and his group utilized the MBH adduct for the efficient stereoselective synthesis of methyl 7-dihydro-trioxacarcinoside B **63**. The key steps in the process were biocatalytic resolution of the MBH adduct, RCM reaction, a substrate-controlled epoxidation, and stereo- and regio-controlled ring opening of epoxide by allyl alcohol, as shown in Scheme 22.[58]



Scheme 22

1.1.7.12. Synthesis of key building blocks for sordarin

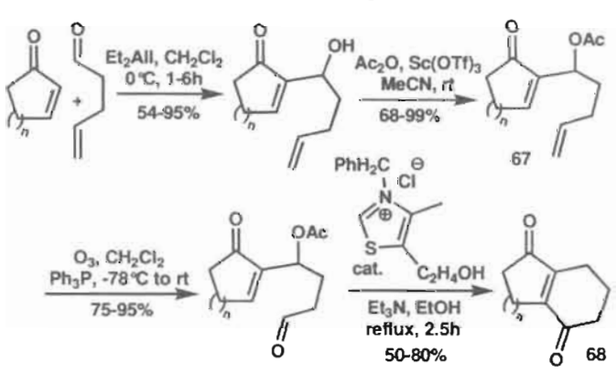
Ciufolini and co-workers utilized the MBH adduct **64** to synthesize ketone **65**, via trialkylsilyl triflate/Et_3N-catalyzed cyclization, which served as a useful building block for the preparation of analogs of the potent antifungal agent, sordarin **66**. It was presumed that the exposure to TIPSOTf induces the formation of the bis-trialkylsilyl derivative, which undergoes a spontaneous intra molecular Diels-Alder reaction to furnish the expected product as mixture of diastereomers **65** (Scheme 23).[59]



Scheme 23

1.1.7.13. Synthesis of bicyclic enediones

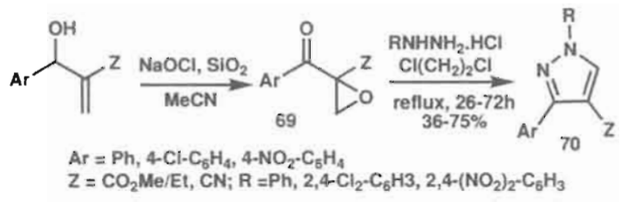
Marko and co-workers demonstrated that bicyclic enediones **68** of various sizes can be efficiently assembled by intramolecular Stetter cyclization of the readily available acetyl derivatives of MBH adducts of cyclic enones and 4-pentenal, as shown in Scheme 24.[60]



Scheme 24

1.1.7.14. Synthesis of 1,3,4-trisubstituted pyrazoles

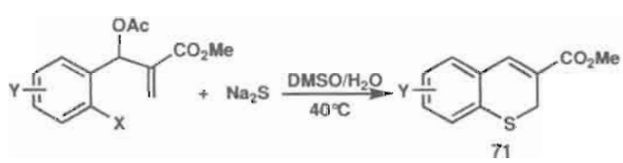
Kim and his group utilized acyloxiranes **69** generated from the MBH adducts for the facile synthesis of 1,3,4-trisubstituted pyrazoles **70** via a reaction with hydrazine derivatives in dichloromethane, as shown in Scheme 25.[61]



Scheme 25

1.1.7.15. Synthesis of 3-carbomethoxy-2H-thiochromenes

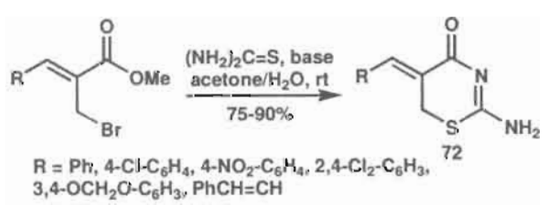
Lee and co-workers reported synthesis of 3-carbomethoxy-2H-thiochromenes **71** from the acetyl derivatives of the MBH adducts by reacting them with Na_2S in $DMSO/H_2O$, as shown in Scheme 26.[62]



Scheme 26

1.1.7.16. Synthesis of 1,3-thiazin-4-ones

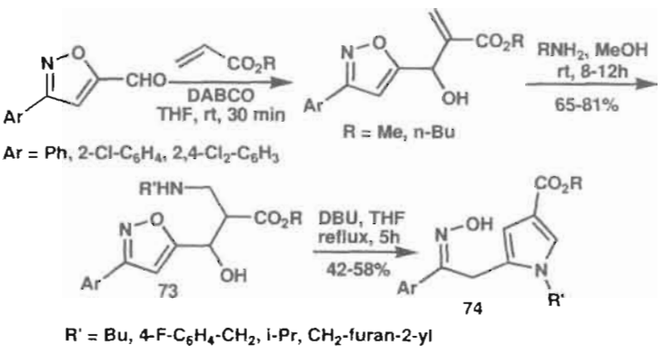
Recently, Sa and co-workers reported a facile synthesis of 1,3-thiazin-4-ones **72** in high yields from the allyl bromides via a reaction of thiourea in the presence of a base in an aqueous medium (Scheme 27).[63]



Scheme 27

1.1.7.17. Synthesis of pyrroles

A DBU-promoted ring transformation of substituted 3-aminopropanol **73** of MBH adducts of 5-isoxazolecarbaldehydes to the pyrroles **74**, via neighboring group participation (NGP), as shown in Scheme 28, was reported by Batra *et al.*[64]

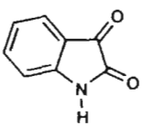


Scheme 28

1.2. The Chemistry of Isatin

1.2.1. Introduction

Isatin (1H-indole-2,3-dione, Figure 16) **75** was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo by nitric and chromic acids. The synthetic versatility of isatin has led to the extensive use of this compound in organic synthesis.



75

Figure 16

Three reviews have been published focusing the chemistry of isatin. The very first review by Sumpter in 1954 [65], second by Popp in 1975 [66], and the third on the utility of isatin as a precursor for the synthesis of other heterocyclic compounds [67a] were reported. In 2001 da Silva *et al.* published one more review[67b] by updating the chemistry of isatin. The synthetic versatility of isatin has stemmed from the interest in the biological and pharmacological properties of its derivatives. In nature, isatin is found in plants of the genus *Isatis*[68], in *Calanthe discolor* LINDL.[69] and in *Couroupita guianensis* Aubl.[70], and has also been found as a component of the secretion from the parotid gland of *Bufo* frogs[71], and in humans as it is a metabolic derivative of adrenaline. [72-74] Substituted isatins are also found in plants, for example the melosatin alkaloids (methoxy phenylpentyl isatins) obtained from the Caribbean tumorigenic plant *Melochia tomentosa* [75-77] as well as from fungi, 6-(3'-

methylbuten- 2'-yl)isatin was isolated from *Streptomyces albus*[78] and 5- (3'-methylbuten-2'-yl)isatin from *Chaetomium globosum*[79]. Isatin has also been found to be a component of coal tar.[80]

1.2.2. Methods for synthesis of isatins

There were many literature methods available for the synthesis of isatin. A few representative methods are given in the following sections.

1.2.2.1. The Sandmeyer methodology

The method developed by Sandmeyer is the oldest and the most frequently used for the synthesis of isatin **75**. It consists in the reaction of aniline **76** with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate to form an isonitrosoacetanilide, which after isolation, when treated with concentrated sulfuric acid, furnishes isatin in >75% overall yield[81] (Scheme 29, Ref. 81).

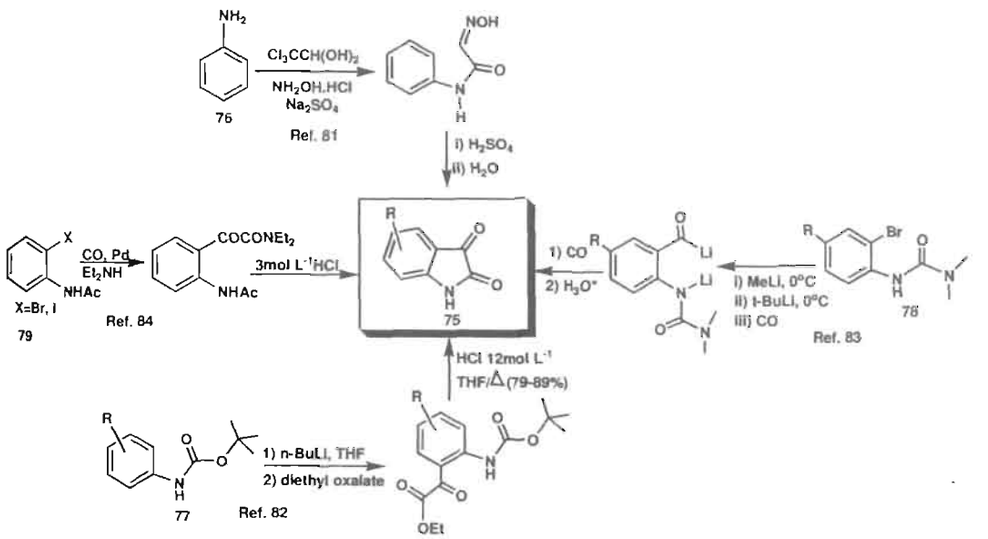
1.2.2.2. Metalation of anilide derivatives

A more recent method for the synthesis of isatins is based upon the directed *ortho*-metalation (DoM) of *N*-pivaloyl- and *N*-(*t*-butoxycarbonyl)-anilines **77**. The corresponding dianions are treated with diethyl oxalate and the isatins are obtained after deprotection and cyclisation of the intermediate α-ketoesters. This method has the advantage of being regioselective for the synthesis of 4-substituted isatins from *meta*-substituted anilines where the substituent is a metalation directing group (*e.g.* OMe) [82] (Scheme 29, Ref. 82).

Recently, a metal-halogen exchange method was described for the synthesis of isatins by lithiation of *o*-bromophenylureas **78**, carbonylation and subsequent intramolecular cyclisation to give the desired products in 71-79% yield[83] (Scheme 29, Ref. 83).

1.2.2.3. Hydrolysis of glyoxylic acid amide

Isatin synthesis based upon a palladium catalyzed double carbonylation of *ortho*-haloacetanilides **79** in the presence of Et_2NH to yield the corresponding glyoxylic acid amide was reported by Yamamoto and coworkers[84]. Hydrolysis of this amide yielded the respective isatin (Scheme 29, Ref. 84).



Scheme 29

1.2.3. Application of isatins in organic synthesis

Many synthetic methodologies have been described for the conversion of isatins to other heterocyclic systems. The reactivity pattern of the isatin can be generalized as one of the following strategies.

a) Partial or total reduction of the heterocyclic ring, leading to indoles and their derivatives.

b) Oxidation of the heterocyclic ring, conversion of isatin to isatoic anhydride.

c) Nucleophilic addition at position C-3, followed by a cyclization process, or by a *spiro*-annelation at position C-3.

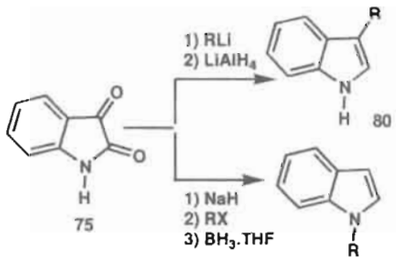
d) Nucleophilic substitution at position C-2.

1.2.4. Reduction of the heterocyclic ring

1.2.4.1. Synthesis of indoles

The reduction of isatins with lithium aluminum hydride in pyridine gave indoles **80** in moderate yields. However, the use of THF as a solvent under an inert atmosphere gave greater yields (86-92%). Isatins can be chemoselectively alkylated at positions 1 or 3.

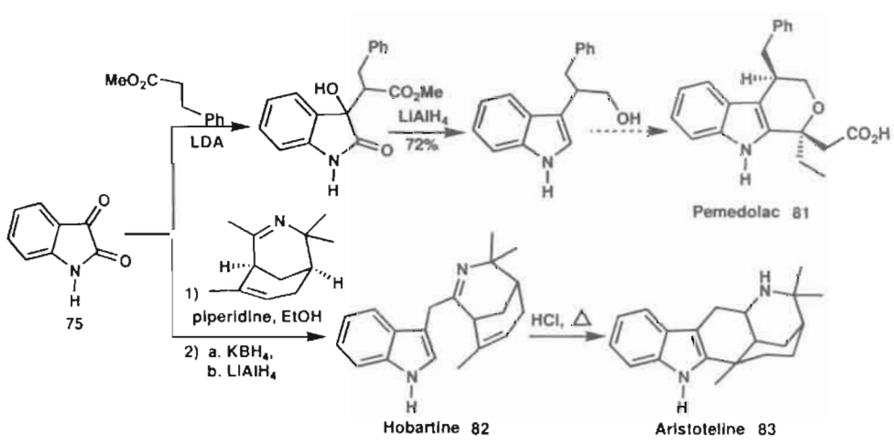
Subsequent reduction of these compounds using metal hydrides leads to 1- or 3-alkylindoles[85] (Scheme 30).



Scheme 30

1.2.4.2. Synthesis of pemedolac and aristoteline

The analgesic drug pemedolac **81**[86] and the synthesis of the alkaloids hobartine **82** and aristoteline **83**[87] were initiated by the C-3 alkylation of isatins to yield dioxindoles that were then reduced to the corresponding indoles by the use of lithium aluminum hydride (Scheme 31).

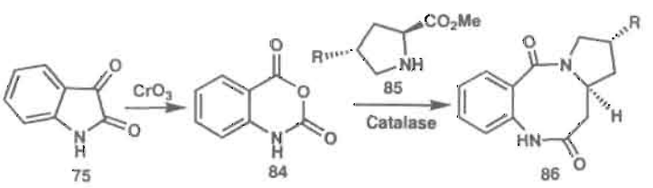


Scheme 31

1.2.5. Oxidation of the heterocyclic ring

The oxidation of isatin **75** using either hydrogen peroxide[88] or chromic anhydride yields isatoic anhydride **84**[89]. Isatoic anhydride **84** can be condensed with proline **85** in polar aprotic solvents at high temperature, or in a reaction catalyzed by the enzyme catalase, to

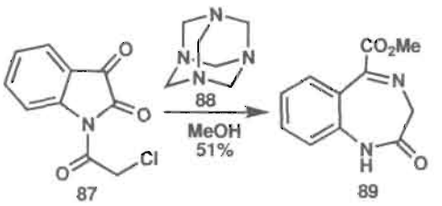
yield a pyrrolo[1,4] benzodiazepine ring **86**, a structural pattern found in some antineoplasic antibiotics[90] (Scheme 32).



Scheme 32

1.2.6. Nucleophilic attack at positions C-2 or C-3

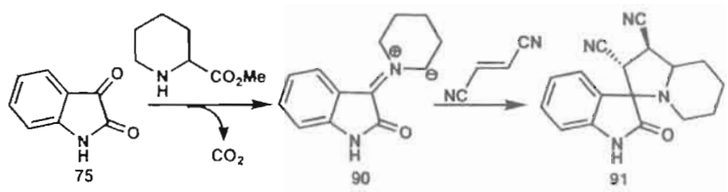
Isatins and derivatives can suffer nucleophilic attack at positions C-2 and/or C-3. The chemoselectivity of these reactions depends on the nature of the nucleophile, on the nature of the substituents attached to the isatin nucleus, and especially of those bonded to the nitrogen atom, as well as upon the solvent and temperature employed. The initial products obtained can suffer further reaction in the presence of a second nucleophilic group to give cyclised products. Compounds bearing the 1,4-benzodiazepine moiety have potential use as anxiolytic agents. One of the methods for the synthesis of this heterocyclic system involves the reaction of 1-α-chloroacetylisatin **87** with hexamethylenetetramine **88** in methanol[91], thus yielding the 1,4- benzodiazepine-5-carboxylic ester **89** via solvolysis of the *N*-acylisatin and the *in-situ* nucleophilic substitution of chloride, generating the glycine amide that subsequently undergoes cyclo-condensation (Scheme 33).



Scheme 33

1.2.6.1. Azomethine ylide generation at C-3

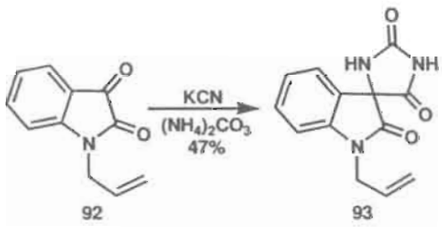
Pipecolic acid, a cyclic amino acid, when reacted with isatin **75** suffers decarboxylation furnishing an azomethine ylide **90**, which reacts with dipolarophiles such as fumaronitrile to yield 3-spirooxindole derivatives **91**[92] (Scheme 34).



Scheme 34

1.2.6.2. Synthesis of spirohydantoins

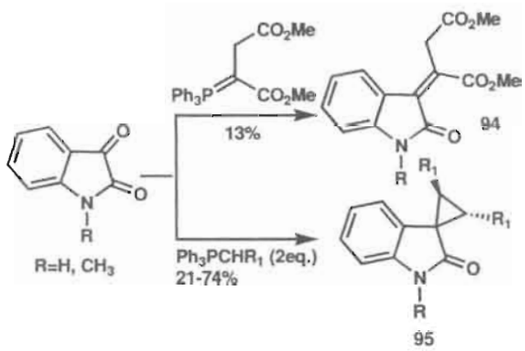
Potassium cyanide and ammonium carbonate react with 1-alkyl or 1-alkenylisatins **92**[93] generating spirohydantoins **93**. These compounds are inhibitors of the enzyme aldose reductase, and have potential use as hypoglycemic agents (Scheme 35).



Scheme 35

1.2.6.3. Wittig reaction at C-3 position of isatins

Isatins can be used as the electrophilic component in the Wittig-Horner reaction with phosphonates and furnish products resulting from attack at C-3 position [94]. 1-Alkyl- and 1-acyl- isatin react with equimolar quantities of a succinyl triphenylphosphorylidene to give dimethyl 2-oxoindolin-3-ylidenesuccinate derivatives **94** in low yields[95] (Scheme 36).

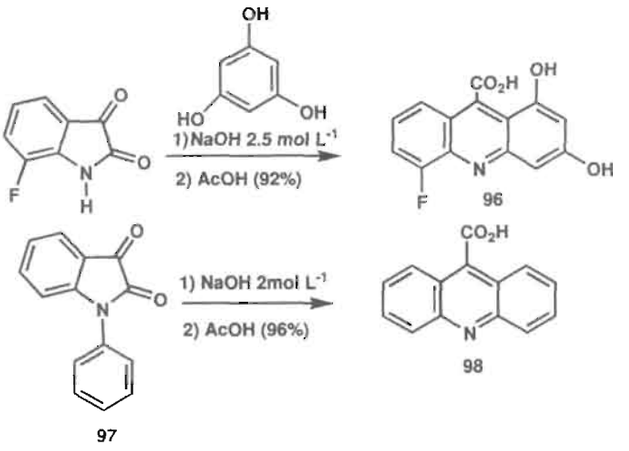


Scheme 36

When the Wittig reaction is carried out with two equivalents of the Wittig reagent, 3-spiro-cyclopropane oxindole **95** is formed[96] (Scheme 36).

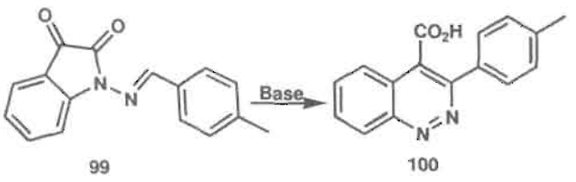
1.2.6.4. Synthesis of acridines

The reaction of isatin with phenols or dihydronaphthalenones[97] yielded acridine **96**. Similar type of product **98** can also be obtained from the treatment of *N*-phenylisatin **97** with aqueous sodium hydroxide[98a] (Scheme 37).



Scheme 37

In a similar procedure, 1-iminobenzylideneisatin **99** furnished cinnoline derivative **100** as shown in Scheme 38.[98b]



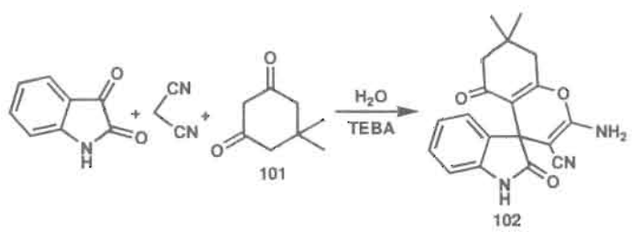
Scheme 38

1.2.7. Recent reports on chemistry of isatins

Several reports based on isatin have appeared focusing on the construction of oxindole core structures. Recent reports on synthetic utility of isatin and its derivatives are discussed in the following sections.

1.2.7.1. Synthesis of spirooxindole scaffold

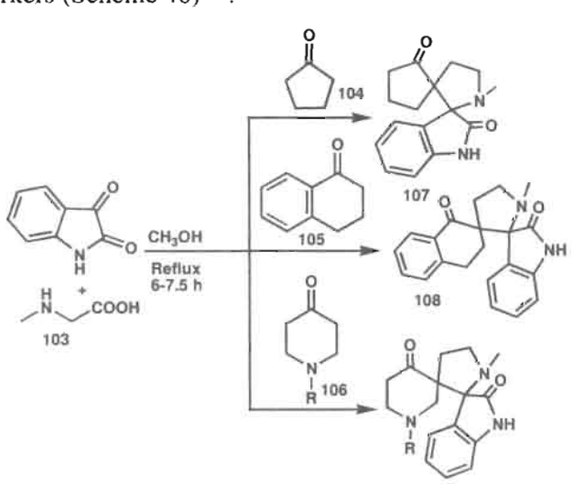
A simple and efficient one-pot three-component synthesis of spirooxindoles scaffold **102** was carried out by Zhu *et al.* following the reaction of isatin, active methylene reagent, and 1,3-dicarbonyl compounds **101** in aqueous medium (Scheme 39)[99].



Scheme 39

1.2.7.2. Synthesis of dispiropyrrolidines

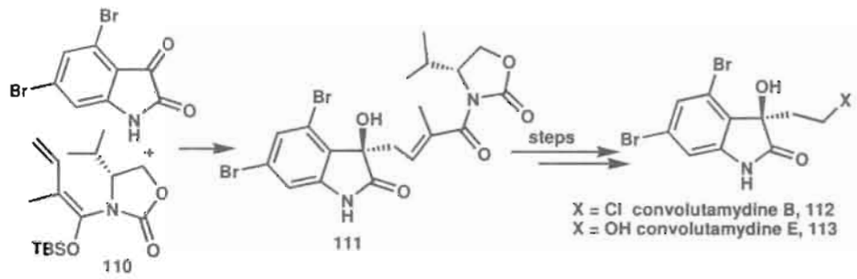
One-pot, three-component tandem reactions of cyclic mono ketones **104-106**, isatin and sarcosine **103** afforded dispiropyrrolidines **107-109** stereoselectively were reported by Perumal and co-workers (Scheme 40)[100].



Scheme 40

1.2.7.3. Synthesis of convolutamydines B and E

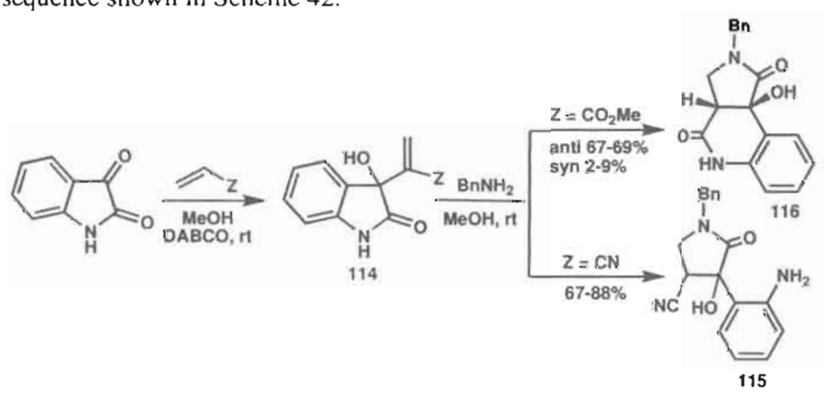
The first enantioselective total synthesis of convolutamydines B **112** and E **113** have been achieved by Kobayashi *et al.* using vinylogous Mukaiyama aldol reaction with isatin and 4-isopropyloxazolidin-2-one derivative **110** as starting materials (Scheme 41)[101].



Scheme 41

1.2.7.4. Synthesis of γ-lactums from MBH adduct of isatin

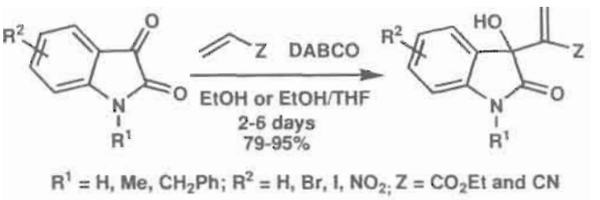
The preparation of 3-aryl-3-hydroxypyrrolidin-2-ones **115** and tricyclic 2-benzyl-9b-hydroxy-3,3a,5,9b-tetrahydro-2H-pyrrolo[3,4-c]quinoline-1,4-diones **116** starting from the MBH adducts of isatin **114** was successfully demonstrated by Kim and coworkers via the reaction sequence shown in Scheme 42.[102]



Scheme 42

1.2.7.5. Isatins as electrophilic component for the MBH reaction

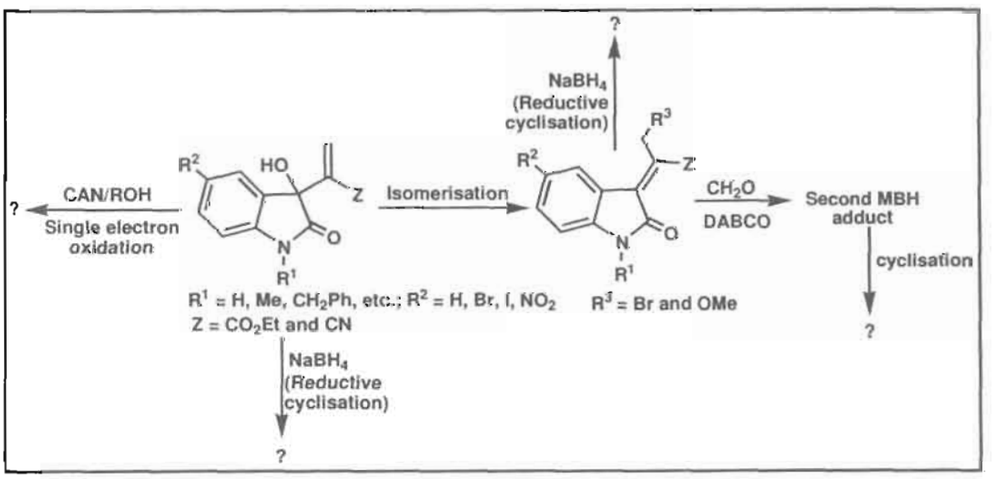
Garden *et al.* first reported that isatin derivatives readily react as the electrophilic component in the MBH reaction giving good to excellent yields of the respective adducts (Scheme 43). It is generally accepted that ketones only take part in the MBH reaction under relatively extreme conditions, with a few exceptions. Isatin on the other hand readily reacts with acrylic acid derivatives in ethanol and or ethanol/THF mixtures in the presence of a catalytic quantity of DABCO.[103]



Scheme 43

1.3. Definition of problem

Literature survey showed that the synthetic transformations and utilities of simple Morita-Baylis-Hillman adducts have been achieved in enormous coverage. From the past reports of our group, there were many synthetic transformations have been achieved, for which simple MBH adducts and their derivatives were utilized[104-108]. Garden *et al.* in the year 2002 reported that isatin and its derivatives readily react as the electrophilic component in the MBH reaction giving an adduct molecule with diverse functionality. However, literature search revealed further synthetic utility of this highly potential MBH adduct of isatin was unexplored until 2005. Hence, we focused our attention for the systematic investigation to bring out novel synthetic transformations of Morita-Baylis-Hillman adduct of isatin to a number of 3-spirooxindole derivatives and related products. The research plans starting from MBH adduct of isatin and its isomerised derivatives and their synthetic use are schematically represented in Scheme 44.



Scheme 44

1.4. References

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Chapter II

Synthesis of functionalized 3-spirocyclopropane-2-indolones from isomerised MBH adducts of isatin

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Chapter II

Synthesis of functionalized 3-spirocyclopropane-2-indolones from isomerised MBH adducts of isatin

2.1. Introduction

Construction of cyclopropane ring systems is of great interest of organic chemists due to its existence as a basic unit in a number of natural products[1]. For instance, some of the natural products and biologically important compounds with cyclopropane ring as core structure are shown in Figure 1.

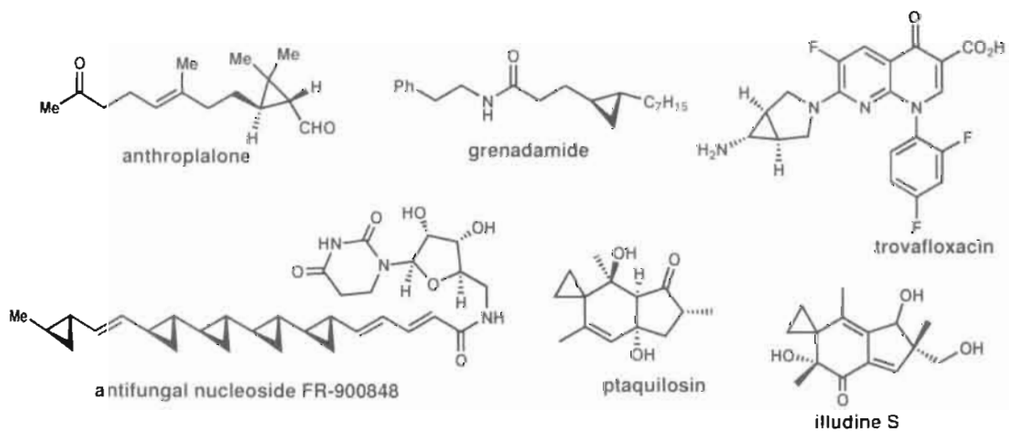


Figure 1

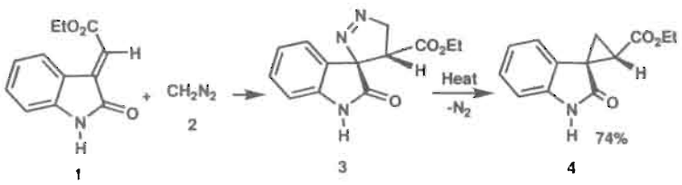
Cyclopropane ring systems are served as versatile building blocks in complex molecular construction. In view of their importance as synthons, numerous synthetic methods have been reported for their synthesis[2-5]. The synthesis of spirocycloindolones are of great interest because they display a variety of biological activities and many of them used as starting materials for alkaloid synthesis[6-9]. Different synthetic strategies are known for the construction of 3-spirocycloalkylindolones[10-21].

2.2. Literature known methods for the synthesis of 3-spirocyclopropane-2-indolones

Since this chapter dealt with the novel method for the synthesis of 3-spirocyclopropane-2-indolones starting from MBH adduct of isatin, literature search revealed that only four methods are known for the construction of 3-spirocyclopropane-2-indalones. Hence, the following sub-sections showed the details of literature known methods for their synthesis.

2.2.1. Using diazomethane via 1,3 dipolar addition-elimination strategy

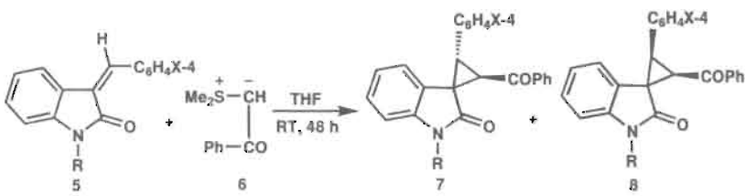
In 1978, Bennet *et al.* first reported the construction of spirocyclopropane using diazomethane via 1,3 dipolar addition-elimination strategy. The reaction of diazomethane **2** with oxoindole-acrylate **1** provided pyrazoline intermediate **3**. The pyrazoline **3** was heated above its melting point or in refluxing xylene, to undergo N_2 loss and to give 3-spirocyclopropane-2-indolone **4** in 74% yield (Scheme 1)[22].



Scheme 1

2.2.2. Utilizing stabilised sulphur ylides

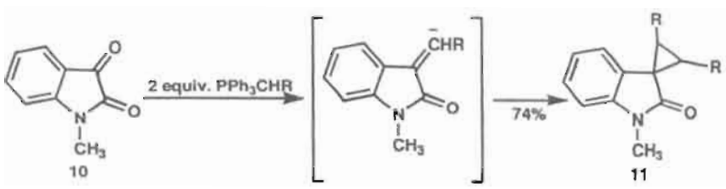
Later in 1979, Croce *et al.* developed a novel method for 3-spirocyclopropane-2-indolone synthesis using stabilised sulphur ylides. The 3-arylmethylene indolin-2-one **5** reacted with carbonyl-stabilized sulphur ylide **6** to yield spiro[cyclopropane-1,3'-indolin-2'-ones] **7** and **8** in the ratio of 2:1 (Scheme 2)[23].



Scheme 2

2.2.3. By Wittig reaction

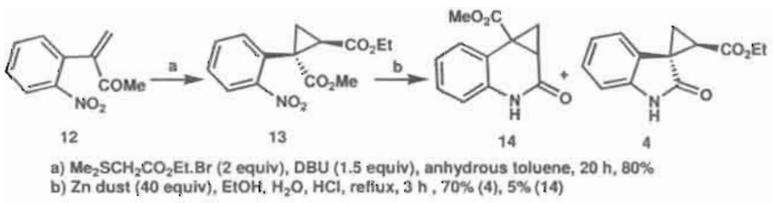
In 1982, Eberle *et al.* found that Wittig reagent adds to 1-methylisatin **10** to give spirocyclopropane ring system in a single operation. Thus, treatment of **10** with 2 equiv. of the phosphorous ylide prepared from 5-bromopentene and triphenylphosphine in ether furnished 74% of spirocyclopropane **11** (Scheme 3)[24].



Scheme 3

2.2.4. Reductive cyclisation using zinc and HCl

Recently in 2007, Ung and Pyne reported cyclopropanation using acrylate and ethyl (dimethyl sulfuranylidene) acetate. Treatment of the acrylate **12** with ethyl (dimethyl sulfuranylidene) acetate yielded the cyclopropane derivative **13** which upon reductive cyclisation using zinc and HCl afforded the spiro compound **4** and a minor side product **14** (Scheme 4)[25].



Scheme 4

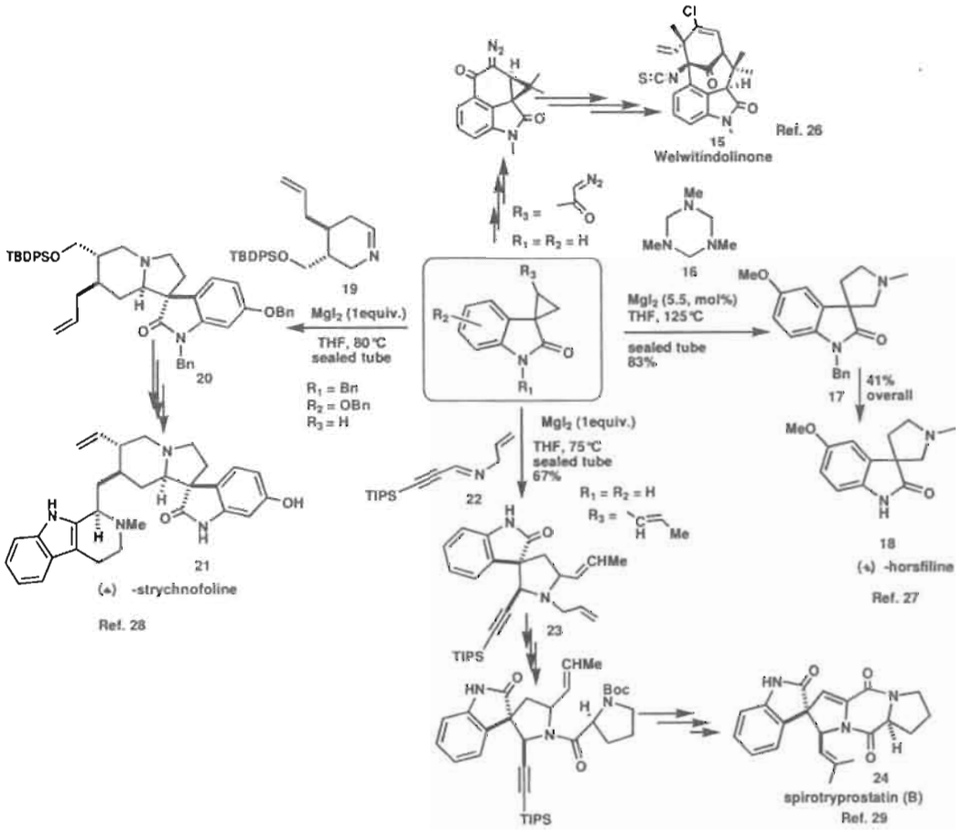
2.3. Applications of 3-spirocyclopropane-2-indolones in organic synthesis

The importances of 3-spirocyclopropane-2-indolones in organic synthesis were demonstrated in several research groups. Few of the representative examples are given in Scheme 5. The synthesis of biologically important carbon skeleton welwitindolinone (antagonists of the P-glycoprotein P-170) **15** was reported utilizing the spirocyclopropane intermediate as shown in Scheme 5[26].

Treatment of 3-spirocyclopropane-2-indolone derivative with 1,3,5-trimethyl-1,3,5-triazinane **16** and 5.5 mol % magnesium iodide in THF at 125 °C in a sealed tube furnished spiro[pyrrolidine-3,3-oxindoles] **17** in 83% yield. Removal of the *N*-benzyl protecting group afforded (±)-horsfiline **18** in 41% overall yield[27].

The magnesium iodide catalyzed coupling of spiro[cyclopropane-1,3-oxindole] with cyclic imine **19** yielded **20** as a single diastereoisomer. The key intermediate **20** upon few more synthetic transformations afforded (±)-strychnofoline **21**[28].

The reation of spiro[cyclopropane-1,3-oxindole] by magnesium iodide catalyzed ring-expansion with *N*-allylimine **22** followed by formation of intermediate **23** which upon further few steps furnished spirotryprostatin (B) **24**[29].



Scheme 5

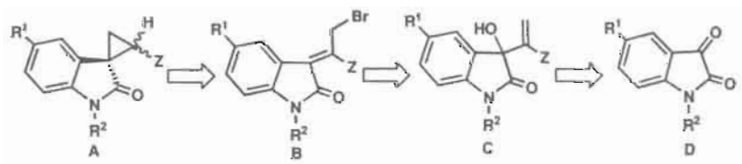
2.4. Objective of present work

Literature search on cyclopropane derivatives reveals that there are number of natural products and biologically active compounds occurred with cyclopropane as core structure. In addition, the compounds containing cyclopropane core have been widely used in number of useful transformations as synthetic intermediate. Hence, the synthesis and chemistry based on cyclopropane ring system are important in synthetic organic chemistry. More over, the search in specific on 3-spirocyclopropane-2-indolones revealed that they have been utilized significantly in synthetic organic chemistry as starting materials for alkaloid synthesis. Further, very few methods for their construction have been reported in the literature. Hence, as part of this research programme, we planned to introduce a new methodology for the construction of 3-spirocyclopropane-2-indolones utilising MBH chemistry. As a result, we developed a novel reductive cyclisation method for the synthesis of functionalized 3-spirocyclopropane-2-indolones from isomerised MBH adducts of isatin. The details of the work are elaborately described in this chapter.

2.5. Results and Discussion

2.5.1. Retrosynthetic analysis

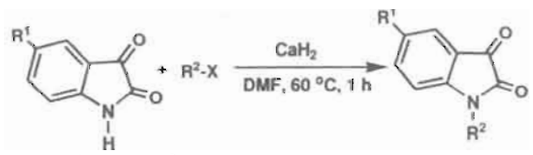
The synthetic strategy for the preparation of 3-spirocyclopropane-2-indolones is depicted in Scheme 6. Reductive cyclization of isomerised bromo derivative of MBH adduct of isatin **B** would provide functionalized 3-spirocyclopropane-2-indolones **A**. The isomerised bromo derivative of MBH adduct of isatin **B** could be synthesized from the MBH adduct of isatin **C** by isomerisation reaction with 46% aqueous HBr under microwave irradiation. In turn, MBH adducts **C** could be prepared from the corresponding substituted isatins **D** by a standard MBH reaction.



Scheme 6

2.5.2. Preparation of MBH adducts of isatin

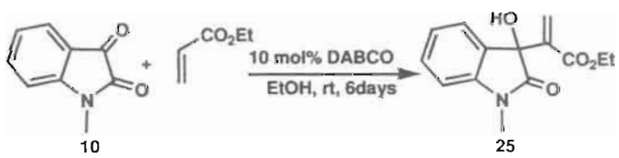
As outlined in the retrosynthetic study, first stage of our target compound synthesis begun with preparation of MBH adduct of isatin. Hence, we initiated the preparation of *N*-alkylation of isatin as shown in Scheme 7. Thus, the alkylation of isatin was conducted using alkyl halide and CaH_2 as base in DMF solvent in 1h reaction time, provided the *N*-alkylated isatin derivatives.



R^1 = H, Br; R^2 = Me, CH_2Ph, CH_2CCH; X = Br, I

Scheme 7

Model substrate for initial studies, the MBH adduct of isatin **25**[30] was prepared by the treatment of *N*-methyl isatin **10** with ethyl acrylate using 10 mole percent of DABCO in ethanol at room temperature in good yield as shown in Scheme 8.



10 25

Scheme 8

The structure of adduct **25** was characterized by ^{1}H NMR spectroscopic analysis. Thus, in the aliphatic region of the spectrum showed two methyl and one methylene signals at δ 1.15, 3.26 and 4.16 respectively. The presence of olefin and aromatic protons at δ 6.25-7.50 were clearly appeared in the spectrum and reproduced in Figure 2.

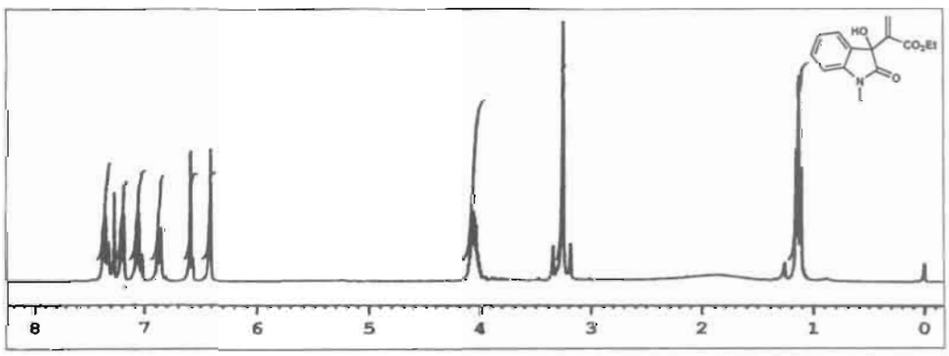


Figure 2 ^{1}H NMR Spectrum of MBH adduct **25**

In a similar way described above, a variety of MBH adducts of isatin were prepared as shown in Figure 3. Some of the MBH adducts of isatin (*N*-propargyl derivative) given in the Figure 3 (**25-32**) were prepared first time by us. However, the standard procedure employed was known in the literature.[30]

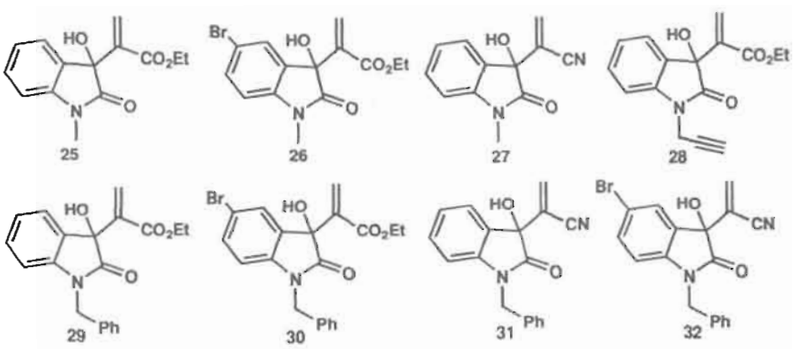


Figure 3

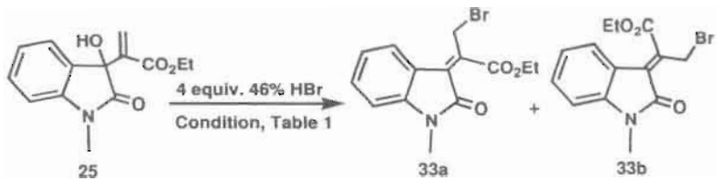
2.5.3. Isomerisation of MBH adducts of isatin with aqueous HBr

Before enter into isomerisation study, we first went through the methods known for the synthesis of bromo isomerisation derivative of simple MBH adducts. It was reported in the literature that the isomerisation of MBH adducts derived from benzaldehye with aqueous HBr[31] is a facile reaction under various conditions such as room temperature stirring in CH_2Cl_2/HBr, CH_2Cl_2/HBr/cat.H_2SO_4, etc. Hence, we utilized aqueous HBr as a reagent for the isomerisation of MBH adduct of isatin.

2.5.3.1. Optimisation study for isomerisation with aqueous HBr

The isomerisation study was initiated with MBH adduct **25** in aqueous HBr. Interestingly, isomerisation procedures reported for simple MBH adduct with HBr failed for isatin derived MBH adduct **25** under conditions such as room temperature stirring in CH_2Cl_2/HBr, CH_2Cl_2/HBr/cat.H_2SO_4, etc. Stirring the adduct **25** in CH_2Cl_2/HBr for a long period (overnight) at RT afforded the unaffected starting material quantitatively (Table 1, entry 1), while the reaction by stirring the adduct **25** in CH_2Cl_2/HBr/cat.H_2SO_4 resulted in decomposition of MBH adduct of isatin (Table 1, entry 2). The reaction of adduct **25** in $CHCl_3$/HBr under reflux condition showed a trace of desired isomerised product formation

(Table 1, entry 4). The trace of product formation under chloroform reflux condition prompted us to carry out a reaction under microwave irradiation. Thus, the pure MBH adduct **25** with aqueous HBr (4 equivalents) embedded on silica gel (0.2 gm) was irradiated in a microwave oven for 3 minutes to afford a 1:2 mixture of *E:Z* isomers of bromo derivative **33a** and **33b** in 95% combined yield after purification by silica gel column chromatography (Scheme 9) (Table 1, entry 5). The geometrical isomers **33a** and **33b** were separated by column chromatography. The proton NMR spectra of the purified individual isomers were used as a tool to distinguish and assign the geometries of the products as discussed in following section.



Scheme 9

Table 1

Entry	Condition	Product	Yield (%)
1	CH_2Cl_2/HBr, 12h, RT	-	-
2	CH_2Cl_2/HBr/cat.H_2SO_4, 1h, RT	-	-
3	CH_2Cl_2/HBr, 1h, reflux	-	-
4	$CHCl_3$/HBr, 1h, reflux	**33a/b**	Trace
5	HBr, MW, 750W, 3 min.	**33a/b**	95

2.5.3.2. Distinction of E/Z isomers 33a/33b by ^{1}H NMR

The characterisation of *E/Z* isomers of bromo derivative **33a** and **33b** was arrived based on proton NMR chemical shift study. The (*E*-) **33a** and (*Z*-) **33b** isomers were distinguished by ^{1}H NMR unambiguously using chemical shift differences of methylene protons attached with bromine atom.

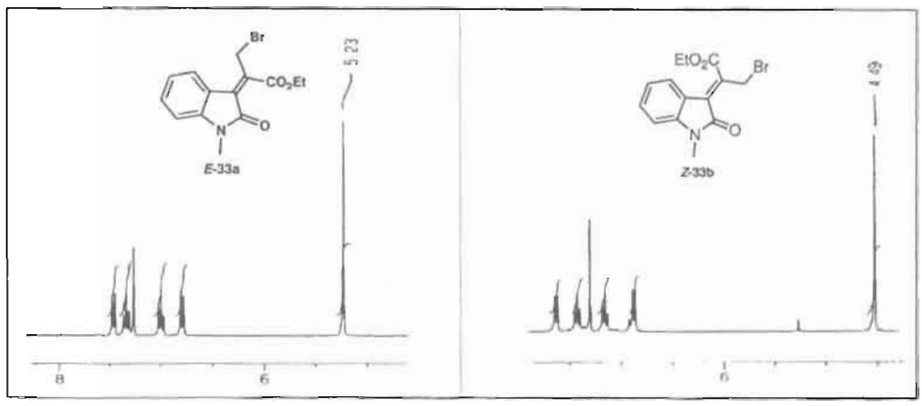
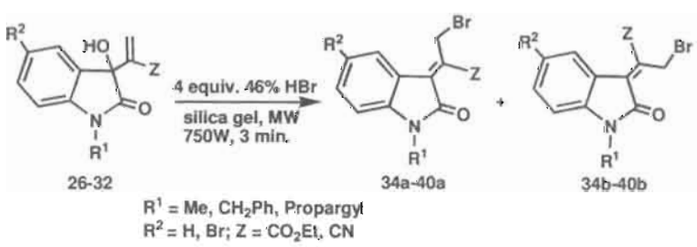


Figure 4 Differentiation of (*E*-) **33a** and (*Z*-) **33b** isomers by ^{1}H NMR Spectrum

Thus, the compound **33a** showed a peak at δ 5.23 which explains the electronic environment and influence of aromatic deshielding ring current effect (Figure 4). On the other hand, the isomer **33b** showed a peak corresponds to methylene protons attached with bromine atom at usual expected chemical shift range δ 4.49 as shown in Figure 4.

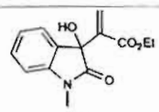
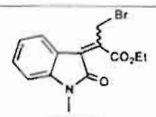
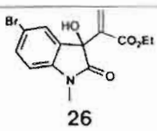
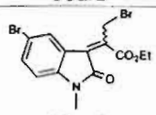
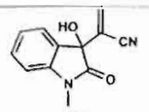
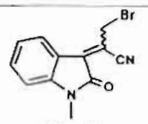
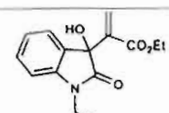
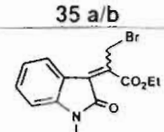
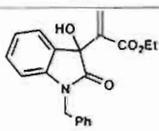
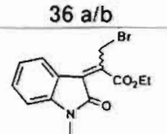
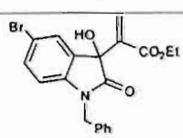
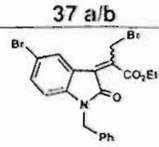
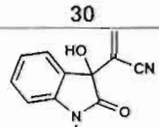
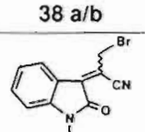
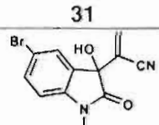
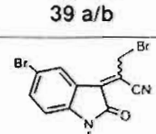
2.5.3.3. Generality of isomerisation reaction

In order to synthesise several isomerised compounds for the subsequent reductive cyclisation study, we carried out reactions under optimized isomerisation condition described above for the MBH adducts **26-32** to afford the corresponding isomerised compounds as *E/Z* mixture **34a/b-40a/b** (Scheme 10). The yields of the reaction and ratio of the isomers are collected in Table 2. All the compounds were purified by silica gel column chromatography and fully characterised by spectral analysis. The ratio of isomers assigned based on ^{1}H NMR study.



Scheme 10

Table 2

Entry	Substrate	Product	Yield (%)	*E*:*Z*
1	 25	 33a/b	95	1:2
2	 26	 34 a/b	93	1:1.5
3	 27	 35 a/b	90	1:1
4	 28	 36 a/b	86	1:1
5	 29	 37 a/b	87	1:2
6	 30	 38 a/b	92	1:2
7	 31	 39 a/b	78	2: 1
8	 32	 40 a/b	85	2: 1

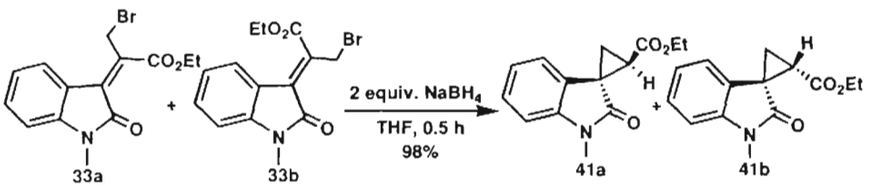
2.5.4. Reductive cyclisation of isomerised bromo derivative of MBH adducts of Isatin with $NaBH_4$

After the successful synthesis of bromo isomerised MBH adducts **33a/b-40a/b**, the stereoselective spirocyclopropane construction was carried out using the mixture of bromo isomerised MBH adducts using $NaBH_4$ as a reducing reagent and reductive cyclisation as a methodology.

2.5.4.1. Optimization of reductive cyclisation for cyclopropanation of MBH derivative 33a/b

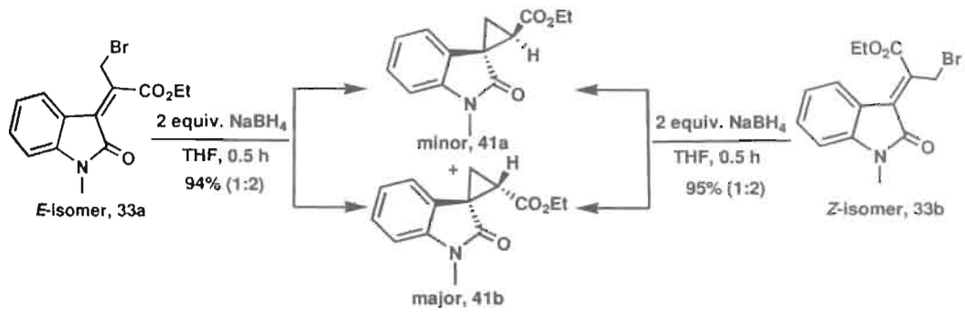
Accordingly, the mixture of compound **33a/b** in dry THF with 4 equivalents of sodium borohydride at RT for 1h afforded functionalized 3-cylopropyl-2-indolones as diastereomeric mixture of isomers **41a** and **41b** in 90% combined yield (Table 3, entry 1). The diastereomers **41a** and **41b** were separable by column chromatography and the ratio of the products (**41a/41b**) was found as 1:2 as estimated by ^1H NMR.

In order to find the optimum reaction time and minimum sodium borohydride requirement, the reductive cyclisation reaction of isomerised compounds **33a/b** with 2 equivalents of $NaBH_4$ in THF for 30 minutes was carried out and the reaction furnished diastereomeric mixture of products **41a/b** in 98% combined yield (Table 3, entry 2). The reaction is shown in Scheme 11.



Scheme 11

To know the selectivity in the formation of diastereo mixture **41a** (minor) and **41b** (major), the reactions from individual isomer of starting material (*E*-) **33a** and (*Z*-) **33b** separately were carried out under optimized condition (Scheme 12).



Scheme 12

Both the reactions of both isomers afforded the diastereomeric mixtures **41a** and **41b** with same ratio and closely similar yields (Table 3, entries 3 and 4). The observation revealed that the both isomers undergo through a common reaction path way and supported in proposing a plausible reaction mechanism.

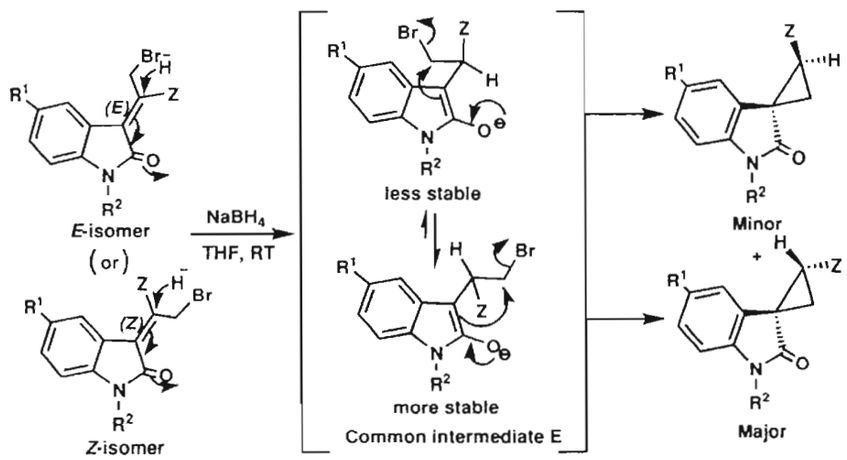
Table 3

Entry	Substrate	Condition	Product	Ratio (a:b)	Yield (%)
1	**33a/33b**	4 equiv. $NaBH_4$ THF, RT, 1 h	**41a/b**	1:2	90
2	**33a/33b**	2 equiv. $NaBH_4$ THF, RT, 0.5 h	**41a/b**	1:2	98
3	**33a**	2 equiv. $NaBH_4$ THF, RT, 0.5 h	**41a/b**	1:2	97
4	**33b**	2 equiv. $NaBH_4$ THF, RT, 0.5 h	**41a/b**	1:2	96

2.5.4.2. A plausible mechanism for cyclopropanation

As mentioned in the optimization study, the reactions of isomerised MBH adduct (*E*-) **33a** and (*Z*-) **33b** afforded the diastereomeric mixture of cyclopropanes as same products (**41a** and **41b**) and in same ratio on exposure to sodium borohydride. Hence, it is understood that both the isomers are undergoing reductive cyclopropanation through a common stable intermediate. The formation of diastereomeric mixture through a common intermediate could be explained based on the plausible mechanism proposed in Scheme 13. Thus, the hydride ion attack on the double bond of the bromo isomerised MBH adducts leads to a common enolate intermediate **E**, which undergoes cyclopropanation. The enolate intermediate **E** could have equilibrium as shown in Scheme 13. The more stable enolate intermediate in which the ester group projects trans to aryl ring affords major isomer. The

sterically less stable enolate intermediate in which the ester group projects same side of aryl ring cyclises to afford minor isomer.

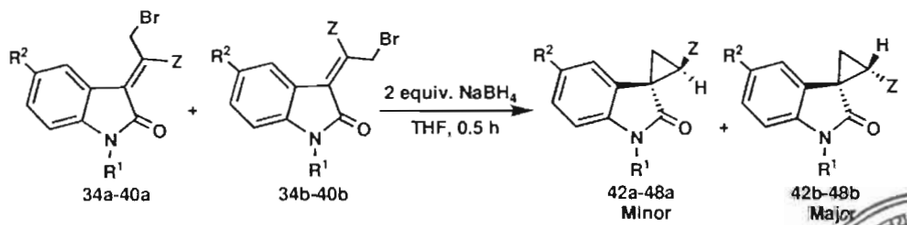


Scheme 13

Hence, we did all the remaining reductive cyclisation experiments by using the mixture of *E/Z* isomerised compounds.

2.5.4.3. Generality of the reductive cyclisation

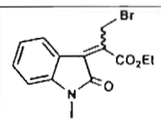
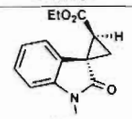
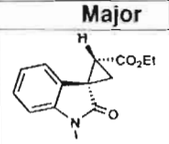
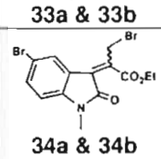
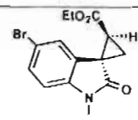
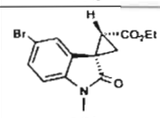
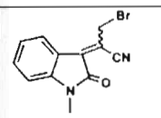
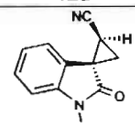
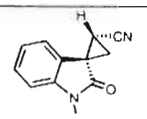
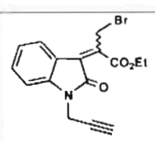
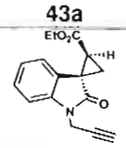
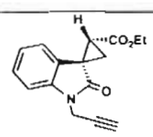
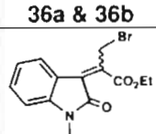
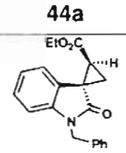
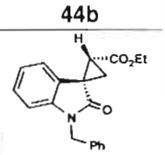
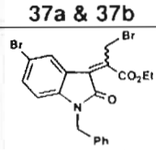
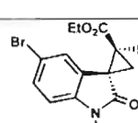
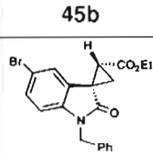
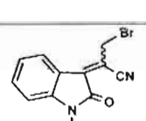
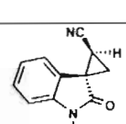
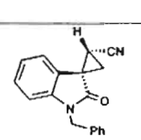
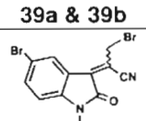
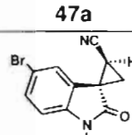
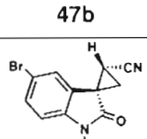
Encouraged by the preliminary results and to show the generality of the reaction, various substitution combinations at aryl ring and *N*-alkyl position of isatin part as well as ester and nitrile groups at activated alkene part of MBH were undertaken. The reaction of isomerised bromo adducts of isatin **34ab-40ab** under optimized conditions afforded the corresponding functionalized 3-spirocylopropyl-2-indolones **42a/42b-48a/48b** in excellent combined yield. The reaction is showed in Scheme 14 and the results are summarized in Table 4.



R^1 = Me, CH_2Ph, Propargyl; R^2 = H, Br; Z = CO_2Et, CN

Scheme 14

Table 4

Entry	Reactant [a] (*E&Z*)	Condition [b]	Products [c]		Ratio[d]	Yield %[e]
			Minor	Major		
1	 **33a & 33b**	2 equiv. $NaBH_4$, THF, 0.5h, RT	 **41a**	 **41b**	1:2	98
2	 **34a & 34b**	2 equiv. $NaBH_4$, THF, 0.5h, RT	 **42a**	 **42b**	1:1.5	96
3	 **35a & 35b**	2 equiv. $NaBH_4$, THF, 0.5h, RT	 **43a**	 **43b**	1:2	94
4	 **36a & 36b**	2 equiv. $NaBH_4$, THF, 0.5h, RT	 **44a**	 **44b**	1:2	88
5	 **37a & 37b**	2 equiv. $NaBH_4$, THF, 0.5h, RT	 **45a**	 **45b**	1:2	93
6	 **38a & 38b**	2 equiv. $NaBH_4$, THF, 0.5h, RT	 **46a**	 **46b**	1:2	95
7	 **39a & 39b**	2 equiv. $NaBH_4$, THF, 0.5 h, RT	 **47a**	 **47b**	1:2.5	98
8	 **40a & 40b**	2 equiv. $NaBH_4$, THF, 0.5 h, RT	 **48a**	 **48b**	1:1.5	86

a. *E/Z* mixture was used as starting material. b. See typical procedure in the experimental part. c. The isomers were separated by column chromatography. d. ratio estimated based on ^1H NMR study. e. combined yield after column purification

2.5.5. Distinction of the minor and major isomers by ^{1}H NMR study

All the reactions in the generality study afforded 1:2 ratios of diastereomeric 3-spirocyclopropane-2-indolones in excellent combined yields. Hence, it was an interesting task for us to distinguish the relative stereochemistry of minor and major products (**41-48a** and **41-48b**). In order to confirm the projection of ester group (α or β) in minor and major isomers (**41-48a** and **41-48b**), ^{1}H NMR chemical shift and coupling constant studies were used as a tool. The chemical shift variation of aromatic protons H_d and $H_{d'}$ was used as a main tool as the structures shown in Figure 5.

For example, the H_d proton appeared at δ 7.51 due to anisotropic influence of ester carbonyl for **42a** while the $H_{d'}$ proton appeared at δ 6.94 due to no influence of ester group in **42b**. To fix the nature of protons of the cyclopropane rings, the coupling constant and chemical shift correlation studies were used as a tool (Table 5). Thus, in compound **42a**, the H_a proton appeared at δ 2.03 (dd, J_{gem}=4.5Hz and J_{cis}=8.7Hz), H_b proton appeared at δ 2.13 (dd, J_{gem}=4.5Hz and J_{trans}=7.2Hz) and H_c proton appeared at δ 2.71 (dd, J_{cis}=8.7 and J_{trans}=7.2Hz). In contrary, for compound **42b**, the $H_{a'}$ proton appeared at δ 1.80 (dd, J_{gem}=5.1Hz and J_{cis}=8.7Hz), $H_{b'}$ proton appeared at δ 2.38 (dd, J_{gem}=5.1Hz and J_{trans}=8.1Hz) and Hc' proton appeared at δ 2.64 (dd, J_{cis}=8.7 and J_{trans}=8.1Hz). Hence, the structure with relative stereochemistry of minor and major compounds **42a** and **42b** was assigned as shown in Figure 5.

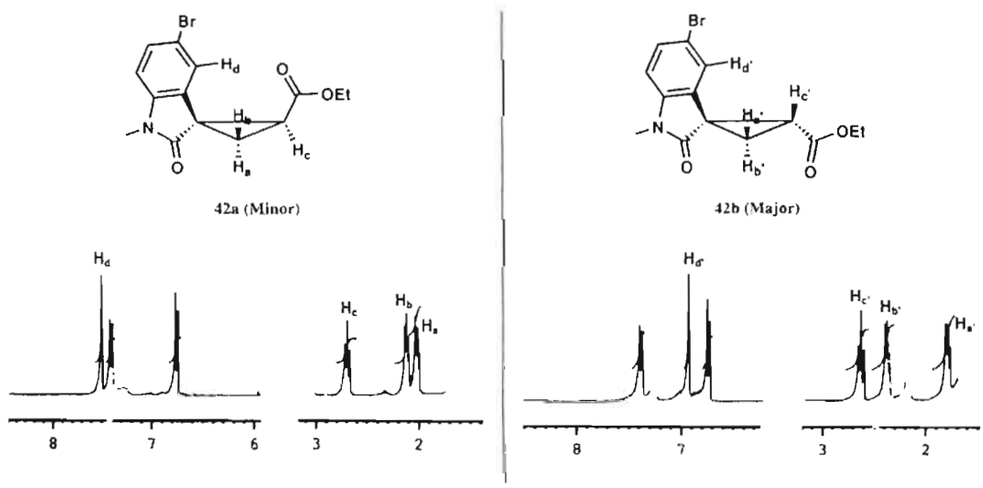


Figure 5

Table 5

Proton	Chemical shift (δ)		Coupling constant (*J* in Hz)	
	42a (Minor)	**42b** (Major)	**42a** (Minor)	**42b** (Major)
a/a'	2.03	1.80	4.5 and 8.7	5.1 and 8.7
b/b'	2.13	2.38	4.5 and 7.2	5.1 and 8.1
c/c'	2.71	2.64	8.7 and 7.2	8.7 and 8.1
d/d'	7.51	6.94	1.8	1.8

2.5.6. Characterization of newly synthesized 3-spirocylopropyl-2-indolones

All the new compounds were thoroughly characterized by following a systematic analysis of spectral (IR, ^{1}H and ^{13}C NMR) and HRMS data (see experimental section). Typical examples of ^{1}H and ^{13}C NMR spectra are explained in the following discussions. The nomenclature numbering for 3-spirocyclopropane-2-indolones systems is shown in the Figure 6. However, the numbering in the ^{13}C NMR spectra was labeled in the increasing order from the up field to down field and assigned appropriately over the structures of the compounds.

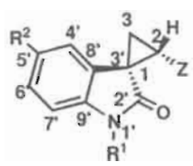


Figure 6

2.5.6.1. Characterization of 3-spirocylopropyl-2-indolones 41a/41b

In the IR spectrum of the compound **41a**, absorption bands at 2968, 2925 and 2863 cm^{-1} supported the presence of cyclopropane ring in the structure. The amide and ester carbonyls caused the absorption bands at 1746 and 1722 cm^{-1}. The aromatic functional group showed the absorption band at 1617 cm^{-1}.

The ^{1}H NMR spectrum of 3-spirocylopropyl-2-indolone **41a** (Figure 7) was analysed as follows. The key evidence for the formation of cyclopropane ring system was confirmed due to the existence of upfield signals as three doublet of doublet peaks at (i) δ 2.01 with

coupling constants $J_{gem/cis}$ = 4.5 and 8.7 Hz, (ii) δ 2.13 with coupling constants $J_{gem/trans}$ = 4.5 and 7.5 Hz, and (iii) δ 2.70 with coupling constants $J_{trans/cis}$ = 7.5 and 8.7 Hz in the aliphatic region of the spectrum. Further, in the aliphatic region, ester methyl protons appeared as a triplet at δ 1.20 with coupling constant J = 6.9Hz and a singlet at δ 3.28 for *N*-methyl protons and a quartet for ester methylene protons at δ 4.13 with coupling constant J = 6.9Hz were clearly visualised. More over, the down field signals due to four aromatic protons appeared as a doublet at δ 6.90 with coupling constant J = 7.8 Hz, two triplets at δ 7.02 and 7.29 with coupling constant J = 7.8 Hz, and another doublet at δ 7.36 with coupling constant J = 7.8 Hz.

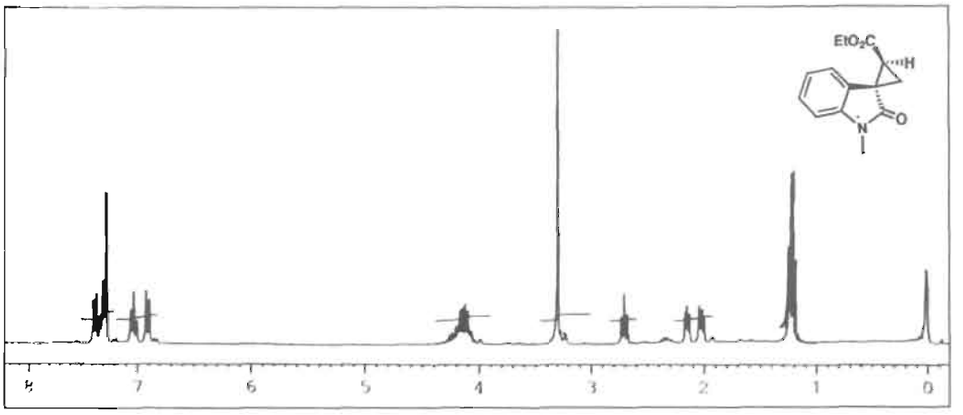


Figure 7 ^{1}H NMR Spectrum of compound **41a**

The ^{13}C NMR spectrum of compound **41a** (Figure 8) clearly showed the spiro-carbon centre at δ 32.94. The carbonyl carbons were resonated at δ 169.03 and δ 175.29 (Figure 8).

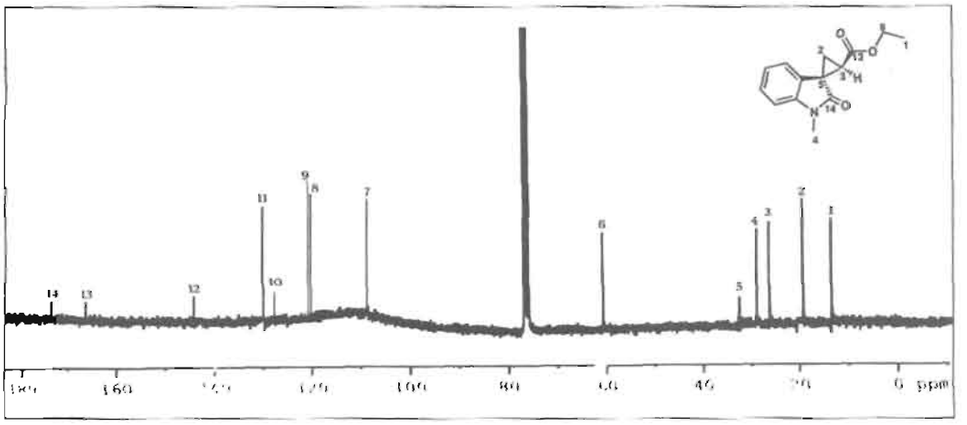


Figure 8 ^{13}C NMR Spectrum of compound **41a**

With these spectral details, final confirmation for the structure of product **41a** was evidenced from mass spectrum (HRMS) by seeing molecular ion peak at m/z 245.1045 (Figure 9).

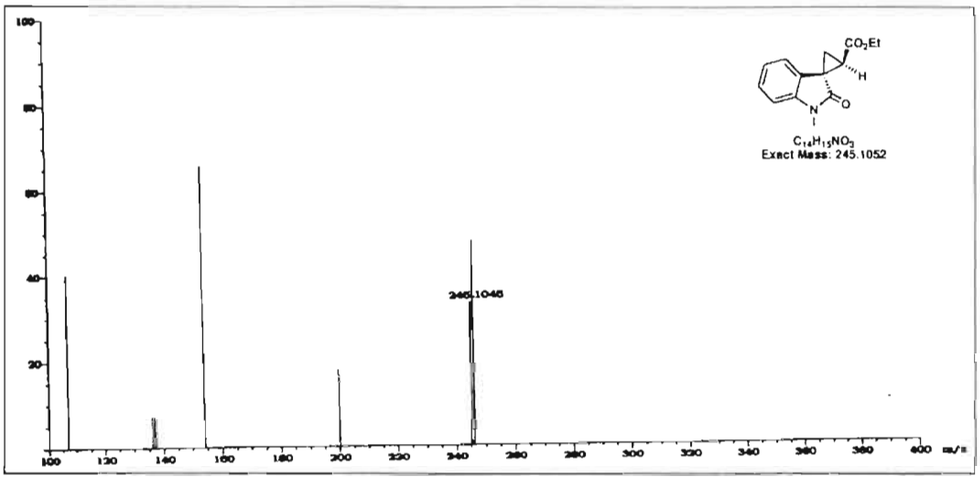


Figure 9 HRMS of compound **41a**

Similarly, IR spectrum of the major isomer **41b** had absorption bands due to cyclopropane ring at 2963, 2937, and 2852 cm^{-1} and for carbonyl functional groups at 1739, 1709 cm^{-1}. The ^1H NMR spectrum of isomer **41b** showed the characteristic signals as appeared in the case of isomer **41a** with slight variation (Figure 10). Thus, a triplet for the ester methyl proton at δ 1.21 with coupling constant J = 6.9Hz, three sets of doublet of doublet for cyclopropane ring system at (i) δ 1.72 with coupling constants $J_{gem/cis}$ = 4.8 and 8.4 Hz, (ii) δ 2.31 with coupling constants $J_{gem/trans}$ = 4.8 and 8.1 Hz, and (iii) δ 2.57 with coupling constants $J_{trans/cis}$ = 8.1 and 8.4 Hz were seen in the up field range by confirming the spirocyclopropyl unit in the product. The peaks for *N*-methyl and ester methylene protons were found at δ 3.19 as singlet and a quartet at δ 4.14 with coupling constants J = 6.9 Hz. The down field aromatic protons appeared as two doublets at δ 6.77 with coupling constants J = 7.2 Hz, and δ 6.82 with coupling constants J = 7.8 Hz. Two triplets were seen at δ 6.98 with coupling constants J = 7.5 Hz, and δ 7.22 with coupling constants J = 7.8 Hz.

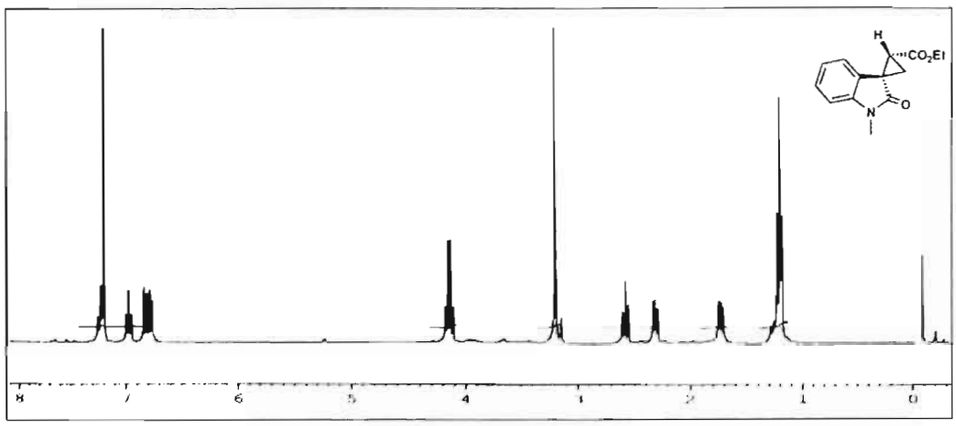


Figure 10 ^{1}H NMR Spectrum of compound **41b**

In ^{13}C NMR spectrum of major diastereomer **41b**, total number of peaks accounted all carbons present in the compound **41b** (Figure 11). The carbon signal due to quaternary spiro centre was visible at δ 32.87. The carbonyl carbons were appeared at δ 168.68 and δ 174.29.

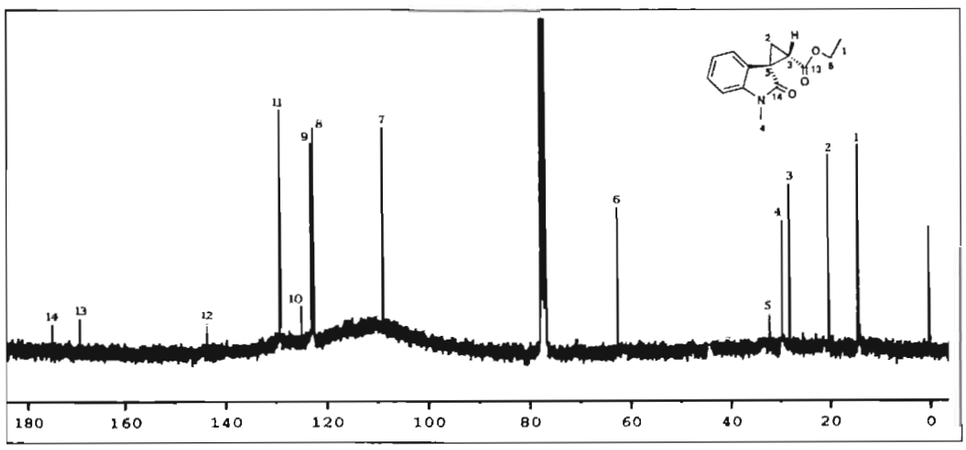


Figure 11 ^{13}C NMR Spectrum of compound **41b**

Final confirmation for the structure of product **41b** was evidenced from mass spectrum (HRMS). Thus, the compound showed a molecular ion peak at m/z 245.1043 (Figure 12).

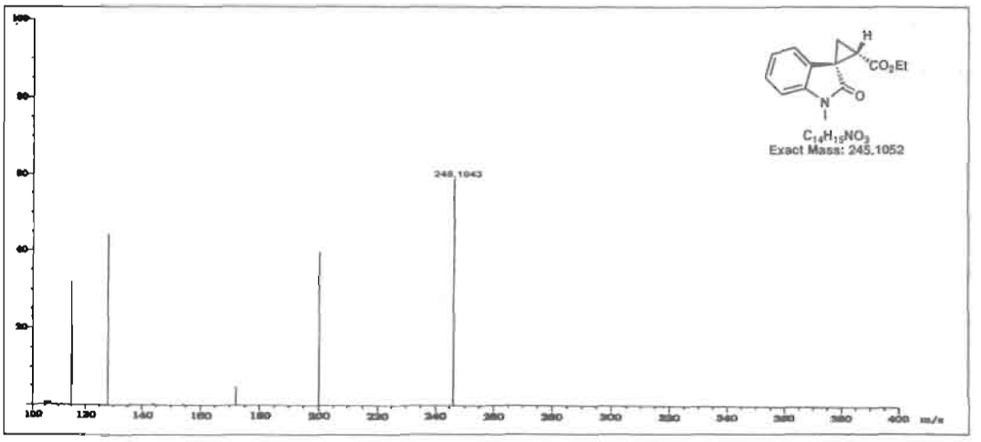


Figure 12 HRMS of compound **41b**

2.5.6.2. Characterization of 3-spirocylopropyl-2-indolones 43a/43b

To demonstrate the structure of nitrile substituted cyclopropane derivatives, products **43a** and **43b** were chosen as substrates and their spectral studies are discussed as follows. The nitrile derivative of minor isomer **43a** showed IR absorption bands at 1701 and 1614 cm^{-1} for the presence of carbonyl and aromatic functional groups respectively. The ^1H NMR spectrum was used to characterize the proton signals unambiguously (Figure 13).

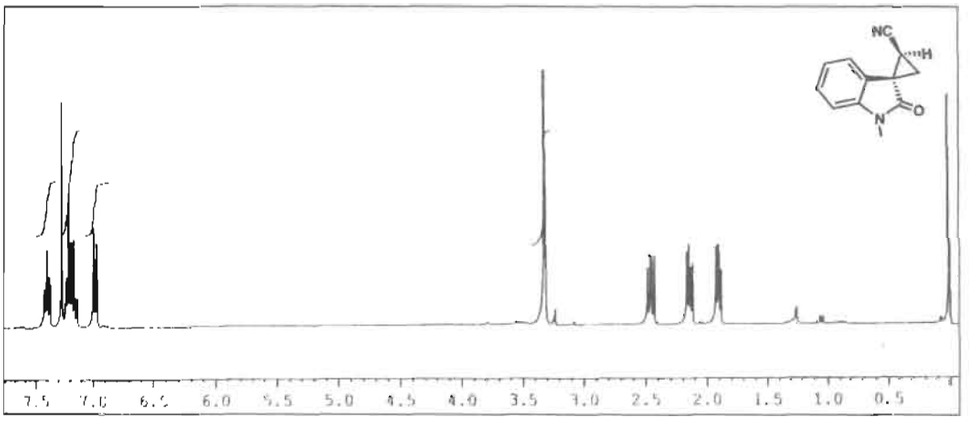


Figure 13 ^1H NMR Spectrum of compound **43a**

Thus, the upfield cyclopropyl protons appeared as three sets of doublet of doublet at (i) δ 1.89 with coupling constant $J_{gem/trans}$ = 4.8 and 6.9 Hz, (ii) δ 2.13 with coupling value $J_{gem/cis}$ = 4.8 and 9.3 Hz, and (iii) δ 2.44 with coupling constant $J_{trans/cis}$ = 6.9 and 9.3 Hz. A singlet

signal was seen at δ 3.30 for the presence of *N*-methyl protons. The four aromatic protons were apparent at δ 6.97 as a doublet with *J* value 7.8 Hz, and a three protons as multiplet around δ 7.12-7.42.

The ^{13}C NMR spectrum accounted total number of carbons as in compound **43a** (Figure 14). Thus, four carbon peaks were visible in aliphatic region. The quaternary spirocarbon was found at δ 31.70. The nitrile carbon appeared at δ 116.85. The carbonyl carbon was occurred at δ 172.97. Final confirmation for the structure of product **43a** was evidenced from mass spectrum (HRMS). Thus, the compound showed a molecular ion peak at m/z 198.0790.

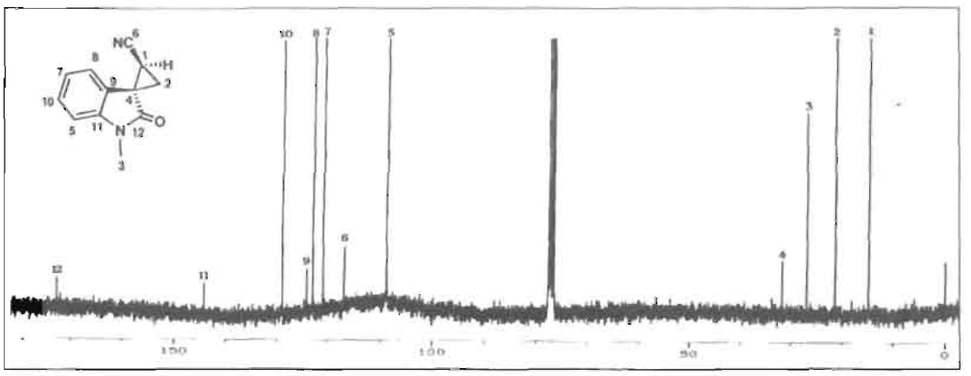


Figure 14 ^{13}C NMR Spectrum of compound **43a**

In the IR spectrum, the nitrile derivative of major isomer **43b** showed absorption band at 3031, 2963, 2916, and 2848 cm^{-1} due to cyclopropane unit. Absorption band for nitrile group was found at 2247 cm^{-1}. The carbonyl and aromatic functional groups had absorption bands at 1705 and 1611 cm^{-1} respectively. The nitrile derivative of major isomer **43b** showed the characteristic signals in its ^{1}H NMR spectrum due to cyclopropane, *N*-methyl and aromatic protons in their respective expected region (Figure 15). Thus, three doublet of doublet signals at (i) δ 1.99 with $J_{gem/cis}$ = 5.1 and 9.3 Hz, (ii) δ 2.19 with $J_{gem/trans}$ = 5.1 and 7.2 Hz, and (iii) δ 2.35 with $J_{trans/cis}$ = 7.2 and 9.3 Hz were indicative of cyclopropane ring protons. The *N*-methyl was appeared as a singlet at δ 3.34. The four aromatic protons were seen at (i) δ 6.79 as doublet with *J* = 7.1 Hz, (ii) δ 6.96 as doublet with *J* = 7.1 Hz, (iii) δ 7.07 as triplet with *J* = 7.8 Hz, and (iv) δ 7.35 as triplet with *J* = 7.8 Hz.

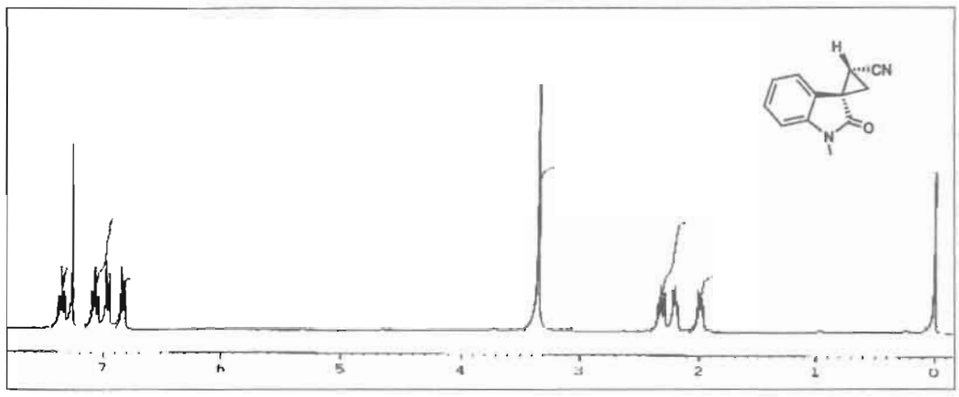


Figure 15 ^{1}H NMR Spectrum of compound **43b**

The ^{13}C NMR spectrum of major isomer **43b** showed the presence of spiro carbon signal at δ 31.83. The nitrile carbon was resonated at δ 115.89. The carbonyl carbon appeared at δ 171.49 (Figure 16). Final confirmation for the structure of product **43b** was evidenced from mass spectrum (HRMS). Thus, the compound showed a molecular ion peak at m/z 198.0795.

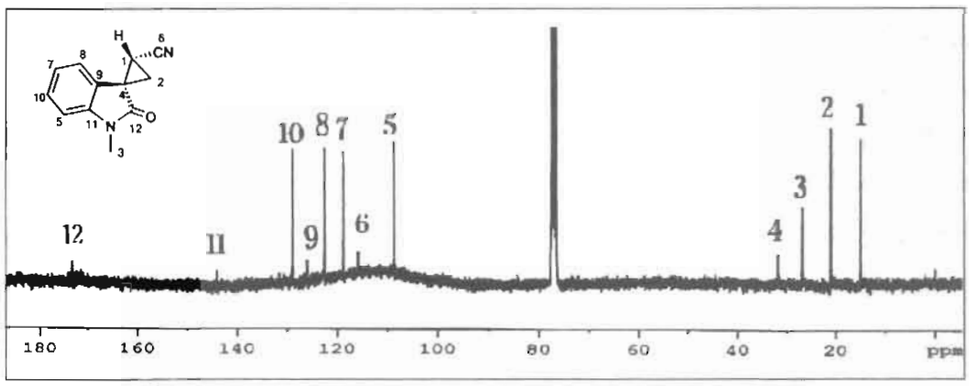


Figure 16 ^{13}C NMR Spectrum of compound **43b**

2.5.6.3. Characterization of *N*-propargyl derivative 44b

The IR spectrum of major isomer **44b** had absorption bands due to cyclopropane ring at 3054, 2986 and 2930 cm^{-1}. Absorption band at 2133 cm^{-1} was due to propargyl group. The amide and ester carbonyls showed absorption bands at 1740 and 1719 cm^{-1}. In ^{1}H NMR spectrum of interesting major isomer of *N*-propargyl derivative **44b**, a triplet at δ 1.26 for ester methyl protons, a doublet of doublet at δ 1.82 for one of the cyclopropane ring protons.

another triplet at δ 2.24 for alkyne proton, two more doublet of doublet at δ 2.39 and 2.66 for remaining cyclopropane ring protons, an ester methylene protons as quartet at δ 4.19 and another methylene protons attached with nitrogen as multiplet around δ 4.48-4.68 clearly accounted all the protons in aliphatic region. The remaining four aromatic protons were seen between δ 6.86-7.34 (Figure 17).

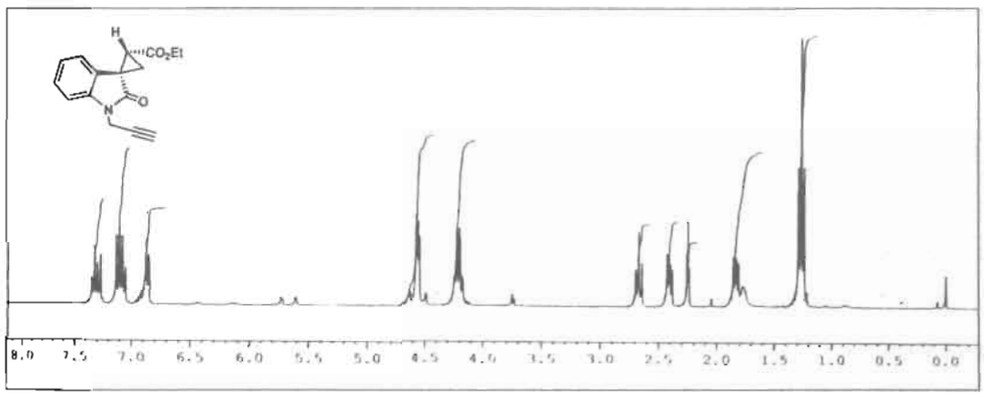


Figure 17 ^{1}H NMR Spectrum of compound **44b**

The ^{13}C NMR spectrum of compound **44b** accounted the total number of carbons present. Thus, the aliphatic carbon signals at δ 14.32 (OCH_2-$\underline{C}H_3$), 21.52 (methine carbon in cyclopropane ring), 29.70 (methylene carbon in cyclopropane ring), 32.42 (quaternary spirocarbon), 33.68 (N-$\underline{C}H_2$-), 47.97 (N-CH_2-$\underline{C}$), 61.62 ($O\underline{C}H_2$-CH_3), and 72.48 (N-CH_2-$C\underline{C}$H) were appeared due to ester methyl and methylene, cyclopropane ring, and *N*-propargyl groups. The presence of two carbonyl carbons resonated at δ 167.04 and 172.55 (Figure 18).

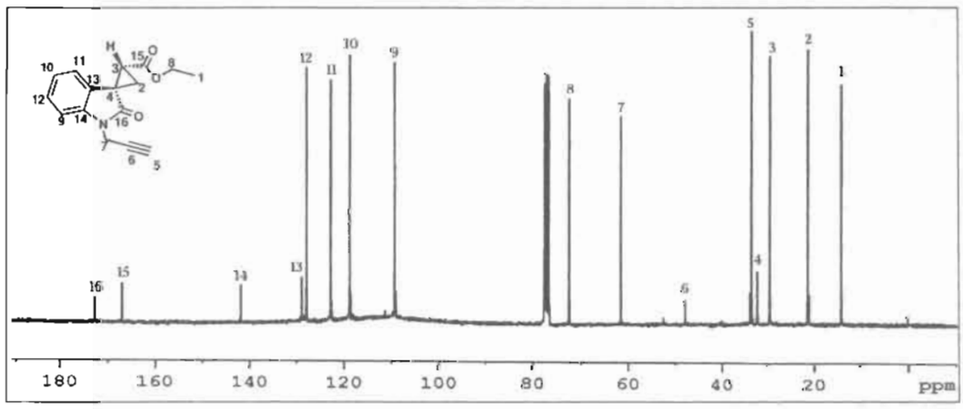


Figure 18 ^{1}**H** NMR Spectrum of compound **44b**

Final proof for the structure of product **44b** was evidenced from mass spectrum (HRMS). Thus, the compound showed a molecular ion peak at m/z 269.1047.

2.5.6.4. Characterization of 3-spirocylopropyl-2-indolones 45a/45b

In the IR spectrum of the compound **45a**, absorption bands at 2927 and 2849 cm^{-1} supported the presence of cyclopropane ring in the structure. The amide and ester carbonyls caused the absorption band at 1721 cm^{-1}. The aromatic functional group showed the absorption band at 1608 cm^{-1}. In the ^1H NMR spectrum of minor isomer of *N*-benzyl derivative **45a**, the ester ethyl group appeared as a triplet and a quartet at δ 1.25 and 4.15 respectively with coupling constant J = 6.9 Hz. The signals due to three diastereotopic cyclopropane ring protons appeared separately at δ (i) 2.08 as a doublet of doublet with coupling constants J = 4.2 (geminal) and 8.4 (vicinal cis) Hz, (ii) 2.18 as a doublet of doublet with coupling constants J = 4.2 (geminal) and 7.5 (vicinal trans) Hz, and (iii) 2.77 as a doublet of doublet with coupling constants J = 7.5 (vicinal trans) and 8.4 (vicinal cis) Hz. The benzyl methylene protons appeared as a singlet at δ 5.10. The remaining aromatic protons appeared in the range at δ 6.84-7.45 (Figure 19).

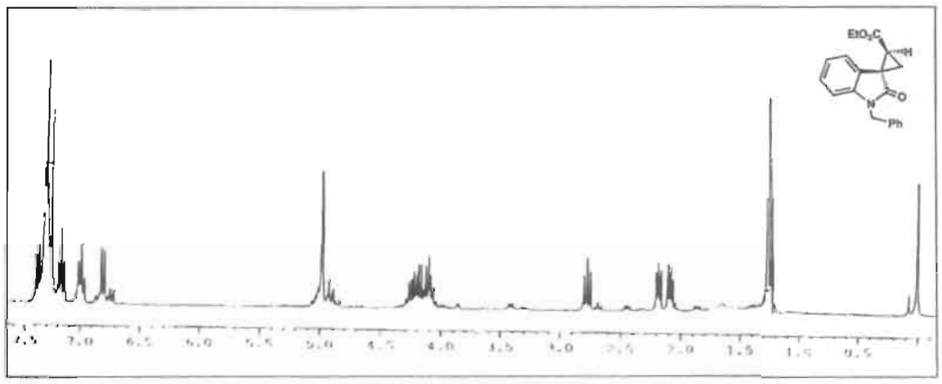


Figure 19 ^1H NMR Spectrum of compound **45a**

The ^{13}C NMR spectrum of the compound **45a** accounted total number of carbons. The peaks at δ 14.35 (OCH_2-$\underline{C}H_3$), δ 21.27 (cyclopropane ring methylene carbon), δ 32.12 (spirocarbon), δ 33.15 (methine carbon of cyclopropane ring), δ 44.52 (N-$\underline{C}H_2$-), and δ 61.51 ($O\underline{C}H_2$-CH_3) in aliphatic region assigned carbons due to ethyl ester, cyclopropane ring, and benzyl methylene groups. Twelve carbon signals due to aromatic carbons were

scattered in the range δ 109.24-143.60. The carbonyl carbons appeared at δ 168.99 and 175.11 (Figure 20). Final evidence for the structure of product **45a** was evidenced from mass spectrum (HRMS). Thus, the compound showed a molecular ion peak at m/z 321.1359.

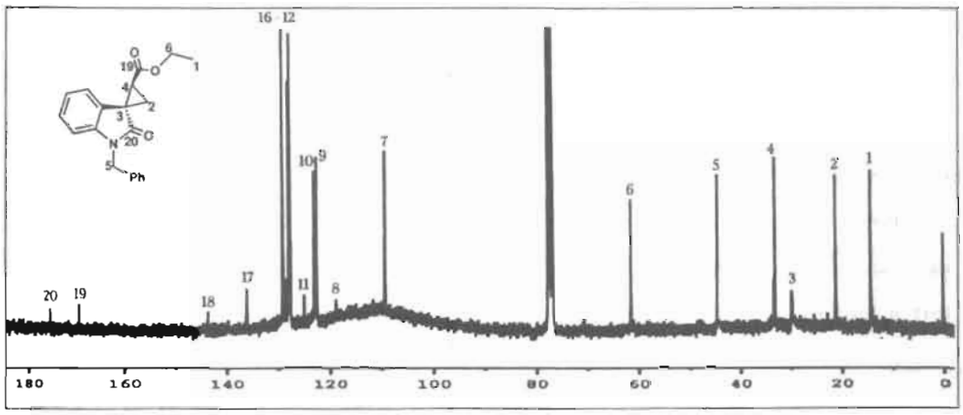


Figure 20 ^{13}C NMR Spectrum of compound **45a**

In the IR spectrum of the compound **45b**, absorption bands at 2983 and 2927 cm^{-1} supported the presence of cyclopropane ring in the structure. The amide and ester carbonyls caused the absorption bands at 1735 and 1705 cm^{-1} respectively. The aromatic functional group showed the absorption band at 1613 cm^{-1}. The ^1H NMR spectrum of major isomer **45b** showed its characteristic signals as in the case of minor compound **45a** with small difference in chemical shifts (Figure 21).

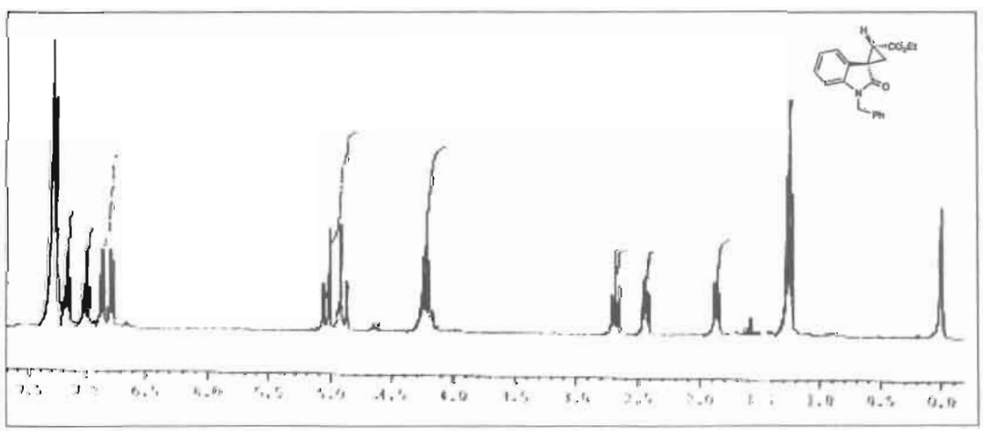


Figure 21 ^1H NMR Spectra of compound **45b**

Thus, in the aliphatic region signals for ester group at δ 1.25 and 4.17 with coupling constant J = 7.1 Hz as a triplet and a quartet were appeared respectively. The cyclopropane ring signals at δ 1.85, 2.43, and 2.68 as the doublet of doublet with coupling constants ($J_{gem/cis}$ = 4.8 and 8.4 Hz), ($J_{gem/trans}$ = 4.8 and 7.8 Hz), and ($J_{trans/cis}$ = 7.8 and 8.4 Hz) were seen respectively. The benzyl methylene protons appeared as two sets of doublets at δ 4.89 and 5.04 with geminal coupling constants J = 15.6 Hz. The remaining aromatic protons appeared in the range of δ 6.76-7.26.

The ^{13}C NMR spectrum of the compound confirmed all the expected carbon signals. Thus, signals for aliphatic carbons at δ 14.38 (OCH_2-$\underline{C}H_3$), δ 21.16 (cyclopropane ring methylene carbon), δ 32.44 (spirocarbon), δ 33.79 (methine carbon in cyclopropane ring), δ 44.25 (N-$\underline{C}H_2$-), and δ 61.63($O\underline{C}H_2$-CH_3), aromatic carbons in the range around δ 109.33-142.95, and carbonyl carbons at δ 167.23 and 173.67 were seen in the spectrum (Figure 22).

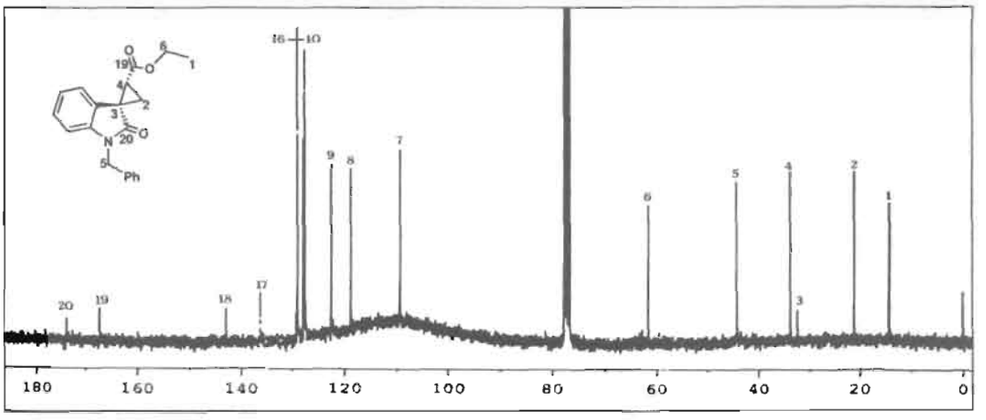
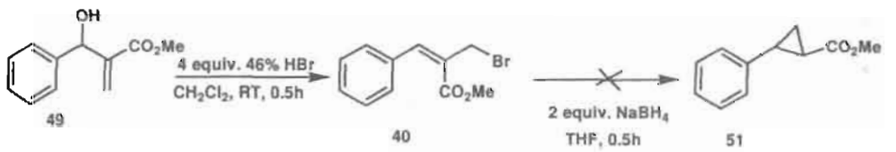


Figure 22 ^{13}C NMR Spectra of compound **45b**

2.5.7. Limitation and applicability of cyclopropanation reaction

To investigate the limitation and applicability of cyclopropanation reaction to the simple MBH adducts, the adduct **49** derived from benzaldehyde with methyl acrylate on isomerisation with aqueous HBr at RT to afford corresponding isomerised product **50** as a single isomer. The isomerised bromo derivative **50** in dry THF upon reduction with 2 equivalents of $NaBH_4$ (optimised conditions) did not yield the expected cyclopropane derivative **51**. Careful repetition and altering the reaction conditions provided only the unreacted starting material. Thus, it is clear that only isomerised bromo derivative of isatins

are suitable substrates for the cyclopropanation under reductive cyclization condition. The reaction is shown in Scheme 15. The reason for the failure of cyclopropanation of substrate 40 is due to non-availability of enolate structure as in isatin derivative.



Scheme 15

2.6. Conclusion

- Synthesis of *E* and *Z* bromo isomerised MBH adducts has been successively carried out.
- A short, novel and facile method for the synthesis of functionalized diastereomeric 3-spirocyclopropane-2-indolones from isomerised bromo derivatives of MBH adducts of isatin by reductive cyclopropanation methodology as a key step has been achieved.
- Distinction of two diastereomeric cyclopropane products obtained in the reaction was characterised applying ^{1}H NMR chemical shift and coupling constant correlation study.
- A plausible mechanism of the reaction was explained.
- All the compounds were thoroughly characterised by spectroscopic methods.
- The limitation of methodology for simple MBH adduct was tested.

2.7. Experimental details

2.7.1. General Considerations

Melting points were recorded on a Buchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300 (^{1}H) and 75(^{13}C) MHz respectively on a Bruker Avance DPX-300 MHz NMR spectrometer. NMR spectra were obtained using chloroform-d_1 as solvent. Chemical shifts are given in δ-scale with tetramethyl silane as internal standard. Coupling constants (J) are reported in hertz (Hz). HRMS were measured at the JMS 600 JEOL Mass Spectrometer. Yields refer to quantities obtained after chromatography. IR spectra were taken on Nicolet (Impact 400D FT-IR) spectrophotometer or Bomem MB-series FT-IR spectrophotometer. Abbreviations used in ^{1}H NMR are: s-singlet, d-doublet, dd-doublet of a doublet, brs-broad singlet, q-quartet and m-multiplet.

Analytical thin layer chromatography (TLC) was performed on glass plates coated with silica gel (Merck) containing 13% calcium sulphate as binder. Column chromatography was done using 100-200 mesh silica gel and appropriate mixture of petroleum ether (60-80 °C) and ethyl acetate was used as solvent system for elution unless otherwise specified. The solvents were removed (under reduced pressure where necessary) using Heidolph or Buchi rotary evaporator. All solvents were distilled prior to use and reactions requiring dry conditions were carried out using dry solvents which were dried according to the literature procedure.[32]

Extraction of the reaction mixtures were done with the appropriate organic solvents, the extraction was repeated with fresh solvent at least three times before the organic layers were combined. Washing of the combined organic layer was also repeated three times in each case (distilled water, 0.2 N hydrochloric acid, saturated sodium bicarbonate solution, brine, *etc*. as required by the procedure).

2.7.2. General Experimental Procedure for *N*-alkylation of isatin

A mixture of isatin (1 mmol), alkyl bromide/iodide (1.5 mmol) and calcium hydride (3 mmol) in DMF was stirred at 60 °C for 1 hour. After completion of the reaction (monitored by TLC), the reaction mixture was poured into water then neutralized with 2N HCl and extracted using ethyl acetate. The organic layer was separated and dried (Na_2SO_4)

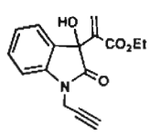
and concentrated *in vacuo*. The crude product obtained was purified by silica gel column chromatography using EtOAc: hexane (20: 80) as eluent to afford the desired *N*-alkylisatin.

2.7.3. General Experimental Procedure for the preparation of MBH adducts of isatin

A mixture of *N*-alkylisatin (1 mmol), 1.5 equiv. of ethyl acrylate (1.5 mmol), 0.02 equiv. of DABCO (0.02 mmol) in EtOH (5 mL) was stirred at RT for 3-6 days. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate. The organic layer was washed successively with 0.2N HCl. The organic layer was separated and dried (Na_2SO_4) and concentrated *in vacuo*. The crude product obtained was purified by silica gel column chromatography using EtOAc: hexane (20: 80) as eluent to afford the desired MBH adduct of *N*-alkylisatin.

2.7.4. Spectral data for MBH adduct of isatin:

Methyl 2-(3-hydroxy-2-oxo-1-(prop-2-ynyl) indolin-3-yl)acrylate **28:**



28

IR (CH_2Cl_2) ν_{max} 3425, 2131, 1718, 1611 cm^{-1}.

^{1}H NMR (300.1 MHz/$CDCl_3$) : δ 1.24 (t, *J* = 7.1 Hz, 3H), 2.28 (t, *J* = 2.2 Hz, 1H), 4.07 (s, OH), 4.11 (q, *J* = 7.1 Hz, 2H), 4.51-4.58 (m, 2H), 6.44 (s, 1H), 6.57 (s, 1H), 7.04-7.09 (m, 2H), 7.18 (d, *J* = 6.48Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H).

^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.31, 29.51, 61.62, 72.61, 76.07, 76.64, 109.65, 123.37, 123.94, 128.18, 129.22, 130.20, 138.89, 142.55, 164.96, 175.37.

HRMS *m/z*: Calcd. for $C_{16}H_{15}NO_4$: 285.1001; Found: 285.0991.

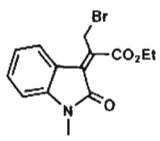
2.7.5. General Procedure for the bromo-isomerisation of MBH adducts of isatin

A mixture of MBH adduct derived from isatin (100mg, 0.382 mmol) was added 4 equiv. of 46% HBr and silica gel (0.2g) to make a slurry. The slurry was subjected to microwave irradiation (750W, 5 sec. pulse) over a period of 3 minutes. The crude mixture was cooled to RT and then extracted with CH_2Cl_2 and the organic phase was washed with water. The organic layer was separated and dried (Na_2SO_4) and concentrated *in vacuo*. The

crude mixture was purified by silica gel column chromatography using a gradient elution with hexane and hexane and EtOAc as eluent to afford pure isomerised bromo derivatives (E/Z-isomers) in 78-95% combined yield.

2.7.6. Spectral data for isomerised MBH adducts:

(*E*)-methyl 3-bromo-2-(1-methyl-2-oxoindolin-3-ylidene)propanoate **33a**:

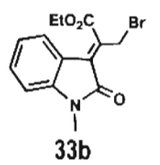


33a

IR (CH_2Cl_2): ν_{max} 1746, 1722, 1617 cm^{-1}.

^{1}H NMR (300.1 MHz/$CDCl_3$) : δ 1.20 (t, *J* = 6.9 Hz, 3H), 3.28 (s, 3H), 4.13 (q, *J* = 6.9 Hz, 2H), 5,23 (s, 2H), 6.90 (d, *J* = 7.8 Hz, 1H, Ar), 7.02 (t, *J* = 7.8 Hz, 1H, Ar), 7.29 (t, *J* = 7.8 Hz, 1H, Ar), 7.36 (d, *J* = 7.8Hz, 1H, Ar).

(*Z*)-methyl 3-bromo-2-(1-methyl-2-oxoindolin-3-ylidene)propanoate **33b**:



33b

IR (CH_2Cl_2): ν_{max} 1739, 1709, 1611, cm^{-1}.

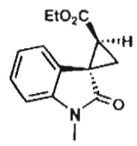
^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.21 (t, *J* = 6.9 Hz, 3H), 3.19 (s, 3H), 4.14 (q, *J* = 6.9 Hz, 2H), 4.49 (s, 2H), 6.77 (d, *J* = 7.2 Hz, 1H, Ar), 6.82 (d, *J* = 7.8 Hz, 1H, Ar), 6.98 (t, *J* = 7.5 Hz, 1H, Ar), 7.22 (t, *J* = 7.8 Hz, 1H, Ar).

2.7.7. General experimental procedure for the synthesis of 3-spirocyclopropane-2-indolones:

A mixture of isomerised bromo derivatives of MBH adducts (40mg, 0.123mmol) in dry tetrahydrofuran (3mL) was added 2 equiv. of sodium borohydride (9.3mg, 0.245 mmol). The mixture was stirred at room temperature until complete disappearance of starting material (TLC, ca. 0.5h). Then, the THF was removed under reduced pressure. The crude material was extracted with ethyl acetate (2x 30mL) and the combined organic layer was washed with water followed by brine. The organic layer was separated and dried (Na_2SO_4) and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography using a gradient elution with hexane and hexane and EtOAc as eluent to afford pure cyclopropane derivatives in 86-98% combined yield.

2.7.8. Spectral data of cyclopropane derivatives

Spiro [cyclopropane-1,3'-[3H] indole]-2-carboxylic acid, 1',2'-dihydro-1'–methyl-2'-oxo-, ethyl ester **41a:**



41a

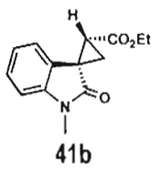
IR (CH_2Cl_2) ν_{max} 2968, 2925, 2863, 1746, 1722, 1617, 1468 cm^{-1}.

^{1}H NMR (300.1 MHz/$CDCl_3$) : δ 1.20 (t, *J* = 6.9 Hz, 3H), 2.01 (dd, *J* = 4.5 and 8.7 Hz, 1H), 2.13 (dd, *J* = 4.5 and 7.5 Hz, 1H), 2.70 (dd, *J* = 7.5 and 8.7 Hz, 1H), 3.28 (s, 3H), 4.13 (q, *J* = 6.9 Hz, 2H), 6.90 (d, *J* = 7.8 Hz, 1H, Ar), 7.02 (t, *J* = 7.8 Hz, 1H, Ar), 7.29 (t, *J* = 7.8 Hz, 1H, Ar), 7.36 (d, *J* = 7.8 Hz, 1H, Ar).

^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.33, 20.89, 26.87, 29.54, 32.94, 61.43, 108.21, 122.40, 122.80, 126.06, 127.86, 144.45, 169.03, 175.29.

HRMS *m/z*: Calcd. for $C_{14}H_{15}NO_3$: 245.1052; Found: 245.1045.

Spiro [cyclopropane-1,3'-[3H] indole]-2-carboxylic acid, 1',2'-dihydro-1'–methyl-2'-oxo-, ethyl ester **41b:**



41b

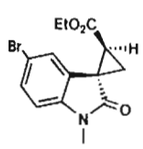
IR (CH_2Cl_2): ν_{max} 3057, 2963, 2937, 2852, 1739, 1709, 1611, 1466 cm^{-1}.

^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.21 (t, *J* = 6.9 Hz, 3H), 1.72 (dd, *J* = 4.8 and 8.4 Hz, 1H), 2.31 (dd, *J* = 4.8 and 8.1 Hz, 1H), 2.57 (dd, *J* = 8.1 and 8.4 Hz, 1H), 3.19 (s, 3H), 4.14 (q, *J* = 6.9 Hz, 2H), 6.77 (d, *J* = 7.2 Hz, 1H, Ar), 6.82 (d, *J* = 7.8 Hz, 1H, Ar), 6.98 (t, *J* = 7.5 Hz, 1H, Ar), 7.22 (t, *J* = 7.8 Hz, 1H, Ar).

^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.36, 20.73, 27.07, 29.42, 32.87, 61.84, 108.82, 122.48, 122.67, 126.53, 127.76, 143.56, 168.68, 174.29.

HRMS *m/z*: Calcd. for $C_{14}H_{15}NO_3$: 245.1052; Found: 245.1043.

Spiro [cyclopropane-1, 3'-[3H] indole]-2-carboxylic acid, 1',2'-dihydro-1' –methyl-5'-bromo-2'-oxo-, ethyl ester **42a:**



42a

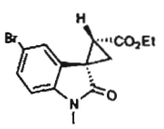
IR (CH_2Cl_2): ν_{max} 2984, 2921, 1717, 1606, 1464 cm^{-1}.

^{1}H NMR (300.1 MHz /$CDCl_3$): δ 1.23 (t, *J* = 6.9 Hz, 3H), 2.03 (dd, *J* = 4.5 and 8.7 Hz, 1H), 2.13 (dd, *J* = 4.5 and 7.2 Hz, 1H), 2.71 (dd, *J* = 7.2 and 8.7 Hz, 1H), 3.26 (s, 3H), 4.17 (q, *J* = 6.9 Hz, 2H), 6.76 (d, *J* = 8.1 Hz, 1H, Ar), 7.42 (d, *J* = 8.1 Hz, 1H, Ar), 7.51 (d, *J* = 1.8 Hz, 1H, Ar).

^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.15, 21.11, 26.76, 29.67, 33.06, 61.50, 108.04, 115.03, 125.86, 127.94, 130.49, 143.30, 168.46, 174.17.

HRMS *m/z*: Calcd. for $C_{14}H_{14}BrNO_3$: 323.0157; Found: 323.0149.

Spiro [cyclopropane-1, 3'-[3H] indole]-2-carboxylic acid, 1',2'-dihydro-1' –methyl-5'-bromo-2'-oxo-,ethyl ester **42b:**



42b

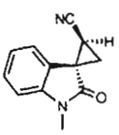
IR (CH_2Cl_2): ν_{max} 2982, 1741, 1712, 1610, 1465 cm^{-1}.

^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.27 (t, *J* = 7.2 Hz, 3H), 1.80 (dd, *J* = 5.1 and 8.7 Hz, 1H), 2.38 (dd, *J* = 5.1 and 8.1 Hz, 1H), 2.64 (dd, *J* = 8.1 and 8.7 Hz, 1H), 3.24 (s, 3H), 4.20 (q, *J* = 7.2 Hz, 2H), 6.75 (d, *J* = 8.1 Hz, 1H, Ar), 6.94 (d, *J* = 1.8 Hz, 1H, Ar), 7.40 (dd, *J* = 8.1 and 1.8 Hz, 1H, Ar).

^{13}C NMR (75.3 MHz/ $CDCl_3$): δ 14.13, 21.32, 26.67, 32.15, 33.39, 61.53, 109.52, 114.85, 121.85, 130.02, 131.02, 142.68, 166.67, 172.75.

HRMS *m/z*: Calcd. for $C_{14}H_{14}BrNO_3$: 323.0157; Found: 323.0142.

Spiro [cyclopropane-1, 3'-[3H] indole-1',2'-dihydro-1'–methyl -2'-oxo-2-nitrile **43a:**



43a

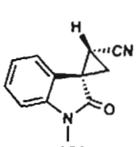
IR (CH_2Cl_2): ν_{max} 3086, 3027, 2236, 1701, 1614, 1469 cm^{-1}.

^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.89 (dd, *J* = 4.8 and 6.9 Hz, 1H), 2.13 (dd, *J* = 4.8 and 9.3 Hz, 1H), 2.44 (dd, *J* = 6.9 and 9.3 Hz, 1H), 3.30 (s, 3H), 6.97 (d, *J* = 7.8 Hz, 1H, Ar), 7.12-7.42 (m, 3H, Ar).

^{13}C NMR (75.3 MHz/ $CDCl_3$): δ 14.78, 21.31, 26.85, 31.70, 108.66, 116.85, 120.91, 122.89, 124.07, 128.83, 144.10, 172.97.

HRMS *m/z*: Calcd. for $C_{12}H_{10}N_2O$: 198.0793; Found: 198.0790.

Spiro [cyclopropane-1, 3'-[3H] indole-1',2'-dihydro-1'–methyl -2'-oxo-2-nitrile **43b:**



43b

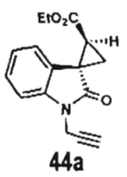
IR (CH_2Cl_2): ν_{max} 3031, 2963, 2916, 2848, 2247, 1705, 1611, 1466 cm^{-1}.

^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.99 (dd, *J* = 5.1 and 9.3 Hz, 1H), 2.19 (dd, *J* = 5.1 and 7.2 Hz, 1H), 2.35 (dd, *J* = 7.2 and 9.3 Hz, 1H), 3.34 (s, 3H), 6.79 (d, *J* = 7.1 Hz, 1H, Ar), 6.96 (d, *J* = 7.1 Hz, 1H, Ar), 7.07 (t, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H, Ar).

^{13}C NMR (75.3 MHz/$CDCl_3$): δ 15.09, 21.14, 26.90, 31.83, 108.41, 115.89, 118.84, 122.56, 126.02, 128.87, 144.17, 171.49.

HRMS *m/z*: Calcd. for $C_{12}H_{10}N_2O$: 198.0793; Found: 198.0795.

Spiro [cyclopropane-1, 3'-[3H] indole]-2-carboxylic acid, 1',2'-dihydro-1'–propargyl-2'-oxo-, ethyl ester **44a:**



44a

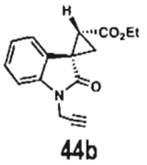
IR (CH_2Cl_2): ν_{max} 3063, 2959, 2927, 2846, 1728, 1706, 1611, 1462 cm^{-1}.

^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.21 (t, *J* = 7.1 Hz, 3H), 2.05 (m, 1H), 2.17 (m, 1H), 2.26 (t, *J* = 2.4 Hz, 1H), 2.74 (m, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.57-4.62 (d, *J* = 2.4 Hz, 2H), 6.75-7.48 (m, 4H, Ar).

^{13}C NMR (75.3 MHz / $CDCl_3$): δ 14.83, 21.72, 29.79, 32.76, 33.29, 47.92, 61.65, 72.54, 109.83, 119.20, 122.85, 127.94, 128.44, 142.21, 167.50, 173.13.

HRMS *m/z*: Calcd. for $C_{16}H_{15}NO_3$: 269.1052; Found: 269.1050.

Spiro [cyclopropane-1, 3'-[3H] indole]-2-carboxylic acid, 1',2'-dihydro-1'–propargyl-2'-oxo-, ethyl ester **44b:**



44b

IR (CH_2Cl_2): ν_{max} 3054, 2986, 2930, 1740, 1719, 1612, 1467 cm^{-1}.

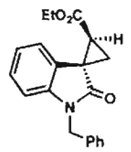
^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.82 (dd, *J* = 5.1 and 8.7 Hz, 1H), 2.24 (t, *J* = 2.4 Hz, 1H), 2.39 (dd, *J* = 5.1 and 8.1 Hz, 1H), 2.66 (dd, *J* = 8.1 and 8.7 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.48-4.68 (d, *J* = 2.4 Hz, 2H), 6.86 (d, *J* = 7.2 Hz, 1H, Ar), 7.05-7.34 (m, 3H, Ar).

^{13}C NMR (75.3 MHz/ $CDCl_3$): δ 14.32, 21.52, 29.70, 32.42, 33.68, 47.97, 61.62, 72.48, 109.37, 118.79, 122.83, 127.91, 128.95, 141.91, 167.04, 172.55.

HRMS *m/z*: Calcd. for $C_{16}H_{15}NO_3$: 269.1052; Found: 269.1047.

Spiro [cyclopropane-1, 3'-[3H] indole]-2-carboxylic acid, 1',2'-dihydro-1'–benzyl -2'-oxo-, ethyl ester **45a:**

IR (CH_2Cl_2): ν_{max} 2927, 2849, 1721, 1608, 1464 cm^{-1}.



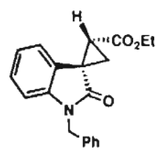
45a

^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.25 (t, *J* = 6.9 Hz, 3H), 2.08 (dd, *J* = 4.2 and 8.4 Hz, 1H), 2.18 (dd, *J* = 4.2 and 7.5 Hz, 1H), 2.77 (dd, *J* = 7.5 and 8.4 Hz, 1H), 4.15 (q, *J* = 6.9 Hz, 2H), 5.10 (s, 2H), 6.84-7.45 (m, 9H, Ar).

^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.35, 21.27, 32.12, 33.15, 44.52, 61.51, 109.24, 118.80, 122.73, 122.95, 124.93, 127.55, 127.79, 127.85, 128.40, 128.99, 136.03, 143.60, 168.99, 175.11.

HRMS *m/z*: Calcd. for $C_{20}H_{19}NO_3$: 321.1363; Found: 321.1359.

Spiro [cyclopropane-1, 3'-[3H] indole]-2-carboxylic acid, 1',2'-dihydro-1' –benzyl -2'-oxo-, ethyl ester **45b:**



45b

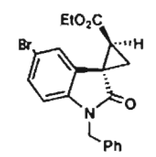
IR (CH_2Cl_2): ν_{max} 2983, 2927, 1735, 1705, 1613, 1466 cm^{-1}.

^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.25 (t, *J* = 7.1 Hz, 3H), 1.85 (dd, *J* = 4.8 and 8.4 Hz, 1H), 2.43 (dd, *J* = 4.8 and 7.8 Hz, 1H), 2.68 (dd, *J* = 7.8 and 8.4 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.89 (d, *J* = 15.6Hz,1H), 5.04 (d, *J* = 15.6 Hz, 1H), 6.76-7.26 (m, 9H, Ar).

^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.38, 21.16, 32.44, 33.79, 44.25, 61.63, 109.33, 118.39, 122.46, 127.38, 127.51, 127.77, 127.82, 128.93(2C), 129.14, 136.14, 142.95, 167.23, 173.67.

HRMS *m/z*: Calcd. for $C_{20}H_{19}NO_3$: 321.1365; Found 321.1363.

Spiro [cyclopropane-1, 3'-[3H] indole]-2-carboxylic acid, 1',2'-dihydro-1'–benzyl-5'-bromo-2'-oxo-, ethyl ester **46a:**



46a

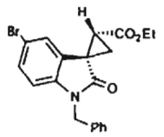
IR (CH_2Cl_2): ν_{max} 2931, 2854, 1727, 1713, 1603, 1473 cm^{-1}.

^{1}H NMR (300.1 MHz/ $CDCl_3$): δ 1.23 (t, *J* = 6.9 Hz, 3H), 2.10 (dd, *J* = 4.5 and 8.7 Hz, 1H), 2.17 (dd, *J* = 4.5 and 7.5 Hz, 1H), 2.78 (dd, *J* = 7.5 and 8.7 Hz, 1H), 4.18 (q, *J* = 6.9 Hz, 2H), 4.99 (2d, *J* = 15.6 Hz, 2H), 6.65 (d, *J* = 8.4 Hz, 1H, Ar), 7.26-7.32 (m, 6H, Ar, Ph), 7.52 (d, *J* = 2.1 Hz, 1H, Ar).

^{13}C NMR (75.3 MHz/ $CDCl_3$): δ 14.15, 21.48, 31.91, 33.24, 44.35, 61.57, 110.36, 115.14, 116.63, 125.98, 127.24 (2C), 127.82, 128.87 (2C), 130.41, 135.29, 142.36, 167.98, 175.01.

HRMS *m/z*: Calcd. for $C_{20}H_{18}BrNO_3$: 399.0470; Found: 399.0466.

Spiro [cyclopropane-1, 3'-[3H] indole]-2-carboxylic acid, 1',2'-dihydro-1'–benzyl-5'-bromo-2'-oxo-, ethyl ester **46b:**



46b

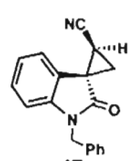
IR (CH_2Cl_2): ν_{max} 3060, 2988, 2925, 1741, 1713, 1617, 1483 cm^{-1}.

^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.86 (dd, *J* = 5.1 and 8.7 Hz, 1H), 2.25 (dd, *J* = 5.1 and 8.1 Hz, 1H), 2.69 (dd, *J* = 8.1 and 8.7 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.87 (d, *J* = 15.6 Hz, 1H), 5.02 (d, *J* = 15.6 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 1H, Ar), 6.95 (d, *J* = 2.1 Hz, 1H), 7.24-7.33 (m, 6H, Ar, Ph).

^{13}C NMR (75.3 MHz/ $CDCl_3$): δ 14.13, 19.81, 32.01, 33.85, 44.09, 61.56, 110.51, 114.96, 121.93, 127.19 (2C), 127.73, 128.80 (3C), 130.36, 131.01, 135.39, 166.58, 172.87.

HRMS *m/z*: Calcd. for $C_{20}H_{18}BrNO_3$: 399.0470; Found: 399.0464.

Spiro [cyclopropane-1, 3'-[3H] indole-1',2'-dihydro-1' –benzyl -2'-oxo-2-nitrile **47a:**



47a

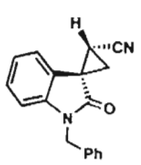
IR (CH_2Cl_2): ν_{max} 3030, 2925, 2855, 2240, 1717, 1612, 1465 cm^{-1}.

^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.94 (dd, *J* = 5.1 and 6.9 Hz, 1H), 2.20 (dd, *J* = 5.1 and 9.3 Hz, 1H), 2.52 (dd, *J* = 6.9 and 9.3 Hz, 1H), 4.95 (s, 2H), 6.87 (d, *J* = 7.8 Hz, 1H, Ar), 6.96 (d, *J* = 7.1 Hz, 1H, Ar), 7.07 (t, *J* = 7.8 Hz, 1H), 7.05-7.34 (m, 8H, Ar, Ph).

^{13}C NMR (75.3 MHz/ $CDCl_3$): 15.00, 21.58, 30.91, 44.50, 109.67, 116.84, 121.00, 122.92, 124.08, 127.34 (2C), 127.88, 128.76, 128.89 (2C), 135.32, 143.27, 173.16.

HRMS *m/z*: Calcd. for $C_{18}H_{14}N_2O$: 274.1106; Found: 274.1103.

Spiro [cyclopropane-1, 3'-[3H] indole-1',2'-dihydro-1' –benzyl -2'-oxo-2-nitrile **47b:**



47b

IR (CH_2Cl_2): ν_{max} 3032, 2928, 2252, 1719, 1618, 1467 cm^{-1}.

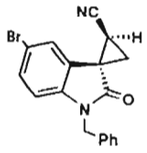
^{1}H NMR (300.1 MHz/$CDCl_3$): δ 2.03 (dd, *J* = 4.8 and 9.0 Hz, 1H), 2.25 (dd, *J* = 4.8 and 7.5 Hz, 1H), 2.35 (dd, *J* = 7.5 and 9.0 Hz, 1H), 4.95-5.08 (2d, *J* = 15.6 Hz, 2H), 6.81-7.33 (m, 9H, Ar, Ph).

^{13}C NMR (75.3 MHz/ $CDCl_3$): 15.35, 21.35, 31.84, 44.48, 109.74, 115.82, 118.93, 122.58, 126.02, 127.55, 127.83 (2C), 128.73, 128.86

(2C), 135.58, 143.18, 171.62.

HRMS ***m/z***: Calcd. for $C_{18}H_{14}N_2O$: 274.1106; Found: 274.1098.

Spiro [cyclopropane-1, 3'-[3H] indole-1',2'-dihydro-1' –benzyl-5'-bromo -2'-oxo-2-nitrile **48a:**



48a

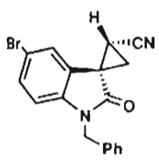
IR (CH_2Cl_2): ν_{max} 2975, 2852, 2249, 1721, 1613, 1479 cm^{-1}.

^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.94 (dd, *J* = 5.1 and 7.2 Hz, 1H), 2.21 (dd, *J* = 5.1 and 9.3 Hz, 1H), 2.55 (dd, *J* = 7.2 and 9.3 Hz, 1H), 4.98 (s, 2H), 6.72 (d, *J* = 8.1 Hz, 1H, Ar), 7.27-7.40 (m, 7H, Ar, Ph).

^{13}C NMR (75.3 MHz /$CDCl_3$): δ 14.18, 21.01, 44.59, 31.56, 109.67, 122.92, 124.23, 127.26, 127.48, 127.87, 128.75, 128.89, 128.99, 131.68, 134.85, 135.44, 142.3, 172.60.

HRMS ***m/z***: Calcd. for $C_{18}H_{13}BrN_2O$: 352.0211; Found: 352.0203.

Spiro [cyclopropane-1, 3'-[3H] indole-1',2'-dihydro-1'–benzyl-5'-bromo-2'-oxo-2-nitrile **48b:**



48b

IR (CH_2Cl_2): ν_{max} 2926, 2853, 2246, 1714, 1614, 1480 cm^{-1}.

^{1}H NMR (300.1 MHz/$CDCl_3$): δ 2.03 (dd, *J* = 5.1 and 9.3 Hz, 1H), 2.29 (dd, *J* = 5.1 and 7.5 Hz, 1H), 2.37 (dd, *J* = 7.5 and 9.3 Hz, 1H), 4.93-5.07 (2d, *J* = 15.6 Hz, 2H), 6.70 (d, *J* = 8.4, 1H, Ar), 6.94 (s, 1H, Ar), 7.26-7.34 (m, 6H, Ar, Ph).

^{13}C NMR (75.3 MHz/$CDCl_3$): δ 15.34, 21.54, 31.63, 44.58, 111.05, 121.23, 121.63, 125.22, 127.26, 127.47, 128.01, 128.11, 128.95, 131.52, 131.67, 135.83, 142.16, 172.03.

HRMS ***m/z***: Calcd. for $C_{18}H_{13}BrN_2O$: 352.0211; Found: 352.0193.

2.8. References

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Chapter III

Activation of the *N*C-H bond of MBH adducts of *N*-substituted isatin with CAN/ROH

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Can. J. Chem. **2009** (In Press).

Chapter III

Activation of the *N*C-H bond of MBH adducts of *N*-substituted isatin with CAN/ROH

3.1. An account on activation of C-H bonds

3.1.1. Introduction

Alkanes are by far the most abundant and the least reactive members of the hydrocarbon family. Consequently, the selective, catalytic, activation and functionalization of carbon-hydrogen and carbon-carbon bonds of alkanes, and of unactivated alkyl groups in general, to form useful functional organics constitutes a Holy Grail in chemistry.[5] Of particular importance are oxidations, since the majority of the commercially important organic chemicals (alcohols, aldehydes, ketones, acids) can, in principle, be derived from alkanes through one or more oxidative functionalization steps.[6]

The lack of reactivity of alkanes (and of unactivated alkyl groups) stems from their unusually high bond energies (C-H bond energy of methane 104 kcal/mol), and most reactions involving the homolysis of a C-H bond occur at fairly high temperatures or under photolytic conditions. Moreover, the selectivity in these reactions is usually low because of the subsequent reactions of the intermediate products, which tend to be more reactive than the alkane itself. Using methane as an example, its homolytic C-H bond energy is 10 kcal/mol higher than that in methanol. Therefore, unless methanol can be removed or protected as soon as it is formed, any oxidation procedure that involves hydrogen atom abstraction from the substrate would normally cause rapid over oxidation of methanol.

Apart from the selectivity with respect to the degree of oxidation, a second selectivity issue arises for C_3 and higher alkanes: the selectivity with respect to the particular C-H bond that is functionalized. Since the homolytic bond energies decrease in the order: primary C-H > secondary C-H > tertiary C-H bonds, radical pathways involving C-H bond homolysis almost always show a marked preference for the functionalization of tertiary C-H bonds. However, many commodity chemicals are terminally functionalized.

The conversion of a C-H bond to C-OH, while carried out routinely in nature by a variety of enzymes[7-9], has not so far found wide application in organic synthesis. Much effort has been devoted to developing reagents for activation of C-H bonds remote from functional groups. This is a challenging goal and the object of continuing interest.

Hence, the C-H bond activation method is one of the challenging synthetic routes in organic synthesis. Activation of C-H bonds particularly by oxidative processes[10-14] and by organometallic reagents[15-21] has been of great interest to organic chemists in recent years. The following sections describe major classifications and some of literature known C-H bond activation methods.

3.1.2. Classification of C-H bond activation reactions

In a broad way, one can classify the C-H activation reactions in two categories.

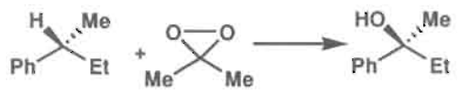
1. C-H activation reactions by compounds other than metal complex
2. C-H activation reactions using metals or their oxides.

In each category a representative examples are given in the following sections (3.1.3. - 3.1.5.).

3.1.3. C-H activation by compounds other than metal complexes

3.1.3.1. C-H activation using Dimethyldioxirane

Adam and co-workers reported the C-H activation of alkane derivative using dimethyldioxirane **1**. Thus, the selective hydroxylation of (-)-2-phenylbutane by dimethyldioxirane **1** furnished (-)-2-phenylbutan-2-ol as shown in Scheme 1.[22]

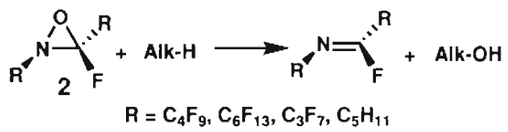


1

Scheme 1

3.1.3.2. C-H activation involving perfluoro-cis-2,3-dialkyloxaziridin

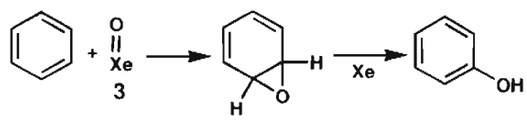
Des Marteau and co-workers reported alkane C-H activation involving perfluoro-cis-2,3-dialkyloxaziridin **2** and alkanes. The reaction provided alkanes functionalized with hydroxyl group as shown in Scheme 2.[23]



Scheme 2

3.1.3.3. C-H activation with xenon compound

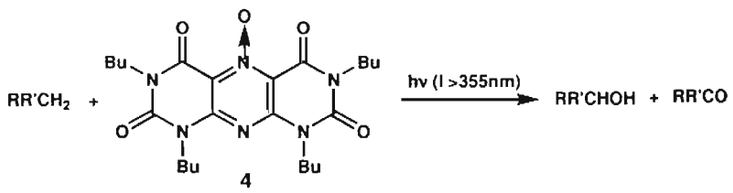
The aromatic C-H bond activation with xenon compound was reported by Kats and co-workers. Oxygen-containing derivatives of xenon **3** (which may be generated by dissolution of XeO_3 or XeF_2 in water or aqueous acetonitrile) oxidized benzene to phenol (Scheme 3).[24]



Scheme 3

3.1.3.4. C-H activation by photooxygenation

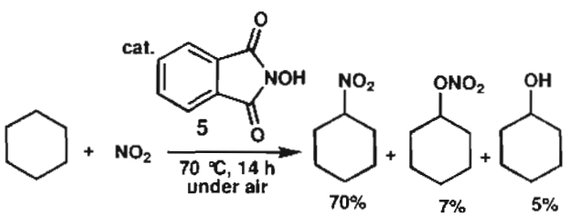
A report following photooxygenation of alkanes to functionalize as alcohols and ketones with heterocyclic *N*-oxides **4** by Sako and co-workers is shown in Scheme 4.[25]



Scheme 4

3.1.3.5. C-H activation using N-hydroxyphthalimide (NHPI)

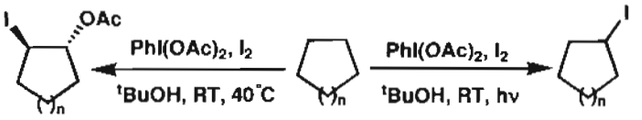
Ishii *et al.* developed a catalytic method for the generation of alkyl radicals from saturated hydrocarbons using *N*-hydroxyphthalimide (NHPI) **5**, which serves as the radical catalyst. The nitration of cyclohexane with NO_2 by NHPI proceeded at 70 °C to give nitrocyclohexane (70%) and cyclohexyl nitrite (7%) along with a small amount of an oxygenated product, cyclohexanol (5%) (Scheme 5). [26]



Scheme 5

3.1.3.6. C-H activation using $PhI(OAc)_2$, I_2, and ^tBuOH

Barluenga *et al.* reported new approaches to selectively produce either iodoalkanes or 1-acetoxy-2-iodocycloalkanes from readily available hydrocarbons. The products iodoalkanes and 1-acetoxy-2-iodocycloalkanes arise from single and double formal C-H bond activation reactions, respectively. This unique reaction manifold can be tuned by treating alkanes with $PhI(OAc)_2$, iodine (I_2), and tert butylalcohol (^tBuOH) simply by using photochemical or thermal conditions (Scheme 6).[27]



Scheme 6

3.1.4. C-H activation reactions promoted by metals or their oxides

Transformations of hydrocarbons which are promoted by solid metals and their oxides play a very important role in chemical industry. Heterogeneous metal-containing catalysts are widely employed for oxidation, dehydrogenation, cracking, isomerization, and many other processes which are performed on saturated as well as aromatic hydrocarbons. Usually such reactions occur only at high temperatures (>200 °C). Metal oxides (Cr_2O_3, Al_2O_3, NiO, etc.) catalyze H-D exchange between alkanes and D_2, as well as between alkanes and deuterated alkanes. In alkyl aromatics, the most reactive side-chain hydrogens are those in benzylic positions. Other types of heterogeneous metal catalysts which have been employed in recent years to activate hydrocarbons include metal clusters,[28] suspended metal catalysts,[29] metal membranes,[30] and supported metals.[31] Both metals and metal oxides catalyze either deep oxidation (to produce carbon dioxide and water) or selective partial

oxidation (to afford alcohols, ketones, and carboxylic acids, as well as "synthesis gas", i.e., CO + H_2) of hydrocarbons with molecular oxygen. In addition to insertion of an oxygen atom into a hydrocarbon molecule, heterogeneous metal catalysts can also promote oxidative condensation, or coupling, of methane.

3.1.5. Transition metal catalyzed coupling reactions under C-H activation

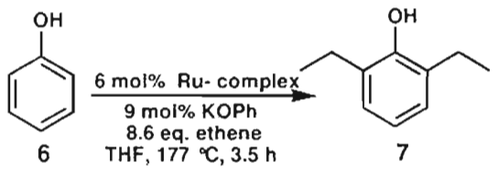
Gerald Dyker published a review article[32] in 1999 on transition metal catalyzed coupling reactions under C-H activation. He listed three kinds of C-H activation by transition metal catalysis as given bellow.

a. Intramolecular C-H activation by a precoordinated transition metal
b. Intramolecular C-H activation through carbon-bound transition metals
c. C-H Activation without cyclometalation

To demonstrate the reaction type, representative examples are discussed in the following section (3.1.5.1 to 3.1.5.3).

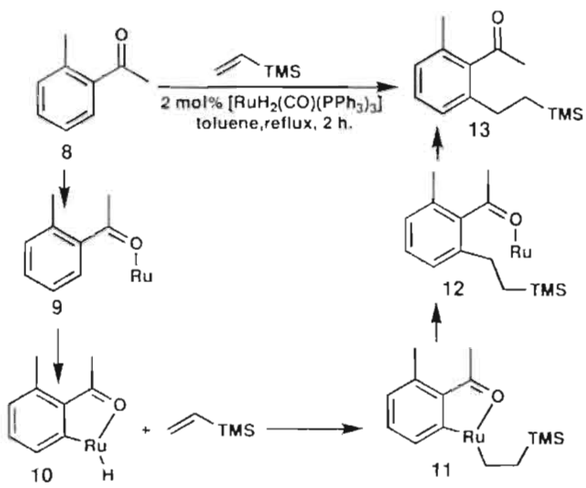
3.1.5.1. Intramolecular C-H activation by a precoordinated transition metal

Lewis and Smith have achieved an initial success in 1986 with the double alkylation of phenol **6** with ethylene selectively in the ortho positions by using an ortho-metalated ruthenium phosphite complex (Scheme 7) .[33]



Scheme 7

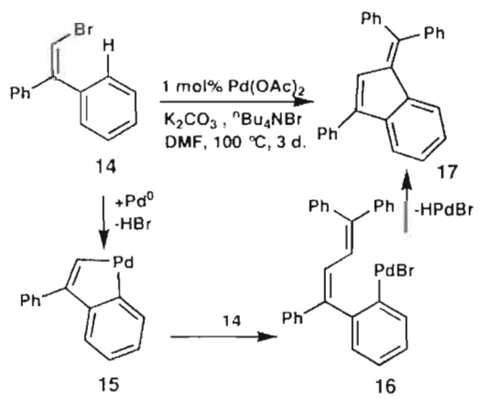
Kakiuchi *et al.* reported the C-H activation using Ru complex. Accordingly, the reaction of acetophenone **8** with vinyl silane yielded regioselectively the ortho product **13** (Scheme 8).[34] The precoordination of metal complex with **8** followed by C-H activation forming the intermediates **9-12**.



Scheme 8

3.1.5.2. Intramolecular C-H activation through carbon-bound transition metals

In this category, Dyker *et al.* in 1996 reported a reaction sequence comprising oxidative addition and C-H activation of phenyl-substituted bromoethene **14** through carbon-bound transition metal intermediates **15** and **16** to form compound **17** (Scheme 9).[35]

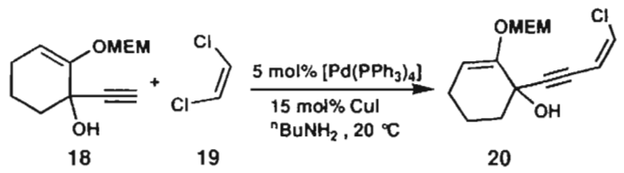


Scheme 9

3.1.5.3. C-H activation without cyclometalation

Numerous examples for transition metal catalyzed C-C coupling with the participation of relatively acidic C-H groups are well known and intensively used. The

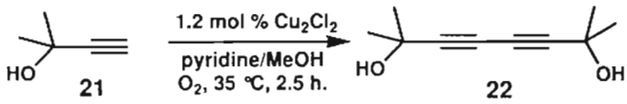
transition metal catalyst can be considered as an organometallic base responsible for the C-H activation. Magnus *et al.* in 1988 reported a coupling reaction catalyzed by Pd. The alkyne derivative **18** with 1,2-dichloroethene **19** afforded C-C coupled product **20** as represented in Scheme 10.[36]



18 19 20

Scheme 10

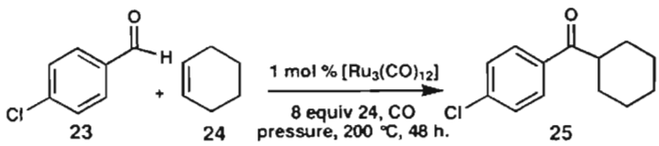
In this context, a classic among C-H activation reactions, the Glaser coupling in which terminal acetylenes are coupled under copper catalysis and oxidation to give butadiynes. In 1962 stansbury *et al.* reported an efficient conversion of the butynol **21** to 1,3-diyne **22** as depicted in Scheme 11. [37]



21 22

Scheme 11

Kondo *et al.* in 1990 reported the coupling of aromatic aldehyde **23** with cyclohexene **24** to form **25** using Ru complex as outlined in Scheme 12. [38]

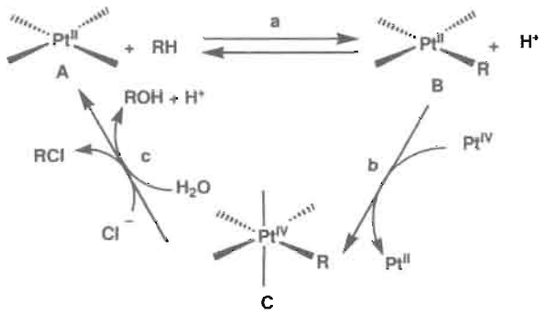


23 24 25

Scheme 12

3.1.6. Alkane oxidation by platinum complexes in aqueous solution

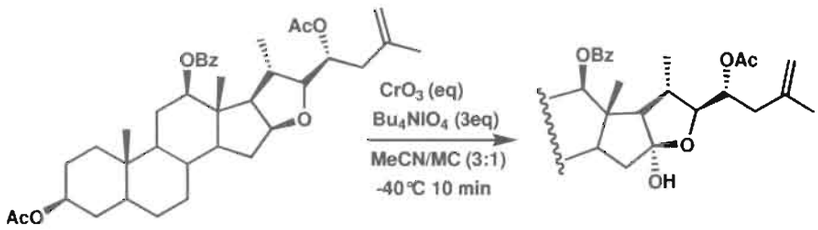
In 1983 Shilov *et al.* proposed a mechanism for platinum catalyzed alkane oxidation consisting of three basic transformations a) activation of the alkane by Pt (II) to generate an alkylplatinum (II) intermediate, b) two-electron oxidation of the alkylplatinum(II) intermediate to generate an alkylplatinum(IV) species, and c) reductive elimination of RX to liberate the oxidized alkane and the Pt (II) catalyst (Scheme 13). [39]



Scheme 13

3.1.7. C-H oxidation protocol for α-hydroxylation of cyclic steroidal ethers

An efficient C-H oxidation protocol for α-hydroxylation of cyclic steroidal ethers with the aid of CrO_3/Bu_4NIO_4 was reported by Fuchs *et al.* in 2004 (Scheme 14).[40]



Scheme 14

3.1.8. Intramolecular rhodium-catalyzed C-H bonds activation

Recently, the activation of α-amino C-H bonds in azacycloalkanes by way of intramolecular rhodium-catalyzed amination was reported by Morin *et al.* (Scheme 15).[41]

Scheme 15

3.2. A brief introduction on Cerium (IV) Ammonium Nitrate (CAN) reagent

3.2.1. Introduction

Cerium (IV) ammonium nitrate (CAN) has emerged as a versatile reagent for a number of synthetic transformations. The most extensively used cerium (IV) reagent in organic chemistry is cerium (IV) ammonium nitrate (CAN). The reasons for its general acceptance as a one-electron oxidant may be attributed due to the following advantages.

- Large reduction potential value of +1.61 V
- Cheap and ready availability
- Low toxicity
- Easy handling
- Experimental simplicity
- Solubility in a number of organic solvents.

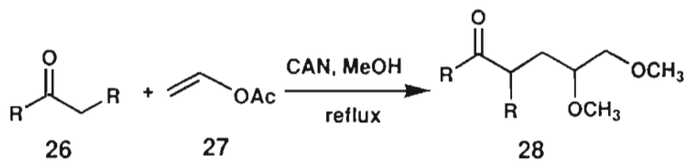
CAN has proved to be very useful to synthetic organic chemists for over four decades. The enormous growth in the use of this reagent is evidenced by the publication of a large number of research papers and several reviews concerning CAN-mediated reactions. [42-52] Due to its wide application in organic synthesis, one can broadly classify the types of reactions and applications under the following categories.

- Reaction involving carbon-carbon bond-formation
- Intramolecular reactions
- Carbon-heteroatoms bond formation
- Reactions involving CAN as a catalytic oxidant
- Protection-deprotection reactions

In each category, selected examples are discussed in the following sections.

3.2.2. Reaction involving carbon-carbon bond-formation

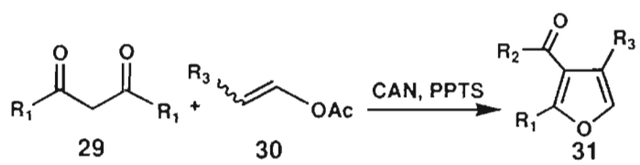
In 1987, Baciocchi *et al.* reported the synthesis of 1,4-dicarbonyl compound **28** by the ceric ammonium nitrate promoted reaction of ketone **26** with vinyl acetate **27** (Scheme 16).[53]



26 27 28

Scheme 16

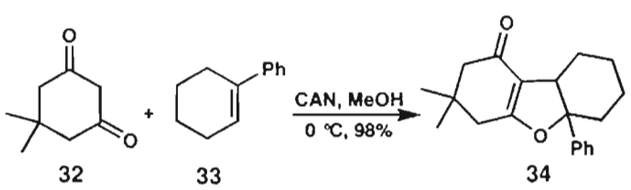
Later, the same group reported the synthesis of 3-acyl and 3-carboalkoxyfuran **31** by the ceric ammonium nitrate promoted addition of 1,3-dicarbonyl compound **29** to vinylic acetate **30** (Scheme 17).[54]



29 30 31

Scheme 17

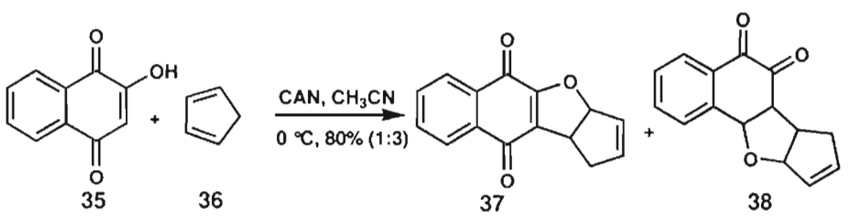
In 1995, Nair *et al.* reported a facile synthesis of dihydrofuran **34** by the cerium (IV) ammonium nitrate mediated oxidative addition of 1,3-dicarbonyl compound **32** to cyclic and acyclic alkene **33**. The reaction afforded the corresponding dihydrofuran derivative in nearly quantitative yield (Scheme 18).[55]



32 33 34

Scheme 18

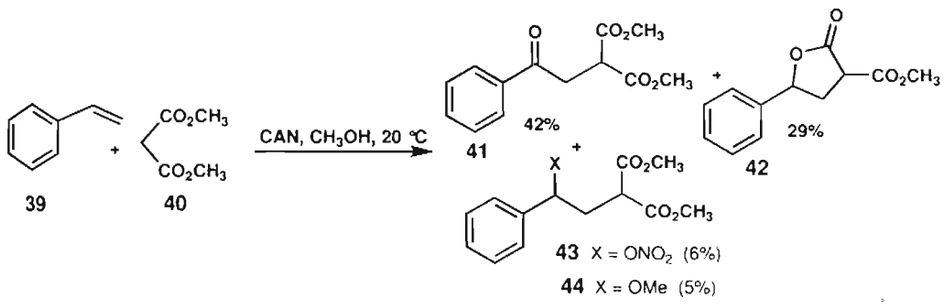
Further an analogous addition of 2-hydroxy-1,4-naphthoquinone **35** to cyclopentadiene **36**, promoted by CAN to form the corresponding furanonaphthoquinone derivatives **37** and **38** was reported (Scheme 19).[56]



35 36 37 38

Scheme 19

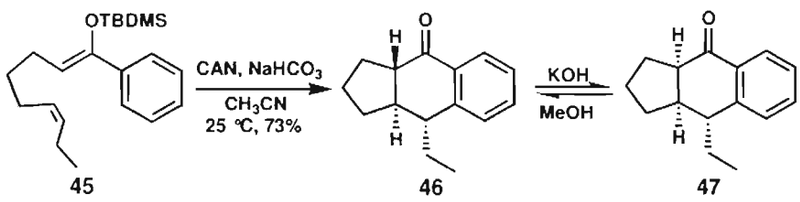
Reports by Nair *et al.* in 1995 and 1997 showed that the use of styrene and dimethyl malonate in CAN mediated C-C bond forming reactions. The addition of dimethyl malonate **40** to styrene **39** occurred via a mechanistically interesting reaction, resulting in the formation of the ketone **41** and the lactone **42** as the major products along with smaller amounts of **43** and **44** (Scheme 20).[57, 58]



Scheme 20

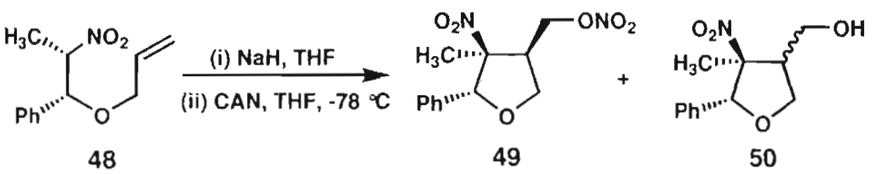
3.2.3. Intramolecular reactions

Snider *et al.* in 1990 reported the oxidative cyclisation of unsaturated silyl enol ethers **45** by CAN affording tricyclic ketones **46** and **47** in high yields and excellent diastereocontrol (Scheme 21).[59]



Scheme 21

Durand *et al.* in 1999 reported that the radical generated by oxidation of the aci-nitro anion formed from **48** underwent intramolecular cyclization, leading to stereoselective formation of 3,4-functionalized tetrahydrofuran derivatives **49** and **50** (Scheme 22).[60] The high stereoselectivities observed in this reaction are indicative of the *5-exo-trig*-radical cyclization rather than an intramolecular [3+2] cycloaddition.



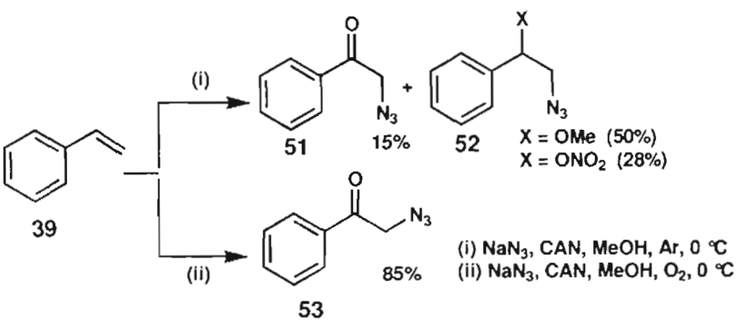
48 49 50

Scheme 22

3.2.4. Reactions involving carbon-heteroatom bond formation

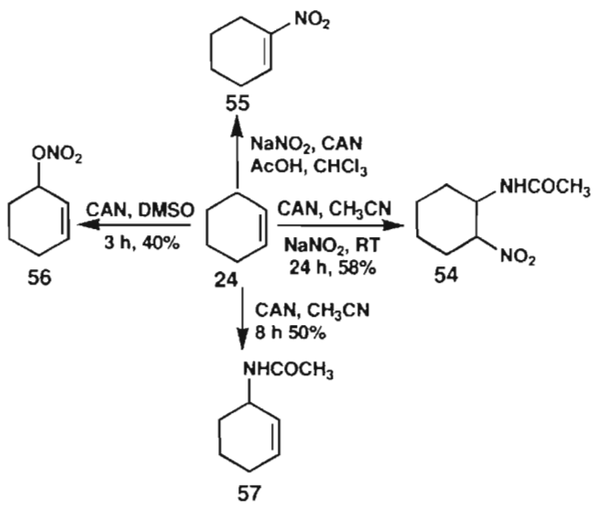
3.2.4.1. Carbon-nitrogen bond formation

Nair *et al.* in 2000 reported that the carbon-nitrogen bond formation of styrene **39** with sodium azide and CAN. The azidomethyl ether **52** was formed as the major product along with small amounts of the azido nitrate and azido ketone, and in oxygen atmosphere, azido ketone **53** was formed exclusively as shown in Scheme 23.[61]



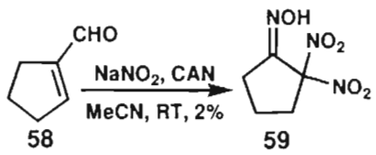
Scheme 23

Nitration of cyclohexene **24** under different conditions using CAN is illustrated in Scheme 24. Briguet *et al.* in 1974 reported the oxidation of cyclohexene **24** by CAN in anhydrous DMSO led to formation of cyclohexene-3-nitrate **56**, whereas in acetonitrile *N*-(cyclohexene-2-yl) acetamide **57** was formed.[62] Later, Hwu *et al.* reported that alkenes could be nitrated with excess sodium nitrite in the presence of CAN and acetic acid in chloroform.[63] They also showed that the same reagent combination can be used for the nitration of allylsilanes by sonication.[64] Simultaneous nitration and acetamidation was achieved in acetonitrile using CAN and sodium nitrite.[65]



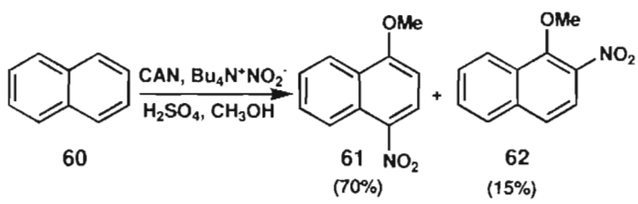
Scheme 24

Smith *et al.* in 1998 attempted nitro acetamidation of cyclopentene carboxaldehyde **58** in acetonitrile using CAN and sodium nitrite. They observed the formation of the unexpected dinitrooxime **59** instead acetamidation (Scheme 25).[66]



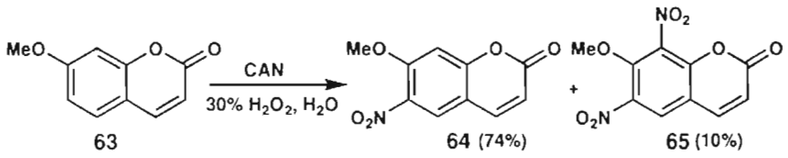
Scheme 25

CAN-mediated nitration of naphthalene **60** in the presence of catalytic amounts of sulfuric acid and *tert*-butylammonium nitrate in methanol afforded 1-nitro-4-methoxynaphthalene **61** as the major product. The suggested mechanism for this reaction involves addition of the nitrite radical to naphthalene and oxidation of the resulting radical to cation followed by quenching with methanol (Scheme 26).[67]



Scheme 26

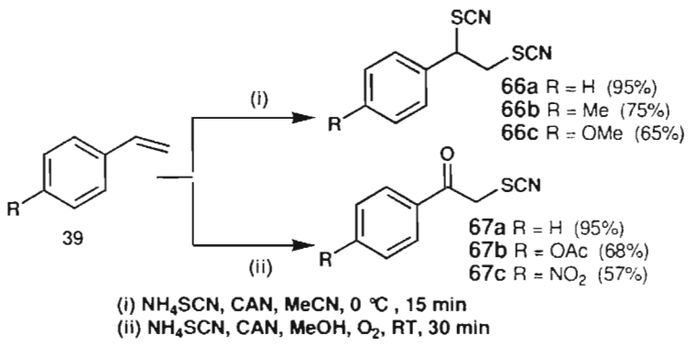
6-Nitrocoumarin **64** was reported to be the sole product formed by nitration of coumarin **63** using one equivalent CAN in acetic acid. The minor dinitro derivative **65** was also obtained in the reaction with the presence of activating groups such as hydroxyl or methoxy on the phenyl ring (Scheme 27).[68]



Scheme 27

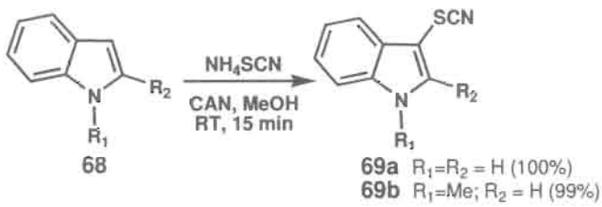
3.2.4.2. Carbon-sulfur bond formation

Thiocyanation of arenes and olefins constitutes an important method for introducing sulfur functionality. Reaction of styrene **39** with ammonium thiocyanate and CAN afforded different products depending on the solvent employed. When the reaction was carried out in acetonitrile at ice bath temperature, dithiocyanate **66** was formed in excellent yield, [69] whereas in methanol, in an atmosphere saturated with oxygen, phenacyl thiocyanate **67** was the predominant product (Scheme 28). [70]



Scheme 28

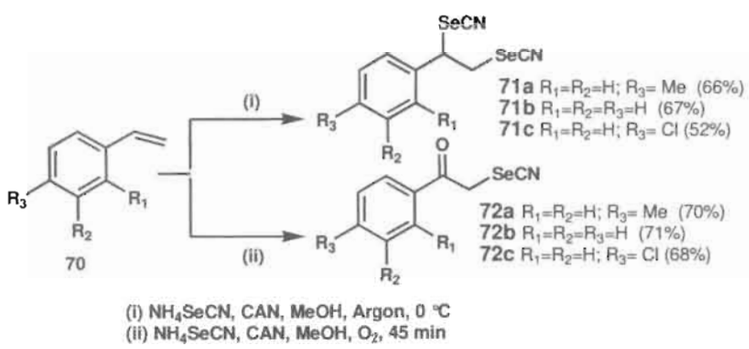
The same combination of reagents mentioned in the previous case effected the thiocyanation of indoles **68** in excellent conversion to yield compounds **69a** and **69b** (Scheme 29).[71]



Scheme 29

3.2.4.3. Carbon-selenium bond formation

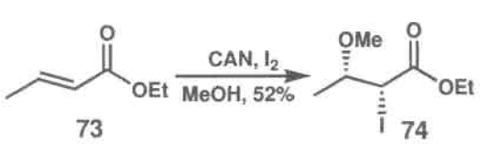
In completely deoxygenated atmosphere, the diselenocyanate **71(a-c)** was formed exclusively, whereas under oxygenated conditions, phenacyl selenocyanate **72(a-c)** was formed as the sole product from the CAN mediated selenocyanation of styrene **70** (Scheme 30).[72-73]



Scheme 30

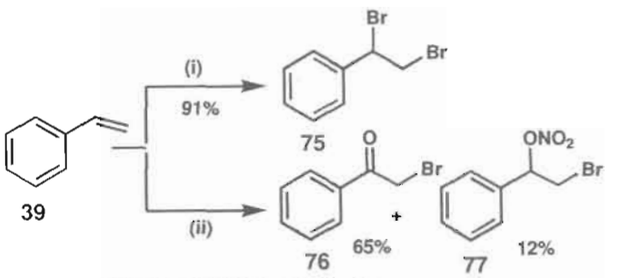
3.2.4.4. Carbon-halogen bond formation

Horiuch *et al.* in 1994 reported that the reaction of α,β-unsaturated ketones and ester **73** with iodine and CAN in methanol, ethanol, or isopropyl alcohol, under reflux conditions afforded the corresponding *β*-alkoxy α-iodo-ketones and esters **74** in very good yields (Scheme 31).[74]



Scheme 31

Nair *et al.* in 2001 reported that the alkenes can be converted to the dibromides using potassium bromide and CAN in a two-phase system of water and dichloromethane. When the solvent used was methanol, acetonitrile, or acetic acid, phenacyl bromide **76** and nitrato bromide **77** were formed (Scheme 32).[75]

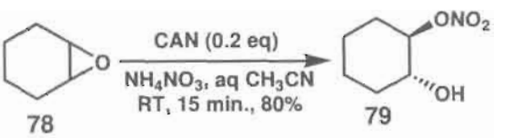


Scheme 32

3.2.5. Reactions involving CAN as a catalytic oxidant

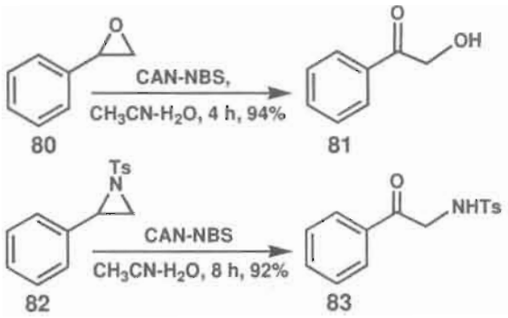
3.2.5.1. Oxidative transformations of epoxides

Iranpoor *et al.* in 1995 reported that the epoxides were converted to the corresponding β-nitrato alcohols **79** by the treatment with catalytic amounts of CAN in the presence of excess nitrate ions, present as ammonium or tetra-*n*-butyl ammonium salt (Scheme 33).[76]



Scheme 33

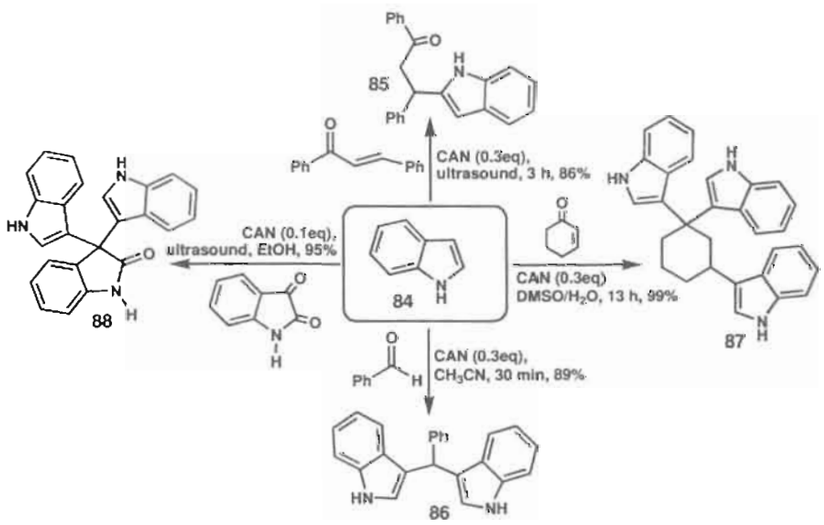
Ring opening of terminal epoxides and terminal aziridines to the corresponding α-hydroxy or α-amino ketones **81** and **83** was effected using CAN and NBS (Scheme 34). The reaction is probably initiated by hydrolysis of the substrate by CAN followed by oxidation with NBS to give the corresponding keto products.[77]



Scheme 34

3.2.5.2. Electrophilic substitution reactions of indoles

CAN mediated electrophilic substitution reactions of indole under different conditions are summarized in Scheme 35. Michael addition of indole to α,β-unsaturated ketones under ultrasonic irradiation afforded the corresponding adduct **85** in excellent yield.[78]



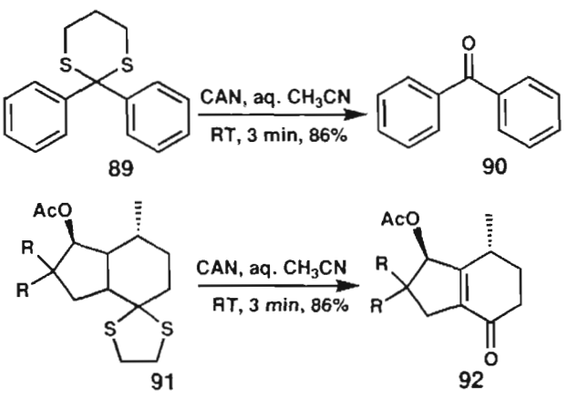
Scheme 35

1,2-addition products of indole **84** were reported by reaction of indole with α,β-unsaturated ketones or aldehydes in the presence of 0.3 equiv of CAN.[79] CAN catalyzed reaction of isatin with indole under sonic waves lead to formation of symmetrical 3,3-(indolyl)indolin-2-one **88**.[80]

3.2.6. Protection-deprotection reactions

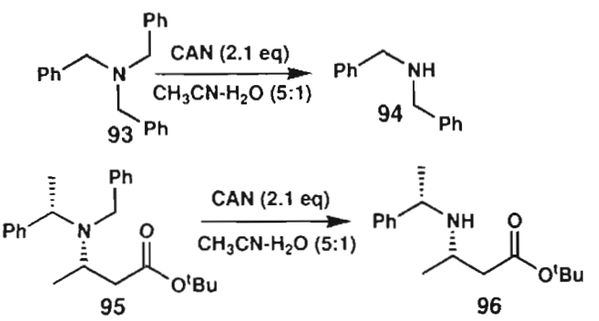
3.2.6.1. Deprotection of carbonyls and amines

In 1972, Ho *et al.* showed that dithioacetals such as **89** and **91** can be unmasked to the parent carbonyl compounds **90** and **92** respectively by employing CAN in aqueous acetonitrile (Scheme 36). [81]



Scheme 36

Treatment of tertiary amines such as **93** with one or more *N*-benzyl protecting groups with aqueous CAN resulted in clean debenzylation to afford the corresponding secondary amines **94** (Scheme 37).[82, 83]

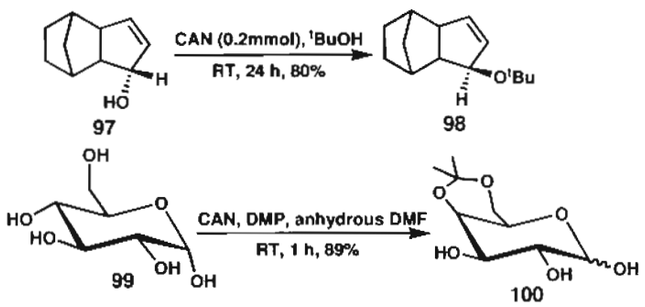


Scheme 37

3.2.6.2. Protection reactions

In contrast to the deprotection sequences, there are only few reports on the protection sequences mediated by CAN. Iranpoor has shown that catalytic amounts of CAN would effect the conversion of allylic alcohol **97** into its corresponding ether **98** in *t*-butanol

(Scheme 38).[84] The wide spectrum of the reactivity of CAN was exemplified by its use in acetalization reactions as well. Acetonation of carbohydrate **99** using 2,2-dimethoxypropane took place in the presence of CAN in anhyd. DMF as solvent (Scheme 38).[85]

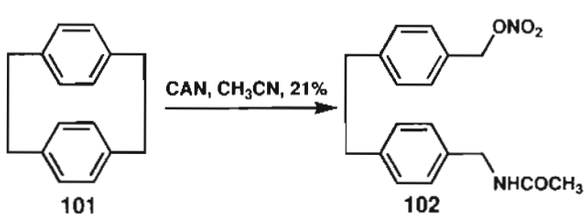


Scheme 38

3.2.7. Miscellaneous transformations

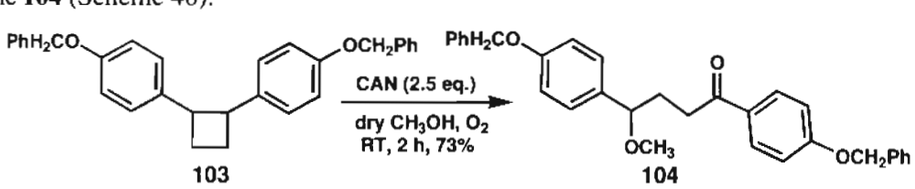
3.2.7.1. Fragmentation reactions

CAN-mediated cleavage of [2.2] paracyclophane **101** resulted in generation of a double benzylic radical cation which is trapped by various nucleophiles to generate products such as **102** (Scheme 39) .[86]



Scheme 39

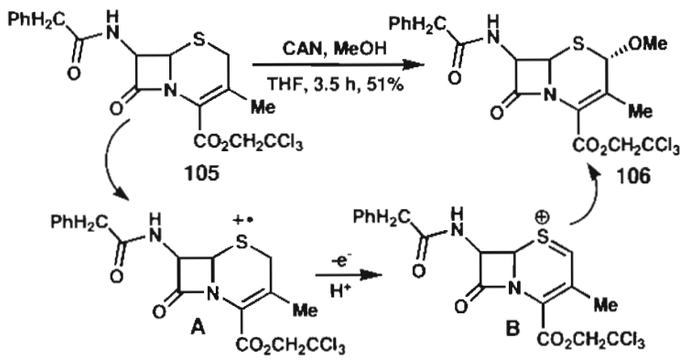
It was found that treatment of cyclobutane **103** with CAN in dry methanol under oxygen atmosphere led to the formation of 1,4-bis(4-(benzyloxy)phenyl)-4-methoxybutan-1-one **104** (Scheme 40).[87]



Scheme 40

3.2.7.2. Alkoxylation reactions

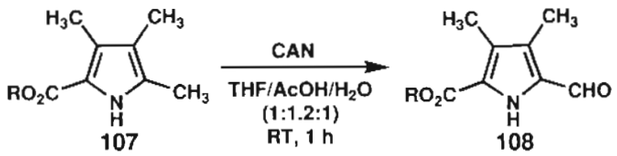
Cephalosporins **105** have been reported to react with CAN in methanol under mild conditions to give corresponding 2-methoxy derivative **106** as a major product.[88] Mechanistically, a single-electron transfer from sulfur to Ce(IV) reagent initiates the reaction forming radical cation **A**. The radical cation **A** subsequently loses a proton and an electron to form **B**. The intermediate **B** then finally quenches with alcohol to form **106** (Scheme 41).



Scheme 41

3.2.7.3. Side-chain oxidations

Lightner *et al.* in 1995 reported oxidation of pyrrole α-methyl derivative **107** to their corresponding formyl derivative **108** with CAN (Scheme 42).[89]



Scheme 42

3.3. Present Work

3.3.1. Introduction

The C-H bond activation method is one of the most challenging reactions in organic synthesis. Activation of C-H bonds particularly by oxidative processes and by organometallic reagents has been of great interest to organic chemists in recent years. Cerium (IV) ammonium nitrate (CAN) has emerged as a versatile reagent for a number of synthetic transformations.

3.3.2. Objective of the present work

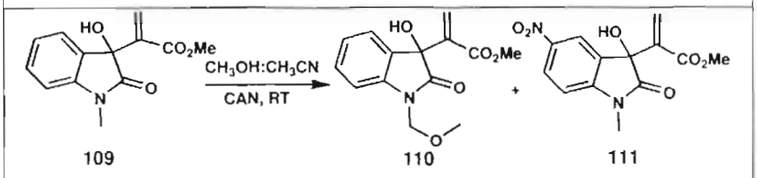
Literature reports on C-H activation shows its wide range of significance in organic synthesis. Because of the reactivity of C-H bond of alkyl group is less and functionalisation of alkyl group is the most important, chemists are interested to discover new routes for C-H activations and alkyl group functionalisation under mild reaction conditions. In this aspect, we have discovered a novel C-H activation method to apply for the system of MBH adducts derived from various *N*-alkyl isatins using ROH/CAN as a reagent. The method delivers *N*C-H bond activation of MBH adducts of *N*-alkyl isatins. The details of the method and study on *N*C-H activation are elaborately dealt in this chapter.

3.3.3. Results and Discussion

3.3.3.1. Reaction optimization and choice of MBH adducts of isatin for NC-H activation

The *N*C-H activation studies were initiated using the MBH adduct of *N*-methylisatin **109** as a model substrate. The preliminary study and results are shown in Table 1. Initially, adduct **109** was treated with 2 equivalents of CAN and excess methanol (10 mL) to afford the *N*C-H activated ether product **110** in trace amount (5 %) (Table 1, entry 1). Repeating the reaction with 3 equivalents of CAN and MeOH (5mL) for 12h afforded **110** in slightly improved yield (10 %) (Table 1, entry 2). Fine-tuning of the reaction conditions is shown in Table 1. Thus, the optimum condition was found as 4 equivalents of CAN and MeOH (1.6 mL, 40 equivalents) and CH_3CN (0.5 mL) and at room temperature for 24h to afford the *N*C-H activated product **110** in 66% yield and nitrated product **111** in 35% yield (Table 1, entry 4).

Table 1. Optimization of *N*C-H bond activation reaction



Entry	MeOH (mL)	CH_3CN (mL)	CAN (equiv.)	Time (h)	Yield (%)	
					110	**111**
1	10.0	-	2.0	12	5	-
2	5.0	-	3.0	12	10	-
3	3.0	3.0	4.0	24	20	35
4	1.6	0.5	4.0	24	66	30

Further to examine the selectivity and structural requirements of *N*-methyl isatin derivatives for *N*C-H activation, we chose different isatin derivatives **109, 112-117** as shown in Figure 1.

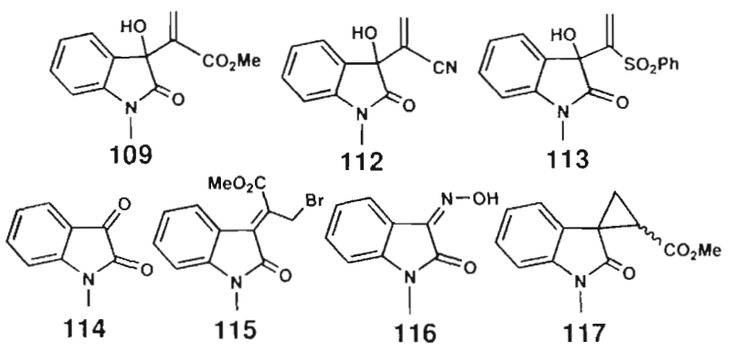


Figure 1

Under optimised condition, MBH adducts **109**, **112** and **113** of *N*-methyl isatin afforded the ether products **110**, **118** and **120** in 24-66 % yields and the nitrated compound **111**, **119** and **121** in trace-30 % yields, respectively (Table 2, entries 1-3). Interestingly, the simple *N*-methyl isatin **114** yielded only the nitrated product **122** in 15 % yields. Other *N*-methylisatin derivatives such as the bromo- derived adduct **115**, oxime derivative of *N*-methyl isatin **116** and *N*-methyl-3-spirocyclopropyl-2-indolone **117** did not yield any *N*C-H activated ether product or nitrated product. The results of the preliminary investigation are summarized in Table 2. Hence, the study showed that the MBH adduct of *N*-methyl isatin was the most suitable substrate for *N*C-H activation reaction.

Table 2

Entry	Substrate	Products		Yield (%)	
		Ether (A)	Nitrates(B)	A	B
1	**109**	**110**	**111**	66	30
2	**112**	**118**	**119**	50	30
3	**113**	**120**	**121**	24	trace
4	**114**	-	**122**	-	15
5	**115**	-	-	-	-
6	**116**	-	-	-	-
7	**117**	-	-	-	-

Excellent preliminary results on *N*C-H activation of MBH adduct of *N*-methyl isatin prompted us to investigate a systematic activation study of various *N*-substituted MBH adducts of isatin derivatives. Thus, we chose various MBH adducts with different *N*-alkyl substitutions such as methyl, methylene and methine which in principle generate 1°, 2° and 3° radical cation intermediates during the *N*C-H activation process thereby providing highly functionalised ether derivatives (Figure 2).

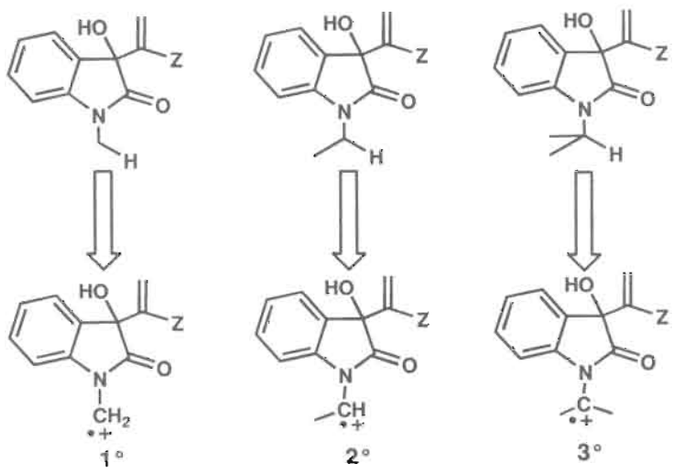
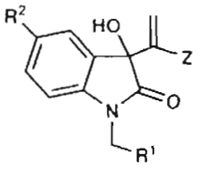


Figure 2

3.3.3.2. *N*C-H activation study of primary methyl radical sources

In order to investigate the *N*C-H activation of MBH adduct of *N*-alkyl isatin via primary radical cation intermediates, MBH adducts **109, 111, 112** and **123** were chosen (Figure 3) and the detailed studies are discussed as follows.



R^1 = H; R^2 = H; Z = CO_2Me **109**

R^1 = H; R^2 = NO_2; Z = CO_2Me **111**

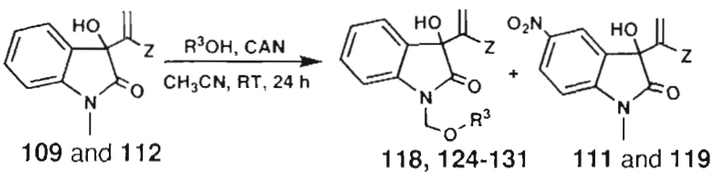
R^1 = H; R^2 = H; Z = CN **112**

R^1 = H; R^2 = Br; Z = CO_2Me **123**

Figure 3

3.3.3.3. *N*C-H activation of MBH adducts of *N*-methyl isatin 109 and 112

As discussed earlier, during optimisation study, the MBH adduct **109** with CAN/MeOH afforded the products **110** (ether) and **111** (nitrate). The observation prompted us to extend the study using adducts **109** and **112** with various saturated and unsaturated alcohols (R^3OH)/CAN (Scheme 43).



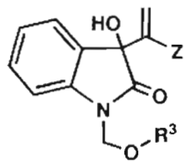
Z = CO_2CH_3, CN

R^3 = CH_3, C_2H_5, propargyl, homopropargyl, ethane-1,2-diol, propane-1,2-diol, benzyl, isopropanol, *t*-butanol, allyol, cinnamylol

Scheme 43

The reactions with various alcohols such as ethanol, propargyl alcohol, homopropargyl alcohol, ethane-1,2-diol, propane-1,3-diol, and benzyl alcohol afforded the *N*C-H activated ethers **118**, **124-131** along with nitrated products **111** and **119** in moderate yield (Table 3, entries 1-9). Notably, the reaction of MBH adduct **109** with 2° and 3°-alcohols (*iso*-propanol and *t*-butanol) did not yield any *N*C-H activated product and only the nitrated product **111** was obtained in good yields (Table 3, entries 10 and 11). However, the reactions with allyl alcohol/CAN and cinnamyl alcohol/CAN did not afford the *N*C-H activated product. Only oxidation of alcohol was observed during the course of the reaction (Table 3, entries 12 and 13). All the new compounds were characterised by spectroscopic (IR, ^1H and ^{13}C NMR) and HRMS data. The results are summarized in Table 3.

Table 3



R^3 = Et; Z =CO_2Me **124**
R^3= H_2C—≡; Z =CO_2Me **125**
R^3 = H_2C ≡; Z =CO_2Me **126**
R^3 = H_2C OH; Z =CO_2Me **127**
R^3 = H_2C OH ; Z =CO_2Me **128**
R^3= CH_2Ph; Z =CO_2Me **129**
R^3 = Me; Z =CN **118**
R^3 = Et; Z =CN **130**
R^3 = H_2C—≡; Z =CN **131**

Entry	MBHA	Alcohol (R^4)	Time (h)	Products		Yield (%)	
				NC-H activation (A)	Nitration (B)	A	B
1	**109**	EtOH	24	**124**	-	52	-
2	**109**	Propargyl	24	**125**	-	51	-
3	**109**	Homopropargyl	24	**126**	**111**	58	25
4	**109**	Ethane-1,2-diol	24	**127**	-	55	-
5	**109**	Propane-1,3-diol	24	**128**	-	67	-
6	**109**	Benzyl alcohol	24	**129**	-	59	-
7	**112**	MeOH	24	**118**	**119**	50	30
8	**112**	EtOH	24	**130**	**119**	53	27
9	**112**	Propargyl	24	**131**	**119**	57	35
10	**109**	*Iso*-Propanol	24	-	**111**	-	54
11	**109**	*t*-Butanol	24	-	**111**	-	65
12	**109**	Allyl alcohol	24	-	-	-	-
13	**109**	Cinnamyl	24	-	-	-	-

All the ether products obtained in the activation study were characterised using morden spectroscopic tools such as IR, NMR and mass spectroscopy. For example, the IR spectrum of ether derivative **124** showed absorption bands at 3382 cm^{-1} for the presence of hydroxy group, 1716 cm^{-1} for carbonyl group, and 1089, 1053 cm^{-1} for the presence of ether linkage in the compound. The ^1H NMR spectrum of compound **124** showed all expected proton signals in their repective chemical shifts. Thus, a triplet at δ 1.20 with a coupling constant J = 6.9Hz for a methyl group, a broad singlet at δ 2.67 for a -OH group, and a multiplet signal at δ 3.65 for oxygen attached methylene and methyl were appeared. The methylene group attached with two electronegative atoms (N and O) was found as closely existing doublets at δ 5.17 and at δ 5.22 with a geminal a coupling constant J = 11.1Hz. The two olefin protons were seen as two singlets at δ 6.43 and at δ 6.58. The four aromatic protons were appeared as two proton multiplet around δ 7.05-7.13, one proton doublet at δ 7.20 with coupling constant J = 7.2Hz, and one proton triplet at δ 7.35 with coupling constant J = 7.2Hz (Figure 4).

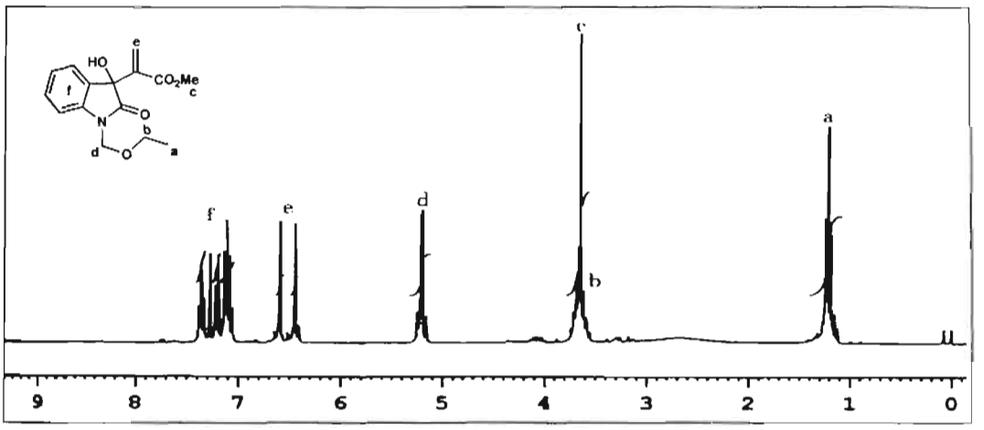


Figure 4 ^{1}H NMR Spectrum of compound **124**

Further, the ^{13}C NMR spectrum of compound **124** had five carbon signals in the aliphatic region between δ 15.10-76.66 for the presence of methine, methylene and methyl carbons. The signals at δ 165.24 and 176.97 confirmed the presence of two carbonyl groups in the compound (Figure 5).

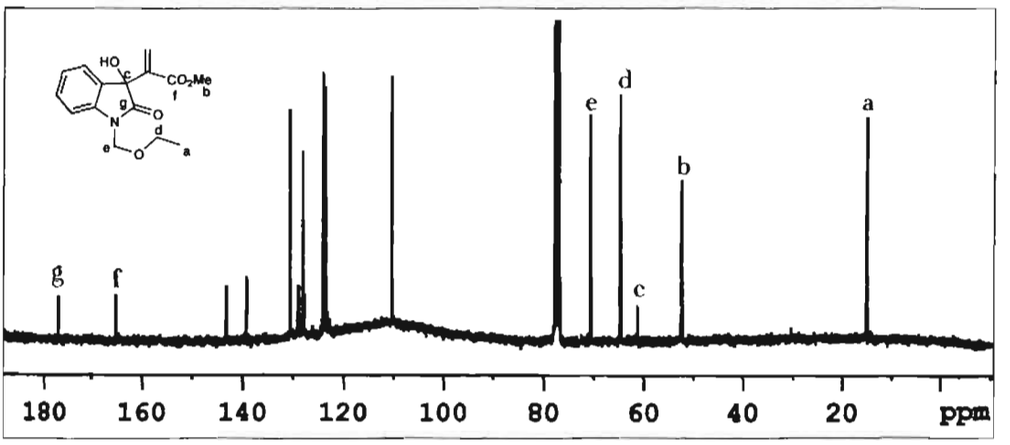


Figure 5 ^{13}C NMR Spectrum of compound **124**

Finally, the mass spectrum (HRMS) showed the molecular ion peak m/z = 291.1088 and confirmed the structure of ether product **124** unambiguously (Figure 6).

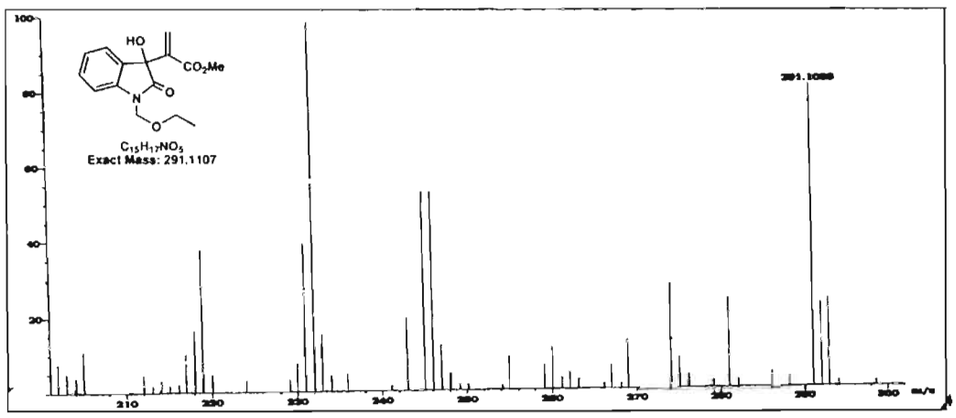


Figure 6 HRMS of compound **124**

Similarly, the structural analysis of propargyl ether derivatives **125** was begun with confirmation of functional groups such as hydroxyl and carbonyl groups with help of IR spectrum. Thus, the hydroxy and carbonyl absorption were found at 3390 cm^{-1} and 1716 cm^{-1} respectively and the propargyl group showed absorption bands at 3311 cm^{-1} (C≡C–H) and 2210 cm^{-1} (–C≡C–). Absorption bands due to the ether linkage were found at 1087 and 1064 cm^{-1}. Further, the structure of compound **125** in which the ether functionality with propargyl alcohol was found clearly in the ^1H NMR spectrum (Figure 7). Thus, a triplet signal centred at δ 2.48 with a coupling constant J = 2.4Hz showed the presence of terminal alkyne proton. The highly deshielded methylene protons attached with two electonegative atoms (O and N) were seen as two doublets at δ 5.20 and δ 5.37 with a coupling constant J = 11.2Hz (geminal coupling).

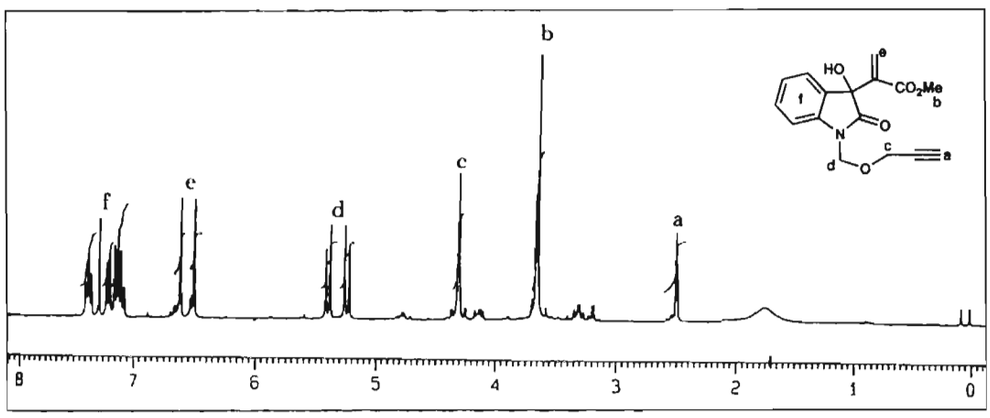


Figure 7 ^1H NMR Spectrum of compound **125**

In addition, the ^{13}C NMR spectrum had all the carbon signals accounting all the carbons in the assigned structure. The two carbonyl carbons were found at δ 165.34 and 176.96. Final evidance for the structure of ether product **125** was arrived based on the mass spectrum (HRMS).Thus, the molecular ion peak m/z = 301.0941 in the mass spectrum confirmed the structure of compound **125** unambiguously.

In the same way, the homopropargyl ether derivative **126** showed all expected absorption bands for the functional groups in its IR spectrum. Thus, the hydroxy and carbonyl stretching absorption were seen at 3406 and 1716 cm^{-1} respectively. The homopropargyl group showed absorption bands at 3320 (C≡C—H) and 2143 cm^{-1} (—C≡C—). Two absorption bands at 1089 and 1050 cm^{-1} were due to ether linkage. The ^{1}H NMR spectrum of **126** is shown in Figure 8. The alkyne proton appeared as triplet at δ 1.95 with a coupling constant J = 2.4Hz. The methylene protons attached with two electronegative atoms (O and N) appeared as two closely appeared doublets (AB quartet) at δ 5.20 and 5.28 with a coupling constant J = 11.1Hz. The olefin hydrogens were resonated as singlet signals at δ 6.46 and 6.59.

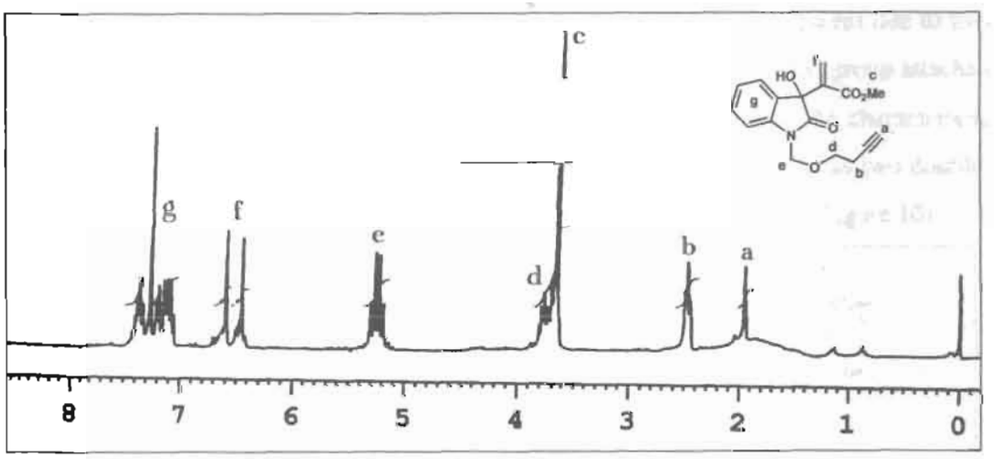


Figure 8 ^{1}H NMR Spectrum of compound **126**

Its ^{13}C NMR spectrum had all the expected carbon signals (Figure 9). The down field signals at δ 165.22 and 176.95 were due to the presence of two carbonyl carbons. The mass spectrum (HRMS) showed a peak at m/z = 315.1101 for compound **126** (Calcd. for $C_{17}H_{17}NO_5$: 315.1107) and confirmed the assigned structure.

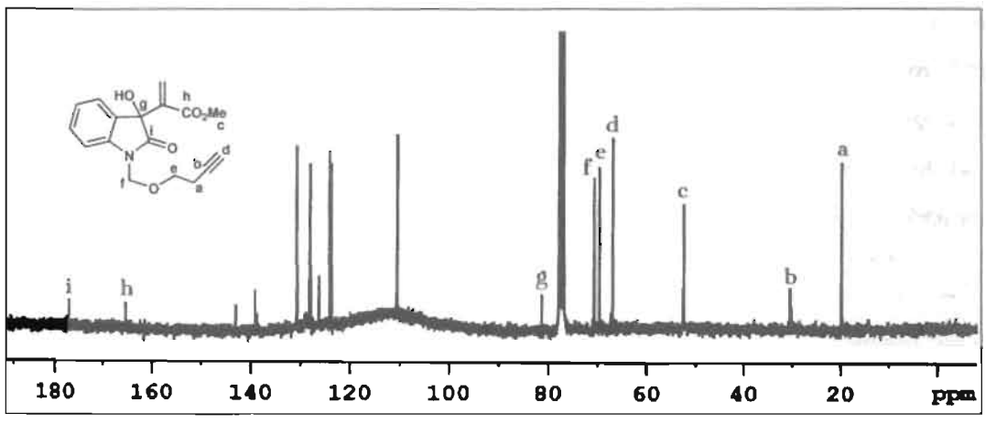


Figure 9 ^{13}C NMR Spectrum of compound **126**

The reaction of MBH adduct **109** with ethane-1,2-diol and propane-1,3-diol afforded corresponding alcoholic ethers **127** and **128**. The ether compound **128** showed the IR absorption bands at 3418 and 1716 cm^{-1} for the presence of hydroxyl and carbonyl groups respectively and bands at 1086 and 1055 cm^{-1} were due to the ether linkage. The ^1H NMR spectrum of compound **128** displayed a quintet signal at δ 1.73 with a coupling constant J = 7.2Hz due to shielded methylene group. A broad singlet at δ 3.11 was apparent due to two hydroxyl protons. Two methylene goups attached with oxygen and a methyl group attached with nitrogen were merged and appeared as a multiplet at δ 3.48-3.80. The characteristic methylene protons attached with nitrogen and oxygen atoms were appeared as two doublet signals (AB quartet) at δ 5.14 and 5.21 with a coupling constant J = 11.4Hz (Figure 10).

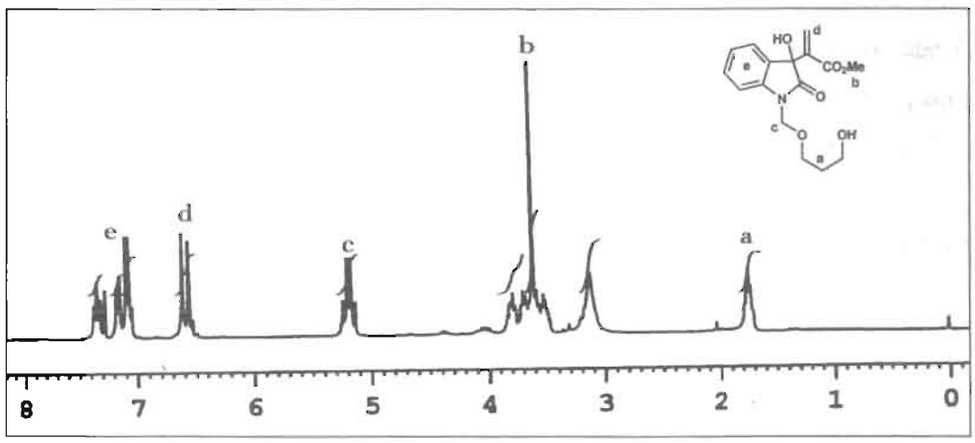


Figure 10 ^1H NMR Spectrum of compound **128**

The ^{13}C NMR of compound **128** was very neet and clear. In the aliphatic region between δ 32.61-76.35 had six signals due to methine, methylene and methyl carbons. The olefin and aromatic carbon signals were scattered in between the chemical shifts range of δ 110.14-143.11. The signals at δ 165.44 and δ 177.23 confirmed the presence of two carbonyl carbons (Figure 11). The final proof for the structure of product **128** was obtained from the mass spectrum (HRMS) by the appearance of mass peak at m/z = 321.1205.

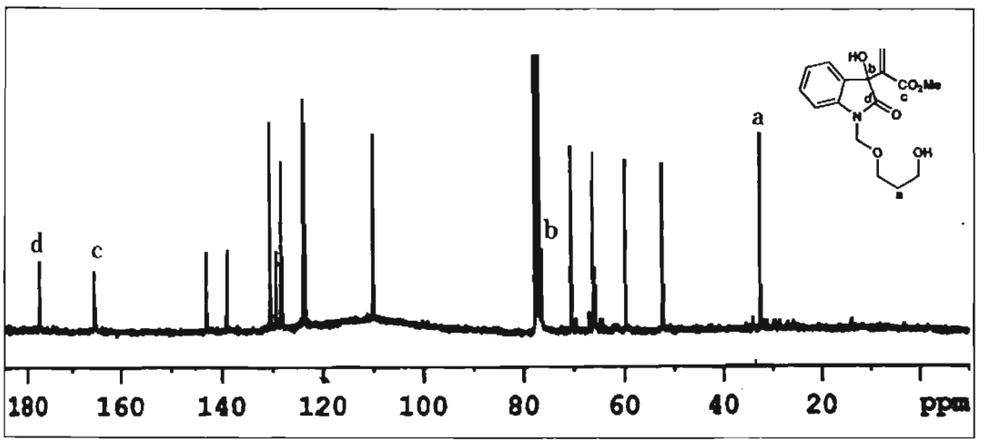


Figure 11 ^{13}C NMR Spectrum of compound **128**

The IR spectrum of nitrile bearing propargyl derivative **131** showed absorption for the presence of hydroxy, nitrile, and carbonyl groups at 3390, 2305, and 1733 cm^{-1} respectively. The propargyl group showed absorption bands (C≡C–H, –C≡C–) at 3312 and 2179 cm^{-1}. Its ^{1}H NMR was very clear. The alkyne proton appeared as a triplet at δ 2.48 with a coupling constant J = 2.4Hz. A doublet signal at δ 4.21 with a coupling constant J = 2.4Hz was representative for methylene protons of the propargyl part. The closely separated two doublets at δ 5.24 and 5.36 with a coupling constant J = 11.1Hz were characteristic for methylene protons attached with nitrogen and oxygen atoms (Figure 12).

The ^{13}C NMR spectrum of compound **131** reflected the presence of total number of carbon of the compound. A carbon signal at δ 174.89 was found due to the presenence of a carbonyl carbon in the compound (Figure 13).

Final structural proof for the ether product **131** was obtained from mass spectrum. Thus, in the mass spectrum (HRMS) a peak at m/z = 258.0992 appeared in consistent with theoritical mass.

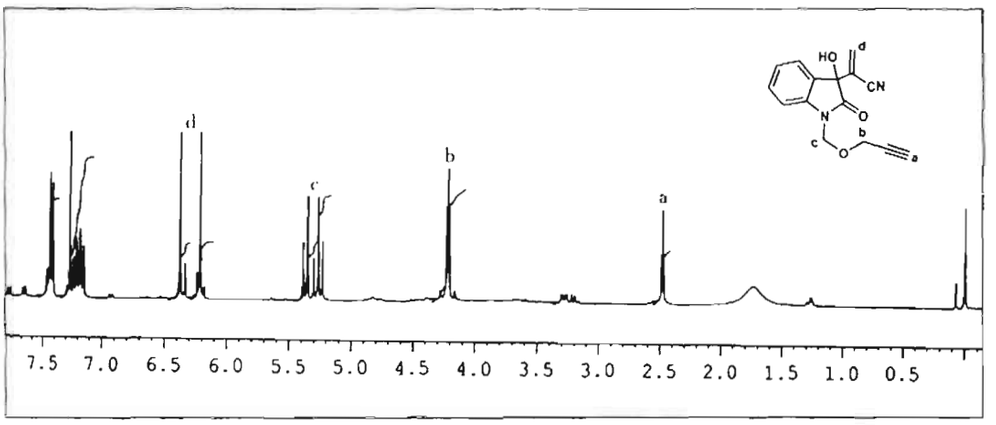


Figure 12 ^{1}H NMR Spectrum of compound **131**

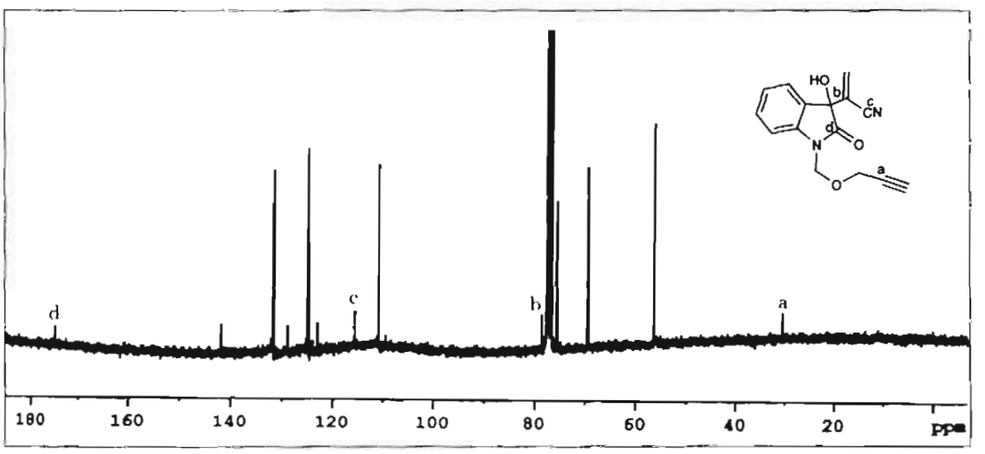


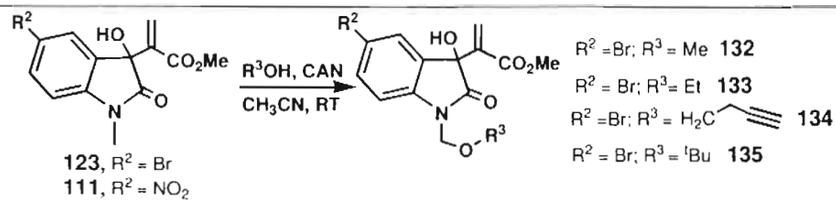
Figure 13 ^{13}C NMR Spectrum of compound **131**

3.3.3.4. Effect of aryl ring substitution on *N*C-H activation of MBH adducts 123 and 111 (Primary radical sources)

In order to circumvent nitration and to check effect of substitution at aryl ring, we examined the activation study with MBH adduct **123** with CAN and alcohols such as methanol, ethanol, homopropargyl alcohol, and t-butanol. The reactions underwent smoothly in enhanced rate (1.5-2 hrs) and afforded the *N*C-H activated compounds **132-135** in good yields (Table 4, entries 1-4). Investigation on effect of substitution and to understand the reactivity pattern of adduct due to electron withdrawing substitution, the reactions with 5-

nitro substituted adduct **111** in methanol and ethanol were tested (Table 4, entries 5 and 6). No *N*C-H activation was found even after allowing the reaction for longer period of time (48 h) and excess of CAN (6 equivalents) reagent. Only starting material was recovered quantitatively, in these cases.

Table 4



Entry	MBHA	Alcohol (R^4)	Time (h)	Products		Yield (%)	
				*N*C-H activation (A)	Nitration (B)	A	B
1	**123**	MeOH	2.0	**132**	-	52	-
2	**123**	EtOH	2.0	**133**	-	51	-
3	**123**		1.0	**134**	-	58	-
4	**123**	^{t}BuOH	1.5	**135**	-	55	-
5	**111**	EtOH	48	-	-	-	-
6	**111**	MeOH	48	-	-	-	-

The IR spectrum of ether **132** had absorption bands due to all the expected functional groups. Thus, the hydroxyl absorption band at 3376 cm^{-1} and a carbonyl absorption band at 1710 cm^{-1} were found. The ^{1}H NMR spectrum of compound **132** showed the *N*C-H activation of adduct **123** with methanol due the presence of two -OMe singlets at δ 3.40 and δ 3.65 and two doublets at δ 5.09 and δ 5.16 with a coupling constant J = 11.0Hz for methylene protons attached with nitrogen and oxygen atoms. The bromo substitution in the aromatic ring of the compound **132** was reflected in the chemical shifts and coupling nature of three aromatic signals. An ortho coupled doublet at δ 6.97 and a meta coupled doublet at δ 7.30 were seen with coupling constants J = 8.3 and 1.8Hz, respectively. A doublet of doublet signal appeared at δ 7.46 with coupling constants J = 8.3 and 1.8Hz (Figure 14). The ^{13}C NMR spectrum had signals at δ 164.73 and 174.37 due to the presence of two carbonyl carbons. A final proof for the structure of the product **132** was arrived from the mass spectrum (HRMS) which had a m/z peak at 355.0051 matching with calculated mass ($C_{14}H_{14}BrNO_5$: 355.0055).

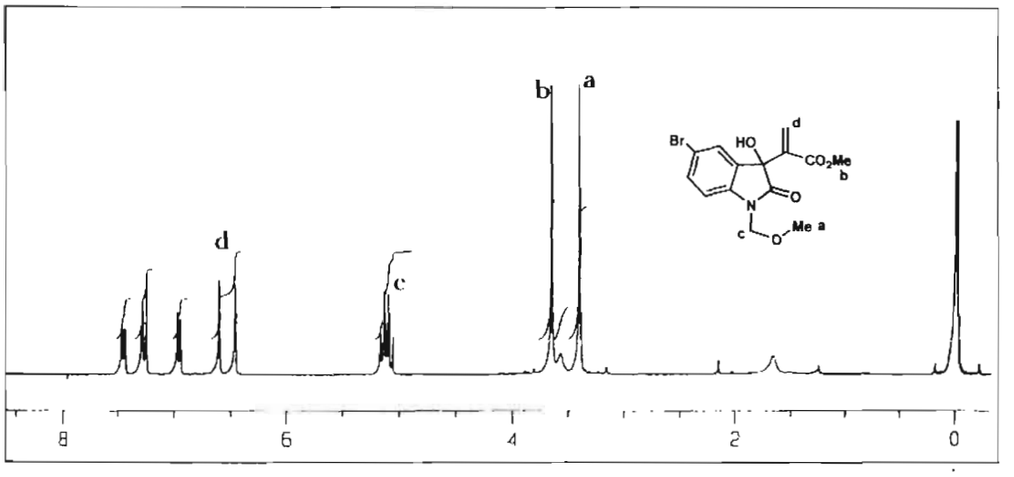


Figure 14 ^{1}H NMR Spectrum of compound **132**

Similarly, the compound **133** obtained from the reaction of adduct **123** and ethanol/CAN showed its IR and ^{1}H NMR spectra with relevant signals. Thus, in IR spectrum absorption bands at 3379 and 1715 cm^{-1} were seen due to hydroxyl and carbonyl groups respectively. The ether linkage in the compound **133** was confirmed due to the presence of absorption bands at 1084 and 1062 cm^{-1}. In ^{1}H NMR spectrum, a triplet at δ 1.19 with a coupling constant J = 7.8Hz confirmed the methyl part of -OEt group. The characteristic methylene protons attached with oxygen and nitrogen atoms appeared as intimately separated doublets at δ 5.13 and δ 5.19 with coupling constant J = 11.1Hz (Figure 15).

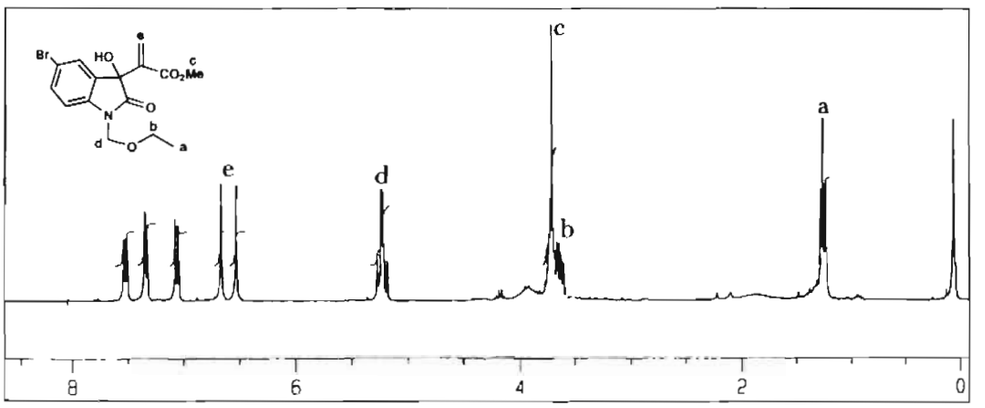


Figure 15 ^{1}H NMR Spectrum of compound **133**

The ^{13}C NMR spectrum identified the presence of two carbonyl carbons in the compound **133** at δ 164.74 and 174.29. The remaining carbon signals in aliphatic, olefinic and aromatic region of the spectrum were consistent with the total number of carbons in assigned structure (Figure 16).

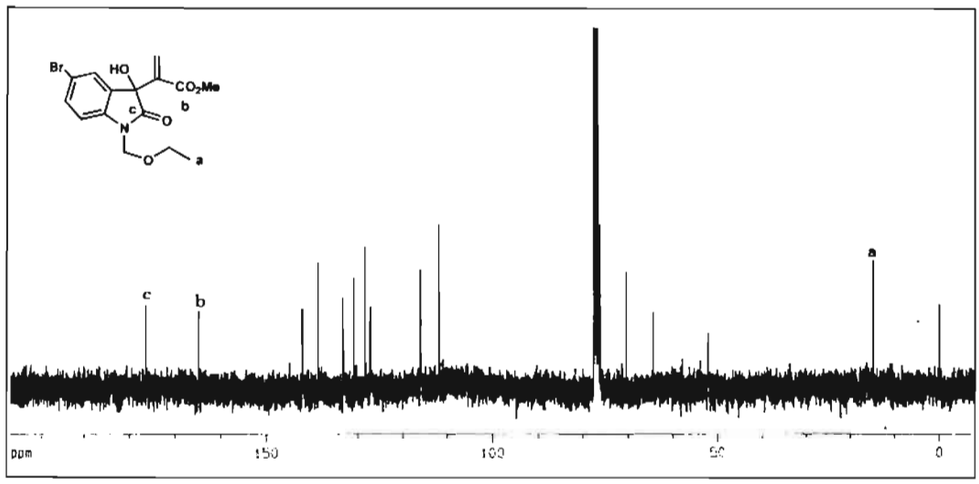
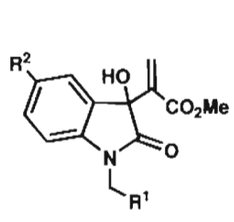


Figure 16 ^{13}C NMR Spectrum of compound **133**

The mass spectrum (HRMS) result was final evidence for the structure of ether product **133** as it showed a m/z peak at 369.0201 which correlates calculated mass ($C_{15}H_{16}BrNO_5$: 369.0212).

3.3.3.5. NC-H activation study of secondary methylene radical sources

To inspect and understand the *N*C-H activation reaction which proceed through a secondary radical intermediate, MBH adducts **136-143** were chosen (Figure 17). The details of the study are discussed in the following sections.

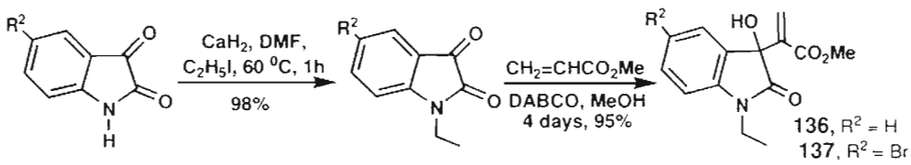


$R^1 = CH_3$; $R^2 = H$ **136**
$R^1 = CH_3$; $R^2 = Br$ **137**
$R^1 = CO_2Me$; $R^2 = H$ **138**
$R^1 = CO_2Et$; $R^2 = H$ **139**
$R^1 = Ph$; $R^2 = H$ **140**
$R^1 = Ph$; $R^2 = Br$ **141**
$R^1 = CCH$; $R^2 = H$ **142**
$R^1 = CCH$; $R^2 = Br$ **143**

Figure 17

3.3.3.6. Activation study of MBH adducts 136 and 137 of *N*-ethyl isatin derivatives

Synthesis of MBH adducts **136/137** is depicted in scheme 44. Accordingly, *N*-ethylation of isatin was carried out with CaH_2 and ethyl iodide in DMF at 60 °C for 1h to afford *N*-ethylisatin in 98% yield. The *N*-ethylisatin with methyl acrylate and DABCO in methanol for four days afforded the desired MBH adducts **136/137** in 95% yield. The structure of the MBH adducts were assigned based on spectroscopic studies.



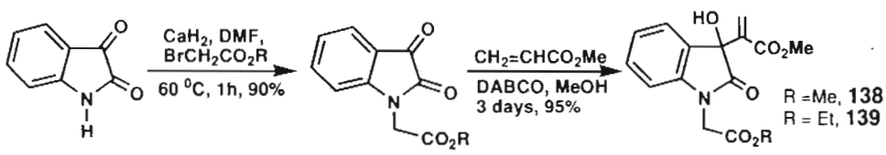
Scheme 44

Activation reaction of adduct **136** with CAN/MeOH in CH_3CN for 24 h provided only the nitrated compound **144** in 56% yield and no *N*C-H activated product was observed (Table 4, entry 1). Experiments with other alcohols such as ethanol, propargyl alcohol and propane-1,3-diol provided only nitrated compound **144** in moderate yields and no *N*C-H activated product was observed in all the cases (Table 4, entries 2-4). The structure of nitrated compound **144** was analyzed by spectroscopic studies. The number of aromatic protons and chemical shifts were the tool for detection of nitration. Accordingly, in the aromatic region, a doublet at δ 6.97 due to ortho coupling (J = 8.6Hz, 1H), a meta coupled doublet at δ 8.04 (J = 2.3Hz) and a doublet of doublet at δ 8.31 (J = 8.6 and 2.3Hz) due to ortho and meta couplings of aromatic protons were appeared. The alkyl and olefin region were similar to that of starting material **136**. To demonstrate and to check effect of electron donating substitution at aryl ring on *N*C-H activation, another adduct **137** was selected. Reactions in methanol and ethanol were carried out (Table 4, entries 5 and 6). To our surprise, we found only a trace of *N*C-H activated product formation **145**, **146** as evidenced from its ^{1}H NMR of crude reaction mixture at regular intervals for 48 h.

3.3.3.7. Activation study of MBH adduct of *N*-methyl/ethyl acetate Isatin 138 and 139

Since, the adduct **136** with electron releasing substitution at α to the *N*C-H bond did not yield any C-H activation products, we considered to evaluate electron withdrawing substitution at α to the *N*C-H bond for *N*C-H activation of MBH adduct such as **138**.

The synthesis of starting materials **138/139** is depicted in scheme 45. Accordingly, the alkylated isatin derivative was synthesized from isatin by the reaction with CaH_2 and methyl-2-bromoacetate in DMF at 60 °C for 1h. The adduct formation of alkylated isatin with methyl acrylate and DABCO in methanol for 3 days afforded the desired adduct in an excellent yield (95%).



Scheme 45

In contrary to the substrates **136** and **137**, activation of adduct **138** with CAN/methanol under optimized reaction condition provided *N*C-H activated product **147** in 58% yield (Table 4, entry 7). The presence of -OMe group due to *N*C-H activation in the product **147** was confirmed from its ^{1}H NMR spectrum. Thus, the methoxy protons were observed at δ 3.63 as a singlet and the methine proton was observed as a singlet at δ 5.96 (Figure 18).

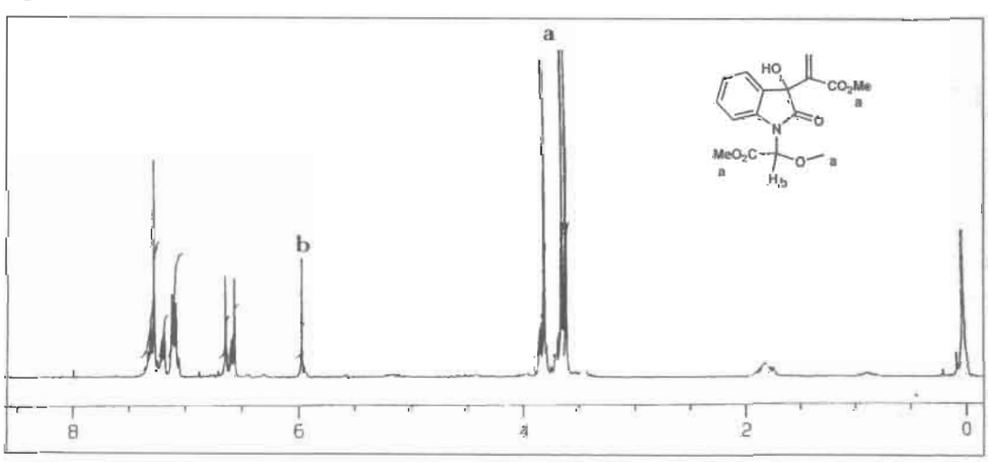


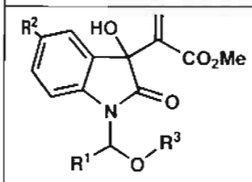
Figure 18 ^{1}H NMR Spectrum of compound **147**

The reactions with ethanol/CAN and propargyl alcohol/CAN were also tested for adduct **138** and the respective *N*C-H activated products **148** and **149** were isolated (Table 4, entries 8 and 9) in moderate to good yields. Similarly, reactions of adduct **139** with benzyl alcohol/CAN and homopropargyl alcohol/CAN afforded the corresponding *N*C-H activated products **150** and **151**, respectively (Table 4, entries 10 and 11) in moderate yields.

3.3.3.8. Activation study on MBH adduct of *N*-benzyl and *N*-propargyl derivatives of isatins 140-141 and 142-143

Having surprise results obtained from adducts **138** and **139**, we were interested to survey the *N*C-H activation of highly functionalized MBH adducts **140-141** and **142-143** of *N*-benzyl and *N*-propargyl isatins, respectively. The desired adducts **140-141** and **142-143** were synthesized using standard procedure described earlier. The adduct **140** with CAN/methanol and CAN/ethanol under optimized reaction conditions yielded neither *N*C-H activated product nor nitrated derivative and the starting material was recovered quantitatively (Table 4, entries 12 and 13). However, the 5-bromo MBH adduct **141** afforded the desired NC-H activated product **152** in 47% yield (Table 4, entry 14).

Table 4



R^1 = Me; R^2 = Br; R^3 = Me **145**

R^1 = Me; R^2 = Br; R^3 = Et **146**

R^1 = CO_2Me; R^2 = H; R^3 = Me **147**

R^1 = CO_2Me; R^2 = H; R^3 = Et **148**

R^1 = CO_2Me; R^2 = H; R^3 = H_2C—≡ **149**

R^1 = CO_2Et; R^2 = H; R^3 = CH_2Ph **150**

R^1 = CO_2Et; R^2=H; R^3 = H_2C—≡ **151**

R^1 = Ph; R^2 = Br; R^3 = Me **152**

R^1 = CCH; R^2 = Br; R^3 = Me **153**

Entry	MBHA	Alcohol (R^4)	Time (h)	Products		Yield (%)	
				*N*C-H activation (A)	Nitration (B)	A	B
1	**136**	MeOH	24	-	**144**	-	56
2	**136**	EtOH	24	-	**144**	-	49
3	**136**	Propargylol	24	-	**144**	-	45
4	**136**	Propane-1,3-diol	24	-	**144**	-	55
5	**137**	MeOH	48	**145**	-	Trace	-
6	**137**	EtOH	48	**146**	-	Trace	-
7	**138**	MeOH	24	**147**	-	58	-
8	**138**	EtOH	24	**148**	-	49	-
9	**138**	Propargylol	24	**149**	-	55	-
10	**139**	Benzylol	24	**150**	-	47	-
11	**139**	Homopropargylol	24	**151**	-	54	-

12	**140**	MeOH	24	-	-	-	-
13	**140**	EtOH	24	-	-	-	-
14	**141**	MeOH	24	**152**	-	47	-
15	**142**	EtOH	24	-	-	-	-
16	**142**	MeOH	24	-	-	-	-
17	**143**	MeOH	2	**153**	-	85	-

In the case of adduct **142,** the reaction mixture became complex (TLC) with CAN/methanol and CAN/ethanol mixture and no *N*C-H activated and nitrated product was obtained (Table 4, entries 15 and 16). However, adduct **143** provided excellent yield of *N*C-H activated product **153** under optimized reaction conditions in 2 hours (Table 4, entry 17). The compound **153** showed all the characteristic signals in its proton NMR spectrum. Thus, the terminal alkyne proton appeared as a doublet at δ 2.61 with a coupling constant J = 2.1Hz. Two singlets were seen at δ 3.48 and δ 3.61 for methoxy protons. A methine proton attached with oxygen and nitrogen atoms appeared as a doublet at δ 6.12 with a coupling constant J = 2.1Hz (Figure 19). The signals at δ 164.54 and δ 175.30 in ^{13}C NMR spectrum appeared due to the presence of two carbonyl carbons. The mass spectrum (HRMS) showed molecular ion peak at m/z = 379.0043.

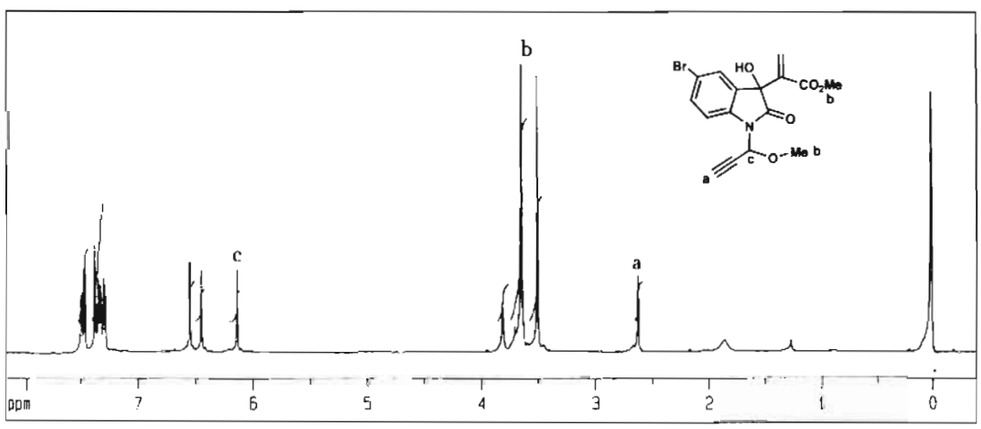
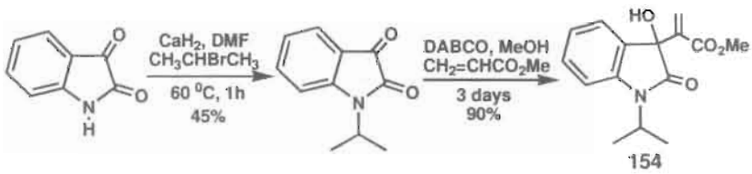


Figure 19 ^{1}H NMR Spectrum of compound **153**

3.3.3.9. *N*C-H activation study of tertiary methine radical source Activation study on MBH adduct of *N*-isopropyl isatin 154

For a comparative study on *N*-alkyl series of isatin derivatives, we chose the MBH adduct of *N*-isopropylisatin **154** as substrate which is believed to precede the *N*C-H activation *via* a tertiary radical intermediate. The synthesis of adduct **154** is depicted in

scheme 46. The *N*-isopropylation of isatin was carried out using CaH_2 and isopropyl bromide in DMF at 60 °C for 1h to afford *N*-isopropyl isatin in 45% yield. *N*-isopropylisatin with methyl acrylate and DABCO in methanol at room temperature afforded MBH adduct **154** in 90% yield.



Scheme 46

The *N*C-H activation of adduct **154** with CAN/MeOH, under optimized condition did not yield any *N*C-H activated product, instead only a moderate yield of nitrated product **155** was obtained (Table 5, entry 1). Similarly, reactions with ethanol, propargyl alcohol and propane-1,3-diol furnished only nitrated compound **155** (Table 5, entries 2-4). The results are collected in Table 5. The structure of nitrated compound **155** was confirmed from its proton NMR data. Thus, the aromatic protons in **155** showed an ortho coupled doublet at δ 7.10 (J = 8.7Hz), a meta coupled doublet at δ 8.03 (J = 2.3Hz) and an ortho-meta coupled doublet of doublet at δ 8.28 (J = 2.3, 8.7Hz) (Figure 20). The alkyl and olefin region were similar to that of starting material **154**. In addition, the ^{13}C NMR spectrum showed signals at δ 164.83 and 176.05 due to two carbonyl carbons. The exact mass value was seen in mass spectrum (HRMS) m/z at 320.1008 which was supportive of final structure.

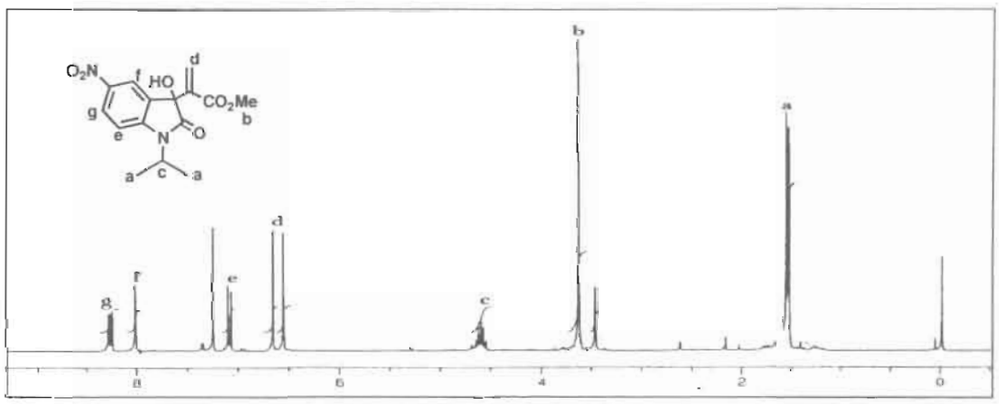
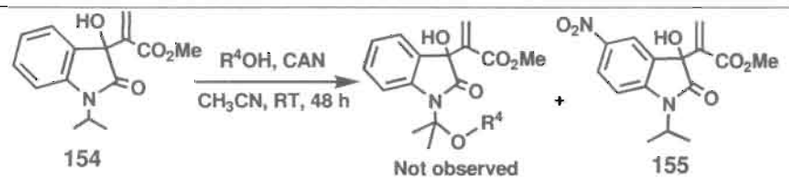


Figure 20 ^1H NMR Spectrum of compound **155**

A detailed spectroscopic data is provided in the experimental part given at the end of this chapter.

Table 5

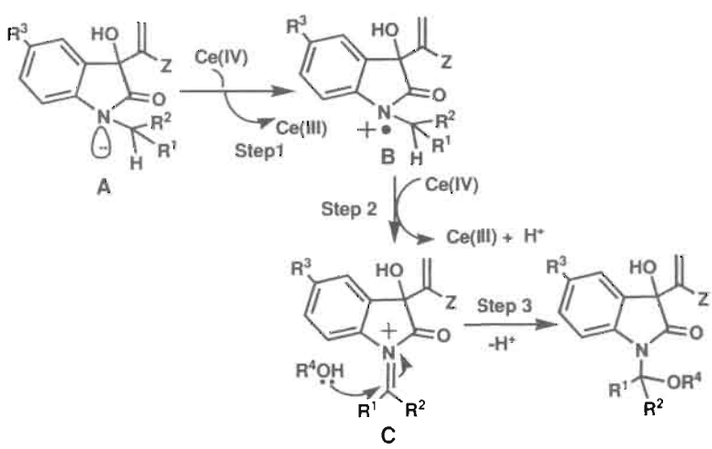


154 Not observed 155

Entry	Alcohol	Product		Yield (%)	
		Ether	Nitrated	Ether	Nitrated
1	MeOH	-	**155**	-	50
2	EtOH	-	**155**	-	39
3	Propargyl-1-ol	-	**155**	-	55
4	Propane-1,3-diol	-	**155**	-	46

3.3.3.10. A plausible mechanism of *N*C-H activation/nitration

A plausible mechanism for the formation of the ether products is delineated in Scheme 47. In the first step, the MBH adduct **A** is oxidised by CAN to form a radical cation[90-92] **B**. Further oxidation of radical cation **B** and liberation of H^+ by CAN produce a cation intermediate **C**, which is quenched by alcohol to afford the *N*C-H activated ether product.



Scheme 47

The proposed mechanism is supported from the results obtained in the studies. It should be noted that comparison of MBH adducts **109**, **123** and **111**, only adduct **123**

underwent *N*C-H activation within 1.5-2.0 h whilst adduct **109** took 24 h for NC-H activation for completion and adduct **111** did not provide any *N*C-H activation product with clear indication of direct involvement of the nitrogen lone pair in the reaction mechanism.

3.3.3.11. Role of nitrogen lone pair for *N*C-H bond activation

The reactivity nature of MBH adducts **136-143** and **154** towards *N*C-H activation can be explained based on the effect of bulky substitution, which reduces the availability of lone pair on nitrogen atom which prevents the first step oxidation and less approach possibility by bulky reagent Ce(IV) towards nitrogen in adducts **136**, **140**, **142** and **154.** The 5-bromo substitution which increases the electron density on nitrogen is clearly found from the reactivity of adducts **137** (trace of NCH activation, 48 h), **141** (47% NC-H activation, 24 h) and **143** (85% *N*C-H activation, 2 h).

However, quite opposite, the nitro substituent having direct resonance with nitrogen lone pair averts the reactivity of the adduct **111**. A pictorial representation for substitution effect and magnitude of nitrogen lone pair is shown in Figure 20. The nitration mechanism of aromatic ring with CAN is well known in the literature.[93]

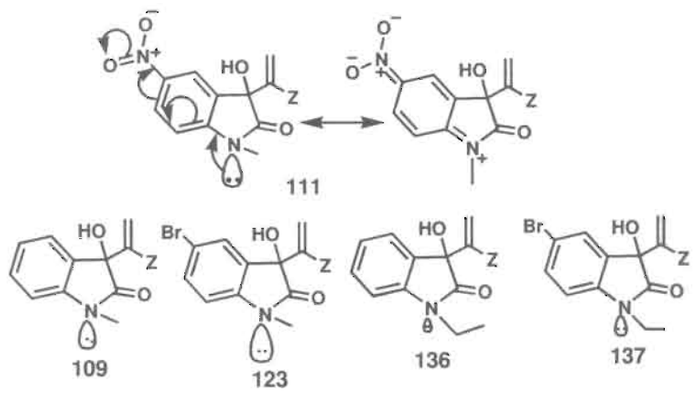


Figure 20

3.3.3.12. Reason for reaction selectivity

The selectivity reason for *N*C-H activation towards MBH adducts alone may probably be due to the conformation favoured by H-bonding in the adduct structure which brings more availability of lone pair on nitrogen atom and avoids resonance with adjacent carbonyl group.

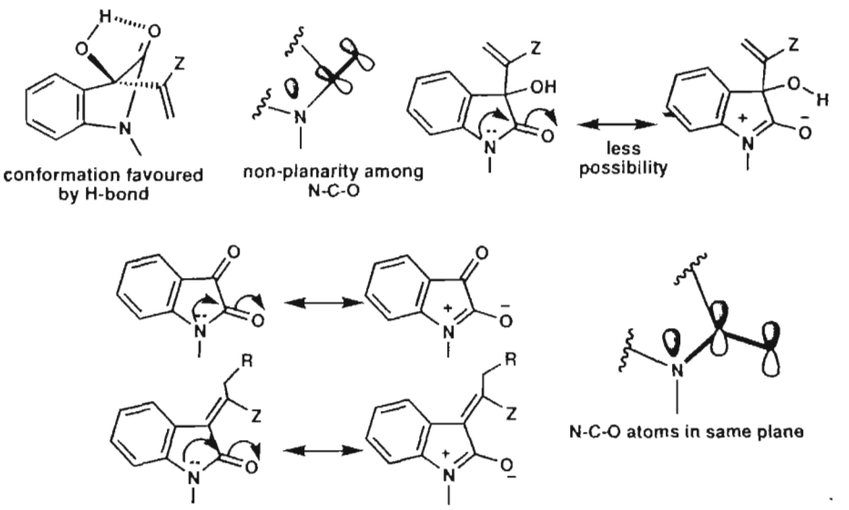


Figure 21

However, the highly planar structure in the compounds **114-117** allows the nitrogen lone pair in the resonance with adjacent carbonyl group. Hence, no *N*C-H activation occurred with simple isatin derivatives. (Figure 21)

3.3.4. Conclusion

- A novel study on *N*C-H activation of various MBH adducts of *N*-substituted isatin with a number of alcohols using CAN as a single electron oxidizing agent was carried out.
- Highly functionalised ether derivatives and nitrated products were synthesised.
- A comparative and reactivity pattern study on *N*C-H activation of MBH adducts of *N*-substituted isatin derivatives viz. *N*-methyl, *N*-ethyl, *N*-methyl acetate, *N*-benzyl, *N*-propargyl and *N*-isopropyl isatins was carried out, thereby the reactions examined substrates with 1°, 2° and 3° radical sources.
- Effect of aryl ring substitution was investigated.
- A plausible mechanism of the reaction was proposed and it was rationalized based on the results obtained.
- Selectivity reason was explained.
- All the products were characterised based on spectroscopic studies.

3.3.5. Experimental Details

3.3.5.1. General experimental procedure for alkylation of isatin

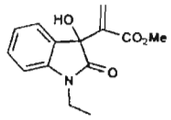
A mixture of isatin (1 mmol), alkyl bromide/iodide (1.5 mmol) and calcium hydride (3 mmol) in DMF was stirred at 60 °C for 1 hour. After completion of the reaction (monitored by TLC), the crude mixture was diluted with water, neutralized with 2N HCl and extracted using ethyl acetate. The organic layer was separated and dried (Na_2SO_4) and concentrated *in vacuo*. The crude product obtained was purified by silica gel chromatography using EtOAc: hexane (20: 80) as eluent to afford the desired *N*-alkylisatin derivatives.

3.3.5.2. General procedure for the preparation of MBH adducts

A mixture of *N*-alkyl isatin (1 mmol), methyl acrylate (1.5 mmol), DABCO (0.02 mmol) in MeOH (5 mL) was stirred at RT for 3-4 days. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate. The organic layer was washed successively with 0.2 N HCl, water and brine. The organic layer was separated and dried (Na_2SO_4) and concentrated *in vacuo*. The crude product obtained was purified by silica gel column chromatography using EtOAc: hexane (20: 80) as eluent to afford the desired MBH adducts of *N*-alkyl isatin.

3.3.6. Spectral data of MBH adducts 136, 138, 142 and 154

Methyl 2-(1-ethyl-3-hydroxy-2-oxoindolin-3-yl) acrylate **136**:



136

Colourless solid; Mp. = 148-150 °C; R_f (25% EtOAc-Hexane) 0.48.

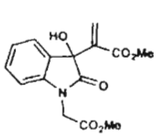
IR (CH_2Cl_2): ν_{max} 3341, 1723, 1615 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.32 (t, *J* = 7.2 Hz, 3H), 2.45 (bs, 1H), 3.62 (s, 3H), 3.74 (q, *J* = 7.2 Hz, 2H), 6.41 (s, 1H), 6.56 (s, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 7.05 (t, *J* = 6.7 Hz, 1H), 7.19 (d, *J* = 6.4 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 12.42, 52.26, 64.53, 70.55, 110.39, 123.62, 124.13, 128.03, 129.08, 130.72, 139.24, 143.27, 165.33, 176.47.

HRMS *m/z*: Calcd. For $C_{14}H_{15}NO_4$: 261.1001; Found: 261.1000.

Methyl 2-(1-methylene carbomethoxy-3-hydroxy-2-oxo indolin-3-yl)acrylate **138**:



138

Colourless waxy solid; R_f (25% EtOAc-Hexane) 0.29.

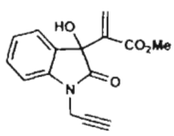
IR (CH_2Cl_2): ν_{max} 3350, 1716, 1615, 1087, 1063 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.64 (s, 3H), 3.78 (s, 3H), 4.41 (bs, 1H), 4.41 (d, J = 17.6 Hz, 1H), 4.61 (d, J = 17.6 Hz, 1H), 6.44 (s, 1H), 6.59 (s, 1H), 6.74 (d, J = 7.8 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 7.06-7.34 (m, 2H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 41.41, 52.14, 52.70, 76.02, 108.66, 123.43, 124.12, 128.31, 129.40, 130.25, 138.48, 142.98, 165.27, 168.26, 176.00.

HRMS *m/z*: Calcd. for $C_{15}H_{15}NO_6$: 305.0899; Found 305.0896.

Methyl 2-(3-hydroxy-2-oxo-1-(prop-2-ynyl) indolin-3-yl)acrylate **142**:



142

Colourless waxy solid; R_f (25% EtOAc-Hexane) 0.34.

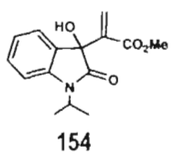
IR (CH_2Cl_2): ν_{max} 3425, 3309, 2131, 1718, 1611 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.28 (t, J = 2.2 Hz, 1H), 3.59 (s, 3H), 4.07 (s, OH), 4.51-4.58 (m, 2H), 6.44 (s, 1H), 6.57(s, 1H), 7.04-7.09 (m, 2H), 7.18 (d, J = 6.48 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 29.51, 52.11, 72.61, 76.07, 76.64, 109.65, 123.37, 123.94, 128.18, 129.22, 130.20, 138.89, 142.55, 164.96, 175.37.

HRMS *m/z*: Calcd. for $C_{15}H_{13}NO_4$: 271.0845; Found: 271.0841.

Methyl 2-(3-hydroxy-1-isopropyl-2-oxoindolin-3-yl)acrylate **154**:



154

Colourless waxy solid; R_f (25% EtOAc-Hexane) 0.42.

IR (CH_2Cl_2): ν_{max} 3353, 1699, 1611 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.52 (d, J = 8.15 Hz, 6H), 3.55 (bs, 1H), 3.61 (s, 3H), 4.58 (sept, J = 7.0 Hz, 1H), 6.42 (s, 1H), 6.56 (s, 1H), 7.02 (d, J = 7.7 Hz, 2H), 7.17 (d, J = 6.6 Hz, 1H), 7.30 (t, J = 6.8 Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 19.05 (2C), 43.26, 51.81, 75.85, 109.77, 122.36, 124.00, 127.64, 129.79 (2C), 139.36, 143.189, 164.84, 176.05.

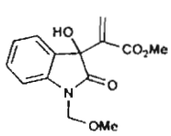
HRMS *m/z*: Calcd. for $C_{15}H_{17}NO_4$: 275.1158; Found: 275.1152.

3.3.7. General experimental procedure for NC-H activation:

A mixture of MBH adduct (1 mmol), 4 equiv. of cerium ammonium nitrate (4 mmol) and 40 equiv. of ROH (1.6 mL) in CH_3CN (0.5 mL) was allowed to stir at RT for 2-48 h. The progress of reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude reaction mixture was extracted with dichloromethane and washed with water and brine. The organic layer was separated and dried (Na_2SO_4) and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography using gradient elution with hexane and hexane and EtOAc to afford pure functionalized ethers and aromatic nitrated products.

3.3.8. Spectral data for NC-H activated compounds

Methyl 2-(3-hydroxy-1-(methoxy methyl)-2-oxoindolin-3-yl) acrylate **110**:



110

Waxy solid; R_f (20% EtOAc-Hexane) 0.35.

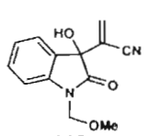
IR (CH_2Cl_2): ν_{max} 3386, 1716, 1085, 1063 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.57 (bs, 1H), 3.41 (s, 3H), 3.65 (s, 3H), 5.13 (d, *J* = 11.1 Hz, 1H), 5.17 (d, *J* = 11.1 Hz, 1H), 6.42 (s, 1H), 6.59 (s, 1H), 7.06-7.10 (m, 2H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 52.49, 53.21, 70.56, 76.66, 110.39, 123.68, 124.13, 127.81, 129.15, 130.62, 139.49, 143.31, 164.83, 176.96.

HRMS *m/z*: Calcd. for $C_{14}H_{15}NO_5$: 277.0950; Found: 277.0947.

2-(3-hydroxy-1-(methoxymethyl)-2-oxoindolin -3-yl)acrylonitrile **118**:



118

Waxy solid; R_f (20% EtOAc-Hexane) 0.44.

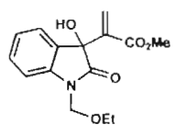
IR (CH_2Cl_2): ν_{max} 3376, 2209, 1726, 1614, 1087 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.36 (s, 3H), 4.07 (s, 1H), 5.10 (d, *J* = 10.9 Hz, 1H), 5.19 (d, *J* = 10.9 Hz, 1H), 6.21 (s, 1H), 6.39 (s, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.17 (t, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 2H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 52.13, 70.72, 76.77, 110.82, 115.56, 123.27, 123.88, 124.86, 126.84, 128.16, 131.55, 142.51, 176.27.

HRMS *m/z*: Calcd. for $C_{13}H_{12}N_2O_3$: 244.0848; Found: 244.0836.

Methyl 2-(1-(ethoxymethyl)-3-hydroxy-2-oxoindolin-3-yl) acrylate **124**:



124

Waxy solid; R_f (20% EtOAc-Hexane) 0.43.

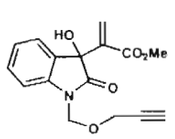
IR (CH_2Cl_2): ν_{max} 3382, 1716, 1089, 1053 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.20 (t, *J* = 6.9 Hz, 3H), 2.67 (bs, 1H), 3.65 (m, 5H), 5.17 (d, *J* = 11.1 Hz, 1H), 5.22 (d, *J* = 11.1 Hz, 1H), 6.43 (s, 1H), 6.58 (s, 1H), 7.05-7.13 (m, 2H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 15.10, 52.26, 64.58, 70.56, 76.66, 110.43, 123.60, 124.09, 128.04, 128.98, 130.63, 139.24, 143.27, 165.24, 176.97.

HRMS *m/z*: Calcd. for $C_{15}H_{17}NO_5$: 291.1107; Found 291.1088.

Methyl 2-(3-hydroxy-2-oxo-1-((prop-2-ynyl oxy)methyl)indolin-3-yl)acrylate **125**:



125

Waxy solid; R_f (20% EtOAc-Hexane) 0.37.

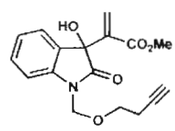
IR (CH_2Cl_2): ν_{max} 3390, 3311, 2210, 1716, 1615, 1087, 1064 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.48 (t, *J* = 2.4 Hz, 1H), 2.67 (bs, 1H), 3.63 (s, 3H), 4.28 (d, *J* = 2.4 Hz, 2H), 5.20 (d, *J* = 11.2 Hz, 1H), 5.37 (d, *J* = 11.2 Hz, 1H), 6.48 (s, 1H), 6.59 (s, 1H), 7.05-7.20 (m, 3H), 7.35 (t, *J* = 7.6 Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 30.50, 52.31, 56.36, 70.28, 75.56, 78.66, 110.73, 123.63, 124.17, 128.13, 129.08, 130.56, 139.34, 143.17, 165.34, 176.96.

HRMS *m/z*: Calcd. for $C_{16}H_{15}NO_5$: 301.0950; Found: 301.0941.

Methyl 2-(1-[(but-3-ynyloxy)methyl]-3-hydr oxy-2-oxoindolin-3-yl) acrylate **126**:



126

Waxy solid; R_f (20% EtOAc-Hexane) 0.47.

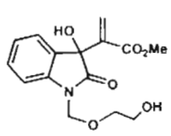
IR (CH_2Cl_2): ν_{max} 3406, 3320, 2123, 1716, 1614, 1089, 1050 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.80 (bs, 1H), 1.95 (t, *J* = 2.4 Hz, 1H), 2.46 (td, *J* = 6.6, 2.4 Hz, 2H), 3.63 (s, 3H), 3.66 (t, *J* = 6.6 Hz, 2H), 5.20 (d, *J* = 11.1 Hz, 1H), 5.28 (d, *J* = 11.1 Hz, 1H), 6.46 (s, 1H), 6.59 (s, 1H), 7.05-7.20 (m, 3H), 7.35 (t, *J* = 7.8 Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 19.84, 30.38, 52.31, 66.90, 69.55, 70.64, 81.34, 110.51, 123.73, 124.12, 126.24, 127.89, 130.71, 139.19, 143.10, 165.22, 176.95.

HRMS *m/z*: Calcd. for $C_{17}H_{17}NO_5$:315.1107; Found: 315.1101.

Methyl 2-(1-((2-hydroxyethoxy)methyl)-3-hydroxy-2-oxoindolin-3-yl)acrylate **127**:



127

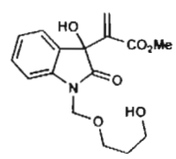
Waxy solid; R_f (20% EtOAc-Hexane) 0.23.

IR (CH_2Cl_2): ν_{max} 3416, 1716, 1614, 1085, 1065 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.67 (bs, 2H), 3.62 (s, 3H), 3.69-3.75 (m, 4H), 5.21 (d, *J* = 11.1 Hz, 1H), 5.28 (d, *J* = 11.1 Hz, 1H), 6.50 (s, 1H), 6.60 (s, 1H), 7.05-7.26 (m, 3H), 7.34 (t, *J* = 6.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$/TMS, 75.3 MHz): δ 52.42, 59.75, 66.15, 70.50, 76.27, 110.13, 123.56, 123.97, 128.35, 129.43, 130.63, 139.04, 143.21, 165.34, 175.63.

HRMS *m/z*: Calcd. for $C_{15}H_{17}NO_6$: 307.1056; Found: 307.1047.

Methyl 2-(1-[(3-hydroxypropoxy)methyl]-3-hydroxy-2-oxoindolin-3-yl) acrylate **128**:



128

Waxy solid; R_f (20% EtOAc-Hexane) 0.28.

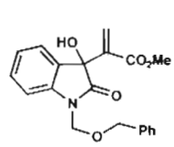
IR (CH_2Cl_2): ν_{max} 3418, 1716, 1613, 1086, 1055 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.73 (quintet, *J* = 7.2 Hz, 2H), 3.11 (bs, 2H), 3.48-3.80 (m, 7H), 5.14 (d, *J* = 11.4 Hz, 1H), 5.21 (d, *J* = 11.4 Hz, 1H), 6.55 (s, 1H), 6.60 (s, 1H), 7.03-7.16 (m, 3H),7.33 (t, *J* = 7.5 Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 32.61, 52.41, 59.81, 66.21, 70.49, 76.35, 110.14, 123.66, 123.98, 128.37, 129.41, 130.53, 139.01, 143.11, 165.44, 177.23.

HRMS *m/z*: Calcd. for $C_{16}H_{19}NO_6$: 321.1212; Found: 321.1205.

Methyl 2-(1-((benzyloxy)methyl)-3-hydroxy-2-oxoindolin-3-yl)acrylate **129**:



129

Waxy solid; R_f (20% EtOAc-Hexane) 0.29.

IR (CH_2Cl_2): ν_{max} 3314, 1716, 1617, 1083, 1055 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.67 (bs, 1H), 3.62 (s, 3H), 4.36 (d, *J* = 11.6 Hz, 1H), 4.72 (d, *J* = 11.6 Hz, 1H), 5.24 (d, *J* = 11.1 Hz, 1H), 5.32 (d, *J* = 11.1 Hz, 1H), 6.47 (s, 1H), 6.59 (s, 1H), 7.08-7.35 (m, 9H).

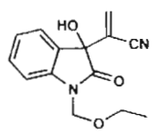
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 52.10, 70. 05, 70.74, 76.37, 110.32, 123.47, 123.88, 127.84 (2C), 128.17 (2C), 128.35 (2C), 128.69, 130.50, 137.48, 138.94, 143.01, 165.00, 176.66.

HRMS *m/z*: Calcd. for $C_{20}H_{19}NO_5$: 353.1263; Found: 353.1254.

2-(1-(ethoxymethyl)-3-hydroxy-2-oxoindolin-3-yl) acrylonitrile **130:**

Waxy solid; R_f (20% EtOAc-Hexane) 0.34.

IR (CH_2Cl_2): ν_{max} 3378, 2917, 2185, 1732, 1613, 1487, 1097 cm^{-1}.



130

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.19 (t, *J* = 7.2Hz, 3H), 1.90 (bs, 1H), 3.57 (q, *J* = 7.2Hz, 2H), 5.15 (d, *J* = 11.1Hz, 1H), 5.25 (d, *J* = 11.1Hz, 1H), 6.21 (s, 1H), 6.36 (s, 1H), 7.14-7.22 (m, 2H), 7.40-7.45 (m, 2H).

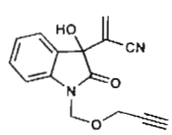
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 15.03, 64.81, 70.71, 76.80, 111.10, 115.65, 123.28, 124.61, 124.93, 126.54, 128.65, 131.62, 142.02, 175.51.

HRMS *m/z*: Calcd. for $C_{14}H_{14}N_2O_3$: 258.1004; Found: 258.0992.

2-(3-hydroxy-2-oxo-1-[(prop-2-yloxy) methyl] indolin-3-yl)acrylonitrile **131:**

Waxy solid; R_f (20% EtOAc-Hexane) 0.42.

IR (CH_2Cl_2): ν_{max} 3390, 3312, 2305, 2179, 1733, 1614, 1073 cm^{-1}.



131

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.80 (bs, 1H), 2.48 (t, *J* = 2.4 Hz, 1H), 4.21 (d, *J* = 2.4 Hz, 2H), 5.24 (d, *J* = 11.1 Hz, 1H), 5.36 (d, *J* = 11.1 Hz, 1H), 6.21 (s, 1H), 6.37 (s, 1H), 7.10-7.29 (m, 2H), 7.42 (d, *J* = 7.5Hz, 2H).

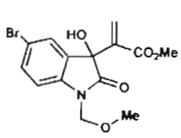
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 30.60, 56.39, 69.52, 75.79, 78.66, 110.91, 115.66, 123.05, 125.00, 126.99, 128.84, 131.61, 132.62, 141.89, 174.89.

HRMS *m/z*: Calcd. for $C_{15}H_{12}N_2O_3$: 268.0848; Found: 268.0840.

Methyl 2-(5-bromo-3-hydroxy-1-(methoxymethyl)-2-oxoindolin-3-yl)acrylate **132:**

Waxy solid; R_f (20% EtOAc-Hexane) 0.47.

IR (CH_2Cl_2): ν_{max} 3376, 1710, 1079, 1060 cm^{-1}.



132

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.40 (s, 3H), 3.58 (s, OH), 3.65 (s, 3H), 5.09 (d, *J* = 11.0 Hz, 1H), 5.16 (d, *J* = 11.0 Hz, 1H), 6.47 (s, 1H), 6.62 (s, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 7.30 (d, *J* = 1.8 Hz, 1H), 7.46 (dd, *J* = 8.3, 1.8 Hz, 1H).

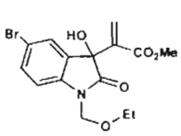
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 52.49, 53.11, 70.57, 76.74, 111.81, 116.05, 126.82, 128.27, 130.82, 133.15, 138.62, 142.13, 164.73, 174.37.

HRMS *m/z*: Calcd. for $C_{14}H_{14}BrNO_5$: 355.0055; Found 355.0051.

Methyl 2-(5-bromo-1-(ethoxymethyl)-3-hydroxy-2-oxoindolin-3-yl)acrylate **133:**

Waxy solid; R_f (20% EtOAc-Hexane) 0.45.

IR (CH_2Cl_2): ν_{max} 3379, 1715, 1084, 1062 cm^{-1}.



133

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.19 (t, *J* = 7.8 Hz, 3H), 1.89 (bs, 1H), 3.45-3.63 (m, 5H), 5.13 (d, *J* = 11.1 Hz, 1H), 5.19 (d, *J* = 11.1 Hz, 1H), 6.47 (s, 1H), 6.60 (s, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 7.28 (d, *J* = 1.9 Hz, 1H), 7.46 (dd, *J* = 8.3, 1.9 Hz, 1H).

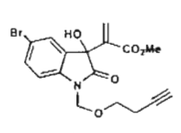
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 14.83, 52.11, 64.43, 70.38, 76.18, 111.82, 116.02, 127.11, 128.27, 130.82, 133.16, 138.60, 142.06, 164.74, 174.29.

HRMS *m/z*: Calcd. for $C_{15}H_{16}BrNO_5$: 369.0212; Found 369.0201.

Methyl 2-(5-bromo-1-((but-3-ynyloxy)methyl)-3-hydroxy-2-oxoindolin-3-yl)acrylate **134:**

Waxy solid; R_f (20% EtOAc-Hexane) 0.39.

IR (CH_2Cl_2): ν_{max} 3390, 2210, 1716, 1085, 1063 cm^{-1};



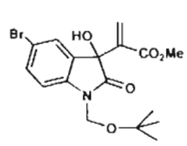
134

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.94 (t, *J* = 2.4 Hz, 1H), 2.46 (td, *J* = 6.7, 2.4 Hz, 2H), 3.61-3.76 (m, 5H), 5.18 (d, *J* = 11.2 Hz, 1H), 5.18 (d, *J* = 11.2 Hz, 1H), 5.25 (d, *J* = 11.2 Hz, 1H), 6.48 (s, 1H), 6.62 (s, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 7.29 (d, *J* = 1.7 Hz, 1H), 7.46 (dd, *J* = 8.3, 1.7 Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 19.30, 30.38, 52.53, 67.28, 69.55, 70.49, 81.05, 110.95, 116.16, 127.14, 128.31, 130.69, 133.21, 138.55, 143.01, 164.78, 176.32.

HRMS *m/z*: Calcd. for $C_{17}H_{16}BrNO_5$: 393.0212; Found 393.0203.

Methyl 2-(1-(t-butoxymethyl)-5-bromo-3-hydroxy-2-oxoindolin-3-yl)acrylate **135:**



135

Waxy solid; R_f (20% EtOAc-Hexane) 0.47.

IR (CH_2Cl_2): ν_{max} 3376, 1710, 1079, 1060 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.23 (s, 9H), 3.58 (s, OH), 3.65 (s, 3H), 5.07 (d, *J* = 10.8 Hz, 1H), 5.30 (d, *J* = 10.8 Hz, 1H),

6.38 (s, 1H), 6.58 (s, 1H), 7.02 (d, J = 8.3 Hz, 1H), 7.29 (d, J = 1.9 Hz, 1H), 7.46 (dd, J = 8.3, 1.9 Hz, 1H).

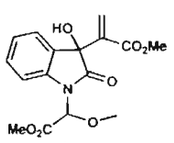
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 28.38, 29.68, 65.27, 75.05, 76.26, 109.85, 114.33, 117.15, 121.47, 127.10, 128.29, 133.15, 138.41, 159.02, 164.98.

HRMS *m/z*: Calcd. for $C_{17}H_{20}BrNO_5$: 397.0525; Found 397.0523.

Methyl 2-(3-hydroxy-1-(methyl 2-methoxyacetate)-2-oxoindolin-3-yl)acrylate **147:**

Waxy solid; R_f (20% EtOAc-Hexane) 0.44.

IR (CH_2Cl_2): ν_{max} 3420, 1718, 1606, 1051 cm^{-1}.



147

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.90 (bs, 1H), 3.59 (s, 3H), 3.63 (s, 3H), 3.79 (s, 3H), 5.96 (s, 1H), 6.55 (s, 1H), 6.63 (s, 1H), 7.04-7.10 (m, 2H), 7.17-7.32 (m, 2H).

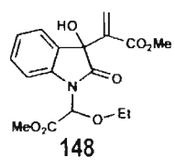
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 46.94, 52.07, 56.87, 76.04, 79.67, 111.40, 123.60, 123.78, 128.10, 128.69, 130.49, 138.65, 140.86, 164.74, 166.95, 176.30.

HRMS *m/z*: Calcd. for $C_{16}H_{17}NO_7$: 335.1005; Found: 335.1001.

Methyl 2-(3-hydroxy-1-(methyl 2-ethoxyacetate)-2-oxoindolin-3-yl)acrylate **148:**

Waxy solid; R_f (20% EtOAc-Hexane) 0.42.

IR (CH_2Cl_2): ν_{max} 3421, 1727, 1615, 1056 cm^{-1}.



148

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.28 (t, J = 7.2 Hz, 3H), 3.97 (bs, 1H), 3.65 (s, 3H), 3.79 (s, 3H), 4.25 (q, J = 7.2 Hz, 2H), 6.02 (s, 1H), 6.44 (s, 1H), 6.59 (s, 1H), 7.06-7.31 (m, 4H).

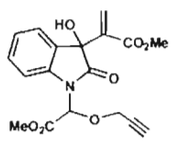
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 14.82, 52.07, 53.77, 62.44, 76.04, 79.67, 110.61, 123.57, 123.77, 127.81, 128.67, 130.43, 137.89, 141.52, 165.47, 166.94, 176.23.

HRMS *m/z*: Calcd. for $C_{17}H_{19}NO_7$: 349.1162; Found: 349.1155.

Methyl 2-(3-hydroxy-1-(methyl 2-(prop-2-ynyloxy)acetate)-2-oxoindolin-3-yl)acrylate **149:**

Waxy solid.;R_f (20% EtOAc-Hexane) 0.48.

IR (CH_2Cl_2): ν_{max} 3294, 2120, 1712, 1610, 1051 cm^{-1}.



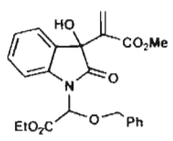
149

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.54 (t, *J* = 2.4 Hz, 1H), 3.57 (bs, 1H), 3.63 (s, 3H), 3.81 (s, 3H), 4.46 (d, *J* = 2.4 Hz, 2H), 6.24 (s, 1H), 6.57 (s, 1H), 6.62 (s, 1H), 7.07-7.13 (m, 2H), 7.19-7.34 (m, 2H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 22.31, 41.50, 52.19, 55.87, 62.70, 75.89, 77.89, 109.29, 111.46, 123.77, 124.13, 128.15, 130.34, 138.75, 140.77, 165.92, 176.14, 176.47.

HRMS *m/z*: Calcd. for $C_{18}H_{17}NO_7$: 359.1005; Found: 359.0996.

Methyl 2-(3-hydroxy-1-(methyl 2-(benzyloxy)acetate)-2-oxoindolin-3-yl)acrylate **150**:



150

Waxy solid; R_f (20% EtOAc-Hexane) 0.43.

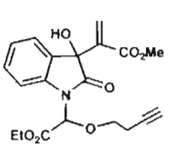
IR (CH_2Cl_2): ν_{max} 3396, 1717, 1084, 1065 cm^{-1};

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.19 (t, *J* = 7.17 Hz, 3H), 3.51 (s, OH), 3.64 (s,3H), 4.24 (q, *J* = 7.17 Hz, 2H), 4.72 (d, *J* = 11.8 Hz, 1H), 4.91 (d, *J* = 11.8 Hz, 1H), 6.03 (s, 1H), 6.44 (s, 1H), 6.64 (s, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.6 Hz 2H), 7.27-7.39 (m, 6H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 14.42, 52.57, 62.86, 70.68, 76.54, 112.27, 114.57, 124.41, 128.66 (2C), 128.81 (2C), 129.33 (2C), 130.71 (2C), 136.68, 141.56, 165.62, 167.22, 177.84.

HRMS *m/z*: Calcd. for $C_{21}H_{20}NO_5$: 366.1341; Found 366.1326.

Methyl 2-(3-hydroxy-1-(methyl 2-(but-3-ynyloxy)acetate)-2-oxoindolin-3-yl)acrylate **151**:



151

Waxy solid; R_f (20% EtOAc-Hexane) 0.46.

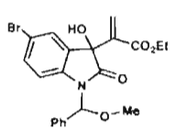
IR (CH_2Cl_2): ν_{max} 3388, 2210, 1718, 1615, 1087, 1064 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.24 (t, *J* = 7.20 Hz, 3H), 1.90 (t, *J* = 2.5 Hz, 1H), 3.56 (s, OH), 3.63 (s,3H), 4.13-4.28 (m, 4H), 6.01 (s, 1H), 6.54 (s, 1H), 6.62 (s, 1H), 7.06-7.29 (m, 4H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 13.96, 19.36, 31.57, 62.52, 66.92, 69.58, 76.04, 78.20, 80.17, 111.67, 123.60, 124.04, 128.05, 128.82, 130.30, 138.43, 140.93, 164.75, 165.98, 176.24.

HRMS *m/z*: Calcd. for $C_{18}H_{18}NO_5$: 328.1185; Found 328.1183.

Methyl 2-(5-bromo-3-hydroxy-1-(methoxy(phenyl) methyl)-2-oxoindolin-3-yl)acrylate **152**:



152

Waxy solid; R_f (20% EtOAc-Hexane) 0.39.

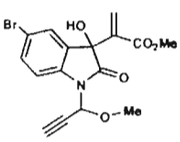
IR (CH_2Cl_2): ν_{max} 3382, 1717, 1085, 1057 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.23 (t, *J* = 7.3 Hz, 3H), 2.15 (s, OH), 3.66 (s, 3H), 4.09 (q, *J* = 7.3 Hz, 2H), 6.48 (s, 1H), 6.53 (s, 1H), 6.58 (s, 1H), 7.19-7.45 (m, 8H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 15.32, 52.10, 65.47, 70.51, 76.37, 110.30, 123.36, 124.28, 127.83 (2C), 128.15 (2C), 128.19 (2C), 128.74, 131.33, 137.46, 139.04, 143.03, 164.51, 175.56.

HRMS *m/z*: Calcd. for $C_{21}H_{20}BrNO_5$: 445.0525; Found 445.0517.

Methyl 2-(5-bromo-3-hydroxy-1-(1-methoxyprop-2-ynyl)-2-oxoindolin-3-yl)acrylate **153**:



153

Waxy solid; R_f (20% EtOAc-Hexane) 0.48.

IR (CH_2Cl_2): ν_{max} 3396, 2212, 1714, 1089, 1055 cm^{-1}.

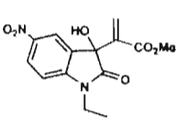
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.61 (d, *J* = 2.1 Hz, 1H), 3.48 (s, 3H), 3.61 (s, 3H), 3.79 (s, OH), 6.12 (d, *J* = 2.1 Hz, 1H), 6.38 (s, 1H), 6.43 (s, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.32 (d, *J* = 1.9 Hz, 1H), 7.46 (dd, *J* = 8.3, 1.9 Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 52.28, 55.89, 56.43, 72.33, 75.06, 75.88, 114.14, 116.35, 126.90, 128.57, 130.95, 132.88, 138.35, 139.48, 164.54, 175.30.

HRMS *m/z*: Calcd. for $C_{16}H_{14}BrNO_5$: 379.0055; Found 379.0043.

3.3.9. Spectral data for nitrated derivatives

Methyl 2-(1-ethyl-3-hydroxy-5-nitro-2-oxoindolin-3-yl) acrylate **144**:



144

Waxy solid; R_f (25% EtOAc-Hexane) 0.48.

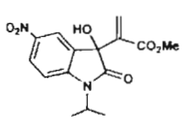
IR (CH_2Cl_2): ν_{max} 3348, 1706, 1611 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.32 (t, *J* = 7.23 Hz, 3H), 2.2 (bs, 1H), 3.62 (s, 3H), 3.77-3.9 (m, 2H), 6.58 (s, 1H), 6.67 (s, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 8.04 (d, *J* = 2.3 Hz, 1H), 8.31 (dd, *J* = 2.3 Hz, *J* = 8.6Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 12.05, 43.65, 52.31, 76.15, 109.64, 120.32, 122.26, 123.10, 128.67, 129.87, 144.46, 144.69, 164.83, 176.05.

HRMS *m/z*: Calcd. for $C_{14}H_{14}N_2O_6$: 306.0852; Found: 306.0841.

Methyl 2-(3-hydroxy-1-isopropyl-5-nitro-2-oxoindolin-3-yl)acrylate **155**:



155

Waxy solid; R_f (25% EtOAc-Hexane) 0.49.

IR (CH_2Cl_2): ν_{max} 3351, 1709, 1612 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.55 (d, *J* = 8.1 Hz, 6H), 3.47 (s, 1H), 3.63 (s, 3H), 4.58-4.63 (m, 1H), 6.56 (s, 1H), 6.67 (s, 1H), 7.1 (d, *J* = 8.7 Hz, 1H), 8.03 (d, *J* = 2.3 Hz, 1H), 8.28 (dd, *J* = 2.3, *J* = 8.7 Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 19.05 (2C), 43.26, 51.81, 75.85, 109.77, 122.36, 124.00, 127.64, 129.87 (2C), 140.46, 143.19, 164.83, 176.05.

HRMS *m/z*: Calcd. for $C_{15}H_{16}N_2O_6$: 320.1008; Found: 320.1008.

3.4. References

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Chapter IV

Part A

Stereoselective synthesis of 3-spiro α-methylene-γ-butyrolactone oxindoles from MBH adducts of isatin

Part B

A facile and efficient synthesis of functionalized γ-butyrolactones from MBH adducts of isatin

This part of work has been published in the following Journals

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Aust. J. Chem. **2007**, *60*, 296-301.

Chapter IV Part A

Stereoselective synthesis of 3-spiro α-methylene-γ-butyrolactone oxindoles from MBH adducts of isatin

4.1.1. Introduction

Oxindoles functionalized at C3 as spirolactones,[1-3] spirocyclicethers and spirocarbo- and heterocyclics are elegant targets in organic synthesis due to their significant biological activities.[5-7] These derivatives have been served as potential intermediates for the synthesis of alkaloids, drug intermediates and clinical pharmaceuticals.[5-7] A few examples of natural products having spirooxindole core structure are shown in Figure 1. Hence, a number of synthetic methods have been developed to expedition of this structural frameworks.[8-22]

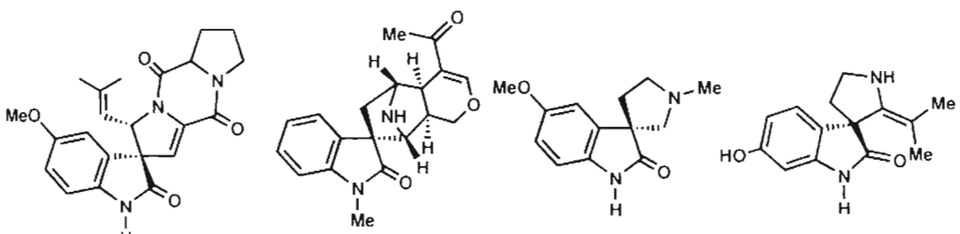


Figure 1

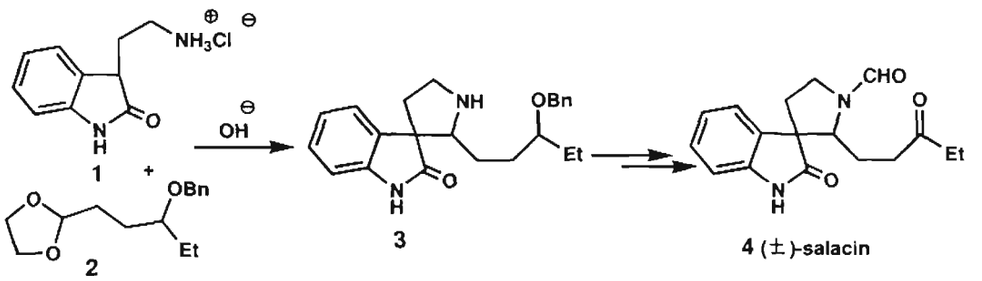
4.1.2. Few of the literature methods for synthesis of Spiro oxindole core structures

Many literature reports have been known for the synthesis of spirooxindole core structures, spirooxindole natural products and closely related compounds. Some of the representative examples are discussed in the following sub-sections.

4.1.2.1. Synthesis of (± -salacin

Salacin **4** was synthesised from oxytryptamine hydrochloride **1**. Condensation of amine **1** with acetal **2**, followed by intramolecular Mannich reaction afforded

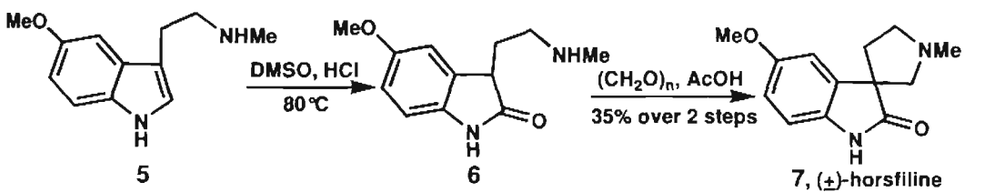
spiro[pyrrolidine-3,3-oxindole] **3**. From spiro[pyrrolidine-3,3-oxindole] **3**, (±)-salacin **4** was obtained in three steps (Scheme 1).[28]



Scheme 1

4.1.2.2 Synthesis of (±)-horsfiline

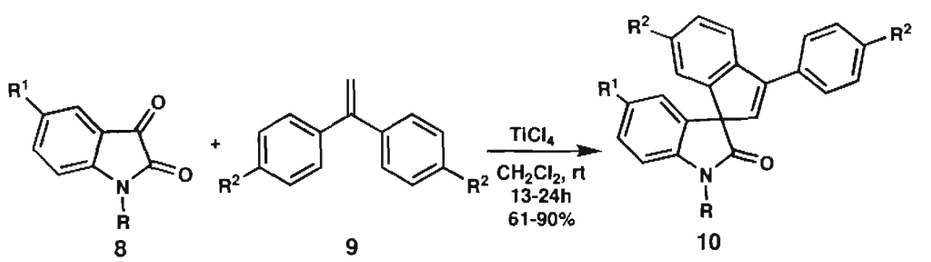
In 1994, Laronze *et al.* achieved the synthesis of horsfiline **7** through an intramolecular Mannich reaction by a spiro cyclization of tryptamine-oxindole **6** with formaldehyde (Scheme 2).[29]



Scheme 2

4.1.2.3 Synthesis of 3-spiro [3'-aryl-1H-indene] oxindoles

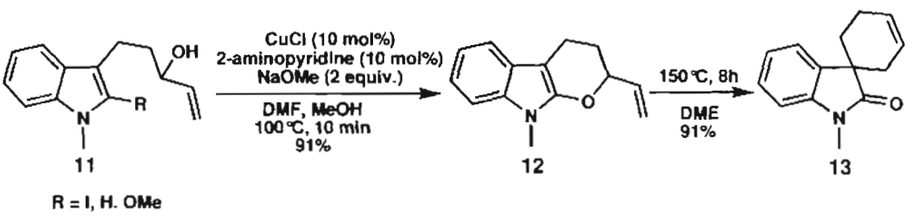
In 2007, Basavaiah *et al.* described a method to synthesis 3-spiro [3'-aryl-1H-indene] oxindole **10** following a tandem Prins and Friedel-Crafts reactions from isatin **8** and alkene **9** (Scheme 3).[8]



Scheme 3

4.1.2.4 Synthesis of spirocyclic oxindoles

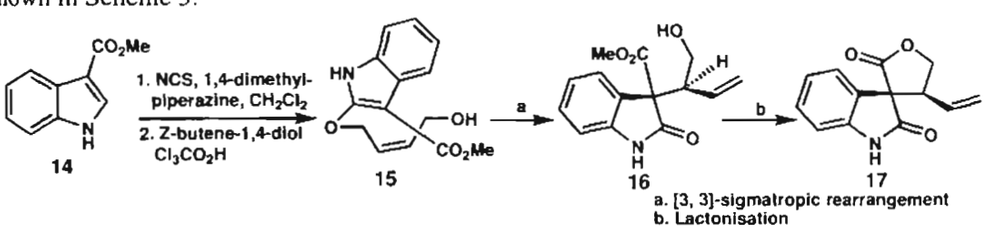
In 2006, Miyamoto *et al.* reported the synthesis of spirocyclic oxindole **13** through intramolecular Ullman coupling and Claisen rearrangement (Scheme 4).[9]



Scheme 4

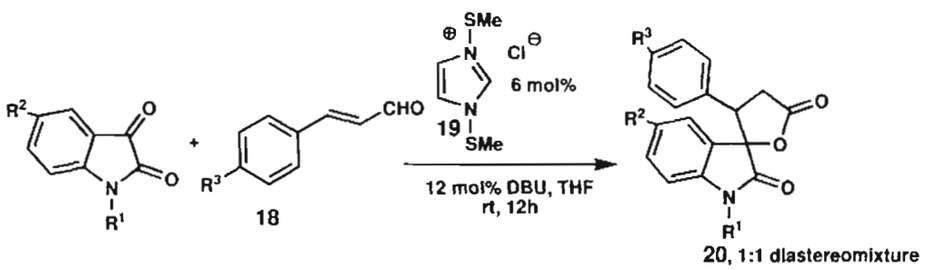
4.1.2.5 Synthesis of Spiro γ-butyrolactones

In 2000 Booker-Milburn *et al.* reported the synthesis of spiro oxindole-lactone **17**. The reaction proceeds via Claisen rearrangement of the indole derivative **14** to give the hydroxy ester derivative **16** which then undergoes spontaneous lactonisation to furnish γ-lactone **17** as shown in Scheme 5.[26]



Scheme 5

In 2006, Nair *et al.* reported that the nucleophilic heterocyclic carbene (NHC) **19** catalyzed annulation of enals and isatins gave 1:1 mixture of diastereomers of γ-spirolactone **20** (Scheme 6). [10]



Scheme 6

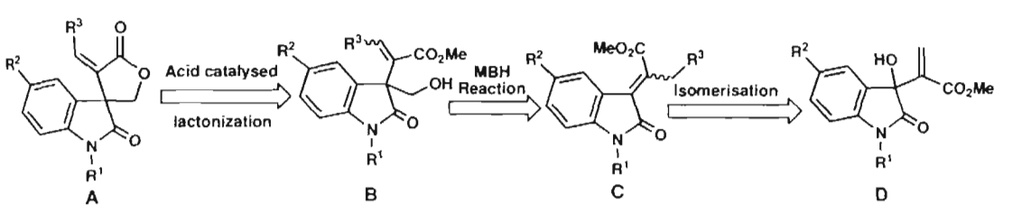
4.1.3 Objective of present work

Literature survey on the synthesis of spiro-oxindoles nucleus shows that oxindoles functionalized at C3 as spirolactones, spirocyclicethers and spirocarbo- and heterocyclics are elegant targets in organic synthesis due to their significant biological activities. These derivatives have been served as potential intermediates for the synthesis of alkaloids, drug intermediates and clinical pharmaceuticals. Although there are number of reports in construction of spiro-oxindole core structures as discussed in the above Schemes 1-6, the synthesis of 3-spiro-α-methylene-γ-butyrolactone oxindole from MBH adduct of isatin derivative is unknown. Hence, the synthesis and characterization of 3-spiro-α-methylene-γ-butyrolactone oxindoles from MBH adduct of isatin are subject matter of this chapter.

4.1.4 Results and Discussion

4.1.4.1 Retrosynthetic analysis

The target 3-spirolactone-oxindoles compounds were synthesized according to retrosynthetic analysis shown in Scheme 7. 3-spiro-α-methylene-γ-butyrolactone oxindoles **A** could be obtained from MBH adduct derivative **B** by an acid catalysed lactonization reaction. The MBH adduct derivative **B** could be obtained through a second MBH reaction with isomerised adducts of MBH adduct of isatin **C** and formaldehyde. The isomerised adduct **C** could be prepared by isomerisation reaction of MBH adducts of isatin **D** with trimethyl orthoformate/Ar-H and a solid acid clay catalyst.

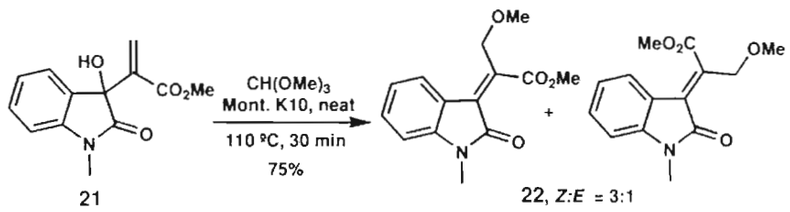


Scheme 7

4.1.4.2 Isomerisation of MBH adducts with trimethyl orthoformate

As per the retrosynthetic analysis, the starting material methoxy derived MBH adduct was prepared as shown in Scheme 8. Accordingly, the reaction of MBH adduct of *N*-methylisatin **21** with excess of trimethyl orthoformate and montmorillonite K10 clay[30-33] as a

catalyst at 110 °C for 0.5 h afforded a 1:3 mixture of *E*- and *Z*- isomers **22** in excellent overall yield (75%).



Scheme 8

The *E*- and *Z* - isomers were inseparable by column chromatography. However, the ratio and distinction of *E* and *Z* isomers were determined based on ^{1}H NMR study. The chemical shifts of methylene protons which is attached with -OMe and olefinic bond of the mixture compound **22** was the key in distinguishing *E*- and *Z*- isomers.

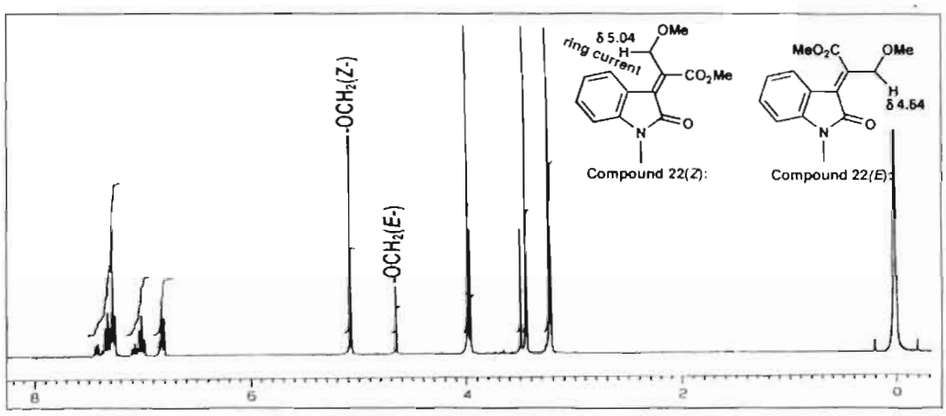


Figure 2 ^{1}H NMR Spectrum of compound **22**(*Z* and *E*, 3:1)

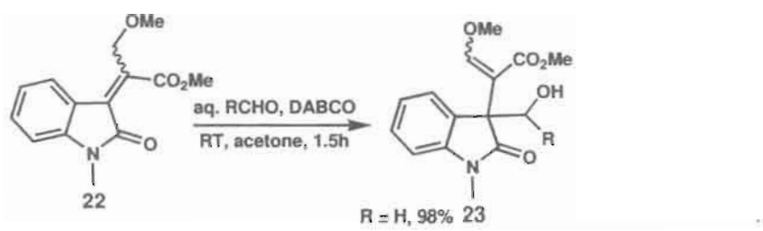
Thus, the methylene protons of *E*-isomer appeared as a singlet at δ 4.64 (peak intensity integrating for 2 protons) whereas Z-isomer showed the methylene peak at δ 5.04 (peak intensity integrating for 0.6 protons) due to ring current of aryl ring (deshielding zone) as shown in Figure 2.

4.1.4.3. Second MBH adduct formation from compound 22

The column purified *E*:*Z* mixture **22** in acetone was subjected to a second MBH adduct formation with 40% aqueous formaldehyde and 1.5 equiv. DABCO at room temperature for 2h to afford adduct **23** in excellent yield (98%). In order to obtain various second MBH adduct **23** (analogs) with various aldehydes, we attempted reactions as shown in

Table 1. To our surprise, attempts to form the second MBH adduct from the isomerised compound **22** with benzaldehyde, *p*-chloro benzaldehyde, *p*-nitrobenzaldehyde, acetaldehyde, heptanaldehyde and *E*-crotonaldehyde (Table 1, entries 1-7) under optimized condition failed. The negative reactions with aldehydes other than formaldehyde can be rationalised due to steric factor at C-3 carbon of isomerised adduct **22**. However, we preceded further investigation with formaldehyde derived second MBH adduct **23** for lactonisation.

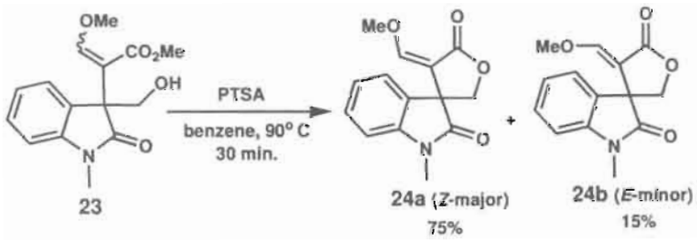
Table 1



Entry	R	% yield of **23**
1	H	98
2	Ph	-
3	p-Cl-C_6H_4-	-
4	p-NO_2-C_6H_4-	-
5	CH_3	-
6	CH_3-$(CH_2)_5$-	-
7	CH_3CH=CH-	-

4.1.4.4. Spiro lactonisation

Subsequent to the synthesis of second MBH adduct **23**, we undertook lactonization with *p*-toluenesulfonic acid (PTSA) as shown in Scheme 9. Thus, exposure of the compound **23** in benzene with PTSA under reflux condition for 30 min. furnished excellent combined yield of 3-spiro-α-methylene-γ-butyrolactone oxindoles **24a** (*Z*- isomer-major, 75%) and **24b** (*E*-isomer-minor, 15%) and the compounds were separated by silica gel column chromatography.



Scheme 9

4.1.4.5. Characterization of 3-spiro-α-methylene-γ-butyrolactone oxindoles 24a and 24b

The structures of spirolactones **24a** and **24b** were arrived based on systematic analysis using modern spectroscopic techniques. The lactone and amide carbonyl functional groups were confirmed in IR spectroscopy with absorption bands at 1753 cm^{-1} (lactone carbonyl) and 1714 cm^{-1} (amide carbonyl). The geometry of compounds **24a** and **24b** was assigned by the analysis of chemical shifts of vinylic olefin protons in ^1H NMR spectra. Accordingly, the Z-vinyl proton of major isomer **24a** was observed as a singlet at δ 7.27 where as *E*-vinyl proton of minor isomer **24b** observed at δ 6.14 as a singlet. The remaining aliphatic and aromatic region of the compounds **24a** and **24b** appeared as similar pattern with slight difference in the δ values. Thus, in the compound **24a**, two singlet signals at δ 3.26 and 3.67 were assigned for -NMe and -OMe protons. Further, the methylene protons in the lactone ring appeared as two separate doublets at δ 4.34 and δ 4.59 with a coupling constant J = 8.8Hz. The remaining four aromatic protons were resonated at δ 6.86 (as a doublet with coupling constant J = 7.8Hz), 7.09 (as a triplet with coupling constant J = 7.5Hz), 7.22 (as a doublet with coupling constant J = 7.4Hz), and 7.32 (as a triplet with coupling constant J = 7.7Hz) (Figure 3).

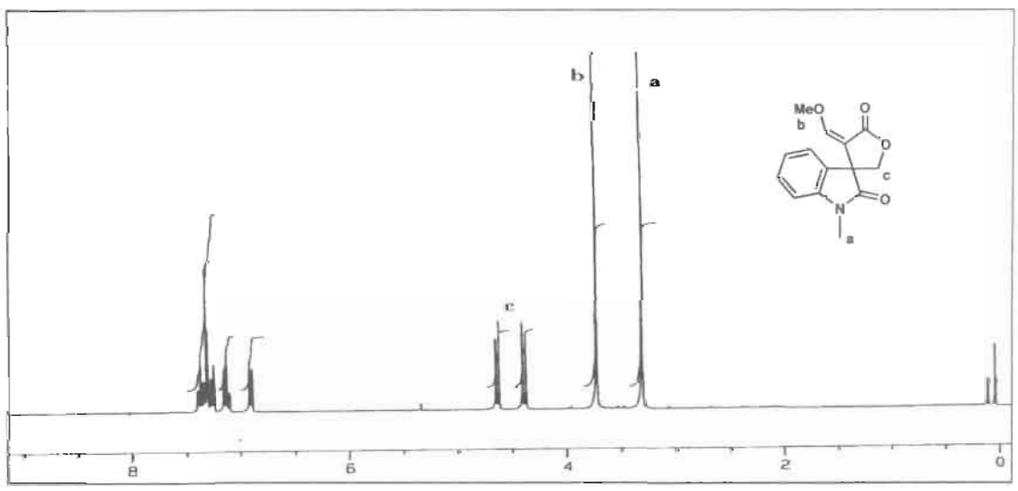


Figure 3 ^1H NMR Spectrum of compound **24a**

In ^{13}C NMR spectrum of the compound **24a**, the quaternary spiro carbon resonated at δ 52.8. The lactone and amide carbonyl carbons appeared at δ 170.8 and 175.2 (Figure 4).

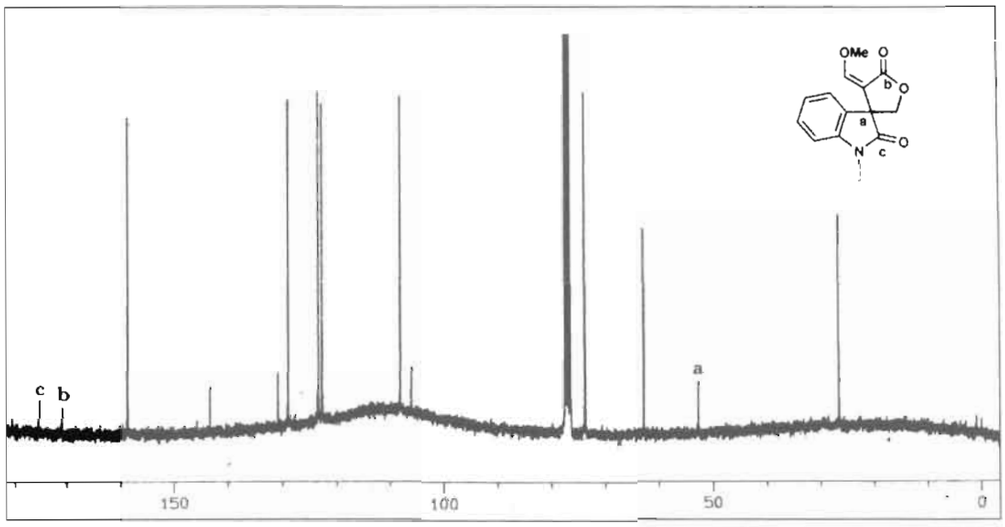


Figure 4 ^{13}C NMR Spectrum of compound **24a**

Further, the mass spectrum (HRMS) of compound **24a** (Figure 5) showed molecular ion peak at m/z = 259.0859 (Calcd. for $C_{14}H_{13}NO_4$: 259.0845).

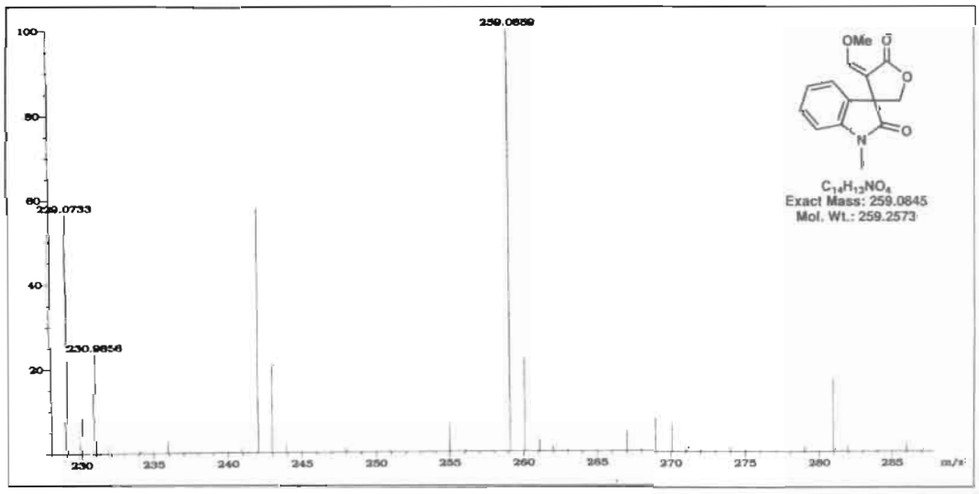


Figure 5 Mass spectrum (HRMS) of compound **24a**

Similarly, in the IR spectrum of minor isomer **24b**, absorption bands at 1755 and 1704 cm^{-1} confirmed the presence of lactone and amide carbonyl functional groups respectively. The ^1H NMR spectrum of minor isomer **24b** showed as discriminate singlet signals at δ 3.24 and δ 3.82 for the presence of the *N*-Me and -OMe protons. The lactone methylene protons

appeared as two well separated doublet signals at δ 4.29 and δ 4.55 with a coupling constant *J* = 8.8Hz (Figure 6).

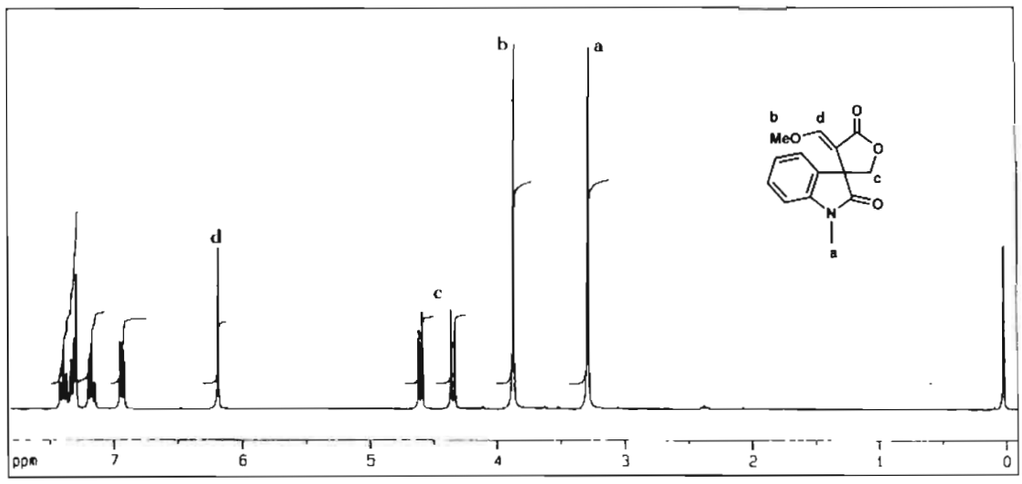


Figure 6 ^{1}H NMR Spectrum of compound **24b**

^{13}C NMR spectrum of compound **24b** had a peak at δ 53.1 for spiro carbon centre. The characteristic carbonyl signals due to the lactone and amide groups were seen clearly at δ 167.2 and 176.5. Rest of the peaks were consistent with assigned structure (Figure 7).

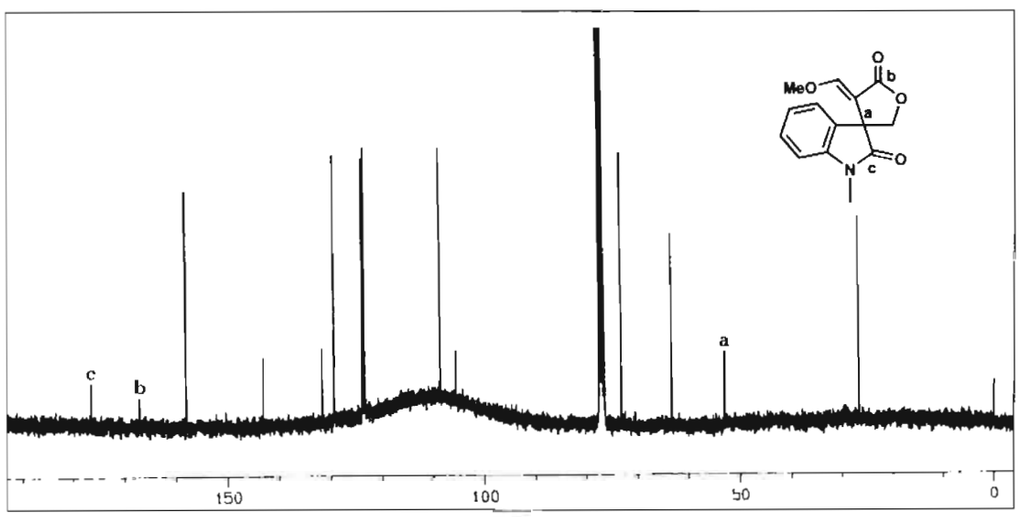


Figure 7 ^{13}C NMR Spectrum of compound **24b**

A concrete evidence for the structure and geometry of the lactones **24a** and **24b** was finally confirmed by a single crystal X-ray analysis (Figure 8)[34].

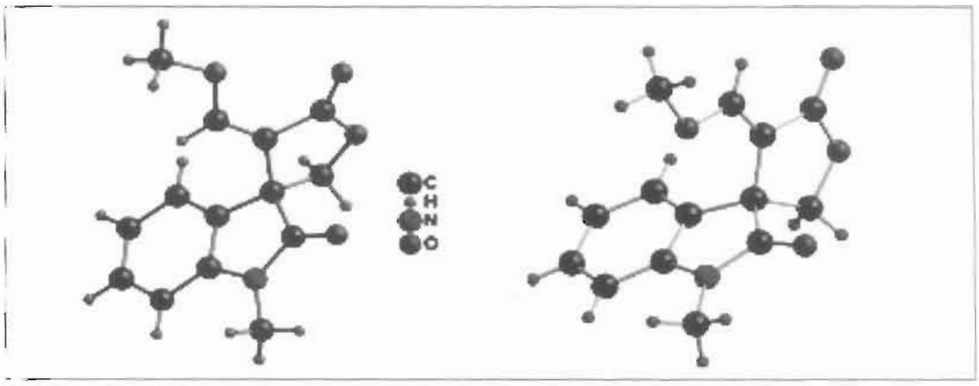
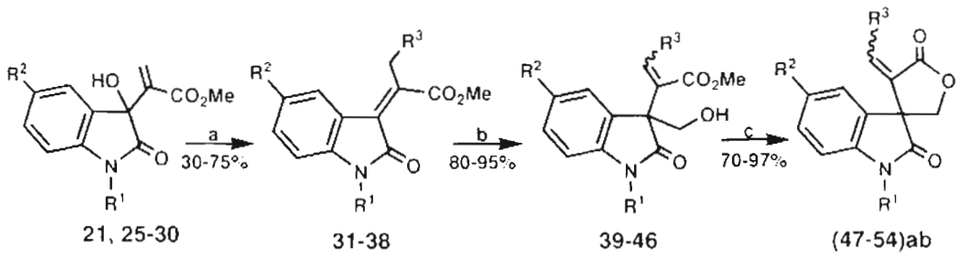


Figure 8 X- Ray crystal structure of spirolactone oxindoles **24a** and **24b**

4.1.4.6. Generality for spiro-α-methylene-γ-butyrolactone oxindoles

Encouraged by preliminary results, we then turned our attention to generalize the synthesis of spiro-α-methylene-γ-butyrolactone oxindoles with a number of MBH adducts of isatin substituted at aryl and *N*-alkyl positions as shown in Scheme 10.



R^1= Me, Et, Propargyl, Bz, Allyl, CO_2Me; R^2=H, Br; R^3= OMe, Ph, O-Propargyl
a. $CH(OMe)_3$ (or) Ar-H (or) propargyl alcohol/Mont. K10, neat, 110 °C, 30 min.
b. aq. HCHO, DABCO, acetone, RT, 2 h; c. PTSA/benzene, 80 °C, 30 min.

Scheme 10

Hence, we first prepared methoxy isomerised MBH derivatives **31-36** from various MBH adduct. The MBH adducts of isatin substituted at aryl and *N*-alkyl positions **25-30** with trimethyl orthoformate, and montmorillonite K10 clay catalyst at 110 °C for 1.5 h afforded the corresponding isomerised compounds **31-36** in moderate to good yields (Table 2, entries 1-6). The isomerisations of MBH adduct **21** with propargyl alcohol and benzene afforded the corresponding isomerised compounds **37** and **38**. It should be noted that the isomerisation reaction with benzene provided poor yield (30%) of compound **38** (Table 2, entry 8). However, the isomerisation with propargyl alcohol furnished very good yield of **37** (68%, Table 2, entry 7).

In continuation of the target compound synthesis, the second MBH adduct formation from isomerised derivatives **31-38** with aqueous formaldehyde and DABCO in acetone were performed and the reactions underwent smoothly to afford corresponding second MBH adducts **39-46** in very good to excellent yields. The formation of second MBH adduct was confirmed based on ^{1}H NMR analysis. Hence, one of the second MBH adducts **40** was analyzed in ^{1}H NMR which established the structure of **40** unambiguously. Thus, a broad singlet at δ 2.0 was found due to hydroxy proton. Two singlets at δ 3.49 and 3.92 were appeared due to methoxy protons. All other protons were seen as expected and the spectrum is reproduced in Figure 9.

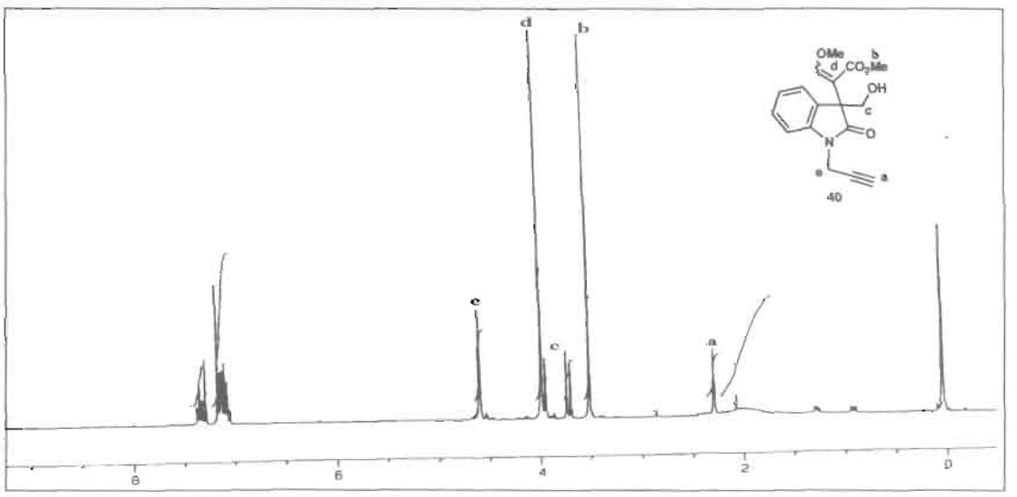
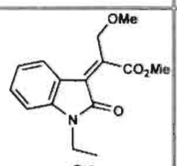
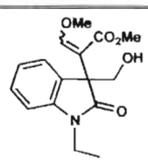
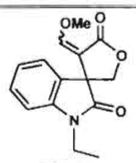
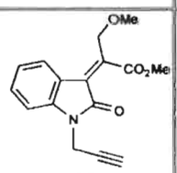
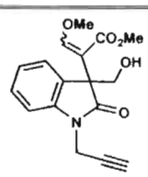
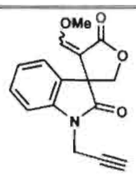
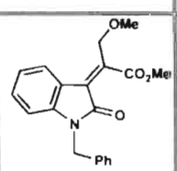
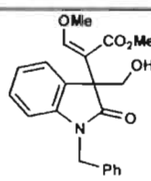
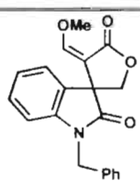
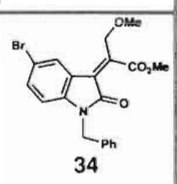
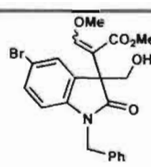
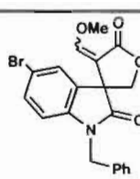
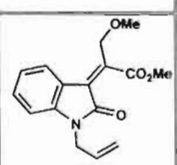
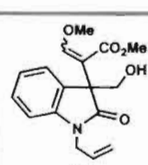
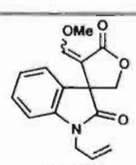
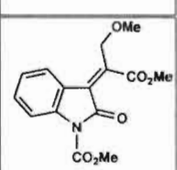
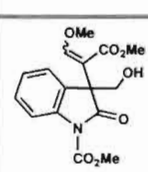
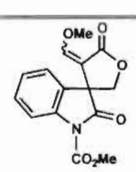
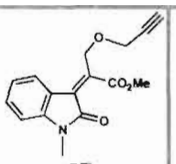
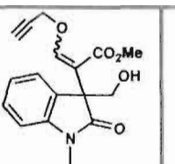
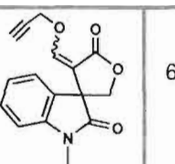
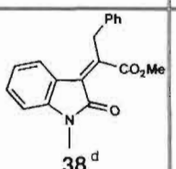
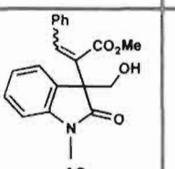
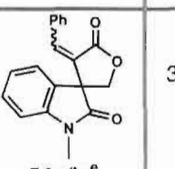


Figure 9 ^{1}H NMR Spectrum of compound **40**

Subsequent to the second MBH adduct formation, lactonization of the silica gel column purified compounds **39-46** in benzene using PTSA were performed and the results are collected in Table 2. The second MBH adduct **39** upon lactonization using PTSA afforded *Z*- and *E*-isomers of 3-spiro α-methylene-γ-butyrolactone-*N*-ethyl oxindole **47a/b,** separable by column chromatography, in excellent combined yield (Table 2, entry 1). Similarly, under optimized conditions, highly functionalized second MBH adducts of *N*-propargyl and *N*-benzyl isatin derivatives **40** and **41** afforded 3-spiro α-methylene-γ-butyrolactone-*N*-propargyl and benzyl oxindole **48a/b** and **49a** respectively in excellent yield (Table 2, entries 2 and 3).

Table 2

Entry	MBH adduct	Products			Yield %[b]		
		Isomerised Product (A)	Second MBH adduct (B)	Lactone Product[a] (C)	(A)	(B)	(C) (*Z*:*E*)[c]
1	**25**	 **31**	 **39**	 **47a/b**	63	97	90 (2:1)
2	**26**	 **32**	 **40**	 **48a/b**	65	93	80 (1:0.2)
3	**27**	 **33**	 **41**	 **49a**	75	95	95
4	**28**	 **34**	 **42**	 **50a/b**	60	98	70 (1:0.3)
5	**29**	 **35**	 **43**	 **51a/b**	67	97	77 (1:0.7)
6	**30**	 **36**	 **44**	 **52a/b**	57	80	67 (2:1)

7	**21**	 **37**	 **45**	 **53a/b**	68	96	84 (2:1)
8	**21**	 **38** [d]	 **46**	 **54a/b** [e]	30	95	97 (1:0.6)

[a]Separable by column chromatography. [b]Yield/ratio was determined after column purification & ^{1}H NMR. [c]Stereochemistry was assigned based on ^{1}H NMR and single crystal X-ray studies. [d]combined yield of the mixture **38** from **21** for 12h was only 30%. [e]Inseparable by column chromatography.

The bromo derivative **42** upon lactonization furnished spirolactones **50a/b** in very good yield (Table 2, entry 4). Likewise, the *N*-allyl compound **43** furnished the corresponding lactone derivatives **51a/b** in good yield (Table 2, entry 5). The MBH adducts bearing carbo methoxy functional group at *N*-H position **44** also furnished the desired spiro lactone **52a/b** in 67% combined yield (Table 2, entry 6). Similarly, the second MBH adducts **45** and **46** upon lactonization using PTSA furnished the corresponding spirooxindole lactone derivatives **53a/b** and **54a/b** in excellent combined yield (Table 2, entries 7 and 8). All the *Z*:*E* isomers of spirolactone compounds **47a/b-53a/b** were separable by column chromatography and thoroughly characterized by spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR and HRMS).

4.1.4.7. Characterization of spiro-α-methylene-γ-butyrolactone oxindoles

4.1.4.7.1. Characterization of major *Z*-isomer 47a

The structure of *N*-ethyl derivative of major Z-isomer of spirolactone **47a** was confirmed by usual spectroscopic techniques. The IR spectrum of **47a** showed the lactone and amide carbonyl absorption bands at 1750 and 1715 cm^{-1} respectively. Its ^{1}H NMR spectrum was very clear. The presence of *N*-ethyl group confirmed from a triplet signal at δ 1.27 with coupling constant J = 7.1Hz and a multiplet at δ 3.85. The methylene protons in the lactone ring appeared as two doublets at δ 4.35 and δ 4.59 with a coupling constant J = 8.8Hz. The

presence of aromatic and olefinic protons were found in the chemical shift range δ 6.87-7.34 integrating five protons (Figure 10).

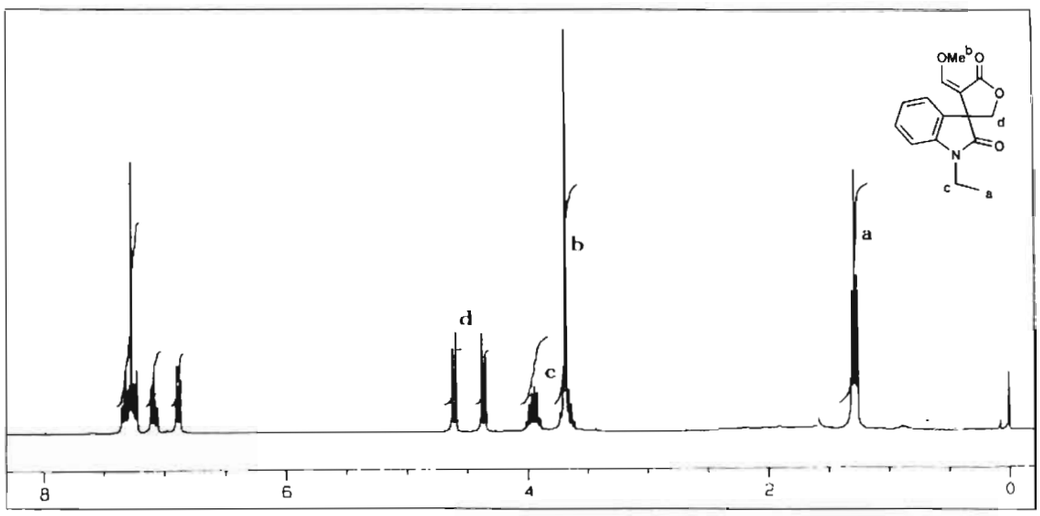


Figure 10 ^{1}H NMR Spectrum of compound **47a**

In the ^{13}C NMR of compound **47a**, carbon signal due to spirocentre resonated at δ 52.9. The quarternary carbon signals in the compound were visible at δ 106.7 and 131.2, 142.4 due to olefinic and aromatic quaternary carbons. The lactone and amide carbonyl carbons displayed signals at δ 170.71 and δ 174.6 (Figure 11). The mass spectrum (HRMS) isomer **47a** (calcd. for $C_{15}H_{15}NO_4$: 273.1001) showed a molecular ion peak at m/z = 273.1006.

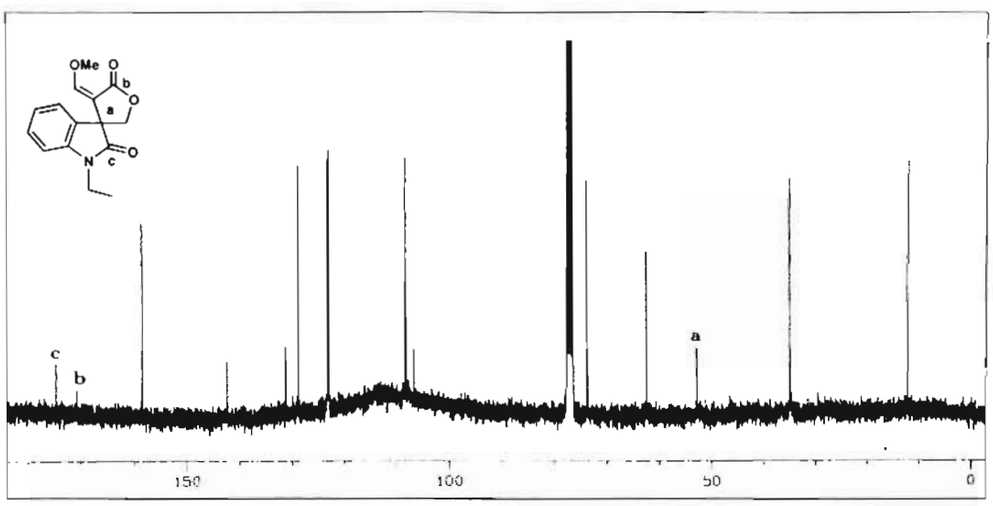


Figure 11 ^{13}C NMR Spectrum of compound **47a**

4.1.4.7.2. Characterization of minor *E*-isomer 47b

Similarly, the IR spectrum of minor *E*-isomer **47b** showed carbonyl absorption at 1755 and 1715 cm^{-1} due to the presence of lactone and amide functional groups. Its ^1H NMR displayed the presence of *N*-ethyl group as a triplet and a quartet at δ 1.30 and 3.77 respectively with coupling constant J = 7.1Hz. The methylene protons of lactone ring occurred as two separate doublets at δ 4.31 and 4.56 with coupling constant J = 8.8Hz. The olefinic proton having *E*-geometry appeared as a singlet at δ 6.13 . All other protons were consistant with assigned structure (Figure 12).

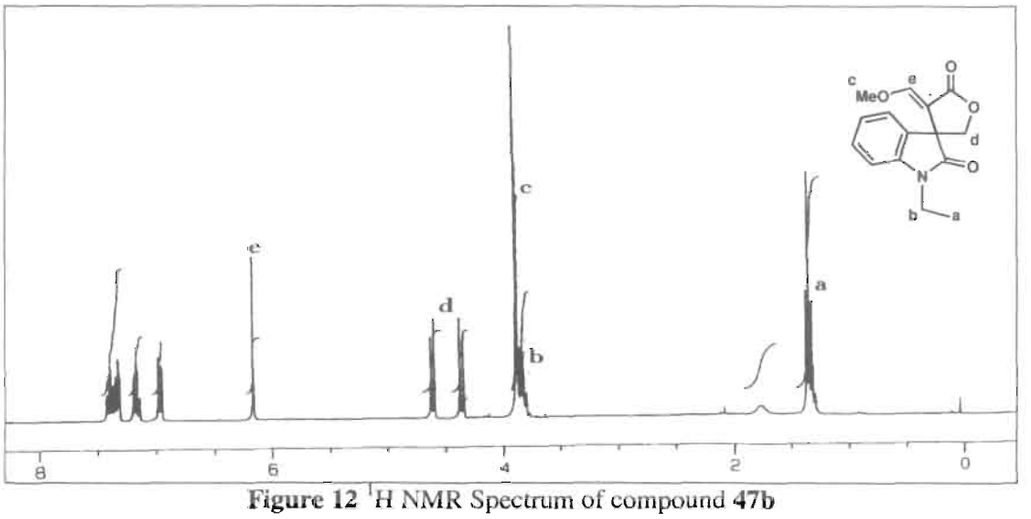


Figure 12 ^1H NMR Spectrum of compound **47b**

The ^{13}C NMR spectrum of lactone **47b** is shown in Figure 13. The quaternary spiro carbon resonated at δ 53.0 and olefinic and aromatic quaternary carbons appeared at δ 105.8, 131.8 and 142.1. The lactone and amide carbonyls appeared at δ 167.1 and 176.1. The mass spectrum (HRMS) of isomer **47b** (Calcd. for $C_{15}H_{15}NO_4$: 273.1001) showed a molecular ion peak at m/z = 273.1003 which confirms the assigned structure.

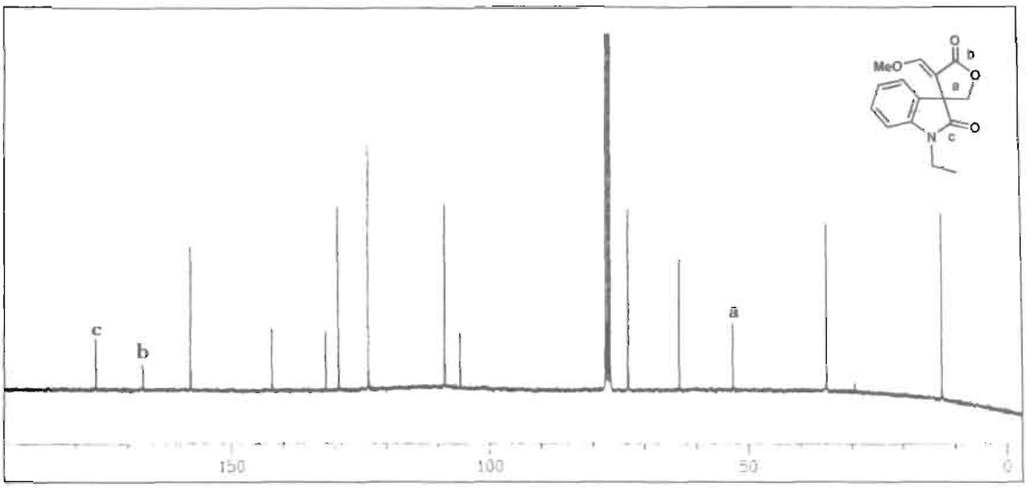


Figure 13 ^{13}C NMR Spectrum of compound **47b**

4.1.4.7.3. Characterization of major *Z*-isomer 50a

In IR spectrum of the major isomer of 5-bromo derivative of spirolactone **50a**, the significant lactone and amide carbonyl absorptions were found at 1744 and 1722 cm^{-1} respectively. The ^1H NMR spectrum was very clear and showed all the charactarestic signals. Thus, a singlet signal was found at δ 3.66 for –OMe protons. The presence of lactone ring and *N*-benzyl methylene protons were observed at δ 4.37-5.22 and the aromatic protons occurred in the chemical shift range δ 6.62-7.34 (Figure 14).

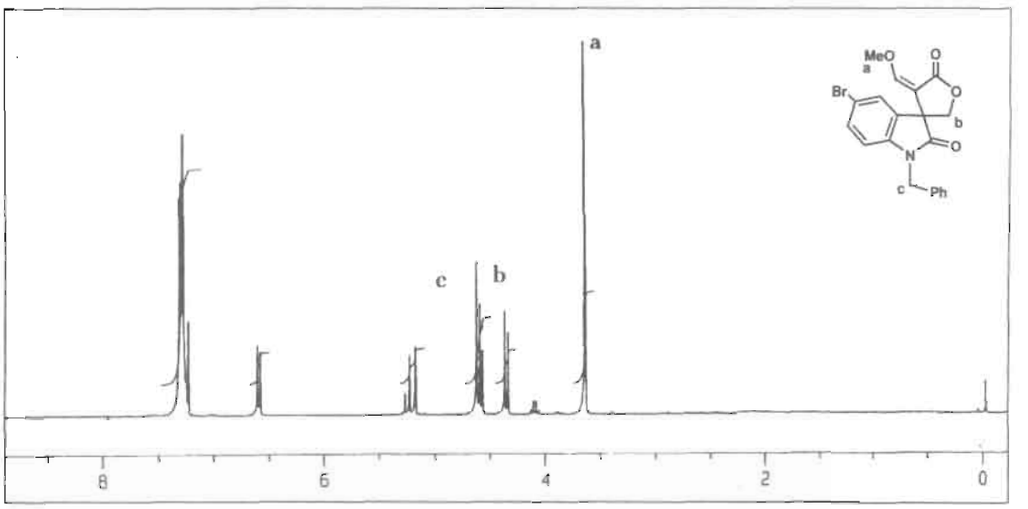


Figure 14 ^1H NMR Spectrum of compound **50a**

In the ^{13}C NMR spectrum, the spiro centre was resonated at δ 52.9. The five quaternary carbons present in the aromatic and olefinic carbons were clearly occurred in the chemical shifts at δ 105.8, 116.1, 132.9, 135.1 and 141.5. The carbonyl carbons were seen at δ 170.4 and 174.9 (Figure 15).

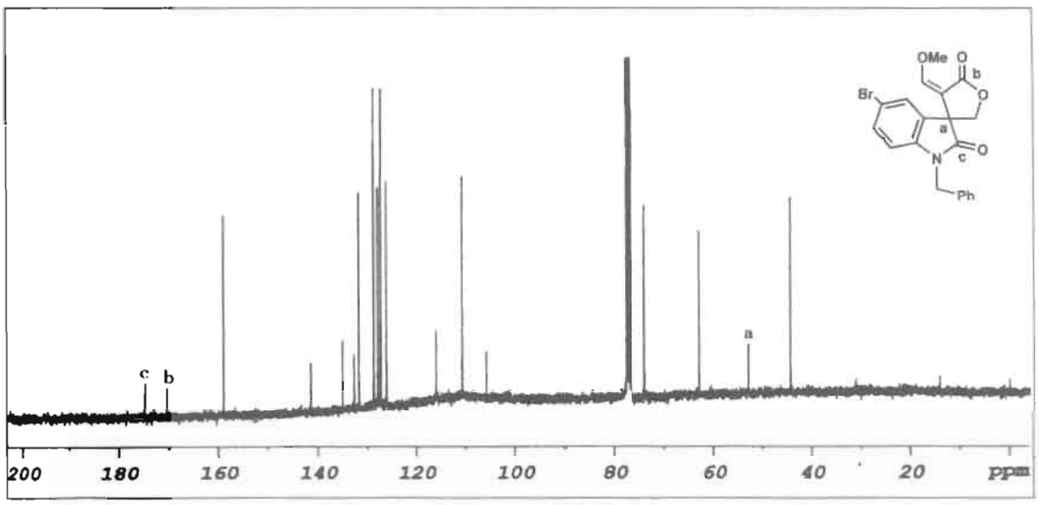


Figure 15 ^{13}C NMR Spectrum of compound **50a**

4.1.4.7.4. Characterization of minor *E*-isomer 50b

Simlarly, the IR spetrum of minor isomer **50b** showed the absorption bands due to spirolactone and amide carbonyl groups at 1751 and 1712 cm^{-1} respectively. The ^{1}H NMR spectrum was neat. A singlet was found at δ 3.85 due to –OMe protons. The methylene protons in the lactone ring were appeared as two well seperated doublets at δ 4.34 and 4.62 with coupling constant J = 8.9Hz. The benzylic methylene protons were found as closely occurring doublets at δ 4.84 and 4.94 with coupling constant J = 5.4Hz. The olefinic proton was appeard as a singlet at δ 6.11. The aromatic protons were seen around δ 6.70-7.41 (Figure 16).

In the ^{13}C NMR spectrum of **50b**, the spiro carbon centre was found at δ 53.1. The carbonyl carbons were resonated at δ 176.6 and 178.4 (Figure 17). Finally, the mass spectrum of the product **50b** (HRMS) confirmed with a m/z peak at 413.0263 (Calcd. for $C_{20}H_{16}BrNO_4$: 413.0263).

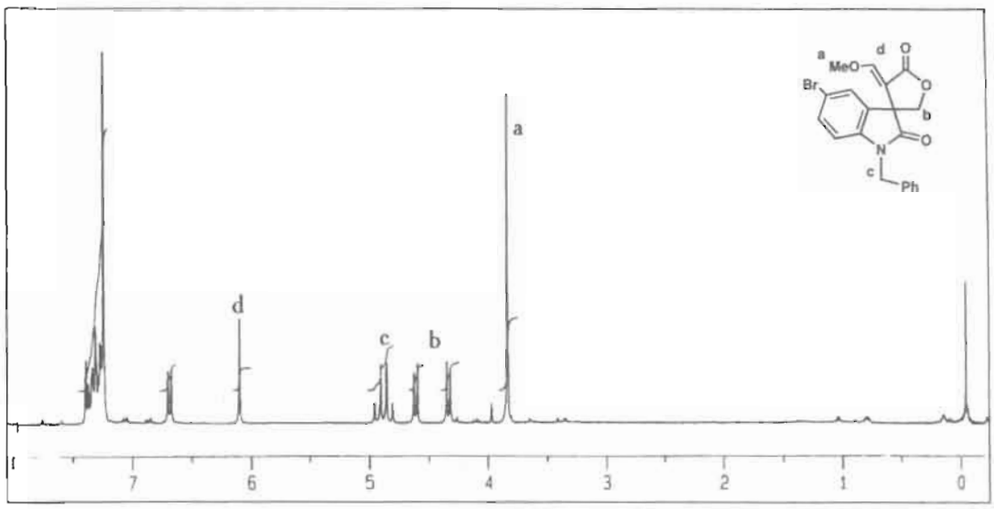


Figure 16 ^{1}H NMR Spectrum of compound **50b**

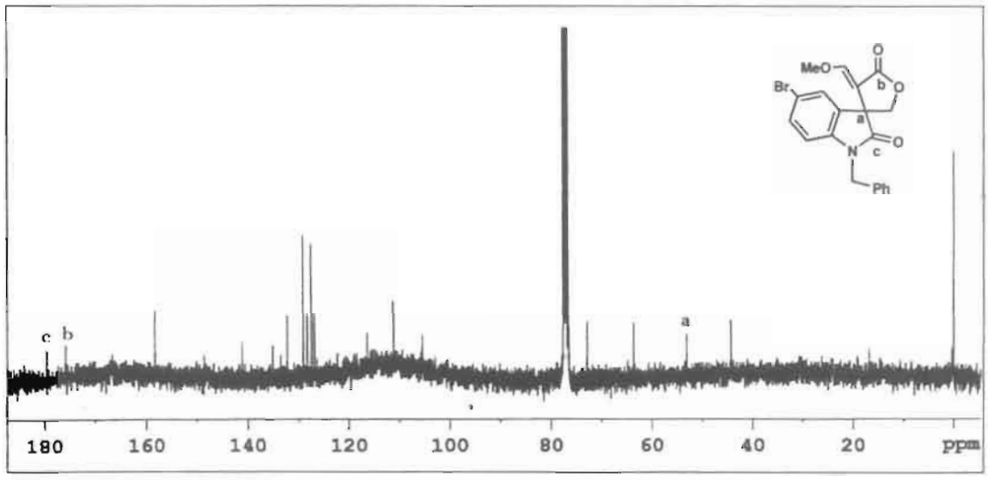


Figure 17 ^{13}C NMR Spectrum of compound **50b**

4.1.4.7.5. Characterization of major *Z*-isomer 51a

The *N*-allyl derivative of spirolactone **51a** (*Z*-major) showed the expected lactone and amide carbonyl absorptions at 1752 and 1714 cm^{-1} respectively. The ^{1}H NMR spectrum is shown in Figure 18. The ester methyl appeared as a singlet at δ 3.68. The protons due to allyl group and lactone methylene displayed their chemical shift in the range between 4.18-5.85 as multiplet signals.

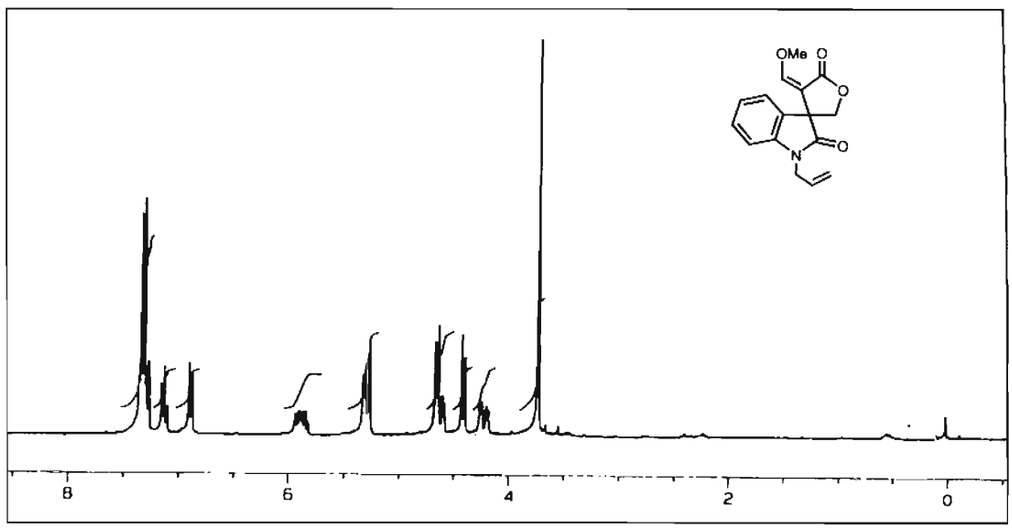


Figure 18 ^{1}H NMR Spectrum of compound **51a**

In its ^{13}C NMR, a signal due to the presence of spiro carbon appeared at δ 52.7. The presence of two carbonyl carbones were visible at δ 170.7 and 174.8. All other carbons were seen as expected and the spectrum is reproduced in Figure 19. The mass spectram (HRMS) had a m/z peak at 285.0992 confirming the calculated molecular mass (Calcd. for $C_{16}H_{15}NO_4$: 285.1001).

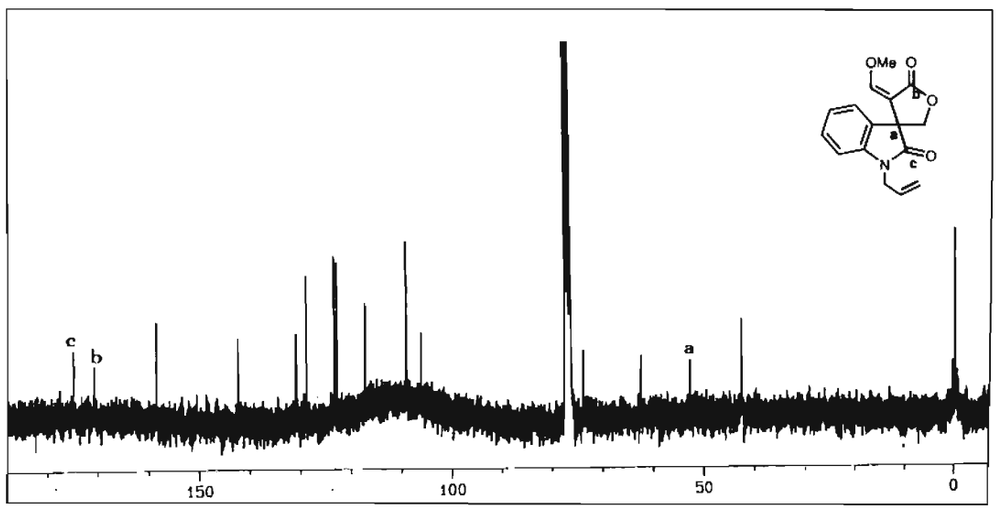
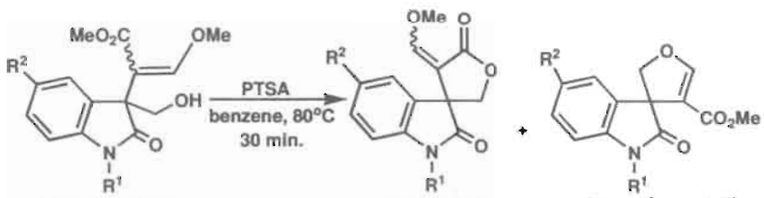


Figure 19 ^{1}H NMR Spectrum of compound **51a**

4.1.5. Synthesis of 3-spirodihydrofuran-*N*-alkyl oxindoles

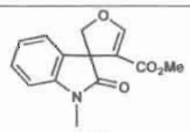
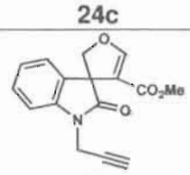
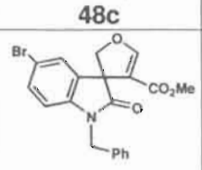
During the course of lactonization of second MBH adducts **23**, **40** and **42** with *p*-toluenesulfonic acid in benzene, in addition to the desired lactone products **24a/b**, **48a/b** and **50a/b,** a minor amount of spirofuran oxindole derivatives (<10%) **24c**, **48c** and **50c** were also isolated. The synthetic transformation and results are shown in Table 3.

Table 3



23, **40** and **42** — **24a/b**, **48a/b** and **50a/b** + **24c**, **48c** and **50c**

R^1=Me, Propargyl and Bn; R^2=H, Br

Entry	Substrate	Product		Yield (%)	
		Lactone (A)	Furan (B)	(A)	(B)
1	**23**	**24a/b**	 **24c**	90	8
2	**40**	**48a/b**	 **48c**	80	7
3	**42**	**50a/b**	 **50c**	70	9

4.1.5.1. Characterization of 3-spirodihydrofuran oxindoles

The structures of 3-spirodihydrofuran compounds were established unambiguously using FTIR and ^{1}H NMR, ^{13}C NMR and mass spectroscopic studies. Thus, in the IR spectrum of compounds **24a/24b**, the lactone and amide carbonyl absorptions were observed at 1753, 1714 and 1755, 1704 cm^{-1}, respectively. However, the FTIR spectrum of compound **24c**

showed only a merged amide and ester carbonyl absorption at 1714 cm^{-1}. Due to the absence of lactone carbonyl absorption at ~1755 cm^{-1} for compound **24c**, the structure was assumed and assigned as 3-spirodihydrofuran **24c**.

Further structural evidence was arrived from the ^1H NMR spectrum of compound **24c**. Accordingly, the olefinic proton in the spiro dihydrofuran ring appeared as a singlet at δ 7.58, the ester -OMe appeared as a singlet at δ 3.53 where as in the spirolactone **24a/24b**, the olefinic proton appeared at δ 7.27/6.14 and -OMe substituent in exocyclic double bond appeared at δ 3.67 and 3.82, respectively (Figure 20). A final proof was arrived based on mass spectrum (HRMS) with m/z peak at 259.0842(Calcd. for $C_{14}H_{13}NO_4$: 259.0845).

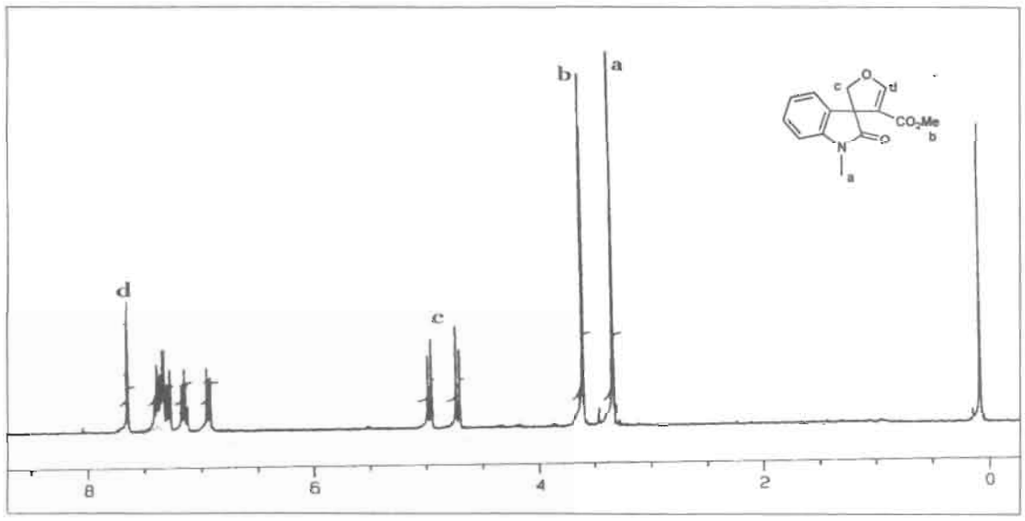


Figure 20 ^1H NMR Spectrum of compound **24c**

Similarly, the structure of spirofuran derivative **50c** was arrived based on spectroscopic analysis. Thus, in IR spectrum of **50c**, the ester and amide carbonyl functional groups were identified due to the merged absorption band at 1717 cm^{-1} and the absence of lactone absorption around 1750 cm^{-1} was observed. Further, the ^1H NMR had a singlet signal due to ester -OMe at δ 3.53. The methylene protons existing in furan ring appeared as two doublet peaks at δ 4.66 and 4.95 with coupling constant J = 9.6Hz. The benzylic methylene protons were seen as two doublets at δ 4.77 and 5.11 with coupling constant J = 15.8Hz (Figure 21).

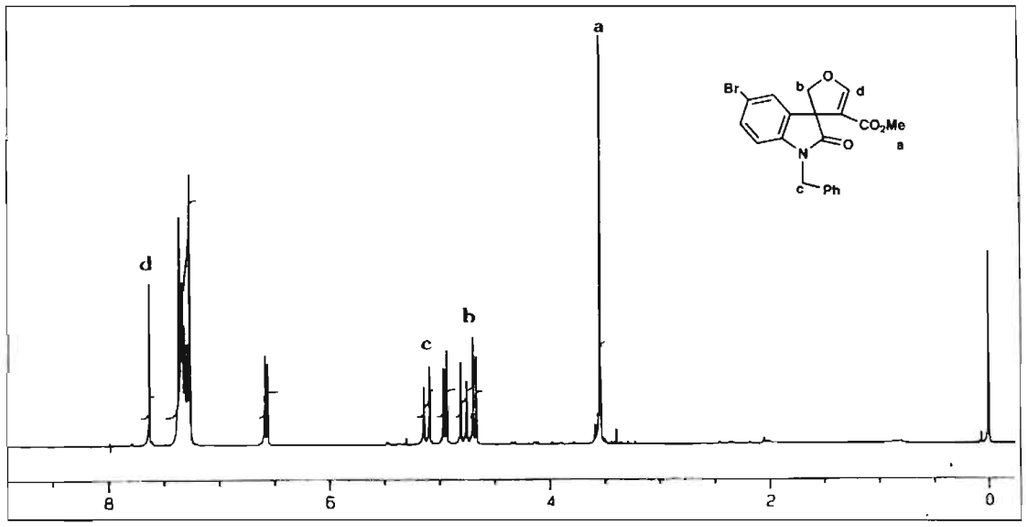


Figure 21 ^{1}H NMR Spectrum of compound **50c**

In the ^{13}C NMR spectrum, the spirocarbon resonated at δ 57.0. The presence of two carbonyl carbons showed down field carbon signals at δ 163.0 and 176.8 (Figure 22). The mass spectrum (HRMS) of spirofuran derivative **50c** showed a m/z peak at 413.0254 (Calcd. for $C_{20}H_{16}BrNO_4$: 413.0263).

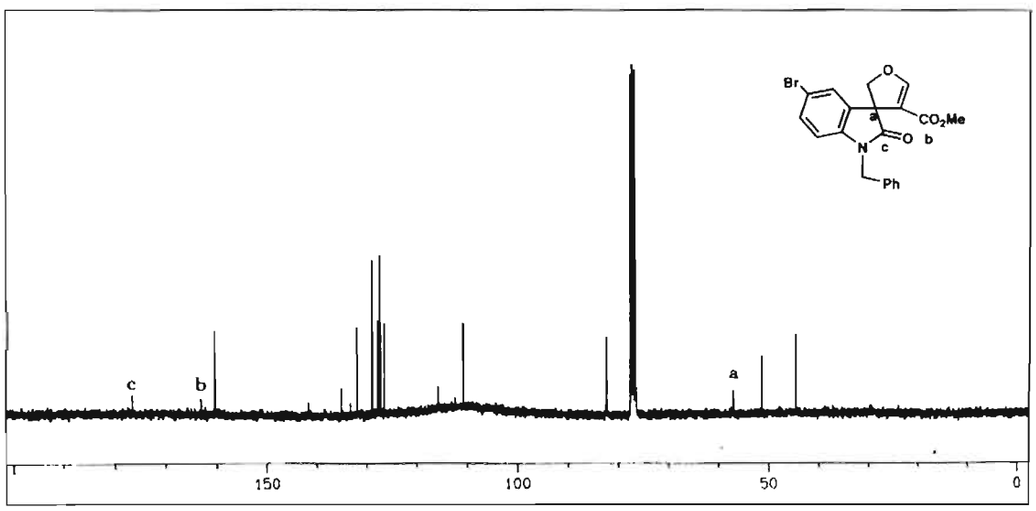
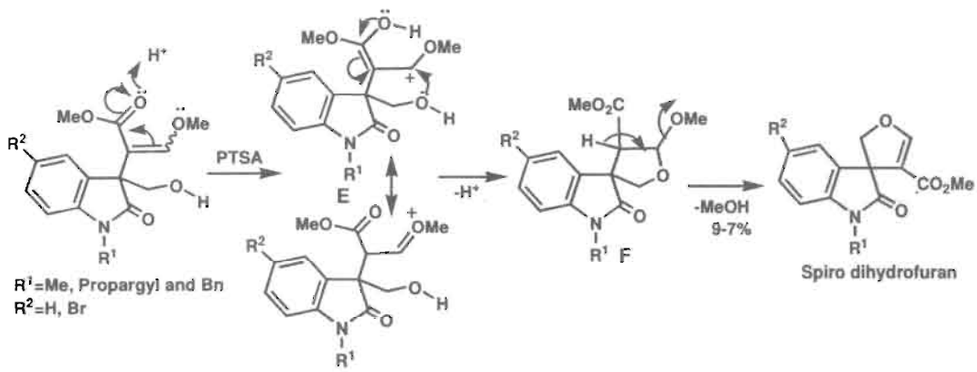


Figure 22 ^{13}C NMR Spectrum of compound **50c**

4.1.5.2. A plausible mechanism for the formation of spiro dihydrofuran derivatives

A plausible mechanism for the formation of minor amounts of dihydro spirofuran oxindole derivatives is depicted in Scheme 11. It is assumed that the protonation of second MBH adduct forms a methoxy-stabilized carbocation **E**. The hydroxyl group of the carbocation **E** cyclizes with loss of a proton to form the intermediate **F** which upon elimination of methanol affords the spirofuran derivatives.



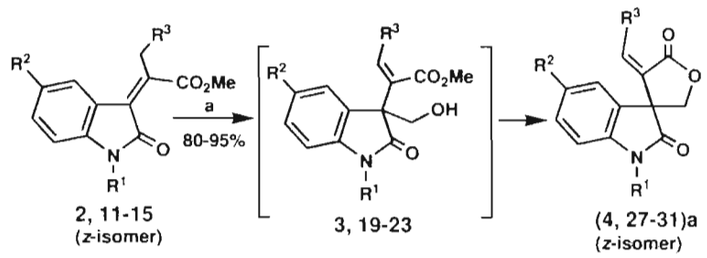
Scheme 11

4.1.6. One-pot base promoted MBH adduct formation- lactonization

Further examination on the lactonization studies, we have developed a base promoted one-pot procedure for the second MBH adducts formation followed by lactonization reaction. The reaction and the results are collected in Table 4. Thus, in a preliminary experiment, the isomerised *Z*-isomer of adduct **22** was treated with 1.5 equiv. DABCO and aqueous formaldehyde in acetone. The mixture was stirred overnight (12h). A one-pot base promoted second MBH adduct formation followed by lactonization occurred smoothly and provided a single *Z*- isomer of the lactone **24a** in excellent yield (90%, Table 4, entry 1).

The formation of *E*-isomer was not observed as per the analysis of TLC and crude and purified ^{1}H NMR spectra of the compounds. In order to show the generality of this observation, reactions with isomerised *Z*-isomers **31-35** with 1.5 equiv. DABCO and aqueous formaldehyde in acetone for 12 h afforded the expected *Z*-isomers of 3-spiro α-methylene-γ-butyrolactone-*N*-alkyl oxindoles **47a-51a** in excellent yields (80-95%) (Table 4, entries 2-6).

Table 4



a. aq. HCHO, DABCO, RT, acetone, 12h

Entry	Substrate	Product	Yield %
1	**23**	**24a**	90
2	**31**	**47a**	92
3	**32**	**48a**	90
4	**33**	**49a**	95
5	**34**	**50a**	80
6	**35**	**51a**	85

4.1.7. Conclusion

- A short and efficient stereoselective synthesis of highly functionalised 3-spiro α-methylene-γ-butyrolactone oxindoles along with minor amounts spirofuran oxindole derivatives from MBH adducts of isatin has been achieved.
- All the new compounds were characterised by modern spectroscopic analysis and single crystal X-ray analysis.
- A plausible mechanism for the formation of a minor amount of spirofuran oxindole derivatives has been explained.
- A one-pot procedure for the second MBH adduct formation followed by lactonization has also been achieved.

Chapter IV Part B

A facile and efficient synthesis of functionalized γ-butyrolactones from MBH adducts of isatin

4.2. Introduction

Various substituted-γ-butyrolactones are important building blocks due to the abundance of the skeleton in a variety of natural products, especially in sesquiterpene lactones and lignans[35-53] (Figure 23). The lactones are also found to be served as valuable synthetic intermediates for the synthesis of many kinds of natural products and biologically important compounds. Some of the lactones showed interesting pharmacological, fungicidal, and plant-growth regulatory activities.[35-62]

4.2.1. Natural occurrence of functionalized lactones

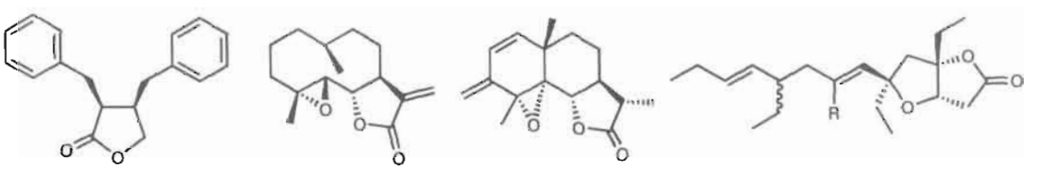


Figure 23

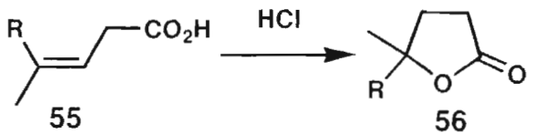
In view of their biological importance, numerous synthetic methods have been reported[63].

4.2.2. Few literature known methods for the synthesis of functionalized γ-butyrolactones

Due to the importance on the lactone core structure, there are several methods known in the literature. Some of the methods for the synthesis of γ-butyrolactones are described in the following sub-sections.

4.2.2.1. By acid catalyzed lactonization

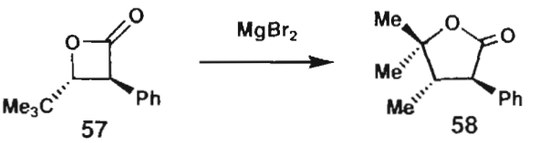
King *et al.* in 1974 reported that the γ,δ-unsaturated carboxylic acid **55** in presence of hydrochloric acid cyclised to furnish γ-butyrolactone **56**[64] core structure as shown in Scheme 12.



Scheme 12

4.2.2.2. By ring enlargement via molecular rearrangement

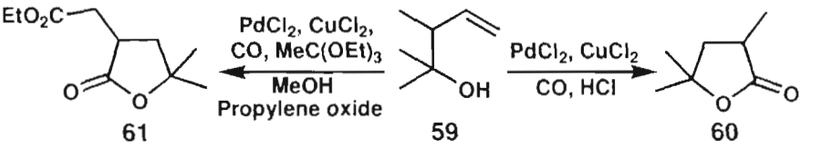
A report by Mulzer *et al.* in 1979 described stereospecific synthesis of γ-butyrolactone **58** by Wagner-Meerwein rearrangement starting from 4-tert-butyl-3-phenyloxetan-2-one **57** (Scheme 13)[65].



Scheme 13

4.2.2.3. By alkoxy carbonylation of 1,3-vinyl alcohol

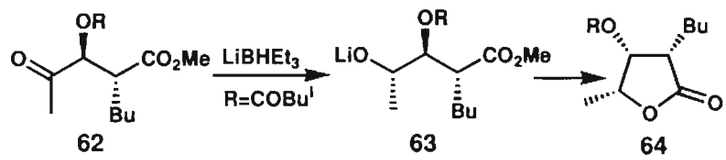
Yoshida *et al.* reported an intramolecular palladium catalyzed oxycarbonylation under mild conditions (room temperature, 1 atm of CO) to afford γ-butyrolactones **60** and **61**[66] as shown in Scheme 14.



Scheme 14

4.2.2.4. In-situ cyclization of γ-hydroxy carboxylic acid intermediate

Mulzer *et al.* reported in-situ cyclization of γ-hydroxy carboxylic ester intermediate **63** to give γ-butyrolactone **64**[67] as shown in Scheme 15.



62 63 64

Scheme 15

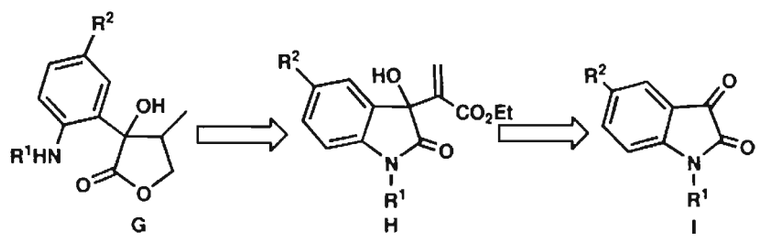
4.2.3. Objective of present work

Construction of γ-butyrolactone core structure is important due to the abundance of the skeleton in a variety of natural products, especially in sesquiterpene lactones and lignans. The lactones are also found to be served as valuable synthetic intermediates for the synthesis of many kinds of natural products and biologically important substances. Some of the literature reports for construction of γ-butyrolactone core structure from MBH adduct have been described in the introduction chapter I (Chapter I, sections 1.1.7.2., 1.1.7.8. and 1.1.7.9.). However, to best of our knowledge no work has been reported on the synthesis of functionalised aryl amine substituted-γ-butyrolactones from MBH of isatin by reductive cyclization methodology. Thus, in this chapter, we wish to give details of the synthesis of functionalized-γ-butyrolactones from MBH adducts of isatin by a simple reductive cyclization method using sodium borohydride reducing reagent in moist tetrahydrofuran.

4.2.4. Results and Discussion

4.2.4.1. Retrosynthetic analysis

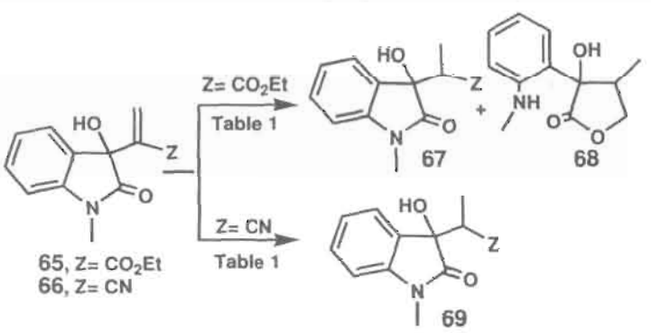
The synthetic strategy of present study is depicted in Scheme 16. Reduction of MBH derivative of isatin **H** would provide functionalized substituted-γ-butyrolactones **G**. The MBH adducts **H** could be synthesized from the corresponding substituted isatins **I** with activated alkenes such as methyl acrylate in the presence of base.



Scheme 16

4.2.4.2. Optimization study for γ-butyrolactone synthesis via reductive cyclization

We have initiated our study with preparation (as detailed in the Chapters II and III) and reductions of the MBH adduct of isatin with sodium borohydride in moist tetrahydrofuran. For comparison of the reactivity of MBH adducts and optimization of the reaction condition, we first synthesized adducts **65** and **66**. The study is shown in Scheme 17. The MBH adducts of isatin for this study were prepared according to literature procedure.[68]



Scheme 17

Initially, the MBH adduct bearing ester group **65** in moist tetrahydrofuran was treated with 1.2 equivalent of sodium borohydride at room temperature for 2h. The reaction afforded chemoselective reduced product **67** in almost quantitative (Table 5, entry 1) yield. Then, the adduct **65** with 2.2 equivalent of sodium borohydride afforded 1:1 ratio of chemoselective reduced product **67** and γ-lactone **68** in 95% combined yield (Table 5, entry 2). Hence, it is inferred that the more equivalents of the reducing agent is required for the complete formation of the lactone. Thus, the optimum condition for the formation of lactone **68** was found as 4 equivalents of sodium borohydride with adduct **65** as shown in Table 5, entry 3. In order to verify the role and effect of solvent, the reactions in methanol and diethyl ether afforded poor yields of the lactone (Table 5, entries 4 and 5) and reaction was found as complex mixture formation (TLC). Hence, the moist tetrahydrofuran is best choice of solvent for the reaction. Experiments with varying THF:H_2O ratio revealed that the best ratio is (4.5mL:0.5mL) in this reaction. To compare the reactivity of the MBH adducts, the adduct bearing nitrile at the activated olefin **66**, on reduction, under optimized condition, furnished only the olefin reduced compound **69** as a sole product as analyzed by NMR(Table 5, entry 6). Experiments with excess of the reducing agent and prolonged reaction time also furnished only compound **69** in

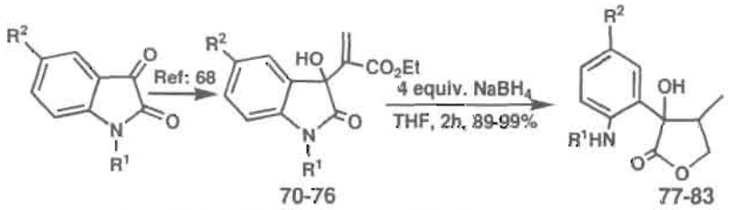
excellent yield (>95%)(Table 5, entry 7). Hence, it is inferred that adduct bearing nitrile **66**, nitrile reduction is more susceptible than the corresponding ester reduction in adduct **65**. The results are summarized in Table 5.

Table 5

Entry	adduct	Condition	Products/ratio	Yield %
1	**65**	1.2 equiv. $NaBH_4$, THF, 2h, RT	(**67**:**68**)1:0	99
2	**65**	2.2 equiv. $NaBH_4$, THF, 2h, RT	(**67**:**68**)1:1	95
3	**65**	4 equiv. $NaBH_4$, THF, 2h, RT	(**67**:**68**)0:1	98
4	**65**	4 equiv. $NaBH_4$, MeOH, 2h, RT	(**67**:**68**)1:2	71
5	**65**	4 equiv. $NaBH_4$, Et_2O, 2h, RT	(**67**:**68**)2:0.5	69
6	**66**	4 equiv. $NaBH_4$, THF, 2h, RT	**69**	99
7	**66**	6 equiv. $NaBH_4$, THF, 4h, RT	**69**	99

4.2.4.3. Generality for the synthesis of γ-butyrolactone

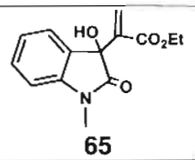
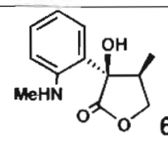
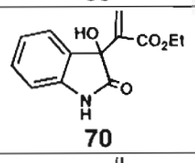
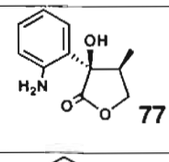
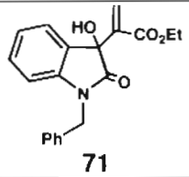
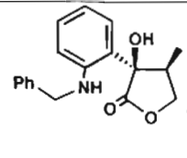
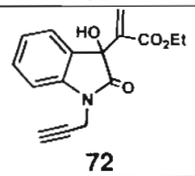
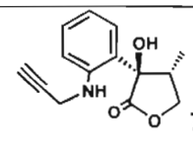
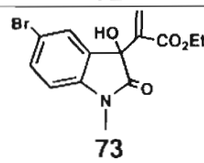
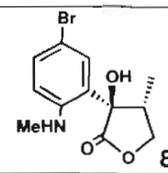
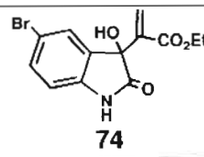
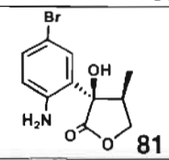
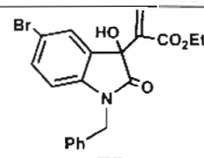
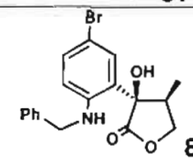
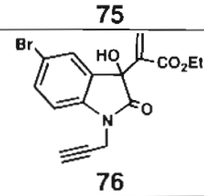
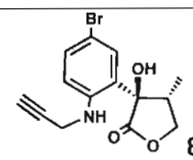
Encouraged by the preliminary results and to show the generality of the reaction, the reaction of adducts **70-76** under optimized conditions afforded the desired aryl amine highly functionalised γ-butyrolactones **77-83** in excellent yield. The general reaction is shown in Scheme 18.



Scheme 18

The lactones **79** and **83** derived from adducts **71** and **76** should be purified rapidly in order to obtain higher yields (Table 6, entries 4 and 8). It should be note worthy that the lactones obtained have substituted aryl amines as one of the substitution at the alpha position of the lactones which could be manipulated for further functionalisation. We have also shown that the presence of functional groups such as benzyl and propargyl in the starting materials are susceptible to the reaction condition affording highly functionalized lactones. The results are summarized in Table 6. All the new compounds were characterized by spectral (IR, ^1H and ^{13}C NMR) and HRMS data.

Table 6

Entry	Reactant	Condition	Product [a]	Yield %[b]
1	 **65**	4 equiv. $NaBH_4$, THF, 2h, RT	 **68**	98
2	 **70**	4 equiv. $NaBH_4$, THF, 2h, RT	 **77**	93
3	 **71**	4 equiv. $NaBH_4$, THF, 2h, RT	 **78**	95
4	 **72**	4 equiv. $NaBH_4$, THF, 2h, RT	 **79**	89
5	 **73**	4 equiv. $NaBH_4$, THF, 1.5h, RT	 **80**	93
6	 **74**	4 equiv. $NaBH_4$, THF, 1h, RT	 **81**	94
7	 **75**	4 equiv. $NaBH_4$, THF, 1.5 h, RT	 **82**	90
8	 **76**	4 equiv. $NaBH_4$, THF, 1.5 h, RT	 **83**	96

a. Racemic mixture; b. Yields refer after column purification.

4.2.4.4. Characterization of 3-hydroxy-4-methyl-3-(2-methylamino-phenyl)-dihydro-furan-2-ones

All the newly synthesized 3-hydroxy-4-methyl-3-(2-methylamino-phenyl)-dihydro-furan-2-one were characterised by spectral means. Some of the representative examples are described as follows. The structure of lactone **68** was arrived based on analysis of spectroscopic data. In the IR spectrum of compound **68**, absorption bands due to the presence of hydroxyl and lactone carbonyl groups were found at 3402 and 1771 cm^{-1} respectively. The ^1H NMR spectrum of the lactone was appeared very neat. In the aliphatic region an upfield signal due to methyl group attached with methine centre appeared as a doublet at δ 0.58 with coupling constant J = 6.9Hz. The methine proton appeared as a multiplet at δ 2.47, which indicated coupling due to its neighbor methylene protons. The methylene protons in the lactone ring appeared as two doublet of doublet signals at δ 3.89 with coupling constants J = 11.1 and 3.9Hz and at δ 4.03 with coupling constants J = 11.1 and 9.9Hz. The one more methyl group attached with nitrogen atom occurred as a singlet signal at δ 3.18. Signals due to OH and NH protons were clearly found from the chemical shifts at δ 3.37 and δ 4.95 respectively. The aromatic region had four protons in the chemical shift range δ 6.82-7.36 (Figure 24). The OH and NH protons were found exchangeable with D_2O in ^1H NMR-D_2O exchange experiment.

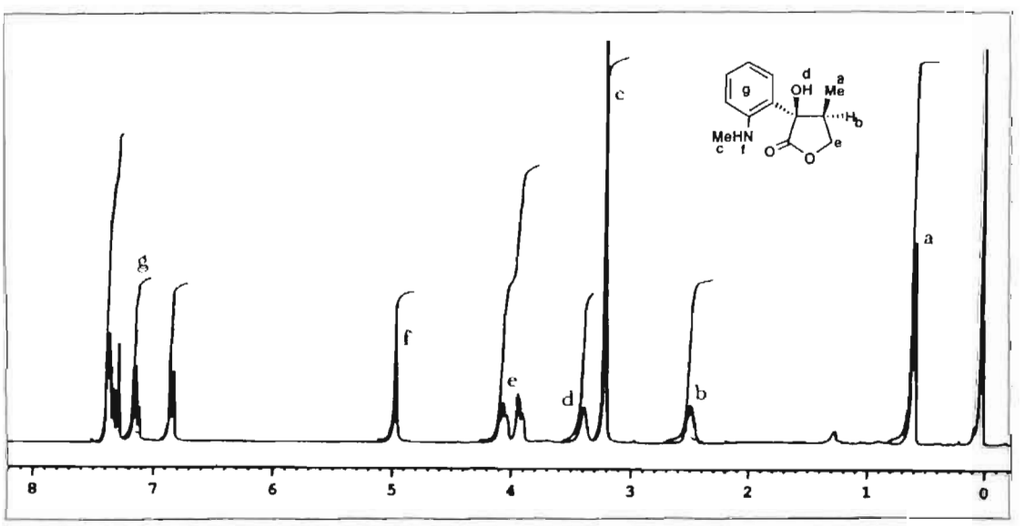


Figure 24 ^1H NMR Spectrum of compound **68**

The ^{13}C NMR spectrum of the γ butyrolactone **68** accounted total number of carbons. The signal at δ 11.38 indicated the methyl carbon at C-4 of the γ-lactone ring. The methine carbon of the γ-butyrolactone core had resonance at δ 26.13. Carbon signals at δ 41.29 and 64.47 were found due to *N*-methyl and methylene in the lactone ring respectively. The quaternary carbon in the lactone ring displayed a peak at δ 79.67. The remaining aromatic carbons were appeared at δ 108.3-129.68 (methine carbons) and δ 130.34, 143.39 (quaternary carbons). The presence of carbonyl carbon in the lactone was confirmed with a carbon peak at δ 177.89 (Figure 25).

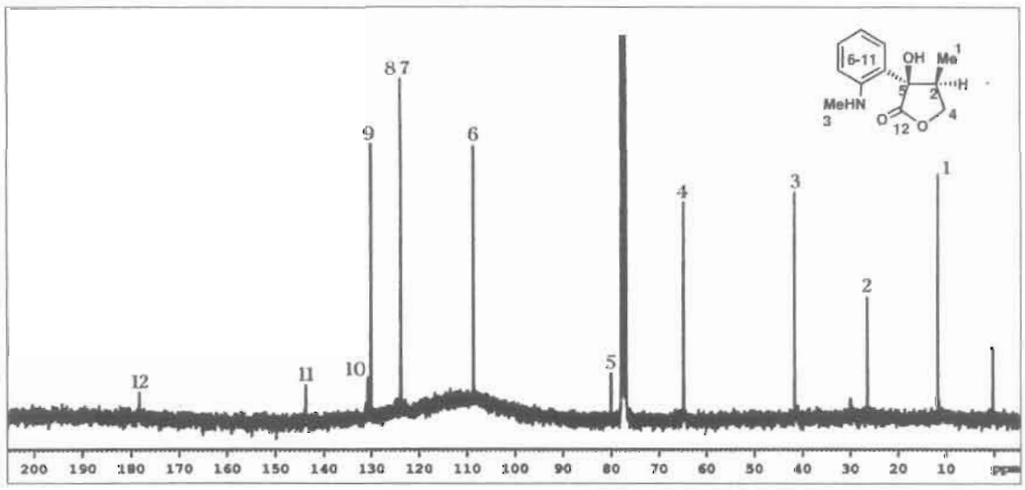


Figure 25 ^{13}C NMR Spectrum of compound **68**

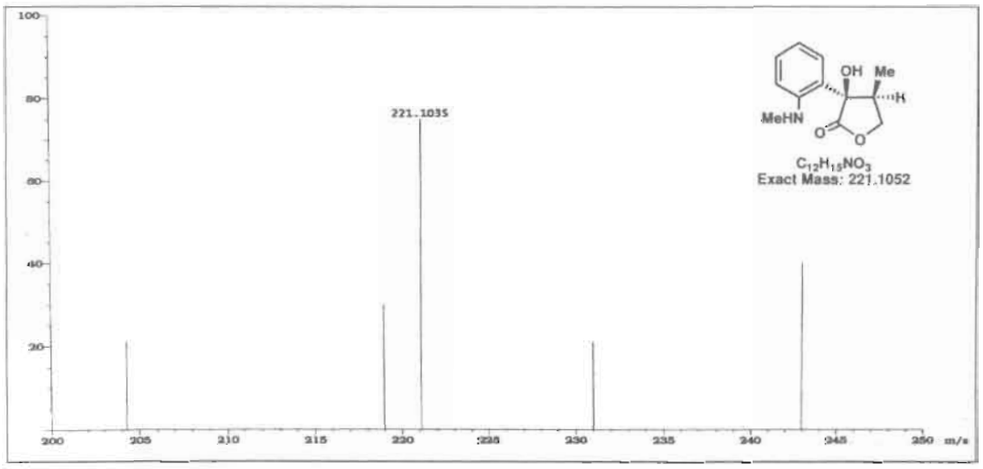


Figure 26 Mass spectrum (HRMS) of compound **68**

A final proof for the structure of γ-butyrolactone **68** was confirmed based on the mass spectrum (HRMS) showing a molecular ion peak at m/z = 221.1035 (Calcd. for $C_{12}H_{15}NO_3$: 221.1054) (Figure 26).

Similarly, in the IR spectrum of the lactone **78**, absorption bands due to -OH and lactone carbonyl functionalities found at 3385 and 1778 cm^{-1} respectively. In ^1H NMR spectrum, a doublet and a multiplet signals at δ 0.62 with coupling constant J = 7.2 and at δ 2.51 were found due to the presence of methyl and methine protons respectively. The presence of two methylene protons, one of lactone ring and another of benzylic methylene part were observed because of characteristic four sets of chemical shifts at δ 3.93 (as doublet of doublet with coupling constants J = 11.1 and 4.5Hz), δ 4.12 (as doublet of doublet with coupling constants J = 11.1and 9Hz, 1H), δ 4.75 (as doublet with a coupling constant J = 15.6Hz) and δ 5.00 (as doublet with a with coupling constant J = 15.6Hz). (Figure 27)

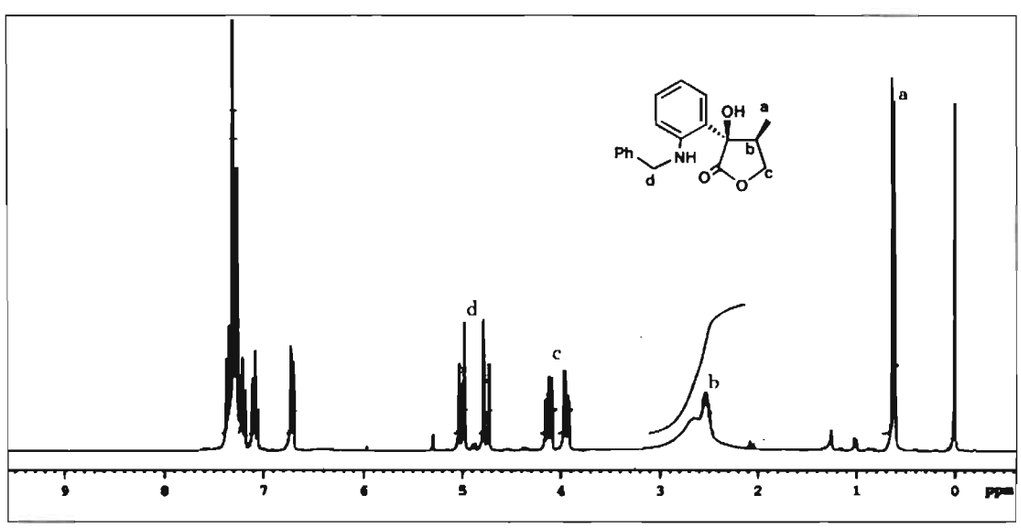


Figure 27 ^1H NMR Spectrum of compound **78**

In its ^{13}C NMR spectrum, a signal due to methyl carbon was found at δ 11.62. The quaternary carbon attached with hydroxyl group occurred at δ 79.63. The lactone carbonyl carbon was found at δ 178.03. All other carbons were found as expected and the spectrum is reproduced in Figure 28. The final evidence for the structure of γ-butyrolactone **78** was confirmed based on the mass spectrum (HRMS) having a molecular ion peak at m/z = 297.1366 (Calcd. for $C_{18}H_{19}NO_3$: 297.1365).

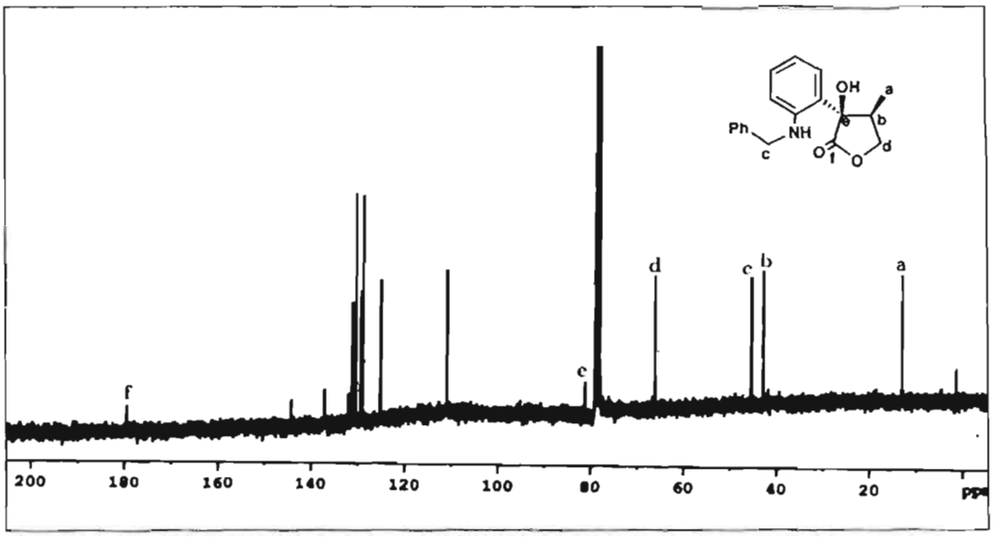


Figure 28 ^{13}C NMR Spectrum of compound **78**

Likewise, the structure of *N*-propargyl derivative of γ-butyrolactone **79** was established using spectroscopic analysis. In IR spectrum of the lactone **79**, the absorption bands at 3427 and 1777cm^{-1} confirmed the presence of hydroxyl group and lactone carbonyl unambiguously. In ^{1}H NMR spectrum, the terminal alkyne proton in the lactone appeared as a triplet at δ 2.17 with coupling constant J = 2.4Hz. The C-5 methylene of the lactone ring appeared as two sets of doublet of doublet at δ 3.72 with coupling constants J = 8.7 and 4.8Hz and at δ 3.84 with coupling constant J = 8.7 and 5.7Hz. (Figure 29)

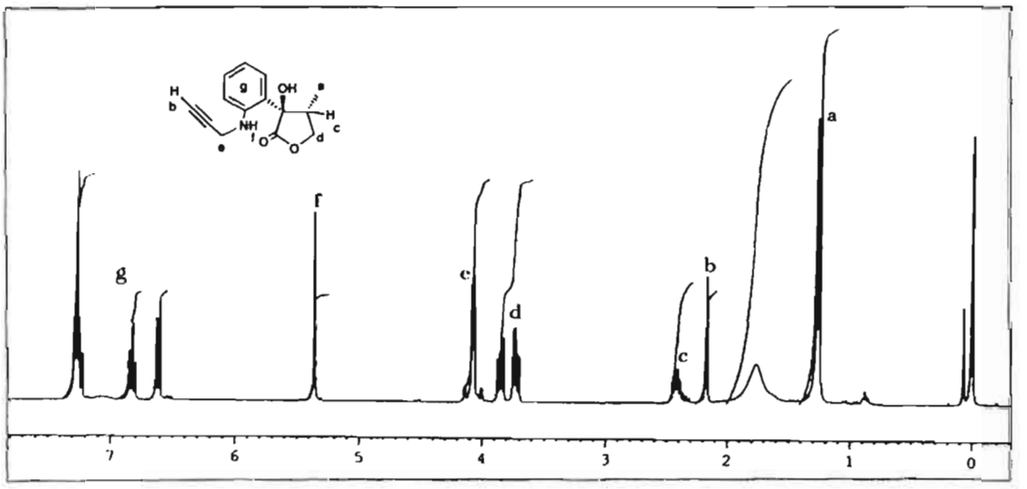


Figure 29 ^{1}H NMR Spectrum of compound **79**

In ^{13}C NMR spectrum, the carbon signals due to C-3 and quaternary carbon in alkyne group were found at δ 78.87 and 87.94 respectively. The lactone carbonyl was seen at δ 172.40 (Figure 30). The mass spectrum (HRMS) of lactone **79** had a molecular ion peak at m/z = 230.0802 (Calcd. for $C_{13}H_{12}NO_3$: 230.0817) resulted as final proof for the assinged structure.

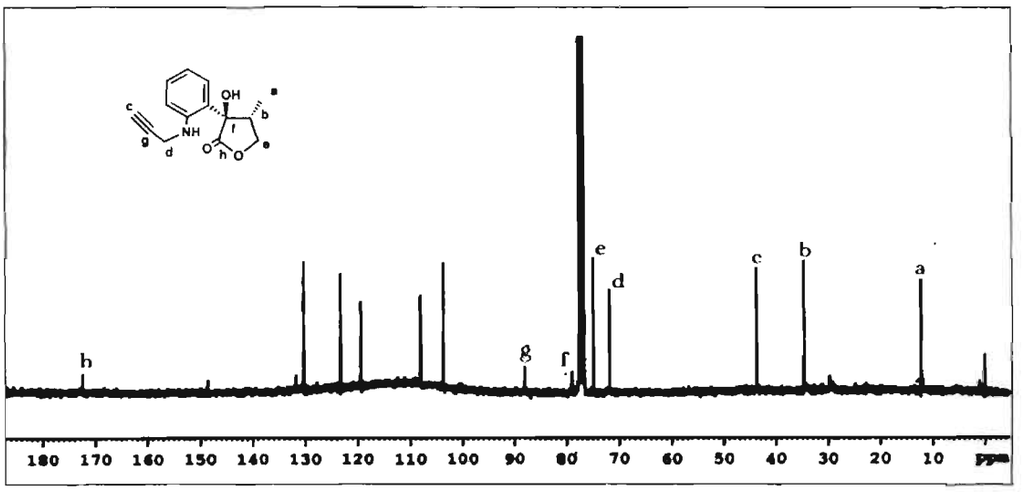


Figure 30 ^{13}C NMR Spectrum of compound **79**

The structure of propargyl lactone derivative in which aryl ring having bromine substitution **83** was analysed by routine spectroscopic techniques. In the IR spectrum, the OH and lactone carbonyl absorption were found at 3391 and 1769 cm^{-1} respectively. Its ^1H NMR spectrum was neat and clear in assigning all the signals present. A triplet signal due to terminal alkyne proton was found at δ 2.18 with coupling constant J = 2.1Hz. The characteristic doublet of doublet pattern expected due to the lactone methylene protons occured at δ 3.74 with coupling constants J = 8.7 and 4.8Hz and at δ 3.85 with coupling constant J = 8.7 and 5.7Hz. (Figure 31)

The ^{13}C NMR spectrum of lactone **83** had the quarternary carbon at δ 79.68. The lactone carbonyl was resonated at δ 180.81. All other carbons were found as expected and the spectrum is reproduced in Figure 32. Finally the structure of lactone **83** was confirmed by mass spectrum (HRMS) in which a molecular ion peak was seen at m/z = 323.0212 (Calcd. for $C_{14}H_{14}BrNO3$: 323.0157).

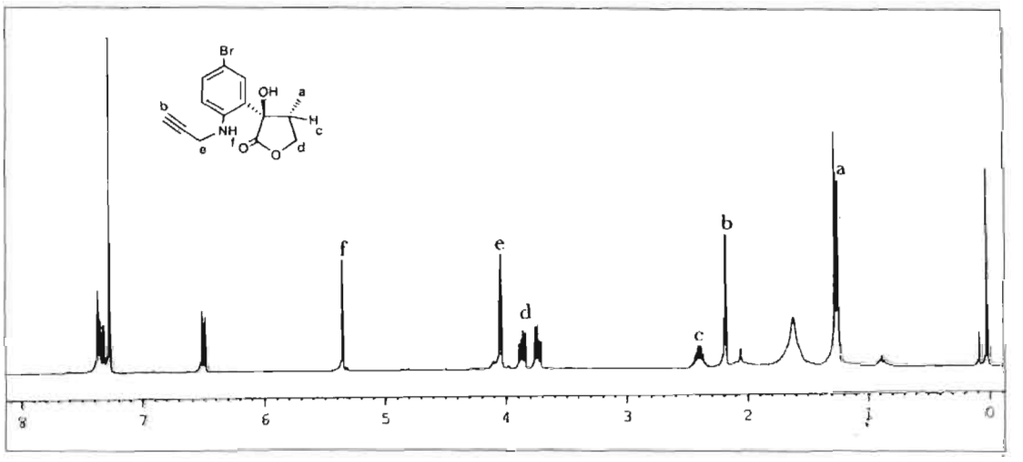


Figure 31 ^{1}H NMR Spectrum of compound **83**

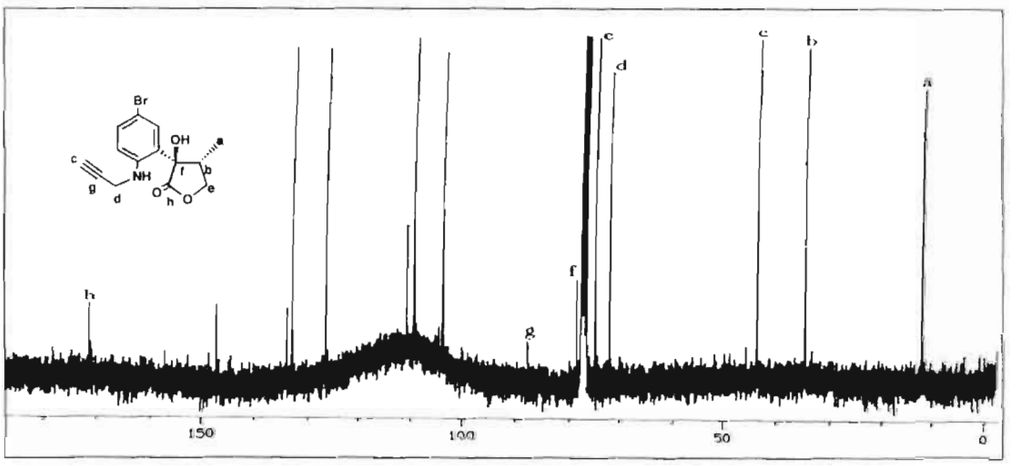


Figure 32 ^{13}C NMR Spectrum of compound **83**

4.2.4.5. Assignment of the relative stereochemistry of the lactones

The relative stereochemistry of the lactones **68** and **80** were arrived based on NOE-irradiation studies. Thus, irradiation of H_c proton at δ 2.47 in compound **68** showed 1.15% enhancement of the H_e proton of the aryl ring while the OH proton showed -3.4% of negative NOE enhancement confirming these are *syn-* and *anti-* relationship with respect to H_a proton. In contrary, we observed that the compounds **79, 80** and **83** showed the opposite relationship as evidenced by NOE correlation and also by comparison of proton NMR chemical shifts of methyl protons which have *anti-* and *syn-* relation with aryl ring in **68** and **80** respectively (H_d at 0.58ppm for **68** and $H_{d'}$ at 0.98 ppm for **80** due to ring current of aryl ring). The reverse in

stereochemistry of the lactones may be due to the substitutions at aryl ring and *N*-alkyl positions which direct the mode of attack of hydride ion which determines the stereochemistry of the products. Thus, the stereochemistry of the products is arrived as shown in Figure 33.

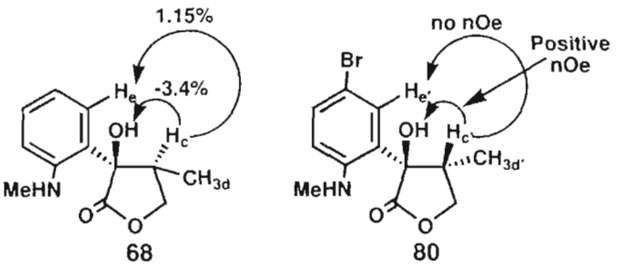


Figure 33

For example, in compound **68**, the H_a and H_b protons appeared as two doublets of doublet at δ 3.89 and δ 4.03 respectively. H_d (Methyl protons) at δ 0.58 appeared as doublet, H_c at δ 2.47ppm appeared as a multiplet. The H_a proton showed coupling constant with H_b proton as 11.1 Hz due to geminal coupling. The H_a and H_b protons had coupling constants with H_c proton as 3.9Hz and 9.9 Hz respectively. The H_d protons had coupling constant with H_c proton as 6.9 Hz. OH proton appeared at δ 3.37 as broad singlet. NH proton was seen at δ 4.95 as a singlet. One aromatic proton at δ 6.82 as a doublet (J = 7.8Hz), remaining three aromatic protons appeared in the range δ 7.09-7.36 as a multiplet. Further, the 2D HOMOCOSY spectrum showed cross peaks between H_c and H_d, H_a and H_c, H_b and H_c and H_{ab} supporting the coupling nature of the protons in the lactone unambiguously. The coupling nature of protons is shown in Figure 34.

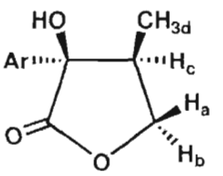
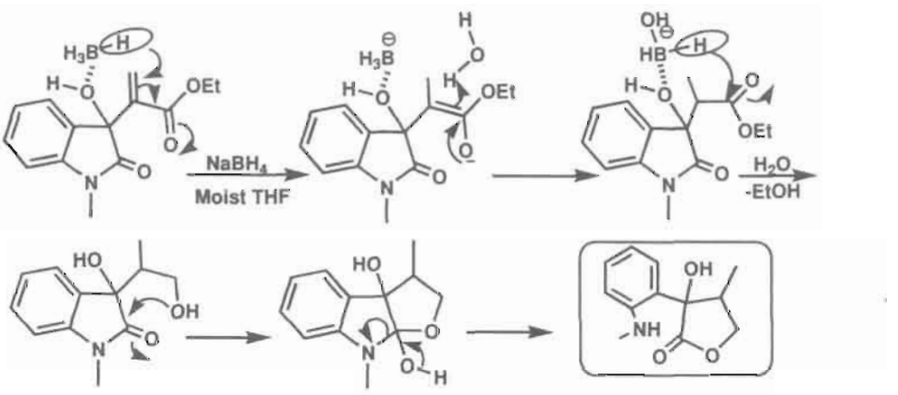


Figure 34

4.2.4.6. A Plausible mechanism of lactonization

The formation of lactones could be explained based on mechanistic studies. A possible pathway for the lactone formation is depicted in scheme 19. A conjugate addition of hydride ion to enone system leads to olefin reduction followed by reduction of ester group to primary

alcohol which undergoes lactonization with cleavage of a weak amide carbonyl group. It is understood that the presence of 3°-alcohol group in the starting material facilitates the hydride addition to the conjugate system by a weak complex formation with the reducing agent preferably.



Scheme 19

4.2.5. Conclusion

- A short, facile and efficient method for the synthesis of functionalized γ-butyrolactones was achieved exploiting MBH adducts of isatin as starting materials by reductive cyclization as a key step.
- All the newly synthesized lactone products were characterized using spectroscopic analysis.
- Assignment of relative stereochemistry of the γ-butyrolactones using NOE and HOMOCOSY experiment study was also explained in detail.
- Finally, a plausible mechanism was proposed for the formation of γ-butyrolactones.

4.3. Experimental Details (Part-A)

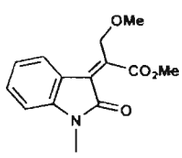
4.3.1. General experimental procedure for isomerisation:

Isomerisation:

A mixture of MBH adducts (100 mg, 0.404 mmol), excess of trimethyl orthoformate (3mL) (or) Ar-H (3mL) (or) propargyl alcohol (3mL) and montmorillonite K-10 Clay (50% w/w) without any solvent was heated at 110 °C for 1.5h. After the reaction (TLC), the crude mixture was purified by a silica gel column chromatography using gradient elution with hexane and hexane and EtOAc (80:20) to afford isomerised products in good yields (68-75%).

4.3.2. Spectral data for Isomerised Baylis-Hillman adducts:

(Z)-methyl 3-methoxy-2-(1-methyl-2-oxoindolin-3-ylidene)propanoate **22:**



22

R_f (20% EtOAc-Hexanes) 0.42.

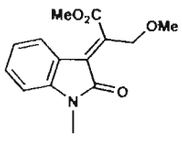
IR (CH_2Cl_2): ν_{max} 1710, 1608 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.22 (s, 3H), 3.43 (s, 3H), 3.96 (s, 3H), 5.04 (s, 2H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.98 (t, *J* = 7.8 Hz, 1H), 7.22-7.31 (m, 2H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 25.9, 52.6, 59.1, 68.2, 108.3, 119.7, 122.4, 122.6, 124.9, 130.4, 141.6, 143.6, 166.9, 167.5.

HRMS *m/z*: Calcd. for $C_{14}H_{15}NO_4$: 261.1001; Found 261.0988.

(E)-methyl 3-methoxy-2-(1-methyl-2-oxoindolin-3-ylidene)propanoate **22:**



R_f (20% EtOAc-Hexanes) 0.42.

IR (CH_2Cl_2): ν_{max} 1710, 1608 cm^{-1}.

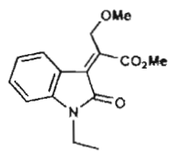
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.20 (s, 3H), 3.48 (s, 3H), 3.95 (s, 3H), 4.64 (s, 2H), 6.82 (d, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 6.9 Hz, 1H), 7.30-7.42 (m, 2H).

(Z)-methyl 2-(1-ethyl-2-oxoindolin-3-ylidene)-3-methoxypropanoate **31:**

R_f (20% EtOAc-Hexanes) 0.38.

IR (CH_2Cl_2): ν_{max} 1713, 1665, 1614 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.26 (t, *J* = 7.0 Hz, 3H), 3.43



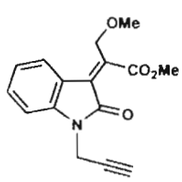
31

(s, 3H), 3.77 (q, J = 7.0 Hz, 2H), 3.96 (s, 3H), 5.04 (s, 2H), 6.79 (d, J = 7.8 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 7.22-7.30 (m, 2H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 12.3, 35.0, 53.2, 54.8, 63.5, 109.2, 119.5, 122.3, 123.2, 125.3, 130.2, 142.5, 143.5, 167.3, 167.8;

HRMS *m/z* : Calcd. for $C_{15}H_{17}NO_4$: 275.1158; Found 275.1147.

(Z)-methyl 3-methoxy-2-(2-oxo-1-(prop-2-ynyl)indolin-3-ylidene)propanoate **32**:



32

R_f (20% EtOAc-Hexanes) 0.41.

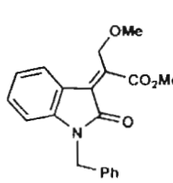
IR (CH_2Cl_2): ν_{max} 3311, 2146, 1716, 1613 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.22 (t, J = 2.4 Hz, 1H), 3.43 (s, 3H), 3.95 (s, 3H), 4.49 (s, 2H), 5.05 (s, 2H), 7.03-71 (m, 2H), 7.26-7.37 (m, 2H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 29.6, 52.7, 57.54, 62.7, 72.2, 97.6, 111.3, 119.77, 122.51, 123.2, 125.27, 130.24, 142.06, 143.51, 166.89, 167.40.

HRMS *m/z* : Calcd. for $C_{16}H_{15}NO_4$: 285.1001; Found 285.0992.

(Z)-methyl 2-(1-benzyl-2-oxoindolin-3-ylidene)-3-methoxypropanoate **33**:



33

R_f (20% EtOAc-Hexanes) 0.47.

IR (CH_2Cl_2): ν_{max} 1717, 1706, 1603 cm^{-1}.

^{1}H NMR($CDCl_3$/TMS, 300.1 MHz): δ 3.45 (s, 3H), 3.98 (s, 3H), 4.92 (s, 2H), 5.10 (s, 2H), 6.69 (d, J = 7.8 Hz, 1H), 6.96 (t, J = 7.8 Hz, 1H), 7.16-7.33 (m, 7H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 44.2, 52.8, 53.9, 62.6, 106.2, 109.3, 122.7, 123.5, 126.8 (2C), 127.6, 128.5 (2C), 129.0, 131.2, 135.4, 142.6, 143.6, 174.8, 175.7.

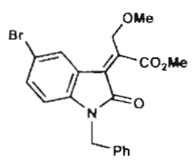
HRMS *m/z*: Calcd. for $C_{20}H_{19}NO_4$: 337.1314; Found 337.1303.

(Z)-methyl 2-(1-benzyl-5-bromo-2-oxoindolin-3-ylidene)-3-methoxypropanoate **34**:

R_f (20% EtOAc-Hexanes) 0.43.

IR (CH_2Cl_2): ν_{max} 1721, 1710, 1605 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.43 (s, 3H), 3.87 (s, 3H), 4.92 (s,



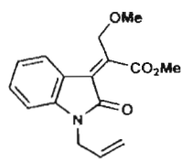
34

2H), 5.04 (s, 2H), 6.63 (d, J = 8.4 Hz, 1H), 7.28-7.34 (m, 8H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 44.4, 52.9, 62.9, 73.8, 105.8, 110.5, 116.2, 126.1, 127.3 (2C), 128.2, 128.8 (2C), 131.8, 132.6, 135.1, 141.7, 143.6, 170.4, 172.8.

HRMS *m/z*: Calcd. for $C_{20}H_{18}BrNO_4$: 415.0419; Found 415.0417.

(Z)-methyl 2-(1-allyl-2-oxoindolin-3-ylidene)-3-methoxypropanoate **35:**



35

R_f (20% EtOAc-Hexanes) 0.47.

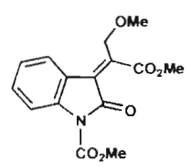
IR (CH_2Cl_2): ν_{max} 1715, 1612 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.54 (s, 3H), 4.08 (s, 3H), 4.45-4.52 (m, 2H), 5.18 (s, 1H), 5.29-5.35 (m, 2H), 5.5 (m, 1H), 6.91 (d, J = 7.5 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 7.35-7.341 (m, 2H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 42.6, 52.77, 52.9, 62.6, 106.20, 109.3, 117.5, 122.8, 123.2, 128.7, 130.63, 131.2, 142.5, 158.4, 173.9, 174.6.

HRMS *m/z*: Calcd. for $C_{16}H_{17}NO_4$: 287.1158; Found 287.1150.

(Z)-methyl 3-(1-(methoxycarbonyl)-2-methoxyethylidene)-2-oxoindoline-1-carboxylate **36:**



36

R_f (20% EtOAc-Hexanes) 0.39.

IR (CH_2Cl_2): ν_{max} 1702, 1607 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.43 (s, 3H), 3.98 (s, 3H), 4.04 (s, 3H), 5.00 (s, 2H), 7.13-7.44 (m, 3H), 7.98 (t, J = 7.8 Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 52.8, 53.4, 59.3, 67.8, 105.7, 108.4, 122.3, 123.6, 129.4, 131.7, 143.3, 143.8, 167.5, 174.9, 175.3.

HRMS *m/z*: Calcd. for $C_{15}H_{15}NO_6$: 305.0899; Found 305.0900.

4.3.3. General experimental procedure for Second Baylis-Hillman adducts formation and lactonisation:

Second Morita-Baylis-Hillman adduct formation:

A mixture of isomerised MBH adducts (100 mg, 0.382 mmol) was treated with 40% aqueous formaldehyde (0.5mL) and DABCO (1.5 equiv.) in acetone (3mL) was stirred for 2hr at RT. The crude mixture was passed through a silica gel column using gradient elution with

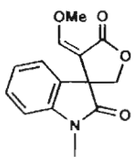
hexane and hexane and EtOAc (70:30) to afford pure adducts as inseparable mixture (combined yield: 80-90%).

Lactonization:

The mixture of second MBH adducts (100 mg, 0.343 mmol) in benzene (5 mL) and PTSA (cat. 0.3 equiv.) was refluxed at 80 °C for 30 minutes. The reaction mixture in CH_2Cl_2 (50ml) was washed with saturated $NaHCO_3$, brine and water. The organic layer was separated, dried (Na_2SO_4) and concentrated under vacuum. The crude mixture was purified by a column chromatography using gradient elution with hexane and hexane and EtOAc (80:20) to afford 3-spiro α-methylene-γ-butyrolactone-*N*-alkyl oxindoles in 70-97% isolated yields.

4.3.4. Spectral data for 3-Spiro α-methylene-γ-butyrolactone oxindole compounds:

Compound 24a:



24a

R_f (20% EtOAc-Hexanes) 0.38.

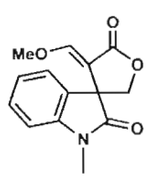
IR (CH_2Cl_2): ν_{max} 1753, 1714, 1667, 1612, 1470, 1048 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.26 (s, 3H), 3.67 (s, 3H), 4.34 (d, *J* = 8.8 Hz, 1H), 4.59 (d, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.27 (s, 1H), 7.32 (t, *J* = 7.7 Hz, 1H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 26.6, 52.8, 62.9, 73.8, 106.2, 108.2, 122.7, 123.4, 128.9, 130.8, 143.3, 158.6, 170.8, 175.2.

HRMS *m/z*: Calcd. for $C_{14}H_{13}NO_4$: 259.0845; Found 259.0845.

Compound 24b:



24b

R_f (20% EtOAc-Hexanes) 0.28.

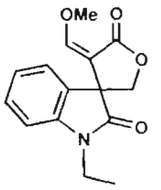
IR (CH_2Cl_2): ν_{max} 1755, 1704, 1657, 1607, 1465, 1071 cm^{-1}.

^{1}H NMR($CDCl_3$/TMS, 300.1 MHz): δ 3.24 (s, 3H), 3.82 (s, 3H), 4.29 (d, *J* = 8.8 Hz, 1H), 4.55 (d, *J* = 8.8 Hz, 1H), 6.14 (s, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H)

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 26.7, 53.1, 63.3, 73.2, 105.6, 108.7, 122.3, 123.4, 129.4, 131.6, 143.0, 158.1, 167.2, 176.5.

HRMS *m/z*: Calcd. for $C_{14}H_{13}NO_4$: 259.0845; Found 259.0840.

Compound 47a:



47a

R_f (20% EtOAc-Hexanes) 0.37.

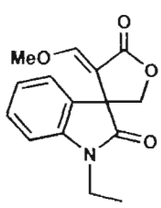
IR(CH_2Cl_2): ν_{max} 1750, 1715, 1667, 1611, 1486, 1051 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.27 (t, *J* = 7.1 Hz, 3H), 3.67 (s, 3H), 3.62-3.98 (m, 2H), 4.35 (d, *J* = 8.8 Hz, 1H), 4.59 (d, *J* = 8.8 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.22-7.34 (m, 3H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 12.3, 35.0, 52.9, 62.5, 73.7, 106.7, 108.3, 122.9, 123.1, 128.9, 131.2, 142.4, 158.4, 170.71, 174.6.

HRMS *m/z*: Calcd. for $C_{15}H_{15}NO_4$: 273.1001; Found 273.1006.

Compound 47b:



47b

R_f (20% EtOAc-Hexanes) 0.26.

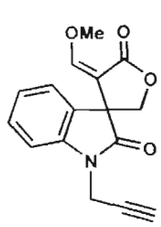
IR (CH_2Cl_2): ν_{max} 1755, 1715, 1652, 1612, 1468, 1073 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.30 (t, *J* = 7.1 Hz, 3H), 3.77 (q, *J* = 7.1 Hz, 2H), 4.31 (d, *J* = 8.8 Hz, 1H), 4.56 (d, *J* = 8.8 Hz, 1H), 6.13 (s, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H),7.29 (d, *J* = 6.8 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 12.7, 35.1, 53.0, 63.3, 73.1, 105.8, 108.8, 123.6 (2C), 129.3, 131.8, 142.1, 157.9, 167.1, 176.1.

HRMS *m/z*: Calcd. for $C_{15}H_{15}NO_4$: 273.1001; Found 273.1003.

Compound 48a:



48a

R_f (20% EtOAc-Hexanes) 0.34.

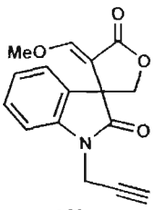
IR (CH_2Cl_2): ν_{max} 3310, 2146, 1747, 1716, 1666, 1613, 1489, 1051 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.55 (t, *J* = 2.5 Hz, 1H), 3.68 (s, 3H), 4.36-4.70 (m, 4H), 7.06 (d, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H),7.25 (d, *J* = 6.9 Hz, 1H), 7.28 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 29.6, 52.7, 62.7, 72.2, 73.6, 98.0, 103.7, 109.2, 122.8, 123.8, 128.9, 130.7, 141.4, 158.7, 170.5, 174.3.

HRMS *m/z*: Calcd. for $C_{16}H_{13}NO_4$: 283.0845; Found 283.0837.

Compound 48b:



48b

R_f (20% EtOAc-Hexanes) 0.37.

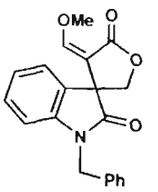
IR (CH_2Cl_2): ν_{max} 3309, 2143, 1752, 1715, 1667, 1612, 1487, 1049 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.28 (t, *J* = 2.5 Hz, 1H), 3.85 (s, 3H), 4.32-4.63 (m, 4H), 6.61 (s, 1H), 6.91-7.41 (m, 4H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 29.9, 53.2, 63.7, 73.1, 73.2, 77.4, 109.7, 111.3, 115.5, 116.6, 123.8, 124.5, 129.7, 158.3, 168.9, 178.3.

HRMS *m/z*: Calcd. for $C_{16}H_{13}NO_4$: 283.0845; Found 283.0835.

Compound 49a:



49a

R_f (20% EtOAc-Hexanes) 0.35.

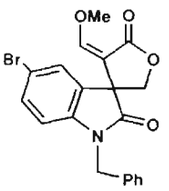
IR (CH_2Cl_2): ν_{max} 1747, 1714, 1667, 1607, 1486, 1050cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.62 (s, 3H), 4.38 (d, *J* = 8.8 Hz, 1H), 4.64 (d, *J* = 8.8 Hz, 1H), 4.65 (d, *J* = 15.6 Hz, 1H), 5.22 (d, *J* = 15.6 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 7.05 (t, *J* = 6.9 Hz, 1H), 7.18-7.33 (m, 8H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 44.2, 52.8, 62.6, 74.1, 106.2, 109.2, 122.8, 123.4, 127.4 (2C), 127.7, 128.7 (2C), 128.8, 130.9, 135.5, 142.4, 158.6, 170.7, 175.3.

HRMS *m/z*: Calcd. for $C_{20}H_{17}NO_4$: 335.1158; Found 335.1153.

Compound 50a:



50a

R_f (20% EtOAc-Hexanes) 0.36.

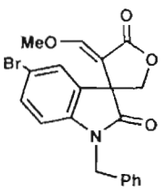
IR (CH_2Cl_2): ν_{max} 1744, 1722, 1668, 1602, 1484, 1053cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.66 (s, 3H), 4.37 (d, *J* = 8.9 Hz, 1H), 4.60 (d, *J* = 15.7 Hz, 1H), 4.63 (d, *J* = 8.9 Hz, 1H), 5.22 (d, *J* = 15.7 Hz, 1H), 6.62 (d, *J* = 8.4 Hz 1H), 7.28-7.34 (m, 8H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 44.4, 52.9, 62.9, 73.8, 105.8, 110.8, 116.1, 126.2, 127.4 (2C), 128.0, 128.9 (2C), 131.8, 132.9, 135.1, 141.5, 159.0, 170.4, 174.9.

HRMS *m/z*: Calcd. for $C_{20}H_{16}BrNO_4$: 413.0263; Found 413.0263.

Compound 50b:



50b

R_f (20% EtOAc-Hexanes) 0.27.

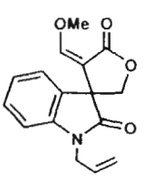
IR (CH_2Cl_2): ν_{max} 1751, 1712, 1668, 1605, 1486, 1054 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.85 (s, 3H), 4.34 (d, *J* = 8.9 Hz, 1H), 4.62 (d, *J* = 8.9 Hz, 1H), 4.84 (d, *J* = 15.4 Hz, 1H), 4.94 (d, *J* = 15.4 Hz, 1H), 6.11 (s, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 7.28-7.41 (m, 7H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 44.3, 53.1, 63.6, 72.88, 105.4, 111.2, 116.4, 126.8, 127.4 (2C), 128.2 (2C), 129.1 (2C), 132.2, 135.1, 141.1, 158.3, 176.6, 178.4.

HRMS *m/z*: Calcd. for $C_{20}H_{16}BrNO_4$: 413.0263; Found 413.0263.

Compound 51a:



51a

R_f (20% EtOAc-Hexanes) 0.36.

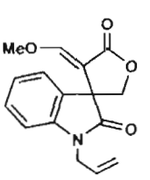
IR (CH_2Cl_2): ν_{max} 1752, 1714, 1668, 1611, 1471, 1047 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.68 (s, 3H), 4.18 (dd, *J* = 5.2 and 16.6 Hz, 1H), 4.38 (d, *J* = 8.8 Hz, 1H), 4.54-4.62 (m, 2H), 5.22-5.28 (m, 2H), 5.79-5.85 (m, 1H), 6.84 (d, *J*=7.8 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.25-7.31 (m, 3H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 42.6, 52.7, 62.6, 74.0, 106.3, 109.1, 117.3, 122.8, 123.3, 128.8, 130.8, 130.9, 142.4, 158.5, 170.7, 174.8.

HRMS *m/z*: Calcd. for $C_{16}H_{15}NO_4$: 285.1001; Found 285.0992.

Compound 51b:



51b

R_f (20% EtOAc-Hexanes) 0.29.

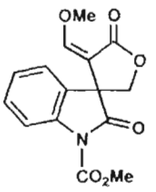
IR (CH_2Cl_2): ν_{max} 1756, 1702, 1659, 1606, 1464, 1071 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.85 (s, 3H), 4.32-4.38 (m, 3H), 4.58 (d, *J* = 9.0 Hz, 1H), 5.26-5.29 (m, 2H), 5.85 (m, 1H), 6.15 (s, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.25-7.35 (m, 2H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 43.2, 52.8, 62.6, 74.0, 106.2, 109.2, 117.4, 122.8, 123.4, 129.3, 131.3, 131.7, 142.4, 158.6, 167.87, 175.7.

HRMS *m/z*: Calcd. for $C_{16}H_{15}NO_4$: 285.1001; Found 285.0993.

Compound 52a:



52a

R_f (20% EtOAc-Hexanes) 0.37.

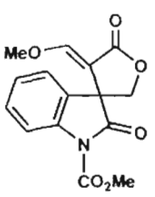
IR (CH_2Cl_2): ν_{max} 1756, 1702, 1659, 1606, 1464, 1071 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.68 (s, 3H), 4.04 (s, 3H), 4.36 (d, J = 8.9 Hz, 1H), 4.63 (d, J = 8.9 Hz, 1H), 7.23-7.40 (m, 4H), 7.93 (t, J = 8.4 Hz, 1H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 52.8, 59.3, 67.8, 74.0, 105.7, 108.6, 122.1, 123.5, 129.2, 132.4, 143.3, 158.5, 167.4, 174.8, 175.7.

HRMS *m/z:* Calcd. for $C_{15}H_{13}NO_6$: 303.0743; Found 303.0732.

Compound 52b:



52b

R_f (20% EtOAc-Hexanes) 0.27.

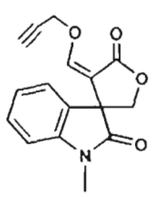
IR (CH_2Cl_2): ν_{max} 1756, 1702, 1659, 1606, 1464, 1071 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.68 (s, 3H), 4.13 (s, 3H), 4.36 (d, J = 8.9 Hz, 1H), 4.61 (d, J = 8.9 Hz, 1H), 7.21-7.42 (m, 4H), 7.92 (t, J = 8.3 Hz, 1H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 53.2, 58.5, 66.9, 73.5, 105.6, 109.7, 122.5, 123.4, 128.7, 131.9, 142.4, 158.6, 167.6, 170.7, 175.3:

HRMS *m/z:* Calcd. for $C_{15}H_{13}NO_6$: 303.0743; Found 303.0740.

Compound 53a:



53a

R_f (20% EtOAc-Hexanes) 0.36.

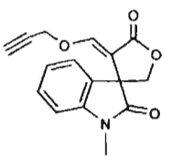
IR (CH_2Cl_2): ν_{max} 2120, 1747, 1715, 1668, 1048 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.42 (t, J = 2.3 Hz, 1H), 3.14 (s, 3H), 4.24-4.27 (m, 3H), 4.50 (d, J = 8.9 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 7.3 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.35 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 26.9, 53.0, 61.9, 74.1, 76.2, 78.1, 108.5, 108.6, 123.0, 123.6, 129.2, 130.79, 143.6, 155.4, 170.5, 175.2.

HRMS *m/z:* Calcd. for $C_{16}H_{13}NO_4$: 283.0845; Found 283.0843.

Compound 53b:



53b

R_f (20% EtOAc-Hexanes) 0.27.

IR (CH_2Cl_2): ν_{max} 2123, 1754, 1713, 1667, 1051 cm^{-1}.

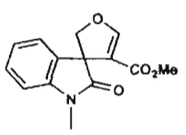
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.52 (t, *J* = 2.3 Hz, 1H), 3.26 (s, 3H), 4.31 (d, *J* = 8.7 Hz, 1H), 4.55-4.65 (m, 3H), 6.34 (s, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 7.12 (t, *J* = 7.3 Hz, 1H), 7.25-7.37 (m, 2H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 26.8, 29.8, 53.2, 61.8, 73.2, 77.9, 106.4, 107.7, 123.5, 123.8, 129.5, 131.4, 143.2, 154.3, 166.5, 176.1.

HRMS *m/z*: Calcd. for $C_{16}H_{13}NO_4$: 283.0845; Found 283.0841.

4.3.5. Spectral data for 3-spiro dihydrofuran compounds:

Compound 24c:



24c

R_f (20% EtOAc-Hexanes) 0.47.

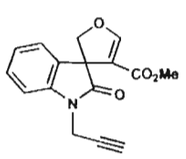
IR (CH_2Cl_2): ν_{max} 1714, 1615, 1492, 1471cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.27 (s, 3H), 3.53 (s, 3H), 4.64 (d, *J* = 9.5 Hz, 1H), 4. 90 (d, *J* = 9.5 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.58 (s, 1H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 26.6, 51.0, 56.7, 85.2, 108.0, 112.7, 113.1, 122.9, 129.0, 131.4, 143.4, 159.4, 162.9, 176.6.

HRMS *m/z*: Calcd. for $C_{14}H_{13}NO_4$: 259.0845; Found 259.0842.

Compound 48c:



48c

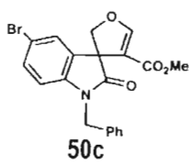
R_f (20% EtOAc-Hexanes) 0.48.

IR (CH_2Cl_2): ν_{max} 2186, 1715, 1615, 1486cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.27 (t, *J* = 2.5 Hz, 1H), 3.51 (s, 3H), 4.51 (dd, *J* = 17.6, 2.5 Hz, 1H), 4.62 (dd, *J* = 17.6, 2.5 Hz, 1H), 4.80 (d, *J* = 9.6 Hz, 1H), 4.91 (d, *J* = 9.6 Hz, 1H), 7.07-7.26 (m, 3H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.59 (s, 1H).

HRMS *m/z*: Calcd. for $C_{16}H_{13}NO_4$: 283.0845; Found 283.0838.

Compound 50c:



50c

R_f (20% EtOAc-Hexanes) 0.48.

IR (CH_2Cl_2): ν_{max} 1717, 1621, 1485 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.53 (s, 3H), 4.66 (d, *J* = 9.6 Hz, 1H), 4.77 (d, *J* = 15.8 Hz, 1H), 4.95 (d, *J* = 9.6 Hz, 1H), 5.11 (d, *J* = 15.8 Hz, 1H), 6.57 (d, *J* = 8.2 Hz, 1H), 7.27-7.35 (m, 7H), 7.62 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 44.5, 51.4, 57.0, 82.3, 110.8, 112.4, 115.8, 126.5, 127.3 (2C), 127.8, 128.8 (2C), 131.9, 133.2, 135.0, 141.6, 160.3, 163.0, 176.8.

HRMS *m/z*: Calcd. for $C_{20}H_{16}BrNO_4$: 413.0263; Found 413.0254.

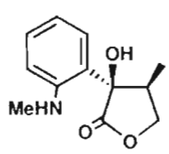
4.4. Experimental Details (Part-B)

4.4.1. General experimental procedure for synthesis of γ-butyrolactones

A mixture of MBH adduct derived from isatin (50mg, 0.191 mmol) in moist tetrahydrofuran (3mL) was added 4 equiv. of sodium borohydride (28.9mg, 0.7mmol) in two portion-wise over a period of 5 min. at room temperature. The mixture was stirred at the same temperature until complete disappearance of starting material (TLC, ca. 2h). Then, the THF was removed under reduced pressure. The crude material was extracted with ethyl acetate (2 x 10mL) and the combined organic layer was washed with water, and brine. The organic layer was separated and dried (Na_2SO_4) and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography using a gradient elution with hexane and hexane and EtOAc as eluent to afford pure product in excellent yield (89-98%).

4.4.2. Spectral data for γ-butyrolactones:

3-Hydroxy-4-methyl-3-(2-methylamino-phenyl)-dihydro-furan-2-one **68**:



68

Colourless solid; M.P: 110°C

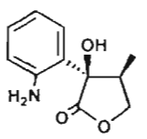
IR (CH_2Cl_2): ν_{max} 3402, 1771, 1710, 1614 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ 0.58 (d, *J* = 6.9 Hz, 3H), 2.47 (m, 1H), 3.18 (s, 3H), 3.37 (bs, 1H, OH), 3.89 (dd, *J* = 11.1 and 3.9 Hz, 1H), 4.03 (dd, *J* = 11.1 and 9.9 Hz, 1H), 4.95 (s, 1H, NH), 6.82 (d, *J* = 7.8 Hz, 1H, Ar), 7.09-7.36 (m, 3H, Ar).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.38, 26.13, 41.29, 64.47, 79.67, 108.31, 123.45, 123.49, 129.68, 130.34, 143.39, 177.89.

HRMS *m/z*: Calcd. for $C_{12}H_{15}NO_3$: 221.1054; Found 221.1035.

3-(2-Amino-phenyl)-3-hydroxy-4-methyl-dihydro-furan-2-one **77**:



77

Colourless viscous liquid, R_f: 0.3 (50:50 Hexane/EtOAc)

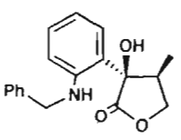
IR (CH_2Cl_2): ν_{max} 3325, 1773, 1713, 1613 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ 0.65 (d, *J* = 7.2 Hz, 3H), 2.48 (m, 1H), 2.77 (bs, 3H, OH and NH_2), 3.83 (dd, *J* = 11.1 and 4.2 Hz, 1H), 4.00 (dd, *J* = 11.1 and 9 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H, Ar), 7.04-7.33 (m, 3H, Ar), 8.24 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.25, 41.34, 64.35, 79.94, 110.27, 123.38, 123.97, 129.68, 130.82, 140.48, 180.01.

HRMS *m/z*: Calcd. for $C_{11}H_{13}NO_3$:207.0895; Found. 207.0881

3-(2-Benzylamino-phenyl)-3-hydroxy-4-methyl-dihydro-furan-2-one **78**:



78

Colourless viscous liquid, R_f: 0.6 (60:40 Hexane/EtOAc).

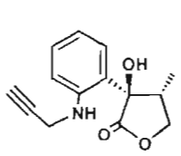
IR (CH_2Cl_2): ν_{max} 3385, 2964, 2941, 2884, 1778, 1703, 1613 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ 0.62 (d, *J* = 7.2 Hz, 3H), 2.51 (m, 1H), 2.59 (bs, 2H, OH and NH), 3.93 (dd, *J* = 11.1 and 4.5 Hz, 1H), 4.12 (dd, *J* = 11.1and 9 Hz, 1H), 4.75 (d, *J* = 15.6, 1H), 5.00 (d, *J* = 15.6 Hz, 1H), 6.71 (d, *J* = 7.8, 1H, Ar), 7.05-7.34 (m, 8H, Ar).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.62, 41.33, 43.91, 64.57, 79.63, 109.39, 123.48, 123.60, 127. 28 (2C), 127.73, 128.83 (3C), 129.62, 135.48, 142.63, 178.03.

HRMS *m/z*: Calcd. for $C_{18}H_{19}NO_3$: 297.1365; Found: 297.1366

3-Hydroxy-4-methyl-3-(2-prop-2-ynylamino-phenyl)-dihydro-furan-2-one **79**:



79

Colourless viscous liquid, R_f: 0.6 (80:20 Hexane/EtOAc)

IR (CH_2Cl_2): ν_{max} 3427, 3297, 2970, 2935, 2883, 1777, 1703, 1610 cm^{-1}.

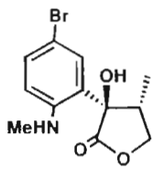
^{1}H NMR: δ 1.26 (d, *J* = 6.9 Hz, 3H), 2.17 (t, *J* = 2.4 Hz, 1H), 2.43 (m, 1H), 3.72 (dd, *J* = 8.7 and 4.8 Hz, 1H), 3.84 (dd, *J* = 8.7 and 5.7

Hz, 1H), 4.07 (2dd, *J* = 18.0, 2.4 Hz, 2H), 5.35 (s, 1H, NH), 6.61 (d, *J* = 7.8 Hz, 1H, Ar), 6.79-7.28 (m, 3H, Ar).

^{13}C NMR: 12.19, 34.60, 43.65, 71.73, 74.82, 78.87, 87.94, 107.94, 119.25, 123.13, 130.15, 148.42, 172.40.

HRMS *m/z*: Calcd. for $C_{13}H_{12}NO_3$: 230.0817; Found: 230.0802

3-Hydroxy-4-methyl-3-(2-methylamino-5-bromo-phenyl)-dihydro-furan-2-one **80:**



80

Colourless viscous liquid, R_f: 0.5 (80:20 Hexane/EtOAc)

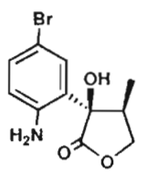
IR (CH_2Cl_2): ν_{max} 3391, 2966, 1769, 1606 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ 0.98 (d, *J* = 6.9 Hz, 3H), 1.99 (bs, OH), 2.65 (m, 1H), 2.85 (s, 3H), 3.16 (dd, *J* = 11.4 and 9 Hz, 1H), 4.02 (dd, *J* = 11.4 and 7.2 Hz, 1H), 5.20 (s, 1H, NH), 6.39 (d, *J* = 9.0 Hz, 1H, Ar), 7.26-7.31 (m, 2H, Ar).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.35, 25.93, 41.18, 64.45, 79.68, 109.22, 112.80, 127.56, 131.85, 132.72, 140.32, 180.81.

HRMS *m/z*: Calcd. for $C_{12}H_{14}BrNO_3$: 299.0157; Found 299.0214.

3-(2-Amino-5-bromo-phenyl)-3-hydroxy-4-methyl-dihydro-furan-2-one **81:**



81

Colourless viscous liquid, R_f: 0.4 (60:40 Hexane/EtOAc)

IR (CH_2Cl_2): ν_{max} 3288, 2957, 2351, 1776, 1721, 1620 cm^{-1}.

^{1}H NMR: δ 0.64 (d, *J* = 6.9 Hz, 3H), 2.42 (m, 1H), 2.89 (bs, 1H, OH), 3.80 (dd, *J* = 10.8 and 3.9 Hz, 1H), 4.00 (dd, *J* = 10.8 and 9.8 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.43 (s, 1H), 8.40 (s, 1H, NH).

^{13}C NMR: 11.21, 41.16, 64.30, 79.98, 109.31, 113.40, 127.35, 132.50, 132.81, 140.00, 190.79.

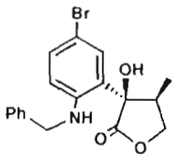
HRMS *m/z*: Calcd. for $C_{11}H_{12}BrNO_3$: 285.0001; Found: 284.9987

3-(2-Benzylamino-5-bromo-phenyl)-3-hydr-oxy-4-methyl-dihydro-furan-2-one **82:**

Colourless viscous liquid, R_f: 0.5 (50:50 Hexane/EtOAc)

IR (CH_2Cl_2): ν_{max} 3405, 2941, 1781, 1718, 1600 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ 0.61 (d, *J* = 6.9, 3H), 1.94 (bs, 2H, OH and NH), 2.5 (m, 1H), 3.92 (dd, *J* = 11.1 and 4.5 Hz, 1H), 4.18



82

(dd, J = 11.1 and 9.6 Hz, 1H), 4.75 (d, J = 15.6 Hz, 1H), 4.98 (d, J = 15.6 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H, Ar), 7.28-7.48 (m, 7H, Ar).

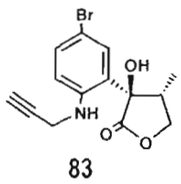
^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.59, 41.11, 64.65, 79.64, 104.78, 116.21, 122.11, 123.44, 127.01, 127.21 (2C), 127.89 (3C), 130.01, 132.39, 141.82, 196.58.

HRMS *m/z*: Calcd. for $C_{18}H_{18}BrNO_3$: 375.0470; Found 375.0470

3-Hydroxy-4-methyl-3-(2-prop-2-ynylamino-5-bromo-phenyl)-dihydro-furan-2-one **83:**

Colourless viscous liquid, R_f: 0.5 (80:20 Hexane/EtOAc)

IR (CH_2Cl_2): ν_{max} 3427, 3297, 2970, 2935, 2883, 1777, 1703, 1610 cm^{-1}.



83

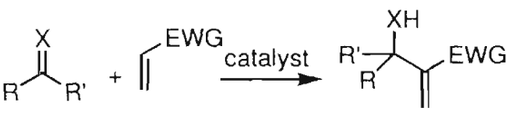
^{1}H NMR: δ 1.24 (d, J = 7.2 Hz, 3H), 2.18 (t, J = 2.1 Hz, 1H), 2.39 (m, 1H), 3.74 (dd, J = 8.7 and 4.8 Hz, 1H), 3.85 (dd, J = 8.7 and 5.7 Hz, 1H), 3.86 (dd, J = 15.9, 2.1 Hz, 2H), 5.34 (s, 1H, NH), 6.48 (d, J = 8.4 Hz, 1H, Ar), 7.32 (dd, J = 8.4, 1.8 Hz, 1H, Ar), 7.36 (d, J = 1.8 Hz,1H).

^{13}C NMR: 11.99, 34.53, 43.66, 72.02, 74.76, 78.34, 87.64, 109.22, 110.80, 126.33, 132.77, 133.74, 147.29, 171.72.

HRMS *m/z*: Calcd. for $C_{14}H_{14}BrNO3$: 323.0157; Found: 323.0212.

SUMMARY

The Morita-Baylis-Hillman (MBH) reaction is an attractive and powerful tool for C-C bond formation reaction. The reaction essentially involves participation of three components which are (i) electrophile, (ii) activated alkene and (iii) tertiary base (Scheme 1). The MBH adduct has been fascinated by synthetic organic chemists in recent years because of its easy preparation and application in the synthesis of densely functionalized molecules. These adducts have been used for the synthesis of important biologically active natural products and related core structures.



R = aryl, alkyl, heteroaryl; R' = H, CO_2R, alkyl
X = O, NR; EWG = electron-withdrawing group

Scheme 1 The Morita-Baylis-Hillman (MBH) reaction

The synthetic versatility of isatin has led to the extensive use of this compound in organic synthesis. Many synthetic methodologies have been described for the conversion of isatins to other heterocyclic systems. The spiro-oxindole ring system is found as core structures of many alkaloids, which displays significant biological activities and are interesting, challenging targets for chemical synthesis by synthetic organic chemists. Construction of such systems can also be appropriate from isatin. Isatin and its derivatives readily undergo MBH reaction to form corresponding MBH adducts (Figure 1) as reported by Garden *et al.* However, literature search showed that the synthetic utility of functionalised MBH adduct of isatin is unexplored. With this background, for the present research work, MBH adducts of isatin have been used as starting materials for novel synthetic transformation which in general afforded novel 3-spiro- and heterocyclic oxindole core structures. Accordingly, the thesis has been divided into four chapters.

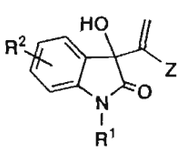
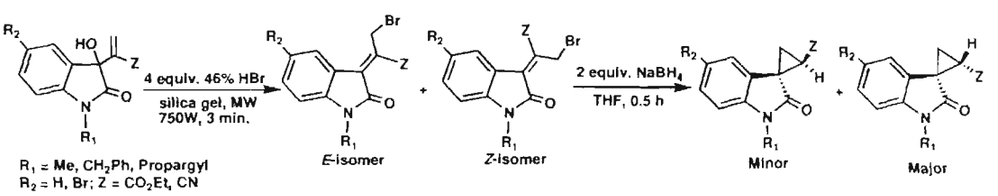


Figure 1 MBH adducts of isatin

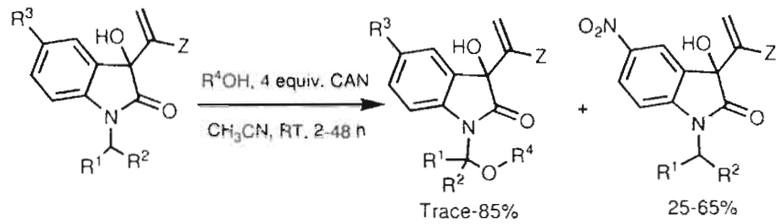
Chapter I of thesis embodied a brief general introductory discussion on the genesis, historical development and synthetic application of MBH-reaction. Followed by the origin, development, synthetic transformations, applications in the synthesis of natural products based on the chemistry of isatin have also been presented.

Syntheses of functionalized 3-spirocyclopropane-2-oxiindolones from bromo isomerised MBH adduct of isatin have been achieved. Initially, we have successfully carried out the isomerisation of MBH adducts of isatin using aqueous HBr under microwave irradiation condition. The mixture of bromo isomerised MBH adducts have been used for the stereoselective synthesis of spiro-3-cyclopropane-2-oxindolones by reductive cyclisation methodology with $NaBH_4$ as a reducing reagent as shown in Scheme 2. Mechanism of the reaction, assignment of stereochemistry of the final products by spectral study has also been discussed. The synthetic strategy, characterization of new compounds by spectral means and experimental details has also been presented at the end of chapter II.



Scheme 2 Syntheses of functionalized 3-spirocyclopropane-2-oxiindolones

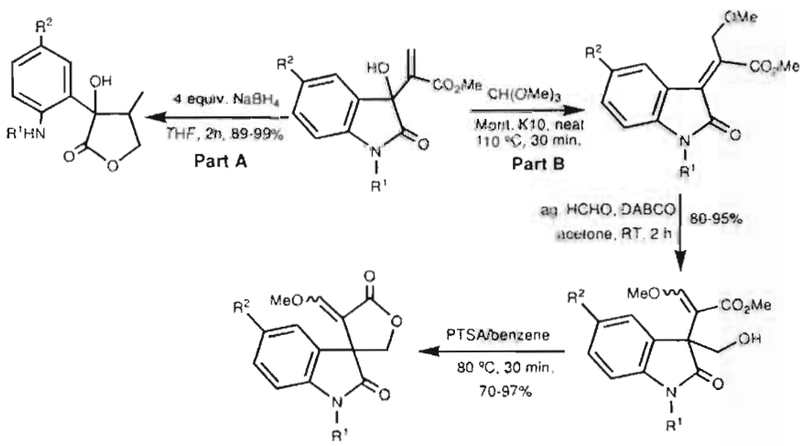
Chapter III of the thesis dealt with activation of the *N*C-H bond of MBH adducts of *N*-substituted isatin with CAN/ROH. A brief introduction on general CH activation and CAN as potential single electron oxidant in organic synthesis is outlined. We have chosen various MBH adducts with different *N*-alkyl substitutions such as methyl, methylene and methine which in principle generate 1°, 2° and 3° radical cation intermediates during the *N*C-H activation process. A systematic and elaborate study has been conducted as depicted in Scheme 3. Mechanism, reactivity and selectivity reason of the activation reaction study have also been discussed. The preparative methods, characterization of new compounds and experimental procedure have been presented in detail at the end of the chapter III.



R^1 = H, CH_3; R^2 = H, CH_3, CO_2Me, benzyl, propargyl;R^3 = H, Br, NO_2, R^4 = CH_3, C_2H_5, propargyl, homopropargyl, ethane-1,2-diol, propane-1,3-diol, benzyl, isopropanol, *t*-butanol; Z = CO_2Me, CN

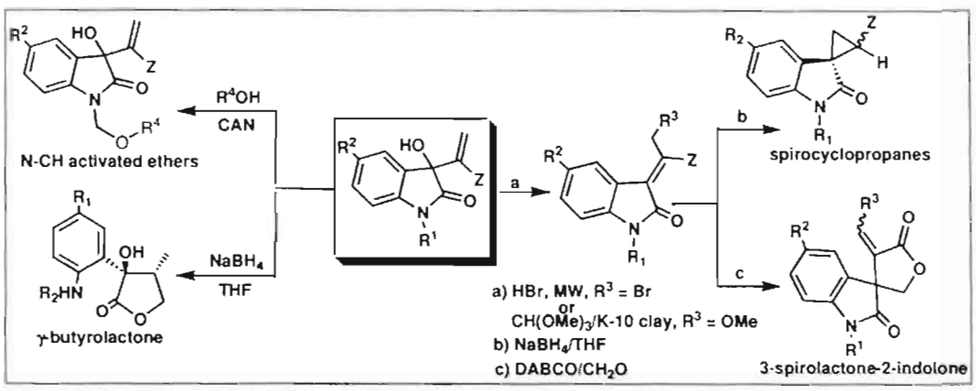
Scheme 3 Activation of the NC-H bond of MBH adducts of *N*-substituted isatin

The chapter IV has been divided into Part A and Part B. Part A contained the detailed synthesis of 3-spiro α-methylene-γ-butyrolactone oxindoles from methoxy isomerised MBH adducts of isatin. The synthesis of spiro-lactones has been achieved by following a three step reaction sequences viz. 1. Isomerisation of the MBH adducts of isatin with trimethyl orthoformate and montmorillonite K10 clay catalyst; 2. A second MBH reaction and 3. An acid catalyzed lactonization. Part B outlined the synthesis of functionalized γ-butyrolactones directly from MBH adducts of isatin by reductive cyclization methodology. Accordingly, synthesis of γ-butyrolactone from MBH adduct of isatin by reductive cyclization method using $NaBH_4$ as a reagent was described. Characterization of new compounds, mechanism of the reaction and detailed experimental procedure has been presented at end of the chapter IV.



Scheme 4 Synthesis of 3-spiro α-methylene-γ-butyrolactone oxindoles and of functionalized γ-butyrolactones

The over-all content of the work carried out in the thesis is shown in Scheme 5.



Scheme 5

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Parts of this Thesis has been Published in the Following Journals

1. Synthesis of functionalized 3-spirocyclopropane-2-indolones from isomerised Baylis-Hillman adducts of isatin. P. Shanmugam*, **V. Vaithiyanathan** and B. Viswambharan *Tetrahedron* **2006**, *62*, 4342-4348.

2. Activation of the NC-H bond of Baylis-Hillman adducts of *N*-methylisatin with CAN/ROH. P. Shanmugam*, **V. Vaithiyanathan** and B. Viswambharan *Tetrahedron Lett.* **2006**, *47*, 6851-6855.

3. A facile stereoselective synthesis of functionalized dihydrofuran-2-one from Baylis-Hillman adducts of isatin. P. Shanmugam*, **V. Vaithiyanathan** and B. Viswambharan *Aust. J. Chem.* **2007**, *60*, 296-301.

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Papers Co-authored

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10. Synthesis of highly functionalised linear pentacyclic compounds from Baylis-Hillman adduct of ninhydrin with azomethine ylides via [3+2] cycloaddition. P. Shanmugam*, S. Madhavan, B. Viswambharan and **V. Vaithiyanathan** *Indian J. Chem., Sec B* **2008**, *47B*, 1113-1116.

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11. Synthesis of highly functionalized allene appended oxindoles and 2-oxo-1,2-dihydro-indol-3-ylidene-2,5-dihydro-furan derivatives via Claisen rearrangement and Cyclization **V. Vaithiyanathan,** K. Selvakumar, P. Shanmugam*, *Synlett* **2009**, (Communicated).

12. A First One-Pot Synthesis, Isomerisation and Synthetic Utility of Mono and Bis Morita-Baylis-Hillman Adducts of 1,1'-Ferrocenedialdehyde. P. Shanmugam*, S. Madhavan, K. Selvakumar, **V. Vaithiyanathan** and B. Viswambharan *Tetrahedron Letters* **2009** (Communicated).

13. A facile and efficient aryl ring Functionalisation of oxindole nucleus via Morita-Baylis-Hillman reaction and isomerisation. P. Shanmugam*, K. Selvakumar and **V. Vaithiyanathan** *Aust. J. Chem.* **2009**, (Communicated).

14. Synthesis of 3-spirocyclopentene oxindoles and 3-spiropyrazole oxindoles via [3+2] annulation method. P. Shanmugam*, K. Selvakumar, **V. Vaithiyanathan** *Tetrahedron Letters* **2009** (Communicated).

Conferences/Poster Presentation/Workshop

1. **Participated** at DST Sponsored National Workshop on Green Chemistry during 15-16 July, 2005 held at Madurai Kamaraj University, Madurai.
2. **Participated and presented two Posters** at the Joint International Conference on Building Bridges, Forging Bonds for 21st Century Organic Chemistry and Chemical Biology (ACS-CSIR OCCB 2006) held between 6th and 9th January 2006 at National Chemical Laboratory, Pune (India)
3. **Presented an oral paper** on CRSI seminar on Recent Advances in chemistry held during10-11, 2006 at Annamalai University, Chidambaram, Tamil Nadu.
4. **Participated** a training programme Sponsored by HRDG, CSIR on **Technological Entrepreneurship** Conducted by Faculty of IIM, Bangalore from February 20 to March 22, 2006 at CLRI Chennai.
5. **Presented a poster** at the FOCY2007 held during January 11-12, 2007 at the Department of Chemistry, Calicut University.
6. **Participated** at DST Sponsored National Workshop on One and Two Dimensional NMR Spectroscopy, during 22-23 February, 2007 held at Madurai Kamaraj University, Madurai.