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**Organic photochemistry: synthetic and computational studies**

**I. The synthesis of novel  $\alpha$ -amino acid precursors *via* the addition of photochemically generated carbon radicals to oximes**

**II. A molecular modeling study of the photochemical [2+2] cycloaddition reactions of 6-allyl-cyclohex-2-en-1-ones and 1-allyl-naphthalen-2(*H*)-ones**

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## ***Abstract***

I: In recent years a large number of synthetic methods have been developed which involve carbon radicals. Although many of these methods are synthetically very useful, they suffer from the significant disadvantage that the generation of the carbon radicals often involves the use of reagents which are based on toxic heavy metals such as tin, or reagents such as peroxides which are hazardous due to their thermal instability.

An alternative method involves the use of a photomediator such as benzophenone, which on irradiation with UV light becomes electronically excited and abstracts a hydrogen atom from a carbon-hydrogen bond in a suitable substrate molecule, thus producing a carbon radical. These radicals are nucleophilic in character and react with electron deficient alkenes or alkynes producing a carbon-carbon bond.

This thesis describes the intermolecular addition of photochemically generated carbon radicals to electron deficient C=N bonds, a process which provides a direct route to  $\alpha$ -amino acid derivatives. Thus a series of oximes and oxime ethers were synthesized and irradiated in the presence of different hydrogen donor molecules, leading to a range of new  $\alpha$ -monosubstituted and  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acid derivatives.

II: Cyclobutane rings are important as they are a common structural feature in a number of naturally occurring molecules. Due to the strain in the ring they can also be used as a starting point for many other transformations. The simplest method for cyclobutane formation remains the photochemical [2+2] cycloaddition reaction which involves 1,4-biradical intermediates in these reactions. For intramolecular reactions an empirical "rule of five" has been used to account for the regiochemistry of these reactions. This rule proves accurate for a range of different systems but there are many exceptions. The biradical conformation control concept also provides a basis for predicting the regiochemical outcome of these reactions and has a more convincing theoretical basis which involves a consideration of the energy and structure of the possible 1,4-biradical intermediates. Triplet biradicals are sufficiently long-lived to allow conformational relaxation to occur. Once ISC occurs, closure or cleavage is very rapid and so further conformational change is unlikely. Low energy biradicals which have a high level of interaction between the singly occupied orbitals, as indicated in the spin density plot, are likely to be product forming; if however the biradical does not have a favorable orientation, a reversion to starting material is likely. Thus predicting the outcome of a cycloaddition reaction involves identifying which biradicals have these structural features. The possible 1,4-biradicals for a series of 6-allyl-cyclohex-2-en-1-ones and 1-allyl-naphthalen-2(*H*)-ones were investigated in an attempt to account for the regio- and stereochemical outcome of their intramolecular [2+2] cycloaddition reactions.

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## II. A molecular modeling study of the photochemical [2+2] cycloaddition reactions of 6-allyl-cyclohex-2-en-1-ones and 1-allyl-naphthalen-2(H)-ones

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*Chapter 1*  
*Introduction*

## 1.0 Introduction

The work described in this section involves the photochemical generation of carbon radicals and their carbon-carbon bond forming reactions with oximes and oxime ethers. The key feature of these reactions is the use of hydrogen abstraction from a carbon-hydrogen bond with a photomediator to form a carbon radical. A brief introduction to the chemistry of carbon radicals and their formation is provided below.

## 1.1 Radicals

Radicals are atomic or molecular species that have one or more unpaired electrons. They are reactive intermediates formed by the homolytic cleavage of bonds (homolysis) so that each fragment has one unpaired electron (**Scheme 1**).



**Scheme 1**

For carbon centred radicals the unpaired electron can occupy a  $p$  orbital or an  $sp^3$  hybrid orbital leading to different shaped radical species. If a  $p$  orbital is involved then a planar geometry is observed; if the unpaired electron is in an  $sp^3$  orbital, a pyramidal geometry is observed (**Figure 1**). The shape is also dependent on the size and electronic properties of adjoining R groups. Simple alkyl radicals adopt a planar geometry, as do radicals with bulky R groups in order to minimise steric interactions. On the other hand the trifluoromethyl radical adopts a pyramidal geometry<sup>[1]</sup>.

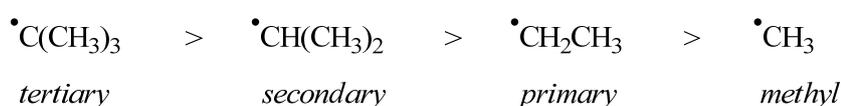


**Figure 1**

Although carbon radicals are neutral species they can exhibit both nucleophilic and electrophilic properties depending on the substituents involved. If there is an electron donating group next to the carbon bearing the unpaired electron, the radical is nucleophilic. Conversely if the carbon carrying the single electron is next to an electron withdrawing group then this radical is electrophilic. The trend in alkyl radical nucleophilicity follows the same pattern as carbocation stability: tertiary > secondary > primary > methyl<sup>[2]</sup>. Conceptually this is correct: electron donating groups increase the electron density of the carbon radical *via* either resonance or the inductive effect, depending on the substituent,

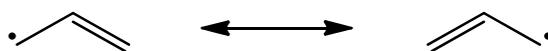
thus making it more nucleophilic. Electron withdrawing groups pull electron density away from the radical thus making it electrophilic. Polar effects play an important role in determining the regiochemical outcome and rate of radical reactions. Fischer and Radom investigated the different factors controlling the addition of carbon-centered radicals to alkenes from both an experimental and theoretical point of view<sup>[3]</sup>.

There are a number of factors which affect radical stability including hyperconjugation, delocalisation and steric effects. The general order of stability of alkyl radicals (**Figure 2**) can be explained by hyperconjugation. The singly occupied  $2p$  orbital interacts with the  $\sigma$  and  $\sigma^*$  orbitals of the adjacent alkyl group in an energetically favourable process. When more alkyl groups are present this effect is enhanced, thus accounting for the stability order<sup>[4]</sup>.



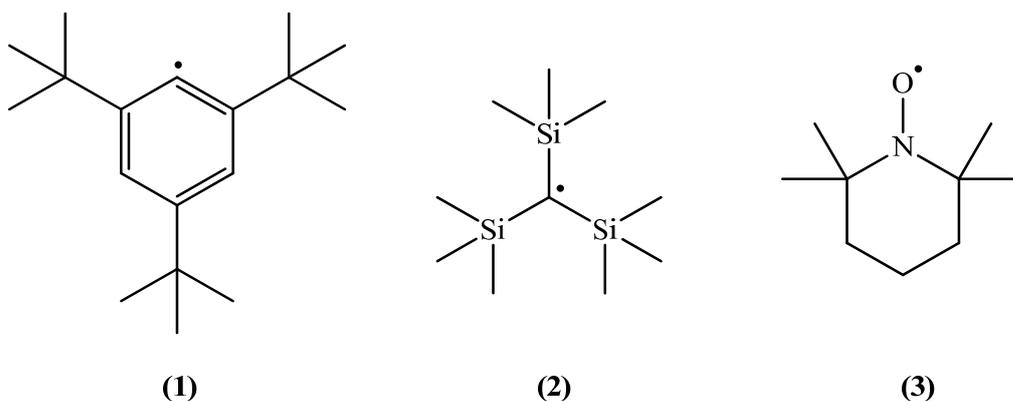
**Figure 2**

When a radical is formed adjacent to an allylic or benzylic group, delocalisation with the conjugated system can occur making the radical more stable and thus lowering its reactivity<sup>[5]</sup> (**Scheme 2**).

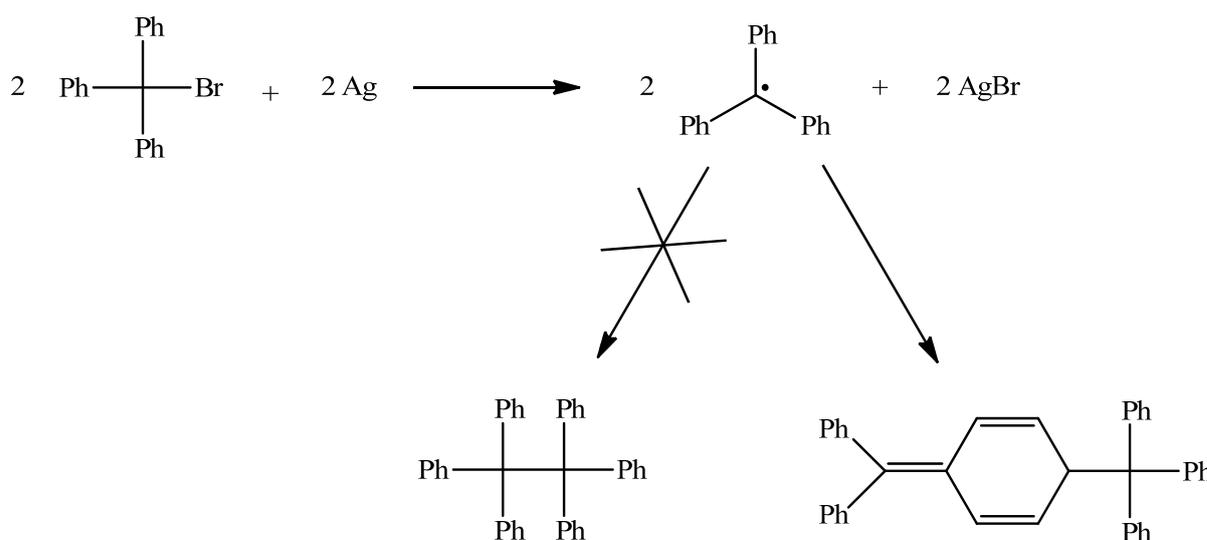


**Scheme 2**

The kinetic stability of radicals is affected by the presence of bulky R groups. These bulky R groups prevent reaction at the radical centres due to steric hindrance. Radicals of this type are termed persistent radicals, and examples include the 2,4,6-tri-*tert*-butylphenyl radical (**1**) which has a half-life of 0.1 s, and the tris(trimethylsilyl)methyl radical (**2**) which has a half-life of 200 s. Other non-carbon radicals, such as the nitroxyl radical TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (**3**), are stable enough to be commercially available.



The first radical identified was the stable triphenylmethyl radical. This was achieved as early as 1900 by Gomberg<sup>[6]</sup> who investigated the reaction of triphenylmethyl bromide with silver in an attempt to make hexaphenylethane; the reaction actually resulted in the formation of a different dimerization product (**Scheme 3**). At first glance the triphenylmethyl radical appears to be stabilised by both resonance and the steric bulk of the phenyl groups. However for resonance stabilisation to occur the phenyl rings would have to be co-planar with the singly occupied *p* orbital. Steric strain prevents this and each of the phenyl rings is twisted out of the plane of the singly occupied *p* orbital. It is thus steric factors that give the triphenylmethyl radical its stability.



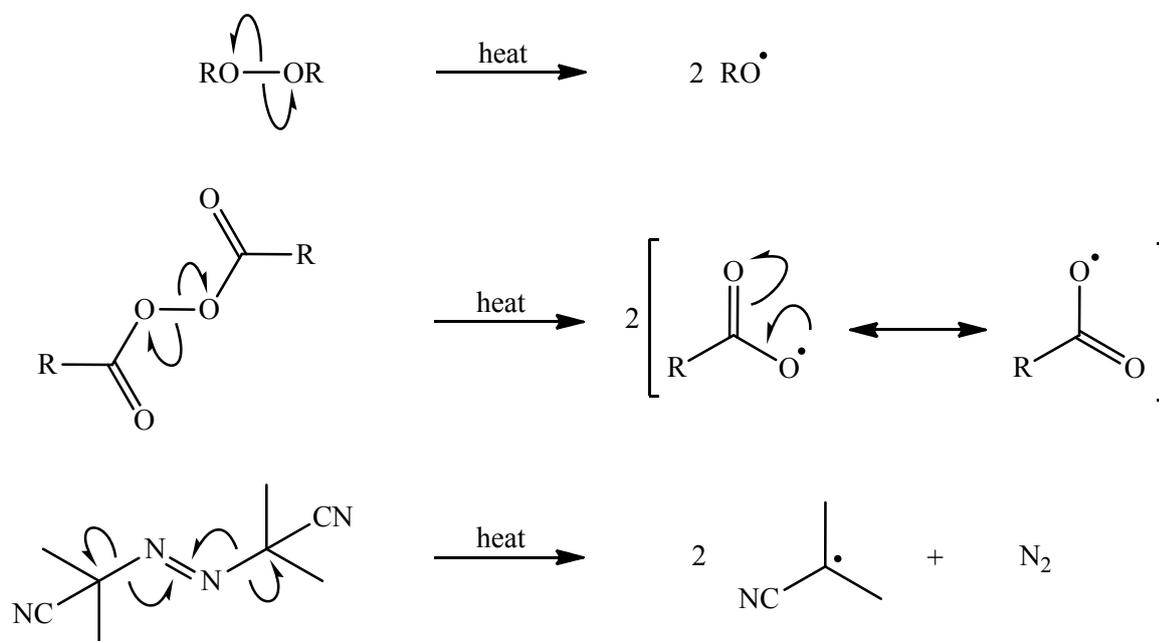
**Scheme 3**

### 1.2 Methods for the generation of carbon radicals

Thermolysis is the process of forming radicals by using heat to break bonds. In the case of carbon-carbon and carbon-hydrogen bonds high temperatures, up to 600 °C, are needed to break these bonds. The petrochemical industry uses this method to break down long chain hydrocarbons. This method although effective, generates large numbers of radicals indiscriminately with very little control over the process. This can be hazardous as explosions can happen. For controlled radical reactions homolysis of relatively weak bonds at lower temperatures is required. Homolysis of bonds with bond energies of 125-165 kJ mol<sup>-1</sup> can be achieved in solution at temperatures up to 150 °C. Diacylperoxides and azo compounds are examples of such compounds and are commonly used as initiators in radical reactions.

Alkyl peroxides have a bond strength of approximately 150 kJ mol<sup>-1</sup>, and when heated form two alkoxy radicals. Larger R groups reduce this bond strength, and thus lower temperatures are needed to form the radicals (**Scheme 4**). Diacylperoxides have lower bond energies of approximately 125 kJ mol<sup>-1</sup> and are more reactive; this is due to the resonance stabilisation of the radical (**Scheme 4**). A

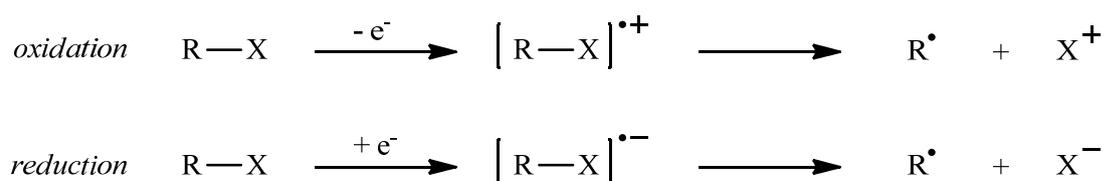
commercially available example is benzoyl peroxide. Thermolysis of azo compounds results in the cleavage of two carbon nitrogen bonds. It is driven by the formation of the stable N<sub>2</sub> molecule and R groups that stabilise the radical formed can lead to faster reaction rates. Traditionally the most effective azo initiator is azobisisobutyronitrile (AIBN) as the tertiary radical formed can be resonance stabilised by the nitrile triple bond (**Scheme 4**).



**Scheme 4**

There are disadvantages to using peroxides and azo compounds however as there are fire and explosion risks involved.

Another method for radical formation involves electron transfer reactions. A neutral molecule can be converted to a radical by the addition or removal of one electron<sup>[1]</sup>. If an electron is lost, a radical cation is formed which breaks down to a radical and a cation. Conversely if an electron is gained, a radical anion is formed which breaks down to give a radical and an anion (**Scheme 5**). Metal ions such as Ag<sup>+</sup> and Fe<sup>2+</sup> which can change their oxidation state by one are commonly used to carry out these reactions. This method is very mild and can be carried out at room temperature; it also leads to the generation of only one radical species, unlike thermolysis which leads to two.



**Scheme 5**

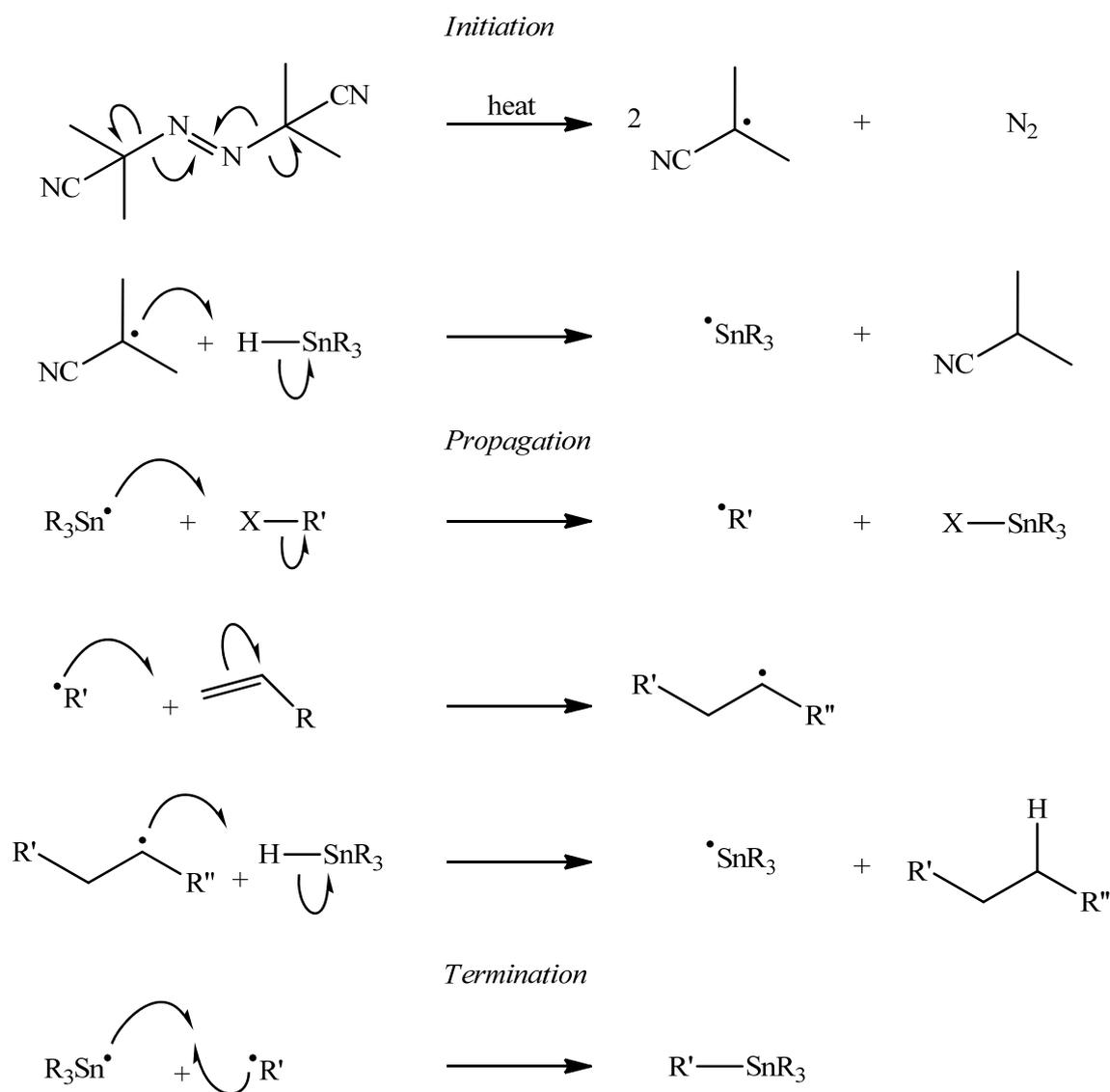
Photolysis is another widely used method for the generation of radicals. When light shines on organic molecules, energy can be absorbed leading to homolysis. This is due to the fact that low energy bonding electrons are promoted to higher energy antibonding orbitals when light energy is absorbed, thus weakening the bond and eventually cleaving it. Only coloured organic molecules are able to absorb visible light and so UV light is required for most organic molecules. Peroxides and diacylperoxides dissociate when light of 350 nm wavelength is employed. Photolysis of the weak C–N bonds of azo compounds can also occur: AIBN for example absorbs light at 345 nm and forms the same radicals observed on thermolysis (**Scheme 4**).

### ***1.3 Hydrogen abstraction as a route to carbon radicals***

#### ***1.3.1 Thermal hydrogen abstraction***

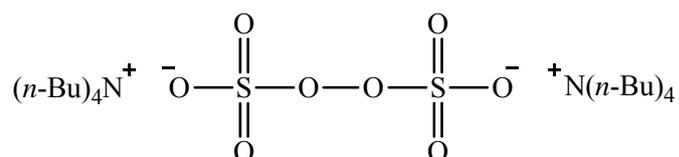
Radical reactions frequently occur by a chain mechanism and incorporate the use of initiator molecules. The first step in this process, termed initiation, involves the homolytic cleavage of bonds as discussed earlier. Homolysis of the C–N bonds in AIBN for example (**Scheme 6**), leads to the formation of two 2-cyanopropyl radicals and a stable molecule of nitrogen. The 2-cyanopropyl radical then abstracts a hydrogen atom from a trialkyltin hydride molecule forming a tin radical. This tin radical reacts with a haloalkane forming a tin-halogen bond and a carbon centred radical. This newly formed radical can then react with another molecule such as an alkene (**Scheme 6**) forming a carbon-carbon bond, or recombination can occur. The driving force in this process is the formation of a tin-halogen bond which is stronger than the tin-hydrogen bond and is thus thermodynamically favoured.

While this type of reaction protocol is well established and synthetically useful, there are drawbacks associated with it. The use of tin compounds is undesirable due to toxicity concerns and disposal of the tin-halogen products generated is also an issue. Related reaction procedures which use peroxides as the initiator are also undesirable due to the explosion risk associated with peroxides in general.



**Scheme 6**

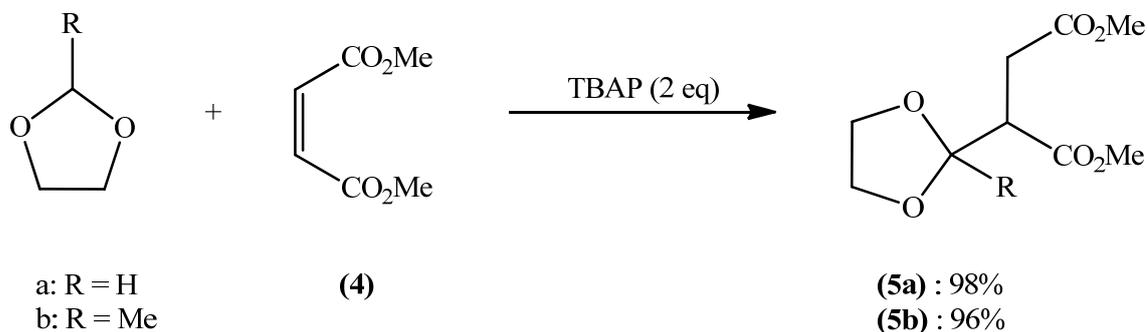
Recently, Kim reported the radical addition of 1,3-dioxolanyl and 2-methyl-1,3-dioxolanyl radicals to a large range of electron deficient alkene systems<sup>[7]</sup>. The reactions are initiated by tetra(*n*-butyl)ammonium peroxydisulfate (TBAP). This is a new type of peroxydisulfate which is soluble in organic solvents as a result of the tetra(*n*-butyl)ammonium cation (**Figure 3**).



**Figure 3**

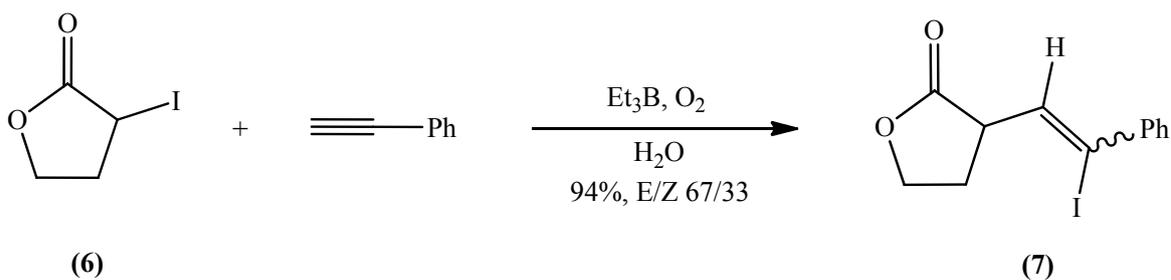
The reactions proceed regioselectively and in excellent yields for both 1,3-dioxolane and 2-methyl-1,3-dioxolane, an example being those with dimethyl maleate (**4**) (**Scheme 7**). The reaction time for

the 1,3-dioxolane reaction was 90 min at 25 °C while the reaction involving 2-methyl-1,3-dioxolane was complete after only 20 min, although this reaction was carried out at a higher temperature (70 °C).



Scheme 7

Trialkylboranes and dialkylzincs (methyl or ethyl), in combination with oxygen, have been shown to be effective initiators for carbon radical formation, leading to new carbon-carbon bond forming reactions<sup>[8-11]</sup>. One such example<sup>[12]</sup> is the addition of  $\alpha$ -iodo- $\gamma$ -butyrolactone (6) to phenylacetylene using triethylborane and oxygen (Scheme 8).



Scheme 8

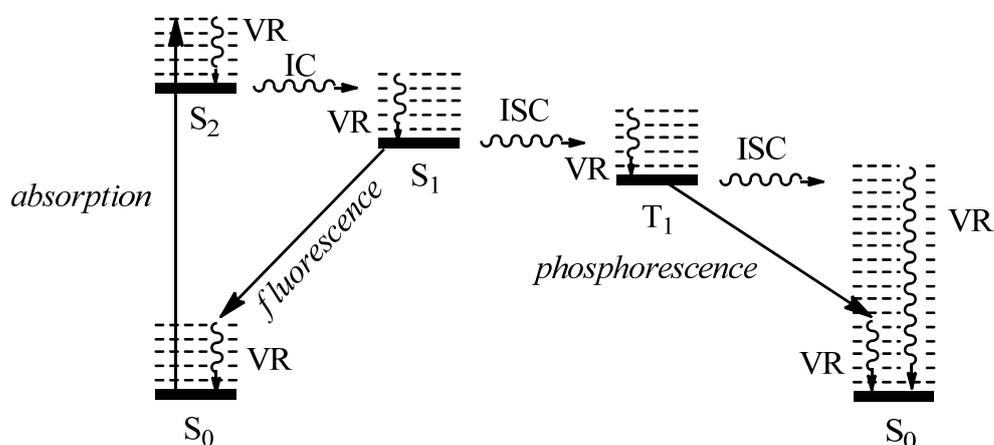
The addition product (7) is formed in excellent yield and as a mixture of *E/Z* isomers. The reaction is carried out using water as a co-solvent. The reaction mechanism for this type of iodine atom transfer reaction is discussed in a later section (Section 1.6).

### 1.3.2 Photochemical hydrogen abstraction

The work described in this thesis involves the formation of carbon radicals using photochemical hydrogen abstraction. The concepts involved are outlined in the following sections.

#### 1.3.2.1 Basic organic photochemistry

When an organic molecule absorbs light energy it enters into an electronically excited state. A range of different processes can then occur to return the molecule back to the ground state. One of the most effective methods of describing the different processes that occur is a Jablonski diagram<sup>[13]</sup> (**Figure 4**). There are two main types of energy transfer process: radiative transfer processes (absorption, fluorescence and phosphorescence) and radiationless energy transfer processes (vibrational relaxation (VR), internal conversion (IC) and intersystem crossing (ISC)).



**Figure 4**

The molecule absorbs a photon of light and is excited from its ground state ( $S_0$ ) into an upper vibrational level of an excited singlet state, such as  $S_2$ . The multiplicity of the molecule remains unchanged so this is a spin-allowed, very fast process ( $k = 10^{18} \text{ s}^{-1}$ ). VR takes the molecule to the lowest vibrational level of  $S_2$ ; this is again a fast process ( $k = 10^{13} \text{ s}^{-1}$ ) as it does not affect the multiplicity of the molecule. The molecule can then go through IC, the transition of an electronically excited molecule to a lower electronic state of the same multiplicity. It is an efficient process as the energy gap between the upper excited states is small and because it is a spin allowed process; it occurs at a rate comparable to VR. The molecule then relaxes to the lowest excited state of  $S_1$  by further VR.

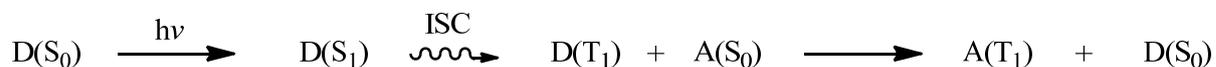
From here there are two photophysical processes which the molecule can undergo, fluorescence or ISC. Fluorescence is an emission that occurs as a result of the transition between  $S_1$  and  $S_0$ . It is an allowed process and thus relatively fast ( $k = 10^6 - 10^9 \text{ s}^{-1}$ ) even though the energy gap is large. ISC is the radiationless transition of the molecule from the  $S_1$  to the  $T_1$  energy state. This is a spin forbidden transition and it is inefficient unless the energy gap between the  $S_1$  and  $T_1$  states is very small. Molecules which contain carbonyl groups have a small  $S_1/T_1$  energy gap and so ISC occurs readily,

the  $\Phi$  (ISC) for benzophenone, for example, being approximately 1. A chemical reaction can occur for a molecule in the  $S_1$  state but would have to be very fast to compete with ISC and fluorescence.

Once in the  $T_1$  energy state phosphorescence can occur. This is a much slower process ( $k = 10^3 - 10^2 \text{ s}^{-1}$ ) as it involves a transition from  $T_1$  to  $S_0$  which is spin forbidden, and in addition the  $T_1/S_0$  energy gap is very large. As this is a slow process the molecule stays in the  $T_1$  state for long enough to allow relatively slow chemical reactions to take place.

The  $n \rightarrow \pi^*$  transition promotes an electron from one of the non-bonding pairs of electrons on the oxygen to the  $\pi^*$  antibonding orbital of the C=O bond. The singly occupied  $n$  orbital localised on the oxygen atom is responsible for the radical nature of the carbonyl group in its  $n \rightarrow \pi^*$ .

Getting molecules into the triplet excited state is thus an important process as the relatively long lifetime of a molecule in  $T_1$  allows chemical reactions time to occur. Carrying this out directly will be inefficient unless there is a carbonyl group present in the molecule. Photosensitization can however be used to populate the  $T_1$  state indirectly. A donor molecule,  $D(S_0)$ , is irradiated and promoted into its excited state,  $D(S_1)$  (**Scheme 9**). Efficient ISC is then required to form the triplet state,  $D(T_1)$ , explaining why most donor molecules contain a carbonyl group with its small  $S_1/T_1$  energy gap. Once in this state the donor molecule can interact with an acceptor molecule,  $A(S_0)$ , and transfer its energy with spin retention, usually through collision, putting the acceptor molecule into its triplet state  $A(T_1)$  and returning the donor molecule to its ground state.



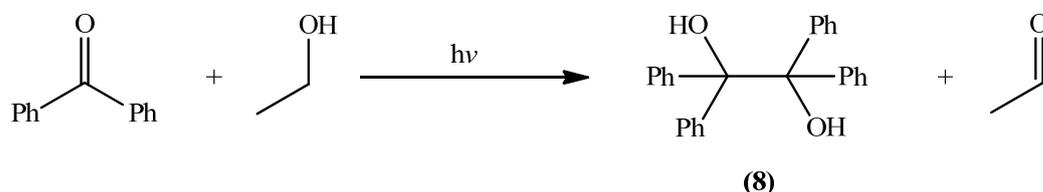
**Scheme 9**

The donor molecule is described as a sensitizer and the acceptor molecule is described as a quencher. For photosensitization to occur the energy of the triplet state of the sensitizer molecule must be larger than the energy of the quencher's triplet state. For the reasons given above ketones are commonly used as sensitizers, with aromatic ketones being particularly important; benzophenone is the most widely used photosensitizer as it has a relatively long triplet lifetime of  $6 \times 10^{-3} \text{ s}$  and a relatively high  $T_1$  energy ( $287 \text{ kJ mol}^{-1}$ )<sup>[14]</sup>.

Although benzophenone is widely used as a photosensitizer, its role in photochemical hydrogen abstraction does not involve this mode of action and so the terms photocatalyst or photomediator are preferred. The term photocatalyst is not the term of choice either as the quantities of benzophenone used are often well above what could be considered catalytic. The term photomediator is thus used to describe the role of benzophenone in the reactions described in this thesis.

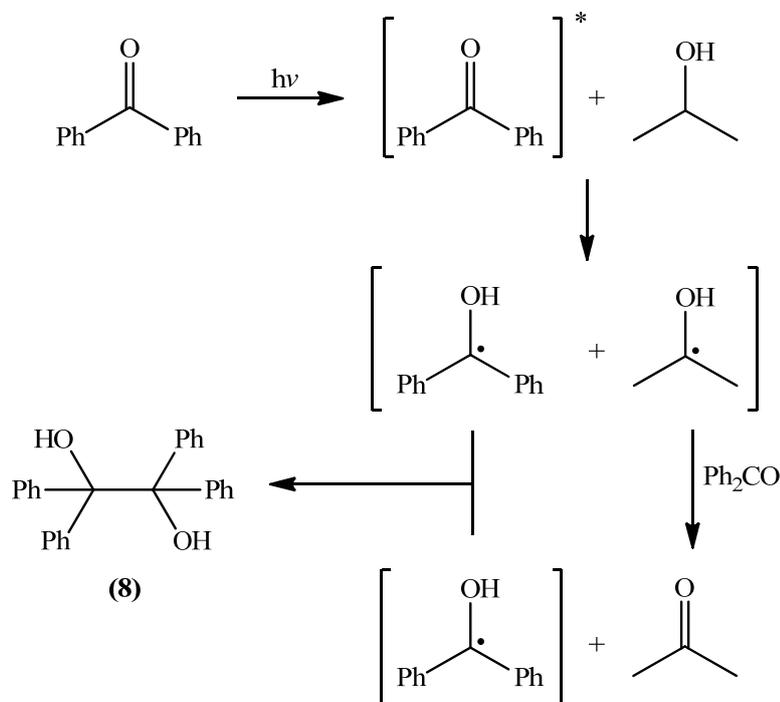
### 1.3.2.2 General reaction mechanism for photochemical hydrogen abstraction

The first photoinduced hydrogen abstraction by an aromatic ketone was observed by Ciamician and Silber<sup>[15]</sup> in 1900. They observed the photoreduction of benzophenone to benzopinacol (**8**), in sunlight using ethanol as a solvent (**Scheme 10**).



**Scheme 10**

Pitts and co-workers explored the mechanism of the photoreduction of benzophenone with 2-propanol<sup>[16]</sup>. They concluded that initially the benzophenone absorbs a photon of light and, as discussed earlier, ends up in the ( $n \rightarrow \pi^*$ ) triplet state (**Scheme 11**). Acting as an alkoxy radical the excited benzophenone abstracts the methine proton from the 2-propanol forming a benzophenone ketyl radical and a hydroxypropyl radical. The latter then undergoes a hydrogen transfer reaction with a molecule of benzophenone in its ground state forming a molecule of acetone and another benzophenone ketyl radical. Dimerisation of these ketyl radicals leads to the efficient formation of benzopinacol. Hammond<sup>[17]</sup> subsequently studied the photoreduction of benzophenone by benzhydrol and confirmed that hydrogen abstraction was occurring *via* the triplet state

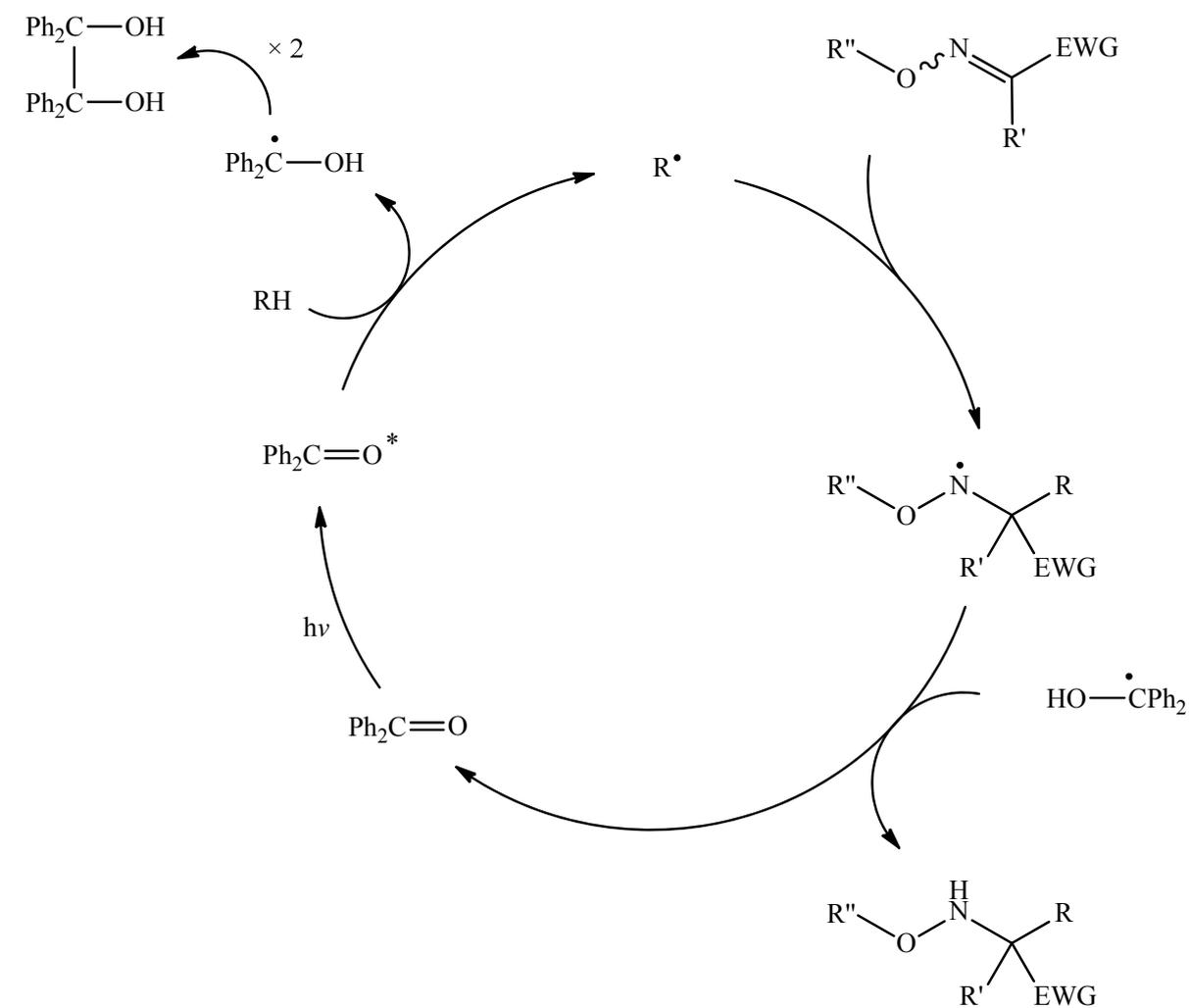


**Scheme 11**

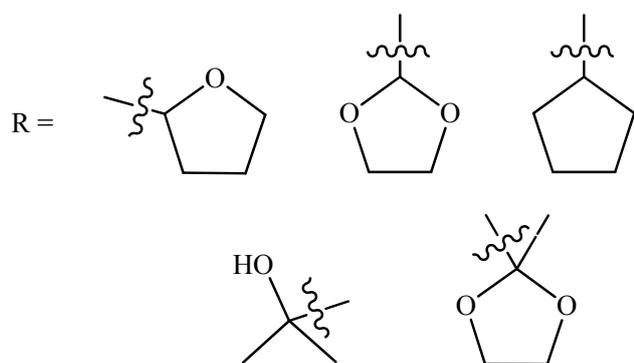
### ***1.3.2.3 Mechanism for reaction of photochemically generated carbon radicals with carbon-nitrogen double bonds***

The work described in this thesis involves the photomediated generation of a carbon radical and its reaction with an electron deficient oxime, or oxime ether, forming a carbon-carbon bond. The main features of the reaction mechanism (**Scheme 12**) are common to almost all reactions of this type including the much more widely studied photomediated addition of carbon radicals to alkenes and alkynes<sup>[18]</sup>, an exception being the series of reactions with methyl 2-(hydroxyimino)(phenyl)acetate where an alternative reaction mechanism operates (**Section 2.10.2, Scheme 85**).

The photomediator, benzophenone, in the presence of UV light is initially excited to an  $n \rightarrow \pi^*$  triplet state. As discussed earlier (**Section 1.3.2**) the carbonyl group in this excited state behaves as an alkoxy radical and abstracts a hydrogen atom from a relatively weak C-H bond. The electronically excited benzophenone is reduced to a ketyl radical, which is needed later on in the reaction cycle but which may also undergo dimerisation to generate a pinacol. If this pinacol formation is prominent for a particular system, large amounts of the photomediator will be required. In the presence of a mono- or disubstituted electron deficient oxime, or oxime ether, the carbon radical undergoes addition forming a carbon-carbon bond and generating an aminyl radical. Back hydrogen transfer from the ketyl radical formed earlier, regenerates benzophenone and forms the product. Another option which must be considered is that the aminyl radical reacts with another molecule of the H-donor, again forming the product but this time generating another carbon radical which can go on to react with a molecule of the unsaturated oxime in a chain mechanism. It has been shown for example, that the reaction of 2-methyl-1,3-dioxolane with DMAD occurs *via* a chain mechanism as a quantum yield of 4.8 is observed<sup>[19]</sup>. This means that for every photon of light absorbed, 4.8 molecules of product are formed, confirming that a chain mechanism is in operation. Due to the large quantities of photomediator required in the reactions involving oximes, and the relatively long reaction times it is unlikely that a chain mechanism is operating for these reactions.



**H-donors**



R' = H, CO<sub>2</sub>Et, Me, Ph, CH<sub>2</sub>CO<sub>2</sub>Me

R'' = H, Bn

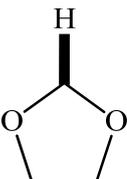
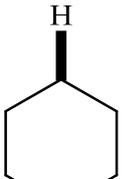
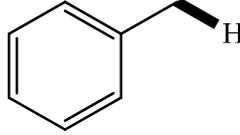
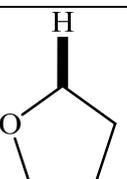
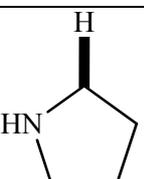
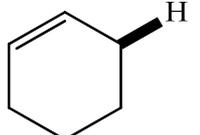
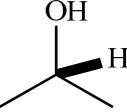
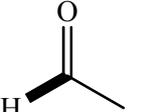
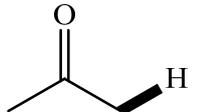
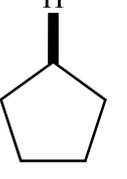
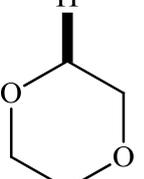
EWG = CO<sub>2</sub>Me, CO<sub>2</sub>Et

**Scheme 12**

### 1.3.2.4 H-Donors

The Evans-Polanyi relationship implies that the rate constant for hydrogen abstraction increases as the bond dissociation energy (BDE) decreases<sup>[20]</sup>. From this, a number of suitable hydrogen donor molecules can be identified by considering BDEs (**Table 1**). There are a number of molecules that have relatively low BDEs but which, due to resonance within the molecule, produce non-nucleophilic radicals (**Table 1**) and thus do not take part in carbon-carbon bond formation with electrophilic multiple bonds. In contrast to this, resonance is the reason why hydrogen abstraction from an aldehyde occurs readily and why the resulting radical has nucleophilic character (**Figure 5**). There are also a number of molecules which are unsuitable as hydrogen donors due to their large BDEs (**Table 2**).

**Table 1 Bond dissociation energies for H-donors<sup>[21]</sup>**

H-Donors which produce nucleophilic C-radicals				H-Donors which produce non-nucleophilic C-radicals	
H-Donor	BDE <sup>a</sup>	H-Donor	BDE <sup>a</sup>	H-Donor	BDE <sup>a</sup>
	381.2		416.3		375.5
	391.6		377.0		341.5
	390.5		374.0		401.7
	400.0		401.7		

<sup>a</sup> kJ mol<sup>-1</sup>



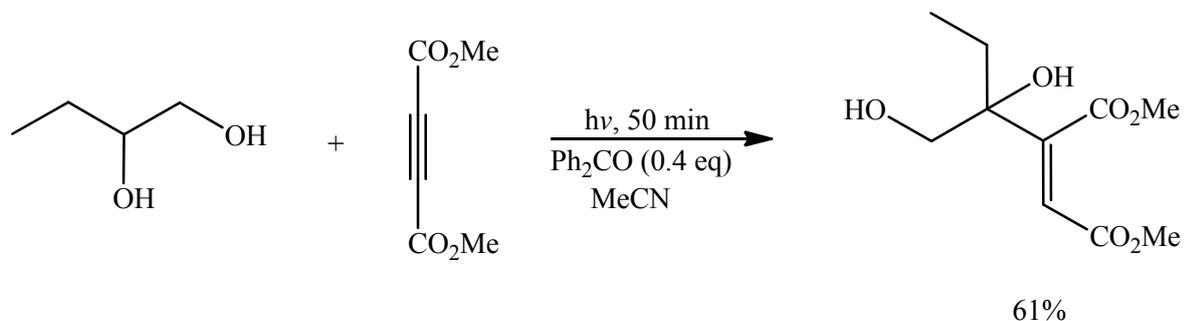
Figure 5

Table 2 Bond dissociation energies for unsuitable H-donors<sup>[21]</sup>

H-Donor	BDE <sup>a</sup>
	544.8
	472.2
	464.8
	423.1

<sup>a</sup> kJ mol<sup>-1</sup>

When a H-donor has more than one type of CH bond, the general order of H-abstraction from CH bonds, primary CH < secondary CH < tertiary CH, determines the regioselectivity of CH abstraction. The reaction of 1,2-butandiol with DMAD<sup>[22]</sup> is an example of where a methine proton is abstracted selectively due to the stability of the tertiary radical formed (**Scheme 13**). As is typical of these reactions, the H-donor is present in large excess so that any secondary radicals formed can engage in an equilibrium with the H-donor which will give the more stable tertiary radical, contributing to the observed selectivity.

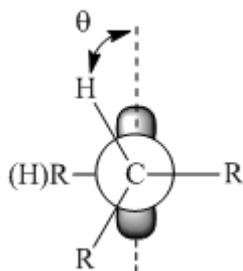


Scheme 13

When 1,2-butandiol is replaced in this reaction by 2-pentanol, a mixture of products is formed. Although the methine CH bond has a lower BDE than the other CH bonds this advantage is off-set by the larger number of other CHs present in the molecule and a complex mixture of products is formed. In general molecules which effectively have just one abstractable H-atom, are the most useful H-donors from a synthetic point of view. Taking into consideration the need for a large excess of H-donor in these reactions, it is clear that it must be relatively volatile so that it can be removed easily from the product.

#### 1.3.2.5 Stereoelectronic Effects

Stereoelectronic effects refer to the way in which the orientation of orbitals influences the result of a reaction. The rate of hydrogen abstraction from a carbon atom adjacent to a nitrogen or oxygen is much quicker than hydrogen abstraction from the corresponding hydrocarbon. Ingold<sup>[23]</sup> showed that for ethers, there were high rates of abstraction from C-H bonds adjacent to the oxygen atom where the dihedral angles between the C-H bond and the *p*-type non-bonding orbital on the oxygen (**Figure 6**) was less than 30°. Abstraction was much slower for C-H bonds which had dihedral angles of about 90°.



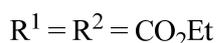
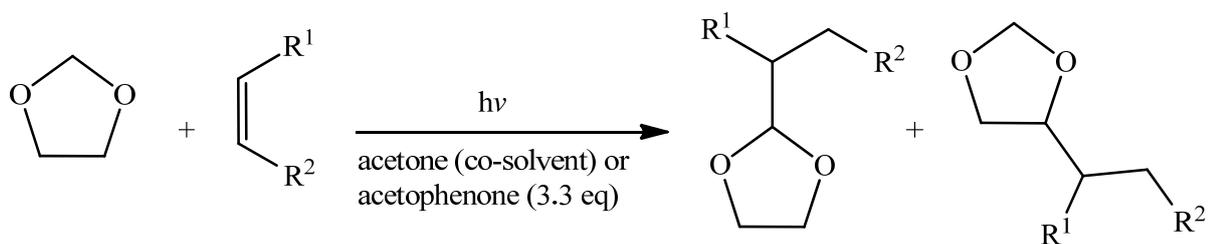
**Figure 6**

Similarly, Scaiano<sup>[24]</sup> showed that for amines, the rate of hydrogen abstraction was quickest when the  $\alpha$ -C-H bonds and the nitrogen lone pair had an eclipsed relationship. He also showed that when a dihedral angle of 60° was present, the C-H bond was less easily cleaved.

## 1.4 Addition of C-radicals to carbon-carbon double bonds

### 1.4.1 Dioxolanes

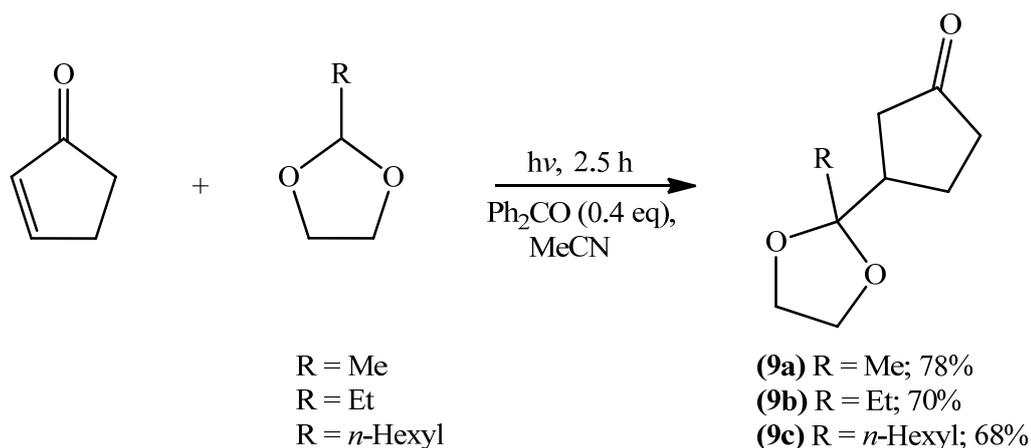
Rosenthal and Elad<sup>[25]</sup> reported the first photomediated generation of carbon radicals from cyclic acetals; they used acetone, acetophenone or benzophenone as photomediators. For the acetophenone initiated addition reaction with diethyl maleate, a 90% yield of the product was obtained. The reaction occurred selectively at the 2-position of the dioxolane. Yields were lower (25-50%) for reactions involving terminal alkenes with some of 4-substituted product being observed, albeit in low yield (**Scheme 14**).



**Scheme 14**

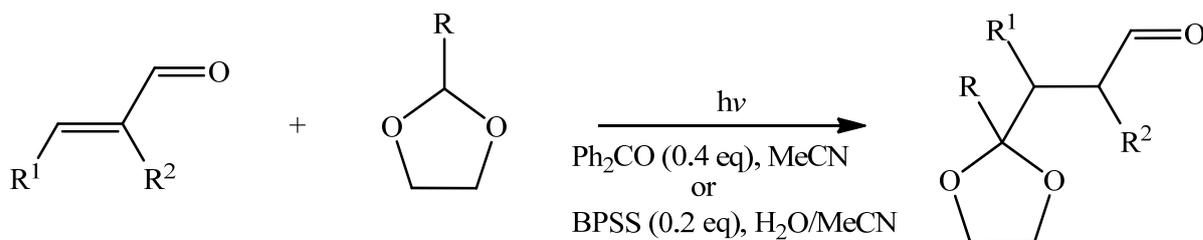
The reactions were carried out using light of wavelength 290 nm. The fact that such light is not able to promote the dioxolane to an excited state, and that 2-propanol and benzopinacol are formed when acetone and benzophenone are used, respectively, indicates that hydrogen atom abstraction from the acetal by the ketone in its ( $n \rightarrow \pi^*$ ) triplet state is involved.

Fagnoni carried out reactions on a range of 2-alkylated-1,3-dioxolanes with both acyclic and cyclic enones<sup>[26]</sup>. Open chain enones gave poor yields (21-49%) for the range of 2-alkyl-1,3-dioxolanes considered. In the case of the 2-phenyl-1,3-dioxolane no alkylation products at all were observed. Much better yields were observed for cyclopentenone (**Scheme 15**) with the benzophenone mediated reaction with 2-methyl-1,3-dioxolane giving a yield of 78%. Again however, no addition products were observed in the case of the 2-phenyl-1,3-dioxolane. This lack of reactivity was attributed to the low nucleophilicity of the benzylic radical formed on hydrogen abstraction. Fagnoni concluded that the yield of the reactions was dependant on the efficiency of the radical trapping, which in turn depends on the structure of the enone. The five- and six-membered cyclic enones gave high yields in short reaction times, whereas the acyclic enones performed poorly giving low yields. This was attributed to the rigidity of the ring structures which allowed better interaction with the radical species<sup>[26]</sup>.



**Scheme 15**

Fagnoni also carried out similar photochemical reactions involving  $\alpha,\beta$ -unsaturated aldehydes, 1,3-dioxolane and 2-alkyl-1,3-dioxolanes<sup>[27]</sup>. The products of these reactions gave monoprotected 1,4-dialdehydes and 1,4-ketoaldehydes respectively (**Scheme 16**).



**Scheme 16**

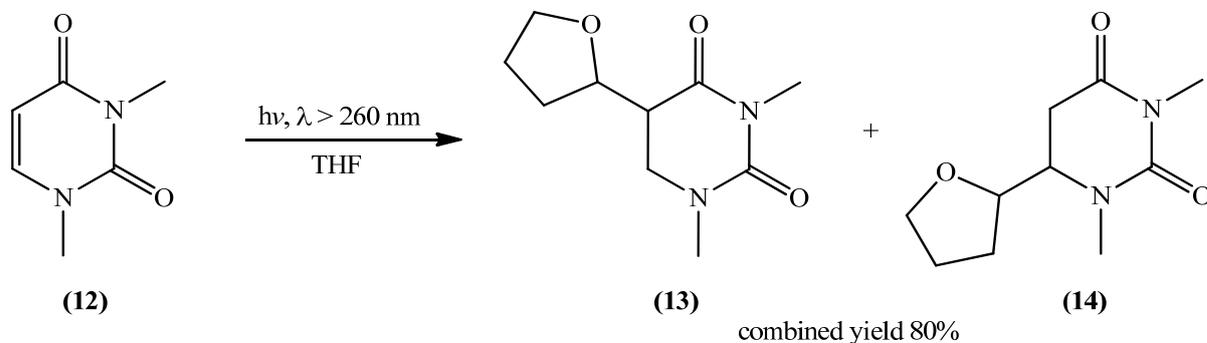
Two different reaction procedures were investigated. Reactions were carried out in an organic medium and also in a mixed aqueous-organic medium. Benzophenone was used to initiate the reactions in the organic medium and a water soluble sensitizer, benzophenone sodium sulfonate (BPSS), was successfully used in the aqueous-organic medium. The reactions proceeded with moderate yields (10-49%) for both reaction systems, but the aqueous-organic medium allowed for a more convenient work up.

#### 1.4.2 Cyclic ethers

Rosenthal and Elad<sup>[28]</sup> also described the addition of THF to a range of terminal alkenes and the electron deficient alkene diethyl maleate (**Scheme 17**).



case by recombination of the resulting ether radical and the enone derived radical. H-abstraction by the carbonyl oxygen leads to  $\beta$ -addition, while abstraction by the  $\beta$ -carbon of the enone leads to  $\alpha$ -addition. Similar results were obtained when the reaction was carried out in the presence of a peroxy initiator.

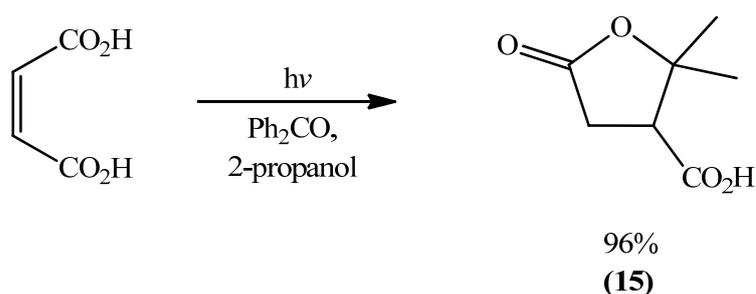


**Scheme 19**

### 1.4.3 Alcohols

The addition of photochemically generated  $\alpha$ -hydroxyalkyl radicals to unsaturated systems is another valuable method of forming carbon-carbon bonds. The process involves hydrogen abstraction from the  $\alpha$ -position of an alcohol by a triplet state ketone and the trapping of the resulting nucleophilic  $\alpha$ -hydroxyalkyl radical with an electron deficient unsaturated substrate.

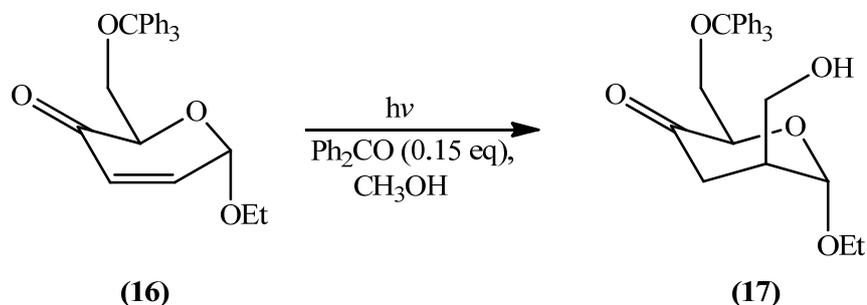
The first synthetically useful application of the process was reported in 1957 when Schenck showed that terebic acid (15) (Scheme 20) could be synthesised *via* the photomediated reaction of the disubstituted alkene maleic acid and 2-propanol<sup>[31]</sup>.



**Scheme 20**

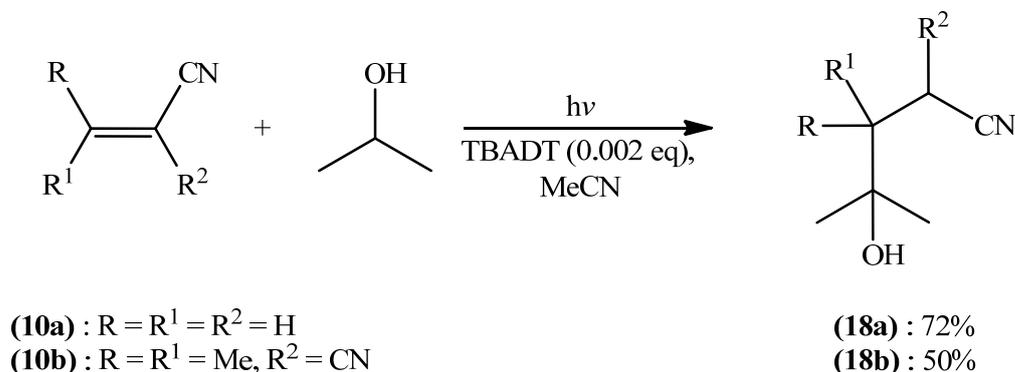
Fraser-Reid<sup>[32]</sup> described the benzophenone promoted photoaddition of methanol to enone (16) which formed (17) in 75% yield. The proposed mechanism involved hydrogen abstraction from the methanol by an excited state benzophenone affording, in the usual way, an  $\alpha$ -hydroxyalkyl radical as well as a ketyl radical. The  $\alpha$ -hydroxyalkyl radical then undergoes addition to (16) at the electron deficient carbon of the enone. The product is formed by back hydrogen transfer from the ketyl radical or

methanol (**Scheme 21**). This reaction shows a high degree of steric control with only addition of the  $\alpha$ -hydroxyalkyl radical on the face opposite to the ethoxy group being observed. When similar reactions were carried out with no axial substituent present at the  $\gamma$ -position, only a small preference for the axial product was evident<sup>[33]</sup>.



**Scheme 21**

The photochemical addition of 2-propanol to the electron deficient alkenes (**10a**) and (**10b**) was achieved by Fagnoni<sup>[29]</sup> (**Scheme 22**). The reactions were carried out in acetonitrile using catalytic amounts of TBADT (0.002 eq) as the photomediator. These reactions again proceeded regioselectively and in good yield.

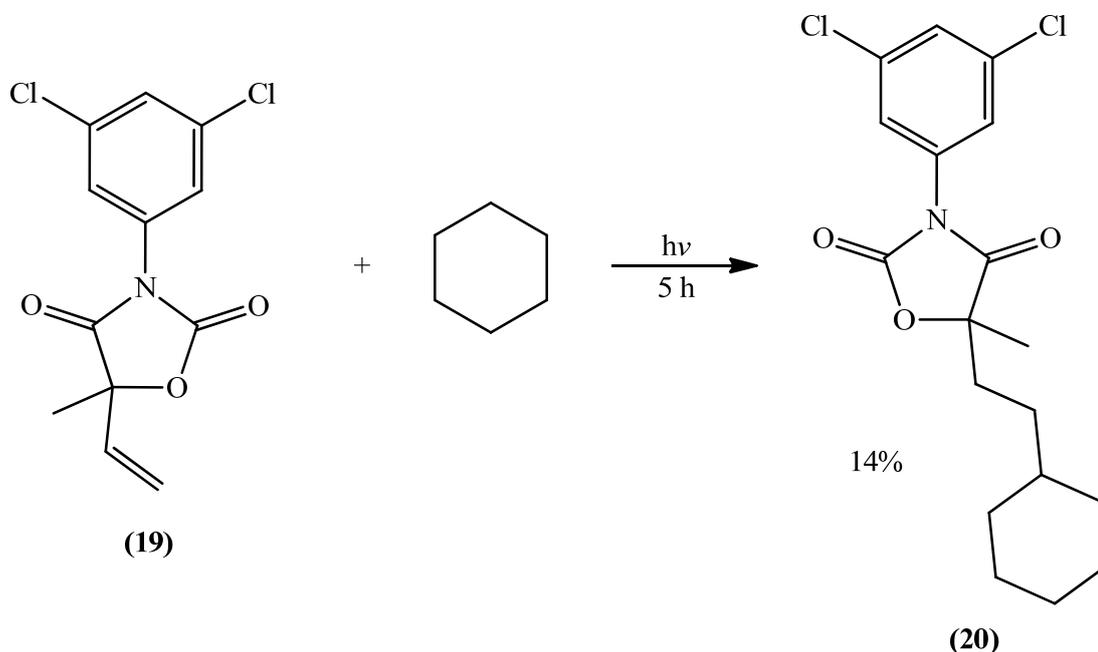


**Scheme 22**

#### 1.4.4 Cycloalkanes

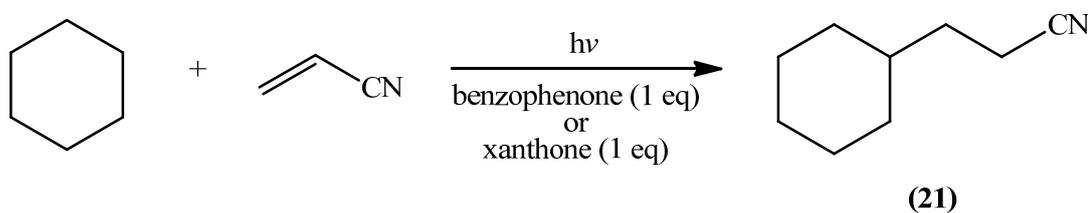
Photochemical reactions that involve the addition of cycloalkanes to electron deficient alkenes are very important synthetically. They provide a method for functionalising molecules that are more generally thought of as solvent molecules as they are so unreactive. Most of the examples discussed above involve the use of a photomediator to generate the carbon radical. One example of the direct generation and subsequent addition of a radical species, involves the irradiation of the herbicide vinclozolin (**19**) in cyclohexane (**Scheme 23**)<sup>[34]</sup>. The suggested mechanism involves one of the carbonyl groups being promoted to its triplet state in which it abstracts a hydrogen atom from the cyclohexane. This cyclohexyl radical then adds to the vinyl group of the vinclozolin. An interesting

feature of this reaction is that the cyclohexyl radical adds to an unactivated alkene, understandably, giving a low yield of the addition product (**20**). The photomediated reaction of 1,3-dioxolanes (**Scheme 14**) with terminal alkenes are other examples of this type of behaviour.



**Scheme 23**

An example of the photomediated addition of cycloalkanes to an electrophilic alkene is given by Fagnoni<sup>[35]</sup>. This involved xanthone or benzophenone based H-abstraction from a cyclic alkane and the reaction of the resulting carbon radical with an  $\alpha,\beta$ -unsaturated nitrile, leading to the formation of a  $\beta$ -cycloalkylnitrile (**21**) (**Scheme 24**). Yields for the reactions were moderate to good depending on the substrate, while substitution at the  $\beta$ -position slowed down the addition. Equimolar amounts of the photomediator with respect to the alkene were used in these reactions.



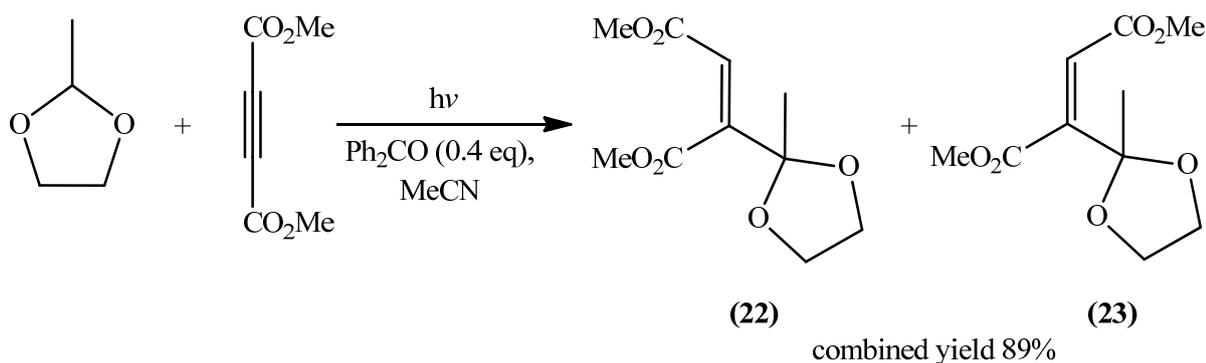
**Scheme 24**

The stereoselective addition of radicals to electron deficient enones carrying chiral auxiliaries is possible: Hoffmann<sup>[36]</sup> for example has demonstrated the stereoselective addition of tertiary amines to menthyloxyfuranone.

## 1.5 Addition of C-radicals to carbon carbon triple bonds

### 1.5.1 Dioxolanes

Geraghty<sup>[19]</sup> has presented work on the radical addition of a series of 2-alkyl-1,3-dioxolanes to both mono- and disubstituted alkynes. Alkyl group substitution at the 2-position was found to improve the rate of reaction: for example, the reaction between DMAD and 2-methyl-1,3-dioxolane is complete in just 15 min, affording *cis* and *trans* addition products, **(22)** and **(23)**, in a combined yield of 89% (**Scheme 25**).

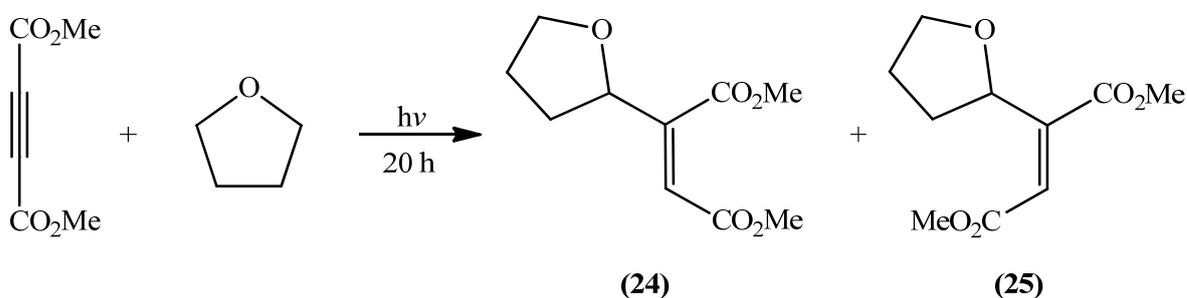


**Scheme 25**

Quantum yield studies indicated that the reaction of 2-methyl-1,3-dioxolane with DMAD occurred with a quantum yield of 4.8, and the reaction of 2-methyl-1,3-dioxolane with methyl propiolate with a quantum yield of 1.4. This suggests that these reactions proceed *via* a chain reaction, in which the alkenyl radical formed when the dioxolanyl radical adds to the alkyne, abstracts a H-atom from a molecule of dioxolane, rather than from the ketyl radical formed from benzophenone. It is suggested that this occurs as a result of efficient H-abstraction from the 2-alkylated dioxolane which is the result of a particularly favourable stereoelectronic interaction between the 2-CH bond and the lone pairs of electrons on the oxygen. A small amount of C-4 alkenylated product is observed in reactions between 1,3-dioxolane and propiolate esters; this was also observed in reactions involving 1-heptene (**Section 1.4.1, Scheme 14**). No C-4 products were obtained however when 2-alkylated dioxolanes were used and this is again attributed to the fact that the C-2 hydrogen atom in these molecules has a more favourable stereoelectronic interaction with the oxygen's lone pairs of electrons than is the case for 1,3-dioxolane itself<sup>[19]</sup>.

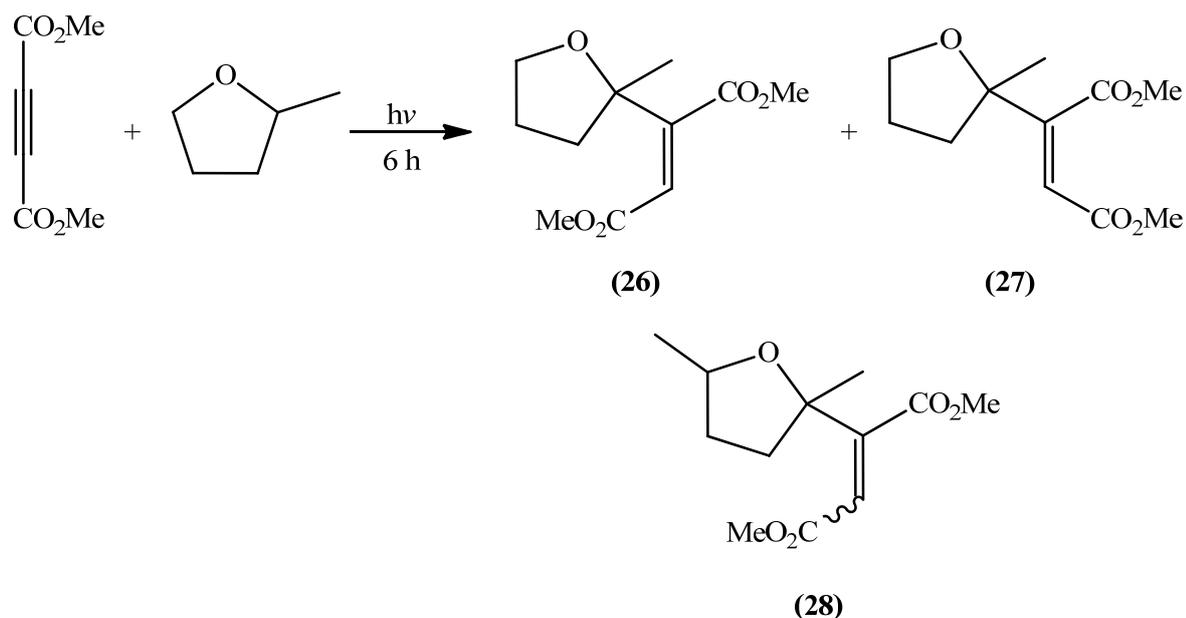
### 1.5.2 Cyclic ethers

The reaction of cyclic ethers with alkynes such as DMAD was first reported by Singh<sup>[37]</sup>. The irradiation of DMAD in THF for 20 h led to the *cis* and *trans* addition products **(24)** and **(25)** (**Scheme 26**). The products were formed in a 1:1 ratio with a combined yield of approximately 60%. As no photomediator was added to the reaction it is reasonable to suggest that an excited state DMAD molecule was responsible for H-abstraction, however this was ruled out as tetrahydropyran failed to react without the addition of acetone. Singh suggested that the carbon radicals were generated by radical forming impurities in the solvent, possibly peroxides, and this was supported by the fact that use of THF which had been dried over lithium aluminium hydride and distilled led to a much slower reaction and a poorer yield (10%).



**Scheme 26**

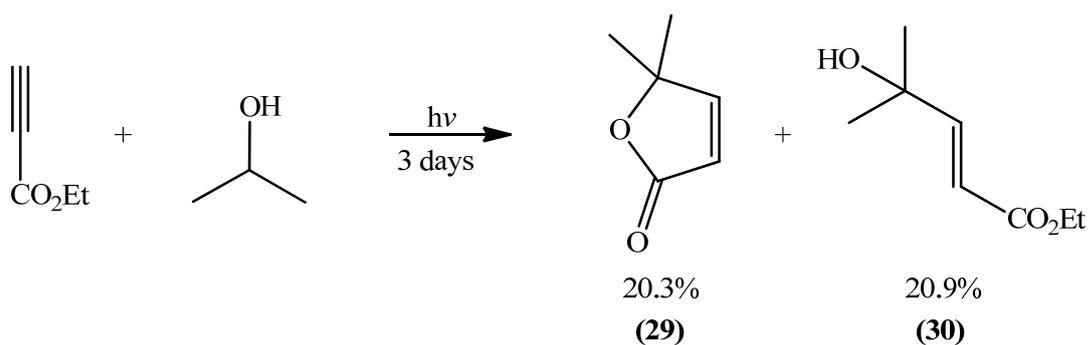
To investigate the effect of an alkyl substituent in the  $\alpha$ -position, a solution of DMAD in 2-methyltetrahydrofuran was irradiated. The reaction was stopped after 6 h at which time three 1:1 adducts, namely the *E* and *Z* isomers, **(26)** and **(27)**, and a minor third product which was tentatively assigned the structure **(28)**, had been formed in approximately 40% yield (**Scheme 27**). In this case the regioselectivity of the reaction is determined by the greater stability of a 3° radical relative to that of a 2° radical. Again this reaction was undertaken in the absence of a photomediator and as before it was suggested that the carbon radicals were generated by impurities in the ether. It is very difficult to see how the product **(28)** could be formed under the conditions involved and so this assignment is presumably incorrect.



**Scheme 27**

### 1.5.3 Alcohols

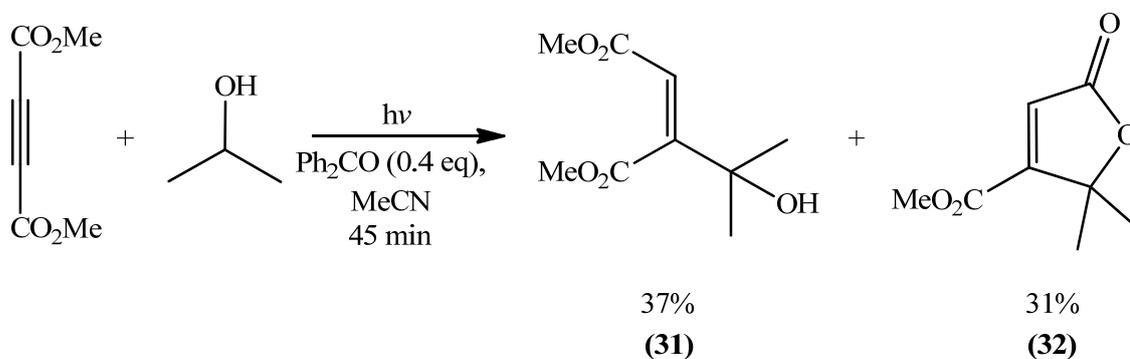
The first example of the photochemical addition of an alcohol to an alkyne was reported by Buchi in 1969<sup>[38]</sup>. Ethyl propiolate was dissolved in a solution of the alcohol and irradiation using a quartz-jacketed mercury lamp was continued until the ethyl propiolate was completely consumed, either in forming low molecular weight products or in polymerization. The reaction of ethyl propiolate and 2-propanol (**Scheme 28**) was complete after 3 days and two products (**29**) and (**30**) were isolated in an overall yield of 41%. The lactone product (**29**) results from the initial formation of the *trans* addition product, followed by its spontaneous cyclization.



**Scheme 28**

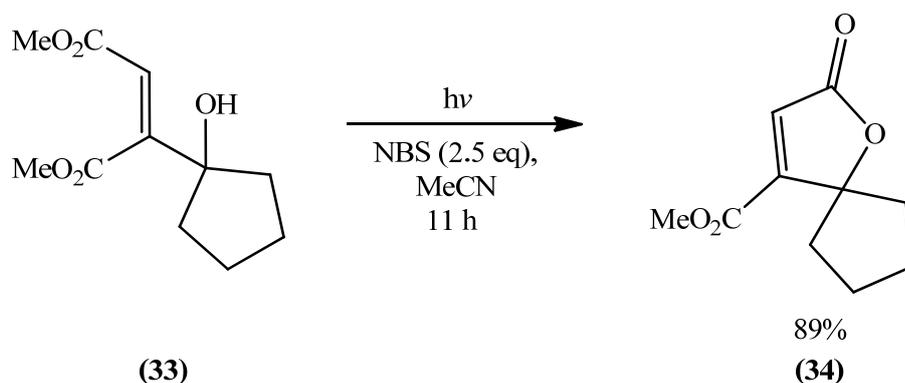
Due to the relatively long reaction times, research in this field was abandoned until relatively recently when it was shown that in the presence of a photomediator, the rate and yield for reactions involving acetylenic esters were greatly enhanced<sup>[22]</sup>. A series of primary and secondary alcohols (cyclic and acyclic), and diols were successfully added to methyl propiolate and dimethyl acetylenedicarboxylate

(DMAD) leading to both *cis* and *trans* addition products in good yields and with short reaction times. The *trans* addition products again spontaneously cyclised, and so the reaction is a particularly direct route to synthetically important  $\gamma$ -butenolides. One such example is the addition of 2-propanol to DMAD in the presence of benzophenone which led to the *cis* addition product (**31**) and lactone (**32**) in a combined yield of 68% (**Scheme 29**).



**Scheme 29**

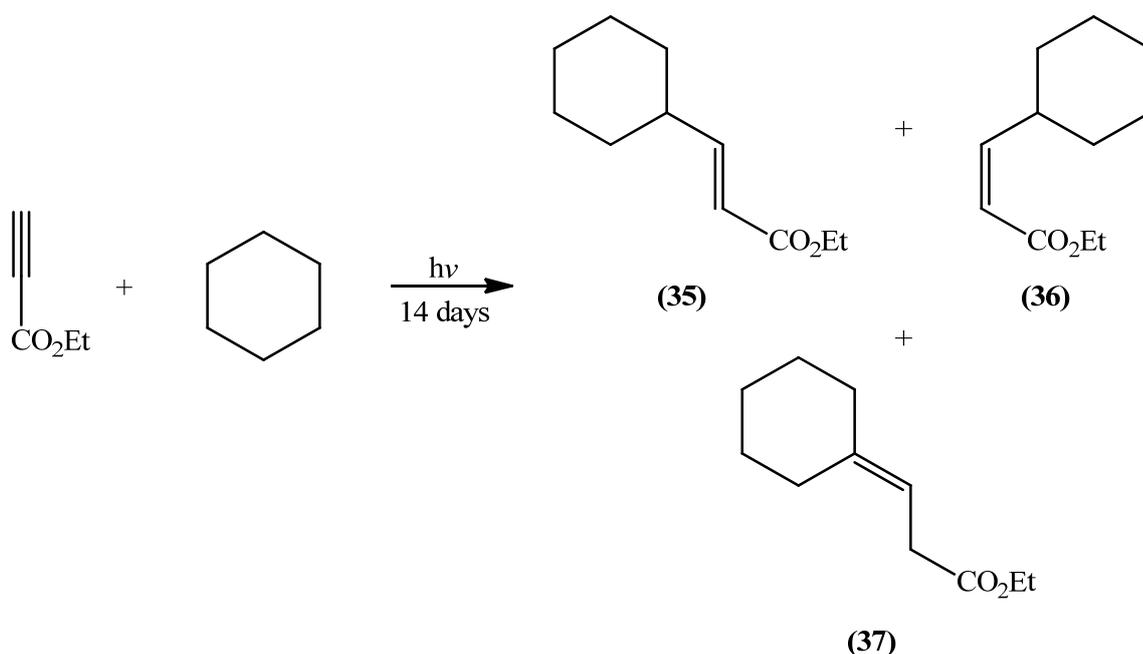
Due to the synthetic importance of  $\gamma$ -butenolides, the photosensitized *E/Z* isomerization of the *cis* addition product (**33**), formed from DMAD and cyclopentanol, was attempted; this proved ineffective as although direct irradiation at 254 nm resulted in isomerization, further photoreaction of the  $\gamma$ -butenolide occurred competitively, leading to the formation of a complex mixture of products. Although not as attractive synthetically, irradiation at 350 nm in the presence of *N*-bromosuccinimide (NBS) led to the isomerised product (**34**) (**Scheme 30**).



**Scheme 30**

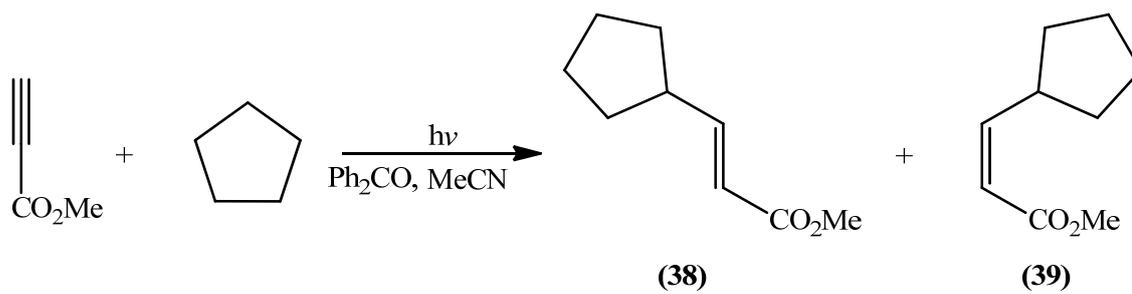
### 1.5.4 Cycloalkanes

The photochemical addition of cycloalkanes to alkynes was first studied by Buchi in 1969<sup>[38]</sup>. He observed that irradiation of ethyl propiolate in cyclohexane led to a mixture of addition products with **(35)**, **(36)** and **(37)** being formed in a 3.9:3.4:1 ratio (**Scheme 31**). The reaction time however was 14 days and only a 10% yield was obtained. At the same time Grovenstein<sup>[39]</sup> noticed that the addition of cyclohexane to DMAD occurred to a small extent (5% yield after 24 h) in the course of an attempted photochemical addition of DMAD to naphthalene in cyclohexane. Again due to the small yields and long reaction times, further work was not carried out in this area until relatively recently.



**Scheme 31**

Geraghty showed that in the presence of a photomediator such as benzophenone, alkynes with electron-withdrawing groups reacted with cycloalkanes to give vinyl cycloalkanes<sup>[40]</sup>. A range of alkynes with electron withdrawing groups attached were reacted with a number of different cyclic alkanes, ranging from C<sub>5</sub>-C<sub>8</sub>. The amounts of photomediator required, was also investigated. The reaction of methyl propiolate and cyclopentane, leading to the *E* and *Z* addition products **(38)** and **(39)**, was initially carried out with 1 equivalent of benzophenone relative to the alkyne, but further investigations showed that as little as 0.15 equivalents of benzophenone was equally effective in this reaction (**Scheme 32**). A further reduction of the amount used to 0.09 equivalents led to a much longer reaction time, but interestingly not a decrease in yield.

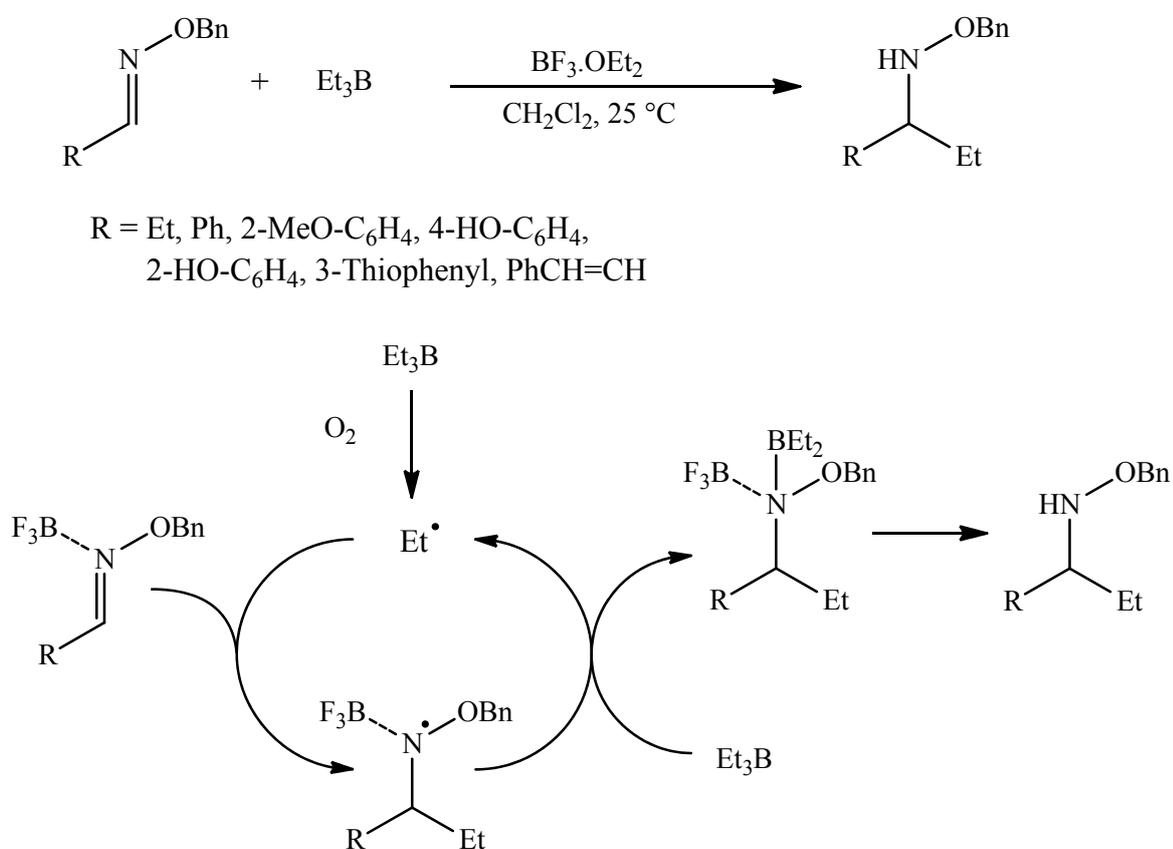


$\text{Ph}_2\text{CO}$	Time	Yield	<i>E/Z</i>
1 eq	2.75 h	86%	1/1.46
0.33 eq	3 h	92%	1/1.33
0.15 eq	3 h	95%	1/1.32
0.09 eq	102 h	91%	1/1.27

**Scheme 32**

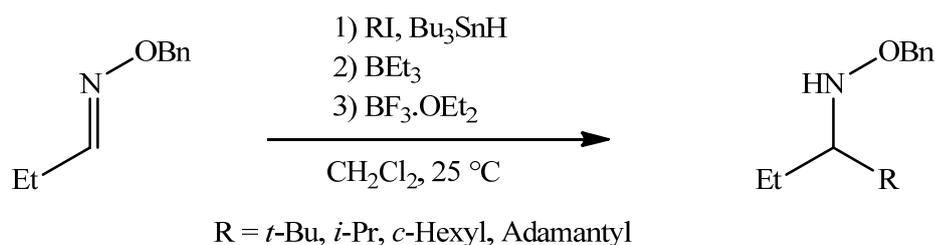
### 1.6 Thermal intermolecular radical addition to carbon nitrogen double bonds

The thermal generation of carbon radicals using reaction systems based on boron or zinc, and their addition to C=N bonds, has been reported. Naito<sup>[41]</sup>, for example, has investigated the addition of boron generated ethyl radicals to a range of aldoxime ethers (**Scheme 33**). The ethyl radical was formed by the reaction of triethylborane and oxygen and then reacted with the iminyl carbon to form a new carbon-carbon bond and an aminyl radical. This was subsequently trapped by another molecule of triethylborane forming a boron complex and releasing another ethyl radical. Hydrolysis gave the products in yields of 41 to 96%. The reactions worked particularly well in the presence of BF<sub>3</sub>.OEt which acts as a Lewis acid.



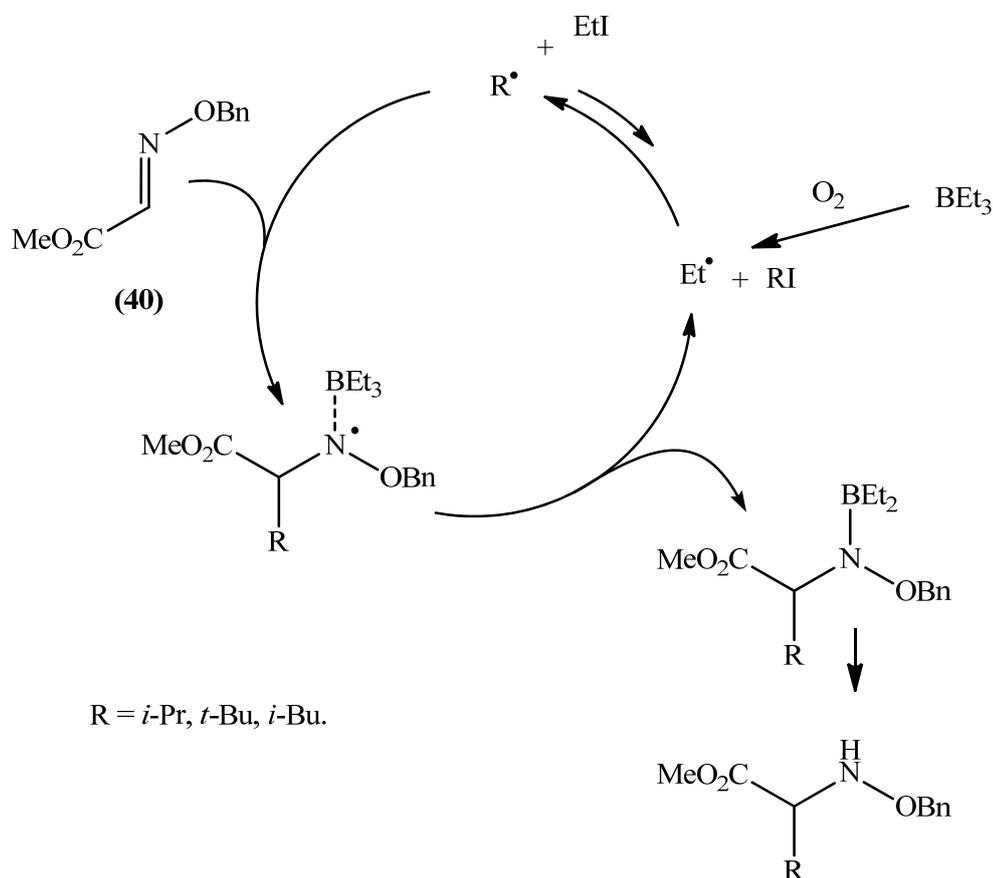
**Scheme 33**

The addition of different alkyl radicals to the oxime bond was achieved using an iodine atom-transfer process (**Scheme 33**). When an alkyl iodide, tributyltin hydride and triethylborane were used, together with BF<sub>3</sub>.OEt, the alkylated products were formed in yields from 41 to 98% (**Scheme 34**).



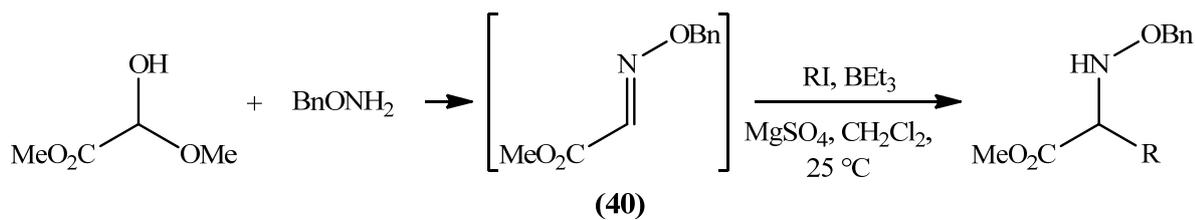
**Scheme 34**

The work was also extended to the glyoxylic oxime ether (**40**) which contains an activating electron withdrawing group<sup>[42]</sup> and so the use of BF<sub>3</sub>·OEt was not required. As before, the reaction proceeded *via* the iodine atom-transfer process (**Scheme 35**). In the absence of tributyltin hydride good reactivity was seen for the stable *i*-propyl and *t*-butyl radicals; however with the less stable methyl and primary *i*-butyl radicals, competitive ethyl radical addition occurred.



**Scheme 35**

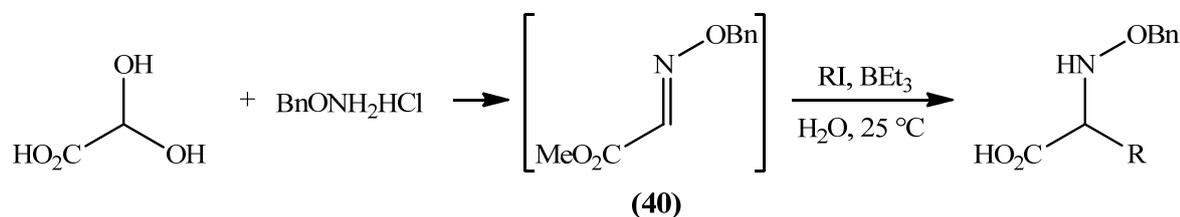
The method was subsequently used for the one pot synthesis of aliphatic  $\alpha$ -amino acid precursors with good success (**Scheme 36**)<sup>[42-43]</sup>. Thus the condensation of methyl 2-hydroxy-2-methoxyacetate and *O*-benzylhydroxylamine afforded (**40**) which on addition of triethylborane and an alkyl iodide gave the amino acid precursors in good yields (52-85%).



R = Et, *t*-Bu, *sec*-Bu, *i*-Pr, *c*-Hexyl, Adamantyl

**Scheme 36**

Further development of this system by Naito's group involved the use of water as the solvent<sup>[44]</sup>. It was shown, for example, that excellent yields (95-99%) of alkylated amino acid precursors were formed in a one pot synthesis using water as the solvent (**Scheme 37**).

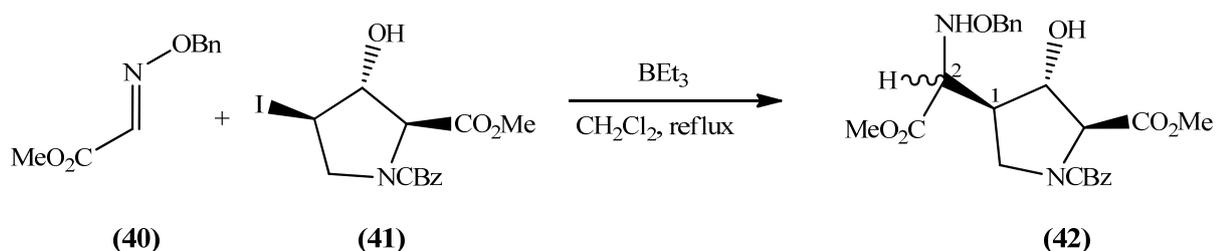


R = *t*-Bu, *sec*-Bu, *i*-Pr, *c*-Hexyl, *c*-Pentyl

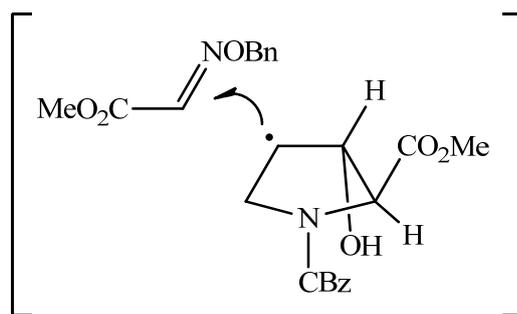
**Scheme 37**

Naito's group also extended this reaction system to more complex alkyl halides that form stabilized primary radicals<sup>[45]</sup>. Thus radicals formed from benzyl iodide and ethyl iodoacetate added to (40) in yields of 62 and 76%, respectively; the radical formed from  $\alpha$ -iodo- $\gamma$ -butyrolactone was successfully added in 46% yield. The addition of pentafluorobenzyl, trichloromethyl and perfluoropropane radicals failed as these radicals are too electrophilic.

The total synthesis of penmacric acid and its stereoisomer was undertaken by Naito<sup>[46]</sup> using the iodine atom-transfer reaction as the key step in the synthetic sequence (**Scheme 38**). The reaction of (40) with the iodoproline derivative (41) in refluxing DCM led to a 1:1 mix of C-2 epimers (42). The stereochemistry at C-1 was controlled by the adjacent hydroxyl group (**Figure 7**).

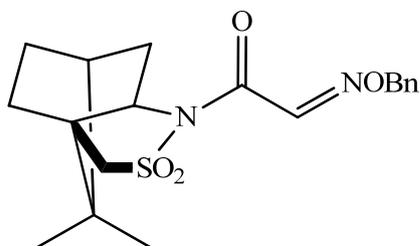


**Scheme 38**



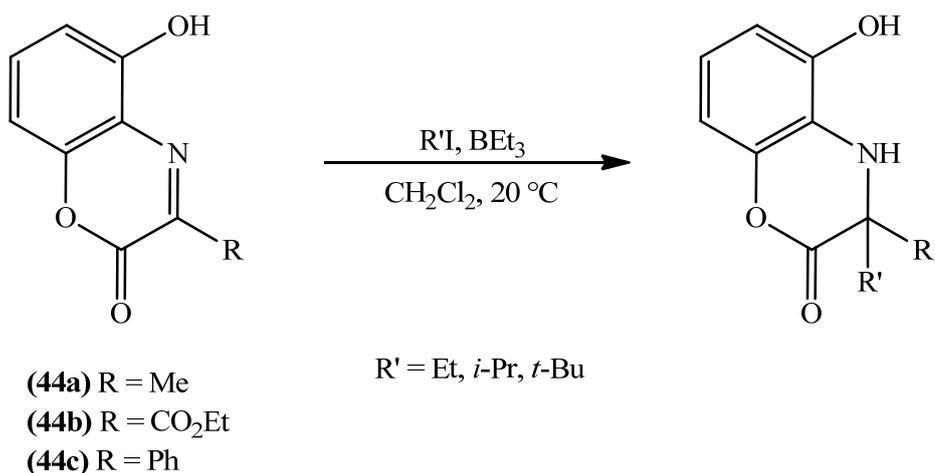
**Figure 7**

Diastereoselective intermolecular carbon radical additions to Oppolzer's camphorsultam derivative of a glyoxylic oxime ether (**43**) have also been developed by Naito's group. They showed that the asymmetric synthesis of  $\alpha$ -amino acids could be achieved using both triethylborane<sup>[47]</sup> and zinc mediated reactions<sup>[48-49]</sup> in organic or aqueous media.



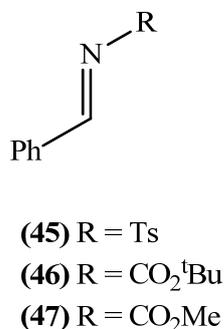
**(43)**

The intermolecular addition of carbon radicals to the iminyl carbon of ketimines provides a novel method of constructing molecules with tetrasubstituted carbons where one of the substituents is an amino group. Miyabe<sup>[11]</sup> investigated the addition of triethylborane generated radicals to a series of ketimines (**44**) (Scheme 39). The substrate (**44a**) was chosen for a number of reasons: firstly, the electron withdrawing effect of the carbonyl group activates the C=N leading to higher yields; secondly, the cyclic structure provides added stability, reducing the chance of hydrolysis of the C=N; thirdly, the aminyl radical could be stabilized by delocalization into the aromatic ring. Ethyl radical addition to (**44a**) worked well giving a yield of 89% after 5 min. The iodine atom-transfer process also worked well for *i*-Pr and *t*-Bu radicals, and when the reactions were carried out in the presence of tributyltin hydride, yields increased from 87 to 96% and from 89 to 97%, respectively, presumably due to the suppression of direct ethyl radical addition. The reaction was then extended to the ketimine (**44b**) that contained a second EWG on the iminyl carbon with yields of 83 to 94% being obtained. Tributyltin hydride was required in the *i*-propyl iodide reaction to suppress direct ethyl radical addition to the imine, however this was not necessary for the *t*-butyl iodide reaction. The reactions with ketimine (**44c**) proceeded well even with the bulky phenyl group attached, with yields of 88 to 96% being obtained.



**Scheme 39**

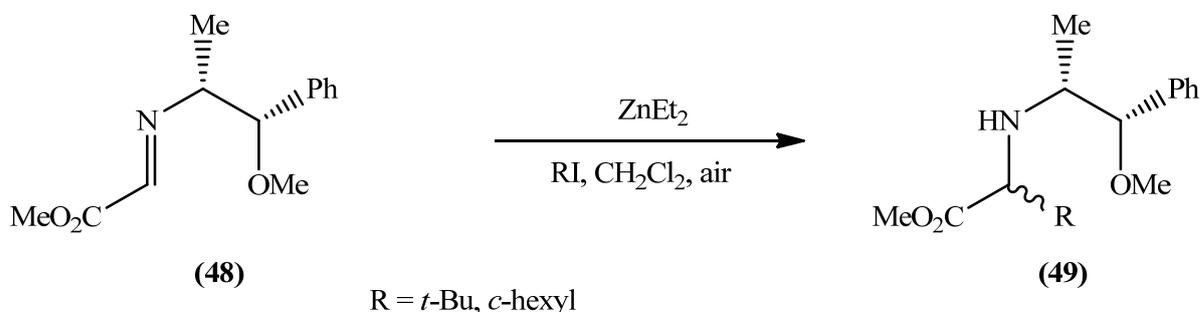
In all cases discussed so far the C=N bond has been activated by either a Lewis acid coordinating to the nitrogen, or the presence of an EWG on the carbon. In theory if the EWG was attached to the nitrogen, it should act as a better radical acceptor. In support of this concept Naito showed that radical addition to *N*-sulfonyl imine (**45**) proceeded well in yields of up to 84%<sup>[50]</sup>. However Takemoto and Miyabe found that the electronically related molecules (**46**) and (**47**) gave poorer yields, with large amounts of unreacted starting material being recovered, together with products resulting from the hydrolysis of the C=N bond<sup>[51]</sup>.



Recently Tomioka<sup>[10]</sup> studied the addition of radicals derived from iodomethyl pivalate, using the iodine atom-transfer process, to such imines. When *N*-Boc-benzaldimine (**46**) was reacted with iodomethyl pivalate and eight equivalents of triethylborane a 42% yield of addition product was obtained. A complex mixture of products was obtained when the reaction was attempted at room temperature using dimethylzinc. However when the reaction temperature was lowered to -78 °C increased yields were observed.

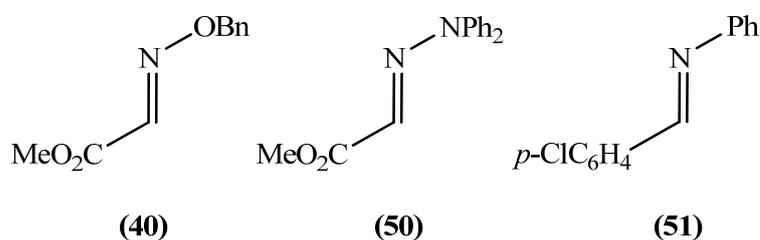
Bertrand's group investigated diethyl zinc mediated radical addition to glyoxylate imines<sup>[52]</sup>. The mechanism for these reactions follows the same path as for the triethylborane reactions (**Scheme 33**). The diethyl zinc reacts with oxygen to form an ethyl radical which can directly add to the imine bond,

or in the presence of a suitable secondary or tertiary alkyl iodide undergo an iodine atom-transfer process, leading to the more stable alkyl radical that subsequently adds to the imine. *t*-Butyl and *c*-hexyl radicals were successfully added to imine (**48**) to form the amino ester (**49**) (Scheme 40). When the temperature for the *t*-butyl iodide reaction was lowered from 20 to -78 °C, the yield increased from 39% (78:22 mixture of diastereomers) to a yield of 71% (95:5 mixture of diastereomers).



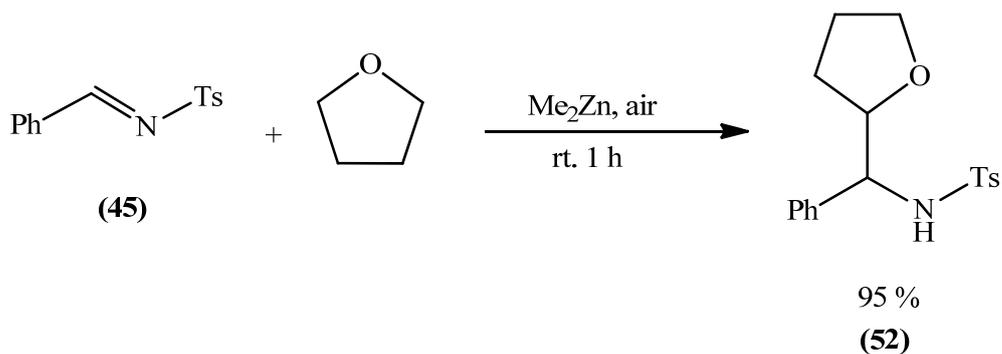
**Scheme 40**

Bertrand then extended this work to include radical acceptors such as the glyoxylic oxime ether (**40**), the hydrazone (**50**) and the aldimine (**51**)<sup>[53]</sup>. The yields and reaction times were comparable to those obtained when triethylborane was used as the radical initiator.



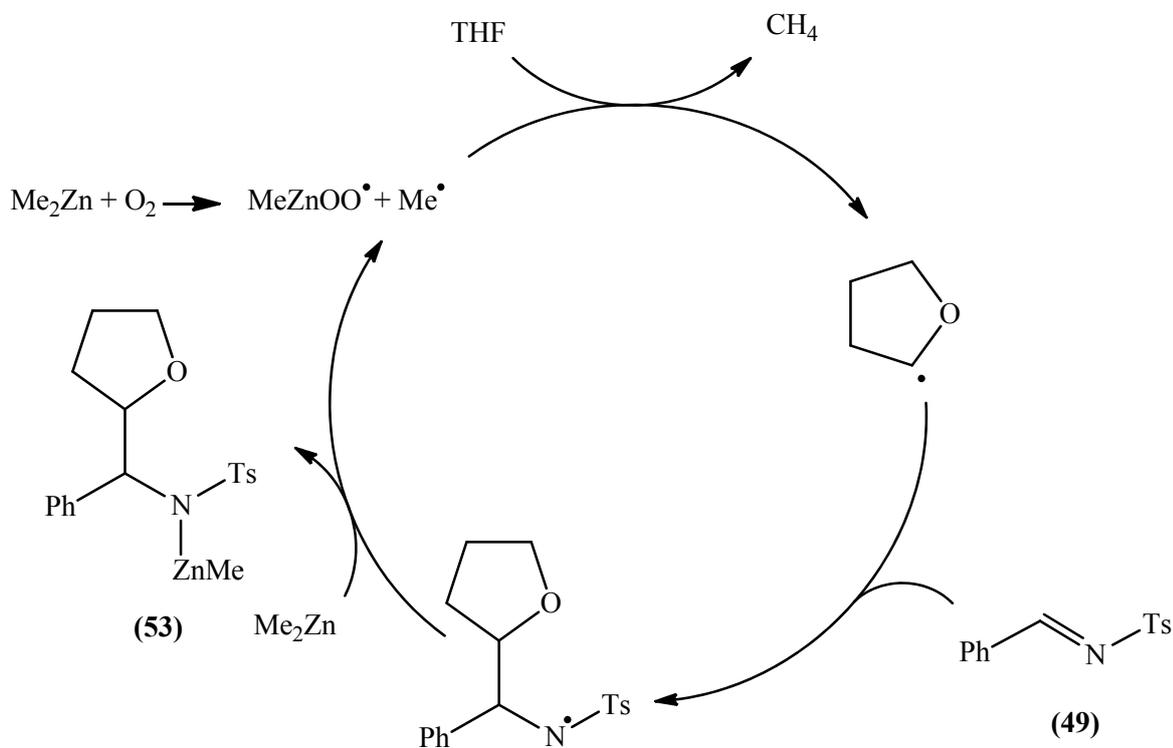
Naito's group further broadened the scope of this work to incorporate the use of zinc metal as the radical initiator, and demonstrated that zinc mediated radical addition to glyoxylic oxime ethers and hydrazones was successful in an aqueous medium<sup>[48]</sup>. The reaction involves a single electron transfer (SET) from the zinc metal as had previously been reported<sup>[50]</sup>.

Tomioka had previously carried out the addition of cyclic ethers and 1,3-dioxolane to imines (**45**) and (**47**) using dimethylzinc (Scheme 41)<sup>[9]</sup>.



**Scheme 41**

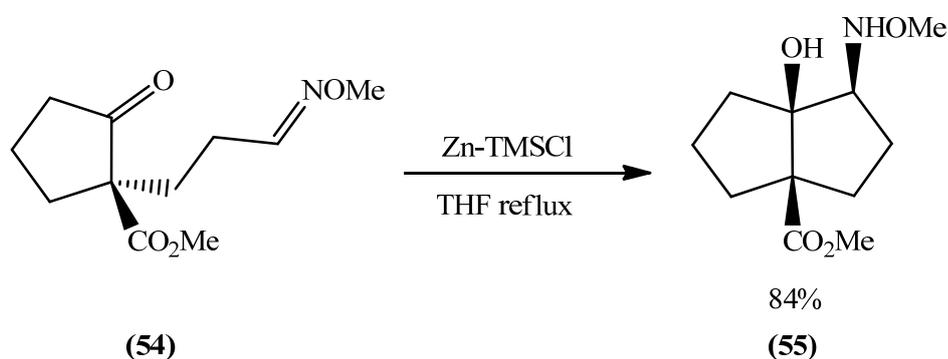
The proposed mechanism for the reaction (**Scheme 42**) involves hydrogen abstraction from the THF molecule by a methyl radical which was rapidly formed by the reaction of the dimethylzinc with molecular oxygen. The THF radical then adds to the imine (**49**) to form the aminyl radical which further reacted with dimethylzinc to form (**53**). Aqueous work up gave the observed product (**52**). Dimethylzinc was shown to be the most effective initiator for this reaction due to the instability of the methyl radical which rapidly abstracted a hydrogen atom. Hydrogen abstraction by ethyl and *i*-propyl radicals was slower which resulted in direct addition to the imine (**49**) becoming competitive with formation of the THF radical.



**Scheme 42**

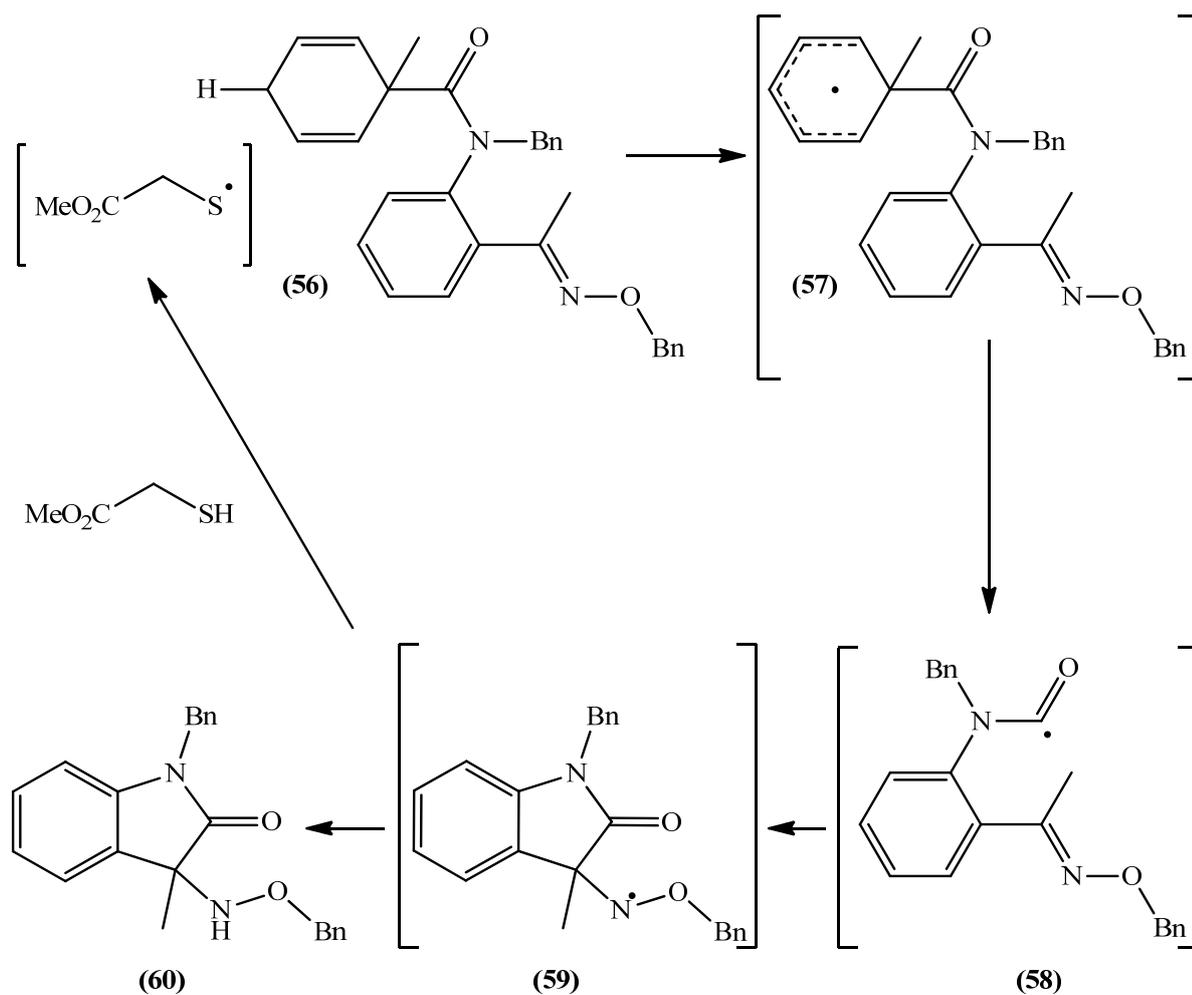
### 1.7 Thermal intramolecular radical addition to carbon nitrogen double bonds

One of the first intramolecular additions of a carbon radical to an oxime was reported by Corey and Pyne in 1983<sup>[54]</sup>. They described a method whereby radicals are generated from ketones *via* reaction with a zinc-trimethylchlorosilane reagent, and this is then followed by intramolecular cyclization. When the oxime ether (**54**) was refluxed in THF in the presence of excess zinc-TMSCl (20 equivalents and 6 equivalents, respectively) the cyclised product (**55**) was formed in 84% yield (**Scheme 43**). The proposed mechanism suggests that the reaction of the zinc-TMSCl with the ketone occurs *via* an electron transfer, with silylation then forming an  $\alpha$ -trimethylsilyloxy radical which cyclises to form a five-membered ring. H-atom abstraction from the solvent completes the reaction.



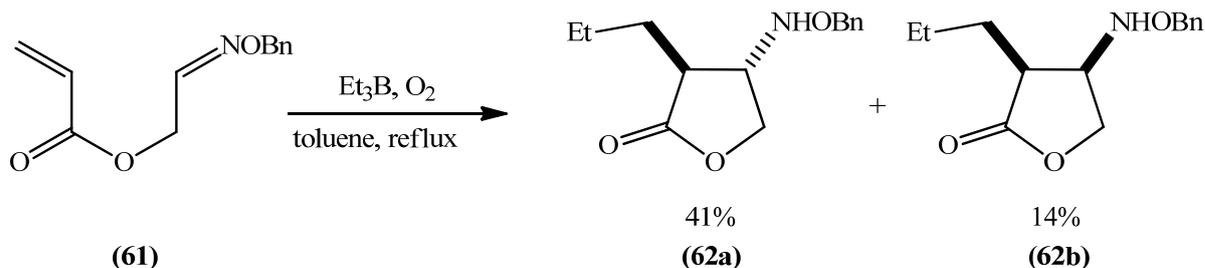
**Scheme 43**

Walton<sup>[55]</sup> showed that the lauroyl peroxide induced decomposition of (**56**) led to indolin-2-ones with a benzyloxyamine substituent in the 3-position (**Scheme 44**). The cyclization was very rapid and took place regioselectively at the carbon atom of the iminyl bond, by a 5-*exo*-trig ring closure. Thus in detail, the electrophilic sulfanyl radical, produced by the reaction of lauroyl peroxide with methyl thioglycolate, abstracts a hydrogen from the bisallylic site of (**56**) forming (**57**), from which loss of toluene gives the carbamoyl radical (**58**). This radical attacks the C=N double bond forming the alkoxyaminyl radical (**59**) which readily abstracts a hydrogen atom from methyl thioglycolate, forming the indole (**60**) and propagating the chain. The reaction gave a yield of 68% after 30 h refluxing in benzene.



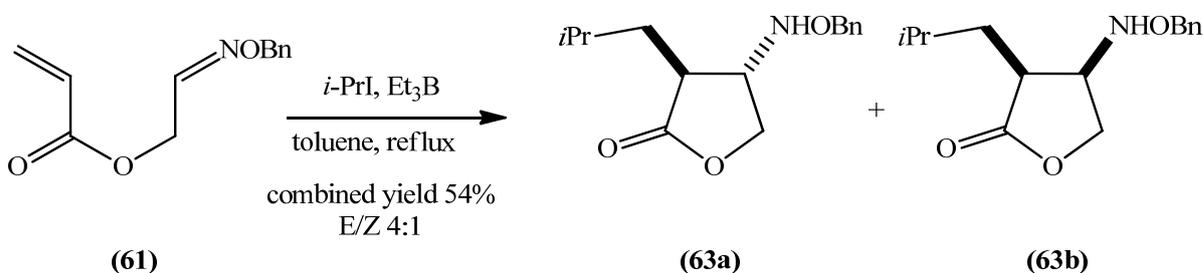
**Scheme 44**

Radical mediated cyclization of imine derivatives is an important method for the construction of various types of cyclic amines. Naito<sup>[56]</sup> investigated the tandem reaction between oxime ethers and carbonyl stabilized radicals, the reaction pathway being similar to that described above (**Scheme 33**). The nucleophilic ethyl radical, formed by the reaction of triethylborane and oxygen, attacks the electron deficient alkene in (**61**), forming a carbonyl stabilized radical which then intramolecularly attacks the oxime ether forming a lactone (**62**) (**Scheme 45**). The aminyl radical is trapped by another triethylborane molecule which is removed by hydrolysis to give the final products, (**62a**) and (**62b**). The *trans* product (**62a**) is formed preferentially due to its lower steric strain.



**Scheme 45**

When the reactions were carried out under iodine atom transfer conditions (**Scheme 35**), the reactions proceeded smoothly to give the isopropylated products (**63a**) and (**63b**) in 54% combined yield and an *E/Z* ratio of 4:1 (**Scheme 46**). It was noted that tributyltin hydride was not required to achieve good yields in these reactions<sup>[56]</sup>, and that no competitive ethyl radical addition occurred.

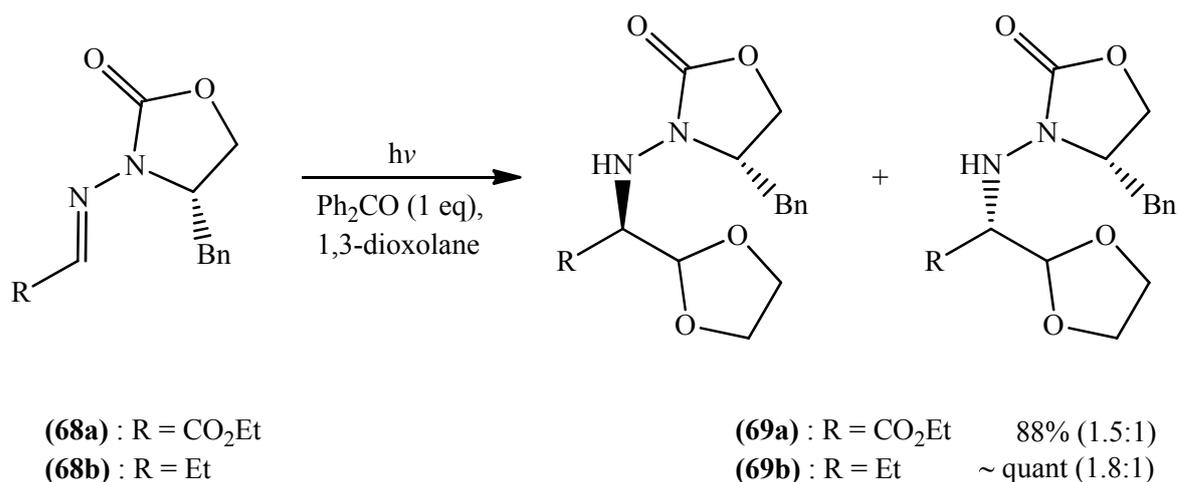


**Scheme 46**

### 1.8 Photochemical intermolecular radical addition to carbon nitrogen double bonds

In contrast to the corresponding thermal reactions discussed above, there are very few reports of the intermolecular addition of photochemically generated carbon radicals to carbon nitrogen double bonds. Alonso<sup>[57]</sup> described the first intermolecular radical addition to ketoxime ethers: when (**64a**) and (**64b**) were irradiated in 1,3-dioxolane in the presence of benzophenone, the addition products (**65a**) and (**65b**), respectively, were obtained in good yields (**Scheme 47**). When the reaction was carried out in the presence of 2-propanol the corresponding addition products were again obtained in yields of 58 and 73%, respectively.



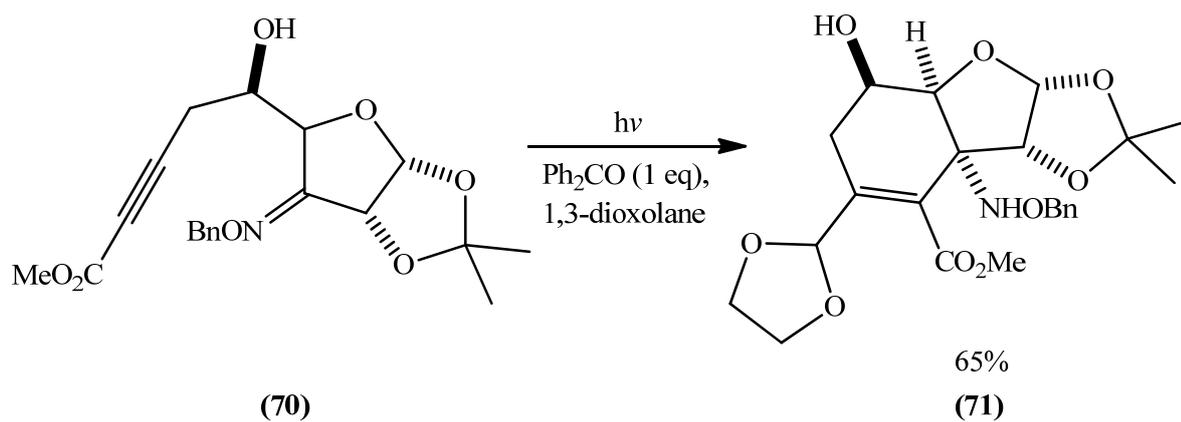


**Scheme 49**

The one pot synthesis of **(69b)** was successfully achieved, initially stirring a solution of propionaldehyde and (S)-3-amino-4-benzyl-1,3-oxazolan-2-one in 1,3-dioxolane, in the presence of catalytic amounts of *p*-TsOH, for 1 h at room temperature, and then irradiation in the presence of benzophenone and InCl<sub>3</sub> at -78 °C. This gave **(69b)** in a 99% yield and 99:1 diastereomeric ratio. It was proposed that the stereochemical outcome of the reaction resulted from the preferential addition of the dioxolanyl radical to the In-coordinated *N*-acyl hydrazone on the face opposite to the benzyl group.

### 1.9 Photochemical intramolecular radical addition to carbon nitrogen double bonds

The intramolecular tandem radical addition/cyclization of acetylenic ketimines was also investigated by Alonso<sup>[59]</sup>. The addition of a thermally generated electrophilic phenylthiyl radical to substrate **(70)** led to the formation of a mixture of products resulting from 5-*exo*-trig and 6-*exo*-trig cyclization involving the mixture of regioisomeric alkenyl radicals initially formed and the imine. To assess the effect of the nature of the initial radical, the phenylthiyl radical was changed to the nucleophilic dioxolan-2-yl radical. Thus, irradiation of a solution of **(70)** in 1,3-dioxolane, in the presence of benzophenone, gave the product **(71)** in 65% yield as a result of a 6-*exo*-trig cyclization process (**Scheme 50**). The formation of the 6-*exo*-trig product only in this reaction is due to the fact that the addition of nucleophilic radicals to alkynes bearing ester groups occurs only at the β-carbon.



**Scheme 50**

### 1.10 Project outline

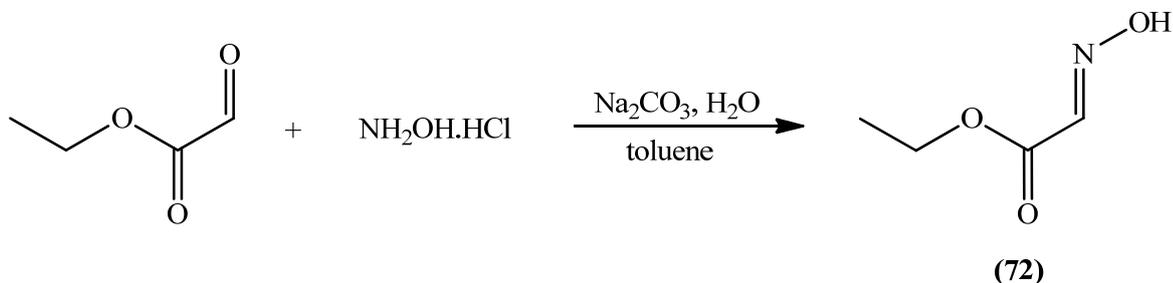
The addition of photochemically generated carbon radicals to carbon nitrogen double bonds has not been extensively studied<sup>[57-58]</sup>. In view of this, the work described in this section of this thesis was designed to explore the synthetic potential of the photomediated addition of a range of hydrogen donors to the carbon-nitrogen double bond in a series of oximes and oxime ethers.

*Chapter 2*  
*Results and Discussion*

## 2.0 Results

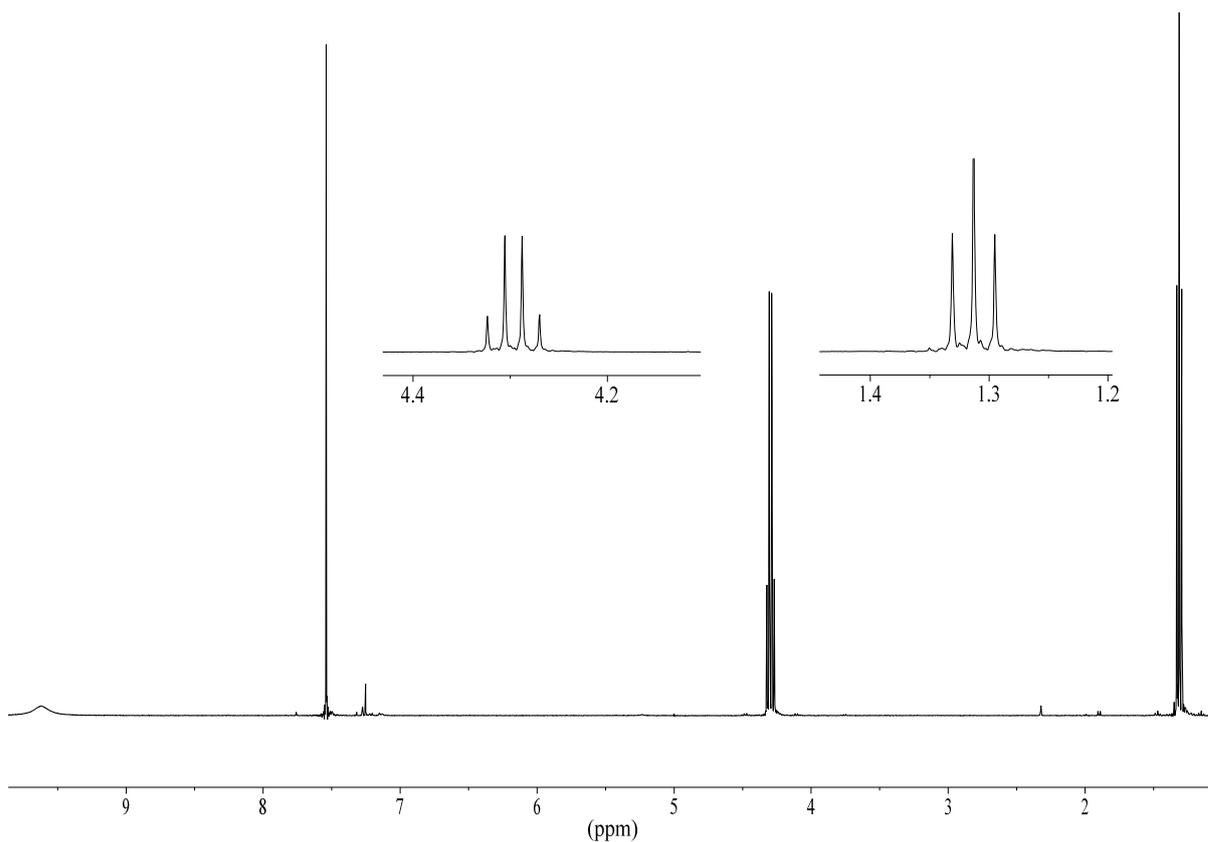
### 2.1 Preparation of oximes

#### 2.1.1 Synthesis of ethyl (2*E*)-(hydroxyimino)acetate (**72**)



**Scheme 51**

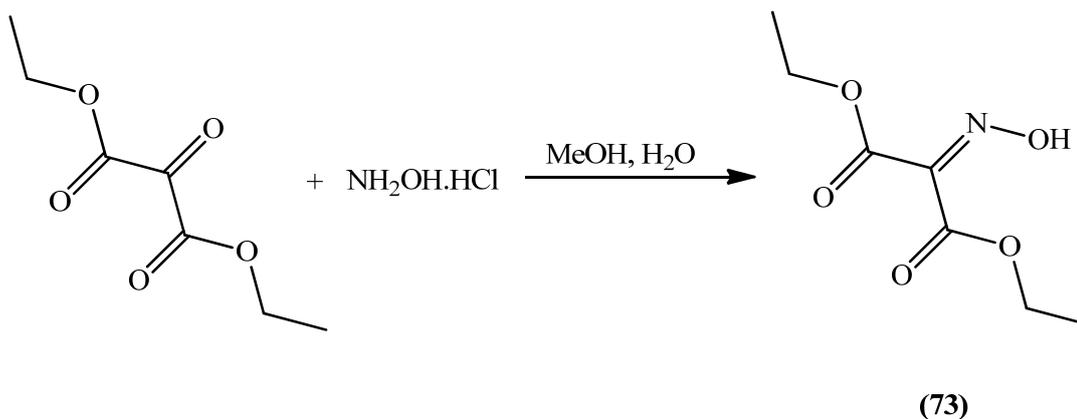
A procedure by Ciufolini<sup>[60]</sup> was used to synthesise ethyl (2*E*)-(hydroxyimino)acetate (**72**). This involved the reaction of hydroxylamine hydrochloride and ethyl glyoxylate, in the presence of  $\text{Na}_2\text{CO}_3$ , in a water/toluene mixture. Normal work-up and chromatography gave ethyl (2*E*)-(hydroxyimino)acetate (**72**) in 50% yield. Spectroscopic data were consistent with those reported<sup>[60]</sup>. The IR spectrum showed the expected OH stretching at  $3331\text{ cm}^{-1}$  along with the carbonyl, iminyl and CO bands at  $1718$ ,  $1623$  and  $1206\text{ cm}^{-1}$ , respectively. The  $^1\text{H-NMR}$  spectrum (**Figure 8**) showed a triplet ( $J_{vic} = 7.1\text{ Hz}$ ) and quartet ( $J_{vic} = 7.1\text{ Hz}$ ) at  $\delta 1.31$  and  $4.30$ , respectively, for the ethyl group, a singlet at  $\delta 7.54$  for the CH and a broad singlet at  $\delta 9.54$  for the OH proton.



**Figure 8**  $^1\text{H-NMR}$  spectrum of (72)

The  $^{13}\text{C-NMR}$  spectrum had four signals: signals at 162.6 and 131.9 ppm corresponded to the carbonyl and iminyl carbons, respectively, with the methylene carbon resonating at 62.0 ppm and the methyl carbon at 14.1 ppm.

### 2.1.2 Synthesis of diethyl (hydroxyimino)malonate (73)

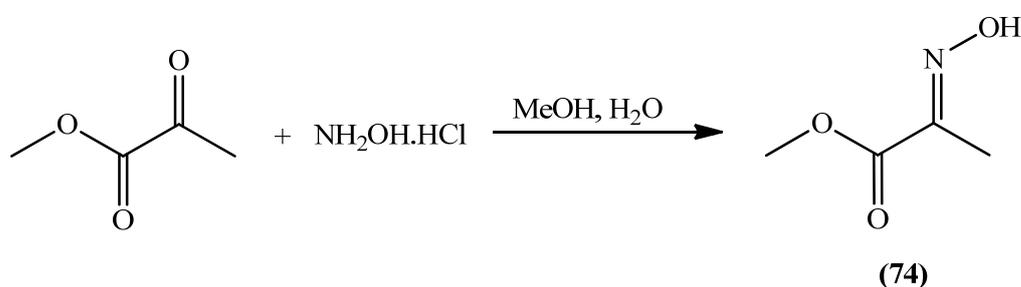


**Scheme 52**

A modified version of a patented procedure from Amersham International<sup>[61]</sup> was used to synthesise diethyl (hydroxyimino)malonate (73). Diethyl ketomalonate in methanol was added to a stirred

aqueous solution of hydroxylamine hydrochloride and the stirring was continued in the dark for 19 h. The product, diethyl (hydroxyimino)malonate (**73**) was isolated in 66% yield after standard workup and column chromatography. Spectroscopic data for the product were consistent with those in the literature<sup>[62]</sup>. The IR spectrum had an OH band at 3345  $\text{cm}^{-1}$ , a carbonyl band at 1721  $\text{cm}^{-1}$  and an iminyl band at 1632  $\text{cm}^{-1}$ , along with the typical CO bands at 1255 and 1091  $\text{cm}^{-1}$ . Analysis of the  $^1\text{H}$ -NMR spectrum showed overlapping multiplets at  $\delta$  1.28-1.38 and 4.31-4.41 due to the ethyl groups and a broad singlet at  $\delta$  10.37 for the OH proton. The  $^{13}\text{C}$ -NMR spectrum had signals at 160.6 and 160.1 ppm due to the carbonyl carbons, signals at 62.8, 62.7, 14.1 and 14.0 ppm for the ethyl groups, and a signal at 144.3 ppm for the iminyl carbon.

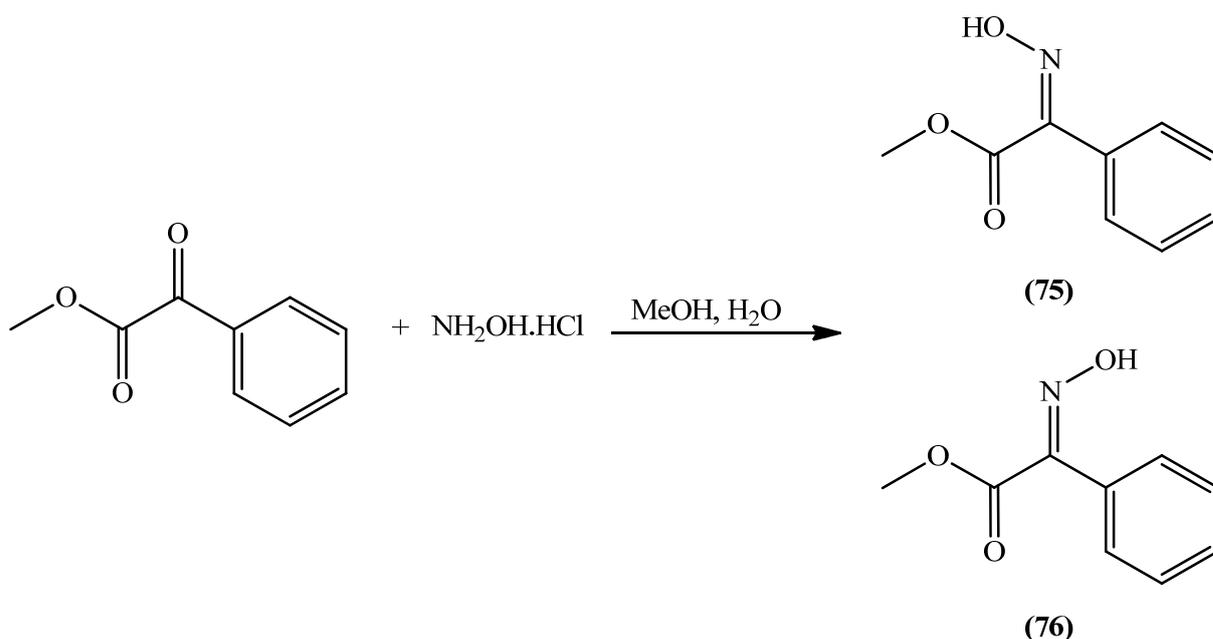
### 2.1.3 Synthesis of methyl (2E)-2-(hydroxyimino)propanoate (**74**)



**Scheme 53**

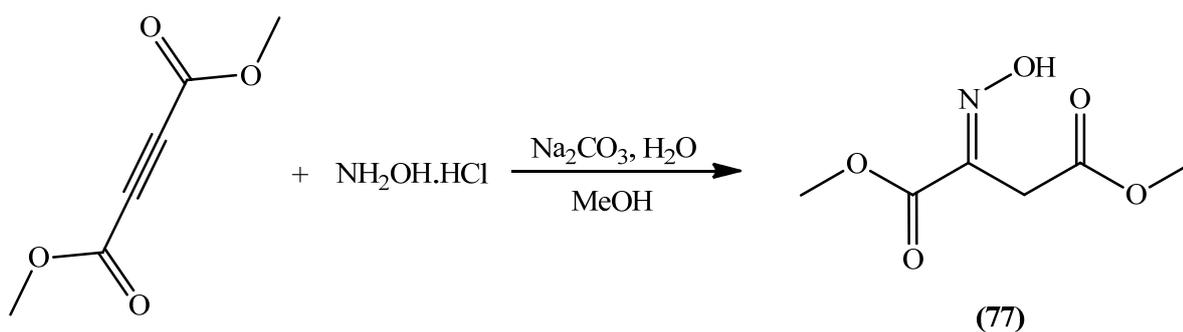
Methyl pyruvate and hydroxylamine hydrochloride were reacted and the product, methyl (2E)-2-(hydroxyimino)propanoate (**74**), isolated, as before (**Section 2.1.2**). This procedure gave methyl (2E)-2-(hydroxyimino)propanoate (**74**) as a white solid, m.p. 72-73 °C, in 76% yield, the spectroscopic data and melting point for which were consistent with those in the literature<sup>[63]</sup>. The IR spectrum showed the expected OH, carbonyl and iminyl bands at 3219, 1720 and 1638  $\text{cm}^{-1}$ , respectively, together with CO bands at 1196 and 1157  $\text{cm}^{-1}$ . In the  $^1\text{H}$ -NMR spectrum singlets at  $\delta$  3.84 and 2.10 corresponded to the methoxy and methyl protons, respectively, and the OH proton appeared at  $\delta$  9.95 as a broad singlet. In the  $^{13}\text{C}$ -NMR spectrum the carbonyl and iminyl carbons resonated at 164.2 and 149.5 ppm, respectively, and the methoxy and methyl carbons appeared at 52.9 and 10.6 ppm, respectively.

#### 2.1.4 Synthesis of (*Z*) and (*E*) methyl 2-(hydroxyimino)(phenyl)acetate, (**75**) and (**76**)

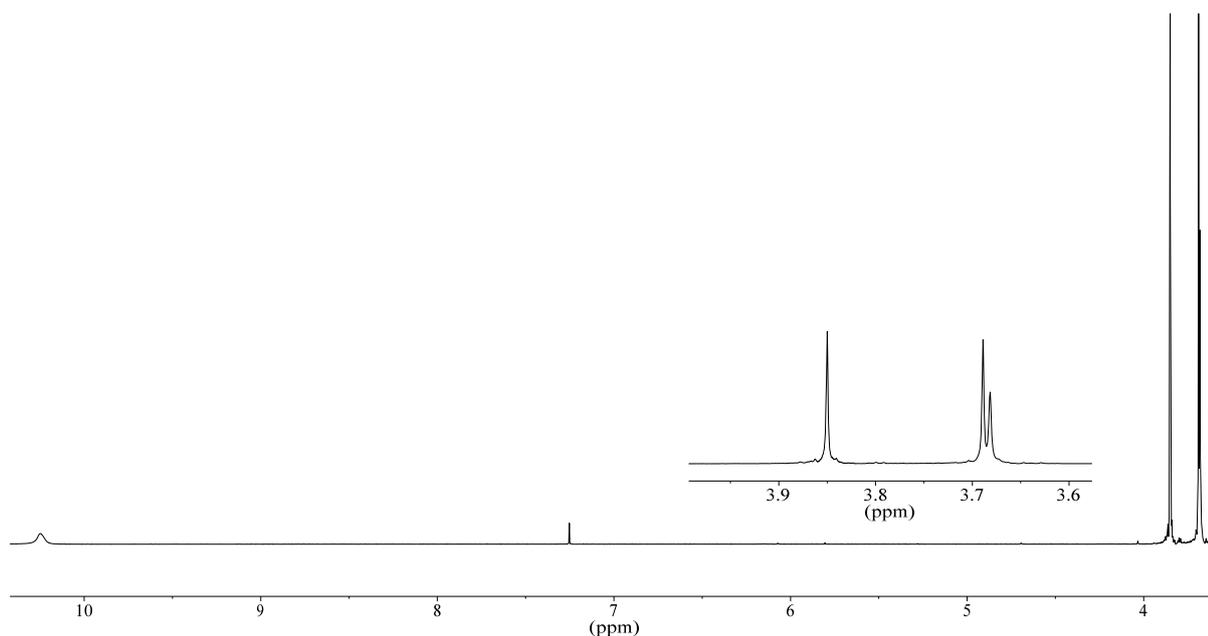


Methyl benzoylformate and hydroxylamine hydrochloride were reacted and the products isolated as before (**Section 2.1.2**), giving a mixture of both *cis* and *trans* (*Z/E*:45/55) methyl (2)-(hydroxyimino)(phenyl)acetate, (**75**) and (**76**), in a total yield of 90%. The spectroscopic data and melting points for both isomers were in line with those in the literature<sup>[64]</sup>. Methyl (2*Z*)-(hydroxyimino)(phenyl)acetate (**75**) was first to elute off the column as a result of intramolecular hydrogen bonding which results in less interaction with the silica compared to the *trans* isomer, methyl (2*E*)-(hydroxyimino)(phenyl)acetate (**76**). The IR spectrum of (**75**) showed OH and carbonyl bands at 3401 and 1730 cm<sup>-1</sup>, and bands at 1217 and 1040 cm<sup>-1</sup> for its CO bonds. The two bands at 719 and 689 cm<sup>-1</sup> were characteristic of a monosubstituted aromatic ring. In the <sup>1</sup>H-NMR spectrum the methoxy protons appeared as a singlet at  $\delta$  3.96 and the aromatic protons as overlapping multiplets at  $\delta$  7.36-7.45 and  $\delta$  7.53-7.57; the OH proton appeared at  $\delta$  9.10. The <sup>13</sup>C-NMR spectrum was as expected with the carbonyl and iminyl carbons resonating at 164.2 and 151.8 ppm, respectively. The aromatic carbons appeared at 130.7, 128.9, 126.5 and 130.1 ppm and the methoxy carbon at 52.7 ppm. The IR, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra for the oxime (**76**) were similar to those for (**75**). Bands at 3211 cm<sup>-1</sup>, at 1732 cm<sup>-1</sup>, and at 1195 and 1052 cm<sup>-1</sup> in the IR spectrum corresponded to the OH, carbonyl and CO functionalities, respectively. The methoxy protons resonated as a singlet at  $\delta$  3.87 and the aromatic protons appeared as overlapping multiplets at  $\delta$  7.42-7.52. The OH proton appeared as a broad singlet at  $\delta$  9.54. The <sup>13</sup>C-NMR spectrum showed signals for the carbonyl and iminyl carbons at 163.8 and 149.7 ppm, respectively; the aromatic carbons appeared at 130.0, 129.3, 128.2 and 128.5 ppm, and the methoxy carbon at 53.1 ppm.

### 2.1.5 Synthesis of 1,4-dimethyl (2E)-2-(hydroxyimino)butanedioate (77)



The procedure of Mitani<sup>[65]</sup> was used to synthesise 1,4-dimethyl (2E)-2-(hydroxyimino)butanedioate (**77**). An aqueous solution of hydroxylamine hydrochloride was added to a solution of dimethyl acetylenedicarboxylate in methanol. Aqueous sodium carbonate was then added at 0 °C and the solution was stirred for 2 h. The product was isolated and chromatographed giving (**77**) in 82% yield. Spectroscopic data were consistent with those in the literature<sup>[65]</sup>. The IR spectrum showed characteristic bands at 3324, 1718 and 1638 cm<sup>-1</sup> for the OH, carbonyl and iminyl groups, respectively, along with bands at 1200 and 1128 cm<sup>-1</sup> for the CO bonds. The <sup>1</sup>H-NMR spectrum (**Figure 9**) had sharp singlets at  $\delta$  3.69 and 3.85 which corresponded to the two methoxy groups, and at  $\delta$  3.68 for the methylene protons. There was also a broad singlet at  $\delta$  10.24 for the OH proton.



**Figure 9** <sup>1</sup>H-NMR spectrum of (**77**)

The <sup>13</sup>C-NMR spectrum had carbonyl signals at 168.5 and 163.3 ppm, an iminyl carbon signal at 145.7 ppm, two methoxy carbon signals at 53.0 and 52.4 ppm, and finally a signal at 30.2 ppm, corresponding to the methylene carbon.

Table 3 NMR data for oximes

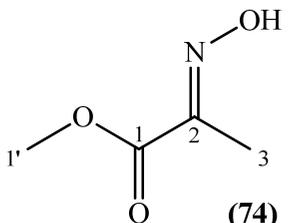
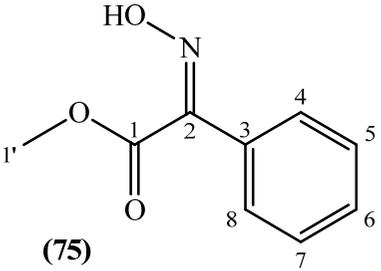
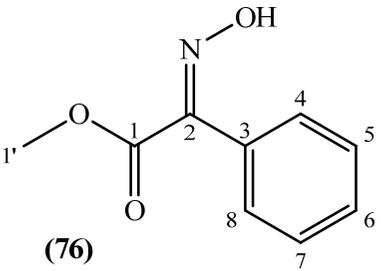
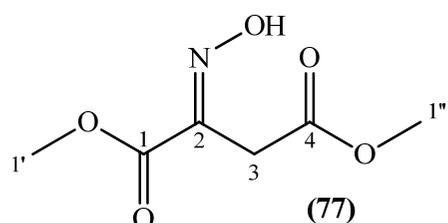
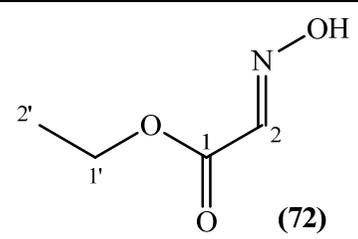
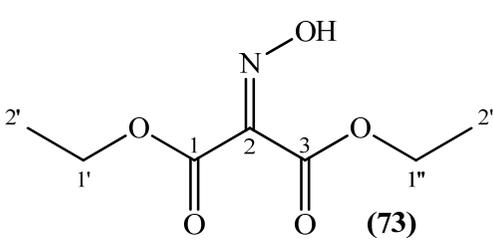
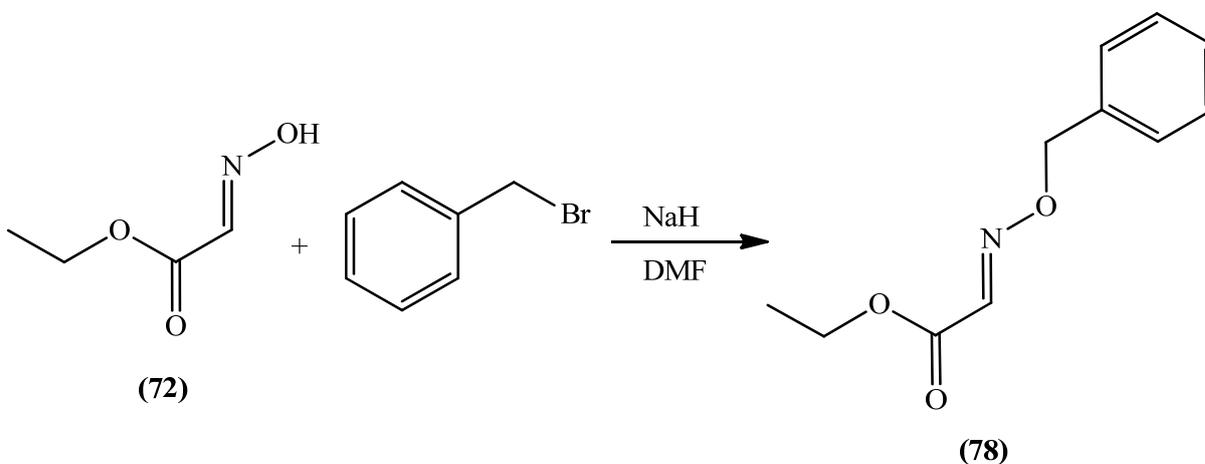
	<sup>1</sup> H-NMR data (δ)			<sup>13</sup> C-NMR data (ppm)			
	OH	H-1'	Other signals	C-2	C-1	C-1'	Other signals
 <p>(74)</p>	9.95 (br s)	3.86 (s)	H-3: 2.10 (s)	149.5	164.2	52.9	C-3: 10.6
 <p>(75)</p>	9.10 (br s)	3.96 (s)	Ar-H: 7.36-7.45 and 7.53-7.57 (overlapping ms)	151.8	164.2	52.7	C-3: 130.1 Ar-CH: 130.7, 128.9 and 126.5
 <p>(76)</p>	9.54 (br s)	3.87 (s)	Ar-H: 7.42-7.52 (overlapping ms)	149.7	163.8	53.1	C-3: 128.5, Ar-CH: 130.0, 129.3 and 128.2

Table 3 (contd.) NMR data for oximes

	<sup>1</sup> H-NMR data (δ)			<sup>13</sup> C-NMR data (ppm)				
	OH	H-1'	Other signals	C-2	C-1	C-1'	Other signals	
 <p>(77)</p>	10.24 (br s)	3.69 (s)	<b>H-3:</b> 3.68 (s), <b>H-1'':</b> 3.85 (s)	145.7	163.3	52.4	<b>C-3:</b> 30.2, <b>C-4:</b> 168.5, <b>C-1'':</b> 53.0.	
 <p>(72)</p>	9.64 (br s)	4.30 (q) <i>J</i> = 7.1 Hz	1.31(t) <i>J</i> = 7.1 Hz	7.54 (s)	141.9	162.6	62.0	14.1
 <p>(73)</p>	10.37 (br s)	4.31-4.41 (ms)	1.28-1.38 (ms)	144.3	160.1/160.6	62.7/62.8	14.0/14.1	

## 2.2 Benzylation of oximes

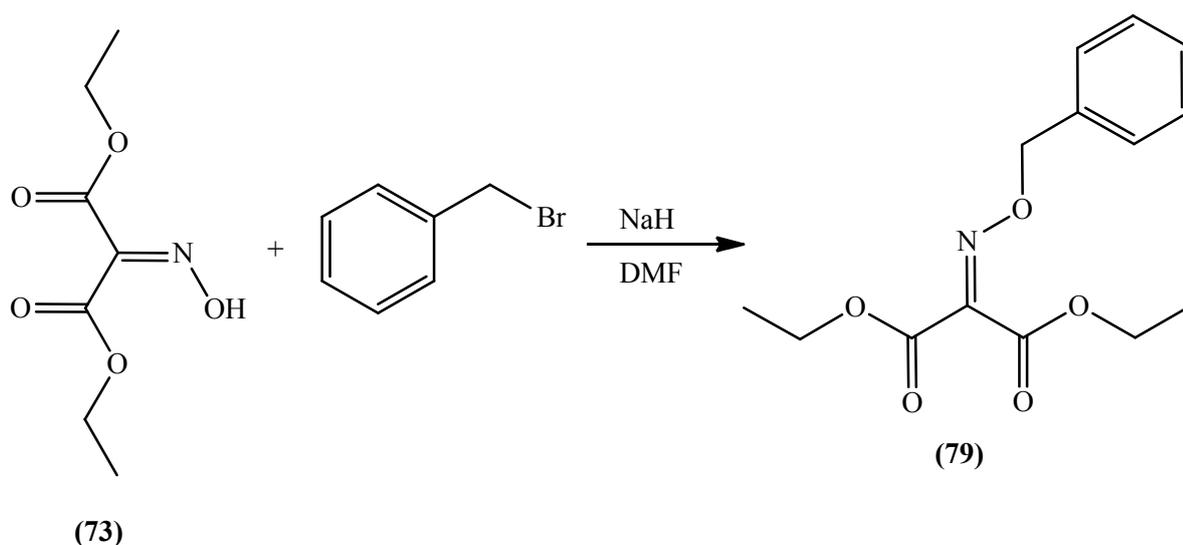
### 2.2.1 Benzylation of ethyl (2E)-2-(hydroxyimino)acetate (72)



Scheme 56

A modified version of the procedure developed by Itsuno<sup>[66]</sup> was used to benzylate the oxime. Sodium hydride and benzyl bromide were added to a stirred solution of (72) in DMF, and the mixture was stirred overnight at 0 °C. The product, ethyl (2E)-[(benzyloxy)imino]acetate (78), was obtained after standard extraction and chromatography in good yield (83%). Spectroscopic data were consistent with those in the literature<sup>[67]</sup>. The IR spectrum had two bands in the carbonyl region at 1740 and 1717 cm<sup>-1</sup> possibly due to contributions from both the *cisoid* and *transoid* conformations of the unsaturated imine. There were also bands at 1598 cm<sup>-1</sup>, and at 1264 and 1194 cm<sup>-1</sup> due to the iminyl and CO groups, respectively. Bands for the monosubstituted aromatic ring appeared at 730 and 696 cm<sup>-1</sup>. The <sup>1</sup>H-NMR spectrum had the expected triplet ( $J_{vic} = 7.1$  Hz) and quartet ( $J_{vic} = 7.1$  Hz) at  $\delta$  1.33 and  $\delta$  4.32, respectively, which corresponded to the ethyl portion of the molecule. The aldiminyl hydrogen resonated at  $\delta$  7.45 as a singlet. The benzylic methylene group appeared as a singlet at  $\delta$  5.29 and the aromatic protons appeared as a series of multiplets at  $\delta$  7.30-7.37. The <sup>13</sup>C-NMR spectrum had signals at 162.1 and 141.3 ppm, which corresponded to the carbonyl and iminyl carbons, respectively. The aromatic, benzylic methylene and ethyl carbons, resonated in their expected positions (Table 4).

### 2.2.2 Benzylation of diethyl (hydroxyimino)malonate (73)



**Scheme 57**

The procedure described above (Section 2.2.1) was utilized to prepare diethyl [(benzyloxy)imino]malonate (79). After chromatography the product was obtained as a clear oil in 67% yield. The IR spectrum contained carbonyl bands at 1743 and 1718  $\text{cm}^{-1}$ , and an iminyl band at 1605  $\text{cm}^{-1}$ , along with the usual CO and aromatic bands. The  $^1\text{H-NMR}$  spectrum (Figure 10) had triplets at  $\delta$  1.30 and 1.32 ( $J_{vic} = 7.1$  Hz) and quartets at  $\delta$  4.34 and 4.33 ( $J_{vic} = 7.1$  Hz) for the ethoxy groups. The methylene and aromatic protons of the benzyl group gave the expected signals (Table 4). The  $^{13}\text{C-NMR}$  spectrum had two signals at 160.6 and 159.7 ppm which corresponded to the carbonyl carbons, and a signal at 144.3 ppm for the iminyl carbon. The ethyl groups gave the expected signals at 62.6 and 62.3 ppm for the methylene carbons, and at 14.1 and 14.2 ppm for the methyl carbons of the ethyl groups. The benzyl group again gave diagnostic signals in the aromatic region, and at 78.8 ppm for the benzylic methylene carbon (Table 4).

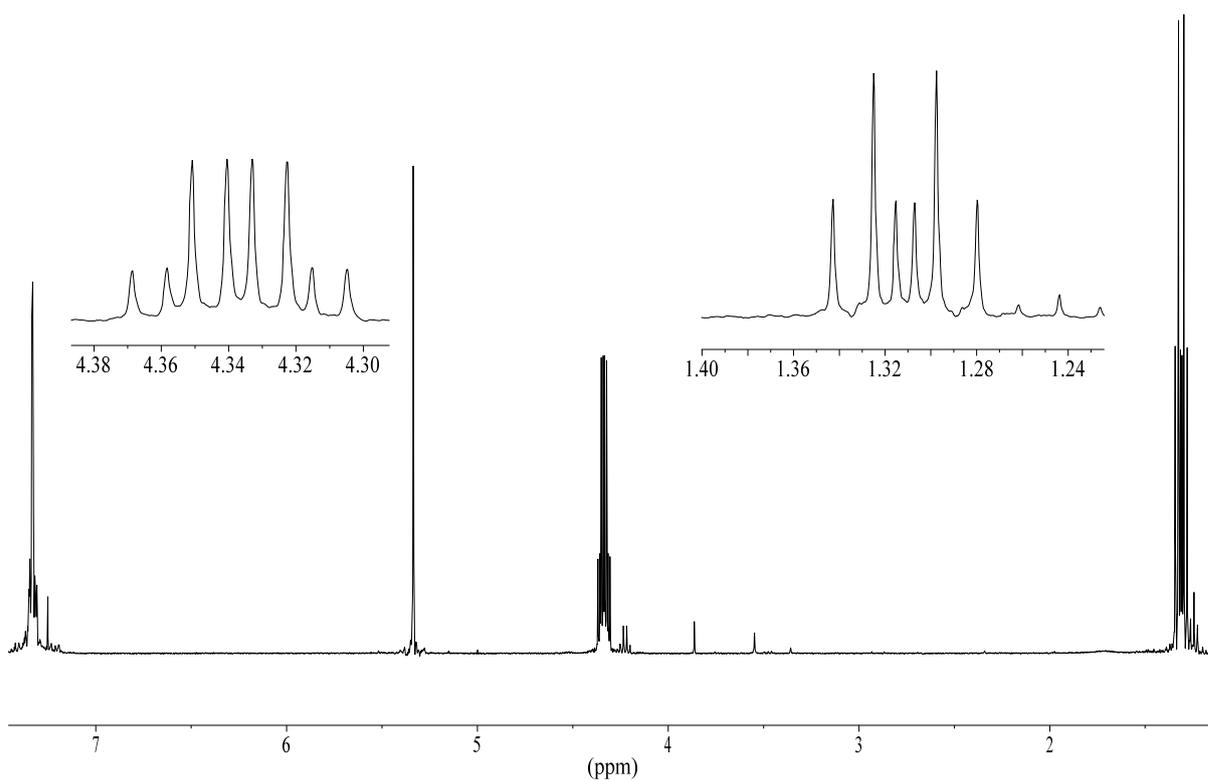
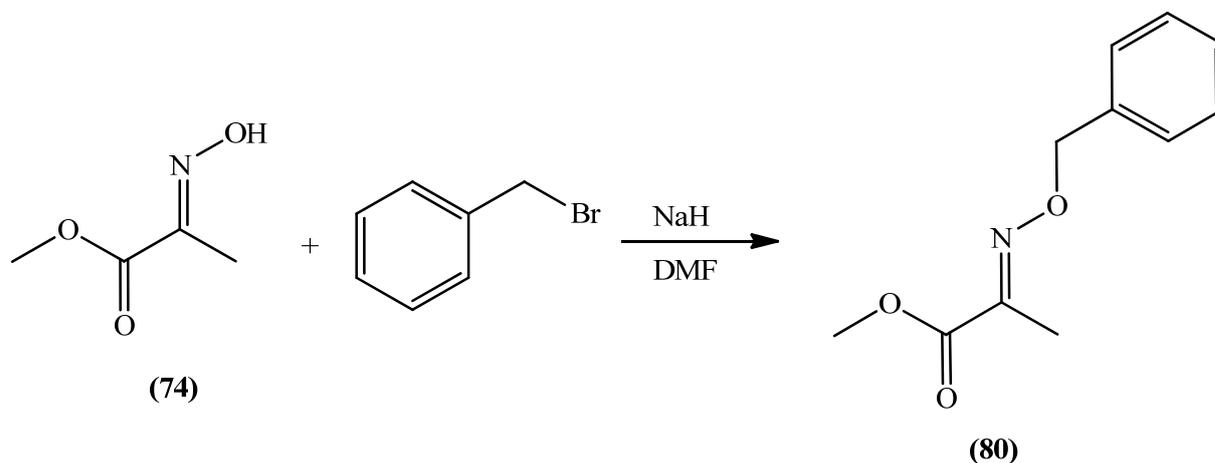


Figure 10  $^1\text{H-NMR}$  spectrum of (79)

### 2.2.3 Benzylation of methyl (2E)-2-(hydroxyimino)propanoate (74)

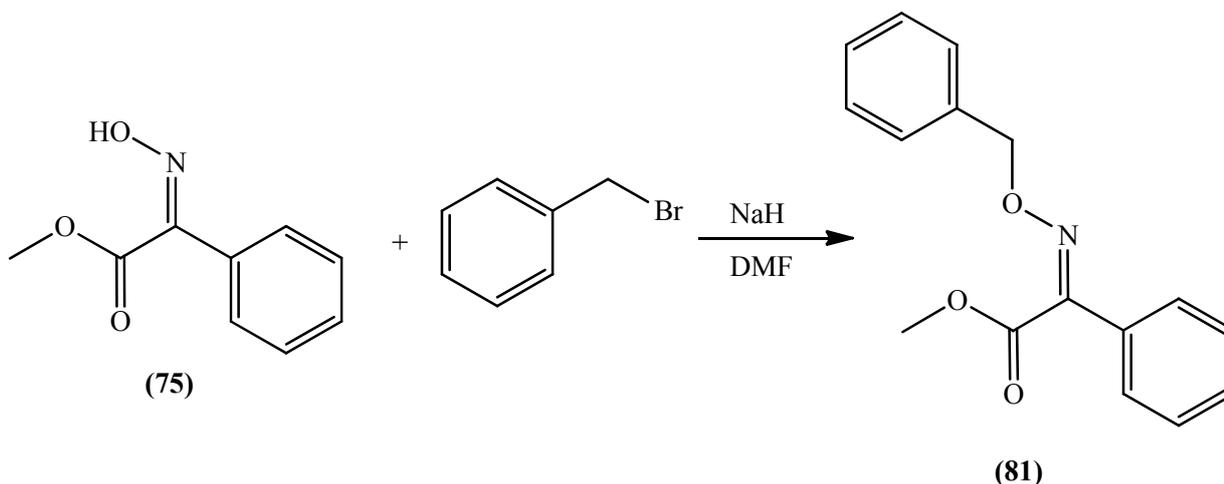


Scheme 58

The benzylation of (74) was carried out as described before (Section 2.2.1) (Scheme 58). The product, methyl (2E)-2-[(benzyloxy)imino]propanoate (80) was obtained as a clear oil in 80% yield and its spectroscopic data were in accordance with those previously reported<sup>[65]</sup>. The IR spectrum had bands indicative of a carbonyl group (1722  $\text{cm}^{-1}$ ), iminyl group (1613  $\text{cm}^{-1}$ ), CO group (1196 and 1151  $\text{cm}^{-1}$ ), and a monosubstituted aromatic ring (718 and 698  $\text{cm}^{-1}$ ). The  $^1\text{H-NMR}$  spectrum had two singlets at  $\delta$

2.09 and 3.85 for the methyl and methoxy groups, respectively, together with another singlet at  $\delta$  5.30 for the methylene group. The aromatic signals were as expected (**Table 4**). The  $^{13}\text{C}$ -NMR spectrum had carbonyl and iminyl signals at 164.4 and 149.4 ppm, respectively, and a methylene signal at 77.7 ppm. The rest of the  $^{13}\text{C}$ -NMR data were as expected (**Table 4**) and confirm the structure.

#### 2.2.4 Benzylation of methyl (2Z)-2-(hydroxyimino)(phenyl)acetate (75)



Scheme 59

The benzylation of methyl (2Z)-2-(hydroxyimino)(phenyl)acetate (**75**) was carried out using the standard procedure (**Section 2.2.1**). The product, methyl (2Z)-[(benzyloxy)imino](phenyl)acetate (**81**), was obtained as a clear oil in 33% yield after chromatography. The IR spectrum is similar to that obtained for (**82**), with carbonyl and iminyl bands at 1738 and 1605  $\text{cm}^{-1}$ , respectively. In the  $^1\text{H}$ -NMR spectrum (**Figure 11**), there were slight variations relative to those in the spectrum of (**82**), in the positions of the methyl and methylene signals with the former resonating at  $\delta$  3.95 and the latter at  $\delta$  5.30. The aromatic signals was also slightly more spread out compared to (**82**) (**Table 4**). The  $^{13}\text{C}$ -NMR spectrum was as expected (**Table 4**) with slight variations in the position of signals relative to those in the spectrum of the *trans* isomer (**82**).

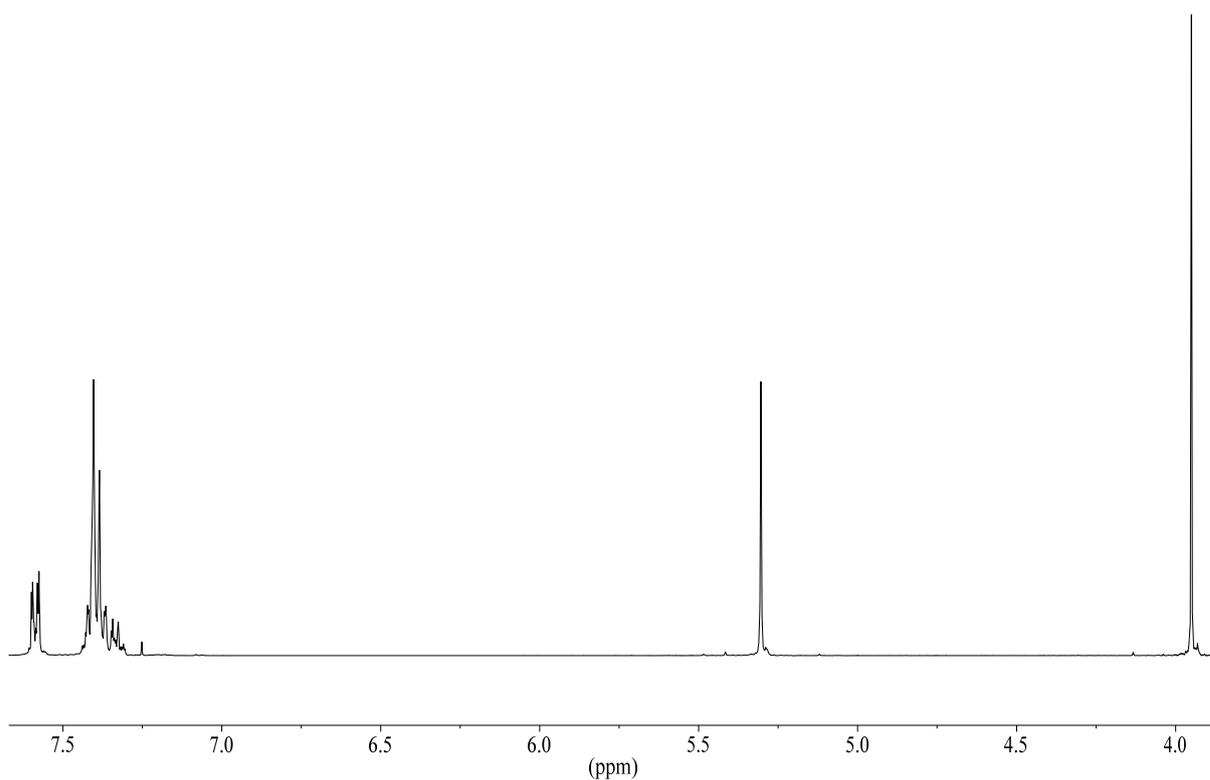
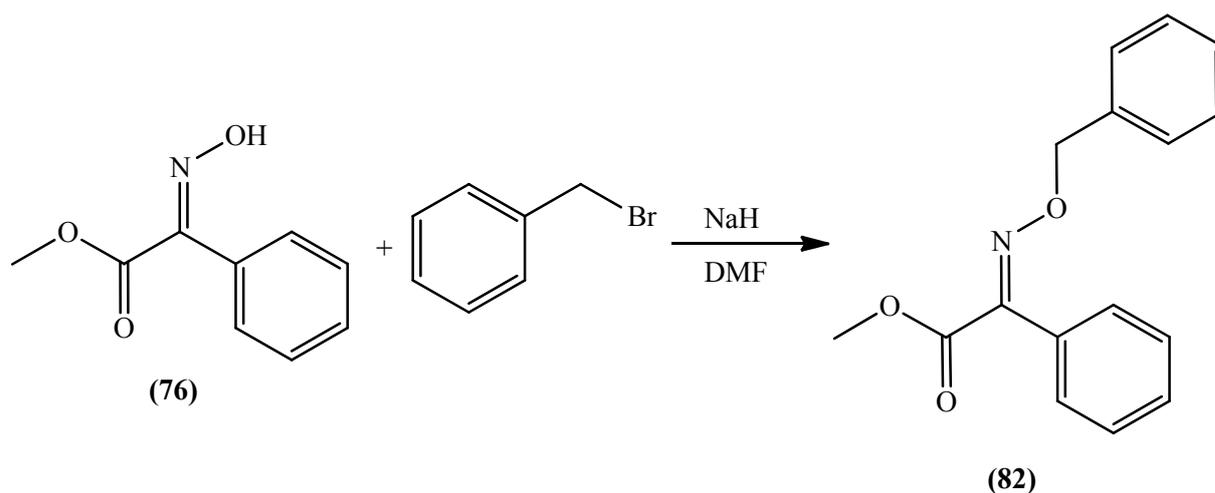


Figure 11  $^1\text{H-NMR}$  spectrum of (81)

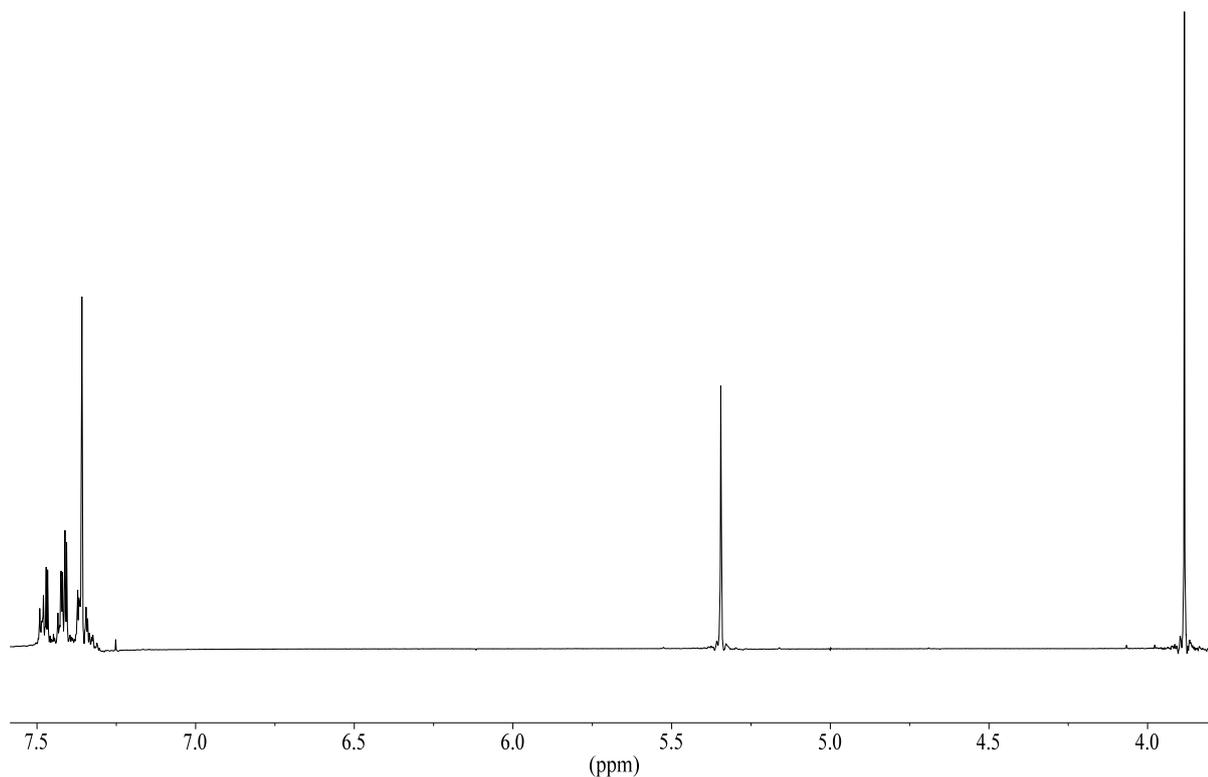
### 2.2.5 Benzylation of methyl (2*E*)-2-(hydroxyimino)(phenyl)acetate (76)



Scheme 60

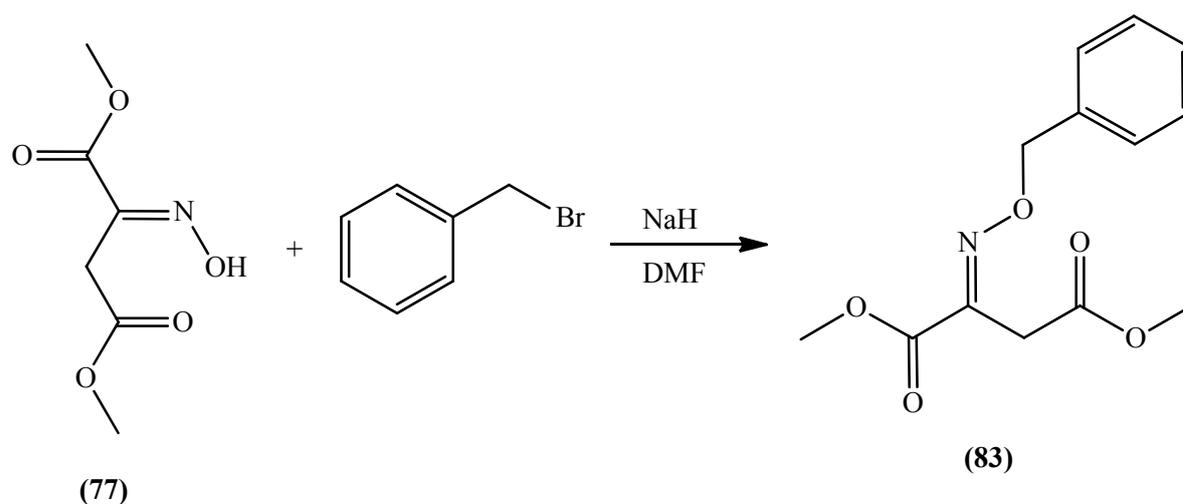
The procedure described above (Section 2.2.1) was again used to synthesize methyl (2*E*)-[(benzyloxy)imino](phenyl)acetate (81) starting from the *trans* oxime (76). A 75% yield of (82), a clear oil, was obtained after chromatography. The spectroscopic data obtained were in agreement with

those in the literature<sup>[68]</sup>. The IR spectrum contained the expected bands for the carbonyl and iminyll bonds at 1726 and 1587  $\text{cm}^{-1}$ , respectively, and for the monosubstituted aromatic rings at 723 and 690  $\text{cm}^{-1}$ , respectively. In the  $^1\text{H}$ -NMR spectrum (**Figure 12**) singlets at  $\delta$  3.88 and 5.37 corresponded to the methyl and methylene protons, respectively, and a series of multiplets ranging from  $\delta$  7.31-7.50 corresponded to the aromatic protons. The  $^{13}\text{C}$ -NMR spectrum contained the expected signals (**Table 4**) including those at 164.1 and 78.2 ppm for the carbonyl and methylene carbons, respectively.



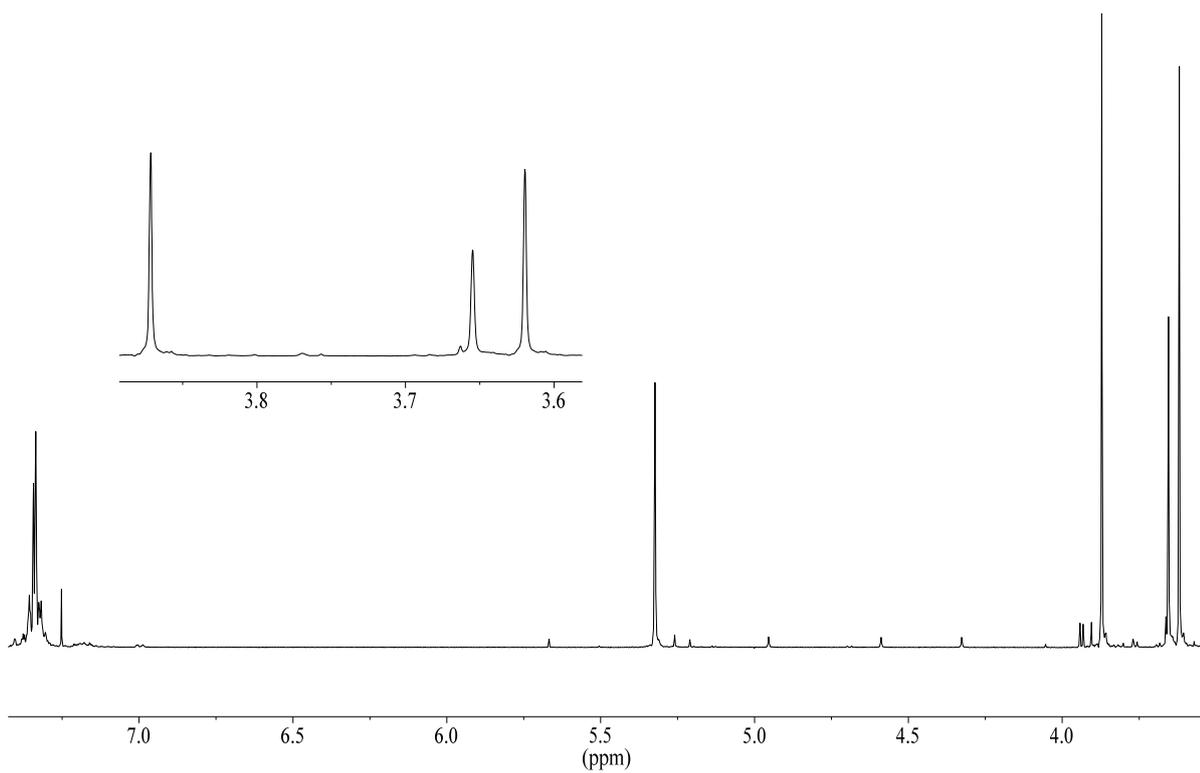
**Figure 12**  $^1\text{H}$ -NMR spectrum of (82)

### 2.2.6 Benzylation of 1,4-dimethyl (2E)-2-(hydroxyimino)butanedioate (77)



**Scheme 61**

A procedure developed by Mitani<sup>[65]</sup> was used to benzylate 1,4-dimethyl (2E)-2-(hydroxyimino)butanedioate (77) (**Scheme 61**). To a suspension of sodium hydride in DMF solutions of benzylbromide and (77) in DMF were added in quick succession at 0 °C under nitrogen. The reaction mixture was stirred for 8 h at 0 °C. Standard work-up and chromatography gave 1,4-dimethyl (2E)-2-[(benzyloxy)imino]butanedioate (83) as a clear oil in 50% yield. Its spectroscopic data correlated well with those in the literature<sup>[65]</sup>. The IR spectrum had two carbonyl bands at 1739 and 1720 cm<sup>-1</sup>, together with an iminyl band at 1604 cm<sup>-1</sup>. The <sup>1</sup>H-NMR spectrum (**Figure 13**) contained singlets at δ 3.61 and 3.87 for the two methoxy groups, and another pair of singlets at δ 3.65 and 5.32 which corresponded to the two methylene groups. The <sup>13</sup>C-NMR spectrum was as expected (**Table 4**).



**Figure 13**  $^1\text{H-NMR}$  spectrum of (83)

Table 4 NMR data for oxime ethers

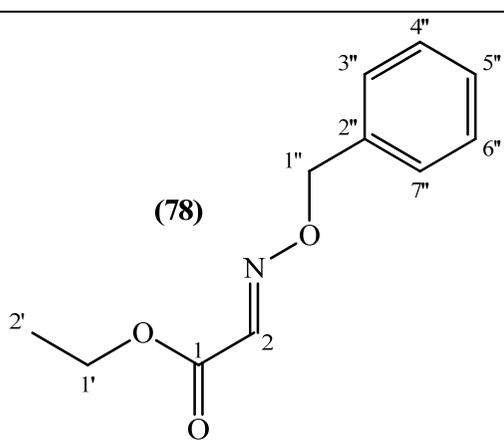
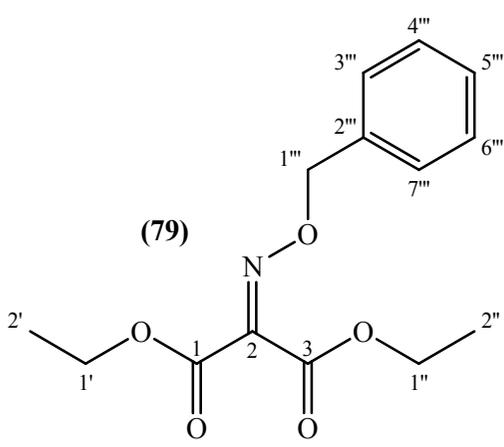
	<sup>1</sup> H-NMR data (δ)					<sup>13</sup> C-NMR data (ppm)					
 <p>(78)</p>	<b>H-1''</b>	<b>H-1'</b>	<b>H-2'</b>	<b>H-2</b>	<b>Ar-H</b>	<b>C-2</b>	<b>C-1</b>	<b>C-1'</b>	<b>C-1''</b>	<b>C-2'</b>	<b>Ar-C</b>
	5.29 (s)	4.32 (q) <i>J</i> = 7.1 Hz	1.33 (t) <i>J</i> = 7.1 Hz	7.54 (s)	7.30-7.37 (overlapping ms)	141.3	162.1	61.8	78.1	14.2	<b>C-2''</b> : 136.0. <b>Ar-CH</b> : 128.7, 128.65 and 128.60.
 <p>(79)</p>	<b>H-1'''</b>	<b>H-1'/ H-1''</b>	<b>H-2'/ H-2''</b>	<b>Ar-H</b>	<b>C-2</b>	<b>C-1/ C-3</b>	<b>C-1'/ C-1''</b>	<b>C-1'''</b>	<b>C-2'/ C-2''</b>	<b>Ar-C</b>	
	5.33 (s)	4.34 and 4.33 (overlapping qs) <i>J</i> = 7.1 Hz	1.27-1.34 (overlapping ts) <i>J</i> = 7.1 Hz	7.31-7.34 (overlapping ms)	144.3	159.7/ 160.6	62.3/ 62.6	78.8	14.1/ 14.2	<b>C-2'''</b> : 135.9. <b>Ar-CH</b> : 128.6, 128.5 and 128.1.	

Table 4 (contd.) NMR data for oxime ethers

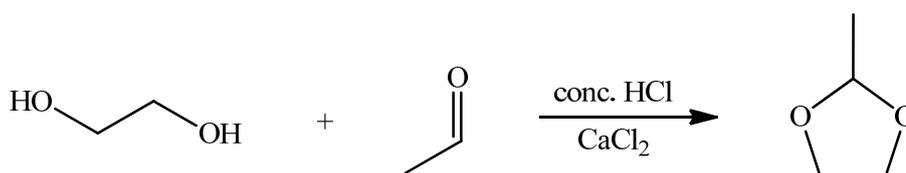
	<sup>1</sup> H-NMR data (δ)			<sup>13</sup> C-NMR data (ppm)				
	H-1'	H-1''	Other signals	C-2	C-1	C-1'	C-1''	Other signals
<p><b>(81)</b></p>	3.88 (s)	5.37 (s)	<p><b>H-3'' to H-7'':</b> 7.31-7.39 (overlapping ms) <b>H-4 to H-8:</b> 7.39-7.50 (overlapping ms)</p>	149.6	164.1	53.1	78.2	<p><b>C-2'':</b> 136.7, <b>C-3:</b> 129.5, <b>Ar-CH:</b> 129.8, 129.3, 128.6, 128.3, 128.2 and 128.1.</p>
<p><b>(82)</b></p>	3.95 (s)	5.30 (s)	<p><b>H-5 to H-7 and H-3'' to H-7'':</b> 7.30-7.42 (overlapping ms) <b>H-4 and H-8:</b> 7.57-7.59 (overlapping ms)</p>	151.2	164.3	52.6	77.1	<p><b>C-2'':</b> 137.4, <b>C-3:</b> 130.2, <b>Ar-CH:</b> 130.6, 128.9, 128.5, 128.0 and 126.4.</p>

Table 4 (contd.) NMR data for oxime ethers

	<sup>1</sup> H-NMR data (δ)				<sup>13</sup> C-NMR data (ppm)					
	H-1'	H-1''	H-3	Other signals	C-2	C-1	C-1'	C-1''	Other signals	
<p>(80)</p>	3.85 (s)	5.30 (s)	2.09 (s)	Ar-H: 7.30-7.37 (overlapping ms)	149.4	164.4	52.8	77.7	C-3: 11.7, C-2'': 136.7. Ar-CH: 128.6, 128.4 and 128.3.	
<p>(83)</p>	3.87 (s)	5.32 (s)	3.65 (s)	H-1''': 3.61 (s), Ar-H: 7.31-7.36 (overlapping ms)	145.7	163.5	168.4	52.3	78.3	C-3: 31.3, C-1': 53.2, C-2''': 136.1, Ar-CH: 128.6, 128.5 and 128.3.

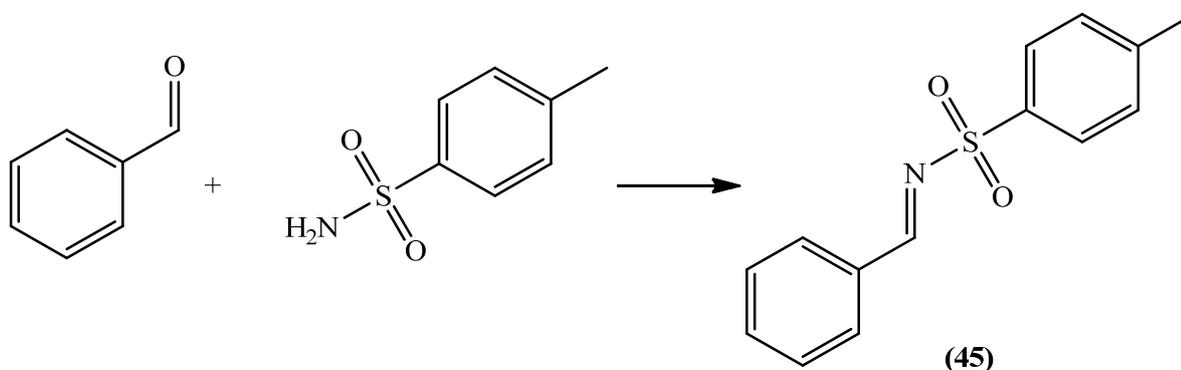
### 2.3 Synthesis of 2-methyl-1,3-dioxolane

A modified version of a method which Riddell<sup>[69]</sup> used was followed in the synthesis of 2-methyl-1,3-dioxolane (**Scheme 62**). Acetaldehyde was slowly added to a cooled solution of ethylene glycol, followed by concentrated HCl. Anhydrous CaCl<sub>2</sub> was then added until one clear liquid layer was visible. Distillation of this liquid layer afforded 2-methyl-1,3-dioxolane as a clear liquid in 43% yield. Spectroscopic data were consistent with those in the literature<sup>[70]</sup>. The IR spectrum showed the typical CO stretching bands at 1146, 1117, 1084 and 1021 cm<sup>-1</sup>. The <sup>1</sup>H-NMR contained a doublet at  $\delta$  1.37 ( $J = 4.8$  Hz) which corresponded to the methyl protons. The methylene protons appeared as multiplets at  $\delta$  3.83-3.86 and 3.87-4.00, and the final signal was a quartet at  $\delta$  4.97 ( $J = 4.8$  Hz) for the methine proton. The <sup>13</sup>C-NMR spectrum had three signals at 101.6, 64.9 and 19.7 ppm which correspond to the methine, methylene and methyl carbons, respectively.



**Scheme 62**

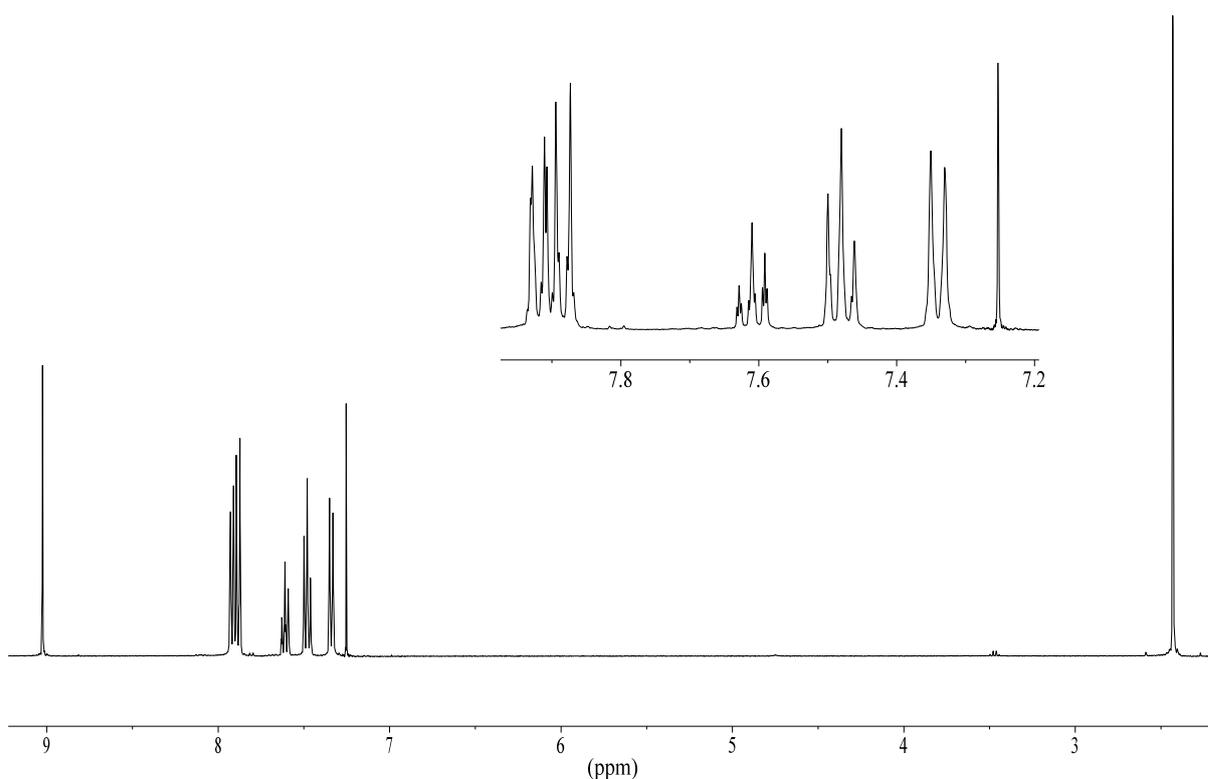
### 2.4 Synthesis of 4-methyl-*N*-[(1*E*)-phenylmethylidene] benzene-1-sulfonamide (**45**)



**Scheme 63**

The synthesis of 4-methyl-*N*-[(1*E*)-phenylmethylidene] benzene-1-sulfonamide (**45**) was achieved using a modified version of the procedure developed by Roy<sup>[71]</sup>. Benzaldehyde and *p*-toluenesulfonamide were refluxed in toluene in the presence of Amberlist and 4 Å molecular sieves, with azeotropic removal of water (**Scheme 63**). Standard work-up and recrystallization from diethyl ether gave 4-methyl-*N*-[(1*E*)-phenylmethylidene] benzene-1-sulfonamide (**45**) in 72% yield as clear crystals (m.p. 116-118 °C). Spectroscopic data were in good agreement with those in the literature<sup>[72]</sup>. Analysis of the IR spectrum showed a band at 1650 cm<sup>-1</sup> for the imine bond, two bands at 1315 and

1154  $\text{cm}^{-1}$  for the sulphur-oxygen double bonds, together with bands at 754 and 668  $\text{cm}^{-1}$  for the monosubstituted aromatic ring. The  $^1\text{H-NMR}$  spectrum (**Figure 14**) contained singlets at  $\delta$  2.43 and 9.02 which corresponded to the methyl and methine protons, respectively. In the aromatic region there were doublets at  $\delta$  7.33 and 7.88 ( $J = 8.2$  Hz) for the four protons on the *para* disubstituted ring of the tosyl group, two triplets at  $\delta$  7.48 and 7.60 ( $J = 7.6$  Hz) which correspond to the protons in the *meta* and *para* positions of the monosubstituted benzene ring, and finally a doublet at  $\delta$  7.91 ( $J = 7.6$  Hz) corresponding to the *ortho* protons of the same ring. The  $^{13}\text{C-NMR}$  spectrum had signals at 170.2 and 21.8 ppm for the iminyl and methyl carbons, respectively, with the aromatic signals resonating at 144.7, 135.0, 132.5, 131.4, 129.9, 128.3 and 128.2 ppm.

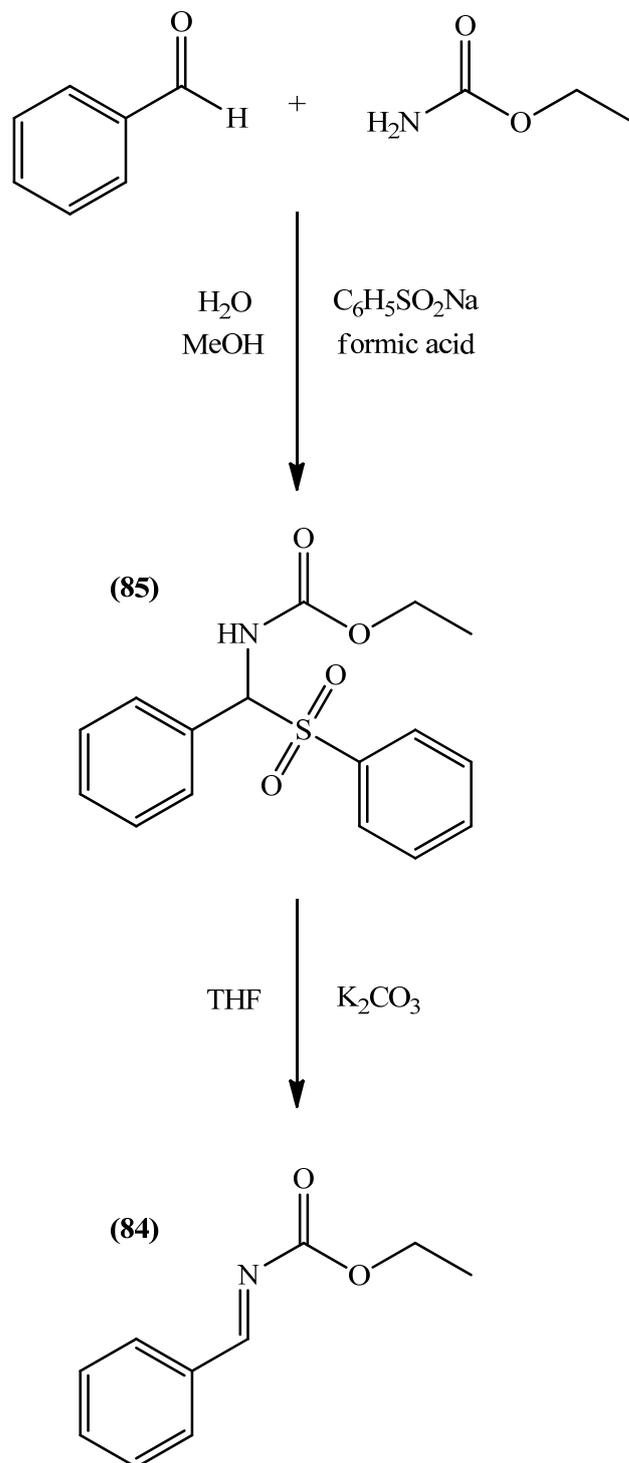


**Figure 14**  $^1\text{H-NMR}$  spectrum of (45)

### 2.5 Synthesis of *N*-(ethoxycarbonyl)benzaldimine (84)

*N*-(Ethoxycarbonyl)benzaldimine (**84**) was prepared in a two step process according to a literature procedure<sup>[73]</sup>. Benzaldehyde in methanol and formic acid were added to an aqueous solution of urethane and sodium benzenesulfinate dihydrate. The mixture was heated for 2 h and then allowed to stir overnight at room temperature. Standard work-up gave ethyl [phenyl(phenylsulfonyl)methyl]carbamate (**85**) in 82% yield. A solution of (**85**) in THF containing anhydrous  $\text{K}_2\text{CO}_3$ , was then refluxed overnight under a nitrogen atmosphere. Standard work-up gave

*N*-(ethoxycarbonyl)benzaldimine (**84**) as a clear oil in 69% yield. Spectroscopic data for both compounds (**84**) and (**85**) were consistent with those in the literature<sup>[73]</sup>.



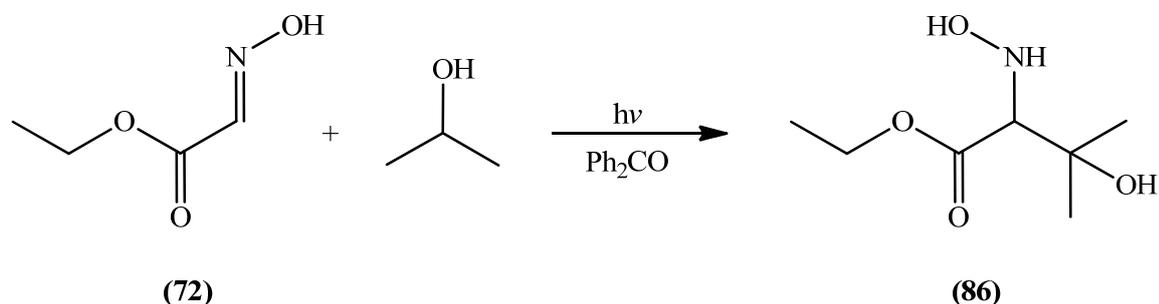
**Scheme 64**

Analysis of the IR spectrum of (**85**) showed bands at  $3349$  and  $1726\text{ cm}^{-1}$  for the NH and carbonyl groups, respectively. It also showed the usual CO stretching bands at  $1232$ ,  $1140$  and  $1082\text{ cm}^{-1}$ , and

aromatic bands at 719 and 690  $\text{cm}^{-1}$ . The  $^1\text{H-NMR}$  spectrum had the expected triplet at  $\delta$  1.12 ( $J = 7.1$  Hz) and quartet at  $\delta$  3.94 ( $J = 7.1$  Hz) for the ethoxy group. The amide and methine protons resonated as overlapping multiplets at  $\delta$  5.85-5.95, and the aromatic protons resonated as a series of multiplets at  $\delta$  7.39 and 7.50-7.87. In the  $^{13}\text{C-NMR}$  spectrum the carbonyl carbon resonated at 154.8 ppm, and the methine carbon at 74.4 ppm. The aromatic signals resonated at 136.9, 134.2, 130.0, 129.6, 129.1, 128.9 and 128.8 ppm. The methyl and methylene carbons appeared at 14.5 and 62.1 ppm, respectively. The IR spectrum for *N*-(ethoxycarbonyl)benzaldimine (**84**) showed the carbonyl band had shifted to 1711  $\text{cm}^{-1}$ , it also had a band at 1627  $\text{cm}^{-1}$  indicative of an imine bond. There was little difference in the CO or aromatic bands compared to (**85**). The  $^1\text{H-NMR}$  spectrum had a triplet at  $\delta$  1.37 ( $J = 7.1$  Hz) and a quartet at  $\delta$  4.31 ( $J = 7.1$  Hz) for the ethoxy group. The methine proton appeared at  $\delta$  8.96 and the aromatic protons as a series of multiplets at  $\delta$  7.39 and 7.50-7.87. In the  $^{13}\text{C-NMR}$  spectrum the iminyl and carbonyl carbons resonated at 171.3 and 163.9 ppm, respectively. The methyl and methylene carbons of the ethoxy group resonated at 14.4 and 63.3 ppm, respectively and the aromatic signals appeared at 134.0, 133.9, 130.5 and 129.0 ppm.

## 2.6 Photochemical reactions of ethyl (2E)-(hydroxyimino)acetate (72)

### 2.6.1 Photochemical reaction of ethyl (2E)-(hydroxyimino)acetate (72) and 2-propanol



Scheme 65

A solution of ethyl (2E)-2-(hydroxyimino)acetate (72), benzophenone and 2-propanol in acetonitrile was degassed, then irradiated in a Rayonet reactor for 1 h, at which time all the starting material had reacted (GC). Analysis of the  $^1\text{H-NMR}$  spectrum of the crude product indicated the presence of the expected addition product and the formation of a large amount of benzopinacol. Chromatography gave ethyl-3-hydroxy-2-(hydroxyamino)-3-methylbutanoate (86) as a clear oil in 80% yield. The assignment of the structure of the product was based on its spectroscopic data. The IR spectrum had bands at 3398, 3282 and  $1725\text{ cm}^{-1}$ , which correspond to the OH, NH and carbonyl groups, respectively. It also contained characteristic CO bands at 1151 and  $1036\text{ cm}^{-1}$ . The  $^1\text{H-NMR}$  spectrum (Figure 15) had singlets at  $\delta$  1.17 and 1.26 for the two methyl groups and a singlet at  $\delta$  3.59 for the methine proton. The ethoxy group showed a triplet at  $\delta$  1.28 ( $J = 7.2\text{ Hz}$ ) for the methyl protons and multiplets at  $\delta$  4.19-4.28 corresponding to the methylene protons. The  $^{13}\text{C-NMR}$  spectrum had a signal at 172.9 ppm for the carbonyl carbon and at 73.7 ppm for the methine carbon; the quaternary carbon resonated at 70.9 ppm. The three methyl carbons resonated at 27.3, 26.5 and 14.3 ppm, and the methylene carbon resonated at 61.4 ppm.

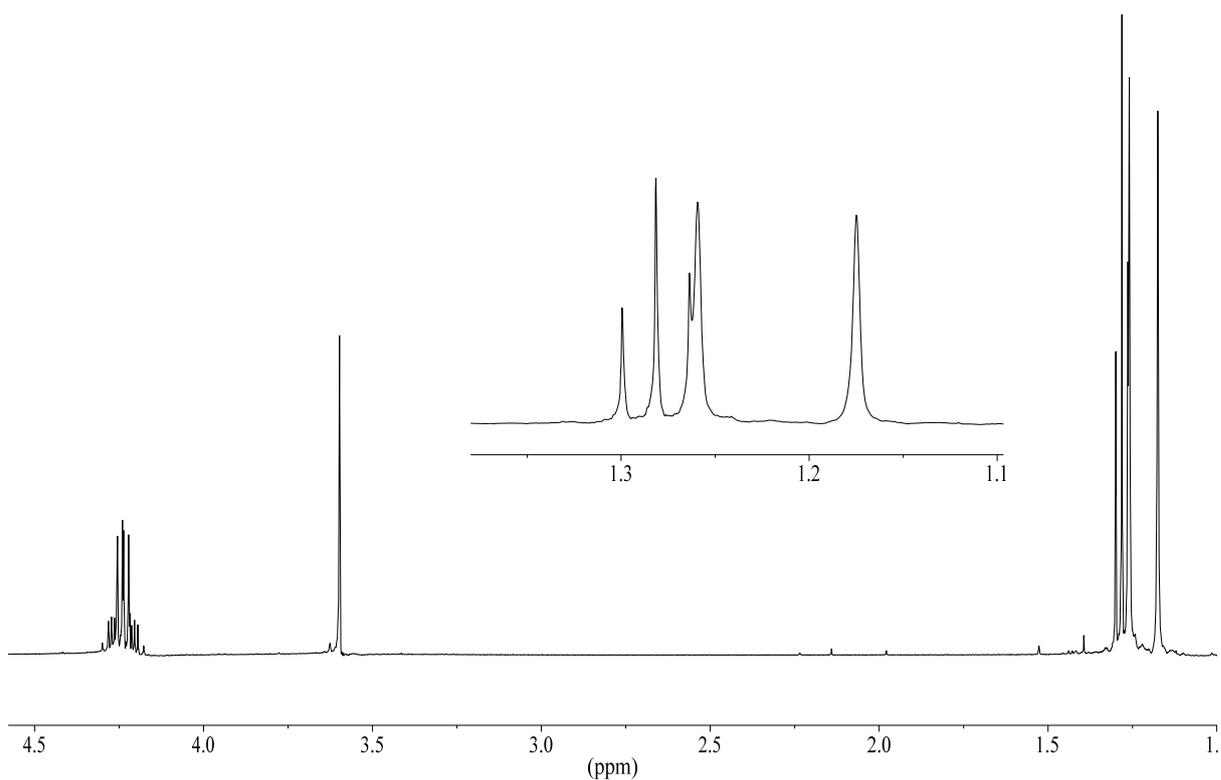
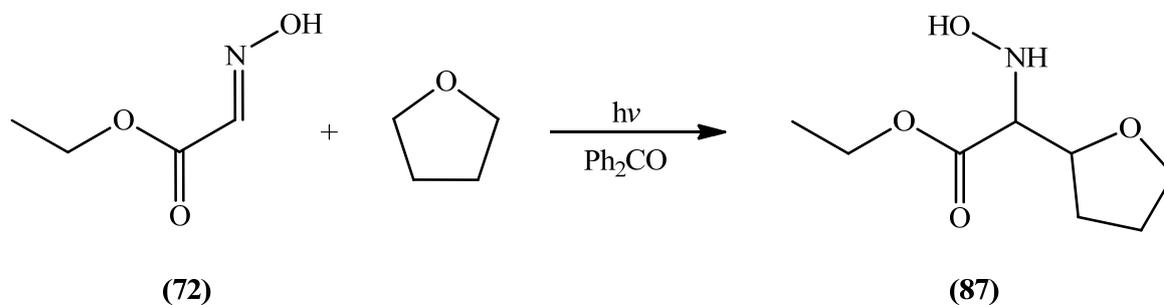


Figure 15  $^1\text{H-NMR}$  spectrum of (86)

### 2.6.2 Photochemical reaction of ethyl (2*E*)-(hydroxyimino)acetate (72) and THF

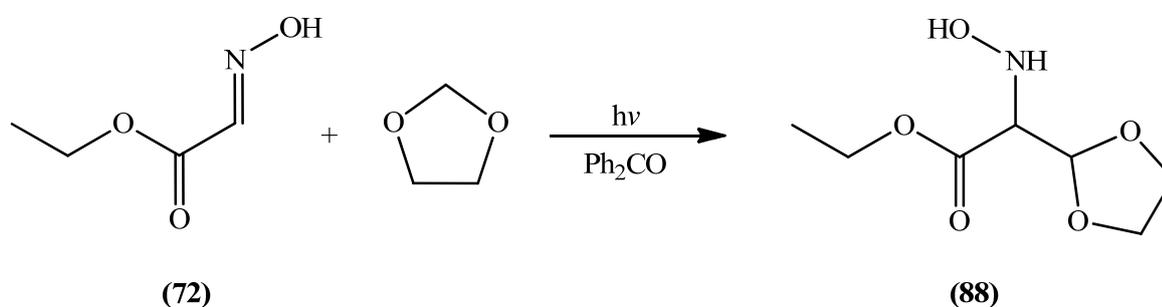


Scheme 66

A solution of ethyl (2*E*)-(hydroxyimino)acetate (72), benzophenone and THF in MeCN was prepared as before (Section 2.6.1). The solution was then irradiated for 1 h at which time all the starting material had reacted (GC). GC analysis indicated that a mixture of diastereomers was formed in a ratio of 1:1.09. Analysis of the  $^1\text{H-NMR}$  spectrum of the crude product indicated that some benzopinacol had formed. Attempts to isolate the individual diastereomers by flash chromatography failed and so the product, ethyl tetrahydrofuran-2-yl(hydroxylamino)acetate (87), was isolated as a mixture of the two diastereomers, and as a clear oil, in 83% yield. The IR spectrum had the expected carbonyl band at  $1731\text{ cm}^{-1}$ , and bands at  $3417$  and  $3271\text{ cm}^{-1}$ , for the OH and NH groups,

respectively. In the  $^1\text{H-NMR}$  spectrum the ethoxy groups appeared as a triplet at  $\delta$  1.24 ( $J = 7.1$  Hz) and quartet at  $\delta$  4.20 ( $J = 7.1$  Hz). The methine protons next to the nitrogen appeared as doublets at  $\delta$  3.57 and 3.75 ( $J = 6.7$  Hz). The methine proton on the tetrahydrofuranyl rings appeared as a series of overlapping multiplets at  $\delta$  3.96-4.05. The methylene protons of the tetrahydrofuranyl rings were present as overlapping multiplets at  $\delta$  3.62-3.82 and 1.75-1.93, and the signals at  $\delta$  5.78 and 6.89, corresponded to the NH and OH protons, respectively. The  $^{13}\text{C-NMR}$  spectrum had signals at 171.7 and 171.6 ppm corresponding to the carbonyl carbons, two methine signals 69.2 and 68.6 ppm, for the carbons adjacent to the nitrogen and two signals for the methine carbon adjacent to the oxygen at 68.7 and 68.6 ppm. The ethoxy groups and remaining carbons on the tetrahydrofuranyl ring gave the expected signals (**Table 5**).

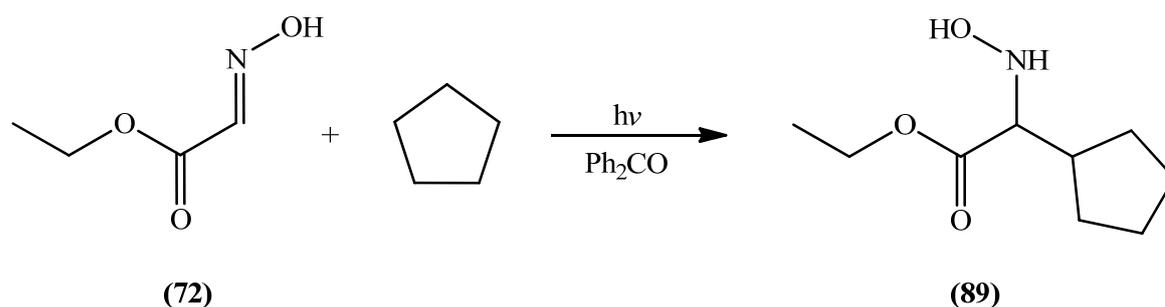
### 2.6.3 Photochemical reaction of ethyl (2E)-(hydroxyimino)acetate (72) and 1,3-dioxolane



**Scheme 67**

A solution of ethyl (2E)-(hydroxyimino)acetate (72), benzophenone and 1,3-dioxolane in MeCN was prepared as before (**Section 2.6.1**). The solution was then irradiated for 1 h at which time all the starting material had reacted (GC). GC analysis also indicated the formation of one product. Analysis of the  $^1\text{H-NMR}$  spectrum of the crude product indicated the formation of a large amount of benzopinacol. Flash column chromatography gave the product, ethyl 1,3-dioxolan-2-yl(hydroxyamino)acetate (88), as a yellow oil in 62% yield. The IR spectrum contained the expected OH, NH and carbonyl bands at 3444, 3274 and 1735  $\text{cm}^{-1}$ , respectively. In the  $^1\text{H-NMR}$  spectrum there was a triplet at  $\delta$  1.30 ( $J = 7.2$  Hz) and quartet at  $\delta$  4.26 ( $J = 7.2$  Hz) which corresponded to the ethoxy group. The methylene protons of the dioxolanyl ring appeared as a series of multiplets  $\delta$  3.82-4.01 and these overlapped with the signal for the methine proton adjacent to the nitrogen. The other methine proton appeared as a doublet at  $\delta$  5.18 ( $J = 3.7$  Hz). The  $^{13}\text{C-NMR}$  spectrum had a signal at 169.8 ppm which corresponded to the carbonyl carbon, signals at 101.6 and 67.8 ppm for the two methine carbons, and signals at 65.6 and 65.5 ppm for the methylene carbons. The ethoxy signals were as expected (**Table 5**).

#### 2.6.4 Photochemical reaction of ethyl (2E)-(hydroxyimino)acetate (72) and cyclopentane



Scheme 68

A solution of ethyl (2E)-(hydroxyimino)acetate (72), benzophenone and cyclopentane in MeCN was prepared as before (Section 2.6.1) and the solution was then irradiated for 2 h, at which time all the starting material had reacted (GC). GC analysis indicated the formation of one product. Analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated the formation of a small amount of benzopinacol. Flash column chromatography gave the product, ethyl cyclopentyl(hydroxyamino)acetate (89), as a yellow oil in 57% yield.

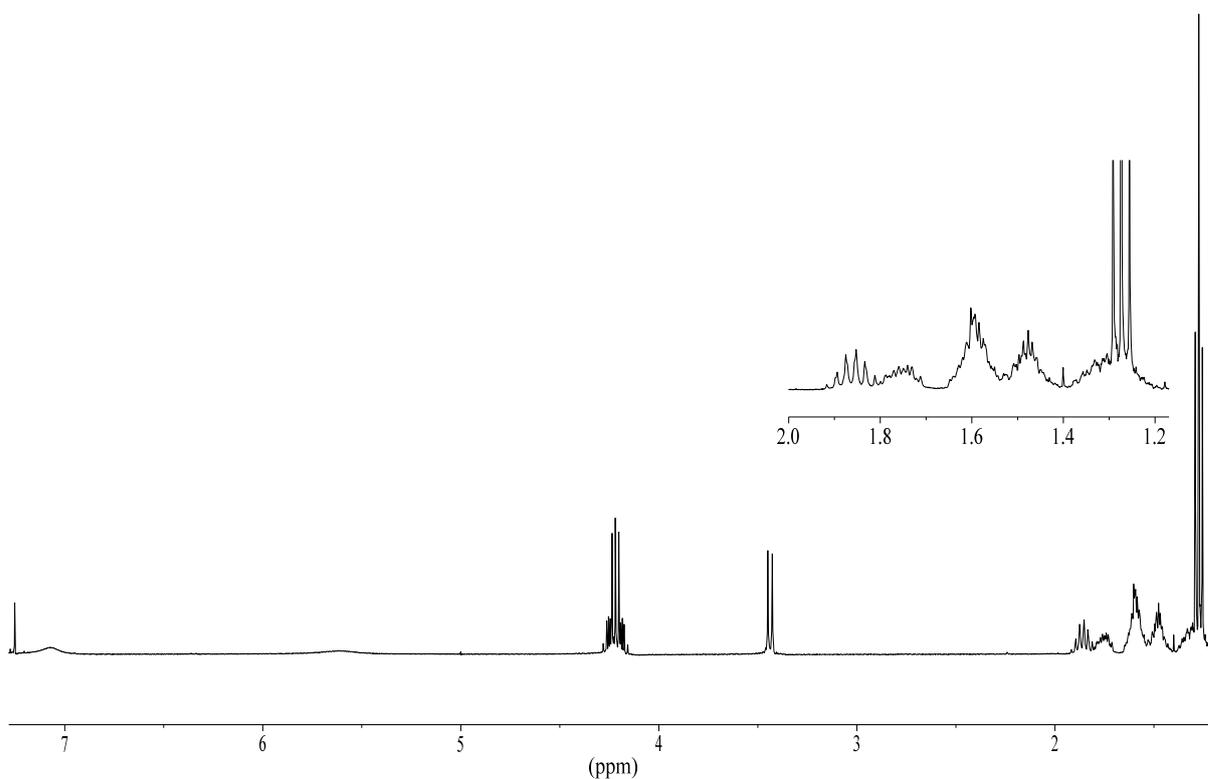


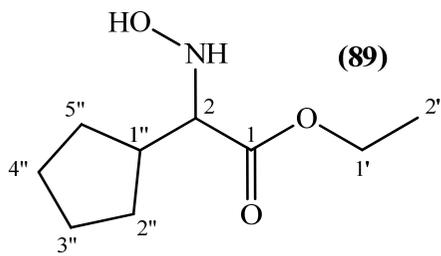
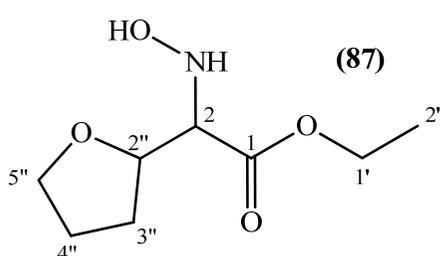
Figure 16 <sup>1</sup>H-NMR spectrum of (89)

Analysis of the IR data confirmed the presence of the OH, NH and carbonyl groups with bands at 3433, 3273 and 1732  $\text{cm}^{-1}$ , respectively; CO bands appeared at 1183, 1159 and 1030  $\text{cm}^{-1}$ . The  $^1\text{H}$ -NMR spectrum (**Figure 16**) showed the cyclopentyl methylene protons as a series of multiplets at  $\delta$  1.30-1.80 and the methine proton as a multiplet at  $\delta$  1.85. The other methine proton appeared as a doublet at  $\delta$  3.43 ( $J = 8.9$  Hz), and the ethoxy group gave the expected triplet for the methyl protons. The methylene protons of the ethoxy appeared as a multiplet due to its proximity to the chiral centre of the molecule. There were also signals for the NH and OH protons (**Table 5**). The  $^{13}\text{C}$ -NMR spectrum further confirmed the structure with a carbonyl signal at 174.0 ppm, two methine carbon signals at 70.4 and 40.0 ppm, and cyclopentyl methylene signals at 30.2, 29.4, 25.1 and 24.9 ppm. The ethoxy signals were as expected (**Table 5**).

Table 5 NMR data for ethyl (2*E*)-(hydroxyimino)acetate products

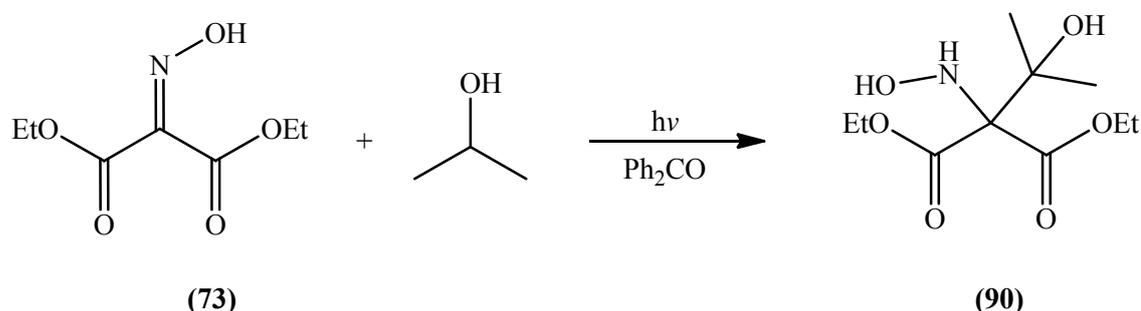
	<sup>1</sup> H-NMR data (δ)					<sup>13</sup> C-NMR data (ppm)				
	OH/NH	H-1'	H-2'	H-2	Other Signals	C-2	C-1	C-1'	C-2'	Other Signals
<p>(86)</p>	–	4.19-4.28 (m)	1.28 (t) <i>J</i> = 7.2 Hz	3.59 (s)	<b>H-1''</b> : 1.17 (s) <b>H-4</b> : 1.26 (s)	73.7	172.9	61.4	14.3	<b>C-3</b> : 70.9, <b>C-1''/C-4</b> : 26.5/27.3.
<p>(88)</p>	–	4.26 (q) <i>J</i> = 7.2 Hz	1.30 (t) <i>J</i> = 7.2 Hz	<b>H-2''</b> : 5.18 (d) <i>J</i> = 3.7 Hz <b>H-2, H-4''/H-5''</b> : 3.82-4.01 (overlapping ms)		67.8	169.8	61.7	14.3	<b>C-2''</b> : 101.6, <b>C-4''/C-5''</b> : 65.5/65.6.

Table 5 (contd.) NMR data for ethyl (2*E*)-(hydroxyimino)acetate products

	<sup>1</sup> H-NMR data (δ)					<sup>13</sup> C-NMR data (ppm)				
	OH/NH	H-1'	H-2'	H-2	Other Signals	C-2	C-1	C-2'	C-1'	Other Signals
 <p>(89)</p>	7.05 (br s)/ 5.56 (br s)	4.17-4.26 (m)	1.25 (t) <i>J</i> = 7.1 Hz	3.43 (d) <i>J</i> = 8.9 Hz	<b>H-1''</b> : 1.85 (m) <b>H-3''/H-4''</b> : 1.30-1.50 (overlapping ms) <b>H-2''/H-5''</b> : 1.51-1.80 (overlapping ms).	70.4	174.0	61.0	14.4	<b>C-1''</b> : 40.0, <b>C-2''/C-5''</b> : 29.4/30.2, <b>C-3''/C-4''</b> : 24.9/25.1.
 <p>(87)</p>	5.78 (br s) 6.89 (br s)	4.20 (q) <i>J</i> = 7.1 Hz	1.24 (t) <i>J</i> = 7.1 Hz	3.57 and 3.75 (ds) <i>J</i> = 6.7 Hz	<b>H-2''</b> : 4.00 (overlapping ms)	69.2 and 68.6	171.7 and 171.6	68.7 and 68.6	14.3	<b>C-2''</b> : 77.1 and 76.8, <b>C-3''</b> : 28.8 and 28.2, <b>C-4''</b> : 25.8 and 25.6, <b>C-5''</b> : 68.7 and 68.6

## 2.7 Photochemical reactions of diethyl (hydroxyimino)malonate (73)

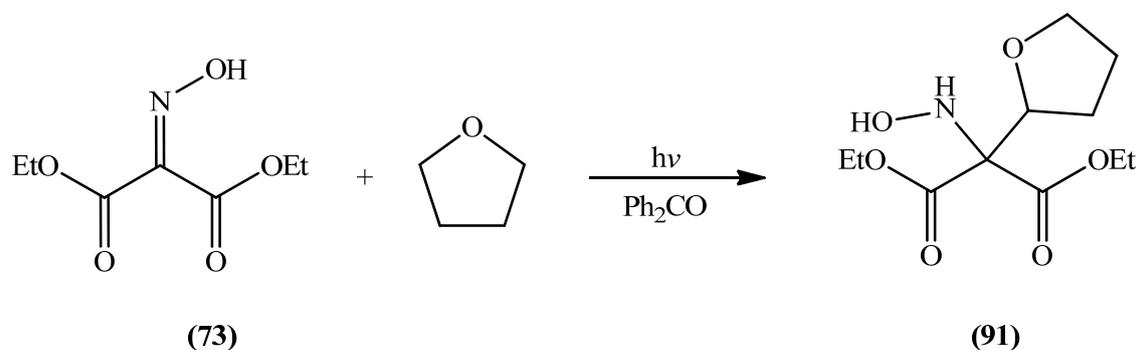
### 2.7.1 Photochemical reaction of diethyl (hydroxyimino)malonate (73) and 2-propanol



**Scheme 69**

A solution of diethyl (hydroxyimino)malonate (**73**), benzophenone and 2-propanol in MeCN was prepared as before (**Section 2.6.1**). It was then irradiated for 1 h at which time all starting material had reacted (GC). No product peak, however, was detected by GC and analysis of the NMR spectrum of the crude reaction product showed that a complex mixture of products had been formed. There was no indication from the  $^1\text{H-NMR}$  spectrum that the expected addition product (**90**) had formed. The mixture was adsorbed onto silica but attempts to isolate any identifiable products *via* flash chromatography failed.

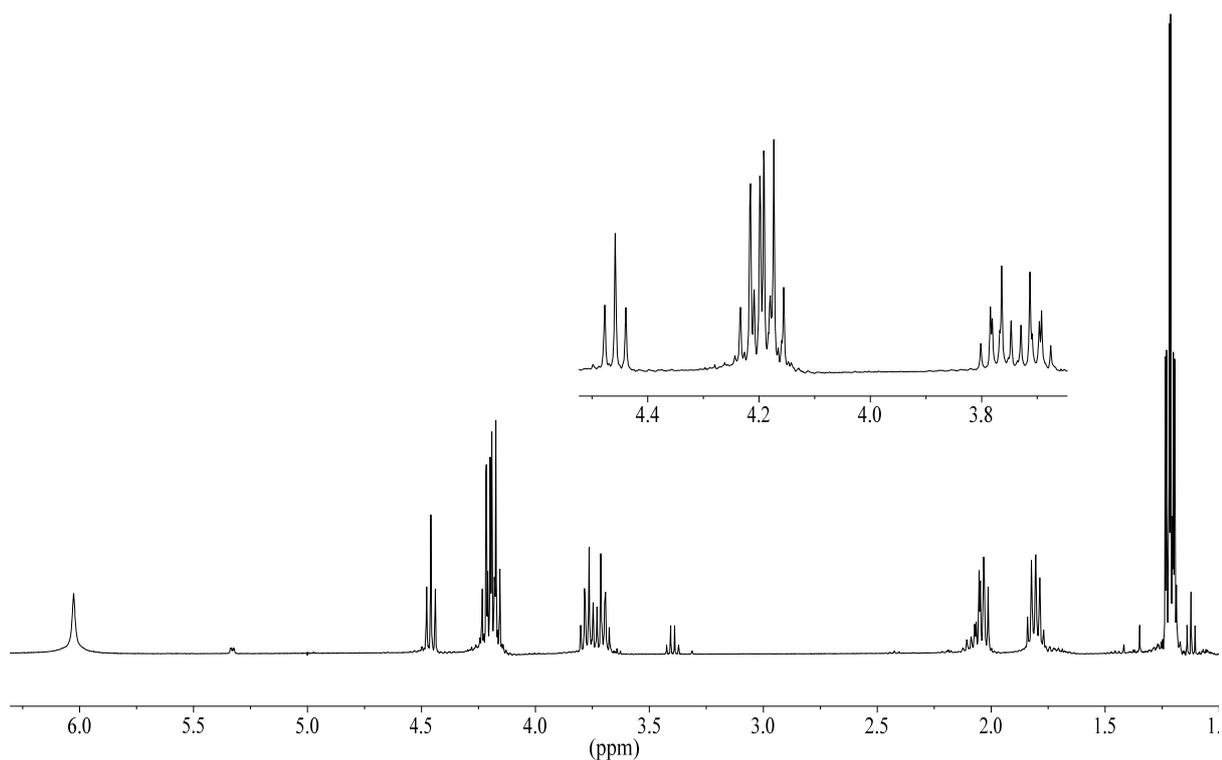
### 2.7.2 Photochemical reaction of diethyl (hydroxyimino)malonate (73) and THF



**Scheme 70**

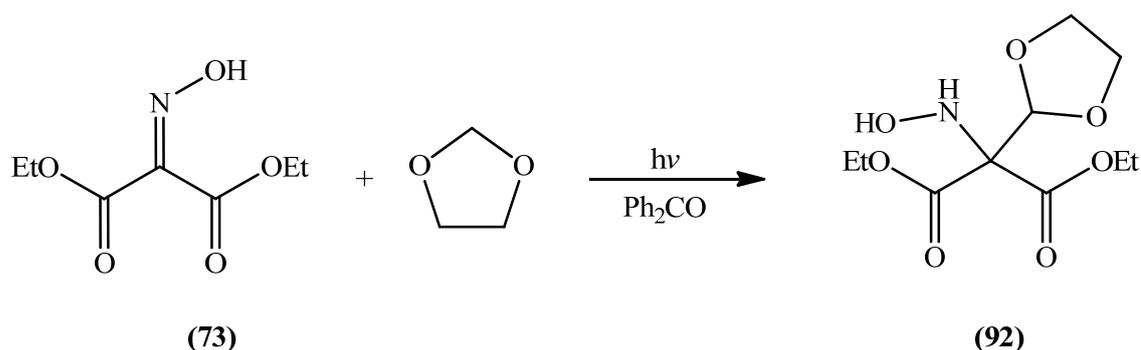
A solution of diethyl (hydroxyimino)malonate (**73**), benzophenone and THF in MeCN was prepared as before (**Section 2.6.1**). It was then irradiated for 1 h at which time all starting material had reacted (GC). NMR analysis of the crude reaction mixture showed that the product (**91**) was formed along with a large amount of benzopinacol. Flash column chromatography gave the product, diethyl (hydroxyamino)(tetrahydrofuran-2-yl)malonate (**91**), as a clear oil in 87% yield. Bands at 3452, 3283 and  $1730\text{ cm}^{-1}$  in the IR spectrum corresponded to the OH, NH and carbonyl groups, respectively. The  $^1\text{H-NMR}$  spectrum (**Figure 17**) showed overlapping triplets at  $\delta$  1.21 and 1.22 ( $J = 7.1\text{ Hz}$ ) and

overlapping quartets at  $\delta$  4.18 and 4.20 ( $J = 7.1$  Hz) for the methyl and methylene protons, respectively, of the ethoxy groups. The methine proton resonated as a triplet at  $\delta$  4.45 ( $J_{cis} = J_{trans} = 7.6$  Hz) and the three methylene groups of the tetrahydrofuranyl ring appeared as a series of multiplets at  $\delta$  1.77-1.84, 2.01-2.12 and 3.68-3.80. In the  $^{13}\text{C}$ -NMR spectrum the two carbonyl signals resonated at 168.2 and 167.2 ppm, the methine carbon appeared at 78.9 ppm, and the quaternary carbon resonated at 75.9 ppm. The methyl and methylene carbons of the ethoxy group were as expected (**Table 6**) and the other methylene carbons resonated at 69.2, 27.5 and 25.9 ppm.



**Figure 17**  $^1\text{H}$ -NMR spectrum of (91)

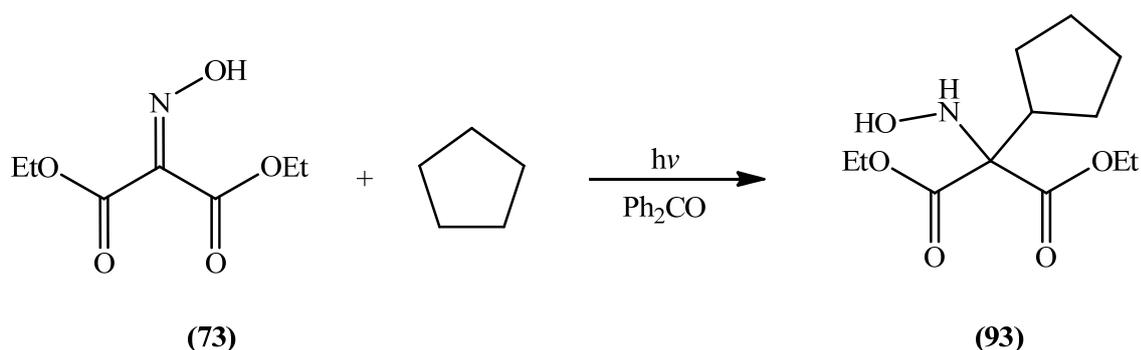
### 2.7.3 Photochemical reaction of diethyl (hydroxyimino)malonate (73) and 1,3-dioxolane



Scheme 71

A solution of diethyl (hydroxyimino)malonate (73), benzophenone and 1,3-dioxolane in MeCN was prepared as before (Section 2.6.1). It was then irradiated for 1 h at which time all starting material had reacted (GC). NMR analysis of the crude reaction mixture showed that the product (92) was formed along with a large amount of benzopinacol. Flash column chromatography gave the product diethyl 1,3-dioxolan-2-yl(hydroxyamino)malonate (92) as a clear oil in 65% yield. Analysis of the IR spectrum confirmed the presence of an OH and NH groups with bands at 3477 and 3294  $\text{cm}^{-1}$ , respectively; a carbonyl band was also present at 1734  $\text{cm}^{-1}$ . In the  $^1\text{H}$ -NMR spectrum there was a triplet at  $\delta$  1.26 ( $J = 7.1$  Hz) and quartet at  $\delta$  4.26 ( $J = 7.1$  Hz) which corresponded to the ethoxy groups. The methylene protons appeared as multiplets at  $\delta$  3.89-3.96 and 4.03-4.09 and the methine proton appeared at  $\delta$  5.59 as a singlet. In the  $^{13}\text{C}$ -NMR spectrum the carbonyl carbons resonated at 166.2 ppm. The methine and quaternary carbons resonated at 103.2 and 75.8 ppm, respectively. The other carbon signals were as expected (Table 6).

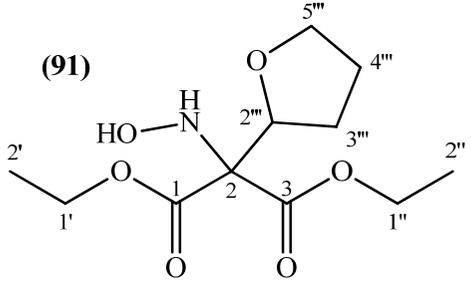
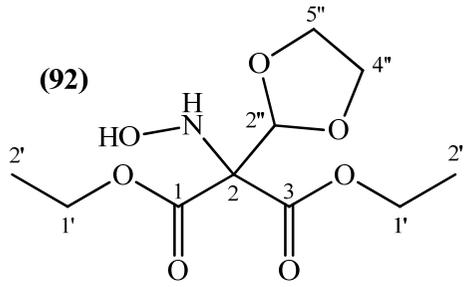
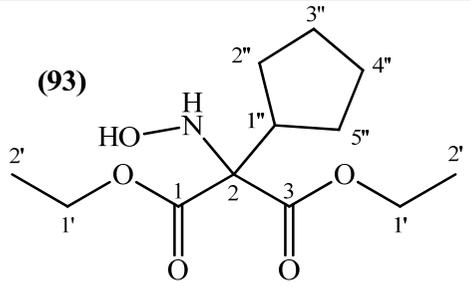
### 2.7.3 Photochemical reaction of diethyl (hydroxyimino)malonate (73) and cyclopentane



Scheme 72

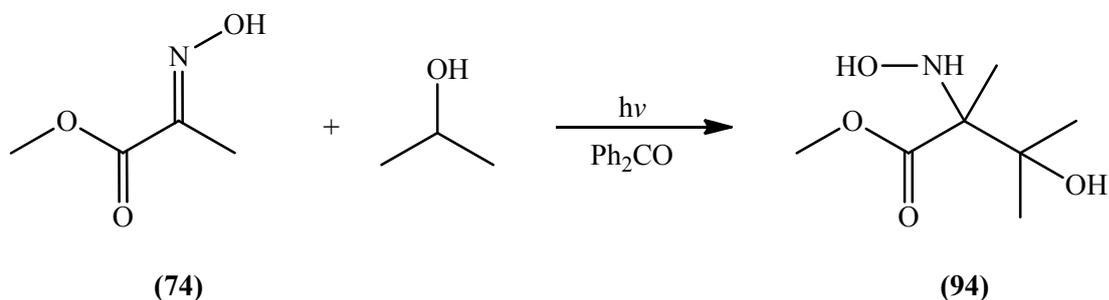
A solution of diethyl (hydroxyimino)malonate (**73**), benzophenone and cyclopentane in MeCN was prepared as before (**Section 2.6.1**) and was irradiated for 4 h at which time no further reaction was observed (GC). NMR analysis of the crude reaction mixture showed that the addition product (**93**) had formed and that the benzophenone had dimerized completely, forming benzopinacol. It also showed that some unreacted starting material was present. Flash column chromatography gave diethyl cyclopentyl(hydroxyamino)malonate (**93**) as a clear oil in 19% yield. Analysis of the IR spectrum indicated the presence of the OH, NH and carbonyl groups due to bands at 3456, 3294 and 1731  $\text{cm}^{-1}$ , respectively, and CO bands were evident at 1231, 1095 and 1019  $\text{cm}^{-1}$ . In the  $^1\text{H}$ -NMR spectrum the methylene protons of the cyclopentyl ring appeared as a series of multiplets at  $\delta$  1.45-1.62 and 1.72-1.81, and the methine proton appeared at  $\delta$  2.43 also as a multiplet. The ethoxy groups gave the expected signals (**Table 6**). In the  $^{13}\text{C}$ -NMR spectrum a signal at 169.6 ppm corresponded to the carbonyl carbons; the quaternary carbon resonated at 76.5 ppm and the methine carbon appeared at 43.0 ppm. The ethoxy signals were as expected (**Table 6**) and two signals were evident at 27.8 and 25.6 ppm for the cyclopentyl methylene carbons.

Table 6 NMR data for diethyl (hydroxyimino)malonate reactions

	<sup>1</sup> H-NMR data (δ)				<sup>13</sup> C-NMR data (ppm)				
	OH/NH	H-1'/H-1''	H-2'/H-2''	Other signals	C-1/ C-3	C-1'/ C-1''	C-2'/ C-2''	C-2	Other signals
<p>(91)</p> 	6.02 (br s)	4.18 and 4.20 (overlapping qs)	1.21 and 1.22 (overlapping ts) $J = 7.1$ Hz	<b>H-2'''</b> : 4.45 (t) $J_{cis} = J_{trans} = 7.6$ Hz, <b>H-4'''</b> : 1.80 (m), <b>H-3'''</b> : 2.03 (m), <b>H-5'''</b> : 3.74 (m).	168.2 and 167.2	62.0 and 61.9	14.0	75.9	<b>C-3'''</b> : 27.5, <b>C-2'''</b> : 78.9, <b>C-5'''</b> : 69.2, <b>C-4'''</b> : 25.9.
<p>(92)</p> 	–	4.26 (q) $J = 7.1$ Hz	1.26 (t) $J = 7.1$ Hz	<b>H-2''</b> : 5.59 (s), <b>H-4''/H-5''</b> : 3.89-3.96/ 4.03-4.09 (ms).	166.2	62.3	14.1	75.8	<b>C-2''</b> : 103.2, <b>C-4''/C-5''</b> : 66.0.
<p>(93)</p> 	5.63 (br s)	4.25 (q) $J = 7.1$ Hz	1.28 (t) $J = 7.1$ Hz	<b>H-1''</b> : 2.43 (m), <b>H-2''-5''</b> : 1.45-1.62 and 1.72-1.81 (ms)	169.6	61.8	14.1	76.5	<b>C-1''</b> : 43.0, <b>C-2''/C-5''</b> : 27.8, <b>C-3''/C-4''</b> : 25.6.

## 2.8 Photochemical reactions of methyl (*E*)-2-(hydroxyimino)propanoate (74)

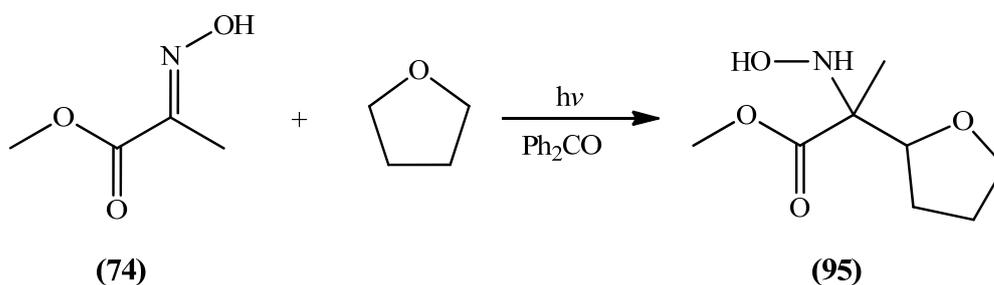
### 2.8.1 Photochemical reaction of methyl (*E*)-2-(hydroxyimino)propanoate (74) and 2-propanol



**Scheme 73**

A solution of methyl (*E*)-2-(hydroxyimino)propanoate (**74**), benzophenone and 2-propanol in MeCN was prepared as before (**Section 2.6.1**). The solution was then irradiated for 3 h at which time all the starting material had reacted (GC). Analysis of the NMR spectrum of the crude product indicated that the addition product (**94**) had formed and that all the benzophenone had dimerized. Dry column vacuum chromatography gave the product, methyl 3-hydroxy-2-(hydroxyamino)-2,3-dimethylbutanoate (**94**), as a clear oil in 33% yield. The IR spectrum contained the expected bands at 3425, 3291 and 1720  $\text{cm}^{-1}$  for the OH, NH and carbonyl groups, respectively, together with the CO bands at 1146, 1108 and 1024  $\text{cm}^{-1}$ . The  $^1\text{H-NMR}$  spectrum had four singlets: at  $\delta$  1.13, 1.14 and 1.33 for the methyl groups, and at  $\delta$  3.71 for the methoxy group. The  $^{13}\text{C-NMR}$  spectrum had a signal at 175.6 ppm for the carbonyl carbon and the two quaternary carbons resonated at 73.9 and 72.0 ppm. The methyl and methoxy carbons were as expected (**Table 7**).

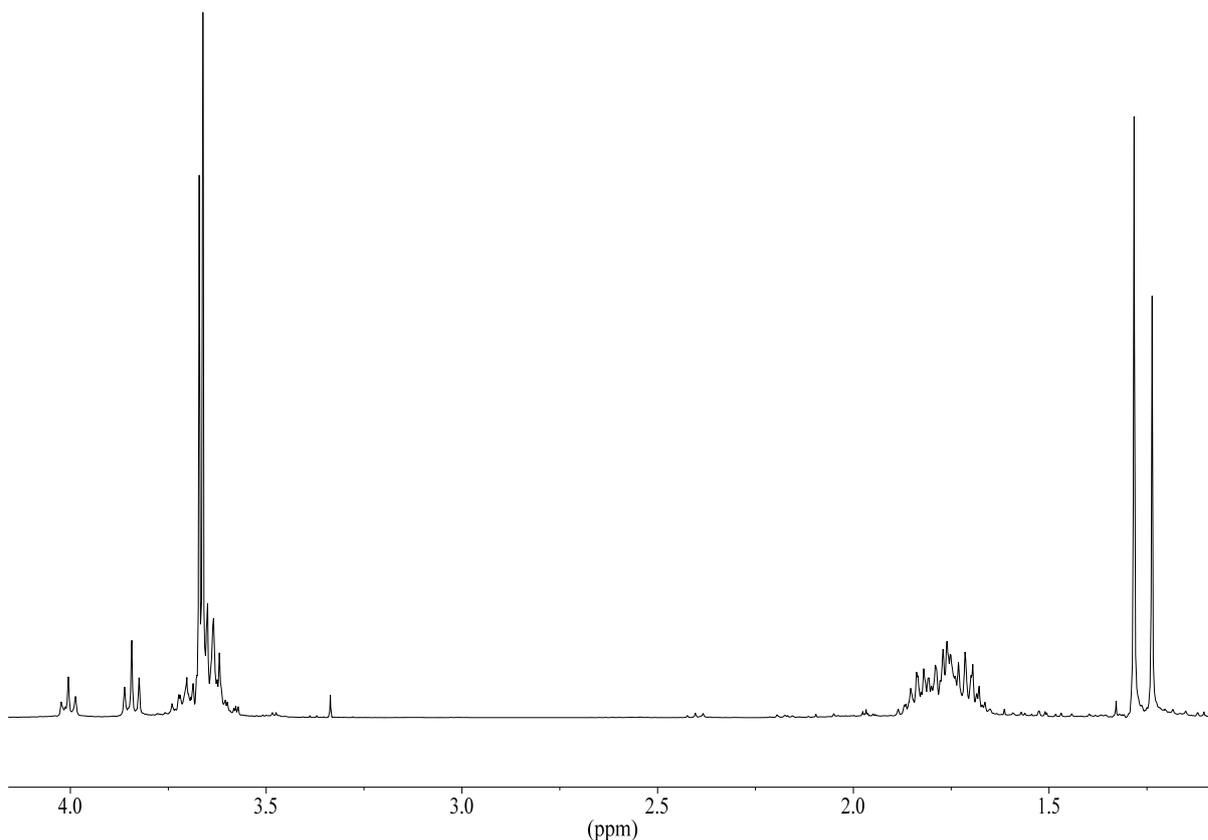
### 2.8.2 Photochemical reaction of methyl (*E*)-2-(hydroxyimino)propanoate (74) and THF



**Scheme 74**

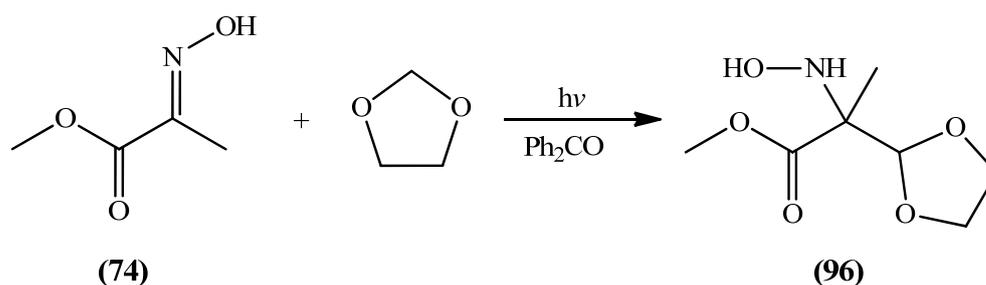
A solution of methyl (*E*)-2-(hydroxyimino)propanoate (**74**) and benzophenone in THF was degassed with  $\text{N}_2$  in the usual manner. Irradiation of the solution led to the formation of a mixture of diastereomers of (**95**) after 3 h. GC analysis showed that the two diastereomers were present in a 1.4:1 ratio and this was confirmed by the  $^1\text{H-NMR}$  spectrum of the crude product. Dry column vacuum

chromatography gave methyl 2-(*N*-hydroxyamino)-2-(tetrahydrofuran-2-yl)propanoate (**95**) as the mixture of diastereomers in 60% yield. No change was noted in the ratio of diastereomers on chromatography. Bands in the IR spectrum at 3436 and 3281  $\text{cm}^{-1}$  were due to the OH and NH bonds, respectively. The carbonyl group gave a band at 1727  $\text{cm}^{-1}$  and the usual CO bands were observed at 1256, 1132 and 1064  $\text{cm}^{-1}$ . The  $^{13}\text{C}$ -NMR spectrum showed two signals at 174.6 and 173.6 ppm for the carbonyl carbons, signals at 81.4 and 80.9 ppm corresponded to the methine carbon adjacent to the oxygen, while signals at 69.0 and 68.9 ppm corresponded to the methylene carbon adjacent to the oxygen. The quaternary carbon resonated at 68.39 and 68.40 ppm and the methoxy carbon gave the expected signals (**Table 7**). The methyl carbons resonated at 16.9 and 15.9 ppm and signals at 26.8, 26.5, 26.0 and 25.7 ppm corresponded to the two methylene groups of the tetrahydrofuran ring. The  $^1\text{H}$ -NMR spectrum (**Figure 18**) showed the expected singlets for the methyl and methoxy groups (**Table 7**). Two triplets at  $\delta$  4.12 and 3.96 ( $J_{cis} = J_{trans} = 7.4$  Hz) corresponded to the methine protons, and overlapping multiplets at  $\delta$  3.74-3.86 and 1.65-1.90 corresponded to the methylene protons.



**Figure 18**  $^1\text{H}$ -NMR spectrum of (**95**)

### 2.8.3 Photochemical reaction of methyl (*E*)-2-(hydroxyimino)propanoate (**74**) and 1,3-dioxolane



**Scheme 75**

A solution of methyl (*E*)-2-(hydroxyimino)propanoate (**74**), benzophenone and 1,3-dioxolane in MeCN was again prepared as before (Section 2.6.1). Irradiation of the solution for 3 h led to the formation of a single product, (**96**) (GC). Dry column vacuum chromatography gave methyl 2-(1,3-dioxolan-2-yl)-*N*-hydroxyalaninate (**96**) as white crystals (m.p. 86-88 °C) in 76% yield. The IR spectrum contained bands at 3265 and 3200  $\text{cm}^{-1}$  due to the OH and NH groups, respectively. A band at 1745  $\text{cm}^{-1}$  corresponded to the carbonyl group, and bands at 1130, 1094 and 1054  $\text{cm}^{-1}$  corresponded to the CO bonds. The  $^1\text{H}$ -NMR spectrum (Figure 19) showed singlets at  $\delta$  1.40 and 3.78 for the methyl and methoxy groups, respectively, a singlet at  $\delta$  5.06 for the methine proton and a series of overlapping multiplets at  $\delta$  3.84-3.98 for the methylene protons. A broad singlet at  $\delta$  5.77 was evident for the hydroxyl and aminyl groups. In the  $^{13}\text{C}$ -NMR spectrum the carbonyl carbon resonated at 172.7 ppm, the methine carbon at 104.3 ppm and the quaternary carbon at 68.6 ppm. The methylene signals were as expected (Table 7) and the signals at 53.7 and 15.6 ppm corresponded to the methoxy and methyl carbon, respectively.

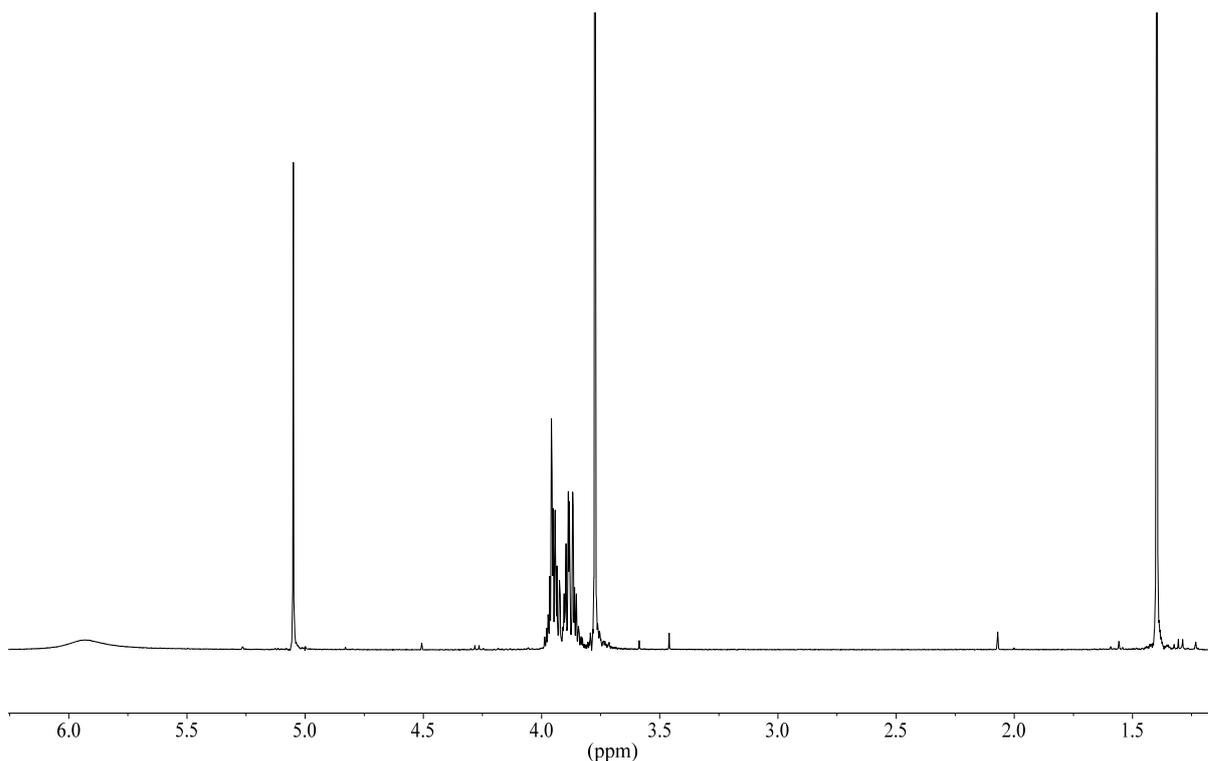
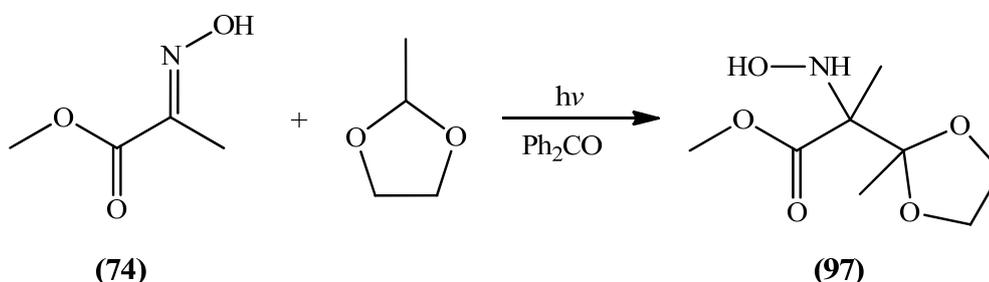


Figure 19  $^1\text{H-NMR}$  spectrum of (96)

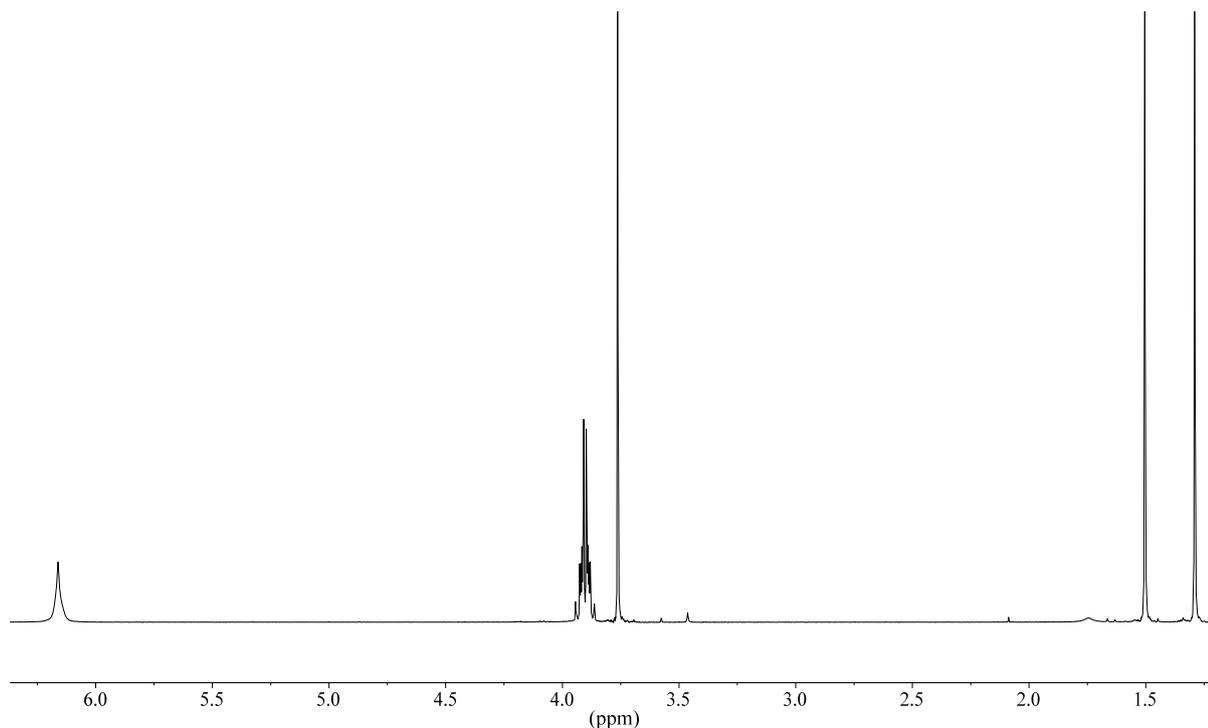
#### 2.8.4 Photochemical reaction of methyl (*E*)-2-(hydroxyimino)propanoate (74) and 2-methyl-1,3-dioxolane



Scheme 76

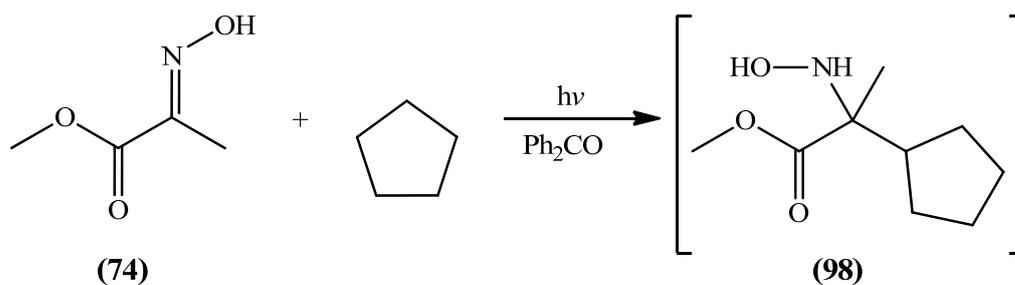
A solution of methyl (*E*)-2-(hydroxyimino)propanoate (74), benzophenone and 2-methyl-1,3-dioxolane in MeCN was prepared as before (Section 2.6.1). The solution was then irradiated for 2 h at which time GC analysis indicated that all the starting material had reacted and that a new product, (97), had formed. Chromatography gave the product, methyl 2-(*N*-hydroxyamino)-2-(2-methyl-1,3-dioxolan-2-yl)propanoate (97), as white crystals (m.p. 120-122 °C) in 53% yield. The IR spectrum showed bands at 3322, 3190 and 1726  $\text{cm}^{-1}$  for the OH, NH and carbonyl groups, respectively, together with CO bands at 1132, 1094 and 1039  $\text{cm}^{-1}$ . The  $^1\text{H-NMR}$  spectrum (Figure 20) had singlets at  $\delta$  1.28 and 1.50 for the methyl groups, and at  $\delta$  3.76 for the methoxy group. The hydroxyl and aminyl protons appeared as a singlet at  $\delta$  6.16 while the methylene protons appeared as multiplets

at  $\delta$  3.88-3.92. Analysis of the  $^{13}\text{C}$ -NMR spectrum showed a signal at 173.3 ppm for the carbonyl carbon and signals at 110.3 and 72.5 ppm for the two quaternary carbons. The other methyl and methylene signals were as expected (**Table 7**).



**Figure 20**  $^1\text{H}$ -NMR spectrum of (**97**)

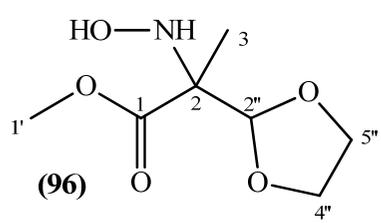
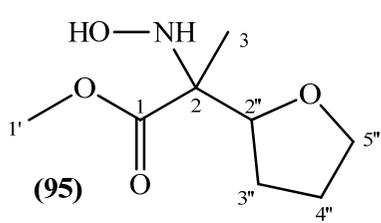
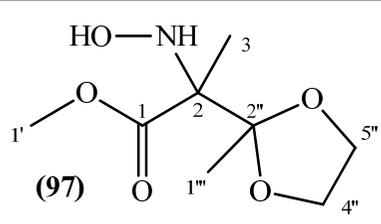
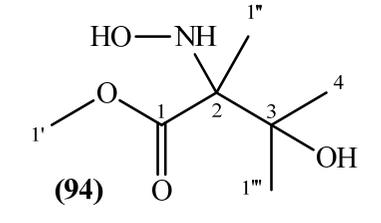
### 2.8.5 Photochemical reaction of methyl (*E*)-2-(hydroxyimino)propanoate (**74**) and cyclopentane



**Scheme 77**

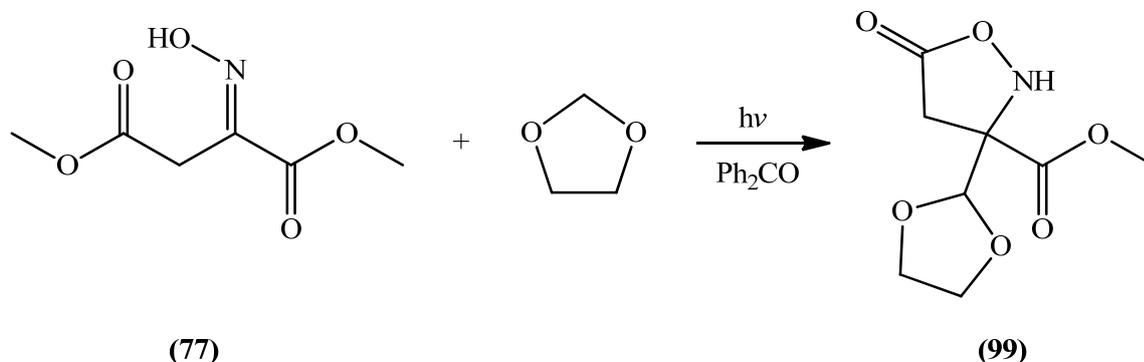
A solution of methyl (*E*)-2-(hydroxyimino)propanoate (**74**), benzophenone and cyclopentane in MeCN was prepared as before (**Section 2.6.1**). The solution was irradiated for 14 h at which time no change was noted (GC). Analysis of the  $^1\text{H}$ -NMR spectrum of the crude product indicated the presence of benzopinacol, starting material and unidentified compounds which were not isolated by chromatography. The expected addition product (**98**) was not formed in this case.

Table 7 NMR data for methyl (2*E*)-2-(hydroxyimino)propanoate reactions

	<sup>1</sup> H-NMR data (δ)					<sup>13</sup> C-NMR data (ppm)					
 <p>(96)</p>	<b>OH/NH</b>	<b>H-3</b>	<b>H-1'</b>	<b>H-2''</b>	<b>Other signals</b>	<b>C-1</b>	<b>C-1'</b>	<b>C-3</b>	<b>C-2</b>	<b>C-2''</b>	<b>Other signals</b>
	5.41-6.13 (br s)	1.40 (s)	3.78 (s)	5.06 (s)	<b>H-4''/H-5'':</b> 3.84-3.98 (ms)	172.7	53.7	15.6	68.6	104.3	<b>C-4''/C-5'':</b> 65.7/65.8
 <p>(95)</p>	<b>OH/NH</b>	<b>H-3</b>	<b>H-1'</b>	<b>H-2''</b>	<b>Other signals</b>	<b>C-1</b>	<b>C-1'</b>	<b>C-3</b>	<b>C-2</b>	<b>C-2''</b>	<b>Other signals</b>
	—	1.24 and 1.28	3.66 and 3.67	3.84 and 4.00 (ts) <i>J</i> = 7.4 Hz	<b>H-3'' - H-4'':</b> 1.65-1.90 (overlapping ms) <b>H-5'':</b> 3.55-3.76 (overlapping ms)	174.6 and 173.6	52.4 and 52.3	16.9 and 15.9	68.40 and 68.39	81.4 and 80.9	<b>C-3'':</b> 26.8 and 26.5, <b>C-4'':</b> 26.0 and 25.7, <b>C-5'':</b> 69.0 and 68.9.
 <p>(97)</p>	<b>OH/NH</b>	<b>H-3</b>	<b>H-1'</b>	<b>H-1''</b>	<b>Other signals</b>	<b>C-1</b>	<b>C-1'</b>	<b>C-3</b>	<b>C-2</b>	<b>C-2''</b>	<b>Other signals</b>
	6.16 (s)	1.28 (s)	3.76 (s)	1.50 (s)	<b>H-4''/H-5'':</b> 3.88-3.92 (ms)	173.3	52.6	16.4	72.5	110.3	<b>C-4''/C-5'':</b> 65.4/65.5, <b>C-1'':</b> 21.3.
 <p>(94)</p>	<b>OH/NH</b>	<b>H-1''</b>	<b>H-1'</b>	<b>H-1''</b>	<b>H-4</b>	<b>C-1</b>	<b>C-1'</b>	<b>C-1''</b>	<b>C-2</b>	<b>C-3</b>	<b>Other signals</b>
	—	1.14 (s)	3.71 (s)	1.13 (s)	1.33 (s)	175.6	52.4	16.4	72.0	73.9	<b>C-1''/C-4:</b> 24.4/26.5

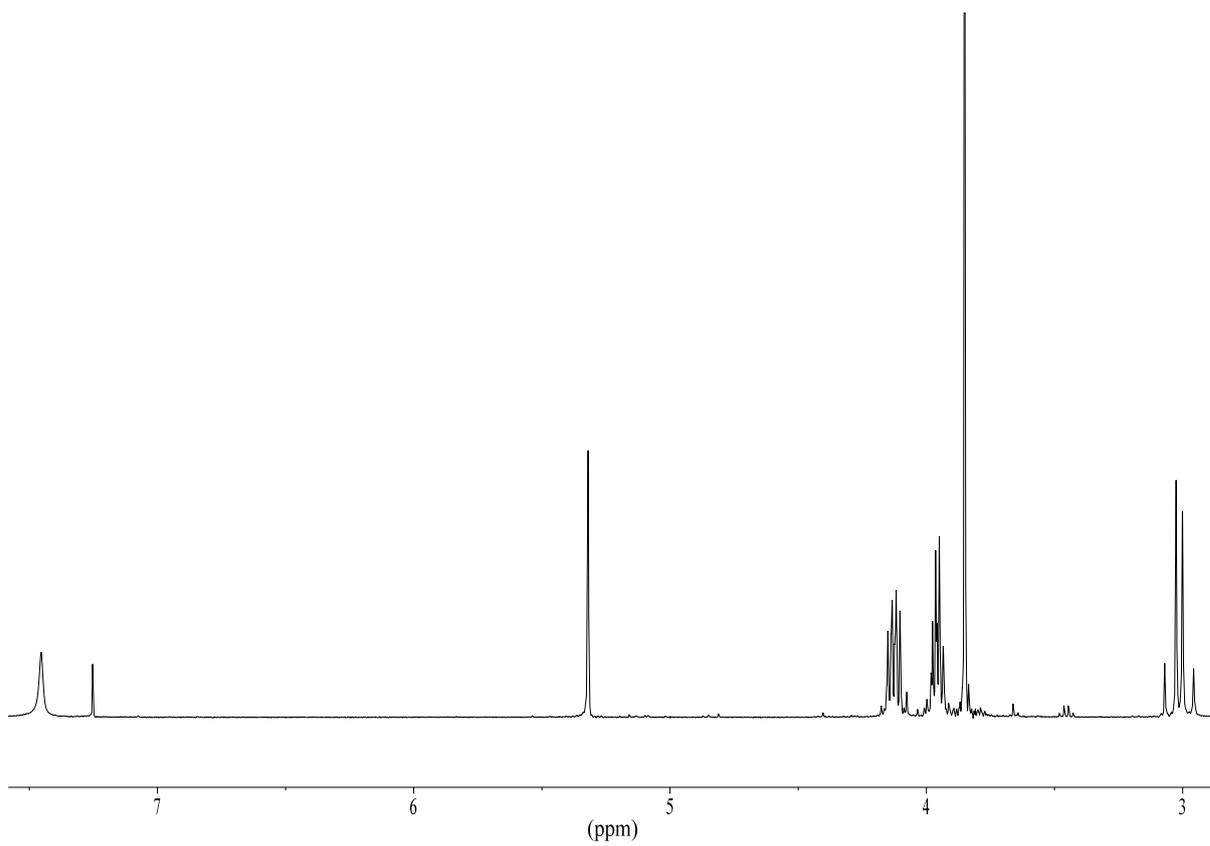
## 2.9 Photochemical reactions of 1,4-dimethyl (2E)-2-(hydroxyimino)butandioate (77)

### 2.9.1 Photochemical reaction of 1,4-dimethyl (2E)-2-(hydroxyimino)butandioate (77) and 1,3-dioxolane



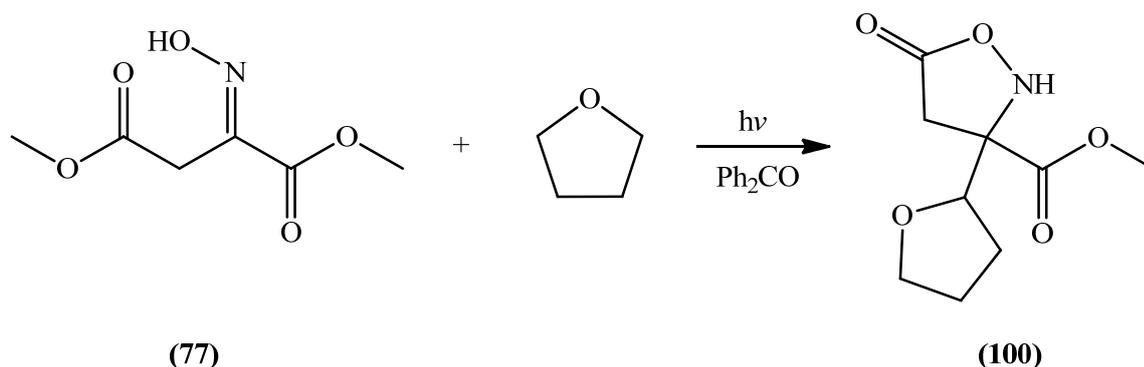
Scheme 78

A solution of 1,4-dimethyl (2E)-2-(hydroxyimino)butandioate (77), benzophenone and 1,3-dioxolane in MeCN was prepared as before (Section 2.6.1) and was then irradiated for 3 h at which time all the starting material had reacted and a single product, (99), had formed (GC). Analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated that a large amount of benzopinacol had formed. Flash column chromatography gave the product, methyl 3-(1,3-dioxolan-2-yl)-5-oxoisoazolidine-3-carboxylate (99), as a yellow oil in 73% yield. Analysis of the IR spectrum showed a band at 3254 cm<sup>-1</sup>, which corresponded to the NH, and two bands at 1789 and 1738 cm<sup>-1</sup> for the two carbonyl groups. There were also CO stretching bands at 1194, 1142 and 1028 cm<sup>-1</sup>. The <sup>1</sup>H-NMR spectrum (Figure 21) had two singlets at δ 3.85 and 5.32, which corresponded to the methyl and methine protons, respectively, a pair of doublets at δ 2.98 and 3.05 (*J* = 17.8 Hz) corresponding to the methylene protons of the oxoisoazolidine ring; the methylene protons of the dioxolanyl ring appeared as expected (Table 8). In the <sup>13</sup>C-NMR spectrum there were signals at 173.8 and 169.7 ppm which corresponded to the two carbonyl carbons. The methine and quaternary carbons resonated at 103.6 and 71.1 ppm, respectively, and the methylene carbons resonated at 66.7, 66.2 and 34.4 ppm. The methoxy carbon appeared in the expected position at 53.9 ppm.



**Figure 21**  $^1\text{H-NMR}$  spectrum of (99)

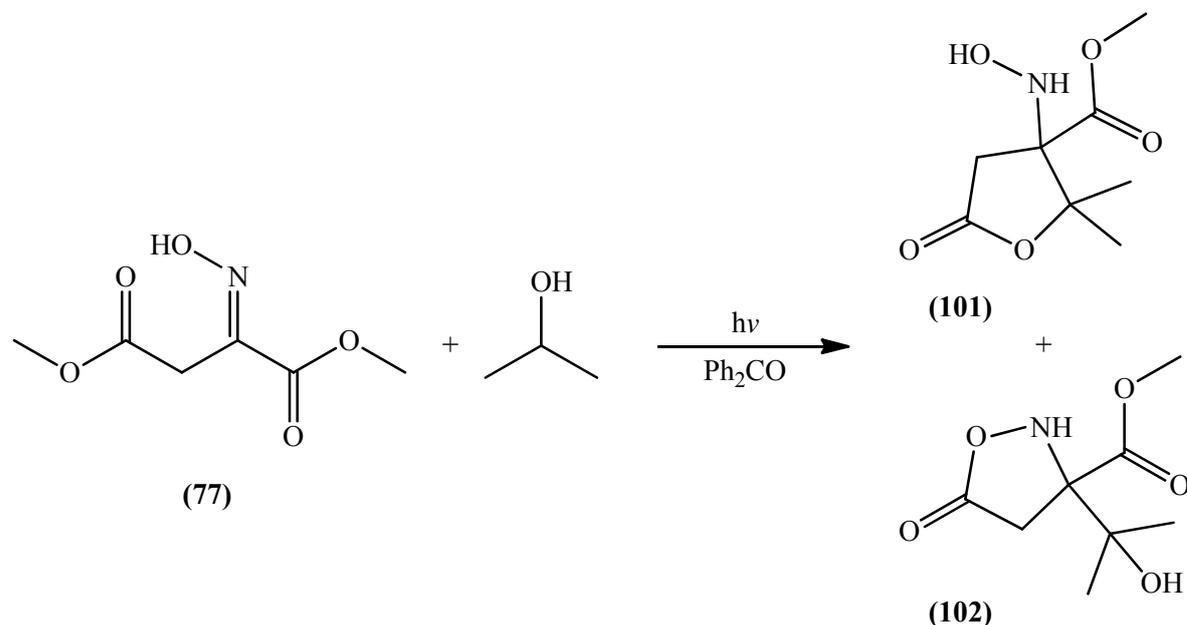
### 2.9.2 Photochemical reaction of 1,4-dimethyl (2E)-2-(hydroxyimino)butandioate (77) and THF



Scheme 79

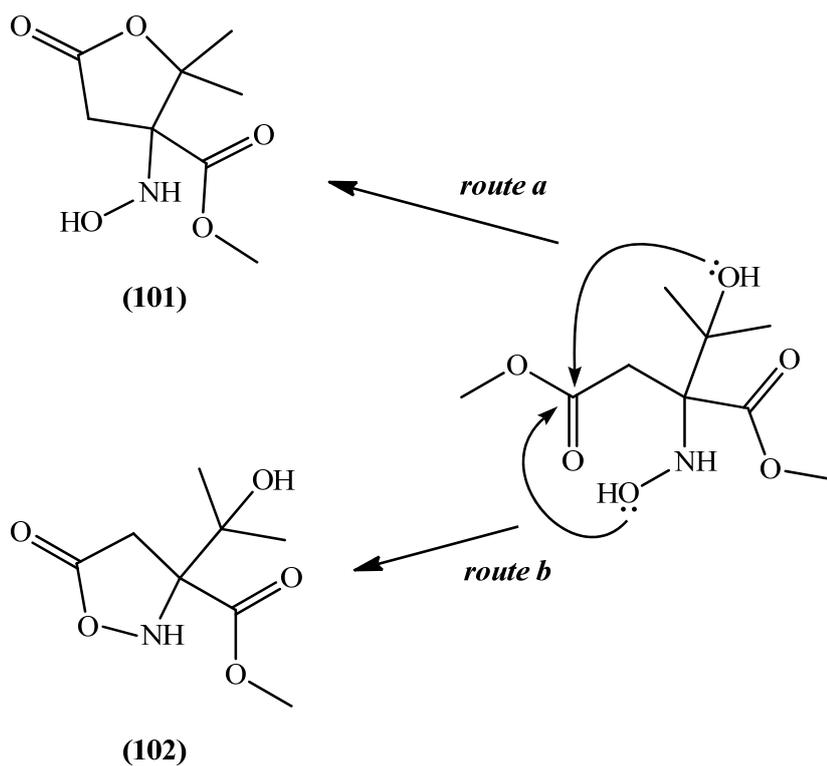
A solution of 1,4-dimethyl (2E)-2-(hydroxyimino)butandioate (77), benzophenone and THF in MeCN was prepared as before (Section 2.6.1). The solution was then irradiated for 3 h at which time all the starting material had reacted (GC). GC analysis indicated the formation of the product, (100), as a mixture of diastereomers in a 1:1 ratio. Analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated that a large amount of benzopinacol had formed. Flash column chromatography gave methyl 5-oxo-3-(tetrahydrofuran-2-yl)-1,2-oxazolidine-3-carboxylate (100) as a clear oil in 83% yield, with no change in the ratio of diastereomers (GC). Analysis of the IR spectrum showed the NH band at 3250 cm<sup>-1</sup>, two carbonyl bands at 1786 and 1733 cm<sup>-1</sup> and CO stretching bands at 1183, 1137 and 1067 cm<sup>-1</sup>. The <sup>1</sup>H-NMR spectrum had a series of overlapping multiplets at δ 1.78-2.05 and 3.72-3.91 which corresponded to the methylene protons of the tetrahydrofuran ring and pairs of doublets at δ 2.85, 2.96, 3.00 and 3.10 (*J* = 17.4 Hz) for the methylene protons of the oxoisoazolidine ring. Two singlets were observed for the methyl protons (Table 8) and a broad singlet was observed at δ 7.42 which corresponded to the NH. In the <sup>13</sup>C-NMR spectrum four carbonyl signals at 174.9, 171.2, 171.0 and 170.7 ppm corresponded to the two different carbonyl groups in the molecule. The methine carbons resonated at 81.0 and 80.4 ppm, and the quaternary carbons resonated as one signal at 71.1 ppm. The methoxy and methylene carbons gave the expected signals (Table 8).

### 2.9.3 Photochemical reaction of 1,4-dimethyl (2E)-2-(hydroxyimino)butandioate (77) and 2-propanol

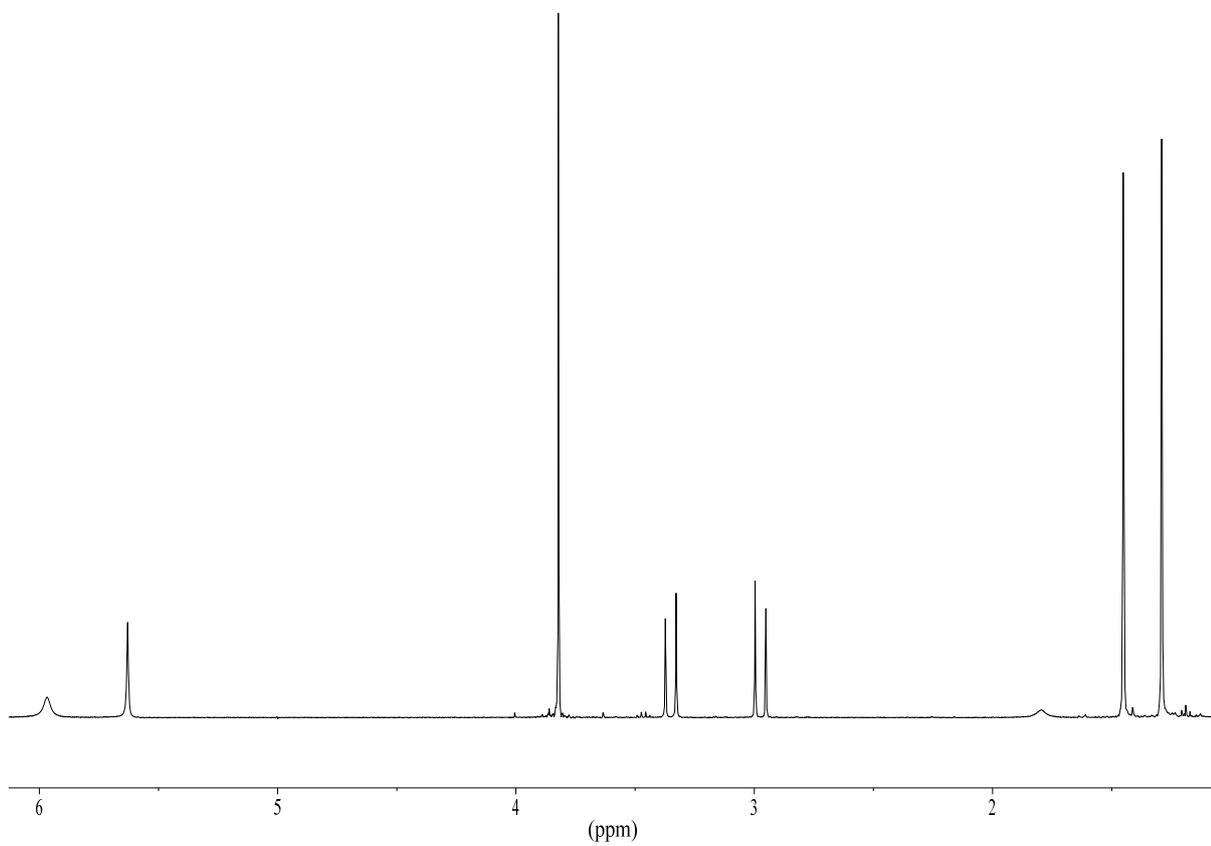


Scheme 80

A solution of 1,4-dimethyl (2E)-2-(hydroxyimino)butandioate (77), benzophenone and 2-propanol in MeCN was prepared as before (Section 2.6.1) and was then irradiated for 2 h at which time the reaction had stopped (GC). Analysis of the  $^1\text{H-NMR}$  spectrum of the crude product indicated that all the benzophenone had dimerized, products (101) and (102) were formed in 1:4 ratio and that unreacted starting material remained. The lactone (101) is formed by the spontaneous attack of the oxygen, from the newly attached hydroxyl group at a carbonyl carbon followed by loss of methanol (Scheme 81, route a). The oxazolidine (102) is formed from the attack of the oxygen from the hydroxyamino group at a carbonyl carbon (Scheme 81, route b). Methyl-3-(hydroxyamino)-2,2-dimethyl-5-oxotetrahydrofuran-3-carboxylate (101) was eluted first on chromatography and was obtained as a clear oil in 14% yield. In the IR spectrum there were bands at 3398 and 3267  $\text{cm}^{-1}$  which corresponded to the OH and NH groups, respectively. Two bands were present at 1773 and 1726  $\text{cm}^{-1}$  which corresponded to the carbonyl groups the former due to the lactone carbonyl; bands due to CO stretching appeared at 1182, 1133 and 1033  $\text{cm}^{-1}$ . In the  $^1\text{H-NMR}$  spectrum (Figure 22) there were singlets in the expected regions for the methyl groups and the methoxy group (Table 8). The methylene protons appeared as a pair of doublets at  $\delta$  2.97 and 3.35 ( $J = 18.1$  Hz). There were also signals for the OH and NH protons at  $\delta$  5.62 and 5.96. In the  $^{13}\text{C-NMR}$  spectrum the carbonyl carbons resonated at 173.9 and 170.6 ppm, the quaternary carbons at 85.1 and 73.9 ppm, and the methyl carbons at 25.2 and 20.5 ppm. The methylene and methoxy carbon appeared as expected (Table 8).



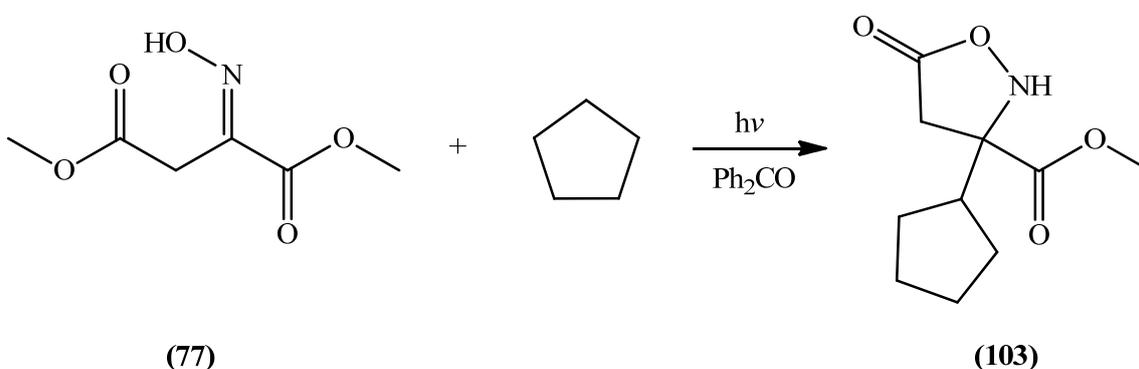
**Scheme 81**



**Figure 22  $^1\text{H-NMR}$  spectrum of (101)**

The second product eluted from the column was methyl-3-(2-hydroxypropan-2-yl)-5-oxo-1,2-oxazolidine-3-carboxylate (**102**); it was obtained as a clear oil in 29% yield. The IR spectrum had bands at 3474 and 3258  $\text{cm}^{-1}$ , for the OH and NH groups, respectively, two bands at 1782 and 1729  $\text{cm}^{-1}$  for the carbonyl groups, and at 1173, 1133 and 1032  $\text{cm}^{-1}$  for the CO bonds. In the  $^1\text{H-NMR}$  spectrum singlets at  $\delta$  1.14 and 1.22 corresponded to the two methyl groups, and a singlet at  $\delta$  3.86 to the methoxy group. The methylene protons appeared as a pair of doublets at  $\delta$  3.01 and 3.36 ( $J = 18.0$  Hz), and the NH proton appeared as a singlet (**Table 8**). In the  $^{13}\text{C-NMR}$  spectrum the carbonyl carbons resonated at 173.6 and 172.3 ppm, the methoxy carbon appeared at 53.9 ppm and the quaternary carbons resonated at 76.0 and 71.9 ppm. The other carbon signals appeared as expected (**Table 8**).

#### 2.9.4 Photochemical reaction of 1,4-dimethyl (2E)-2-(hydroxyimino)butandioate (77) and cyclopentane



**Scheme 82**

A solution of 1,4-dimethyl (2E)-2-(hydroxyimino)butandioate (**77**), benzophenone and cyclopentane in MeCN was prepared as before (**Section 2.6.1**). It was irradiated for 4 h at which time all of the benzophenone had dimerised. Analysis of the  $^1\text{H-NMR}$  spectrum of the crude product indicated that a complex mixture of products had formed, together with benzopinacol and unreacted starting material. A singlet at  $\delta$  3.77 for the methoxy group and signals at  $\delta$  2.76-3.04 for the methylene protons of the oxazolidine ring indicated that the mixture contained traces of the addition product, (**103**). Attempts to isolate the product *via* flash chromatography failed.

Table 8 NMR data for 1,4-diethyl (2*E*)-(hydroxyimino)butandioate reactions

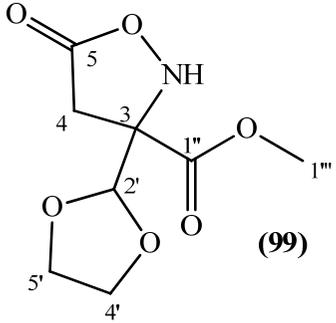
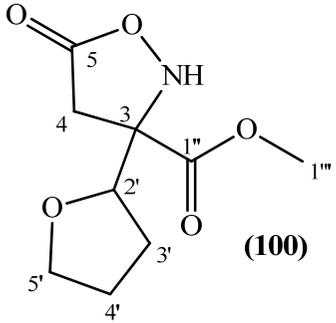
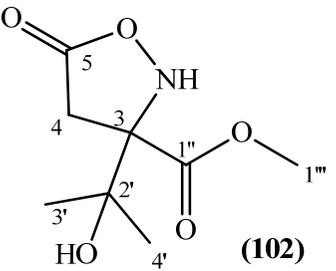
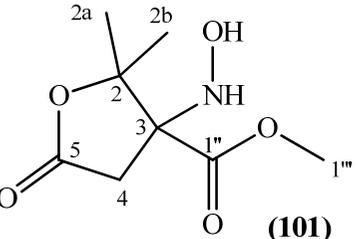
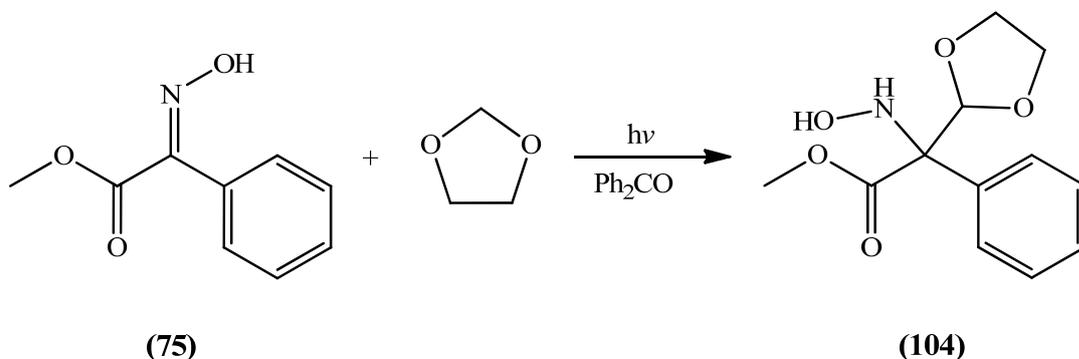
	<sup>1</sup> H-NMR data (δ)					<sup>13</sup> C-NMR data (ppm)					
	NH	H-2'	H-1'''	H-4	Other Signals	C-5	C-1''	C-1'''	C-4	C-3	Other Signals
 <p>(99)</p>	7.45 (s)	5.32 (s)	3.85 (s)	2.98 and 3.05 (ds) <i>J</i> = 17.8 Hz	<b>H-4'/H-5'</b> : 3.91-4.01/ 4.09-4.18 (ms)	173.8	169.7	53.9	34.4	71.1	<b>C-2'</b> : 103.6, <b>C-4'/C-5'</b> : 66.2/66.7.
 <p>(100)</p>	7.42 (br s)	4.19 and 4.26 (ts) <i>J</i> = 6.8 Hz	3.80 and 3.81 (s)	2.85, 2.96, 3.00 and 3.10 (ds) <i>J</i> = 17.4 Hz	<b>H-3' and H-4'</b> : 1.78-2.05 (overlapping ms) <b>H-5'</b> : 3.72-3.91 (overlapping ms)	174.9 and 171.2	171.0 and 170.7	53.7 and 53.6	36.8 and 36.5	71.1	<b>C-2'</b> : 81.0 and 80.4 <b>C-3'</b> : 26.7 and 26.4 <b>C-4'</b> : 26.0 and 25.8 <b>C-5'</b> : 69.6 and 69.4

Table 8 (contd.) NMR data for 1,4-diethyl (2*E*)-(hydroxyimino)butandioate reactions

	<sup>1</sup> H-NMR data (δ)				<sup>13</sup> C-NMR data (ppm)				
	OH/NH	H-4	H-1'''	Other Signals	C-5	C-1''	C-1'''	C-3	Other Signals
 <p>(102)</p>	5.62 (s)/ 5.96 (s)	2.97 and 3.35 (ds) <i>J</i> = 18.1 Hz	3.82 (s)	<b>H-3'/H-4'</b> : 1.29 (s) / 1.45 (s)	173.9	170.6	53.2	73.9	<b>C-4</b> : 35.8, <b>C-2'</b> : 85.1, <b>C-3'/C-4'</b> : 20.5/25.2.
 <p>(101)</p>	NH	H-4	H-1'''	Other Signals	C-5	C-1''	C-1'''	C-3	Other Signals
	7.81 (br s)	3.01 and 3.36 (ds) <i>J</i> = 18.0 Hz	3.86 (s)	<b>H-2a/H-2b</b> : 1.14 (s) / 1.22 (s)	173.6	172.3	53.9	71.9	<b>C-4</b> : 33.8, <b>C-2</b> : 76.0, <b>C-2a/C-2b</b> : 15.3/25.1.

## 2.10 Photochemical reactions of methyl (2E)-(hydroxyimino)(phenyl)acetate (75)

### 2.10.1 Photochemical reaction of methyl (2E)-(hydroxyimino)(phenyl)acetate (75) and 1,3-dioxolane



Scheme 83

A solution of methyl (2E)-(hydroxyimino)(phenyl)acetate (**75**), benzophenone and 1,3-dioxolane in MeCN was prepared as before (Section 2.6.1) and was then irradiated for 6 h at which time no change was occurring (GC). Analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated that a complex mixture of products had formed and that the benzophenone had dimerised completely. Flash column chromatography gave the product, methyl-1,3-dioxolan-2-yl(hydroxyamino)phenylacetate (**104**), in 25% yield. In the IR spectrum there were bands at 3418, 3271 and 1736 cm<sup>-1</sup> which corresponded to the OH, NH and carbonyl groups, respectively, together with the CO stretching bands at 1122, 1089 and 1037 cm<sup>-1</sup>. In the <sup>1</sup>H-NMR spectrum (Figure 23) the methyl and methine protons appeared as singlets at δ 3.83 and 5.68, respectively, and the methylene protons appeared as a series of multiplets at δ 3.59, 3.71 and 3.77-3.87. The aromatic protons appeared in the characteristic region as a series of multiplets (Table 9). In the <sup>13</sup>C-NMR spectrum the aromatic signals were as expected (Table 9), the carbonyl carbon resonated at 171.7 ppm and the quaternary carbon resonated at 74.4 ppm. The methine carbon resonated at 104.1 ppm and the methylene and methoxy carbons gave the expected signals (Table 9).

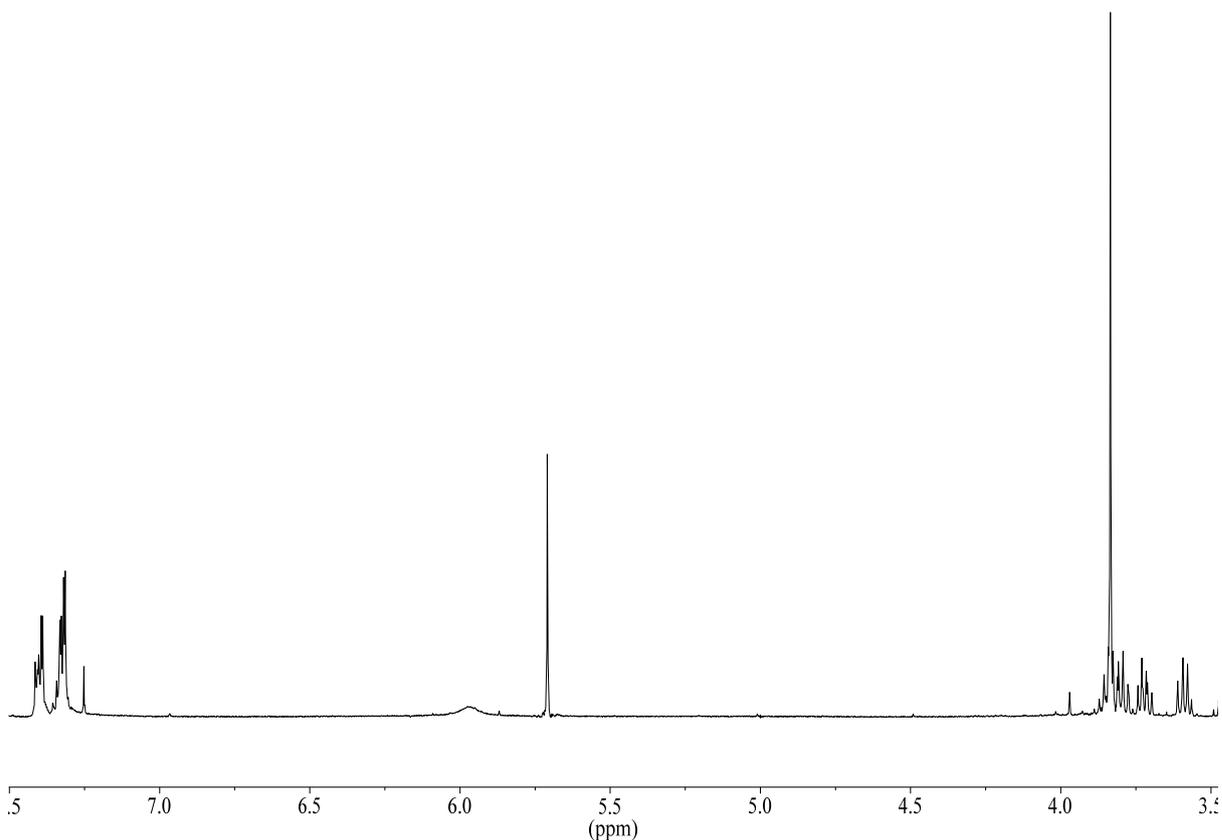
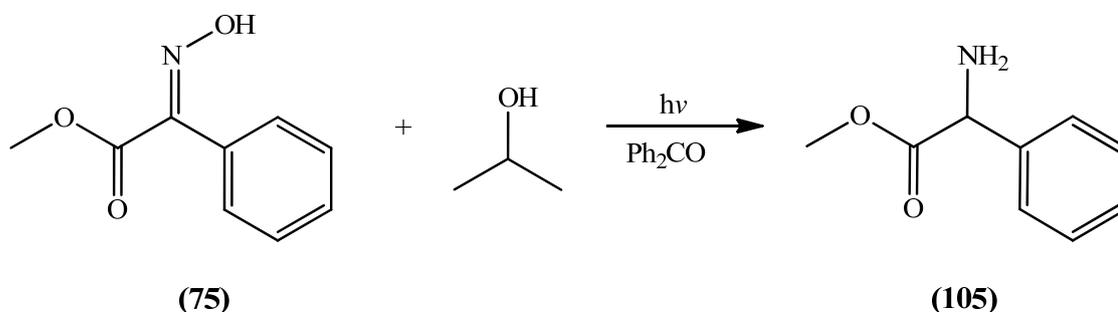


Figure 23  $^1\text{H-NMR}$  spectrum of (104)

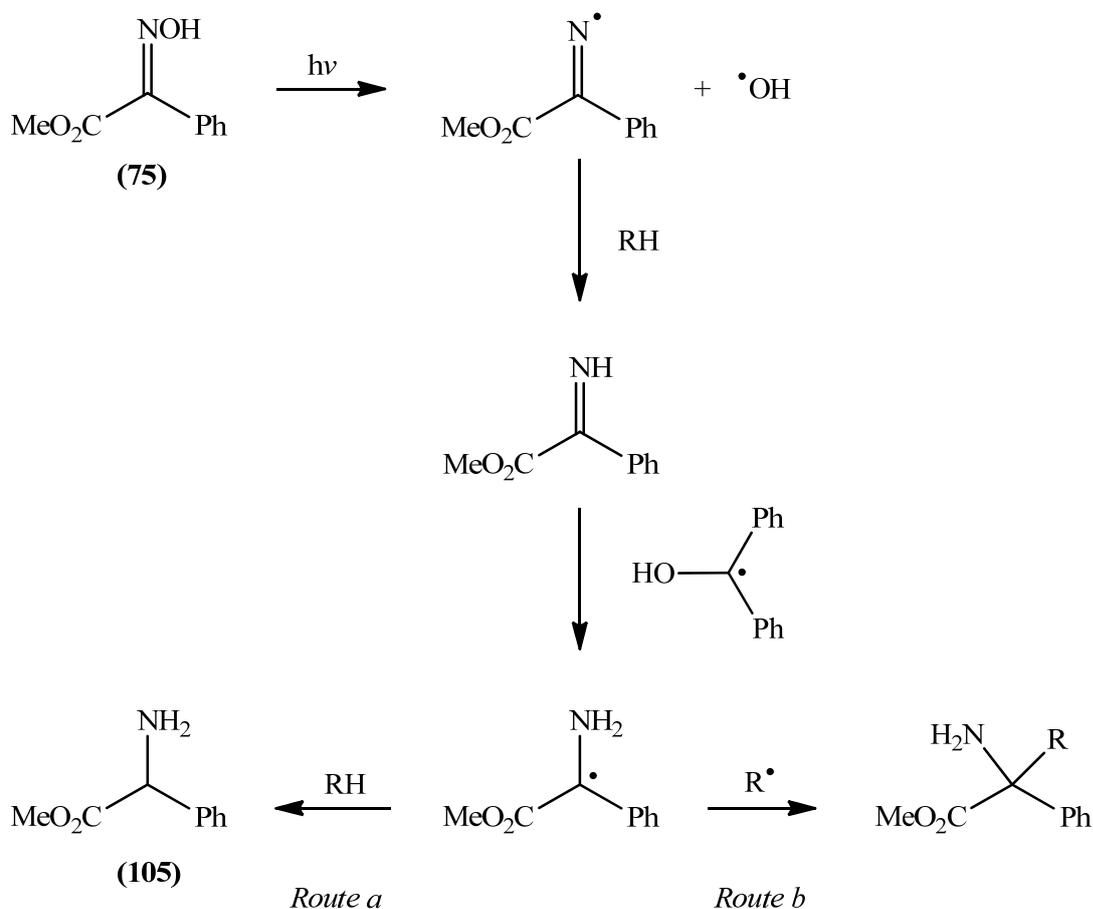
2.10.2 Photochemical reaction of methyl (2*E*)-(hydroxyimino)(phenyl)acetate (75) and 2-propanol



Scheme 84

A solution of methyl (2*E*)-(hydroxyimino)(phenyl)acetate (75) and benzophenone in 2-propanol was degassed and then irradiated for 6 h at which time no further change was occurring (GC). Analysis of the  $^1\text{H-NMR}$  spectrum of the crude product indicated that all the benzophenone had dimerised and a small amount of unreacted starting material remained. Flash column chromatography gave the product, methyl 2-amino-2-phenylacetate (105), as a clear oil in 33% yield. Spectroscopic data were consistent with those in the literature<sup>[74]</sup>. It is very difficult to see how this product is formed if the classical photomediated reaction mechanism is followed. In *lieu* of this an alternative mechanism is proposed (Scheme 85, Route a). Homolysis of the NO bond leads to the formation of an iminyl and hydroxyl radical. This iminyl radical then abstracts a proton from the solvent, in this case 2-propanol, forming

the imine. This then reacts with a ketyl radical, reforming benzophenone and the tertiary benzylic radical. Further hydrogen abstraction from another solvent molecule leads to the formation of **(105)**.



**Scheme 85**

In the IR spectrum there were bands at  $3376$  and  $3306\text{ cm}^{-1}$  due to the symmetrical and unsymmetrical stretching of the  $\text{NH}_2$ , a band at  $1733\text{ cm}^{-1}$  for the carbonyl group and CO stretching bands at  $1220$ ,  $1167$  and  $1072\text{ cm}^{-1}$ . In the  $^1\text{H-NMR}$  spectrum (**Figure 24**) the methine and methoxy protons appeared as singlets at  $\delta$  4.58 and 3.65, respectively. There was a broad singlet at  $\delta$  2.18 for the aminyl protons and the aromatic protons appeared as a series of multiplets at  $\delta$  7.22-7.33. In the  $^{13}\text{C-NMR}$  spectrum the carbonyl carbon resonated at  $174.5\text{ ppm}$  and the aromatic signals were as expected (**Table 9**). The methine and methoxy carbons resonated at  $58.8$  and  $52.5\text{ ppm}$ , respectively.

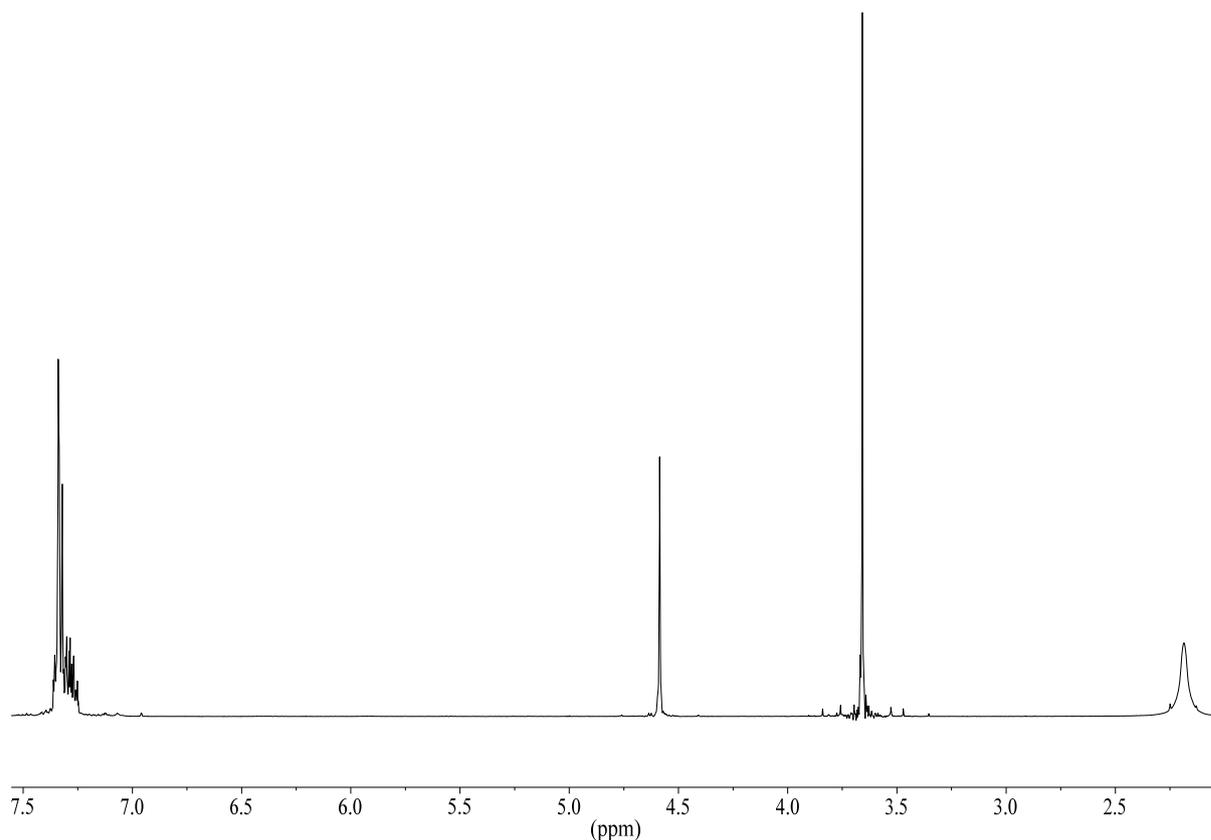
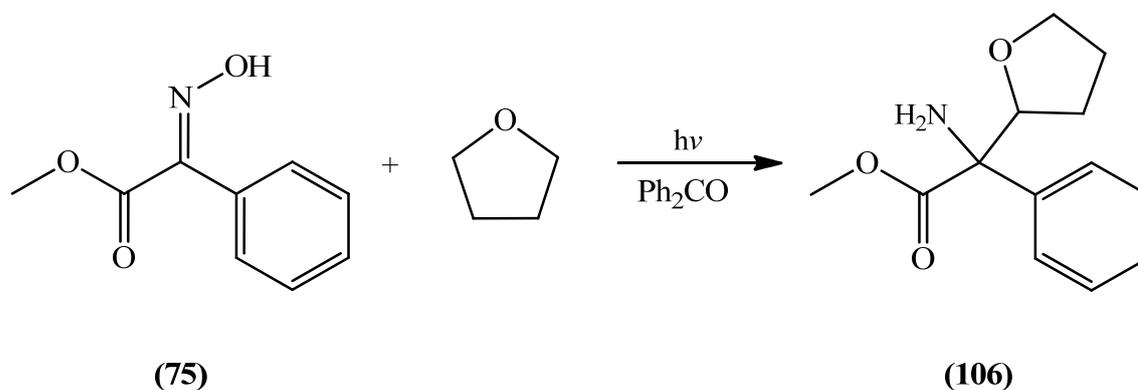


Figure 24  $^1\text{H-NMR}$  spectrum of (105)

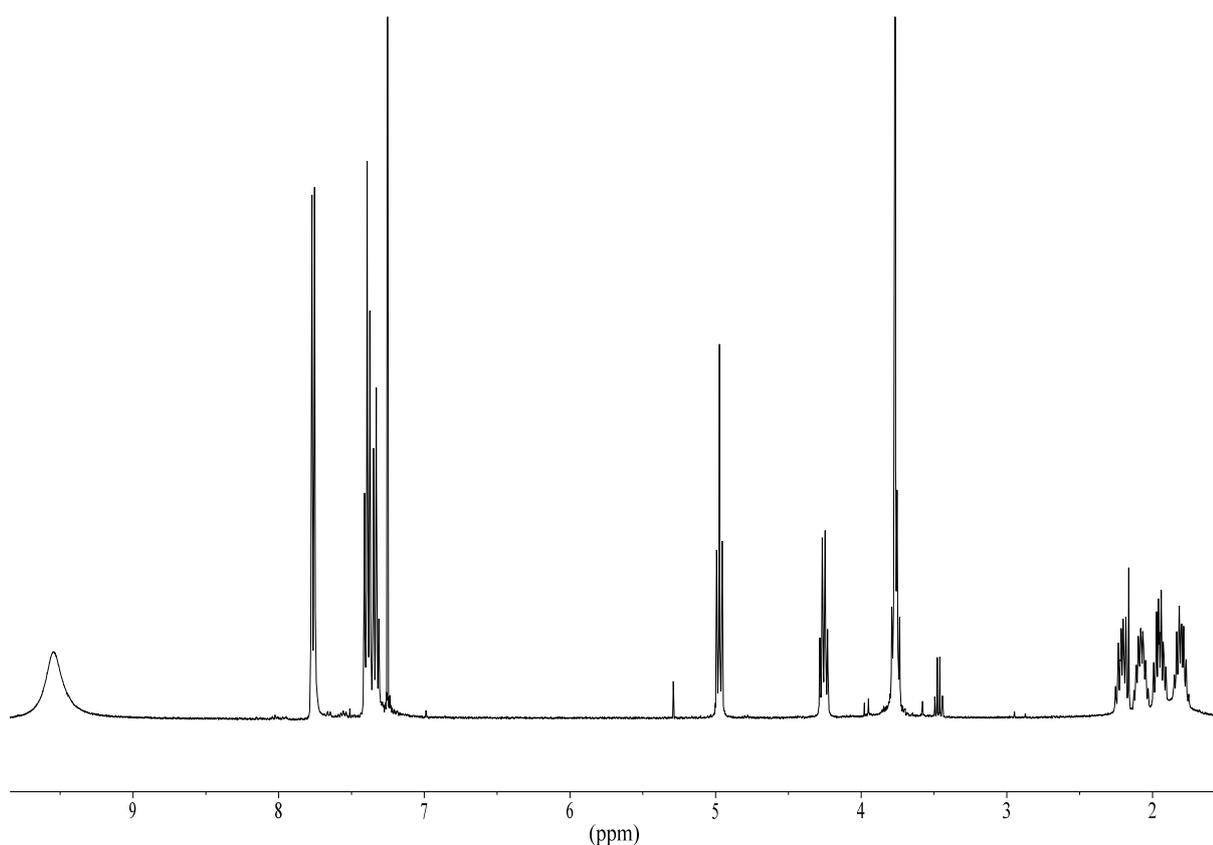
### 2.10.3 Photochemical reaction of methyl (2E)-(hydroxyimino)(phenyl)acetate (75) and THF



Scheme 86

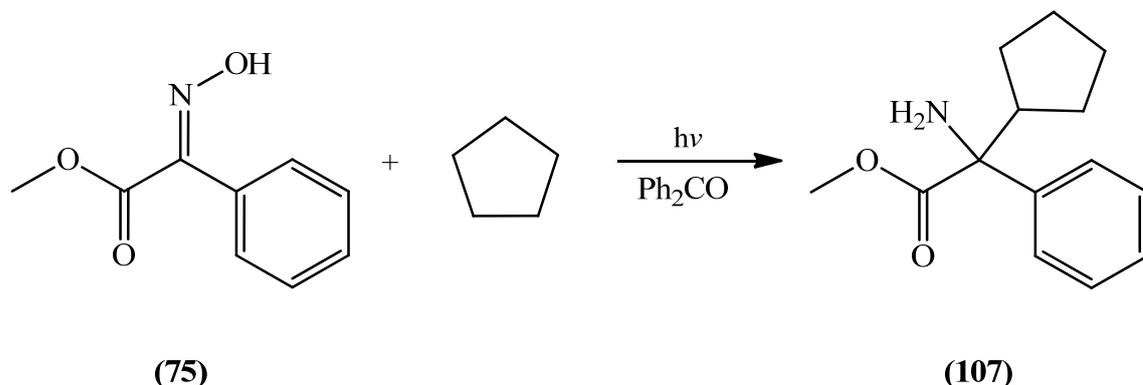
A solution of methyl (2E)-(hydroxyimino)(phenyl)acetate (**75**), benzophenone and THF in MeCN was prepared as before (Section 2.6.1). It was then irradiated for 3 h at which time no further change was noted in the reaction (GC). GC analysis indicated that a range of products was formed which was confirmed by analysis of the  $^1\text{H-NMR}$  of the crude product which showed a complex mixture of products had formed. Flash chromatography gave methyl amino(tetrahydrofuran-2-yl)phenylacetate (**106**) as a clear oil in 11% yield as a single diastereomer. This product is again formed *via* the

mechanism proposed above (**Scheme 85, Route b**). Instead of the tertiary benzylic radical abstracting a proton from the solvent, it combines with the tetrahydrofuranyl radical formed through hydrogen abstraction by an excited benzophenone. In the IR spectrum there were weak bands at 3382 and 3322  $\text{cm}^{-1}$  due to the symmetrical and unsymmetrical stretching of the  $\text{NH}_2$  group, a band at 1731  $\text{cm}^{-1}$  for the carbonyl group, and CO stretching bands at 1233, 1179 and 1063  $\text{cm}^{-1}$ . There were also two bands at 729 and 698  $\text{cm}^{-1}$  for the monosubstituted benzene ring. In the  $^1\text{H-NMR}$  spectrum (**Figure 25**) there were a series of multiplets at  $\delta$  1.75-2.25 which corresponded to four of the tetrahydrofuranyl protons. The other methylene protons of the ring resonated as multiples at  $\delta$  3.75 and 4.24. The methoxy protons appeared as a singlet at  $\delta$  3.75 and the aromatic signals were as expected (**Table 9**). The methine proton appeared as a triplet at  $\delta$  4.97 ( $J_{cis} = J_{trans} = 7.8$  Hz). In the  $^{13}\text{C-NMR}$  spectrum the carbonyl carbon resonated at 169.2 ppm and the aromatic signals appeared at 132.4, 129.3, 129.2 and 126.7 ppm. The methine and methoxy carbons resonated in the expected regions (**Table 9**) and the quaternary carbon appeared at 69.0 ppm. The methylene carbons of the tetrahydrofuranyl ring resonated at 69.9, 26.9 and 26.0 ppm.



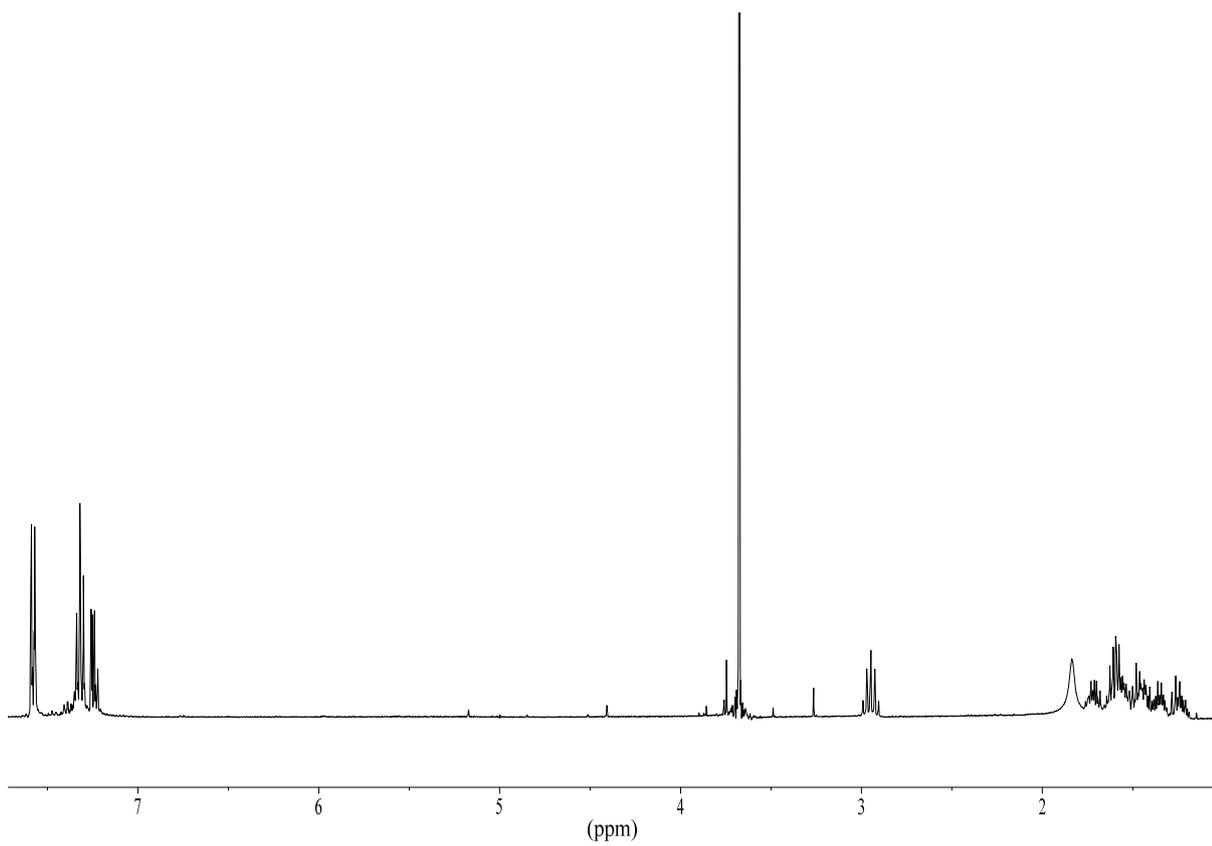
**Figure 25**  $^1\text{H-NMR}$  spectrum of (106)

**2.10.4 Photochemical reaction of methyl (2E)-(hydroxyimino)(phenyl)acetate (75) and cyclopentane**



**Scheme 87**

A solution of methyl (2E)-(hydroxyimino)(phenyl)acetate (**75**), benzophenone and cyclopentane in MeCN was prepared as before (**Section 2.6.1**) and was then irradiated for 6 h at which time no further change was occurring (GC). Analysis of the <sup>1</sup>H-NMR of the crude product indicated a complex mixture of products and some benzopinacol was formed. Flash chromatography gave methyl amino(cyclopentyl)phenylacetate (**107**) as a clear oil in 23% yield. This was formed following the route described above (**Scheme 85, Route b**). In the IR spectrum there were weak bands at 3392 and 3332 cm<sup>-1</sup> due to the symmetrical and unsymmetrical stretching of the NH<sub>2</sub> group, a band at 1727 cm<sup>-1</sup> for the carbonyl group and CO stretching bands at 1226, 1174 and 1020 cm<sup>-1</sup>. There were also two bands at 730 and 698 cm<sup>-1</sup> for the monosubstituted benzene ring. In the <sup>1</sup>H-NMR spectrum (**Figure 26**) there was a series of overlapping multiplets at δ 1.18-1.78 which corresponded to the methylene protons of the cyclopentyl ring and a broad singlet at δ 1.78-1.90 for the aminyl protons. The methoxy protons appeared as a singlet at δ 3.69 and the methine proton appeared as a quintet at δ 2.95 ( $J_{cis} = J_{trans} = 8.66$  Hz). The aromatic protons appeared as a series of overlapping multiplets (**Table 9**). In the <sup>13</sup>C-NMR spectrum the carbonyl carbon resonated at 176.2 ppm and the aromatic signals appeared at 143.2, 128.3, 127.3 and 125.9 ppm. The methine and methoxy carbons resonated at 47.4 and 52.5 ppm, respectively, and the quaternary carbon at 65.6 ppm. The methylene carbons of the cyclopentyl ring were as expected (**Table 9**).



**Figure 26  $^1\text{H-NMR}$  spectrum of (107)**

Table 9 NMR data for methyl (2*E*)-(hydroxyimino)(phenyl)acetate reactions

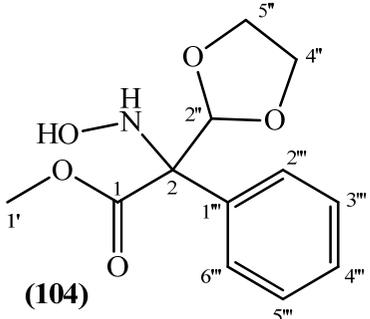
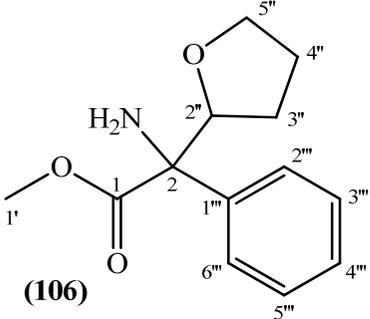
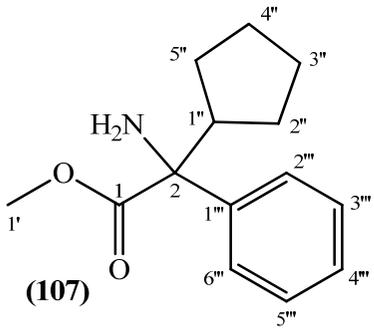
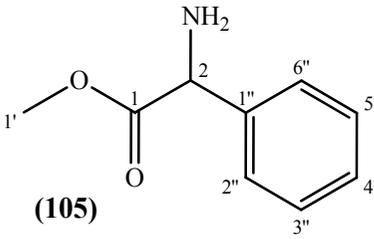
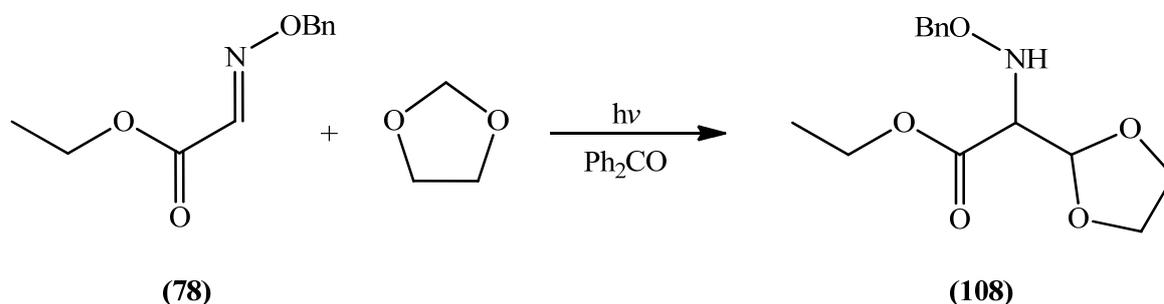
	<sup>1</sup> H-NMR data (δ)					<sup>13</sup> C-NMR data (ppm)					
	OH/NH	H-1'	H-2''	H-2'''/ H-6'''	Other signals	C-1	C-1'	C-2	C-2''	C-1'''	Other signals
 <p>(104)</p>	5.97 (br s)	3.83 (s)	5.68 (s)	7.39-7.41 (ms)	<b>H-4'' and H-5'':</b> 3.59, 3.71 and 3.77-3.87 (ms) <b>H-3'''-H-5''':</b> 7.31-7.34 (overlapping ms)	171.7	52.7	74.4	104.1	134.7	<b>C-4''/C-5'':</b> 65.5/65.9, <b>Ar-CH:</b> 128.5, 128.3 and 127.8.
 <p>(106)</p>	9.52 (br s)	3.75 (s)	4.97 (t) <i>J</i> = 7.8 Hz	7.76 (d) <i>J</i> = 7.3 Hz	<b>H-3''-H-4'':</b> 1.75-2.25 (overlapping ms) <b>H-5'':</b> 3.75 and 4.24 (ms) <b>H-3'''-</b> <b>H-5''':</b> 7.30-7.41 (overlapping ms)	169.2	53.8	69.0	80.7	132.4	<b>C-3'':</b> 26.9, <b>C-4'':</b> 26.0, <b>C-5'':</b> 69.9, <b>Ar-CH:</b> 129.3, 129.2 and 126.7.

Table 9 (contd.) NMR data for methyl (2E)-(hydroxyimino)(phenyl)acetate reactions

	<sup>1</sup> H-NMR data (δ)					<sup>13</sup> C-NMR data (ppm)					
	NH <sub>2</sub>	H-1'	H-1''	H-2''- H-5''	Other signals	C-1	C-1'	C-2	C-1''	C-1'''	Other signals
 <p>(107)</p>	1.77-1.90 (br s)	3.69 (s)	2.95 (quintet) <i>J</i> = 8.66 Hz	1.18-1.78 (overlapping ms)	<b>H-2'''/H-6'''</b> : 7.57 (d) <i>J</i> = 7.2 Hz <b>H-3'''-H-5'''</b> : 7.21-7.37 (overlapping ms)	176.2	52.5	65.6	47.4	143.2	<b>C-2''/C-5''</b> : 26.9/27.9, <b>C-3''/C-4''</b> : 26.0/26.3, <b>Ar-CH</b> : 128.3, 127.3 and 125.9.
 <p>(105)</p>	2.18 (s)	52.5 (s)	4.58 (s)	<b>Ar-H</b> : 7.22-7.33 (overlapping ms)	174.5	52.5	58.8	140.3	<b>Ar-CH</b> : 128.9, 128.1 and 126.9.		

## 2.11 Photochemical reactions of ethyl (2E)-[(benzyloxy)imino]acetate (78)

### 2.11.1 Photochemical reaction of ethyl (2E)-[(benzyloxy)imino]acetate (78) and 1,3-dioxolane



Scheme 88

A solution of ethyl (2E)-[(benzyloxy)imino]acetate (78), benzophenone and 1,3-dioxolane in MeCN was prepared as before (Section 2.6.1) and the solution was then irradiated for 2.5 h at which time all the starting material had reacted (GC). GC analysis indicated the formation of a single product, (108). <sup>1</sup>H-NMR analysis of the crude product indicated that a large amount of benzopinacol had formed. Chromatography gave ethyl [(benzyloxy)amino](1,3-dioxolan-2-yl)acetate (108) as a clear oil in 75% yield. In the IR spectrum there were bands at 3266 and 1736 cm<sup>-1</sup>, which corresponded to the NH and carbonyl groups, respectively. There were also CO bands at 1199, 1147 and 1023 cm<sup>-1</sup> and bands at 740 and 696 cm<sup>-1</sup> which corresponded to the monosubstituted aromatic ring. In the <sup>1</sup>H-NMR spectrum (Figure 27) the benzylic methylene protons appeared as a singlet at δ 4.72, and the methine proton on the dioxolanyl ring appeared as a doublet at δ 5.13 (*J* = 4.2 Hz). The methylene protons of the dioxolanyl ring and the methine proton adjacent to the nitrogen appeared as overlapping multiplets at δ 3.81-3.97. The aromatic protons also appeared as a series of overlapping multiplets at δ 7.27-7.34. There was a broad singlet at δ 6.21 for the aminyl proton and the ethoxy signal was as expected (Table 10). In the <sup>13</sup>C-NMR spectrum the carbonyl carbon resonated at 170.1 ppm and the aromatic carbons appeared in the characteristic region (Table 10). The methine carbons resonated at 101.6 and 66.9 ppm, and the methylene carbons of the dioxolanyl ring appeared at 65.6 and 65.5 ppm. The ethoxy signals were as expected at 61.5 and 14.3 ppm, together with the benzylic methylene carbon at 76.4 ppm.

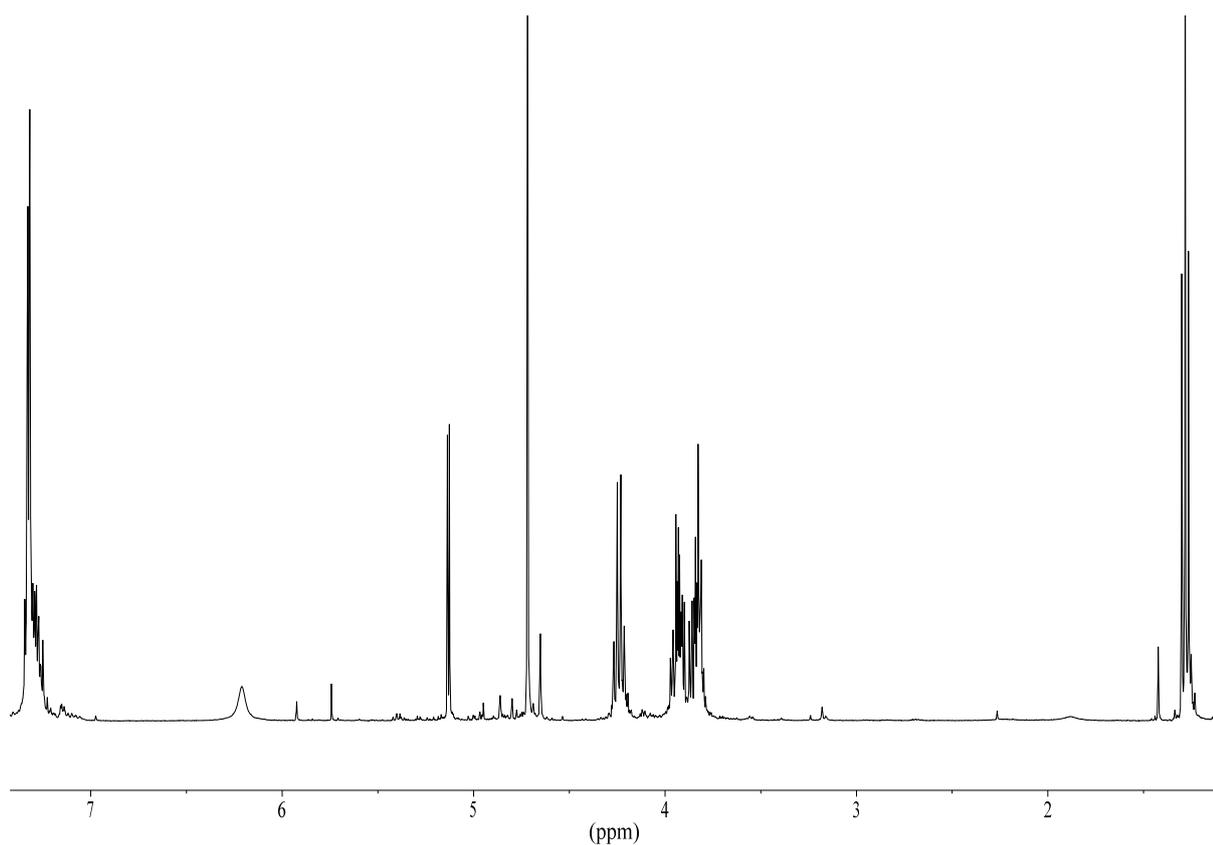
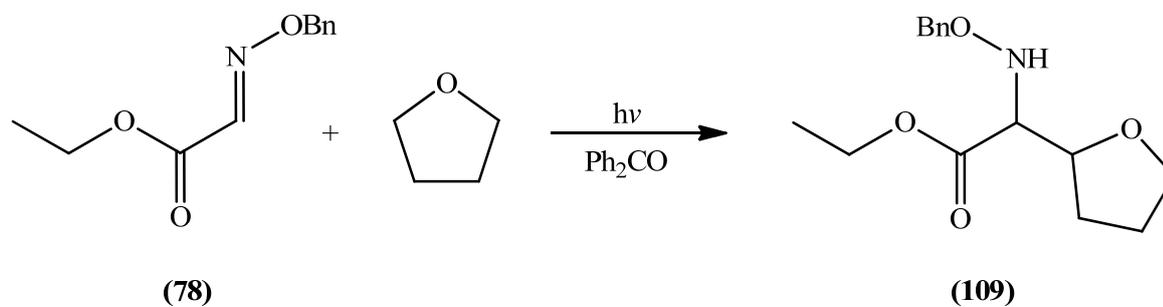


Figure 27  $^1\text{H-NMR}$  spectrum of (108)

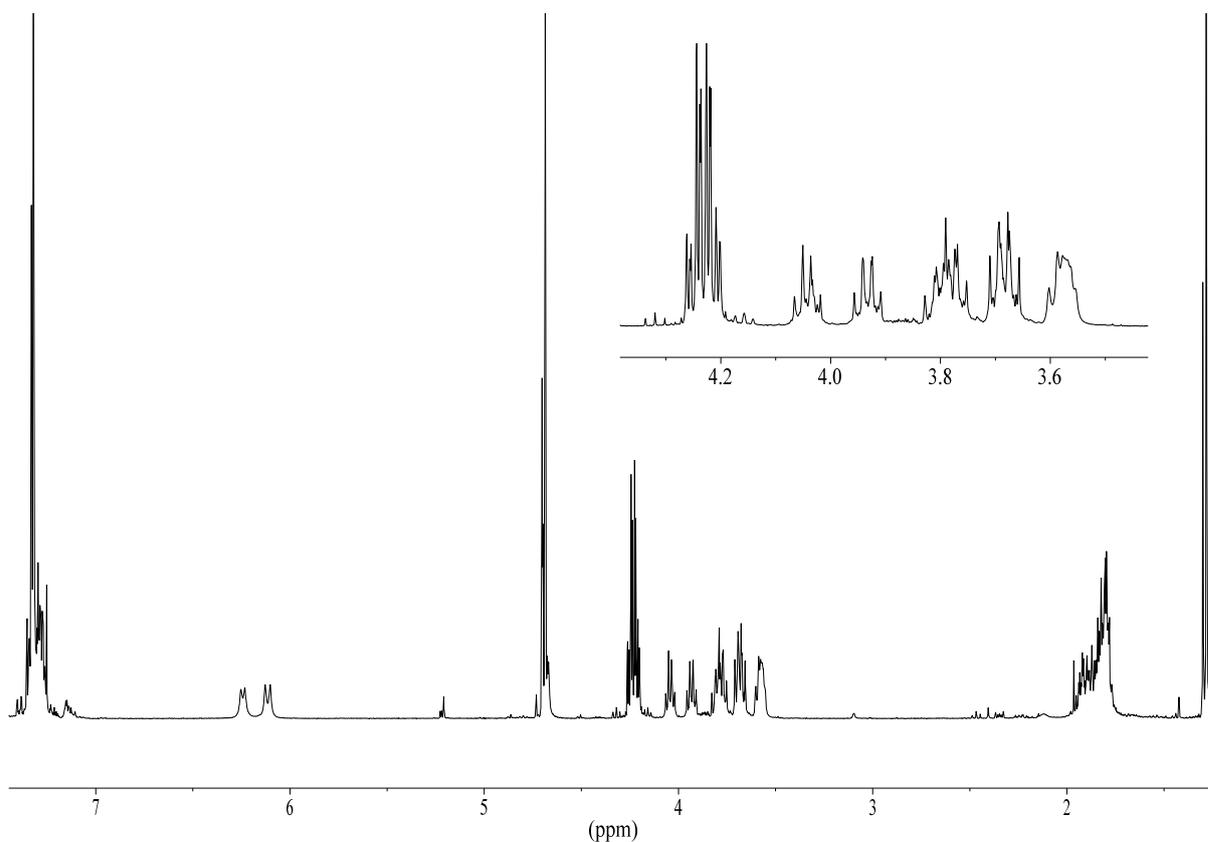
### 2.11.2 Photochemical reaction of ethyl (2*E*)-[(benzyloxy)imino]acetate (78) and THF



Scheme 89

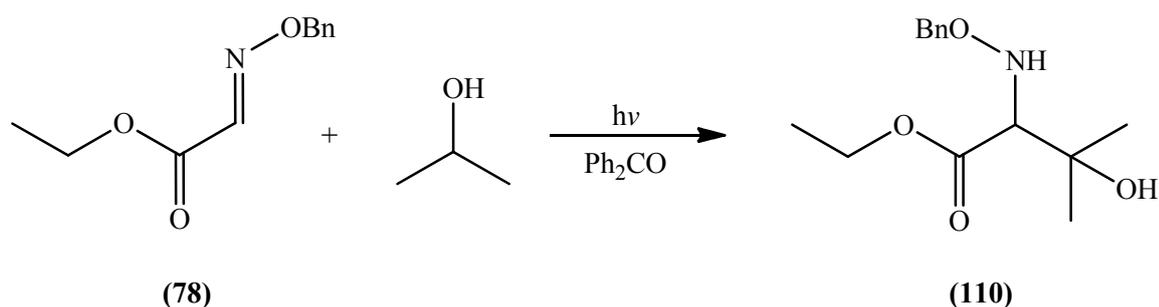
A solution of ethyl (2*E*)-[(benzyloxy)imino]acetate (**78**), benzophenone and THF in MeCN was prepared as before (Section 2.6.1). The solution was then irradiated for 3 h at which time all the starting material had reacted (GC). GC analysis indicated the formation of (**109**) as a mixture of diastereomers in a ratio of 1:1.06. Analysis of the  $^1\text{H-NMR}$  of the crude product indicated that most of the benzophenone had dimerised. Chromatography gave ethyl [(benzyloxy)amino](tetrahydrofuran-2-yl)acetate (**109**) as a clear oil in 73% yield, with no change in the diastereomeric ratio (GC). In the IR spectrum there were bands at 736 and 696  $\text{cm}^{-1}$ , for the monosubstituted aromatic ring, at 1255, 1062 and 1032  $\text{cm}^{-1}$ , for the CO bonds and at 3276 and 1732  $\text{cm}^{-1}$ , for the NH and carbonyl groups,

respectively. In the  $^1\text{H}$ -NMR spectrum (**Figure 28**) there was a triplet at  $\delta$  1.28 ( $J = 7.1$  Hz) and overlapping quartets at  $\delta$  4.22 and 4.24 ( $J = 7.2$  Hz) which corresponded to the ethoxy groups. The methylene protons adjacent to the oxygen in the tetrahydrofuran ring appeared as a series of multiplets at  $\delta$  3.69 and 3.79 and the other methylene protons of this ring appeared as overlapping multiplets at  $\delta$  1.79-1.96. The tetrahydrofuran methine protons appeared as quartets at  $\delta$  3.93 and 4.03 ( $J_{cis} = J_{trans} = J_{gem} = 6.4$  Hz), and the methine protons adjacent to the nitrogen appeared as multiplets at  $\delta$  3.54-3.63. The aminyl protons appeared as doublets at  $\delta$  6.10 and 6.23 ( $J = 9.2$  Hz). Overlapping multiplets were evident for the aromatic protons (**Table 10**) and the benzylic methylene protons appeared as multiplets at  $\delta$  4.67-4.70. In the  $^{13}\text{C}$ -NMR spectrum there were signals at 172.1 and 172.0 ppm for the carbonyl carbons, a single signal for the *ipso* carbons at 137.8 ppm, together with signals for the other aromatic carbons at 128.65, 128.6, 128.4, 128.3, 127.9 and 127.8 ppm. The methine carbons adjacent to the nitrogen resonated at 77.2 and 77.1 ppm and the tetrahydrofuran methine protons at 67.7 and 67.6 ppm. The methylene carbons of the tetrahydrofuran ring appeared at 68.8, 68.5, 28.9, 28.7, 25.9 and 25.3 ppm. The benzylic methylene signals and the ethoxy signals were as expected (**Table 10**).



**Figure 28**  $^1\text{H}$ -NMR spectrum of (109)

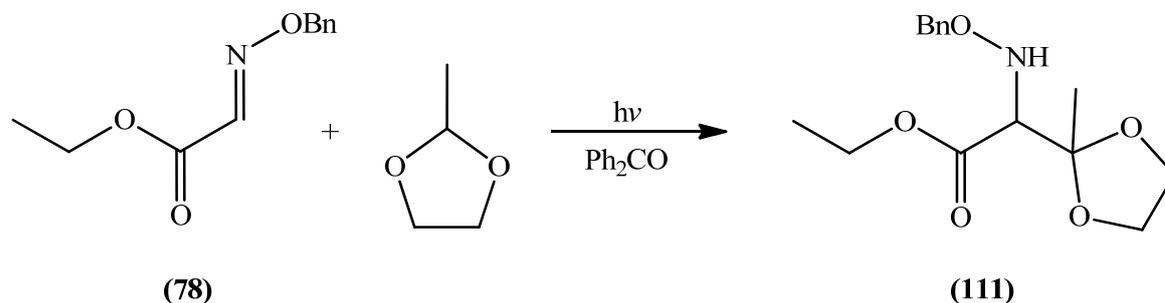
### 2.11.3 Photochemical reaction of ethyl (2*E*)-[(benzyloxy)imino]acetate (78) and 2-propanol



Scheme 90

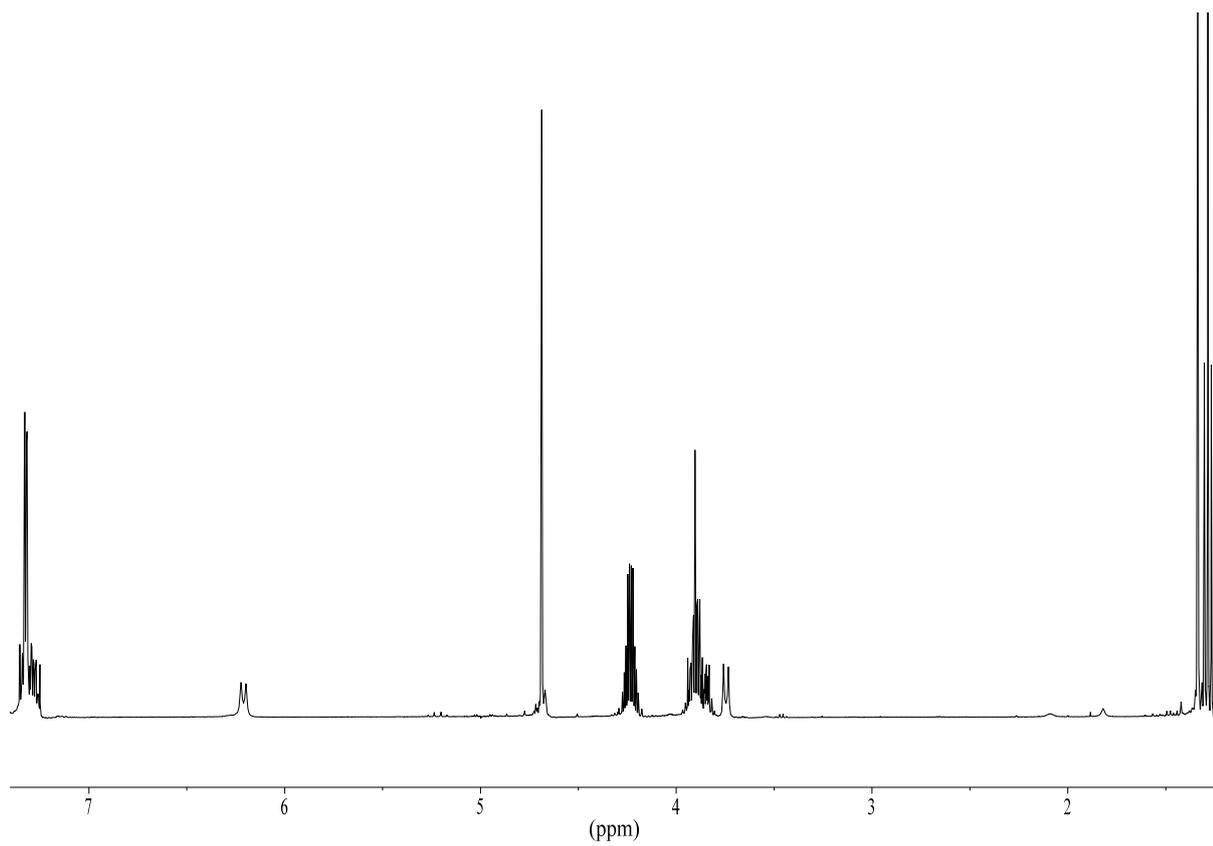
A solution of ethyl (2*E*)-[(benzyloxy)imino]acetate (78), benzophenone and 2-propanol in MeCN was prepared as before (Section 2.6.1). The solution was then irradiated for 2 h at which time all the starting material had reacted (GC). GC analysis indicated the formation of a single product, (110), while analysis of the NMR of the crude product indicated that a large amount of benzopinacol had formed. Flash chromatography gave ethyl-2-benzyloxyamino-3-hydroxy-3-methyl butanoate (110) as a clear oil in 65% yield. In the IR spectrum there were bands at 3491, 3276 and 1728  $\text{cm}^{-1}$ , which corresponded to the OH, NH and carbonyl groups, respectively. CO bands were evident at 1207, 1152 and 1022  $\text{cm}^{-1}$ , and there were two bands at 738 and 696  $\text{cm}^{-1}$  for the monosubstituted aromatic ring. In the  $^1\text{H-NMR}$  spectrum singlets at  $\delta$  1.10 and 1.24 corresponded to the *geminal* methyl groups, and further singlets at  $\delta$  3.53 and 4.67 corresponded to the methine and benzylic protons, respectively. There were broad singlets at  $\delta$  2.85 and 6.31, for the hydroxyl and aminyl protons, respectively. A triplet at  $\delta$  1.28 ( $J = 7.1$  Hz) and multiplets at  $\delta$  4.20-4.28 were evident for the ethoxy group, and overlapping multiplets in the usual position corresponded to the aromatic protons (Table 10). In the  $^{13}\text{C-NMR}$  spectrum the carbonyl carbon resonated at 173.2 ppm and the aromatic signals appeared as expected (Table 10). The benzylic methylene carbon resonated at 76.1 ppm, and the methine and quaternary carbons resonated at 71.8 and 70.7 ppm, respectively. The *geminal* methyl carbons resonated at 26.8 and 26.7 ppm and the ethoxy group gave the expected signals at 61.4 and 14.3 ppm.

#### 2.11.4 Photochemical reaction of ethyl (2*E*)-[(benzyloxy)imino]acetate (78) and 2-methyl-1,3-dioxolane



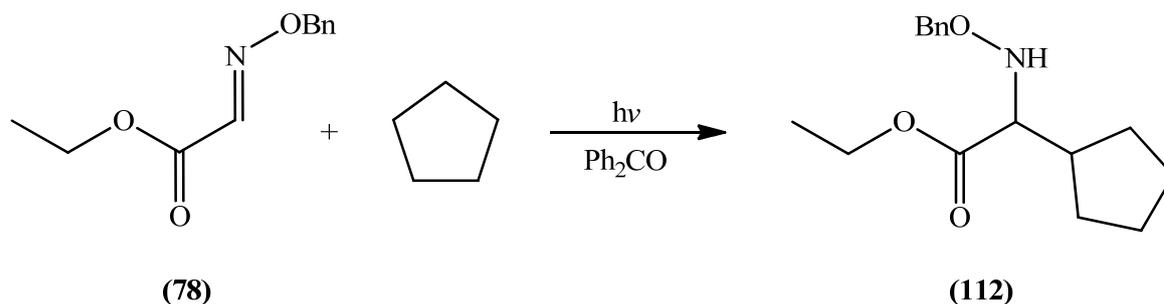
Scheme 91

A solution of ethyl (2*E*)-[(benzyloxy)imino]acetate (78), benzophenone and 2-methyl-1,3-dioxolane in MeCN was prepared as before (Section 2.6.1) and the solution was then irradiated for 1 h at which time all the starting material had reacted (GC). GC analysis indicated the formation of a single product, (111), and analysis of the  $^1\text{H-NMR}$  spectrum indicated that most of the benzophenone had dimerised. Flash chromatography gave ethyl [(benzyloxy)amino](2-methyl-1,3-dioxolan-2-yl)acetate (111) as a clear oil in 79% yield. In the IR spectrum there were bands at 3271 and 1735  $\text{cm}^{-1}$ , for the NH and carbonyl groups, respectively, together with the CO bands at 1204, 1151 and 1034  $\text{cm}^{-1}$ . There were also the usual bands at 736 and 696  $\text{cm}^{-1}$  which corresponded to the monosubstituted aromatic ring. In the  $^1\text{H-NMR}$  spectrum (Figure 29) there were singlets at  $\delta$  1.33 and 4.68, for the methyl and benzylic methylene groups, respectively. Doublets at  $\delta$  3.74 and 6.20 ( $J = 10.1$  Hz) corresponded to the methine and aminyl protons, respectively. The aromatic protons appeared as a series of overlapping multiplets, as did the methylene protons of the dioxolanyl ring (Table 10). The ethoxy group appeared as a triplet at  $\delta$  1.28 ( $J = 7.2$  Hz) and multiplets at  $\delta$  4.20-4.26. In the  $^{13}\text{C-NMR}$  spectrum the aromatic signals appeared at 137.7, 128.7, 128.4 and 127.9 ppm and the carbonyl carbon resonated at 171.5 ppm. The quaternary, benzylic methylene and methine carbons resonated as expected (Table 10). The ethoxy carbons gave the expected signals at 61.2 and 14.3 ppm, and the methyl carbon resonated at 23.1 ppm.



**Figure 29  $^1\text{H-NMR}$  spectrum of (111)**

### 2.11.5 Photochemical reaction of ethyl (2E)-[(benzyloxy)imino]acetate (78) and cyclopentane



Scheme 92

A solution of ethyl (2E)-[(benzyloxy)imino]acetate (78), benzophenone and cyclopentane in MeCN was prepared as before (Section 2.6.1). The solution was then irradiated for 5 h at which time all the starting material had reacted (GC). GC analysis indicated the formation of a single product, (112), and <sup>1</sup>H-NMR analysis of the crude product indicated that some benzopinacol had formed. Dry column vacuum chromatography gave ethyl [(benzyloxy)amino](cyclopentyl)acetate (112) as a yellow oil in 45% yield. In the IR spectrum there were bands at 3261 and 1733 cm<sup>-1</sup> which corresponded to the NH and carbonyl groups, respectively. The CO bands appeared at 1251, 1180 and 1025 cm<sup>-1</sup>, and the bands at 736 and 696 cm<sup>-1</sup> corresponded to the monosubstituted aromatic ring. In the <sup>1</sup>H-NMR spectrum the ethoxy group gave a triplet at δ 1.27 (*J* = 7.2 Hz) and multiplets at δ 4.20-4.28. The cyclopentyl methine and methylene protons appeared as a series of overlapping multiplets at δ 1.29-1.89. The methine proton adjacent to the nitrogen appeared as a triplet at δ 3.37 (*J* = 10.0 Hz) and the aminyl proton appeared as a doublet at δ 5.96 (*J* = 10.0 Hz). The benzylic protons appeared as a singlet at δ 4.67 and the aromatic protons appeared as a series of multiplets at δ 7.28-7.33. In the <sup>13</sup>C-NMR spectrum the carbonyl carbon resonated at 174.4 ppm and the four cyclopentyl methylene carbons resonated at 30.2, 29.5, 25.1 and 25.0 ppm. The cyclopentyl methine carbon appeared at 40.0 ppm. The benzylic methylene carbon appeared at 76.0 ppm and the methine carbon adjacent to the nitrogen resonated at 68.5 ppm. The ethoxy and aromatic signals appeared as expected (Table 10).

Table 10 NMR data for ethyl (2E)-(benzyloxyimino)acetate reactions

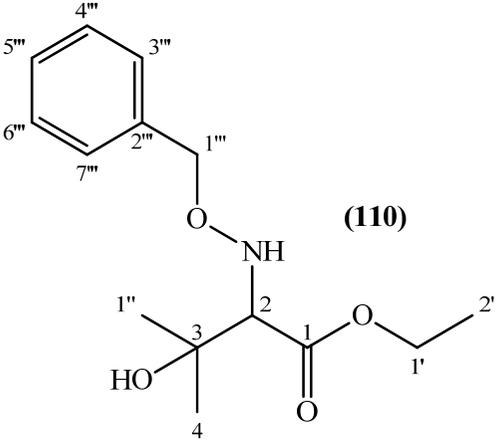
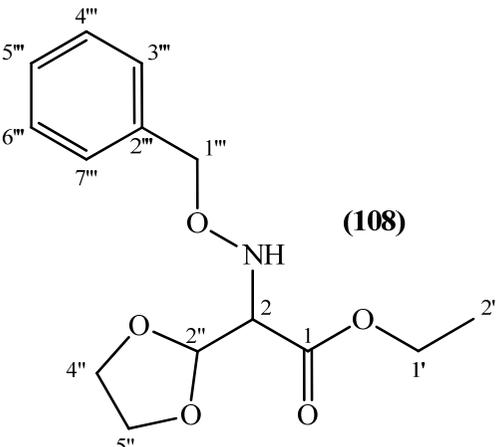
	<sup>1</sup> H-NMR data (δ)					<sup>13</sup> C-NMR data (ppm)					
	NH	H-1'	H-2'	H-2	Other Signals	C-2	C-1	C-1'	C-2'	C-2'''	Other Signals
 <p>(110)</p>	6.31 (s)	4.20-4.28 (ms)	1.28 (t) <i>J</i> = 7.1 Hz	3.53 (s)	<b>H-1''/H-4:</b> 1.10 (s)/1.24 (s) <b>H-1''':</b> 4.67 (s) <b>Ar-H:</b> 7.26-7.33 (overlapping ms) <b>OH:</b> 2.85 (s)	71.8	173.2	61.4	14.3	137.6	<b>C-3:</b> 70.7, <b>C-1''/C-4:</b> 26.7/26.8, <b>H-1''':</b> 76.1, <b>Ar-CH:</b> 128.7, 128.4 and 128.0
 <p>(108)</p>	6.21 (s)	4.23 (q) <i>J</i> = 7.2 Hz	1.28 (t) <i>J</i> = 7.2 Hz		<b>H-2'':</b> 5.13 (d) <i>J</i> = 4.2 Hz <b>H-2, H-4''/H-5'':</b> 3.81-3.97 (overlapping ms) <b>H-1''':</b> 4.72 (s) <b>Ar-H:</b> 7.27-7.34 (overlapping ms)	66.9	170.1	61.5	14.3	137.5	<b>C-2'':</b> 101.6, <b>C-4''/C-5'':</b> 65.5/65.6, <b>H-1''':</b> 76.4, <b>Ar-CH:</b> 128.6, 128.4 and 128.1

Table 10 (contd.) NMR data for ethyl (2*E*)-(hydroxyimino)acetate products

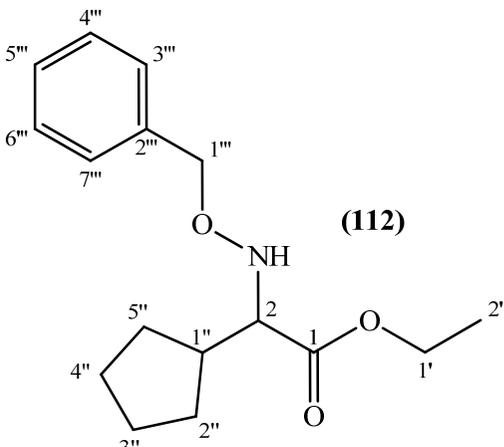
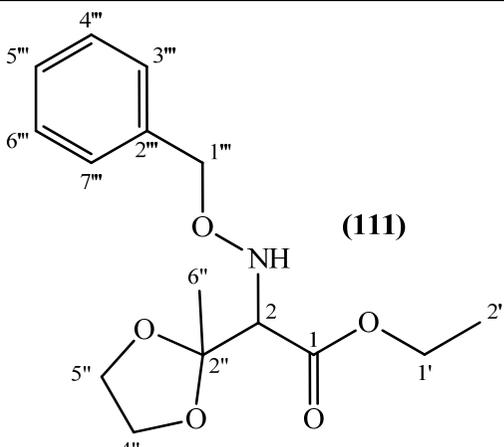
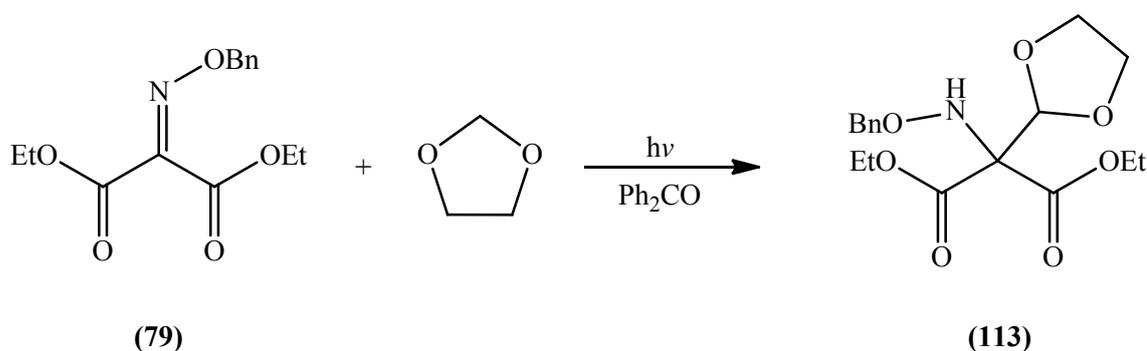
	<sup>1</sup> H-NMR data (δ)					<sup>13</sup> C-NMR data (ppm)					
	NH	H-1'	H-2'	H-2	Other Signals	C-2	C-1	C-1'	C-2'	C-2'''	Other Signals
 <p>(112)</p>	5.96 (d) <i>J</i> = 10.0 Hz	4.20-4.28 (ms)	1.27 (t) <i>J</i> = 7.2 Hz	3.37 (t) <i>J</i> = 10.0 Hz	<b>H-1''-H-5''</b> : 1.29-1.87 (overlapping ms), <b>H-1'''</b> : 4.67 (s) <b>Ar-H</b> : 7.28-7.33 (overlapping ms)	68.5	174.4	61.0	14.4	138.0	<b>C-1''</b> : 40.0, <b>C-2''/C-5''</b> : 29.5/30.2, <b>C-3''/C-4''</b> : 25.0/25.1, <b>H-1'''</b> : 76.0, <b>Ar-CH</b> : 128.7, 128.3 and 127.8
 <p>(111)</p>	6.20 (d) <i>J</i> = 10.0 Hz	4.20-4.26 (ms)	1.28 (t) <i>J</i> = 7.2 Hz	3.74 (d) <i>J</i> = 10.0 Hz	<b>H-6''</b> : 1.33 (s) <b>H-4''/H-5''</b> : 3.83-3.94 (overlapping ms) <b>H-1'''</b> : 4.68 (s) <b>Ar-H</b> : 7.25-7.35 (overlapping ms)	70.0	171.5	61.2	14.3	137.7	<b>C-2''</b> : 107.9, <b>C-4''/C-5''</b> : 65.2/65.4, <b>C-6''</b> : 23.1, <b>H-1'''</b> : 76.2, <b>Ar-CH</b> : 128.7, 128.4 and 127.9

Table 10 (contd.) NMR data for ethyl (2E)-(benzyloxyimino)acetate reactions

	<sup>1</sup> H-NMR data (δ)					<sup>13</sup> C-NMR data (ppm)					
	NH	H-1'	H-2'	H-2	Other Signals	C-2	C-1	C-1'	C-2'	C-2'''	Other Signals
<p style="text-align: center;"><b>(109)</b></p>	6.10 and 6.23 (ds) <i>J</i> = 9.2 Hz	4.22 and 4.24 (overlapping qs) <i>J</i> = 7.1 Hz	1.28 (t) <i>J</i> = 7.1 Hz	3.54-3.63 (ms)	<b>H-2''</b> : 3.93 and 4.03 (qs), <i>J</i> = 6.4 Hz <b>H-5''</b> : 3.69 and 3.79 (ms) <b>H-3'' and H-4''</b> : 1.79-1.96 (overlapping ms) <b>H-1'''</b> : 4.67-4.70 (ms) <b>Ar-H</b> : 7.26-7.33 (overlapping ms)	77.2 and 77.1	172.1 and 172.0	61.2 and 61.1	14.4 and 14.3	137.8	<b>C-2''</b> : 67.7 and 67.6, <b>C-3''</b> : 28.9 and 28.7, <b>C-4''</b> : 25.9 and 25.3, <b>C-5''</b> : 68.8 and 68.5, <b>H-1'''</b> : 76.3 and 76.2, <b>Ar-CH</b> : 128.65, 128.60, 128.4, 128.3, 127.9 and 127.8

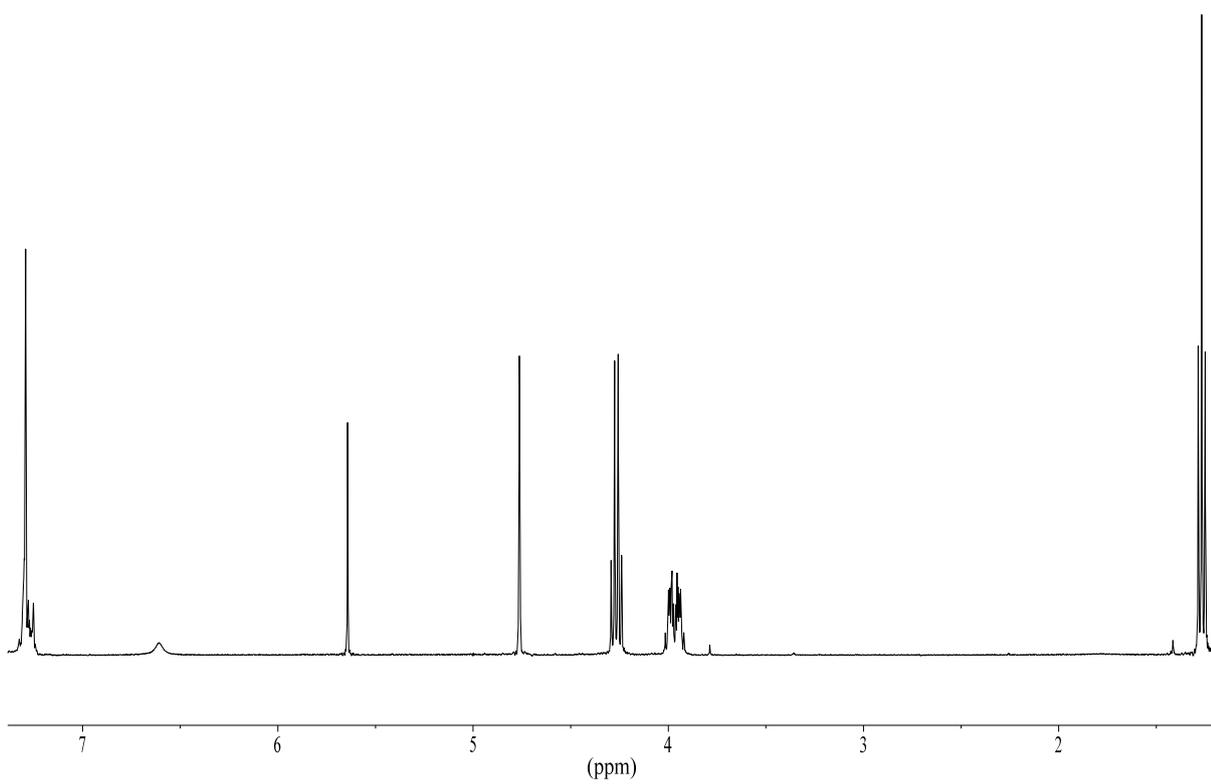
## 2.12 Photochemical reactions of diethyl [(benzyloxy)imino]malonate (79)

### 2.12.1 Photochemical reaction of diethyl [(benzyloxy)imino]malonate (79) and 1,3-dioxolane



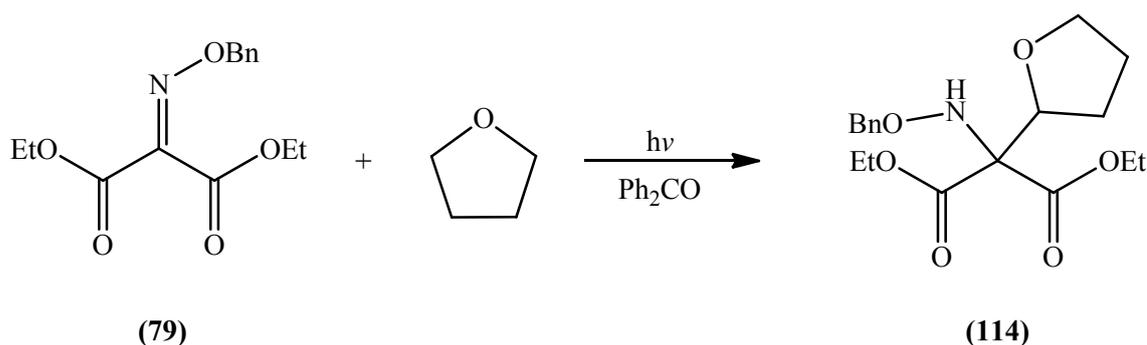
Scheme 93

A solution of diethyl [(benzyloxy)imino]malonate (**79**), benzophenone and 1,3-dioxolane in MeCN was prepared as before (Section 2.6.1) and the solution was then irradiated for 1 h at which time all the starting material had reacted (GC). Analysis of the NMR spectrum of the crude product indicated the formation of a single product, (**113**), and that a large amount of benzophenone had dimerised. Flash chromatography gave diethyl [(benzyloxyamino)(1,3-dioxolan-2-yl)malonate (**113**) as a clear oil in 89% yield. In the IR spectrum there were bands at 3274 and 1735  $\text{cm}^{-1}$  which corresponded to the NH and carbonyl groups, respectively. The CO bonds gave the expected bands at 1224, 1095 and 1034  $\text{cm}^{-1}$  and two bands at 742 and 699  $\text{cm}^{-1}$  were characteristic of a monosubstituted aromatic ring. In the  $^1\text{H-NMR}$  spectrum (Figure 30) there were singlets at  $\delta$  4.76 and 5.64 which corresponded to the benzylic protons and the methine proton, respectively. The two ethoxy groups appeared as a triplet at  $\delta$  1.27 ( $J = 7.1$  Hz) and a quartet at  $\delta$  4.26 ( $J = 7.1$  Hz), and the aminyl proton appeared as a broad singlet at  $\delta$  6.60. The dioxolanyl methylene groups appeared as a series of overlapping multiplets, as did the aromatic protons (Table 11). In the  $^{13}\text{C-NMR}$  spectrum the two carbonyl carbons resonated at 166.0 ppm. The aromatic carbons resonated at 137.1, 128.4, 128.35 and 127.9 ppm, and the benzylic methylene carbon at 77.0 ppm. The methine and quaternary carbons resonated at 102.5 and 75.1 ppm, respectively, and the methylene carbons appeared as a single signal at 65.9 ppm. The ethoxy groups were as expected (Table 11).



**Figure 30** <sup>1</sup>H-NMR spectrum of (113)

### 2.12.2 Photochemical reaction of diethyl [(benzyloxy)imino]malonate (79) and THF



Scheme 94

A solution of diethyl [(benzyloxy)imino]malonate (79), benzophenone and THF in MeCN was prepared as before (Section 2.6.1). The solution was then irradiated for 1 h at which time all the starting material had reacted (GC). GC analysis indicated the formation of a single product, (114), and analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated that a large amount of benzopinacol had formed. Flash chromatography gave diethyl [(benzyloxy)amino](tetrahydrofuran-2-yl)malonate (114) as a clear oil in 77% yield. In the IR spectrum, bands at 3270 and 1733 cm<sup>-1</sup> indicated the presence of an NH and carbonyl group, respectively. Bands at 1260, 1065 and 1032 cm<sup>-1</sup> corresponded to the CO bonds, and bands at 740 and 698 cm<sup>-1</sup> were characteristic of a monosubstituted aromatic ring. In the <sup>1</sup>H-NMR spectrum (Figure 31) the methyl protons of the ethoxy groups appeared as a triplet at δ 1.27 (*J* = 7.1 Hz) and the methylene protons appeared as overlapping multiplets at δ 4.21-4.27. There were multiplets at δ 1.75-1.92, 2.16-2.22 and 3.71-3.83 which corresponded to the methylene protons of the tetrahydrofuran ring, the latter being due to the protons adjacent to the oxygen. The methine proton appeared as a triplet at δ 4.58 (*J*<sub>cis</sub> = *J*<sub>trans</sub> = 7.4 Hz) and there was a broad singlet for the aminyl proton at δ 6.55. The benzylic and aromatic protons appeared as expected (Table 11). In the <sup>13</sup>C-NMR spectrum the carbonyl carbons resonated at 167.8 and 166.9 ppm, and the aromatic signals appeared at 137.3, 128.4, 128.3 and 127.9 ppm. The methine and quaternary carbons resonated at 78.6 and 75.5 ppm, respectively, and the benzylic methylene carbon appeared at 76.9 ppm. The three remaining tetrahydrofuran methylene carbons and ethoxy carbons resonated as expected (Table 11).

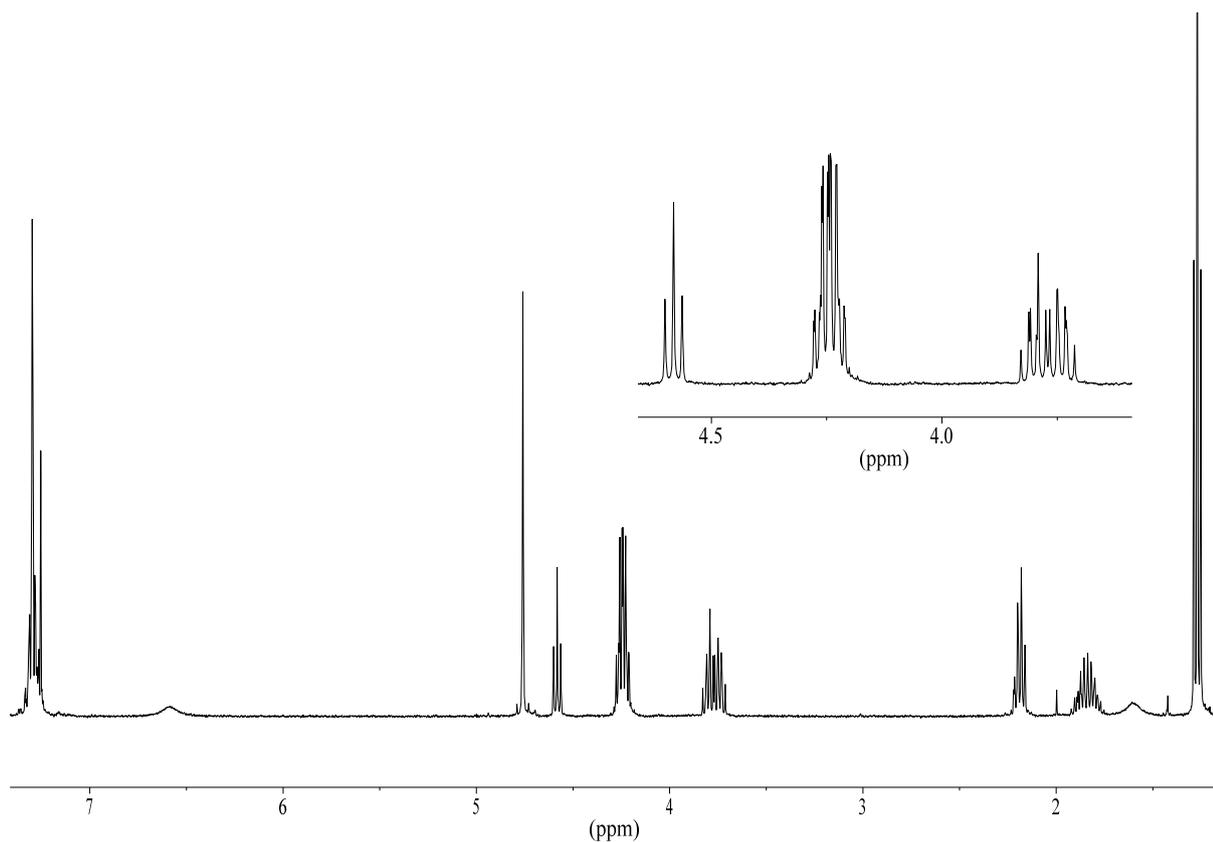
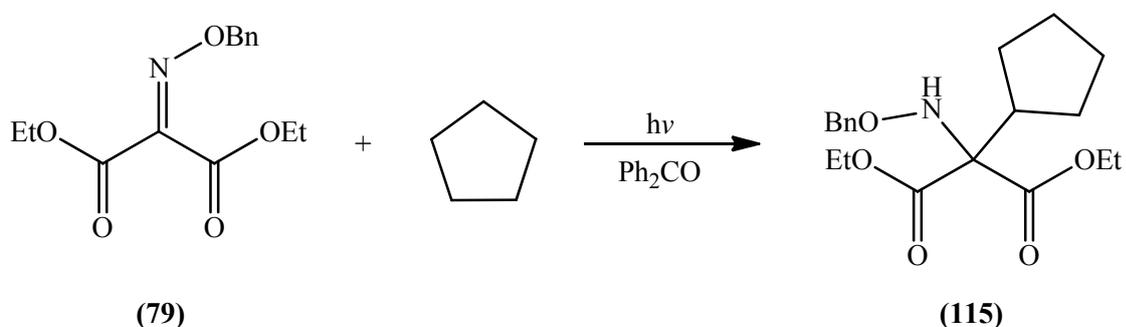


Figure 31  $^1\text{H-NMR}$  spectrum of (114)

### 2.12.3 Photochemical reaction of diethyl [(benzyloxy)imino]malonate (79) and cyclopentane

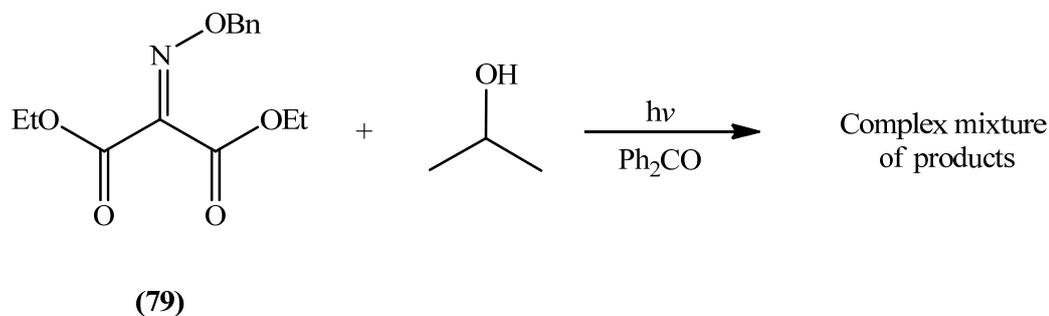


Scheme 95

A solution of diethyl [(benzyloxy)imino]malonate (79), benzophenone and cyclopentane in MeCN was prepared as before (Section 2.6.1) and the solution was then irradiated for 2 h at which time no further reaction was observed (GC). Analysis of the  $^1\text{H-NMR}$  spectrum of the crude product indicated that all the benzophenone had dimerised. Flash chromatography gave diethyl [(benzyloxy)amino](cyclopentyl)malonate (115) as a clear oil in 29% yield. In the IR spectrum there were bands at  $3270$  and  $1733\text{ cm}^{-1}$ , which corresponded to the NH and carbonyl groups, respectively. The characteristic monosubstituted aromatic bands were at  $744$  and  $698\text{ cm}^{-1}$ , and the CO stretching

bands appeared at 1249, 1097 and 1032  $\text{cm}^{-1}$ . In the  $^1\text{H}$ -NMR spectrum the ethoxy protons appeared as the usual triplet at  $\delta$  1.26 ( $J = 7.1$  Hz) and quartet at  $\delta$  4.22 ( $J = 7.2$  Hz). The methylene protons of the cyclopentyl ring appeared as overlapping multiplets at  $\delta$  1.49-1.61 and 1.76-1.86; the methine proton also appeared as a multiplet at  $\delta$  2.69. The other signals in the spectrum corresponded to the aminyl, benzylic protons and the aromatic protons, and appeared in the expected regions of the spectrum (**Table 11**). In the  $^{13}\text{C}$ -NMR spectrum the carbonyl carbons resonated at 168.8 ppm and the aromatic carbons resonated at 137.5, 128.4, 128.2 and 127.8 ppm. Only two signals were evident for the cyclopentyl methylene carbons at 27.8 and 25.6 ppm due to the symmetry in the molecule. The methine and quaternary carbons resonated at 42.5 and 75.4 ppm, respectively. The benzylic carbon and ethoxy carbons appeared in the expected regions (**Table 11**).

#### 2.12.4 Photochemical reaction of diethyl [(benzyloxy)imino]malonate (79) and 2-propanol



**Scheme 96**

A solution of diethyl [(benzyloxy)imino]malonate (**79**), benzophenone and 2-propanol in MeCN was prepared as before (**Section 2.6.1**). The solution was then irradiated for 1 h at which time all the starting material had reacted (GC). Analysis of the  $^1\text{H}$ -NMR spectrum of the crude product showed that a complex mixture of products had formed but attempts to isolate any identifiable products *via* flash chromatography, failed.

Table 11 NMR data for diethyl (benzyloxymino)malonate reactions

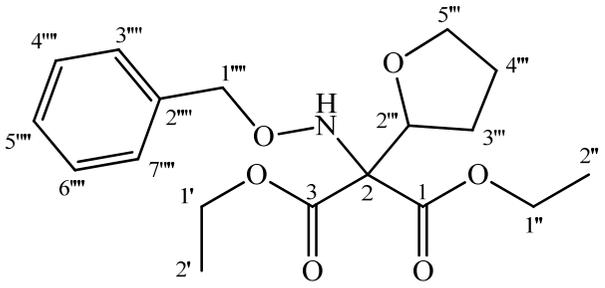
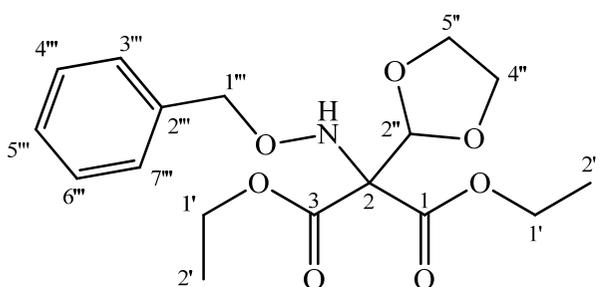
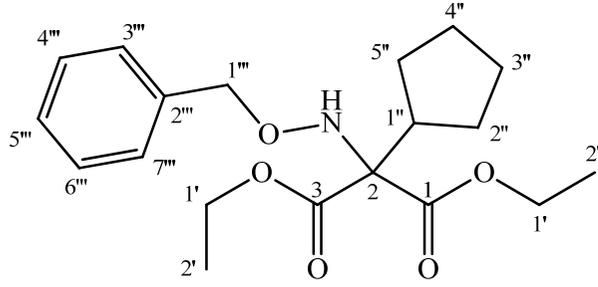
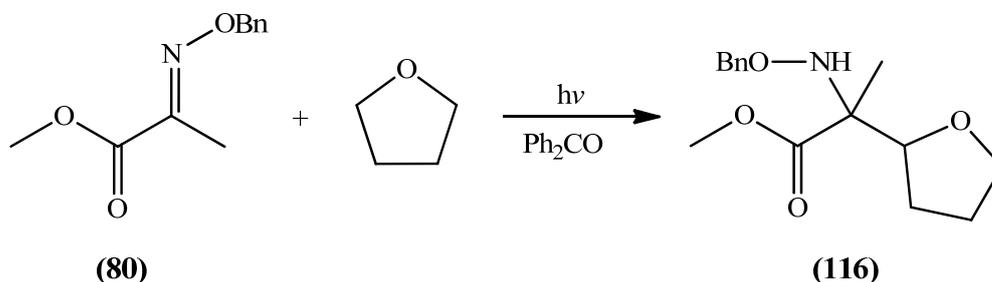
	<sup>1</sup> H-NMR data (δ)				<sup>13</sup> C-NMR data (ppm)					
	NH	H-1'/H-1''	H-2'/H-2''	Other signals	C-1/ C-3	C-1'/ C-1''	C-2'/ C-2''	C-2	C-2'''	Other signals
 <p style="text-align: center;"><b>(114)</b></p>	6.55 (br s)	4.21-4.27 (ms)	1.27 (t) <i>J</i> = 7.1 Hz	<b>H-2'''</b> : 4.58 (t) <i>J</i> <sub>cis</sub> = <i>J</i> <sub>trans</sub> = 7.4 Hz, <b>H-4'''</b> : 1.83 (m), <b>H-3'''</b> : 2.18 (m), <b>H-5'''</b> : 3.76 (m), <b>H-1'''</b> : 4.75 (s), <b>H-3''' - H-7'''</b> : 7.27-7.33 (overlapping ms).	167.8 and 166.9	61.9	14.2	75.5	137.3	<b>C-3'''</b> : 27.7, <b>C-2'''</b> : 78.6, <b>C-5'''</b> : 69.2, <b>C-4'''</b> : 26.1, <b>C-1'''</b> : 76.9, <b>Ar-CH</b> : 128.4, 128.3 and 127.9.
 <p style="text-align: center;"><b>(113)</b></p>	6.60 (br s)	4.26 (q) <i>J</i> = 7.1 Hz	1.27 (t) <i>J</i> = 7.1 Hz	<b>H-2''</b> : 5.64 (s), <b>H-4''/H-5''</b> : 3.78-4.01 (overlapping ms), <b>H-1''</b> : 4.76 (s), <b>Ar-H</b> : 7.25-7.29 (overlapping ms).	166.0	62.1	14.1	75.1	137.1	<b>C-2''</b> : 102.5, <b>C-4''/C-5''</b> : 65.9, <b>C-1''</b> : 77.0, <b>Ar-CH</b> : 128.4, 128.35 and 127.9.

Table 11 (contd.) NMR data for diethyl (benzyloxyimino)malonate reactions

	<sup>1</sup> H-NMR data (δ)				<sup>13</sup> C-NMR data (ppm)					
	NH	H-1'	H-2'	Other signals	C-1/ C-3	C-1'	H-2'	C-2	C-2'''	Other signals
 <p style="text-align: center;"><b>(115)</b></p>	6.20 (s)	4.22 (q) $J = 7.2$ Hz	1.26 (t) $J = 7.1$ Hz	<b>H-1''</b> : 2.69 (m), <b>H-2''-5''</b> : 1.49- 1.61 and 1.78- 1.84 (2 × ms) <b>H-1'''</b> : 4.75 (s), <b>Ar-H</b> : 7.26-7.33 (overlapping ms).	168.8	61.6	14.2	75.4	137.5	<b>C-1''</b> : 42.5, <b>C-2''/C-5''</b> : 27.8, <b>C-3''/C-4''</b> : 25.6. <b>C-1'''</b> : 76.6, <b>Ar-CH</b> : 128.4, 128.2 and 127.8.

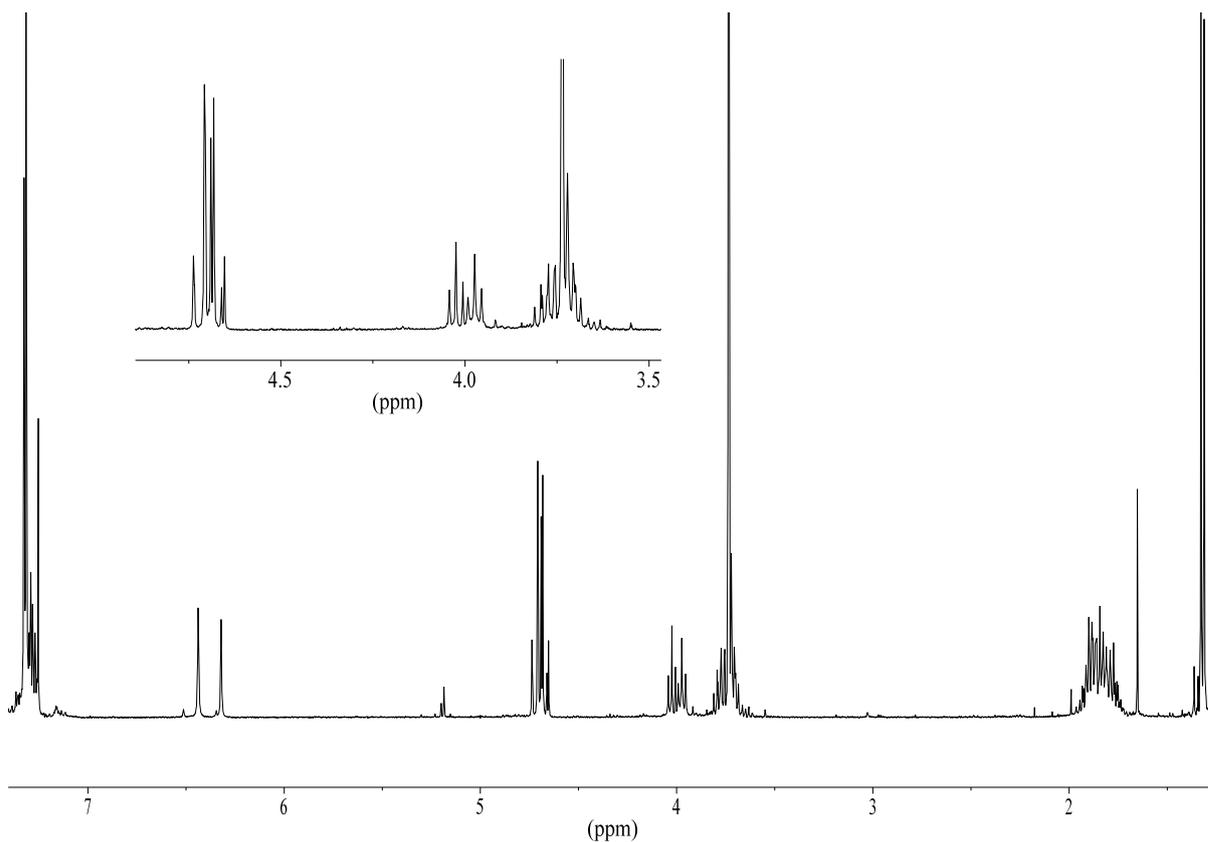
## 2.13 Photochemical reactions of methyl (2E)-2-[(benzyloxy)imino]propanoate (80)

### 2.13.1 Photochemical reaction of methyl (2E)-2-[(benzyloxy)imino]propanoate (80) and THF



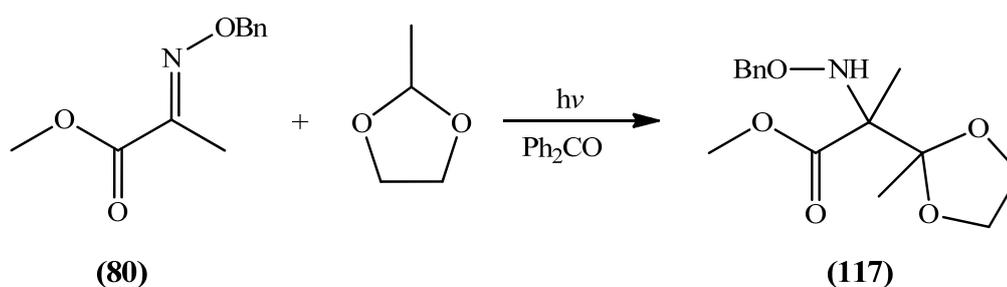
Scheme 97

A solution of methyl (2E)-2-[(benzyloxy)imino]propanoate (**80**), benzophenone and THF in MeCN was prepared as before (**Section 2.6.1**). The solution was then irradiated for 6 h at which time all the starting material had reacted (GC). GC analysis indicated the formation of (**116**) as a mixture of diastereomers in 1.1:1 ratio and analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated that a large amount of benzopinacol had formed. Chromatography gave methyl 2-[(benzyloxy)amino]-2-(tetrahydrofuran-2-yl)propanoate (**116**) as a clear oil in 68% yield with no change in diastereomeric ratio (GC). In the IR spectrum characteristic bands were present at 737 and 698 cm<sup>-1</sup> for the monosubstituted aromatic ring, at 1256, 1138 and 1069 cm<sup>-1</sup> for the CO bonds, and at 3270 and 1728 cm<sup>-1</sup> for the NH and carbonyl groups, respectively. In the <sup>1</sup>H-NMR spectrum (**Figure 32**) singlets at δ 1.31 and 1.38, and at δ 3.72 and 3.73, corresponded to the methyl and methoxy protons, respectively. The methylene protons adjacent to the oxygen in the tetrahydrofuranyl ring appeared as overlapping multiplets at δ 3.68-3.79, with the other methylene protons of this ring appeared as overlapping multiplets at δ 1.73-1.92. The methine protons appeared as triplets at δ 3.84 and 4.00 ( $J_{cis} = J_{trans} = 7.1$  Hz), and the benzylic protons appeared as overlapping pairs of doublets at δ 4.67, 4.68, 4.71 and 4.72 ( $J = 11.7$  Hz). The aminyl protons appeared as singlets and the aromatic signals appeared as a series of overlapping multiplets (**Table 12**). In the <sup>13</sup>C-NMR spectrum both carbonyl carbons resonated as a single signal at 173.9 ppm. The aromatic carbons gave the expected signals (**Table 12**) and the methine carbons resonated at 81.5 and 81.4 ppm. The methyl and methoxy carbons resonated at 16.9 and 16.1 ppm, and at 52.4 and 52.3 ppm, respectively. The quaternary carbons resonated at 68.7 and 68.2 ppm, and the benzylic carbons appeared at 77.2 and 77.1 ppm. The other methylene carbon signals appeared as expected (**Table 12**).



**Figure 32**  $^1\text{H-NMR}$  spectrum of **(116)**

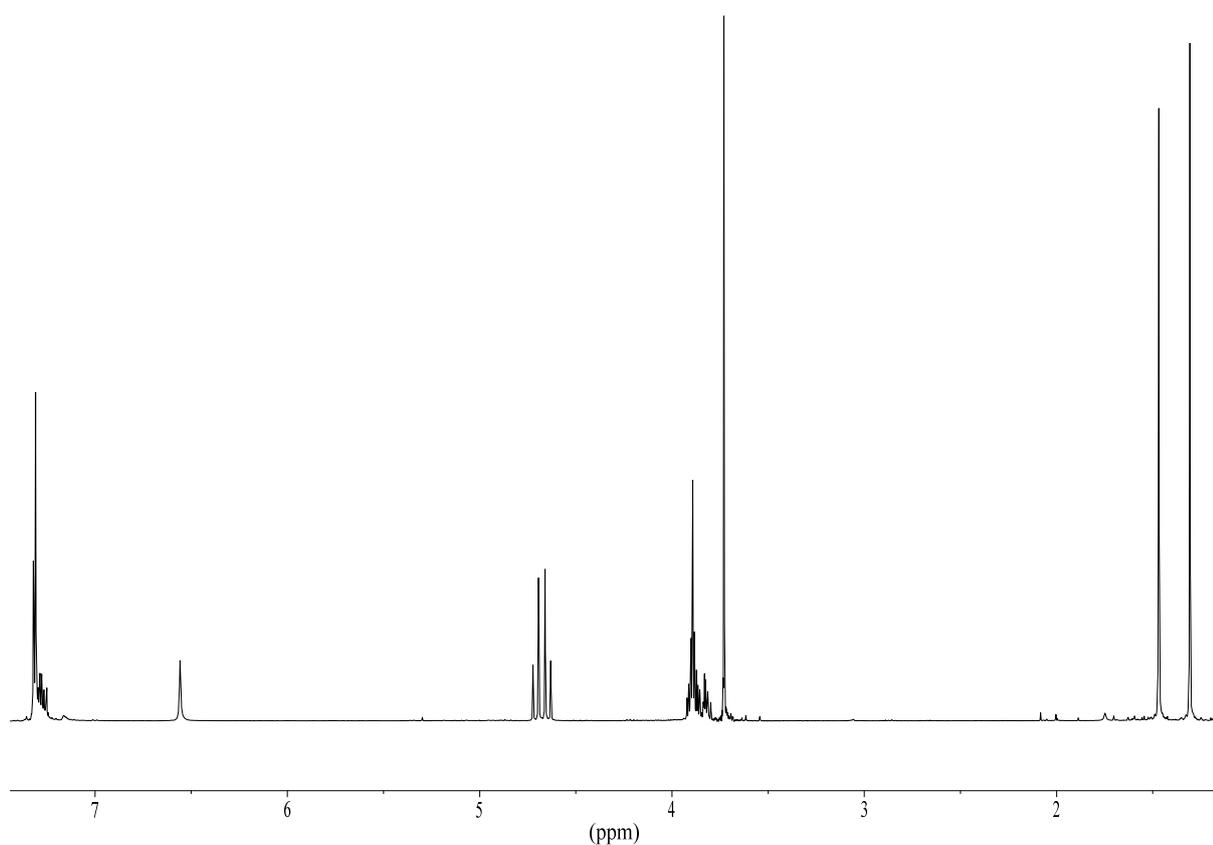
**2.13.2 Photochemical reaction of methyl (2E)-2-[(benzyloxy)imino]propanoate (**80**) and 2-methyl-1,3-dioxolane**



**Scheme 98**

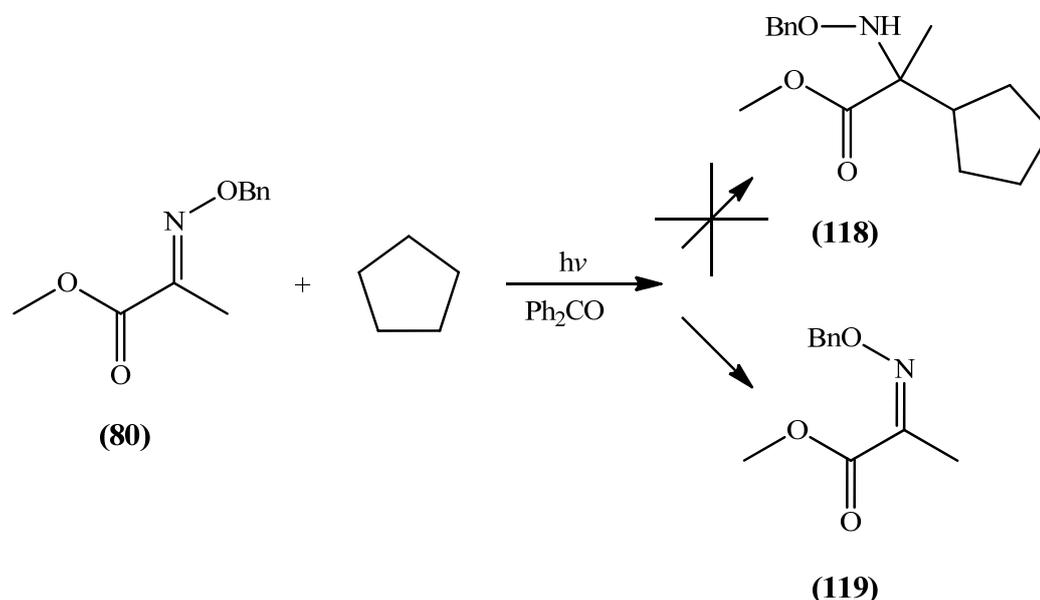
A solution of methyl (2E)-2-[(benzyloxy)imino]propanoate (**80**), benzophenone and 2-methyl-1,3-dioxolane in MeCN was prepared as before (**Section 2.6.1**). It was then irradiated for 2 h at which time all the starting material had reacted (GC). GC analysis indicated the formation of a single product, (**117**), and analysis of the  $^1\text{H-NMR}$  spectrum of the crude product indicated the formation of a large amount of benzopinacol. Chromatography gave methyl 2-[(benzyloxy)amino]-2-(2-methyl-1,3-dioxolan-2-yl)propanoate (**117**) as a clear oil in 71% yield. In the IR spectrum there were the characteristic NH and carbonyl bands at 3281 and 1729  $\text{cm}^{-1}$ , respectively, together with CO bands at

1140, 1097 and 1042  $\text{cm}^{-1}$ . Monosubstituted aromatic bands were present at 733 and 698  $\text{cm}^{-1}$ . In the  $^1\text{H}$ -NMR spectrum (**Figure 33**) there were four singlets; at  $\delta$  1.30 and 1.46 corresponding to the methyl protons, at  $\delta$  3.72 for the methoxy protons and at  $\delta$  6.55 for the aminyl proton. The benzylic group appeared as a pair of doublets at  $\delta$  4.65 and 4.71 ( $J = 11.7$  Hz). The dioxolanyl methylene protons and the aromatic protons appeared as overlapping multiplets in their respective regions (**Table 12**). In the  $^{13}\text{C}$ -NMR spectrum the carbonyl carbon resonated at 173.7 ppm and the aromatic carbons gave the expected signals at 137.9, 128.7, 128.3 and 127.8 ppm. The quaternary carbons resonated at 110.5 and 72.1 ppm, the former attached to the oxygens in the dioxolanyl ring. The benzylic carbon appeared at 77.3 ppm and the other methylene carbons resonated as a single signal at 65.5 ppm. The methyl and methoxy carbons appeared as expected (**Table 12**).



**Figure 33**  $^1\text{H}$ -NMR spectrum of (117)

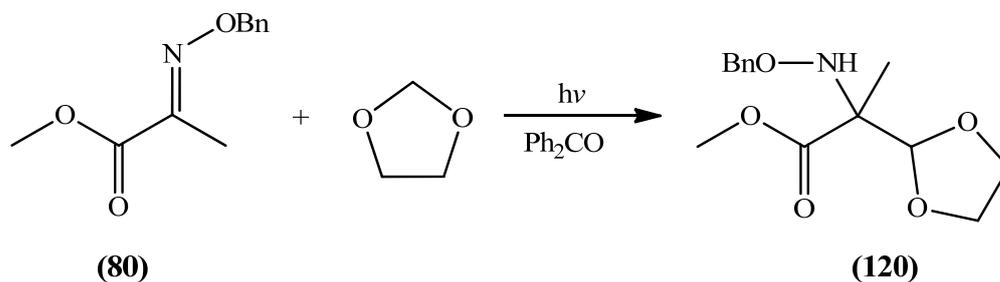
### 2.13.3 Photochemical reaction of methyl (2*E*)-2-[(benzyloxy)imino]propanoate (**80**) and cyclopentane



Scheme 99

A solution of methyl (2*E*)-2-[(benzyloxy)imino]propanoate (**80**), benzophenone and cyclopentane in MeCN was prepared as before (Section 2.6.1). It was then irradiated for 8 h at which time no further reaction was occurring (GC). GC analysis indicated that no product had formed but a peak with similar retention time to that of the starting material was present. This peak was due to methyl (2*Z*)-2-[(benzyloxy)imino]propanoate (**119**), formed by *E/Z* photoisomerisation in the photostationary state. The *E/Z* ratio was 1:1.9 (GC). Spectroscopic data for (**119**) were consistent with those in the literature<sup>[57]</sup>. In the IR spectrum there were bands at 1737 and 1605  $\text{cm}^{-1}$  which corresponded to the carbonyl and iminyl bonds, respectively. CO bands appeared at 1196, 1158 and 1044  $\text{cm}^{-1}$  and the characteristic monosubstituted aromatic bands appeared at 733 and 696  $\text{cm}^{-1}$ . In the  $^1\text{H-NMR}$  spectrum singlets at  $\delta$  2.04, 3.82 and 5.11 corresponded to the methyl, methoxy and methylene protons, respectively. The aromatic protons appeared as a series of overlapping multiplets at  $\delta$  7.29-7.35. In the  $^{13}\text{C-NMR}$  spectrum the carbonyl and iminyl carbons resonated at 164.4 and 148.3 ppm, respectively, and the aromatic signals appeared at 137.6, 128.4, 127.9 and 127.8 ppm. The benzylic carbon resonated at 76.3 ppm, and the methoxy and methyl carbons appeared at 52.3 and 17.1 ppm, respectively.

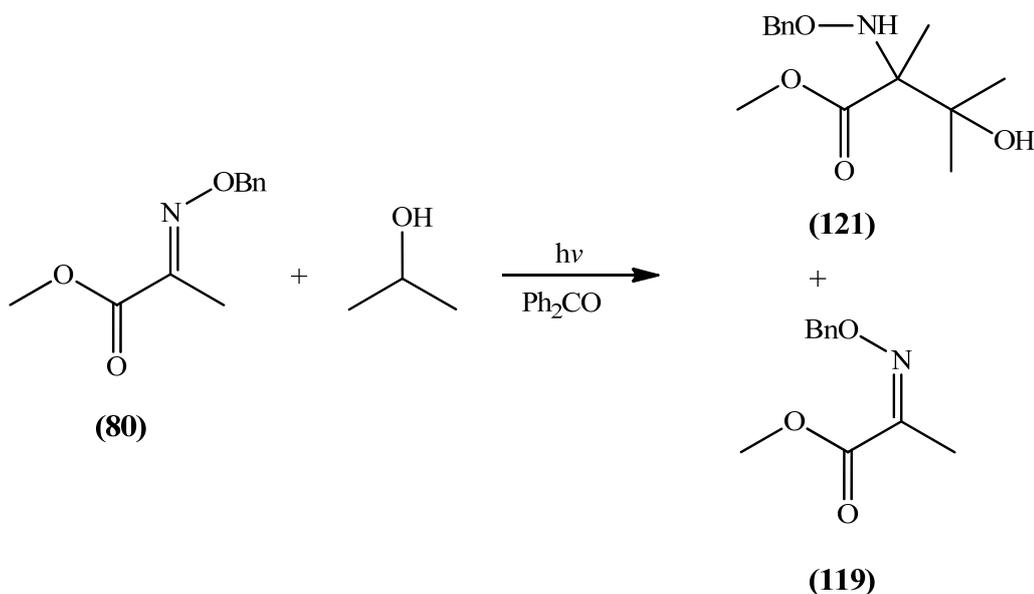
#### 2.13.4 Photochemical reaction of methyl (2*E*)-2-[(benzyloxy)imino]propanoate (**80**) and 1,3-dioxolane



Scheme 100

A solution of methyl (2*E*)-2-[(benzyloxy)imino]propanoate (**80**), benzophenone and 1,3-dioxolane in MeCN was prepared as before (Section 2.6.1) and it was then irradiated for 2 h at which time all the starting material had reacted (GC). GC analysis indicated the formation of a single product, (**120**), and analysis of the NMR spectrum of the crude product indicated the formation of a large amount of benzopinacol. Flash chromatography gave methyl 2-[(benzyloxy)amino]-2-(1,3-dioxolan-2-yl)propanoate (**120**) as a clear oil in 68% yield; its spectroscopic data were consistent with those published by Alonso<sup>[57]</sup>. Alonso carried out this reaction in neat 1,3-dioxolane with 1 equivalent of benzophenone and the reaction was complete after 2 h. The isolated yield for the reaction was 74% and only slightly higher than if the reaction was carried out using MeCN as solvent. In the IR spectrum bands at 3282 and 1735  $\text{cm}^{-1}$  corresponded to the NH and carbonyl groups, respectively. Bands at 1259, 1103 and 1040  $\text{cm}^{-1}$  corresponded to the CO bonds, and two bands at 734 and 698  $\text{cm}^{-1}$  were due to the monosubstituted aromatic ring. In the  $^1\text{H}$ -NMR spectrum singlets at  $\delta$  1.38 and 3.74 corresponded to the methyl and methoxy protons, respectively. The dioxolanyl methylene protons appeared as overlapping multiplets at  $\delta$  3.83-3.95 and the benzylic methylene protons appeared as a pair of doublets at  $\delta$  4.68 and 4.73 ( $J = 11.6$  Hz). The methine, aminyl and aromatic protons appeared as expected (Table 12). In the  $^{13}\text{C}$ -NMR spectrum the methyl and methoxy carbons resonated at 15.3 and 52.5 ppm, respectively, and the methine carbon appeared at 104.1 ppm. The quaternary and benzylic carbons appeared at 68.6 and 77.3 ppm, respectively, with the other methylene signals appearing at 65.7 and 65.6 ppm. The carbonyl and aromatic carbons appeared as expected (Table 12).

### 2.13.5 Photochemical reaction of methyl (2E)-2-[(benzyloxy)imino]propanoate (80) and 2-propanol



Scheme 101

A solution of methyl (2E)-2-[(benzyloxy)imino]propanoate (80), benzophenone and 2-propanol in MeCN was prepared as before (Section 2.6.1). It was then irradiated for 4 h at which time no further reaction was occurring (GC). GC analysis indicated the presence of the Z isomer (119), and (121). Analysis of the  $^1\text{H-NMR}$  spectrum of the crude product indicated that all the benzophenone had dimerised. First to elute on chromatography was (119); it was obtained in 20% yield and its spectroscopic data were identical to those given above (Section 2.13.3). The addition product methyl 2-[(benzyloxy)amino]-3-hydroxy-2,3-dimethylbutanoate (121) eluted next as a clear oil and was obtained in 22% yield. Its spectroscopic data were consistent with those in the literature<sup>[57]</sup>. Also carried out this reaction in neat 2-propanol with 1 equivalent of benzophenone and the reaction was complete in just 2 h. An isolated yield of 58% of (121) and 4% of the unreacted starting material was obtained<sup>[57]</sup>. In this instance the use of MeCN as solvent has a bigger influence on the outcome of the reaction as a much lower yield was obtained after a longer reaction time. In the IR spectrum there were OH and NH bands at 3544 and 3276  $\text{cm}^{-1}$ , respectively, together with CO bands at 1254, 1152 and 1039  $\text{cm}^{-1}$ . A carbonyl band appeared at 1724  $\text{cm}^{-1}$  and monosubstituted aromatic bands appeared at 738 and 698  $\text{cm}^{-1}$ . In the  $^1\text{H-NMR}$  spectrum singlets appeared for the methyl and methoxy protons (Table 12). There was a broad singlet at  $\delta$  2.95 for the hydroxyl proton and a pair of doublets at  $\delta$  4.68 and 4.73 ( $J = 11.7$  Hz) for the benzylic methylene protons. The aromatic protons appeared as a series of overlapping multiplets at  $\delta$  7.29-7.38. In the  $^{13}\text{C-NMR}$  spectrum the methyl carbons resonated at 26.5, 24.3 and 16.4 ppm, and the methoxy carbon at 52.5 ppm. The quaternary carbons appeared at 73.8 and 72.1 ppm, and the benzylic methylene carbon resonated at 77.3 ppm. The aromatic signals appeared as expected (Table 12) and the carbonyl carbon appeared at 176.0 ppm.

Table 12 NMR data for methyl (2*E*)-2-(benzyloxyimino)propanoate reactions

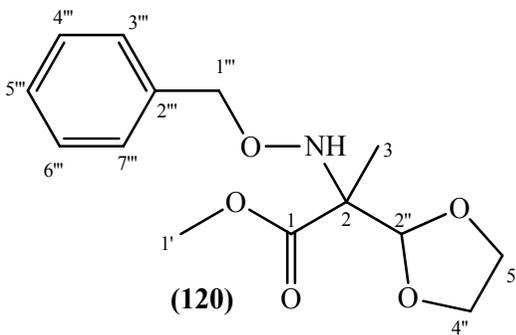
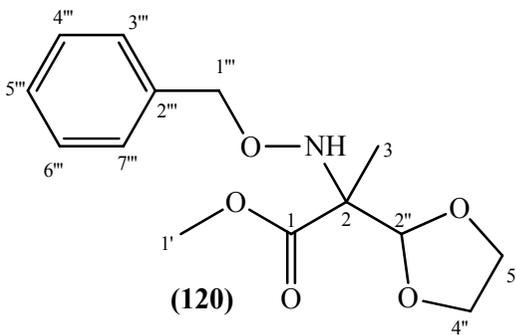
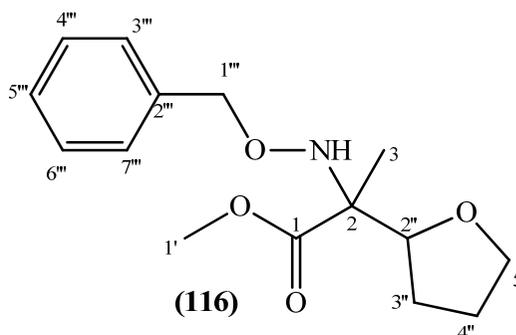
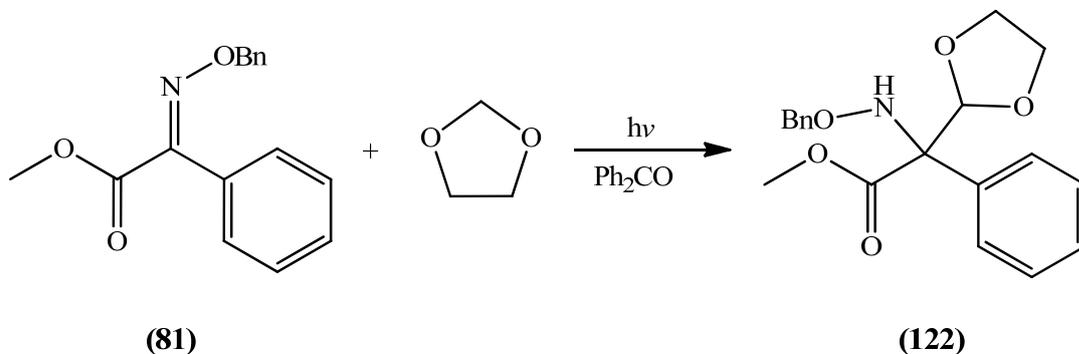
 (120)	<sup>1</sup> H-NMR data (δ)					<sup>13</sup> C-NMR data (ppm)						
	NH	H-3	H-1'	H-2''	Other signals	C-1	C-1'	C-3	C-2	C-2''	C-2'''	Other signals
 (120)	6.28 (s)	1.38 (s)	3.74 (s)	5.05 (s)	<b>H-4''/H-5''</b> : 3.83-3.95 (ms), <b>H-1'''</b> : 4.68 and 4.73 (ds) <i>J</i> = 11.6 Hz, <b>Ar-H</b> : 7.25-7.33 (overlapping ms)	172.6	52.5	15.3	68.6	104.1	137.5	<b>C-4''/C-5''</b> : 65.6/65.7, <b>C-1'''</b> : 77.3, <b>Ar-CH</b> : 128.5, 128.4 and 127.9.
 (116)	6.32 and 6.43 (s)	1.31 and 1.38 (s)	3.72 and 3.73 (s)	3.84 and 4.00 (ts) <i>J</i> = 7.4 Hz	<b>H-3''-H-4''</b> : 1.73-1.92 (overlapping ms) <b>H-5''</b> : 3.68-3.79 (overlapping ms) <b>H-1'''</b> : 4.67, 4.68, 4.71 and 4.72 (ds) <i>J</i> = 11.7 Hz, <b>Ar-H</b> : 7.26-7.32 (overlapping ms)	173.9	52.4 and 52.3	16.9 and 16.1	68.7 and 68.2	81.5 and 81.4	137.8 and 137.9	<b>C-3''</b> : 26.9 and 26.6, <b>C-4''</b> : 26.1 and 25.8, <b>C-5''</b> : 69.2 and 69.0, <b>C-1'''</b> : 77.2 and 77.1, <b>Ar-CH</b> : 128.9, 128.6, 128.5, 128.4, 128.3 and 127.8.

Table 12 (contd.) NMR data for methyl (2*E*)-2-(benzyloxyimino)propanoate reactions

	<sup>1</sup> H-NMR data (δ)					<sup>13</sup> C-NMR data (ppm)						
	NH	H-3	H-1'	H-6''	Other signals	C-1	C-1'	C-3	C-2	C-2''	C-2'''	Other signals
<p>(117)</p>	6.55 (s)	1.30 (s)	3.72 (s)	1.46 (s)	<b>H-4''/H-5''</b> : 3.84-3.90 (ms), <b>H-1'''</b> : 4.65 and 4.71 (ds) <i>J</i> = 11.7 Hz, <b>Ar-H</b> : 7.26-7.33 (overlapping ms)	173.7	52.5	16.7	72.1	110.3	137.9	<b>C-4''/C-5''</b> : 65.5, <b>C-6''</b> : 21.4. <b>C-1'''</b> : 77.3, <b>Ar-CH</b> : 128.7, 128.3 and 127.8.
<p>(121)</p>	2.95 (br s)	1.14 (s)	3.76 (s)	1.24 (s)/ 1.39 (s)	<b>H-1'''</b> : 4.68 and 4.73 (ds) <i>J</i> = 11.7 Hz, <b>Ar-H</b> : 7.29-7.38 (overlapping ms)	176.0	52.5	16.4	72.1	73.8	137.6	<b>C-1''''/C-4</b> : 24.3/26.5, <b>C-1'''</b> : 77.3, <b>Ar-CH</b> : 128.7, 128.4 and 127.4.

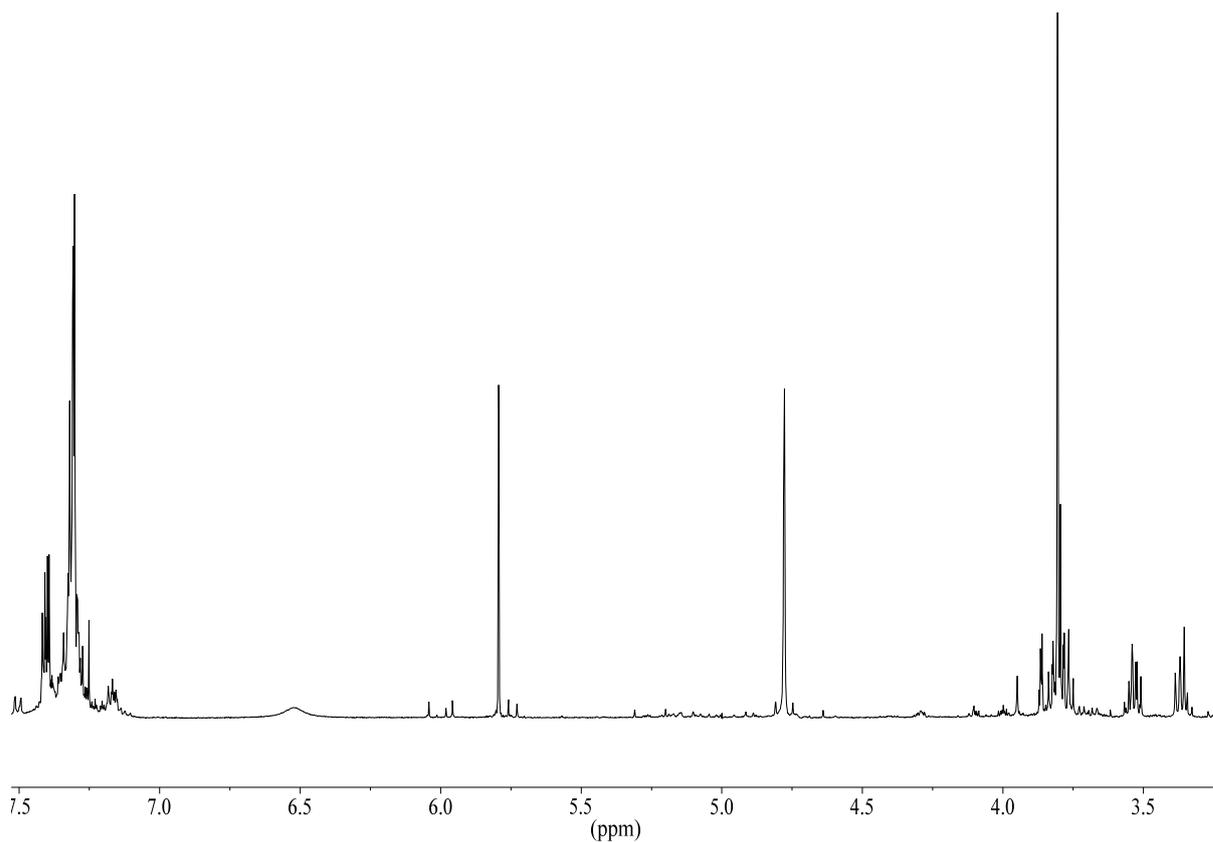
## 2.14 Photochemical reactions of methyl (2E)-[(benzyloxy)imino](phenyl)acetate (81)

### 2.14.1 Photochemical reaction of methyl (2E)-[(benzyloxy)imino](phenyl)acetate (81) and 1,3-dioxolane



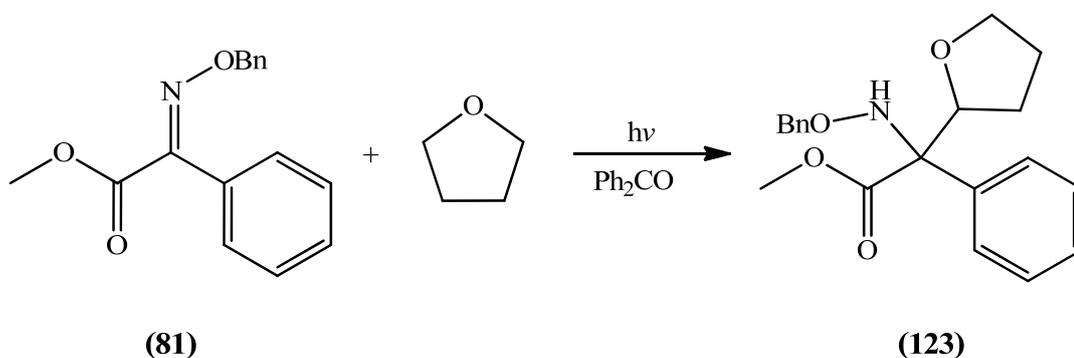
Scheme 102

A solution of methyl (2E)-[(benzyloxy)imino](phenyl)acetate (**81**), benzophenone and 1,3-dioxolane in MeCN was prepared as before (Section 2.6.1) and was then irradiated for 2 h at which time all the starting material had reacted (GC). GC analysis indicated the formation of a single product, (**122**), and analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated that most of the benzophenone had dimerised. Chromatography gave methyl [(benzyloxy)amino](1,3-dioxolan-2-yl)phenylacetate (**122**) as a clear oil in 79% yield. In the IR spectrum there were bands at 3256 and 1735 cm<sup>-1</sup> which corresponded to the NH and carbonyl bonds, respectively. The CO bands appeared at 1139, 1094 and 1018 cm<sup>-1</sup> and bands for the monosubstituted aromatic systems in the molecule at 728 and 696 cm<sup>-1</sup>. The <sup>1</sup>H-NMR spectrum (Figure 34) contained singlets corresponding to the methoxy and benzylic methylene groups, respectively (Table 13). The methine proton signal appeared at δ 5.79 and there was a broad singlet at δ 6.52 which corresponded to the aminyl proton. The methylene protons appeared as a series of overlapping multiplets at δ 3.37, 3.54 and 3.75-3.86 and the aromatic protons appeared as a series of overlapping multiplets at δ 7.15-7.49. In the <sup>13</sup>C-NMR spectrum the carbonyl carbon resonated at 171.6 ppm and the methine carbon appeared at 103.3 ppm. Signals at 137.5 and 134.6 ppm corresponded to the two *ipso* carbons of the aromatic systems, the former due to that in the benzyl group. The other aromatic signals appeared as expected (Table 13), and the benzylic methylene carbon resonated at 76.9 ppm. The quaternary and methoxy carbons resonated at 74.2 and 52.6 ppm, respectively, and the other methylene carbon signals appeared at 65.7 and 65.5 ppm.



**Figure 34**  $^1\text{H-NMR}$  spectrum of **(122)**

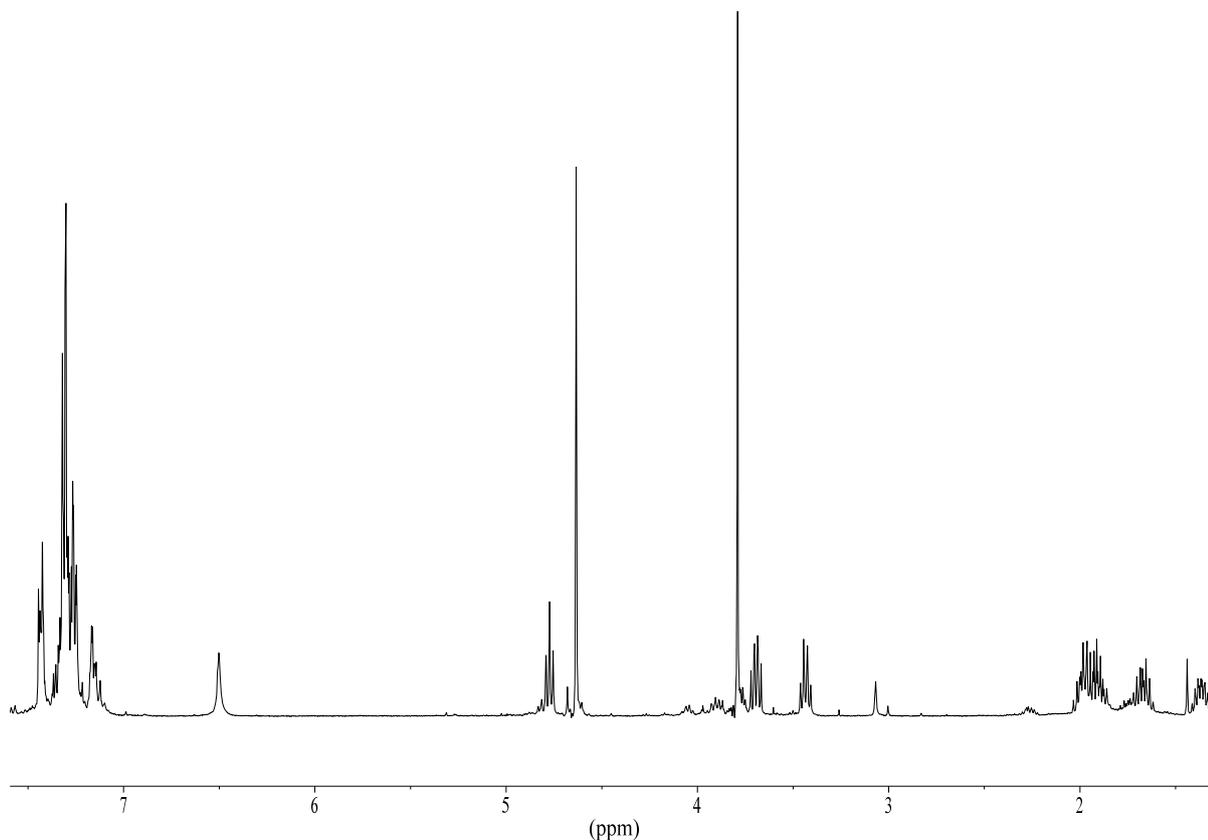
**2.14.2 Photochemical reaction of methyl (2E)-[(benzyloxy)imino](phenyl)acetate (**81**) and THF**



**Scheme 103**

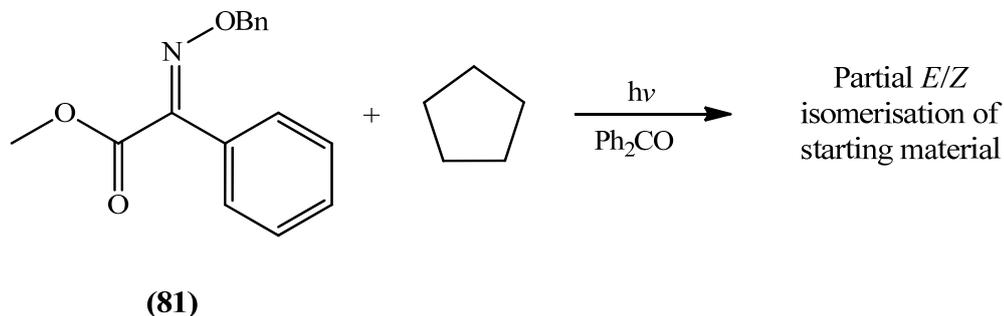
A solution of methyl (2E)-[(benzyloxy)imino](phenyl)acetate (**81**), benzophenone and THF in MeCN was prepared as before (**Section 2.6.1**). It was then irradiated for 2 h at which time no further change was occurring (GC). Analysis of the  $^1\text{H-NMR}$  spectrum of the crude product indicated that no benzophenone remained, that a large amount of starting material also remained unreacted, but that there were some product signals present in a 1:1.2 diastereomeric ratio. Flash column chromatography gave one diastereomer of methyl [(benzyloxy)amino](tetrahydrofuran-2-yl)phenylacetate (**123**) as a

clear oil in 16% yield. None of the second diastereomer was isolated. In the IR spectrum there were the characteristic bands for the monosubstituted rings at 731 and 696  $\text{cm}^{-1}$ , and the CO bands appeared at 1139, 1066 and 1024  $\text{cm}^{-1}$ . The carbonyl and NH bands appeared at 1728 and 3271  $\text{cm}^{-1}$ , respectively. In the  $^1\text{H-NMR}$  spectrum (**Figure 35**) there were multiplets at  $\delta$  1.28, 1.57 and overlapping multiplets at  $\delta$  1.79-1.91 which corresponded to the methylene protons of the tetrahydrofuranyl ring which were not adjacent to the oxygen. Two quartets at  $\delta$  3.36 ( $J_{gem} = J_{cis} = J_{trans} = 7.2$  Hz) and  $\delta$  3.60 ( $J_{gem} = J_{cis} = J_{trans} = 7.1$  Hz) corresponded to the methylene protons adjacent to the oxygen in the ring. Singlets corresponding to the methoxy and benzylic methylene protons were present (**Table 13**), and a triplet at  $\delta$  4.68 ( $J_{cis} = J_{trans} = 7.4$  Hz) appeared for the methine proton. The aminyl proton appeared as a singlet at  $\delta$  6.42 and the aromatic protons appeared as a series of overlapping multiplets at  $\delta$  7.03-7.35. In the  $^{13}\text{C-NMR}$  spectrum the carbonyl carbon resonated at 172.6 ppm and the methine carbon signal appeared at 82.0 ppm. Signals at 137.6 and 136.6 ppm corresponded to the two *ipso* carbons of the aromatic systems, the former due to the benzylic aromatic system. The other aromatic signals and the benzylic carbon appeared as expected (**Table 13**); the methoxy and quaternary carbons resonated at 52.5 and 74.0 ppm, respectively. The final three signals appeared at 69.2, 24.3 and 22.5 ppm corresponded to the methylene carbons of the tetrahydrofuranyl ring.



**Figure 35**  $^1\text{H-NMR}$  spectrum of (123)

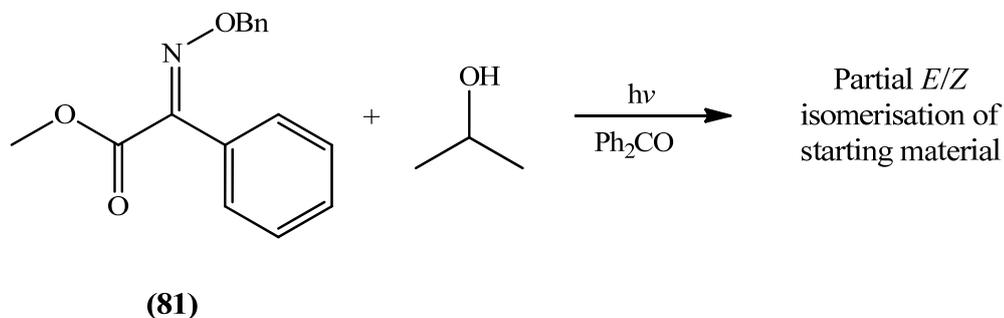
**2.14.3 Photochemical reaction of methyl (2E)-[(benzyloxy)imino](phenyl)acetate (81) and cyclopentane**



**Scheme 104**

A solution of methyl (2E)-[(benzyloxy)imino](phenyl)acetate (**81**), benzophenone and cyclopentane in MeCN was prepared as before (**Section 2.6.1**). It was then irradiated for 4 h at which time no further change in the reaction was occurring (GC). Analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated partial *E/Z* photoisomerisation had occurred (*E/Z* ratio = 2.8/1 ratio, NMR), but that no addition products had formed. No attempts were made to isolate the isomers as the NMR spectrum of the mixture corresponded to those of pure (**81**) and (**82**).

**2.14.4 Photochemical reaction of methyl (2E)-[(benzyloxy)imino](phenyl)acetate (81) and 2-propanol**



**Scheme 105**

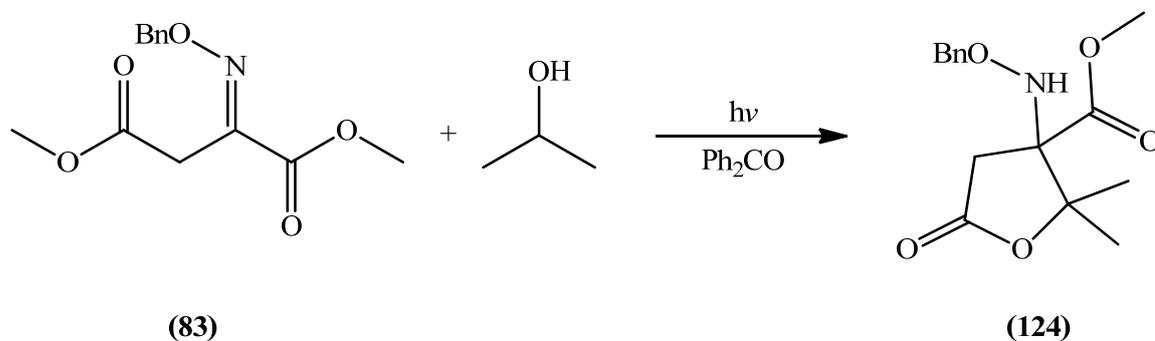
A solution of methyl (2E)-[(benzyloxy)imino](phenyl)acetate (**81**), benzophenone and 2-propanol in MeCN was prepared as before (**Section 2.6.1**). It was then irradiated for 3 h at which time no further change was occurring (GC). Analysis of the NMR spectrum of the crude product again indicated partial *E/Z* photoisomerisation had occurred (*E/Z* ratio = 2.4/1 ratio NMR), but that no addition products formed.

Table 13 NMR data for methyl (2E)-(benzyloxyimino)(phenyl)acetate reactions

	<sup>1</sup> H-NMR data (δ)					<sup>13</sup> C-NMR data (ppm)					
	NH	H-1'	H-2''	H-4''/ H-5''	Other signals	C-1	C-1'	C-2	C-2''	C-1'''	Other signals
<p>(122)</p>	6.52 (br s)	3.80 (s)	5.79 (s)	3.37 (m), 3.54 (m), 3.75-3.86 (ms)	<b>H-1''''</b> : 4.77 (s) <b>Ar-H</b> : 7.15-7.49 (overlapping ms)	171.6	52.6	74.2	103.3	134.6	<b>C-4''/C-5''</b> : 65.5/65.7, <b>C-</b> <b>1''''</b> : 76.9, <b>C-</b> <b>2''''</b> : 137.5, <b>Ar-</b> <b>CH</b> : 128.4, 128.3, 128.2, 127.9, 127.8 and 127.5.
<p>(123)</p>	6.42 (s)	3.70 (s)	4.68 (t) $J = 7.8$ Hz	1.28 (m) and 1.57 (m)	<b>H-3''</b> : 1.79-1.91 (overlapping ms) <b>H-5''</b> : 3.36 (q) $J_{gem} = J_{cis} = J_{trans} =$ 7.2 Hz, 3.60 (q) $J_{gem} = J_{cis} = J_{trans} =$ 7.1 Hz <b>H-1''''</b> : 4.54 (s) <b>Ar-H</b> : 7.03-7.35 (overlapping ms)	172.6	52.5	74.0	82.0	136.6	<b>C-3''</b> : 24.3, <b>C-</b> <b>4''</b> : 22.5, <b>C-</b> <b>5''</b> : 69.2, <b>C-</b> <b>1''''</b> : 76.6, <b>C-</b> <b>2''''</b> : 137.6, <b>Ar-</b> <b>CH</b> : 128.5, 128.4, 128.1, 127.9, 127.8 and 127.7.

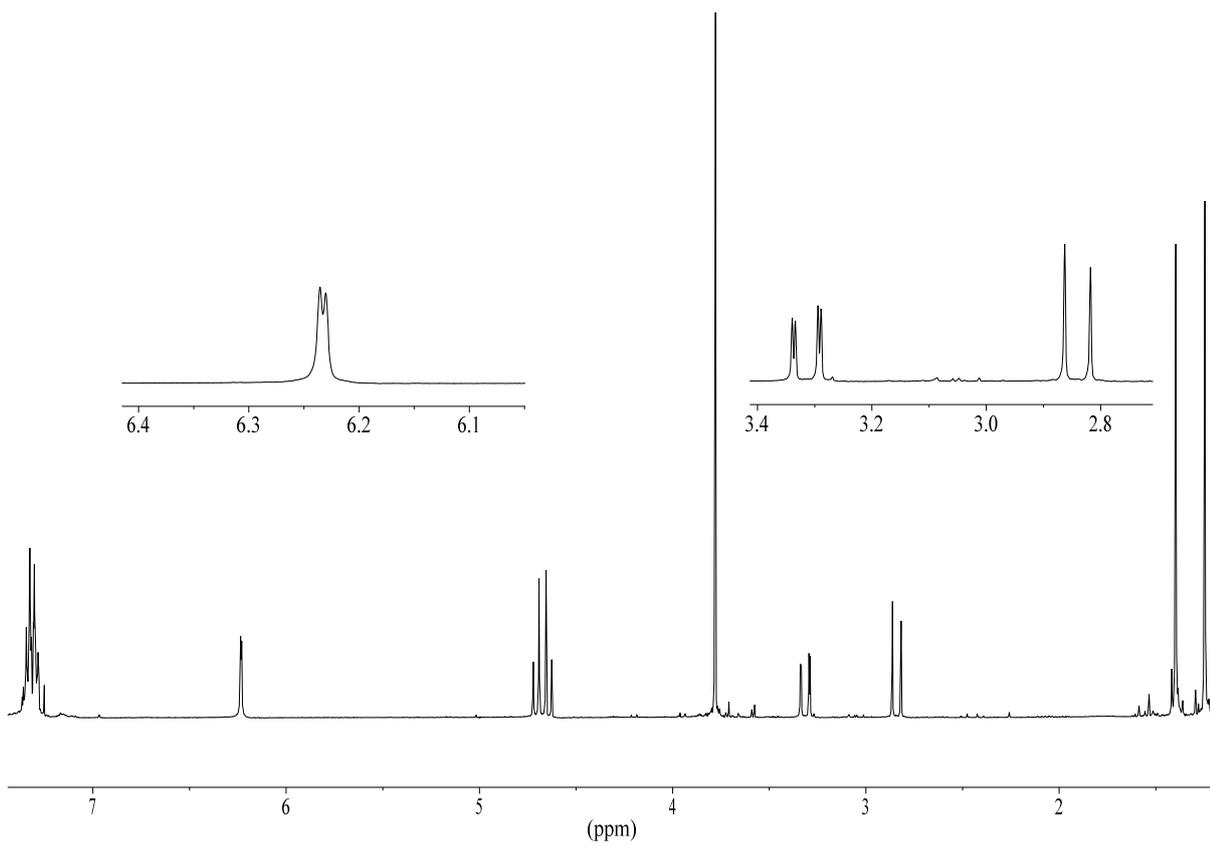
## 2.15 Photochemical reactions of 1,4-dimethyl (2E)-2-[(benzyloxy)imino]butandioate (**83**)

### 2.15.1 Photochemical reaction of 1,4-dimethyl (2E)-2-[(benzyloxy)imino]butandioate (**83**) and 2-propanol



Scheme 106

A solution of 1,4-dimethyl (2E)-2-[(benzyloxy)imino]butandioate (**83**), benzophenone and 2-propanol in MeCN was prepared as before (Section 2.6.1). It was then irradiated for 2 h at which time no further reaction was occurring (GC). Analysis of the  $^1\text{H-NMR}$  spectrum of the crude product indicated that all the benzophenone had dimerized, that some starting material remained, and that (**124**) had formed. On chromatography the unreacted starting material was eluted first and was obtained in a 51% yield. It was followed by methyl 3-[(benzyloxy)amino]-2,2-dimethyl-5-oxotetrahydrofuran-3-carboxylate (**124**) which was obtained as a clear oil in 26% yield. In the IR spectrum of (**124**) there were bands at 726 and 698  $\text{cm}^{-1}$  characteristic of the monosubstituted aromatic ring, with CO bands appearing at 1176, 1135 and 1028  $\text{cm}^{-1}$ . The lactone carbonyl band was present at 1779  $\text{cm}^{-1}$  and the ester carbonyl band appeared at 1736  $\text{cm}^{-1}$ ; the NH band appeared at 3269  $\text{cm}^{-1}$ . In the  $^1\text{H-NMR}$  spectrum (Figure 36) there were singlets at  $\delta$  1.24 and 1.39, and at  $\delta$  3.77 which corresponded to the methyl and methoxy groups, respectively. The benzylic methylene protons appeared as a pair of doublets at  $\delta$  4.64 and 4.71 ( $J = 11.9$  Hz). One of the methylene protons on the lactone ring appeared as a doublet at  $\delta$  2.83 ( $J = 18.0$  Hz) due to geminal coupling; the methylene proton *trans* to the nitrogen appeared as a double doublet at  $\delta$  3.32 ( $J = 18.0$  Hz and  $J = 2.2$  Hz) due to long-range W coupling with the aminyl proton. The aminyl proton in turn appeared as a doublet at  $\delta$  6.23 ( $J = 2.2$  Hz) and the aromatic protons appeared as a series of overlapping multiplets at  $\delta$  7.27-7.34. In the  $^{13}\text{C-NMR}$  spectrum the carbonyl carbons resonated at 173.4 and 170.5 ppm, and the aromatic carbons appeared at 136.6, 128.8, 128.6 and 128.3 ppm. The quaternary carbon of the *geminal* dimethyl group resonated at 84.8 ppm, and the other quaternary carbon resonated at 73.1 ppm. The two methyl carbons and methoxy carbons resonated at 25.0, 20.6 and 53.1 ppm, respectively, and the benzylic and ring methylene carbons appeared at 77.6 and 35.6 ppm, respectively.



**Figure 36**  $^1\text{H-NMR}$  spectrum of (124)

## 2.16 Photochemical reactions of molecules with EWG on the nitrogen

Although attaching the EWG to the nitrogen end of the imine bond should make the imine more susceptible to attack by the nucleophilic carbon radical due to the larger  $\delta^+$  on the iminyl carbon (**Figure 37**), mixed results have been reported with molecules of this kind (**Section 1.6**)<sup>[9-10, 52-53]</sup>. However all reactions reported involved the thermal generation of the radicals, and so in an attempt to investigate the effect of the photochemical generation the carbon radicals in relation to this type of system, reactions were undertaken with ethyl[(1*E*)-phenylmethylene]carbamate (**84**) and 4-methyl-*N*-[(1*E*)-phenylmethylidene] benzene-1-sulfonamide (**45**).

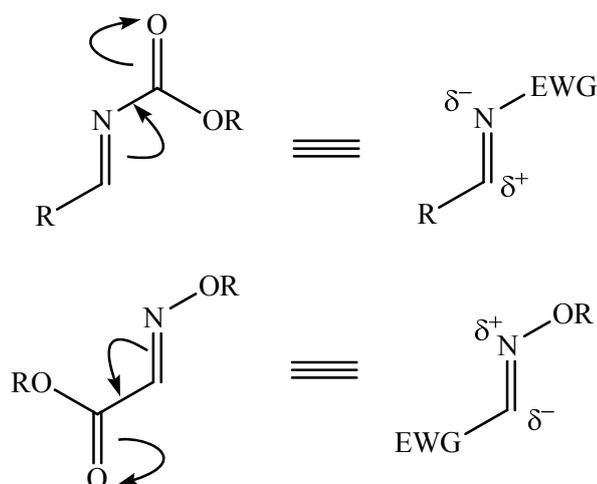
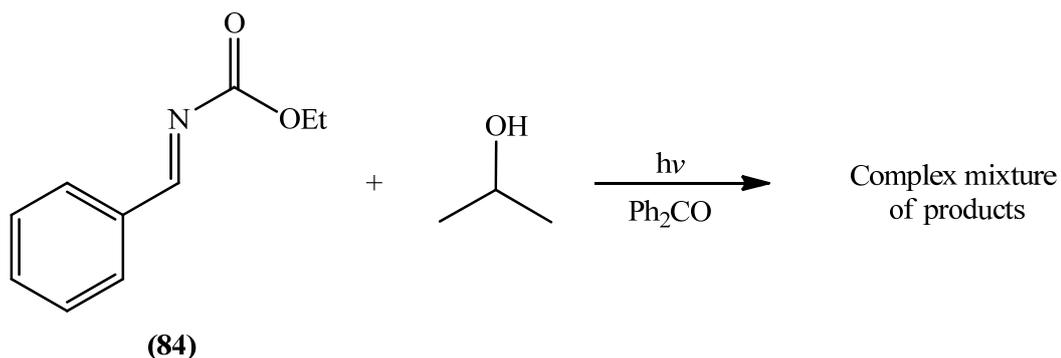


Figure 37

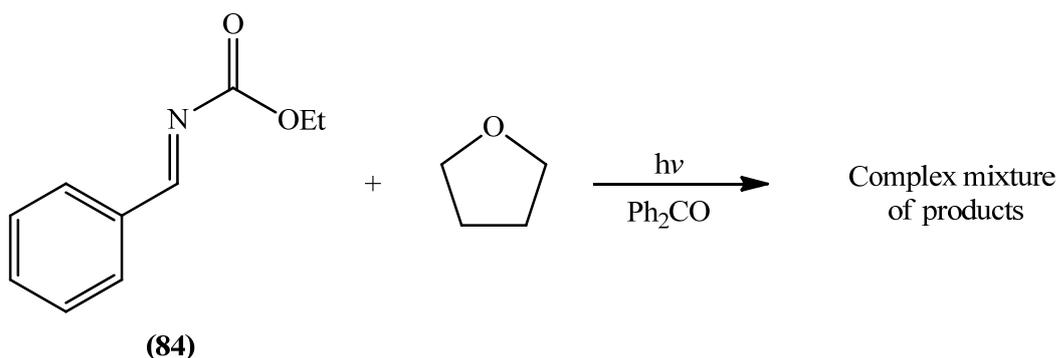
### 2.16.1 Photochemical reaction of ethyl[(1*E*)-phenylmethylene]carbamate (**84**) and 2-propanol



Scheme 107

A solution of ethyl[(1*E*)-phenylmethylene]carbamate (**84**), benzophenone and 2-propanol in MeCN was prepared as before (**Section 2.6.1**). It was then irradiated for 1 h at which time the starting material had reacted (GC). GC analysis indicated that no product peaks had been formed. Analysis of the NMR spectrum of the crude product indicated the formation of a complex mixture of products.

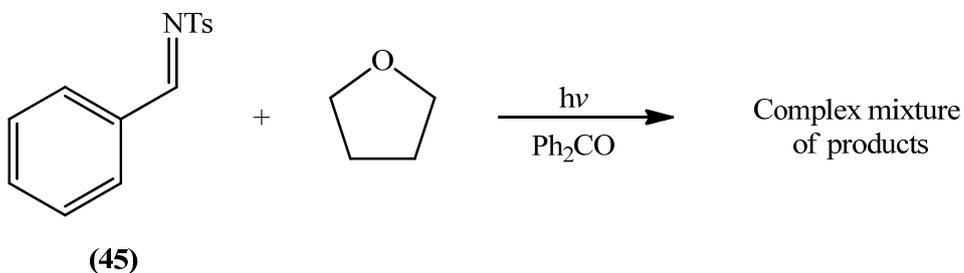
### 2.16.2 Photochemical reaction of ethyl[(1E)-phenylmethylene]carbamate (84) and THF



**Scheme 108**

A solution of ethyl[(1E)-phenylmethylene]carbamate (**84**) and benzophenone in THF was prepared as before (**Section 2.6.1**). It was then irradiated for 15 min at which time the starting material had reacted (GC). GC analysis indicated that no small molecule volatile products had been formed and analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated the formation of a complex mixture of products.

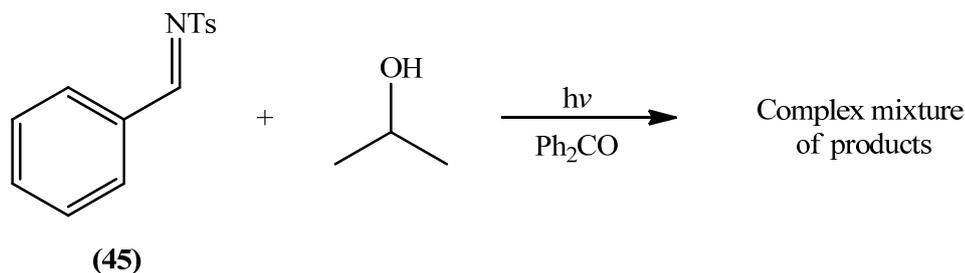
### 2.16.3 Photochemical reaction of 4-methyl-N-[(1E)-phenylmethylidene]benzene-1-sulfonamide (45) and THF



**Scheme 109**

A solution of 4-methyl-N-[(1E)-phenylmethylidene]benzene-1-sulfonamide (**45**) and benzophenone in THF was prepared as before (**Section 2.6.1**). It was then irradiated for 30 min at which time the starting material had reacted (GC). Analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated a complex mixture of products had formed.

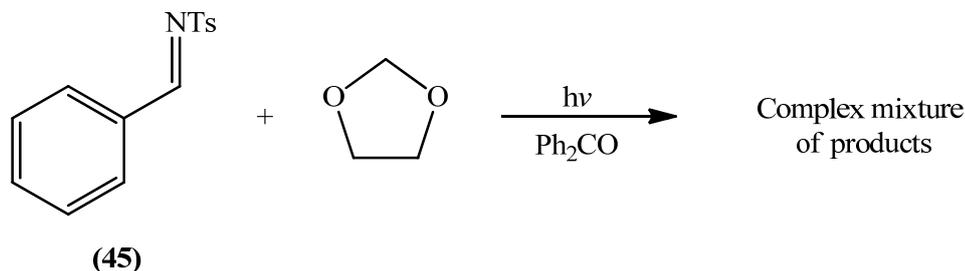
**2.16.4 Photochemical reaction of 4-methyl-*N*-[(1*E*)-phenylmethylidene]benzene-1-sulfonamide (45) and 2-propanol**



**Scheme 110**

A solution of 4-methyl-*N*-[(1*E*)-phenylmethylidene]benzene-1-sulfonamide (**45**), benzophenone and 2-propanol in MeCN was prepared as before (**Section 2.6.1**). It was then irradiated for 1 h at which time the starting material had reacted (GC). Analysis of the NMR spectrum of the crude product indicated a complex mixture of products had formed.

**2.16.5 Photochemical reaction of 4-methyl-*N*-[(1*E*)-phenylmethylidene]benzene-1-sulfonamide (45) and 1,3-dioxolane**



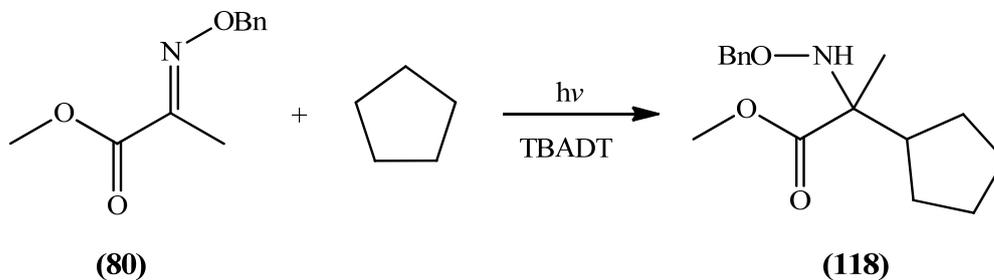
**Scheme 111**

A solution of 4-methyl-*N*-[(1*E*)-phenylmethylidene]benzene-1-sulfonamide (**45**), benzophenone and 1,3-dioxolane in MeCN was prepared as before (**Section 2.6.1**). It was then irradiated for 1 h at which time the starting material had reacted (GC). Analysis of the NMR spectrum of the crude product indicated a complex mixture of products had formed.

It is disappointing these experiments didn't lead to any 'addition product' formation as similar experiments had been carried out with thermally generated radicals and thus comparisons could have been made. As to why these experiments may not have worked, polymerisation of the starting material may have occurred once radical formation had started. Another reason may have been that the products formed were not photostable leading to degradation in the presence of UV light.

## 2.17 TBADT mediated reactions

### 2.17.1 Photochemical reaction of methyl (2E)-2-[(benzyloxy)imino]propanoate (80) and cyclopentane



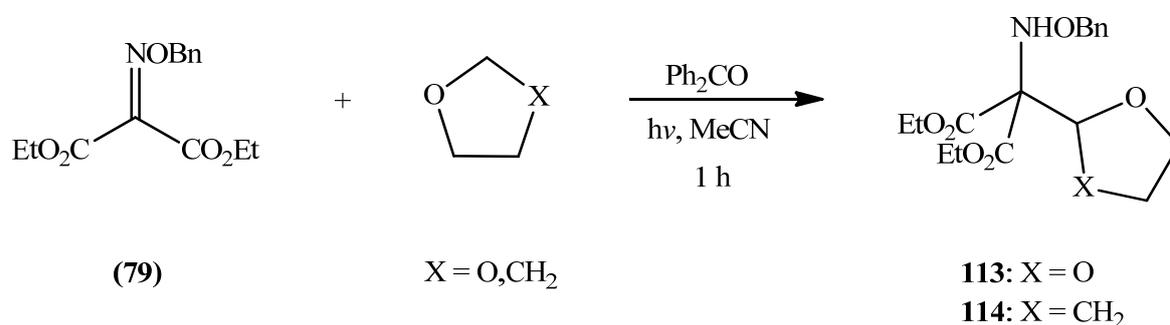
Scheme 112

A solution of methyl (2E)-2-[(benzyloxy)imino]propanoate (**80**), TBADT and cyclopentane in MeCN was prepared as before (Section 2.6.1). It was then irradiated for 25 h at which time the reaction was stopped, GC analysis indicating the formation of (**125**), the presence of unreacted starting material and the fact that no further reaction was occurring. In contrast to the same reaction mediated by benzophenone (Section 2.12.3), TBADT gives an addition product whereas benzophenone gives only a photoisomerisation product. Standard work-up and chromatography gave methyl 2-[(benzyloxy)amino]-2-(cyclopentyl)propanoate (**125**) as a clear oil in 25% yield. In the IR spectrum there were bands at 1251, 1140 and 1044  $\text{cm}^{-1}$ , which corresponded to the CO bonds, and a band at 1727  $\text{cm}^{-1}$  for the carbonyl group. The NH band appeared at 3280  $\text{cm}^{-1}$  and the monosubstituted aromatic bands appeared at 733 and 696  $\text{cm}^{-1}$ . In the  $^1\text{H-NMR}$  spectrum singlets at  $\delta$  1.32 and 3.69 corresponded to the methyl and methoxy protons, respectively. The cyclopentyl methylene protons appeared as a series of overlapping multiplets at  $\delta$  1.42-1.69 and the methine proton signal appeared as a multiplet at  $\delta$  2.00. The benzylic methylene protons appeared as a pair of doublets at  $\delta$  4.65 and 4.72 ( $J = 12.0$  Hz), together with the aminyl proton which appeared as a singlet at  $\delta$  6.09. The aromatic signals appeared as a series of overlapping multiplets at  $\delta$  7.26-7.39. In the  $^{13}\text{C-NMR}$  spectrum the carbonyl carbon resonated at 175.9 ppm and the aromatic carbons gave signals at 137.9, 128.5, 128.4 and 127.8 ppm. The benzylic methylene carbon resonated at 77.1 ppm, with the cyclopentyl methylene carbons appearing at 27.2, 26.9, 25.5 and 25.3 ppm. The quaternary and methine carbons appeared at 68.0 and 45.4 ppm, respectively, and the methyl and methoxy carbons at 16.8 and 52.1 ppm, respectively.

## 2.18 Solar Photochemistry

The use of sunlight as a possible source of UV irradiation makes the photomediated addition of H-donors to electron deficient multiple bonds attractive from a clean/green aspect<sup>[75]</sup>. Oelgemoller<sup>[76]</sup> carried out a series of photochemical reactions, including the photoacylation of naphthoquinone with butyraldehyde. He found that all reactions could be carried out on multigram-to-kilogram scale using cheap and commercially available starting materials giving high yields. These reactions yielded important key intermediates for industrial applications.

Some solar photochemical reactions, using basic equipment, were undertaken to test the feasibility of these reactions.



**Scheme 113**

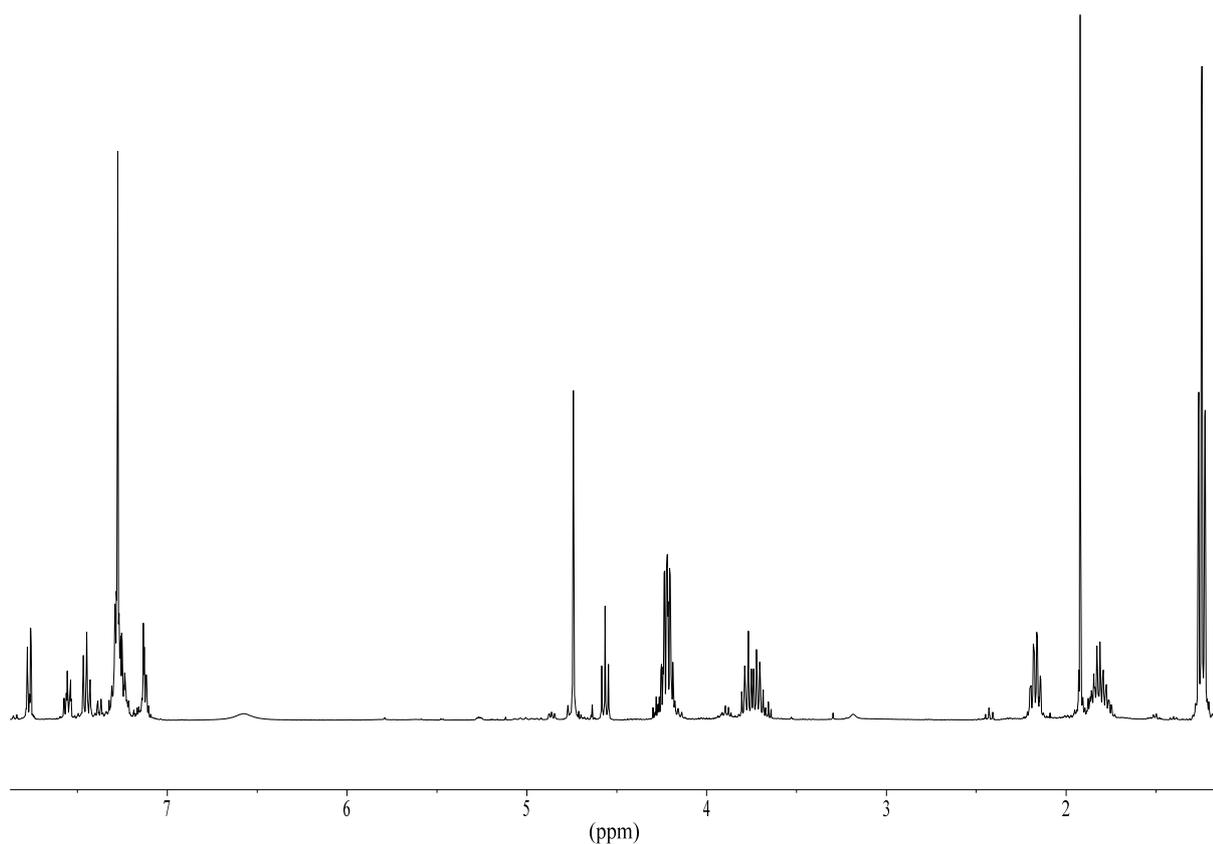
A solution of (79), benzophenone and 1,3-dioxolane in MeCN was prepared as before in the standard way (Section 2.6.1). It was then exposed to direct sunlight (Figure 38) for 1 h at which time the reaction was complete with GC and NMR analysis indicating that the oxime ether (79) had been completely consumed and that (113) was the only product formed. No attempt was made to isolate the product as it was clear from both the GC and NMR that 100% conversion had taken place.



**Figure 38**

A solution of (79), benzophenone and THF in MeCN were also prepared as before (Section 2.6.1) and exposed to direct sunlight (Figure 36) for 1 h at which time the reaction was complete with GC and NMR analysis (Figure 39) indicating that (79) had been completely consumed and that (114) was the only product formed. Allowing for the presence of benzopinacol, benzophenone and some acetonitrile the  $^1\text{H-NMR}$  spectrum of the product was identical to that obtained for the product produced using the Rayonet reactor.

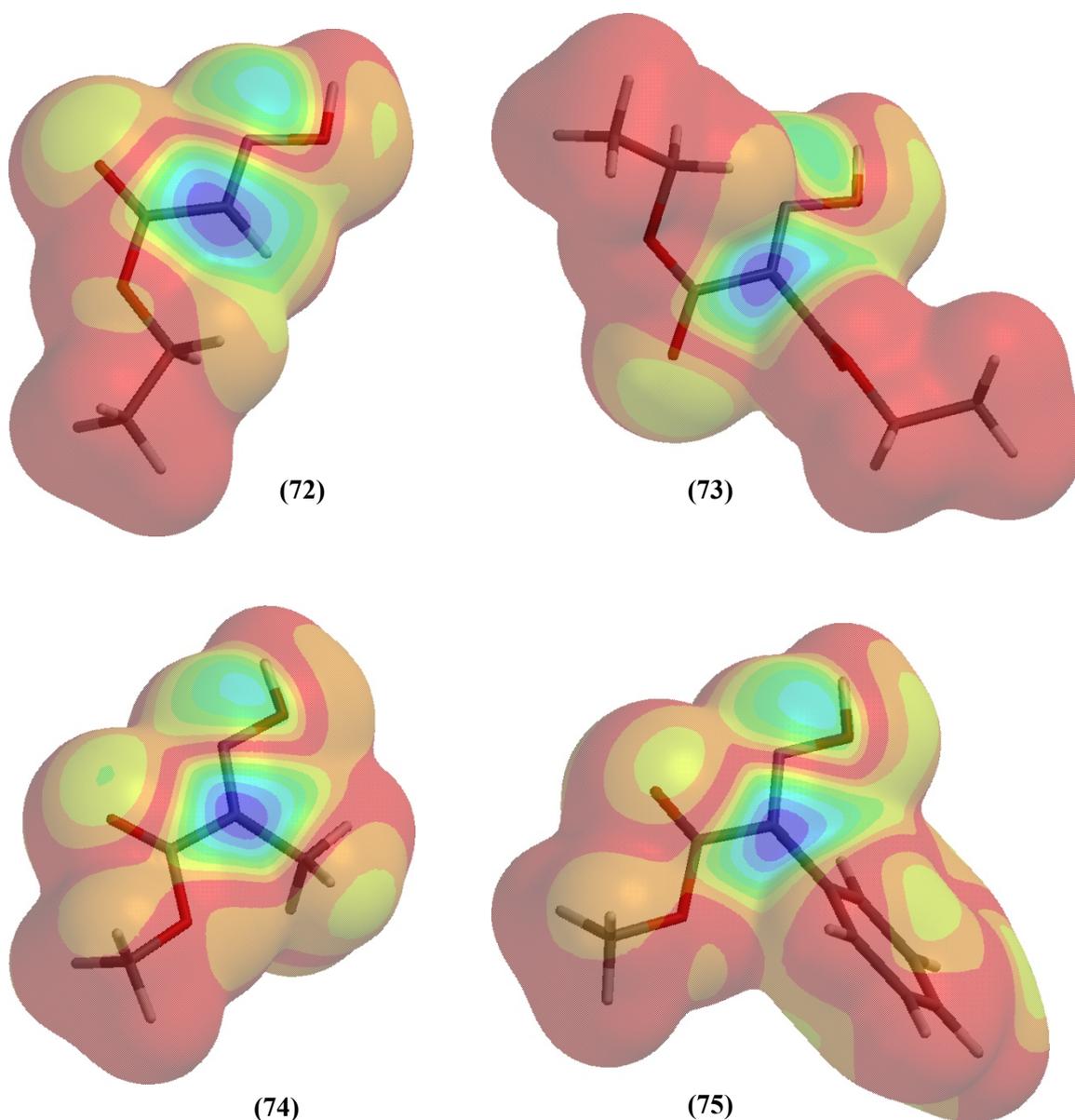
Interestingly, compared to the reaction carried out in the Rayonet reactor much less benzopinacol had formed using sun-light as the UV source.



**Figure 39** crude NMR spectrum of solar reaction of (79) and THF

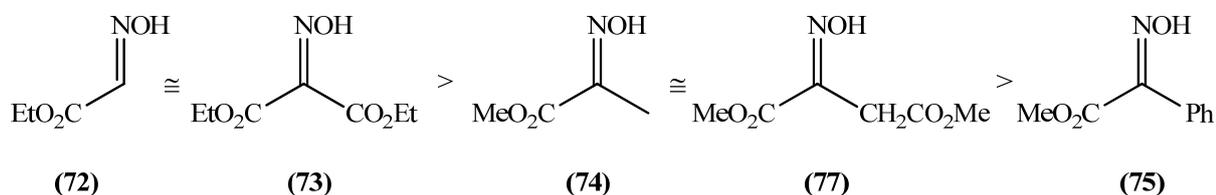
## 2.19 Comparison of C=N systems

The addition of nucleophilic C-radicals to the oximes considered here and in other work<sup>[11, 48, 57]</sup>, involve reaction at the C-atom. This is even true of systems with an EWG, or EWGs on the oximes C-atom, such as (72-75) and (77), for which the EWG effect might be expected to be most pronounced at the  $\beta$ -atom of the conjugated system, that is the N-atom. Clearly the inductive effect of the N-atom is the major factor in determining the regiochemistry of radical additions. This is confirmed by the electron density surface maps for the LUMOs of (72)-(75). The LUMO map shows which regions of a molecule are most electron deficient and depicts them in blue. For oximes (72)-(75), these electrophilic regions are located over the C-atom of the oxime bond. The EWGs simply activate the oxime bond to nucleophilic attack by lowering its electron density in a general way.



### 2.19.1 Reactivity of oximes

In general, a definite order of reactivity, based on both yield and reaction time, is evident for the oxime systems considered (**Scheme 114**).



**Scheme 114**

The aldoxime (**72**) and hydroxyimino malonate (**73**) had approximately the same reactivity and were the most reactive of the systems investigated. Although the malonate has a second EWG which should increase the reactivity, this extra reactivity is offset by the steric crowding around the reactive carbon centre. The behaviour of (**72**) and (**73**) thus suggests that both steric and electronic effects are important in determining the reactivity of these systems in relation to radical addition. The hydroxyimino propanoate (**74**) and the hydroxyimino butandioate (**77**) also displayed similar reactivity but were less reactive than (**72**) and (**73**). As both systems have only one activating EWG and also have a large non-activating group joined to the active centre, their reactivity fits into the pattern established by (**72**) and (**73**). The hydroxyimino phenyl acetate (**75**) was the least reactive of the systems considered, presumably due to the even greater steric crowding around its iminyl carbon provided by the phenyl group.

All reactions with aldoxime (**72**) were carried out using 0.5 equivalents of the photomediator benzophenone and all the reactions were complete after 1 h (**Table 14**). Good yields were obtained for the THF and 2-propanol reactions, however lower yields were obtained for the reactions of 1,3-dioxolane and cyclopentane.

**Table 14 Summary of reactions involving oxime (72)**

Oxime	H-Donor	Reaction time <sup>a</sup>	Eq photomediator	% Yield <sup>b</sup>
<b>(72)</b>	THF	1 h	0.5	83
	1,3-dioxolane	1 h	0.5	62
	2-propanol	1 h	0.5	80
	cyclopentane	1 h	0.5	57

<sup>a</sup>GC, <sup>b</sup>Isolated yield

The reactions of hydroxyimino malonate (**73**) (**Table 15**) with THF and 1,3-dioxolane again proceeded rapidly and in good yield. However reactions with 2-propanol led to a complex mixture of products, and reactions involving cyclopentane gave lower yields even when 1 equivalent of benzophenone was employed as the photomediator.

**Table 15 Summary of reactions involving oxime (73)**

Oxime	H-Donor	Reaction time <sup>a</sup>	Eq photomediator	% Yield <sup>b</sup>
<b>(73)</b>	THF	1 h	0.5	87
	1,3-dioxolane	1 h	0.5	65
	2-propanol	1 h	0.5	-
	cyclopentane	4 h	1.0	19

<sup>a</sup>GC, <sup>b</sup>Isolated yield

Achieving reasonable yields with the ketoxime (**74**) (**Table 16**) required 1 equivalent of benzophenone, as preliminary experiments showed that benzophenone dimerization was particularly competitive for these systems, with reaction times varying from 2-4 h. The best yield, 76%, was obtained in the 1,3-dioxolane reaction, with THF giving a lower yield of 60%. No addition products were obtained with cyclopentane and the reaction with 2-propanol gave a low yield of 33%.

**Table 16 Summary of reactions involving ketoxime (74)**

Oxime	H-Donor	Reaction time <sup>a</sup>	Eq photomediator	% Yield <sup>b</sup>
<b>(74)</b>	THF	3 h	1.0	60
	1,3-dioxolane	3 h	1.0	76
	2-propanol	3 h	1.0	33
	cyclopentane	4 h	1.0	-

<sup>a</sup>GC, <sup>b</sup>Isolated yield

The series of reactions with ketoxime (**77**) (**Table 17**) again required 1 equivalent of benzophenone; reaction times were in line with those observed for (**74**). The reactions with THF and 1,3-dioxolane again gave the best yields, with a lower yield being obtained for the reaction with 2-propanol. The reaction with cyclopentane again failed to work.

**Table 17 Summary of reactions involving ketoxime (77)**

Oxime	H-Donor	Reaction time <sup>a</sup>	Eq photomediator	% Yield <sup>b</sup>
(77)	THF	3 h	1.0	83
	1,3-dioxolane	3 h	1.0	73
	2-propanol	2 h	1.0	43
	cyclopentane	4 h	1.0	-

<sup>a</sup>GC, <sup>b</sup>Isolated yield

Only 1,3-dioxolane gave an addition product with ketoxime (75) (Table 18) and even here the yield obtained was very low. THF, 2-propanol and cyclopentane gave photoreduction products. It would appear then that the normal addition process is very slow for (75) allowing other reaction channels to compete. It should be emphasized however that reactions involving (75) lead to the formation of a complex mixture of products (GC) and so it is possible that the products obtained were simply those most easily separated by chromatography on silica. It is not clear why cyclopentane affords photoreduction products in this case and not with ketoximes (74) and (77), where no reaction at all is observed.

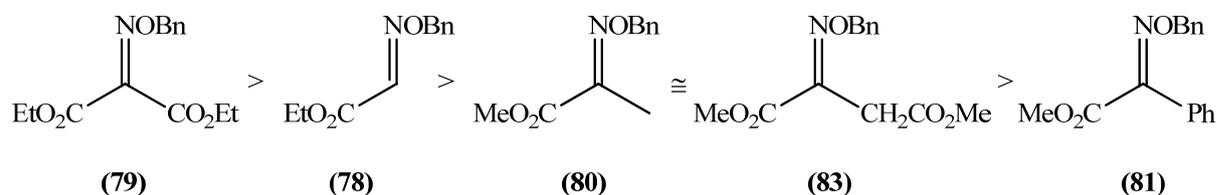
**Table 18 Summary of reactions of oxime (75)**

Oxime	H-Donor	Reaction time <sup>a</sup>	Eq photomediator	% Yield <sup>b</sup>
(75)	THF	3 h	1.0	11 <sup>c</sup>
	1,3-dioxolane	6 h	1.0	25
	2-propanol	6 h	1.0	33 <sup>c</sup>
	cyclopentane	6 h	1.0	23 <sup>c</sup>

<sup>a</sup>GC, <sup>b</sup>Isolated yield, <sup>c</sup>yield of photoreduction product

### 2.19.2 Reactivity of benzylated oximes

For the series of benzyl protected oximes considered, the order of reactivity (**Scheme 115**) followed the same pattern as that for the free oximes, with the exception that the benzyloxyimino malonate (**79**) was slightly more reactive than the aldoxime ether (**78**).



**Scheme 115**

The reactions of (**79**) with THF and 1,3-dioxolane occurred efficiently with 0.5 equivalents of benzophenone, and were complete in 1 h (**Table 19**); the cyclopentane reaction was complete in 2 h. The yields were high for both the THF and 1,3-dioxolane reactions, a lower yield being obtained for the cyclopentane reaction. The reaction with 2-propanol gave a complex mixture of products which was also the case for the reaction involving the corresponding free oxime, (**73**). It is not clear why a complex mixture of products is obtained in the 2-propanol reactions for these systems. The presence of the benzyl group, on the basis of these results has little effect on the addition reaction.

**Table 19 Summary of reactions involving oxime (79)**

Oxime	H-Donor	Reaction time <sup>a</sup>	Eq photomediator	% Yield <sup>b</sup>
<b>(79)</b>	THF	1 h	0.5	77
	1,3-dioxolane	1 h	0.5	89
	2-propanol	1 h	0.5	-
	Cyclopentane	2 h	0.5	29

<sup>a</sup>GC, <sup>b</sup>Isolated yield

In keeping with the behaviour of the corresponding aldoxime (**72**), 0.5 equivalents of benzophenone was sufficient to effectively promote reaction of (**78**) with all the H-donors, the reaction times varying from 1-5 h (**Table 20**). The reaction with 2-methyl-1,3-dioxolane, in line with previously published work by Geraghty<sup>[19]</sup>, was complete in just 1 h and gave a higher yield, 79%, than the 1,3-dioxolane itself.

**Table 20 Summary of reactions involving aldoxime (78)**

Oxime	H-Donor	Reaction time <sup>a</sup>	Eq photomediator	% Yield <sup>b</sup>
<b>(78)</b>	THF	3 h	0.5	73
	1,3-dioxolane	2.5 h	0.5	75
	2-methyl-1,3-dioxolane	1 h	0.5	79
	2-propanol	2 h	0.5	65
	Cyclopentane	5 h	0.5	45

<sup>a</sup>GC, <sup>b</sup>Isolated yield

As with the corresponding free oxime (**74**) the reactions of the benzylated ketoxime (**80**) required 1 equivalent of benzophenone; this resulted in reaction times varying from 2-7.5 h (**Table 21**). Also in keeping with the trends seen earlier, the reaction of (**80**) with 2-methyl-1,3-dioxolane gave a higher yield of 71% compared to the 1,3-dioxolane itself. The cyclopentane reaction again failed to give an addition product using benzophenone as the photomediator. Remarkably however, the use of TBADT as photomediator, in catalytic amounts<sup>[29]</sup> (2 mol%) gave the cyclopentane addition product in 25% after 25 h.

**Table 21 Summary of reactions involving oxime (80)**

Oxime	H-Donor	Reaction time <sup>a</sup>	Eq photomediator	% Yield <sup>b</sup>
<b>(80)</b>	THF	6 h	1.0	68
	1,3-dioxolane	2 h	1.0	68
	2-methyl-1,3-dioxolane	2 h	1.0	71
	2-propanol	4 h	1.0	22
	Cyclopentane	7.5 h	1.0	-
		25 h	0.02 <sup>c</sup>	25

<sup>a</sup>GC, <sup>b</sup>Isolated yield, <sup>c</sup>TBADT

Only one reaction was carried out with ketoxime (**83**): the reaction with 2-propanol was complete in 2 h and gave a 27% yield of the addition product, methyl 3-[(benzyloxy)amino]-2,2-dimethyl-5-oxotetrahydrofuran-3-carboxylate (**124**). The outcome of this reaction indicates that the reactivity of ketoxime (**83**) is similar to that of ketoxime (**80**).

The reactions of oxime (**81**) required 1 equivalent of benzophenone, with reaction times ranging from 2-4 h (**Table 22**). There were significant differences in the behaviour of the benzylated oxime (**81**) compared to that of the free oxime (**75**). The reaction of THF with (**81**) gave an addition product

whereas that with (75) gave a reduction product. 1,3-Dioxolane gave an addition product with both (75) and (81), but a much larger yield was obtained in the latter case. Reduction was the outcome of irradiation of (75) in 2-propanol and cyclopentane whereas *E/Z* isomerisation occurred on irradiation of (81) in the same solvents.

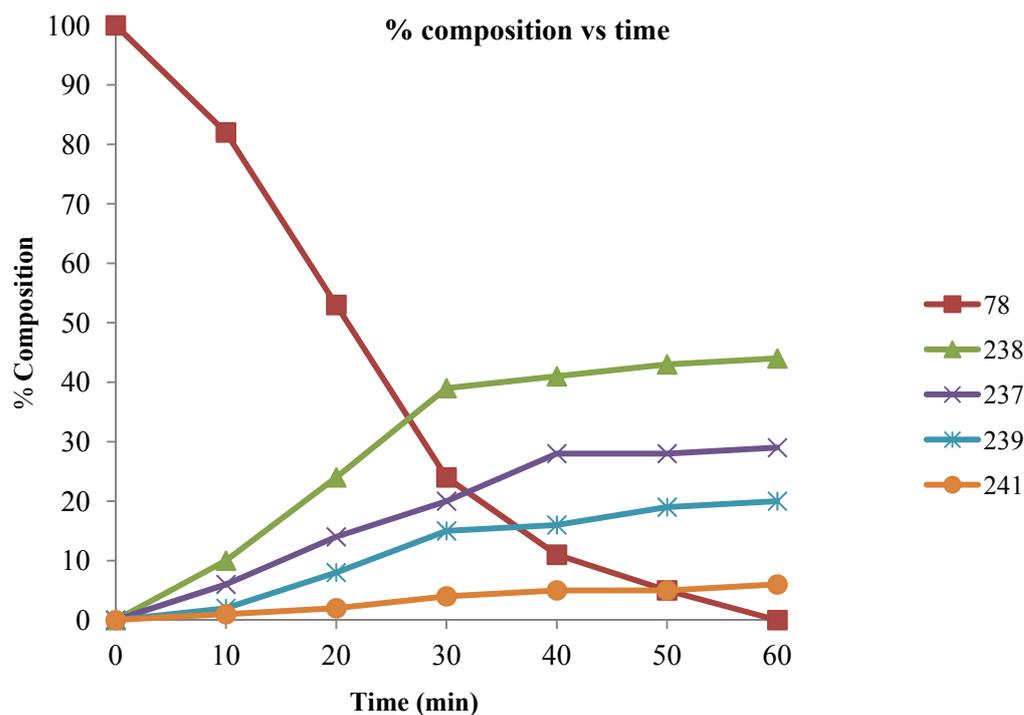
**Table 22 Summary of reactions of oxime (81)**

Oxime	H-Donor	Reaction time <sup>a</sup>	Eq photomediator	% Yield <sup>b</sup>
(81)	THF	2 h	1.0	16
	1,3-dioxolane	2 h	1.0	79
	2-propanol	3 h	1.0	- <sup>c</sup>
	Cyclopentane	4 h	1.0	- <sup>c</sup>

<sup>a</sup>GC, <sup>b</sup>Isolated yield, <sup>c</sup> partial *E/Z* isomerisation occurred

### 2.19.3 Relative reactivity of H-donors in reaction with benzylated oximes

An experiment designed to assess the relative reactivities of the different H-donors used was undertaken. The benzylated oxime (78) and benzophenone (1 equivalent) were dissolved in a mixture made up of equimolar amounts of THF, 1,3-dioxolane, 2-propanol and cyclopentane. GC analysis was used to monitor the concentrations of the different products formed as a function of time (**Figure 40**). The experiment confirmed the reactivity pattern already observed, with the THF adduct (**238**) being formed to the greatest extent followed by the 1,3-dioxolane adduct (**237**), the 2-propanol adduct (**239**), and finally the cyclopentane addition product (**241**).



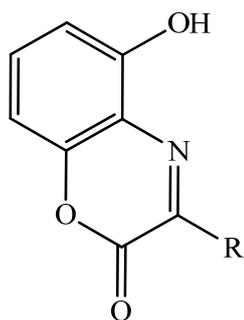
**Figure 40**

From the BDEs of the H-donors (**Section 1.3.2.3, Table 1**) 1,3-dioxolane has the lowest BDE value ( $381.2 \text{ kJ mol}^{-1}$ ) for the abstractable hydrogens on C-2 and so should be the most reactive. THF however, whose BDE is only  $10.4 \text{ kJ mol}^{-1}$  higher has more abstractable hydrogens compared to 1,3-dioxolane and is in fact the most reactive. 2-Propanol has only one abstractable hydrogen with a BDE of  $390.5 \text{ kJ mol}^{-1}$  and so is less competitive compared to both THF and 1,3-dioxolane. Cyclopentane, although having ten hydrogens is least reactive due to its larger BDE of  $400.0 \text{ kJ mol}^{-1}$ .

## **2.20 A comparison of the addition of thermally and photochemically generated carbon radicals to C=N bonds**

The addition of photochemically generated carbon radicals to C=N bonds has been investigated by Alonso using range of ketoximes<sup>[57, 59]</sup> and hydrazones<sup>[58]</sup>. In all cases he found that 1 equivalent of benzophenone was necessary to mediate the reactions successfully. This finding is consistent with the results presented in this thesis for the ketoxime substrates **(74)**, **(75)** and **(77)**, and the ketoxime ethers **(80)**, **(81)** and **(83)** where 1 equivalent of photomediator was required. We have now found however, for the aldoxime **(72)**, the aldoxime ether **(78)**, and the hydroxyimino malonates **(73)** and **(79)**, that the amount of photomediator used can be lowered to 0.5 equivalents without loss of reactivity, or yield. Miyabe<sup>[11]</sup> has described the addition of, trialkylborane and dialkyl zinc, generated carbon radicals to the ketimines **(44a-c)**. These molecules are electronically similar to the ones considered in this thesis and so some tentative comparisons can be made. He obtained a high yield of addition products for all the substrates tested with reaction times of only 5 min, including **(44c)** which has the bulky phenyl

group attached to the reactive carbon. This is in contrast to the results reported here for the ketimines (**75**) and (**81**) where in general low yields of addition products were obtained after long reaction times. Good yields were however obtained for the reactions involving hydroxyimino malonates (**73**) and (**79**) which have two EWGs attached, and this is in line with what Miyabe found for (**44b**). In general slightly lower yields were obtained for reactions with ketoximes (**74**) and (**80**) which is again in contrast with what Miyabe found for (**44a**). Overall it would appear that the thermally generated radicals, at least in the case of the C=N bonds enjoy an advantage over those generated photochemically.



**(44a)** R = Me

**(44b)** R = CO<sub>2</sub>Et

**(44c)** R = Ph

### 2.21 Synthetic potential of reaction

The synthesis of  $\alpha$  and  $\beta$ -amino acids which do not occur naturally is an important area of research<sup>[77-78]</sup>. Naturally occurring peptides and proteins are normally constructed from only twenty naturally occurring  $\alpha$ -amino acids, and so unnatural amino acids are becoming important building blocks for the synthesis of novel peptides and peptidomimetics<sup>[79]</sup>. The methodology employed in the reactions described here leads in a highly convergent manner to a range of different  $\alpha$ -amino acid precursors, thus demonstrating considerable synthetic potential and warranting further investigation.

The use of 1,3-dioxolane as a hydrogen donor in this series of reactions is interesting synthetically. The reaction corresponds to an umpolung reaction which using classical chemistry would require a three step synthetic sequence using dithiane protection of the carbonyl group followed by deprotonation using lithium and finally reformation of the carbonyl group. The products formed are protected aldehydes which can be used in further synthetic manipulations.

C-H activation is an important concept that has been studied in conventional organic chemistry. In photochemical reactions C-H activation occurs easily and is well established<sup>[80]</sup>.

## 2.22 Conclusions and future work

It can be concluded from the work presented in this thesis that photochemically generated carbon radicals add to the C-terminus of electron deficient oximes and oxime ethers in good yield and with relatively short reaction times when there is a hydrogen atom or second EWG attached to the reaction centre. More sterically hindered systems, in general, give lower yields and require extended reaction times. Of the hydrogen donors used, THF and 1,3-dioxolane performed best with lower yields being obtained for 2-propanol and cyclopentane. For the sterically hindered systems, 1 equivalent of benzophenone was necessary for the reactions, whereas less photomediator, typically 0.5 equivalents, was sufficient with systems which were less hindered or had two EWGs.

The need to remove benzophenone and/or benzopinacol by chromatography remains a major drawback in these reaction systems, and for this reason work has been carried out by us in relation to the synthesis of silica supported photomediators which can be separated from the reaction product by simple filtration and recycled. It has been shown that these supported photomediators work well for alkene and alkyne substrates. Some exploratory work has been carried out with the oxime ether (**80**) and three hydrogen donors, THF, 1,3-dioxolane and 2-propanol, with all reactions working well<sup>[81]</sup>. A logical extension of this work would be to develop supported photomediators for use with reactive oximes and oxime ethers. The use of such photomediators may also help to reduce the level of dimerisation of the photomediator, a process which removes it from the reaction cycle and which is much more rapid in reactions involving oximes than in those involving alkenes or acetylenes. Dimerization would be significantly more difficult for benzophenone related molecules which are surface bound, as long as the surface density is kept low. The relative success of the reaction carried out with the polyoxometalate, TBADT, also suggests that this photomediator may be worth consideration as a replacement for benzophenone.

*Chapter 3*  
*Experimental*

### ***3.0 Experimental***

#### ***3.1 General Experimental Section***

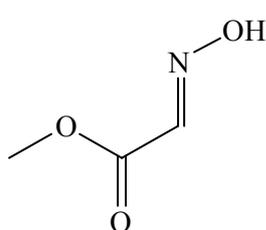
Photochemical reactions were carried out in cylindrical pyrex tubes using a Rayonet photochemical reactor, RPR-100, fitted with sixteen RPR-3500 Å lamps. Infra-red spectra (IR) were measured for neat samples with a Perkin Elmer Spectrum 100 FT-IR spectrometer. Mass spectrometry was carried out using a Waters LCT Premier XE spectrometer. <sup>1</sup>H-NMR and <sup>13</sup>C-NMR experiments were carried out using a JOEL GXFT 400 MHz instrument. All samples were run at probe temperatures using deuterated chloroform as solvent, and tetramethylsilane (TMS) as internal standard unless otherwise stated. Melting points were measured on a Stuart Scientific SMP 1 melting point apparatus. Flash column chromatography was carried out with Aldrich silica gel, pore size 60 Å 40-63 μm, with gradient elution using ether/pet. ether (40-60 °C) unless otherwise stated. Dry column vacuum chromatography was carried out with Merck silica gel, pore size 60 Å 15-40 μm, with gradient elution using ether/pet. ether (40-60 °C). TLC analysis was carried out on pre-coated silica gel plates (Merck silica gel 60 F<sub>254</sub>). Spots were visualized using 254 nm light. The solvents used were obtained from a Pure Solv MD-5 solvent purification system, or were distilled and dried according to literature procedures. Distillation of reaction products was carried out using a Büchi B-580 kugelrohr distillation unit. All boiling point ranges are glass oven temperatures. Gas chromatography analysis was carried out with a Varian 3900 chromatograph using a Restek RTx-5, crossbound 5% diphenyl/95% dimethyl polysiloxane (15 m × 0.25 mm × 0.25 μm) column. Unless otherwise stated the temperature profile was as follows: 60 °C for 1 min; 60 to 100 °C at 20 °C/min; 100 to 200 °C at 30 °C/min; 200 °C subsequently for 10 min.

### 3.3 Synthesis of oximes

#### 3.2.1 Synthesis of ethyl (2E)-(hydroxyimino)acetate<sup>[60]</sup> (72)

A mixture of hydroxylamine hydrochloride (6.80 g, 97.9 mmol) and Na<sub>2</sub>CO<sub>3</sub> (10.40 g, 97.9 mmol) in water (30 ml) was stirred and heated gently until the salts completely dissolved. A solution of ethyl glyoxylate in toluene 50% w/w (10.00 g, 48.9 mmol) was then added to the reaction mixture in one portion. The mixture began to reflux vigorously. When boiling subsided, toluene (25 ml) was added and the solution was stirred overnight. The toluene layer was separated, dried with MgSO<sub>4</sub> and removed under reduced pressure. Flash column chromatography (pet. ether/ether, 50/50) gave ethyl (2E)-(hydroxyimino)acetate as a clear oil in 50% yield (2.92 g). Spectroscopic data were consistent with those in the literature<sup>[60]</sup>.

#### Ethyl (2E)-(hydroxyimino)acetate (72)

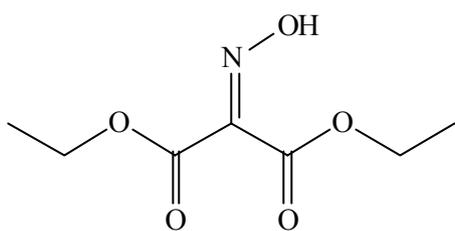


**IR**  $\nu_{\max}$  (cm<sup>-1</sup>): 3331 (OH), 1718 (C=O), 1623 (C=N), 1258, 1206 and 1027 (CO). **<sup>1</sup>H-NMR** ( $\delta$ ): 1.31 (t,  $J$  = 7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 4.30 (q,  $J$  = 7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 7.54 (s, 1H, CH), 9.64 (br s, 1H, OH). **<sup>13</sup>C-NMR** (ppm): 162.6 (C=O), 141.9 (C=N), 62.0 (OCH<sub>2</sub>CH<sub>3</sub>), 14.1 (OCH<sub>2</sub>CH<sub>3</sub>).

#### 3.2.2 Synthesis of diethyl (hydroxyimino)malonate (73)

A modified version of a published procedure<sup>[61]</sup> was used to synthesise diethyl (hydroxyimino)malonate. To a stirred solution of hydroxylamine hydrochloride (0.39 g, 6.8 mmol) in water (2 ml), diethyl ketomalonate (1.00 g, 6.8 mmol) and methanol (13 ml) was added. The reaction mixture was stirred in the dark for 19 h. The methanol was removed under reduced pressure, water (10 ml) was added and the pH was adjusted to 7. The solution was then saturated with NaCl and extracted with DCM (3 × 20 ml). The DCM washings were combined, dried with MgSO<sub>4</sub> and the solvent was removed under reduced pressure. Flash column chromatography (pet. ether/ether, 50/50) gave the product, diethyl (hydroxyimino)malonate (**73**), as a clear oil in 66% yield (0.85 g). Spectroscopic data were consistent with those in the literature<sup>[62]</sup>.

### Diethyl (hydroxyimino)malonate (73)

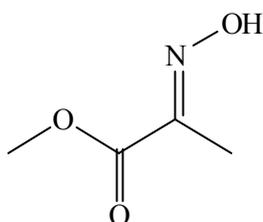


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3345 (OH), 1721 (C=O), 1632 (C=N), 1255, 1091 and 1012 (CO).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.28-1.38 (ms, 6H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 4.31-4.41 (ms, 4H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 10.37 (br s, 1H, OH).  **$^{13}\text{C-NMR}$**  (ppm): 160.6 and 160.1 ( $2 \times \text{C=O}$ ), 144.3 (C=N), 62.8 and 62.7 ( $2 \times \text{OCH}_2\text{CH}_3$ ), 14.1 and 14.0 ( $2 \times \text{OCH}_2\text{CH}_3$ ).

### 3.2.3 Synthesis of methyl (2E)-2-(hydroxyimino)propanoate (74)

A solution of hydroxylamine hydrochloride (7.00 g, 100.0 mmol) in water (10 ml), methyl pyruvate (10.50 g, 100.0 mmol) and methanol (65 ml) was prepared as before (**Section 3.2.2**). The reaction mixture was stirred in the dark for 20 h. The methanol was removed under reduced pressure, water (100 ml) was added and the pH was adjusted to 7. The solution was then saturated with NaCl and extracted with DCM until no further product was detected (TLC). The DCM washings were combined, dried with  $\text{MgSO}_4$  and the solvent was removed under reduced pressure. Column chromatography (pet. ether/ether, 50/50) gave the product, methyl (2E)-2-(hydroxyimino)propanoate (**74**), in a 76% yield (8.94 g) as white crystals (m.p. 72-73 °C; lit m.p. 72.0-72.8 °C<sup>[63]</sup>). Spectroscopic data and melting points were consistent with those in the literature<sup>[63]</sup>.

### Methyl (2E)-2-(hydroxyimino)propanoate (74)

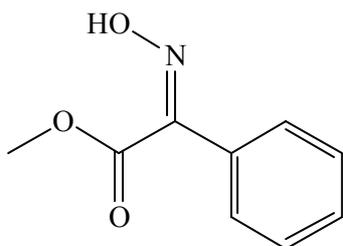


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3219 (OH), 1720 (C=O), 1638 (C=N), 1196, 1157 and 1024 (CO).  **$^1\text{H-NMR}$**  ( $\delta$ ): 2.10 (s, 3H,  $\text{CCH}_3$ ), 3.84 (s, 3H,  $\text{OCH}_3$ ), 9.95 (br s, 1H, OH).  **$^{13}\text{C-NMR}$**  (ppm): 164.2 (C=O), 149.5 (C=N), 52.9 ( $\text{OCH}_3$ ), 10.6 ( $\text{CCH}_3$ ).

### 3.2.4 Synthesis of (Z) and (E) methyl 2-(hydroxyimino)(phenyl)acetate, (75) and (76)

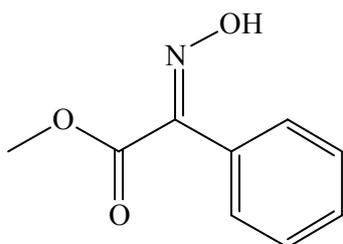
A solution of hydroxylamine hydrochloride (3.50 g, 50.0 mmol) in water (5 ml), methyl benzoylformate (8.20 g, 50.0 mmol) and methanol (33 ml) was prepared as before (Section 3.2.2). The reaction mixture was stirred in the dark for 20 h. The methanol was removed under reduced pressure, water (100 ml) was added and the pH was adjusted to 7. The solution was then saturated with NaCl and extracted with DCM until no further product was detected (TLC). The DCM washings were combined, dried with MgSO<sub>4</sub> and the solvent was removed under reduced pressure. Flash column chromatography (pet. ether/ether, 100/0 to 80/20) gave methyl (2Z)-(hydroxyimino)(phenyl)acetate (**75**) in a 40% yield (3.57 g) as white crystals (m.p. 82-83 °C; lit. m.p. 80.6-81.3 °C<sup>[65]</sup>) and methyl (2E)-(hydroxyimino)(phenyl)acetate (**76**) in a 50% yield (4.47 g.) as white needles (m.p. 151-153 °C; lit. m.p. 149-150 °C<sup>[64]</sup>). Spectroscopic data were consistent with those in the literature<sup>[64]</sup>.

#### Methyl (2Z)-(hydroxyimino)(phenyl)acetate (75)



**IR**  $\nu_{\max}$  (cm<sup>-1</sup>): 3401 (OH), 1730 (C=O), 1217, 1040 and 1023 (CO), 719 and 689 (monosubstituted Ar). **<sup>1</sup>H-NMR** ( $\delta$ ): 3.96 (s, 3H, OCH<sub>3</sub>), 7.36-7.45 (overlapping ms, 3H, Ar-H), 7.53-7.57 (overlapping ms, 2H, Ar-H), 9.10 (s, 1H, OH). **<sup>13</sup>C-NMR** (ppm): 164.2 (C=O), 151.8 (C=N), 130.7, 128.9 and 126.5 (Ar-C), 130.1 (Ar<sub>ipso</sub>), 52.7 (OCH<sub>3</sub>).

#### Methyl (2E)-(hydroxyimino)(phenyl)acetate (76)

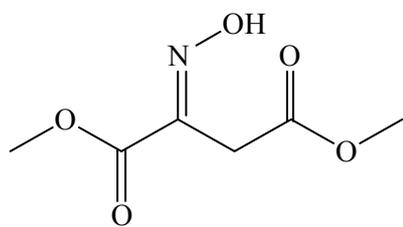


**IR**  $\nu_{\max}$  (cm<sup>-1</sup>): 3211 (OH), 1732 (C=O), 1195, 1052 and 1009 (CO), 716 and 691 (monosubstituted Ar). **<sup>1</sup>H-NMR** ( $\delta$ ): 3.87 (s, 3H, OCH<sub>3</sub>), 7.42-7.52 (overlapping ms, 5H, Ar-H), 9.54 (br s, 1H, OH). **<sup>13</sup>C-NMR** (ppm): 163.8 (C=O), 149.7 (C=N), 130.0, 129.3 and 128.2 (Ar-C), 128.5 (Ar<sub>ipso</sub>), 53.1 (OCH<sub>3</sub>).

### 3.2.5 Synthesis of 1,4-dimethyl (2E)-2-(hydroxyimino)butanedioate (77)

1,4-dimethyl (2E)-2-(hydroxyimino)butanedioate (**77**) was prepared according to the literature procedure<sup>[65]</sup>. Hydroxylamine hydrochloride (1.25 g, 18.0 mmol) in water (8 ml) was added to dimethyl acetylenedicarboxylate (2.13 g, 15.0 mmol) in methanol (30 ml). Sodium carbonate (0.95 g, 9.0 mmol) in water (10 ml) was then added at 0 °C and the solution was stirred for 2 h. The methanol was removed under reduced pressure and the residue was extracted with DCM (2 × 50 ml). The DCM washings were then combined, dried with MgSO<sub>4</sub> and the solvent was removed under reduced pressure. Flash column chromatography (pet. ether/ether, 50/50) gave the product, 1,4-dimethyl (2E)-2-(hydroxyimino)butanedioate (**77**), as a clear oil in 82% yield (2.15 g). Spectroscopic data were consistent with those in the literature<sup>[65]</sup>.

#### 1,4-Dimethyl (2E)-2-(hydroxyimino)butanedioate (77)



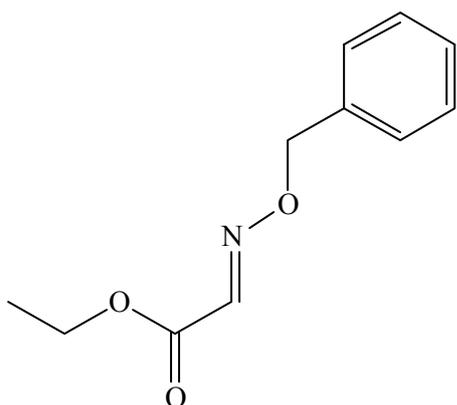
**IR**  $\nu_{\max}$  (cm<sup>-1</sup>): 3324 (OH), 1718 (C=O), 1638 (C=N), 1200, 1128 and 1003 (CO). **<sup>1</sup>H-NMR** ( $\delta$ ): 3.68 (s, 2H, CH<sub>2</sub>), 3.69 (s, 3H, CH<sub>2</sub>COOCH<sub>3</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 10.24 (s, 1H, OH). **<sup>13</sup>C-NMR** (ppm): 168.5 and 163.3 (2 × C=O), 145.7 (C=N), 53.0 and 52.4 (2 × OCH<sub>3</sub>), 30.2 (CH<sub>2</sub>).

### 3.3 Benzylation of oximes

#### 3.3.1 Benzylation of ethyl (2E)-2-(hydroxyimino)acetate (72)

Ethyl (2E)-[(benzyloxy)imino]acetate (**78**) was synthesized *via* a modified literature procedure<sup>[66]</sup>. Ethyl (2E)-2-(hydroxyimino)acetate (**72**) (1.17 g, 10.0 mmol) was dissolved in DMF (30 ml), NaH (0.48 g, 12.0 mmol) was added and the mixture was stirred at room temperature for 1 h. Benzylbromide (2.04 g, 12.0 mmol) was then added and the mixture was stirred overnight at 0 °C. Saturated brine solution (30 ml) was added and the products were extracted with DCM (4 × 50 ml). The combined organic layers were dried with MgSO<sub>4</sub> and removed under reduced pressure. Flash column chromatography (pet. ether/ether, 100/0 to 80/20) gave the product ethyl (2E)-[(benzyloxy)imino]acetate (**78**) as a yellow oil in 83% yield (1.73 g). Spectroscopic data were consistent with those in the literature<sup>[67]</sup>.

#### Ethyl (2E)-[(benzyloxy)imino]acetate (78)

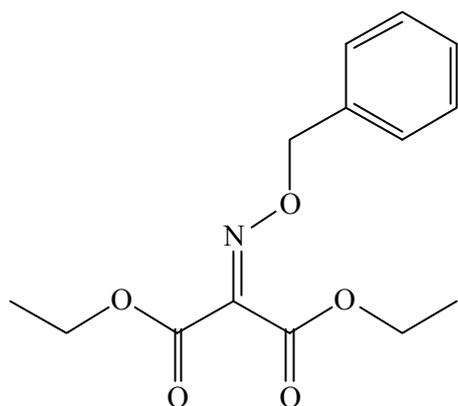


**IR**  $\nu_{\max}$  (cm<sup>-1</sup>): 1740 and 1717 (C=O), 1598 (C=N), 1264, 1194 and 1039 (CO), 730 and 696 (monosubstituted Ar). **<sup>1</sup>H-NMR** ( $\delta$ ): 1.33 (t,  $J$  = 7.1 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 4.32 (q,  $J$  = 7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.29 (s, 2H, OCH<sub>2</sub>Ph), 7.30-7.37 (ms, 5H, 5 × Ar-H), 7.54 (s, 1H, CH). **<sup>13</sup>C-NMR** (ppm): 162.1 (C=O), 141.3 (C=N), 136.0 (Ar<sub>ipso</sub>), 128.7, 128.65 and 128.6 (Ar-C), 78.1 (OCH<sub>2</sub>Ph), 61.8 (OCH<sub>2</sub>CH<sub>3</sub>), 14.2 (OCH<sub>2</sub>CH<sub>3</sub>).

#### 3.3.2 Benzylation of diethyl (hydroxyimino)malonate (73)

Diethyl [(benzyloxy)imino]malonate (**79**) was synthesized as described above (Section 3.3.1). Diethyl (hydroxyimino)malonate (**73**) (0.95 g, 5.0 mmol) was dissolved in DMF (30 ml), NaH (0.24 g, 6.0 mmol) was added and the reaction was stirred at room temperature for 1 h. Benzylbromide (1.02 g, 6.0 mmol) was then added and the reaction was stirred overnight at 0 °C. Saturated brine solution (30 ml) was added and the products were then extracted with DCM (4 × 50 ml). The DCM washings were combined, dried with MgSO<sub>4</sub> and the solvent was removed under reduced pressure. Flash column chromatography (pet. ether/ether, 100/0 to 80/20) gave the product, diethyl [(benzyloxy)imino]malonate (**79**), as a clear oil in 67% yield (0.93 g).

### Diethyl [(benzyloxy)imino]malonate (79)

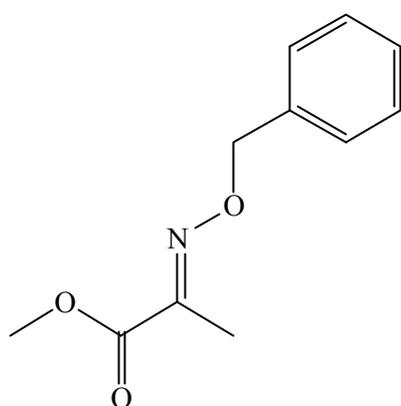


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 1743 and 1718 (C=O), 1605 (C=N), 1251, 1173 and 1099 (CO), 737 and 697 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.30 and 1.32 (overlapping ts,  $J = 7.1$  Hz, 6H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 4.34 and 4.33 (overlapping qs,  $J = 7.1$  Hz, 4H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 5.33 (s, 2H,  $\text{OCH}_2\text{Ph}$ ), 7.31-7.34 (ms, 5H,  $5 \times \text{Ar-H}$ ).  **$^{13}\text{C-NMR}$**  (ppm): 160.6 and 159.7 ( $2 \times \text{C=O}$ ), 144.3 (C=N), 135.9 ( $\text{Ar}_{\text{ipso}}$ ), 128.6, 128.5 and 128.1 (Ar-C), 78.8 ( $\text{OCH}_2\text{Ph}$ ), 62.6 and 62.3 ( $2 \times \text{OCH}_2\text{CH}_3$ ), 14.1 and 14.2 ( $2 \times \text{OCH}_2\text{CH}_3$ ). HRMS (ESI) calcd. for  $\text{C}_{14}\text{H}_{17}\text{NO}_5\text{Na}$  [ $\text{M}+\text{Na}$ ] $^+$ : 302.1004; found: 302.1011.

### 3.3.3 Benzylation of methyl (2E)-2-(hydroxyimino)propanoate (74)

Methyl (2E)-2-[(benzyloxy)imino]propanoate (**80**) was synthesized as described above (Section 3.3.1). Methyl (2E)-2-(hydroxyimino)propanoate (**74**) (1.17 g, 10.0 mmol) was dissolved in DMF (30 ml), NaH (0.48 g, 12.0 mmol) was added and the reaction was stirred at room temperature for 1 h. Benzylbromide (2.04 g, 12.0 mmol) was added and the reaction was stirred overnight at 0 °C. Saturated brine solution (30 ml) was added and the products were extracted with DCM ( $4 \times 50$  ml). The DCM washings were then combined, dried with  $\text{MgSO}_4$  and the solvent was removed under reduced pressure. Flash column chromatography (pet. ether/ether, 100/0 to 80/20) gave methyl (2E)-2-[(benzyloxy)imino]propanoate (**80**) as a clear oil in 80% yield (1.66 g). Spectroscopic data were consistent with those in the literature<sup>[65]</sup>.

### Methyl (2E)-2-[(benzyloxy)imino]propanoate (80)

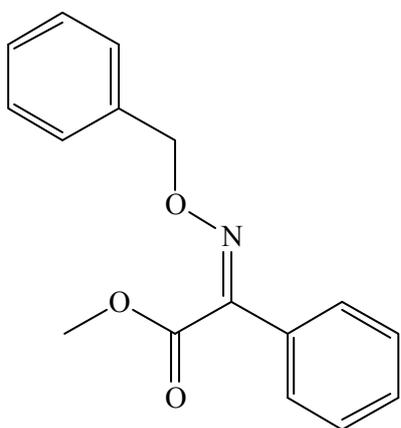


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 1722 (C=O), 1613 (C=N), 1196, 1151 and 1081 (CO), 718 and 698 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 2.09 (s, 3H,  $\text{CH}_3$ ), 3.85 (s, 3H,  $\text{OCH}_3$ ), 5.30 (s, 2H,  $\text{OCH}_2\text{Ph}$ ), 7.30-7.37 (ms, 5H,  $5 \times \text{Ar-H}$ ).  **$^{13}\text{C-NMR}$**  (ppm): 164.4 (C=O), 149.4 (C=N), 136.7 ( $\text{Ar}_{\text{ipso}}$ ), 128.6, 128.4 and 128.3 (Ar-C), 77.7 ( $\text{OCH}_2\text{Ph}$ ), 52.8 ( $\text{OCH}_3$ ), 11.7 ( $\text{CH}_3$ ).

### 3.3.5 Benzylolation of methyl (2Z)-2-(hydroxyimino)(phenyl)acetate (75)

Methyl (2Z)-[(benzyloxy)imino](phenyl)acetate (**81**) was synthesized as described above (Section 3.3.1). Methyl (2Z)-2-(hydroxyimino)(phenyl)acetate (**75**) (0.18 g, 1.0 mmol) was dissolved in DMF (30 ml), NaH (0.05 g, 1.2 mmol) was added and the reaction was stirred at room temperature for 1 h. Benzylbromide (0.20 g, 1.2 mmol) was then added and the reaction was stirred overnight at 0 °C. Most of the solvent was removed under reduced pressure, water (10 ml) was added and the product was extracted with DCM (2 × 30 ml). The DCM washings were then combined, dried with MgSO<sub>4</sub> and the solvent was removed under reduced pressure. Flash column chromatography (pet. ether/ether, 100/0 to 80/20) gave methyl (2Z)-[(benzyloxy)imino](phenyl)acetate (**81**) as a clear oil in 33% yield (0.09 g).

#### Methyl (2Z)-[(benzyloxy)imino](phenyl)acetate (**81**)

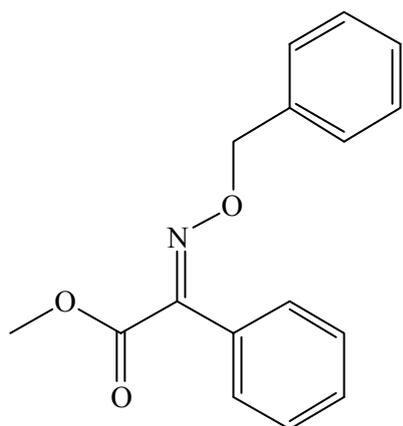


**IR**  $\nu_{\max}$  (cm<sup>-1</sup>): 1738 (C=O), 1605 (C=N), 1220, 1182 and 1006 (CO), 734 and 689 (monosubstituted Ar). **<sup>1</sup>H-NMR** ( $\delta$ ): 3.95 (s, 3H, CH<sub>3</sub>), 5.30 (s, 2H, OCH<sub>2</sub>Ph), 7.30-7.42 and 7.57-7.59 (overlapping ms, 10H, 10 × Ar-H). **<sup>13</sup>C-NMR** (ppm): 164.3 (C=O), 151.2 (C=N), 137.4 (CH<sub>2</sub>Ar<sub>ipso</sub>), 130.2 (Ar<sub>ipso</sub>), 130.6, 128.9, 128.5, 128.0 and 126.4 (Ar-C), 77.1 (OCH<sub>2</sub>Ph), 52.6 (OCH<sub>3</sub>). **HRMS (ESI)** calcd. for C<sub>16</sub>H<sub>16</sub>NO<sub>3</sub> [M+H]<sup>+</sup>: 270.1130; found: 270.1124.

### 3.3.4 Benzylolation of methyl (2E)-2-(hydroxyimino)(phenyl)acetate (76)

Methyl (2E)-[(benzyloxy)imino](phenyl)acetate (**82**) was synthesized as described above (Section 3.3.1). Methyl (2E)-2-(hydroxyimino)(phenyl)acetate (**76**) (1.79 g, 10.0 mmol) was dissolved in DMF (30 ml), NaH (0.48 g, 12.0 mmol) was added and the reaction was stirred at room temperature for 1 h. Benzylbromide (2.04 g, 12.0 mmol) was then added and the reaction was stirred overnight at 0 °C. Saturated brine solution (30 ml) was added and the products were then extracted with DCM (4 × 50 ml). The DCM washings were combined, dried with MgSO<sub>4</sub> and the solvent was removed under reduced pressure. Flash column chromatography (pet. ether/ether, 100/0 to 80/20) gave the product, methyl (2E)-[(benzyloxy)imino](phenyl)acetate (**82**), as a clear oil in 75% yield (2.03 g). Spectroscopic data were consistent with those in the literature<sup>[68]</sup>.

### Methyl (2E)-[(benzyloxy)imino](phenyl)acetate (**82**)

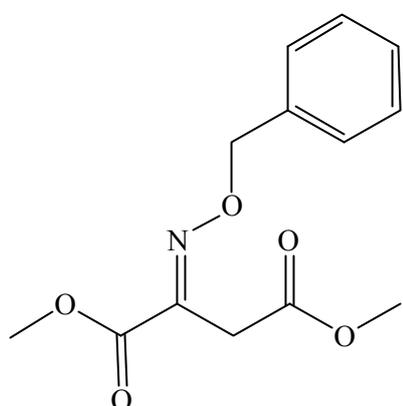


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 1726 (C=O), 1587 (C=N), 1209, 1087 and 1064 (CO), 723 and 690 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 3.88 (s, 3H, CH<sub>3</sub>), 5.37 (s, 2H, OCH<sub>2</sub>Ph), 7.31-7.50 (overlapping ms, 10H, 10  $\times$  Ar-H).  **$^{13}\text{C-NMR}$**  (ppm): 164.1 (C=O), 149.6 (C=N), 136.7 (CH<sub>2</sub>Ar<sub>ipso</sub>), 129.5 (Ar<sub>ipso</sub>), 129.8, 129.3, 128.6, 128.3, 128.2 and 128.1 (Ar-C), 78.2 (OCH<sub>2</sub>Ph), 53.1 (OCH<sub>3</sub>).

### 3.3.6 Benzylation of 1,4-dimethyl (2E)-2-(hydroxyimino)butanedioate (**77**)

1,4-Dimethyl (2E)-2-[(benzyloxy)imino]butanedioate (**83**) was prepared according to a literature procedure<sup>[65]</sup>. To a DMF (20 ml) suspension of NaH (0.12 g, 5.0 mmol), a DMF (4 ml) solution of benzylbromide (0.85 g, 5.0 mmol) was added, and was immediately followed by a DMF (6 ml) solution of 1,4-dimethyl (2E)-2-(hydroxyimino)butanedioate (**77**) (0.87 g, 5.0 mmol) at 0 °C under a nitrogen atmosphere. The reaction was stirred for 8 h at 0 °C. Most of the solvent was removed under reduced pressure. Water (10 ml) was then added and the product was extracted with DCM (4  $\times$  30 ml). The DCM washings were combined, dried with MgSO<sub>4</sub> and the solvent was removed under reduced pressure. Flash column chromatography (pet. ether/ether, 100/0 to 80/20) gave 1,4-dimethyl (2E)-2-[(benzyloxy)imino]butanedioate (**83**) as a clear oil in 50% yield (0.67 g). Spectroscopic data were consistent with those in the literature<sup>[65]</sup>.

### 1,4-Dimethyl (2E)-2-[(benzyloxy)imino]butanedioate (**83**)

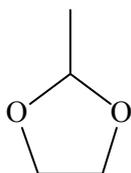


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 1739 and 1720 (C=O), 1604 (C=N), 1200, 1172 and 1126 (CO), 727 and 697 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 3.61 (s, 3H, OCH<sub>3</sub>), 3.65 (s, 2H, CH<sub>2</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 5.32 (s, 2H, OCH<sub>2</sub>Ph), 7.31-7.36 (ms, 5H, 5  $\times$  Ar-H).  **$^{13}\text{C-NMR}$**  (ppm): 168.4 and 163.5 (2  $\times$  C=O), 145.7 (C=N), 136.1 (Ar<sub>ipso</sub>), 128.6, 128.5 and 128.3 (Ar-C), 78.3 (OCH<sub>2</sub>Ph), 53.2 and 52.3 (2  $\times$  OCH<sub>3</sub>), 31.3 (CH<sub>2</sub>).

### 3.4 Synthesis of 2-methyl-1,3-dioxolane

2-Methyl-1,3-dioxolane was synthesized using a modified literature procedure<sup>[69]</sup>. Concentrated HCl (1 ml) was added to a stirred, cooled solution of ethylene glycol (55.70 g, 0.9 mol) and acetaldehyde (19.60 g, 450.0 mmol). Anhydrous CaCl<sub>2</sub> (110.00 g) was then added until one liquid layer remained. This was then decanted from the remaining solid and dried over K<sub>2</sub>CO<sub>3</sub>. The liquid was filtered and distilled yielding 2-methyl-1,3-dioxolane as a clear colourless liquid in 43% yield (17.21 g) b.p. 82-84 °C. Spectroscopic data were consistent with those in the literature<sup>[70]</sup>.

#### 2-Methyl-1,3-dioxolane

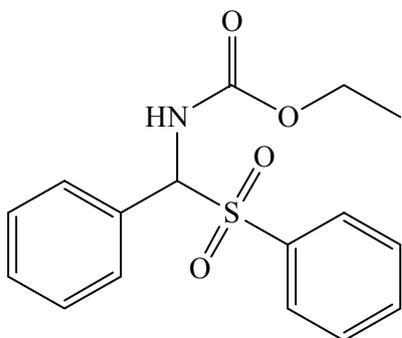


**IR**  $\nu_{\max}$  (cm<sup>-1</sup>): 1146, 1117, 1084 and 1021 (CO). **<sup>1</sup>H-NMR** ( $\delta$ ): 1.37 (d,  $J$  = 4.8 Hz, 3H, CH<sub>3</sub>), 3.83-3.86 (ms, 2H, CH<sub>2</sub>), 3.87-4.00 (ms, 2H, CH<sub>2</sub>), 4.97 (q,  $J$  = 4.8 Hz, 1H, CH). **<sup>13</sup>C-NMR** (ppm): 101.6 (CH), 64.9 (CH<sub>2</sub>), 19.7 (CH<sub>3</sub>).

### 3.5 Synthesis of *N*-(ethoxycarbonyl)benzaldimine (84)

*N*-(Ethoxycarbonyl)benzaldimine (**84**) was prepared according to a literature procedure<sup>[73]</sup>. Benzaldehyde (6 ml, 29.0 mmol) in methanol (20 ml) and 88% formic acid (10 ml) were added to a solution of urethane (4.46 g, 50.0 mmol) and sodium benzenesulfinate dihydrate (10.02 g, 50.0 mmol) in water (50 ml). The mixture was heated at 65-75 °C for 2 h and then allowed to stir overnight at room temperature. The resulting white precipitate was filtered, washed with water (30 ml), pet. ether (30 ml) and diisopropyl ether (30 ml), and then dried in vacuo to give an 82% yield (7.64 g) of *N*-(ethoxycarbonyl)(phenylsulfonyl)benzylamine (**85**).

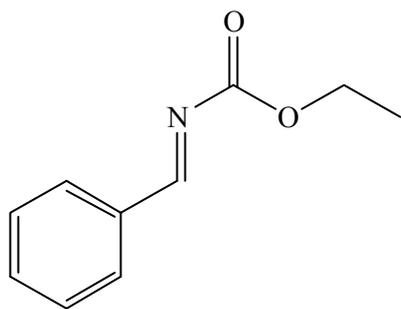
#### *N*-(Ethoxycarbonyl)(phenylsulfonyl)benzylamine (85)



**IR**  $\nu_{\max}$  (cm<sup>-1</sup>): 3349 (NH), 1726 (C=O), 1302 and 1140 (O=S=O), 1232, 1170 and 1082 (CO), 719 and 690 (monosubstituted Ar). **<sup>1</sup>H-NMR** ( $\delta$ ): 1.12 (t,  $J$  = 7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 3.94 (q,  $J$  = 7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.85-5.95 (ms, 2H, CHNH), 7.39 (m, 5H, Ar-H), 7.50-7.87 (ms, 5H, Ar-H). **<sup>13</sup>C-NMR** (ppm): 154.8 (C=O), 136.9, 134.2, 130.0, 129.6, 129.1, 128.9 and 128.8 (Ar-C), 74.4 (CH), 62.1 (OCH<sub>2</sub>CH<sub>3</sub>), 14.5 (OCH<sub>2</sub>CH<sub>3</sub>).

A solution of sulfone (**85**) (1.16 g, 3.6 mmol) in THF (40 ml) containing anhydrous  $K_2CO_3$  (3.00 g, 21.6 mmol), was then refluxed for 15 h under a nitrogen atmosphere. The mixture was then allowed to cool to room temperature and vacuum filtered. The solvent was removed under reduced pressure to yield *N*-(ethoxycarbonyl)benzaldimine (**84**) as a clear oil in 69% yield (0.44 g). Spectroscopic data were consistent with those in the literature<sup>[73]</sup>.

#### *N*-(Ethoxycarbonyl)benzaldimine (**84**)

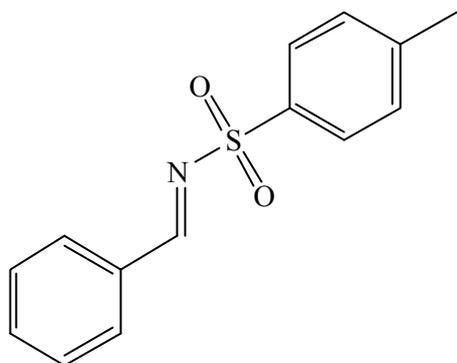


**IR**  $\nu_{\max}$  ( $cm^{-1}$ ): 1711 (C=O), 1627 (C=N), 1244, 1199 and 1039 (CO), 754 and 688 (monosubstituted Ar).  **$^1H$ -NMR** ( $\delta$ ): 1.37 (t,  $J = 7.1$  Hz, 3H,  $OCH_2CH_3$ ), 4.31 (q,  $J = 7.1$  Hz, 2H,  $OCH_2CH_3$ ), 7.43-7.55 (ms, 3H,  $3 \times Ar-H$ ), 7.91 (ms, 2H,  $2 \times Ar-H$ ), 8.96 (s, 1H, CH).  **$^{13}C$ -NMR** (ppm): 171.3 (C=N), 163.9 (C=O), 134.0, 133.9, 130.5 and 129.0 (Ar-C), 63.3 ( $OCH_2CH_3$ ), 14.4 ( $OCH_2CH_3$ ).

#### 3.6 Synthesis of 4-methyl-*N*-[(*E*)-phenylmethylidene]benzene-1-sulfonamide (**45**)

4-Methyl-*N*-[(*E*)-phenylmethylidene]benzene-1-sulfonamide (**45**) was prepared using a similar method to that described previously<sup>[71]</sup>. A mixture of benzaldehyde (0.62 g, 6.0 mmol) and *p*-toluenesulfonamide (1.00 g, 6.0 mmol) was dissolved in toluene (45 ml), Amberlist (0.30 g) and 4 Å molecular sieves (0.30 g) were added and the reaction was refluxed for 56 h with a Dean-Stark apparatus attached. The reaction was cooled, filtered and the toluene was removed under reduced pressure. Unreacted benzaldehyde was removed *via* kugelrohr distillation and the product was recrystallized in diethyl ether to give 4-methyl-*N*-[(*E*)-phenylmethylidene]benzene-1-sulfonamide (**45**) in 72% yield (1.09 g) as clear crystals (m.p. 116-118 °C; lit. m.p. 109-110 °C<sup>[72]</sup>). Spectroscopic data were consistent with those in the literature<sup>[72]</sup>.

#### 4-Methyl-*N*-[(*E*)-phenylmethylidene]benzene-1-sulfonamide (**45**)



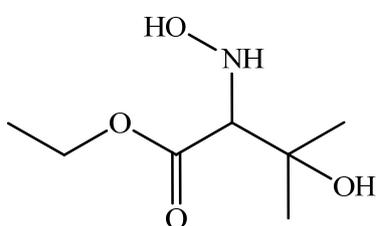
**IR**  $\nu_{\max}$  ( $cm^{-1}$ ): 1650 (C=N), 1315 and 1154 (O=S=O), 754 and 668 (monosubstituted Ar).  **$^1H$ -NMR** ( $\delta$ ): 2.43 (s, 3H,  $CH_3$ ), 7.33 (d,  $J = 8.2$  Hz, 2H,  $2 \times Ar-H$ ), 7.48 (t,  $J = 7.6$  Hz, 2H,  $2 \times Ar-H$ ), 7.60 (t,  $J = 7.6$  Hz, 1H,  $2 \times Ar-H$ ), 7.88 (d,  $J = 8.7$  Hz, 2H,  $2 \times Ar-H$ ), 7.91 (d,  $J = 7.6$  Hz, 2H,  $2 \times Ar-H$ ), 9.02 (s, 1H, CH).  **$^{13}C$ -NMR** (ppm): 170.2 (C=N), 144.7, 135.0, 132.5, 131.4, 129.9, 128.3 and 128.2 (Ar-C), 21.8 ( $CH_3$ ).

### 3.7 Photochemical reactions of ethyl (2E)-(hydroxyimino)acetate (72)

#### 3.7.1 Photochemical reaction of ethyl (2E)-(hydroxyimino)acetate (72) with 2-propanol

Ethyl (2E)-2-(hydroxyimino)acetate (**72**) (0.20 g, 1.7 mmol), benzophenone (0.15 g, 0.85 mmol), 2-propanol (10.20 g, 170.0 mmol) and MeCN (40 ml) were added to a cylindrical pyrex tube and the solution was degassed with N<sub>2</sub> gas for 20 min. The solution was then irradiated for 1 h at which time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.45 g) was adsorbed onto silica (30 g). Flash chromatography (pet. ether/ether, 100/0 to 40/60) gave ethyl 3-hydroxy-2-(hydroxyamino)-3-methylbutanoate (**86**) as a clear oil in 80% yield (0.24 g).

#### Ethyl 3-hydroxy-2-(hydroxyamino)-3-methylbutanoate (86)

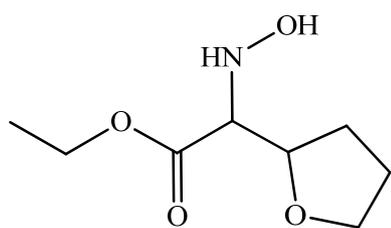


**IR**  $\nu_{\max}$  (cm<sup>-1</sup>): 3398 (OH), 3282 (NH), 1725 (C=O), 1207, 1151 and 1036 (CO). **<sup>1</sup>H-NMR** ( $\delta$ ): 1.17 (s, 3H, CCH<sub>3</sub>), 1.26 (s, 3H, CCH<sub>3</sub>), 1.28 (t,  $J = 7.2$  Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 3.59 (s, 1H, CH), 4.19-4.28 (ms, 2H, OCH<sub>2</sub>CH<sub>3</sub>). **<sup>13</sup>C-NMR** (ppm): 172.9 (C=O), 73.7 (CH), 70.9 (C), 61.4 (OCH<sub>2</sub>CH<sub>3</sub>), 27.3 and 26.5 (2  $\times$  CCH<sub>3</sub>), 14.3 (OCH<sub>2</sub>CH<sub>3</sub>). **HRMS (ESI)** calcd. for C<sub>9</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>Na [M+MeCN+Na]<sup>+</sup>: 241.1164; found: 241.1152.

#### 3.7.2 Photochemical reaction of ethyl (2E)-(hydroxyimino)acetate (72) with THF

A solution of ethyl (2E)-(hydroxyimino)acetate (**72**) (0.20 g, 1.7 mmol), benzophenone (0.15 g, 0.85 mmol) and THF (12.25 g, 170.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). The solution was then irradiated for 1 h at which time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.52 g) was adsorbed onto silica (30 g). Flash chromatography (pet. ether/ether, 100/0 to 40/60) gave ethyl tetrahydrofuran-2-yl(hydroxylamino)acetate (**87**) as a clear oil in 83% yield (0.27 g), and as a mixture of diastereomers (1:1.09, GC).

### Ethyl tetrahydrofuran-2-yl(hydroxylamino)acetate (**87**)

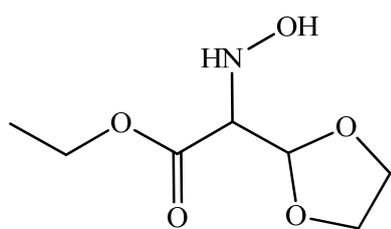


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3417 (OH), 3271 (NH), 1731 (C=O), 1195, 1064 and 1027 (CO).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.24 (t,  $J = 7.1$  Hz, 6H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 1.75-1.93 (overlapping ms, 8H,  $2 \times \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 3.57 and 3.75 (ds,  $J = 6.7$  Hz, 2H,  $2 \times \text{CHN}$ ), 3.62-3.82 (overlapping ms, 4H,  $2 \times \text{OCH}_2\text{CH}_2$ ), 4.00 (overlapping ms, 2H,  $2 \times \text{OCH}$ ), 4.20 (q,  $J = 7.1$  Hz, 4H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 5.78 (br s, 2H,  $2 \times \text{NH}$ ), 6.89 (br s, 2H,  $2 \times \text{OH}$ ).  **$^{13}\text{C-NMR}$**  (ppm): 171.7 and 171.6 ( $2 \times \text{C=O}$ ), 77.1 and 76.8 ( $2 \times \text{OCH}$ ), 69.2 and 68.6 ( $2 \times \text{NCH}$ ), 68.7 and 68.6 ( $2 \times \text{OCH}_2\text{CH}_2$ ), 61.3 and 61.2 ( $2 \times \text{OCH}_2\text{CH}_3$ ), 28.8 and 28.2 ( $2 \times \text{CHCH}_2\text{CH}_2$ ), 25.8 and 25.6 ( $2 \times \text{CH}_2\text{CH}_2\text{CH}_2$ ), 14.3 ( $2 \times \text{OCH}_2\text{CH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}_4\text{Na}$   $[\text{M}+\text{MeCN}+\text{Na}]^+$ : 253.1164; found: 253.1159.

#### 3.7.3 Photochemical reaction of ethyl (2E)-(hydroxyimino)acetate (**72**) with 1,3-dioxolane

A solution of ethyl (2E)-(hydroxyimino)acetate (**72**) (0.20 g, 1.7 mmol), benzophenone (0.15 g, 0.85 mmol) and 1,3-dioxolane (12.58 g, 170 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). The solution was then irradiated for 1 h at which time all the starting material had reacted. The solvent was removed under reduced pressure and the remaining mixture (0.55 g) was adsorbed onto silica (30 g). Flash column chromatography (pet. ether/ether, 100/0 to 40/60) gave the product, ethyl 1,3-dioxolan-2-yl(hydroxyamino)acetate (**88**), as a yellow oil in 62% yield (0.20 g).

### Ethyl 1,3-dioxolan-2-yl(hydroxyamino)acetate (**88**)

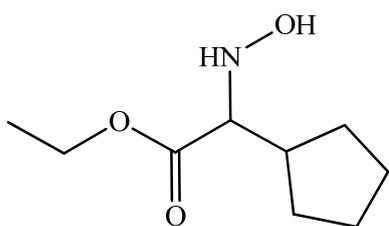


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3444 (OH), 3274 (NH), 1735 (C=O), 1196, 1145 and 1027 (CO).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.30 (t,  $J = 7.2$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 3.82-4.01 (ms, 5H,  $\text{OCH}_2\text{CH}_2\text{O}$  and  $\text{CHNH}$ ), 4.26 (q,  $J = 7.2$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ), 5.18 (d,  $J = 3.7$  Hz, 1H,  $\text{OCHO}$ ).  **$^{13}\text{C-NMR}$**  (ppm): 169.8 (C=O), 101.6 (OCHO), 67.8 (CHNH), 65.6 and 65.5 ( $\text{OCH}_2\text{CH}_2\text{O}$ ), 61.7 ( $\text{OCH}_2\text{CH}_3$ ), 14.3 ( $\text{OCH}_2\text{CH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_9\text{H}_{16}\text{N}_2\text{O}_5\text{Na}$   $[\text{M}+\text{MeCN}+\text{Na}]^+$ : 255.0957; found: 255.0950.

#### 3.7.4 Photochemical reaction of ethyl (2E)-(hydroxyimino)acetate (**72**) with cyclopentane

A solution of ethyl (2E)-(hydroxyimino)acetate (**72**) (0.20 g, 1.7 mmol), benzophenone (0.15 g, 0.85 mmol) and cyclopentane (11.92 g, 170.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). The solution was then irradiated for 2 h at which time all the starting material had reacted. The solvent was removed under reduced pressure and the remaining mixture (0.48 g) was adsorbed onto silica (30 g). Flash column chromatography (pet. ether/ether, 100/0 to 40/60) gave ethyl cyclopentyl(hydroxyamino)acetate (**89**) as a yellow oil in 57% yield (0.18 g).

### Ethyl cyclopentyl(hydroxyamino)acetate (**89**)



**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3433 (OH), 3273 (NH), 1732 (C=O), 1183, 1159 and 1030 (CO).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.25 (t,  $J = 7.1$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.30-1.80 (overlapping ms, 8H, cyclopentyl  $\text{CH}_2$ ), 1.85 (m, 1H,  $\text{CHCHNH}$ ), 3.43 (d,  $J = 8.9$  Hz, 1H,  $\text{NHCH}$ ), 4.17-4.26 (m, 2H,  $\text{OCH}_2\text{CH}_3$ ), 5.56 (br s, 1H,  $\text{NH}$ ), 7.05 (br s, 1H,  $\text{OH}$ ).  **$^{13}\text{C-NMR}$**  (ppm): 174.0 (C=O), 70.4 (CHNH), 61.0 ( $\text{OCH}_2\text{CH}_3$ ), 40.0 (CHCHNH), 30.2 and 29.4 (both  $\text{CHCH}_2\text{CH}_2$ ), 25.1 and 24.9 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ), 14.4 ( $\text{OCH}_2\text{CH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_9\text{H}_{18}\text{NO}_3$   $[\text{M}+\text{H}]^+$ : 188.1287; found: 188.1293.

### 3.8 Photochemical reactions of diethyl (hydroxyimino)malonate (**73**)

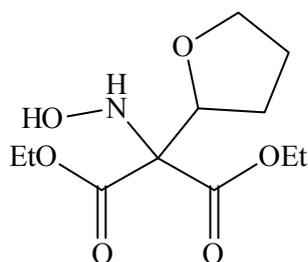
#### 3.8.1 Photochemical reaction of diethyl (hydroxyimino)malonate (**73**) with 2-propanol

A solution of diethyl (hydroxyimino)malonate (**73**) (0.20 g, 1.0 mmol), benzophenone (0.10 g, 0.5 mmol) and 2-propanol (6.30 g, 105.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). It was then irradiated for 1 h at which time all starting material had reacted (GC). Analysis of the  $^1\text{H-NMR}$  spectrum of the crude product indicated a complex mixture of products. The mixture (0.29 g) was adsorbed onto silica (30 g) but attempts to isolate any identifiable products *via* flash chromatography failed.

#### 3.8.2 Photochemical reaction of diethyl (hydroxyimino)malonate (**73**) with THF

A solution of diethyl (hydroxyimino)malonate (**73**) (0.20 g, 1.0 mmol), benzophenone (0.10 g, 0.5 mmol) and THF (7.57 g, 105.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). It was then irradiated for 1 h at which time all starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.46 g) was adsorbed onto silica (30 g). The product, diethyl (hydroxyamino)(tetrahydrofuran-2-yl)malonate (**91**), was isolated by flash column chromatography (pet. ether/ether, 100/0 to 30/70) as a clear oil in 87% yield (0.24 g).

### Diethyl (hydroxyamino)(tetrahydrofuran-2-yl)malonate (**91**)

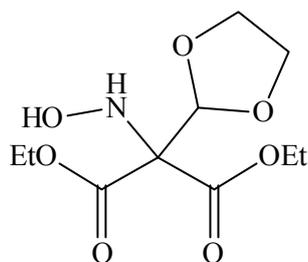


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3452 (OH), 3283 (NH), 1730 (C=O), 1257, 1051 and 1025 (CO).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.21 and 1.22 (overlapping ts,  $J = 7.1$  Hz, 6H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 1.77-1.84 (ms, 2H,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 2.01-2.12 (ms, 2H,  $\text{CHCH}_2\text{CH}_2$ ), 3.68-3.80 (ms, 2H,  $\text{OCH}_2\text{CH}_2$ ), 4.18 and 4.20 (overlapping qs,  $J = 7.1$  Hz, 4H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 4.45 (t,  $J_{\text{cis}} = J_{\text{trans}} = 7.6$  Hz, 1H, CH), 6.02 (broad s, 2H, NHOH).  **$^{13}\text{C-NMR}$**  (ppm): 168.2 and 167.2 ( $2 \times \text{C=O}$ ), 78.9 (CH), 75.9 (C), 69.2 ( $\text{OCH}_2\text{CH}_2$ ), 62.0 and 61.9 ( $2 \times \text{OCH}_2\text{CH}_3$ ), 27.5 ( $\text{CHCH}_2\text{CH}_2$ ), 25.9 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 14.0 ( $2 \times \text{OCH}_2\text{CH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_{13}\text{H}_{22}\text{N}_2\text{O}_6\text{Na}$  [ $\text{M}+\text{MeCN}+\text{Na}$ ] $^+$ : 325.1376; found: 325.1385.

### 3.8.3 Photochemical reaction of diethyl (hydroxyimino)malonate (**73**) with 1,3-dioxolane

A solution of diethyl (hydroxyimino)malonate (**73**) (0.20 g, 1.0 mmol), benzophenone (0.10 g, 0.5 mmol) and 1,3-dioxolane (7.80 g, 105.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). It was then irradiated for 1 h at which time all starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.45 g) was adsorbed onto silica (30 g). Flash column chromatography (pet. ether/ether, 100/0 to 50/50) gave the product, diethyl 1,3-dioxolan-2-yl(hydroxyamino)malonate (**92**), as a clear oil in 65% yield (0.18 g).

### Diethyl 1,3-dioxolan-2-yl(hydroxyamino)malonate (**92**)

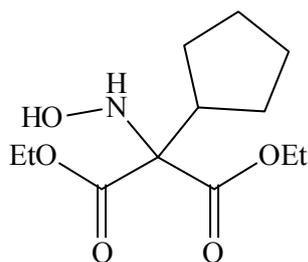


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3477 (OH), 3294 (NH), 1734 (C=O), 1228, 1095 and 1017 (CO).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.26 (t,  $J = 7.1$  Hz, 6H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 3.89-3.96 and 4.03-4.09 ( $2 \times$  ms, 4H,  $\text{OCH}_2\text{CH}_2\text{O}$ ), 4.26 (q,  $J = 7.1$  Hz, 4H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 5.59 (s, 1H CH).  **$^{13}\text{C-NMR}$**  (ppm): 166.2 (C=O), 103.2 (CH), 75.8 (C), 66.0 ( $\text{OCH}_2\text{CH}_2\text{O}$ ), 62.3 ( $\text{OCH}_2\text{CH}_3$ ), 14.1 ( $\text{OCH}_2\text{CH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_7\text{Na}$  [ $\text{M}+\text{MeCN}+\text{Na}$ ] $^+$ : 327.1168; found: 327.1175.

### 3.8.4 Photochemical reaction of diethyl (hydroxyimino)malonate (**93**) with cyclopentane

A solution of diethyl (hydroxyimino)malonate (**73**) (0.20 g, 1.0 mmol), benzophenone (0.19 g, 1.0 mmol) and cyclopentane (7.57 g, 105.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). It was then irradiated for 4 h at which time no further reaction was observed (GC). The solvent was removed under reduced pressure and the remaining mixture (0.52 g) was adsorbed onto silica (30 g). The product diethyl cyclopentyl(hydroxyamino)malonate (**93**) was isolated by flash column chromatography (pet. ether/ether, 100/0 to 30/70) as a clear oil in 19% yield (0.05 g).

### Diethyl cyclopentyl(hydroxyamino)malonate (**93**)



**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3456 (OH), 3294 (NH), 1731 (C=O), 1231, 1095 and 1019 (CO).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.28 (t,  $J = 7.1$  Hz, 6H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 1.45-1.62 and 1.72-1.81 ( $2 \times$  ms, 8H, cyclopentyl  $\text{CH}_2$ ), 2.43 (m, 1H, CH), 4.25 (q,  $J = 7.1$  Hz, 4H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 5.63 (broad s, 2H, NHOH).  **$^{13}\text{C-NMR}$**  (ppm): 169.6 (C=O), 76.5 (C), 61.8 ( $\text{OCH}_2\text{CH}_3$ ), 43.0 (CH), 27.8 ( $\text{CHCH}_2\text{CH}_2$ ), 25.6 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ), 14.1 ( $\text{OCH}_2\text{CH}_3$ ). **HRMS (ESI)**

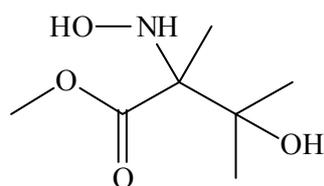
calcd. for  $\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}_5\text{Na}$  [ $\text{M}+\text{MeCN}+\text{Na}$ ] $^+$ : 323.1583; found: 323.1589.

### 3.9 Photochemical reactions of methyl (*E*)-2-(hydroxyimino)propanoate (**74**)

#### 3.9.1 Photochemical reaction of methyl (*E*)-2-(hydroxyimino)propanoate with 2-propanol

A solution of methyl (*E*)-2-(hydroxyimino)propanoate (**74**) (0.26 g, 2.0 mmol), benzophenone (0.36 g, 2.0 mmol) and 2-propanol (1.44 g, 20.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). The solution was then irradiated for 3 h at which time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.67 g) was adsorbed onto silica (20 g). Dry column vacuum chromatography (pet. ether/ether, 100/0 to 60/40) gave methyl 3-hydroxy-2-(hydroxyamino)-2,3-dimethylbutanoate (**94**) as a clear oil in 33% yield (0.16 g).

#### Methyl 3-hydroxy-2-(hydroxyamino)-2,3-dimethylbutanoate (**94**)



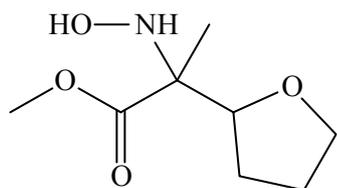
**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3425 (OH), 3291 (NH), 1720 (C=O), 1146, 1108 and 1024 (CO).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.13 (s, 3H,  $\text{CCH}_3$ ), 1.14 (s, 3H,  $\text{NHCCH}_3$ ), 1.33 (s, 3H,  $\text{CCH}_3$ ), 3.71 (s, 3H,  $\text{OCH}_3$ ).  **$^{13}\text{C-NMR}$**  (ppm): 175.6 (C=O), 73.9 (COH), 72.0 (C), 52.4 ( $\text{OCH}_3$ ), 26.5 and 24.4 ( $2 \times \text{CCH}_3$ ), 16.4

( $\text{CCH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_9\text{H}_{18}\text{N}_2\text{O}_4\text{Na}$  [ $\text{M}+\text{MeCN}+\text{Na}$ ] $^+$ : 241.1164; found: 241.1152.

#### 3.9.2 Photochemical reaction of methyl (*E*)-2-(hydroxyimino)propanoate (**74**) with THF

Methyl (*E*)-2-(hydroxyimino)propanoate (**74**) (0.30 g, 2.5 mmol) and benzophenone (0.45 g, 2.5 mmol) were dissolved in THF (35 ml, 430.0 mmol) and the solution was degassed with  $\text{N}_2$  gas for 20 min. It was then irradiated for 3 h at which time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (1.25 g) was adsorbed onto silica (22 g). Dry column vacuum chromatography (pet. ether/ether, 100/0 to 60/40) gave the product, methyl 2-(*N*-hydroxyamino)-2-(tetrahydrofuran-2-yl)propanoate (**95**), in 60% yield (0.29 g) as a mixture of diastereomers (1:1.4, GC).

### Methyl 2-(*N*-hydroxyamino)-2-(tetrahydrofuran-2-yl)propanoate (**95**)

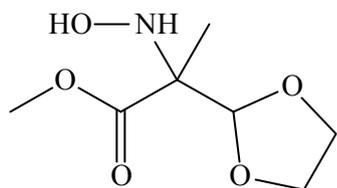


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3437 (OH), 3281 (NH), 1727 (C=O), 1256, 1133 and 1065 (CO).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.24 and 1.28 (2  $\times$  s, 6H, 2  $\times$  CCH<sub>3</sub>), 1.65-1.90 (overlapping ms, 8H, 2  $\times$  CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.55-3.76 (overlapping ms 4H, 2  $\times$  OCH<sub>2</sub>CH<sub>2</sub>), 3.66 and 3.67 (2  $\times$  s, 6H, 2  $\times$  OCH<sub>3</sub>), 3.84 and 4.00 (2  $\times$  t,  $J_{\text{cis}} = J_{\text{trans}} = 7.4$  Hz, 2H, 2  $\times$  CH).  **$^{13}\text{C-NMR}$**  (ppm): 174.6 and 173.6 (2  $\times$  C=O), 81.4 and 80.9 (2  $\times$  CH), 69.0 and 68.9 (2  $\times$  OCH<sub>2</sub>CH<sub>2</sub>), 68.4 and 68.39 (2  $\times$  C), 52.4 and 52.3 (2  $\times$  OCH<sub>3</sub>), 26.8, 26.5, 26.0 and 25.7 (2  $\times$  CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 16.9 and 15.9 (2  $\times$  CCH<sub>3</sub>). **HRMS (ESI)** calcd. for C<sub>10</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>Na [M+MeCN+Na]<sup>+</sup>: 253.1164; found: 253.1161.

#### 3.9.3 Photochemical reaction of methyl (*E*)-2-(hydroxyimino)propanoate (**74**) with 1,3-dioxolane

A solution of methyl (*E*)-2-(hydroxyimino) propanoate (**74**) (0.30 g, 2.5 mmol), benzophenone (0.45 g, 2.5 mmol) and 1,3-dioxolane (5.30 g, 71.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). It was then irradiated for 3 h at which time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (1.10 g) was adsorbed onto silica (20 g). Dry column vacuum chromatography (pet. ether/ether, 100/0 to 60/40) gave methyl 2-(1,3-dioxolan-2-yl)-2-(hydroxyamino)propanoate (**96**) as white crystals (m.p. 86-88 °C) in 76% yield (0.36 g).

### Methyl 2-(1,3-dioxolan-2-yl)-2-(hydroxyamino)propanoate (**96**)

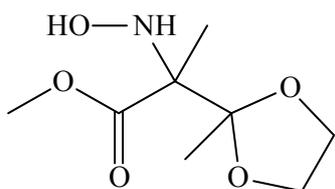


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3266 (OH), 3200 (NH), 1745 (C=O), 1130, 1095 and 1054 (CO).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.40 (s, 3H, CCH<sub>3</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.84-3.98 (ms, 4H, OCH<sub>2</sub>CH<sub>2</sub>O), 5.06 (s, 1H, CH), 5.77 (br s, 2H, NHOH).  **$^{13}\text{C-NMR}$**  (ppm): 172.7 (C=O), 104.3 (CH), 68.6 (C), 65.8 and 65.7 (OCH<sub>2</sub>CH<sub>2</sub>O), 53.7 (OCH<sub>3</sub>), 15.6 (CCH<sub>3</sub>). **HRMS (ESI)** calcd. for C<sub>9</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>Na [M+MeCN+Na]<sup>+</sup>: 255.0957; found: 255.0948.

#### 3.9.4 Photochemical reaction of methyl (*E*)-2-(hydroxyimino)propanoate (**74**) with 2-methyl-1,3-dioxolane

A solution of methyl (*E*)-2-(hydroxyimino) propanoate (**74**) (0.12 g, 1.0 mmol), benzophenone (0.09 g, 0.5 mmol) and 2-methyl-1,3-dioxolane (1.76 g, 20.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). It was then irradiated for 2 h at which time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.35 g) was adsorbed onto silica (20 g). Dry column vacuum chromatography (pet. ether/ether, 100/0 to 60/40) gave the product, methyl 2-(*N*-hydroxyamino)-2-(2-methyl-1,3-dioxolan-2-yl)propanoate (**97**), as white crystals (m.p. 120-122 °C) in 53% yield (0.11 g).

### Methyl 2-(*N*-hydroxyamino)-2-(2-methyl-1,3-dioxolan-2-yl)propanoate (**97**)



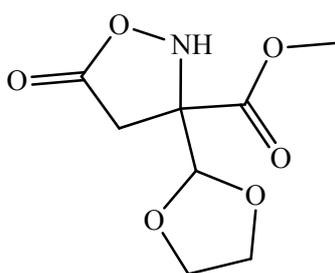
**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3322 (OH), 3190 (NH), 1726 (C=O), 1132, 1094 and 1039 (CO). **<sup>1</sup>H-NMR** ( $\delta$ ): 1.28 (s, 3H,  $\text{NHCCH}_3$ ), 1.50 (s, 3H,  $\text{CCH}_3$ ), 3.76 (s, 3H,  $\text{OCH}_3$ ), 3.88-3.92 (ms, 4H,  $\text{OCH}_2\text{CH}_2\text{O}$ ), 6.16 (s, 2H,  $\text{NHOH}$ ). **<sup>13</sup>C-NMR** (ppm): 173.3 (C=O), 110.3 (OCO), 72.5 (C), 65.5 and 65.4 ( $\text{OCH}_2\text{CH}_2\text{O}$ ), 52.6 ( $\text{OCH}_3$ ), 21.3 ( $\text{OCCH}_3$ ), 16.4 ( $\text{NHCCH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}_5\text{Na}$  [ $\text{M}+\text{MeCN}+\text{Na}$ ] $^+$ : 269.1113; found: 269.1107. CHN calcd. for  $\text{C}_8\text{H}_{15}\text{NO}_5$ : C, 46.82; H, 7.37; N, 6.83%. Found: C, 46.78; H, 7.53; N, 7.20%.

### 3.10 Photochemical reactions of 1,4-dimethyl (2*E*)-2-(hydroxyimino)butandioate (**77**)

#### 3.10.1 Photochemical reaction of 1,4-dimethyl (2*E*)-2-(hydroxyimino)butandioate (**77**) with 1,3-dioxolane

A solution of 1,4-dimethyl (2*E*)-2-(hydroxyimino)butandioate (**77**) (0.20 g, 1.1 mmol), benzophenone (0.20 g, 1.1 mmol) and 1,3-dioxolane (8.14 g, 110.0 mmol) in MeCN (40 ml) was prepared as before (Section 3.7.1). The solution was then irradiated for 3 h at which time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.52 g) was adsorbed onto silica (30 g). Flash column chromatography (pet. ether/ether, 100/0 to 40/60) gave methyl 3-(1,3-dioxolan-2-yl)-5-oxoisoazolidine-3-carboxylate (**99**) as a yellow oil in 73% yield (0.16 g).

### Methyl 3-(1,3-dioxolan-2-yl)-5-oxoisoazolidine-3-carboxylate (**99**)

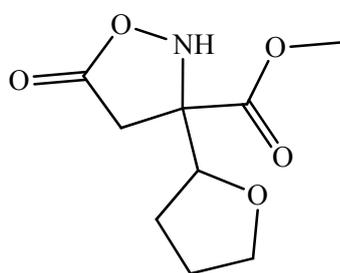


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3254 (NH), 1789 (ring C=O), 1738 (ester C=O), 1194, 1142 and 1028 (CO). **<sup>1</sup>H-NMR** ( $\delta$ ): 2.98 and 3.05 (ds,  $J = 17.8$  Hz, 2H,  $\text{C}(\text{O})\text{CH}_2$ ), 3.85 (s, 3H,  $\text{OCH}_3$ ), 3.91-4.01 (ms, 2H,  $\text{OCH}_2$ ), 4.09-4.18 (ms, 2H,  $\text{OCH}_2$ ), 5.32 (s, 1H,  $\text{CH}$ ), 7.45 (s, 1H,  $\text{NH}$ ). **<sup>13</sup>C-NMR** (ppm): 173.8 and 169.7 (C=O), 103.6 (CH), 71.1 (C), 66.7 and 66.2 ( $\text{OCH}_2\text{CH}_2\text{O}$ ), 53.9 ( $\text{OCH}_3$ ), 34.4 ( $\text{CH}_2$ ). **HRMS (ESI)** calcd. for  $\text{C}_8\text{H}_{12}\text{NO}_6$  [ $\text{M}+\text{H}$ ] $^+$ : 218.0665; found: 218.0668.

### 3.10.2 Photochemical reaction of 1,4-dimethyl (2E)-2-(hydroxyimino)butandioate (77) with THF

A solution of 1,4-dimethyl (2E)-2-(hydroxyimino)butandioate (**77**) (0.20 g, 1.1 mmol), benzophenone (0.20 g, 1.1 mmol) and THF (7.93 g, 110.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). The solution was then irradiated for 3 h at which time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.65 g) was adsorbed onto silica (30 g). Flash column chromatography (pet. ether/ether, 100/0 to 40/60) gave the product, methyl 5-oxo-3-(tetrahydrofuran-2-yl)-1,2-oxazolidine-3-carboxylate (**100**), as a clear oil in 83% yield (0.17 g) with a dr of 1:1 (GC).

#### Methyl 5-oxo-3-(tetrahydrofuran-2-yl)-1,2-oxazolidine-3-carboxylate (**100**)

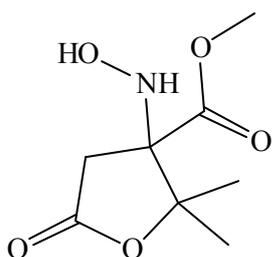


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3250 (NH), 1786 (ring C=O), 1733 (ester C=O), 1183, 1137 and 1067 (CO). **<sup>1</sup>H-NMR** ( $\delta$ ): 1.78-2.05 (overlapping ms, 8H,  $2 \times \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 2.85, 2.96, 3.00 and 3.10 (overlapping ds,  $J = 17.4$  Hz, 4H,  $2 \times \text{C}(\text{O})\text{CH}_2$ ), 3.72-3.91 (overlapping ms, 4H,  $2 \times \text{OCH}_2$ ), 3.80 and 3.81 ( $2 \times$  s, 6H,  $2 \times \text{OCH}_3$ ), 4.19 and 4.26 ( $2 \times$  t,  $J = 6.8$  Hz, 2H, OCH), 7.42 (br s, 2H,  $2 \times \text{NH}$ ). **<sup>13</sup>C-NMR** (ppm): 174.9, 171.2, 171.0 and 170.7 ( $4 \times \text{C}=\text{O}$ ), 81.0 and 80.4 ( $2 \times \text{OCH}$ ), 71.1 ( $2 \times \text{C}$ ), 69.6 and 69.4 ( $2 \times \text{OCH}_2$ ), 53.7 and 53.6 ( $2 \times \text{OCH}_3$ ), 36.8 and 36.5 ( $2 \times \text{C}(\text{O})\text{CH}_2$ ), 26.7, 26.4, 26.0 and 25.8 ( $2 \times \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$ ). **HRMS (ESI)** calcd. for  $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_5\text{Na}$  [ $\text{M}+\text{MeCN}+\text{Na}$ ] $^+$ : 279.0957; found: 279.0952.

### 3.10.3 Photochemical reaction of 1,4-dimethyl (2E)-2-(hydroxyimino)butandioate (77) with 2-propanol

A solution of 1,4-dimethyl (2E)-2-(hydroxyimino)butandioate (**77**) (0.20 g, 1.1 mmol), benzophenone (0.20 g, 1.1 mmol) and 2-propanol (6.60 g, 110.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). The solution was then irradiated for 2 h at which time all the benzophenone had dimerized (NMR). The solvent was removed under reduced pressure and the remaining mixture (0.50 g) was adsorbed onto silica (30 g). Flash column chromatography (pet. ether/ether, 100/0 to 40/60) gave the products, methyl-3-(hydroxyamino)-2,2-dimethyl-5-oxotetrahydrofuran-3-carboxylate (**101**) (0.03 g) and methyl-3-(2-hydroxypropan-2-yl)-5-oxo-1,2-oxazolidine-3-carboxylate (**102**), (0.07 g) as clear oils in a combined 43% yield.

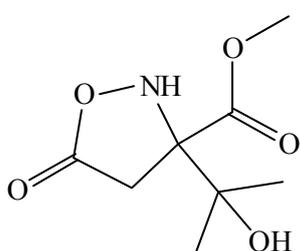
**Methyl-3-(hydroxyamino)-2,2-dimethyl-5-oxotetrahydrofuran-3-carboxylate (101)**



**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3398 (OH), 3267 (NH), 1773 (lactone C=O), 1726 (ester C=O), 1182, 1133 and 1033 (CO).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.29 (s, 3H,  $\text{CH}_3$ ), 1.45 (s, 3H,  $\text{CH}_3$ ), 2.97 and 3.35 (ds,  $J = 18.1$  Hz, 2H,  $\text{CH}_2$ ), 3.82 (s, 3H,  $\text{OCH}_3$ ), 5.62 (s, 1H, NH), 5.96 (s, 1H, OH).  **$^{13}\text{C-NMR}$**  (ppm): 173.9 and 170.6 (C=O), 85.1 ( $\text{C}(\text{CH}_3)_2$ ), 73.9 (CNH), 53.2 ( $\text{OCH}_3$ ), 35.8 ( $\text{CH}_2$ ), 25.2 and 20.5 ( $2 \times \text{CH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_5\text{Na}$  [ $\text{M}+\text{MeCN}+\text{Na}$ ] $^+$ :

267.0957; found: 267.0964.

**Methyl-3-(2-hydroxypropan-2-yl)-5-oxo-1,2-oxazolidine-3-carboxylate (102)**



**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3474 (OH), 3258 (NH), 1782 (ring C=O), 1729 (ester C=O), 1173, 1133 and 1032 (CO).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.14 (s, 3H,  $\text{CH}_3$ ), 1.22 (s, 3H,  $\text{CH}_3$ ), 3.01 and 3.36 (ds,  $J = 18.0$  Hz, 2H,  $\text{CH}_2$ ), 3.86 (s, 3H,  $\text{OCH}_3$ ), 7.81 (s, 1H, NH).  **$^{13}\text{C-NMR}$**  (ppm): 173.6 and 172.3 (C=O), 76.0 ( $\text{C}(\text{CH}_3)_2$ ), 71.9 (CNH), 53.9 ( $\text{OCH}_3$ ), 33.8 ( $\text{CH}_2$ ), 25.1 and 15.3 ( $2 \times \text{CH}_3$ ).

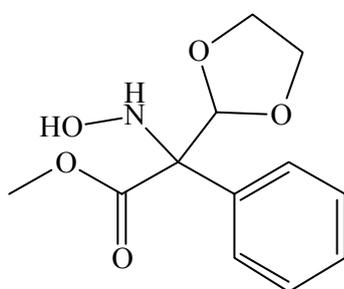
**HRMS (ESI)** calcd. for  $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_5\text{Na}$  [ $\text{M}+\text{MeCN}+\text{Na}$ ] $^+$ : 267.0957; found: 267.0962.

### 3.11 Photochemical reactions of methyl (2E)-(hydroxyimino)(phenyl)acetate (75)

#### 3.11.1 Photochemical reaction of methyl (2E)-(hydroxyimino)(phenyl)acetate (75) with 1,3-dioxolane

A solution of methyl (2E)-(hydroxyimino)(phenyl)acetate (**75**) (0.20 g, 1.1 mmol), benzophenone (0.20 g, 1.1 mmol) and 1,3-dioxolane (8.14 g, 110.0 mmol) in MeCN (40 ml) was prepared as before (Section 3.7.1). It was then irradiated for 6 h at which time the reaction had stopped (GC). The solvent was removed under reduced pressure and the remaining mixture (0.67 g) was adsorbed onto silica (30 g). Flash column chromatography (pet. ether/ether, 100/0 to 60/40) gave methyl-1,3-dioxolan-2-yl(hydroxyamino)phenylacetate (**104**) as a yellow oil in 25% yield (0.07 g).

#### Methyl-1,3-dioxolan-2-yl(hydroxyamino)phenylacetate (104)

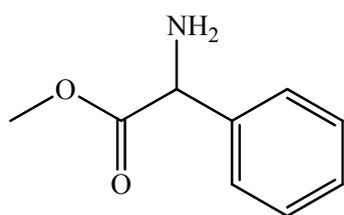


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3418 (OH), 3271 (NH), 1736 (C=O), 1122, 1089 and 1037 (CO), 730 and 701 (monosubstituted Ar). **<sup>1</sup>H-NMR** ( $\delta$ ): 3.59, 3.71 and 3.77-3.87 (ms, 4H, OCH<sub>2</sub>CH<sub>2</sub>O), 3.83 (s, 3H, OCH<sub>3</sub>), 5.68 (s, 1H, CH), 5.97 (br s, 1H, NH) 7.31-7.34 (overlapping ms, 3H, Ar-H<sub>meta</sub> and Ar-H<sub>para</sub>), 7.39-7.41 (overlapping ms, 2H, Ar-H<sub>ortho</sub>). **<sup>13</sup>C-NMR** (ppm): 171.7 (C=O), 134.7 (Ar<sub>ipso</sub>), 128.5, 128.3 and 127.8 (Ar-C), 104.1 (CH), 74.4 (C), 65.9 and 65.5 (OCH<sub>2</sub>CH<sub>2</sub>O), 52.7 (OCH<sub>3</sub>). **HRMS (ESI)** calcd. for C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>Na [M+MeCN+Na]<sup>+</sup>: 317.1113; found 317.1118.

#### 3.11.2 Photochemical reaction of methyl (2E)-(hydroxyimino)(phenyl)acetate (75) with 2-propanol

Methyl (2E)-(hydroxyimino)(phenyl)acetate (**75**) (0.20 g, 1.1 mmol) and benzophenone (0.20 g, 1.1 mmol) were dissolved in 2-propanol (40 ml, 520.0 mmol). The solution was degassed with N<sub>2</sub> for 20 min. It was then irradiated for 6 h at which time no change was occurring (GC). The solvent was removed under reduced pressure and the remaining mixture (0.41 g) was adsorbed onto silica (40 g). Flash column chromatography (pet. ether/ether, 70/30) gave the product, methyl 2-amino-2-phenylacetate (**105**), as a clear oil in 33% yield (0.06 g). Spectroscopic data were consistent with those in the literature<sup>[74]</sup>.

#### Methyl 2-amino-2-phenylacetate (105)

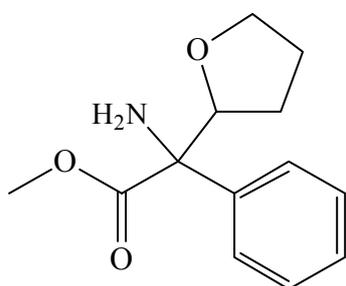


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3376 and 3306 (NH<sub>2</sub>), 1733 (C=O), 1220, 1167 and 1072 (CO), 729 and 696 (monosubstituted Ar). **<sup>1</sup>H-NMR** ( $\delta$ ): 2.18 (s, 2H, NH<sub>2</sub>), 3.65 (s, 3H, OCH<sub>3</sub>), 4.58 (s, 1H, CH), 7.22-7.33 (ms, 5H, Ar-H). **<sup>13</sup>C-NMR** (ppm): 174.5 (C=O), 140.3 (Ar<sub>ipso</sub>), 128.9, 128.1 and 126.9 (Ar-C), 58.8 (CH), 52.5 (OCH<sub>3</sub>).

### 3.11.3 Photochemical reaction of methyl (2E)-(hydroxyimino)(phenyl)acetate (75) with THF

A solution of methyl (2E)-(hydroxyimino)(phenyl)acetate (**75**) (0.20 g, 1.1 mmol), benzophenone (0.20 g, 1.1 mmol) and THF (7.93 g, 110.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). It was then irradiated for 3 h at which time no change was occurring (GC). GC analysis indicated the formation of a complex mixture of products. The solvent was removed under reduced pressure and the remaining mixture (0.62 g) was adsorbed onto silica (30 g). Flash chromatography (pet. ether/ether, 70/30) gave methyl amino(tetrahydrofuran-2-yl)phenylacetate (**106**), as a single diastereomer and as a clear oil in 11% yield (0.03 g).

#### Methyl amino(tetrahydrofuran-2-yl)phenylacetate (106)

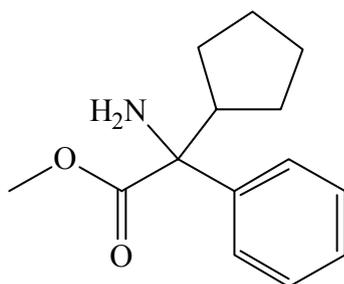


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3382 and 3322 ( $\text{NH}_2$ ), 1731 ( $\text{C}=\text{O}$ ), 1233, 1179 and 1063 ( $\text{CO}$ ), 729 and 698 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.75-2.25 (ms, 4H,  $\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 3.75 (m, 1H,  $\text{OCHH}$ ), 3.75 (s, 3H,  $\text{OCH}_3$ ), 4.24 (m, 1H,  $\text{OCHH}$ ), 4.97 (t,  $J_{\text{cis}} = J_{\text{trans}} = 7.8$  Hz, 1H,  $\text{CH}$ ), 7.30-7.41 (overlapping ms, 3H,  $\text{Ar-H}_{\text{meta}}$  and  $\text{Ar-H}_{\text{para}}$ ), 7.76 (d,  $J = 7.3$  Hz, 2H,  $\text{Ar-H}_{\text{ortho}}$ ), 9.52 (br s, 2H,  $\text{NH}_2$ ).  **$^{13}\text{C-NMR}$**  (ppm): 169.2 ( $\text{C}=\text{O}$ ), 132.4 ( $\text{Ar}_{\text{ipso}}$ ), 129.3, 129.2 and 126.7 ( $\text{Ar-C}$ ), 80.7 ( $\text{CH}$ ), 69.9 ( $\text{OCH}_2$ ), 69.0 ( $\text{C}$ ), 53.8 ( $\text{OCH}_3$ ), 26.9 ( $\text{CHCH}_2\text{CH}_2$ ), 26.0 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ). **HRMS (ESI)** calcd. for  $\text{C}_{13}\text{H}_{18}\text{NO}_3$   $[\text{M}+\text{H}]^+$ : 236.1287; found: 236.1295

### 3.11.4 Photochemical reaction of methyl (2E)-(hydroxyimino)(phenyl)acetate (75) with cyclopentane

A solution of methyl (2E)-(hydroxyimino)(phenyl)acetate (**75**) (0.20 g, 1.1 mmol), benzophenone (0.20 g, 1.1 mmol) and cyclopentane (7.70 g, 110.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). It was then irradiated for 6 h at which time the reaction had stopped (GC). The solvent was removed under reduced pressure and the remaining mixture (0.54 g) was adsorbed onto silica (40 g). Flash column chromatography (pet. ether/ether, 70/30) gave the product, methyl amino(cyclopentyl)phenylacetate (**107**), as a yellow oil in 23% yield (0.06 g).

### Methyl amino(cyclopentyl)phenylacetate (107)



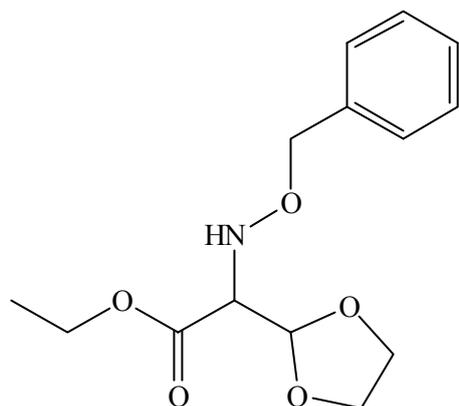
**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3392 and 3332 ( $\text{NH}_2$ ), 1727 ( $\text{C}=\text{O}$ ), 1226, 1174 and 1020 ( $\text{CO}$ ), 730 and 698 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.18-1.78 (overlapping ms, 8H, cyclopentyl  $\text{CH}_2$ ), 1.77-1.90 (br s, 2H,  $\text{NH}_2$ ), 2.95 (m, 1H, CH), 3.69 (s, 3H,  $\text{OCH}_3$ ), 7.21-7.37 (overlapping ms, 3H, Ar- $\text{H}_{\text{meta}}$  and Ar- $\text{H}_{\text{para}}$ ), 7.57 (d,  $J = 7.2$  Hz, 2H, Ar- $\text{H}_{\text{ortho}}$ ).  **$^{13}\text{C-NMR}$**  (ppm): 176.2 ( $\text{C}=\text{O}$ ), 143.2 ( $\text{Ar}_{\text{ipso}}$ ), 128.3, 127.3 and 125.9 (Ar-C), 65.6 (C), 52.5 ( $\text{OCH}_3$ ), 47.4 (CH), 27.9, 26.9, 26.3 and 26.0 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ). **HRMS (ESI)** calcd. for  $\text{C}_{14}\text{H}_{20}\text{NO}_2$  [ $\text{M}+\text{H}$ ] $^+$ : 234.1494; found: 234.1496.

### 3.12 Photochemical reactions of ethyl (2E)-[(benzyloxy)imino]acetate (78)

#### 3.12.1 Photochemical reaction of ethyl (2E)-[(benzyloxy)imino]acetate (78) with 1,3-dioxolane

A solution of ethyl (2E)-[(benzyloxy)imino]acetate (**78**) (0.20 g, 1.0 mmol), benzophenone (0.10 g, 0.5 mmol) and 1,3-dioxolane (1.48 g, 20.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). The solution was then irradiated for 2.5 h at which time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.35 g) was adsorbed onto silica (20 g). Dry column vacuum chromatography (pet. ether/ether, 100/0 to 60/40) gave ethyl [(benzyloxy)amino](1,3-dioxolan-2-yl)acetate (**108**) as a clear oil in 75% yield (0.21 g).

### Ethyl [(benzyloxy)amino](1,3-dioxolan-2-yl)acetate (108)

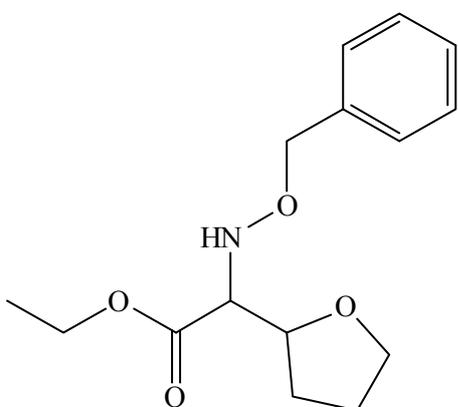


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3266 (NH), 1736 ( $\text{C}=\text{O}$ ), 1199, 1147 and 1023 ( $\text{CO}$ ), 740 and 696 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.28 (t,  $J = 7.2$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 3.81-3.97 (ms, 5H,  $\text{OCH}_2\text{CH}_2\text{O}$  and  $\text{CHNH}$ ), 4.23 (q,  $J = 7.2$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ), 4.72 (s, 2H,  $\text{OCH}_2\text{Ph}$ ), 5.13 (d,  $J = 4.2$  Hz, 1H,  $\text{OCHO}$ ), 6.21 (s, 1H, NH), 7.27-7.34 (ms, 5H,  $5 \times \text{Ar-H}$ ).  **$^{13}\text{C-NMR}$**  (ppm): 170.1 ( $\text{C}=\text{O}$ ), 137.5 ( $\text{Ar}_{\text{ipso}}$ ), 128.6, 128.4 and 128.1 (Ar-C), 101.6 (OCH), 76.4 ( $\text{OCH}_2\text{Ph}$ ), 66.9 (NCH), 65.6 and 65.5 ( $\text{OCH}_2\text{CH}_2\text{O}$ ), 61.5 ( $\text{OCH}_2\text{CH}_3$ ), 14.3 ( $\text{OCH}_2\text{CH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_{14}\text{H}_{19}\text{NO}_5\text{Na}$  [ $\text{M}+\text{Na}$ ] $^+$ : 304.1161; found: 304.1172.

### 3.12.3 Photochemical reaction of ethyl (2E)-[(benzyloxy)imino]acetate (78) with THF

A solution of ethyl (2E)-[(benzyloxy)imino]acetate (**78**) (0.20 g, 1.0 mmol), benzophenone (0.10 g, 0.5 mmol) and THF (1.44 g, 20 mmol) in MeCN (40 ml) was prepared as before (Section 3.7.1). The solution was then irradiated for 3 h at which time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.35 g) was adsorbed onto silica (20 g). Dry column vacuum chromatography (pet. ether/ether, 100/0 to 50/50) gave ethyl [(benzyloxy)amino](tetrahydrofuran-2-yl)acetate (**109**) as a clear oil in 73% yield (0.20 g) and as a mixture of diastereomers 1:1.06 (GC).

#### Ethyl [(benzyloxy)amino](tetrahydrofuran-2-yl)acetate (**109**)

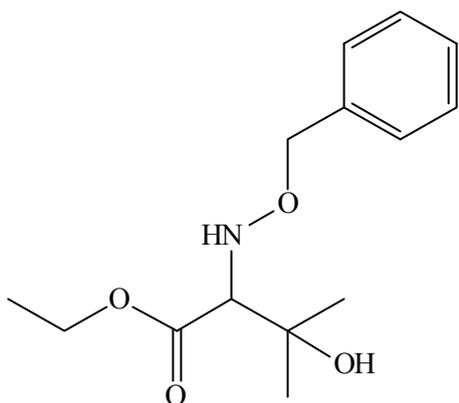


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3276 (NH), 1732 (C=O), 1255, 1062 and 1032 (CO), 736 and 696 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.28 (t,  $J = 7.1$  Hz, 6H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 1.79-1.96 (overlapping ms, 8H,  $2 \times \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 3.54-3.63 (ms, 2H,  $2 \times \text{CHNH}$ ), 3.69 and 3.79 ( $2 \times$  m, 4H,  $2 \times \text{OCH}_2\text{CH}_2$ ), 3.93 and 4.03 ( $2 \times$  m, 2H,  $2 \times \text{OCH}$ ), 4.22 and 4.24 (overlapping qs,  $J = 7.1$  Hz, 4H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 4.69 (m, 4H,  $2 \times \text{OCH}_2\text{Ph}$ ), 6.10 and 6.23 ( $2 \times$  d,  $J = 9.2$  Hz, 2H,  $2 \times \text{CHNH}$ ), 7.26-7.33 (m, 10H,  $10 \times \text{Ar-H}$ ).  **$^{13}\text{C-NMR}$**  (ppm): 172.1 and 172.0 ( $2 \times \text{C=O}$ ), 137.8 ( $2 \times \text{Ar}_{\text{ipso}}$ ), 128.65, 128.6, 128.4, 128.3, 127.9 and 127.8 (Ar-C), 77.2 and 77.1 ( $2 \times \text{NHCH}$ ), 76.3 and 76.2 ( $2 \times \text{OCH}_2\text{Ph}$ ), 68.8 and 68.5 ( $2 \times \text{OCH}_2\text{CH}_2$ ), 67.7 and 67.6 ( $2 \times \text{OCHCH}_2$ ), 61.2 and 61.1 ( $2 \times \text{OCH}_2\text{CH}_3$ ), 28.9 and 28.7 ( $2 \times \text{CHCH}_2\text{CH}_2$ ), 25.9 and 25.3 ( $2 \times \text{CH}_2\text{CH}_2\text{CH}_2$ ), 14.4 and 14.3 ( $2 \times \text{OCH}_2\text{CH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_{15}\text{H}_{21}\text{NO}_4\text{Na}$  [ $\text{M}+\text{Na}$ ] $^+$ : 302.1368; found: 302.1363.

### 3.12.4 Photochemical reaction of ethyl (2E)-[(benzyloxy)imino]acetate (78) with 2-propanol

A solution of ethyl (2E)-[(benzyloxy)imino]acetate (**78**) (0.20 g, 1.0 mmol), benzophenone (0.10 g, 0.5 mmol) and 2-propanol (1.20 g, 20.0 mmol) in MeCN (40 ml) was prepared as before (Section 3.7.1). The solution was then irradiated for 2 h at which time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.33 g) was adsorbed onto silica (40 g). Flash column chromatography (pet. ether/ether, 100/0 to 60/40) gave ethyl 2-benzyloxyamino-3-hydroxy-3-methyl butanoate (**110**) as a clear oil in 65% yield (0.17 g).

### Ethyl 2-benzyloxyamino-3-hydroxy-3-methyl butanoate (**110**)



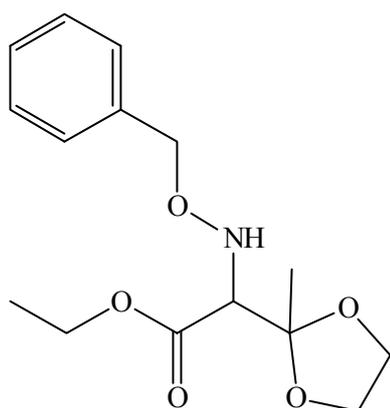
**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3491 (OH), 3276 (NH), 1728 (C=O), 1207, 1152 and 1022 (CO), 738 and 696 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.10 (s, 3H, CCH<sub>3</sub>), 1.24 (s, 3H, CCH<sub>3</sub>), 1.28 (t,  $J$  = 7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 2.85 (s, 1H, OH), 3.53 (s, 1H, CH), 4.20-4.28 (ms, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.67 (s, 2H, OCH<sub>2</sub>Ph), 6.31 (s, 1H, NH), 7.26-7.33 (ms, 5H, 5  $\times$  Ar-H).  **$^{13}\text{C-NMR}$**  (ppm): 173.2 (C=O), 137.6 (Ar<sub>ipso</sub>), 128.7, 128.4 and 128.0 (Ar-C), 76.1 (OCH<sub>2</sub>Ph), 71.8 (CH), 70.7 (C), 61.4 (OCH<sub>2</sub>CH<sub>3</sub>), 26.8 and 26.7 (2 $\times$ CCH<sub>3</sub>), 14.3 (OCH<sub>2</sub>CH<sub>3</sub>). **HRMS (ESI)** calcd.

for C<sub>14</sub>H<sub>21</sub>NO<sub>4</sub>Na [M+Na]<sup>+</sup>: 290.1368; found: 290.1356.

### 3.12.2 Photochemical reaction of ethyl (2E)-[(benzyloxy)imino]acetate (**78**) with 2-methyl-1,3-dioxolane

A solution of ethyl (2E)-[(benzyloxy)imino]acetate (**78**) (0.20 g, 1.0 mmol), benzophenone (0.10 g, 0.5 mmol) and 2-methyl-1,3-dioxolane (1.76 g, 20.0 mmol) in MeCN (40 ml) was prepared as before (Section 3.7.1). The solution was then irradiated for 1 h at which time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.44 g) was adsorbed onto silica (40 g). Flash column chromatography (pet. ether/ether, 100/0 to 65/35) gave the product, ethyl [(benzyloxy)amino](2-methyl-1,3-dioxolan-2-yl)acetate (**111**), as a clear oil in 79% yield (0.23 g).

### Ethyl [(benzyloxy)amino](2-methyl-1,3-dioxolan-2-yl)acetate (**111**)



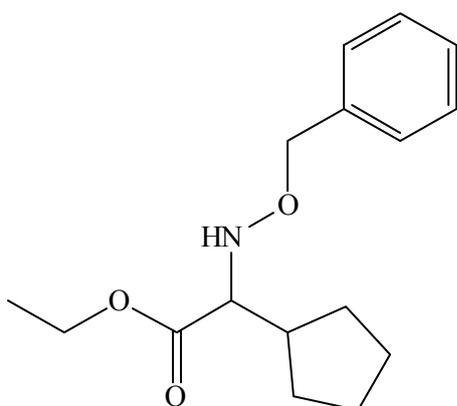
**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3271 (NH), 1735 (C=O), 1204, 1151 and 1034 (CO), 736 and 696 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.28 (t,  $J$  = 7.2 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.33 (s, 3H, CCH<sub>3</sub>), 3.74 (d,  $J$  = 10.0 Hz, 1H, CH), 3.83-3.94 (ms, 4H, OCH<sub>2</sub>CH<sub>2</sub>O), 4.20-4.26 (ms, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.68 (s, 2H, OCH<sub>2</sub>Ph), 6.20 (d,  $J$  = 10.0 Hz, 1H, NH), 7.25-7.35 (m, 5H, 5  $\times$  Ar-H).  **$^{13}\text{C-NMR}$**  (ppm): 171.5 (C=O), 137.7 (Ar<sub>ipso</sub>), 128.7, 128.4 and 127.9 (Ar-C), 107.9 (C), 76.2 (OCH<sub>2</sub>Ph), 70.0 (CH), 65.4 and 65.2 (OCH<sub>2</sub>CH<sub>2</sub>O), 61.2 (OCH<sub>2</sub>CH<sub>3</sub>), 23.1 (CCH<sub>3</sub>), 14.3 (OCH<sub>2</sub>CH<sub>3</sub>). **HRMS (ESI)** calcd.

for C<sub>15</sub>H<sub>22</sub>NO<sub>5</sub> [M+H]<sup>+</sup>: 296.1498; found: 296.1509.

### 3.12.5 Photochemical reaction of ethyl (2E)-[(benzyloxy)imino]acetate (78) with cyclopentane

A solution of ethyl (2E)-[(benzyloxy)imino]acetate (**78**) (0.20 g, 1.0 mmol), benzophenone (0.10 g, 0.5 mmol) and cyclopentane (1.40 g, 20.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). The solution was then irradiated for 5 h at which time no further reaction was observed (GC). The solvent was removed under reduced pressure and the remaining mixture (0.28 g) was adsorbed onto silica (20 g). Dry column vacuum chromatography (pet. ether/ether, 100/0 to 90/10) gave the product, ethyl [(benzyloxy)amino](cyclopentyl)acetate (**112**), as a yellow oil in 45% yield (0.13 g).

#### Ethyl [(benzyloxy)amino](cyclopentyl)acetate (**112**)



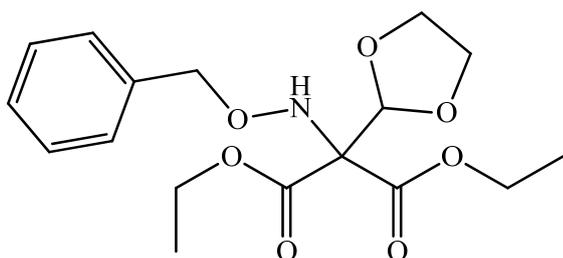
**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3261 (NH), 1733 (C=O), 1251, 1180 and 1025 (CO), 736 and 696 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.27 (t,  $J = 7.2$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.29-1.87 (ms, 9H, cyclopentyl CH and  $\text{CH}_2$ ), 3.37 (t,  $J = 10.0$  Hz, 1H, NHCH), 4.20-4.28 (ms, 2H,  $\text{OCH}_2\text{CH}_3$ ), 4.67 (s, 2H,  $\text{OCH}_2\text{Ph}$ ), 5.96 (d,  $J = 10.0$  Hz, 1H, NH), 7.28-7.33 (ms, 5H,  $5 \times \text{Ar-H}$ ).  **$^{13}\text{C-NMR}$**  (ppm): 174.4 (C=O), 138.0 ( $\text{Ar}_{\text{ipso}}$ ), 128.7, 128.3 and 127.8 (Ar-C), 76.0 ( $\text{OCH}_2\text{Ph}$ ), 68.5 (CHNH), 60.8 ( $\text{OCH}_2\text{CH}_3$ ), 40.0 (CHCHNH), 30.2 and 29.5 ( $2 \times \text{CHCH}_2\text{CH}_2$ ), 25.1 and 25.0 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ), 14.4 ( $\text{OCH}_2\text{CH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_{16}\text{H}_{24}\text{NO}_3$  [ $\text{M}+\text{H}$ ] $^+$ : 278.1756; found: 278.1768.

### 3.13 Photochemical reactions of diethyl [(benzyloxy)imino]malonate (79)

#### 3.13.1 Photochemical reaction of diethyl [(benzyloxy)imino]malonate (79) with 1,3-dioxolane

A solution of diethyl [(benzyloxy)imino]malonate (**79**) (0.20 g, 0.7 mmol), benzophenone (0.07 g, 0.35 mmol) and 1,3-dioxolane (5.18 g, 70.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). The solution was then irradiated for 1 h at which time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.50 g) was adsorbed onto silica (40 g). Flash column chromatography (pet. ether/ether, 100/0 to 50/50) gave diethyl [(benzyloxy)amino](1,3-dioxolan-2-yl)malonate (**113**) as a clear oil in 89% yield (0.22 g).

### Diethyl [(benzyloxy)amino](1,3-dioxolan-2-yl)malonate (**113**)

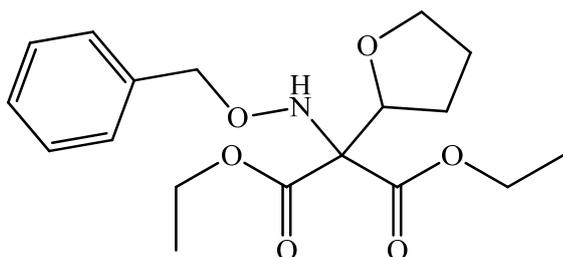


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3274 (NH), 1735 (C=O), 1224, 1095 and 1034 (CO), 742 and 699 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.27 (t,  $J = 7.1$  Hz, 6H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 3.78-4.01 (ms, 4H,  $\text{OCH}_2\text{CH}_2\text{O}$ ), 4.26 (q,  $J = 7.1$  Hz, 4H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 4.76 (s, 2H,  $\text{OCH}_2\text{Ph}$ ), 5.64 (s, 1H CH), 6.60 (broad s, 1H, NH), 7.25-7.29 (ms, 5H,  $5 \times \text{Ar-H}$ ).  **$^{13}\text{C-NMR}$**  (ppm): 166.0 (C=O), 137.1 ( $\text{Ar}_{\text{ipso}}$ ), 128.4, 128.35 and 127.9 (Ar-C), 102.5 (CH), 77.0 ( $\text{OCH}_2\text{Ph}$ ), 75.1 (C), 65.9 ( $\text{OCH}_2\text{CH}_2\text{O}$ ), 62.1 ( $\text{OCH}_2\text{CH}_3$ ), 14.1 ( $\text{OCH}_2\text{CH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_{17}\text{H}_{24}\text{NO}_7$   $[\text{M}+\text{H}]^+$ : 354.1553; found: 354.1568.

#### 3.13.2 Photochemical reaction of diethyl [(benzyloxy)imino]malonate (**79**) with THF

A solution of diethyl [(benzyloxy)imino]malonate (**79**) (0.20 g, 0.7 mmol), benzophenone (0.07 g, 0.35 mmol) and THF (5.04 g, 70.0 mmol) in MeCN (40 ml) was prepared as before (Section 3.7.1). The solution was then irradiated for 1 h at which time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.34 g) was adsorbed onto silica (40 g). Flash column chromatography (pet. ether/ether, 100/0 to 50/50) gave the product, diethyl [(benzyloxy)amino](tetrahydrofuran-2-yl)malonate (**114**), as a clear oil in 77% yield (0.19 g).

### Diethyl [(benzyloxy)amino](tetrahydrofuran-2-yl)malonate (**114**)

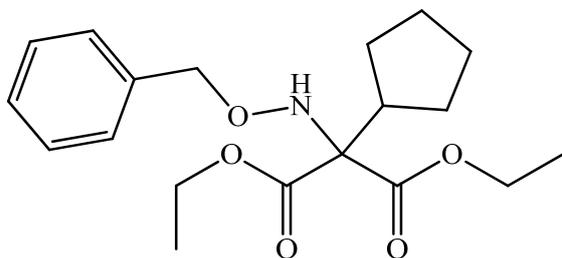


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3270 (NH), 1733 (C=O), 1260, 1065 and 1032 (CO), 740 and 698 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.27 (t,  $J = 7.1$  Hz, 6H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 1.75-1.92 (ms, 2H,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 2.16-2.22 (ms, 2H,  $\text{CHCH}_2\text{CH}_2$ ), 3.71-3.83 (ms, 2H,  $\text{OCH}_2\text{CH}_2$ ), 4.21-4.27 (m, 4H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 4.58 (t,  $J_{\text{cis}} = J_{\text{trans}} = 7.4$  Hz, 1H, CH), 4.75 (s, 2H  $\text{OCH}_2\text{Ph}$ ), 6.55 (broad s, 1H, NH), 7.27-7.33 (m, 5H,  $5 \times \text{Ar-H}$ ).  **$^{13}\text{C-NMR}$**  (ppm): 167.8 and 166.9 (C=O), 137.3 ( $\text{Ar}_{\text{ipso}}$ ), 128.4, 128.3 and 127.9 (Ar-C), 78.6 (CH), 76.9 ( $\text{OCH}_2\text{Ph}$ ), 75.5 (C), 69.0 ( $\text{OCH}_2\text{CH}_2$ ), 61.9 ( $\text{OCH}_2\text{CH}_3$ ), 27.7 ( $\text{CHCH}_2\text{CH}_2$ ), 26.1 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 14.2 ( $\text{OCH}_2\text{CH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_{18}\text{H}_{25}\text{NO}_6\text{Na}$   $[\text{M}+\text{Na}]^+$ : 374.1580; found: 374.1570.

### 3.13.3 Photochemical reaction of diethyl [(benzyloxy)imino]malonate (79) with cyclopentane

A solution of diethyl [(benzyloxy)imino]malonate (**79**) (0.20 g, 0.7 mmol), benzophenone (0.07 g, 0.35 mmol) and cyclopentane (4.90 g, 70.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). The solution was then irradiated for 2 h at which time no further reaction was occurring (GC). The solvent was removed under reduced pressure and the remaining mixture (0.31 g) was adsorbed onto silica (40 g). Flash column chromatography (pet. ether/ether, 100/0 to 50/50) gave the product, diethyl [(benzyloxy)amino](cyclopentyl)malonate (**115**), as a clear oil in 29% yield (0.07 g).

#### Diethyl [(benzyloxy)amino](cyclopentyl)malonate (**115**)



**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3270 (NH), 1733 (C=O), 1249, 1097 and 1032 (CO), 744 and 698 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.26 (t,  $J = 7.1$  Hz, 6H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 1.49-1.61 and 1.78-1.84 (overlapping ms, 8H, cyclopentyl  $\text{CH}_2$ ), 2.69 (m, 1H, CH), 4.22 (q,  $J = 7.2$  Hz, 4H,  $2 \times \text{OCH}_2\text{CH}_3$ ), 4.75 (s, 2H

$\text{OCH}_2\text{Ph}$ ), 6.20 (s, 1H, NH), 7.26-7.33 (ms, 5H,  $5 \times \text{Ar-H}$ ).  **$^{13}\text{C-NMR}$**  (ppm): 168.8 (C=O), 137.5 ( $\text{Ar}_{\text{ipso}}$ ), 128.4, 128.2 and 127.8 (Ar-C), 76.6 ( $\text{OCH}_2\text{Ph}$ ), 75.4 (C), 61.6 ( $\text{OCH}_2\text{CH}_3$ ), 42.5 (CH), 27.8 ( $\text{CHCH}_2\text{CH}_2$ ), 25.6 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ), 14.2 ( $\text{OCH}_2\text{CH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_{19}\text{H}_{27}\text{NO}_5\text{Na}$   $[\text{M}+\text{Na}]^+$ : 372.1787; found: 372.1783.

### 3.13.4 Photochemical reaction of diethyl [(benzyloxy)imino]malonate with 2-propanol

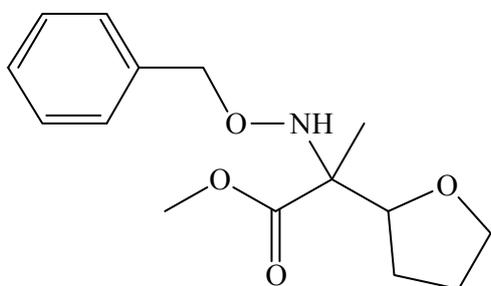
A solution of diethyl [(benzyloxy)imino]malonate (0.20 g, 0.7 mmol), benzophenone (0.07 g, 0.35 mmol) and 2-propanol (4.20 g, 70.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). The solution was then irradiated for 1 h at which time all the starting material had reacted (GC). NMR analysis of the crude reaction mixture showed a complex mixture of products. The mixture (0.29 g) was adsorbed onto silica (40 g) however attempts to isolate any identifiable products *via* flash chromatography failed.

### 3.14 Photochemical reactions of methyl (2E)-2-[(benzyloxy)imino]propanoate (80)

#### 3.14.1 Photochemical reaction of methyl (2E)-2-[(benzyloxy)imino]propanoate (80) with THF

A solution of methyl (2E)-2-[(benzyloxy)imino]propanoate (**80**) (0.20 g, 1.0 mmol), benzophenone (0.18 g, 1.0 mmol) and THF (1.44 g, 20.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). It was then irradiated for 6 h at which time no change was occurring in the reaction (GC). The solvent was removed under reduced pressure and the remaining mixture (0.58 g) was adsorbed onto silica (40 g). Flash column chromatography (pet. ether/ether, 95/5 to 70/30) gave the product, methyl 2-[(benzyloxy)amino]-2-(tetrahydrofuran-2-yl)propanoate (**116**), as a mixture of diastereomers 1:1.1 (GC) and as a clear oil in 68% yield (0.19 g).

#### Methyl 2-[(benzyloxy)amino]-2-(tetrahydrofuran-2-yl)propanoate (116)



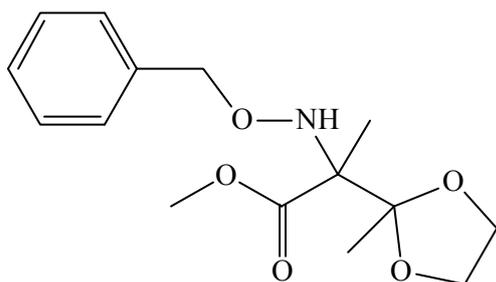
**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3270 (NH), 1728 (C=O), 1256, 1138 and 1069 (CO), 737 and 698 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.31 and 1.38 (2  $\times$  s, 6H, 2  $\times$  CCH<sub>3</sub>), 1.73-1.92 (overlapping ms, 8H, 2  $\times$  CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.68-3.79 (overlapping ms, 4H, 2  $\times$  OCH<sub>2</sub>CH<sub>2</sub>), 3.72 and 3.73 (2  $\times$  s, 6H, 2  $\times$  OCH<sub>3</sub>), 3.84 and 4.00 (2  $\times$  ts,  $J_{\text{cis}} = J_{\text{trans}} = 7.1$  Hz,

2H, 2  $\times$  CH), 4.67, 4.68, 4.71 and 4.72 (overlapping ds,  $J = 11.6$  Hz, 4H, 2  $\times$  OCH<sub>2</sub>Ph), 6.32 and 6.43 (2  $\times$  s, 2H, NH), 7.26-7.32 (ms, 10H, 10  $\times$  Ar-H).  **$^{13}\text{C-NMR}$**  (ppm): 173.9 (2  $\times$  C=O), 137.8 and 137.9 (2  $\times$  Ar<sub>ipso</sub>), 128.9, 128.6, 128.5, 128.4, 128.3 and 127.8 (Ar-C), 81.5 and 81.4 (2  $\times$  CH), 77.2 and 77.1 (2  $\times$  OCH<sub>2</sub>Ph), 69.2 and 69.0 (2  $\times$  OCH<sub>2</sub>CH<sub>2</sub>), 68.7 and 68.2 (2  $\times$  C), 52.4 and 52.3 (2  $\times$  OCH<sub>3</sub>), 26.9, 26.6, 26.1 and 25.8 (2  $\times$  CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 16.9 and 16.1 (2  $\times$  CCH<sub>3</sub>). **HRMS (ESI)** calcd. for C<sub>15</sub>H<sub>22</sub>NO<sub>4</sub> [M+H]<sup>+</sup>: 280.1550; found: 280.1549.

#### 3.14.2 Photochemical reaction of methyl (2E)-2-[(benzyloxy)imino]propanoate (80) with 2-methyl-1,3-dioxolane

A solution of methyl (2E)-2-[(benzyloxy)imino]propanoate (**80**) (0.20 g, 1.0 mmol), benzophenone (0.18 g, 1.0 mmol) and 2-methyl-1,3-dioxolane (1.76 g, 20.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). It was then irradiated for 2 h at which time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.64 g) was adsorbed onto silica (20 g). Dry column vacuum chromatography (pet. ether/ether, 100/0 to 60/40) gave methyl 2-[(benzyloxy)amino]-2-(2-methyl-1,3-dioxolan-2-yl)propanoate (**117**) as a clear oil in 71% yield (0.21 g).

### Methyl 2-[(benzyloxy)amino]-2-(2-methyl-1,3-dioxolan-2-yl)propanoate (117)

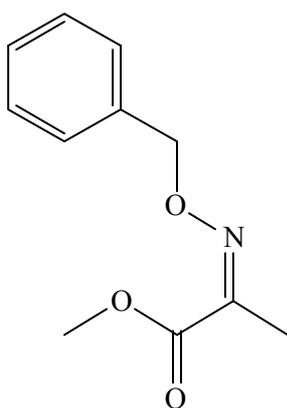


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3281 (NH), 1729 (C=O), 1140, 1097 and 1042 (CO), 733 and 698 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.30 (s, 3H,  $\text{NCCH}_3$ ), 1.46 (s, 3H,  $\text{OCCH}_3$ ), 3.72 (s, 3H,  $\text{OCH}_3$ ), 3.84-3.90 (ms, 4H,  $\text{OCH}_2\text{CH}_2\text{O}$ ), 4.65 and 4.71 (ds,  $J = 11.7$  Hz, 2H,  $\text{CH}_2$ ), 6.55 (s, 1H, NH), 7.26-7.33 (ms, 5H,  $5 \times \text{Ar-H}$ ).  **$^{13}\text{C-NMR}$**  (ppm): 173.7 (C=O), 137.9 ( $\text{Ar}_{\text{ipso}}$ ), 128.7, 128.3 and 127.8 (Ar-C), 110.5 (OCO), 77.3 ( $\text{OCH}_2\text{Ph}$ ), 72.1 (NC), 65.5 ( $\text{OCH}_2\text{CH}_2\text{O}$ ), 52.5 ( $\text{OCH}_3$ ), 21.4 ( $\text{OCCH}_3$ ), 16.7 ( $\text{NCCH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_{15}\text{H}_{21}\text{NO}_5\text{Na}$   $[\text{M}+\text{Na}]^+$ : 318.1317; found: 318.1325.

### 3.14.3 Photochemical reaction of methyl (2E)-2-[(benzyloxy)imino]propanoate (80) with cyclopentane

A solution of methyl (2E)-2-[(benzyloxy)imino]propanoate (**80**) (0.20 g, 1.0 mmol), benzophenone (0.18 g, 1.0 mmol) and cyclopentane (1.40 g, 20.0 mmol) in MeCN (40 ml) was prepared as before (Section 3.7.1). The solution was then irradiated for 7.5 h at which time no change was occurring (GC). The solvent was removed under reduced pressure and the remaining mixture (0.47 g) was adsorbed onto silica (30 g). Flash column chromatography (pet. ether/ether, 95/5 to 70/30) gave methyl (2Z)-2-[(benzyloxy)imino]propanoate (**119**) as a clear oil in 65% yield (0.13 g).

### Methyl (2Z)-2-[(benzyloxy)imino]propanoate (119)

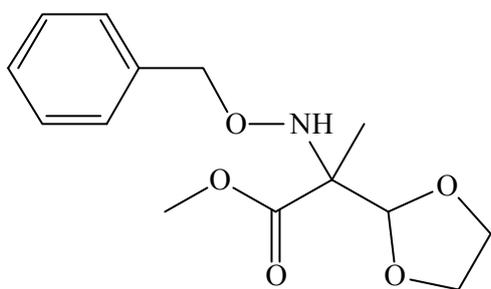


**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 1737 (C=O), 1605 (C=N), 1196, 1158 and 1044 (CO), 733 and 696 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 2.04 (s, 3H,  $\text{CH}_3$ ), 3.82 (s, 3H,  $\text{OCH}_3$ ), 5.11 (s, 2H,  $\text{CH}_2$ ), 7.29-7.35 (ms, 5H,  $5 \times \text{Ar-H}$ ).  **$^{13}\text{C-NMR}$**  (ppm): 164.4 (C=O), 148.3 (C=N), 137.6 ( $\text{Ar}_{\text{ipso}}$ ), 128.4, 127.9 and 127.8 (Ar-C), 76.3 ( $\text{OCH}_2\text{Ph}$ ), 52.3 ( $\text{OCH}_3$ ), 17.1 ( $\text{CH}_3$ ).

### 3.14.4 Photochemical reaction of methyl (2E)-2-[(benzyloxy)imino]propanoate (80) with 1,3-dioxolane

Methyl (2E)-2-[(benzyloxy)imino]propanoate (**80**) (0.20 g, 1.0 mmol), benzophenone (0.18 g, 1.0 mmol) and 1,3-dioxolane (1.48g, 20.0 mmol) in MeCN (40 ml) was prepared as before (Section 3.7.1). The solution was then irradiated for 2 h at which the reaction time all the starting material had reacted (GC). The solvent was removed under reduced pressure and the remaining mixture (0.43 g) was adsorbed onto silica (30 g). Flash column chromatography (pet. ether/ether, 95/5 to 70/30) gave the product, methyl 2-[(benzyloxy)amino]-2-(1,3-dioxolan-2-yl)propanoate (**120**), as a clear oil in 68% yield (0.19 g). Spectroscopic data were consistent with those in the literature<sup>[57]</sup>.

#### Methyl 2-[(benzyloxy)amino]-2-(1,3-dioxolan-2-yl)propanoate (120)



**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3282 (NH), 1735 (C=O), 1259, 1103 and 1040 (CO), 734 and 698 (monosubstituted Ar). **<sup>1</sup>H-NMR** ( $\delta$ ): 1.38 (s, 3H, CH<sub>3</sub>), 3.74 (s, 3H, OCH<sub>3</sub>), 3.83-3.95 (ms, 4 H, OCH<sub>2</sub>CH<sub>2</sub>O), 4.68 and 4.73 (pair of ds,  $J = 11.6$  Hz, 2H, OCH<sub>2</sub>Ph), 5.05 (s, 1H, CH), 6.28 (s, 1H, NH), 7.25-7.31 (ms, 5H, 5  $\times$  Ar-H). **<sup>13</sup>C NMR** (ppm): 172.6 (C=O), 137.5 (Ar<sub>ipso</sub>), 128.5, 128.4 and 127.9 (Ar-C), 104.1 (CH), 77.3 (OCH<sub>2</sub>Ph), 68.6 (C), 65.7 and 65.6 (OCH<sub>2</sub>CH<sub>2</sub>O), 52.5 (OCH<sub>3</sub>), 15.3 (CH<sub>3</sub>).

### 3.14.5 Photochemical reaction of methyl (2E)-2-[(benzyloxy)imino]propanoate (80) with 2-propanol

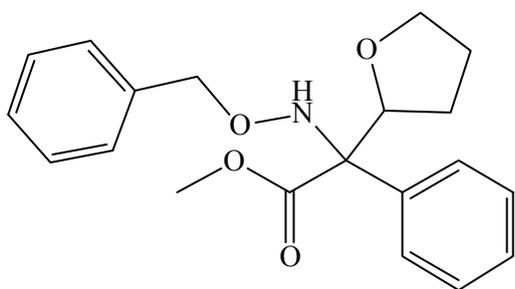
A solution of methyl (2E)-2-[(benzyloxy)imino]propanoate (**80**) (0.20 g, 1.0 mmol), benzophenone (0.18 g, 1.0 mmol) and 2-propanol (1.20 g, 20.0 mmol) in MeCN (40 ml) was prepared as before (Section 3.7.1). The solution was then irradiated for 4 h at which time no change was occurring (GC). The solvent was removed under reduced pressure and the remaining mixture (0.44 g) was adsorbed onto silica (20 g). Dry column vacuum chromatography (pet. ether/ether, 100/0 to 60/40) gave methyl (2Z)-2-[(benzyloxy)imino]propanoate (**119**) in 20% yield (0.04 g) and the addition product, methyl 2-[(benzyloxy)amino]-3-hydroxy-2,3-dimethylbutanoate (**121**), as a clear oil in 22% yield (0.06 g). Spectroscopic data were consistent with those in the literature<sup>[57]</sup>, and in the case of (**119**) with those described above (Section 3.14.3).



### 3.15.2 Photochemical reaction of methyl (2*E*)-[(benzyloxy)imino](phenyl)acetate (**81**) with THF

A solution of methyl (2*E*)-[(benzyloxy)imino](phenyl)acetate (**81**) (0.20 g, 0.7 mmol), benzophenone (0.13 g, 0.7 mmol) and 1,3-dioxolane (5.04 g, 70.0 mmol) in MeCN (40 ml) was prepared as before (Section 3.7.1). It was then irradiated for 2 h at which time no change was occurring and two products (d.r. = 1.1.2) had formed (GC). The solvent was removed under reduced pressure and the remaining mixture (0.54 g) was adsorbed onto silica (40 g). Flash column chromatography (pet. ether/ether, 70/30) gave one of the diastereomers of methyl [(benzyloxy)amino](tetrahydrofuran-2-yl)phenylacetate (**123**), as a clear oil in 16% yield (0.04 g). None of the other diastereomer was isolated.

#### Methyl [(benzyloxy)amino](tetrahydrofuran-2-yl)phenylacetate (**123**)



**IR**  $\nu_{\max}$  (cm<sup>-1</sup>): 3271 (NH), 1728 (C=O), 1139, 1066 and 1024 (CO), 731 and 696 (monosubstituted Ar). **<sup>1</sup>H-NMR** ( $\delta$ ): 1.28 and 1.57 (ms, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.57 1.79-1.91 (overlapping ms, 2H, CHCH<sub>2</sub>CH<sub>2</sub>), 3.36 (q,  $J_{\text{gem}} = J_{\text{cis}} = J_{\text{trans}} = 7.2$  Hz, 1H, OCHHCH<sub>2</sub>), 3.60 (q,  $J_{\text{gem}} = J_{\text{cis}} = J_{\text{trans}} = 7.1$  Hz, 1H, OCHHCH<sub>2</sub>), 3.70 (s, 3H, OCH<sub>3</sub>), 4.54 (s, 2H, OCH<sub>2</sub>Ph), 4.68 (t,  $J_{\text{cis}} = J_{\text{trans}} = 7.4$  Hz, 1H, CH), 6.42 (s, 1H, NH), 7.03-7.35 (overlapping ms, 10H, 10 × Ar-H). **<sup>13</sup>C-NMR** (ppm): 172.6 (C=O), 137.6 (Ar<sub>ipso</sub>CH<sub>2</sub>), 136.6 (Ar<sub>ipso</sub>), 128.5, 128.4, 128.1, 127.9, 127.8 and 127.7 (Ar-C), 82.0 (CH), 76.6 (OCH<sub>2</sub>Ph), 74.0 (C), 69.2 (OCH<sub>2</sub>CH<sub>2</sub>), 52.5 (OCH<sub>3</sub>), 24.3 (CHCH<sub>2</sub>CH<sub>2</sub>), 22.5 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>). **HRMS (ESI)** calcd. for C<sub>20</sub>H<sub>23</sub>NO<sub>4</sub>Na [M+Na]<sup>+</sup>: 364.1525; found: 364.1520.

### 3.15.3 Photochemical reaction of methyl (2*E*)-[(benzyloxy)imino](phenyl)acetate (**81**) with cyclopentane

A solution of methyl (2*E*)-[(benzyloxy)imino](phenyl)acetate (0.20 g, 0.7 mmol), benzophenone (0.13 g, 0.7 mmol) and cyclopentane (4.90 g, 70.0 mmol) in MeCN (40 ml) was prepared as before (Section 3.7.1) and was then irradiated for 4 h at which time no change was occurring (GC). The solvent was removed under reduced pressure and analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated partial *E/Z* photoisomerisation had occurred (*E/Z* = 2.8/1), but that no addition products had formed. The NMR data for the mixture corresponded to those of pure (**81**) and (**82**).

### 3.15.4 Photochemical reaction of methyl (2*E*)-[(benzyloxy)imino](phenyl)acetate (**81**) with 2-propanol

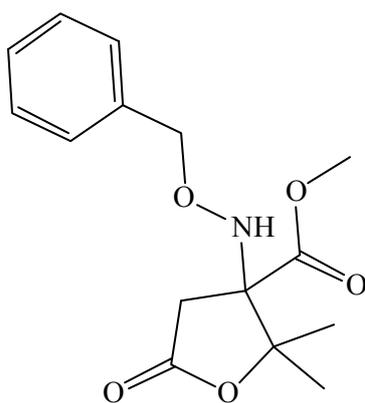
A solution of methyl (2*E*)-[(benzyloxy)imino](phenyl)acetate (0.20 g, 0.7 mmol), benzophenone (0.13 g, 0.7 mmol) and 2-propanol (4.20 g, 70.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). It was then irradiated for 3 h at which time no change was occurring (GC). The solvent was removed under reduced pressure and analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated that partial *E/Z* photoisomerisation had occurred (*E/Z* = 2.4/1), but that no addition products had formed.

### 3.16 Photochemical reactions of 1,4-dimethyl (2*E*)-2-[(benzyloxy)imino]butandioate (**83**)

#### 3.16.1 Photochemical reaction of 1,4-dimethyl (2*E*)-2-[(benzyloxy)imino]butandioate (**83**) with 2-propanol

A solution of 1,4-dimethyl (2*E*)-2-[(benzyloxy)imino]butandioate (**83**) (0.20 g, 0.75 mmol), benzophenone (0.13 g, 0.75 mmol) and 2-propanol (4.50 g, 75.0 mmol) in MeCN (40 ml) was prepared as before (**Section 3.7.1**). The solution was then irradiated for 2 h at which time all the benzophenone had dimerized (NMR). The solvent was removed under reduced pressure and the remaining mixture (0.41 g) was adsorbed onto silica (30 g). Flash column chromatography (pet. ether/ether, 100/0 to 50/50) gave the product, methyl 3-[(benzyloxy)amino]-2,2-dimethyl-5-oxotetrahydrofuran-3-carboxylate (**124**), as a clear oil in 27% yield (0.06 g).

#### Methyl 3-[(benzyloxy)amino]-2,2-dimethyl-5-oxotetrahydrofuran-3-carboxylate (**124**)



**IR**  $\nu_{\max}$  (cm<sup>-1</sup>): 3269 (NH), 1779 (lactone C=O), 1736 (ester C=O), 1176, 1135 and 1028 (CO), 726 and 698 (monosubstituted Ar). **<sup>1</sup>H-NMR** ( $\delta$ ): 1.24 (s, 3H, CH<sub>3</sub>), 1.39 (s, 3H, CH<sub>3</sub>), 2.83 (d, *J* = 18.0 Hz, 1H, C(O)CHH), 3.32 (dd, *J* = 18.0 Hz, and *J* = 2.2 Hz, 2H, C(O)CHH), 3.77 (s, 3H, OCH<sub>3</sub>), 4.64 and 4.71 (ds, *J* = 11.9 Hz, 2H, OCH<sub>2</sub>Ph), 6.23 (d, *J* = 2.2 Hz, 1H, NH), 7.27-7.34 (ms, 5H, 5 × Ar-H). **<sup>13</sup>C-NMR** (ppm): 173.4 and 170.5 (C=O), 136.6 (Ar<sub>ipso</sub>), 128.8, 128.6 and 128.3 (Ar-C), 84.8 (C(CH<sub>3</sub>)<sub>2</sub>), 77.6 (OCH<sub>2</sub>Ph), 73.1 (NC), 53.1 (OCH<sub>3</sub>), 35.6 (CH<sub>2</sub>), 25.0 and 20.6 (2 × CH<sub>3</sub>). **HRMS (ESI)** calcd. for C<sub>15</sub>H<sub>19</sub>NO<sub>5</sub>Na [M+Na]<sup>+</sup>: 316.1161; found: 316.1170.

### **3.17 Photochemical reactions of alternative imines**

#### **3.17.1 Photochemical reaction of ethyl[(1E)-phenylmethylene]carbamate (84) and 2-propanol**

A solution of ethyl[(1E)-phenylmethylene]carbamate (**84**) (0.20 g, 1.1 mmol), benzophenone (0.10 g, 0.55 mmol) and 2-propanol (6.60 g, 110 mmol) in MeCN (40 ml) was prepared as before (**Section 2.6.1**). It was then irradiated for 1 h at which time the starting material had reacted (GC). GC analysis indicated that no product peaks had formed and analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated the formation of a complex mixture of products.

#### **3.17.2 Photochemical reaction of ethyl[(1E)-phenylmethylene]carbamate (84) and THF**

A solution of ethyl[(1E)-phenylmethylene]carbamate (**84**) (0.20 g, 1.1 mmol), and benzophenone (0.10 g, 0.55 mmol) in THF (40 ml) was prepared as before (**Section 2.6.1**). It was then irradiated for 15 min at which time the starting material had reacted (GC). GC analysis indicated that no product peaks had been formed and analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated the formation of a complex mixture of products.

#### **3.17.3 Photochemical reaction of 4-methyl-N-[(1E)-phenylmethylidene]benzene-1-sulfonamide (45) and THF**

A solution of 4-methyl-N-[(1E)-phenylmethylidene]benzene-1-sulfonamide (**45**) (0.10 g, 0.38 mmol) and benzophenone (0.07 g, 0.38 mmol) in THF (40 ml) was prepared as before (**Section 2.6.1**). It was then irradiated for 30 min at which time the starting material had reacted and GC analysis indicated that no product peaks had formed. Analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated the formation of a complex mixture of products.

#### **3.17.4 Photochemical reaction of 4-methyl-N-[(1E)-phenylmethylidene]benzene-1-sulfonamide (45) and 2-propanol**

A solution of 4-methyl-N-[(1E)-phenylmethylidene]benzene-1-sulfonamide (**45**) (0.20 g, 0.7 mmol), benzophenone (0.12 g, 0.7 mmol) and 2-propanol (4.20 g, 70 mmol) in MeCN (40 ml) was prepared as before (**Section 2.6.1**). It was then irradiated for 1 h at which time the starting material had reacted (GC). Analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated that a complex mixture of products had formed.

### ***3.17.5 Photochemical reaction of 4-methyl-N-[(1E)-phenylmethylidene]benzene-1-sulfonamide (45) and 1,3-dioxolane***

A solution of 4-methyl-N-[(1E)-phenylmethylidene]benzene-1-sulfonamide (**45**) (0.20 g, 0.7 mmol), benzophenone (0.12 g, 0.7 mmol) and 1,3-dioxolane (5.18 g, 70 mmol) in MeCN (40 ml) was prepared as before (**Section 2.6.1**). It was then irradiated for 1 h at which time the starting material had reacted (GC). Analysis of the <sup>1</sup>H-NMR spectrum of the crude product indicated that it was a complex mixture of products.

### ***3.18 Tetrabutylammonium decatungstate (TBADT) mediated reactions***

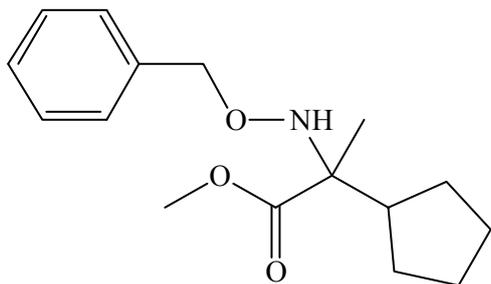
#### ***3.18.1 Synthesis of TBADT<sup>[36]</sup>***

Sodium tungstate dihydrate (16.0 g, 48.5 mmol) was added to boiling H<sub>2</sub>O (100 ml). The solution was quickly acidified with 3M HCl (34 ml) with rapid stirring. Tetrabutylammonium bromide (6.40 g, 19.8 mmol) in water (10 ml) was added after 2 min of stirring. A white precipitate was observed which was vacuum filtered. The precipitate was washed sequentially with boiling water (3 × 40 ml), ethanol (3 × 60 ml) and ether (2 × 100 ml), and was then dried in air to give TBADT (14.95 g, 91% pure UV). Recrystallization in boiling MeCN (9.0 g in 6 ml) gave TBADT as a white powder in 90% yield (97.5% pure, UV); this was used without further purification.

#### ***3.18.2 Photochemical reaction of methyl (2E)-2-[(benzyloxy)imino]propanoate (80) with cyclopentane***

A solution of methyl (2E)-2-[(benzyloxy)imino]propanoate (**80**) (0.20 g, 1.0 mmol), TBADT (66.50 mg, 0.02 mmol) and cyclopentane (1.40 g, 20.0 mmol) in MeCN (20 ml) was prepared as before (**Section 3.7.1**). The solution was then irradiated for 25 h at which time no change was occurring (GC). The TBADT was removed by filtration through neutral alumina (20 g). The solvent was removed under reduced pressure and the remaining mixture (0.21 g) was adsorbed onto silica (30 g). Flash column chromatography (pet. ether/ether, 95/5 to 70/30) gave methyl 2-[(benzyloxy)amino]-2-(cyclopentyl)propanoate (**118**) as a clear oil in 25% yield (0.07 g).

### Methyl 2-[(benzyloxy)amino]-2-(cyclopentyl)propanoate (**118**)



**IR**  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3280 (NH), 1727 (C=O), 1251, 1140 and 1044 (CO), 733 and 696 (monosubstituted Ar).  **$^1\text{H-NMR}$**  ( $\delta$ ): 1.32 (s, 3H,  $\text{CCH}_3$ ), 1.42-1.69 (ms, 8H, cyclopentyl  $\text{CH}_2$ ), 2.00 (m, 1H, CH), 3.69 (s, 3H,  $\text{OCH}_3$ ), 4.65 and 4.72 (ds,  $J = 12.0$  Hz, 2H,  $\text{OCH}_2\text{Ph}$ ), 6.09 (s, 1H, NH), 7.26-7.39 (ms, 5H,  $5 \times \text{Ar-H}$ ).  **$^{13}\text{C NMR}$**  (ppm): 175.9 (C=O), 137.9 ( $\text{Ar}_{\text{ipso}}$ ), 128.5, 128.4 and 127.8 (Ar-C), 77.1 ( $\text{OCH}_2\text{Ph}$ ), 68.0 (C), 52.1 ( $\text{OCH}_3$ ), 45.4 (CH), 27.2, 26.9, 25.5 and 25.3 (cyclopentyl  $\text{CH}_2$ ), 16.8 ( $\text{CH}_3$ ). **HRMS (ESI)** calcd. for  $\text{C}_{16}\text{H}_{24}\text{NO}_3$   $[\text{M}+\text{H}]^+$ : 278.1756; found: 278.1757.

### 3.19 Solar reactions

#### 3.19.1 Photochemical reaction of diethyl [(benzyloxy)imino]malonate (**79**) with 1,3-dioxolane

A solution of diethyl [(benzyloxy)imino]malonate (**79**) (0.10 g, 0.35 mmol), benzophenone (0.03 g, 0.17 mmol) and 1,3-dioxolane (2.59 g, 35.0 mmol) in MeCN (20 ml) was prepared as before (**Section 3.7.1**). The solution was then irradiated in direct sunlight for 1 h at which time all the starting material had reacted (GC). Analysis of the  $^1\text{H-NMR}$  spectrum of the crude product indicated that (**113**) was the only addition product formed. No attempt was made to isolate the product.

#### 3.19.2 Photochemical reaction of diethyl [(benzyloxy)imino]malonate (**79**) with THF

A solution of diethyl [(benzyloxy)imino]malonate (**79**) (0.10 g, 0.35 mmol), benzophenone (0.03 g, 0.17 mmol) and THF (2.52 g, 35.0 mmol) in MeCN (20 ml) was prepared as before (**Section 3.7.1**). The solution was then irradiated in direct for 1 h at which time all the starting material had reacted (GC). Analysis of the  $^1\text{H-NMR}$  spectrum of the crude product indicated that (**114**) was the only addition product formed. No attempt was made to isolate the product.

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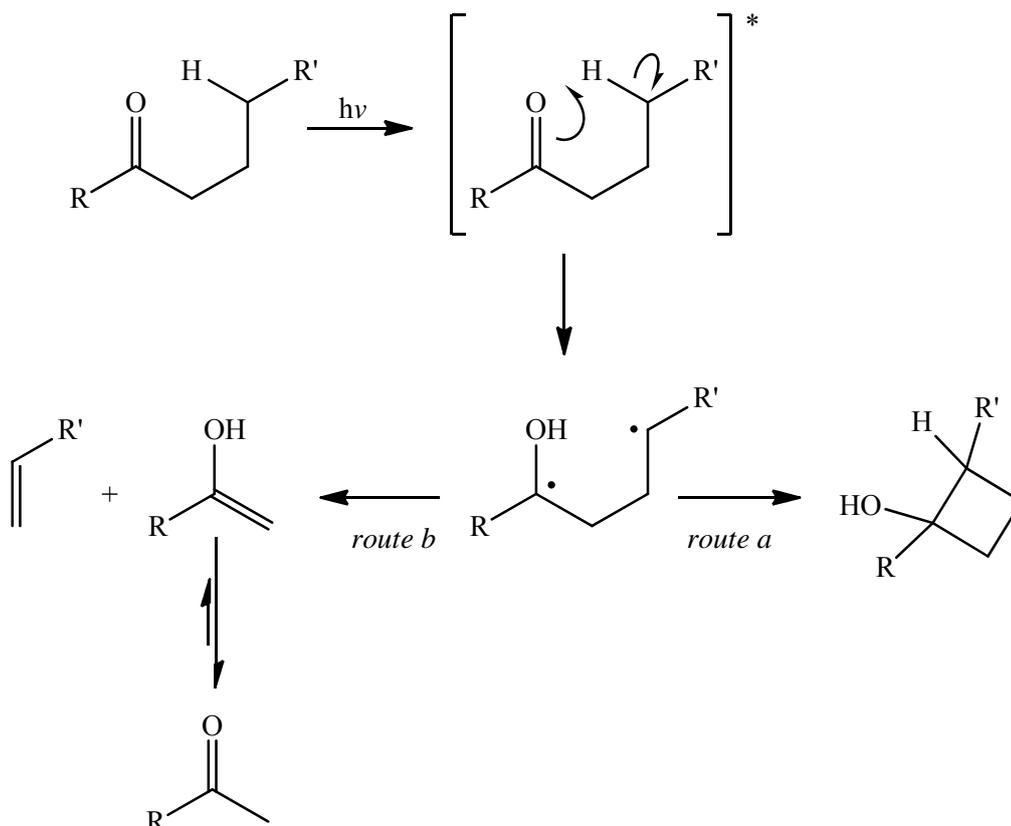
**II. A molecular modeling study of the photochemical [2+2]  
cycloaddition reactions of 6-allyl-cyclohex-2-en-1-ones and 1-allyl-  
naphthalen-2(*H*)-ones**

## 1.1 Introduction

Organic photochemistry is an important tool in the arsenal of a synthetic chemist as it provides a relatively simple method for making highly strained molecules, in particular cyclobutanes, which are not accessible, or are difficult to make, *via* other methods. 1,4-Biradicals are key intermediates in a number of different photochemical processes such as Norrish-Yang cyclizations, Paterno-Buchi reactions and [2+2] enone-alkene cycloadditions. This section of the thesis deals with the concept that biradical conformation control is the key determining factor in the regio- and stereochemical outcome of these reactions. A brief outline of the processes mentioned above is provided below.

## 1.2 Norrish -Yang cyclization

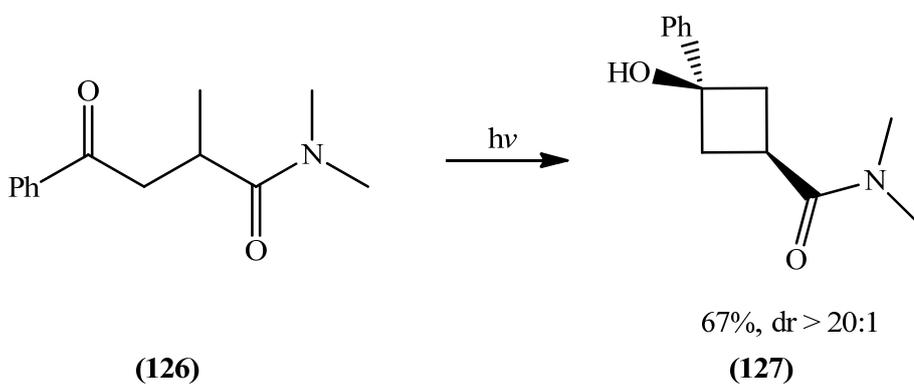
The Norrish-Yang cyclization<sup>[1-2]</sup> involves the irradiation of a molecule which contains a carbonyl group, which once in its excited state intramolecularly abstracts a hydrogen atom from the  $\gamma$ -carbon forming a 1,4-biradical. Two processes can happen from this point: ring closure, forming a cyclobutanol (Norrish-Yang cyclization) (**Scheme 116, route a**), or bond cleavage leading to an alkene and a ketone (Norrish Type II reaction) (**Scheme 116, route b**)<sup>[3]</sup>.



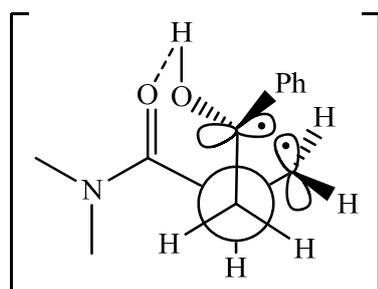
**Scheme 116**

Norrish-Yang cyclizations have been exploited synthetically. Thus Wessig<sup>[4]</sup> showed that irradiation of the  $\gamma$ -ketoamide (**126**) gave the corresponding cyclobutanol product (**127**) in a 67% yield (**Scheme**

**117).** The low rate of Norrish Type II cleavage and the high diastereoselectivity observed was attributed to intramolecular hydrogen bonding in the biradical intermediate between the newly formed hydroxyl group and the carbonyl group of the amide (**Figure 41**). This conformation of the biradical prevents the singly occupied *p*-orbital and the  $\beta$  C-C bond adopting the eclipsed arrangement that is required for cleavage; it also accounts for the *cis* relationship of the amide and hydroxyl groups in the Norrish-Yang product (**127**).

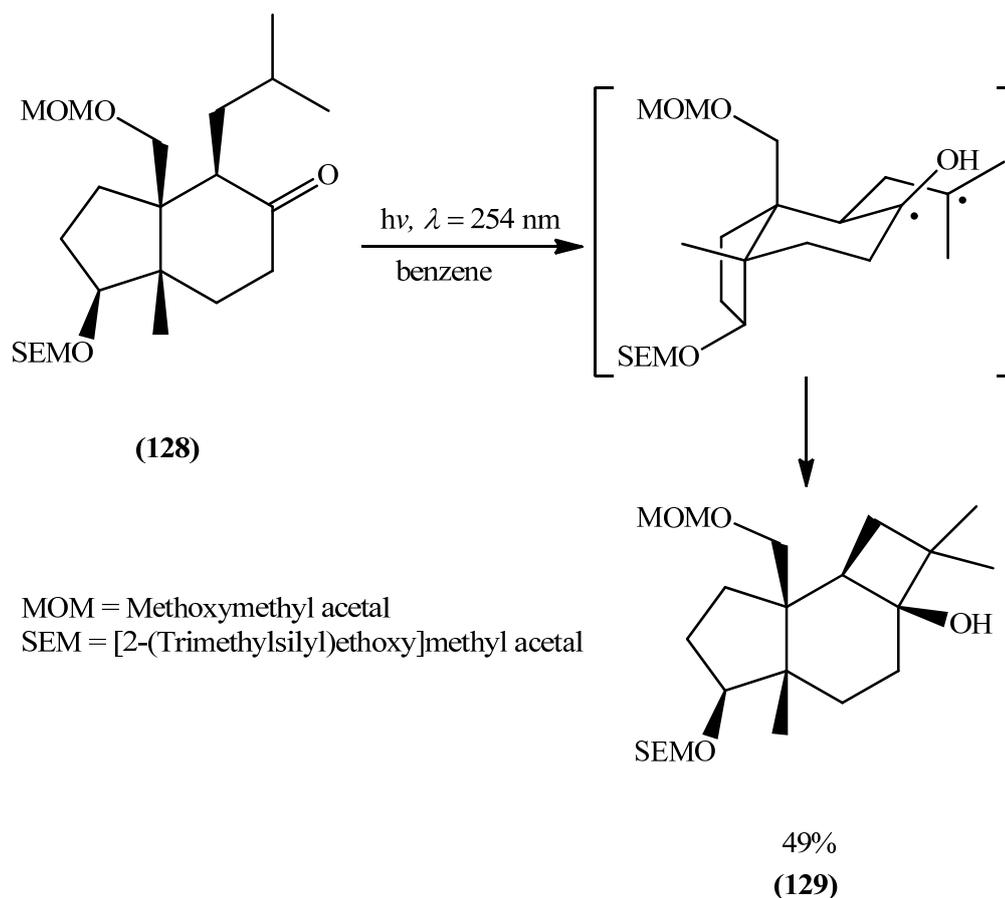


**Scheme 117**



**Figure 41**

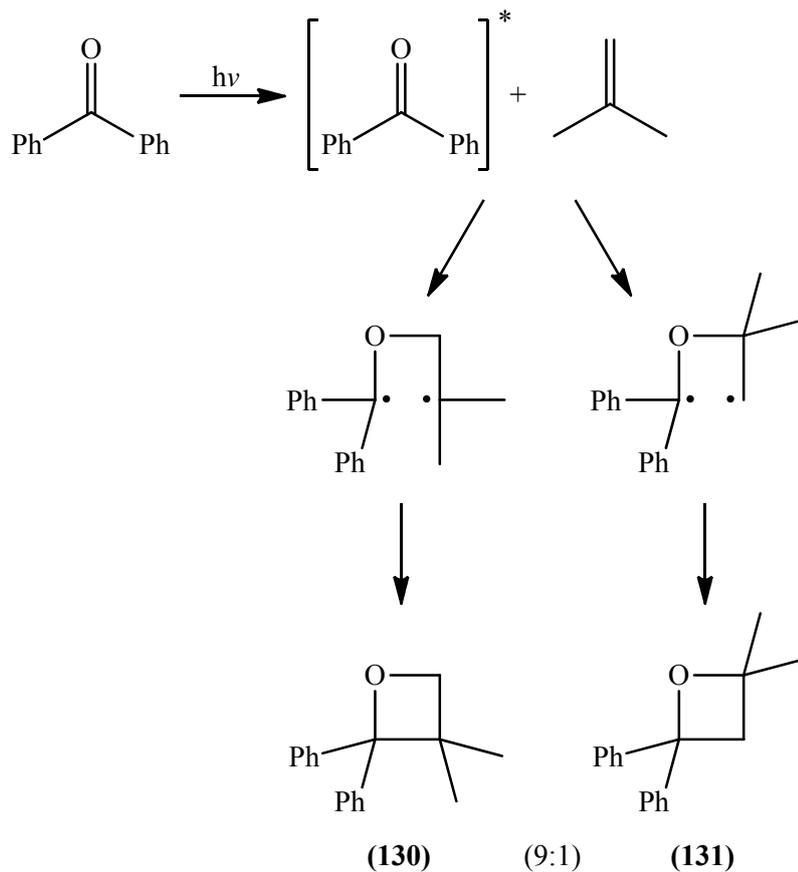
The Norrish-Yang cyclization of **(128)** (**Scheme 118**)<sup>[5]</sup> is a key step in the synthesis of the natural product (-)-punctatin A. The reaction proceeded in 49% yield with only about 20% of the Norrish Type II cleavage products being observed.



Scheme 118

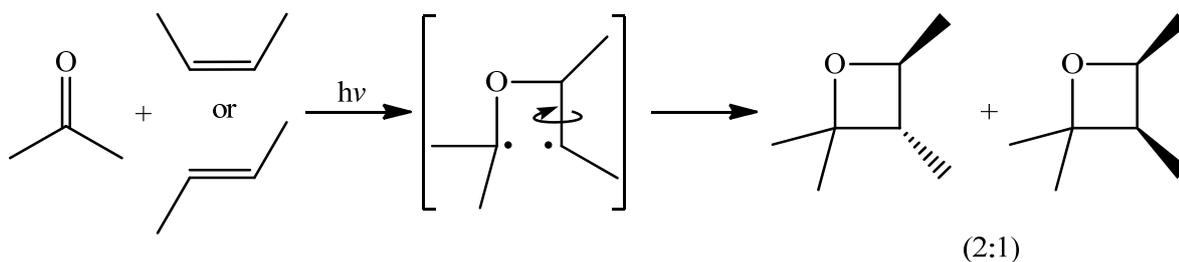
### 1.3 The Paterno-Buchi reaction

The Paterno-Buchi reaction results in the formation of an oxetane ring. The reaction proceeds first by the excitation of an aldehyde, or ketone, to its excited  $S_1$  state. ISC then occurs transferring the molecule to the  $T_1$  state. It is in this state that the carbonyl group, behaving like an alkoxy radical, reacts with a ground state alkene forming the oxetane ring. Thus the reaction of benzophenone and 2-methylpropene (**Scheme 119**)<sup>[6]</sup>, for example, leads to the formation of (**130**) and (**131**) in 93% yield, with the major product being (**130**). The regiochemical outcome of the reaction is dictated by the stability of the 1,4-biradical intermediates formed; the  $3^\circ/3^\circ$  biradical is more stable than the  $3^\circ/1^\circ$  biradical and is thus involved in the formation of the major product.



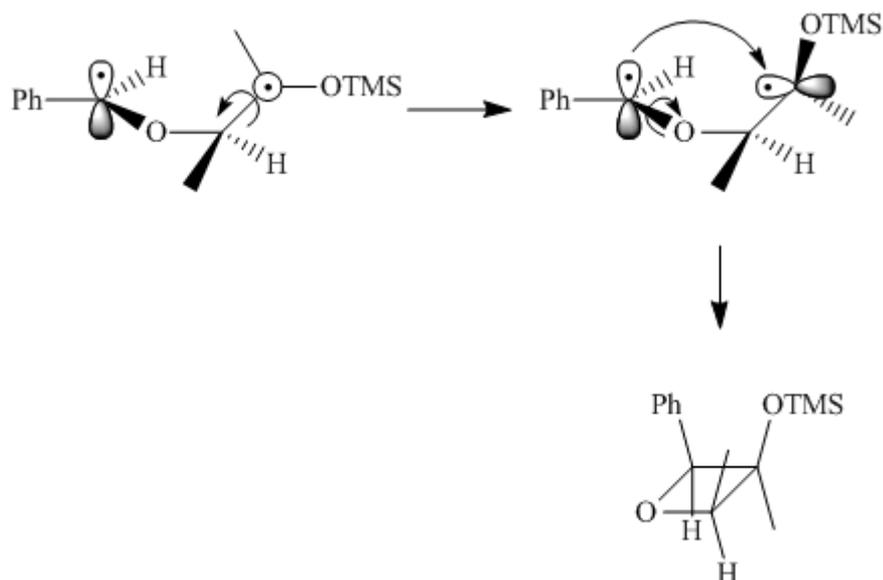
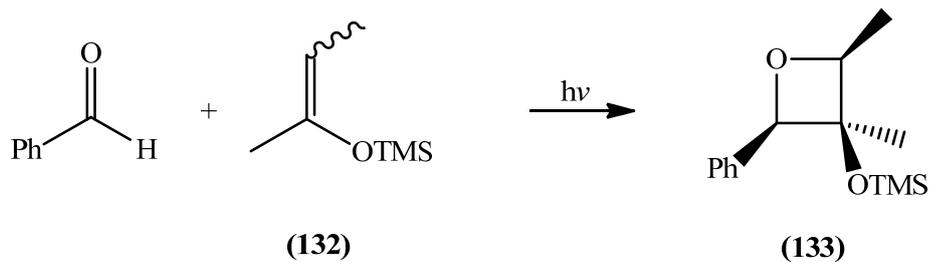
**Scheme 119**

Carless<sup>[7]</sup> investigated the addition of both *cis* and *trans* but-2-ene to acetone. He found that there was a loss of stereochemical ‘memory’ in oxetane formation as the ratio of *cis* and *trans* products was independent of the starting but-2-ene (**Scheme 120**). This supports the idea that a 1,4-biradical is formed as an intermediate, as it would have a sufficiently long lifetime for bond rotation to occur.



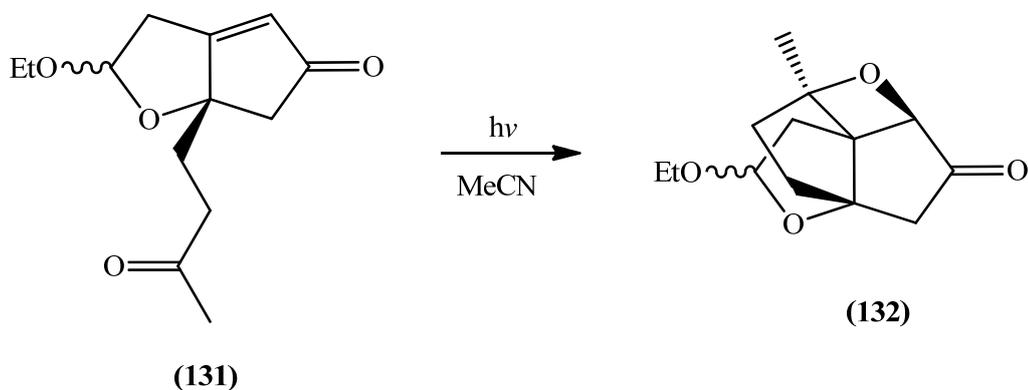
**Scheme 120**

D’Auria<sup>[8]</sup> recently used a frontier orbital approach to account for the stereoselectivity in the reaction of benzaldehyde and the silyl enol ether (**132**) (**Scheme 121**). He carried out DFT calculations on the two possible stereoisomers which can be formed after initial bond formation and concluded that the stereochemistry of the ring closure is controlled by frontier orbital interactions in the lower energy biradical (**Scheme 121**).



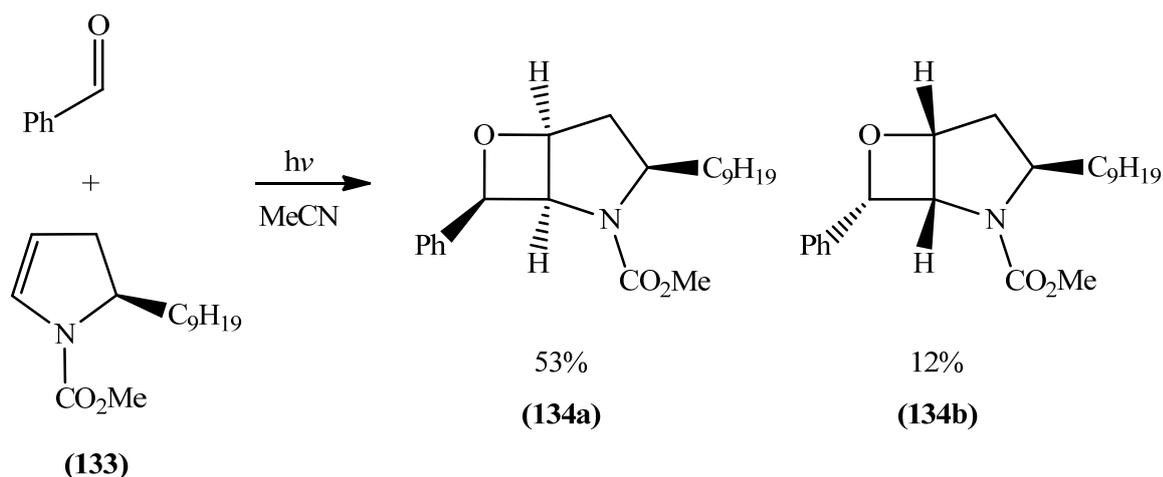
Scheme 119

The potential of Paterno-Buchi reactions as a route to oxetanes has led to many synthetic applications. For example an intramolecular Paterno-Buchi reaction (Scheme 122) was used to construct the core framework of merrilactone A, a naturally occurring molecule isolated from *Illicium mirrillianum* A<sup>[9]</sup>. The bicyclic molecule (131) was irradiated in MeCN, using light of wavelength greater than 300 nm, giving (132) in 93% yield.



Scheme 122

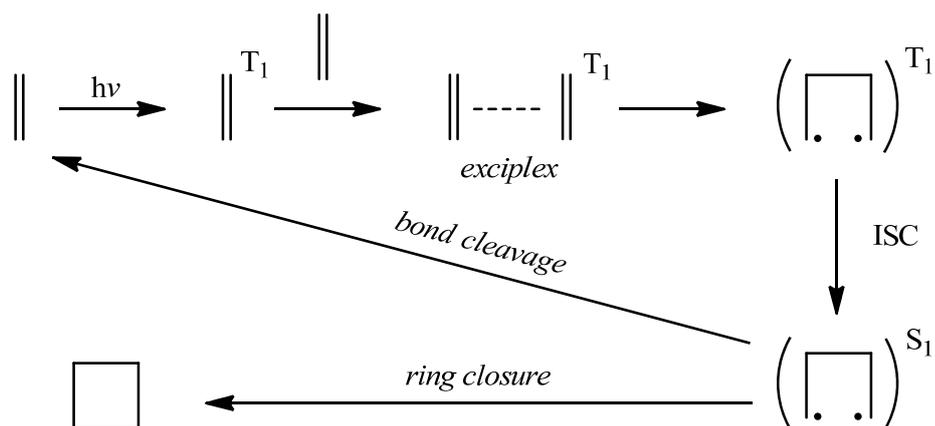
Bach utilised an intermolecular Paterno-Buchi reaction in a short total synthesis of (+)-preussin, an antifungal pyrrolidinol alkaloid (**Scheme 123**)<sup>[10]</sup>. The photochemical reaction of the dihydropyrrole (**133**) and benzaldehyde afforded, (**134a**), (**134b**), and a third product which was not isolated. The major product (**134a**) is not the obvious product as addition occurs on the same face as the nonyl side chain. An argument based on product stability was advanced to account for this and was supported by molecular mechanics calculations which showed a preference for a configuration in which the alkyl chain and the phenyl group were oriented parallel to each other.



**Scheme 123**

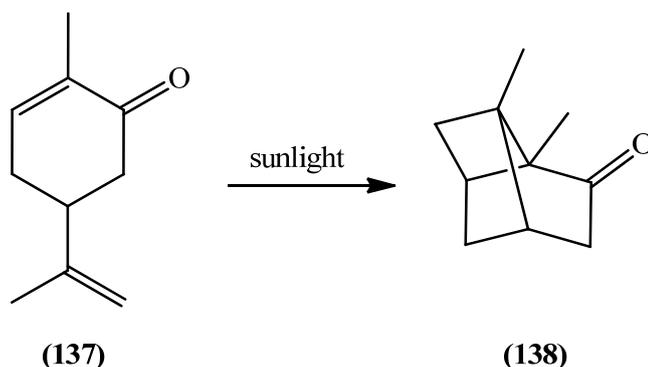
#### 1.4 Enone-alkene cycloadditions

The generally accepted mechanism for [2+2] cycloaddition reactions is sometimes referred to as the “Corey-De Mayo” mechanism (**Scheme 124**)<sup>[11]</sup>. The alkene is irradiated with uv light and is excited to its S<sub>1</sub> state, efficient ISC then putting it into its T<sub>1</sub> state. This excited alkene interacts with an alkene in its ground state forming initially an excited state complex and then a triplet biradical. Once ISC occurs again, and depending on the orientation of the singly occupied orbitals in the biradical, it will undergo ring closure or cleavage.



**Scheme 124**

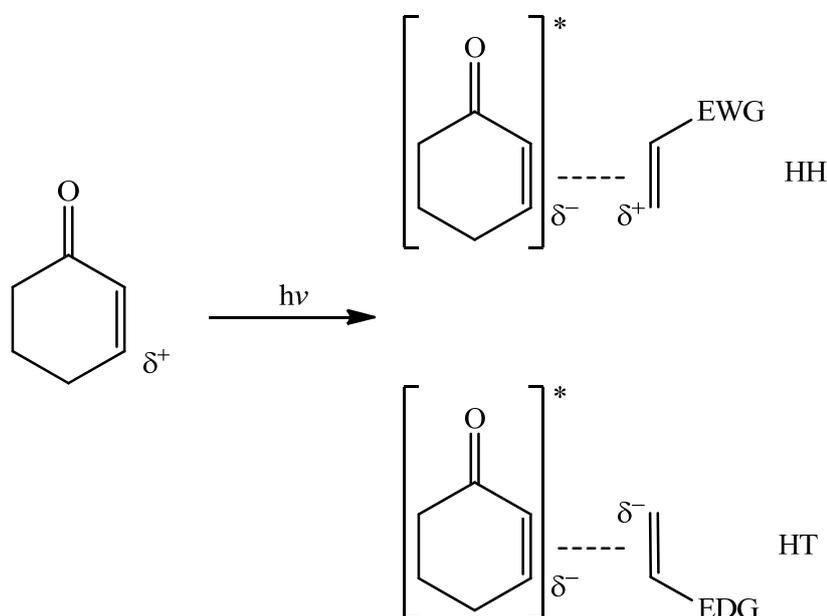
Interestingly, the first example of an enone-alkene cycloaddition was an intramolecular reaction, reported by Ciamician in 1908<sup>[12]</sup>. He observed that carvone camphor (**138**) was obtained by the irradiation of carvone (**137**) in “Italian sunlight” (**Scheme 125**).



**Scheme 125**

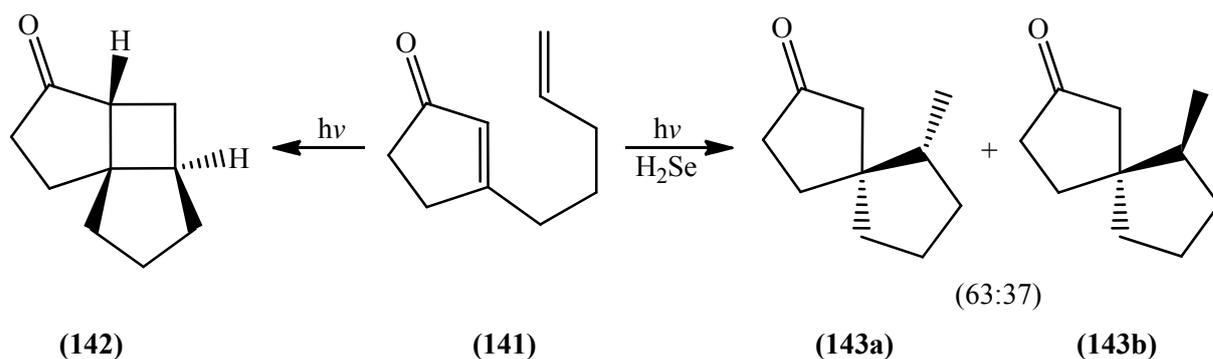
Corey proposed the first version of the “Corey-De Mayo” mechanism for [2+2] cycloaddition reactions in 1964<sup>[13]</sup> after studying the reactions of cyclohexenones with a variety of electron rich and electron deficient alkenes (**Scheme 126**). In terms of regiochemistry he found that electron rich alkenes reacted in a head-to-tail (HT) manner while the electron poor alkenes reacted in a head-to-head (HH) manner. His hypothesis was that the lowest triplet state of the enone had some negative charge on the  $\beta$ -carbon and that a Coulombic interaction between the polarised triplet enone and ground state electron-poor or electron-rich alkenes held the molecule in an excited complex or ‘exciplex’ that accounted for the regiochemistry of the reactions. Although it was believed for many years that [2+2] cycloaddition reactions involved exciplexes, kinetic studies of the reactions of a number of enone systems with various alkenes in different solvents led to a revision of the mechanism<sup>[14]</sup>. It was shown that there was very little difference in the rates of reaction in polar and non-polar solvents. As exciplexes are polar in nature, differences should have been observed in both the rate and/or the product distribution. As this was not observed, the involvement of exciplexes as

intermediates was no longer considered likely. In intramolecular [2+2] cycloaddition reactions, the idea that an exciplex could be involved as an intermediate is particularly unlikely due to strain that would exist within the intramolecular exciplex.



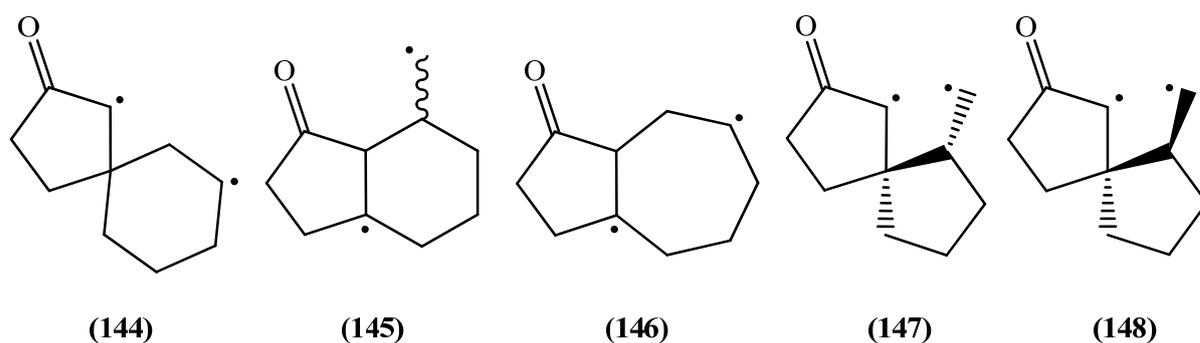
**Scheme 126**

Paralleling Paterno-Buchi reactions, [2+2] cycloadditions lead to the formation of *cis* and *trans* cycloadducts, again suggesting that 1,4-biradicals are also intermediates in [2+2] cycloaddition reactions<sup>[13]</sup>. Following on from this, Bauslaugh<sup>[15]</sup> proposed that the regiochemical outcome of these cycloadditions was dependent on the geometry of the 1,4-biradicals, and their relative rates of cyclization and fragmentation. In an attempt to identify the important 1,4-biradicals in intramolecular [2+2] cycloadditions, Wheedon<sup>[16]</sup> carried out photoreactions in the presence of hydrogen selenide as a radical trap. He irradiated a solution of 3-(4'-pentenyl)cyclopent-2-enone in toluene (**Scheme 127**) forming the tricyclic ketone (**142**). When the reaction was repeated in the presence of hydrogen selenide only the spiroketones (**143a**) and (**143b**) were obtained.



Scheme 127

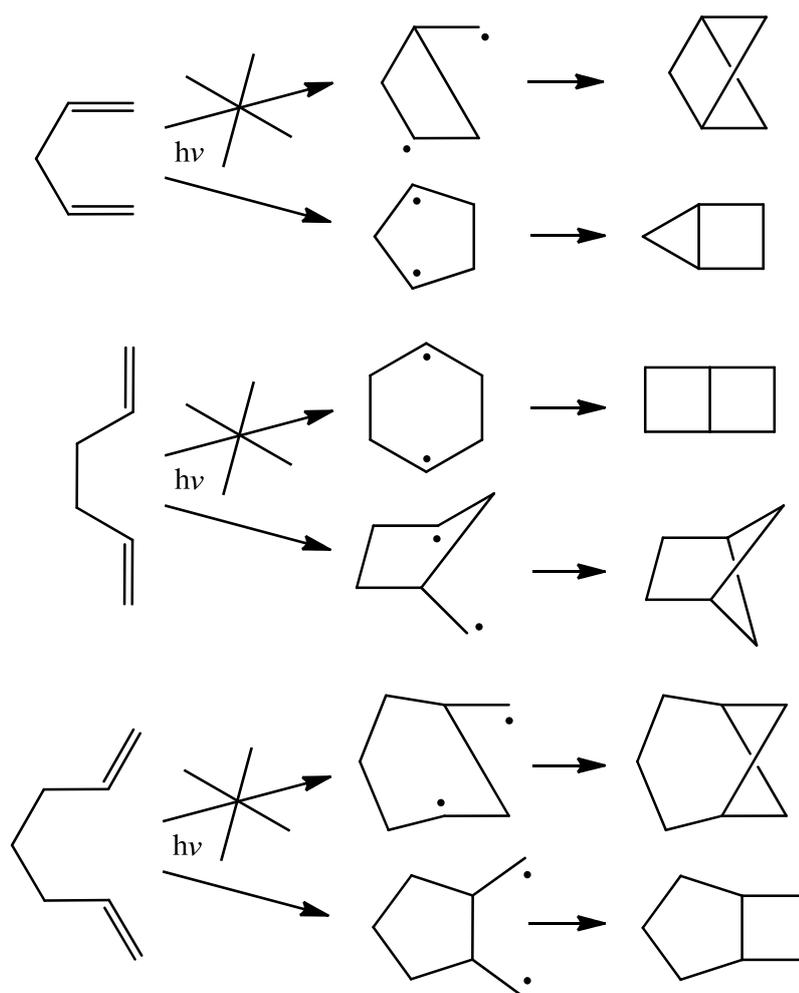
The 1,4-biradicals (144)-(148) could potentially be formed during the photoreaction of (141). As no crossed products were observed in the photoreaction of (141), biradicals (144) and (145) are either not formed, or else revert back completely to starting material. The fact that no structures of this type were isolated when the reactions were carried out in the presence of hydrogen selenide would indicate that they are not formed. Again, as only products derived from the biradicals (147) and (148) were isolated, the biradical (146) is either not formed, or else undergoes bond cleavage at a rate which is too fast for competitive trapping with hydrogen selenide. Wheedon concluded that (147) was the only product forming precursor, as the stereochemistry of biradical (148) does not allow for ring closure and so when formed, this biradical reverts to starting material. In relation to the computational work presented in this thesis, it is important to note that  $1^\circ$  radicals can play an important role in product formation in intramolecular [2+2] cycloaddition reactions. Prior to this work of Weedon, the involvement of  $1^\circ$  radicals in product formation was discounted on the basis that they were too unstable.



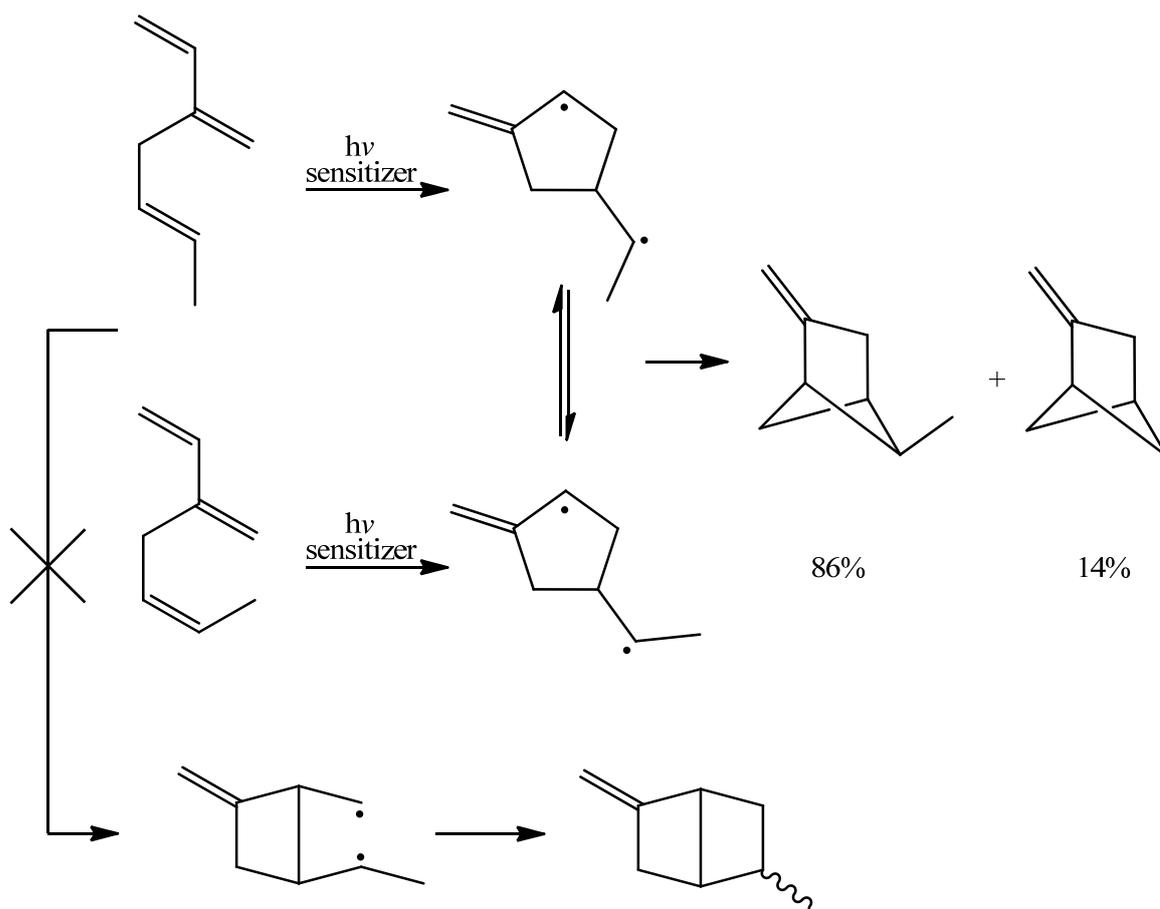
The regiochemistry of intramolecular [2+2] cycloaddition reactions can be predicted using the so called 'rule of five' which states that if possible, product formation will occur *via* a five-membered ring biradical. This rule was first introduced by Srinivasan<sup>[17]</sup> (Scheme 128) and Hammond<sup>[18]</sup> (Scheme 129) after studying the regiochemical outcome of intramolecular cycloaddition reactions of a series of polyenes.

Hammond found that starting from either the *cis* or *trans* isomer of 3-methylene-1,6-heptadiene gave the same ratio of cycloadducts (**Scheme 129**). From this he concluded that a common biradical intermediate was formed which allowed bond rotation about the 5,6 carbon-carbon bond. He felt that the selectivity reflected kinetic control of the first addition step and that the preference for the formation of five-membered rings reflected the fact that the bonding carbon atoms in the 5-membered ring biradical are, on average, closer together than those in the biradical leading to the alternative regioisomeric product<sup>[18]</sup>.

Gleiter<sup>[19]</sup> provided a frontier orbital based explanation for the ‘rule of five’. This analysis suggested that dienes containing an even number of bridging carbons would lead to a crossed product, whereas if there was an odd number of bridging carbons, a parallel product would be formed. The frontier orbital analysis which underpins this approach is based on the concept that exciplexes play a pivotal role in the alignment of the alkene units. The fact that exciplexes are now not considered to play a role in [2+2] cycloadditions eliminates this frontier orbital approach as a theoretical basis for the empirical rule of five.



**Scheme 128**

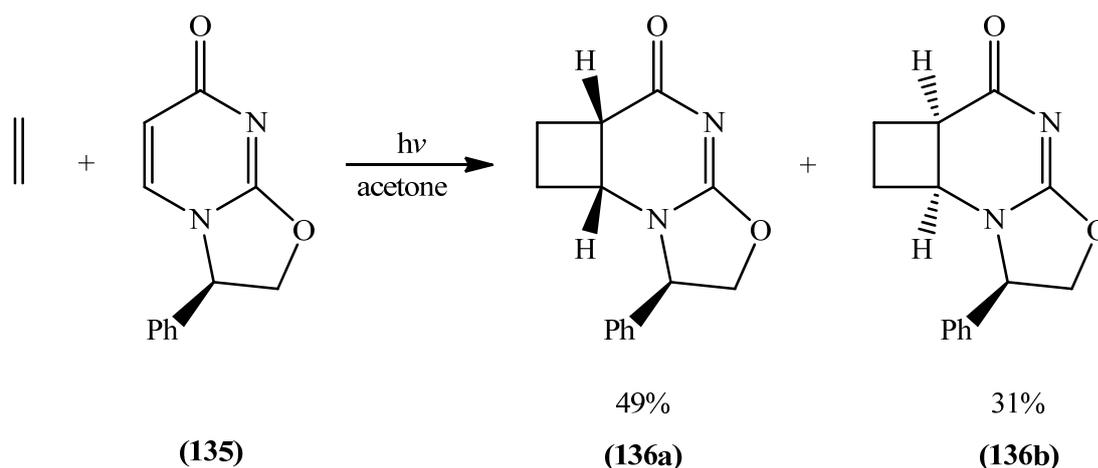


**Scheme 129**

Spin orbital coupling (SOC) is an important factor in the efficiency of ISC of a biradical from its  $T_1$  to  $S_0$  state. Carlacci et al<sup>[20]</sup> and Michle<sup>[21]</sup> have shown that a  $90^\circ$  angle between the singly occupied orbitals is important for efficient ISC to occur. While this is an important factor in ISC it may not help to predict the outcome of the [2+2] cycloaddition reaction. The orientation of the molecule may allow for efficient ISC to occur, however, it may not be orientated for ring closure and so when this efficient ISC occurs cleavage will predominate.

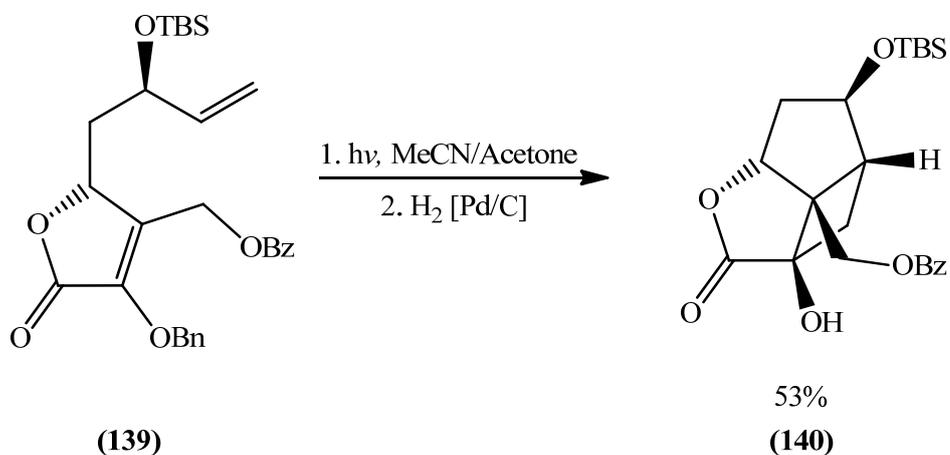
A similar observation was made by Griesbeck<sup>[22]</sup> and Kutateladze<sup>[23]</sup> in relation to the rate and efficiency of ISC in Paterno Buchi reactions.

Cyclobutane formation is probably the most widely used photochemical reaction in terms of organic synthesis. Thus for example, a key step in the synthesis of 2-aminocyclobutane-1-carboxylic acids was the [2+2] photocycloaddition of ethylene and the chiral uracil derivative (**135**) (**Scheme 130**)<sup>[24]</sup>. The reaction was carried out by bubbling ethylene through a solution of (**135**) in acetone while irradiating it with a 400W medium-pressure mercury lamp fitted with a Pyrex filter. This led to a mixture of products (**136a**) and (**136b**) in yields of 49 and 31%, respectively.



**Scheme 130**

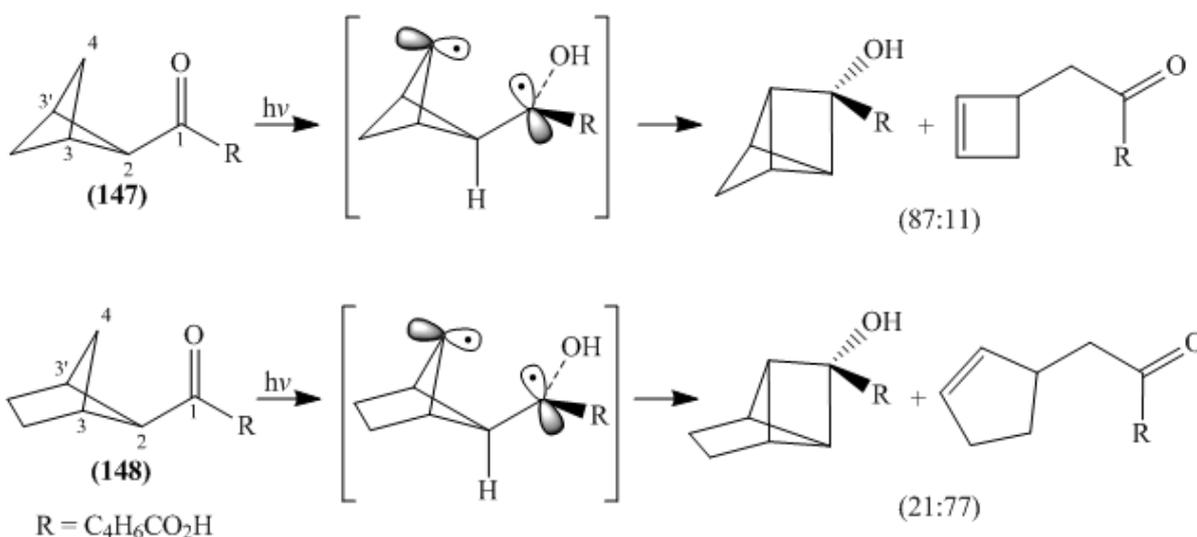
A recent example of the use of an intramolecular [2+2] photocycloaddition as a key step in the total synthesis of a natural product is provided by Bach (**Scheme 131**)<sup>[25]</sup>. He used this method to construct the tricyclic core of (+)-lactiflorin. The photochemical reaction of (139) went to completion in 2 h when acetone was used as a co-solvent and gave a mixture of regioisomers (parallel/crossed  $\approx$  75:25). As these regioisomers proved to be inseparable, hydrogenolysis of the benzyl ether was undertaken, after which chromatography gave the parallel product (140) as a single diastereomer in 53% yield over the two steps.



**Scheme 131**

### 1.6 Biradical conformation control

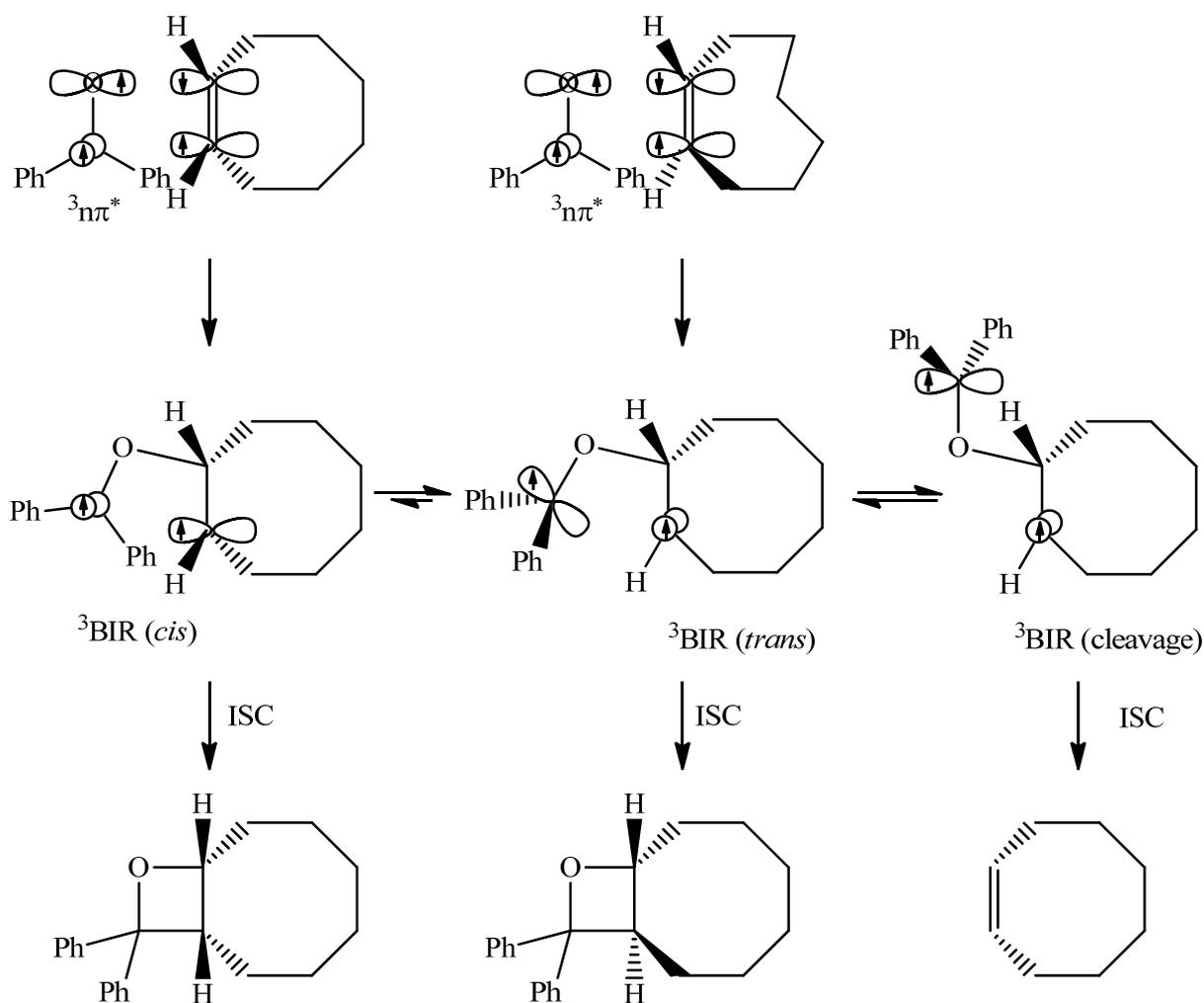
Biradical conformation control is based on the concept that the spatial relationship of the singly occupied orbitals in the intermediate biradical is an important factor in deciding the regiochemical outcome of [2+2] cycloaddition reactions<sup>[26-28]</sup>, as it determines whether the biradical will undergo bond cleavage, reforming starting material, or ring closure forming a cyclobutane. This concept has also been applied in the context of other photochemical reactions. In an attempt to obtain qualitative data pertaining to the  $\beta$ -cleavage ring closure ratio in Norrish/Yang reactions, Scheffer<sup>[27]</sup> investigated the solid state photochemical reactions of (147) and (148) (Scheme 132). He found that for (147) the ring closure product predominated, whereas for (148)  $\beta$ -cleavage was the major pathway. By measuring the angle between the singly occupied orbital on C1, and the C2-C4 vector and the angle between the singly occupied orbital on C4 and the C2-C3 bond, he found that in the case of (147) the singly occupied orbital on C1 was better aligned for ring closure as there was a small angle between the singly occupied orbital on C1, and the C2-C4 vector. In the case of (148), the angle between the singly occupied orbital on C4 and the C2-C3 bond was small leading to the cleavage products predominating.



Scheme 132

Adam<sup>[26]</sup> investigated the Paterno-Buchi reaction of benzophenone with *cis* and *trans* isomers of cyclooctene (Scheme 133) and observed an unusual temperature dependent diastereoselectivity. In the reaction of benzophenone with *cis*-cyclooctene, as the temperature increased from -95 °C to 110 °C, the *trans*-oxetane cycloadduct is increasingly favoured. In the reaction of benzophenone with *trans*-cyclooctene, however, as the temperature is increased the *trans* geometry is retained and only at temperatures of 60 °C is a small amount (up to 10%) of the *cis*-cycloadduct observed. Adam concluded that the conversion between <sup>3</sup>BIR (*cis*) and <sup>3</sup>BIR (*trans*) is kinetically hindered and thus,

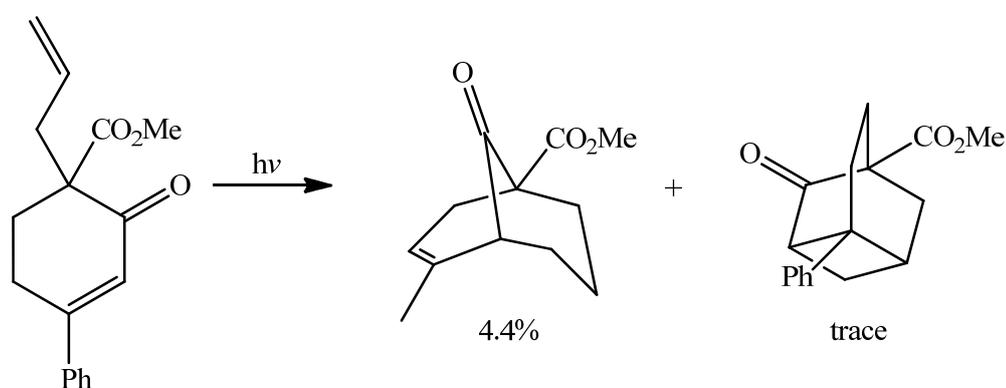
temperature dependent. The conformer  $^3\text{BIR}$  (*cis*) is higher in energy due to the unfavourable orientation of the phenyl ring and the eclipsed interactions in the cyclooctyl ring. The  $^3\text{BIR}$  (*trans*) conformer is much less hindered and so after ISC the *trans*-oxetane is the preferred photoproduct at higher temperatures for *cis*-cyclooctene, and at all temperatures for *trans*-cyclooctene. A third biradical conformer was proposed to account for the *trans* to *cis* isomerisation also observed in these reactions. The conformer  $^3\text{BIR}$  (cleavage), where the radical centres assume an antiperiplanar arrangement, are not set up for bond formation and so cleavage occurs reforming the less strained *cis*-cyclooctene product.



**Scheme 133**

The biradical conformation control concept has also been successfully utilized in predicting the outcome of a series of intramolecular enone-ene cycloaddition reactions which fail to follow the “rule of five”. Geraghty *et al*<sup>[28]</sup> studied the photochemical reactions of a series of 6-alkenyl-3-phenylcyclohex-2-ones and undertook a molecular modelling study of all the possible 1,4-biradical intermediates. This involved the use of conformational searching and B3LYP/6-31G\* DFT

calculations to determine the energy and structure of all potentially important biradicals, and the identification of the product forming biradical on the basis that the formation of high energy biradicals will not be competitive, and that of the possible low energy biradicals, the one with the most suitably orientated singly occupied orbitals will be product forming. The approach successfully accounted for the change in regioselectivity that occurs when the length of the methylene chain linking the alkene bonds is altered. The calculations were performed on the biradicals in the triplet state, as further conformational relaxation is unlikely to occur following ISC, due to the very short life of the singlet biradical. The importance of various other structural parameters of the biradicals, such as the interradical distance was also considered, but the molecular modelling studies clearly showed that biradical energy and the orientation of the singly occupied orbitals were the key product determining factors.



**Scheme 134**

In addition to successfully accounting for the regiochemical outcome of the [2+2] cycloaddition reactions, this molecular modelling approach also provided an explanation of why in some cases the biradicals underwent hydrogen abstraction rather than cyclobutane formation. The irradiation of 1,3-phenyl-6-(2'-propenyl)cyclohex-2-en-1-one, for example, led to the formation of the hydrogen abstraction product and only trace amounts of the cycloadduct (**Scheme 134**). The major weakness of those results presented is that the products were isolated in low yields, in some cases as low as 4.4%, with polymerization of the starting materials being the major reaction pathway. This lessens the validity of these results as a demonstration of the importance of the biradical conformation control.

It was subsequently found<sup>[29]</sup> however that simple 6-alkenylcyclohex-2-en-1-ones gave [2+2] cycloadducts in very high, and in some cases almost quantitative yield. Molecular modelling studies of the possible 1,4-biradicals formed have now been undertaken with a view to evaluating the use of biradical conformation control in accounting for the regiochemical and stereochemical outcome of these reactions, and the results are presented in this thesis. A brief outline of the relevant aspects of molecular modelling is provided below.

## ***1.7 Molecular Modelling***

Molecular modelling is a very useful tool for analysing and visualising chemical structures. It has been used to predict the behaviour of molecules and the outcome of reactions, and to study intermediates which by their nature are too unstable to be studied experimentally. In relation to this work, molecular modelling is used to determine the energy, conformation and distribution of different 1,4-biradicals, information about which is impossible to obtain experimentally due to their short lifetimes. In 1959 Dreiding introduced scaled hand-held models which allowed people to visualise molecules in 3-D. Ten years later, space-filling Corey-Pauling-Koltun (CPK) models were introduced which allowed people to see how much space molecules occupied. While these models are useful they cannot be used to determine most of the important physical properties of a chemical system. With the development of faster, more powerful computers virtual models can provide information not only about the structures but also about the energies of molecules. As a result of this molecular modelling is becoming an increasingly important tool in understanding all aspects of organic chemistry.

### ***1.7.1 Molecular mechanics***

Molecular mechanics (MM) involves a mathematical model which represents a molecule as a set of balls and springs that correspond to its atoms and bonds, respectively; it is based on Newtonian mechanics. The energy of the molecule is closely related to the geometry as the springs resist being over stretched (or compressed) from their natural length or angle, and the balls seek to avoid being forced too close together. The MM approach involves expressing the energy of a molecule as a function of its resistance to bond bending or stretching, or atom overcrowding. As the electrons are not considered specifically, electronic properties such as charge distribution cannot be calculated using molecular mechanics<sup>[30]</sup>. For a given system, the energy of different conformations is calculated to obtain the minimum energy conformation. This structure optimisation (energy minimisation) procedure will eventually find an energy minimum corresponding to a low energy conformation<sup>[31]</sup>. Molecular mechanics is often used to locate a low energy structure which is then used as a starting point for quantum mechanical calculations. One of the advantages that it enjoys relative to quantum mechanical methods is that it can be successfully used with molecules containing thousands of atoms.

### 1.7.2 Quantum mechanics

On a fundamental level, quantum mechanics (QM) deals with the movement of electrons in atoms or molecules under the influence of electromagnetic forces exerted by nuclear charges<sup>[32]</sup>. As was stated previously, molecular mechanics calculations ignore the role of electrons when calculating the characteristics of a molecule. QM models explicitly incorporate electrons into the model using the Schrödinger equation, and are thus inherently more realistic.

First proposed in 1925 the Schrödinger equation provides a means for describing the behaviour of electrons in a molecule, but can only be solved for one electron systems such as a hydrogen atom. For the equation to be a useful tool, certain approximations have to be introduced to account for multiple electron systems. Brief descriptions of the most important approximations are as follows<sup>[33]</sup>:

**Born-Oppenheimer Approximation:** This approximation assumes that nuclei, compared to electrons, are static. Nuclei of course, are not static, just moving much more slowly than electrons. However by fixing the position of the nuclei in this way, the Schrödinger equation can be simplified allowing systems of more than one electron to be studied. The internal energy of a molecule can be calculated by adding the solution of the Schrödinger equation to the internuclear repulsion.

**Hartree-Fock Approximation:** This assumes that the electrons move independently of one another. In practice, electrons are believed to move in molecular orbitals which are established by assuming that the electron is moving within an average field due to all the surrounding electrons.

**Linear Combination of Atomic Orbitals Approximation:** Molecules are constructed from atoms and so it is reasonable to assume that molecular orbitals are made from atomic orbitals belonging to the atoms in the molecules. The Hartree-Fock approximation gives a set of equations, each involving coordinates for a single electron. The Linear Combination of Atomic Orbitals approximation (LCAO) transforms the set of single electron equations into an algebraic form which describes the electronic structure of the molecule.

The application of these approximations provides a starting point for most of the quantum models commonly employed to determine the properties of molecules. A brief summary of some of these models is provided below.

### **1.7.2.1 *Ab initio* methods**

The term, *ab initio* means “from the beginning” in Latin and refers to the fact that these methods do not involve any empirical or semi-empirical parameters in their equations, but are derived straight from theoretical principals. The simplest kind of *ab initio* calculation is the Hartree-Fock calculation, a method implemented by selecting a so-called “basis set” which consists of the mathematical functions necessary to construct the atomic orbitals which when combined form the molecular orbitals<sup>[34]</sup>. The Hartree-Fock approach provides a solution to the Schrödinger equation by replacing actual electron-electron interactions with the interaction between a single electron and the average field created by all the other electrons<sup>[33]</sup>.

### **1.7.2.2 *Semi-empirical* methods**

Semi-empirical methods are simplified versions of the Hartree-Fock model, which combine the use of both theory and experimental data. To reduce the number of computational operations the calculations are restricted to the valence electrons and these are again represented by basis sets. Semi-empirical methods reduce the overall computation time by assuming there is no overlap between atomic orbitals of different atomic centres, thus simplifying the evaluation of electron repulsion terms. Some commonly used methods are AM1 and PM3, with the AM1 method, in conjunction with a Monte-Carlo conformational search technique, being one of the computational methods used in this work.

### **1.7.2.3 *Density Functional Theory***

Density Functional Theory (DFT) models are used to determine the electronic structure of matter in terms of electron density instead of molecular wavefunctions. Electron density has the advantage of being an experimentally measurable quantity, unlike a wavefunction, and can be calculated by X-ray or electron diffraction techniques. Electron density models are based on three spatial variables while a wavefunction is based on four variables, three spatial and one spin coordinate for every electron. Thus, while the complexity of the wavefunction increases with the number of electrons, the electron density will have the same number of variables, irrespective of the size of the system<sup>[33]</sup>.

DFT is based on work published in 1964 by Hohenburg and Kohn<sup>[35]</sup> and in 1965 by Kohn and Sham<sup>[36]</sup>. Hohenburg and Kohn developed, then proved two theorems that are implemented using the so-called Kohn-Sham equations. The first Hohenburg-Kohn theorem states that all the properties of a molecule in a ground electronic state are determined by the ground state electronic density. The second theorem states that any electron density calculation must give an energy greater than, or equal to, the true energy of the molecule.

The Kohn-Sham equations are used to express the ground state electronic energy as the sum of the electrons' kinetic energy, their Coulombic interaction, the electron-nuclear interaction energy, and the exchange-correlation energy<sup>[33]</sup>. Of these components, only the kinetic energy does not depend on the electron density. Regrettably, the calculation also involves an unknown exchange/correlation functional which effectively is a rule that transforms a function into a number, and this can only be approximated. Nevertheless, DFT calculations are among the most successful quantum mechanical approaches available.

### ***1.7.3 Conformational searching***

When a molecule is optimized to a low energy structure, there is no way of knowing if the structure is a local or global low energy form. One way to solve this problem is to use conformational searching to find all the low energy forms of a molecule. In general there are two main methods of achieving this. Systematic methods are used for molecules with only a small amount of conformational freedom as finding the low energy forms involves folding rings and rotating around bonds one at a time. The alternative semi-random, or Monte Carlo method finds a low energy conformer, then randomly changes the conformation to generate a different starting geometry for a second optimization. The result of the second optimization is compared to that of the first: if the energy of the second structure is greater by a pre-determined amount than that of the first, the second structure is dumped. If the situation is reversed, the first structure is dumped. If the second structure is the same as the first it is again dumped. A new starting geometry is then generated and the process continues. Overall this generates a set of low energy forms in an energy window above that of the global minimum. The process stops when the repeated calculations fail to generate any new low energy forms. This approach involves a large number of calculations but is an efficient way of locating all low energy conformations. As a result of the large number of calculations required, these must be based on molecular mechanics or semi-empirical quantum mechanical methods; *ab initio*, Hartree-Fock and density functional methods cannot be used. For larger molecules this is the method used as systematic methods are impractical.

### ***1.8 Aims of the project***

The aim of the project was to use the biradical conformation control concept to account for the regio- and stereochemical outcome of a series of intramolecular [2+2] enone-ene cycloaddition reactions which had previously been carried out in Galway<sup>[29]</sup> and which occurred in very high yield. This involved analysis of the cycloadditions in terms of the structures and relative energies of the biradicals potentially involved.

*Chapter 2*  
*Results and Discussion*

## 2.1 Key concepts

The purpose of the work described here is to determine whether the biradical conformation control principle can account for the behaviour of anti-“rule of five” 6-alkenylcyclohex-2-en-1-ones and 1-allyl-naphthalen-2(*H*)-ones. The photocycloaddition reactions of a series of 6-alkenylcyclohex-2-en-1-ones were carried out and the structure of the products determined (**Table 23**)<sup>[29]</sup>. This involved the irradiation of 0.3 M solutions of enone in methanol through pyrex using 350 nm lamps in a Rayonet reactor. The reactions were monitored by GC, with the exception of the reactions involving (**155**), (**156**) and (**157**) which were followed by NMR and IR spectroscopies. The products were isolated by flash chromatography and the structures were assigned on the basis of their NMR and IR spectra.

Photocycloaddition reactions involving 1-allyl-naphthalen-2(*H*)-ones which were previously published by Geraghty<sup>[37]</sup> were also investigated in the same manner (**Table 35**).

Molecular modelling calculations were carried out using Spartan '06 (Wavefunction Inc., Irvine, CA, 2006) and Spartan '10 (Wavefunction Inc., Irvine, CA, 2010). A Monte Carlo based semi-empirical AM1 calculation was used to obtain the low energy conformer(s) for each of the biradicals. The lowest energy conformer(s) were then further refined using a DFT (B3LYP/6-31G\*) optimization which provided the energy and spin density overlap values which determine whether a particular biradical was involved in cycloadduct formation.

The core principle in the work described in this thesis is that the regiochemical and stereochemical outcome of intramolecular [2+2] cycloaddition reactions is determined by the behaviour of the 1,4-biradical intermediates involved. The evidence from trapping studies<sup>[16]</sup> is that all possible biradicals, including those involving 1° radicals, may be involved in cycloadduct formation. In terms of the Hammond postulate the formation of the 1,4-biradicals will involve a late biradical-like transition state which will be closer in energy to the biradical than the starting material. As a result, the formation of high energy biradicals will not be competitive with that of lower energy biradicals and they will not have the opportunity to play a product determining role in cycloadduct formation. The stereoelectronically based biradical conformation control principle suggests that of the possible low energy biradicals, the product will be formed *via* that, or those, whose structure(s) holds the singly occupied *p*-orbitals in a bond forming orientation. The work presented here is based on the idea that the level of interaction between the singly occupied orbitals can be evaluated on the basis of the electron density value at which overlap between these orbitals occurs; the existence of spin density overlap (SDO) at a high electron density value is an indication of a high level of interaction and thus of an orbital orientation which on stereoelectronic grounds is likely to be bond forming. Low energy biradicals in which the singly occupied *p*-orbitals are not orientated in this way will undergo bond cleavage and reform starting material.

Table 23 Photocycloadditions of 6-alkenylcyclohex-2-en-1-ones

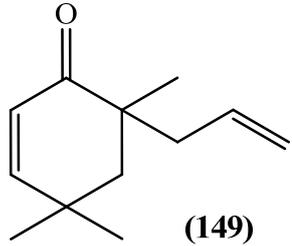
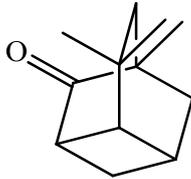
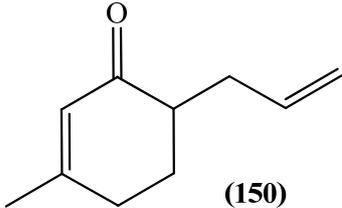
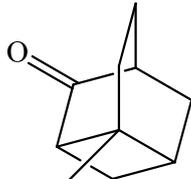
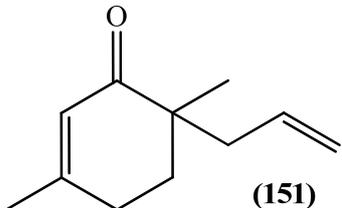
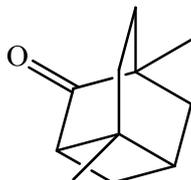
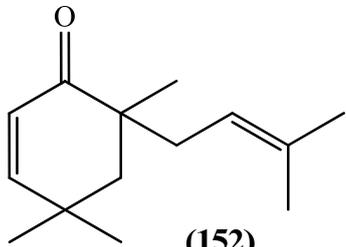
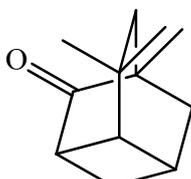
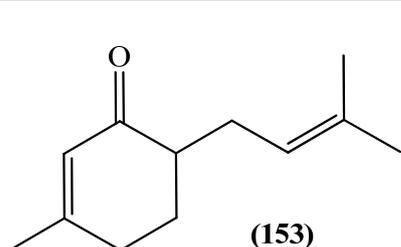
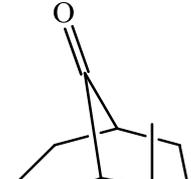
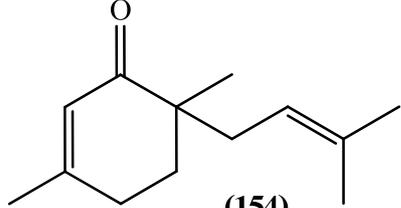
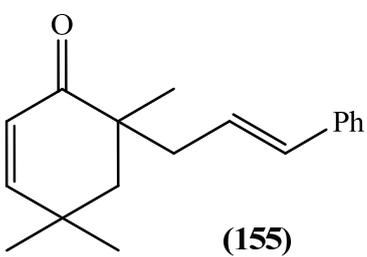
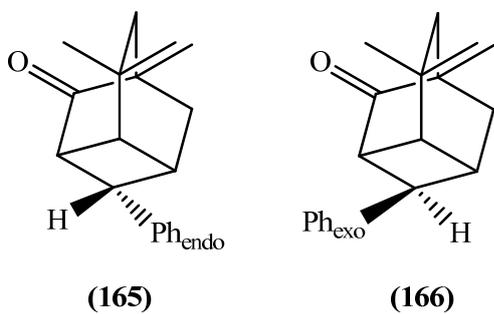
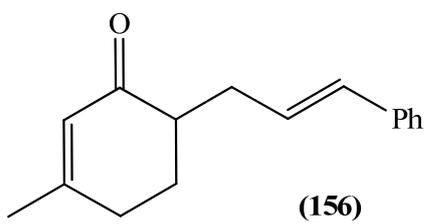
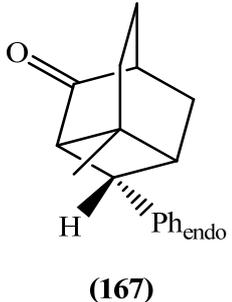
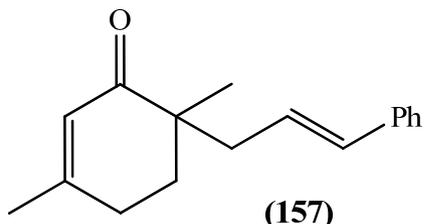
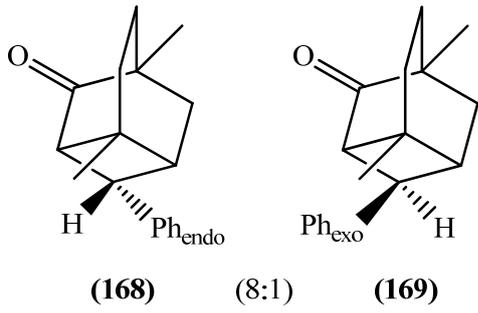
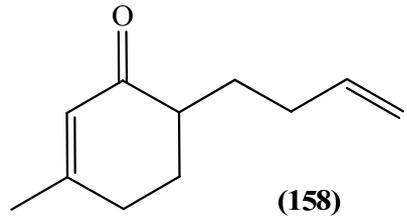
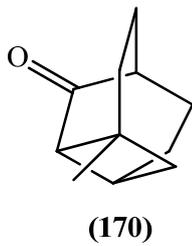
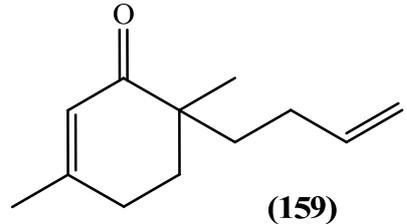
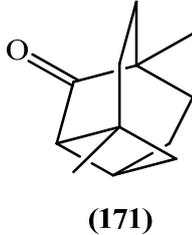
Enone	Time	Product	Yield
 <p>(149)</p>	20 h	 <p>(160)</p>	84%
 <p>(150)</p>	9 h	 <p>(161)</p>	90%
 <p>(151)</p>	13 h	 <p>(162)</p>	89%
 <p>(152)</p>	28 h	 <p>(163)</p>	91%
 <p>(153)</p>	72 h	 <p>(164)</p>	4%
 <p>(154)</p>	72 h	complex mixture	-

Table 23 (contd.) Photocycloadditions of 6-alkenylcyclohex-2-en-1-ones

Enone	Time	Product	Yield
 <p>(155)</p>	16 h	 <p>(165) (166)</p>	<p>165 53%</p> <p>166 46%</p>
 <p>(156)</p>	16 h	 <p>(167)</p>	94%
 <p>(157)</p>	16 h	 <p>(168) (8:1) (169)</p>	168 73%
 <p>(158)</p>	0.5 h	 <p>(170)</p>	95%
 <p>(159)</p>	1.5 h	 <p>(171)</p>	96%

## 2.2 Intramolecular [2+2] cycloaddition reactions of 6-alkenyl-2-cyclohexene-1-ones

### 2.2.1 Intramolecular [2+2] cycloaddition of 6-allyl-6,4,4-trimethyl-2-cyclohexene-1-one (149)

Irradiation of the enone (**149**) leads to the formation of the anti-“rule of five” adduct (**160**) in 84% yield (**Table 23**). AM1 based conformational searching identified unique low energy conformations for the 1°/2° parallel, the 1°/2° crossed and the 2°/2° crossed biradicals, and two low energy forms for the parallel 2°/2° biradical (**Table 24**). The term ‘parallel’ and ‘crossed’ are used when referring to the orientation of the alkene subunits when they align for initial bond formation in the different biradicals. The term parallel is used when the alkene subunits align in a head to head fashion while the term crossed is used when they align in a head to tail manor. The 2°/2° crossed biradical is the lowest in energy but due to its low spin density overlap (SDO) ( $9.5 \times 10^{-4}$  electrons/au<sup>3</sup>) (**Figure 42**), it is not considered to be product forming. The involvement of the 1°/2° crossed biradical in product formation is also ruled out as its relative energy is too high and so its formation will not be competitive. This analysis suggests that the reaction will give an anti-“rule of five” product, probably *via* the 1°/2° parallel biradical which has the lowest relative energy and has the highest SDO ( $3.80 \times 10^{-3}$  electrons/au<sup>3</sup>) (**Figure 43**) of the parallel biradicals (**Table 24**).

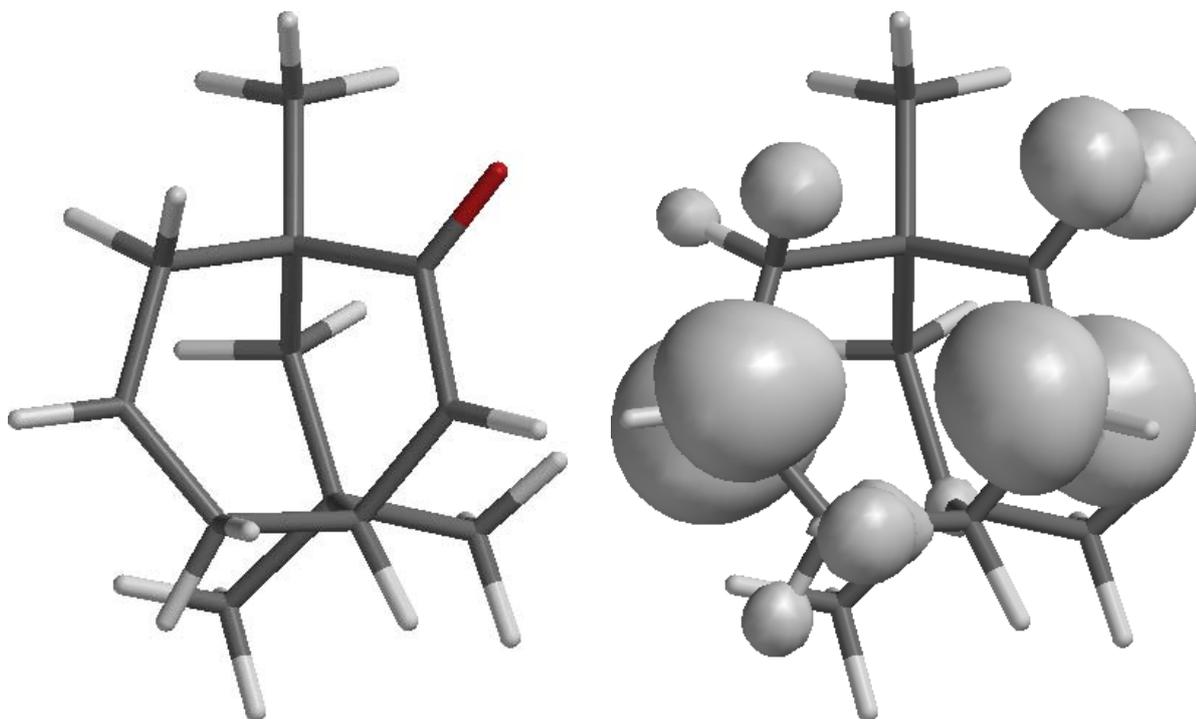


Figure 42

**Table 24** Computational results for biradicals obtained from 6-allyl-6,4,4-trimethyl-2-cyclohexene-1-one (**149**)

	1°/2° parallel	2°/2° parallel (a)	2°/2° parallel (b)	1°/2° crossed	2°/2° crossed
Relative energy (kJ mol <sup>-1</sup> )	15.4	28.2	28.2	65.0	0.0
Spin density overlap <sup>a</sup>	3.80×10 <sup>-3</sup>	3.40×10 <sup>-3</sup>	2.67×10 <sup>-3</sup>	3.80×10 <sup>-3</sup>	9.50×10 <sup>-4</sup>
IRD (Å) <sup>b</sup>	3.00	3.15	3.12	3.08	3.15
IPA <sup>c</sup>	54.4	82.3	84.1	78.2	129.8
Cleavage angle <sup>d</sup>	11.9/29.7	53.6/15.6	60.1/4.7	57.3/27.1	68.8/11.4
Radical/ $\alpha$ -H distance (Å) <sup>e</sup>	No short radical/ $\alpha$ -H distances				
Singlet biradical optimization <sup>f</sup>	S M	S M	S M	“rule of five” product	S M
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )	 0.0 kJ mol <sup>-1</sup> <b>(160)</b>			 15.0 kJ mol <sup>-1</sup>	
Experimental result	anti-“rule of five” product <b>(160)</b> formed				

<sup>a</sup> The electron density value (electrons/au<sup>3</sup>) at which overlap between the singly occupied orbitals begins, <sup>b</sup> Inter-radical distance, <sup>c</sup> Angle between the planes to which the singly occupied orbitals are orthogonal, <sup>d</sup> Torsion angle between the initially formed carbon-carbon bond and the singly occupied orbitals. If the radical is non planar an average torsion angle is provided, <sup>e</sup> The distance between one carbon radical and a hydrogen  $\alpha$  to the other radical, <sup>f</sup> The structure resulting when the optimised structure of the biradical in the triplet state is re-optimised as a singlet biradical.

A number of other structural parameters were considered. The interradical distances (IRD) (**Table 24**) for all the low energy biradicals are very similar (3.00-3.15 Å) and thus this parameter is not product determining. It has been suggested that the angle between the singly occupied orbitals, which is equal to the angle between the central planes of the singly occupied orbitals (IPA), can be used as an indicator of orbital interaction and a “90° rule” has been advanced as a method of identifying a product forming biradical<sup>[38]</sup>. In this regard it is worth noting that the interplanar angle (IPA) (**Table 24**) values for the 2°/2° parallel orbitals, 82.3 and 84.1° most closely approximate the ideal 90° angle. However, overall the IPA has to be viewed as a crude indicator of orbital interaction, a feature that is more accurately reflected by an SDO value. Once formed it is the closure/cleavage ratio for a particular biradical which determines whether it will be product forming. The analysis provided above takes a positive view of whether a biradical is likely to undergo ring closure on the basis of its SDO value. It is however possible that the regiochemical and stereochemical outcome of the reaction is determined by the fact that certain biradicals undergo efficient bond cleavage reforming the starting material. A co-planar relationship of the initially formed carbon-carbon bond and one (or both) of the singly occupied orbitals would allow for efficient cleavage of the biradicals. The torsion angle between these structural features, in this work referred to as the “cleavage angle” (CA), provides an indication of how well they approximate a co-planar relationship, a value of 0° corresponding to perfect co-planarity. Analysis of the computational data obtained for the biradicals derived from (**149**) (**Table 24**) does not suggest that the size of the cleavage angle is an important product determining parameter, with only the 2°/2° parallel (b) biradical involving a particularly small cleavage angle (4.7°). At best this provides another reason, in addition to its SDO value, why this biradical is not product forming despite the fact that on the basis of energy its formation should be competitive.

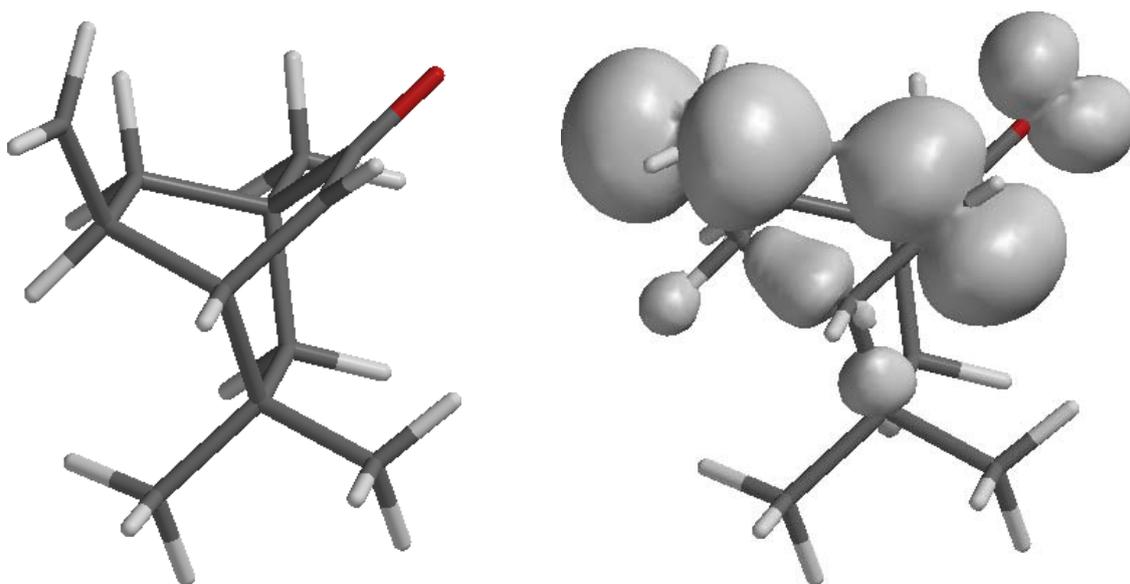


Figure 43

Previous studies<sup>[28]</sup> have shown that a short distance between one carbon radical and a hydrogen  $\alpha$  to the other carbon radical (Radical/ $\alpha$ -H distance, **Table 24**) can open up another reaction channel for the biradicals, hydrogen abstraction. This parameter was thus evaluated in the course of the computational work, but in the case of **(149)** none of the biradicals involve a short radical/ $\alpha$ -H distance and so hydrogen abstraction products are neither expected nor obtained. The mechanistic model on which this computational analysis is based involves biradical formation and conformational relaxation, ISC to a singlet biradical, and ring closure or bond cleavage which is so rapid that further conformational relaxation is not possible. An attractive possibility is that energy minimization/structure optimisation algorithm used by Spartan might mimic the process by which a singlet biradical forms either a cycloadduct or a hydrogen abstraction product, or reverts back to starting material. If so, the identification of a possible product forming triplet biradical followed by optimization of the structurally identical biradical as a singlet, might provide a very direct method of predicting the outcome of the reaction. Unfortunately in the case of **(149)** there is no correlation between the outcome of the reaction and of the optimization of the singlet biradicals, as with one exception all the low energy singlet biradicals revert to starting material on optimization. Interestingly the highest energy biradical (at least in the  $T_1$  state) the  $1^\circ/2^\circ$  crossed biradical, optimizes to the “rule of five” regioisomer which is not formed on irradiation of **(149)**.

### 2.2.2 Intramolecular [2+2] cycloaddition of 6-allyl-3-methyl-2-cyclohexene-1-one (150)

Irradiation of the enone (**150**) leads to the formation of the anti-“rule of five” adduct (**161**) in 90% yield (**Table 23**). Conformational searching identified unique low energy conformations for the  $1^\circ/2^\circ$  parallel, the  $1^\circ/2^\circ$  crossed and the  $2^\circ/2^\circ$  crossed biradicals, and two low energy forms for the parallel  $2^\circ/3^\circ$  biradical (**Table 25**). The  $2^\circ/2^\circ$  crossed biradical has the lowest energy but its SDO ( $7.3 \times 10^{-4}$  electrons/au<sup>3</sup>) (**Figure 44**) is too small for ring closure to occur. In terms of product forming potential, the  $1^\circ/3^\circ$  crossed biradical can also be discounted as its relative energy is too large for its formation to be competitive. This means that cycloadduct formation involves the parallel biradicals, again leading to the formation of the anti-“rule of five” product (**161**). All three parallel biradicals could be considered to be product forming; however the most likely candidate is the  $2^\circ/3^\circ$  parallel (b) biradical as it has the highest SDO ( $3.02 \times 10^{-3}$  electrons/au<sup>3</sup>) and a relative energy that is low energy enough for competitive formation to occur. Considering the other structural parameters, the IRD values are again very similar (3.05-3.20 Å) and don't provide a basis for predicting the reaction outcome. Interestingly the biradical which emerges as the most likely to be product forming, the  $2^\circ/3^\circ$  parallel (b) biradical, is also that with an IPA  $87.5^\circ$ , which is closest to that preferred by the “ $90^\circ$  rule”. The CA is again not particularly helpful, the only clear cut conclusion being that the value of  $3.7^\circ$  for the  $1^\circ/2^\circ$  parallel biradical rules it out as a likely product forming intermediate. The short radical/ $\alpha$ -H distance in  $2^\circ/3^\circ$  parallel (a) biradial is presumably responsible for why optimization of the corresponding singlet biradical leads to the hydrogen abstraction product. However it would appear that this channel, even if available, is only competitive if cycloadduct formation is disfavoured by poor SDO value which is not the case here. Interestingly in this case optimization of the singlet form of the  $2^\circ/3^\circ$  parallel (b) biradical does result in the experimentally observed anti-“rule of five” product (**161**).

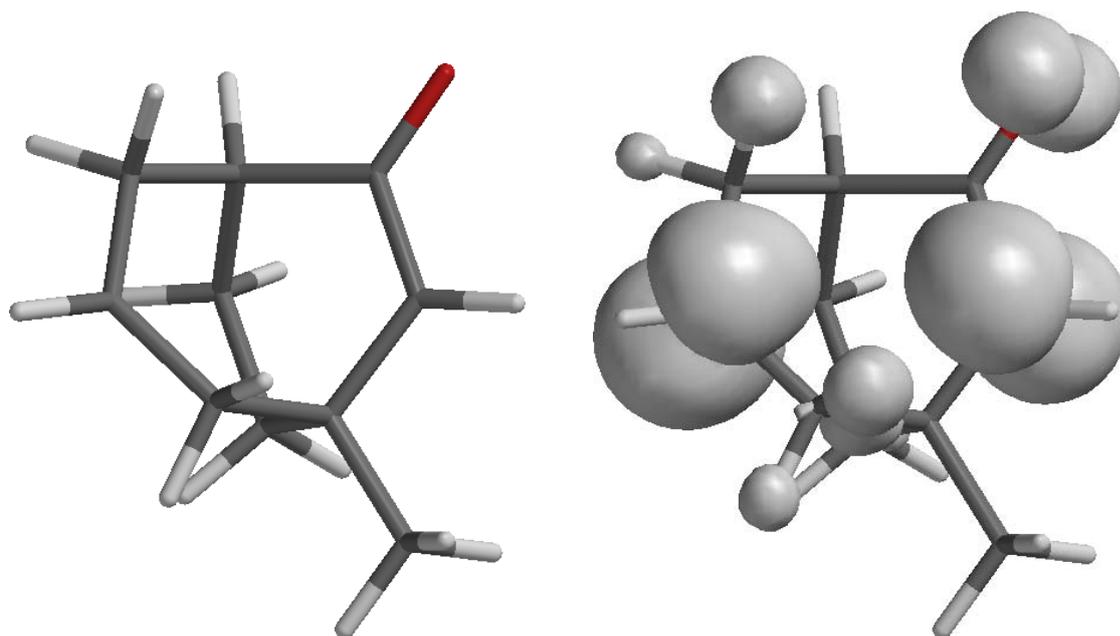


Figure 44

**Table 25\*** Computational results for biradicals obtained from 6-allyl-3-methyl-2-cyclohexene-1-one (150)

	1°/2° parallel	2°/3° parallel (a)	2°/3° parallel (b)	1°/3° crossed	2°/2° crossed
Relative energy (kJ mol <sup>-1</sup> )	19.3	8.1	19.1	46.9	0.0
Spin density overlap	2.78×10 <sup>-3</sup>	1.85×10 <sup>-3</sup>	3.02×10 <sup>-3</sup>	4.23×10 <sup>-3</sup>	7.3×10 <sup>-4</sup>
IRD (Å)	3.08	3.14	3.20	3.03	3.18
IPA	57.8	80.3	87.5	59.1	134.5
Cleavage angle	3.7/32.4	9.6/58.6	55.5/11.4	13.7/30.8	64.3/14.8
Radical/ $\alpha$ -H distance (Å)		2.73			
Singlet biradical optimization	S M	H-abs	anti-“rule of five” product	S M	S M
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )	 0.0 kJ mol <sup>-1</sup> <b>(161)</b>			 2.1 kJ mol <sup>-1</sup>	
Experimental result	anti-“rule of five” product <b>(161)</b> formed				

\* See **Table 24** for glossary of terms

### 2.2.3 Intramolecular [2+2] cycloaddition of 6-allyl-3,6-dimethyl-2-cyclohexen-1-one (151)

Irradiation of the enone (**151**) leads to the formation of the anti-“rule of five” adduct (**162**) in 89% yield (**Table 23**). Conformational searching identified individual low energy conformations for the  $1^\circ/2^\circ$  parallel and the  $2^\circ/2^\circ$  crossed biradicals, and two low energy conformations for both the  $2^\circ/3^\circ$  parallel and the  $1^\circ/3^\circ$  crossed biradicals (**Table 26**). The  $2^\circ/2^\circ$  crossed biradical has the lowest energy but its SDO ( $8.3 \times 10^{-4}$  electrons/au<sup>3</sup>) does not allow for ring closure. Both  $1^\circ/3^\circ$  crossed biradicals are excluded from consideration on energy grounds, as their relative energies are too high for formation to be competitive. It follows that this reaction involves parallel biradicals and thus gives an anti-“rule of five” product probably through the  $2^\circ/3^\circ$  parallel (b) biradical as its relative energy does not prohibit its competitive formation and its SDO ( $2.97 \times 10^{-3}$  electrons/au<sup>3</sup>) (**Figure 45**) allows for ring closure. Again, the most likely candidate for product formation, the  $2^\circ/3^\circ$  parallel biradical, has an IPA ( $87.5^\circ$ ) which is the closest to the angle preferred by the “90° rule”. The short radical/ $\alpha$ -H distance in  $2^\circ/3^\circ$  parallel (a) biradical is again presumably responsible for why optimization of the corresponding singlet biradical leads to the hydrogen abstraction product. The similar angles, low energy biradical conformations and singlet optimization results obtained for (**150**) and (**151**) are not surprising. The structural difference, a methyl group in the 6-position in (**151**), does not interfere with the conformation of the reactive centre and so the structural features are similar. Illustrating this point, singlet optimization of the  $1^\circ/3^\circ$  crossed (a) biradical derived from (**151**) gives the “rule of five” product which was also the result obtained for the corresponding biradical formed from (**150**).

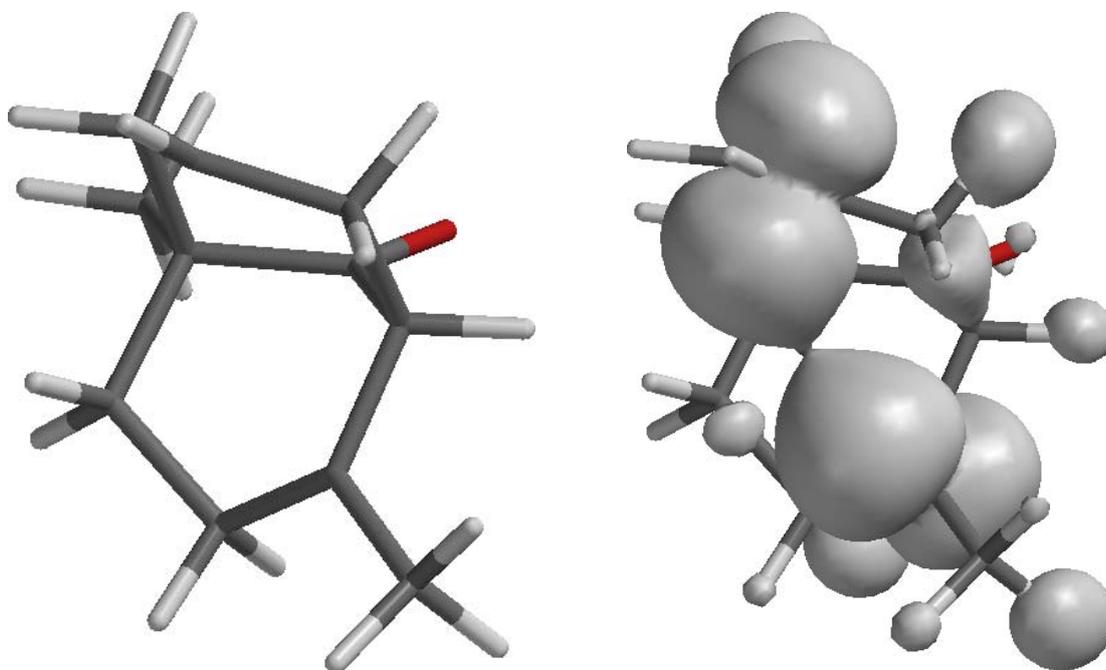


Figure 45

Table 26\* Computational results for biradicals obtained from 6-allyl-3,6-dimethyl-2-cyclohexen-1-one (151)

	1°/2° parallel	2°/3° parallel (a)	2°/3° parallel (b)	1°/3° crossed (a)	1°/3° crossed (b)	2°/2° crossed
Relative energy (kJ mol <sup>-1</sup> )	14.2	6.7	17.9	41.2	41.7	0.0
Spin density overlap	2.62×10 <sup>-3</sup>	2.01×10 <sup>-3</sup>	2.97×10 <sup>-3</sup>	2.46×10 <sup>-3</sup>	4.02×10 <sup>-3</sup>	8.3×10 <sup>-4</sup>
IRD (Å)	3.10	3.12	3.20	3.05	3.06	3.15
IPA	58.2	79.3	87.5	74.6	76.1	133.0
Cleavage angle	3.7/32.5	57.7/8.6	55.1/10.5	80.3/55.1	9.3/47.8	14.0/65.6
Radical/ $\alpha$ -H distance (Å)		2.67				
Singlet biradical optimization	S M	H-abs	S M	“rule of five” product	SM	S M
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )						
Experimental result	anti-“rule of five” product (162) formed					

\* See Table 24 for glossary of terms

#### 2.2.4 Intramolecular [2+2] cycloaddition of 6-(3-methyl-2-butenyl)-4,4,6-trimethyl-2-cyclohexen-1-one (152)

Irradiation of the enone (**152**) leads to the formation of the anti-“rule of five” adduct (**163**) in 91% yield (**Table 23**). Individual low energy conformations for the  $3^\circ/2^\circ$  crossed, the  $2^\circ/2^\circ$  crossed and the  $2^\circ/2^\circ$  parallel biradicals, and two low energy conformations for the  $3^\circ/2^\circ$  parallel biradical were identified by conformational searching (**Table 27**). The  $3^\circ/2^\circ$  crossed and the  $2^\circ/2^\circ$  crossed biradicals are, due to their high relative energies, ruled out of consideration as their formation is not competitive. It is clear then that the reaction involves parallel biradical(s) and should give the anti-“rule of five” product. The involvement of the  $2^\circ/2^\circ$  parallel biradical is unlikely as the energy gap between it and the  $3^\circ/2^\circ$  parallel (a) biradical is large ( $37.9 \text{ kJ mol}^{-1}$ ). The best candidate is the  $3^\circ/2^\circ$  parallel (a) biradical (**Figure 46**) as it is lowest in energy and has a high SDO ( $3.41 \times 10^{-3} \text{ electrons/au}^3$ ). Interestingly the other low energy biradical,  $3^\circ/2^\circ$  parallel (b) biradical, has an IPA ( $86.3^\circ$ ) which is much closer to the “ $90^\circ$  rule” compared to the situation for the  $3^\circ/2^\circ$  parallel (a) biradicals which has an IPA of  $57.7^\circ$ . As both conformers have almost the same energy it is probable that both contribute to product formation. It is also interesting to note that on optimisation the singlet  $3^\circ/2^\circ$  parallel (b) biradical gives the observed anti-“rule of five” product while the  $3^\circ/2^\circ$  parallel (a) biradical reverts back to starting material. For this series of biradicals, there were no short radical/ $\alpha$ -H distances so hydrogen abstraction products are neither expected nor obtained.

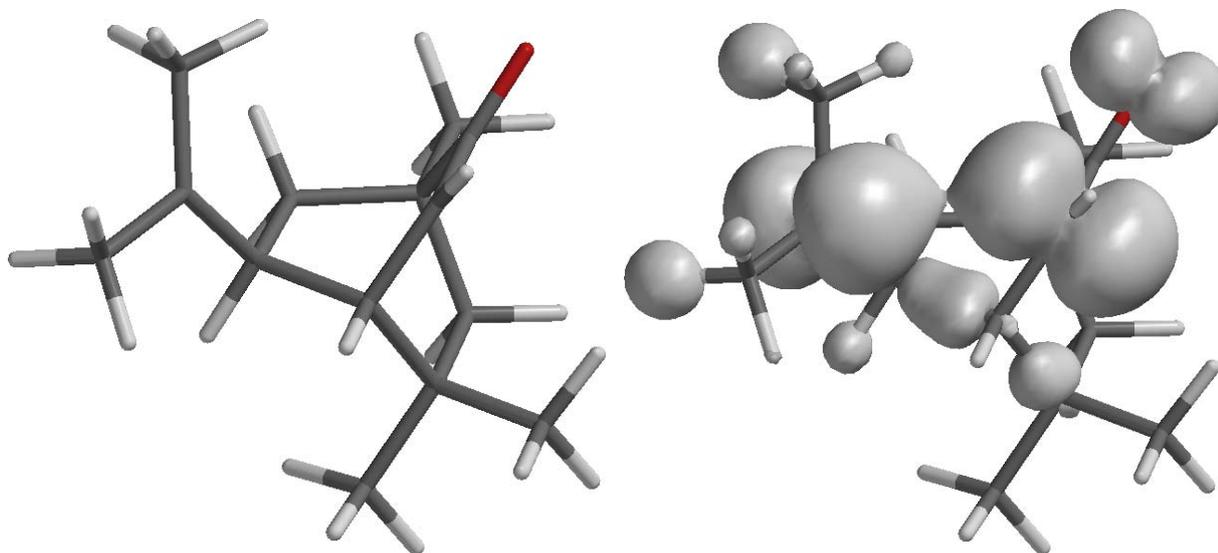


Figure 46

Table 27\* Computational results for biradicals obtained from 6-(3-methyl-2-butenyl)-4,4,6-trimethyl-2-cyclohexen-1-one (152)

	3°/2° parallel (a)	3°/2° parallel (b)	2°/2° parallel	3°/2° crossed	2°/2° crossed
Relative energy (kJ mol <sup>-1</sup> )	0.0	2.6	37.9	46.3	31.6
Spin density overlap	$3.41 \times 10^{-3}$	$2.81 \times 10^{-3}$	$2.91 \times 10^{-3}$	$2.51 \times 10^{-3}$	$4.7 \times 10^{-4}$
IRD (Å)	3.02	3.10	3.10	3.18	3.19
IPA	57.7	86.3	84.1	89.2	141.8
Cleavage angle	7.3/29.6	77.3/30.0	57.4/3.3	70.3/33.3	56.7/12.1
Radical/ $\alpha$ -H distance (Å)	no short radical/ $\alpha$ -H distances				
Singlet biradical optimization	S M	anti-“rule of five” product	S M	“rule of five” product	S M
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )	 0.0 kJ mol <sup>-1</sup> <b>(163)</b>		 24.6 kJ mol <sup>-1</sup>		
Experimental result	anti-“rule of five” product <b>(163)</b> formed				

\* See Table 24 for glossary of terms

### 2.2.5 Intramolecular [2+2] cycloaddition of 3-methyl-6-(3-methyl-2-butenyl)-2-cyclohexen-1-one (153)

Irradiation of the enone (**153**) leads to the formation of a complex mixture of products after 72 h, from which the hydrogen abstraction product (**161**) was isolated in 4% yield (**Table 23**). Conformational searching identified individual low energy conformers for the 3°/2° parallel and 2°/3° parallel biradicals, and two low energy conformers each for the 3°/3° crossed and 2°/2° crossed biradicals. The 3°/2° parallel biradical has the lowest energy and so would be expected to be formed in large amounts, this may well be the case but due to its low SDO ( $1.00 \times 10^{-3}$  electrons/au<sup>3</sup>) ring closure would be inefficient. The CA (20°) may contribute to the efficiency of this cleavage. All of the crossed biradicals have relative energies which are too large to allow for efficient formation. The 2°/3° parallel biradical has a relative energy which allows for its formation but due to its low SDO ( $1.49 \times 10^{-3}$  electrons/au<sup>3</sup>) ring closure would not be expected. However in this conformation there is a short radical/ $\alpha$ -H distance (2.68 Å) and through a six-membered chair transition state (**Figure 47**) hydrogen abstraction can, and does occur. In this instance, optimization of the singlet form of the biradical correctly predicts the formation of the hydrogen abstraction product. Interestingly, the 2°/2° crossed (b) biradical has a very short IRD (2.91 Å), an IPA (85.5°) close to 90° and a high SDO ( $4.24 \times 10^{-3}$  electrons/au<sup>3</sup>) all factors associated with ring closure. This is presumably why on optimization of the singlet form of this biradical it gives the “rule of five” product. As stated earlier however the relative energy of this biradical would not allow for its competitive formation.

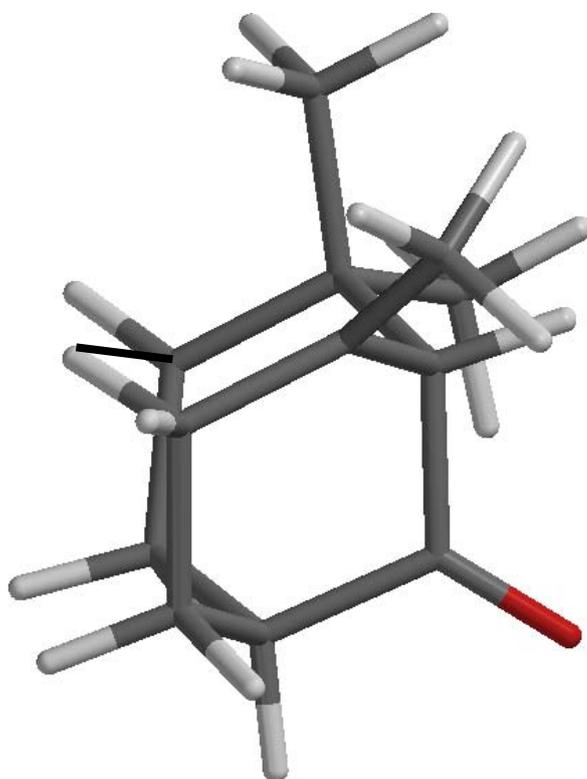


Figure 47

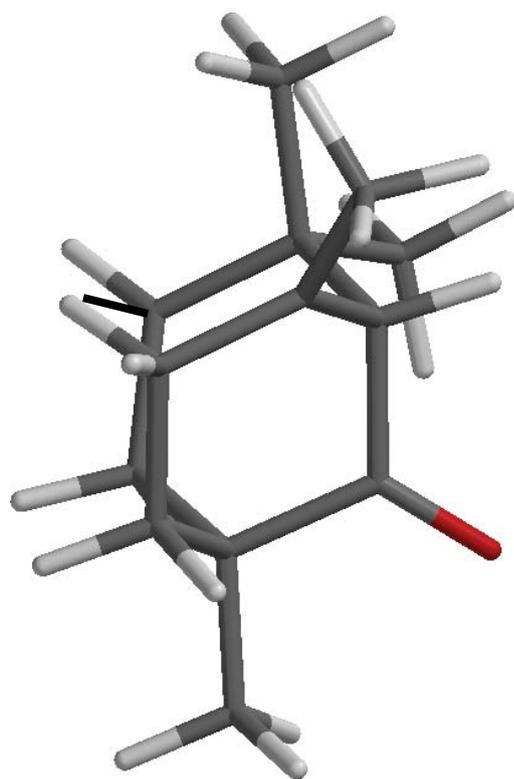
Table 28\* Computational results for biradicals obtained from 3-methyl-6-(3-methyl-2-butenyl)-2-cyclohexen-1-one (153)

	3°/2° parallel	2°/3° parallel	3°/3° crossed (a)	3°/3° crossed (b)	2°/2° crossed (a)	2°/2° crossed (b)
Relative energy (kJ mol <sup>-1</sup> )	0.0	18.9	33.0	33.4	29.8	36.5
Spin density overlap	1.00×10 <sup>-3</sup>	1.49×10 <sup>-3</sup>	2.84×10 <sup>-3</sup>	3.89×10 <sup>-3</sup>	6.4×10 <sup>-4</sup>	4.24×10 <sup>-3</sup>
IRD (Å)	3.20	3.15	3.15	3.09	3.17	2.91
IPA	58.1	88.1	56.0	51.8	139.6	85.5
Cleavage angle	20.0/33.3	58.5/25.2	10.9/45.5	30.0/31.6	59.8/13.1	67.1/12.7
Radical/α-H distance (Å)		2.68				
Singlet biradical optimization	S M	H-abs	S M	S M	S M	“rule of five” product
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )						
Experimental result	hydrogen abstraction product (164) formed					

\* See Table 24 for glossary of terms

### 2.2.6 Intramolecular [2+2] cycloaddition of 3,6-dimethyl-6-(3-methyl-2-butenyl)-2-cyclohexen-1-one (154)

Irradiation of the enone (**154**) again led to the formation of a complex mixture of products after an extended reaction time from which no identifiable product could be isolated (**Table 23**). Individual low energy conformers were identified for the 3°/3° crossed and 2°/2° crossed biradicals, and two low energy conformers were identified for both the 3°/2° parallel and 2°/3° parallel biradicals (**Table 29**) using the AM1 conformational searching method. The 3°/2° parallel (a) and 3°/2° parallel (b) biradicals are within an energy window which should allow competitive formation, but are ruled out on the basis of their low SDO values (**Table 29**). The 2°/3° parallel (a), 2°/3° parallel (b), 3°/3° crossed and 2°/2° crossed biradicals have relative energies which are too high to allow them to participate in product formation. As for the enone (**153**), which gave a hydrogen abstraction product in low yield (4%), the 2°/3° parallel (a) biradical has the hydrogen abstraction channel open to it due to its short radical/ $\alpha$ -H distance (2.68 Å) and the availability of a six-membered chair transition state for hydrogen abstraction (**Figure 48**). The failure to isolate the hydrogen abstraction product in this case may be due to the difficulty of the chromatography. The 3°/3° crossed biradical also has a short radical/ $\alpha$ -H distance (2.88 Å) and so hydrogen abstraction could in principal occur. A chair-like transition state is not available in this case and so the hydrogen abstraction channel would be inefficient. Overall (**154**) gives a complex mixture of products after a very long reaction time. Enone (**153**) and (**154**) are the only systems investigated in which two tri-substituted alkenes are interacting and both give complex mixture after long reaction times. In neither case are there biradicals which are ideal candidates for cycloadduct formation, either because of energy or SDO considerations. The formation of a number of unidentified products suggests that other unidentified reaction pathways are in operation for these two systems.



**Figure 48**

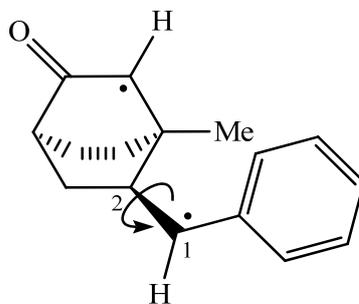
Table 29\* Computational results for biradicals obtained from 3,6-dimethyl-6-(3-methyl-2-butenyl)-2-cyclohexen-1-one (154)

	3°/2° parallel (a)	3°/2° parallel (b)	2°/3° parallel (a)	2°/3° parallel (b)	3°/3° crossed	2°/2° crossed
Relative energy (kJ mol <sup>-1</sup> )	0.0	2.2	18.0	32.4	25.5	31.1
Spin density overlap	$9.7 \times 10^{-4}$	$1.19 \times 10^{-3}$	$1.75 \times 10^{-3}$	$2.34 \times 10^{-3}$	$2.27 \times 10^{-3}$	$6.4 \times 10^{-4}$
IRD (Å)	3.23	3.22	3.14	3.26	3.14	3.16
IPA	58.4	61.5	85.1	86.5	85.6	139.6
Cleavage angle	33.5/18.6	16.1/33.5	57.7/16.2	58.0/11.4	69.5/54.9	59.2/13.3
Radical/ $\alpha$ -H distance (Å)			2.68		2.88	
Singlet biradical optimization	S M	S M	H-abs	S M	H-abs	S M
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )	 13.1 kJ mol <sup>-1</sup>			 0.0 kJ mol <sup>-1</sup>		
Experimental result	complex mixture of products formed					

\* See Table 24 for glossary of terms

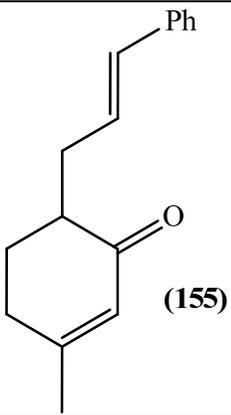
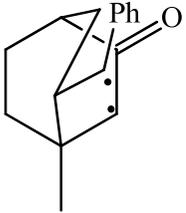
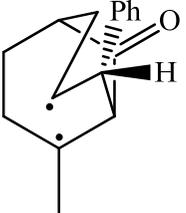
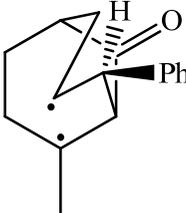
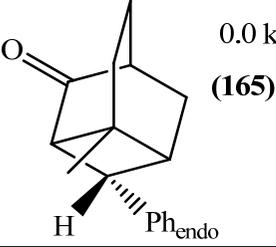
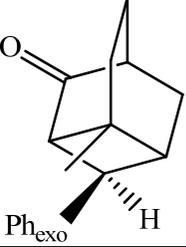
### 2.2.7 Intramolecular [2+2] cycloaddition of 3-methyl-6-[(E)-3-phenyl-2-propenyl]-2-cyclohexen-1-one (155)

The cycloaddition reaction of **(155)** is significantly more complicated than those considered above as both regiochemistry and stereochemistry have to be considered. Irradiation of the enone **(155)** led to the formation of the anti-“rule of five” product **(165)** in 94% yield (**Table 23**). Conformational searching identified two low energy conformers for the 2°/2° parallel biradical and unique low energy forms for both the 2°/3° parallel (Ph<sub>endo</sub>) (available if bond cleavage reforms the starting material in the *cis* form) and 2°/3° parallel (Ph<sub>exo</sub>) biradicals (**Table 30**). For the crossed biradicals, single low energy forms were identified for the 2°/2° crossed (Ph<sub>endo</sub>) and 2°/2° crossed (Ph<sub>exo</sub>) biradicals, and three low energy conformers were identified for the 2°/3° crossed biradical (**Table 30**). On the basis of energy only the 2°/2° parallel biradical can be involved in bond formation and this accounts for the formation of the anti-“rule of five” product in the reaction. An evaluation of the physical characteristics of the other biradicals is not necessary as the relative energy values are too large for competitive formation. Although neither of the 2°/2° parallel biradicals identified are particularly suited for bond closure on the basis of SDO, rotation about the benzylic bond allows for better SDO of the orbitals and thus facilitates ring closure. A series of calculations were undertaken whereby the benzyl group was rotated around the C1-C2 bond of the biradical (**Figure 49**) in 20° increments and the relative energies of the structures generated were obtained (**Figure 50**). There are two rotation options for the lowest energy biradical, the 2°/2° parallel (a) biradical: rotation of the bulky phenyl group towards (**A→B**, **Figure 50**), or away from the methyl group (**A→C**, **Figure 50**). Rotation away from the methyl group to position **C** (**Figure 50**) is not only more energetically favourable than rotation towards the methyl group, but results in better SDO and leaves the phenyl group in an *endo* position, *trans* to the methyl group across the cyclobutane ring. This is precisely the geometry of the product formed. The extra stability and thus longer lifetime of the 1,4-biradical, which includes a benzylic radical, might even allow for this bond rotation to occur in the S<sub>1</sub> state following ISC. Overall this process allows for the formation of the more stable cycloadduct **(165)** due to the avoidance of a transannular interaction in the cyclobutane ring between the phenyl and methyl groups.



**Figure 49**

**Table 30\*** Computational results for biradicals obtained from 3-methyl-6-[(*E*)-3-phenyl-2-propenyl]-2-cyclohexen-1-one (155)

 <p style="text-align: right;"><b>(155)</b></p>				
	2°/2° parallel (a)	2°/2° parallel (b)	2°/3° parallel (Ph <sub>endo</sub> )	2°/3° parallel (Ph <sub>exo</sub> )
Relative energy (kJ mol <sup>-1</sup> )	0.0	15.9	59.4	55.9
Spin density overlap	1.22×10 <sup>-3</sup>	7.8×10 <sup>-4</sup>	1.33×10 <sup>-3</sup>	1.80×10 <sup>-3</sup>
IRD (Å)	3.09	3.29	3.19	3.14
IPA	63.1	61.7	86.1	89.0
Cleavage angle	31.9/33.2	9.1/33.5	12.8/66.4	58.2/19.6
Radical/ $\alpha$ -H distance (Å)			2.70	2.76
Singlet biradical optimization	S M	S M	H-abs	S M
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )	 <p style="text-align: center;"><b>(165)</b> 0.0 kJ mol<sup>-1</sup></p>		 <p style="text-align: center;">6.9 kJ mol<sup>-1</sup></p>	
Experimental result	anti-“rule of five” Ph <sub>endo</sub> product <b>(165)</b> formed			

**Table 30 (contd.) Computational results for biradicals obtained from 3-methyl-6-[(E)-3-phenyl-2-propenyl]-2-cyclohexen-1-one (155)**

	2°/3° crossed (a)	2°/3° crossed (b)	2°/3° crossed (c)	2°/2° crossed (Ph <sub>endo</sub> )	2°/2° crossed (Ph <sub>exo</sub> )
Relative energy (kJ mol <sup>-1</sup> )	26.3	26.7	59.4	58.0	54.6
Spin density overlap	9.8×10 <sup>-4</sup>	3.36×10 <sup>-3</sup>	1.75×10 <sup>-3</sup>	1.28×10 <sup>-3</sup>	9.6×10 <sup>-4</sup>
IRD (Å)	3.05	3.06	3.16	3.12	3.18
IPA	81.4	78.0	48.2	125.4	130.7
Cleavage angle	50.5/64.8	9.5/48.6	10.0/9.8	11.3/72.7	15.1/70.4
Radical/α-H distance (Å)	No short radical/α-H distances				
Singlet biradical optimization	S M	S M	S M	S M	S M
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )					
Experimental result	anti-“rule of five” Ph <sub>endo</sub> product ( <b>165</b> ) formed				

\* See **Table 24** for glossary of terms

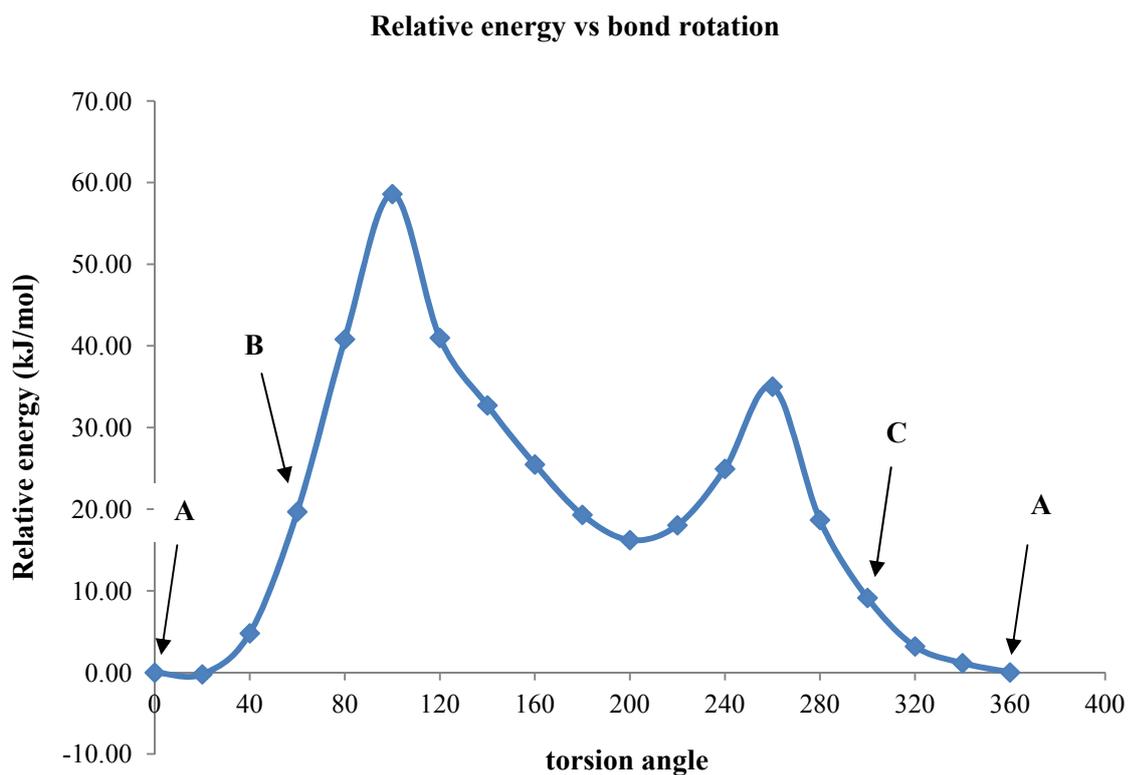
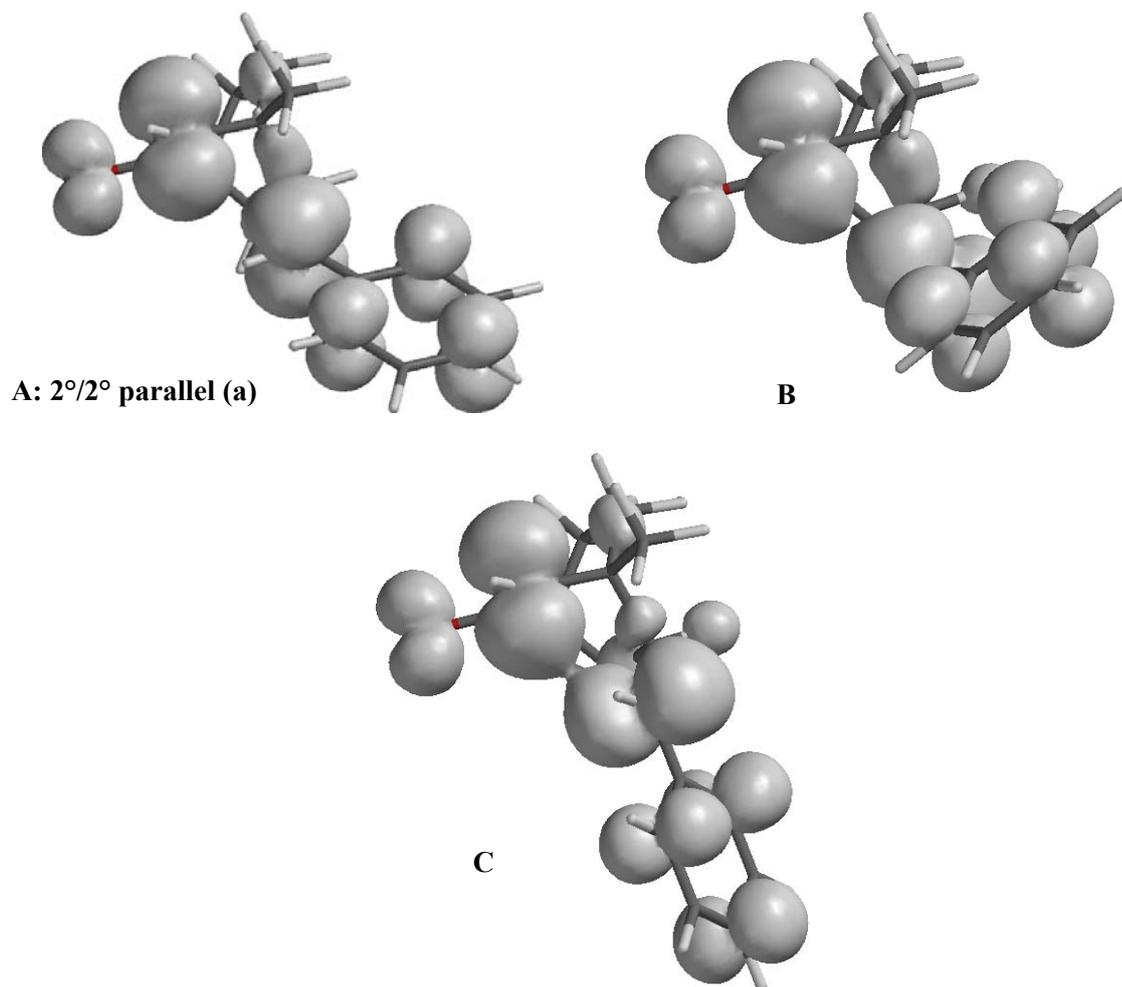
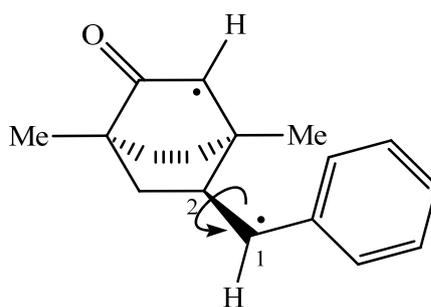


Figure 50



### 2.2.8 Intramolecular [2+2] cycloaddition of 3,6-dimethyl-6-[(E)-3-phenyl-2-propenyl]-2-cyclohexen-1-one (156)

Irradiation of the enone (**156**) led to the formation of the anti-“rule of five” products (**166**) and (**167**) in an 8:1 ratio, with the cycloadduct (**166**) being isolated in 73% yield (**Table 23**). Conformational searching identified two low energy conformers for the 2°/2° parallel biradical and unique low energy forms for both the 2°/3° parallel (Ph<sub>endo</sub>) and 2°/3° parallel (Ph<sub>exo</sub>) biradicals. For the crossed biradicals, single low energy forms were identified for the 2°/2° crossed (Ph<sub>endo</sub>) and 2°/2° crossed (Ph<sub>exo</sub>) biradicals, and three low energy conformers were identified for the 2°/3° crossed biradical. As with the previous case only the 2°/2° parallel biradical can be involved in bond formation on the basis of energy grounds thus accounting for the formation of the anti-“rule of five” products. The arguments presented previously (**Section 2.2.7**) can again be used to account for the high stereoselectivity of the process, rotation of the benzylic group about the C1-C2 bond (**Figure 51**) allows for better interaction of the orbitals and thus facilitates ring closure. The energy profile (**Figure 52**), generated as indicated above, shows that rotating away from the methyl group to C is more energetically favourable (**Figure 52**); it results in an enhanced SDO at a lower energy value and orientates the molecule for ring closure with the phenyl group in the *endo* position and *trans* to the methyl group across the cyclobutane ring. Interestingly the energy profiles for the 2°/2° parallel biradicals from enones (**156**) and (**157**) are very similar in appearance which would indicate they should display similar reactivities. The addition of the methyl group in the 6-position has little effect on the overall stereoselectivity of the reaction as the major product, (**166**), has the Ph group again in the *endo* position. The fact that similar reactivity was observed supports the idea that rotation of the phenyl group away from the methyl group is the determining factor in the stereoselectivity of both reactions.



**Figure 51**

Table 31\* Computational results for biradicals obtained from 3,6-dimethyl-6-[(*E*)-3-phenyl-2-propenyl]-2-cyclohexen-1-one (**156**)

	2°/2° parallel (a)	2°/2° parallel (b)	2°/3° parallel (Ph <sub>endo</sub> )	2°/3° parallel (Ph <sub>exo</sub> )
Relative energy (kJ mol <sup>-1</sup> )	0.0	16.7	63.4	58.8
Spin density overlap	1.37×10 <sup>-3</sup>	6.2×10 <sup>-4</sup>	1.54×10 <sup>-3</sup>	1.91×10 <sup>-3</sup>
IRD (Å)	3.12	3.30	3.15	3.12
IPA	61.2	61.1	88.6	87.1
Cleavage angle	24.5/33.1	12.9/29.7	64.2/11.4	57.4/18.0
Radical/ $\alpha$ -H distance (Å)			2.65	2.71
Singlet biradical optimization	S M	S M	H-abs	S M
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )	 0.0 kJ mol <sup>-1</sup> ( <b>166</b> )		 7.2 kJ mol <sup>-1</sup> ( <b>167</b> )	
Experimental result	anti-“rule of five” products ( <b>166</b> ):( <b>167</b> ) (8:1) formed			

Table 31 (contd.) Computational results for biradicals obtained from 3,6-dimethyl-6-[(*E*)-3-phenyl-2-propenyl]-2-cyclohexen-1-one (157)

	2°/3° crossed (a)	2°/3° crossed (b)	2°/3° crossed (c)	2°/2° crossed (Ph <sub>endo</sub> )	2°/2° crossed (Ph <sub>exo</sub> )
Relative energy (kJ mol <sup>-1</sup> )	26.4	26.5	26.9	61.2	63.2
Spin density overlap	3.36×10 <sup>-3</sup>	8.1×10 <sup>-4</sup>	3.19×10 <sup>-3</sup>	2.78×10 <sup>-3</sup>	1.06×10 <sup>-3</sup>
IRD (Å)	3.03	3.04	3.06	3.01	3.12
IPA	61.1	78.7	78.2	103.9	129.4
Cleavage angle	1.9/31.2	70.0/52.8	3.1/45.8	13.6/81.1	11.0/67.4
Radical/ $\alpha$ -H distance (Å)	No short radical/ $\alpha$ -H distances				
Singlet biradical optimization	S M	S M	S M	“rule of five” product	S M
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )					
Experimental result	anti-“rule of five” products (166):(167) (8:1) formed				

\* See Table 24 for glossary of terms

### Relative energy vs bond rotation

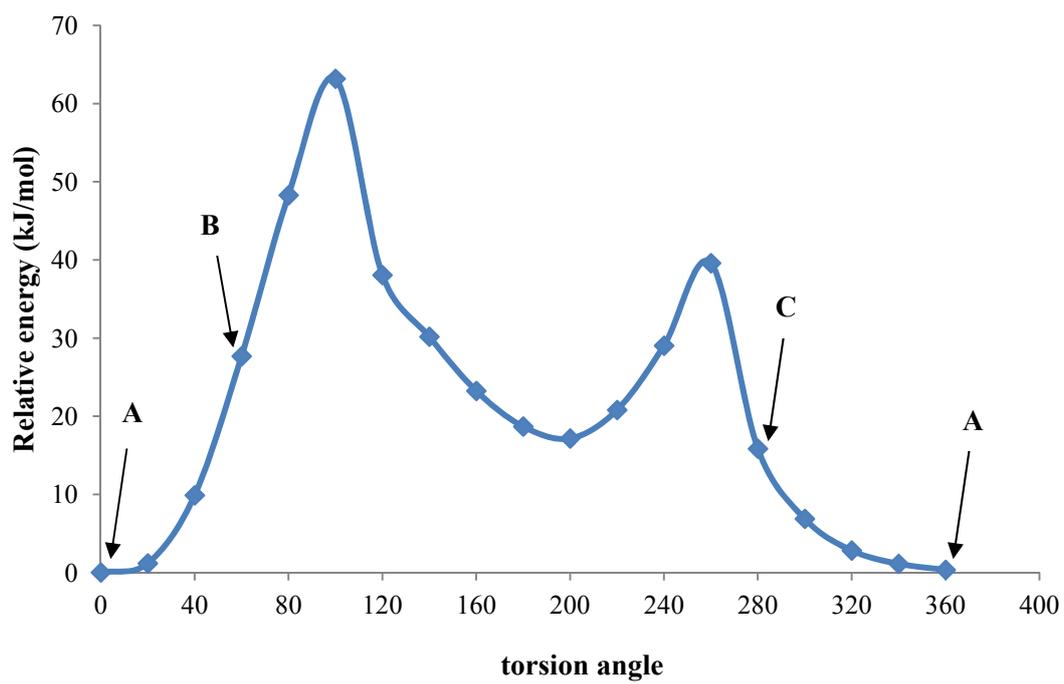
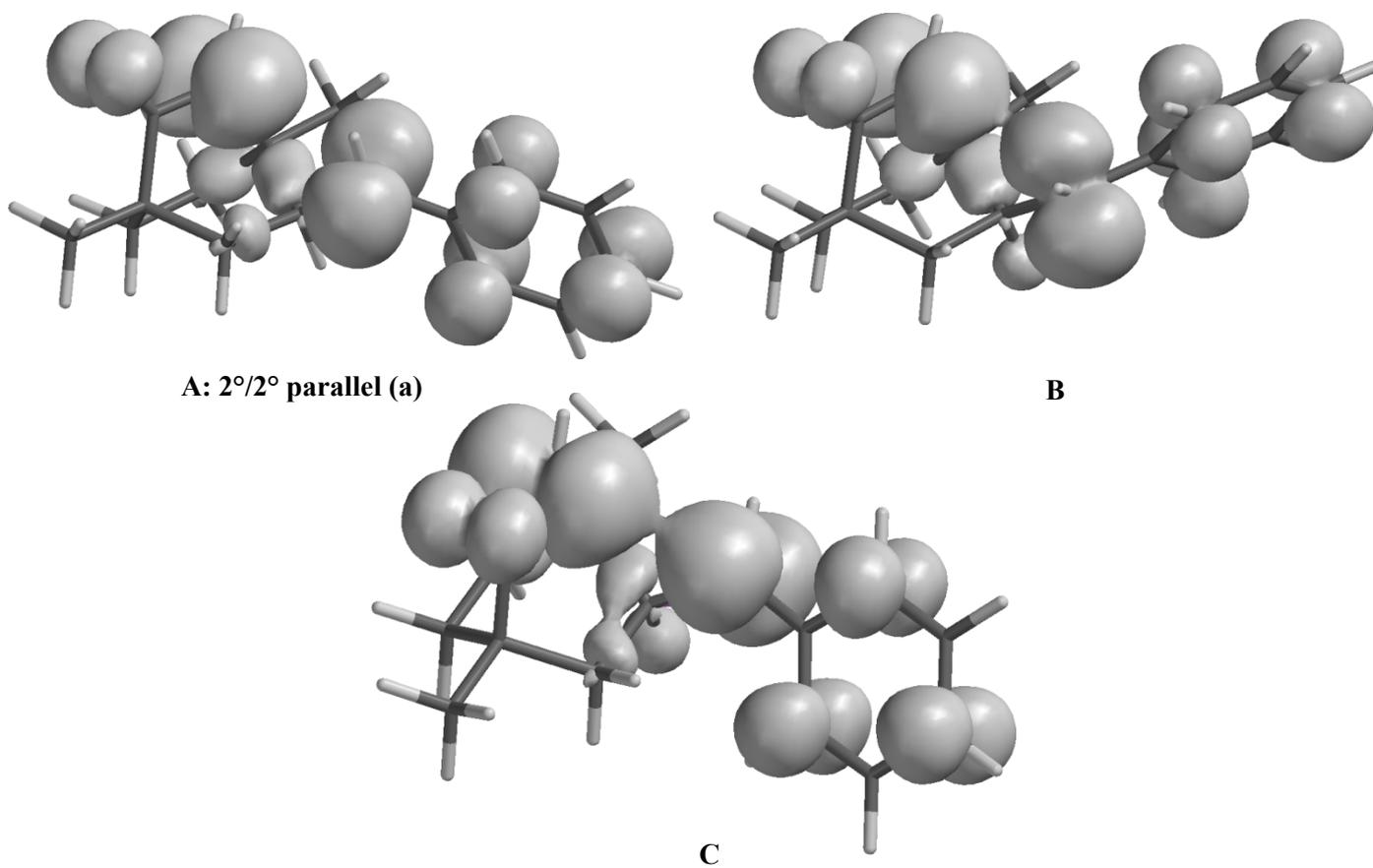
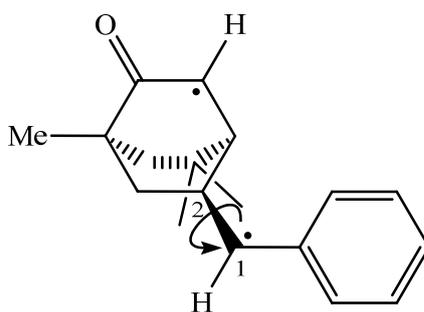


Figure 52



### 2.2.9 Intramolecular [2+2] cycloaddition of 6-[(E)-3-phenyl-2-propenyl]-4,4,6-trimethyl-2-cyclohexen-1-one (157)

Irradiation of the enone (**157**) led to the formation of the anti-“rule of five” products (**168**) and (**169**) in 53% and 46% yield, respectively (**Table 23**). Conformational searching identified two low energy conformers for the 2°/2° parallel biradical, two low energy conformers for the 2°/2° parallel (Ph<sub>endo</sub>) biradical, and three low energy conformers for the 2°/2° parallel (Ph<sub>exo</sub>) biradical. Three low energy conformers were identified for the 2°/2° crossed biradical, while unique low energy conformers were identified for the 2°/2° crossed (Ph<sub>endo</sub>) and 2°/2° crossed (Ph<sub>exo</sub>) biradicals (**Table 32**). As has been seen before, on the basis of energy only the 2°/2° parallel biradical is involved in product formation, thus accounting for the regiochemistry of the process. As there is no methyl group in the 3-position the phenyl group can rotate with equal ease in both directions. The usual series of calculations were undertaken whereby the benzyl group was rotated around the C1-C2 bond (**Figure 53**) in 20° increments and the relative energies of the structures generated were obtained. The energy profile (**Figure 54**) indicates that rotation is equally hindered in both directions and that SDO overlap increases to essentially the same extent in both directions. Experimentally, this leads to the almost equal formation of the Ph<sub>endo</sub> and Ph<sub>exo</sub> products, (**168**) and (**169**) respectively.



**Figure 53**

In the three enones (**156**), (**157**) and (**158**) a stable benzylic radical is formed as an intermediate. The direction in which rotation about the benzylic bond can occur determines the stereochemical outcome of the process. This rotation could occur in the T<sub>1</sub> state but, as pointed out above the stability and relatively long lifetime of the benzylic radical may allow the rotation to take place as well in the S<sub>1</sub> state prior to ring closure.

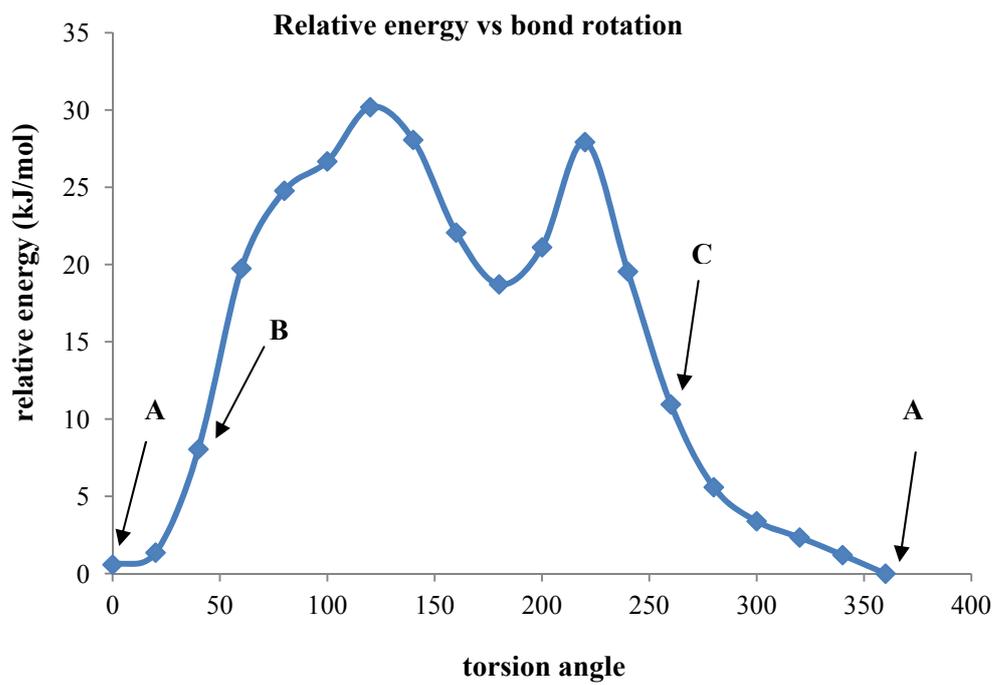
Table 32\* Computational results for parallel biradicals obtained from 6-[(*E*)-3-phenyl-2-propenyl]-4,4,6-trimethyl-2-cyclohexen-1-one (**157**)

	2°/2° parallel (a)	2°/2° parallel (b)	2°/2° parallel (a) (Ph <sub>endo</sub> )	2°/2° parallel (b) (Ph <sub>endo</sub> )	2°/2° parallel (a) (Ph <sub>exo</sub> )	2°/2° parallel (b) (Ph <sub>exo</sub> )	2°/2° parallel (c) (Ph <sub>exo</sub> )
Relative energy (kJ mol <sup>-1</sup> )	0.0	18.3	84.6	84.7	77.3	89.7	92.8
Spin density overlap	2.53×10 <sup>-3</sup>	1.44×10 <sup>-3</sup>	2.01×10 <sup>-3</sup>	2.46×10 <sup>-3</sup>	3.45×10 <sup>-3</sup>	4.54×10 <sup>-3</sup>	3.67×10 <sup>-3</sup>
IRD (Å)	3.03	3.16	3.17	3.22	3.14	3.03	3.04
IPA	55.7	56.3	88.8	88.2	83.7	59.0	72.0
Cleavage angle	5.2/30.2	2.3/29.9	69.1/4.8	64.5/11.5	53.6/15.7	29.3/20.2	45.9/2.6
Radical/ $\alpha$ -H distance (Å)	No short radical/ $\alpha$ -H distances						
Singlet biradical optimization	S M	S M	S M	S M	S M	S M	S M
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )							
Experimental result	anti-“rule of five” products <b>(168):(169)</b> (53:46) formed						

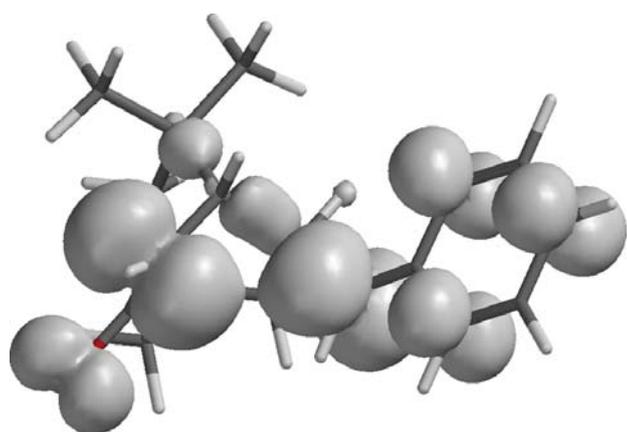
Table 32 (contd.) Computational results for crossed biradicals obtained from 6-[(*E*)-3-phenyl-2-propenyl]-4,4,6-trimethyl-2-cyclohexen-1-one (155)

	2°/2° crossed (a)	2°/2° crossed (b)	2°/2° crossed (c)	2°/2° crossed (Ph <sub>endo</sub> )	2°/2° crossed (Ph <sub>exo</sub> )				
Relative energy (kJ mol <sup>-1</sup> )	49.8	50.2	50.7	55.9	68.0				
Spin density overlap	2.99×10 <sup>-3</sup>	9.4×10 <sup>-4</sup>	2.40×10 <sup>-3</sup>	1.38×10 <sup>-3</sup>	8.0×10 <sup>-4</sup>				
IRD (Å)	3.07	3.07	3.03	3.12	3.16				
IPA	54.3	74.5	38.5	123.7	130.1				
Cleavage angle	7.8/18.3	62.1/25.0	30.6/5.5	76.8/10.1	65.2/10.0				
Radical/ $\alpha$ -H distance (Å)	No short radical/ $\alpha$ -H distances								
Singlet biradical optimization	S M	S M	S M	S M	S M				
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )									
Experimental result	anti-“rule of five” products <b>(168):(169)</b> (53:46) formed								

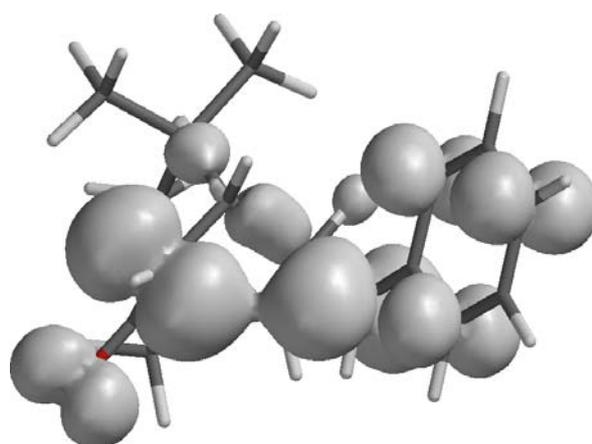
\* See Table 24 for glossary of terms



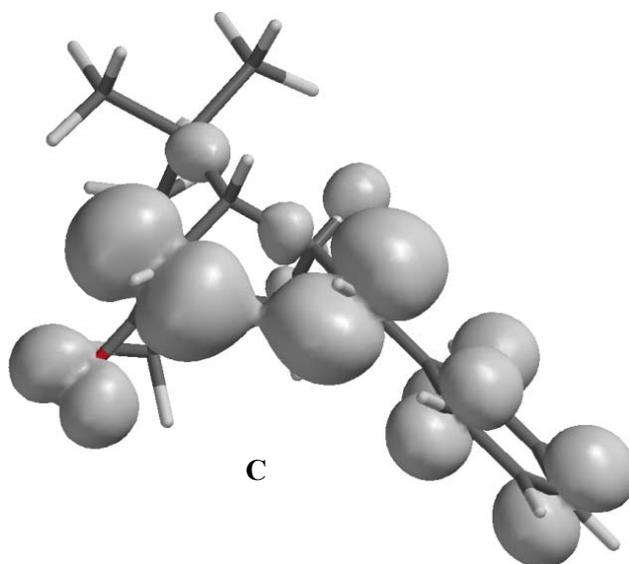
**Figure 54**



**A: 2°/2° parallel (a)**



**B**



**C**

### 2.2.10 Intramolecular [2+2] cycloaddition of 6-(3-butenyl)-3-methyl-2-cyclohexen-1-one (158)

Irradiation of the enone (**158**), which has an extra methylene between the alkene bonds, led to the formation of the “crossed” product (**170**) in 95% yield (**Table 23**). This is an inversion of the regiochemistry observed for the previous systems investigated where the “parallel”, anti-“rule of five” product was formed. Conformational searching identified a number of different low energy forms for each of the possible biradicals. Six low energy forms were identified for the  $2^\circ/3^\circ$  parallel biradical, four low energy forms were identified for the  $1^\circ/3^\circ$  crossed biradical and three low energy forms, were identified for both the  $1^\circ/2^\circ$  parallel and the  $2^\circ/2^\circ$  crossed biradicals (**Table 33**). The  $2^\circ/2^\circ$  crossed (a) biradical has the lowest energy but has a very low SDO ( $8.5 \times 10^{-4}$  electrons/au<sup>3</sup>) (**Figure 55**) and so is discounted on that basis. The  $2^\circ/2^\circ$  crossed (c) biradical has a high SDO ( $6.33 \times 10^{-3}$  electrons/au<sup>3</sup>) but its relative energy ( $29.4 \text{ kJ mol}^{-1}$ ) is too high for its formation to be competitive. The  $2^\circ/2^\circ$  crossed (b) biradical has the best potential to be product forming, being a low energy biradical (relative energy  $1.6 \text{ kJ mol}^{-1}$ ) with a significant SDO ( $4.38 \times 10^{-3}$  electrons/au<sup>3</sup>) (**Figure 56**). Of the parallel biradicals the  $2^\circ/3^\circ$  parallel (a), (c), (d), (e), and  $1^\circ/2^\circ$  parallel (c), biradicals have low SDOs, with most also being unattractive in terms of energy (**Table 33**). The  $2^\circ/3^\circ$  parallel (f),  $1^\circ/2^\circ$  parallel (a) and (b) biradicals show high SDOs but their formation will not be competitive on energy grounds. The most competitive parallel biradical,  $2^\circ/3^\circ$  parallel (b), has an energy, which is  $17.6 \text{ kJ mol}^{-1}$  higher than the  $2^\circ/2^\circ$  crossed (b) biradical and it also has a lower SDO value (**Table 33**). The  $2^\circ/2^\circ$  crossed (b) biradical is thus the product forming biradical accounting for the regioselective formation of the “crossed product”.

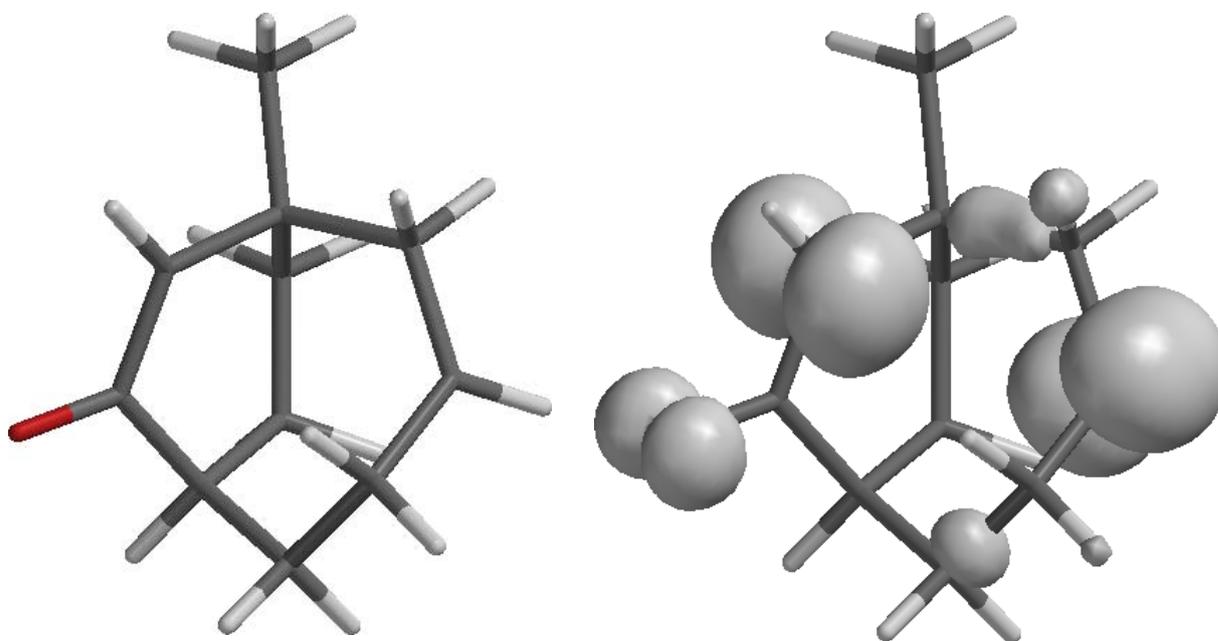
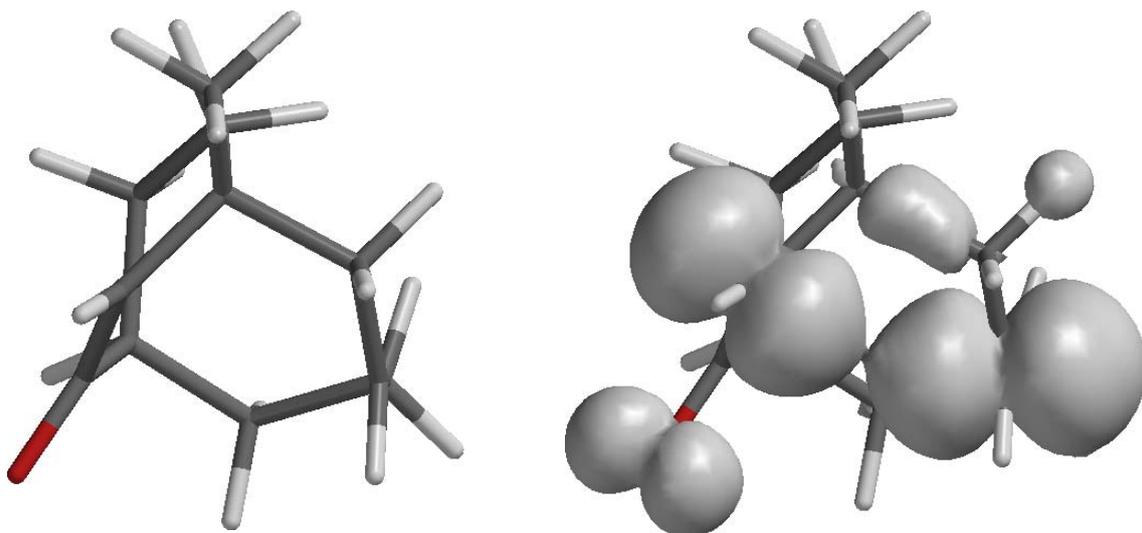
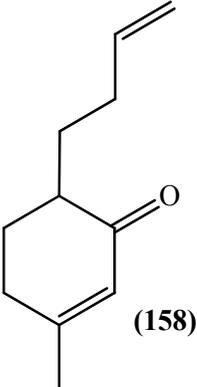
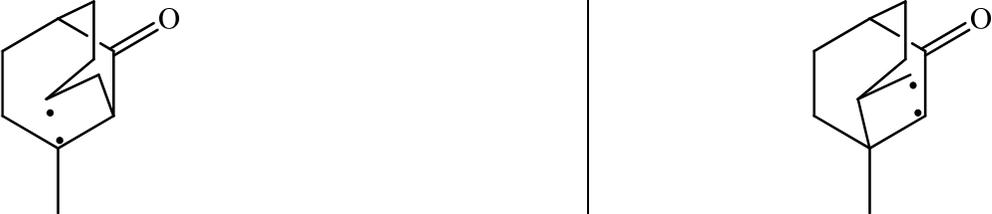
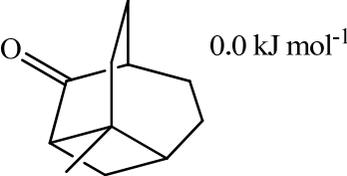


Figure 55



**Figure 56**

Table 33\* Computational results for parallel biradicals obtained from 6-(3-butenyl)-3-methyl-2-cyclohexen-1-one (158)

 <p>(158)</p>									
	2°/3° parallel (a)	2°/3° parallel (b)	2°/3° parallel (c)	2°/3° parallel (d)	2°/3° parallel (e)	2°/3° parallel (f)	1°/2° parallel (a)	1°/2° parallel (b)	1°/2° parallel (c)
Relative energy (kJ mol <sup>-1</sup> )	16.2	19.2	20.6	22.2	23.6	25.8	23.7	24.1	29.3
Spin density overlap	2.75×10 <sup>-3</sup>	3.42×10 <sup>-3</sup>	5.50×10 <sup>-4</sup>	1.91×10 <sup>-3</sup>	1.18×10 <sup>-3</sup>	4.20×10 <sup>-3</sup>	5.13×10 <sup>-3</sup>	4.43×10 <sup>-3</sup>	1.50×10 <sup>-3</sup>
IRD (Å)	3.17	3.08	3.36	3.32	3.26	3.12	2.91	2.92	3.21
IPA	53.8	64.7	64.1	60.9	80.3	65.2	47.1	80.1	39.8
Cleavage angle	22.6/13.8	8.4/39.0	19.2/72.6	11.1/20.2	41.8/83.1	15.2/20.8	14.6/11.9	68.3/15.9	3.3/13.4
Radical/ $\alpha$ -H distance (Å)	3.19	2.83							
Singlet biradical optimization	S M	S M	S M	S M	S M	S M	parallel product	parallel product	S M
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )	 <p>0.0 kJ mol<sup>-1</sup></p>								
Experimental result	crossed product (161) formed								

**Table 33 (contd.) Computational results for crossed biradicals obtained from 6-(3-butenyl)-3-methyl 2-cyclohexen-1-one (158)**

	1°/3° crossed (a)	1°/3° crossed (b)	1°/3° crossed (c)	1°/3° crossed (d)	2°/2° crossed (a)	2°/2° crossed (b)	2°/2° crossed (c)
Relative energy (kJ mol <sup>-1</sup> )	25.1	30.3	44.2	59.6	0.0	1.6	29.4
Spin density overlap	3.01×10 <sup>-3</sup>	2.64×10 <sup>-3</sup>	3.06×10 <sup>-3</sup>	3.19×10 <sup>-3</sup>	8.50×10 <sup>-4</sup>	4.38×10 <sup>-3</sup>	6.33×10 <sup>-3</sup>
IRD (Å)	3.13	3.10	2.92	2.92	3.19	2.94	2.82
IPA	75.7	46.3	64.1	67.9	146.6	45.8	48.4
Cleavage angle	50.3/10.0	7.3/11.1	72.0/36.2	66.3/13.6	1.3/28.8	6.2/23.1	17.8/8.1
Radical/α-H distance (Å)	3.84						
Singlet biradical optimization	H-abs	S M	S M	S M	S M	C P	C P
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )							
Experimental result	crossed product <b>(170)</b> formed						

\* See **Table 24** for glossary of terms

### 2.2.11 Intramolecular [2+2] cycloaddition of 6-(3-butenyl)-3,6-dimethyl-2-cyclohexen-1-one (159)

Irradiation of the enone (**159**), which also has an extra methylene between the alkene bonds, again led to the formation of the “crossed” product (**171**) in 96% yield (**Table 23**). The addition of a methyl group in the 6-position has no effect on the regiochemistry of the reaction; which is the same as that of the enone (**158**), with the crossed product again being formed regiospecifically. A large number of low energy conformers were identified by conformational searching: four low energy forms were identified for both the 1°/3° crossed and the 2°/2° crossed biradicals, while six low energy conformers were identified for the 2°/3° parallel biradical and three low energy forms were found for the 1°/2° parallel biradical. Of the crossed biradicals, the 2°/2° crossed (a) biradical is the most attractive; it has lowest energy of all the biradicals and has a high SDO ( $4.46 \times 10^{-3}$  electrons/au<sup>3</sup>) (**Figure 57**). Compared to this the six 2°/3° parallel biradicals can be ruled out on either high relative energy grounds or low SDO values (**Table 34**). Of the 1°/2° parallel biradicals, the 1°/2° parallel (a) biradical is the most competitive in terms of bond formation having a short IRD (2.92 Å) and significant SDO ( $4.40 \times 10^{-3}$  electrons/au<sup>3</sup>). Comparing the values for this biradical with those for the most competitive crossed biradical, the 2°/2° crossed (a) biradical shows that the IRDs are essentially identical, and that the former has a slightly poorer SDO. The energy difference between the two biradicals however,  $18.3 \text{ kJ mol}^{-1}$  in favour of the crossed biradical, provides a rationale for the fact that a crossed product is obtained.

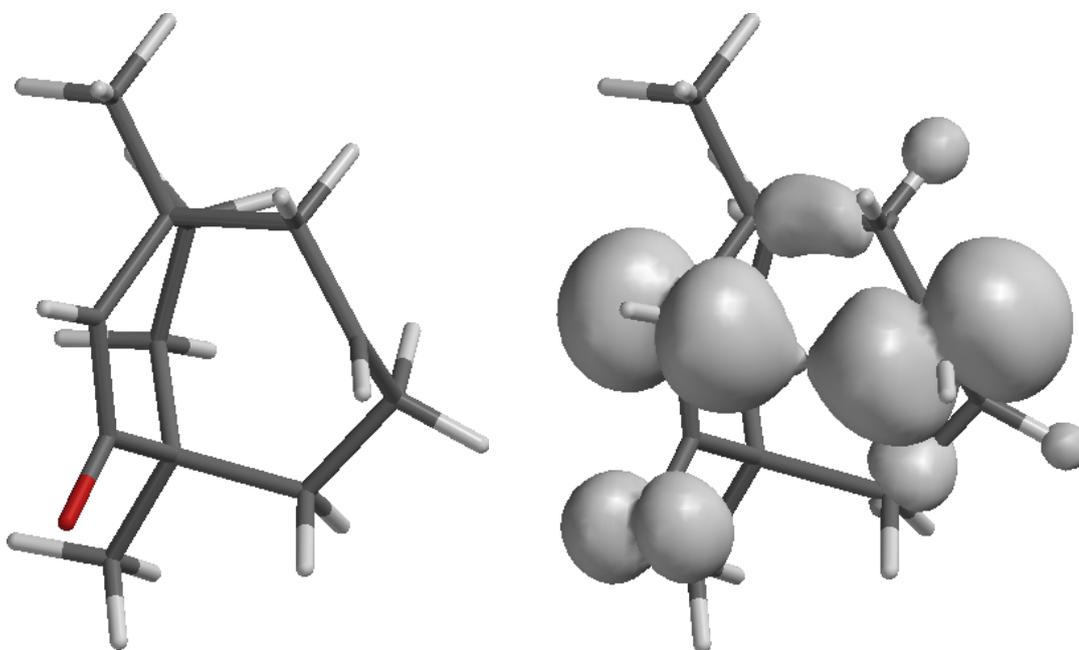


Figure 57

**Table 34\* Computational results for biradicals obtained from 6-(3-butenyl)-3,6-dimethyl-2-cyclohexen-1-one (159)**

<p>(159)</p>									
	2°/3° parallel (a)	2°/3° parallel (b)	2°/3° parallel (c)	2°/3° parallel (d)	2°/3° parallel (e)	2°/3° parallel (f)	1°/2° parallel (a)	1°/2° parallel (b)	1°/2° parallel (c)
Relative energy (kJ mol <sup>-1</sup> )	13.2	16.8	17.8	19.9	21.2	23.8	18.3	18.9	23.3
Spin density overlap	2.84×10 <sup>-3</sup>	3.44×10 <sup>-3</sup>	6.7×10 <sup>-4</sup>	1.97×10 <sup>-3</sup>	1.21×10 <sup>-3</sup>	4.09×10 <sup>-3</sup>	4.40×10 <sup>-3</sup>	4.94×10 <sup>-3</sup>	1.55×10 <sup>-3</sup>
IRD (Å)	3.16	3.08	3.31	3.31	3.26	3.12	2.92	2.92	3.21
IPA	53.9	65.7	67.3	61.4	78.6	66.1	46.9	82.2	39.7
Cleavage angle	15.8/22.5	11.5/5.2	72.1/23.8	20.2/13.0	83.2/40.6	14.9/22.1	10.0/13.9	70.6/15.5	2.4/13.1
Radical/ $\alpha$ -H distance (Å)	No short radical/ $\alpha$ -H distances								
Singlet biradical optimization	S M	S M	S M	S M	S M	S M	parallel product	parallel product	S M
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )	<p>0.0 kJ mol<sup>-1</sup></p>								
Experimental result	Crossed product (171) formed								

Table 34 (contd.) Computational results for biradicals obtained from 6-(3-butenyl)-3,6-dimethyl-2-cyclohexen-1-one (159)

	1°/3° crossed (a)	1°/3° crossed (b)	1°/3° crossed (c)	1°/3° crossed (d)	2°/2° crossed (a)	2°/2° crossed (b)	2°/2° crossed (c)	2°/2° crossed (d)
Relative energy (kJ mol <sup>-1</sup> )	18.3	23.1	37.6	52.5	0.0	4.8	25.6	31.5
Spin density overlap	3.06×10 <sup>-3</sup>	2.66×10 <sup>-3</sup>	3.19×10 <sup>-3</sup>	3.25×10 <sup>-3</sup>	4.46×10 <sup>-3</sup>	6.0×10 <sup>-4</sup>	6.38×10 <sup>-3</sup>	6.0×10 <sup>-5</sup>
IRD (Å)	3.12	3.10	2.92	2.92	2.93	3.18	2.82	3.53
IPA	55.9	46.4	67.0	70.3	46.5	145.3	49.4	162.1
Cleavage angle	25.7/9.1	11.6/6.9	72.4/31.2	66.9/10.8	6.5/24.4	31.5/5.5	7.1/20.0	5.6/19.9
Radical/ $\alpha$ -H distance (Å)			2.79					
Singlet biradical optimization	S M	S M	H-abs	S M	Crossed product	S M	Crossed product	S M
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )	 4.7 kJ mol <sup>-1</sup> <b>(171)</b>							
Experimental result	Crossed product <b>(171)</b> formed							

\* See Table 24 for glossary of terms

### 2.3 Intramolecular [2+2] cycloaddition reactions of 1-alkenyl-1-methyl-2(1H)-naphthalenones

1-Alkenyl-1-methyl-2(1H)-naphthalenones are related to the 6-alkenyl-2-cyclohexen-1-ones discussed previously (Sections 2.2.1-2.2.11) in that they contain the same alkenyl substituted cyclohexenone sub-unit. The presence of the fused benzene ring provides an opportunity to assess how robust the biradical conformation control concept is in accounting for the photochemical behaviour of related but structurally distinct systems. A low level computational approach (MM) has been used previously<sup>[29]</sup> to study the photochemistry of some alkenyl naphthalenones; the work described here is a more rigorous evaluation (for example, in the use of conformational searching and QM calculations) of the applicability of the biradical conformation control concept to these systems.

**Table 35 Photocycloadditions of 1-allyl-naphthalen-2(H)-ones**

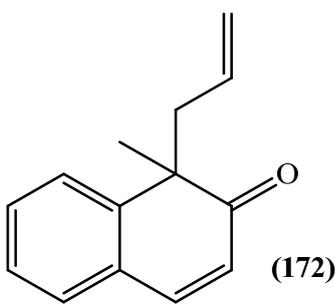
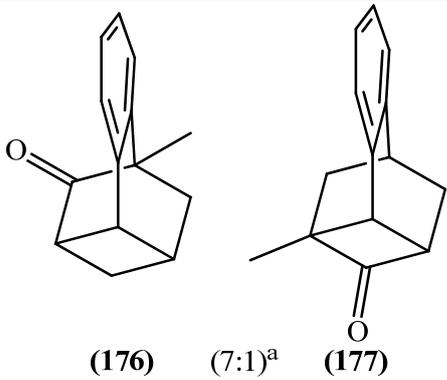
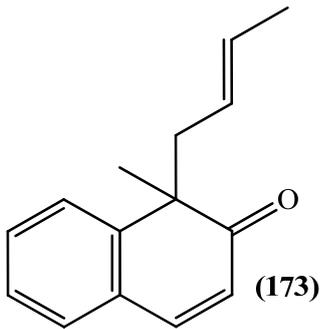
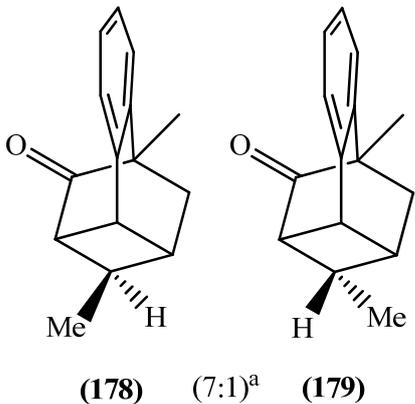
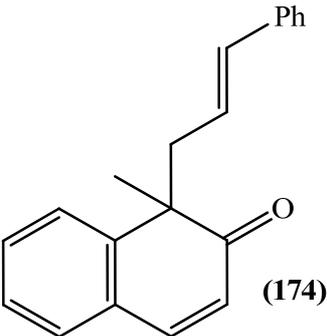
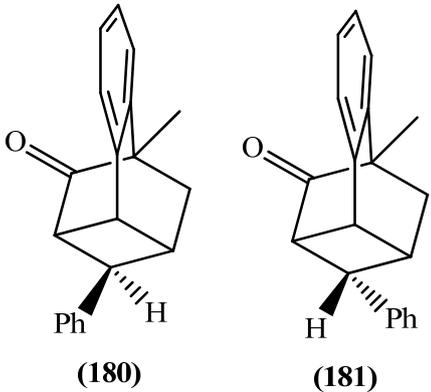
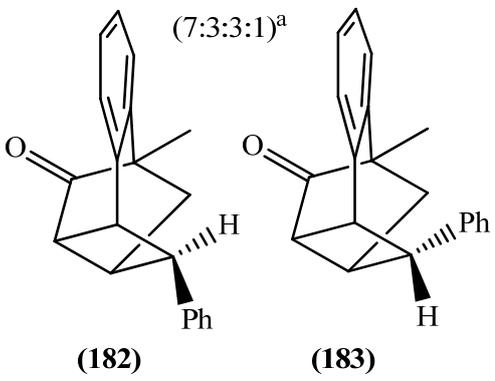
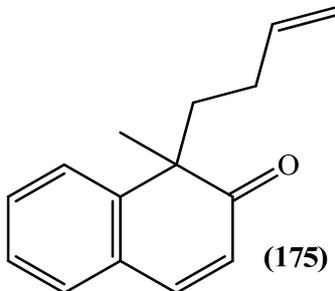
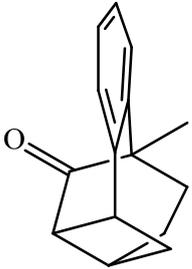
Enone	Time	Product	Yield	Ref
 <p>(172)</p>	111 h	 <p>(176) (7:1)<sup>a</sup> (177)</p>	(176) 80% <sup>b</sup> (177) 3% <sup>b</sup>	[39]
 <p>(173)</p>	48 h	 <p>(178) (7:1)<sup>a</sup> (179)</p>	(178) 74% <sup>b</sup> (179) 3% <sup>b</sup>	[37]

Table 35 (contd.) Photocycloadditions of 1-allyl-naphthalen-2(H)-ones

Enone	Time	Product	Yield	Ref
 <p>(174)</p>	80 h	 <p>(180) (181)</p>  <p>(182) (183)</p> <p>(7:3:3:1)<sup>a</sup></p>	<p>(180)-(183) 94%<sup>c</sup> (180) 7%<sup>b</sup> (181) 3%<sup>b</sup> (182) 5%<sup>b</sup> (183) 3%<sup>b</sup></p>	[37]
 <p>(175)</p>	17 h	 <p>(184)</p>	<p>100%<sup>c</sup> 66%<sup>b</sup></p>	[37]

<sup>a</sup> GC, <sup>b</sup> Isolated yield, <sup>c</sup> crude yield

### 2.3.1 Intramolecular [2+2] cycloaddition of 1-methyl-1-(2-propenyl)-2(1H)-naphthalenone (172)

Irradiation of the naphthalenone (**172**) led to the formation of the anti-“rule of five” product (**176**) and a cyclobutanone (**177**) in a ratio of 10:1 (**Table 35**). Conformational searching identified unique low energy conformers for the four possible parallel and crossed biradicals. Both crossed biradicals are excluded from consideration on energy grounds, as their relative energies are too high for formation to be competitive. In keeping with the experimental result it follows that this reaction involves parallel biradicals and thus gives an anti-“rule of five” product. Although the 1°/2° parallel biradical has an SDO ( $2.99 \times 10^{-3}$  electrons/au<sup>3</sup>) which is higher than the 2°/2° parallel biradical its relative energy is far too high to be considered in product formation (**Table 36**). This means that the products are derived from the 2°/2° parallel biradical (**Figure 59**). The structure of the 2°/2° parallel biradical also provides an explanation for the formation of the minor product, the cyclobutanone (**177**), as it allows SDO between the singly occupied orbital on C-7, and the singly occupied orbitals on C-4a and C-10 which arise due to the delocalization of the benzylic radical (**Figure 58**). This allows for the formation of the standard [2+2] cycloadduct (**176**) and the cyclobutane (**185**) (**Scheme 135**) which subsequently rearranges to the cyclobutanone (**177**)

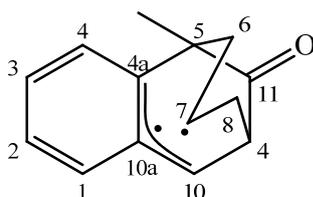


Figure 58

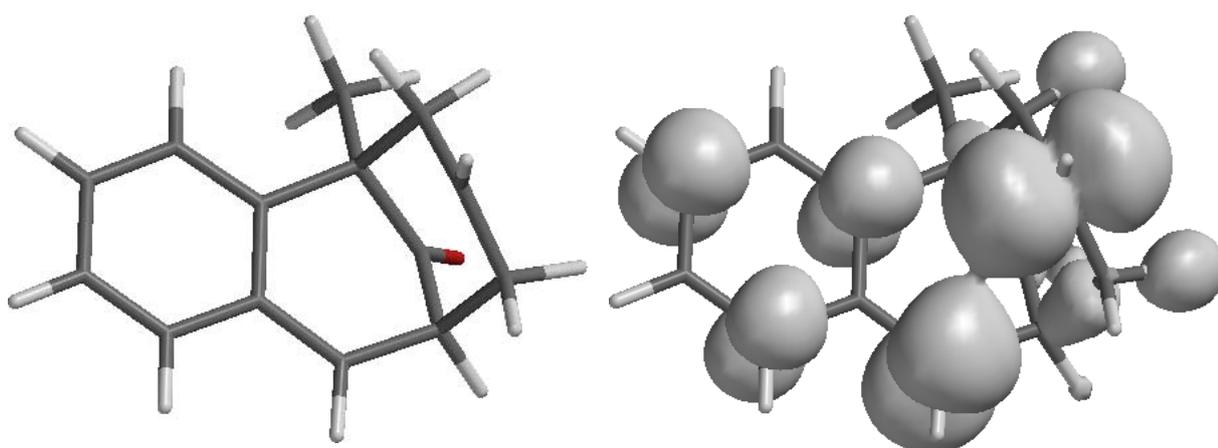
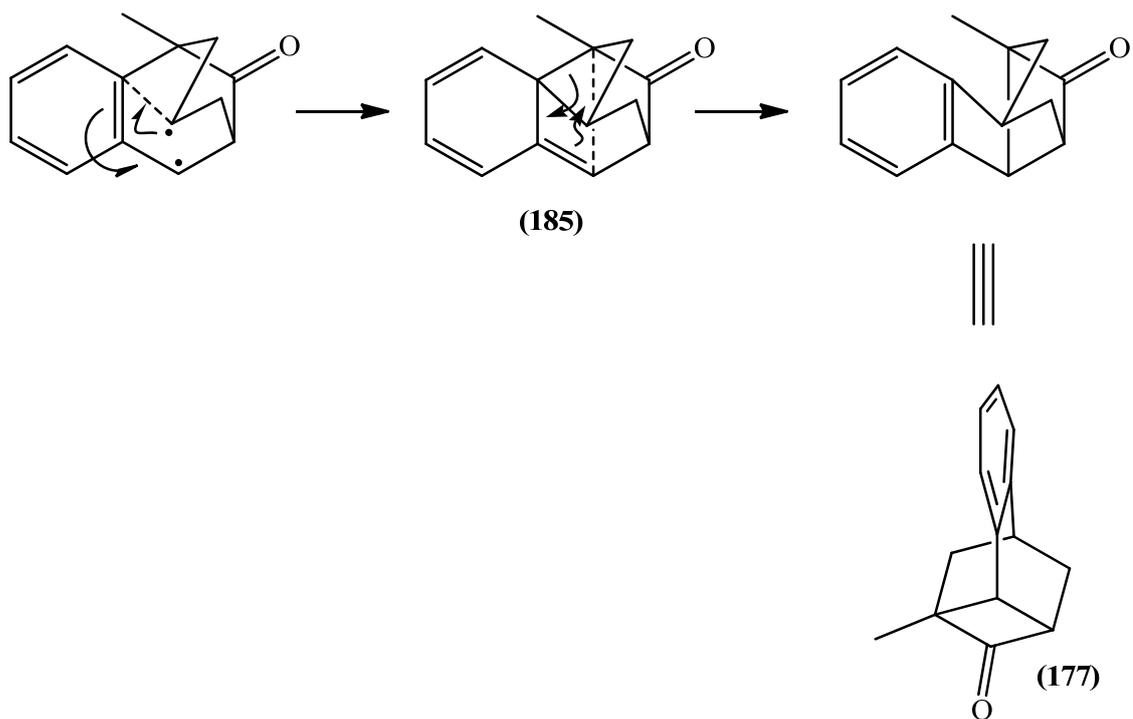


Figure 59



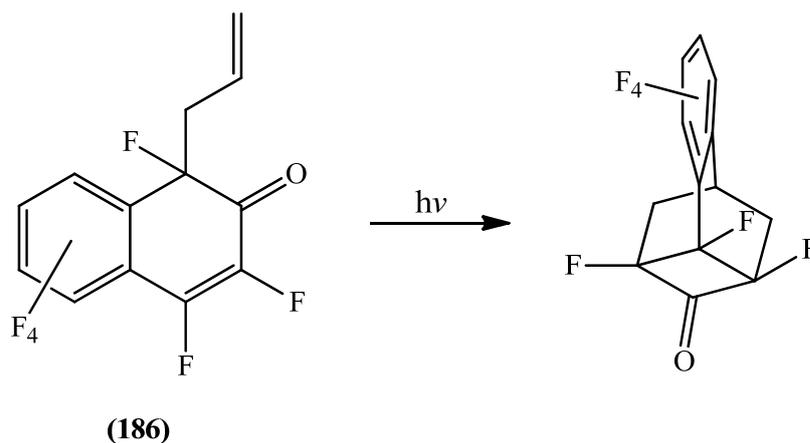
Scheme 135

**Table 36\*** Computational results for biradicals obtained from 1-methyl-1-(2-propenyl)-2(1*H*)-naphthalenone (172)

	2°/2° parallel	1°/2° parallel	1°/2° crossed	2°/2° crossed
Relative energy (kJ mol <sup>-1</sup> )	0.0	43.2	37.2	25.7
Spin density overlap	2.66×10 <sup>-3</sup>	2.99×10 <sup>-3</sup>	2.95×10 <sup>-3</sup>	3.65×10 <sup>-3</sup>
IRD (Å)	3.07	3.07	3.03	2.96
IPA	74.6	54.4	47.7	96.8
Cleavage angle	0.9/49.8	5.8/29.4	12.4/13.5	11.2/94.2
Radical/β-C distance (Å)	3.12			
Singlet biradical optimization	anti-“rule of five” product	SM	SM	“rule of five” product
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )	 0.0 kJ mol <sup>-1</sup> (176)	 -5.4 kJ mol <sup>-1</sup> (177)	 18.1 kJ mol <sup>-1</sup>	
Experimental result	anti-“rule of five” and cyclobutanone products (176):(177) (10:1) formed			

\* See **Table 24** for glossary of terms

A similar rearrangement has been observed for the perfluorinated naphthalenone **(186)** (**Scheme 136**)<sup>[40]</sup>. The mechanism suggested for rearrangement involved the first (and to date the only) example of a Woodward-Hoffmann allowed [3,5] sigmatropic shift. The potential for C-7/C-4a bond formation in the 2°/2° parallel biradical (**Figure 59**), demonstrated by the molecular modelling results described here, avoids the need to implicate a [3,5] sigmatropic shift in the naphthalenone/cyclobutanone rearrangement. There is also a correlation between the relative amounts of **(176)** and **(177)** formed and the level of SDO at C-7 and C-4a.



**Scheme 136**

### 2.3.2 Intramolecular [2+2] cycloaddition of 1-methyl-1-((2E)-but-2-en-1-yl)-2(1H)-naphthalenone (173)

Irradiation of the naphthalenone (**173**) led to the formation of the anti-“rule of five” products (**178**) and (**179**) in a ratio of 7:1 (**Table 35**). Only trace amounts of the “rule of five” products and the cyclobutanone were observed. Conformational searching identified unique low energy conformers for the three parallel biradicals and also for the three crossed biradicals. The 2°/2° parallel (Me<sub>exo</sub>) and the 2°/2° parallel (Me<sub>endo</sub>) biradicals have the lowest relative energies with only a 2.2 kJ mol<sup>-1</sup> difference between them. This accounts for the anti-“rule of five” being formed as the major product. The three crossed biradicals have relative energies that prohibit their formation from being competitive (**Table 37**). The 2°/2° parallel (Me<sub>exo</sub>) biradical has a slightly higher SDO ( $2.68 \times 10^{-3}$  electrons/au<sup>3</sup>) (**Figure 60**) compared to that of the 2°/2° parallel (Me<sub>endo</sub>) biradical ( $2.53 \times 10^{-3}$  electrons/au<sup>3</sup>) and so accounts for the formation of (**178**) in larger amounts. The cyclobutanone product was formed in trace amounts (NMR, IR) but was not isolated. The SDO plot for the 2°/2° parallel (Me<sub>exo</sub>) biradical (**Figure 60**) suggests its formation is again possible, but provides no clear indication of why less of the cyclobutanone is formed in this case. It is always possible that the failure to isolate this product is related to difficulties on chromatography.

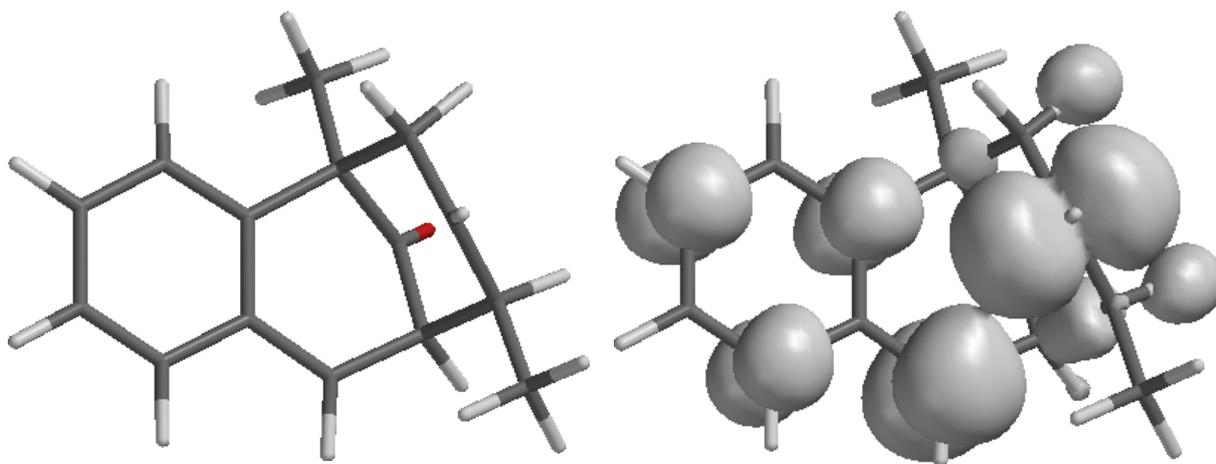


Figure 60

The cycloaddition reactions of (**155**)-(157) involve benzylic radicals which can generate either *exo* or *endo* adducts as a result of rotation about the benzylic bond. The corresponding radical for (**173**) is the 2°/2° parallel biradical but this is not involved for energy reasons (**Table 37**). The stereoselective formation of (**178**) with its *exo* methyl group can best be understood in terms of the formation of the 2°/2° parallel (Me<sub>exo</sub>) biradical and subsequent ring closure, a process which is energetically and stereoelectronically favourable. The formation of small amounts of (**179**) with its *endo* methyl group must occur *via* the 2°/2° parallel (Me<sub>endo</sub>) biradical which is available by reversion of some of the 2°/2° parallel (Me<sub>exo</sub>) biradical to starting material in the *cis* form and subsequent biradical formation.

Table 37\* Computational results for biradicals obtained from 1-methyl-1-((*2E*)-but-2-en-1-yl)-2(1*H*)-naphthalenone (**173**)

	2°/2° parallel	2°/2° parallel (Me <sub>exo</sub> )	2°/2° parallel (Me <sub>endo</sub> )
Relative energy (kJ mol <sup>-1</sup> )	27.2	0.0	2.2
Spin density overlap	2.75×10 <sup>-3</sup>	2.68×10 <sup>-3</sup>	2.53×10 <sup>-3</sup>
IRD (Å)	3.09	3.07	3.08
IPA	53.6	73.2	77.8
Cleavage angle	7.3/30.0	0.4/47.3	1.2/53.8
Radical/β-C distance (Å)		3.12	3.12
Singlet biradical optimization	SM	SM	anti-“rule of five” product
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )	 0.0 kJ mol <sup>-1</sup> <b>(178)</b>		 0.1 kJ mol <sup>-1</sup> <b>(179)</b>
Experimental result	anti-“rule of five” products <b>(178):(179)</b> (7:1) formed		

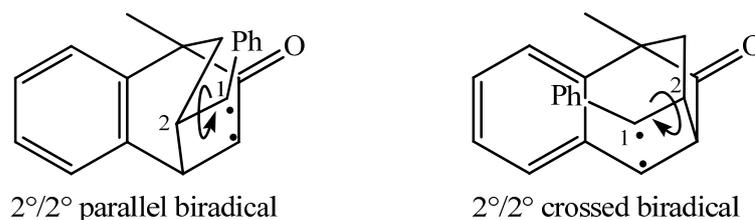
Table 37(contd.) Computational results for biradicals obtained from 1-methyl-1-((2E)-but-2-en-1-yl)-2(1H)-naphthalenone (173)

	2°/2° crossed	2°/2° crossed (Me <sub>exo</sub> )	2°/2° crossed (Me <sub>endo</sub> )
Relative energy (kJ mol <sup>-1</sup> )	21.7	26.7	26.5
Spin density overlap	3.28×10 <sup>-3</sup>	3.75×10 <sup>-3</sup>	1.04×10 <sup>-3</sup>
IRD (Å)	3.03	2.96	3.14
IPA	48.0	96.8	129.6
Cleavage angle	8.0/14.9	10.9/71.0	9.3/68.6
Radical/β-C distance (Å)	no short Radical/β-C distances		
Singlet biradical optimization	SM	“rule of five” product	SM
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )			
Experimental result	anti-“rule of five” products (178):(179) (7:1) formed		

\* See Table 24 for glossary of terms

### 2.3.3 Intramolecular [2+2] cycloaddition of 1-methyl-1-((2E)-3-phenylprop-2-en-1-yl)-2(1H)-naphthalenone (174)

Irradiation of the naphthalenone (**174**) led to the formation of the anti-“rule of five” products (**180**) and (**181**), and the “rule of five” products (**182**) and (**183**), in a 7:3:3:1 ratio (**Table 35**). Conformational searching indentified a single low energy form for both the 2°/2° parallel (Ph<sub>exo</sub>) and the 2°/2° parallel (Ph<sub>endo</sub>) biradicals, and two low energy conformers for the 2°/2° parallel biradical. In the case of the crossed biradicals, unique conformers were identified for the 2°/2° crossed (Ph<sub>exo</sub>) and the 2°/2° crossed (Ph<sub>endo</sub>) biradicals, and two low energy conformers for the 2°/2° crossed biradical. The 2°/2° crossed (Ph<sub>exo</sub>) and the 2°/2° crossed (Ph<sub>endo</sub>) biradicals can be ruled out due to their large relative energies which make their formation uncompetitive. The same conclusion can be reached about the 2°/2° parallel (Ph<sub>exo</sub>) and 2°/2° parallel (Ph<sub>endo</sub>) biradicals which also have large relative energies. The energy difference between the 2°/2° crossed (a) and the 2°/2° parallel (b) biradicals is quite small (5.4 kJ mol<sup>-1</sup>) and so the formation of both of these biradicals is competitive. Their SDOs are also comparable leading to the formation of a mixture of anti-“rule of five” and “rule of five” products. As we have seen in earlier cases the stability of the benzylic radical allows for bond rotation to occur prior to bond closure or cleavage. For both the 2°/2° parallel and the 2°/2° crossed biradicals, a series of calculations were undertaken whereby the phenyl group was rotated around the benzylic bond of the biradical (**Figure 61**) in 20° increments and the relative energies of the structures generated were obtained (**Figure 62 and 63**). In its lowest energy conformation, the 2°/2° parallel (a) biradical is orientated for the formation of (**180**). A slight rotation about the benzylic bond to **X** (**Figure 62**), does not change this orientation but enhances the SDO without significantly increasing the energy. Rotation of the bulky phenyl group in the opposite direction eventually enhances the SDO (**Y**) allowing for the formation of (**181**) (**Figure 62**). However this involves a more significant increase in energy and so (**181**) is formed in lesser amounts. The lowest energy conformer of the 2°/2° crossed (a) biradical is orientated for the formation of (**182**); a slight rotation to **N** (**Figure 63**) enhances the SDO without changing the orientation. Rotation in the opposite direction, to **M**, allows for the formation of (**183**) but significantly increases the energy, and so (**183**) is the minor product. The fact that the rearranged cyclobutanone product is not isolated, or even observed in trace amounts, is not surprising in this instance. It can only be formed through either the 2°/2° parallel (Ph<sub>exo</sub>) or the 2°/2° parallel (Ph<sub>endo</sub>) biradicals, neither of which are formed due to their high relative energies.



**Figure 61**

Table 38\* Computational results for biradicals obtained from 1-methyl-1-((*2E*)-3-phenylprop-2-en-1-yl)-2(1*H*)-naphthalenone (**174**)

	2°/2° parallel (a)	2°/2° parallel (b)	2°/2° parallel (Ph <sub>exo</sub> )	2°/2° parallel (Ph <sub>endo</sub> )
Relative energy (kJ mol <sup>-1</sup> )	5.4	23.5	27.4	35.0
Spin density overlap	2.32×10 <sup>-3</sup>	1.34×10 <sup>-3</sup>	2.65×10 <sup>-3</sup>	2.05×10 <sup>-3</sup>
IRD (Å)	3.08	3.20	3.07	3.11
IPA	55.61	58.01	76.51	81.83
Cleavage angle	1.8/30.2	0.8/30.5	1.2/51.1	1.8/60.0
Radical/β-C distance (Å)			3.14	3.10
Singlet biradical optimization	SM	SM	SM	Step 1 CB formation
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )	 2.1 kJ mol <sup>-1</sup> <b>(180)</b>		 0.0 kJ mol <sup>-1</sup> <b>(181)</b>	
Experimental result	anti-“rule of five” ( <b>180</b> ),( <b>181</b> ) and “rule of five” products ( <b>182</b> ) and ( <b>183</b> ) (7:3:3:1) formed			

**Table 38 (contd.)** Computational results for biradicals obtained from 1-methyl-1-((2*E*)-3-phenylprop-2-en-1-yl)-2(1*H*)-naphthalenone (174)

	2°/2° crossed (a)	2°/2° crossed (b)	2°/2° crossed (Ph <sub>exo</sub> )	2°/2° crossed (Ph <sub>endo</sub> )
Relative energy (kJ mol <sup>-1</sup> )	0.0	19.8	53.9	55.1
Spin density overlap	2.75×10 <sup>-3</sup>	1.62×10 <sup>-3</sup>	3.56×10 <sup>-3</sup>	1.12×10 <sup>-3</sup>
IRD (Å)	3.03	3.18	2.97	3.14
IPA	50.2	51.5	82.8	127.5
Cleavage angle	5.3/14.6	14.1/27.2	10.8/71.7	9.3/70.3
Radical/β-C distance (Å)	no short Radical/β-C distances			
Singlet biradical optimization	SM	SM	“rule of five” product	SM
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )				
Experimental result	anti-“rule of five” (180),(181) and “rule of five” products (182) and (183) (7:3:3:1) formed			

\* See **Table 24** for glossary of terms

Relative energy vs bond rotation in the 2°/2° parallel biradical

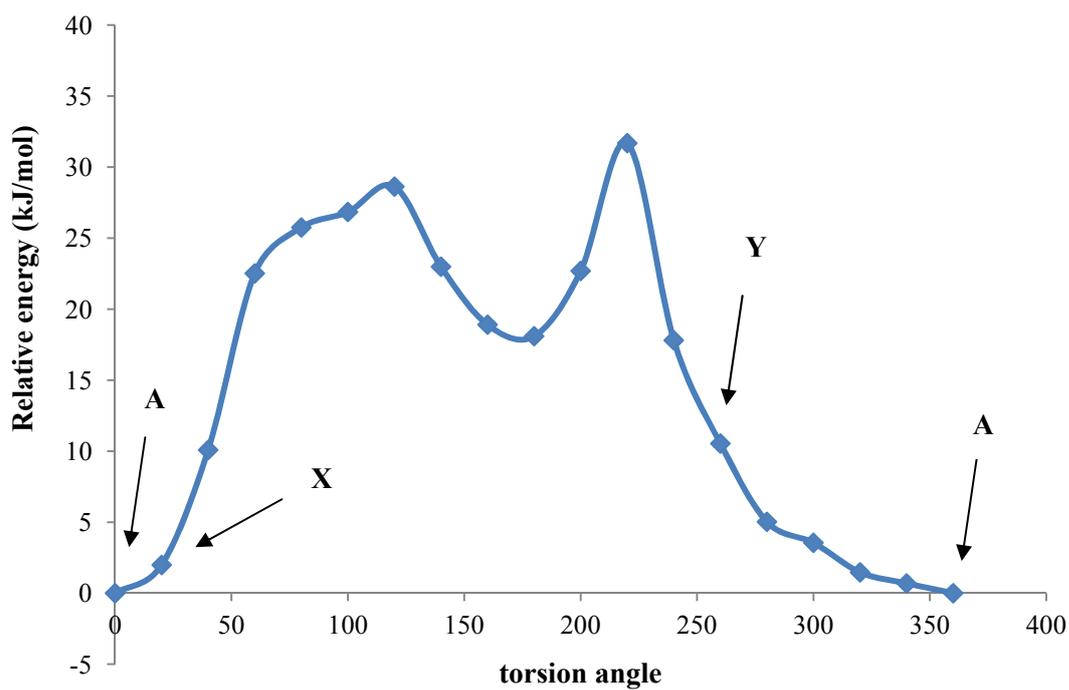
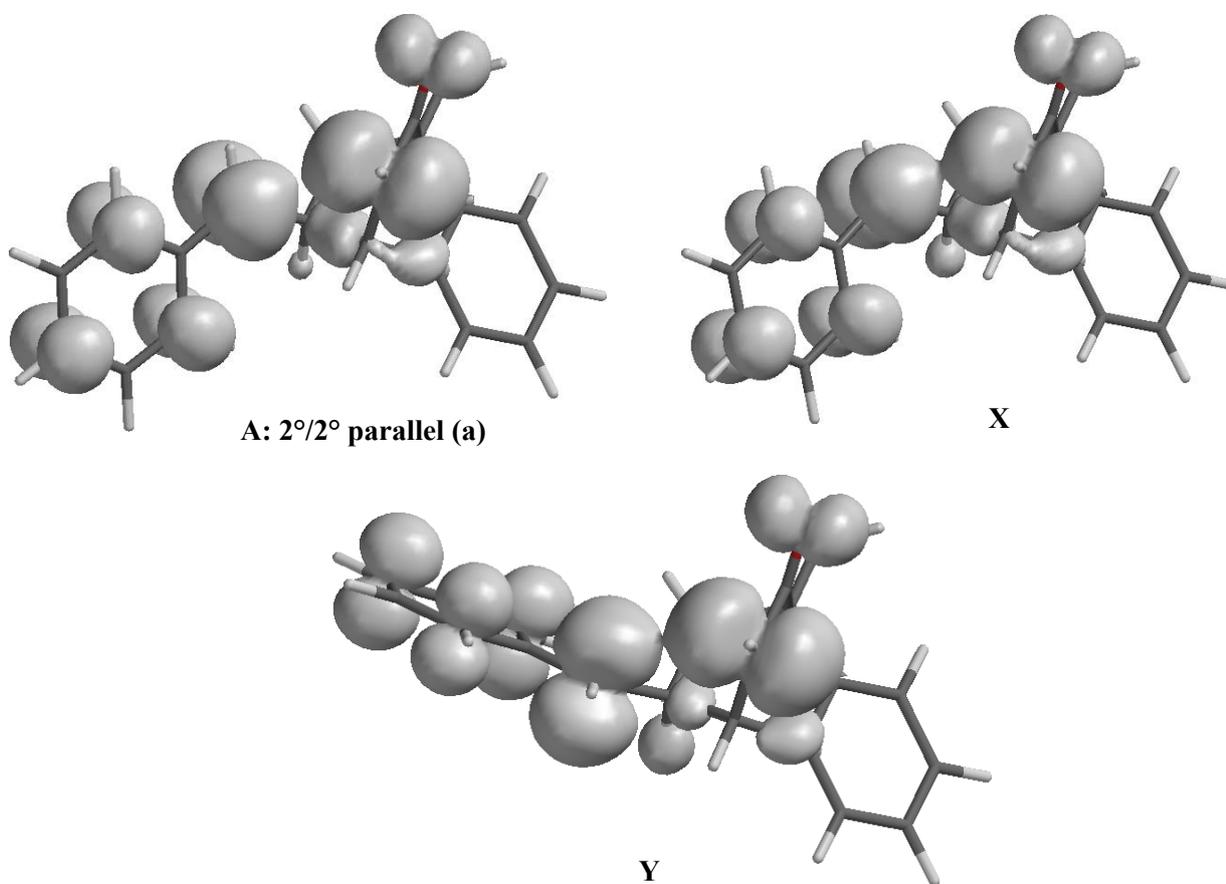
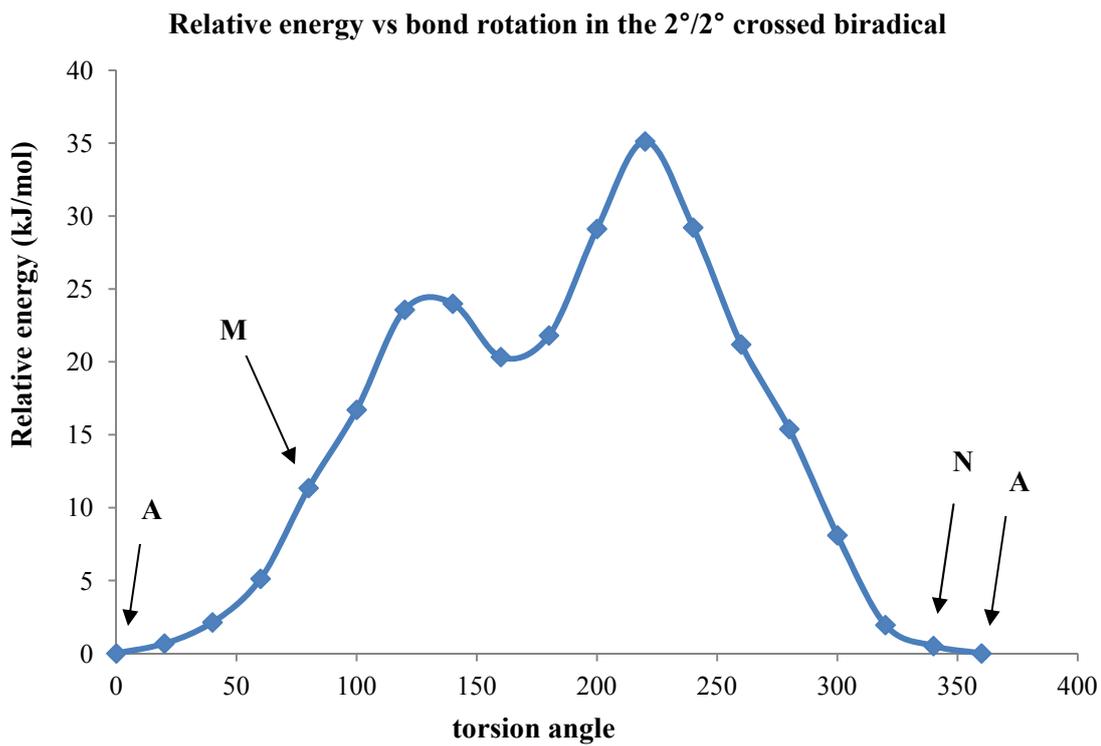
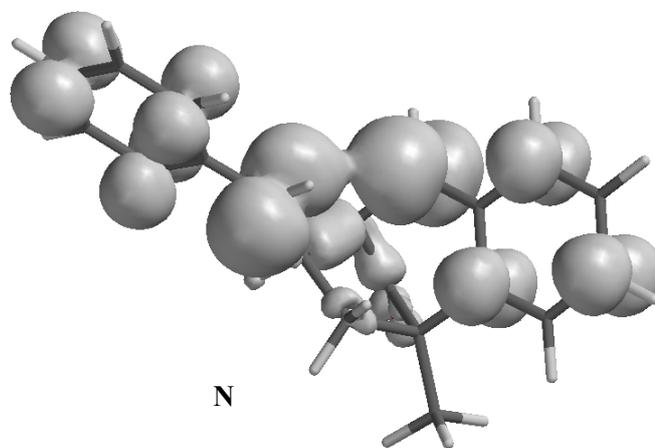
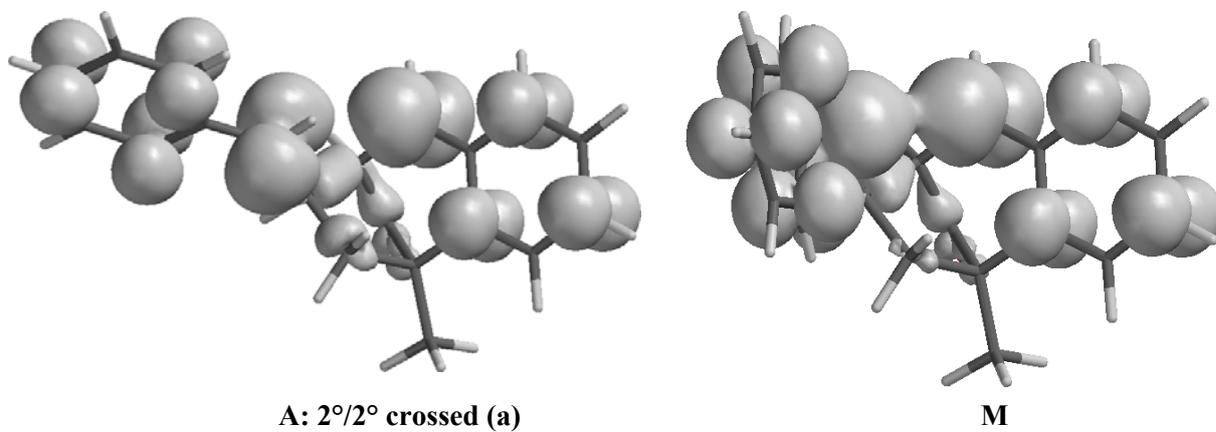


Figure 62



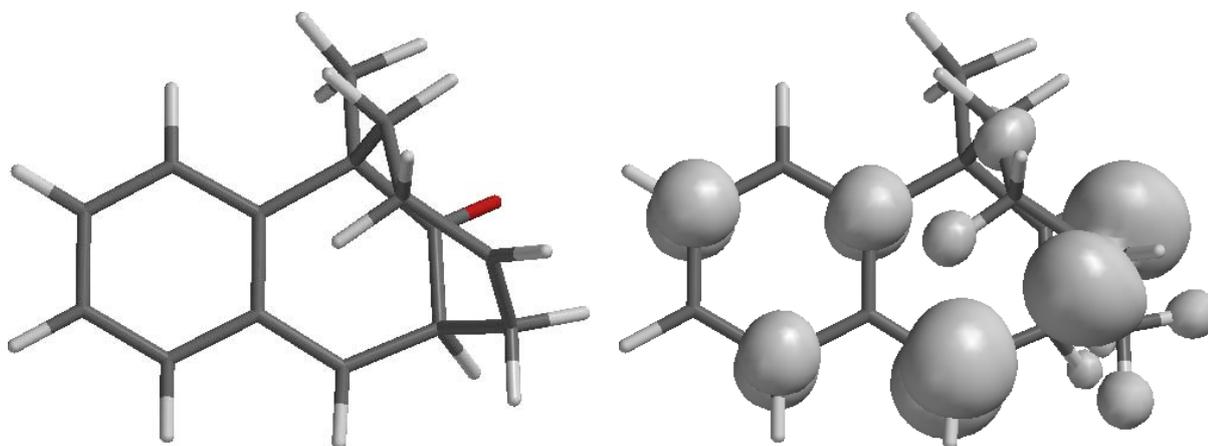


**Figure 63**



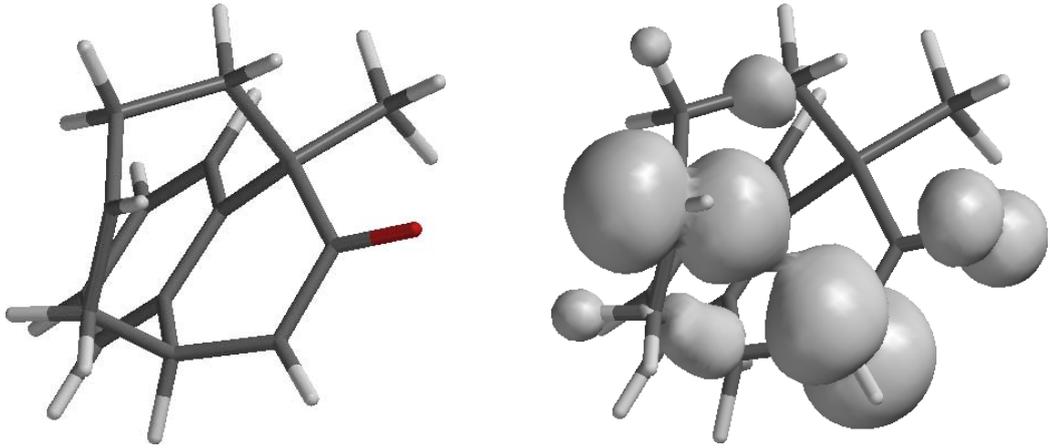
#### 2.3.4 Intramolecular [2+2] cycloaddition of 1-methyl-1-(but-3-en-1-yl)-2(1H)-naphthalenone (175)

Irradiation of the naphthalenone (**175**) led to the formation of the crossed product (**184**) (**Table 35**). This is an inversion of the regiochemistry observed for the naphthalenone (**172**), which has one less methylene in the linking chain, and gave the parallel anti-“rule of five” product. This result is consistent with what was observed for the enone (**158**) which also had an extra methylene in the chain linking the alkene units and gave the crossed product. Conformational searching identified unique low energy conformers for the 1°/2° parallel and the 1°/2° crossed biradicals, and two low energy conformers for both the 2°/2° parallel and the 2°/2° crossed biradicals. The 1°/2° parallel and the 2°/2° crossed (b) biradicals are immediately ruled out on energy grounds. The 2°/2° parallel (a) biradical has the lowest relative energy but due to its low SDO ( $1.00 \times 10^{-3}$  electrons/au<sup>3</sup>) (**Figure 64**) ring closure will not occur and bond cleavage will predominate.



**Figure 64**

Both the 2°/2° parallel (b) and the 1°/2° crossed biradicals have very similar SDO values (**Table 39**), but the 1°/2° crossed biradical has a lower energy relative to that of the 2°/2° parallel (b) which suggests that the crossed product should predominate. The 2°/2° crossed (a) biradical has a relative energy which also allows for its competitive formation and an SDO value ( $4.67 \times 10^{-3}$  electrons/au<sup>3</sup>) (**Figure 65**) that is much higher compared to the other competing biradicals. It seems probable that it is this biradical which is responsible for formation of the crossed cycloadduct (**184**).



**Figure 65**

Table 39\* Computational results for biradicals obtained from 1-methyl-1-(but-3-en-1-yl)-2(1H)-naphthalenone (175)

	2°/2° parallel (a)	2°/2° parallel (b)	1°/2° parallel	1°/2° crossed	2°/2° crossed (a)	2°/2° crossed (b)
Relative energy (kJ mol <sup>-1</sup> )	0.0	9.2	37.4	2.1	13.3	45.8
Spin density overlap	1.00×10 <sup>-3</sup>	2.87×10 <sup>-3</sup>	1.73×10 <sup>-3</sup>	2.65×10 <sup>-3</sup>	4.67×10 <sup>-3</sup>	6.18×10 <sup>-3</sup>
IRD (Å)	3.26	3.17	3.27	3.07	2.93	2.84
IPA	106.8	70.0	79.8	39.6	46.6	54.3
Cleavage angle	24.4/82.6	33.3/36.9	11.9/53.7	0.5/6.5	5.3/21.6	3.6/30.4
Radical/β-C distance (Å)	no short Radical/β-C distances					
Singlet biradical optimization	SM	SM	SM	SM	crossed product	crossed product
Resulting cycloadduct structure; relative energy (kJ mol <sup>-1</sup> )	 0.0 kJ mol <sup>-1</sup>			 10.5 kJ mol <sup>-1</sup> <b>(184)</b>		
Experimental result	crossed product <b>(184)</b> formed					

\* See Table 24 for glossary of terms

#### ***2.4 Conclusions and future work***

We have shown that the biradical conformation control concept can be successfully used to account for the regioselectivity and stereoselectivity of the intramolecular [2+2] cycloaddition reactions of a series of 6-alkenylcyclohex-2-en-1-ones and 1-alkenyl-1-methyl-2(1*H*)-naphthalenones.

The concept that the optimization of the singlet form of the biradicals might provide an indication of the outcome of these cycloaddition reactions would appear to be worth exploring further. The failure of the energy minimization algorithm used by Spartan to accurately mimic the processes by which the biradicals react is however, disappointing. Future work could include the evaluation of different optimization algorithms or the use of a different process entirely such as molecular dynamics. Future work might also include extending this type of analysis to systems which obey the “rule of five” to check on its applicability in those cases.

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