SYNTHESIS OF \( \beta \)-LACTAM-4-YLIDENES AND THEIR APPLICATION AS
SYNTHONS FOR NOVEL \( \beta \)-LACTAM SYNTHETIC METHODOLOGIES

By

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$\beta$-LACTAM-4-YLIDENES
This thesis is dedicated with gratitude to
my parents
for their immeasurable sacrifices
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ABSTRACT

The first portion of this thesis deals with the chemistry of the imino-triazoline, imino-thiadiazoline, and imino-oxadiazoline systems. All three systems have the cyclic cis azo function as a common feature, but it was found that each system has its own characteristic chemistry.

Upon quaternization of the $sp^2$ ring carbon the stability of the resulting cyclic azo compounds increased in the following order: triazolines < thiadiazolines < oxadiazolines. Thus, the reaction of the imino-triazoline with benzoyl cyanide formed the aziridine. Moreover, the imino-triazoline system did not form a stable spiro-$\beta$-lactam triazoline when treated with diphenylketene.

On the other hand, the quaternization of the imino-thiadiazoline $sp^2$ ring carbon did not always lead to $N_2$ extrusion. The reaction of the imino-thiadiazoline with diphenylketene led to $N_2$ extrusion followed by electrocyclic ring closure to form the spiro-$\beta$-lactam thirane as the only product, if the substituent on nitrogen was a phenyl group. Replacing the phenyl group on nitrogen by a benzyl group led to the isolation of both the spiro-$\beta$-lactam thiadiazoline and the product of $N_2$ extrusion, the corresponding spiro-$\beta$-lactam thirane. The spiro-$\beta$-lactam thiadiazoline loses $N_2$ thermally to form the thirane as the only product.

The chemistry of the oxadiazoline system was very different. Imino-oxadiazolines reacted with different substituted ketenes to form the corresponding spiro-$\beta$-lactam oxadiazolines. Quaternization of the $sp^2$ ring carbon did not lead to $N_2$ extrusion; the spiro-$\beta$-lactam oxadiazoline system (172) was very stable at room temperature. The thermolysis of the spiro-$\beta$-lactam oxadiazoline system (172) at 100°C gave products derived from the novel $\beta$-lactam-4-ylidene (181), as an intermediate.
Product analysis implied the generation of the carbene 181 quantitatively.

The second portion of this thesis deals with a study on the scope of the spiro-β-lactam oxadiazoline system (172), as a source for β-lactam-4-yldenes (181). This oxadiazoline system (172) proved to be an excellent source for the β-lactam-4-ylidene (181), in the sense that it is a mild, bottleable, and a quantitative source.

On the other hand, the chemistry and scope of the novel β-lactam-4-ylidene (181) were studied. The β-lactam-4-yldenes (181) were trapped inter- and intra-molecularly by insertion and addition reactions. Carbene trapping experiments were carried out to form the novel spiro-β-lactam cyclopropenes, spiro-β-lactam cyclopropanes, various carbene insertion products and fused bicyclic β-lactams.

Thus, the β-lactam-4-ylidene (181) proved to be an excellent synthon for novel β-lactam systems that could not be synthesized, in a single step, otherwise.
ACKNOWLEDGEMENTS

The list of individuals who contributed to the evolution of this thesis is long indeed.

Initially, I wish to record my thanks to my parents for their faith in me, their support and their immeasurable sacrifices.

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Chapter 1

INTRODUCTION

Your thoughts and my words are waves from a sealed memory that keeps records of our yesterdays.

K. Gibran

1.1.0.0.0 ■ β-Lactams in perspective

β-Lactams (1) are 4-membered cyclic amides. Though the first member was synthesized in 1907 by Staudinger, the emergence of β-lactams as a class was not realized until the discovery of penicillin (2), in the early 1940's, which possesses the β-lactam ring as a key feature. Penicillin (2) was the first microbial metabolite to show sufficient separation between toxicity to the bacterial cell and toxicity to the mammalian host to permit its use in the systematic treatment of bacterial infections of humans and animals.

The increasing therapeutic role of β-lactam antibiotics (they constitute about 60% of the antibiotic market) and the discovery of significant new members of the series through chemical synthesis or fermentation screening programs, has led to exponential growth of the literature describing the chemistry and biology of these species. The excitement and interest in the β-lactam antibiotics has been raised to a peak by the recent discovery of the so called non-classical β-lactam antibiotics such as

I
clavulanic acid (3), thienamycin (4)\textsuperscript{9,10,11} and monobactams (sulfazecin) (5), whose biological properties are conspicuously unique.

Not surprisingly, therefore, many laboratories in academia and pharmaceutical industry are continuing the search for new and improved synthetic methodologies that could lead to more efficient synthetic routes to $\beta$-lactams.

1.1.1.0.0 $\textbf{Nomenclature}$

In the literature, monocyclic $\beta$-lactams are usually referred to as azetidin-2-ones, 2-azetidinones, or 2-oxoazetidines (1). However, the fused bicyclic systems 6a and 7a have been given the trivial names "penam"\textsuperscript{13} and "cepham"\textsuperscript{14}, respectively.

Similarly, the terms oxapenam, oxacepham, azapenam, azacepham, carbapenam, and carbacepham were coined for the bicyclic $\beta$-lactams 6b, 7b, 6c, 7c, 6d, 7d, respectively.\textsuperscript{15,16} The penem and cephem nuclei are derived by introducing a double bond into the penam and the cephem nuclei, respectively.\textsuperscript{17}

Penicillins are acylated derivatives of 6-aminopenicillanic acid (6-APA) which is itself an example of a substituted penam.\textsuperscript{17} Also, cephalosporins are acyl derivatives of 7-aminoccephalosporanic acid (7-ACA) which is an example of a substituted cephem.\textsuperscript{18} When the cephem ring is substituted with a methoxy group the resultant 7-methoxycephalosporin is called a cephamycin.\textsuperscript{17}
Moreover, the terms clavams and clavens have also been used in the literature to describe oxapepams and oxapenems respectively; clavulanic acid (3) and its derivatives are derived from the parent clavam ring.\(^{19}\)

The term monobactam is used to describe a derivative of 3-β-aminomonobactamic acid (3-AMA) (8). Sulfazecin (5) is an example of a monobactam.

A synthetic compound in this series that is of current interest is azthreonam (SQ-26,776) (9).\(^{20}\)

This trivial system of nomenclature cannot be conveniently broadened to apply to distant analogs and homologs of penicillins and cephalosporins, especially if the position of the heteroatom of the non-β-lactam ring is altered. For example, the clavam analogue with oxygen at the 2-position was referred to as "iso-clavam", by Stoodley.\(^{21}\) Similarly, analogues of penams with sulfur moved to the 2-position have been termed
"iso-penam". Also, this system of nomenclature is inadequate in the case of fused β-lactams, having no bridgehead nitrogen atom (10).

Due to this discrepancy other trivial systems of nomenclature have been introduced.15,16 In these systems fused β-lactams 9 and 10 may be called "alkanam"16 (alkam)15 and "isoalkanam"16 (neoalkam)15, respectively. Thus, β-lactams containing 7 and 8 atoms in the bicyclic system (9) (e. g. 6 and 7) may be given generic names, heptanam16 (heptam)15 and octanam16 (octam)15, respectively. In this nomenclature penam 6a is 1-thiaheptam15 and cepham 7a is 1-thiaoctam15.

Although the old trivial nomenclature is inadequate, it is still the one which is widely used in the literature, presumably because it is a statement that reflects the source and structure of the metabolite. The systematic name is generally avoided because of its complexity, but it is essential to define a compound precisely. Thus, clavulanic acid was the name given to the β-lactamase inhibitor from S. clavuligerus rather than: (2R, 5R)-3-(Z-β-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

1.1.2.0.0 ■ Structure

Simple azetidin-2-ones are usually colourless, low-melting solids or oils. A number of monocyclic azetidin-2-ones have been studied by X-ray crystallography. The results indicated that the ring is essentially planar with the nitrogen atom slightly (0.003 Å) out of the mean plane of its substituents except where steric factors enforce greater
deviations from planarity.\textsuperscript{22-29} Representative data are given for 1-(2-bromophenyl) azetidin-2-one (11).\textsuperscript{28,29} The N-CO distance of 1.38 Å in 11 is rather greater than that of a normal amide (ca. 1.32 Å). This has been attributed to ring strain and to inhibition of normal amide resonance.\textsuperscript{29}

Investigations by NMR spectroscopy have shown low energy barriers to inversion at nitrogen in β-lactams, even at -40 °C.\textsuperscript{30} Electron delocalizing substituents on nitrogen (N-aryl, N-acyl) lower the inversion barrier by lowering the energy of the transitional, "flat", geometry with the three substituents of the nitrogen all in the same plane. Substituents bearing unshared electron pairs (N-halo, N-amino, N-nitroso) raise the inversion barrier.\textsuperscript{29,31}

A number of theoretical\textsuperscript{32-34} (including ab initio\textsuperscript{35-37}) studies have been reported on the β-lactam structure. Recently, Palomo, \textit{et. al.}\textsuperscript{37} reported ab initio calculations which predict that azetidin-2-one exists in two interconverting conformers with pyramidal and planar geometry at the nitrogen, 12a and 12b, respectively. The calculated "inversion barrier" with respect to the planar conformer is 1.66 kcal/mol (data are for structure 12 with R = H).

Analysis of the molecular orbitals and net atomic charges as they change with
respect to pyramidalization of the nitrogen was also reported.\textsuperscript{37} For example the energy of the LUMO orbitals, which have a substantial contribution from the antibonding $\pi^*$ orbital of the carbonyl group, decrease strongly as the dihedral angle $\omega$ decreases (mistake in Palomo's paper: p. 485 increase instead of decrease). The result suggests that the more pyramidal the nitrogen, the easier the nucleophilic attack on the carbonyl group. This argument supports the pyramidalization of nitrogen in the early stages of the nucleophilic attack on the carbonyl group of the azetidin-2-one by OH$^-$, suggested by Petrongolo, et. al.\textsuperscript{35,36} and clarifies the cause for the high reactivities of penicillins which have a dihedral angle around 136° (135.7° for benzyl-penicillin),\textsuperscript{38,39} and cephalosporins which have a dihedral angle around 157° (156.8° for the $\Delta^3$-cephalosporin cephaloridine).\textsuperscript{39} Moreover, calculations have been performed on simple $\beta$-lactams to illustrate the energy that monocyclic $\beta$-lactams need to resemble the pyramidal conformations present in antibacterial agents.\textsuperscript{37,38,39}

In summary, strain in the five or six membered ring fused to the $\beta$-lactam ring tends to distort the hybridization at the $\beta$-lactam nitrogen and causes the hybridization to be more pyramidal.\textsuperscript{40} The nitrogen is calculated to be several tenths of an angstrom out of the plane of its three substituents in the more strained bicycles, whereas, as mentioned earlier in this section, it is essentially in the plane in the monocyclic models. The more strained structures tend to have higher $\nu$ (C=O) because amide resonance is hampered as the nitrogen becomes less sp$^2$ hybridized.\textsuperscript{40} In other words, due to the strain in the $\beta$-lactam ring, the non-polar conformer 12a is more populated compared to the polar conformer 12b. This relationship was originally conceived by Woodward in an attempt to interpret the properties of penicillin.\textsuperscript{2}

Therefore, one of the most important physiochemical properties used in quantitative structure-activity relationships of $\beta$-lactam compounds is the characteristic carbonyl group stretching frequency in the infrared. As expected, the carbonyl band
maximum, ν (C=O), is shifted to higher frequencies in compounds with higher biological activity. This fact has been interpreted in terms of dominance of contributor 12a and the relative unimportance of contributor 12b in most biologically active β-lactam compounds.⁴⁰,⁴¹

1.1.3.0.0 ■ Synthetic Methodologies

The construction of naturally occurring or unnatural β-lactams, with attendant control of functional groups and stereochemistry, has been the goal of synthetic organic chemists for the past 50 years. Figure 1 shows the structures of a number of β-lactam antibiotics, all of which have been synthesized.⁴²-⁴⁴

There are diverse synthetic routes to β-lactams, and in principle the 4-membered heterocycle could be constructed by the formation of one, two, three, or all four bonds of the ring system during the process of cyclization. Except for the last one all

![](image-url)

**Figure 1.** Structures of some representative β-lactam antibiotics that have been synthesized.
of the possibilities have been realized. Thus far, the synthesis of the β-lactams can be
differentiated into the following five fundamental methods.\textsuperscript{16,29,45-48}

1. Cyclization of the requisite acyclic precursors by \textit{closure of one bond}.

(i) \textbf{Formation of N-C\textsubscript{2} bond}:

\[
\begin{align*}
\text{O} & \quad \text{N} & \quad \text{H} & \quad \text{R}^1 & \quad \text{O} \\
\text{R}^2 & \quad 18 & & & \quad 1
\end{align*}
\]

(ii) \textbf{Formation of N-C\textsubscript{4} bond}:

\[
\begin{align*}
\text{X} & \quad \text{N} & \quad \text{H} & \quad \text{R}^1 & \quad \text{O} \\
\text{19} & & & \quad 1
\end{align*}
\]

(iii) \textbf{Formation of C\textsubscript{2}-C\textsubscript{3} bond}:

\[
\begin{align*}
\text{(CO)}_3\text{Fe} & \quad \text{N} & \quad \text{H} & \quad \text{R}^1 & \quad \text{O} \\
\text{20} & & & \quad 1
\end{align*}
\]

(iv) \textbf{Formation of C\textsubscript{3}-C\textsubscript{4} bond}:
2. Cyclization of the requisite acyclic precursor by closure of two bonds.

(i) Formation from [3+1] fragments:

PhS
\[ \text{CO} \quad \text{N} \quad \text{R}^1 \]  
\[ \text{PhS} \quad \text{CH}_2\text{I}_2 \]  
\[ \text{CO} \quad \text{N} \quad \text{R}^1 \]

(ii) Formation from [2+2] fragments:

a) Formation of N-C$_2$ and C$_3$-C$_4$ bonds:
b) Formation of N-C₄ and C₇-C₃ bonds:

\[ \text{R}^2 \cdots \text{N} \cdots \text{R}^3 \]

\[ O \equiv C \equiv N \quad 26 \]

\[ \text{R}^2 \quad \text{N} \quad \text{R}^3 \]

\[ \text{O} \quad \text{N} \quad \text{R}^1 \]

3. Ring expansions

\[ \text{HO} \quad \text{N} \quad \text{R}^1 \]

\[ \text{X} \]

\[ \text{Base} \]

\[ \text{O} \quad \text{N} \quad \text{R}^1 \]

\[ \text{I} \]

4. Ring contractions

\[ \text{X} \quad \text{Y} \quad \text{R}^1 \]

\[ \text{Base} \quad (\text{NaOCH}_3) \]

\[ \text{CH}_3O \quad \text{Y} \quad \text{N} \quad \text{R}^1 \]

\[ \text{O} \quad \text{N} \quad \text{R}^1 \]

\[ \text{I} \]

5. Oxidation of azetidines
Due to the exhaustive literature on the synthesis of β-lactam systems, this section will be focused on the synthetic method relevant to the thesis project. Therefore, emphasis will be put only on the cyclocondensation reaction of the Schiff base with a ketene or a ketene equivalent.

The addition of a two-atom component to an imine function provides one of the most important and versatile routes to β-lactams. The first synthesis of a β-lactam, reported by Staudinger in 1907, was by the addition of a ketene to an imine and there are now many examples of this type of approach. Ketenes are most frequently generated in situ from acid chlorides by dehydrodehalogenation, but have also been produced from diazo ketones, by heating of alkoxyacetylenes and, in the case of certain cyanoketenes, by thermolysis of the cyclic precursors 30 and 31.

The order of reactivity of several ketenes towards benzophenone anil, determined by Staudinger, is shown below. Ketene itself is much less reactive than the substituted ketenes, for the reaction takes place only under extremely brutal conditions (180 - 200°C). Also, mono-alkyl and -phenyl substituted ketenes are not highly reactive.
\[ \text{C} = \text{O} \quad \text{32} \quad \text{33} \quad \text{34} \quad \text{35} \]

with imines. This could be due to their great tendency to polymerize even under very mild conditions.\(^{46a}\)

Moreover, there are numerous reports in the literature in which the substituted acetic acid itself is used as a ketene equivalent under the influence of a suitable activating agent. For example, mixed anhydrides formed with chloroformates, trifluoroacetic acid,\(^{49}\) chlorophosphates,\(^{50,51}\) chlorophosphamides\(^{50}\) cyanuric chloride,\(^{52}\) saccharyl chloride,\(^{53}\) triphenylphosphine and carbon tetrabromide\(^{54}\) have all been employed as modifications to the acid chloride route.

Also, in the past decade intense research activity has surrounded ester-imine condensations (eq 1).\(^{48}\) Gilman and Speeter in 1943 described the preparation of 1,4-diphenyl-2-azetidinone (38) by condensation of the Reformatsky reagent derived from ethyl \(\alpha\)-bromoacetate (36) with N-phenylbenzaldimine (37).\(^{55}\) Presumably the recent intense interest in this reaction is owed to the ability of the modern synthetic chemist to manipulate the reactivity patterns of enolates.\(^{48}\) Thus, the condensation has been conducted with lithium, aluminum, boron, zinc, tin, and zirconium enolates.\(^{48}\)

Considerable diversity in imine structure is also possible. For example, cyclic imines and conjugated imines such as cinnamylidineaniline react with ketenes or ketene equivalents to afford \(\beta\)-lactams. N-acylhydrazones can be used, but phenylhydrazones
(39) and O-alkyi oximes (40) do not give β-lactams. However, Sharma, et. al. recently reported the reaction of phenylhydrazones with phenoxyacetyl chloride to form β-lactams.\textsuperscript{56} Furthermore, the reactivity of imine substrates substituted with heteroatoms at the carbon atom has been investigated with respect to reactivity with ketenes. Imino chloride 41 was found to be unreactive.\textsuperscript{46a} However, imidates\textsuperscript{57} (imino esters), thioimidates,\textsuperscript{2,46a} and amidines\textsuperscript{58} have found wide applications in the synthesis of functionalized β-lactams.

\textbf{1.1.3.1.0 Mechanistic Aspects of the [2+2] Ketene - Imine Reaction}

Figure 2. A possible mode of attack of a voracious nucleophile on a ketene animal.

Tidwell, et. al.\textsuperscript{59} used the animated ketene form 43, in an attempt to show the high reactivity of such species, (Figure 2).

"Having no arms, these creatures have limited stability and fall easy prey to their natural enemies, the Greater Hump-backed Nucleophiles".\textsuperscript{59}
The reactions of ketenes or ketene equivalents with imines, discussed in section 1.1.3.0, all involve the imine acting as a nucleophile. The ester-imine reaction however, is believed to involve a nucleophilic attack of the enolate anion, derived from the ester, on the electrophilic carbon of the imine followed by cyclization, (Scheme 1, path-a). Alternatively, the enolate could fragment to afford a ketene, (Scheme 1, path-b).

\[
\begin{align*}
\text{R}_3\text{CH(X)CO}_2\text{R} & \quad \xrightarrow{-\text{ROZnBr}} \quad \text{R}_3\text{CH}=\text{C}=\text{O} \\
44 & \quad X = \text{Br} \\
& \quad X = \text{ZnBr} \\
\text{R}^4\text{CH}=\text{NR}^1 & \xrightarrow{\text{path-a}} \quad \text{R}^4\text{CH}=\text{NR}^1 \\
\text{RO}_2\text{C} & \quad \xrightarrow{-\text{ROZnBr}} \quad \text{N}(\text{ZnBr})\text{R}^1 \\
\text{N}(\text{ZnBr})\text{R}^1 & \xrightarrow{\text{path-a}} \quad \text{R}^3\text{R}^4\text{N} \quad \text{RO}_2\text{C} \\
\end{align*}
\]

Scheme 1

Stereochemical studies have shown that the main route is path-a (Scheme 1), that the ester-imine condensation is reversible, and that the stereochemistry depends on the solvent polarity. Increased solvent polarity favours the cis β-lactam, (Scheme 2).

Although the ketene-imine cycloaddition route to β-lactams has received considerable attention, the exact mechanism and the stereochemical consequences of this reaction are still being debated.\(^{29,45,60}\) The interaction of acid chlorides with imines in the presence of bases such as triethylamine may involve prior formation of a ketene followed by cycloaddition to the imine,\(^{60}\) but it can also be considered to involve interaction of the imine with the acid chloride to give an immonium ion (46). This ion is then cyclized by deprotonation under the influence of the base. Clearly, the distinction between these routes is a rather fine one and the mechanism involved in a particular case may well
depend on the reactants and the timing of mixing (Scheme 3).^{60}

Moreover, the stereochemistry of the product can often not be predicted with confidence. For example, some reports describe the cycloaddition to be
stereospecific,\textsuperscript{61-63} while others observe mixtures of cis- and trans-2-azetidinones.\textsuperscript{64} Bose, et. al. reported that the stereospecificity generally depends on the experimental conditions employed.\textsuperscript{57a} For example, products having trans stereochemistry appear to be preferred when the amine is added to a solution of the acid halide and the imine, while cis products often predominate when the acid halide is added to a solution of the amine and the imine. It is generally assumed that the latter method involves a ketene intermediate and the former an acylium ion.\textsuperscript{65} However, it is not completely clear whether either of these methods involve a bona fide ketene intermediate or even if the tertiary amine or its conjugate acid have an influence on product stereochemistry.

If a ketene is involved then two extreme mechanisms can be envisaged (Scheme 4), concerted [2+2] cycloaddition or the more generally accepted formation of a dipolar intermediate 47, (Scheme 4). Intermediate 47 can close to the β-lactam or can interact with a second molecule of ketene to give 2:1 adducts, 48 and 49, which are
sometimes formed as side products. The course of the reaction is governed by the nature of the substituents in the reacting species. The reactivities of the ketenes, as mentioned in section 1.1.3.0, vary considerably from one member to another, and in some cases the ketene dimer is formed first and then reacts with the imine to give the 6-membered heterocycles, 48 and 49.66,67

1.1.3.1.1 Concerted [2+2] Imine - Ketene Cycloaddition

Most alkenes cannot be induced to undergo a [2+2] cycloaddition reaction thermally, a finding that is readily rationalized by the forbidden nature of the $[\pi 2s + \pi 2s]$ addition and the steric difficulties associated with the allowed $[\pi 2s + \pi 2a]$ pathway (Figure 3).68,69

However, ketenes are especially reactive in [2+2] cycloadditions because they offer a low degree of steric hinderance at the carbonyl group carbon center and a low-energy LUMO. In a ketene-imine reaction the important interaction is HOMO ketenophile (imine) / LUMO ketene. Regioselectivity is determined by the fact that the

![Diagram showing HOMO and LUMO interactions](image)

Figure 3. (2s + 2a) pathway. Figure 4.

larger lobe of the HOMO of the ketenophile overlaps with the larger lobe of the LUMO of
the ketene, (Figure 4).\textsuperscript{68,69}

Ketenes are known to add to alkenes with retention of the cis-trans geometry about the alkene component and with the orientation and stereochemistry that yields the sterically \textit{most hindered} product.\textsuperscript{70-72} The \([\pi2s + \pi2a]\) transition state 51, (Scheme 5), accounts for the characteristics of the reaction. The least hindered approach of the reactants leads to the most hindered product. The electron-deficient carbon end of the carbonyl \(\pi\) orbital (perpendicular to the page) in 51 impinges directly on the alkene \(\pi\) bond in the \(s + a\) approach; this interaction is considered to provide a key stabilizing influence.\textsuperscript{68,69,73,74} An alternative geometry of approach has been proposed for the alkene-ketene cycloaddition with the allowed \(\pi2s + \pi2s + \pi2s\) pericyclic path.\textsuperscript{75} The product stereochemistry is the same as that for the \(2s + 2a\) cycloaddition.\textsuperscript{68}

Despite the success of the concerted \([\pi2s + \pi2a]\) pericyclic pathway in explaining the stereochemistry of numerous ketene additions,\textsuperscript{68,69,76} it is generally accepted that the imine-ketene cycloaddition occurs by a stepwise path via intermediate 47.\textsuperscript{29,60,68,77,78} The formation of 47 is also consistent with frontier orbital control of regioselectivity. That is, the atoms with the larger coefficients on the HOMO (ketenophile) and the LUMO (ketene) are the first to become bonded.

\subsection*{1.1.3.1.2 Non-concerted [2+2] Imine-Ketene Reaction}
There have been a large number of theoretical studies on ketenes in recent years.\textsuperscript{76,79-87} The net charges on the atoms, in a recent study using 3TO - 3G optimized geometries, are shown in Figure 5.\textsuperscript{87} The position of attack by various reagents on ketenes will be determined by the energies of the various transition states for addition, but the charge distributions shown in Figure 5 can be used to indicate that the oxygen and C\textsubscript{\beta} are susceptible to attack by electrophiles, while nucleophiles will be attracted to C\textsubscript{\alpha}, just as in the case of a more typical carbonyl group.\textsuperscript{87} The ketene HOMO and LUMO\textsuperscript{76} (50a and 50b, respectively) further suggest that electrophilic attack will occur from above the plane of the ketene skeleton, while nucleophilic attack will occur in the plane,\textsuperscript{59,76} (Figure 6).

Therefore, the nucleophilic attack of the nonbonding electrons of the imine nitrogen atom on the ketene would involve reaction with the LUMO of the ketene 50b. The substituents on the ketene are expected to determine the preferred direction of the attack. According to Tidwell, \textit{et. al.} the approach of the imine nitrogen, on the ketene LUMO (50b), should be from the least hindered side in the plane of the ketene.\textsuperscript{88} The interaction of the ketene
LUMO, with the lone-pair electrons of the imine-nitrogen, is expected to be through the p-lobe, on the sp-hybridized carbon (Cα), which is anti to the large substituent. Brady, et al. suggest that the above approach will give the zwitterionic intermediate 47a (Scheme 6) since the imine would prefer the trans conformation, T, (Scheme 6). The dipolar intermediate may be represented by several different resonance structures. Structure 47a would be expected to be a major contributor to the resonance hybrid. A conrotatory ring closure of 47a results in the β-lactam with cis configuration. Earlier, Moore, et al. suggested a similar mechanistic paradigm based on their observations on the reactions of cyanoketenes with imines. They concluded that the stereoselectivity of all the cycloadditions resulting in the 2-azetidinones is directly related to the steric bulk of the
N-substituent of the imine.\textsuperscript{91} The relative contributions of the zwitterions 47a and 47b, and thus also the 2-azetidinone products (cis and trans respectively) are significantly influenced by the bulk of the N-substituent.\textsuperscript{91} However, Brady suggests that the structure of the intermediate is determined not only by steric but also by electronic effects.\textsuperscript{90} When both R\textsuperscript{2} and R\textsuperscript{3} are cation stabilizing groups, or R\textsuperscript{2} is a cation - destabilizing group, the resonance contribution of 47a should be enhanced by these substituents, resulting in only the cis isomer of the β-lactam. When R\textsuperscript{2} is a better cation - stabilizing group than R\textsuperscript{3}, resonance structure 47b should make more of a contribution to the dipolar intermediate. Thus, the thermodynamically controlled ring closure of 47b results in the formation of the trans isomer, which has been shown to be the more stable isomer by epimerization studies.\textsuperscript{90,92}

Moreover, if the substituent on the ketene is a good carbanion-stabilizing

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {\textbf{47a}};
  \node at (2,-2) {\textbf{47d}};
  \node at (0,-4) {\textbf{cis}};
  \node at (2,-4) {\textbf{trans}};
  \node at (-2,0) {\textbf{Scheme 7}};
  \draw[<->] (0,0) -- (2,0);
  \draw[<->] (0,-2) -- (2,-2);
  \draw[<->] (0,-4) -- (2,-4);
\end{tikzpicture}
\end{center}

group. resonance structure 47d (Scheme 7) of the dipolar intermediate could be expected to be a major contributor to the resonance hybrid. Hence, the more thermodynamically stable trans isomer should be formed predominantly.

When the imine is locked in the cisoid configuration, such as with thiazoline,
the dipolar intermediate will result in the trans isomer, regardless of the relative

\[
\begin{align*}
\text{trans isomer} \\
\text{Scheme 8}
\end{align*}
\]

contributions of 51a or 51b, \(^{90,93}\) (Scheme 8). Also, 1-oxa-cepham (52), prepared by the
annelation of 2-aryl-1,3-oxazines, was formed as the trans stereoisomer only.\(^{93,95}\) This
annelation method was also utilized to synthesize the aza-analogues. The aza-cepham
substructure has been reported by several workers. Among these the 1-aza(N-H) cephem
(53) was reported by Wolfe, \textit{et al.}\(^ {96}\) with trans stereochemistry of the \(\beta\)-lactam
substituents. Bose and co-workers reported the synthesis of analogous compounds having
C\(_6\)-aryl or C\(_6\)-thiomethyl substituents (54).\(^ {97,98}\)

It should be further noted that a zwitterionic intermediate in a diphenylketene /
imine cycloaddition has been detected by matrix isolation.\(^ {99}\) In an elegant experiment
Moore was able to trap the zwitterionic intermediate intramolecularly according to
Scheme 9.\(^ {91}\) The 2 + 4 product (60) was obtained when the steric bulk of the R substituent
on nitrogen was increased; hence favouring intermediate 57b.
Although in many cases the formation of the zwitterionic intermediate is certain, it should be emphasized that the course of the reaction is governed by the nature of the substituents in the reacting species.

1.1.3.2.0 **Enantioselectivity in the [2+2] imine-ketene reaction**

During the β-lactam [2+2] construction two new centers of asymmetry, C₃ and C₄, are created and therefore four diastereomers could possibly be formed, (+)-cis, (-)-cis (+)-trans, and (-)-trans. The synthesis of an optically pure β-lactam is essential because
the antibacterial activity is shown by one enantiomer only. In a recent review, Meyers has highlighted the importance and art of synthesis of chiral non-racemic compounds.\textsuperscript{100} The Staudinger reaction is a very promising approach since, in many cases, its stereoselectivity can be controlled in favor of the cis configuration as necessary for the synthesis of many β-lactam antibiotics.\textsuperscript{101,102}

Recently, Bose has described the enantiospecific synthesis of β-lactams via cycloaddition using chiral imines derived from chiral amines as well as aldehydic compounds.\textsuperscript{102-104} For example, Schiff bases from cinnamaldehyde and a d-threonine ester have been used to achieve high diastereoselectivity in the cycloaddition reaction.\textsuperscript{104,105} Also, complete diastereoselectivity in β-lactam formation was achieved by annelating a Schiff base from optically active aldehyde and an achiral amine.\textsuperscript{103,108-110}

On the other hand, Evans, \textit{et al.} have used a chiral substituent in the amido portion of the ketene. The chiral auxiliary 61 was synthesized from l-phenylglycine. A 95:5 mixture of the two cis diastereomers was obtained.\textsuperscript{111} Also, the complementary chiral auxiliary 62 prepared from norphedrine was utilized and only one diastereomer was obtained in greater than 95 % yield.\textsuperscript{111} The problem of removing the chiral directing group was solved by Cooper, \textit{et al.}\textsuperscript{112a} who have used the tartrimide 63 as a chiral directing group. These tartaric systems could be removed by opening the imide to the amide followed by application of a routine PCl\textsubscript{5} cleavage methodology.\textsuperscript{112a} By changing R' and R'' several derivatives of 63 were prepared; the best induction was achieved with R' = R'' = PhCOO and R' = R'' = PhCH\textsubscript{2}O, both produced 86:14 ratios of two
diastereomers.

The Lilly group\textsuperscript{112a} could not explain the chiral induction into their products by the method described earlier by the Roche workers.\textsuperscript{106} The Roche group postulated that the induction was a result of a preferential direction of rotation of the initial planar zwitterionic intermediate (described in section 1.1.3.1.2), (Scheme 10). According to the

\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme10.png}
\end{center}

\textbf{Scheme 10}

\begin{flushright}
Lilly group,\textsuperscript{112a} it would be more appropriate to postulate an orthogonal approach to the geometry of the transition state. This approach could occur from either the $\alpha$ or $\beta$ faces, and as such, the intermediates 64a and 64b are the two chiral isomers (Scheme 11). These isomers would then undergo a conrotatory bond closure with concomitant assumption of planarity. Transition state 64a could only give the $\beta$-lactam with both protons $\alpha$, and vice versa. Thus, according to the Lilly group, the origin of chirality occurred at the acylation of the imine, not from the direction of rotation, and was controlled sterically by the asymmetry of the substituent groups on the nitrogen.

The Lilly group supported their observations with MNDO calculations. These semi-empirical calculations led to the discovery of a relatively low energy transition intermediate (Scheme 11). The energy of this zwitterion (64) was about 22 kcal/mol above that of the reactants. \textit{The two ends of the molecule were nearly perpendicular to each other} (64, Scheme 11). The product from the model reaction was N-methyl-3,4-dimethyl-azetidin-2-one. Its energy was 26 kcal/mol below that of the starting molecules.
and 48 kcal/mol lower than that of the transition intermediate (64).\textsuperscript{112a}

Very recently, Hegedus \textit{et al.} adopted a similar mechanism to explain stereoselectivity in the imine - ketene cycloaddition reaction.\textsuperscript{112b} This mechanism seems to be a hybrid of the two proposed mechanisms in sections 1.1.3.1.1 and 1.1.3.1.2. That is, it is an orthogonal \(\pi2s + \pi2a\) cycloaddition but stepwise reaction rather than concerted.

1.1.4.0.0 ■ Ring Modifications

It is often necessary to prepare \(\beta\)-lactams with particular substituents at \(N_1\), \(C_3\), and \(C_4\), as in the preparation of fused \(\beta\)-lactams from monocyclic precursors. In this section ring modifications at \(N_1\) and \(C_3\) will be introduced briefly while modifications at
C₄ will be dealt with in more detail due to their particular importance and relevance to the thesis project.

1.1.4.1.0 Modifications at N₁

The reactions of N-unsubstituted azetidin-2-ones or their derived anions with a variety of soft electrophiles results in N-substitution.²⁹ N-Alkylation has been achieved with various alkyl halides in the presence of a strong base such as sodamide, sodium hydride or potassium-t-butoxide.²⁹ Also, under phase transfer conditions potassium hydroxide was used for alkylation with alkyl halides.²⁹ N-alkylation also was reported to occur with aldehydes.²⁹ N-acylation occurs with acyl chlorides and triethyl amine or with ketenes.¹¹³ Isocyanates gave the corresponding urea in low yields.¹¹⁴ Nitrosation was achieved in acetic acid to give N-nitroso-β-lactams.²⁹

More recently, the Merck research group pioneered the synthesis of the carbapenem structure of thienamycin with the key step being an efficient carbenoid insertion reaction into the N-H bond (eq 2).¹¹⁵,¹¹⁶

\[
\begin{align*}
\text{OH} & \\
\text{66} & \\
\text{67} & \\
\text{CO}_2\text{PNB} & \\
\end{align*}
\]

This process has been applied also to the synthesis of carbacephems.¹¹⁷-¹¹⁹ Moreover, intermolecular carbenoid insertion followed by intramolecular displacement of acetate gave the clavulanic acid derivative 69 in one step from 4-acetoxy azetidin-2-one (68), (eq 3).¹²⁰

Miller, et. al. recently reported the ring closure of the N-benzyloxy-β-lactam
1.1.4.2.0 Modification at C₃

N-Substituted β-lactams are deprotonated at C₃ using a strong base, such as lithium diisopropyl amide (LDA), at low temperatures. The resulting anions have been quenched with various electrophiles including ketones, esters, reactive alkyl halides, trimethylsilyl chloride, and various other electrophiles. Deprotonation of the corresponding position in penicillins and cephalosporins with subsequent epimerization and/or quenching with electrophiles has been reviewed.

A diazo group at the 6-position in penicillins (73) was utilized to provide access to a variety of analogues with different substituents at these positions (Scheme 12). The stereoselective formation of 75, from the diazo compound 73, where Y is sulfur or oxygen has been reported by several workers. The 6-halopenicillanate (74) and the 6,6-dihalo analogue have also been prepared. Similar reactions were carried out on the
Scheme 12

Several mechanisms have been proposed for this reaction. Nitrogen loss to form a carbenoid in the presence of a metal catalyst has been suggested. However, Sheehan has shown that, under his reaction conditions, the thiol reacts with 73 to form an azo intermediate which then loses nitrogen. The reaction of 73 with acrylonitrile, methyl-, ethyl- or tert-butyl-acrylate was found to produce the corresponding 6-spiropyrazolines, with or without Cu(AcAc)$_2$. It has been further suggested that the formation of the 6-spirocyclopropane, when vinyl ethers were used, possibly occurs through 1-pyrazoline intermediates. More recently, the method has been applied for the synthesis of 6-spiro epoxy-penicillins by the reaction of 73 with oxalyl halides. Also, 7-spiro-epoxycephalosporins have been synthesized by the same method.

1.1.4.3.0 Modifications at C$_4$

The main strategies (Scheme 13) for β-lactam synthesis usually involve the construction of an appropriately substituted monocyclic β-lactam (76) followed by chemical manipulations at N$_1$ and C$_4$ and subsequent ring closure to form the bicyclic ring system 78 in the last step of the synthesis. While N$_1$ (section 1.1.4.1.0) and C$_3$ (section 1.1.4.2.0) display natural reactivity, the C$_4$-position does not show similar characteristics. However, several reactions have been reported in which a substituent attached to the C$_4$-position is displaced without disruption of the ring.
1.1.4.3.1 ▪ Good leaving group at C₄ (4-acetoxy-2-azetidinones)

4-Acetoxy-2-azetidinone\(^{135}\) (77) is a widely accepted as an efficient and versatile precursor for various C₄ substituted β-lactams. β-Lactam 77 readily undergoes displacement of the acetoxy group with oxygen, sulfur, nitrogen,\(^{29,135-137}\) carbon,\(^{29,136,138,139}\) hydrogen\(^{140,141}\) and various other nucleophiles.\(^{29}\) The replacement of the acetoxy group by a variety of nucleophiles provides an easy access to a wide variety of bicyclic β-lactam precursors (Scheme 13).\(^{29,44,120,134,138}\) Due to the racemization of the starting 4-acetoxy-2-azetidinones, it is widely accepted that 80 is the reactive intermediate.\(^{29,135,140}\) Moreover, it has been speculated that 79 is present as an intermediate even if R is not a hydrogen atom.\(^{138a,139d,142}\) In a study on the

structure-reactivity relationship in monocyclic β-lactams, O'Ferrell, \textit{et al.}\(^{143}\) have shown that an N-H azetidinone with a good leaving group at C₄ reacts much more rapidly than the N-methyl analogue with aqueous sodium hydroxide or methanolic sodium methoxide.
This difference in rate is because, as shown by Fedor,\textsuperscript{144} the N-H azetidinones undergo a
1,2-elimination to form the neutral 1-azetinone intermediate \textbf{80}.\textsuperscript{143}

The most direct access to 4-acetoxyazetidin-2-ones is the addition of
chlorosulfonyl isocyanate (CSI) to the corresponding vinyl acetate.\textsuperscript{145} However, apart
from the low yields reported and the lack of stereoselectivity in the cycloaddition step,
CSI is reactive towards several functional groups and such a process, to prepare β-lactams
with a substituent at the C\textsubscript{3} position, is not usually feasible.\textsuperscript{146}

In an attempt to control the stereochemistry, the annelation of cinnamylidene
Schiff base (\textbf{81}) with an activated acetic acid was attempted. Ozonolysis of the styryl
moiety followed by a Baeyer-Villiger oxidation of the resulting methyl ketone \textbf{82} led to

\[
\begin{align*}
\text{Ph} & \quad \text{R} \\
\text{N} & \quad \text{R}^3 \\
\text{H} & \quad \text{H} \\
\text{R} & \quad \text{R}^3 \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{R} & \quad \text{R}^3 \\
\text{O} & \quad \text{OAc} \\
\end{align*}
\]

the 4-acetoxy-azetidin-2-one (\textbf{77}), (eq 5).\textsuperscript{147,148} Also, the Reformatsky type reaction
(section 1.1.3.0.0) has been recently used as the first step of this method.\textsuperscript{149} The Merck
group\textsuperscript{150} has eliminated the ozonolysis step by annelating an acid chloride with a
keto-imine, thus providing direct access to the C\textsubscript{4} keto-substituted β-lactam\textsuperscript{151} on the route
to 4-benzyloxy- azetidin-2-one.\textsuperscript{150} Other reports deal with the conversion of a carboxy
group by lead tetraacetate oxidative decarboxylation of the acid.\textsuperscript{152} Other related and
shorter, but lower yielding, pathways have been reported by Georg, \textit{et. al.} Scheme 14.\textsuperscript{153}
Moreover, Palomo, \textit{et. al.}\textsuperscript{154} recently reported an acid chloride - imino ester condensation
producing the ester of \textbf{85} which, upon saponification and further decarboxylation -
aeetoxylation\textsuperscript{155}, furnished \textbf{77}.\textsuperscript{154} Reinhoudt, \textit{et. al.} reported the acetoxylation of a
1-benzyloxy β-lactam at C\textsubscript{4} by a reduction - oxidation sequence \textit{via} a 1-hydroxyazetidine
Intermediate.\(^{156}\) Electrochemical oxidation was also used for the synthesis of the 4-acetoxy-2-azetidinones 77. Mori, et. al. electrolyzed the β-lactam 86 to produce 77;

the reaction is assumed to proceed through intermediates 87 and 88 (eq 6).\(^{157}\) This reaction could not be applied to β-lactams having oxidation-labile functions at C₃.\(^{157}\) More recently, Mori et. al. resolved this problem by reporting the electrolysis of 4-carboxy-2-azetidinone to synthesize the 4-acetoxy β-lactam (eq 7). This reaction was effective for β-lactams with oxidation-labile substituents at C₃.\(^{158}\) Moreover, N-alkyl β-lactams were electrolyzed in methanol to afford products with a methoxy group at the endo- (C₄) and the exo-cyclic carbons alpha to nitrogen.\(^{159}\) Therefore, N-unsubstituted β-lactams seem to be more appropriate for these electrochemical reactions.\(^{159b}\) Also,
osmium trichloride catalyzed oxidation of the C₄-H bond in β-lactams with peracetic acid in acetic acid gave the corresponding 4-acetoxy β-lactams.¹⁶⁰

Furthermore, Easton, et. al. described a method in which a benzoyloxy¹⁶¹ or an acetoxy¹⁶² group could be introduced directly at the C₄ position of N-alkyl and N-aryl β-lactams.¹⁶¹,¹⁶² The method involved a copper catalysed reaction of a 4-unsubstituted β-lactam with t-butyl perbenzoate or peracetate to afford the corresponding 4-benzoyloxy or acetoxy β-lactams. The suggested mechanism involves an initial hydrogen atom transfer from the β-lactam (C₄) to t-butoxy radical, followed by benzoate or acetate incorporation at the site of hydrogen abstraction.¹⁶¹,¹⁶² It should be noted that the problem of a competing reaction on the exocyclic carbon α to nitrogen, encountered by Mori, et. al.,¹⁵⁹ is faced here also.¹⁶¹

Though the results of these methods are quite interesting, most of them require high substrate specificity. Hence, these methods are complementary and the search continues for an ideal, more general method.

1.1.4.3.2 Reactive intermediate at C₄

The displacement of the acetoxy group in the reactions of 4-acetoxy β-lactam (77) with nucleophiles is believed to occur via an elimination - addition mechanism involving azetinones 79 or 80, as reactive intermediates (section 1.1.4.3.1). In an attempt to prove the existence of 80 and to provide a concise route to fused bicyclic β-lactams, its capture with 1,3-dienes had been tried.¹³⁹d Meyers et. al. obtained a cycloadduct from the
reaction of 3-siloxy-1,3-pentadiene with 4-acetoxyazetidinone.\textsuperscript{139e} The reaction was speculated to occur by a hetero Diels-Alder reaction \textit{via} the azetidinone intermediate (80). However, it has been speculated by others that if 80 is not rapidly captured, the ring opens to produce vinyl isocyanates.\textsuperscript{139d,163} On the other hand, Olofson \textit{et. al.}'s clever attempt to detect azetidiones 92 was fruitful.\textsuperscript{164} The substructure of azetidiones 92 was observed spectroscopically, at low temperature; infra-red and $^{13}$C NMR spectra were obtained.\textsuperscript{164}

Furthermore, a free radical \textit{reactive intermediate}, has been generated at C$_4$ in some of the attempts to synthesize the more stable \textit{reactive intermediate}, 4-acetoxy $\beta$-lactam 77, section 1.1.4.3.1. Beckwith, \textit{et. al.}\textsuperscript{165} reported the formation of fused bi- and tri-cyclic $\beta$-lactams by free radical ring closure.\textsuperscript{165} Heating the thioether (93) with tributylstannane and a trace of azobisisobutyronitrile (AIBN) produced the reduction product 95 (48 %), the bicyclic compound 97 (26 %) and starting material (22 %).\textsuperscript{165} This unusual behavior (\textit{endo closure instead of exo}) was explained in terms of the possible strain engendered by the azetidinonoyl ring in the exo transition structures.\textsuperscript{165} The formation of the carbacephem ring employing the same method was reported earlier by Kametani, \textit{et. al.}\textsuperscript{166} who also could not detect the carbapenam, \textit{formed by exo-ring closure}.\textsuperscript{166} More recently, the phenylselenyl group was used as a progenitor to generate a free radical at C$_4$.\textsuperscript{167} Kametani reported the radical cyclization onto a propargyl group leading to the synthesis of carbapenems (10 %) again \textit{via} an endo closure.\textsuperscript{167}

It is noteworthy that other radical ring closures (\textit{radical center on the side chain}) leading to fused $\beta$-lactam systems behave similarly (\textit{endo closure}).\textsuperscript{168} Bachi, \textit{et. al.} reported similar behavior when the side chain radical method was employed to form oxacephams.\textsuperscript{169a,b} However, regio-control of the mode of side chain radical cyclization
was reported with changes in the substitution on the alkene or alkyne.\textsuperscript{169c,d} Parsons, \textit{et. al.} observed a strange effect of the concentration on the mode of cyclization, exo verses endo, in the side chain radical reaction.\textsuperscript{170}

From the forgoing, the functionalization at the C\textsubscript{4}- position of β-lactams becomes an increasingly interesting task. Out of the C\textsubscript{4} reactive intermediates utilized so far, \textit{the C\textsubscript{4} carbene is yet to be reported}.\textsuperscript{171}

1.2.0.0.0 ■ Carbenes in perspective

Carbenes are neutral, divalent carbon intermediates. They are regarded as short-lived and highly reactive and they play a prominent role in the broad field of reactive intermediates.\textsuperscript{172} Indications of a divalent intermediate sprinkled through the early literature\textsuperscript{173} associated with the work of Bucher and Curtius (1885),\textsuperscript{174} Staudinger and Kupfer (1912),\textsuperscript{175} Rice and Glasebrook (1934)\textsuperscript{176}, and Meerwein \textit{et. al.} (1942).\textsuperscript{177} The
modern development in the field was ignited by the work of Hine (1950) who proposed that the alkaline hydrolysis of chloroform involves *a new* intermediate, CCl$_2$.$^{178}$ Doering and Hoffman (1954) were able to generate CCl$_2$ in non-aqueous medium and under conditions which made addition to alkenes the major pathway, making 1,1-dichlorocyclopropanes in good yields.$^{179}$ Doering also coined the term "carbene" for this divalent reactive intermediate. These developments led to an explosive growth of interest in the field.

1.2.1.0.0 ■ Definitions and nomenclature

A carbene carbon (99) uses two of its four valence orbitals to form two covalent bonds to other groups. The other two non-bonding orbitals contain two electrons between them. Hence, carbenes may exist in triplet and singlet states. If the pair of electrons are in the same *in-plane* molecular orbital ($\sigma^2$) with paired spins, then the carbene is a singlet (101); if the two electrons have parallel spins and occupy an *in-plane* ($\sigma$) orbital and an orbital ($p$) perpendicular to the molecular plane, then the carbene is a triplet (100).

The simplest carbene, :CH$_2$, is usually called methylene. Derivatives are sometimes called methylenes; thus, :CHCl is chloromethylene, and so on. More commonly, the derivatives are named carbenes, for example, chlorocarbene (:CHCl), phenylcarbene (:CHPh), and so on. The word carbene includes the divalent carbon. Carbenes in which the electron - deficient carbon is part of a ring may be named by use of the replacement name prefix, *carbena*. Locant 1 is assigned to *carbena*, except in cyclic systems with fixed numbering. Alternatively, these (and acyclic) c-:benes may be named by use of the suffix -ylidene; for example :CH$_2$ (methylene or carbene) is also called methylidene. The numbering starts from the divalent carbon; for example, carbene 98 is
called 4-chloro-2- cyclohexenyldene.\textsuperscript{180}

1.2.2.0.0 \textbf{Electronic and molecular structure}

![Diagram](image)

\textbf{Figure 7.}

The possible arrangements of two electrons between orbitals of different energies are as shown in Figure 8. Following Hund’s rule, the electron configuration with one electron in each of these orbitals will minimize electron repulsion and have the lowest energy. Hence, the ground state in methylene (99, $R^1 = R^2 = H$) is a triplet, 100. However, the in-plane orbital in 100 is not a pure $p$ orbital but a hybrid of $s$ and $p$. This mixing decreases the energy of this hybrid orbital and makes it part of the $\sigma$ system, while the
$p$-orbital perpendicular to the plane is, to a first approximation, unaffected.\textsuperscript{181} Hence, the σ orbital becomes $sp^2$-like, and the molecule is bent. Herzberg's early studies on the electronic spectra of methylene have shown the singlet to be bent with the H-C-H angle being 102.4°.\textsuperscript{182} Herzberg originally concluded that the triplet structure is linear or nearly so;\textsuperscript{182} however, it is now generally believed that the triplet is bent with an angle around 133.8°.\textsuperscript{183} These equilibrium bond angles have been determined experimentally and supported by extensive ab-initio calculations.\textsuperscript{184} Several physical methods have been used to provide direct information about the spin multiplicity. Among these techniques are, for example, electron paramagnetic resonance (EPR),\textsuperscript{185} electron nuclear double resonance (ENDOR),\textsuperscript{187} and optical spectroscopy, either in low temperature glasses\textsuperscript{188} or in the liquid phase with increasing time resolution.\textsuperscript{189}

Since triplet carbenes contain two unpaired electrons, one in a (σ) and one in a (π) orbital, at the same carbon atom, geometrical isomerism should be feasible if the divalent carbon can be held rigidly in two different orientations of an asymmetric environment. There are many reported examples in which the divalent carbon was held rigidly by conjugation of its partially filled π orbital with an adjacent π system. Geometric isomerism has been observed in carbenes in which the divalent carbon is conjugated with aryl, vinyl, or carbonyl moieties.\textsuperscript{190} The two naphthylmethylene (102a,b) were the first carbenes for which geometrical isomerism was observed.\textsuperscript{191}

\begin{align*}
\text{102a} & \quad \text{102b} \\
\begin{array}{c}
\text{H} \quad \text{C}^+ \quad \text{H} \\
\text{\includegraphics[width=0.2\textwidth]{naphthylmethylene102a.png}} \quad \text{\includegraphics[width=0.2\textwidth]{naphthylmethylene102b.png}}
\end{array}
\end{align*}

These results established beyond any doubt that these triplet carbenes are bent.\textsuperscript{190}

Although one might expect bending of the carbene molecule to cause a change of the lowest electronic state from triplet to singlet as the electrons pair in the lower -
energy orbital (σ), the ground state remains triplet (for methylene). The singlet remains the state of higher- energy due to the energy cost because of electron repulsion if both electrons are paired in the σ orbital; unless the energy gap between the σ and p is larger than this cost the electrons will remain in the separate orbitals with spins parallel. Changes in the energies of these orbitals could invert the state spin multiplicities from their usual order of triplet below singlet. There are two distinct ways to affect the energies of these orbitals. The first is through a change in geometry, primarily the bond angle at the carbene carbon atom. Calculations predict that as this angle contracts, the energy of the singlet carbene decreases relative to that of the triplet. Angle reduction was sufficient to make the singlet the ground state in three membered rings. The second variable that controls the singlet - triplet gap is related to electronic perturbation. The ground state of CXY is determined by which substituents X and Y are used. It is widely believed that the singlet state is stabilized by electron withdrawing substituents and by substituents donating π(p) lone pairs to the empty carbenic p(π) orbital. The triplet state is favored by substituents more electropositive than carbon and by sterically bulky substituents, which prefer large X-C-Y angles.

1.2.2.1.0 ■ Substituted carbenes

According to Houk the mixing of a relatively high-lying π orbital of a donor substituent with the p(π) carbene orbital, will stabilize the singlet (103a) more than the triplet, since two π electrons from the donor are stabilized through this mixing. Although such a mixing occurs in the triplet (103b), the stabilization is less due to a partial counteracting destabilization of one π electron of the carbene (Figure 9).

On the other hand, the influence of π-acceptors depends on the geometry of the carbene. If the acceptor-π* orbital is parallel to the carbene p(π) orbital (Figure 10),
then the acceptor can only stabilize the triplet (104a). Putting the $\pi^*$ orbital perpendicular to the carbene $p(\pi)$ orbital, i.e. parallel to the carbene $\sigma$ orbital, permits greater stabilization of the singlet (105b) than the triplet (105a), (Figure 11).\(^{194}\)

Goddard, \textit{et. al.} have found a correlation between the singlet - triplet splitting and the $sp^n$ hybridization in non-bonding $\sigma$ orbitals of carbenes.\(^{192}\) The more
electronegative substituents induce an increase of the s-character in the non-bonding 
\( \sigma \)-orbital for the triplet state as compared to the singlet.\textsuperscript{192}

Rough estimates of carbene singlet - triplet gaps can be predicted by using 
Houk's simple relationship, (eq 8).\textsuperscript{194}

\[
E(s) - E(t) = 84.5 \Sigma \sigma_R^\circ + 13
\]

The empirical resonance substituent constant, \( \sigma_R^\circ \), is available for a large number of 
substituents.\textsuperscript{196}

Spectroscopic studies on a variety of carbenes led to the conclusion that 
halomethylenes are ground state singlets with bond angles in the range 100-110\(^\circ\), whereas 
methylenes, arylmethylenes, and alkylmethylenes are ground state triplets with bond 
angles 130-150\(^\circ\) and have excited singlet states with angles of 100-110\(^\circ\).\textsuperscript{192,194} 
Biarylmethylenes have a smaller singlet - triplet splitting (S-T gap for diphenylmethylenes 
\( \approx 5 \text{ kcal mol}^{-1}, 21 \text{ kJ mol}^{-1} \)), and some are ground state singlets.\textsuperscript{197} At present, the singlet 
- triplet gap in the parent methylene can be considered to have been determined with 
considerable accuracy to be 9 kcal mol\(^{-1}\) (38 kJ mol\(^{-1}\)).\textsuperscript{183,184,198}

1.2.3.0.0 ■ **Reactions of carbenes**

Singlet and triplet electronic configurations of carbenes are reflected in their 
physical properties. Other than the two different geometries (as seen in section 1.2.2.0.0), 
as well as the diamagnetism of the singlet compared to the paramagnetism of the triplet, 
since the 1950's it has been recognized that the singlet and triplet carbenes can be readily 
distinguished by their chemical reactivities.\textsuperscript{172}

Among the characteristic reactions of carbenes are singlet triplet intersystem
crossing, addition to unsaturated bonds and insertion into single bonds, such as C-H, C-C,

<table>
<thead>
<tr>
<th><strong>Table 1. Typical carbone reactions</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S-T INTERCONVERSION:</strong> XYC((\uparrow\downarrow)) (\rightarrow) XYC((\uparrow\uparrow))</td>
</tr>
<tr>
<td><strong>INSERTION:</strong> XYC: + R-H (\rightarrow)</td>
</tr>
</tbody>
</table>
| **ADDITION:** XYC: + \(\begin{array}{c}
\text{X} \\
\text{Y}
\end{array}\) \(\rightarrow\) |
| **DIMERIZATION:** 2 XYC: \(\rightarrow\) XYC=XY |
| **REARRANGEMENT:** |

C-O, C-Cl, Si-Cl, Si-H, N-H or O-H, (Table 1). Classical mechanistic criteria, particularly the fate of stereochemistry, chirality, or an isotopic label, have been instrumental in establishing the exact mechanisms for reactions of various carbenes with several types of substrates.

The chemical behavior of a carbone depends on its electronic state. The state in which the carbone is produced depends on the substituents (Section 1.2.2) and on the method of generation: singlets normally form in thermal reactions and in photochemical reactions without triplet sensitizers; triplets form by irradiation in the presence of a sensitizer (Scheme 15).

It is widely believed that spin-state-specific mechanisms can be assigned to the reactions of carbenes. For example, many carbenes with heteroatom substituents have
singlet ground states (Section 1.2.2.1.0), the excited triplet states being experimentally inaccessible. These carbenes undergo concerted, stereospecific cycloadditions with alkenes\textsuperscript{199} and insert readily into O-H bonds.\textsuperscript{172,200,201} Stepwise, nonstereospecific addition to alkenes, reaction with oxygen,\textsuperscript{202} and hydrogen atom abstraction\textsuperscript{203} are characteristic of carbenes that react from their triplet ground states.\textsuperscript{172,204} Other spin-state-specific reactions have been characterized and used to differentiate \textsuperscript{1}CH\textsubscript{2} and \textsuperscript{3}CH\textsubscript{2}. With chloroform, for example, \textsuperscript{1}CH\textsubscript{2} undergoes mainly \textit{net} C-Cl bond insertion, while \textsuperscript{3}CH\textsubscript{2} undergoes mainly C-H bond insertion.\textsuperscript{205} Moreover, Creary reported the regioselectivity in the addition of singlet and triplet carbenes to 1,1-dimethylallene as a probe for carbene multiplicity.\textsuperscript{206} The singlet carbenes add preferentially to the more substituted bond of 1,1-dimethylallene, to give methylenecyclopropanes as the major products. In contrast, the triplet carbenes gives the thermodynamically preferred regioisomeric addition products, isopropylidenecyclopropanes.\textsuperscript{206}

1.2.3.1.0 ■ Singlet-triplet interconversion

It appears that singlet - triplet interconversion of the parent methylene is slow enough for specific interception of each spin state.\textsuperscript{172,207} Many substituted carbenes, aryl carbenes for example, exhibit reactions commonly associated with both the singlet and
triplet states, for example, addition to alkenes with partial loss of configurational integrity.\textsuperscript{204,208,209} It appears that the spin-state equilibration (intersystem crossing) of arylcarbenes is faster than (or competitive with) chemical reactions (Scheme 15). In solution, at room temperature, the singlet to triplet conversion of diarylcarbenes has been found\textsuperscript{210,211} to proceed with a rate constant of the order of $10^{10}$ s$^{-1}$, while the reverse triplet to singlet conversion step is roughly 3 orders of magnitude slower. A similar value of $k_{ST}$ has been reported for fluorenylidene,\textsuperscript{212} boraanthrylidene,\textsuperscript{208} and anthronylidene\textsuperscript{204}. These singlet carbenes may (and often do) intersystem cross to a lower energy triplet before they are consumed in bimolecular reactions. On the other hand, if the singlet - triplet energy gap is small, equilibration and reaction from the upper state does occur. For example, although phenylcarbene has a triplet ground state,\textsuperscript{213} the reaction of phenylcarbene with alkenes gives cyclopropanes with greater than 95 \% stereospecificity.\textsuperscript{214} This was explained in terms of rapid singlet - triplet equilibration and higher reactivity of the singlet towards alkenes.\textsuperscript{215} Moss and Dolling demonstrated that this stereospecificity was not affected by dilution.\textsuperscript{216} Creary found that even sensitization did not affect the stereospecificity.\textsuperscript{217} Very recently, Kirmse reported almost no effect of sensitization on the stereospecificity of addition of phenylcarbene to (E)-$\beta$-deuterio-$\alpha$-methylstyrene, which is considered an efficient triplet trap.\textsuperscript{218} Thus, even with a potent acceptor, triplet $\rightarrow$ singlet crossing is faster than the intermolecular addition of triplet phenylcarbene. However, in a recent communication, Kirmse and Houk reported rapid intramolecular addition reaction of triplet arylcarbenes with double bonds (106).\textsuperscript{219} Therefore, in contrast to intermolecular addition reactions, the intramolecular triplet phenylcarbene addition reaction is faster than the triplet $\rightarrow$ singlet interconversion.\textsuperscript{218,219} Thus, the carbene (106) addition was moderately stereoselective in direct photolysis but converged to give an equal mixture of the two cyclopropane isomers (108) upon sensitization.\textsuperscript{218,219} Moreover, direct photolysis in methanol (singlet-spin-specific
reagent) led to predominant intermolecular OH insertion to form 107; sensitization enhanced the formation of the cyclopropane 108 at the expense of the singlet product, 107,

(eq 9)\(^{218}\)

In a study on the environmental factors affecting the dynamics of the singlet-triplet interconversions, Eisenthal reported an increase in the intersystem crossing rate constant \(k_{ST}\) of diphenylcarbene with decreasing polarity of the solvent. For example, \(k_{ST} = 3.2 \times 10^9 \text{ s}^{-1}\) in acetonitrile, and \(k_{ST} = 10.5 \times 10^9 \text{ s}^{-1}\) in hydrocarbons.\(^{220}\) A similar observation of the rate constant for formation of the ground triplet of another carbene, fluorenylidene, in two solvents has also been reported.\(^{221}\) The solvent effect on the stereospecificity of formation of 108 from 106 was rather small.\(^{218}\) Eisenthal, \textit{et. al.} used the electronic nature of the singlet and triplet states to explain the solvent effect found on the rate of singlet to triplet intersystem crossing of diphenylcarbene.\(^{220}\) The singlet state, being highly polar (in fact it is often described as \textit{zwitterionic})\(^{222}\), will be strongly stabilized in polar solvents whereas the less polar triplet will only experience a weak stabilization.\(^{220}\) Thus, it is expected that the singlet-triplet energy gap, \(\Delta E_{ST}\), will decrease as the solvent polarity increases. This smaller gap can arise in principle either from forces that stabilize the singlet more than the triplet, or by forces that destabilize the triplet more than the singlet, (Figure 12)\(^{208}\) (Section 1.2.2). Moreover, it has been widely observed that in a relatively inert solvent (benzene, for example) in the presence of a reagent specific for the singlet carbene (methanol, for example) equilibration with and reaction from the singlet state occurs, even if the ground state is the triplet.\(^{204}\) Furthermore, if the intermolecular and intramolecular factors affecting the intersystem
crossing dynamics of the carbene are in favor of the singlet, the singlet can be electrophilic, nucleophilic or ambiphilic.

1.2.3.2.0 ■ Addition to alkenes / Carbenic selectivities

It has long been known that most carbenes are electrophilic species.\textsuperscript{172} Doering described methylene as "the most indiscriminate reagent known in organic chemistry".\textsuperscript{223} However, electron-donor substituents on the carbene can render it ambiphilic or even nucleophilic.\textsuperscript{224,225} From theory, CH\textsubscript{2} has a freer p-orbital than CCl\textsubscript{2}, and therefore CH\textsubscript{2} would be classified as more electrophilic and less selective than CCl\textsubscript{2}.\textsuperscript{172,226} Skell showed that alkenes react with CCl\textsubscript{2} in the order: tetraalkyl > trialkyl > monoalkyl.\textsuperscript{172,226} Moss has systematized this reactivity order for a variety of carbenes, and has introduced a selectivity index, m\textsubscript{CXY}, (eq 10).\textsuperscript{227,228}

\[
\log \left(\frac{k_i}{k_0}\right)_{CXY} = m_{CXY} \log \left(\frac{k_i}{k_0}\right)_{CCl_2}
\]

In the first term of eq 10, k\textsubscript{i} are the rate constants for addition of the carbene under investigation, :CXY, to the six di-, tri-, and tetra- methylethenes which constitute a standard set of alkenes, and k\textsubscript{0} is the rate constant for its reaction with (CH\textsubscript{3})\textsubscript{2}C=CH\textsubscript{2}. The
logarithms are then plotted against similar measurements for \( :CCl_2 \) and the slope of the resulting line is the selectivity index (eq 10). Furthermore, Moss correlated the dependence of \( m_{CXY} \) on the \( X^- \) and \( Y^-\) substituents to \( \sigma^* \) and \( \sigma_i \) (eq 11).

\[
m_{CXY} = -1.10 \sum_{X,Y} \sigma^*_R + 0.53 \sum_{X,Y} \sigma_i - 0.31
\]

From eq 11 Moss constructed a carbene selectivity spectrum, locating both known and uninvestigated carbenes according to the magnitude of \( m_{CXY} \) (Figure 13). Houk showed that these room temperature selectivities of carbenes (\( m_{CXY} \)) are correlated with carbene stabilities. Thus, whereas \( CH_2 \) is unselective, donor substituents stabilize carbenes and increase their selectivities. However, eq 11 was calibrated with carbenes that are primarily electrophilic and alkenes that are primarily electron rich; thus, eq 11 cannot be expected to correlate the selectivities of nucleophilic carbenes quantitatively. More recently, Moss reported the FMO approach as a general method to rationalize carbenic philicity in a semiquantitative fashion.

1.2.3.2.1 Mechanism of the \([1+2]\) cycloaddition
In the [1+2] cycloaddition of any singlet carbene to an alkene, the carbene is inherently both an electrophile and a nucleophile. Figure 14 shows the geometry of the

![Diagram of HOMO-LUMO interaction](image)

Figure 14a. $\Delta \varepsilon_E$

Figure 14b. $\Delta \varepsilon_N$

Figure 14c. $\Delta \varepsilon_E = \Delta \varepsilon_N$

HOMO-LUMO interaction that occurs on bringing a carbene and an alkene together.\(^{228}\)

The carbene HOMO is the orbital $\sigma$ and the LUMO is the orbital $p$ discussed earlier. What determines the carbene’s expressed philicity is whether, in the transition state, it is the $[\text{LUMO}_{\text{carbene}} - \text{HOMO}_{\text{alkene}} = \Delta \varepsilon_E] (p_{\text{carbene}} - \pi_{\text{alkene}})$, electrophilic carbene orbital interaction (Figure 14a) or the, $[\text{HOMO}_{\text{carbene}} - \text{LUMO}_{\text{alkene}} = \Delta \varepsilon_N] (\sigma_{\text{carbene}} - \pi_{\text{alkene}}^*)$, nucleophilic carbene orbital interaction that is dominant (Figure 14b).\(^{229}\) If both interactions are comparably important, the carbene will exhibit ambiphilic selectivity (Figure 14c).\(^{229}\) According to FMO theory, the stabilization of a cycloaddition transition state (TS) depends inversely on the differential energies of the interacting "frontier molecular orbitals" (Figure 14).\(^{69,229}\)

Placing a basic unshared pair of electrons on an
atom next to the carbene center will raise the carbene LUMO (p-orbital); \( \Delta \varepsilon_E \) becomes larger, the reaction is slower and more selective. If the adjacent lone pair is basic enough, the dominant interaction will become carbene HOMO with alkene LUMO (Figure 14b); the carbene is now nucleophilic.\textsuperscript{229} Houk and Rondan calculated the geometry of the transition state using STO-3G basis sets.\textsuperscript{224} They discovered a relationship between the carbenic philicity and the angle \( \alpha \), the calculated angle of tilt of the CXY plane with respect to the original ethene plane at the addition transition state (Figure 15).\textsuperscript{224,228} For a

![Figure 15](image)

*Figure 15.*

*pure* electrophilic approach, \( \alpha \) would be 0° (Figure 14a); a *pure* nucleophilic approach would have \( \alpha = 90° \). In fact, \( \alpha \) is 36° for CCl\(_2\) and increases smoothly to 58° for C(OH)\(_2\).\textsuperscript{224,228}

Another question posed for the alkene addition reaction is one of stereochemistry. If the carbene is a singlet the ring formation would be concerted; thus, the addition would be stereospecific.\textsuperscript{199b,230} With a triplet carbene, however, the spin state of one of the electrons must change (110) before bonding can be completed. Thus, a mixture of products should result if intersystem crossing in the intermediate (109) takes long enough for bond rotation to occur (111) (Scheme 16).\textsuperscript{230} It should be noted that the singlet is not required to react stereospecifically simply because it can, nor must the triplet necessarily add with loss of stereochemistry.\textsuperscript{230,231} A carbene-alkene dipolar adduct (113)\textsuperscript{232} has been proposed by Doyle and Liu in an attempt to explain the
non-stereospecific addition reaction of chlorophenylcarbene with diethyl maleate (Scheme 16).

Thus, bond rotation can occur to form 114. Turro and Moss have described weakly interacting carbene-alkene complexes as encounter pairs that are stabilized by weak charge-transfer interactions.233,234 Also, Liu has proposed a similar carbene-alkene complex to explain alkene-dependent 1,2-hydrogen migration of benzylic alcohohalocarbenes.235-237 Recently, Wiberg, et al. have proposed an electron transfer mechanism to explain the predominant inversion of configuration in an intramolecular
carbene addition to an alkene. This mechanism was based on Hoffmann's description of an unsymmetrical activated complex in the carbene-alkene reaction and on Zurawski's ab initio calculations, which suggested that the reaction began via an electron transfer from the alkene to the carbene, followed by a reverse transfer while the second bond was being formed. This description suggests that a two-step process proceeding via a trimethylene diradical may be energetically close to the normal concerted (not synchronous) process.

1.2.3.2.2 ■ Energetics of the [1+2] cycloaddition

Experimental data have indicated that enthalpic variations do not always control reactivity and selectivity. Skell and Cholod reported that the relative rates of CCl₂ cycloadditions to alkylethylenes were paralleled by the differences in entropies, not enthalpies, of activation. Skell proposed that more reactive alkenes have earlier, loose, entropy-dominated transition states. Turro and Moss calculated the absolute rate constants, k_{abs}, for the addition of several arylhalocarbenes to alkyl-ethenes (=10⁻⁴⁻⁻¹⁰ M⁻¹s⁻¹). The dependence of k_{abs} on temperature was examined; Arrhenius correlations afforded negative activation energies for the reactions of PhCCI with trimethyl- and tetramethyl-ethenes. Also, measurements of k_{abs} as a function of pressure afforded volumes of activation (ΔV^*). Values for PhCCI addition are = -14 ± 3 cm³mol⁻¹. For comparison values of ΔV^* for Diels-Alder reactions often reach = -40 cm³mol⁻¹. According to Moss the smaller values of ΔV^* for carbene reactions are consistent with early, loose transition states where bond formation is not far advanced. To interpret the negative E_a, the increase in rate constant with a decrease in temperature, two approaches have been suggested. The first postulates an intermediate, reversibly-formed carbene/alkene π-complex. Conversion of this complex to products involves a second
barrier which is below the energy of the reactants\textsuperscript{234,241}. This π-complex has later been adopted by Liu et al.\textsuperscript{235-237} (Section 1.2.3.2.1). The second interpretation of the origin of the negative $E_a$ was provided by Houk.\textsuperscript{242,243} According to Houk, reactions of very energetic species are likely to have negative activation energies. In such cases, there are no enthalpic barriers and $ΔH$ decreases continually along the reaction coordinates. For reaction of CBr$_2$ with Me$_2$C=CMMe$_2$, for example, there are only entropy imposed barriers. Nevertheless, selectivity can still arise, due to the substantial free energy barriers to such addition ($ΔG^e > 0$) because of a dominant unfavorable entropy of activation.\textsuperscript{242,243} The role of entropy has been postulated earlier by Skell\textsuperscript{226} and more recently by Giese.\textsuperscript{244} However, carbene-alkene complexes have never been observed\textsuperscript{229,235-237} experimentally, nor is their existence supported by Houk's calculations,\textsuperscript{242} which suggest that no stable complexes, other than possible solvent "cage" complexes, are formed between alkenes and CCl$_2$ or more reactive carbenes.\textsuperscript{242}

1.2.3.2.3  ■  [1+2] Versus [1+4] Cycloaddition

The normal mode of carbene cycloaddition to dienes and polyenes is [1+2]. Very few examples of the [1+4] addition have been reported.\textsuperscript{245} Although the [1+4] chelotropic reaction is symmetry allowed, the [1+2] addition is preferred experimentally as well as theoretically.\textsuperscript{246} Consequently, reports of [1+4] addition must be viewed skeptically, because their occurrence could be due to addition of a triplet carbene,\textsuperscript{245d} to form an intermediate ylide,\textsuperscript{247} or to the vinylcyclopropane - cyclopentene rearrangement.\textsuperscript{172,245a}

1.2.3.3.0  ■  Insertion reactions

1.2.3.3.1  ■  C-H Insertion
The C-H insertion of singlet carbenes is generally believed to proceed via a one-step process involving a three-center cyclic transition state 115 (eq 12).\textsuperscript{172,248}

\[
\begin{align*}
\text{C:} \uparrow\uparrow & \quad + \quad \text{H} \\
\rightarrow & \quad \text{C}:::\text{C}:::\text{H} \\
\rightarrow & \quad -\text{C}::\text{C}::\text{H} & (12)
\end{align*}
\]

115

Therefore, singlet-state carbenes insert into the C-H bond with retention of configuration. The triplet carbene would behave as a free radical; insertion is known to proceed via hydrogen abstraction followed by coupling of the radical pair 116 (eq 13) and therefore is usually accompanied by large amounts of products derived from all possible radical reactions.

Theoretical calculations by Hoffmann, \textit{et. al.}\textsuperscript{249a} suggest that attack of the singlet carbene on the C-H bond occurs, through the vacant \textit{p} orbital (electrophilic attack), at the hydrogen end of the C-H bond, and that transfer of the hydrogen to the incoming \textit{CH}_2 runs ahead of C-C bond making.\textsuperscript{249}

Intramolecular C-H bond insertion by carbenes to form rings is also known.\textsuperscript{172a} Ring formation occurs with the ring size preference 5 > 6 > 3 >> 4.\textsuperscript{172a,250}

Insertion of the carbene into an adjacent C-H bond, better known as 1,2-hydrogen migration, leads to alkenes (eq 14). These rearrangements take place from the singlet state, and the preferential stereochemistry is that shown in 117.\textsuperscript{251} The migrating hydrogen is aligned with the LUMO (\textit{p}-orbital) of the singlet carbene.\textsuperscript{181}

Liu, \textit{et. al.} reported substituent effects in the 1,2-H migration in
benzylchlorocarbene (X-C₆H₄CH₂-C-Cl). The rearrangement was found to accelerate with electron-donating groups (CH₃, OCH₃) and to decelerate with electron-withdrawing groups (Cl).²³⁶ According to Liu this result confirms the hydride-like character of the 1,2-H shift, since electron-donating groups can better stabilize the partial positive charge developed in the transition state.²³⁶

Theoretical calculations have deduced energy barriers to this rearrangement ranging from 0 to 27 kcal mol⁻¹.²⁵² Recently, Liu, et. al. provided an estimate of 1.1±1 kcal mol⁻¹ for the height of the barrier to a 1,2-H shift in a dialkylcarbene.²⁵³ Earlier, Liu, et. al. estimated the barrier to be 6.4±2 and 4.7±2 kcal mol⁻¹ in Ph-CH₂-C-Cl and Ph-CH₂-C-Br, respectively.²³⁷ The absolute rate constant for the 1,2-H migration in benzylbromocarbene has been determined to be kₐₑₛₜ ²₅⁰ = 5.6 x 10⁷ s⁻¹.²⁵⁴

Several factors affect the product E/Z-isomer ratio. It is believed that a carbene solvent complex, if formed, would be expected to cause a decreased preference for the less stable olefin isomer.¹⁷²ι

A similar 1,2-carbon migration has been observed but only if constraints such as ring strain are imposed on the reacting system.²⁵⁵-²⁵⁷ However, intermolecular carbene insertion into C-C single bonds has eluded discovery.²⁵⁸

1.2.3.3.2 • C-H / C-Cl Insertion

It is widely believed that a singlet carbene abstracts a chlorine from HCl₂ (eq
15) while a triplet abstracts a hydrogen (eq 16).\(^{187}\) According to Roth, the rate of the
electrophilic attack of a singlet carbene on a chlorocarbon should depend markedly on the
nature of the carbene-\(\alpha\) substituents; electron withdrawing groups, for example, would
reduce the energy of the transition state 120. Roth explained that H-abstraction by triplet
carbene should not show similar substituent effects.\(^{187}\) Warkentin \textit{et al.}\(^{256}\) reported that a
carbene-\(\alpha\) substituent that can stabilize a positive charge (a cyclopropyl moiety, for
example) reduces a carbene’s electrophilicity and attack occurs on the hydrogen in
HCCl\(_3\).\(^{256}\) Thus, the overall product of attack of singlet dicyclopropylcarbene on HCCl\(_3\)
was that of C-H insertion. Warkentin suggested a nonsynchronous concerted process
involving charge separation in the sense of 121 but with a geometry resembling 122.\(^{256}\)

\[ \text{1.2.3.3} \text{ } O=I I \text{ Insertion} \]

It has long been held that the reaction of carbenes with alcohols to give ethers
is characteristic of the singlet state.\(^{172}\) Triplet carbenes are believed to abstract hydrogen
atoms from alcohols to form radical pairs that eventually go on to products. This simple
description of spin-selective carbene chemistry has recently been challenged by the
suggestion that triplet diphenylcarbene reacts in one step with MeOH to give
diphenylmethyl methyl ether. Spin inversion is thought to occur as the system
progresses along the reaction coordinate. This latter hypothesis has not been generally
accepted by the carbene community. Spin-state equilibration of arylcarbenes
followed by singlet state reaction with O-H continues to be the preferred pathway. In
any event, the formation of ethers proceeds much faster from singlet than from triplet
carbenes. The rates at which spin-equilibrated carbenes react with O-H bonds decrease
sharply as $\Delta G_{ST}$ increases.

Three mechanistic sequences have been considered likely for the reaction of

![Scheme 18](image)

Scheme 18

singlet carbenes with O-H bonds (Scheme 18). There is no experimental support for the
concerted three-center interaction, *path-c*. The choice of either the ylide or the
carbocation route appears to depend primarily on the electrophilic versus nucleophilic
character of the carbene. Experimental support for *path-a* has been reported for
acceptor-substituted vinylcarbenes, cyclopentadienylidene, and fluorenylidene. *Path-b* has also been demonstrated for the reaction of donor-substituted vinylcarbenes,
cycloheptatrienylidene, and more recently by the direct spectroscopic observation of
carbenium ions from the reaction of carbenes with methanol.\textsuperscript{245,267}

Generally the O-H insertion of singlet carbenes is very efficient and proceeds at a rate near the diffusion controlled limit.\textsuperscript{264} Recently, Moss reported the observed \textit{pseudo-first-order} rate constants for (MeO)\textsubscript{2}C: decay in 1M solutions of alcohol in CH\textsubscript{3}CN, reflecting the carbene's reactivity as a function of the alcohol's structure and acidity (Table 2).\textsuperscript{268} FCOMe was much less reactive towards hexafluoroisopropyl alcohol

<table>
<thead>
<tr>
<th>substrate</th>
<th>pK\textsubscript{a}</th>
<th>(K_{eq}, \text{s}^{-1} \text{ (MeO)}\textsubscript{2}C: )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH\textsubscript{3}CH\textsubscript{2}OH</td>
<td>15.90</td>
<td>3.2 ± 0.9 \times 10\textsuperscript{4}</td>
</tr>
<tr>
<td>CH\textsubscript{3}OH</td>
<td>15.54</td>
<td>8.8 ± 0.2 \times 10\textsuperscript{4}</td>
</tr>
<tr>
<td>CICH\textsubscript{2}CH\textsubscript{2}OH</td>
<td>14.31</td>
<td>9.1 ± 1.0 \times 10\textsuperscript{5}</td>
</tr>
<tr>
<td>FCH\textsubscript{2}CH\textsubscript{2}OH</td>
<td>14.20</td>
<td>2.3 ± 0.2 \times 10\textsuperscript{6}</td>
</tr>
<tr>
<td>F\textsubscript{2}CCH\textsubscript{2}OH</td>
<td>12.37</td>
<td>6.3 ± 0.9 \times 10\textsuperscript{7}</td>
</tr>
<tr>
<td>(F\textsubscript{2}C)\textsubscript{2}CHOH</td>
<td>9.30</td>
<td>6.7 ± 0.7 \times 10\textsuperscript{8}</td>
</tr>
<tr>
<td>CH\textsubscript{3}COOH</td>
<td>4.76</td>
<td>2.4 ± 0.4 \times 10\textsuperscript{9}</td>
</tr>
</tbody>
</table>

Table 2. Pseudo-first-order rate constants for reaction of dimethoxycarbene with 1M hydroxyl substrates in CH\textsubscript{3}CN solution at 20°.

than (MeO)\textsubscript{2}C: (K\textsubscript{eq} = 9 \times 10\textsuperscript{3} \text{s}^{-1} for carbene decay in 1M ROH / CH\textsubscript{3}CN).\textsuperscript{268}

Scialiano, \textit{et. al.} reported a hydrogen bonding effect in the insertion reaction of arylchlorocarbenes with alcohols. Hydrogen bonded oligomers, which are increasingly formed as the methanol concentration is increased, are substantially more reactive towards the carbene than methanol monomers.\textsuperscript{269} The authors presumed a decrease in O-H bond dissociation energy with H-bonding.\textsuperscript{269} A solvent effect was observed; the efficiency of methanol as a quencher was reduced in acetonitrile compared to isooctane as a solvent. This solvent effect was explained by the ability of acetonitrile to form H-bonds with MeOH and hence, decrease the abundance of methanol oligomers.\textsuperscript{269} The rate constant for the reaction of p-methoxyphenylchloro carbene with methanol oligomers was (4.3±0.4) \times 10\textsuperscript{9} \text{M}^{-1}\text{s}^{-1}(per methanol unit). The reaction rate constant with methanol monomer was 2 \times 10\textsuperscript{7} \text{M}^{-1}\text{s}^{-1} in isooctane and 6.5 \times 10\textsuperscript{6} \text{M}^{-1}\text{s}^{-1} in acetonitrile. The activation energy \(E_a = -4.7\pm0.3 \text{ kcal mol}^{-1}\) was obtained for the reaction of
p-methoxyphenylchloro carbene with 0.23 M methanol in acetonitrile. The activation energy for similar reaction with tert-butyl alcohol was $E_a = +3.23 \pm 0.60$ kcal mol$^{-1}$, reflecting the dominant role of steric effects.\textsuperscript{172,269,*}

1.2.4.0.0 ■ Formation of carbenes

The methods of carbene generation have been investigated in detail.\textsuperscript{172} The most widely used methods are summarized in Table 3.\textsuperscript{172} Other methods are also known; cyclopropenes (126) are known to undergo thermal or photochemical reversible ring

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{Table 3. Some methods for the generation of carbenes.} & & & & & \\
\hline
12 & CHCl$_3$ + RO$^-$ & $\xrightarrow{k_1 \rightarrow k_2}$ & ROH + Cl$_3$C$^-$ & Cl$^-$ + Cl$_2$C$^-$ & \\
13 & HR$^1$R$^2$CX + M & $\rightarrow$ & R$^1$R$^2$CMX & $\rightarrow$ & MX + R$^1$R$^2$C$^-$ \\
\text{X=Halogen} & & & & & \\
\text{M= RLi, RSn, Zn(Cu), (form carbenoids); Hg (forms free carbenes)} & & & & & \\
14 & & & & & \\
\hline
15 & \begin{array}{c}
\text{R}\text{^1} \\
\text{R}\text{^2}
\end{array} & \text{C} & \text{N} & \text{N} & \text{Ts} & \begin{array}{c}
\text{base} \\
\Delta
\end{array} & \begin{array}{c}
\text{R}\text{^1} \\
\text{R}\text{^2}
\end{array} & \text{C} & \text{N} & \text{N} & \text{Ts} & \begin{array}{c}
\text{hu, or} \\
\Delta
\end{array} & \text{Ts}^- + [16] \\
\hline
16 & & & & & \\
\hline
17 & & & & & \\
\hline
\end{tabular}
\end{table}

\textsuperscript{* For competitive insertion and 1 or addition experiments see reference 270.}
\textsuperscript{* For a more detailed review on the carbene reactions see reference 172.}
opening to produce vinyl carbenes (127). The carbene 127 is usually a planar ground state triplet, but the initial species from thermal (or photochemical) cyclopropene ring opening must be a singlet.

In most cases the ring opening only occurs at a reasonable rate at 150 - 180°C. However, if X or Y is an electron withdrawing group, with R and Z being alkyl groups, the ring opens at ambient temperatures or below. Electron withdrawing groups at C₃ (R and/or Z) should slow down the ring opening. This destabilizing interaction could be due to the allylic interaction with the empty p-orbital of the developing σ² carbene; 128 represents the extreme of charge separation.

The cyclopropene - vinylcarbene interconversions can be viewed as electrocyclic reactions. The vinylcarbene can be trapped with an alkyne to generate another cyclopropene which can be re-opened and trapped and so on...

Each of the numerous methods for carbene generation has its limitations. Up-to-date there is no general method, but all methods are complementary. Except for a few exceptions, carbenes have been regarded as short-lived and highly reactive intermediates; therefore, the carbenes should be generated in situ. Thus, mildness is essential.

The diazirine and the diazo compounds are very important sources of carbenes. They both share the formation of a nitrogen molecule (bond energy 226 kcal.mol⁻¹) as a large driving force to carbenes. However, both compounds are dangerous to prepare and are not safe to handle. A third class that shares the "nitrogen" driving force, not as yet well recognized, is the Δ³-1,3,4-oxadiazoline system. Oxadiazolines are
easy to prepare, generally stable at room temperature, and reasonably safe to handle. They lose nitrogen thermally to produce carbonyl ylides, which can fragment to produce carbenes. The following section will focus on the oxadiazoline \( \rightarrow \) carbonyl ylide \( \rightarrow \) carbene process.

1.2.4.1.0 \( \textbf{Oxadiazoline} \rightarrow \textbf{carbonyl ylide} \rightarrow \textbf{carbene} \)

Although the \( \Delta^3\)-1,3,4-oxadiazoline ring system has been known since the 1960’s,\(^{276,277}\) it wasn’t until recently that oxadiazolines have been recognized as good carbene precursors.\(^{278-281}\)

The mechanism of thermolysis of the \( \Delta^3\)-1,3,4-oxadiazolines has been investigated. Small solvent effects and small aryl substituent effects on the rate constants for thermolysis were interpreted in terms of concerted extrusion of \( \text{N}_2\).\(^{282}\) A stepwise scission of the C-N bonds has also been suggested\(^{283}\) but later ruled out.\(^{284}\) The formation of ylides from the thermal decomposition of \( \Delta^3\)-1,3,4-oxadiazoline, is now well established.\(^{276-282}\) Warkentin, \textit{et. al.} were able to trap the ylide generated from an oxadiazoline with methanol-d\(_4\); thus, providing direct evidence for the intermediacy of a carbonyl ylide.\(^{278}\)

1.2.4.1.1 \( \textbf{Carbonyl ylides: structure and reactions} \)

\[
\begin{align*}
\text{129} & \quad (0^\circ, 0^\circ) \\
\text{130} & \quad (0^\circ, 90^\circ) \\
\text{131} & \quad (90^\circ, 90^\circ)
\end{align*}
\]

(*\text{\textsuperscript{\textdagger}} ) stands for the diradical and dipolar character of the carbonyl ylides

Carbonyl ylides can adopt many different geometries; however, normally
parent 1,3-dipoles are at their energy minimum when they are planar (0°,0°- conformation, 129), a geometry that maximizes π-bonding.285,286 However, Kellog,287 studying the

geometry of thiocarbonyl ylides, concluded, that at least for certain examples, a symmetric thiocarbonyl ylide is not planar (129) but tilted (132). Because of the steric congestion the planar structure is untenable, and congestion is relieved by tilting one of the p-orbitals upwards by an angle φ and the other downward by the same angle. Schwan and Warkentin288 have reached a similar conclusion for some azomethine ylides. Houk286 studied the effect of substituents on the geometry of the carbonyl ylides, and concluded the following:

\[
D \left( \begin{array}{c}
\text{C}_1 \\
\text{O}_2 \\
\text{C}_3 \\
\end{array} \right) A
\]

A donor group at atom 1 or an acceptor at atom 3 causes an increase in the bonding between atoms 1 and 2 and an increase in the antibonding between atoms 2 and 3. This is equivalent to noting that resonance structure 133a is an increasingly important contributor relative to 133b.286

133a

This conclusion implies that rotation becomes successively more easy as donor or acceptor substituents are added, until in the 1,1-diamino- 3,3- dicyanocarbonyl ylide, the (0°,90°) species is more stable than the planar species.

If the (0°,0°) conformation is the major contributor than its fate would be best
represented by (Scheme 19).

However, as the out-of-plane rotation becomes increasingly easy the tendency of the carbonyl ylide to fragment thermally, to the corresponding carbonyl and carbene moieties, increases, with the formation of the more stable carbene governing the direction of fragmentation (Figure 16).

Some substituent effects on the the carbonyl ylide reactions have been studied experimentally by Warkentin et al. It was observed that putting a phenyl group at one
end of the carbonyl ylide considerably reduces the rate of fragmentation of 134a. Instead it cyclizes to the oxirane with an estimated rate constant of $k^{31^\circ} = 1.3 \times 10^6 \text{ s}^{-1}$ and in the presence of a dipolarophile cycloaddition occurs with estimated rate constants of $1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ and $1 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ to norbornadiene and to dimethylacetylene dicarboxylate,

![Chemical Structures]

respectively.\textsuperscript{281} A major competitive process in the case of 134b is fragmentation of the carbonyl ylide to carbonyl compounds and carbenes.\textsuperscript{281} Also, acyloxycarbenes were generated upon thermolysis of 134c and dialkoxycarbenes were generated from 135\textsuperscript{289} and 136\textsuperscript{290} as the major thermolysis products. By thermolyzing 134b in acetone-$d_6$, Warkentin \textit{et. al.} were able to demonstrate that the fragmentation of carbonyl ylides is reversible.\textsuperscript{280}
Chapter 2

RESULTS AND DISCUSSION

And when the shadow fades and is no more, the light that lingers becomes a shadow to another light.

K. Gibran

2.1.0.0.0 ■ OBJECTIVES:

The primary objective of this study was to prepare a mild, bottleable precursor to β-lactam-4-ylidenes. It was felt that the oxadiazoline system would be the best source of carbonyl ylides on the route to carbenes.

The second objective was to study the thermal chemistry of the spiro β-lactam oxadiazoline system. In general, oxadiazolines are known to lose N₂ thermally to form carbonyl ylides which in turn could fragment to form carbenes, (Chapter 1). Exploring the strength of the oxadiazoline system as a β-lactam-4-ylidene generator and the applications of the β-lactam-4-ylidenes as synthons for more elaborate β-lactam structures, were the core aims of the study.

A third objective was to compare the chemistry of the oxadiazoline to the triazoline and the thiadiazoline analogues.

The first section of this chapter deals briefly with the synthesis and reactions of the triazolines and thiadiazolines.

2.2.0.0.0 ■ Triazolines

The phenyliminotriazoline (137), reported by Warkentin and Taguchi, was treated with p-nitrobenzoyl chloride, in dry methylene chloride at room temperature. This led to the formation of the corresponding salt, 138, characterized by its typical infrared
absorptions at 1720 cm\(^{-1}\) (N-C-N), and 1655 cm\(^{-1}\) (C=O, amide). This salt (138) hydrolyzed back to the starting material, 137, when exposed to moisture (eq 17). Amidines are known to form salts easily\(^{292}\) however, formation of a stable covalent bond by nucleophilic attack at the imino-carbon is almost impossible in symmetric amidine systems. This is due to two factors:

i) The tendency to form salts due to the extra stabilization by resonance, 139.

\[ \begin{align*}
139a & \quad \text{R} \quad \text{NH}_2 \\
& \quad \text{NH}_2 \\
\end{align*} \quad \begin{align*}
139b & \quad \text{R} \quad \text{NH}_2 \\
& \quad \text{NH}_2 \\
\end{align*} \]

ii) The tendency to hydrolyze due to the gem-diamino functionality (*masked carbonyl*), (eq 18).

\[ \begin{align*}
\text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \quad \text{R}^4 \quad \text{Nu} \quad \text{H}_2\text{O} \quad \text{O} \\
\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \text{R}^5 \quad \text{Nu} \\
\end{align*} \]

Reduction of the nucleophilicity of one of the nitrogens could reduce the extra
stabilization of an amidine to that of an imine. This suggests that, for such a reaction, a suitable amidine could be one that would form an amidinium ion (140) less stable than corresponding ions from symmetric amidines 139. Therefore, formally the amidine

![Chemical structure](image)

system would become imine-like and could undergo nucleophilic attack on the amidinium cation (140) to form a product less prone to hydrolysis than the product from the parent amidine. It is important to realize that the type of nucleophile is also important. The approaching base should be a poor leaving group for a covalent bond to be affected. However, treatment of 137 with benzoyl cyanide did not lead to reaction, probably because of 137’s reduced basicity. Moreover, it is believed that the imino phenyl group exerts conjugative and inductive effects on the amidinium cation making it less stable.292 Therefore, a more nucleophilic triazoline (141) was synthesized.

2.2.1.0.0 □ Synthesis of 5, 5-dimethyl-4-benzyl-3-benzylimino-Δ1-1,2,4-triazoline (141).

The method employed by Taguchi and Warkentin,291 to synthesize 137 was employed to synthesize the benzyl analogue (141) according to Scheme 20. Oxidation of the N,N'-dibenzyl guanylhydrazone of acetone (146) by lead tetraacetate, LTA, in dry methylene chloride afforded the title compound in 20 % yield, based on the acetone -4-benzyl-thiosemicarbazone 147. The preparation of 146 was achieved via several steps as
outlined in Scheme 20, and as developed by Taguchi and Warkentin\textsuperscript{291} for the phenyl analogue (137). The \textsuperscript{1}H NMR spectrum of the product showed one singlet at $\delta$(ppm) 1.28 for the gem-dimethyl, a strong piece of evidence for the cyclic structure 141. The low field resonance of C-5, $\delta$(ppm) = 101.01, confirms the presence of the azo function (Table 4). Spectroscopic data did not imply the presence of two stereoisomers. Based on previous results for the phenyl analogue,\textsuperscript{291,293} it was assumed that the E-isomer, if
present, would be in minor amounts due to the steric congestion of the benzyllic groups.

2.2.1.1.0 Reactions of 141

2.2.1.1.1 Synthesis of 1-Benzyl-2-(N-p-nitrobenzoyl) benzylamino-2-cyano-3,3-dimethylaziridine (147).

Treatment of 141 with p-nitrobenzoyl cyanide in dry acetonitrile at room temperature gave the aziridine 147 in low yields, with recovery of the unreacted starting material. The $^1$H NMR spectrum of 147 confirms the quaternization of the $sp^2$ ring carbon of 141 by the presence of two singlets at $\delta$(ppm) 1.46 and 1.60. This confirms that the two methyl groups have become magnetically non-equivalent. Further evidence comes from the presence of a pair of distinguishable $ab$-quartets for the benzyllic hydrogens at $\delta$(ppm):

![Scheme 21](image-url)
4.09 (H₃), 5.05 (H₅) J = 15.2 Hz; 4.43 (H₆), 4.59 (H₇), J = 15.1 Hz; this proves the formation of an asymmetric center. The lack of a ¹³C NMR resonance in the 100 - 110 ppm region provides evidence that the product does not have the azo functional group.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Selected ¹³C NMR data for 141 and 147</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(CDCl₃)</td>
</tr>
<tr>
<td></td>
<td>159.34 (C=N)</td>
</tr>
<tr>
<td></td>
<td>101.01 (C₅)</td>
</tr>
<tr>
<td></td>
<td>52.58, 44.61 (CH₂)</td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(CCl₄)</td>
</tr>
<tr>
<td></td>
<td>150.94 (C=O)</td>
</tr>
<tr>
<td></td>
<td>116.01 (C≡N)</td>
</tr>
<tr>
<td></td>
<td>97.62 (C₂), 75.54 (C₃)</td>
</tr>
</tbody>
</table>

(Table 4). Presumably N₂ extrusion from 148 occurred after quaternization of the sp² ring carbon of 141, leading to an azomethine ylide intermediate (149) which underwent rapid electrocyclic ring closure to give 147, (Scheme 21).

2.2.1.1.2 Reaction of 141 with diphenylketene: Formation of N-benzyl-2, 2-diphenylethananamide (153).

Treatment of 141 with diphenylacetyl chloride in the presence of triethylamine (Scheme 22) took a different pathway. It is believed that a (2π + 2π) cyclocondensation reaction occurred to give 150 (Scheme 22) presumably as a transient intermediate, followed by nitrogen loss to give the ylide (151) which led to a 4-amino-β-lactam product (152). Evidence for the β-lactam comes from the infrared absorption of the crude product.
at 1765 cm\(^{-1}\). However, like other 4-amino-\(\beta\)-lactams\(^{58}\) this product is so sensitive to moisture that it hydrolyzes during the work-up to give 153 as the only isolable product. This mode of hydrolysis, breaking the C-C bond in 3,3-diphenyl-4-amino-2-azetidinones as opposed to breaking the C-N bond in 3,3-dimethyl-substituted \(\beta\)-lactams, was observed previously by Bose, et al.\(^{58}\) who proposed the mechanism outlined in Scheme 23. We prefer to assume the presence of the protonated (Et\(_3\)NH\(^{+}\)Cl\(^{-}\) was present) intermediate 152\(^{a}\) (eq 19) instead of 152. This intermediate (152\(^{a}\)) can undergo a unimolecular ring opening to give 152\(^{b}\) which can lead to the product 153. The amido aldehyde, or ketone, (158) was not formed, 153 was the sole product. Rupture of the bond between C\(_3\) and C\(_4\) would form a transient carbanion on C\(_3\) in the Bose mechanism. Such a carbanion is stabilized by a carbonyl and two phenyl groups (154, Scheme 23) (enol form in eq. 19).
Scheme 23
2.3.0.0.0 ■ Thiadiazoline

2.3.1.0.0 □ Synthesis of 5, 5-dimethyl-2-benzylimino-Δ³-1, 3, 4-thiadiazoline (159).

The synthesis of 5,5-dimethyl-2-benzylimino-Δ³-1,3,4- thiadiazoline (159) was accomplished by the oxidation of acetone-4-benzyl-thiosemicarbazone (160), prepared as in eq 20, on active manganese dioxide to give the title compound, 159, in 59 % yield together with 6 % of the thione isomer, 161, as a side product (eq 20). ¹H NMR data showed a gem-dimethyl singlet at δ(ppm) 1.80 for 159 and at δ(ppm) 1.45 for 161. Assignment of 159 and 161 was accomplished through use of the characteristic infrared absorption of the iminothiadiazoline (159) at 1640 cm⁻¹, and that for the triazolinethione (161) at 1300 cm⁻¹.

The aryl analogues of 159 (aryliminothiadiazolines) have been prepared by Landquist and co-workers,²⁹⁴ but the triazolinethione isomers have not been detected previously when manganese dioxide was used as the oxidizing agent.
2.3.1.1.0 ◊ Reaction of 159 with diphenylketene: Formation of Spiro \( \beta \)-lactam thiadiazoline (162) and spiro \( \beta \)-lactam-thiirane (164).

Treating thiadiazoline 159 with diphenylacetyl chloride in the presence of triethylamine at -23°C afforded the spiro-\( \beta \)-lactams 162 and 164 in a ratio of 2.4:1.0 (Scheme 24). In contrast to the presumed 4-amino-\( \beta \)-lactam product (152), the 4-thio-\( \beta \)-lactam products 162 and 164 survived the work-up procedure. Lactam 162 is a stable solid at room temperature, but in solution (chloroform) it loses nitrogen gas slowly to give 164. Mass spectrometry (even CI/MS) failed to give evidence for the presence of \( \text{N}=\text{N} \) in 162. However, \(^{13}\text{C}\) NMR data showed the quaternary ring carbons shifted downfield \( \delta \text{ (ppm)} \) \( C_4 = 134.65, C_6 = 106.77 \) due to the presence of the cis-azo functionality. Surprisingly, the \(^1\text{H}\) NMR spectrum of 162 showed the benzylic protons as accidentally equivalent, \( \delta \text{ (ppm)} \) 4.40 (s, 2H, CH\(_2\)), giving a singlet which turns into an ab-quartet for 164, \( \delta \text{ (ppm)} \) 4.16 (d), 4.86 (d), J= 16.1 Hz. Yamamoto, et al.\(^{295}\) reported the formation of a thiirane by the cycloadDITION reaction of the phenyl analogue of 159, phenyl-iminothiadiazoline, with diphenylketene. However, the same reaction under the
conditions employed for the benzyl analogue 159 did not afford the intermediate spiro β-lactam thiadiazone, the phenyl analogue of 162.

Furthermore, thiadiazone 162 was dissolved in dimethylacetylene dicarboxylate and stirred at room temperature in an attempt to trap the thiocarbonyl ylide intermediate (163) by a 1,3-dipolar cycloaddition reaction to form 165. However, after 24 hours the only product obtained was the thiirane 164. Presumably the thiocarbonyl ylide 163 does not have the (0°, 0°) geometry as the energy minimum conformation, but the ylide is twisted to relieve the steric congestion. Thus, electrocyclization to the thiirane could be the fastest and the least energy demanding route such an ylide can select.

2.4.0.0.0 Oxadiazones

2.4.1.0.0 Synthesis of 1, 7, 8-triaza-2-oxo-5-oxaspiro[3.4]oct-7-enes (172).

The synthesis of 1, 7, 8-triaza-5-oxa-2-oxospiro[3.4]oct-7-enes, or spiro-β-lactam-oxadiazones (172), was accomplished by the [2+2] cycloaddition of imino-oxadiazones (171) to substituted ketenes or ketene equivalents (eq 22). The 2-imino-Δ^3^-1, 3, 4-oxadiazones (171) were synthesized by the procedure reported previously; they were formed in good yields by the lead tetraacetate oxidation of the corresponding 4-substituted semicarbazones (168). Semicarbazones 168 have been synthesized by route-B if R^1 = Me and by route-A for the rest. The reported imino-oxadiazones lacked ^13^C NMR data and these values are hereby reported in Table 5. The ^13^C NMR chemical shift of C5 in the region (δ(ppm) 120-124) clearly indicates the presence of the cis azo function along with the imino group in the (δ(ppm) 158-165) region.

It should be noted that the oxidations of 168 have been conducted in dry methylene chloride or dry benzene (Scheme 25). However, if absolute methanol, a nucleophilic solvent, is used, the 2-phenylamino-2-methoxy oxadiazone (173) was
obtained (eq 21) presumably by a nucleophilic attack on intermediate 170. The $^1$H NMR spectrum of the crude product, after work-up, indicated the presence of 171 and 173 in a ratio of 1:7. The tendency of 173 to lose methanol to produce 171 during manipulation of the mixture precluded its isolation. The structures fit the $^1$H NMR data of the mixture, one singlet at δ(ppm) 1.67 for the gem-dimethyl signal of 171, and two methyl signals, δ(ppm) 1.50 and 1.57, from 173. It is noteworthy that 173 was transformed completely into 171 and methanol at room temperature in chloroform during one week.

Spiro β-lactam oxadiazolines (172) have been prepared in good to excellent
Table 5. $^{13}$CNMR data for imino-oxadiazelines 171

<table>
<thead>
<tr>
<th>Compounds 171</th>
<th>$C_5$</th>
<th>$C\equiv N$</th>
<th>Substituents at N and $C_5$</th>
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<td><img src="image" alt="" /></td>
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<td></td>
</tr>
<tr>
<td>a</td>
<td>122.54</td>
<td>159.68</td>
<td>23.59 (2 x CH$_3$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>142.99 (Ph)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>128.88 (Ph)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>126.64 (Ph)</td>
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<td></td>
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<td></td>
<td>124.61 (Ph)</td>
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<td></td>
</tr>
<tr>
<td>d</td>
<td>122.11</td>
<td>158.99</td>
<td>23.66 (2 x CH$_3$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>158.43 (Ph)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>135.62 (Ph)</td>
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<td></td>
<td></td>
<td></td>
<td>126.90 (Ph)</td>
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<td></td>
<td></td>
<td></td>
<td>114.01 (Ph)</td>
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<td><img src="image" alt="" /></td>
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<td></td>
</tr>
<tr>
<td>b</td>
<td>120.70</td>
<td>162.70</td>
<td>23.32 (2 x CH$_3$)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>52.04 (CH$_2$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>138.52 (Ph)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>128.23 (Ph)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>127.46 (Ph)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>126.78 (Ph)</td>
</tr>
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<td><img src="image" alt="" /></td>
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<td></td>
</tr>
<tr>
<td>c</td>
<td>120.20</td>
<td>163.63</td>
<td>35.30 (NCH$_3$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23.46 (2 x CH$_3$)</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>126.19</td>
<td>162.14</td>
<td>138.75 (Ph)</td>
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<tr>
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<td></td>
<td></td>
<td>128.16, 127.52</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>126.68 (Ph)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>52.09, 46.73, 38.99,</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>37.09, 36.94, 36.58,</td>
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<td>36.02, 34.41, 34.01,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27.19, 26.81, 26.12</td>
</tr>
</tbody>
</table>
yields (eq 22).

172 (a) $R^1 = R^2 = R^3 = Ph$; (b) $R^1 = PhCH_2$, $R^2 = R^3 = Ph$; (c) $R^1 = Me$, $R^2 = R^3 = Ph$; (d) $R^1 = Ph$, $R^2 = R^3 = Me$; (e) $R^1 = R^2 = R^3 = Me$; (f) $R^1 = PhCH_2$, $R^2 = R^3 = Ph$, $R^4, R^5 =$ adamantyl; (g) $R^1 = Ph$, $R^2 = OPh$, $R^3 = H$; (h) $R^1 = Ph$, $R^2 = H$, $R^3 = OPh$; (i) $R^1 = MeOC_6H_4$, $R^2 = OPh$, $R^3 = H$; (j) $R^1 = Ph$, $R^2 = N_3 (H)$, $R^3 = H (N_3)$; (k) $R^1 = MeOC_6H_4$, $R^2 = R^3 = Cl$; (l) $R^1 = MeOC_6H_4$, $R^2 = R^3 = Me$; (m) $R^1 = Ph$, $R^2 = CH_3 (OPh)$, $R^3 = OPh$; (n) $R^1 = Ph$, $R^2 = OPh (CH_3)$, $R^3 = CH_3 (OPh)$; (o) $R^1 = Ph$, $R^2 = OMe (H)$, $R^3 = H (OMe) (major)$; (p) $R^1 = Ph$, $R^2 = H (OMe)$, $R^3 = OMe (H) (minor)$; (q) $R^1 = R^2 = R^3 = Ph$, $R^4 = Ph$, (Me). $R^5 = Me$, (Ph); (r) $R^1 = R^2 = R^3 = Ph$, $R^4 = Me$, (Ph), $R^5 = Ph$, (Me); (s) $R^1 = Ph_2HCC=O$, $R^2 = R^3 = Ph$.

($R^4 = R^5 = Me$ if not specified); all 172 were synthesized according to equation 22 except 172h, m, and n, these were synthesized by transformation of 172g.

In contrast to the thiadiazoline analogue, quaternization of the imidate (171) $sp^2$ ring
carbon afforded a *stable* oxadiazoline. The structures fit the $^1$H NMR data; quaternization of the sp$^2$ ring carbon is manifested by the presence of two magnetically *equiv.* equivalent methyl groups. The $^{13}$C NMR data (Table 6) provide evidence for the retention of the azo function in all of the structures 172 ($C_4$ and $C_6$ in the $\delta$(ppm) 120 region). Moreover, carbonyl absorption in the $\delta$(ppm) 165 - 175 region of the $^{13}$C spectra is characteristic of amides. Infrared absorptions (Table 6) in the 1750 - 1775 cm$^{-1}$ region provide strong evidence for a $\beta$-lactam carbonyl. Of the absorptions noted in the experimental (Chapter 3), a weak but sharp band in the 1600 cm$^{-1}$ region corresponds to the N=N stretching frequency. The fragmentation pattern in mass spectrometry (see Experimental, Chapter 3), to afford ketenes and isocyanates, supports the four-membered ring structure. Chemical ionization mass spectra showed an (M$^+$+1) peak for all the structures 172.

Those spectra firmly identified the spiro-fused skeleton of 172 in all of them because the structure of 172a was confirmed by single crystal X-ray diffraction (Figure A1-1, Appendix I).

2.4.1.1.0 □ Mechanism and Stereochemistry of the Imino-oxadiazoline Ketene reaction.

The mechanism of the reaction of imines with acid chlorides in the presence of a base to form $\beta$-lactams is covered with uncertainty; hence the rationale for the stereo*selectivity observed remains obscure (see Section 1.1.3.1.0). This uncertainty is, in part, due to the high reactivity of ketenes and the necessity to generate the less stable members *in situ*, usually from acid chlorides and tertiary amines.$^{112b}$ This raises the possibility that species such as acid chloride, the tertiary amine, the amine hydrochloride salt, N-acylammonium, or N-acyliminium species may play a role in the reaction.$^{29,45,112b}$ Several experiments have been performed in an attempt to establish the presence or absence of a ketene intermediate$^{300}$ (Section 1.1.3.1.0). As mentioned earlier (Section
**Table 6.** $^{13}$C NMR for C=O, C₃, C₄, and C₆ carbons and infrared stretching frequency for the C=O in spiro β-lactam oxadiazolines 172

<table>
<thead>
<tr>
<th>Cpd.</th>
<th>C=O</th>
<th>C₃</th>
<th>C₄</th>
<th>C₆</th>
<th>IR (C=O, cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>172a</td>
<td>166.80</td>
<td>76.13</td>
<td>125.17</td>
<td>122.61</td>
<td>1770 (KBr)</td>
</tr>
<tr>
<td>172b</td>
<td>168.53</td>
<td>76.03</td>
<td>124.82</td>
<td>122.31</td>
<td>1770 (KBr)</td>
</tr>
<tr>
<td>172c</td>
<td>168.18</td>
<td>75.99</td>
<td>124.58</td>
<td>122.22</td>
<td>1782 (KBr)</td>
</tr>
<tr>
<td>172d</td>
<td>170.61</td>
<td>60.81</td>
<td>124.93</td>
<td>121.19</td>
<td>1758 (KBr)</td>
</tr>
<tr>
<td>172e</td>
<td>172.57</td>
<td>60.72</td>
<td>124.91</td>
<td>120.63</td>
<td>1779 (KBr)</td>
</tr>
<tr>
<td>172f</td>
<td>168.81</td>
<td>43.05</td>
<td>123.09</td>
<td>115.00</td>
<td>1772 (KBr)</td>
</tr>
<tr>
<td>172g</td>
<td>162.13</td>
<td>88.21</td>
<td>129.66</td>
<td>122.85</td>
<td>1792 (KBr)</td>
</tr>
<tr>
<td>172h</td>
<td>162.48</td>
<td>84.20</td>
<td>122.57</td>
<td>122.37</td>
<td>1785 (film)</td>
</tr>
<tr>
<td>172i</td>
<td>162.41</td>
<td>87.68</td>
<td>125.30</td>
<td>122.39</td>
<td>1784 (KBr)</td>
</tr>
<tr>
<td>172j</td>
<td>160.13</td>
<td>73.93</td>
<td>129.22</td>
<td>121.09</td>
<td>1778 (KBr)</td>
</tr>
<tr>
<td>172k</td>
<td>159.07</td>
<td>86.03</td>
<td>124.94</td>
<td>121.65</td>
<td>1810 (film)</td>
</tr>
<tr>
<td>172l</td>
<td>170.65</td>
<td>60.36</td>
<td>125.08</td>
<td>120.95</td>
<td>1770 (KBr)</td>
</tr>
<tr>
<td>172m</td>
<td>165.55</td>
<td>92.86</td>
<td>123.66</td>
<td>121.94</td>
<td>1777 (film)</td>
</tr>
<tr>
<td>172n</td>
<td>165.33</td>
<td>93.50</td>
<td>123.73</td>
<td>122.04</td>
<td>1780 (film)</td>
</tr>
<tr>
<td>172o</td>
<td>162.99</td>
<td>91.65</td>
<td>122.45</td>
<td>121.72</td>
<td>1782 (KBr)</td>
</tr>
<tr>
<td>172p</td>
<td>163.78</td>
<td>87.59</td>
<td>121.92</td>
<td>114.39</td>
<td>1780 (film)</td>
</tr>
</tbody>
</table>

1.1.3.1.0), the sequence of reagent addition could govern the fate of the acid chloride and thus determine the transition intermediate for this reaction. It is generally assumed that N-acyliminium species are involved when the amine is added to a solution of the acid
chloride and the imine, while a ketene intermediate is obtained when the acid chloride is added to a solution of the amine and the imine (Section 1.1.3.1.0).

Two chiral centers may be generated in the cycloaddition process, and both the relative and absolute stereochemistries of these two centers are often of critical concern in the use of this reaction in the synthesis of biologically active β-lactams. However, the stereochemical outcome of this reaction is hard to predict and depends on the structure of the imine, on the ketene precursor, on the sequence of reagent addition, on the solvent, and on the nature of the base used to produce the ketene from the acid chloride (Section 1.1.3.1.2). It is generally observed that the reaction of a simple imine with a ketene leads to a β-lactam with the relative stereochemistry, of the C₃ and C₄ substituents, being cis (Section 1.1.3.1.0). The cis stereochemistry can be obtained by a concerted imine-ketene cycloaddition, but a non-concerted mechanism leading to a zwitterionic intermediate seems to be the more acceptable mechanism (see Section 1.1.3.1.0).

However, if the substituent on the imine sp² ring carbon can stabilize the charge (e.g., Ph, OMe, SMe), then the zwitterionic intermediate may undergo isomerization producing the thermodynamically more stable β-lactam with a trans configuration of the substituents at C₃ and C₄. This is, in fact, the stereoselectivity observed with imidates and thioimidates, and in some cases with benzaldehyde imines.⁵⁷c,d,112b

The synthesis of the spiro-β-lactam oxadiazolines (172) was accomplished by the addition of the acid chloride to a solution of the imino-oxadiazoline (171) and triethylamine. Based on the mode of addition of the reagents, a ketene intermediate is expected. Moreover, a concerted cycloaddition is unlikely due to steric as well as electronic factors. The steric bulk of the imino-oxadiazolines (171) and their ability, being imidates, to stabilize the positive charge increase the likelihood for the formation of a zwitterionic intermediate.
Attack of the imino-oxadiazoline should occur from the less hindered side of
the ketene with the plane of the imino-oxadiazoline perpendicular to that of the ketene, as
depicted in transition state 174 (Scheme 26). The imino-oxadiazolines 171 can have

![Diagram of chemical reactions](image)

Scheme 26

either the E or Z configurations at the exocyclic nitrogen. However, the configuration of
representative structures of 171 have been confirmed by X-ray crystallography to be the Z
isomers. Lead tetraacetate oxidation of semicarbazones yields only one isomer, the E
isomer has not been observed.\textsuperscript{296,298,299} Since it is not clear from molecular models why
the R\textsuperscript{1} / O steric interaction should be smaller than the R\textsuperscript{1} / N interaction, Warkentin \textit{et. al.}
rationalized the stereospecific ring closure of the semicarbazones to be due to ring closure
occurring from an organo-lead intermediate.\textsuperscript{298} Given that the imine geometry is Z, the
nucleophilic attack of the imino-oxadiazolines 171 on the LUMO of the ketene carbonyl
group, which is coplanar with the ketene substituents, leads to zwitterionic intermediate
175a. Rotation of the imine into the plane of the ketene in concert with a conrotatory ring closure (path a) produces the β-lactam in which the N=N group and the large group on the ketene are cis (172(I)). This is in fact the stereochemistry observed for 172g, where \( L = \text{OPh}, S = H, R^1 = \text{Ph}, R^4 = R^5 = \text{CH}_3 \). Also, isomerization of β-lactam 172g using fluoride ion, in dry tetrahydrofuran, led to the formation of 172h as the major product and 172g as the minor (eq 23). Therefore, closure of intermediate 175a led to the kinetic product

\[
\begin{align*}
172g & \quad \text{Bu}_4\text{NF}, \text{THF} \\
172h &
\end{align*}
\]

172(I) or 172g. Thus 172h, with OPh and O being cis, is the thermodynamic product. Alkyl N-phenylformimidates are known to react with phenoxyacetyl chloride in the presence of triethylamine to produce trans-β-lactams (OPh trans to O). However, the formation of the trans configuration has been attributed to the ability of the imidate alkoxy substituent to stabilize the positive charge, thus enabling bond rotation before ring closure. This implies that the imino-oxadiazolines 171 are not acting as imidates, at least in the case of 172g. Intermediate 175a is closing to form 172(I). In the case of 172g, if 175b is formed it should be expected to undergo bond rotation to form 175c followed by a conrotatory bond closure to produce the thermodynamic product 172h. The reaction was stereospecific, 172g was the sole product. This result could be explained in two ways. First, the presence of the azo function, in the imino-oxadiazoline, is rendering the imidate-portion incapable of stabilizing the positive charge, thus making 175a a more important contributor than 175b. Second, 175b is the major contributor but, under the reaction conditions, bond rotation to form 175c is slower than ring closure. Slow bond
rotation might be explainable by considering the steric interactions due to the bulkiness of the oxadiazoline ring. Thus, both of these factors could be rendering the imino-oxadiazoline system more like an imine than an imidate.

Similarly, 172i (R^1 = MeOC\_6H\_4) was synthesized from 171d and phenoxyacetyl chloride. The β-lactam was formed as a single isomer in 88 % yield. Due to the stereospecificity and the high yield it should be safe to predict a similar stereochemistry for 172i as that for 172g. Therefore, the phenoxy group should be trans to the oxadiazoline oxygen. Moreover, the reaction of azidoacetyl chloride with imino-oxadiazoline 171a led to a very low yield of the β-lactam 172j (≈20 %, as a single isomer), eq 22. Also, the reaction of 171a with methoxyacetyl chloride led to 172o and 172p, two isomers in a total yield of 25 % and a ratio of 10:1, respectively. Both reactions were attempted under different conditions of temperature and concentration, but nothing seemed to increase the yield. The low yield in this reaction could be due to two reasons. First, due to the instability of those ketenes, they tend to dimerise before they react with the imino-oxadiazoline. Second, due to the formation of a different intermediate which does not involve a ketene, thus following a different mechanism. The reaction of the azidoacetyl chloride was low yielding but stereospecific. Methoxyacetyl chloride, on the other hand, produced two isomers in a ratio of 1 : 10. Therefore, the prediction of the stereochemistry, in these two cases, is hard and cannot be assigned with complete confidence. If the mechanism is similar to that for 172g, then 172j should have the azido group trans to the oxadiazoline oxygen (O), 172o (major isomer) should have the methoxy group trans to the O, and 172p (minor isomer) should have the methoxy group cis to the O.

The other, with one chiral center, spiro-β-lactam oxadiazolines (172) were synthesized in good to excellent yields. However, it should be noted that 171b (R^1 = CH\_2Ph) did not produce the β-lactam when treated with isobutyryl chloride in the
presence of triethylamine, the imino-oxadiazoline 171b was recovered unchanged. This
could be due to the instability of the dimethylketene; presumably, its dimerization was
faster than the reaction with 171b. Spiro-β-lactam oxadiazoline 172b was produced in 80
% yield when 171b was allowed to react with diphenylacetyl chloride under the same
conditions. Moreover, phenylacetyl chloride did not produce the β-lactam when treated
with 171a or 171b. This could also be due to the ketene tendency to dimerize or
polymerize (see Section 1.1.3.0.0).

The reaction of 171e (R1 = H) with diphenylacetyl chloride in the presence of
excess triethylamine did not produce 176. The only product obtained was the β-lactam

\[
\text{Ph}_2\text{CHCOCI} \quad \text{Et}_3\text{N}, -23^\circ\text{C} \quad \text{176}
\]

172s, in ≈ 40 % yield (eq 24). It should be noted that the molar ratio of triethylamine to
171e was 3 : 1. The ratio of 171e to the diphenylacetyl chloride was 1 : 1.2; however,
171e was always in large excess since diphenylacetyl chloride was added dropwise. The
experimental conditions could imply that the ketene (or the acid chloride) has reacted with
the imino-oxadiazoline (171e) to form an amide-like intermediate (C=N-C=O), this could
undergo cycloaddition with another ketene molecule to afford 172s. However, the initial
formation of 176 followed by a nucleophilic attack of 176 on a ketene (or acid chloride)
cannot be ruled out.

2.4.2.0.0 ■ Thermolysis of 172: rate constants

Spiro β-lactam oxadiazolines (172) with alkyl substituents (dimethyl or
adamantyl) at C₆ proved to be stable at room temperature. However, at 100°C they decomposed to form the ketone in quantitative yields. The disappearance of the dimethyl substituents and their replacement with the acetone signal was obvious from ¹H NMR spectroscopy. In the case where C₆ is part of an adamantyl group the formation of adamantanone was proved by GC/MS (EI) on the product after decomposition. Presumably the fragmentation occurs by a concerted loss of N₂ to form the β-lactam carbonyl ylide (177), followed by fragmentation to the ketone and the β-lactam-4-ylidene (181). Steric congestion in the (0°, 0°) conformation (177) and/or charge separation caused by inductive and/or resonance charge stabilization caused by the β-lactam-nitrogen, are two factors that could lower the energy barrier for rotation about the ylide's O-C bonds (Section 1.2.4.1.1), hence increasing the population of the (0°, 90°) conformation; a conformation which usually leads to fragmentation generating carbenes (Scheme 27).

![Diagram](image)

(0°, 0°)
177

The only identifiable product after the thermolysis of the spiro-β-lactam oxadiazolines, 172, in dry benzene, was the ketone which was formed in 100% yield, (Scheme 27). The 2,4-azetidine-dione (179), which could form via path-b, has not been observed. This shows that path-a in Scheme 27 is the only pathway taken by this carbonyl ylide.
Therefore, the thermolysis of 172 leads to the carbonyl ylide which does not undergo any of the known (0°, 0°) ylide reactions (Section 1.2.4.1.1, Scheme 19), but only undergoes fragmentation and the fragmentation is unidirectional to form the ketone quantitatively. This can only mean that the second product is the β-lactam-4-ylidene (181) which should also be formed quantitatively. Trapping experiments on this β-lactam-4-ylidene are in the following sections of this Chapter.

In order to study the scope of this reaction for the use of 172 as a β-lactam building block, we studied the effect of the substituents on the rate of the thermolysis. Table 7 shows the thermolysis rate constants of 15 spiro-β-lactam-oxadiazolines (see Appendix II for raw data and graphs). It is clear that the substituents effect is steric as well as electronic. The bulky adamantyl group in 172f retarded the rate by a factor of = 15 compared to dimethyl at that site; Table 7, entries 6 and 2 respectively.

On the other hand, a hydrogen and a phenoxy group at C3, entry 7, Table 7, enhanced the rate by a factor of = 6 compared to diphenyl at that site; entry 1, Table 7. In
Table 7.
Substituent effect on the rate of decomposition of fifteen spiro-β-lactam-oxadiazolines
(thermolysis in benzene at 100°C)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>R⁵</th>
<th>Rate constants sec⁻¹ (100 °C)</th>
<th>k_rel</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (a)</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>CH₃</td>
<td>CH₃</td>
<td>2.80 x 10⁻⁴</td>
<td>40.6</td>
</tr>
<tr>
<td>2 (b)</td>
<td>PhCH₂</td>
<td>Ph</td>
<td>Ph</td>
<td>CH₃</td>
<td>CH₃</td>
<td>1.00 x 10⁻⁴</td>
<td>14.5</td>
</tr>
<tr>
<td>3 (c)</td>
<td>CH₃</td>
<td>Ph</td>
<td>Ph</td>
<td>CH₃</td>
<td>CH₃</td>
<td>1.20 x 10⁻⁴</td>
<td>17.4</td>
</tr>
<tr>
<td>4 (d)</td>
<td>Ph</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>1.10 x 10⁻⁴</td>
<td>15.9</td>
</tr>
<tr>
<td>5 (e)</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>3.90 x 10⁻⁵</td>
<td>5.65</td>
</tr>
<tr>
<td>6 (f)</td>
<td>PhCH₂</td>
<td>Ph</td>
<td>Ph</td>
<td>Adamantyl</td>
<td></td>
<td>6.90 x 10⁻⁶</td>
<td>1.00</td>
</tr>
<tr>
<td>7 (g)</td>
<td>Ph</td>
<td>OPh</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>1.79 x 10⁻³</td>
<td>259</td>
</tr>
<tr>
<td>8 (h)</td>
<td>Ph</td>
<td>H</td>
<td>OPh</td>
<td>CH₃</td>
<td>CH₃</td>
<td>3.40 x 10⁻⁴</td>
<td>49.3</td>
</tr>
<tr>
<td>9 (i)</td>
<td>MeOPh</td>
<td>OPh</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>1.26 x 10⁻³</td>
<td>183</td>
</tr>
<tr>
<td>10 (j)</td>
<td>Ph</td>
<td>N₃</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>1.66 x 10⁻³</td>
<td>241</td>
</tr>
<tr>
<td>11 (k)</td>
<td>MeOPh</td>
<td>Cl</td>
<td>Cl</td>
<td>CH₃</td>
<td>CH₃</td>
<td>1.82 x 10⁻³</td>
<td>264</td>
</tr>
<tr>
<td>12 (m)</td>
<td>Ph</td>
<td>CH₃</td>
<td>OPh</td>
<td>CH₃</td>
<td>CH₃</td>
<td>4.80 x 10⁻⁴</td>
<td>69.6</td>
</tr>
<tr>
<td>13 (n)</td>
<td>Ph</td>
<td>OPh</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>7.40 x 10⁻⁴</td>
<td>107</td>
</tr>
</tbody>
</table>

sec⁻¹ (50°C)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>R⁵</th>
<th>Rate constants sec⁻¹ (50 °C)</th>
<th>k_rel</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 (q)</td>
<td>PhCH₂</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>CH₃</td>
<td>1.30 x 10⁻⁴</td>
<td>29.0</td>
</tr>
<tr>
<td>15 (r)</td>
<td>PhCH₂</td>
<td>Ph</td>
<td>Ph</td>
<td>CH₃</td>
<td>Ph</td>
<td>4.48 x 10⁻⁶</td>
<td>1.00</td>
</tr>
</tbody>
</table>

order to determine if the increase in rate is due to the phenoxy group, electronic effect, or
due to the hydrogen, steric effect, β-lactams 172m and 172n were synthesized. From entries 12 and 13 it is clear that one isomer decomposes about twice as fast as the other. Isomers 172m and 172n were synthesized by treating the lithium enolate (182) of β-lactam 172g with methyl iodide (Scheme 28); the two isomers were formed with 172n being the minor isomer. If the two isomers were synthesized under thermodynamic control, compound 172m (the major isomer) should be more stable, and this is true, entry 12. Also, isomerization of compound 172g using fluoride ion, in dry tetrahydrofuran, led to the formation of 172h as the major product and 172g as the minor (Section 2.4.1.1.0, eq 23). The rate of decomposition for 172h (major isomer) is about five times slower than that of 172g (minor isomer). Therefore, the isomerization experiment led to the thermodynamic product (172h). This implies that 172g, the product of the ketene-imine cyclocondensation reaction, is the kinetic product (see Section 2.4.1.1.0). If it is assumed that equilibrium has been achieved (eq 23), then the equilibrium concentrations can be obtained from the \(^1\)H NMR spectrum of the mixture. Thus, the free energy difference between 172h and 172g could be approximated to be around 0.85 kcal/mole (Figure 17).

\[ \Delta G^\circ = -2.303 \ RT \log K = -4.576 \times 10^{-3} \times 298 \log ([172h]/[172g]) \]

\[ \Delta G^\circ = -4.576 \times 10^{-3} \times 298 \log (4.2) = 0.85 \text{ kcal/mole.} \]

Since the freedoms of motion are similar in both systems, the entropy factors could be considered similar. Also, since the change in stereochemistry (at C3) is not on
the reaction centers (C₄ and C₆, during loss of N₂), there is no reason why the transition states should be very different; they are identical if they come late on the reaction coordinate. Therefore, the only obvious reason for the difference in the stability of 172g and that of 172h must be due to a difference in ground state stability (ΔG⁰). The same reasoning could be applied for 172m and 172n. In any case, comparison of the two kinetic products one with H (entry 7, 172g), the other with CH₃ (entry 13, 172n) shows that the one with H is about 2.5 times faster than the one with CH₃. This rate difference implies that the steric effects are fairly important.

The electronic factor also plays a role. Replacing one of the C₃ methyl groups in 172d (entry 4) by the phenoxy substituent in 172m or 172n enhanced the rate by a factor of ≈ 4 and ≈ 7, respectively. Moreover, the electronic factor is also manifested in entry 5, Table 7. A methyl group on the β-lactam nitrogen retarded the rate by a factor of ≈ 3 compared to a phenyl group (entry 4, Table 7). Making the β-lactam nitrogen more basic did not enhance the fragmentation, implying that the lone pairs on nitrogen are not nucleophilically inducing the oxadiazoline ring-opening. But, the increase in the rate upon replacing a methyl group by a phenyl group cannot be due to steric interactions. Thus, these changes in the rate of fragmentation could be due to slight perturbations in the
hybridizations of both rings.

On the other hand, putting a phenyl substituent at C₆ would change the electronic distribution in the carbonyl ylide. The (0°,0°) conformation might become more important due to charge delocalization. The β-lactam synthesis produced the two diastereomers (172q and 172r) in about 60 % total yield and in a ratio of 1 : 1.53. The two isomers decomposed if left in chloroform at room temperature. The major of the two isomers was decomposing faster than the minor, there was a build up of acetophenone and of the [1,4] sigmatropic H-rearrangement product (183, Scheme 29). The transition state

![Chemical structures](image)

Scheme 29

for the ketene - imino-oxadiazoline reaction should resemble 174 (Scheme 30). Transition state 174 reveals that the substituents R⁴ and R⁵ are far from the reaction centers and might not have an effect on the cycloaddition. However, rotation of the imino-oxadiazoline into the plane of the ketene in concert with a conrotatory ring closure, should be slightly affected by R⁴ and R⁵. Therefore, in order to have the least hindered approach the transition state (174) with R⁵ = CH₃ should be favored over R⁵ = Ph. This implies that isomer (B) should be thermodynamically favoured, Scheme 30 (174 with R⁵ =
CH$_3$ and R$^4$ = Ph), over isomer (A) (174 with R$^2$ = Ph and R$^4$ = CH$_3$). According to AM1 calculations isomer B is 1.2 kcal/mole more stable than isomer A.

The presence of the [1,4] hydrogen migration product suggests two structural features of the carbonyl ylide. First, a geometry close to the (0°,0°) conformation should be possible for the [1,4] H~ migration to occur; second, the methyl group should be endo. The endo methyl group should also be preferred due to steric factors. Therefore, ylide 177a should be generated from A and ylide 177b should be generated from B. But, the major isomer decomposes about 30 times faster than the minor (see Table 7); this could imply that the kinetic product (A) is the major isomer and not (B), the thermodynamic product. Thus, the difference in the rate of decomposition between A and B could be due
to a difference in the steric interactions during cycloreversion, due to a difference in the stability of the ground states (AM1 calculations predict a difference of 1.2 kcal/mole), or to both. However, it is not perceivable why the generation of ylide 177a should be that much faster than the generation of ylide 177b. It should be emphasized that the assignments of A and B are in compliance with the least hindered approach, required by transition state 174, but the assignments could be reversed because they were not confirmed spectroscopically.

In order to study the mode of fragmentation as to whether one of the isomers (A or B, Scheme 30) is losing acetophenone to form the carbene while the other isomer is doing the [1,4] sigmatropic rearrangement, or whether both isomers are decomposing to both products, a thermolysis experiment was conducted. By following the decomposition of the mixture, at 50°C, by 1H NMR for 90 minutes, the major isomer was found to be almost completely decomposed while the minor isomer was decomposing at a much slower rate. The decrease in the major isomer was 64% of the increase in the two products (acetophenone and 183). Also, the buildup of the two products was in the ratio of 1 : 3.25 (183 : acetophenone). This means that the starting material is decomposing to give 1 part of 183 product to 3.25 parts of the carbene.

2.4.3.0.0 ☐ β-LACTAM-4-YLIDENES: ADDITION REACTIONS
2.4.3.1.0 ☐ β-lactam-4-yldenenes: Addition to alkynes

The thermolysis of 172a in benzene at 100°C (sealed tube), in the presence of dimethyl acetylenedicarboxylate (2.0 M), afforded the highly strained spiro-β-lactam cyclopropene system 184 in ca. 33% yield (Scheme 31). Due to the symmetry in compound 184 the two ester groups appeared as a singlet in the 1H NMR spectrum. Infrared showed two sharp C=O absorptions one at 1750 cm⁻¹ (C=O, β-lactam, Table 11), and the other at 1730 cm⁻¹ (2 x C=O, esters). Moreover, the 13C NMR showed two (C=O)
signals one at $\delta = 167.63$ (C=O, $\beta$-lactam) and the two magnetically equivalent ester C=O groups at $\delta 158.33$ (Table 8). The structure of 184 was confirmed by single crystal X-ray diffraction (Figure A1-9, Appendix I). Similarly, the unsymmetric spiro-$\beta$-lactam cyclopropene (185) was produced, also in ca. 35 % yield, by thermolysis of the N-benzyl analogue of 172a, spiro-$\beta$-lactam oxadiazoline 172b, in the presence of ethyl phenylpropiolate (Scheme 31). The $^1$H NMR spectrum showed two overlapping diastereotopic methylene groups, for the benzyl and the ethyl substituents, thus confirming the generation of a new chiral center. The structure of 185 was firmly identified by $^1$H NMR, $^{13}$C NMR (Table 8), infrared (Table 11) and high resolution mass spectroscopy, and confirmed by comparing the spectroscopic data of 185 to those of 184.

These novel spiro-$\beta$-lactam cyclopropene systems must enclose enormous strain energy (see Figures A1-9, 10, 11, 12, Appendix I). This should enhance the reactivity of both the $\beta$-lactam and the cyclopropene ring. Therefore, the cyclopropene
Table 8. $^{13}$C NMR for C₁, C₂, C₅, and C₆ in spiro β-lactam cyclopropenes 184 and 185.

<table>
<thead>
<tr>
<th>Cpd.</th>
<th>C=O</th>
<th>C₁</th>
<th>C₂</th>
<th>C₃</th>
<th>C₆</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="structure" /></td>
<td>167.63</td>
<td>119.81</td>
<td>119.81</td>
<td>66.03 (C₆)</td>
<td>64.13 (C₃)</td>
</tr>
<tr>
<td><img src="image2" alt="structure" /></td>
<td>169.55</td>
<td>112.51</td>
<td>125.00</td>
<td>70.97</td>
<td>60.92</td>
</tr>
</tbody>
</table>

might be expected to undergo the ring-opening to form vinyl carbenes at a relatively low temperature.

2.4.3.1.1 □ Thermolysis of spiro-β-lactam-cyclopropene 184: Formation of 187b

Thermolysis of 184 at 154°C in benzene (sealed tube) afforded a product to which structure 187b could be assigned. Formation of 187b can be rationalized as depicted in Scheme 32. The well-known ring opening of cyclopropenes to vinyl carbenes (Section 1.2.4) is the first step, forming 186. Both carbenes (186) presumably revert to 184 but 186a also inserts into a phenyl CH-bond to form 187a which undergoes allylic rearrangement to the more stable 187b. That carbene attack had occurred on a C-phenyl (187) and not the N-phenyl (188) group was clear from the mass spectrum, which did not contain the signal for diphenylketene radical cation characteristic of 3,3-diphenyl-β-lactams. The infrared spectrum showed that the β-lactam ring had
remained intact (1810 cm⁻¹) and both the H and ¹³C NMR spectra indicated that the product cannot have structure 187a. Although 187a would appear to be a necessary intermediate, isomerization to the more stable 187b is not surprising given that the H-moiety that migrates is allylic, benzylic, and ester - activated in 187a.

2.4.3.2.0  β-lactam-4-ylidene: Addition to alkenes

Cyclopropane derivatives have been known for more than 100 years, but it
wasn't until recently that these structural fragments have been recognized as building blocks for organic synthesis. To realize the benefits of such a pseudo-functional group many ways have been developed for their creation or incorporation. For most cases the cyclopropyl group is not the final goal, but an intermediate to acyclic or ring systems commonly needed in natural products chemistry.

Despite intense activity in the area of β-lactam chemistry since 1943, especially in developing methods for functionalizing the C-4 carbon, to our knowledge, there is only one example to date of a 4-spiro β-lactam cyclopropane\textsuperscript{301}. The compound was not formed via a carbene reaction. Though the result is quite interesting, the applications of this reaction are limited due to the high substrate specificity, the number of steps required, and the formation of the imino-lactone as an important side product.\textsuperscript{301}

Four novel spiro β-lactam cyclopropanes (189-192) were synthesized by

\begin{align*}
\text{189} & \quad \text{190} \\
\text{191} & \quad \text{192}
\end{align*}

addition of a β-lactam-4-ylidene to systems with a carbon - carbon double bond.
2.4.3.2.1 □ Addition to Acrylonitrile:

The thermolysis of the spiro β-lactam oxadiazoline (172g) (0.33 M) in neat acrylonitrile afforded three of the four possible isomers of 189 in a total yield of ca. 70% in a ratio of 1 : 2.5 : 1.4, based on 1H NMR spectroscopy. The thermolysis was conducted in a sealed NMR tube at 100°C. After 50 minutes no more N₂ bubbles were observed and the 1H NMR spectrum confirmed the consumption of more than 95% of the starting material. The products were separated by chromatography and characterized by 1H NMR, 13C NMR, infrared, and high resolution mass spectrometry. Table 9 contains the cyclopropyl 1H NMR chemical shifts and coupling constants for one of the isomers 189. The isomer reported in Table 9 has clearly separated ab-quartets whereas the other two isomers have overlapping multiplets. Moreover, the 13C NMR confirmed the cyclopropane substructure of the three by displaying an upfield chemical shift for the C-2 carbon, δ(ppm) 2.96 (Fraction # 2), 4.33 (Fraction # 3), 2.44 (Fraction # 4), (Table 10). Infrared stretching frequencies, in the 1760-1790 cm⁻¹ region, confirmed the presence of a β-lactam moiety in all isomers 189 (Table 11). NOE experiments were performed, on all three isomers, in an attempt to identify the different stereo- and regio-isomers. Irradiating the proton at C-6 and in a different experiment irradiating the proton at C-1 failed to provide a convincing result as to the identity of each isomer.

Although, from previous reports, the thermolysis of oxadiazolines is supposed to generate carbonyl ylides (Section 1.2.4.1), loss of acetone to form the 4-diazo-β-lactam could also be considered as another possible mode of fragmentation for this novel oxadiazoline (172). 4-Diazo-β-lactams would undergo a 1,3-dipolar cycloaddition reaction with dipolarophiles to form cyclicazo compounds on the route to cyclopropanes. In order to provide evidence against the intermediacy of a diazo-compound, the reaction of 172g with styrene, a poorer dipolarophile, was attempted.
Table 9. Proton chemical shifts and coupling constants for the cyclopropyl moiety in 189 and 190.

<table>
<thead>
<tr>
<th>R</th>
<th>$H_a$</th>
<th>$H_b$</th>
<th>$H_c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = CN</td>
<td>1.88, $J_{ab}$ = 7.9 Hz</td>
<td>2.14, $J_{ba}$ = 7.9 Hz</td>
<td>2.50, $J_{ca}$ = 6.9 Hz</td>
</tr>
<tr>
<td>F#2</td>
<td>$J_{ac}$ = 6.9 Hz</td>
<td>$J_{bc}$ = 10.0 Hz</td>
<td>$J_{cb}$ = 10.0 Hz</td>
</tr>
<tr>
<td>R = Ph</td>
<td>1.84, tr, $J$ = 7.6 Hz</td>
<td>1.67, $J_{bc}$ = 7.6 Hz</td>
<td>2.72, $J_{ca}$ = 7.6 Hz</td>
</tr>
<tr>
<td>F#1</td>
<td>($J_{ab}$ = $J_{ac}$ = 7.6 Hz)</td>
<td>$J_{bc}$ = 10.1 Hz</td>
<td>$J_{cb}$ = 10.1 Hz</td>
</tr>
<tr>
<td>R = Ph</td>
<td>1.75, $J_{ab}$ = 7.9 Hz</td>
<td>2.13, $J_{ba}$ = 7.9 Hz</td>
<td>3.10, $J_{ca}$ = 7.4 Hz</td>
</tr>
<tr>
<td>F#2</td>
<td>$J_{ac}$ = 7.4 Hz</td>
<td>$J_{bc}$ = 10.3 Hz</td>
<td>$J_{cb}$ = 10.3 Hz</td>
</tr>
</tbody>
</table>

2.4.3.2.2 □ Addition to Styrene:

The spiro-cyclopropane annellated β-lactam (190) was obtained in 74 % total yield. Two of the four possible isomers were obtained in a ratio of 5.2 : 1. The two isomers were separated by chromatography and their structures confirmed by $^1$H NMR, $^{13}$C NMR, infrared and high resolution mass spectrometry (HRMS). HRMS was done on the (M$^+$ - CO) fragment due to the absence of the molecular ion for both isomers in EI. The $^1$H NMR data in Table 9 reveal the chemical shifts and coupling constants of the cyclopropyl protons for the two isolated fractions of 190. Moreover, the $^{13}$C NMR spectra confirmed the presence of the cyclopropane by showing an upfield shift for the C-2
Table 10. $^{13}$C NMR for C=O, C$_1$, C$_2$, C$_3$, and C$_6$ in spiro $\beta$-lactam cyclopropanes 189, 190, 191, and 192.

<table>
<thead>
<tr>
<th>Cpd.</th>
<th>Isomer</th>
<th>C=O</th>
<th>C$_1$</th>
<th>C$_2$</th>
<th>C$_3$</th>
<th>C$_6$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F#2</td>
<td>162.72</td>
<td>10.25</td>
<td>2.96</td>
<td>54.31</td>
<td>82.71</td>
</tr>
<tr>
<td></td>
<td>F#3</td>
<td>163.39</td>
<td>10.42</td>
<td>4.33</td>
<td>54.08</td>
<td>83.37</td>
</tr>
<tr>
<td></td>
<td>F#4</td>
<td>x</td>
<td>12.68</td>
<td>2.44</td>
<td>54.87</td>
<td>82.28</td>
</tr>
</tbody>
</table>

|      | Major  | 164.90 | 24.08  | 7.40   | 55.79  | 84.19  |
|      | Minor  | 164.22 | 21.86  | 9.48   | 56.42  | 81.45  |

|      | 168.81 | 19.47  | 13.80  | 60.71  | 70.02  |

|      | F#5    | 168.87 | 167.45 | 26.97  | 59.75  | 82.74  |
|      | 165.14 | 26.86  | 26.86  | 59.75  | 82.74  |
|      | F#7    | 166.50 | 26.46  | 58.01  | 83.51  |
|      | 166.00 | 23.37  | 23.37  | 58.01  | 83.51  |
|      | 165.99 |        |        |        |        |

Cyclopropyl carbon $\delta$(ppm) 7.40 (major isomer), 9.48 (minor isomer) (Table 10). Infrared spectra confirmed the presence of the $\beta$-lactam moiety in both isomers (187, Table 11). Once again NOE experiments, on both isomers, were not confirmative as to the identity of the isomers. Moreover, the styrene experiment was done with and without added...
Table 11. Infrared $\beta$-lactam carbonyl frequencies for spiro $\beta$-lactam cyclopropanes 189, 190, 191, 192 and cyclopropanes 184, 185.

<table>
<thead>
<tr>
<th>Cpd.</th>
<th>Isomer</th>
<th>IR (C=O, cm$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td>F#2</td>
<td>1775 (film)</td>
</tr>
<tr>
<td><img src="image2.png" alt="Image" /></td>
<td>F#3</td>
<td>1760 (KBr)</td>
</tr>
<tr>
<td><img src="image3.png" alt="Image" /></td>
<td>F#4</td>
<td>1790 (film)</td>
</tr>
<tr>
<td><img src="image4.png" alt="Image" /></td>
<td>Major</td>
<td>1760 (KBr)</td>
</tr>
<tr>
<td><img src="image5.png" alt="Image" /></td>
<td>Minor</td>
<td>1758 (KBr)</td>
</tr>
<tr>
<td><img src="image6.png" alt="Image" /></td>
<td></td>
<td>1755 (KBr)</td>
</tr>
<tr>
<td><img src="image7.png" alt="Image" /></td>
<td>F#5</td>
<td>1775 (film)</td>
</tr>
<tr>
<td><img src="image8.png" alt="Image" /></td>
<td>F#6</td>
<td>1775 (film)</td>
</tr>
<tr>
<td><img src="image9.png" alt="Image" /></td>
<td>mixture</td>
<td>1775 (film)</td>
</tr>
<tr>
<td><img src="image10.png" alt="Image" /></td>
<td>F#7</td>
<td>1775 (film)</td>
</tr>
<tr>
<td><img src="image11.png" alt="Image" /></td>
<td>184</td>
<td>1750 (KBr)</td>
</tr>
<tr>
<td><img src="image12.png" alt="Image" /></td>
<td>R$^1$ = Ph, R$^2$ = R$^3$ = COOMe</td>
<td></td>
</tr>
<tr>
<td><img src="image13.png" alt="Image" /></td>
<td>185</td>
<td>1745 (film)</td>
</tr>
<tr>
<td><img src="image14.png" alt="Image" /></td>
<td>R$^1$ = CH$_2$Ph, R$^2$ = Ph, R$^3$ = COOEt</td>
<td></td>
</tr>
</tbody>
</table>
Rh$_2$(OAc)$_4$, to give the same result. The latter experiment is not definitive for the absence of the diazo intermediate because the evidence that Rh$_2$(OAc)$_4$ is an effective catalyst for cyclopropanation with diazo compounds other than diazo-carbonyls is limited to simple structures.$^{302}$ However, this experiment adds some weight to the carbonyl ylide $\rightarrow$ carbene side of the argument.

On the other hand, if the reactive intermediate is not a 1,3 dipole, it could still be a 1,2 dipole (181). β-Lactams with a leaving group in the 4-position have recently received much attention (Section 1.1.4.3). The reaction apparently occurs via an elimination - addition mechanism involving an azetinone-like intermediate (79, see Section 1.1.4.3). Presumably the carbene 181 is stabilized by delocalization of the N-electrons but the contribution of the dipolar structure (181b) must be small, given that the carbonyl group decreases the basicity of the β-lactam nitrogen and taking into account the fact that a diamino-carbene has only a small negative charge (0.03 e) on the carbene carbon.$^{275}$ AM1 calculations, on the β-lactam-4-ylidene with R$^1$ = R$^2$ = R$^3$ = Ph, showed a positive charge (0.076) at the carbenic site. AM1 also showed a positive charge (0.065) at the carbenic site of the β-lactam-4-ylidene with R$^1$ = R$^2$ = R$^3$ = H. Further support for the generation of a carbene comes from the reaction of 172a with 4-bromo-1-butene.
2.4.3.2.3 Addition to 4-bromo-1-butene:

Two features are embedded in 4-bromo-1-butene; first, the double bond is almost non-activated and should be a very poor dipolarophile and second, the Br substituent is a good leaving group for $S_N2$ displacement by a nucleophile. Therefore, it is to be expected that if the reactive intermediate is a 1,3-dipole no cycloaddition reaction should occur with such a bad dipolarophile or at least the reaction yield should be very low. Moreover, if the major contributor to the reactive intermediate (181) is the 1,2 dipole (181b), with a negative charge on carbon, no reaction should occur on the electron rich double bond. However, an $S_N2$ displacement could be expected at the bromine-bearing carbon atom of the molecule to produce compounds such as 193 and/or 194 (Scheme 33). Compound 193 can arise by a nucleophilic substitution of the bromide by 181, followed by abstraction of a proton by bromide ion to form 193 and HBr. The 4-bromo $\beta$-lactam (194) could be formed if the nucleophilic substitution of bromide is followed by an
ion-pair collapse, of the bromide and the 4-carbocationic-β-lactam intermediate. Upon thermolysis of 172a (0.14 mmol) in 4-bromot-butene (0.5 mL), the only product obtained was the spiro β-lactam cyclopropane (191) with no evidence for an S_N2 displacement at the bromine site to form 193, 194 (Scheme 33), or their decomposition products. GC/MS (EI) of the crude product showed only one major peak with the adduct molecular weight. Also the major product isolated by chromatography was the expected spiro β-lactam cyclopropane. ^1H NMR showed two multiplets at δ(ppm) 3.14 and 1.76 for the two diastereotopic methylene groups CH_2Br and CH_2, respectively. The cyclopropane protons resonated at δ(ppm) 0.85, (CHR), 1.27 and 1.34 (CH_2). The assignment of the different proton chemical shifts was accomplished by a 2D ^1H-^13C correlation experiment (see Table 10 for the cyclopropyl ^13C data). Absorption at 1755 cm⁻¹ (Table 11), by the carbonyl group, in the infrared spectrum confirmed the β-lactam structure. The yield obtained was 60 % and there was only one isomer of the two expected.

This result infers that intermediate 181 must have a carbenic character. Thus, the question of the stereoselectivity of this carbene's additions to alkenes follows. The reaction of 172g with dimethyl maleate was attempted.

### 2.4.3.2.4 Addition to dimethyl maleate / fumarate:

To our surprise, the thermolysis of the spiro β-lactam oxadiazoline (172g) in dimethyl maleate afforded four products, two trans and two cis isomers, 192a, 192b, 192c, 192d. The total yield was 43 %, distributed over the 4 isomers; 2 trans, 5 % and 19 %, and 2 cis, 13 % and 6 %. The assignment of the cis and trans isomers was accomplished by their specific coupling constants noted in Table 12. ^13C chemical shifts (Table 10) of the cyclopropane were shifted downfield, δ(ppm) 23 - 27 ppm, due to the deshielding effect of the two ester groups. Again the infrared spectra proved the presence of the β-lactam moiety by showing absorptions at 1775 cm⁻¹ for all isomers 192.
Table 12. Proton chemical shifts and coupling constants of the cyclopropyl-group in 192.

<table>
<thead>
<tr>
<th>Isomer</th>
<th>H₂ δ (ppm)</th>
<th>H₃ δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F#5 (trans)</td>
<td>3.27 (d, J = 7 Hz)</td>
<td>2.96 (d, J = 7 Hz)</td>
</tr>
<tr>
<td>F#6 (trans)</td>
<td>3.23 (d, J = 7 Hz)</td>
<td>2.99 (d, J = 7 Hz)</td>
</tr>
<tr>
<td>F#6* (cis)</td>
<td>3.00 (d, J = 11 Hz)</td>
<td>2.93 (d, J = 11 Hz)</td>
</tr>
<tr>
<td>F#7 (cis)</td>
<td>2.66 (d, J = 11 Hz)</td>
<td>2.63 (d, J = 11 Hz)</td>
</tr>
</tbody>
</table>

Although stereoselectivity is evident, the 24% trans (192a and 192b) and 19c % cis (192c and 192d) result shows no stereospecificity. Analysis of the volatiles showed the presence of dimethyl maleate and acetone. A ¹H NMR spectrum of the crude product showed no evidence of maleate isomerization to the fumarate. Also, GC analysis showed no fumarate and isomerization of the starting material is ruled out.

The same experiment was conducted in dimethyl fumarate as a solvent. Dimethyl fumarate is a solid with a melting point of 103-104°C; therefore, the two solids,
172g and the fumarate, were mixed and heated, in an evacuated sealed tube, at 111°C. After about 50 minutes the $^1$H NMR spectrum confirmed the consumption of more than 95 % of 172g. Purification by chromatography, using 25 % ethyl acetate in hexane as eluent, afforded two fractions. The first fraction corresponded to the fumarate while the second fraction was a mixture of the two trans products (192a and 192b) in a total of 36 % yield. The cis isomer was not present. The two trans isomers were formed in a ratio of 2.7:1.

Analysis of the non-stereospecific maleate results could lead to several explanations.

Normally a non-stereospecific carbene addition is considered a triplet carbene reaction. However, the thermal generation of the carbene could rule out a triplet reaction, unless the singlet - triplet energy gap is small enough for state equilibration to occur rapidly. The geometric requirements, in the β-lactam-4-ylidene system, play against a small energy-gap. The four membered ring should accommodate the singlet (smaller angle) preferentially to the triplet (larger angle) and hence, stabilize the former more than the latter (see Section 1.2.2). Following the same train of thought, the presence of the nitrogen alpha to the carbenic site should preferentially stabilize the singlet. Moreover, as will be seen in the following section, the β-lactam-4-ylidenes (181) insert readily into alcohol OH-bonds to form 4-alkoxy-β-lactams in quantitative yields. The reaction of a carbene with an alcohol is considered a singlet specific reaction (see Section 1.2.3). A quantitative singlet specific reaction does not mean that the triplet is not present, but it certainly implies that if the triplet is present then the singlet - triplet energy gap should be small enough for populating the singlet state. Also, the singlet - triplet energy gap does not have to stay the same in different solvents, an increase in polarity should stabilize the singlet more than the triplet (see Section 1.2.3.1.0). Therefore, if there is spin state equilibration in methanol - benzene this does not mean that this equilibration can take
place in dimethylmaleate, for example.

In summary, the thermal generation, the geometric requirements, the presence of the nitrogen in the alpha position, and the O-H bond insertion are all singlet state criteria. However, the triplet reaction with the alkenes cannot be ruled out due to a possible small singlet - triplet energy gap and hence, state equilibration. This argument implies that if the reaction is due to a triplet carbene, then the triplet is more reactive than the singlet towards maleate, to our knowledge, there is no precedence for that.

A second possibility is that the intermediate has the zwitterionic resonance form (181b) as a major contributor. This possibility is not supported by the previously discussed experiment, with the 4-bromo-1-butene probe (Scheme 33). Furthermore, a zwitterionic intermediate would represent an unnatural charge distribution by putting a positive charge alpha to a carbonyl group, this electronic destabilization would be augmented if the strain energy required to develop a partial double bond in the ring (181) is added.

Moreover, the β-lactam-4-ylidene could be forming a carbene alkene complex which leads to a carbene - alkene dipolar adduct similar to that suggested by Doyle and Liu (Section 1.2.3.2.1). This carbene - alkene dipolar adduct could allow bond rotation and thus the formation of the thermodynamically more stable product. Another possible singlet non-concerted cycloaddition could occur through an electron transfer reaction similar to that proposed by Wiberg (see Section 1.2.3.2.1).

2.4.4.0.0 ■ β-LACTAM-4-YLIDENE: INSERTION REACTIONS

2.4.4.1.0 □ β-lactam-4-yldenes: Intermolecular insertion reactions

Since the generation of the carbenes, β-lactam-4-yldienes (181), from the spiro β-lactam oxadiazolines (172) is quantitative (R^4 = R^5 = Me), it is conceivable that the β-lactam-4-ylidene system (172) can be an efficient synthon for the
4-acetoxy-2-azetidinone building block (see Section 1.1.4.3.0) as well as a direct synthon for other carbene insertion reactions.

The thermolysis of the spiro β-lactam oxadiazolines 172a (0.15 M) in benzene in the presence of acetic acid (0.40 M) produced, after ca. 8 hours, the 4-acetoxy-β-lactam (195) in quantitative yield. After bulb to bulb distillation the ¹H NMR spectrum of the volatiles showed the presence of only the excess acetic acid and acetone. The ¹H NMR spectrum of the residue was that expected for β-lactam 195. A singlet at δ(ppm) 7.02 corresponding to H-4 and a singlet at 1.72 corresponding to the ester OCH₃ group were obtained. The ¹³C chemical shifts (Table 13) show two carbonyl groups at δ(ppm) 165.57 and 170.07 for the β-lactam and the ester, respectively, as well as deshielding at C-4, the point of acetoxy attachment, (δ(ppm) 83.22) relative to that at C-3 (δ(ppm) 72.87).

Furthermore, the thermolysis of 172a (0.15 M) in benzene with methanol (12.0 M) added, afforded 196. As with compound 195, the 4-methoxy β-lactam (196) was obtained quantitatively. The ¹H NMR spectrum showed a singlet at δ(ppm) 5.75 corresponding to H-4 and a singlet at 3.23 corresponding to the methoxy group. Moreover, the ¹³C NMR spectrum showed the C-3 chemical shift (δ(ppm) 71.86) comparable to that of 195 (Table 13), but with C-4 considerably more deshielded (δ(ppm) 90.68).

Similar results were obtained when the spiro β-lactam oxadiazoline 172g was thermolyzed in the presence of methanol or ethanol. The 4-methoxy and the 4-ethoxy-β-lactams, 197 and 198, respectively were obtained in quantitative yields.
Table 13. $^{13}$C NMR of C=O, C$_3$, C$_4$, and infrared frequencies of the β-lactam carbonyl for the 4-alkoxy-β-lactams 195, 196, 197, 198, 200.

<table>
<thead>
<tr>
<th>Cpd.</th>
<th>Isomer</th>
<th>C=O</th>
<th>C$_3$</th>
<th>C$_4$</th>
<th>IR (C=O, cm$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image.png" alt="Chemical Structure" /></td>
<td>196</td>
<td>166.13</td>
<td>71.86</td>
<td>90.68</td>
<td>1753 (KBr)</td>
</tr>
<tr>
<td><img src="image.png" alt="Chemical Structure" /></td>
<td>195</td>
<td>165.57</td>
<td>72.87</td>
<td>83.22</td>
<td>1768 (film)</td>
</tr>
<tr>
<td><img src="image.png" alt="Chemical Structure" /></td>
<td>197</td>
<td>trans 163.94</td>
<td>84.61</td>
<td>83.67</td>
<td>1770 (film)</td>
</tr>
<tr>
<td>cis 163.07</td>
<td>81.79</td>
<td>88.23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image.png" alt="Chemical Structure" /></td>
<td>198</td>
<td>trans 161.15</td>
<td>87.55</td>
<td>84.54</td>
<td>1770 (film)</td>
</tr>
<tr>
<td>cis 161.15</td>
<td>84.01</td>
<td>81.61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image.png" alt="Chemical Structure" /></td>
<td>200</td>
<td>166.45</td>
<td>72.99</td>
<td>86.32</td>
<td>1767 (KBr)</td>
</tr>
</tbody>
</table>
Compound 197 was formed in a cis : trans ratio of 1 : 2.6 and compound 198 was formed in a cis : trans ratio of 1 : 4. The stereochemistry was assigned from the coupling constants, between H-3 and H-4, with $J_{\text{cis}} = 3.6$ Hz and $J_{\text{trans}} = 0 - 1$ Hz.

An attempt to trap HCN using acetone cyanohydrin was unsuccessful. Again, the thermolysis of 172a (0.15 M) in benzene in the presence of acetone cyanohydrin (ca. 0.75 M) produced 200 instead of 199, the product of HCN insertion. The

4-alkoxy-β-lactam (200) is the result of a direct OH insertion on the β-lactam carbenic site. No HCN insertion product was formed, 200 was produced in > 95% yield (Scheme 34). The $^1$H NMR spectrum showed a singlet at δ(ppm) 3.39 corresponding to H-4 and...
two magnetically non-equivalent methyl groups at $\delta$(ppm) 1.51 and 1.08. $^{13}$C NMR spectroscopy showed C₃ and C₄ at 72.99 and 86.32; chemical shifts comparable to those in the other 4-alkoxy-$\beta$-lactams (Table 13). The presence of the nitrile group (C≡N) was depicted by the carbon chemical shift at $\delta$(ppm) 120.23. Also, infrared spectroscopy showed absorptions at 2240 cm$^{-1}$ and at 1767 cm$^{-1}$, thus confirming the presence of the nitrile and the $\beta$-lactam moieties, respectively. Such a structure (200) could be considered to be a result of carbonyl ylide trapping product by HCN. However, due to the fact that this carbonyl ylide has not been trapped by acetic acid, methanol, or ethanol, it is highly unlikely that in this case it is trapped quantitatively.

The reaction of the $\beta$-lactam-4-ylidenes (181) with electron poor olefins, like acrylonitrile, could mean that the carbene is nucleophilic. Therefore, if OH insertion proceeded by proton transfer (nucleophilic carbene insertion mechanism into OH-bonds, see Section 1.2.3.3.3), and subsequent ion pair collapse, the loss of CN$^-$ from (CH$_3$)$_2$(CN)O$^-$ is too slow to compete.

Furthermore, the thermolysis of 172b in neat CCl$_4$ at 100 °C in a sealed tube produced a product which could be the 4-chloro-2-azetidinone (202, Scheme 35). Decomposition of 202 upon manipulation precluded its isolation. Evidence in favor of the
formation of 202 comes from the $^1$H NMR spectrum of the crude product which showed the disappearance of the two doublets, at $\delta$(ppm, CCl$_4$) 4.54 ($J = 15.3$ Hz) and 4.10 ($J = 15.3$ Hz), due to the diastereotopic benzylic methylene group of the spiro $\beta$-lactam oxadiazoline (172b), and their replacement by a new pair of doublets, at $\delta$(ppm, CCl$_4$) 4.85 ($J = 15.3$ Hz) and 4.11 ($J = 15.3$ Hz), presumably due to the diastereotopic benzylic methylene of 202. Further evidence comes from the infrared spectrum of the crude product which showed absorption in the $\beta$-lactam carbonyl region (1785 cm$^{-1}$). The yield of 202 was calculated from the $^1$H NMR spectrum (sealed NMR tube) after the thermolysis. If the oxadiazoline (172b) is considered to have decomposed to form acetone in 95% yield then the relative integrals of the acetone peak to the new doublet of doublets gives the yield as $\approx$ 78%. GC/MS(EI) of the crude product showed a chromatogram of eight peaks. Two peaks corresponded to diphenylketene, with 91% fit with the MS library search result, yet with different retention times (11.196 and 21.824 min). This shows that the product is not surviving the GC temperature. One peak ($R_t$ = 25.596 min) corresponded to ($M^+ - \text{Cl} =$ 428), another ($R_t$ = 25.888 min) corresponded to ($M^+ - 3\text{Cl} =$ 358). However, the major peak corresponded to the $\beta$-lactam-4-ylidene structure ($M^+ - \text{CCl}_4 =$ 311). Also, one of the peaks corresponded to hexachloroethane (203). This latter compound should be due to the coupling of two trichloromethyl radicals formed after a homolytic Cl-C bond cleavage to form 201 (Scheme 35) or it could be generated by thermolysis of 202 in the GC inlet system.

2.4.4.2.0 β-lactam-4-ylidenes: Intramolecular insertion reactions.

From the foregoing, the importance of the $\beta$-lactam-4-ylidenes (181) as building blocks for fused bicyclic $\beta$-lactams such as that in Figure 18, with $T$ being an intramolecular carbene trap, is apparent.
2.4.4.2.1 Synthesis of oxapenam (209) and the oxacepham (217)

The oxapenam nucleus (209) was successfully synthesized by the same carbene methodology (Scheme 36 and eq 25). Semicarbazide hydrochloride (166) was condensed with acetone to form the 4-unsubstituted semicarbazone (167), as in Schemes 25 and 36. Transamination with ethanolamine occurred at ≈ 150°C and was completed after about half an hour to produce the 4-substituted acetone semicarbazone (204). Lead tetraacetate oxidation of the alcohol 204 led to the formation of the spirow bicyclic amino-alkoxy oxadiazoline (211) via 210 (eq 26). Therefore, alcohol (204) was protected as the tert-butyldimethylsilylether derivative (205, Scheme 36) in quantitative yield. Oxidation of 205 led to the imino-oxadiazoline (206). The 2-imino-Δ³-1, 3, 4-oxadiazoline (206) was converted to the β-lactam (207) upon treatment with the acid chlorides a,b, and c and triethylamine. The deprotection of (207a) with tetrabutylammonium fluoride afforded the alcohol 208a in 82 % yield. β-Lactams (208) now have an intramolecular trapping group (O-H) attached in place to afford a five membered ring via a carbene to alcohol insertion. The oxapenam (209) was indeed formed, in 50 % yield, upon thermolysis of 208a (0.15 M) in benzene (eq 25); see Table 14 for selected ¹³C NMR and IR data. Reducing the concentration of 208a to 0.008 M did not increase the yield of the oxapenam, on the contrary a slight decrease in the yield was observed. This phenomenon could be due to the tendency of 208a to undergo an
intramolecular insertion reaction in the form of oligomers. Oligomers of alcohols are believed to be more reactive towards carbenes than monomers, presumably because hydrogen bonding in the former causes weakening in the OH-bond (see Section 1.2.3.3.3). However, it is to be expected that at high concentrations the intermolecular starts to
compete with the intramolecular insertion reaction. Therefore, a compromise in the concentration should be sought.

Deprotection of 207b and 207c led to 208b and 208c, respectively. Contrary to 208a the thermolysis of 208b and 208c did not lead to the oxapenam skeleton, the analogues of 209 (Scheme 37). This could be due to several reasons; one reason could be the presence of a hydrogen or a chlorine, alpha to the carbenic site, that can migrate to form a highly strained product that could decompose under the reaction conditions. Another possibility could be that the oxapenam skeletons obtained are not stable under the reaction conditions.

Therefore, the intramolecular carbene insertion method works quite well with neutral substituents (like phenyl) but the presence of a heteroatom (like O, Cl) and/or a hydrogen atom on the alpha carbon seems to preclude the formation and/or isolation of an oxapenam substructure. Due to the absence of a major product from 208b,c, the
Table 14. $^{13}$C NMR of $\beta$-lactam ring carbons and infrared frequencies of the $\beta$-lactam carbonyl for the oxapenam (209) and the oxacephams (217) and (225).

<table>
<thead>
<tr>
<th>Cpd.</th>
<th>C=O</th>
<th>C$_5$</th>
<th>C$_6$</th>
<th>IR (C=O, cm$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 209" /></td>
<td>179.82</td>
<td>92.93</td>
<td>70.73</td>
<td>1785 (film)</td>
</tr>
<tr>
<td><img src="image" alt="Structure 217" /></td>
<td>169.08</td>
<td>85.65</td>
<td>72.25</td>
<td>1750 (KBr)</td>
</tr>
<tr>
<td><img src="image" alt="Structure 225" /></td>
<td>166.50 (β-lactam)</td>
<td>86.38</td>
<td>73.77</td>
<td>1762 (KBr)</td>
</tr>
</tbody>
</table>

The oxacephem nucleus (217) was also synthesized by the same method. Surprisingly the oxacephem yield in this case was only 30 %, even when the concentration of 216 in benzene was only 0.007 M. In order to determine if the low yield is due to product instability, the isolated oxacephem (217) was re-exposed to the same reaction conditions (100°C, with benzene as a solvent, in a sealed tube). During 9 hours the oxacephem (217) did not change, implying that the low yield is not due to product decomposition.
The spiro β-lactam oxadiazoline (215b) was synthesized by the reaction of phenoxyacetyl chloride with 214 in the presence of excess triethylamine. This led to only one diasteromer of 215b, presumably with the same stereochemistry at C-3 as that for 172g (PhO and the oxadiazoline "O" being trans). Deprotection of 215b by tetrabutylammonium fluoride afforded 218 and 219 (Scheme 39). Presumably the fluoride ion is causing isomerization by deprotonating the C-3 site. Fluoride ion in THF is a very strong base.\textsuperscript{303,304} Therefore, 215 was deprotected by the acetic acid / H\textsubscript{2}O / THF method,\textsuperscript{304} and 218 was produced quantitatively (Scheme 39). It is noteworthy that 218 was produced in minor amounts by the fluoride deprotection method. This implies that the ketene - imine cycloaddition to form 215b occurs under kinetic control, as for 172g. The thermolysis of 218, and in a separate experiment the thermolysis of 219, like thermolysis of their analogue 208b, did not produce the β-lactam fused bicyclic structures (Scheme 40). Loss of entropy as well as increase in enthalpy (strain energy) might be leading to a high energy transition state to form the β-lactam fused bicyclic structures. The rate constants for the decomposition were not determined but it was evident that 219 was decomposing at a much slower rate than 218. A similar rate difference was observed
for 172g and 172h (Section 2.4.2.0.0).

In order to get around this problem, we attempted to trap the carbene intermolecularly by acetic acid in the hope that it would afford the 4-acetoxy-2-azetidinone. This intermediate would then, presumably, undergo
displacement of the acetoxy group, at the C-4 position, by the internal hydroxy moiety.

The thermolysis of 218 was conducted in acetic acid / benzene (1:1) at a concentration of 0.33 M. The disappearance of 218 was monitored with $^1$H NMR; after four hours the decomposition was over. Bulb to bulb distillation, at 0.02 mm of Hg,
afforded a yellowish oily residue and a clear volatile liquid. The $^1$H NMR of the volatiles showed the presence of acetone, acetic acid and benzene. The residue was a mixture of products; purification on the Chromatotron, using 25% ethyl acetate in hexane, afforded three products. The first fraction was (220a) which could be the result of insertion of the carbene into acetic acid and esterification of the free hydroxyl group. This result was not expected because esterification of acetic acid is known to take place only in the presence of a strong mineral acid. The other fraction was composed of the two expected carbene insertion products, the cis and trans isomers 221a and 221b, respectively. β-Lactam 220 was obtained in 9.5% yield as the cis isomer only. β-Lactam 221 was obtained in a total yield of 37% with a cis : trans ratio of 1 : 1.55. The oxacepham target was not obtained.

When the thermolysis was done in neat acetic acid the product ratios changed, but still the oxacepham was not among the products. The first fraction was 220b, obtained in 15.2% yield and the second fraction was the cis isomer (220a), obtained in 19.6%
yield. The third fraction (10.5 \%) was 221b. A fourth fraction was isolated but it was too small to be identified, most probably it is the cis isomer (221a).

Furthermore, when the protected alcohol (215a) was thermolyzed in (50:50) acetic acid / benzene, product 222 was obtained. Neither the deprotected 4-acetoxy-\(\beta\)-lactam nor the oxacepham were produced.

An inter - intra molecular competition experiment was conducted. The thermolysis of 218 in the presence of methanol (12 M) in benzene, did not afford any of the intramolecular insertion products. The only two compounds isolated were the products of the intermolecular insertion of methanol into the carbene, the cis and trans isomers 223a and 223b, respectively. The two products were separated by chromatography to give 43 \% of the trans (223b) and 19 \% of the cis (223a); total yield = 62 \% with a cis : trans ratio of 1 : 2.3.

2.4.4.2.2 □ Synthesis of anhydro-oxacepham (225): intramolecular carboxylic acid
The anhydro-oxacepham 225 was generated from the intramolecular insertion reaction of the β-lactam-4-ylidene into the carboxylic acid OH-group. Oxidation of the alcohol (216a) by Sharpless’ method using RuO₄, a mild oxidizing agent, generated the carboxylic acid (224) in 74% yield (Scheme 41). Due to the insolubility of 224 in benzene, the thermolysis was conducted in acetone in a sealed tube. The anhydro-oxacepham (225) was formed in 45% yield. It is well known that carbonyl ylides decompose to carbenes and carbonyl compounds reversibly (section 1.2.4.1.1). Therefore, using acetone as a solvent could increase the chances of trapping the carbonyl ylide. However, we were unable to detect any of the products that could be the result of an inter- or intra-molecular entrapment of the carbonyl ylide by the acid 224. Probably in all the intramolecular cases the ylides are in fact trapped but the products do not survive the reaction conditions.
2.4.4.2.3 Reaction with ester: Synthesis of 1-aza-5-p-nitro-phenyl-4, 7-dioxa-9-oxo-8, 8-diphenylbicyclo [4.3.0] non-5-ene (230).

The successful intramolecular insertion reactions of the β-lactam-4-yldenes (181), with alcohol and carboxylic acid moieties, led us to broaden the scope of our investigation to include esters. Carbene insertions into C-X bonds, where X = Cl, OR, SR, or NR₂, have been frequently reported in the literature.¹²¹,¹⁷² Also, heterocyclic and acyclic compounds have been reported to form as a result of the addition of carbenes to carbon-heteroatom multiple bonds.

The ester, spiro-β-lactam oxadiazoline (228), was successfully synthesized according to Scheme 42. The semicarbazone 204 was allowed to react with p-nitrobenzoyl chloride in the presence of triethylamine to form the ester 226 in 85% yield. Oxidation of 226, with lead tetraacetate, led to the imino-oxadiazoline (227) in 85% yield. The reaction of 227 with diphenylketene afforded the β-lactam-4-ylidene precursor with an intramolecular ester moiety (228, Scheme 42). All the structures in Scheme 42 fit their respective spectroscopic data.
It was expected that a nucleophilic attack of the ester oxygen on the carbene would occur, to give an ylide, subsequent rearrangement of which should give 229.

\[
\text{228, } \text{Ar} : _{\text{p-NO}_2 \text{C}_6 \text{H}_4}
\]

\[
\text{C}_6 \text{H}_6, \Delta
\]

Scheme 43

However, the thermolysis of 228 in benzene did not lead to the formal O-carbonyl insertion product 229, the only product obtained was 230 (Scheme 43). This fused bicyclic compound (230) could be formed according to the mechanism outlined in Scheme 44. Carbene addition occurs on the ester-carbonyl to form the oxirane (231). Homolytic bond cleavage, as shown in 231 (Scheme 44), leads to the diradical 232. β-scission generates the resonance stabilized diradical 233 and ring closure of 233 leads to the fused bicyclic product 230 (Scheme 44). The stucture of 230 has been deduced from its $^1$H NMR, $^{13}$C NMR, IR, and HRMS spectra, and confirmed by single crystal X-ray diffraction (Figure A1-13).

Although carbene’s formal insertion into C-O bonds and addition onto aldehydic and ketonic C=O bonds are known reactions, the insertion or addition reactions of carbenes with esters, to our knowledge, are unknown.
2.4.5.0.0 □ β-Lactam-4-Ylidenes: 1,2 ~ H-migration

The synthesis and isolation of azetinones (80 and 92) have been attempted by several workers, yet failure was the result (Section 1.1.4.3.2). However, the substructure of azetinones 92 was observed spectroscopically at low temperature (see Section 1.1.4.3.2). Also, the substructure of 80 has been postulated as an intermediate in the nucleophilic substitution reactions on β-lactams with a good leaving group at C-4 (see Section 1.1.4.3.2).

β-lactam-4-y'ldenes with a hydrogen at C-3 or N-1 could be perceived as
potentially excellent precursors for either 80 or 92 (Scheme 45). A simple 1,2 hydrogen migration should lead to the azetinone nucleus (Scheme 45). The approach taken involved the generation of 181 and the capture of 92, in situ, by two methods; Michael addition and Diels-Alder cycloaddition.

As described in Section 2.4.4.1.0, the thermolysis of 172g (0.39 M) in benzene in the presence of methanol (12 M) led to the insertion product, 4-methoxy β-lactam, in 100 % yield. The 4-methoxy-β-lactam (197) was formed as a mixture of the cis and trans isomers in a ratio of 1 to 2.6, respectively (eq 27). It should be expected that at a lower concentration of methanol the carbene 181 should have a better chance to undergo a 1,2-hydrogen migration forming 92, before encountering a methanol molecule which would lead to 197.

Therefore, the thermolysis was conducted in methanol-d₄ in the hope of obtaining 197-D₃, the product expected from a Michael addition of CD₃OD on 92. Isomer 197-D₄ should be expected from the direct attack of the carbene (181) on CD₃OD. The experiment has been performed initially at high CD₃OD concentration (12.00 M) to insure the formation of 197-D₄. The ¹H NMR spectrum of 197-D₄ (trans and cis) would provide the trans and cis chemical shifts for the proton at C-3. It is clear from Table 15 that the chemical shifts at δ (ppm) 5.26 and 5.30 correspond to the proton at C-3 in the trans and cis isomers (197a and 197b), respectively. Therefore, at low CD₃OD concentration, if 197-D₃ is formed then the ¹H NMR should give singlets at 5.68 and 5.44 for the cis and trans isomers, respectively.
Table 15. $^1$H NMR chemical shifts and coupling constants for β-lactams 197 and 197-D4

<table>
<thead>
<tr>
<th>197a (trans)</th>
<th>197b (cis)</th>
<th>197-D4 (trans)</th>
<th>197-D4 (cis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhO</td>
<td>PhO</td>
<td>PhO</td>
<td>PhO</td>
</tr>
<tr>
<td>H</td>
<td>OCH$_3$</td>
<td>H</td>
<td>OCD$_3$</td>
</tr>
<tr>
<td>O</td>
<td></td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>N</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
</tr>
<tr>
<td>δ = 5.44 ppm</td>
<td>J = 0.63 Hz</td>
<td>δ = 5.68 ppm</td>
<td>J = 3.60 Hz</td>
</tr>
<tr>
<td>br. s, δ = 5.26 ppm</td>
<td></td>
<td>d, δ = 5.33 ppm, J = 3.60 Hz</td>
<td></td>
</tr>
</tbody>
</table>

Three experiments were conducted at different concentrations (Table 16). At low CD$_3$OD concentrations (entry 1, Table 16) there was no evidence for the formation of 197-D3 or 197-D4. No major product was formed, thus the fate of the carbene 181 was left undetermined. Increasing the concentration of the carbene precursor to 0.33 M but keeping its ratio to CD$_3$OD low (1 : 1.2), did not provide either of the expected products (197-D3,4). However, keeping the concentration of 172g the same (0.33 M, entry 3, Table 16) and increasing the ratio of 172g to CD$_3$OD to 1 : 10 (entry-3, Table 16) afforded about 70% of 197-D4, the product of direct carbene insertion into CD$_3$OD. Again, product
Table 16. Thermolysis of 172g in the presence of CD$_3$OD at different concentrations.

<table>
<thead>
<tr>
<th>Entry</th>
<th>172g</th>
<th>CD$_3$OD</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.04 M</td>
<td>0.06 M</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>0.33 M</td>
<td>0.40 M</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>0.33 M</td>
<td>3.30 M</td>
<td>Carbene trapped =70 % 197-D4</td>
</tr>
<tr>
<td>4</td>
<td>0.33 M</td>
<td>12.0 M</td>
<td>Carbene trapped 100 % 197-D4</td>
</tr>
</tbody>
</table>

197-D3 was not detected.

The second experiment conducted in the same regard, was the thermolysis of 172g in the presence of 1,3-diphenyl isobenzofuran, 234 (eq 28). If azetinone 92 is formed it would be trapped, in situ, as the 2π + 4π cycloadduct 235 (eq 28).

The thermolysis of 172g did not take the course leading to 235. Instead of 235, two isomeric 1 : 1 adducts of 92 and 234 were isolated. Spectroscopic data (IR, $^1$H NMR, $^{13}$C NMR, MS) for both isomers were very similar. Infrared spectra of both isomers indicated a higher β-lactam carbonyl frequency (1800 cm$^{-1}$) than in 172g (1792 cm$^{-1}$) and the presence of another carbonyl group (1740 cm$^{-1}$) and an absorption at around 1670 cm$^{-1}$, characteristic of the CC double bond in 4-alkylidene β-lactams. Single crystal X-ray diffraction showed that one of the isomers was Z-4-(1-(2-benzoylphenyl)-1-phenyl) methylene-1-phenyl-3-phenoxyazetidine-2-one, 236 (eq 29). The other product could be identified, from its spectra, as the corresponding E-isomer, 237 (eq 29). In view of the fact that β-lactam-4-ylenes have been shown to add to CC double bonds (Section 2.4.3.2.0), as in styrene (Section 2.4.3.2.2) and
4-bromo-1-butene (Section 2.4.3.2.3), analogous cyclopropanation could occur in the first step, to form 238, presumably as a mixture of all possible isomers. As a special

divinylcyclopropane, with heteroatom substituents and phenyl groups as well, isomers 238 are not expected to be stable at 100°C. A reasonable mechanism for formation of 236
and 237 (Scheme 47) begins with an expected vinylcyclopropane bond cleavage in 238, leading to diradical 239, which undergoes β-scission to form 236 and 237.

There isn’t any precedent for formation of 4-methylene β-lactams by a carbene route. Moreover, the reaction is an unusual one for carbenes of any kind representing, in a purely formal sense, the coupling of two different carbenes.

2.5.0.0.0 AM1 calculations on the β-lactam ylides.

2.5.1.0.0 β-Lactam Carbonyl ylide.

AM1 calculations were performed on the β-lactam carbonyl ylide (178) (formed from spiro-β-lactam oxadiazoline 172a) in order to study the relationship between the ylide’s conformation and its reactions. Experiments have shown (Section 2.4.2.0.0) that the β-lactam carbonyl ylide’s main reaction is fragmentation to form the β-lactam-4-ylidene (181). Presumably, fragmentation occurs by a concerted loss of N₂ to form the β-lactam carbonyl ylide (178), followed by fragmentation to the ketone and the β-lactam-4-ylidene, 181, (Section 2.4.2.0.0). Steric congestion in the (0°, 0°) conformation (177) and/or charge separation caused by inductive and/or resonance charge stabilization caused by the β-lactam-nitrogen, are two factors that could lower the energy barrier for rotation about the ylide’s O-C bonds (Section 1.2.4.1.1), hence increasing the population of the (0°, 90°) conformation; a conformation which usually leads to fragmentation generating carbenes (Section 1.2.4.1.1, Scheme 27).

The bond lengths, bond angles, and dihedral angles from the AM1 predicted energy minimum conformation, for the β-lactam carbonyl ylide, are shown in Figure 19.

Analysis of the results show that the carbonyl ylide does not have the (0°, 0°) geometry as the energy minimum conformation, the dihedral angle "dcba" is 146.01° (34°). This twisting could be due to steric interactions and/or to charge localization. The charge at site "d" is -0.052 whereas at site "b" it is -0.047. Also, bond c-b (1.308 Å) is
shorter than bond c-d (1.363 Å). Both the charge distribution and the bond lengths suggest some charge localization in the energy minimum conformation. The negative charge at site "d" causes pyramidalization at that site (dihedral "gfde" is 132.17°, Figure 19). The twisted conformation, the localized charge, and the pyramidalization at site "d" are criteria for fragmentation.

Starting from the energy minimum conformation, the dihedral angle "dcba" was rotated by 30° increments. This rotation led to fragmentation between the (0°, 95°) and (0°, 120°) conformations. The fragmentation occurred unidirectionally to form the β-lactam-4-ylidene and acetone. Thus, the experimental observations were reproduced. Figure 20 shows the heat of formation of the energy minimum conformation (0°, 34°) with respect to the (0°, 0°) and the (0°, 90°) conformations. It should be noted that the O-C bond length "cd" increases from 1.346 Å → 1.363 Å → 1.409 Å when going from (0°, 0°) → (0°, 34°) → (0°, 90°) conformations, respectively.

On the other hand, putting a phenyl substituent at C₆ seems to have changed the electronic distribution in the carbonyl ylide. Experimentally, the ylide from
oxadiazoline 172q or r led to fragmentation, but in competition with [1,4] H~migration (see Section 2.4.2.0.0). Therefore, the replacement of the methyl group by a phenyl group has increased the life time of the ylide.

The β-lactam carbonyl ylide from 172 (q or r) was fully optimized by AM1.

Bond lengths, bond angles, and dihedral angles for the energy minimum conformation, as predicted by AM1, are shown in Figure 21. The structure of the, AM1 predicted, energy minimum conformation was twisted by 48° (dihedral angle "ij:ba" = 131.94°). Also, the methyl and the benzyl were syn (Figure 21). As for the methyl analogue, a 30° increment
dihedral twist was applied. However, after a 360° dihedral twist, the ylide did not fragment. It should be noted that the negative charge is concentrated at site "b" (-0.144, Figure 21), instead of site "d" as for the methyl analogue (Figure 19).

Thus, the theoretical results are in parallel with the experimental observations.

Moreover, according to AM1 the (0°, 0°) conformation is higher than the (0°, 48°) conformation by only 5.24 kcal. (Figure 22). Therefore, the rotation is easier than for the methyl analogue (7.66 kcal.); thus, this could be one of the factors in favor of the [1,4] H ~ migration.

2.5.2.0.0 □ β-Lactam thio carbonyl ylide

The sulfur analogue of 172a was also studied. Experimentally, 162 and its phenyl analogue do not fragment to carbenes; in both cases the thiiranes were formed quantitatively (see Section 2.3.1.1.0). Furthermore, the β-lactam thio carbonyl ylide (163) did not undergo a 1, 3 dipolar cycloaddition reaction with dimethylacetylene dicarboxylate. This result led to the belief that the structure of the energy minimum conformation of this sulfur ylide is twisted.

The sulfur analogue of 172a was fully optimized by AM1. Bond lengths, bond angles, and dihedral angles for the energy minimum conformation, as predicted by
AM1, are shown in Figure 23. The structure of the AM1 predicted, energy minimum conformation was twisted by 23° (dihedral angle "dcba" = 22.80°). In contrast to the oxygen analogue, the "d" site was not pyramidal (dihedral angle "gfdc" = 180.03°, Figure 23). As for the oxygen analogue, a 30° increment dihedral twist was applied. However, after a 360° dihedral twist, the ylide did not fragment. Figure 24 shows that the (0°, 0°)

![Figure 23. Energy minimum conformation for the thiocarbonyl ylide after full optimization by AM1; selective bond lengths (Å), bond angles (°), and dihedral angles (°) are shown above.](image)

![Figure 24. A plot showing the heat of formation of the energy minimum conformation (0°, 23°) with respect to the (0°, 0°) and the (0°, 90°) conformations.](image)

conformation is very close in energy to the (0°, 23°), but lower than the (0°, 90°) by 4.48 kcal. (Figure 24).
In summary, the AM1 calculations are in accord with experimental results. AM1 predicted that the carbonyl ylides would fragment to form the β-lactam-4-ylidenes, for the dimethyl case. Also, when one methyl was replaced by a phenyl, AM1 did not fail to predict that the resulting ylide would be more stable. Moreover, AM1 predicted a stable ylide if the oxygen was replaced by a sulfur, in accord with experimental results. Therefore, AM1's consistency, in reflecting experimental observations, makes, at least, the relative energy differences between the different conformations reliable.

2.6.0.0.0 ■ Conclusion

It can be concluded that while the imino-triazolines, imino-thiadiazolines, and imino-oxadiazolines are very similar systems, their chemistry is drastically different.

Upon quaternization of the $sp^2$ ring system, the imino-triazoline system extrudes $N_2$ to form the azomethine ylide. The reaction of the imino-triazoline with benzoylcyanide formed the aziridine. Moreover, the imino-triazoline system did not form a stable spiro-β-lactam triazoline when treated with diphenylketene.

On the other hand the quaternization of the imino-thiadiazoline $sp^2$ ring carbon did not lead to $N_2$ extrusion in all cases. The reaction of the imino-thiadiazoline with diphenylketene led to $N_2$ extrusion followed by electrocyclic ring closure to form the spiro-β-lactam thirane as the only product, if the substituent on nitrogen was a phenyl group. Replacing the phenyl group on nitrogen by a benzyl group led to the isolation of both the spiro-β-lactam thiadiazoline and the product of $N_2$ extrusion, the corresponding spiro-β-lactam thirane. The spiro-β-lactam thiadiazoline loses $N_2$ thermally to form the thirane as the only product.

The chemistry of the oxadiazoline system was very different. Imino-oxadiazolines reacted with different substituted ketenes to form the corresponding spiro-β-lactam oxadiazolines. Quaternization of the $sp^2$ ring carbon did not lead to $N_2$
extrusion; the spiro-β-lactam oxadiazoline system was very stable at room temperature. The thermolysis of the spiro-β-lactam oxadiazoline system at 100°C led to the novel β-lactam-4-ylidene, as the only product. Therefore, cycloreversion to N₂ and a carbonyl ylide is followed by clean, unidirectional fragmentation of the ylide. Contrary to the sulfur ylide, the carbonyl ylide did not lead to electrocyclic ring closure.

The substituents effect on the thermolysis rate constants was also studied. For example, putting a phenyl group at C₆, the opposite end of the carbonyl ylide, considerably enhanced the thermolysis rate, but the [1,4] H-migration started competing with carbene generation.

AM1 calculations have shown that the β-lactam carbonyl ylide has a twisted energy minimum conformation with some charge localization. Also, AM1 predicted that a dihedral twist of 95 - 120° should cause the ylide to fragment to form the β-lactam-4-ylidene and the ketone. Thus, AM1 predictions reflect the experimental observations.

In summary the spiro-β-lactam oxadiazolines have been synthesized in good yields and they have proven to be an excellent source of β-lactam-4-yldenes.

The novel β-lactam-4-yldenes proved to be a building block for novel β-lactam systems that could not be synthesized otherwise. The β-lactam-4-yldenes were trapped inter- and intra-molecularly by insertion and addition reactions as summarized in Scheme 48.
Scheme 48
CHAPTER 3

EXPERIMENTAL

For in revery you cannot rise above your achievements nor fall lower than your failures.

K. Gibran

3.0.0.0.0 ■ General

Melting points (mp) were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM-500, Bruker AM-200, or an EM-390 spectrometer, with the AM-500 and the AM-200 being equipped with a 5mm dual frequency $^1$H-$^{13}$C probe; the EM-390 is equipped with a 5 mm H-probe. Proton spectra were acquired at 500.14 MHz on the AM-500, 200.13 MHz on the AM-200, or at 90 MHz on the EM-390 spectrometer. Unless otherwise noted, chloroform-d was used as a solvent and tetramethylsilane (TMS) was used as an internal standard. The chemical shifts are reported in $\delta$ values (ppm), followed in brackets by the multiplicity symbol (s= singlet, d= doublet, t= triplet, q= quintet, m= multiplet), the coupling constants where appropriate, the number of protons, and the type of group. $^{13}$C NMR spectra were acquired at 125.76 MHz on the Bruker AM-500 or at 50.32 MHz on the Bruker AM-200 spectrometer. The solvent was chloroform-d unless otherwise noted and the peaks are calibrated against the 77.00 ppm peak of CDCl$_3$. Chemical shifts are reported in $\delta$ values (ppm), followed in brackets by the the type of carbon.

Infrared spectra (IR) obtained with a Perkin-Elmer model 283 instrument, are reported in wavenumbers (cm$^{-1}$), calibrated against the 1601.4 cm$^{-1}$ band of a polystyrene film.
Ultraviolet (uv) spectra were obtained with a Hewlett-Packard model 8451A diode array spectrophotometer. Methylene chloride (HPLC grade) was used as solvent in all cases.

Low resolution EI and CI mass spectra (LRMS) were obtained using a VG Analytical ZAB-E double focussing mass spectrometer. Typical experimental conditions were as follows: resolution = 1000, electron energy = 70 eV, source temperature = 200°C, and source pressure = 2 x 10^-6 mbar for EI and 4 x 10^-5 mbar for CI. Elemental composition determinations were made with a resolution of 5000. GC / MS experiments were performed using a Hewlett-Packard Mass Selective Detector (bench top quadrupole mass spectrometer) operated in EI mode only.

Gas chromatographic analysis were done on a Varian VISTA 6000 instrument equipped with an off-column flash injector and a flame ionization detector (FID) at 300°C.

Analytical thin-layer chromatography (TLC) was conducted by using plastic-backed, Merck Kieselgel 60 F_{254}, 0.2 mm silica plates or plastic-backed Polygram ALOX, N/uv_{254}, 0.2 mm neutral alumina plates. Compounds were visualized by means of UV light (254 nm) or I₂ vapor. Preparative chromatographic separations were conducted by centrifugal chromatography carried out on silica (Merck Kieselgel 60 PF_{254}) coated plates (coating 2 or 4 mm. thick) spinning in a Chromatotron model 17924T apparatus, or by flash chromatographic separations using E. Merck silica gel 60, 230-400 mesh.

The flow rate, for the reagent addition (where appropriate), was controlled using a syringe pump, Harvard Apparatus Pump 22.

Solvents and reagents were used as received without purification, unless otherwise noted. Tetrahydrofuran was freshly distilled from benzophenone ketyl. Triethylamine was distilled from KOH and stored over KOH. Benzene was distilled from P₂O₅ and stored over molecular sieves. Methylene chloride was freshly distilled from P₂O₅. Reactions demanding H₂O or O₂ free atmosphere were conducted under an
atmosphere of dry nitrogen in oven-dried glassware. All extracts were dried over MgSO₄.

3.1.0.0.0 ■ Triazolines

3.1.1.0.0 □ Synthesis of 5, 5-dimethyl-4-benzyl-3-benzylimino-Δ¹- 1, 2, 4-triazoline (141).

Triazoline 141 was synthesized following the procedure outlined, by Taguchi and Warkentin,²⁹⁰ for the phenyl analogue 137.

(i) Acetone-4-benzyl-thiosemicarbazone:

¹H NMR (90 MHz, CDCl₃) δ 8.49 (br. s, 1H, NH), 7.74 (br. s, 1H, NH), 7.44 - 7.18 (m, 5H, Ar), 4.93 (d, 2H, CH₂), 1.95 (s, 3H, CH₃), 1.88 (s, 3H, CH₃).

(ii) Thiosemicarbazone-methyl iodide-salt:

¹H NMR (90 MHz, CDCl₃) δ 8.95 (br. s, 1H, S=CNHN), 7.55 - 7.21 (m, 5H, Ar), 4.75 (br. s, 1H, NH), 2.85 (s, 3H, CH₃), 2.25 (br. s, 6H, 2 x CH₃).

(iii) Triazoline 141:

Obtained as a yellow oil, in 20 % yield (based on the acetone 4-benzyl-thiosemicarbazone); IR (neat) ν 1685 cm⁻¹ (C=N); ¹H NMR (200.13 MHz, CDCl₃) δ 7.43 - 7.20 (m, 10H, Ar), 5.32 (s, 2H, CH₂), 4.51 (s, 2H, CH₂), 1.36 (s, 6H, CH₃); ¹H NMR (90 MHz, CCl₄) δ 7.43 - 7.03 (m, 10H, Ar), 5.17 (s, 2H, CH₂), 4.40 (s, 2H, CH₂), 1.27 (s, 6H, CH₃); ¹³C NMR(125.76 MHz, CDCl₃ = 77.2 ppm) δ 159.34 (C=N), 141.99 (C₁, Ar), 137.72 (C₁, Ar), 128.63 (Ar), 128.57 (Ar), 128.54 (Ar), 128.51 (Ar), 128.39 (Ar), 128.02 (Ar), 127.62 (Ar), 126.49 (Ar), 101.01 (C₅), 52.58 (CH₂), 44.61 (CH₂), 23.73 (2 x CH₃).

3.1.1.1.0 □ Reactions of 5, 5-dimethyl-4-benzyl-3-benzylimino-Δ¹- 1, 2, 4-triazoline (141).

3.1.1.1.1 □ Synthesis of 1-benzyl-2-(N-p-nitrobenzoyl)-benzylimino-2-cyano-3,
3-dimethylaziridine (147).

The benzylimino-triazoline (141) (1.71 mmol) was dissolved in dry acetonitrile (1 mL). To this solution a solution of p-nitrobenzoyl cyanide (1.71 mmol) in acetonitrile (6 mL) was added. The mixture was left stirring, under nitrogen, at room temperature for 2 days, after which acetonitrile was pumped out and the viscous oil was titurated with petroleum ether in ether (ratio 2 : 3). Purification by centrifugal chromatography afforded the aziridine 147, as a thick yellow oil, in a yield of = 30 % based on the starting material consumed; IR (neat) ν 2240 cm⁻¹ (C≡N), 1670 cm⁻¹ (C=O), 1525 cm⁻¹ (NO₂, st as), 1348 cm⁻¹ (NO₂, st sy); ¹H NMR (500.13 MHz, CDCl₃) δ 8.32 (d, J = 8.7 Hz, 2H, Ar), 7.81 (d, J = 8.7 Hz, 2H, Ar), 7.50 - 6.99 (m, 10H, Ar), 5.05 (d, J = 15.1 Hz, 1H, CH₂), 4.59 (d, J = 15.2 Hz, 1H, CH₂), 4.43 (d, J = 15.1 Hz, 1H, CH₂), 4.09 (d, J = 15.2 Hz, 1H, CH₂), 1.74 (s, 3H, CH₃), 1.55 (s, 3H, CH₃); ¹³C NMR (125.76 MHz, CDCl₃ = 96.7 ppm) δ 150.94 (C=O, +ve), 149.37 (C₄, p-NO₂C₆H₄, +ve), 141.67 (C₁, Ar, +ve), 140.15 (C₁, Ar, +ve), 138.61 (C₁, Ar, +ve), 129.10 (Ar, -ve), 128.84 (Ar, -ve), 128.35 (Ar, -ve), 128.04 (Ar, -ve), 127.22 (Ar, -ve), 126.85 (Ar, -ve), 124.62 (Ar, -ve), 116.01 (C≡N, +ve), 97.62 (C₂, +ve), 75.54 (C₃, +ve), 53.07 (CH₂, +ve), 46.42 (CH₂, +ve), 28.67 (CH₃, -ve), 26.10 (CH₃, -ve); LRMS: m/z (EI) 440 (M⁺, 3 %), 324 (4 %), 173 (13 %), 149 (22 %), 91 (100 %), (CI, NH₃) 441 (M⁺ + 1, 100 %), 369 (13 %), 353 (29 %), 326 (7 %), 91 (5 %); HRMS: Calculated for C₂₆H₂₄N₄O₃ 440.1848, observed, 440.1840.

The p-nitrobenzoyl cyanide required was prepared from p-nitrobenzoyl chloride and CuCN, according to the method by Piechucki.³⁰⁶

3.1.1.1.2 □ Reaction of 141 with diphenylketene: Formation of N-Benzyl-2, 2-diphenylethanamide or N-benzylidiphenylacetamide (153).

(i) Diphenylacetyl chloride.

A mixture of diphenyl acetic acid (21.2g, 0.1 mol) and SOCl₂ (17.8g, 0.15 mol) was heated under reflux on a steam bath for 1 hour. The excess SOCl₂ was removed
under vacuum. Recrystallization from petroleum ether yielded 20.8 g (90%) of the
diphenylacetyl chloride, mp. 55 - 57°C.

(ii) Formation of 153.

Diphenylacetyl chloride (3.0 mmol) was dissolved in dry methylene chloride
(10 mL) and added dropwise to a stirred solution containing the triazoline, 141, (2.5
mmol) and triethylamine (6.0 mmol) in dry methylene chloride (20 mL) under nitrogen
atmosphere at ~ -23°C. The resulting reaction mixture was stirred overnight at room
temperature and washed with saturated sodium bicarbonate solution and brine. The
aqueous layers were re-washed twice with methylene chloride. The combined organic
layers were dried (MgSO₄) and filtered. Removal of the solvent afforded an oily residue
which, upon addition of ether / hexane, produced a white solid. This was further purified
by recrystallization from ethylacetate / hexane. The white solid was obtained in 65%
yield; mp 126°C; IR (KBr) ν 3260 cm⁻¹ (N-H), 1639 cm⁻¹ (C=O); ¹H NMR (90 MHz,
CDCl₃) δ 7.55 - 7.25 (m, 15H, Ar), 5.95 (br.s, 1H, N-H), 4.94 (s, 1H, C-H), 4.48 (d, 2H,
CH₂); ¹³C NMR (125.76 MHz, CDCl₃) δ 171.93 (C=O), 139.58 (2 x C₁, Ar), 138.33 (C₁,
Ar), 129.11 (Ar), 128.99 (Ar). 128.87 (Ar), 127.82 (Ar), 127.70 (Ar), 127.50 (Ar), 59.45
(C-H), 44.03 (CH₂); LRMS: m/z (EI) 301 (M⁺, 17%), 167 (Ph₂CH, 100%), 152 (13%),
91 (PhCH₂, 29%), (Cl, NH₃) 319 ((M + NH₄)⁺, 3%), 302 (M⁺ + 1, 100%), 226 (5%),
167 (7%), 106 (5%).

3.2.0.0.0 □ Thiadiazoines

3.2.1.0.0 ☐ Synthesis of 5,5-dimethyl-2-benzylimino-Δ⁳-1, 3, 4-thiadiazoline (159).

(i) Acetone 4-Benzyl-thiosemicarbzone.

The 4-benzyl-thiosemicarbazide required in the synthesis was prepared by the
modification of the method by Tisler. Benzyl isothiocyanate (0.1 mol) was dissolved in
60 mL of 95% ethanol. To the vigorously stirred solution hydrazine monohydrate (0.12
mol) was added in one portion. The solution was thoroughly mixed and cooled with ice for 15 minutes. The precipitate obtained was recrystallized from ethanol (95 % yield), mp 128-129°C. Acetone 4-benzyl-thiosemicarbazone (160) was prepared by heating under reflux 4-benzyl-thiosemicarbazide (0.1 mol) with 40 mL of acetone in 95 mL of 95 % ethanol until dissolution was effected. On cooling, the thiosemicarbazone (160) crystallized out in a pure state, mp 145-146°C, in 82 % yield. 

(ii) Synthesis of 159.

The oxidation of the acetone 4-benzyl-thiosemicarbazone (160) was accomplished based on the method by Landquist. Thiosemicarbazone 160 was dissolved (0.05 mol) in dry benzene (800 mL). Active manganese dioxide (1.25 mol) was added in one portion to the stirring solution. After 2 hours of stirring at room temperature, manganese dioxide was filtered and washed with benzene. Benzene was evaporated on the rotary evaporator and the product was purified by flash chromatography, using 30 % ether in hexane, to afford 159 (59 % yield) and the thione isomer (161) as a side product (6 % yield). 159: IR (film) v 1640 cm\(^{-1}\) (C=N); \(^1\)H NMR (90 MHz, CDCl\(_3\)) δ 7.55 - 7.20 (m, 5H, Ar), 1.80 (s, 6H, 2 x CH\(_3\)). 161: IR: (film) v 1300 cm\(^{-1}\) (C=S); \(^1\)H NMR (90 MHz, CDCl\(_3\)) δ 7.37 (s, 5H, Ar), 1.45 (s, 6H, 2 x CH\(_3\)).

Active manganese dioxide was prepared by the method in the "Textbook of Practical Organic Chemistry", Vogel.\(^{308}\)

3.2.1.1.0 □ Reactions of 5,5-dimethyl-2-benzylimino-\(\Delta^3\)-1, 3, 4-thiadiazoline (159) with diphenylketene to form 162 and 164.

Diphenylacetyl chloride (3.0 mmol), prepared as in Section 3.1.1.1.2, was dissolved in dry methylene chloride (10 mL) and added dropwise to a stirred solution containing the thiadiazoline, 159, (2.5 mmol) and triethylamine (6.0 mmol) in dry methylene chloride (20 mL) under nitrogen atmosphere at \(-23°C\). The resulting reaction
mixture was stirred overnight at room temperature and washed with saturated sodium bicarbonate solution and brine. The aqueous layers were re-washed twice with methylene chloride. The combined organic layers were dried (MgSO₄) and filtered. Removal of the solvent afforded an oily residue the ¹H NMR spectrum of which showed the two products 162 and 164 in a ratio of 2.4 : 1.0. In chloroform 162 loses N₂ slowly, to produce 164. Addition of ether/hexane, caused the selective precipitation of the thiaazolone 162, as a white solid. Purification on the Chromatotron, using 20% ether in hexane as eluent, afforded two fractions. F#1 showed the same ¹H NMR spectrum as the white solid above (162), F#3 was 164.

3.2.1.1.1 □ Synthesis of 1, 7, 8-triata-1-benzyl-6, 6-dimethyl-2 -oxo-3, 3-diphenyl-5-thiaspiro [3.4] oct-7-ene, or spiro β-lactam thiaazolone (162).

IR (film) ν 1765 cm⁻¹ (C=O); ¹H NMR (500.13 MHz, C₆D₆) δ 7.40 - 7.20 (m, 15H, Ar), 4.40 (s, 2H, CH₂), 1.75 (s, 3H, CH₃), 1.63 (s, 3H, CH₃); ¹³C NMR (125.76 MHz, CDCl₃) δ 168.59 (C=O), 138.36 (2 x C₁, Ar), 135.02 (C₁, Ar), 134.65 (C₄), 129.00 (Ar), 128.59 (Ar), 128.51 (Ar), 128.18 (Ar), 128.11 (Ar), 127.31 (Ar), 127.74 (Ar), 127.66 (Ar), 106.77 (C₆), 77.56 (C₃), 43.57 (CH₂), 29.83 (CH₃), 29.12 (CH₃); LRMS: m/z (El) 385 (M⁺ - N₂, 3 %), 353 (M⁺ - N₂ - S, 5 %), 262 (11 %), 237 (11 %), 220 (M⁺ - N₂ - S - PhCH₂NCO, 97 %), 205 (220 - CH₃, 85 %), 194 (Ph₂CCO, 15 %), 165 (C₁₃H₉⁺ = 9-fluorenyl, 35 %), 129 (10 %), 91 (PhCH₂, 100 %), 65 (15 %), (Cl, NH₃) 386 (M⁺ - N₂, 6 %), 354 (M⁺ - N₂ - S, 100 %), 220 (9 %), 144 (20 %), 91 (10 %).

3.2.1.1.2 □ Synthesis of 4-aza-4-benzyl-2, 2-dimethyl-6, 6-diphenyl-1-thiaspiro [2.3] hexan-5-one (164).

IR (film) ν 1765 cm⁻¹ (C=O); ¹H NMR (500.13 MHz, CDCl₃) δ 7.44 - 7.17 (m, 15H, Ar), 4.86 (d, J = 16.1 Hz, 1H, CH₂), 4.16 (d, J = 16.1 Hz, 1H, CH₂), 1.46 (s, 3H, CH₃), 1.14 (s, 3H, CH₃); ¹³C NMR (125.76 MHz, CDCl₃) δ 171.15 (C=O), 138.21 (C₁, Ar), 137.13 (C₁, Ar), 135.78 (C₁, Ar), 129.61 (Ar), 128.70 (Ar), 128.16 (Ar), 127.81 (Ar), 127.75 (Ar),
127.61 (Ar), 127.41 (Ar), 87.45 (C₃), 72.17 (C₆), 46.00 (C₂), 44.57 (CH₂), 29.23 (CH₃), 
26.76 (CH₃); LRMS: m/z (EI) 385 (M⁺, 3 %), 353 (M⁺ - S, 5 %), 262 (11 %), 237 (11 %), 
220 (M⁺ - S - PhCH₂NCO, 97 %), 205 (220 - CH₃, 85 %), 194 (Ph₂CCO, 15 %), 165 
(C₁₃H₉⁺ = 9-fluorenyl, 35 %), 129 (10 %), 91 (PhCH₂, 100 %), 65 (15 %), (CI, NH₃) 386 
(M⁺, 6 %), 354 (M⁺ - S, 100 %), 220 (9 %), 144 (20 %), 91 (10 %).

3.3.0.0.0 ■ Oxadiazolines

3.3.1.0.0 □ Semicarbazones

Unsubstituted semicarbazones were prepared from ketones and semicarbazide hydrochloride according to a standard procedure.²⁶¹ A 4-substituted semicarbazone was obtained either by the reaction of the appropriate ketone with 4-substituted semicarbazide or by Borsche’s method.³¹⁰,³¹¹ Semicarbazones (168) with R¹ = Ph, PhCH₂ or C₆H₄OCH₃ were prepared by transamination (Borsche’s method).²⁹⁷,³¹⁰,³¹¹ The semicarbazone with R¹ = Me was prepared by the reaction of methyl isocyanate with hydrazine following Vogelsang’s procedure.³¹² The 4-methyl semicarbazide obtained reacted with the ketone to give the semicarbazone under acetic acid catalysis.³¹²

3.3.2.0.0 □ General procedure for the synthesis of 5, 5-disubstituted 2-alkyl (or aryl)-imino-Δ³-1, 3, 4-oxadiazolines (171).

(i)   □ Method-1

For the arylimino oxadiazolines.²⁹⁶

(ii)  □ Method-2

For the alkylimino oxadiazolines.³¹¹

(iii) □ Method-3

For iminoxadiazoline with R¹ = H (171e).³¹³

Method-1 has been used for the synthesis of 171a, method-2 was used for 171b, 171c,
171d, 171f, 171g and method-3 was used for the hydrolytically sensitive 171e.

3.3.3.0.0 □ Synthesis of 1, 7, 8-triaza-5-oxa-2-oxospiro[3.4]oct-7-enes (172) or spiro-β-lactam oxadiazoines.

**Spiro-β-lactam-oxadiazoines:**

![Structure of 172](image)

**172**, $R^4 = R^5 = \text{Me}$ if not specified

172 (a) $R^1 = R^2 = R^3 = \text{Ph}$; (b) $R^1 = \text{PhCH}_2$, $R^2 = R^3 = \text{Ph}$; (c) $R^1 = \text{Me}$, $R^2 = R^3 = \text{Ph}$; (d) $R^1 = \text{Ph}$, $R^2 = R^3 = \text{Me}$; (e) $R^1 = R^2 = R^3 = \text{Me}$; (f) $R^1 = \text{PhCH}_2$, $R^2 = R^3 = \text{Ph}$, $R^4, R^5 = \text{adamantyl}$; (g) $R^1 = \text{Ph}$, $R^2 = \text{OPh}$, $R^3 = \text{H}$; (h) $R^1 = \text{Ph}$, $R^2 = \text{H}$, $R^3 = \text{OPh}$; (i) $R^1 = \text{MeOC}_6\text{H}_4$, $R^2 = \text{OPh}$, $R^3 = \text{H}$; (j) $R^1 = \text{Ph}$, $R^2 = N_3$ (H), $R^3 = H$ (N$_3$); (k) $R^1 = \text{MeOC}_6\text{H}_4$, $R^2 = R^3 = \text{Cl}$; (l) $R^1 = \text{MeOC}_6\text{H}_4$, $R^2 = R^3 = \text{Me}$; (m) $R^1 = \text{Ph}$, $R^2 = \text{CH}_3$, $R^3 = \text{OPh}$; (n) $R^1 = \text{Ph}$, $R^2 = \text{OPh}$, $R^3 = \text{CH}_3$; (o) $R^1 = \text{Ph}$, $R^2 = \text{OMe}$, $R^3 = H$ (major); (p) $R^1 = \text{Ph}$, $R^2 = H$, $R^3 = \text{OMe}$ (minor); (q) $R^1 = R^2 = R^3 = \text{Ph}$, $R^4 = \text{Ph}$, (Me), $R^5 = \text{Me}$, (Ph); (r) $R^1 = R^2 = R^3 = \text{Ph}$, $R^4 = \text{Me}$, (Ph); (s) $R^1 = \text{PhH}_2\text{HCC}=\text{O}$, $R^2 = R^3 = \text{Ph}$. ($R^4 = R^5 = \text{Me}$ if not specified); all 172 are synthesized according to the following procedure except 172h, m, and n, these were synthesized by transformation of 172g.

General procedure for the [2+2] cycloaddition reaction to form spiro-β-lactam-oxadiazoines (172):

*The acid chlorides required for the synthesis were purchased from Aldrich,*
unless otherwise noted. Diphenylacetyl chloride was synthesized according to the method described in Section 3.1.1.2. Azidoacetyl chloride was synthesized starting from ethyl chloroacetate following the method described by Bertho and Maier.\textsuperscript{314}

The acid chloride (3.0 mmol) was dissolved in dry methylene chloride (10 mL) and added dropwise to a stirred solution containing the imino-oxadiazoline (2.5 mmol) and triethylamine (6.0 mmol) in dry methylene chloride (20 mL) under nitrogen atmosphere at = -23°C. The resulting reaction mixture was stirred overnight at room temperature and washed with saturated sodium bicarbonate solution and brine. The aqueous layers were re-washed twice with methylene chloride. The combined organic layers were dried (MgSO\textsubscript{4}) and filtered. Removal of the solvent afforded the β-lactams (172) in almost clean form. These were further purified by centrifugal chromatography, with diethyl ether in hexanes (1:4) as eluent. This procedure was used for all the spiro β-lactam-oxadiazolines (172) unless otherwise noted.

(i) 1, 7, 8-Triaza-6, 6-dimethyl-5-oxa-2-oxo-1, 3, 3-triphenylspiro [3.4] oct-7-ene (172a).

White solid, in 90 % yield; mp 154 °C; IR (KBr) v 1770 cm\textsuperscript{-1} (C=O), 1595 cm\textsuperscript{-1} (N=N);

\textsuperscript{1}H NMR (500.14 MHz, CDCl\textsubscript{3}) δ 7.10-7.50 (m, 15H, Ar), 1.38 (s, 3H, CH\textsubscript{3}), 1.39 (s, 3H, CH\textsubscript{3}); \textsuperscript{13}C NMR (125.78 MHz, CDCl\textsubscript{3}) δ 166.80 (C=O), 136.39 (N-C\textsubscript{1}, Ar), 134.64 (C\textsubscript{1}, Ar), 133.38 (C\textsubscript{1}, Ar), 129.39 (Ar), 128.75 (Ar), 128.69 (Ar), 128.42 (Ar), 128.33 (Ar), 128.02 (Ar), 127.57 (Ar), 123.27 (Ar), 125.17 (C\textsubscript{4}), 122.61 (C\textsubscript{4}), 76.13 (C\textsubscript{3}), 24.40 (CH\textsubscript{3}), 24.30 (CH\textsubscript{3}); LRMS: m/z (EI) 355 (M+ - N\textsubscript{2}, 1%), 269 (M+ - N\textsubscript{2} - acetone, 68 %), 236 (M+ - N\textsubscript{2} - PhNCO, 7 %), 194 (Ph\textsubscript{2}CCO, 60 %), 119 (PhNCO, 35 %), 165 (C\textsubscript{13}H\textsubscript{9}+ = 9-fluorenyl, 100 %), (Cl, NH\textsubscript{3}) 384 (M+ + 1, 100 %); structure confirmed by single crystal X-ray diffraction.
(ii) 1, 7, 8-Triaza-1-benzyl-6, 6-dimethyl-5-oxa-2-oxo-3, 3-diphenylspiro [3.4] oct-7-ene (172b).

White solid, in 80 % yield; mp 101-102°C; IR (KBr) v 1770 cm\(^{-1}\) (C=O), 1600 cm\(^{-1}\) (N=N); \(^1\)H NMR (500.14 MHz, CDCl\(_3\)) \(\delta\) 7.20 - 7.55 (m, 15H, Ar), 4.66 (d, J=15Hz, 1H, CH\(_2\)), 4.53 (d, J=15Hz, 1H, CH\(_2\)), 1.45 (s, 3H, CH\(_3\)), 1.35 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (125.78 MHz, CDCl\(_3\)) \(\delta\) 168.53 (C=O), 136.81 (C\(_1\), Ar), 135.36 (C\(_1\), Ar), 135.13 (C\(_1\), Ar), 128.73 (Ar), 128.60 (Ar), 128.41 (Ar), 128.36 (Ar), 128.00 (Ar), 127.80 (Ar), 127.65 (Ar), 124.82 (C\(_4\)), 122.31 (C\(_6\)), 76.03 (C\(_3\)), 24.67 (CH\(_3\)), 24.32 (CH\(_3\)); LRMS: m/z (EI) 397 (M\(^+\), 3 %), 341 (M\(^+\) - N\(_2\) - CO, 11 %), 265 (9 %), 236 (18 %), 194 (Ph\(_2\)CO, 100 %), 165 (C\(_{13}\)H\(_9\)\(^+\) = 9-fluorenyl, 83 %), 132 (30 %), 91 (PhCH\(_2\), 87 %), (Cl, NH\(_3\)) 415 ((M + NH\(_4\))\(^+\), 28 %), 398 (M\(^+\)+1, 100 %), 360 (11 %), 345 (27 %), 302 (71 %), 267 (20 %), 206 (32 %), 194 (Ph\(_2\)CO, 17 %), 167 (43 %), 108 (15 %), 99 (40 %).

(iii) 1, 7, 8-Triaza-1, 6, 6-trimethyl-5-oxa-2-oxo-3, 3-diphenylspiro [3.4] oct-7-ene (172c).

The above procedure was followed however, the starting 5,5-dimethyl-2-(methylimino)-Δ\(^3\)-1,3,4-oxadiazoline (171c) could not be separated from its hydrolysis product 5,5-dimethyl-Δ\(^3\)-1, 3, 4-oxadiazolin-2-one. The two compounds were in the ratio of 1.33:1.00; the mixture was used with the appropriate number of moles considering the above ratio. (An alternative procedure is to leave the mixture, imino-oxadiazoline and the oxadiazolinone, at room temperature for few days. At that time the oxadiazolinone would have decomposed to the azine and CO\(_2\); the azine could be distilled (at room temperature, 0.3 mm of Hg) leaving the pure imino-oxadiazoline behind.)

Imino-oxadiazoline (171c) reacted with diphenylacetyl chloride to afford the title compound, a white solid, in 65 % yield; mp 138-139ºC; IR (KBr) v 1782 cm\(^{-1}\) (C=O),
1595 cm\(^{-1}\) (N=N); \(^1\)H NMR (200.13 MHz, CDCl\(_3\)) \(\delta\) 7.34 (br s, 10H, Ar), 2.73 (s, 3H, NCH\(_3\)), 1.60 (s, 3H, CH\(_3\)), 1.56 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (125.78 MHz, CDCl\(_3\)) \(\delta\) 168.18 (C=O), 136.77 (C\(_1\), Ar), 135.28 (C\(_1\), Ar), 128.63 (Ar), 128.51 (Ar), 128.41 (Ar), 128.34 (Ar), 128.28 (Ar), 127.94 (Ar), 127.88 (Ar), 127.82 (Ar), 124.58 (C\(_4\)), 122.22 (C\(_6\)), 75.99 (C\(_3\)), 25.32 (NCH\(_3\)), 24.36 (CH\(_3\)), 24.30 (CH\(_3\)); LRMS: m/z (EI) 293 (M\(^+\) - N\(_2\), 3 %), 236 (M\(^+\) - N\(_2\) - MeNCO, 33 %), 221 (5 %), 207 (47 %), 194 (Ph\(_2\)CCO, 41 %), 193 (19 %), 165 (C\(_{13}\)H\(_9\)\(^+\) = 9-fluorenyl, 100 %), 133 (13 %), 119 (10 %), (Cl, NH\(_3\)) 339 ((M + NH\(_4\))\(^+\), 54 %), 322 (M\(^+\)+1, 100 %), 226 (12 %), 208 (8 %), 167 (10 %).

(iv) 1, 7, 8-Triaza-3, 3, 6, 6-tetramethyl-5-oxa-2-oxo-1-phenylspiro [3.4] oct-7-ene (172d).

White solid, in 60 % yield; mp 99-100\(^\circ\)C; IR (KBr) v 1758 cm\(^{-1}\) (C=O), 1590 cm\(^{-1}\) (N=N); \(^1\)H NMR (200.13 MHz, CDCl\(_3\)) \(\delta\) 6.95-7.40 (m, 5H, Ar), 1.66 (s, 3H, CH\(_3\)), 1.46 (s, 3H, CH\(_3\)), 1.43 (s, 3H, CH\(_3\)), 1.32 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (125.78 MHz, CDCl\(_3\)) \(\delta\) 170.61 (C=O), 134.84 (N-C\(_1\), Ar), 129.31 (Ar), 126.22 (Ar), 120.48 (Ar), 124.93 (C\(_4\)), 121.19 (C\(_6\)), 60.81 (C\(_3\)), 25.93 (CH\(_3\)), 23.76 (CH\(_3\)), 18.76 (CH\(_3\)), 17.20 (CH\(_3\)); LRMS: m/z (EI) 203 (M\(^+\)-N\(_2\)-CO, 3 %), 145 (203 - acetone, 100 %), 130 (20 %), 104 (10 %), 77 (20 %); (Cl, NH\(_3\)) 277 ((M + NH\(_4\))\(^+\), 12 %), 260 (M\(^+\)+1, 100 %), 232 (13 %), 203 (10 %), 145 (85 %).

(v) 1, 7, 8-Triaza-1, 3, 3, 6, 6-pentamethyl-5-oxa-2-oxospiro [3.4] oct-7-ene (172e).

The procedure is similar to the one used for 172c above, (iii). The 5,5 dimethyl-2-(methylimino)-\(\Delta^3\)-1, 3, 4-oxadiazoline (171e) reacted with isobutyryl chloride to afford the title compound, a white solid, in 60 % yield; mp 87-88\(^\circ\)C; IR (KBr) v 1779 cm\(^{-1}\) (C=O), 1568 cm\(^{-1}\) (N=N); \(^1\)H NMR (200.13 MHz, CDCl\(_3\)) \(\delta\) 2.63 (s, 3H, NCH\(_3\)), 1.64 (s, 3H, CH\(_3\)), 1.47 (s, 3H, CH\(_3\)), 1.35 (s, 3H, CH\(_3\)), 1.21 (s, 3H, CH\(_3\)); \(^{13}\)C NMR
(125.78 MHz, CDCl₃) δ 172.57 (C=O), 124.91 (C₄), 120.63 (C₆), 60.72 (C₃), 25.48 (CH₃), 24.98 (CH₃), 23.98 (NCH₃), 18.59 (CH₃), 17.06 (CH₃), ¹H - ¹³C correlation experiment proved the chemical shifts of the NCH₃ and the other methyl substituents to be as shown; LRMS: m/z (El) 169 (M⁺ - N₂, 2 %), 141 (169 - CO, 7 %) 83 (141 - acetone, 100 %), 68 (32 %), (Cl, NH₃) 215 ((M + NH₄)⁺, 6 %), 198 (M⁺+1, 100 %), 170 (5 %), 83 (45 %).

(vi) 6, 6-Adamantylidene-1, 7, 8-triaza-1-benzyl-5-oxa-2-oxo-3, 3-diphenylspiro [3.4] oct-7-ene (172f).

Following the above procedure starting from 5,5-adamantylidene-2-(benzylimino)-Δ³-1, 3, 4-oxadiazoline (171g) and diphenylacetyl chloride, the title compound was obtained as a white solid, in 46 % yield: mp 159-160°C; IR (KBr) ν 1772 cm⁻¹ (C=O), 1595 cm⁻¹ (N=N); ¹H NMR (200.13 MHz, CDCl₃) δ 7.36 - 7.26 (m, 15 H, Ar), 4.64 (d, J = 16.2 Hz, 1 H, CH₂), 4.04 (d, J = 16.2 Hz, 1 H, CH₂), 2.52 (m, 2 H, adamantyl), 2.07 - 1.28 (m, 12 H, adamantyl); ¹³C NMR (50.32 MHz, CDCl₃) δ 168.61 (C=O), 136.84 (C₁, Ar), 135.57 (C₁, Ar), 134.98 (C₁, Ar), 128.53 (Ar), 128.41 (Ar), 128.29 (Ar), 128.19 (Ar), 128.08 (Ar), 127.60 (Ar), 127.51 (Ar), 123.09 (C₄), 115.00 (C₆), 43.05 (C₃), 37.78 (-ve), 37.55 (-ve), 36.93 (+ve), 35.12 (+ve), 34.89 (+ve), 33.81 (+ve), 33.57 (+ve), 27.15 (-ve), 26.30 (-ve) (adamantyl); LRMS: m/z (El) 488 (M⁺ - 1, 13 %), 356 (M⁺ - PhCH₂NCO, 6 %), 284 (23 %), 194 (Ph₂CCO, 100 %), 166 (22 %), 150 (36 %), 134 (60 %), 91 (20 %), (Cl, CH₄) 490 (M⁺+1, 10 %), 328 (M⁺ - PhCH₂NCO - N₂, 8 %), 298 (12 %), 225 (11 %), 194 (Ph₂CCO, 100 %), 150 (36 %), 134 (16 %), 91 (10 %).

(vii) Trans-1, 7, 8-triaza-6, 6-dimethyl-5-oxa-2-oxo-1-phenyl-3-phenoxySpiro [3.4] oct-7-ene (172g).

White solid, in 98 % yield, only one diastereomer; mp 95-96°C; IR (KBr) ν 1792 cm⁻¹ (C=O), 1594 cm⁻¹ (N=N); ¹H NMR (200.13 MHz, CDCl₃) δ 7.40 - 7.00 (m, 10 H, Ar),
5.49 (s, 1 H, CH), 1.56 (s, 3 H, CH₃), 1.48 (s, 3 H, CH₃); ¹³C NMR (125.78 MHz, CDCl₃) δ 162.13 (C=O), 156.99 (O-C₁, Ar), 133.24 (N-C₁, Ar), 129.30 (Ar), 127.33 (Ar), 123.13 (Ar), 121.91 (Ar), 116.14 (Ar), 129.66 (C₆), 122.85 (C₆), 88.21 (C₃), 24.35 (CH₃), 23.93 (CH₃); LRMS: m/z (EI) 267 (M⁺-N₂-CO, 4 %), 209 (267-acetone, 87 %), 180 (76 %), 134 (20 %), 105 (70 %), 77 (100 %), (Cl, CH₄) 324 (M⁺+1, 10 %), 254 (9 %), 230 (40 %), 209 (100 %), 180 (42 %), 132 (46 %), 104 (24 %), 71 (75 %); structure confirmed by single crystal X-ray diffraction.

(viii) Cis-1, 7, 8-triaza-6, 6-dimethyl-5-oxa-2-oxo-1-phenyl-3-phenoxy spiro [3.4] oct-7-ene (172h).

Thick yellow oil, IR (film) ν 1785 cm⁻¹(C=O), 1595 cm⁻¹ (N=N); ¹H NMR (200.13 MHz, CDCl₃) δ 7.40 - 6.96 (m, 10H, Ar), 5.79 (s, 1H, CH), 1.56 (s, 3H, CH₃), 1.38 (s, 3H, CH₃); ¹³C NMR (50.32 MHz, CDCl₃) δ 162.48 (C=O), 156.75 (O-C₁, Ar), 133.51 (N-C₁, Ar), 129.75 (Ar), 129.36 (Ar), 127.14 (Ar), 123.00 (Ar), 121.14 (Ar), 115.50 (Ar), 122.57 (C₆), 122.37 (C₆), 84.20 (C₃), 24.35 (CH₃), 24.08 (CH₃); LRMS: m/z (EI) 209 (M⁺- N₂- CO - acetone, 95 %), 180 (100 %), 132 (18 %), 105 (33 %), 77 (34 %), (Cl, NH₂) 341 ((M + NH₄)⁺, 50 %), 326 (7 %), 308 (11 %), 210 (M⁺ + 1 - N₂- CO - acetone, 100 %), 180 (32 %), 118 (11 %).

(ix) Trans-1, 7, 8-triaza-1-p-methoxyphenyl-6, 6-dimethyl-5-oxa-2-oxo-3-phenoxy spiro [3.4] oct-7-ene (172i)

Following the above procedure starting from 5, 5-dimethyl-2-(p-methoxyphenylimino)-A³-1, 3, 4-oxadiazoline (171d) and phenoxyacetyl chloride, the title compound was obtained, as a pale yellow solid, in 88 % yield: mp 97-98°C; IR (KBr) ν 1784 cm⁻¹ (C=O), 1590 cm⁻¹ (N=N); ¹H NMR (200.13 MHz, CDCl₃) δ 7.30 - 6.84 (m, 9H, Ar), 5.50 (s, 1H, CH), 3.79 (s, 3H, OCH₃), 1.51 (CH₃), 1.42 (CH₃); ¹³C
NMR (50.32 MHz, CDCl₃) δ 162.41 (C=O), 159.09 (O-C₁ or O-C₄, Ar), 156.99 (O-C₁ or O-C₄, Ar), 129.66 (Ar), 125.18 (Ar), 123.00 (Ar), 115.93 (Ar), 114.57 (Ar), 125.30 (C₄), 122.39 (C₆), 87.68 (C₃), 55.45 (OCH₃), 24.35 (2 x CH₃); LRMS: m/z (EI) 325 (M⁺ - N₂, 5 %), 283 (M⁺ - Me₂CN₂, 11 %), 239 (8 %), 227 (13 %), 221 (48 %), 210 (14 %), 176 (M⁺ - N₂ - MeOC₆H₄NCO, 7 %), 149 (MeOC₆H₄NCO, 41 %), 134 (HPhOCCO, 86 %), 123 (23 %), 94 (17 %), 72 (100 %), (Cl, CH₄) 383 (6 %), 354 (M⁺+1, 4 %), 340 (13 %), 284 (25 %), 256 (17 %), 222 (100 %), 190 (11 %), 162 (33 %), 134 (11 %), 95 (7 %), 72 (12 %).

(x) (cis or trans) 1, 7, 8-Triaza-3-azido-6, 6-dimethyl-5-oxa-2-oxo-1-phenylspiro [3.4] oct-7-ene (172j)

The azidoacetyl chloride, see the general procedure above, (1.06 mmol) was dissolved in dry methylene chloride (3 mL) and added dropwise, at 0°-5°C, over a period of one hour (using a syringe pump) to a stirred solution of the 5, 5-dimethyl-2-(phenylimino)-Δ³-1, 3, 4-oxadiazoline (171a, 1.06 mmol) and triethylamine (TEA, 1.06 mmol) in dry methylene chloride (6.5 mL) under nitrogen atmosphere. The resulting reaction mixture was stirred overnight at room temperature. Methylene chloride was removed and the resulting crude brown oil was titurated twice with diethyl ether. Evaporation of ether left an orange oil which was purified by centrifugal chromatograph (Chromatotron, 2 mm silica plate) with a mixture of hexane and ethyl acetate as eluent (5:1). Fraction #1, the major component, was the starting material (171a); fraction #2 was the title compound, a white solid, formed in 20 % yield: mp 99-100°C; IR (KBr) ν 2110 cm⁻¹ (N₃), 1778 cm⁻¹ (C=O, β-lactam), 1595 cm⁻¹ (N=N); ¹H NMR (200 MHz, CDCl₃) δ 7.10-7.45 (m, 5H, Ar), 4.65 (s, 1 H, CH), 1.67 (s, 3 H, CH₃), 1.54 (s, 3 H, CH₃); ¹³C NMR (50.32 MHz, CDCl₃) δ 160.13 (C=O), 133.41 (N-C₁, Ar), 129.33 (Ar), 127.16 (Ar), 123.14 (?), 120.83 (Ar), 129.22 (C₆), 121.09 (C₆), 73.93 (C₃), 24.69 (CH₃), 23.53 (CH₃); LRMS: m/z (EI) 244 (M⁺ - N₂, trace), 176 (3 %), 161 (M⁺ - HN₃CCO - N₂, 12 %), 146 (11 %),
130 (28 %), 119 (PhNCO, 33 %), 103 (M⁺ - HN₃CCO - N₂ - acetone, 100 %), 91 (14 %),
77 (22 %), (Cl, NH₃) 290 (M⁺+(NH₄)⁺, 100 %), 273 (7 %), 230 (11 %), 217 (25 %), 161
(8 %), 119 (10 %), 99 (13 %).

(xi) 1, 7, 8-Triaza-3, 3-dichloro-1-p-methoxyphenyl-6, 6-dimethyl-5-oxa-2-oxospiro
[3.4] oct-7-ene (172k).

Yellow oil, in 74 % yield; IR (neat) ν 1810 cm⁻¹ (C=O), 1610 cm⁻¹ (N=N); ¹H NMR (200
MHz, CDCl₃) δ 7.01 (AA’BB’, 4H, Ar), 3.78 (s, 3H, OCH₃), 1.67 (s, 3H, CH₃), 1.60 (s,
3H, CH₃); ¹³C NMR (50.32 MHz, CDCl₃), δ 159.07 (C=O), 158.29 (O-C₄, Ar), 124.71
(N-C₁, Ar), 123.44 (Ar), 114.65 (Ar), 124.94 (C₄), 121.65 (C₂), 86.03 (C₃), 55.44 (OCH₃),
25.18 (CH₃), 23.43 (CH₃); LRMS: m/z (EI) 301 (M⁺-N₂, 10 %), 303 (M⁺ + 2 - N₂, 6 %),
273 (7 %), 238 (15 %), 215 (21 %), 168 (22 %), 149 (CH₃OC₆H₄NCO, 100 %), 134 (38%
), 106 (18 %), 92 (14 %), 78 (16 %), 63 (12 %), (Cl, NH₃) 347 ((M + NH₄)⁺, 100 %),
349 ((M + 2 + NH₄)⁺, 60 %), 351 ((M + 4 + NH₄)⁺, 11 %), 301, 303, (17 %, 12 %), 268,
270 (49 %, 16 %), 238 (14 %), 216 (30 %), 174 (8 %), 149 (12 %), 123 (8 %).

(xii) 1, 7, 8-Triaza-1-p-methoxyphenyl-3, 3, 6, 6-tetramethyl-5-oxa-2-oxospiro [3.4]
oct-7-ene (172l).

White solid, in 92 % yield; mp 89-90°C; IR (KBr) ν 1770 cm⁻¹ (C=O), 1583 cm⁻¹ (N=N);
¹H NMR (200.13 MHz, CDCl₃) δ 7.00 (AA’BB’, 4H, Ar), 3.77 (s, 3H, OCH₃), 1.54 (s,
3H, CH₃), 1.46 (s, 3H, CH₃), 1.44 (s, 3H, CH₃), 1.32 (s, 3H, CH₃); ¹³C NMR (50.32 MHz,
CDCl₃) δ 170.65 (C=O), 158.08 (O-C₄, Ar), 126.84 (N-C₁, Ar), 123.50 (Ar), 114.33 (Ar),
125.08 (C₄), 120.95 (C₆), 60.36 (C₃), 55.39 (OCH₃), 25.58 (CH₃), 23.89 (CH₃), 18.55
(CH₂), 17.03 (CH₃); LRMS: m/z (EI) 261 (M⁺-N₂, 16 %), 246 (12 %), 191 (261 -
Me₂CCO, 50 %), 175 (261-acetone-CO), 163 (25 %), 149 (MeC₆H₄NCO, 59 %), 133 (38
%), 106 (11 %), 92 (18 %), 70 (42 %), (Cl, CH₄) 290 (M⁺+1, 28 %), 281 (21 %), 248 (20
(xiii & xiv) **Synthesis of 172m and 172n:**

An oven dry 25 mL round bottom flask was equipped with a magnetic stirrer bar, flushed with dry nitrogen, and sealed with a septum. The flask was swept with a constant stream of nitrogen *via* a needle attached to a bubbler. Using a syringe, 9 mL of dry THF was added followed with dry di-isopropylamine (0.32 mL, 2.3 mmol). After cooling the flask in an ice bath, n-butyl-lithium (2.3 mmol), solution in hexane, was added dropwise using a syringe. The mixture was stirred under nitrogen for 15 minutes.

The procedure for the preparation of 172m,n is based on the method by Durst. The LDA (2.3 mmol) solution was added, *via canula*, to a stirred solution of the spiro-β-lactam oxadiazoline 172g (2 mmol) in 125 mL of dry THF at -78 °C. The colour changed from yellow to orange and after 10 minutes to red. After about 15 minutes iodoethane (6 mmol) was added. The reaction mixture was stirred at -78 °C, under dry nitrogen atmosphere, for 2 hours before it was allowed to warm to room temperature over a period of 3 hours. The reaction mixture was quenched with 100 mL of 10 % HCl and extracted three times with CH$_2$Cl$_2$. The combined organic layer was washed once with brine and was dried over MgSO$_4$. Evaporation of the solvent left behind a brown slurry. Purification on the Chromatotron with 25 % diethyl ether in hexane afforded three fractions. F#1 one isomer in 3.4 % yield, F#2 second isomer in 26 % yield, F#3 starting material recovered in 12 % yield.

N.B. n-butyl-lithium was titrated 3 times with diphenyl acetic acid before it was used.

(xiii) **F#1:** Trans-1,7,8-triaza-3, 6, 6-trimethyl-5-oxa-2-oxo-3-phenoxy-1-phenylspiro
[3.4] oct-7-ene (172m).

Thick yellow oil, IR (film) $\nu$ 1777 cm$^{-1}$ (C=O); $^1$H NMR (200.13 MHz, CDCl$_3$) $\delta$ 7.37 -
7.05 (m, 10H, Ar), 1.73 (s, 3H, CH₃), 1.70 (s, 3H, CH₃), 1.62 (s, 3H, CH₃); ¹³C NMR (50.32 MHz, CDCl₃) δ 165.55 (C=O), 154.35 (O-C₁, Ar), 134.12 (N-C₁, Ar), 129.33 (Ar), 129.25 (Ar), 126.58 (Ar), 120.46 (Ar), 120.19 (Ar), 123.66 (C₄), 121.94 (C₆), 92.86 (C₃), 25.44 (CH₃), 23.58 (CH₃), 15.53 (CH₃); LRMS: m/z (EI) 309 (M⁺-N₂, trace), 223 (32 %), 180 (58 %), 149 (11 %), 130 (10 %), 105 (48 %), 77 (Ph, 100 %), (Cl, NH₃) 310 (M⁺-N₂ +1, 3 %), 224 (100 %), 180 (12 %), 147 (5 %), 94 (6 %).

(xiv) F#2: Cis-1, 7, 8-triaza-3, 6, 6-trimethyl-5-oxa-2- oxo-3-phenoxy-1-phenylspiro[3.4]oct-7-ene (172n).

Yellow oil; IR (film) ν 1780 cm⁻¹ (C=O), 1595 cm⁻¹ (N=N); ¹H NMR (200.13 MHz, CDCl₃) δ 7.33 - 7.04 (m, 10H, Ar), 1.67 (s, 3H, CH₃), 1.59 (s, 3H, CH₃), 1.56 (s, 3H, CH₃); ¹³C NMR (50.32 MHz, CDCl₃) δ 165.33 (C=O), 154.11 (O-C₁, Ar), 133.51 (N-C₁, Ar), 129.09 (Ar), 129.05 (Ar), 126.70 (Ar), 123.44 (Ar), 120.82 (Ar), 120.38 (Ar), 123.73 (C₄), 122.04 (C₆), 93.50 (C₃), 25.05 (CH₃), 23.36 (CH₃), 15.77 (CH₃); LRMS: m/z (EI) 224 (20 %), 180 (30 %), 130 (10 %), 105 (28 %), 88 (11 %), 86 (63 %), 84 (100 %), 77 (49 %), (Cl, NH₃) 355 ((M + NH₄)⁺, 2 %) 310 (M⁺-N₂, 16 %), 224 (100 %), 210 (11 %), 180 (10 %), 147 (12 %), 105 (6 %).

(xv & xvi) Synthesis of 172o and 172p:

Following the above procedure for the ketene - imine reaction; the reaction of 5. 5-dimethyl-2-(phenylimino)-Δ³-1, 3, 4-oxadiazoline (171a) with methoxyacetyl chloride, in the presence of triethylamine, afforded a low yield of the title compounds mixed with the starting material. Chromatography failed to separate the large amount of the imino-oxadiazoline (171a) from the minor product mixture. Therefore, most of the excess of 171a was removed by tituration with hexane. Purification of the hexane insoluble residue, on the Chromatotron using 20 % ether in hexane, afforded three
fractions. F#1 was the starting material (171a) F#2 was the minor β-lactam product (172p), and F#3 was the major β-lactam product (172o). The two diastereomers (172o,p) were obtained in a total of 20% yield and in a ratio of 10:1 (172o : 172p), as determined from the \(^1\)H NMR spectrum of the crude product.

(xv) **Major isomer:** Trans-1, 7, 8-triaza-trans-3-methoxy-6,
White solid, mp 70°C; IR (KBr) 1782 (C=O), 1592 (N=N); \(^1\)H NMR (200.13 MHz, CDCl\(_3\)) \(\delta 7.32 - 7.17\) (m, 5H, Ar), 4.79 (s, 1H, C-H), 3.63 (s, 3H, OCH\(_3\)), 1.62 (s, 3H, CH\(_3\)), 1.54 (s, 3H, CH\(_3\)); \(^1\)C NMR (50.32 MHz, CDCl\(_3\)) \(\delta 162.99\) (C=O), 133.59 (N-C\(_1\), Ar), 129.11 (Ar), 126.66 (Ar), 120.64 (Ar), 122.45 (C\(_4\)), 121.72 (C\(_6\)), 91.65 (C\(_3\)), 58.76 (OCH\(_3\)), 24.55 (CH\(_3\)), 23.57 (CH\(_3\)); LRMS: m/z (EI) 147 (M\(^+\) - N\(_2\) - CO - acetone, 41%), 132 (13%), 104 (55%), 77 (Ph, 100%), (Cl, NH\(_3\)) 262 (M\(^+\) + 1, 2%), 234 (M\(^+\) - N\(_2\) + 1, 11%), 148 (M\(^+\) - N\(_2\) - CO - acetone + 1, 100%), 94 (10%).

(xvi) **Minor Isomer:** Cis-1, 7, 8-triaza-3-methoxy-6,
Thick colourless oil, IR (film) \(\nu\) 1780 (C=O); \(^1\)H NMR (200.13 MHz, CDCl\(_3\)) \(\delta 7.34 - 7.19\) (m, 5H, Ar), 5.05 (s, 1H, C-H), 3.68 (s, 3H, OCH\(_3\)), 1.66 (s, 3H, CH\(_3\)), 1.56 (s, 3H, CH\(_3\)); \(^1\)C NMR (50.32 MHz, CDCl\(_3\)) \(\delta 163.78\) (C=O), 133.99 (N-C\(_1\), Ar), 129.29 (Ar), 126.68 (Ar), 120.30 (Ar), 121.92 (C\(_4\)), 114.39 (C\(_6\)), 87.59 (C\(_3\)), 58.47 (OCH\(_3\)), 25.14 (CH\(_3\)), 23.84 (CH\(_3\)); LRMS: m/z (EI) 147 (M\(^+\) - N\(_2\) - CO - acetone, 43%), 132 (12%), 104 (57%), 77 (Ph, 100%), (Cl, NH\(_3\)) 262 (M\(^+\) + 1, 5%), 234 (M\(^+\) - N\(_2\) + 1, 9%), 148 (M\(^+\) - N\(_2\) - CO - acetone + 1, 100%), 94 (10%).

(xvii) 1, 7, 8-Triaza-1-benzyl-3, 6-dimethyl-5-oxa-2-oxo-1,6-diphenylspiro [3.4]
oct-7-ene (172q and 172r).

(a) Acetophenone 4-benzylsemicarbazone:

The synthesis was accomplished according to the procedure referenced in Section 3.3.1.0.0. The title compound was obtained as a white solid; mp 140-141°C; IR (KBr) ν 1680 (C=O), 1515 (C=N); ¹H NMR (200.13 MHz, CDCl₃) δ 9.76 (br. s, 1H, CONHN), 7.66 - 7.22 (m, 10H, Ar), 6.78 (br. t, 1H, NHCH₂), 4.56 (br. d, 2H, CH₂), 2.23 (s, 3H, CH₃); ¹³C NMR (50.32 MHz, CDCl₃) δ 157.14 (C=O), 145.91 (C=N), 139.32 (C₁, Ar), 138.35 (C₁, Ar), 128.63 (Ar), 128.38 (Ar), 128.15 (Ar), 127.16 (Ar), 126.97 (Ar), 125.83 (Ar), 43.36 (CH₂), 13.62 (CH₃).

(b) Synthesis of 2-benzylimino-5-methyl-5-phenyl-Δ³-1, 3, 4-oxadiazoline (171f):

The synthesis was accomplished according to the method-2 referenced in Section 3.2.2.0.0. The oxadiazoline, 171f, was obtained in 81 % yield as a thick yellow oil; IR (film) ν 1712 cm⁻¹ (C=N), 1600 cm⁻¹ (N=N); ¹H NMR (200.13 MHz, CDCl₃) δ 7.41 - 7.25 (m, 10H, Ar), 4.76 (s, 2H, CH₂), 1.83 (s, 3H, CH₃); ¹³C NMR (50.32 MHz, CDCl₃) δ 162.66 (C=N), 138.25 (C₁, Ar), 135.34 (C₁, Ar), 129.01 (Ar), 128.51 (Ar), 128.07 (Ar), 127.35 (Ar), 126.64 (Ar), 124.53 (Ar), 121.66 (C₃), 52.07 (CH₂), 24.69 (CH₃); LRMS: m/z (EI) 237 (M⁺ - N₂, trace), 146 (M⁺ - N₂ - Ph₂CH₂, 13 %), 106 (30 %), 104 ((PhCCH₃)⁺, 100 %), 91 (PhCH₂, 20 %), 77 (18 %), (CI, NH₃) 268 (M⁺+3, 100 %), 210 (5 %), 120 (80 %), 91 (11 %).

(c) Spiro-β-lactam oxadiazolines: diastereomers 1, 7, 8-triaza-1-benzyl-6-methyl-5-oxa-2-oxo -3, 3, 6-triphenylspiro [3.4] oct-7-ene (172q and 172r):

The synthesis was accomplished following the general method described above. The two diastereomers were obtained in 60 % total yield and in a ratio of 1 : 1.53 (172r : 172q), as
determined from the $^1$H NMR spectrum of the crude product. The mixture could not be separated, purification by chromatography was always giving acetophenone as the first fraction; IR (film) ν 1775 (C=O), 1600 (N=N); $^1$H NMR (200.13 MHz, CDCl$_3$) δ 7.39 - 6.79 (m, 20H, Ar), 4.65 (d, J = 16 Hz, 1H, CH$_3$; minor isomer), 4.32 (d, J = 16 Hz, 1H, CH$_2$; minor isomer), 4.03 (d, J = 16 Hz, 1H, CH$_2$; major isomer), 3.91 (d, J = 16 Hz, 1H, CH$_2$; major isomer), 1.77 (s, 3H, CH$_3$; major isomer), 1.63 (s, 3H, CH$_3$; minor isomer); LRMS: m/z (EI) 433 (M$^+$-N$_2$+2, 3 %), 312 (M$^+$-N$_2$-PhCH$_2$NCO, 6 %), 284 (13 %), 194 (Ph$_2$CCO, 11 %), 165 (C$_{12}$H$_9^+$ = 9-fluorenyl, 27 %), 91 (PhCH$_2^+$, 100 %), (Cl, NH$_3$) 432 (M$^+$ - N$_2$ + 1, 100 %), 312 (31 %), 138 (40 %).

(d) Thermolysis of 172q and 172r: Formation of 1-benzyl-4- (1-phenyl-1-ethenox)-3, 3-diphenylazetidin-2-one (183) by [1,4] sigmatropic H-migration.

$^1$H NMR (200.13 MHz, CDCl$_3$) δ 7.43 - 6.70 (m, 20H, Ar), 5.99 (s, 1H, CH), 4.74 (d, J = 3.4 Hz, 1H, C=CH$_2$), 4.19 (d, J = 3.4 Hz, 1H, C=CH$_2$), 4.86 (d, J = 16 Hz, 1H, CH$_2$Ph), 4.29 (d, J = 16 Hz, 1H, CH$_2$Ph).

(xviii) 1, 7, 8-triaza-6, 6-dimethyl-5-oxa- 2-oxo-1-diphenylacetyl-3, 3-diphenylspiro [3.4] oct-7-ene (172s).

The general procedure for the [2 + 2] cycloaddition reaction, described in Section 3.3.3.0.0, was followed; using imino-oxadiazoline 171e and diphenylacetyl chloride. The β-lactam (172s) was obtained as a white solid, in 38 % yield; mp 135-136°C; IR (film) ν 1808 cm$^{-1}$ (C=O, β-lactam), 1730 (C=O), 1600 (N=N); $^1$H NMR (200.13 MHz, CDCl$_3$) δ 7.30 - 6.85 (m, 20H, Ar), 5.97 (s, 1H, CH), 1.76 (s, 3H, CH$_3$), 1.47 (s, 3H, CH$_3$); $^{13}$C NMR (50.32 MHz, CDCl$_3$) δ 169.46 (C=O), 166.06 (C=O, β-lactam), 137.24 (2 x C$_1$, Ar), 137.08 (C$_1$, Ar), 135.56 (C$_1$, Ar), 129.50 (Ar), 129.34 (Ar), 129.05 (Ar), 128.84 (Ar), 128.76 (Ar), 128.55 (Ar), 128.36 (Ar), 128.28 (Ar), 128.21 (Ar), 127.96 (Ar), 127.86 (C$_4$),
127.69 (C₆), assignment of C₄ and C₆ is tentative, 75.59 (C₃), 58.21 (Ph₂HCC=O), 24.95 (CH₃), 22.48 (CH₂); LRMS: m/z (EI) 501 (M⁺, 1 %), 307 (M⁺ - Ph₂CCO, trace %), 279 (307 - N₂, trace %), 237 (M⁺ - Ph₂HCCONCO, 3 %), 194 (Ph₂CCO, 50 %), 167 (Ph₂CH, 100 %), 139 (6 %), (Cl, NH₃) 519 ((M + NH₄)⁺, 20 %), 502 (M⁺ + 1, 1 %), 449 (12 %), 310 (7 %), 265 (30 %), 237 (16 %), 212 (22 %), 167 (100 %), 99 (11 %).

3.3.4.0.0 • β-Lactam-4-Ylidenes: Addition to Alkynes

• General procedure for the generation of the β-lactam-4-ylidenes: Thermolysis of spiro-β-lactam oxadiazolines, 172, in the presence of an alkyne.

For a small scale reaction, the spiro-β-lactam oxadiazolines, 172, (≈0.10 mmol), the alkyne (1.0 mmol), and benzene (0.25 mL), were mixed all together in a medium-walled NMR tube. After three cycles of degassing, at liquid nitrogen temperature, and thawing at room temperature, the tube was sealed under vacuum (10⁻² mm of Hg). The thermolysis was carried out in a constant temperature oil bath, maintained at 100 ± 0.2°C, for 10 hours. At the end of the reaction, the solvent and the excess of the alkyne were distilled by the bulb to bulb method, at high vacuum. The residue was then purified on the Chromatotron (2 mm silica plate), using 25 % ether in hexane as the eluent.

3.3.4.1.0 • 4-aza-1,2-bis (methoxycarbonyl)-5-oxo-4, 6, 6-triphenylspiro [2.3] hex-1-ene (184).
The spiro-β-lactam cyclopropene was synthesized following the above procedure. The product (184) was obtained as a yellow solid, in 33 % yield; mp 128-129°C; IR (KBr) ν 1750 (C=O, β-lactam), 1730 (C=O, ester), 1720 (C=O, ester); UV (CH₂Cl₂) λ_max 248 nm, log ε 4.32; ¹H NMR (500 MHz, CDCl₃) δ 7.46-7.11 (m, 15H, Ar), 3.75 (s, 6H, 2 x OMe); ¹³C NMR (125.76 MHz, CDCl₃) δ 167.63 (C=O, β-lactam), 158.33 (2 x C=O, ester), 137.00 (2 x (C₁, Ar)), 135.82 (N-C₁, Ar), 129.56 (Ar), 128.53 (Ar), 128.02 (Ar), 127.79 (Ar), 127.24 (Ar), 125.55 (Ar), 119.81 (C₁, C₂), 66.03, 64.13 (C₃, C₆), 53.43 (2 x OMe); LRMS: (EI) 439 (M⁺, trace), 411 (M⁺- CO, 11 %), 379 (13 %), 348 (18 %), 320 (M⁺-PhNCO, 100 %), 293 (24 %), 249 (13 %), 178 (31 %), 165 (C₁₅H₉⁺= 9-fluorenyl, 73 %), 119 (PhNCO, 15 %), 77 (47 %), (Cl, NH₃) 457 ((M + NH₄)⁺, 16 %), 440 (M⁺+1, 100 %), 410 (23 %), 382 (5 %), 352 (6 %), 323 (7 %), 294 (6 %), 246 (5 %), 167 (28 %), 119 (10 %), 94 (12 %); structure confirmed by single crystal X-ray diffraction.

3.3.4.1.1 □ Thermolysis of spiro-β-lactam cyclopropene 181:

Formation of 184b.

The spiro-β-lactam cyclopropene, 184, (0.06 mmol) in dry benzene (0.4 mL) was sealed into a glass tube after three cycles of freeze-pump-thaw degassing. The tube was then immersed in a bath of refluxing anisole (154°C). After about 3 minutes at 154°C, the colour changed from light yellow to dark green. The yellow colour returned
upon cooling the tube to room temperature. At 154°C, the green colour persisted for about 4 hours, after that the colour went back to yellow, when hot or when cold. After heating for 8 hours, the tube was opened and the solvent was pumped out. TLC showed two fluorescent spots and another very polar spot. Purification on the Chromatotron (2 mm silica plate), using 25 % ether in hexane gave, as the only identifiable product, the first fluorescent fraction: White solid, in 25 % yield; mp 165 - 166°C; IR (KBr) ν 1810 cm⁻¹ (C=O, β-lactam), 1732 cm⁻¹, 1712 cm⁻¹ (C=O, esters), 1685 cm⁻¹ (C=C); UV: λ_max (CH₂Cl₂, HPLC) 232 nm, log ε 4.16, λ 258 nm, log ε 4.05; ¹H NMR (200.13 MHz, CDCl₃) δ 7.56 - 7.22 (m, 14H, Ar), 4.96 (s, 1H, CH), 3.73 (s, 3H, OCH₃), 3.50 (s, 3H, OCH₃); ¹³C NMR (125.76 MHz, CDCl₃) δ 171.89 (C=O, +ve), 165.41 (C=O, +ve), 164.70 (C=O, +ve), 150.64 (C₇, Ar, +ve), 135.69 (Ar, +ve), 135.18 (Ar, +ve), 130.26 (C₆, +ve), 130.94 - 117.18 (Ar, -ve), 121.16 (Ar, +ve), 98.87 (C₅, +ve), 78.12 (C₃, +ve), 52.74 (OCH₃), 51.11 (OCH₃), 44.11 (C₄); LRMS (EI) 439 (M⁺, 3 %), 411 (M⁺ - CO, 5 %), 380 (M⁺ - CH₃COO, 26 %), 352 (M⁺ - CH₂COO - CO, 100 %), 320 (M⁺ - PhNCO, 38 %), 291 (15 %), 160 (8 %), 84 (35 %), (Cl, NH₃) 457 ((M + NH₄)⁺, 100 %), 440 (M⁺ + 1, 40 %), 412 (M⁺ - CO + 1, 40 %), 380 (22 %), 352 (40 %), 320 (9 %); HRMS: Calculated for C₂₇H₂₁NO₅ 439.1420, observed 439.1418.

3.3.4.2.0 □ 4-Aza-4-benzyl-1-ethoxycarbonyl-2, 6, 6-triphenylspiro [2.3] hex-1-ene (185).

![Diagram](image_url)

The spiro-β-lactam cyclopropene (185) was synthesized following the above procedure.
The product (185) was obtained as a yellow oil, IR (film) ν 1745 (C=O), 1710 (C=O); \(^1\)H NMR (200.13 MHz, CDCl\(_3\)) δ 7.46 - 7.01 (m, 20H, Ar), 4.41 - 4.04 (m, 4H, CH\(_2\)Ph and CH\(_2\)CH\(_3\)) 1.26 (t, J = 7.2 Hz, 3H, CH\(_3\)); \(^{13}\)C NMR (50.32 MHz, CDCl\(_3\)) δ 169.55 (C=O, \(\beta\)-lactam), 159.46 (C=O, ester), 138.69 (C\(_1\), Ar), 138.20 (C\(_1\), Ar), 137.24 (C\(_1\), Ar), 135.97 (C\(_1\), Ar), 131.70 (Ar), 131.50 (Ar), 128.69 (Ar), 128.56 (Ar), 128.35 (Ar), 128.29 (Ar), 127.67 (Ar), 127.50 (Ar), 127.32 (Ar), 127.29 (Ar), 127.16 (Ar), 125.00 (C\(_2\)), 112.51 (C\(_1\)), 70.97 (C\(_3\)), 61.45 (OCH\(_2\)), 60.92 (C\(_6\)), 43.02 (PhCH\(_2\)), 14.08 (CH\(_3\)); LRMS: m/z (El) 485 (M\(^+\), 6 %), 457 (M\(^+\) - CO, 9 %), 384 (M\(^+\) - CO - COOCH\(_2\)CH\(_3\), 7 %), 352 (M\(^+\) - PhCH\(_2\)NCO, 19 %), 322 (12 %), 194 (Ph\(_2\)CCO, 11 %), 165 (C\(_{13}\)H\(_9\)+ = 9-fluorenyl, 27 %), 133 (PhCH\(_2\)NCO, 29 %), 105 (22 %), 91 (PhCH\(_2\), 100 %), (Cl, NH\(_3\)) 503 (M + NH\(_4\))\(^+\), 3 %), 486 (M\(^+\) + 1, 100 %), 353 (M\(^+\) - PhCH\(_2\)NCO + 1, 5 %), 167 (17 %), 108 (18 %), 91 (20 %); HRMS: Calculated for C\(_{33}\)H\(_{27}\)N\(_3\)O\(_3\) 485.1991, observed 485.2000.

3.3.5.0.0 ■ \(\beta\)-Lactam-4-Ylidenes: Addition to Alkenes.

■ General procedure for the generation of the \(\beta\)-lactam-4-ylidenes: Thermolysis of spiro-\(\beta\)-lactam oxadiazolines, 172, in the presence of an alkene.

For a small scale reaction, the spiro-\(\beta\)-lactam oxadiazolines, 172, (=0.1 mmol) and the alkene, used as the solvent, (0.5 mL), were mixed all together in a medium-walled NMR tube. After three cycles of degassing, at liquid nitrogen temperature, and thawing at room temperature, the tube was sealed under vacuum (10\(^{-2}\) mm of Hg). The thermolysis was carried out in a constant temperature oil bath, maintained at 100 ± 0.2°C, for 55 minutes if 172g was the carbene source, and for 10 hours if the oxadiazolone was 172a. At the end of the reaction, the solvent (the excess alkene) was distilled by the bulb to bulb method, at high vacuum. The residue was then purified on the Chromatotron (2 mm silica plate), using 25 % ether in hexane as the eluent.

3.3.5.1.0 □ Addition to Acrylonitrile: Synthesis of 4-aza-1-
cyano-6-phenoxy-4-phenylspiro [2.3] hexan-5-one (189).

The spiro-β-lactam cyclopropane (189) was synthesized following the above procedure. The product (189) was obtained as a mixture of regio- and stereo-isomers. Four fractions were separated but the first fraction was too small to be identified. The isomers were obtained in a ratio of 1 : 2.5 : 1.4, as determined from the $^1$H NMR spectrum of the mixture.

(i) F#2

Yellow oil in 14 % yield; IR (film) ν 1775 cm$^{-1}$ (C=O), 2260 cm$^{-1}$ (C≡N); $^1$H NMR (200.13 MHz, CDCl$_3$) δ 7.38 - 7.08 (m, 10H, Ar), 5.61 (s, 1H, CH), 2.50 (dd, J = 6.9, 10.0 Hz, 1H, CH₂CN), 2.14 (dd, J = 7.9, 10.0 Hz, 1H, CH₂, trans), 1.88 (dd, J = 6.9, 7.9 Hz, 1H, CH₂, cis); $^{13}$C NMR (50.32 MHz, CDCl$_3$) δ 162.72 (C=O), 156.90 (O=C₁, Ar), 134.89 (N-C₁, Ar), 129.83 (Ar), 129.79 (Ar), 126.27 (Ar), 123.12 (Ar), 118.67 (Ar), 116.26 (Ar), 117.85 (C≡N), 82.71 (C₆), 54.31 (C₃), 10.25 (H-C=C=N), 2.96 (CH₂); LRMS: m/z (EI) 290 (M⁺, 2 %), 262 (M⁺- C=O, 31 %), 233 (48 %), 194 (10 %), 180 (30 %), 165 (6 %), 144 (12 %), 117 (65 %), 104 (33 %), 77 (phenyl⁺, 100 %), (Cl, NH$_3$) 308 ((M + NH$_4$)+, 100 %), 262 (6 %), 199 (8 %); HRMS: Calculated for C$_{18}$H$_{14}$N$_2$O$_2$ 290.1055, observed 290.1050.

(ii) F#3

White solid, in 35 % yield; IR (KBr) ν 1760 cm$^{-1}$ (C=O), 2240 cm$^{-1}$ (CN); $^1$H NMR (200.13 MHz, CDCl$_3$) δ 7.45 - 7.05 (m, 10H, Ar), 5.43 (s, 1H, CH), 2.13 - 2.00 (m,
2H, CHCN.CH₂), 1.92 - 1.82 (m, 1H, CH₂); δ¹³C NMR (50.32 MHz, CDCl₃) δ 163.39 (C=O), 156.78 (O-C₁, Ar), 133.51 (N-C₁, Ar), 129.84 (Ar), 129.43 (Ar), 127.73 (Ar), 123.15 (Ar), 122.99 (Ar), 115.61 (Ar), 116.85 (C=Н), 83.37 (С₆), 54.08 (С₂), 19.42 (НС-C=N), 4.33 (CH₂); LRMS: m/z (EI) 290 (М⁺, 3 %), 262 (М⁺- С=О, 48 %), 233 (68 %), 209 (6 %), 180 (36 %), 144 (11 %), 117 (61 %), 104 (29 %), 77 (100 %), (Cl, NH₃) 308 ((М + NH₄)⁺, 100 %), 291 (М⁺ + 1, 4 %), 263 ((М⁺ - CO + 1, 6 %), 199 (10 %); HRMS: Calculated for C₁₈H₁₄N₂O₂ 290.1055, observed 290.1047.

(iii) Ф#4

Yellow oil, in 20 % yield, IR (film) ν 1790 cm⁻¹ (C=O), 2260 cm⁻¹ (C≡N); δ¹H NMR* (200.13 MHz, CDCl₃) δ 7.47 - 7.05 (m, 10H, Ar), 5.39 (s, 1H, CH₁), 2.24 (t, J = 7 Hz, 1H, CH₂, trans), 2.09 (dd, J=7, 10 Hz, 1H, CH₆C≡N), 1.85 (dd, J=7, 10 Hz, 1H, CH₂, cis); δ¹³C NMR (50.32 MHz, CDCl₃) δ 156.72 (O-C₁, Ar), 129.90 (Ar), 129.53 (Ar), 127.33 (Ar), 123.14 (Ar), 116.31 (Ar), 115.71 (Ar), 119.37 (C≡N), 82.28 (С₆), 54.87 (С₂), 12.68 (С₁), 2.44 (С₂); LRMS: m/z (EI) 290 (М⁺, 3%), 262 (М⁺- CO, 68 %), 233 (100 %), 209 (8 %), 180 (52 %), 144 (16%), 117 (93 %), 104 (40 %), 103 (20 %), 84 (41 %), 77 (92 %), (Cl, NH₃) 308 ((М + NH₄)⁺, 100 %), 291 (М⁺+1, 13 %), 263 (10 %), 233 (6 %), 216 (8 %), 199 (79 %), 183 (8 %), 160 (18 %), 118 (8 %), 94 (27 %); HRMS: Calculated for C₁₈H₁₄N₂O₂ 290.1055, observed 290.1060.

3.3.5.2.0 □ Addition to Styrene: Synthesis of 4-aza-6- phenoxy-1, 4-diphenylspiro

[2.3] hexan-5-one (190).
The *spiro*-β-lactam cyclopropane (190) was synthesized following the above procedure. Two out of the four possible isomers were obtained in a total yield of 74 %, and in a ratio of 5.2 : 1.

(i) **Data for the major isomer:**

White solid; in 62 % yield; mp 136°C; IR (KBr) ν 1760 cm\(^{-1}\) (C=O); \(\text{\(^1\)H NMR (200 MHz, CDCl}_3\) δ 7.35-6.70 (m, 15H, Ar), 5.50 (s, 1H, CH), 2.72 (dd, J = 7.6, 10.1 Hz, 1H, CHPh), 1.84 (tr, 1H, CH\(_2\), J = 7.6 Hz), 1.67 (dd, J = 7.6, 10.1, 1H, CH\(_2\)); \(\text{\(^13\)C NMR (50.32 MHz, CDCl}_3\) δ 164.90 (C=O), 157.56 (O-C\(_1\), Ar), 135.36 (C\(_1\), Ar), 135.25 (C\(_1\), Ar), 129.69 (Ar), 129.46 (Ar), 128.46 (Ar), 128.28 (Ar), 127.07 (Ar), 125.77 (Ar), 122.53 (Ar), 122.39 (Ar), 115.78 (Ar), 84.19 (C\(_6\), 55.79 (C\(_3\), 24.08 (C\(_1\), C-Ph), 7.40 (C\(_2\));

LRMS: m/z (EI) 313 (M\(^+\) - CO, 4 %), 238 (10 %), 196 (100 %), 165 (25 %), 144 (6 %), 104 (21 %), 77 (45 %), (Cl, NH\(_3\)) 359 ((M + NH\(_4\))\(^+\), 8 %), 342 (M\(^+\)+1, 100 %), 314 (M\(^+\) - N\(_2\)+ 1, 29 %), 248 (12 %), 196 (8 %), 94 (6 %); HRMS: Calculated for C\(_{22}\)H\(_{19}\)N\(_4\)O\(_1\) (C\(_{23}\)H\(_{19}\)N\(_4\)O\(_2\) - CO) 313.1467, observed 313.1457.

(ii) **Data on the minor isomer:**

White solid, 12 % yield; mp 162 °C; IR (KBr) ν 1758 cm\(^{-1}\) (C=O); \(\text{\(^1\)H NMR (200.13 MHz, CDCl}_3\) δ 7.41 - 7.05 (m, 15H, Ar), 4.99 (s, 1H, CH), 3.10 (dd, J = 7.4, 10.3 Hz, 1H, CHPh), 2.13 (dd, J = 7.9, 10.3 Hz, 1H, CH\(_2\), cis), 1.75 (dd, J = 7.4, 7.9 Hz, 1H, CH\(_2\), trans); \(\text{\(^13\)C NMR (50.32 MHz, CDCl}_3\) δ 164.22 (C=O), 157.35 (O-C\(_1\), Ar), 137.42 (C\(_1\), Ar), 136.42 (C\(_1\), Ar), 129.53 (Ar), 128.77 (Ar), 126.93 (Ar), 126.63 (Ar), 125.13 (Ar), 122.51 (Ar), 118.40 (Ar), 117.04 (Ar), 116.48 (Ar), 81.45 (C\(_6\)), 56.42 (C\(_3\), 20.86 (C\(_1\)), 9.48 (C\(_2\));

LRMS: m/z (EI) 313 (M\(^+\) - CO, 1 %), 238 (11 %), 196 (100 %), 165 (22 %), 100 (16 %), 75 (13 %), (Cl, NH\(_3\)) 359 ((M + NH\(_4\))\(^+\), 11 %), 342 (M\(^+\)+1, 100 %), 314 (M\(^+\) - N\(_2\)+ 1, 10 %), 250 (9 %), 196 (14 %), 167 (13 %), 134 (12 %), 94 (33 %), 72 (15 %); HRMS: Calculated for C\(_{22}\)H\(_{19}\)N\(_4\)O\(_1\) (C\(_{23}\)H\(_{19}\)N\(_4\)O\(_2\) - CO) 313.1467, observed 313.1453.
3.3.5.3.0 □ Addition to 4-bromo-1-butene: Synthesis of 4-aza-1-(2-bromoethyl)-4, 6, 6-triphenylspiro [2.3] hexan-5-one (191).

The spiro-β-lactam cyclopropane (191) was synthesized following the above procedure. One out of the two possible isomers was obtained as a white solid, in 60% yield; IR (KBr) ν 1755 cm⁻¹ (C=O); ¹H NMR (200 MHz, CDCl₃) δ 7.42-6.90 (m, 15H, Ar), 3.14 (m, 2H, CH₂Br), 1.76 (m, 2H, CH₂), 1.30 (m, 2H, CH₂, C₂), 0.88 (m, 2H, CH₂, C₁); 2D ¹³C-¹H correlation was used to interpret the ¹H NMR spectrum; ¹³C NMR (50.32 MHz, CDCl₃) δ 168.81 (C=O, +ve), 138.18 (C₁, Ar, +ve), 137.72 (C₁, Ar, +ve), 135.82 (C₁, Ar, +ve), 129.54 (Ar, -ve), 128.82 (Ar, -ve), 128.64 (Ar, -ve), 128.22 (Ar, -ve), 128.07 (Ar, -ve), 127.65 (Ar, -ve), 127.53 (Ar, -ve), 127.05 (Ar, -ve), 124.22 (Ar, -ve), 70.02 (C₃ or C₆, +ve), 60.71 (C₃ or C₆, +ve), 31.90 (CH₂, +ve), 31.81 (CH₂, +ve), 19.47 (C₁, -ve), 13.80 (C₂, +ve); GC/MS: m/z (EI) 405 (M⁺-C=O, Br = 81, 9.8%), 403 (M⁺-C=O, Br = 79, 6.6%), 165 (C₁₃H₉⁺ = 9-fluorenyl, 100%); LRMS: m/z 431, 433 (M⁺, 2%), 403, 405 (M⁺-CO, 14%), 312, 314 (M⁺-PhNCO, 8%), 269 (40%), 205 (49%), 165 (C₁₃H₉⁺ = 9-fluorenyl, 100%), 115 (11%), 77 (39%), (Cl, NH₃) 449, 451 ([M + NH₄⁺], 56%), 432, 434 (M⁺+1, 100%), 404 (14%), 354 (33%), 352 (30%), 316 (13%), 270 (17%), 205 (11%), 165 (19%), 94 (13%); HRMS: Calculated for C₂₅H₂₂Br₁N₁O₁, 431.0885, observed 431.0883.

3.3.5.4.0 □ Addition to Dimethyl Maleate: Synthesis of two cis and two trans isomers
of 4-aza-1, 2-bis (methoxycarbonyl)-6-phenoxy-4-phenyl spiro [2.3] hexan-5-one (192). 

The spiro-β-lactam cyclopropane (192) was synthesized following the above procedure. Purification by chromatography, using 25 % ether in hexane as eluent, afforded four very minor products that are not 192; these compounds were not identified. When the polarity of the eluent was increased to 25 % ethyl acetate in hexane, three fractions were separated F#5, F#6, and F#7. F#6 is a mixture of two isomers of 192, one cis and the other trans. Thus, all four possible isomers were obtained. The total yield was 43 %, distributed over the four isomers; two trans, 5 % and 19 %, and two cis, 13 % and 6 %.

(i) Fraction #5 (trans), a colourless oil, was obtained in 5 % yield; IR (film) ν 1775 (C=O, β-lactam), 1730 (C=O, esters); 1H NMR (200.13 MHz, CDCl₃) δ 7.36 - 7.00 (m, 10H, Ar), 5.38 (s, 1H, CH), 3.69 (s, 3H, OCH₃), 3.39 (s, 3H, OCH₃), 3.27 (d, J=7 Hz, 1H, CH), 2.96 (d, J=7 Hz, 1H, CH); 13C NMR (50.32 MHz, CDCl₃) δ 168.87 (C=O), 167.45 (C=O), 165.14 (C=O), 157.62 (O-C₁, Ar, +ve), 134.10 (N-C₁, Ar, +ve), 129.63 (Ar, -ve), 129.09 (Ar, -ve), 127.43 (Ar, -ve), 123.81 (Ar, -ve), 123.03 (Ar, -ve), 117.12 (Ar, -ve), 82.74 (C₆, -ve), 59.75 (C₃, +ve), 52.63 (OCH₃, -ve), 52.20 (OCH₃, -ve), 26.97 (C₁ or C₂, -ve), 26.86 (C₁ or C₂, -ve); LRMS: m/z (El) 353 (M⁺ - CO, 10 %), 293 (9 %), 262 (M⁺ - PhNCO, 8 %), 234 (M⁺ - CO - PhNCO, 11 %), 175 (35 %), 149 (41 %), 91 (42 %), 77 (Ph, 100 %), (Cl, NH₃) 419 (20 %), 382 (M⁺+1, 17 %), 354 (M⁺ - CO + 1, 28 %), 313 (83 %), 286 (100 %).
%, 194 (23 %), 166 (7 %), 134 (HPhOCO, 6 %), 108 (30 %), 91 (13 %); HRMS: 
Calculated for C_{20}H_{19}N_{1}O_{5} (C_{21}H_{19}N_{1}O_{6} - CO) 353.1263, observed 353.1258.

(ii) Fraction # 6, a yellow oil, was obtained in 32.5 % yield as a mixture of two products 
on one trans and the other cis in ratio 1.6 : 1 ratio, respectively, by 1H NMR spectroscopy. 
GC/MS: showed two peaks with the title compounds molecular weight. The GC ratio was 
1.65 : 1, with the major peak (trans) coming out first followed by the cis; IR (neat) of the 
mixture: ν 1775 (br., C=O), 1730 (br., C=O); 1H NMR (500 MHz, CDCl₃):

"trans" (20 % yield) δ 7.41 - 7.00 (m, 10H, Ar), 5.52 (s, 1H, CH), 3.78 (s, 3H, OCH₃), 
3.22 (s, 3H, OCH₃), 3.23 (d, J=7 Hz, 1H, CH), 2.99 (d, J=7 Hz, 1H, CH); GC/MS: first 
peak (trans), m/z (EI) 381 (M⁺, ≈ 0.5 %), 353 (M⁺- C=O, 30 %), 293 (19 %), 262 (M⁺- 
PhNCO, 13 %), 234 (M⁺ - PhNCO - CO, 27 %), 228 (13 %), 188 (28 %), 175 (53 %), 144 
(53 %), 129 (14 %), 104 (31 %), 77 (Ph⁺, 100 %), 51 (40 %).

"cis" (12.5 % yield) δ 7.41 - 7.00 (m, 10H, Ar), 6.24 (s, 1H, CH), 3.75 (s, 3H, OCH₃), 
3.70 (s, 3H, OCH₃), 3.00 (d, J=11 Hz, 1H, CH), 2.93 (d, J=11 Hz, 1H, CH); GC/MS: 
second peak (cis), m/z (EI) 381 (M⁺, 1 %), 353 (M⁺- C=O, 19 %), 293 (18 %), 262 (M⁺- 
PhNCO, 14 %), 234 (M⁺ - PhNCO - CO, 23 %), 200 (23 %), 175 (44 %), 169 (39 %), 144 
(40 %), 104 (25 %), 77 (Ph⁺, 100 %), 51 (31 %).

(iii) Fraction #7 (cis) was obtained as a yellow oil, in 6.5 % yield; IR (film) ν 1775 (C=O, 
β-lactam), 1730 (C=O, esters); 1H NMR (200.13 MHz, CDCl₃) δ 7.38 - 7.03 (m, 10H, Ar), 
5.38 (s, 1H, CH), 3.52 (s, 3H, OCH₃), 3.45 (s, 3H, OCH₃), 2.66 (d, J=11 Hz, 1H, CH), 
2.63 (d, J=11 Hz, 1H, CH) ; 13C NMR (50.32 MHz, CDCl₃) δ 166.50 (C=O), 166.00 
(C=O), 165.99 (C=O), 156.97 (O-C₁, Ar), 133.94 (N-C₁, Ar), 129.82 (Ar), 128.54 (Ar), 
128.46 (Ar), 127.94 (Ar), 122.93 (Ar), 115.86 (Ar), 83.51 (C₆), 58.01 (C₃), 52.04 (OCH₃),
51.92 (OCH₃), 26.46 (C₁ or C₂), 23.37 (C₁ or C₂); GC/MS: one peak (pure) m/z (EI) 381 (M⁺, 1.5 %), 353 (M⁺- C=O, 21 %), 293 (13 %), 262 (M⁺- PhNCO, 9 %), 234 (M⁺- PhNCO - CO, 18 %), 228 (9 %), 188 (25 %), 169 (20 %), 144 (23 %), 129 (10 %), 104 (16 %), 77 (Ph⁺, 100 %), 51 (29 %); LRMS: m/z (EI) 353 (M⁺ - CO, 4 %), 234 (M⁺ - PhNCO - CO, 7 %), 149 (25%), 77 (100%), (Cl, NH₃) 399 ((M + NH₄)⁺, 7 %), 382 (M⁺+1, 40 %), 354 (M⁺ - CO + 1, 98 %), 322 (36 %), 290 (20 %), 259 (10 %), 228 (26 %), 205 (11 %), 175 (18 %), 119 (PhNCO, 42 %), 94 (100 %); HRMS: Calculated for C₂₀H₁₉N₁O₅ (C₂₁H₁₉N₁O₆ - CO) 353.1264, observed 353.1275.

*The equation \[ \delta_A - \delta_B = \frac{1}{2} [(v_4 - v_1)(v_3 - v_2)]^{1/2} \] was used to determine the chemical shifts of this dd.

3.3.5.5.0 Addition to Dimethyl Fumarate: Synthesis of 4-aza-1, 2-bis (methoxycarbonyl)-6-phenoxy-4-phenylspiro [2.3] hexan-5-one (192), two trans isomers.

Dimethyl fumarate is a solid with a melting point of 103-104°C; therefore, the two solids, 172g and the fumarate, were mixed and sealed into a glass tube after three cycles of freeze-pump-thaw degassing. The tube was then immersed in a constant temperature oil bath, maintained at 111 ± 0.2°C, for 55 minutes. After about 55 minutes the ¹H NMR spectrum confirmed the consumption of more than 95 % of 172g. Purification by chromatography, using 25 % ethyl acetate in hexane as eluent, afforded two fractions. The first fraction corresponded to the fumarate while the second fraction was a mixture of the two trans products (192a and 192b) in a total of 36 % yield. The cis isomer was not present. The two trans isomers were formed in a ratio of 2.7:1.

3.3.6.0.0 β-Lactam-4-Ylidenes: Insertion Reactions.
3.3.6.1.0 □ Intermolecular Insertion Reactions.

**General procedure for the generation of the β-lactam-4-yldenes: Thermolysis of spiro-β-lactam oxadiazolines, 172, in the presence of an R-OH trap.**

For a small scale reaction, the spiro-β-lactam oxadiazolines, 172, (~0.1 mmol), the carbene trap (1.0 mmol), and the solvent (0.25 mL), were mixed all together in a medium-walled NMR tube. After three cycles of degassing, at liquid nitrogen temperature, and thawing at room temperature, the tube was sealed under vacuum (10⁻² mm of Hg). The thermolysis was carried out in a constant temperature oil bath, maintained at 100 ± 0.2°C, for 55 minutes if 172g was the carbene source, and for 10 hours if the oxadiazoline was 172a or 172b. At the end of the reaction, the solvent and the excess carbene-trap were distilled by the bulb to bulb method, at high vacuum. Unless otherwise noted, the residue was the required carbene insertion product, obtained in a pure state with no need for further purification.

3.3.6.1.1 □ Thermolysis of 172a; insertion into acetic acid: 4-Acetoxy-1, 3, 3-triphenyl-azetidin-2-one (195).

The 4-acetoxy β-lactam (195) was synthesized following the above procedure with modifications in the concentrations: The oxadiazoline, 172a, (0.064 mmol) was dissolved in C₆D₆ (0.5 mL) and acetic acid (11 μL, 0.19 mmol) was added (see procedure above). The residue after bulb to bulb distillation was the expected product (195), obtained as a
thick colorless oil, in 100 % yield; IR (film) v 1768 cm\(^{-1}\) (C=O), 1745 cm\(^{-1}\) (C=O); \(^1\)H NMR (200.13 MHz, CDCl\(_3\)) \(\delta\) 7.85 - 7.16 (m, 15H, Ar), 7.02 (s, 1H, CH), 1.72 (s, 3H, OCH\(_3\)); \(^13\)C NMR (50.32 MHz, CDCl\(_3\)) \(\delta\) 170.07 (C=O, CH\(_2\)COO), 165.57 (C=O, C\(_2\)), 137.08 (N-C\(_1\), Ar), 136.38 (C\(_1\), Ar), 135.92 (C\(_1\), Ar), 129.31 (Ar), 128.90 (Ar), 128.66 (Ar), 128.24 (Ar), 127.96 (Ar), 127.91 (Ar), 127.84 (Ar), 125.07 (Ar), 117.08 (Ar), 83.22 (C\(_4\)), 72.87 (C\(_3\)), 20.38 (CH\(_3\)COO); LRMS: m/z (EI) 270 (M\(^+\) - CH\(_3\)COO - CO, 2 %), 238 (M\(^+\) - PhNCO, 12 %), 196 (100 %), 165 (C\(_{13}\)H\(_9\)\(^+\) = 9-fluorenyl, 32 %), 84 (23 %), (Cl, NH\(_3\)) 358 (M\(^+\) + 1, 18 %), 315 (M\(^+\) - CH\(_3\)CO +1, 11 %), 298 (M\(^+\) - CH\(_3\)COOH, 100 %), 270 (80 %), 238 (8 %), 196 (47 %), 167 (15 %), 136 (6 %), 94 (7 %).

3.3.6.1.2 □ Thermolysis of 172a; insertion into methanol: 4-Methoxy-1, 3, 3-triphenyl-azetidin-2-one (196).

The 4-methoxy β-lactam (196) was synthesized following the above procedure. The residue obtained after bulb to bulb distillation did not require any purification. β-Lactam (196) was obtained as a white solid, > 95 % yield; mp 89-90 ºC; IR (KBr) v 1753 cm\(^{-1}\) (C=O); \(^1\)H NMR (500 MHz, CDCl\(_3\)), 7.6-7.1 (m, 15H, Ar), 5.75 (s, 1H, CH), 3.23 (s, 3H, OCH\(_3\)); \(^13\)C NMR (125.76 MHz, CDCl\(_3\)) \(\delta\) 166.13 (C=O), 138.25 (N-C\(_1\), Ar), 137.21 (C\(_1\), Ar), 136.23 (C\(_1\), Ar), 129.21 (Ar), 128.93 (Ar), 128.67 (Ar), 128.24 (Ar), 127.93 (Ar), 127.76 (Ar), 127.61 (Ar), 124.79 (Ar), 117.42 (Ar), 90.68 (C\(_4\)), 71.86 (C\(_2\)), 54.81 (OCH\(_3\)); LRMS: m/z (EI) 329 (M\(^+\), 5 %), 210 (M\(^+\) - PhNCO, 68 %), 194 (Ph\(_2\)CCO, 100 %), 165 (C\(_{13}\)H\(_9\)\(^+\) = 9-fluorenyl, 78 %), 105 (18 %), 77 (36 %); HRMS calculated for C\(_{22}\)H\(_9\)NO\(_2\) 329.1416, observed 329.1411.

3.3.6.1.3 □ Thermolysis of 172g; insertion into methanol:

4-Methoxy-3-phenoxy-1-phenylazetidin-2-one (197), cis / trans mixture.

The 4-methoxy β-lactams (197) were synthesized following the above procedure. The
proton NMR spectrum of the residue, obtained after bulb to bulb distillation, showed the cis and trans isomers of 197 to be the only products of this reaction. The cis and trans isomers were not separated, but their ratio was determined, from the $^1$H NMR spectrum of the mixture, to be 1 : 2.6, respectively. β-Lactams 197 were obtained as a yellow oil; IR (film) ν 1770 cm$^{-1}$ (C=O); $^1$H NMR (200 MHz, CDCl$_3$) δ 7.57 - 7.06 (m, 10H, Ar), 5.71 (d, J = 3.6 Hz, 1H, CH, cis), 5.46 (d, J = 0.8 Hz, 1H, CH, trans), 5.33 (d, J = 3.6 Hz, 1H, CH, cis), 5.28 (d, J = 0.8 Hz, 1H, CH, trans), 3.55 (s, 3H cis, 3H trans, OCH$_3$); $^{13}$C NMR (50.32 MHz, CDCl$_3$) δ 163.07 (C=O, cis), 160.94 (C=O, trans), 157.40, 157.07 (O-C$_1$, Ar, cis and trans), 136.70 (N-C$_1$, Ar, cis and trans), 129.76 (Ar), 129.65 (Ar), 129.31 (Ar), 125.34 (Ar), 125.31 (Ar), 122.55 (Ar), 117.57 (Ar), 117.47 (Ar), 115.70 (Ar), 115.56 (Ar), 88.23 (C$_4$, cis), 84.61 (C$_3$, trans), 83.67 (C$_4$, trans), 81.79 (C$_3$, cis), these last four assignments are tentative, 54.53 (OCH$_3$, cis), 53.83 (OCH$_3$, trans); LRMS: m/z (EI) 269 (M$^+$, 13 %), 150 (M$^+$ - PhNCO, 100 %), 135 (15 %), 104 (15 %), 84 (15 %), 77 (60 %), (Cl, NH$_3$) 270 (M$^+$ + 1, 90 %), 287 ((M + NH$_4$)$^+$, 100 %), 270 (M$^+$ + 1, 90 %), 178 (18 %), 150 (28 %), 138 (6 %), 136 (14 %), 94 (11 %); HRMS: Calculated for C$_{16}$H$_{15}$N$_1$O$_3$, 269.1052, observed 269.1056.

3.3.6.1.4 □ Thermolysis of 172g; insertion into ethanol:

4-Ethoxy-3-phenoxy-1-phenylazetidin-2-one (198), cis / trans mixture.

The 4-ethoxy β-lactams (198) were synthesized following the above procedure. The proton NMR spectrum of the residue, obtained after bulb to bulb distillation, showed the cis and trans isomers of 198 to be the only products of this reaction. The cis and trans isomers were not separated, but their ratio was determined, from the $^1$H NMR spectrum of the mixture, to be 1 : 4, respectively. β-Lactams 198 were obtained as a yellow oil; IR (film) ν 1770 cm$^{-1}$ (C=O), $^1$H NMR (200.132 MHz, CDCl$_3$) δ 7.55 - 7.06 (m, 10H, Ar), 5.70 (d, J = 3.6 Hz, 1H, CH, cis), 5.46 (br. s, 1H, CH, trans), 5.30 (d, J = 3.6 Hz, 1H, CH,
cis), 5.24 (br. s, 1H, CH, trans), 3.78 (m, 2H cis, 2H trans, CH₂), 1.30 (tr, J = 7 Hz, 3H, CH₃, trans), 1.17 (tr, J = 7 Hz, 3H, cis); ¹³C NMR (50.32 MHz, CDCl₃) δ 161.15 (C=O), 157.08 (O-C₁, Ar, cis and trans), 136.62 (N-C₁, Ar, cis and trans), 129.74 (Ar), 129.61 (Ar), 129.28 (Ar), 125.24 (Ar), 122.49 (Ar), 117.66 (Ar), 117.46 (Ar), 115.62 (Ar), 112-113.51 (Ar), 87.55 (C₃, trans), 84.54 (C₄, trans), 84.01 (C₃, cis), 81.61 (C₄, cis), 63.26 (CH₂, cis), 63.04 (CH₂,trans), 15.24 (CH₃, cis and trans); MS: m/z (EI) 283 (M⁺, 15 %), 164 (M⁺ - PhNCO, 100 %), 149 (M⁺ - PhO(H)COO, 10 %), PhO(H)COO, 11 %), 136 (53 %), 121 (17 %), 107 (25 %), 93 (16 %), 77 (76 %), (Cl, NH₃) 301 ((M + NH₄)⁺, 9 %), 284 (M⁺+1, 100 %), 164 (19 %), 150 (7 %), 94 (9 %).

3.3.5.1.5 □ Thermolysis of 172b; insertion into acetone cyanohydrin:

1-Benzyl-4-(2-cyano-2-propoxy)-3, 3-diphenyl azetidin-2-one (200).

The 4-alkoxy β-lactam (200) was synthesized following the above procedure with modifications in the concentrations: The oxadiazoline, 172a, (0.081 mmol) was dissolved in C₆D₆ (0.5 mL) and acetone cyanohydrin (22.2 μL, 0.24 mmol) was added (see above procedure). The residue after bulb to bulb distillation was the O-H insertion product (200), along with some of the excess acetone cyanohydrin. Therefore, the β-lactam (200) was purified on the Chromatotron (2 mm silica plate) using 25 % ethyl acetate in hexane as eluent. The product (200) was obtained as a white solid, > 95 % yield; mp 155-156°C;

IR (KBr) ν 2240 cm⁻¹ (CN), 1767 cm⁻¹ (C=O); ¹H NMR (200.13 MHz, CDCl₃) δ 7.67 - 7.17 (m, 15H, Ar), 3.39 (s, 1H, CH), 1.51 (s, 3H, CH₃), 1.08 (s, 3H, CH₃); ¹³C NMR (50.32 MHz, CDCl₃) δ 166.45 (C=O), 136.59 (C₁, Ar), 136.24 (C₁, Ar), 136.00 (C₁, Ar), 130.08 (Ar), 129.24 (Ar), 129.13 (Ar), 129.03 (Ar), 128.12 (Ar), 127.89 (Ar), 127.79 (Ar), 125.24 (Ar), 118.16(Ar), 120.23 (CN), 86.32 (C₄), 72.99 (C₃), 70.34 (CCN), 27.90 (CH₂), 27.44 (CH₃); LRMS: m/z (EI) 383 (M⁺, 1 %), 263 (M⁺ - PhNCO, 24 %), 205 (6 %), 194 (Ph₂CCO, 100 %), 165 (C₁₃H₉⁺= 9-fluorenyl, 93 %), 152 (22 %), 139 (7 %), 115 (6 %), 93
(12 %), 77 (19 %), (Cl, NH₃) 400 ((M + NH₄)⁺, 3 %), 383 (M⁺+1, 100 %), 342 (14 %),
325 (18 %), 300 (15 %), 270 (16 %), 194 (Ph₂CCO, 23 %), 167 (71 %), 119 (PhNCO, 13
%), 94 (34 %); HRMS: Calculated for C₂₅H₂₂N₃O₂ 382.1681, observed 382.1696.

3.3.6.1.6 □ Thermolysis of 172b; insertion into carbon tetrachloride:
1-Benzyl-4-chloro-4-trichloromethyl-3, 3-diphenyl azetidin-2-one (202).
The 4-chloro β-lactam (202) was synthesized following the above procedure with the
following modifications: The oxadiazoline, 172b, was dissolved in 0.5 mL of CCl₄,
carbene-trap used as solvent, (see above procedure). The residue, obtained after
evaporation of the solvent, was a yellow oil; IR (film) ν 1785 cm⁻¹ (C=O, β-lactam); ¹H
NMR (90 MHz, CDCl₃) δ 7.67 - 7.17 (m, 15H, Ar), 4.85 (d, J = 15.3 Hz, 1H, CH₂), 4.11
(d, J = 15.3 Hz, 1H, CH₂); GC/MS (EI) product was not surviving the GC temperature.
One peak (Rₜ= 25.596 min) corresponded to (M⁺ - Cl, = 428), another (Rₜ= 25.888 min)
corresponded to (M⁺ - 3Cl, = 358). However, the major peak corresponded to the
β-lactam-4-ylidene structure (M⁺ - CCl₄, = 311). Also, one of the peaks corresponded to
hexachloroethane.

3.3.6.2.0 ■ Intramolecular Insertion Reactions
3.3.6.2.1 □ Synthesis of Oxapenam (206)
(i) Synthesis of acetone 4-(2-hydroxyethyl) semicarbazone (204).
The procedure for the preparation of the semicarbazone (204) is based on that of Iwao.³¹⁷
Ethanolamine (8.9 mL, 0.15 mol) was introduced into a round bottom flask fitted with a
condensor, a thermometer, and a nitrogen bubbler. The acetone semicarbazone (14.15 g,
0.123 mol) was then added and the mixture was heated until the temperature reached
140°C. The solution (the semicarbazone dissolved in ethanolamine at 140°C) was stirred
at 140°C for 30 minutes and then left to cool to room temperature. The crude acetone
4-(2-hydroxyethyl) semicarbazone (204) crystallized out as the flask was swirled at room temperature. The crude off white solid of 204 was recrystallized from benzene to produce the pure title compound (204) in 60% yield; mp 91-92°C; IR (KBr) ν 3500 - 3150 cm⁻¹ (HO, HN), 1650 cm⁻¹ (C=O), 1550 (C=N); ¹H NMR (200.13 MHz, CDCl₃) δ 7.92 (br. s, 1H, CONH₂N), 6.55 (br. s, 1H, CNHCO), 3.76 (t, J = 5 Hz, 2H, CH₂O), 3.46 (q, J = 5.5 Hz, 2H, CH₂N), 3.24 (br. s, 1H, OH), 1.97 (s, 3H, CH₃), 1.84 (s, 3H, CH₃); ¹³C NMR (50.32 MHz, CDCl₃) δ 157.86 (C=O), 148.15 (C=N), 62.38 (CH₂O), 42.31 (CH₂N), 24.93 (CH₃), 16.44 (CH₃).

(ii) Synthesis of the tert-butyldimethylsilyl ether derivative of semicarbazone 204, (205).

The method for the protection of the hydroxyl group with tert-butyldimethylsilyl chloride is based on that of Corey. However, 205 was not formed if the conditions described by Corey were employed. Instead of imidazole as catalyst and dimethylformamide as solvent, triethylamine was used as the base and dry methylene chloride was used as the solvent. The tert-butyldimethylsilyl chloride (3.62 g, 24 mmol) was dissolved in dry methylene chloride (30 mL) and added dropwise, over a period of two hours (using a syringe pump), to a stirred solution containing the acetone 4-(2-hydroxyethyl) semicarbazone, 204, (2.55 g, 16 mmol) and triethylamine (4.0 mL, 29 mmol) in dry methylene chloride (100 mL) under nitrogen atmosphere at 0°C (ice bath). The resulting reaction mixture was stirred overnight at room temperature. Evaporation of the solvent (methylene chloride) afforded a white solid. This crude product was titurated three times with ether. Removal of the ether afforded the protected semicarbazone (205) which was dried under high vacuum for 4 hours. Semicarbazone 205 was obtained in pure form, as a white solid, in a quantitative yield (100%); mp 63-64°C; IR (KBr) ν 1675 (C=O), 1530 (C=N); ¹H NMR (200.13 MHz, CDCl₃, ref.= CH₂Cl₂= 5.32 ppm) δ 8.31 (br.
s, 1H, CONH\(_{2}\)N), 6.57 (br. t, 1H, CNH\(_{2}\)), 3.72 (t, J = 5.3 Hz, 2H, \(\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cd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(Ar), 128.16 (Ar), 128.00 (Ar), 127.61 (Ar), 124.73 (C₄), 121.85 (C₆), 75.82 (C₃), 60.46 (OCH₂), 41.87 (NCH₂), 25.82 (3 x CH₃), 25.18 (CH₃), 24.18 (CH₃), 18.24 (C-Si), -5.50 (Si(CH₃)₂); LRMS: m/z (EI) 450 (M⁺- CH₃, 1.6 %), 408 (M⁺- C₄H₉, 65.8 %), 380 (M⁺- (CH₃)₂C - N₂, 13 %), 338 (380 - (CH₃)₂C, 38 %), 310 (338 - CO, 42 %), 279 (13 %), 237 (37 %), 194 (Ph₂CCO, 100 %), 165 ((C₁₃H₉⁺= 9-fluorenyl, 74 %), 144 (35 %), 100 (48 %), (Cl, NH₃) 466 (M⁺+1, 100 %), 438 (10 %), 396 (48 %), 371 (32 %), 265 (31 %), 202 (40 %), 167 (21 %), 99 (27 %).

(v) Deprotection of 207a: Synthesis of 1, 7, 8-triaza-1-(2-hydroxyethyl)-6, 6-dimethyl-5-oxa-2-oxo-3, 3-diphenylspiro [3.4] oct-7-ene (208a).

The removal of the silyl protecting group in 207a was accomplished by a procedure based on that of Corey.⁶⁰⁴ tetra-n-Butylammonium fluoride (2.1 mmol) in THF (2.1 mL) was added dropwise to a stirred solution of the protected alcohol, 207a, (0.62 g, 1.33 mmol) in THF (1 mL), at 0°C. After 5 hours of stirring at room temperature the THF was removed on the rotary evaporator. The residue was dissolved in CH₂Cl₂ (4 mL) and 0.1 N HCl (2 mL) was added. The aqueous layer was extracted three times with methylene chloride.

The organic layers combined and washed with saturated sodium bicarbonate solution and brine. The aqueous layers were combined and re-extracted twice with methylene chloride. The organic layers were combined and dried (MgSO₄) and filtered. Purification on the Chromatotron (4 mm silica plate), using 40 % ethylacetate in hexane as the eluent, afforded the deprotected alcohol (208a) as a white solid, in 82 % yield (for deprotection), mp 142-143 °C; IR (KBr) v 3620-3440 cm⁻¹ (OH, br), 1770 cm⁻¹ (C=O); ¹H NMR (200 MHz, CDCl₃, ref: CH₂Cl₂ = 5.32 ppm) δ 7.40-7.25 (m, 10H, Ar), 3.85 (t, 2H, OCH₂), 3.25-3.15 (br m, 3H, NCH₂OH), 1.65 (s, 3H, CH₃), 1.54 (s, 3H, CH₃); ¹³C NMR (50.323 MHz, CDCl₃) δ 168.95 (C=O), 136.23 (C₁, Ar), 134.58 (C₁, Ar), 128.52 (Ar), 128.31 (Ar), 128.18 (Ar), 127.86 (Ar), 127.80 (Ar), 124.12 (C₄), 122.42 (C₆), 75.39 (C₃), 60.15
(OCH₂), 43.60 (NCH₂), 25.04 (CH₃), 24.15 (CH₃); LRMS: m/z (El) 265 (M⁺-N₂-acetone, 30 %), 236 (10 %), 194 (Ph₂CCO, 63 %), 165 (C₁₃H₉⁺ = 9-fluorenyl, 100 %), 139 (10 %), 115 (7 %), (Cl, NH₃) 369 ((M + NH₄)⁺, 11 %), 352 (M⁺+1, 85 %), 324 (12 %), 299 (31 %), 256 (27 %), 238 (49 %), 212 (52 %), 186 (100 %), 167 (53 %), 142 (25 %), 105 (46 %), 88 (23 %), 72 (90 %).

(vi) Synthesis of 6,6-diphenyl-oxapenam (209)

![Chemical structure of 6,6-diphenyl-oxapenam](image)

The alcohol 208a (0.021 g, 5.87 x 10⁻⁵ mol) was dissolved in benzene (0.4 mL), conc. = 0.147 M, (in a different experiment 208a (0.138 g, 3.92 x 10⁻⁴) was dissolved in 50 mL of benzene, conc. = 7.84 x 10⁻³ M) and sealed into a glass tube after three cycles of freeze-pump-thaw degassing. The tube was then immersed in a constant temperature oil bath, maintained at ±0.0 ± 0.2°C, for 10 hours. Removal of the solvent afforded a yellow oil. Purification on the Chromatotron (2 mm silica plate), using 35 % ethylacetate in hexane, afforded the oxapenam (209) as a white solid, in an average of 50 % yield (the thermolysis at high dilution afforded a slightly lower yield); mp 113-114°C; IR (film) ν 1785 cm⁻¹ (C=O); ¹H NMR (200 MHz, CDCl₃) δ 7.60-7.00 (m, 10H, Ar), 5.57 (s, 1H, CH), 4.15-3.87 (m, 2H, CH₂O), 3.76-3.66 (m, 1H, CH₂N), 3.10-2.98 (m, 1H, CH₂N); ¹³C NMR (50.32 MHz, CDCl₃) δ 179.82 (C=O), 139.43 (Ar), 136.05 (Ar), 128.9-126.5 (Ar), 92.93 (C₅), 70.73 (C₆), 69.29 (C₂), 45.15 (C₃); LRMS: m/z (El) 265 (M⁺, 43 %), 194 (Ph₂CCO, 57 %), 165 (C₁₃H₉⁺ = 9-fluorenyl, 100 %), 152 (12 %), 139 (9 %), 115 (8 %).
89 (5 %), 70 (11 %), (Cl, NH₃) 283 ((M + NH₄)⁺, 33 %), 266 (M⁺+1, 100 %), 238 (14 %), 212 (31 %), 194 (39 %), 182 (30 %), 167 (95 %), 152 (6 %), 136 (8 %), 111 (9 %); HRMS: calculated for C₁₇H₁₅NO₂ 265.1103, observed 265.1122.

3.3.6.2.2 Synthesis of 3, 4, 9-triaza-2, 2-dimethyl-1, 6-dioxaspiro [4.4] non-3-ene (211).

![Chemical Structure](image)

The semicarbazonate, 204, (1.0 g, 6.29 mmol) was dissolved in dry methylene chloride (40 mL) and added dropwise to an ice cold stirred solution of lead tetraacetate (3.35 g, 7.55 mmol) in 70 mL of methylene chloride. During the 30 minutes addition, the reaction flask was swept with a slow stream of dry Nitrogen. The mixture was kept stirring at room temperature for two hours. The color of the mixture changed from yellow to near colorless after two hours. Cold water (70 mL) was added and the mixture was filtered through a wet celite cake, to remove the lead oxide. This solution was then washed with ice cold saturated sodium bicarbonate solution and brine. The organic layer was dried (MgSO₄) and filtered. Evaporation of the solvent afforded a thick yellow oil. The crude product was distilled on the Kugelrohr at 60 - 70°C and 0.5 mm of Hg. The distillate was a light yellow clear oil. The ¹H NMR spectrum was not that for a pure 211; also, the IR showed an absorption at 1710 cm⁻¹ suggesting the presence of the imine. However, purification on the Chromatotron, using either in hexane as the eluent (starting with 20 % ether in hexane and gradually increasing the polarity to 40 % ether in hexane) afforded 211 as the major product. The oxadiazoline 211 was obtained as a pale yellow oil, in 20
% yield (one trial); IR (neat) ν 3350 (br., N-H), 1580 (N=N); ^1^H NMR (500.14 MHz, CDCl₃) δ 4.26 (br. dd, ^3^J = 7.5 Hz, ^2^J = -14.6 Hz, 1H, OCH₂), 4.19 (dd, ^3^J = 7.5 Hz, ^2^J = -14.6 Hz, 1H, OCH₂), 3.48 (m, 2H, NCH₂), 2.88 (br. s, 1H, N-H), 1.52 (s, 3H, CH₃), 1.48 (s, 3H, CH₃); ^1^3^C NMR (50.32 MHz, CDCl₃) δ 139.06 (C₅), 117.47 (C₂), 67.70 (OCH₂), 44.53 (NCH₂), 24.48 (CH₃), 24.26 (CH₃); LRMS: m/z (EI) 129 (M⁺ - N₂, 16 %), 99 (15 %), 88 (100 %), 84 (63 %), 71 (49 %), (Cl, NH₃) 175 ((M + NH₄)⁺, 12 %), 158 (M⁺ + 1, 21 %), 130 (7 %), 105 (100 %), 88 (45 %), 72 (10 %).

3.3.6.2.3 (i) Synthesis of 1, 7, 8-triaza-1- (2-tert-butyl- dimethylsilyloxy ethyl)-6, 6-dimethyl-5-oxa-2-oxo-3-phenoxySpiro [3.4] oct-7-ene (207b). The general procedure for the [2 + 2] cycloaddition reaction, described in Section 3.3.3.0.0, was followed. The β-lactam (207b) was obtained as a yellow oil, in 80 % yield; IR (neat) ν 1794 cm⁻¹ (C=O), 1600 cm⁻¹ (N=N); ^1^H NMR (200.13 MHz, CDCl₃, CH₂Cl₂= 5.32 ppm) δ 7.34 - 7.00 (m, 5H, Ar), 5.38 (s, 1H, CH), 3.74 (m, 2H, OCH₂), 3.26 (br. tr, J = 6.1 Hz, 2H, NCH₂), 1.68 (s, 3H, CH₃), 1.54 (s, 3H, CH₃), 0.94 (s, 9H, 3 x CH₃), 0.11 (s, 6H, 2 x CH₃); ^1^3^C NMR (50.32 MHz, CDCl₃) δ 163.70 (C=O, β-lactam), 156.73 (O-C₁, Ar), 129.35 (C₃, Ar), 122.66 (C₄, Ar), 115.64 (C₂, Ar), 122.13 (C₅, Ar), 121.88 (C₆), 87.41 (C₇), 60.31 (OCH₂), 41.62 (NCH₂), 25.66 (3 x CH₃), 24.74 (CH₃), 24.02 (CH₃), 18.06 (Si-C), -5.64 (Si(CH₃)₂).

(ii) Deprotection of 207b: Synthesis of 1, 7, 8-triaza-1- (2-hydroxyethyl)-6, 6-dimethyl-5-oxa-2-oxo-3-phenoxySpiro [3.4] oct-7-ene (208b). The removal of the silyl protecting group in 207b was accomplished by a procedure described above for the formation of 208a (Section 3.3.6.2.1 (v)). The alcohol 208b was obtained as a white solid in 32 % yield; mp 118 - 119°C; ^1^H NMR (200.13 MHz, CDCl₃) δ 7.30 - 6.83 (m, 5H, Ar), 5.62 (s, 1H, CH), 4.56 (m, 2H, OCH₂), 3.34 (m, 2H, NCH₂),
2.17 (br. s, 1H, O-H), 1.72 (s, 3H, CH₃), 1.59 (s, 3H, CH₃); ¹³C NMR (50.32 MHz, CDCl₃) δ 166.94 (C=O, β-lactam), 157.10 (O-C₁, Ar), 129.51 (C₃, Ar), 122.70 (C₄, Ar), 116.26 (C₂, Ar), 124.28 (C₄), 123.90 (C₆).

3.3.6.2.4 □ (i) Synthesis of 1, 7, 8-triaza-1-(2-tert-butyl(dimethyl)silyloxy ethyl)-3, 3-dichloro-6, 6-dimethyl-5-oxa-2-oxospiro[3.4]oct-7-ene (207c)

The general procedure for the [2 + 2] cycloaddition reaction, described in Section 3.3.3.0.0, was followed. The β-lactam (207c) was obtained as a yellow oil, in 75% yield; IR (neat) ν 1812 cm⁻¹ (C=O); ¹H NMR (200.13 MHz, CDCl₃= Ref. = 7.24 ppm) δ 3.63 (tr, J = 6.0 Hz, 2H, OCH₂), 3.17 (m, 2H, NCH₂), 1.68 (s, 3H, CH₃), 1.51 (s, 3H, CH₃), 0.83 (s, 9H, 3 x CH₃), 0.00 (s, 6H, 2 x CH₂); ¹³C NMR (50.32 MHz, CDCl₃) δ 160.32 (C=O, β-lactam), 123.88 (C₄), 121.53 (C₆), 86.22 (C₃), 60.00 (OCH₂), 42.50 (NCH₂), 25.74 (3 x CH₂), 24.95 (CH₃), 24.11 (CH₃), 18.16 Si-C, -5.59 (Si(CH₃)₂).

(ii) Deprotection of 207c: Synthesis of 1, 7, 8-triaza-3, 3-dichloro-1-(2-hydroxyethyl)-6, 6-dimethyl-5-oxa-2-oxospiro[3.4]oct-7-ene (208c).

The removal of the silyl protecting group in 207c was accomplished by a procedure described above for the formation of 208a (Section 3.3.6.2.1 (v)). The alcohol 208c was obtained as a yellow oil in 25% yield; IR (neat) ν 3420 cm⁻¹ (br OH), 1807 (C=O, β-lactam); ¹H NMR (200.13 MHz, CDCl₃= Ref. = 7.24 ppm) δ 3.75 (br. tr, 2H, OCH₂), 3.25 (m, 2H, NCH₂), 2.40 (br. s, 1H, O-H), 1.74 (s, 3H, CH₃), 1.55 (s, 3H, CH₃); ¹³C NMR (50.32 MHz, CDCl₃) δ 160.89 (C=O, β-lactam), 124.54 (C₄), 121.16 (C₆), 86.00 (C₃), 59.75 (OCH₂), 43.37 (NCH₂), 25.05 (CH₂), 23.95 (CH₃).

3.3.6.2.5 □ Synthesis of Oxacepham 217.

(i) Acetone 4-(3-hydroxypropyl) semicarbazone (210).
The procedure for the preparation of the semicarbazone (210) is similar to the procedure described above for the 2-hydroxyethyl analogue, 204, (Section 3.3.6.2.1(i)). Acetone 4-(3-hydroxypropyl) semicarbazone (210) was obtained as a white solid in 15 % yield; mp 97 - 98 °C; IR (KBr) 1640 (C=O), 1550 (C=N); $^1$H NMR (200.13 MHz, CDCl$_3$) δ 8.71 (br. s, 1H, NH), 6.42 (br. t, 1H, NH), 3.96 (br. s, 1H, OH), 3.64 (t, 2H, OCH$_2$), 3.48 (q, 2H, NCH$_2$), 1.96 (s, 3H, CH$_3$), 1.70 (qn, 2H, CH$_2$); $^{13}$C NMR (50.32 MHz, CDCl$_3$) δ 158.09 (C=O), 147.97 (C=N), 58.50 (OCH$_2$), 35.49 (NCH$_2$), 33.02 (CH$_2$), 25.09 (CH$_3$), 16.49 (CH$_3$).

(ii) Synthesis of the tert-butyldimethylsilyl ether derivative of semicarbazone 210, (213).

The method for the protection of the hydroxyl group with tert-butyldimethylsilyl chloride is similar to the procedure described above for the 2-hydroxyethyl analogue, 205, (Section 3.3.6.2.1(ii)). The protected alcohol was obtained as a yellow oil in 100 % yield, IR (neat) ν 1675 cm$^{-1}$ (C=O), 1535 (C=N); $^1$H NMR (200.13 MHz, CDCl$_3$, ref: CH$_2$Cl$_2$= 5.32 ppm) δ 9.11 (br. s, 1H, NH), 6.38 (br. t, 1H, NH), 3.72 (t, 2H, OCH$_2$), 3.40 (q, 2H, NCH$_2$), 1.95 (s, 3H, CH$_3$), 1.90 (s, 3H, CH$_3$), 1.77 (qn, 2H, CH$_2$), 0.92 (s, 9H, 3 x CH$_3$), 0.08 (s, 6H, Si(CH$_3$_2)); $^{13}$C NMR (50.32 MHz, CDCl$_3$) δ 156.98 (C=O), 146.56 (C=N), 60.84 (OCH$_2$), 36.64 (NCH$_2$), 32.51 (CH$_2$), 25.61 (3 x CH$_3$), 25.50 (CH$_3$), 24.83 (CH$_3$), 16.39 (C-Si), -5.73 (Si(CH$_3$_2)).

(iii) 5, 5-Dimethyl-2-(3-tert-butyldimethylsilyloxy propyl)-imino-$\Delta^3$-1, 3, 4-oxadiazoline (214).

The synthesis was accomplished according to the method-2 referenced in Section 3.2.2.0.0. The oxadiazoline, 214, was obtained as a yellow oil, in 95 % yield; IR (neat) ν 1712 cm$^{-1}$(C=N), 1520 (N=N); $^1$H NMR (200.13 MHz, CDCl$_3$, ref: residual CHCl$_3$= 7.24
(iv) 1, 7, 8-Triaza-1-(3-tert-butyldimethylsilyloxy propyl)-5-oxa-2-oxo-3,
3-diphenylspiro [3.4] oct-7-ene (215a).

The general procedure for the [2 + 2] cycloaddition reaction, described in Section
3.3.3.0.0, was followed. The β-lactam (215a) was obtained as an orange oil, in 72 %
yield; IR (neat) ν 1786 cm⁻¹(C=O), 1600 cm⁻¹(N=N); ¹H NMR (200.13 MHz, CDCl₃, ref:
CH₂Cl₂= 5.32 ppm) δ 7.40 - 7.20 (br. m, 10H, Ar), 3.65 (t, 2H, OCH₂), 3.23 (br t, 2H,
NCH₂), 1.81 (br m, 2H, CH₂), 1.64 (s, 3H, CH₃), 1.54 (s, 3H, CH₃), 0.88 (s, 9H, 3 x CH₃)
0.04 (s, 6H, Si(CH₃)₂); ¹³C NMR (50.32 MHz, CDCl₃) δ 168.06 (C=O), 136.64 (N-C₁,
Ar), 135.05 (C₁, Ar), 128.64 (Ar), 128.39 (Ar), 128.21 (Ar), 128.18 (Ar), 128.7 (Ar),
127.5 (Ar), 124.74 (C₄), 121.86 (C₆), 75.60 (C₃), 60.15 (OCH₂), 36.50 (NCH₂), 31.64
(CH₂), 25.84 (3 x CH₃), 24.99 (CH₃), 24.18 (CH₃), 18.18 (C-Si), -5.51 (Si(CH₃)₂); LRMS:
m/z (EI) 422 (M⁺ - (CH₃)₂C, 4 %), 365 (16 %), 269 (6 %), 194 (Ph₂CCO, 42 %), 165
(C₁₃H₉⁺= 9-fluorenyl, 43 %), 115 (17 %), 73 (100 %), (Cl, NH₃) 480 (M⁺+1, 8 %), 410
(18 %), 366 (73 %), 327 (100 %), 269 (31 %), 183 (33 %), 167 (79 %), 132 (21 %), 83 (38 %).

(v) Deprotection of 215a: 1, 7, 8-Triaza-6, 6- dimethyl-5-oxa- 2-oxo-3,
3-diphenyl-1-(3-hydroxypropyl) spiro [3.4] oct-7-ene (216a).
The removal of the silyl protecting group in 215a was accomplished by a procedure described above for the formation of 208a (Section 3.3.6.2.1 (v)). The alcohol 216a was obtained as a white solid, in 100 % yield; mp 82 - 83°C; IR (KBr) v 1773 (C=O), 1597 (N=N); \(^1\)H NMR (200.13 MHz, CDCl\(_3\)) \(\delta\) 7.36 - 7.24 (m, 10H, Ar), 3.67 (t, 2H, OCH\(_2\)), 3.24 (t, 2H, NCH\(_2\)), 2.64 (br. s, 1H, OH), 1.70 (m, 2H, CH\(_2\)), 1.61 (CH\(_3\)), 1.51 (CH\(_3\)); \(^13\)C NMR (50.32 MHz, CDCl\(_3\)) \(\delta\) 168.79 (C=O), 136.25 (C\(_1\), Ar), 134.77 (C\(_1\), Ar), 128.26 (Ar), 128.05 (Ar), 127.92 (Ar), 127.56 (Ar), 127.47 (Ar), 124.37 (C\(_4\)), 121.97 (C\(_6\)), 75.34 (C\(_3\)), 58.70 (OCH\(_2\)), 35.67 (NCH\(_2\)), 30.94 (CH\(_2\)), 24.79 (CH\(_3\)), 23.92 (CH\(_3\)); LRMS: m/z (El) 365 (M\(^+\), 7 %), 236 (M\(^+\) - N\(_2\) - HO(CH\(_2\))\(_3\)NCO, 8 %), 194 (Ph\(_2\)COCO, 30 %), 165 (C\(_{13}\)H\(_9\)\(^+\)= 9-fluorenyl, 68 %), 149 (40 %), 142 (49 %), 115 (16 %), 100 (23 %), 89 (35 %), 73 (100 %), (Cl, NH\(_3\)) 366 (M\(^+\)+1, 5 %), 280 (M\(^+\) - N\(_2\) - acetone + 1, 100 %), 252 (8 %), 194 (Ph\(_2\)COCO, 15 %), 167 (24 %), 86 (14 %).

(vi) Synthesis of 7, 7-diphenyl-oxacepham (217).

![Chemical Structure](image)

The alcohol 216a (0.1006 g, 2.756 x 10\(^{-4}\) mol) was dissolved in benzene (40 mL), conc. = 0.007 M, and sealed into a glass tube after three cycles of freeze-pump-thaw degassing. The tube was then immersed in a constant temperature oil bath, maintained at 100 ± 0.2°C, for 10 hours. Removal of the solvent afforded a yellow oil. Purification on the Chromatotron (2 mm silica plate), using 20 % ethylacetate in hexane, afforded the oxacepham (217) as a white solid, in 27 % yield, mp 166 - 167 °C; IR (KBr) v 1750 cm\(^{-1}\) (C=O), 1598 cm\(^{-1}\) (N=N); \(^1\)H NMR (200.13 MHz, CDCl\(_3\)) \(\delta\) 7.48 - 7.27 (m, 10H, Ar), 5.37
(s, 1H, CH), 4.15 - 3.97 (m, 2H, OCH2 ?), (m, 1H, NCH2), 3.16 - 3.01 (m, 1H, NCH2).
1.99 - 1.75 (m, 1H, CH2), 1.53 - 1.43 (m, 1H, CH2); 13C NMR (50.32 MHz, CDCl3) δ 169.08 (C=O), 139.59 (C1, Ar), 136.46 (C4, Ar), 128.74 (Ar), 128.28 (Ar), 128.07 (Ar), 127.37 (Ar), 127.19 (Ar), 126.84 (Ar), 85.65 (C6), 72.25 (C7), 65.19 (C2), 37.55 (C4), 24.00 (C3); LRMS: m/z (EI) 279 (M+, 20 %), 194 (Ph2CCO, 23 %), 165 (C13H9+ = 9-fluorenyl, 75 %), 152 (18 %), 139 (8 %), 115 (9 %), 84 (M+ - Ph2CCO - H, 100 %), 75 (7 %), (Cl, NH3) 280 (M+ + 1, 100 %), 194 (Ph2CCO, 13 %), 167 (23 %), 86 (14 %);
HRMS: Calculated for C18H17N1O2 279.1259, observed 279.1270. It should be noted that the oxacephem (217) was isolated and re-heated at 100°C in benzene for 10 hours; there was no change.

3.3.6.2.6 (i) Synthesis of 1, 7, 8-triaza-1-(2-tert-butyl-dimethylsilyloxy propyl)-6, 6-dimethyl-5-oxa-2-oxo-3-phenoxyspiro [3.4] oct-7-ene (215b)

The general procedure for the [2 + 2] cycloaddition reaction, described in Section 3.3.3.0.0, was followed. The β-lactam (215b) was obtained as a yellow oil, in 60 % yield; IR (neat) ν 1800 cm⁻¹ (C=O), 1600 cm⁻¹ (N=N); 1H NMR (200.13 MHz, CDCl3, ref. = CH2Cl2= 5.32 ppm) δ 7.30 - 6.96 (m, 5H, Ar), 5.34 (s, 1H, CH), 3.64 (tr., J = 5.8 Hz, 2H, OCH2), 3.21 (m, 2H, NCH2), 1.77 (m, 2H, CH2), 1.65 (s, 3H, CH3), 1.51 (s, 3H, CH3), 0.88 (s, 9H, 3 x CH3), 0.04 (s, 6H, Si(CH3)2); 13C NMR (50.32 MHz, CDCl3) δ 163.75 (C=O), 156.83 (O-C1, Ar), 129.47 (C3, Ar), 122.75 (C4), 115.71 (C2, Ar), 122.26 (C4), 122.07 (C6), C4 and C6 could be reversed, 87.40 (C3), 59.89 (OCH2), 36.53 (NCH2), 31.28 (CH2), 25.77 (3 x CH3), 24.81 (CH3), 24.18 (CH3), 18.11 (C-Si), -5.55 (Si(CH3)2); LRMS: m/z (EI) 362 (M+ - (CH3)3C, trace), 292 (8 %), 264 (M+ - N2 - (CH3)3C - (CH3)2C, 6 %), 200 (9 %), 142 (63 %), 107 (43 %), 73 (100 %), (Cl, NH3) 420 (M+ + 1, 3 %), 404 (8 %), 350 (M+ - N2 - (CH3)2C + 1, 25 %), 306 (M+ - N2 - acetone - C=O + 1, 100 %), 246 (19 %), 216 (49 %), 190 (20 %), 147 (20 %), 74 (22 %).
(ii) Deprotection of 215b:

**Method a: Synthesis of 1, 7, 8-triaza-6, 6-dimethyl-5-oxa-2-oxo-3-phenoxy-1-(3-hydroxypropyl) spiro [3.4] oct-7-ene (218 / 219).**

The removal of the silyl protecting group in 215b was accomplished by a procedure described above for the formation of 208a (Section 3.3.6.2.1 (v)). The two alcohol diastereomers 218 and 219 were formed in a total of 50% yield and in a ratio of 1 : 1.5, respectively.

**218:**

The minor isomer 218 was obtained as a yellow oil, in 20% yield; IR (neat) ν 3460 cm⁻¹ (br. O-H), 1785 cm⁻¹ (C=O), 1595 cm⁻¹ (N=N); ¹H NMR (200.13 MHz, CDCl₃) δ 7.34 - 6.96 (m, 5H, Ar), 5.37 (s, 1H, CH), 3.73 (m, 2H, OCH₂), 3.25 (m, 2H, NCH₂), 2.37 (br. s, 1H, OH), 1.72 (m, 2H, CH₂), 1.65 (CH₃), 1.51 (CH₃); ¹³C NMR (50.32 MHz, CDCl₃) δ 164.90 (C=O), 156.84 (O-C₁, Ar), 129.60 (C₃, Ar), 122.97 (C₄, Ar), 115.82 (C₂, Ar), 122.58 (C₄), 122.07 (C₆), C₄ and C₆ could be reversed, 87.50 (C₃), 58.86 (OCH₂), 35.79 (NCH₂), 30.73 (CH₂), 24.94 (CH₃), 24.24 (CH₃); LRMS: m/z (EI) 219 (M⁺ - N₂ - acetone, 8%), 191 (10%), 165 (17%), 134 (HPheOCCO, 25%), 105 (70%), 84 (219 - HPheOCCO - H, 100%), 77 (88%), (Cl, NH₃) 306 (M⁺ + 1, 3%), 220 (M⁺ - N₂ - acetone + 1, 50%), 192 (220 - C=O, 100%), 167 (10%), 102 (18%), 86 (19%).

**219:**

The major isomer 219 was obtained as a yellow oil, in 30% yield; IR (neat) ν 3470 (br. OH), 1790 cm⁻¹ (C=O), 1598 cm⁻¹ (N=N); ¹H NMR (200.13 MHz, CDCl₃) δ 7.31 - 6.88 (m, 5H, Ar), 5.68 (s, 1H, CH), 3.73 (tr., J = 5.8 Hz, 2H, OCH₂), 3.28 (m, 2H, NCH₂), 2.05 (br. s, 1H, OH), 1.77 (qu, J = 6.4 Hz, 2H, CH₂), 1.65 (s, 3H, CH₃), 1.33 (s, 3H, CH₃); ¹³C NMR (50.32 MHz, CDCl₃) δ 165.25 (C=O), 156.72 (O-C₁, Ar), 129.82 (C₃, Ar), 122.84 (C₄, Ar), 115.38 (C₂, Ar), 122.33 (C₄), 122.13 (C₆), C₄ and C₆ could be reversed, 84.24
(C₃), 58.95 (OCH₂), 36.08 (NCH₂), 30.88 (CH₂), 25.19 (CH₃), 23.96 (CH₃); LRMS: m/z (EI) 219 (M⁺ - N₂ - acetone, 5 %), 191 (219 - C=O, 10 %), 134 (HPhOCCO, 32 %), 105 (80 %), 86 (64 %), 84 (219 - HPhOCCO - H, 100 %), 77 (53 %), (Cl, NH₃) 306 (M⁺ + 1, 6 %), 278 (M⁺ - N₂ + 1, 3 %), 253 (6 %), 236 (10 %), 220 (M⁺ - N₂ - acetone + 1, 34 %), 192 (220 - C=O, 100 %), 134 (9 %), 105 (11 %), 94 (13 %), 83 (8 %).

**Method b: Synthesis of 218.**

In order to avoid isomerizing the starting material (215b), the removal of the silyl protecting group in 215b, was accomplished using acetic acid / water / tetrahydrofuran (3:1:1), instead of the fluoride ion, by a procedure based on that of Corey.³⁰⁴ The protected alcohol, 215b, (0.786 g, 1.87 mmol) was dissolved in THF (4 mL) and H₂O (4 mL). Acetic acid (12 mL, 0.21 mol) was then added and the solution was stirred at room temperature. After 24 hours TLC showed the disappearance of the starting material (215b). The flask was cooled to 0°C in an ice bath and sodium hydroxide (210 mL, 0.21 mol, 1.0 N solution) was added. The water layer was saturated with NaCl and extracted three times with ether. The ether layers were combined and washed with saturated solution of sodium bicarbonate and brine. The aqueous layers were combined and washed twice with ether. The combined organic layers were dried (MgSO₄) and filtered. Purification on the Chromatotron (4 mm silica plate), using 40% ethylacetate in hexane, afforded the deprotected alcohol (218) as the only product in quantitative yield. Isomer 219 was not obtained.

3.3.6.2.7 □ Thermolysis of 218 in the presence of acetic acid:
(i) Formation of 4-acetoxy-3-phenoxy-1-(3-acetoxypropyl) azetidin-2-one (220a: cis, 220b: trans).

(ii) Formation of 4-acetoxy-3-phenoxy-1-(3-hydroxypropyl) azetidin-2-one (221a: cis, 221b: trans).

(a) • Thermolysis of 218 in 1:1 benzene / acetic acid.

The alcohol 218 (0.05 g, 0.164 mmol) was dissolved in benzene / acetic acid (0.25 mL / 0.25 mL) and sealed into a medium walled NMR tube after three cycles of freeze-pump-thaw degassing. The tube was then immersed in a constant temperature oil bath, maintained at 100 ± 0.2°C, for 4 hours. Removal of the benzene and the excess acetic acid afforded a yellow oil. This residue was a mixture of products; purification on the Chromatoutron (2 mm silica plate), using 25 % ethyl acetate in hexane, afforded three products. The first fraction was (220a) obtained in 9.5 % yield. The other fraction was a mixture of the cis and trans isomers 221a and 221b, respectively. Isomers 221a and 221b were obtained in a total yield of 37 %, and in a cis : trans ratio of 1 : 1.55, as determined by proton NMR spectroscopy.

220a, cis:

Yellow oil, in 9.5 % yield; IR (film) ν 1780, 1740 cm⁻¹ (br, C=O); ¹H NMR (200 MHz, CDCl₃) δ 7.47 - 6.96 (m, 5H, Ar), 6.32 (d, J=3.4 Hz, 1H, CH), 5.30 (d, J=3.4 Hz, 1H, CH), 4.14 (br tr, J=6 Hz, 2H, OCH₂), 3.57 - 3.29 (m, 2H, NCH₂), 2.08 (s, 3H, CH₃COO), 2.06
(s, 3H, CH₂COO), 1.98 (m, 2H, CH₂); ¹³C NMR (50.32 MHz, CDCl₃) δ 170.63 (C=O), 2
x esters), 165.46 (C=O, β-lactam), 157.13 (O-C₁, Ar), 129.60 (Ar), 122.61 (Ar), 115.67
(Ar), 81.26 (C₆), 79.59 (C₃), 61.51 (OCH₂), 38.32 (NCH₂), 27.02 (CH₂), 20.86 (CH₃).
20.72 (CH₃); LRMS: m/z (EI) 178 (M⁺ - CH₂COO(CH₂)₃NCO, 16 %), 149 (11 %), 136
(178 - CH₂CO + 1, 100 %), 102 (27 %), 77 (19 %), (Cl, NH₃) 339 (M + NH₄)⁺, 6 %), 322
(M⁺+1, 8 %), 279 (322 -CH₂CO, 38 %), 234 (100 %), 204 (12 %), 174 (15 %), 136 (37
%), 102 (16 %).

221a, cis and 221b, trans:
Yellow oil, in 37 % yield; ¹H NMR (200 MHz, CDCl₃) δ 5.35 - 6.96 (m, 5H, Ar), 6.34 (d,
J=3.4 Hz, 1H, CH, cis), 6.03 (br. s, 1H, CH, trans), 5.31 (d, J=3.4 Hz, 1H, CH, cis), 5.18
(br. s, 1H, CH, trans), 3.76 - 3.18 (m’s, CH₂O, CH₂N, cis and trans), 2.21 (s, 3H,
CH₂COO, trans), 2.06 (s, 3H, CH₂COO, cis), 2.02 - 1.65 (m’s, CH₂, cis and trans);
LRMS: m/z (EI) 178 (M⁺ - HO(CH₂)₃NCO, 17 %), 149 (8 %), 136 (178 - CH₂CO + 1,
100 %), 105 (9 %), 94 (9 %), 77 (23 %), (Cl, NH₃) 280 (M⁺+1, 68 %), 237 (M⁺ - CH₂CO
+ 1, 24 %), 220 (100 %), 178 (14 %), 136 (41 %), 115 (59 %), 86 (13 %).

(b) • Thermolysis of 218 in neat acetic acid.
The procedure is similar to that used for the thermolysis in acetic acid / benzene with the
following modifications: The alcohol 218 (0.05 g, 1.64 mmol) was dissolved in 1 mL of
acetic acid (see the above procedure). Purification led to three products. The first fraction
was 220b, obtained in 15.2 % yield, the second fraction was the cis isomer (220a)
obtained in 19.6 % yield, and the third fraction was 221b obtained in 10.5 % yield.

220b, trans:
Colourless oil, in 15.2 % yield; IR (film) ν 1780, 1750, 1735 cm⁻¹ (br., C=O); ¹H NMR
(500 MHz, CDCl₃) δ 7.35 - 6.95 (m, 5H, Ar), 6.03 (d, J=0.5 Hz, 1H, CH), 5.16 (br. s, 1H, CH), 4.17 - 4.08 (m, 2H, CH₂O), 3.55 - 3.49 (m, 1H, CH₂N), 3.28 - 3.23 (m, 1H, CH₂N), 2.20 (s, 3H, CH₃COO), 2.06 (s, 3H, CH₃COO), 2.01 - 1.93 (m, 2H, CH₂); ¹³C NMR (50.323 MHz, CDCl₃) δ 170.95 (C=O, ester), 170.39 (C=O, ester), 163.45 (C=O, C₂), 156.90 (O-C₁, Ar), 129.73 (Ar), 122.64 (Ar), 115.45 (Ar), 84.90 (C₄), 81.42 (C₃), 61.71 (CH₂O), 38.49 (CH₂N), 27.04 (CH₂), 20.84 (CH₂COO), 20.75 (CH₃COO); LRMS: m/z (EI) 178 (M⁺ - CH₃COO(CH₂)₂NCO, 16 %), 149 (11 %), 136 (178 - CH₃CO + 1, 100 %), 105 (7 %), 77 (21 %), (Cl, NH₃) 339 ((M + NH₄)⁺, 6 %), 322 (M⁺+1, 12 %), 279 (322 - CH₃CO, 30 %), 234 (100 %), 220 (10 %), 174 (17 %), 136 (40 %), 102 (12 %).

220a, cis:

yield: 19.6 %

221b, trans:

yellow oil, in 10.5 % yield; IR (film) ν 3460 (br., OH), 1775 (br., 2 x C=O); ¹H NMR (200.13 MHz, CDCl₃) δ 7.36 - 6.96 (m, 5H, Ar), 6.03 (br. s, 1H, CH), 5.18 (br. s, 1H, CH), 3.69 (m, 2H, CH₂O), 3.67 - 3.55 (m, 1H, CH₂N), 3.32 - 3.19 (m, 1H, CH₂N), 2.21 (s, 3H, CH₃COO), 1.91 - 1.71 (m, 2H, CH₂); ¹³C NMR (50.32 MHz, CDCl₃) δ (C=O did not appear, too dilute) 156.94 (O-C₁, Ar), 129.76 (Ar), 122.73 (Ar), 115.55 (Ar), 84.87 (C₃), 81.41 (C₄), 59.24 (CH₂O), 37.76 (CH₂N), 30.65 (CH₂), 20.78 (CH₃); LRMS: m/z (EI) 178 (M⁺ - HO(CH₂)₂NCO, 17 %), 149 (20 %), 136 (178 - CH₃CO + 1, 100 %), 105 (11 %), 77 (24 %), (Cl, NH₃) 280 (M⁺+1, 30 %), 262 (M⁺ - CO + 1, 13 %), 237 (M⁺ - CH₃CO + 1, 24 %), 220 (100 %), 178 (19 %), 136 (45 %), 115 (71 %), 86 (9 %).

3.3.6.2.8 □ Thermolysis of 215a in the presence of acetic acid: Synthesis of 4-acetoxy-1-(3-tert-butyldimethylsilyloxy propyl)-3, 3-diphenyl-azetidin-2-one (222).
The protected alcohol 215a (0.076 g, 0.158 mmol) was dissolved in benzene/acetic acid (1.5 mL / 1.5 mL) and sealed into a medium walled NMR tube after three cycles of freeze-pump-thaw degassing. The tube was then immersed in a constant temperature oil bath, maintained at 100 ± 0.2°C, for 12 hours. Removal of the benzene and the excess acetic acid afforded a yellow oil. This residue was a mixture of products; purification on the Chromatotron (2 mm silica plate), using 20 % ether in hexane, afforded 222 as a yellow oil, in 57 % yield; IR (film) ν 1765 cm⁻¹ (C=O); ¹H NMR (200 MHz, CDCl₃, ref. = CH₂Cl₂ = 5.32 ppm) δ 7.78 - 7.23 (m, 10H, Ar), 6.54 (s, 1H, CH), 3.65 (t, J=6 Hz, 2H, CH₂O), 3.43 (m, 2H, CH₂N), 1.86 (m, 2H, CH₂), 1.73 (s, 3H, CH₃COO), 0.89 (s, 9H, 3 x CH₃), 0.03 (s, 6H, 2 x CH₃); ¹³C NMR (50.32 MHz, CDCl₃) δ 170.13 (C=O, ester), 168.17 (C=O, C₂), 137.64 (C₁, Ar), 136.40 (C₁, Ar), 128.73 (Ar), 128.39 (Ar), 128.12 (Ar), 127.77 (Ar), 127.66 (Ar), 127.51 (Ar), 84.75 (C₄), 72.90 (C₃), 60.07 (CH₂O), 37.87 (CH₂N), 30.91 (CH₂), 25.84 (3 x CH₂), 20.49 (CH₃COO), 18.22 (C₃Si), -5.48 (2 x CH₃Si); LRMS: m/z (El) 396 (M⁺ - (CH₃)₃C, 4 %), 354 (8 %), 238 (M⁺ - TBDMSO(CH₂)₃NCO, 12 %), 196 (100 %), 167 (20 %), 84 (38 %), (Cl, NH₂) 454 (M⁺+1, 4 %), 411 (M⁺ - CH₂CO + 1, 27 %), 394 (M⁺ - CH₃COO, 100 %), 366 (22 %), 238 (11 %), 216 (18 %), 196 (80 %), 167 (20 %), 91 (8 %), 74 (10 %).

3.3.6.2.9 □ Inter / Intra-molecular competition experiment. Thermolysis of 218 in the presence of methanol:
The alcohol 218 (0.05 g, 0.164 mmol) was dissolved in benzene / methanol (0.25 mL / 0.25 mL) and sealed into a medium walled NMR tube after three cycles of freeze-pump-thaw degassing. The tube was then immersed in a constant temperature oil bath, maintained at 100 ± 0.2°C, for 4 hours. Removal of the benzene and the excess methanol afforded a yellow oil. This residue was purified on the Chromatotron (2 mm silica plate), using 50% ethyl acetate in hexane as eluent, to afford two products. The first fraction was the trans isomer (223b) obtained in 43% yield. The other fraction was the cis isomer (223a), obtained in 19% yield.

(i) Formation of trans-4-methoxy-3-phenoxy-1-(3-hydroxypropyl)-azetidin-2-one (223b).

Yellow oil, in 43% yield; IR (film) ν 3700 - 3100 (br OH); 1765 (C=O); ¹H NMR (200.13 MHz, CDCl₃) δ 7.36 - 7.00 (m, 5H, Ar), 5.02 (br. s, 1H, CH), 4.92 (d, J=0.5 Hz, 1H, CH), 3.72 (t, J=6 Hz, 2H, CH₂O), 3.56 (m, 2H, CH₂N), 3.54 (s, 3H, CH₃O), 2.21 (br. s, 1H, OH), 1.86 (quintet, J=6 Hz, 2H, CH₂); ¹³C NMR (50.32 MHz, CDCl₃) δ 164.66 (C=O), 157.04 (O-C₁, Ar), 129.71 (Ar), 122.37 (Ar), 115.41 (Ar), 89.35 (C₄), 84.42 (C₃), 59.18 (OCH₃), 56.18 (CH₂O), 37.51 (CH₂N), 30.44 (CH₂); LRMS: m/z (El) 219 (M⁺ - CH₃OH, 8%), 150 (M⁺ - HO(CH₂)₃NCO, 100%), 105 (17%), 90 (9%), 77 (41%), (CI, NH₃) 252 (M⁺+1, 100%), 220 (35%), 192 (18%), 150 (37%), 102 (13%).

(ii) Formation of cis-4-methoxy-3-phenoxy-1-(3-hydroxypropyl)-azetidin-2-one (223a).
Yellow oil, in 19% yield; IR (film) ν 3700 - 3200 (br OH), 1760 (C=O); \(^1\)H NMR (200.13 MHz, CDCl\(_3\)) δ 7.35 - 7.03 (m, 5H, Ar), 5.21 (d, J=3.3 Hz, 1H, CH), 5.15 (d, J=3.3 Hz, 1H, CH), 3.74 (t, J=6 Hz, 2H, CH\(_2\)O), 3.52 - 3.41 (m, 2H, CH\(_2\)N), 3.49 (s, 3H, CH\(_3\)O), 2.05 (br. s, 1H, OH), 1.86 (quintet, J=6 Hz, 2H, CH\(_2\)); \(^1\)C NMR (50.32 MHz, CDCl\(_3\)) δ 166.88 (C=O), 157.48 (O-C\(_1\), Ar), 129.56 (Ar), 122.35 (Ar), 115.62 (Ar), 86.85 (C\(_3\)), 81.87 (C\(_4\)), 59.42 (OCH\(_3\)), 56.21 (CH\(_2\)O), 37.87 (CH\(_2\)N), 30.64 (CH\(_2\)); LRMS: m/z (EI) 251 (M\(^+\), trace), 219 (M\(^+\) - CH\(_3\)OH, 20%), 150 (M\(^+\) - HO(CH\(_2\))\(_3\)NCO, 100%), 107 (18%), 77 (64%), (Cl, NH\(_3\)) 252 (M\(^+\)+1, 22%), 237 (28%), 220 (M\(^+\) - OCH\(_3\), 100%), 192 (11%), 150 (M\(^+\) - HO(CH\(_2\))\(_3\)NCO, 83%), 115 (78%), 86 (13%).

3.3.6.2.10 Synthesis of anhydro-oxacepham (225).

(i) Oxidation of 215a: Synthesis of 1, 7, 8-triaza-1-(2-propanoic acid)-6, 6-dimethyl-5-oxa-2-oxo-3, 3-diphenylspiro [3.4] oct-7-ene (224).

The oxidation procedure, for the synthesis of the carboxylic acid (224) is based on that of Sharpless.\(^{305}\) A 10 mL flask was charged with a magnetic stirrer, CCl\(_4\) (0.63 mL), CH\(_3\)CN (0.63 mL), and the alcohol 215a (0.116 g, 3.16 mmol). When the solution was affected, H\(_2\)O (0.95 mL) was added, two phases could be observed and the alcohol stayed in solution. NaIO\(_4\) (0.278 g, 1.30 mmol) was added, but did not dissolve completely even with vigorous stirring. To this suspension RuCl\(_3\).nH\(_2\)O (1.6 mg, 6.96 \(\mu\)mol, calculation based on n = 1)\(^{305}\) was added. The color changed from colorless to brown, and after 30 minutes changed to a brown - off - white color. After two hours of vigorous stirring at room temperature, CH\(_2\)Cl\(_2\) (10 mL) along with H\(_2\)O (2 mL) were added. The insoluble solid was filtered through a celite pad. The two layers were separated after saturating the aqueous layer with NaCl. The aqueous layer was extracted three times with methylene chloride. The combined organic layers were dried (MgSO\(_4\)) and filtered. Evaporation of the solvent left a pale white solid. An attempt to purify this
solid on the Chromatotron (silica plate) was unsuccessful, the compound decomposed. This solid does not dissolve in chloroform, therefore, titration with chloroform removed the impurities. The acid (224) was obtained in a pure form, as a white solid, in 74 % yield; mp 163 - 164 °C; IR (KBr) ν = 2940 cm⁻¹ (br, OH), 1763 cm⁻¹ (C=O, β-lactam), 1718 cm⁻¹ (C=O, acid), 1598 cm⁻¹ (N=N); ¹H NMR (200.13 MHz, acetone-d₆, TMS) δ 7.39 - 7.27 (m, 10H, Ar), 3.55 - 3.28 (m, 2H, NCH₂), 2.85 (br. s, 1H, COOH ?), 2.79 - 2.56 (m, 2H, CH₂), 1.65 (s, 3H, CH₃), 1.53 (s, 3H, CH₃); ¹³C NMR (50.32 MHz, acetone-d₆= 30.50 ppm) δ 171.89 (C=O, acid), 168.25 (C=O, β-lactam), 137.95 (C₁, Ar), 136.48 (C₁, Ar), 129.17 (Ar), 129.03 (Ar), 128.79 (Ar), 128.40 (Ar), 123.33 (Ar), 128.33 (C₄), 125.42 (C₆), 76.33 (C₃), 35.92 (CH₂N), 33.47 (CH₂), 25.14 (CH₃), 24.32 (CH₃); LRMS: m/z (El) 380 (M⁺ + 1, trace), 265 (M⁺ - N₂ - acetone, 20 %), 194 (Ph₂CCO, 40 %), 165 (C₁₃H₉⁺= 9-fluorenyl, 100 %), 101 (44 %), (Cl, NH₃) 397 (M + NH₄⁺, 10 %), 380 (M⁺+1, 18 %), 352 (M⁺ - N₂ + 1, 5 %), 327 (8 %), 311 (11 %), 294 (M⁺ - N₂ - acetone + 1, 14 %), 266 (M⁺ - N₂ - acetone - CO, 100 %), 227 (40 %), 186 (18 %), 167 (14 %), 76 (12 %).

(ii) Synthesis of 2-oxo-7, 7-diphenyl-oxacepham or 7, 7-diphenyl-anhydro-oxacepham (225).

![Chemical Structure](image)

The carboxylic acid 224 (0.046 g, 0.121 mmol) was dissolved in dry acetone (20 mL) and sealed into a glass tube after three cycles of freeze-pump-thaw degassing. The tube was then immersed in a constant temperature oil bath, maintained at 100 ± 0.2°C, for 12 hours. Removal of the solvent afforded a thick yellow oil. Purification on the Chromatotron (2
mm silica plate), using 35% ethylacetate in hexane, afforded the anhydro-oxacepham (225) as the major product. β-Lactam (225) was obtained as a white solid, in 45.3% yield; mp 195-196°C (d); IR (KBr) ν 1762 cm\(^{-1}\) (br C=O, β-lactam and ester); \(^1\)H NMR (200.13 MHz, CDCl\(_3\)) δ 7.43 - 7.25 (m, 10H, Ar), 6.05 (s, 1H, CH), 4.14 - 3.94 (m, 1H, NCH\(_2\)), 3.59 - 3.47 (m, 1H, NCH\(_2\)), 2.79 - 2.71 (m, 2H, CH\(_2\)); \(^13\)C NMR (50.32 MHz, CDCl\(_3\)) δ 169.25 (C=O, ester), 166.50 (C=O, β-lactam), 138.06 (C\(_1\), Ar), 134.20 (C\(_1\), Ar), 129.06 (Ar), 128.56 (Ar), 128.15 (Ar), 128.01 (Ar), 127.91 (Ar), 126.50 (Ar), 86.38 (C\(_6\)), 73.77 (C\(_7\)), 36.13 (CH\(_2\)N), 29.49 (CH\(_2\)); LRMS: m/z (EI) 293 (M\(^+\), 5%), 196 (100%), 165 (C\(_{13}\)H\(_9\)\(^{+}\)=9-fluorenlyl, 65%), 149 (50%), 115 (6%), 98 (7%), 85 (8%), 71 (16%), (Cl, NH\(_3\)) 311 (M + NH\(_4\))\(^+\), 3%), 294 (M\(^{+1}\), 22%), 266 (M\(^+\) - CO + 1, 100%), 196 (36%), 165 (12%); HRMS: Calculated for C\(_{18}\)H\(_{15}\)N\(_1\)O\(_3\) 293.1052, observed 293.1052.

3.3.6.2.11 Synthesis of 1-aza-5-p-nitrophenyl-4,7-dioxa-9-oxo-8, 8-diphenylbicyclo[4.3.0] non-5-ene (230).

(i) Acetone 4-p-nitrobenzoyloxyethyl semicarbazone (226):

The alcohol precursor, acetone 4-(2-hydroxyethyl) semicarbazone (204), (12.6 mmol) and triethylamine (16.6 mmol) were dissolved in 60 mL of dry methylene chloride. To the stirred solution, p-nitrobenzoylchloride (13.8 mmol) dissolved in 30 mL of dry methylene chloride was added dropwise under nitrogen atmosphere and at 0°C. A syringe pump was used for the dropwise addition which took 2 hours, during that time the temperature was kept at 0°C. After overnight stirring at RT, the mixture was washed twice with concentrated NaHCO\(_3\) and once with brine. The combined water layers were extracted twice with methylene chloride. The combined organic layers were dried over anhydrous MgSO\(_4\). After evaporation of the solvent the crude product obtained was a yellow solid, (3.24 g, 85% yield). Recrystallization from absolute ethanol afforded the title compound in 63% yield; mp. 143 - 144°C; IR (KBr) ν 1718 cm\(^{-1}\)(C=O), 1662 cm\(^{-1}\)
(C=N, C=O); $^1$H NMR (200.13 MHz, CDCl$_3$) δ 8.42 (br. s, 1H, CONH), 8.25 (AA'BB', 4H, Ar), 6.53 (br. tr., 1H, CH$_2$NH), 4.48 (tr, J = 5.4 Hz, 2H, CH$_2$O), 3.73 (br. q, 2H, CH$_2$N), 1.95 (s, 3H, CH$_3$), 1.85 (s, 3H, CH$_3$); $^{13}$C NMR (50.32 MHz, CDCl$_3$) δ 164.55 (C=O, ester), 156.78 (C=O, amide), 150.44 (C=N), 147.73 (C$_4$, NO$_2$Ph), 135.36 (C$_1$, O=C-Ph), 130.72, 123.44 (Ar), 65.20 (CH$_2$O), 38.39 (CH$_2$N), 25.19 (CH$_2$), 16.45 (CH$_3$).

(ii) 5, 5-Dimethyl-2-(p-nitrobenzoyloxyethyl)-imino-Δ$^3$-1, 3, 4-oxadiazole (227).

The synthesis was accomplished according to the method-2 referenced in Section 3.2.2.0.0. The oxadiazoline, 227, was obtained as a brown solid, in 85 % yield: mp 84-85°C; IR (KBr) ν 1720 cm$^{-1}$ (C=O), 1600 (N=N); $^1$H NMR (200.13 NH Hz, CDCl$_3$) δ 8.25 (AA'BB', 4H, Ar), 4.65 (t, J = 6 Hz, 2H, OCH$_2$), 3.84 (t, J = 6 Hz, 2H, NCH$_2$), 1.61 (s, 3H, CH$_3$); $^{13}$C NMR (50.32 MHz, CDCl$_3$) δ 164.60 (C=O), 163.46 (C=N), 150.55 (C$_4$, NO$_2$-Ph), 135.44 (C$_1$, Ar-C=O), 130.78 (Ar), 123.47 (Ar), 121.27 (C$_3$), 65.22 (CH$_2$O), 47.13 (CH$_2$N), 23.52 (2 x CH$_3$); LRMS: m/z (EI) 194 (p-NO$_2$C$_6$H$_4$COOCH$_2$CH$_2$-), 150 (p-NO$_2$C$_6$H$_4$CO, 68 %), 104 (30 %), 84 ((NCOC(CH$_2$)$_2$)$^+$, 100 %), (Cl, NH$_3$) 307 (M$^+$+1, 100 %), 280 (42 %), 211 (14 %), 193 (11 %), 150 (11 %), 120 (8 %).

(iii) 1, 7, 8-Triaza-6, 6-dimethyl-1-(p-nitrobenzoyloxyethyl)-5-oxa-2-oxo-3, 3-diphenylspiro [3.4] oct-7-ene (228).

The general procedure for the [2 + 2] cycloaddition reaction, described in Section 3.3.3.0.0, was followed. The β-lactam (228) was obtained as a white solid, in 80 % yield; mp 136 - 137 °C; IR (KBr) ν 1780 (C=O, β-lactam), 1732 (C=O, ester); $^1$H NMR (500.13 MHz, CDCl$_3$) δ 8.19 (AA'BB', 4H, Ar), 7.33 - 7.24 (m, 10H, Ar), 4.55 - 4.50 (m, 1H, OCH$_2$), 4.47 - 4.42 (m, 1H, OCH$_2$), 3.58 - 3.52 (m, 1H, NCH$_2$), 3.47 - 3.43 (m, 1H, NCH$_2$), 1.58 (s, 3H, CH$_3$), 1.46 (s, 3H, CH$_3$); $^{13}$C NMR (50.32 MHz, CDCl$_3$) δ 168.38 (C=O), 164.44 (C=O), 150.60 (C$_4$, NO$_2$Ph), 136.16 (C$_1$, Ar-C=O), 134.98 (C$_1$, Ar), 134.50
(C1, Ar), 131.00 (Ar), 128.52 (Ar), 128.26 (Ar), 128.23 (Ar), 127.91 (Ar), 127.84 (Ar), 123.47 (Ar), 124.67 (C4), 122.20 (C6), 76.19 (C3), 62.30 (CH2O), 38.29 (CH2N), 25.28 (CH3), 24.13 (CH3); LRMS: m/z (EI) 414 (M+ - N2 - acetone, 27 %), 280 (12 %), 236 (11 %), 194 (Ph2CCO, 77 %), 165 (C13H9+= 9-fluorenyl, 100 %), 150 (p-NO2C6H4CO, 37 %), 104 (23 %), 76 (13 %), (Cl, NH3) 415 (M+ - N2 - acetone + 1, 6 %), 385 (12 %), 194 (Ph2CCO, 24 %), 167 (58 %), 120 (100 %), 94 (9 %).

(iv) 1-Aza-5-p-nitrophenyl-4, 7-dioxao-9-oxo-8, 8-diphenylbicyclo [4.3.0] non-5-ene (230).

The ester 228 (0.495 g, 1.00 mmol) was dissolved in benzene (30 mL), conc. = 0.007 M, and sealed into a glass tube after three cycles of freeze-pump-thaw degassing. The tube was then immersed in a constant temperature oil bath, maintained at 100 ± 0.2°C, for 12 hours. Removal of the solvent afforded an orange oil. Purification on the Chromatotron (4 mm silica plate), using 40 % ether in hexane as eluent, afforded 230 as the major product. The bicyclic compound (230) was obtained as an orange solid, in 49 % yield; mp 191 °C; IR (KBr) ν 1745 cm⁻¹(C=O), 1670 cm⁻¹(C=O); ¹H NMR (200.13 MHz, CDCl₃) δ 8.06 (AA’BB’, 4H, Ar), 7.58 - 7.26 (m, 10H, Ar), 4.18 (t, J = 5 Hz, 2H, CH2O), 3.92 (t, J = 5 Hz, 2H, CH2N); ¹³C NMR (50.32 MHz, CDCl₃) δ 166.36 (C=O, +ve), 144.74 (C4, NO2-Ph, +ve), 140.60 (C1, Ar-C=O, +ve), 137.66 (2 x C1, Ar, +ve), 129.12 (Ar, -ve), 128.75 (Ar, -ve), 126.41 (Ar, -ve), 123.90 (Ar, -ve), 123.36 (Ar, -ve), 139.27 (C6, +ve), 116.56 (C5, +ve), 89.25 (C8, +ve), 63.22 (OCH2, C3, +ve), 40.76 (NCH2, C2, +ve); LRMS: m/z (EI) 414 (M⁺, 100 %), 398 (7 %), 236 (O2NC6H4COOCH2CH2NCO, 14 %), 208 (236 - CO, 18 %), 194 (Ph2CCO, 14 %), 165 (C13H9+= 9-fluorenyl, 42 %), 104 (7 %), 72 (13 %), (Cl, NH3) 432 ((M + NH4)⁺, 3 %), 415 (M⁺ + 1, 100 %), 385 (15 %), 240 (14 %), 167 (21 %), 127 (12 %); HRMS: Calculated for C24H18N2O5 414.1216, observed 414.1232; structure confirmed by single crystal X-ray diffraction.
3.3.6.3.0 □ 1,2 ~ Hydrogen migration: Attempts to generate and trap azetinone.

3.3.6.3.1 □ Thermostlysis of 172g in the presence of CD$_3$OD: 4-Methoxy-3-phenoxy-1-phenylazetidin-2-one-d$_4$ (197-D4), cis / trans mixture.

The 4-methoxy β-lactam-d$_4$ (197-D4) were synthesized following the procedure in Section 3.3.6.1.0. The proton NMR spectrum of the residue, obtained after bulb to bulb distillation, showed the cis and trans isomers of 197-D4 to be the only products of this reaction. The cis and trans isomers were not separated, but their ratio was determined, from the $^1$H NMR spectrum of the mixture, to be 1 : 2.5, respectively. The mixture, a yellow oil, was obtained in quantitative yield (100%); IR (film) ν 1770 cm$^{-1}$ (C=O); $^1$H NMR (200.13 MHz, CDCl$_3$) δ 7.56 - 7.06 (m, 10H, Ar), 5.30 (s, 1H, H-3, cis), 5.27 (s, 1H, H-3, trans); $^{13}$C NMR (50.32 MHz, CDCl$_3$) δ 160.91 (C=O, cis and trans), 157.30 (O-C$_1$, Ar, cis), 156.99 (O-C$_1$, Ar, trans), 136.62 (N-C$_1$, Ar, cis and trans), 129.73 (Ar, trans), 129.61 (Ar, cis), 129.28 (Ar, cis and trans), 125.28 (Ar, cis and trans), 122.49 (Ar, cis and trans), 117.49 (Ar, trans), 117.39 (Ar, cis), 115.59 (Ar, cis), 115.43 (Ar, trans), 83.38 (C$_2$), 81.57 (C$_4$), 65.80 (OCD$_3$); LRMS: m/z (EI) 273 (M$^+$, 37%), 211 (M$^+$ - C=O - OCD$_3$, 12%), 154 (M$^+$ - PhNCO, 100%), 125 (7%), 77 (9%), (Cl, NH$_3$) 291 ((M + NH$_4$)$^+$, 92%), 274 (M$^+$, 100%), 213 (10%), 154 (81%), 94 (7%).

3.3.6.3.2 □ Thermostlysis of 172g in the presence of 1,3-diphenyl isobenzofuran:
Formation of Z-4-(1-(2-benzoylphenyl)-1-phenyl)methylene-1-phenyl-3-phenoxyazetidine-2-one (236).

The oxadiazoline 172g (27.6 mg, 0.085 mmol) and 1, 3-diphenyl isobenzofuran (70 mg, 0.256 mmol) were dissolved in benzene (0.5 mL), and sealed into a glass tube after three cycles of freeze-pump-thaw degassing. The tube was then immersed in a constant temperature oil bath, maintained at 100 ± 0.2°C, for 1 hour. Removal of the solvent afforded a yellow oil. Purification on the Chromatotron (2 mm silica plate), using
5 % ether in hexane as eluent, afforded three fractions; F#1 was the excess diene.

(i) **F#2:**

IR (film) ν 1800 cm⁻¹ (C=O), 1665 cm⁻¹ (C=O, C=C), ¹H NMR (200.132 MHz, CDCl₃) δ 7.58 - 6.72 (m, 24H, Ar), 5.61 (s, 1H, CH); ¹³C NMR (125.76 MHz, CDCl₃) δ 162.10 (C=O, β-lactam), 139.85 (Ar, +ve), 132.98 (Ar, -ve), 132.32 (Ar, -ve), 130.32 (Ar), 130.02 (Ar, -ve), 129.84 (Ar, -ve), 129.56 (Ar, -ve), 129.44 (Ar, -ve), 128.84 (Ar, -ve), 128.31 (Ar, -ve), 127.99 (Ar, -ve), 127.79 (Ar, -ve), 127.35 (Ar, -ve), 127.09 (Ar, -ve), 126.09 (Ar, -ve), 123.01 (Ar, -ve), 121.77 (Ar, -ve), 117.24 (Ar, -ve), 128.14 (C₄, is taken from a normal carbon spectrum, not spin sort, assignment is tentative) C₅ not assigned, 84.68 (C₃, -ve); LRMS: m/z (El) 507 (M⁺, 10 %), 414 (6 %), 388 (M⁺- PhNCO, 34 %), 370 (8 %), 311 (10 %), 270 (M⁺- β-lactam, 100 %), 241 (20 %), 193 (9 %), 165 (26 %), 144 (27 %), 116 (9 %), 105 (56 %), 77 (92 %), (Cl, NH₂) 508 (M⁺ + 1, 100 %), 388 (M⁺- PhNCO, 12 %), 270 (M⁺- β-lactam, 10 %).

(ii) **F#3:**

IR (film) ν 1800 cm⁻¹ (C=O), 1740 cm⁻¹ (C=C, tent.), 1670 cm⁻¹ (C=O, tent.); ¹H NMR (200.13 MHz, CDCl₃) δ 7.72 - 6.86 (m, 24H, Ar), 6.07 (br. s, 1H, CH); ¹³C NMR (125.76 MHz, CDCl₃) δ 189.28 (C=O, Ketone), 166.96 (C=O, β-lactam), 157.34 (O-C₁, Ar), 137.93 (2 x C₁, Ar), 137.24 (C₁, Ar), 136.53 (C₁, Ar), 132.67 (Ar), 131.90 (Ar), 130.02 (Ar), 129.85 (Ar), 129.29 (Ar), 128.90 (Ar), 128.33 (Ar), 128.13 (Ar), 127.79 (Ar), 126.70 (Ar), 126.57 (Ar), 126.13 (Ar), 122.39 (Ar), 122.22 (C₄), 118.10 (C₅, C=C), the assignment of C₄ and C₅ is tentative, 84.82 (C₃); LRMS: m/z (El) 507 (M⁺, 10 %), 414 (12 %), 388 (M⁺- PhNCO, 68 %), 311 (15 %), 270 (M⁺- β-lactam, 100 %), 241 (10 %), 209 (18 %), 144 (30 %); structure confirmed by single crystal X-ray diffraction.

3.3.7.0.0 ■ Thermolysis of 172: Determination of the thermolysis rate constants.
(i) Thermolysis of 172 except 172q and 172r.

In a typical procedure, a solution of 172 (25 mg, \( \approx 0.1 \) mmol) in C\(_6\)D\(_6\) (0.5 mL), containing toluene as an internal standard, was sealed into a medium-walled NMR tube after three freeze-pump-thaw cycles at 10\(^{-2}\) torr. The tube was heated at 100°C for \( \approx \) 8 hours, at which time the methyl signals from 172 had disappeared and replaced quantitatively by the ketone signal. Concentration vs. time data were obtained by recording the \(^1\)H NMR (200 MHz) spectra over about 6 time intervals. The integral of the disappearing methyl signals were measured and normalized against the toluene integral. The resultant plot of \( \ln \left( \frac{(A-x)}{A} \right) \) vs. \( t \) in all cases yielded a straight line through at least four half-lives, (see Appendix II for graphs and data).

(ii) Thermolysis of 172q and 172r.

The above procedure was used except that the thermolysis was done in the NMR probe (250 MHz), at 50°C. The spectra were collected every 10.5 min using a "kinetics" Bruker computer program. Also, instead of toluene, anisole was used as the internal reference. Anisole was used because the methyl groups in toluene and acetophenone have the same chemical shift in benzene (see Appendix II for graphs and data).
Appendix I

X-ray Crystallographic Data

4.1.0.0.0 1, 7, 8-triaza-6, 6-dimethyl-5-oxa-2-oxo-1, 3, 3-triphenylspiro [3.4] oct-7-ene (172a).

Figure AI-1. 50 % thermal ellipsoid probabilities are shown for spiro-β-lactam oxadiazoline 172a; H-atoms are represented as spheres of arbitrary size.

Figure AI-2. Selected bond lengths (Å) for spiro-β-lactam oxadiazoline 172a with estimated standard deviations in parentheses.
Figure A1-3. Selected bond angles ($^\circ$) for spiro-$\beta$-lactam oxadiazoline 172a with estimated standard deviations in parentheses.

Figure A1-4. Selected dihedral angles ($^\circ$) for spiro-$\beta$-lactam oxadiazoline 172a.

DIHEDRAL ANGLES

Plane-1  Plane-2 = 90.9
Plane-1  Plane-3 = 36.1
Plane-1  Plane-4 = 118.0
Plane-1  Plane-5 = 91.8
Plane-2  Plane-3 = 92.5
4.2.0.0.0  ■ Trans-1, 7, 8-triaza-6, 6-dimethyl-5-oxa-2-oxo-1-phenyl-3-phenoxy-spiro[3.4]oct-7-ene (172g).

Figure A1-5. 50% thermal ellipsoid probabilities are shown for \textit{spiro}-\alpha-\beta\textnormal{-lactam oxadiazoline} 172g; H-atoms are represented as spheres of arbitrary size.

Figure A1-6. Selected bond lengths (Å) for \textit{spiro}-\beta\textnormal{-lactam oxadiazoline} 172g with estimated standard deviations in parentheses.
Figure A1-7. Selected bond angles (°) for spiro-β-lactam oxadiazoline 172g, with estimated standard deviations in parentheses.

Figure A1-8. Selected dihedral angles (°) for spiro-β-lactam oxadiazoline 172g.
4.3.0.0.0 • 4-aza-1, 2-bis (methoxycarbonyl)-5-oxo-4, 6, 6-triphenylspiro [2.3] hex-1-ene (184).

Figure AI-9. 50% thermal ellipsoid probabilities are shown for \textit{spiro-\beta\text{-lactam}} cyclopropene 184; H-atoms are represented as spheres of arbitrary size.

Figure AI-10. Selected bond lengths (Å) for \textit{spiro-\beta\text{-lactam}} cyclopropene 184 with estimated standard deviations in parentheses.
Figure AI-11. Selected bond angles (°) for spiro-β-lactam cyclopropene 184, with estimated standard deviations in parentheses.

Figure AI-12. Selected dihedral angles (°) for spiro-β-lactam cyclopropene 184.

DIHEDRAL ANGLES

Plane-1 ° Plane-2 = 90.1
Plane-2 ° Plane-3 = 15.1
Plane-2 ° Plane-4 = 20.8
Plane-1 ° Plane-5 = 173.0
Plane-2 ° Plane-5 = 92.2
4.4.0.0.0 1-aza-5-p-nitrophenyl-4, 7-dioxa-9-oxo-8, 8-diphenylbicyclo [4.3.0] non-5-ene (230).

Figure AI-13. 30% thermal ellipsoid probabilities are shown for the fused-bicyclic compound 230; H-atoms are represented as spheres of arbitrary size.

Figure AI-14. Selected bond lengths (Å) for the fused-bicyclic compound 230, with estimated standard deviations in parentheses.
Figure A1-15. Selected bond angles (°) for the fused-bicyclic compound 230, with estimated standard deviations in parentheses.

Figure A1-16. Selected dihedral angles (°) for the fused-bicyclic compound 230.

DIHEDRAL ANGLES

Plane-1  ⊖ Plane-2 = 60.5
Plane-1  ⊖ Plane-3 = 110.8
Plane-1  ⊖ Plane-4 = 12.5
Plane-2  ⊖ Plane-3 = 82.7
Plane-2  ⊖ Plane-4 = 49.7
Plane-3  ⊖ Plane-4 = 111.6
4.5.0.0.0 • Z-4-(1-(2-benzoylphenyl)-1-phenyl) methylene-1-phenyl-3-phenoxazetidine-2-one (236).

Figure AI-17. 30% thermal ellipsoid probabilities are shown for the 4-alkylylidene β-lactam 236; H-atoms are represented as spheres of arbitrary size.

Figure AI-18. Selected bond lengths (Å) for 4-alkylylidene β-lactam 236 with estimated standard deviations in parentheses.
Figure A1-19. Selected bond angles (°) for 4-alkylylidene β-lactam 236 with estimated standard deviations in parentheses.

Figure A1-20. Selected dihedral angles (°) for 4-alkylylidene β-lactam 236.
Appendix II
Thermolysis Data and Graphs

5.1.0.0.0 ■ Plot of the first order thermolysis (at 100°C) of 1, 7, 8-triaza-6,
6-dimethyl-5-oxa-2-oxo-1, 3, 3-triphenylspiro [3.4] oct-7-ene (172a)

Figure AII-1. Plot of \( \ln \left( \frac{A-x}{A} \right) \) versus time for spiro-β-lactum oxadiazoline 172a.

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>( \ln \left( \frac{A-x}{A} \right) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>3000</td>
<td>-0.870</td>
</tr>
<tr>
<td>5400</td>
<td>-1.523</td>
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<tr>
<td>7440</td>
<td>-2.163</td>
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<td>9360</td>
<td>-2.688</td>
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<tr>
<td>11160</td>
<td>-3.124</td>
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Regression Output

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<tr>
<td>Std Err of Y Est</td>
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<tr>
<td>R Squared</td>
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<tr>
<td>No. of Observations</td>
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<tr>
<td>Degrees of Freedom</td>
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</tr>
<tr>
<td>X Coefficient</td>
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<tr>
<td>Std Err of Coef.</td>
<td>1.95E-06</td>
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</tbody>
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5.2.0.0.0  ▲ Plot of the first order thermolysis (at 100°C) of 1, 7, 8-triaza-1-benzyl-6, 6-dimethyl-5-oxa-2-oxo-3, 3-diphenylspiro [3.4] oct-7-ene (172b).

![Graph](image-url)

**Figure AII-2.** Plot of \( \ln \left( \frac{(A-x)}{A} \right) \) versus time for spiro-\(\beta\)-lactam-oxadiazoline 172b.

<table>
<thead>
<tr>
<th>Time (sec)</th>
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</thead>
<tbody>
<tr>
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<td>7440</td>
<td>-0.753</td>
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<td>9360</td>
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<td>11160</td>
<td>-1.135</td>
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**Regression Output**

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<td>R Squared</td>
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<td>No. of Observations</td>
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<tr>
<td>Degrees of Freedom</td>
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</tr>
<tr>
<td>X Coefficient</td>
<td>-0.0001</td>
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<tr>
<td>Std Err of Coef.</td>
<td>2.03E-06</td>
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5.3.0.0.0 ■ Plot of the first order thermolysis (at 100°C) of 1, 7, 8-triaza-1, 6, 6-trimethyl-5-oxa-2-oxo-3, 3-diphenylspiro [3.4] oct-7-ene (172c)

![Graph](image)

**Figure AIII-3.** Plot of \( \ln \left( \frac{A-x}{A} \right) \) versus time for spiro-\( \beta \)-lactam oxadiazoline 172c.

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>Ln ( \left( \frac{A-x}{A} \right) )</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2640</td>
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<tr>
<td>4800</td>
<td>-0.619</td>
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<tr>
<td>7260</td>
<td>-0.926</td>
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<tr>
<td>9840</td>
<td>-1.234</td>
</tr>
<tr>
<td>12060</td>
<td>-1.461</td>
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</table>

**Regression Output**

- Constant: 0
- Std Err of Y Est: 0.02566
- R Squared: 0.9978
- No. of Observations: 6
- Degrees of Freedom: 5
- X Coefficient: -0.00012
- Std Err of Coef.: 1.42E-06
5.4.0.0.0 Plot of the first order thermolysis (at 100°C) of 1, 7, 8-triaza-3, 3, 6, 6-tetramethyl-5-oxa-2-oxo-1-phenylspiro [3.4] oct-7-ene (172d)

Figure AH-4. Plot of ln \((A-x)/A\) versus time for spiro-β-lactam oxadiazoline 172d.

<table>
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<th>Time (sec)</th>
<th>Ln ((A-x)/A)</th>
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<td>2640</td>
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<td>7260</td>
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<td>9840</td>
<td>-1.008</td>
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<td>12060</td>
<td>-1.234</td>
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Regression Output

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<tr>
<td>Std Err of Y Est</td>
<td>0.03791</td>
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<tr>
<td>R Squared</td>
<td>0.9933</td>
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<tr>
<td>No. of Observations</td>
<td>6</td>
</tr>
<tr>
<td>Degrees of Freedom</td>
<td>5</td>
</tr>
<tr>
<td>X Coefficient</td>
<td>-0.00011</td>
</tr>
<tr>
<td>Std Err of Coef.</td>
<td>2.1E-06</td>
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</tbody>
</table>
5.5.0.0.0 Plot of the first order thermolysis (at 100°C) of 1, 7, 8-triaza-1, 3, 3, 6, 6-pentamethyl-5-oxa-2-oxospiro [3.4] oct-7-ene (172e)

![Graph](image)

**Figure AII-5.** Plot of ln ((A-x)/A) versus time for spiro-β-lactam oxadiazoline 172e.

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>Ln ((A - x) / A)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
<td>2820</td>
<td>-0.103</td>
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<tr>
<td>4980</td>
<td>-0.213</td>
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<tr>
<td>7980</td>
<td>-0.317</td>
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<tr>
<td>10140</td>
<td>-0.392</td>
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<tr>
<td>12780</td>
<td>-0.486</td>
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<th>Regression Output</th>
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<tbody>
<tr>
<td>Constant</td>
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<tr>
<td>Std Err of Y Est</td>
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<tr>
<td>R Squared</td>
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<tr>
<td>No. of Observations</td>
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<tr>
<td>Degrees of Freedom</td>
</tr>
<tr>
<td>X Coefficient</td>
</tr>
<tr>
<td>Std Err of Coef.</td>
</tr>
</tbody>
</table>
5.6.0.0.0 Plot of the first order thermolysis (at 100°C) of 6, 6-adamantyl-1, 7, 8-triaca-1-benzyl-5-oxa-2-oxo-3, 3-diphenylspiro [3.4] oct-7-ene (172f).

Figure AII-6. Plot of ln ((A-x)/A) versus time for spiro-β-lactam oxadiazoline 172f.

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>Ln ((A-x)/A)</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>2820</td>
<td>-0.016</td>
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<tr>
<td>6720</td>
<td>-0.043</td>
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<tr>
<td>9720</td>
<td>-0.096</td>
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<td>14760</td>
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<td>18360</td>
<td>-0.108</td>
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**Regression Output**

- Constant: 0
- Std Err of Y Est: 0.01580
- R Squared: 0.8935
- No. of Observations: 6
- Degrees of Freedom: 5
- X Coefficient: -6.9E-06
- Std Err of Coef.: 5.96E-07
5.7.0.0.0  Plot of the first order thermolysis (at 100°C) of 1, 7, 8-triaza-6, 6-dimethyl-5-oxa-2-oxo-1-phenyl-trans-3-phenoxysspiro [3.4] oct-7-ene (172g)

Figure AII-7. Plot of ln \((A-x)/A\) versus time for spiro-\(\beta\)-lactam oxadiazoline 172g.

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>(\text{Ln}{(A - x) / A})</th>
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<tbody>
<tr>
<td>0</td>
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<td>960</td>
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<tr>
<td>1440</td>
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<tr>
<td>2100</td>
<td>-3.73</td>
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</table>

Regression Output

- Constant: 0
- Std Err of Y Est: 0.05094
- R Squared: 0.9989
- No. of Observations: 4
- Degrees of Freedom: 3
- X Coefficient: -0.00179
- Std Err of Coef.: 1.87E-05
5.8.0.0.0 ■ Plot of the first order thermolysis (at 100°C) of 1, 7, 8-triaza-6, 6-dimethyl-5-oxa-2-oxo-1-phenyl-cis-3-phenoxySpiro [3.4] oct-7-ene (172h)

![Graph](image)

Figure AII-8. Plot of \( \ln \left( \frac{A-x}{A} \right) \) versus time for spiro-\( \beta \)-lactam oxadiazoline 172h.

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>( \ln \left( \frac{A-x}{A} \right) )</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>900</td>
<td>-0.33</td>
</tr>
<tr>
<td>1500</td>
<td>-0.52</td>
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<tr>
<td>2100</td>
<td>-0.72</td>
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<td>-0.96</td>
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<tr>
<td>3600</td>
<td>-1.21</td>
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<tr>
<td>4560</td>
<td>-1.51</td>
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**Regression Output**

- Constant: 0
- Std Err of Y Est: 0.02645
- R Squared: 0.9974
- No. of Observations: 7
- Degrees of Freedom: 6
- X Coefficient: -0.00034
- Std Err of Coef.: 3.8E-06
5.9.0.0.0 • Plot of the first order thermolysis (at 100°C) of 1, 7, 8-triaza-1-p-methoxyphenyl-6, 6-dimethyl-5-oxa-2-oxo-trans-3-phenoxyetho [3.4] oct-7-ene (172i).

![Graph](image_url)

Figure AII-9. Plot of \( \ln\left(\frac{A-x}{A}\right) \) versus time for spiro-\(\beta\)-lactam oxadiazoline 172l.

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>( \ln\left(\frac{A-x}{A}\right) )</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>720</td>
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</tr>
<tr>
<td>1080</td>
<td>-1.45</td>
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<tr>
<td>1320</td>
<td>-1.73</td>
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<tr>
<td>1560</td>
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<tr>
<td>1800</td>
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<tr>
<td>2100</td>
<td>-2.45</td>
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**Regression Output**

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<tr>
<td>X Coefficient</td>
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<tr>
<td>Std Err of Coef.</td>
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5.10.0.0.0. Plot of the first order thermolysis (at 100°C) of 1, 7, 8-triaza-3-azido trans-6, 6- dimethyl-5-oxa-2-oxo-1-phenylspiro [3.4] oct-7-ene (172j).

![Graph showing ln((A-x)/A) versus time](image)

Figure AII-10. Plot of ln((A-x)/A) versus time for spiro-β-lactam oxadiazoline 172j.

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>Ln {(A - x) / A}</th>
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<tr>
<td>1380</td>
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<td>2100</td>
<td>-3.37</td>
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### Regression Output

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<tr>
<td>Degrees of Freedom</td>
<td>4</td>
</tr>
<tr>
<td>X Coefficient</td>
<td>-0.00166</td>
</tr>
<tr>
<td>Std Err of Coef.</td>
<td>3.56E-05</td>
</tr>
</tbody>
</table>
5.11.0.0.0 ■ Plot of the first order thermolysis (at $100^\circ$C) of 1, 7, 8-triaca-3, 3-dichloro-1-p-methoxyphenyl-6, 6-dimethyl-5-oxa-2-oxospiro [3.4] oct-7-ene (172k).

![Graph](image)

**Figure AII-11.** Plot of $\ln \left( \frac{(A-x)}{A} \right)$ versus time for *spiro*-β-lactam oxadiazoline 172k.

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>$\ln \left( \frac{(A-x)}{A} \right)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>660</td>
<td>-1.43</td>
</tr>
<tr>
<td>1020</td>
<td>-2.04</td>
</tr>
<tr>
<td>1380</td>
<td>-2.63</td>
</tr>
<tr>
<td>1740</td>
<td>-3.13</td>
</tr>
<tr>
<td>2100</td>
<td>-3.62</td>
</tr>
</tbody>
</table>

**Regression Output**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0</td>
</tr>
<tr>
<td>Std Err of Y Est</td>
<td>0.1687</td>
</tr>
<tr>
<td>R Squared</td>
<td>0.9833</td>
</tr>
<tr>
<td>No. of Observations</td>
<td>6</td>
</tr>
<tr>
<td>Degrees of Freedom</td>
<td>5</td>
</tr>
<tr>
<td>X Coefficient</td>
<td>-0.00182</td>
</tr>
<tr>
<td>Std Err of Coef.</td>
<td>5.13E-05</td>
</tr>
</tbody>
</table>
5.12.0.0.0 • Plot of the first order thermolysis (at 100°C) of 1, 7, 8-triaza-3, 6, 6-trimethyl-5-oxa-2-oxo-cis-3-phenoxy-1-phenylspiro [3.4] oct-7-ene (172m).

Figure AII-12. Plot of ln \((A-x)/A\) versus time for spirolactam oxadiazoline 172m.

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>Ln ((A - x) / A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>900</td>
<td>-0.40</td>
</tr>
<tr>
<td>1260</td>
<td>-0.64</td>
</tr>
<tr>
<td>1860</td>
<td>-0.92</td>
</tr>
<tr>
<td>2460</td>
<td>-1.19</td>
</tr>
<tr>
<td>3480</td>
<td>-1.65</td>
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</tbody>
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Regression Output

<table>
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<tr>
<th>Description</th>
<th>Value</th>
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</thead>
<tbody>
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<td>Constant</td>
<td>0</td>
</tr>
<tr>
<td>Std Err of Y Est</td>
<td>0.02642</td>
</tr>
<tr>
<td>R Squared</td>
<td>0.9980</td>
</tr>
<tr>
<td>No. of Observations</td>
<td>6</td>
</tr>
<tr>
<td>Degrees of Freedom</td>
<td>5</td>
</tr>
<tr>
<td>X Coefficient</td>
<td>-0.00048</td>
</tr>
<tr>
<td>Std Err of Coef.</td>
<td>5.39E-06</td>
</tr>
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</table>
5.13.0.0.0  Plot of the first order thermolysis (at 100°C) of 1, 7, 8-triaz-3, 6, 6-trimethyl-5-oxa-2-oxo-trans-3-phenoxy-1-phenylspiro [3.4] oct-7-ene (172n).

Figure AII-13. Plot of ln \((A-x)/A\) versus time for \textit{spiro}-\textit{β}-lactam oxadiazoline 172n.

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>Ln {(A - x) / A}</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>900</td>
<td>-0.70</td>
</tr>
<tr>
<td>1260</td>
<td>-0.94</td>
</tr>
<tr>
<td>1620</td>
<td>-1.23</td>
</tr>
<tr>
<td>2220</td>
<td>-1.65</td>
</tr>
<tr>
<td>3060</td>
<td>-2.25</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Regression Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
</tr>
<tr>
<td>Std Err of Y Est</td>
</tr>
<tr>
<td>R Squared</td>
</tr>
<tr>
<td>No. of Observations</td>
</tr>
<tr>
<td>Degrees of Freedom</td>
</tr>
<tr>
<td>X Coefficient</td>
</tr>
<tr>
<td>Std Err of Coef.</td>
</tr>
</tbody>
</table>
5.14.0.0.0 ■ Plot of the first order thermolysis (at 50°C) of 1, 7, 8-triaca-1-benzyl-6-methyl-5-oxa-2-oxo-3, 3, 6-triphenylspiro [3.4] oct-7-ene (172r).

Figure AII-14. Plot of ln ((A-x) / A) versus time for spiro-β-lactam oxadiazoline 172q.
<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>( \text{Ln}{(A - x) / A} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>630</td>
<td>-0.14</td>
</tr>
<tr>
<td>1260</td>
<td>-0.11</td>
</tr>
<tr>
<td>1890</td>
<td>-0.22</td>
</tr>
<tr>
<td>2520</td>
<td>-0.23</td>
</tr>
<tr>
<td>3150</td>
<td>-0.44</td>
</tr>
<tr>
<td>3780</td>
<td>-0.57</td>
</tr>
<tr>
<td>4410</td>
<td>-0.65</td>
</tr>
<tr>
<td>5040</td>
<td>-0.75</td>
</tr>
<tr>
<td>5670</td>
<td>-0.82</td>
</tr>
<tr>
<td>6300</td>
<td>-0.64</td>
</tr>
<tr>
<td>6930</td>
<td>-0.94</td>
</tr>
<tr>
<td>7560</td>
<td>-1.04</td>
</tr>
<tr>
<td>8190</td>
<td>-1.07</td>
</tr>
<tr>
<td>8820</td>
<td>-1.05</td>
</tr>
<tr>
<td>9450</td>
<td>-1.22</td>
</tr>
<tr>
<td>10080</td>
<td>-1.34</td>
</tr>
<tr>
<td>10710</td>
<td>-1.17</td>
</tr>
<tr>
<td>11340</td>
<td>-1.28</td>
</tr>
<tr>
<td>11970</td>
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<td>12600</td>
<td>-1.46</td>
</tr>
<tr>
<td>13230</td>
<td>-1.53</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Regression Output</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Constant</strong></td>
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<tr>
<td><strong>Std Err of Y Est</strong></td>
</tr>
<tr>
<td><strong>R Squared</strong></td>
</tr>
<tr>
<td><strong>No. of Observations</strong></td>
</tr>
<tr>
<td><strong>Degrees of Freedom</strong></td>
</tr>
<tr>
<td><strong>X Coefficient</strong></td>
</tr>
<tr>
<td><strong>Std Err of Coef.</strong></td>
</tr>
</tbody>
</table>
5.15.0.0.0 ■ Plot of the first order thermolysis (at 50°C) of 1, 7, 8-triaza-1-benzyl-6-methyl-5-oxa-2-oxo -3, 3, 6-triphenylspiro [3.4] oct-7-ene (172r).

Figure AII-15. Plot of ln [(A-x)/A] versus time for spiro-β-lactam oxadiazoline 172r.
<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>Ln {(A - x) / A}</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
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<tr>
<td>630</td>
<td>-0.04</td>
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<tr>
<td>1260</td>
<td>-0.07</td>
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<td>1890</td>
<td>-0.05</td>
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<td>2520</td>
<td>-0.01</td>
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<tr>
<td>3150</td>
<td>-0.05</td>
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<tr>
<td>3780</td>
<td>-0.08</td>
</tr>
<tr>
<td>4410</td>
<td>-0.07</td>
</tr>
<tr>
<td>5040</td>
<td>-0.13</td>
</tr>
<tr>
<td>5670</td>
<td>-0.11</td>
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<tr>
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<td>-0.11</td>
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<tr>
<td>6930</td>
<td>-0.17</td>
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<tr>
<td>7560</td>
<td>-0.08</td>
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<tr>
<td>8190</td>
<td>-0.12</td>
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<td>8820</td>
<td>-0.11</td>
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<tr>
<td>9450</td>
<td>-0.08</td>
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<tr>
<td>10080</td>
<td>-0.13</td>
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<td>10710</td>
<td>-0.14</td>
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<tr>
<td>11340</td>
<td>-0.15</td>
</tr>
<tr>
<td>11970</td>
<td>-0.08</td>
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<tr>
<td>12600</td>
<td>-0.18</td>
</tr>
<tr>
<td>13230</td>
<td>-0.10</td>
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</tbody>
</table>

**Regression Output**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
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<td>0</td>
</tr>
<tr>
<td>Std Err of Y Est</td>
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<tr>
<td>R Squared</td>
<td>0.3164</td>
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<tr>
<td>No. of Observations</td>
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<tr>
<td>Degrees of Freedom</td>
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<tr>
<td>X Coefficient</td>
<td>-1.3E-05</td>
</tr>
<tr>
<td>Std Err of Coef.</td>
<td>1.08E-06</td>
</tr>
</tbody>
</table>
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260• see reference 172-k, pp. 320-333 for a summary of arguments.


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