NOVEL 1,3-DIPOLAR CYCLOADDITION REACTIONS OF ACYCLIC CARBONYL YLIDES AND RELATED CHEMISTRY

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CERTIFICATE

This is to certify that the work embodied in the thesis entitled "**Novel 1,3-Dipolar Cycloaddition Reactions of Acyclic Carbonyl Ylides and Related Chemistry**" has been carried out by **Ms. Sindhu Mathai** under my supervision at the Organic Chemistry Division of the Regional Research Laboratory (CSIR), Trivandrum, and the same has not been submitted elsewhere for any other degree.

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LIST OF ABBREVIATIONS

Ac	: acetyl
acac	: acetyl acetonate
bs	: broad singlet
d	: doublet
DMAD	: dimethyl acetylenedicarboxylate
Et	: ethyl
h	: hour(s)
HOMO	: highest occupied molecular orbital
HRMS	: high-resolution mass spectrum
Hz	: hertz
IR	: infrared
J	: coupling constant
LUMO	: lowest unoccupied molecular orbital
m	: multiplet
Me	: methyl
NPM	: *N*-phenyl maleimide
g	: gram
mL	: milliliter
mp	: melting point
NMR	: nuclear magnetic resonance
nOe	: nuclear Overhauser effect spectroscopy
o	: ortho
oct	: octanoate
p	: para
Ph	: phenyl
Pr	: n-propyl
RT	: room temperature
s	: singlet
t	: triplet
Tf	: triflyl (trifluoromethanesulfonyl)
Ts	: *p*-toluene sulfonyl
tert	: tertiary

CHAPTER 1

AN INTRODUCTION TO THE CHEMISTRY OF CARBENES, CARBENOIDS AND CARBONYL YLIDES

1.1. Introduction

Carbon-carbon and carbon-heteroatom bond-forming reactions constitute the central events in organic synthesis. With few exceptions, such reactions rely on the use of transient species, known as reactive intermediates. The most commonly used reactive intermediates are cations, anions and radicals. Other reactive intermediates, *viz.*, carbenes, nitrenes, ylides and zwitterions, although known for a long time, have received the attention of organic chemists only recently. The importance of carbenes stems from their diverse range of reactivity. They can form zwitterions by reacting with activated carbon-carbon double bonds or triple bonds. Carbenes are also known to form 1,3-dipoles or ylides with heteroatom containing organic compounds which are valuable tools in synthetic organic chemistry, especially for the synthesis of heterocyclic compounds. Carbonyl ylides, a well known example of 1,3-dipoles, have gained much interest in recent years due to their potential role as intermediates in a variety of reactions, including the formation of oxiranes and five membered heterocycles.[1]

Recently, intermolecular or intramolecular reactions of carbenes and metallocarbenes with carbonyl compounds were found to be an efficient method for carbonyl ylide formation, thus providing a convenient synthetic route to oxygenated five membered heterocycles or complex polycyclic oxygen heterocycles. The focal theme of the present study is the exploration of the reactivity of acyclic carbonyl ylides generated from aldehydes and dicarbomethoxycarbene with various dipolarophiles. In order to put things in perspective, a brief introduction to the

chemistry of carbenes, carbenoids and carbonyl ylides is needed as a prelude, and it is provided in the following passages.

The most common reactive intermediates of organic chemistry are charged species, such as carbocations or carbanions. However, there are two important groups of formally neutral electron-deficient reactive intermediates, *viz.*, radicals, in which the trivalent carbon centre has a single non-bonding electron, and carbenes* with two non-bonding electrons on its divalent carbon centre. The first attempts to prepare carbenes, known in the early literature as methylenes, were made by Dumas and Regnault in 1839, when they tried to synthesize methylene by dehydrating methanol using phosphorous pentoxide[2]. Later, in 1861 Butlerov suggested the intermediacy of methylene[2] when he prepared ethylene by the reaction of methyl iodide with copper. In 1862, Geuther established that dichloromethylene can be produced by the basic hydrolysis of chloroform.[3] Modern work in the field of methylenes began around 1910 with the investigations of Staudinger on the decomposition of diazo compounds.[4] The consistent use of these fascinating species as transient intermediates[2,5] and their important role in the field of synthetic organic chemistry, however, began only after their introduction into organic chemistry by Doering in the 1950s.[6]

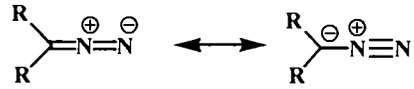
1.1.1. General Methods for the Generation of Carbenes

Elimination or fragmentation reactions, which usually involve the breaking of rather weak bonds and the formation of stable byproducts, remain the most efficient methods for the generation of carbenes.

Diazo compounds, known for over a century since the first preparation of ethyl diazoacetate[7] by Curtius in 1883, are probably the most widely used carbene precursors. They possess a 1,3-dipolar structure (Figure 1) and are readily prepared from a variety of precursors. They decompose to carbenes with loss of nitrogen under thermal or photochemical conditions or under the influence of certain transition metal

*The word 'carbene' was apparently conceived by Woodward, Doering and Winstein, and was first introduced at a meeting of the American Chemical Society in 1951.

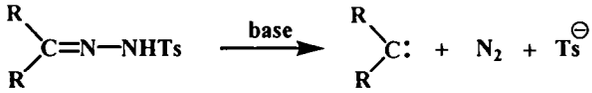
catalysts.



1 2

Figure 1. *1,3-dipolar nature of the diazo group indicating possibility for resonance stabilization.*

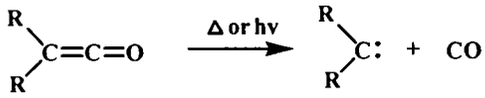
In a similar way, tosyl hydrazones also generate carbenes under basic conditions (Scheme 1).[8]



3 4

Scheme 1

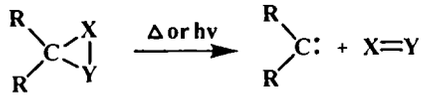
Ketenes are known to decompose under photolytic or thermal conditions to generate carbenes (Scheme 2).



5 4

Scheme 2

Photolysis or thermolysis of small rings have been shown to generate carbenes (Scheme 3).[9]

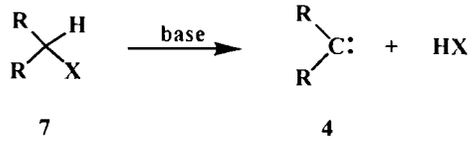


6 4

X–Y = O-CR_2, R_2C–CR_2, N=N

Scheme 3

Organic halides under strong basic conditions undergo α-elimination and generate carbenes (Scheme 4).[10]

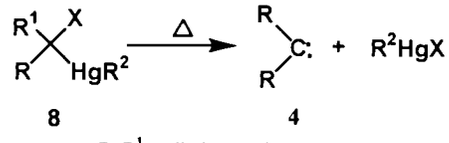


7 4

X = good leaving group

Scheme 4

Another method employed involves the thermolysis of Seyferth reagents (Scheme 5).[11]



8 4

R, R^1 = alkyl or aryl
R^2 = aryl
X = halide

Scheme 5

1.1.2. Structure and Reactivity

Carbenes are neutral divalent carbon species with only six electrons in their valence shell, two in each bond and two nonbonding electrons which are often represented as $:CR_2$ (as though they are lone pairs). Carbenes are usually thought of as being sp^2-hybridized. Since the non-bonding electrons can have their spins paired or parallel, there is the possibility of two electronic arrangements or spin states (Figure 2). The singlet carbene has the spins of its non-bonding electrons paired. This electron pair is in an sp^2-orbital leaving a vacant *p*-orbital on the carbene-carbon. In triplet carbenes, however, the two non-bonding electrons have parallel spins.

In general, triplet is often the ground state even though the energy difference between singlet and triplet states is not very high (estimated to be 32-42 KJ/mol for methylene). Depending upon the mode of generation, a carbene may initially be formed in either state, no matter which one is lower in energy.

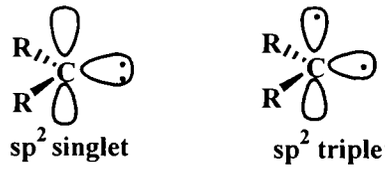


Figure 2. *Electronic structures of R_2C: showing sp^2 singlet and triplet states*

Carbenes are electron deficient intermediates, the carbon atom having only six electrons in its outer shell. Therefore, carbenes are expected to be highly electrophilic in their reactions. However, the nature of the substituents affects the chemical reactivity of carbene intermediates. Not surprisingly the more electron withdrawing the substituents, the more strongly electrophilic the carbene (Figure 3).

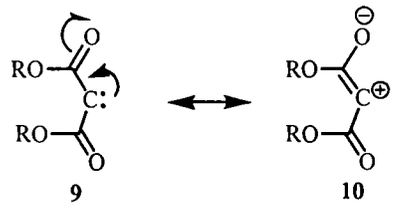


Figure 3

Similarly, very strong π-donor substituents such as amino groups can make the carbene electron rich and consequently render it nucleophilic in its reactions (Figure 4).

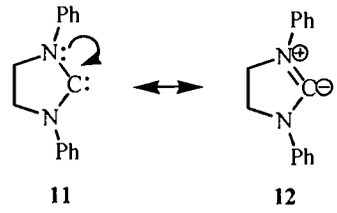
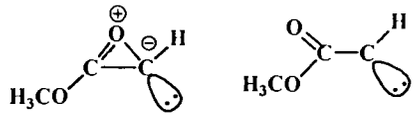


Figure 4

Furthermore, since carbenes are high energy species, they can assume more stable structures. As a case in point, one set of MO calculations[12] arrives at structure **A** as a better description of carbomethoxycarbene than the conventional structure **B** (Figure 5).



A B

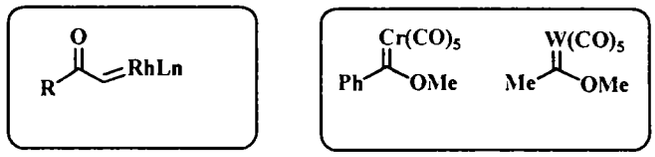
Figure 5

1.2. Carbenoids

In general, the term carbenoid refers to the transition-metal bound carbene formed by metal-catalyzed decomposition of diazo compounds. Carbenes formed by this process cannot be considered as true carbenes because it appears that they remain complexed with the metal used to generate them. Organic chemists have recognized that carbenoids[13] can be very good substitutes for free carbenes in many of the reactions which are ascribed to them.

It has been known that the addition of certain copper salts to solutions of diazo compounds leads to evolution of nitrogen and formation of products of the same general type as those formed in thermal and photochemical decomposition of diazoalkanes. There is, however, no evidence to show that free carbene intermediates are involved in such reactions. Instead, complexes of the carbene unit with the metallic catalyst seem to be the actual reactants. Such complexes are examples of carbenoid species.

Several metal ions exert a catalytic effect on the decomposition of diazo compounds. While rhodium and copper carbenoids are unstable, some transition metals such as tungsten and chromium form stable and isolable carbenoids (Figure 6).

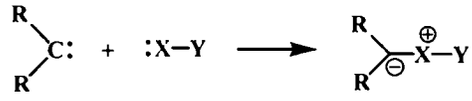


Rhodium carbene complex Stable 'Fischer carbenes'

Figure 6

1.3. Ylides

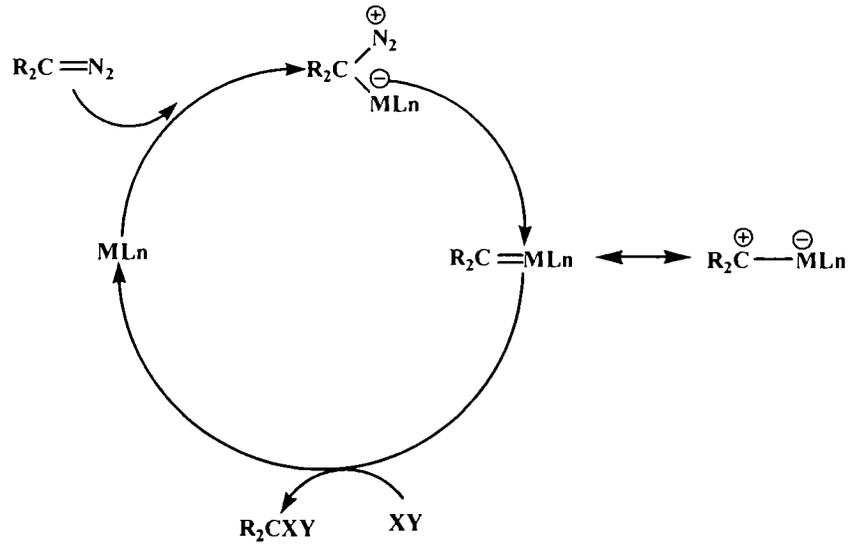
Ylides[14] are defined as reactive intermediates, which are known to undergo a number of synthetically useful transformations to form stable products. Ylides can be viewd as species in which a positively charged heteroatom 'X' (O, I, S, Se, N, P etc.) is connected to an atom possessing an unshared pair of electrons. Even though several methods are available for the generation of ylides, except for phosphorus ylides, the reaction of a heteroatom *via* its lone pair with a carbene remains the most efficient method for ylide formation (Scheme 6).



4 13 14

Scheme 6

The method of generation (thermal, photochemical or base induced elimination), as well as the high reactivity and the lack of selectivity with functionalized organic compounds diminishes the synthetic utility of free carbenes in ylide- forming process. Therefore it is often preferable to use metal-complexed carbenes (carbenoids) in which the metal and the ligands with which it is associated can potentially influence the reactivity of the carbene. Carbenoids are themselves often transient intermediates. An efficient method for generating carbenoids involves the metal catalyzed decomposition of a diazo (often an α-diazocarbonyl) compound. The metal complex used acts as a Lewis acid and accepts electron density from the diazocarbon at a vacant coordination site on the metal (Scheme 7). This is followed by the concomitant loss of nitrogen due to the back donation of electron density from the metal to carbene-carbon. As the intermediate metallocarbene can be considered to be electrophilic at carbon, it can accept electron density from a suitable donor XY with eventual loss of the metal-ligand complex which therefore functions as a catalyst.[15]



Scheme 7

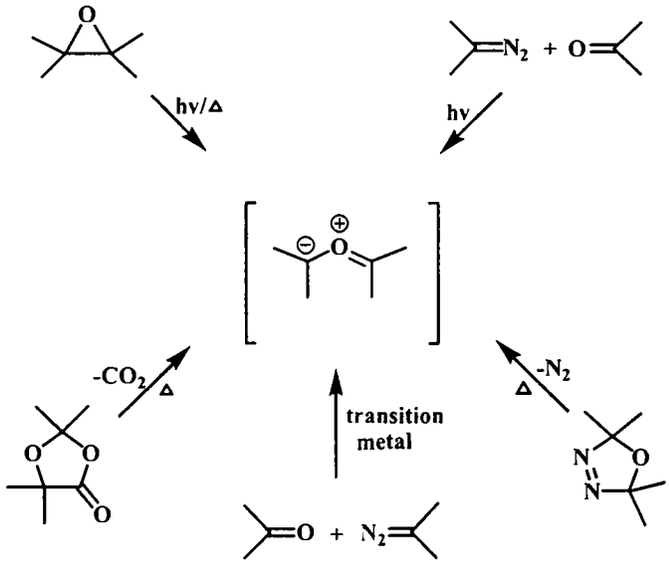
Among the metallocarbenes which generate ylides, those formed by the use of copper and rhodium salts are particularly important.[16] Until 1970, catalytic decomposition reactions of diazo compounds were usually carried out in the presence of copper in different oxidation states. As a result of a systematic screening of transition-metal compounds, Rh(II) carboxylates[17] have emerged as highly efficient catalysts for ylide generation from diazo compounds.

Ylides are known to form by the reaction of metallocarbenes with nucleophilic species like ethers, thioethers, amines etc. Compounds containing heteroatoms in the sp^2 or sp state of hybridization interact similarly with carbenes. Examples of such functional groups include aldehydes, esters, ketones, imines, thiocarbonyl compounds and nitriles.

1.3.1. Carbonyl Ylides

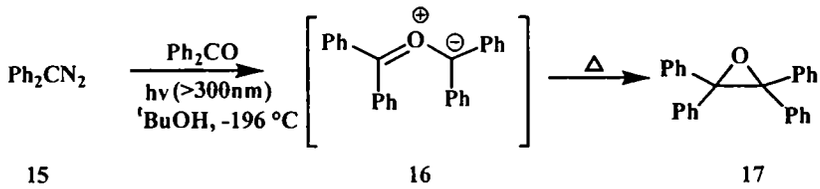
Although the chemistry of a wide range of ylides has been studied in detail, we will be concerned only with carbonyl ylides, since the subject matter of the thesis is mainly focused on the generation and reactivity of the latter. Several methods are available in the literature for the generation of carbonyl ylides. The most common methods involve the thermolysis or photolysis of epoxides possessing electron

withdrawing substituents,[18] the thermal extrusion of nitrogen from 1,3,4-oxadiazoline[19] and the loss of carbon dioxide from 1,3-dioxolan-4-ones[20] (Scheme 8).



Scheme 8

However, the reaction of carbenes with carbonyl compounds represents the most useful approach to the generation of carbonyl ylides. Quite a number of recent studies support the intermediacy of carbonyl ylides in reactions involving the interaction of a carbene with carbonyl oxygen. In an elegant experiment, by Tomioka, where diphenyl diazomethane in 5% benzophenone/*tert*-butyl alcohol was irradiated, the transient formation of a blue species in the reaction mixture was reminiscent of a carbonyl ylide which had been previously detected in the low-temperature irradiation of oxirane (Scheme 9).[21]



15 16 17

Scheme 9

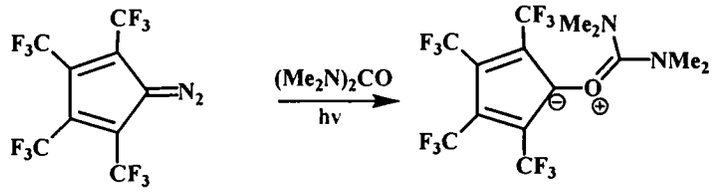
Olah and co-workers have irradiated dideuteriodiazomethane with monomeric formaldehyde in an ether solution and found evidence supporting the formation of

carbonyl ylide.[22] A carbonyl ylide formation has also been detected in the photolysis of 9-diazofluorene (Scheme 10).[23]

18 19

Scheme 10

Very few examples of stable carbonyl ylides have been reported in the literature. One particularly interesting case, however, involves an ylide stabilized by a "push-pull" electronic substitution pattern.[24] Irradiation of diazotetrakis(trifluoromethyl)cyclopentadiene in the presence of tetramethyl urea produced the carbonyl ylide **21** as a crystalline solid. The structure of this species has been elucidated by X-ray crystallographic analysis (Scheme 11).

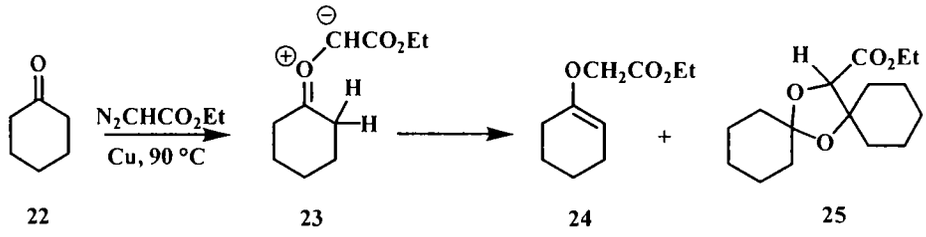


20 21

Scheme 11

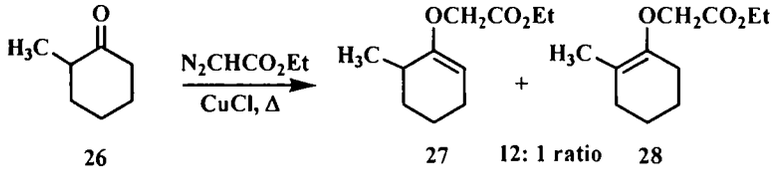
1.3.2. Proton Transfer

One characteristic reaction of carbonyl ylides derived from the metal catalyzed reaction of diazoalkanes with ketones consists of an intramolecular proton transfer to give enol ethers. In 1953 Kharasch and co-workers reported the first example for this kind of reaction. Treatment of ethyl diazoacetate in cyclohexanone with a catalytic amount of copper powder at 90 °C afforded two products (Scheme 12).[25]



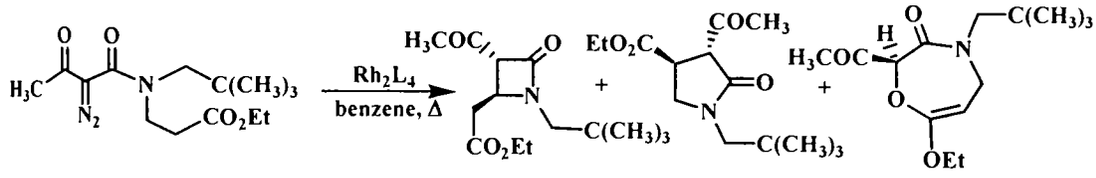
Scheme 12

The mechanism proposed for the formation of enol ether **24** invokes the generation of a copper carbenoid which then adds to the carbonyl oxygen of cyclohexanone to produce carbonyl ylide **23**. The latter then undergoes an intramolecular proton transfer. The adduct **25** was formed *via* 1,3-dipolar cycloaddition of ylide across the carbonyl group of cyclohexanone. Proton-transfer reactions were found to occur with high regiospecificity.[26] When unsymmetrical ketones were used, formation of the least substituted enol ether is the dominant pathway. For example, the reaction of 2-methyl cyclohexanone with ethyl diazoaceate in the presence of a copper catalyst results primarily in the formation of enol ethers **27** and **28** (Scheme 13).



Scheme 13

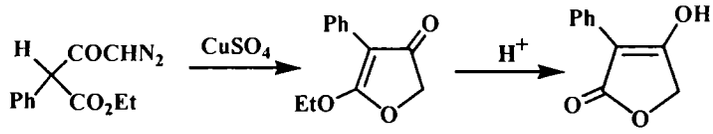
Interestingly, this reaction has been applied as a versatile methodology for the synthesis of many biologically active compounds. Doyle and coworkers have reported the synthesis of β-lactam compounds through intramolecular C-H insertion induced by the Rh(II) acetate catalyzed decomposition of *N*-alkyl diazoacetoacetamides.[27] Products **30** and **31** were formed by C-H insertions of the rhodium carbenoid derived from **29**. In addition to these compounds, heterocycle **32** was also formed from the suspected carbonyl ylide intermediate which then undergoes a proton transfer (Scheme 14).



29 30 31 32

Scheme 14

Bien and Gillon have prepared 3(2H)-furanones by the proton transfer reaction of carbonyl ylide.[28] For example, the copper sulfate catalyzed decomposition of ethyl 2-phenyl-4-diazoacetoacetate **33** gave 5-ethoxy-4-phenyl-3(2H)-furanone **34** as well as 4-hydroxy-3-phenyl-2(5H)furanone **35**. The formation of furanone **35** can be attributed to hydrolysis of **34** during workup (Scheme 15).

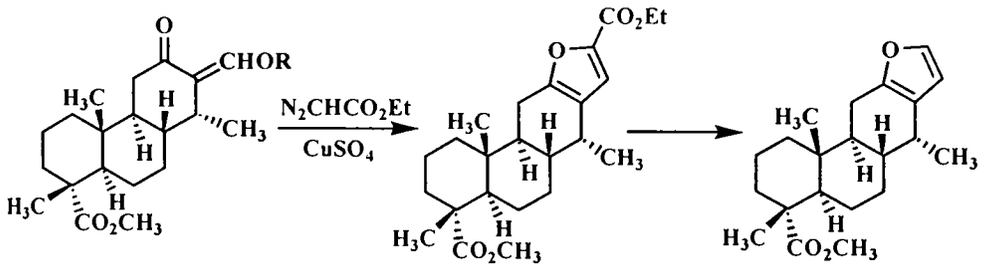


33 34 35

Scheme 15

1.3.3. Cyclization of α, β-Unsaturated Carbonyl Ylides

The carbonyl ylide formation/cycloaddition sequence is synthetically valuable, since it offers a fast access to highly functionalized oxygen-containing five membered rings. Spencer and co-workers have used this strategy in their synthesis of the tetracyclic furanoid diterpene methyl vinhaticoate.[29] Treatment of ketone **36** with ethyl diazoacetate in the presence of copper sulfate at 160 °C afforded the furoate **37** as the major product. This was selectively hydrolyzed and decarboxylated to give the natural product **38** (Scheme 16).



36 37 38

Scheme 16

1.3.4. 1,3-Dipolar Cycloaddition Reactions

The history of 1,3-dipoles goes back to Curtius, who discovered diazoacetic ester in 1883. Büchner was the first to describe a 1,3-dipolar cycloaddition reaction by studying the reaction of diazoacetic ester with α,β-unsaturated esters.[30] In 1893, he suggested that the product of the reaction of methyl diazoacetate and methyl acrylate was a 1-pyrazoline and that the isolated 2-pyrazole was formed after rearrangment of the 1-pyrazole.[31] After this elegant observation, in 1898 nitrones and nitrile oxides were discovered by Beckmann, and Werner and Buss, respectively.[32] Thus, the chemistry of 1,3-dipolar species has evolved for more than 100 years, and a variety of different 1,3-dipoles have been discovered. However, the general application of 1,3-dipoles in organic chemistry was first established by the pioneering efforts of Huisgen in the 1960s.[33]

A 1,3-dipole is defined as an *a-b-c* structure that undergoes 1,3-dipolar cycloaddition reactions and is portrayed by a dipolar structure as outlined in Figure 7.[34]

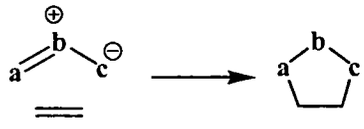
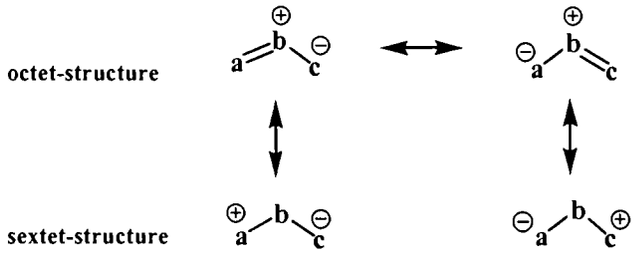


Figure 7

Generally, 1,3-dipoles can be divided into two different types: the allyl anion type and the propargyl/allenyl anion type. The allyl anion type is characterized by four

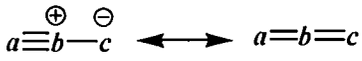
electrons in three parallel p_z orbitals perpendicular to the plane of the dipole and the 1,3-dipole is bent. Different resonance structures are possible, where two structures have an electron octect and two other structures in which *a* or *c* has an electron sextet (Figure 8).



The allyl anion type

Figure 8

If an extra π orbital is located in the plane orthogonal to the allenyl anion type molecular orbital (MO), it comes under the propargyl/allenyl anion type category. This class of dipoles is linear and the central atom *b* is limited to nitrogen (Figure 9).



Propargyl/allenyl anion type

Figure 9

According to the two resonance sextet structures ascribed to the allyl anion type dipoles, as shown in Figure 8, both termini may show electrophilicity. Thus, 1,3-dipoles are ambivalent nucleophiles and electrophiles. In dipoles like nitrile ylide or diazomethane, the nucleophilic character is predominant and so these cycloadd to electron deficient multiple bonds with ease. Per contra, ozone shows electrophilic character in its reactions and thus adds to electron rich multiple bonds. In between these two extremes, there is a broad range in which nucleophilic and electrophilic characters are more or less balanced.

The transition state of the concerted 1,3-dipolar cycloaddition reaction is controlled by the frontier molecular orbitals (FMO) of the substrates. Sustmann has

classified 1,3-dipolar cycloaddition reaction into three types on the basis of the relative FMO energies between the dipole and the alkene (Figure 10).[35]

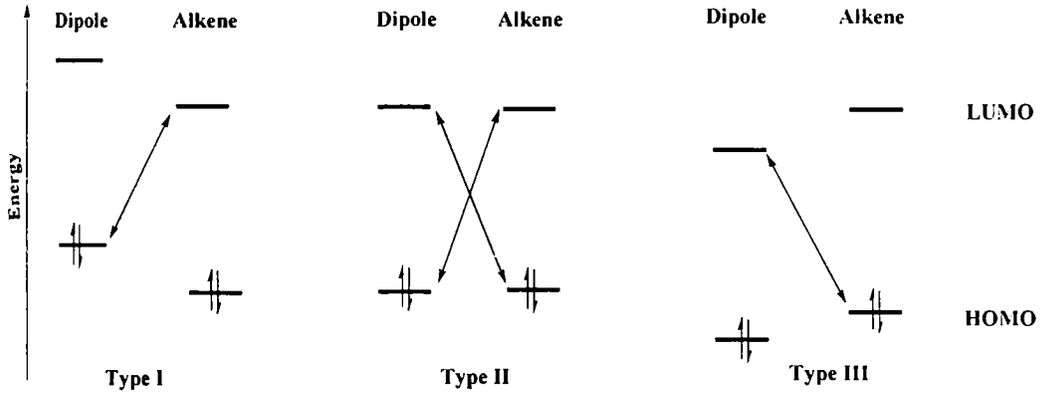


Figure 10

In Type I 1,3-dipolar cycloaddition reactions, the dominant FMO interaction is that of the $HOMO_{diploe}$ with the $LUMO_{alkene}$ as outlined in Figure 10. In Type II, since the FMO energies of the dipole and alkene are similar, both the HOMO-LUMO interactions are to be considered. However, 1,3-dipolar cycloaddition reactions of Type III are dominated by the interaction between the $LUMO_{dipole}$ and the $HOMO_{alkene}$.

Azomethine ylides and azomethine imines are typical examples for 1,3-dipolar reactions of Type I. The reactions of nitrones are normally classified as Type II. 1,3-Dipolar cycloaddition reactions of nitrile oxides are also classified as Type II, but they are better classified as borderline to type III, since nitrile oxides have relatively low lying HOMO energies. Examples of Type III interactions are 1,3-dipolar cycloaddition reactions of ozone and nitrous oxide. However, the introduction of electron-donating or electron-withdrawing substituents on the dipole or the alkene can alter the relative FMO energies, and therefore the reaction type dramatically. The 1,3-Dipolar cycloaddition reaction of *N*-methyl-*C*-phenyl nitrone with methyl acrylate is controlled by the $HOMO_{dipole}$-$LUMO_{alkene}$ interaction, whereas the reaction of the same nitrone with methyl vinyl ether is controlled by the $LUMO_{dipole}$-$HOMO_{alkene}$ interaction.

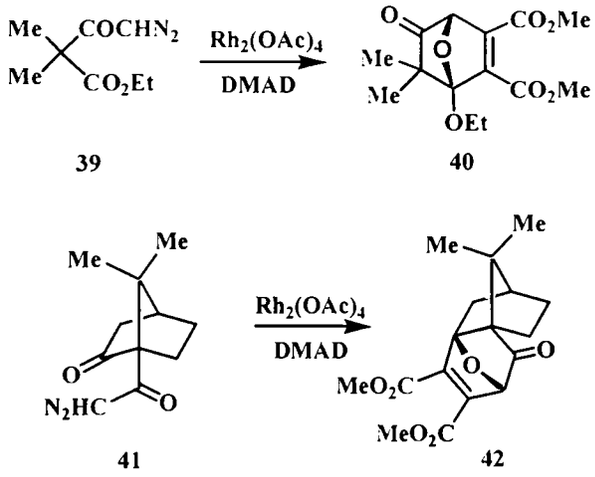
By considering the stereospecificity of the 1,3-dipolar cycloaddition reaction, Huisgen has suggested a concerted mechanism for the reaction. Huisgen *et al.* have later shown that certain 1,3-dipolar cycloaddition reactions can take place in a stepwise fashion involving an intermediate and in these cases the stereospecificity of the reaction may be lost.

1.4. Cyclic Carbonyl Ylides

Intramolecular carbene-carbonyl cyclization represents one of the most effective methods for generating carbonyl ylides. The methodology for the generation of a carbonyl ylide and its intramolecular trapping was initially demonstrated by Ibata and co-workers[37] and this has culminated in the development of a very versatile protocol for the construction of highly functionalized complex organic compounds. Intramolecular carbene-carbonyl cyclization can lead to carbonyl ylide intermediates of various ring sizes, *viz.*, five, six, and seven-membered rings, and their synthetic applications are illustrated in the respective sections.

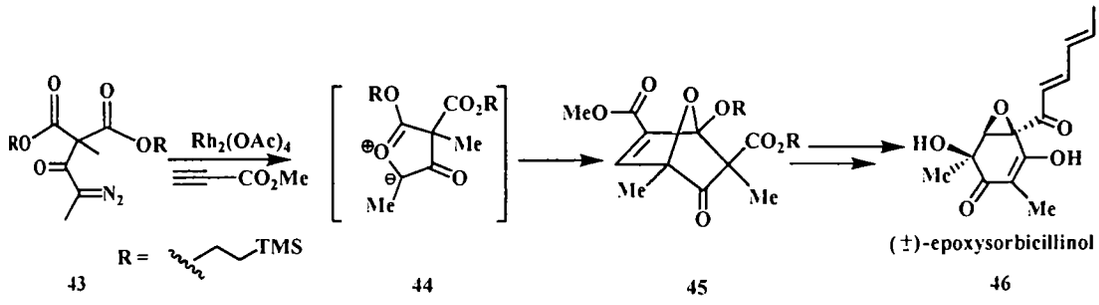
1.4.1. Five Membered Ring Carbonyl Ylides

When a diazo functionality, located at the γ-position with respect to a carbonyl group of a substrate, is exposed to an appropriate transition metal catalyst, a five membered carbonyl ylide is formed as a transient species through transannular cyclization of the emerging carbene/carbenoid onto the neighbouring keto carbonyl oxygen. Padwa *et al.* have shown the generation and reaction of five membered cyclic carbonyl ylides by studying the transition metal catalyzed decomposition of the diazocompounds **39** and **40** and the subsequent trapping of the transient intermediates with DMAD (Scheme 17).[38]



Scheme 17

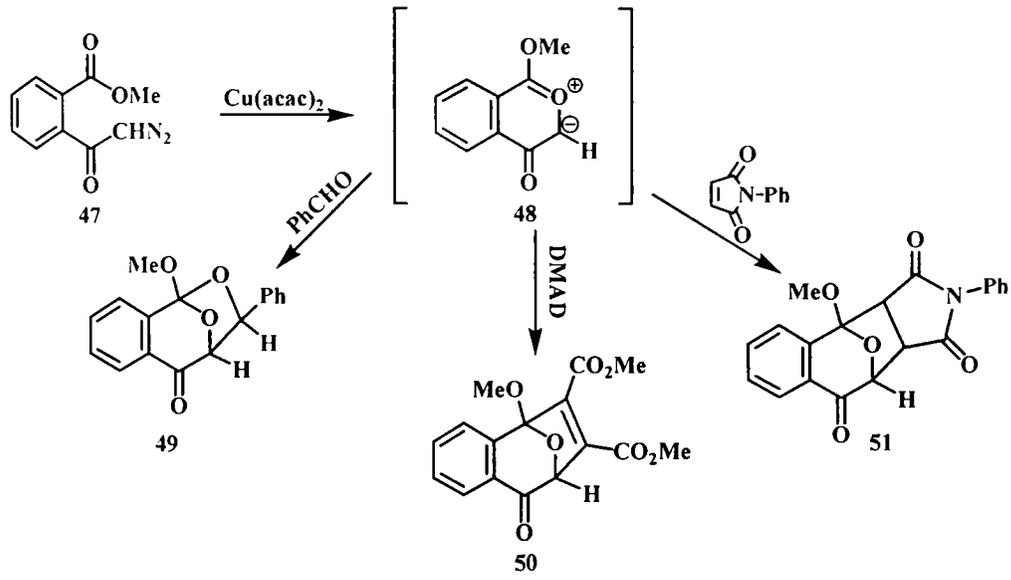
Only a few examples of the formation of five-membered ring carbonyl ylides using ester carbonyl groups have been reported. The utility of this process has been demonstrated in the first total synthesis of the biologically active natural product, (±)-epoxysorbicillinol,[39] a novel vertinoid polyketide possessing an epoxide functionality (Scheme 18).



Scheme 18

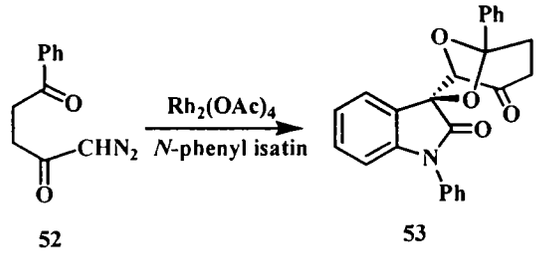
1.4.2. Six Membered Ring Carbonyl Ylides

Ibata and co-workers were the first to study the reactivity of the carbonyl ylide generated by the transition metal catalyzed decomposition of *o*-alkoxycarbonyl-α-diazoacetophenone in the presence of various dipolarophiles (Scheme 19).[37a,b]



Scheme 19

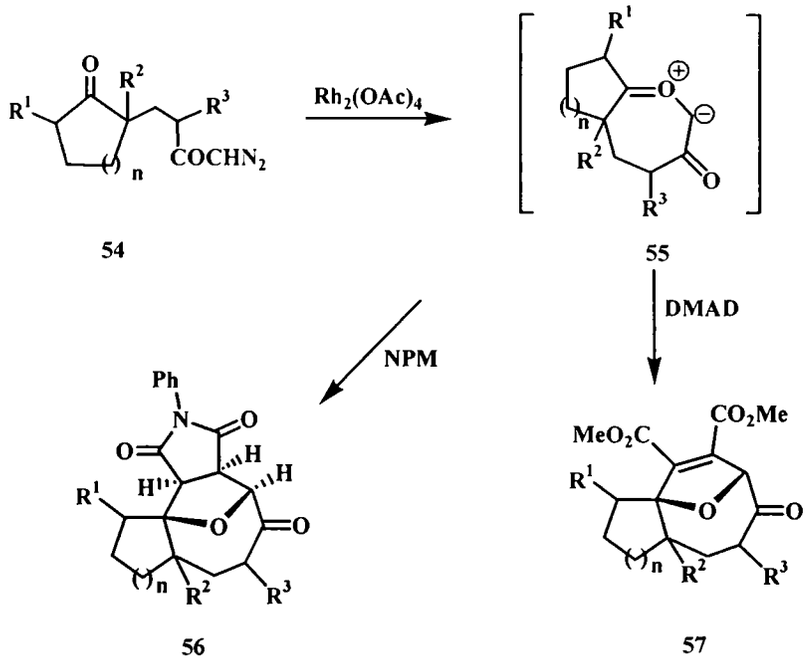
Symmetrical and unsymmetrical 1,2-diones exhibit diverse cycloaddition modes in reactions with carbonyl ylides to yield highly oxygenated novel spirocompounds.[40] Typically, the six membered ylide generated from the known diazo ketone **52** on reaction with *N*-phenyl isatin afforded the spiro-oxindole derivative **53**. As anticipated, the ylide reacted exclusively with the more electrophilic carbonyl in the isatin and only the *endo*-adduct was formed in every case (scheme 20).[41]



Scheme 20

1.4.3. Seven Membered Ring Carbonyl Ylides

There has been very little work on cycloadditions involving seven membered ring carbonyl ylides, barring a few examples in which a seven-membered ring carbonyl ylide was trapped by dipolarophiles like DMAD and NPM (Scheme 21).[38]

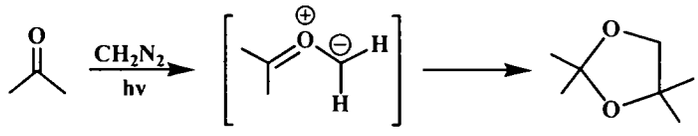


Scheme 21

1.5. Generation and Trapping of Acyclic Carbonyl Ylides

In contrast to the substantial amount of work on the generation and cycloaddition of cyclic carbonyl ylides, there is only limited amount of work on the formation of ylides through intermolecular reactions between diazo ester compounds and aldehydes or ketones in the presence of transition metal catalysts. These transient intermediates can undergo electrocyclization to form oxiranes or 1,3-dipolar cycloaddition with dipolarophiles. The latter process has been utilized for the synthesis of heterocycles. Since a detailed description of the acyclic carbonyl ylide chemistry is given in Chapter 2, only a peripheral historic outline is given in this chapter.

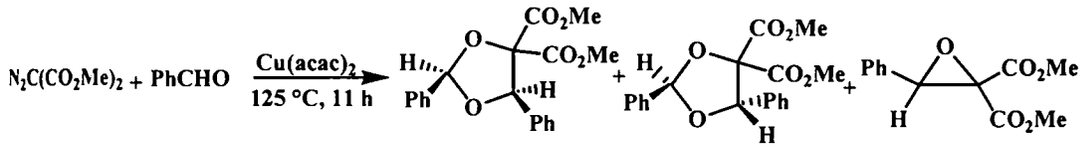
In 1963, Bradley and Ledwith investigated the irradiation of diazomethane in acetone and found that 2,2,4,4-tetramethyl-1,3-dioxolane **59** was formed as the major product (Scheme 22).[42]



58 59

Scheme 22

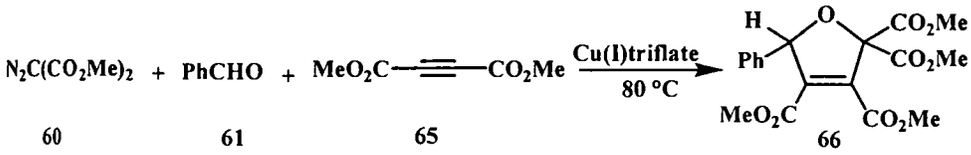
The reaction of carboalkoxycarbenes with carbonyl compounds dates back to the first report in 1885 by Büchner and Curtius.[43] The products of the reaction were characterized as dioxolanes by Dieckmann[44] in 1910. These reactions evoked very little interest until two decades ago, when Huisgen and de March investigated the chemistry in detail and demonstrated the intermediacy of a carbonyl ylide by trapping it with DMAD.[45] These workers examined the reaction of dimethyl diazomalonate with benzaldehyde at 125 °C. The reaction mixture contained dioxolanes and epoxide (Scheme 23). The yield of these products was significantly improved by the use of a transition metal catalyst.



60 61 62 63 64

Scheme 23

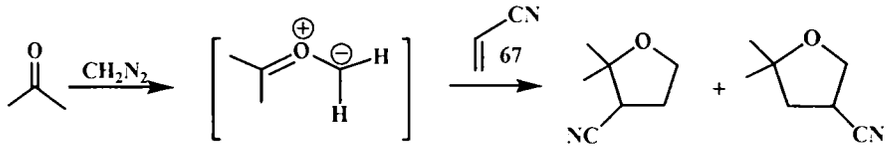
These carbonyl ylides were also found to react efficiently with dimethyl acetylenedicarboxylate to produce dihydrofurans (Scheme 24).



60 61 65 66

Scheme 24

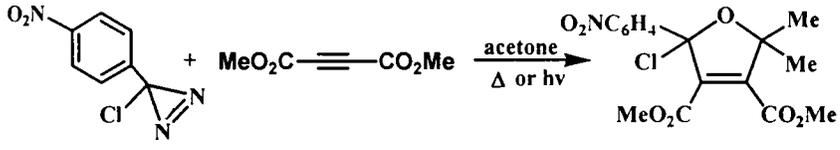
More recently, Turro has reported that the irradiation of diazomethane in acetone in the presence of acrylonitrile gave a 2:1 mixture of cycloadducts (Scheme 25).[46]



58 68 69

Scheme 25

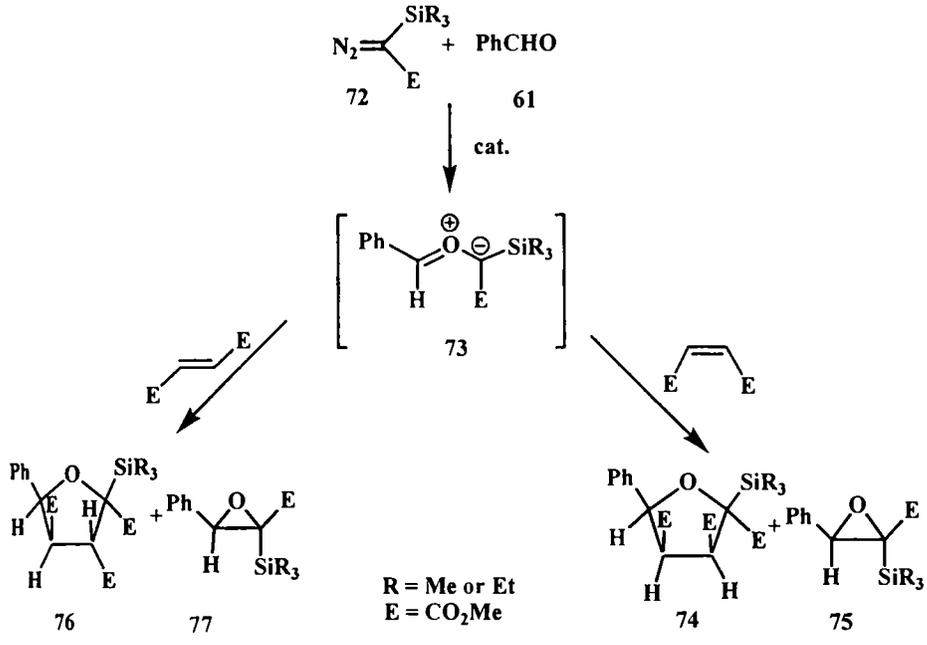
Ibata and Lu have employed chlorodiazirines as precursors for electrophilic carbenes which react with aldehydes and ketones to form carbonyl ylides.[47] One example involves the photolytic or thermal decomposition of 3-chloro-3-*p*-nitrophenyldiazirine in the presence of a mixture of acetone and dimethyl acetylenedicarboxylate to give the dihydrofuran derivative (Scheme 26).



70 65 71

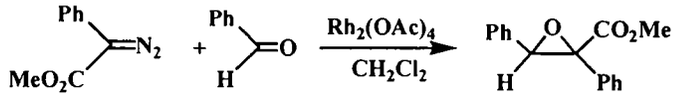
Scheme 26

Maas has studied the generation of acyclic carbonyl ylides and their trapping by maleate and fumarate (Scheme 27).[48]



Scheme 27

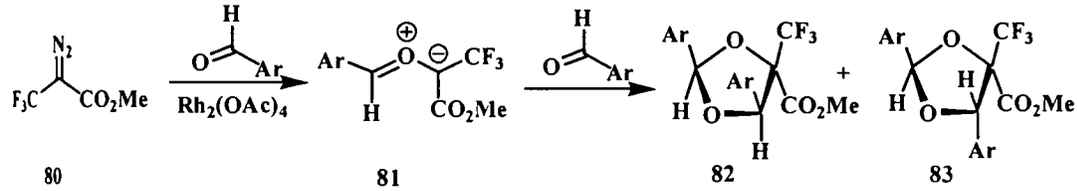
Doyle has reported a stereospecific epoxidation *via* carbonyl ylide intermediates using Rh(II) acetate catalyzed reaction of phenyl and styryl diazoacetates with aldehydes and ketones (Scheme 28).[49]



78 61 79 (66%)

Scheme 28

Very recently Jiang *et al.* have utilized this reaction in a highly diastereoselective synthesis of dioxolanes (Scheme 29).[50]



80 81 82 83

Scheme 29

1.6. Definition of the Problem

From the literature survey presented above, it is evident that the catalytic generation of carbonyl ylides from diazo compounds, especially in the intramolecular reactions, has significantly broadened their application in synthetic organic chemistry. However, intermolecular reactions emanating from transition metal catalyzed decomposition of diazo compounds in the presence of aldehydes or ketones have received only limited attention. In other words, when compared to the well exploited 1,3-dipolar cycloadditions of cyclic carbonyl ylides, the synthetic utility of acyclic carbonyl ylides remains practically unexplored. Against this background, it was of interest to undertake a series of investigations in this area. In the first instance, an exploration of the reaction of acyclic carbonyl ylides with dipolarophiles like activated styrenes appeared very attractive. In the context of the earlier work involving cyclic carbonyl ylides and 1,2- and 1,4-diones carried out in our laboratry,

naturally, it was of interest to explore the reaction of these compounds with acyclic carbonyl ylides.

Thus the first phase of the present investigation was mainly concerned with the dipolar cycloaddition reactions of the acyclic carbonyl ylides, generated from aldehydes and dicarbomethoxycarbene, with activated styrenes with a view to develop a synthesis of fully substituted tetrahydrofurans. In the second phase, we extended the present reaction to 1,2-diones, 1,4-diones and isatins. These results comprise the subject matter of the second and third chapter. The final phase of the work involved a limited investigation of the dipolar cycloaddition reactions of azomethine ylide with 1,2-diones. Details of these studies are presented in the following chapters.

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CHAPTER 2

STEREOSELECTIVE SYNTHESIS OF SUBSTITUTED TETRAHYDROFURANS *VIA* ACYCLIC CARBONYL YLIDE ADDITION TO ACTIVATED STYRENES

2.1. Introduction

1,3-Dipolar cycloaddition reactions provide the most versatile and convenient entry into the synthesis of five membered heterocyclic compounds. This class of reactions has undergone impressive development by the monumental efforts of Huisgen and coworkers.[1] As already discussed in chapter 1, these reactions are bimolecular in nature and involve the addition of a 1,3-dipole to a multiple π-bond system leading to five membered heterocycles (Figure 1).

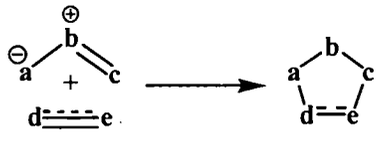


Figure 1

Cycloaddition reactions utilizing carbonyl ylides are important and concise methods for the stereoselective synthesis of oxygen-containing five membered rings. The catalytic generation of carbonyl ylides from diazocompounds has significantly broadened their applicability in organic synthesis.[2] These dipolar species are, in general, reactive intermediates which can undergo [3+2] dipolar cycloaddition reactions. Among the various methods[3] available for carbonyl ylide formation, the interaction of a carbene with the oxygen atom of a carbonyl group appears to be the most effective one. This can be readily accomplished by the transition metal catalyzed decomposition of an α-diazo ketone, in the presence of a carbonyl group. If the reacting carbonyl and the carbene moiety are present in the same molecule, it will

result in cyclic carbonyl ylide formation, the chemistry of which has been extensively explored.[4]

Acyclic carbonyl ylides are formed by the bimolecular reaction of carbene and an aldehyde or a ketone (Figure 2).

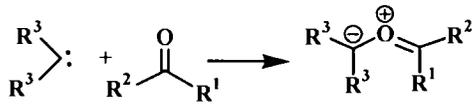
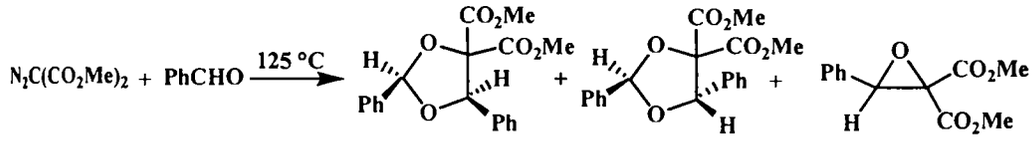


Figure 2

In comparison to their cyclic counterparts, the formation and reactions of acyclic carbonyl ylides have attracted only limited attention until very recently. The information available in the literature is presented in the following passages. Although acyclic carbonyl ylide chemistry mainly depends on the catalytic decomposition of diazo compounds, for the sake of completeness, their formation by other methods is also discussed in this section.

Büchner and Curtius[5] were the first to report the reaction of dicarbomethoxycarbenes with carbonyl compounds. The products of the reaction were characterized as dioxolanes by Dieckmann[6] in 1910. Later, Huisgen and de March studied the reaction of dimethyl diazomalonate with benzaldehyde at 125 °C (Scheme 1).[7]

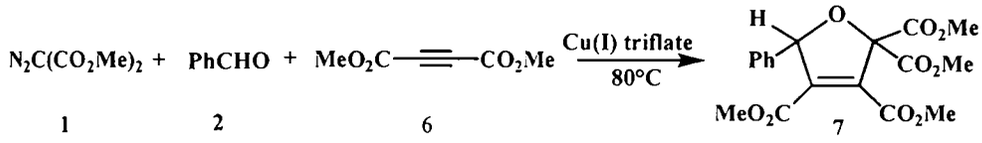


1 2 3 4 5

Scheme 1

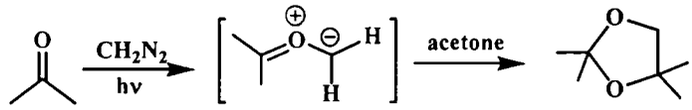
The reaction mixture contained dioxolanes **3, 4** and epoxide **5**. The yields of these products were significantly improved by the use of a transition metal catalyst viz., copper acetyl acetonate. Benzaldehyde plays a double role, first as a constituent of the carbonyl ylide, and subsequently as a dipolarophile in the trapping of the dipole.

On further investigation they found out that the ylide could be trapped by dimethyl acetylenedicarboxylate (Scheme 2).



Scheme 2

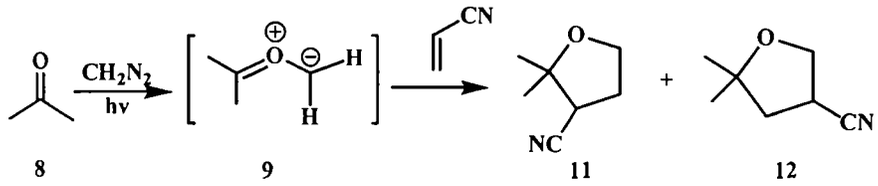
It has been reported by Bradley and Ledwith[8] that the irradiation of diazomethane in acetone resulted in the formation of 2,2,4,4-tetramethyl-1,3-dioxolane as the major product (Scheme 3).



Scheme 3

Irradiation of diazomethane results in the generation of a singlet carbene, which attacks the carbonyl oxygen of acetone to give carbonyl ylide intermediate. The ylide then undergoes a 1,3-dipolar cycloaddition reaction across carbonyl group of another molecule of acetone to give the heterocycle.

Irradiation of diazomethane in acetone in the presence of acrylonitrile gave a 2:1 mixture of **11** and **12** (Scheme 4).[9]

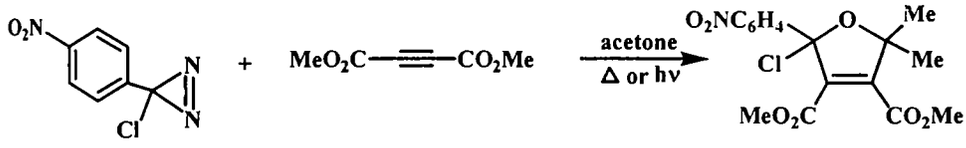


Scheme 4

The ylide **9** is produced by the electrophilic attack of the singlet carbene with the ketone, which is intercepted by the more reactive dipolarophile present in the reaction mixture. The fact that the reaction of the unsymmetrical dipolarophile gives a 2:1 mixture of two regioisomers indicates that in the HOMO of the carbonyl ylide, the

electron density at the unsubstituted carbon is greater than that at the substituted carbon atom.

Ibata and Liu[10] have devised another method for the generation of electrophilic carbenes. When 3-chloro-3-*p*-nitrophenyldiazirine **13** was decomposed thermally or photolytically in the presence of a mixture of acetone and dimethyl acetylenedicarboxylate, a three component reaction occurred to form the dihydrofuran derivative **14** (Scheme 5). The reaction takes place by the ylide formation, *via* the interaction between phenyl chlorocarbene and acetone.

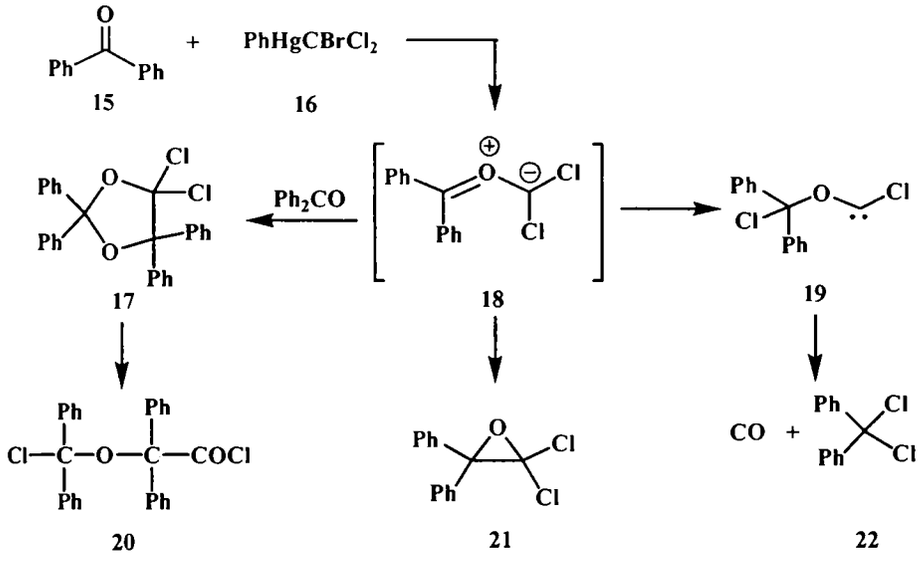


13 6 14

Scheme 5

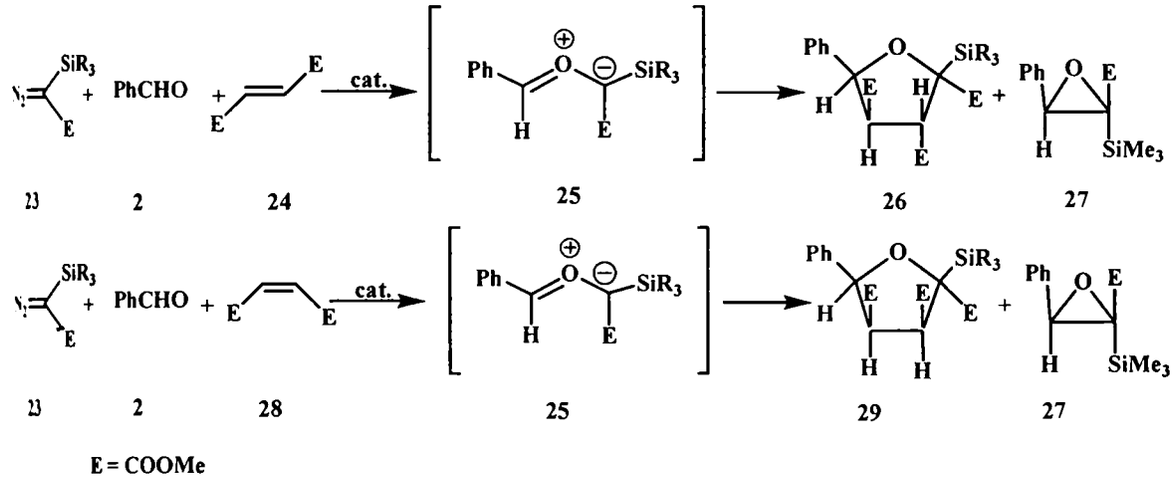
It was also observed that in the absence of a dipolarophile the carbonyl ylide cyclizes to form epoxide. Electron withdrawing substituents on the carbene were found to increase the rate of ylide formation and to decrease the rate of cyclization to the epoxide, thus enhancing the dipolar cycloaddition reaction.

A mixture of products was obtained on treatment of phenyl(bromodichloromethyl)mercury with an excess of benzophenone.[11] Although the mechanism for the product formation remains tentative, the evidence suggests that attack of dichlorocarbene on the ketone occurs to generate a dichlorocarbonyl ylide **18**. Once formed, it can follow three distinct paths to deliver different products (Scheme 5).



Scheme 6

There are only a few reports on the addition of acyclic carbonyl ylide to a C=C double bond. Maas,[12] has succeeded in obtaining the cycloaddition product in the reaction of aldehyde and α-diazo(trialkylsilyl)acetic esters with maleate and fumarate (Scheme 7).

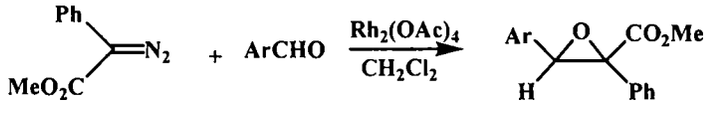


Scheme 7

When $Rh_2(pfb)_4$ or $[Ru_2(CO)_4(\mu\text{-}OAc)_2]_n$ was used as the catalyst, the reaction afforded the corresponding tetrahydrofuran as the sole product. In contrast, CuOTf-catalyzed reaction yielded only the oxirane. It is likely to result from the carbonyl

ylide by a conrotatory 4π-electrocyclization, and therefore, the (2α, 3β) configuration must be assumed. In the case of maleate and fumarate, the reaction was found to be stereoselective. The diastereoselectivity of the 1,3-dipolar cycloaddition between **25** and dimethyl maleate is especially noteworthy. It appears that π-attractive interactions between the phenyl ring and an ester carbonyl function in the transition state have dominated over the repulsive steric interaction between the SiR_3 and the other CO_2Me group of the dipolarophile.

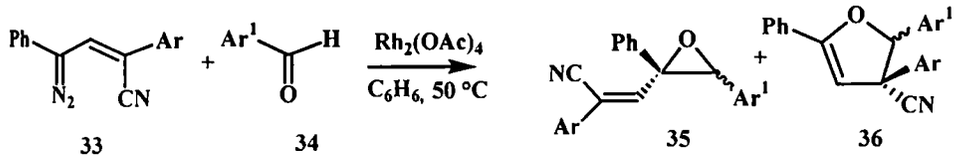
Recently, Doyle[13] and coworkers have reported the exclusive formation of oxiranes by the ring closure of phenyldiazoacetate derived carbonyl ylide with an equivalent amount of aldehyde (Scheme 8).



30 **31** **32(50-86%)**

Scheme 8

Hamaguchi *et al.* have reported the first example of the reaction of a vinylcarbonyl ylide with substituted benzaldehydes[14] (Scheme 9).



33 **34** **35** **36**

24 - 57% **14 - 54%**

Z/E = 0.77 - 2.9 **Z/E = 0.0 - 1.6**

Scheme 9

The formation of oxirane and dihydrofuran may be occurring from the two structural variations of the intermediate ylide which are in equilibrium as shown in Figure 3.

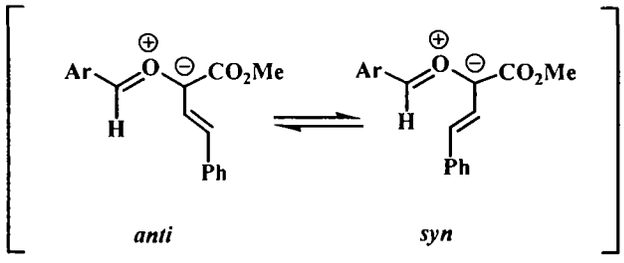
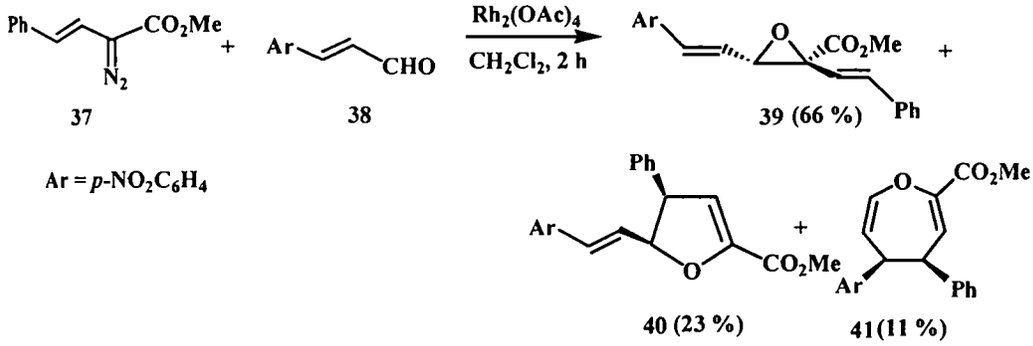


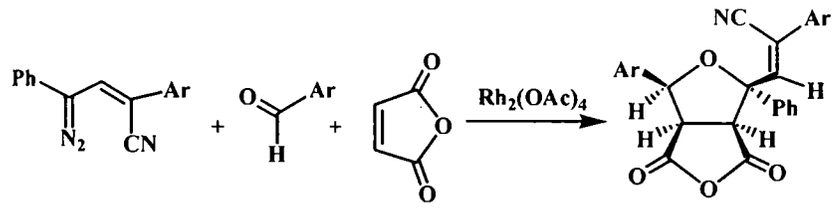
Figure 3

Not surprisingly, both the oxirane and the dihydrofuran were obtained nonstereospecifically. Extending the conjugation in the intermediate ylide allowed access to seven-membered ring heterocycles.[15] The reaction of styryldiazoacetate with *p*-nitrocinnamaldehyde gave a mixture of products in which oxirane, dihydrofuran, and oxepine were formed in competition. Only one isomer of each compound was formed (Scheme 10).



Scheme 10

Attempts have also been made towards trapping of vinyl carbonyl ylides using reactive dipolarophiles. The Rh(II)-catalyzed reaction of **33** with *p*-chlorobenzaldehyde in the presence of maleic anhydride at 50 °C produced the single cycloadduct **43** along with small amounts of oxiranes and dihydrofuran derivatives[14] (Scheme 11).

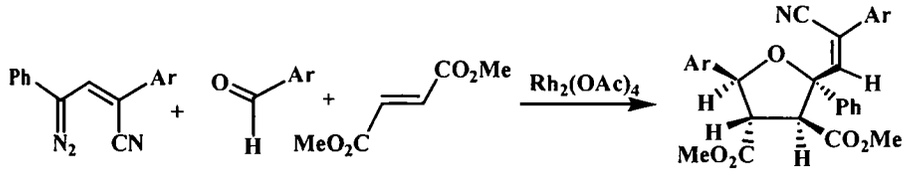


33 31 42 43 (71 %)

Ar = *p*-ClC$_6$H$_4$

Scheme 11

The same ylide was also trapped by dimethyl fumarate to give the cycloadduct **44** along with trace amounts of oxiranes and dihydrofuran derivatives (Scheme 12).

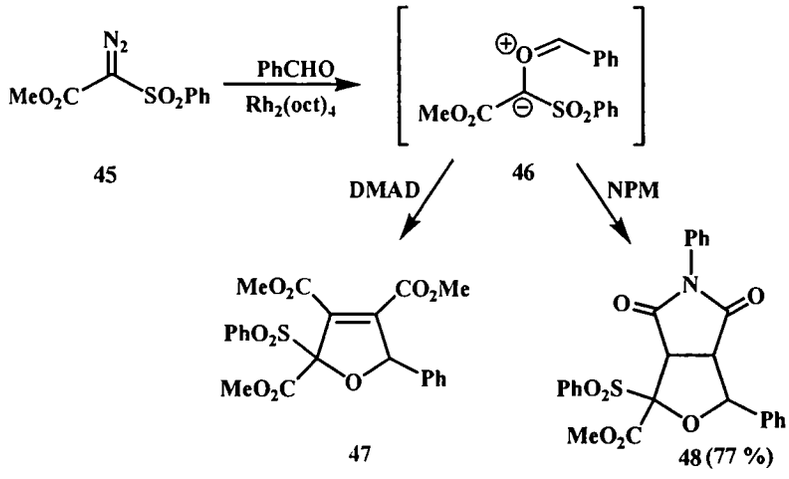


33 31 24 44

Ar = *p*-ClC$_6$H$_4$

Scheme 12

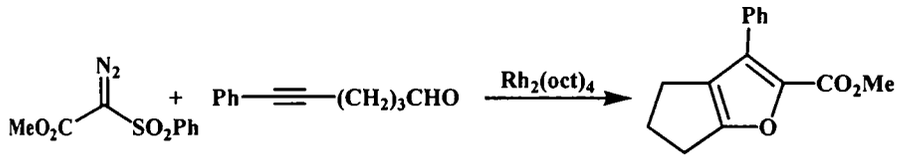
The carbonyl ylide generated by the reaction of diazo ester **45** and aldehyde was trapped by dimethyl acetylenedicarboxylate and *N*-phenyl maleimide thus leading to the formation of substituted heterocyclic compounds[16] (Scheme 13).



45 46 47 48 (77 %)

Scheme 13

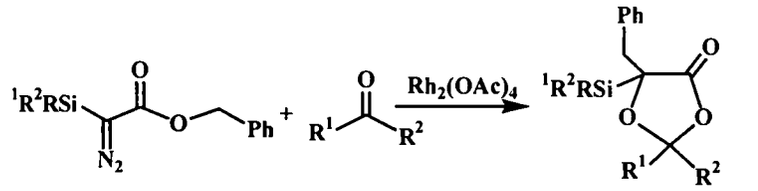
The intramolecular version of this reaction was also investigated. In the resence of aldehyde having an alkynyl group, the decomposition of the diazo ester **45** rnished the annulated furan **50** in moderate yield. No separate step for the imination of phenyl sulphinic acid was required as elimination was found to occur nder the reaction conditions (Scheme 14).



45 49 50 (36 %)

Scheme 14

Bolm *et al.* have investigated the intermolecular metal catalyzed reaction of enzyl 2-trialkylsilyl-2-diazoacetate with various acyclic and cyclic ketones (Scheme 5).[17]

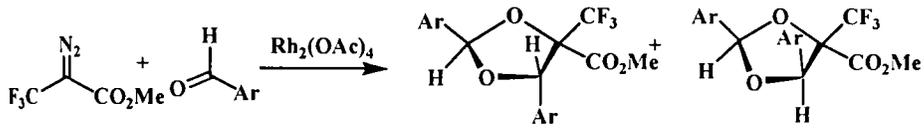


51 52 53 (51-98 %)

R^1, R^2 = alkyl

Scheme 15

In an experiment by Jiang *et al.* methyl diazo (trifluoromethyl)acetate was reated with two equivalents of aryl aldehyde in CH_2Cl_2 with Rh(II) acetate catalyst. he reaction furnished products of carbonyl ylide cycloaddition in high yield[18] Scheme 16). However, the reaction of aryl aldehydes bearing a substituent group in e *meta* or *para* position, diastereoselectively gave a single cycloadduct, identified as e out of the four possible diastereomers. The *ortho* substituted aryl aldehydes also forded **56** as the major product in the ratio 9:1.



55 31 56 57

Ar = *o*-ClC$_6$H$_4$ 91% (91:9)

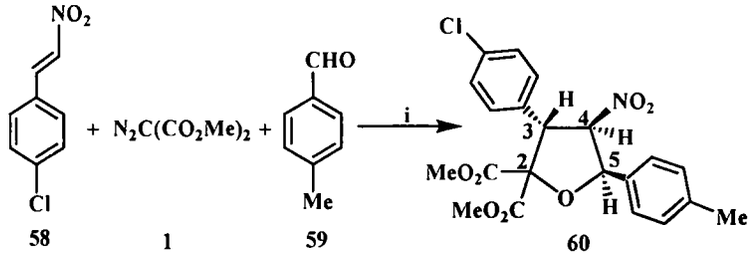
Scheme 16

2.2. The Present Work

It is evident from the foregoing discussion (see also, chapter 1-general introduction) that the cycloaddition reactions of acyclic carbonyl ylides has received only limited attention. The perception that such reactions involving activated alkenes would constitute an effective method for the construction of highly substituted tetrahydrofuran derivatives provided additional impetus for undertaking the studies discussed in this chapter. Essentially, the present work is an exploration of the reactivity of the ylides derived from dicarbomethoxycarbene and aldehydes towards activated styrenes, with a view to develop a stereoselective synthesis of fully substituted tetrahydrofuran derivatives. The results of the work carried out with such systems are presented in the following pages.

2.3. Results and Discussion

Our studies were initiated by the Rh(II) catalyzed reaction of dimethyldiazomalonate with *p*-tolualdehyde and 4-chloro-*β*-nitrostyrene. A facile reaction occurred to afford the single cycloadduct **60** (Scheme 17). The product was purified by chromatography on a silica gel column using a mixture of hexane-ethyl acetate (90:10) to afford the product in 76% yield.



58 1 59 60

i. $Rh_2(OAc)_4$, dry benzene, argon, 80 °C, 16 h, 76%

Scheme 17

The compound **60** was characterized on the basis of spectroscopic data. The IR spectrum showed the carbonyl absorption at 1742 cm^{-1}. The asymmetrical and symmetrical absorptions of the NO_2 group showed strong bands at 1553 and 1371 cm^{-1}, respectively. In the ^1H NMR spectrum, the methyl protons on the aromatic ring resonated at δ2.33, while the protons of the carbomethoxy groups showed signals at δ 3.36 and δ3.93. The signals due to the protons at C-3, C-4 and C-5 positions of the tetrahydrofuran ring were discernible at δ5.18, δ5.68 and δ6.16, respectively. In the ^{13}C NMR spectrum, the peak corresponding to the two ester carbonyls were discernible at δ167.0 and δ168.1. The signal which appeared at δ 93.7 is attributed to the carbon bearing the NO_2 group. Peaks due to the methoxy carbons were discernible at δ53.4 and δ53.6, while the signal due to the methyl carbon was visible at δ21.3. All other signals were also in good agreement with the proposed structure.

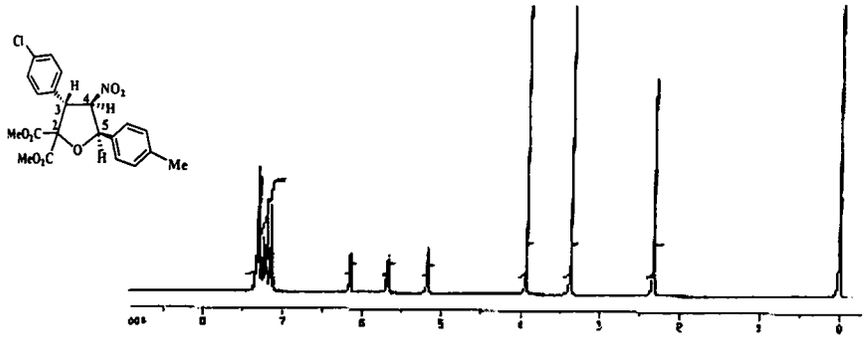


Figure 4. *^1H NMR Spectrum of 60*

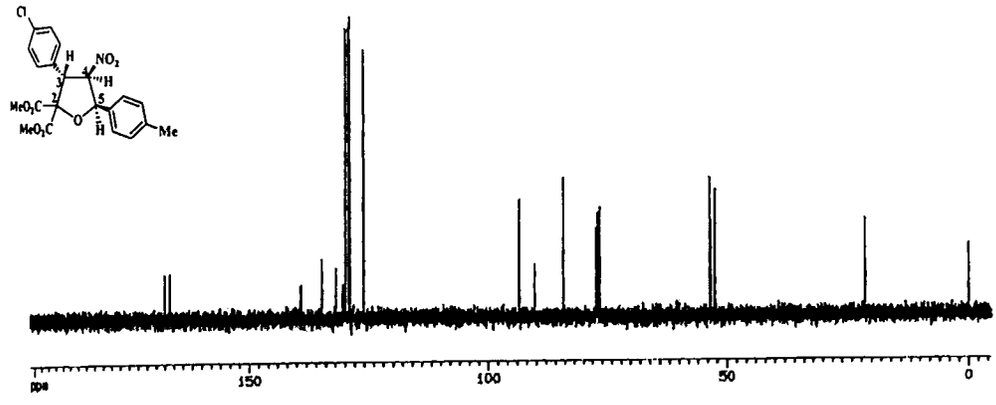


Figure 5. *^{13}C NMR Spectrum of 60*

The relative stereochemistry of **60** was determined on the basis of coupling constants of the three protons of the tetrahydrofuran ring. In the ^{1}H NMR spectrum, the *J* value of 7.3 Hz for C5-H (δ 6.16) and C4-H (δ 5.70) was diagnostic for their *cis* relationship as attested by literature report.[19] Further support for the stereochemical assignment was obtained by ^{1}H nOe difference spectroscopic studies (Figure 6).

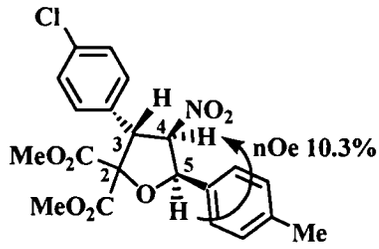
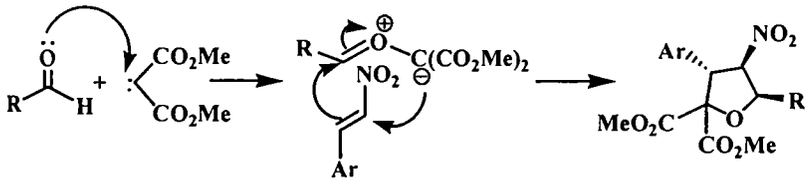


Figure 6

Irradiation of the C5-H signal of compound **60** at δ 6.16 enhanced the peak of C4-H at δ 5.70. On the other hand, irradiation of the C3-H peak at δ 5.28 did not show nOe on C4-H and C5-H signals, thus indicating its *trans* relationship with those protons.

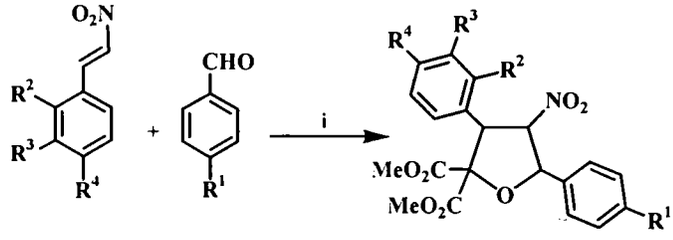
Mechanistically the reaction may be considered to involve the Huisgen dipolar cycloaddition of the carbonyl ylide, formed by the reaction of the carbene and the aldehyde, to the *β*-nitrostyrene, the latter being a good dipolarophile (Scheme 18). The diastereoselectivity of the reaction may be rationalized by the concerted nature of the carbonyl ylide cycloaddition and the observed stereochemistry of the products may be attributed to the preferred *trans* geometry of the ylide and the dipolarophile.



Scheme 18

The reaction was found to be general with different *β*-nitrostyrenes and aldehydes and the products were obtained in moderate yields (Scheme 19). In all cases,

The structure of the product was established by spectroscopic analysis; IR, ^{1}H NMR and ^{13}C NMR data were completely consistant with the assigned structure.

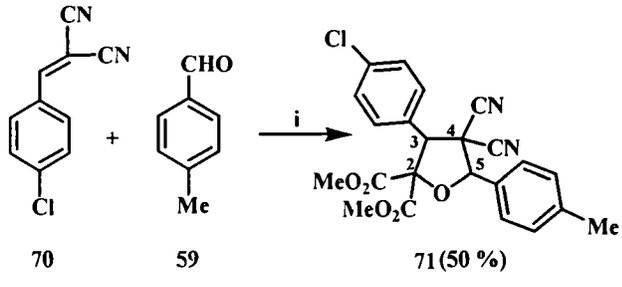


i. $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, dry benzene, argon, 80°C, 16 h

$R^1 = R^2 = R^3 = H$, $R^4 = Cl$	**61** (47 %)
$R^1 = CH_3$, $R^2 = R^4 = H$, $R^3 = NO_2$	**62** (60 %)
$R^1 = CH_3$, $R^2 = R^3 = R^4 = H$	**63** (57 %)
$R^1 = R^2 = R^3 = R^4 = H$	**64** (47 %)
$R^1 = CH_3$, $R^2 = R^3 = H$, $R^4 = F$	**65** (67 %)
$R^1 = R^2 = R^3 = H$, $R^4 = F$	**66** (50 %)
$R^1 = CH_3$, $R^2 = R^3 = H$, $R^4 = OMe$	**67** (38 %)
$R^1 = CH_3$, $R^2 = H$, $R^3 = R^4 = Cl$	**68** (58 %)
$R^1 = R^2 = H$, $R^3 = R^4 = Cl$	**69** (45 %)

Scheme 19

In view of the success of this reaction, we decided to extend it to other styrenes also. The reaction of 4-chloro-benzylidene malononitrile with the carbonyl ylide generated from *p*-tolualdehyde and dicarbomethoxycarbene furnished the cycloadduct **71** in moderate yield (Scheme 20).



70 **59** **71 (50 %)**

i. $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, dry benzene, argon, 80°C, 16 h

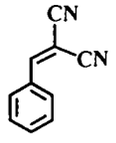
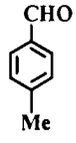
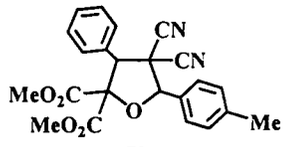
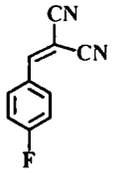
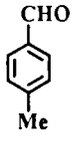
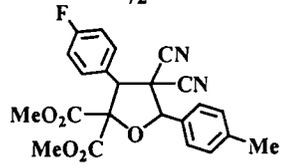
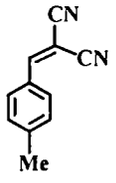
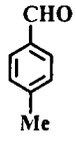
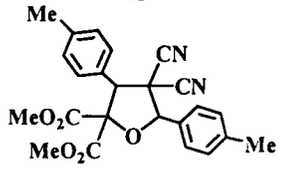
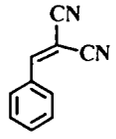
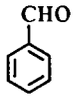
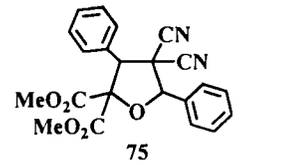
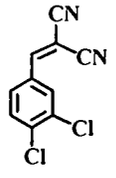
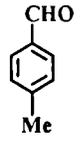
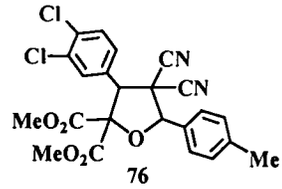
Scheme 20

The structure of the adduct **71** was established by spectroscopic methods. The IR spectrum displayed absorption at 2254 cm^{-1} which is characteristic of a cyano group. The peak which appeared at 1758 cm^{-1} was assigned to the ester carbonyls

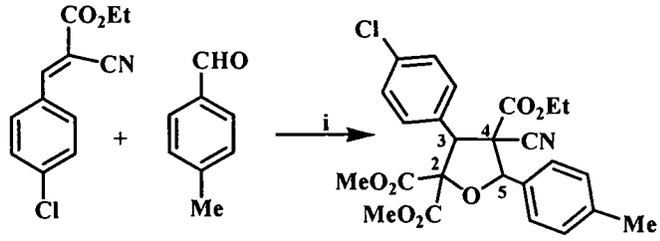
present in the compound. In the ^{1}H NMR spectrum, the singlet signal due to *p*-methyl protons was seen at δ 2.40. Protons of the two methoxy groups resonated at δ 3.36 and δ 3.95. The singlet signals at δ 5.22 and δ 5.95 were assigned respectively to the protons at C-3 and C-5 of the tetrahydrofuran ring. In the ^{13}C NMR spectrum, the signals corresponding to ester carbonyls were discernible at δ 166.22 and δ 166.18. The two cyano groups resonated at δ 112.2 and δ 111.2. All the other signals in the ^{1}H NMR and ^{13}C NMR spectra were also in good agreement with the assigned structure.

The reaction was found to be applicable to dicyanostyrenes with different substituents on the aromatic ring; the corresponding tetrahydrofuran derivatives were obtained in moderate yields (Table 1).

Table 1

Entry	Styrene	Aldehyde	Product	Yield (%)
1			 72	49
2			 73	50
3			 74	40
4			 75	43
5			 76	44

Subsequent to these investigations, we turned our attention to cyanocinnamates. nder the usual experimental conditions, 77 underwent facile 1,3-dipolar ycloaddition with the same carbonyl ylide generated from diazomalonate and *p*-lualdehyde (Scheme 21).



77 59 78 (55%)

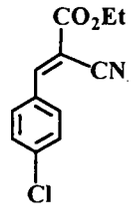
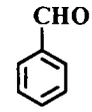
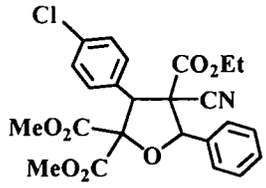
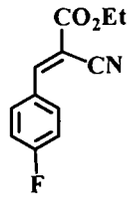
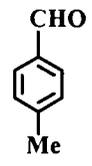
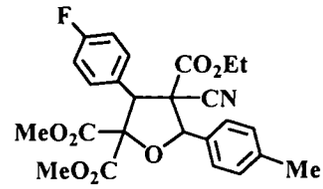
i. $Rh_2(OAc)_4$, dry benzene, argon, 80°C, 16 h

Scheme 21

Characterization of the product was accomplished on the basis of spectroscopic nalysis. In the IR spectrum of the cycloadduct **78**, the peaks which appeared at 1744 m^{-1} and 1738 cm^{-1} were attributed to the ester carbonyls present in the molecule. The bsorbtion due to cyano group was observed at 2250 cm^{-1}. In the ^{1}H NMR spectrum of e compound, methyl protons of the ethylester functionality were discernible as a plet at δ 0.82. The methyl protons on the aromatic ring displayed a singlet at δ 2.38. wo singlet signals at δ 3.40 and δ 3.94 were being attributed to the methoxy protons. e methylene protons of the ester functionality displayed two multiplets centred at δ 6-3.97 and δ 3.64-3.70. The signals due to the protons at C-3 and C-5 were scernible at δ 5.14 and δ 6.16 respectively. In the ^{13}C NMR spectrum, the signals e to the ester carbonyls were visible at δ 167.5, δ 167.0 and δ 165.2. The resonance gnal for the cyano group was visible at δ 115.6. The methyl carbon on the aromatic ng resonated at δ 21.3.

With this system we have carried out only two additional experiments and the sults are shown in the Table 2.

Table 2

Entry	Styrene	Aldehyde	Product	Yield (%)
1			 **79**	45
2			 **80**	55

Our attempts to extend the 1,3-dipolar cycloaddition of acyclic carbonyl ylides to simple styrenes were unsuccessful. In all cases, either cyclopropanation and/or epoxide formation occurred; no dipolar cycloaddition was observed. Therefore no further work was done in this area.

2.4. Theoretical Calculations

In order to explain the observed reactivity of activated styrenes and acyclic carbonyl ylides, we did some theoretical calculations using semi-emprical MNDO method with the aid of TITAN software (version 1). The correlation diagram for the reaction of the styrene **61** with the ylide is given in Figure 7.

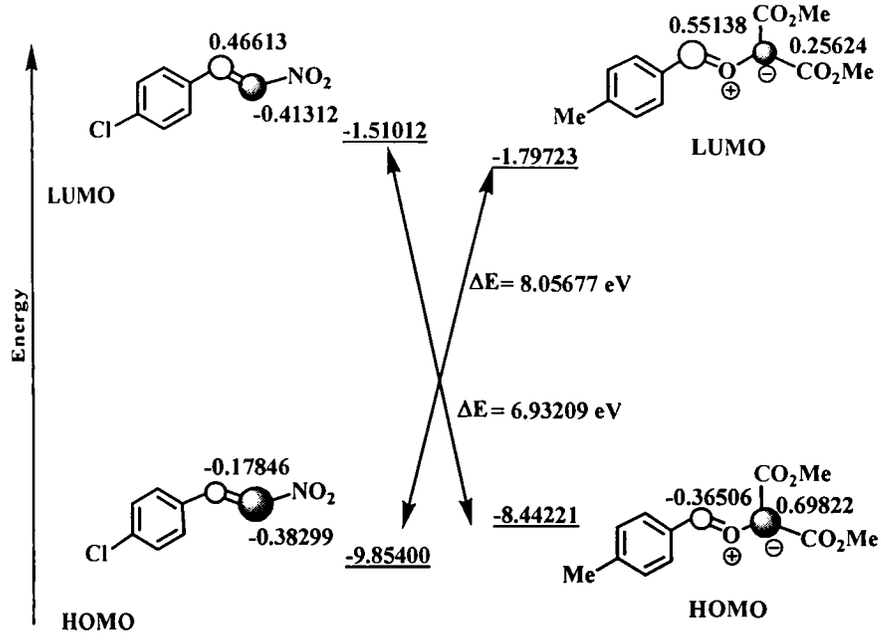


Figure 7. *Molecular orbital correlation diagram of styrene* ***60*** *and the acyclic carbonyl*

From the correlation diagram, it is clear that HOMO of the dipole and LUMO the dipolarophile are the interacting molecular orbitals. The observed regioselectivity is also explained on the basis of symmetry considerations.

Conclusion

In conclusion, we have demonstrated that carbonyl ylides generated from carbomethoxycarbene and aldehydes react efficiently with activated styrenes leading highly substituted tetrahydrofuran derivatives. It is conceivable that the latter will be amenable to a number of synthetically useful transformations. The reaction may also find application in the synthesis of natural products containing tetrahydrofuran core work.

Experimental Details

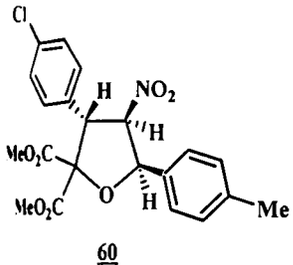
General: All the reactions were carried out in oven-dried glasswares. Progress each reaction was monitored by Thin Layer Chromatography (TLC). Purification of products was effected using column chromatography on silica gel and mixtures of hexane-ethyl acetate were used for elution. NMR spectra were recorded at 300 (^{1}H)

and 75 (^{13}C) MHz respectively on a Bruker DPX-300 MHz NMR spectrometer. IR spectra were recorded on a Nicolet Impact 400D FT-IR spectrophotometer. Melting points were recorded on a Büchi melting point apparatus and are uncorrected. High-resolution mass spectra were recorded under EI/HRMS (at 5000 resolution) using JEOL JMS 600H mass spectrometer. Elemental analyses were done using Perkin Elmer-2400 CHNS analyser. Solvent used for the experiment (benzene) was distilled and dried by employing standard procedures.

Dimethyl diazomalonate was prepared from dimethyl malonate using Reigitz[20] diazotization protocol.

Dimethyl (3R,4R,5R)-3-(4-chlorophenyl)dihydro-5-(4-methylphenyl)-4-nitro-2,2(3H)-furandicarboxylate 60

To the mixture of 4-chloro-β-nitrostyrene (0.220 g, 1.20 mmol), *p*-tolualdehyde (0.036 g, 0.30 mmol) and dimethyl diazomalonate (0.047 g, 0.30 mmol) in 5mL of dry benzene, 2 mol % Rh(II) acetate was added and refluxed for about 16 h under an argon atmosphere. The reaction mixture was then subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixtures to afford the product **60** (0.099 g, 76 %) as a colorless crystalline solid. It was recrystallized from dichloromethane-hexane solvent system, **mp** 158-159 °C.



60

IR (KBr) ν_{max}: 3036, 2955, 2854, 1742, 1553, 1492, 1438, 1371, 1303, 1249, 1115, 1027, 811, 670, 609 cm^{-1}.

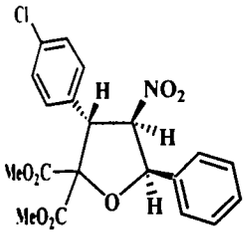
^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.36 (s, 3H), 3.93 (s, 3H), 5.18 (d, 1H, J = 6.2 Hz), 5.68 (overlapping doublets, 1H, J_1 = 7.2 Hz, J_2 = 6.4 Hz), 6.16 (d, 1H, J = 7.3 Hz), 7.14-7.35 (m, 8H).

^{13}C NMR ($CDCl_3$) δ 21.3, 52.6, 53.4, 53.6, 84.4, 90.5, 93.7, 126.2, 129.0, 129.3, 129.9, 130.6, 131.9, 134.8, 139.3, 167.0, 168.1.

nal. Calcd for $C_{21}H_{20}ClNO_7$: C, 58.14; H, 4.65; N, 3.23. Found: C, 58.58; H, 4.70; N, 47.

Dimethyl (3R,4R,5R)-3-(4-chlorophenyl)dihydro-5-phenyl-4-nitro-2,2(3H)-furandicarboxylate 61

The reaction of 4-chloro-β-nitrostyrene (0.220 g, 1.20 mmol), benzaldehyde 032 g, 0.30 mmol) and dimethyl diazomalonate (0.047 g, 0.30 mmol), according to e general procedure, described for **60**, afforded the product **61** (0.059 g, 47 %) as a olorless crystalline solid, **mp** 147 °C.



61

IR (KBr) ν_{max}: 3079, 3032, 2955, 1760, 1553, 1501, 1465, 1444, 1382, 1310, 1253, 1134, 1093, 1062, 1025, 855, 808, 756, 710, 612 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 3.36 (s, 3H), 3.94 (s, 3H), 5.18 (d, 1H, J = 6.1 Hz), 5.7 (overlapping doublets, 1H, J_1 = 7.1 Hz, J_2 = 6.3 Hz), 6.19 (d, 1H, J = 7.3 Hz) 7.28-7.35 (m, 9H).

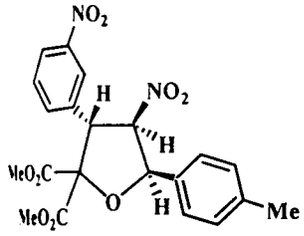
^{13}C NMR ($CDCl_3$) δ 52.6, 53.5, 53.7, 84.4, 90.5, 93.7, 126.3, 128.6, 129.1, 129.5, 130.0, 131.9, 133.6, 134.9, 168.1.

nal. Calcd for $C_{20}H_{18}ClNO_7$: C, 57.22; H, 4.22; N, 3.34. Found: C, 57.42; H, 4.00; N, 55.

Dimethyl (3R,4R,5R)-3-(3-nitrophenyl)dihydro-5-(4-methylphenyl)-4-nitro-2,2 3H)-furandicarboxylate 62

The reaction of 3-nitro-β-nitrostyrene (0.233 g, 1.20 mmol), p-tolualdehyde 36 g, 0.30 mmol) and dimethyl diazomalonate (0.036 g, 0.30 mmol), according to e general procedure, afforded the product **62** (0.080 g, 60 %) as a colorless ystalline solid, **mp** 188-190 °C.

IR (KBr) ν_{max}: 3036, 2955, 1755, 1634, 1539, 1445, 1357, 1297, 1236, 1108, 818 cm^{-1}.



62

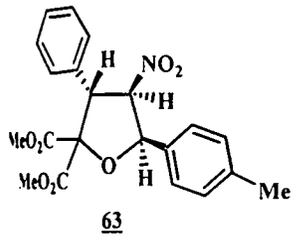
^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 3.45 (s, 3H), 3.94 (s, 3H), 5.27 (d, 1H, J = 7.4 Hz), 5.81 (overlapping doublets, 1H, J_1 = 7.7 Hz, J_2 = 7.5 Hz), 6.23 (d, 1H, J = 7.8 Hz), 7.15-7.26 (m, 5H), 7.58 (overlapping doublets, 1H, J_1 = 7.8 Hz, J_2 = 8.8 Hz), 7.76 (d, 1H, J = 7.1 Hz), 8.22 (s, 1H).

^{13}C NMR ($CDCl_3$) δ 21.4, 52.8, 53.2, 53.8, 84.0, 90.0, 93.0, 123.2, 123.8, 126.4, 129.4, 129.9, 130.6, 135.3, 139.5, 148.5, 166.8, 168.0.

Anal. Calcd for $C_{21}H_{20}N_2O_9$: C, 56.76; H, 4.54; N, 6.30. Found: C, 56.70; H, 4.32; N, 6.32.

Dimethyl (3R,4R,5R)-3-(phenyl)dihydro-5-(4-methylphenyl)-4-nitro-2,2(3H)-furandicarboxylate 63

The reaction of β-nitrostyrene (0.179 g, 1.20 mmol), *p*-tolualdehyde (0.036 g, 0.30 mmol) and dimethyl diazomalonate (0.047 g, 0.30 mmol), according to the general procedure, afforded the product **63** (0.068 g, 57 %) as a colorless crystalline solid, **mp** 148 °C.



63

IR (KBr) ν_{max}: 3022, 2955, 2854, 1762, 1613, 1566, 1519, 1445, 1283, 1054, 939 cm^{-1}.

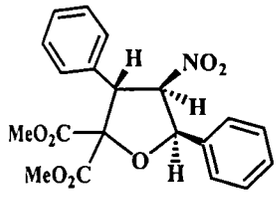
^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.26 (s, 3H), 3.93 (s, 3H,), 5.22 (d, 1H, J = 5.46 Hz), 5.69 (overlapping doublets, 1H, J_1 = 6.9 Hz, J_2 = 5.58 Hz), 6.18 (d, 1H, J = 7.0 Hz), 7.14-7.34 (m, 9H).

^{13}C NMR ($CDCl_3$) δ 21.3, 52.4, 53.6, 54.2, 84.8, 90.9, 94.3, 126.2, 128.5, 128.6, 128.9, 129.2, 130.7, 133.8, 139.1, 167.1, 168.1.

ınal. Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.31; H, 4.81; N, .71.

)imethyl (3R,4R,5R)-3-(phenyl)dihydro-5-phenyl-4-nitro-2,2(3H)-'urandicarboxylate 64

The reaction of *β*-nitrostyrene (0.179 g, 1.20 mmol), benzaldehyde (0.032 g, 0.30 mmol) and dimethyl diazomalonate (0.047 g, 0.30 mmol), according to the general procedure, afforded the product **64** (0.054 g, 47 %) as a colorless crystalline solid, **mp** 130-131 °C.



64

IR (KBr) ν_{max}: 2982, 2955, 1748, 1566, 1445, 1371, 1283, 1108 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 3.27 (s, 3H), 3.95 (s, 3H), 5.23 (d, 1H, J = 5.3 Hz), 5.71 (overlapping doublets, 1H, J_1 = 6.7 Hz, J_2 = 5.6 Hz), 6.21 (d, 1H, J = 7.0 Hz), 7.35-7.36 (m, 10H).

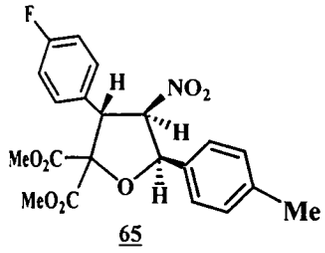
^{13}C NMR ($CDCl_3$) δ 52.4, 53.6, 54.3, 84.8, 91.0, 94.3, 126.3, 128.4, 128.6, 128.7, 128.9, 129.4, 133.7, 133.8, 167.1, 168.1.

Anal. Calcd for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.26; H, 5.06; N, 3.83.

Dimethyl (3R,4R,5R)-3-(4-fluorophenyl)dihydro-5-(4-methylphenyl)-4-nitro-2,2(3H)-furandicarboxylate 65

The reaction of 4-fluoro-*β*-nitrostyrene (0.201 g, 1.20 mmol), *p*-tolualdehyde (0.036 g, 0.30 mmol) and dimethyl diazomalonate (0.047 g, 0.30 mmol), according to the general procedure, afforded the product **65** (0.084 g, 67 %) as a colorless crystalline solid, **mp** 148-149 °C.

IR (KBr) ν_{max}: 3027, 2960, 2929, 2856, 1750,



65

1620, 1558, 1517, 1439, 1351, 1289, 1243, 1113, 1077, 1020, 974, 932, 860, 818, 756, 741, 632 cm^{-1}.

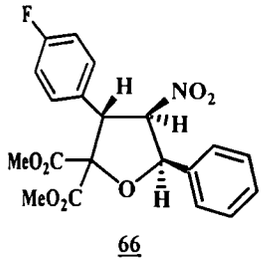
^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 3.36 (s, 3H), 3.93 (s, 3H), 5.19 (d, 1H, J = 6.2 Hz), 5.68 (overlapping doublets, 1H, J_1 = 7.1Hz, J_2 = 6.4 Hz), 6.16 (d, 1H, J = 7.3 Hz), 7.03- 7.36 (m, 8H).

^{13}C NMR ($CDCl_3$) δ 21.3, 52.6, 53.3, 53.6, 84.4, 94.0, 115.8, 116.1, 126.3, 129.3, 130.4, 130.5, 130.7, 167.1, 168.2.

Anal. Calcd for $C_{21}H_{20}FNO_7$: C, 60.43; H, 4.83; N, 3.36. Found: C, 60.54; H, 4.83; N, 3.42.

Dimethyl (3R,4R,5R)-3-(4-fluorophenyl)dihydro-5-phenyl-4-nitro-2,2(3H)-furandicarboxylate 66

The reaction of 4-fluoro-β-nitrostyrene (0.201 g, 1.20 mmol), benzaldehyde (0.032 g, 0.30 mmol) and dimethyl diazomalonate (0.047 g, 0.30 mmol) according to the general procedure, afforded the product **66** (0.061 g, 50 %) as a colorless crystalline solid, **mp** 140 °C.



66

IR (KBr) ν_{max}: 3068, 3032, 2996, 2970, 2950, 1744, 1615, 1558, 1522, 1444, 1387, 1300, 1289, 1237, 1170, 1118, 1067, 1031, 963, 943, 922, 855, 751, 705, 643, 596, 539 cm^{-1}.

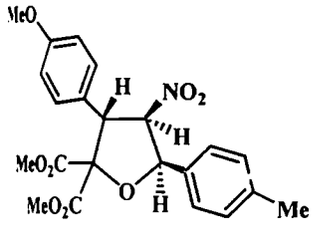
^{1}H NMR ($CDCl_3$) δ 3.35 (s, 3H), 3.94 (s, 3H), 5.23 (d, 1H, J = 5.94 Hz), 5.69 (overlapping doublets, 1H, J_1 = 6.4 Hz, J_2 = 6.8 Hz), 6.22 (d, 1H, J = 7.2 Hz), 7.03-7.09 (m, 2H), 7.25-7.35 (m, 7H).

^{13}C NMR ($CDCl_3$) δ 52.5, 53.3, 53.6, 84.3, 90.5, 93.9, 115.7, 116.0, 126.2, 128.5, 129.2, 129.4, 130.2, 130.4, 133.5, 164.3, 166.9, 168.1.

nal. Calcd for $C_{20}H_{18}FNO_7$: C, 59.55; H, 4.50; N, 3.47. Found: C, 59.72; H, 4.34; N, 3.70.

Dimethyl (3R,4R,5R)-3-(4-methoxyphenyl)dihydro-5-(4-methylphenyl)-4-nitro-2,2(3H)-furandicarboxylate 67

The reaction of 4-methoxy-β-nitrostyrene (0.215 g, 1.20 mmol), *p*-tolualdehyde (0.036 g, 0.30 mmol) and dimethyl diazomalonate (0.047 g, 0.30 mmol), according to the general procedure, afforded the product **67** (0.049 g, 38 %) as a colorless crystalline solid, **mp** 115 °C.



67

IR (KBr) ν_{max}: 3022, 2955, 2939, 1744, 1615, 1563, 1532, 1460, 1444, 1372, 1268, 1232, 1222, 1186, 1118, 1082, 1041, 927, 860, 803, 736, 684 cm^{-1}.

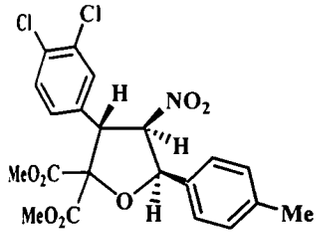
^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 3.35 (s, 3H), 3.79 (s, 3H), 3.93 (s, 3H), 5.14 (d, 1H, J = 5.9 Hz), 5.65 (overlapping doublets, 1H, J_1 = 6.1 Hz, J_2 = 6.9 Hz), 6.15 (d, 1H, J = 7.17 Hz), 6.86 (d, 2H, J = 8.7 Hz), 7.26-7.14 (m, 6H).

^{13}C NMR ($CDCl_3$) δ 21.2, 52.4, 53.4, 53.4, 55.1, 84.3, 90.6, 94.2, 114.1, 125.3, 126.1, 129.1, 129.6, 130.7, 139.0, 159.6, 167.1, 168.2.

nal. Calcd for $C_{22}H_{23}NO_8$: C, 61.53; H, 5.40; N, 3.26. Found: C, 61.84; H, 5.33; N, 3.46.

Dimethyl (3R,4R,5R)-3-(3,4-dichlorophenyl)dihydro-5-(4-methylphenyl) 4-nitro-2,2(3H)-furandicarboxylate 68

The reaction of 3,4-dichloro-β-nitrostyrene (0.261 g, 1.20 mmol), *p*-tolualdehyde (0.036 g, 0.30 mmol) and dimethyl diazomalonate (0.047 g, 0.30 mmol), according to the general procedure, afforded the product **68** (0.082 g, 58 %) as a colorless crystalline solid, **mp** 175 °C.



68

IR (KBr) ν_{max}: 3025, 2984, 2921, 1741, 1562, 1481, 1464, 1455, 1293, 1284, 1222, 1126, 1037, 942, 895, 750, 617 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.43 (s, 3H), 3.91 (s, 3H), 5.10 (d, 1H, J = 6.93 Hz), 5.66 (overlapping doublets, 1H, J_1 = 7.2 Hz, J_2 = 7.35 Hz), 6.12 (d, 1H, J = 7.62 Hz), 7.11-7.43 (m, 7H).

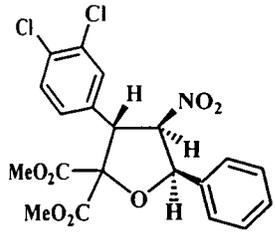
^{13}C NMR ($CDCl_3$) δ 21.4, 52.7, 52.9, 53.7, 84.1, 90.1, 93.2, 126.4, 128.0, 129.3, 130.5, 130.6, 130.8, 133.2, 133.4, 139.3, 166.8, 168.0.

Anal. Calcd for $C_{21}H_{19}Cl_2NO_7$: C, 53.86; H, 4.09; N, 2.99. Found: C, 54.29; H, 3.63; N, 2.76.

Dimethyl (3R,4R,5R)-3-(3,4-dichlorophenyl)dihydro-5-phenyl-4-nitro-2,2(3H)-furandicarboxylate 69

The reaction of 3,4-dichloro-β-nitrostyrene (0.261 g, 1.20 mmol), benzaldehyde (0.032 g, 0.30 mmol) and dimethyl diazomalonate (0.047 g, 0.30 mmol), according to the general procedure, afforded the product **69** (0.061 g, 45 %) as a colorless crystalline solid, **mp** 155 °C.

IR (KBr) ν_{max}: 3027, 2996, 2965, 2924, 1739, 1563, 1482, 1460, 1455, 1294, 1284, 1222, 1129, 1077, 1041, 937, 891, 803 751, 617 cm^{-1}.



69

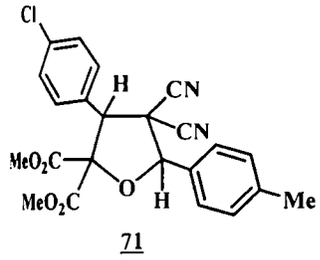
^{1}H NMR ($CDCl_3$) δ 3.45 (s, 3H), 3.94 (s, 3H), 5.13 (d, 1H, J = 6.8 Hz), 5.70 (overlapping doublets, 1H, J_1 = 6.9 Hz, J_2 = 7.5 Hz), 6.18 (d, 1H, J = 7.5 Hz), 7.19-7.46 (m, 8H).

^{13}C NMR ($CDCl_3$) δ 52.7, 52.9, 53.6, 84.1, 90.2, 93.3, 126.3, 127.8, 128.5, 129.5, 130.5, 130.7, 133.1, 133.2, 133.2, 133.4, 166.6, 167.9.

Anal. Calcd for $C_{20}H_{17}Cl_2NO_7$: C, 52.88; H, 3.77; N, 3.08. Found: C, 52.46; H, 3.68; N, 3.29.

Dimethyl-3-(4-chlorophenyl)dihydro-5-(4-methylphenyl)-4,4-dicyano-2,2(3H)-furandicarboxylate 71

The reaction of (4-chlorobenzylidene) malononitrile (0.094 g, 0.50 mmol), *p*-tolualdehyde (0.060 g, 0.50 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol), according to the general procedure, afforded the product **71** (0.119 g, 54%) as a colorless crystalline solid, **mp** 158 °C.



71

IR (KBr) ν_{max}: 2955, 2913, 2246, 1750, 1625, 1594, 1108, 1113, 1020, 932, 746 cm^{-1}.

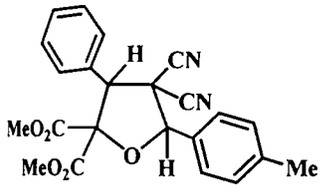
^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.36 (s, 3H), 3.95 (s, 3H), 5.08 (s, 1H), 5.95 (s, 1H), 7.18-7.48 (m, 8H).

^{13}C NMR ($CDCl_3$) δ 166.2, 166.2, 140.5, 136.3, 130.9, 130.6, 129.7, 129.4, 128.7, 126.2, 112.2, 111.2, 90.6, 87.9, 59.2, 54.3, 53.0, 48.7, 21.4.

Anal. Calcd for $C_{23}H_{19}ClN_2O_5$: C, 62.95; H, 4.36; N, 6.38. Found: C, 63.02; H, 4.26; N, 6.41.

Dimethyl-3-(phenyl)dihydro-5-(4-methylphenyl)-4,4-dicyano-2,2(3H)-furandicarboxylate 72

The reaction of benzylidenemalononitrile (0.077 g, 0.50 mmol), *p*-tolualdehyde (0.060 g, 0.50 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol), according to the general procedure, afforded the product **72** (0.099 g, 49 %) as a colorless crystalline solid, **mp** 158 °C.



72

IR (KBr) ν_{max}: 3012, 2955, 2251, 1750, 1620, 1522, 1460, 1439, 1310, 1243, 1103, 1067, 1020, 974, 756 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.28 (s, 3H), 4.00 (s, 3H), 5.24 (s, 1H), 6.00 (s, 1H), 7.25-7.50 (m, 9H).

^{13}C NMR ($CDCl_3$) δ 166.3, 166.2, 140.3, 132.2, 129.9, 129.6, 129.5, 129.4, 129.1, 128.7, 126.2, 112.4, 111.1, 90.7, 87.8, 59.7, 54.2, 52.8, 48.8, 21.4.

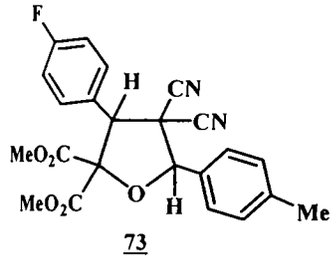
Anal. Calcd for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93. Found: C, 68.04; H, 4.57; N, 7.06.

Dimethyl-3-(4-fluorophenyl)dihydro-5-(4-methylphenyl)-4,4-dicyano-2,2(3H)-furandicarboxylate 73

The reaction of (4-fluorobenzylidene)malononitrile (0.086 g, 0.50 mmol), *p*-tolualdehyde (0.060 g, 0.50 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol), according to the general procedure, afforded the product **73** (0.105 g, 50 %) as a colorless crystalline solid, **mp** 183 °C.

IR (KBr) ν_{max}: 3022, 2960, 2251, 1760, 1610, 1512, 1439, 1294, 1227, 1170, 1129, 1098, 948, 803 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 3.37 (s, 3H),



73

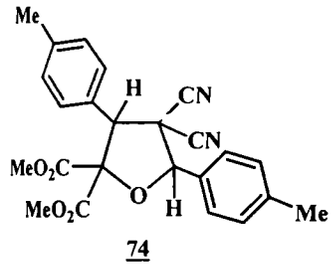
3.97 (s, 3H), 5.24 (s, 1H), 5.95 (s, 1H), 7.13-7.48 (m, 8H).

^{13}C NMR ($CDCl_3$) δ 166.2, 164.9, 161.6, 140.4, 131.5, 131.4, 129.6, 126.1, 116.4, 116.1, 112.2, 111.1, 90.6, 87.8, 59.0, 54.2, 52.9, 48.8, 21.3.

Anal. Calcd for $C_{23}H_{19}FN_2O_5$: C, 65.40; H, 4.53; N, 6.63. Found: C, 65.39; H, 4.45; N, 6.66.

Dimethyl-3-(4-methylphenyl)dihydro-5-(4-methylphenyl)-4,4-dicyanao-2,2(3H)-furandicarboxylate 74

The reaction of (4-methyl benzylidene) malononitrile (0.084 g, 0.50 mmol), *p*-tolualdehyde (0.060 g, 0.50 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol), according to the general procedure, afforded the product **74** (0.084 g, 40 %) as a colorless liquid.



74

IR (neat) ν_{max}: 3024, 2994, 2960, 2252, 1762, 1612, 1514, 1434, 1290, 1226, 1170, 1125, 1084, 951, 806, 794 cm^{-1}.

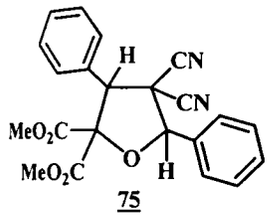
^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 2.39 (s, 3H), 3.32 (s, 3H), 3.95 (s, 3H), 5.22 (s, 1H), 5.98 (s, 1H), 7.20-7.32 (m, 8H).

^{13}C NMR ($CDCl_3$) δ 166.4, 140.6, 140.0, 129.9, 129.61, 129.59, 129.4, 129.3, 126.6, 126.2, 112.5, 111.2, 90.6, 87.7, 59.5, 54.2, 52.1, 49.3, 21.4, 21.2.

HRMS (EI): m/z Calcd for $C_{24}H_{22}N_2O_5$ [M+]: 418.1528. Found: 418.1508.

Dimethyl-3-(phenyl)dihydro-5-phenyl-4,4-dicyano-2,2(3H)-furandicarboxylate 75

The reaction of benzylidenemalononitrile (0.077 g, 0.50 mmol), benzaldehyde (0.053 g, 0.50 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol), according to the general procedure, afforded the product **75** (0.084 g, 43%) as a colorless liquid.



75

IR (neat) ν_{max}: 3024, 2990, 2920, 2251, 1759, 1564, 1480, 1456, 1413, 1290, 1284, 1222, 1129, 1041, 891, 803, 751, 705, 617 cm^{-1}

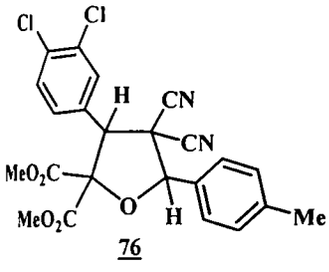
^{1}H NMR ($CDCl_3$) δ 3.39 (s, 3H), 3.98 (s, 3H), 5.12 (s, 1H), 6.00 (s, 1H), 7.35-7.61 (m, 10H).

^{13}C NMR ($CDCl_3$) δ 48.6, 53.0, 54.4, 59.2, 87.8, 90.7, 111.1, 112.1, 126.3, 126.7, 129.0, 129.4, 129.5, 130.5, 130.9, 131.7, 136.3, 166.1, 166.2.

HRMS (EI): m/z Calcd for $C_{22}H_{18}N_2O_5$ [M+]: 389.1137. Found: 389.1055.

Dimethyl-3-(3,4-dichlorophenyl)dihydro-5-(4-methylphenyl)-4,4-dicyanao-2,2(3H)-furandicarboxylate 76

The reaction of (3,4-dichlorobenzylidene)malononitrile (0.112 g, 0.50mmol), p-tolualdehyde (0.060 g, 0.50 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol), according to the general procedure, afforded the product **76** (0.104 g, 44 %) as a colorless liquid.



76

IR (neat) ν_{max}: 2955, 2924, 2259, 1750, 1615, 1563, 1517, 1475, 1439, 1294, 1237, 1110, 1036, 943, 824, 668 cm^{-1}.

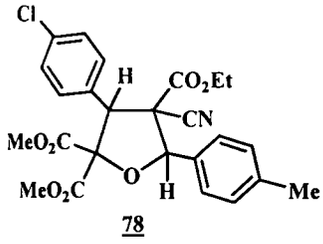
^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 3.44 (s, 3H), 3.96 (s, 3H), 5.17 (s, 1H), 5.93 (s, 1H), 7.25-7.63 (m, 7H).

^{13}C NMR ($CDCl_3$) δ 167.3, 166.1, 140.8, 140.6, 134.8, 133.5, 131.9, 131.0, 129.8, 129.7, 128.5, 126.6, 112.3, 112.0, 90.7, 86.6, 58.3, 54.2, 53.2, 48.8, 21.5.

HRMS (EI): m/z Calcd for $C_{23}H_{18}N_2O_5Cl_2$ [M+]: 472.0592. Found: 472.0539.

4-Ethyl-2,2-dimethyl-3-(4-chlorophenyl)-4-cyano-5-(4-methylphenyl) dihydrofuran-2,2,4(3H)-tricarboxylate 78

The reaction of ethyl-3-(4-chlorophenyl)-2-cyanoacrylate (0.118 g, 0.50 mmol), *p*-tolualdehyde (0.060 g, 0.50 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol), according to the general procedure, afforded the product **78** (0.134 g, 55 %) as a colorless crystalline solid. The product was further purified by recrystallization from dichloromethane-hexane solvent system, colorless crystalline solid, **mp** 164 °C.



78

IR (KBr) ν_{max}: 2953, 2250, 1744, 1738, 1511, 1439, 1367, 1288, 1232, 1120, 1041, 1009, 817 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3H, J = 7.2 Hz), 2.38 (s, 3H), 3.40 (s, 3H), 3.64-3.70 (m, 1H), 3.86-3.97 (m, 1H), 3.94 (s, 3H), 5.14 (s, 1H), 6.16 (s, 1H), 7.19 (d, 2H, J = 8.0 Hz), 7.37-7.39 (m, 6H).

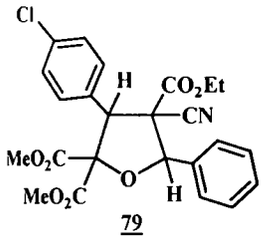
^{13}C NMR ($CDCl_3$) δ : 13.2, 21.3, 52.7, 53.6, 56.8, 59.5, 63.3, 89.3, 91.4, 115.6, 126.2, 128.8, 129.1, 130.5, 131.7, 132.0, 135.2, 139.3, 165.2, 167.0, 167.5.

Anal. Calcd for $C_{25}H_{24}ClNO_7$: C, 61.79; H, 4.98; N, 2.88. Found: C, 61.41; H, 5.00; N, 3.00.

4-Ethyl-2,2-dimethyl-3-(4-chlorophenyl)-cyano-5-phenyl dihydrofuran-2,2,4(3H)-tricarboxylate 79

The reaction of ethyl-3-(4-chlorophenyl)-2-cyanoacrylate (0.118 g, 0.50 mmol), benzaldehyde (0.053 g, 0.50 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol), according to the general procedure, afforded the product **79** (0.106 g, 45%) as a colorless crystalline solid, **mp** 148-150 °C.

IR (KBr) ν_{max}: 2953, 2250, 1751, 1738, 1563,



79

1491, 1463, 1439, 1284, 1243, 1118, 1093, 870, 777, 705 cm^{-1}.

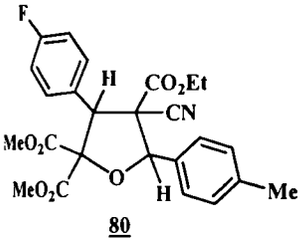
^{1}H NMR ($CDCl_3$) δ 0.79 (t, 3H, J = 7.2 Hz), 3.39 (s, 3H), 3.61-3.67 (m, 1H), 3.78-3.84 (m, 1H), 3.94 (s, 3H), 5.12 (s, 1H), 6.19 (s, 1H), 7.39-7.68 (9H).

^{13}C NMR ($CDCl_3$) δ 13.2, 52.7, 53.6, 56.8, 59.4, 63.3, 89.2, 91.5, 115.4, 126.3, 128.4, 128.8, 129.4, 131.7, 132.0, 133.5, 135.2, 165.2, 166.9, 167.4.

Anal. Calcd for $C_{24}H_{22}ClNO_7$: C, 61.09; H, 4.70; N, 2.97. Found: C, 61.47; H, 4.56; N, 3.20

4-Ethyl-2,2-dimethyl-3-(4-fluorophenyl)-4-cyano-5-(4-methylphenyl) dihydrofuran-2,2,4(3H)-tricarboxylate 80

The reaction of ethyl (4-fluorophenyl)-2-cyanoacrylate (0.110 g, 0.50 mmol), *p*-tolualdehye (0.060 g, 0.50 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol), according to the general procedure, afforded the product **80** (0.129 g, 55 %) as a colorless crystalline solid, **mp** 158 °C.



80

IR (KBr) ν_{max}: 2995, 2913, 2246, 1755, 1615, 1512, 1279, 1232, 1124, 1051, 860 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 0.81 (t, 3H, J = 7.14 Hz), 2.36 (s, 3H), 3.37 (s, 3H), 3.63-3.69 (m, 1H), 3.76-3.87 (m, 1H), 3.92 (s, 3H), 5.12 (s, 1H), 6.12 (s, 1H), 7.06-7.46 (m, 8H).

^{13}C NMR ($CDCl_3$) δ : 13.2, 21.3, 52.7, 53.6, 56.7, 59.6, 63.3, 89.2, 91.5, 115.6, 126.2, 129.0, 129.5, 130.5, 132.1, 132.3, 139.3, 161.3, 165.3, 167.1, 167.6.

Anal. Calcd for $C_{25}H_{24}FNO_7$: C, 63.96; H, 5.15; N, 2.98. Found: C, 63.59; H, 4.93; N, 3.27.

2.7. References

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CHAPTER 3

THE THREE COMPONENT REACTION OF DICARBOMETHOXYCARBENE, ALDEHYDES AND QUINONOID COMPOUNDS: SYNTHESIS OF NOVEL SPIRODIOXOLANES

3.1. Introduction

The focal theme of the chapter is the cycloaddition of acyclic carbonyl ylides to 1,2-quinones and therefore it is considered essential to give a brief review of the chemistry of the latter.

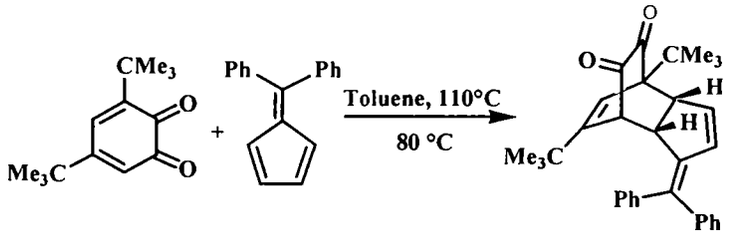
Quinones are versatile organic compounds endowed with rich and fascinating chemistry; many of them are important therapeutic agents. The importance of quinones stems from their potential biological activity. They play a vital role in electron transport in the respiratory and photosynthetic elements of biological systems as well as in a number of redox processes in Nature.[1]

Their reactivity profile in cycloaddition reactions is quite interesting both from the synthetic and theoretical standpoints. In Diels-Alder reactions, they can function as carbodienes, heterodienes or dienophiles. In addition to the conventional cycloaddition reactions, quinones are also known to undergo cycloaddition reactions with various 1,3-dipoles and zwitterions. The electronic and steric features of the substituents on the quinone play an important role in the cycloaddition reactions of 1,2-benzoquinones. Recent investigations in our laboratory have highlighted the influence of these factors on the cycloaddition reactions of 1,2-benzoquinones.[2-5]

The different reactivity profiles exhibited by 1,2-benzoquinones in cycloaddition reactions are briefly outlined in the following sections.

3.1.1. Diels-Alder Reactions of 1,2-Benzoquinones

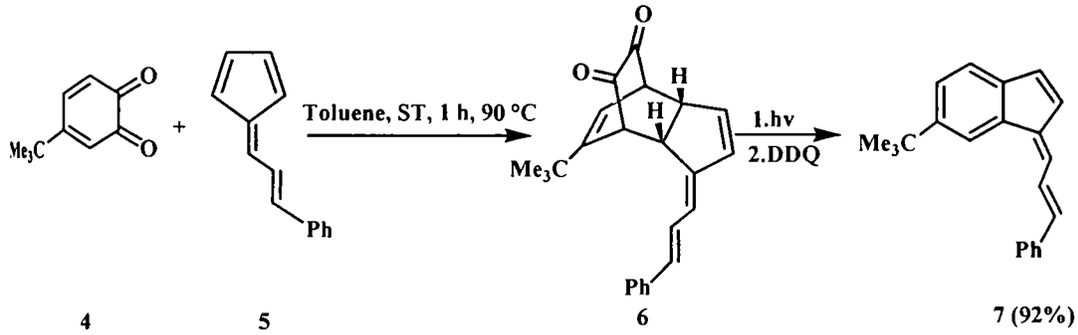
3,5-Di-*tert*-butyl-1,2-benzoquinone **1** was found to undergo a facile cycloaddition with pentafulvene **2** to afford bicyclo[2.2.2]octene dione **3** in high yield (Scheme 1).[2]



1 2 3 (90%)

Scheme 1

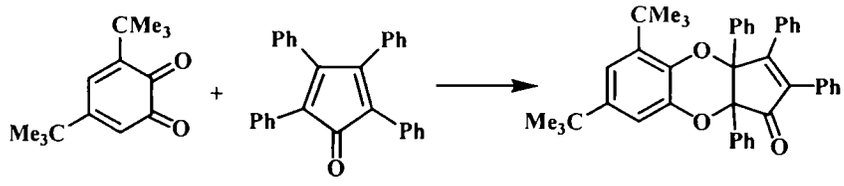
It is interesting to note that 1,2-benzoquinones can undergo inverse electron demand Diels-Alder reaction with 6-(2-phenylethenyl) fulvene **5**. The diones obtained by these reactions undergo photolytic double decarbonylation reactions, lending an efficient route to the highly substituted indenes, which show interesting chemical and physical properties (Scheme 2).[3]



4 5 6 7 (92%)

Scheme 2

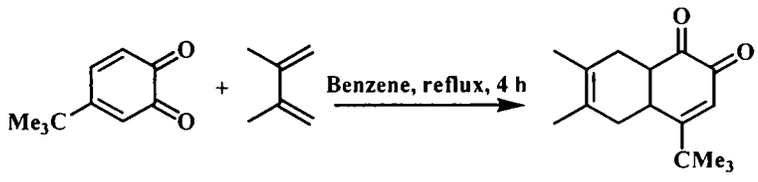
The heterodiene moiety present in 1,2-benzoquinones are highly activated so that they can participate in Diels-Alder reactions. 3,5-Di-*tert*-butyl-1,2-benzoquinone **1** when treated with tetracyclone **8** led to the formation of benzodioxin derivative (Scheme 3).[4]



1 8 9

Scheme 3

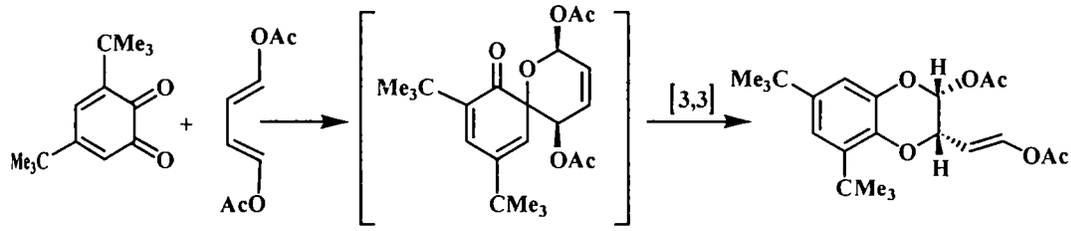
It has been reported that 1,2-benzoquinone functions as an electron deficient dienophile in its reaction with 2,3-dimethyl butadiene **10** (Scheme 4).[5]



4 10 11 (55%)

Scheme 4

1,2-Benzoquinones can serve as heterodienophiles in cycloaddition reactions due to the presence of two activated carbonyl groups. Electron rich dienes such as 1,4-diacetoxy-1,3-butadiene, undergo hetero Diels-Alder reaction with substituted 1,2-benzoquinones to give benzodioxin adducts.[6] The reaction proceeds by a two step mechanism; the initial [4+2] adduct **13** is positioned for [3,3] sigmatropic rearrangement leading to the benzodioxin **14** (Scheme 5).



1 12 13 14 (90%)

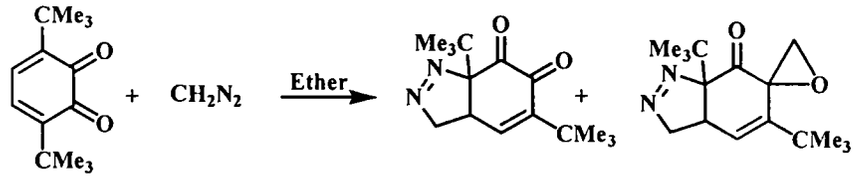
Scheme 5

3.1.2. Dipolar Cycloaddition Reactions of 1,2-Benzoquinones

The presence of two potentially dipolarophilic functionalities *viz.*, C=C and C=O, renders 1,2-benzoquinones very interesting from the vantage point of dipolar

Cycloadditions. In contrast to the large amount of work carried out on the Diels-Alder cycloadditions of 1,2-quinones, very little is known about their dipolar cycloadditions. Literature reports in this area mainly constitute the reactions of diazomethane, nitrile oxides and certain mesoionic compounds.[7]

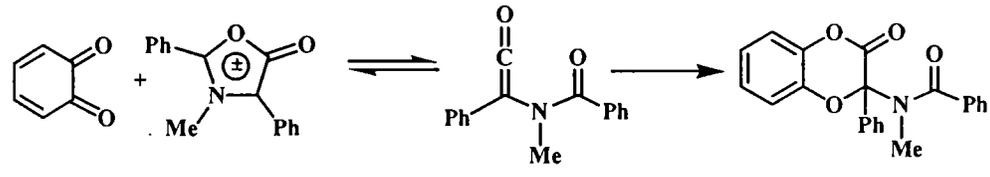
The reaction of 3,6-di-*tert*-butyl-1,2-benzoquinone **15** with diazomethane has been reported to afford the corresponding indazole **16**. Spirooxirane **17** was also formed along with the indazole, when excess of diazomethane was used (Scheme 6).[8]



15 16 17

Scheme 6

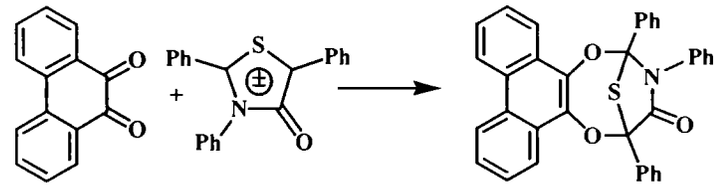
Mesoionic compounds have been extensively utilized as substrates in 1,3-dipolar cycloadditions. The anhydro-5-hydroxy-1,3-oxazoliumhydroxide or münchnone **19** reacts with unsubstituted 1,2-benzoquinone **18** affording the lactone **21**. Conceivably the reaction occurs *via* the open chain ketene form of münchnone **19** (Scheme 7).[9]



18 19 20 21

Scheme 7

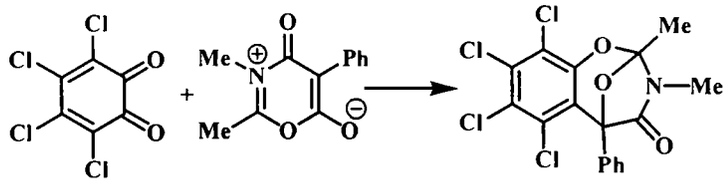
Phenanthrenequinone was also found to react smoothly with the mesoisomünchnone **23** (Scheme 8).[10]



22 23 24

Scheme 8

The reaction of 4-oxo-4[H]-1,3-oxazinium-6-olate with *o*-chloranil led to the :rmation of **27** (Scheme 9).[11-12]

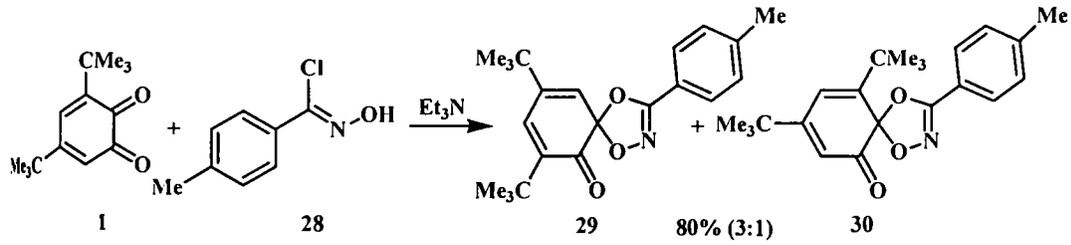


25 26 27

Scheme 9

Presumably this reaction also occurs *via* the open chain ketene form of the :pole.

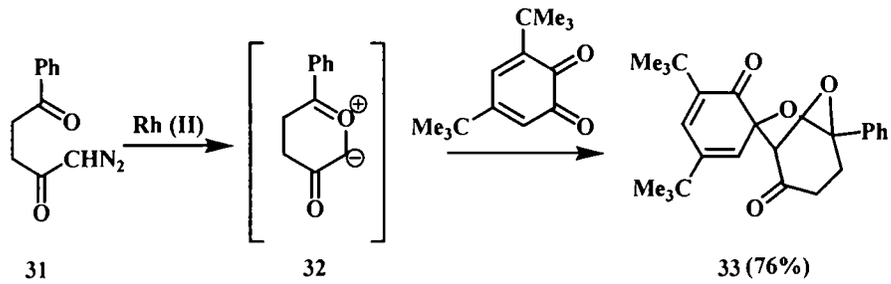
Another important class of dipolar species that has been added to 1,2-:nzoquinones is nitrile oxides. This reaction was studied in detail in our laboratory :d it was found that aryl nitrile oxides undergo facile cycloaddition with 1,2-:nzoquinones, the reaction generally occurring across the carbon-oxygen double :nd.[13] The reaction of di- and tri- substituted 1,2-benzoquinones with aryl nitrile :ides afforded a regioisomeric mixture of mono spirodioxolanes. An illustrative :ample is given in Scheme 10.



1 28 29 80% (3:1) 30

Scheme 10

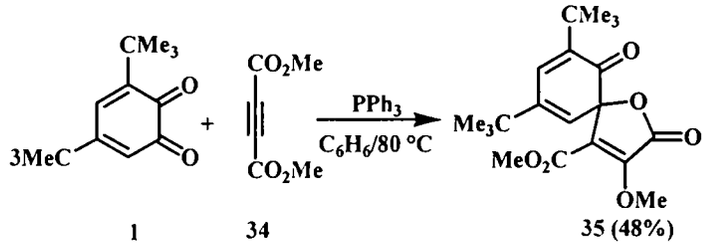
Recent work in our laboratory has shown that cyclic carbonyl ylides generated om diazoketones undergo a facile dipolar cycloaddition with *o*-quinones (Scheme 1).[14]



31 32 33 (76%)

Scheme 11

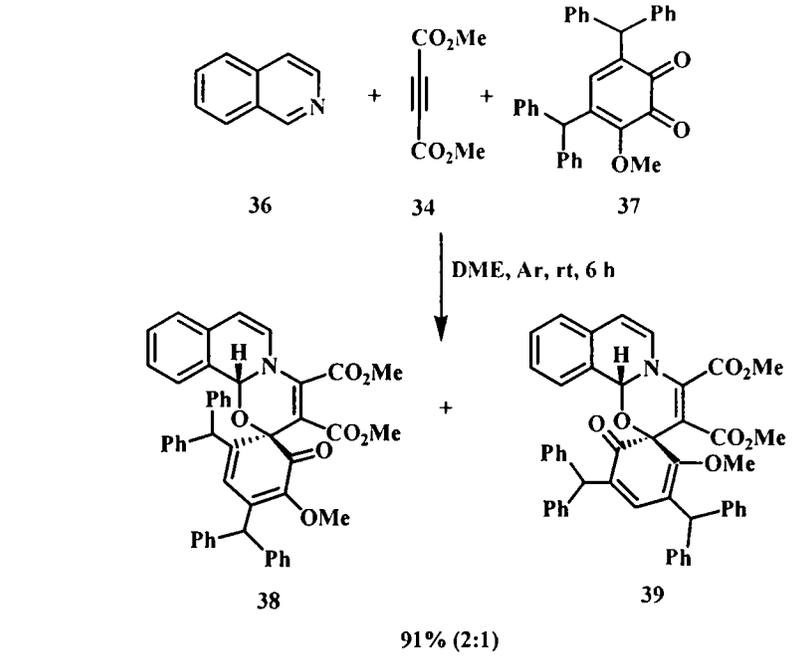
Research in our laboratory has shown that *o*-quinones are efficient traps for witterionic species generated from DMAD and triphenylphosphine (Scheme 12).[15]



1 34 35 (48%)

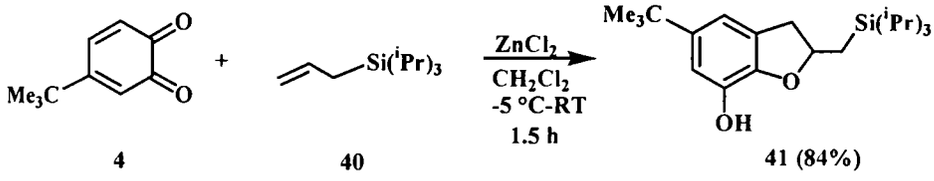
Scheme 12

In related investigations, it has been shown that zwitterionic species generated the addition of isoquinoline to DMAD can be trapped by the quinone carbonyls Scheme 13).[16]



Scheme 13

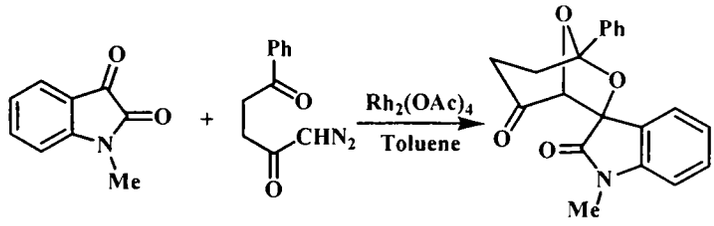
In the presence of Lewis acids, allylsilanes undergo a formal [2+3] oaddition with 1,2-benzoquinones to yield benzofuran derivative (Scheme 14).[17]



Scheme 14

Isatins

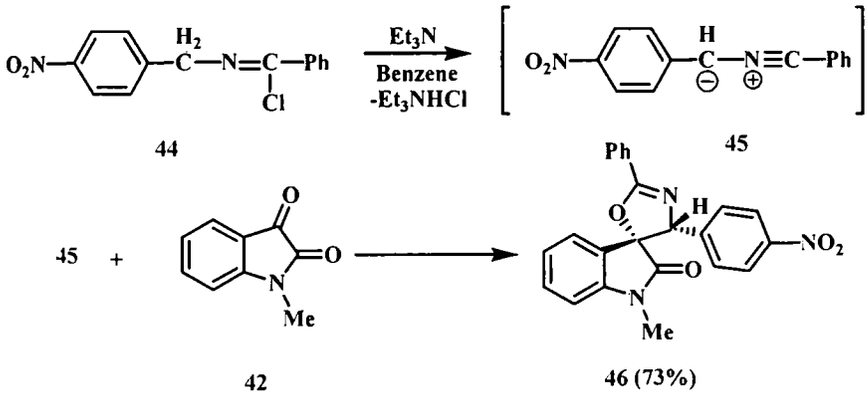
Isatin and its derivatives are known to exhibit interesting pharmacological vities. *N*-alkylated isatins act as antimicrobials,[18] excitatory amino acid antagonists munomodulators and anti-cancer agents,[19] ulcer inhibitors, acetylcholinesterase bitors for the treatment of memory dysfunction, and reversible and competitive bitors of monoamine oxidase **A** and **B**. In spite of the enormous utility offered by class of quinonoid compounds, their chemistry remains underexplored. estigations by our group have shown that cyclic carbonyl ylide dipoles add to these tems leading to novel spirooxindole structures (Scheme 15).[20]



42 31 43(67%)

Scheme 15

Similarly, isatins have been shown to participate in a facile 1,3-dipolar addition ith nitrile ylides. Base catalyzed reaction of 4-nitro-*N*-benzyl benzimidoylchloride 4 and *N*-methyl isatin **42** in benzene at room temperature resulted in the formation oxazoline fused spirooxindole derivative **46** in 73% yield. As expected, the [2+3] cloaddition occurred across the more electrophilic ketonic carbonyl (Scheme 16).[21]

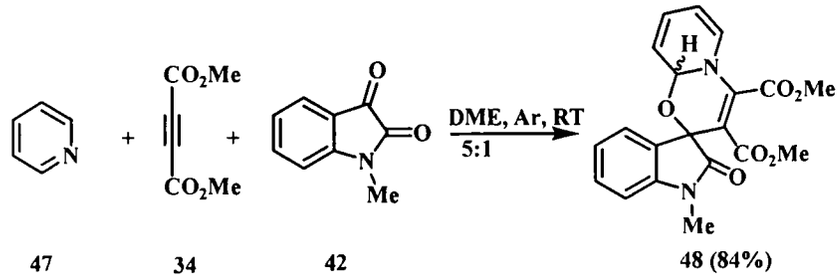


44 45

42 46 (73%)

Scheme 16

Isatins serve as very good dipolarophiles for 1,4-dipoles also (Scheme 17).[16]



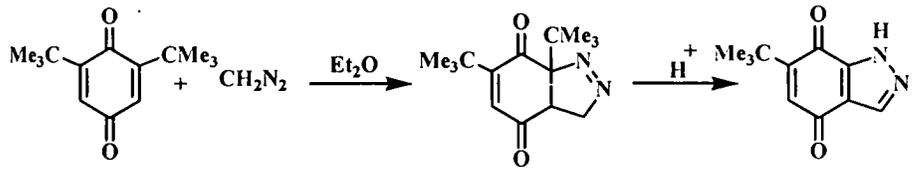
47 34 42 48 (84%)

Scheme 17

1,4-Quinones

Although the chemistry of 1,4-quinones has been the subject of extensive stigations, very little information is available on the dipolar cycloaddition ctions of these species. A selective coverage of the literature is presented here.

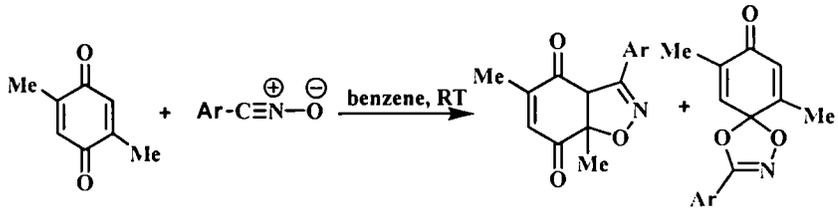
The reaction of diazomethane with 2,6-di-*tert*-butyl-1,4-benzoquinone afforded corresponding indazole derivative which under acidic conditions underwent lkylation to yield **51** (Scheme 18).[22]



49 50 51

Scheme 18

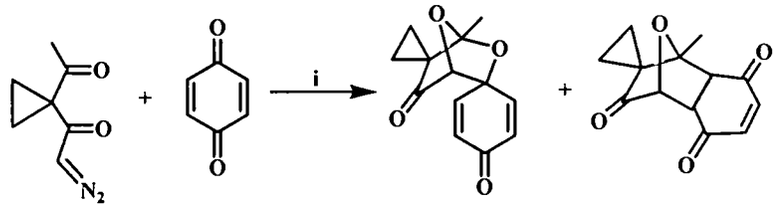
p-Quinones are known to react both as carbo and hetero dipolarophiles. An strative example is the reaction of aryl nitrile ylide with 2,5-dimethyl *p*-quinone **52** afford the products **54** and **55** as depicted in the following scheme.[23]



52 53 54 55

Scheme 19

Cyclic carbonyl ylides also react with *p*-quinones leading to both C=O and C addition products (Scheme 20).[24]



56 57 58 59

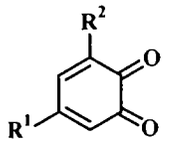
i. $Rh_2(OAc)_4$, CH_2Cl_2, RT, 6 h, 41%, (1:1.7)

Scheme 20

The Present Work

The literature survey presented above has revealed that although the reactions various 1,3-dipoles including cyclic carbonyl ylides with quinonoid compounds has n studied in detail, there has been no work on the addition of acyclic carbonyl des to 1,2- and 1,4- diones. In view of this, and in the context of our general interest the chemistry of quinonoid compounds, we have explored the reaction of the latter h carbonyl ylides generated from aldehydes and dicarbomethoxycarbene. The ults of our work constituting a detailed study of the cycloaddition reactions of ious 1,2-diones such as substituted 1,2-benzoquinones, phenanthrene quinone and ins with various acyclic carbonyl ylides are presented in this chapter. The liminary results obtained with 1,4-quinones are also presented.

The 1,2- and 1,4-diones selected for the present study are shown in Figure 1.

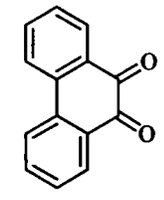


i

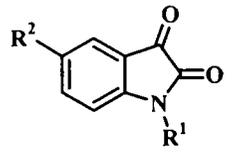
ia: R^1 = ^{t}Butyl, R^2 = H

ib: R^1 = R^2 = ^{t}Butyl

ic: R^1 = ^{t}Butyl, R^2 = diphenylmethyl



ii



iii

iiia: R^1 = R^2 = H

iiib: R^1 = Me; R^2 = H

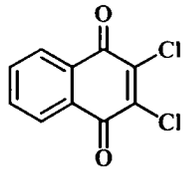
iiic: R^1 = ^{n}Pr; R^2 = H

iiid: R^1 = Et, R^2 = H

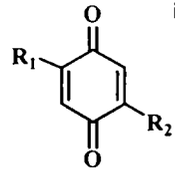
iiie : R^1 = Me, R^2 = Br

iiif: R^1 = Ph, R^2 = H

iiig: R^1 = allyl, R^2 = H



iv



v

va: R^1= R^2 = Me

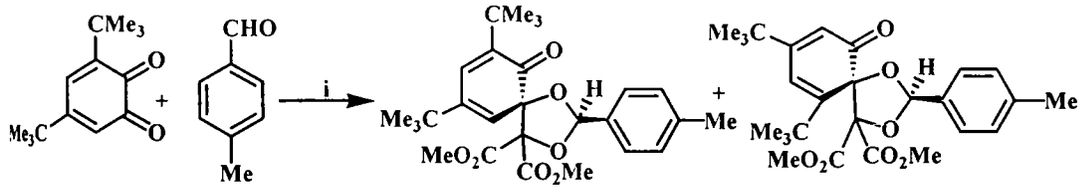
vb: R^1 = R^2 = H

Figure 1

3.5. Results and Discussion

3.5.1. Reaction of Acyclic Carbonyl Ylides with *o*-Quinones

Our studies commenced by the Rh(II) catalyzed decomposition of dimethyl azomalonate in the presence of *p*-tolualdehyde and 3,5-di-*tert*-butyl-1,2-enzoquinone. A facile reaction occurred, affording a regioisomeric mixture of oxolanes **61** and **62** (Scheme 21).



1 60 61 (44 %) 62 (15 %)

i. $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, dry benzene, argon, 80 °C, 14 h.

Scheme 21

The products were separated by chromatography on silica gel column and haracterized by spectroscopic analysis. In the IR spectrum of **61**, the keto-group sorbed at 1646 cm^{-1} and the ester carbonyl group showed absorption at 1745 cm^{-1}. the ^1H NMR spectrum, resonance signals for the two *tert*-butyl groups were visible singlets at δ 1.14 and δ 1.25. Methyl protons on the aromatic ring were discernible δ 2.37. The singlet signals due to the protons of the two methoxy groups were served at δ 3.73 and δ 3.80. The acetal proton furnished a singlet at δ 6.78. Two finic protons were discernible as doublets at δ 5.72 and δ 6.87. The two signals ich appeared as doublets at δ 7.19 and δ 7.60 correspond to the aromatic protons. In ^{13}C NMR spectrum, the signal due to the *p*-methyl carbon was descernible at δ 5. The peak at δ 53.0 was assigned to the two carbomethoxy carbons. The signal at 4.0 was attributed to the spirocarbon. The ester carbonyl groups resonated at δ 7.0 and the keto-group signal was observed at δ 198.2. All other signals were also good agreement with the proposed structure. Final confirmation of the structure and reochemistry of **61** was obtained by single crystal X-ray analysis (Figure 2).

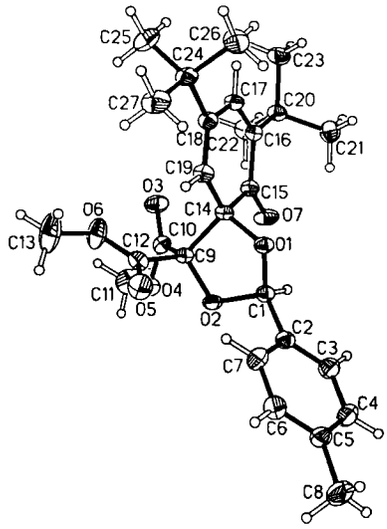
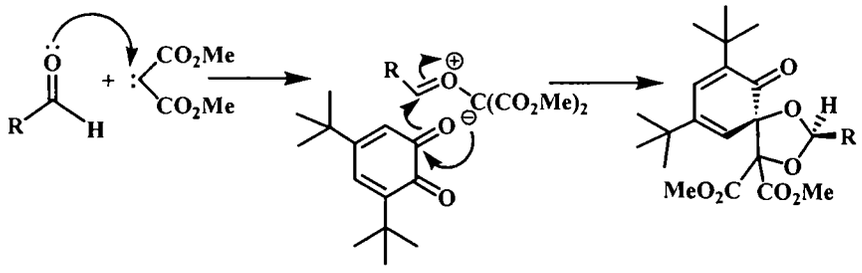


Figure 2. *Single crystal X-ray structure of* ***61***

The IR spectrum of compound **62** displayed a strong absorption at 1659 cm^{-1} ributable to the keto group. The peak observed at 1752 cm^{-1} corresponds to the ester bonyl groups present in the compound. In the ^{1}H NMR spectrum, the peaks served at δ 1.12 and δ 1.21 correspond to the *tert*-butyl groups, while the signal due he methyl group on the aromatic ring was visible at δ 2.39. The two carbomethoxy ups displayed signals at δ 3.71 and δ 3.75. The acetal proton resonated at δ 6.59. e doublet that appeared at δ 6.37 can be attributed to the olefinic proton which is in jugation with the carbonyl group. The signal at δ 5.74 can be assigned to the other finic proton. The ^{13}C NMR spectrum of **62** manifested a sharp peak at δ 204.6 igned to the keto-group. Ester carbonyl signal was visible at δ 167.6. The signals at 2.8 and δ 53.5 were attributed to the two carbomethoxy carbons. The methyl bon on the aromatic ring resonated at δ 21.4. All the other signals were also in d agreement with the proposed structure. The relative stereochemistry of **62** was igned by comparison of the chemical shift of the acetal proton (δ 6.59) to that of corresponding proton in **61** (δ 6.78).

Mechanistically the reaction may be considered to involve the formation of a bonyl ylide by the reaction of the carbene, generated by Rh(II) catalyzed

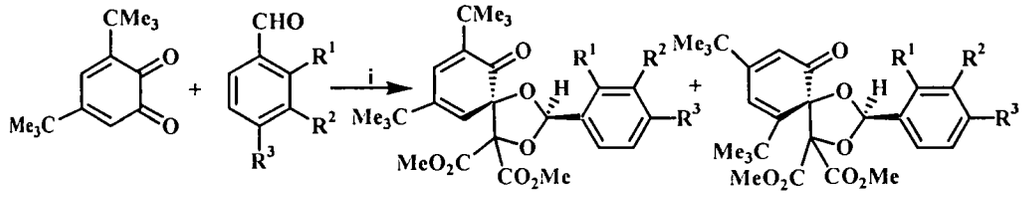
decomposition of dimethyl diazomalonate, and the aldehyde and its trapping by the quinone carbonyls (Scheme 22). The diastereoselectivity of the reaction may be rationalized by the concerted nature of the carbonyl ylide cycloadition and, the observed relative stereochemistry of the products may be attributed to the preferred *trans* geometry of the ylide.



Scheme 22

The reaction was found to be general with respect to a variety of aromatic aldehydes, especially those containing electron donating groups, and 1,2-benzoquinones. The dioxolane derivatives were obtained in moderate to excellent yields. In all cases, the structure of the products was established by spectroscopic analysis; IR, ^{1}H NMR and ^{13}C NMR data were completely consistent with the assigned structure.

With 3,5-di-*tert*-butyl-1,2-benzoquinone, the dipolar cycloaddition reaction resulted in the formation of two regioisomeric dioxolanes in the ratio 3:1. The results are presented in Scheme 23.



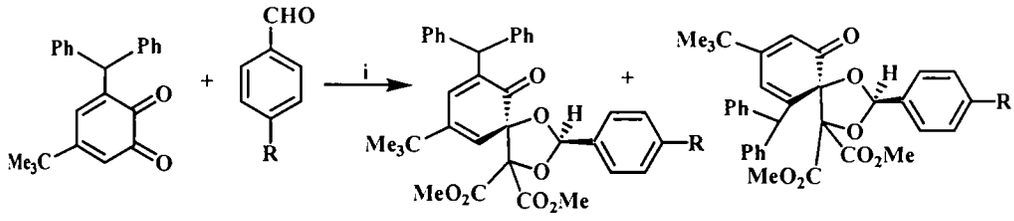
1 63a-65a 63b-65b

i. $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, dry benzene, argon, 80 °C, 14 h

63a, 63b. $R^1 = R^2 = R^3 = H$, 62 % (3:1)
64a, 64b. $R^1 = R^3 = H$, $R^2 = OMe$, 40 % (3:1)
65a, 65b. $R^1 = R^3 = OMe$, $R^2 = H$, 34 % (3:1)

Scheme 23

With 3-(diphenylmethyl)-5-*tert*-butyl-1,2-benzoquinone, the ratio of the two regioisomers was found to change with aldehyde substituent (Scheme 24).



66a-67a 66b-67b

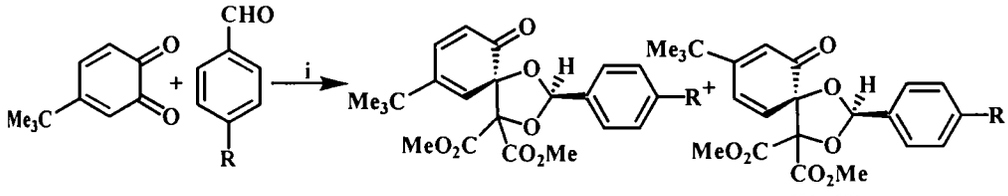
i. $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, dry benzene, argon, 14 h

66a, 66b. R = Me, 74 % (2:1)

67a, 67b. R = H, 65 % (1:1.4)

Scheme 24

As anticipated, the addition of acyclic carbonyl ylides to 4-*tert*-butyl-1,2-benzoquinone afforded regioisomeric mixture of the products in the ratio 1:1(Scheme 25).



68a-69a 68b-69b

i. $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, dry benzene, argon, 14 h

68a, 68b. R = Me, 41 % (1:1)

69a, 69b. R = H, 45 % (1:1)

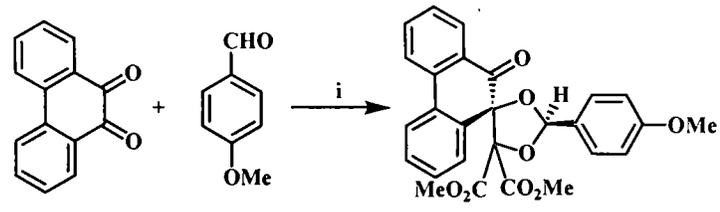
Scheme 25

When aromatic aldehydes with electron withdrawing substituents were used in the reaction, complex and interactable mixtures resulted; therefore the reaction was not pursued.

3.2. Dipolar Cycloaddition Reaction of Acyclic Carbonyl Ylides with Phenanthrenequinone

Subsequent to the above investigations, we turned our attention to the addition of acyclic carbonyl ylides to phenanthrenequinone. We initiated our experiments by treating a mixture of dimethyl diazomalonate, *p*-anisaldehyde and

Phenanthrenequinone with a catalytic amount of Rh(II) acetate in refluxing benzene under an atmosphere of argon for 14 h. The reaction afforded the corresponding dioxolane derivative **71** as a single diastereoisomer in 73 % yield (Scheme 26).



22 **70** **71 (73 %)**

i. $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, dry benzene, argon, 14 h

Scheme 26

The cycloadduct **71** was characterized by spectroscopic methods. The IR spectrum of **71** showed a strong band at 1708 cm^{-1} which can be assigned to the keto group in the product. The two ester carbonyls appeared at 1748 cm^{-1}. The ^1H NMR spectrum was in good agreement with the assigned structure. Signals due to the methoxy and carbomethoxy protons were discernible at δ 3.18, δ 3.60, and δ 3.85. The acetal proton of the dioxolane ring showed its resonance signal as a singlet at δ 6.71. The ^{13}C NMR spectrum was also in good agreement with the assigned structure. The peaks at δ 165.8 and δ 164.8 were typical of the two ester carbonyls. The signal at δ 197.2 was assigned tc the keto-group present in the compound. All the other signals were also in good agreement with the assigned structure.

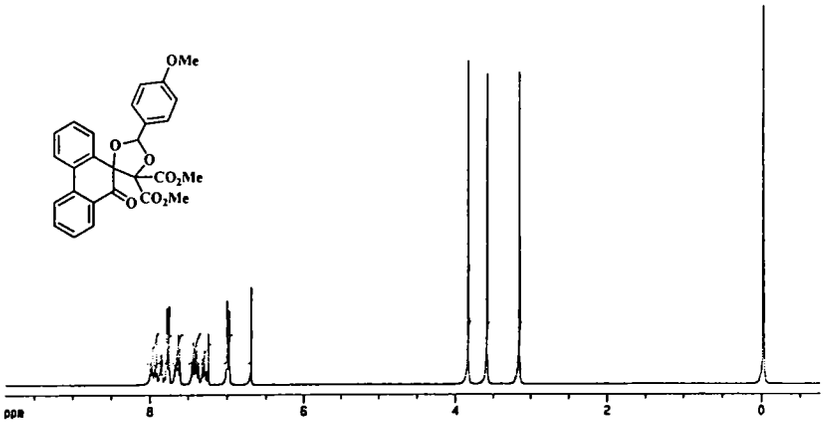


Figure 3. *^1H NMR Spectrum of 71*

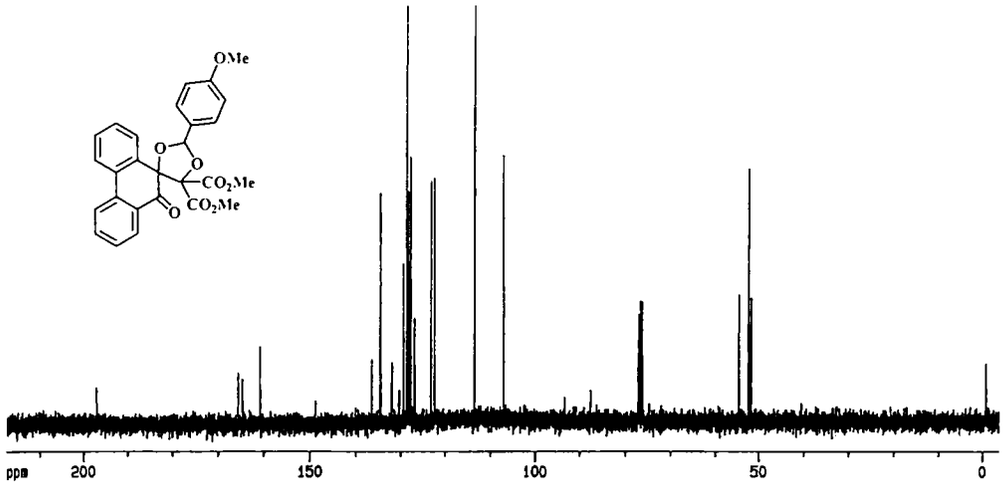


Figure 4. *^{13}C NMR Spectrum of 71*

To establish the relative stereochemistry of **71**, we resorted to single crystal X-ray analysis (Figure 5).

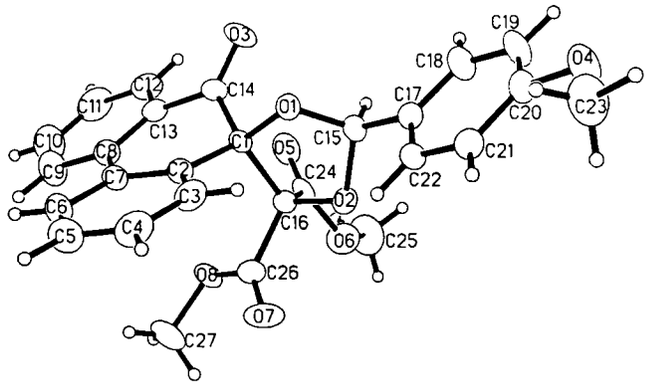
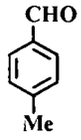
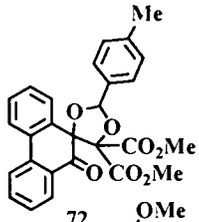
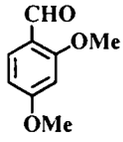
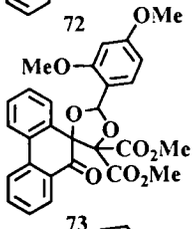
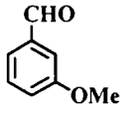
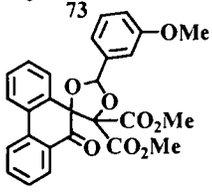
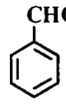
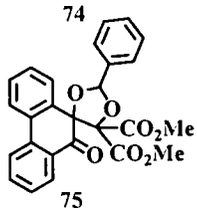


Figure 5. *Single crystal X-ray structure of 71*

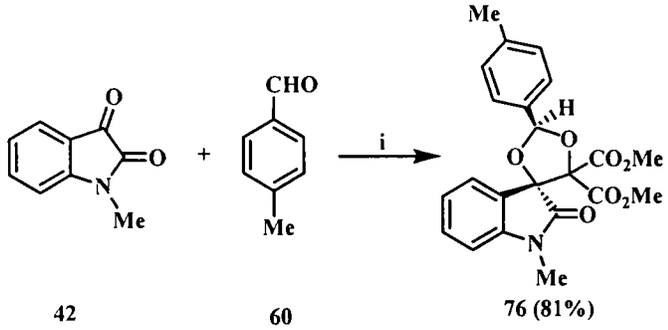
The reaction was extended to a number of other aldehydes; in all cases good yields of the spiro-dioxolane derivatives were obtained and the results are summarized in Table 1.

Table 1

Entry	Aldehyde	Product	Yield (%)
1		 72	85
2		 73	78
3		 74	68
4		 75	49

3. Dipolar Cycloaddition Reaction of Acyclic Carbonyl Ylides with Isatins

In the next phase of our studies we investigated the reaction with another class quinonoid compounds; isatin and its derivatives. When *N*-methylisatin was allowed react with the acyclic carbonyl yilde generated by the reaction of *p*-tolualdehyde dicarbomethoxycarbene, a product was formed in high yield (Scheme 27).



42 60 76 (81%)

i. $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, dry benzene, argon, 16 h

Scheme 27

The structure of the product was assigned by routine spectroscopic methods. e IR spectrum of **76** showed strong bands at 1757 cm^{-1} and 1728 cm^{-1} due to the ter and the lactam carbonyls repectively. In the ^1H NMR spectrum, resonance signal e to the methyl group on the aromatic ring was seen as a singlet at δ 2.36, while the nal due to the *N*-methyl protons appeared at 3.19. Signals due to the two methoxy oups were discernible at δ 3.64 and δ 3.80. The sharp singlet observed at δ 6.94 can assigned to the acetal proton. The ^{13}C NMR spectrum was also in agreement with structure proposed, with the lactam carbonyl displaying a signal at δ 173.8. The o ester carbonyls gave signals at δ 166.9. The characteristic peak of spirocarbon s observed at δ 85.6. The signals due to the carbomethoxy groups were visible at δ l and δ 52.9. The signals that appeared at 26.2 and δ 21.4 were assigned to the *N*-thyl and *C*-methyl respectively. In this case also the relative stereochemistry was tablished by single crystal X-ray analysis (Figure 6).

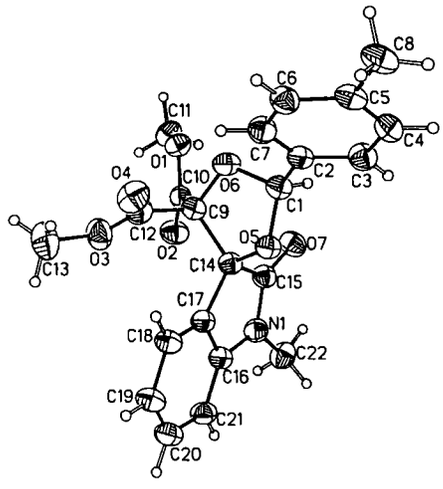


Figure 6. *Single crystal X-ray structure of 76*

The regiospecificity observed in this reaction is attributable to the higher ctrophilicity of the keto-group compared to the amide carbonyl. The reaction was und to be general with various isatin derivatives and aromatic aldehydes yielding the iro-oxindole as a single stereoisomer in good yields. These results are summarised Table 2.

Table 2

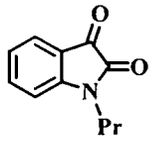
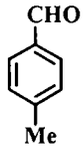
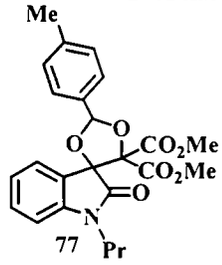
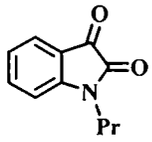
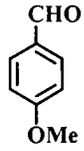
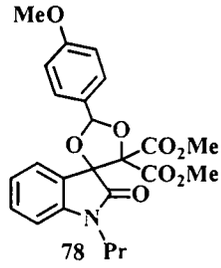
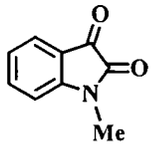
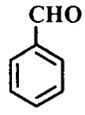
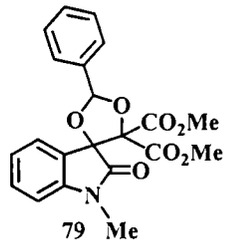
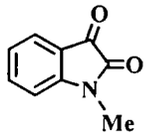
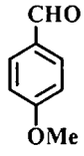
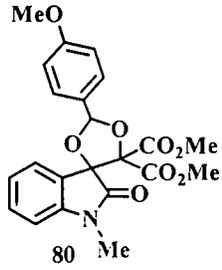
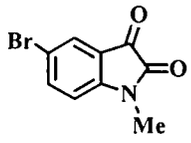
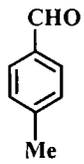
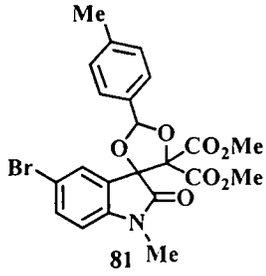
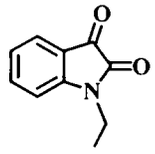
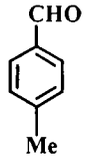
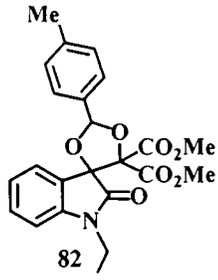
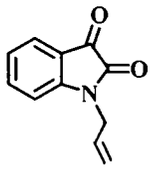
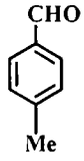
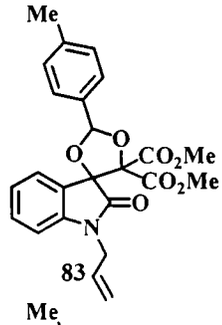
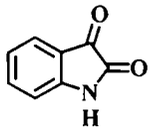
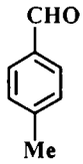
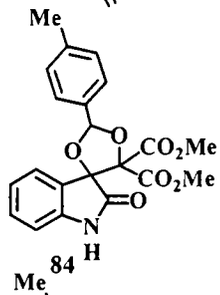
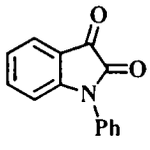
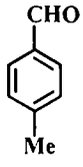
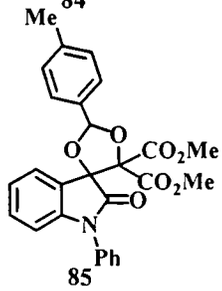
Entry	Isatin	Aldehyde	Product	Yield (%)
1			 77	95
2			 78	93
3			 79	76
4			 80	63
5			 81	82

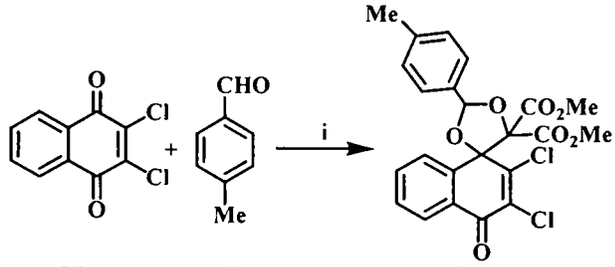
Table 2 (contd.)

Entry	Isatin	Aldehyde	Product	Yield (%)
6			 82	78
7			 83	87
8			 84	20
9			 85	98

3.5.4. Dipolar Cycloaddition Reaction of Acyclic Carbonyl Ylides with 1,4-Quinones

In view of the encouraging results obtained in the reaction of 1,2-diones with the acyclic carbonyl ylides generated by the reaction of aldehydes and dicarbomethoxycarbene, it was considered obligatory to extend the same to 1,4-diones. A limited investigation was conducted and it is discussed in this section. The reaction of 2,3-dichloro-1,4-naphthoquinone with acyclic carbonyl ylide generated from *p*-

ialdehyde and dicarbomethoxycarbene constituted our initial experiment (Scheme 8).



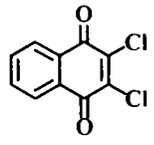
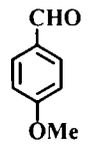
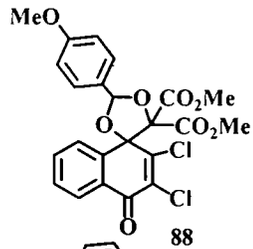
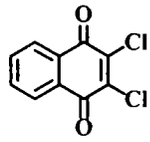
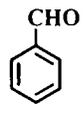
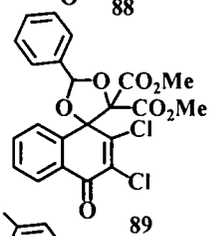
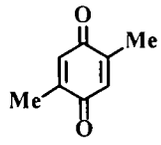
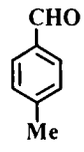
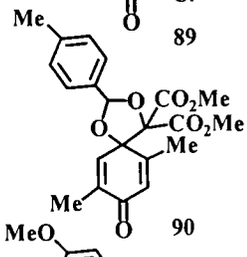
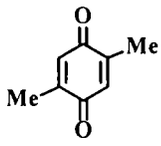
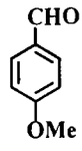
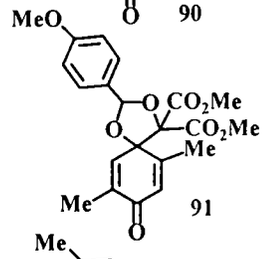
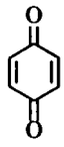
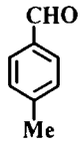
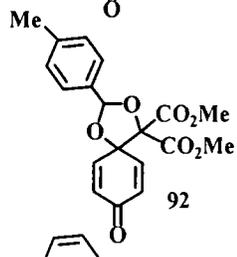
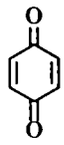
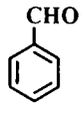
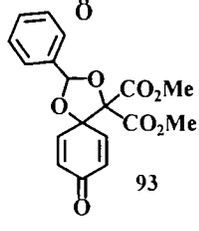
86 60 87 (77 %)

i. $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, dry benzene, argon, 16 h

Scheme 28

The structure of the adduct **87** was established by spectroscopic methods. The R spectrum displayed strong absorptions at 1762 cm^{-1} and 1688 cm^{-1} corresponding the ester and enone carbonyls, respectively. The ^1H NMR spectrum was in nsonance with the structure proposed. The methyl protons resonated at δ 2.45, while e peaks due to the carbomethoxy protons appeared at δ 3.13 and δ 3.78. Signal due the acetal proton was descernible as a siglet at δ 6.76. The ^{13}C NMR spectrum was so in good agreement with the structure proposed. The peak at δ 176.2 corresponds the carbonyl group which remained intact during the reaction. Two ester carbonyls sonated at δ 164.5 and δ 163.3. The peak at δ 86.7 was typical of a spirocarbon. The rbomethoxy carbons resonated at δ 54.3 and δ 52.8. The methyl carbon displayed gnal at δ 21.5. All the other signals were also in good agreement with the structure oposed. The reaction was studied with a few other quinones and carbonyl ylides and e results are presented in Table 3.

Table 3

Entry	1,4-Quinone	Aldehyde	Product	Yield (%)
1			 88	54
2			 89	57
3			 90	56
4			 91	51
5			 92	20
6			 93	16

6. Theoretical Calculations

From the results presented in the previous sections, it is clear that acyclic arbonyl ylides add across either one of the C=O bonds of the *o*-quinones. In order to

plain the observed mode of cycloaddition, we have carried out some calculations ing semi-emprical MNDO method with the aid of TITAN software (version 1).

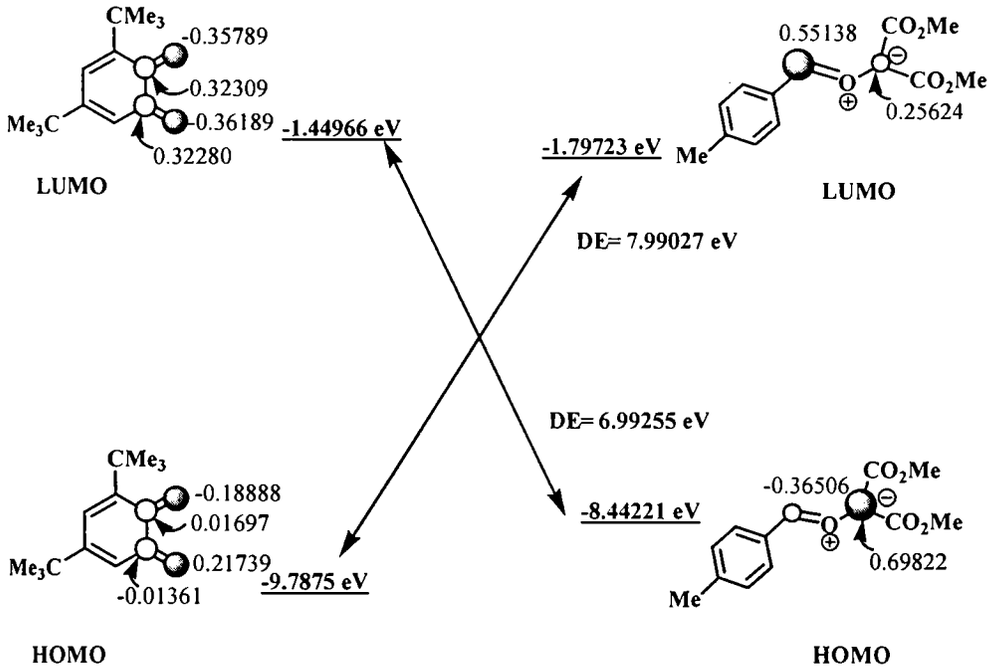


Figure 7. *Molecular orbital correlation diagram of 3,5-di-tert-butyl-1,2-benzoquinone 1 and the acyclic carbonyl ylide.*

From Figure 7, it is clear that the predominant interaction is between the HOMO of the dipole and the LUMO of the dipolarophile, which leads to the pathway, favored both in terms of energetics and symmetry considerations.

In the case of *p*-quinones also, the predominant interaction is between HOMO of the dipole and LUMO of the dipolarophile as evident from the molecular orbital correlation diagram (Figure 8).

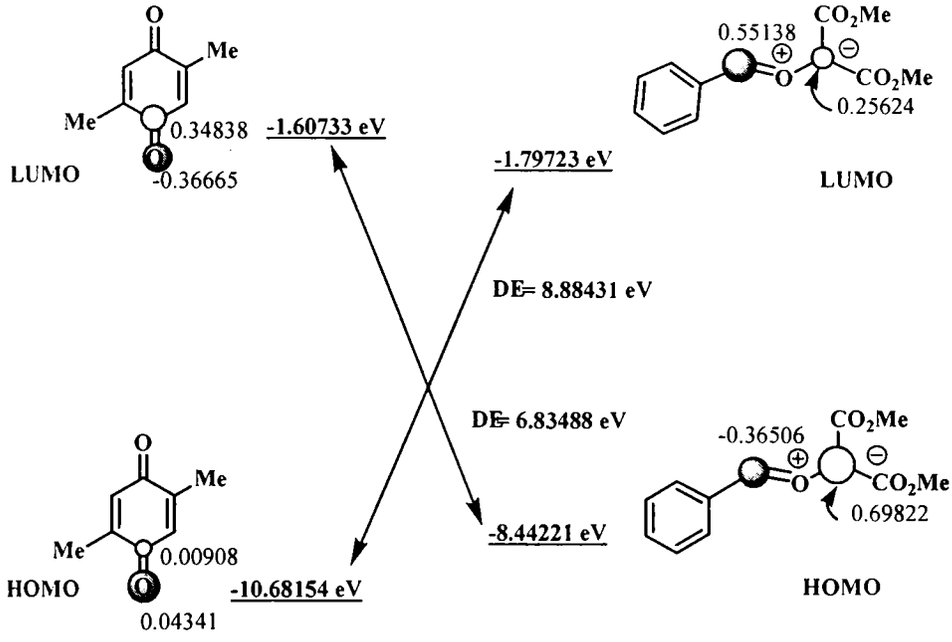


Figure 8. *Molecular orbital correlation diagram of 2,5-dimethyl-1,4-benzoquinone and the cyclic carbonyl ylide.*

17. Conclusion

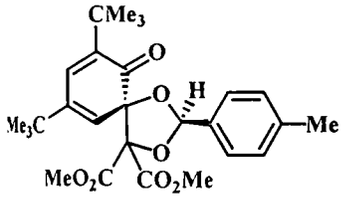
In conclusion we have demonstrated that carbonyl ylides generated from carbomethoxycarbene and aldehydes react efficiently with 1,2-quinones as well as 1,4-quinones leading to novel spirodioxolanes. In all cases the cycloaddition is highly regio- and stereoselective. With isatins the ylide preferencially adds to the more electron deficient carbonyl group making it regiospecific. Here also the reaction is stereoselective and affords novel spirooxindole derivatives in high yields. Results of the theoretical calculations carried out strongly support the observed reactivity of the quinonoid compounds towards carbonyl ylides. It is conceivable that the novel three component reactions described herein will find wider application in organic synthesis.

18. Experimental Details

General: General information about the experiments is given in Section 2.6 of Chapter 2.

Dimethyl 7,9-bis(1,1-dimethylethyl)-10-oxo-2-(4-methylphenyl)-1,3-dioxaspiro[4.5] deca-6,8-diene 4,4-dicarboxylate 61 and Dimethyl 6,8-bis (1,1-dimethylethyl)-10-oxo-2-(4-methylphenyl)-1,3-dioxaspiro[4.5] deca-6,8-diene 4,4-dicarboxylate 62: Typical Procedure and spectral data

A mixture of 3,5-di-*tert*-butyl-1,2-benzoquinone **1** (0.1 g, 0.45 mmol), *p*-tolualdehyde **60** (0.054 g, 0.45 mmol), dimethyl diazomalonate (0.079 g, 0.5 mmol) and 2 mol% of $Rh_2(OAc)_4$ was refluxed in 5 mL of dry benzene under argon atmosphere for 14 h. The solvent was then removed under *vacuo* and the residue on chromatographic separation on silica gel using hexane-ethyl acetate (95:5) gave the spirodioxolanes **61** (0.094 g, 44%) and **62** (0.032 g, 15%) as yellow crystalline solids. The products were recrystallized from ethyl acetate-hexane solvent system, **mp** 160 °C.



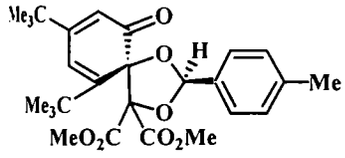
61

IR (KBr) ν_{max}: 2965, 2866, 1745, 1646, 1427, 1374, 1288, 1228, 1122, 1069, 1003, 963, 937, 817, 791, 738, 645 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 7.60 (d, 2H, J = 8.0 Hz), 7.19 (d, 2H, J = 7.9 Hz), 6.87 (d, 1H, J = 2.2 Hz), 6.78 (s, 1H), 5.72 (d, 1H, J = 2.2 Hz), 3.80 (s, 3H), 3.73 (s, 3H), 2.37 (s, 3H), 1.25 (s, 9H), 1.14 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 198.2, 167.0, 147.1, 143.5, 139.6, 134.4, 132.8, 128.9, 127.8, 123.4, 123.3, 107.1, 84.0, 53.0, 34.9, 34.6, 29.3, 28.5, 21.5.

Elemental analysis calcd. for $C_{27}H_{34}O_7$: C, 68.92, H, 7.28, Found: C, 69.00, H, 7.41.



62

mp 102 °C

IR (KBr) ν_{max}: 2959, 2919, 2866, 1752, 1659, 1639, 1580, 1440, 1387, 1295, 1222, 1129, 1016, 963, 824, 658, 492 cm^{-1}.

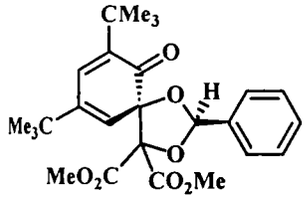
^{1}H NMR ($CDCl_3$) δ 7.56 (d, 2H, J = 8.0 Hz), 7.20 (d, 2H, J = 8.0 Hz), 6.59 (s, 1H). 6.37 (d, 1H, J = 1.41 Hz), 5.74 (d, 1H, J = 1.41 Hz), 3.75 (s, 3H), 3.71 (s, 3H), 2.39 (s, 3H), 1.21 (s, 9H), 1.12 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 204.6, 167.6, 153.1, 139.1, 131.9, 128.9, 126.8, 123.4, 117.2, 107.1, 53.5, 52.8, 37.7, 35.5, 30.7, 28.1, 21.4.

Elemental analysis calcd. for $C_{27}H_{34}O_7$: C, 68.92, H, 7.28,Found: C, 68.80, H, 7.52.

Dimethyl 7,9-bis(1,1-dimethylethyl)-10-oxo-2-(phenyl)-1,3-dioxaspiro[4.5] deca-6,8-diene 4,4-dicarboxylate 63a and Dimethyl 6,8-bis(1,1-dimethylethyl)-10-oxo-2-(phenyl)-1,3-dioxaspiro[4.5]deca-6,8-diene 4,4-dicarboxylate 63b.

A mixture of 3,5-di-*tert*-butyl-1,2-benzoquinone **1** (0.1 g, 0.45 mmol), benzaldehyde (0.048 g, 0.45 mmol) and dimethyl diazomalonate (0.079 g, 0.5 mmol) was allowed to react in the presence of 2 mol% of $Rh_2(OAc)_4$ according to the general procedure, to afford the spirodioxolanes **63a** (0.096 g, 47%) and **63b** (0.032 g, 15 %) as yellow viscous liquids.



63a

IR (neat) ν_{max}: 2960, 2872, 1750, 1677, 1512, 1460, 1258, 1134, 793, 705 cm^{-1}.

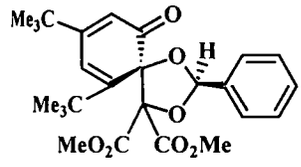
^{1}H NMR ($CDCl_3$) δ 7.73-7.72 (m, 2H), 7.40-7.38 (m, 3H), 6.88 (d, 1H, J = 2.1 Hz), 6.80 (s, 1H), 5.72 (d, 1H, J = 2.1 Hz), 3.81 (s, 3H), 3.74 (s, 3H), 1.25 (s, 9H), 1.15 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 198.1, 167.2, 166.9, 147.2,

143.5, 135.6, 134.0, 129.8, 128.2, 127.9, 123.2, 107.6, 106.9, 91.6, 84.1, 53.0, 52.9, 34.9, 34.6, 29.2, 28.4.

RMS (EI): m/z Calcd for $C_{26}H_{32}O_7$[M+]: 456.2148. Found: 456.2226.

IR (neat) ν_{max}: 2960, 2872, 1750, 1698, 1590, 1434, 1372, 1253, 1108, 1062, 1015, 824, 736 cm^{-1}.



63b

^{1}H NMR ($CDCl_3$) δ 7.81-7.66 (m, 3H), 7.42-7.35 (m, 3H), 6.64 (s, 1H), 6.38 (d, 1H, J = 1.5 Hz), 5.75 (d, 1H, J = 1.6 Hz), 3.75 (s, 3H), 3.72 (s, 3H), 1.21 (s, 9H), 1.12 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 204.5, 164.5, 164.0, 146.3, 143.7, 135.5, 129.9, 127.9, 126.8, 123.4, 122.1, 117.2, 106.9, 92.0, 53.6, 52.8, 37.7, 35.5, 30.4, 28.0

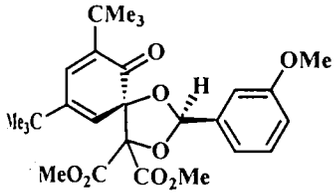
RMS (EI): m/z Calcd for $C_{26}H_{32}O_7$[M+]: 456.2148. Found: 456.2057.

Dimethyl 7,9-bis(1,1-dimethylethyl)-10-oxo-2-(3-methoxyphenyl)-1,3-dioxaspiro 4.5] deca-6,8-diene 4,4-dicarboxylate 64a and Dimethyl 6,8-bis(1,1-dimethylethyl) 10-oxo-2-(3-methoxyphenyl)-1,3-dioxaspiro[4.5] deca-6,8-diene 4,4-dicarboxylate 64b.

A mixture of 3,5-di-*tert*-butyl-1,2-benzoquinone **1** (0.1 g, 0.45 mmol), *m*-anisaldehyde (0.061 g, 0.45 mmol) and dimethyl diazomalonate (0.079 g, 0.5 mmol) was allowed to react in the presence of 2 mol% of $Rh_2(OAc)_4$ according to the general procedure, to afford the spirodioxolanes **64a** (0.070 g, 30%) and **64b** (0.023 g, 10%) as yellow viscous liquids.

IR (neat) ν_{max}: 2959, 2873, 1752, 1677, 1601, 1463, 1369, 1269, 1124, 793 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 7.31-7.23 (m, 2H), 6.93-



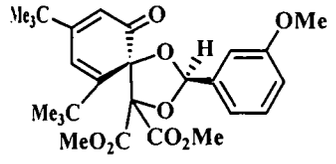
64a

6.87 (m, 2H), 6.78 (s, 1H), 6.67 (s, 1H), 5.72 (d, 1H, J = 2.1 Hz), 3.84 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 1.25 (s, 9H), 1.14 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 196.4, 167.1, 166.9, 159.6, 147.2, 143.6, 137.9, 129.2, 129.1, 123.2, 120.5, 119.6, 116.5, 112.6, 107.5, 102.5, 83.9, 55.1, 53.0, 52.9, 34.7, 34.6, 29.2, 28.5.

RMS (EI): m/z Calcd for $C_{27}H_{38}O_8$[M+]: 486.2253 Found: 486.2265.

IR (neat) ν_{max}: 2960, 1756, 1672, 1602, 1463, 1367, 1268, 1113, 1052, 960, 874, 787, 726, 692, 499 cm^{-1}.



64b

^{1}H NMR ($CDCl_3$) δ 7.33-7.22 (m, 2H), 6.93-6.87 (m, 2H), 6.60 (s, 1H), 6.39 (s, 1H), 5.74 (s, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 1.21 (s, 9H), 1.13 (s, 9H).

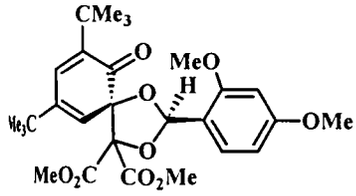
^{13}C NMR ($CDCl_3$) δ 204.4, 163.9, 163.4, 153.0, 136.2, 129.2, 123.4, 122.1, 120.3, 119.2, 117.1, 116.6, 106.8, 92.0, 91.0, 55.2, 53.5, 52.7, 35.5, 35.3, 30.6, 28.0.

RMS (EI): m/z Calcd for $C_{27}H_{34}O_8$[M+]: 486.2253 Found: 486.2274.

Dimethyl 7,9-bis(1,1-dimethylethyl)-10-oxo-2-(2,4-dimethoxyphenyl)1,3-dioxaspiro[4.5] deca-6,8-diene 4,4-dicarboxylate 65a and Dimethyl 6,8-bis(1,1-dimethylethyl)-10-oxo-2-(2,4-dimethoxyphenyl)-1,3-dioxaspiro[4.5] deca-6,8-diene 4,4-dicarboxylate 65b

A mixture of 3,5-di-*tert*-butyl-1,2-benzoquinone **1** (0.1 g, 0.45 mmol), 2,4-dimethoxy benzaldehyde (0.075 g, 0.45 mmol) and dimethyl diazomalonate (0.079 g, 0.5 mmol) was allowed to react in the presence of 2 mol% of $Rh_2(OAc)_4$ according to

the general procedure, to afford the spirodioxolanes **65a** (0.062 g, 25%) and **65b** (0.020 g, 8%), **mp** 68 °C.



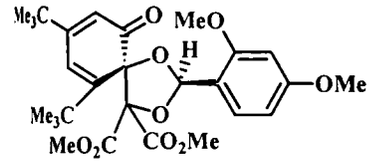
65a

IR (KBr) ν_{max}: 2959, 1746, 1660, 1615, 1510, 1460, 1372, 1280, 1208, 1156, 1126, 1059, 939, 843, 796 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 7.88 (d, 1H, J = 8.6 Hz), 7.08 (s, 1H), 6.85 (s, 1H), 6.54 (d, 1H, J = 8.7 Hz), 6.40 (s, 1H), 5.72 (s, 1H), 3.81 (s, 6H), 3.79 (s, 3H), 3.68 (s, 3H), 1.22 (s, 9H), 1.14 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 198.1, 167.3, 167.1, 162.0, 159.3, 146.8, 143.6, 134.2, 129.7, 123.7, 116.3, 104.6, 102.0, 98.0, 83.9, 55.5, 55.2, 52.9, 34.8, 34.6, 29.2, 28.4.

Anal. Calcd for $C_{28}H_{36}O_9$: C, 65.10; H, 7.02. Found: C, 64.83; H, 7.30.



65b

IR (neat) ν_{max}: 2959, 1762, 1677, 1603, 1508, 1463, 1372, 1267, 1158, 1126, 1032, 944, 837 cm^{-1}.

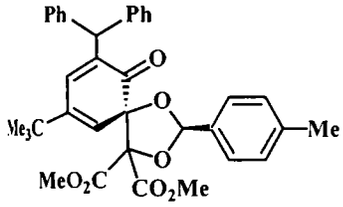
^{1}H NMR ($CDCl_3$) δ 7.98 (d, 1H, J = 8.6 Hz), 7.11 (s, 1H), 6.83 (s, 1H), 6.55 (bs, 1H), 6.34 (s, 1H), 5.88 (s, 1H), 3.83 (s, 6H), 3.79 (s, 3H), 3.78 (s, 3H), 1.22 (s, 9H), 1.16 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 197.7, 167.3, 166.9, 162.0, 159.1, 145.8, 143.7, 134.2, 130.7, 128.9, 123.7, 119.4, 104.9, 102.1, 97.9, 83.7, 55.3, 55.2, 53.0, 52.9, 34.8, 34.7, 30.0, 28.5.

HRMS (EI): m/z Calcd for $C_{28}H_{36}O_9$[M+]: 516.2359, Found: 516.2386.

Dimethyl 7-benzhydryl-9-*tert*-butyl-10-oxo-2-(4-methylphenyl)-1,3-dioxaspiro[4.5] deca-6,8-diene 4,4-dicarboxylate 66a and Dimethyl 6-benzhydryl-8-*tert*-butyl-10-oxo-2-(4-methylphenyl)-1,3-dioxaspiro[4.5] deca-6,8-diene 4,4-dicarboxylate 66b

A mixture of 3-diphenylmethyl-5-*tert*-butyl-1,2-benzoquinone (0.148 g, 0.45 mmol), *p*-tolualdehyde (0.054 g, 0.45 mmol) and dimethyl diazomalonate (0.079 g, .5 mmol) was allowed to react in the presence of 2 mol% of $Rh_2(OAc)_4$ according to he general procedure, to afford the spirodioxolanes **66a** (0.131 g, 50%) and **66b** 1.065 g, 25%).



66a

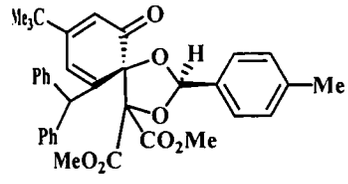
IR (neat)ν_{max}: 2965, 1755, 1682, 1439, 1284, 1232, 1124, 1067, 787, 705 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 7.56 (d, 2H, J = 7.9 Hz), 7.33-7.06 (m, 12H), 6.61 (s, 1H), 6.49 (bs, 1H), 5.75 (d, 1H, J = 1.8 Hz), 5.47 (s, 1H), 3.81 (s, 3H), 3.57 (s, 3H), 2.36 (s, 3H), 1.10 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 197.2, 166.9, 166.8, 147.0, 141.6, 141.5, 139.7, 139.4, 138.9, 132.3, 129.3, 128.8, 128.7, 128.3, 127.7, 126.5, 123.3, 106.7, 91.7, 83.5, 52.9, 52.8, 49.2, 34.6, 28.2, 21.3.

HRMS (EI): m/z Calcd for $C_{36}H_{36}O_7$ [M+]: 580.2461. Found: 580.2458

mp 66 °C



66b

IR (KBr)ν_{max}: 3027, 2960, 1760, 1677, 1501, 1439, 1232, 1124, 1072, 1015, 736, 705cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 7.27-7.00 (m, 12H), 6.79 (bs, 2H), 6.38 (s, 1H), 6.18 (s, 1H), 6.00 (s, 1H), 4.96 (s, 1H), 3.75 (s, 3H), 3.55 (s, 3H), 2.34 (s, 3H), 1.11 (s, 9H).

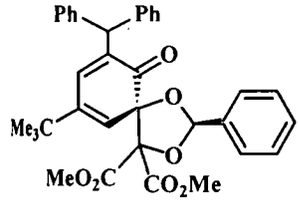
^{13}C NMR ($CDCl_3$) δ 202.3, 166.1, 164.3, 162.0, 149.2, 143.2, 142.5, 138.8, 131.7, 129.9, 128.6,

128.4, 128.2, 128.1, 127.9, 126.6, 125.7, 118.9, 107.2, 94.6, 88.8, 53.6, 53.4, 52.9, 35.5, 28.0, 21.4.

:MS (EI): m/z Calcd for $C_{36}H_{36}O_7$ [M+]: 580.2461. Found: 580.2447

imethyl 7-benzhydryl-9-*tert*-butyl-10-oxo-2-(phenyl)-1,3-dioxaspiro[4.5] deca-8-diene 4,4-dicarboxylate 67a and Dimethyl 6-benzhydryl-8-*tert*-butyl-10-oxo-2-phenyl)-1,3-dioxaspiro[4.5] deca-6,8-diene 4,4-dicarboxylate 67b

A mixture of 3-diphenymethyl-5-*tert*-butyl-1,2-benzoquinone (0.148 g, 0.45 mmol), benzaldehyde (0.048 g, 0.45 mmol) and dimethyl diazomalonate (0.079 g, 0.5 mmol) was allowed to react in the presence of 2 mol% of $Rh_2(OAc)_4$ according to the general procedure, to afford the spirodioxolanes **67a** (0.097 g, 38%) and **67b** (0.070 g, 27%) as yellow crystalline solids, recrystallized from ethyl acetate-hexane solvent mixture.



67a

mp 124 °C

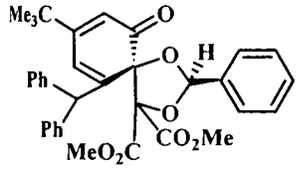
IR (KBr) ν_{max}: 2965, 2948, 1755, 1672, 1473, 1268, 1118, 1002, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 7.68 (bs, 2H), 7.39-7.11 (m, 13H), 6.65 (s, 1H), 6.51 (s, 1H), 5.75 (s, 1H), 5.48 (s, 1H), 3.83 (s, 3H), 3.58 (s, 3H), 1.20 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 197.1, 167.0, 166.7, 165.5, 147.3, 141.7, 139.0, 138.8, 129.9, 129.5, 129.4, 129.0, 128.9, 128.7, 128.5, 128.3, 127.9, 123.3, 107.8, 106.8, 96.3, 83.7, 53.1, 53.0, 49.4, 31.4, 28.2.

Anal. Calcd for $C_{35}H_{34}O_7$: C, 74.19; H, 6.05; Found: C, 74.40; H, 6.15

mp 136 °C



67b

IR (KBr) ν_{max}: 2960, 1755, 1677, 1455, 1227, 1124, 1010, 705 cm^{-1}.

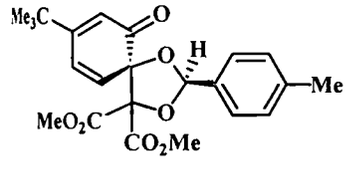
^{1}H NMR ($CDCl_3$) δ 7.27-7.02 (m, 13H), 6.77-6.76 (m, 2H), 6.41 (s, 1H), 6.18 (bs, 1H), 6.01 (bs, 1H), 4.94 (s, 1H), 3.75 (s, 3H), 3.57 (s, 3H), 1.11 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 202.0, 165.8, 164.1, 162.0, 149.1, 142.9, 142.2, 134.4, 129.6, 128.9, 128.2, 128.0, 127.8, 126.5, 126.3, 118.8, 106.9, 94.9, 88.6, 53.5, 53.3, 52.9, 35.4, 27.9.

inal. Calcd for $C_{35}H_{34}O_7$: C, 74.19; H, 6.05; Found: C, 74.24; H, 6.32.

imethyl 8-*tert*-butyl-2-(4-methylphenyl)-10-oxo-1,3-dioxaspiro[4.5]deca-6,8-iene-4,4-dicarboxylate 68a and Dimethyl 7-*tert*-butyl-2-(4-methylphenyl)-0-oxo-1,3-dioxaspiro[4.5]deca-6,8-diene-4,4-dicarboxylate 68b

A mixture of 4-*tert*-butyl-1,2-benzoquinone (0.074 g, 0.45 mmol), *p*-tualdehyde (0.054 g, 0.45 mmol) and dimethyl diazomalonate (0.079 g, 0.5 mmol) as allowed to react in the presence of 2 mol% of $Rh_2(OAc)_4$ according to the general rocedure, to afford the spirodioxolanes **68a** and **68b** as an inseparable mixture (0.077 41 %).

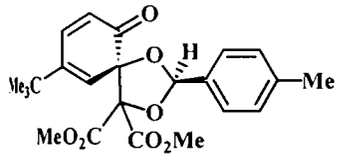


68a

and

IR (neat) ν_{max}: 2968, 2875, 1748, 1674, 1586, 1497, 1438, 1431, 1393, 1272, 1129, 1058, 998, 921, 795, 729 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 7.61-7.55 (m, 4H), 7.21-7.19 (m, 4H), 7.08-7.05 (m, 1H), 6.75 (s, 1H), 6.73 (s, 1H), 6.55-6.51 (m, 1H), 6.15-6.08 (m, 2H), 5.95 (bs, 1H), 5.80 (bs, 1H), 3.82 (s, 6H), 3.75 (s, 6H), 2.36 (s, 6H), 1.20 (s, 9H), 1.14 (s,



68b

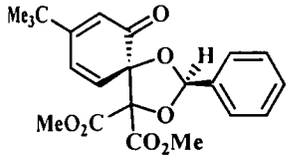
9H).

^{13}C NMR ($CDCl_3$) δ 203.8, 197.4, 168.1, 165.8, 161.7, 139.9, 139.8, 130.4, 129.2, 128.9, 128.1, 127.9, 127.5, 126.5, 126.4, 120.0, 107.6, 106.9, 90.0, 89.9, 53.6, 53.3, 53.1, 52.8, 34.7, 34.5, 28.4, 28.3.

HRMS (EI): m/z Calcd for $C_{23}H_{26}O_7$ [M+]: 414.1678. Found: 414.1631.

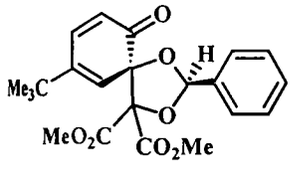
Dimethyl 8-*tert*-butyl-2-(phenyl)-10-oxo-1,3-dioxaspiro[4.5]deca-6,8-diene-4,4-dicarboxylate 69a and Dimethyl 7-*tert*-butyl-2-(phenyl)-10-oxo-1,3-dioxaspiro [4.5]deca-6,8-diene-4,4-dicarboxylate 69b

A mixture of 4-*tert*-butyl-1,2-benzoquinone (0.074 g, 0.45 mmol), benzaldehyde (0.048 g, 0.45 mmol) and dimethyl diazomalonate (0.079 g, 0.5 mmol) was allowed to react in the presence of 2 mol% of $Rh_2(OAc)_4$ according to the general procedure to afford the spirodioxolanes **69a** and **69b** as an inseparable mixture (0.083 g, 45 %).



69a

and



69b

IR (neat) ν_{max}: 3039, 2968, 1755, 1673, 1579, 1497, 1459, 1431, 1393, 1272, 1129, 1058, 998, 921, 795, 729 cm^{-1}.

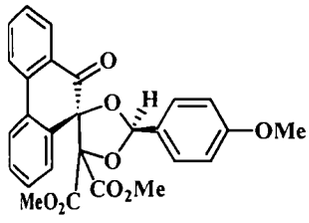
^{1}H NMR ($CDCl_3$) δ 7.73-7.67 (m, 4H), 7.39-7.38 (bs, 6H), 7.08-7.02 (m, 1H), 6.77 (s, 1H), 6.76 (s, 1H), 6.56-6.52 (m, 1H), 6.15- 6.08 (m, 2H), 5.95 (bs, 1H), 5.79 (bs, 1H), 3.80 (s, 6H), 3.74 (s, 6H), 1.18 (s, 9H), 1.13 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 198.6, 198.0, 166.9, 166.7, 166.6, 162.2, 139.9, 139.4, 135.2, 134.2, 132.4, 129.9, 129.6, 128.5, 128.4, 128.2, 128.0, 127.7, 125.6, 124.8, 118.9, 107.1, 106.5, 91.4, 83.4, 82.2, 53.1, 53.0, 52.9, 35.3, 34.5, 28.2, 27.8.

HRMS (EI): m/z Calcd for $C_{22}H_{24}O_7$ [M+]: 400.1522. Found: 400.1498.

Dimethyl 2'-(4-methoxylphenyl)-10'-oxospiro [1,3-dioxolane-4,9'(10'H)-phenanthrene]-5',5'-dicarboxylate 71

Phenanthrenequinone (0.104 g, 0.5 mmol), *p*-anisaldehyde (0.068 g, 0.5 mmol) and dimethyl diazomalonte (0.087 g, 0.55 mmol) was allowed to react with 2 mol% of $Rh_2(OAc)_4$ under an atmosphere of argon at reflux condition for 14 h. The solvent was then removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethyl acetate (80:20) gave the spirodioxolane **71** (0.173 g, 68%) as a colorless crystalline solid, **mp** 177 °C.



71

IR (KBr) ν_{max}: 2962, 1748, 1708, 1620, 1526, 1458, 1256, 1108, 1047, 845 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 8.01-7.86 (m, 3H), 7.78 (d, 2H, J = 8.6 Hz), 7.70-7.62 (m, 2H), 7.48-7.28 (m, 3H), 7.00 (d, 2H, J = 8.7 Hz), 6.71 (s, 1H), 3.85 (s, 3H), 3.60 (s, 3H), 3.18 (s, 3H).

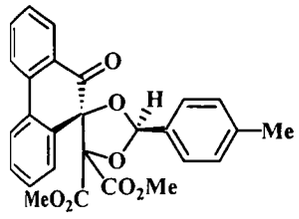
^{13}C NMR ($CDCl_3$) δ 197.2, 165.8, 164.8, 161.0, 136.6, 134.7, 132.2, 129.7, 129.0, 128.7, 128.6, 128.5, 128.1, 127.2, 123.5, 122.7, 113.9, 107.5, 94.1, 88.0, 55.2, 53.1, 52.5.

Anal. Calcd for $C_{27}H_{22}O_8$: C, 68.35; H, 4.67. Found: C, 68.50; H, 4.84.

Dimethyl 2'-(4-methylphenyl)-10'-oxospiro [1,3-dioxolane-4,9'(10'H) phenanthrene]-5',5'-dicarboxylate 72

The reaction of phenanthrenequinone (0.104 g, 0.5 mmol), *p*-tolualdehyde (0.060 g, 0.5 mmol) and dimethyl diazomalonte (0.087 g, 0.55 mmol) with 2 mol% of $Rh_2(OAc)_4$ under the general procedure, gave the spirodioxolane **72** (0.195 g, 85%) as colorless crystalline solid, **mp** 128 °C.

IR (KBr) ν_{max}: 2965, 2929, 1760, 1687, 1510, 1472, 1432, 1375, 1301, 1235, 1209, 1117, 1090,



72

1016, 953, 940, 748 cm^{-1}.

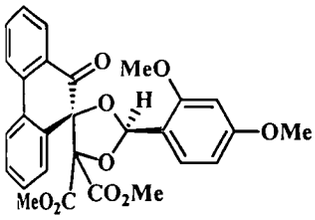
^{1}H NMR ($CDCl_3$) δ 8.00-7.83 (m, 3H), 7.73 (d, 2H), 7.67-7.60 (m, 2H), 7.46-7.37 (m, 2H), 7.29-7.21 (m, 3H), 6.71 (s, 1H), 3.59 (s, 3H), 3.16 (s, 3H), 2.39 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 196.9, 165.5, 164.6, 139.7, 136.5, 134.6, 132.1, 129.5, 129.1, 128.6, 128.5, 128.4, 127.8, 127.2, 123.4, 122.6, 107.4, 93.7, 88.1, 52.9, 52.4, 21.4.

:nal. Calcd for $C_{27}H_{22}O_7$: C, 70.73; H, 4.84. Found: C, 70.97; H, 4.45.

)imethyl 2'-(2,4-dimethoxylphenyl)-10'-oxospiro [1,3-dioxolane-4,9'(10'H)-henanthrene]-5',5'-dicarboxylate 73

The reaction of phenanthrenequinone (0.104 g, 0.5 mmol), 2,4-:imethoxybenzaldehyde (0.083 g, 0.5 mmol) and dimethyl diazomalonte (0.087 g, :5 mmol) with 2 mol% of $Rh_2(OAc)_4$ under the general procedure, gave the :irodioxolane **73** (0.197 g, 78%) as a colorless crystalline solid, **mp** 186 °C.



73

IR (KBr) ν_{max}: 3056, 2962, 1753, 1688, 1615, 1451, 1436, 1281, 1240, 1128, 1115, 1074, 1033, 948, 901, 753 cm^{-1}.

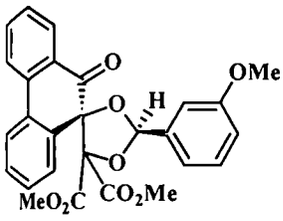
^{1}H NMR ($CDCl_3$) δ 8.02-7.85 (m, 3H), 7.70- 7.62 (m, 3H), 7.47-7.26 (m, 3H), 7.00 (s, 1H), 6.97-6.87 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.61 (s, 3H), 3.18 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 197.1, 165.9, 164.8, 153.8, 152.6, 134.7, 132.2, 130.6, 129.6, 128.8, 128.6, 128.4, 128.1, 124.1, 123.5, 122.7, 116.4, 113.3, 112.5, 102.9, 88.0, 56.6, 55.8, 53.1, 52.5.

:alcd for $C_{28}H_{24}O_9$: C, 66.66; H, 4.80. Found: C, 66.26; H, 4.73.

imethyl 2'-(3-methoxylphenyl)-10'-oxospiro [1,3-dioxolane-4,9'(10'H) henanthrene]-5',5'-dicarboxylate 74

The reaction of phenanthrenequinone (0.104 g, 0.5 mmol), 3-ethoxybenzaldehyde (0.068 g, 0.5 mmol) and dimethyl diazomalonte (0.087 g, 0.55 mmol) with 2 mol% of $Rh_2(OAc)_4$ under the general procedure, gave the spirodioxolane **74** (0.161 g, 68%) as a colorless viscous liquid.



74

IR (neat) ν_{max}: 3012, 2955, 2846, 1755, 1693, 1600, 1460, 1439, 1398, 1274, 1144, 1051, 943, 891, 731 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 8.00-7.84 (m, 3H), 7.68- 7.59 (m, 3H), 7.43-7.25 (m, 3H), 7.00-6.94 (m, 2H), 6.74 (s, 1H), 3.83 (s, 3H), 3.59 (s, 3H), 3.16 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 197.0, 165.7, 164.6, 159.7, 137.7, 136.5, 134.5, 132.1, 129.7, 129.6, 128.7, 123.5, 122.7, 120.1, 119.6, 115.9, 112.3, 107.2, 93.8, 88.0, 55.3, 53.1, 52.5.

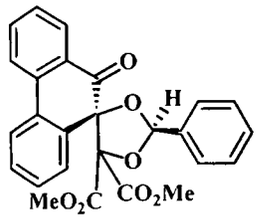
HRMS (EI): m/z Calcd for $C_{27}H_{22}O_8$ [M+]: 474.1314. Found: 474.1244.

imethyl 2'-(phenyl)-10'-oxospiro [1,3-dioxolane-4,9'(10'H)-phenanthrene] 5',5'-dicarboxylate 75

The reaction of phenanthrenequinone (0.104 g, 0.5 mmol), benzaldehyde (0.053 g, 0.5 mmol) and dimethyl diazomalonte (0.087 g, 0.55 mmol) with 2 mol% of $Rh_2(OAc)_4$ under the general procedure gave the spirodioxolane **75** (0.108 g, 49%) as coloress viscous liquid.

IR (neat) ν_{max}: 3068, 2965, 1755, 1693, 1610, 1444, 1434, 1279, 1237, 1134, 1108, 1077, 1036, 953, 901, 756 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 8.00-7.83 (m, 5H), 7.60-7.32



75

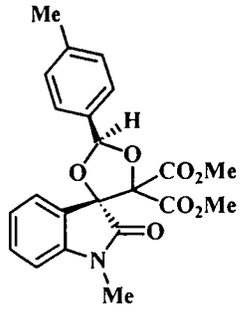
(m, 8H), 6.77 (s, 1H), 3.54 (s, 3H), 3.12 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 196.9, 165.4, 164.4, 136.3, 134.7, 134.6, 131.9, 129.8, 129.5, 128.3, 128.3, 127.7, 127.1, 123.4, 122.6, 107.1, 93.6, 87.8, 52.8, 52.3.

HRMS (EI): m/z Calcd for $C_{26}H_{20}O_7$ [M+]: 444.1209. Found: 444.1206.

Dimethyl 1',2'-dihydro-1'-methyl-2-(4-methylphenyl)-2'-oxospiro[1,3-dioxolane-4,3'-[3H]indole]-5',5'-dicarboxylate 76

A mixture of *N*-methyl isatin (0.081 g, 0.5 mmol), *p*-tolualdehyde (0.060 g, 0.5 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) in 5 mL of dry benzene was refluxed with 2 mol% of Rh(II) acetate under an atmosphere of argon for 16 h. The residue obtained after the removal of the solvent was subjected to chromatography on silica gel column using hexane-ethyl acetate (80:20) as the solvent to afford the product **76** (0.166 g, 81%) as a colorless crystalline solid, **mp**168-169 °C.



76

IR (KBr) ν_{max}: 2962, 1757, 1728, 1616, 1457, 1440, 1384, 1371, 1299, 1243, 1032 cm^{-1}.

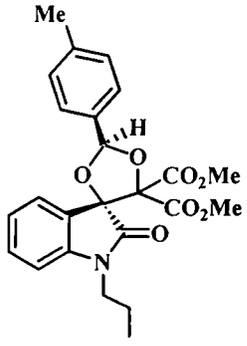
^{1}H NMR ($CDCl_3$) δ 7.69 (d, 2H, J = 7.1 Hz), 7.38-7.19 (m, 4H), 7.04-6.99 (m, 1H), 6.94 (s, 1H), 6.83 (d, 1H, J = 7.5 Hz), 3.80 (s, 3H), 3.64 (s, 3H), 3.19 (s, 3H), 2.36 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 173.8, 166.9, 145.3, 139.9, 132.4, 131.5, 128.9, 127.9, 125.2, 122.8, 122.7, 108.9, 106.3, 88.9, 85.6, 53.1, 52.9, 26.2, 21.4.

Anal. Calcd for $C_{22}H_{21}NO_7$: C, 64.23; H, 5.14; N, 3.40. Found: C, 63.94; H, 5.03; N, 3.43.

methyl 1',2'-dihydro-1'-^{n}propyl-2-(4-methylphenyl)-2'-oxospiro[1,3-dioxolane-'-[3H]indole]-5',5'-dicarboxylate 77

The reaction between *N*-^{n}propyl isatin (0.095 g, 0.5 mmol), *p*-tolualdehyde 060 g, 0.5 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) in the presence Rh(II) acetate under the procedure described for compound **76** afforded the product (0.209 g, 95%) as a colorless crystalline solid, **mp** 123 °C.



77

IR (KBr) ν_{max}: 2975, 1762, 1620, 1445, 1263, 1148, 1034 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 7.69 (d, 2H, *J* = 7.7 Hz), 7.35-7.19 (m, 4H), 7.04-7.01 (m, 1H), 6.91 (s, 1H), 6.83 (d, 1H, *J* = 7.8 Hz), 3.77 (s, 3H), 3.73-3.68 (m, 1H), 3.63 (s, 3H), 3.57-3.47 (m, 1H), 2.35 (s, 3H), 1.77-1.70 (m, 2H), 1.00 (t, 3H, *J* = 7.3 Hz).

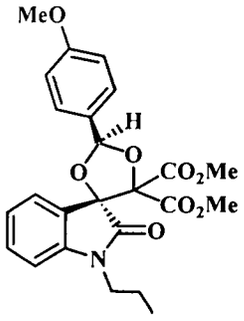
^{13}C NMR ($CDCl_3$) δ 173.4, 166.7, 144.8, 139.6, 132.5, 131.2, 128.8, 128.1, 127.7, 125.1, 122.3, 108.9, 106.0, 88.7, 85.3, 52.8, 41.7, 21.2, 20.4, 11.2.

Anal. Calcd for $C_{24}H_{25}NO_7$: C, 65.59; H, 5.73; N, 3.19. Found: C, 65.43; H, 5.85; N, 3.19.

Dimethyl 1',2'-dihydro-1'-^{n}propyl-2-(4-methoxylphenyl)-2'-oxospiro [1,3-dioxolane-4,3'-[3H]indole]-5',5'-dicarboxylate 78

The reaction between *N*-^{n}propyl isatin (0.095g, 0.5 mmol), *p*-anisaldehyde 0.068 g, 0.5 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) in the presence of Rh(II) acetate under the procedure described for compound **76** afforded the product 8 (0.212 g, 93%) as a colorless crystalline solid, **mp** 161-163 °C.

IR (KBr) ν_{max}: 2967, 2876, 1757, 1723, 1620, 1469, 1374, 1289, 1244, 1130, 1038, 839 cm^{-1}.



78

^{1}H NMR ($CDCl_3$) δ 7.75 (d, 2H, J = 8.6 Hz), 7.34-7.24 (m, 2H), 7.03-6.84 (m, 5H), 3.81 (s, 3H), 3.79 (s, 3H), 3.75-3.70 (m, 1H), 3.67 (s, 3H), 3.60-3.51 (m, 1H), 1.79- 1.72 (m, 2H), 1.02 (t, 3H, J = 7.4 Hz).

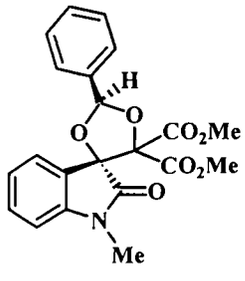
^{13}C NMR ($CDCl_3$) δ 173.6, 167.1, 166.9, 161.1, 144.9, 131.4, 129.9, 129.6, 127.3, 125.2, 124.8, 122.6, 113.7, 109.1, 106.1, 88.8, 85.3, 55.2, 53.1, 53.0, 41.8, 20.5, 11.5.

ial. Calcd for $C_{24}H_{25}NO_8$: C, 63.29; H, 5.53; N, 3.08. Found: C, 63.43; H, 5.37; N, 11.

methyl 1',2'-dihydro-1'-methyl-2-(phenyl)-2'-oxospiro[1, 3-dioxolane-4, 3'-H]indole]-5', 5'-dicarboxylate 79

The reaction between *N*-methyl isatin (0.081 g, 0.5 mmol), benzaldehyde 053 g, 0.5 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) in the presence Rh(II) acetate under the procedure described for compound **76** afforded the product (0.150 g, 76%) as a colorless crystalline solid, **mp** 169-170 °C.

IR (KBr) ν_{max}: 3022, 2948, 2840, 1755, 1735, 1620, 1472, 1378, 1290, 1256, 1128, 1054, 1013, 919 cm^{-1}.



79

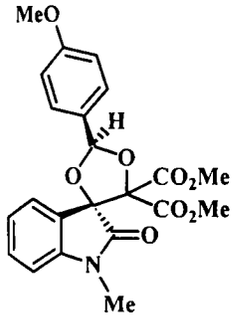
^{1}H NMR ($CDCl_3$) δ 7.83-7.80 (m, 2H), 7.42-7.34 (m, 4H), 7.24 (d, 1H, J = 7.5 Hz), 7.05-6.99 (m, 1H), 6.97 (s, 1H), 6.84 (d, 1H, J = 7.8 Hz), 3.79 (s, 3H), 3.65 (s, 3H), 3.17 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 173.6, 166.8, 166.7, 145.1, 135.1, 131.6, 130.0, 128.2, 128.2, 127.9, 124.9, 122.8, 122.2, 108.9, 106.1, 88.6, 85.5, 53.1, 52.9, 26.1.

al. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.65; H, 4.97; N, 4.

imethyl 1',2'-dihydro-1'-methyl-2-(4-methoxylphenyl)-2'-oxospiro[1,3-oxolane-4,3'-[3H]indole]-5',5'-dicarboxylate 80

The reaction between *N*-methyl isatin (0.081 g, 0.5 mmol), *p*-anisaldehyde 068 g, 0.5 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) in the presence Rh(II) acetate under the procedure described for compound **76** afforded the product (0.135 g, 63%) as a colorless crystalline solid, **mp** 163 °C.



80

IR (KBr) ν_{max}: 2962, 1757, 1728, 1616, 1467, 1440, 1384, 1299, 1243, 1129, 1032 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 7.76 (d, 2H, J = 8.6 Hz), 7.35 (t, 1H, J = 7.7 Hz), 7.25 (d, 1H, J = 7.2 Hz), 7.06-7.01 (m, 1H), 6.94-6.84 (m, 4H), 3.81 (s, 3H), 3.79 (s, 3H), 3.67 (s, 3H), 3.21 (s, 3H).

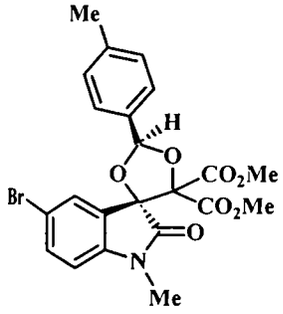
^{13}C NMR ($CDCl_3$) δ 173.3, 167.2, 166.6, 161.5, 143.7, 131.4, 129.9, 129.7, 127.3, 125.4, 124.6, 122.3, 113.8, 109.2, 106.4, 88.9, 85.5, 55.3, 53.1, 53.2, 26.3.

nal. Calcd for $C_{22}H_{21}NO_8$: C, 61.82; H, 4.95; N, 3.28. Found: C, 62.71; H, 5.55; N, 40.

imethyl 5'-bromo-1'-methyl 2'-oxo-2-(4-methylphenyl)-1',2'-dihydrospiro[1,3-oxolane-4,3'-indole]-5,5-dicarboxylate 81

The reaction between 5-bromo-*N*-methyl isatin (0.120 g, 0.5 mmol), *p*-ualdehyde (0.060 g, 0.5 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) the presence of Rh(II) acetate under the procedure described for compound **76** forded the product **81** (0.204 g, 82%) as a colorless crystalline solid, **mp** 175 °C.

IR (KBr) ν_{max}: 2955, 2829, 1750, 1729, 1610, 1485, 1438, 1364, 1303, 1243, 1121, 994 cm^{-1}.



81

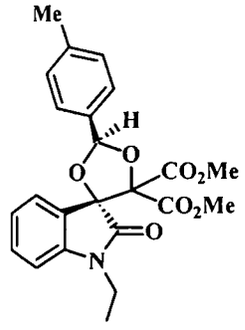
^{1}H NMR ($CDCl_3$) δ 7.69 (d, 2H, *J* = 8.0 Hz), 7.53-7.49 (m, 1H), 7.36-7.21 (m, 3H), 6.93 (s, 1H), 6.74 (d, 1H, *J* = 8.3 Hz), 3.80 (s, 3H), 3.73 (s, 3H), 3.20 (s, 3H), 2.39 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 173.4, 166.8, 144.4, 140.1, 134.3, 132.1, 129.1, 128.6, 127.9, 124.5, 115.4, 110.2, 106.7, 89.0, 85.2, 53.1, 53.1, 26.3, 21.4.

nal. Calcd for $C_{22}H_{20}BrNO_7$: C, 53.89; H, 4.11; N, 2.86. Found: C, 53.24; H, 3.70; N, 95.

imethyl 1',2'-dihydro-1'-ethyl-2-(4-methylphenyl)-2'-oxospiro[1,3-dioxolane-3'-[3H]indole]-5',5'-dicarboxylate 82

The reaction between *N*-ethyl isatin (0.088 g, 0.5 mmol), *p*-tolualdehyde (0.060 .0.5 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) in the presence of h(II) acetate under the procedure described for compound **76** afforded the product **82** .166 g, 78%) as a colorless crystalline solid, **mp** 126-128 °C.



82

IR (KBr) ν_{max}: 2982, 1752, 1723, 1615, 1479, 1378, 1297, 1249, 1121 cm^{-1}.

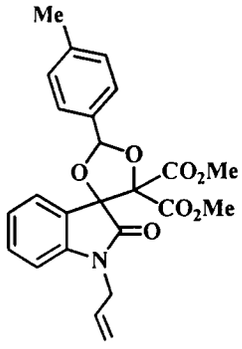
^{1}H NMR ($CDCl_3$) δ 7.69 (d, 2H, *J* = 8.0 Hz), 7.36-7.31 (m, 1H), 7.26-7.19 (m, 3H), 7.02-6.70 (m, 1H), 6.94 (s, 1H), 6.84 (d, 1H, *J* = 7.8 Hz), 3.77 (s, 3H), 3.74-3.67 (m, 1H), 3.64 (s, 3H), 3.56-3.49 (m, 1H), 2.36 (s, 3H), 1.02 (t, 3H, *J* = 7.4 Hz).

^{13}C NMR ($CDCl_3$) δ 173.5, 166.8, 144.8, 139.8, 131.3, 128.9, 127.9, 125.1, 122.5, 109.0, 106.1, 88.4, 85.7, 53.0, 52.9, 41.7, 21.3, 20.5, 11.4.

RMS (EI): m/z Calcd for $C_{23}H_{23}N_2O_7$ [M+]: 439.1504. Found: 439.1505.

imethyl 1',2'-dihydro-1'-allyl-2-(4-methylphenyl)-2'-oxospiro[1,3-dioxolane-3'-[3H]indole]-5',5'-dicarboxylate 83

The reaction between *N*-allyl isatin (0.094 g, 0.5 mmol), *p*-tolualdehyde (0.060 g, 0.5 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) in the presence of Rh(II) acetate under the procedure described for compound **76** afforded the product **83** (0.190 g, 87%) as a colorless liquid.



83

IR (neat) ν_{max}: 2962, 2928, 1765, 1730, 1619, 1500, 1465, 1444, 1368, 1291, 1236, 1194, 1131, 1034, 992, 950 cm^{-1}.

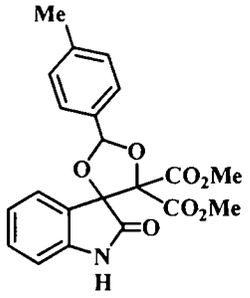
^{1}H NMR ($CDCl_3$) δ 7.16 (d, 2H, J = 8.0 Hz), 7.31-7.10 (m, 3H), 7.07-6.96 (m, 2H), 6.93 (s, 1H), 6.80 (d, 1H, J = 7.8 Hz), 5.84- 5.78 (m, 1H), 5.35-5.20 (m, 2H), 4.46-4.32 (m, 1H), 4.16-4.10 (m, 1H), 3.74 (s, 3H), 3.61 (s, 3H), 2.34 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 173.3, 166.6, 166.5, 144.4, 139.7, 132.3, 131.2, 130.8, 129.4, 128.8, 127.7, 125.6, 124.6, 122.5, 117.8, 109.6, 106.1, 88.7, 85.3, 52.9, 42.2, 21.1.

Dimethyl 1',2'-dihydro-2-(4-methylphenyl)-2'-oxospiro[1,3-dioxolane-4,3'-[3H]indole]-5',5'-dicarboxylate 84

The reaction between isatin (0.074 g, 0.5 mmol), *p*-tolualdehyde (0.060 g, 0.5 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) in the presence of Rh(II) acetate under the procedure described for compound **76** afforded the product **84** (0.040 g, 20%) as a colorless viscous liquid.

IR (neat) ν_{max}: 3464, 3063, 2955, 2994, 1750, 1729, 1620, 1589, 1501, 1465, 1439, 1305, 1243, 1124, 1082, 1010, 953 cm^{-1}.



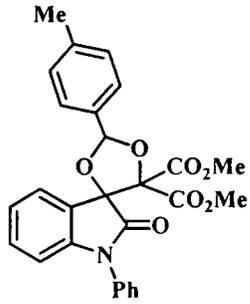
84

^{1}H NMR ($CDCl_3$) δ 9.03 (bs, 1H), 7.68 (d, 2H, *J* = 7.8 Hz), 7.28-7.16 (m, 4H), 7.00-6.84 (m, 3H), 3.79 (s, 3H), 3.67 (s, 3H), 2.33 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 176.0, 166.9, 166.8, 142.6, 139.9, 132.0, 131.5, 128.9, 127.9, 125.2, 122.7, 111.2, 108.5, 106.2, 88.5, 85.9, 53.2, 53.1, 21.4.

imethyl 1',2'-dihydro-1'-phenyl-2-(4-methylphenyl)-2'-oxospiro[1,3-dioxolane-3'-[3H]indole]-5',5'-dicarboxylate 85

The reaction between *N*-phenyl isatin (0.112 g, 0.5 mmol), *p*-tolualdehyde 0.060 g, 0.5 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) in the presence f Rh(II) acetate under the procedure described for compound **76** afforded the product 5 (0.228 g, 98%) as a colorless viscous liquid.



85

IR (neat) ν_{max}: 3052, 2955, 2927, 1754, 1729, 1615, 1506, 1472, 1432, 1375, 1301, 1244, 1210, 1124, 1090, 1016, 953, 942, 759, 708 cm^{-1}.

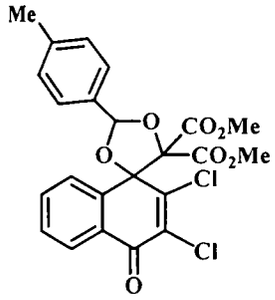
^{1}H NMR ($CDCl_3$) δ 7.73 (d, 2H, *J* = 8.0 Hz), 7.54-7.39 (m, 4H), 7.33-7.19 (m, 5H), 7.00 (s, 1H), 6.77 (d, 2H, *J* = 7.9 Hz), 3.78 (s, 3H), 3.67 (s, 3H), 2.36 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 172.9, 166.8, 145.2, 139.7, 133.5, 131.9, 129.5, 128.8, 127.8, 126.4, 125.1, 123.0, 109.9, 106.2, 88.8, 85.4, 53.2, 53.0, 21.2.

RMS (EI): m/z Calcd for $C_{27}H_{23}NO_7$ [M+]: 473.1471. Found: 473.1474.

imethyl 2-(4-methylphenyl)-4'-oxo-4'H-spiro[1,3-dioxolane-4,1'-naphthalene]-5-dicarboxylate 87

The reaction between **86** (0.114 g, 0.5 mmol), *p*-tolualdehyde (0.060 g, 0.5 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) in the presence of Rh(II) acetate under the procedure described for compound **76** afforded the product **87** (0.184 g, 77%) as a colorless crystalline solid, **mp** 155 °C.



87

IR (KBr) ν_{max}: 2962, 2921, 2861, 1762, 1688, 1600, 1431, 1276, 1222, 1135, 1081, 1020, 960, 926 cm $^{-1}$.

^{1}H NMR ($CDCl_3$) δ 8.15-8.12 (m, 1H), 7.66 (d, 2H, J = 8.0 Hz), 7.53-7.46 (m, 3H), 7.32 (d, 2H, J = 7.9 Hz), 6.76 (s, 1H), 3.78 (s, 3H), 3.13 (s, 3H), 2.45 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 176.2, 164.5, 163.3, 149.8, 140.4, 140.0, 133.2, 131.4, 129.6, 129.4, 127.2, 126.9, 126.6, 107.4, 92.7, 86.7, 54.3, 52.8, 21.5.

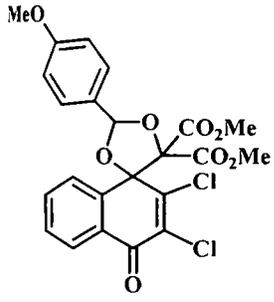
nal. Calcd for $C_{23}H_{18}Cl_2O_7$: C, 57.88; H, 3.80. Found: C, 58.14; H, 3.43

imethyl 2-(4-methoxyphenyl)-4'-oxo-4'H-spiro[1,3-dioxolane-4,1'-naphthalene]-5-dicarboxylate 88

The reaction between **86** (0.114 g, 0.5 mmol), *p*-tolualdehyde (0.068 g, 0.5 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) in the presence of Rh(II) acetate under the procedure described for compound **76** afforded the product **88** (0.133 g, 54%) as a colorless crystalline solid, **mp** 142 °C.

IR (KBr) ν_{max}: 2860, 2846, 1770, 1760, 1620, 1589, 1522, 1439, 1403, 1300, 1263, 1144, 1072, 1036, 963, 912, 834, 710 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 8.04 (d, 1H, J = 6.9 Hz),



88

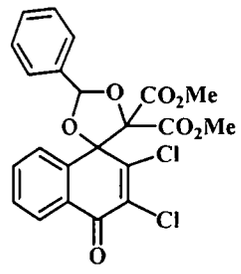
7.64-7.45 (m, 5H), 6.98-6.88 (m, 2H), 6.66 (s, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.04 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 175.9, 164.4, 163.1, 160.9, 149.7, 140.2, 134.6, 133.0, 132.7, 130.0, 129.5, 128.5, 128.0, 127.9, 126.8, 125.9, 114.0, 107.2, 93.0, 86.5, 55.2, 54.2, 52.6.

al. Calcd for $C_{23}H_{18}Cl_2O_8$: C, 56.00; H, 3.68. Found: C, 55.99; H, 3.71.

methyl 2-phenyl-4'-oxo-4'H-spiro[1,3-dioxolane-4,1'-naphthalene]-5,5 carboxylate 89

The reaction between **86** (0.114 g, 0.5 mmol), benzaldehyde (0.053 g, 0.5 mol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) in the presence of Rh(II) etate under the procedure described for compound **76** afforded the product **89** 132 g, 57%) as a colorless crystalline solid, **mp** 175 °C.



89

IR (KBr) ν_{max}: 2955, 1755, 1681, 1607, 1452, 1283, 1236, 1155, 1061, 1020, 953, 791, 697 cm^{-1}.

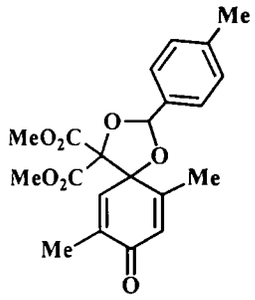
^{1}H NMR ($CDCl_3$) δ 8.2 (d, 1H, J = 7.9 Hz), 7.79-7.76 (m, 2H), 7.51-7.49 (m, 6H), 6.78 (s, 1H), 3.88 (s, 3H), 3.12 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 176.1, 164.4, 163.1, 140.6 140.2, 134.2, 132.7, 130.1, 130.0, 129.6, 128.7, 128.4, 127.1, 126.9, 126.5, 107.2, 92.7, 86.7, 54.3, 52.8.

al. Calcd for $C_{22}H_{16}Cl_2O_7$: C, 57.04; H, 3.48. Found: C, 56.92; H, 3.32.

imethyl 6,9-dimethyl-2-(4-methylphenyl)-8-oxo-1,3-dioxospiro [4.5]deca-6,9-iene-4,4-dicarboxylate 90

The reaction between 2,5-dimethyl 1,4-benzoquinone (0.068 g, 0.5 mmol), *p*-ualdehyde (0.068 g, 0.5 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) the presence of Rh(II) acetate under the procedure described for compound **76** forded the product **90** (0.108 g, 56%) as a colorless viscous liquid.



90

IR (neat) ν_{max}: 2955, 1755, 1688, 1661, 1445, 1384, 1249, 1121, 1074, 663 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 7.47 (d, 2H, J = 8.0 Hz), 7.21 (d, 2H, J = 8.0 Hz), 6.81 (s, 1H), 6.62 (s, 1H), 6.16 (s, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 2.38 (s, 3H), 1.94 (s, 3H), 1.82 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 185.2, 165.9, 164.5, 140.2, 139.3, 138.5, 131.9, 128.9, 128.5, 126.2, 125.9, 107.2, 105.3, 90.6, 83.0, 53.3, 53.2, 21.2, 19.6, 15.4.

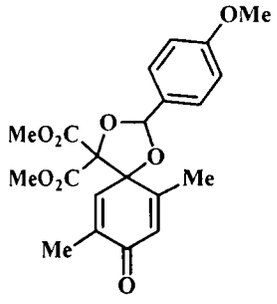
RMS (EI): m/z Calcd for $C_{21}H_{22}NO_7$[M+]:386.1365. Found: 386.1399.

imethyl 6,9-dimethyl-2-(4-methoxylphenyl)-8-oxo-1,3-dioxospiro[4.5]deca-6,9-iene-4,4-dicarboxylate 91

The reaction between 2,5-dimethyl 1,4-benzoquinone (0.068 g, 0.5 mmol), *p*-isaldehyde (0.068 g, 0.5 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) the presence of Rh(II) acetate under the procedure described for compound **76** forded the product **91** (0.103 g, 51%) as a colorless viscous liquid.

IR (neat) ν_{max}: 2948, 2840, 1755, 1688, 1654, 1526, 1438, 1391, 1256, 1189, 1135, 1081.

^{1}H NMR ($CDCl_3$) δ 7.52 (d, 2H, J = 8.7 Hz), 6.92, (d, 2H, J = 8.7 Hz), 6.79 (s, 1H), 6.59 (s, 1H), 6.10 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.74



91

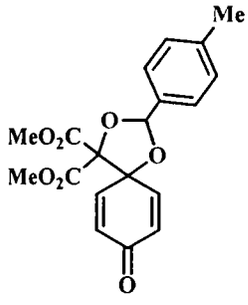
(s, 3H), 1.93 (s, 3H), 1.84 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 185.3, 166.1, 164.7, 155.4, 140.3, 138.6, 128.9, 128.0, 127.7, 113.8, 105.4, 90.4, 83.0, 55.2, 53.3, 53.2, 19.7, 15.6.

HRMS (EI): m/z Calcd for $C_{21}H_{22}O_8$ [M+]: 402.1314. Found: 402.1320.

2-(4-Methylphenyl)-8-oxo-1,3-dioxospiro[4.5]deca-6,9-diene-4,4-dicarboxylate 92

The reaction between 1,4-benzoquinone (0.054 g, 0.5 mmol), *p*-tolualdehyde (0.068 g, 0.5mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) in the presence of Rh(II) acetate under the procedure described for compound **76** afforded the product **92** (0.036 g, 20%) as a colorless viscous liquid.



92

IR (neat) ν_{max}: 2068, 1755, 1667, 1438, 1294, 1243, 1108 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 7.44 (d, 2H, J = 7.9 Hz), 7.21 (d, 2H, J = 7.9 Hz), 7.10-6.91 (m, 2H), 6.53 (s, 1H), 6.38-6.23 (m, 2H), 3.82 (s, 3H), 3.71 (s, 3H), 2.38 (s, 3H).

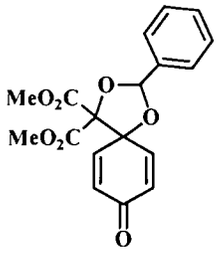
^{13}C NMR ($CDCl_3$) δ 184.1, 165.3, 145.9, 143.4, 141.2, 133.1, 131.2, 130.1, 129.2, 126.5, 106.2, 89.4, 79.6, 53.4, 53.2, 21.4.

HRMS (EI): m/z Calcd for $C_{19}H_{18}O_7$ [M+]: 357.0974. Found: 357.0935.

2-Phenyl-8-oxo-1,3-dioxospiro[4.5]deca-6,9-diene-4,4-dicarboxylate 93

The reaction between 1,4-benzoquinone (0.054 g, 0.5 mmol), benzaldehyde (0.053 g, 0.5 mmol) and dimethyl diazomalonate (0.087 g, 0.55 mmol) in the presence of Rh(II) acetate under the procedure described for compound **76** afforded the product **93** (0.028 g, 16%) as colorless viscous liquid.

IR (neat) ν_{max}: 2955, 1750, 1682, 1636, 1439,



93

1289, 1243, 1289, 1243, 1118, 772, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 7.58-7.54 (m, 2H), 7.42-7.39 (m, 3H), 7.06-7.05 (m, 1H), 6.93-6.89 (m, 1H), 6.56 (s, 1H), 6.38-6.34 (m, 1H), 6.27-6.23 (m, 1H), 3.81 (s, 3H), 3.70 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 184.0, 165.1, 164.4, 143.1, 141.1, 135.9, 130.1, 129.7, 128.9, 129.4, 128.3, 127.8, 126.8, 105.9, 89.1, 79.5, 53.3, 53.2.

3.9. References

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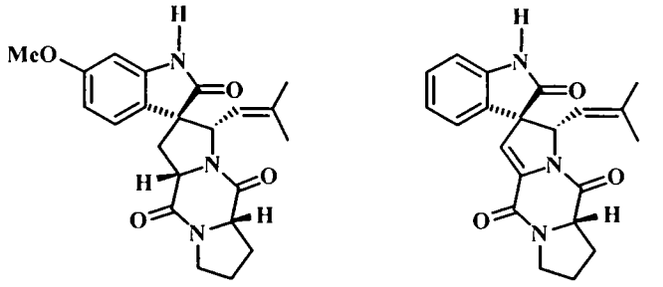
CHAPTER 4

1,3-DIPOLAR CYCLOADDITION REACTION OF AZOMETHINE YLIDE TO 1,2-DIONES: A FACILE SYNTHESIS OF SPIRO-OXINDOLES

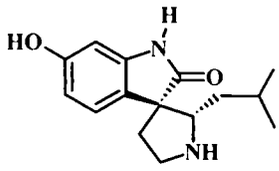
4.1. Introduction

As already mentioned in the previous chapters, 1,3-dipolar cycloaddition reactions constitute one of the most efficient methods for the synthesis of five membered heterocycles. Among the various dipoles, azomethine ylides have received substantial attention in recent years.[1] The synthetic importance of azomethine ylides stems from their use for the preparation of five membered nitrogen heterocycles, which are ubiquitous in Nature and often found as subunits of bioactive natural products. It is especially noteworthy that nitrogen containing heterocycles form the basic skeleton of numerous alkaloids and therapeutic agents.[2,3] Pyrrolidine, pyrrolizidine and oxindole alkaloids constitute a class of compounds with significant biological activity. Spiro[pyrrolidine/oxindole] ring system is common to most oxindole alkaloids.[4] Spirotryprostatine **A** and Spirotryprostatine **B**[5] contain spiropyrrolidinyl-oxindole skeletons. Both the compounds inhibit the cell cycle in the G2/M phase, and Spirotryprostatine **B** shows cytotoxic activity on the growth of human leukemia cell lines. (+)-Elacomine[6] and (-)-Horsfiline[7] are other examples of compounds containing 3,3'-spiro-oxindole skeleton (Figure 1).

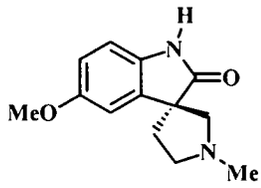


(-)-Spirotryprostatine A

(-)-Spirotryprostatine B



(+)-Elacomine



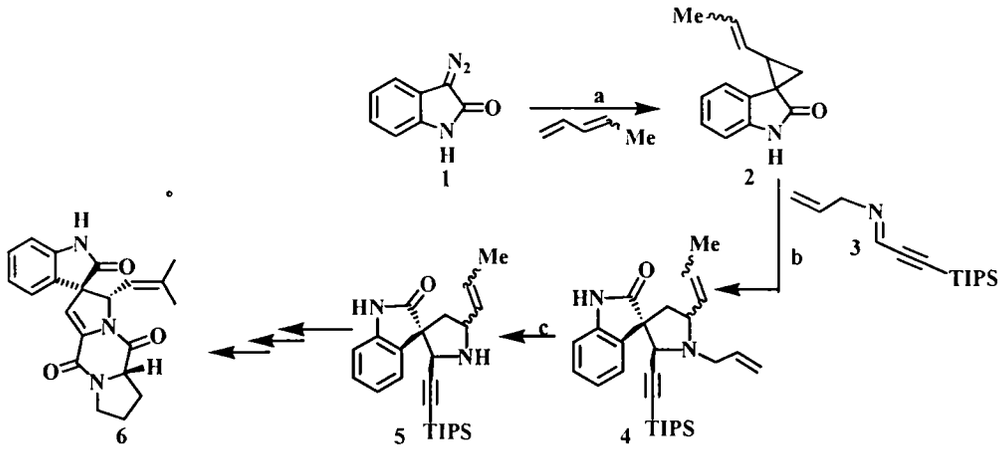
(-)-Horsfiline

Figure 1

Most of the oxindole alkaloids possess a common basic framework derived from tryptamine and are characterized by a unique spiro fusion to a pyrrolidine ring at the 3-position of the oxindole core.

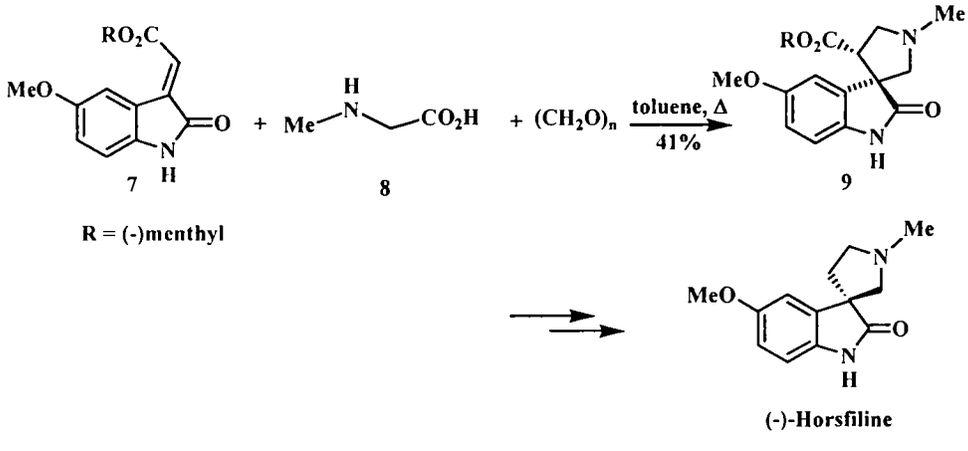
A number of strategies have been devised to provide access to the spiro[oxindole-3,3'-pyrrolidine] core.[8] The approaches that are most relevant to our studies are outlined below.

Very recently Carreira *et al.* have developed a novel approach to spiro[oxindole-3,3'-pyrrolidines] by the MgI_2-catalyzed ring expansion reaction of spiro[cyclopropane-1,3'-oxindoles] and aldimines (Scheme 1).[9]



Scheme 1

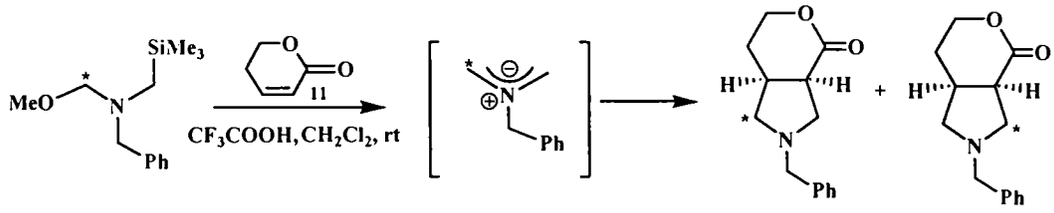
Palmisano has used 1,3-dipolar cycloaddition reaction as a method for the construction of the spiro[pyrrolidine-3,3'-oxindole] system in the context of natural product synthesis. Dipolar cycloaddition of **6** with *N*-methyl-azomethine ylide prepared *in situ* from formaldehyde and sarcosine yielded **8**. Hydrolysis of the ester and decarboxylation afforded (-) Horsfiline (Scheme 2).[10]



Scheme 2

Although several methods[11-14] are available for the generation of azomethine ylides, the most commonly used ones are those based on the fluoride-mediated

desilylation. Non-stabilized azomethine ylides are generated by acid-mediated desilylation of α-silyl amines bearing an appropriate leaving group. Trifluoroacetic acid is a strong enough acid to initiate the reaction, and is usually the reagent of choice (Scheme 3).[15]



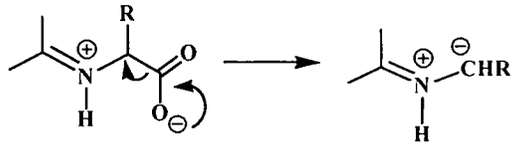
10 12 13 14

* = ^{13}C

Scheme 3

In the above reaction, two cycloaddition products are formed in the ratio 1:1 as indicated by ^{13}C labelling (*) of the precursor.

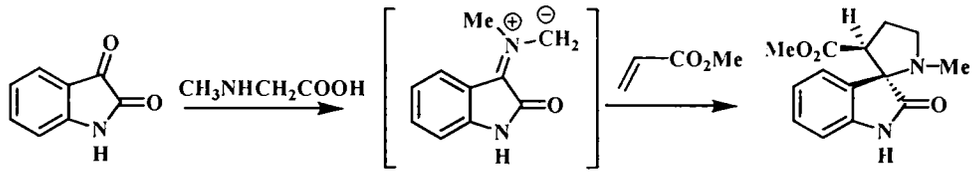
Grigg *et al.* have reported the formation of azomethine ylides from amino acid esters *via* Schift base formation.[16] It is conceivable that the imine undergoes decarboxylation *via* the zwitterionic form **15** generating the 1,3-dipole **16** (Scheme 4).



15 16

Scheme 4

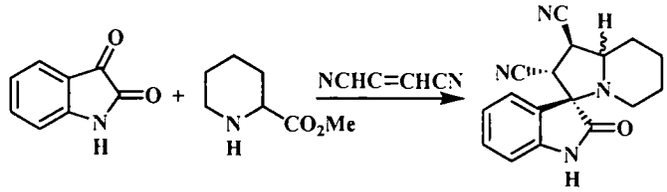
They have also studied the reaction of azomethine ylides generated by the condensation of 1,2-dicarbonyl compounds with α-amino acids or amines. For example, isatin **17** when treated with sarcosine in the presence of menthyl/methyl acrylate, afforded a single cycloadduct **19** in good yield *via* the azomethine ylide **18** (Scheme 5).[17]



17 18 19

Scheme 5

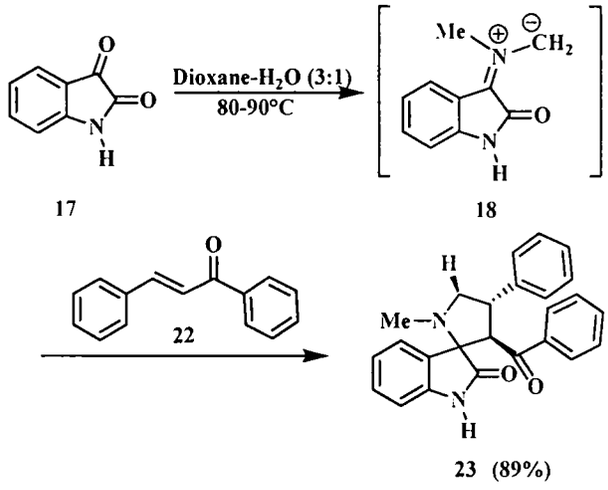
Similarly when isatin, pipecolic acid and fumaronitrile were heated in MeOH, the cycloadduct **21** was obtained in 76% yield (Scheme 6).[16b]



17 20 21

Scheme 6

It has been reported that azomethine ylide **18**, generated by the decarboxylative condensation of isatin with sarcosine, was trapped by chalcone **22** to afford the heterocycle **23** (Scheme 7).[18]



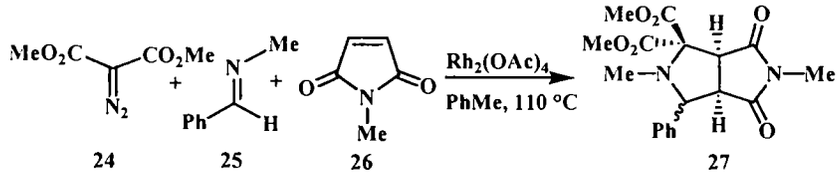
17 18

23 (89%)

Scheme 7

Padwa and co-workers have explored the reactivity of azomethine ylide generated by the reaction of carbenes or carbenoids with imines. Typically, Rh(II)

acetate-catalyzed reaction of dimethyl diazomalonate **24** in the presence of the imine **25** and *N*-methyl maleimide afforded the bicyclic imide **27** in good yield with a modest preference for the *exo* isomer (Scheme 8).[19]

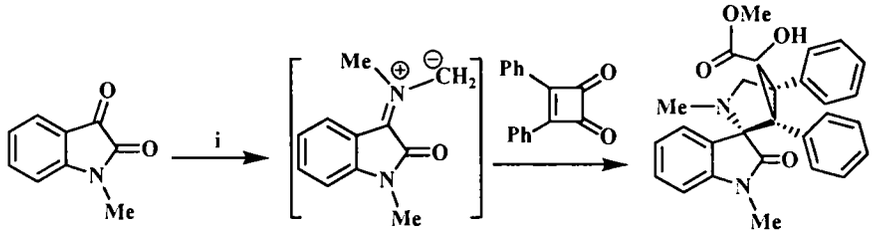


24 25 26 27

50% *exo* 30% *endo*

Scheme 8

The addition of azomethine ylide, derived from sarcosine and isatin with 3,4-diphenylcyclobutene-1,2-dione has been investigated in our laboratory. The reaction in MeOH:H_2O system at 90 °C proceeded smoothly to afford a product in 58% yield and it was characterized as the spiropyrrolidine derivative **30** (Scheme 9).[20]

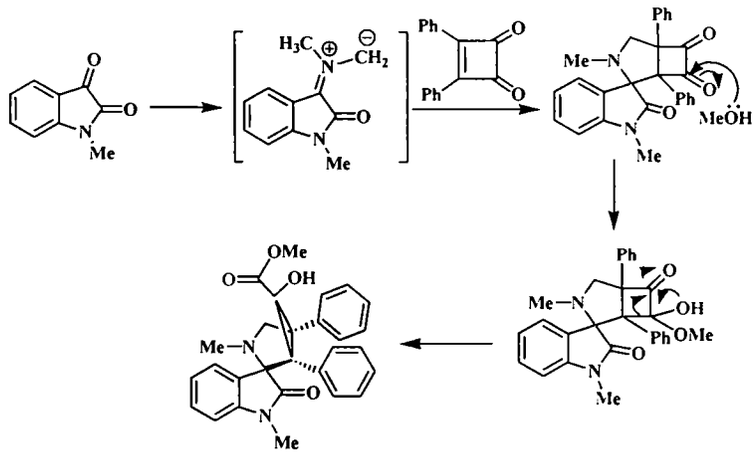


28 + $CH_3NHCH_2CO_2H$ 29 30 (58%)

i. MeOH:H_2O (3:1), 90°C, 24 h

Scheme 9

A mechanistic rationale for the reaction is outlined in Scheme 10.



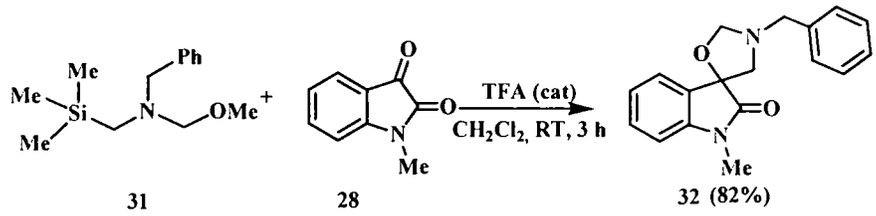
Scheme 10

4.2. The Present Work

The literature survey revealed that, although the chemistry of azomethine ylides has been explored in detail, their reactivity towards carbonyl compounds has received only scant attention. Earlier work from our own group indicated that azomethine ylides generated by the condensation of derivatives of isatins and sarcosine react with substituted cyclobutene 1,2-diones. But the reactivity of azomethine ylides towards isatins has not been investigated. Against this literature scenario, and in the context of our general interest in the chemistry of 1,2- diones (see chapter 3), it was decided to explore the reactivity of the latter towards azomethine ylide generated by the acid catalyzed decomposition of *N*-methoxymethyl-*N*-(trimethyl-silylmethyl)benzylamine. Isatins, acenaphthene quinone and phenanthrene quinone are the 1,2-diones selected for our study. The results of this investigation form the subject matter of this chapter.

4.3. Results and Discussion

Our studies were initiated by exposing *N*-methyl isatin to *N*-methoxymethyl-*N*-(trimethyl-silylmethyl)benzylamine, in the presence of catalytic amount of trifluoroacetic acid; a facile reaction occurred to afford the oxazolidine derivative in excellent yield (Scheme 11).



31 28 32 (82%)

Scheme 11

The structure of the product **32** was established by spectroscopic analysis. The IR spectrum showed a strong absorption peak at 1722 cm^{-1} corresponding to amide carbonyl. In the ^1H NMR spectrum, the peak corresponding to the *N*- methyl protons was discernible as a singlet at δ 3.17. The benzylic protons gave two separate doublets at δ 3.26 and δ 3.44. The two doublets at δ 4.10 and δ 4.19 correspond to the methylene protons adjacent to the spirocarbon. The methylene protons positioned between oxygen and nitrogen showed two doublets at δ 4.79 and δ 4.84. The aromatic protons displayed signals between δ 6.72 and δ 7.44. In the ^{13}C NMR spectrum, the amide carbonyl was found to resonate at δ 176.9. The signal due to methylene carbon flanked by oxygen and nitrogen was descernible at δ 89.4, while the spirocarbon showed its resonace peak at δ 80.1. All the other signals were also in good agreement with the assigned structure. The HRMS data of the compound was also found to be satisfactory.

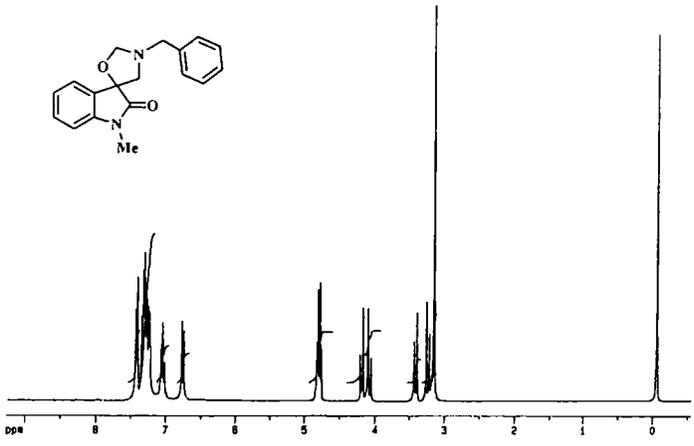


Figure 2. *^1H NMR Spectrum of 32*

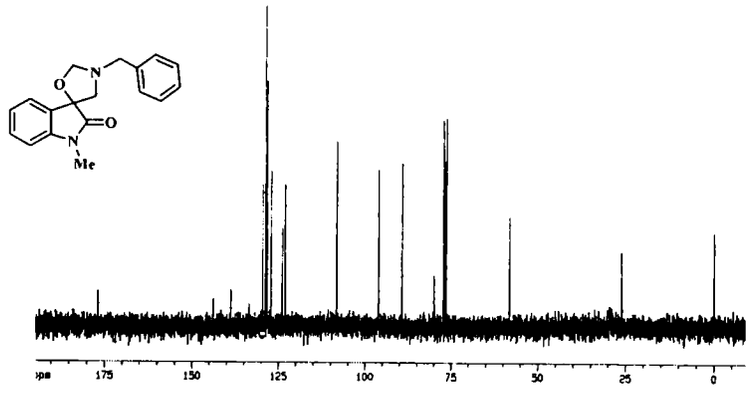
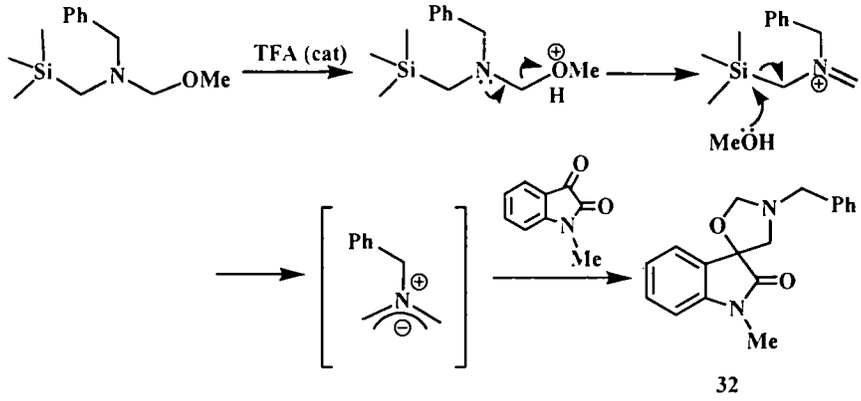


Figure 3. *^{13}C NMR Spectrum of 32*

Mechanistically, the reaction can be considered to take place by the acid catalyzed decomposition of *N*-methoxymethyl-*N*-(trimethyl-silylmethyl)benzylamine to form azomethine ylide *in situ*. Subsequent addition of this unstable species to the keto carbonyl of isatin affords the product **32** (Scheme 12).

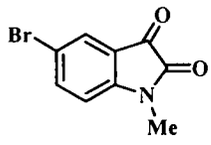
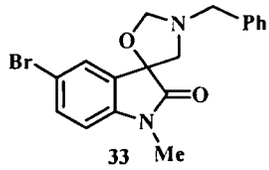
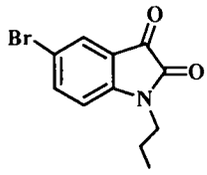
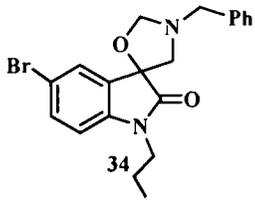
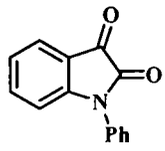
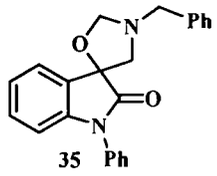
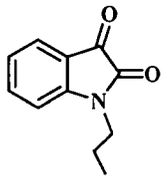
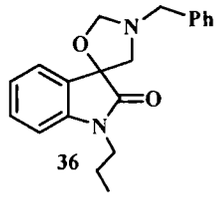
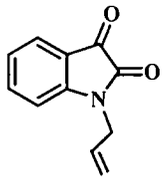
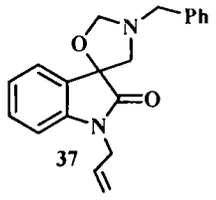


Scheme 12

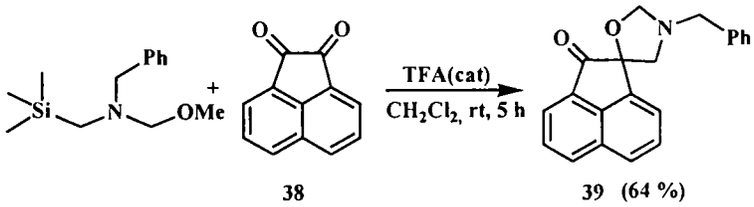
The chemoselectivity of the reaction can be attributed to the higher electrophilicity of the keto-group *vis* a *vis* the amide carbonyl.

The reaction was found to be applicable to a number of *N*-substituted isatins and high yields of oxazolidine derivatives were obtained in all cases (Table 1).

Table 1

Entry	Isatin	Product	Yield (%)
1		 33	94
2		 34	96
3		 35	93
4		 36	86
5		 37	94

Subsequently, we turned our attention to other 1,2-diones. Reaction with acenaphthenequinone afforded the addition product in good yield (Scheme 13).

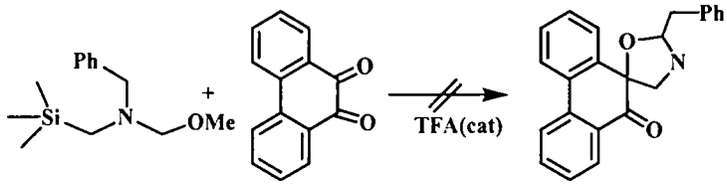


38 39 (64 %)

Scheme 13

The structure of the product was elucidated by spectroscopic data. The IR spectrum of **39** manifested a strong band at 1733 cm^{-1} due to the carbonyl group. In the ^1H NMR spectrum of the compound, the benzylic protons were descernible as two doublets at δ 3.36 and δ 3.46. The resonance peaks due to protons of the methylene group attached to the spirocarbon also appeared as two doublets at δ 4.16 and δ 4.26. The singlet signal that appeared at δ 4.88 corresponds to the methylene protons flanked by oxygen and nitrogen. Signals due to aromatic protons were discernible between δ 7.21 and δ 8.07. In the ^{13}C NMR spectrum, the carbonyl carbon showed its resonance peak at δ 204.0. The signal that appeared at δ 84.0 is characterstic of a spirocarbon. All other signals were also in good agreement with the proposed structure.

When the reaction was attempted with phenanthrenequinone, no addition was observed (Scheme 14).



Scheme 14

4.4. Conclusion

In conclusion, we have demonstrated that the unstable azomethine ylide generated by the acid catalyzed decomposition of *N*-methoxymethyl-*N*-(trimethylsilylmethyl)benzylamine undergoes facile cycloaddition to 1,2-diones, such as isatins and acenaphthenequinone to furnish oxazolidine derivatives in high yields. It is conceivable that these compounds, by virtue of the presence of the oxindole moiety, a structural constituent of many biologically active natural products, may exhibit interesting biological activity. Further investigations in this area will be undertaken by other members of the group.

4.5. Experimental Details

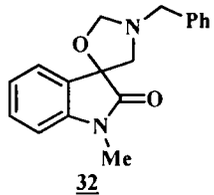
General information about the experiments is given in Section 2.6 of chapter 2. *N*-methoxymethyl-*N*-(trimethyl-silyl)benzylamine was purchased from Lancaster. Gravity column was performed using neutral alumina and mixtures of hexane-ethyl acetate were used for elution.

4.5.1. General Procedure for the Synthesis of Oxazolidines

To a mixture of isatin (0.30 mmol) and *N*-methoxymethyl-*N*-(trimethyl-silyl)benzylamine (0.33 mmol) in 5mL of dry dichloromethane was added 10 mol% of trifluoroacetic acid. The reaction mixture was allowed to stir for 3 h. After stirring, solvent was removed *in vacuo*. The product was purified by column chromatography on neutral alumina to afford the oxazolidine.

3'-Benzyl-1-methyl spiro[indole-3, 5'-[1, 3]oxazolidin]-2(1H)-one 32

To a mixture of *N*-methyl isatin (0.048 g, 0.3 mmol) and *N*-methoxymethyl-*N*-(trimethyl-silyl)benzylamine (0.078 g, 0.33 mmol) in 5 mL of dry dichloromethane added 10 mol% of trifluoroacetic acid. Stirred at room temperature for 3 h. Solvent was removed and the product was purified by column chromatography on neutral alumina using 95:5 hexane-ethylacetate mixture to afford the product **32** (0.072 g, 82 %) as a pale yellow viscous liquid.



32

IR(neat)$_{\nu max}$: 2962, 2924, 1722, 1623, 1492, 1470, 1382, 1354, 1096, 915, 751 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 3.17 (s, 3H), 3.26 (d, 1H, J = 12.2 Hz), 3.44 (d, 1H, J = 12.2 Hz), 4.10 (d, 1H, J = 13.1 Hz), 4.19 (d, 1H, J = 13.0 Hz), 4.79 (d, 1H, J = 5.7 Hz), 4.84 (d, 1H, J = 5.7 Hz), 6.72 (d, 1H, J = 7.8 Hz), 7.06 (t, 1H, J = 7.6 Hz), 7.24-7.44 (m, 7H).

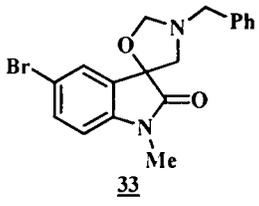
^{13}C NMR ($CDCl_3$) δ 176.9, 143.9, 138.9, 129.7, 128.9, 128.5, 127.3, 124.0, 123.2,

112.0, 108.3, 89.4, 80.1, 61.7, 58.3, 26.3.

HRMS (EI): m/z Calcd for $C_{18}H_{18}N_2O_2$ [M+]: 294.1368. Found: 294.1182.

3'-Benzyl-5-bromo-1-methyl spiro[indole-3, 5'-[1, 3]oxazolidin]-2(1H)-one 33

5-Bromo *N*-methyl isatin (0.072 g, 0.3 mmol) and **31** (0.078 g, 0.33 mmol) were allowed to react in the presence of 10 mol% of trifluoroacetic acid under the experimental conditions described in the general procedure to afford the product **33** (0.105 g, 94 %) as a colorless viscous liquid.



33

IR(neat)$_{vmax}$: 2929, 2880, 1728, 1612, 1497, 1467, 1349, 1272, 1234, 1102, 1009, 915, 817, 707 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 3.13 (s, 3H), 3.24 (d, 1H, *J* = 12.1 Hz), 3.42 (d, 1H, *J* = 12.2 Hz), 4.07 (d, 1H, *J* = 13.1 Hz), 4.18 (d, 1H, *J* = 13.1 Hz), 4.78 (d, 1H, *J* = 5.7 Hz), 4.81 (d, 1H, *J* = 5.6 Hz), 6.65 (d, 1H, *J* = 8.2 Hz), 7.28-7.45 (m, 7H).

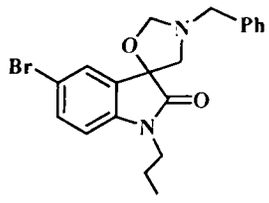
^{13}C NMR ($CDCl_3$) δ 176.1, 142.7, 138.5, 132.3, 132.1, 128.8, 128.4, 127.3, 127.1, 115.6, 109.7, 89.4, 79.8, 61.6, 58.0, 26.2.

3'-Benzyl-5-bromo-1-^{n}propyl spiro[indole-3, 5'-[1, 3]oxazolidin]-2(1H)-one 34

5-Bromo *N*-^{n}propyl isatin (0.080 g, 0.3 mmol) and **31** (0.078 g, 0.33 mmol) were allowed to react in the presence of 10 mol% of trifluoroacetic acid under the experimental conditions described in the general procedure to afford the product **34** (0.116 g, 96 %) as a colorless viscous liquid.

IR(neat)$_{vmax}$: 2968, 2935, 1728, 1612, 1486, 1431, 1349, 1267, 1118, 1003, 817 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, *J* = 7.4 Hz), 1.61-1.73 (m, 2H), 3.25 (d, 1H, *J* = 12.2 Hz),



<u>34</u>

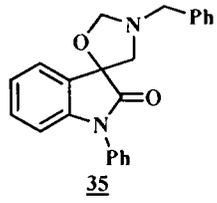
3.42 (d, 1H, J = 12.2 Hz), 3.58-3.63 (m, 2H), 4.09 (d, 1H, J = 13.1 Hz), 4.19 (d, 1H, J = 13.1 Hz), 4.79 (d, 1H, J = 5.6 Hz), 4.81 (d, 1H, J = 5.6 Hz), 6.67 (d, 1H, J = 8.3 Hz), 7.23-7.46 (m, 7H).

^{13}C NMR ($CDCl_3$) δ 176.2, 142.1, 138.5, 132.3, 132.2, 128.8, 128.3, 127.2, 115.3, 109.9, 89.5, 79.8, 61.7, 57.9, 41.6, 20.4, 11.2.

HRMS (EI): m/z Calcd for $C_{20}H_{21}N_2O_2Br$ [M+]: 400.0786. Found: 400.0808

3'-Benzyl-1-phenyl spiro[indole-3, 5'-[1, 3]oxazolidin]-2(1H)-one <u>35</u>

N-Phenyl isatin (0.067 g, 0.3 mmol) and **31** (0.078 g, 0.33 mmol) were allowed to react in the presence of 10 mol% trifluoroacetic acid under the experimental conditions described in the general procedure to afford the product **35** (0.099 g, 93%) as a colorless viscous liquid.



<u>35</u>

IR(neat)$_{\nu max}$: 3058, 3027, 1734, 1620, 1600, 1501, 1465, 1377, 1336, 1201, 1108, 1056, 1010, 922, 756, 694 cm^{-1}.

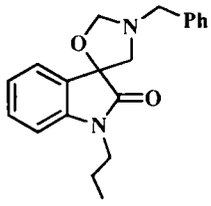
^{1}H NMR ($CDCl_3$) δ 3.36 (d, 1H, J = 12.3 Hz), 3.56 (d, 1H, J = 12.3 Hz), 4.13 (d, 1H, J = 13.1 Hz), 4.23 (d, 1H, J = 13.1 Hz), 4.83 (d, 1H, J= 5.8 Hz), 4.88 (d, 1H, J = 5.8 Hz), 6.77 (d, 1H, J = 7.8 Hz), 7.22-7.48 (m, 13H).

^{13}C NMR ($CDCl_3$) δ 176.1, 143.7, 138.8, 134.1, 129.9, 129.5, 128.9, 128.4, 127.9, 127.2, 126.3, 124.2, 123.5, 109.5, 89.4, 80.1, 62.1, 58.2.

HRMS (EI): m/z Calcd for $C_{23}H_{20}N_2O_2$ [M+]: 356.1525. Found: 356.1487

3'-Benzyl-1-^{n}propyl spiro[indole-3, 5'-[1, 3]oxazolidin]-2(1H)-one 36

N-^{n}propyl isatin (0.057 g, 0.3 mmol) and **31** (0.078 g, 0.33 mmol) were allowed to react in the presence of 10 mol% of trifluoroacetic acid under the experimental conditions described in the general procedure to afford the product **36** (0.083 g, 86 %) as colorless viscous liquid.



36

IR(neat)$_{\nu max}$: 2962, 2929, 1728, 1618, 1492, 1470, 1371, 1212, 1135, 1003, 921, 751 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, *J* = 7.4 Hz), 1.65-1.74 (m, 2H), 3.28 (d, 1H, *J*= 12.2 Hz), 3.44 (d, 1H, *J* = 12.2 Hz), 3.63-3.66 (m, 2H), 4.12 (d, 1H, *J* = 13.1 Hz), 4.22 (d, 1H, *J* = 13.1 Hz), 4.81 (d, 1H, *J* = 5.8 Hz), 4.85 (d, 1H, *J* = 5.8 Hz), 6.79 (d, 1H, *J* = 7.8 Hz), 7.05 (t, 1H, *J* = 7.5 Hz), 7.24-7.42 (m, 7H).

^{13}C NMR ($CDCl_3$) δ 176.7, 143.4, 129.8, 128.9, 128.5, 127.5, 127.6, 124.4, 123.1, 108.6, 89.0, 80.2, 61.2, 58.2, 41.6, 20.7, 11.4.

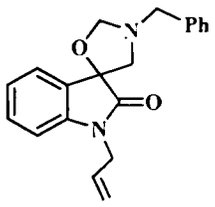
HRMS (EI): m/z Calcd for $C_{20}H_{22}N_2O_2$ [M+]: 322.1681. Found: 322.1701

3'-Benzyl-1-allyl spiro[indole-3, 5'-[1, 3]oxazolidin]-2(1H)-one 37

N-Allyl isatin (0.056 g, 0.3 mmol) and **31** (0.078 g, 0.33 mmol) were allowed to react in the presence of 10 mole% of trifluoroacetic acid under the experimental conditions described in the general procedure; product **37** (0.090 g, 94%) was obtained as a colorless viscous liquid.

IR(neat)$_{\nu max}$: 2929, 2877, 1724, 1615, 1496, 1457, 1362, 1186, 1160, 922, 881, 751 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 3.26 (d, 1H, *J* = 12.2 Hz), 3.43 (d, 1H, *J* = 12.2 Hz), 4.09 (d, 1H, *J* = 13.1 Hz), 4.19 (d, 1H, *J* = 13.1 Hz), 4.25-4.27 (m,



37

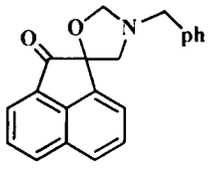
2H), 4.78 (d, 1H, J = 5.7 Hz), 4.82 (d, 1H, J = 5.7 Hz), 5.16-5.23 (m, 2H), 5.73-5.85 (m, 1H), 6.75(d, 1H, J = 7.8 Hz), 7.19-7.43 (m, 8H).

^{13}C NMR ($CDCl_3$) δ 176.4, 142.9, 138.7, 130.9, 130.0, 129.4, 128.7, 128.2, 127.1, 123.9, 122.9, 117.5, 108.9, 89.2, 79.8, 61.6, 58.0, 42.1.

HRMS (EI): m/z Calcd for $C_{20}H_{20}N_2O_2$ [M+]: 320.1525. Found: 320.1563.

Cycloadduct 39

10 mol% of trifluoroacetic acid was added to a solution containing a mixture of acenaphthenequinone and *N*-methoxymethyl-*N*-(trimethyl-silylmethyl)benzylamine in 5mL of dry benzene. The resulting solution was refluxed for 5 h. The solvent was removed *in vacuo* and the product was purified by chromatography on neutral alumina using 95:5 mixture of ethyl acetate and hexane solution to afford the product in 64 % yield as a colorless viscous liquid.



39

IR(neat)$_{vmax}$: 2929, 2858, 1733, 1612, 1508, 1470, 1371, 1343, 1261, 1157, 1053, 1014, 921, 784, 696 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 3.36 (d, 1H, J = 12.3 Hz), 3.46 (d, 1H, J = 12.2 Hz), 4.16 (d, 1H, J = 13.0 Hz), 4.26 (d, 1H, J = 13.0 Hz), 4.90 (s, 2H). 7.21-7.35(m, 3H), 7.46 (d, 2H, J = 7.6 Hz), 7.62-7.74 (m, 3H), 7.81-7.86 (m, 1H), 7.94 (d, 1H, J = 7.0 Hz), 8.08 (d, 1H, J = 8.2 Hz).

^{13}C NMR ($CDCl_3$) δ 204.0, 141.9, 140.1, 138.9, 131.6, 129.0, 128.9, 128.5, 128.3, 127.3, 125.3, 121.9, 120.2, 89.6, 84.0, 61.4, 58.2.

HRMS (EI): m/z Calcd for $C_{21}H_{17}NO_2$ [M+]: 315.1259. Found: 315.0386.

4.6. References

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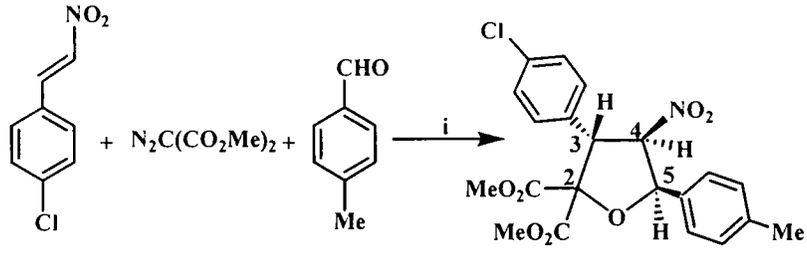
SUMMARY

The thesis entitled "**Novel 1,3-Dipolar Cycloaddition Reactions of Acyclic Carbonyl Ylides and Related Chemistry**" embodies the results of the investigations carried out to explore the reactivity of acyclic carbonyl ylides, generated by the reaction of dicarbomethoxy carbene and aldehydes towards dipolarophiles such as activated styrenes, 1,2-and 1,4-quinones.

A general introduction to the chemistry of carbenes, carbenoids and carbonyl ylides is given in chapter 1, and it is intended to provide a qualitative understanding of these topics. A definition of the problems addressed in the thesis is also included in this chapter.

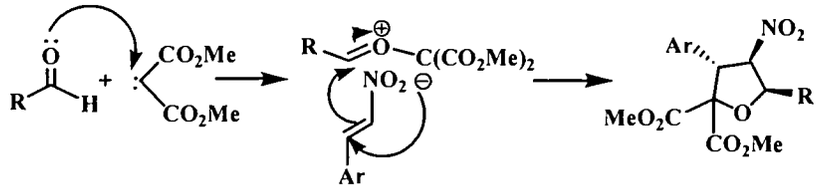
The second chapter discusses the stereoselective synthesis of highly substituted tetrahydrofuran derivatives by the three component reaction of acyclic carbonyl ylides with activated styrenes. The Rh(II) catalyzed reaction of dimethyl diazomalonate in the presence of *p*-tolualdehyde and 4- chloro-*β*-nitrostyrene afforded a single cycloadduct in 76 % yield (Scheme 1).



i. $Rh_2(OAc)_4$, dry benzene, argon, 80°C, 16 h, 76%

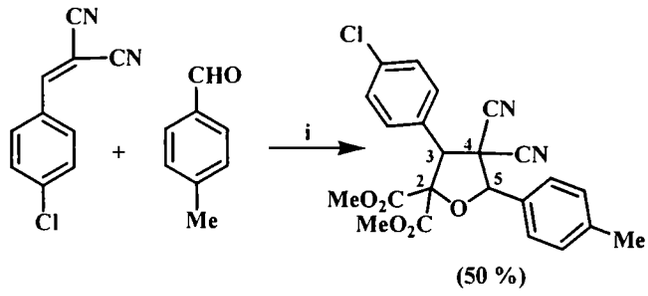
Scheme 1

Mechanistically, the reaction may be considered to involve the Huisgen dipolar cycloaddition of the carbonyl ylide, formed by the reaction of the carbene and the aldehyde, to the *β*-nitrostyrene, the latter being a good dipolarophile (Scheme 2).



Scheme 2

The reaction of 4-chloro-benzylidene malononitrile with the carbonyl ylide, generated from *p*-tolualdehyde and dicarbomethoxycarbene, furnished the tetrahydrofuran derivative in moderate yield (Scheme 3).

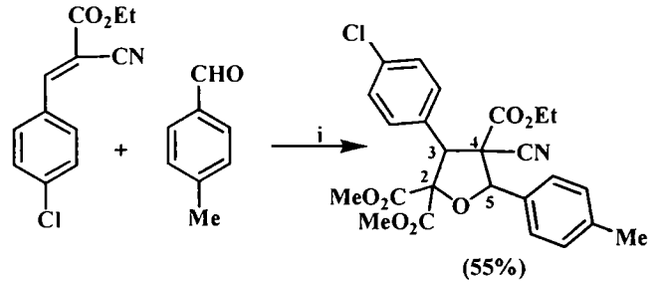


(50 %)

i. $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, dry benzene, argon, 80°C, 16 h

Scheme 3

Similar addition of the acyclic carbonyl ylide to cyanocinnamates also afforded the corresponding cycloadduct (Scheme 4).



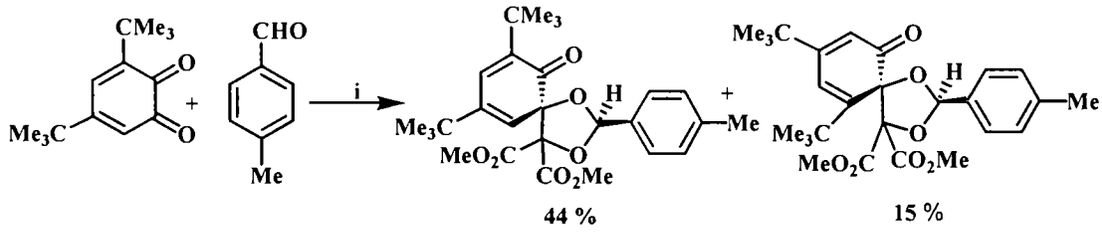
(55%)

i. $Rh_2(OAc)_4$, dry benzene, argon, 80°C, 16 h

Scheme 4

The third chapter of the thesis is focused on the reactivity of the carbonyl ylides towards various 1,2-diones, such as, *o*-benzoquinones, phenanthrenequinone and isatins. Our studies in this area were initiated by the Rh(II) catalyzed decomposition of dimethyl diazomalonate in the presence of *p*-tolualdehyde and 3,5-di-*tert*-butyl-1,2-

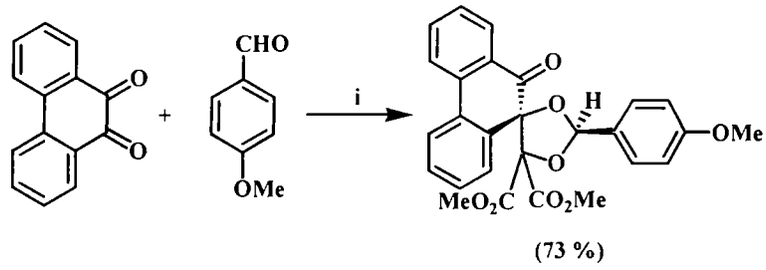
benzoquinone. A facile reaction occurred, affording a regioisomeric mixture of dioxolanes (Scheme 5).



i. $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, dry benzene, argon, 80 °C, 14 h.

Scheme 5

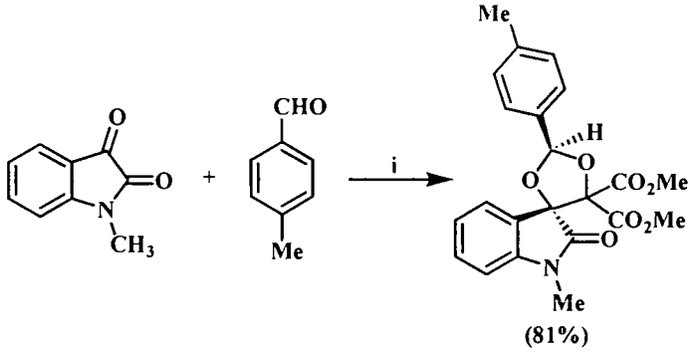
Phenanthrenequinone also reacted with the carbonyl ylide in the same way to afford the dioxolane derivative in very good yield (Scheme 6).



i. $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, dry benzene, argon, 14 h

Scheme 6

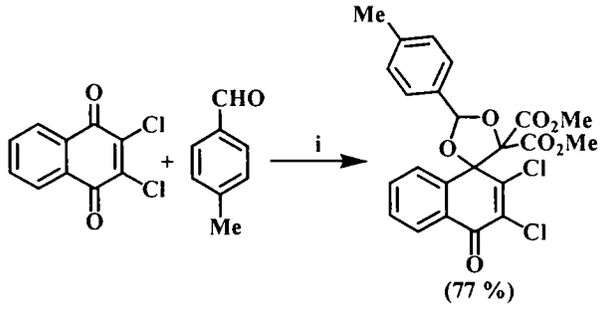
The cycloaddition of acyclic carbonyl ylides with istatins, illustrated by the following example, is also discussed in chapter 3 (Scheme 7).



i. $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, dry benzene, argon, 16 h

Scheme 7

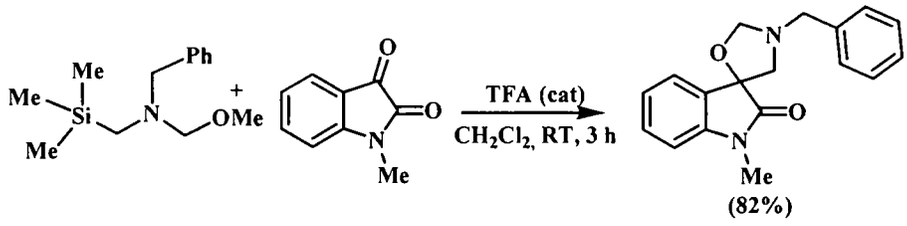
In a limited investigation, the reaction was extended to 1,4-diones also, and the results are included in this chapter. The following example is illustrative (Scheme 8).



i. $N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, dry benzene, argon, 16 h

Scheme 8

The reactivity of azomethine ylide towards isatins is addressed in the fourth and final chapter. As shown in the following example, azomethine ylide generated by the acid catalyzed decomposition of *N*-methoxymethyl-*N*-(trimethyl-silylmethyl)benzylamine, underwent a very efficient cycloaddition to isatins (Scheme 9).



Scheme 9

In conclusion, we have explored the reactivity pattern of acyclic carbonyl ylides derived from dicarbomethoxycarbene and aldehydes towards activated styrenes with a view to develop a stereoselective synthesis of highly substituted tetrahydrofuran derivatives. It was also found that the ylide could be trapped by various 1,2- and 1,4-diones to form dioxolane derivatives. It is noteworthy that the cycloaddition is highly regio- and stereoselective. With isatins the ylide preferentially adds to the more electron defficient carbonyl group making it regiospecific.

In related work we have shown that azomethine ylide undergoes facile cycloaddition to isatins to afford novel spiro-oxindole derivatives, a structural constituent of many biologically active natural products.

It is conceivable that the novel three component reactions described in the thesis will find wider application in organic synthesis.