Chapter 3

The Reaction of Dimethoxycarbene-DMAD Zwitterion with 1,2-Diones - Synthesis of Dihydrofurans and Spirodihydrofurans

3.1 Introduction

Nucleophilic carbenes have attracted considerable attention in recent years due to their versatile chemistry and potential applications in organic synthesis. Of these, the diamino- and dialkoxy-substituted carbenes are the most extensively studied group of carbenes. The present chapter describes a new multicomponent reaction (MCR) based on the reactivity of dimethoxycarbene-dimethyl acetylenedicarboxylate (DMAD) zwitterion with 1,2-dicarbonyl compounds. Before going into the details, a brief overview of the generation and reactivity patterns of dialkoxy carbenes is described in the following sections.

3.2 Dialkoxy carbenes

Dialkoxy carbenes are species having two oxygen atoms directly attached to the carbene carbon. These have singlet ground states as a consequence of donation of the lone-pair on the alkoxy oxygen atom into the formally vacant $p$-orbital of the carbene carbon (Chapter 1, Scheme 43). This kind of electronic delocalization not only stabilizes the ground state, but also the transition states and the dipolar intermediates arising from the reactions of the carbene and renders it nucleophilic. The various methods for the generation of dialkoxy carbenes are outlined below.

3.2.1 Generation of dialkoxy carbenes

Dialkoxy carbenes were first generated by Hoffmann in 1971 by the thermolysis of norbornadiene ketals. This method, however, is limited to the preparation of only a few alkoxy carbenes and is unsuitable for unsymmetrical carbenes (Scheme 1).
Later, Moss and co-workers showed that dimethoxycarbene could be photochemically or thermally generated from dimethoxy diazirine. The latter is prepared by the reaction of methoxychloro diazirine with sodium methoxide in DMF (Scheme 2). However, this method is also not very useful for synthetic applications because the explosive diazirines are generally available only as dilute solutions in solvents such as pentane.

Warkentin in 1992, identified 2,2-dimethoxy-5,5-dimethyl-Δ³-1,3,4-oxadiazoline 10 as a shelf stable, thermal source of dimethoxycarbene. Since then, this method has been the most useful one for the generation of dialkoxo and other heteroatom substituted carbenes. These carbene precursors are easily accessible by the oxidation of alkoxy carbonyl hydrazones of acetone with lead tetraacetate (LTA) or phenyl iodonium acetate. Electrochemical oxidation of ketone hydrazones to oxadiazolines is also known. The LTA oxidation affords a mixture of 2-acetoxy-2-methoxy-5,5-dimethyl-Δ³-1,3,4-oxadiazoline 8 and an acyclic azo compound 9, which on acid catalyzed displacement reaction with a suitable alcohol affords the required oxadiazoline 10 along with unchanged 9. Selective removal of the latter is achieved by hydrolysis with aqueous base. The advantage of this method is that a single acetoxy substrate 8 can serve as the source of different oxadiazolines (Scheme 3).
Scheme 3

The oxadiazoline 10 undergoes thermolysis at ca 100 °C in solution to afford the corresponding dialkoxycarbenes. The carbonyl ylide 12, formed by the initial decomposition of oxadiazoline, undergoes successive fragmentation to the corresponding singlet carbene (Scheme 4).

Scheme 4

Very recently, Warkentin has reported the generation of dimethoxycarbene 16 at 40-50 °C by the thermolysis of 2,5-dihydro-2,2-dimethoxy-5-methyl-5-(p-methoxy)phenyl-1,3,4-oxadiazole 15 (Scheme 5). The lower temperature of this reaction permits the isolation of products that might not survive at 100 °C.
The chemistry of dialkoxycarbenes, especially dimethoxycarbene, was the subject of extensive investigations by Hoffmann and later by Warkentin, a brief account of which is given in the following passages.

3.2.2 Reactions of dialkoxy carbene

Hoffmann studied the reactivity of dimethoxycarbene towards electron-deficient alkenes and demonstrated that the carbene undergoes insertion to form cyclopropane derivatives as shown below. The retention of stereochemistry observed in the reaction of dimethoxycarbene with olefins is diagnostic of its singlet ground state (Scheme 6).\(^\text{13}\)

\[\begin{align*}
\text{Scheme 6}
\end{align*}\]

Recent studies, however, have shown that the reactivity of the dialkoxycarbenes towards electron-deficient alkenes largely depends on the method of their generation. For example, Warkentin has demonstrated that dimethoxycarbene generated from the oxadiazoline 15 at 50 °C in benzene reacts with dimethyl dicyanofumarate 24 to form the zwitterionic intermediate 25 which in turn can react with another molecule of dimethoxycarbene to yield products such as 26 and 27 (Scheme 7).\(^\text{12}\)
Reaction of dimethoxycarbene with electron-deficient alkynes to afford 1:2 adducts has already been described in chapter 1, scheme 44 of this thesis. Formation of similar 1:2 adducts was observed by Hoffmann with heterocumulenes like aryl isocyanates and aryl isothiocyanates 36 (resulting in the formation of substituted hydantoins and thiohydantoins), 14 aryl acetylenes 30, diphenyl ketene 32 13 and 2,3-butanedione 34 15 as shown below. In all these cases dimethoxycarbene generated from 1 reacts with one molecule of the electrophile to form a 1,3-dipolar intermediate which then adds on to another molecule of the electrophile followed by ring closure to give the 1:2 adduct (Scheme 8).

The 1:2 adduct formation between dimethoxycarbene and dimethyl acetylenedicarboxylate has been exploited in our laboratory for the construction of a variety of heterocyclic and carbocyclic systems, the details of which are given in this chapter.
Dimethoxycarbene can react in different ways with the carbonyl group. For example, it undergoes nucleophilic addition to the carbonyl groups of acid chlorides\(^{13}\) and cyclic anhydrides\(^{16}\) to form dipolar intermediates which can rearrange to form the final product (Scheme 9).

A different kind of reactivity was observed by Warkentin with 9-fluorenone 43 and adamantane thione 46 leading to the formation of dialkoxyoxiranes and thiiranes respectively (Scheme 10).\(^{17}\)
1,3-Dicarbonyl compounds were also found to undergo reaction with dimethoxycarbene resulting in the formation of an inserted product and the alkene formed by methanol elimination. Related insertions into alcohols and phenols afford the corresponding orthoformates (Scheme 11).  

Dimethoxycarbene was also found to react with quinonoid compounds such as p-chloranil to afford products resulting from the nucleophilic addition of the carbene to the carbonyl group (Scheme 12).  

Another class of reactions in which dimethoxycarbene is known to participate efficiently is the [4+1] cycloaddition reaction. Hoffmann and Lilienblum in 1977 observed an intramolecular cheletropic elimination reaction between dimethoxycarbene and tetracyclone 55 leading to the formation of the product 56 (Scheme 13). This reaction seems to be the first example of [4+1] cycloaddition of dimethoxycarbene.
Dimethoxycarbene generated from 1 has been intercepted with tetrazines to afford the corresponding pyrazole 59 via the [4+1] cycloaddition of the carbene followed by subsequent cycloreversion as shown below (Scheme 14).  

[4+1] cycloaddition of dimethoxycarbene with the bisketene generated by the thermolysis of cyclobutenedione 60 has led to the formation of cyclopentenedione derivative 62 (Scheme 15).

Rigby reported the [4+1] cycloaddition of dialkoxycarbenes to vinyl isocyanates and vinyl ketenes leading to the formation of hydroindolones and highly substituted cyclopentenones respectively (Scheme 16).
In the formation of 64, it is presumed that addition of the second equivalent of the carbene occurs via a fast NH insertion subsequent to ring formation. Both these types of cycloadditions are general for oxygen, nitrogen and sulfur based nucleophilic carbenes.

Very recently inter- and intramolecular [4+1] cycloadditions between electron-deficient dienes and dialkoxycarbenes were reported by Spino and co-workers. The reactions led to formation of the corresponding cyclopentene derivatives in low yields (Scheme 17).²⁵

![Scheme 17](image_url)

Dienes tethered to oxadiazoline, on thermolysis gave good yields of bicyclic adducts as shown below. [4+1] annulation was possible with enone 73 to give the bicyclic orthoester 74 in 82% isolated yield (Scheme 18).²⁵

![Scheme 18](image_url)

Thermolysis of other dialkoxy substituted oxadiazolines was also studied by Warkentin. For example, thermolysis of oxadiazoline substituted with alkyne functionality 75 underwent an interesting rearrangement to furnish the tricyclic product 77 in good yield (Scheme 19).²⁶
The bis-oxadiazoline 78 on thermolysis in presence of DMAD afforded the benzofused tricyclic compound 80 in moderate yield (Scheme 20).^{27}

Warkentin observed that the thermolysis of 2-cinnamylloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline 81 afforded the products 85 and 86 via a β-scission of the carbene formed as shown in the scheme below (Scheme 21).^{28}

Very recently the same group has studied the temperature dependence of the reactions of allyloxy(methoxy) carbene in solution. It was observed that at 50 °C, fragmentation to a radical pair is not important but the carbene tends to undergo...
dimerization followed by a Claisen rearrangement to afford 89 in major amounts as illustrated below (Scheme 22). \(^\text{29}\)

![Scheme 22](image)

Work in our laboratory has shown that the zwitterion formed from dimethoxycarbene and DMAD can react with electrophilic compounds like aldehydes and electron-deficient styrenes to form dihydrofurans and cyclopentenone derivatives respectively (Scheme 23). \(^\text{30}\)

![Scheme 23](image)

The zwitterion was also found to react efficiently with 1,4-dienones to yield divinyl dihydrofuran which in turn underwent an interrupted Nazarov reaction to yield bicyclic lactones such as 94 (Scheme 24). \(^\text{31}\)

![Scheme 24](image)

As the present study is concerned with the addition of the dimethoxycarbene-DMAD zwitterion to 1,2-dicarbonyl compounds like diaryl 1,2-diones, isatins and
cyclobutenediones, a brief introduction to the latter two species with emphasis on their dipolar cycloaddition reactions is presented in the following section.

3.3 Isatins and Cyclobutenediones

Isatins are a class of versatile substrates which can be used for the synthesis of a large variety of pharmacologically important compounds. They have been found in the mammalian tissues and serve as a modulator in many biochemical processes. There are many methods for the synthesis of isatins and their N-alkylated derivatives, among which the reaction of alkyl halide in DMF in presence of calcium hydride as a base is the most convenient one for the preparation of N-alkyl isatins. Isatin is also an important raw material for drug synthesis, for example in the synthesis of the analgesic drug pemedolac, the key intermediate is formed by the alkylation of isatin at C-3 followed by reduction with LAH (Scheme 25).

![Scheme 25](image)

Work in our laboratory has shown that the carbonyl group of isatins can act as versatile 2π-component and can undergo a variety of [3+2] cycloadditions leading to spirooxindole derivatives. The scheme below summarizes the results in this area. Both cyclic and acyclic carbonyl ylides underwent facile cycloaddition with the carbonyl group of isatin to afford products 98 and 99 respectively. Azomethine ylide generated from 102 also reacted with isatin to form the cycloadduct 103. Nucleophilic addition of allyl triisopropylsilane 100 to the Lewis acid co-ordinated keto carbonyl of isatin afforded the product 101 (Scheme 26). In all cases the 1,3-dipole reacts with the more electrophilic carbonyl of the isatin to generate the spirooxindole derivatives. Spirooxindole is a common motif of alkaloids with significant biological activity.
In addition to these, the azomethine ylide generated by the reaction of isatin with \( \alpha \)-amino acids has been intercepted with electrophilic carbon-carbon\(^{37a,b} \) and carbon-oxygen double bonds to yield spiropyrrolidines\(^{37c} \).

![Diagram of chemical reactions involving isatins and zwitterions](image)

Scheme 26

The addition of unconventional dipoles or zwitterions to isatins has also been utilized to afford a variety of heterocyclic spirooxindole derivatives as shown below. The spirooxadiazoline 107 is formed by the reaction of triphenylphosphine-DEAD zwitterion with isatins. The addition of isocyanide-DMAD zwitterion led to the formation of spiroiminolactone 104 while the addition of pyridine-DMAD zwitterion to isatin resulted in the formation of the spirooxindole derivative 106. Similar reaction with isoquinoline-DMAD zwitterion resulted in the formation of the product 105 (Scheme 27).\(^{38} \)
Another versatile class of 1,2-dicarbonyl compounds are the cyclobutene 1,2-diones. During the last two decades a variety of simple and powerful methods have been developed for the conversion of cyclobutenediones into highly functionalized molecules of synthetic importance. The following section will highlight the dipolar cycloaddition reactions in which these species participate.

Cyclobutenediones have been shown to react with excess of diazomethane to give cycloadducts as shown below (Scheme 28).
Cyclobutenediones, despite their weak dipolarophilic behaviour towards benzonitrile oxide, on prolonged heating (30-40 h) with excess of mesitonitrile oxide III, afforded mono, bis and tris adducts (Scheme 29).\(^{41}\) Interestingly the dipole preferentially attacks the carbonyl dipolarophile.

**Scheme 29**

Investigations in our laboratory have shown that azomethine ylide generated by decarboxylative condensation of sarcosine 115 with N-methylisatin 96 adds to cyclobutenedione 108 to afford the spiropyrrolidine derivative 116 (Scheme 30).\(^{37c}\)

**Scheme 30**

Recent work in our laboratory has demonstrated that zwitterions generated from pyridine and DMAD as well as isocyanide and DMAD can add to one of the carbonyl groups of the cyclobutenedione to yield highly substituted benzene derivatives and spiropyran derivatives respectively. While the first reaction takes place by the addition of the pyridine-DMAD zwitterion to the carbonyl group of the dione followed by ring opening and rearrangement, the latter occurs via a pseudo four-component reaction of the isocyanide-DMAD zwitterion with the carbonyl group. An illustrative example is shown below (Scheme 31).\(^{42}\)
3.4 Statement of the Problem

The carbonyl group of 1,2-dicarbonyl compounds is a potentially reactive functional moiety mainly due to the inherent coulombic repulsion between the adjacent carbonyls. In view of the sustained interest in the area of nucleophilic carbenes and the quest to develop new multicomponent methodologies for heterocyclic synthesis, we have explored the reactivity pattern of 1,2-dicarbonyl compounds like diaryl 1,2-diones, cyclobutenediones and N-substituted isatins towards the 1,3-dipolar species generated by the addition of dimethoxycarbene to DMAD. The results obtained are discussed in the following sections.

3.5 Results and Discussions

The diaryl 1,2-diones, except m-dinitrobenzil, required for our studies were prepared by the base catalyzed reaction of the corresponding aldehydes with thiamine hydrochloride as catalyst followed by oxidation of the resulting benzoins using concentrated nitric acid (Scheme 32).
The diaryl 1,2-diones were obtained in moderate yields. These were purified to remove the trace amount of carboxylic acid by column chromatography on silica gel.

The \textit{m}-dinitrobenzil required for our studies was prepared by the nitration of benzil using the conventional nitration procedure.

In our initial experiment, we exposed benzil 119 to the zwitterionic species generated from DMAD 79 and dimethoxycarbene, the latter being generated \textit{in situ} by the thermolysis of the oxadiazoline 42 in dry toluene in a sealed tube for 24 h. Concentration of the reaction mixture followed by column chromatography of the residue on silica gel using hexanes-ethyl acetate solvent mixture (80:20) afforded the product 120 in 83\% yield (Scheme 33).

\begin{center}
\begin{eqnarray*}
&\begin{array}{ccc}
\text{O} & \text{CO}_2\text{Me} & \text{M} \\
\text{N} & \text{N} & \text{O}\text{Me}_2 \\
\text{O} & \text{Me} & \text{O} \\
\text{O} & \text{Me} & \text{CO}_2\text{Me}
\end{array} & + & \begin{array}{c}
\text{CO}_2\text{Me} \\
\text{Me} \\
\text{N}=\text{N} \\
\text{O}\text{Me}_2 \\
\text{O} \\
\text{Me}
\end{array} & \rightarrow & \begin{array}{c}
\text{MeO}_2\text{C} \\
\text{CO}_2\text{Me} \\
\text{OMe} \\
\text{OMe} \\
\text{OMe}
\end{array}
\end{eqnarray*}
\end{center}

\text{(i) Toluene, sealed tube, 110 °C, 24 h, 83%}

\textbf{Scheme 33}

The structure of the product 120 was established by spectroscopic analysis. In the IR spectrum of 120 the vibrational stretching of the ester and benzoyl carbonyl groups were discernible at 1743 and 1686 cm\(^{-1}\) respectively. In the \textsuperscript{1}H NMR spectrum, the methoxy protons resonated as sharp singlets at \(\delta\ 3.68\) and 3.06 while the protons of the carbomethoxy groups resonated at \(\delta\ 3.83\) and 3.73. The \textsuperscript{13}C NMR spectrum displayed the characteristic signal for the ester and benzoyl carbonyl carbons at \(\delta\ 167.9, 167.3\) and 192.3 respectively. The compound gave satisfactory mass spectral analysis also.
Final confirmation of the structure of 120 was obtained from single crystal X-ray analysis (Figure 3).
The reaction was found to be general with a number of diaryl 1,2-diones and the results are summarized in table 1. It is noteworthy that highly electron deficient diaryl diones 125 and 128 (entries 3 and 4) underwent a carbene insertion followed by rearrangement to yield the products 127 and 129 in major amounts while highly electron-rich 4,4'-dimethoxy diaryl dione 132 did not undergo any reaction (entry 5, Table 1).

The reaction of thenil 130 with DMAD and dimethoxycarbene was found to be temperature dependant. Treatment of thenil 130 with DMAD 79 and oxadiazoline 42 under the usual reaction conditions led to the formation of the dihydrofuran 131 in only 15% yield. However, when oxadiazoline 15, known to generate the carbene at 50 °C, was used in place of 42 the product 131 was formed in 71% yield (Scheme 34).
Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Dihydrofuran</th>
<th>Inserted Product</th>
</tr>
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<tbody>
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<td><img src="image2" alt="Dihydrofuran 122" /></td>
<td><img src="image3" alt="Inserted Product (0)" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image4" alt="Substrate 123" /></td>
<td><img src="image5" alt="Dihydrofuran 124" /></td>
<td><img src="image6" alt="Inserted Product (0)" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="image7" alt="Substrate 125" /></td>
<td><img src="image8" alt="Dihydrofuran 126" /></td>
<td><img src="image9" alt="Inserted Product 127 (66%)" /></td>
</tr>
<tr>
<td>4</td>
<td><img src="image10" alt="Substrate 128" /></td>
<td><img src="image11" alt="Dihydrofuran 129" /></td>
<td><img src="image12" alt="Inserted Product 129 (96%)" /></td>
</tr>
<tr>
<td>5</td>
<td><img src="image13" alt="Substrate 132" /></td>
<td></td>
<td><img src="image14" alt="Inserted Product (0)" /></td>
</tr>
</tbody>
</table>

Reaction conditions: Oxadiazoline (2 equiv), DMAD (1.5 equiv), Dry Toluene, Sealed tube, 24 h

Mechanistically, it is conceivable that the zwitterionic intermediate I initially formed by the 1:1 interaction of dimethoxycarbene 16 and DMAD 79 adds to one of the carbonyl groups of the dione leading to a new zwitterionic species II and cyclization of the latter yields the dihydrofuran product 120. Alternatively, a cycloaddition of the zwitterion with the C=O can also lead to the dihydrofuran (Scheme 35).
Subsequently the reaction of the zwitterion, I with 3,4 diaryl cyclobutene-1,2-diones was investigated. The cyclobutenediones required for our studies were prepared by a reported protocol starting from commercially available squaric acid (Scheme 36).

Scheme 35

<table>
<thead>
<tr>
<th>Ar</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenyl</td>
<td>![Ph structure](attachment:Ph Structure.png)</td>
</tr>
<tr>
<td>4-methylphenyl</td>
<td>![4-MePh structure](attachment:4-MePh Structure.png)</td>
</tr>
<tr>
<td>4-chlorophenyl</td>
<td>![4-ClPh structure](attachment:4-ClPh Structure.png)</td>
</tr>
<tr>
<td>4-bromophenyl</td>
<td>![4-BrPh structure](attachment:4-BrPh Structure.png)</td>
</tr>
<tr>
<td>4-methoxyphenyl</td>
<td>![4-OMePh structure](attachment:4-OMePh Structure.png)</td>
</tr>
</tbody>
</table>

Scheme 37

It is known that dimethoxycarbene, reacts with the bisketene formed from cyclobutenedione to form a cyclopentenedione (See scheme 15). In a prototype experiment 3,4-ditolyl cyclobutene-1,2-dione, 133 was treated with DMAD 79 and oxadiazoline 42 in dry toluene in a sealed tube. The reaction afforded the product 134 in 53\% yield (Scheme 37).
The product 134 was characterized on the basis of spectroscopic analysis. The IR spectrum of 134 showed characteristic vibrations at 1730 and 1671 cm\(^{-1}\) corresponding to the ester and ketone carbonyls respectively. In the \(^1\)H NMR spectrum the carbomethoxy protons displayed their signals at \(\delta\) 3.87 and 3.73 while the methoxy protons adjacent to the ketone carbonyl were discernible at \(\delta\) 3.51 and 2.68. The protons of the remaining two methoxy groups resonated at \(\delta\) 3.57 and 3.55. The \(^{13}\)C NMR spectrum of 134 revealed signals due to the spirocarbon at \(\delta\) 100.2, the ester carbons at \(\delta\) 162.7 and 162.3 and the ketone carbonyl at \(\delta\) 195.9. The compound gave satisfactory elemental analysis also.

![Figure 4: \(^1\)H NMR spectrum of compound 134](image)
Final confirmation of the structure of 134 was obtained by single crystal X-ray analysis (Figure 6).

To test the generality of the reaction, other substituted cyclobutenediones were prepared and were subjected to the same reaction conditions. The formation of the spirodihydrofuran derivative was observed in all the cases and the results are presented in table 2.
Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
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<td><img src="135" alt="Image" /></td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td><img src="136" alt="Image" /></td>
<td><img src="135" alt="Image" /></td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td><img src="138" alt="Image" /></td>
<td><img src="139" alt="Image" /></td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td><img src="140" alt="Image" /></td>
<td><img src="141" alt="Image" /></td>
<td>42</td>
</tr>
</tbody>
</table>

Reaction conditions: Oxadiazoline (2 equiv), DMAD (1.5 equiv), Dry Toluene, Sealed tube, 24 h

Mechanistically the reaction may be envisaged as involving two stages. The initial [4+1] cycloaddition between the carbene and the bisketene formed by the thermolysis of the cyclobutenedione can deliver the cyclopentenedione A. The latter then undergoes 1,3-dipolar cycloaddition with the zwitterion B to yield the spiroadduct. Alternatively, a [3+2] cycloaddition of the zwitterion with the C=O can also lead to the spirodihydrofuran (Scheme 38).
Encouraged by the interesting results obtained with benzils and cyclobutene diones, we extended our investigations to N-substituted isatins. The latter were prepared by the reaction of isatins with alkyl bromides in presence of calcium hydride in dry DMF as the solvent. The isatins employed in the present study are shown below (Scheme 39).
In the first experiment, N-methyl isatin 96, DMAD 79 and oxadiazoline 42 were heated in dry toluene in a sealed tube. Processing of the reaction mixture as usual followed by column chromatography of the crude product on silica gel afforded the product 142 in 54% yield (Scheme 40).

![Scheme 40]

The structure of the adduct 142 was ascertained by spectroscopic methods. In the $^{1}$H NMR spectrum, signals due to the carbomethoxy and methoxy protons were discernible as sharp singlets at $\delta$ 3.91, 3.65, 3.62 and 3.43. The amide and ester carbonyl groups gave $^{13}$C resonance signals at $\delta$ 171.0, 162.2 and 160.0 respectively, supporting the IR absorptions at 1678 and 1745 cm$^{-1}$. The resonance signal due to the spirocarbon was found at $\delta$ 86.4 in the $^{13}$C NMR spectrum. The compound gave satisfactory mass analysis also.

![Figure 7 $^{1}$H NMR spectrum of compound 142]
The reaction was found to be general with other N-substituted isatins and the results are presented in table 3. A mechanistic postulate analogous to the one suggested for the reaction of benzils could be invoked to explain the formation of the products. Formation of the hydroxy ester 151 (entry 4) can be explained along the following lines. Dimethoxycarbene first adds to the carbonyl group of the isatin to form the epoxide which during column chromatography on SiO₂ rearranges to the hydroxy ester 151 (Scheme 41). It may be mentioned that similar reaction was observed by Warkentin with fluorenone where the oxirane formed undergoes hydrolysis on silica to afford the hydroxy ester.¹⁷ᵃ

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**Figure 8** $^{13}$C NMR spectrum of compound 142

The reaction was found to be general with other N-substituted isatins and the results are presented in table 3. A mechanistic postulate analogous to the one suggested for the reaction of benzils could be invoked to explain the formation of the products. Formation of the hydroxy ester 151 (entry 4) can be explained along the following lines. Dimethoxycarbene first adds to the carbonyl group of the isatin to form the epoxide which during column chromatography on SiO₂ rearranges to the hydroxy ester 151 (Scheme 41). It may be mentioned that similar reaction was observed by Warkentin with fluorenone where the oxirane formed undergoes hydrolysis on silica to afford the hydroxy ester.¹⁷ᵃ
Table 3

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Spirooxindoles</th>
<th>Yield (%)</th>
<th>Inserted Product</th>
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<td>(0)</td>
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<tr>
<td>2.</td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
<td>50</td>
<td>(0)</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td>48</td>
<td>(0)</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td>32</td>
<td>151 Me 48%</td>
</tr>
</tbody>
</table>

Reaction conditions: Oxadiazoline (2 equiv), DMAD (1.5 equiv), Dry Toluene, Sealed tube, 24 h

Subsequently, the reaction of phenanthrenequinone was investigated. Treatment of 152 with DMAD 79 and oxadiazoline 42 in a sealed tube in dry toluene for 24 h followed by column chromatography on silica gel afforded the ring enlarged compound 153 as the major product. A small amount of the spiroadduct 154 was also obtained (Scheme 42).

![Scheme 42](image9)

(i) Toluene, sealed tube, 110 °C, 24 h

Scheme 42
The IR spectrum of the product 153 showed characteristic carbonyl absorption peaks at 1667 and 1607 cm⁻¹. In the ¹H NMR spectrum, the methoxy protons provided sharp singlet at δ 3.50 corresponding to the six methoxy protons. The ¹³C NMR spectrum showed resonance at δ 197.5 and 52.1 corresponding to the carbonyl and methoxy carbons respectively. The IR spectrum of product 154 showed sharp peaks at 1742 and 1694 cm⁻¹ corresponding to the ester and benzoyl carbonyls respectively. In the ¹H NMR spectrum, the ester methoxy groups provided singlets at δ 3.83 and 3.49. The ¹³C NMR spectrum of the product showed peaks at δ 160.7 and 161.2 corresponding to the ester carbonyls. The ¹³C resonance signal at δ 86.4 corresponded to the spirocarbon.

3.6 Conclusion

In conclusion, our studies clearly show that the zwitterion formed from dimethoxycarbene and DMAD can efficiently add to cyclic and acyclic 1,2-diones. The products formed are potentially amenable to further transformations. Spiroannulated oxindole derivatives form an important structural unit of biologically active natural products such as the mycotoxin triptoquivaline.⁴⁵

3.7 Experimental Details

General information about experiments is given in Section 2 of Chapter 2. Benzil and phenanthrenequinone were purchased from Aldrich Co. and were used without further purification. All other substituted dicarbonyl compounds were prepared following known literature procedures.

General Procedure for the Synthesis of Diaryl-1,2-diones

To a 20 mL reaction vial, was added an aqueous solution of 0.13 g thiamine hydrochloride, 1.5 mL 95% ethanol, 0.25 mL 3M sodium hydroxide solution and 0.75 mL pure benzaldehyde. The mixture is heated to 60 °C and stirring was continued for 12 hours. After completion of the reaction, the mixture was poured into ice-cold water and was extracted with dichloromethane (3 x 10 mL). The combined organic extract was washed with water, brine and then dried over anhydrous sodium sulphate. After removal
of the solvent on a rotary evaporator, 2-3 mL concentrated nitric acid was added and the mixture was heated to 100 °C for 1-2 h. After completion of the reaction, the mixture was poured to ice-cold water and the product (diaryl-1,2-dione) was filtered and washed with water.

**General Procedure for the Reaction of Diaryl-1,2-diones with Oxadiazoline and DMAD**

Diaryl-1,2-dione (0.48 mmol), dimethyl acetylenedicarboxylate (102 mg, 0.72 mmol) and oxadiazoline (0.96 mmol) in 2 mL dry toluene was degassed and heated at 110 °C in a sealed tube for 24 h. After completion, the solvent was removed on a rotary evaporator and the residue was subjected to column chromatography on silica gel (100-200 mesh) using hexanes/ethyl acetate solvent mixtures to furnish the pure products. All dihydrofurans were eluted with 80:20 hexanes/ethyl acetate solvent mixture.

**Dimethyl-2-benzoyl-5,5-dimethoxy-2-phenyl-2,5-dihydrofuran-3,4-dicarboxylate 120:**

Benzil 119 (100 mg, 0.48 mmol), dimethyl acetylenedicarboxylate 79 (102 mg, 0.72 mmol) and oxadiazoline 42 (154 mg, 0.96 mmol) were heated in dry toluene (2 mL) in a sealed tube. The reaction was processed as described in the general procedure to afford the dihydrofuran 120 (169 mg, 83%) as a white crystalline solid, mp 124-125 °C (recrystallized from CH₂Cl₂-hexanes).

IR (KBr) νmax: 3077, 2954, 2845, 1743, 1686, 1594, 1573, 1449, 1434, 1331, 1295, 1187 cm⁻¹.

**¹H NMR:** δ 7.89 (d, 2H, J = 7.5 Hz), 7.49-7.42 (m, 3H), 7.36-7.33 (m, 5H), 3.83 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 3.06 (s, 3H).

**¹³C NMR:** δ 192.3, 167.9, 167.3, 155.9, 135.6, 133.9, 133.8.
130.2, 129.3, 129.2, 128.9, 128.7, 128.4, 128.3, 111.2, 53.1, 53.0, 52.9, 52.8.

**Elemental analysis** Calcd for C\textsubscript{23}H\textsubscript{22}O\textsubscript{8}: C = 64.78, H = 5.20; Found: C = 64.72, H = 5.19.

**Mass spectrometric analysis (HRMS-EI)** m/z calcd for C\textsubscript{23}H\textsubscript{22}O\textsubscript{8}: 426.1315, found: 426.1319.

**Dimethyl-2-(4-fluorobenzoyl)-2(4-fluorophenyl)-5,5-dimethoxy-2,5-dihydrofuran-3,4-dicarboxylate 122:**

4,4'-Difluoro benzil 121 (117 mg, 0.41 mmol), dimethyl acetylenedicarboxylate 79 (102 mg, 0.72 mmol) and oxadiazoline 42 (154 mg, 0.96 mmol) were heated in dry toluene (2 mL) in a sealed tube. The reaction was processed as described in the general procedure to afford the dihydrofuran 121 (123 mg, 65%) as a colourless viscous liquid.

**IR (thin film)** ν\textsubscript{max}: 2954, 2928, 2851, 1743, 1686, 1619, 1491, 1434, 1357, 1341, 1207, 1146, 1108 cm\textsuperscript{-1}.

**\textsuperscript{1}H NMR:** δ 7.95-7.91 (m, 2H), 7.43-7.38 (m, 2H), 7.05-7.00 (m, 4H), 3.84 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H), 3.07 (s, 3H).

**\textsuperscript{13}C NMR:** δ 193.5, 167.3, 155.4, 134.4, 134.3, 134.1, 134.0, 133.9, 129.3, 128.9, 124.5, 116.6, 116.1, 115.9, 111.0, 53.5, 53.4, 52.8, 52.6.

**Mass spectrometric analysis (HRMS-EI):** m/z calcd for C\textsubscript{23}H\textsubscript{20}F\textsubscript{2}O\textsubscript{8}: 462.1126; found: 462.1125.

**Dimethyl-2,2-Dimethoxy-5-(4-methylbenzoyl)-5-p-tolyl-2,5-dihydrofuran-3,4-dicarboxylate 124:**

4,4'-Dimethyl benzil 123 (114 mg, 0.48 mmol), dimethyl acetylenedicarboxylate 79 (102 mg, 0.72 mmol) and oxadiazoline 42 (154 mg, 0.96 mmol) in dry toluene were heated in a sealed tube. Usual processing of the reaction mixture afforded the dihydrofuran 124 (98 mg, 45%) as a colourless viscous liquid.
IR (thin film) $\nu_{\text{max}}$: 2959, 2922, 2856, 1743, 1686, 1604, 1444, 1264, 1192, 1125, 1042, 970 cm$^{-1}$.

$^1$H NMR: $\delta$ 7.80 (d, 2H, $J = 8.07$ Hz), 7.31-7.25 (m, 2H), 7.14-7.11 (m, 4H), 3.82 (s, 3H), 3.73 (s, 3H), 3.66 (s, 3H), 3.05 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H).

$^{13}$C NMR: $\delta$ 194.9, 162.1, 161.9, 144.2, 143.5, 138.5, 134.7, 133.4, 131.2, 130.3, 129.9, 128.3, 126.8, 124.1, 111.1, 53.1, 52.3, 51.7, 50.6, 40.2, 25.1, 21.3.

Mass spectrometric analysis (HRMS-El) $m/z$ calcd for C$_{35}$H$_{26}$O$_8$: 454.1628; found: 454.1625.

Dimethyl-2,2-dimethoxy-5-(4-trifluoromethylbenzoyl)-5-(4-trifluoromethyl)phenyl-2,5-dihydrofuran-3,4-dicarboxylate 126 and 2,2-Dimethoxy-1,3-bis(4-(trifluoromethyl)phenyl)propane-1,3-dione 127:

4,4'-Trifluoromethyl benzil 125 (171 mg, 0.48 mmol), dimethyl acetylenedicarboxylate 79 (102 mg, 0.72 mmol) and oxadiazoline 42 (154 mg, 0.96 mmol) were heated in dry toluene (2 mL) in a sealed tube. Usual processing of the reaction mixture afforded the products in increasing order of polarity. Elution with 2:98 ethyl acetate/hexanes solvent mixtures afforded the product 127 (133 mg, 66%) as a colourless viscous liquid. Further elution with 20:80 ethyl acetate/hexanes solvent mixture afforded 126 (84 mg, 31%) as a colourless viscous liquid.

IR (thin film) $\nu_{\text{max}}$: 2964, 2845, 1743, 1696, 1619, 1444, 1408, 1326, 1264, 1176, 1135, 1068 cm$^{-1}$.

$^1$H NMR: $\delta$ 8.02-7.97 (m, 2H), 7.68-7.56 (m, 6H), 3.85 (s, 3H), 3.76 (s, 3H), 3.69 (s, 3H), 3.08 (s, 3H).

$^{13}$C NMR: $\delta$ 193.2, 162.2, 161.9, 140.8, 131.0, 130.5, 129.9, 128.8, 127.2, 125.5, 125.4, 124.7, 124.6, 124.5, 111.0, 55.5, 52.7, 52.5, 51.8, 51.4, 50.8, 50.7, 29.7.
Mass spectrometric analysis (FAB): \( m/z \) calcd for 
\( \text{C}_{25}\text{H}_{20}\text{F}_{6}\text{O}_{8} \ [\text{M+H}]^{+} \): 563.1062; found: 563.1064.

**IR** (thin film) \( \nu_{\text{max}} \): 2964, 2918, 2851, 1831, 1676, 1614, 1578, 1413, 1326, 1249, 1161, 1130, 1068, 1011 cm\(^{-1}\).

**\(^1\text{H NMR}\):** \( \delta \) 7.64-7.62 (m, 8H), 3.55 (s, 6H).

**\(^{13}\text{C NMR}\):** \( \delta \) 189.4, 131.2, 130.6, 128.8, 127.1, 126.5, 126.4, 126.3, 54.9, 30.5, 30.0.

Mass spectrometric analysis (HRMS-El): \( m/z \) calcd for 
\( \text{C}_{19}\text{H}_{14}\text{F}_{6}\text{O}_{4} \): 420.0796; found: 420.0791.

2,2-Dimethoxy-1,3-bis(3-nitrophenyl)propane-1,3-dione 129:

3,3'-Dinitro benzil 128 (145 mg, 0.48 mmol), dimethyl acetylenedicarboxylate 79 (102 mg, 0.72 mmol) and oxadiazoline 42 (154 mg, 0.96 mmol) were heated in dry toluene (2 mL) in a sealed tube. Usual processing of the reaction mixture afforded the product 129 (172 mg, 96%) as a yellow oil.

**IR** (thin film) \( \nu_{\text{max}} \): 2959, 1686, 1532, 1346, 1228, 1120 cm\(^{-1}\).

**\(^1\text{H NMR}\):** \( \delta \) 8.39 (s, 2H), 8.20 (d, 2H, \( J = 8.06 \text{ Hz} \)), 7.81-7.78 (m, 2H), 7.56 (uneven triplet, 2H, \( J_1 = 8.06 \text{ Hz} \), \( J_2 = 8.54 \text{ Hz} \)), 3.61 (s, 6H).

**\(^{13}\text{C NMR}\):** \( \delta \) 189.5, 148.9, 136.3, 135.6, 133.9, 131.7, 130.7, 130.1, 129.4, 128.7, 125.7, 124.4, 123.9, 121.3, 52.2.

Mass spectrometric analysis (HRMS-El): \( m/z \) calcd for 
\( \text{C}_{17}\text{H}_{14}\text{N}_{2}\text{O}_{8} \): 374.0750, found: 374.0738.
Dimethyl-2,2-dimethoxy-5-(thiophen-2-yl)-5-(thiophene-2-carbonyl)-2,5-
dihydrofuranc-3,4-dicarboxylate 131:

Thenil 130 (107 mg, 0.48 mmol), dimethyl acetylenedicarboxylate 79 (102 mg, 0.72 mmol) and oxadiazoline 15 (242 mg, 0.96 mmol) were heated in dry toluene (2 mL) in a sealed tube. Usual processing of the reaction mixture afforded the product 131 (149 mg, 71%) as a yellow oil.

IR (thin film) $\nu_{\text{max}}$: 2958, 2850, 1743, 1717, 1665, 1614, 1434, 1408, 1305, 1259, 1130 cm$^{-1}$.

$^1$H NMR: $\delta$ 7.85 (d, 2H, $J = 3.18$ Hz), 7.66 (d, 1H, $J = 4.47$ Hz), 7.34 (d, 1H, $J = 4.41$ Hz), 7.08-7.04 (m, 1H), 6.93 (uneven triplet, 1H, $J_1 = 4.68$ Hz, $J_2 = 3.87$ Hz), 3.84 (s, 3H), 3.79 (s, 3H), 3.67 (s, 3H), 3.18 (s, 3H).

$^{13}$C NMR: $\delta$ 186.7, 161.6, 161.5, 142.2, 140.5, 139.2, 136.1, 135.1, 133.3, 131.2, 128.1, 127.9, 127.2, 127.0, 126.6, 115.9, 111.2, 55.6, 52.6, 52.3, 51.8.

Mass spectrometric analysis (HRMS-EI): $m/z$ calcd for C$_{10}$H$_{18}$O$_8$S$_2$: 438.0443; found: 438.0449.

General Procedure for the Synthesis of Substituted Cyclobutene-1,2-diones from Squaric Acid

A solution of thionyl chloride (6.2 g, 0.052 mol) in anhydrous benzene (10 mL) was added dropwise to a suspension of commercially available squaric acid (3 g, 0.026 mol) in anhydrous benzene (10 mL) at 80 °C. After the addition of roughly half of the SOCl$_2$ solution, 3 drops of distilled DMF was syringed in to the reaction vessel, followed by the remaining portion of SOCl$_2$ solution. The reaction mixture was heated under reflux for 12 h, cooled and the excess thionyl chloride was removed by bubbling a steady stream of dry N$_2$ gas through the reaction mixture. The dark residue of squaryl chloride (2.8 g, 72%) obtained was used as such for the next step.
To a solution of squaryl chloride (1 g, 0.007 mol) in anhydrous dichloromethane (10 mL) was added the aromatic hydrocarbon (0.021 mol) at 0 °C. Anhydrous AlCl₃ (0.021 mol) was added in portions at 0 °C and the reaction mixture was kept at that temperature for 5 h. It was treated with cold water (10 mL), extracted with dichloromethane (3 x 10 mL) and the combined organic layer was dried over anhydrous sodium sulfate. Dichloromethane was distilled off on a rotavapor and the residue was subjected to chromatography on silica gel column using hexanes-ethyl acetate (95:5) as eluent to afford the substituted cyclobutenediones as yellow fluffy solids.

**General Procedure for the Reaction of Cyclobutenediones with Oxadiazoline and DMAD**

3,4-Diaryl cyclobutene 1,2-dione (0.38 mmol), dimethyl acetylenedicarboxylate (81 mg, 0.57 mmol) and oxadiazoline (122 mg, 0.76 mmol) in 2 mL dry toluene was heated in a sealed tube for 24 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography (silica gel, 100-200 mesh; 80:20 hexanes/ethyl acetate) to give pure products.

**6,7-Bis-(4-methyl-phenyl)-2,2,9,9-tetramethoxy-8-oxo-1-oxa-spiro[4.4]nona-3,6-diene-3,4-dicarboxylic acid dimethyl ester 134:**

3,4-Ditoly cyclobutene 1,2-dione 133 (100 mg, 0.38 mmol), DMAD 79 (81 mg, 0.57 mmol) and oxadiazoline 42 (122 mg, 0.76 mmol) in dry toluene (2 mL) was heated in a sealed tube for 24 h. The reaction mixture was processed as described in the general procedure to afford the spirodihydrofurans 134 (111 mg, 53%) as a colourless crystalline solid, mp 131-132 °C (recrystallized from CH₂Cl₂-hexanes).

![Image](image.png)

**IR** (thin film) \(\nu_{max}: 3000, 2954, 2850, 1730, 1671, 1609, 1506, 1434, 1352, 1331, 1274, 1207, 1182, 1130 \text{ cm}^{-1}.

**¹H NMR:** \(\delta 7.18-7.04 \text{ (m, 8H), 3.87 (s, 3H), 3.73 (s, 3H), 3.57 (s, 3H), 3.55 (s, 3H), 3.51 (s, 3H), 2.68 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H).}

**¹³C NMR:** \(\delta 195.9, 162.7, 162.3, 141.3, 138.8, 138.6, 138.2.\)
129.7, 129.5, 129.1, 128.8, 128.7, 127.2, 122.9, 100.2, 93.7, 52.9, 52.5, 51.5, 51.4, 50.2, 21.4, 21.3.

**Elemental analysis** Calcd for C\textsubscript{30}H\textsubscript{32}O\textsubscript{2}: C = 65.21, H = 5.84; Found: C = 65.25, H = 5.96.

**2,2,9,9-Tetramethoxy-8-oxo-6,7-diphenyl-1-oxa-spiro[4.4]nona-3,6-diene-3,4-dicarboxylic acid dimethyl ester 135:**

3,4-Diphenylecyclobutene 1,2-dione 108 (88 mg, 0.38 mmol), DMAD 79 (81 mg, 0.57 mmol) and oxadiazoline 42 (122 mg, 0.76 mmol) in dry toluene (2 mL) was heated in a sealed tube for 24h. Usual processing of the reaction mixture afforded the spirodihydrofuran 135 (159 mg, 80%) as a colourless oil.

**IR (thin film)** $v_{\text{max}}$: 2954, 2845, 1727, 1671, 1480, 1439, 1362, 1326, 1274, 1130, 1068, 975 cm$^{-1}$.

**$^1$H NMR:** δ 7.27-7.08 (m, 10H), 3.78 (s, 3H), 3.75 (s, 3H), 3.57 (s, 6H), 3.51 (s, 3H), 2.58 (s, 3H).

**$^{13}$C NMR:** δ 195.6, 163.1, 162.2, 141.5, 138.5, 132.4, 129.9, 129.5, 129.0, 128.9, 128.7, 128.6, 128.4, 128.3, 127.9, 122.9, 100.1, 52.9, 52.7, 52.5, 51.7, 51.4, 50.1.

**Mass spectrometric analysis (HRMS-EI):** $m/z$ calcd for C\textsubscript{28}H\textsubscript{28}O\textsubscript{10}: 524.1683; found: 524.1685.

**6,7-Bis-(4-chloro-phenyl)-2,2,9,9-tetramethoxy-8-oxo-1-oxa-spiro[4.4]nona-3,6-diene-3,4-dicarboxylic acid dimethyl ester 137:**

3,4-Dichlorophenyl cyclobutene 1,2-dione 136 (115 mg, 0.38 mmol), DMAD 79 (81 mg, 0.57 mmol) and oxadiazoline 42 (122 mg, 0.76 mmol) in dry toluene was heated in a sealed tube. Usual processing of the reaction mixture led to the spirodihydrofuran 137 (112 mg, 50%) as a yellow oil.

**IR (thin film)** $v_{\text{max}}$: 3000, 2958, 2850, 1732, 1671, 1635, 1593, 1439, 1351, 1336, 1284, 1124 cm$^{-1}$. 

2,2,9,9-Tetramethoxy-8-oxo-6,7-diphenyl-1-oxa-spiro[4.4]nona-3,6-diene-3,4-dicarboxylic acid dimethyl ester 135:

3,4-Diphenylecyclobutene 1,2-dione 108 (88 mg, 0.38 mmol), DMAD 79 (81 mg, 0.57 mmol) and oxadiazoline 42 (122 mg, 0.76 mmol) in dry toluene (2 mL) was heated in a sealed tube for 24h. Usual processing of the reaction mixture afforded the spirodihydrofuran 135 (159 mg, 80%) as a colourless oil.

**IR (thin film)** $v_{\text{max}}$: 2954, 2845, 1727, 1671, 1480, 1439, 1362, 1326, 1274, 1130, 1068, 975 cm$^{-1}$.

**$^1$H NMR:** δ 7.27-7.08 (m, 10H), 3.78 (s, 3H), 3.75 (s, 3H), 3.57 (s, 6H), 3.51 (s, 3H), 2.58 (s, 3H).

**$^{13}$C NMR:** δ 195.6, 163.1, 162.2, 141.5, 138.5, 132.4, 129.9, 129.5, 129.0, 128.9, 128.7, 128.6, 128.4, 128.3, 127.9, 122.9, 100.1, 52.9, 52.7, 52.5, 51.7, 51.4, 50.1.

**Mass spectrometric analysis (HRMS-EI):** $m/z$ calcd for C\textsubscript{28}H\textsubscript{28}O\textsubscript{10}: 524.1683; found: 524.1685.
Chapter 3: Dihydrofurans and Spirodihydrofurans

\[ ^1H \text{ NMR: } \delta 7.23-7.17 \text{ (m, 8H)}, 3.87 \text{ (s, 3H)}, 3.75 \text{ (s, 3H)}, 3.57 \text{ (s, 6H)}, 3.51 \text{ (s, 3H)}, 2.65 \text{ (s, 3H)}. \]

\[ ^13C \text{ NMR: } \delta 195.0, 162.9, 162.1, 132.7, 131.7, 131.5, 131.4, 131.0, 130.1, 129.9, 129.5, 129.2, 128.9, 128.7, 128.5, 128.4, 128.3, 123.3, 100.2, 53.3, 53.0, 52.8, 52.7, 51.9, 51.8. \]

Mass spectrometric analysis (HRMS-FAB): \( m/z \) calcd for \( C_{28}H_{26}Cl_2O_7 \) [M+2+H]: 595.0903; found: 595.0900.

6,7-Bis-(4-bromo-phenyl)-2,2,9,9-tetramethoxy-8-oxo-1-oxa-spiro[4.4]nona-3,6-diene-3,4-dicarboxylic acid dimethyl ester 139:

3.4 Dibromophenyl cyclobutene 1,2-dione 138 (146 mg, 0.38 mmol), DMAD 79 (81 mg, 0.57 mmol) and oxadiazoline 42 (122 mg, 0.76 mmol) in dry toluene (2 mL) was heated in a sealed tube for 24h. Usual processing of the reaction mixture afforded the spirodihydrofuran 139 (227 mg, 88%) as a yellow oil.

\[ \text{IR (thin film) } \nu_{\max}: 2959, 2923, 2850, 1743, 1681, 1650, 1599, 1444, 1279, 1135, 1063 \text{ cm}^{-1}. \]

\[ ^1H \text{ NMR: } \delta 7.23-7.17 \text{ (m, 8H)}, 3.87 \text{ (s, 3H)}, 3.76 \text{ (s, 3H)}, 3.57 \text{ (s, 6H)}, 3.51 \text{ (s, 3H)}, 2.66 \text{ (s, 3H)}. \]

\[ ^13C \text{ NMR: } \delta 195.0, 162.9, 162.2, 132.7, 131.6, 131.4, 131.5, 131.1, 130.2, 129.9, 129.8, 129.4, 129.2, 128.9, 128.8, 128.5, 128.5, 128.3, 123.2, 100.2, 53.2, 53.1, 52.9, 52.8, 51.9, 51.8. \]

Mass spectrometric analysis (HRMS-FAB): \( m/z \) calcd for \( C_{28}H_{26}Br_2O_7 \) [M+2+H]: 682.9893; found: 682.9899.

6,7-Bis-(4-methoxy-phenyl)-2,2,9,9-tetramethoxy-8-oxo-1-oxa-spiro[4.4]nona-3,6-diene-3,4-dicarboxylic acid dimethyl ester 141:

3.4-Dimethoxyphenyl cyclobutene 1,2-dione 140 (112 mg, 0.38 mmol), DMAD 79 (81 mg, 0.57 mmol) and oxadiazoline 42 (122 mg, 0.76 mmol) in dry toluene (2 mL) was heated in a sealed tube for 24h. Usual processing of the reaction mixture led to the spirodihydrofuran 141 (93 mg, 42%) as a yellow oil.
**General Procedure for the Synthesis of N-alkyl Substituted Isatins**

To a solution of isatin (500 mg, 3.39 mmol) in dry DMF (10 mL) was added powdered calcium hydride (472 mg, 11.21 mmol) and the mixture was stirred with gentle warming (40 °C-50 °C) for half an hour. The alkylation agent (16.99 mmol) was added to the reaction mixture at room temperature and was stirred for 4-5 h. The reaction mixture was then poured slowly to a solution of brine (0.2 N HCl was added dropwise to NaCl solution). Extraction was done using ethyl acetate several times. Evaporation of the solvent left a residue which was then subjected to chromatography on a silica gel column using 80:20 hexanes-ethyl acetate solvent mixtures to afford the N-alkyl derivative of isatin.

**General Procedure for the Reaction of N-Substituted Isatins with Oxadiazoline and DMAD**

A mixture of N-alkyl isatin (0.31 mmol), dimethyl acetylenedicarboxylate (132 mg, 0.93 mmol) and oxadiazoline (198 mg, 1.24 mmol) was refluxed in 2 mL dry toluene in a sealed tube for 24 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography (silica gel, 100-200 mesh;
neutralized by adding triethyl amine) using 70:30 hexanes/ethyl acetate to give the pure product.

**Spiro[1'-methylindole-1(2H)-4-dimethoxy-2,3-bis(methoxycarbonyl)furan]-2-one 142:**

A mixture of N-methyl isatin 96 (50 mg, 0.31 mmol), DMAD 79 (132 mg, 0.93 mmol) and oxadiazoline 42 (198 mg, 1.24 mmol) was refluxed in dry toluene (2 mL) in a sealed tube for 24h. Processing of reaction mixture as specified in the general procedure afforded product 142 (63 mg, 54%) as a yellow oil.

**IR** (thin film) $\nu_{\text{max}}$: 2945, 2850, 1745, 1678, 1602, 1457, 1270, 1162, 1055 cm$^{-1}$.

**$^1$H NMR:** $\delta$ 7.37-6.83 (m, 4H), 3.91 (s, 3H), 3.65 (s, 3H), 3.62 (s, 3H), 3.43 (s, 3H), 3.25 (s, 3H).

**$^{13}$C NMR:** $\delta$ 171.0, 162.2, 160.0, 143.6, 140.5, 130.8, 126.5, 125.0, 124.9, 123.1, 108.6, 86.4, 53.2, 52.8, 52.6, 52.5, 52.4, 51.9, 50.6, 50.5, 50.3, 26.5.

**Mass spectrometric analysis (HRMS-El):** $m/z$ calcd for C$_{14}$H$_{19}$NO$_8$: 377.1111; found: 377.1115.

**Spiro[1'-ethylindole-1(2H)-4-dimethoxy-2,3-bis(methoxycarbonyl)furan]-2-one 144:**

A mixture of N-ethyl isatin 143 (55 mg, 0.31 mmol), DMAD 79 (132 mg, 0.93 mmol) and oxadiazoline 42 (198 mg, 1.24 mmol) was refluxed in dry toluene (2 mL) in a sealed tube for 24h. Usual processing of the reaction mixture afforded the product 144 (61 mg, 50%) as a yellow oil.

**IR** (thin film) $\nu_{\text{max}}$: 2948, 2847, 1730, 1681, 1613, 1485, 1465, 1249, 1150, 1051 cm$^{-1}$.

**$^1$H NMR:** $\delta$ 7.33-6.84 (m, 4H), 3.91 (s, 3H), 3.62 (s, 3H), 3.58 (s, 3H), 3.49 (s, 3H), 3.14 (m, 2H), 1.31 (t, 3H, $J = 7.19$ Hz).

**$^{13}$C NMR:** $\delta$ 171.2, 162.4, 160.1, 143.7, 140.6, 136.3, 130.9, 126.6,
Spiro[1'-propylindole-1(2H)-4-dimethoxy-2,3-bis(methoxycarbonyl)furan]-2-one 146:

A mixture of N-propyl isatin 45 (60 mg, 0.31 mmol), DMAD 79 (132 mg, 0.93 mmol) and oxadiazoline 42 (198 mg, 1.24 mmol) was refluxed in dry toluene (2 mL) in a sealed tube for 24 h. Usual processing of the reaction mixture afforded the product 146 (63 mg, 50%) as yellow oil.

\[ \text{IR (thin film) } \nu_{\text{max}}: 2955, 2890, 2850, 1730, 1681, 1613, 1472, 1450, 1310, 1250, 1190, 1050 \text{ cm}^{-1}. \]

\[ ^1H\text{ NMR: } \delta 7.3-6.78 (m, 4H), 3.85 (s, 3H), 3.70 (m, 2H), 3.70 (s, 3H), 3.55 (s, 3H), 3.43 (s, 3H), 1.66 (m, 2H), 0.99 (t, 3H, J = 7.37 Hz). \]

\[ ^13C\text{ NMR: } \delta 171.9, 162.9, 160.7, 135.7, 130.3, 128.9, 126.9, 123.8, 120.1, 109.6, 86.4, 55.9, 54.6, 51.9, 51.7, 35.1, 15.6, 12.3. \]

**Mass spectrometric analysis (HRMS-EI):** m/z calcd for C\textsubscript{19}H\textsubscript{21}NO\textsubscript{8}: 391.1267; found: 391.1269.

Spiro[1'-benzylindole-1(2H)-4-dimethoxy-2,3-bis(methoxycarbonyl)furan]-2-one 148:

A mixture of N-benzyl isatin 147 (74 mg, 0.31 mmol), DMAD 79 (132 mg, 0.93 mmol) and oxadiazoline 42 (198 mg, 1.24 mmol) was refluxed in dry toluene (2 mL) in a sealed tube for 24 h. Usual processing of the reaction mixture afforded the product 148 (67 mg, 48%) as yellow oil.

\[ \text{IR (thin film) } \nu_{\text{max}}: 2955, 2847, 1742, 1679, 1620, 1495, 1445, 1256, 1182, 1128, 980 \text{ cm}^{-1}. \]

\[ ^1H\text{ NMR: } \delta 7.33-7.16 (m, 9H), 5.12 (d, 1H, J = 9 Hz), 4.66 (d, 1H, 4.66 (d, 1H,
Spiro[1'-methyl-5-bromo-indole-1(2H)-4-dimethoxy-2,3-
  bis(methoxycarbonyl)furan]-2-one 150 and 5-bromo-1-methyl-3-carbomethoxy-3-
  hydroxy-indol-2-one 151:

A mixture of 5-bromo N-methyl isatin 149 (74 mg, 0.31 mmol), DMAD 79 (132
mg, 0.93 mmol) and oxadiazoline 42 (198 mg, 1.24 mmol) was refluxed in dry toluene
(2 mL) in sealed tube for 24 h. Usual processing of the reaction mixture led to isolation
of two products in increasing polarities. Elution with 85:15 hexane/ EtOAc gave the
product 151 (44 mg, 48%) as colourless oil. Further elution with 70:30
hexane/ethylacetate yielded the product 150 (45 mg, 32%) as a yellow oil.

IR (thin film) \( \nu_{\text{max}} \): 2949, 2849, 1744, 1678, 1609, 1485, 1444,
1227, 1279, 980 cm\(^{-1}\).

\( ^1\text{H NMR} \): \( \delta \) 7.25-7.22 (m, 2H), 6.48-6.40 (m, 1H), 3.81 (s, 3H),
3.69 (s, 3H), 3.62 (s, 3H), 3.40 (s, 3H), 3.25 (s, 3H).

\( ^{13}\text{C NMR} \): \( \delta \) 171.1, 162.1, 160.0, 142.6, 141.5, 130.7, 126.6,
125.0, 124.9, 52.7, 52.5, 51.8, 50.7, 50.6, 26.5.

Mass spectrometric analysis (HRMS-El): \( m/z \) calcd for
C\(_{18}\)H\(_{18}\)BrNO\(_8\): 455.0216; found: 455.0218.

\( \text{IR (thin film) } \nu_{\text{max}} \): 3451, 2954, 2650, 1734, 1618, 1470, 1347,
1260, 1152, 1113, 1105, 980 cm\(^{-1}\).

\( ^{1}\text{H NMR} \): \( \delta \) 7.85-7.82 (m, 2H), 7.41-7.38 (m, 1H), 6.49 (s, 1H).
6,6-Dimethoxy-dibenzo[a,c]cycloheptene-5,7-dione 153 and Spiro[phenanthrene-1(2H)-4-dimethoxy-2,3-bis(methoxycarbonyl)furan]-2-one 154:

A mixture of 152 (100 mg, 0.48 mmol), DMAD 79 (102 mg, 0.72 mmol) and oxadiazoline 42 (154 mg, 0.96 mmol) was refluxed in dry toluene (2 mL) in sealed tube for 24 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography (silica gel 100-200 mesh, neutralized by adding triethyl amine) using hexanes-ethyl acetate solvent mixture to afford the products in increasing order of polarities. Elution with hexane gave the product 153 (77 mg, 57%) as an amorphous solid. Further elution with 90:10 hexanes/ethyl acetate afforded the product 154 as a colourless liquid (21 mg, 10%).

**IR (thin film)** $\nu_{\text{max}}$: 2921, 2850, 1667, 1607, 1482, 1380, 1250, 1130, 1100, 1031, 980 cm$^{-1}$.

$^1$H NMR: $\delta$ 8.57 (d, 2H, $J = 8.26$ Hz), 7.92-7.89 (m, 2H), 7.57-7.4 (m, 4H), 3.50 (s, 6H).

$^{13}$C NMR: $\delta$ 197.5, 136.4, 132.9, 127.2, 126.7, 124.2, 123.3, 54.7, 52.1.

**Mass spectrometric analysis (HRMS-EI):** $m/z$ calcd for C$_{17}$H$_{14}$O$_4$: 282.0892, found: 282.0899.

**IR (thin film)** $\nu_{\text{max}}$: 2955, 2850, 1742, 1694, 1600, 1380, 1120, 1010, 985 cm$^{-1}$.

$^1$H NMR: $\delta$ 7.99-7.88 (m, 3H), 7.64-7.53 (m, 2H), 7.40-7.27 (m, 8H).
3.8 References


