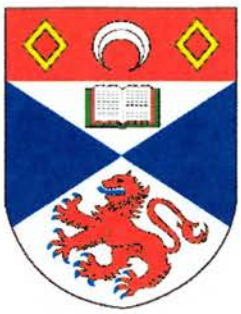
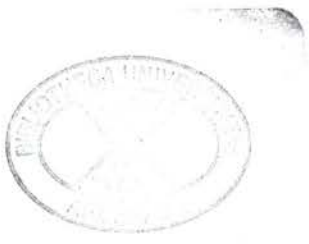


Evaluating the Reactivity of Cyclohexadiene Derivatives For Free-Radical Syntheses.

A thesis presented by Leon V. Jackson to the University of St. Andrews for the degree of Doctor of Philosophy.

October 2001



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Declarations

I, Leon Valentine Jackson hereby certify that this thesis has been composed by myself, that it is a record of my own work and that it has not been accepted in partial or complete fulfilment of any other degrees or professional qualifications.

Signed Date 26 Oct 2001

I was admitted to the Faculty of Science at the University of St. Andrews under Ordinance General No. 12 on the 1st October 1997 and as a candidate for the degree of PhD. On the 1st October 1998.

Signed Date 26 Oct. 2001

I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate to the degree of PhD.

Signed Date 26 Oct. 2001

Declaration

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Contents

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Many people have provided a great deal of guidance, assistance and support during the time it has taken me to complete this PhD. The greatest and most enduring presence was that of my supervisor, Professor John Walton. His relentless pursuit of excellence and constant thirst for knowledge is both exemplary and inspirational. Without his support this PhD would not have been possible.

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The final acknowledgement goes to Andrea, who has provided me with a level of emotional support that can only be given, not expected.

Abbreviations and Symbols

AIBN	2,2'-Azobisisobutyronitrile
DTBP	Di-*tert*-butyl peroxide
bp	Boiling Point
Bu_3SnH	Tributyltin hydride
BuLi	*n*-Butyl Lithium
Bz	Benzyl
DCC	Dicyclhexylcarbodiimide
DCM	Dichloromethane
DPPH	2,2-Diphenyl-1-picrylhydrazyl
DMAP	Dimethylaminopyridine
EPR	Electron Paramagnetic Resonance
Ether	Diethyl Ether
GC/MS	Gas Chromatography/Mass Spectrometry
GLC	Gas Liquid Chromatography
hfs	Hypefine splitting constants
Im	Imidazole
$In^{\bullet}$	Initiator
Light Petroleum	40/60 Petroleum Ether
M^+	Molecular Ion
MeOH	Methanol
mp	Melting point
Mol	Mole
Ms	Mesyl
m/z	Mass to charge ratio
NMR	Nuclear Magnetic Resonance
r.t.	Room Temperature
s, d, t, q, q^I	Singlet, doublet, triplet, quartet, quintet
TBS	*t*-Butyldimethylsilane
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	Tetramethylethylene diamine
Ts	Tosyl

Abstract

A summary of the tin hydride method for generating radicals in organic synthesis is presented, followed by an illustrative guide to the many alternative methods available for mediating radical reactions. Particular emphasis is placed upon recent developments in the field of organic radical precursors, which are free from metal encumbrances. This is followed by two chapters describing our efforts to advance current research in the use of pro-aromatic compounds as free-radical precursors.

A range of 1-alkylcyclohexa-2,5-diene-1-carboxylic acids have been prepared, using the Birch reduction/alkylation methodology, and shown to generate the corresponding alkyl radical using Electron Paramagnetic Resonance (EPR) spectroscopy. Radical dissociation rates for 1-alkylcyclohexa-2,5-diene-1-carboxylic acids containing linear, branched and cyclic substituents, as well as allyl, propargyl, cyanomethyl and benzyl alternatives were studied using a novel EPR technique.

For each carboxylic acid, EPR spectra for the corresponding cyclohexadienyl radicals were observed at lower temperatures, which were replaced by spectra due to the ejected carbon-centred radicals at higher temperatures. Rate constants (k_d), for the release of carbon-centred radicals from the cyclohexadienyl radicals, were determined from radical concentration measurements. The rate of cyclohexadienyl radical dissociation increased with branching in the 1-alkyl substituents and with enhanced electron delocalisation in the ejected carbon-centred radical, however, the dissociation rate decreased when 3,5- and 2,6-dimethyl-substitution was introduced onto the cyclohexadienyl ring.

Rate data for the abstraction of a bis-allylic hydrogen from the cyclohexadienyl acids was obtained for ethyl, *n*-propyl and isopropyl radicals. These results indicated a sharp drop in the rate of hydrogen abstraction as the degree of branching in the attacking radical increased.

A variety of 1-carbamoyl-1-methylcyclohexa-2,5-dienes have been prepared and analysed for their radical donating properties. EPR studies confirmed the formation

of the delocalised cyclohexadienyl radical at low temperatures, and as the EPR cavity temperature was increased, the radical induced homolysis of these compounds was encouraged in order to release the associated aminoacyl radicals. Measurements of concentration data from the acquired EPR spectra enabled the rate of dissociation for several of these aminoacyl radicals to be calculated.

The released aminoacyl radicals were also examined for their ability to take part in intramolecular cyclisations. Suitably unsaturated compounds were confirmed to take part in 4-*exo-trig* and 5-*exo-trig* cyclisations, in order to yield β- and γ- lactams.

Chapter 1

Introduction

The Use of Radicals in Organic Synthesis

The majority of reactions in organic chemistry centre around the interactions between positively and negatively charged species, including partially polarised compounds. The latter are formed by inductive or mesomeric effects of neighbouring atoms, which are held together by covalent bonds.

However, organic compounds can also participate in radical reactions, an area of chemistry that has grown in importance over the last three decades.[1-4] These radical reactions involve the homolytic cleavage of covalent bonds with the production of highly reactive intermediates, which possess an unpaired electron.

Radicals have been recognised as synthetically useful for some time, mainly for their unique ability to construct polycyclic molecules via tandem radical cyclisations. These reactions result in the conversion of comparatively simple starting materials into more complex and potentially useful molecules.[5] Other important radical reactions include intramolecular ring closures to produce monocyclic products, additions of radicals to centres of unsaturation and radical decarboxylations.

There are several positive characteristics that make radicals favourable as intermediates in organic synthesis. They are neutral species; therefore solvation has no great effect. In addition, reactions can be carried out in more polar, hindered environments that often prove to be more effective at furnishing the desired products.[3] Radical processes also have the potential to be high yielding due to their ability to take part in radical chain mechanisms.

Generally, radical procedures can be performed under relatively mild reaction conditions, without the presence of acid or base. This helps prevent any unwanted, secondary reactions occurring within the reactants and removes the necessity to protect many vulnerable functional groups prior to an experiment.

The conventional method of generating a radical in organic synthesis involves treating an alkyl halide or selenide with a stoichiometric equivalent of tributyltin hydride.

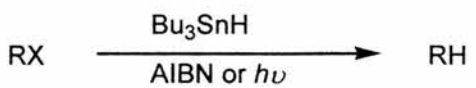
Due to the increased interest in these radical processes it follows that commercially available organotin hydrides are important reagents for synthesis. These tin compounds have numerous advantages, including good initiation rates and the generation of high product yields. However, the toxicity of organotin compounds must also be taken into account and this proves to be a major drawback.[1]

Organostannanes are known to break down during radical reactions and generate highly toxic tin residues, which are difficult to separate from the end product. These residues are potent neurotoxins, a factor that commonly rules against their use in the pharmaceuticals industry. Furthermore, carbon-centred radicals are able to quickly abstract a hydrogen atom from the organotin hydrides. This can potentially cause problems when a rearrangement, or radical addition to a point of unsaturation, is required before the hydrogen abstraction.

It is clear that an alternative, non-toxic reagent, with the ability to replace tin in many applications, would be highly desirable. Many techniques have been employed in an attempt to improve the removal of toxic organotin residues or find new methodologies to generate radicals without the presence of tin. The purpose of this introduction is to review the tin hydride method in more detail and examine some of the alternative methods which have been developed for generating radicals suitable for preparative purposes.

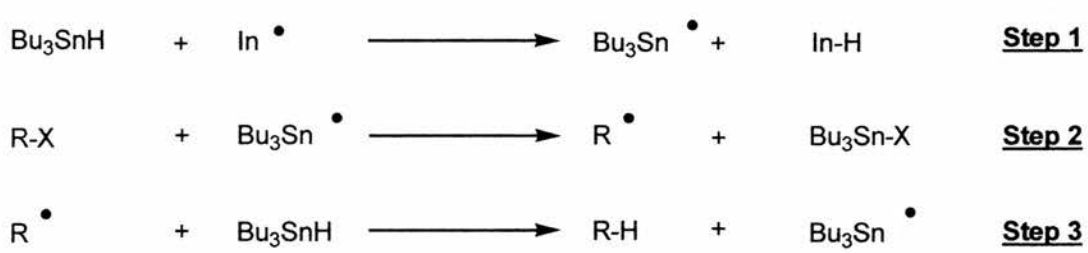
Radical Formation Using Tin Hydride

The reduction of an alkyl halide, RX, to RH (Scheme 1) was discovered in the 1960's.[6] This is a classic example of a radical chain reaction which requires the presence of tributyltin hydride.



X=Cl, Br, I **Scheme 1**

The Sn-H bond is relatively weak and can be broken homolytically when exposed to UV radiation, or when heated in the company of a catalytic amount of AIBN. The resulting radical, $Bu_3Sn^{\bullet}$, has a high affinity for halogens and can readily abstract chlorine, bromine or iodine atoms from alkyl halides, giving the desired carbon-centred radical, $R^{\bullet}$, together with the tin by-product which contains the very strong Sn-X bond. The resulting alkyl radical can abstract hydrogen from the remaining tin hydride to give the desired product, RH, and regenerate the tin radical in what is known as the chain transfer step. This allows the chain mechanism to continue (Scheme 2).[7]



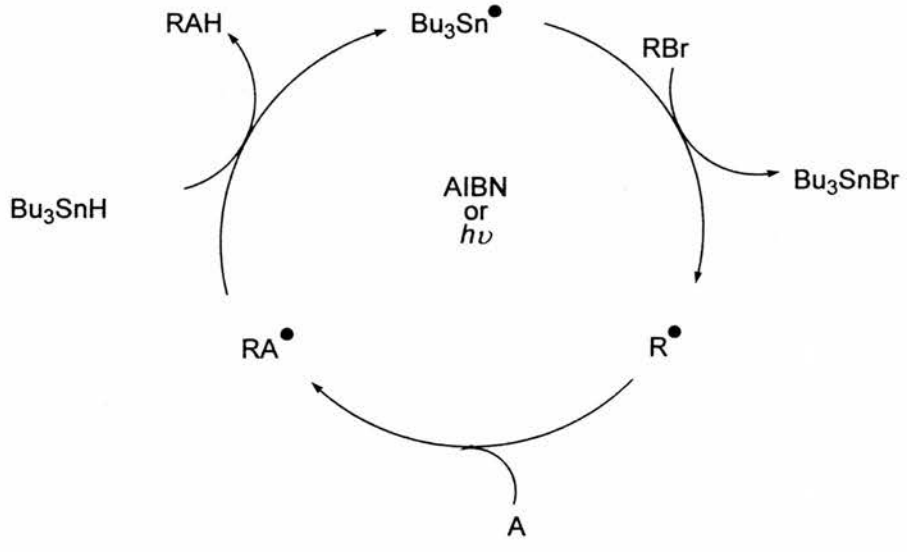
Scheme 2

The success of this type of mechanism relies on the ability to consume and then regenerate the intermediate radical, known as the chain carrier. This chain carrier can then react further with the alkyl halide to allow this mechanism to continue in a cycle.

Radicals are highly reactive intermediates, indeed it is feasible that two radicals could meet and form a covalent bond. However, this event is very rare in chain mechanisms as the nature of the reaction supplies the chain carrier in very low concentrations. As

a result, the probability of two radicals meeting in solution, in a so-called termination step, is minimal and accordingly the radical mainly interacts with the alkyl halide to form the desired product.

From a synthetic point of view, it is more beneficial for an alkyl radical to be intercepted either inter- or intramolecularly by an alkene, **A**. Thus the radical chain mechanism can be modified to the sequence of steps illustrated in Scheme 3.



Scheme 3

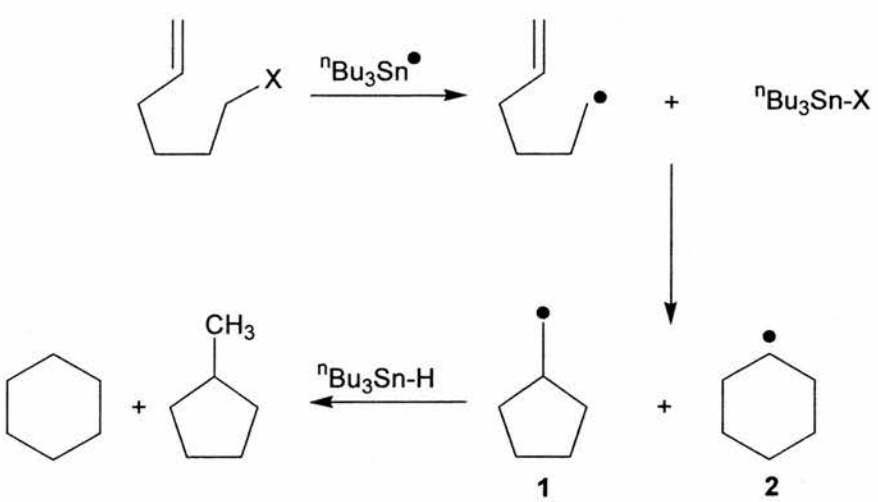
The alkyl radical can therefore act in two ways; either hydrogen abstraction from the tin hydride occurs to give the undesired reduction product (RH), or addition to an alkene can take place prior to H-abstraction, to give the more functional RAH.[8] Clearly it is advantageous to develop a method favouring the radical addition to an alkene, therefore several techniques have been developed to control this competition.

Stork describes various methods in his proposed synthetic route to Prostaglandin $F_{2\alpha}$.[9] He suggests that a large excess of the alkene be used to encourage the radical addition, and that the tributyltin hydride should be added portionwise to maintain a low concentration of the tin hydride in the reaction mixture. A further solution to the inconvenience caused by the excellent hydrogen donating ability of tributyltin hydride is to use an organotin reagent that possesses no Sn-H bond, for example hexamethylditin, Me_6Sn_2.[10, 11] When exposed to radiation the tin-tin bond is cleaved,

generating the organotin radical, which can then react in the conventional manner. This procedure can be effectively incorporated in many organic syntheses, although an additional hydrogen source is occasionally required to avoid polymerisation.

Intramolecular cyclisation

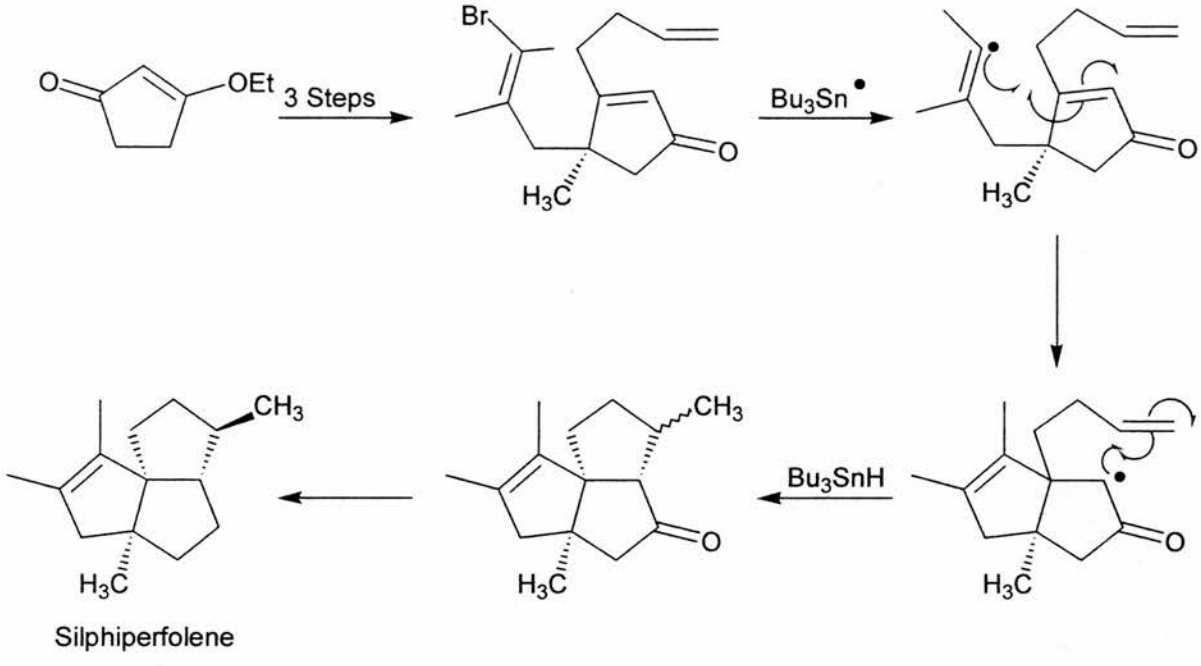
Intramolecular radical additions to multiple bonds are particularly useful in organic synthesis. This phenomenon has been studied a great deal and can provide unique, cyclised products from relatively simple starting materials.[12, 13] An important prototype is the cyclisation of the hex-5-enyl radical to the cyclopentylmethyl radical (Scheme 4). It must be noted that the 5-*exo* mode of cyclisation to give product **1** is favoured, and that relatively little of the 6-*endo* compound **2** is formed. The latter would be expected to be more stable, being a secondary radical and having an unstrained cyclohexane ring. This synthetically important result can be explained in terms of an early transition state having little product character. Thus, stereoelectronic factors govern the cyclisation, and the best overlap between the radical orbital and π orbital of the double bond is achieved when in the five membered ring transition state.[14, 15]



Scheme 4

Tandem cyclisations have been imaginatively used in the preparation of polycyclic compounds. This fascinating area of radical chemistry was developed by Curran and his co-workers when they derived a novel method for synthesising (±)-hirsutene in 1985.[16] Curran subsequently went on to publish a very thorough and informative

review on this subject area,[2] which led to the synthesis of a large variety of diverse natural products, including several other triquinanes. An example of Curran's work can be seen in the radical construction of silphiperfolene (Scheme 5).[17]



Scheme 5

Radical mechanisms can also be used for reduction, deoxygenation and intramolecular hydrogen abstraction. It can therefore be seen that radicals are very useful tools, however, the toxicity of tin residues makes these methods inappropriate for the syntheses of drugs, medicines and other formulations intended for human consumption.

New tin reagents which aid product isolation

A large proportion of research has centred around the generation of alternative tin compounds that facilitate the removal of toxic residues from the end product. The creation of innovative purification techniques, which improve the extraction of tin deposits from these radical mixtures, has also been a priority.

An original solution for the removal of tin compounds is the use of a potassium fluoride precipitation technique, introduced by Jacobus in 1979.[18] Addition of a saturated solution of KF to the product mixture results in the cleavage of all Sn-Br,

Sn-I and Sn-Sn bonds and the formation of Sn-F bonds in their place. The organotin fluorides are known to exist in hexameric arrays, which readily precipitate out of solution. Filtration removes the majority of the tin residues, however, even after column chromatography there remains about 2 mol% of tin contamination.[19] This primitive method of removing toxic residues also gave problems when using silyl protecting groups (deprotection) and esters (transesterification).

Fluorine has been the centrepiece in other tin removal solutions. A novel procedure, adapted by Curran and his co-workers, relies on the immiscibility of dichloromethane and perfluorocyclohexane. It employs fluorous reagent **3** (Scheme 6), which can be prepared in a three-step synthesis.[20] The reaction is carried out in trifluoromethylbenzene, which is evaporated off upon completion and replaced with a mixture of dichloromethane and perfluorocyclohexane. The fluorous tin by-products remain in the fluorocarbon layer, while the desired organic product passes into the dichloromethane where it can be isolated from any tin contamination.

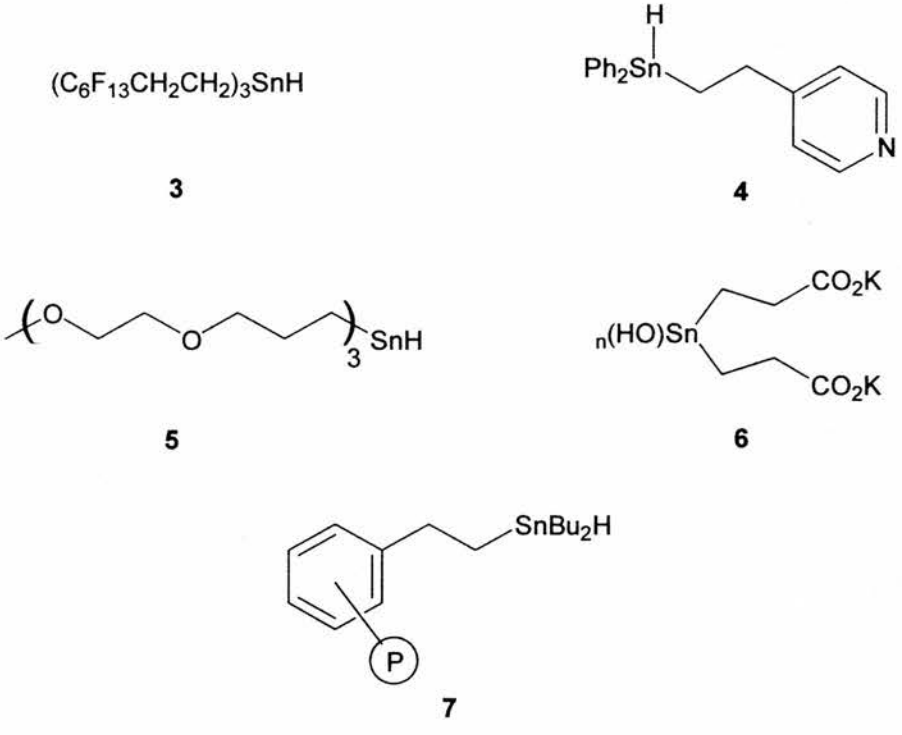
Clive has recently developed a novel pyridylstannane **4**, which contains the tin functionality.[21] This compound is readily soluble in polar organic solvents, yet the tin-halogen by-products have very low R_f values in ethyl acetate:hexane (1:3), which allows the desired product to be effectively isolated by chromatography. These reagents can be used to form products in comparable yields to those obtained using the tin hydride method.

Converse techniques generate tin residues that are very non-polar and therefore elute before the desired product. An example of this technique uses an excess of sodium cyanoborohydride in *tert*-butyl alcohol on the product mixture.[22] This regenerates the organotin hydride and subsequent column chromatography of the mixture elutes the tin hydride first, which can be reused, followed by the virtually tin free product. However, this procedure requires heating in refluxing *tert*-butanol, which is not compatible with heat sensitive substrates.

Breslow has also tried to improve the surrounding structure of tin and its residues in order to assist purification.[23] The water-soluble tin hydride **5** was originally reported in 1990 and enabled radical reactions to be conducted in environmentally friendly,

aqueous solutions. Several provisional reactions were carried out using this modified tin compound, which generated reduction products in varying yields of between 37% and 84%. The polarity of the tin hydride should facilitate product isolation, however, the synthesis of the tin precursor is a rather lengthy process and it is not commercially available.

Collum and co-workers have subsequently described an improved water-soluble tin reagent **6**.[24] This novel compound has provided consistently high yields, comparable to that of the conventional Bu_3SnH/AIBN method, when performing basic reductions and cyclisations. Regretfully these compounds must still be synthesised in the lab prior to use and this prevents them from becoming a popular replacement.

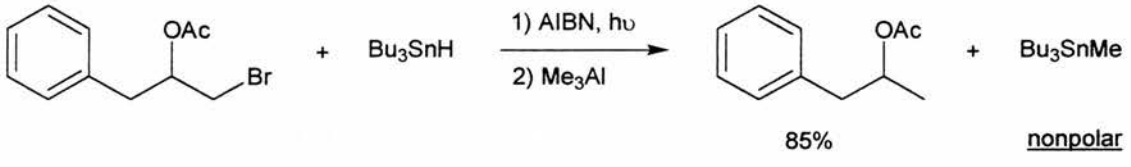


Scheme 6

Polymer supported tin hydrides are arguably the most effective precursors for isolating a desired organic product free from tin residues. The polymers are insoluble in the chosen reaction solvent; therefore the organic product can be isolated simply by filtration, followed by the removal of the reaction solvent. The recovered polymeric tin halides can generally be recycled back to the tin hydride for further use. Neumann[25, 26] has reported polymers of type **7** to be of general use in synthesis.

However, these reagents are not commercially available and therefore must be prepared prior to use, which can prove a rather complex task.

Renaud has recently developed a novel work up procedure, which successfully leads to the complete removal of tin residues.[27] It was discovered that contamination by tin derivatives did not occur when working with an excess of Me_3Al in the reaction mixture. Trialkyltin halides react with Me_3Al at room temperature to give a rapid and clean formation of methyltrialkyltin.[28] Tetraalkyltin derivatives are highly non-polar compounds that can be washed easily from silica gel with hexane; therefore, it is possible to transform the trialkyltin halides formed during the radical reaction by a one-pot treatment with Me_3Al (Scheme 7). The methyltributylstannane is easily separated from the product by filtration over a short column of silica gel with hexane as eluent. Unfortunately, this procedure cannot be considered for all reactions as several functional groups (aldehydes and ketones) will interact with the Me_3Al and break down.



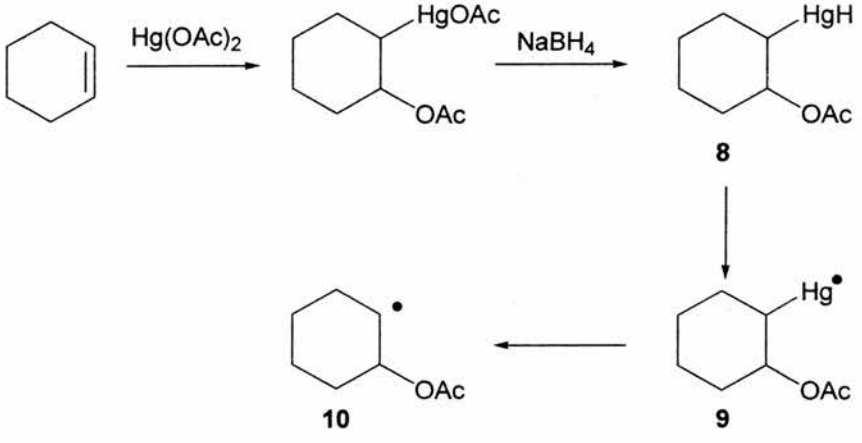
Scheme 7

Alternative metal chain carriers

It is clear that a non-toxic alternative to tin would be a great asset to the synthetic community and a great deal of investigation has focused on finding new methods to generate radicals. Primarily, scientists have looked at different metal centres, which possess similar characteristics to that of organotin hydrides without the toxicity issues. Mercury, cobalt, manganese and samarium exhibit radical behaviour under specific conditions and have been exhaustively studied over the previous fifteen years in an attempt to find a compliant replacement for tin.

The mercury method

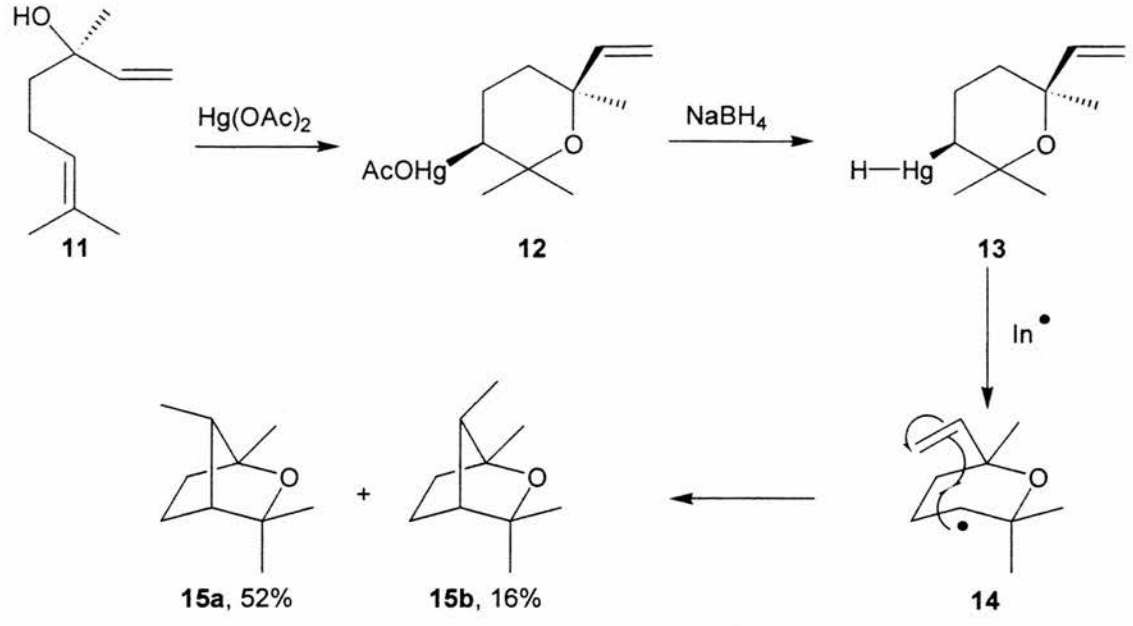
Organomercury compounds possess the ability to function as sources of radicals for use in synthesis.[11] The organomercury hydride is prepared *in situ* by the action of mercury(II) acetate on alkenes, followed by reduction using sodium borohydride to provide the weak Hg-H bond (Scheme 8). The resultant hydride **8** can undergo Hg-H bond dissociation, analogous to tributyltin hydride, producing the labile alkylmercury radical **9**. This decomposes spontaneously to release mercury and form the alkyl radical **10**.



Scheme 8

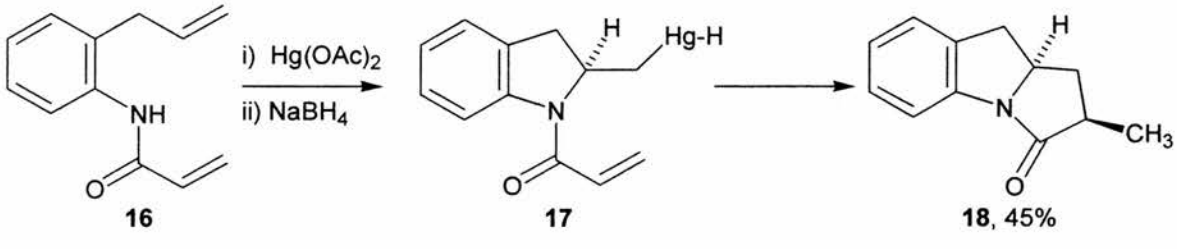
The radical generated using the mercury salt behaves in a similar fashion to a radical generated with the aid of tin. It can therefore take part in various additions to alkenes, cyclisations and radical cascades.

An illustration of the preparation and reactivity of these compounds can be seen in Schemes 9 and 10. Linalool, **11**, was treated with mercury(II) acetate to give the monocyclic organomercury compound **12**, which was formed by electrophilic attack of mercury acetate on the electron-rich double bond in **11**, followed by intramolecular attack by the OH group.[29] The organomercury hydride **13** was formed upon reduction using sodium borohydride and enabled homolysis of the C-Hg bond to give radical **14**. This radical promptly underwent a 5-*exo* cyclisation before abstracting hydrogen from **13** to form the bicyclic compound **15** as two isomers in a 68% yield.



Scheme 9

Danishefsky and co-workers[30] have also used alkyl mercurials in the synthesis of the benzoannelated tricyclic compound **18**. Aryl amide **16** was converted to the hydride **17** by treatment with mercury(II) acetate followed by sodium borohydride. The amide functionality acts as a nucleophile by attacking the carbon bearing the acetyl group, thus generating the first ring. The intermediate hydride **17** was not isolated, but allowed to fragment in order to form the primary radical which rapidly cyclised to yield the tricyclic product **18** in a 45% yield.



Scheme 10

The mercury method holds several advantages over the more traditional use of tin. The conditions for an organomercury reaction are significantly milder than those dictated by tin, requiring only room temperature with no dependence on high intensity light. The reaction times with mercury compounds are also significantly faster, with the average reaction completing in the order of minutes rather than hours. Finally, the

straightforward separation of any mercury residues from the end product appears to make this process a worthwhile alternative to toxic tin. However, the organomercury hydride is a better hydrogen donor than trialkyltin hydride, therefore the mercury technique can only be employed in syntheses involving very reactive alkenes. In addition, the reduced yields and the handling issues associated with mercury have limited the application of this procedure.

The cobalt procedure

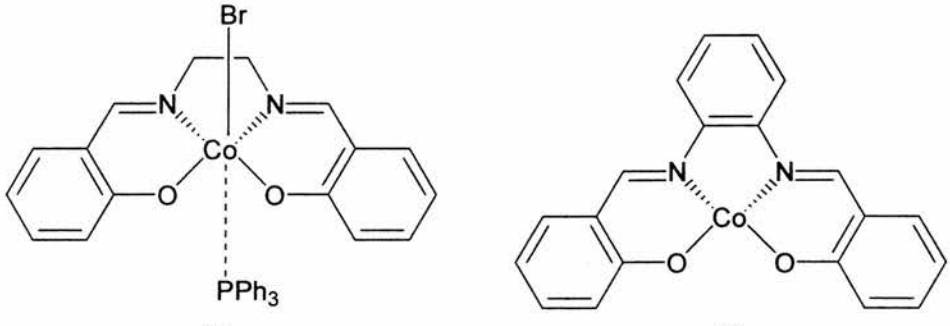
Cobalt is the core transition element in vitamin B_{12}. The mechanism of this complex biological product has been studied in immense detail and investigations demonstrated that the reactions are triggered by the homolytic cleavage of the carbon-cobalt bond.[31, 32] This information tells synthetic chemists that: -

i) Cobalt forms weak covalent bonds with carbon leading to relatively stable organocobalt compounds.

ii) Homolysis of these organocobalt molecules could provide a good source of carbon radicals.

Researchers therefore began to examine some of the free radical chemistry of organocobalt complexes in more detail.

Most radical activity has been observed using two forms of cobalt complex which model the vitamin B_{12} structure, these are bromotriphenylcobalt(III) salen **19** and cobalt(II) salophen **20** (Scheme 11). These organocobalt compounds can be used to generate alkyl, aryl and acyl radicals that are suitable for use in organic syntheses.

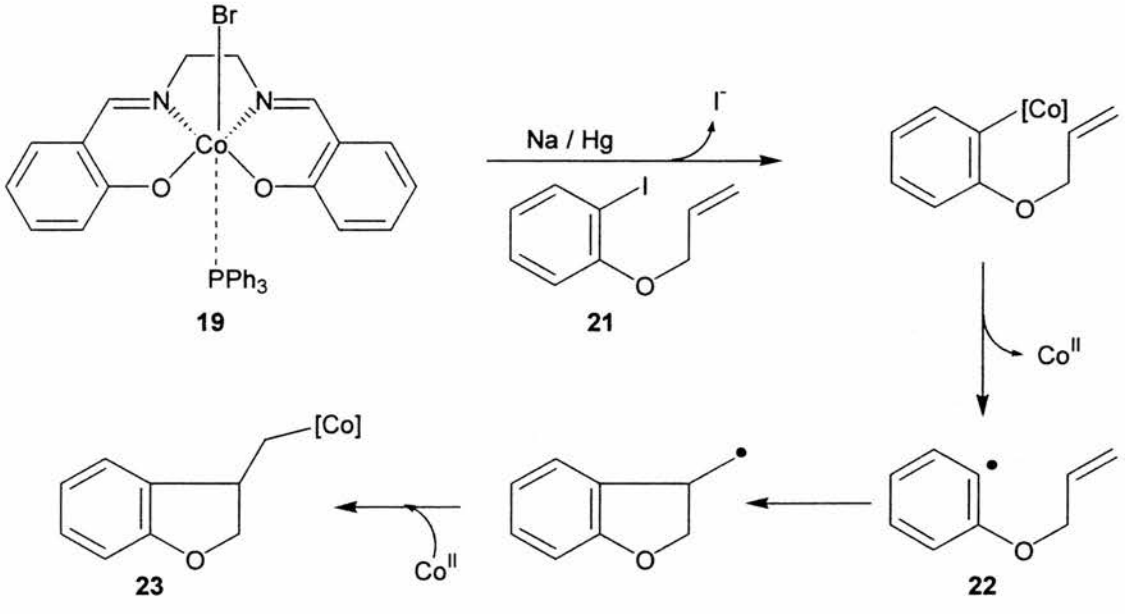


19 $BrCo^{III}(salen)PPh_3$

20 $Co^{II}(salophen)$

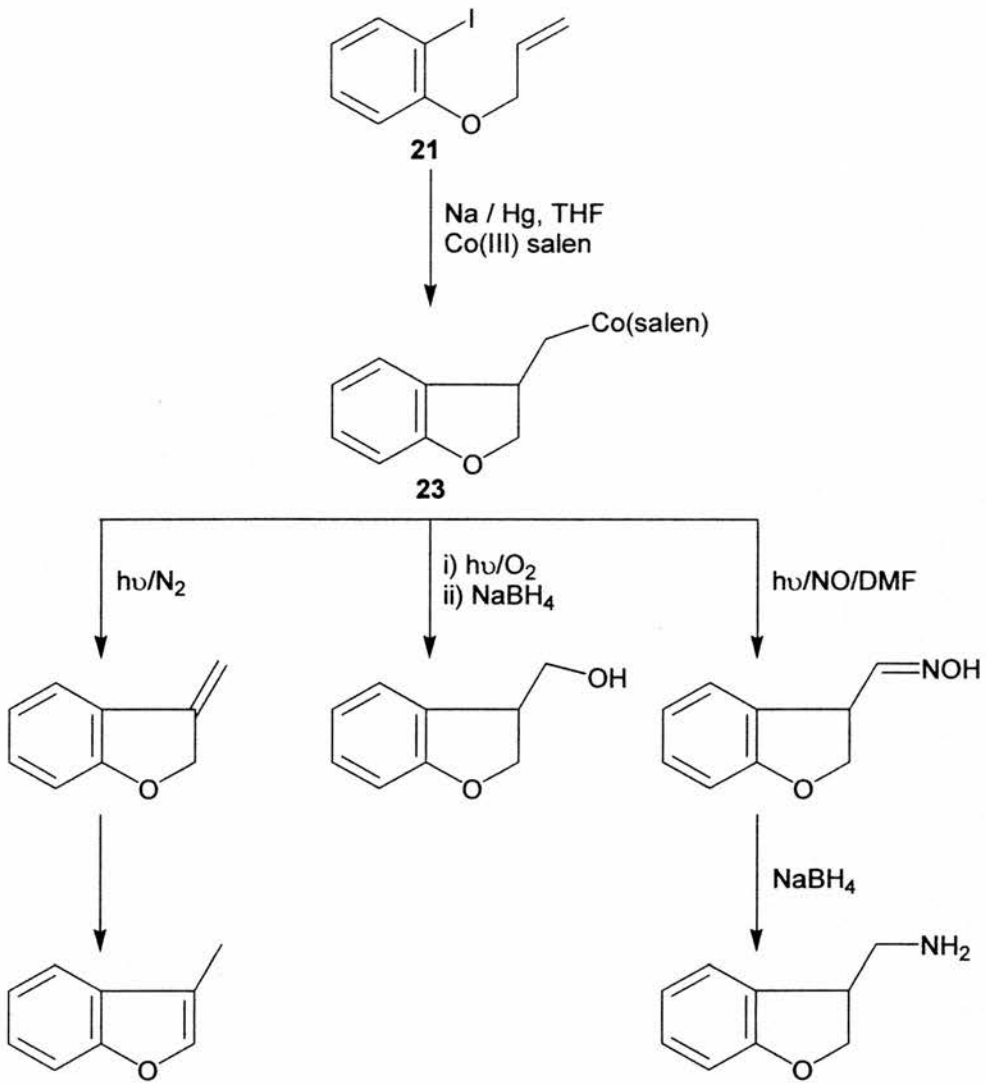
Scheme 11

The 5-*exo* cyclisation of allyl 2-iodophenyl ether **21** using Co(III) salen is a popular example of how these reactions progress (Scheme 12). Cobalt complex **19** was treated with a small amount of sodium amalgam in THF. This was followed by the addition of aryl iodide **21** in order to deliver benzofuran **23**, which was isolated in 65% yield.[33] The mechanism for this reaction involves reduction of the cobalt(III) complex using the sodium amalgam to generate a cobalt(I) species which transfers an electron to the carbon-iodine bond of compound **21**. This results in the displacement of the iodide anion and formation of an aryl radical **22** which cyclises onto the proximate double bond, forming a primary radical. This radical is then trapped by the cobalt(II) species to give **23**. The action of the salophen complex was essentially identical.



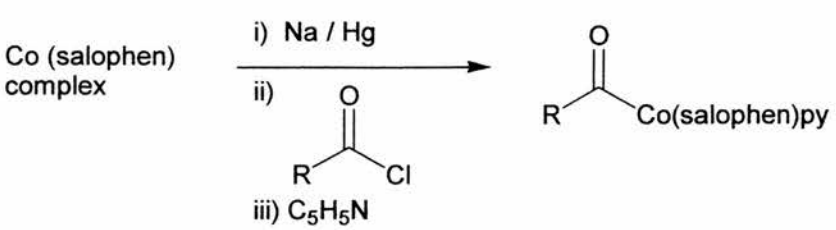
Scheme 12

The true advantage of using a cobalt complex can be observed after cyclisation has occurred. The product **23** contains a further weak cobalt-carbon bond and can consequently undergo a further homolysis in the presence of a different radical trapping agent in order to introduce a distinct functionality at the radical centre. This illustrates that functionality can be maintained within the cyclisation product in contrast to the trialkyltin hydride reductions (Scheme 13).[34]

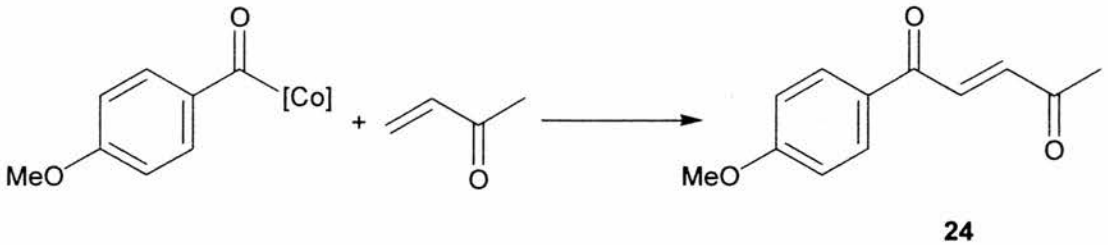


Scheme 13

Organocobalt reagents also function as sources of acyl radicals which are prepared by the reduction of the cobalt (salophen) complex using sodium amalgam, followed by treatment with the appropriate acid chloride and chromatographic purification in the presence of pyridine (Scheme 14).[35] When heated, these complexes readily generate acyl radicals which can add to various activated alkenes before β-elimination occurs to generate the conjugate enone **24** (Scheme 15).



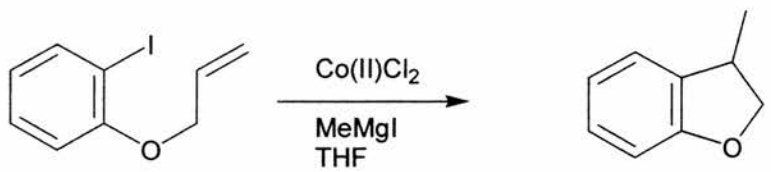
Scheme 14



24

Scheme 15

An alternative to using a cobalt salen or salophen complex has been described by Jones.[36] The iodide **21** was converted to dihydrobenzofuran **25** in a 54% yield when added to anhydrous $Co(II)Cl_2$ in THF, followed by the addition of a Grignard reagent, MeMgI, prior to refluxing the mixture (Scheme 16). The mechanism involves the formation of an organocobalt species that is derived from the reaction of the Grignard reagent and cobalt(II) chloride. This complex reacts with the aryl iodide to generate the corresponding aryl radical, which undergoes 5-*exo* cyclisation to give **25**.



21 **25**, 54%

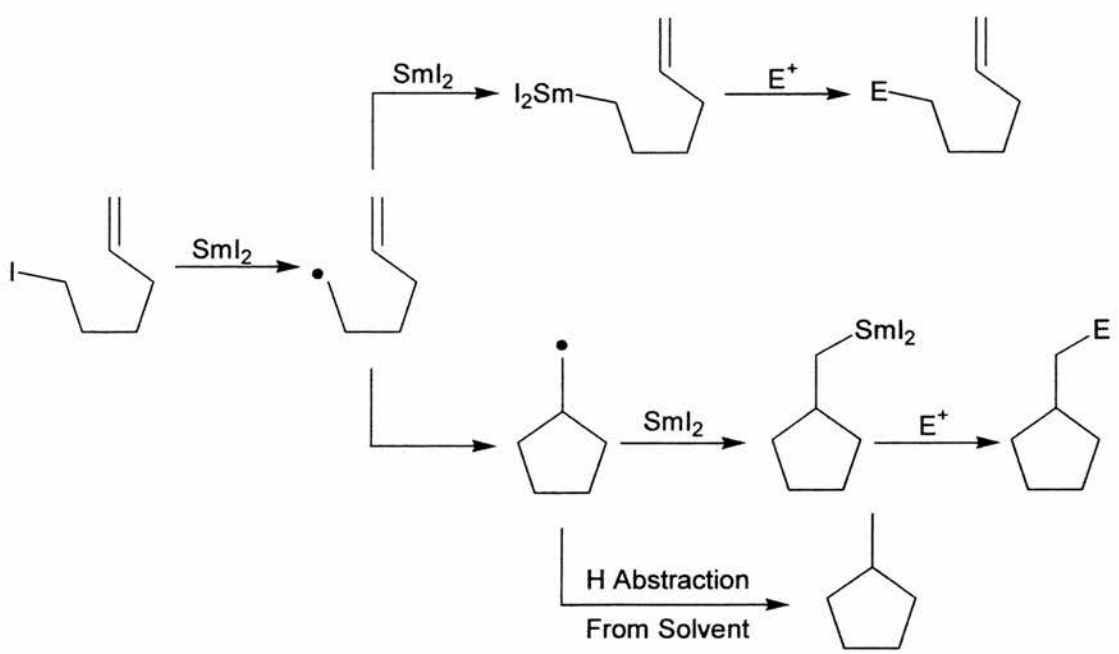
Scheme 16

Organocobalt compounds serve well as sources for alkyl radicals. Cobalt residues are straightforward to remove from the required products and reaction yields are comparable to equivalent reactions using tin precursors. This solution does have its disadvantages, as cobalt is also a heavy metal and therefore toxic if ingested in unusual amounts. The cleavage of the cobalt complex from the end product in order to add the extra functionality can also prove difficult on occasion.

The reductive approach: samarium(II) iodide

Samarium(II) iodide, SmI_2, has established itself as a versatile reagent with numerous applications since its introduction by Kagan in the late 1970's.[37] Over the last decade this compound has become increasingly popular as a mediator in radical reactions due to its selectivity, efficiency and simplicity of use.[38]

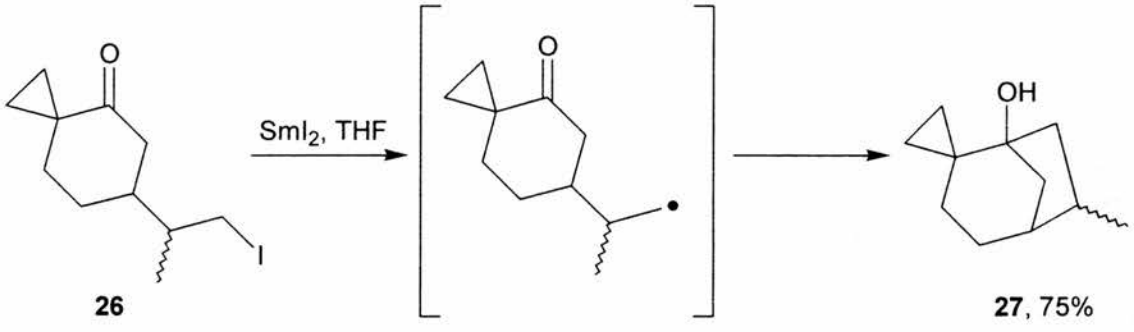
Generally, samarium diiodide reactions involve an alkyl halide, which accepts an electron from SmI_2 in order to displace the halide and form the designated alkyl radical (Scheme 17). The pathway of the mechanism is very reliant on the reaction conditions. Initially, hydrogen abstraction from the solvent could occur to give the reduced alkyl product. However, the conversion of the alkyl radical to a new species *via* an inter- or intramolecular rearrangement is also plausible if the rate of this modification is fast. Finally, samarium(II) iodide can interact with any intermediate radical in a reductive manner to form the corresponding organosamarium compound. This can be beneficial as it allows synthetic chemists to perform further transformations in an attempt to create unique products. Unfortunately this ability also brings about the limitation of SmI_2 as a radical precursor, as any desired radical reaction must take place significantly faster than reduction to the anion in order to achieve the desired goal.



Scheme 17

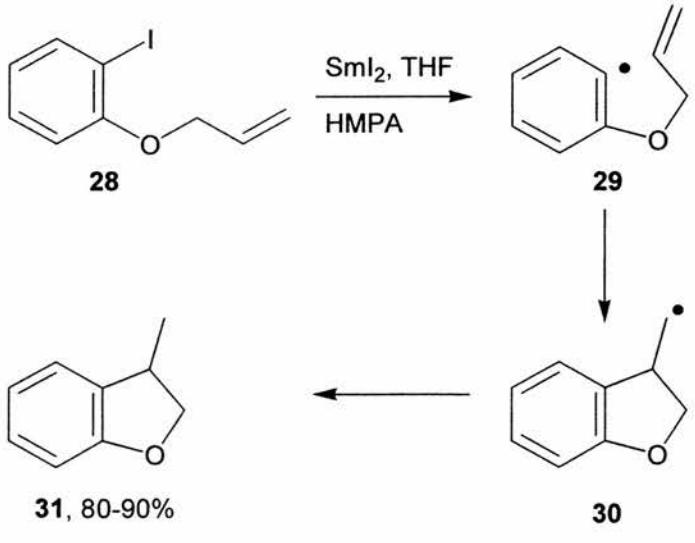
Molander demonstrated that iodoethylspiro-[2.5]-cyclooctanone **26** could be treated with SmI_2 in THF in order to produce the adduct **27** in 75% yield (Scheme 18).[39] The primary alkyl radical generated by electron transfer interacts with the ketyl group in order to create the third ring. Evidence suggests that the samarium ketyl intermediate

is not formed, as this would fragment the cyclopropane ring. As an alternative, hydrogen abstraction from the solvent occurs to yield **27**.



Scheme 18

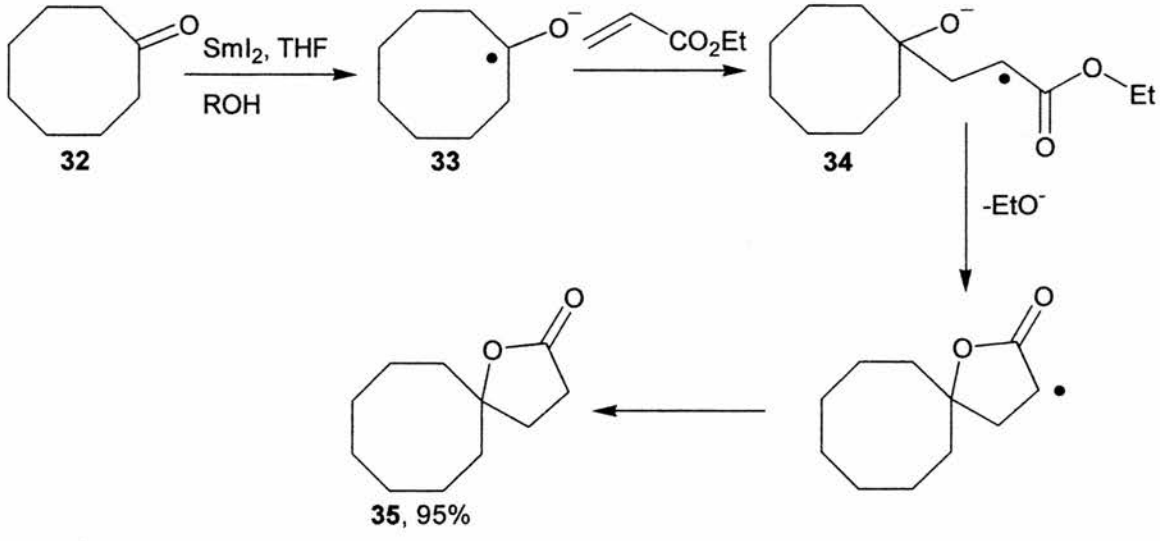
Samarium(II) iodide has also proved to be useful in the generation of aryl and vinyl radicals. For example, *O*-allyl-2-iodophenol **28** was allowed to react with an excess of SmI_2 in the presence of HMPA; the dihydropyran **31** was isolated in an 80 - 90% yield (Scheme 19).[40] SmI_2 donates an electron in order to break the carbon-iodine bond. Cyclisation of the ensuing aryl radical **29** results in the formation of the ring-closed species **30**, which can abstract hydrogen from the solvent to give **31**. Alkenyl and aryl radicals show the greatest potential as useful radical intermediates for SmI_2-promoted cyclisation reactions as their rate of reduction to the organosamarium compound is comparatively less than that of hydrogen abstraction from a solvent.



Scheme 19

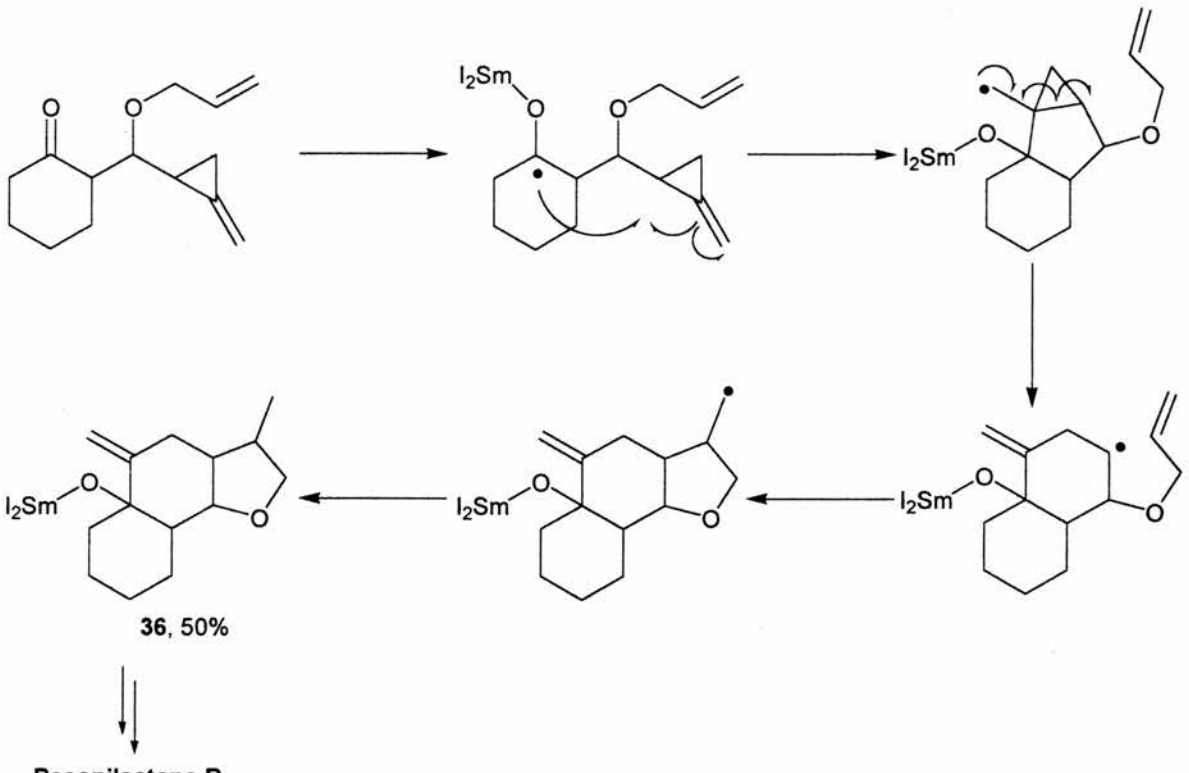
It is also recognized that samarium(II) iodide can take part in ketyl-alkene coupling reactions which join aldehydes and ketones to alkenes and alkynes (Scheme 20).[41]

When ketones of type **32** are treated with SmI_2, an electron transfer results in the formation of a radical anion **33** which is a strong nucleophile, and therefore adds readily to an electrophilic alkene to give the intermediate radical **34**. Nucleophilic attack at the remaining ketyl functionality closes the γ-lactone to give the cyclised product **35** in a 95% yield. This cross-coupling reaction is most efficient when using unsaturated esters, as they are good acceptors of nucleophilic radicals.



Scheme 20

The examples presented clearly illustrate that samarium(II) iodide has many potential uses in organic synthesis. When compared directly with the traditional tin hydride methods, SmI_2 exhibits easier work-up procedures and the potential to form *in situ* organosamarium intermediates, which could be used to insert further functionality on to the end product in preparation for future reactions. However, a majority of studies have involved simple molecules and cyclisations, while comparatively little research has been attempted on samarium(II) iodide mediated tandem processes. Fortunately, examples of radical cascades and natural product syntheses involving SmI_2 are finally surfacing. Watson and Kilburn have recently provided a novel method for the synthesis of a eudesmane tricyclic framework **36**, a precursor in the preparation of paeonilactone B, using these concepts (Scheme 21).[42]

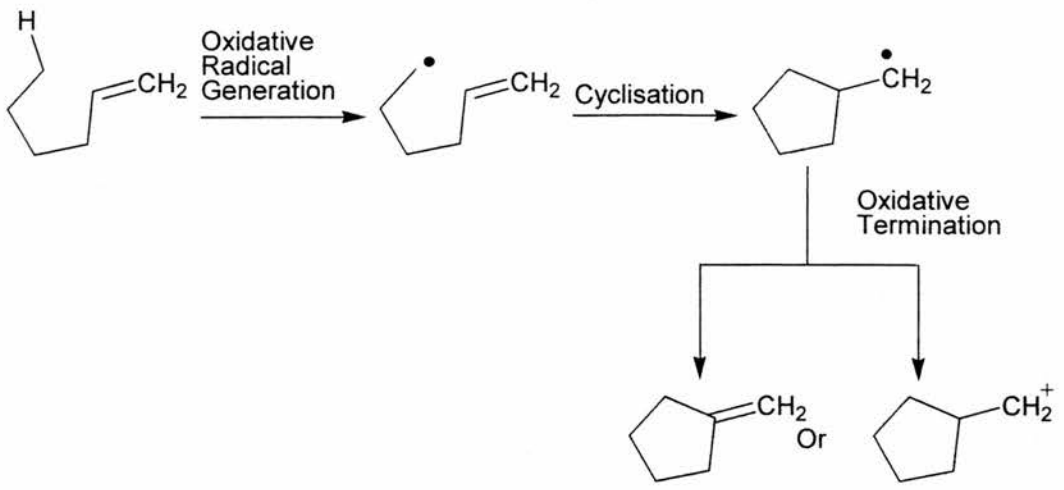


Scheme 21

Oxidative radical formation: the manganese method

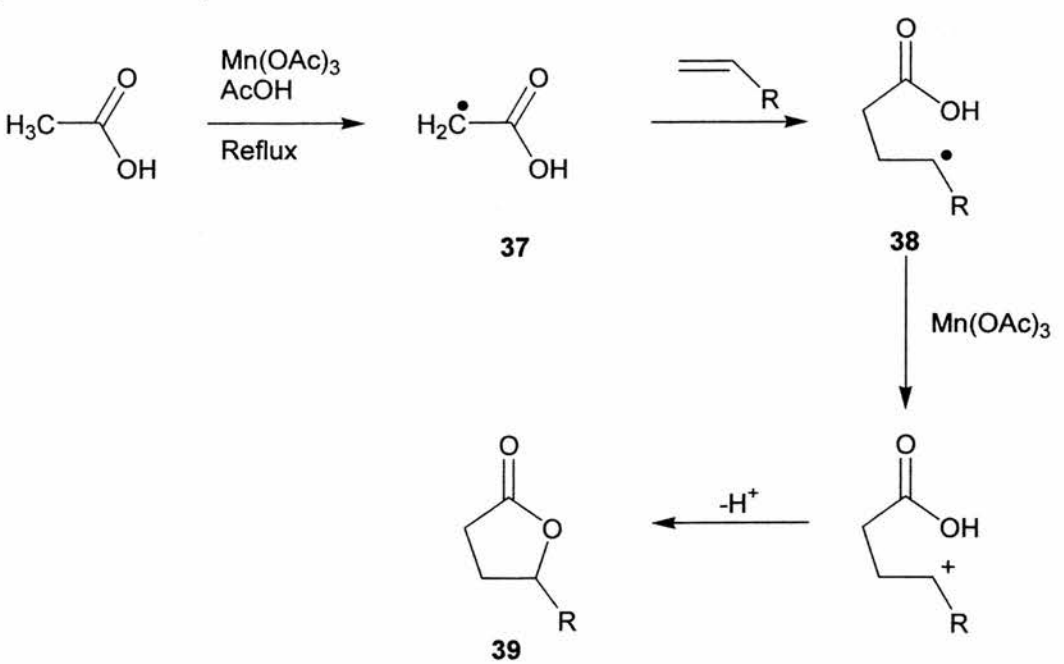
Radical chemistry using oxidative methods holds several advantages over the traditional use of tin compounds. As intended, work-up procedures are usually straightforward in order to efficiently remove unwanted heavy metal residues from the end product. Furthermore, oxidative termination of the intermediate radical can provide highly functionalised and versatile products, which allow synthetic chemists to perform supplementary reactions.

The oxidative formation of a radical involves the formal loss of a hydrogen atom; in practice this is accomplished by the loss of a proton and subsequent oxidation of the ensuing alkyl anion with a one-electron oxidant to generate the desired radical (Scheme 22). An advantage of this method for radical generation is the simplicity and availability of the precursor. However, there is a disadvantage as the required product is susceptible to further deprotonation and oxidation.



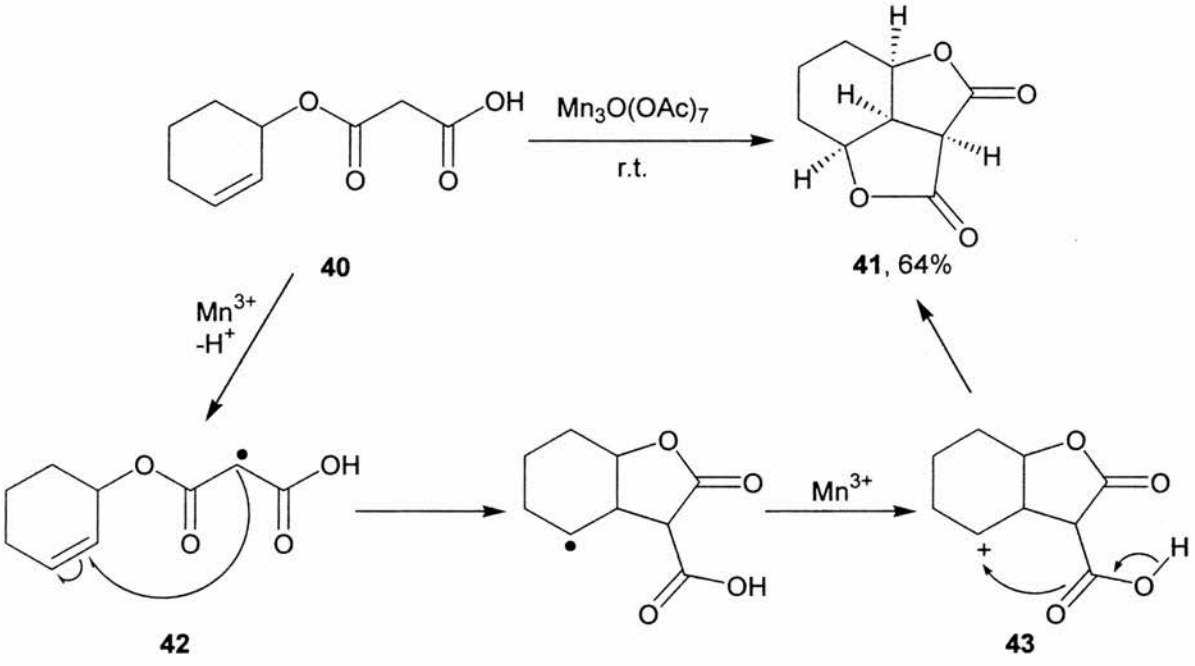
Scheme 22

The oxidative addition of acetic acid to alkenes was first reported by Heiba[43] and Bush[44] in 1968. This procedure involved the use of manganous acetate, $Mn(OAc)_3$, as a one-electron oxidant in order to generate the carboxymethyl radical **37** (Scheme 23). This radical can add to an electron rich alkene to give radical **38**, which is prone to oxidation by a second equivalent of $Mn(OAc)_3$ to furnish the corresponding cation. The neighbouring carboxylic acid group finally attacks this ionic intermediate in order to close the 5-membered ring and generate the γ-lactone **39**. This approach provided the basis for oxidative free-radical cyclisations, an area that has been extensively explored over the past three decades.



Scheme 23

The optimal solvent for oxidative cyclisation is acetic acid. Unfortunately, this prevents the use of Mn(III) based radical precursors in the cyclisation of unsaturated acids, as the acetic acid would be oxidised preferentially. However, Corey performed a series of experiments on unsaturated β-keto acids under milder conditions in order to demonstrate how these novel manganese complexes could be used with no competitive oxidation of the solvent.[45] For example, using $Mn_3O(OAc)_7$ in the presence of acetic acid at ambient temperature, the half-malonate ester of cyclohex-2-en-1-ol **40** was converted to the bis(δ-lactone) **41** in a 64% yield (Scheme 24).



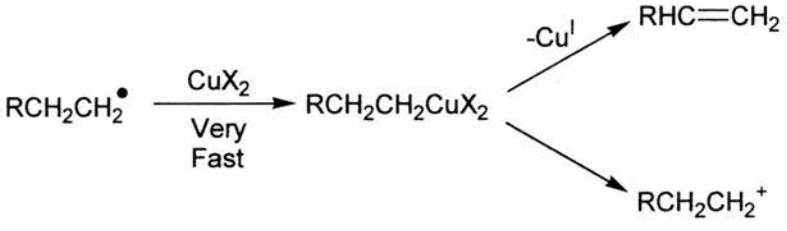
Scheme 24

The half-malonate ester is initially oxidised to form radical **42**, which rapidly undergoes intramolecular addition with the double bond. The resultant secondary radical is subject to a further oxidation step due to the presence of excess Mn(III) in order to generate the cation **43**. The carboxylic acid functionality can readily attack this cation to form the final ring and deliver the desired lactone **41**.

Commercially available $Mn(OAc)_3 \bullet 2H_2O$ has been used for the majority of oxidative cyclisations. It rapidly oxidises tertiary radicals to cations, which readily lose a proton in order to form the alkene or react with acetic acid to give acetate esters. However, $Mn(OAc)_3$ oxidises primary and secondary radicals very slowly so that hydrogen atom abstraction from the solvent becomes the dominant process. The

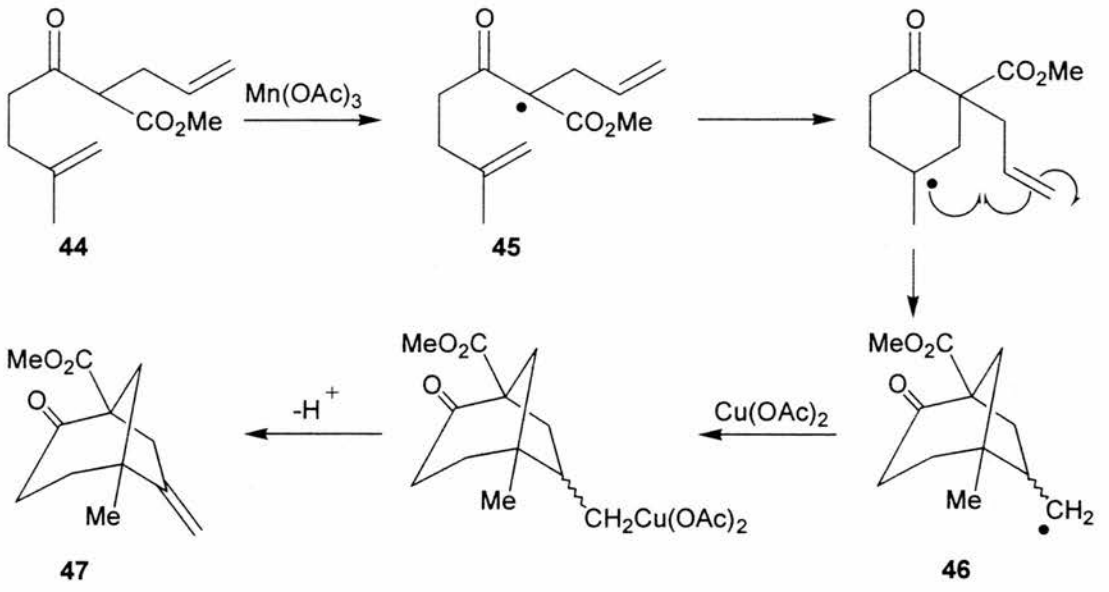
result is a loss of functionality in the end product, which is a great disadvantage for synthetic chemists who need to perform further reactions on this reduced product.

In the early 1970's, Kochi demonstrated that Cu(II) reacts rapidly with radicals to give alkylcopper(III) intermediates. These react further with the loss of Cu(I) in order to form the alkene, by oxidative elimination, or the carbocation (Scheme 25).[46] Heiba found that the use of $Cu(OAc)_2$ as a co-oxidant was compatible with $Mn(OAc)_3$ and that Cu(II) oxidised the secondary and primary radicals to alkenes much faster than their Mn(III) equivalents.[47]



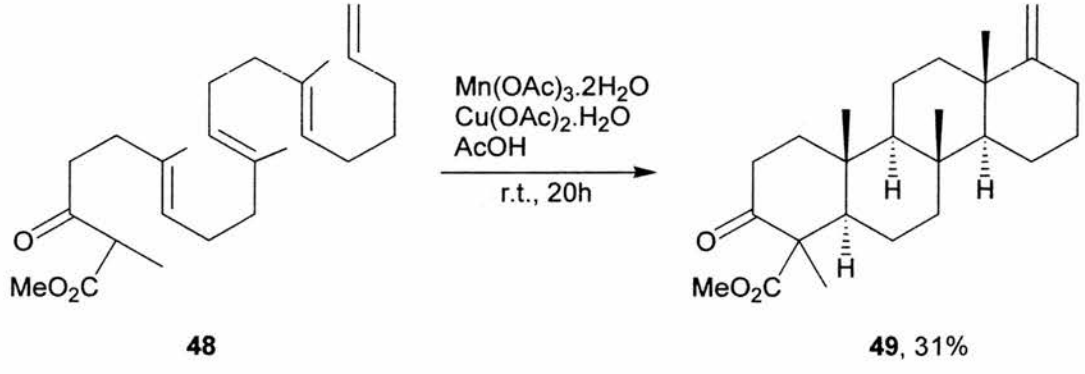
Scheme 25

Snider has provided many examples of using $Cu(OAc)_2$ in conjunction with $Mn(OAc)_3$ in his recent review.[48] The β-keto ester **44** can form the radical **45** in the presence of $Mn(OAc)_3$ (Scheme 26). This radical undergoes selective 6-*endo* cyclisation, followed by 5-*exo* cyclisation to form the primary radical **46**, which is rapidly oxidised by the co-oxidant, $Cu(OAc)_2 \bullet H_2O$, resulting in the elimination of a proton to yield the unsaturated β-keto ester **47**. The Cu(I) produced in this oxidation is readily oxidised to Cu(II) by Mn(III) and therefore only a catalytic amount of $Cu(OAc)_2 \bullet H_2O$ is required.



Scheme 26

$Mn(OAc)_3$ can also be used to create more complex targets with excellent stereocontrol using tandem oxidative cyclisations. Zoretic has developed a very efficient tetra cyclisation leading to a *trans* decalin ring system (Scheme 27).[49] β-Keto ester **48** was converted into the tetracyclic compound **49** in 31% yield. The stereoselectivity of the reaction was profound as only one isomer of a possible sixty-four was liberated. Functionality was added to the released product by oxidative termination with $Cu(OAc)_2$ in order to furnish the *exo*-cyclic double bond.



Scheme 27

These examples illustrate the synthetic potential of Mn(III) based oxidative radical reactions. The starting materials are readily available, although substrates are restricted to 1,3-dicarbonyl compounds. Mono and tandem cyclisations proceed in high yields with excellent control of regio- and stereochemistry before oxidative

termination, using $Cu(OAc)_2$, inserts a double bond into the product to release highly functionalised polycyclic products.

A wide variety of alternative one-electron oxidants have been used for generating free radicals including Ce(IV), Fe(III) and V(V).[48] All of these oxidants are capable of forming radicals from 1,3-dicarbonyl compounds and their increased solubility in solvents such as methanol and acetonitrile make them attractive alternatives to manganous acetate. However, further development is needed in these areas in order to assess the scope, limitations and mechanisms of these reactions.

The use of silane derivatives

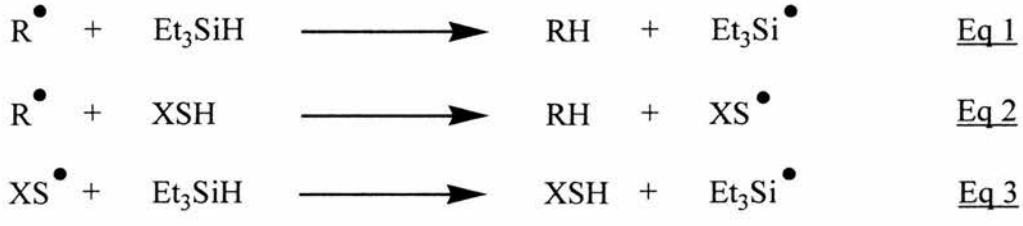
Silicon is the obvious alternative to tin as a radical chain carrier. It resides in the same group as tin in the periodic table and should theoretically have very similar properties. Silicon centred radicals are proficient at abstracting halogens from alkyl halides in order to generate the corresponding alkyl radical. However, the silicon-hydrogen bond strength is greater than that of its tin counterpart, this reduces the efficiency of hydrogen abstraction and therefore disrupts the chain process.

Investigations have focused around triethylsilane and diphenylsilane as alternatives to organotin hydrides. Barton and Jaszberenyi reported that diphenylsilane could be used to reduce alkyl bromides and isonitriles in excellent yields.[50] However, the corresponding iodides and chlorides were reduced in poor yields while nitro-adamantane and phenylselenyl derivatives were completely unreactive. The reaction procedure involved radical initiation using either triethylborane-oxygen or AIBN in refluxing toluene; both methods are not particularly attractive as they involve high temperatures (110 °C), which primarily contradict the use of a radical procedure.

Triethylsilane has also been described as an alternative to tributyltin hydride.[51-53] Again, reaction methods require high temperatures and large quantities of initiator to create and maintain the radical chain reaction. It is therefore unlikely that either triethylsilane or diphenylsilane will be used independently to mediate radical reactions.

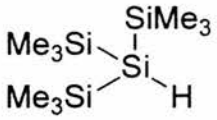
It was Roberts who first devised a practicable use of trialkylsilanes in free-radical reactions.[54] He postulated that alkyl radicals are nucleophilic species and the hydrogen atom in triethylsilane was also electron rich. Therefore, the abstraction of hydrogen from triethylsilane by an alkyl radical, to give the reduced product, was unfavourable (Eq 1, Scheme 28).

This problem was overcome by adding a catalytic amount of an alkanethiol, such as *tert*-dodecanethiol (XSH), in union with triethylsilane, to the reaction mixture. Nucleophilic alkyl radicals abstract hydrogen from thiols much more readily than from trialkylsilanes,[55] the resulting thiyl radical is electrophilic and therefore much more eager to abstract hydrogen from the trialkylsilane in order to regenerate the thiol, along with the chain carrying trialkylsilyl radical, to give the reduced alkyl product in yields greater than 90% (Eq 2 and 3, Scheme 28). This procedure is known as polarity-reversal catalysis and has been used to great effect in many radical procedures.[56]



Scheme 28

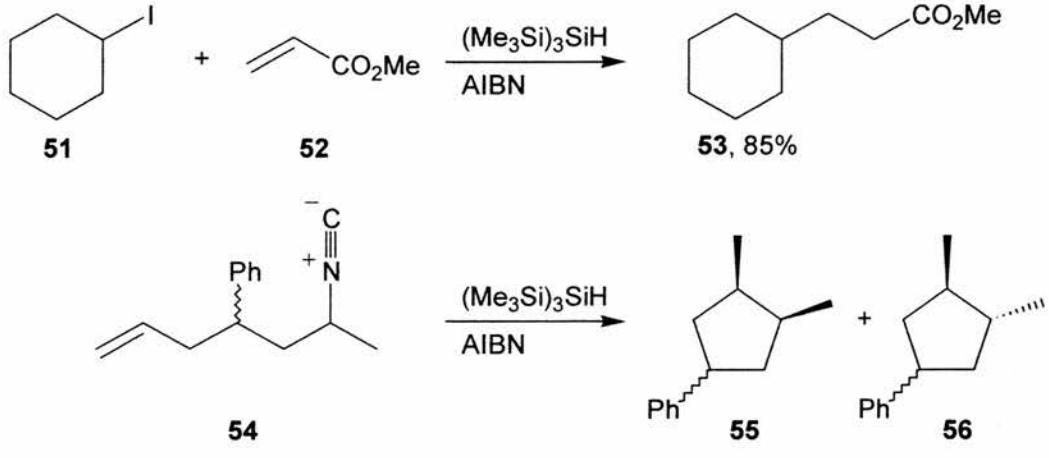
Chatgilialoglu and co-workers introduced the most successful and widely used alternative for tin hydride in 1988.[57-59] Tris(trimethylsilyl)silane **50**, originally discovered in 1965 by Gilman,[60] was ignored for the first twenty years before Chatgilialoglu drew attention to its greater hydrogen donating abilities than the conventional trialkylsilanes, due to stabilisation of the resulting silyl radical. This is achieved *via* back bonding into the adjacent, vacant, d orbitals that are present on each of the silicon atoms.



50

Tris(trimethylsilyl)silane is a non-toxic compound which has the additional advantage of furnishing fewer direct-reduction products than analogous trialkyltin compounds as the Si-H bond is slightly stronger (≈ 5 kcal mol^{-1}) than the equivalent Sn-H bond. This higher bond energy prevents rapid reduction of intermediate radicals and often allows radical reactions to be performed with a stoichiometric amount of the silane in the initial reaction mixture, rather than the tedious portionwise addition of tributyltin hydride.

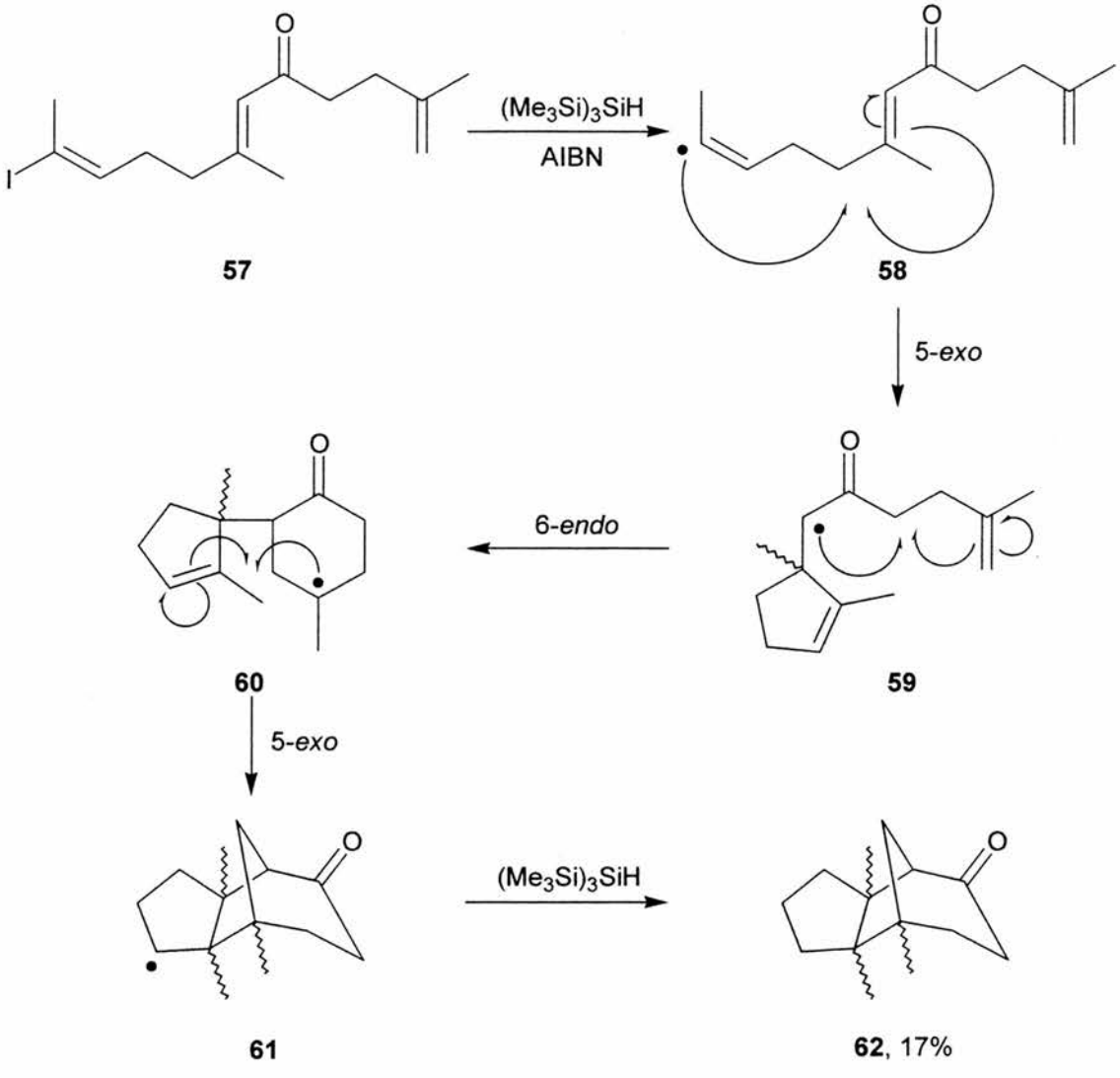
Several examples of inter- and intramolecular radical additions to activated alkenes using tris(trimethylsilyl)silane have been reported; two model syntheses are given in Scheme 29. The reaction of cyclohexyl iodide **51** and methyl acrylate **52** afforded the desired product **53** in 85% yield, which was comparable to that obtained by the tin method.[58] The $(Me_3Si)_3SiH$ technique does not allow primary alkylamines to be used as alkyl radical precursors in the formation of C-C bonds; the amine must initially be converted to isocyanide **54** in order to generate the desired alkyl radical, which readily cyclises to furnish a mixture of *cis* **55** and *trans* **56** isomers in a 78% yield.[61]



Scheme 29

Curran has also put tris(trimethylsilyl)silane to good use in a 'Round trip radical cyclisation'.[62] This unique form of radical cascade initiates and terminates the radical

sequence at the same carbon atom in order to construct polycyclic ring systems from an unsaturated acyclic precursor (Scheme 30).



Scheme 30

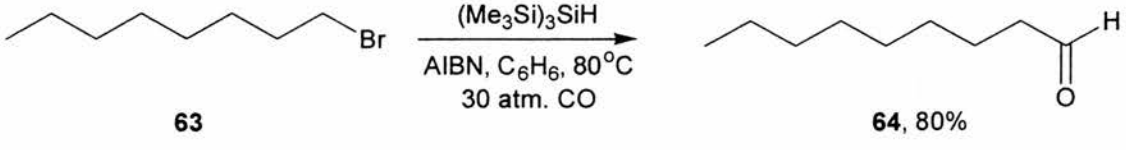
Initial attempts by Curran to cyclise iodide **57** with tributyltin hydride were unsuccessful, yielding mainly the reduced monocyclic product derived from **59**. This was attributed to premature reduction of the intermediate radical by tributyltin hydride. The implementation of a tris(trimethylsilyl)silane methodology prevented early reduction to give the tricyclic compound **62**.

When iodide **57** was treated with $(Me_3Si)_3SiH$ and AIBN in refluxing benzene, the vinyl radical **58** was released which rapidly cyclised in 5-*exo* fashion to generate a new carbon-centred radical **59**. The presence of a carbonyl substituent adjacent to this

secondary radical influenced the next cyclisation step. Ordinarily a 5-*exo* cyclisation would occur, however, the literature states that a 6-*endo* cyclisation took place to generate radical **60** in two isomeric forms. The final phase involves a further 5-*exo* cyclisation on to the initial radical site to complete the 'Round Trip' and generate radical **61**. This is reduced by $(Me_3Si)_3SiH$ to regenerate the chain carrier and deliver the polycyclic product **62** in a 17% yield.

Free radical carbonylation reactions have recently gained distinction as a promising method for the introduction of carbonyl functionality into a molecule. Extensive research has been carried out in this area using organotin compounds as radical mediators.[63] However, these processes must be carried out under very high pressures in order to encourage the alkyl radicals to capture carbon monoxide instead of abstracting hydrogen from the tin hydride. In order to reduce the carbon monoxide pressure in this process, it becomes essential to employ a radical mediator which has a poorer hydrogen donating ability. Tris(trimethylsilyl)silanes are therefore attractive alternatives.[64]

The conversion of octyl bromide **63** to its corresponding aldehyde **64** is a typical example of free radical carbonylation (Scheme 31).[64] The alkyl halide **63** was refluxed in benzene in the presence of tris(trimethylsilyl)silane and AIBN under 30 atmospheres pressure of carbon monoxide to give **64**, which was isolated in a yield of 80%. When this reaction was carried out using tin hydride methods, the optimal pressure of carbon monoxide was 50 atmospheres and afforded the aldehyde in a reduced yield of 63%.

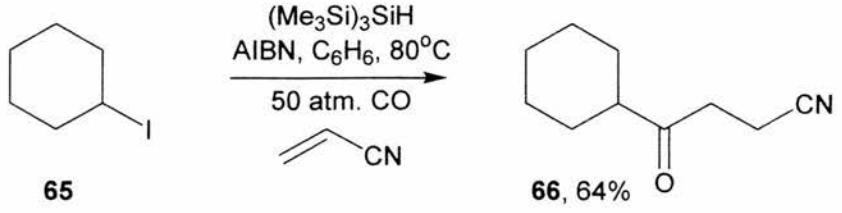


63 **64**, 80%

Scheme 31

This use of tris(trimethylsilyl)silane allows chemists to carry out further radical additions subsequent to carbonylation. It has been reported that the acyl radical, resulting from carbonylation of an alkyl halide, can add to an available alkene prior to hydrogen abstraction in order to form the corresponding ketone in good yields. For

example, cyclohexyl iodide **65** was converted to the β-cyano ketone **66** in a 64% yield as shown in Scheme 32.[64]

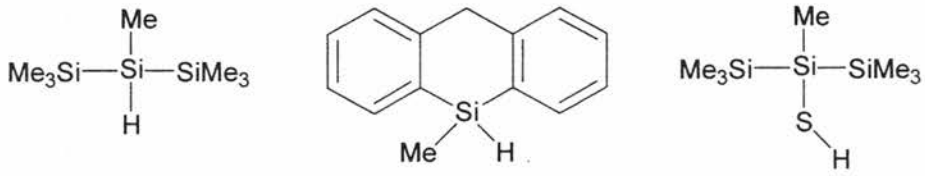


65 **66**, 64%

Scheme 32

It is clear that tris(trimethylsilyl)silane is a versatile reagent which can mediate a wide range of radical reactions. Its reduced ability to donate hydrogen presents new opportunities for cascade reactions and radical carbonylations within a non-toxic environment. However, few reagents in organic synthesis come complete with no disadvantages, and tris(trimethylsilyl)silane is no exception. The silyl radicals generated from this reagent are very efficient at hydrosilylating double and triple bonds, therefore reducing yields by forming unwanted side products.[65] Tris(trimethylsilyl)silane is also a very expensive reagent as its preparation is low yielding and the reagent is quite difficult to handle. Fortunately, Chatgilialoglu has reported the catalytic use of tris(trimethylsilyl)silane, using sodium borohydride to regenerate the reagent from the silicon-halogen by-products.[66] This procedure gives yields comparable to the stoichiometric methods previously described, yet reduces costs and waste.

A diverse range of organosilanes have been synthesised since their introduction into the chemical community. This has given radical chemists the ability to tune this radical mediator to suit individual experimental requirements. The incorporation of different side chains on to the central silicon has a direct effect on the strength of the Si-H bond. Therefore it is feasible to weaken this bond dramatically in order to accelerate hydrogen abstraction and enable direct reduction products to be obtained. Equally, it is possible to increase this bond strength to prevent premature reduction and promote inter- or intramolecular additions. However, if the Si-H bond strength is increased too much, the radical chain breaks down and yields are greatly reduced. Examples of these custom-made silanes can be seen in Scheme 33.

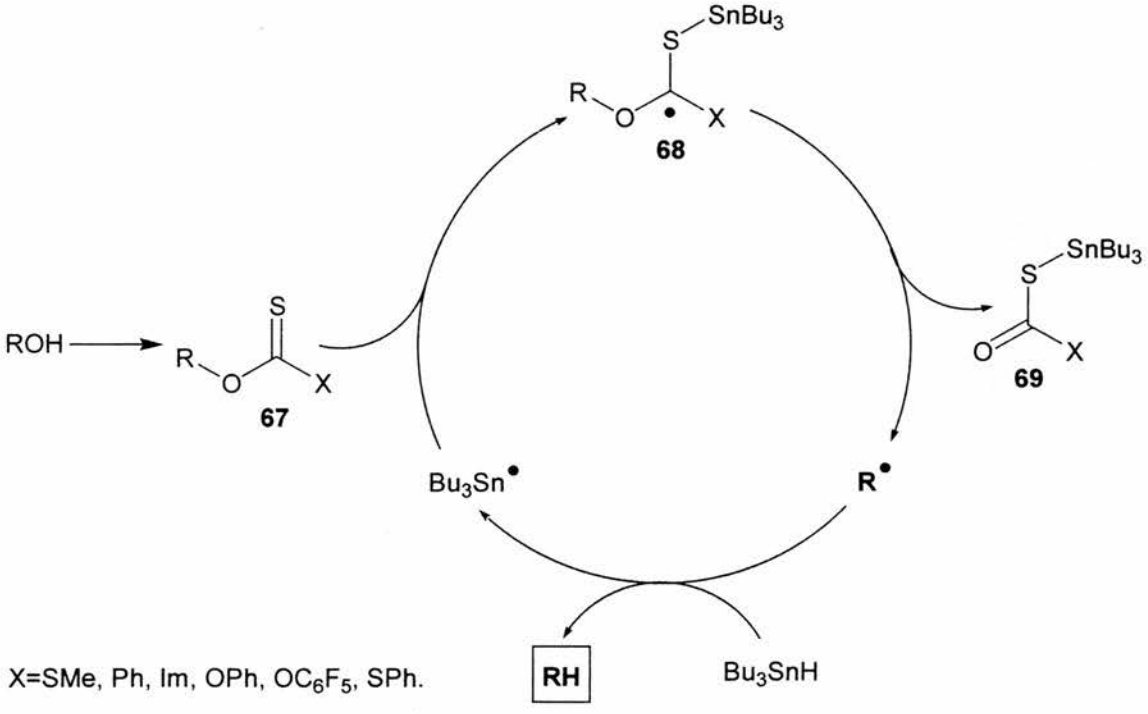


Scheme 33

Organic Alternatives to Toxic Tin

The radical properties of sulfur compounds

The Barton-McCombie reaction of organotin hydrides with thiocarbonyl compounds has been widely used as a means of generating radicals from alcohols and a mild method of deoxygenation.[67] The method requires the initial conversion of an alcohol into a thiocarbonyl ester **67**. These esters are straightforward to prepare in good yields before the thiocarbonyl sulfur is readily attacked by tributyltin hydride, in the presence of an initiator (AIBN), to form the C-centred radical **68**. Finally, a radical fragmentation results in the formation of the alkyl radical $\mathbf{R}^{\bullet}$ and the corresponding carbonyl compound **69** (Scheme 34).[68]

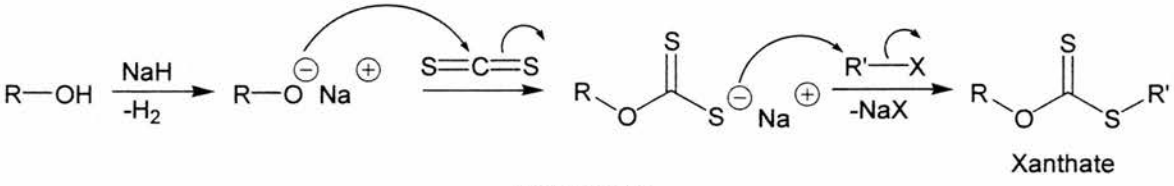


Scheme 34

There have been many examples for the use of this deoxygenation method in an array of diverse areas, including the synthesis of steroids, carbohydrates, terpenoids and nucleosides.[69] The major advantage of this procedure is the use of very cheap reagents, however, the reappearance of organotin hydride in the mechanism prevents this procedure being used outside of a laboratory.

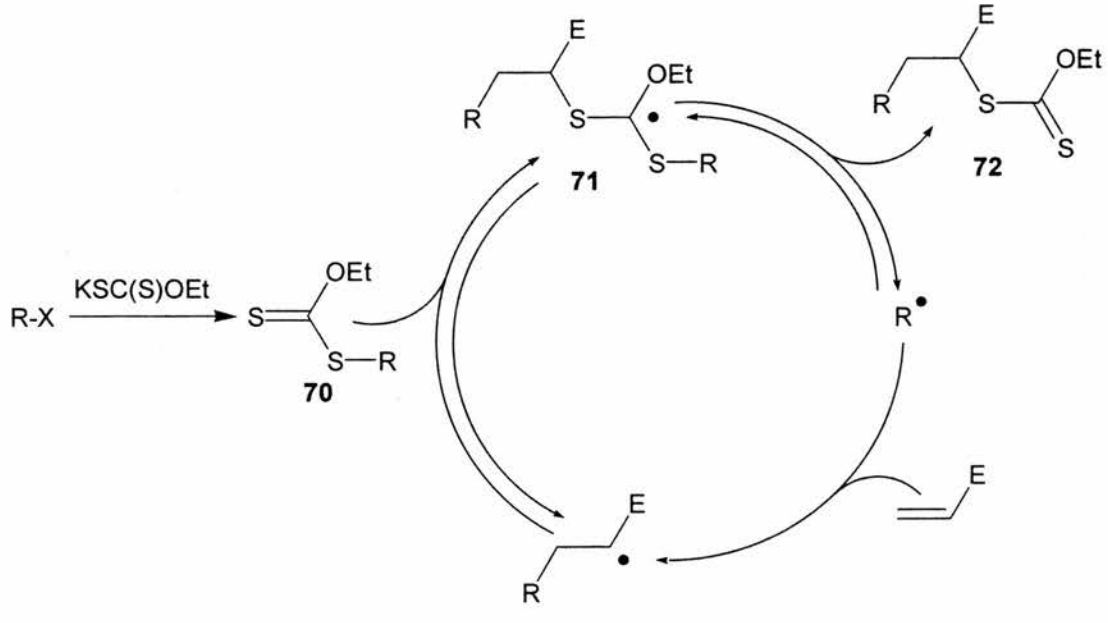
Xanthates

Dithiocarbonates (xanthates) can be prepared from alcohols using a three-step reaction sequence (Scheme 35). Their ability to take part in radical processes, without organotin compounds, has been extensively investigated in attempts to eliminate the monopoly of tin hydride in this area.[68]



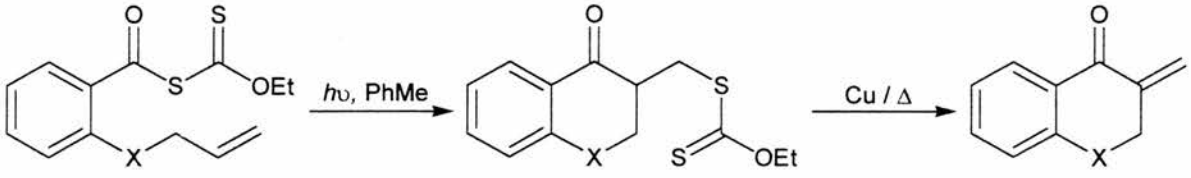
Scheme 35

The addition of a radical to a methoxy- or ethoxyxanthate **70** delivers the corresponding tertiary radical **71**. This radical intermediate does not fragment in the usual Barton-McCombie mode to give a methyl or ethyl radical, but undergoes a C-S bond scission to generate R$^{\bullet}$ and the new xanthate **72**. The released radical can then add to an alkene or cyclise before continuing the chain by addition to more of the starting xanthate **70** (Scheme 36). The chain reaction is initiated using a catalytic amount of peroxide to give xanthate **72** as the major product. The xanthate functionality can finally be removed by reduction with dilauroyl peroxide in propan-2-ol or treatment with DBU in order to furnish the required, metal free, addition product.



Scheme 36

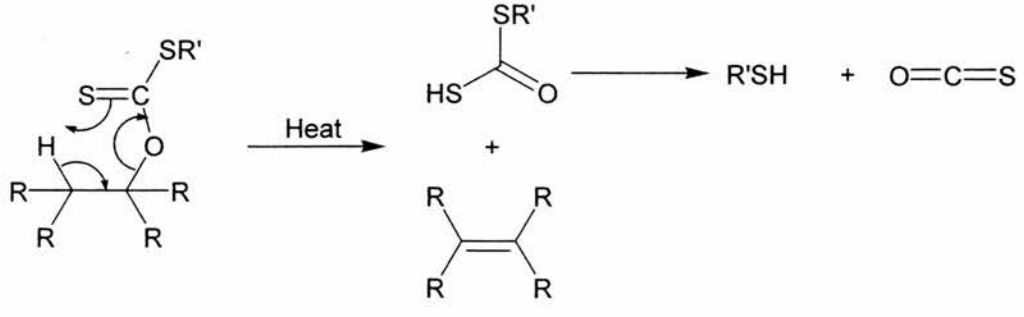
The corresponding *S*-acyl xanthates **73** are also convenient precursors of acyl radicals and can be useful agents for additions and cyclisations.[68] Their preparation involves the treatment of an acid chloride with a xanthate salt, such as potassium ethyl xanthate, to furnish the xanthic anhydride. Irradiating the *S*-acyl xanthate with visible light generates the acyl radical, which can then be captured in an inter- or intramolecular fashion by using appropriate alkene traps (Scheme 37). In this example, the xanthate group is easily removed with base or by heating with copper powder to yield the alkene function.



73 **X=O**, 70% **X=S**, 93% **X=O**, 40%

Scheme 37

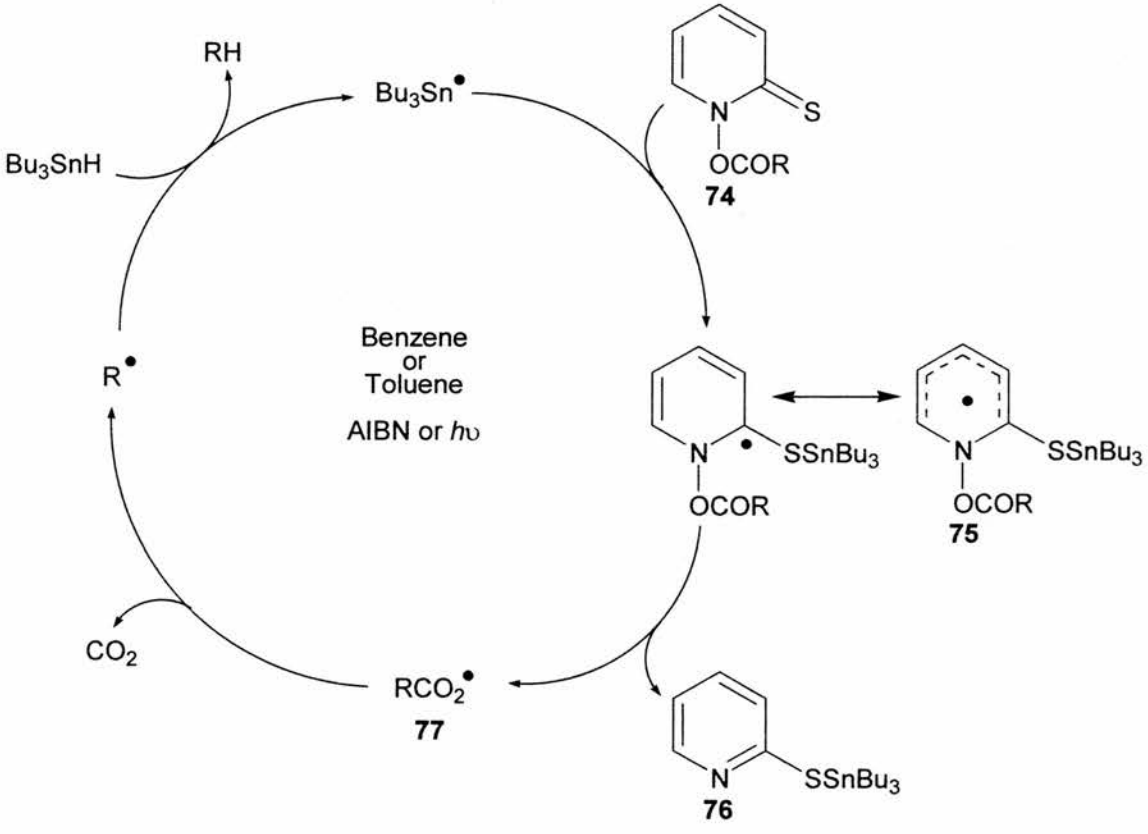
There are many advantages to using a xanthate procedure over more traditional radical methods. The lack of heavy or toxic metals in the process makes it a desirable and cleaner route, along with the economic rewards of using cheap and readily available starting materials. Furthermore, the end product from one reaction can be used as a starting point for another radical sequence; or using the rich chemistry of sulfur, we can modify this product further. However, the main problem with xanthates is their instability. On heating, these molecules can undergo an intramolecular elimination to form an alkene in the Chugaev reaction (Scheme 38).[70, 71]



Scheme 38

Barton's thiohydroxamic esters

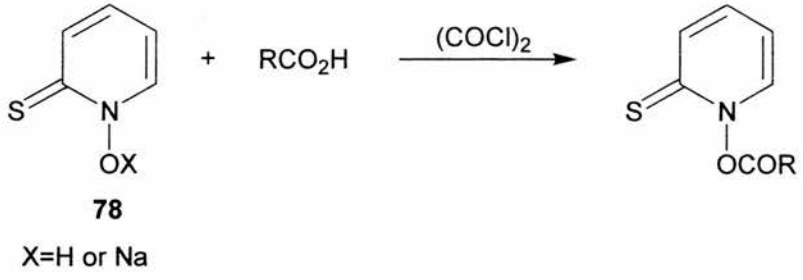
A solution to the thermal rearrangement problems of xanthates in radical procedures is the use of its modified relative, the thiohydroxamic ester **74**. These *O*-acyl derivatives of the thiohydroxamic acid *N*-hydroxypyridine-2-thione were initially shown to generate carbon-centred radicals under mild conditions in the presence of tributyltin hydride and AIBN (Scheme 39).[72]



Scheme 39

The tin radical adds to the sulfur of the thiocarbonyl functionality to form the delocalised radical **75**, which readily fragments to give stannyl-2-pyridylsulfide **76** as a by-product and the corresponding alkoxycarbonyl radical **77**. Carbon dioxide is finally liberated to deliver the carbon-centred radical R$^{\bullet}$, which abstracts hydrogen from the tin hydride to give the reduction product RH and the chain-carrying tin radical. This reaction is highly favourable due to the susceptibility of the thione function towards tin.[73] The generation of an aromatic pyridine ring, formation of two strong C=O bonds and entropy gain of creating four products from two reactants also act as a strong thermodynamic driving force.[72]

Thiohydroxamic esters are prepared by esterifying mixtures of commercially available 2-mercaptopyridine N-oxide **78** and carboxylic acids which are activated by oxalyl chloride (Scheme 40). The resultant esters are not ordinarily isolated, but reacted immediately.



78

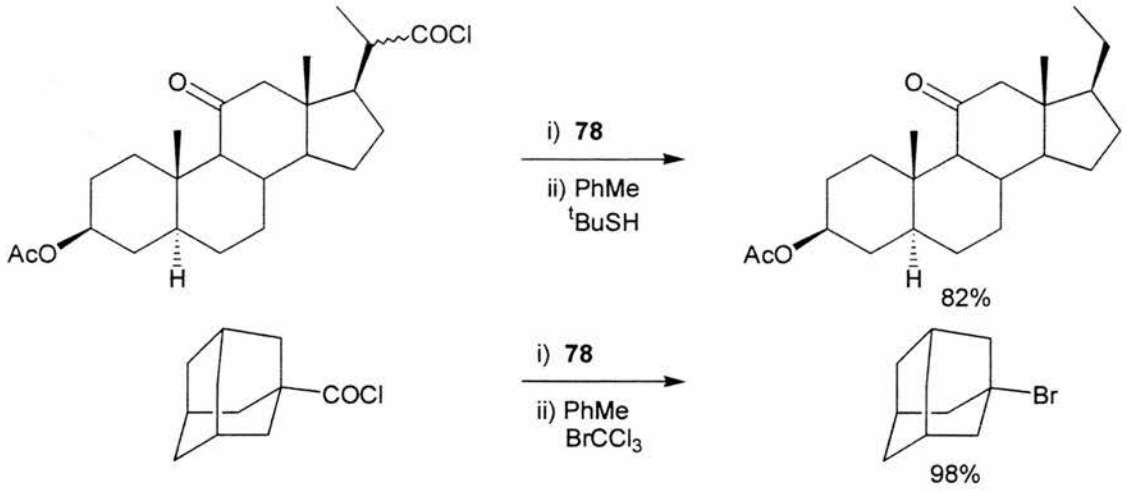
X=H or Na

Scheme 40

The Barton esters were originally used in collaboration with organotin hydrides to generate alkyl radicals. However, the use of toxic metals in these mechanisms must be avoided, therefore several alternative reagents have been derived to initiate the chain reaction illustrated in Scheme 39.

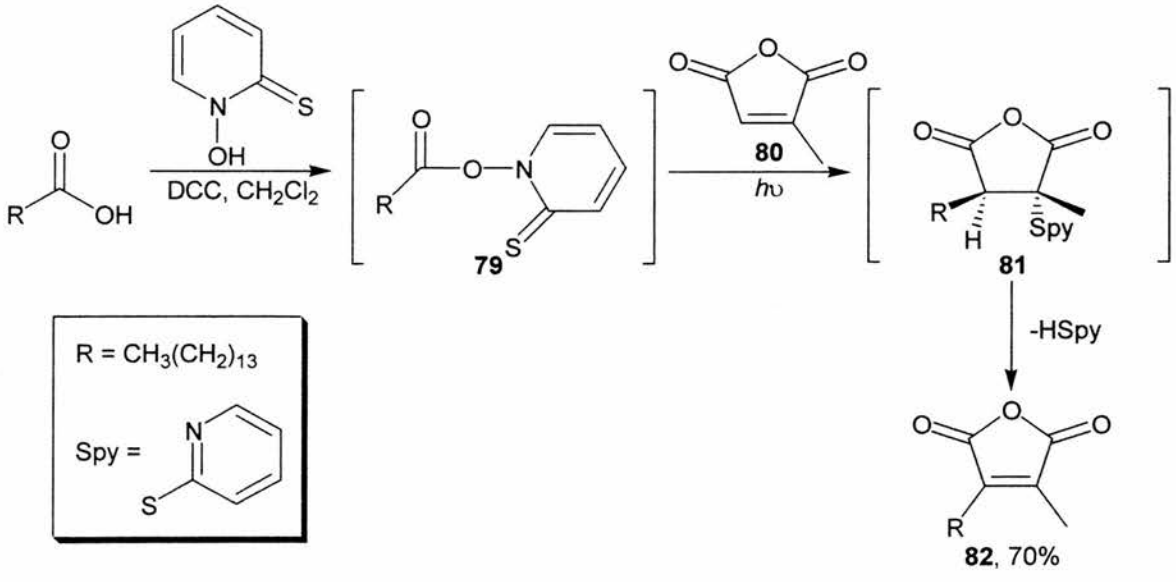
Thiols can be used, commonly 2-methylpropane-2-thiol, to replace tin hydride with little loss of efficiency and improved purification of products. The success of this initiator is due to the susceptibility of the thione functionality to attack from a sulfur-centred radical. Chain reactions can also be instigated using bromotrichloromethane or carbon tetrachloride to generate the alkyl bromides and chlorides respectively. This process is a mild method for the decarboxylative halogenation of carboxylic acids, brought about by the trichloromethyl radical ($^{\bullet}CCl_3$) being 'thiophilic' and forming strong bonds with sulfur. Examples of these radical reactions can be seen in Scheme 41.[72]

Since their introduction, there have been numerous diverse applications of thiohydroxamic esters in organic synthesis, including the conversion of carboxylic acids into thiols,[74] cyanides[75] and isocyanates,[75] as well as reductive decarboxylations. Two examples, illustrating the use of these esters in synthesis, can be seen in Schemes 42 and 43.



Scheme 41

Chaetomellic anhydrides are a precursor to chaetomellic acids, which can be found in several plants, and have shown potent inhibitory behaviour towards cell transformation and PFTase activity in animals. Several approaches have been reported for the total synthesis of chaetomellic anhydride A, including cobalt-mediated radical coupling and organocuprate addition to alkynes. Each attempt gave the desired anhydride yet proved highly inefficient. Samadi has recently described a more proficient one step synthesis using Barton radical decarboxylations (Scheme 42).[76]

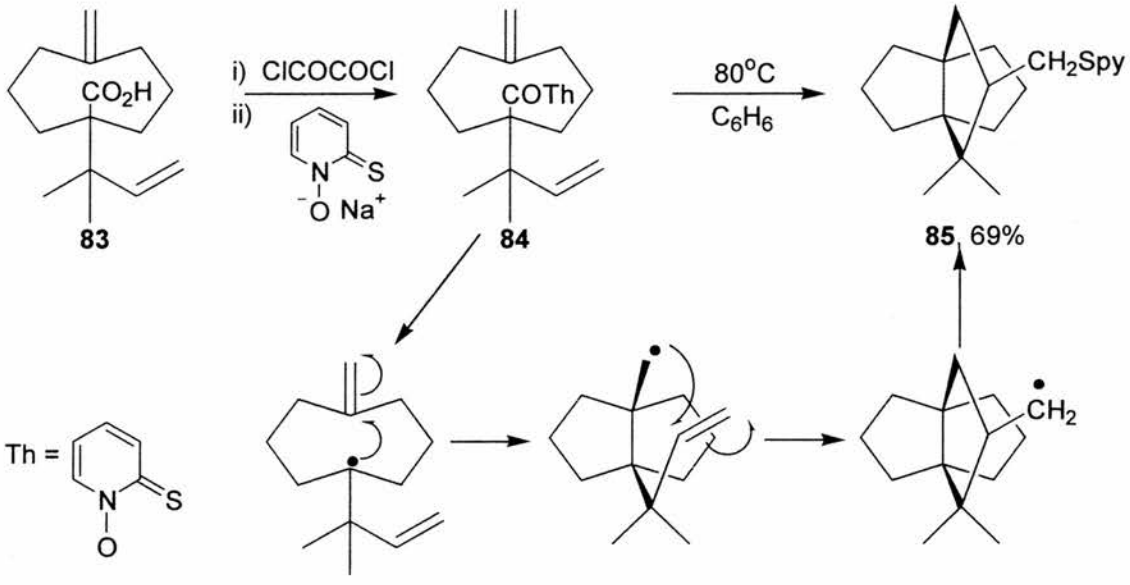


Scheme 42

The readily available pentadecanoic acid was converted into its thiohydroxamic ester **79** *via* a DCC coupling method. The resultant ester was irradiated in the presence of

citraconic anhydride **80** for a short period of time in order to generate the intermediate addition product **81**. This intermediate slowly underwent complete β-elimination of the 2-pyridylthio function to release the desired chaetomellic anhydride **82** in a 70% yield.

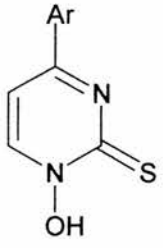
Curran has also put Barton's thiohydroximate radical procedure to good use in his synthesis of a novel [3.3.3]propellane (Scheme 43).[77] A customised cyclooctane carboxylic acid **83**, was initially converted into the acid chloride, using oxalyl chloride, before acylation was carried out with the sodium salt of *N*-hydroxypyridinethione. The resultant thiohydroximate **84** was refluxed in benzene for twelve hours in order to initiate the transannular cyclisations and furnish cyclised product **85** in a 69% yield. The rich chemistry of sulfur allowed further reactions to be carried out on the cyclised product in order to furnish a range of [3.3.3] propellanes.



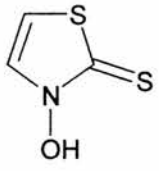
Scheme 43

One of the major factors restricting the use thiohydroxamic esters is instability. A desired thiohydroxamic ester must be prepared immediately before it is used in a radical process, as it will break down if stored for more than a few hours. In an attempt to stabilise the thiohydroxamic ester, a range of alternative compounds have been studied.

1-Acyloxy-2(1*H*)-pyrimidine-2-thiones **86** have been developed and studied by Liebscher.[78] These novel heterocyclic *O*-acyl thiohydroxamate compounds show sufficient stability for isolation and storage for several days without decomposition, while possessing the ability to serve as radical precursors. *N*-Hydroxythiazole-2(3*H*)-thione **87** exhibits similar durability and reactivity. However, these alternatives often need more vigorous reaction conditions to facilitate initiation, or require the presence of organotin compounds.



86

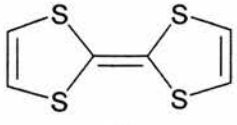


87

Sulfur based reagents exhibit optimum performance when used in conjunction with tin hydrides. Nevertheless, several practical, metal-free, systems have been discovered and used with great effect in natural product synthesis and transannular cyclisations. An additional inconvenience with using this chemistry stems from the potent odour which accompanies the use of thiols and many other sulfur compounds. This odour is barely tolerable in laboratory experiments, but would be an environmental cataclysm on an industrial scale.

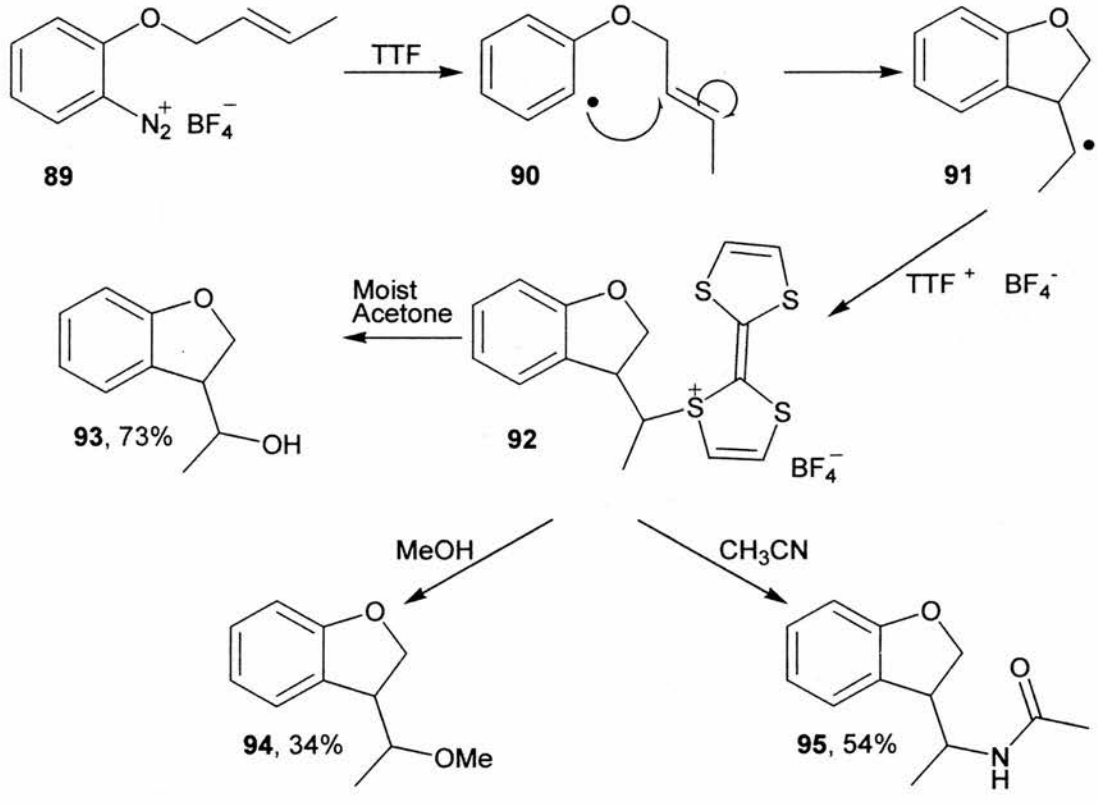
Tetrathiafulvalene as a radical initiator

The use of tetrathiafulvalene (TTF) **88** as a metal replacement in aryl radical reactions has been extensively studied by Murphy.[79] Traditionally, aryldiazonium salts were used in conjunction with copper(I) in order to generate the aryl radicals. However, in a novel breakthrough, the organic TTF can be used to replace copper in these procedures as the initial electron donor.



88

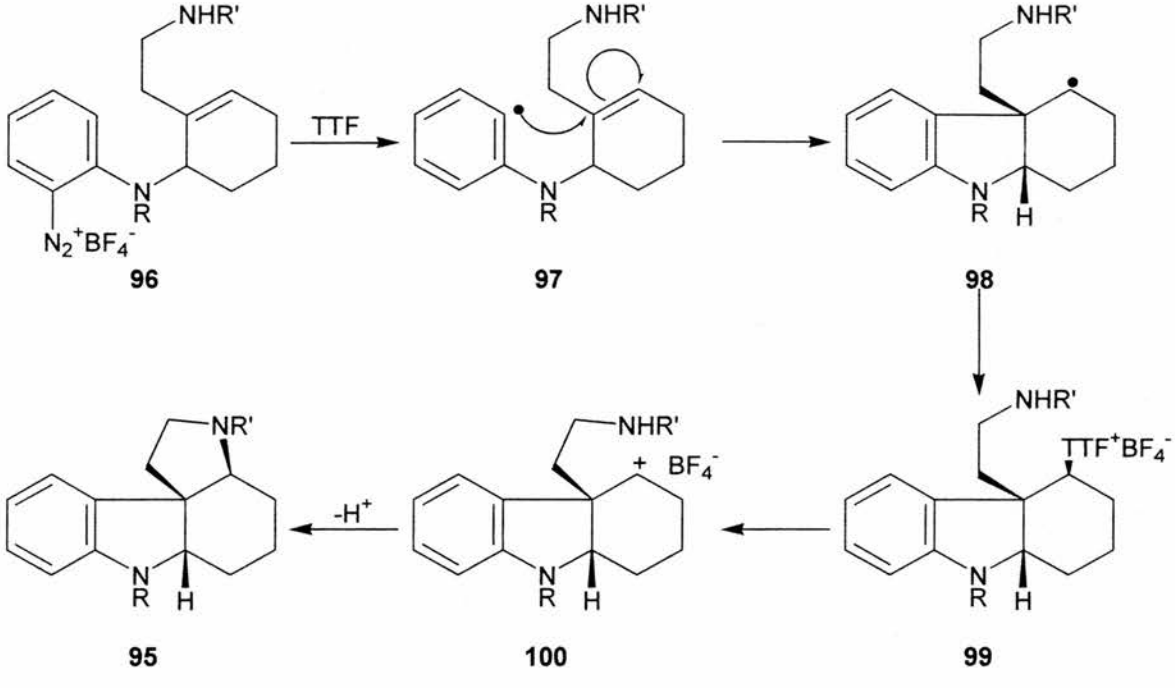
Tetrathiafulvalene will readily donate an electron to an aryldiazonium tetrafluoroborate **89** in order to expel nitrogen and form the aryl radical **90**. *5-Exo* cyclisation of this intermediate gives the alkyl radical **91**, which is ultimately trapped by the TTF radical cation in order to furnish the crystalline product **92** (Scheme 44). [80, 81] In the presence of moist acetone, the TTF salt **92** was converted into the corresponding alcohol **93** in good yield. Methyl ether **94** was formed when using methanol as the solvent, and it was also possible to use acetonitrile as the solvent to furnish amide **95**.[82]



Scheme 44

As TTF is regenerated at the end of a reaction sequence *via* an S_N1 reaction, it is possible to use the radical initiator in catalytic amounts. However, research has shown that the catalytic properties of TTF are poor under mild conditions as the turnover number remains very low. This is due to attack on the intermediate radical-cation and the intermediate sulfonium salt **92**.

Murphy carried out investigations into the use of this radical-polar crossover reaction in the synthesis of more complex molecules. The tetracycle **95** is a common subunit in alkaloid natural products such as aspidospermidine, strychnine and vinblastine. Murphy used the TTF mediated sequence in Scheme 45 to generate this base unit and provide a clean radical method of generating these important natural products.[83, 84]



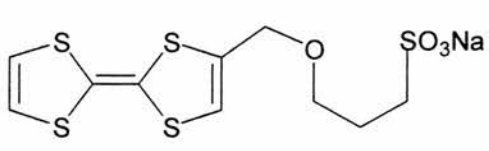
R = H, Me, Bz
R' = H, Me

Scheme 45

When the diazonium salt **96** was treated with TTF, the intermediate aryl radical **97** was generated, which readily cyclised to give alkyl radical **98**. This radical was trapped by the TTF radical cation and oxidised in order to give the carbocation **100**. Finally, the carbocation was open to attack by the proximate nitrogen lone pair in order to close the final ring and form the tetracycle **95** with an all *cis* stereochemistry. The stereoselectivity is derived from the preference of the internal nucleophile to attack the less hindered face of the carbocation **100**.

Tetrathiafulvalene's success as a radical initiator can be credited to its ability to act as an effective electron donor and its sufficiently lethargic rate of radical trapping. This allows the aryl radical to cyclise before the adduct radical is trapped. Recent efforts have focused on understanding how these properties can be controlled by using alternative electron donors based on TTF derivatives.[85, 86]

There have also been attempts to generate both water-soluble TTF analogues **101** and polymer-supported TTF **102**. The water-soluble reagent is easily prepared from TTF and can be reacted with soluble diazonium chlorides. The organic product is simple to extract, making this an attractive procedure for industrial use.[87] Polymer-supported TTF makes purification even simpler, filtration extracts the polymer-bound TTF, which can be regenerated using sodium borohydride with a minimal drop in activity.[88]



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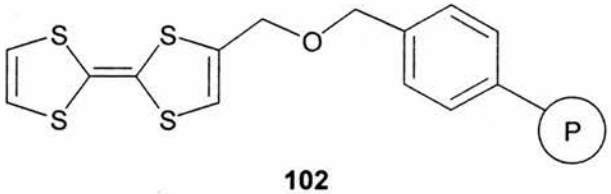
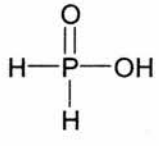


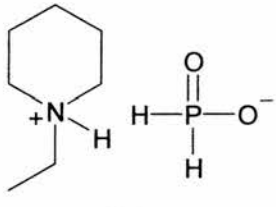
102

The major limitation of using TTF as a radical initiator is the requirement for arenediazonium salts as starting materials.

Hypophosphorus acid and its *N*-ethylpiperidine salt



103

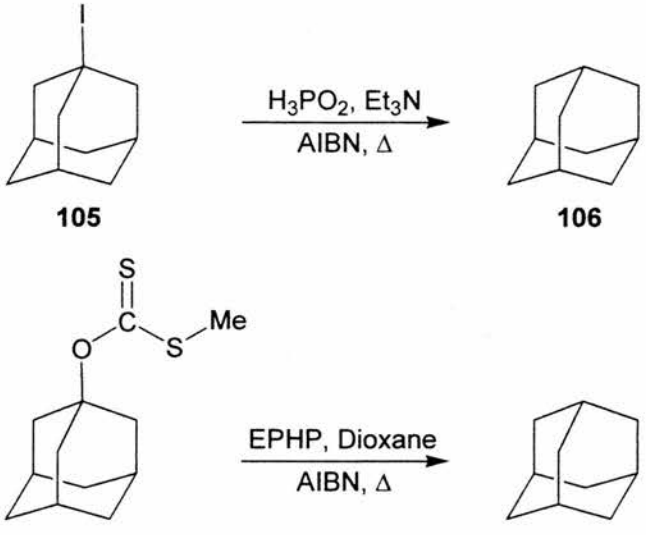


104

Phosphorus centred radicals derived from H_3PO_2 **103** and its *N*-ethylpiperidine hypophosphite salt (EPHP) **104** were first described by Barton and Jang.[89, 90] The phosphorus compounds contain weak P- H bonds which readily fragment upon initiation to give phosphorus centred radicals, which were initially used in a series of functional group reductions such as deoxygenations, deaminations and dehalogenations.

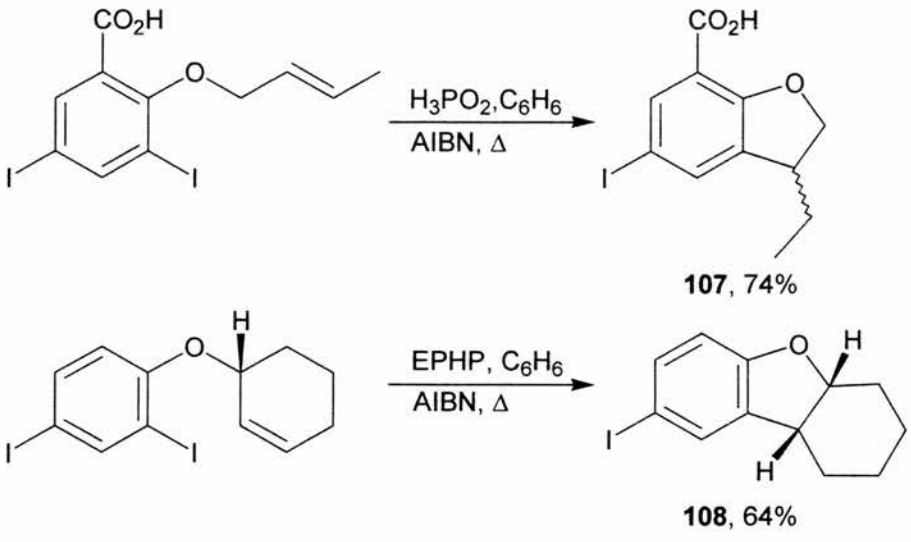
Commercially available hypophosphorus acid was used to dehalogenate 1-iodoadamantane **105** in the presence of triethylamine and a catalytic amount of AIBN to give quantitative yields of adamantane **106** (Scheme 46). The triethylamine was used to neutralise the acidity of the reaction mixture. However, hypophosphorus acid is used as an aqueous solution, therefore water-sensitive substrates give the

hydrolysed products. In order to avoid hydrolysis, a crystalline salt of hypophosphorus acid was prepared by removing the water from commercial, 50% aqueous, hypophosphorus acid under vacuum and slowly adding *N*-ethylpiperidine at 0°C to afford the hygroscopic *N*-ethylpiperidine salt. This salt allowed a range of alcohols to be deoxygenated in high yields.[91]



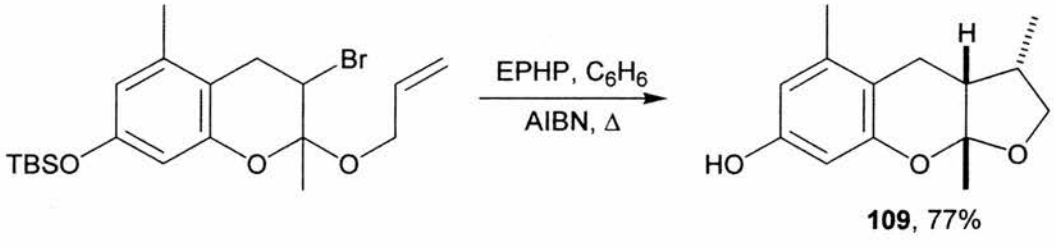
Scheme 46

Initial reports revealed little information on the C-C bond forming abilities of these novel phosphorus reagents. Therefore Murphy looked at a number of simple aryl and alkyl iodides as substrates for C-C bond formation (Scheme 47).[92] The reactions were carried out in refluxing benzene and initiated using AIBN. The released phosphorus-centred radical has a high affinity for iodine and rapidly abstracts the halide to form the aryl radical, which undergoes a 5-*exo*-trig cyclisation to give the bicyclic **107** and tricyclic **108** products in good yields.



Scheme 47

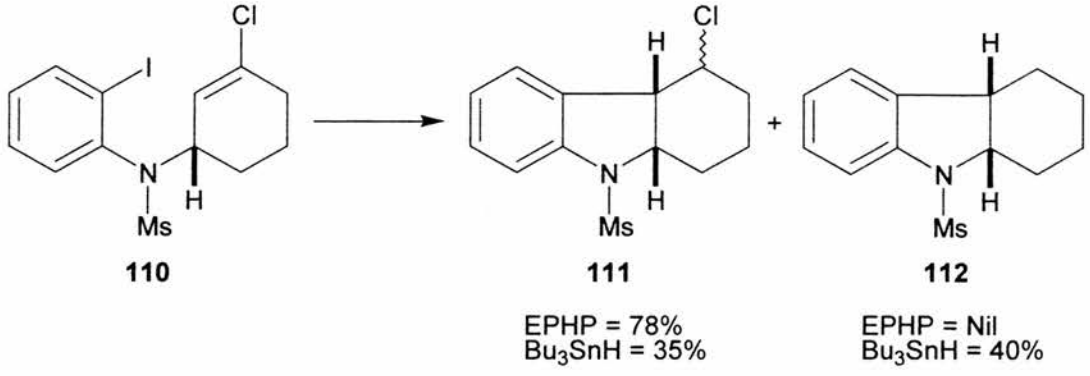
The use of *N*-ethylpiperidine hypophosphite in natural product synthesis is currently under investigation and shows great promise as a clean alternative to organotin hydrides. The recent total synthesis of alboatrin **109**, a phytotoxic metabolite, illustrates how this reagent can be utilised in the pharmaceutical industry to form specific stereoisomers of compounds in high yields (Scheme 48).[93]



Scheme 48

Phosphorus-based reagents appear to be good replacements for tributyltin hydride. They are inexpensive reactants, which can be removed from the organic product with a simple aqueous wash to give high yields of the desired compound. Hypophosphite radicals also show very limited reactivity towards aryl chlorides, in contrast to tin compounds. This greater halide selectivity could have enormous potential in organic synthesis by providing the ability to dictate a point of radical attack, while leaving other halide functionalities free for further reaction. Thus, iodochloride **110** undergoes clean cyclisation to **111** in a 78% yield when using a phosphorus reagent, but the corresponding reaction with tributyltin hydride affords **111** in a reduced yield

of 35%, which is contaminated by large quantities of the dehalogenated by-product **112** (Scheme 49).



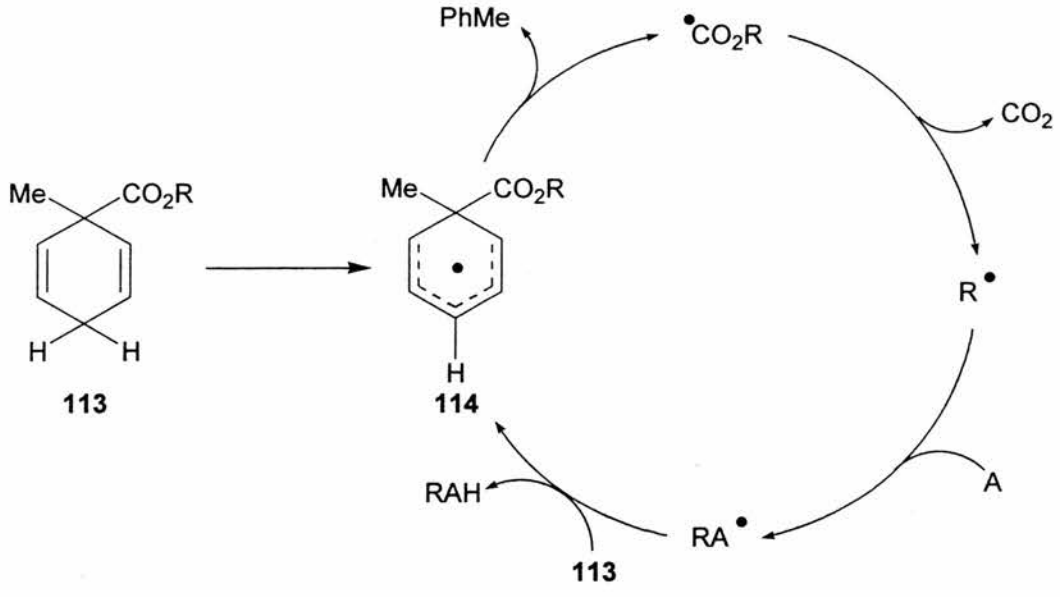
Scheme 49

1-Alkylcyclohexa-2,5-diene-1-carboxylates

The abstraction of a hydrogen atom from a suitably designed reagent, rather than a halogen or chalcogen, could be used in the initial stages of propagation. However, the arbitrary selectivity of C-centred radicals when abstracting hydrogen has caused problems with regioselectivity and consequently inhibited the design of multipurpose reagents. The recent introduction of "pro-aromatic" compounds in radical procedures has provided a potential solution.[94, 95]

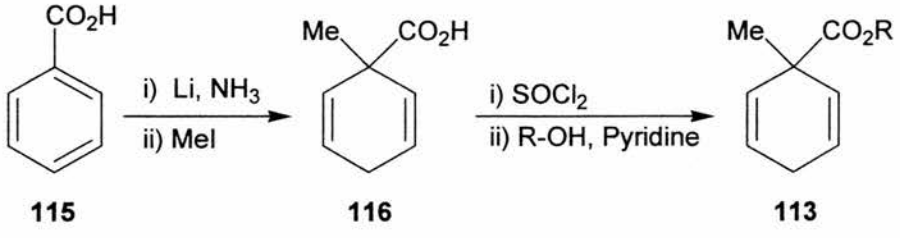
1-Methylcyclohexa-2,5-diene-1-carboxylate esters **113** readily generate radicals which are able to participate in radical chain reactions (Scheme 50). These esters contain two *bis*-allylic hydrogen atoms, which can be abstracted with an appropriate initiator such as dibenzoyl peroxide, to produce the delocalised cyclohexadienyl radical **114**. A high thermodynamic driving force makes it highly favourable for this radical to dissociate by C-C bond scission, reforming the aromatic ring and liberating the alkoxycarbonyl radical $^{\bullet}CO_2R$. Decarboxylation releases the alkyl radical $R^{\bullet}$ which is then free to cyclise or undergo free radical addition to an alkene (A), and hence be transformed to a new C-centred radical $RA^{\bullet}$, before abstracting a further *bis*-allylic hydrogen from **113** to give the addition product and regenerate the delocalised radical **114**. The attractive features of this scheme are the slower H-transfer step in comparison to organotin hydrides, thus allowing more time for intermolecular

additions, and the formation of only one benign by-product, toluene, which is easily removed due to its volatility.



Scheme 50

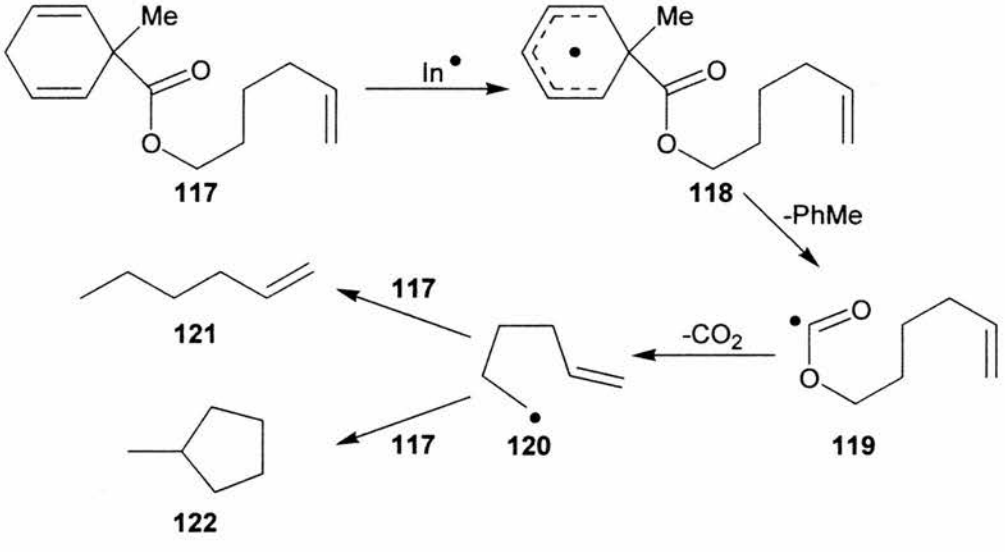
A range of 1-methylcyclohexa-2,5-diene-1-carboxylate esters were synthesised to produce a variety of alkyl radicals, using the well-known Birch reduction/alkylation of benzoic acid. The best results were obtained by adding lithium metal to a solution of benzoic acid **115** in liquid ammonia and quenching with an excess of 1-iodomethane to furnish 1-methylcyclohexe-2,5-diene-1-carboxylic acid **116** in good yields of approximately 80% . Conversion to the esters was then straightforward, by transforming the carboxylic acid into its corresponding acid chloride and reacting this with the relevant alcohol (Scheme 51).[95]



Scheme 51

The radical decomposition of the hex-5-enyl ester **117** illustrates the use of cyclohexadienyl esters in intramolecular additions (Scheme 52). When ester **117** was

exposed to a radical initiator at 140°C in *tert*-butylbenzene, it surrendered a *bis*-allylic hydrogen to form the delocalised cyclohexadienyl radical **118**. The high temperature induced a prompt dissociation into the alkoxycarbonyl radical **119**, which released CO_2 in order to deliver the required hex-5-enyl radical **120**. If the rate of hydrogen abstraction from the starting ester **117** is high, the hex-5-enyl radical will rapidly remove a *bis*-allylic hydrogen to give the direct reduction product, hex-5-ene **121,** and regenerate the chain-carrying cyclohexadienyl radical. However, a lower rate of hydrogen abstraction allows an intramolecular addition to take place prior to hydrogen abstraction in order to furnish methyl cyclopentane **122**. The major product of this reaction was methyl cyclopentane **122**, suggesting that the rate of hydrogen abstraction from 1-methylcyclohexa-2,5-diene-1-carboxylate esters is low.

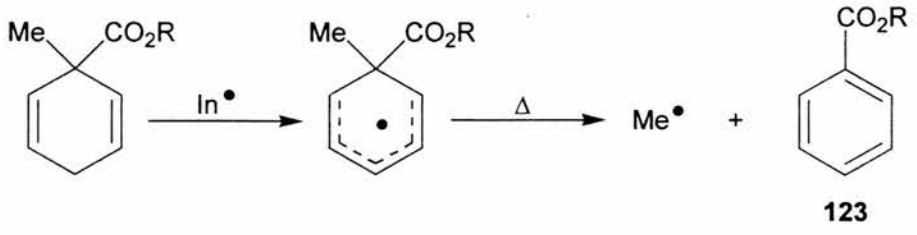


Scheme 52

Using the known rate constant for cyclisation of a primary hex-5-enyl radical,[96] the rate constant for hydrogen abstraction from **117** by a primary alkyl radical was determined, by measuring the ratio of **121 : 122**. This radical clock method gave a rate constant of 0.82 x 10^5 $dm^3mol^{-1}s^{-1}$ at 140°C, which is approximately 150 times slower than the rate constant of hydrogen abstraction from tributyltin hydride.[97]

The yields of products from the methyl esters were greatly reduced due mainly to the competitive loss of a methyl radical from the delocalised cyclohexadienyl radical, giving the corresponding benzoate ester **123** in yields comparable to the desired product (Scheme 53). In order to inhibit this dissociation, the methyl functionality

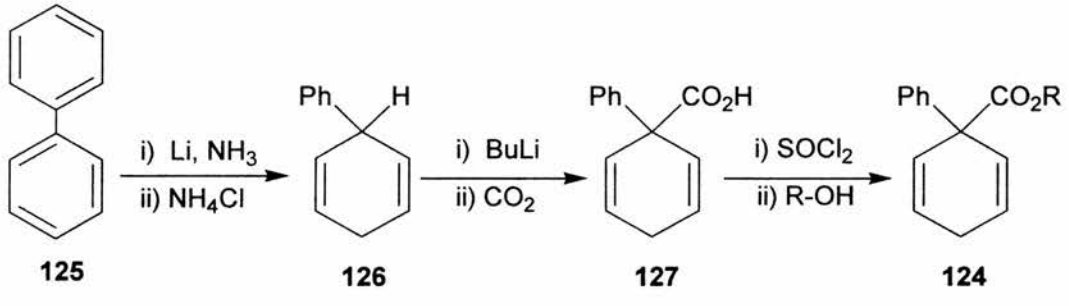
was replaced with a phenyl group, because phenyl radicals are thermodynamically destabilised and would deter the unwanted cleavage.[98]



123

Scheme 53

1-Phenylcyclohexa-2,5-diene-1-carboxylate esters **124** were prepared using cheap and commercially available biphenyl **125** as the foundation (Scheme 54). The Birch reduction of biphenyl was performed in a similar procedure to that previously mentioned, quenching the reaction mixture with ammonium chloride to give 1,4-dihydrobiphenyl **126** in high yields. The treatment of dihydrobiphenyl with BuLi, followed by the pouring of the resultant mixture onto crushed dry ice, furnished the desired 1-phenylcyclohexa-2,5-diene-1-carboxylic acid **127** as the major product. Conversion of this carboxylic acid to the required ester was then carried out in a similar manner to that described for the methyl analogues.[98]

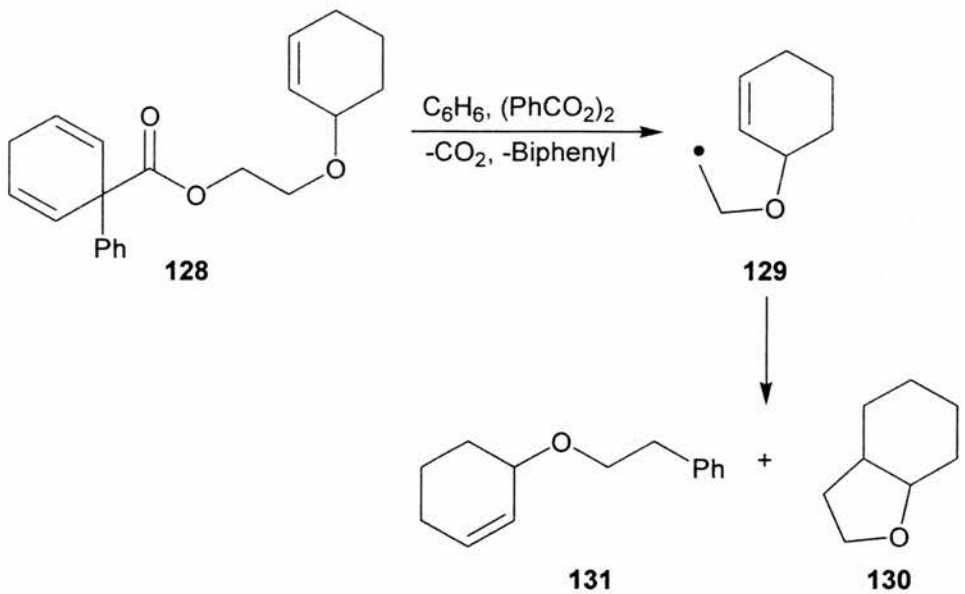


125 **126** **127** **124**

Scheme 54

A range of 1-phenylcyclohexa-2,5-diene-1-carboxylate esters were synthesised in order to examine their ability to take part in chain reactions, and to confirm the suppression of any competing rearrangement. The ethoxycyclohexene derivative **128** was synthesised and isolated in a 30% yield from the phenyl carboxylic acid **127**. This was refluxed in benzene, together with dibenzoyl peroxide as the radical initiator, in order to generate radical **129**, which underwent a 5-*exo* cyclisation to give 7-oxabicyclo[4.3.0]nonane **130** and biphenyl as the major products, which were easily separated using chromatography (Scheme 55). The unwanted β-scission to

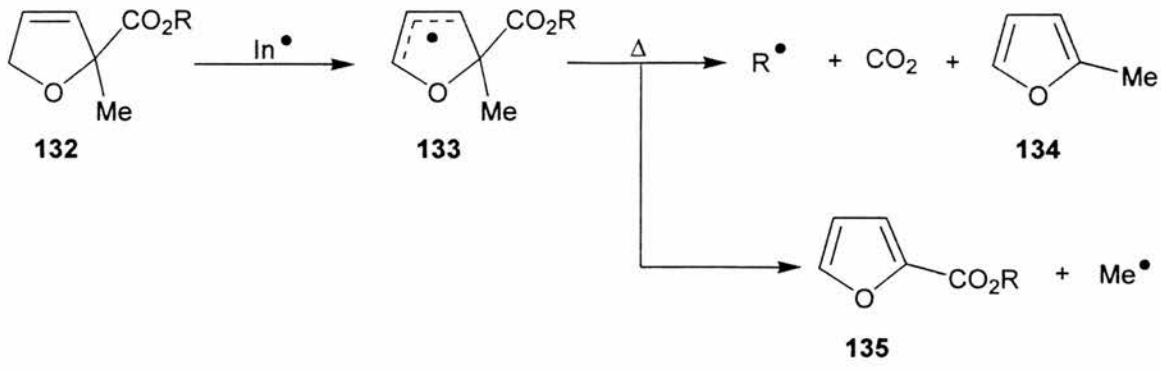
give the phenyl radical was not observed. However, small amounts of the phenyl-ethoxycyclohexene **131** were obtained, presumably from addition of radical **129** to the solvent.



Scheme 55

The radical induced fragmentation of 1-alkylcyclohexa-2,5-diene-1-carboxylate esters can be used as a source of alkyl radicals. The slow hydrogen abstraction rates allow inter- and intramolecular additions to occur before reduction and the by-products are easily removed from the desired product. However, the synthesis and purification of the cyclohexadienyl esters was rather lengthy and gave variable yields. The radical procedure required large amounts of radical initiator in order to maintain the reaction cycle and generally gave poor yields of rearranged product.

Additional research by Binmore examined the radical donating properties of the analogous esters of 2,5-dihydrofuran-2-carboxylic acids **132**.[94, 95] These compounds were synthesised in a similar way to the cyclohexadienyl esters, using the Birch reduction/alkylation of furoic acid in order to generate the initial 2,5-dihydrofuran-2-carboxylic acid. The esters contained allylic hydrogens, which were readily abstracted by an initiator radical to produce the delocalised dihydrofuranyl radical **133**. β-Scission of this radical intermediate gave the alkyl radical $\mathbf{R}^{\bullet}$, CO_2 and 2-methyl furan **134** as an easily removable side product (Scheme 56).

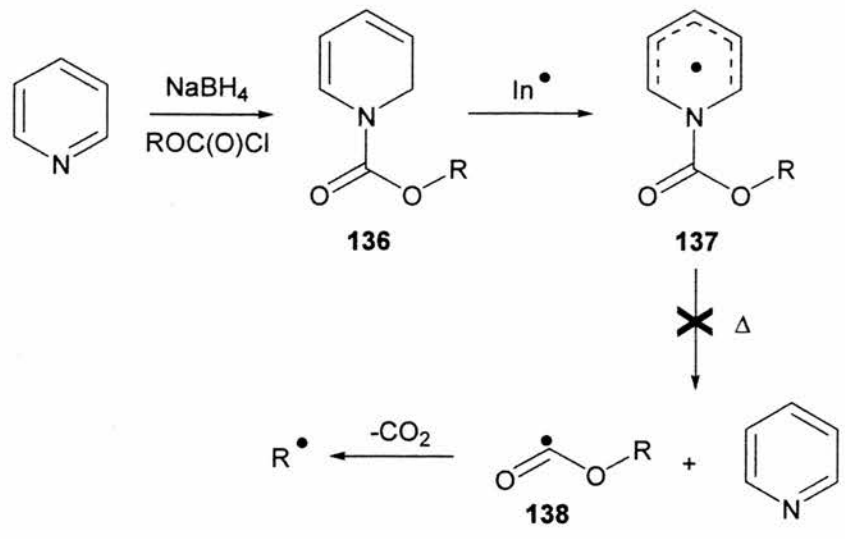


Scheme 56

Unfortunately, when the dihydrofuranyl esters were used in radical addition reactions, evidence for the competitive loss of a methyl radical to furnish the furanyl ester **135** was significant. As large amounts of radical initiator were still required in order to maintain the chain reaction, it was concluded that there were no additional benefits from the incorporation of a furan analogue into these systems, which were not already present when using the cyclohexadienyl derivatives, therefore research in this area was discontinued.

N-Carboalkoxy-1,2-dihydropyridines **136** were studied by Baguley as an alternative to the cyclohexadienyl esters.[99] These compounds can be prepared in good yields by the treatment of pyridine with sodium borohydride in methanol and addition of the appropriate chloroformate (Scheme 57). It was anticipated that allylic hydrogen atom abstraction would give the corresponding delocalised radical **137**, which would generate an alkyl radical by N-C bond scission followed by decarboxylation of the resulting alkoxycarbonyl radical **138**. The by-product, pyridine, could be efficiently removed using an acid wash, and there was no additional alkyl functionality which could compete with the desired N-C bond scission.

EPR analysis of a range of 1,2-dihydropyridines, in the presence of a radical initiator, confirmed the presence of the delocalised aza-cyclohexadienyl radical **137**. However, these compounds gave no evidence for the generation of alkyl radicals, either in the EPR experiments or in a range of radical reactions with various alkenes.

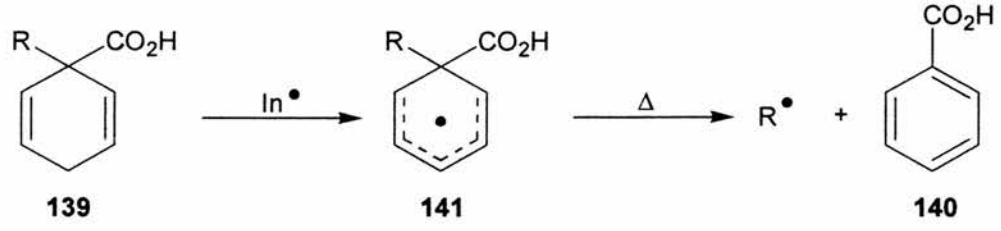


Scheme 57

Although radicals were detected at lower temperatures, it was confirmed that when the temperature was increased, the major route of decomposition was by the non-radical, β-elimination of formate ester **136** with the concomitant production of pyridine.

1-Alkylcyclohexa-2,5-diene-1-carboxylic acids 139

Cyclohexadienyl acids **139** held the potential to be more efficient precursors for radical sources. These compounds could be synthesised in high yields using Birch methodologies, and used directly in radical procedures to yield the desired alkyl radical and benzoic acid **140** as the easily removable side product (Scheme 58). [100, 101] The competitive β-scission would be inhibited, as the hydroxyformyl radical has a low thermodynamic stability.

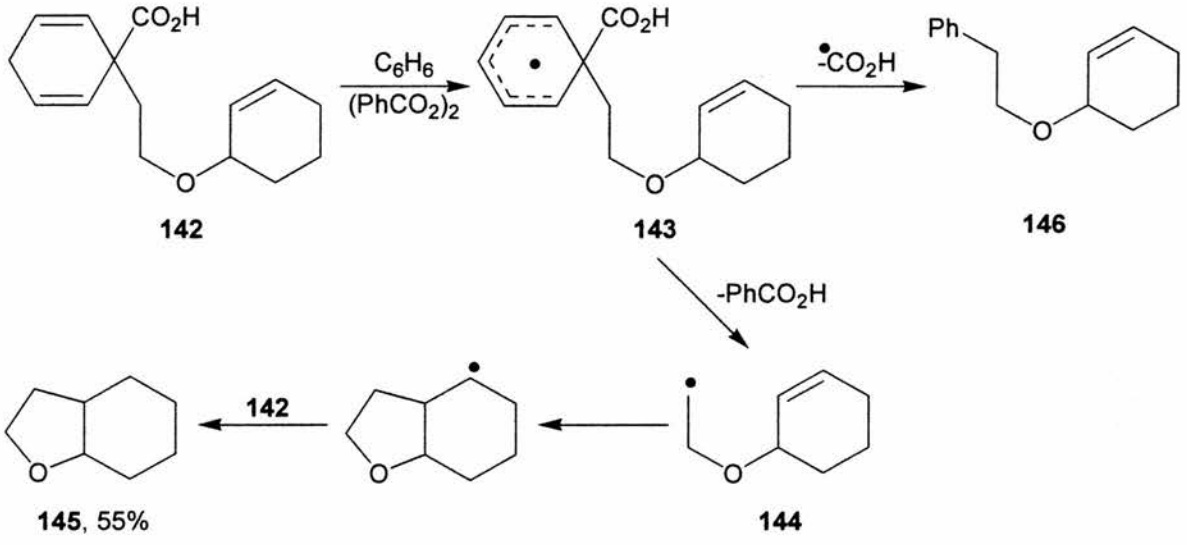


Scheme 58

Treatment of the carboxylic acids with DTBP in the presence of UV light generated the delocalised radicals **141**, which were observed by EPR spectroscopy. When the

temperature of the EPR cavity was increased, the spectrum of **141** was replaced with a new spectrum consistent with the pattern expected for R•. This provided evidence that the cyclohexadienyl carboxylic acids could undergo hydrogen abstraction with an appropriate initiator and that these delocalised radicals could fragment.

1-Alkylcyclohexa-2,5-diene-1-carboxylic acids can participate in radical chain reactions in order to undergo inter- and intramolecular additions. The unsaturated ether analogue **142** was synthesised in an attempt to compare the radical properties of cyclohexadienyl acids with those illustrated by tin hydride (Scheme 59).

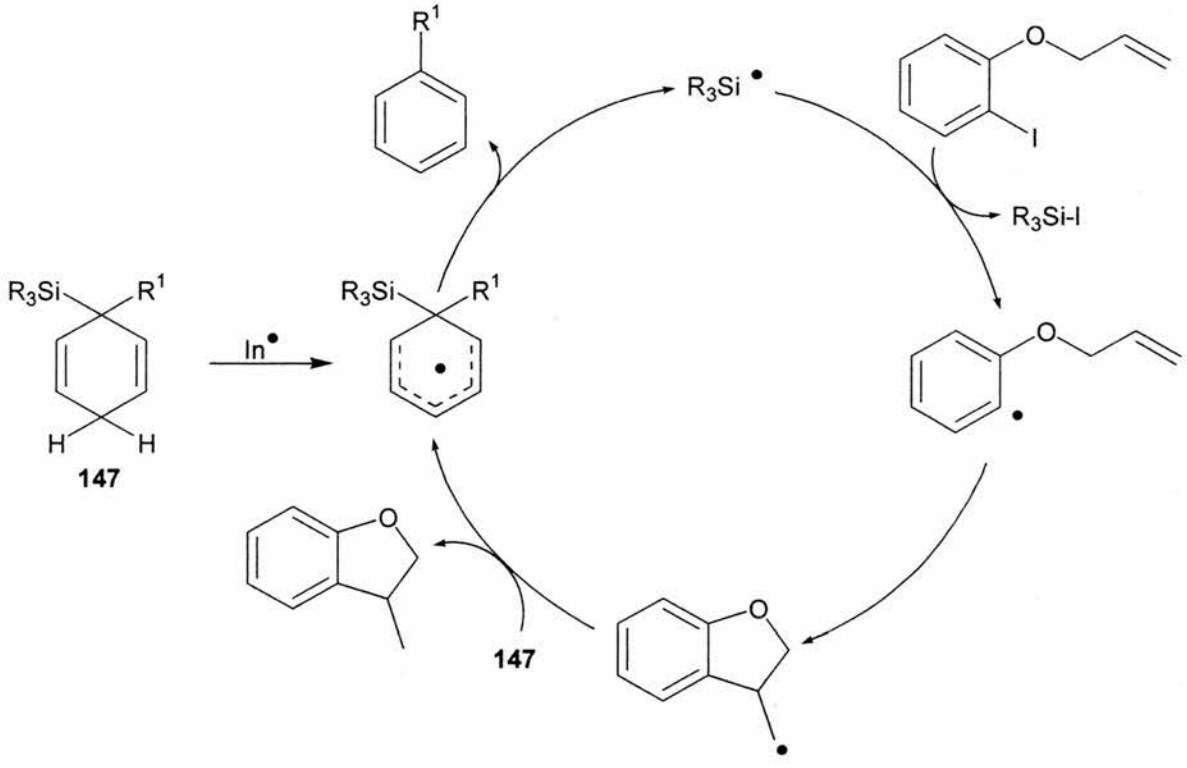


Scheme 59

The carboxylic acid was dissolved in benzene and refluxed in the presence of dibenzoyl peroxide to generate the delocalised radical **143**. 5-*Exo* cyclisation of the derived alkyl radical **144** yielded the bicyclic compound **145** in a 55% yield, which was comparable to the 60% yield attained when using tributyltin hydride with the corresponding bromide. There was no evidence of the prematurely reduced product, however, the presence of moderately large amounts of the 2-phenylethoxy cyclohexene **146** suggested that the unwanted release of a hydroxyformyl radical •CO_2H was more prolific than anticipated when generating a primary radical. [101]

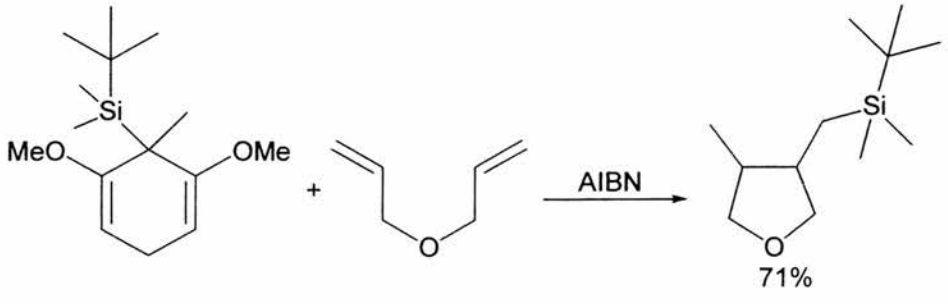
Recently, Studer discussed the formation of silylated cyclohexadienes **147** as alternatives to tin hydrides in various radical reactions. These compounds differ from

the cyclohexadienyl acids as they release a silyl radical which can propagate a radical reaction by dehalogenating an alkyl halide to give the desired alkyl radical and the halogenated silane as a by-product. The liberated radical is then free to undergo addition or cyclisation before it is reduced by abstraction of a *bis*-allylic hydrogen from the silylated cyclohexadiene **147** (Scheme 60).[102]



Scheme 60

The hydrosilylation/cyclisation of dienes is a well-known process, which relies heavily on transition metals. Studer has evolved the use of silylated cyclohexadienes to provide a metal-free alternative for the hydrosilylation of alkenes, which is both high yielding and friendly to the environment (Scheme 61).[103]



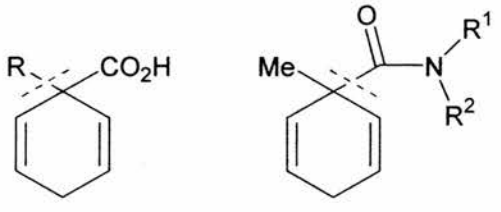
Scheme 61

1-Alkylcyclohexa-2,5-diene-1-carboxylic acids and their silylated analogues have demonstrated their ability to take part in radical reactions and provide good yields of addition products. However, further investigation is required in order to evaluate their scope for generating radicals with differing functionality, and to compare their capabilities with those of organotin hydrides.

Aims and Objectives of the Research

It has been established that 1-alkylcyclohexa-2,5-diene-1-carboxylic acids **139** can generate straightforward alkyl radicals which are able to participate in radical additions and cyclisations. The purpose of my research was to further investigate these alternative sources for radical generation, expanding the range of diverse radicals that can be generated using these precursors and assessing their associated rates of reaction.

This thesis describes our efforts to analyse two main radical reagents (**139** and **148**, Scheme 62), each of which is discussed separately in the following chapters.



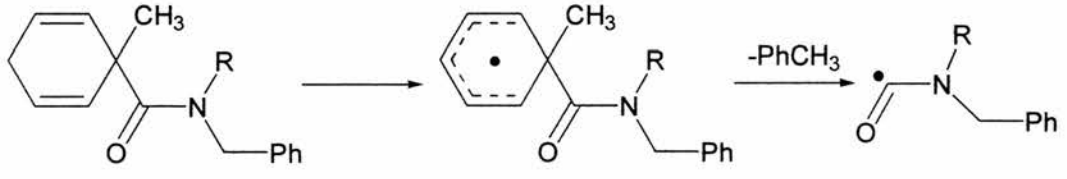
139 **148**

Scheme 62

The bulk of our research has concentrated on the synthesis and kinetic analysis of 1-alkylcyclohexa-2,5-diene-1-carboxylic acids **139**. Previous research in this area focused on the release of secondary, tertiary or resonance stabilised radicals with the major goal being the release of radicals which could undergo 5-*exo* cyclisations, or free radical addition to an alkene, before being reduced. EPR spectroscopy has previously been used on a basic level to detect the delocalised cyclohexadienyl radical at low temperatures and then confirm the rearrangement and consequential release of the desired alkyl radical when the EPR cavity temperature was raised. This research describes the synthesis of many new cyclohexadienyl acids that release several distinct classes of radical with varied stability and functionality. The thesis also demonstrates how a novel EPR technique has been developed, in order to allow the relative dissociation rates, and energies of activation, for these cyclohexadienyl compounds to be measured in an efficient and accurate manner.

The synthesis and radical generating ability of several amido-cyclohexadienes **148** have also been investigated in the latter half of this work. These compounds exhibited the potential to release aminoacyl radicals that could undergo 5-*exo* and 4-*exo* cyclisations to furnish γ- and β-lactams respectively. These desirable lactam structures are found in many natural products but remain difficult to generate using regular procedures in organic synthesis due to the intermolecular strain associated with the formation of the four-membered ring.

A number of 1-carbamoyl-1-methylcyclohexa-2,5-dienes have been synthesised and evaluated using EPR techniques. This confirmed their ability to generate the delocalised cyclohexadienyl radicals **149** and release the aminoacyl radicals **150** (Scheme 63). Product analysis of these compounds after radical initiation, established their ability to undergo radical cyclisation in order to form the desired lactam rings. Unfortunately, due to time limitations, it was not possible to complete full investigations of these compounds, but it is anticipated that research in this area will be continued.



148 **149** **150**

Scheme 63

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Chapter 2

1-Alkylcyclohexa-2,5-diene-1-carboxylic Acids.

Electron Paramagnetic Resonance Spectroscopy

Electron paramagnetic resonance spectroscopy (EPR) records the magnetic resonance spectrum of unpaired electrons and can therefore be applied to systems that are intrinsically paramagnetic such as organic and inorganic radicals. Unpaired electrons have both charge and angular momentum (spin), these combine to give a magnetic moment, which can align with or against an applied magnetic field. Thus, unpaired electrons in a magnetic field will produce a magnetic resonance spectrum.

EPR provides a very sensitive method for detecting and identifying radical species. The technique was first reported by Zavoisky[1] in 1945, who made use of the microwave apparatus that became available after World War II. This innovation allowed physical organic chemists to monitor the formation and disappearance of a variety of radicals and to eventually quantify radical reactions and determine rates of reaction in solution.

The EPR spectrum of a paramagnetic compound in an external magnetic field $\boldsymbol{B}$ can be described using a Hamiltonian operator (Eq 1):

$$\boldsymbol{H} = \boldsymbol{H}_{EZ} + \boldsymbol{H}_{NZ} + \boldsymbol{H}_{EN} + \boldsymbol{H}_{Q} \qquad \textbf{(1)}$$

$\boldsymbol{H}_{EZ}$ is the electronic Zeeman operator, which represents the interaction between electron spin $\boldsymbol{S}$ and the external field. The electron is a quantum mechanical particle which has two magnetic spin quantum states of $m_s = -1/2$ and $m_s = +1/2$. The magnetic moment, μ, is derived from the spin state using the equation $\mu = -g\beta\boldsymbol{S}$, where $\boldsymbol{S}$ is the electron spin, g is the gyromagnetic ratio and β is the Bohr magneton ($= 9.274\text{x}10^{-24}$ J T^{-1}). The interaction of this magnetic moment with the applied magnetic field can therefore be described by (Eq 2):

$$\boldsymbol{H}_{EZ} = -\mu \,.\, \mathbf{B} = g\beta\boldsymbol{S} \,.\, \mathbf{B} \qquad \textbf{(2)}$$

For a free electron in a magnetic field, $g=g_e=2.00232$ (the Landé g factor), therefore the magnetic moments are $\pm 1/2 g_e\beta$ in the magnetic field direction. As a result, the

interaction between these magnetic moments and the applied magnetic field, $\mathbf{B_0}$, produces two distinct energy states with a difference in energy $\Delta E = g\beta\mathbf{B}$. If electromagnetic radiation with a frequency equal to this value of ΔE is applied, absorption takes place and transitions from the lower energy state to the higher energy state and vice-versa occur (Figure 1). In a field of 3,400 Gauss, the Larmor frequency of a free electron will be 9.2 GHz, therefore EPR spectra are recorded in the microwave region of the magnetic resonance spectrum.

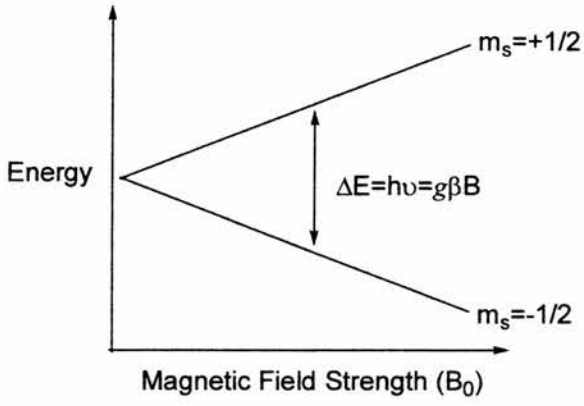


Figure 1

However, the spin state of a free electron is influenced by its local atomic environment, which in turn affects the *g*-value of the electron and its magnetic moment. The effective magnetic moment of a free radical is therefore the product of a coupling between its spin and orbital angular momentum. This results in the molecular electron having a different effective magnetic moment from that of a free electron.

The nuclear Zeeman operator, $\boldsymbol{H_{NZ}}$, represents the interaction of the nuclear spin with the external magnetic field $\mathbf{B_0}$. This value is very small and often negligible as the nuclear magneton is approximately 1836 times smaller than the Bohr magneton. As a result, the nuclear Zeeman energy is very much smaller than its electronic counterpart and can generally be ignored.

The term $\boldsymbol{H_{EN}}$ describes the hyperfine interaction between the electron spin and local nuclear spins. Hyperfine splitting into a number of distinct lines can occur when there

is an interaction between the electron magnetic moment and the magnetic moments of neighbouring magnetic nuclei and, analogous to NMR, the number of lines arising from hyperfine splitting is dependent on the number of nuclear spin orientations.

If a paramagnetic compound contains one magnetic nucleus in close proximity to the free electron, the unpaired electron will experience a local magnetic field. Electron resonance will occur when the total field, made up of contributions by the spectrometer and any local fields, is equal to ΔE. As a result, several absorption lines are observed as the spin states of the magnetic nucleus can align with or against that of the electron and applied field. As a general rule, the spectrum will contain $(2nI+1)$ lines, where I is the spin quantum number of the magnetic nucleus and n is the number of nuclei present.

The splittings between these lines brought about by a common magnetic nucleus can be measured to give hyperfine splittings or a-values. The size of an a value is affected by the structure of the radical (Eq 3), therefore detailed analysis of the number and positions of spectral lines can lead to the determination of the physical and electronic structure of the observed radical.

$$\boldsymbol{H_{EN} = a \,.\, S_Z \,.\, I_Z} \qquad \textbf{(3)}$$

Where a defines the hyperfine coupling and S_Z/I_Z are the electron/nuclear spin operators respectively.

$\boldsymbol{H_Q}$ describes the nuclear quadrupolar energy. This occurs when some nuclei with spins of 1 or more possess an electric quadrupole moment, as the distribution of charge density inside the nucleus is not spherical. This does not occur in the organic molecules being described within this thesis and can be effectively ignored.

The result of eliminating these operations from the Hamiltonian operator given in Eq 1, gives a simplified equation for the spectrum observed using EPR (Eq 4):

$$\boldsymbol{H = g\beta B_0 \,.\, S_Z + a \,.\, S_Z \,.\, I_Z} \qquad \textbf{(4)}$$

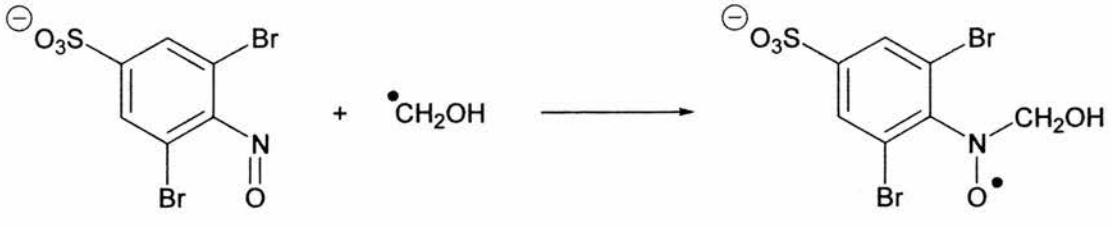
In solids, the radical is fixed and can be orientated in any direction with respect to the applied magnetic field. This means that the *a* and *g*-values can take on a series of different quantities. However, in solution molecular tumbling averages the values of *a* and *g* therefore simplifying the observed isotropic spectrum.

Quantitative measurements using EPR spectroscopy

The determination of radical concentrations in a mixture can be performed in a similar way to NMR by measuring the absorption intensity of the observed signal, which is directly proportional to the radical concentration. However, measurement of this value is relatively more difficult than in NMR as the highly reactive radicals exist in very low concentrations and often cannot be observed at all. Several techniques exist in order to help overcome this. For example, using pulse photolysis to generate higher concentrations of radicals by applying several short bursts of high energy UV light. A more common method is the employment of a technique known as spin trapping (Scheme 1).

Scheme 1

The trapping of a reactive radical (R•) to form a more stable and longer lived radical (R-Trap•), known as a spin adduct, is the main principal behind spin trapping. The spin adduct has a longer lifetime within the EPR spectrometer and can therefore be observed, in order to deduce some information about the structure of the initial radical R•. There are many diverse classes of spin traps, yet the more common forms are either nitroso compounds (R-NO), which react with radicals to give the more stable nitroxides (Scheme 2), or nitrones.



Scheme 2

The EPR spectrum displayed by the spin adduct often proves to be complicated. The α-oxygen atom does not split the signal as I = 0 for the major isotope ^{16}O. However, the β-nitrogen has I = 1 and will give three lines in the ratio 1:1:1, which are then split by the magnetic nuclei of the trapped radical $R^{\bullet}$ to give the complex spectrum. Radicals can therefore be detected using nitroso spin traps, but the structural information obtained is generally limited as the spectra may be difficult to interpret and the original trapped radical is far away from the spin centre in the detected spin adduct radical, which provides no detailed structural information beyond the γ position.

Attempts to calculate kinetic data using the spin trapping technique have been implemented on several occasions, with a varying degree of success. The spin adduct is often a persistent radical, which builds up within the sample as the reaction time increases. Quantifying this rate of increase should therefore give a rate for the formation of the initial organic radical $R^{\bullet}$. Unfortunately, the rate of radical addition between the spin trap and free radical, to give the spin adduct, is not infinite and must also play a part in any kinetic calculations, along with the rate of decay of the spin adduct as it degrades through disproportionation, oxidation and other processes. These features are constantly taking place throughout the EPR experiment and should therefore be accounted for in any derived rate equations, a laborious task that often proves difficult and leads to a large degree of error.[2, 3]

In order to improve accuracy flash photolysis techniques have been employed, which involve the generation of a radical within the EPR cavity using intermittent illumination.[2] The EPR spectrometer is forced to continuously monitor one part of the EPR spectrum, rather than making a large sweep of the many different frequencies. It is routine to observe the tip of the largest peak within the spectrum, which is generated when a pulse of high intensity UV light or a laser initiates the radical reaction. As with most small organic radicals, they decay extremely rapidly, therefore the spectrometer continuously observes the absorption intensity at the selected point and gives an average measurement of the radical decay. This technique has been used to measure the rates of biomolecular radical combination and disproportionation reactions.

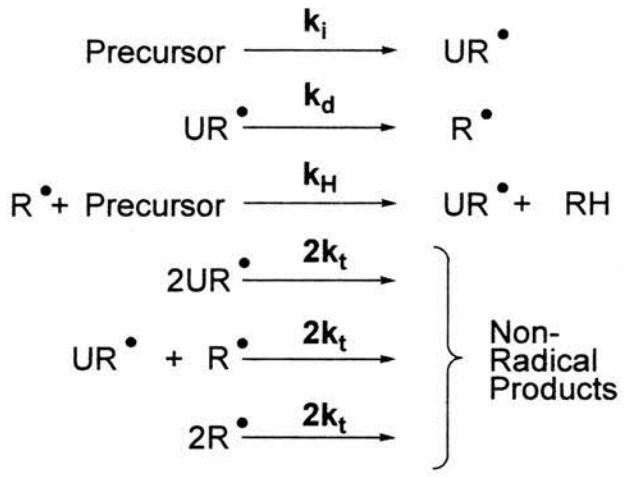
The rates of termination in these reactions are found to be very fast and the rate constants are diffusion controlled which means they are practically independent of radical structure. Fischer and co-workers used this information to accurately calculate the $2k_t$ values of many radicals and to correct them for solvent viscosity.[4] These values have become very important when calculating radical kinetics and are referred to frequently throughout this work.

New techniques in kinetic EPR spectroscopy

It became apparent that recent developments in computer software, with regard to the acquisition and manipulation of EPR spectra, could make it possible to design a new approach to measuring radical concentration data. This has previously been a very laborious and manual task, which proved to be both inaccurate and difficult due to the large amounts of background noise that commonly exists when observing transient radicals.

When EPR peaks derived from both the unrearranged radical **UR$^\bullet$** and its associated rearranged radical **R$^\bullet$** can be simultaneously observed on a single EPR spectrum, it is possible to use new computer software to filter out any background noise and double integrate the differential spectrum to give the associated area under the EPR peak. This area can then be converted into a value of radical concentration by direct comparison to a standard, with known radical concentration.

A need to calculate the reaction kinetics for the radical rearrangement of 1-alkylcyclohexa-2,5-diene-1-carboxylic acids into their related alkyl radicals provided a good opportunity to develop this proposed technique, and to confirm the potential of these original radical precursors to replace organostannanes in organic synthesis.



Scheme 3

The mechanism for radical rearrangement of the cyclohexadienyl acids can be simplified into its component parts (Scheme 3). Fischer confirmed in his work that the rate of termination was independent of radical structure, providing the radicals are small. Therefore all rates of termination are believed to be equal and diffusion controlled. This assumption, coupled with a Steady State approximation on the mechanism of rearrangement (Appendix 1), allows an equation to be derived which can be used to calculate the values of k_d and k_H from concentration measurements of the two transient radicals obtained from the EPR spectrum (Eq 5).

$$\frac{k_d}{2k_t} = \frac{k_H}{2k_t}\frac{[R^\bullet]}{[UR^\bullet]}[AH] + [R^\bullet] + \frac{[R^\bullet]^2}{[UR^\bullet]} \qquad (5)$$

k_d = Rate of dissociation

k_H = Rate of hydrogen abstraction

$2k_t$ = Diffusion controlled termination rate (Values obtained from Fischer's work)[4]

[AH] = Initial sample concentration of 1-alkylcyclohexa-2,5-diene-1-carboxylic acid

[UR•] = Measured concentration of the delocalised cyclohexadienyl radical

[R•] = Measured concentration of the released alkyl radical

The derived equation contains two unknowns, k_H and k_d. In order to solve this equation, two separate sets of data are required with differing values of [R•], [UR•]

and [AH]. However, for most of the cyclohexadienyl acids used in the following experiments, a significant change in sample concentration [AH] had little effect on the concentrations of the transient radicals and therefore k_H must be very small and can be deemed negligible. This further simplifies the Steady State equation to contain only one unknown, k_d, which can be directly calculated by measuring the peak areas in the EPR spectrum (Eq 6).

$$\frac{k_d}{2k_t} = [R^\bullet] + \frac{[R^\bullet]^2}{[UR^\bullet]} \qquad (6)$$

Measuring radical concentration using EPR spectroscopy

In order to calculate the relevant values of k_d for the cyclohexadienyl acids, a simple and accurate method of determining the transient radical concentration was required. As discussed, the area underneath a signal in the EPR spectrum is directly proportional to the radical concentration at that specific point. Previous methods of calculating this area involved a lot of manual effort and often gave inaccurate results. However, in this age of computer technology there is a good supply of new software packages available, which are making the collection and interpretation of EPR spectra more simple.

The arrival of a new Bruker EMX 10/12 EPR spectrometer and it associated software, WinEPR, provided the opportunity to manipulate EPR spectra on-screen, so that measurements of hyperfine splitting and *g*-value could be found quickly. The ability to enhance the spectrum and filter out any background noise also proved useful when taking measurements from the spectra of often obscured transient radicals. However, the major advantage of the new software package was the capacity to select a small portion of the EPR differential spectrum and double integrate it in order to gain data on peak area in an analogous manner to that used in NMR.

The EPR spectrum of 1-*n*-propylcyclohexa-2,5-diene-1-carboxylic acid serves as a good example of how the individual spectra were manipulated to give the required data on radical concentration. Figure 2 displays a small section of the spectra

acquired when photolysing the *n*-propyl acid within the EPR cavity at 345 K. The selected portion shows peaks that are generated by both the delocalised cyclohexadienyl radical **1** and the released n-propyl radical **2** as indicated.

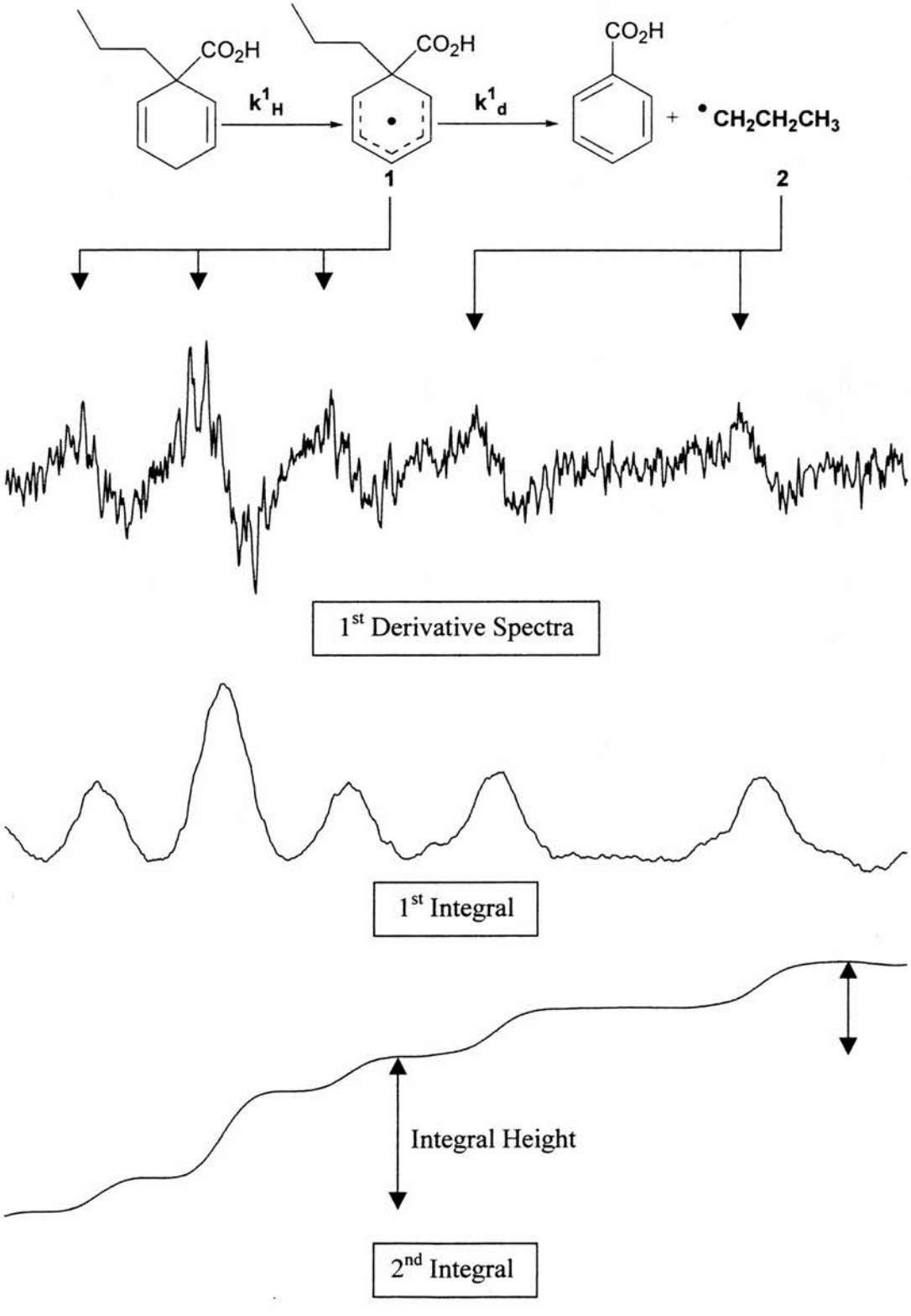


Figure 2

The 1st derivative spectrum, produced after the initial EPR experiment, could be filtered to remove any excess noise, though a majority of this noise was eliminated during the first integration. Integration was straightforward using the WinEPR software, despite the fact that the spectrum resulting from the 1st integration often gave a warped baseline. Fortunately the software package contained a flexible baseline correction facility, which allowed us to reset the baseline so that a second integration could be applied, giving the familiar step diagram which is analogous to that found in NMR. Measurement of the integral heights was simplified by using the pointer incorporated into the computer program, and these readings gave the accurately measured double integral values necessary to calculate the transient radical concentrations.

In order to convert the observed double integral values into actual radical concentrations, it became necessary to employ a standard solution which contained a stable radical of known concentration. Previous research used a standard solution of 2,2-diphenyl-1-picrylhydrazyl (DPPH) in toluene, which had a known concentration of approximately 10^{-4} M. A stock DPPH solution, of known concentration, was prepared and a 250 μl aliquot was placed in the cleaned EPR tube before being thoroughly degassed with N_2. This sample was inserted into the resonant cavity, which was held at a fixed temperature, and the EPR spectrum acquired using identical experimental parameters of both power and modulation to those used with the cyclohexadienyl acid, in order to give the well-resolved spectrum of DPPH (Figure 3). This spectrum was double integrated in a similar manner to that dictated by the cyclohexadienyl acid and gave a new double integral value, which had an accurately known concentration.

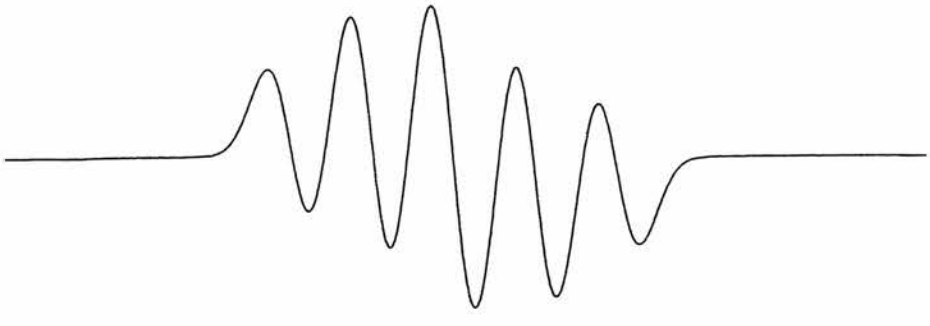


Figure 3

The double integrals of the two transient radicals can be directly compared to the double integral of DPPH, as the experimental parameters were identical. Placing these respective values into the derived equation (Eq 7), allows the relationship between concentration and double integral value to be determined, and therefore enables accurate concentrations for each transient radical to be calculated.

$$[R^{\bullet}] = [DPPH] \times \frac{di\,(R^{\bullet})}{di\,(DPPH)} \times \frac{Gain\,(DPPH)}{Gain\,(R^{\bullet})} \times \frac{[\Delta H\,(R^{\bullet})]^2}{[\Delta H\,(DPPH)]^2} \times \frac{Ruby\,(DPPH)}{Ruby\,(R^{\bullet})} \times \frac{T\,(R^{\bullet})}{T\,(DPPH)} \times F$$

(Eq 7)

[DPPH] = Known concentration of DPPH

di ($R^{\bullet}$) = Double integral value for part of the $R^{\bullet}$ spectrum

Gain ($R^{\bullet}$) = EPR Gain used during spectrum acquisition

ΔH ($R^{\bullet}$) = Field range of double integrated portion of the spectrum (G)

Ruby ($R^{\bullet}$) = Height of the ruby signal (Equal to 1 in all our experiments)

T ($R^{\bullet}$) = Absolute temperature at which the spectra was acquired (K)

F = Factor, inverse fraction for the portion of spectrum integrated

The acquired concentration data can finally be fed into the derived Steady State equation (Eq 6) to give a value for $k_d/2k_t$ for the cyclohexadienyl radical at a specific temperature.

Calibration of the EPR spectrometer

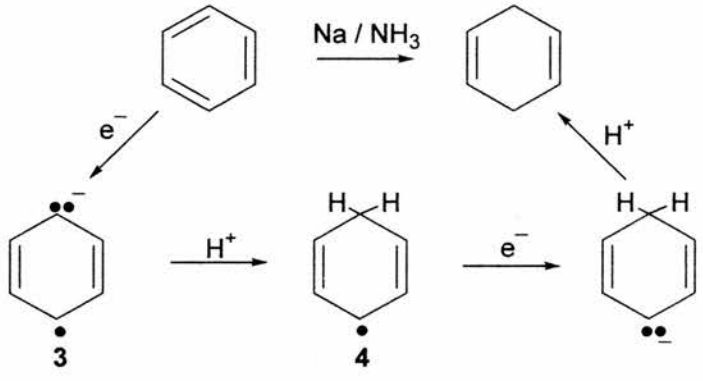
In order to gain accurate kinetic data for the 1-alkylcyclohexadienyl acids, it was important to keep all individual EPR experiments uniform. Small differences in sample size and positioning within the EPR cavity could have a marked effect on the absorption intensity in the produced EPR spectrum. In an attempt to reduce these factors to a minimum, all samples were prepared using 250 µl of the preferred solvent. A series of EPR experiments was also carried out on a test sample to find the optimum distance to place an EPR tube within the cavity to gain the strongest spectra. This distance was maintained in all experiments to give both the strongest possible spectrum, and to maintain experimental consistency.

The temperature of the resonance cavity was controlled by a cryostat, which used liquid N_2 to cool the system, or heated air to increase temperature. The use of high powered UV light on the EPR sample, while inside the resonant cavity, served as an additional source of heat which slightly increased the temperature from that dictated by the cryostat. Attempts to cool the UV light by passing it through a quartz condenser, cooled by water, had only a slight affect.

The precise measurement of temperature within the EPR cavity was crucial in order maintain accuracy. Therefore a temperature calibration curve was plotted, comparing the dial temperature on the cryostat with the actual temperature within the resonant cavity while the UV light was both activated and deactivated. This calibration was carried out for both the liquid nitrogen cooling system and the compressed air heating system to give equations for the precise temperature within the EPR cavity when the UV light was activated. All stated temperatures have therefore been corrected using the appropriate equation.

The Birch reduction

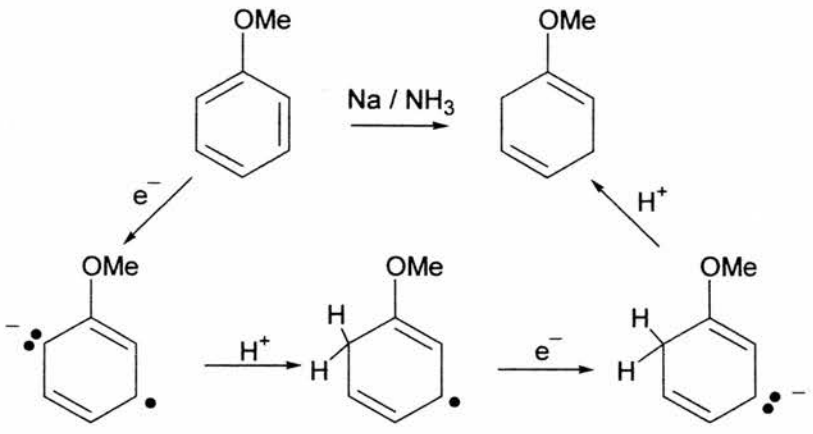
Aromatic compounds can be reduced to the corresponding, non-conjugated, cyclohexadienes by alkali metal-ammonia reductions which are commonly referred to as Birch reductions.[5, 6] As a result, benzene can be transformed into cyclohexa-1,4-diene using Na and NH_3 in high yields (Scheme 4).



Scheme 4

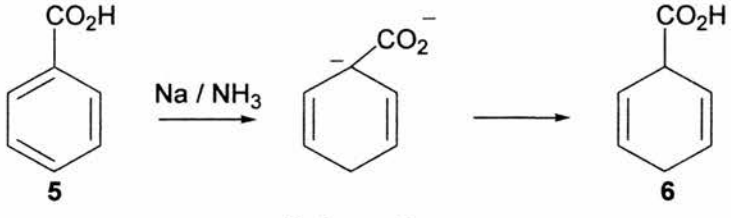
The mechanism for this reduction involves the transfer of an electron from the metal to the ammonia thus forming a solution of solvated electrons, distinguished by a deep blue colouration. An electron is able to add to the aromatic ring to form the radical anion **3**, which readily abstracts a proton from a proton source, such as EtOH, to give radical **4**. This radical can accept a further electron from the solution and protonate to give the desired product.

If the aromatic ring is substituted, there is a potential for many regioisomeric cyclohexadienes to be produced, however, only one form is generally observed. It is well established that an aromatic ring with an electron donating substituent will commonly form the cyclohexadienes with the substituent attached at an olefinic carbon. Thus the Birch reduction of methoxybenzene results in the formation of 1-methoxycyclohexa-1,4-diene (Scheme 5).



Scheme 5

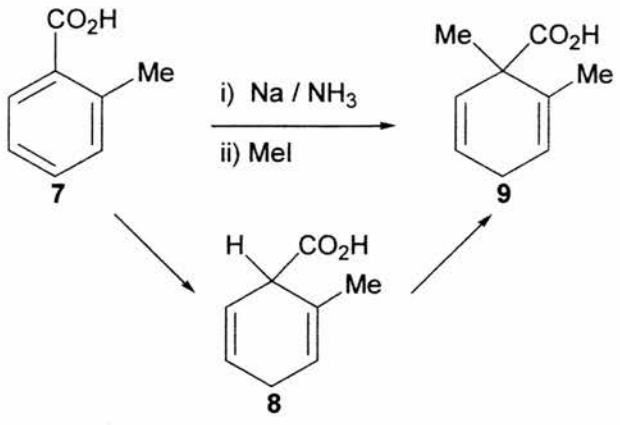
The presence of an electron withdrawing substituent on the benzene ring increases the relative rate of reduction. The substituent is generally bonded to a saturated carbon in the final cyclohexadienes; hence treatment of benzoic acid **5** under Birch conditions gives 1,4-dihydrobenzoic acid **6** (Scheme 6).



5 **6**

Scheme 6

In an extension of this work, Birch found that it was possible to perform his alkali metal reductions on multisubstituted precursors. For example, *o*-toluic acid **7** could be converted into the corresponding cyclohexadiene **8** (Scheme 7). Further treatment of this product with potassium amide in NH_3, and subsequent quenching with methyl iodide furnished 1,2-dimethylcyclohexa-2,5-diene-1-carboxylic acid **9**.[7] It has subsequently been proved that this reaction can be carried out in one step by treating *o*-toluic acid with Na in NH_3 and quenching directly with methyl iodide. This type of reaction is known as a Birch reduction/alkylation.

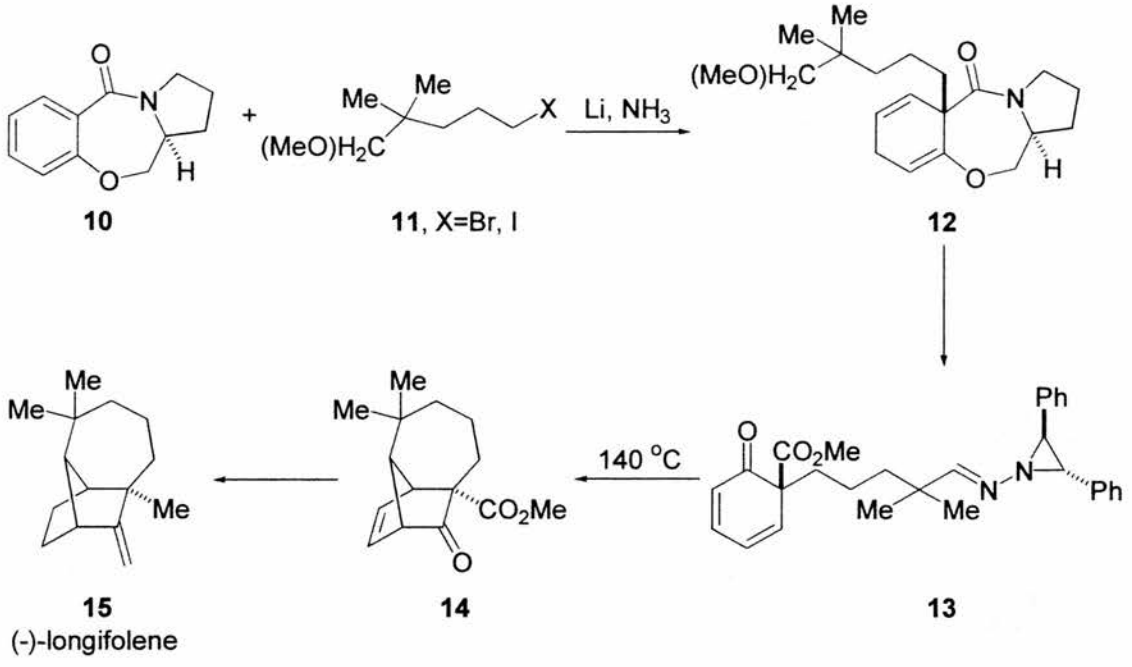


Scheme 7

Birch reduction/alkylation processes have proved to be of significant use in organic chemistry, as they convert relatively simple aromatic precursors into more useful cyclohexadienyl compounds and generate a chiral centre simultaneously. The availability of a wide range of substituents on the precursor benzoic acid derivative, and the uniformly high degree of diastereoselection in the chiral alkylation step, make this approach unusually versatile for the asymmetric synthesis of many natural products and related materials.

Schultz has comprehensively studied this area of research and has provided many examples for the use of asymmetric Birch reduction/alkylation strategies in the synthesis of natural products.[8] The formation of the tricyclic sesquiterpene longifolene **15**, found in several *Pinus* species, offers a suitable example (Scheme 8).[9]

The initial step involved the Birch reduction/alkylation of benzoxazepinone **10** with the associated alkyl halide **11** in a yield of 96%. Cyclohexadiene **12** was converted into a cyclohexa-2,4-dien-1-one ring system *via* a general procedure to give the aziridinyl imine **13**. Heating at 140 °C instigated fragmentation to give the intermediate diazoalkane, which underwent a 1,3-dipolar cycloaddition before expelling N_2 to give the tricyclic ketone **14**. This ketone was readily converted into the desired natural product (-)-longifolene **15**.



Scheme 8

We required an effective method for preparing 1-alkylcyclohexa-2,5-diene-1-carboxylic acids. Previous research has revealed that the Birch reduction/alkylation of benzoic acid is suitable for this purpose.[10, 11] The reduction of benzoic acid with Li metal in a solution of NH_3 is straightforward, and the addition of a range of alkyl halides would result in the formation of many varied carboxylic acids which could be tested for their abilities as radical precursors.

Results and Discussion

This section discusses the synthesis and subsequent reactions of 1-alkylcyclohexa-2,5-diene-1-carboxylic acids. In order to simplify presentation, each acid has been analysed and discussed individually, in combination with the applicable EPR spectra and all executed radical reactions.

General procedure for the preparation of EPR samples

All EPR samples were prepared in a similar fashion, often using 250 μl of di-*tert*-butyl peroxide (DTBP) as both the solvent and radical initiator. However, several compounds proved insoluble in DTBP and were therefore prepared using only 50 μl of DTBP in 200 μl of *t*-butylbenzene as a co-solvent. On occasion, it became apparent that the temperature of the resonant cavity would be set below the freezing point of both DTBP and *t*-butylbenzene in order to gain the necessary kinetic information. In these cases, an alternative co-solvent with a lower freezing point was utilised. The kinetic data obtained from each experiment was always corrected for any change in solvent viscosity using Fischer's values for $2k_t$.[4]

To prepare the EPR sample, an accurately measured quantity of the 1-alkylcyclohexa-2,5-diene-1-carboxylic acid was placed in a clean and dry quartz EPR tube, before a total of 250 μl of the designated solvent was added. The sample was mixed thoroughly, to ensure all of the carboxylic acid was taken up into solution, before a steady flow of N_2 was passed through the sample for a total of 15 minutes in order to remove any air from the sample, which could cause broadening of the EPR spectra. Once degassed, the sample was rapidly sealed and used in the selected EPR experiment.

General procedure for the Birch reduction/alkylation

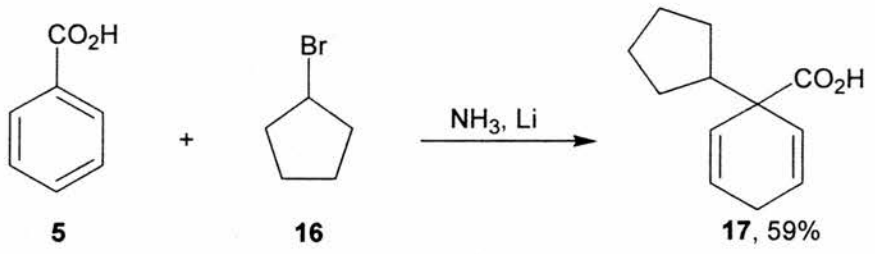
In order to make a varied range of diverse cyclohexadienyl acids, we performed numerous Birch reactions using benzoic acid and its analogues as the standard aromatic component, alkylating with a wide range of alkyl halides.

During the reaction, addition of benzoic acid to NH_3 often proved quite a volatile process and required care and attention to prevent any losses of reactants. Freshly cut Li metal was washed in petroleum ether to remove any traces of paraffin oil and added portionwise to the ammonia mixture while stirring constantly. After complete addition of Li, the reaction mixture was allowed to stir for a further 10 minutes until a persistent blue colouration was formed, before the dropwise addition of the alkyl halide decolourised the solution and formed the desired 1-alkylcyclohexa-2,5-diene-1-carboxylic acid.

The alkyl halide was often added without dilution in any solvent. However, several experiments reacted violently when the concentrated reactant was added. This was overcome by diluting the alkyl halide in a small quantity of ether. The decolourised solution was allowed to stand for several hours while all of the NH_3 evaporated, before the remaining products were dissolved in 2 M NaOH and washed with ether. The basic fraction was acidified using 2 M H_2SO_4 in order to release the cyclohexadienyl acid, which was taken up into ether. The resultant organic fraction was washed with water and dried, before the solvent was removed, to furnish the desired 1-alkylcyclohexa-2,5-diene-1-carboxylic acid in moderate yields.

1-Cyclopentylcyclohexa-2,5-diene-1-carboxylic acid 17

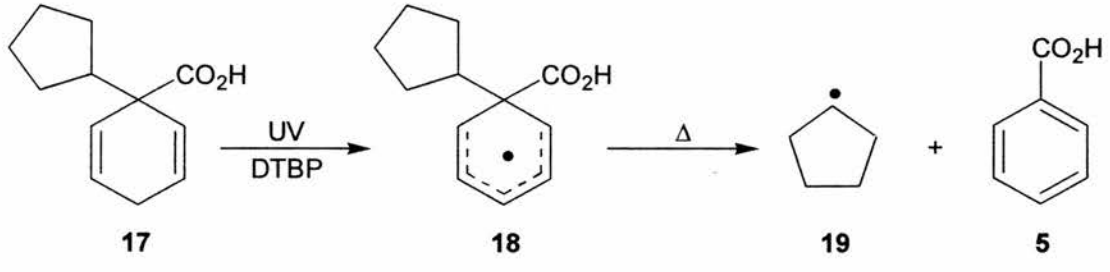
Synthesis of 1-cyclopentylcyclohexa-2,5-diene-1-carboxylic acid 17[10, 12]



Scheme 9

1-Cyclopentylcyclohexa-2,5-diene-1-carboxylic acid **17** was prepared using the adapted Birch reduction/alkylation procedure (Scheme 9). The cyclopentyl acid had previously been synthesised by Baguley using cyclopentyl bromide **16** as the quenching alkyl halide. This procedure was duplicated on a smaller 5 g scale to furnish the cyclohexadienyl acid, which was purified using column chromatography to give the desired product in a yield of 59%.

EPR study of 1-cyclopentylcyclohexa-2,5-diene-1-carboxylic acid 17



Scheme 10

The EPR samples were prepared in a similar fashion to that stated in the general procedure, using 250 μl DTBP as both the solvent and radical initiator. Approximately 10 mg of **17** was initially used in exploratory experiments to assess the generated spectra and to optimise the conditions of the EPR cavity. The degassed sample was placed in the EPR cavity and its initial EPR spectrum was obtained without any UV light to verify the absence of any radicals. The cavity was then cooled to 240 K before the sample was exposed to high intensity UV in order to

generate the *t*-butoxyl radicals from DTBP. This radical removed a *bis*-allylic hydrogen from **17** and furnished the delocalised cyclohexadienyl radical **18** (Scheme 10). The EPR spectrum was recorded and a spectrum corresponding to the delocalised acid radical **18** was observed (Figure 4). There were no discernable peaks due to the released cyclopentyl radical **19**.

The EPR cavity was allowed to heat up to a temperature of 320 K before, again, exposing the sample to UV and recording the EPR spectrum. On this occasion, the spectrum had changed in appearance and could now be assigned to the released cyclopentyl radical **19**, with only a very weak trace of the signal from the delocalised acid radical.

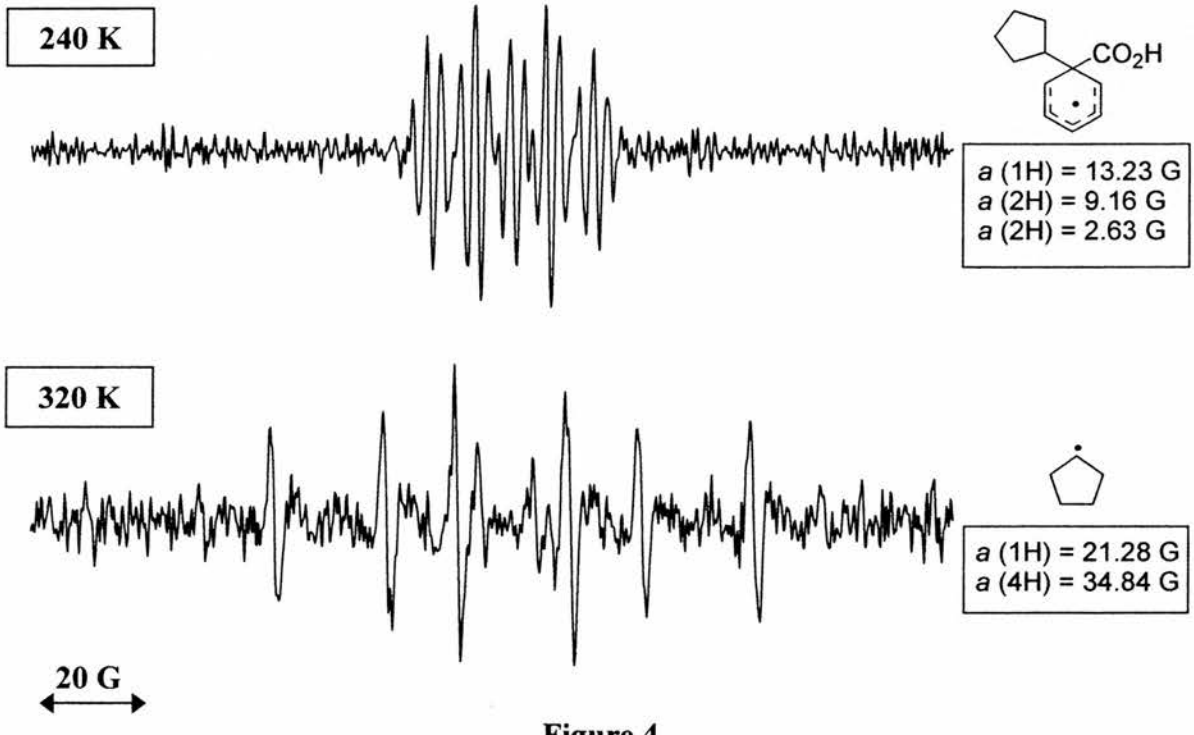


Figure 4

It was noted that as the temperature of the cavity increased, the spectrum due to the delocalised acid radical **18** weakened and was gradually replaced by that of the corresponding cyclopentyl radical **19**. On lowering the temperature, the inverse process was observed and the spectrum of the delocalised acid radical was restored.

In order to gain kinetic information using our EPR protocol, measurements had to be recorded when both of the transient radicals could be distinguished on the same

spectrum. Therefore the cavity temperature was adjusted once again in small increments of 5 K, in order to determine the temperature range at which both radicals could be observed. For the cyclopentyl acid, this range was 277-307 K.

A new EPR sample was prepared with an accurately measured concentration of the cyclohexadienyl acid. The degassed sample was placed in the EPR cavity and allowed to cool to 277 K before exposure to UV. Initially the full spectrum was recorded, displaying mainly the delocalised acid radical **18**, with small peaks derived from the rearranged cyclopentyl radical **19**. Analysis of the entire spectrum proved very difficult using the software available, as it became impossible to obtain a flat baseline after the initial integration. It was also apparent that the peaks became significantly weaker towards the end of the spectra as the supply of cyclopentyl acid was exhausted. In order to combat this, it was decided to focus on a specific part of the spectrum where signals from both radicals **18** and **19** could be observed, but did not interfere with each other.

To prevent the spectra from becoming progressively weaker due to continuous use of the same sample, a stock solution of the cyclopentyl acid was prepared, providing ten equal samples with a known concentration. Each sample was degassed thoroughly with N_2, before EPR spectra were recorded at individual temperatures, using a fresh sample for each new temperature setting (Figure 5). These spectra were finally double integrated using the WinEPR software to give the required data for peak area.

The concentrations of the two transient radicals, at each temperature, were determined by direct comparison to standard DPPH spectra using the novel method described earlier. The derived values for transient radical concentration were placed into the Steady State equation to give a value for log $k_d/2k_t$ at each temperature. Data for the diffusion-controlled rates ($2k_t$) have previously been determined for many solvents by Fischer and co-workers.[4] This data allowed us to correct the calculated k_d values for solvent viscosity and provided the observed values for log k_d at each temperature (Table 1).

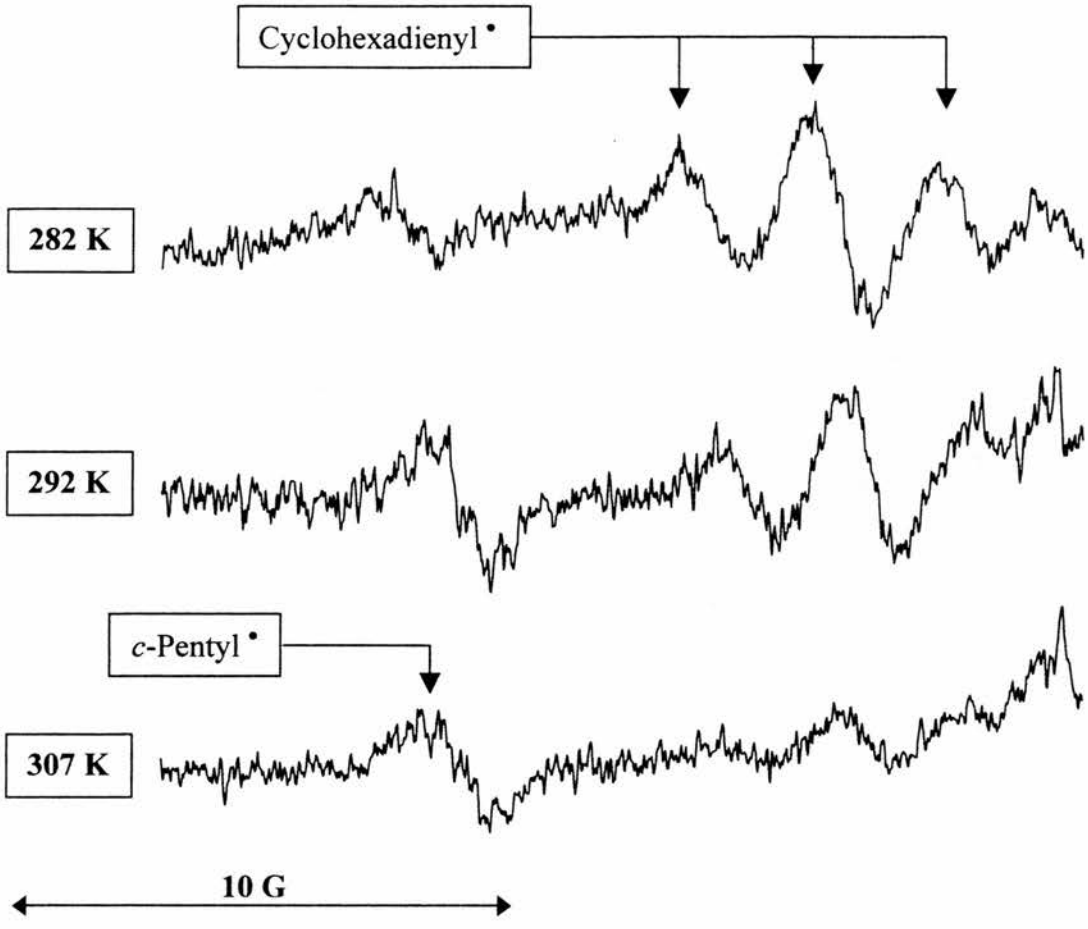


Figure 5

T/K	[19]	[18]	log $k_d/2k_t$	$10^3/T$	log $2k_t$[a] DTBP	k_d
277	5.036E-08	2.575E-07	-7.220	3.613	9.529	2.03E+02
282	1.007E-07	3.815E-07	-6.895	3.548	9.564	4.67E+02
287	9.229E-08	1.710E-07	-6.847	3.485	9.599	5.64E+02
292	7.914E-08	1.031E-07	-6.854	3.424	9.632	5.99E+02
292	9.044E-08	1.984E-07	-6.880	3.424	9.632	5.64E+02
297	1.194E-07	1.180E-07	-6.619	3.365	9.664	1.11E+03
302	1.046E-07	6.252E-08	-6.554	3.308	9.695	1.38E+03
307	1.107E-07	5.176E-08	-6.459	3.254	9.725	1.84E+03

Table 1

[a]$2k_t$ values from work of Fischer and co-workers, corrected for solvent viscosity.[4]

The variation in the rate of a chemical reaction with temperature can be represented quantitatively using the Arrhenius equation. By plotting the calculated values of log k_d against $10^3/T$, and implementing a line of best fit, it was possible to obtain the

associated gradient and intercept of this line, which are both related to the values of activation energy (E_d) and pre-exponential factor (A_d) for 1-cyclopentylcyclohexa-2,5-diene-1-carboxylic acid (Figure 6, Table 2).

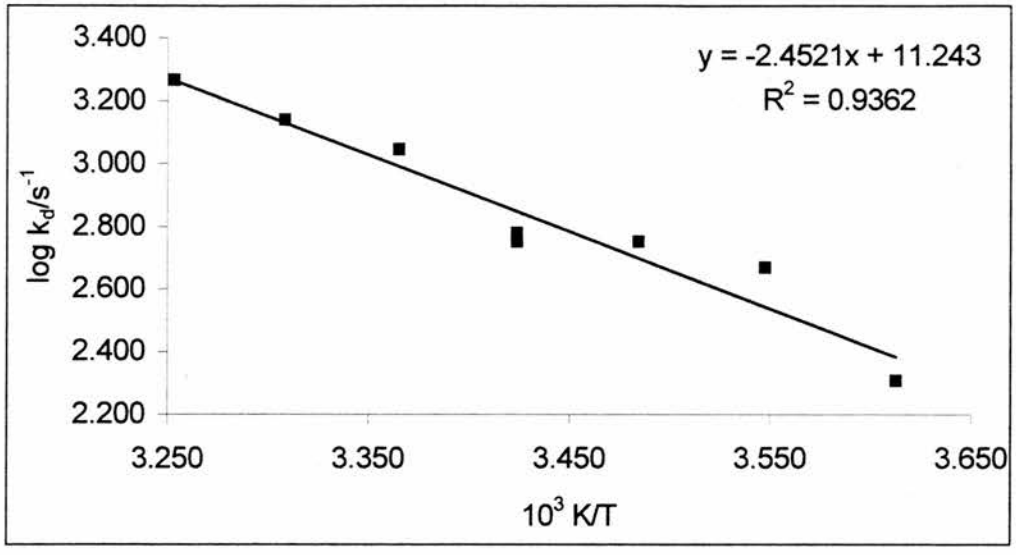


Figure 6

R^2 = Accuracy of line of best fit (1.0 = perfect fit)

Released Radical	10^{-3} k_d / s^{-1} (300K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
c-$C_5H_9^{\bullet}$	1.14	11.24	11.22

Table 2

EPR study of 1-cyclopentylcyclohexa-2,5-diene-1-carboxylic acid 17 using a different sample concentration

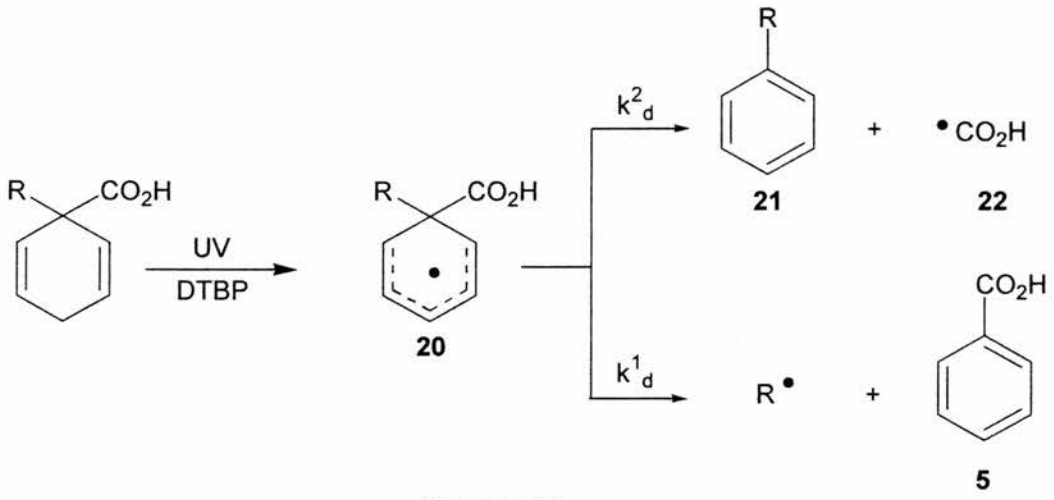
The Steady State equation derived in Appendix 1 relies heavily on the assumption that k_H is negligible. In order to confirm this belief, a second set of spectra was acquired, using a sample that contained a different concentration of the cyclopentyl acid. If k_H was significant for the cyclopentyl acid, any change in acid concentration would have a direct effect on the ratio of transient radicals observed by EPR and the relative values of k_d.

The new sample, containing 1 mg of the cyclopentyl acid in 250 μl of DTBP, was prepared and placed into the EPR resonator, which was held at 292 K. The sample was photolysed and its EPR spectrum recorded using identical parameters to those employed in the previous set of experiments. The peaks due to both the delocalised cyclohexadienyl radical and its released cyclopentyl derivative were double integrated and compared with the values gained using the 10 mg sample. No significant difference in k_d values could be observed, therefore k_H was deemed negligible for the 1-cyclopentylcyclohexa-2,5-diene-1-carboxylic acid **17**.

Product analysis of the cyclopentyl acid 17 after photolysis

Previous research with 1-methylcyclohexa-2,5-diene-1-carboxylates demonstrated that the delocalised cyclohexadienyl radical could rearrange, *via* two routes, in order to regain its aromaticity.[13] The desirable cleavage of the alkoxycarbonyl functionality in order to yield the required alkyl radical was the major process. However, the competitive cleavage of the methyl group, to furnish a methyl radical and the associated benzoate ester, served to reduce yields significantly. Replacing the methyl group with phenyl functionality eventually solved this problem, as the competitive cleavage of the carbon-carbon bond to release the undesirable phenyl radical requires a large amount of energy and therefore does not occur.

The rearrangement of the delocalised cyclohexadienyl acids **20** could also proceed in two directions (Scheme 11). The desirable dissociation, k^1_d, releases the alkyl radical $\mathbf{R}^\bullet$ and benzoic acid as the easily removable side product. However, a competitive dissociation route also exists, k^2_d, which results in the release of a hydroxyformyl radical **22** and the formation of the alkylbenzene **21**. The success of the 1-alkylcyclohexa-2,5-diene-1-carboxylic acids as free radical precursors, and the accuracy of our calculated kinetic data, relies heavily upon the opinion that this competitive rearrangement is a very minor process, which can subsequently be deemed negligible.



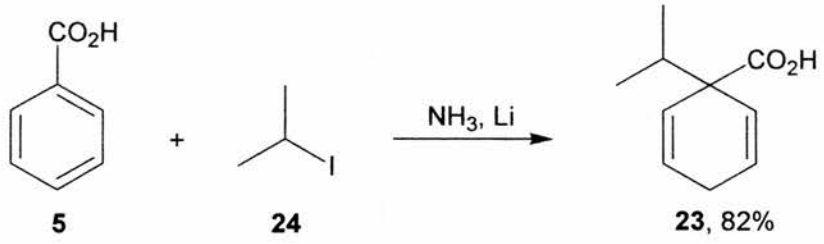
Scheme 11

In an attempt to investigate the magnitude of this competing dissociation, a known quantity of the cyclopentyl acid was placed in a quartz tube and dissolved in DTBP. This sample was heated to 300 K and photolysed for two hours using a 400 W UV lamp in order to facilitate the complete rearrangement of the cyclohexadienyl acid. The sample was analysed by NMR, in an attempt to locate any peaks derived from the cyclopentylbenzene; unfortunately, the large excess of DTBP and *t*-butanol reduced the size of the desired peaks in the spectrum and made it impossible to gain a positive identification. Removal of the excess solvents would result in the loss of the desired alkylbenzene, therefore GLC was proposed as an alternative method of identifying and measuring the concentration of alkylbenzene produced in the radical reaction.

In order to calculate the extent of the undesirable dissociation, we needed to compare the relative amounts of benzoic acid and alkylbenzene produced during the photolysis. This would provide a ratio of k^1_d:k^2_d and establish whether k^2_d can be legitimately ignored. Initial attempts to analyse the photolysed sample proved disappointing as the benzoic acid adhered to the GLC column. However, conversion of the benzoic acid into the methyl benzoate, by adding MeOH and a catalytic amount of H_2SO_4, resolved this problem and subsequent GLC analysis confirmed the presence of both the methyl benzoate and a small amount of the *c*-pentylbenzene. The retention times of these peaks were compared with authentic samples and the relative peak areas calculated to give a ratio of k^1_d:k^2_d greater than 500:1. This confirms that the degree of competitive dissociation for the cyclopentyl acid **17** is negligible.

1-Isopropylcyclohexa-2,5-diene-1-carboxylic acid 23

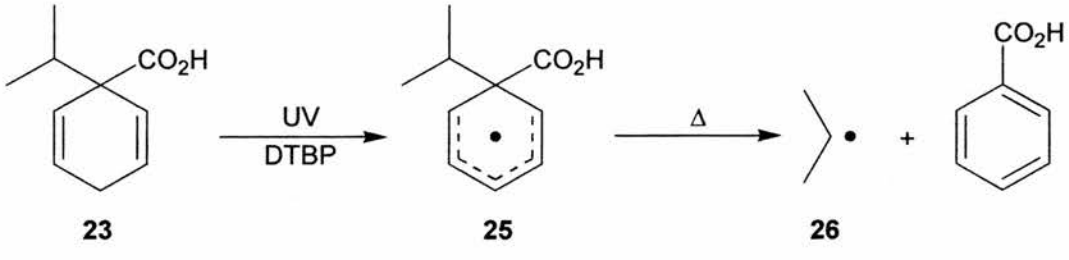
Synthesis of 1-isopropylcyclohexa-2,5-diene-1-carboxylic acid 23[11]



Scheme 12

1-Isopropylcyclohexa-2,5-diene-1-carboxylic acid **23** was prepared by Baguley using the adapted Birch reduction/alkylation procedure (Scheme 12).[10] The cyclohexadienyl acid was formed in good yield when quenching the reaction mixture with 2-iodopropane **24**. The crude product, provided by Baguley, was purified for EPR analysis by washing with both alkali and acid before a saturated solution of sodium thiosulfate was used to eliminate any iodine present. Recrystallisation from pentane gave large cubic crystals of the highly pure 1-isopropylcyclohexa-2,5-diene-1-carboxylic acid in a yield of 82%.

EPR study of 1-isopropylcyclohexa-2,5-diene-1-carboxylic acid 23



Scheme 13

The EPR samples were prepared using the previously stated general procedure. Initially, a sample was made using approximately 10 mg of the acid and 250 μl DTBP. However, the pure isopropyl acid showed limited solubility in this solvent at room temperature, and would therefore be very sparingly soluble at the lower temperatures required to gain kinetic data. A new sample was prepared using a co-solvent in

which the carboxylic acid was more soluble. The adapted sample used 200 µl *t*-BuPh as the bulk solvent, to aid solubility, and 50 µl DTBP as the radical initiator. Approximately 10 mg of the cyclohexadienyl acid was initially used in exploratory experiments to assess the generated spectra and optimise the conditions of the EPR cavity.

The degassed sample was placed in the EPR cavity before a spectrum was recorded in the absence of UV light. No signal was detected and this confirmed the absence of any unwanted background radicals. The temperature of the EPR cavity was decreased to 245 K, and the sample allowed to equilibrate to its surrounding temperature, before a second EPR spectrum was recorded using UV light to initiate the radical reaction. At this low temperature, a clear spectrum consistent with that of the delocalised acid radical was observed and its relevant *a*-values were measured (Figure 7). There were no obvious peaks from the released isopropyl radical at this temperature.

In order to encourage the fragmentation of the isopropyl radical, the EPR cavity was heated to a temperature of 300 K before repeating the experiment and recording the EPR spectrum. This altered the appearance of the observed EPR spectrum significantly, as the spectrum due to the delocalised acid radical weakened to be replaced by that of the isopropyl radical.

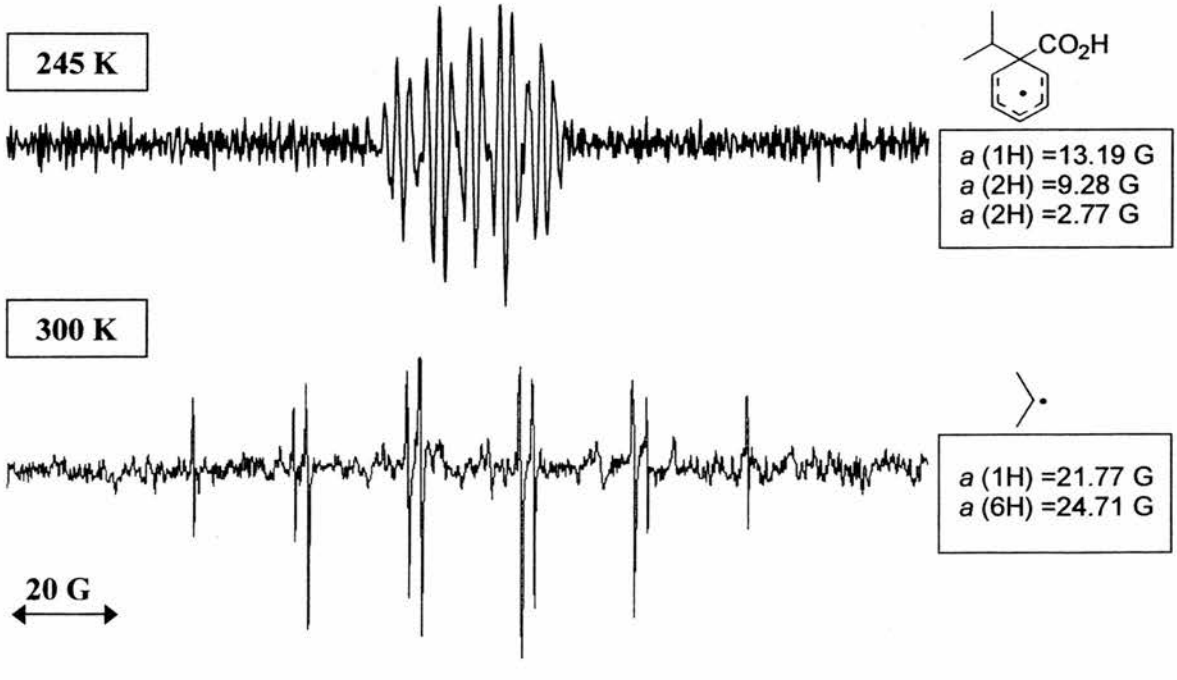


Figure 7

The EPR spectra for both the delocalised cyclohexadienyl radical and the dissociated isopropyl radical could be seen concurrently in the temperature range of 250-290 K. Therefore, in order to gain the required kinetic information, a stock solution of the isopropyl acid in *t*-BuPh and DTBP was prepared, with an accurately measured concentration, and identical samples of this solution were used to record a number of EPR spectra within the stated temperature range. Again, in order to simplify integration, only a small portion of the spectrum was analysed where peaks from both spectra could be observed without any constructive or destructive interference.

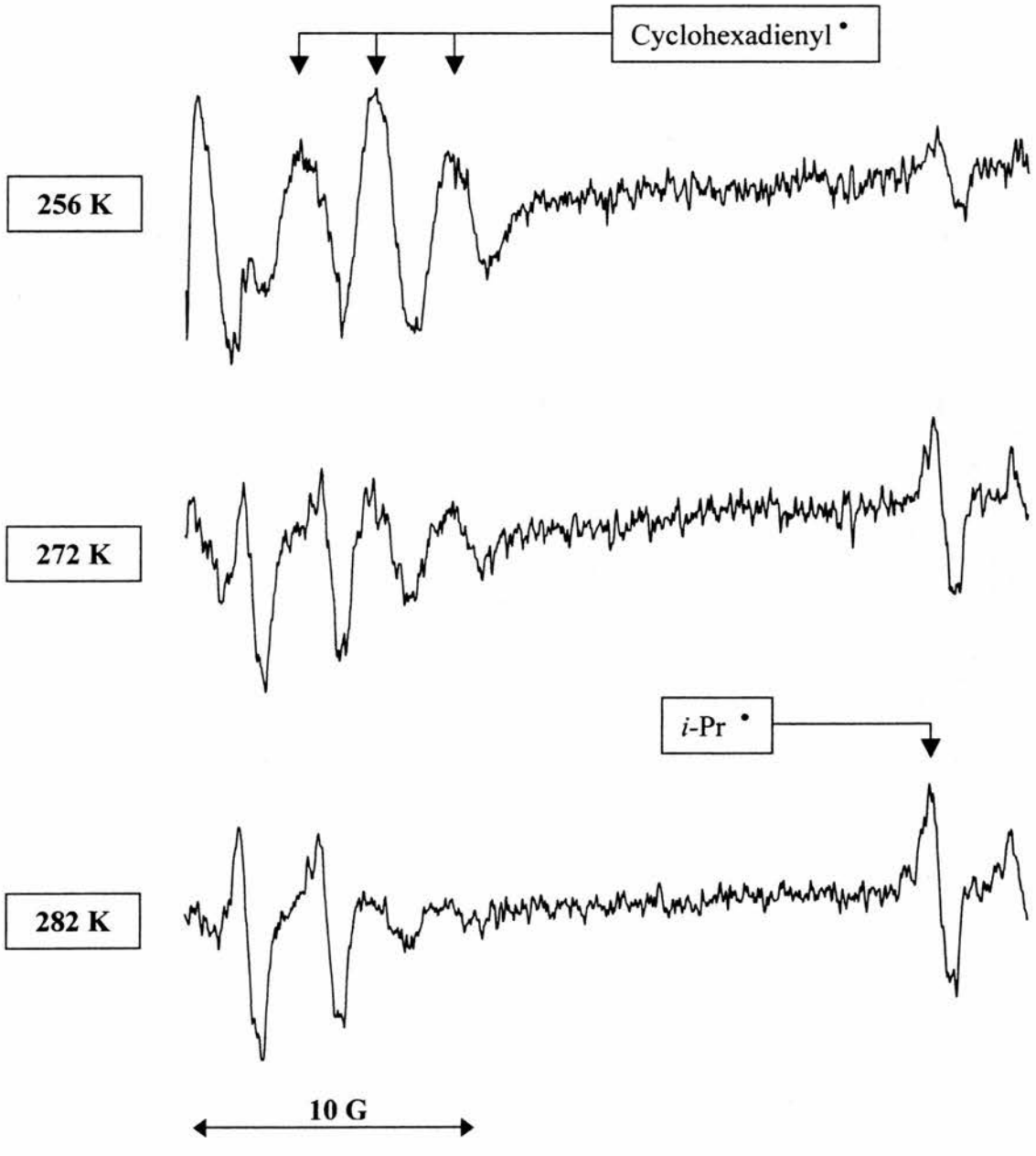


Figure 8

The acquired spectra were processed and integrated using the WinEPR software, and the retrieved data was placed into the Steady State equation in order to give values for log $k_d/2k_t$ at each temperature. The bulk solvent used in these experiments was *t*-BuPh, therefore new values for the diffusion controlled rate were found, from Fischer's work, and substituted into the equation to give corrected values of k_d for the isopropyl cyclohexadienyl acid (Table 3).

T/K	[26]	[25]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ *t*-BuPh	k_d
256	2.459E-08	2.344E-07	-7.566	3.900	9.216	4.47E+01
261	3.012E-08	1.533E-07	-7.443	3.824	9.277	6.82E+01
267	3.380E-08	1.183E-07	-7.362	3.751	9.334	9.39E+01
272	3.908E-08	9.304E-08	-7.256	3.681	9.388	1.36E+02
277	5.603E-08	7.856E-08	-7.018	3.613	9.438	2.63E+02
282	6.578E-08	4.958E-08	-6.815	3.548	9.484	4.67E+02

Table 3

The values of log k_d were plotted against $10^3/T$, as dictated by the Arrhenius equation, to give the associated values of activation energy (E_d) and pre-exponential factor (A_d) for the isopropyl acid (Figure 9, Table 4). The k_d value at 300 K is similar to that observed for the cyclopentyl radical, however, the energy of activation is slightly higher as the cyclopentyl group is slightly more bulky and therefore breaks away from the cyclohexadienyl acid more readily. Again, the relative value of log A_d is very close to 13.

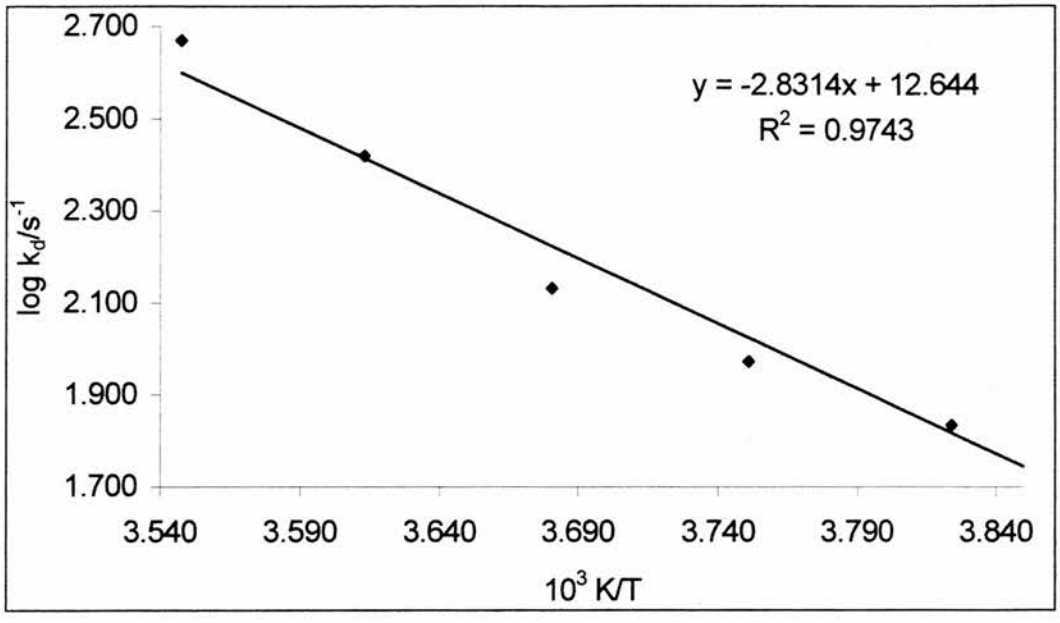


Figure 9

Released Radical	10^{-3} k_d / s^{-1} (300 K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
i-$Pr^{\bullet}$	1.56	12.64	12.96

Table 4

EPR study of 1-isopropylcyclohexa-2,5-diene-1-carboxylic acid 23 using a different sample concentration

In the original Steady State equation, $k_d/2k_t$ can be calculated if the acid concentration, transient radical concentration and rate of hydrogen abstraction (k_H) are known (Eq 8).

$$\frac{k_d}{2k_t} = \frac{k_H [R^{\bullet}] [AH]}{2k_t [UR^{\bullet}]} + [R^{\bullet}] + \frac{[R^{\bullet}]^2}{[UR^{\bullet}]} \qquad \textbf{(8)}$$

The assumption that k_H was negligible, removed this unknown from Eq 8 and allowed us to apply data derived from the EPR spectra in order to find values of k_d using the simplified Eq 9. Therefore, the accuracy of this calculated value for k_d relies upon the value of k_H being very small.

$$\frac{k_d}{2k_t} = [R^\bullet] + \frac{[R^\bullet]^2}{[UR^\bullet]} \quad \textbf{(9)}$$

It is clear from Eq 9 that the value of k_d is independent of the initial acid concentration, providing k_H is negligible. Therefore, in order to confirm that k_H could legitimately be ignored, a new set of EPR spectra were acquired using the exact EPR parameters of the previous experiment, substituting the 10 mg samples with a modified stock solution which provided ten samples, each containing only 1 mg of the isopropyl acid.

The acquired spectra were double integrated using the WinEPR software and the concentration of each transient radical calculated by direct comparison to a standard solution of DPPH. This concentration data was used in the steady state equation (Eq 9) to give new values of k_d at each temperature (Table 5).

T/K	[26]	[25]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ t-BuPh	k_d
256	1.303E-08	9.488E-08	-7.829	3.900	9.216	2.44E+01
261	1.839E-08	5.024E-08	-7.600	3.824	9.277	4.76E+01
267	1.852E-08	3.623E-08	-7.553	3.751	9.334	6.05E+01
272	2.058E-08	1.991E-08	-7.378	3.681	9.388	1.02E+02
277	1.887E-08	2.508E-08	-7.480	3.613	9.438	9.06E+01

Table 5

When the k_d values for the 10 mg and 1 mg samples are compared directly, a slight difference can be seen (Table 6). This suggests that k_H is small, but not negligible for the isopropyl acid, consequently Eq 9 cannot be applied and we must solve Eq 8 in order to gain accurate values for both k_H and k_d.

[23] mol dm^{-3}	T/K	[26]	[25]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ *t*-BuPh	k_d
0.013	256	1.303E-08	9.488E-08	-7.829	3.900	9.216	2.44E+01
0.13	256	1.060E-08	1.126E-07	-7.936	3.900	9.216	1.91E+01

[23] mol dm^{-3}	T/K	[26]	[25]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ *t*-BuPh	k_d
0.013	261	1.839E-08	5.024E-08	-7.600	3.824	9.277	4.76E+01
0.13	261	1.822E-08	8.369E-08	-7.654	3.824	9.277	4.20E+01

[23] mol dm^{-3}	T/K	[26]	[25]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ *t*-BuPh	k_d
0.013	267	1.852E-08	3.623E-08	-7.553	3.751	9.334	6.05E+01
0.13	267	2.520E-08	5.172E-08	-7.426	3.751	9.334	8.09E+01

[23] mol dm^{-3}	T/K	[26]	[25]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ *t*-BuPh	k_d
0.013	272	2.058E-08	1.991E-08	-7.378	3.681	9.388	1.02E+02
0.13	272	3.098E-08	4.380E-08	-7.277	3.681	9.388	1.29E+02

[23] mol dm^{-3}	T/K	[26]	[25]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ *t*-BuPh	k_d
0.013	277	1.887E-08	2.508E-08	-7.480	3.613	9.438	9.06E+01
0.13	277	2.920E-08	3.209E-08	-7.254	3.613	9.438	1.53E+02

Table 6

Eq 8 has two unknowns and must be solved simultaneously (Appendix 2). The values of k_H and k_d at a set temperature are independent of acid concentration, this means that the data from both sets of EPR spectra can be placed into Eq 8 in order to give two different equations which can be solved simultaneously to give accurate values of log k_H and log k_d at each temperature (Table 7).

$10^3/T$	log $2k_t$	x_1	y_1	x_2	y_2	$k_H/2k_t$	$k_d/2k_t$	log k_H	log k_d
	t-BuPh	[23] = 0.13		[23] = 0.013					
3.900	9.216	1.22E-02	1.16E-08	1.79E-03	1.48E-08	-3.08E-07	1.54E-08	–	1.40
3.824	9.277	2.83E-02	2.22E-08	4.76E-03	2.51E-08	-1.24E-07	2.57E-08	–	1.69
3.751	9.334	6.33E-02	3.75E-08	6.65E-03	2.80E-08	1.67E-07	2.69E-08	2.56	1.76
3.681	9.388	9.19E-02	5.29E-08	1.34E-02	4.19E-08	1.40E-07	4.00E-08	2.54	1.99
3.613	9.438	1.18E-01	5.58E-08	9.78E-03	3.31E-08	2.09E-07	3.10E-08	2.76	1.93

Table 7

These new values for log k_H and log k_d can be represented on an Arrhenius plot of log k_H/k_d against $10^3/T$. The two different rate constants fall on different lines, and the application of a line of best fit allows us to calculate new values for E_d, log A_d and k_d at 300 K which take hydrogen abstraction into account. Values for E_H, log A_H and k_H at 340 K can also be calculated using the Arrhenius equation. These values correlate well with those specified in the literature for H-abstraction from 1,4-cyclohexadienes.

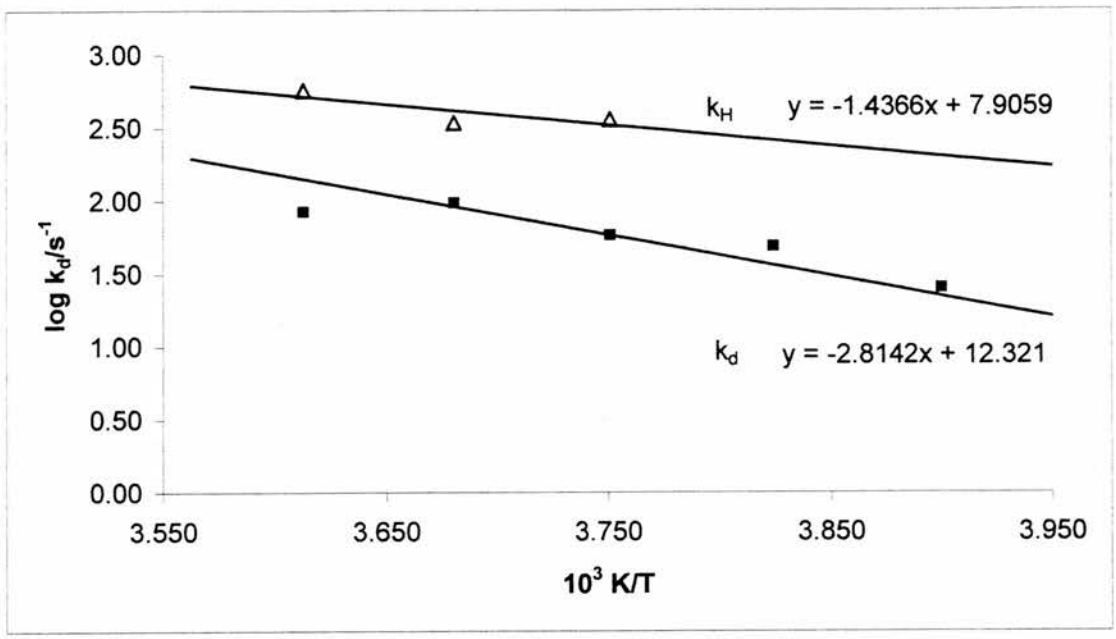


Figure 10

Released Radical	10^{-3} k_d / s^{-1} (300 K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
i-Pr$^{\bullet}$	0.842	12.32	12.88

10^{-3} k_H * (340 K)	Log A_H *	E_H / kcal mol^{-1}
4.805	7.9	6.57

Table 8, * = dm^3 mol^{-1} s^{-1}

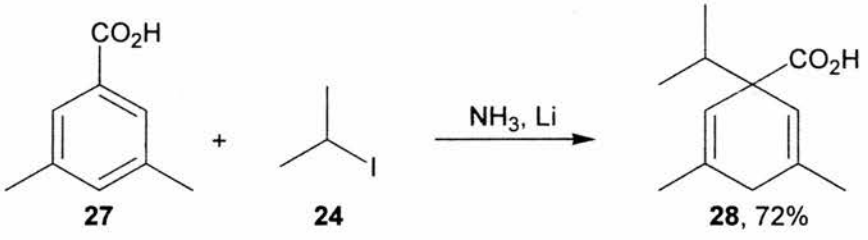
The effect of changing the concentration of the isopropyl acid **23** was very small due to the low rate of H-abstraction. Meaningful results could only be obtained for three temperatures at the lower end of the dissociation range and the error limits on these kinetic parameters are consequently high.

Product analysis of the isopropyl acid 23 after photolysis

The isopropyl acid was photolysed in the presence of DTBP at 300 K for a period of two hours, in order to ensure the complete rearrangement of the radical precursor. All benzoic acid in the resultant mixture was converted into the methyl benzoate using the previously discussed technique, before the sample was analysed by GLC. Comparison of the acquired GLC trace with that of authentic samples of methyl benzoate and isopropylbenzene, confirmed that none of the alkyl benzene was formed and therefore dissociation *via* the k^2_d pathway was insignificant.

1-Isopropyl-3,5-dimethylcyclohexa-2,5-diene-1-carboxylic acid 28

Synthesis of 1-isopropyl-3,5-dimethylcyclohexa-2,5-diene-1-carboxylic acid 28



Scheme 14

In an attempt to encourage the rearrangement of the delocalised cyclohexadienyl radical, and increase the value of k_d for the production of secondary radicals, it was proposed that analogous compounds could be made which possessed a bulky group *meta-* to the released alkyl chain. This should increase steric hindrance in the radical precursor and therefore weaken the carbon-carbon bond attaching the isopropyl group to the cyclohexadienyl framework.

The presence of a large alkyl functionality on the cyclohexadienyl ring, for example a *t*-butyl group, would affect the Birch reduction/alkylation and give poor yields as the alkyl halide would have inhibited access to the anionic intermediate. Therefore the methyl analogue was prepared using 3,5-dimethyl benzoic acid **27** as the starting material and reacting this with 2-iodopropane **24** under the Birch reduction/alkylation conditions specified in the general procedure (Scheme 14). The cyclohexadienyl acid **28** was isolated using a standard aqueous workup and washed with a saturated solution of sodium thiosulfate to remove any iodine before recrystallisation from pentane gave the title compound in a 72% yield.

EPR study of 1-isopropyl-3,5-dimethylcyclohexa-2,5-diene-1-carboxylic acid 28

An EPR sample was prepared in a similar fashion to that described for the unsubstituted isopropyl acid. The degassed sample was used in exploratory EPR experiments to confirm the acid's ability to generate the delocalised cyclohexadienyl radical and release the desired isopropyl radical. At 240 K, the spectrum assigned to the delocalised radical was observed with no significant peaks derived from the

released isopropyl radical. However, as the temperature of the EPR cavity was increased, the spectrum attributable to the delocalised radical weakened to be replaced by the spectrum of an isopropyl radical, as anticipated, at about 290 K.

In order to gain kinetic data for this substituted isopropyl acid, the set of EPR experiments were repeated using a stock solution, with a known concentration, of the dimethyl isopropyl acid. EPR spectra were recorded within the range of 251-282K, and processed in the now routine manner using the computer software described in the general procedure (Figure 11).

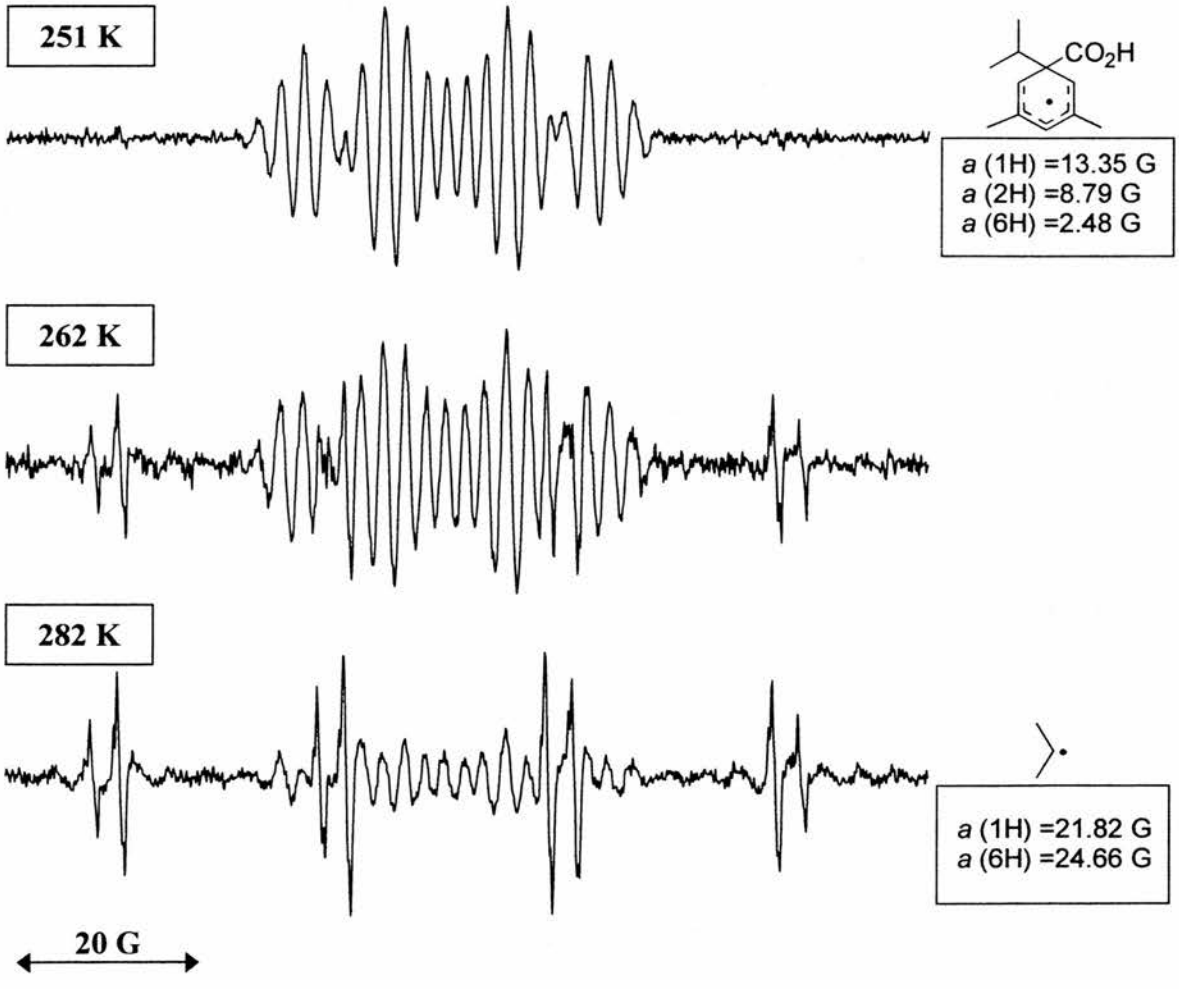


Figure 11

The double integral data was substituted into the Steady State equation to give the required values of log $k_d/2k_t$ at each temperature, and these values were adjusted for

solvent viscosity to give corrected values of k_d for 1-isopropyl-3,5-dimethylcyclohexa-2,5- diene-1-carboxylic acid **28** (Table 9).

T/K	[*i*-Pro˙]	[Acid˙]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ *t*-BuPh	k_d
292	1.136E-08	7.284E-09	-7.536	3.424	9.569	107.718
287	1.108E-08	8.043E-09	-7.580	3.485	9.528	88.785
282	9.139E-09	1.232E-08	-7.798	3.548	9.484	48.548
277	7.906E-09	1.381E-08	-7.905	3.613	9.438	34.057
272	6.647E-09	2.026E-08	-8.054	3.681	9.388	21.559
267	5.098E-09	1.659E-08	-8.176	3.751	9.334	14.394
261	3.975E-09	2.279E-08	-8.331	3.824	9.277	8.841
256	2.203E-09	4.057E-08	-8.634	3.900	9.216	3.820
251	1.851E-09	4.973E-08	-8.717	3.979	9.150	2.714

Table 9

An Arrhenius plot of log k_d against $10^3/T$ was drawn, using the information in Table 9, and a line of best fit applied (Figure 12). The equation of this line was used to generate accurate values of E_d and log A_d for this substituted acid (Table 10).

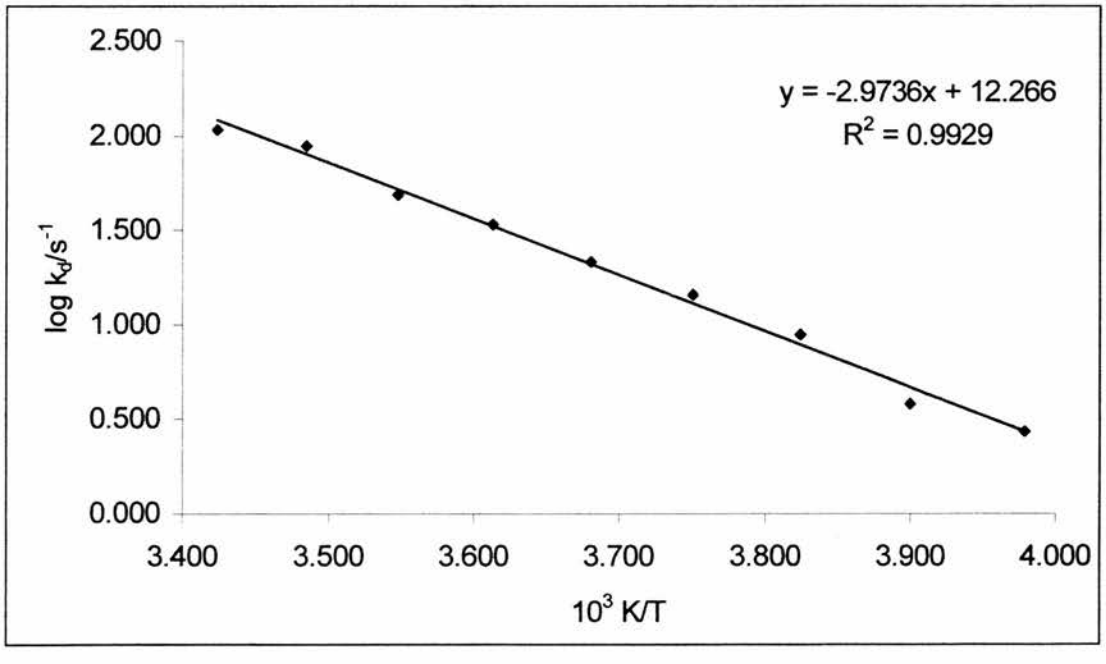


Figure 12

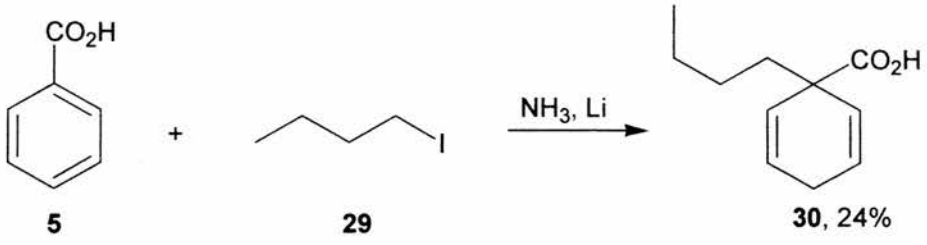
Released Radical	10^{-3} k_d / s^{-1} (300 K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
i-Pr$^{\bullet}$	1.19	12.27	13.61

Table 10

It can be seen that the value of k_d at 300 K is lower than that for the unhindered acid and this is confirmed by the relatively higher energy of activation. This indicates that the addition of methyl groups at the -3 and -5 positions of the cyclohexadienyl ring has no beneficial effect on the overall rate of dissociation for the delocalised cyclohexadienyl radical.

1-*n*-Butylcyclohexa-2,5-diene-1-carboxylic acid 30

Synthesis of 1-*n*-butylcyclohexa-2,5-diene-1-carboxylic acid 30



5 **29** **30**, 24%

Scheme 15

1-*n*-Butylcyclohexa-2,5-diene-1-carboxylic acid **30** was prepared using the general procedure described at the beginning of this section (Scheme 15). Benzoic acid **5** was reacted with freshly distilled 1-iodobutane **29** under Birch conditions to give the impure cyclohexadienyl acid. The product was washed with large amounts of saturated thiosulfate solution to remove all traces of iodine, before it was successfully purified by column chromatography [SiO_2, light petroleum-EtOAc (4:1)] to give the carboxylic acid in a yield of 24% as oily, colourless crystals. Attempts to recrystallise the cyclohexadienyl acid, using a range of solvents, were unsuccessful as the acid failed to crystallise out of solution.

EPR study of 1-*n*-butylcyclohexa-2,5-diene-1-carboxylic acid 30

An EPR sample was prepared in the conventional manner, by dissolving acid **30** in DTBP which acted as both the solvent and photolytic initiator. The sample was degassed using N_2 and employed in a range of exploratory EPR experiments to assess the acids ability to generate the delocalised cyclohexadienyl radical and release the desired *n*-butyl radical. At lower temperatures it was possible to see the spectrum assigned to the delocalised radical (Figure 13). However, as the temperature of the EPR cavity was increased, there was no apparent change in the spectrum, only an increase in noise and an apparent weakening of the delocalised radical spectrum which could be attributed to a Boltzmann effect. The anticipated spectrum of the *n*-butyl radical was not observed using this EPR sample at any of the temperatures in our accessible range.

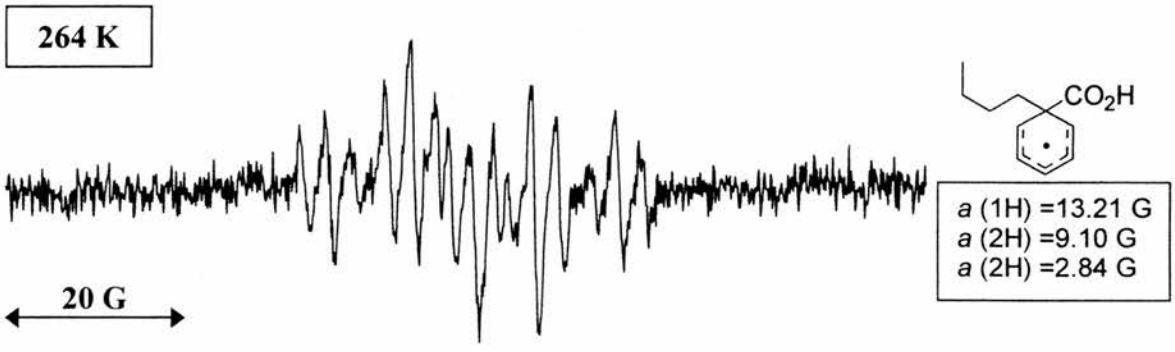


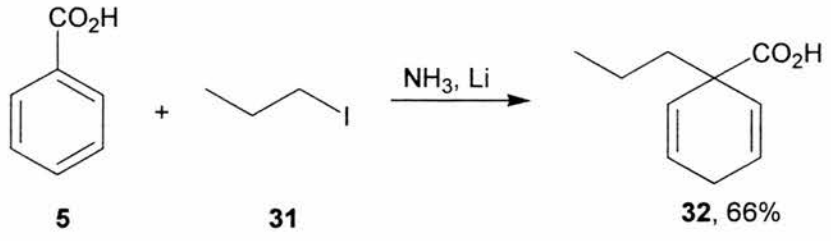
Figure 13

It was thought that the release of a primary radical from a cyclohexadienyl acid must occur at significantly higher temperatures than the 360 K allowed using DTBP as a solvent. Therefore a separate sample was made using 200 μl of hexadecane as the bulk solvent in conjunction with 50 μl of DTBP as the initiator. This allowed us to increase the temperature of the EPR cavity in an attempt to find a spectrum attributable to the n-butyl radical. However, after increasing the cavity temperature to over 390 K there was no evidence for the desired spectrum.

EPR is a particularly sensitive technique with regard to purity. It is thought that a small number of impurities within the *n*-butylcyclohexa-2,5-diene-1-carboxylic acid were weakening the spectrum of the released *n*-butyl radical and making it difficult to observe amongst the background noise. All attempts to purify the sample by distillation, chromatography and recrystallisation have failed to produce the high purity sample required to observe these transient radicals in our EPR system.

1-*n*-Propylcyclohexa-2,5-diene-1-carboxylic acid 32

Synthesis of 1-*n*-propylcyclohexa-2,5-diene-1-carboxylic acid 32[14, 15]



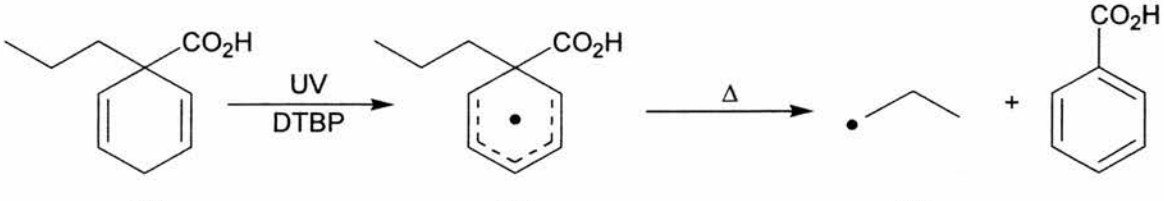
5 **31** **32**, 66%

Scheme 16

The synthesis of an *n*-propyl derivative was proposed in order to further assess the properties of the cyclohexadienyl acids and their ability to dissociate, leading to the production of primary radicals. Recent success in the formation and purification of the *iso*-propyl analogue suggested that the *n*-propyl cyclohexadienyl acid might recrystallise with greater ease, therefore providing stronger EPR spectra at the higher temperatures required to instigate bond dissociation.

The addition of 1-iodopropane **31** to benzoic acid **5** under the standard Birch conditions gave a high yield of brown oil, identified by NMR spectroscopy as primarily the *n*-propyl cyclohexadienyl acid (Scheme 16). The subsequent washing of this impure compound, with saturated sodium thiosulfate solution, removed most of the brown colouration of iodine to leave a pink oil, which was distilled on a Kugelrohr to afford the pure *n*-propylcyclohexa-2,5-diene-1-carboxylic acid **32** as a white powder in a yield of 66%.

EPR study of 1-*n*-propylcyclohexa-2,5-diene-1-carboxylic acid 32



32 **33** **34**

Scheme 17

The EPR samples were prepared as stated in the general procedure, using DTBP as both the solvent and radical initiator. A sample containing approximately 10 mg of the *n*-propyl cyclohexadienyl acid **32** was initially used in exploratory experiments in order to confirm the ability of this acid to furnish the primary n-propyl radical **34**, and to optimise the EPR settings to give a clear and strong spectrum. The degassed sample was placed in the EPR cavity before an initial spectrum was recorded in the absence of UV light, to confirm the absence of any background radicals. The cavity was then cooled to 270 K, and the sample allowed to equilibrate to this temperature, before the UV light was activated and the first spectrum of the delocalised cyclohexadienyl radical **33** was observed.

The recorded spectra had similar parameters to previous examples of the cyclohexadienyl radical. There were no observed peaks that could be associated with the released primary radical at this low temperature, therefore the temperature was increased to 320 K, in order to encourage the radical rearrangement and deliver the *n*-propyl radical spectrum. However, even at this higher temperature there appeared little evidence of the desired radical species. A higher EPR cavity temperature was necessary and this required the use of hot air to heat the cavity, rather than liquid nitrogen which was used to cool the system down.

Compressed air was passed over the EPR heating element and the thermostat set at 370 K. This was the upper limit when using DTBP as the solvent, as it boils above this temperature. After allowing a small time period for the sample to warm up and equilibrate to this higher temperature, the UV light was activated and a spectrum recorded. This spectrum appeared with a greater amount of noise than those obtained at lower temperatures, however, additional peaks, associated with the *n*-propyl radical **34**, could clearly be observed.

Attempts to improve the signal to noise ratio using the same sample proved futile, as the higher temperature gave the samples a very short lifetime when under UV light. The repeated spectrum exhibited only vague and broad signals as all of the initial cyclohexadienyl acid had rearranged into benzoic acid and the products derived from *n*-propyl radical addition. This highlighted the importance of making a stock solution of the *n*-propyl acid, as a new sample would be required for each EPR experiment.

A series of preliminary EPR experiments were carried out in an attempt to optimise the conditions of the spectrometer, so that a strong EPR spectrum could be obtained with minimal background noise. A temperature range of 330 – 380 K allowed us to observe all the stages of rearrangement, from the initial appearance of the *n*-propyl radical **34** through to the complete conversion of the cyclohexadienyl radical **33** into the relatively more unstable primary radical (Figure 14).

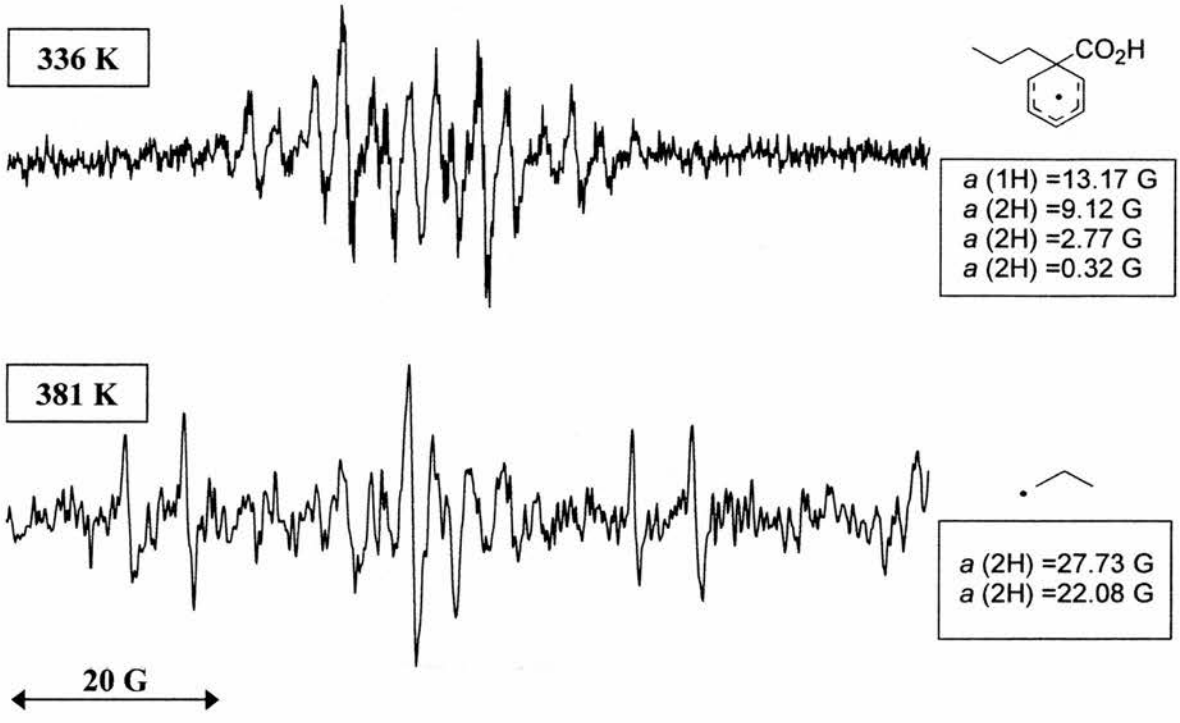


Figure 14

The short lifetime of the samples meant that a relatively fast conversion time was necessary to prevent sample decay within the time period of the EPR experiment. However, as the conversion time of the experiment was decreased, the signal to noise ratio in the resultant spectra increased. In order to combat this, it was possible to focus on a small, 20 G, section of the produced EPR spectrum, where peaks applicable to both the *n*-propyl and cyclohexadienyl radical could be observed. To gain kinetic data, these individual peaks must not interfere constructively or destructively with each other, as that would provide inaccurate peak areas when integrating the signals. Recording the spectrum over a smaller range of 20 G enabled us to significantly reduce conversion time, with little effect on the background noise in our experiments.

A stock solution of the *n*-propyl cyclohexadienyl acid in DTBP was prepared, which supplied several equal samples containing an accurately measured acid concentration (4 mg per 200 μl sample). The EPR samples were degassed using N_2 prior to insertion into the EPR cavity. The temperature of the cavity was raised to approximately 345 K, and the sample allowed to equilibrate at this temperature, before the UV light was activated and an initial EPR spectrum recorded, using a sweep width of 100 G. Signals due to both the cyclohexadienyl radical and the released *n*-propyl radical were observed clearly at this temperature, which allowed us to choose a 20 G area where both of the transient radicals could be observed.

The EPR parameters were modified using the information gained in the previous experiment, reducing the sweep width to 20 G, and therefore allowing the conversion time to be reduced significantly. A fresh EPR sample was prepared from the stock solution and the cavity temperature reduced to 335 K before a new EPR experiment was run, providing well defined peaks for both the delocalised cyclohexadienyl radical **33** and the rearranged *n*-propyl radical **34**.

A range of spectra were recorded using these new parameters. The temperature within the EPR cavity was gradually increased at 5 K intervals, and a fresh EPR sample was employed for each experiment (Figure 15). The peaks derived from the cyclohexadienyl radical weakened as the temperature increased, to be replaced by the peaks associated with the n-propyl radical. The observed peaks were double integrated using the available WinEPR software and these double integrals converted into concentration data using the calculation previously discussed.

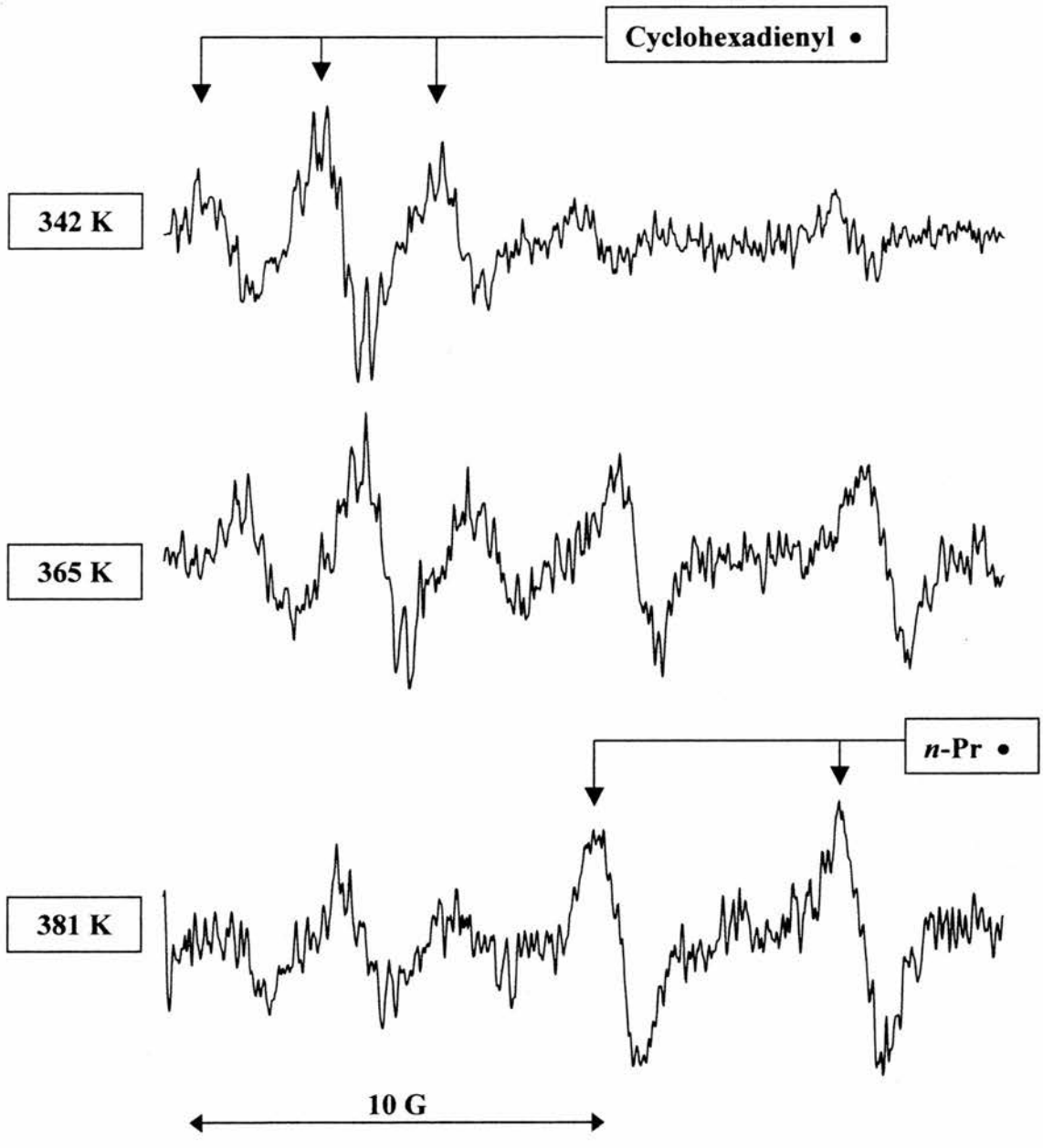


Figure 15

The calculated transient radical concentrations were placed into the previously derived Steady State equation to give a value for log $k_d/2k_t$ at each recorded temperature. The values for $2k_t$ were found using Fischer's paper,[4] which allowed us to calculate values of log k_d for the *n*-propylcyclohexadienyl-1-carboxylic acid at each temperature, which have been corrected for solvent viscosity (Table 11).

T/K	[34]	[33]	log $k_d/2k_t$	$10^3/T$	log $2k_t$	k_d
336	6.407E-08	1.086E-06	-7.168	2.974	9.877	5.12E+02
342	7.931E-08	9.472E-07	-7.066	2.925	9.904	6.89E+02
348	1.440E-07	8.792E-07	-6.776	2.877	9.930	1.43E+03
353	2.019E-07	9.500E-07	-6.611	2.831	9.955	2.21E+03
359	2.507E-07	7.599E-07	-6.477	2.786	9.979	3.18E+03
365	3.246E-07	7.237E-07	-6.328	2.743	10.003	4.73E+03
370	3.752E-07	5.050E-07	-6.184	2.701	10.026	6.94E+03
376	5.944E-07	7.674E-07	-5.977	2.661	10.048	1.18E+04
381	4.461E-07	4.190E-07	-6.036	2.621	10.069	1.08E+04

Table 11

The variation in the values of log k_d, with respect to temperature, can be represented using an Arrhenius plot (Figure 16). The equation for the line of best fit can subsequently be used to calculate the associated values of activation energy and the pre-exponential factor for 1-*n*-propylcyclohexa-2,5-diene-1-carboxylic acid **32** (Table 12).

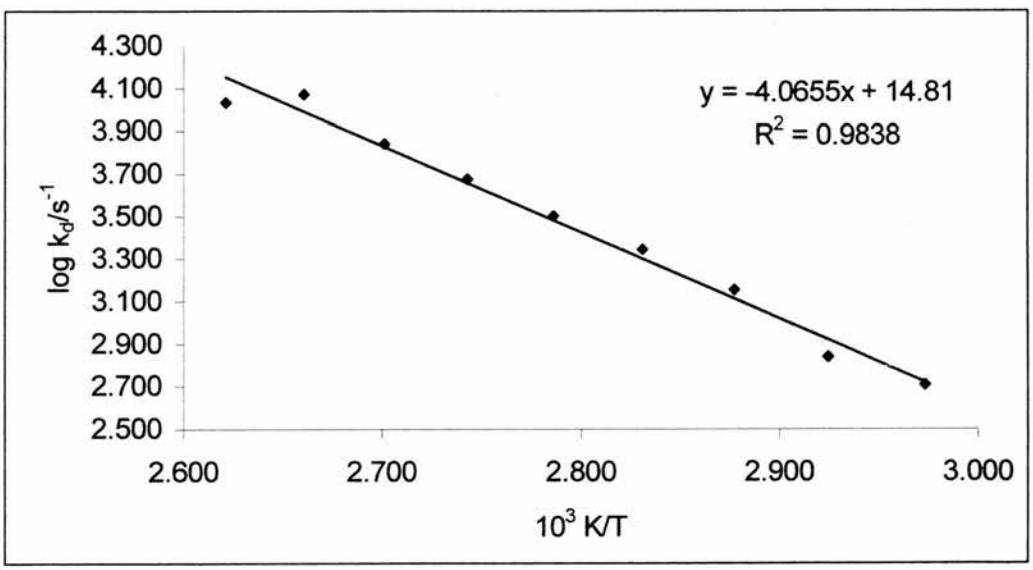


Figure 16

Released Radical	10^{-3} k_d / s^{-1} (300 K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
n-Pr$^\bullet$	0.017	14.81	18.60

Table 12

The low value of k_d, accompanied by the high value of E_d, makes it clear to see that the liberation of a primary radical through rearrangement is significantly less favourable than the release of a more stabilised and bulky secondary radical. This was expected for the 1-alkylcyclohexa-2,5-diene-1-carboxylic acids and confirmed that this novel procedure for gaining kinetic information was legitimate.

EPR study using a lower sample concentration

The slower rate of dissociation, revealed in the previous experiment, suggested that hydrogen abstraction might well have a greater opportunity to take place within our detectable range for this primary radical precursor. As previously stated, if H-abstraction is significant enough to be detected, the value of k_d will alter in response to a change in sample concentration. Therefore attempts were made to prepare a sample containing 30 mg of the acid in 200 μl of DTBP. Unfortunately, there were problems with dissolving this large amount of solid in such a small volume of liquid. Therefore, a new EPR sample was prepared using 0.3 mg of the *n*-propyl acid in 200 μl of DTBP. This amount of acid was taken up completely by the DTBP to give greater than a ten-fold decrease in acid concentration over the previous 4 mg sample, which would highlight any dependence of the peak areas on sample concentration.

The sample was degassed in the usual manner and placed in the EPR resonator, which was maintained at 355 K, before the spectrum was recorded using the 20 G sweep width determined in the previous set of experiments. It was critical to keep all of the experimental parameters identical to those used previously with the 4 mg sample, in order to maintain parity. The resultant spectrum made it clear that there was indeed a difference between the relative peak sizes and k_d values for the *n*-propyl acid.

This revelation indicated that the rate of hydrogen abstraction was a significant factor, and it proved possible to measure this value of k_H by comparing the spectra for a range of acid concentrations at a set temperature. In order to gather this data, the EPR study described above was repeated using a different stock solution, which supplied ten equal samples containing approximately 0.3 mg of the cyclohexadienyl acid.

The EPR experiments were prepared in the usual manner and the spectra recorded at temperatures matching those determined previously with the 4 mg sample. A fresh sample was used at each temperature and the experimental parameters were preserved to maintain uniformity (Figure 17). The recorded spectra were analysed and integrated, using the WinEPR software, to give a new range of values for the peak areas, which were translated into concentration data and used to derive an additional set of data for k_d (Table 13).

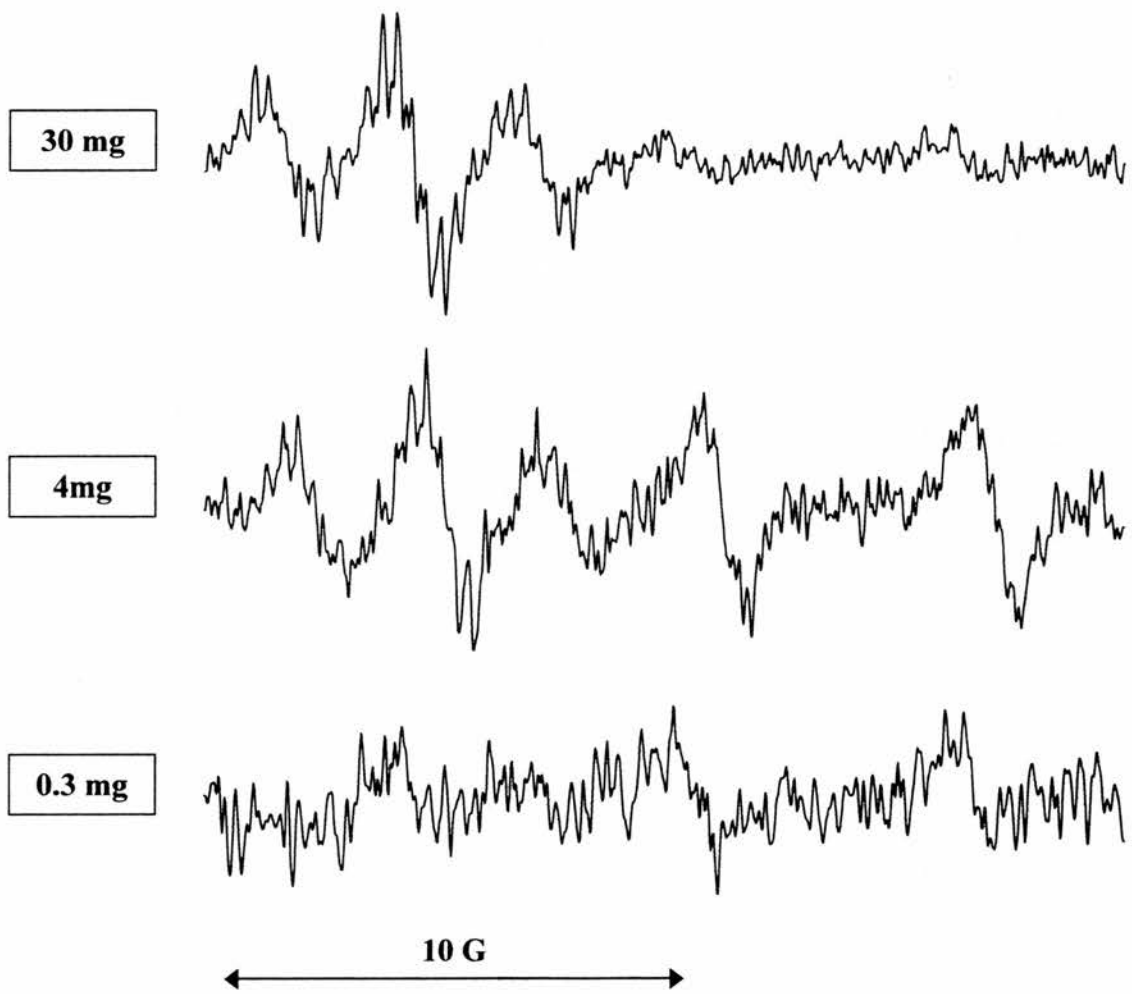


Figure 17

All spectra recorded at 355 K

T/K	[34]	[33]	log $k_d/2k_t$	$10^3/T$	log $2k_t$	k_d
336	6.221E-08	2.767E-07	-7.118	2.974	9.877	5.74E+02
348	7.198E-08	2.188E-07	-7.019	2.877	9.930	8.14E+02
353	9.851E-08	1.229E-07	-6.751	2.831	9.955	1.60E+03
359	1.086E-07	1.776E-07	-6.757	2.786	9.979	1.67E+03
365	1.097E-07	9.663E-08	-6.630	2.743	10.003	2.36E+03

Table 13

The two values of k_d at each temperature were compared directly to confirm that there was an appreciable difference in the rate of dissociation throughout the temperature range (Table 14). As a result, the data on transient radical concentration was used once again to solve the more complex Steady State equation (eq 8) in the manner described for the *iso*-propyl analogue, to give new values for log k_H and log k_d (Table 15).

[32] mol dm^{-3}	T/K	[34]	[33]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ DTBP	k_d
0.009	336	6.221E-08	2.767E-07	-7.118	2.974	9.877	5.74E+02
0.109	336	6.407E-08	1.086E-06	-7.168	2.974	9.877	5.12E+02

[32] mol dm^{-3}	T/K	[34]	[33]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ DTBP	k_d
0.009	348	7.198E-08	2.188E-07	-7.019	2.877	9.930	8.14E+02
0.109	348	1.440E-07	8.792E-07	-6.776	2.877	9.930	1.43E+03

[32] mol dm^{-3}	T/K	[34]	[33]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ DTBP	k_d
0.009	353	9.851E-08	1.229E-07	-6.751	2.831	9.955	1.60E+03
0.109	353	2.019E-07	9.500E-07	-6.611	2.831	9.955	2.21E+03

[32] mol dm^{-3}	T/K	[34]	[33]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ DTBP	k_d
0.009	359	1.086E-07	1.776E-07	-6.757	2.786	9.979	1.67E+03
0.109	359	2.507E-07	7.599E-07	-6.477	2.786	9.979	3.18E+03

[32] mol dm^{-3}	T/K	[34·]	[33·]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ DTBP	k_d
0.009	365	1.097E-07	9.663E-08	-6.630	2.743	10.003	2.36E+03
0.109	365	3.246E-07	7.237E-07	-6.328	2.743	10.003	4.73E+03

Table 14

$10^3/T$	log $2k_t$	x^1	y^1	x^2	y^2	$k_H/2k_t$	$k_d/2k_t$	log k_H	log k_d
	DTBP	[32] = 0.109		[32] = 0.009					
2.974	9.877	5.90E-03	6.79E-08	2.02E-03	7.62E-08	-2.15E-06	8.06E-08	--	2.78
2.877	9.930	1.64E-02	1.68E-07	2.96E-03	9.57E-08	5.36E-06	7.98E-08	4.66	2.83
2.831	9.955	2.13E-02	2.45E-07	7.21E-03	1.77E-07	4.80E-06	1.43E-07	4.64	3.11
2.786	9.979	3.30E-02	3.33E-07	5.50E-03	1.75E-07	5.77E-06	1.43E-07	4.74	3.14
2.743	10.003	4.49E-02	4.70E-07	1.02E-02	2.34E-07	6.81E-06	1.65E-07	4.84	3.22

Table 15

The new data for log k_H and log k_d was plotted against $10^3/T$ to give a new Arrhenius plot for the *n*-propyl cyclohexadienyl acid (Figure 18). The equations of the lines of best fit were used, in conjunction with the Arrhenius equation, to calculate corrected values for the associated activation energies (E_d and E_H) and their pre-exponential factors, which took into account the H-abstraction (Table 16).

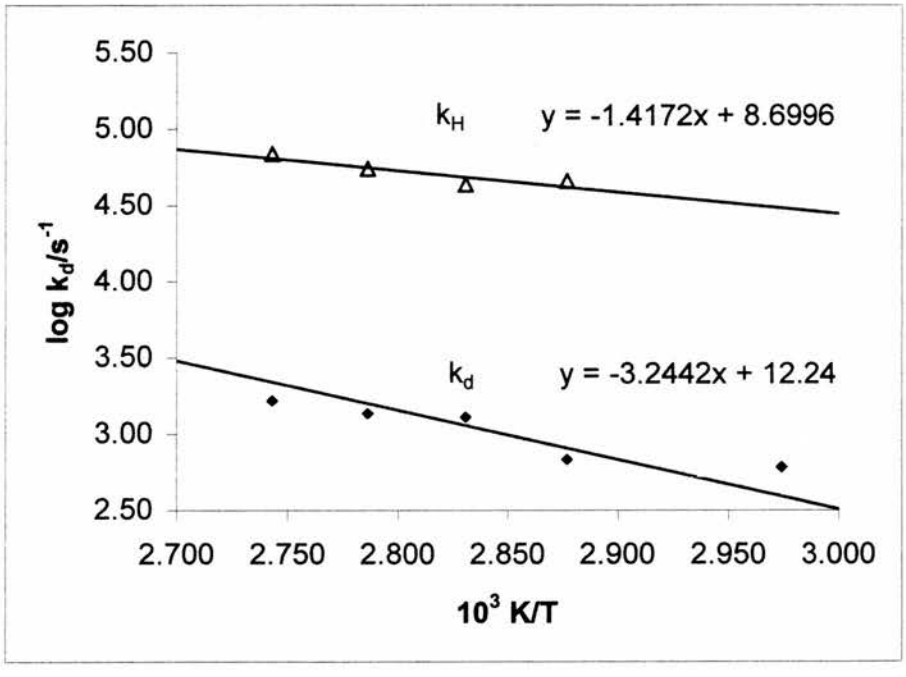


Figure 18

Released Radical	10^{-3} k_d / s^{-1} (300 K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
n-$Pr^{\bullet}$	0.15	12.24	13.05

10^{-5} k_H * (340 K)	Log A_H *	E_H / kcal mol^{-1}
0.34	8.7	6.49

Table 16, * = dm^3 mol^{-1} s^{-1}

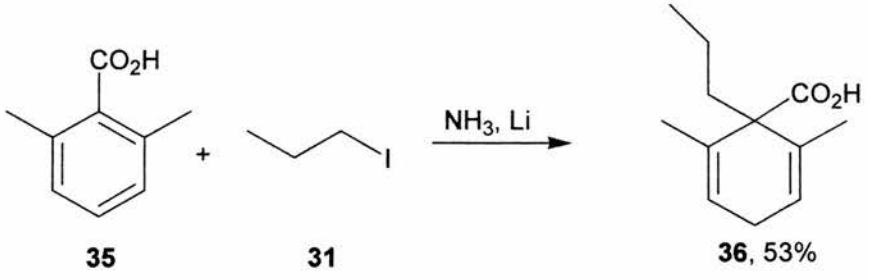
The new values for k_d and E_d are slightly different to the previous set of data where H-abstraction was ignored. The corrected value of k_d remains significantly lower than that found for the *i*-Pr radical, confirming that the rate of dissociation is dramatically reduced when releasing a primary radical, this has the direct effect of increasing the energy of activation. The rate of hydrogen abstraction for the *n*-propyl radical is a lot larger than that calculated for the isopropyl radical. This was expected as the secondary radical is relatively more stable than the primary radical due to steric factors and hyperconjugation. The energy for hydrogen abstraction remains similar for both the primary and secondary radical.

Product analysis of the *n*-propyl acid 32 after photolysis

The *n*-propyl acid was photolysed in the presence of DTBP at 300 K for a period of two hours, in order to ensure the complete rearrangement of the radical precursor. All benzoic acid in the resultant mixture was converted into the methyl benzoate using the previously discussed technique, before the sample was analysed by GLC. Comparison of the acquired GLC trace with that of authentic samples of methyl benzoate and *n*-propylbenzene, confirmed the presence of a small amount of the alkyl benzene. Calculations on the ratio between benzoic acid and the alkyl benzene confirmed that benzoic acid was the major product in a ratio of 22 : 1. Therefore diversion of the dissociation down the k^2_d pathway can be neglected.

1-*n*-Propyl-2,6-dimethyl-cyclohexa-2,5-diene-1-carboxylic acid 36

Synthesis of 1-*n*-propyl-2,6-dimethyl-cyclohexa-2,5-diene-1-carboxylic acid 36



35 **31** **36**, 53%

Scheme 18

The *n*-propyl cyclohexadienyl acid has demonstrated its ability to furnish the primary *n*-propyl radical under the applied photolytic conditions. The relatively higher activation energy required to release this radical, reduces the rate of dissociation significantly and results in low product yields when this radical precursor is used in basic addition reactions. The low yields can be attributed to the break down of the radical chain mechanism, provoked by the low rate of dissociation. This restraint can be overcome, to a certain extent, by using larger amounts of radical initiator within the reaction system. However, this can often prove expensive when used in large-scale operations.

The introduction of two methyl groups onto the basic ring structure, to increase the value of k_d, was a theory investigated previously with the 1-*iso*-propyl-3,5-dimethyl-cyclohexa-2,5-diene-1-carboxylic acid **28**. The incorporation of an obstructing side group was proposed to increase steric hindrance and therefore encourage bond dissociation. Unfortunately, there was no observed increase in reaction rate with the *iso*-propyl analogue.

A potential improvement on this model involved the relocation of the methyl functionality to the 2- and 6- positions of the cyclohexadienyl ring. This would place a methyl group adjacent to the point of bond dissociation, therefore providing a larger steric interaction between the alkyl side chain and the methyl groups, which could conceivably have a more direct effect on the rate of dissociation.

The 1-*n*-propyl-2,6-dimethyl-cyclohexa-2,5-diene-1-carboxylic acid **36** was prepared by the addition of 1-iodopropane **31** to 2,6-dimethyl benzoic acid **35** under the standard Birch conditions described in the general procedure (Scheme 18). The desired product was isolated, in a moderate yield, as a pale yellow solid before it was washed with a saturated solution of sodium thiosulfate and recrystallised from pentane to give the pure *n*-propyl dimethyl acid as white crystals, in a yield of 53%.

EPR study of 1-*n*-propyl-2,6-dimethyl-cyclohexa-2,5-diene-1-carboxylic acid 36

The purified *n*-propyl analogue was prepared for EPR analysis as stated in the general procedure, using DTBP as both the solvent and radical initiator. Previous EPR experiments with the *n*-propyl acids required a high temperature to encourage rearrangement from the cyclohexadienyl radical into the primary *n*-propyl radical. Therefore the EPR cavity was heated using warm air to help attain these high temperatures.

The sample was degassed thoroughly before its EPR spectrum was acquired at a temperature of 260 K, in the presence of UV. The observed spectrum held many similarities to those of previous delocalised cyclohexadienyl radicals, however, closer analysis revealed additional hfs from the methyl groups in the 2- and 6- positions (Figure 19). The identity of the spectra was confirmed as that belonging to the substituted cyclohexadienyl radical *via* EPR simulation.

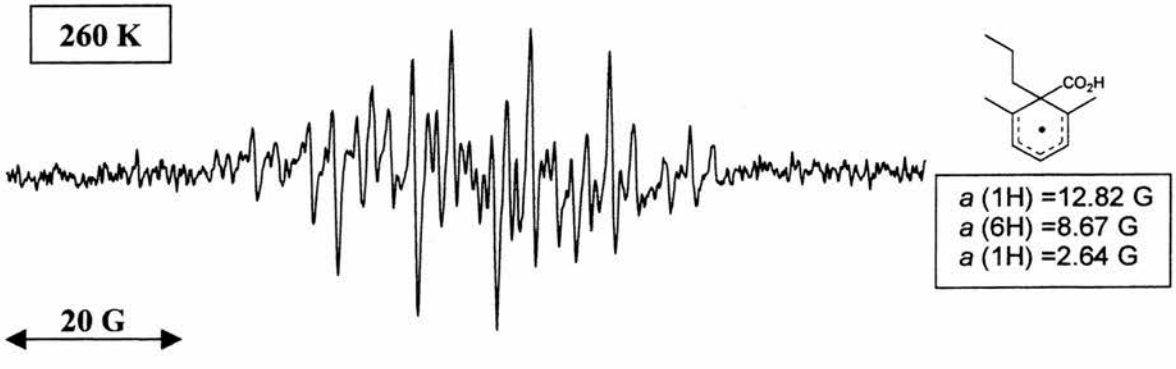
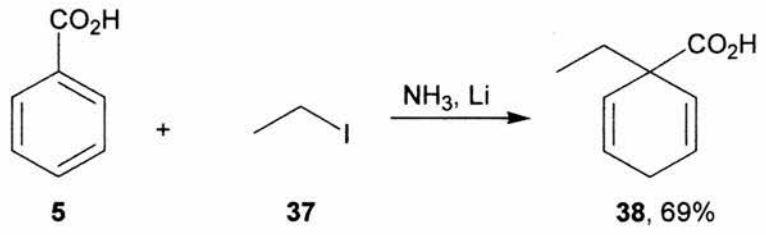


Figure 19

The temperature of the EPR cavity was raised in an attempt to encourage bond dissociation. Surprisingly, only the 2,6-dimethylcyclohexadienyl radical could be observed over the accessible temperature range ($T \leq 370$ K), suggesting that dissociation required higher temperatures, outside of our machine capabilities. It follows that the k_d for this acid radical is significantly lower than that of the unsubstituted *n*-propyl acid **32**. It was concluded that the desired steric assistance to dissociation was minor, and outweighed by the additional stabilisation of the cyclohexadienyl radical due to methyl stabilisation. This latter effect would be expected to increase the activation energy of the dissociation step, as observed.

1-Ethylcyclohexa-2,5-diene-1-carboxylic acid 38

Synthesis of 1-ethylcyclohexa-2,5-diene-1-carboxylic acid 38[12, 15]



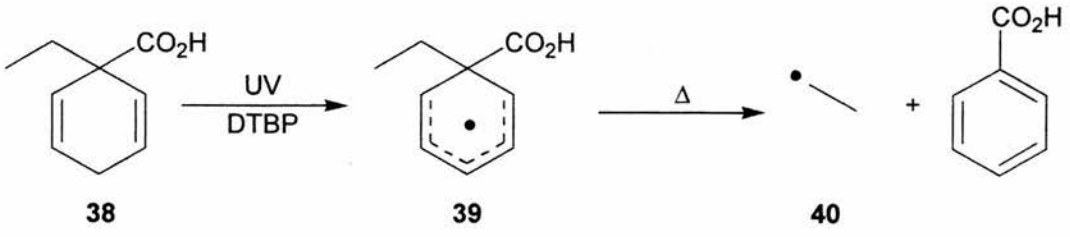
5 **37** **38**, 69%

Scheme 19

The recent success associated with the isolation and kinetic study of the *n*-propyl acid, fuelled our interest in the release of primary radicals from the cyclohexadienyl skeleton. The potential for measuring values of both k_d and k_H using the novel EPR procedure was of great interest and highlighted the need for more exploration in this area.

The synthesis of 1-ethylcyclohexa-2,5-diene-1-carboxylic acid **38** followed the general Birch procedure described at the opening of this chapter (Scheme 19). The dropwise addition of iodoethane **37** to the Birch mixture of benzoic acid **5** and lithium, in ammonia, proved to be too volatile. Therefore the haloalkane was diluted using an equal volume of diethyl ether, to prevent excessive bumping within the reaction vessel. Subsequent addition proved to be trouble-free and yielded a yellow oil, which was identified as the desired ethyl acid **38** by NMR. The oil was taken up into diethyl ether and washed using a saturated thiosulfate solution to remove any excess iodine, before finally being concentrated at the Buchi and distilled using a Kügelrohr apparatus. The 1-ethylcyclohexa-2,5-diene-1-carboxylic acid was isolated as a pale yellow oil in a yield of 69%.

EPR study of 1-ethylcyclohexa-2,5-diene-1-carboxylic acid 38



38 **39** **40**

Scheme 20

An EPR sample (10 mg in 250 μl DTBP) was prepared in the usual fashion and degassed for a suitable period using N_2, before being placed in the EPR resonator and used in exploratory experiments. Previous research on the *n*-propyl cyclohexadienyl acid **32** suggested that a high temperature, in excess of 320 K, would be required to favour the cleavage of the carbon-carbon bond and release the primary radical (Scheme 20). However, initial spectra were recorded at lower temperatures, while illuminating with UV light, in order to observe a strong spectrum of the delocalised cyclohexadienyl radical **39** (Figure 20). The well-resolved spectrum allowed accurate readings of hyperfine splitting to be recorded and confirmed the absence of any background radical signals.

Figure 20

A fresh sample was placed in the EPR cavity and allowed to heat to approximately 360 K, before the UV light was activated and the spectrum recorded. At this higher temperature, the peaks derived from the delocalised cyclohexadienyl radical remained a prominent feature and therefore distorted the central portion of the acquired spectrum. However, closer examination around the outer limits of the delocalised spectra revealed two additional peaks, which were unobstructed by other signals and

recognised as belonging to the released ethyl radical **40**. These peaks could be integrated and used to gain the desired kinetic data for the 1-ethylcyclohexa-2,5-diene-1-carboxylic acid.

The spectra acquired at higher temperatures were relatively weak due to both the Boltzmann factor and a rapid deterioration of the EPR sample. A gradual build up of benzoic acid on the walls of the EPR tube also inhibited the amount of UV light passing through the sample to initiate the reaction. It was therefore vital to carry out the EPR experiments, and record all necessary peaks, in the quickest time possible without sacrificing any accuracy due to increased noise levels. This was achieved by selecting a small, 40 G, section of the EPR spectrum where the unhindered peaks of both transient radicals could be observed. It was then possible to decrease the acquisition time, without losing any spectra quality or increasing the signal to noise ratio.

A stock solution of the 1-ethylcyclohexa-2,5-diene-1-carboxylic acid was prepared in order to provide ten uniform EPR samples, each containing 6 mg of the acid in 250 μl DTBP. The individual samples were degassed in the conventional manner and photolysed within the EPR cavity to produce a spectrum at a specific temperature in the range 330 – 370 K. The EPR spectra were recorded over the 40 G sweep width, established previously, using a fresh sample for each temperature change. In the interests of maintaining consistency, all experimental parameters were held constant (Figure 21).

The peaks generated by the primary ethyl radical **40** are clearly shown, along with a considerable distortion and weakening in the spectrum of the delocalised cyclohexadienyl radical **39** as the temperature increases. A single peak from the ethyl radical and an unimpeded peak from the delocalised radical were double integrated using WinEPR software. This information was converted into concentration data and used in calculating the values for k_d at each temperature setting, correcting for solvent viscosity (Table 17).

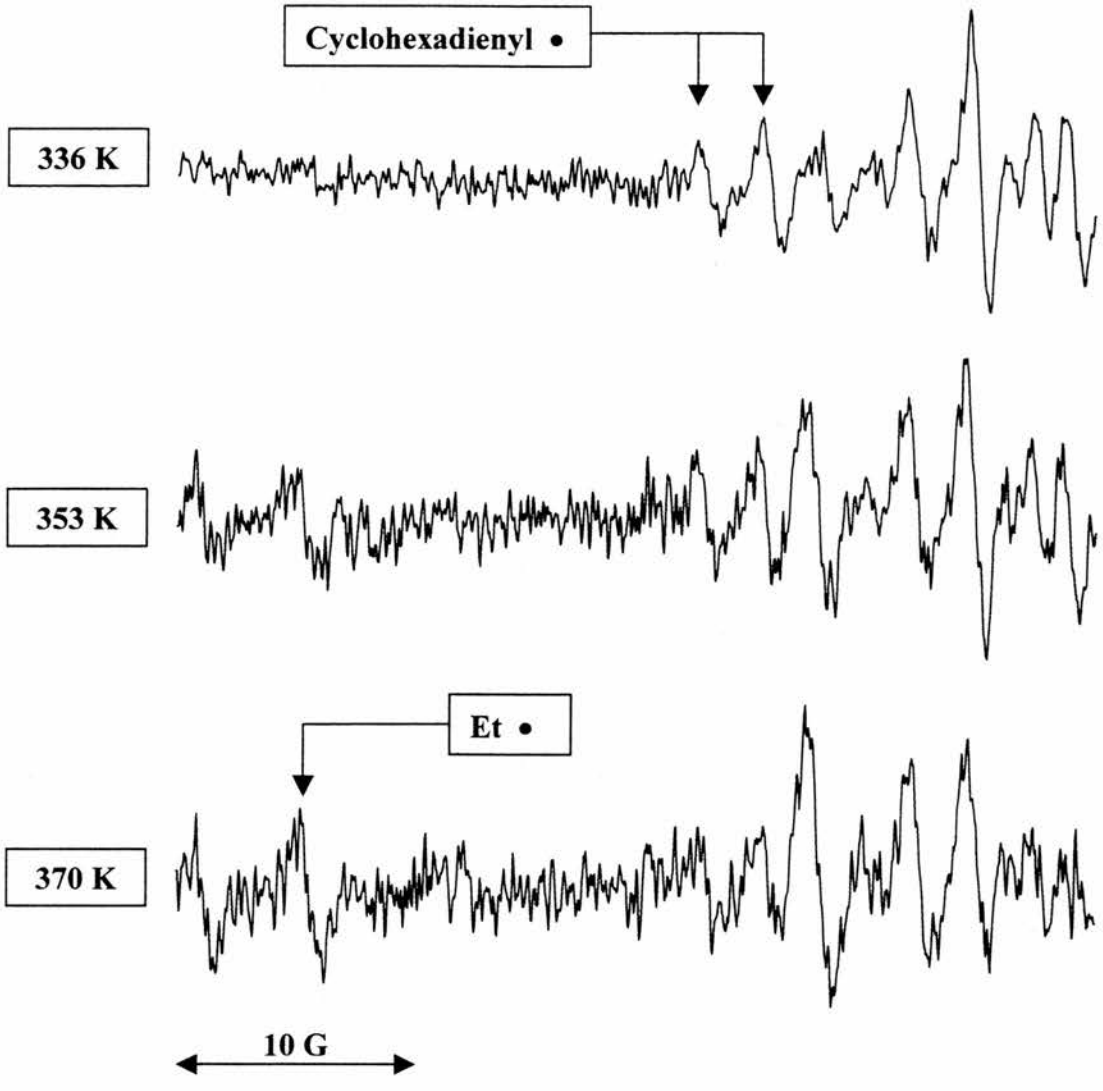


Figure 21

T/K	[40]	[39]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ DTBP	k_d
336	2.050E-07	6.050E-07	-6.562	2.974	9.877	2.07E+03
342	2.300E-07	5.750E-07	-6.492	2.925	9.904	2.58E+03
348	2.500E-07	5.450E-07	-6.438	2.877	9.930	3.10E+03
353	2.900E-07	5.000E-07	-6.339	2.831	9.955	4.13E+03
359	3.400E-07	4.450E-07	-6.222	2.786	9.979	5.72E+03
365	3.700E-07	4.100E-07	-6.152	2.743	10.003	7.09E+03
370	3.950E-07	3.800E-07	-6.094	2.701	10.026	8.55E+03

Table 17

This information was transferred on to an Arrhenius plot, in order to confirm that the relationship between log k_d and temperature was linear (Figure 22). The equation of the applied trendline was used to calculate a value for the energy of dissociation (E_d)

and the associated pre-exponential factor for 1-ethylcyclohexa-2,5-diene-1-carboxylic acid **38** (Table 18).

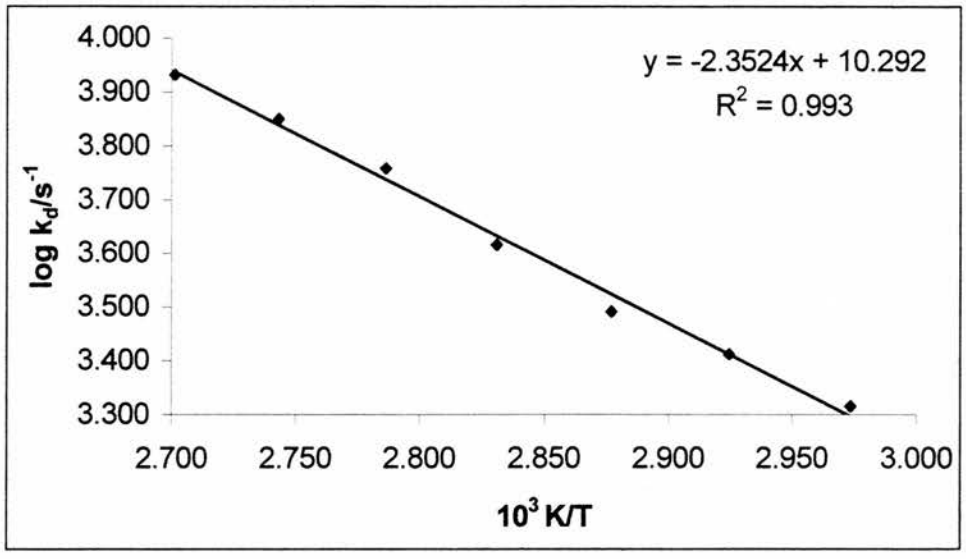


Figure 22

Released Radical	10^{-3} k_d / s^{-1} (300 K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
$Et^{\bullet}$	0.276	10.29	10.76

Table 18

The k_d value displayed in Table 18 seems extraordinarily high when compared with that observed for the *n*-propyl radical, this leads to a rather low value for the energy of dissociation. It was suspected that the rate of hydrogen abstraction for the ethyl acid was significant, leading to a large degree of error when calculating the Steady State equation. In order to confirm this belief, more data was collected using a range of EPR sample concentrations.

EPR study of 38 using different sample concentrations

A new EPR sample (0.6 mg of acid in 250 μl DTBP) was prepared in the conventional fashion and placed in the EPR resonator at 350 K. The EPR spectrum was acquired, using identical parameters to the previous experiment, while illuminating the sample with UV light. The resulting spectrum was compared directly with the spectrum retrieved at the same temperature using the original 6 mg sample. A notable difference in relative peak intensities was observed, which confirmed the presence of a sizeable hydrogen abstraction rate.

In order to determine the value of k_H for this compound, it became necessary to repeat the entire set of EPR experiments, using samples with a different acid concentration. This would give a set of contrasting results for transient radical concentration at each temperature, which could be placed into the Steady State equation. In order to improve accuracy, it was decided that the experiment should be repeated using a total of four distinct concentrations, so that the observed values of k_H could then be averaged.

Stock solutions were prepared in the conventional manner, providing individual samples that contained approximately 0.6 mg, 1 mg and 3 mg of the ethyl acid in 250 μl of DTBP. Each grouping was then employed in the EPR experiments described for the 6 mg sample, using a fresh EPR sample at each temperature setting, and maintaining the experimental parameters of the EPR spectrometer to aid in reproducibility (Figure 23).

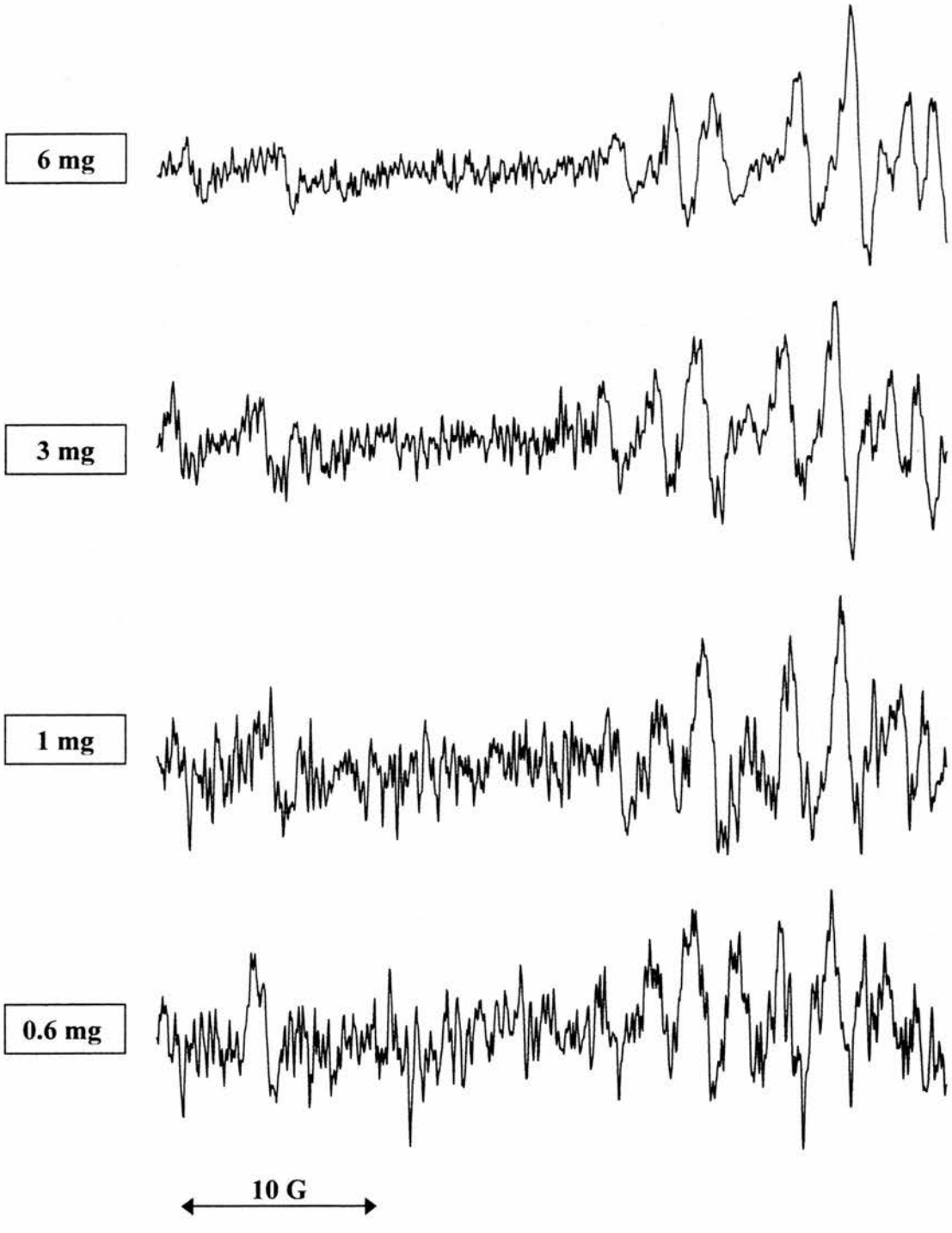


Figure 23

Spectra of 1-ethylcyclohexa-2,5-diene-1-carboxylic acid 38 at 353 K, with four distinct concentrations

The recorded spectra were individually analysed and double integrated, using WinEPR software, to give the areas of the selected peaks. This information was converted into a radical concentration and placed into the Steady State equation described previously. The derived equations contained k_d and k_H as two unknowns and could be simplified into an expression for a straight line plot, following the form y = mx + c. For the ethyl acid, transient radical concentrations were recorded at four separate concentrations over the entire temperature range, therefore a plot of $([r^\bullet]^2/[ur^\bullet])+[r^\bullet]$ against $([ah].[r^\bullet])/[ur^\bullet]$ at each temperature should provide a straight line, where the gradient of this line is equal to $k_H/2k_t$ and its intercept on the y-axis is equal to $k_d/2k_t$ (Table 19, Figure 24).

T/K	[38]	[40]	[39]	(ah.r)/ur x	$(r^2/ur)+r$ y	$2k_t$	k_H	k_d
342	0.2	1.26E-07	6.12E-07	4.047E-02	1.518E-07	8.02E+09	1.45E+04	1.93E+03
342	0.1	1.51E-07	4.49E-07	3.251E-02	2.019E-07			
342	0.03	1.51E-07	3.21E-07	1.586E-02	2.222E-07			
342	0.02	1.31E-07	2.27E-07	1.139E-02	2.067E-07			

T/K	[38]	[40]	[39]	(ah.r)/ur x	$(r^2/ur)+r$ y	$2k_t$	k_H	k_d
348	0.2	1.690E-07	5.759E-07	5.769E-02	2.186E-07	8.51E+09	1.70E+04	3.05E+03
348	0.1	2.048E-07	4.457E-07	4.444E-02	2.989E-07			
348	0.03	1.956E-07	2.687E-07	2.453E-02	3.38E-07			
348	0.02	1.536E-07	1.728E-07	1.752E-02	2.902E-07			

T/K	[38]	[40]	[39]	(ah.r)/ur x	$(r^2/ur)+r$ y	$2k_t$	k_H	k_d
353	0.2	2.342E-07	5.852E-07	7.866E-02	3.2786E-07	9.02E+09	1.93E+04	5.32E+03
353	0.1	3.122E-07	4.292E-07	7.035E-02	5.3935E-07			
353	0.03	2.602E-07	2.341E-07	3.746E-02	5.4936E-07			
353	0.02	2.081E-07	1.561E-07	2.627E-02	4.8576E-07			

T/K	[38]	[40]	[39]	(ah.r)/ur x	$(r^2/ur)+r$ y	$2k_t$	k_H	kd
359	0.2	2.643E-07	5.193E-07	1.001E-01	3.989E-07	9.54E+09	2.30E+04	8.97E+05
359	0.1	3.965E-07	3.369E-07	1.138E-01	8.631E-07			
359	0.03	2.908E-07	1.982E-07	4.944E-02	7.174E-07			
359	0.02	2.432E-07	7.928E-08	6.043E-02	9.892E-07			

T/K	[38]	[40]	[39]	(ah.r)/ur x	$(r^2/ur)+r$ y	$2k_t$	k_H	k_d
365	0.2	3.544E-07	4.429E-07	1.573E-01	6.381E-07	1.01E+10	2.85E+04	1.18E+04
365	0.1	3.759E-07	2.657E-07	1.368E-01	9.077E-07			
365	0.03	3.222E-07	1.731E-07	6.272E-02	9.218E-07			
365	0.02	2.954E-07	1.127E-07	5.161E-02	1.069E-06			

Table 19

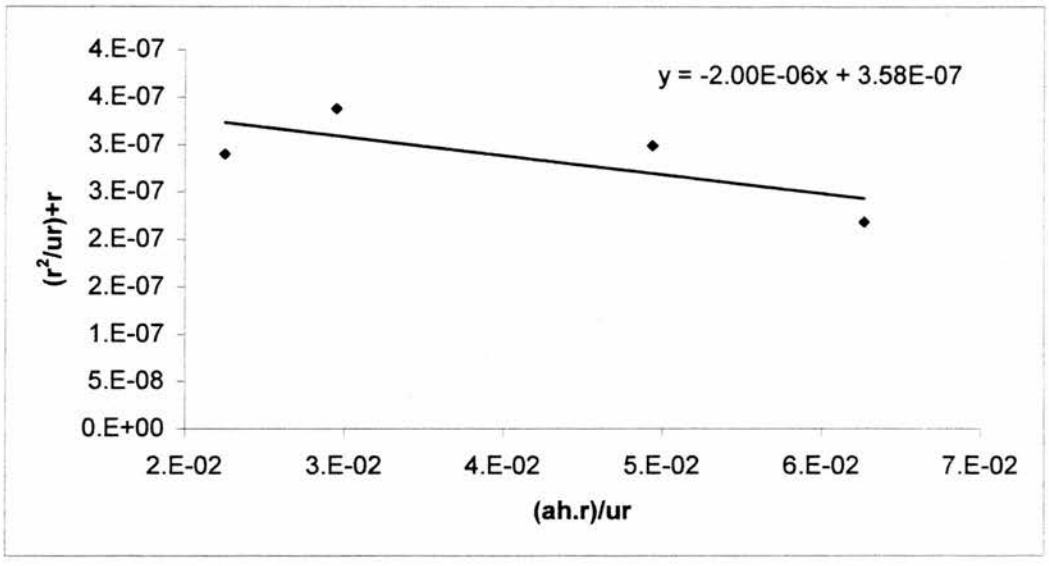


Figure 24. Example of plot derived from data at 348 K

This technique allowed us to calculate the average values of k_H and k_d at each temperature and finally plot log k_H and log k_d against $10^3/T$, in order to give general equations for k_H and k_d for the ethyl cyclohexadienyl acid (Figure 25). Analysis of this Arrhenius plot enabled us to calculate the dissociation rate constant at 300 K and the rate of H-abstraction at 340 K (Table 20).

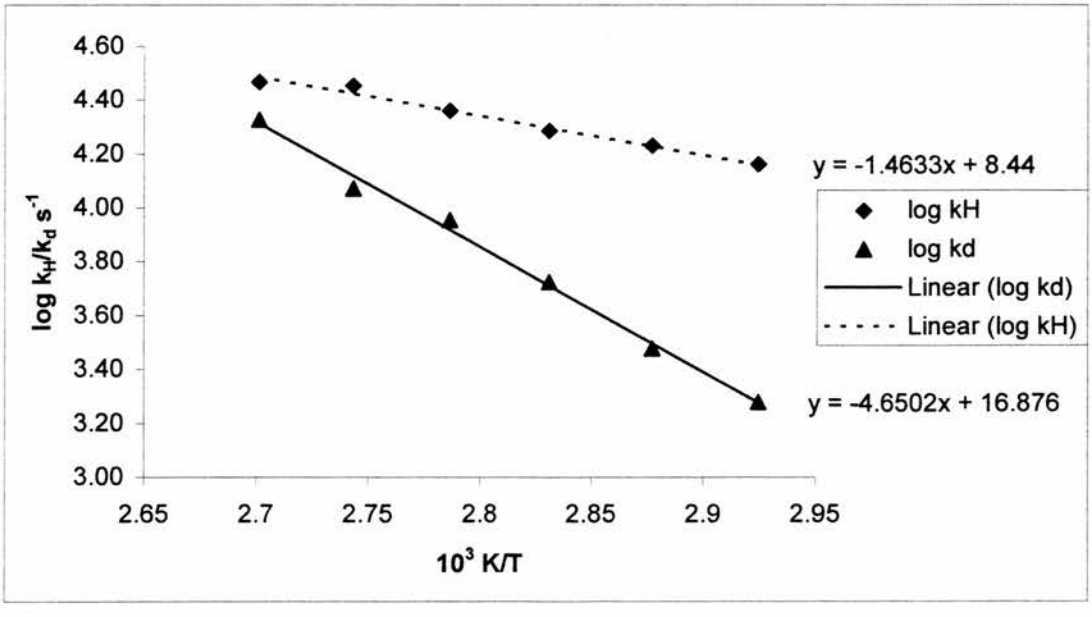


Figure 25

Released Radical	10^{-3} k_d / s^{-1} (300 K)	Log A_d/ s^{-1}	E_d/ kcal mol^{-1}	10^{-5} k_H * (340 K)	Log A_H *	E_H / kcal mol^{-1}
$Et^{\bullet}$	0.023	16.88	21.28	0.14	8.44	6.70

Table 20, * = dm^3 mol^{-1} s^{-1}

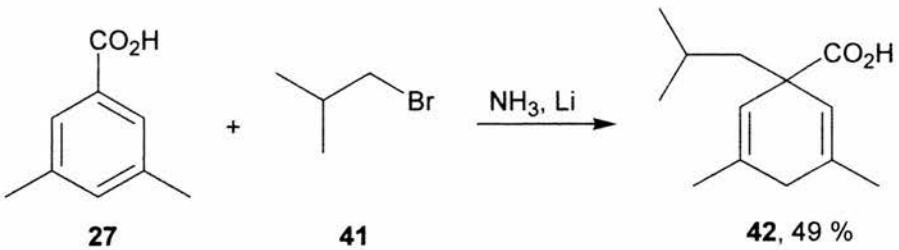
This lower value of k_d is in the area expected for the release of a primary radical. The rate of hydrogen abstraction is also similar to that expected for an ethyl radical and is significantly higher than that found for the isopropyl analogue due to the relative instability of the primary radical in solution. These results authenticate the use of this modified procedure in measuring the value of k_d and k_H, and display the merits of recording several results over a range of sample concentrations in order to improve accuracy.

Product analysis of the ethyl acid 38 after photolysis

The ethyl acid was photolysed, in the presence of DTBP, at 300 K for a period of two hours in order to ensure the complete rearrangement of the radical precursor. All benzoic acid in the resultant mixture was converted into the methyl benzoate using the previously discussed technique, before the sample was analysed by GLC. Comparison of the acquired GLC trace with that of authentic samples of methyl benzoate and ethylbenzene, confirmed the presence of a small amount of the alkyl benzene. Calculations on the ratio between benzoic acid and the alkyl benzene confirmed that benzoic acid was the major product in a ratio of 20 : 1. Therefore diversion of the dissociation down the k^2_d pathway can be neglected.

1-*iso*-Butyl-3,5-dimethyl-cyclohexa-2,5-diene-1-carboxylic acid 42

Synthesis of 1-*iso*-butyl-3,5-dimethyl-cyclohexa-2,5-diene-1-carboxylic acid 42

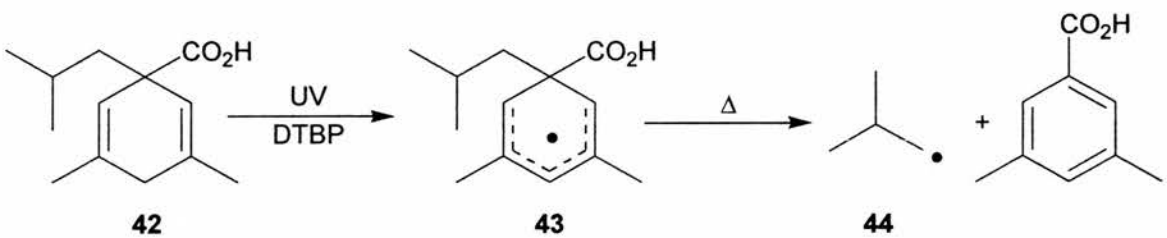


27 **41** **42**, 49 %

Scheme 21

1-*Iso*-butyl-3,5-dimethyl-cyclohexa-2,5-diene-1-carboxylic acid **42** was prepared using the Birch reduction/alkylation methodology described previously (Scheme 21). The addition of 1-bromo-2-methylpropane **41** to 3,5-dimethylbenzoic acid **27** proceeded readily under Birch conditions to give an impure white solid, which was recrystallised from pentane to furnish the desired carboxylic acid as white plates in a yield of 49%.

EPR study of 1-*iso*-butyl-3,5-dimethyl-cyclohexa-2,5-diene-1-carboxylic acid 42



42 **43** **44**

Scheme 22

The EPR sample was prepared in the usual manner, employing DTBP as the bulk solvent. This sample was degassed with nitrogen before being placed in the EPR resonator, which was cooled to a temperature of 240 K. An initial EPR recording, without UV initiation, confirmed the absence of any background radicals within the sample. The spectrum recorded at 240 K, in the presence of UV, was very similar to those previously observed for other cyclohexadienyl acids and confirmed the existence of the delocalised cyclohexadienyl radical **43**. The presence of two methyl

groups, attached to the cyclohexadienyl ring, provided a more complex septet splitting, which was measured using the WinEPR software.

A number of EPR spectra were recorded at this lower temperature, in an attempt to optimise the EPR parameters, before a new sample was prepared and the temperature of the cavity increased to 320 K. As expected, this significant increase in cavity temperature encouraged the release of the *iso*-butyl radical and delivered a very different EPR spectrum, with a reduced set of peaks from the cyclohexadienyl radical and the introduction of new peaks, both outside the cyclohexadienyl spectrum and superimposed upon it. The splittings of these new peaks were measured and compared favourably with the literature values for the *iso*-butyl radical **44**. This confirmed the ability of 1-*iso*-butyl-3,5-dimethyl-cyclohexa-2,5-diene-1-carboxylic acid to rearrange and supply the primary *iso*-butyl radical when initiated.

Closer examination of the spectra derived from the cyclohexadienyl and *iso*-butyl radicals confirmed that there were peaks within each spectrum that did not overlap and interfere with each other. Thus, measurements of the growth and decline of these peak integrals could be used to gain kinetic information.

A stock solution of the *iso*-butyl acid was prepared, containing an accurately measured quantity of the purified carboxylic acid (0.1 g acid, 2.5 ml of DTBP). This stock solution provided ten identical samples of 250 μl for the kinetic experiments, and each sample was degassed thoroughly before use.

EPR spectra were recorded in the temperature range of 297 K – 328 K, at increments of 5 K (Figure 26). A new sample was used for each different temperature setting and the experimental parameters were kept constant in order to maintain uniformity. The acquired spectra were double integrated using the WinEPR software and the integral heights of the independent radical peaks were measured and converted into concentration data, by comparison with a standard DPPH sample of known concentration.

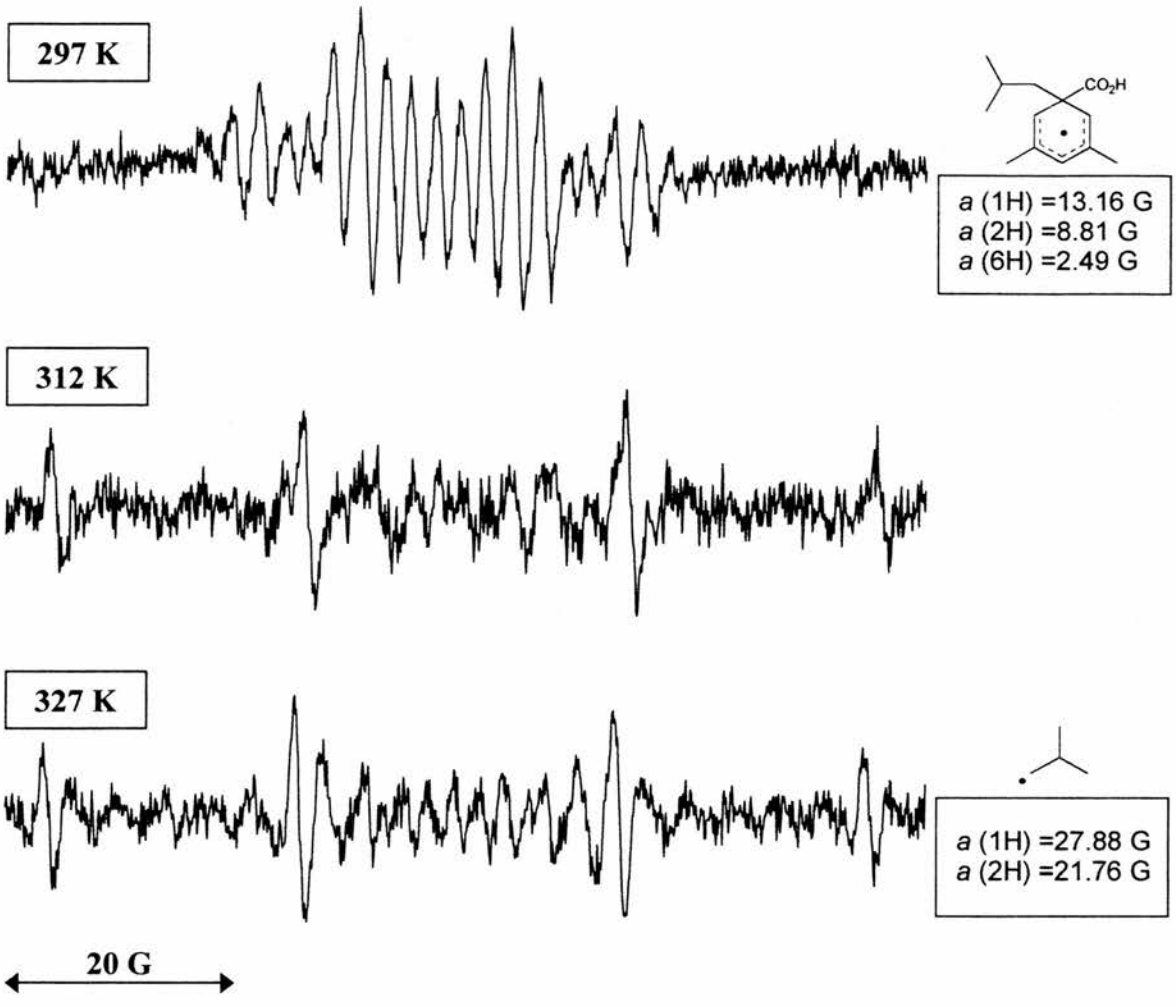


Figure 26

The concentration data for these transient radicals were placed into the previously derived Steady State equation, in order to give values for log $k_d/2k_t$ at each recorded temperature. By substituting the value of $2k_t$ for DTBP, found in the work by Fischer, it was possible to calculate values of log k_d for the *iso*-butyl carboxylic acid, which was corrected for solvent viscosity at each temperature (Table 21).

T/K	[44]	[43]	log $k_d/2k_t$	$10^3/T$	log $2k_t$	k_d
297	4.294E-08	8.158E-07	-7.345	3.365	9.894	353.840
302	6.374E-08	4.266E-07	-7.135	3.308	9.893	573.275
307	8.792E-08	3.517E-07	-6.959	3.254	9.940	957.760
312	8.755E-08	2.627E-07	-6.933	3.201	9.984	1125.746
318	1.028E-07	2.398E-07	-6.833	3.149	10.016	1522.011
318	1.516E-07	3.537E-07	-6.664	3.149	9.976	2047.590
323	2.205E-07	3.308E-07	-6.435	3.099	9.985	3546.765
328	2.480E-07	2.029E-07	-6.259	3.051	9.991	5400.383

Table 21

The rate data derived from the Steady State expression can be represented on an Arrhenius plot in order to give values for the energy of activation and the pre-exponential factor (Figure 27, Table 22). This information allows us to compare these acids directly with each other and will enable several conclusions to be derived, with regard to the ability of the *iso*-butyldimethyl carboxylic acid to rearrange and release the primary *iso*-butyl radical.

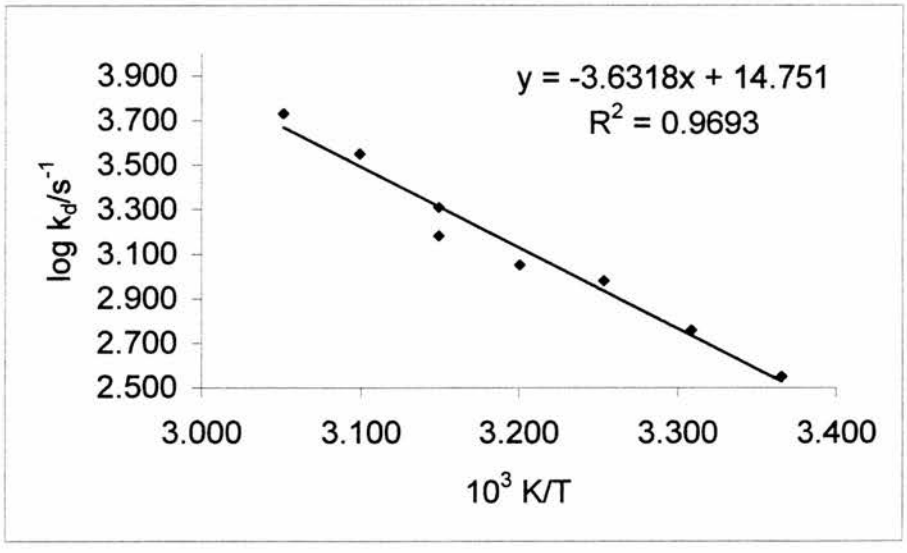


Figure 27

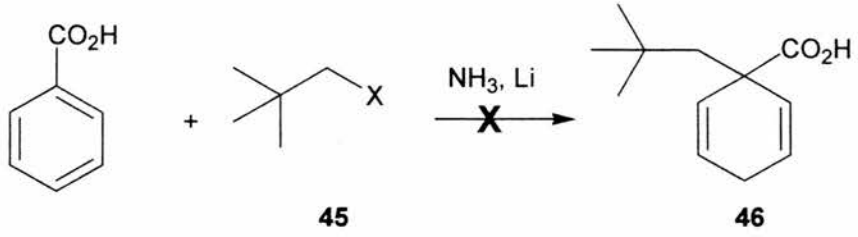
Released Radical	10^{-3} k_d / s^{-1} (300 K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
i-Bu$^\bullet$	0.425	14.75	16.62

Table 22

As anticipated, the value of k_d is lower than those found for the more stable secondary radicals. The release of an *iso*-butyl radical has a similar activation energy to the accompanying cleavage of the n-propyl radical, yet it is much smaller than that found for the ethyl radical precursor. This suggests that a slight increase in steric bulk encourages the cleavage of the carbon-carbon bond, therefore the *iso*-butyl radical is released more readily than the ethyl radical. The activation energy remains significantly higher than those exhibited by other secondary, tertiary and resonance stabilised radicals.

1-Neopentylcyclohexa-2,5-diene-1-carboxylic acid 46

Attempted synthesis of 1-neopentylcyclohexa-2,5-diene-1-carboxylic acid 46



45 **46**

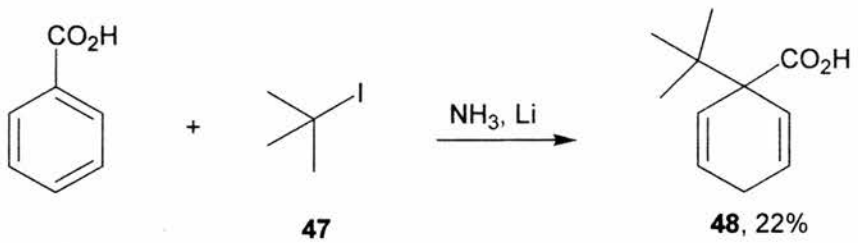
X = Br, I **Scheme 23**

Following the successful preparation and analysis of the *iso*-butyl acid, it was decided that a slightly more bulky compound should be prepared so that any stereogenic effect on the rate of bond dissociation could be assessed. The neopentyl analogue **46** contains a larger alkyl side chain, but would still release a primary radical, so that the kinetic data for both the *iso*-butyl and neopentyl acids could be directly compared.

The Birch reduction/alkylation of benzoic acid was performed, quenching with neopentyl bromide **45** in order to form the desired cyclohexadienyl acid **46** (Scheme 23). We were disappointed to find that after work-up of the reaction mixture only unreacted benzoic acid and the neopentyl bromide were obtained in addition to 1,4-dihydrobenzoic acid. In an attempt to rectify this situation, the experiment was repeated using neopentyl iodide, but none of the desired product was acquired.

1-*t*-Butylcyclohexa-2,5-diene-1-carboxylic acid 48

Synthesis of 1-*t*-butylcyclohexa-2,5-diene-1-carboxylic acid 48[10]



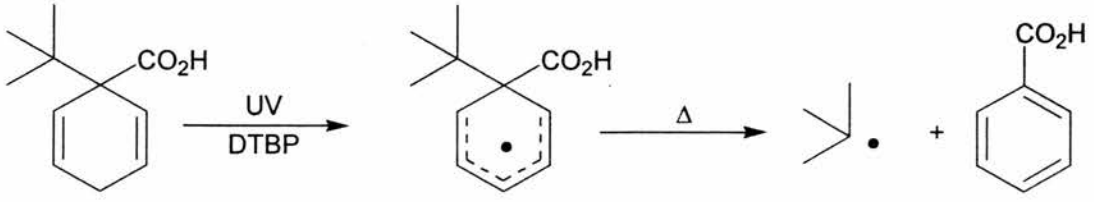
47 **48**, 22%

Scheme 24

Previous experiments by Baguley had demonstrated that it was possible to synthesise the *t*-butyl cyclohexadienyl acid **48**. The *t*-butyl side chain contains a quaternary carbon adjacent to the cyclohexadienyl ring and is therefore considerably more bulky than the any of the substituents used previously. Radical dissociation of this side chain would release a relatively more stable tertiary radical. In an attempt to study the effects of releasing a relatively more stable, and considerably more bulky, tertiary centre on the rate of bond dissociation, we decided to repeat Baguley's synthesis of 1-*t*-butylcyclohexa-2,5-diene-1-carboxylic acid and to evaluate its associated values of k_d and activation energy.

The procedure described by Baguley, for the formation of the *t*-butyl acid, used *t*-butyl iodide **47** to quench the reactive benzoic acid/NH_3 mixture. Previous attempts using *t*-butyl bromide furnished the desired product in a reduced yield. Therefore a Birch reduction/alkylation was performed on benzoic acid, quenching with *t*-butyl iodide, to give the title compound, which was purified by column chromatography to remove all traces of unreacted benzoic acid and 1,4-dihydrobenzoic acid (Scheme 24). The low yield of 22% was comparable to that attained by Baguley and can be attributed to the large steric strain associated with creating a bond between two quaternary carbons.

EPR study of 1-*t*-butylcyclohexa-2,5-diene-1-carboxylic acid 48



48 **49** **50**

Scheme 25

The EPR sample was prepared as described in the general procedure, using DTBP as both the solvent and radical initiator. This initial sample contained approximately 10 mg of the *t*-butyl acid and was easily taken up into solution. The sample was degassed for a suitable period before it was placed into the EPR cavity, which was held at a temperature of 270 K. An initial scan of the sample, in the absence of UV, confirmed that there were no discernable peaks due to background radicals in the sample. The experiment was repeated in the presence of UV light and furnished a very strong spectrum, which was identified as the central region of the released *t*-butyl radical **50** (Figure 28). This result seemed promising as the spectra confirmed that the *t*-butyl cyclohexadienyl acid rearranged to release the *t*-butyl radical at a lower temperature than any of the previous cyclohexadienyl acid analogues. However, in order to measure the radical kinetics of this compound, using the novel EPR method, we needed to locate a temperature range where both the unrearranged cyclohexadienyl radical **49** and rearranged *t*-butyl radical **50** could be observed on the same spectrum. The temperature of the EPR cavity was reduced to 240 K and the spectrum acquisition was repeated in an attempt to locate the cyclohexadienyl radical. Again, only the spectrum of the *t*-butyl radical could be seen.

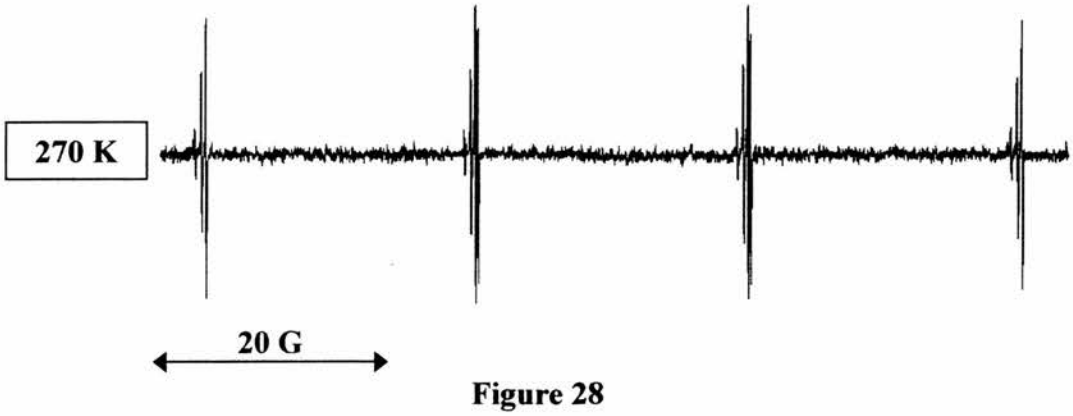


Figure 28

The freezing point of DTBP is approximately 235 K. In order to observe the EPR spectrum for the cyclohexadienyl radical **49** we had to fall below this temperature; therefore a new sample was prepared using 50 μl DTBP in approximately 200 μl of *n*-propane. *n*-Propane is a gas at room temperature, therefore the sample was prepared in a novel manner by placing approximately 10 mg of the acid and 50 μl of DTBP in a clean EPR tube, which had been fitted with a ground glass joint. The sample tube was connected to a vacuum line and frozen using a dewar of liquid N_2 before the dewar was taken away and all air within the sample was removed. This process of freezing and degassing was repeated several times to remove all air from the sample. Finally, the sample was again frozen in liquid N_2 while a measure of *n*-propane was passed from a reservoir into the cooled sample. The degassed sample was sealed using an oxygen/methane torch and used directly in the EPR spectrometer.

The EPR cavity was kept below 200 K to prevent the *n*-propane from boiling and breaking the tube. Spectra were recorded at a range of temperatures between 110 K and 200 K, but delivered no spectra that could be identified as the delocalised cyclohexadienyl radical. It was thought that the cyclohexadienyl acid had little solubility in the *n*-propane at these low temperatures. Therefore, in a final attempt to observe this radical, a new sample was prepared using 50 μl DTBP, 25 μl *t*-butyl benzene and approximately 200 μl of cyclopropane as the bulk co-solvent. This sample was prepared in an identical manner to that explained previously and the sealed, degassed sample was placed into the EPR resonator at 160 K. The EPR spectra was acquired in the presence of UV light and delivered a new spectrum, which was identified as that from the delocalised cyclohexadienyl radical.

This success in locating the spectra for the cyclohexadienyl radical meant that the kinetics could finally be measured using our EPR method. In order to gain this kinetic data, a range of spectra were recorded using several new samples in the temperature range of 180 – 211 K (Figure 29). The acquired spectra displayed signals for both the cyclohexadienyl and *t*-butyl radicals. Therefore integration of these peaks using the WinEPR software and conversion of these values into relative radical concentrations, allowed us to calculate the value of k_d at each temperature by using the derived Steady State equation (Table 23).

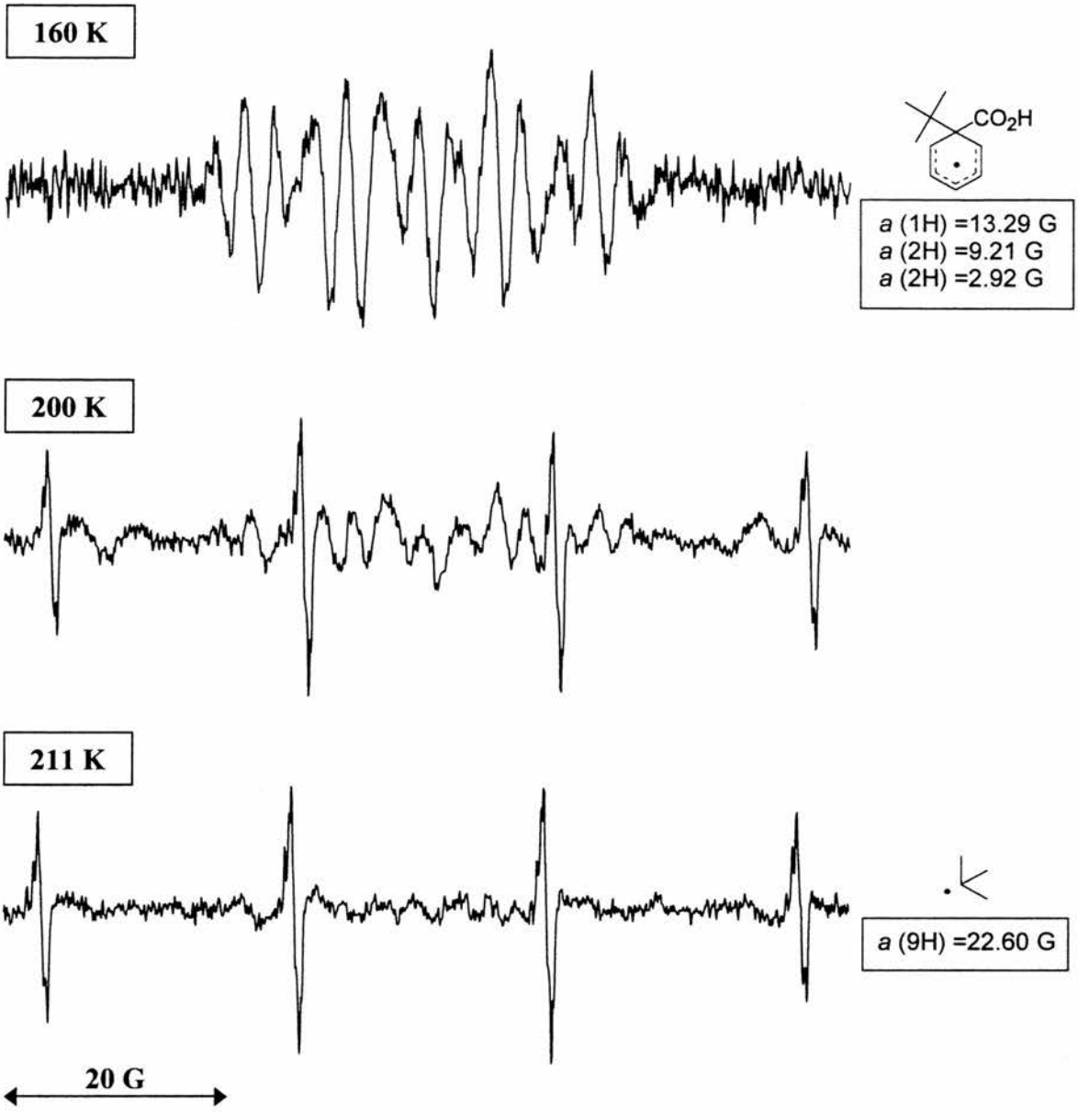


Figure 29

T/K	[50]	[49]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ c-C_3H_6	k_d
180	1.130E-09	2.980E-08	-8.931	5.556	10.042	1.29E+01
185	5.899E-09	3.830E-08	-8.167	5.403	10.072	8.03E+01
190	9.033E-09	4.168E-08	-7.959	5.259	10.100	1.38E+02
195	1.403E-08	2.937E-08	-7.683	5.121	10.127	2.78E+02
200	1.413E-08	2.013E-08	-7.619	4.991	10.152	3.41E+02
200	1.364E-08	2.202E-08	-7.656	4.991	10.152	3.13E+02
205	1.788E-08	1.593E-08	-7.421	4.867	10.176	5.69E+02
211	1.846E-08	1.487E-08	-7.383	4.750	10.199	6.55E+02

Table 23

The values of log k_d against $10^3/T$ can be plotted in the usual fashion on an Arrhenius plot, and a line of best fit applied, to give values for the pre-exponential factor and energy of activation for the rearrangement of the delocalised cyclohexadienyl radical in order to release the *t*-butyl radical (Figure 30, Table 24).

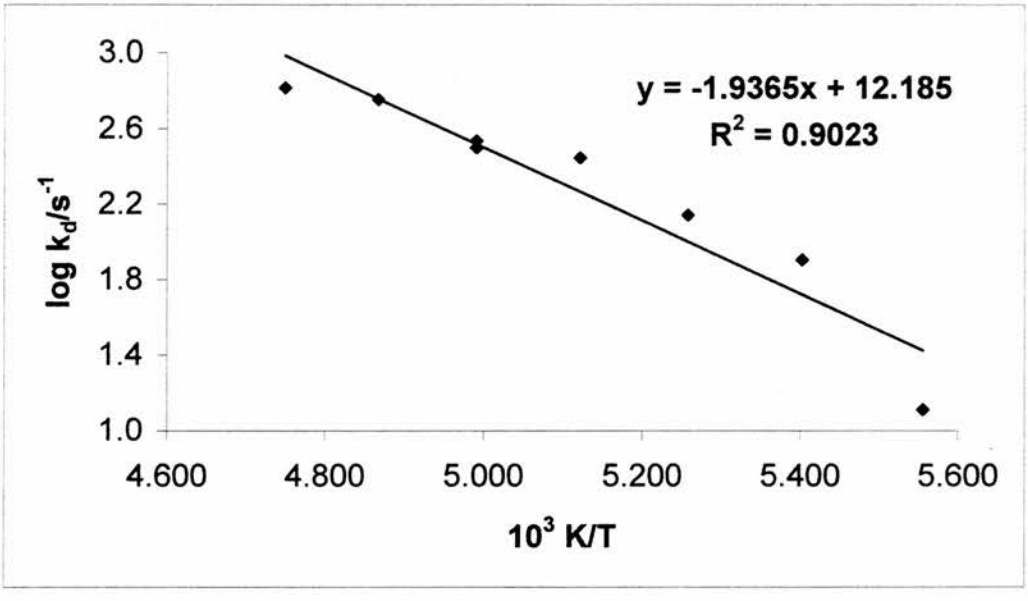


Figure 30

Released Radical	10^{-3} k_d / s^{-1} (300 K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
t-Bu$^{\bullet}$	526.83	12.19	8.86

Table 24

The relative value of k_d for the *t*-butyl acid is considerably larger than that observed for the release of a secondary or primary radical. This was expected, as the tertiary radical is much more stable than its secondary or primary equivalent and is also considerably more bulky. These factors reduce the energy required to break the carbon-carbon bond and therefore allow the dissociation to proceed at a greater rate.

EPR study of 1-*t*-butylcyclohexa-2,5-diene-1-carboxylic acid 48 using a different sample concentration

A second set of spectral data was acquired, using a sample containing a different concentration of the *t*-butyl acid. If k_H was significant for the *t*-butyl analogue, any change in acid concentration would have a direct effect on the ratio of transient radicals observed by EPR and their relative values of k_d.

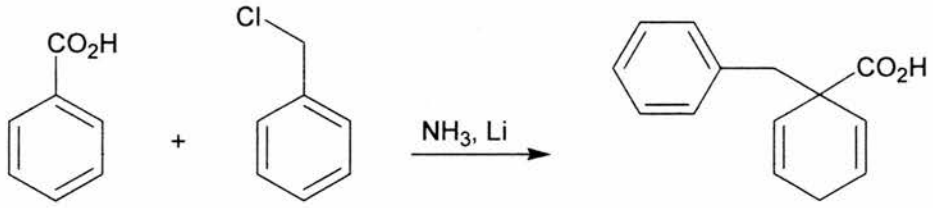
A new sample containing 1 mg of the *t*-butyl acid was prepared and placed into the EPR resonator, which was held at 200 K. The sample was photolysed and its EPR spectrum recorded, using identical parameters to those employed in the previous set of experiments. The peaks due to both the delocalised cyclohexadienyl radical and the released *t*-butyl radical were double integrated and compared with the values gained using the 10 mg sample. No significant difference in k_d values could be observed, therefore k_H was deemed negligible for the 1-*t*-butylcyclohexa-2,5-diene-1-carboxylic acid **48**.

Product analysis of the *t*-butyl acid 48 after photolysis

The *t*-butyl acid was photolysed, in the presence of DTBP, at 300 K for a period of two hours in order to ensure the complete rearrangement of the radical precursor. All benzoic acid in the resultant mixture was converted into the methyl benzoate, using the previously discussed technique, before the sample was analysed by GLC. Comparison of the acquired GLC trace with that of authentic samples of methyl benzoate and *t*-butylbenzene, confirmed that none of the alkyl benzene was formed and therefore dissociation *via* the k^2_d pathway was insignificant.

1-Benzylcyclohexa-2,5-diene-1-carboxylic acid 52

Synthesis of 1-benzylcyclohexa-2,5-diene-1-carboxylic acid 52[16]



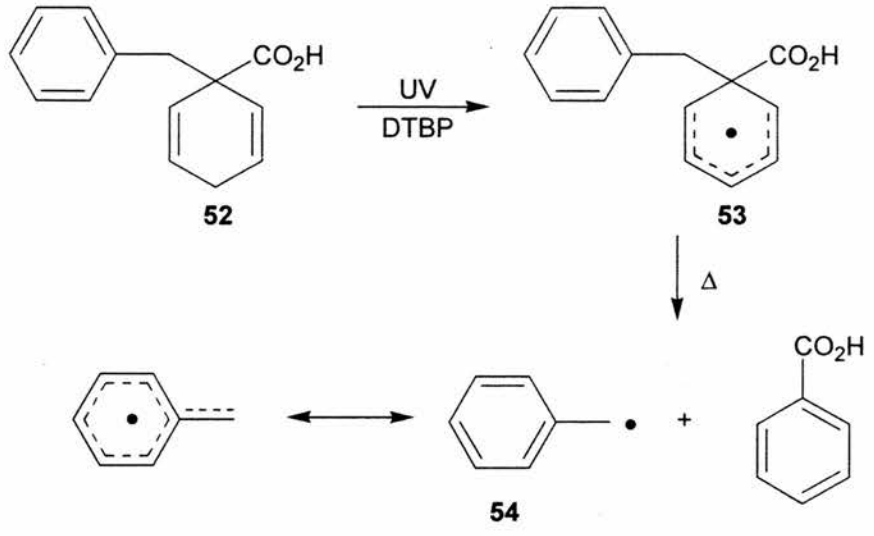
51 **52**, 41 %

Scheme 26

Experimentation confirmed that cyclohexadienyl acids that released primary, secondary and tertiary radicals, displayed marked differences in their rates of dissociation and resultant energies of activation. This was almost certainly due to both the relative stability of the released radical and the degree of steric hindrance, which weakens the carbon-carbon bond attaching the substituent to the cyclohexadienyl ring. In order to further test the effect of radical stability on the rate of dissociation, several acids were synthesised which held the potential to release resonance stabilised radicals.

The synthesis of 1-benzylcyclohexa-2,5-diene-1-carboxylic acid is a well documented procedure which has been carried out by several chemists in moderate yields.[10, 17, 18] The Birch reduction/alkylation was carried out in a similar fashion to that described in the general procedure, quenching with benzyl chloride **51** to give the desired benzyl cyclohexadienyl acid **52** (Scheme 26). This acid was recrystallised in pentane to give several batches of the desired acid with varying degrees of purity. The samples that exhibited greatest purity were pooled together and gave an overall yield of 41%. Benzyl halides are particularly susceptible to nucleophilic substitution reactions. Consequently, benzyl chloride could be used to generate good yields of the desired acid rather than the equivalent bromide or iodide.

EPR study of 1-benzylcyclohexa-2,5-diene-1-carboxylic acid 52



Scheme 27

It was anticipated that low temperatures would be required in order to observe the EPR spectra for the delocalised cyclohexadienyl radical **53**, as the resonance stabilised benzyl radical **54** would break away from the cyclohexadienyl ring relatively easily (Scheme 27). This requirement for low temperatures dictated that the sample solvent should be cyclopropane. Therefore an EPR sample containing 10 mg of the pure benzyl acid was prepared (50 μl DTBP, 200 μl cyclopropane). The sample was degassed using the freeze/thaw technique described for the *t*-butyl acid and then placed into the EPR cavity, which was held at 150 K.

An initial EPR experiment was performed with the UV light activated and produced a well-defined, complex spectrum which was attributed to the delocalised 1-benzylcyclohexa-2,5-diene-1-carboxylic acid **53** after computer simulation using Bruker's Simfonia software (Figure 31).

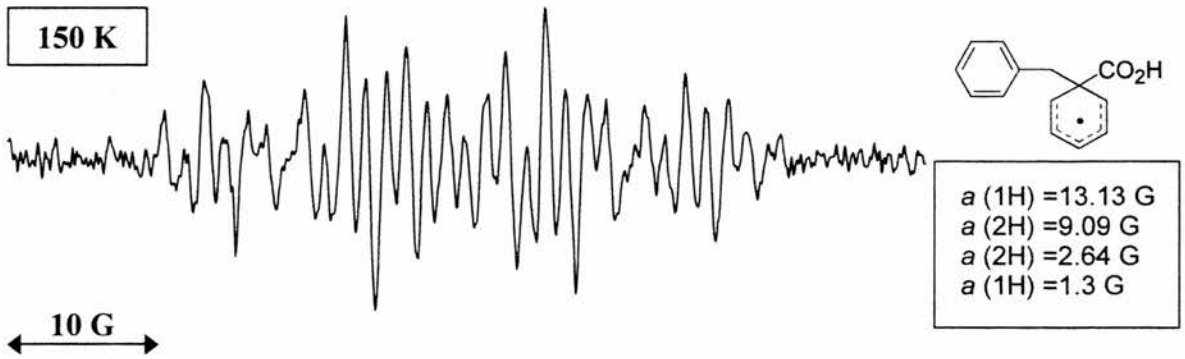


Figure 31

It was interesting to note that at these low temperatures, only one of the methylene hydrogen atoms coupled with the unpaired electron to give a long range hfs. This suggests that the radical adopts a preferred conformation about the carbon-carbon bond that attaches the cyclohexadienyl ring to the benzyl side chain. This conformation places only one H-atom in a position where it can interact with the SOMO of the cyclohexadienyl radical. Increasing the temperature within the EPR cavity has the effect of broadening the EPR lines, as internal rotation about the bond increases and becomes too fast for the EPR timescale.

The temperature of the EPR resonator was increased to 210 K, in an attempt observe the released benzyl radical. A spectrum was recorded in the presence of UV light and revealed a new spectrum, recognised as that belonging to the benzyl radical **54** (Figure 32).

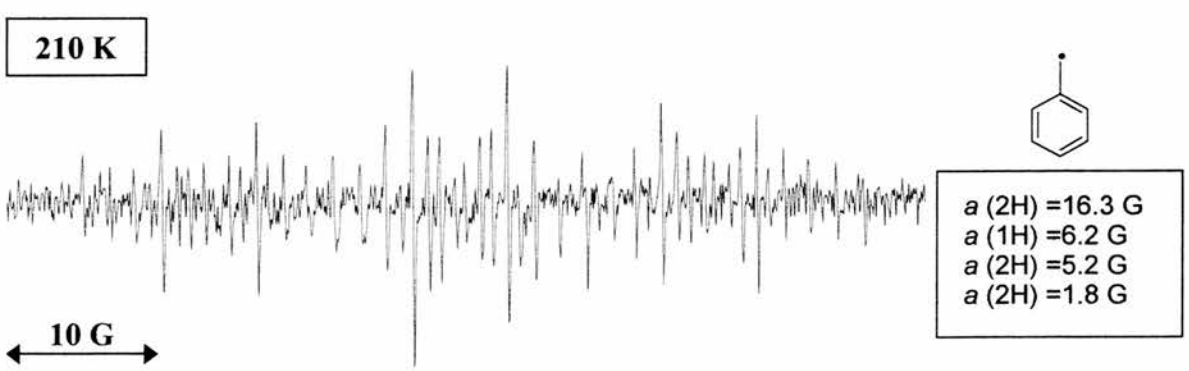
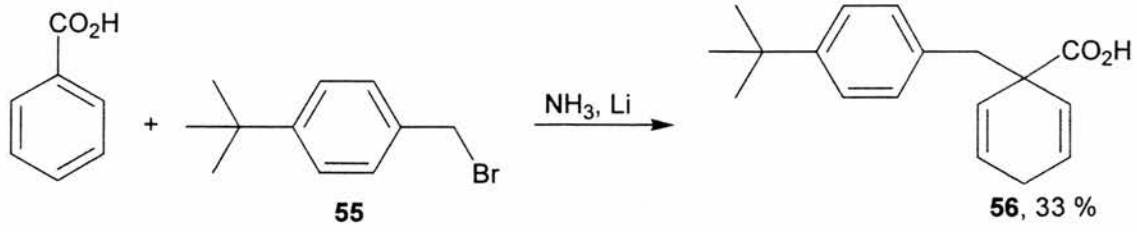


Figure 32

To gain kinetic information, several spectra were recorded at temperatures in the range 150 K – 210 K, in an attempt to observe both the unrearranged and rearranged radicals on the same spectra. Unfortunately, the major peaks in the benzyl radical spectrum overlapped considerably with those found for the delocalised cyclohexadienyl radical. The peaks that did not interfere with the cyclohexadienyl spectrum proved too small and sharp to be useful for concentration measurements. This prevented us from calculating the rate of dissociation for 1-benzylcyclohexa-2,5-diene-1-carboxylic acid.

1-(4-*t*-Butylbenzyl)-cyclohexa-2,5-diene-1-carboxylic acid 56

Synthesis of 1-(4-*t*-butylbenzyl)-cyclohexa-2,5-diene-1-carboxylic acid 56



55 **56**, 33 %

Scheme 28

Previous attempts to integrate the benzyl radical spectrum proved fruitless as the peaks were very sharp and small due to excessive splitting from the aromatic ring. In order to simplify this spectrum, we decided to place a *t*-butyl functionality in the *para*-position of the aromatic ring to remove the 6.2 G splitting from the acquired spectrum and therefore reduce the number of peaks significantly. This reduction in peak number should have the knock-on effect of increasing peak intensity.

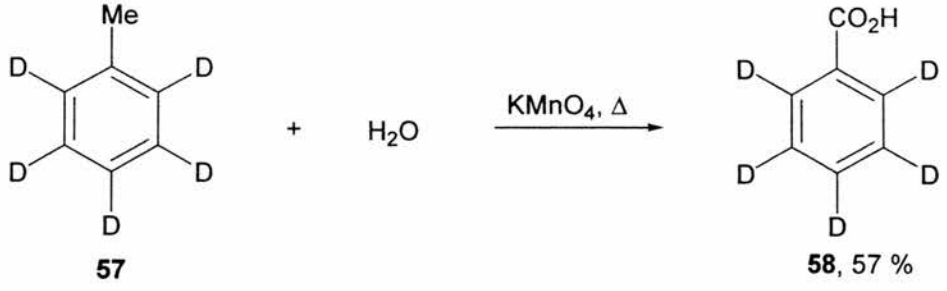
The synthesis of the *t*-butyl analogue **56** was performed using the general procedure for a Birch reduction/alkylation of benzoic acid, quenching the reactive Birch solution with 4-*t*-butylbenzyl bromide **55** (Scheme 28). 1-(4-*t*-Butylbenzyl)-cyclohexadiene-1-carboxylic acid **56** was purified for EPR analysis by recrystallising from pentane and was isolated in a moderate yield of 33%.

EPR study of 1-(4-*t*-butylbenzyl)-cyclohexa-2,5-diene-1-carboxylic acid 56

Attempts to prepare an EPR sample of the *t*-butylbenzyl acid in 200 μl of DTBP were unsuccessful as the cyclohexadienyl acid showed very little solubility in the chosen solvent. It was anticipated that the desired spectra would appear at low temperatures; therefore several attempts were made at preparing samples using cyclopropane, *n*-propane and *n*-heptane as co-solvents. Again, a lack of solubility prevented us from acquiring any EPR spectra. Finally, samples were prepared using 50 μl of DTBP, approximately 150 μl of cyclopropane and 50 μl of *t*-butylbenzene in an attempt to improve solubility. Unfortunately the cyclohexadienyl acid refused to be taken up into solution and prevented us from recording any EPR spectra.

1-Benzyl-2,3,4,5,6-pentadeutero-cyclohexa-2,5-diene-1-carboxylic acid 58

Synthesis of pentadeuterobenzoic acid 58[19]



57 **58**, 57 %

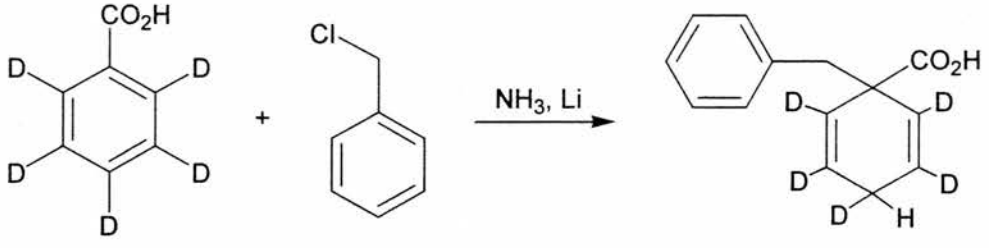
Scheme 29

The spectrum for the delocalised 1-benzylcyclohexa-2,5-diene-1-carboxylic acid **53** is both wide and complicated, due to the presence of a long range splitting by one of the benzylic hydrogen atoms. In order to simplify the spectrum of the cyclohexadienyl radical, we prepared a pentadeuterated cyclohexadiene. The hyperfine splitting values for deuterons are considerably smaller than those exhibited by protons, therefore, substituting deuterons for protons in the cyclohexadiene structure will have the effect of narrowing the overall spectrum while broadening the individual peaks. This gives reduced resolution in the cyclohexadienyl radical spectrum, but might allow us to integrate several of the larger peaks in the benzyl radical spectrum, as these will no longer interfere with the reduced cyclohexadienyl signals.

The precursor required for the synthesis of the deuterated benzyl acid is pentadeuterobenzoic acid **58**. This compound was prepared using an adaptation of the procedure developed by Clarke and co workers (Scheme 29).[19] A mixture of D_5-toluene **57** and water was refluxed in the presence of potassium permanganate for four hours. As the reaction progressed, the intense purple colour of permanganate faded to give a dark grey solution, containing the grey precipitate of manganese dioxide. Steam distillation of this solution removed all of the unreacted D_5-toluene and some of the water. Filtration of the hot residue removed all traces of the manganese dioxide and decolourising with animal charcoal gave a clear, colourless solution of water, which contained the deuterated benzoic acid **58**. This solution was acidified using

concentrated HCl and the organic layer was separated using several portions of ether. The pentadeuterobenzoic acid was isolated in a yield of 57%.

Synthesis of 1-benzyl-2,3,4,5,6-pentadeutero-cyclohexa-2,5-diene-1-carboxylic acid 59[20]

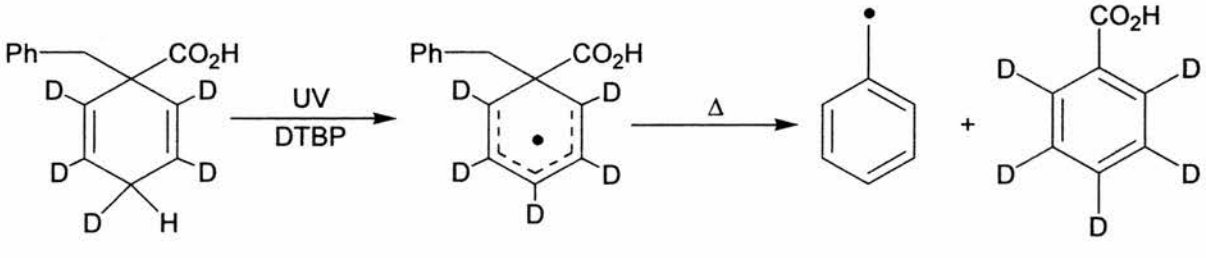


58 **51** **59**, 56 %

Scheme 30

The synthesis of the 1-benzylpentadeuterocyclohexadienyl acid **59** was carried out following the general procedure for a Birch reduction/alkylation outlined above, replacing benzoic acid with the pentadeuterobenzoic acid **58** which had previously been prepared (Scheme 30). The reaction mixture was allowed to stir for 10 min before quenching with benzyl chloride **51** to give 1-benzyl-2,3,4,5,6-pentadeutero-cyclohexa-2,5-diene-1-carboxylic acid **59**, which was purified by recrystallisation from pentane and isolated in a yield of 56%.

EPR study of 1-benzyl-2,3,4,5,6-pentadeutero-cyclohexa-2,5-diene-1-carboxylic acid 59



59 **60** **54**

Scheme 31

Previous experiments with the analogous benzyl acid directed us to prepare the EPR samples in a solvent that had a low freezing point. A 10 mg sample was therefore prepared in a similar fashion to that described for the benzyl analogue, using 50 μl of

DTBP and approximately 200 μl of cyclopropane. The degassed sample was placed in the EPR resonator at 150 K and a spectrum acquired in the absence of UV light. The lack of any signal in the EPR spectrum confirmed the absence of any transient background radicals; therefore, the EPR experiment was repeated with the UV light activated to furnish a spectrum, which contained one very broad signal with very little resolution. It was anticipated that the spectrum for the deuterated cyclohexadienyl radical **60** would be both narrow and less well resolved, however, due to the lack of resolved fine structure, it proved difficult to confirm that this signal was brought about by the cyclohexadienyl radical.

The temperature of the EPR cavity was raised to 180 K and the EPR spectrum acquired. On this occasion we observed both the broad signal and several sharp, well-defined peaks that could be attributed to the released benzyl radical **54**. Closer examination of the broad signal revealed a significant reduction in size, therefore the concentration of the radical creating the broad signal must also have reduced. Further analysis at higher temperatures confirmed a steady decrease in the size of the broad signal, which increased in size again when the temperature was lowered to 165 K. This evidence confirmed our suspicion that the broad signal was actually derived from the deuterated cyclohexadienyl radical.

Fresh samples were prepared using an accurately measured mass of the deuterated benzyl acid. These samples were thoroughly degassed and sealed before being used to gather EPR spectra at a range of different temperatures (Figure 33)

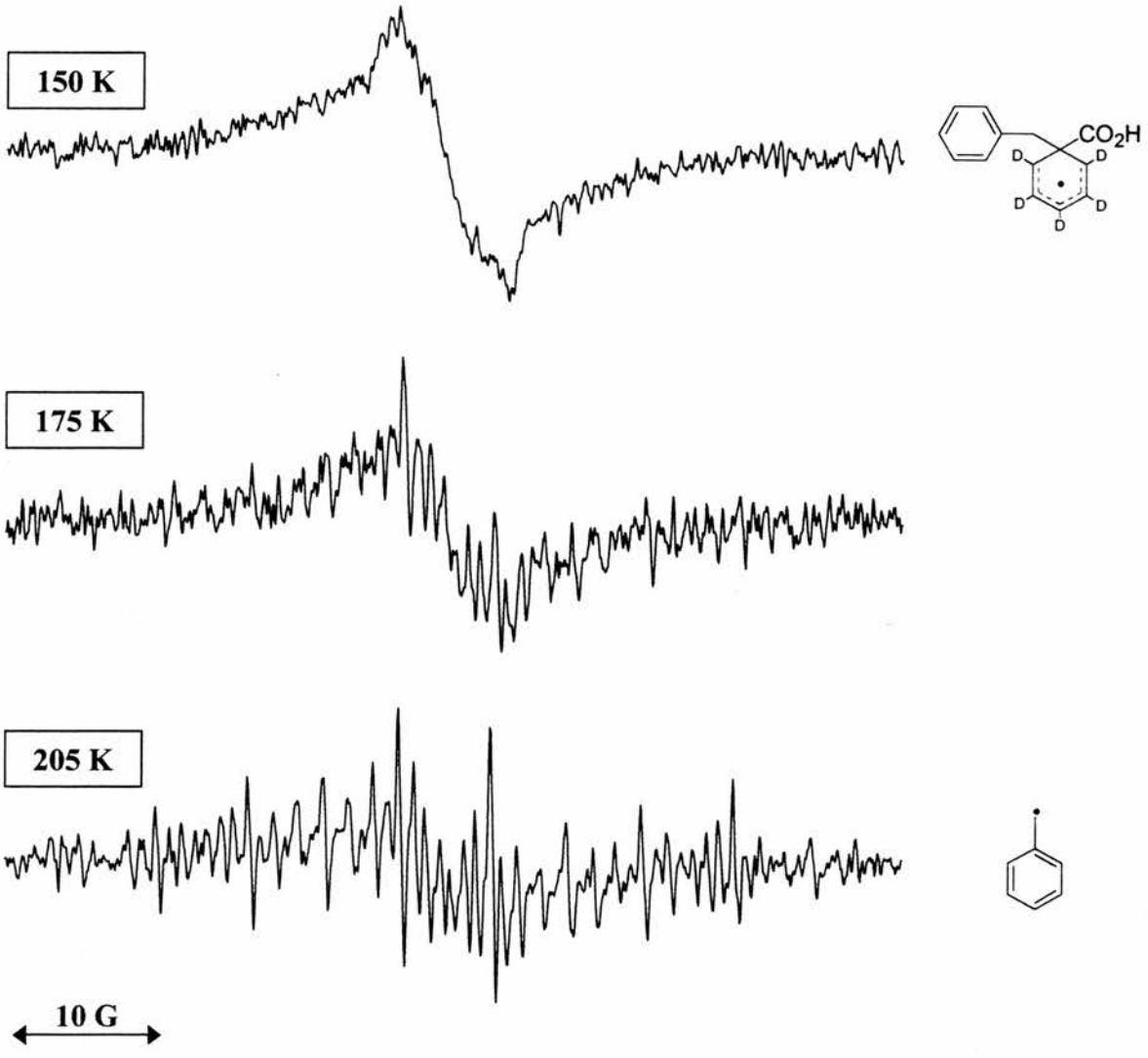


Figure 33

In order to calculate the required kinetic data, the double integrals for the spectra associated with both the benzyl and deuterated cyclohexadienyl radicals had to be measured. Integrating peaks from the benzyl radical **54** created little problem, as several of the larger peaks no longer interfered with the diminished spectrum of the deuterated cyclohexadienyl radical. However, gaining an accurate double integral value for the deuterated cyclohexadienyl radical **60** proved problematic, as a background signal seemed to develop as the EPR experiments progressed. The added hindrance of several peaks in the benzyl radical spectrum being superimposed on the cyclohexadienyl spectrum, suggested that it was impossible to gain an accurate double integral value for the unrearranged acid.

Despite these problems, several techniques were developed which allowed us to calculate the double integral value of the cyclohexadienyl radical with reasonable accuracy. The WinEPR software proved invaluable when separating the benzyl radical peaks from the broad peak representing the cyclohexadienyl radical. Resolution enhancement techniques within the program, allowed us to remove all high frequency peaks attributed to both background noise and the benzyl radical, leaving the broad signal attributed to the cyclohexadienyl radical and the developed background signal untouched. Subsequent double integration of this enhanced, broad, signal proved relatively simple.

It also proved possible to calculate the approximate double integral value of the background radical, which developed as the experiments progressed. This was accomplished by photolysing a sample at high temperature for several minutes in order to use up all of the cyclohexadienyl acid. The temperature of the EPR resonator was then reduced to the temperature range in which the kinetic spectra were acquired and the EPR experiment repeated in the presence of UV light. The resultant EPR spectrum contained a broad signal, which could only be derived from a background radical, as all of the cyclohexadienyl radical had been used up at the higher temperature. The double integral of this background radical was calculated and subtracted from all of the derived double integral values for the cyclohexadienyl acid.

Using these techniques, it was possible to gain concentration data for the benzyl radical and a corrected concentration value for the deuterated cyclohexadienyl radical. These figures were placed into the derived Steady State equation in order to generate values for k_d at each temperature (Table 25).

T/K	[54]	[60]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ c-C_3H_6	k_d
165	5.081E-10	3.110E-09	-9.228	6.072	9.941	5.16E+00
175	1.150E-09	2.252E-09	-8.760	5.718	10.010	1.78E+01
185	2.165E-09	1.820E-09	-8.324	5.403	10.072	5.59E+01
205	3.110E-09	5.000E-10	-7.649	4.867	10.176	3.37E+02

Table 25

The data acquired from substituting the values of radical concentration into the Steady State equation can be represented in an Arrhenius plot of log k_d against $10^3/T$ (Figure

34). This chart compares the change in dissociation rate with any associated change in temperature. The points fall on a straight line, confirming a linear correlation between dissociation rate and temperature for the benzyl cyclohexadienyl acid. The equation of this line can be used to calculate values for the pre-exponential factor, activation energy and the dissociation rate at 300 K (Table 26).

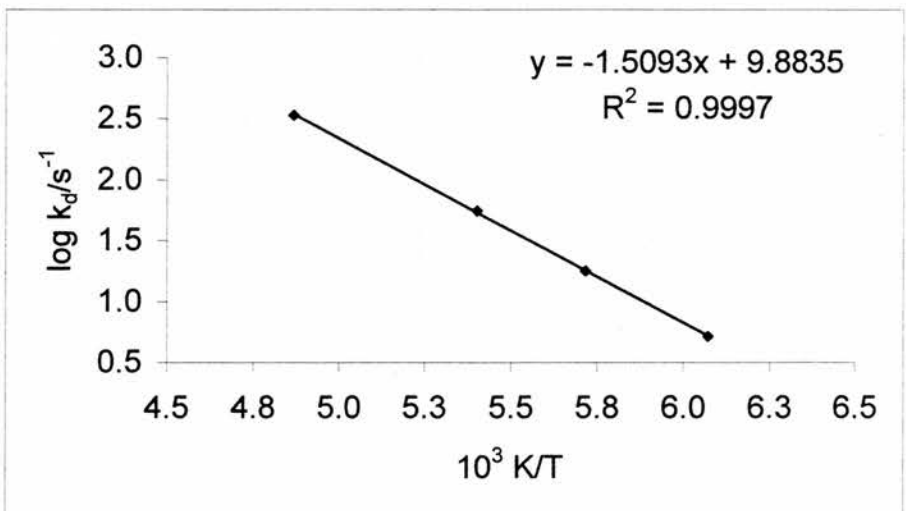


Figure 34

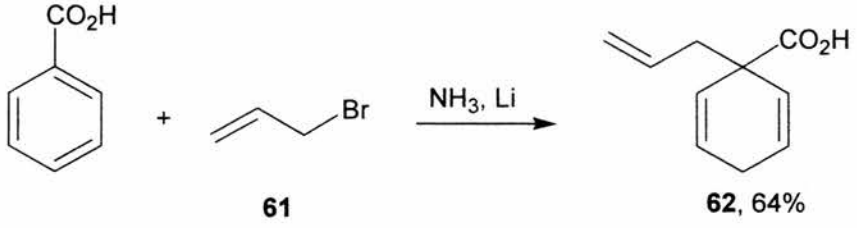
Released Radical	10^{-3} k_d / s^{-1} (300 K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
$PhCH_2^{\bullet}$	70.15	9.88	6.90

Table 26

The significantly lower temperatures required to observe the deuterated cyclohexadienyl radical indicate how readily the bond connecting the benzyl side chain to the cyclohexadienyl ring fragments. The energy of activation is significantly lower than any of the previously tested cyclohexadienyl acids, and this is represented by a large increase in the value of k_d at 300 K. The benzyl radical is clearly a highly stabilised species, due to its ability to delocalise the radical around the aromatic π-system. However, it should be noted that the values of k_d and E_d are less accurate for the 1-benzyl-2,3,4,5,6-pentadeutero-cyclohexa-2,5-diene-1-carboxylic acid, due to the degradation in data quality when obtaining the double integral value for the broad signal, associated with the cyclohexadienyl radical. This is highlighted by the low value of log A_d, which should be closer to 13, and accounts for a reduction in the experimentally measured k_d value when compared to the *t*-butyl analogue.

1-Allylcyclohexa-2,5-diene-1-carboxylic acid 62

Synthesis of 1-allylcyclohexa-2,5-diene-1-carboxylic acid 62[21]

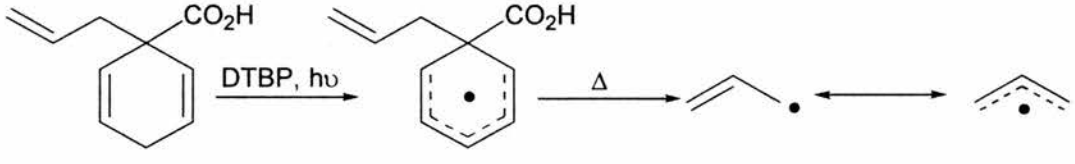


61 **62**, 64%

Scheme 32

The allyl derivative was prepared using the general Birch reduction/alkylation procedure, quenching with allyl bromide **61**, to give a yellow oil after aqueous workup (Scheme 32). This oil was purified by Kugelrohr distillation to furnish a colourless oil, identified as 1-allylcyclohexa-2,5-diene-1-carboxylic acid **62** in a yield of 64%.

EPR study of 1-allylcyclohexa-2,5-diene-1-carboxylic acid 62



62 **63** **64**

Scheme 33

The initial EPR sample was prepared using DTBP as both the solvent and radical initiator. However, the allyl acid had a limited solubility in this solvent at room temperature and raised fears that the allyl acid would fall out of solution when placed in the EPR cavity that was maintained at a low temperature of 250 K. A new sample was prepared using approximately 10 mg of the cyclohexadienyl acid and 50 μl of DTBP in 200 μl of *t*-butylbenzene to encourage solubility. Using this solvent mixture, the acid was completely solvated, which allowed it to be degassed with N_2 and its spectrum observed using the EPR spectrometer.

The EPR cavity was maintained just above the freezing point of the sample solvent. At 215 K, a spectrum was recorded in the absence of UV to confirm the absence of

any background radicals before an initial spectrum was recorded using UV to initiate the radical reaction (Scheme 33). A strong and well-resolved spectrum was recorded at this temperature, which identified through both simulation and from literature hyperfine splitting values as the allyl radical **64** (Figure 35). This confirmed that the intermediate cyclohexadienyl radical **63** could rapidly rearrange to release the resonance stabilised allyl radical, but also dictated that a different sample solvent was required, with a lower freezing point, so that the EPR spectra of the delocalised cyclohexadienyl radical could be observed and kinetic data recorded.

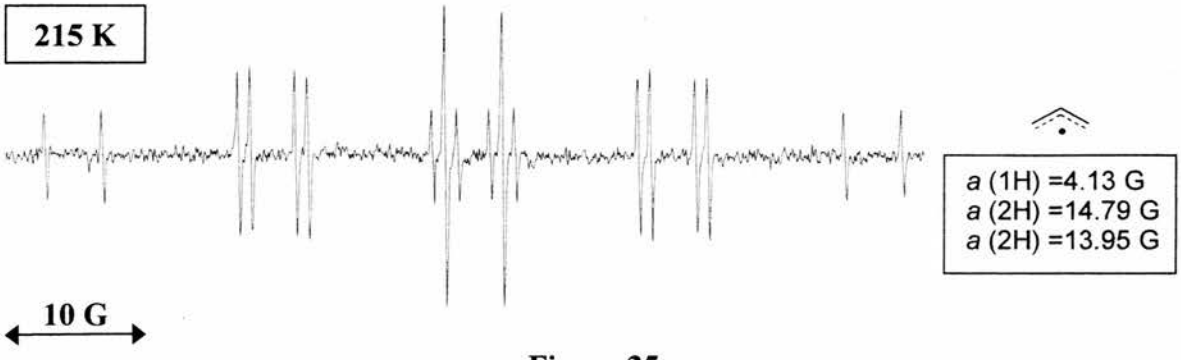


Figure 35

A new sample was prepared (10 mg acid, 50 µl DTBP and 200 µl cyclopropane), but again problems were found in sufficiently dissolving the acid in this solution. Therefore a small amount of *t*-butylbenzene was added to make the solution monophasic. The sample was degassed in the usual manner and placed into the EPR cavity, which was held at a temperature of 160 K, before a spectrum was recorded using UV to initiate the radical reaction. At this lower temperature, the rate of release of the allyl radical was vastly reduced and a clear spectrum for the delocalised cyclohexadienyl radical **63** was observed (Figure 36).

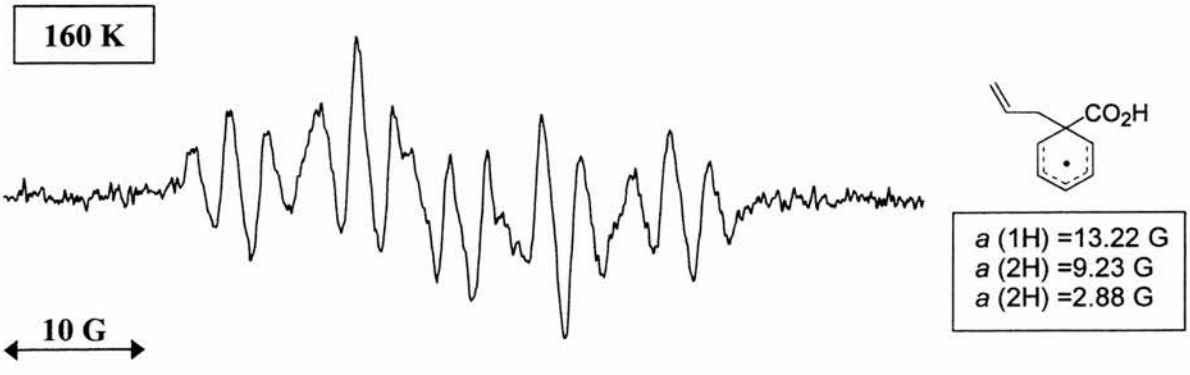


Figure 36

Further experimentation with this sample allowed us to locate a narrow temperature range where the recorded spectra progressively changed from the delocalised radical to that of the allyl radical. Several peaks in the spectra of both transient radicals were confirmed not to interfere with any other peaks in the spectrum, and could therefore be measured using the EPR method to gain kinetic data. It was possible to focus on a small part of the spectrum (35 G), in order to isolate these peaks, so that spectra could be gathered quickly and accurately with very little noise.

Several samples were prepared using the previously stated solvent system and an accurately known mass of the cyclohexadienyl acid. These samples were degassed using the conventional freeze/thaw technique and finally sealed. EPR spectra were acquired at a range of cavity temperatures from 185 – 221 K, using a fresh sample at each new temperature (Figure 37).

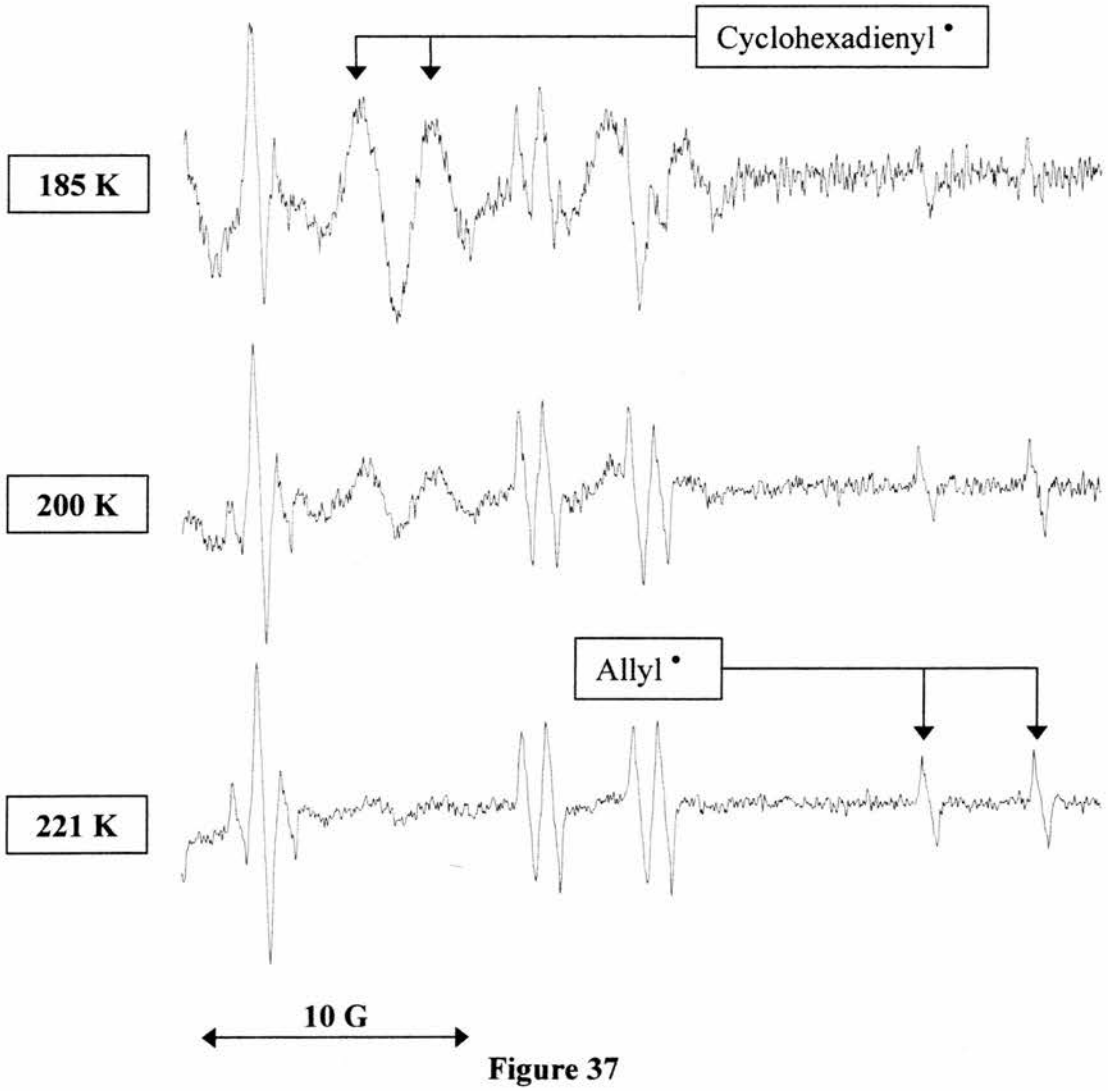


Figure 37

The recorded spectra were double integrated, using the WinEPR software, to give the relative peak areas for the unhindered peaks of both the delocalised cyclohexadienyl **63** and allyl **64** radicals. These peak areas were converted into concentration information and placed in the derived Steady State equation to give values of k_d for the 1-allylcyclohexa-2,5-diene-1-carboxylic acid at each individual temperature (Table 27).

T/K	[64]	[63]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ c-C_3H_6	k_d
190	5.259E-08	5.548E-07	-7.240	5.259	10.100	7.25E+02
195	1.154E-07	4.975E-07	-6.847	5.121	10.127	1.90E+03
200	1.676E-07	4.050E-07	-6.625	4.991	10.152	3.36E+03
205	2.277E-07	2.553E-07	-6.366	4.867	10.176	6.47E+03
211	2.587E-07	1.908E-07	-6.215	4.750	10.199	9.64E+03
216	2.999E-07	1.751E-07	-6.090	4.637	10.221	1.35E+04
221	3.035E-07	1.443E-07	-6.026	4.530	10.242	1.65E+04

Table 27

The value of log k_d at each temperature can be plotted against $10^3/T$ in an Arrhenius plot, in order to display the trend connecting temperature and rate of dissociation (Figure 38). The points fall on a straight line, confirming a linear relationship, and the addition of a line of best fit to this plot provides a general equation which allows us to calculate the value of k_d at any temperature and can also give us values for the pre-exponential factor (A_d) and energy of activation (E_d) (Table 28).

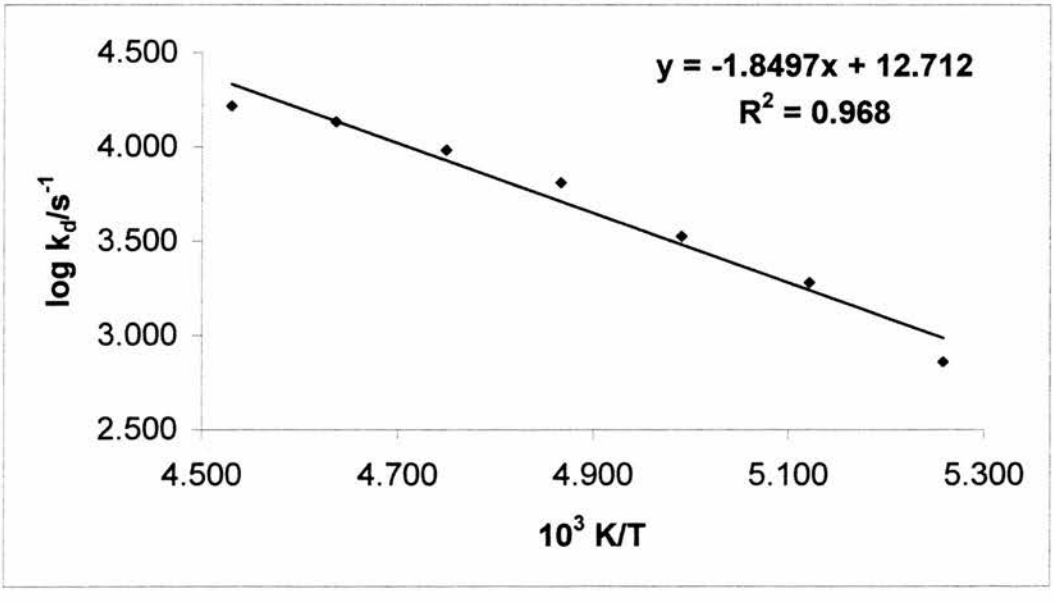


Figure 38

Released Radical	10^{-3} k_d / s^{-1} (300 K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
Allyl$^{\bullet}$	6701	12.71	8.46

Table 28

The value of k_d at 300 K confirms that resonance stabilisation of the released radical has a profound effect on the rate of dissociation. The free-radical is stabilised over three carbon centres, which makes it a lot more stable in solution than the branched alkyl radicals discussed previously. However, it was anticipated that the benzyl radical, which is stabilised over seven carbon atoms, would display a greater stability effect and therefore have a larger value of k_d than the allyl analogue. This is clearly not the case as the k_d value for the benzyl analogue is significantly smaller than predicted, due to the large experimental errors encountered when using the pentadeuterated carboxylic acid.

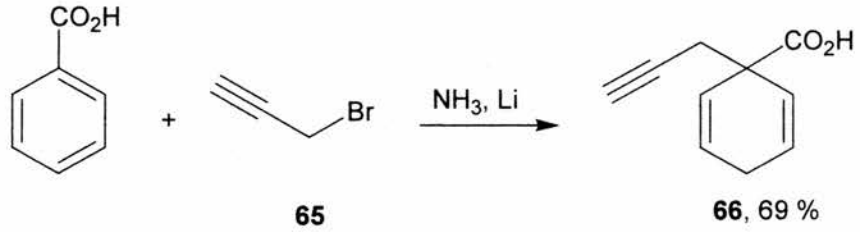
EPR study of 1-allylcyclohexa-2,5-diene-1-carboxylic acid using different sample concentrations

Due to the difficulties in handling cyclopropane at such low temperatures, it proved impossible to prepare a stock solution which had a uniform concentration. In order to maintain equality, the individual EPR samples were prepared using exactly the same quantities of DTBP, *t*-butylbenzene and cyclopropane. The amount of allyl acid added to the samples was also measured carefully to keep the samples as uniform as possible.

In order to confirm that a change in concentration had a negligible effect on the overall ratio of peak heights, several samples were prepared with a concentration of approximately 1 mg and analysed in similar EPR experiments. The recorded spectrum was reduced in size, yet the ratio of the double integrals and their respective k_d values remained constant, confirming a negligible effect of sample concentration and verifying that the rate of hydrogen abstraction is too small to be measured using this technique.

1-Propargylcyclohexa-2,5-diene-1-carboxylic acid 66

Synthesis of 1-propargylcyclohexa-2,5-diene-1-carboxylic acid 66



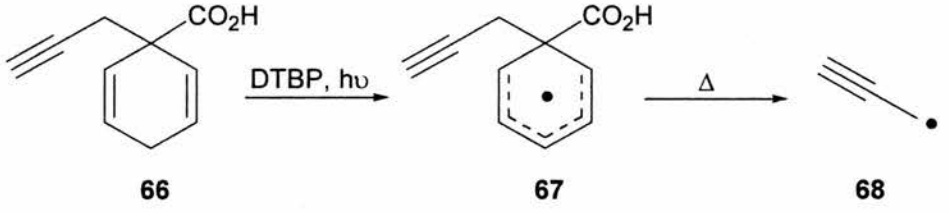
65 **66**, 69 %

Scheme 34

The formation of a propargyl radical is of great significance in organic synthesis as the triple bond acts a good foundation for further reaction, after radical addition. It was therefore necessary to study the ability of 1-propargylcyclohexa-2,5-diene-1-carboxylic acid **66** to furnish the moderately stabilised propargyl radical under mild conditions.

The synthesis of the propargyl acid was carried out using the modified Birch reduction/alkylation procedure described earlier, quenching with propargyl bromide **65** to furnish a dark brown oil after washing (Scheme 34). A sample of this oil was removed and purified by micro distillation, at low pressure, to yield a white solid which was identified as the pure 1-propargylcyclohexa-2,5-diene-1-carboxylic acid **66** by NMR spectroscopy.

EPR study of 1-propargylcyclohexa-2,5-diene-1-carboxylic acid 66



66 **67** **68**

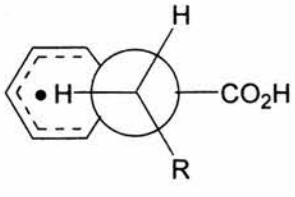
Scheme 35

It was predicted that cleavage of the carbon-carbon bond, to release the propargyl radical **68**, would occur at a low cavity temperature as the propargyl radical had increased stability from resonance. Therefore an initial sample was prepared using 10

mg of the pure carboxylic acid, 50 μl DTBP and ca. 200 μl of cyclopropane. The degassed sample was placed in the EPR cavity, which was maintained at a temperature of 170 K, and an experimental spectrum recorded using UV light to initiate the radical reaction. The acquired spectrum appeared very similar to that expected for the delocalised cyclohexadienyl radical **67**, however, closer inspection confirmed the presence of additional peaks which were derived from the long range interaction of hydrogens from the 1-substitutent (Figure 39). This γ-splitting suggests that only one of the two available methylene hydrogen's can couple with the unpaired electron. Simulation of this spectrum, incorporating an additional splitting value, gave a precise match for the acquired spectrum.

Figure 39

As the temperature of the resonant cavity was progressively increased to 190 K, the EPR lines broadened and the spectrum adopted the common form observed for the cyclohexadienes discussed previously. It was concluded that at low temperatures, the radical adopted a preferred conformation about the ring-CH_2 bond, in which only one H-atom was favourably placed for interaction with the SOMO (Scheme 36). At higher temperatures, the rate of internal rotation about this bond became fast on the EPR timescale and the lines broadened.



Scheme 36

The rearrangement of the delocalised cyclohexadienyl radical **67** into the propargyl radical **68** was first observed when the EPR cavity was held at 193 K. Heating the cavity to a temperature of 230 K encouraged the rapid conversion of the cyclohexadienyl acid into benzoic acid and consequently released the propargyl radical, to give a complete spectrum of the released radical with no significant peaks from the unrearranged precursor (Figure 40). This information dictated a range of 193 K – 221 K for gathering concentration information, where both transient radicals could be observed simultaneously.

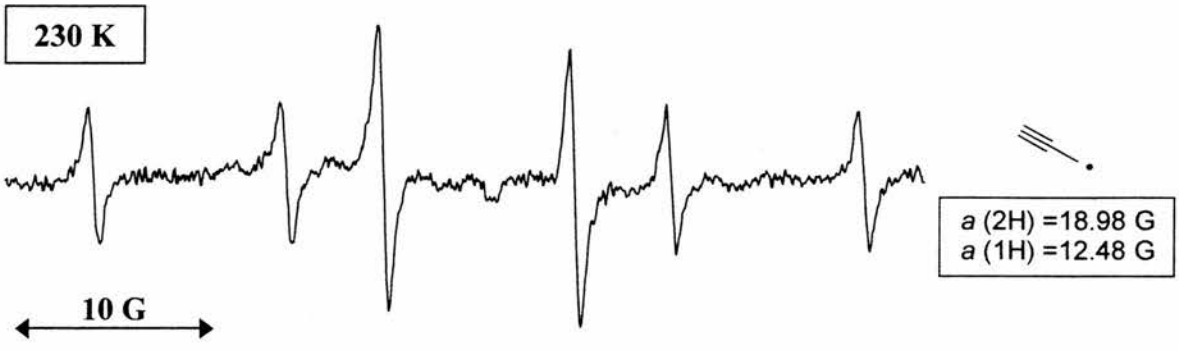


Figure 40

A small portion of 20 G was selected, where unhindered peaks from both transient radicals could be observed. This reduced scan width allowed us to acquire spectra very quickly and with minimal background noise. Several samples containing equal amounts of propargyl acid **66** in a DTBP/cyclopropane solvent system were prepared before a number of EPR experiments were performed at a range of temperatures within the 193 K – 222 K boundaries. A fresh sample was used at each new temperature setting and the acquired spectra were analysed and double integrated, using the WinEPR software, to give relative values of peak area. These values were converted into concentration data, which was placed into the derived Steady State equation to give values of k_d for 1-propargylcyclohexa-2,5-diene-1-carboxylic acid at a range of different temperatures (Table 29).

T/K	[68]	[67]	$k_d/2k_t$	$10^3/T$	log $2k_t$ c-C_3H_6	k_d
193	8.403E-09	1.111E-07	9.038E-09	5.181	10.115	117.765
198	9.669E-09	8.164E-08	1.081E-08	5.051	10.140	149.436
202	1.725E-08	1.003E-07	2.022E-08	4.950	10.160	292.230
207	2.619E-08	9.411E-08	3.348E-08	4.831	10.183	510.701
217	1.495E-08	8.541E-09	4.110E-08	4.608	10.227	693.023
221	1.987E-08	6.638E-09	7.937E-08	4.525	10.243	1389.369

Table 29

The values for log k_d were plotted against $10^3/T$ to give the Arrhenius plot (Figure 41). Again, all of the points fell on a straight line, indicating a linear relationship between the rate of dissociation and temperature. A line of best fit was applied to the plot, and the equation of this line used to generate values for activation energy (E_d) and the exponential factor (A_d) (Table 30).

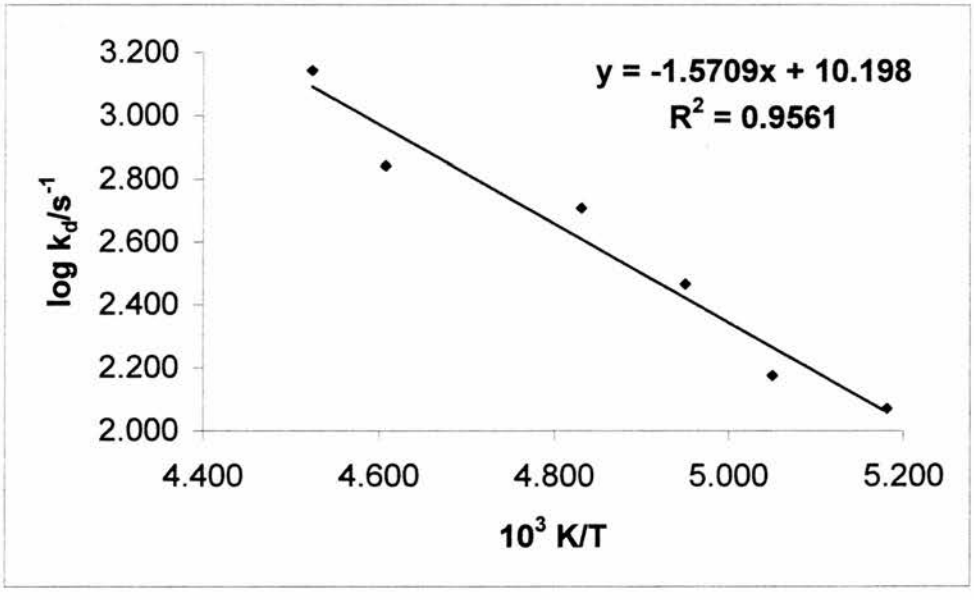


Figure 41

Released Radical	10^{-3} k_d / s^{-1} (300 K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
Propargyl$^\bullet$	90.14	10.20	7.19

Table 30

The rate of dissociation at 300 K appears suspiciously high for the propargyl acid. It was originally predicted that the k_d value for the propargyl analogue would be significantly lower than that of its benzyl predecessor. Conversely, this data suggests that the value of k_d is much higher. In order to confirm this fact, a new set of experiments were carried out

It became apparent that a sample containing the propargyl acid, DTBP and *t*-butylbenzene could be used to good effect, replacing cyclopropane as the major solvent. This brought about several advantages, namely a much simpler sample preparation and the ability to prepare a stock solution so that all samples held exactly the same concentration of the propargyl acid. This would maintain equality throughout the experiments and provide more accurate results.

In order to acquire as many points possible for the Arrhenius plot, we decided to record the entire width of the propargyl radical spectrum (60 G). This enabled us to integrate several groups of peaks for each transient radical and therefore supplied two sets of results for every spectrum acquired. This should again improve accuracy when calculating the energy of activation and k_d at 300 K.

The stock solution was prepared, providing ten samples of equal volume and acid concentration. Each sample was degassed thoroughly and used only once to record EPR spectra at a range of temperatures (Figure 42). The EPR spectra were analysed and double integrated using the software available, to give relative values for peak intensity. These values were converted into radical concentration data for the two transient radicals present in the EPR sample, to give values of k_d for the propargyl acid **66** at each temperature (Table 31).

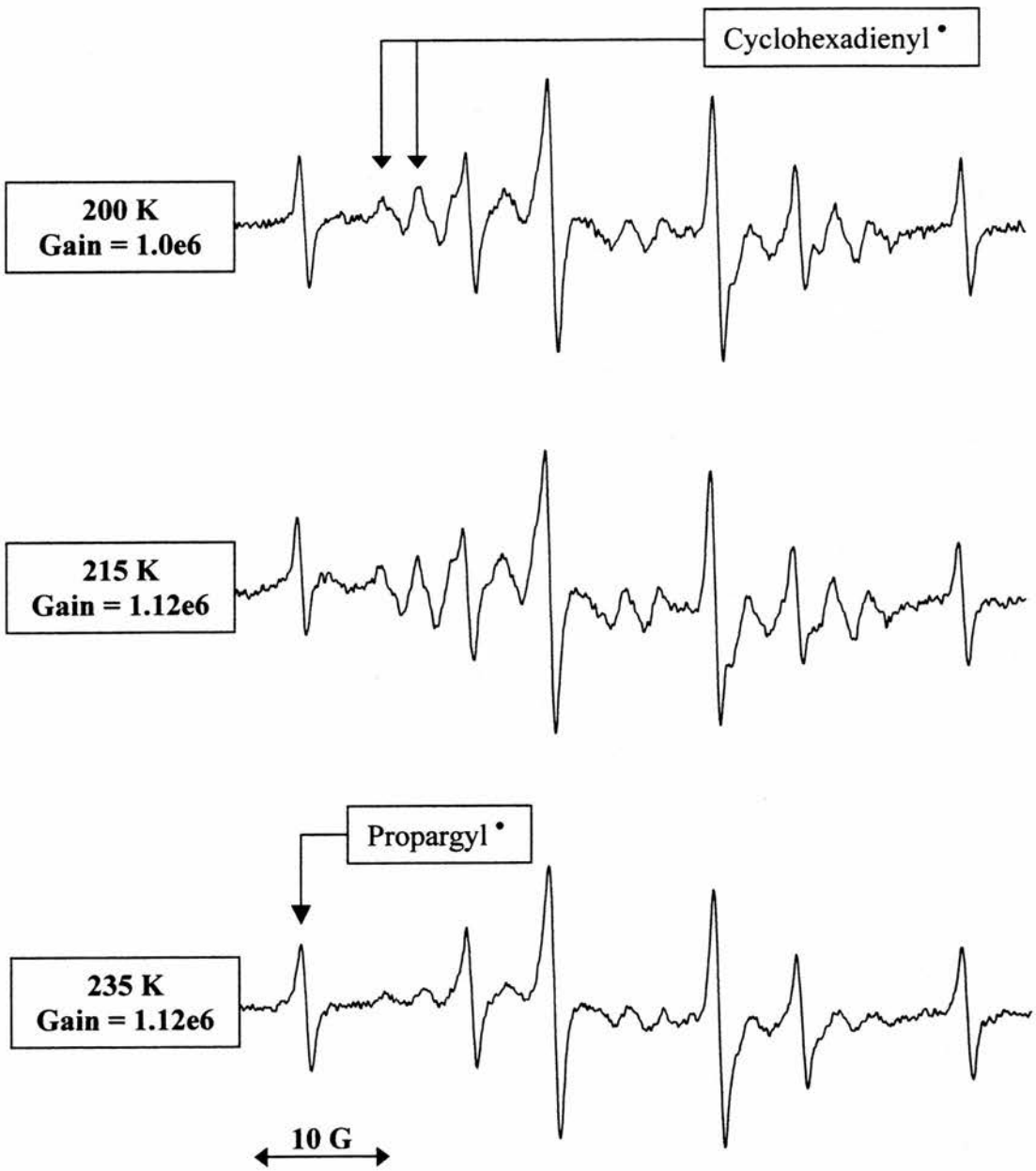

Cyclohexadienyl •
200 K
Gain = 1.0e6
215 K
Gain = 1.12e6
Propargyl •
235 K
Gain = 1.12e6
10 G

Figure 42

T/K	[68]	[67]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ *t*-BuPh	k_d
236	3.354E-08	9.062E-09	-6.802	4.237	8.922	1.32E+02
231	1.457E-08	7.447E-09	-7.366	4.330	8.834	2.94E+01
226	1.435E-08	1.275E-08	-7.516	4.428	8.738	1.67E+01
221	1.338E-08	2.013E-08	-7.652	4.530	8.635	9.61E+00
216	1.028E-08	2.488E-08	-7.838	4.637	8.524	4.85E+00
216	1.196E-08	1.739E-08	-7.695	4.637	8.524	6.74E+00
211	1.419E-08	2.451E-08	-7.650	4.750	8.402	5.66E+00
205	1.060E-08	2.045E-08	-7.794	4.867	8.271	3.00E+00
200	9.302E-09	2.540E-08	-7.896	4.991	8.128	1.71E+00
195	7.274E-09	2.356E-08	-8.021	5.121	7.972	8.92E-01
236	4.377E-08	1.927E-08	-6.844	4.237	8.922	1.20E+02
231	1.865E-08	7.319E-09	-7.179	4.330	8.834	4.51E+01
226	1.877E-08	1.256E-08	-7.329	4.428	8.738	2.56E+01
221	1.568E-08	1.369E-08	-7.473	4.530	8.635	1.45E+01
216	1.178E-08	2.512E-08	-7.762	4.637	8.524	5.78E+00
216	1.364E-08	1.295E-08	-7.553	4.637	8.524	9.35E+00
211	1.576E-08	2.535E-08	-7.593	4.750	8.402	6.46E+00
205	1.068E-08	2.513E-08	-7.818	4.867	8.271	2.84E+00
200	8.773E-09	2.924E-08	-7.943	4.991	8.128	1.53E+00
195	6.406E-09	2.492E-08	-8.094	5.121	7.972	7.55E-01

Table 31

All values of log k_d were plotted against $10^3/T$ to form the Arrhenius plot (Figure 43). It is clear to see that all points fit rather well to the best fit line, confirming a linear relationship, and the equation of this line was used to calculate a more accurate value for k_d at 300 k, E_d and A_d (Table 32).

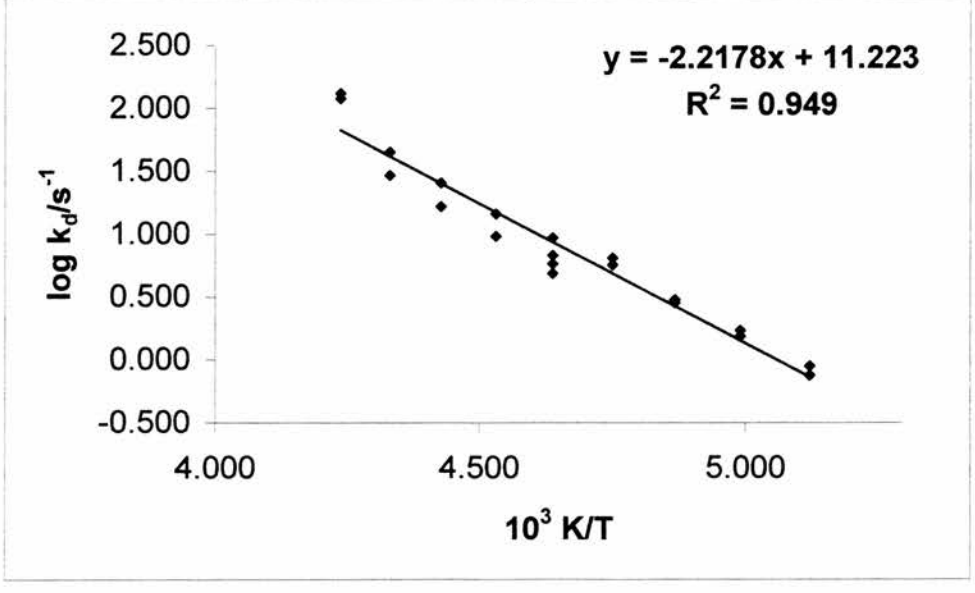


Figure 43

Released Radical	10^{-3} k_d / s^{-1} (300 K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
Propargyl$^{\bullet}$	6.619	11.22	10.15

Table 32

This new value for k_d at 300 K fits much better with that expected for a radical with only limited resonance stabilisation. The propargyl acid has a higher rate of dissociation than when releasing primary and secondary radicals. However, the steric bulk found in a tertiary radical provides a higher value of k_d and make it relatively more stable in solution. The larger resonance stabilisation available to the allyl and benzyl radicals give these compounds a much larger rate of dissociation compared with that of the propargyl analogue.

The inconsistency observed between the two EPR experiments, using cyclopropane or *t*-butylbenzene as co-solvents, was attributed to changes in solubility of the acid in these two solvents. The propargyl acid was sparingly soluble in DTBP, although it did appear to dissolve in cyclopropane. However, it was postulated that at the low temperatures required to acquire the kinetic spectrum, some of the acid may have fallen out of solution and altered the sample concentration. This could have a direct effect on the steady state calculation and could give abnormally high values of k_d. It has previously been demonstrated that *t*-butyl benzene acts as a very good solvent for the cyclohexadienyl acids and has displayed no solubility limits in any of the previous experiments. This evidence, coupled with the ability to prepare a stock solution of the EPR samples, suggest that the latter data, using *t*-butyl benzene as the co-solvent, is more accurate.

EPR study of 1-propargylcyclohexa-2,5-diene-1-carboxylic acid 66 using a different sample concentration

In order to confirm that k_H was negligible for the propargyl acid, a second set of spectra were acquired using a sample containing a different concentration of the propargyl acid. If k_H was significant, any change in acid concentration should have a

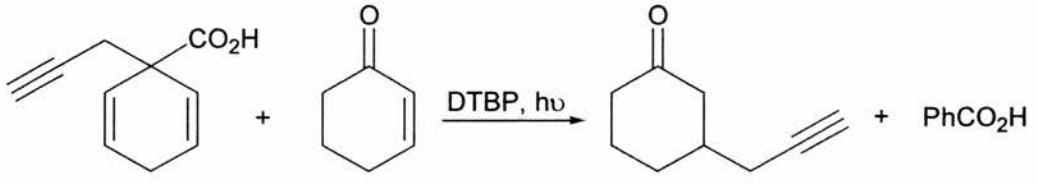
direct effect on the ratio of transient radicals observed by EPR and their relative values of k_d.

A new sample, containing 1 mg of the propargyl acid, was prepared and placed into the EPR resonator, which was held at 221 K. The sample was photolysed and its EPR spectrum recorded using identical parameters to those employed in the previous set of experiments. The peaks due to both the delocalised cyclohexadienyl radical and the released propargyl radical were double integrated and compared with the values gained using the 10 mg sample. No significant difference in k_d values could be observed, therefore k_H was deemed to be negligible.

Product analysis of the propargyl acid 66 after photolysis

The propargyl acid was photolysed, in the presence of DTBP, at 300 K for a period of two hours in order to ensure the complete rearrangement of the radical precursor. All benzoic acid in the resultant mixture was converted into the methyl benzoate, using the previously discussed technique, before the sample was analysed by GLC. Comparison of the acquired GLC trace with that of authentic samples of methyl benzoate and propargylbenzene, confirmed that none of the alkyl benzene was formed and therefore dissociation *via* the k^2_d pathway was insignificant.

Photolytically initiated radical addition of 1-propargylcyclohexa-2,5-diene-1-carboxylic acid to cyclohexenone.



66 **69** **70**, 45%

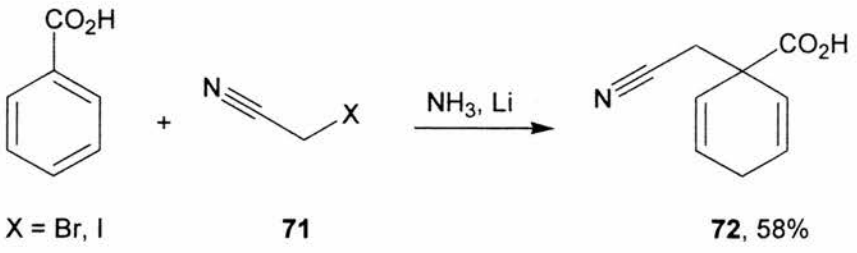
Scheme 37

The addition of the propargyl radical **66** to cyclohexenone **69** was carried out on a small scale in order to confirm the ability of these radical precursors to take part in free radical additions (Scheme 37). A small amount of the propargyl acid and cyclohexenone was placed into a quartz EPR tube and dissolved in excess DTBP. A

high-powered UV lamp was used to photolytically initiate the radical reaction, over a five hour period, before the sample was analysed by GC/MS. Inspection of the GC/MS trace revealed many compounds in the product mixture which were derived from impurities within the solvent and the varied addition products of DTBP. However, two major peaks could be identified from their mass spectra as benzoic acid and the desired product 3-prop-2-ynyl-cyclohexanone **70**. Calculation of the experimental yield was not possible using NMR spectroscopy due to the many impurities in the product mixture. Therefore a GC/MS yield was measured showing this small scale reaction to be 45% efficient.

1-Cyanomethylcyclohexa-2,5-diene-1-carboxylic acid 72

Synthesis of 1-cyanomethylcyclohexa-2,5-diene-1-carboxylic acid 72



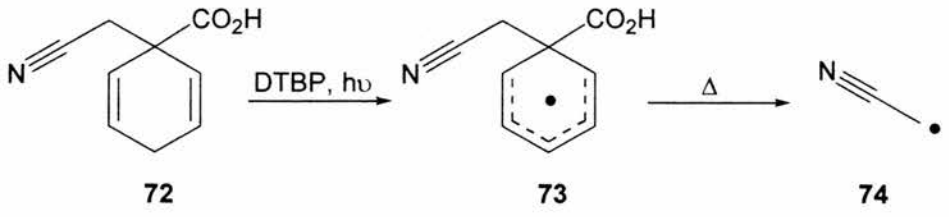
X = Br, I **71** **72**, 58%

Scheme 38

The synthesis of the cyanomethyl acid **72** was reasonably straightforward. Initially a small scale Birch reduction/alkylation was performed using the general procedure outlined previously, quenching the reactive Birch complex with a mixture of iodoacetonitrile **71** in dry ether (Scheme 38). The addition of the halide was rather violent, even when diluted in a significant volume of dry ether, however, the deep blue colour of the Birch mixture faded to leave a dark brown solution after complete addition. The brown precipitate remaining after all NH_3 had evaporated was dissolved in an ether/water mixture and washed as previously described to leave a dark brown oil. Further washing with thiosulfate solution and decolourising the remaining organic layer with charcoal, before removing the solvent under vacuum, furnished a pale yellow powder, which was recrystallised from pentane to give the title compound as white plates in a yield of 58%.

In order to gather more of the pure cyanomethyl acid, the Birch reduction/alkylation was repeated on a larger scale, quenching with bromoacetonitrile. On this occasion, addition of the halide was less violent and produced a large quantity of an impure black oil after the initial aqueous wash. A small portion of this oil was decolourised using charcoal and purified by microdistillation, under high vacuum, to furnish a white solid, identified as the 1-cyanomethylcyclohexa-2,5-diene-1-carboxylic acid **72**.

EPR study of 1-cyanomethylcyclohexa-2,5-diene-1-carboxylic acid 72



72 **73** **74**

Scheme 39

It was predicted that the cyanomethyl acid would have similar EPR properties to its propargyl analogue. Therefore initial EPR spectra were recorded using a mixture of DTBP and *t*-butylbenzene as the solvent. As predicted, the recorded spectrum at 245 K was identified as the delocalised cyclohexadienyl radical **73**, although many of the peaks had slight shoulders on them as a result of unresolved structure, derived from long-range hyperfine splitting from a methylene hydrogen (Figure 44). Manipulation of the EPR parameters failed to resolve this splitting and therefore measurements could not be recorded.

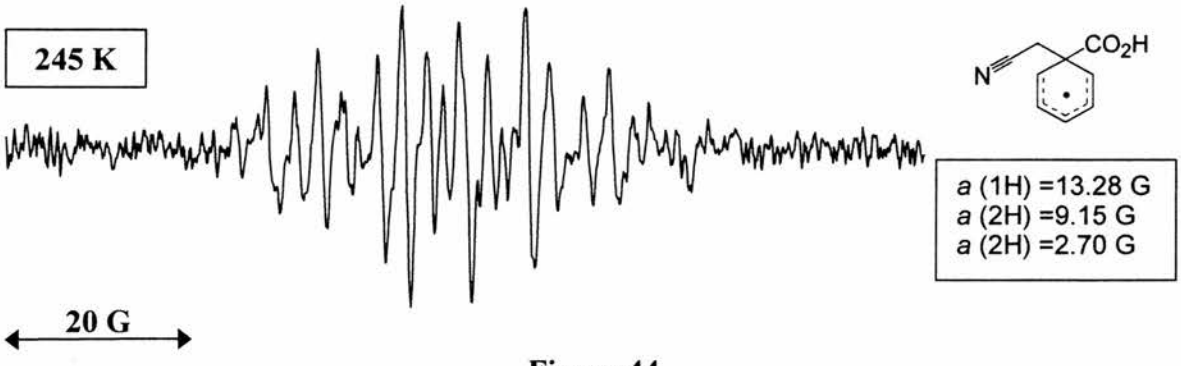


Figure 44

In order to encourage the cleavage of the carbon-carbon bond, to release the cyanomethyl radical **74**, the EPR cavity was heated to 270 K. At this higher temperature, very small peaks were observed outside of the original spectra, but further heating to 300 K failed to increase the size of these peaks and the observed spectrum could not be characterised as that of the released alkyl radical.

The issue of solubility was raised once again; the cyanomethyl carboxylic acid was not easily dissolved in the DTBP/*t*-butylbenzene mixture and this suggested that the acid fell out of solution when cooled in the EPR cavity. The inability to see the

cyanomethyl radical **74** also suggested that the released alkyl radical was very sparingly soluble in the sample solvent. A new sample was prepared using 10 mg of the cyanomethyl acid, 240 μl of DTBP and 10 μl of MeOH to increase solubility. It was encouraging to see that the cyclohexadienyl acid was readily dissolved in this new solvent and subsequent EPR experiments in the temperature range of 245 K – 290 K confirmed the appearance of a new radical species as the temperature of the cavity was increased (Figure 45). Literature values for the hyperfine splittings of a cyanomethyl radical, in conjunction with EPR simulation confirmed this new radical species to be that of the released cyanomethyl radical **74**.

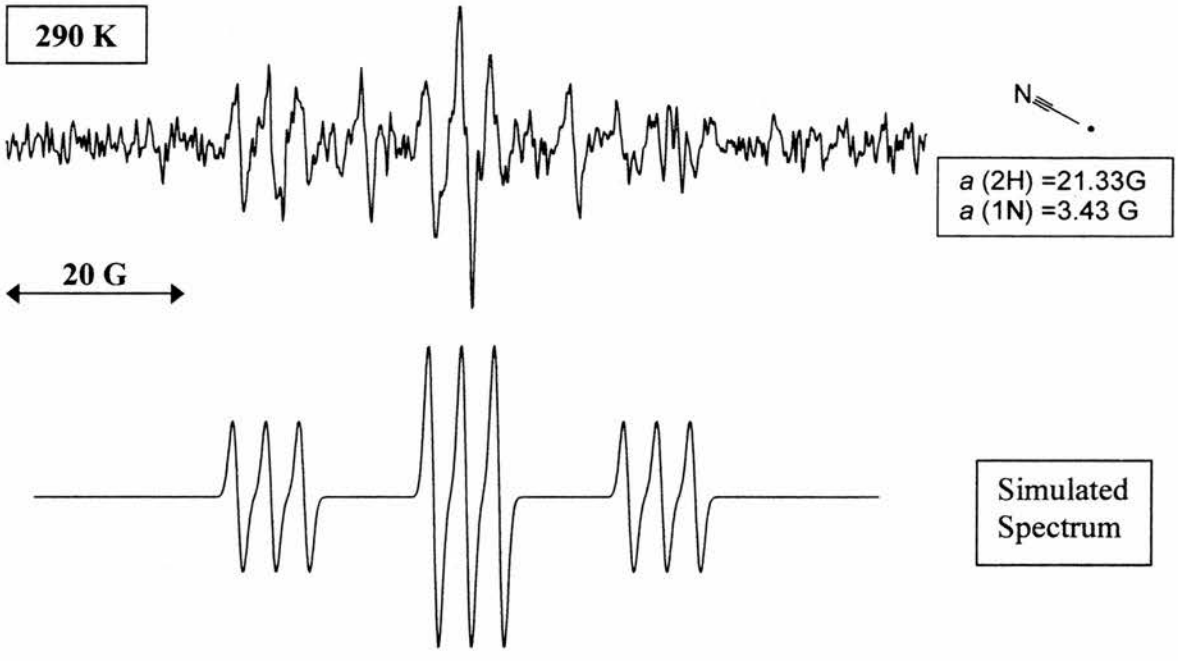


Figure 45

A stock solution of the cyanomethyl acid in the DTBP/MeOH solution was prepared, providing ten equal samples containing approximately 8 mg of the cyclohexadienyl acid. Each sample was analysed by EPR, in the presence of UV, at a different temperature in the range of 246 K – 282 K, in order to map the rearrangement of the delocalised cyclohexadienyl radical into the cyanomethyl radical and benzoic acid. To help improve accuracy and reduce sample degradation, we focused on a small portion of the spectrum, with a scan width of 25 G, where unhindered peaks from both transient radicals could be observed (Figure 46). This allowed us to reduce the

background noise within the spectrum without dramatically increasing the acquisition time.

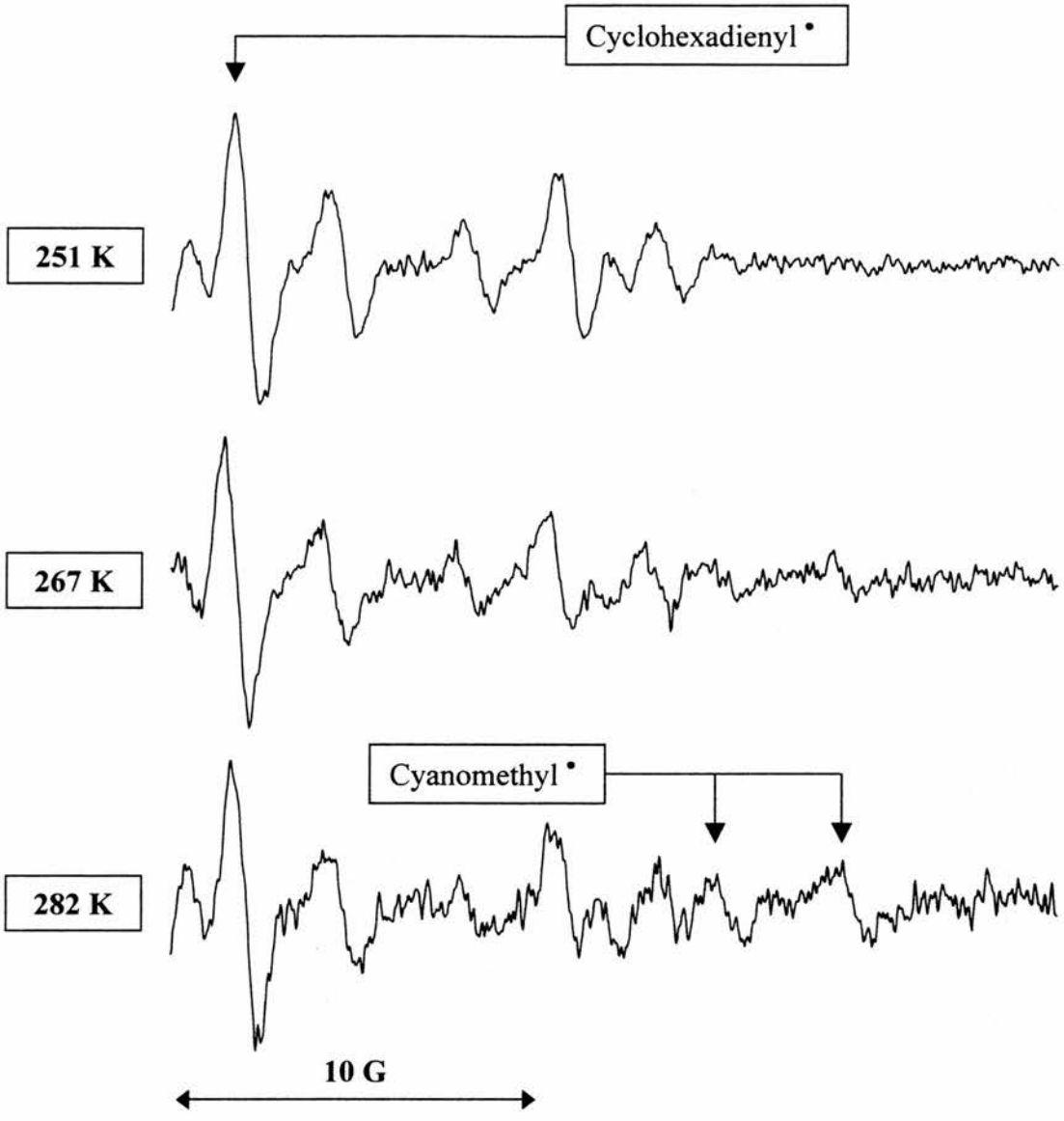


Figure 46

All spectra were analysed and double integrated, using the previously described technique, to give relative peak areas for each of the transient radicals. The peak areas were compared with those found from a known concentration of DPPH, to give the relative concentrations of each radical. These were placed into the derived Steady State equation to give the values of k_d at each temperature for 1-cyanomethylcyclohexa-2,5-diene-1-carboxylic acid **72** (Table 33).

T/K	[74]	[73]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ *t*-BuPh	k_d
246	9.022E-09	2.254E-07	-8.028	4.062	9.284	1.80E+01
251	9.082E-09	1.734E-07	-8.020	3.979	9.329	2.04E+01
256	1.864E-08	1.868E-07	-7.688	3.900	9.372	4.83E+01
261	2.143E-08	1.814E-07	-7.620	3.824	9.414	6.21E+01
267	2.247E-08	1.389E-07	-7.583	3.751	9.453	7.42E+01
272	2.699E-08	1.123E-07	-7.475	3.681	9.492	1.04E+02
277	3.084E-08	1.179E-07	-7.410	3.613	9.529	1.31E+02
282	4.749E-08	8.308E-08	-7.127	3.548	9.564	2.74E+02

Table 33

The Arrhenius plot of log k_d against $10^3/T$ was plotted, in order to confirm the linear relationship between the rate of dissociation and temperature (Figure 47). The equation for the line of best fit was then used, in conjunction with the Arrhenius equation, to give values for k_d at 300 K, activation energy and the pre-exponential factor (Table 34).

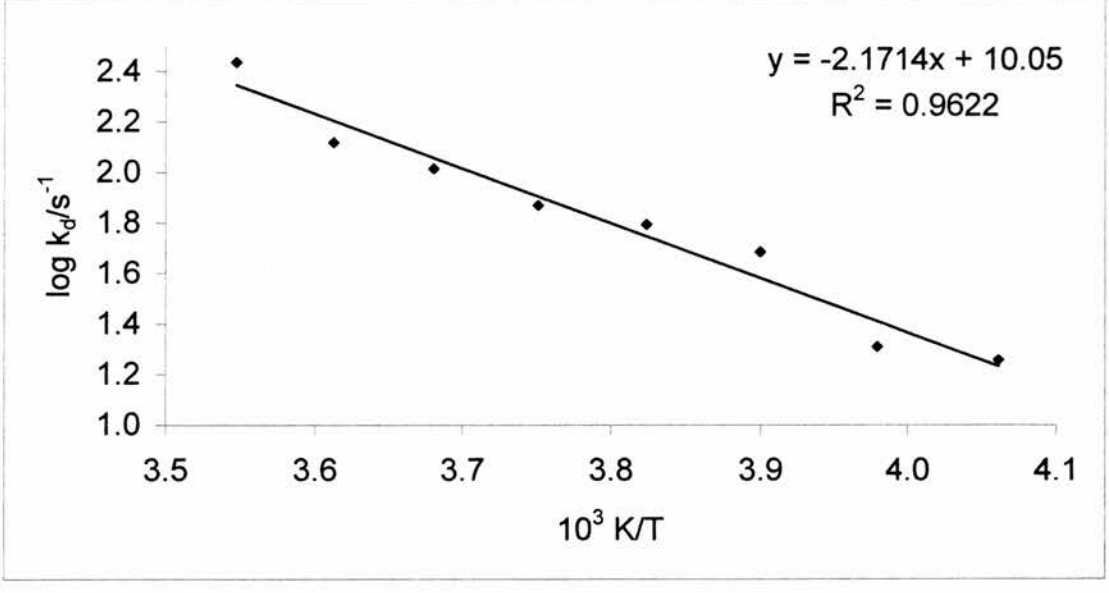


Figure 47

Released Radical	10^{-3} k_d / s^{-1} (300 K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
Cyanomethyl$^\bullet$	0.635	10.05	9.94

Table 34

The value of k_d at 300 K is an order of magnitude lower than the value observed for the release of a propargyl radical. This suggests that the relative amount of stabilisation offered by the nitrile group is significantly less than that provided by a conventional alkyne. This scenario was expected, as it is common knowledge that the p-orbitals of nitrogen do not interact as efficiently with the π orbitals of the triple bond, therefore reducing the degree of resonance stabilisation. This reduced stability is further demonstrated by an observed increase in hfs between the radical and the α-CH_2 group. As the CH_2 group acquires more methylene character, the observed hfs value moves closer to 23 G. From our experimental results, $a(2H)_{propargyl}$ = 18.98 G and $a(2H)_{cyanomethyl}$ = 21.33 G. The value of k_d for the release of a cyanomethyl radical remains higher than that associated with the release of an unstabilised primary radical. This confirms that the nitrile function does offer a degree of resonance stabilisation.

EPR study of 1-cyanomethylcyclohexa-2,5-diene-1-carboxylic acid using different sample concentrations

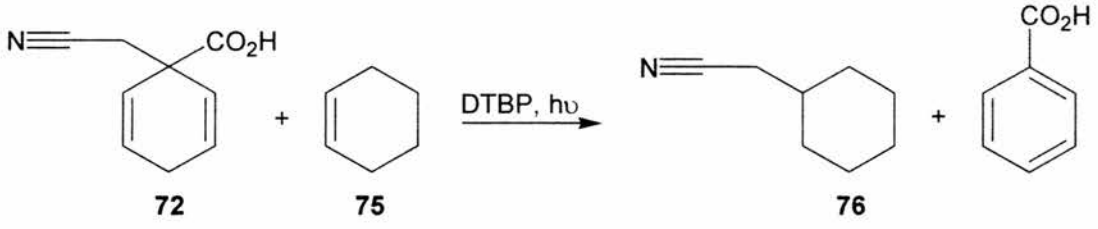
A stock solution of the cyanomethyl derivative was prepared, using DTBP/MeOH as the solvent, in order to provide ten equal samples containing 4 mg of the cyanomethyl acid, 50 % less acid than those in the previous experiment. The samples were analysed by EPR before their double integrals were calculated and compared to those found in the previous set of experiments. There was no observable change in the values of k_d at each temperature, or in the ratio of unrearranged:rearranged radical. This confirmed that the value of k_H was too small to measure using the EPR technique.

Product analysis of the cyanomethyl acid 72 after photolysis

The cyanomethyl acid was photolysed, in the presence of DTBP, at 300 K for a period of two hours in order to ensure the complete rearrangement of the radical precursor. All benzoic acid in the resultant mixture was converted into the methyl benzoate, using the previously discussed technique, before the sample was analysed by GLC. Comparison of the acquired GLC trace with that of authentic samples of methyl

benzoate and benzoacetonitrile, confirmed that none of the alkyl benzene was formed and therefore dissociation *via* the k^2_d pathway was insignificant.

Photolytically initiated radical addition of 1-cyanomethylcyclohexa-2,5-diene-1-carboxylic acid to cyclohexene.

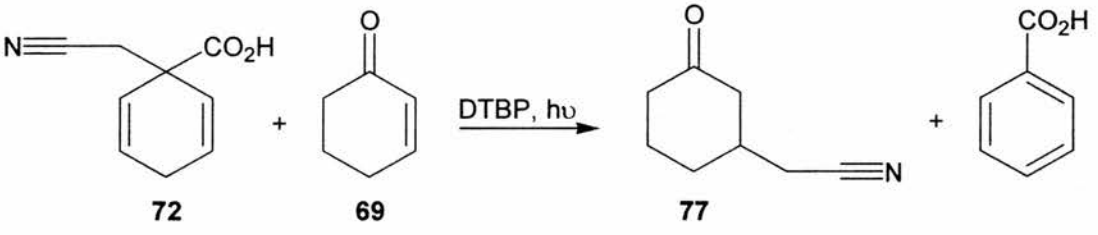


72 **75** **76**

Scheme 40

1-Cyanomethylcyclohexa-2,5-diene-1-carboxylic acid was dissolved in cyclohexene **75** and photolysed, over a period of five hours, in the presence of DTBP (Scheme 40). Analysis of the resultant mixture by GC/MS revealed an assorted mixture of addition products from the interaction of the *t*-butoxyl radical with cyclohexene and the [2+2] radical cycloaddition of cyclohexene. However, two minor peaks located on the trace were identified as benzoic acid and that of the desired adduct **76**. Unfortunately, it was not possible to measure a yield of the desired product by either NMR spectroscopy or GC/MS due to the large amounts of background noise.

Photolytically initiated radical addition of 1-cyanomethylcyclohexa-2,5-diene-1-carboxylic acid to cyclohexenone.



72 **69** **77**

Scheme 41

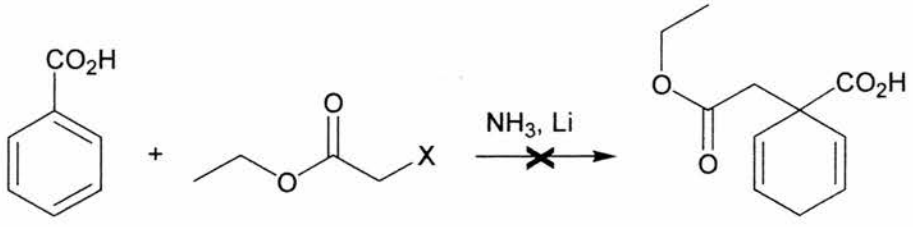
In an attempt to encourage radical addition of the cyanomethyl radical to an alkene, we photolysed a mixture of the cyanomethyl acid **72** in the presence of cyclohexenone **69** (Scheme 41). Cyclohexenone contains a double bond which is relatively more electron deficient than the previously evaluated cyclohexene, therefore it should have a greater affinity for the cyanomethyl radical. Analysis of the resultant product

mixture by GC/MS revealed a large number of diverse products from the interaction of DTBP and its *t*-butoxyl radicals with the solvent, however, only one compound contained nitrogen, and this compound was identified as (2-oxo-cyclohexyl)-acetonitrile **77**.

NMR and GC/MS yield measurements were not possible for this radical addition due to the large number of impurities. However, there was no evidence of the unreacted cyanomethyl acid in the GC/MS and the peak sizes for benzoic acid and adduct **77** were very similar. This suggests that the radical reaction went to completion, and furnished equivalent amounts of benzoic acid and (2-oxo-cyclohexyl)-acetonitrile **77** in high yields.

1-Ethoxycarbonylmethyl-cyclohexa-2,5-diene-1-carboxylic acid 79

Attempted synthesis of 1-ethoxycarbonylmethyl-cyclohexa-2,5-diene-1-carboxylic acid 79



X = Br, I **78** **79**

Scheme 42

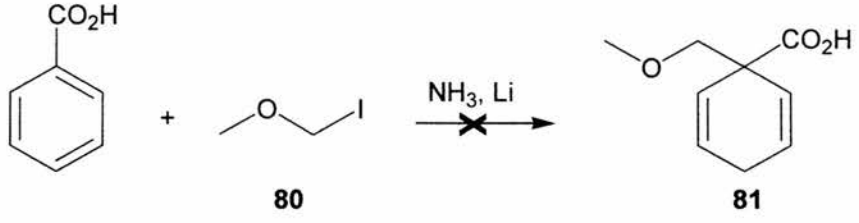
The release of radicals containing differing functionalities, and the measurement of their associated rates of dissociation, would be of great use for synthetic chemists. It would deliver new methods for generating novel radicals and demonstrate the capacity of these cyclohexadienyl compounds to take place in a variety of diverse chemical reactions.

The formation of a cyclohexadienyl acid containing ester functionality was initially attempted. The rearrangement of the cyclohexadienyl radical would potentially furnish a primary radical, which could be stabilised by resonance onto the carbonyl group. Regrettably, all efforts to form the ethoxycarbonylmethyl acid **79**, using the Birch reduction/alkylation procedure failed (Scheme 42). The Birch reaction was attempted on several occasions, quenching with both ethyl bromoacetate and ethyl iodoacetate **78**. On each occasion, the addition of the halide decolourised the deep blue Birch mixture to give a pale yellow solution with a brown precipitate. Isolation of the precipitate and subsequent washing and concentration of the pale solvent yielded only unreacted benzoic acid and 1,4-dihydrobenzoic acid.

It was thought that the carbonyl group of the halide interacted more readily with the reactive Birch complex and quenched the reaction before the halide had the opportunity to form its carbon-carbon bond.

1-Methoxymethylcyclohexa-2,5-diene-1-carboxylic acid 81

Attempted synthesis of 1-methoxymethylcyclohexa-2,5-diene-1-carboxylic acid 81



80 **81**

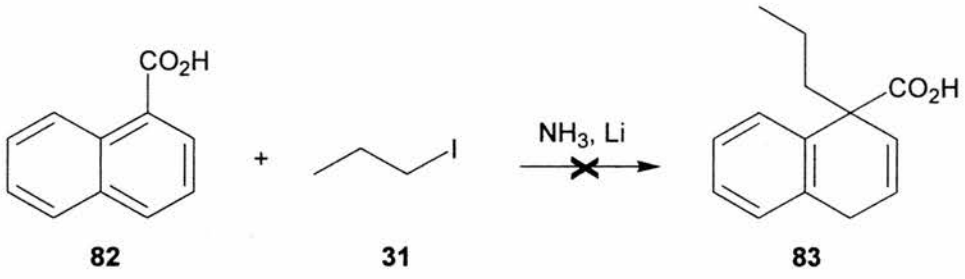
Scheme 43

The recent failure to synthesise the ethoxycarbonylmethyl acid derivative *via* the Birch reduction/alkylation methodology, led us to investigate the formation of a similar cyclohexadienyl acid which had a reduced amount of functionality in the 1-substituent (Scheme 43).

The ether side chain does not possess a carbonyl group, it was therefore anticipated that quenching of the reactive Birch solution with a halogenated ether would furnish the desired cyclohexadienyl acid. However, all attempts to form the 1-methoxymethylcyclohexa-2,5-diene-1-carboxylic acid **81** by quenching the Birch mixture with 1-iodomethylmethyl ether **80** failed, yielding only unreacted benzoic acid.

1-*n*-Propyl-1,4-dihydronaphthalene-1-carboxylic acid 83

Attempted synthesis of 1-*n*-propyl-1,4-dihydronaphthalene-1-carboxylic acid 83[22]



82 **31** **83**

Scheme 44

The preparation of a dihydronaphthalene carboxylic acid would help increase our understanding of cyclohexadienyl derivatives as radical precursors. It was postulated that the dihydronaphthalenes would exhibit subtle differences in their dissociation rates when compared with their equivalent cyclohexadienes, therefore providing a novel option in the design of synthetic radical reactions.

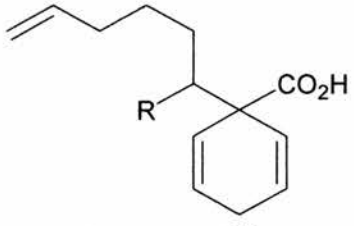
Impure α-naphthoic acid was recrystallised from rectified spirit (ethanol with 5% water) in order to furnish needle-like crystals of the pure acid precursor **82**, which was used directly in a small scale Birch reduction/alkylation, quenching with 1-iodopropane **31** (Scheme 44). The resultant solution was left overnight, to allow all NH_4 to evaporate, before the product mixture was washed with both acid and a saturated thiosulfate solution. Column chromatography of the impure product, eluting with 5% ethyl acetate in light petroleum, isolated several compounds which were identified by NMR analysis as 1,4-dihydronaphthoic acid and a compound derived from the multiple addition of the 1-iodopropane to naphthoic acid. There was no evidence of the desired adduct **83**.

It was clear that additional work was required in this area; therefore this branch of study was passed on to a different research student as our attention was drawn to developing the 'ideal' cyclohexadienyl acid. The multiple addition compound detected in the end product suggests that the desired dihydronaphthoic acid can be synthesised if the Birch reduction/alkylation is controlled.

1-(1-Propyl-hex-5-enyl)-cyclohexa-2,5-diene-1-carboxylic acid 91

All previously calculated documentation for the 1-alkylcyclohex-2,5-diene-1-carboxylic acids was analysed and evaluated in order to establish several mechanistic conclusions, which are discussed to a greater degree in the conclusions section of this thesis (Chapter 2, p. 191 – 192). It was established that in order to gain a high experimental yield when using a cyclohexadienyl acid as the radical precursor, k_d and k_H needed to be high. This would encourage the efficient release of the desired alkyl radical, and maintain the chain reaction.

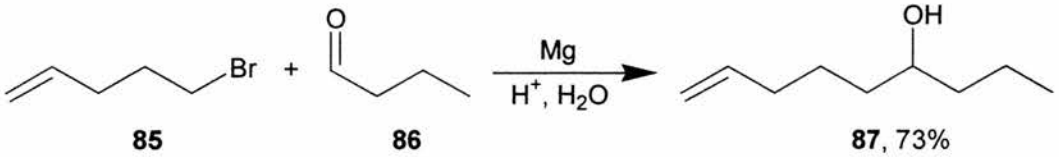
These conclusions led to the design of an 'ideal' cyclohexadienyl model **84**, which readily fragments, after radical initiation, to furnish a secondary radical. This radical should rapidly cyclise in order to form a primary radical intermediate, which abstracts hydrogen rapidly from the starting acid to maintain the radical cycle.



84

In order to confirm our logic, we attempted to synthesise an ideal cyclohexadienyl acid, so that it could be tested for its radical donating abilities.

Preparation of non-1-en-6-ol 87



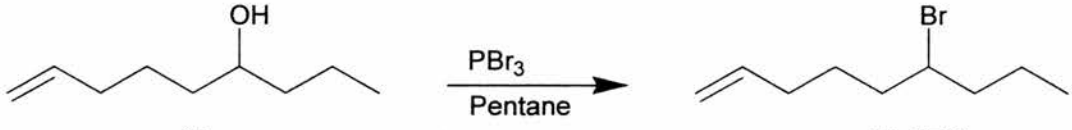
85 **86** **87**, 73%

Scheme 45

In order to synthesise the desired 1(1-propyl-hex-5-enyl)-cyclohexadienyl acid, it was necessary to prepare the alkyl halide that would be used to quench the Birch reaction. The precursor to this halide was non-1-en-6-ol **87**.

The desired alcohol was initially prepared on a small scale using a general Grignard procedure (Scheme 45). 5-Bromopentene **85** was added to a suspension of magnesium turnings in dry ether in order to generate the Grignard reagent. The reactive complex was cooled using an ice bath, before addition of the distilled butyraldehyde **86** in order to furnish the desired alcohol **87**. The impure product was acidified and washed before Kugelrohr distillation delivered the pure non-1-en-6-ol **87** as a colourless oil with a distinctive, sweet smell in a yield of 69%. This procedure was subsequently repeated on a larger scale to give **87** in an increased yield of 73%.

Preparation of 6-bromo-non-1-ene 88



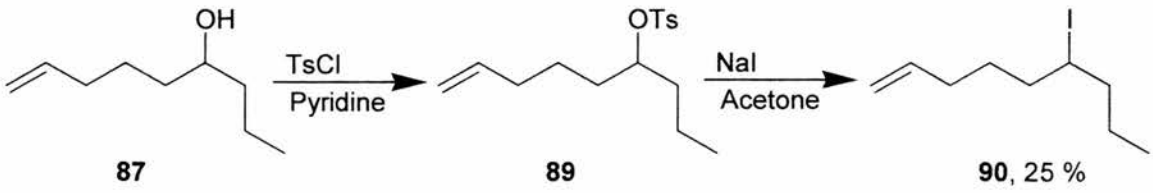
87 **88**, 57 %

Scheme 46

In order to add this manufactured side chain to benzoic acid, in the Birch reaction, the alcohol functionality had to be converted into a halide. The bromination of secondary alcohols is commonly carried out using HBr, however, the presence of an alkene functionality in the starting alcohol prevents this method from being used. An alternative, milder bromination using phosphorus tribromide is well documented and often progresses in high yields for primary alcohols, though a significant reduction in yield is observed for secondary compounds (Scheme 46).

Non-1-en-6-ol and pyridine were dissolved in a small amount of dry pentane and cooled to –10 °C using an acetone/dry ice bath. Phosphorus tribromide was slowly added to the solution before the cooling bath was removed. The resultant solution was allowed to stir at room temperature for 24 h before a conventional work-up yielded a mixture of the products. Kugelrohr distillation of the product mixture furnished 6-bromo-non-1-ene **88** in varying yields of between 35 – 57%. Several experimental modifications were made in an attempt to improve the yield for this reaction and encourage secondary bromination. Unfortunately the yields remained low and unpredictable.

Attempted preparation of 6-iodo-non-1-ene 90

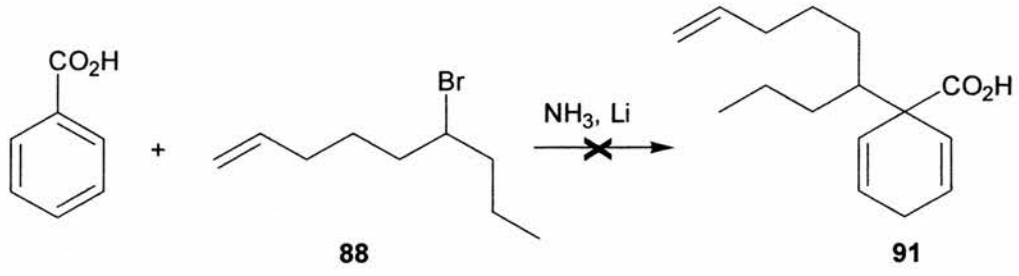


Scheme 47

The erratic yields encountered when brominating, using phosphorus tribromide, encouraged us to try different methods of halogenation. Alcohol **87** was converted into the corresponding tosylate **89** by cooling the alcohol, dissolved in excess pyridine, and adding *p*-toluenesulfonyl chloride (Scheme 47). The subsequent mixture was stirred overnight before quenching with water to deliver a mixture of unreacted alcohol and the tosylate **89**.

The crude product was dissolved in acetone before NaI was added. The resultant solution was refluxed for 20 h and washed with both thiosulfate and brine to give a mixture of the unreacted starting material **87** and the desired 6-iodo-non-1-ene **90** in roughly equal amounts. The overall yield for the production of the halide was 25%; this is significantly lower than our average yield for bromination. We therefore decided to persevere with bromination of the alcohol in order to generate the large amounts of alkyl halide necessary for the Birch reduction/alkylation.

Attempted synthesis of 1-(1-propyl-hex-5-enyl)-cyclohexa-2,5-diene-1-carboxylic acid 91

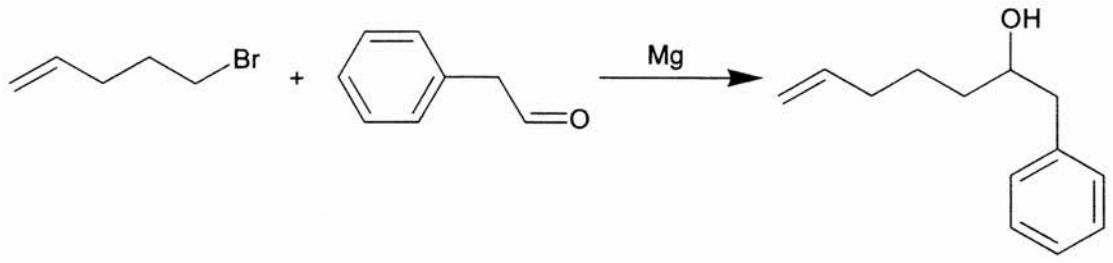


Scheme 48

A large quantity of the brominated alkene was prepared and purified by Kugelrohr distillation, in order to supply the necessary quantities for the Birch reduction/alkylation. 6-Bromo-non-1-ene **88** was dissolved in a small quantity of dry ether and slowly added to the reactive Birch solution containing benzoic acid (Scheme 48). Addition of **88** caused the mixture to decolourise and furnished a white solid after solvent evaporation. Analysis of this solid by NMR and GC/MS, after a basic aqueous work-up, allowed us to identify both unreacted benzoic acid and 1,4-dihydrobenzoic acid as the major reaction products. There was no evidence for the formation of the desired 1-(1-propyl-hex-5-enyl)-cyclohexa-2,5-diene-1-carboxylic acid **91**.

1-(1-Benzyl-hex-5-enyl)-cyclohexa-2,5-diene-1-carboxylic acid 95

Preparation of 1-phenyl-hept-6-en-2-ol 93

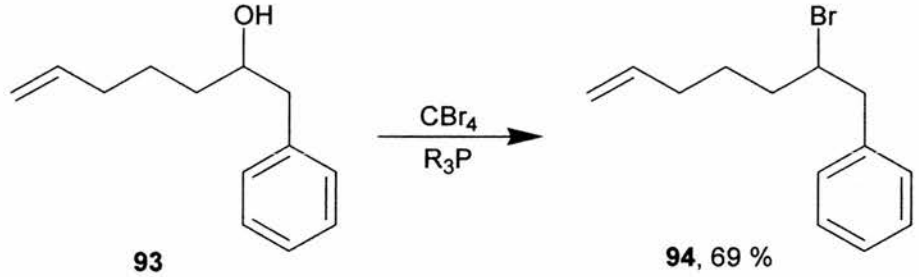


85 **92** **93**, 82 %

Scheme 49

The Grignard reaction between 5-bromopentene **85** and distilled phenyl acetaldehyde **92** was carried out in a similar manner to that described previously for non-1-en-6-ol **87** (Scheme 49). The Grignard reagent formed readily and addition of the phenyl acetaldehyde progressed efficiently to furnish a relatively pure product in a good yield of 92%. Purification of this crude product, *via* vacuum distillation, gave the pure 1-phenyl-hept-6-en-2-ol **93** as a colourless oil in an overall yield of 82%.

Preparation of 2-bromo-hept-6-enyl-benzene 94[23]



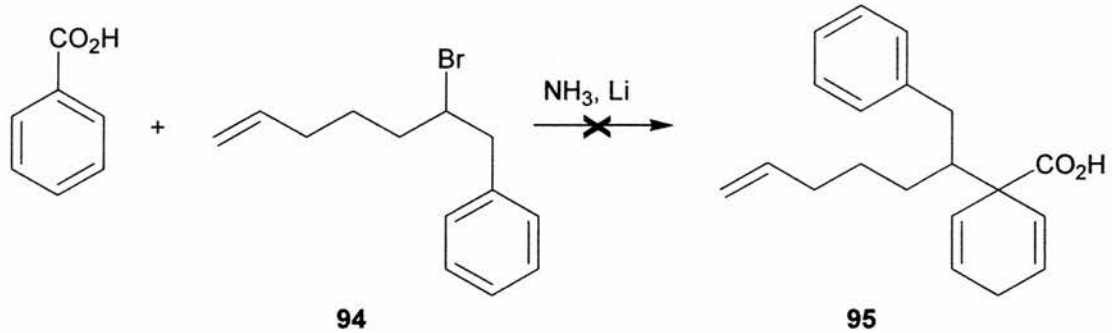
93 **94**, 69 %

Scheme 50

Initial attempts to brominate the secondary alcohol of **93** using the previously described phosphorus tribromide method proved relatively unsuccessful. On each occasion, the yield of brominated alkene **94** was below 40%. A literature search provided an alternative method for the bromination of a secondary alcohol using carbon tetrabromide (CBr_4) and tri-*n*-octylphosphine (Scheme 50).[23] The alcohol was added to a small amount of dry ether, containing CBr_4, and cooled using an ice bath. Tri-*n*-octylphosphine was added slowly to the mixture, which resulted in the

formation of bromide **94** as a yellow oil. NMR spectroscopic analysis of the crude product identified several impurities, which were removed by vacuum distillation in order to isolate the desired 2-bromo-hept-6-enyl-benzene **94** in a yield of 69%. Unfortunately, small impurities remained in the product after several distillation attempts, although these were considered to have no detrimental effect on the ensuing Birch reaction.

Attempted synthesis of 1-(1-benzyl-hex-5-enyl)-cyclohexa-2,5-diene-1-carboxylic acid 95



94 **95**

Scheme 51

Addition of the halogenated alkene **94** to benzoic acid was attempted using the Birch reduction/alkylation technique described previously (Scheme 51). A three-fold excess of the quenching halide was recommended in order to furnish the optimum yield of cyclohexadienyl acid. However, due to difficulties in bromination and isolation of the precursor, we decided to attempt the Birch reaction using a reduced amount of benzoic acid (2.5 g) and a two-fold excess of the alkene.

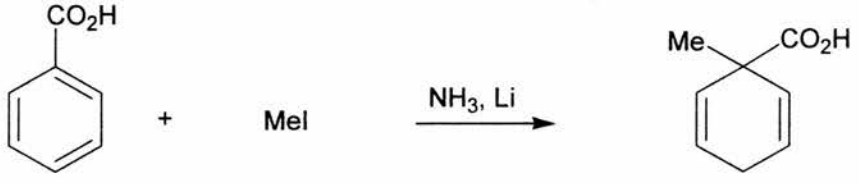
Addition of 2-bromo-hept-6-enyl-benzene **94** to the reactive Birch solution progressed smoothly and decolourised the reaction mixture, as expected, to leave a white powder after aqueous work-up. However, NMR spectroscopic and GC/MS analysis of the crude product revealed large quantities of unreacted benzoic acid and small amounts of 1,4-dihydrobenzoic acid, with no evidence for the formation of carboxylic acid **95**.

The experiment was repeated on several different occasions using freshly prepared and purified starting materials, unfortunately the desired cyclohexadienyl acid **95** was never formed. Time restraints prevented any further research in this area.

1-Methylcyclohexa-2,5-diene-1-carboxylic acid 97

With the intention of investigating the limits of this novel EPR technique for calculating values of k_d and k_H, and completing our series for the release of primary radicals, we decided to synthesise the methyl cyclohexadienyl acid. Our ability to detect the released methyl radical using the available EPR equipment was questionable, however, it should be possible to gauge an educated estimate for the rate of dissociation of this unstable radical from the cyclohexadienyl precursor.

Synthesis of 1-methylcyclohexa-2,5-diene-1-carboxylic acid 97[13, 14]



96, 79%

Scheme 52

The methyl acid was prepared by reacting benzoic acid with methyl iodide under the Birch reduction/alkylation conditions specified in the general procedure (Scheme 52). The cyclohexadienyl acid **96** was isolated using a standard aqueous workup and washed with a saturated solution of sodium thiosulfate to remove any iodine before Kugelrohr distillation gave the pure compound as a pale yellow oil in a yield of 79 %.

EPR study of 1-methylcyclohexa-2,5-diene-1-carboxylic acid 96

The EPR sample for the methyl carboxylic acid was prepared in the conventional manner (10 mg acid, 200 μl DTBP) and degassed thoroughly with N_2. The sample was placed into the EPR cavity and the system temperature increased to 381 K, just short of the boiling point of DTBP, before an experimental spectrum was recorded in the presence of UV light. The high temperature caused the sample to degrade quickly, and made the spectrum rather noisy. However, close examination of the

spectrum confirmed the presence of the delocalised cyclohexadienyl radical with no real evidence for the release of the methyl radical.

This information confirmed that the temperature of the EPR cavity was not sufficient to encourage the complete cleavage of the methyl radical from the cyclohexadienyl precursor. Small peaks from the methyl radical could well be hidden underneath the noise within the spectrum; however, a conservative estimate allows us to forecast that the peaks due to the delocalised cyclohexadienyl radical are **at least** ten times larger than those attributed to the released methyl radical. This estimation allows us to calculate a maximum value for the rate of dissociation, although the true rate is probably much smaller (Table 35).

T/K	$[CH_3^{\cdot}]$	[Acid$^{\cdot}$]	log $k_d/2k_t$	$10^3/T$	log $2k_t$	k_d
381	≤1.181E-08	1.181E-07	≤-7.886	2.621	10.069	≤1.52E+02

Table 35

The estimated value for k_d can be represented on an Arrhenius plot of log k_d against $10^3/T$. As only one point is known, it is not possible to apply a line of best fit. However, statistical mechanics state that for many unimolecular reaction, log $A_d \approx 13$. This allows us to draw an approximate line which crosses through the calculated log k_d value for the methyl acid, and intercepts the Y-Axis at 13. The equation of this line can be used to calculate a maximum value for the rate of dissociation at 300 K, and a minimum value of activation energy (Table 36).

Released Radical	10^{-3} k_d / s^{-1} (300 K)	Log A_d / s^{-1}	E_d / kcal mol $^{-1}$
$Me^{\bullet}$	≤0.0002	13.00	≥18.88

Table 36

The value of k_d demonstrates how small the rate of dissociation is when compared with those found for secondary, tertiary and resonance stabilised radicals. This illustrates how unfavourable the cleavage of the methyl radical is from these cyclohexadienyl compounds.

Summary and Mechanistic Conclusions

EPR spectroscopic study of 1-alkylcyclohexa-2,5-diene-1-carboxylic acids

A range of 1-alkylcyclohexa-2,5-diene-1-carboxylic acids have been prepared, in varying yields, using the Birch reduction/alkylation reaction. Photolysis of the acids, in the presence of a radical initiator, generated the corresponding cyclohexadienyl radicals which were observed by EPR over a specific temperature range. The hyperfine splittings (hfs) and *g*-factors for each radical are recorded in Table 37.

Acid	Released radical	T/K	g-factor	$a(H^4)$	$a(H^{2,6})$	$a(H^{3,5})$	$a(H^{other})$
96	Me·	220[a]	2.003	13.20	9.20	2.70	--
38	Et·	295[b]	2.0026	13.13	9.13	2.72	--
32	*n*-Pr·	270[b]	2.003	13.17	9.12	2.77	0.32 (4H)
30	*n*-Bu·	245[b]	2.003	13.21	9.10	2.84	--
23	*i*-Pr·	220[a]	2.0027	13.19	9.28	2.77	--
17	*c*-C_5H_9·	215[a]	2.003	13.23	9.16	2.63	--
48	*t*-Bu·	145[c]	2.0027	13.29	9.21	2.92	--
62	Allyl·	160[c]	2.0026	13.22	9.23	2.88	--
66	Propargyl·	170[d]	2.0026	13.30	9.18	2.65	1.32 (1H)
72	Cyanomethyl·	245[e]	2.003	13.28	9.15	2.70	--
59	Benzyl·	150[d]	2.003	13.13	9.09	2.64	1.30 (1H)
42	*i*-Bu· (dimethyl)	290[a]	2.003	13.16	8.81	--	2.49 (6H)
28	*i*-Pr· (dimethyl)	240[b]	2.003	13.35	8.79	--	2.48 (6H)
36	*n*-Pr· (dimethyl)	340[b]	2.003	12.82	--	2.64	8.70 (6H)

Table 37

All hfs in G (10 G = 1.0 mT). [a] Solvent PhBu-*t*. [b] Solvent neat DTBP. [c] Solvent cyclopropane + ca. 20 % PhBu-*t*. [d] Solvent cyclopropane. [e] Solvent PhBu-*t* + trace MeOH.

The hfs were very similar for all cyclohexadienyl radicals and were not very sensitive to the nature of the 1-substituent. In a few cases, small long range hfs from hydrogens of the 1-substituent were resolved, however, these disappeared due to signal broadening as the temperature of the EPR cavity increased.

Kinetic EPR study of the dissociation of 1-substitued cyclohexadienyl radicals

EPR spectroscopy was used to map the rearrangement of the cyclohexadienyl radicals into benzoic acid and its released alkyl radical. Concentration data for the two transient radicals were derived using Bruker's WinEPR software over a range of different temperatures, and this information was translated into a rate of dissociation using the derived Steady State equation.

The rate of hydrogen abstraction was confirmed negligible for most of the cyclohexadienyl acids; this enabled us to use a simplified Steady State equation to gain the values of k_d. However, when the value of k_H was significant, measurements of the transient radical concentrations were carried out using two (or more) different sample concentrations to give values of $k_d/2k_t$ and $k_H/2k_t$ simultaneously.

An Arrhenius plot of log k_d against $10^3/T$ over a range of temperatures, allowed us to determine the pre-exponential factor (log A_d), energy of activation (E_d) and rate of dissociation (k_d) at 300 K for each of the cyclohexadienyl acids. This information, corrected for solvent viscosity, is recorded in Table 38.

Acid	Released radical	10^{-3} k_d s^{-1} (300K)	log A_d s^{-1}	E_d kcal mol^{-1}
96	Me·	≤0.0002	13.00	≥18.88
38	Et·	0.023	16.88	21.28
32	*n*-Pr·	0.026	12.24	14.84
23	*i*-Pr·	0.842	12.32	12.88
17	*c*-C_5H_9·	1.140	11.24	11.22
48	*t*-Bu·	527.0	12.19	8.86
62	Allyl·	3454.0	12.71	8.46
66	Propargyl·	6.619	11.22	10.15
72	Cyanomethyl·	0.635	10.05	9.94
59	Benzyl·	70.20	9.88	6.90
42	*i*-Bu· (dimethyl)	0.425	14.75	16.62
28	*i*-Pr· (dimethyl)	0.218	12.27	13.61

Table 38

All values are corrected for solvent viscosity using Fischer's values for $2k_t$.[4]

The measured Arrhenius pre-exponential factors for the cyclohexadienyl acids are spread over a considerable range (log (A_d/s^{-1}) 9.88 – 16.88). This can be attributed to the relatively short temperature ranges of the individual experiments (40 ± 10 K) giving a localised cluster of points on the Arrhenius plot. Accurate A-factors could not be obtained with this technique due to the long extrapolations involved, and this led to small discrepancies in the calculations of k_d.

Statistical mechanics dictate that the A-factor (log A) is approximately 13 for many unimolecular reactions. Deviations from this 'normal' value were not extreme, hence it is probable that the true A-factors are close to this value for all of the dissociations (Figure 48). Table 39 shows the activation energies and k_d values at 300 K for each of the acids when the A-factors are forced to take on the value of 13.

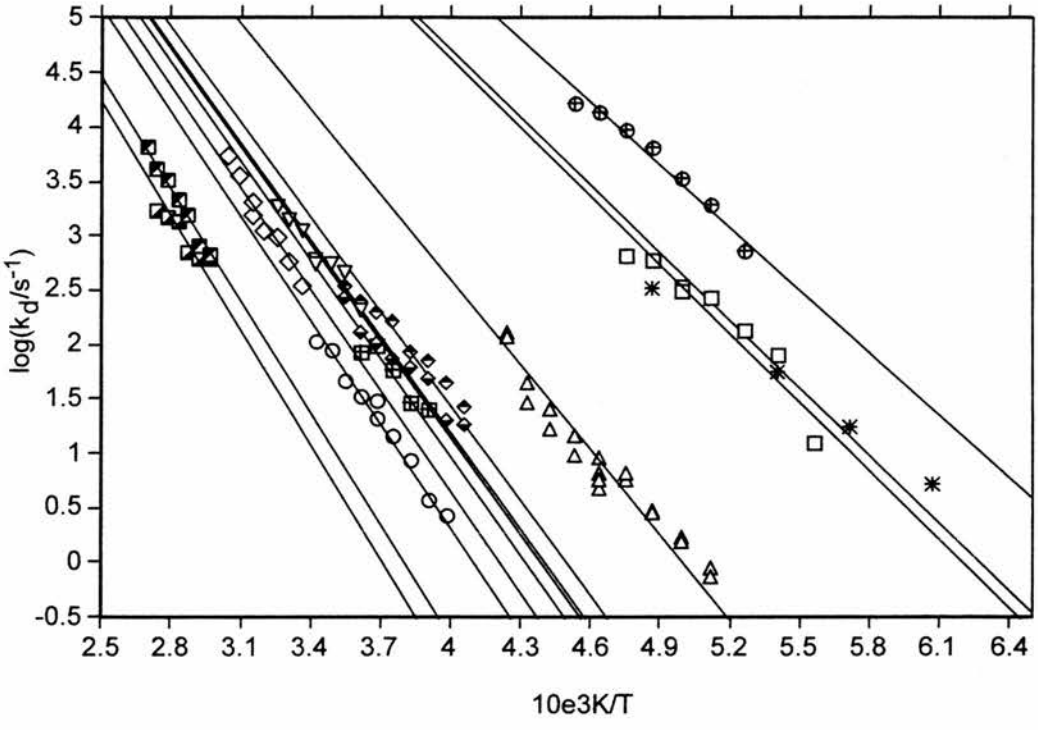


Figure 48

Lines have been constrained to intersect the y-axis at logA =13.0. Crossed circles; allyl-substituted radical ***62****. Open squares; t-butyl-substituted radical* ***48****. Stars; benzyl-substituted radical from acid* ***59****. Triangles apex-up; propargyl-substituted radical* ***66****. Diamonds top and bottom filled; cyanomethyl-substituted radical* ***72****. Triangles apex-down; cyclopentyl-substituted radical* ***17****. Crossed squares; isopropyl-substituted radical* ***28****. Open diamonds; isobutyl radical from acid* ***42****. Open circles; isopropyl radical from acid* ***23****. Squares filled left; ethyl-substituted radical* ***38****. Squares filled right; n-propyl-substituted radical* ***32****.*

Acid	Released radical	*log A_d s^{-1}	*10^{-3} k_d s^{-1} (300K)	*E_d kcal mol^{-1}
96	Me·	13.00	≤0.0002	≥18.88
38	Et·	13.00	0.120	14.97
32	*n*-Pr·	13.00	0.023	15.95
23	*i*-Pr·	13.00	1.017	13.70
17	*c*-C_5H_9·	13.00	1.287	13.56
48	*t*-Bu·	13.00	1012	9.59
62	Allyl·	13.00	4291	8.73
66	Propargyl·	13.00	21.27	11.89
72	Cyanomethyl·	13.00	1.448	13.49
59	Benzyl·	13.00	1238	9.47
42	*i*-Bu· (dimethyl)	13.00	0.503	14.12
28	*i*-Pr· (dimethyl)	13.00	0.257	14.52

Table 39

* Values derived assuming all log A values = 13.0 s^{-1}.

The experimental k_d values confirm that the ease of fragmentation increased dramatically with the degree of branching on the 1-substituent. This can be clearly seen, as the release of *t*-Bu$^\bullet$ was over four orders of magnitude faster than that of a primary alkyl radical at 300 K. Similarly, comparison of the dissociation data for both the allyl and benzyl radicals, with that for the dissociation of primary radicals, highlighted that electron delocalisation in the released radical led to an increased dissociation rate. This suggests that both the thermodynamic stabilisation of the released radical and the steric strain in the initial cyclohexadienyl radicals are important factors in controlling the fragmentation rates.

Surprisingly, dimethyl substitution on the cyclohexadienyl ring caused a reduction in k_d for the dissociation of both *i*-Pr$^\bullet$ and *n*-Pr$^\bullet$. It was originally contemplated that dimethyl substitution would offer additional steric assistance to dissociation. However, the experimental results confirm that this must have been minor and offset by the additional stabilisation gained by the cyclohexadienyl radical due to methyl substitution.

In order to explore the influences which control these dissociations, all cyclohexadienyl radical structures, and their products derived from the two available fragmentation modes, were evaluated using AM1 and PM3 semi-empirical molecular orbital calculations.[24, 25] All structures were fully optimised with respect to their geometric variables to give accurate measurements for bond lengths and bond angles. The theoretical enthalpies of dissociation (ΔH_o) for each of the cyclohexadienyl acids *via* both fragmentation paths were also calculated (Table 40).

Acid	Released radical	R-C_1Bond Å	ΔH_o (AM1) $\rightarrow R^{\bullet} + PhCO_2H$	ΔH_o (AM1) $\rightarrow {}^{\bullet}CO_2H + PhR$	ΔH_o (PM3) $\rightarrow R^{\bullet} + PhCO_2H$	ΔH_o (PM3) $\rightarrow {}^{\bullet}CO_2H + PhR$
96	Me	1.535	33.4	29.0	19.0	7.6
38	Et	1.544	11.1	15.8	9.2	7.6
32	*n*-Pr	1.543	12.0	15.8	19.1	7.1
23	*i*-Pr	1.556	1.8	14.6	0.4	5.5
17	*c*-C_5H_9	1.547	3.5	15.5	-0.1	5.2
48	*t*-Bu	1.565	-7.2	13.7	-8.9	4.3
62	Allyl	1.545	1.1	17.1	0.4	7.0
66	Propargyl	1.548	4.9	15.1	5.6	7.2
72	Cyanomethyl	1.545	8.8	14.5	7.8	6.5
59	Benzyl	1.545	-0.6	22.8	-1.7	10.4
42	*i*-Bu	1.546	9.0	14.4	8.9	4.3

Table 40

Bond lengths calculated using AM1 method.

All C_1-CO_2H AM1 computed distances were 1.520 ± 0.003 Å

The acquired data illustrate how the bond connecting the 1-substituent to the cyclohexadienyl ring varies in length depending on the steric bulk of the attached R group. This bond was longest when R = *t*-Bu (1.565 Å), and progressively reduced in length as the 1-substituent changed to smaller compounds such as R = *i*-Pr (1.556 Å), to R = Et (1.544 Å) and finally R = Me (1.535 Å). The lengthening of this bond with increasing size of the attached substituent gave a clear signal that frontal strain in the radicals played an important part in dictating the ease of fragmentation.

The AM1 calculated reaction enthalpies (ΔH_o) for the dissociation of the cyclohexadienyl radical into $R^{\bullet}$ and benzoic acid suggest that an increase in branching of the 1-substituent led to a reduction in ΔH_o. Therefore, when R = Me, the fragmentation is endothermic (33.4 kcal mol^{-1}), however, with increased branching of

the substituent to R = *t*-Bu, this becomes an exothermic reaction (-7.2 kcal mol^{-1}). The computed ΔH_o values for the alternative dissociation to $^{\bullet}CO_2H$ and the alkyl benzene were all endothermic and showed comparatively little sensitivity towards the nature of R. These computed values of ΔH_o concurred with our experimental findings, showing that dissociation of the cyclohexadienyl radical to $R^{\bullet}$ and benzoic acid is more favoured for all substituents (except Me). The data calculated using the PM3 technique corresponded less well with the experimental observations, as they implied that the undesired dissociation would be favoured for all unbranched alkyl substituents.

A plot of the AM1 computed ΔH_o values against the experimental activation energies ($^{*}E_d$) is shown in Figure 49. It can be seen that the data divides into two groups with the points for primary and delocalised radicals, all of type RCH_2, fall on the lower line, and points for branched radicals on the upper line.

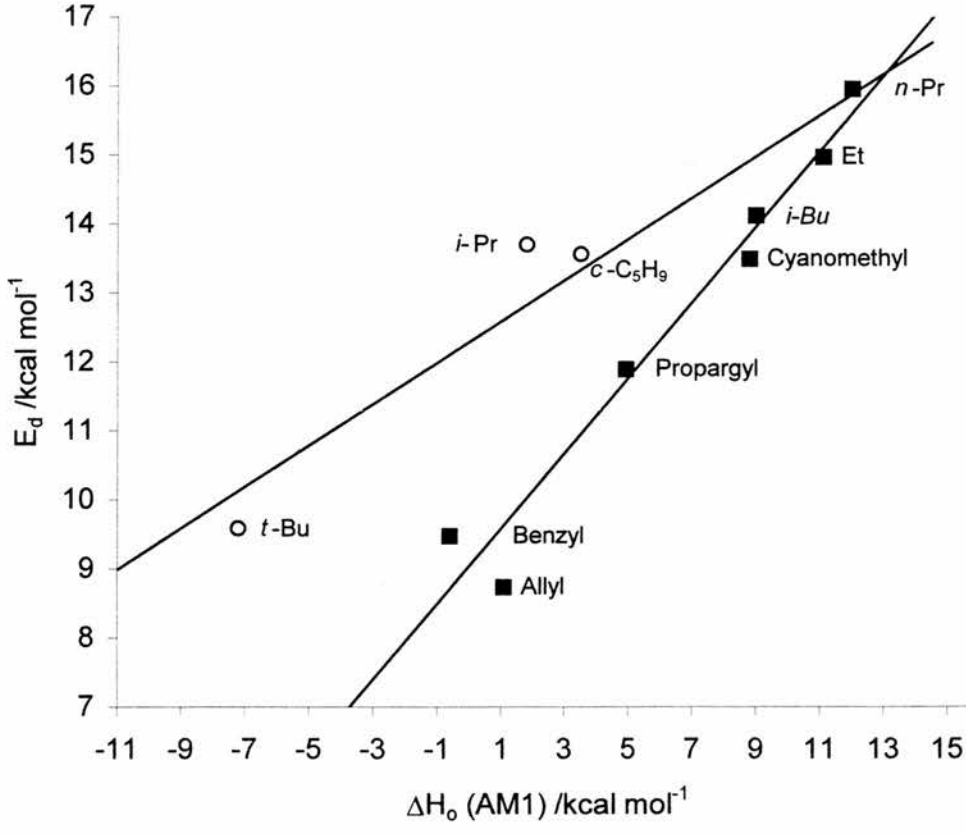


Figure 49

Steric effects are expected to be minimal for all of the radicals which are attached to the cyclohexadienyl ring by a CH_2 group, hence the lower line expresses the reduction in activation energy associated with increasing resonance stabilisation of the ejected radical.

Increased branching in R will cause an increase in the frontier strain of the initial cyclohexadienyl radical. In addition, methyl substitution on the α-carbon of the released radical will have a stabilisation effect due to hyperconjugation. The extent of both these effects dictate the observed dissociation energy, therefore the upper line expresses the reduction in activation energy associated with increasing branching and hyperconjugation.

EPR study of hydrogen abstraction from 1-substitued cyclohexadienyl radicals

The values of transient radical concentrations for the *n*-alkyl cyclohexadienyl acids were significantly affected by major changes in sample concentrations, hence k_H values could be accurately determined for H-abstraction by $Et^{\bullet}$ and *n*-$Pr^{\bullet}$ (Figure 50). The effect of concentration change on the 1-isopropylcyclohexadienyl acid was small due to the reduced rate of H-abstraction. However, experiments with this acid gave some meaningful results in the middle of the dissociation range, although the error limits on these derived kinetic parameters were high. Concentration experiments on the *t*-butyl cyclohexadienyl acid revealed no observable difference in the transient radical concentration, confirming that k_H for the *t*-Bu radical is even lower.

Rate constants for H-abstraction (k_H) were derived from the Steady State equation, solving simultaneously, and corrected for solvent viscosity. The calculated values of k_H can be seen in Table 41, where they are compared to a range of literature values for other radicals which are abstracting hydrogen from cyclohexa-1,4-diene.[26-31] The calculated log A_H values were normal for bimolecular reactions of this type. However, as indicated previously, the Arrhenius parameters were not particularly reliable due to the limited temperature ranges.

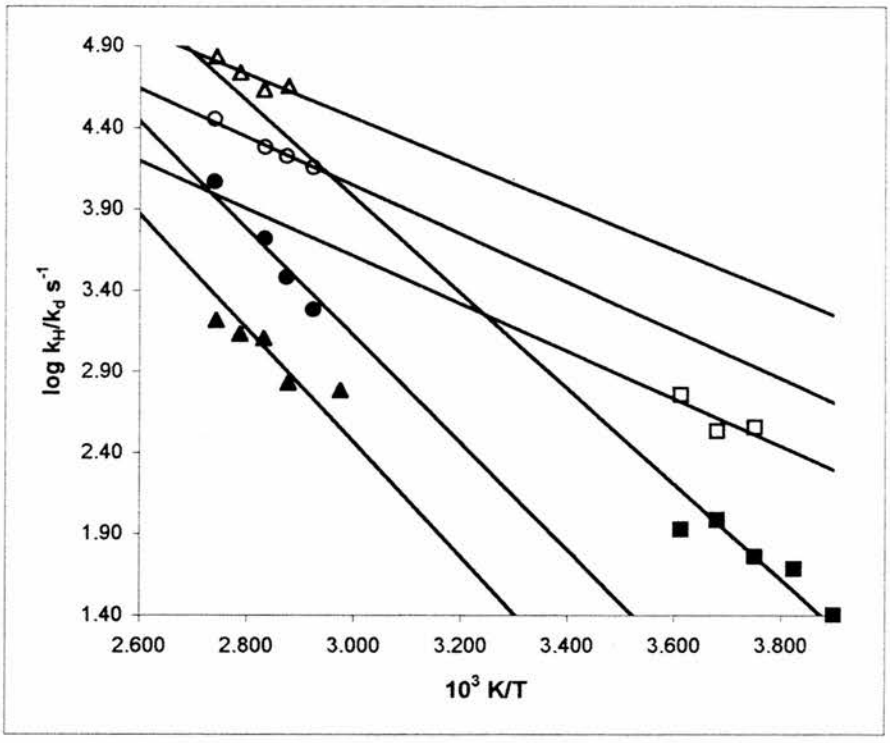
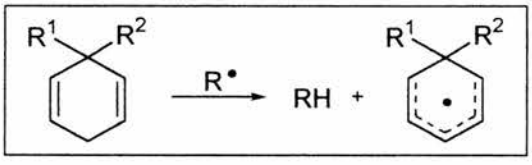


Figure 50

Filled = k_d, *Outline* = k_H

Square = *i*-Pr; *Triangle* = *n*-Pr; *Circle* = Et



R·	^{1}R	^{2}R	$10^{-5}k_H^{\dagger}$	(T/K)	log $A_H^{\dagger}$	E_H kcal mol^{-1}	Ref. No.
Me·	H	H	1.30	(300)	9.10	5.50	26
Et·	H	H	0.58	(300)	--	--	26
*Et·	CO_2H	Et	0.14	(340)	8.44	6.70	*
*n-Pr·	CO_2H	n-Pr·	0.34	(340)	8.70	6.49	*
Hex-5-enyl	H	H	2.30	(323)	--	--	27
Hex-5-enyl	CO_2H	Hex-5-enyl	0.20	(421)	--	--	11
C_6H_{11}·	H	H	5.00	(323)	--	--	27
*i-Pr·	CO_2H	i-Pr·	0.05	(340)	7.90	6.57	*
t-Bu·	H	H	0.04	(300)	--	--	26
Cyclopropyl	H	H	79	(298)	--	--	30
CCl_3·	H	H	0.30	(300)	--	--	26
t-BuO·	H	H	540	(295)	--	--	28, 29

Table 41

* *Compounds discussed in this thesis,* † = $dm^3\ mol^{-1}\ s^{-1}$

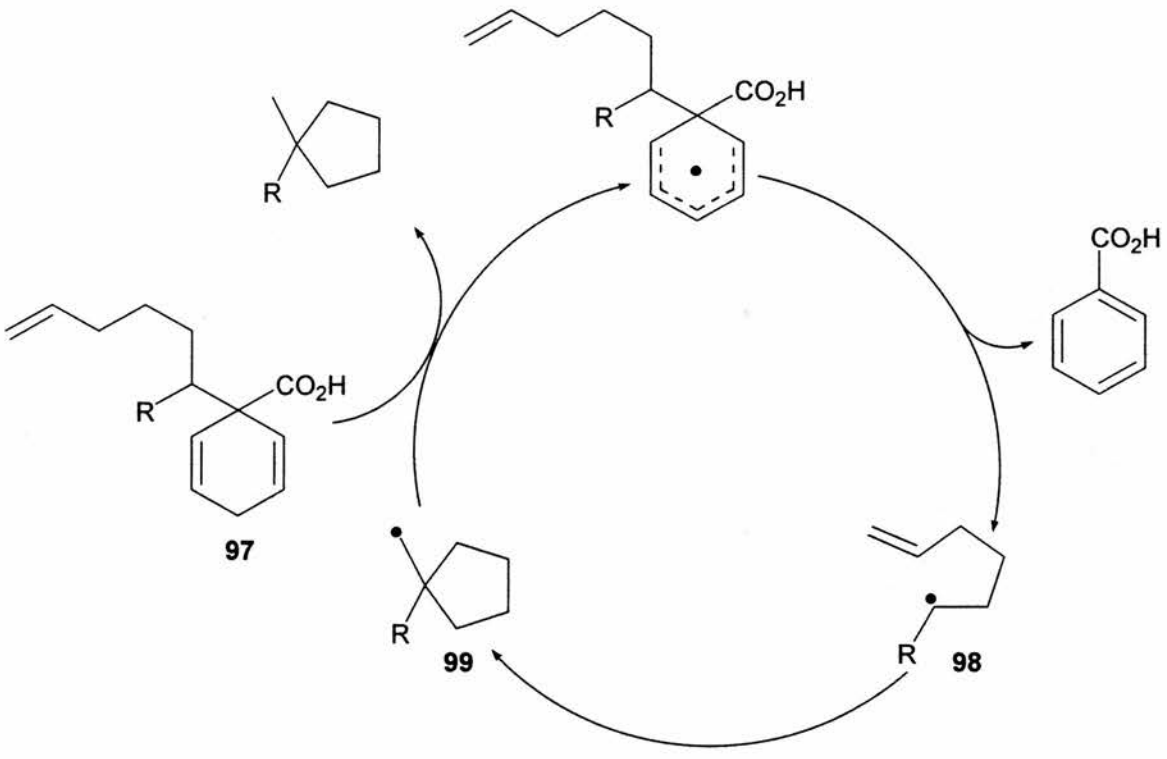
When comparing the different k_H values, it should be noted that cyclohexa-1,4-diene has four bis-allylic hydrogens in comparison with the two bis-allylic hydrogens of the 1,1-disubstitued analogues. Hence, for comparison purposes, the k_H values for the literature data should be reduced by a statistical factor of 2.

As expected, the C-centred alkyl radicals show a large reduction in k_H along the series $Me^{\bullet} > Et^{\bullet} \sim n\text{-}Pr^{\bullet} > i\text{-}Pr^{\bullet} > t\text{-}Bu^{\bullet}$ which is accompanied by a parallel increase in the enthalpies of hydrogen abstraction. It was initially assumed that 1,1-disubstitution onto the cyclohexadienyl ring would have little effect on k_H as the substituents are comparatively remote from the site of H-abstraction. However, the k_H values for the substituted cyclohexadienyl acids are somewhat smaller, even after taking account for the statistical factor. It can therefore be concluded that substitution of this kind leads to a small reduction in the rate of H-abstraction by C-centred radicals.

Mechanistic conclusion

Dissociation of the cyclohexadienyl radical to release the 1-substituent, avoiding alkyl benzene production, was found to be most efficient for branched or resonance stabilised $R^{\bullet}$. Unfortunately, the rate of hydrogen donation by the cyclohexadienyl acids to branched radicals is comparatively slow. Therefore adduct radicals, formed from the addition of the released alkyl radical to an alkene, will not be able to sustain chain reactions effectively and will inevitably give reduced yields.

However, *in situ* transformations of $R^{\bullet}$ that furnish primary or vinyl radicals should be well suited to this methodology. It can be concluded that the most useful cyclohexadienyl acids **97** will contain a branched 1-substituent, which delivers a branched radical **98** upon fragmentation with a high value of k_d. The intermediate radical is readily transformed to a primary radical **99**, *via* cyclisation, which abstracts hydrogen from the starting acid **97** with a high value of k_H (Scheme 53). The premature reduction of the released alkyl radical **98** to give the alkene will not occur for these compounds as the k_H values of the cyclohexadienyl acids are almost 2 orders of magnitude less than for H-donation by organotin hydrides.[32]



Scheme 53

This 'ideal' scenario would provide high rates of dissociation and H-abstraction, which would maintain the chain reaction and provide high yields of the cyclised product. Unfortunately all attempts to synthesise various acids of the form **97** proved unsuccessful and lack of time prevented any further progress in this area.

Experimental

^{1}H NMR spectra were recorded using a Varian Gemini spectrometer at 200 MHz or a Bruker AM 300 spectrometer at 300 MHz. The majority of the ^{13}C NMR spectra were performed at 75 MHz using the Bruker previously mentioned. All samples were dissolved in deuterated chloroform, unless otherwise stated, and run using tetramethylsilane (δ_H=δ_C=0) as an internal reference. EI mass spectra were obtained with 70 eV electron impact ionisation and CI spectra were obtained with isobutene as the target gas on a VG Autospec spectrometer. GC/MS analyses were run on a Finnigan Incos 50 quadrupole instrument coupled to a Hewlett Packard HP 5890 chromatograph fitted with a 25 m HP 17 capillary column (50 % phenyl methyl silicone). When calculating yields from GC data, the detector response was calibrated using known amounts of authentic materials (or close analogues). EPR spectra were obtained with a Bruker EMX 10/12 spectrometer operating at 9.5 GHz with 100 kHz modulation. Samples of the substrate (0.3 to 40 mg) and di-*tert*-butyl peroxide (0.01 to 0.5 cm^3) or *tert*-butylbenzene (0.5 cm^3) in 4 mm quartz tubes, were de-aerated by bubbling nitrogen for 20 min, and photolysed in the resonant cavity by light from a 500 W super pressure mercury arc lamp. For reactions performed in cyclopropane, the solution was degassed on a vacuum line using the freeze-pump-thaw technique, and the tube was flame sealed. In all cases where spectra were obtained, hfs were assigned with the aid of computer simulations using the Bruker Simfonia software package. For kinetic measurements, carboxylic acid samples were used in 'single shot' experiments, i.e. new samples were prepared for each temperature and each acid concentration, to minimise sample degradation effects. Signals were double integrated using the Bruker WinEPR software and radical concentrations were calculated by reference to a known concentration of DPPH as described previously.

All NaOH and HCl solutions were approximately 2 M. THF and ether were distilled under nitrogen from sodium benzophenone ketyl prior to use. Where dry DCM was used, it was distilled over CaH_2. Petroleum ether refers to the fraction boiling between 40 and 60 °C. Other organic compounds were used as received. Column chromatography was performed using BDH silica gel (40 – 63 μm) eluting with the given solvent mixture.

Synthesis of 1-cyclopentylcyclohexa-2,5-diene-1-carboxylic acid 17[10, 12]

Ammonia (300 cm^3) was added to benzoic acid (5 g, 41 mmol) with careful stirring. To this, Li (0.9 g, 0.130 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of bromocyclopentane (19.38 g, 0.131 mol). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure leaving a white solid which was recrystallised from pentane, yielding the title compound as fine white crystals (4.62 g, 59 %); mp 98-100 °C (lit.,[12] 96°C); δ_H(200 MHz, $CDCl_3$) 1.2-1.4 (2 H, m, methylene-H, cyclopentyl ring), 1.4-1.7 (6 H, m, methylene-H, cyclopentyl ring), 2..3-2.5 (1 H, m, *tert*-H, cyclopentyl ring), 2.6-2.7 (2 H, s, allylic-H), 5.7-5.9 (4 H, m, olefinic-H); δ_C(75 MHz, $CDCl_3$) 25.7, 26.5, 27.2 (5 × methylene-C), 47.8 (*tert*-CH), 49.8 (quaternary-C), 125.9, 126.4 (4 × olefinic-C), 180.2 (carbonyl-C).

Photolysis of cyclopentyl acid 17

Carboxylic acid **17** (0.01 g, 0.05 mmol) was dissolved in DTBP (250 µl) and the mixture photolysed at 300 K for 2h. MeOH (200 µl) was added to the sample, along with a catalytic amount of H_2SO_4, before the mixture was sonicated at 60 °C for 1 h. A sample of the reaction mixture was submitted for analysis by GLC; methyl benzoate (Ret. time = 109 mm, Area = 9784), cyclopentylbenzene (Ret. Time = 20 mm, Area = 12). Ratio of methyl benzoate : cyclopentylbenzene is 815 : 1.

Synthesis of 1-isopropylcyclohexa-2,5-diene-1-carboxylic acid 23[11, 12]

Ammonia (300 cm^3) was added to benzoic acid (5 g, 41 mmol) with ca
reful stirring. To this, Li (0.9 g, 0.130 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of 2-iodopropane (22.09 g, 0.130 mol). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150

cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure leaving a pale yellow solid which was recrystallised in pentane, yielding the title compound as colourless prisms (5.58 g, 82%); mp 81-82 °C (lit.,[12] 82 °C); δ_H(300 MHz, $CDCl_3$) 0.87 (6 H, d, *J* 7, 2 × CH_3), 2.1 (1 H, septet, *J* 7, CH), 2.65 (2 H, s, allylic-H), 5.74-5.85 (4 H, m, olefinic-H); δ_C(75 MHz, $CDCl_3$) 17.8 (*i*-propyl-CH_3), 27.0 (*i*-propyl-CH), 36.2 (allylic-CH), 52.3 (quaternary-C), 125.7 (olefinic-CH), 182.2 (carbonyl-C).

Photolysis of the isopropyl acid 23

Carboxylic acid **23** (0.01 g, 0.05 mmol) was dissolved in DTBP (250 μl) and the mixture photolysed at 300 K for 2h. MeOH (200 μl) was added to the sample, along with a catalytic amount of H_2SO_4, before the mixture was sonicated at 60 °C for 1h. A sample of the reaction mixture was submitted for analysis by GLC; methyl benzoate (Ret. time = 111 mm, Area = 9652), no alkylbenzene peaks were observed.

Synthesis of 1-isopropyl-3,5-dimethylcyclohexa-2,5-diene-1-carboxylic acid 28

Ammonia (300 cm^3) was added to 3,5-dimethylbenzoic acid (5 g, 33 mmol) with careful stirring. To this, Li (0.7 g, 0.10 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of 2-iodopropane (18.38 g, 0.10 mol) in dry ether (5 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a white solid (5.02 g). The product was successfully purified by recrystallisation in pentane, yielding the title compound (4.59 g, 72%) as white needles; mp 94-95 °C; δ_H(300 MHz, $CDCl_3$) 0.79-0.82 (6 H, d, *J* 6, 2 × CH_3), 1.78 (6 H, s, 2 × ring CH_3), 2.0-2.23 (1 H, septet, *J* 6, $CHMe_2$), 2.48 (2 H, s, allylic-H), 5.45 (2H, s, olefinic-H); δ_C(75 MHz, $CDCl_3$) 17.3 (CH_3), 22.9 (ring CH_3), 36.1 ($CHMe_2$), 36.3 (allylic-C), 54.2

(quaternary-C), 119.4 (CH), 134.2 (quaternary-C), 181.6 (C=O). (Found MH^+ 195.1389, $C_{12}H_{19}O_2$ requires MH^+ 195.1385).

Synthesis of 1-*n*-butylcyclohexa-2,5-diene-1-carboxylic acid 30

Ammonia (300 cm^3) was added to benzoic acid (5 g, 41 mmol) with careful stirring. To this, Li (0.9 g, 0.130 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of 1-iodobutane (22.04 g, 0.122 mol). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a yellow oil which decomposed on distillation. The product was successfully purified by chromatography [SiO_2, light petroleum-EtOAc (4:1)] to give the carboxylic acid **30** (1.74 g, 24%) as oily, colourless crystals; mp 59 °C; δ_H(300 MHz, $CDCl_3$) 0.94 (3 H, t, *J* 6, CH_3), 1.26 (4 H, m, 2 × CH_2), 1.75 (2 H, t, *J* 4, CH_2C), 2.68 (2 H, s, allylic-H), 5.75-5.98 (4 H, m, olefinic-H); δ_C(75 MHz, $CDCl_3$) 14.0 (CH_3), 19.6-26.4 (3 × CH_2), 26.1 (CH_2), 39.3 (quaternary-C), 126.0-126.8 (4 × CH), 180.5 (C=O). (Found MH^+ 181.1235, $C_{11}H_{17}O_2$ requires MH^+ 181.1229).

Synthesis of 1-*n*-propylcyclohexa-2,5-diene-1-carboxylic acid 32[14, 15]

Ammonia (300 cm^3) was added to benzoic acid (5 g, 41 mmol) with careful stirring. To this, Li (0.9 g, 0.130 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of 1-iodopropane (20.9 g, 0.123 mol) in dry ether (5 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, washed with a saturated solution of sodium thiosulfate, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a pink oil which was purified by distillation to yield the title compound (4.47 g, 66%) as a white powder; mp 47 °C (lit.[15] 46-48.5 °C);

δ_H(300 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 6, CH_3), 1.28 (2 H, m, CH_2), 1.67 (2 H, m, CH_2C), 2.65 (2 H, s, allylic-H) 5.69-5.98 (4 H, m, olefinic-H), 11.10 (1 H, bs, -OH); δ_C(75 MHz, $CDCl_3$) 14.1 (CH_3), 17.4 (CH_2), 26.0 (CH_2), 41.7 (CH_2), 47.7 (quaternary-C), 125.8, 126.7 (4 × CH), 181.6 (C=O).

Photolysis of the *n*-propyl acid 32

Carboxylic acid **32** (0.01 g, 0.05 mmol) was dissolved in DTBP (250 μl) and the mixture photolysed at 300 K for 2h. MeOH (200 μl) was added to the sample, along with a catalytic amount of H_2SO_4, before the mixture was sonicated at 60 °C for 1h. A sample of the reaction mixture was submitted for analysis by GLC; methyl benzoate (Ret. time = 111 mm, Area = 1322), *n*-propylbenzene (Ret. Time = 17.5 mm, Area = 58). Ratio of methyl benzoate : *n*-propylbenzene is 23 : 1.

Synthesis of 1-*n*-propyl-2,6-dimethylcyclohexa-2,5-diene-1-carboxylic acid 36

Ammonia (300 cm^3) was added to 2,6-dimethylbenzoic acid (5 g, 33 mmol) with careful stirring. To this, Li (0.69 g, 0.10 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of 1-iodopropane (16.98 g, 0.10 mol) in dry ether (5 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a white solid (4.21 g). The product was successfully purified by recrystallisation in pentane, yielding the title compound (3.42 g, 53%) as white plates; mp 96-97 °C; δ_H(300 MHz, $CDCl_3$) 0.91 (3 H, t, *J* 6, CH_3), 0.97-1.13 (2 H, m, CH_2), 1.70 (6 H, s, 2 × CH_3), 1.79-1.88 (2 H, m, CH_2), 2.72 (2 H, s, allylic-H), 5.72 (2H, s, olefinic-H); δ_C(75 MHz, $CDCl_3$) 14.3 (CH_3) 16.6 (CH_2), 19.3 (2 × ring CH_3), 27.1 (CH_2), 32.5 (allylic-C), 55.2 (quaternary-C), 123.5 (CH), 130.3 (quaternary-C), 179.9 (C=O). (Found: MH^+ 195.1382, $C_{12}H_{19}O_2$ requires MH^+ 195.1385).

Synthesis of 1-ethylcyclohexa-2,5-diene-1-carboxylic acid 38[12, 15]

Ammonia (300 cm^3) was added to benzoic acid (5 g, 41 mmol) with careful stirring. To this, Li (0.9 g, 0.130 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of iodoethane (20.8 g, 0.133 mol) in dry ether (5 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a yellow oil (7.26 g) which was purified by washing with a solution of saturated sodium thiosulfate followed by distillation to yield the title compound (4.32 g, 69%) as a pale yellow oil; δ_H(300 MHz, $CDCl_3$) 0.46 (2 H, d, CH_2), 0.85 (3 H, t, *J* 6, CH_3), 1.74 (2 H, q, *J* 6, CH_2), 2.65 (2 H, s, allylic-H), 5.69-5.98 (4 H, m, olefinic-H), 8.80 (1 H, bs, CO_2H); δ_C(75 MHz, $CDCl_3$) 10.2 (CH_3), 25.8 (CH_2) 27.4 (allylic-C), 46.4 (quaternary-C), 125.8-126.9 (4 × CH), 180.7 (C=O).

Photolysis of the ethyl acid 38

Carboxylic acid **38** (0.01 g, 0.05 mmol) was dissolved in DTBP (250 µl) and the mixture photolysed at 300 K for 2h. MeOH (200 µl) was added to the sample, along with a catalytic amount of H_2SO_4, before the mixture was sonicated at 60 °C for 1h. A sample of the reaction mixture was submitted for analysis by GLC; methyl benzoate (Ret. time = 114 mm, Area = 5225), ethylbenzene (Ret. Time = 16 mm, Area = 254). Ratio of methyl benzoate : ethylbenzene is 20 : 1.

Synthesis of 1-isobutyl-3,5-dimethylcyclohexa-2,5-diene-1-carboxylic acid 42

Ammonia (300 cm^3) was added to 3,5-dimethylbenzoic acid (5 g, 33 mmol) with careful stirring. To this, Li (0.7 g, 0.10 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of 1-bromo-2-methylpropane (13.7 g, 0.10 mol) in dry ether (5 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH

and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a white solid (5.19 g, 76 %) which was purified by recrystallisation from pentane to yield the title compound (3.36 g, 49%) as white plates; mp 71 °C; δ_H(300 MHz, $CDCl_3$) 0.75-0.89 (6 H, d, *J* 6, 2 × CH_3), 1.50 - 1.63 (2 H, d, *J* 6, CH_2), 1.8 (6 H, s, 2 × ring CH_3), 2.2 (1 H, m, $CHMe_2$), 2.48 (2 H, s, allylic-H), 5.45 (2H, s, olefinic-H); δ_C(75 MHz, $CDCl_3$) 17.3 (*2* × CH_3), 22.9 (ring CH_3), 36.1 ($CHMe_2$), 36.3 (allylic-C), 45.2 (CH_2) 54.2 (quaternary-C), 119.4 (olefinic-C), 134.2 (quaternary-C), 181.6 (C=O); (Found : MH^+ 209.1549, $C_{13}H_{21}O_2$ requires MH^+ 209.1542).

Attempted preparation of 1-neopentylcyclohexa-2,5-diene-1-carboxylic acid 46

Ammonia (300 cm^3) was added to benzoic acid (5 g, 41 mmol) with careful stirring. To this, Li (0.9 g, 0.130 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of 1-bromo-2,2-dimethylpropane (24.0 g, 0.123 mol) in dry ether (5 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a white solid identified as unreacted benzoic acid and 1,4-dihydrobenzoic acid by NMR. The reaction was repeated quenching with 1-iodo-2,2-dimethylpropane (24.9 g, 0.123 mol), again, only starting materials were isolated.

Synthesis of 1-*t*-butylcyclohexa-2,5-diene-1-carboxylic acid 48[10]

Ammonia (600 cm^3) was added to benzoic acid (10 g, 82 mmol) with careful stirring. To this, Li (1.7 g, 0.246 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of *t*-butyl iodide (30.01 g, 0.164 mol). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with

ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure leaving a pale yellow solid which was chromatographed [SiO_2, light petroleum-EtOAc (4:1)] to give the carboxylic acid **48** (3.2 g, 22%) as colourless needles; mp 100-102 °C (lit.[10] 101 °C); δ_H (300 MHz, $CDCl_3$) 1.00 (9 H, s, $C(CH_3)_3$), 2.57-2.63 (2 H, s, allylic-H), 5.88-6.10 (4 H, m, olefinic-H); δ_C (75 MHz, $CDCl_3$) 26.0 (3 × CH_3), 26.2 (CH_2), 38.6 (quaternary-C), 52.9 (quaternary-C), 125.5, 126.2 (4 × CH), 180.4 (C=O).

Photolysis of the *t*-butyl acid 48

Carboxylic acid **48** (0.01 g, 0.05 mmol) was dissolved in DTBP (250 μl) and the mixture photolysed at 300 K for 2h. MeOH (200 μl) was added to the sample, along with a catalytic amount of H_2SO_4, before the mixture was sonicated at 60 °C for 1h. A sample of the reaction mixture was submitted for analysis by GLC; methyl benzoate (Ret. time = 109 mm, Area = 8245), no alkylbenzene peaks were observed.

Synthesis of 1-benzylcyclohexa-2,5-diene-1-carboxylic acid 52[16, 33]

Ammonia (600 cm^3) was added to benzoic acid (10 g, 82 mmol) with careful stirring. To this, Li (1.6 g, 0.231 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of benzyl chloride (29.2 g, 0.233 mol) in dry ether (5 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a white solid (8.56 g) which was purified by recrystallisation from pentane to yield the title compound (7.24 g, 41%) as white needles; mp 76-77 °C (lit. [16] 76-77 °C); δ_H(300 MHz, $CDCl_3$) 2.27-2.63 (2 H, m, allylic-H), 3.03 (2 H, s, benzylic-H), 5.80-5.90 (4 H, m, olefinic-H), 7.11-7.29 (5 H, m, aromatic-H); δ_C(75 MHz, $CDCl_3$) 25.0 (allylic-C), 46.1 (CH_2), 48.8 (quaternary-C), 126.5, 126.7, 127.9, 130.7, 131.4 (9 × CH), 136.1 (C), 179.7 (C=O).

Synthesis of 1-(4-*t*-butylbenzyl)-cyclohexa-2,5-diene-1-carboxylic acid 56

Ammonia (300 cm^3) was added to benzoic acid (5 g, 41 mmol) with careful stirring. To this, Li (0.9 g, 0.130 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of *t*-butylbenzyl bromide (24.4 g, 0.123 mol) in dry ether (5 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a white solid (4.23 g) which was purified by recrystallisation from pentane to yield the title compound (3.65 g, 33%) as white powder; mp 271 °C; δ_H(300 MHz, $CDCl_3$) 1.25 (9 H, s, *t*-butyl-H), 2.14-2.40 (2 H, m, allylic-H), 2.88 (2 H, s, benzylic-H), 5.46-5.83 (4 H, m, olefinic-H), 6.90-7.12 (4 H, m, aromatic-H); δ_C(75 MHz, $CDCl_3$) 25.2 (allylic-C), 28.2 (3 × CH_3), 39.4 (quaternary-C), 47.1 (CH_2), 48.4 (quaternary-C), 126.1, 126.4, 127.6, 130.2 (8 × CH), 137.2 (C), 138.4 (C), 177.9 (C=O).

Synthesis of pentadeutero benzoic acid 58[19]

Potassium permanganate (36 g, 0.23 mol) was placed in a 1 l. flask fitted with a stirrer and reflux condenser. Water (350 cm^3) and D_5-toluene (10 g, 99.8 mmol) were added before the mixture was slowly heated to boiling with continual stirring. The mixture decolourised over a period of 4 h and the resultant product was steam distilled until no oil passed over with the water in order to eliminate any unreacted D_5-toluene. The hot mixture was filtered with suction and the cake of hydrated manganese dioxide was washed with hot water (3 × 100 cm^3). The combined filtrate was decolourised (charcoal) before being acidified by the cautious addition of excess conc. HCl to yield a white precipitate. The product was extracted using dry ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a white solid (7.23 g, 57%); mp 121 °C (lit.[34] 119-120 °C); δ_H(300 MHz, C_3D_6O) blank; δ_C(75 MHz, C_3D_6O) 127.9, 129.8, 133.6 (aromatic C); 172.5 (carbonyl C).

Synthesis of 1-benzyl-2,3,4,5,6-pentadeuterio-cyclohexa-2,5-diene-1-carboxylic acid 59[20]

Ammonia (300 cm^3) was added to deuterated benzoic acid (5 g, 39 mmol) with careful stirring. To this, Li (0.9 g, 0.130 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of benzyl chloride (15.62 g, 0.123 mol) in dry ether (5 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a white solid (5.16 g) which was purified by recrystallisation from pentane to yield the title compound (4.81 g, 56 %) as a white solid; mp 76-77 °C; δ_H(200 MHz, $CDCl_3$) 2.32, 2.51 (1 H, m, allylic-H), 3.06 (2 H, bs, CH_2), 6.8-7.8 (5 H, m, aromatic-H), 10.34 (1 H, bs, CO_2H); δ_C(75 MHz, $CDCl_3$) 25.3 (allylic-C), 46.4 (CH_2), 48.6 (quaternary-C), 126.3 – 132.1 (9 × CH/CD), 137.4 (C), 180.3 (C=O). (Found: MH^+ 220.1390, $C_{14}H_{10}D_5O_2$ requires MH^+ 220.1381).

Synthesis of 1-allylcyclohexa-2,5-diene-1-carboxylic acid 62[21]

Ammonia (300 cm^3) was added to benzoic acid (5 g, 41 mmol) with careful stirring. To this, Li (0.9 g, 0.130 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of allyl bromide (14.9 g, 0.123 mol) in dry ether (5 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a pale yellow oil (8.14 g) which was purified by distillation to yield the title compound (4.28 g, 64%) as a colourless oil; δ_H(300 MHz, $CDCl_3$) 2.46 (2 H, d, CH_2), 2.65 (2 H, s, bisallylic-H), 5.09 (2 H, d, allyl-CH_2), 5.66 (1 H, m, allyl-CH), 5.69-5.98 (4 H, m, olefinic-H), 11.19 (1 H, bs, CO_2H); δ_C(75 MHz, $CDCl_3$) 26.0 (CH_2), 44.0 (allylic-CH_2), 47.5 (quaternary-C), 118.3 (CH_2), 126.1, 126.3 (4 × CH), 132.7 (CH), 180.8 (C=O).

Synthesis of 1-propargylcyclohexa-2,5-diene-1-carboxylic acid 66

Ammonia (300 cm^3) was added to benzoic acid (5 g, 41 mmol) with careful stirring. To this, Li (0.9 g, 0.130 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of propargyl bromide (26.45 g, 0.124 mol) in dry ether (5 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a brown oil (9.13 g). A small portion of this impure product was distilled under reduced pressure to furnish the title compound as a white solid in a yield of 69 %; mp 74 °C; δ_H(300 MHz, $CDCl_3$) 2.0-2.04 (1 H, s, acetylenic-H), 2.57-2.63 (2 H, s, allylic-H), 2.69-2.72 (2 H, s, CH_2CCH), 5.81-6.02 (4 H, m, olefinic-H); δ_C(75 MHz, $CDCl_3$) 26.3 (CH_2), 30.0 (CH_2), 47.3 (quaternary-C, ring), 70.9 (CH), 79.7 (quaternary-C, chain), 125.5, 127.2, 128.5, 129.2 (4 × CH), 178.9 (C=O). (Found MH^+ 163.0766, $C_{10}H_{11}O_2$ requires MH^+ 163.0759).

Photolysis of the propargyl acid 66

Carboxylic acid **66** (0.01 g, 0.05 mmol) was dissolved in DTBP (250 μl) and the mixture photolysed at 300 K for 2h. MeOH (200 μl) was added to the sample, along with a catalytic amount of H_2SO_4, before the mixture was sonicated at 60 °C for 1h. A sample of the reaction mixture was submitted for analysis by GLC; methyl benzoate (Ret. time = 108 mm, Area = 8372), no alkylbenzene peaks were observed.

Radical addition of 1-propargylcyclohexa-2,5-diene-1-carboxylic acid 66 to cyclohexenone.

1-Propargyl-cyclohexa-2,5-diene-1-carboxylic acid (22.3 mg, 0.14 mmol) was placed in a quartz tube along with DTBP (250 μl) and cyclohexenone (31 mg, 0.27 mmol). The contents of the quartz tube were photolysed for 5 hours using a 400 Watt mercury lamp and a portion analysed by GC/MS; peak no. 572, octahydro-biphenylene-1,5-

dione, *m/z* (relative intensity), 192 (M^+) (2), 164 (3), 136 (16), 108 (18), 96 (77), 79 (63), 68 (50), 55 (68), 39 (100), 27 (80), 18 (29); peak no. 378, benzoic acid, 122 (M^+) (66), 105 (93), 77 (100), 51 (56); peak no. 346, 3-*tert*-butoxy-cyclohexanone, 170 (M^+) (1), 114 (14), 97 (24), 86 (17), 69 (33), 57 (100), 41 (66), 29 (22), 18 (39); peak no. 321, 3-prop-2-ynyl-cyclohexanone **70**, 136 (M^+) (9), 121 (4), 108 (13), 97 (46), 79 (32), 69 (26), 55 (38), 41 (100), 27 (47), 18 (87); peak no. 252, unidentified product. GC/MS yield of product **70** was 45 %.

Synthesis of 1-cyanomethyl-cyclohexa-2,5-diene-1-carboxylic acid 72

Ammonia (300 cm^3) was added to benzoic acid (3.73 g, 31 mmol) with careful stirring. To this, Li (0.64 g, 0.091 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of iodoacetonitrile (10.2 g, 0.061 mol) in dry ether (20 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, washed with a saturated solution of sodium thiosulfate, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a brown oil (3.96 g) which was purified by decolourising with charcoal and recrystallisation from pentane to yield the title compound (2.93 g, 58%) as white plates; mp 110 °C; δ_H(300 MHz, $CDCl_3$) 2.76 (2 H, s, allylic-H), 2.81 (2 H, s, CH_2), 5.72-6.17 (4 H, m, 4 × CH); δ_C(75 MHz, $CDCl_3$) 26.1 (CH_2), 28.3 (allylic-C), 45.8 (quaternary-C), 116.5 (CN), 123.4, 129.4 (CH), 177.3 (C=O); *m/z* (relative intensity) 163 (M^+, 6), 123 (100), 122 (29), 117 (35), 115 (47), 105 (27), 91 (35), 79 (66), 77(55), 51 (19); (Found: M^+ 163.0638 $C_9H_9O_2N$ requires *M*, 163.0633).

Synthesis of 1-cyanomethylcyclohexa-2,5-diene-1-carboxylic acid 72

Ammonia (300 cm^3) was added to benzoic acid (5 g, 41 mmol) with careful stirring. To this, Li (0.9 g, 0.130 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of bromoacetonitrile (14.76 g, 0.123 mol) in dry ether (20 cm^3). The reaction mixture was stirred for 60 min and then left whilst

the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a black oil (9.39 g) which was purified by decolourising a small sample with charcoal and micro distillation to yield the title compound as a white solid; mp 110 °C.

Photolysis of the cyanomethyl acid 72

Carboxylic acid **72** (0.01 g, 0.05 mmol) was dissolved in DTBP (250 µl) and the mixture photolysed at 300 K for 2h. MeOH (200 µl) was added to the sample, along with a catalytic amount of H_2SO_4, before the mixture was sonicated at 60 °C for 1h. A sample of the reaction mixture was submitted for analysis by GLC; methyl benzoate (Ret. time = 110 mm, Area = 9645), no alkylbenzene peaks were detected.

Radical addition of 1-cyanomethylcyclohexa-2,5-diene-1-carboxylic acid 72 to cyclohexene.

1-Cyanomethylcyclohexa-2,5-diene-1-carboxylic acid (10 mg, 0.06 mmol) was placed in a quartz tube along with DTBP (150 µl) and cyclohexene (100 µl). The contents of the quartz tube were photolysed for 5 hours using a 400-Watt mercury lamp and a portion analysed by GC/MS; peak no. 412, dodecahydro-biphenylene, *m/z* (relative intensity), 162 (M^+, 1), 81 (100), 66 (5), 53 (15), 41 (19), 27 (8); peak no. 381, unidentified product; peak no. 364 benzoic acid; peak no. 284, cyclohexyl-acetonitrile **76**, 122 (M^+, 1), 108 (2), 96 (1), 83 (65), 67 (9), 55 (100), 41 (74), 27 (33), 18 (22); peak no. 236, *tert*-butoxy-cyclohexane, 156 (M^+, 1), 141 (3), 100 (9), 82 (4), 57 (100), 41 (52), 29 (40), 18 (5).

Radical addition of 1-cyanomethylcyclohexa-2,5-diene-1-carboxylic acid 72 to cyclohexenone.

1-Cyanomethylcyclohexa-2,5-diene-1-carboxylic acid (13 mg, 0.08 mmol) was placed in a quartz tube along with DTBP (150 µl) and cyclohexenone (100 µl). The contents

of the quartz tube were photolysed for 5 hours using a 400-Watt mercury lamp and a portion analysed by GC/MS; peak no. 572, octahydro-biphenylene-1,5-dione; peak no. 410, (2-oxocyclohexyl)-acetonitrile **77**, *m/z* (relative intensity) 137 (M^+, 16), 122 (16), 97 (19), 69 (18), 55 (100), 41 (73), 27 (26), 18 (46); peak no. 374, benzoic acid; peak no. 342, 3-*tert*-butoxy-cyclohexanone.

Attempted synthesis of 1-ethoxycarbonylmethyl-cyclohexa-2,5-diene-1-carboxylic acid 79

Ammonia (300 cm^3) was added to benzoic acid (5 g, 41 mmol) with careful stirring. To this, Li (0.9 g, 0.130 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of ethyl bromoacetate (20.54 g, 0.123 mol). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a white solid (6.03 g) shown by ^1H NMR to be a mixture of benzoic acid and 1,4-dihydrobenzoic acid. The reaction was repeated, quenching with ethyl iodoacetate, but only starting materials were isolated.

Attempted preparation of 1-methoxymethylcyclohexa-2,5-diene-1-carboxylic acid 81

Ammonia (300 cm^3) was added to benzoic acid (3.27 g, 27 mmol) with careful stirring. To this, Li (0.56 g, 54 mmol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of iodomethylmethyl ether (9.22 g, 0.054 mol) in dry ether (5 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a white solid (2.78 g) identified as 1,4-dihydrobenzoic acid by NMR spectroscopy.

Attempted preparation of 1-*n*-propyl-1,4-dihydronaphthalene-1-carboxylic acid 83[22]

Ammonia (300 cm^3) was added to purified α-naphthoic acid (5.0 g, 29 mmol) with careful stirring. To this, Li (0.61 g, 87 mmol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of 1-iodopropane (13.81 g, 81 mmol) in dry ether (5 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3) and washed with a saturated thiosulfate solution before the ethereal extracts were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a white solid (5.45 g). The impure mixture was separated using column chromatography, eluting with 5 % ethyl acetate in petroleum ether, yielding starting material (0.63 g, 12 %), 1,4-dihydronaphthoic acid (1.40 g, 28%) and 1,3-dipropyl-1,4-dihydronaphthalene-1-carboxylic acid (1.25 g, 17 %) δ_H(300 MHz, $CDCl_3$) 0.93 (6 H, t, *J* 5, 2 × CH_3), 1.21-1.63 (4 H, m, 2 × CH_2), 1.80-2.07 (2 H, m, CH_2), 2.28-2.89 (4H, m, allylic –CH_2/*n*-propyl-CH_2), 5.80 (1 H, m, CH), 7.18-7.35 (4 H, m, aromatic-H); δ_C(75 MHz, $CDCl_3$) 14, 15 (2 × CH_3), 19, 21, 31, 34 (4 × CH_2), 38 (allylic-CH_2), 50 (quaternary-C) 122, 123, 126, 127, 129 (4 × CH), 134, 135, 136 (quaternary-C), 181 (C=O).

Preparation of non-1-en-6-ol 87

5-Bromopent-1-ene (5.0 g, 34 mmol) dissolved in dry ether (20 cm^3) was added dropwise to a rapidly stirred suspension of Mg turnings (0.90 g, 37 mmol) in dry ether (20 cm^3), and the resulting mixture refluxed gently for 1.5 h. The grey solution was cooled using an ice bath before butyraldehyde (2.45 g, 34 mmol) dissolved in dry ether (20 cm^3) was added dropwise, instigating an exothermic reaction. The resulting mixture was allowed to warm to r.t. before it was refluxed for 2h and finally left to stir overnight at r.t. Ice (100 cm^3) and HCl (100 cm^3) were added to the solution and the product was extracted with ether (3 × 100 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated to give a yellow oil (4.3 g). The impure mixture was purified by distillation to furnish the title compound as a colourless oil

(3.53 g, 73 %); bp 95-100 °C at 0.4 mmHg; δ_H(300 MHz, $CDCl_3$) 0.92 (3 H, t, *J* 4, CH_3), 1.24-1.59 (8 H, m, 4 × CH_2), 2.06 (2 H, m, CH_2), 3.61 (1 H, m, CH), 4.96 (2 H, m, olefinic-CH_2), 5.79 (1 H, m, olefinic-CH) 8.64 (1 H, bs, -OH); δ_C(75 MHz, $CDCl_3$) 14 (CH_3), 21, 25, 33, 37, 40 (5 × CH_2), 71 (CH), 114 (olefinic-CH_2), 139 (olefinic-CH); (Found: MH^+ 142.1352 $C_9H_{18}O$ requires MH^+ 142.1358).

Preparation of 6-bromo-non-1-ene 88

PBr_3 (1.9 g, 7 mmols) dissolved in dry pentane (5 cm^3) was added dropwise to a stirred solution of non-1-en-6-ol **87** (2.0 g, 14 mmols) and pyridine (0.56 g, 7 mmol) dissolved in dry pentane (10 cm^3) which was cooled to –10 °C. After addition, the mixture was stirred for 1.5h at 0 °C before the temperature was allowed to rise to r.t. and the solution stirred overnight. The reaction contents were added to ether (100 cm^3), washed with H_2O (100 cm^3), and the ether layer dried ($MgSO_4$) before the solvent was removed to yield a brown oil (2.79 g) which was shown by NMR spectroscopy to be a mixture of the unreacted starting material and the desired product **88**. The brown oil was purified by vacuum distillation in order to furnish the desired product **88** as a pale yellow oil (1.64 g, 57%); δ_H(300 MHz, $CDCl_3$) 0.96 (3 H, m, CH_3), 1.33-1.89 (8 H, m, 4 × CH_2), 2.08 (2 H, m, CH_2), 4.04 (1 H, m, CH), 4.92-5.08 (2 H, m, olefinic-CH_2), 5.70-5.89 (1 H, m, olefinic-CH); δ_C(75 MHz, $CDCl_3$) 13 (CH_3), 21, 27, 32, 38, 41 (5 × CH_2), 58 (CH), 114 (olefinic-CH_2), 138 (olefinic-CH).

Preparation of 6-tosyl-non-1-ene 89

Non-1-en-6-ol **87** (1.5 g, 11 mmol) was dissolved in pyridine (30 cm^3) and cooled to -10 °C before adding *p*-toluenesulphonyl chloride (3.3 g, 17 mmol). The resulting mixture was allowed to warm to r.t. and left stirring for 24h. The reaction contents were added to H_2O (100 cm^3) and the product was extracted with ethyl acetate (2 × 100 cm^3). The organic extracts were combined, dried ($MgSO_4$) and the solvent evaporated to yield an orange oil which was identified by NMR as a mixture of the desired tosylate and unreacted starting material (2.2 g, 67 %); δ_H(200 MHz, $CDCl_3$) 0.77-1.00 (3 H, m, CH_3), 1.16-1.79 (8 H, m, 4 × CH_2), 1.86-2.17 (2 H, m, CH_2), 2.44 (3 H, s, tosyl-CH_3), 4.58 (1 H, q^i, *J* 6, CH), 4.85-5.09 (2 H, m, olefinic-CH_2), 5.55-

5.91 (1 H, m, olefinic-CH), 7.25-7.40 (2 H, d, *J* 8, aromatic-H), 7.75-7.85 (2 H, d, *J* 8, aromatic-H).

Preparation of 6-iodo-non-1-ene 90

The tosylate **90** (2.2 g, 7 mmol) was dissolved in Analar acetone (30 cm^3) to which sodium iodide (2.4 g, 16 mmol) was added and the resulting mixture was refluxed for 20h. The acetone was evaporated and ethyl acetate (100 cm^3) was added to the residue, which was washed with a saturated solution of sodium thiosulfate (100 cm^3) and brine (100 cm^3) before being dried ($MgSO_4$). The remaining solvent was evaporated to yield a pale yellow oil (1.23 g) which was purified by distillation to furnish the title compound as a colourless oil (0.44 g, 25%); bp 100-105 °C at 0.4 mmHg; δ_H (300 MHz, $CDCl_3$) 0.96 (3 H, t, *J* 8, CH_3), 1.36-1.79 (8 H, m, 4 × CH_2), 2.12 (2 H, m, CH_2), 4.13 (1 H, m, CH), 4.94-5.08 (2 H, m, olefinic-CH_2), 5.72-5.89 (1 H, m, olefinic-CH); δ_C(75 MHz, $CDCl_3$) 13 (CH_3), 22, 28, 32, 39, 41 (5 × CH_2), 63 (CH), 114 (olefinic-CH_2), 137 (olefinic-CH).

Attempted synthesis of 1-(1-propyl-hex-5-enyl)-cyclohexa-2,5-diene-1-carboxylic acid 91

Ammonia (200 cm^3) was added to benzoic acid (3 g, 25 mmol) with careful stirring. To this, Li (0.6 g, 86 mmol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of 6-bromo-non-1-ene (10.25 g, 50 mmol) in dry ether (10 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (100 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a white solid (1.76 g) which was identified by NMR spectroscopy and GC/MS as unreacted starting material and 1,4-dihydrobenzoic acid.

Preparation of 1-phenyl-hept-6-en-2-ol 93

5-Bromopent-1-ene (10.0 g, 67 mmol) dissolved in dry ether (20 cm^3) was added dropwise to a rapidly stirred suspension of Mg turnings (1.79 g, 73 mmol) in dry ether (30 cm^3), and the resulting mixture refluxed gently for 1.5 h. The grey solution was cooled using an ice bath before freshly distilled phenyl acetaldehyde (8.05 g, 67 mmol) dissolved in dry ether (50 cm^3) was added dropwise, instigating an exothermic reaction. The resulting mixture was allowed to warm to r.t. before it was refluxed for 2h and finally left to stir overnight at r.t. Ice (100 cm^3) and H_2SO_4 (100 cm^3) were added to the solution and the product was extracted with ether (3 × 100 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated to give a yellow oil (11.73 g). The impure mixture was purified by distillation to furnish the title compound as a colourless oil (9.63 g, 82 %); bp 120-125 °C at 0.4 mmHg; δ_H(300 MHz, $CDCl_3$) 1.44-1.67 (4 H, m, 2 × CH_2), 2.08-2.18 (2 H, m, CH_2), 2.60-2.88 (2 H, m, benzylic-CH_2) 3.82 (1 H, m, CH), 4.91-5.08 (2 H, m, olefinic-CH_2), 5.73-5.89 (1 H, m, olefinic-CH) 7.18-7.39 (5 H, m, aromatic-H); δ_C(75 MHz, $CDCl_3$) 25.4, 34.1, 36.6, 44.5 (4 × CH_2), 72.9 (CH), 115.0 (CH_2), 127.1, 128.8, 129.5 (5 × CH), 138.5 (quaternary-C), 139.0 (CH); (Found: MH^+ 190.1355 $C_9H_{18}O$ requires MH^+ 190.1358).

Preparation of 2-bromo-hept-6-enyl-benzene 94 [23]

Tri-*n*-octylphosphine (20.57 g, 55 mmol) was added to a stirred solution of 1-phenyl-hept-6-en-2-ol **93** (5.27 g, 28 mmol) and carbon tetrabromide (18.41 g, 56 mmol) in dry ether (80 cm^3). An immediate exothermic reaction took place and the initially colourless mixture turned yellow. After complete addition, the mixture was gently refluxed for 1.5h before the remaining carbon tetrabromide and ether were removed by distillation, yielding a brown oil (48.78 g) which was a mixture of several different compounds. This mixture was purified by vacuum distillation to furnish the title compound as a pale yellow oil (4.81 g, 69 %); bp 105-110 °C at 0.4 mmHg; δ_H(300 MHz, $CDCl_3$) 1.60-2.02 (4 H, m, 2 × CH_2), 2.11-2.28 (2 H, m, CH_2), 3.31 (2 H, m, benzylic-CH_2) 4.34 (1 H, m, CH), 5.03-5.17 (2 H, m, olefinic-CH_2), 5.83-5.97 (1 H, m, olefinic-CH) 7.20-7.40 (5 H, m, aromatic-H); δ_C(75 MHz, $CDCl_3$) 27.1, 33.4, 37.9, 46.1 (4 × CH), 57.8 (CH), 115.3 (CH_2), 126.8, 128.9, 129.8 (5 × CH), 138.8 (quaternary-C), 139.1 (CH)

Attempted synthesis of 1-(1-benzyl-hex-5-enyl)-cyclohexa-2,5-diene-1-carboxylic acid 95

Ammonia (200 cm^3) was added to benzoic acid (2.6 g, 21 mmol) with careful stirring. To this, Li (0.424 g, 61 mmol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of 2-bromo-hept-6-enyl-benzene **94** (10.58 g, 42 mmol) in dry ether (10 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (100 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a white solid (2.29 g) which was identified by NMR spectroscopy and GC/MS as unreacted starting material and 1,4-dihydrobenzoic acid.

Synthesis of 1-methylcyclohexa-2,5-diene-1-carboxylic acid 96[13, 14]

Ammonia (300 cm^3) was added to benzoic acid (5 g, 41 mmol) with careful stirring. To this, Li (0.92 g, 133 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of methyl iodide (17.46 g, 123 mmol) in dry ether (20 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, washed with a saturated solution of sodium thiosulfate, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a yellow oil (5.06 g). The crude product was purified by distillation yielding the title compound as a pale yellow oil (4.45 g, 79%); bp 85-90 °C at 0.4 mmHg; δ_H(300 MHz; $CDCl_3$) 1.40 (3 H, s, CH_3), 2.67 (2 H, s, CH_2), 5.79-5.91 (4 H, m, 4 × CH); δ_C(75 MHz, $CDCl_3$) 27 (CH_3), 28 (allylic-C), 44 (quaternary-C), 125, 129 (4 × CH), 183 (C=O).

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CHAPTER 3

1-Carbamoyl-1-methyl-cyclohexa-2,5-dienes.

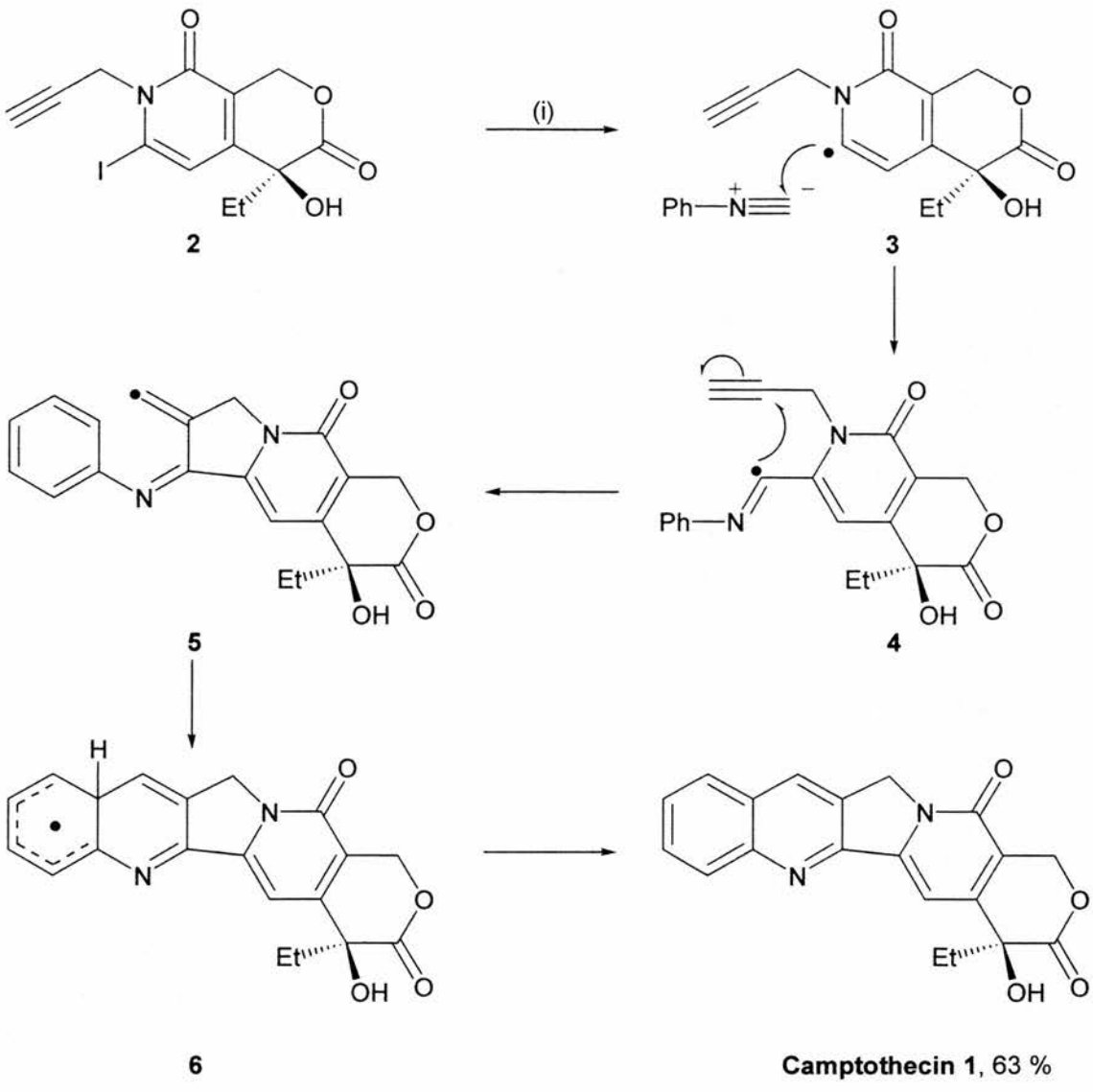
Introduction

Radical pathways to heterocycle formation

Radical cyclisations have played an important part in synthetic organic chemistry, particularly in natural product synthesis, for several years. Their use in the creation of many diverse heterocycles continues to be an area of great interest, which has lead to the introduction of various new cyclisation methodologies. However, the traditional use of tributyltin hydride or the related triorganostannanes continues to dominate the field of radical cyclisations in heterocyclic chemistry.[1]

Several complex heterocyclic systems have been constructed using radical cyclisations. These reactions hold a variety of advantages over non-radical methods, which often require labour intensive multi-step syntheses. The radical cyclisations do not generally suffer from steric hindrance or racemisation problems and can generally be carried out in neutral organic solutions, furthermore, radical cascade reactions allow the construction of two or more rings in a one-pot reaction.

An example of a heterocyclic radical cascade reaction can be seen in Curran's recent work towards the synthesis of the important anticancer alkaloid camptothecin **1** (Scheme 1).[2, 3] In this procedure, rings B and C are assembled in a one-pot reaction by photolysis of *N*-propargyl-6-iodo-2-pyridone **2** in the presence of phenyl isocyanide and hexamethylditin. Initially, the pyridone radical **3** is formed by halogen abstraction, which rapidly undergoes bimolecular addition to the reactive isonitrile in order to generate the new radical **4**. 5-*Exo-dig* cyclisation onto the proximate alkyne closes ring C in order to furnish the vinyl radical **5**, which cyclises onto the benzene ring to form ring B and generate the resonance stabilised π-radical **6**. The oxidation of this intermediate radical into the pentacyclic camptothecin **1** remains unclear. However, this methodology has been used to furnish camptothecin, and a wide range of analogues containing substituents on the alkyne, benzene ring A and the pyridone ring, in high yields.[4]



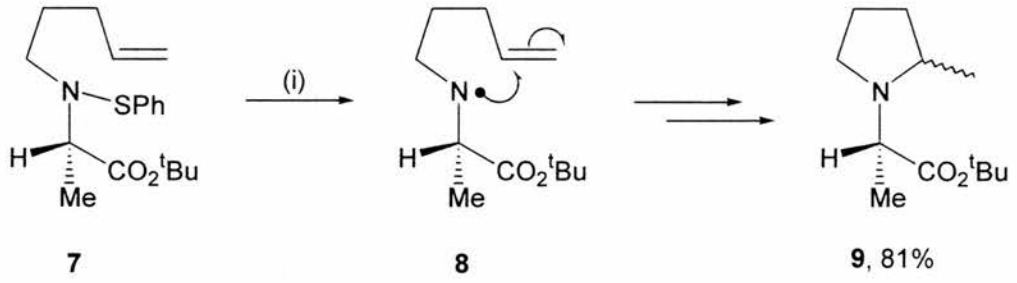
Scheme 1
(i), PhNC, $(Me_3Sn)_2$, PhH, sun lamp, 70 °C, 8 h

Radical formation of nitrogen heterocycles

The synthesis of nitrogen heterocycles, using a radical methodology, remains an area of increasing interest to synthetic chemists. The formation of pyrrolidines by 5-*exo* cyclisation is well suited to the use of radicals, which can be generated in a number of positions relative to the nitrogen atom.

Bowman and co-workers looked at the formation of aminyl radicals and demonstrated how an α-amino acid aminyl radical **8**, derived from the sulfenamide precursor **7**, can undergo 5-*exo-trig* cyclisation onto a suitably placed *N*-alkenyl of α-alkenyl chain,

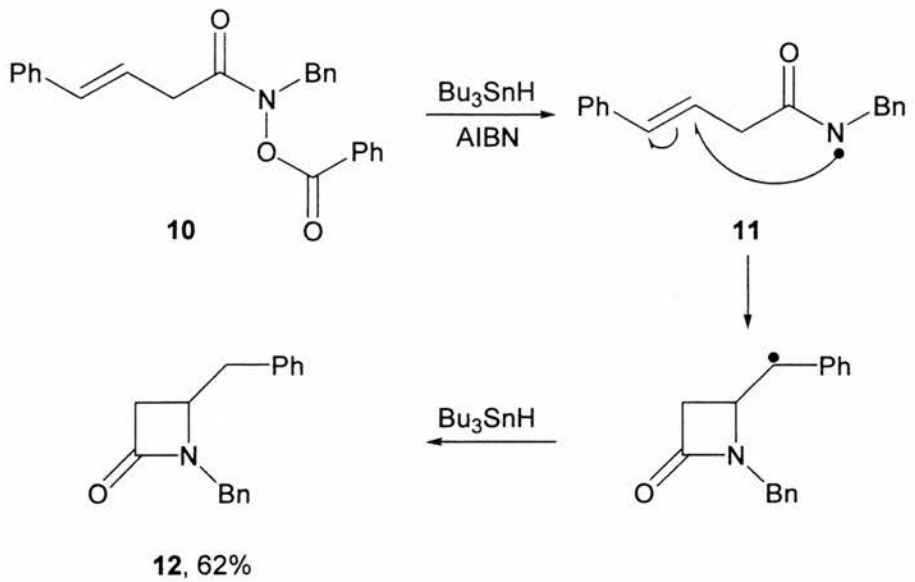
with reasonable diastereoselectivity, in order to generate the corresponding pyrrolidine **9** in high yields (Scheme 2).[5] The α-ester of the amino acid encourages the aminyl radical to behave electrophilically in order to facilitate cyclisation onto the alkene.



7 **8** **9**, 81%

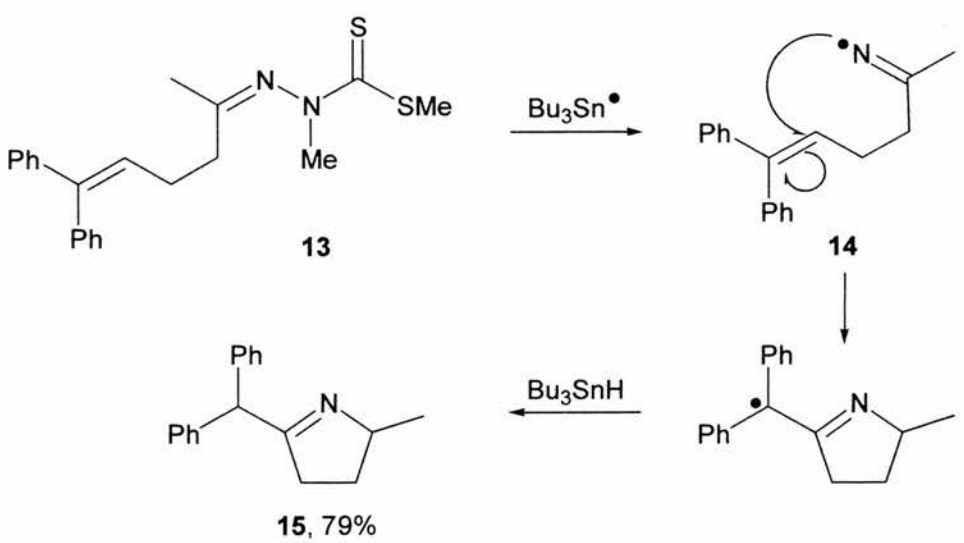
Scheme 2
(i), Bu_3SnH, AIBN, PhMe, reflux, 6 h.

Amidyl radicals are known to be highly reactive intermediates, which are considerably more electrophillic than their aminyl relatives. Therefore, radical cyclisations involving amidyl radicals tend to be much more favourable. Amidyl radical **11**, generated from the tributyltin mediated homolysis of the *O*-benzoyl hydroxamic acid derivative **10**, readily undergoes 4-*exo-trig* cyclisation in order to furnish the highly strained β-lactam **12**, together with the uncyclised direct reduction product (Scheme 3).[6] The formation of the γ-lactam using amidyl radical cyclisation techniques has also been extensively studied.[7] The incorporation of laser flash photolysis techniques allowed researchers to calculate the associated reaction kinetics, in order to confirm that cyclisations of amidyl radicals occur much more rapidly than those involving carbon-centred radicals. However, current research suggests that this cyclisation is reversible.[8]



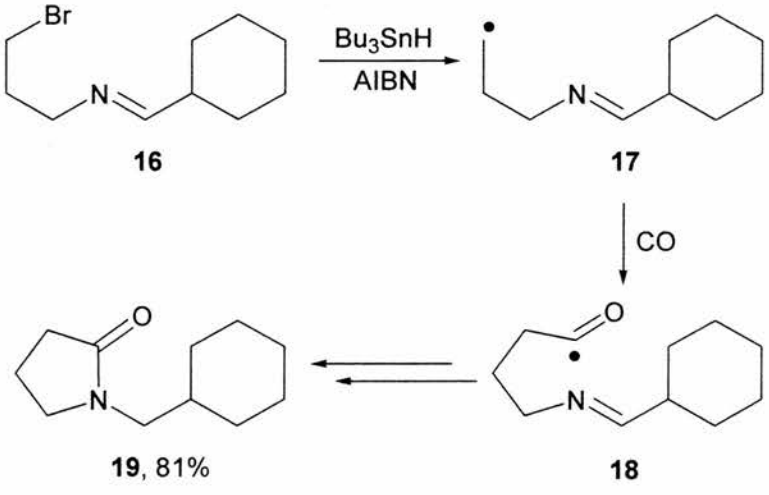
Scheme 3

Newcomb and co-workers have also investigated iminyl radicals **14** for their ability to take part in radical cyclisations.[9] Heating of the xanthic hydrazone **13**, in the presence of a stoichiometric quantity of tributyltin hydride and AIBN, released the tin radical which readily adds to the thione sulfur and encourages *N-N* homolytic cleavge in order to generate the iminyl radical **14**. 5-*Exo-trig* cyclisation of this intermediate, followed by reduction, formed the desired pyrroline in a yield of 79%.



Scheme 4

Conversely, radical attack onto the C=N bond can provide an alternative route to the formation of nitrogen heterocycles. Several novel examples of this procedure have been published, however, this type of alkyl radical cyclisation often presented little selectivity, providing mixtures of nitrogen containing heterocycles *via* 5-*exo and* 6-*endo* cyclisations.[10-12] Ryu and co-workers adapted these systems by introducing a polar component in order to improve selectivity. They predicted that the incorporation of an acyl radical, δ- to the heteroatom, would promote an *N*-phillic acyl radical cyclisation (Scheme 5).[13]



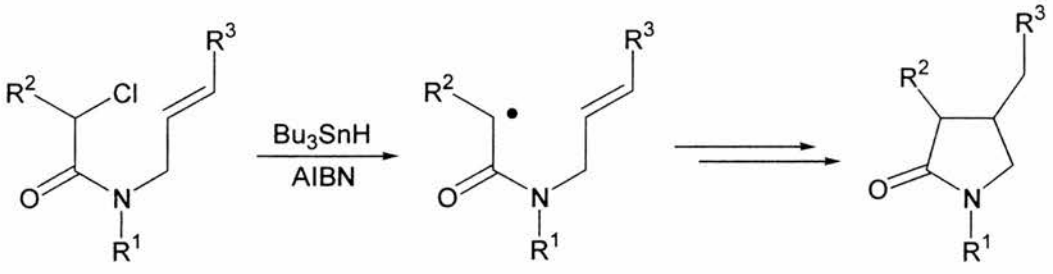
Scheme 5

Alkyl radical **17** was generated from the halogenated precursor **16** using tributyltin hydride and AIBN. An atmosphere of carbon monoxide, at high pressure, encourages radical addition in order to deliver the intermediate acyl radical **18**, which in turn undergoes a 5-*exo* cyclisation, onto the nitrogen of the imine group, to furnish the pyrrolidin-2-one **19**. Product analysis confirmed the absence of both the uncyclised carbonylation/reduction product and the undesired five-membered ring, which would result from attack of the unmodified alkyl radical. This suggests that the intermediate radical **17** is reluctant to undergo 4-*exo* cyclisation onto the nitrogen of the imine, or 5-*endo* cyclisation onto the imine carbon. This allows time for the slow addition of carbon monoxide in order to generate the acyl radical and facilitate the 4 + 1 type carbonylation-annulation.

A major area of research regarding the formation of substituted pyrrolidines, pyrrolidinones and pyroglutamates has evolved around the formation of radicals β- to

the nitrogen atom, and their subsequent cyclisation onto β-alkenes. This strategy has been employed in the formation of a range of substituted γ-lactams.[14, 15]

When an unsaturated haloamide **20** was treated with tributyltin hydride, in the presence of AIBN, the intermediate alkyl radical **21** was formed, which could interact with the β-alkene to form moderate yields of pyrrolidinone **22**, along with the uncyclised, direct reduction product (Scheme 6). Further work in this field by Parsons revealed that the nature of the *N*-protecting group (R^1), along with the substituents attached at the site of radical generation (R^2) and at the acceptor double bond (R^3), have a significant effect upon the yields of cyclisation products found. Optimisation of substituents R^2 and R^3 eventually led to the successful cyclisation of secondary haloamides without bulky *N*-protecting groups.[15]

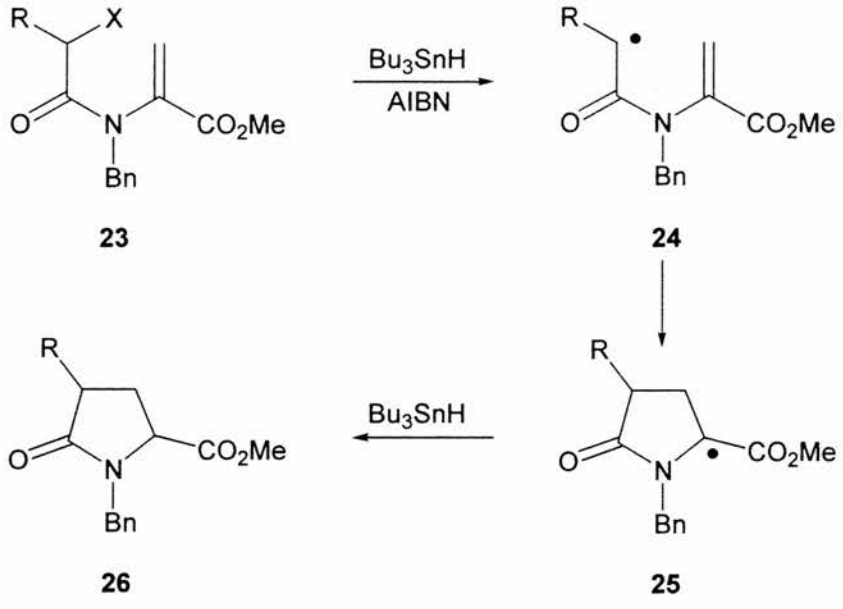


20 **21** **22**

R^1=H, Bn, Me
R^2=Cl, H, Me, Ph
R^3=H, CO_2Et

Scheme 6

The application of this methodology has been further advanced by both Parsons and Ikeda, who demonstrated that the β-radical could undergo a geometrically disfavoured 5-*endo-trig* mode of cyclisation onto an α-alkene, in order to generate both pyrrolidinones and pyroglutamates from the *N*-vinyl precursors (Scheme 7).[16-18] Hence, reaction of dehydroalanine **23** with an equivalent amount of Bu_3SnH resulted in the formation of the primary alkyl radical **24**, which underwent a 5-*endo-trig* cyclisation to form the relatively stable captodative radical **25**. Hydrogen abstraction from Bu_3SnH regenerated the chain carrier and released the desired pyroglutamates **26** in moderate yields.

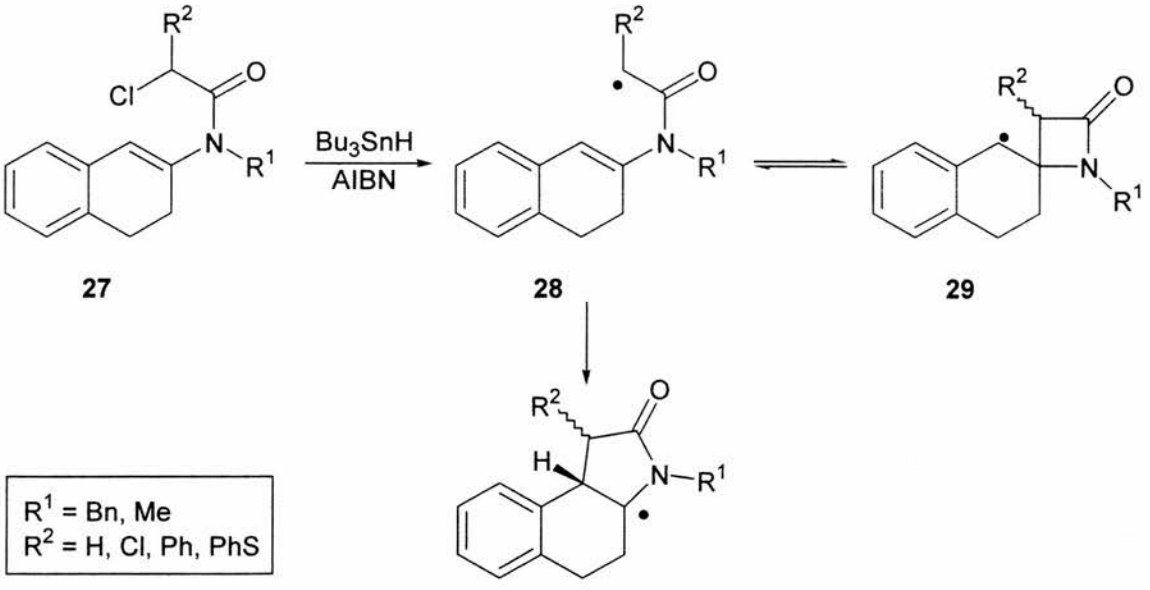


Scheme 7

It was subsequently discovered that the intermediate radical **25** could be trapped, using various alkenes, in order to furnish the α-substituted pyroglutamates in moderate yields.[17]

The presence of a radical β to nitrogen, and a proximate α-alkene, can also be used to generate highly strained 4-membered heterocyclic rings by 4-*exo-trig* cyclisation. In order to control the regioselectivity of these Bu_3SnH mediated cyclisations, the substituents at the points of radical formation had to be selected prudently.[19, 20] Ikeda demonstrated this with his recent work on the cyclisations of 2-chloro-*N*-(3,4-dihydro-2-naphthyl)-*N*-methylacetamides **27**.[21]

Previous research had confirmed that a radical stabilising group, such as phenyl, at the terminus of the *N*-vinyl group lead to an increase in the formation of the β-lactam. [19] However, Ikeda demonstrated that the nature of the substituent attached to the initially formed carbamoylmethyl radical **28** also played an important role (Scheme 8).

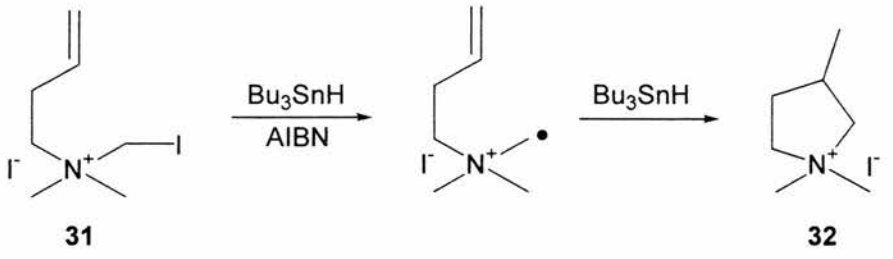


Scheme 8

When R^2 = H or Cl in **28**, the formation of the β-lactam was favoured; however, when this substituent was replaced by one which aided radical stabilisation, such as methyl, phenyl or thiophenyl, the γ-lactam became the dominant product. The explanations for these results were based on the known reversibility of the 4-*exo-trig* cyclisation. 4-*Exo-trig* cyclisation is the kinetically favoured process, when compared to the 5-*endo-trig* alternative, as it produces the resonance stabilised benzyl radical **29**. When R^2 = H or Cl, the subsequent reduction of this intermediate radical is faster than the ring-opening step and hence the β-lactam is formed. However, when R^2 is a radical stabilising group, the ring opening of **29** occurs rapidly to give the relatively stabilised initial radical **28**, therefore reduction takes place after the thermodynamically more stable radical **30** has been formed by 5-*endo-trig* cyclisation of **28** to give the γ-lactam. This rationale was confirmed by an observed increase in the relative amounts of γ-lactam produced when the radical cyclisation was performed in a higher boiling solvent.

The synthesis of pyrrolidines and their analogues by cyclisation of radicals β- to the nitrogen atom is now a common procedure. However, the synthesis of pyrrolidines by cyclisation of radicals α- to the nitrogen onto γ-alkenes is rare. A novel procedure based on this variant has been described by Della, who used *N*,*N*-dialkyl-*N*-

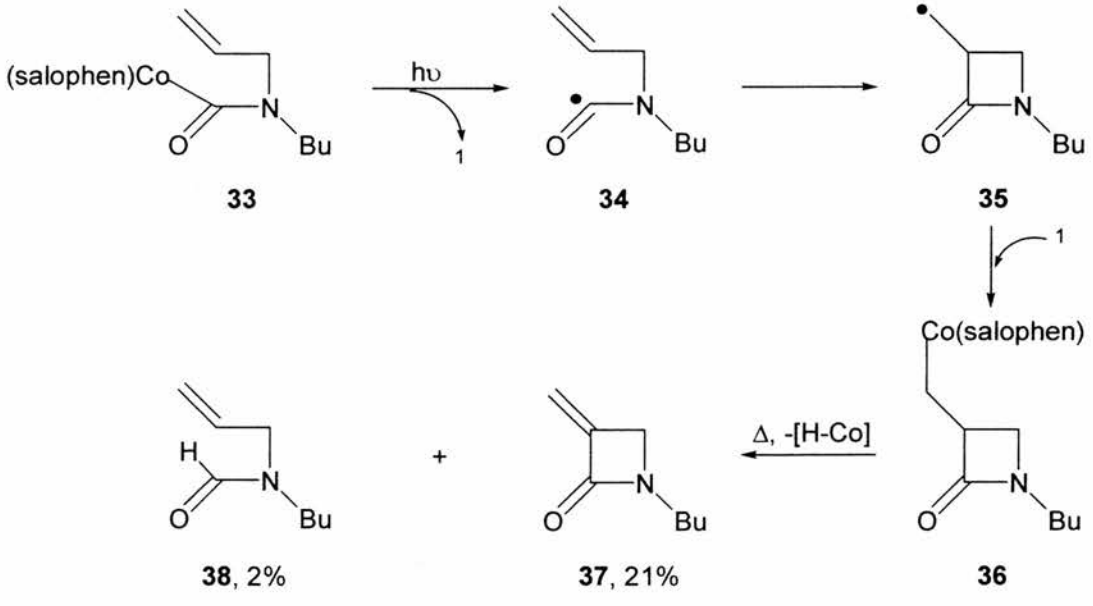
(iodomethyl)-but-3-enylamine salts **31** for the synthesis of 5-membered ring ammonium salts **32** (Scheme 9).[22]



31 **32**

Scheme 9

The study of carbamoyl radicals is a relatively new area of research and has conventionally followed the radical properties of formamide-derived species and their abilities to add to alkenes.[23, 24] Carbamoylcobalt(III) salophens have recently been used by Pattenden to generate heteroatom-substituted acyl radicals, which allow the direct synthesis of a variety of cyclic and acyclic compounds, including both γ- and β-lactams.[25] Detailed studies of homolytic reactions involving organocobalt reagents confirmed their ability to generate carbamoyl radicals, which could be trapped by alkenes or undergo facile cyclisations onto β- and γ- alkenes in order to furnish β- and γ- lactams (Scheme 10).



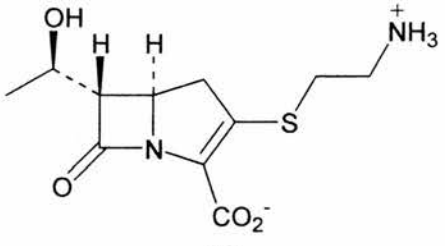
33 **34** **35** **36** **38**, 2% **37**, 21%

[1] = Co(II) salophen

Scheme 10

The carbamoyl derivative **33** was irradiated with UV light in order to release the carbamoyl radical **34**. This highly reactive intermediate rapidly underwent a 4-*exo-trig* cyclisation to close the β-lactam ring and form the β-lactamidomethyl radical **35**. Radical **35** was trapped by the cobalt(II) salophen species to give **36**, which was finally added to refluxing toluene in order to release the β-lactam **37** in a yield of 21%. The uncyclised formamide **38** was also isolated as a minor product in a yield of 2%.

A similar procedure was carried out on an analogous compound, which possessed an alkene γ- to the nitrogen atom. Photolysis of this organocobalt precursor gave the reactive carbamoyl radical which underwent a 5-*exo-trig* cyclisation to furnish the desired γ-lactam in good yield. The information derived from these initial studies was exploited by Pattenden and co-workers, leading to the novel, radical based, synthesis of (±) thienamycin **39**.[26]

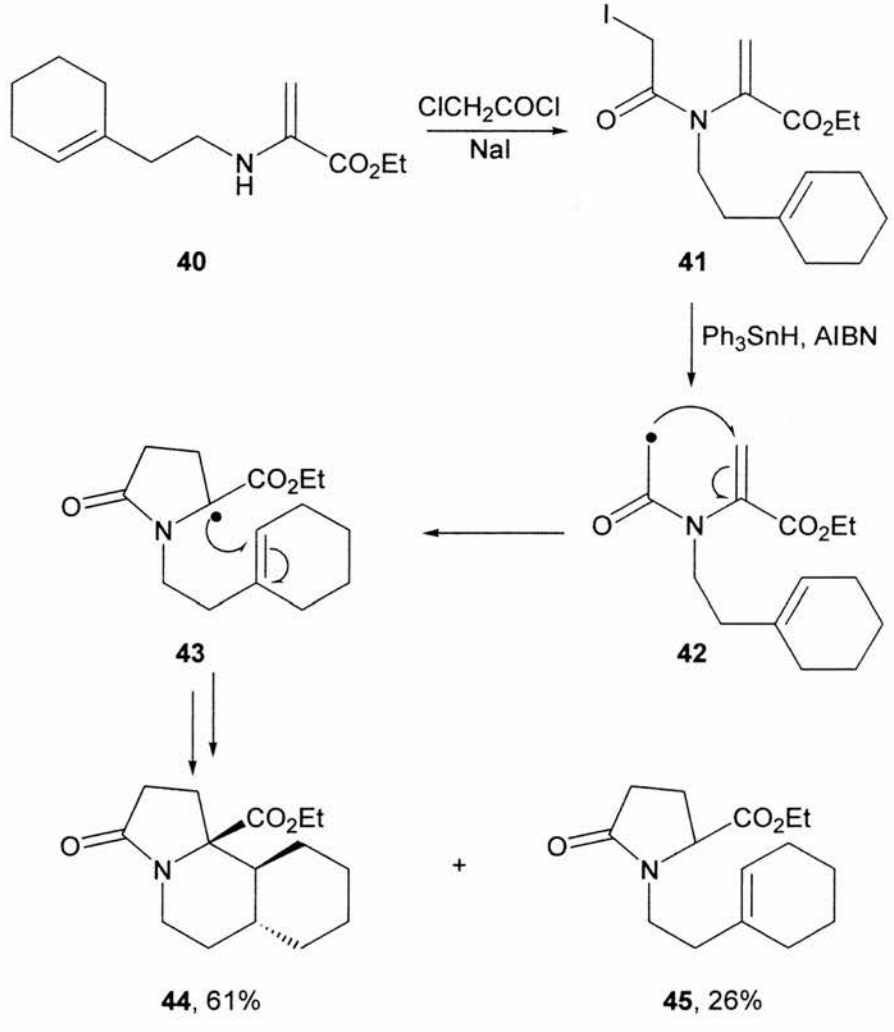


39

Combinations of many of the previously discussed methodologies for heterocyclic ring formation have been used in tandem radical cyclisations in order to synthesise various polycyclic nitrogen heterocycles. Generally, the tandem cyclisation is planned around a central nucleophilic nitrogen atom, which can undergo a range of alkylations to attach extra chains containing either the radical generating group or a chain containing unsaturated functionality for the radical intermediate to cyclise onto. The simplicity of alkylation reactions onto nitrogen atoms provides a fast and facile route into the synthesis of complex heterocyclic targets.

Parsons and co-workers demonstrated this process in the formation of the tricyclic pyrrolizidinone **44** (Scheme 11).[27, 28] The starting amide **40** was acylated using α-iodoacetyl chloride in order to generate the radical precursor **41**. Standard radical initiation using triphenyltin hydride and AIBN released the stabilised radical **42**,

which has been extensively studied and confirmed to undergo the unusual 5-*endo-trig* cyclisation to furnish the second radical intermediate **43**. The second cyclisation of radical **43** is an example of a stabilised radical preferring to undergo the thermodynamically favoured 6-*endo-trig* cyclisation rather than the faster 5-*exo-trig* process in order to furnish the desired tricyclic compound **44** in a yield of 61%. The mono-cyclised by-product **45** was also isolated as a minor product in a yield of 26%.



Scheme 11

Many examples for the use of this protocol in the synthesis of interesting and physiologically important heterocycles have been reported in the literature. However, a majority of these procedures involve the use of tin compounds to initiate and maintain the radical chain process. As discussed in Chapter 1, organotin compounds are toxic and have many undesirable physical properties, which are detrimental to their use in industry. It is therefore important to find alternative methods for generating these radical intermediates.

Alternatives to organotin compounds

The development of heterocyclic synthesis using radical processes is dependant on the general advances in radical synthetic methodology of non-heterocyclic systems, and the use of Bu_3SnH continues to dominate this field. However, purification issues prevent their use in industry.

The majority of alternative procedures developed to produce organic radicals in the absence of organotin hydrides have previously been discussed in Chapter 1. Many of these procedures have been effectively modified and employed in the formation of heterocyclic compounds, including the use of tributylgermanium hydrides, tris(trimethylsilyl)silane, tetrathiafulvalenes and solid phase, polymer supported, Bu_3SnH.

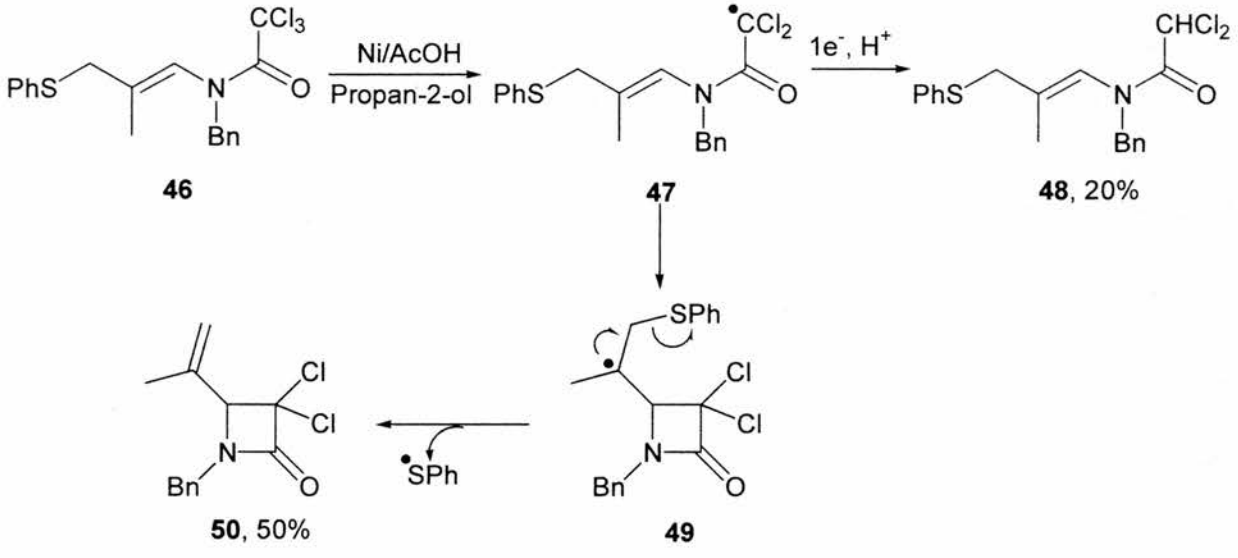
The reduction method: nickel powder

The formation of radicals using metal induced redox methodologies has been an area of intense study over recent years. They hold many advantages over the traditional use of tributyltin hydride, including their ability to introduce additional functionality into a molecule after the radical sequence.

For reductive processes, the difficulty commonly lies in finding a system which is able to readily transfer one electron to the radical precursor, while having a second electron transfer which remains sufficiently slow to allow the radical intermediate to undergo cyclisation. Recent studies by Zard *et al* have highlighted the use of nickel powder in these radical systems and illustrated their use in the construction of γ- and β-lactams (Scheme 12).[29]

The radical precursor **46** was prepared by the condensation of the appropriate aldehyde with benzylamine, followed by acylation of the resulting imine with trichloroacetyl chloride. When **46** was subjected to nickel powder and acetic acid, in refluxing propan-2-ol, the intermediate radical anion was formed which fragmented to give radical **47**. The second one-electron reduction, leading to the reduced product

48, was relatively slow, this allowed sufficient time for the 4-*exo-trig* cyclisation to occur in order to generate the β-lactam radical **49**, which rapidly underwent a fragmentation, with the loss of a stabilised phenylsulfide radical, to prevent further ring opening and furnish the highly functionalised β-lactam **50**. The presence of two chlorine atoms at the 3-position of the β-lactam proved useful for further reaction.



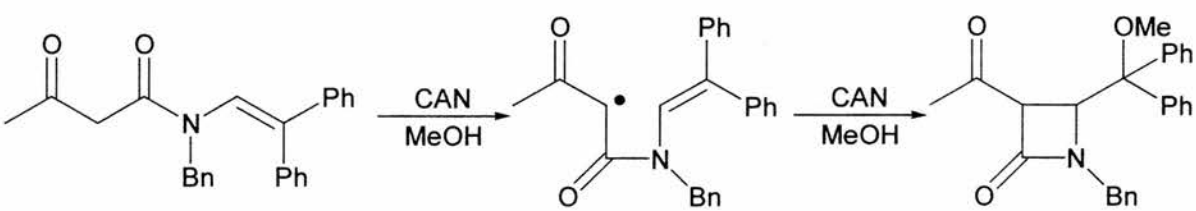
Scheme 12

The reversible nature of the β-lactam cyclisation dictated that a second irreversible step was necessary, after the initial cyclisation. The rapid loss of the stabilised sulfide radical prevented any ring opening and therefore none of the competing 5-*endo-trig* cyclisation product was observed. Attempts to trap the β-lactam radical, using an alkene, gave mixtures of both the β- and γ-lactam products due to the slower reaction time associated with an intermolecular addition. This favoured the re-opening of radical **49** and allowed the irreversible 5-*endo-trig* cyclisation to occur.

This synthetic procedure avoids the use of tributyltin hydride and provides a short synthetic route to a number of alkaloids. However, the presence of acetic acid in this technique proves to be a limiting factor when synthesising lactams with acid sensitive functionality.

The oxidation protocol: cerium(IV) ammonium nitrate

The use of cerium(IV) ammonium nitrate (CAN) in oxidative radical generation was first investigated by Heiba and Dessau.[30] The oxidative process uses metal salts with adjacent, stable, oxidation states to remove an electron from a dicarbonyl radical precursor **51** in order to generate the carbon centred radical **52**, which is immune to further oxidation due to its electrophilic nature. These carbon centred radicals can efficiently add to electron rich alkenes to produce an adduct which is more susceptible to oxidation. The resulting cation is finally attacked by a nucleophile or loses a proton to generate the appropriate alkene **53** (Scheme 13).[31, 32]



51 **52** **53**, 48%

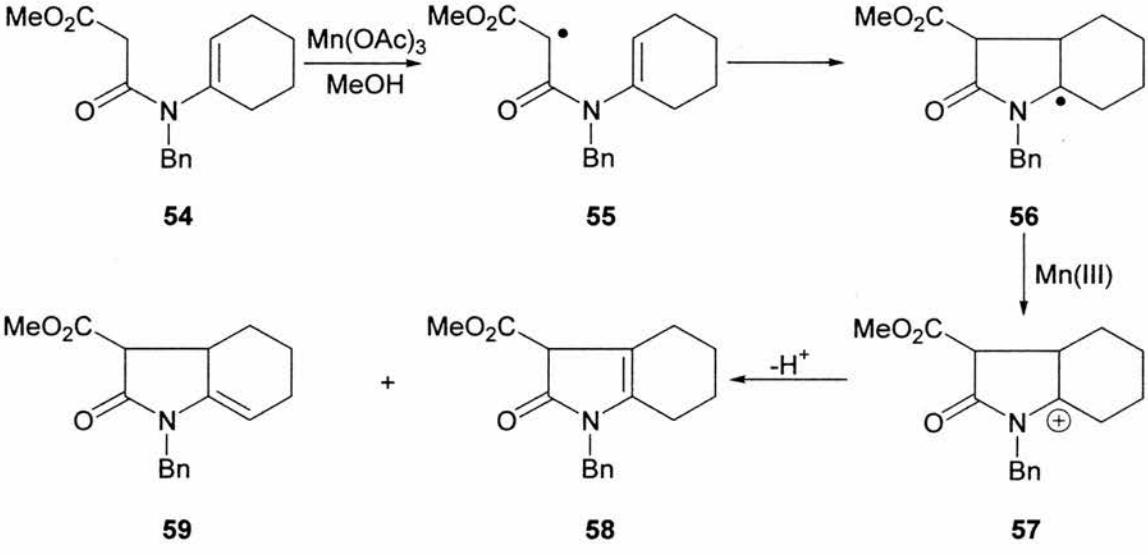
Scheme 13

The reaction of enamides with CAN provides a novel method for generating functionalised β- and γ-lactams in moderate yields. The presence of a ketone moiety at the C-4 position of the final β-lactam could render these compounds susceptible to further modification into useful synthetic intermediates. However, the requirement for a dicarbonyl radical precursor could prove problematic in some scenarios.

Manganese(III) acetate

$Mn(OAc)_3$ occupies a unique position among the one electron oxidants and has served as a key reagent in the synthesis of a number of important natural products.[33] The most commonly used precursors for Mn(III)-based cyclisations have included β-keto esters and malonic esters which readily undergo enolisation. However, recent studies have developed the use of the less acidic β-amido esters, which have demonstrated their ability to take part in 5-*exo*, 5-*endo* and 4-*exo* cyclisations to give pyrrolidines and β- or γ-lactams.[34, 35]

The major advantage of a manganese(III) process is the flexibilirty to choose between acetic acid or methanol as the reaction solvent. Methanol provides slightly milder reaction conditions which will have a reduced effect on functionalised side chains. Hence, when β-amido ester **54** and $Mn(OAc)_3$ were refluxed in boiling methanol, oxidation took place with the formal loss of a hydrogen atom (together with manganese(II)) to give the carbamoylmethyl radical **55** (Scheme 14). 5-*Endo-trig* cyclisation of this intermediate radical, formed the tertiary radical **56**, which was particularly susceptible to oxidation by reaction with a further equivalent of manganese(III). The resultant acyliminium ion **57** then underwent deprotonation to give alkenes **58** or **59**.[36, 37]

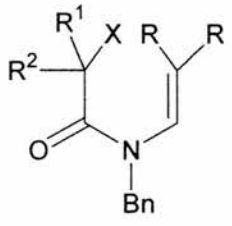


Scheme 14

Recent modification of this procedure by Parsons and co-workers has significantly reduced the severity of the reaction conditions, by replacing methanol with a dilute mixture of the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate in dichloromethane.[38] This averts solubility problems, and allows the manganese(III) mediated radical reactions to be carried out at lower temperatures. In addition, it also avoids the large degree of aqueous waste produced when removing acetic acid from the end products.

Several supplementary oxidation techniques have been studied over recent years, including copper(I) chloride/bipyridine systems[36] and dichlorotris-(triphenylphosphine)-ruthenium(II) complexes.[39] These metal complexes require

halo-enamides of type **60** in order to generate the associated carbamoylmethyl radicals, which have demonstrated their ability to undergo 4-*exo* and 5-*endo* radical cyclisations to form a variety of highly substituted β- and γ-lactams.



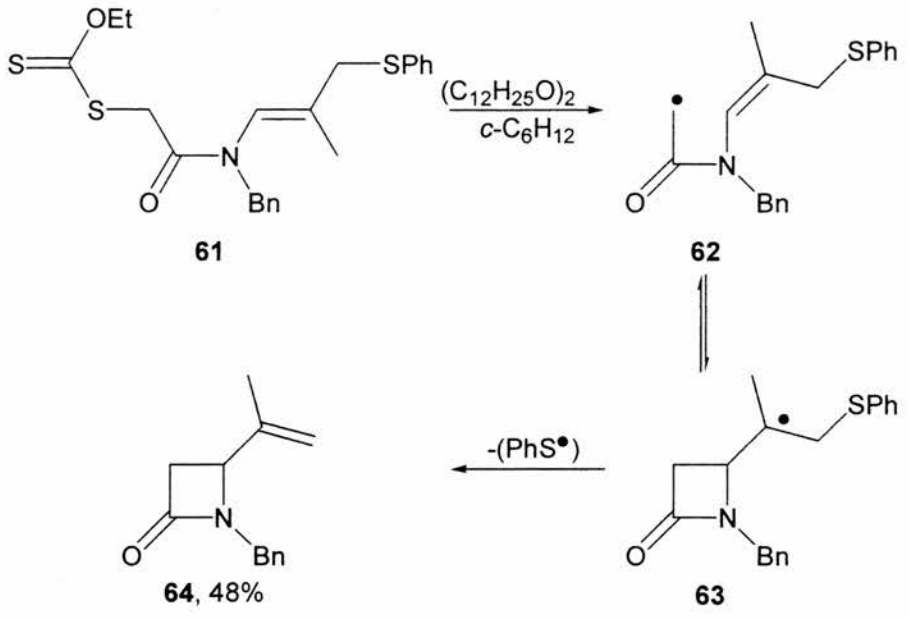
60
R=R=CH_3
R=R=$(CH_2)_5$

The use of xanthates

As part of their work studying the radical chemistry of Xanthates, Zard and co-workers found that their strategy could be utilised in the formation of β-lactams. The xanthate methodology held several advantages over the previously discussed processes, including:

(i) The creation of radicals *via* initiation with organic peroxides or light, without the intervention of heavy metals.
(ii) An intermediate radical that has a relatively long lifetime, therefore allowing it to undergo difficult cyclisations, or additions, to unactivated olefins.
(iii) The release of a final product that has xanthate functionality, opening up a route into the rich chemistry of sulfur for subsequent reactions.

When the *N*-alkenylacetamide **61** (prepared by the acylation of an imine with chloroacetyl chloride, followed by displacement of the chloride with a xanthate salt) was initiated using lauroyl peroxide, the xanthate group was abstracted to release the carbamoylmethyl radical **62**. The reversible and thermodynamically unfavourable 4-*exo* cyclisation was pushed to completion by the rapid β-elimination of a phenylthiyl radical from intermediate **63** to yield the desired β-lactam **64** in a yield of 48% (Scheme 15).[40]

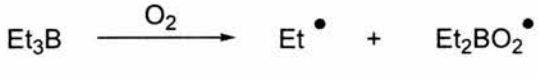


Scheme 15

The reversibility of both xanthate transfer and β-lactam cyclisation initially prevented the isolation of the cyclised product, as the intermediate β-lactam radical was not sufficiently stabilised to shift the equilibrium in favour of the β-lactam structure. In order to favour the formation of the β-lactam, a phenylthiyl group was required, which rapidly, and irreversibly, fragmented upon 4-*exo*-*trig* cyclisation to give the β-lactam **64**. This process prevents the transfer of the useful xanthate group onto the final product, but provides an equally functionalised alkene in its place.

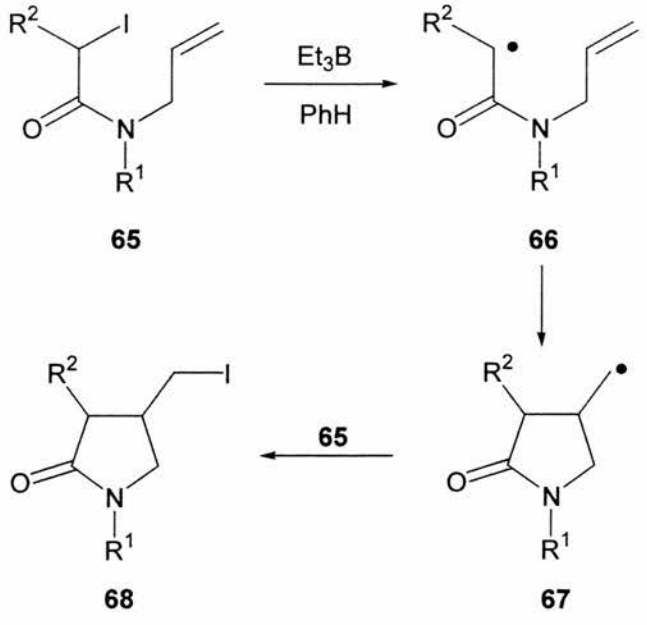
Triethylborane mediated atom transfer

It is known that triethylborane can rearrange to produce ethyl radicals when in the presence of oxygen (Scheme 16). These ethyl radicals can in turn be used to abstract an iodine atom from an iodoalkane in order to generate the desired alkyl radical, which can undergo inter- or intramolecular additions before abstracting iodine from another molecule of starting material to regenerate the intermediate radical. This process is known as iodine atom transfer.[41]



Scheme 16

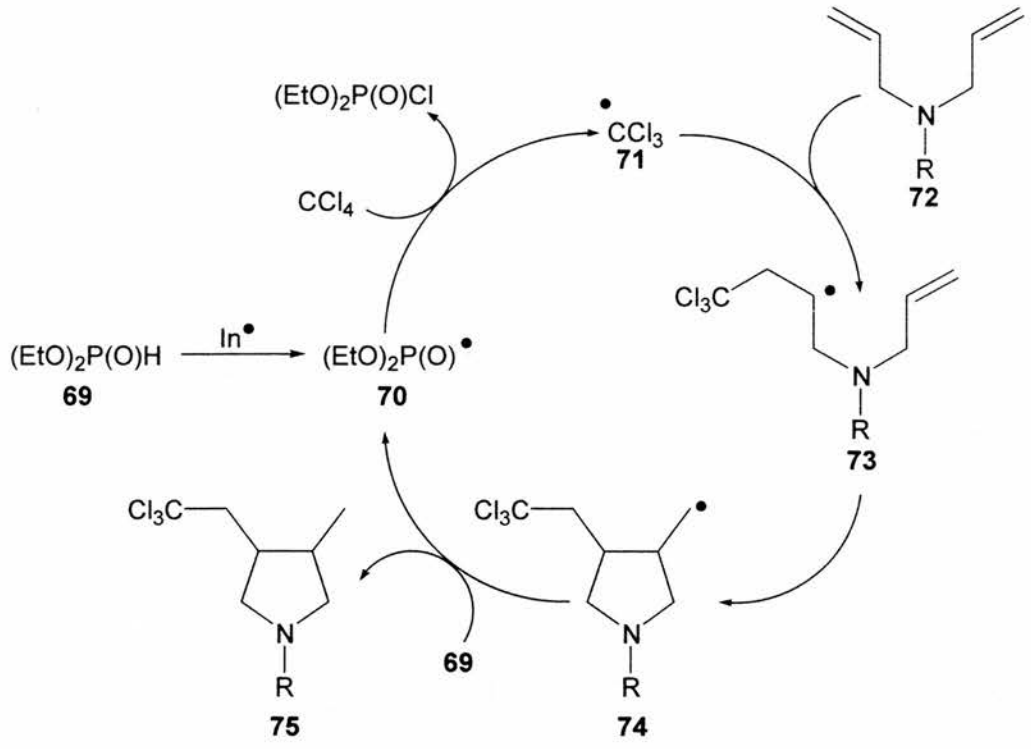
This property has been utilised in the radical cyclisations of 2-iodo-*N*-(prop-2-enyl)acetamides **65**, which undergo iodine atom transfer cyclisation when refluxed in the presence of Et_3B to produce 4-(iodomethyl)pyrrolidin-2-ones **68** in high yields (Scheme 17).[42] The cyclised radical **67** abstracts iodine from the starting material **65** to yield the product iodide **68** and regenerate the intermediate radical **66**.



Scheme 17

Radical cyclisations involving phosphonyl radicals

Preliminary research by Murphy, into the use of hypophosphorous acid and 1-ethylpiperidine hypophosphite in radical processes, initiated the development of diethyl phosphite and diphenylphosphine oxide, for use in radical cyclisation reactions, by Parsons and co-workers (Scheme 18).[43] Heating the starting phosphite **69** with peroxides readily formed phosphonyl radical **70**. This radical abstracted a weakly held halogen atom from an organohalide, in this case carbon tetrachloride, to release a trichloromethyl radical **71**. The addition of this electrophilic radical to the electron rich double bond of diene **72**, generated the secondary radical **73**, which rapidly underwent a 5-*exo-trig* cyclisation to generate primary radical **74**. Hydrogen abstraction from the initial starting phosphite **69** regenerated the phosphonyl radical **70** and furnished the cyclised pyrrolidine **75**.



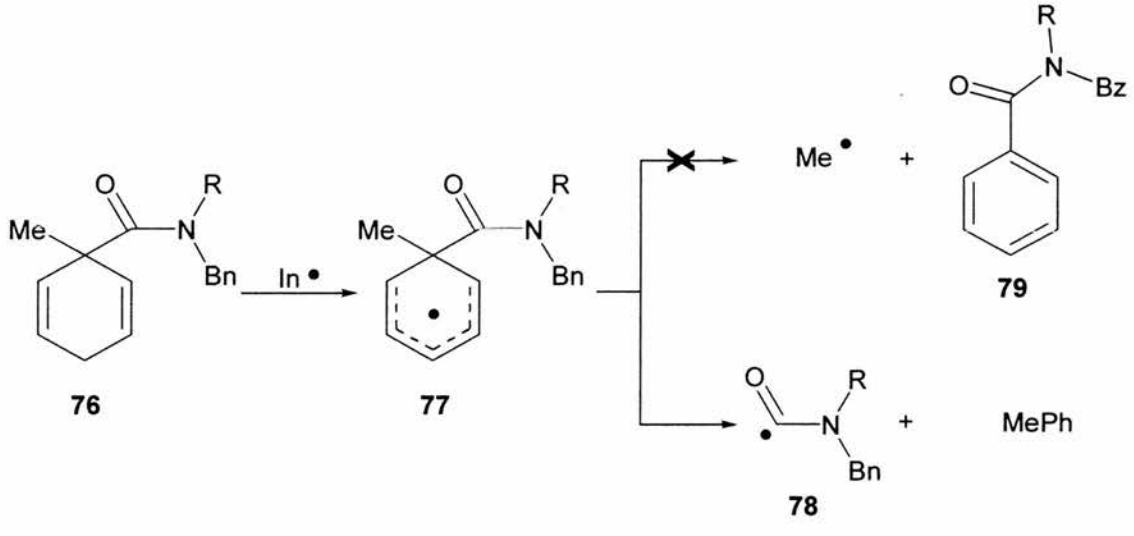
Scheme 18

This area of research is currently in its infancy and research shows that the cyclisation reactions are strongly affected by the solvent. However, the use of these reagents have a number of advantages over the use of tributyltin hydride, with regard to reduced toxicity and simplified purification due to the polarity of phosphorous chloride by-products. Future investigations could potentially increase reaction yields in order to provide a viable alternative to organotin compounds in these important cyclisations.

Generation of aminoacyl radicals from "proaromatic" compounds

Previous research confirmed that the esters of 1-methylcyclohexa-2,5-diene-1-carboxylic acid and of 2,5-dihydrofuran-2-carboxylic acid selectively furnished alkyl radicals upon induced homolysis.[44] These reagents were employed, with varying success, in radical additions to alkenes and in cyclisations. The main limitation of this process was the unwanted, competitive, dissociation of the intermediate 1-methyl-1-carboxylatocyclohexadienyl radicals that generated the methyl radical and benzoate esters as by-products.

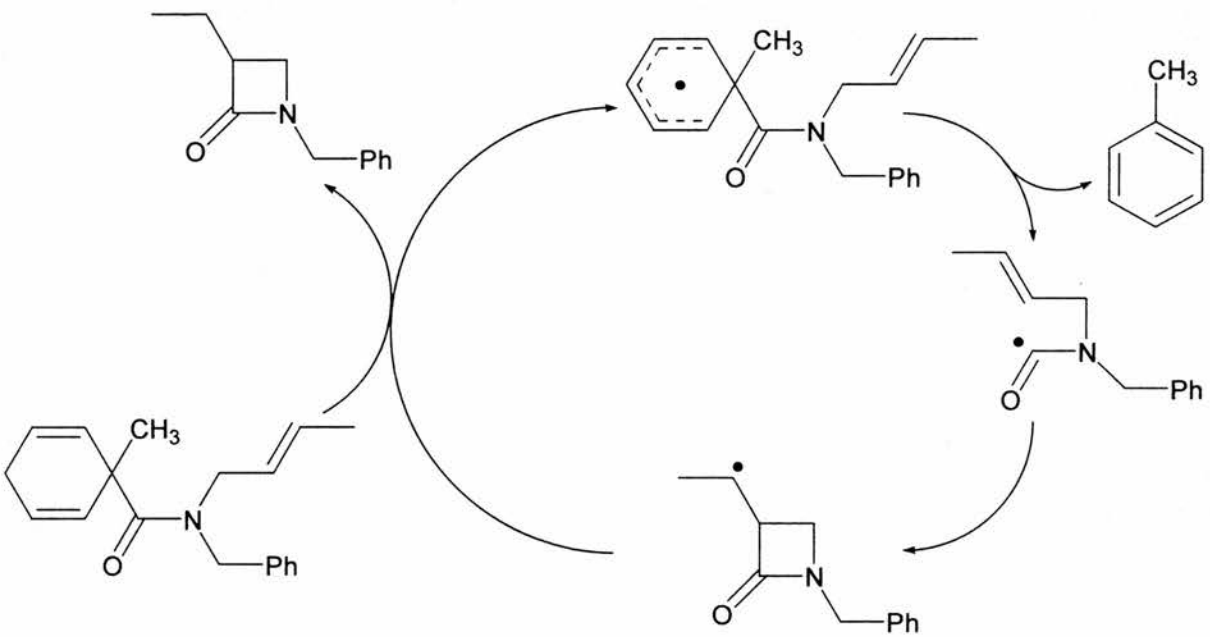
It was considered that the analogous amides **76** might function as good sources of aminoacyl radicals **78**, due to the increased stability of these radical intermediates in comparison to their alkoxyacyl alternatives (Scheme 19). This would favour the desired dissociation of the delocalised radical **77** to aminoacyl radical **78** and toluene, rather than the alternative dissociation of Me$^{\bullet}$ with production of amide **79**. The driving force for the reaction would be restoration of aromaticity to the six membered ring, and the toluene by-product should be efficiently removed by vacuum distillation or chromatography.



Scheme 19

In order to assess the abilities of the amidocyclohexadienes to undergo radical induced fragmentation, and release the desired aminoacyl radical, a number of 1-carbamoyl-1-methylcyclohexa-2,5-dienes were synthesised and tested using the previously discussed EPR spectroscopic techniques.

Pattenden had previously described the ability of aminoacyl radicals to undergo 4-*exo-trig* and 5-*exo-trig* cyclisations, using cobalt chemistry, in order to afford both β- and γ-lactams.[26] Therefore, in an attempt to advance this work, a number of suitably unsaturated amidocyclohexadienes were synthesised and investigated in an attempt to find new, metal free, methods for generating these physiologically important structures (Scheme 20).



Scheme 20

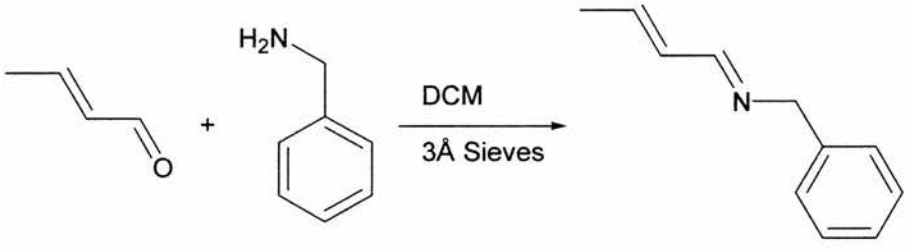
Results and Discussion

This section discusses the synthesis and subsequent radical reactions of several 1-carbamoyl-1-methylcyclohexa-2,5-dienes. The research carried out with each diene is assessed and discussed individually, in combination with the applicable EPR, in order to simplify presentation.

N-Benzyl-*N*-but-2-enyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 86

Previous work by Pattenden and co-workers indicated that the *N*-benzyl-*N*-but-2-enyl-formamide radical could be generated using cobalt salophen chemistry.[26] This radical was able to undergo 4-*exo*-*trig*-cyclisation in order to generate the β-lactam ring which has numerous applications in natural product synthesis. We were therefore interested to observe whether this important radical intermediate, and its cyclised product, could be generated using pro-aromatic chemistry.

Synthesis of *N*-benzyl-*N*-but-2-enylidineamine 81[26]

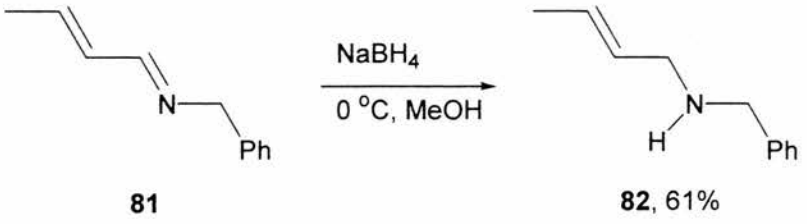


80 **81**, 98%

Scheme 21

The addition of benzylamine to but-2-enal **80** was carried out using a simplistic procedure described by Pattenden (Scheme 21).[26] Stirring the two reactants in dry DCM, over 3Å molecular sieves, generated the desired product **81** as a yellow oil in a crude yield of 98%. The slightly impure product contained traces of unreacted starting materials, however, further purification was not performed as these slight impurities were considered to be of little consequence in the following reaction.

Synthesis of *N*-benzyl-*N*-but-2-enylamine 82[26]

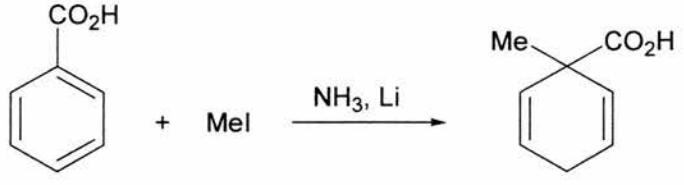


81 **82**, 61%

Scheme 22

A sodium borohydride reduction was performed on imine **81** in order to selectively reduce the imine and generate the corresponding amine **82**. The reaction followed a procedure described by Pattenden, where the impure imine was stirred at 0 °C while $NaBH_4$ was slowly added portionwise (Scheme 22). The resultant mixture was allowed to warm to room temperature and stirred for 18 h before the addition of excess concentrated HCl liberated the amine. The impure compound was dissolved in water and washed with ether before the addition of potassium hydroxide forced the desired product to fall out of solution. Finally, the amine was extracted with ether, and the combined organic phases concentrated, to furnish the title compound as a pale yellow oil. Purification by Kugelrohr distillation generated amine **82** as a colourless liquid in a yield of 61%.

Synthesis of 1-methylcyclohexa-2,5-diene-1-carboxylic acid 84[44, 45]

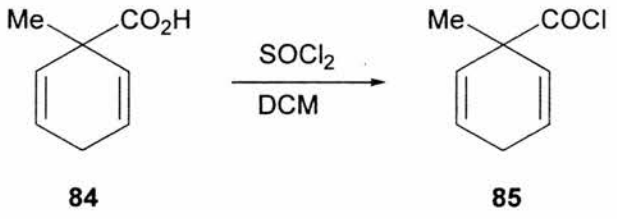


83 **84**, 79 %

Scheme 23

1-Methyl cyclohexadienyl acid **84** was prepared by reacting benzoic acid **83** with methyl iodide, under the Birch reduction/alkylation conditions specified in Chapter 2 (Scheme 23). The cyclohexadienyl acid **84** was isolated, using a standard aqueous workup, and washed with a saturated solution of sodium thiosulfate to remove any traces of iodine, before Kugelrohr distillation gave the pure acid as a pale yellow oil in a yield of 79 %.

Synthesis of 1-methylcyclohexa-2,5-diene-1-carbonyl chloride 85

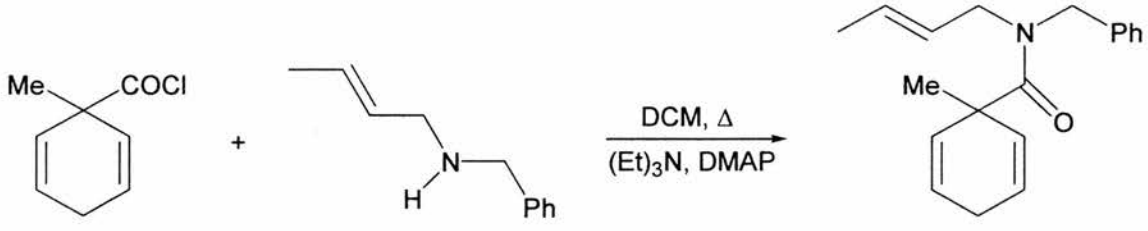


84 **85**

Scheme 24

The conversion of carboxylic acid **84** into the corresponding acid chloride **85** proved initially to be rather problematic, as each attempt yielded only unreacted starting materials. However, systematic adjustment of solvent volume and the use of completely dry apparatus eventually provided a favourable reaction environment, which yielded the desired acid chloride **85** in high yields. The conversion of the carboxylic acid into the acid chloride was straightforward to follow by ^{1}H NMR spectroscopy as the original multiplet at 5.85 ppm was split into two multiplets at 5.70 and 6.00 ppm after complete halogenation.

Synthesis of *N*-benzyl-*N*-but-2-enyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 86

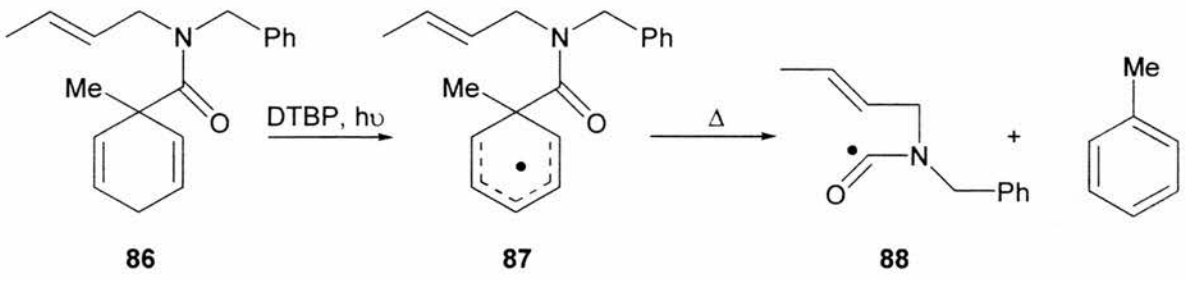


85 **82** **86**, 72 %

Scheme 25

In order to generate the desired amido cyclohexadiene **86**, the crude acid chloride **85** was added dropwise to a mixture of dichloromethane, purified amide **82**, triethylamine and a catalytic amount of DMAP (Scheme 25). The resultant solution was refluxed for 5h before a basic workup yielded the impure product, which was purified by column chromatography to furnish *N*-benzyl-*N*-but-2-enyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide **86** as a pale yellow oil in a yield of 72 %.

EPR analysis of *N*-benzyl-*N*-but-2-enyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 86



86 **87** **88**

Scheme 26

Previous research on the 1-alkyl cyclohexadienyl acids, outlined in Chapter 2, used EPR spectroscopy to confirm the ability of the acids to release alkyl radicals. We were interested in determining whether allylic hydrogen abstraction from the analogous cyclohexadienyl amide **86**, generating the delocalised cyclohexadienyl radical **87**, would be a feasible process, which would result in the release of the aminoacyl radical **88** and toluene (Scheme 26). EPR spectroscopy was employed, once again, in order to observe the formation of these transient radicals.

An EPR sample was prepared, as described previously for the cyclohexadienyl acids, (10 mg of amide, 200 μl DTBP) and degassed with N_2 for approximately 20 mins. The sample was placed in the EPR cavity, which was held at a temperature of 250 K, and a preliminary EPR spectrum acquired with the UV light activated in order to initiate the radical reaction. It soon became clear that the cyclohexadienyl amides would readily generate the delocalised cyclohexadienyl radical **87**, which was observed as an intense, well resolved EPR spectrum that was straightforward to characterise (Figure 1).

Figure 1

The temperature of the EPR cavity was gradually increased to 336 K, in order to encourage the scission of the carbon-carbon bond and resultant release of the aminoacyl radical **88**. The intensity of the acquired EPR spectrum at this higher temperature was significantly reduced due to the Boltzmann factor. However, it was still possible to recognise several peaks from the delocalised cyclohexadienyl radical **87** together with additional, broad, peaks from a new radical species. A further increase in cavity temperature to 360 K removed most of the peaks associated with the delocalised cyclohexadienyl radical and revealed a new spectrum which was characterised, by EPR simulation and comparison to literature hfs values, as the desired aminoacyl radical **88** (Figure 2).

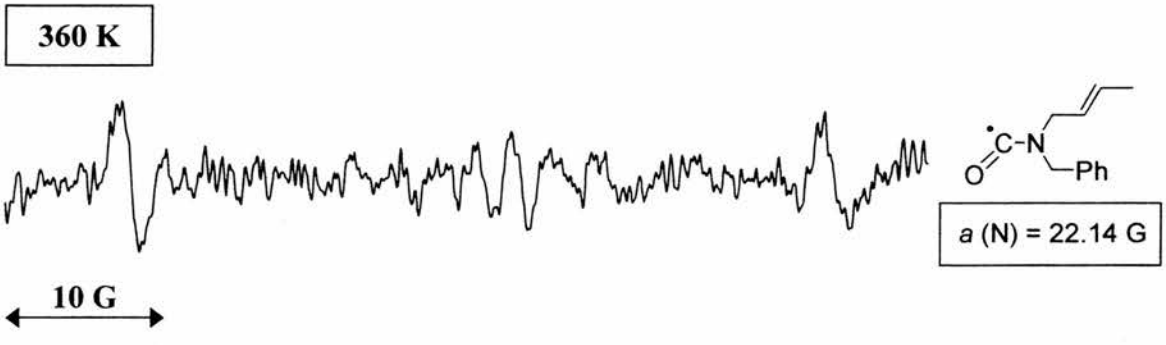


Figure 2

Further analysis of the EPR sample allowed us to locate a narrow temperature range where the recorded spectra progressively changed from the delocalised radical, to that of the rearranged aminoacyl radical. It was also possible to focus on a small, 26 G, section of the acquired spectra where peaks from both transient radical species could

be observed. This allowed us to acquire spectra quickly, therefore limiting the degree of sample degradation throughout data collection, and reducing background noise.

A stock solution of the amide **86** in DTBP was prepared, supplying ten equivalent EPR samples, which contained approximately 10 mg of the amide each. Each EPR sample was degassed using N_2 before EPR spectra were acquired in the temperature range of 300 – 330 K, using a fresh sample at each new temperature.

The recorded spectra were double integrated using the WinEPR software, as described for the cyclohexadienyl acids in Chapter 2, to give relative peak areas for both radical **87** and **88** respectively. These peak areas were converted into concentration data and placed into the derived Steady State equation to give values of k_d for the cyclohexadienyl amide at each individual temperature (Table 1).

T/K	[88]	[87]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ DTBP	k_d
308	2.302E-08	1.584E-07	-7.579	3.247	9.729	1.41E+02
314	3.468E-08	2.472E-07	-7.403	3.188	9.760	2.28E+02
319	6.027E-08	3.109E-07	-7.143	3.132	9.791	4.45E+02
325	5.630E-08	2.340E-07	-7.156	3.077	9.821	4.62E+02
331	6.331E-08	1.555E-07	-7.050	3.025	9.850	6.30E+02
336	7.829E-08	9.265E-08	-6.840	2.974	9.877	1.09E+03

Table 1

The value of log k_d at each temperature was plotted against $10^3/T$ in an Arrhenius plot, which displayed the trend between temperature and dissociation rate for the cyclohexadienyl amide **86** (Figure 3). The points all fall on a straight line, and the equation of this applied line was used to calculate the energy of dissociation (E_d), pre-exponential factor (A_d) and rate of dissociation at the desired temperature of 300 K (Table 2).

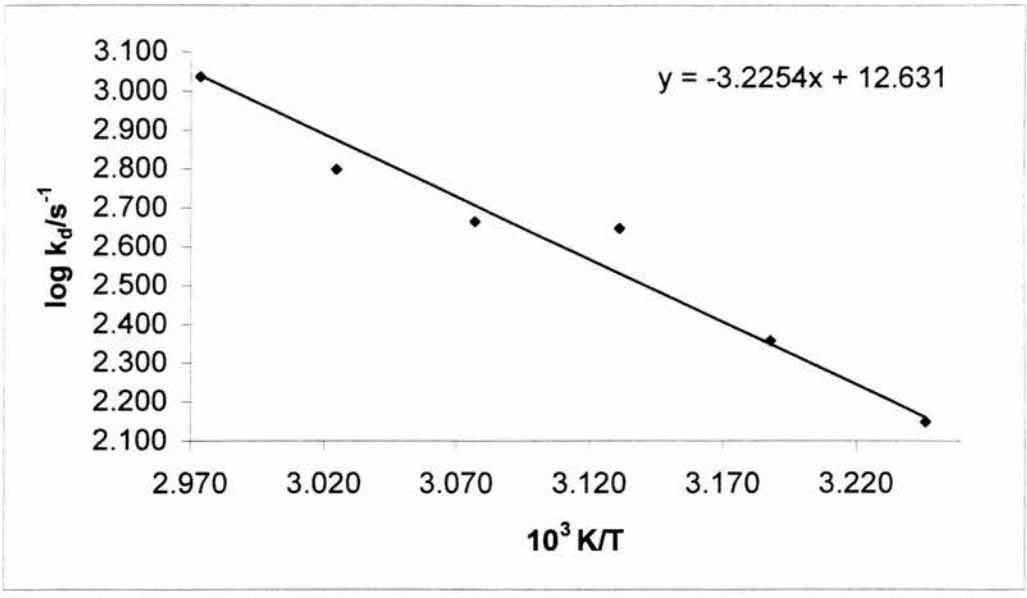


Figure 3

Released Radical	10^{-3} k_d / s^{-1} (300K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
88	0.073	12.63	14.76

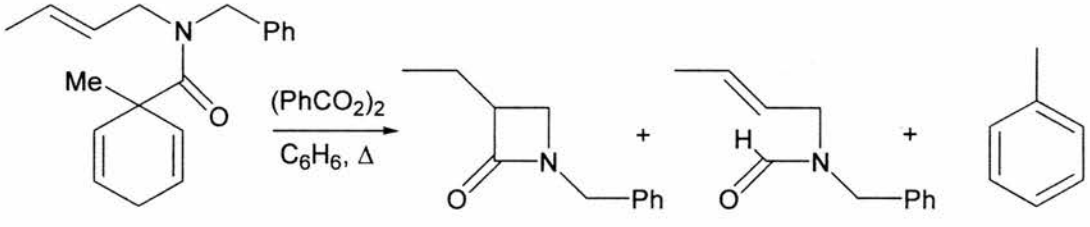
Table 2

The value of E_d seems moderately high for the release of the aminoacyl radical **88**, the rate of this dissociation appears to be slightly higher than those found for the release of a primary alkyl radical from the analogous cyclohexadienyl acids. This reflects the slight increase in stability of the released aminoacyl radical **88** and suggests that the carbon-carbon bond in the cyclohexadienyl amide **86** is marginally weaker than in the cyclohexadienyl acids. This leads to a higher rate of bond dissociation and a reduced degree of competitive fragmentation to release the methyl radical and generate the unwanted benzylamide.

EPR analysis of *N*-benzyl-*N*-but-2-enyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 86 using a different sample concentration

In order to assess the rate of hydrogen abstraction from the starting amide, a new stock solution was prepared which supplied ten equal samples containing 1 mg of the cyclohexadienyl amide **86**. The EPR experiments described above were repeated using identical experimental parameters and cavity temperatures, in order to provide a second set of kinetic data. The peaks due to both the delocalised cyclohexadienyl radical and the released aminoacyl radical were double integrated and compared with the values gained using the 10 mg sample. No significant difference in k_d values could be observed, therefore k_H was deemed negligible for amido-cyclohexadiene **86**.

Thermally initiated radical cyclisation of *N*-benzyl-*N*-but-2-enyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide 86



86 **89**, 34% **90**, 31%

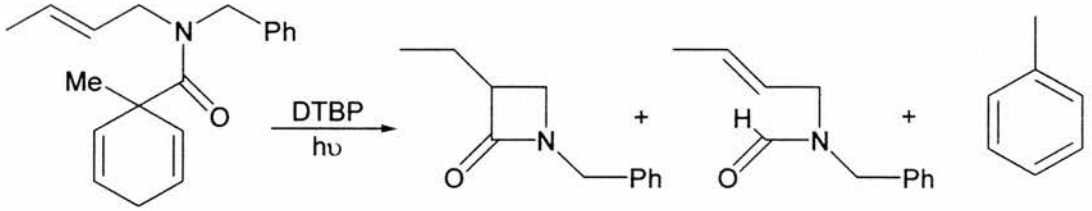
Scheme 27

After obtaining amide **86** in its purest form, the radical fragmentation of this compound was investigated. We were hopeful that the slow rate of hydrogen abstraction from the initial cyclohexadienyl amide **86**, along with the appropriate proximity of the double bond, would encourage the released aminoacyl radical to undergo a 4-*exo-trig*-cyclisation in order to generate the β-lactam (Scheme 27).

Refluxing a mixture of amide **86** and dibenzoyl peroxide in benzene initiated the radical reaction and furnished a mixture of products, which were analysed by GC/MS and ^{1}H NMR spectroscopy. Column chromatography of this mixture allowed us to separate out a majority of the impurities. However, GC/MS of this purified compound revealed the presence of both the cyclised **89** and uncyclised **90** products. Preparative TLC of this impure mixture allowed us to isolate and characterise both of

the products, and to calculate approximate yields using the crude product NMR spectroscopic data.

Photolytically initiated radical cyclisation of *N*-benzyl-*N*-but-2-enyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide 86



86 **89**, 42% **90**, 38%

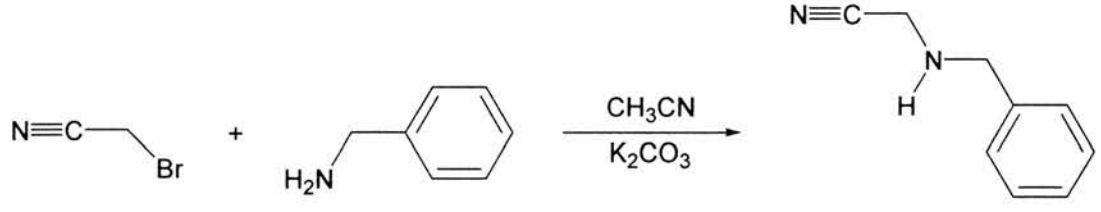
Scheme 28

We were interested in observing any change in product yields for the alternative, photolytic, radical fragmentation of cyclohexadienyl amide **86** (Scheme 28). Irradiation of the amide in the presence of DTBP furnished a mixture of products, which were analysed by GC/MS. A mixture of the cyclised β-lactam **89** and the uncyclised formamide **90** was detected in a similar ratio to that observed for the thermally initiated reaction, and the lack of any peak from the starting amide confirmed the complete rearrangement of the cyclohexadiene. GC/MS yields were measured by comparison of the peak areas to that of a known quantity of a formamide standard, verifying that the major product was the cyclised compound **89** in a yield of 42% and the minor, uncyclised product **90** was formed in a yield of 38%. Careful analysis of the GC/MS plot gave no evidence for the formation of benzylamide *via* the competitive dissociation of a methyl radical.

N-Benzyl-*N*-cyanomethyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 93

The success in generating an aminoacyl radical from the standard cyclohexadienyl framework, led us to continue this area of investigation in an attempt to generate further aminoacyl compounds that contain different categories of functionality. The incorporation of a cyanomethyl group into the released radical seemed a rather attractive prospect as this compound would contain a triple bond and an additional nitrogen functionality which would act as an excellent site for subsequent reactions, after radical addition. It was also postulated that the released aminoacyl radical could undergo 4-*exo*-*dig*-cyclisation in order to yield a functionalised β-lactam ring with an exocyclic double bond.

Synthesis of benzylaminoacetonitrile 92[46]



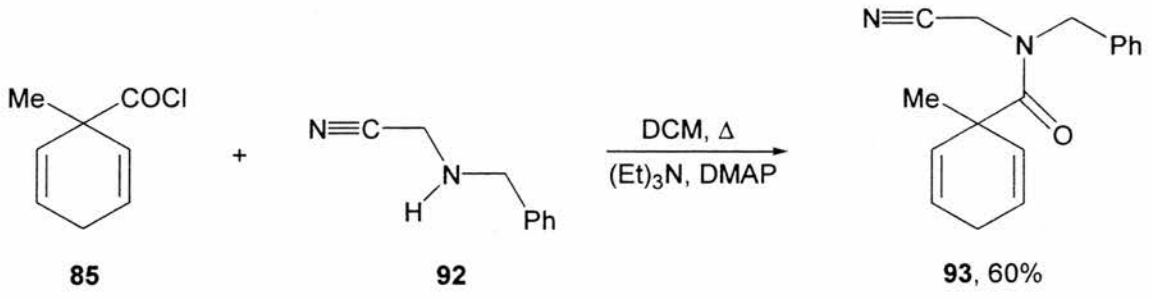
91 **92**, 87 %

Scheme 29

A literature search highlighted the many diverse methods available for the formation of benzylaminoacetonitrile **92**; however, Pandey and co-workers described a relatively simple reaction for the addition of a halogenated nitrile **91** to an amine by refluxing in acetonitrile in the presence of potassium carbonate (Scheme 29). This novel technique had been used to form a range of amines, although the formation of benzylaminoacetonitrile **92** had not previously been attempted.

The slow addition of the alkyl halide **91** to a refluxing mixture of benzylamine, acetonitrile and K_2CO_3 proceeded smoothly, giving a slightly impure oil after 12h reflux. The crude product was purified using column chromatography, eluting with 10% ethyl acetate in hexane, in order to furnish benzylaminoacetonitrile **92** as a colourless liquid in a yield of 87% .

Synthesis of *N*-benzyl-*N*-cyanomethyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 93

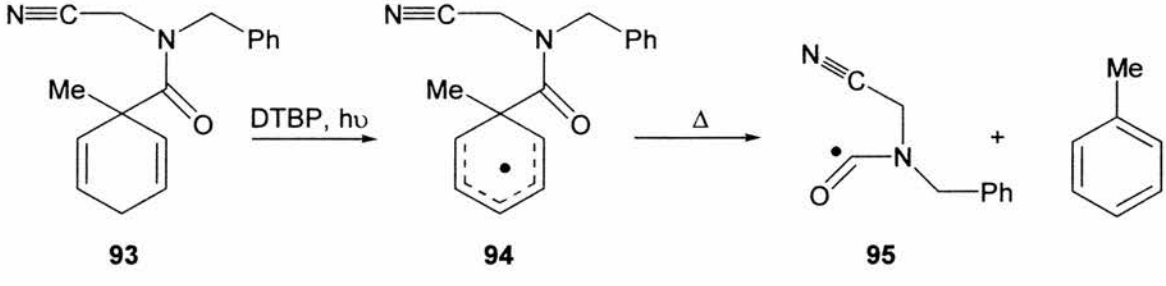


85 **92** **93**, 60%

Scheme 30

The cyclohexadienyl amide **93** was formed as previously described, by adding the previously synthesised methyl acid chloride **85** to a mixture of dichloromethane, purified benzylaminoacetonitrile **92**, triethylamine and a catalytic amount of DMAP (Scheme 30). The resultant solution was refluxed for 5 h before a basic workup yielded the impure product, which was isolated by column chromatography, eluting with 5% ethyl acetate in hexane, to furnish *N*-benzyl-*N*-cyanomethyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide **93** as a yellow oil in a yield of 60%.

EPR analysis of *N*-benzyl-*N*-cyanomethyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 93



93 **94** **95**

Scheme 31

The pure cyanomethyl amide **93** was analysed in the conventional manner using EPR spectroscopy. An initial sample was prepared (10 mg cyclohexadienyl amide, 200 µl DTBP) and degassed before being placed into the EPR resonator, which was held at a temperature of 250 K. A preliminary EPR experiment, using UV light to initiate the radical reaction, delivered an intense and well-resolved spectrum that was attributed to the delocalised cyclohexadienyl radical **94** after simulation (Figure 4).

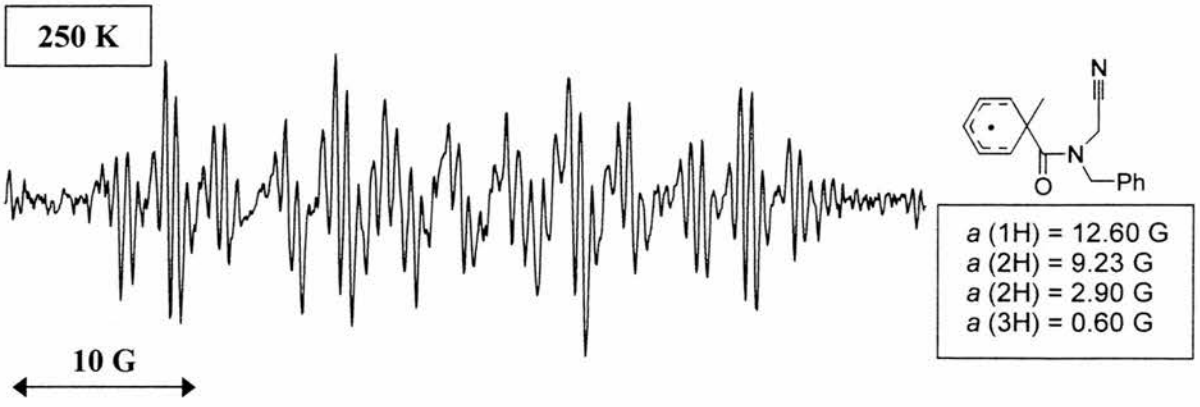


Figure 4

As the temperature of the EPR cavity was increased to 360 K, the acquired EPR spectrum changed significantly. However, the new spectrum did not correspond to that expected for the released aminoacyl radical **95**, and simulation did not help with the elucidation of a possible structure for this unknown species. After several attempts at purifying the cyclohexadienyl amide and repeating the EPR spectra at higher temperatures, it was confirmed that spectra for the released aminoacyl radical **95**, or its cyclised derivative, could not observed as they were replaced by this unknown radical species. This factor prevented us from acquiring any kinetic data for cyanomethyl amide **93**.

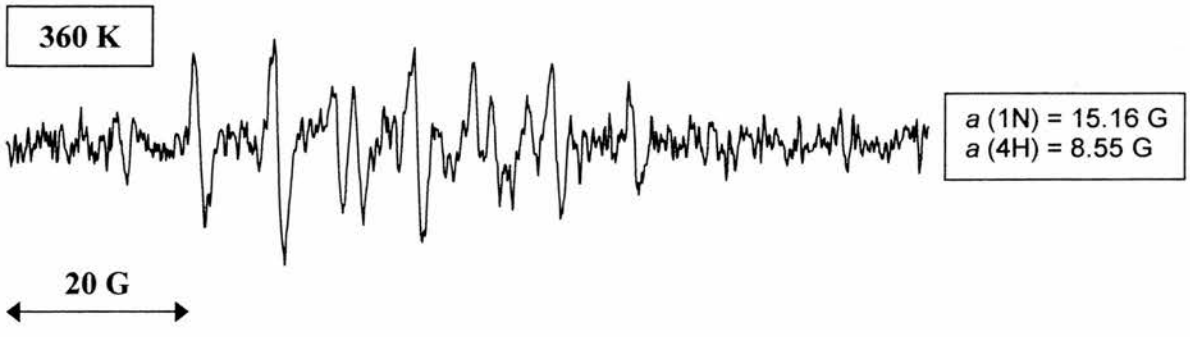
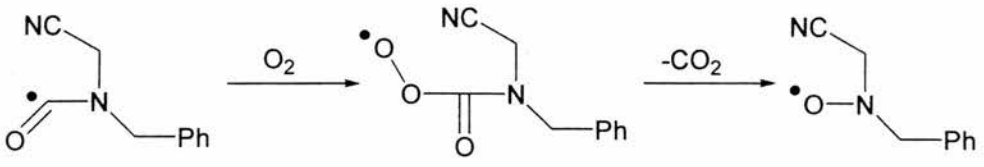


Figure 5

The g-factor of the unknown radical intermediate was consistent with that expected for a nitroxide radical (2.0062). It was therefore proposed that the unknown radical species could be a nitroxide radical, formed by the addition of oxygen to the

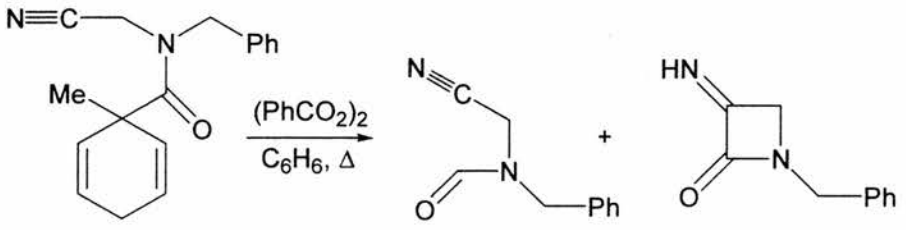
aminoacyl radical **95**, and an ensuing decarboxylation to yield nitroxide **96** (Scheme 32).



95 **96**

Scheme 32

Thermally initiated radical fragmentation of *N*-benzyl-*N*-cyanomethyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide 93



93 **97**, 57% **98**

Scheme 33

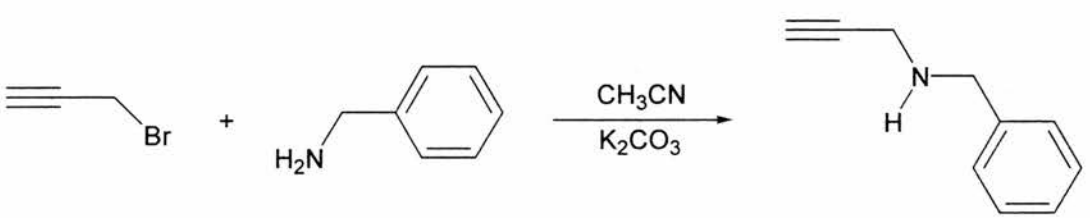
In order to verify the ability of the cyclohexadienyl amide **93** to rearrange into toluene and the desired aminoacyl radical **95**, a thermally induced radical fragmentation was performed (Scheme 33). Refluxing a mixture of the pure cyclohexadienyl amide **93** and dibenzoyl peroxide in benzene, initiated the radical reaction and furnished a mixture of products, which were analysed by GC/MS and ^{1}H NMR spectroscopy. Column chromatography of this mixture, eluting with 10% ethyl acetate in light petroleum, allowed us to isolate the desired *N*-benzyl-*N*-cyanomethyl formamide **97** as a colourless oil in a yield of 57%. However, there was no evidence for the formation of the cyclised compound **98**.

Attempts to generate aminoacyl radical **95** photolytically, using DTBP as the radical initiator, gave similar results, although there were significant amounts of unreacted starting material detected in the GC/MS due to premature termination of photolysis.

N-Benzyl-*N*-prop-2-ynyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 101

Our inability to detect the released aminoacyl radical using EPR spectroscopy for the cyanomethyl analogue **93**, directed our attempts to synthesise another cyclohexadienyl amide. The propargyl amide **101** is structurally similar to the previously synthesised cyanomethyl compound; however, it was hoped that the released aminoacyl radical could be observed using EPR spectroscopy, therefore allowing us to calculate the dissociation rates of these novel radical precursors.

Synthesis of prop-2-ynyl-benzylamine 100[47]

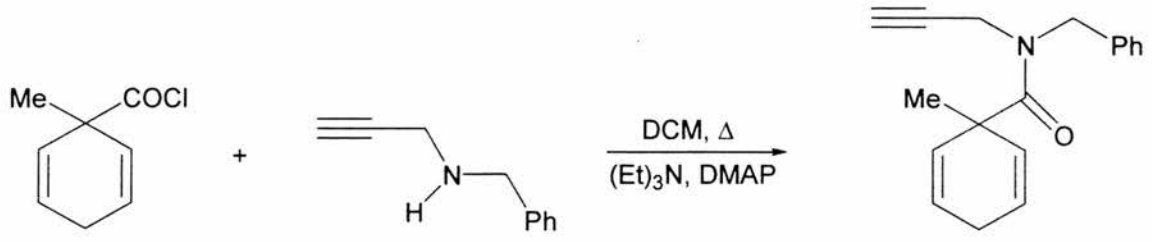


99 **100**, 48 %

Scheme 34

The amine was prepared in a similar fashion to the previously synthesised cyanomethyl analogue **92**. Prop-2-ynyl benzylamide **100** had previously been synthesised by Gordon and co-workers using this method in moderate yields of 45%.[47] Following this procedure, 3-bromopropyne **99** was added to a refluxing mixture of acetonitrile containing benzylamine and potassium carbonate. After continuous reflux for 12h, the solid residue was removed by filtration and washed with several portions of ethyl acetate in order to yield the crude product. Column chromatography, eluting with 10% ethyl acetate in hexane, allowed us to isolate the desired amine **100** in a yield of 48 %.

Synthesis of *N*-benzyl-*N*-prop-2-ynyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 101

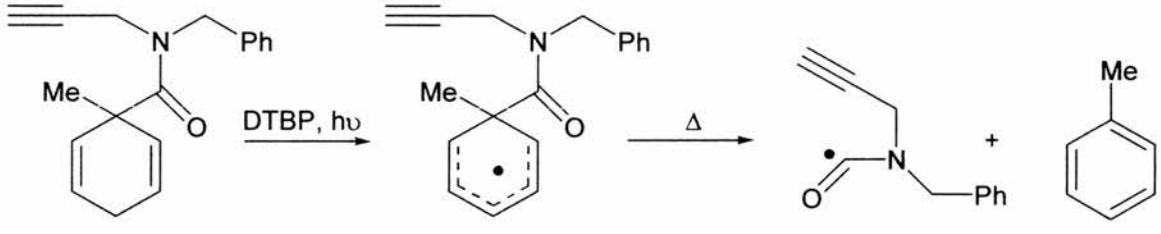


85 **100** **101**, 53 %

Scheme 35

The amido-cyclohexadiene **101** was synthesised by the addition of the previously prepared methyl acid chloride **85** to a mixture of dichloromethane, purified prop-2-ynyl benzylamine **100**, triethylamine and a catalytic amount of DMAP (Scheme 35). The resultant solution was refluxed over a period of 5 h, before an aqueous workup yielded the impure product. Purification by column chromatography, eluting with 5% ethyl acetate in hexane, allowed us to isolate *N*-benzyl-*N*-prop-2-ynyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide **101** as a yellow oil in a yield of 53 %.

EPR analysis of *N*-benzyl-*N*-prop-2-ynyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 101



101 **102** **103**

Scheme 36

The prop-2-ynyl amide **101** was analysed using EPR spectroscopy, in an attempt to gain kinetic data for the release of the functionalised aminoacyl radical **103**. An initial sample was prepared (10 mg prop-2-ynyl amide, 200 μl DTBP) and degassed before being placed into the EPR resonator, which was held at a temperature of 250 K. An initial EPR spectrum was acquired, using UV light to initiate the radical reaction, and delivered a well-resolved spectrum that was recognised as belonging to

the delocalised cyclohexadienyl amide **102**. The acquired spectrum appeared very similar to those observed previously for other cyclohexadienyl amides, a factor that is validated by the similar values of hfs.

Figure 6

As the temperature of the EPR cavity was systematically increased to encourage rearrangement, the spectrum of the detected transient radical changed. However, as observed previously with the cyanomethyl derivative, the new spectrum did not correspond to that expected for the released aminoacyl radical **103**, and simulation did not help us elucidate a possible structure for this unknown species. The spectra for the released aminoacyl radical, or its cyclised derivative, could not be observed as they were replaced by this unknown radical species. This prevented us from acquiring any kinetic data.

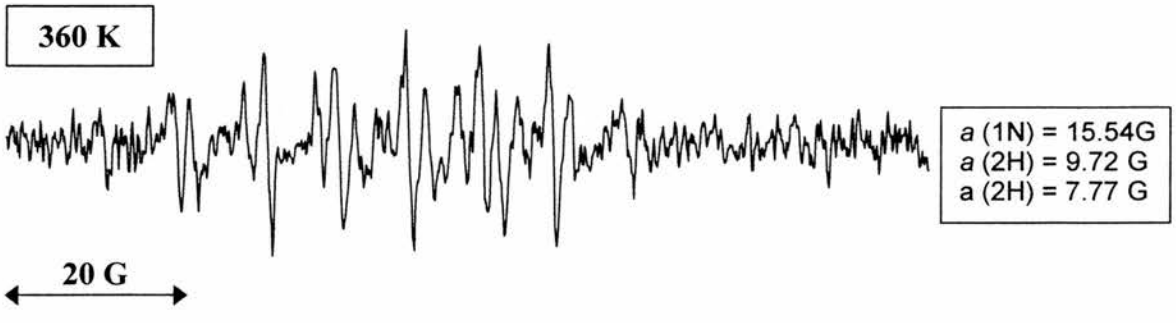
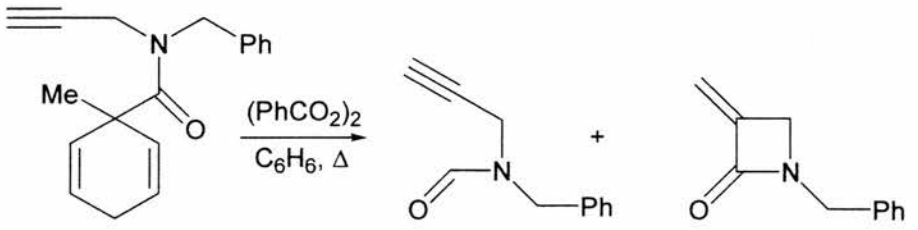


Figure 7

Thermally initiated radical fragmentation of *N*-benzyl-*N*-prop-2-ynyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide 101



101 **104**, 64% **105**

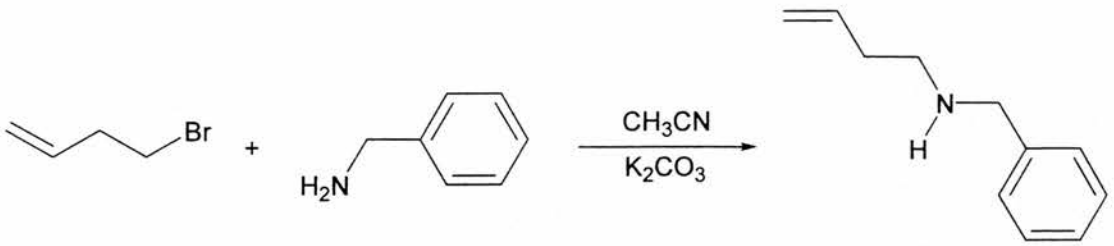
Scheme 37

The thermally induced radical fragmentation of amide **101** was performed in order to confirm the release of the desired aminoacyl radical **103**. Refluxing a mixture of the pure cyclohexadienyl amide and dibenzoyl peroxide in benzene, initiated the radical reaction and furnished a mixture of products, which were analysed by GC/MS and ^{1}H NMR spectroscopy. Column chromatography of this mixture, eluting with 10% ethyl acetate in light petroleum, allowed us to isolate the desired *N*-benzyl-*N*-prop-2-ynyl formamide **104** as a colourless oil in a yield of 64%. The GC/MS spectra also confirmed the presence of a significant amount of unreacted starting material. This suggests that the reaction needs more than one equivalent of the initiator in order to maintain the reaction cycle, a factor which is attributable to the aminoacyl radicals low rate of hydrogen abstraction from the starting cyclohexadiene. There was no evidence for the formation of the cyclised compound **105**.

The photolytically induced radical fragmentation, using four equivalents of DTBP as the radical initiator, gave a similar GC/MS to the previous thermal fragmentation. The amount of unreacted starting material detected in the GC/MS spectrum was reduced considerably when using larger amounts of radical initiator, however, it was proposed that gradual darkening of the sample during photolysis, restricted the passage of UV light through the sample and consequently prevented complete fragmentation.

N-Benzyl-*N*-but-3-enyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 108

Synthesis of but-3-enylbenzylamine 107

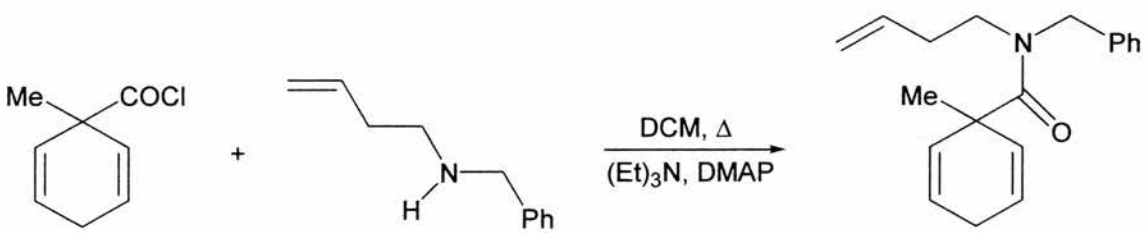


106 **107**, 38 %

Scheme 38

The unsaturated amine **107** was prepared as previously discussed, adding 4-bromobut-1-ene **106** to a refluxing mixture of acetonitrile containing benzylamine and potassium carbonate. After continuous reflux for 12 h, the solid residue was removed by filtration and washed with several portions of ethyl acetate in order to yield the crude product. Column chromatography, eluting with 10% ethyl acetate in hexane, allowed us to isolate the desired amine **107** in a yield of 38 %.

Synthesis of *N*-benzyl-*N*-but-3-enyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 108



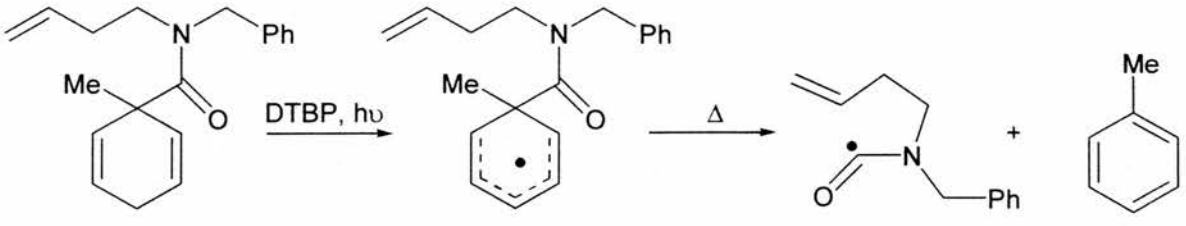
85 **107** **108**, 60 %

Scheme 39

The amido-cyclohexadienyl compound **108** was synthesised in the conventional manner, by the addition of the previously prepared methyl acid chloride **85** to purified but-3-enylbenzylamine **107** in order to furnish the impure product as a dark brown oil (Scheme 39). Purification by column chromatography, eluting with 10% ethyl acetate

in hexane, allowed us to isolate *N*-benzyl-*N*-but-3-enyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide **108** as a pale yellow oil in a yield of 60 %.

EPR analysis of *N*-benzyl-*N*-but-3-enyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 108



108 **109** **110**

Scheme 40

All of the preceding amides have delivered intense and well-resolved EPR spectra for the delocalised cyclohexadienyl radical, when initiated photolytically. However, only the but-2-enyl amide analogue has provided sufficient evidence for the release of an aminoacyl radical as the temperature of the EPR cavity was increased. It was anticipated that the but-3-enyl amide **108** would give strong EPR spectra for both transient radicals **109** and **110** in an accessible temperature range, enabling us to calculate rates of dissociation for this novel radical precursor (Scheme 40).

A preliminary EPR sample was prepared in the customary fashion (10 mg cyclohexadienyl amide, 200 μl DTBP), before being placed in the EPR cavity, which was held at a temperature of 250 K. The EPR spectrum, which was recorded in the presence of UV, had similar hfs to all of the previous cyclohexadienyl compounds and therefore confirmed the presence of the delocalised cyclohexadienyl radical **109** at this temperature (Figure 8).

Figure 8

As the temperature of the EPR cavity was systematically increased to a maximum of 360 K, the spectrum attributed to the cyclohexadienyl radical **109** diminished in size and was replaced by a simple N triplet (a(1N)=22.11 G) which could be assigned to the released aminoacyl radical **110**.

As predicted, both the cyclohexadienyl and released aminoacyl radicals could be observed using EPR spectroscopy within the accessible temperature. As a result, it was possible to measure the relative concentrations of these transient radicals at specific temperatures in order to calculate data for the rate of dissociation of this cyclohexadienyl amide.

Sample degradation proved to be a major issue at higher cavity temperatures. However, using the previously acquired data, it was possible to locate a small section of the EPR spectra where unimpeded peaks from both of the transient radicals could be observed. A reduction in the sweep width of the EPR experiment enabled us to acquire the EPR spectra swiftly and with minimal background noise.

A stock solution of the cyclohexadienyl amide **108** in DTBP was prepared, supplying ten equal samples containing 10 mg of the amide, for EPR analysis. Several EPR experiments were carried out using the same experimental parameters in the temperature range of 305-340 K, employing a new sample at each temperature (Figure 9). The acquired EPR data was processed using the WinEPR software, in order to give relative values of concentration for each transient radical. This information was placed into the derived Steady State equation in order to deliver a rate of dissociation (k_d) for each temperature setting (Table 3).

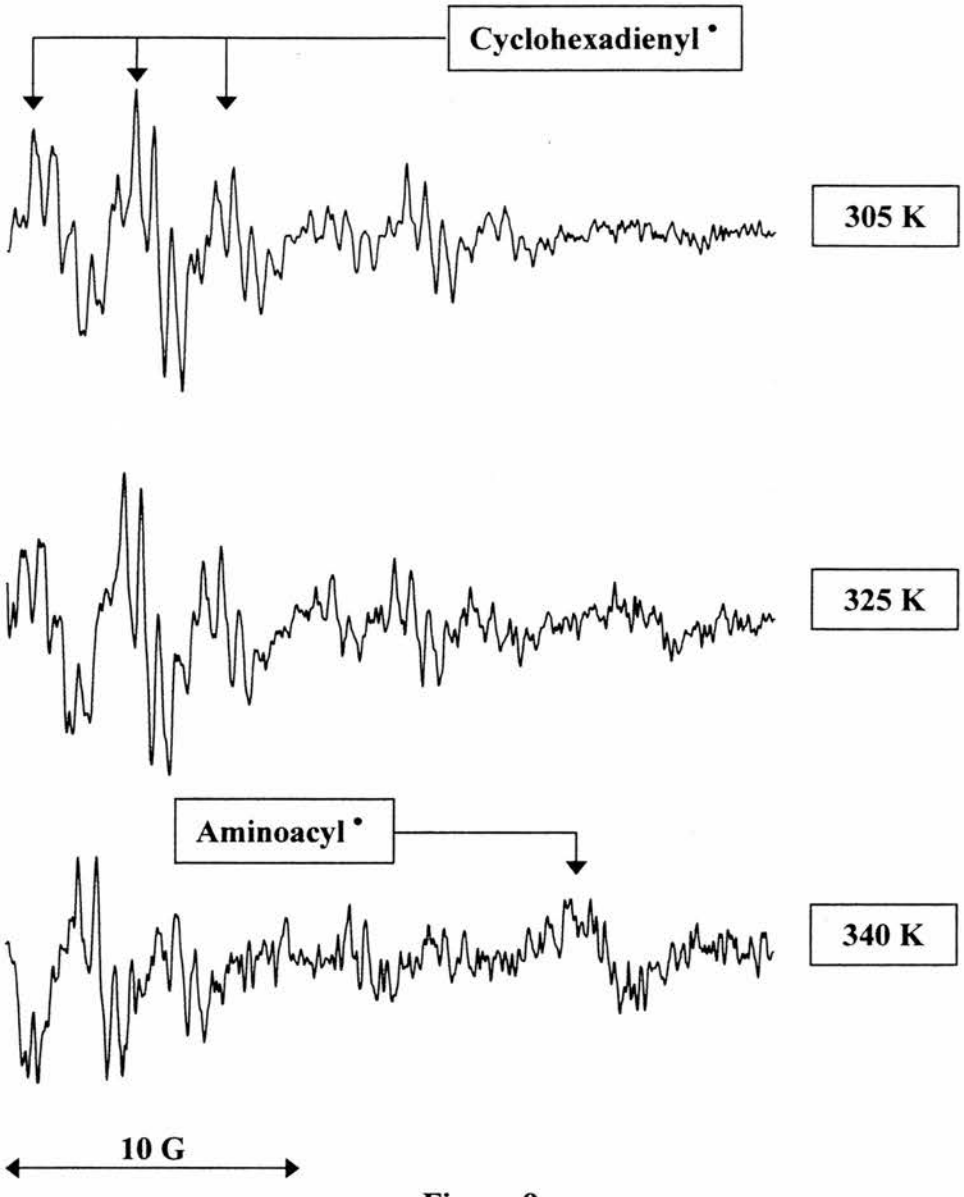


Figure 9

T/K	[110]	[109]	log $k_d/2k_t$	$10^3/T$	log $2k_t$ DTBP	k_d
308	2.069E-08	3.774E-07	-7.661	3.247	9.729	1.17E+02
314	3.576E-08	4.258E-07	-7.412	3.188	9.760	2.23E+02
319	4.058E-08	3.167E-07	-7.339	3.132	9.791	2.83E+02
325	5.115E-08	3.289E-07	-7.228	3.077	9.821	3.91E+02
331	4.692E-08	3.031E-07	-7.266	3.025	9.850	3.83E+02
336	6.694E-08	2.798E-07	-7.081	2.974	9.877	6.25E+02
342	7.172E-08	2.399E-07	-7.031	2.925	9.904	7.47E+02
348	9.972E-08	2.024E-07	-6.827	2.877	9.930	1.27E+03
353	6.399E-08	1.706E-07	-7.056	2.831	9.955	7.94E+02
359	6.971E-08	1.371E-07	-6.978	2.786	9.979	1.00E+03

Table 3

The values for k_d at each temperature can be represented on an Arrhenius plot of log k_d against $10^3/T$ (Figure 10). It can clearly be seen that the majority of these values fall on a straight line, and this allows us to calculate values for the pre-exponential factor (A_d), energy of dissociation (E_d) and the approximate value of k_d at a predetermined temperature (Table 4). However, two points at the highest temperatures do not follow the applied line of best fit. It was proposed that the higher temperature encouraged the aminoacyl radical to undergo a 5-*exo-trig* cyclisation, in order to give a different radical centre that was too weak to be detected by EPR. This had the net effect of reducing the observed concentration of aminoacyl radical **110** and therefore reducing the value of k_d. In order to acquire an accurate prediction for k_d, the two highest temperature points were omitted from the linear regression analysis.

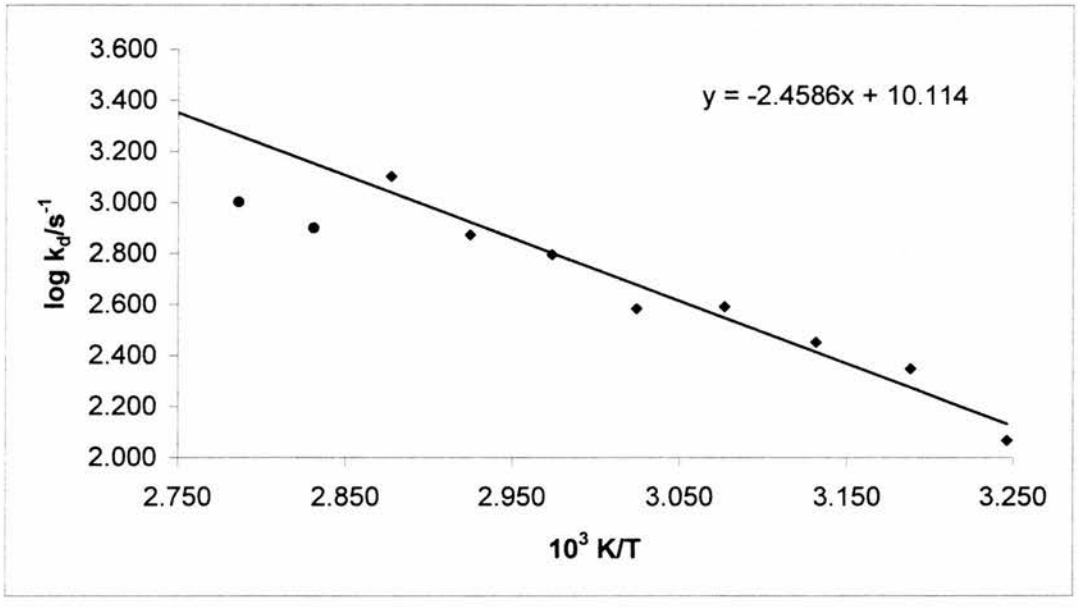


Figure 10

Released Radical	10^{-3} k_d / s^{-1} (300K)	Log A_d / s^{-1}	E_d / kcal mol^{-1}
110	0.08	10.11	11.25

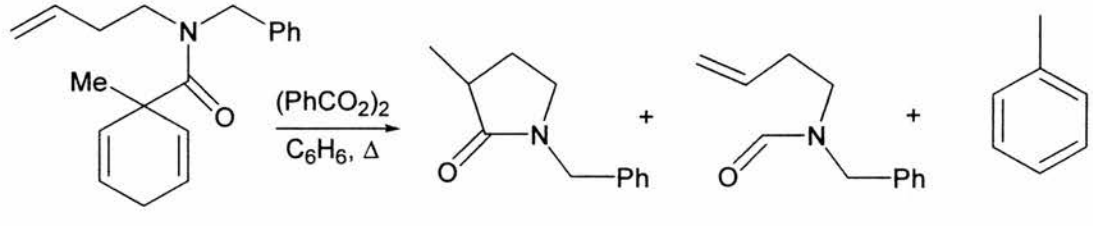
Table 4

The observed value of k_d is very similar to that calculated for the but-2-enyl derivative, this was to be expected as the released aminoacyl radicals have very similar structures. Again, the observed values of k_d and E_d confirm how the carbon-carbon bond in the cyclohexadienyl amides is slightly weaker than that associated with the cyclohexadienyl acids. The practically identical values of k_d for both the but-2-enyl and but-3-enyl cyclohexadienyl derivatives illustrate the accuracy of this EPR method for predicting bond dissociation rates.

EPR analysis of *N*-benzyl-*N*-but-3-enyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 108 using a different sample concentration

In order to assess the rate of hydrogen abstraction from the starting amide **108**, a new stock solution was prepared which supplied ten equal samples containing 1 mg of the cyclohexadienyl amide. The EPR experiment, described above, was repeated using identical experimental parameters and cavity temperatures in order to provide a second set of EPR spectra, which were processed accordingly using the WinEPR software. Comparison of the two sets of kinetic data revealed no significant difference in k_d values, therefore k_H was deemed negligible for this cyclohexadienyl amide.

Thermally initiated radical cyclisation of *N*-benzyl-*N*-but-3-enyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide 108



108 **111**, 53% **112**, 37%

Scheme 41

The purified amide **108** was tested for its ability to release the associated aminoacyl radical **110** when the reaction was thermally initiated using dibenzoyl peroxide. It was hoped that the proximate double bond in the released aminoacyl radical,

accompanied by a comparatively low rate of hydrogen abstraction, would promote 5-*exo-trig*-cyclisation to give the γ-lactam **111**.

Refluxing a mixture of the amide **108** and dibenzoyl peroxide in benzene initiated the radical reaction and furnished a mixture of products, which were analysed by GC/MS and ^{1}H NMR spectroscopy. Column chromatography of this mixture allowed us to separate out a majority of the impurities, however, GC/MS of this purified compound revealed the presence of both the cyclised **111** and uncyclised **112** products. Preparative TLC of this mixture, using 5% ethyl acetate in hexane as the developing solvent, allowed us to isolate and characterise both the cyclised and uncyclised products in yields of 53% and 37% respectively (yields calculated using the crude product NMR data).

The radical fragmentation was also studied using *t*-butyl peroxyoxalate as an alternative thermal initiator and DTBP as a photolytic initiator, in an attempt to observe any change in the ratio of the generated cyclised and uncyclised products. The experiments were carried out under similar reaction conditions, and GC/MS analysis of these products displayed comparable data to that observed when using dibenzoyl peroxide. This confirms that there is no significant benefit derived from using different sources of radical initiation.

Summary and Conclusions

Synthesis and EPR analysis of 1-carbamoyl-1-methylcyclohexa-2,5-dienes

Several functionalised amines were prepared using various techniques and added to 1-methylcyclohexa-2,5-diene-1-carboxylic acid in order to generate the associated amido cyclohexadienes in reasonable yields. Photolysis of the amido cyclohexadienes, in the presence of a radical initiator, generated the corresponding cyclohexadienyl radicals, which were observed by EPR at a specific temperature setting. The hyperfine splittings for each cyclohexadienyl radical are recorded in Table 5, all g-factors were assumed to be equal to those calculated for the cyclohexadienyl acids (2.0027).

Amide	T/K	g-factor	$a(H^4)$	$a(H^{2,6})$	$a(H^{3,5})$	$a(H^{other})$	a(N)
86	250	2.0027	12.61	9.19	2.65	0.62	0.62
93	250	2.0027	12.60	9.23	2.90	0.60	--
101	250	2.0027	12.75	9.25	2.64	0.64	0.64
108	250	2.0027	12.71	9.24	2.66	0.65	0.65

Table 5

All hfs in G (10 G = 1.0 mT). All spectra recorded using neat DTBP as the solvent.

The hfs for each cyclohexadienyl radical were very similar and exhibited little sensitivity to the nature of the carbamoyl substituent. The long-range splittings from nitrogen and the methyl substituted at the 1-position gave additional splittings in the observed, low temperature, spectra. However, these minor splittings disappeared due to signal broadening as the temperature and EPR modulation were increased.

An increase in the cavity temperature of the EPR spectrometer led to a change in the observed EPR spectrum of each amido cyclohexadiene. For amides **86** and **108**, this change could be attributed to the release of the desired aminoacyl radical and the formation of toluene. However, for amides **93** and **101**, the spectrum of an unknown radical was revealed. Simulation of these unknown spectra and approximate measurement of their g-factors allowed us to speculate that they were derived from a nitroxide radical, which could be formed when the released aminoacyl radical reacts

with oxygen. The observed hyperfine splittings and g-factors for the released radicals are recorded in Table 6.

Amide	T/K	g-factor	a(N)	a(2H)	a(2H)	a(4H)
86	360	2.0019	22.14	--	--	--
93	360	2.0062	15.16	--	--	8.55
101	360	2.0062	15.54	9.72	8.77	--
108	360	2.0018	22.11	--	--	--

Table 6

It was possible to use EPR spectroscopy to gain kinetic data for the rate of dissociation of amido cyclohexadienes **86** and **108**. Recording several EPR spectra over a range of temperatures, and measuring the designated peak areas using Bruker's WinEPR software, allowed us to establish concentration data for the two transient radicals. This information was translated into a rate of dissociation using the derived Steady State equation. The rate of hydrogen abstraction was confirmed negligible for both amido cyclohexadienes; therefore the simplified Steady State equation was used.

An Arrhenius plot of log k_d against $10^3/T$ allowed us to determine the pre-exponential factor (log A_d), energy of activation (E_d) and rate of dissociation (k_d) at 300 K for both of the amido cyclohexadienes. This information, corrected for solvent viscosity, is recorded in Table 7.

Amide	10^{-3} k_d s^{-1} (300K)	log A_d s^{-1}	E_d kcal mol^{-1}	*log A_d s^{-1}	*10^{-3} k_d s^{-1} (300K)	*E_d kcal mol^{-1}
86	0.073	12.63	14.76	13.00	0.069	15.30
108	0.080	10.11	11.25	13.00	0.044	15.57

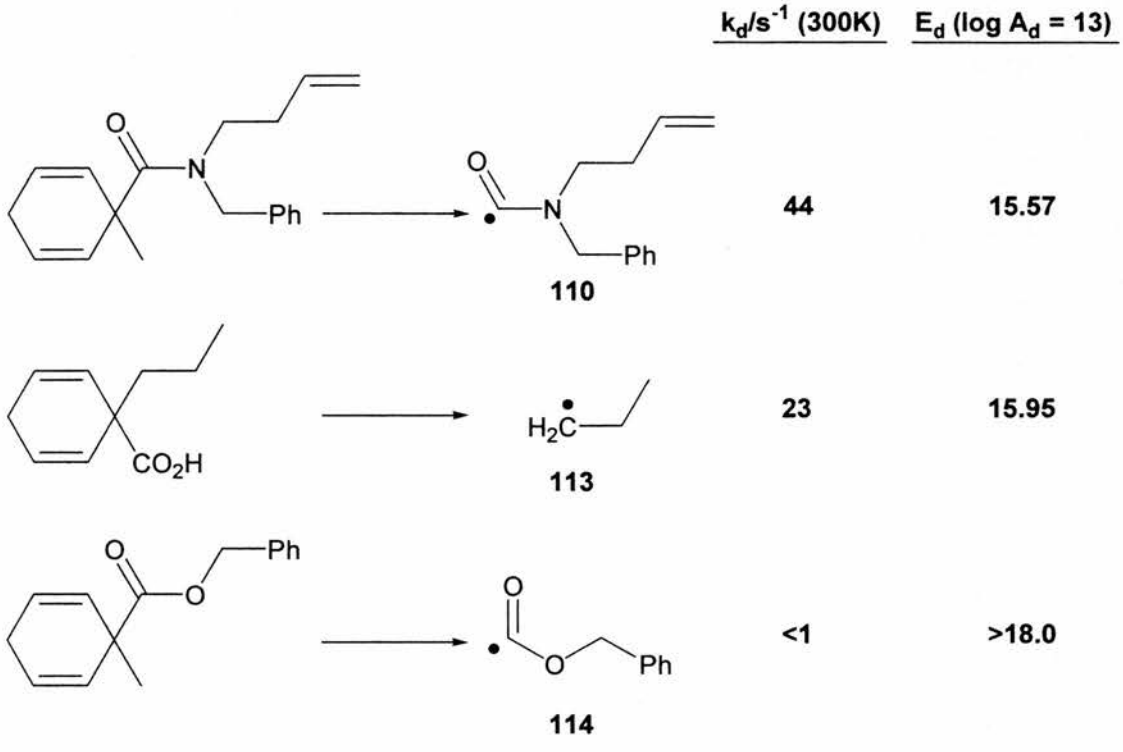
Table 7

All values are corrected for solvent viscosity using Fischer's values for $2k_t$.[48]

* Data derived assuming all log (A_d/s^{-1}) values = 13.0 s^{-1}.

The experimentally measured values of k_d are very similar for both of the analysed cyclohexadienyl compounds. This was expected as the released aminoacyl radicals have very similar structures. When the observed values of k_d were corrected to account for a pre-exponential factor of 13.0, the new values of k_d remained reasonably

constant at approximately double the value of k_d observed for the release of a primary alkyl radical from a cyclohexadienyl acid. The larger value of k_d and reduced value of E_d highlight the slight increase in stability of the released aminoacyl radical **110** when compared with that of a released primary alkyl radical **113** or alkoxyacyl radical **114**. This also suggests a weakening of the carbon-carbon bond which attaches the substituent to the cyclohexadienyl ring (Scheme 42).



Scheme 42

Radical cyclisation and synthesis of β- and γ-lactams

Thermally and photolytically initiated radical fragmentations of the amido cyclohexadienes confirmed the efficient release of the relevant aminoacyl radical, which abstracts hydrogen in order to generate the associated formamide. Amide **86** fragmented to release an aminoacyl radical with an alkene β- to the nitrogen atom. Therefore, 4-*exo-trig* cyclisation was allowed to proceed in order to generate the corresponding β-lactam in a yield of 34%, this physiologically important compound was isolated and characterised. There was no evidence for the formation of a γ-lactam derived from the competing, unfavourable, 5-*endo-trig* cyclisation. Amides **93** and **101** also included points of unsaturation β- to the nitrogen atom, however, after

radical initiated fragmentation there was no evidence for the formation of the cyclised product. This was attributed to the extra strain associated with forming a 4-membered ring that contains an exocyclic double bond.

Finally, amide **108** underwent radical fragmentation to release an aminoacyl radical, which had an alkene positioned γ- to the nitrogen atom. This facilitated 5-*exo-trig* cyclisation in order to form the relevant γ-lactam in a yield of 53%. There was no evidence for the formation of the unwanted aromatic amides of type **79** throughout these photolytically and thermally induced radical fragmentations. This suggests that the unwanted fragmentation of the delocalised cyclohexadienyl radical to release $Me^{\bullet}$ was negligible.

In summary, 1-carbamoyl-1-methylcyclohexa-2,5-dienes have confirmed their ability to be good sources of aminoacyl radicals, with no competition from the alternative dissociation of methyl radicals. Suitably designed alkenylaminoacyl radicals can undergo 4- and 5-*exo-trig* cyclisations to form both β- and γ-lactams respectively in moderate yields. Kinetic EPR studies confirm the dissociation rate constants for these compounds to be in the order of 10^2 within the accessible temperature range.

Consequently, these amides provide a tin-free route to the synthesis of small and possibly medium sized lactams, which are suitable for conversion into useful, biologically active compounds. Strict time restraints prevented the completion of research in this interesting area of radical chemistry; however, continuation of this work should provide an enhanced view of the significance of these compounds in the synthesis of natural products.

Experimental

Synthesis of *N*-benzyl-*N*-but-2-enylidineamine 81[26]

Benzylamine (7.64 g, 71 mmol) was added dropwise over 1 min to a stirred solution of but-2-enal **80** (5.0 g, 71 mmol) in dry dichloromethane (50 cm^3) over 3 Å molecular sieves. The mixture was stirred under an atmosphere of nitrogen for 24h and then filtered through magnesium sulfate. The filtrate was evaporated to dryness under reduced pressure to leave the title compound **81** (11.06 g, 98%) as a yellow liquid; δ_H(300 MHz, $CDCl_3$) 1.85 (3 H, d, *J* 5, CH_3), 4.56 (2 H, s, NCH_2), 6.04-6.37 (2 H, m, 2 × CH), 7.23 (5 H, m, ArH), 7.96 (1 H, m, CH); δ_C (75 MHz, $CDCl_3$) 17.8 (CH_3), 64.4 (CH_2), 126.1, 126.5, 127.6, 127.7, 128.0 (5 × Ar-CH), 128.1 (CH), 135.9 (quaternary-C), 140.4 (CH), 163.1 (CH).

Synthesis of *N*-benzyl-*N*-but-2-enylamine 82[26]

Sodium borohydride (0.99 g, 26 mmol) was added portionwise over 1 min to a stirred and cooled (0 °C) solution of the crude imine **81** (11.06 g, 70 mmol) in dry methanol (100 cm^3) under an atmosphere of nitrogen. The solution was allowed to warm to ambient temperature and then stirred for 18h, during which time the yellow colour of the solution faded. The solution was cooled (0 °C) before concentrated HCl was added dropwise until the mixture attained pH 1. The resulting suspension was evaporated under reduced pressure to leave a white solid residue. The residue was dissolved in water (100 cm^3) and the resulting aqueous solution was washed with ether (2 × 100 cm^3). The remaining aqueous solution was brought to pH 10 by careful addition of potassium hydroxide pellets, and the liberated amine was extracted with ether (3 × 100 cm^3). The combined organic phases were dried ($MgSO_4$) and then evaporated to dryness under reduced pressure to leave a pale yellow liquid (10.10 g). The impure product was purified by distillation to yield the title amine **82** (6.87 g, 61%) as a colourless liquid; δ_H(300 MHz, $CDCl_3$) 1.51 (1 H, bs, NH), 1.72 (3 H, d, *J* 5, CH_3), 3.22 (2 H, m, CH_2), 3.78 (2 H, s, CH_2), 5.58 (2 H, m, 2 × CH), 7.32 (5 H, m, ArH); δ_C(75 MHz, $CDCl_3$) 18 (CH_3), 58 (CH_2), 64.4 (CH_2), 126.3, 126.9, 127.6, 127.9, 128.4 (5 × Ar-CH), 128.6 (CH) 135.8 (quaternary-C), 140.4 (CH).

Synthesis of 1-methylcyclohexa-2,5-diene-1-carboxylic acid 84[44, 45]

Ammonia (300 cm^3) was added to benzoic acid **83** (5 g, 41 mmol) with careful stirring. To this, Li (0.92 g, 133 mol) was added portionwise until a persistent blue solution formed, followed by the dropwise addition of methyl iodide (17.46 g, 123 mmol) in dry ether (20 cm^3). The reaction mixture was stirred for 60 min and then left whilst the NH_3 evaporated. The product was dissolved in dilute NaOH and washed with ether (150 cm^3) before the alkaline fraction was neutralized with excess HCl. The product was extracted with ether (3 × 150 cm^3), the ethereal extracts combined, washed with a saturated solution of sodium thiosulfate, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a yellow oil (5.06 g). The crude product was purified by distillation yielding the title compound **84** as a pale yellow oil (4.45 g, 79 %); bp 85-90 °C at 0.4 mmHg; δ_H(300 MHz; $CDCl_3$) 1.40 (3 H, s, CH_3), 2.67 (2 H, s, CH_2), 5.79-5.91 (4 H, m, 4 × CH); δ_C(75 MHz, $CDCl_3$) 27 (CH_3), 28 (allylic-C), 44 (quaternary-C), 125, 129 (4 × CH), 183 (C=O).

Synthesis of 1-methylcyclohexa-2,5-diene-1-carbonyl chloride 85

Thionyl chloride (10.28 g, 87 mmol) dissolved in dry DCM (20 cm^3) was added to 1-methylcyclohexa-2,5-diene-1-carboxylic acid **84** (3.0 g, 22 mmol) dissolved in dry dichloromethane (20 cm^3). This mixture was refluxed for 5h before the solvent was evaporated to give the corresponding acid chloride **85** (3.42 g, 99 %) as a yellow oil; δ_H(200 MHz, $CDCl_3$) 1.44 (3 H, s, CH_3), 2.73 (2H, bs, CH_2), 5.67-5.79 (2 H, m, 2 × CH), 5.92-6.06 (2 H, m, 2 × CH).

Synthesis of *N*-benzyl-*N*-but-2-enyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 86

The acid chloride **85** (2.0 g, 13 mmol) was dissolved in dry dichloromethane (10 cm^3) and added dropwise to a mixture of *N*-benzyl-*N*-but-2-enylamine **82** (1.6 g, 10 mmol), triethylamine (1.0 g, 10 mmol) and a catalytic amount of DMAP in dry dichloromethane (20 cm^3). The resultant mixture was refluxed for 5h before washing with H_2O (2 × 100 cm^3) and drying ($MgSO_4$). The solvent was evaporated to give the

impure product (2.36 g) as a brown oil, which was purified by column chromatography, eluting with 2 % ethyl acetate in light petroleum, in order to furnish the title compound **86** (2.02 g, 72%) as a pale yellow oil; δ_H(300 MHz, $CDCl_3$) 1.38 (3 H, s, CH_3), 1.68 (3 H, bs, CH_3), 2.67 (2 H, m, allylic-H), 3.70-3.97 (2 H, m, CH_2), 4.48-4.72 (2 H, m, benzylic-CH_2), 5.25-5.48 (2 H, m, 2 × CH), 5.70-5.81 (4 H, bs, 4 × CH), 7.08-7.34 (5 H, m, Ar H); δ_C(75 MHz, $CDCl_3$) 17.7 (CH_3), 25.8 (CH_2), 28.8 (CH_3), 45.0 (quaternary-C), 47.7 (CH_2), 48.6 (CH_2), 122.9, 125.7, 126.9, 127.3, 127.4, 127.8, 128.4, 128.6, 129.4, 130.0, 130.6 (11 × CH), 138.0 (quaternary C), 173.5 (C=O); (Found M^+ 281.1776, $C_{19}H_{23}NO$ requires M^+, 281.1780).

Thermally initiated radical cyclisation of *N*-benzyl-*N*-but-2-enyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide 86

Amide **86** (0.5 g, 1.8 mmol) was dissolved in benzene (10 cm^3) and heated to reflux before dibenzoyl peroxide (0.5 g) was added portionwise over a period of 24 h. After complete addition, the solvent was evaporated before dissolving the impure product in ether (50 cm^3), washing with NaOH (2 × 50 cm^3), HCl (2 × 50 cm^3) and water (2 × 50 cm^3) and drying ($MgSO_4$). The solvent was evaporated under reduced pressure to yield a brown oil (0.42 g), which was purified by column chromatography, eluting with 5% ethyl acetate in light petroleum. A sample of the purified product was submitted for analysis by GC/MS; peak no. 902, cyclised β-lactam **89** (34%), *m/z* (relative intensity) 189 (6), 160 (3), 133 (38), 119 (3), 105 (50), 91 (100), 77 (16), 65 (37), 55 (22), 41 (46), 39 (43), 27 (33), 18 (24); peak no. 908, uncyclised *N*-benzyl-*N*-but-2-enylformamide **90** (31 %), 189 (7), 160 (1), 148 (2), 134 (36), 115 (2), 106 (34), 98 (30), 91 (100), 79 (39), 77 (17), 70 (33), 65 (49), 55 (27), 39 (46), 28 (95), 18 (31); peak no. 914, unidentified, 189 (20), 160 (6), 134 (21), 118 (13), 106 (28), 98 (28), 91 (100), 79 (25), 77 (19), 70 (18), 65 (44), 55 (26), 39 (56), 28 (77), 18 (100). The cyclised product **89** (34 %)† was finally isolated as a colourless oil by preparative TLC, eluting with 2% ethyl acetate in pentane; δ_H(300 MHz, $CDCl_3$) 0.98 (3 H, t, *J* 4.6, CH_3), 1.51-1.90 (2 H, m, CH_2), 2.84 (1 H, m, CH), 3.12-3.27 (2 H, m, CH_2), 4.38 (2 H, m, benzyllic-CH_2), 7.19-7.41 (5 H, m, ArH); δ_C(75 MHz, $CDCl_3$) 11.2 (CH_3), 21.9 (CH_2), 44.5 (CH_2), 45.8 (benzyllic-CH_2), 51.3 (CH), 127.8, 128.1, 128.8 (5 × CH), 135.8 (quaternary-C), 170.6 (C=O); (Found M^+ 189.1149, $C_{12}H_{15}NO$ requires M^+ 189.1154). The uncyclised *N*-benzyl-*N*-but-2-enylformamide **90** (31%) was also

isolated as a colourless oil; δ_H(300 MHz, $CDCl_3$) 1.77 (3 H, br d, *J* 6, CH_3), 3.74 (2 H, br s, CH_2), 4.34 (1 H, br s, NC*H*HPh), 4.51 (1 H, br s, NCH*H*Ph), 5.24-5.71 (2 H, br m, 2 × CH), 7.18-7.42 (5 H, m, Ar H), 8.30 (1 H, s, HC=O); δ_c(75 MHz, $CDCl_3$) 17.7 (CH_3), 44.8 (CH_2), 48.6 (CH_2), 124.6, 125.6 (2 × CH), 127.6, 128.3, 128.6 (7 × CH), 135.8 (quaternary-C), 162.6 (C=O). The formamide spectral assignments were consistent with those found in the literature.[26] [†]Yield calculated using original ^1H NMR and GC/MS data.

Photolytically initiated radical cyclisation of *N*-benzyl-*N*-but-2-enyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide 86

Amide **86** (0.2 g, 0.7 mmol) was dissolved in DTBP (250 μl) and added to a quartz EPR tube. The tube was capped and irradiated with light from a 400 W high pressure Hg lamp for 2 h. Analysis of the reaction mixture by GC/MS indicated that all of the cyclohexadienyl amide had been consumed, leaving identical peaks in the GC/MS to those observed with the thermally initiated radical reaction. GC/MS yield measurements, using a formamide standard, confirmed that the cyclised compound **89** was formed in a yield of 42% and the uncyclised **90** in a yield of 38%.

Synthesis of benzylaminoacetonitrile 92[46]

Bromoacetonitrile **91** (4.85 g, 40 mmol) was added dropwise to a refluxing solution of benzylamine (4.39 g, 41 mmol) in dry acetonitrile (75 cm^3) containing anhydrous K_2CO_3 (8.37 g, 61 mmol). After 12h of reflux, the reaction mixture was allowed to cool and the solid material filtered off, washed with ethyl acetate and the combined filtrates concentrated to yield the impure product (5.82 g), which was purified by column chromatography, eluting with 10% ethyl acetate in hexane, to give the corresponding secondary amine **92** (5.14 g, 87%) as a colourless liquid; ν_{max}/cm^{-1} 3350 (NH), 2234 (CN) and 1734 (NH); δ_H(300 MHz, $CDCl_3$) 1.72 (1 H, bs, NH) 3.54 (2 H, s, CH_2), 3.91 (2 H, s, benzylic-CH_2), 7.36 (5 H, m, Ar H); δ_C(75 MHz, $CDCl_3$) 36.0 (CH_2), 52.1 (CH_2), 117.6 (CN), 127.6, 128.3, 128.5 (5 × CH), 137.8 (quaternary-C).

Synthesis of *N*-benzyl-*N*-cyanomethyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 93

Acid chloride **85** (2.16 g, 16 mmol) was dissolved in dry dichloromethane (20 cm^3) and added dropwise to a mixture of benzylaminoacetonitrile **92** (2.28 g, 16 mmol), triethylamine (1.58 g, 16 mmol) and a catalytic amount of DMAP in dry dichloromethane (20 cm^3). The resultant mixture was refluxed for 5h before washing with H_2O (2 × 100 cm^3) and drying ($MgSO_4$). The solvent was evaporated to give the impure product (3.31 g) as a brown oil, which was purified by column chromatography, eluting with 5 % ethyl acetate in hexane, in order to furnish the title compound **93** (2.54 g, 60%) as a pale yellow oil; δ_H(300 MHz, $CDCl_3$) 1.26 (3 H, s, CH_3), 2.63 (2 H, s, allylic-H), 3.99 (2 H, s, CH_2), 4.64 (2 H, s, benzylic-CH_2), 5.79-5.86 (4 H, m, 4 × CH), 7.18-7.39 (5 H, m, Ar H); δ_C(75 MHz, $CDCl_3$) 22.1 (CH_3), 33.4 (CH_2), 34.7 (CH_2), 46.1 (quaternary-C), 54.6 (CH_2), 114.4 (CN), 127.3, 127.5, 127.8, 128.3, 128.6, 129.2, 129.7, 130.1, 130.4 (9 × CH), 137.2 (quaternary C), 170.2 (C=O); *m/z* (relative intensity), 266 (M^+, 1), 251 (1), 175 (2), 173 (2), 93 (74), 91 (100) 77 (53), 65 (37), 51 (32), 39 (36); (Found M^+ 266.1416, $C_{17}H_{18}N_2O$ requires M^+ 266.1419).

Thermally initiated radical fragmentation of *N*-benzyl-*N*-cyanomethyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide 93

Amide **93** (0.5 g, 1.9 mmol) was dissolved in benzene (10 cm^3) and heated to reflux before dibenzoyl peroxide (0.5 g) was added portionwise over a period of 24 h. After complete addition, the solvent was evaporated before dissolving the impure product in ether (50 cm^3), washing with NaOH (50 cm^3), HCl (50 cm^3) and water (2 × 50 cm^3) and drying ($MgSO_4$). The solvent was evaporated under reduced pressure to yield a brown oil (0.38 g), which was analysed, by ^1H NMR and GC/MS; peak no. 104, toluene, *m/z* (relative intensity) 91 (M^+, 100), 65 (18), 52 (14), 39 (48), 27 (11); peak no. 687, benzoic acid (from initiator); peak no. 768, biphenyl (from initiator); peak no. 882, *N*-benzyl-*N*-cyanomethyl formamide **97**, 174 (M^+, 16), 134 (71), 106 (83), 91 (100), 79 (97), 65 (76), 51 (61), 39 (81), 28 (92), 18 (13); peak no. 913, benzoic acid phenyl ester (from initiator); peak no. 1097, unreacted cyclohexadienyl amide **93**

(See above for spectral assignments). The crude product was finally purified by column chromatography, eluting with 10% ethyl acetate in light petroleum, to give the uncyclised *N*-benzyl-*N*-cyanomethyl formamide **97** (0.19 g, 57 %) as a colourless oil; δ_H(300 MHz, $CDCl_3$) 4.12 (2 H, s, CH_2), 4.55 (2 H, s, benzylic-CH_2), 7.24-7.49 (5 H, m, Ar H), 8.31 (1 H, s, HC=O); δ_C(75 MHz, $CDCl_3$) 29.4 (CH_2), 51.1 (CH_2), 114.3 (CN), 127.9, 128.9, 129.3 (5 × CH), 133.5 (quaternary C), 162.0 (C=O); (Found M^+ 174.0786, $C_{10}H_{10}N_2O$ requires M^+ 174.0793).

Photolytically initiated radical cyclisation of *N*-benzyl-*N*-cyanomethyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide 93

Amide **93** (0.2 g, 0.75 mmol) was dissolved in DTBP (250 μl) and added to a quartz EPR tube. The tube was capped and irradiated with light from a 400 W high pressure Hg lamp for 2h. Analysis of the reaction mixture by GC/MS confirmed the presence of both *N*-benzyl-*N*-cyanomethyl formamide **97** (peak no. 895) and the unreacted cyclohexadienyl amide **93** (peak no. 1128) in an approximate ratio of 2:1(see above for spectral interpretation). The only detectable impurities were those derived from the photolytic breakdown of DTBP.

Synthesis of prop-2-ynyl-benzylamine 100[47]

3-Bromopropyne **99** (6.45 g, 54 mmol) was added dropwise to a refluxing solution of benzylamine (5.76 g, 54 mmol) in dry acetonitrile (75 cm^3) containing anhydrous K_2CO_3 (11.19 g, 81 mmol). After 12 h of reflux, the reaction mixture was allowed to cool and the solid material filtered off, washed with ethyl acetate and the combined filtrates concentrated to yield the impure product (5.25 g), which was purified by column chromatography, eluting with 10% ethyl acetate in hexane, to give the corresponding secondary amine **100** (3.78 g, 48%) as a colourless liquid; δ_H(200 MHz, $CDCl_3$) 1.60 (1 H, bs, NH) 2.29 (1 H, s, CH), 3.43 (2 H, s, CH_2), 3.88 (2 H, s, benzylic-CH_2), 7.21-7.45 (5 H, m, Ar H); δ_C(75 MHz, $CDCl_3$) 31.3 (CH_2), 53.1 (benzylic-CH_2), 72.4 (quaternary-C), 81.5 (CH), 127.0, 128.3, 128.8, (5 × CH), 139.8 (quaternary C).

Synthesis of *N*-benzyl-*N*-prop-2-ynyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 101

Acid chloride **85** (3.10 g, 22 mmol) was dissolved in dry dichloromethane (20 cm^3) and added dropwise to a mixture of prop-2-ynyl-benzylamine **100** (3.19 g, 22 mmol), triethylamine (2.23 g, 23 mmol) and a catalytic amount of DMAP in dry dichloromethane (20 cm^3). The resultant mixture was refluxed for 5h before washing with H_2O (2 × 100 cm^3) and drying ($MgSO_4$). The solvent was evaporated to give the impure product (3.97 g) as a brown oil, which was purified by column chromatography, eluting with 10 % ethyl acetate in hexane, in order to furnish the title compound **101** (3.09 g, 53%) as a pale yellow oil; δ_H(300 MHz, $CDCl_3$) 1.41 (3 H, s, CH_3), 2.24 (1 H, s, CH), 2.73 (2 H, bs, allylic-H), 4.16 (2 H, s, CH_2), 4.80 (2 H, s, benzylic-CH_2), 5.75-5.84 (4 H, m, 4 × CH), 7.18-7.42 (5 H, m, Ar H); δ_C(75 MHz, $CDCl_3$) 21.9 (CH_3), 32.1 (CH_2), 33.2 (CH_2), 45.2 (quaternary-C), 55.1 (CH_2), 72.8 (quaternary-C), 80.9 (CH), 126.8, 127.2, 127.8, 128.2, 128.7, 129.0, 129.5, 130.1, 130.6 (9 × CH), 139.2 (quaternary C), 172.2 (C=O); *m/z* (relative intensity), 174 (3), 172 (6), 134 (3), 105 (5), 93 (26), 91 (100) 77 (27), 65 (20), 51 (11), 39 (23), 28 (8), 18 (29); (Found M^+ 265.1465, $C_{18}H_{19}NO$ requires M^+ 265.1467).

Thermally initiated radical fragmentation of *N*-benzyl-*N*-prop-2-ynyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide 101

Amide **101** (0.5 g, 1.9 mmol) was dissolved in benzene (10 cm^3) and heated to reflux before dibenzoyl peroxide (0.5 g) was added portionwise over a period of 24 h. After complete addition, the solvent was evaporated before dissolving the impure product in ether (50 cm^3), washing with NaOH (50 cm^3), HCl (50 cm^3) and water (2 × 50 cm^3) and drying ($MgSO_4$). The solvent was evaporated under reduced pressure to yield a brown oil (0.47 g), which was analysed, by ^1H NMR and GC/MS; peak no. 190, toluene; peak no. 692, benzoic acid (from initiator); peak no. 772, biphenyl (from initiator); peak no. 843, *N*-benzyl-*N*-prop-2-ynylformamide **104**, *m/z* (relative intensity) 173 (M^+, 6), 144 (2), 134 (65), 128 (12), 115 (9), 106 (42), 91 (64), 79 (58), 65 (50), 51 (35), 39 (100), 28 (88); peak no. 915, benzoic acid phenyl ester (from initiator); peak no. 1086, unreacted cyclohexadienyl amide **101** (See above for

spectral assignments). The crude product was finally purified by column chromatography, eluting with 10% ethyl acetate in light petroleum, to give the uncyclised *N*-benzyl-*N*-prop-2-ynyl formamide **104** as a colourless oil (NMR yield of 64%); δ_H(300 MHz, $CDCl_3$) 2.24 (1 H, s, CH), 4.07 (2 H, s, CH_2), 4.55 (2 H, s, benzylic-CH_2), 7.23-7.42 (5 H, m, Ar H), 8.30 (1 H, s, HC=O); δ_C(75 MHz, $CDCl_3$) 30.6 (CH_2), 50.3 (CH_2), 72.4 (C≡CH), 78.4 (C≡CH), 127.8, 128.6, 129.0 (5 × CH), 135.0 (quaternary C), 162.0 (C=O); (Found M^+ 173.0838, $C_{11}H_{11}NO$ requires M^+ 173.0841)

Photolytically initiated radical cyclisation of *N*-benzyl-*N*-prop-2-ynyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide 101

Amide **101** (0.5 g, 1.9 mmol) was dissolved in benzene (2 cm^3), which contained DTBP (1.10 g, 7.5 mmol). The resultant solution was placed into a quartz tube, heated to 60 °C using a paraffin oil bath and the sample irradiated with light from a 400 W high pressure Hg lamp over a 3h period. Analysis of the reaction mixture by GC/MS confirmed the presence of both *N*-benzyl-*N*-prop-2-ynyl formamide **104** (peak no. 843) and the unreacted cyclohexadienyl amide **101** (peak no. 1086) in an approximate ratio of 2:1(see above for spectral interpretation). The only detectable impurities were those derived from the photolytic breakdown of DTBP.

Synthesis of but-3-enyl-benzylamine 107

4-Bromobut-1-ene **106** (5.0 g, 37 mmol) was added dropwise to a refluxing solution of benzylamine (4.0 g, 37 mmol) in dry acetonitrile (75 cm^3) containing anhydrous K_2CO_3 (8.30 g, 60 mmol). After 12h of reflux, the reaction mixture was allowed to cool and the solid material filtered off, washed with ethyl acetate and the combined filtrates concentrated to yield the impure product (3.92 g), which was purified by column chromatography, eluting with 10% ethyl acetate in hexane, to give the corresponding secondary amine **107** (2.24 g, 38%) as a colourless liquid; δ_H(200 MHz, $CDCl_3$) 1.48 (1 H, bs, NH) 2.30 (2 H, q, *J* 7, CH_2), 2.71 (2 H, t, *J* 7, CH_2), 3.79 (2 H, s, benzylic-CH_2), 5.00-5.18 (2 H, m, CH_2), 5.67-5.91 (1 H, m, CH), 7.20-7.40 (5 H, m, Ar H); δ_C(75 MHz, $CDCl_3$) 26.2 (CH_2), 34.6 (CH_2), 51.1 (benzylic-CH_2), 115.7 (CH_2), 127.2, 128.3, 128.6 (5 × CH), 134.9 (CH), 136.7 (quaternary-C).

Synthesis of *N*-benzyl-*N*-but-3-enyl-(1-methyl)-cyclohexa-2,5-diene-1-carboxamide 108

Acid chloride **85** (2.0 g, 14.5 mmol) was dissolved in dry dichloromethane (10 cm^3) and added dropwise to a mixture of but-3-enylbenzylamine **107** (2.24 g, 14.0 mmol), triethylamine (1.45 g, 14.2 mmol) and a catalytic amount of DMAP in dry dichloromethane (20 cm^3). The resultant mixture was refluxed for 5h before washing with H_2O (2 × 100 cm^3) and drying ($MgSO_4$). The solvent was evaporated to give the impure product (3.13 g) as a brown oil, which was purified by column chromatography, eluting with 10 % ethyl acetate in hexane, in order to furnish the title compound **108** (2.44 g, 60%) as a pale yellow oil; δ_H(300 MHz, $CDCl_3$) 1.37 (3 H, s, CH_3), 2.27 (2 H, m, CH_2), 2.69 (2 H, bs, allylic-H), 3.21-3.50 (2 H, m, CH_2), 4.67 (2 H, s, benzylic-CH_2), 4.99 (2 H, d, *J* 7, CH_2), 5.59-5.84 (5 H, m, 5 × CH), 7.10-7.46 (5 H, m, Ar H); δ_C(75 MHz, $CDCl_3$) 25.7 (CH_2), 28.8 (CH_3), 31.3 (CH_2), 32.8 (CH_2), 44.9 (quaternary-C), 51.0 (CH_2), 116.3 (CH_2), 126.8, 127.2, 128.3, 128.6, 130.3 (9 × CH), 135.4 (CH), 137.7 (quaternary-C), 173.6 (C=O); *m/z* (relative intensity), 281 (M^+ 1), 240 (1), 190 (2), 188 (19), 174 (1), 160 (1), 148 (3), 93 (21), 91 (100) 77 (19), 65 (20), 51 (4), 39 (11), 28 (4), 18 (3); (Found M^+ 281.1784, $C_{19}H_{23}NO$ requires M^+ 281.1780).

Thermally initiated radical cyclisation of *N*-benzyl-*N*-but-3-enyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide 108

Amide **108** (0.5 g, 1.8 mmol) was dissolved in benzene (10 cm^3) and heated to reflux before dibenzoyl peroxide (0.5 g) was added portionwise over a period of 24 h. After complete addition, the solvent was evaporated before dissolving the impure product in ether (50 cm^3), washing with NaOH (50 cm^3), HCl (50 cm^3) and water (2 × 50 cm^3) and drying ($MgSO_4$). The solvent was evaporated under reduced pressure to yield a brown oil (0.56 g), which was analysed, by ^1H NMR and GC/MS; peak no. 187, toluene; peak no. 699, benzoic acid (from initiator); peak no. 771, biphenyl (from initiator); peak no. 895 (37%), *N*-benzyl-*N*-but-3-enylformamide **112**, *m/z* (relative intensity) 189 (M^+, 2), 148 (16), 134 (2), 130 (2), 119 (2), 106 (2), 98 (2), 91 (100), 77 (4), 65 (20), 51 (6), 39 (21), 28 (13), 18 (10); peak no. 915 (53%), 1-benzyl-3-methyl-

pyrrolidin-2-one **111**, 189 (M^+, 69), 174 (10), 160 (12), 146 (5), 132 (13), 118 (10), 106 (23), 98 (25), 91 (100), 77 (10), 65 (32), 55 (19), 51 (12), 39 (35), 28 (23), 18 (9); peak no. 1118, unreacted cyclohexadienyl amide **108** (See above for spectral assignments). The crude product was finally purified by column chromatography, eluting with 10% ethyl acetate in light petroleum, and by preparative TLC to give the cyclised γ-lactam, 1-benzyl-3-methyl-pyrrolidin-2-one **111** (53%) as a colourless oil; δ_H(300 MHz, $CDCl_3$) 1.24 (3 H, d, *J* 7, CH), 1.60 (2 H, m, CH_2), 2.52 (1 H, s^t, *J* 7, CH), 3.19 (2 H, m, CH_2), 4.47 (2 H, m, benzylic-CH_2), 7.21-7.37 (5 H, m, Ar H); δ_C(75 MHz, $CDCl_3$) 16.4 (CH_3), 27.1 (CH_2), 36.8 (CH), 44.6 (CH_2), 46.8 (CH_2), 127.5, 128.1, 128.6 (5 × CH), 136.7 (quaternary C), 177.4 (C=O); (Found M^+ 189.1158, $C_{12}H_{15}NO$ requires M^+ 189.1154). The uncyclised formamide **112** was also isolated as a colourless oil (37%); δ_H (300 MHz, $CDCl_3$) 1.68 (2 H, m, CH_2), 3.14-3.27 (2H, m, CH_2), 4.40 (1 H, br s, NC*H*HPh), 4.56 (1 H, br s, NCH*H*Ph), 5.01-5.19 (2 H, m, CH_2), 5.59-5.85 (1 H, m, CH), 7.18-7.41 (5 H, m, Ar H), 8.25 (1 H, s, HC=O); δ_C(75 MHz, $CDCl_3$) 32.6 (CH_2), 45.4 (CH_2), 51.5 (benzylic-CH_2), 118.1 (olefinic-CH_2), 127.9, 128.2, 128.9 (5 × CH), 134.0 (CH), 136.4 (quaternary-CH), 163.8 (HC=O); (Found M^+ 189.1149, $C_{12}H_{15}NO$ requires M^+ 189.1154). The experiment was repeated using *t*-butyl peroxyoxalate (1.9 mmol) as the thermally activated radical initiator to give similar products in comparable yields.

Photolytically initiated radical cyclisation of *N*-benzyl-*N*-but-3-enyl-(1-methyl)-cyclohexa-2,5-diene-1- carboxamide 108

Amide **108** (0.5 g, 1.8 mmol) was dissolved benzene (2 cm^3), which contained DTBP (1.3 g, 9 mmol). The resultant solution was placed into a quartz tube, heated to 60 °C using a paraffin oil bath and the sample irradiated with light from a 400 W high pressure Hg lamp over a 4h period. Analysis of the reaction mixture by GC/MS confirmed the presence of both 1-benzyl-3-methyl-pyrrolidin-2-one **111** and the uncyclised *N*-benzyl-*N*-but-3-enylformamide **112** in an approximate ratio of 2:1(see above for spectral interpretation). The only detectable impurities were those derived from the photolytic breakdown of DTBP, with no evidence for the competitive release of methyl radicals to form *N*-benzyl-*N*-but-3-enylbenzamide.

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