NOVEL HETEROCYCLIC CONSTRUCTIONS MEDIATED BY NUCLEOPHILIC CARBENES AND RELATED CHEMISTRY

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IN CHEMISTRY UNDER THE FACULTY OF SCIENCE

BY

BINDU S.

UNDER THE SUPERVISION OF

Dr. G . VIJAY NAIR

ORGANIC CHEMISTRY DIVISION

REGIONAL RESEARCH LABORATORY (CSIR)

THIRUVANANTHAPURAM-695 019

KERALA, INDIA

APRIL 2003

REGIONAL RESEARCH LABORATORY (CSIR)
GOVERNMENT OF INDIA
TRIVANDRUM-695 019, INDIA

Dr. G. Vijay Nair, F. A. Sc.
Director-Grade Scientist

Telephone: 91-471-2490406; Fax: 91-471-2491712

CERTIFICATE

This is to certify that the work embodied in the thesis entitled "**Novel Heterocyclic Constructions Mediated by Nucleophilic Carbenes and Related Chemistry**" has been carried out by **Ms. Bindu S.** 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.

G. Vijay Nair
(Thesis Supervisor)

Trivandrum
April 2003

email: vijaynair_2001@yahoo.com; gvn@csrrltrd.ren.nic.in

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PREFACE

Carbon-Carbon and Carbon-Heteroatom bond forming reactions are of crucial importance in organic synthesis and enormous efforts have been devoted to develop new methodologies for the same. The traditional synthesis of complex organic molecules employs stepwise formation of bonds and involves multiple steps. Besides the sequential synthesis, in several instances, the desired product can also be obtained in one pot reactions of three or more starting compounds. Such reactions in which more than two starting materials react to form a product in such a way that the majority of the atoms of the starting materials can be found in the product are called multicomponent reactions (MCRs). A number of advantages make MCRs attractive both in organic and combinatorial synthesis *viz.*, simple procedures, facile execution, atom economy, convergence and ecofriendliness and they offer great promise in the synthesis of heterocycles.

The chemistry of nucleophilic carbenes such as dialkoxycarbenes and *N*-heterocyclic carbenes has been the subject of intense investigations recently. In the context of our general interest in devising new methods for heterocyclic construction and in designing novel multicomponent reactions based on nucleophilic species, we have carried out a detailed and systematic investigation of the reactivity pattern of the 1:1 zwitterions, generated *in situ* from nucleophilic carbenes such as dimethoxycarbene and *N*-heterocyclic carbenes and dimethyl acetylenedicarboxylate. The results of our investigations constitute the subject matter of the thesis entitled **"NOVEL HETEROCYCLIC CONSTRUCTIONS MEDIATED BY NUCLEOPHILIC CARBENES AND RELATED CHEMISTRY"**.

The thesis is divided into four chapters. Relevant references are given at the end of each chapter.

A general introduction to carbenes, carbenoids and nucleophilic carbenes is presented in Chapter 1. A brief introduction to multicomponent

reactions and the definition of the present research problem is also provided in this chapter.

The second chapter presents the results of our investigations of the reaction of 1:1 zwitterion of dimethoxycarbene and DMAD with various carbonyl compounds. General information on the experimental procedures is given this chapter.

The third chapter describes a facile one pot synthesis of bicyclic lactones by the "interrupted Nazarov reaction" of divinyl dihydrofurans obtained by the multicomponent reaction of 1,4-dienones with dimethoxycarbene and DMAD.

The results of our investigations on the application of *N*-heterocyclic carbenes in multicomponent reaction with DMAD and aromatic aldehydes leading to the one pot synthesis of 2-oxy-maleate and furanone derivatives are disclosed in the fourth chapter.

It may be mentioned that each chapter of the thesis is presented as an independent unit and therefore the structural formulae, schemes and figures are numbered chapter wise.

A summary of the work is given towards the end of the thesis.

ABBREVIATIONS

Ac	: acetyl
acac	: acetyl acetonate
CDI	: N, N'-carbonyl diimidazole
Cy	: cyclohexyl
d	: doublet
dd	: doublet of doublet
DABCO	: 1,4-diaza bicyclo[2.2.2]octane
DBN	: 1,5-diazabicyclo[4.3.0]non-5-ene
DBU	: 1,8-diazabicyclo[5.4.0]undec-7-ene
DME	: 1,2-dimethoxyethane
DMF	: dimethyl formamide
DMAD	: dimethyl acetylenedicarboxylate
EI	: electron impact
Et	: ethyl
ee	: enantiomeric excess
HRMS	: high-resolution mass spectrum
Hz	: hertz
IR	: infrared
J	: coupling constant
KHDMS	: potassium hexamethyl disilazide
m	: multiplet
Me	: methyl
mg	: milligram
mL	: milliliter
mp	: melting point
NMR	: nuclear magnetic resonance
o	: ortho
p	: para
Ph	: phenyl
Pr	: n-propyl
s	: singlet
t	: triplet
Ts	: *p*-toluene sulfonyl
tert	: tertiary
TEMPO	: 2,2,6,6-tetramethyl-1-piperidin-1-oxyl
TPP	: triphenyl phosphine
^{t}Bu	: tertiary butyl

CHAPTER 1

AN INTRODUCTION TO THE CHEMISTRY OF CARBENES, CARBENOIDS AND NUCLEOPHILIC CARBENES

1.1 Introduction

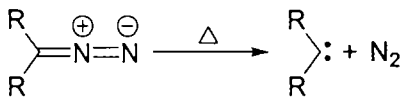
Nucleophilic carbenes such as dialkoxycarbenes and *N*-heterocyclic carbenes (NHCs) have gained considerable attention recently and the exploration of their reactivity profiles has become a major area of current research.[1] The central theme of the present study is the application of nucleophilic carbenes in multicomponent reactions (MCRs). In order to put things in perspective, a brief introduction to the chemistry of carbenes, carbenoids and nucleophilic carbenes is given in the following sections. This is followed by a brief introduction to multicomponent reactions.

1.1.1 Carbenes

Carbenes are neutral divalent derivatives of carbon with only six electrons in their valence shell. The first attempts to prepare carbenes 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 prepared ethylene by the reaction of methyl iodide with copper and he suggested that the product formation is occurring *via* the intermediacy of methylene.[2] In 1862 Geuther established that dichlorocarbene 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 recent growth in carbene chemistry started in the 1950s when Doering introduced carbenes to organic chemistry.[5] Since then, these fascinating species have played a crucial role in many important synthetic organic reactions.

1.1.2 Common Methods for the Preparation of Carbenes

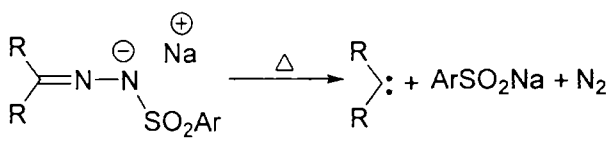
A large number of methods are available in the literature for the generation of carbenes and some of the most general ones are discussed below. The common method employed involves the decomposition of diazo compounds under photolysis, thermolysis or metal ion catalysis (Scheme 1).[6]



1 **2**

Scheme 1

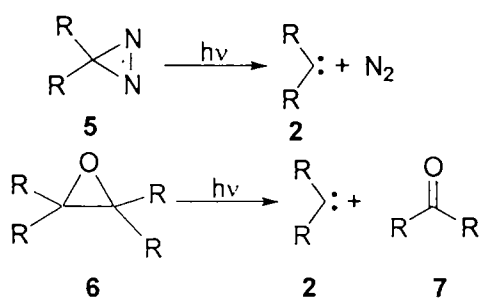
An extension of the above method uses salts of sulfonyl hydrazones under photolytic or thermal conditions (Scheme 2).[7]



3 **2** **4**

Scheme 2

Although not of any synthetic value, the photolysis of diazirines and epoxides have been shown to generate carbenes (Scheme 3).[8]

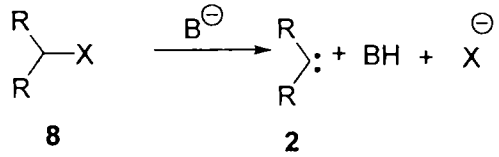


5 **2**

6 **2** **7**

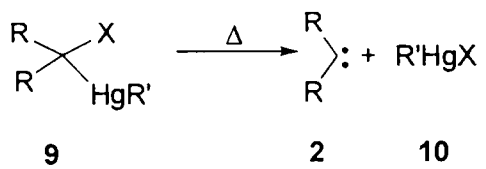
Scheme 3

Organic halides under strong basic conditions or on reaction with organometallic compounds generate carbenes (Scheme 4).[9]



Scheme 4

Another method employed involves the thermolysis of Seyferth reagents (Scheme 5).[10]



R = alkyl, aryl etc.; R' = aryl

Scheme 5

1.1.3 Structure and Reactivity Profiles of Carbenes

Depending on the spin multiplicity, carbenes are divided into singlet and triplet states. Singlet carbenes feature a filled and a vacant orbital, thereby showing ambiphilic character while triplet carbenes have two singly occupied orbitals and are generally regarded as diradicals (Figure 1).

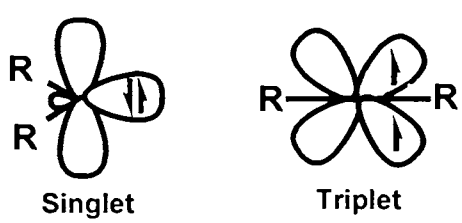
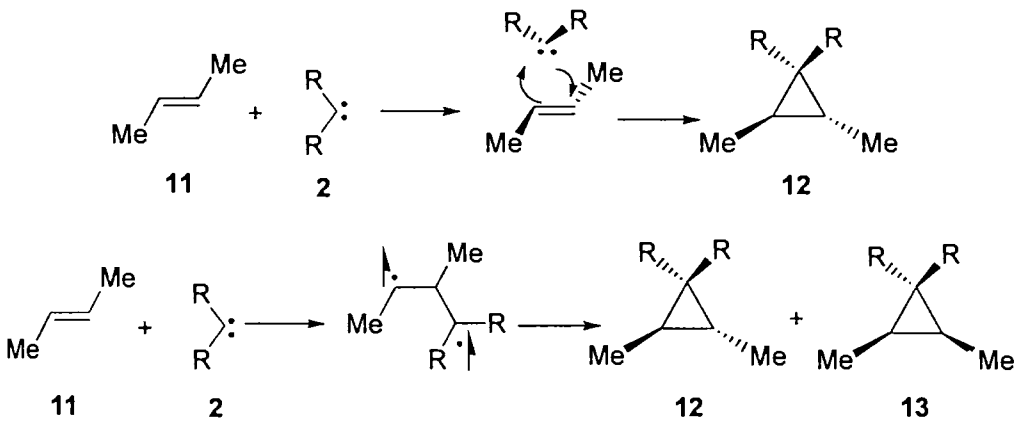


Figure 1

1.1.3a Addition Reactions of Carbenes

Carbene additions to alkenes are the best studied reactions of these intermediates and the addition results in the formation of a cyclopropane derivative. Both singlet and triplet carbenes undergo this reaction and it is possible to find out the spin state of the carbene by observing differences in the stereochemistry of the products formed. A one step mechanism is possible for singlet carbenes thereby affording a single cyclopropane derivative having the

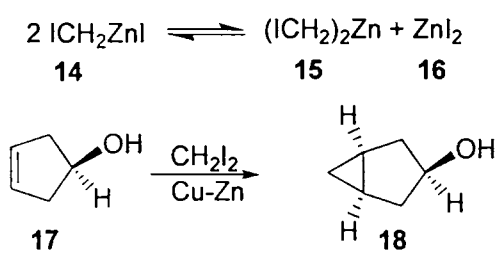
same stereochemistry as the starting olefin. In the case of triplet carbenes, due to the intermediacy of diradicals, the cyclopropanes formed will be mixtures of the two possible stereoisomers (Scheme 6).[11]



Scheme 6

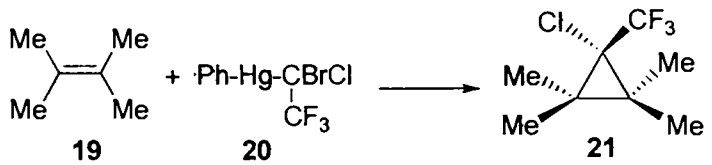
Several methods have been developed for the synthesis of cyclopropanes from alkenes by the addition of carbenes. Some of these methods are discussed below.

A very effective method for converting an alkene to cyclopropane by transfer of a methylene involves the use of methylene iodide and Zn-Cu couple system, commonly known as Simmons-Smith reagent. The addition is stereo specific and the active species involved is believed to be the iodomethylzinc iodide in equilibrium with (*bis*) iodomethyl zinc (Scheme 7).[12]



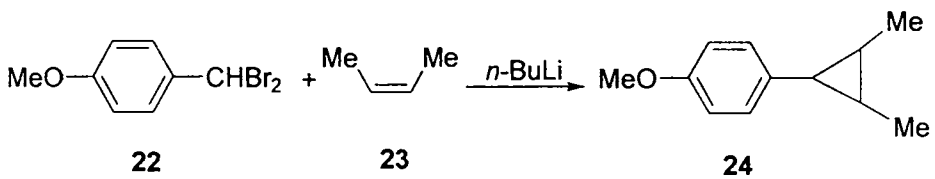
Scheme 7

Seyferth reagents are also found to be effective for cyclopropanation (Scheme 8).[10]



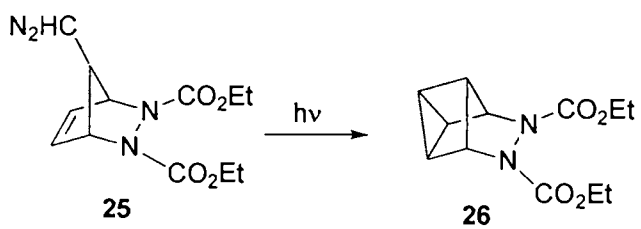
Scheme 8

The α-elimination of organic halides with strong bases in the presence of an alkene is also used as a method for generating cyclopropanes, but this method is seldom used in organic synthesis (Scheme 9).[13]



Scheme 9

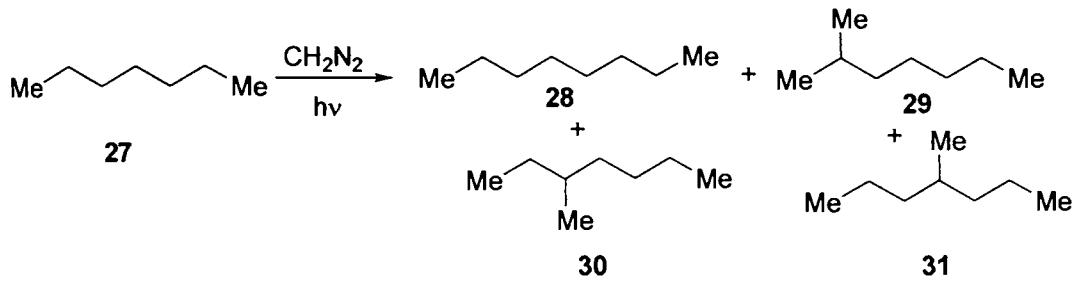
Intramolecular cyclopropanation reactions are considered to be important in organic synthesis, since this method provides an easy access to highly strained ring compounds (Scheme 10).[14]



Scheme 10

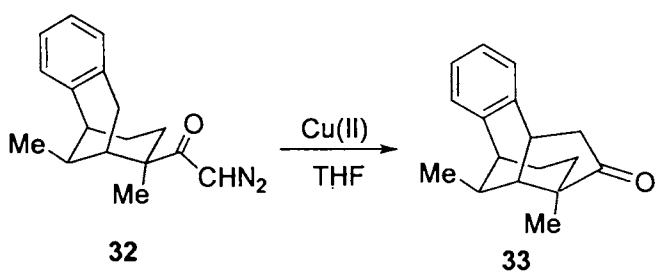
1.1.3b Insertion Reactions of Carbenes

The most common carbene insertion reactions involve C-H bonds and in these reactions the reactive intermediate interposes itself into an existing bond. Due to the high energy of the intermediates involved, these reactions are found to be very unselective (Scheme 11).[15]



Scheme 11

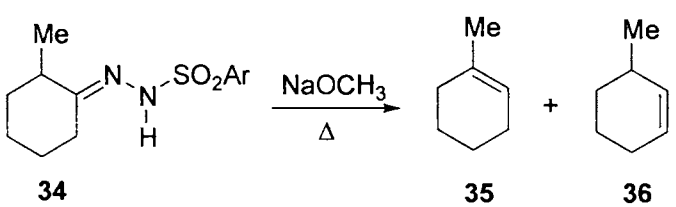
Intramolecular insertion reactions of carbenes into C-H bonds are synthetically useful for the preparation of strained molecules or cage systems (Scheme 12).[16]



Scheme 12

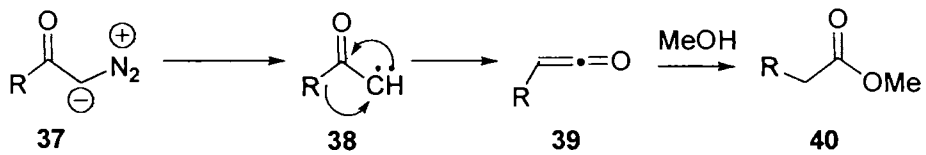
1.1.3c Rearrangement Reactions of Carbenes

The presence of a vacant *p*-orbital enables carbenes to undergo facile rearrangement reactions. The most common among them is the migration of hydrogen to generate an alkene (Scheme 13).[17]



Scheme 13

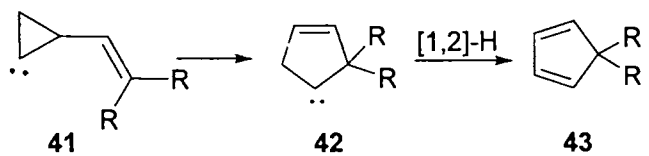
The best known carbene rearrangement is the Wolff rearrangement of diazo ketones to ketenes (Scheme 14).[18]



37 38 39 40

Scheme 14

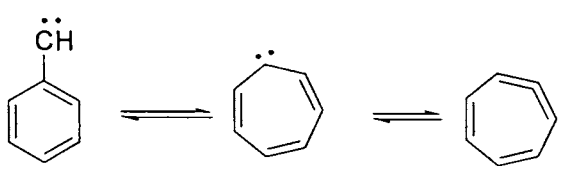
Another rearrangement reaction involving carbenes is the Skattebøl rearrangement in which a vinyl cyclopropylidene undergoes rearrangement to form a cyclopentadiene (Scheme 15).[19]



41 42 43

Scheme 15

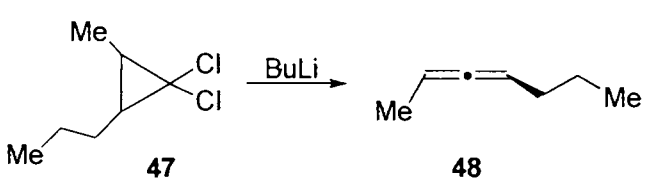
Similarly aryl carbenes undergo a series of rearrangements when generated in gas phase to afford cycloheptatrienylidene, which on further rearrangement affords a highly strained cycloheptatetraene derivative (Scheme 16).[20]



44 45 46

Scheme 16

Cyclopropylidenes, generated under suitable conditions, undergo rearrangement to afford allene derivatives. For instance, the dihalocyclopropane **47** undergoes rearrangement in presence of butyl lithium to afford the allene derivative **48** (Scheme 17).[21]

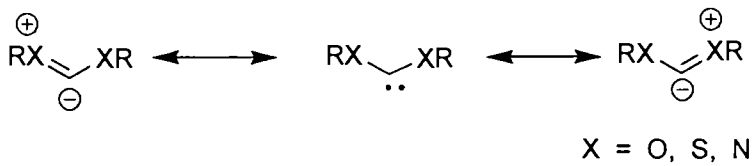


47 48

Scheme 17

1.1.3d Nucleophilic Carbenes

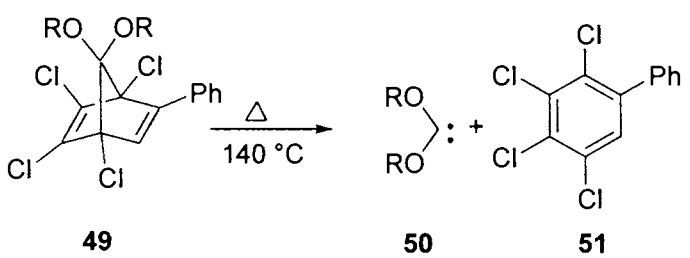
Nucleophilic carbenes are characterized by the presence of substituents having donor atoms such as oxygen, nitrogen and sulfur. The nucleophilicity of these species is a direct consequence of the donation of lone pairs of heteroatoms into the formally vacant *p*-orbital of the carbene carbon. This strongly stabilizes the singlet state and imparts dipolar character (Scheme 18).[22]



Scheme 18

1.1.3e Generation and Reactivity Patterns of Dialkoxycarbenes

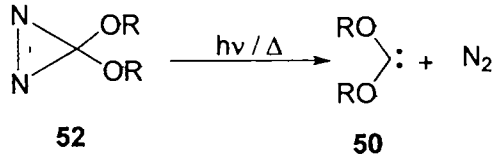
Only a few general methods are available in the literature for the generation of dialkoxycarbenes. The first method developed by Hoffmann in 1971, is based on the thermolysis of norbornadiene ketals. The method is limited to the preparation of only a few alkoxycarbenes and is unsuitable for unsymmetrical carbenes. Moreover the by-products from thermolysis of **49** can interfere with the isolation of products from the reactions of dialkoxycarbenes (Scheme 19).[23]



49 **50** **51**

Scheme 19

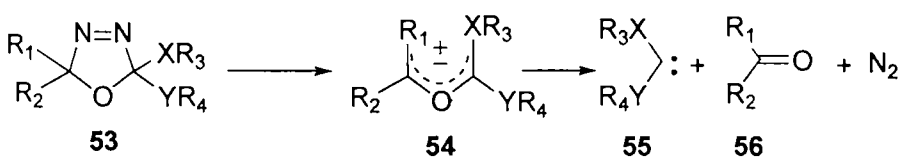
Later, Moss and coworkers have developed a method based on the photolysis or thermolysis of dialkoxy diazirines. The hazardous nature of these compounds, however, precludes their use in synthetic chemistry (Scheme 20).[24]



52 50

Scheme 20

The identification of Δ^3-1,3,4-oxadiazolines as a versatile source of various nucleophilic carbenes by Warkentin can be considered as a milestone in the development of the chemistry of dialkoxycarbenes.[25] The oxadiazolines undergo thermolysis at *ca* 100 °C in solution to afford the corresponding heteroatom substituted carbenes. The initial event in the thermal decomposition of oxadiazolines is a cycloreversion, forming carbonyl ylides of type **54**. These dipolar intermediates, with a few exceptions, are not trapped under the reaction conditions. Instead, they undergo successive fragmentation to the corresponding stable singlet carbenes. The ready accessibility and stability of oxadiazolines make them attractive source of dialkoxycarbenes (Scheme 21).[26]

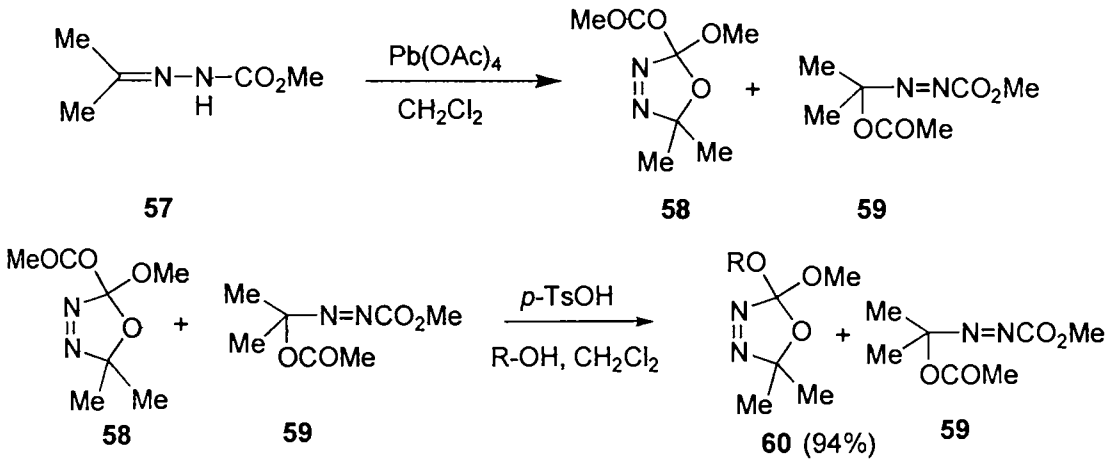


53 54 55 56

Scheme 21

These carbene precursors are readily available by the oxidation of alkoxycarbonyl hydrazones of acetone with lead tetraacetate (LTA).[27] The use of other oxidizing agents like phenyl iodonium acetate has been reported.[28] Electrochemical oxidation of ketone hydrazones to oxadiazolines is also known.[29] The LTA oxidation affords a mixture of 2-acetoxy-2-methoxy-5,5-dimethyl Δ^3-1,3,4-oxadiazoline **58** and an acyclic azo compound **59**, which on acid catalyzed displacement reaction with a suitable alcohol affords the required oxadiazoline **60** along with unchanged **59**. Selective removal of the latter is achieved by hydrolysis with aqueous base. The advantage of this

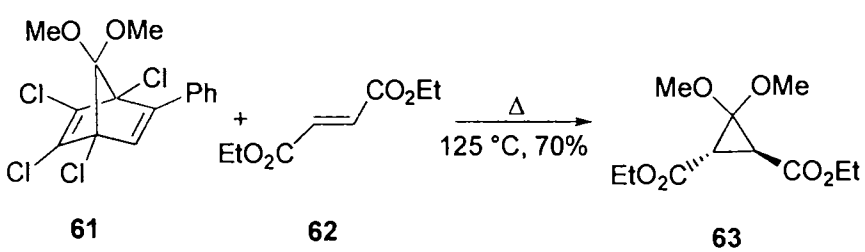
method is that a single acetoxy substrate **58** can serve as the source of different oxadiazolines (Scheme 22).[30]



Scheme 22

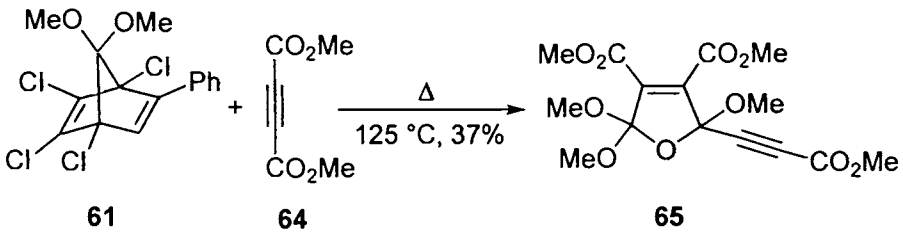
The chemistry of dialkoxycarbenes, especially dimethoxycarbene was the subject of intense investigations by Hoffmann and later by Warkentin, a brief account of which is given in the following passages.

The reactivity of dimethoxycarbene towards electron deficient alkenes and alkynes was studied by Hoffmann. He has demonstrated that dimethoxycarbene, generated by the thermolysis of the acetal **61** undergoes facile addition to diethyl maleate or fumarate to afford the corresponding cyclopropane derivative (Scheme 23).[31]



Scheme 23

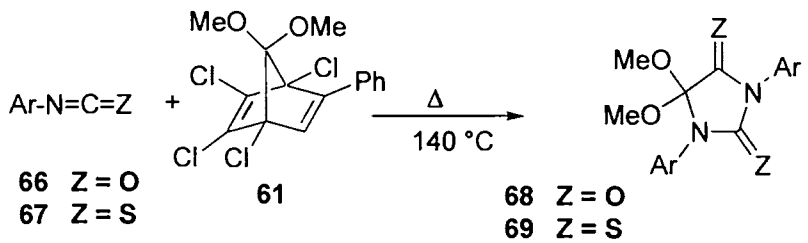
Similarly, the addition of dimethoxycarbene to an electron deficient alkyne such as dimethyl acetylenedicarboxylate afforded the dihydrofuran derivative **65** in low yield (Scheme 24).[31]



61 64 65

Scheme 24

The addition of dimethoxycarbene to heterocumulenes such as aryl isocyanates and aryl isothiocyanates leads to the formation of substituted hydantoins and thiohydantoins respectively (Scheme 25).[32]



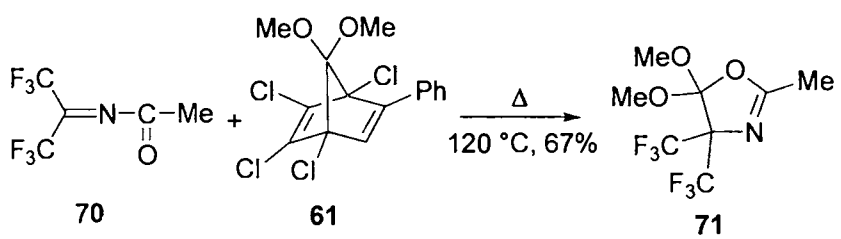
66 Z = O
67 Z = S

61

68 Z = O
69 Z = S

Scheme 25

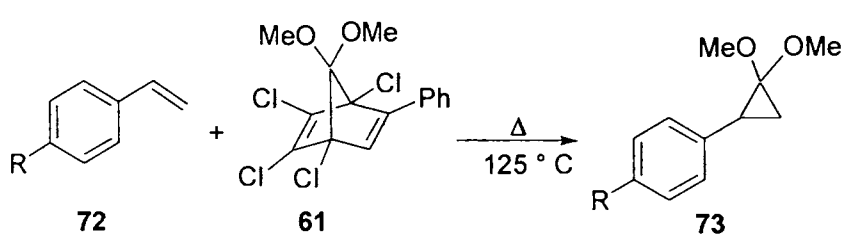
Dialkoxycarbenes undergo addition reactions with acylimines affording oxazolines (Scheme 26).[33]



70 61 71

Scheme 26

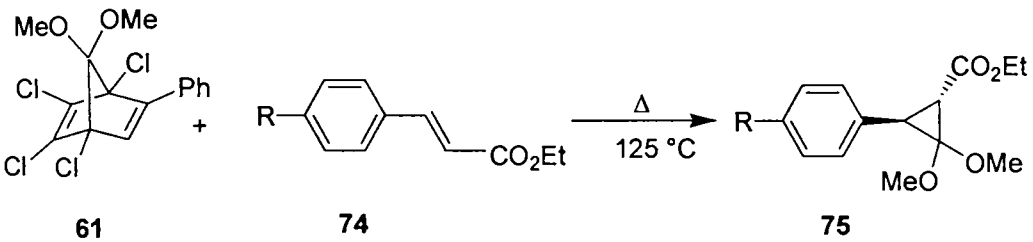
Styrenes were also found to undergo reaction with dimethoxycarbene to afford cyclopropane derivatives (Scheme 27).[31]



72 61 73

Scheme 27

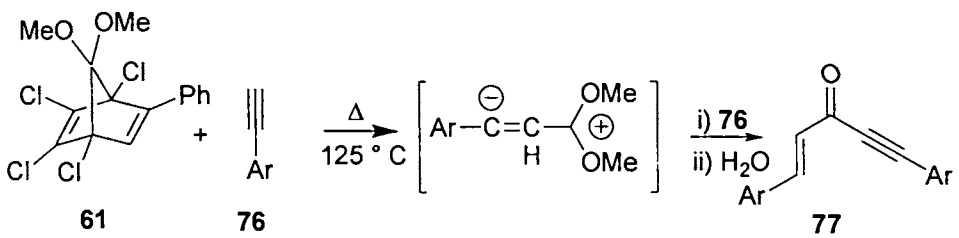
Under similar reaction conditions, α,β-unsaturated esters also afforded cyclopropane derivatives (Scheme 28).[31]



61 74 75

Scheme 28

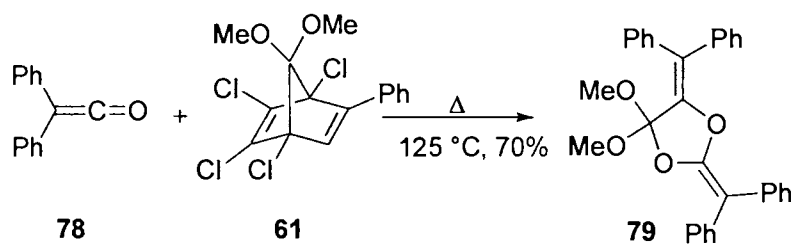
Dimethoxycarbene on reaction with aryl acetylenes furnished the corresponding 1:2 adduct as shown in Scheme 29.[31]



61 76 77

Scheme 29

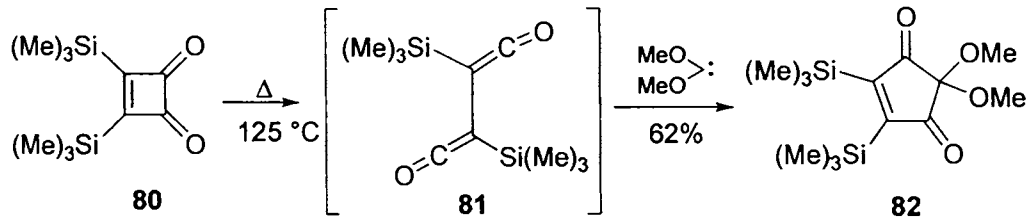
The addition of dimethoxycarbene to diphenyl ketene afforded the cyclized product **79** in good yield (Scheme 30).[31]



78 61 79

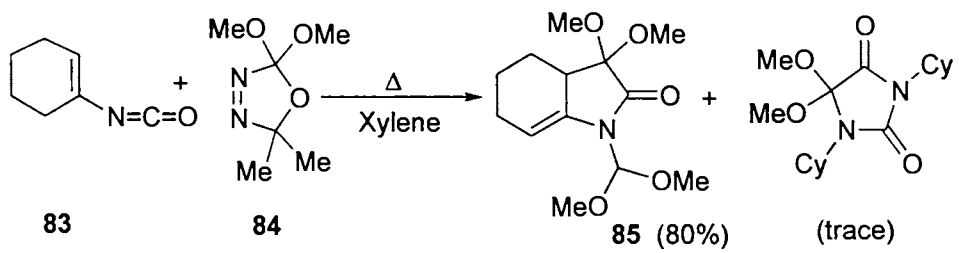
Scheme 30

Warkentin has demonstrated that bisketene generated by the thermolysis of cyclobutenedione **80** undergoes facile addition to dimethoxycarbene to afford cyclopentenedione derivative **82** (Scheme 31).[34]



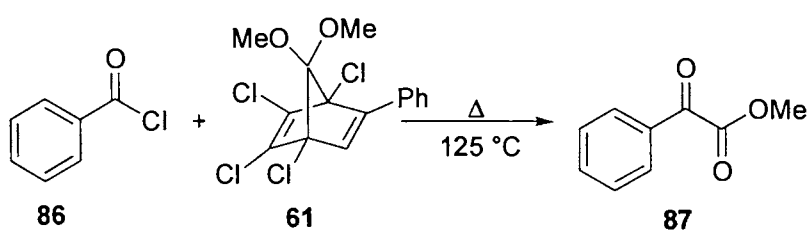
Scheme 31

Recently, Rigby has reported the [4+1] cycloaddition of dimethoxycarbene with vinyl isocyanates leading to the formation of hydroindolone derivatives along with the by-product **68** (Scheme 32).[35]



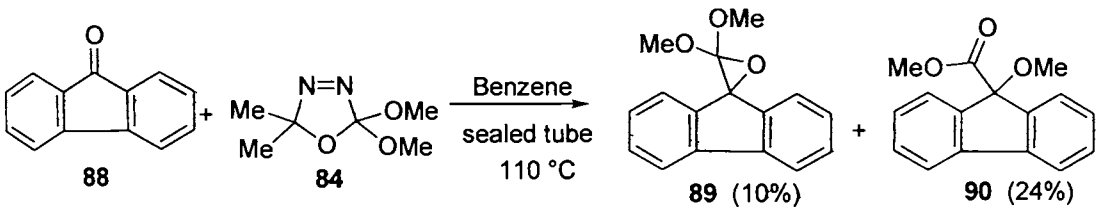
Scheme 32

Hoffmann has reported the reaction of dimethoxycarbene with benzoyl chloride **86** affording methyl benzoyl formate **87** (Scheme 33).[31]



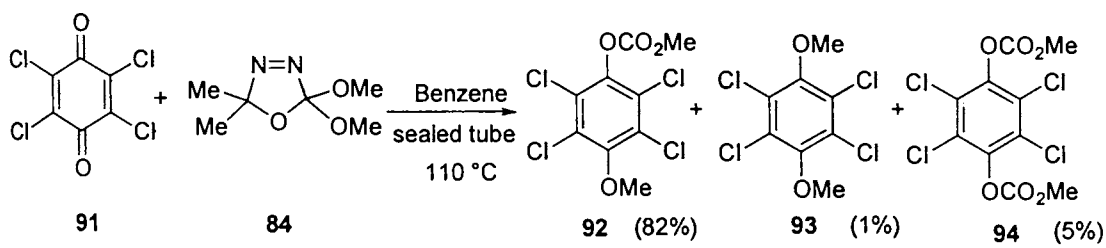
Scheme 33

The reaction of dimethoxycarbene generated by the thermolysis of oxadiazoline **84** with 9-flourenone afforded 9-(dimethoxy methylene)-fluorene oxide **89** and methyl 9-methoxyfluorene-9-carboxylate **90** (Scheme 34).[36]



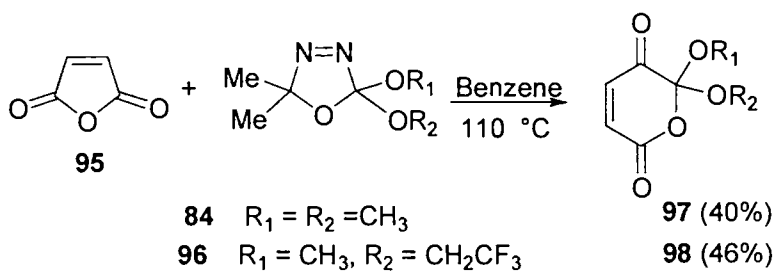
Scheme 34

Dimethoxycarbene was found to react with quinonoid compounds such as *p*-chloranil to afford products resulting from nucleophilic addition of the carbene to the carbonyl group (Scheme 35).[37]



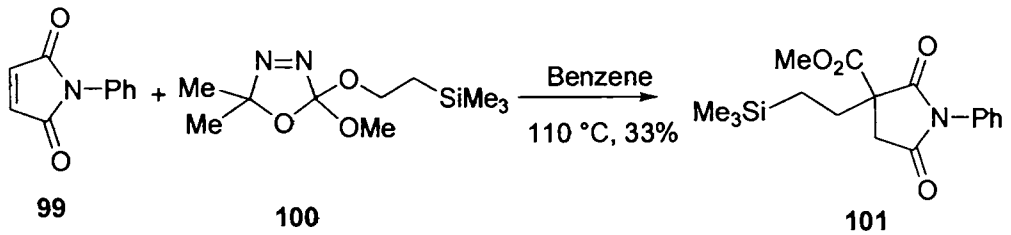
Scheme 35

A variety of cyclic anhydrides are reported to react with dialkoxycarbenes leading to the corresponding ring enlarged products (Scheme 36).[38]



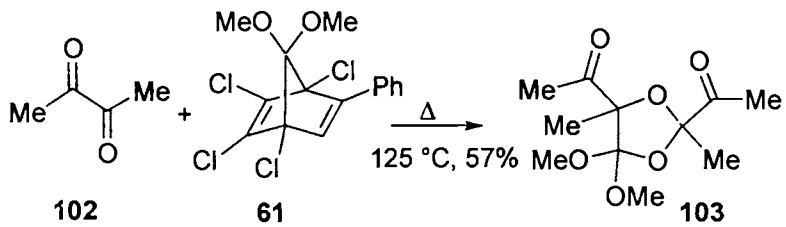
Scheme 36

However, the reaction of methoxy(trimethylsilyl)ethoxycarbene, generated by the thermolysis of oxadiazoline **100** with *N*-phenyl maleimide, followed a different reaction pathway leading to the formation of product **101** *via* the migration of the trimethylsilyl group (Scheme 37).[39]



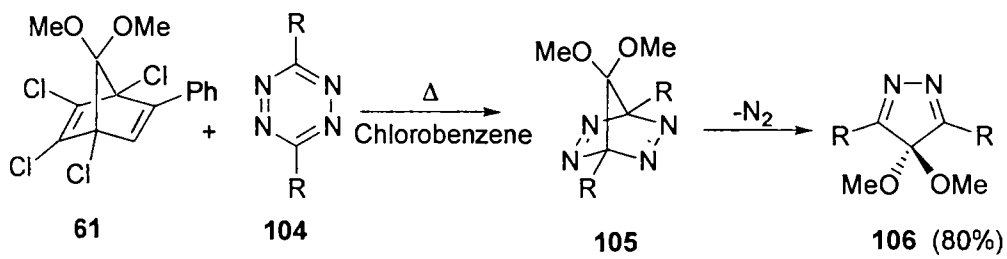
Scheme 37

1,2-diones such as 2,3-butanedione reacts with dimethoxycarbene to form the cyclic compound **103** as shown in Scheme 38.[33]



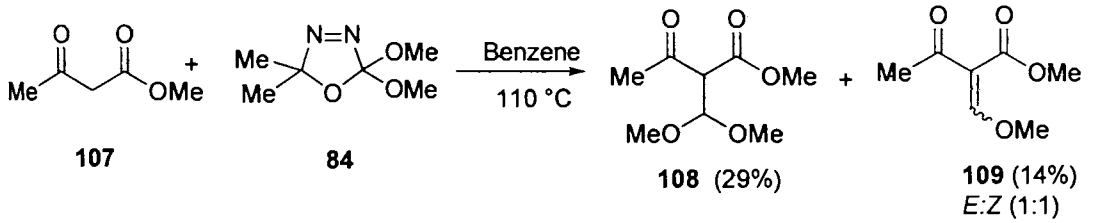
Scheme 38

Dimethoxycarbene generated from the acetal **61** has been intercepted with triazines to afford the corresponding pyrazole *via* the [4+1] cycloaddition of carbene followed by subsequent cycloreversion (Scheme 39).[40]



Scheme 39

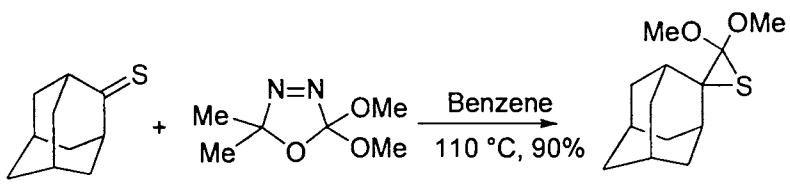
1,3-dicarbonyl compounds were also found to undergo reaction with dialkoxycarbenes. The reaction of methylacetoacetate with oxadiazoline **84** afforded the corresponding carbene inserted product **108** along with the alkene **109** formed by methanol elimination. Related insertions into alcohols and phenols afford the corresponding orthoformates (Scheme 40).[41]



107 84 **108** (29%) **109** (14%) *E*:*Z* (1:1)

Scheme 40

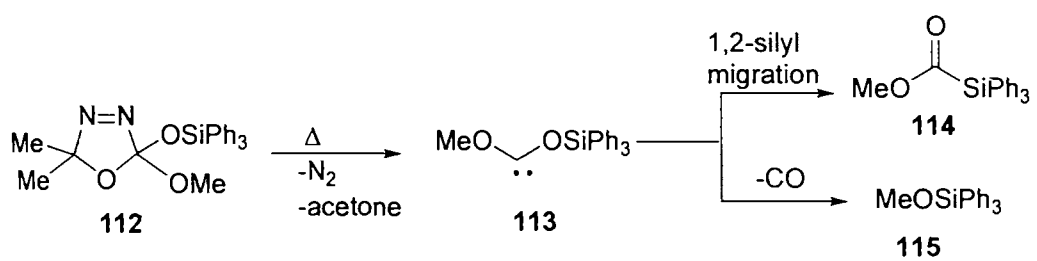
Warkentin and co-workers have shown that the carbene generated by the thermolysis of the oxadiazoline **84** reacts with adamantane thione **110** to afford 1,1-dimethoxy thiirane **111** as a stable solid in excellent yield (Scheme 41).[42]



110 **84** **111**

Scheme 41

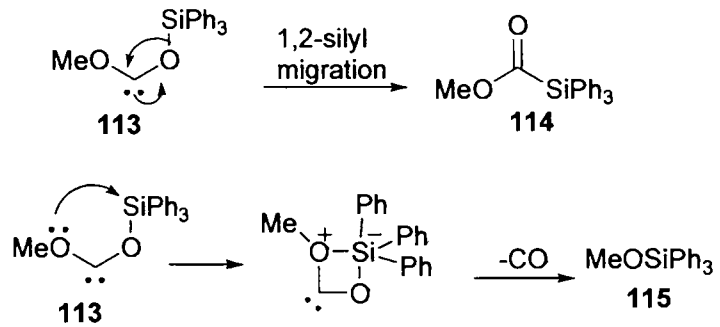
They have also shown that the thermolysis of 2-methoxy-2-triphenyl siloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline affords methyl triphenylsilyl formate and methyl triphenylsilyl ether *via* methoxy triphenyl siloxy carbene (Scheme 42).[43]



112 **113** **114** **115**

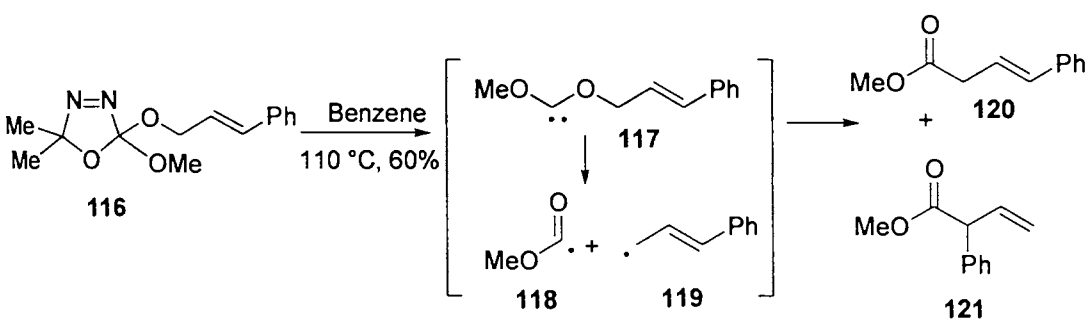
Scheme 42

A probable mechanism for this transformation is depicted in Scheme 43.



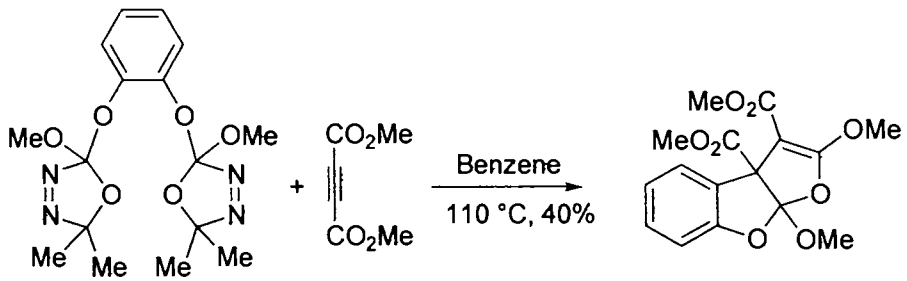
Scheme 43

Similarly the thermolysis of 2-cinnamyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline afforded the products **120** and **121** in the ratio 2:1. The carbene generated under the reaction conditions undergoes a "β-scission" to afford radical pairs, which on subsequent rearrangement and recombination afforded the corresponding products. The formation of free radical intermediates in this reaction was confirmed by interception using radical scavengers such as TEMPO (Scheme 44).[44]



Scheme 44

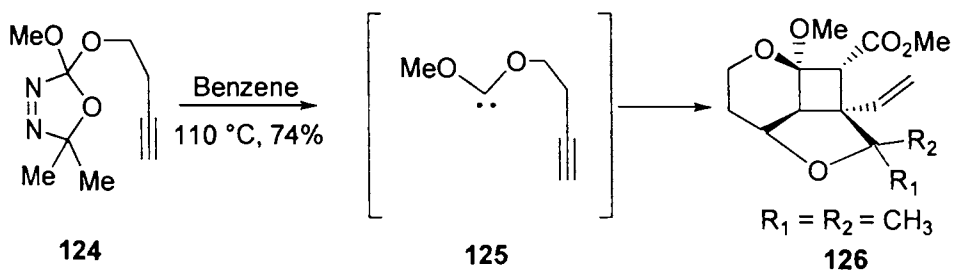
In a mechanistically intriguing reaction, the thermolysis of *bis* oxadiazoline **122** in presence of DMAD afforded the benzofused tricyclic compound **123** in moderate yield (Scheme 45).[45]



122 64 123

Scheme 45

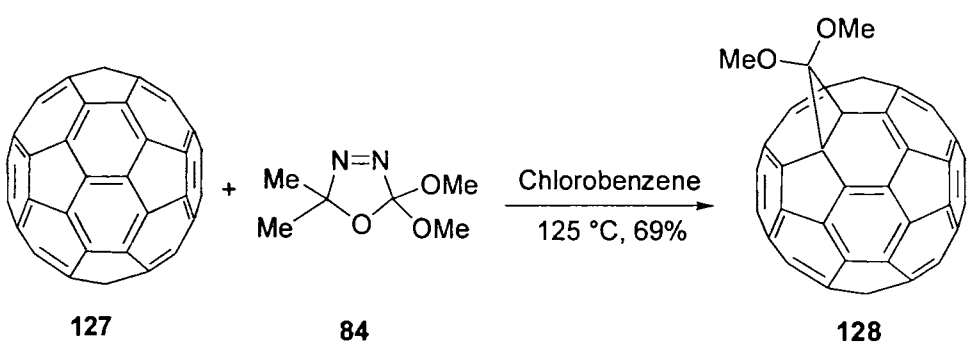
Similarly, it has been reported that on thermolysis, oxadiazolines substituted with alkyne functionalities undergo an interesting rearrangement to furnish the tricyclic product **126** in good yield (Scheme 46).[46]



124 125 126

Scheme 46

The reaction of dimethoxycarbene with C_{60} fullerene was reported to afford the dimethoxy methanofullerene derivative (Scheme 47).[47]

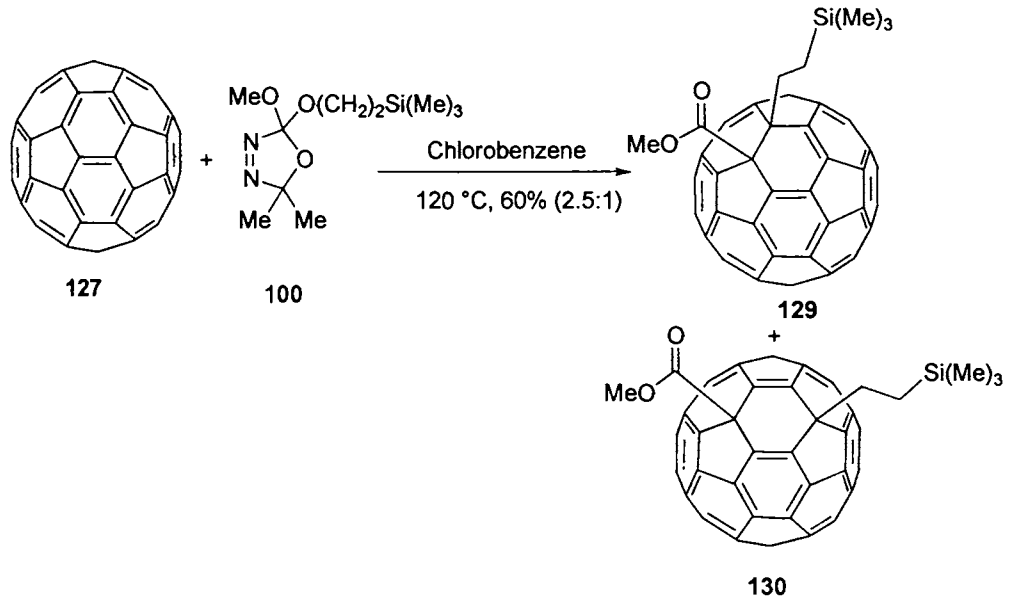


127 84 128

Scheme 47

The thermolysis of methoxy(2-trimethylsilyl)ethoxycarbene in presence of C_{60}, however, did not afford the dialkoxy methanofullerene derivative;

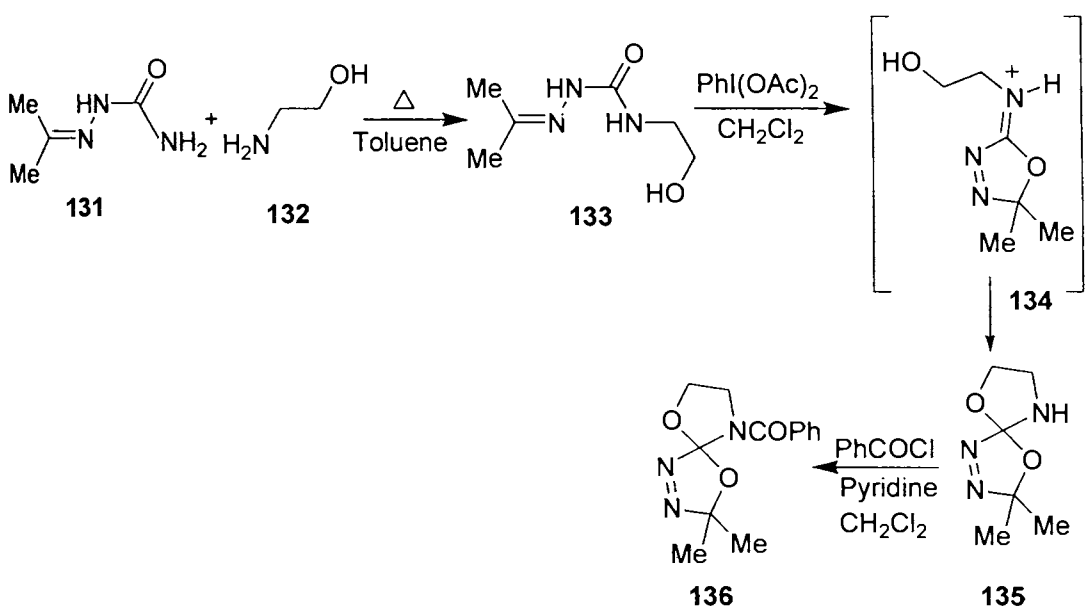
instead it afforded the products **129** and **130** *via* rearrangement reactions (Scheme 48).[47]



Scheme 48

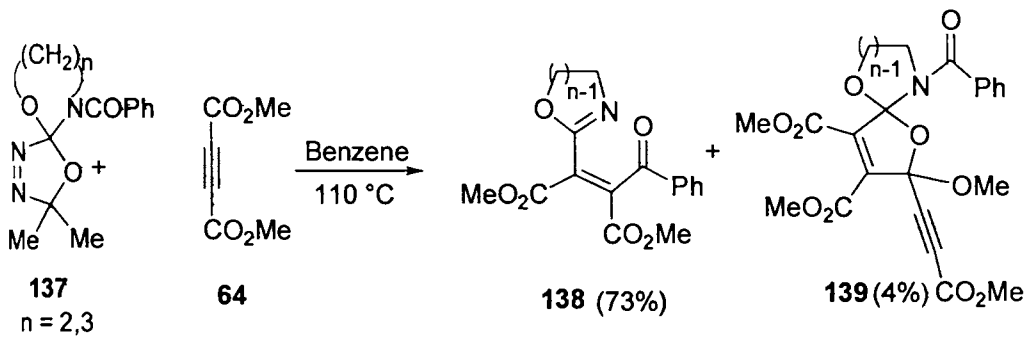
1.1.3f Generation and Reactivity Patterns of Alkoxyamino Carbenes

Warkentin has demonstrated that alkoxy aminocarbenes can be generated by the thermolysis of alkoxyamino oxadiazolines of the type **136**, the synthesis of which is outlined in Scheme 49.[48]



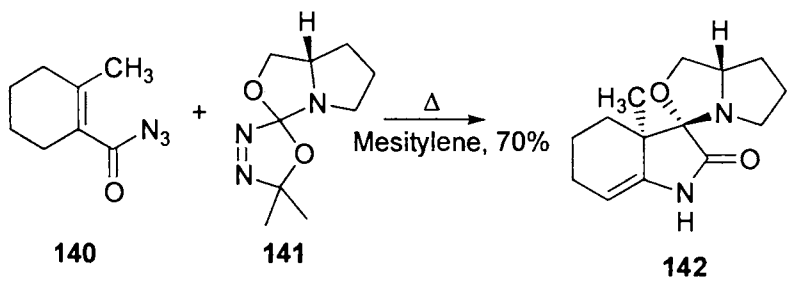
Scheme 49

The reaction of these carbenes with activated triple bonds has been reported (Scheme 50).[48]



Scheme 50

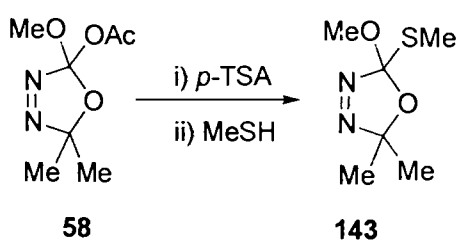
Recently Rigby and coworkers have investigated the [4+1] cycloaddition of alkoxy amino carbenes with vinyl isocyanates and this strategy has been applied for the synthesis of enantiopure hydroisatin (Scheme 51).[49]



Scheme 51

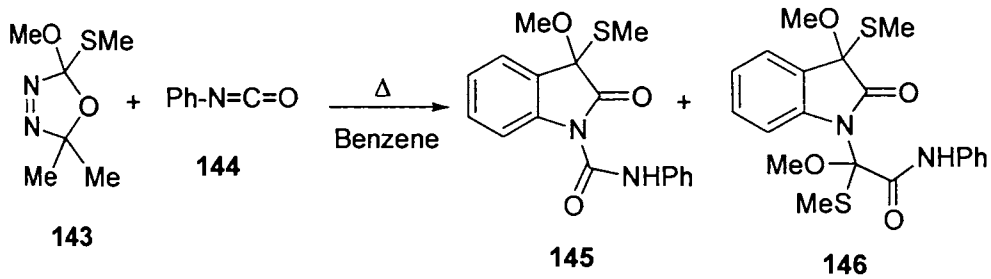
1.1.3g Generation and Reactivity Pattern of Alkoxy Alkylthiocarbenes

The alkoxy alkylthiocarbenes can be conveniently prepared from the precursor **143**, which in turn was obtained from the acetoxy oxadiazoline **58** by acid catalyzed exchange reaction with the corresponding thiol (Scheme 52).[50]



Scheme 52

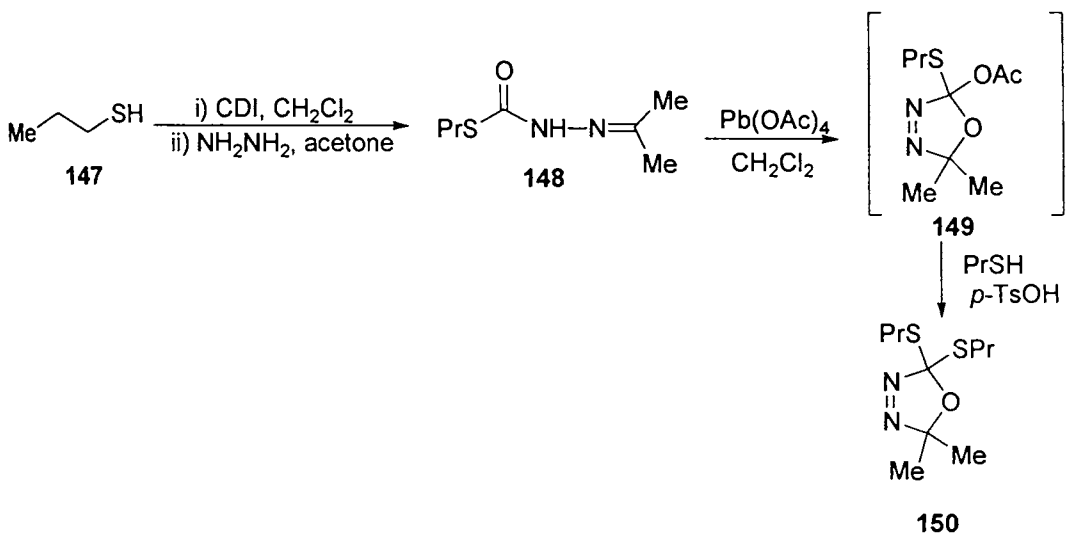
The alkoxy alkylthio oxadiazolines undergo thermolysis at 60-80 °C in solution to generate alkoxy thiocarbenes and they have been intercepted with suitable electrophiles such as DMAD, phenyl isocyanate, ethyl crotonate *etc.* A typical example involving phenyl isocyanate is shown in Scheme 53.[50]



Scheme 53

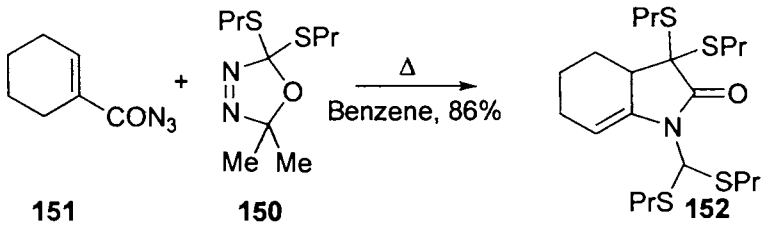
1.1.3h Generation and Reactivity Patterns of Dithiocarbenes

Dithiocarbenes are generated by the thermolysis of the corresponding dithio oxadiazolines, which in turn are prepared by a slight modification of the Warkentin protocol as depicted in Scheme 54.[51]



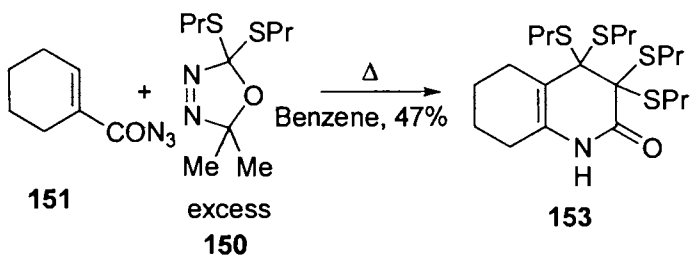
Scheme 54

The thermolysis of the dithio oxadiazoline **150** in presence of acyl azide afforded the corresponding hydroindolone derivative **152** in good yield (Scheme 55).[52]



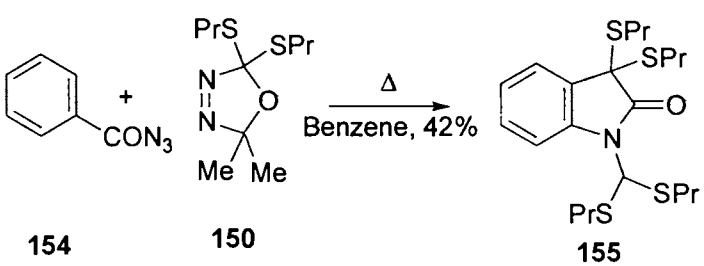
Scheme 55

The use of excess of oxadiazoline, however, afforded the hydropyridone derivative **153** (Scheme 56).[52]



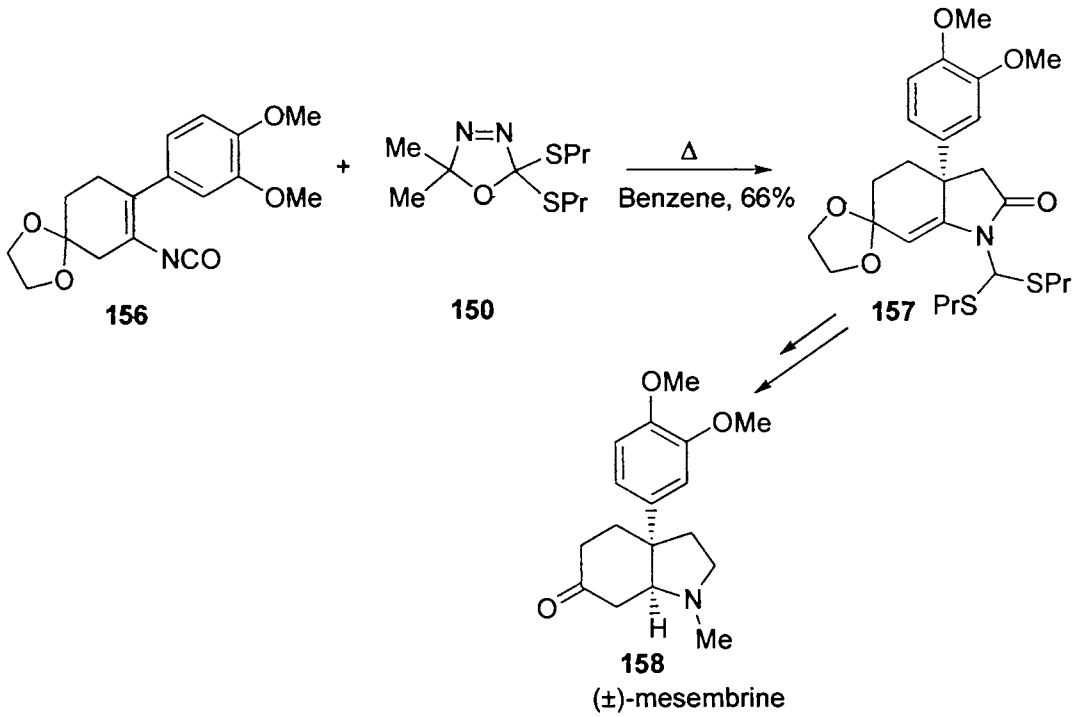
Scheme 56

The *bis* (alkylthio)carbenes undergo a [4+1] cycloaddition with aryl isocyanates to furnish isatin derivatives (Scheme 57).[53]



Scheme 57

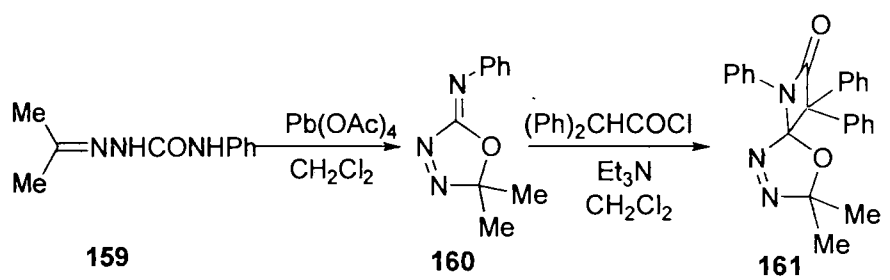
Rigby and coworkers have applied the strategy of [4+1] cycloaddition of dithiocarbenes with functionalized vinyl isocyanates in the total synthesis of (±) mesembrine **158** (Scheme 58).[54]



Scheme 58

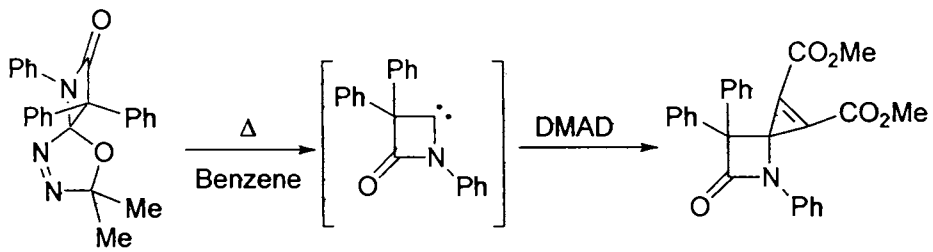
1.1.3i Generation and Reactivity Pattern of β-Lactam-4-ylidenes

Warkentin has shown that β-lactam ylidenes can be generated by the thermolysis of spiro fused β-lactam oxadiazolines of the type **161**. These compounds are prepared by the [2+2] cycloaddition of an imino oxadiazoline **160** with a ketene generated *in situ* (Scheme 59).[55]



Scheme 59

The β-lactam ylidene **162** generated by the thermolysis of **161** is reported to react with activated and unactivated alkenes and alkynes affording the cyclopropane derivatives. A typical example involving DMAD is shown below (Scheme 60).[56]



161 162 163 (33%)

Scheme 60

1.1.3j Generation and Reactivity Patterns of Diaminocarbenes

An introduction to the generation and reactivity profiles of diaminocarbenes is presented in Chapter 4 (see section 4.1 in Chapter 4).

1.2 Multicomponent Reactions

Conventional preparative procedures in organic synthesis involve stepwise formation of individual bonds and are often tedious and involve many synthetic steps. Reactions in which more than two starting materials react to form a product in such a way that the majority of the atoms of the starting materials can be found in the product are called multicomponent reactions (MCRs).[57] The reagents employed may be different molecules or they may be different functional groups of the same reagent. These reactions can either be carried out in solution or on a solid support.

Multicomponent reactions are further classified in to three basic types as shown in Table 1.

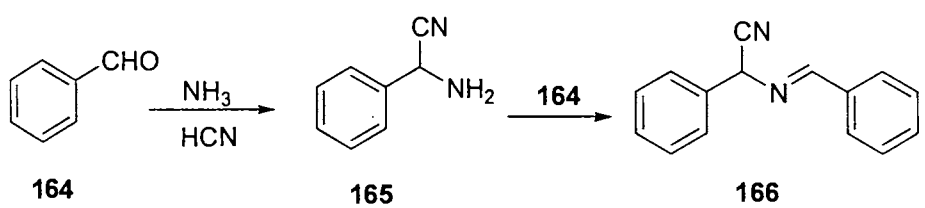
MCR type	General Reaction Scheme
I	A+B ⇌ C ⇌ .....O ⇌ P
II	A+B ⇌ C ⇌ D.....O ⇌ P
III	A → B+C → D → ....O → P

Table 1

In the type I MCRs, the starting materials, intermediates and products are in a mobile equilibrium. MCRs whose elementary reactions involve either equilibria or partial irreversible reactions and whose last step is irreversible belong to type II. Reactions of this type are preparatively advantageous as the

total equilibrium is shifted to the side of the products by the last irreversible step. Type III MCRs comprise sequences of elementary reactions and they seldom occur in preparative chemistry. A number of advantages make MCRs attractive both in organic and combinatorial synthesis *viz.*, simple procedures, facile execution, atom economy, convergence and ecofriendliness. MCRs offer great promise in the synthesis of heterocycles and are especially remarkable for their ease of execution and come closer to ideal synthesis defined by Wender.[58]

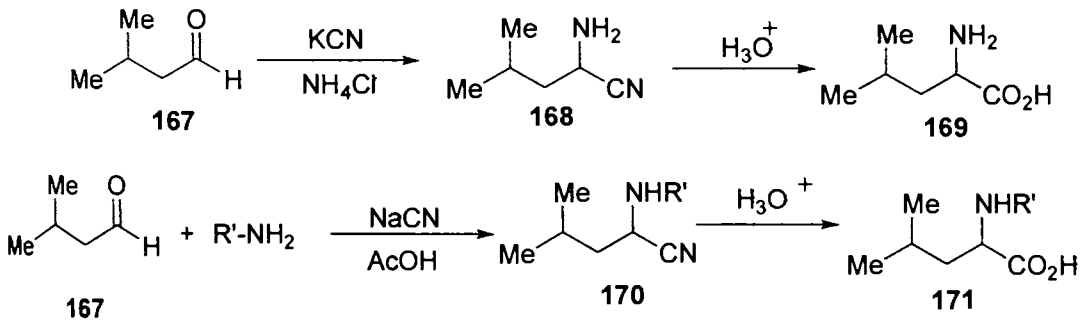
The history of MCRs can be traced to the work of Laurent and Gerhardt when they prepared "benzoylazotide" from bitter almond oil and ammonia. In this reaction, benzaldehyde undergoes a Strecker reaction with hydrocyanic acid and ammonia to give aminobenzyl cyanide **165** whose Schiff base with benzaldehyde has been isolated as the so called "benzoylazotide" (Scheme 61).[59]



164 **165** **166**

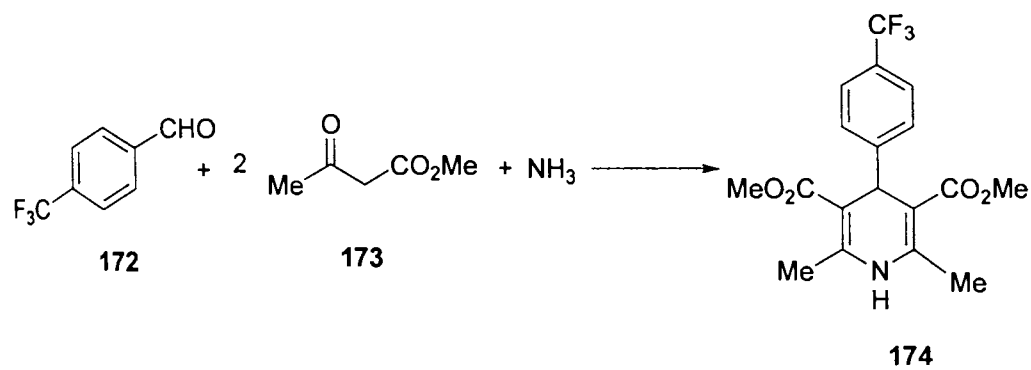
Scheme 61

The Strecker amino acid synthesis, reported in the 1850s is considered as another important multicomponent reaction. This involves the three component condensation of ammonia, an aldehyde and hydrogen cyanide to afford an α-amino nitrile which on subsequent hydrolysis furnishes the α-amino acid derivative. Safer, milder and more selective reaction conditions have been developed and the reaction has been extended to include primary and secondary amines (Scheme 62).[60]



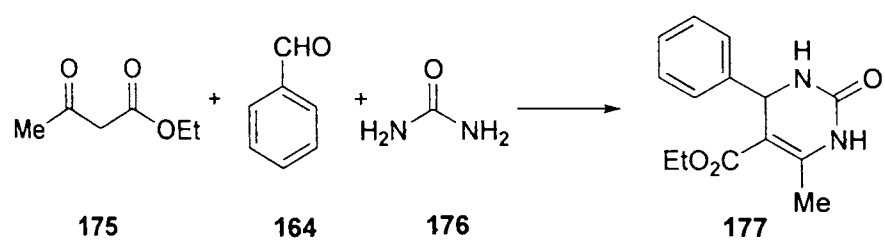
Scheme 62

The synthesis of 1,4-dihydropyridines of the type **174** from ammonia, aldehyde and acetoacetic ester has been reported a century ago by Hantzsch and coworkers (Scheme 63).[61] Recently, this methodology has been applied to the synthesis of Nifedipin®, an important drug used in cardiovascular therapy.



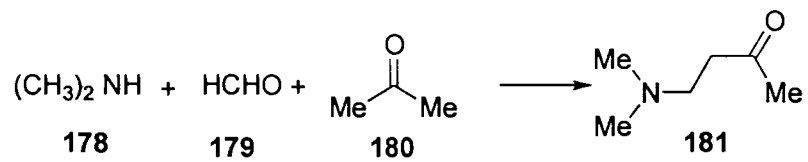
Scheme 63

The Biginelli condensation of an aldehyde, β-keto ester and urea leading to the synthesis of dihydropyrimidines is considered as another important multicomponent reaction. The dihydropyrimidine derivatives are compounds with important biological properties and they play a prominent role as calcium antagonistic reagents (Scheme 64).[62]



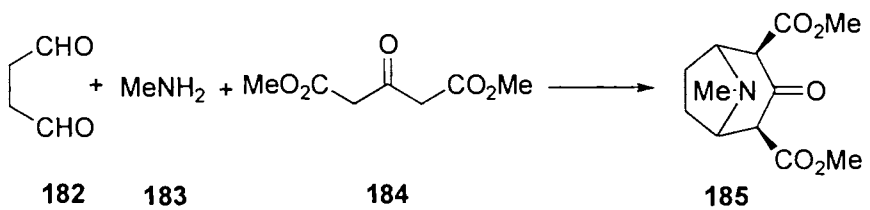
Scheme 64

A commonly used and important multicomponent reaction is the Mannich reaction, which involves a one pot synthesis of amino methylated carbonyl compounds from formaldehyde, secondary amine and ketones (Scheme 65). This reaction has proved to be extremely valuable in the total synthesis of several natural products.[63]



Scheme 65

Robinson's Tropinone synthesis from succinic aldehyde, methylamine and dimethyl acetonedicarboxylate provides a spectacular example of the application of MCRs in natural product synthesis (Scheme 66).[64]

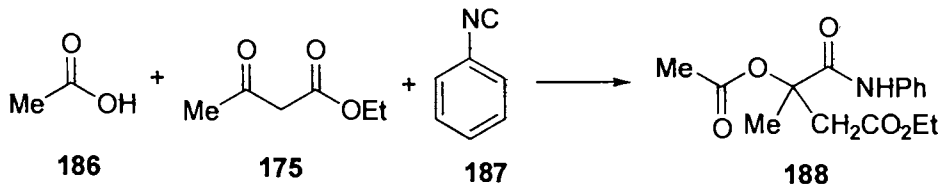


Scheme 66

Among the large class of multicomponent reactions reported so far, the major and the most successful ones are isocyanide based multicomponent reactions (IMCRs). The most important IMCRs are the Passerini 3-component reaction (P-3CR) and the Ugi 4-component reaction (U-4CR), a brief account of which is given in the following sections.

1.2.1 Passerini Reaction

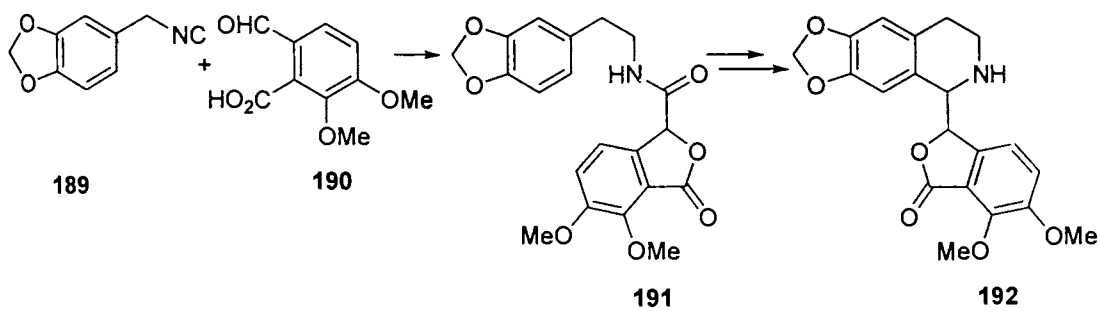
The formation of α-acyloxy carboxamides **188** by the three component reaction between isocyanides, carboxylic acids and carbonyl compounds is known as the Passerini reaction, an example of which is given in the following scheme (Scheme 67).[65]



186 175 187 188

Scheme 67

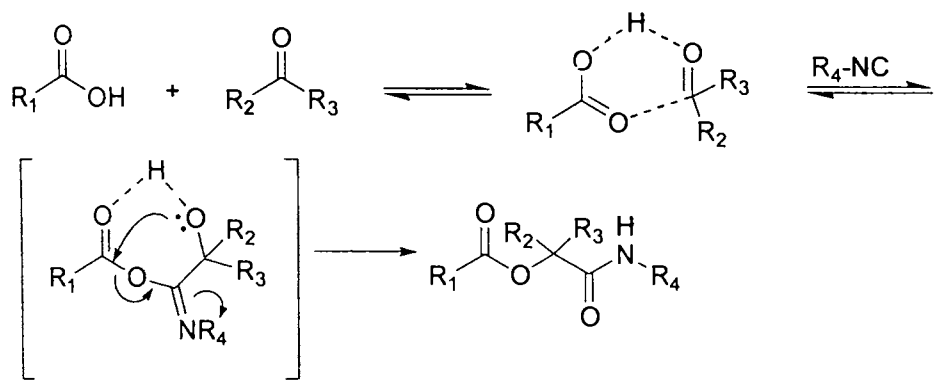
The reaction has been applied to the total synthesis of many natural products; a typical example involving the total synthesis of an alkaloid (±)-hydrastine **192** is outlined below (Scheme 68).[66]



189 190 191 192

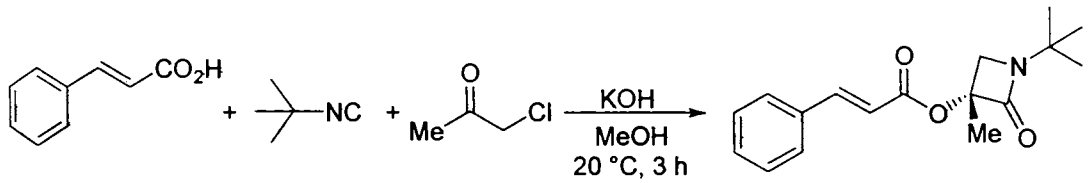
Scheme 68

The Passerini reaction is accelerated in aprotic solvents, indicating a non-ionic mechanism. A mechanistic rationale for this reaction is shown in Scheme 69.



Scheme 69

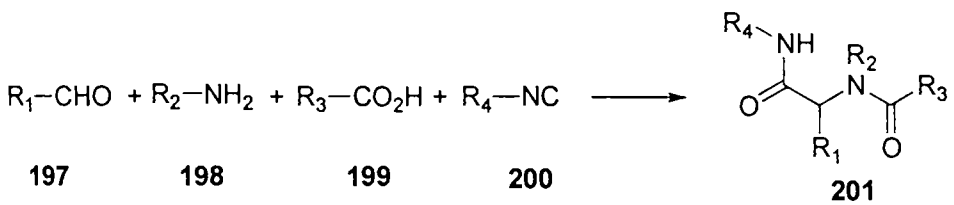
A variant of this reaction employing an α-chloroketone **195**, isocyanide **194** and carboxylic acid **193** has been applied to the synthesis of azetidinones (Scheme 70).[67]



Scheme 70

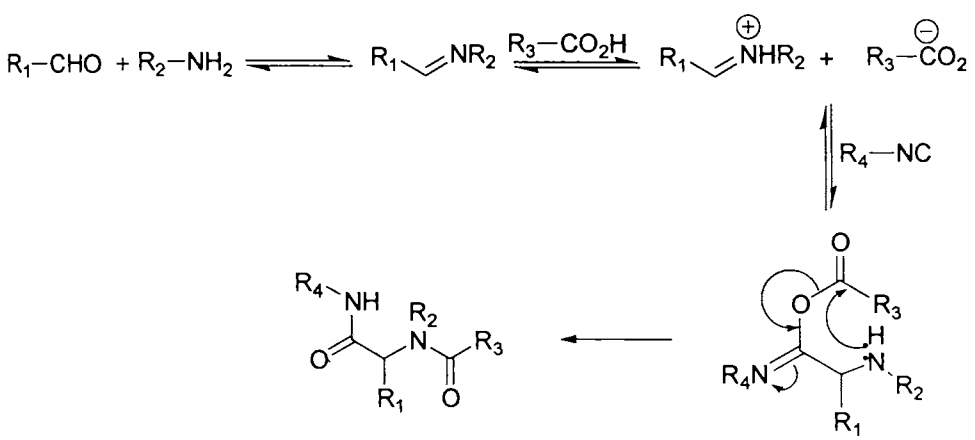
1.2.2 Ugi Reaction

In 1959, Ugi and coworkers reported the most important IMCR.[68] The characteristic feature of the Ugi reaction is the α-addition of an iminium ion and the conjugate base of a carboxylic acid to an isocyanide, followed by spontaneous rearrangement of the α-adduct to yield an α-amino carboxamide derivative. Carbonyl compounds and amines, or their condensation products, serve as precursors to the iminium ion (Scheme 71).



Scheme 71

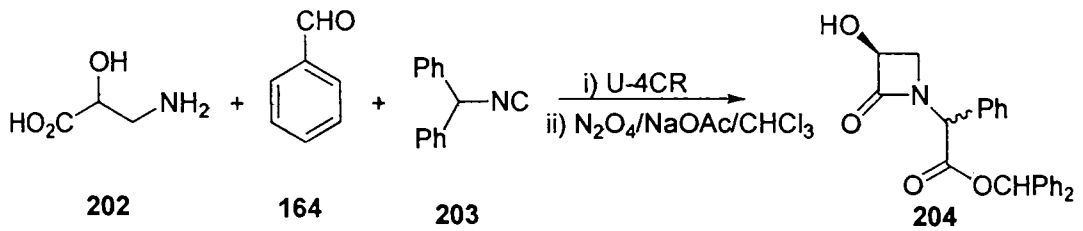
The mechanism for this reaction is shown below (Scheme 72).



Scheme 72

Any known type of C-isocyanide can be used as the isocyanide component and the only restriction for the acid component is that it must be

able to rearrange irreversibly from the intermediate α-adduct of the isocyanide to deliver a stable product. The Ugi 4CR has been widely applied for the synthesis of β-lactams and β-lactam containing antibiotics (Scheme 73).[69]



202 164 203 204

Scheme 73

Work in our laboratory has revealed that the 1:1 intermediate formed by the addition of isocyanides to DMAD could be intercepted by a range of electrophiles thereby constituting novel multicomponent reactions. Details of this work are presented in Chapter 2 (see section 2.2 in Chapter 2).

1.3 Definition of the Problem

It is evident from the literature survey presented above that the chemistry of nucleophilic carbenes especially dialkoxy, alkoxyamino, diamino, alkoxythio, and dithiocarbenes has been investigated to a lesser extent. In particular, the potential use of these carbenes in multicomponent reactions has not been studied so far. Against this literature background and in view of our sustained interest in devising novel multicomponent reactions employing nucleophilic species, we undertook a detailed investigation of the formation of zwitterions by the reaction of nucleophilic carbenes with activated acetylenes and the interception of these zwitterions with various electrophiles in one pot. The carbenes selected for our study include dimethoxycarbene and *N*-heterocyclic carbenes such as 1,3-dimesityl-imidazolin-2-ylidene and 1,3-dimesityl-imidazol-2-ylidene. The activated alkyne of choice was dimethyl acetylenedicarboxylate (DMAD). The electrophiles employed in the study are various carbonyl compounds such as aldehydes, ketones, and α,β-unsaturated carbonyl compounds.

In the initial phase of our study we have undertaken a systematic investigation of the reactivity pattern of the 1:1 intermediate formed by the addition of dimethoxycarbene and DMAD with various carbonyl compounds. To make the study more comprehensive, we have carried out some investigations on the chemistry of the adducts formed in the aforementioned multicomponent reactions. These results comprise the subject matter of second and third chapters.

The last phase of our study was focused on the reaction of *N*-heterocyclic carbenes towards DMAD and aromatic aldehydes and the results constitute the subject matter of the fourth chapter.

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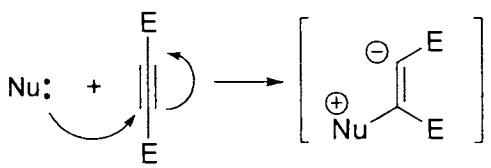
CHAPTER 2

THE REACTION OF DIMETHOXYCARBENE AND DIMETHYL ACETYLENEDICARBOXYLATE WITH CARBONYL COMPOUNDS: SYNTHESIS OF DIHYDROFURAN DERIVATIVES

2.1 Introduction

The 1,3-dipolar cycloaddition reactions offer one of the most versatile and convergent approaches for the synthesis of five membered heterocyclic compounds.[1] The monumental work of Huisgen has established this general concept and over the years many structurally diverse groups of heterocyclic compounds have been synthesized by this methodology.[2] Apart from the conventional dipoles which have been studied in detail, there is another class of reactive species called zwitterionic intermediates which also react with various dipolarophiles to afford heterocyclic compounds. Zwitterionic species are neutral compounds having formal electrical charges of opposite sign delocalized on nonadjacent atoms and it is not possible to represent these species by uncharged canonical forms. Nucleophilic addition of donors that contain no active hydrogen atoms are generally initiated *via* zwitterionic intermediates, which can undergo stabilization by rearrangement, cyclization or addition reaction (Scheme 1).[3]



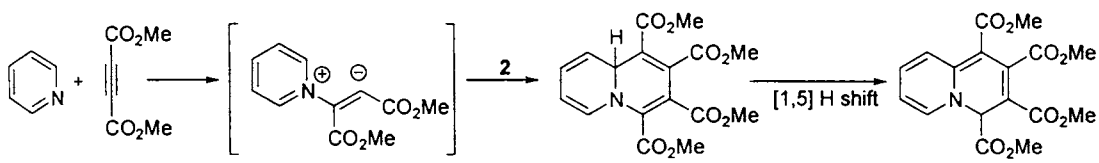
Nu = TPP, R-NC, DMSO, etc.
E = $-CO_2Me$, $-SO_2R$, -CN, -COR, etc.

Scheme 1

The reaction of these intermediates with electrophiles provides direct access to a wide range of heterocyclic compounds, a concise historical account of such reactions is presented in the following sections.

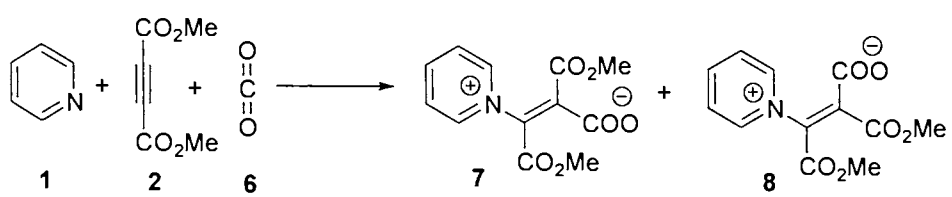
2.1.1 Addition of Aromatic Tertiary Amines

As early as 1932, Diels and Alder showed that aromatic amines such as pyridine react readily with dimethyl acetylenedicarboxylate (DMAD) to form stable adducts.[4] However, the structure of the adducts was conclusively established only after many years by Acheson and coworkers (Scheme 2).[5]



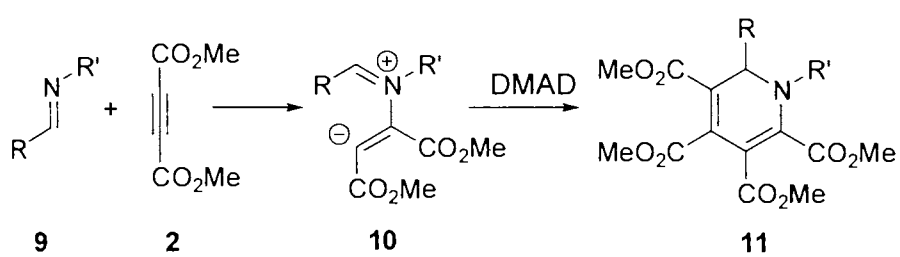
Scheme 2

Later, mechanistic studies by the same group have proved that the zwitterionic intermediate **3** could be trapped by CO_2 to form *cis* and *trans* isomeric betaines (Scheme 3).[6]



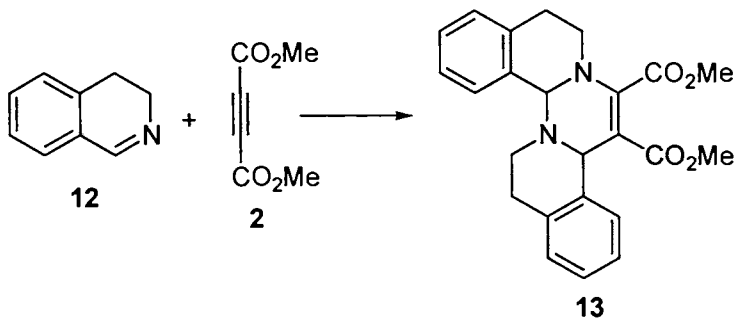
Scheme 3

Huisgen has demonstrated the use of imines as donors in the reaction with DMAD leading to the dihydropyridine derivative **11** (Scheme 4). He has classified the second step in this reaction as a 1,4 dipolar cycloaddition.[7]



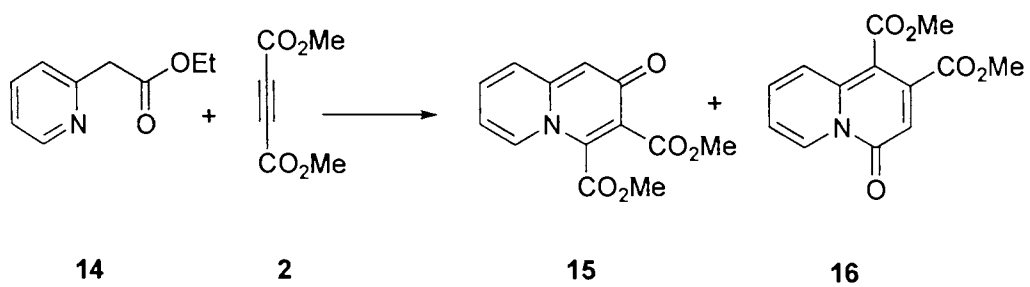
Scheme 4

The 1,4-dipole thus formed can be intercepted with a suitable excess of imine; in the case of dihydroisoquinoline, the reaction afforded the pentacyclic compound **13** (Scheme 5).[8]



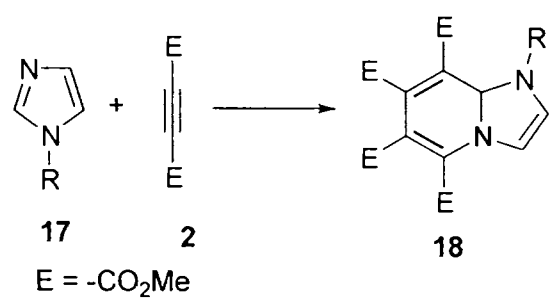
Scheme 5

Another study by Winterfeldt has shown that aromatic tertiary amines substituted with suitable receptors react with DMAD to afford various heterocyclic derivatives; a typical example involving ethyl pyridyl acetate is shown in Scheme 6.[9]



Scheme 6

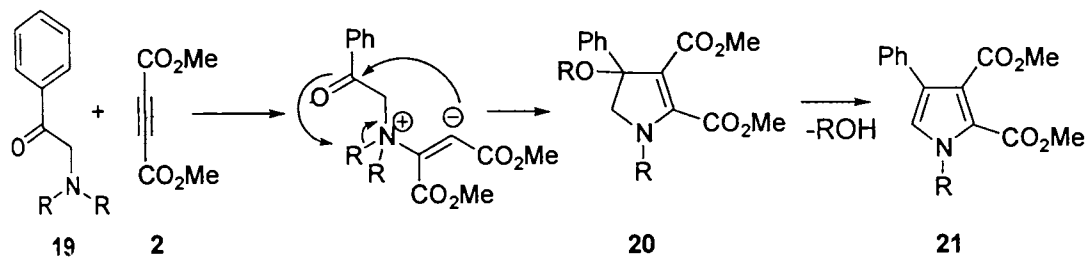
Heteroaromatic compounds such as thiazoles and imidazoles also participate in reactions with DMAD affording products as illustrated in Scheme 7.[10]



Scheme 7

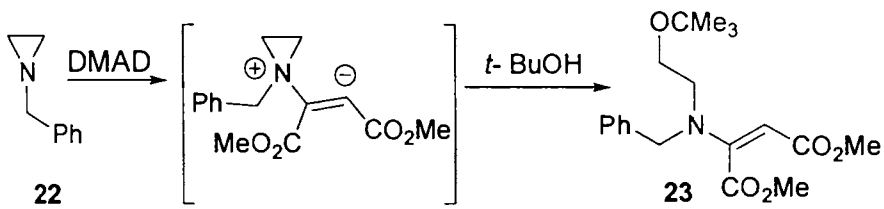
2.1.2 Addition of Aliphatic Tertiary Amines

The reaction of trialkyl amines with DMAD afforded pyrrole derivative **21** (Scheme 8).[11]



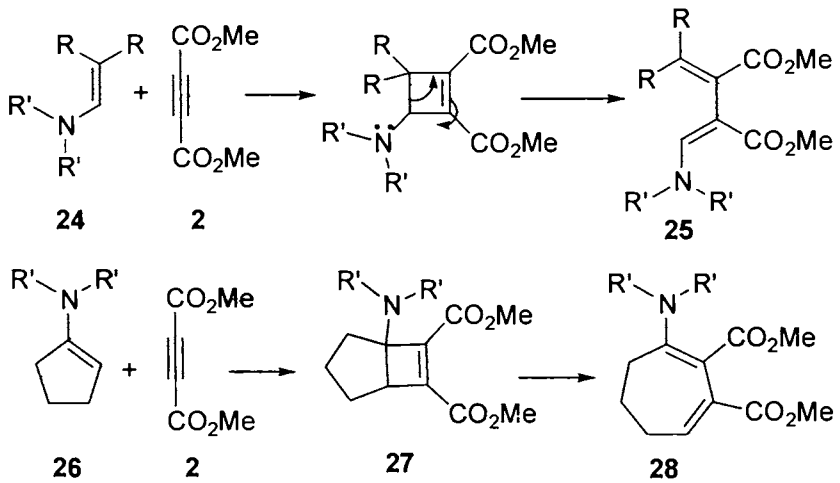
Scheme 8

Aziridines have also been known to react with DMAD to give products, which arise through either a C-N or C-C bond cleavage. *N*-benzyl aziridine on reaction with DMAD in *t*-BuOH afforded the ether derivative by a C-N bond cleavage (Scheme 9).[12]



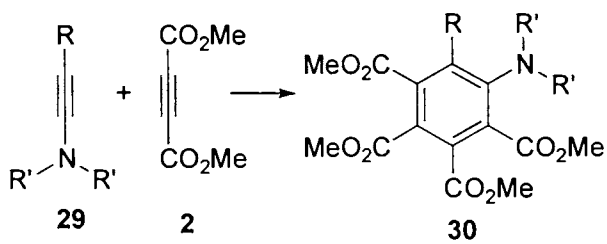
Scheme 9

The reactivity of enamines towards acetylenic esters was investigated by several groups and these studies have revealed that the reaction generally proceeds *via* a cyclic four membered adduct which undergoes further rearrangement to give the dienamine derivative **25**.[13] Cyclic enamines undergo ring expansion *via* a similar intermediate affording ring enlarged products and this methodology has been successfully employed in the synthesis of some biologically active compounds (Scheme 10).[14]



Scheme 10

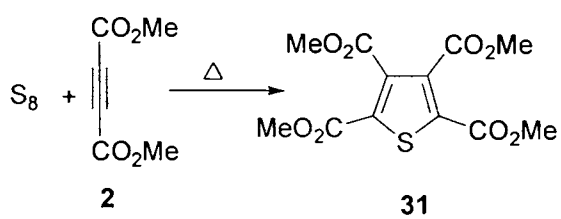
Alkynyl amines undergo facile addition to DMAD to form benzene derivatives (Scheme 11).[15]



Scheme 11

2.1.3 Addition of Sulfur Compounds

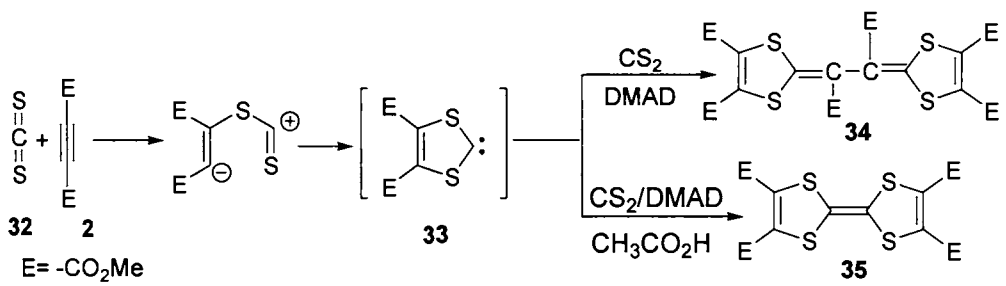
The reactivity of elemental sulfur towards acetylenic esters was studied by Michael in 1895, and this afforded 2,3,4,5-thiophene tetracarboxylate (Scheme 12).[16]



Scheme 12

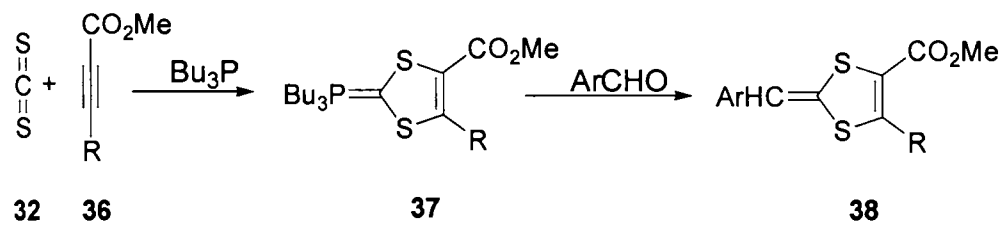
The reaction of acetylenic esters with carbon disulfide afforded an array of products depending on the conditions employed. Thus at 100 °C, DMAD

reacts with CS_2 to form a 2:3 adduct **34** and a 2:2 adduct **35** in presence of acetic acid, presumably through a dithiocarbene intermediate (Scheme 13).[17]



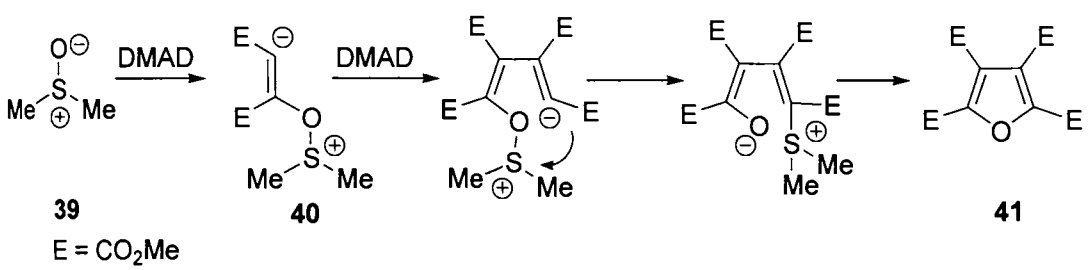
Scheme 13

However, in the presence of aromatic aldehydes and tributyl phosphine, the reaction afforded 2-benzylidene-1,3-dithioles (Scheme 14).[18]



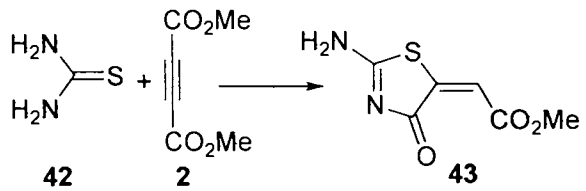
Scheme 14

Winterfeldt has reported the reaction of dimethyl sulfoxide with DMAD leading to tetramethylfuran tetracarboxylate **41** as depicted in Scheme 15.[19]



Scheme 15

Acetylenic esters react with thiourea to afford thiazolin-4-one **43** (Scheme 16).[20]



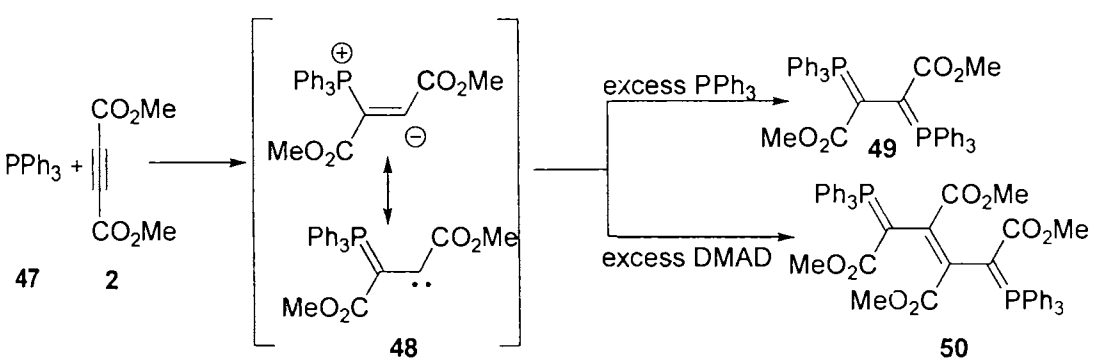
Scheme 16

The reaction of sulfoxonium ylide with acetylenic esters resulted in the formation of stable, open chain ylides (Scheme 17).[21]

Scheme 17

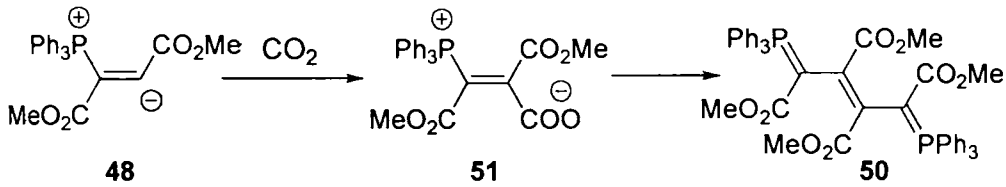
2.1.4 Addition of Phosphines

The reactivity of various phosphine derivatives towards acetylenic esters was studied by Tebby and coworkers and they have shown that triphenyl phosphine (TPP) reacts with DMAD to form a 2:1 adduct, *i.e.* a dialkylidene diphosphorane **49**. In the absence of excess of phosphine the product **50** was isolated (Scheme 18).[22]



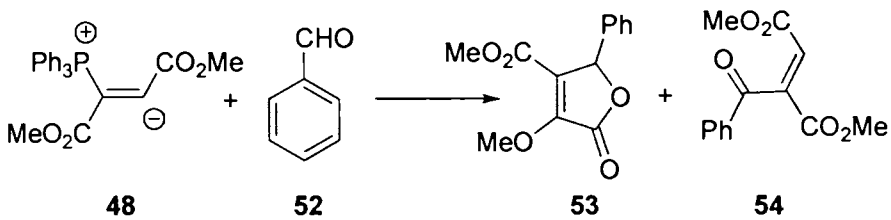
Scheme 18

Attempts have been made to intercept the 1:1 zwitterion of DMAD and TPP with CO_2, in which case a betaine is formed, which on subsequent decarboxylation afforded the product **50** (Scheme 19).[23]



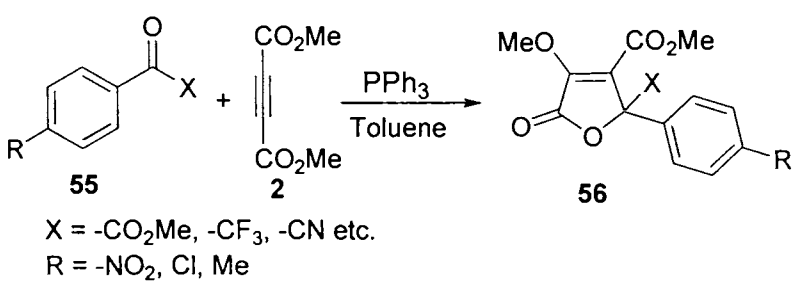
Scheme 19

Winterfeldt has shown that the 1:1 zwitterion of TPP and DMAD could be trapped by benzaldehyde to afford two products **53** and **54** (Scheme 20).[24]



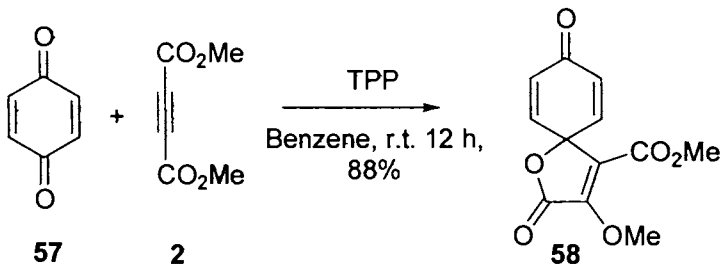
Scheme 20

In a modification of the Winterfeldt protocol, Nozaki and coworkers have established the catalytic use of TPP in this reaction and have extended it to activated carbonyl compounds such as α-keto esters and α-keto nitriles affording lactones in good yields (Scheme 21).[25]



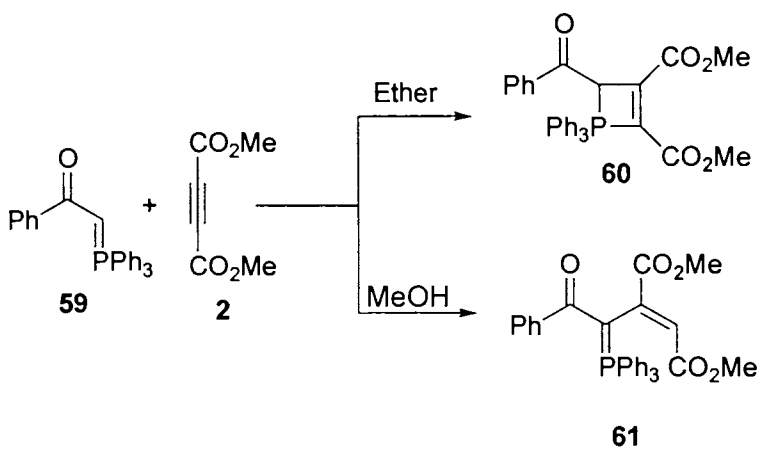
Scheme 21

Studies in our laboratory have shown that the 1:1 intermediate formed by the addition of triphenylphosphine to DMAD undergoes facile reaction with quinonoid compounds to afford highly functionalized *γ-spiro* lactones in high yields. A typical example involving *p*-benzoquinone is shown in Scheme 22.[26]



Scheme 22

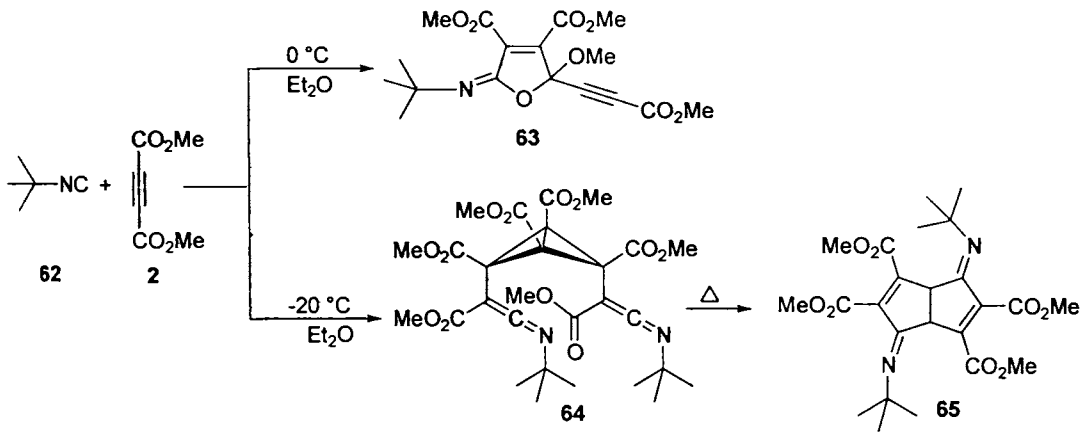
Triphenyl alkylidene phosphorane was also reported to react with acetylenic esters, and the reaction was found to be sensitive to the nature of the solvent employed. Thus the reaction of triphenyl phosphorylidene acetophenone with DMAD in an aprotic solvent such as ether gave the phosphorane **60** while the reaction in methanol afforded **61** as the product (Scheme 23).[27]



Scheme 23

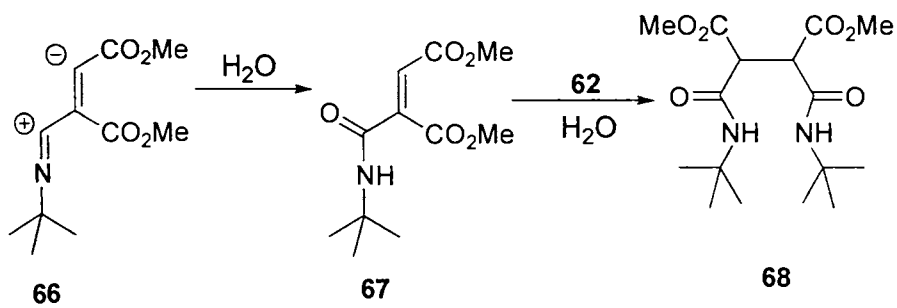
2.1.5 Addition of Isocyanides

Several groups have explored the addition of isocyanides to acetylenic esters in detail and these reactions are of particular interest, in view of the variety of products that are formed. Winterfeldt has reported the formation of pyrrole derivatives by the reaction of *t*-butyl isocyanide with DMAD. The reaction at 0 °C afforded the dihydrofuran derivative **63** while at -20 °C gave the bicyclobutane derivative **64** which on thermal isomerization furnished the bicyclic compound **65** (Scheme 24).[28]



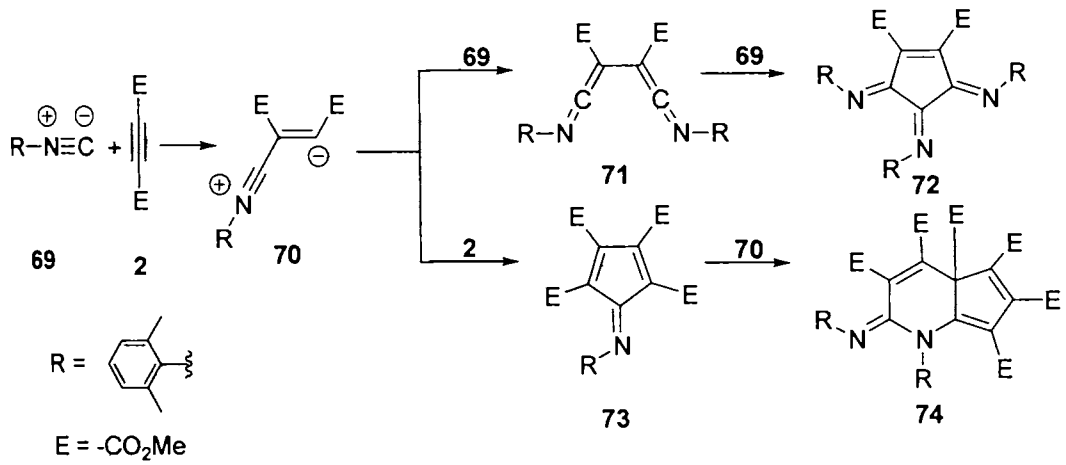
Scheme 24

When the reaction was carried out in a protic solvent such as water, a symmetrical *bis* amide **68** was isolated (Scheme 25).[28]



Scheme 25

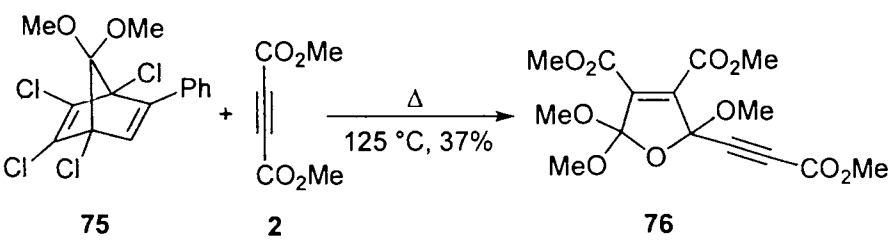
Suzuki and coworkers have shown that complex mixtures of products were formed in the reaction of 2,6-dimethyl phenyl isocyanide and 4-bromo-2,6,-dimethyl phenyl isocyanide with DMAD. [29a] The products include the 2:1 adduct **71** and a 3:1 adduct **72**. In addition, a 2:3 adduct **74** was obtained by the reaction of the zwitterion with the intermediate compound **73** (Scheme 26). Subsequently, George and coworkers have investigated the reaction of cyclohexyl isocyanide with DMAD and studied the thermal isomerization of the different cycloadducts formed.[29b]



Scheme 26

2.1.6 Addition of Dialkoxycarbenes

The reactivity of dialkoxycarbenes towards DMAD was studied by Hoffmann who has shown that the dihydrofuran derivative **76** was formed in low yield (Scheme 27).[30]



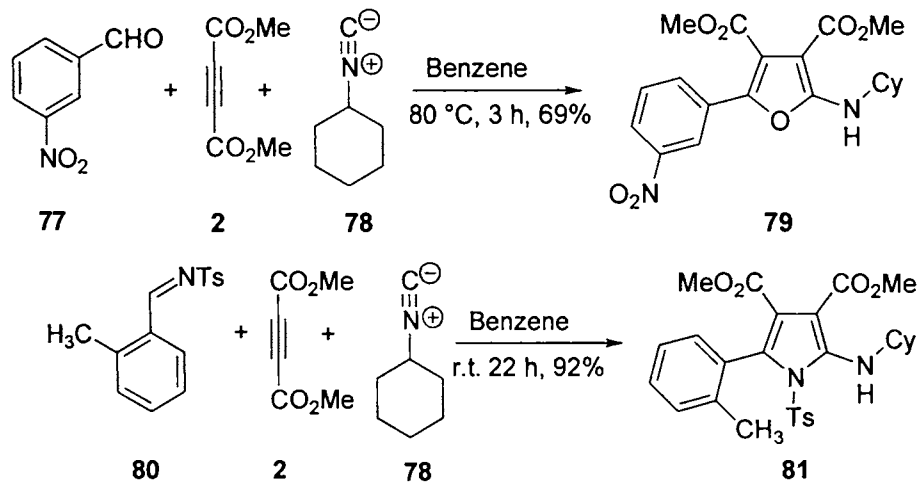
Scheme 27

A brief account of the reactivity of dialkoxycarbenes is presented in Chapter 1 (see Chapter 1, Section 1.1.3 e.).

2.2 Interception of the Zwitterionic Intermediate with a Third Component

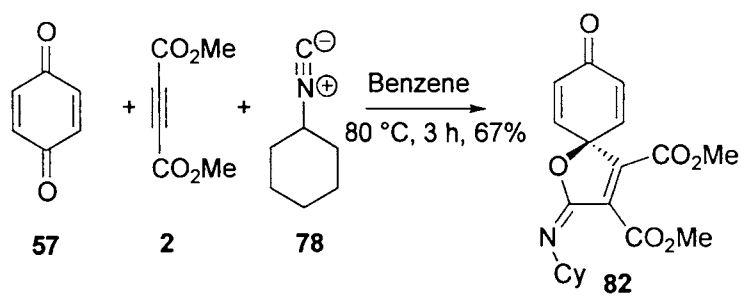
There have been attempts to intercept the 1:1 zwitterion of isocyanides and DMAD with a third component but these were essentially unsuccessful.[31] Recent studies in our laboratory have shown that the 1:1 intermediate formed by the addition of isocyanides to DMAD could be intercepted with various electrophiles, ranging from aldehydes to quinones, affording a variety of heterocyclic compounds, thereby constituting novel multicomponent reactions (MCRs). Thus, the reaction of cyclohexyl isocyanide, DMAD and 3-nitro

benzaldehyde afforded the 2-aminofuran derivative in good yield.[32] The use of *N*-tosylimines as the third component afforded novel pyrrole derivatives (Scheme 28).[33]



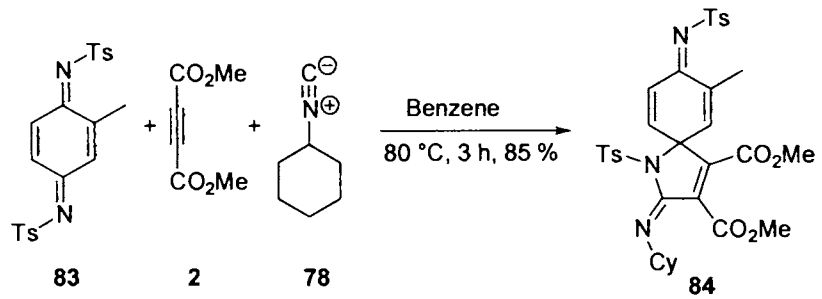
Scheme 28

The reaction of the zwitterionic intermediate with quinonoid compounds furnished novel imino lactones; a typical example involving *p*-benzoquinone is shown in Scheme 29.[34]



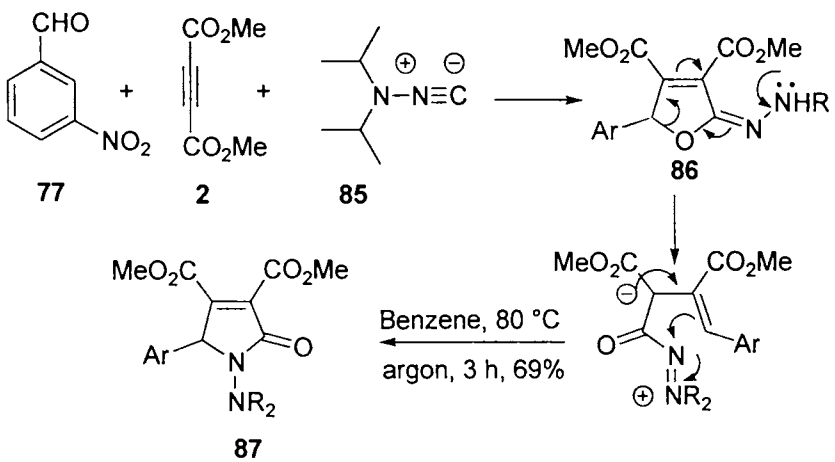
Scheme 29

p-Quinoneimines also displayed analogous reactivity affording the *spiro* dihydropyrrole derivative **84** (Scheme 30).



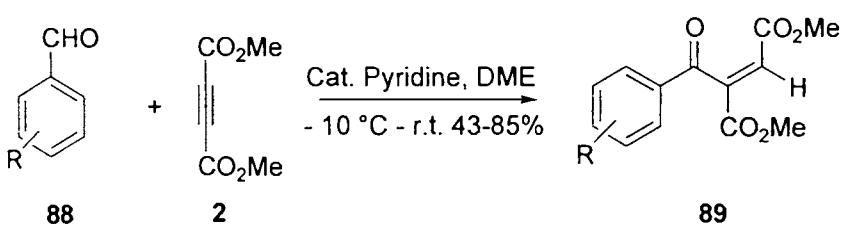
Scheme 30

When *N*-isocyanides were employed in the above described multicomponent reactions, the initially formed dihydrofuran derivative **86** underwent a Dimroth rearrangement to afford the pyrrolinone derivative **87** (Scheme 31).[35]



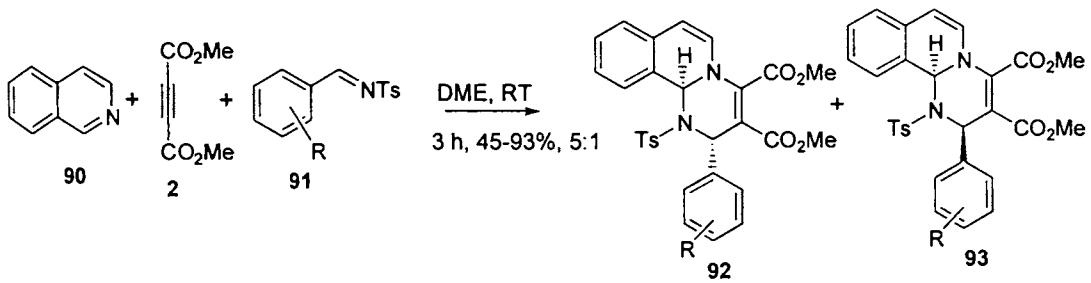
Scheme 31

The use of pyridine as the nucleophile in these reactions constituted a novel two component reaction affording 2-benzoyl but-2-enoates in good yields (Scheme 32).[36] In this reaction pyridine acts as a catalyst and on completion of the reaction, it gets eliminated.



Scheme 32

However, under similar conditions, isoquinoline took part in a multicomponent reaction, in the sense that the initially formed 1:1 intermediate underwent 1,4-dipolar cycloaddition with the electrophiles employed. The dipolar cycloaddition of the zwitterion with *N*-tosylimines is shown in Scheme 33.[37]



Scheme 33

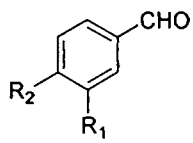
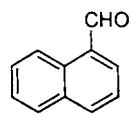
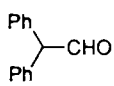
2.3 The Present Work

It is clear from the literature survey presented above that, a range of nucleophiles can add to DMAD forming 1:1 zwitterionic intermediates. Results from our laboratory have established novel protocols for the interception of the 1:1 zwitterions formed by the addition of isocyanides and various aromatic tertiary amines to DMAD with a number of electrophiles. However, no efforts have been made to study the reactivity profile of the 1:1 zwitterionic intermediate formed by the addition of nucleophilic carbenes such as dialkoxycarbenes to DMAD. Against this literature scenario, and in the context of our general interest in devising novel multicomponent reactions, it was of interest to study the reactivity profile of the zwitterionic intermediate of dialkoxycarbene and DMAD with various electrophiles, following the lines of a multicomponent reaction. The electrophiles which have been selected for our study include aldehydes, ketones, and α,β-unsaturated carbonyl compounds, and dimethoxycarbene was employed as the nucleophilic carbene. The results of our explorations in this avenue and the usefulness of the process leading to novel dihydrofuran derivatives are presented here.

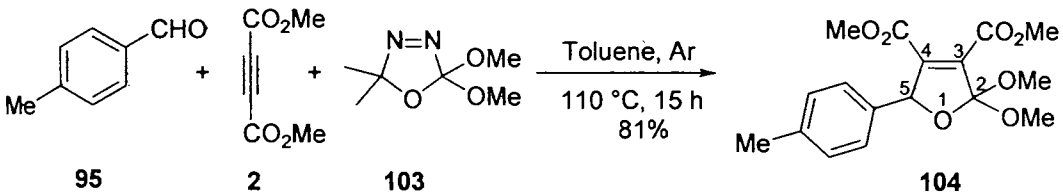
2.4 Results and Discussion

The aldehydes selected for our studies are listed below (Table 1).

Table -1

		**100**	
52	R_1=R_2= H	**101**	
77	R_1= NO_2, R_2= H		
94	R_1= Cl, R_2= H	**102**	
95	R_1= H, R_2= CH_3		
96	R_1= H, R_2= Cl		
97	R_1= H, R_2= OCH_2Ph		
98	R_1= H, R_2= OCH_3		
99	R_1= R_2= Cl		

In our initial experiment, we exposed *p*-tolualdehyde to the zwitterionic species resulting from the reaction of DMAD and dimethoxycarbene, the latter being generated *in situ* by the thermolysis of 2,2-dimethoxy-Δ^3-1,3,4-oxadiazoline in refluxing toluene following the Warkentin prescription.[38] A facile reaction leading to the formation of dihydrofuran derivative **104** in 81% yield occurred (Scheme 34).



Scheme 34

The structure of the product **104** was elucidated by spectroscopic analysis. The IR spectrum showed characteristic peaks at 1735 and 1725 cm^{-1} corresponding to the two carbomethoxy groups. In the ^1H NMR spectrum, the signal due to the *p*-methyl group was seen at δ 2.34 as a singlet, and the sharp singlets at δ 3.40 and δ 3.46 were attributed to the protons of the two methoxy groups. The peaks corresponding to protons of the two carbomethoxy groups were seen at δ 3.65 and δ 3.87. The benzylic proton resonated as a sharp singlet at δ 5.84. The aromatic protons afforded two separate doublets at δ 7.14 (J = 7.9 Hz) and δ 7.24 (J = 7.9 Hz). In the ^{13}C NMR spectrum, signal due to the *p*-methyl carbon was discernible at δ 21.2 while signals at δ 50.9 and δ 51.4 were assigned to the carbons of the methoxy groups. The carbomethoxy carbon signals were seen at δ 52.3 and δ 52.6. The resonance signal corresponding to the benzylic carbon was present at δ 83.9 while the resonance peaks corresponding to C-2, C-3 and C-4 were visible at δ 123.9, 141.1 and 138.7 respectively. The peaks at δ 161.6 and δ 162.4 were attributed to the ester carbonyls. All the other signals were also in good agreement with the proposed structure.

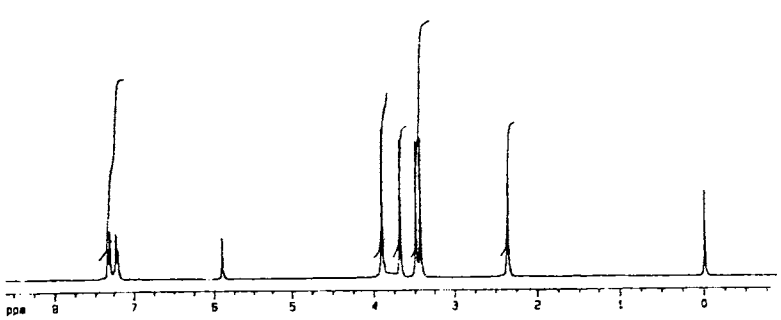


Figure 1 ^1H NMR of 104

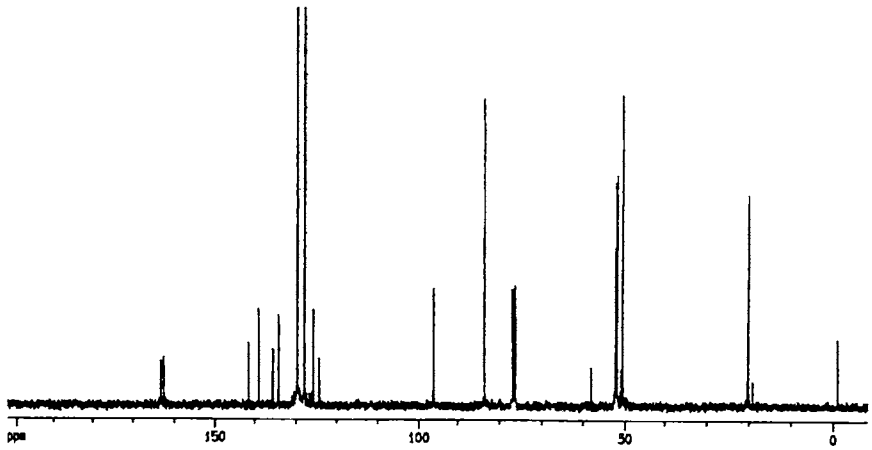
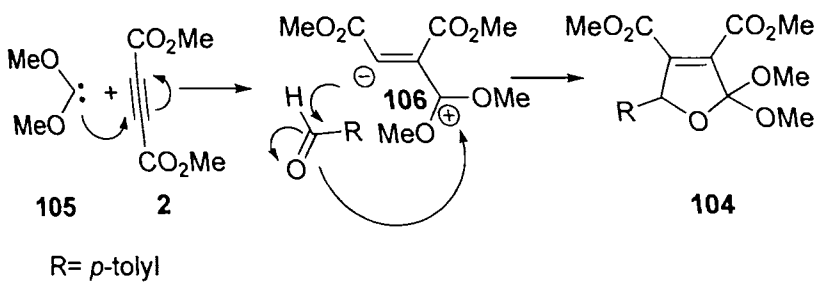


Figure 2 ^{13}C NMR of 104

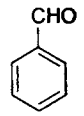
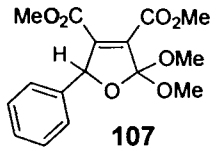
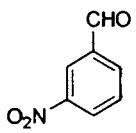
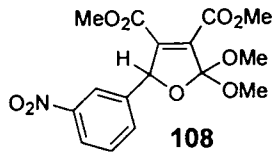
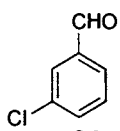
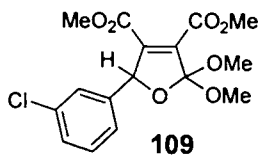
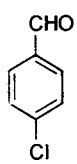
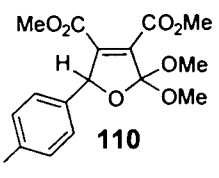
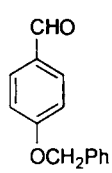
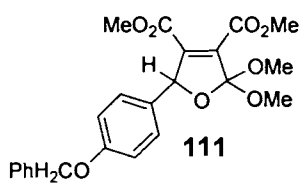
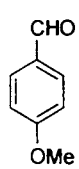
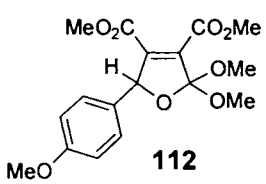
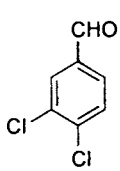
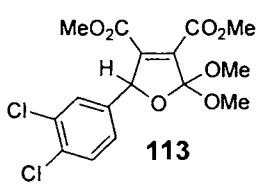
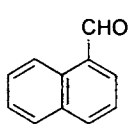
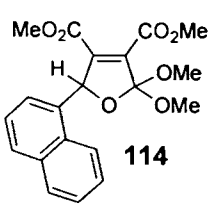
Mechanistically, the reaction is considered to involve the initial formation of a 1:1 zwitterionic intermediate by the reaction of dimethoxycarbene with DMAD. The zwitterion **106** adds to the carbonyl group to afford a dipolar species, which undergoes cyclization to furnish the product. In another perspective, the reaction may be considered to involve the 1,3 dipolar cycloaddition of **106** with the carbonyl group (Scheme 35).



Scheme 35

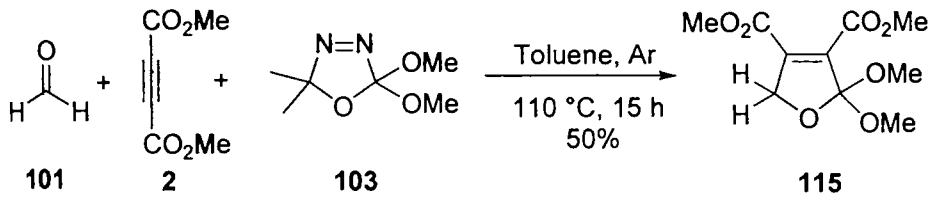
The reaction was found to be applicable to a number of aromatic aldehydes containing both electron donating and electron withdrawing groups; the dihydrofuran derivatives were obtained in moderate to excellent yields (Table 2). In all cases, the structure of the product was established by spectroscopic analysis; IR, ^{1}H NMR and ^{13}C NMR data were completely consistent with the assigned structure.

Table 2

Entry	Aldehyde	Products	Yield (%)*
1	 **52**	 **107**	81
2	 **77**	 **108**	77
3	 **94**	 **109**	75
4	 **96**	 **110**	66
5	 **97**	 **111**	69
6	 **98**	 **112**	43
7	 **99**	 **113**	70
8	 **100**	 **114**	90

Reaction conditions: Toluene, Ar, 110 °C, 15 h
* = isolated yield

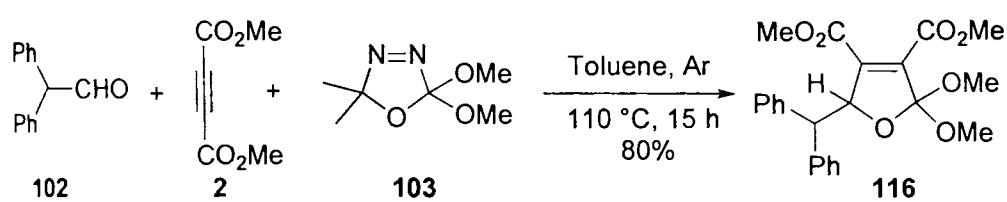
The reaction was found to be applicable to aliphatic aldehydes also. Paraformaldehyde on reaction with DMAD and dimethoxy carbene, generated from the oxadiazoline **103**, afforded the dihydrofuran derivative **115** in 50% yield (Scheme 36).



Scheme 36

The IR spectrum of **115** showed characteristic carbonyl absorption peak at 1735 cm^{-1}. The ^1H NMR spectrum showed sharp singlets at δ 3.34, δ 3.72, δ 3.75, and δ 4.02, corresponding to four methoxy protons. In the ^{13}C NMR spectrum, the characteristic peaks corresponding to two ester carbonyls were discernible at δ 164.2 and δ 162.1 while the peak corresponding to the orthoester carbon was seen at δ 123.6. All the other signals were also in good agreement with the proposed structure.

When diphenylacetaldehyde was employed as the aldehyde component in the multicomponent reaction with DMAD and dimethoxycarbene, the corresponding dihydrofuran derivative was obtained in excellent yield (Scheme 37).

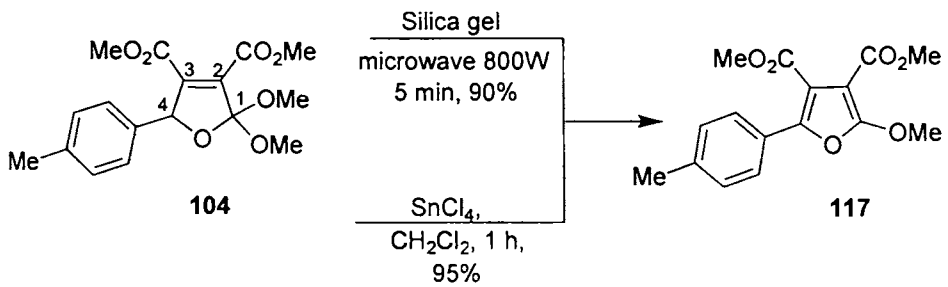


Scheme 37

As in the case of other dihydrofuran derivatives, the structure of the product was established by spectroscopic analysis. The IR spectrum of **116** showed characteristic peak at 1735 cm^{-1} corresponding to two carbomethoxy groups. In the ^1H NMR spectrum, the methoxy groups showed sharp singlets at δ3.05, δ3.33, δ3.49, and δ3.58. The two doublets at δ5.69 (J = 6.4 Hz) and

δ4.43 (J = 6.4 Hz) were attributed to the two methine protons. In the ^{13}C NMR spectrum, the ester carbonyls resonated at δ 163.4 and δ 162.3. All the other signals were also in good agreement with the assigned structure.

It was observed that the dihydrofuran derivatives obtained by the above mentioned multicomponent reactions lost methanol slowly on standing at room temperature for several hours, to afford the corresponding furan derivatives. Subsequently, it was found that either microwave irradiation or the addition of a Lewis acid catalyst accelerated this transformation. A typical example involving the dihydrofuran **104** is shown in Scheme 38.

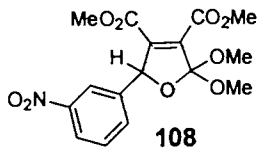
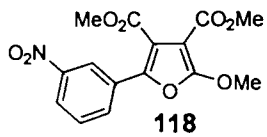
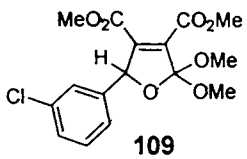
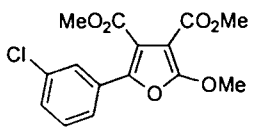
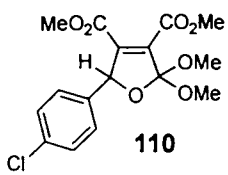
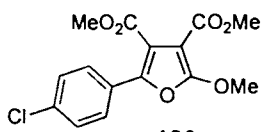
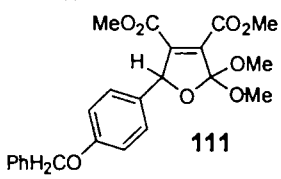
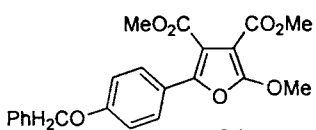
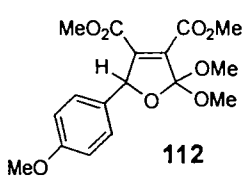
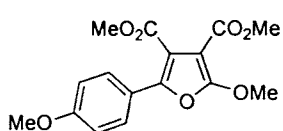
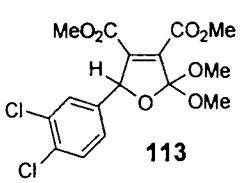
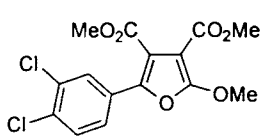
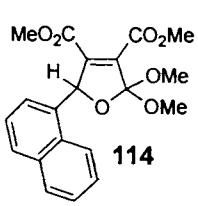
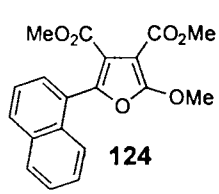


Scheme 38

The IR spectrum of **117** showed strong carbonyl absorption peaks at 1732 and 1707 cm^{-1}. In the ^{1}H NMR spectrum, the peaks at δ 4.19 and δ 3.88 were assigned to the protons corresponding to the two carbomethoxy groups while the sharp singlet at δ 3.81 was assigned to the protons of the methoxy group. In the ^{13}C NMR spectrum, the peaks corresponding to the two ester carbonyls were discernible at δ 164.9 and δ 162.2, while the carbon bearing the methoxy group in the furan ring resonated at δ 160.6. All other signals were in good agreement with the proposed structure and the compound gave satisfactory micro analysis data.

The reaction was found to be applicable to almost all dihydrofuran derivatives prepared, and the results are summarized in Table 3. The structure of the products was established by spectroscopic analysis; the compounds gave satisfactory microanalysis data also.

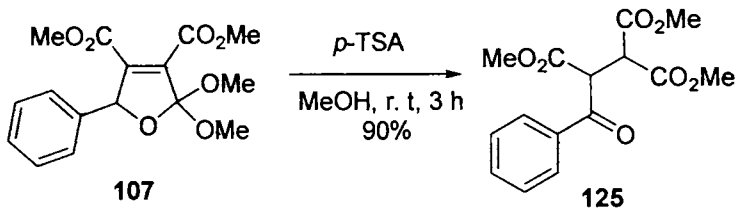
Table 3

Entry	Substrate	Product	Yield (%)*
1	 108	 118	85
2	 109	 119	88
3	 110	 120	90
4	 111	 121	88
5	 112	 122	85
6	 113	 123	90
7	 114	 124	92

Reaction conditions: $SnCl_4$, CH_2Cl_2, 1 h
* = isolated yield

It is worthy of note that either thermolysis or the use of an acid catalyst such as *p*-TSA did not transform the dihydrofurans to the furan derivatives. As illustrated in Scheme 39, when *p*-TSA was employed the reaction afforded the

ring opened product **125** in 90% yield, while attempted thermolysis left the dihydrofuran **107** unchanged.

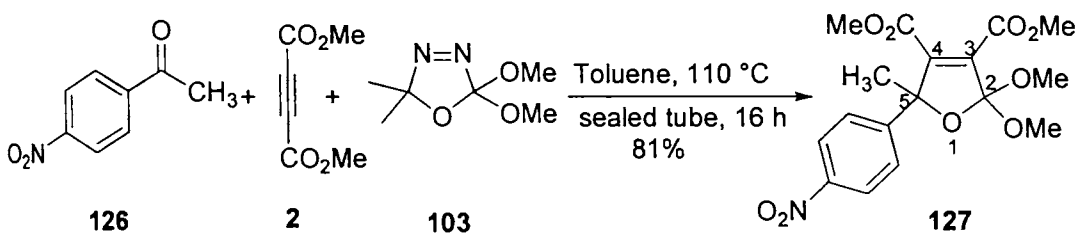


107 125

Scheme 39

2.4.1 Reaction with Ketones

In view of the encouraging results obtained in the case of aldehydes, it was of interest to extend the present reaction to ketones also. When *p*-nitro acetophenone was treated with DMAD and the carbene precursor **103**, in refluxing toluene under argon atmosphere for 16 h, a facile reaction leading to the formation of the dihydrofuran derivative **127** in 81% yield occurred (Scheme 40).

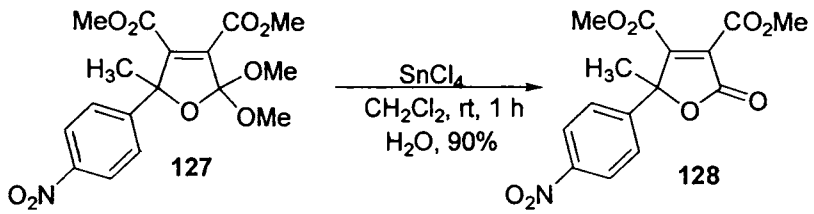


126 2 103 127

Scheme 40

The IR spectrum of **127** showed strong and broad carbonyl absorption peaks at around 1735 cm^{-1} corresponding to two carbomethoxy groups. In the ^1H NMR spectrum, the peaks due to the four methoxy groups were discernible at δ3.81, δ3.73, δ3.46 and δ3.43, while the peak at δ2.01 was assigned to the methyl group. ^{13}C NMR spectrum showed characteristic peaks at δ 161.9 and δ161.6 due to the resonance of two ester carbonyls. The peaks at δ 122.8 and δ86.6 were assigned to C-2 and C-4 carbons of the dihydrofuran ring. All the other signals were in good agreement with the proposed structure.

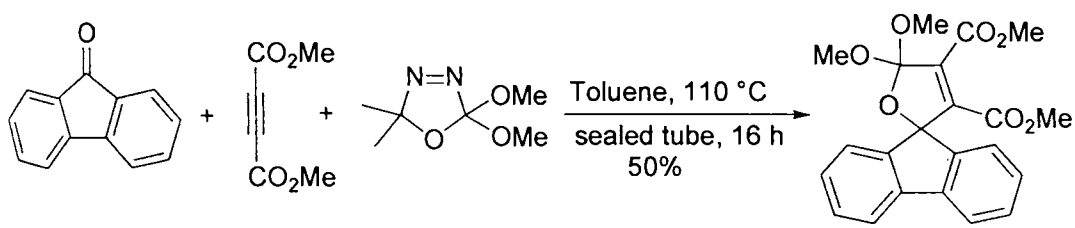
The dihydrofuran derivative **127** on reaction with Lewis acid catalyst afforded the furanone derivative **128** in high yield (Scheme 41).



Scheme 41

In this case also, the structure of the product was established by spectroscopic analysis. IR spectrum of **128** showed peaks corresponding to both the lactone and ester moieties at 1796 and 1748 cm^{-1}. In the ^1H NMR spectrum, the protons corresponding to two carbomethoxy groups were seen as singlets at δ 3.93 and δ 4.07, while the resonance of the methyl group was visible at δ 2.15. In the ^{13}C NMR spectrum, the peaks corresponding to the lactone and ester carbonyls were discernible at δ 165.1, δ 160.4 and δ 160.1. All other signals were also in good agreement with the assigned structure.

When fluorenone was employed in the multicomponent reaction with DMAD and dimethoxycarbene, the corresponding dihydrofuran derivative was obtained in moderate yield (Scheme 42).



129 **2** **103** **130**

Scheme 42

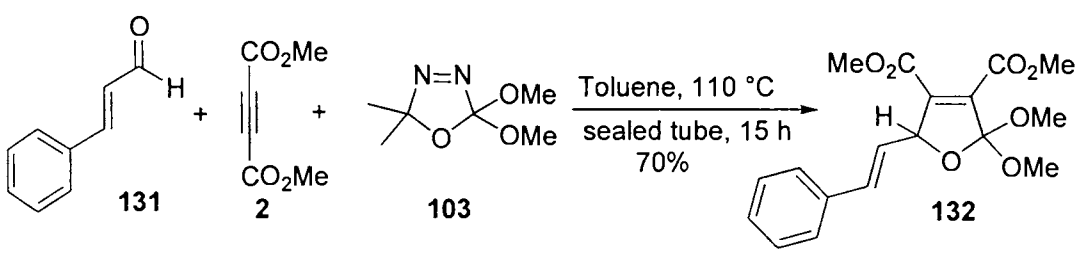
Inexplicably, acetophenone and *p*-chloro acetophenone did not furnish any dihydrofuran derivatives when treated with DMAD and dimethoxycarbene; the ketones and DMAD were recovered quantitatively.

2.4.2 Reaction with α,β-Unsaturated Carbonyl Compounds

In the next phase of our studies we turned our attention to α,β-unsaturated carbonyl compounds to examine the chemoselectivity in the multicomponent reaction of these compounds with DMAD and dimethoxycarbene. The α,β-unsaturated carbonyl compounds selected for our studies include various substituted cinnamaldehydes and chalcones.

2.4.3 Reaction with α,β-Unsaturated Aldehydes

We initiated our experiments by treating cinnamaldehyde with DMAD and 2,2-dimethoxy oxadiazoline in refluxing toluene under argon atmosphere for 15 hours and the reaction afforded the corresponding dihydrofuran derivative **132** in about 70% yield (Scheme 43). No product resulting from the addition of the zwitterion to the conjugated double bond was observed.

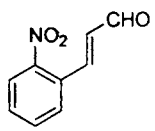
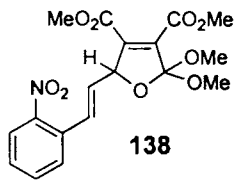
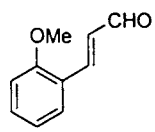
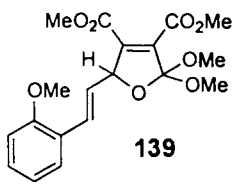
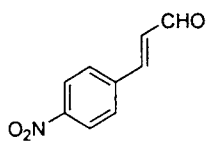
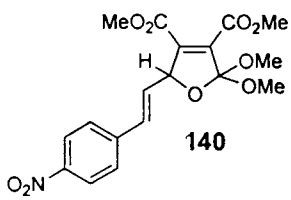
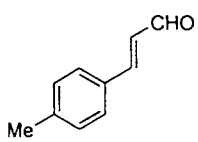
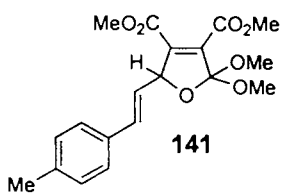
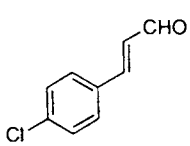
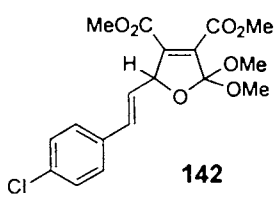


Scheme 43

The structure of the product was confirmed by spectroscopic methods. The IR spectrum of **132** showed strong carbonyl absorption peak at 1746 cm^{-1}. The ^{1}H NMR spectrum was in good agreement with the assigned structure. Signals due to the methoxy and carbomethoxy protons were discernible at δ3.44, δ3.51, δ3.71 and δ3.74. The methine proton in the dihydrofuran ring showed its resonance peak as a singlet at δ4.83. The ^{13}C NMR spectrum was also in good agreement with the assigned structure. The peaks at δ 163.9 and δ 161.7 were typical of the two ester carbonyls. The peaks at δ 103.7 and δ 122.0 were assigned to the methine carbon and the carbon attached to two methoxy groups. All other signals were in good agreement with the proposed structure. The reaction was extended to a number of other substituted

cinnamaldehydes; moderate yields of dihydrofuran derivatives were obtained and the results are summarized in Table-4.

Table 4

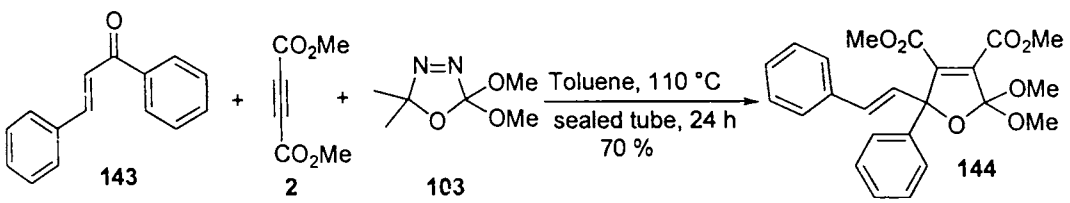
Entry	Aldehyde	Products	Yield (%)*
1	 **133**	 **138**	60
2	 **134**	 **139**	40
3	 **135**	 **140**	50
4	 **136**	 **141**	38
5	 **137**	 **142**	60

Reaction conditions: Toluene, Ar, 110 °C, 15 h

* = isolated yield

2.4.4 Reaction with Chalcones

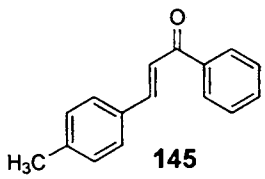
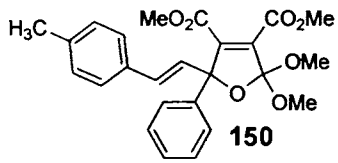
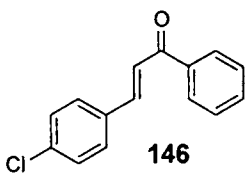
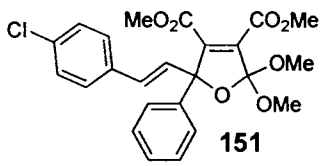
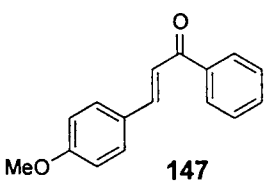
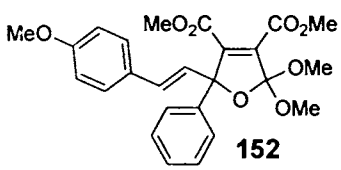
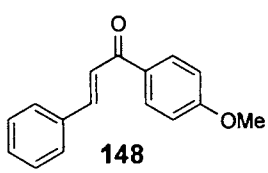
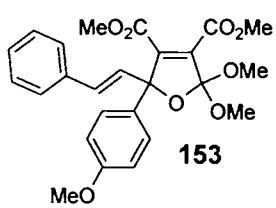
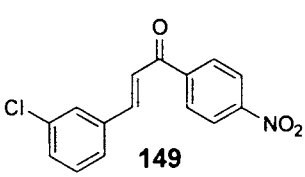
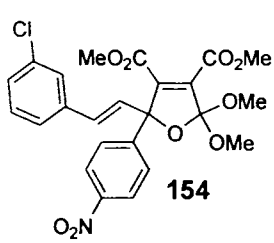
Prompted by the successful participation of cinnamaldehydes in the multicomponent reaction with DMAD and dimethoxycarbene, it was reasonable to extend the reaction to α,β-unsaturated ketones such as chalcones also. In a typical reaction, benzylidene acetophenone was treated with DMAD and 2,2-dimethoxy oxadiazoline in refluxing toluene under argon for 24 hours and this resulted in the formation of the corresponding dihydrofuran derivative **144** in 70% yield (Scheme 44).



Scheme 44

Characterization of the product is based on conventional spectroscopic data. The IR spectrum of **144** showed carbonyl absorption peaks at 1728 and 1740 cm^{-1}, corresponding to two carbomethoxy groups. In the ^1H NMR spectrum, the signals corresponding to two methoxy groups were seen as singlets at δ 3.33 and δ 3.49, while the peaks corresponding to the carbomethoxy protons were discernible at δ 3.75 and δ 3.86. In the ^{13}C NMR spectrum, typical ester carbonyl peaks were visible at δ 162.4 and δ 162.1. The two quaternary carbons α to the ring oxygen were seen at δ 89.8 and δ 123.1. All other signals were also in good agreement with the proposed structure; the compound gave satisfactory HRMS data also. The reaction was found to be applicable to a number of substituted chalcones, and the dihydrofuran derivatives were obtained in good yields. As usual, the products were characterized on the basis of spectroscopic analysis. The results are summarized in Table 5.

Table 5

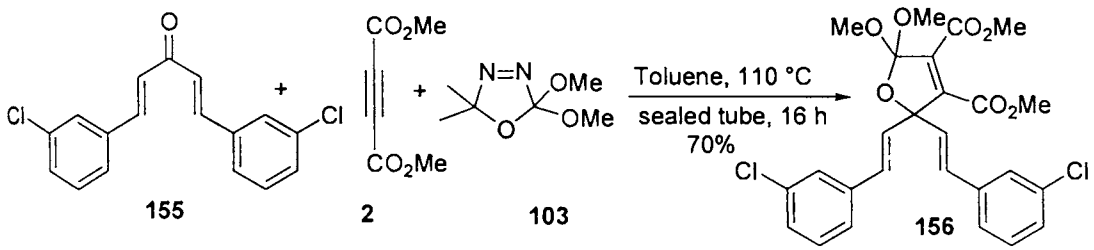
Entry	Substrate	Products	Yield (%)*
1	 **145**	 **150**	**60**
2	 **146**	 **151**	**65**
3	 **147**	 **152**	**38**
4	 **148**	 **153**	**50**
5	 **149**	 **154**	**69**

Reaction conditions: Toluene, Ar, 110 °C, 24 h

* = isolated yield

2.4.5 Reaction with 1,4-Dienones

1,4-Dienones are a group of organic compounds whose participation in many organic reactions has been studied in detail; the most important is the cationic electrocyclization reaction termed Nazarov reaction. The multicomponent reaction of 1,4-dienone **155**, DMAD and dimethoxycarbene, generated *in situ* from **103**, afforded the distyrenyl dihydrofuran derivative **156** in good yield (Scheme 45). As usual, the structure of the product **156** was established by spectroscopic methods.



Scheme 45

The dihydrofuran derivatives thus formed appeared to be suitable substrates for cationic electrocyclic reactions such as the interrupted Nazarov reaction. A literature survey has shown that such a reaction involving dihydrofuran derivatives has not been reported so far. In this context, we undertook an investigation of the reactivity of divinyl dihydrofurans in interrupted Nazarov reaction and the results of our studies are presented in Chapter 3 (see Chapter 3, Section 3.4.2).

2.5 Conclusion

In conclusion, it has been shown that the one pot reactions of carbonyl compounds, DMAD and dimethoxycarbene offer an easy route for the synthesis of highly functionalized dihydrofuran derivatives in good yields, thereby constituting novel multicomponent reactions. It is interesting to note that furan and dihydrofuran motifs are present in a number of biologically active natural products and other heterocyclic compounds. It is conceivable that the novel multicomponent reactions described herein will find application in

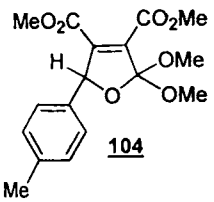
the synthesis of a variety of heterocyclic compounds, and in natural product synthesis.

2.6 Experimental

General: Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz respectively on a Bruker DPX-300 MHz NMR spectrometer. Chemical shifts (δ) are reported relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling constant (J) is reported in Hertz (Hz). Mass spectra were recorded under EI/HRMS (at 5000 resolution) using JEOL JMS 600H mass spectrometer. IR spectra were recorded on a Nicolet Impact 400D FT-IR spectrophotometer. Elemental analyses were performed on a Perkin Elmer-2400 Elemental Analyzer. Dimethyl acetylenedicarboxylate (DMAD) was purchased from Aldrich Chemical Co. and was used without further purification. The dimethoxycarbene precursor, 2,2-dimethoxy-Δ^3-1,3,4-oxadiazoline was prepared according to a known literature procedure.[38] Commercial grade solvents were distilled prior to use. Analytical thin layer chromatography was performed on glass plates coated with silica gel containing calcium sulfate binder. Gravity column chromatography was performed using 100-200 mesh silica gel and mixtures of hexane-ethyl acetate were used for elution.

Dimethyl-2,2-dimethoxy-5-(4-methylphenyl)-2,5-dihydro-3,4 furandicarboxylate 104

A mixture of *p*-tolualdehyde **95** (100 mg, 0.83 mmol), DMAD **2** (177 mg, 1.24 mmol) and oxadiazoline **103** (265 mg, 1.66 mmol) was refluxed in dry toluene under argon for 15 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate solvent mixture to afford **104** as a colorless viscous liquid (226 mg, 80%).



104

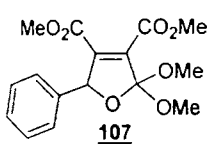
IR (neat) ν_{max}: 3015, 2944, 2843, 1735, 1725, 1607, 1513, 1445, 1251, 1102, 983, 808, 750 cm^{-1}.

^{1}H NMR: δ 7.24 (d, J = 7.9, 2H), 7.14 (d, J = 7.9, 2H), 5.84 (s, 1H), 3.87 (s, 3H), 3.65 (s, 3H), 3.46 (s, 3H), 3.40 (s, 3H), 2.34 (s, 3H).

^{13}C NMR: δ 162.4, 161.6, 141.1, 138.7, 133.8, 129.3, 127.6, 125.4, 123.9, 83.9, 52.6, 52.3, 51.4, 50.9, 21.2.

Dimethyl-2, 2-dimethoxy-5-phenyl-2,5-dihydro-3,4-furandicarboxylate 107

A mixture of benzaldehyde **52** (100 mg, 0.94 mmol), DMAD **2** (200 mg, 1.40 mmol) and oxadiazoline **103** (448 mg, 2.88 mmol) was refluxed in dry toluene under argon for 15 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate solvent mixture to **107** as a colorless viscous liquid (265 mg, 80%).



107

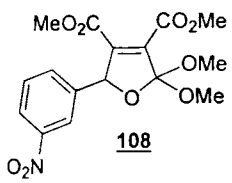
IR (neat) ν_{max}: 3016, 2962, 2847, 1742, 1728, 1694, 1445, 1351, 1283, 1249, 1115, 1081, 1027, 980, 919, 798, 703 cm^{-1}.

^{1}H NMR: δ 7.35-7.28 (m, 5H), 5.87 (s, 1H), 3.86 (s, 3H), 3.63 (s, 3H), 3.36 (s, 3H), 3.26 (s, 3H).

^{13}C NMR: δ 162.2, 161.4, 140.5, 136.7, 135.3, 128.8, 128.5, 127.5, 123.9, 83.9, 52.5, 52.2, 50.9, 50.8.

Dimethyl-2,2-dimethoxy-5-(3-nitrophenyl)-2,5-dihydro-3,4 furandicarboxylate 108

A mixture of 3-nitrobenzaldehyde **77** (100 mg, 0.66 mmol), DMAD **2** (141 mg, 0.99 mmol) and oxadiazoline **103** (211 mg, 1.32 mmol) was refluxed in dry toluene under argon for 15 h. The solvent was removed under vacuum and the residue subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate solvent mixture to afford **108** as a pale yellow viscous liquid (186 mg, 77%).



108

IR (neat) ν_{max}: 3090, 3001, 2955, 2854, 1748, 1728, 1640, 1539, 1445, 1351, 1263, 1202, 1162, 1115, 1047, 1013, 987, 912, 818, 744 cm^{-1}.

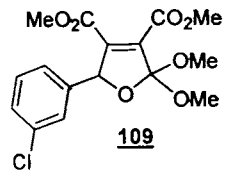
^{1}H NMR: δ 8.78 (s, 1H), 8.33-8.27 (m, 2H), 7.62 (t, J = 8, 1H), 4.27 (s, 1H) 3.78 (s, 3H), 3.70 (s, 3H), 3.51 (s, 6H).

^{13}C NMR: δ 163.2, 160.6, 147.7, 135.3, 130.1, 129.7, 128.7, 125.4, 124.6, 121.7, 119.9, 104.6, 55.5, 52.8, 52.4, 51.5, 50.8.

Dimethyl-2,2-dimethoxy-5-(3-chlorophenyl)-2,5-dihydro-3,4-furandicarboxylate 109

A mixture of 3-chlorobenzaldehyde **94** (100 mg, 0.71 mmol), DMAD **2** (151 mg, 1.1 mmol) and oxadiazoline **103** (227 mg, 1.42 mmol) was refluxed in dry toluene under argon for 15 h. The solvent was removed under vacuum and the residue subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate solvent mixture to afford analytically pure **109** as a colorless viscous liquid (189 mg, 75%).

IR (neat) ν_{max}: 3070, 2996, 2948, 2840, 1742, 1730, 1647, 1566, 1438, 1330, 1290, 1196, 1094, 987, 784, 724 cm^{-1}.



109

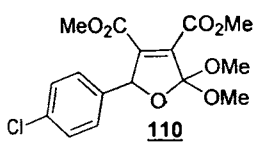
^{1}H NMR: δ 7.37-7.27 (m, 4H), 5.83 (s, 1H), 3.88 (s, 3H), 3.68 (s, 3H), 3.49 (s, 3H), 3.41 (s, 3H).

^{13}C NMR: δ 162.3, 161.2, 139.8, 139.0, 136.0, 134.5, 129.8, 129.1, 128.4, 125.7, 124.2, 83.3, 52.8, 52.4, 51.2, 50.9.

Dimethyl-2,2-dimethoxy-5-(4-chlorophenyl)-2,5-dihydro-3,4-furandicarboxylate 110

A mixture of 4-chlorobenzaldehyde **96** (100 mg, 0.71 mmol), DMAD **2** (151 mg, 1.1 mmol) and oxadiazoline **103** (227 mg, 1.42 mmol) was refluxed in dry toluene under argon for 15 h. The solvent was removed under vacuum and the residue subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate solvent mixtures to afford **110** as a colorless viscous liquid (167 mg, 66%).

IR (neat) ν_{max}: 3002, 2962, 2847, 1755, 1721, 1634, 1600, 1492, 1438, 1337, 1256, 1196, 1115, 1054, 1027, 899, 784, 690 cm^{-1}.



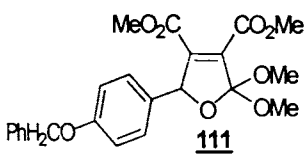
110

^{1}H NMR: δ 7.87 (d, J = 8.6, 2H), 7.38 (d, J = 8.6, 2H), 5.83 (s, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 3.40 (s, 6H).

^{13}C NMR: δ 164.8, 161.9, 160.7, 141.8, 132.8, 128.2, 125.8, 124.5, 122.6, 115.3, 58.4, 52.7, 52.5, 51.4.

Dimethyl-2,2-dimethoxy-5-(4-benzyloxyphenyl)-2,5-dihydro-3,4-furandicarboxylate 111

A mixture of 4-benzyloxy benzaldehyde **97** (100 mg, 0.47 mmol), DMAD **2** (100 mg, 0.70 mmol) and oxadiazoline **103** (150 mg, 0.94 mmol) was refluxed in dry toluene under argon for 15 h. The solvent was removed under vacuum and the residue subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate solvent mixture to afford **111** as a colorless viscous liquid (138 mg, 69%).



111

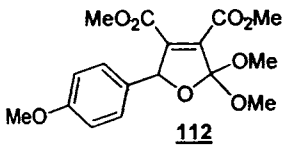
IR (neat) ν_{max}: 3009, 2948, 2845, 1755, 1721, 1681, 1627, 1519, 1431, 1283, 1243, 1189, 1121, 987, 933, 852, 751, 697 cm^{-1}.

^{1}H NMR: δ 7.14-6.92 (m, 9H), 5.83 (s, 1H), 5.03 (s, 2H), 3.87 (s, 3H), 3.65 (s, 3H), 3.46 (s, 3H), 3.40 (s, 3H).

^{13}C NMR: δ 162.4, 161.7, 159.3, 141.1, 136.7, 135.2, 129.1, 129.0, 128.5, 128.2, 127.9, 127.4, 125.3, 123.9, 83.7, 69.9, 52.6, 52.3, 51.1, 51.0.

Dimethyl-2,2-dimethoxy-5-(4-methoxyphenyl)-2,5-dihydro-3,4-furandicarboxylate 112

A mixture of 4-methoxy benzaldehyde **98** (100 mg, 0.73 mmol), DMAD **2** (156 mg, 1.1 mmol) and oxadiazoline **103** (233 mg, 1.46mmol) was refluxed in dry toluene under argon for 15 h. The solvent was removed under vacuum and the residue subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate solvent mixture to afford **112** as a colorless viscous liquid (102 mg, 43%).



112

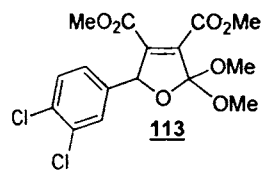
IR (neat) ν_{max}: 2999, 2948, 2854, 1748, 1729, 1607, 1519, 1465, 1256, 1189, 1232, 1108, 976, 782 cm^{-1}.

^{1}H NMR: δ 7.98 (d, J = 8.8, 2H), 7.46 (d, J = 8.8, 2H), 4.09 (s, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 3.58 (s, 3H), 3.36 (s, 3H).

^{13}C NMR: δ 164.8, 162.2, 160.4, 159.8, 142.8, 128.6, 127.3, 121.3, 114.6, 113.8, 68.5, 55.1, 52.3, 51.5, 51.4.

Dimethyl-2,2-dimethoxy-5-(3,4-dichlorophenyl)-2,5-dihydro-3,4-furandicarboxylate 113

A mixture of 3,4-dichlorobenzaldehyde **99** (100 mg, 0.57 mmol), DMAD **2** (121 mg, 0.85 mmol) and oxadiazoline **103** (182 mg, 1.14mmol) was refluxed in dry toluene under argon for 15 h. The solvent was removed under vacuum and the residue subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate solvent mixture to afford **113** as a colorless viscous liquid (156 mg, 70%).



113

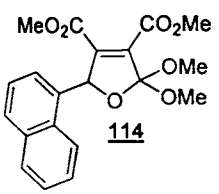
IR (neat) ν_{max}: 2998, 2952, 2839, 1732, 1672, 1606, 1560, 1474, 1434, 1401, 1334, 1281, 1241, 1202, 1175, 1109, 1036, 983, 917, 811, 764, 665 cm^{-1}.

^{1}H NMR: δ 7.49-7.42 (m, 2H), 7.27-7.22 (m, 1H), 5.81 (s, 1H), 3.89 (s, 3H), 3.70 (s, 3H), 3.49 (s, 3H), 3.40 (s, 3H).

^{13}C NMR: δ 162.2, 161.1, 139.2, 137.4, 136.8, 133.1, 132.8, 130.6, 129.7, 126.8, 124.3, 82.8, 52.8, 52.5, 51.3, 50.9.

Dimethyl-2,2-dimethoxy-5-(1-naphthyl)-2,5-dihydro-3,4-furandicarboxylate 114

A mixture of 1-naphthaldehyde **100** (100 mg, 0.60 mmol), DMAD **2** (129 mg, 0.90 mmol) and oxadiazoline **103** (192 mg, 1.20 mmol) was refluxed in dry toluene under argon for 15 h. The solvent was removed under vacuum and the residue subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate solvent mixture to afford **114** as a colorless viscous liquid (214 mg, 90%).



114

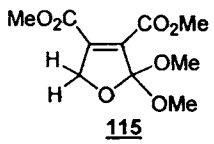
IR (neat) ν_{max}: 2999, 2942, 2843, 1740, 1731, 1681, 1432, 1332, 1276, 1232, 1113, 976, 782 cm^{-1}.

^{1}H NMR: δ 8.22 (d, J = 8.2, 1H), 7.87-7.82 (m, 2H), 7.58-7.41 (m, 4H), 6.75 (s, 1H), 3.91 (s, 3H), 3.61 (s, 3H), 3.51 (s, 3H), 3.27(s, 3H).

^{13}C NMR: δ 162.3, 161.9, 141.5, 136.1, 133.8, 132.7, 131.7, 129.6, 128.7, 126.6, 126.2, 125.9, 125.2, 124.2, 123.2, 79.7, 52.7, 52.4, 51.3, 50.9.

Dimethyl-2,2-dimethoxy-2,5-dihydro-3,4-furandicarboxylate 115

A mixture of paraformaldehyde **101** (100 mg, 3.3 mmol), DMAD **2** (710 mg, 5.00 mmol) and oxadiazoline **103** (1.05 g, 6.60 mmol) was refluxed in dry toluene under argon for 15 h. The solvent was removed under vacuum and the residue subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate solvent mixture to afford **115** as a colorless viscous liquid (406 mg, 50%).



115

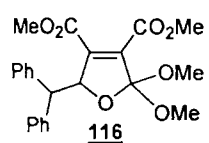
IR (neat) ν_{max}: 3002, 2955, 2054, 1735, 1613, 1445, 1330, 1256, 1074, 960, 804, 757, 703 cm^{-1}.

^{1}H NMR: δ 4.73 (d, J = 9, 1H), 4.49 (d, J = 9, 1H), 4.02 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 3.34 (s, 3H)

^{13}C NMR: δ 164.2, 162.1, 146.7, 144.6, 124.5, 123.6, 58.5, 51.7, 51.4.

Dimethyl-2,2-dimethoxy-5-(diphenylmethyl)-2,5-dihydro-3,4-furandicarboxylate 116

A mixture of diphenyl acetaldehyde **102** (100 mg, 0.50 mmol), DMAD **2** (108 mg, 0.76 mmol) and oxadiazoline **103** (160 mg, 1.00 mmol) was refluxed in dry toluene under argon for 15 h. The solvent was removed under vacuum and the residue subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate solvent mixture **116** as a colorless viscous liquid (164 mg, 80%).



116

IR (neat) ν_{max}: 3012, 2984, 2857, 1735, 1685, 1625, 1515, 1438, 1261, 1086, 973, 910, 850, 790, 670 cm^{-1}.

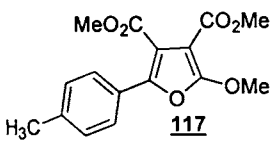
^{1}H NMR: δ 7.38-7.20 (m, 10H), 5.69 (d, J = 6.4, 1H), 4.43 (d, J = 6.4, 1H), 3.58 (s, 3H), 3.49 (s, 3H), 3.33 (s, 3H), 3.05 (s, 3H).

^{13}C NMR: δ 163.4, 162.3, 145.5, 142.2, 138.0, 128.2, 126.8, 127.7, 123.8, 91.2, 58.4, 52.7, 52.2, 51.7, 48.4.

Dimethyl-2-(methoxy)-5-(4-methylphenyl)-3,4-furandicarboxylate 117

$SnCl_4$ (58 mg, 0.22 mmol) was added to a solution of the dihydrofuran **104** (150 mg, 0.44 mmol) in anhydrous dichloromethane. After stirring for 1 h at ambient temperature, water was added to the reaction mixture and it was

extracted with dichloromethane. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. After the removal of solvent, the residue was subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate mixture to afford analytically pure **117** as a colorless crystalline solid (127 mg, 95%), m.p. 112-113 °C (recrystallized from CH_2Cl_2-hexane).



117

IR (KBr) ν_{max}: 3012, 2956, 1732, 1707, 1601, 1457, 1264, 1095, 952, 814, 750 cm^{-1}.

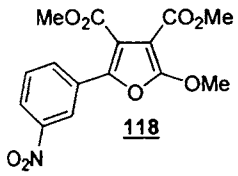
^{1}H NMR: δ 7.46 (d, J = 8, 2H), 7.17 (d, J = 8, 2H), 4.19 (s, 3H), 3.88 (s, 3H), 3.81 (s, 3H), 2.36 (s, 3H)

^{13}C NMR: 164.9, 162.2, 160.6, 142.5, 138.6, 129.6, 129.4, 125.8, 125.5, 58.4, 52.5, 51.5, 21.4.

Analysis calculated for $C_{16}H_{16}O_6$: C, 63.15, H, 5.90; Found: C, 63.0, H, 5.21.

Dimethyl-2-(methoxy)-5-(3-nitrophenyl)-3, 4- furandicarboxylate 118

$SnCl_4$ (52 mg, 0.20 mmol) was added to a solution of the dihydrofuran **108** (150 mg, 0.40 mmol) in anhydrous dichloromethane. After stirring for 1 h at ambient temperature, water was added to the reaction mixture and it was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. After the removal of solvent, the residue was subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate mixture to afford analytically pure **118** as a yellow crystalline solid (114 mg, 85%), m.p. 184-185 °C (recrystallized from CH_2Cl_2-hexane).



118

IR (KBr) ν_{max}: 3007, 2952, 2840, 1738, 1703, 1600, 1524, 1469, 1441, 1345, 1221, 1103, 1048, 985, 820, 763 cm^{-1}.

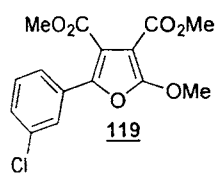
^{1}H NMR: δ 8.44 (s, 1H), 8.15 (d, J = 7.4, 1H), 7.92 (d, J = 7.1, 1H), 7.57 (t, J = 7.8, 1H), 4.25 (s, 3H), 3.94 (s, 3H), 3.83 (s, 3H).

^{13}C NMR: δ 164.2, 161.7, 148.6, 146.9, 139.3, 130.6, 130.2, 129.8, 122.8, 120.1, 55.8, 52.9, 51.7.

Analysis calculated for $C_{15}H_{13}NO_8$: C, 53.74, H, 3.91, N, 4.18; Found: C, 54.02, H, 3.93, N, 4.31.

Dimethyl-2-(methoxy)-5-(3-chlorophenyl)-3,4-furandicarboxylate 119

$SnCl_4$ (55 mg, 0.21 mmol) was added to a solution of the dihydrofuran **109** (150 mg, 0.42 mmol) in anhydrous dichloromethane. After stirring for 1 h at ambient temperature, water was added to the reaction mixture and it was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. After the removal of solvent, the residue was subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate mixture to afford analytically pure **119** as a colorless crystalline solid (120 mg, 88%). m.p. 100-101 °C (recrystallized from CH_2Cl_2-hexane).



119

IR (KBr) ν_{max}: 3009, 2962, 2840, 1735, 1721, 1600, 1573, 1485, 1438, 1357, 1243, 1108, 1054, 966, 885, 784, 724 cm^{-1}.

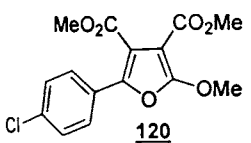
^{1}H NMR: δ 7.55 (s, 1H), 7.47-7.44 (m, 1H), 7.33-7.26 (m, 2H) 4.21 (s, 3H), 3.91 (s, 3H), 3.81 (s, 3H).

^{13}C NMR: δ 164.4, 161.9, 160.8, 140.3, 134.8, 130.2, 130.0, 128.4, 125.3, 125.2, 116.2, 58.5, 52.72, 51.6.

Analysis calculated for $C_{15}H_{13}ClO_6$: C, 55.48, H, 4.04; Found: C, 55.69, H, 4.08.

Dimethyl-2-(methoxy)-5-(4-chlorophenyl)-3,4- furandicarboxylate 120

$SnCl_4$ (55 mg, 0.21 mmol) was added to a solution of the dihydrofuran **110** (150 mg, 0.42 mmol) in anhydrous dichloromethane. After stirring for 1 h at ambient temperature, water was added to the reaction mixture and it was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. After the removal of solvent, the residue was subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate mixture to afford analytically pure **120** as a colorless crystalline solid (122 mg, 90%), m.p. 105-106 °C (recrystallized from CH_2Cl_2-hexane).



120

IR (KBr) ν_{max}: 3015, 2999, 2949, 1734, 1729, 1607, 1470, 1426, 1338, 1245, 1089, 1039, 821,794, 689 cm^{-1}.

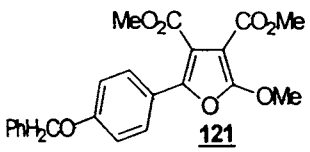
^{1}H NMR: δ 7.52 (d, J = 8.6, 2H), 7.34 (d, J = 8.5, 2H), 4.19 (s, 3H), 3.89 (s, 3H), 3.81 (s, 3H).

^{13}C NMR: δ 163.9, 161.8, 160.6, 142.1, 134.4, 132.8, 128.9, 126.9, 126.6, 123.1, 58.4, 52.5, 51.5.

Analysis calculated for $C_{15}H_{13}ClO_6$: C, 55.48, H, 4.04; Found: C, 55.43, H, 4.12.

Dimethyl-2-(methoxy)-5-(4-benzyloxyphenyl)-3,4-furandicarboxylate 121

$SnCl_4$ (45 mg, 0.17 mmol) was added to a solution of the dihydrofuran **111** (150 mg, 0.35 mmol) in anhydrous dichloromethane. After stirring for 1 h at ambient temperature, water was added to the reaction mixture and it was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. After the removal of solvent, the residue was subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate mixture to afford analytically pure **121** as a colorless crystalline solid (122 mg, 88%), m.p. 111-112 °C (recrystallized from CH_2Cl_2-hexane).



121

IR (KBr) ν_{max}: 3030, 2943, 2854, 1738, 1688, 1607, 1482, 1413, 1351, 1219, 1176, 1107, 1051, 1013, 826, 780, 716, 698 cm^{-1}.

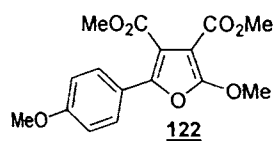
^{1}H NMR: δ 7.52-6.90 (m, 9H), 5.06 (s, 2H), 4.15 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H).

^{13}C NMR: δ 167.2, 164.6, 159.1, 136.7, 128.6, 127.1, 127.4, 127.4, 121.7, 115.1, 104.9, 70.1, 58.4, 52.3, 49.6.

Analysis calculated for $C_{22}H_{20}O_7$: C, 66.66, H, 5.09; Found: C, 66.83, H, 5.04.

Dimethyl-2-(methoxy)-5-(4-methoxyphenyl)-3,4-furandicarboxylate 122

$SnCl_4$ (54 mg, 0.21 mmol) was added to a solution of the dihydrofuran **112** (150 mg, 0.42 mmol) in anhydrous dichloromethane. After stirring for 1 h at ambient temperature, water was added to the reaction mixture and it was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. After the removal of solvent, the residue was subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate mixture to afford analytically pure **122** as a colorless crystalline solid (114 mg, 85%), m.p. 121-122 °C. (recrystallized from CH_2Cl_2-hexane).



122

IR (KBr) ν_{max}: 3002, 2955, 2840, 1735, 1681, 1512, 1431, 1256, 1101, 1034, 973, 790, 650 cm^{-1}.

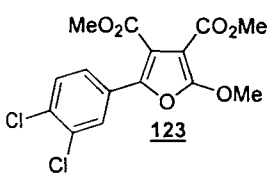
^{1}H NMR: δ 7.54 (d, J = 8.7, 2H), 6.90 (d, J = 8.7, 2H), 4.17 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H).

^{13}C NMR: δ 164.6, 162.1, 160.04, 143.0, 140.1, 127.3, 123.3, 121.4, 113.1, 55.7, 55.1, 52.1, 51.6

Analysis calculated for $C_{16}H_{16}O_7$: C, 60.0, H, 5.05; Found: C, 60.4, H, 5.14.

Dimethyl-2-(methoxy)-5-(3,4-dichlorophenyl)-3,4- furandicarboxylate 123

$SnCl_4$ (50 mg, 0.19 mmol) was added to a solution of the dihydrofuran **113** (150 mg, 0.38 mmol) in anhydrous dichloromethane. After stirring for 1 h at ambient temperature, water was added to the reaction mixture and it was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. After the removal of solvent, the residue was subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate mixture to afford analytically pure **123** as a colorless crystalline solid (122 mg, 90%), m.p. 124-125 °C (recrystallized from CH_2Cl_2-hexane).



123

IR (KBr) ν_{max}: 3002, 2962, 2837, 1735, 1682, 1560, 1464, 1281, 1109, 1036, 983, 764, 665 cm^{-1}.

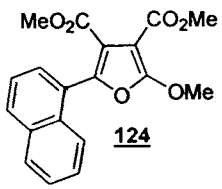
^{1}H NMR: δ 7.66 (s, 1H), 7.43 (s, 2H), 4.21 (s, 3H), 3.82 (s, 3H), 3.71 (s, 3H).

^{13}C NMR: δ 164.2, 161.7, 160.8, 139.5, 133.1, 130.7, 126.9, 124.4, 122.6, 116.5, 58.6, 52.7, 51.6.

Analysis calculated for $C_{15}H_{12}O_6Cl_2$: C, 50.16, H, 3.37; Found: C, 50.20, H, 3.15.

Dimethyl-2-(methoxy)-5-(1-naphthyl)-3,4-furandicarboxylate 124

$SnCl_4$ (52 mg, 0.20 mmol) was added to a solution of the dihydrofuran 114 (150 mg, 0.40 mmol) in anhydrous dichloromethane. After stirring for 1 h at ambient temperature, water was added to the reaction mixture and it was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. After the removal of solvent, the residue was subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate mixture to afford **124** as a colorless viscous liquid (125 mg, 92%).



124

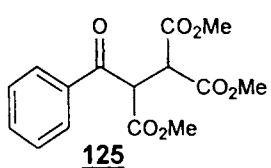
IR (neat) ν_{max}: 3012, 2840, 1726, 1607, 1451, 1345, 1239, 1095, 1052, 802, 777, 652 cm^{-1}.

^{1}H NMR: δ 7.91-7.85 (m, 3H), 7.63 (d, J = 6.6 1H), 7.51-7.48 (m, 3H), 4.13 (s, 3H), 3.84 (s, 3H), 3.64 (s, 3H).

^{13}C NMR: δ 163.6, 162.1, 161.2, 143.6, 133.5, 131.7, 130.2, 129.0, 128.4, 126.7, 126.1, 125.1, 124.9, 117.8, 79.7, 58.4, 52.0, 51.5.

Methyl 2,3-*bis* methoxycarbonyl-4-oxo-4-phenyl-butyrate 125

p-TsOH (26 mg, 0.15 mmol) was added to a solution of the dihydrofuran derivative **107** (50 mg, 0.15 mmol) in methanol and the resulting solution was stirred at r.t. for 3 h. After the removal of the solvent, the residue was extracted with dichloromethane and subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate solvent mixture to afford **125** (41 mg, 90%) as a colorless crystalline solid, m.p 86-87 °C.



125

IR (KBr) ν_{max}: 2956, 2847, 1755, 1744, 1728 1590, 1432, 1301, 1258, 1117, 1002, 939, 889, 764, 696 cm^{-1}.

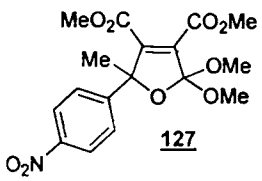
^{1}H NMR: δ 8.09-8.06 (m, 2H), 7.60-7.47 (m, 3H), 5.21 (d, J = 11, 1H), 4.50 (d, J = 11, 1H), 3.80 (s, 3H), 3.66 (s, 6H).

^{13}C NMR: δ 192.4, 168.0, 167.6, 167.3, 135.7, 133.8, 129.2, 128.6, 53.0, 52.9, 52.8, 51.5.

Dimethyl-2,2-dimethoxy-2-methyl-2-(4-nitrophenyl)-2,5-dihydro-3,4-furandicarboxylate 127

A mixture of 4-nitro acetophenone **126** (100 mg, 0.64 mmol), DMAD **2** (136 mg, 0.96 mmol) and oxadiazoline **103** (204 mg, 1.28 mmol) was refluxed

in dry toluene under argon for 16 h. The solvent was removed under vacuum and the residue subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate solvent mixture to afford **127** as a colorless viscous liquid (214 mg, 81%).



127

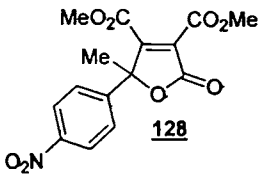
IR (neat) ν_{max}: 2996, 2969, 2847, 1735, 1672, 1607, 1526, 1438, 1344, 1270, 1121, 980, 858, 789, 696 cm^{-1}.

^{1}H NMR: δ 8.19 (d, J = 8.7, 2H), 7.72 (d, J = 8.7, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 3.46 (s, 3H), 3.43 (s, 3H), 2.01 (s, 3H).

^{13}C NMR: δ 161.9, 161.6, 148.13, 147.6, 143.5, 135.5, 127.1, 123.2, 122.8, 86.6, 52.4, 51.2, 50.6, 24.2.

Dimethyl-2oxo-2-methyl-2-(4-nitrophenyl)-2,5-dihydro-3,4-furandicarboxylate 128

$SnCl_4$ (34 mg, 0.13 mmol) was added to a solution of the dihydrofuran **127** (100 mg, 0.26 mmol) in anhydrous dichloromethane. After stirring for 1 h at ambient temperature, water was added to the reaction mixture and it was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. After the removal of solvent, the residue was subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate mixture to afford analytically pure **128** as a colorless solid (78 mg, 90%), m.p 134-135 °C (recrystallized from CH_2Cl_2-hexane).



128

IR (KBr) ν_{max}: 3097, 2955, 2861, 1796, 1748, 1667, 1607, 1533, 1452, 1364, 1283, 1047, 980, 789 cm^{-1}.

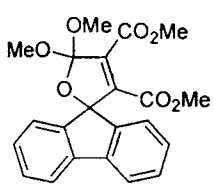
^{1}H NMR: δ 8.60 (d, J = 8.7, 2H), 8.60 (d, J = 8.7, 2H), 4.07 (s, 3H), 3.93 (s, 3H), 2.15 (s, 3H).

^{13}C NMR: δ 165.1, 160.4, 160.1, 158.7, 148.2, 143.1, 127.3, 126.7, 123.9, 86.3, 53.3, 53.1, 24.3.

HRMS (EI) Calculated for $C_{24}H_{24}O_7$: 335.0641 Found: 335.0638.

Dimethyl 5',5'-dimethoxy spiro [9H-fluorene-9,2'(5'H)-furan]-3,4-dicarboxylate 130

A mixture of flourenone **129** (100 mg, 0.55 mmol), DMAD **2** (117 mg, 0.83 mmol) and oxadiazoline **103** (176 mg, 1.10 mmol) was refluxed in dry toluene under argon for 16 h. The solvent was removed under vacuum and the residue subjected to chromatography on a silica gel column using 80:20 hexane-ethyl acetate solvent mixture to afford **130** as a colorless viscous liquid. (109 mg, 50%).



130

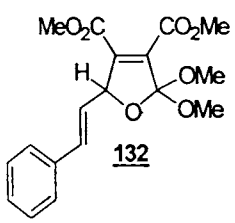
IR (neat) ν_{max}: 3009, 2948, 2847, 1735, 1674, 1452, 1337, 1290, 1175, 1135, 1034, 987, 939, 789, 764 cm^{-1}.

^{1}H NMR: δ 7.62 (d, J = 7.4, 2H), 7.49 (d, J = 7.4, 2H), 7.38 (t, J = 7.4, 2H), 7.26 (t, J = 7.4, 2H), 3.82 (s, 3H), 3.55 (s, 6H), 3.37(s, 3H).

^{13}C NMR: δ 162.2, 160.9, 143.1, 143.0, 140.7, 136.9, 129.9, 128.1, 124.7, 123.3, 120.1, 91.8, 52.6, 52.1, 51.4.

Dimethyl-2,2-dimethoxy-5-(phenylethenyl)-2,5-dihydro-3,4-furandicarboxylate 132

A mixture of cinnamaldehyde **131** (100 mg, 0.76 mmol), DMAD **2** (161 mg, 1.1 mmol) and oxadiazoline **103** (243 mg, 1.5 mmol) was refluxed in dry toluene in a sealed tube for 15 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford **132** as a colorless viscous liquid (185 mg, 70%).



132

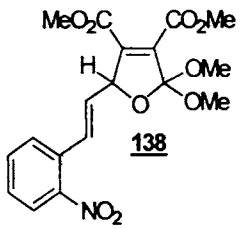
IR (neat) ν_{max}: 3000, 2956, 2848, 1746, 1695, 1644, 1638, 1593, 1447, 1256, 1205, 1105, 1020, 766, 702 cm^{-1}.

^{1}H NMR: 7.39-7.27 (m, 5H), 6.77 (d, J = 15.7, 1H), 6.17-6.09 (m, 1H), 5.51 (d, J = 7.2, 1H), 3.99 (s, 3H), 3.78 (s, 3H), 3.48 (s, 3H), 3.41 (s, 3H).

^{13}C NMR: 163.9, 161.7, 148.0, 144.5, 133.4, 132.4, 131.7, 130.6, 129.2, 126.6, 122.0, 102.4, 54.9, 52.0, 50.5.

Dimethyl-2,2-dimethoxy-5-(2-nitrophenylethenyl)-2,5-dihydro-3,4-furandicarboxylate 138

A mixture of 2-nitrocinnamaldehyde **133** (100 mg, 0.58 mmol), DMAD 2 (123 mg, 0.87 mmol) and oxadiazoline **103** (185 mg, 1.20 mmol) was refluxed in dry toluene in a sealed tube for 15 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford **138** as a colorless viscous liquid (121 mg, 60%).



138

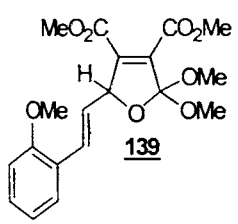
IR (neat) ν_{max}: 3056, 2867, 1735, 1647, 1600, 1512, 1472, 1404, 1351, 1216, 1061, 953, 778 cm^{-1}.

^{1}H NMR: δ 7.98-7.95 (m, 1H), 7.61-7.57 (m, 1H), 7.46-7.42 (m, 1H), 7.30-7.25 (m, 1H), 6.15 (dd, J = 6.7, 15.6, 1H), 5.56 (dd, J = 1.1, 6.7, 1H), 5.30 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.52 (s, 3H), 3.40 (s, 3H).

^{13}C NMR: δ 163.3, 162.2, 136.9, 135.5, 131.7, 130.8, 130.7, 128.7, 126.7, 121.2, 103.5, 55.4, 52.2, 51.1, 50.6, 50.5.

Dimethyl-2,2-dimethoxy-5-(2-methoxyphenylethenyl)-2,5-dihydro-3,4-furandicarboxylate 139

A mixture of 2-methoxycinnamaldehyde **134** (100 mg, 0.61 mmol) DMAD **2** (130 mg, 0.92 mmol) and oxadiazoline **103** (195 mg, 1.22 mmol) was refluxed in dry toluene in a sealed tube for 15 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford **139** as a colorless viscous liquid (92 mg, 40%).



139

IR (neat) ν_{max}: 3063, 2948, 2847, 1742, 1634, 1593, 1438, 1249, 1108, 1027, 784, 757 cm^{-1}.

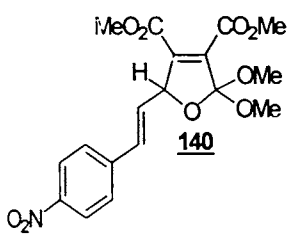
^{1}H NMR: δ 7.60-7.53 (m, 1H), 7.27-7.22 (m, 2H), 7.02-6.76 (m, 3H), 4.15 (s, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.41 (s, 3H).

^{13}C NMR: δ 164.2, 162.5, 157.8, 148.2, 144.3, 132.3, 131.0, 129.8, 127.1, 126.4, 121.9, 115.0, 102.9, 54.8, 52.2, 51.1, 50.7, 50.6.

HRMS (EI) Calculated for $C_{19}H_{22}O_8$: 378.1315 Found: 378.1292

Dimethyl-2,2-dimethoxy-5-(4-nitrophenylethenyl)-2,5-dihydro-3,4-furandicarboxylate 140

A mixture of 4-nitrocinnamaldehyde **135** (100 mg, 0.56 mmol), DMAD **2** (119 mg, 0.84 mmol) and oxadiazoline **103** (179 mg, 1.12 mmol) was refluxed in dry toluene in a sealed tube for 15 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford **140** as a colorless viscous liquid (110 mg, 50%).



140

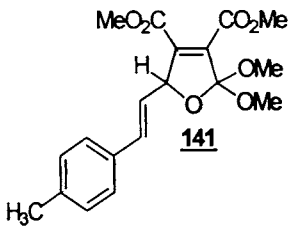
IR (neat) ν_{max}: 2956, 2848, 1740, 1600, 1542, 1447, 1256, 1020, 874, 746, 715 cm^{-1}.

^{1}H NMR: δ 8.18 (d, J = 8.6, 2H), 7.52 (d, J =8.6, 2H), 6.84 (d, J = 15.8, 1H), 6.37 (dd, J = 6.6, 15.8, 1H), 5.54 (d, J = 6, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.52 (s, 3H), 3.47 (s, 3H).

^{13}C NMR: δ 162.3, 161.3, 147.4, 142.2, 138.5, 136.4, 131.6, 128.2, 127.4, 123.7, 119.0, 81.6, 52.8, 52.6, 51.3, 51.2.

Dimethyl-2,2-dimethoxy-5-(4-methylphenylethenyl)-2,5-dihydro-3,4-furandicarboxylate 141

A mixture of 4-methyl cinnamaldehyde **136** (100 mg, 0.68 mmol), DMAD **2** (144 mg, 1.02 mmol) and oxadiazoline **103** (217 mg, 1.36 mmol) was refluxed in dry toluene in a sealed tube for 15 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford **141** as a colorless viscous liquid (93 mg, 38%).



141

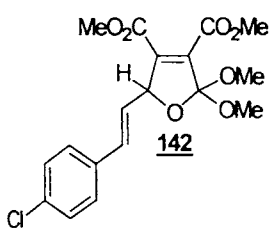
IR (neat) ν_{max}: 3012, 2948, 2834, 1735, 1675, 1445, 1270, 1128, 980, 798, 697 cm^{-1}.

^{1}H NMR: δ 7.35(d, J = 8, 2H), 7.08 (d, J = 8, 2H), 6.93 (d, J = 15.6, 1H), 6.48 (dd, J = 6.6, 15.8, 1H), 4.91 (d, J = 6, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.59 (s, 3H), 3.39 (s, 3H), 2.29 (s, 3H).

^{13}C NMR: δ 162.5, 162.1, 142.9, 137.8, 135.4, 133.6, 131.3, 128.4, 127.1, 123.0, 119.1, 89.9, 52.6, 52.5, 51.5, 51.1, 21.2.

Dimethyl-2,2-dimethoxy-5-(4-chlorophenylethenyl)-2,5-dihydro-3,4-furandicarboxylate 142

A mixture of 4-chlorocinnamaldehyde **137** (100 mg, 0.60 mmol), DMAD **2***r* (127 mg, 0.9 mmol) and oxadiazoline **103** (192 mg, 1.20 mmol) was refluxed in dry toluene in a sealed tube for 15 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford **142** as a colorless viscous liquid (118 mg, 60%).



142

IR (neat) ν_{max}: 3012, 2955, 2840, 1742, 1708, 1640, 1485, 1438, 1317, 1249, 1108, 1013, 838, 744, 663cm^{-1}.

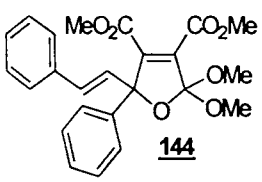
^{1}H NMR: δ 7.87 (d, J = 8.4, 2H), 7.37 (d, J = 8.4, 2H), 6.8 (m, 1H) 6.3(d, J = 15.6, 1H) 4.22 (d, J = 6, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 3.36 (s, 6H).

^{13}C NMR: δ 163.3, 162.1, 146.9, 141.2, 135.6, 134.8, 132.6, 129.6, 128.7, 127.8, 126.8, 103.0, 55.4, 52.1, 51.1, 50.5.

HRMS (EI) Calculated for $C_{18}H_{19}O_7Cl$: 382.0819 Found: 382.0899.

Dimethyl-2,2-dimethoxy-5-phenyl-5-(phenylethenyl)-2,5-dihydro-3,4-furandicarboxylate 144

A mixture of chalcone **143** (100 mg, 0.48 mmol), DMAD **2** (102 mg, 0.72 mmol) and oxadiazoline **103** (243 mg, 0.96 mmol) was refluxed in dry toluene in a sealed tube for 24 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford **144** as a colorless viscous liquid (142 mg, 70%).



144

IR (neat) ν_{max}: 3002, 2955, 2847, 1740, 1728, 1452, 1431, 1283, 987, 933, 752, 703 cm^{-1}.

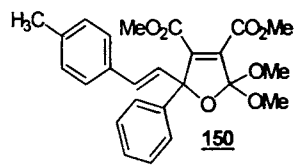
^{1}H NMR: δ 7.21-7.47 (m, 10H), 6.92 (d, J = 16, 1H), 6.76 (d, J = 16, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.49 (s, 3H), 3.33 (s, 3H).

^{13}C NMR: δ 162.4, 162.1, 142.9, 140.1, 136.4, 135.6, 134.4, 131.4, 128.6, 128.4, 128.3, 126.8, 123.7, 123.1, 89.8, 52.5, 52.4, 51.4, 50.0.

HRMS (EI) Calculated for $C_{24}H_{24}O_7$: 424.1522 Found: 424.1534

Dimethyl-2,2-dimethoxy-5-phenyl-5-(4-methylphenylethenyl)-2,5-dihydro-3,4-furandicarboxylate 150

A mixture of chalcone **145** (100 mg, 0.44 mmol), DMAD **2** (95 mg, 0.67 mmol) and oxadiazoline **103** (140 mg, 0.88 mmol) was refluxed in dry toluene in a sealed tube for 24 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford **150** as a colorless viscous liquid (186 mg, 60%).



150

IR (neat) ν_{max}: 3012, 2948, 2834, 1735, 1675, 1445, 1270, 1128, 980, 697 cm^{-1}.

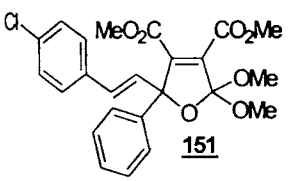
^{1}H NMR: δ 7.46-7.44 (m, 2H), 7.33-7.31 (m, 5H), 7.12 (d, J = 7.9, 2H), 6.88 (d, J = 16, 1H), 6.70 (d, J = 16, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 3.48 (s, 3H), 3.33 (s, 3H), 2.03 (s, 3H).

^{13}C NMR: δ 162.5, 162.1, 142.9, 140.1, 137.8, 135.7, 134.6, 133.5, 131.3, 129.3, 129.2, 128.3, 127.1, 126.8, 123.0, 89.9, 52.6, 52.5, 51.5, 51.1, 21.2.

HRMS (EI) Calculated for $C_{25}H_{26}O_7$: 438.1679 Found: 438.1671

Dimethyl-2,2-dimethoxy-5-phenyl-5-(4-chlorophenylethenyl)-2,5-dihydro-3,4-furandicarboxylate 151

A mixture of chalcone **146** (100 mg, 0.41 mmol), DMAD **2** (87 mg, 0.61 mmol) and oxadiazoline **103** (153 mg, 0.96 mmol) was refluxed in dry toluene in a sealed tube for 24 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford **151** as a colorless viscous liquid (122 mg, 65%).



151

IR (neat) ν_{max}: 3015, 2948, 2840, 1735, 1667, 1492, 1324, 1263, 1175, 1020, 966, 845, 730 cm^{-1}.

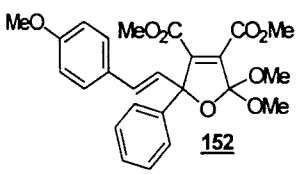
^{1}H NMR: δ 7.45-7.26 (m, 9H), 6.88 (d, J = 16, 1H), 6.75 (d, J = 16, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 3.49 (s, 3H), 3.32 (s, 3H).

^{13}C NMR: δ 162.3, 162.1, 142.8, 140.1, 136.1, 135.7, 135.3, 134.6, 133.8, 128.4, 128.2, 127.0, 125.5, 123.1, 89.7, 52.7, 52.4, 51.2, 50.7.

HRMS (EI) Calculated for $C_{24}H_{23}ClO_7$: 458.1132, Found: 458.1109.

Dimethyl-2,2-dimethoxy-5-phenyl-5-(4-methoxyphenylethenyl)-2,5-dihydro-3,4-furandicarboxylate 152

A mixture of chalcone **147** (100 mg, 0.41 mmol), DMAD **2** (89mg, 0.62 mmol) and oxadiazoline **103** (131.2 mg, 0.96 mmol) was refluxed in dry toluene in a sealed tube for 24 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford **152** as a colorless viscous liquid (70 mg, 38%).



152

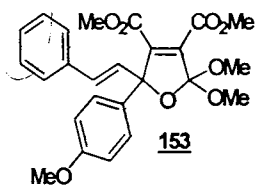
IR (neat) ν_{max}: 3009, 2955, 1742, 1613, 1512, 1276, 1182, 1034, 966, 912, 811, 703 cm^{-1}.

^{1}H NMR: δ 7.44-7.34 (m, 2H), 7.31-7.26 (m, 5H), 6.87-6.81 (m, 3H), 6.65 (d, J = 16, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H), 3.48 (s, 3H), 3.33 (s, 3H).

^{13}C NMR: δ 162.4, 162.2, 159.6, 143.3, 140.3, 135.3, 131.0, 129.2, 128.2, 128.0, 127.3, 127.1, 126.1, 123.0, 89.9, 55.1, 52.7, 52.4, 51.6. 51.1.

Dimethyl-2,2-dimethoxy-5-(4-methoxyphenyl)-5-(4-chlorophenylethenyl)-2,5-dihydro-3,4-furandicarboxylate 153

A mixture of chalcone **148** (100 mg, 0.41 mmol), DMAD **2** (89mg, 0.62 mmol) and oxadiazoline **103** (131.2 mg, 0.96 mmol) was refluxed in dry toluene in a sealed tube for 24 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford **153** as a colorless viscous liquid (930 mg, 50%).



153

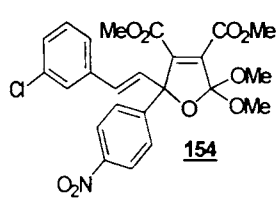
IR (neat) ν_{max}: 3009, 2955, 1731, 1674, 1607, 1512, 1438, 1256, 1175, 1115, 1027, 906, 744 cm^{-1}.

^{1}H NMR: 7.44-7.22 (m, 7H), 6.94-6.83 (m, 3H), 6.74 (d, J = 16, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.43 (s, 3H), 3.23 (s, 3H).

^{13}C NMR: δ 162.5, 162.1, 159.6, 142.9, 140.3, 136.4, 135.3, 132.4, 131.1, 128.5, 128.3, 128.3, 128.0, 126.8, 122.9, 89.6, 55.1, 52.7, 52.6, 51.4, 51.1.

Dimethyl-2,2-dimethoxy-5-(4-nitrophenyl)-5-(3-chlorophenylethenyl)-2,5-dihydro-3,4-furandicarboxylate 154

A mixture of chalcone **149** (100 mg, 0.34 mmol), DMAD **2** (74mg, 0.52 mmol) and oxadiazoline **103** (108 mg, 0.68 mmol) was refluxed in dry toluene in a sealed tube for 24 h The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford **154** as a colorless viscous liquid (118 mg, 60%).



154

IR (neat) ν_{max}: 2996, 2948, 1735, 1607, 1533, 1438, 1357, 1270, 1115, 973, 858, 757 cm^{-1}.

^{1}H NMR: δ 8.21 (d, J = 8.9, 2H), 7.69 (d, J = 8.9, 2H), 7.60-7.57 (m, 1H), 7.41-7.35 (m, 2H), 7.26-7.23 (m, 2H), 6.75 (d, J = 16, 1H), 3.89 (s, 3H), 3.76 (s, 3H), 3.54 (s, 3H), 3.38 (s, 3H).

^{13}C NMR: δ 162.1, 161.6, 147.8, 147.0, 140.6, 137.2, 134.1, 133.7, 129.5, 129.4, 128.9, 128.7, 128.6, 128.1, 127.1, 123.5, 88.7, 52.8, 52.0, 51.0.

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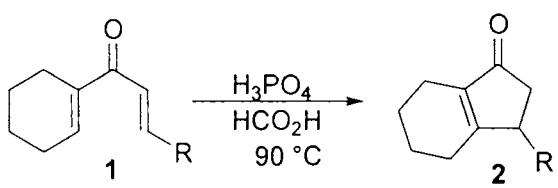
CHAPTER 3

SYNTHESIS OF BICYCLIC LACTONES *via* AN INTERRUPTED NAZAROV REACTION OF *gem* DIVINYL DIHYDROFURANS

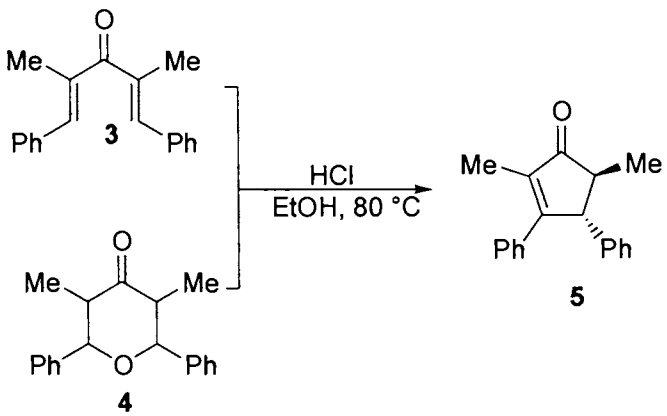
3.1 Introduction

The Nazarov reaction, named after the eminent Russian chemist I. N. Nazarov, constitutes a well-known method for the construction of 2-cyclopentenones.[1] The reaction is formulated as the acid catalyzed closure of divinyl ketones to cyclopentenones under the influence of very strong acids such as sulfuric acid or phosphoric acid (Scheme 1). Modern variants of this reaction employ Lewis acids such as tin tetrachloride, boron trifluoride diethyletherate, aluminium chloride, or ferric chloride in chlorocarbon solvents.[2]



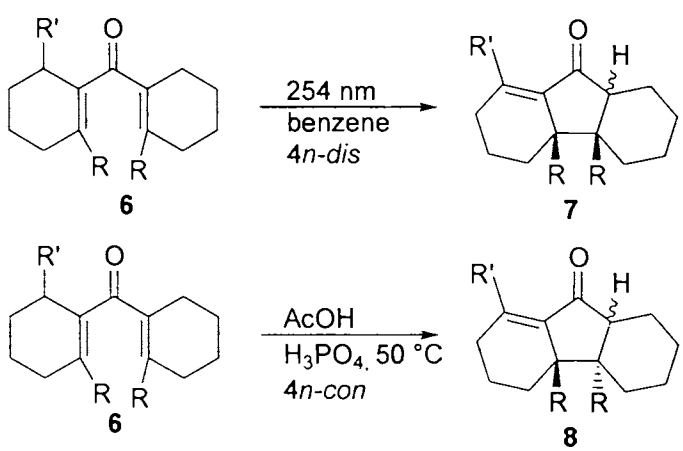
Scheme 1

A wide variety of precursors which can transform to divinyl ketones or their functional equivalents under specific reaction conditions can be successfully employed in this reaction. It is this structural diversity of precursors that lends versatility to Nazarov reaction. A specific example involving a tetrahydropyran is shown below (Scheme 2).[3]



Scheme 2

Both spectroscopic and stereochemical studies have established Nazarov cyclization as a pericyclic reaction belonging to the class of electrocyclizations, specifically the 4π electrocyclic closure of a 3-hydroxy pentadienylic cation.[4] The intermediacy of carbocations in these reactions has been proved by the isolation of products derived from Wagner-Meerwein rearrangement. The relative configuration of the substituents on the newly formed bond of the five membered ring can be easily predicted from orbital symmetry rules governing electrocyclic reactions. This can be visualized in the reaction of *bis*-(1-cyclohexenyl) ketones under both thermal (*con* rotatory) and photochemical (*dis* rotatory) conditions.[5] The newly formed double bond normally occupies the most substituted position obeying the Saytzeff rule (Scheme 3).

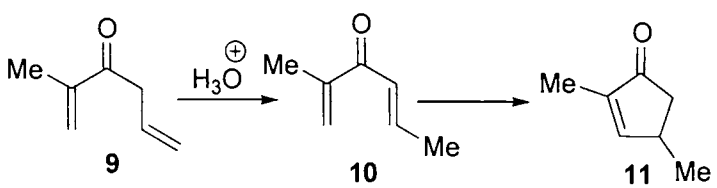


Scheme 3

Nazarov reaction can be further classified into six categories depending on the structure of the precursors employed; a) cyclization of divinyl and allyl vinyl ketones, b) cyclization of silylated (stannylated) divinyl ketones, c) *in situ* generation/cyclization of divinyl ketones, d) solvolytic generation/cyclization of divinyl ketones or equivalents, e) reaction of alkyne-based precursors of divinyl ketones, f) coupling reactions to generate and cyclize divinyl ketones.

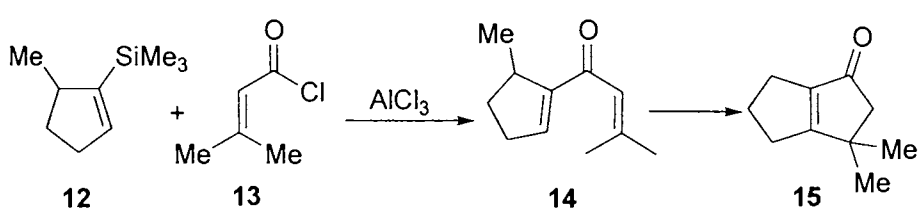
3.1a Cyclization of Divinyl and Allyl Vinyl Ketones

The tautomeric divinyl and allyl vinyl ketones are equivalent precursors for acid promoted cyclizations (Scheme 4).[6] Allyl vinyl ketones are produced by the mercuric ion catalyzed hydration of dienynes, the latter being prepared by the dehydration of vinyl acetylide adducts of ketones.



Scheme 4

In another approach, monocyclic precursors were prepared by the acylation of cycloalkenyl silanes with the corresponding α,β-unsaturated acid chlorides (Scheme 5).[7]

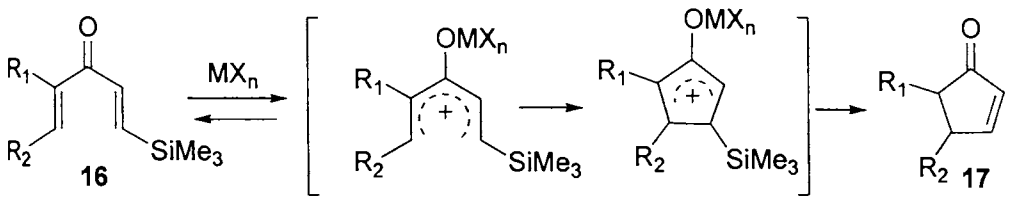


Scheme 5

3.1b Cyclization of Silylated (Stannylated) Divinyl Ketones

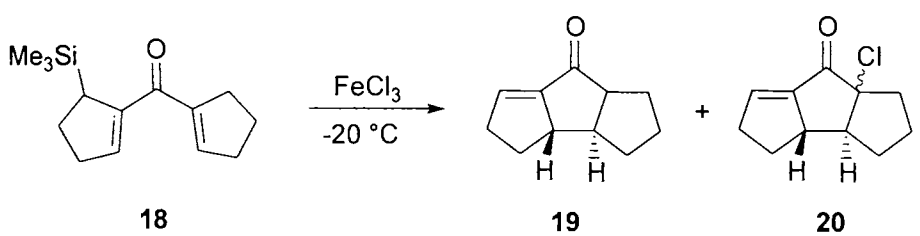
Denmark has demonstrated that the scope and synthetic utility of Nazarov reaction can be greatly enhanced by employing β-silyl or α'-silyl divinyl ketones as precursors.[8] The strategic placement of a trialkylsilyl or stannyl group can control the collapse of the intermediate cyclopentenylic

cation, thereby suppressing cationic rearrangements. An additional feature gained by this strategy is that the final position of the newly formed double bond in the cyclopentenone ring can be fixed. This is particularly significant in the preparation of simple cyclopentenones in which the double bond resides in the least substituted position (Scheme 6).



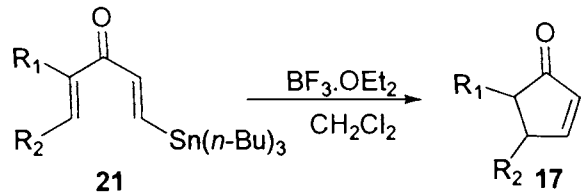
Scheme 6

A wide range of Lewis acids can effectively promote the silicon directed Nazarov reaction, the most commonly used one is anhydrous iron (III) chloride at low temperatures (Scheme 7). Lewis acids such as boron trifluoride and zirconium tetrachloride were also found to be equally effective for this reaction.[9]



Scheme 7

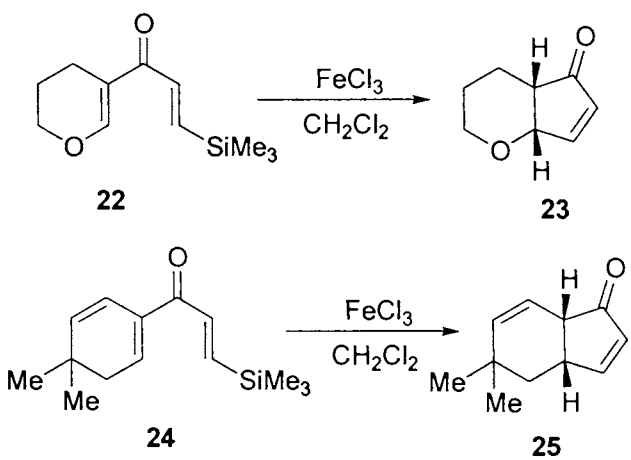
The use of tin derivatives in Nazarov cyclization has also been reported. Trialkyltin substituted divinyl ketones undergo cyclization in a similar fashion as the silyl substituted divinyl ketones in silicon directed Nazarov cyclization, and it is reported that these reactions are best promoted by boron trifluoride (Scheme 8).[10]



21

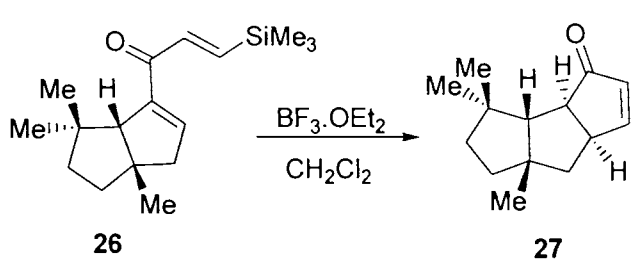
Scheme 8

A wide range of substrates such as cyclic, acyclic, heterocyclic and unsaturated carbocyclic divinyl ketones can participate in silicon directed Nazarov cyclization.[11] In all these, the newly formed double bond was found to be exclusively in the less substituted position. Two specific examples are shown in Scheme 9.

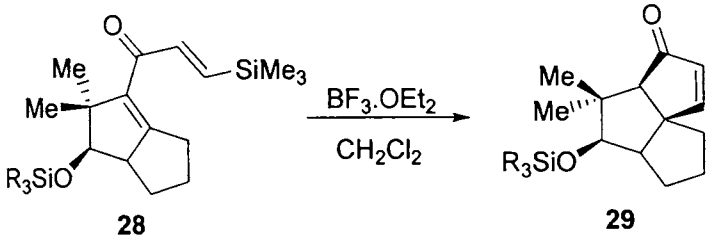


Scheme 9

Cyclopentenone annulation with chiral substrates has been extensively studied and has been applied to the synthesis of linear and angular triquinanes (Scheme 10).[11]



26 27

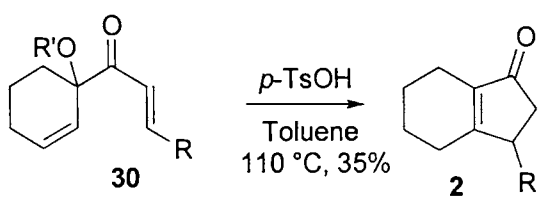


28 29

Scheme 10

In situ Generation/Cyclization of Divinyl Ketones

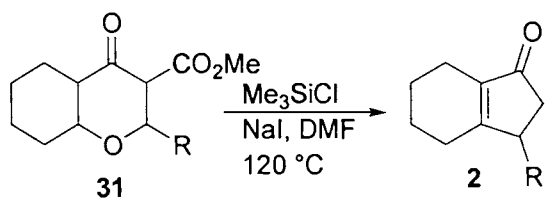
α-Oxygenated enones are precursors of divinyl ketones. These compounds on treatment with acid at elevated temperatures afforded the cyclopentenone derivatives *via* the Nazarov cyclization *albeit* in low yields (Scheme 11).[12]



30 2

Scheme 11

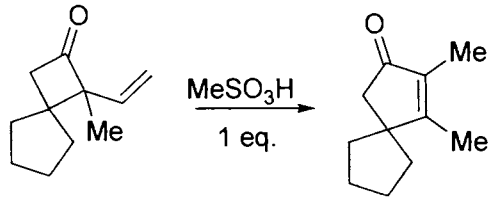
Similarly the double β-elimination of tetrahydro-4-pyranone **31** in presence of trimethylsilyl chloride or trimethylsilyl triflate afforded the corresponding cyclized product **2** (Scheme 12).[13]



31 2

Scheme 12

The acid catalyzed rearrangement of α-vinyl cyclobutanones furnishes divinyl ketones. However, in presence of equivalent amount of acids, the reaction proceeds further to afford Nazarov products (Scheme 13).[14]

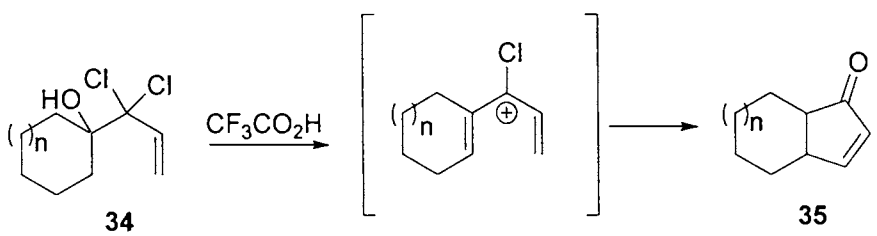


32 33

Scheme 13

3.1d Solvolytic Generation/Cyclization of Divinyl Ketones or Equivalents

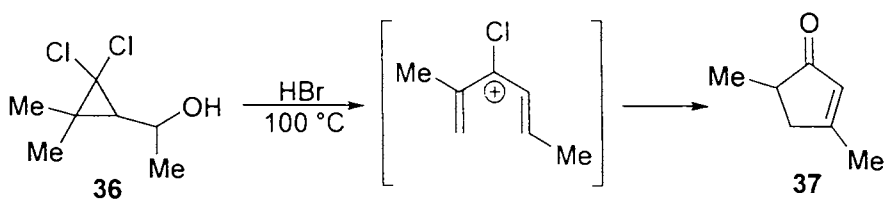
Dihalo-homoallylic alcohols under strong acidic conditions transform to the 3-halo-pentadienylic cations, which undergo Nazarov cyclization affording cyclopentenone derivatives (Scheme 14).[15]



34 35

Scheme 14

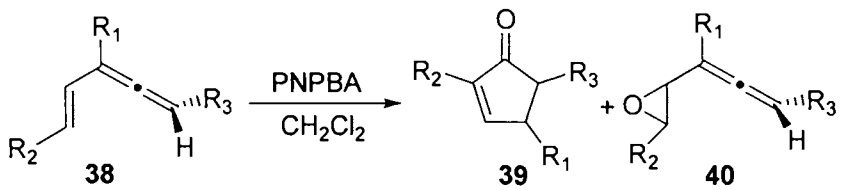
Similar intermediates can also be generated from substituted dihalocyclopropanes (Scheme 15).[16]



36 37

Scheme 15

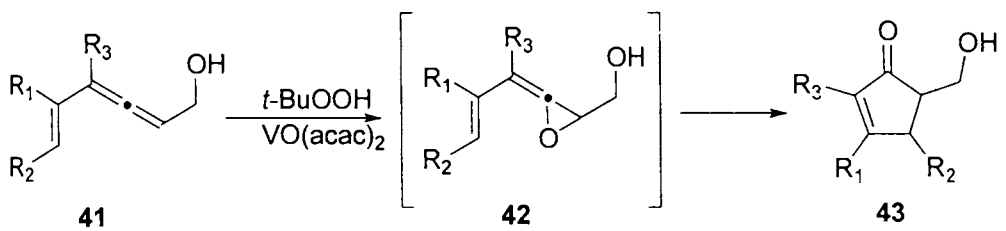
Peracid epoxidation of vinyl allenes bearing allenic substituents leads to the formation of cyclopentenones (Scheme 16).[17]Allenes lacking substituents afforded the epoxides exclusively.



PNPBA = *p*-nitroperoxy benzoic acid

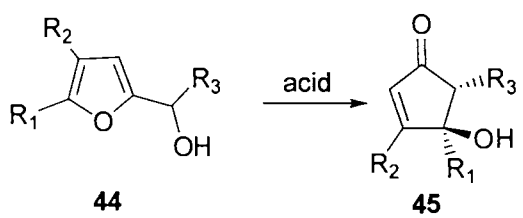
Scheme 16

Here the unproductive oxidation of the vinyl double bond can be suppressed by introducing hydroxyl substituents in the substrate, and this furnishes the cyclopentenones in good yields. The reaction presumably goes through a vinylallene oxide **42** (Scheme 17).[18]



Scheme 17

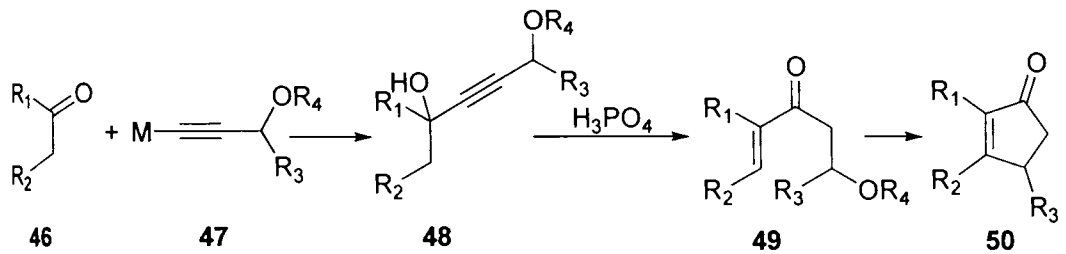
The acid catalyzed rearrangement of 2-furyl alcohols, readily available from furfural by Grignard addition, constitutes a versatile synthesis of hydroxy cyclopentenones *via* the Nazarov cyclization (Scheme 18).[19]



Scheme 18

3.1e Reaction of Alkyne-Based Precursors of Divinyl Ketones

Ynediols obtained by the addition of propargylic alcohols and ethers to ketones, undergo acid catalyzed cyclization to afford cyclopentenones.[20] The advantage of the method is that it works under fairly mild conditions, and for many years this reaction constituted the method of choice for cyclopentenone annulation (Scheme 19).

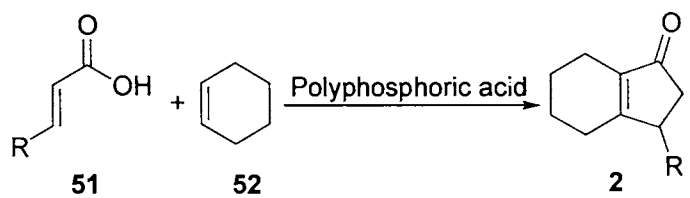


46 47 48 49 50

Scheme 19

3.1f Coupling Reactions to Generate and Cyclize Divinyl Ketones.

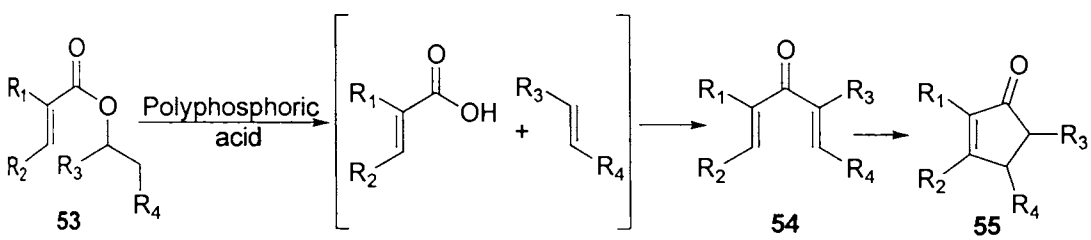
Earlier methods used under this category involved the Friedel-Crafts reaction of cycloalkenes with α,β-unsaturated acids (Scheme 20).[21]



51 52 2

Scheme 20

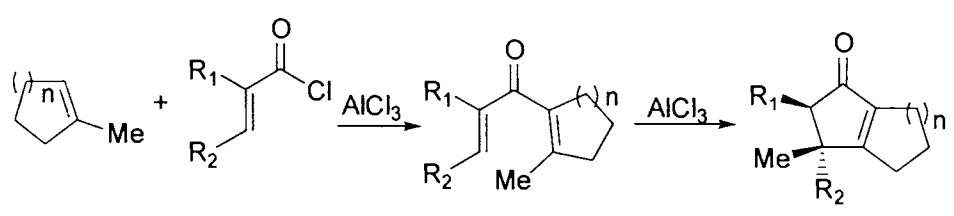
Under these conditions, α,β-unsaturated esters undergo fragmentation and subsequent Friedel-Crafts reaction to generate divinyl ketones and the latter take the Nazarov route to afford cyclopentenone derivatives (Scheme 21).[22]



53 54 55

Scheme 21

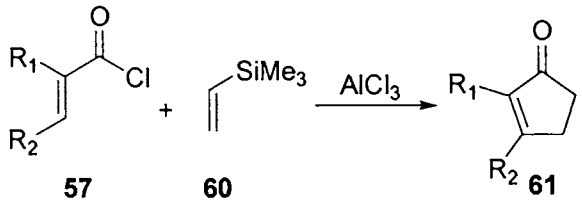
Another method employed involves the use of acyl halides in coupling reactions to generate the divinyl ketones (Scheme 22).[23]



56 57 58 59

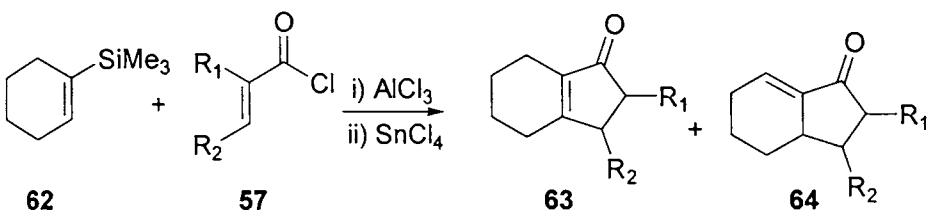
Scheme 22 G8552

A significant improvement in the utility of this approach involved the use of vinyl silanes for the preparation of intermediate divinyl ketones (Scheme 23).[24]



Scheme 23

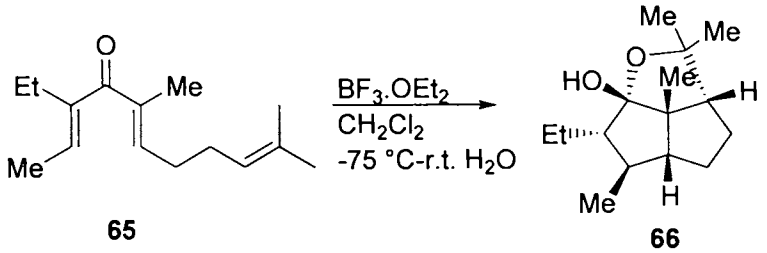
Substituted acryloyl chlorides in combination with cyclic vinyl silanes have also been used in Nazarov Cyclization (Scheme 24).[7, 25]



Scheme 24

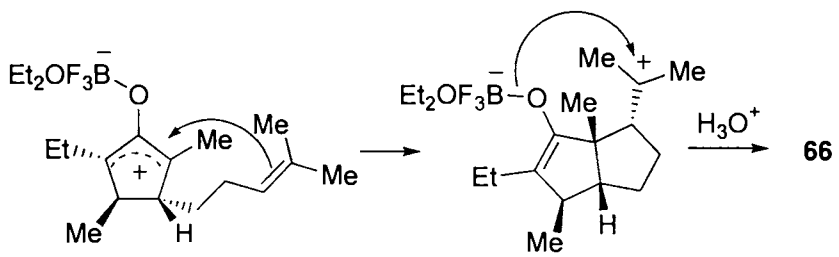
3.2 Interrupted Nazarov Reaction

Interrupted Nazarov reaction is a close variant of Nazarov cyclization, introduced by West in 1998.[26] It is well known that Nazarov cyclization proceeds *via* oxyallyl intermediates. The central feature of this reaction is a carbon-carbon bond formation *via* the conrotatory electrocyclization of a pentadienylic cation and the creation of two new stereocenters. Some or all the stereochemical information is lost in the subsequent deprotonation or desilylation steps. In the interrupted Nazarov reaction, the stereochemical integrity is retained by trapping the oxyallyl zwitterion with pendant nucleophiles. In the initial report, West and coworkers have utilized the interrupted Nazarov reaction for the synthesis of functionalized polycyclic ring systems.[26] The reaction involved the trapping of the Nazarov oxyallyl intermediate with an attached olefin moiety and this process efficiently transformed the acyclic, achiral trienones to diquinanes with six new stereocenters (Scheme 25).



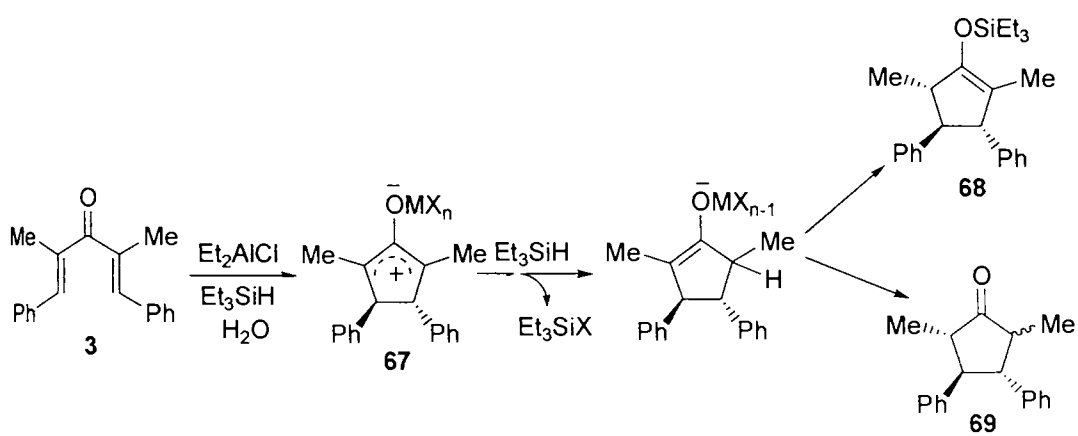
Scheme 25

A mechanistic rationale for this transformation is given in Scheme 26.



Scheme 26

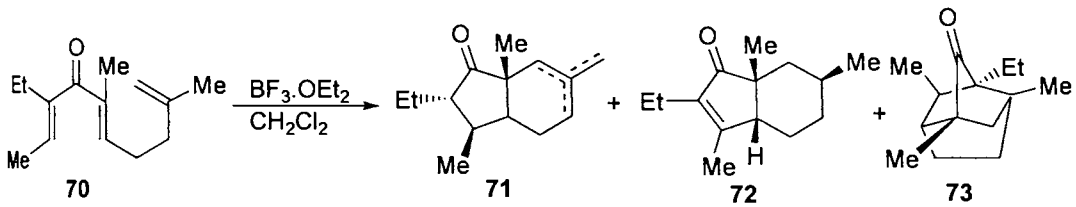
The "reductive" Nazarov reaction, another variant of interrupted Nazarov cyclization was reported by West and co-workers. The reaction involved the treatment of divinyl ketones with a reducing agent such as triethyl silane in the presence of a Lewis acid.[27] The reaction is presumed to occur *via* the oxyallyl intermediate **67** which undergoes intermolecular hydride transfer and *O*-silylation to afford the products **68** and **69** (Scheme 27).



Scheme 27

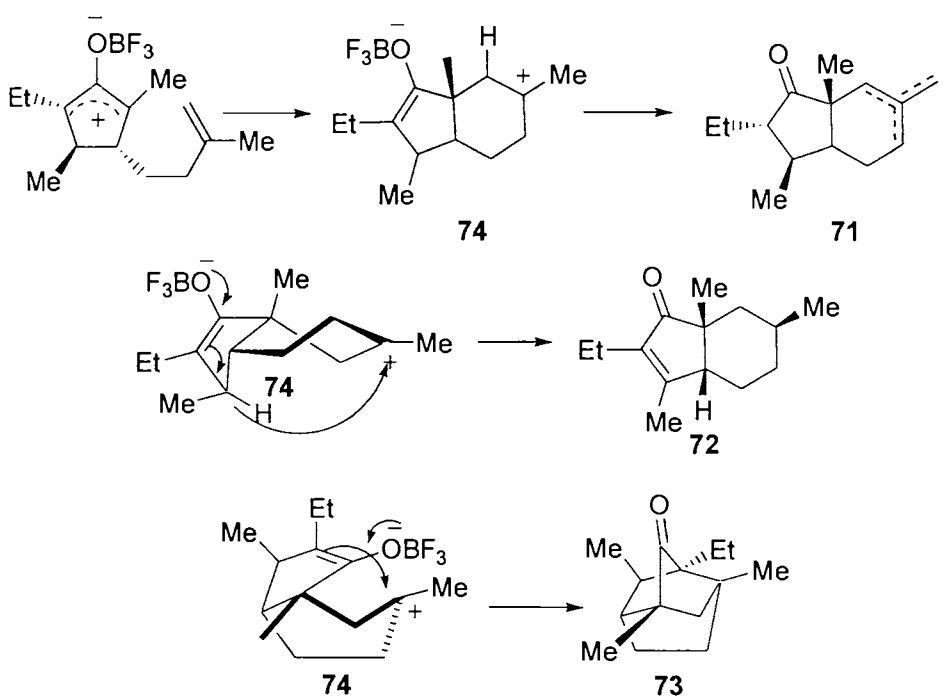
In related studies West has shown that the trienone **70**, on treatment with $BF_3.OEt_2$ at -78 °C underwent an interrupted Nazarov reaction to afford the

hydrindenone regioisomers **71** along with two other products **72** and **73** (Scheme 28).[28]



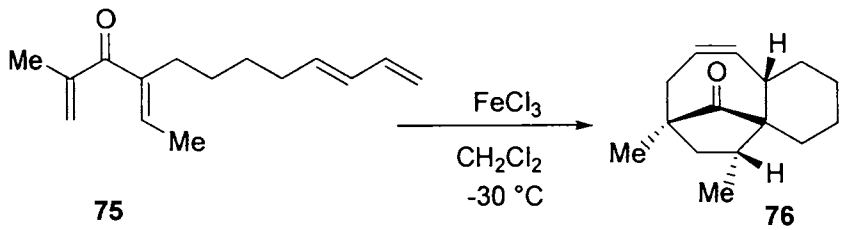
Scheme 28

The initial event in this reaction is the interception of the oxyallyl intermediate with the pendant alkene to form a tertiary carbocation **74** which undergoes further rearrangements to afford all the three products as shown in the following scheme (Scheme 29).



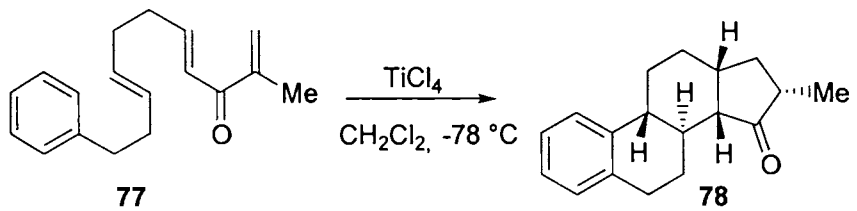
Scheme 29

In another study, West has demonstrated the formation of complex polycyclic ring systems bearing several stereocenters by the [4+3] trapping of the Nazarov oxyallyl intermediate with a suitable pendant diene moiety (Scheme 30).[29]



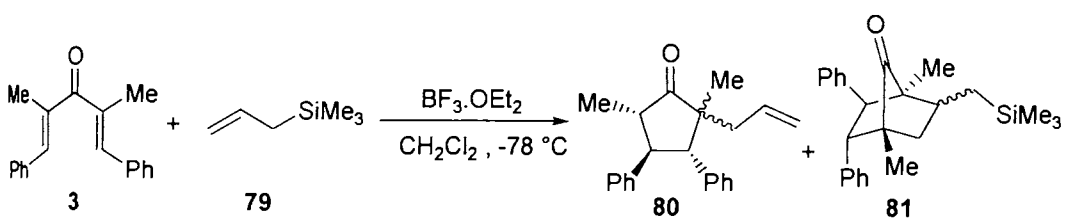
Scheme 30

The same strategy has been elegantly applied to the diastereoselective synthesis of tetra- or pentacyclic ring systems from simple aryl trienone precursors (Scheme 31).[30]



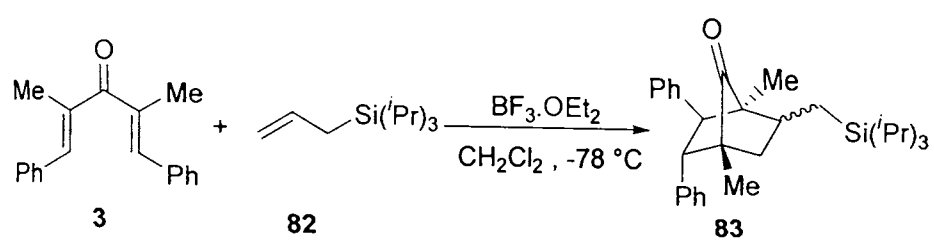
Scheme 31

Intermolecular trapping of the Nazarov oxyallyl intermediate with allyl silanes was also reported by West and co-workers.[31] The reaction afforded the allylated cyclopentanone derivative **80** and a bicyclo[2.2.1]heptanone derivative **81**, formed *via the [3+2] addition of the oxyallyl cation and the* alkene (Scheme 32).



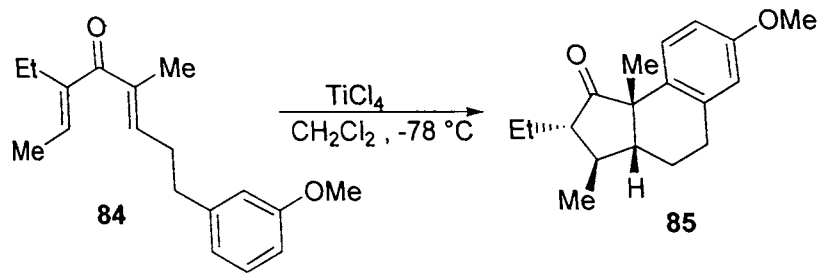
Scheme 32

Allyl silanes with bulkier substituents, however, afforded only the [3+2] adduct (Scheme 33).



Scheme 33

Divinyl ketones with pendant aryl moieties have also been reported to undergo interrupted Nazarov reaction, thus offering a simple and efficient route to the diastereoselective synthesis of benzohydrindanes in high yields (Scheme 34).[32]



Scheme 34

3.3 The Present Work

It is evident from the literature survey presented above that, the substrates which undergo interrupted Nazarov reaction include only the divinyl ketone derivatives. The participation of divinyl dihydrofurans in such interrupted Nazarov reactions has not been reported so far. Against this background, and with the reasonable assumption that a similar reaction will occur in the case of divinyl dihydrofuran derivatives, we undertook some investigations in this area and the results are presented in the following section.

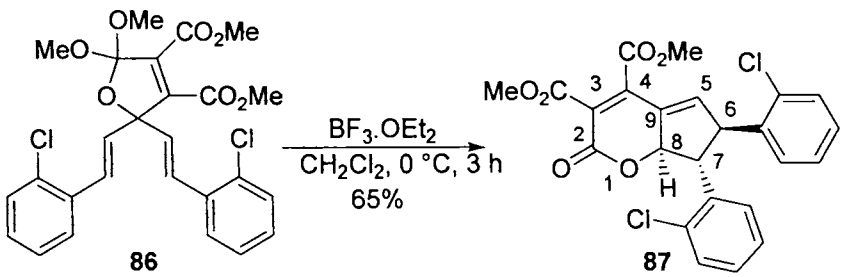
3.4 Results and Discussion

3.4.1 Interrupted Nazarov Reaction of Divinyl Dihydrofurans

The divinyl dihydrofurans selected for our studies have been prepared by a multicomponent reaction of 1,4-dienones, DMAD and dimethoxycarbene which in turn is generated by the thermolysis of 2,2-dimethoxy Δ^3-1,3,4-oxadiazoline, following the Warkentin prescription.[33] (see Section 2.4.5 of Chapter 2 and Section 3.4.2 of this Chapter for the synthesis of various divinyl dihydrofurans).

Our studies were set in motion by exposing the divinyl dihydrofuran derivative **86** with a stoichiometric amount of $BF_3.OEt_2$ in dichloromethane.

The reaction furnished a single bicyclic lactone **87**, presumably resulting from an interrupted Nazarov reaction (Scheme 35).



Scheme 35

The structure of the product **87** was ascertained by spectroscopic analysis. The IR spectrum showed characteristic absorption peaks at 1745 cm^{-1}, 1738 cm^{-1} and 1728 cm^{-1} due to the lactone and ester carbonyls respectively. In the ^1H NMR spectrum, the carbomethoxy groups were discernible as a sharp singlet at δ 3.91. The methine proton adjacent to the ring oxygen resonated as a triplet at δ 3.88 (J = 8 Hz). The olefinic proton signal at C-5 appeared as a singlet at δ 6.82 while the C-7 proton resonated as a doublet at δ 5.02 (J = 8 Hz). The doublet at δ 5.91 (J = 8 Hz) was assigned to the C-6 proton. Aromatic protons were visible as a multiplet between δ 7.19 and δ 7.35. In the ^{13}C NMR spectrum, the characteristic signal due to the lactone carbonyl was observed at δ 163.8 and the ester carbonyls provided peaks at δ 162.7 and δ 160.3 The two benzylic carbons C-6 and C-7 resonated at δ 59.4 and δ 53.1 whereas the C-7 carbon was discernible at δ 87.0 All the other signals were also in good agreement with the proposed structure. The purity of the compound was attested by satisfactory microanalytical data. Final proof for the structure and stereochemistry of the product was obtained from single crystal X-ray analysis (Figure 1).

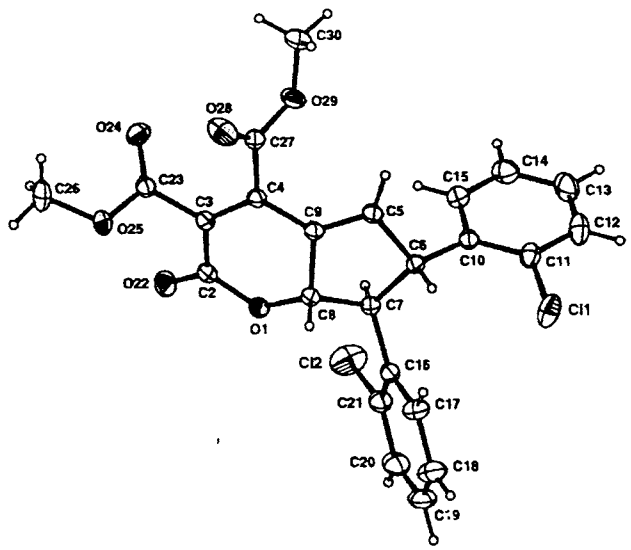


Figure 1 X- Ray Crystal Structure of 87

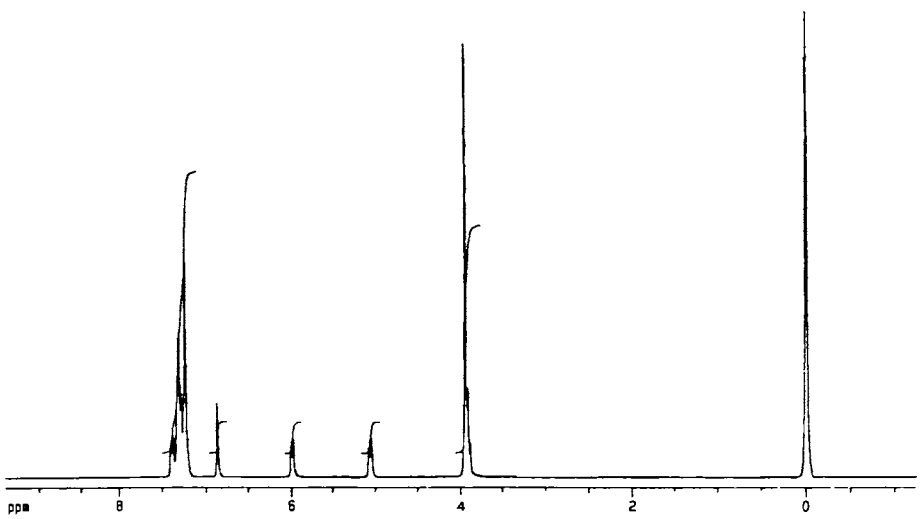


Figure 2 ^{1}H NMR Spectrum of 87

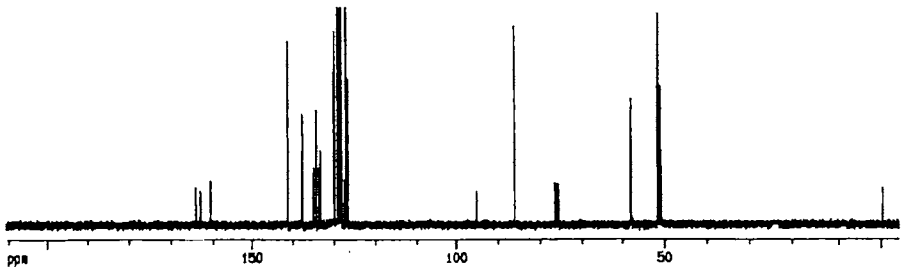
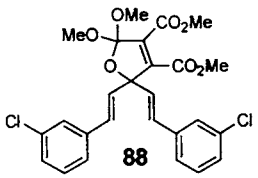
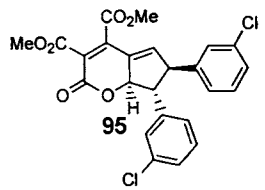
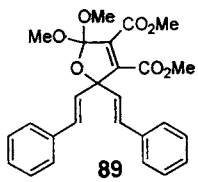
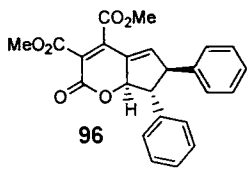
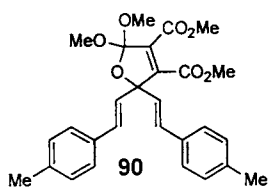
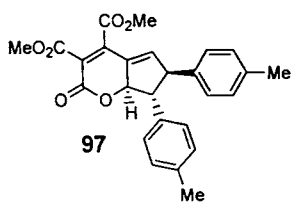
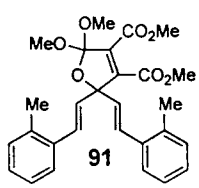
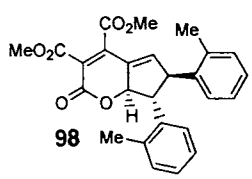
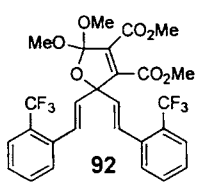
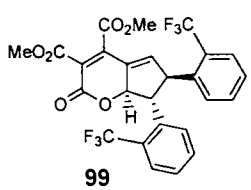
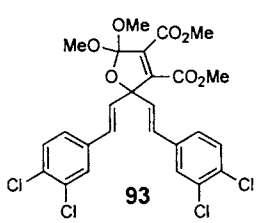
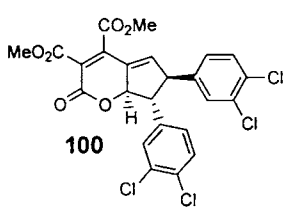
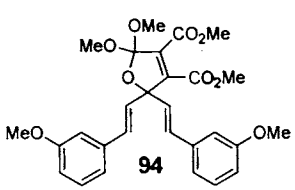
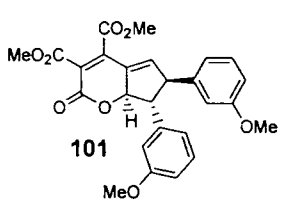


Figure 3 ^{13}C NMR Spectrum of 87

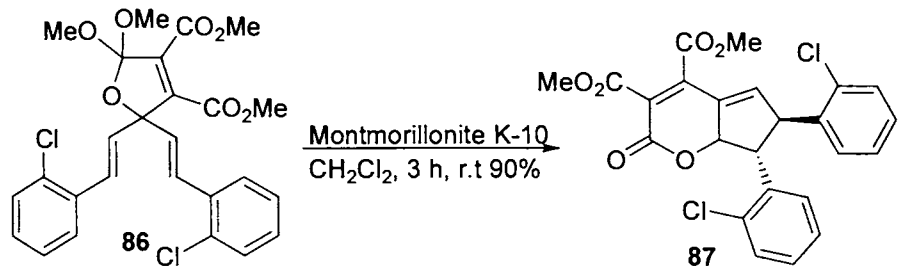
To explore the scope and generality of the reaction, a variety of substituted divinyl ketones were subjected to the reaction under identical conditions. In all the cases, bicyclic lactones were obtained in moderate to excellent yields; the results are summarized in Table 1. Since we are not observing a substantial difference in the product yields in this reaction as shown in Table 1, it may be concluded that the substituents on the aromatic ring do not play any significant role in the cyclization.

Table 1

Entry	Substrate	Product	Yield (%)*
1	 88	 95	65
2	 89	 96	60
3	 90	 97	81
4	 91	 98	60
5	 92	 99	60
6	 93	 100	79
7	 94	 101	60

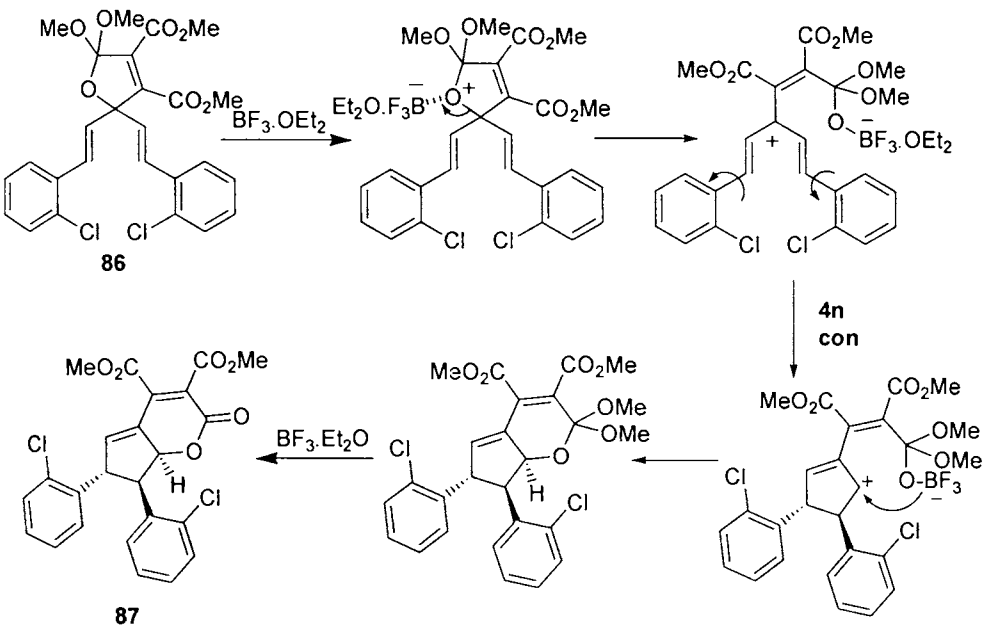
Reaction conditions: $BF_3.OEt_2$, CH_2Cl_2, 0 °C, 3 h
* = isolated yield

Similar reaction occurred when $SnCl_4$ was employed as the Lewis acid. When the reaction was carried out in the presence of Montmorillonite K-10 clay, a similar reaction occurred and the bicyclic lactone was obtained in excellent yield (Scheme 36).



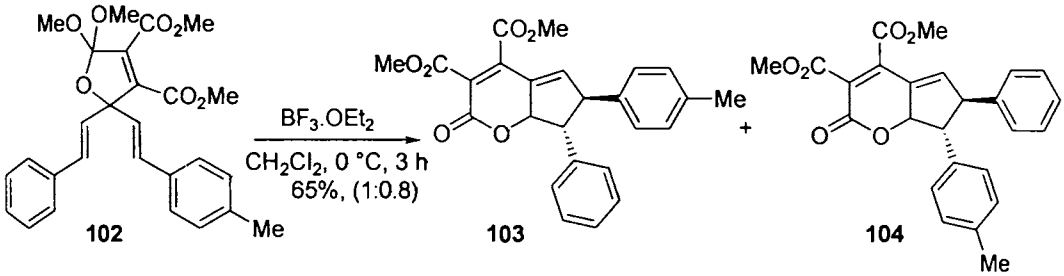
Scheme 36

A mechanistic rationale for this reaction is given in Scheme 37. Initial coordination of the Lewis acid to the dihydrofuran derivative **86** yields the diallyl cation which undergoes a facile 4π conrotatory electrocyclic closure resulting in a new C-C bond, two new stereocenters and an allyl cation. This allyl cation is trapped by the pendant orthoester borate, establishing a new C-O bond, and elimination of methanol from the intermediate delivers the bicyclic lactone **87**.



Scheme 37

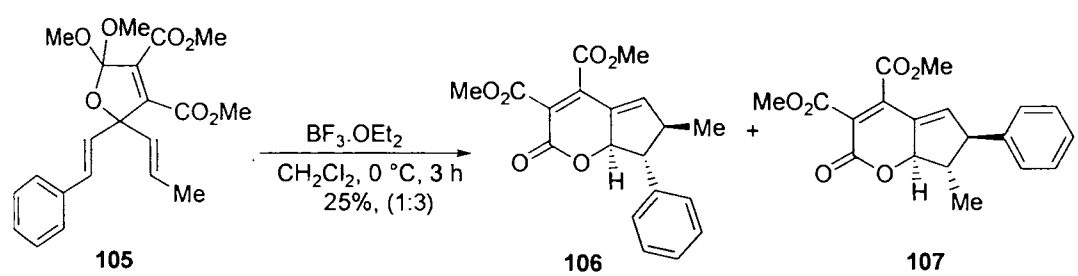
Not surprisingly, the rearrangement reaction of distyrenyl dihydrofuran **102** with unsymmetrical substitution on the aromatic ring afforded an inseparable mixture of regioisomers **103** and **104** (Scheme 38).



Scheme 38

The products **103** and **104** were characterized by spectroscopic methods. The IR spectrum displayed characteristic lactone and ester carbonyl vibrations at 1748 cm^{-1} and 1728 cm^{-1}. In the ^1H NMR spectrum, the methyl group was discernible at δ 2.31, while the carbomethoxy groups showed a sharp singlet at δ 3.90.The methine proton adjacent to the ring oxygen presented a multiplet between δ 3.46 and δ 3.53. Similarly the two benzylic protons also appeared as multiplets centered at δ 4.07 and δ 5.53. The olefinic proton was discernible as a multiplet between δ 6.80 and δ 6.83. In the ^{13}C NMR spectrum, the characteristic lactone and ester carbonyl peaks were seen at δ 168.1, δ 162.9 and δ 161.9.

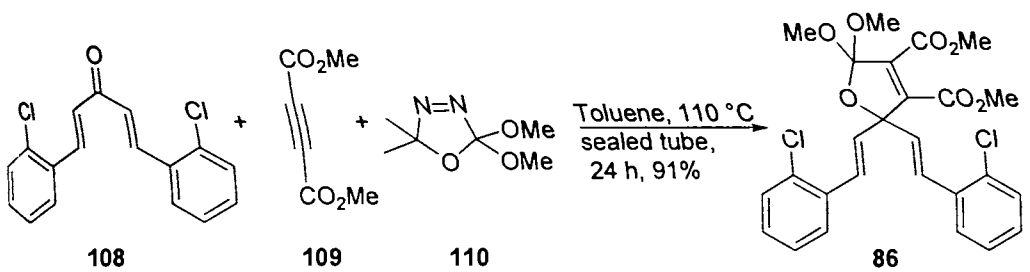
The dihydrofuran **105** with a non-styrenyl substituent also gave the corresponding bicyclic lactone *albeit* in very low yields. This may be attributed to the relative instability of the cationic intermediate formed in the reaction (Scheme 39).



Scheme 39

3.4.2 Synthesis of Divinyl Dihydrofurans

The dihydrofurans which served as starting materials for our investigations were synthesized by the multicomponent reaction of a dienone, dimethyl acetylenedicarboxylate (DMAD) and dimethoxycarbene. In a pilot experiment, the dienone **108** was treated with DMAD and 2,2-dimethoxy Δ^3-1,3,4-oxadiazoline in refluxing toluene under sealed tube conditions to afford the distyrenyl dihydrofuran derivative **86** in 91% yield (Scheme 40).



Scheme 40

The structure of the product **86** was established by spectroscopic analysis. The IR spectrum showed lactone and carbonyl vibrations at 1735 cm^{-1} and 1728 cm^{-1} respectively. In the ^1H NMR spectrum, the protons corresponding to the methoxy groups appeared as a sharp singlet at δ 3.56, while the peak corresponding to the carbomethoxy groups was discernible at δ 3.85. The olefinic protons provided two doublets centered at δ 6.53 (J = 16 Hz) and δ 7.26 (J = 16 Hz). The aromatic protons were visible as a multiplet between δ 7.56 and δ 6.96. The ^{13}C NMR spectrum showed characteristic peaks corresponding to the two ester carbonyls at δ 162.3 and δ 161.8. The sp^2 carbons attached to the two carbomethoxy groups resonated at δ 141.4 and δ 135.3. The peak corresponding to the orthoester carbon was discernible at δ 123.2 while the *spiro* carbon signal was seen at δ 87.8. All the other signals were also in good agreement with the assigned structure. Satisfactory HRMS data was also obtained for the compound.

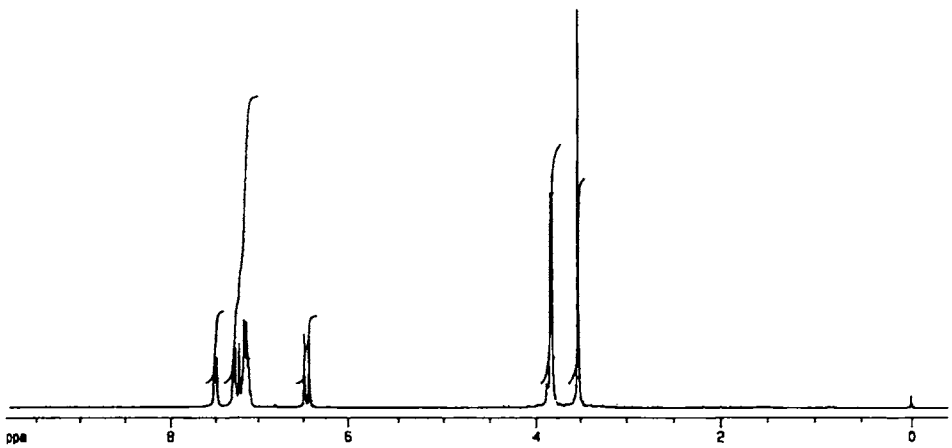


Figure 4 ^{1}H NMR Spectrum of 86

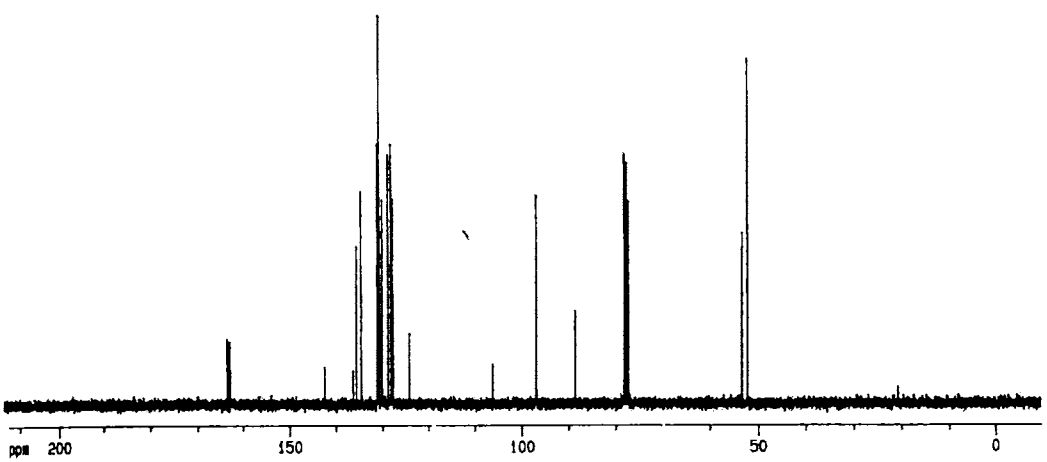
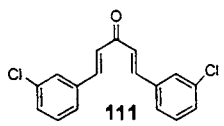
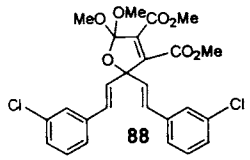
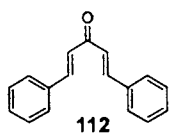
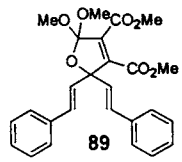
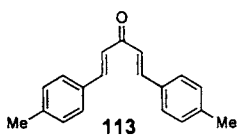
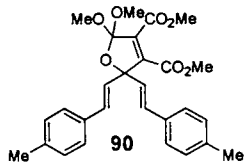
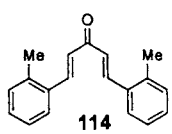
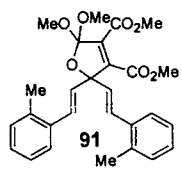
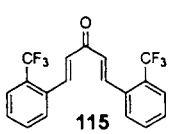
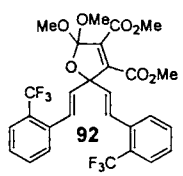
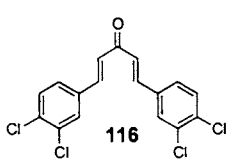
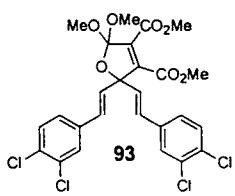
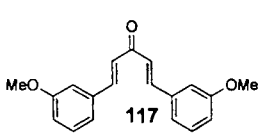
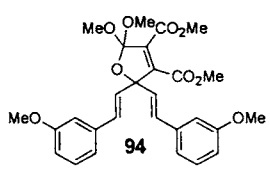
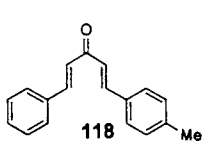
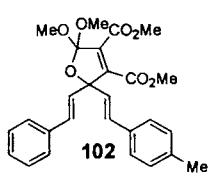


Figure 5 ^{13}C NMR Spectrum of 86

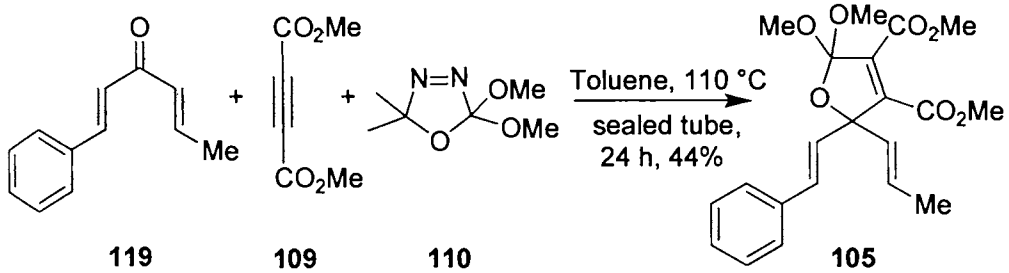
The reaction was found to be applicable to a number of substituted divinyl ketones and the distyrenyl dihydrofurans were obtained in moderate to good yields (Table 2).

Table-2

Entry	Substrate	Product	Yield (%)*
1	 111	 88	70
2	 112	 89	73
3	 113	 90	46
4	 114	 91	53
5	 115	 92	81
6	 116	 93	77
7	 117	 94	41
8	 118	 102	65

Reaction conditions: Sealed Tube, 110 °C, 24 h
* isolated yield

The reaction was found to occur with an alkyl substituted dienone **119**, but the dihydrofuran derivative **105** was obtained only in moderate yield (Scheme 41).



Scheme 41

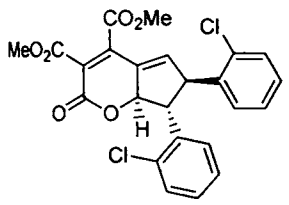
In conclusion, we have uncovered a facile method for the synthesis of highly substituted dihydrofuran derivatives and it has been shown that the latter undergo an interrupted Nazarov reaction in the presence of Lewis acids to afford cyclopentenolactone derivatives. It is worthy of mention that, the basic cyclopentenolactone moiety is a recurring structural motif in a number of biologically active monoterpenoids such as artemesia lactone, vulgaris lactone and ilexlactone.

3.5 EXPERIMENTAL

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

Dimethyl *trans*-6,7-*bis* (2-chlorophenyl) 2,6,7,7a-tetrahydro-oxocyclopenta [b]pyran-3,4-dicarboxylate 87

A solution of the dihydrofuran derivative **86** (100 mg, 0.19 mmol) in 15 ml of dry CH_2Cl_2 was cooled to 0 °C and $BF_3.OEt_2$ (27 mg, 0.19 mmol) was added. After stirring for 3 h, the reaction mixture was passed through a short pad of silica. The solvent was removed and the residue on silica gel column chromatography using 70:30 hexane-ethyl acetate solvent mixture afforded analytically pure bicyclic lactone **87** as a colorless crystalline solid (58 mg, 65%), m.p 189-190 °C (recrystallized from CH_2Cl_2-hexane).



87

IR (KBr) ν_{max}: 3015, 2955, 2850, 1745, 1738, 1728, 1630, 1594, 1479, 1437, 1393, 1277, 1098, 1052, 993, 758, 703 cm^{-1}.

^{1}H NMR: δ 7.35-7.19 (m, 8H), 6.82 (s, 1H), 5.91 (d, J = 8, 1H), 5.02 (d, J = 8, 1H), 3.91 (s, 6H), 3.88 (t, J = 8.3, 1H).

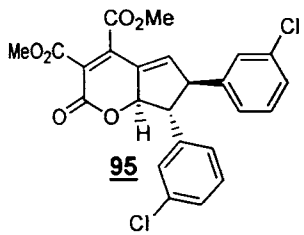
^{13}C NMR: δ 163.8, 162.7, 160.3, 141.6, 138.1, 135.3, 134.6, 134.0, 133.7, 130.5, 130.3, 129.5, 129.0, 128.9, 128.7, 127.5, 127.0, 87.0, 59.4, 53.1, 52.9, 52.3.

Analysis calculated for $C_{24}H_{18}Cl_2O_6$: C, 60.90 H, 3.88; Found: C, 61.26 H, 3.93.

Crystal data for 87: $C_{24}H_{18}Cl_2O_6$ FW = 473.28. The crystal used for the X-ray study has the dimensions of 0.65 x 0.50 x 0.25 mm^3. Monoclinic, space group P21/a. Unit cell dimensions: a = 14.338 (8) Å, α = 90°; b = 9.405 (6) Å, β = 110.70 (3)°; c = 17.465 (8) Å, γ = 90°; Vol = 2925.51(6) $Å^3$. Density (calcd.) = 1.427 mg/mm^3. Absorption coefficient = 0.334 mm^{-1}. R indicecs R1 = 0.0656, wR2 = 0.01214.

Dimethyl *trans*-6,7-*bis* (3-chlorophenyl) 2,6,7,7a-tetrahydro-oxocyclopenta [b]pyran-3,4-dicarboxylate 95

A solution of the dihydrofuran derivative **88** (100 mg, 0.19 mmol) in 15 ml of dry CH_2Cl_2 was cooled to 0 °C and $BF_3.OEt_2$ (27 mg, 0.19 mmol) was added. After stirring for 3 h, the reaction mixture was passed through a short pad of silica. The solvent was removed and the residue on silica gel column chromatography using 70:30 hexane-ethyl acetate solvent mixture afforded bicyclic lactone **95** as a yellow viscous liquid (58 mg, 65%).



95

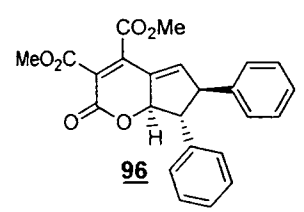
IR (neat) ν_{max}: 3015, 2953, 2854, 1740, 1730, 1715, 1632, 1595, 1570, 1440, 1280, 1096, 1046, 996, 891, 786, 696 cm^{-1}.

^{1}H NMR: δ 7.23-6.93 (m, 8H), 6.78 (s, 1H), 5.53 (d, J = 8.2, 1H), 4.05 (d, J = 8.7, 1H), 3.86 (s, 6H), 3.47 (t, J = 8.5, 1H).

^{13}C NMR: δ 163.8, 162.7, 160.2, 142.3, 140.6, 139.6, 134.9, 130.2, 128.7, 128.1, 128.0, 127.7, 127.6, 126.3, 125.8, 87.9, 61.2, 56.5, 53.3, 53.1.

Dimethyl *trans*-6,7-*bis* (phenyl) 2,6,7,7a-tetrahydro-oxocyclopenta[b]pyran -3,4-dicarboxylate 96

A solution of the dihydrofuran derivative **89** (100 mg, 0.22 mmol) in 15 ml of dry CH_2Cl_2 was cooled to 0 °C and $BF_3.OEt_2$ (31 mg, 0.22 mmol) was added. After stirring for 3 h, the reaction mixture was passed through a short pad of silica. The solvent was removed and the residue on silica gel column chromatography using 70:30 hexane-ethyl acetate solvent mixture afforded bicyclic lactone **96** as a colorless viscous liquid (53 mg, 60%).



96

IR (neat) ν_{max}: 3029, 2948, 2870, 1748, 1733, 1728, 1600, 1568, 1438, 1283, 1067, 990, 764, 703 cm^{-1}.

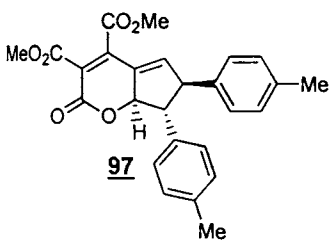
^{1}H NMR: δ 7.31-7.06 (m, 10H), 6.83 (t, J = 1.9, 1H), 5.58-5.54 (m, 1H), 4.14-4.06 (m, 1H), 3.89 (s, 6H), 3.54 (t, J = 8.5, 1H).

^{13}C NMR: δ 164.0, 162.9, 160.5, 141.9, 140.5, 137.8, 135.5, 128.8, 128.7, 128.2, 127.8, 127.5, 127.5, 88.3, 61.6, 57.0, 53.1, 53.0

HRMS (EI) Calculated for $C_{24}H_{20}O_6$: 404.1260, Found: 404.1234.

Dimethyl *trans*-6,7-*bis* (4-methylphenyl) 2,6,7,7a-tetrahydro-oxocyclopenta [b]pyran-3,4-dicarboxylate 97

A solution of the dihydrofuran derivative **90** (100 mg, 0.20 mmol) in 15 ml of dry CH_2Cl_2 was cooled to 0 °C and $BF_3.OEt_2$ (29 mg, 0.20 mmol) was added. After stirring for 3 h, the reaction mixture was passed through a short pad of silica. The solvent was removed and the residue on silica gel column chromatography using 70:30 hexane-ethyl acetate solvent mixture afforded bicyclic lactone **97** as a colorless viscous liquid (71 mg, 81%).



97

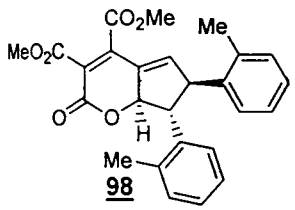
IR (neat) ν_{max}: 3036, 2969, 2921, 1748, 1721, 1715, 1640, 1526, 1452, 1276, 1216, 1108, 1061, 1000, 825, 737 cm^{-1}.

^{1}H NMR: δ 7.07-6.94 (m, 8H), 6.79 (t, J = 1.8, 1H), 5.49 (d, J = 8.2, 1H), 4.03 (d, J = 8.7, 1H), 3.87 (s, 6H), 3.46 (t, J = 8.5, 1H), 2.30 (s, 6H).

^{13}C NMR: δ 163.9, 162.9, 160.4, 142.1, 137.7, 136.9, 135.6, 134.9, 129.7, 129.4, 129.3, 128.1, 127.6, 127.5, 127.4, 127.1, 88.3, 56.6, 52.7, 20.9.

Dimethyl *trans*-6,7-*bis* (2-methylphenyl) 2,6,7,7a-tetrahydro-oxocyclopenta [b]pyran-3,4-dicarboxylate 98

A solution of the dihydrofuran derivative **91** (100 mg, 0.20 mmol) in 15 ml of dry CH_2Cl_2 was cooled to 0 °C and $BF_3.OEt_2$ (29 mg, 0.20 mmol) was added. After stirring for 3 h, the reaction mixture was passed through a short pad of silica. The solvent was removed and the residue on silica gel column chromatography using 70:30 hexane-ethyl acetate solvent mixture afforded bicyclic lactone **98** as a colorless crystalline solid (53 mg, 60%), m.p 63-64 °C (recrystallized from CH_2Cl_2-hexane).



98

IR (KBr) ν_{max}: 3035, 2961, 2860, 1755, 1728, 1715, 1640, 1594, 1451, 1283, 1101, 1060, 993, 764, 700cm^{-1}.

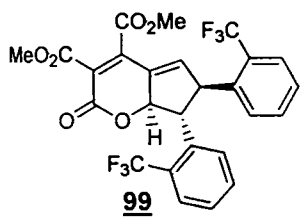
^{1}H NMR: δ 7.38-6.68 (m, 8H), 6.79 (s, 1H), 5.69 (d, J = 8.1, 1H), 4.32 (d, J= 8.4, 1H), 3.90 (s, 6H), 3.98-3.86 (m, 1H), 1.81 (s, 3H),1.73 (s, 3H)

^{13}C NMR: δ 164.0, 162.9, 160.9, 142.6, 139.5, 137.1, 136.8, 135.6, 128.5, 127.6, 127.4, 127.2, 127.1, 126.8, 126.3, 125.9, 89.1 57.9, 54.5, 53.1, 52.9, 19.4.

HRMS (EI) Calculated for $C_{26}H_{24}O_6$: 432.1573, Found: 432.1603.

Dimethyl *trans*- 6, 7-*bis* (2-triflouromethylphenyl) 2, 6, 7, 7a-tetrahydro-oxocyclopenta[b]pyran-3, 4-dicarboxylate 99

A solution of the dihydrofuran derivative **92** (100 mg, 0.17 mmol) in 15 ml of dry CH_2Cl_2 was cooled to 0 °C and $BF_3.OEt_2$ (24 mg, 0.17 mmol) was added. After stirring for 3 h, the reaction mixture was passed through a short pad of silica. The solvent was removed and the residue on silica gel column chromatography using 70:30 hexane-ethyl acetate solvent mixture afforded bicyclic lactone **99** as a colorless crystalline solid (55 mg, 60%), m.p 221-222 °C (recrystallized from CH_2Cl_2-hexane).



99

IR (neat) ν_{max}: 3015, 2948, 2921, 1748, 1731, 1707, 1626, 1526, 1451, 1310, 1107, 1047, 905, 777, 676 cm^{-1}.

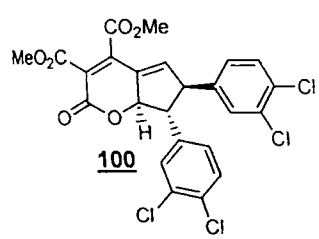
^{1}H NMR: δ 7.64-7.26 (m, 8H), 6.69 (m, 1H), 5.66 (d, J = 7.3, 1H), 4.56 (m, 1H), 4.09 (t, J = 7.4, 1H), 3.90 (s, 6H).

^{13}C NMR: δ 163.8, 162.7, 160.0, 141.2, 139.0, 132.5, 132.0, 130.2, 128.9, 128.5, 128.3, 127.6, 127.5, 126.0, 125.9, 125.6, 125.5, 125.4, 90.7, 56.8, 54.8, 53.3, 53.1.

HRMS (EI) Calculated for $C_{26}H_{18}F_6O_6$: 540.1026, Found: 540.1007.

Dimethyl *trans*-6,7-*bis* (3,4-dichloro-phenyl) 2,6,7,7a-tetrahydro-oxocyclopenta[b]pyran-3,4-dicarboxylate 100

A solution of the dihydrofuran derivative **93** (100 mg, 0.17 mmol) in 15 ml of dry CH_2Cl_2 was cooled to 0 °C and $BF_3.OEt_2$ (24 mg, 0.17 mmol) was added. After stirring for 3 h, the reaction mixture was passed through a short pad of silica. The solvent was removed and the residue on silica gel column chromatography using 70:30 hexane-ethyl acetate solvent mixture afforded bicyclic lactone **100** as a pale yellow viscous liquid (72 mg, 79%).



100

IR (neat) ν_{max}: 3020, 2961, 2848, 1748, 1732, 1712, 1640, 1478, 1444, 1276, 1222, 1114, 1067, 1037, 838, 750 cm^{-1}.

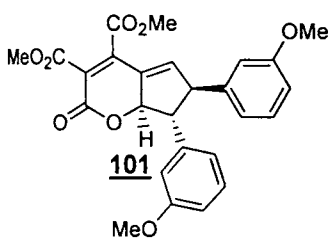
^{1}H NMR: δ 7.39-6.89 (m, 6H), 6.76 (s, 1H), 5.51 (d, J = 8.2, 1H), 4.01 (d, J = 8.8, 1H), 3.90 (s, 6H), 3.41 (t, J = 8.5, 1H)

^{13}C NMR: δ 163.6, 162.5, 159.9, 140.1, 139.8, 137.3, 134.7, 133.0, 132.1, 130.9, 130.8, 129.5, 129.3, 128.8, 127.3, 126.9, 87.5, 60.7, 55.7, 53.2, 53.0.

HRMS (EI) Calculated for $C_{24}H_{16}Cl_4O_6$: 539.9701, Found: 539.9734.

Dimethyl *trans*-6,7-*bis* (3-methoxy-phenyl) 2,6,7,7a-tetrahydro-oxocyclopenta[b]pyran-3,4-dicarboxylate 101

A solution of the dihydrofuran derivative **94** (100 mg, 0.19 mmol) in 15 ml of dry CH_2Cl_2 was cooled to 0 °C and $BF_3.OEt_2$ (27 mg, 0.19 mmol) was added. After stirring for 3 h, the reaction mixture was passed through a short pad of silica. The solvent was removed and the residue on silica gel column chromatography using 70:30 hexane-ethyl acetate solvent mixture afforded bicyclic lactone **101** as a yellow viscous liquid (52 mg, 60%).



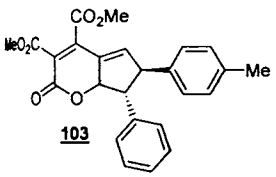
IR (neat) ν_{max}: 3016, 2955, 2847, 1748, 1735, 1715, 1620, 1587, 1499, 1452, 1270, 1169, 1067, 811, 710 cm^{-1}.

^{1}H NMR: δ 7.26-6.65 (m, 8H), 6.60 (s, 1H), 5.54 (d, J = 8.2, 1H), 4.11-4.04 (m, 1H), 3.88 (s, 6H), 3.73 (s, 6H), 3.50 (t, J = 8.4,1H).

^{13}C NMR: δ 163.9, 162.9, 160.3, 159.9, 141.7, 142.1, 139.5, 135.5, 129.8, 129.7, 128.3, 127.8, 119.9, 113.8, 112.8, 88.2, 61.3, 56.9, 55.1, 55.0, 53.0, 52.8.

Dimethyl *trans*-6-(phenyl)-7-(4-methylphenyl) 2,6,7,7a-tetrahydro-oxocyclopenta[b]pyran-3,4-dicarboxylate and Dimethyl *trans*-6-(4-methylphenyl)-7-(phenyl) 2,6,7,7a-tetrahydro-oxocyclopenta[b]pyran-3,4-dicarboxylate 103 and 104

A solution of the dihydrofuran derivative **102** (100 mg, 0.21 mmol) in 15 ml of dry CH_2Cl_2 was cooled to 0 °C and $BF_3.OEt_2$ (30 mg, 0.21 mmol) was added. After stirring for 3 h, the reaction mixture was passed through a short pad of silica. The solvent was removed and the residue on silica gel column chromatography using 70:30 hexane-ethyl acetate solvent mixture afforded the bicyclic lactones **103** and **104** (inseparable mixture of regioisomers) as a colorless viscous liquid (57 mg, 65%, 1: 0.8).



103

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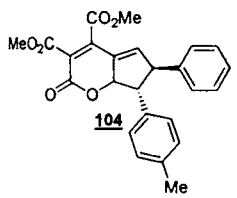


104

IR (neat) ν $_{max}$: 3023, 2961, 2870, 1748, 1728, 1640, 1606, 1594, 1485, 1438, 1397, 1283, 1094, 1060, 898, 804, 710 cm^{-1}.

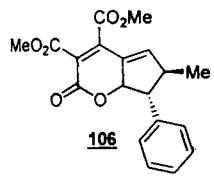
^{1}H NMR: δ 7.88-6.95 (m, 9H), 6.83-6.80 (m, 1H), 5.56-5.51 (m, 1H), 4.09-4.05 (m, 1H), 3.90 (s, 6H), 3.53-3.46 (m, 1H), 2.31 (s, 3H).

^{13}C NMR: δ 168.1, 162.9, 161.9, 142.3, 142.0, 140.7, 137.9, 137.6, 137.1, 135.5, 129.5, 129.4, 128.8, 128.7, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 88.4, 88.3, 61.7, 61.4, 57.0, 56.7, 53.1, 53.0, 24.9, 21.1.

HRMS (EI) Calculated for $C_{25}H_{22}O_6$: 418.1416 Found: 418.1418.

Dimethyl *trans*-6-(methyl)-7-(4-phenyl) 2,6,7,7a-tetrahydro-oxocyclopenta[b]pyran-3,4-dicarboxylate 106 and Dimethyl *trans*-6-(4-phenyl)-7-(methyl) 2,6,7,7a-tetrahydro-oxocyclopenta[b]pyran-3,4-dicarboxylate 107

A solution of the dihydrofuran derivative **105** (100 mg, 0.25 mmol) in 15 ml of dry CH_2Cl_2 was cooled to 0 °C and $BF_3.OEt_2$ (36 mg, 0.25 mmol) was added. After stirring for 3 h, the reaction mixture was passed through a short pad of silica. The solvent was removed and the residue on silica gel column chromatography using 70:30 hexane-ethyl acetate solvent mixture afforded the bicyclic lactones **106** and **107** (inseparable mixture of regioisomers) as a colorless viscous liquid (20 mg, 25%, 1: 3).



106

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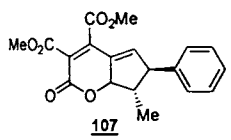


107

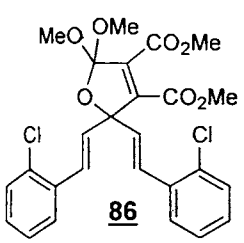
IR (neat) ν_{max}: 3016, 2955, 2847, 1742, 1735, 1715, 1620, 1438, 1249, 1162, 1013, 811, 710 cm^{-1}.

^{1}H NMR: δ 7.47-7.26 (m, 5H), 6.25-6.23 (m, 1H), 5.37-5.30 (m, 1H), 4.61-4.56 (m, 1H), 3.86-3.83 (m, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 1.33 (d, 3H, J = 6.5, 1H).

^{13}C NMR: δ 170.0, 167.2, 166.0, 139.2, 138.6, 131.7, 128.8, 128.2, 122.2, 122.1, 122.0, 113.3, 95.3, 92.7, 92.3, 84.7, 83.7, 79.9, 56.4, 52.8, 52.7, 52.6, 20.9, 20.4.

Dimethyl 2,2-*bis* [2-(2-chlorophenyl) ethenyl]-2,5-dihydro-5,5-dimethoxy-3, 4-furandicarboxylate 86

A mixture of dieneone **108** (100 mg, 0.33 mmol), DMAD **109** (70 mg, 0.49 mmol) and oxadiazoline **110** (106 mg, 0.65 mmol) was refluxed in dry toluene in a sealed tube for 24 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford the dihydrofuran derivative **86** (154 mg, 91%) as a pale yellow viscous liquid.



86

IR (neat) ν_{max}: 3002, 2948, 2847, 1735, 1728, 1681, 1600, 1479, 1445, 1283, 1182, 1128, 1047, 980, 764, 697 cm^{-1}.

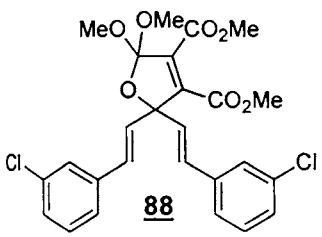
^{1}H NMR: δ 7.56-6.96 (m, 8H), 7.26 (d, J = 16, 2H), 6.53 (d, J = 16, 2H), 3.85 (s, 6H), 3.56 (s, 6H).

^{13}C NMR: δ 162.3, 161.8, 141.4, 135.3, 134.5, 133.6, 130.1, 129.7, 129.0, 127.8, 127.1, 126.8, 123.2, 87.8, 52.7, 51.6.

HRMS (EI) Calculated for $C_{26}H_{24}O_7Cl_2$: 518.0899 Found: 518.0902.

Dimethyl 2,2-*bis* [2-(3-chlorophenyl) ethenyl]-2,5-dihydro-5,5-dimethoxy-3, 4-furandicarboxylate 88

A mixture of dieneone **111** (100 mg, 0.33 mmol), DMAD **109** (70 mg, 0.49 mmol) and oxadiazoline **110** (106 mg, 0.65 mmol) was refluxed in dry toluene in a sealed tube for 24 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford the dihydrofuran derivative **88** (119 mg, 70%) as a pale yellow viscous liquid.



88

IR (neat) ν_{max}: 3012, 2948, 2840, 1738, 1728, 1674, 1600, 1566, 1472, 1438, 1270, 1115, 980, 784, 683 cm^{-1}.

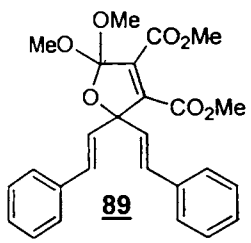
^{1}H NMR: δ 7.38-7.24 (m, 8H), 6.76 (d, J = 15.9, 2H), 6.53 (d, J = 15.9, 2H), 3.85 (s, 6H), 3.50 (s, 6H).

^{13}C NMR: δ 162.4, 161.6, 141.0, 138.0, 135.5, 134.6, 130.4, 130.1, 129.8, 128.8, 128.4, 128.1, 126.7, 125.0, 123.1, 87.6, 52.8, 52.5, 51.4, 50.6.

HRMS (EI) Calculated for $C_{26}H_{24}O_7Cl_2$: 518.0899 Found: 518.0902.

Dimethyl 2,2-*bis* [2-(phenyl) ethenyl]-2,5-dihydro-5,5-dimethoxy-3,4-furandicarboxylate 89

A mixture of dieneone **112** (100 mg, 0.42 mmol), DMAD **109** (90 mg, 0.63 mmol) and oxadiazoline **110** (134 mg, 0.84 mmol) was refluxed in dry toluene in a sealed tube for 24 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixtures to afford the dihydrofuran derivative **89** (71 mg, 73%) as a colorless viscous liquid.



89

IR (neat) ν_{max}: 3110, 2915, 2847, 1735, 1728, 1681, 1600, 1452, 1270, 1121, 980, 764, 703 cm^{-1}.

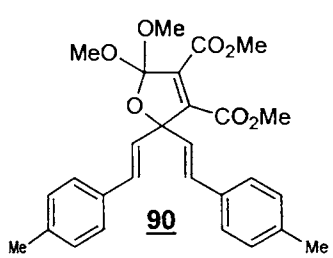
^{1}H NMR: δ 7.41-7.21 (m, 10H), 6.82 (d, J = 16, 2H), 6.52 (d, J = 16, 2H), 3.81 (s, 6H), 3.51 (s, 6H).

^{13}C NMR: δ 162.5, 161.8, 142.1, 136.2, 134.8, 131.7, 130.1, 128.5, 128.2, 128.1, 127.5, 126.8, 126.4, 123.0, 87.9, 52.7, 52.6, 51.4.

HRMS (EI) Calculated for $C_{26}H_{26}O_7$: 450.1678, Found: 450.1655.

Dimethyl 2,2-*bis* [2-(4-methylphenyl) ethenyl]-2,5-dihydro-5,5-dimethoxy-3, 4-furandicarboxylate 90

A mixture of dieneone **113** (100 mg, 0.38 mmol), DMAD **109** (81 mg, 0.57 mmol) and oxadiazoline **110** (121 mg, 0.76 mmol) was refluxed in dry toluene in a sealed tube for 24 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford the dihydrofuran derivative **90** (83 mg, 46%) as a colorless viscous liquid.



90

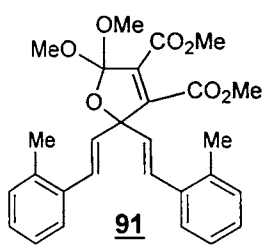
IR (neat) ν_{max}: 3002, 2948, 2860, 1735, 1715, 1618, 1512, 1438, 1263, 1175, 1121, 987, 811, 663cm^{-1}.

^{1}H NMR: δ 7.30-7.10 (m, 10H), 6.80 (d, J = 16, 2H), 6.45 (d, J = 16, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.49 (s, 6H), 2.34 (s, 6H).

^{13}C NMR: δ 162.5, 161.9, 142.6, 137.8, 134.6, 133.5, 132.8, 131.7, 130.1, 129.2, 126.8, 123.0, 88.1, 52.6, 51.4, 21.3.

Dimethyl 2,2-*bis* [2-(2-methylphenyl) ethenyl]-2,5-dihydro-5,5-dimethoxy-3, 4-furandicarboxylate 91

A mixture of dieneone **114** (100 mg, 0.38 mmol), DMAD **109** (81 mg, 0.57 mmol) and oxadiazoline **110** (121 mg, 0.76 mmol) was refluxed in dry toluene in a sealed tube for 24 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford the dihydrofuran derivative **91** (96 mg, 53%) as a colorless viscous liquid.



91

IR (neat) ν_{max}: 3022, 2955, 2853, 1741, 1721, 1687, 1444, 1269, 1181, 1121, 993, 960, 797, 753cm^{-1}.

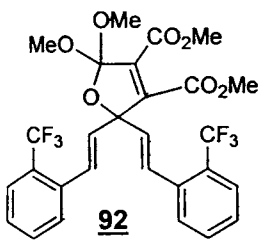
^{1}H NMR: δ 7.45-7.13 (m, 8H), 7.09 (d, J = 15.9, 2H), 6.41 (d, J = 15.9, 2H), 3.83 (s, 6H), 3.37 (s, 6H), 2.01 (s, 6H).

^{13}C NMR: δ 162.3, 161.9, 142.8, 135.6, 135.4, 134.2, 130.2, 129.6, 128.9, 127.9, 126.0, 125.8, 123.0, 88.2, 52.5, 51.3, 19.7.

HRMS (EI) Calculated for $C_{28}H_{30}O_7$: 478.1992, Found: 478.1978

Dimethyl 2,2-*bis* [2-(2-triflouromethylphenyl) ethenyl]-2,5-dihydro-5,5-dimethoxy-3, 4-furandicarboxylate 92

A mixture of dieneone **115** (100 mg, 0.27 mmol), DMAD **109** (57 mg, 0.40 mmol) and oxadiazoline **110** (86 mg, 0.54 mmol) was refluxed in dry toluene in a sealed tube for 24 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column 90:10 hexane-ethyl acetate solvent mixture to afford the dihydrofuran derivative **92** (128 mg, 81%) as a colorless viscous liquid.



92

IR (neat) ν_{max}: 3050, 2957, 2854, 1740, 1728, 1573, 1503, 1442, 1317, 1279, 1116, 981, 774 cm^{-1}

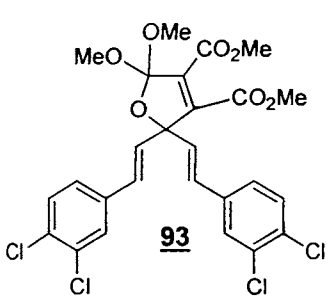
^{1}H NMR: δ 7.63-7.32 (m, 8H), 7.26 (d, J = 15.8, 2H), 6.53 (d, J = 15.8, 2H), 3.85 (s, 6H), 3.53 (s, 6H).

^{13}C NMR: δ 162.2, 161.8, 141.1, 135.7, 135.4, 131.9, 131.7, 128.4, 128.0, 127.7, 127.6, 126.0, 125.8, 125.7, 125.7, 123.2, 122.3, 87.59, 52.6, 51.3.

HRMS (EI) Calculated for $C_{28}H_{24}O_7F_6$: 586.1426 Found: 586.1377

Dimethyl 2,2-*bis* [2-(3,4-dichlorophenyl) ethenyl]-2,5-dihydro-5,5-dimethoxy-3,4-furandicarboxylate 93

A mixture of dieneone **116** (100 mg, 0.27 mmol) DMAD **109** (57 mg, 0.40 mmol) and oxadiazoline **110** (86 mg, 0.54 mmol) was refluxed in dry toluene in a sealed tube for 24 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixtures to afford the dihydrofuran derivative **93** (122 mg, 77%) as a pale yellow viscous liquid.



93

IR (neat) ν_{max}: 3008, 2955, 2847, 1740, 1728, 1687, 1485, 1451, 1283, 1121, 1040, 993, 932, 797, 683 cm^{-1}.

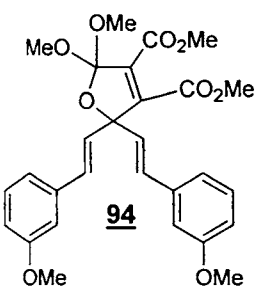
^{1}H NMR: δ 7.47-7.21 (m, 6H), 6.73 (d, J = 15.9, 2H), 6.52 (d, J = 15.9, 2H), 3.86 (s, 6H), 3.50 (s, 6H).

^{13}C NMR: δ 162.2, 161.4, 140.4, 136.1, 135.7, 132.7, 131.8, 130.4, 129.3, 129.1, 128.8, 128.4, 125.8, 123.1, 87.3, 52.7, 51.4.

HRMS (EI) Calculated for $C_{26}H_{22}Cl_4O_7$: 586.0120, Found: 586.0090.

Dimethyl 2,2-*bis* [2-(3-methoxyphenyl) ethenyl]-2,5-dihydro-5,5-dimethoxy-3,4-furandicarboxylate 94

A mixture of dieneone **117** (100 mg, 0.34 mmol), DMAD **109** (72 mg, 0.51 mmol) and oxadiazoline **110** (108 mg, 0.68 mmol) was refluxed in dry toluene in a sealed tube for 24 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford the dihydrofuran derivative **94** (71 mg, 41%) as a yellow viscous liquid.



94

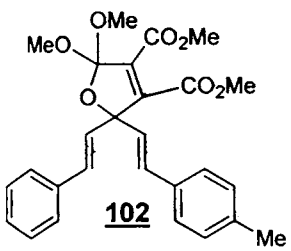
IR (neat) ν_{max}: 3008, 2961, 2847, 1741, 1721, 1680, 1163, 1586, 1451, 1175, 1128, 1053, 979, 929, 797, 710 cm^{-1}.

^{1}H NMR: δ 7.51-6.78 (m, 8H), 6.79 (d, J = 16, 2H), 6.50 (d, J = 16, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.80 (s, 6H), 3.50 (s, 6H).

^{13}C NMR: δ 161.1, 159.7, 141.0, 137.6, 134.9, 131.7, 129.5, 127.7, 123.0, 119.4, 113.7, 112.1, 87.8, 55.1, 52.6, 51.3.

Dimethyl 2,2-phenyl [2-(4-methylphenyl) ethenyl]-2,5-dihydro-5,5-dimethoxy-3,4-furandicarboxylate 102

A mixture of dieneone **118** (100 mg, 0.40 mmol) DMAD **109** (85 mg, 0.60 mmol) and oxadiazoline **110** (128 mg, 0.80 mmol) was refluxed in dry toluene in a sealed tube for 24 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixture to afford the dihydrofuran derivative **102** (120 mg, 65%) as a pale yellow viscous liquid.



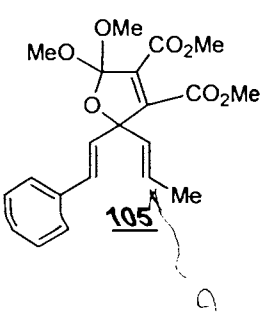
IR (neat) ν_{max}: 3043, 2989, 2948, 1742, 1721, 1681, 1445, 1276, 1121,1034, 933, 825, 764 cm^{-1}.

^{1}H NMR: δ 7.40-7.08 (m, 8H), 6.85-6.76 (m, 2H), 6.76-6.43 (m, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.26 (s, 6H), 2.31 (s, 3H).

^{13}C NMR: δ 162.3, 161.7, 142.3, 137.8, 136.2, 134.6, 133.4, 131.6, 131.5, 129.1, 128.4, 127.5, 126.7, 126.6, 126.4, 122.9, 87.9, 52.4, 51.2, 21.1

Dimethyl 2,2-phenyl [2-(4-methylphenyl) ethenyl]-2,5-dihydro-5,5-dimethoxy-3,4-furandicarboxylate 105

A mixture of dieneone **119** (100 mg, 0.40 mmol), DMAD **109** (85 mg, 0.60 mmol) and oxadiazoline **110** (128 mg, 0.80 mmol) was refluxed in dry toluene in a sealed tube for 24 h. The solvent was removed under vacuum and the residue was subjected to chromatography on a silica gel column using 90:10 hexane-ethyl acetate solvent mixtures to afford the dihydrofuran derivative **105** (120 mg, 44%) as a pale yellow viscous liquid.



IR (neat) ν_{max}: 3043, 2955, 2847, 1735, 1721, 1681, 1431, 1337, 1263, 1108, 1020, 973, 764 cm^{-1}.

^{1}H NMR: δ 7.45-7.27 (m, 5H), 6.36-6.21 (m, 2H), 5.64 (dd, J = 1.6, 15.1, 2H), 3.90 (s, 3H), 3.82 (s, 3H), 3.49 (s, 3H), 3.44 (s, 3H), 1.81 (dd, J = 6.6, 1.5, 3H).

^{13}C NMR: δ 162.0, 160.9, 141.3, 134.7, 131.7, 130.3, 128.8, 128.3, 128.2, 127.6, 123.6, 123.1, 121.9, 88.3, 84.2, 81.9, 52.8, 52.4, 50.8, 20.0.

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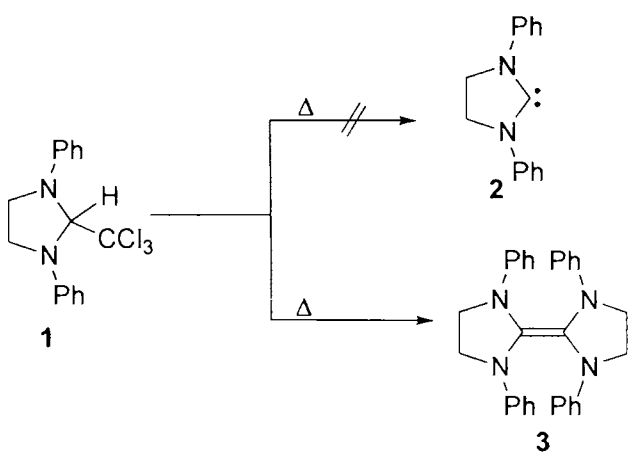
CHAPTER 4

MULTICOMPONENT REACTIONS OF *N*-HETEROCYCLIC CARBENES (NHCs) WITH DIMETHYL ACETYLENEDICARBOXYLATE AND AROMATIC ALDEHYDES

4.1 Introduction

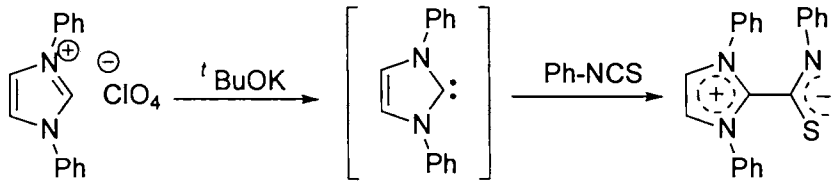
Ever since the isolation and characterization of a stable crystalline diaminocarbene by Arduengo in 1991, there has been growing interest in the exploration of the structure and chemical reactivities of *N*-heterocyclic carbenes.[1] The history of NHCs can be traced to the work of Wanzlick in the 1960s.[2] He had recognized earlier that electron rich imidazole nucleus can stabilize a carbene center at the 2-position between two nitrogens, and he tried to prepare the 1,3-diphenyl imidazolin-2-ylidene from **1** by the thermal elimination of chloroform. At that time he could not isolate any carbene, but isolated a dimeric electron rich olefin **3** (Scheme 1).



Scheme 1

Although Wanzlick was unsuccessful in isolating aminocarbenes, he demonstrated that imidazolium salts such as **4** could be deprotonated by

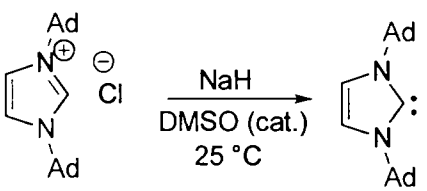
potassium tertiary butoxide to afford the corresponding imidazol-2-ylidenes which were subsequently trapped with electrophiles such as isocyanates and isothiocyanates, thereby proving the intermediacy of aminocarbenes in these reactions (Scheme 2).[3]



4 5 6

Scheme 2

A major breakthrough in this area occurred when Arduengo isolated a stable crystalline diaminocarbene in 1991. When *bis* (1-adamantyl) imidazolium chloride **7** was deprotonated with sodium hydride in tetrahydrofuran in the presence of a catalytic amount of dimethyl sulfoxide anion, the carbene **8** precipitated as a colorless crystalline and thermally stable compound (Scheme 3).[1]



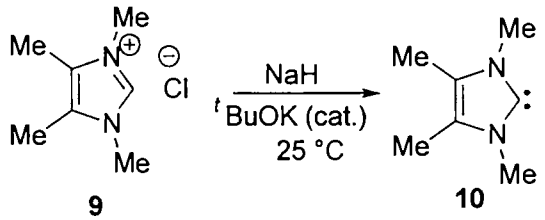
7 **8**

Ad = adamantyl

Scheme 3

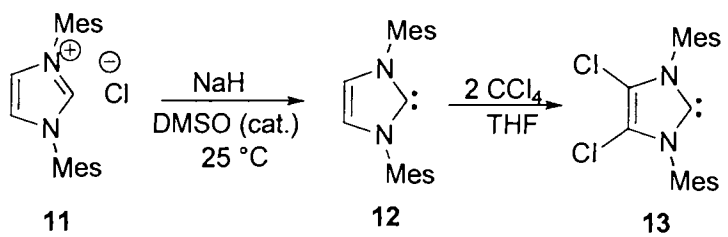
In the ^{13}C NMR spectrum, the low field position of the signal for the carbene carbon (δ = 211.4) was diagnostic, and single crystal X-ray analysis unequivocally confirmed the structure of **8**. The unusual stability of **8** was explained on the basis of a number of factors *viz.*, the large singlet-triplet energy gap in imidazol-2-ylidene (~80 kcal/mol), π-interactions in the imidazole ring, and electronegativity effects from the nitrogen. In addition to the electronic factors, it was believed initially that steric effects also play a

major role in stabilizing the carbene **8**. Later Arduengo has demonstrated that stable carbenes of the type **10** could be prepared by the deprotonation of imidazolium salts bearing less bulky substituents in the 1 and 3 positions (Scheme 4).[4]



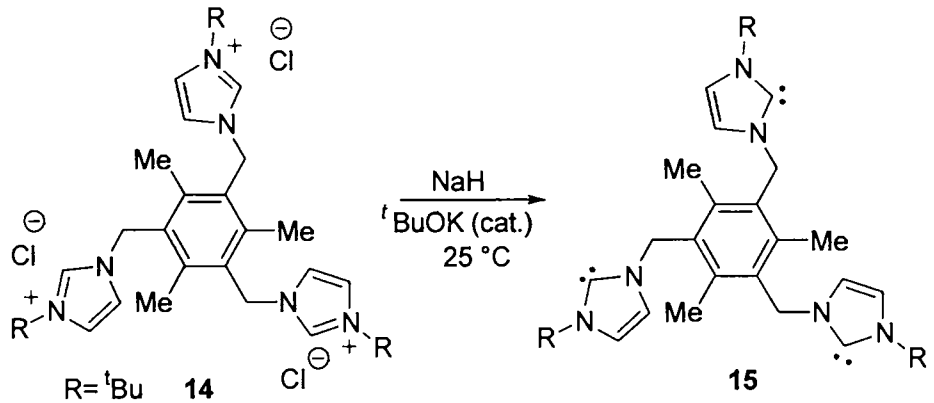
Scheme 4

Since then a wide variety of aminocarbenes have been synthesized, including the first air stable carbene in 1997. A solid sample of the stable carbene **13** exposed to air did not show any decomposition even after two days (Scheme 5).[5]



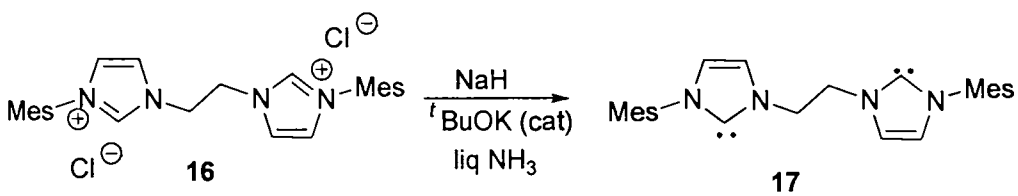
Scheme 5

The synthesis of a *tris* carbene, in which the imidazolylidene units are attached to a benzene ring, has also been reported. The carbene **15** was synthesized by deprotonation of the corresponding imidazolium chloride with sodium hydride in presence of a catalytic amount of potassium tertiary butoxide (Scheme 6).[6]



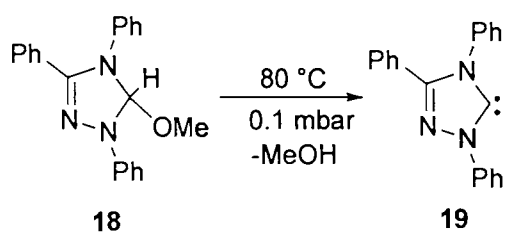
Scheme 6

Similarly, a stable *bis* carbene **17** was also prepared by employing the same strategy (Scheme 7).[7]



Scheme 7

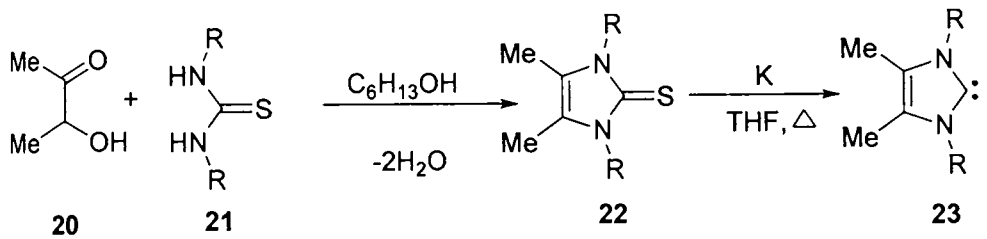
Enders and coworkers have reported the synthesis of the stable triazolylidene **19** by the thermal elimination of methanol from 5-methoxy-1,3,4-triphenyl-4,5-dihydro-1H-1,2,4-triazole **18** (Scheme 8).[8]



Scheme 8

As described above, the general method for the synthesis of aminocarbenes involves the deprotonation of the corresponding azolium salts by a suitable base. Later Kuhn and coworkers have developed a novel and versatile method for the synthesis of alkyl substituted *N*-heterocyclic carbenes using a completely different strategy. In this method the carbene **23** is

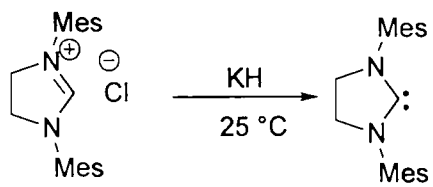
generated by the reaction of imidazole-2(3H)-thiones **22** obtained from aldol **20** and thiourea with potassium in THF (Scheme 9).[9]



20 **21** **22** **23**

Scheme 9

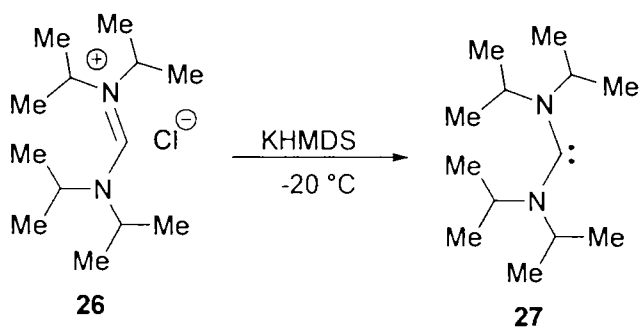
Later, Arduengo and coworkers have reported the synthesis of imidazolin-2-ylidenes by the deprotonation of *bis*-(mesityl) imidazolinium chloride **24** with potassium hydride. The X-ray structure of **25** has confirmed the monomeric nature of the molecule (Scheme 10).[10]



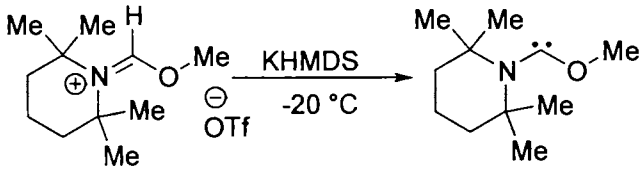
24 **25**

Scheme 10

The synthesis of stable acyclic diaminocarbenes was reported by Alder in 1998; this was followed by the isolation of stable alkoxyamino and aminothiocarbenes.[11] The aminocarbenes were prepared by the deprotonation of the corresponding amidinium salts with lithium amide bases, and these carbenes were found to undergo slow dimerization at ambient temperatures (Scheme 11).



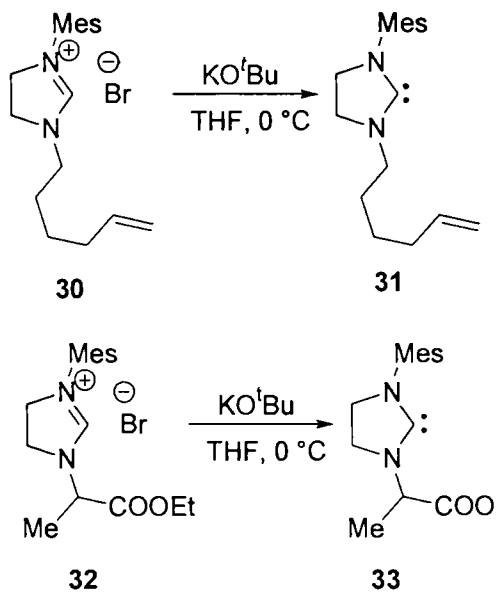
26 **27**



28 29

Scheme 11

The synthesis of *N*-heterocyclic carbenes with pendant alkenes and active C-H sites has been reported by Fürstner and co-workers. They have isolated the stable carbenes and established the structure by single crystal X-ray analysis (Scheme 12).[12]



Scheme 12

4.2 Reactivity Patterns of *N*-Heterocyclic Carbenes

By virtue of their strong σ-donating ability, *N*-heterocyclic carbenes have found impressive use as ligands in the preparation of catalysts in organometallic chemistry. It is worthy of note that the aminocarbene incorporated ruthenium alkylidene catalysts were found to be more versatile than the conventional Grubbs' catalyst in olefin metathesis reactions.[13] The application of NHCs in organometallic chemistry is treated only superficially

here, since it is only of peripheral relevance to the present work and excellent reviews on the subject are available in the literature.[14]

Following the Brønsted-Lowry concept, Alder and coworkers have determined the nucleophilicity and basicity of various aminocarbenes. They have reported the *p*Ka of 1,3-diisopropyl-4,5-dimethyl-imidazol-2-ylidene as 24 in DMSO-d_6 and found that it is a much stronger base than DBN, DBU and proton sponge but weaker than phosphazene bases.[15] Recently Streitweiser has calculated the *p*Ka of 1,3-ditertiary butyl imidazole-2-ylidene in THF as 20 which is much less than that of the dimesityl derivative reported by Alder.[16]

As early as 1958, Breslow recognized the role of *N*-heterocyclic carbenes as nucleophilic catalysts in enzymatic reactions. He has shown that the vitamin B_1 enzyme cofactor thiamin **34**, a naturally occurring thiazolium salt, plays a key role in biochemical transformations (Figure 1).[17]

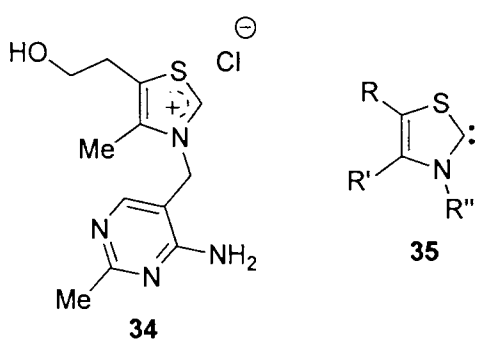
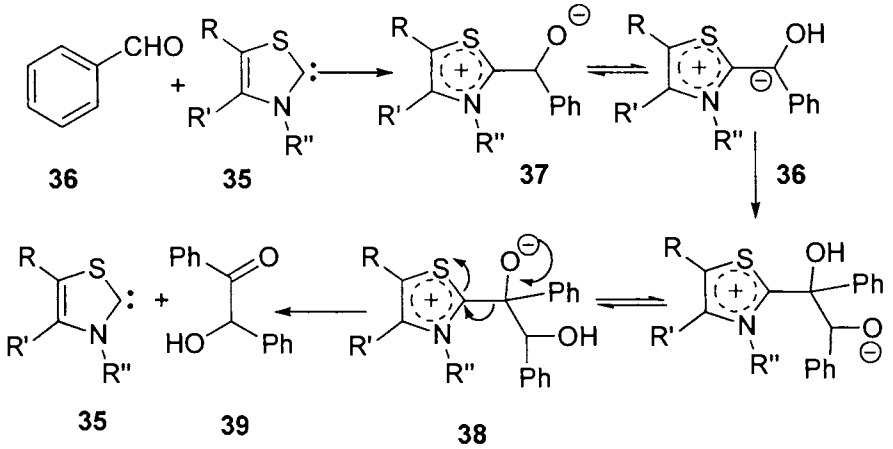


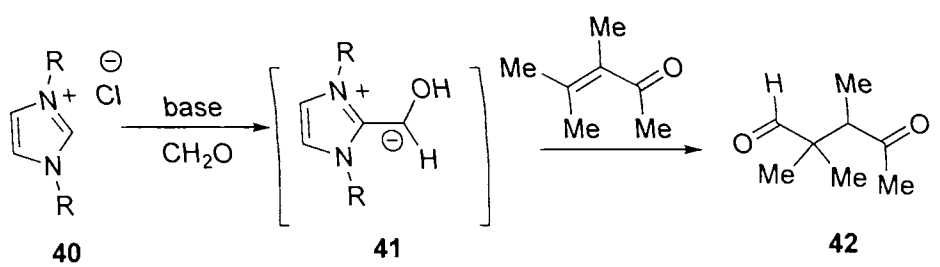
Figure 1

As thiamine diphosphate, it catalyzes the decarboxylation of pyruvic acid to active acetaldehyde as well as the benzoin condensation of aromatic aldehydes. The active species involved in this reaction was found to be the thiazolylidene **35** (Scheme 13).



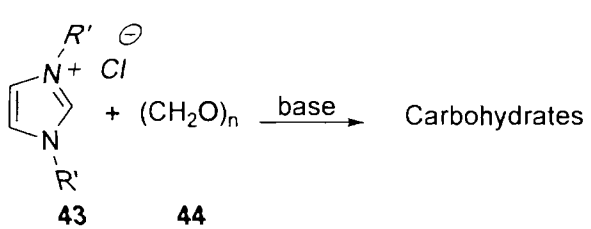
Scheme 13

Upon addition of an ylidene catalyst such as imidazolium, thiazolium or triazolium salts, aliphatic aldehydes are also reported to undergo benzoin type condensation known as Stetter reaction. When α,β-unsaturated ketones are employed, the reaction is called Michael-Stetter reaction; a typical reaction involving an imidazolium salt, an α,β-unsaturated ketone and an aldehyde is shown in Scheme 14.[18]



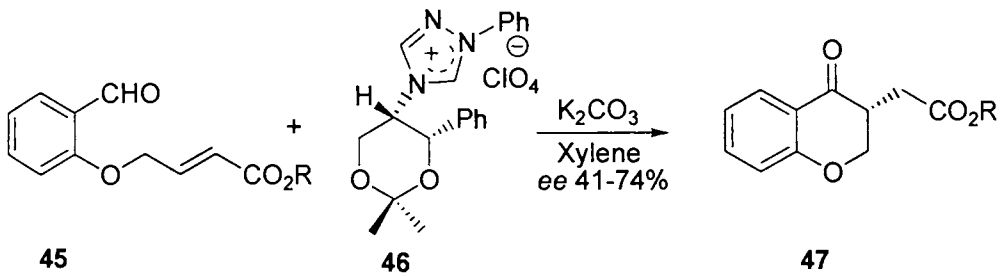
Scheme 14

The formoin condensation under ylidene catalysis affords carbohydrates (Scheme 15).[19]



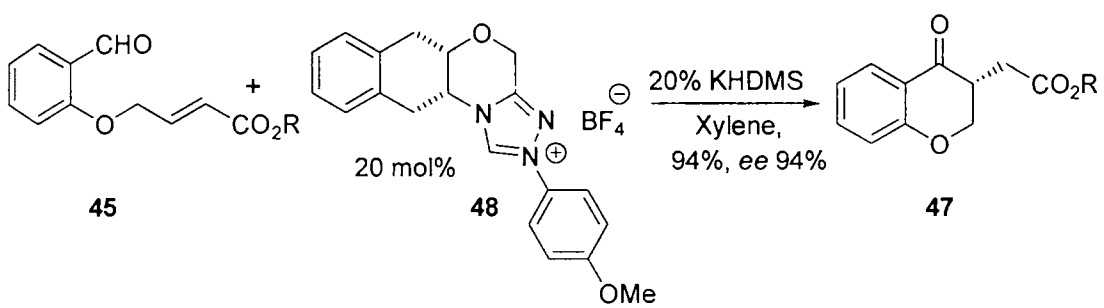
Scheme 15

Asymmetric versions of Michael-Stetter reactions employing chiral azolium salts have also been reported (Scheme16).[20]



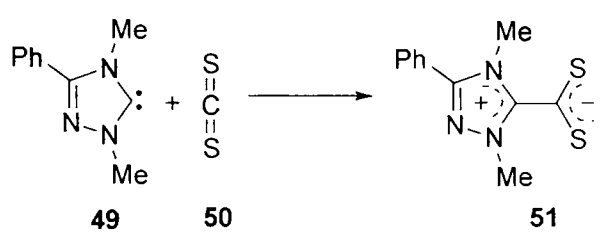
Scheme 16

In a recent study, the asymmetric intramolecular Michael-Stetter reaction using another chiral triazolium salt **48** has been reported with improved yields and enantioselectivity (Scheme 17).[21]



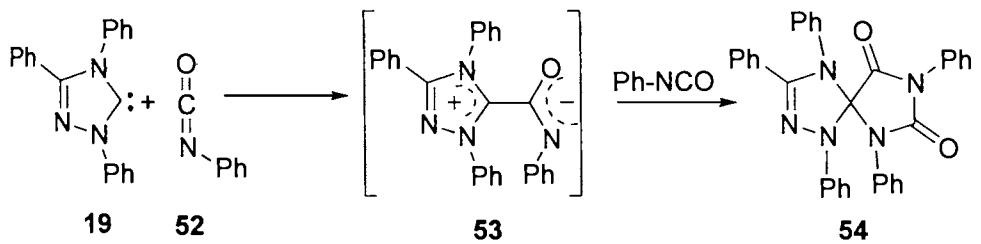
Scheme 17

The addition of stable imidazole-2-ylidenes and triazolylidenes to heterocumulenes such as carbondioxide, carbon disulfide and phenyl isothiocyanate afforded the corresponding betaines (Scheme 18).[22]



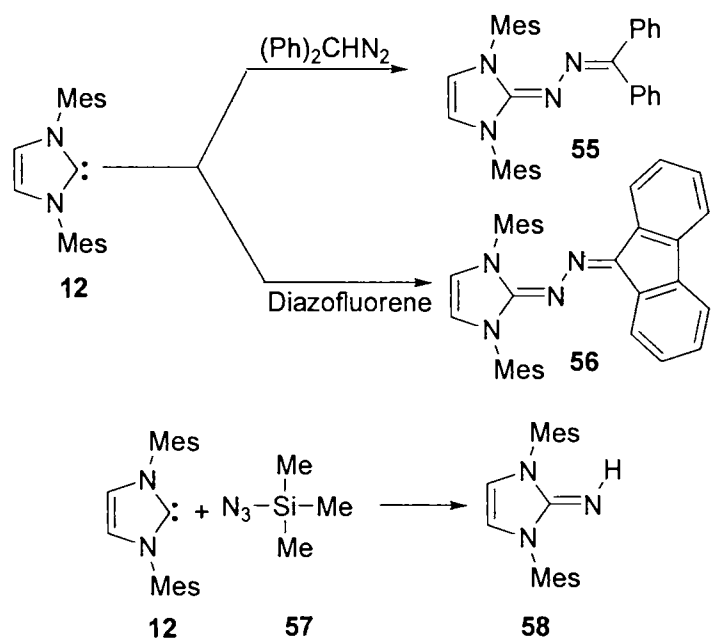
Scheme 18

The reaction of triazolylidene **19** with excess phenyl isocyanate led to the formation of the spiro compound **54**, presumably *via* a [3+2] cycloaddition with the intermediate betaine **53** (Scheme 19).[22]



Scheme 19

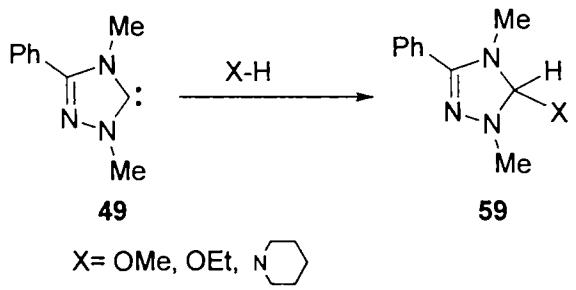
The reaction of 1,3-dimesityl imidazole-2-ylidene with diazo compounds such as diazofluorene and diphenyl diazomethane afforded the corresponding azines as the addition products, while the reaction of the carbene with azido trimethylsilane furnished the imine **58** (Scheme 20).[23]



Scheme 20

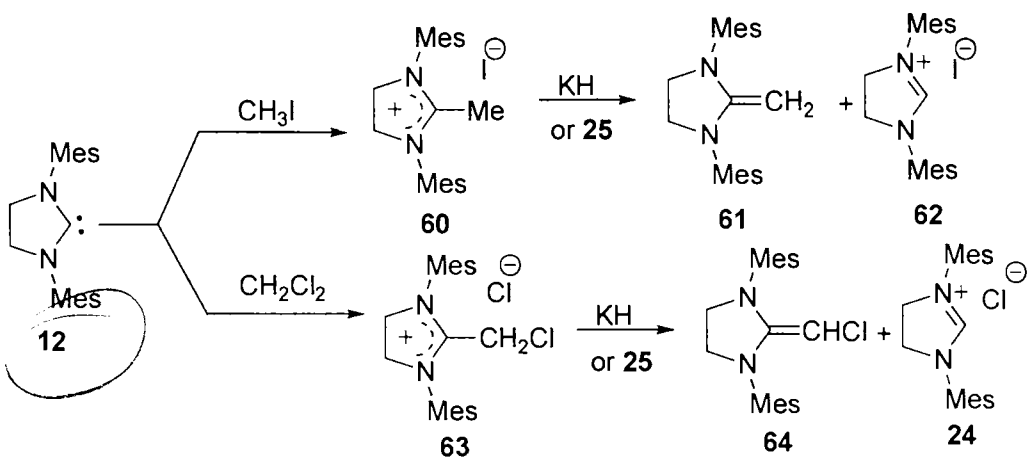
Insertion of stable aminocarbenes such as triazolylidene into strongly polar X-H bonds has been reported to afford the corresponding 1,1-addition

products in quantitative yields. However, the insertion of such species into unpolarised C-H bonds is not reported so far (Scheme 21).[8]



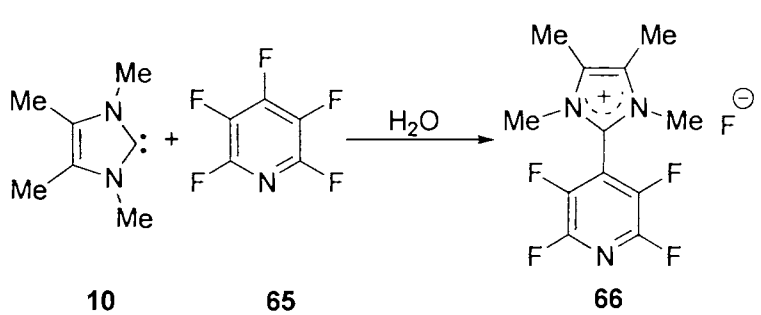
Scheme 21

Imidazolin-2-ylidene **25** has been reported to react with methyl iodide and methylene chloride to afford the olefins **61** and **64** along with the corresponding imidazolinium salts (Scheme 22).[5]



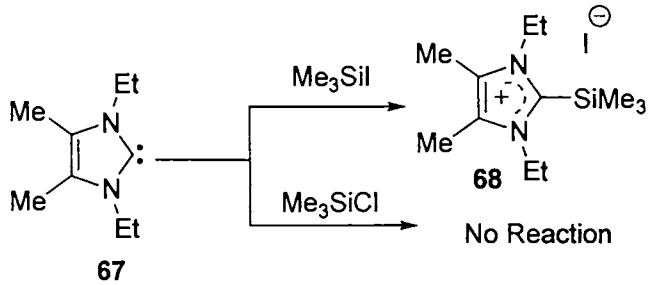
Scheme 22

The reaction of imidazol-2-ylidene **10** with pentafluoro pyridine afforded the corresponding substituted product **66** in good yield (Scheme 23).[24]



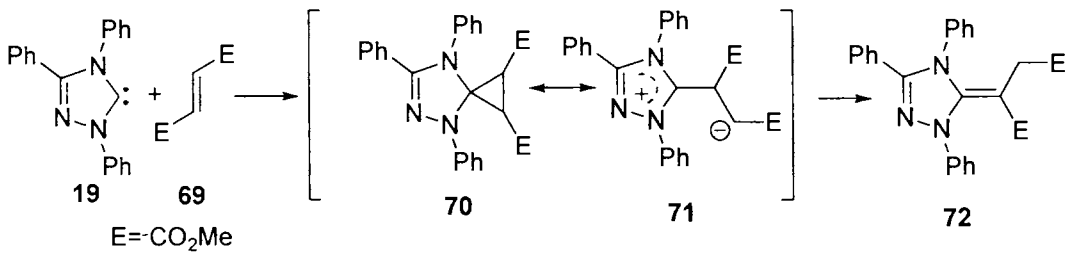
Scheme 23

Similarly the addition of carbene **67** to trimethylsilyl iodide afforded the corresponding addition product. However no reaction was observed with trimethylsilyl chloride (Scheme 24).[25]



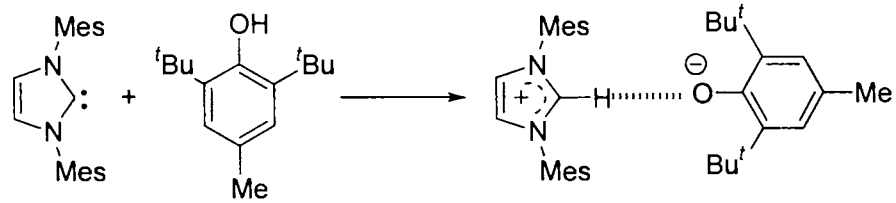
Scheme 24

The reactivity of stable diaminocarbenes towards C-C multiple bonds has also been studied by Enders and coworkers, who have shown that unlike other singlet carbenes, the triazolylidene **19** did not furnish any cyclopropane derivative with dimethyl fumarate; instead it afforded the methylene triazoline derivative **72**. According to these workers, the initial event in this reaction is the [2+1] cycloaddition of the carbene with the alkene to form the cyclopropane derivative **70** which undergoes rapid ring opening to afford the zwitterionic intermediate **71**. This zwitterion on subsequent [1,2] hydrogen shift affords the methylene triazoline derivative **72** (Scheme 25).[8]



Scheme 25

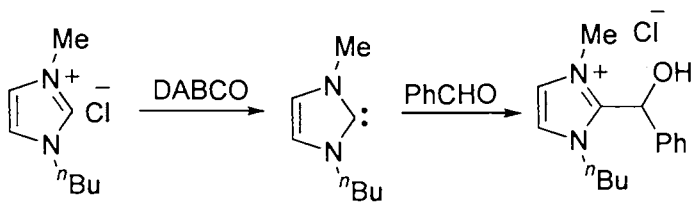
Recently, the *N*-heterocyclic carbene **12** was reported to form stable crystalline compounds with organic acids such as phenols (Scheme 26).[26]



12 73 74

Scheme 26

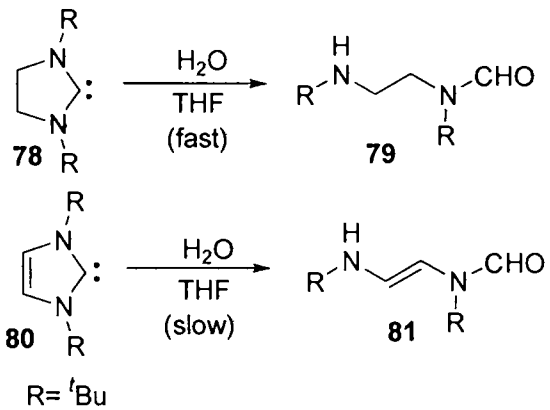
A number of imidazolium salts have found widespread use as ionic liquids. Afonso and coworkers have reported the beneficial properties of imidazolium salts as ionic liquids in Baylis Hillmann reaction.[27] However, in a recent study, it was shown that the use of imidazolium salts as ionic liquids in Baylis Hillman reaction results in low yields of products due to side reactions of the carbene generated with aldehydes[28] as shown in Scheme 27. Thus the study has demonstrated that the deprotonation of imidazolium salts requires only mild bases such as DABCO and 3-hydroxyquinuclidine.



75 76 77

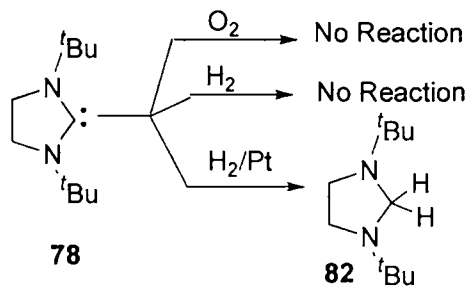
Scheme 27

The reactivity of stable diaminocarbenes towards water, oxygen and hydrogen has also been investigated. The imidazolin-2-ylidene **78** was found to undergo instant hydrolysis on exposure to moist THF while the aromatic congener **80** took days to get hydrolysed to the corresponding aldehyde (Scheme 28).[29]



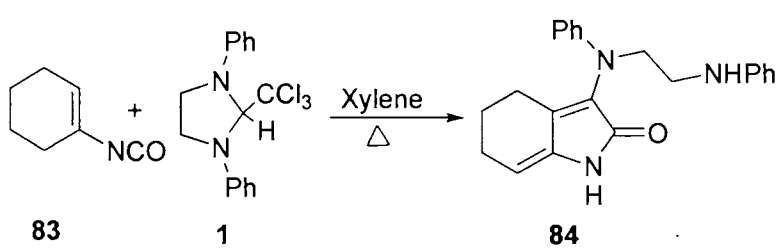
Scheme 28

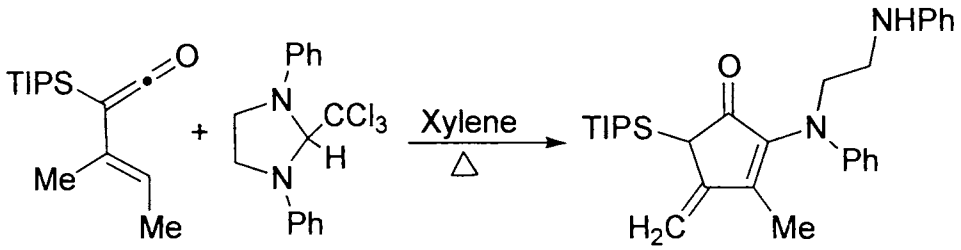
The carbenes **78** and **80** were found to be inert towards oxygen and hydrogen, but in the presence of a platinum or palladium catalyst, they underwent slow hydrogenation (Scheme 29).[29]



Scheme 29

Rigby has shown that the reaction of *N*-heterocyclic carbenes with vinyl isocyanates and vinyl ketenes led to functionalized hydroindolone and cyclopentenone derivatives (Scheme 30).[30]





85 1 86

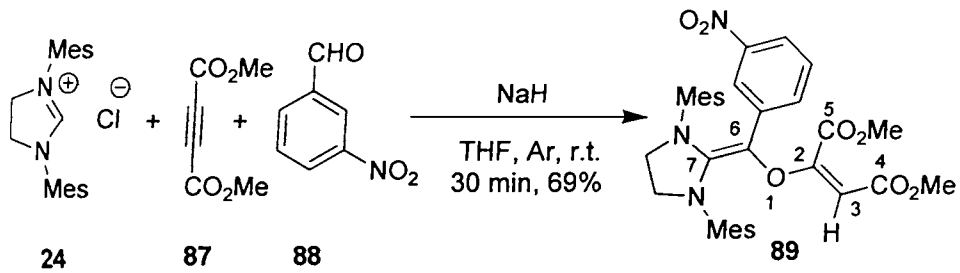
Scheme 30

4.3 The Present Work

The literature survey has revealed that although the chemistry of *N*-heterocyclic carbenes has been explored in some detail most of the studies were focused on the coordination behavior of these species as strong σ-donor ligands. Against this literature background, and in the context of our general interest in devising novel multicomponent reactions based on nucleophilic carbenes (see Chapter 2), it was of interest to examine the reactivity pattern of *N*-heterocyclic carbenes in multicomponent reactions. The NHCs covered in the present study are 1,3-dimesityl-imidazolin-2-ylidene and 1,3-dimesityl-imidazol-2-ylidene and the electrophiles of our choice include a variety of aromatic aldehydes and dimethyl acetylenedicarboxylate (DMAD). The results of our explorations in this avenue are presented in the following section.

4.4 Results and Discussion

Our studies commenced by exposing 3-nitrobenzaldehyde to DMAD and 1,3-dimesityl imidazolin-2-ylidene, generated *in situ* by the reaction of 1,3-dimesityl-imidazolinium chloride with sodium hydride in THF under argon atmosphere. A facile reaction leading to the formation of 2-oxymaleate derivative **89** occurred (Scheme 31).



Scheme 31

The structure of the product **89** was established by spectroscopic analysis. The IR spectrum showed strong carbonyl absorption peaks at 1742 and 1730 cm^{-1} corresponding to two ester carbonyls. In the ^1H NMR spectrum, the peaks corresponding to protons of the aryl methyl groups were discernible as singlets at δ2.01, δ2.21 and δ2.38. The carbomethoxy protons resonated as singlets at δ 3.48 and δ 3.69 while the methylene protons of the dihydro imidazole displayed two triplets centered at δ 3.75 and δ 3.89. The peak corresponding to the olefinic proton was discernible as a singlet at δ4.75 while the aromatic protons afforded signals between δ 6.46 and δ 7.36. In the ^{13}C NMR spectrum, the two ester carbonyls were found to resonate at δ 165.8 and δ163.5. The olefinic carbons C-3 and C-6 showed peaks at δ97.9 and δ117.3. All the other signals were in good agreement with the assigned structure. The HRMS data of the compound was also found to be satisfactory. Final proof for the structure assigned for **89** was derived from single crystal X-ray analysis (Figure 2).

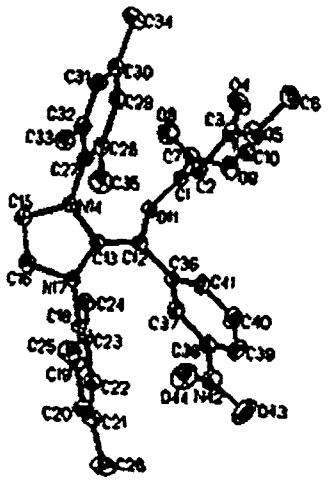


Figure 2 X- Ray Crystal Structure of 89

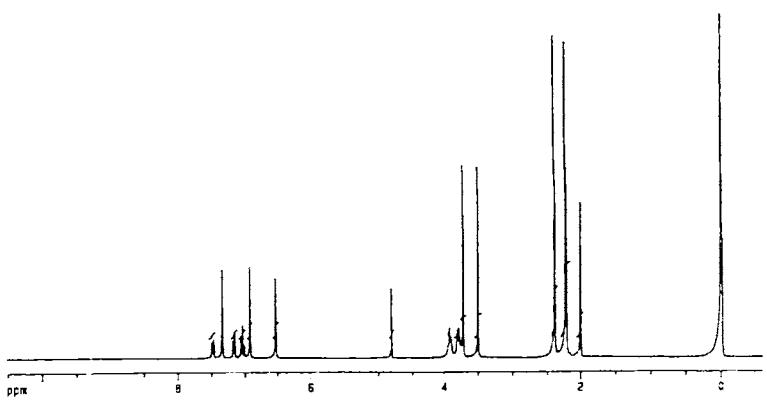


Figure 3 ^{1}H NMR Spectrum of 89

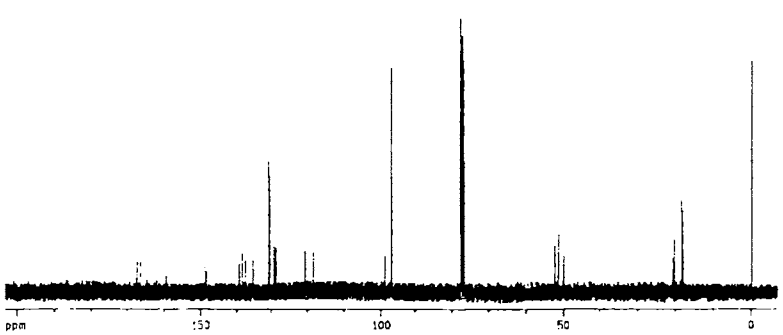
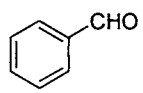
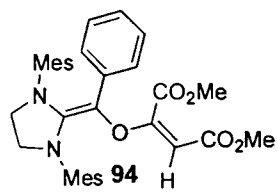
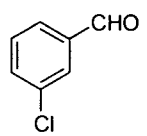
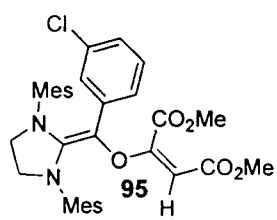
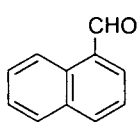
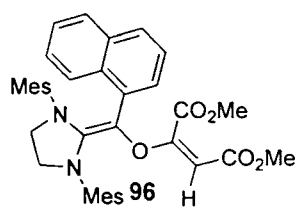
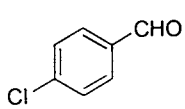
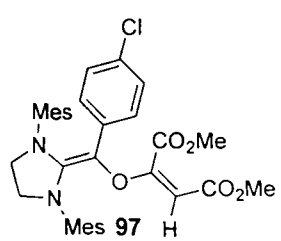
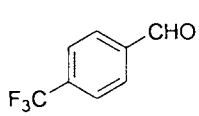
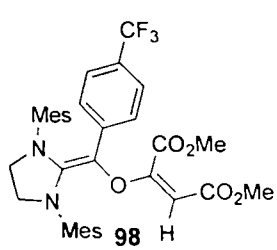


Figure 4 ^{13}C NMR Spectrum of 89

The reaction was found to be applicable to a number of substituted aromatic aldehydes; reasonable yields of maleate derivatives were obtained in all cases (Table 1).

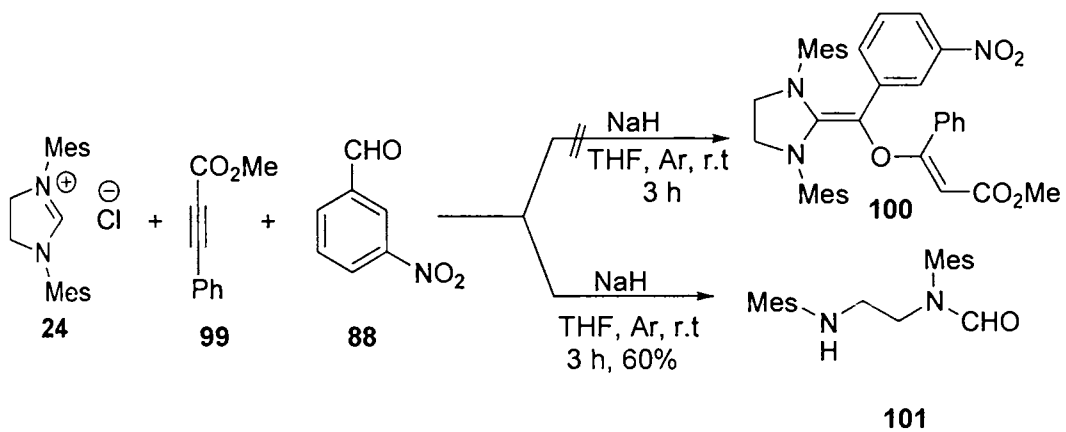
Table 1

Entry	Substrate	Product	Yield(%)*
1	 **36**	 **94**	53
2	 **90**	 **95**	80
3	 **91**	 **96**	62
4	 **92**	 **97**	60
5	 **93**	 **98**	60

Reaction conditions: NaH, THF, Ar, r.t, 3 h.

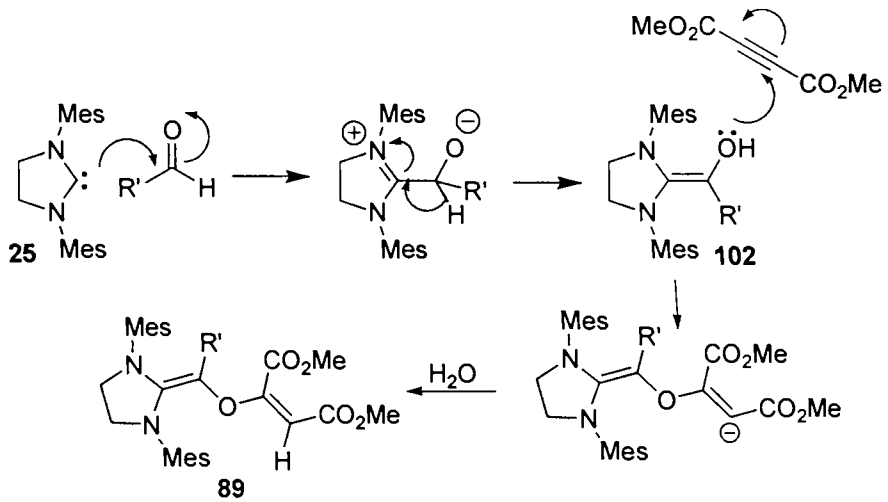
* =isolated yield

The reaction takes place in solvents such as benzene and toluene also, but the products were obtained in much higher yields when the reaction was carried out in THF. Similarly the rate of the reaction was found to be accelerated at higher temperatures, but in some cases the reaction afforded intractable mixtures. Also the use of alkynes other than DMAD did not afford any maleate derivatives. In these cases, the only isolable product was **101** derived from the hydrolysis of the carbene (Scheme 32).



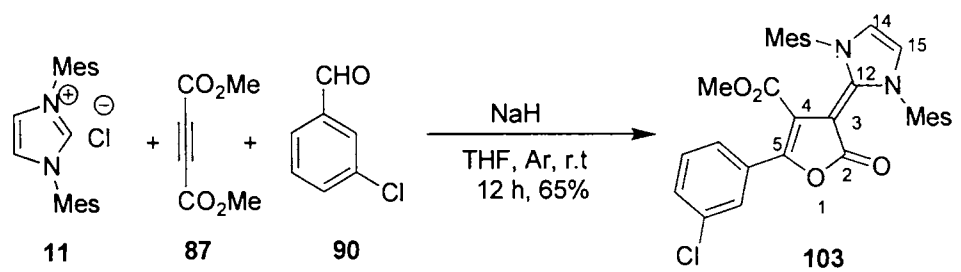
Scheme 32

A mechanistic rationale for this reaction is given in Scheme 33. Presumably, unlike in the case of nucleophiles such as isocyanides and dimethoxycarbene, the initial event in this reaction is the addition of diaminocarbene to the aldehyde to form an electron rich enaminol intermediate **102**. The latter, due to steric reasons, undergoes a conjugate addition to the activated alkyne through the harder oxygen atom, followed by proton abstraction to furnish the product. It is conceivable that the addition of diaminocarbene to DMAD is reversible at r.t. and the thermodynamic stability of **102** drives the reaction towards product formation.



Scheme 33

The reaction was found to be sensitive to the nature of the carbene employed. When the less nucleophilic 1,3-dimesityl imidazol-2-ylidene is employed, the reaction followed a different but interesting pathway leading to the furanone derivative **103** in good yield (Scheme 34).



Scheme 34

The structure of the product **103** was elucidated by spectroscopic analysis. The IR spectrum showed a peak at 1694 cm^{-1} corresponding to the lactone and the carbomethoxy groups. In the ^{1}H NMR spectrum, the peaks corresponding to the aryl methyl groups were discernible as singlets at δ 2.19, and δ 2.30. The protons of the carbomethoxy group resonated as a singlet at δ 3.37 while the aromatic protons afforded two separate multiplets in the region δ 6.93-6.12 and δ 7.36-7.29. In the ^{13}C NMR spectrum, signals due to the aryl methyl carbons were visible at δ 18.6 and δ 21.1 while signals at δ 71.2 and δ 111.1 were assigned to the C-3, C-14 and C-15 carbons. The signals due to

the ester and lactone carbonyls were seen at δ 164.1 and δ 165.3. All the other signals were also in good agreement with the proposed structure; the HRMS data of the compound was also found to be satisfactory. Final proof for the structure assigned for **103** was derived from single crystal X-ray analysis (Figure 5).

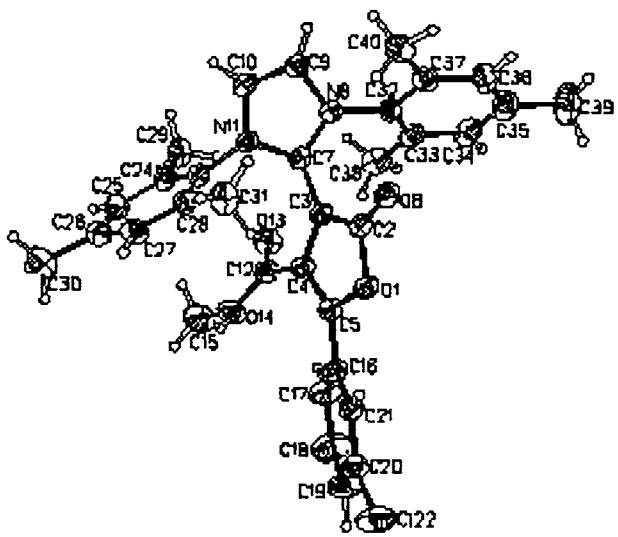
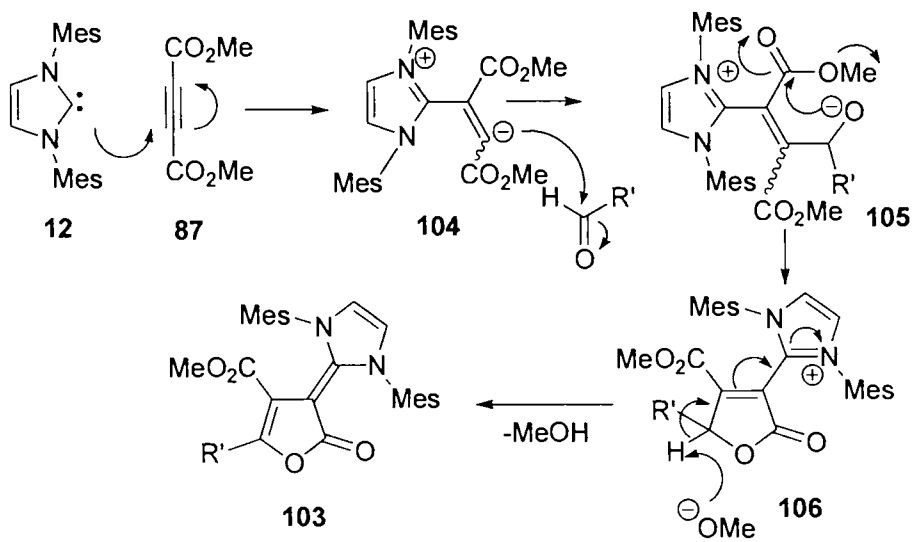


Figure 5 X- Ray Crystal Structure of 103

A plausible mechanism for this reaction is given in the following scheme (Scheme 35).

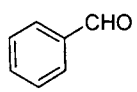
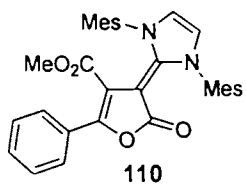
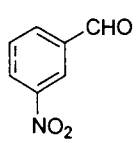
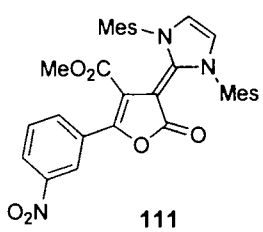
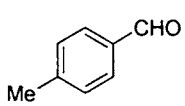
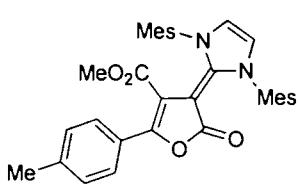
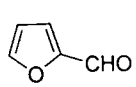
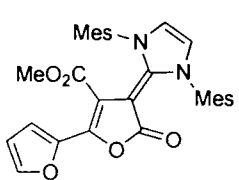
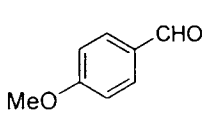
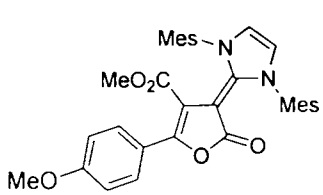


Scheme 35

It is conceivable that the addition is initiated by the formation of the

zwitterion **104**, from the carbene and DMAD, which adds to the aldehyde to form another zwitterionic species **105**. This ion, presumably for steric reasons, adds to the ester carbonyl of DMAD in preference to the iminium ion to afford **106**, which subsequently eliminates a proton to furnish the furanone derivative **103**. The reaction was found to be applicable to a number of substituted aromatic aldehydes and the results are summarized in Table 2.

Table 2

Entry	Substrate	Product	Yield(%)*
1	 **36**	 **110**	**57**
2	 **88**	 **111**	**79**
3	 **107**	 **112**	**45**
4	 **108**	 **113**	**42**
5	 **109**	 **114**	**25**

Reaction conditions: NaH, THF, Ar, r.t. 12 h.
* =isolated yield

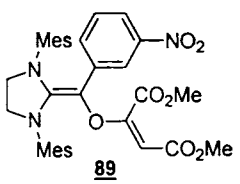
In conclusion, we have unraveled some interesting reactivity profiles of the *N*-heterocyclic carbenes **25** and **12** thus constituting novel multicomponent reactions which offer a simple and efficient route to the one pot synthesis of highly functionalized 2-oxymaleate and furanone derivatives. It is worthy of mention that a wide range of biologically active molecules contain dihydroimidazole and furanone moieties as the central core.

4.5 Experimental

General information about the experiments is given in Section 2.6 of Chapter 2. The carbene precursors 1,3-dimesityl-imidazolinium chloride and 1,3-dimesityl-imidazolium chlorides were prepared by a known literature procedure.[32] Gravity column was performed using basic alumina and mixtures of hexane-ethylacetate were used for elution.

Dimethyl 2-[[1,3-bis (2,4,6-trimethylphenyl)-1-imidazolidinylidene] (3-nitrophenyl) methoxy]-2-butenedioate 89

NaH (16 mg, 0.66 mmol) was added to a suspension of the carbene precursor **24** (226 mg, 0.66 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (69 mg, 0.49 mmol) and the aldehyde **88** (50 mg, 0.33 mmol) and the resulting solution was stirred for 30 minutes. The reaction mixture was then passed through a short pad of Celite®. After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford **89** (136 mg, 69%) as a red crystalline solid (recrystallized from hexane-CH_2Cl_2 solvent mixture), m.p. 149-150 °C.



89

IR (KBr) ν_{max}: 3015, 2942, 2850, 1742, 1730, 1620, 1592, 1472, 1351, 1283, 1052, 845, 737 cm^{-1}.

^{1}H NMR: δ 7.36 (d, J = 7.9, 1H), 7.25 (s, 1H), 7.08 (d, J = 7.9, 1H), 6.95 (t, J = 7.9, 1H), 6.84 (s, 2H), 6.46 (s, 2H), 4.75 (s, 1H), 3.89 (t, J = 7.7, 2H), 3.75 (t, J = 7.9, 2H), 3.69 (s, 3H), 3.48 (s, 3H), 2.38 (s, 6H), 2.21 (s, 9H), 2.01 (s, 3H).

^{13}C NMR: δ 165.8, 163.5, 157.8, 147.2, 146.8, 137.9, 137.5, 136.9, 136.3, 136.1, 134.1, 129.8, 129.5, 128.3, 127.7, 119.7, 117.3, 97.9, 52.1, 51.3, 51.1, 49.8, 20.9, 20.0, 18.7, 18.3.

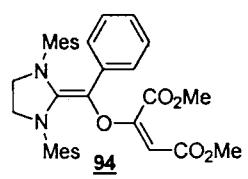
HRMS (EI) Calculated for $C_{34}H_{37}N_3O_7$: 599.2631 Found: 599.2591.

Crystal data for 89: $C_{34}H_{37}N_3O_7$, FW = 599.67, the crystal used for the X-ray study has the dimensions of 0.40 x 0.22 x 0.10 mm^3. Monoclinic, space group P2 (1)/c. Unit cell dimensions: a = 8.3507(2) Å, α = 90°; b = 16.5312(3) Å, β = 94.2560(10)°; c = 22.7552(5) Å, γ = 90°; Vol = 3132.63(12) $Å^3$. Density (calcd.) = 1.271 mg/mm^3. Absorption coefficient = 0.089 mm^{-1}. R indicecs R1 = 0.1555, wR2 = 0.1439

Dimethyl-2-[[1,3-bis(2,4,6-trimethylphenyl)-1-imidazolidinylidene] (phenyl)methoxy]-2-butenedioate 94

NaH (22 mg, 0.94 mmol) was added to a suspension of the carbene precursor **24** (322 mg, 0.94 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (99 mg, 0.70 mmol) and the aldehyde **36** (50 mg, 0.47 mmol) and the resulting solution was stirred for 3 h. The reaction mixture was then passed through a short pad of Celite®. After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate mixture to afford **94** (205 mg,

53%) as a yellow crystalline solid (recrystallized from hexane-CH_2Cl_2 solvent mixture), m.p. 150-151 °C.



94

IR (KBr) ν_{max}: 3013, 2948, 2854, 1742, 1721, 1627, 1592, 1485, 1352, 1283, 1135, 1040, 858, 690 cm^{-1}.

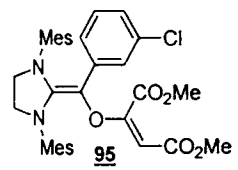
^{1}H NMR: δ 6.82-6.74 (m, 6H), 6.62-6.57 (m, 1H,), 6.49 (s, 2H), 4.76 (s, 1H), 3.81-3.68 (m, 4H), 3.65 (s, 3H), 3.45 (s, 3H), 2.38 (s, 6H), 2.03 (s, 3H), 2.21 (s, 9H).

^{13}C NMR: δ 165.9, 163.2, 158.3, 145.1, 138.6, 136.2, 135.1, 134.1, 134.1, 129.6, 126.6, 124.9, 123.3, 111.1, 97.4, 51.7, 51.3, 50.8, 49.8, 20.8, 20.5, 18.5, 18.2.

HRMS (EI) Calculated for $C_{34}H_{38}N_2O_5$: 554.2780, Found: 554.2791

Dimethyl-2-[[1,3-bis(2,4,6-trimethylphenyl)-1-imidazolidinylidene] (3-chlorophenyl) methoxy]-2-butenedioate 95

NaH (22 mg, 0.70 mmol) was added to a suspension of the carbene precursor **24** (239 mg, 0.70 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (99 mg, 0.53 mmol) and the aldehyde **90** (50 mg, 0.35 mmol) and the resulting solution was stirred for 3 h. The reaction mixture was then passed through a short pad of Celite®. After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford **95** (164 mg, 80%) as a yellow crystalline solid (recrystallized from hexane-CH_2Cl_2 solvent mixture), m.p. 135-136 °C.



95

IR (KBr) ν_{max}: 3012, 2948, 2860, 1742, 1627, 1587, 1479, 1290, 1142, 1058, 848, 737 cm^{-1}.

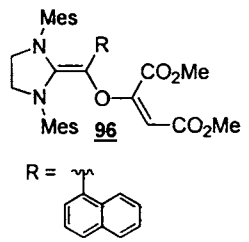
^{1}H NMR: δ 6.90-6.49 (m, 8H), 4.74 (s, 1H), 3.80-3.83 (m, 2H), 3.76-3.74 (m, 2H), 3.69 (s, 3H), 3.44 (s, 3H), 2.35 (s, 6H) 2.19 (s, 9H), 2.05 (s, 3H).

^{13}C NMR: δ 166.0, 163.2, 158.1, 146.5, 138.3, 138.2, 136.6, 136.4, 136.3, 135.4, 134.0, 132.0, 129.7, 129.5, 129.1, 128.2, 125.2, 123.0, 122.6, 121.7, 109.9, 105.0, 97.7, 51.9, 51.4, 51.0, 49.9, 20.9, 20.6, 18.6, 18.3, 18.2.

HRMS (EI) Calculated for $C_{34}H_{37}N_2O_5Cl$: 588.2391, Found: 588.2388.

Dimethyl-2-[[1,3-bis(2,4,6-trimethylphenyl)-1-imidazolidinylidene] (1-naphthyl) methoxy]-2-butenedioate 96

NaH (22 mg, 0.64 mmol) was added to a suspension of the carbene precursor **24** (219 mg, 0.64 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (68 mg, 0.48 mmol) and the aldehyde **91** (50 mg, 0.32 mmol) and the resulting solution was stirred for 3 h. The reaction mixture was then passed through a short pad of Celite®. After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford **96** (164 mg, 62%) as a yellow crystalline solid (recrystallized from hexane-CH_2Cl_2 solvent mixture), m.p. 170-171 °C.



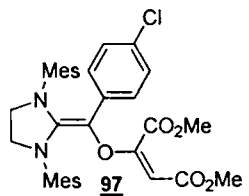
IR (KBr) ν_{max}: 3010, 2955, 2860, 1744, 1717, 1627, 1485, 1371, 1290, 1135, 1047, 791, 765 cm^{-1}.

^{1}H NMR: δ 8.07 (d, J = 8.2, 1H), 7.47 (d, J = 7.7, 1H), 7.32-7.21 (m, 4H), 7.11 (d, J = 7, 1H), 6.96-6.88 (m, 4H), 5.05 (s, 1H), 3.80-3.65 (m, 4H), 3.52 (s, 3H). 3.40 (s, 3H), 2.51 (s, 6H), 2.19 (s, 9H), 1.81 (s, 3H).

^{13}C NMR: δ 166.1, 162.9, 158.4, 146.2, 138.7, 136.5, 134.9, 133.5, 132.3, 131.7, 129.6, 128.7, 128.1, 127.7, 126.5, 126.2, 124.8, 124.3, 109.3, 97.9, 50.8, 50.7, 50.6, 50.2, 20.9, 20.3, 18.4.

Dimethyl-2-[[1,3-bis(2,4,6-trimethylphenyl)-1-imidazolidinylidene] (4-chlorophenyl)methoxy]-2-butenedioate 97

NaH (22 mg, 0.70 mmol) was added to a suspension of the carbene precursor **24** (239 mg, 0.70 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (99 mg, 0.53 mmol) and the aldehyde **92** (50 mg, 0.35 mmol) and the resulting solution was stirred for 3 h. The reaction mixture was then passed through a short pad of Celite®. After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford **97** (124 mg, 60%) as a yellow crystalline solid (recrystallized from hexane-CH_2Cl_2 solvent mixture), m.p. 135-136 °C.



97

IR (KBr) ν_{max}: 3012, 2942, 2845, 1742, 1627, 1485, 1438, 1290, 1209, 1135, 1054, 845, 757 cm^{-1}.

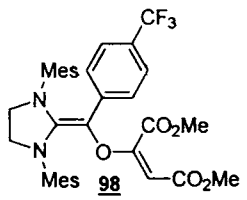
^{1}H NMR: δ 6.95-6.51 (m, 8H), 4.72 (s, 1H), 3.84-3.68 (m, 4H), 3.65 (s, 3H), 3.45 (s, 3H), 2.32 (s, 6H), 2.23 (s, 9H), 2.20 (s, 3H).

^{13}C NMR: δ 165.7, 163.0, 158.0, 145.6, 143.3, 138.4, 138.3, 136.9, 136.1, 135.7, 134.2, 132.9, 129.6, 129.2, 128.5, 126.7, 126.0, 97.8, 51.6, 51.2, 50.7, 49.8, 20.7, 20.4, 18.3, 18.1.

HRMS (EI) Calculated for $C_{34}H_{37}N_2O_5Cl$: 588.2391, Found: 588.2362.

Dimethyl-2-[[1,3-bis(2,4,6-trimethylphenyl)-1-imidazolidinylidene] (4-trifluoromethylphenyl)methoxy]-2-butenedioate 98

NaH (13 mg, 0.56 mmol) was added to a suspension of the carbene precursor **24** (191 mg, 0.56 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (61 mg, 0.43 mmol) and the aldehyde **93** (50 mg, 0.28 mmol) and the resulting solution was stirred for 3 h. The reaction mixture was then passed through a short pad of Celite®. After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford **98** (104 mg, 60%) as a yellow crystalline solid (recrystallized from hexane-CH_2Cl_2 solvent mixture), m.p. 138-139 °C.



98

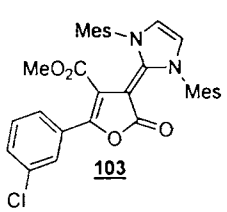
IR (KBr) ν_{max}: 3010, 2962, 2845, 1728, 1634, 1438, 1256, 1128, 1027, 798 cm^{-1}.

^{1}H NMR: δ 6.93-6.54 (m, 8H), 4.73 (s, 1H), 3.83-3.68 (m, 4H), 3.68 (s, 3H), 3.47 (s, 3H), 2.30 (s, 6H), 2.21 (s, 9H), 2.19 (s, 3H).

^{13}C NMR: δ 165.8, 163.0, 158.2, 145.6, 143.3, 138.1, 136.7, 136.2, 136.1, 135.7, 134.0, 129.8, 129.4, 128.5, 126.7, 126.0, 123.8, 123.6, 123.5, 97.6, 52.0, 51.3, 51.0, 49.9, 20.9, 20.3, 18.5, 18.2.

Methyl-2-(3-chlorophenyl)-4-[1,3-dihydro-1,3-bis(2,4,6-trimethylphenyl)-1H-imidazol-2-ylidene]-4,5-dihydro-5-oxo-3-furancarboxylate 103

NaH (17 mg, 0.71 mmol) was added to a suspension of the carbene precursor **11** (241 mg, 0.71 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (74 mg, 0.53 mmol) and the aldehyde **90** (50 mg, 0.35 mmol), and the resulting solution was stirred for 12 h. The reaction mixture was then passed through a short pad of Celite.® After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford **103** (126 mg, 65%) as a yellow crystalline solid (recrystallized from hexane-CH_2Cl_2), m.p. 279-280 °C.



103

IR (KBr) ν_{max}: 3012, 2928, 2850, 1694, 1600, 1533, 1479, 1371, 1216, 1047, 906, 852, 798, 730 cm^{-1}.

^{1}H NMR: δ 7.36-7.29 (m, 2H), 6.93-6.12 (m, 8H), 3.37 (s, 3H), 2.30 (s, 6H), 2.19 (s, 12H).

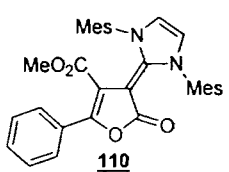
^{13}C NMR: δ 165.3, 164.1, 148.4, 140.2, 139.3, 135.3, 133.5, 132.8, 132.3, 130.5, 129.7, 129.3, 128.7, 127.2, 126.6, 125.2, 120.9, 111.1, 71.2, 50.5, 21.1, 18.6.

HRMS (EI) Calculated for $C_{33}H_{31}N_2O_4Cl$: 554.1972, Found: 554.1946.

Crystal data for 103: $C_{33}H_{31}N_2O_4Cl$ FW = 555.05, the crystal used for the X-ray study has the dimensions of 0.40 x 0.33 x 0.24 mm^3. Orthorhombic, space group $P2_12_12_1$. Unit cell dimensions: a = 11.05750 (10) Å, $\alpha = 90^\circ$; b = 15.0539 (2) Å, $\beta = 90^\circ$; c = 17.5750 (5) Å, $\gamma = 90°$; Vol = 2925.51(6) $Å^3$. Density (calcd.) = 1.260 mg/mm^3. Absorption coefficient = 0.170 mm^{-1}. R indicecs R1 = 0.0639, wR2 = 0.0971.

Methyl-2-(phenyl)-4-[1,3-dihydro-1,3-bis(2,4,6-trimethylphenyl)-1H-imidazol-2-ylidene]-4,5-dihydro-5-oxo-3-furancarboxylate 110

NaH (23 mg, 0.94 mmol) was added to a suspension of the carbene precursor **11** (319 mg, 0.94 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (100 mg, 0.70 mmol) and the aldehyde **36** (50 mg, 0.47 mmol), and the resulting solution was stirred for 12 h. The reaction mixture was then passed through a short pad of Celite.® After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford **110** (139 mg, 57%) as a yellow crystalline solid (recrystallized from hexane-CH_2Cl_2), m.p. 295-296 °C.



110

IR (KBr) ν_{max}: 3010, 2962, 2842, 1688, 1607, 1539, 1485, 1378, 1303, 1070, 1040, 906, 865, 750 cm^{-1}.

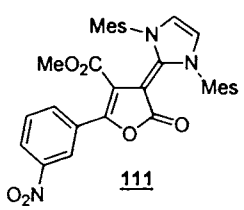
^{1}H NMR: δ 7.38-7.36 (m, 2H), 7.19-7.07(m, 3H), 6.91-6.93 (m, 6H), 3.33 (s, 3H), 2.29 (s, 6H), 2.20 (s, 12H).

^{13}C NMR: δ 165.5, 164.4, 148.3, 142.1, 139.1, 130.9, 129.6, 127.5, 127.3, 126.9, 111.1, 71.2, 50.5, 23.6, 21.1, 18.6.

HRMS (EI) Calculated for $C_{33}H_{32}N_2O_4$: 520.2362, Found: 520.2355.

Methyl-2-(3-nitrophenyl)-4-[1,3-dihydro-1,3-bis(2,4,6-trimethylphenyl)-1H-imidazol-2-ylidene]-4,5-dihydro-5-oxo-3-furancarboxylate 111

NaH (16 mg, 0.66 mmol) was added to a suspension of the carbene precursor **11** (224 mg, 0.66 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (71 mg, 0.49 mmol) and the aldehyde **88** (50 mg, 0.33 mmol), and the resulting solution was stirred for 12 h. The reaction mixture was then passed through a short pad of Celite.® After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford **111** (187 mg, 79%) as a yellow crystalline solid (recrystallized from hexane-CH_2Cl_2), m.p. 250-251 °C.



111

IR (KBr) ν_{max}: 3018, 2935, 2852, 1701, 1607, 1526, 1321, 1229, 1040, 906, 852, 747 cm^{-1}.

^{1}H NMR: δ 8.30 (s, 1H), 7.91 (d, J = 7.4, 1H), 7.77 (d, J = 7.4, 1H), 7.34 (t, J = 8, 1H), 7.03 (s, 3H), 6.96 (s, 3 H), 3.46 (s, 3H,), 2.29 (s, 6H), 2.21 (s, 12H).

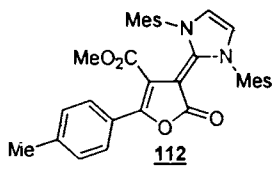
^{13}C NMR: δ 165.1, 163.8, 147.9, 139.5, 138.5, 132.4, 129.7, 128.6, 121.6, 121.1, 120.7, 118.6, 113.7, 113.1, 77.2, 50.9, 21.2, 18.6.

HRMS (EI) Calculated for $C_{33}H_{31}N_3O_6$: 565.2212, Found: 565.2197.

Methyl-2-(4-methyl)-4-[1,3-dihydro-1,3-bis(2,4,6-trimethylphenyl)-1H-imidazol-2-ylidene]-4,5-dihydro-5-oxo-3-furancarboxylate 112

NaH (20 mg, 0.84 mmol) was added to a suspension of the carbene precursor **11** (285 mg, 0.84 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (88 mg, 0.62 mmol) and the aldehyde **107** (50 mg, 0.42 mmol), and the resulting solution was stirred for 12 h. The

reaction mixture was then passed through a short pad of Celite.® After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford **112** (94 mg, 45%) as a yellow crystalline solid (recrystallized from hexane-CH_2Cl_2), m.p. 255-256 °C.



112

IR (KBr) ν_{max}: 3018, 2962, 2854, 1686, 1533, 1371, 1229, 1303, 1162, 1074, 1034, 912, 854 cm^{-1}.

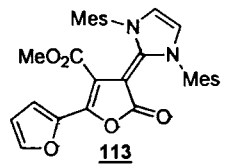
^{1}H NMR: δ 7.26 (d, J = 8.3, 2H), 6.98-6.91(m, 8H), 3.32 (s, 3H), 2.28 (s, 6H), 2.19 (s, 3H), 2.07 (s, 9H).

^{13}C NMR: δ 165.4, 164.3, 148.2, 142.5, 138.94, 136.5, 135.1, 132.2, 130.1, 129.5, 128.1, 127.3, 120.6, 110.4, 70.9, 50.3, 21.2, 21.0. 18.5.

HRMS (EI) Calculated for $C_{34}H_{34}N_2O_4$: 534.2518, Found: 534.2521.

Methyl-2-(1-furyl)-4-[1,3-dihydro-1,3-bis(2,4,6-trimethylphenyl)-1H-imidazol-2-ylidene]-4,5-dihydro-5-oxo-3-furancarboxylate 113

NaH (25 mg, 1.04 mmol) was added to a suspension of the carbene precursor **11** (353 mg, 1.04 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (111 mg, 0.78 mmol) and the aldehyde **108** (50 mg, 0.52 mmol), and the resulting solution was stirred for 12 h. The reaction mixture was then passed through a short pad of Celite.® After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford **113** (113 mg, 42%) as a yellow crystalline solid (recrystallized from hexane-CH_2Cl_2). m.p. 268-269 °C.



113

IR (KBr) ν_{max}: 3018, 2962, 2854, 1688, 1546, 1485, 1378, 1290, 1155, 1040, 926, 845, 751 cm^{-1}.

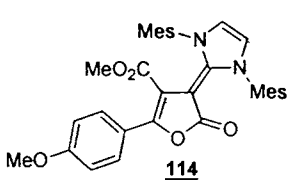
^{1}H NMR: δ 7.25-7.22 (d, J = 9, 1H), 6.97-6.92 (m, 6H), 6.43-6.42 (m, 1H), 6.28-6.26 (m, 1H), 3.43 (s, 3H), 2.30 (s, 6H), 2.19 (s, 12H).

^{13}C NMR: δ 164.9, 164.0, 148.0, 146.1, 141.2, 139.1, 135.2, 133.8, 132.1, 130.0, 129.6, 120.8, 111.1, 110.5, 108.1, 70.4, 50.5, 21.1, 18.5.

HRMS (EI) Calculated for $C_{31}H_{30}N_2O_5$: 510.2154, Found: 510.2155.

Methyl-2-(4-methoxy)-4-[1,3-dihydro-1,3-bis(2,4,6-trimethylphenyl)-1H-imidazol-2-ylidene]-4,5-dihydro-5-oxo-3-furancarboxylate 114

NaH (17 mg, 0.72 mmol) was added to a suspension of the carbene precursor **11** (217 mg, 0.72 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (78 mg, 0.55 mmol) and the aldehyde **109** (50 mg, 0.36 mmol), and the resulting solution was stirred for 12 h. The reaction mixture was then passed through a short pad of Celite.® After the removal of the solvent, the residue was subjected to chromatography on a basic alumina column using 80:20 hexane-ethyl acetate solvent mixture to afford **114** (49 mg, 25%) as a yellow crystalline solid (recrystallized from hexane-CH_2Cl_2), m.p. 189-190 °C.



114

IR (KBr) ν_{max}: 3019, 2952, 2851, 1670, 1529, 1492, 1378, 1250, 1173, 1032, 892, 845, 791, 731, 616 cm^{-1}.

^{1}H NMR: δ 7.35-7.34 (m, 2H), 6.94-6.92 (m, 6H), 6.73-6.70 (m, 2H), 3.74 (s, 3H), 3.33 (s, 3H), 2.29 (s, 6H), 2.16 (s, 12H).

^{13}C NMR: δ 165.5, 158.9, 148.7, 143.1, 139.0, 135.4, 132.5, 130.0, 129.6, 129.1, 128.5, 120.6, 113.1, 109.8, 70.7, 55.1, 50.2, 21.1, 18.5.

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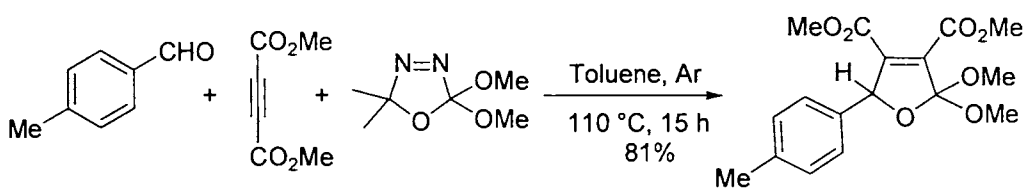
SUMMARY

The thesis entitled **"NOVEL HETEROCYCLIC CONSTRUCTIONS MEDIATED BY NUCLEOPHILIC CARBENES AND RELATED CHEMISTRY"** embodies the results of the investigations carried out to explore the reactivity patterns of the 1:1 zwitterions, generated *in situ* from various nucleophilic carbenes and dimethyl acetylenedicarboxylate (DMAD) towards aldehydes and ketones.

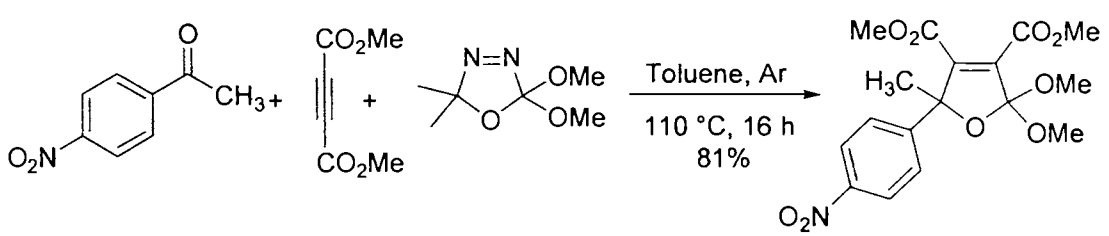
A general introduction to carbenes, carbenoids and nucleophilic carbenes is presented in Chapter 1. A brief introduction to multicomponent reactions and the definition of the present work is also provided in this chapter.

The second chapter describes the addition of the 1:1 zwitterionic intermediate of dimethoxycarbene, generated *in situ* by the thermolysis of 2,2-dimethoxy-Δ^3-1,3,4-oxadiazoline and DMAD, to various carbonyl compounds such as aldehydes, ketones and α,β-unsaturated carbonyl compounds. The addition of the zwitterionic intermediate to *p*-tolualdehyde affording the corresponding dihydrofuran derivative in 81% yield is illustrative (Scheme 1).



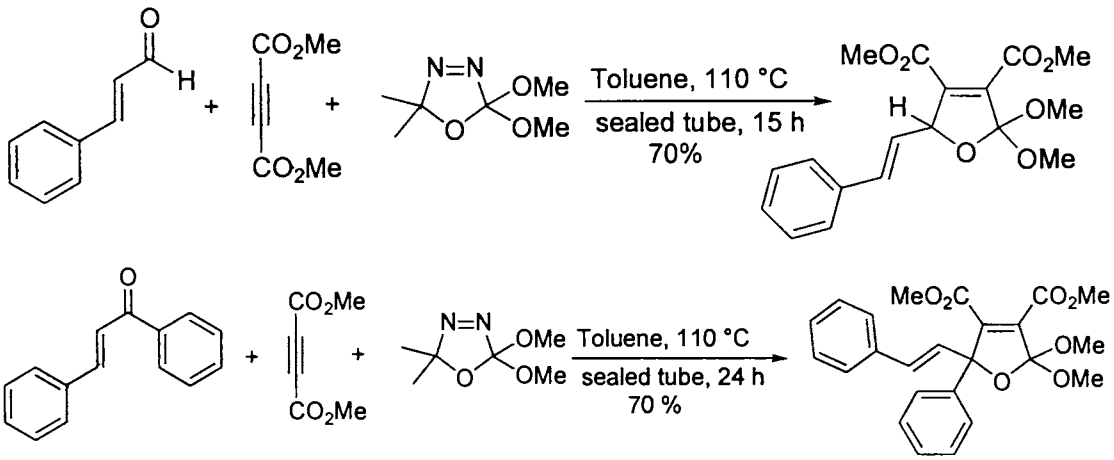
Scheme 1

The addition of the zwitterionic intermediate to ketones such as *p*-nitro acetophenone afforded the dihydrofuran derivative in excellent yield (Scheme 2).



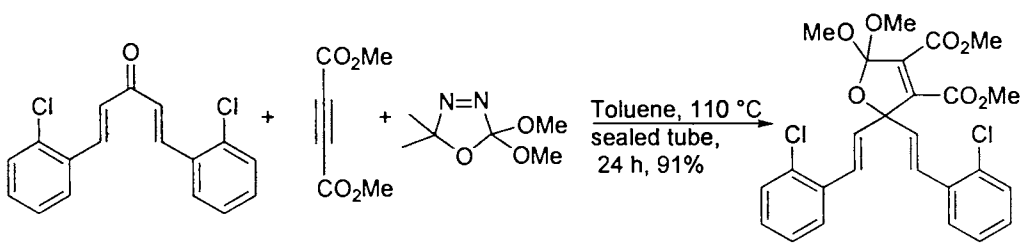
Scheme 2

Similar addition of zwitterionic intermediate to α,β-unsaturated carbonyl compounds such as cinnamaldehydes and chalcones also furnished the corresponding dihydrofuran derivatives (Scheme 3).



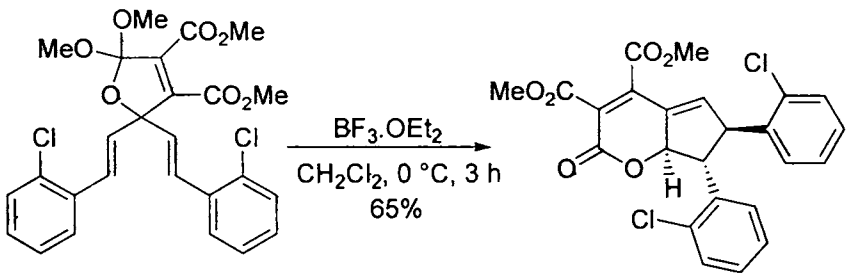
Scheme 3

The third chapter describes a novel approach to the synthesis of bicyclic lactones *via* the interrupted Nazarov reaction of divinyl dihydrofuran derivatives. The divinyl dihydrofurans are readily prepared by the multicomponent reaction of 1,4-dienones, DMAD and dimethoxycarbene (Scheme 4).



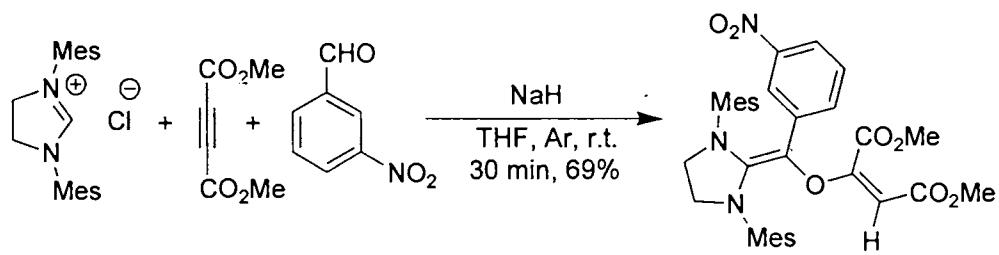
Scheme 4

The divinyl dihydrofurans when exposed to a Lewis acid such as $BF_3.OEt_2$, underwent the interrupted Nazarov reaction to afford the respective bicyclic lactone derivatives in good yield (Scheme 5).



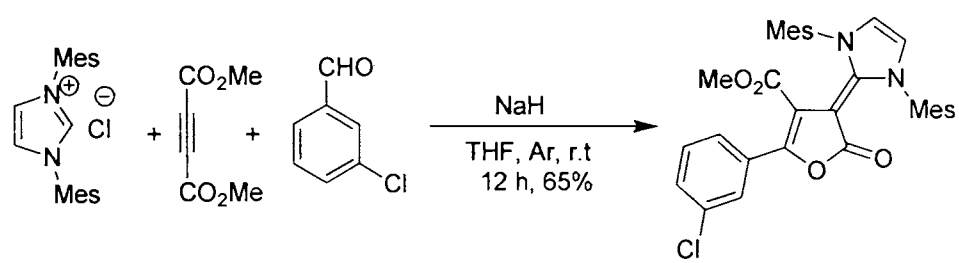
Scheme 5

The results of our investigations on the reaction of *N*-heterocyclic carbenes such as 1,3-dimesityl-imidazolin-2-ylidene and 1,3-dimesityl-imidazol-2-ylidene towards DMAD and aromatic aldehydes are presented in Chapter 4. The reaction of the 1,3-dimesityl-imidazolin-2-ylidene, generated *in situ* with DMAD and 3-nitro benzaldehyde afforded the 2-oxy-maleate derivative in good yield (Scheme 6).



Scheme 6

The reaction was found to be sensitive to the nature of the carbene employed. When the less nucleophilic 1,3-dimesityl imidazol-2-ylidene is employed as the carbene, the reaction followed a different pathway leading to the furanone derivative in good yield (Scheme 7).



Scheme 7

In conclusion, we have unravelled novel reactivity patterns of 1:1 zwitterionic intermediates generated by the addition of various nucleophilic

carbenes to DMAD and thus devised one pot synthesis of highly functionalized dihydrofuran derivatives, bicyclic lactones, 2-oxy-maleate and furanone derivatives. It is interesting to note that dihydrofuran and lactone motifs are present in a number of biologically active natural products and other heterocyclic compounds. It is conceivable that the novel multicomponent reactions described herein will find application in the synthesis of a variety of heterocyclic compounds, and in natural product synthesis.