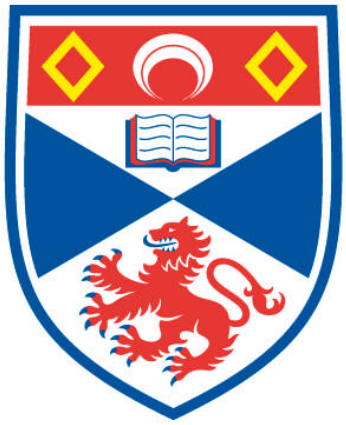
OXIME DERIVATIVES: VERSATILE REAGENTS FOR RADICAL-MEDIATED SYNTHESES OF HETEROCYCLES

Fernando Portela-Cubillo

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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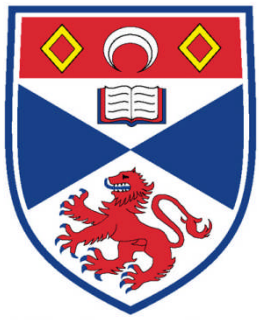

Oxime Derivatives: Versatile Reagents for Radical-Mediated Syntheses of Heterocycles

A thesis presented by Fernando Portela-Cubillo to the University of St Andrews in application for the degree of Doctor of Philosophy.

December 2008

To Beatriz

Declaration

I Fernando Portela-Cubillo, hereby certify that this thesis, which is approximately 64500 words in length, has been written by me, that it is record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

I was admitted as a researcher student in January, 2005 and as a candidate for the degree of PhD in January 2006; the higher study for which this is a record was carried out in the University of St Andrews between 2005 and 2008.

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Table of Contents

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Abbreviations and Symbols

AIBN	2,2 Azobis(isobutyronitrile)
ACCN	1-1'-Azobis(cyclohexane-carbonitrile)
Å	Angstrom(s)
°C	Degrees Celsius
CHD	Cyclohexadiene
CI	Chemical ionization
DCM	Dichloromethane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DLP	Dilauryl peroxide
DMAP	*N*,*N*-4-Dimethylaminopyridine
DMN	1,5-Dimethoxynaphthalene
δ	Chemical shift
DMSO	Dimethyl sulfoxide
DMF	Dimethylformamide
DTBP	Di-*tert*-butyl peroxide
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
emimPF_6	1-Ethyl-3-methylimidazolium hexafluorophosphate
equi	Equivalents
ESR	Electron spin resonance
ES	Electrospray
EtOAc	Ethyl acetate
g	Gram(s)
G	Gauss
GHz	GigaHertz

h	Hours
hfs	Hyperfine splitting
HRMS	High-resolution mass spectrometry
HT	Hydrogen transfer
hν	Photons
IL	Ionic liquid
In	Radical initiator
IR	Infrared
J	Coupling constant
K	kelvin(s)
kcal	Kilocalories
LFP	Laser flash photolysis
M	Concentration mol L^{-1}
MAOS	Microwave assisted organic synthesis
MAP	*p*-Methoxyacetophenone
MHz	MegaHertz
min	Minute(s)
μL	Microlitres
mL	Millilitres
mmol	Millimoles
mp	Melting point
MOM	Methoxymethyl
MW	Microwave
m/z	Mass over charge ratio
NBS	*N*-Bromosuccinimide
nm	Nanometers
NMP	*N*-methylpyrrolidinone

NMR	Nuclear magnetic resonance
R	Generic group
R_f	Retention factor
rt	Room temperature
s, d, t, q, qt	Singlet, doublet, triplet, quartet, quintuplet
s	Second(s)
S_N1	Unimolecular nucleophilic substitution
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TTMSS	Tris(trimethylsilyl)silane
UV	Ultraviolet
V-061	2,2'-Azobis[2-(2-imidazolin-2-yl)propane]
V-65	2,2'-Azobis(2,4-dimethylvaleronitrile)
V-70	2,2'-Azobis(4-methoxy-2,4-dimethylvaleronitrile)
V-501	4,4'-azobis(4-cyanopentanoic acid)
v	Wavenumber, cm^{-1}
W	Watts

Abstract

A summary of tin hydride mediated reactions in generating radicals in organic synthesis is presented, together with some of the many alternative methods now available for conducting radical reactions. Particular attention has been given to the iminyl radical and the development of tin-free organic radical precursors. This introduction is followed by three chapters describing research on the development of two new sources of iminyl radicals and their application in syntheses of aza-heterocyles.

O-Phenyl oxime ethers are the first iminyl radical precursors described in the thesis. Microwave thermolyses of oxime ethers released iminyl and phenoxyl radicals under comparatively mild conditions and with short reaction times. Few microwave-assisted synthetic methods, based around radical intermediates, are known. The mild and neutral conditions associated with radical chemistry, and the ability of radicals to perform intramolecular cyclisations, together with the virtues of MAOS, make their combination a very useful tool in syntheses of aza-heterocycles. A comprehensive study of intramolecular additions of iminyl radicals onto several radical acceptors, alkenes, alkynes, phenyl rings and indoles, is described. Furthermore, a wide range of nitrogen heterocyles with potential biological activity was prepared making use of this methodology.

Intramolecular iminyl radical cyclisation onto imines *via* microwave irradiation was another process extensively studied. Microwave assisted syntheses of dihydroquinazolines and quinazolines are described. The precursor *O*-phenyl oxime ethers enable imine formation to be assimilated with iminyl radical generation before subsequent cyclisation. Clean, fast and high yielding methodology was therefore developed for the syntheses of these highly interesting heterocycles which form the basis of many pharmaceutical products.

Dioxime oxalates were the second type of precursor investigated as sources of iminyl radicals. Homolytic cleavage of their N-O oxime bonds occurred on photolysis releasing two molecules of CO_2 and two iminyl radicals in a clean and atom-efficient process. A facile route to dioxime oxalates with a range of radical acceptors in suitable positions is described.

ESR spectroscopy was used to demonstrate that dioxime oxalates dissociate on photolysis to give iminyl radicals in the presence of photosensitizer. This technique also confirmed the proposed mechanisms of radical cyclisation onto double bonds and several 2-azacyclopentylmethyl radicals were characterized by ESR spectroscopy. In several instances both the uncyclized iminyl radical, and the cyclised C-radical, could be simultaneously detected, and their concentrations determined.

ESR spectroscopy was then profitably used to determine *5-exo*-cyclization rate constants of iminyl radicals onto double bonds.

Finally, the syntheses of several heterocycles from dioxime oxalates are described. Photolytic dissociation of dioxime oxalates containing alkenyl groups yielded iminyl radicals that ring closed to 3,4-dihydro-2*H*-pyrroles in toluene solution. The syntheses of phenanthridines, and the natural product trisphaeridine, were also accomplished by UV irradiation of dioxime oxalates containing aromatic rings as the radical acceptor.

Chapter 1

General Introduction

1.0 Radicals in organic synthesis.

Radical reactions involve homolytic bond-breaking processes in which the two electrons in a covalent bond are divided symmetrically producing highly reactive intermediates called "free radicals" which each contain one unpaired electron. They have an odd number of electrons and can combine, in order to "pair" the electrons to give stable non radical products.

Historically, it is accepted that the first radical was identified by Gomberg[1] in 1900, in the form of a trivalent compound, triphenylmethyl. However, the beginnings of synthesis by radical pathways did not appear until 1937 with Hey and Waters[2] and the homolytic phenylation of aromatic substrates.

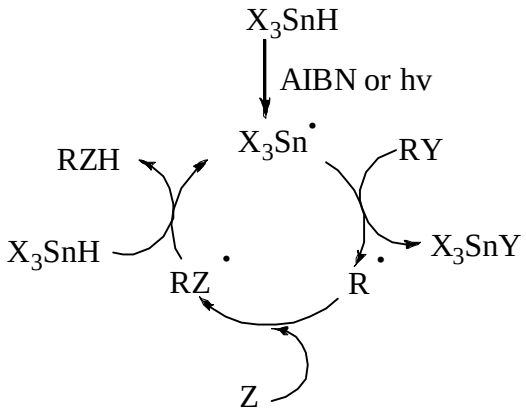
The use of free radical reactions in organic synthesis has undergone an extraordinary development in recent years and a number of books[3,4] and reviews[5,6] have been published on the topic. At the beginning of the 1980s, the place of radical reactions in organic synthesis was limited to a few important functional group transformations such as the Barton-McCombie reaction.[7] However, during the last two decades, radical C-C bond-forming reactions have grown in importance to the point where they are now routinely considered in strategy level planning of complex targets.

The high level of interest in radical chemistry in organic synthesis is a consequence of the mild, neutral reaction conditions, the compatibility of these conditions with various functional groups, the body of kinetic data that is available and the level of regio- and stereo-selectivity that can now be achieved.

2.0 Tin hydride for free-radical generation.

Ever since the original discovery of radical generation by organotin hydride[8], a spiral of applications has wound inexorably upward. At present, tributyltin hydride is the most popular reagent for conducting radical chain reactions. Rates of initiation and propagation reactions are well known, and many reactions to make carbon-carbon bonds have been developed using this reagent. Intra- or inter-molecular reactions of alkyl or aryl halide, selenide or sulphide precursors to form reduced products are possible.

The use of tin hydride is a chain process, requiring only a small quantity of radical initiator (Scheme 1).

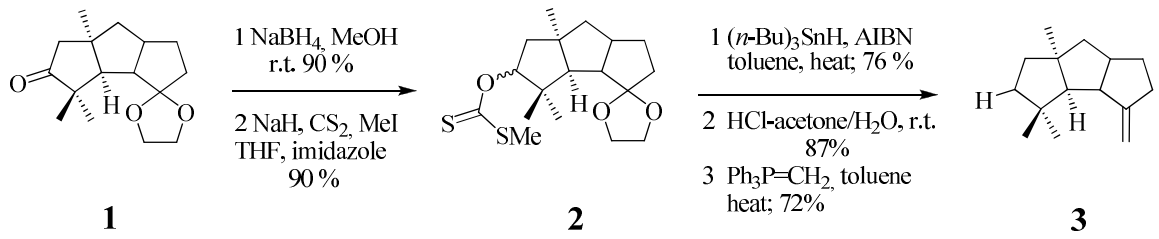


Scheme 1

The tin hydride bond can be broken homolytically by the presence of a catalytic amount of AIBN producing $\mathbf{Bu_3Sn^{\bullet}}$ radical, which has a high affinity for halogens and can readily abstract chlorine, bromine or iodine atoms from alkyl halides. A site-specific radical $\mathbf{R^{\bullet}}$ is generated from an organic substrate **RY** by atom or group abstraction. The carbon-centered radical $\mathbf{R^{\bullet}}$ can undergo addition to a multiple bond generating a new radical $\mathbf{RZ^{\bullet}}$ and intramolecular addition is particularly fast. The radical $\mathbf{RZ^{\bullet}}$ then reacts with tin hydride to generate the reduced product **RZH** and regenerate $\mathbf{Bu_3Sn^{\bullet}}$.

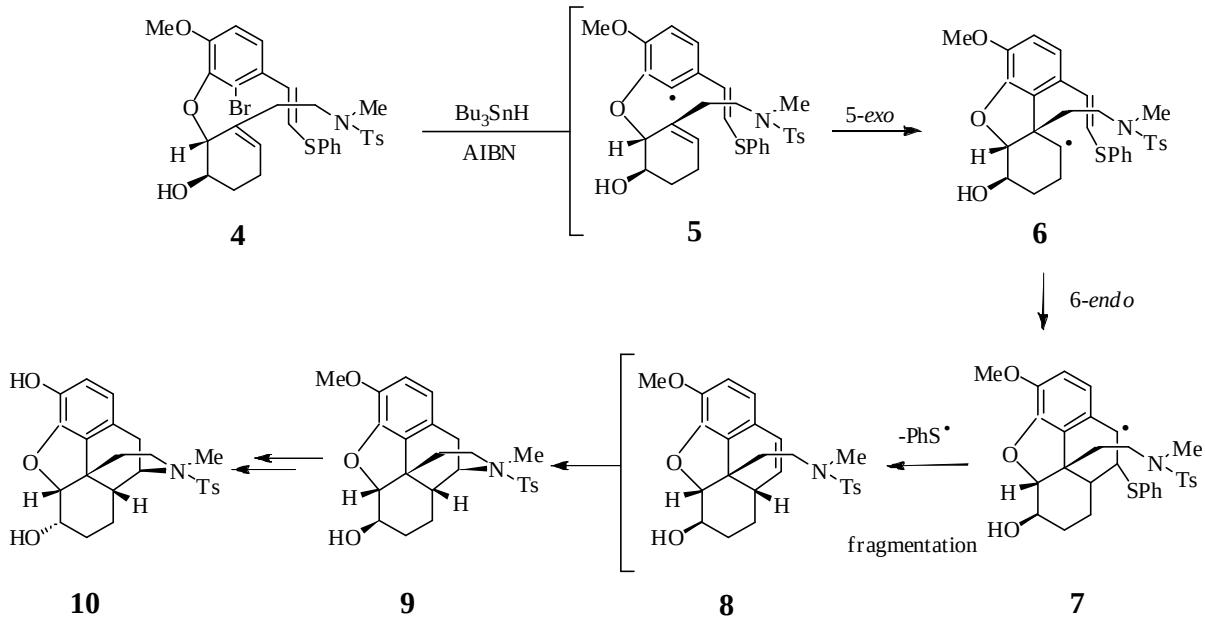
The tin hydride method has several virtues. It is extremely mild and selective. The laboratory simplicity and kinetic understanding of the tin hydride method also make it easy to use. Most important, the kinetic behaviour of tin hydride is such that, when a radical $\mathbf{R^{\bullet}}$ is generated from a reactive radical precursor in the presence of a low concentration of tin hydride, it has a reasonably long lifetime within which to react ($\mathbf{R^{\bullet} \rightarrow RZ}$) before being trapped ($\mathbf{R^{\bullet} \rightarrow RH}$).

Barton and McCombie [7] in the early 1970s made use of this superlative flexibility of organotin reagents in their radical deoxygenation reaction. The Barton-McCombie reaction involve the use of a thiocarbonyl derivative of the alcohol such as xanthate and has found numerous applications because the hydroxyl function is ubiquitous in natural products and in synthetic intermediates. One example is presented in the novel and stereospecific synthesis of the marine natural product (±)-Δ-canellen **3** from *p*-cresol by Singh[9]. After rapidly assembling the desired carbon framework, it was necessary to remove the carbonyl group from the tricyclic intermediate which was accomplished using Barton's deoxygenation (Scheme 2).



Scheme 2

However, during the past decades, radical C-C and C-heteroatom bond-formations have grown in importance.[10,11] Free radical reactions have played a dominant and determining role in the development of polycyclic ring synthesis via tandem radical cyclisations, particularly when they are carried out in an intramolecular and sequential ring-forming fashion. For example, Parker et al.[12] incorporated a tin hydride-mediated bicyclisation of an aryl radical in the synthesis of (±) morphine (Scheme 3). Reaction of aryl bromide **4** with tributyltin hydride chemoselectively breaks the carbon-bromine bond to generate the reactive aryl radical **5**, which undergoes 5-*exo* cyclisation onto the trisubstituted alkene to give a stable *cis*-fused ring product **6**. The resulting cyclic secondary radical then undergoes a 6-*endo* cyclisation to form the tetracyclic radical **7**. This mode of cyclization produces a less strained ring system than that obtained from the alternative 5-*exo* cyclisation, and also generates a resonance-stabilized benzylic radical. Finally, rapid fragmentation of radical **7** occurs to break the weak C-S bond. The fragmentation introduces an alkene double bond **8**, which is required for the subsequent cyclization reaction.



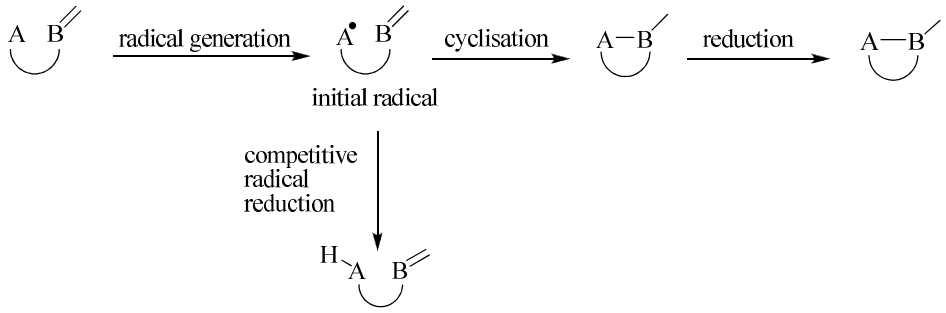
Scheme 3

This radical reaction has accomplished two cyclizations and a fragmentation in one reaction. The mild reaction conditions are also compatible with the alcohol functional group and this does not need to be protected before cyclisation.

The downside of tin hydrides is their toxicity [13,14] and the difficulty in handling and removal of tin compounds.[6,15] For years, this toxicity has kept radical chemistry from being implemented in the production of medicines and food stuffs. It is, therefore highly desirable to develop new alternatives, which could replace tin in some, if not all applications.

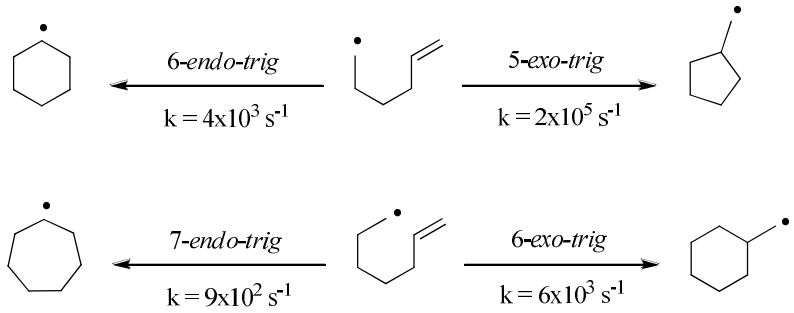
2.1 Radical cyclizations.

One of the most important reactions in radical chemistry and indeed organic synthesis is the formation of rings.[16,17] Most antibiotics and natural products contain at least one ring and many are bicyclic or tricyclic systems. Free radicals are advantageous in that they quite readily cyclise onto a range of functional groups including carbon-carbon multiple bonds, carbonyl groups, imines and aromatic rings. In general intramolecular addition is much faster than intermolecular addition. The general scheme to conduct a selective radical cyclisation is summarised below (Scheme 4).



Scheme 4

Cyclisation to give 5-membered rings is among the fastest, and by far the most widely used, ring forming process in radical chemistry. Closure of the 5-hexenyl radical, the simplest example, has been studied and often serves as a standard clock against which the rates of other radical reactions are measured. This rearrangement can in principle lead either to a cyclopentylmethyl radical by a 5-*exo-trig* ring closure or to the more stable cyclohexyl radical through the alternative 6-*endo-trig* mode (Scheme 5).[18,19] It is the former, with a rate constant of $2 \times 10^5\ s^{-1}$ at 25 °C, that predominates by a factor of about 50, indicating that the process is under kinetic control. 5-Membered rings are therefore less subject to competitive reduction leading to uncyclised by-products.

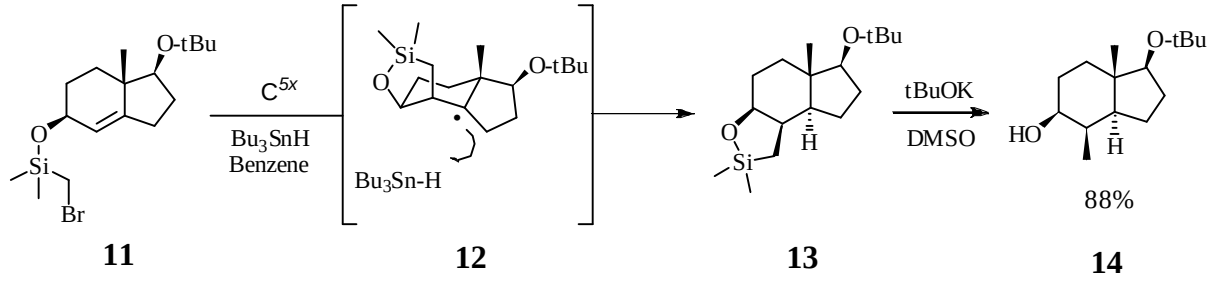


Scheme 5

This regioselectivity is in agreement with Baldwin´s rules [20] of cyclisation which state that 5-*exo*-cyclisation is a favoured process.

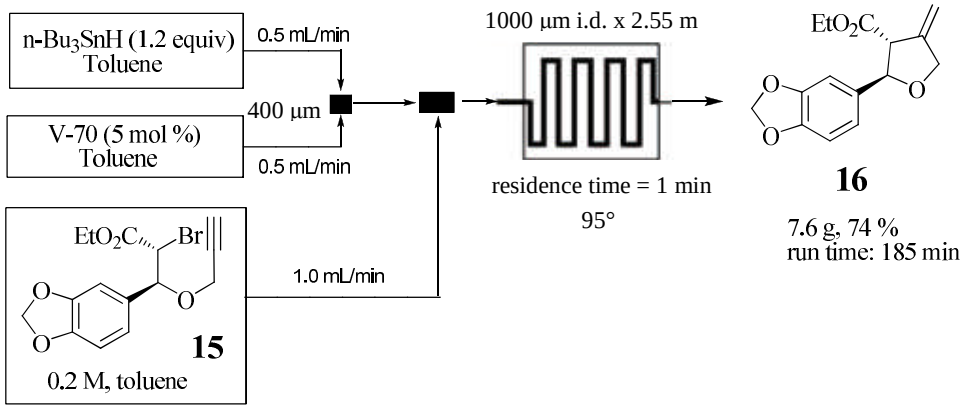
One example of 5-*exo* cyclisation is described in Scheme 6. Stork and Khan[21] exploited the ease of 5-membered ring formation to transfer stereochemical information from an allylic alcohol to control the configuration of the adjacent carbon. Protection of the allylic hydroxyl group as its bromodimethylsilyl ether **11** provides a precursor for an effective reductive cyclisation. Not only have two new chiral centres been established with total control, because the final hydrogen atom transfer from the stannane occurs from the less

hindered *exo*-face of **12**, but the *trans* hydrindane **13** is also generated in the process (Scheme 6).



Scheme 6

Recently, tributyltin hydride-mediated radical reactions of organic halides were successfully carried out in a continuous flow system using a microreactor by Ryu et al.[22] The reactions proceeded within a very short period of time, coupled with quickly decomposing radical initiators such as V-65 and V-70. The continuous flow reaction was applied to gram synthesis of the tetrahydrofuran **16**, key intermediate for the synthesis of furofuran lignans [23] (Scheme 7).

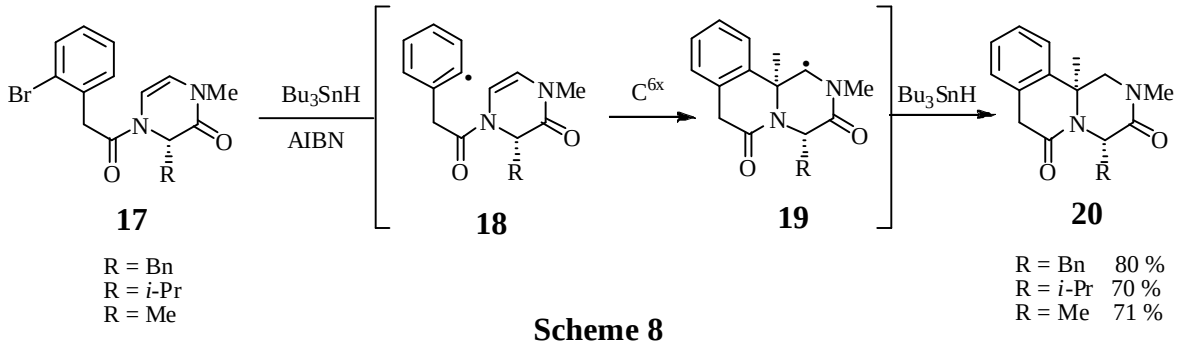


Scheme 7

The 5-*exo* radical cyclisation of unsaturated α-bromo ester **15** was completed in 1 min reaction time. To achieve multigram quantities, the microflow system was run for a total of 185 min, which gave 7.6 g of the tetrahydrofuran **16**.

6-Membered ring radical cyclisations are less general than cyclisations leading to 5 membered rings. However, they still have an important place in synthesis. One example involving 6-*exo* cyclisation is the formation of amino acid derived heterocycles which can be used as peptidomimetic scaffolds.[24] Amino acids were used to synthesise a range of enamido

radical precursors **17**. The aryl radicals **18** were generated using Bu_3SnH and these cyclised with a 6-*exo* selectively to afford the peptide mimics **20** after hydrogen abstraction in good yields. Only one diastereoisomer was obtained in each case and this was explained by the radical approaching from the opposite face of the amino acid's side chain (Scheme 8).

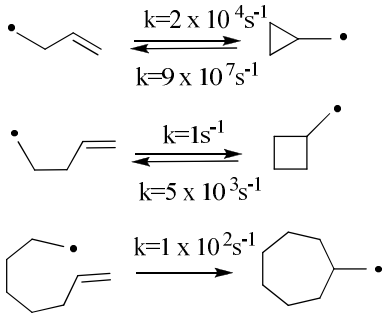


Scheme 8

2.2 Unusual radical cyclisation.

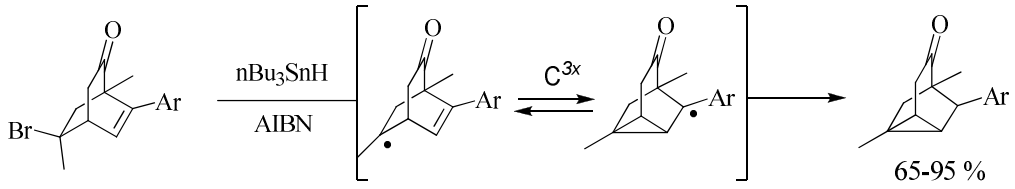
As has been described earlier, radical cyclisation is most often applied to the formation of five- and six- membered rings. Nevertheless, "odd" type cyclisations have become a good alternative to ionic reactions in the synthesis of 3-, 4-, 7- and larger membered rings.[25,26]

Experimental rate constants relevant to unusual cyclisation of model radicals are shown in Scheme 9. It is apparent that reverse ring-opening processes are dynamically opposed to both 3-*exo* [27] and 4-*exo* [28] cyclisations. Preparation of three- or four- membered rings can, therefore, only be achieved by the intramolecular addition route, for precursors containing substituents, or structural factors, which favour cyclisation and/or disfavour ring-opening. The rate constants of cyclisation rapidly diminish as ring size increases.[19] Furthermore, although *exo* cyclisation usually is faster than *endo* cyclisation, the difference gets smaller as ring size increases.



Scheme 9

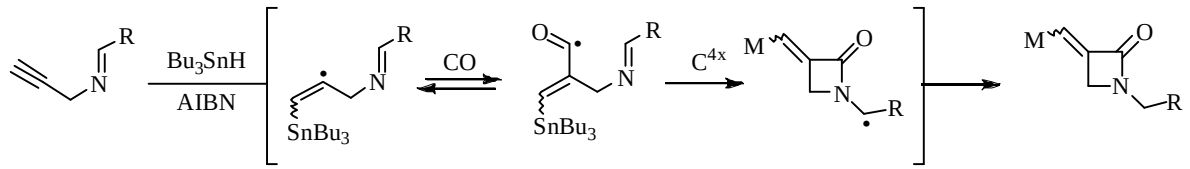
One example of the 3-*exo* cyclisation has been recently described by Srikrishna et al.[29] in the successful synthesis of tricyclooctan-4-ones **24**. The bromide **21**, on treatment with Bu_3SnH and AIBN furnished the tricyclic compound **24** via 3-*exo-trig* radical cyclisation. Because of the presence of a radical-stabilizing group, such as an aryl or arylethynyl group on the olefin, the equilibrium was shifted to the cyclised form (Scheme 10). The electrophilicity of the olefin was increased enough for it to act as a very good internal radicophile.



21 **22** **23** **24**

Scheme 10

4-*Exo* cyclisation has been extensively used in the synthesis of cyclobutanes, cyclobutanols, cyclobutanones and specially β-lactams. β-Lactams are a family of antibiotics and appear in many other natural products such as clavulanic acid. 4-*Exo-trig* cyclisation routes to the ring system are remarkable for their variety and range. One of these pathways, is the addition of acyl radical onto an imine acceptor. Ryu and co-workers [30] made used of their elegant radical cabonylation process in the synthesis of tin containing β-lactams **29**. The reactions were carried out with the precursor azaenyne **25**, Bu_3SnH and the presence of AIBN as an initiator under 90 atm. of CO at 90 °C. Addition of an organometallic radical gave vinyl radical **26**, which picked up CO to generate acyl radical **27**. The latter underwent a 4-*exo* cyclisation onto the N atom of the imine and subsequent H abstraction from the Bu_3SnH gave the β-lactams **29** in excellent yields (Scheme 11).

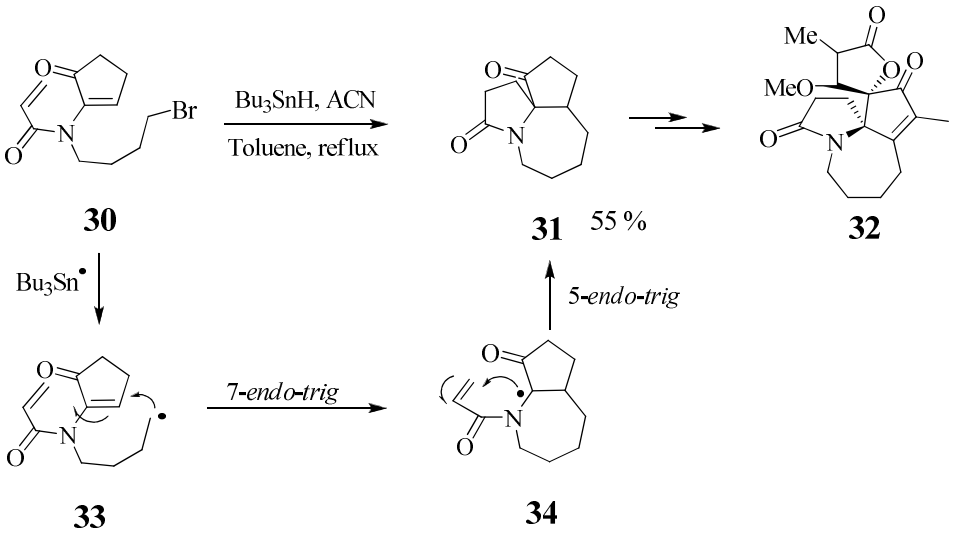


25 **26** **27** **28** **29**

Scheme 11

Radical cyclisations to give 7-membered rings have also been carried out. In a very recent example, Ishibashi et al [31] have described a concise total synthesis of (±)-stemonamide

using a radical cascade as a key step. The tricyclic skeleton **31** was obtained by a Bu_3SnH-mediated radical cascade of that involves 7-*endo-trig* cyclisation of alkyl radical **33** and a subsequent 5-*endo-trig* cyclisation of the resulting α-amidoyl radical **34** (Scheme 12).



Scheme 12

Radical cyclisation promoted by Bu_3SnH has been proved to be extremely versatile, reliable and efficient, in the synthesis of several carbocycles and heterocycles.

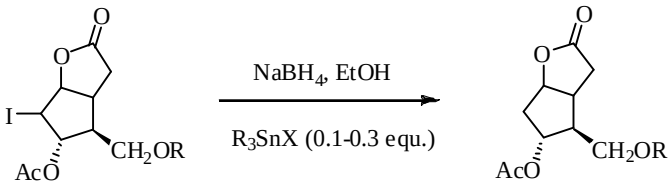
Unfortunately, tin-based chemistry is associated with two critical drawbacks, that is, the toxicity of organotin compounds and the problems very often encountered in product purification. The qualitative removal of organotin residues from the reaction products is usually a difficult task, and this disadvantage, along with the high toxicity of those residues, can severely limit the application of tin reagents, for example for the synthesis of pharmaceuticals. It is therefore no surprise that alternative ways of carrying out radical reactions are under intensive investigation, in a search for both efficient purification protocols and, above all, tin substitutes.

2.3 New tin reagents which aid product isolation.

2.3.1 Catalytic tin hydride Reactions.

Tin hydrides are usually employed in stoichiometric amounts. The products, once formed by these procedures, must be separated from a full one equivalent of trialkyltin halide. However, several processes using catalytic amounts of organotin species in radical reactions have been reported to date. The observation that reduction of organotin halides by lithium aluminium hydride occurs very rapidly[32] suggested that organotin halides might be used as

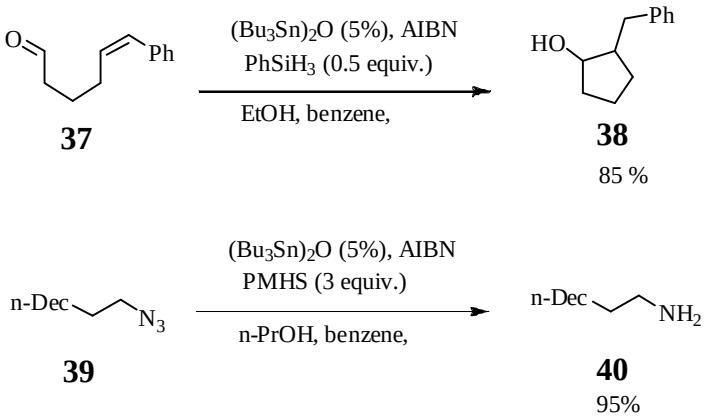
hydrogen carriers. However the use of a stoichiometric amount of the reactive aluminium hydride greatly limits the method. In 1975 Corey[33] developed a catalytic process for the generation of the valuable prostaglandin precursor **36** from the halolactone **35** using the milder sodium borohydride (Scheme 13).



35 **36**

Scheme 13

A further improvement to the catalytic procedure was established by Stork[34], who used sodium cyanoborohydride as the stoichiometric reducing agent in *t*-butanol. In the late nineties, Fu et al.[35,36] introduced the development of Bu_3SnH-catalyzed reactions by using the commercially available phenylsilane ($PhSiH_3$) or polymethylhydrosiloxane (PMHS) to generate the tin hydride. Reductive cyclisations of enals and enols or reduction of azides to amines were performed with catalytic $(Bu_3Sn)_2O$ (Scheme 14). However, since $PhSiH_3$ and PMHS do not reduce tin halides, these methods are limited to the recycling of tin alkoxides and tin amides.



37 **38** 85 %

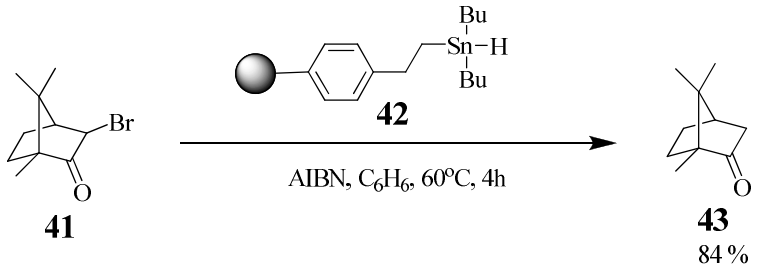
39 **40** 95%

Scheme 14

2.3.2 Modified tin hydrides.

In order to avoid contamination of the products by tin-products as well as to simplify separation procedures, some authors have investigated several polymer-supported organotin hydrides. Neumann and co-workers[37] reported the use of polymer **42** to reduce bromides,

thiocarbonates and isonitriles. Apart from the simpler work up, the by-products can be separated by simple filtration, the polymer reagent can be regenerated for multiple uses.



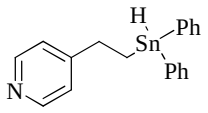
41 **43** 84 %

Scheme 15

Modified tin hydrides for which the corresponding tin halides are readily separated from the organic reaction products, have been designed. The alkyl groups in these compounds are replaced by special phase makers.

The pyridylstannane[38] **44** is readily soluble in polar organic solvents, the tin-halogen by-products have very low R_f values in ethyl acetate:hexane (1:3), which allows the desired product to be efficiently isolated by chromatography. These reagents can be used to form products in comparable yields to those obtained using the standard tin hydride method.

Curran[39] introduced fluorous tin hydrides such as tris[2-(perfluorohexyl)ethyl]tin hydride reagent **45** as a versatile reducing agent with the advance of an easy separation of the tin by-products from the reduced compound by liquid extraction. The reaction is carried out in trifluoromethylbenzene, which is evaporated off upon completion and replaced with a mixture of dichloromethane and perfluoromethylcyclohexane. 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 (Figure 1).



44

$(C_6F_{13}CH_2CH_2)_3SnH$

45

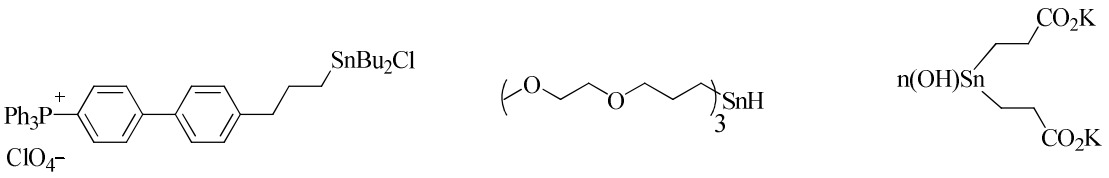
Figure 1

Charette et al[40] have described the use of the phosphonium-supported tin reagent as an effective solubility control group for tin reagents involved in radical–mediated processes such as dehalogenations and cyclisation reactions. The phosphonium reagents are typically very soluble in chlorinated solvents, and they can be precipitated out of solution by ether,

hexane or toluene addition. The tin by-products can be removed by a simple phase separation and recycled if needed. The reduction of halides using tin chloride **46** proceeded very well under Stork's[34] conditions. Several aryl and alkyl bromides were converted to the reduced product in high yields. After standard work up, the crude product was dissolved in DCM and the tin residues were precipitated upon hexane addition. Filtration of the mixture and concentration of the solution led to tin-free product.

Breslow[41] developed a new water-soluble tri(methoxyethoxypropyl)tin hydride **47** to perform tin radical chemistry in water. The trialkyl species are easily recovered. Acidifying the water to pH < 2 with HCl regenerates the trialkyl chloride, which is extracted into $CHCl_3$, distilled, and reduced with BH_3 in THF, regenerating the tri(methoxyethoxypropyl)tin hydride.

Collum and co-workers[42] have described an improved water-soluble tin reagent **48** which can be reduced in situ with $NaBH_4$ to a tin hydride that can be used in radical dehalogenation reactions. This novel compound has provided consistently high yields, comparable to those of conventional Bu_3SnH/AIBN method.



46 **47** **48**

Figure 2

Regretfully all these modified compounds must be synthesised in the lab prior to use and this prevents them from becoming popular replacements. Furthermore, the problems of tin toxicity and tin garbage remain a constant menace. Hence, alternatives ways of carrying out radical processes are of great interest.

3.0 Alternatives to tin hydride.

3.1 Oganosilicon-, germanium-hydrides.

Silicon and germanium are in the same periodic column as tin, and the radical chemistry associated with these elements is in many ways similar. The increased strength of the bonding to hydrogen and carbon translates into slower kinetics and less efficient chain processes as compared with organotin derivatives (Figure 3).

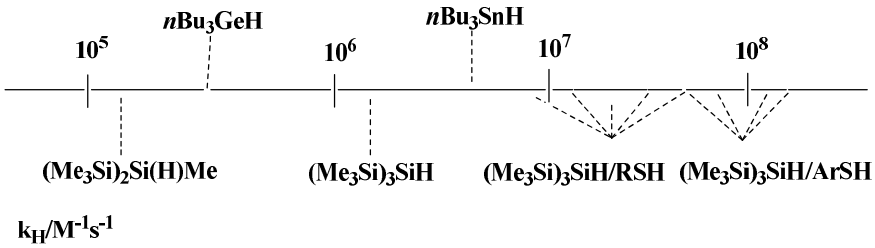
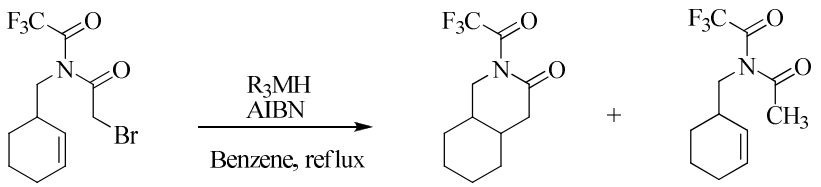


Figure 3. Rate constants for H-atom abstraction from a variety of reducting systems by primary alkyl radicals at 80ºC.

According to the kinetic studies carried out by Chatgilialoglu and Newcomb[43] H – atom abstraction from tri-*n*-butylgermane by a given carbon-centred radical is 10-20 times slower than from tri-*n*-butyltin hydride, and from triethylsilane and other simple silanes it becomes too slow to be useful. Modified triethylsilanes, and more concretely, TTMSS[44] are the best alternative to the tin hydrides. Organogermanium compounds and TTMSS are more expensive than triorganotin hydrides but this is compensated by a lesser toxicity and a greater ease of purification of the reaction mixture.

3.1.1 Radical reactions with germanium.

Tributylgermanium hydride derives its principal benefit from the low reactivity of its metal-hydrogen bond. This reagent does become interesting when a desired radical transformation cannot be accomplished efficiently using organotin procedure. For instance, in the construction of γ- and δ-lactams by 5- and 6-*exo* type cyclisations, starting from bromoacetamides **49** by Stork and Mah[45] (Scheme 16).



49 **50** **51**

Bu_3SnH	65 %	24 %
Ph_3GeH	85 %	-----

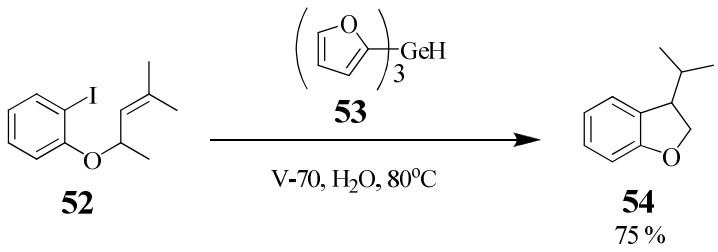
Scheme 16

The cyclisation step is compounded by the existence of two rotamers, only one of which can cyclise, and the rate of rotation around the amide bond is slower than hydrogen

abstraction from the stannane.[46] Substitution of tributyltin hydride by the slower reducing triphenylgermane, affords the cyclised product **50** in much better yields and none of the reduced product **51**.

The most potent Ge-based H-donor towards C-radicals to date is $(TMS)_3GeH$,[47] which reduces primary C-radicals about three times faster than Bu_3SnH. $(TMS)_3GeH$ has been used in radical dehalogenation, in Barton-McCombie reductions, in deaminations via isonitriles and in deselenatons.[48]

Oshima [49] reported tri-2-furylgermane **53** as a potent tin hydride substitute for radical dehalogenations, deoxygenations and cyclisations. The reactions are generally conducted in THF using Et_3B/O_2 as radical initiator. However, it can be used in environmentally friendly aqueous solution in the presence of V-70 [2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile)]. A suspension of o-iodophenol **52,** tri-2-furylgermane **53** and initiator in water was stirred at 80°C for 4.5 h, affording the desired cyclised product **54** (Scheme 17).



52 **53** **54** 75 %

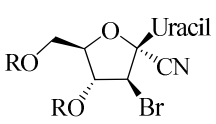
Scheme 17

However, although these reagents have some advantages, they are not an ideal alternative to organotin hydride, not least due to the cost, and are therefore not used very often in preparative radical chemistry.

3.1.2 Radical reactions with silicon.

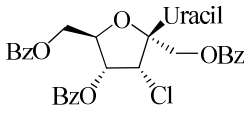
Trialkylsilanes R_3SiH represent a viable alternative to trialkyltin hydrides. Silicon-centred radicals are extremely efficient in abstracting halogens from alkyl halides, in order to generate the alkyl radicals. However, H-abstraction from simple trialkylsilanes by C-radicals is too slow to participate in radical chain reactions at ordinary temperature because the silicon-hydrogen bond is usually too strong for efficient H-abstraction. Moreover alkyl radicals are nucleophilic species and the hydrogen atom in triethylsilane is also electron rich. Therefore, the abstraction of hydrogen from ethylsilane by an alkyl radical to give the reduced product is disfavoured and this disrupts the chain process.

In the late eighties Chatgilialoglu introduced a modified organosilicon hydride, which constitutes the most successful tin hydride substitute to date, tris(trimethylsilyl)silane (TTMSS).[44,50] [$(TMS)_3SiH$] is commercially available and can satisfactorily replace tin hydrides in the more common radical reactions because of its greater hydrogen donating ability compared to trialkylsilanes. This is due to stabilisation of the resulting silyl radical achieved by back-bonding into the adjacent, vacant, d-orbital on each of the silicon atoms. TTMSS is an effective reducing agent for the removal of a variety of functional groups Examples of dehalogenation and reductive removal of chalcogen groups are shown in Figure 4, for bromide **55**,[51,52] chloride **56**,[53] and selenide **57**[54] by reaction with $(Me_3Si)_3SiH$ in the presence of AIBN as an initiator.

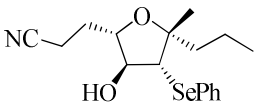


R, R = TIPDS

55



56



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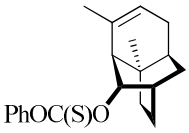
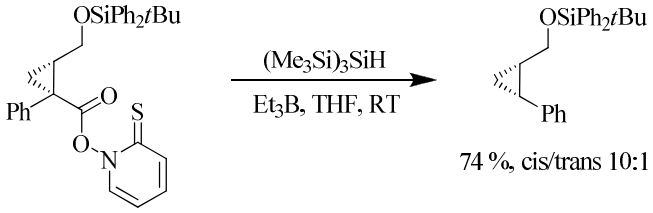


58

Figure 4

The use of TTMSS in the deoxygenation of secondary alcohols, after conversion to thiocarbonyl derivatives (e.g. phenylthiocarbonate **58**), has important applications in nucleoside chemistry, where it can be very useful in going from the ribose to the 2-deoxyribose series, a common step in medicinal chemistry. The need for non-toxic reagents to achieve this step is evident since the compounds have to be tested for biological assays.

A variety of acyl derivatives, such as acyl chlorides,[55] phenylseleno esters,[56] or N-hydroxypiridine-2-thione esters,[57] can be used for decarbonylation and reductive decarboxylation. One example is the decarboxylation of the chiral *cis*-cyclopropane **59.** Another feature of the radical reactivity of $(Me_3Si)_3SiH$ is the diastereoselective outcome. The H abstraction from the sterically demanding TTMSS preferably occurs from the less hindered side of the intermediate cyclopropyl radical, thus affording a very high *cis*-selectivity **60** (Scheme 18).

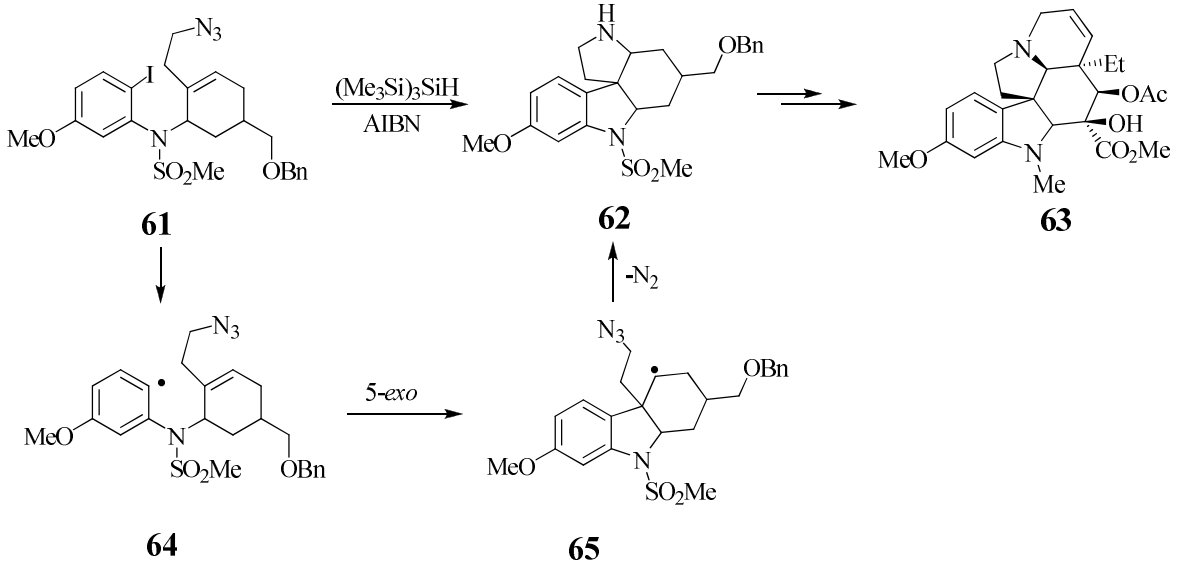


59 **60**

Scheme 18

Moreover, since the Si-H bond is approximately 5 kcal/mol stronger than the Sn-H bond of tributyltin hydride, the less reactive $(TMS)_3SiH$ often allows radical reactions using a stoichiometric amount of the silane in the initial reaction mixture to be performed, preventing in some cases, premature reduction of intermediate radicals by tributyltin hydride.[58] The reactions are generally conducted, by analogy with tin hydride mediated reactions, using AIBN as initiator in benzene or toluene.

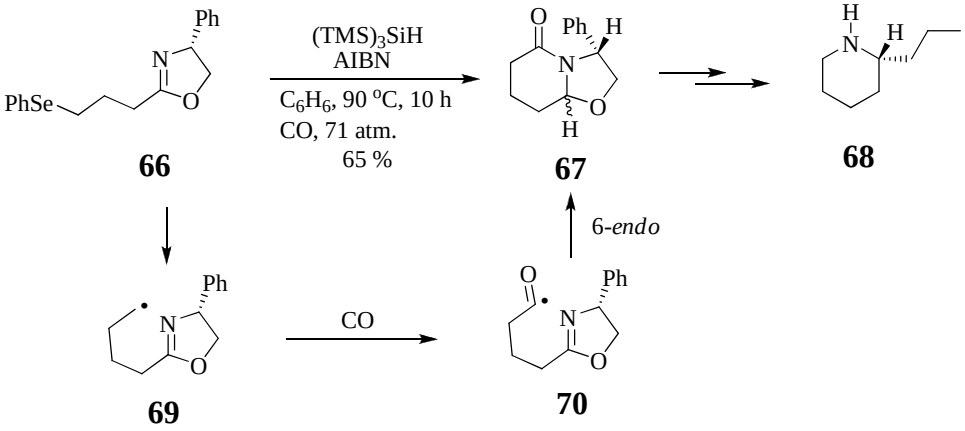
Murphy[59] and co-workers made use of the TTMSS properties in the formal total synthesis of the important anti-cancer agent (±)-vindoline **63** (Scheme 19). Intramolecular tandem radical cyclisation was achieved from iodoaryl azide **61** by reaction with TTMSS in the presence of AIBN. Aryl radical **64** cyclised in a 5-*exo* fashion generating a new C-centred radical **65** which attacked the azide group, assembling the tetracycle **62** in 65 % yield.



Scheme 19

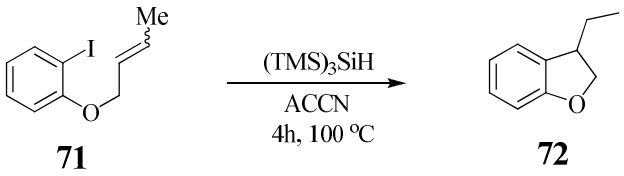
Free radical carbonylation has gained distinction as a promising method for introduction of carbonyl groups into molecules. Extensive research has been carried out in this area using organotin compounds as radical mediators.[60] However, these processes must be carried out under high pressures in order to encourage the alkyl radical to react with carbon monoxide instead of abstracting hydrogen from the tin hydride. Due to the stronger Si-H bond in TTMSS compared to tin hydride, direct reduction is less of a problem and this allows the pressure of CO to be reduced. Ryu and co-workers[61] reported the formal synthesis of (R)-(-)-coniine **68** based on the free-radical-mediated carbonylation and 6-*endo* cyclisation of the resultant acyl radical onto the oxazoline nitrogen (Scheme 20). Thus, treatment of oxazoline **66** with carbon monoxide in the presence of TTMSS and AIBN provided bicyclic

lactam **67** in 65 % yield. Interestingly the 6-*endo* cyclisation onto nitrogen is preferred over 5-*exo* cyclisation which may be ascribed to the "polarity-matched" combination of an acyl radical and an imine N-C bond.



Scheme 20

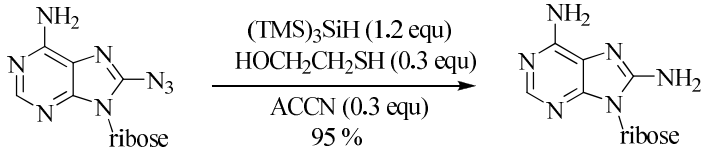
The use of water as solvent is not only because it is cheap, safe, and environmentally friendly but also because of increased reaction rate and selectivity.[62] Recently, Chatgilialoglu et al.[63] have reported the successful use of $(Me_3Si)_3SiH$ in a variety of radical-based transformations in water. Two different methods were described, depending on the hydrophilic or hydrophobic character of substrates. For water-insoluble compounds, a heterogeneous mixture of the substrate, TTMSS and 1,1'-azobis(cyclohexane-carbonitrile) (ACCN) in water was heated at 100 °C for 4 hours. Dehalogenation and deoxygenation of alcohols, Barton-McCombie reaction, worked as efficiently as previously reported in organic solvents. Furthermore, the reaction conditions were also applied for a radical cyclisation; 1-allyloxy-2-iodobenzene **71** affording the cyclised compound **72** in 85 % yield (Scheme 21).



Scheme 21

On the other hand, when the mentioned conditions were used for the reduction of water-soluble compounds, no reaction was observed. The problem was solved using the amphiphilic 2-mercaptoethanol ($HOCH_2CH_2SH$) in combination with TTMSS. The reduction

of hydrophilic substrates in water has the advantage of an easy separation of the silane by-products. One example reported by Chatgilialoglu, was the reduction of water soluble azides **73** to primary amines **74** in excellent yields (Scheme 22).

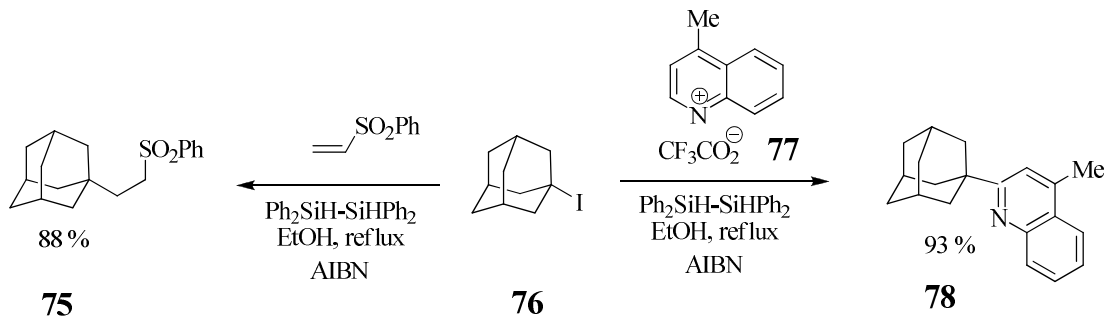


73 **74**

Scheme 22

Although tris(trimethylsilyl)silane shows great versatility and can be used to mediate a number of useful reactions, its use entails some disadvantages. For example the silyl radicals generated from this reagent are very efficient at hydrosilylating double and triple bonds, leading to reduced yields by forming unwanted side products.[64] Other disadvantages are that TTMSS is easily oxidized by air and it is rather expensive. Nevertheless, it constitutes the best alternative to tin hydrides nowadays.

Other organosilanes have been extensively studied as tin hydride substitutes.[65] 1,1,2,2-Tetraphenyldisilane deserves special mention. Introduced by Togo and co-workers,[66] it is an air-stable crystalline solid, made by treating chlorodephenylsilane with magnesium. It tolerates mildly acidic substances such as pyridinium salts and reactions can be run in refluxing alcohols. When adamantyl iodide **76**, $Ph_4Si_2H_2$, AIBN and lepidinium trifluoroacetate **77**, were refluxed in ethanol the corresponding alkylated heteroaromatic base **78** was obtained in excellent yield. In the same way, Giese-type addition to a carbon-carbon double-bond was carried out giving the corresponding reductive addition product **75** (Scheme 23).

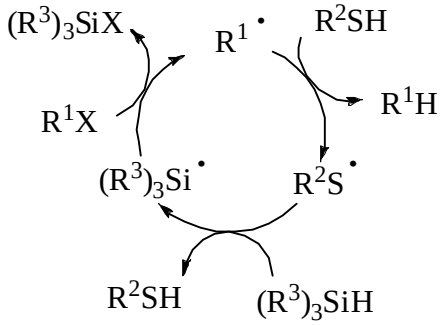


75 **76** **78**

Scheme 23

3.2 Polarity reversal catalysis.

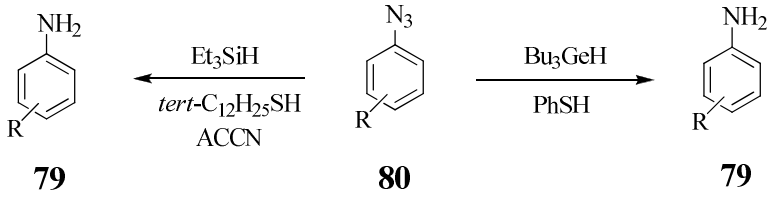
Polarity reversal catalysis (PRC) by thiols has successfully been applied in reductive radical chain reactions using stoichiometric amounts of trialkylsilane by Roberts and co-workers [67] and further developed by Bowman.[68] In addition to the inherent strength of the Si-H bond, the difficulty in abstraction of the electron-rich hydrogen is compounded by the fact that alkyl radicals are themselves generally nucleophilic in character. The polarity mismatch that also obtains with stannanes is compensated by the weakness of the Sn-H bond. The S-H bond in aliphatic thiols is as strong as the Si-H bond in triethylsilane but has the reverse polarity. The rate of hydrogen atom transfer from a thiol to a nucleophilic alkyl radical becomes comparable to that from tributylstannane. In the chain, the C-radical $R^{1\bullet}$ is readily reduced by the thiol catalyst to provide the corresponding reduced product R^1H, along with the thiyl radical $R^2S^{\bullet}$. The thiyl radical is then reduced with a trialkylsilane $(R^3)_3SiH$ to generate the thiol catalyst R^2SH along with the silyl radical $(R^3)_3Si^{\bullet}$ which is able to propagate the chain reaction (Scheme 24).



Scheme 24

Spagnolo et al. investigated the radical aryl azide reduction using Et_3SiH[69] and Bu_3GeH.[70] To circumvent the poor hydrogen-donating properties of these compounds, the procedures were carried out following "polarity reversal catalysis". It was proved that electron-rich and electron-poor aryl azides **80** in refluxing toluene remained unaffected upon treatment with Et_3SiH or Bu_3GeH in the presence of a radical initiator such as AIBN or ACCN. This fact was due to inhibition of the chain reaction caused by the inefficiency of the nucleophilic silane and germane towards the derived N-silyl and N-germylaminyl radicals, which are predicted to have nucleophilic properties as well. They extended the (PRC) technique to the silane using *tert*-dodecanethiol as a catalyst in the presence of ACCN and

catalytic amounts of benzenethiol with germanes, affording aryl amines **79** in excellent yields (Scheme 25).

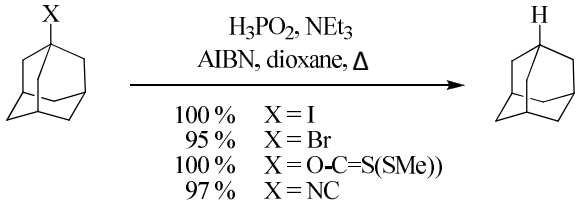


79 **80** **79**

Scheme 25

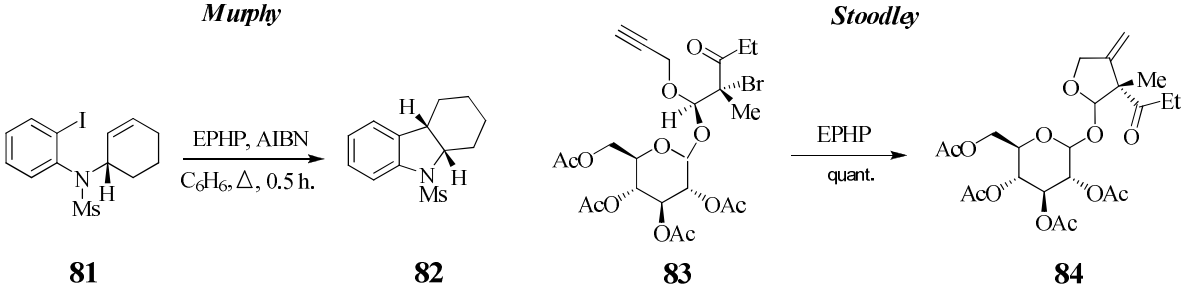
3.3 Phosphorus reagents.

Recent developments in radical reactions involving phosphorous reagents have attracted the attention of several research groups.[71] The use of hypophosphorous acid and its salts in reductive radical chain was first studied by Barton and Jaszberenyi.[72] Phosphorous acid and its salts contain weak P-H bonds which can be readily abstracted by radical initiators to produce phosphorus-centred radicals. These were initially used in reductive radical chain reactions such as deamination *via* isonitriles, deoxygenation *via* xanthates or thiocarbonates and dehalogenations (Scheme 26).



Scheme 26

The best salt proved to be the *N*-ethylpiperidinium salt (EPHP). Murphy and Stoodley simultaneously reported that EPHP could mediate formation of carbon-carbon bonds. This was demonstrated by a 6-*exo*-*trig* cyclisation in the synthesis of the carbazole **82** from aryl iodide **81** by Murphy,[73] and, through a 5-*exo*-*dig* cyclisation of the alkyl α-keto radical obtained from **83,** by Stoodley,[74] which afforded the carbohydrate **84** in quantitative yield (Scheme 27).

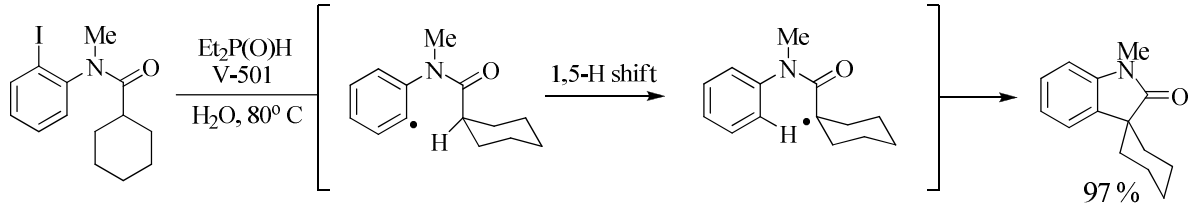


81 **82** **83** **84**

Scheme 27

Kita et al[75] reported the use of EPHP as a water-soluble chain carrier in the C-C bond forming radical reaction of hydrophobic substrates in water in an efficient radical process. It was based in the use of a water-soluble radical initiator VA-061, the chain carrier EPHP, and surfactant cetyltrimethylammonium bromide CTAB. This surfactant is essential to solubilise the hydrophobic substrate in water.

Murphy,[76,77] introduced a water-soluble phosphine oxide which permits higher isolated yields than the corresponding reaction using EPHP, with no additional additive. Upon using diethylphosphine oxide (DEPO), they carried out an efficient synthesis of indolones in water (Scheme 28). Treatment of aryl iodide **85** with DEPO in the presence of a water soluble radical initiator V-501, gives the aryl radical **86** which undergoes 1,5- hydrogen shift. Subsequent homolytic aromatic substitution of **87** onto the phenyl ring yields indolone **88** in excellent yield.

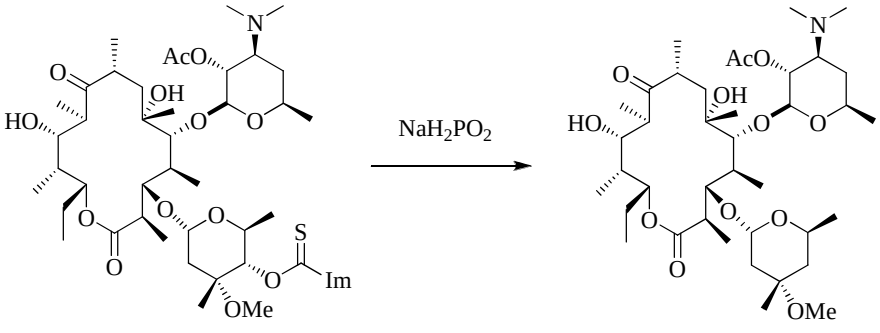


85 **86** **87** **88**

Scheme 28

Because DEPO is more lipophilic than hypophosphorous acid yet is still water soluble, it can facilitate the interaction between the water-soluble mediator and initiator and the lipophilic substrates without requiring a phase-transfer agent. Moreover, its pK_a is 6, thus ensuring that this almost neutral excess reagent can be extracted into base during workup.

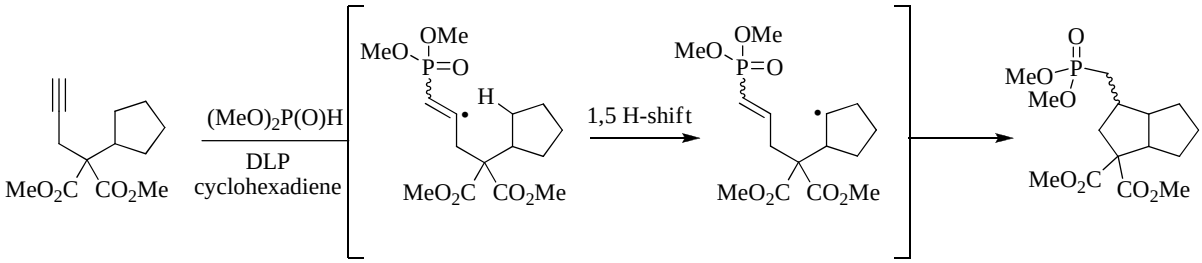
Probably, one of the most impressive synthetic achievements of the P-based radical mediators is the deoxygenation of an erythromycin B derivative **89** toward the industrial synthesis of ABT-229 **90**, a potent motilin receptor agonist. Clean deoxygenation was accomplished on a 15 kg scale by using NaH_2PO_2 in an aqueous alcohol and phase transfer agent (Scheme 29).[78]



89 **90**

Scheme 29

Addition of a phosphorus-centred radical onto an unsaturated carbon-carbon bond is one of the most common reactions for the preparation of organophosphorus compounds. Phosphonyl radicals have subsequently been involved in tandem and cascade process. Parsons et al.[79] have investigated extensively the formation of carbocycles by reaction of 1,6-dienes with ethyl phosphites and AIBN. They were able to prepare the corresponding cyclic organophosphorus derivatives in good yields. More recently Renaud[80] introduced a new tandem process based on the addition of phosphonyl radicals onto alkyne, radical translocation and final cyclisation onto the vinylphosphonate affording the synthesis of various cyclopentanes (Scheme 30).

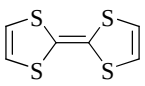


Scheme 30

The efficiency of the radical processes, the low cost of the phosphorus reagents, their ease of separation from reaction products and their environmentally friendly character gives a strong and renewed relevance to the development of radical reactions involving phosphorus.

3.4 The radical-polar crossover reaction.

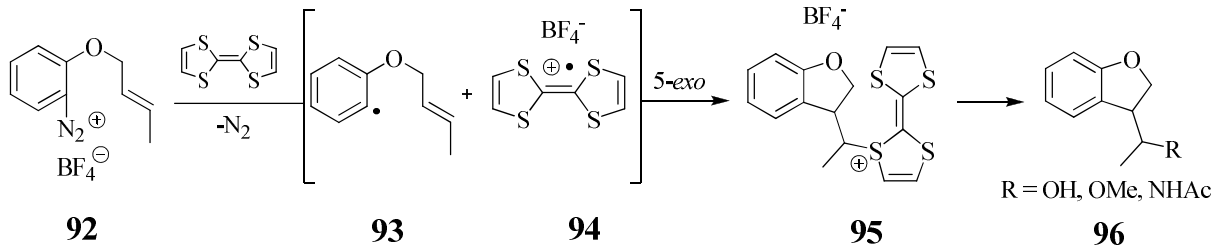
The use of neutral ground-state organic molecules as powerful reducing agents is a novel and attractive idea, which has been extensively investigated by Murphy and co-workers.[81] A representative of this class of neutral molecules is tetrathiafulvalene (TTF) **91.**



91

Traditionally, aryldiazonium salts were used in conjunction with copper (I) in order to generate aryl radicals. However, the organic TTF can be used to replace copper in this procedure as the initial electron donor. Tetrathiafulvalene will readily donate an electron to the aryldiazonium tetrafluoroborate **92** in order to expel nitrogen and form the aryl radical **93**. 5-*Exo* cyclisation of this intermediate gives the alkyl radical which is ultimately trapped by the TTF radical cation in order to furnish the crystalline product **95** (Scheme 31).[82] In the

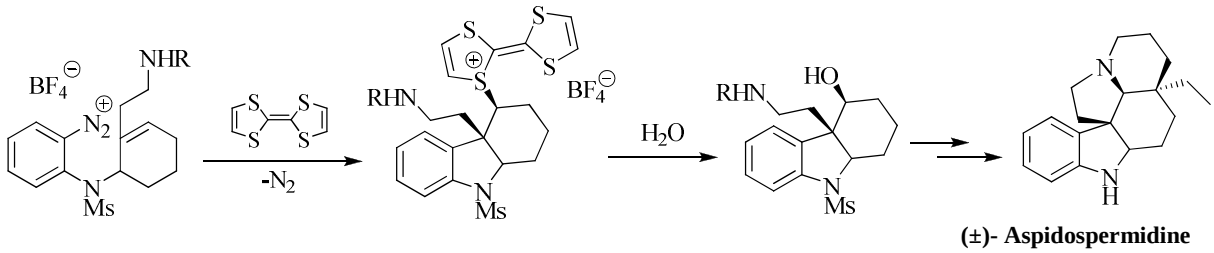
presence of moist acetone, the TTF salt was converted into the corresponding alcohol. Methyl ether was formed when using methanol as the solvent, and it was also possible to use acetonitrile as the solvent to furnish amides [83].



Scheme 31

As TTF is regenerated at the end of a reaction sequence via S_N1 attack of a nucleophile, 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 **95**.

An interesting application of the radical-polar crossover reaction to the synthesis of aspidosperma alkaloids is depicted in Scheme 32 and relies on solvolysis of the intermediate TTF salt to give the secondary alcohol with overall retention of configuration.[84]

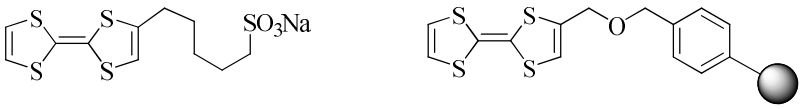


Scheme 32

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.

There have been attempts to generate both water-soluble TTF analogues **97** and polymer supported TTF **98**. The water-soluble reagent is easily prepared from TTF and can be reacted with water soluble diazonium chlorides. The organic product is simple to extract, making this an attractive procedure for industrial use.[85] Polymer-supported TTF makes

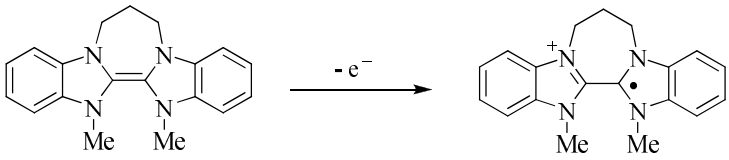
purification even simpler, filtration extracts the polymer-bound TTF, which can be regenerated using sodium borohydride with a minimal drop in reactivity[86] (Figure 5).



97 **98**

Figure 5

The major limitation of using TTF as a radical initiator is the requirement for arenediazonium salts as starting materials. Attempts to extend this reaction to the much more common aryl halides or to alkyl halides have been carried out, the "dimer" **99** being one of the most successful reagents (Scheme 33).

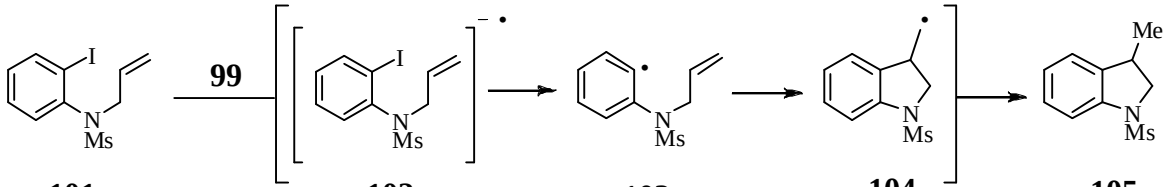


99 **100**

Scheme 33

Compound **99** is a more powerful reducing agent than TTF. The driving force for electron donation derives from the considerable aromatization energy[87] residing in the corresponding radical cation **100**, and the presence of nitrogen, which is helpful to the creation of a good electron donor.[88] Thus, electron loss from **99** would initially afford radical cation **100**, which features the double stabilization.

To prove the efficiency of this super electron donor, several aryl iodides were treated with **99**. For instance, initial electron transfer from **99** to aryl iodide **101**, would afford the radical anion **102.** Dissociation of **102** would then give the aryl radical which undergoes 5-*exo* cyclisation onto the double bond yielding indoline **105** in excellent yield (Scheme 34).[89]



101 **102** **103** **104** **105**

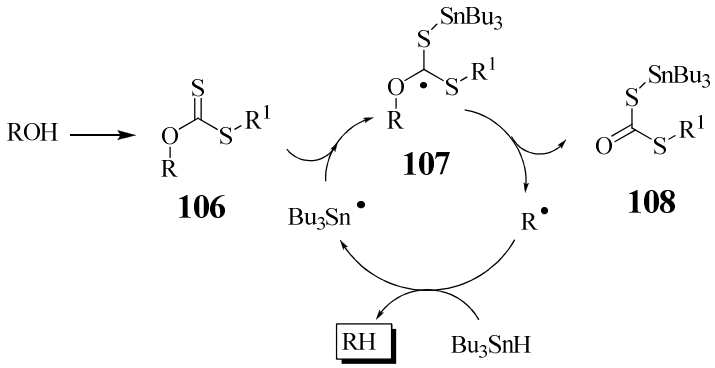
Scheme 34

The use of neutral ground state organic molecules as powerful reducing agents, has proved to be an excellent method in the generation of aryl radicals and its application in radical cyclisation. The very mild and neutral reaction conditions, the absence of metals, their selectivity, tolerance of other functional groups, tunability, ease of attachment to solid supports and ease of regeneration, make these reducing agents very attractive for use in synthetic chemistry.[90]

3.5 Xanthates and related derivatives as radical precursors.

3.5.1 The Barton-McCombie deoxygenation

Xanthates and related thiocarbonyl derivatives made their entry into synthetic radical chemistry in the early 1970s. Barton and McCombie introduced a radical deoxygenation using organotin hydride and thiocarbonyl compounds.[7] The Barton-McCombie reaction represents a major milestone in the application of radical processes to synthetic problems. It has been widely used in organic synthesis, especially for the modification of carbohydrates, and as a convenient source of radicals from alcohols in general. The method requires the conversion of an alcohol into a xanthate **106** which is readily attacked by tributyltin hydride in the presence of a radical initiator AIBN to give the carbon-centred radical adduct **107** undergoing a preferential β-scission of the carbon-oxygen bond to form alkyl radical **R**$^{\bullet}$ and the carbonyl co-product **108** (Scheme 35).[91]

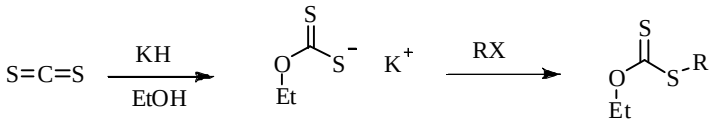


Scheme 35

The Barton-McCombie reaction allows spectacular deoxygenations, especially in complex carbohydrates. Moreover the use of cheap reagents is another advantage of this procedure; however, the reappearance of organotin hydrides in the reaction mechanism prevents this method being used outside laboratories.

3.5.2 Degenerative transfer of xanthates.

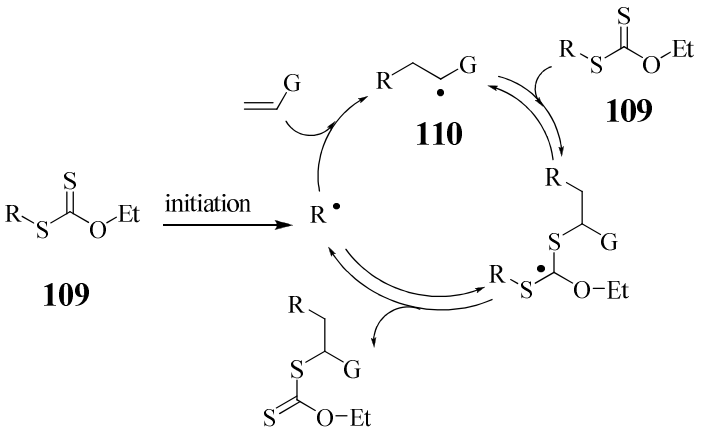
Zard and co-workers have made a very intensive study of the homolytic chemistry of a variety of xanthates.[91,92] *O*-Ethyldithiocarbonates, for example, promote tin-free radical chain addition very efficiently. [93-95] No heavy or toxic metals are involved in such a process and the starting materials are cheap and readily available. For instance, *O*-ethyldithiocarbonate **109** can be made by nucleophilic displacement of an alkyl halide with potassium *O*-ethyl xanthate (Scheme 36).



109

Scheme 36

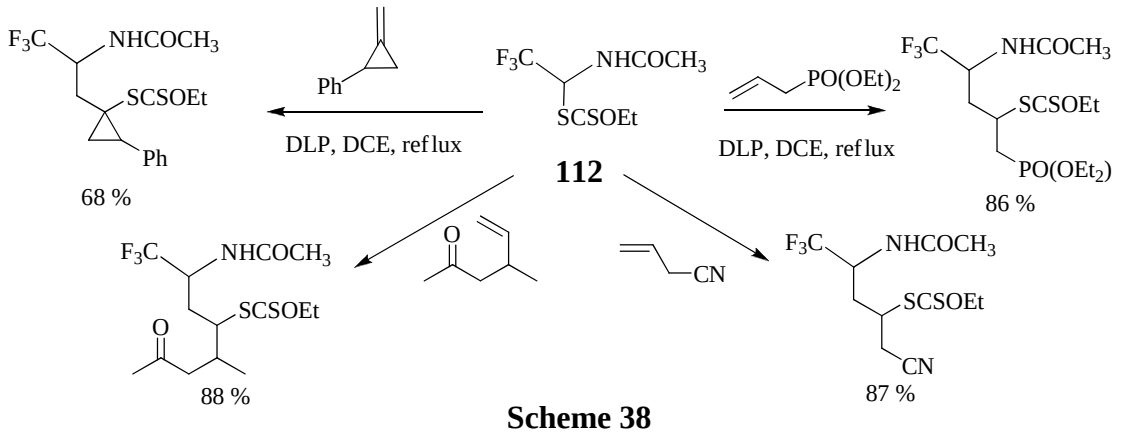
On chemical or photochemical initiation, *O*-ethyldithiocarbonate **109** cannot undergo β-scission on the carbon-oxygen bond since it would produce an ethyl radical, which is thermodynamically unstable; a radical $\mathbf{R}^{\bullet}$ is thus generated. $\mathbf{R}^{\bullet}$ reacts with an alkene placed in the medium, leading to an adduct radical **110**, which in turn reacts with the starting xanthate **109** to generate, after two reversible steps, $\mathbf{R}^{\bullet}$ and the new xanthate **111**. The released radical can then add to the alkene before continuing the chain by addition to more xanthate **109** (Scheme 37). The chain reaction is initiated mainly, using a catalytic amount of peroxide, to give the xanthate **111** as the major product which can be employed as a starting point for another radical sequence, or modified further. The xanthate functionality can also be removed by reduction with dilauroyl peroxide in propan-2-ol or treatment with DBU in order to furnish the required addition product. The array of functionality that can be obtained by using the xanthate procedure is quite amazing and has many interesting applications.



111

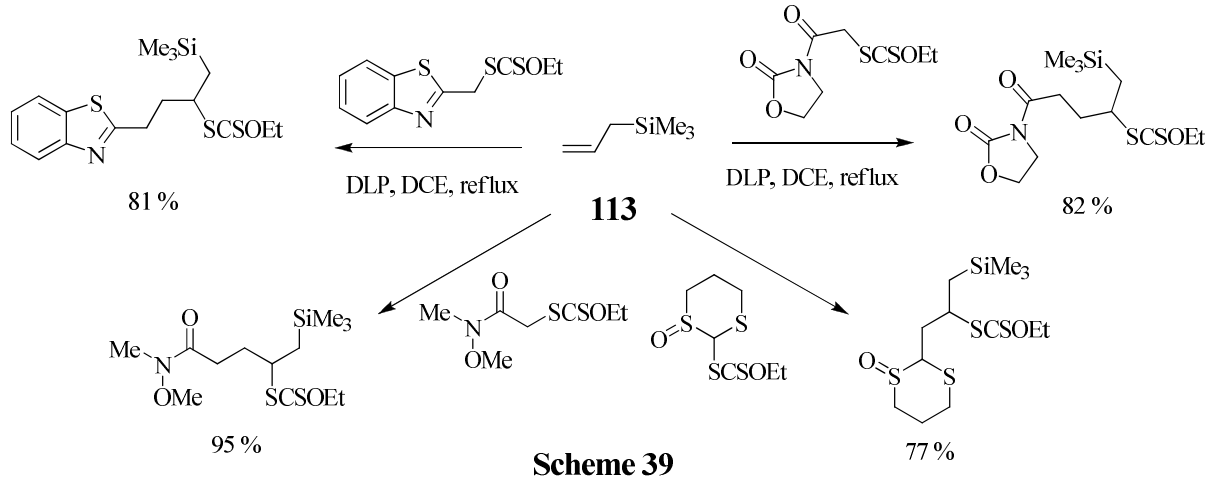
Scheme 37

The most important synthetic asset of the xanthate transfer methodology lies in the ability to induce carbon-carbon bond formation by intermolecular addition to unactivated olefins. This is possible because the initial radical has a comparatively long lifetime in the medium. For instance, xanthate **112** can add efficiently to a large assortment of olefins (Scheme 38).[96]



Scheme 38

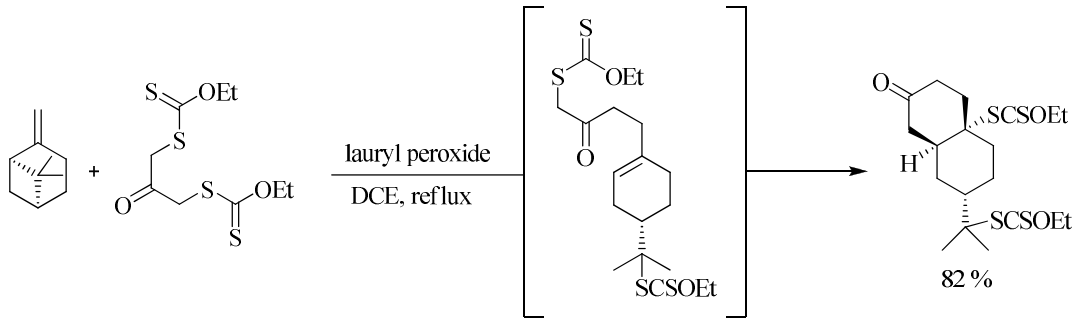
Alternatively, one can start with a given olefin **113**, and consider the great diversity of xanthates that can be added to it (Scheme 39).[97-100]



Scheme 39

If intermolecular addition onto double un-reactive olefins is feasible, the construction of rings by intramolecular addition should be readily achieved. One example can be found in the cascade sequence depicted in Scheme 40. Zard and co-workers[101] made use of an intermolecular addition, which causes the scission of the cyclobutane ring and places an

olefinic bond in a position allowing it to capture the radical produced from the second xanthate in an intramolecular mode.

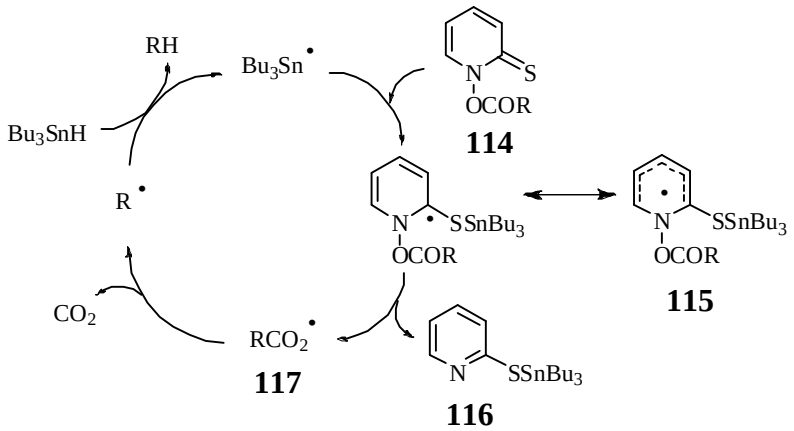


Scheme 40

Xanthates and analogues are good precursors not only to carbon-centred radicals. Xanthate precursors to acyl, alkoxycarbonyl and nitrogen centred radicals have been reported and found numerous applications in synthesis.[102]

3.5.3 Barton's thiohydroxamic esters.

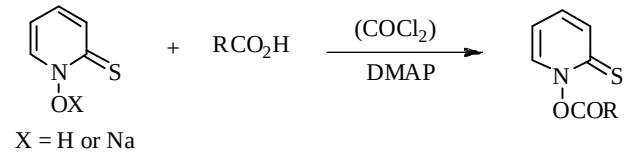
Reductive decarboxylation of carboxylic acids can be performed efficiently by use of thiohydroxamic acid esters **114**, which have been shown to be facile sources of carbon centred radicals under mild conditions.[103] Treatment of *O*-esters of thiohydroxamic acids with tributyltin hydride in presence of AIBN, or photochemically, results in the formation of delocalised radical **115**. Radical **115** fragments to give the pyridylstannane **116** as a by-product and alkoxycarbonyl radical **117** which extrudes carbon dioxide generating carbon-centred radical **R**.• This radical abstracts hydrogen from tin hydride to give the reduction product RH and the chain-carrying tin radical (Scheme 41).



Scheme 41

The success of this methodology is due to the well known affinity of tin for sulphur, as well as for the passage from thiocarbonyl to carbonyl, the weakness of the N-O bond, aromatisation of the pyridine nucleus as a favourable thermodynamic driving force, and gain of entropy upon fragmentation in creating three products from two reactants.

Thiohydroxamic esters **114** are readily obtained from the reaction of a slight excess of commercially available 2-sulfanylpyridine N-oxide **118** and carboxylic acids which are activated by oxalyl chloride in the presence of a catalytic amount of DMAP (Scheme 42). The esters formed are not usually isolated but reacted in situ with *tri*-n-butylstannane in order to obtain the reduced hydrocarbon.

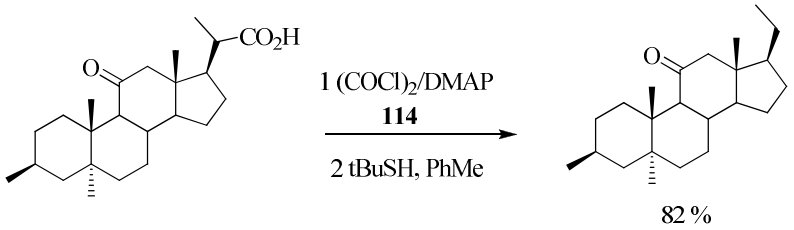


X = H or Na

118

Scheme 42

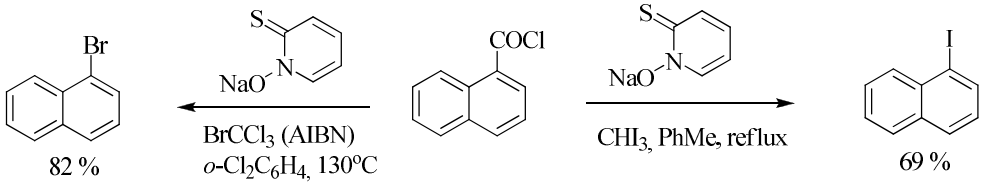
The disadvantage of this method is the use of organotin hydrides to generate alkyl radicals, therefore alternative reagents have been used in order to initiate the chain reaction. For example the use of the poorly nucleophilic *t*-butylmercaptan was found to be a valuable alternative for the decarboxylative reduction of carboxylic acids. The success of this initiator is due to the affinity of the thione functionality for sulphur centred radicals. The decomposition of thiohydroxamic esters **114** serves as initiator for the reaction which proceeds *via* a radical chain mechanism.



82 %

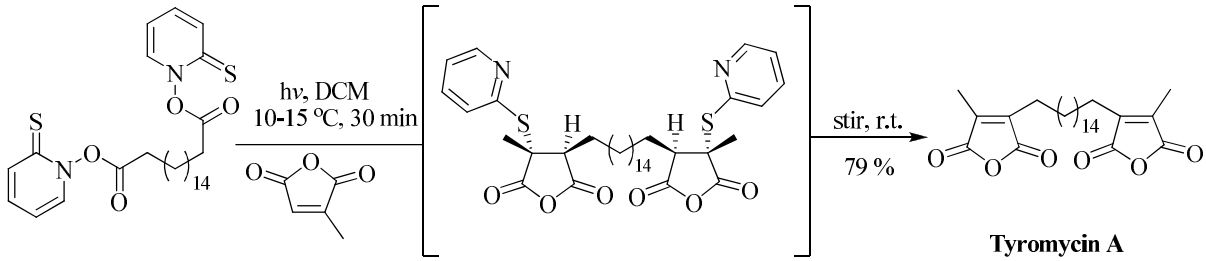
Scheme 43

Another, very useful modification of the Barton decarboxylation consists in performing the reaction in the presence of carbon tetrachloride or bromotrichloromethane, as solvent or co-solvent. This leads cleanly to the formation of the corresponding chloride or bromide. Decarboxylative iodinations can be achieved using iodoform or ethyl iodoacetate as the iodine transfer agent (Scheme 44).[104]



Scheme 44

Interception, by an internal or external olefin, of the carbon radical formed upon decarboxylation represents a mild yet powerful means of creating new C-C bonds. Samadi et al[105] reported an efficient double Barton radical decarboxylation in the one step total synthesis of *tyromycin A*. The bis-thiohydroxamic ester was irradiated in the presence of citraconic anhydride, and the resulting product was stirred for two days to ensure complete elimination affording the desired product in good yield (Scheme 45).



Scheme 45

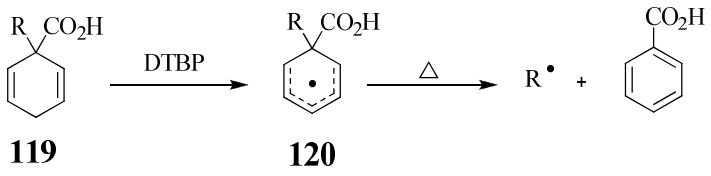
3.6 Functionalized Cyclohexa-2,5-dienes in Radical Chain Reactions.

The main attributes for a clean radical precursor include independence from use of toxic metals, afford single radicals under mild conditions and should not produce toxic or smelly by-products. A potential method of avoiding tin dependence consists of arranging hydrogen abstraction from a suitable reagent containing activated C-H bonds, as the first step of chain propagation, rather than halogen transfer as with tin reagents. Carbon-centered radicals are unselective in H-abstraction propagation steps. However several series of "pro-aromatic" appropriately substituted cyclohexadienes and related compounds deliver the required selectivity by means of bisallylic activation of hydrogen, simultaneously taking advantage of the re-aromatisation as the driving force for extrusion of some desired initial radicals. This new generation of initiator compounds can therefore be cleanly used in reductive radical chain reactions.[106]

3.6.1 Alkylcyclohexa-2,5-diene-1-carboxylic acid.

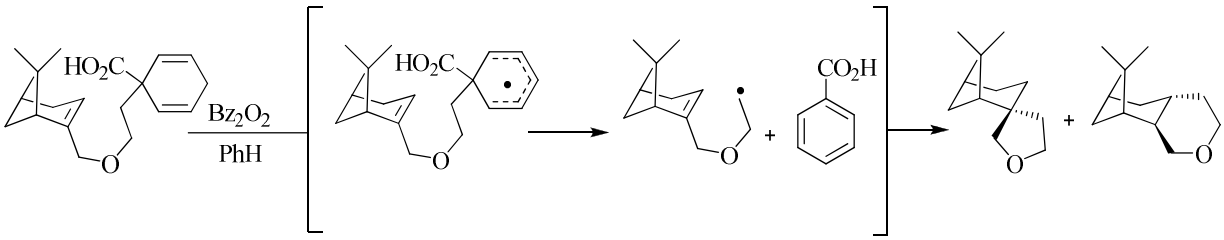
1-Alkylcyclohexa-2,5-diene-1-carboxylic acids **119** are efficient precursors for radical generation. Photolysis of carboxylic acid **119** with DTBP generated the delocalised radical

120 which underwent β-scission, at increased temperatures, yielding the desired alkyl radical accompanied by the easily removable benzoic acid (Scheme 46).



Scheme 46

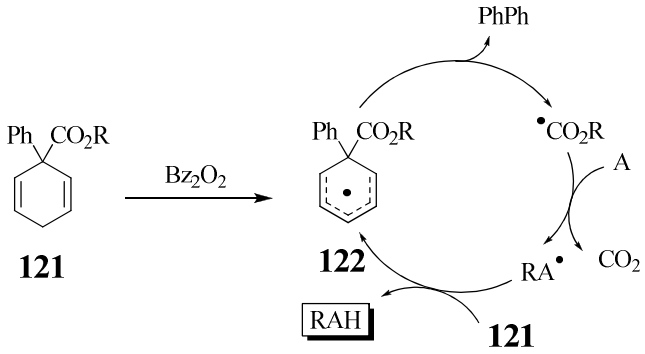
Scheme 47 shows that ring closure of the radical derived from myrtenyl containing acid took place in both 5-*exo* and 6-*endo* modes to afford cyclic ethers in moderate yields.[107]



Scheme 47

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

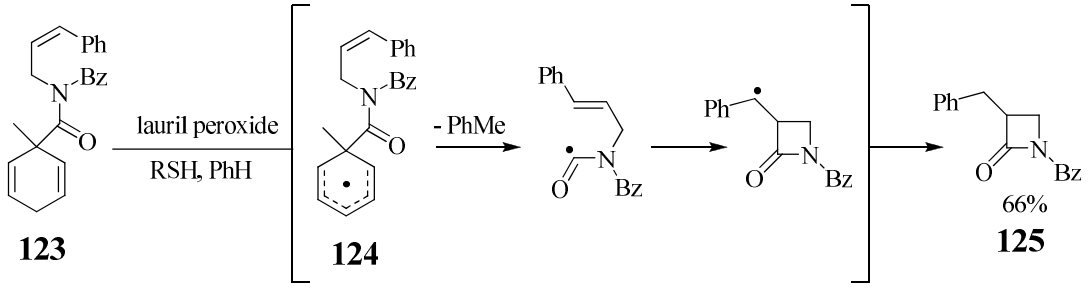
1-Phenylcyclohexa-2,5-diene-1-carboxylates, containing bisallylic activation, have been shown to undergo radical induced fragmentation to give the alkyl radical **R•** and toluene, in the presence of radical initiator dibenzoyl peroxide (Scheme 48).



Scheme 48

Phenylcyclohexa-2,5-diene-1-carboxylates **121** afforded cyclohexadienyl radicals **122** which mainly underwent β-scission above 80 °C to produce the alkoxycarbonyl radicals **•CO₂R**. The latter underwent decarboxylation, thus generating the alkyl radical **R•** This alkyl radical then reacted to give **RA•**, which abstracted hydrogen from more **121** to give the product **RAH** and delocalised radical **122**, hence continuing the chain process.[108]

In seeking to extend the scope further Walton and co-workers[109] proposed the analogous carbamoylcyclohexadienes **123** as sources of carbamoyl radicals, anticipating that the thermodynamic stability of carbamoyl radicals would prevent decarbonylation from occurring at moderates temperatures, and hence they could be incorporated in radical chain cyclizations. Carbamoyl radicals underwent 4-*exo* cyclisations, generating carbon centred radical which were reduced. However, since the reduction of carbon-centred radicals with cyclohexadiene is slow, they showed that more efficient chains were obtained using polarity reversal catalysis (Scheme 49).

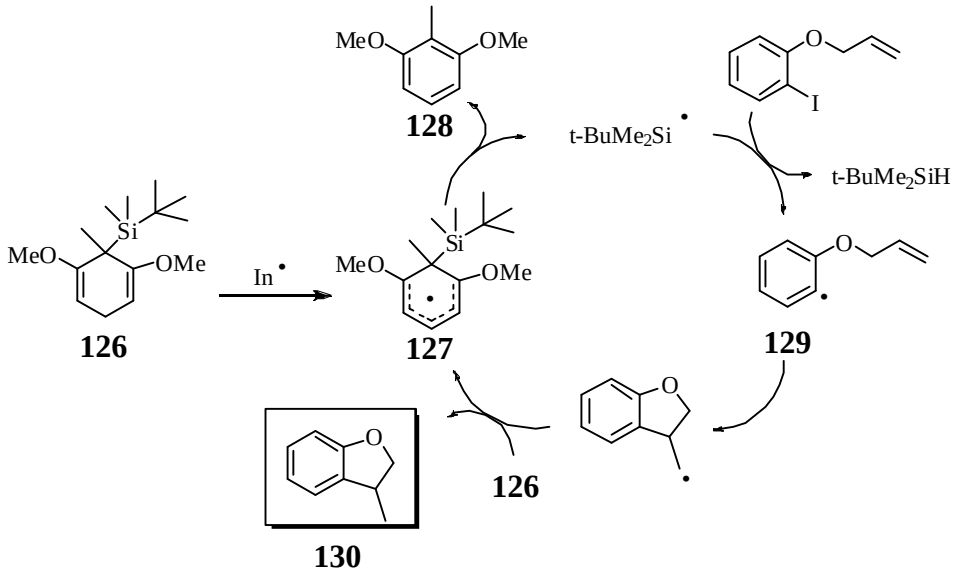


123 **124** **125**

Scheme 49

3.6.3 Silylated cyclohexadienes as radical reducing agents.

Based on the observations made by Walton on the use of cyclohexadienes as free radical mediators, Studer[110] introduced new silylated cyclohexadienes which can act as efficient hydrogen donors suitable to replace tin hydride in radical chain reductions. For example *t*-butyldimethylsilyl derivative **126** in the presence of radical initiator such as AIBN in n-hexane produced the corresponding cyclohexadienyl radical **127** (Scheme 50).

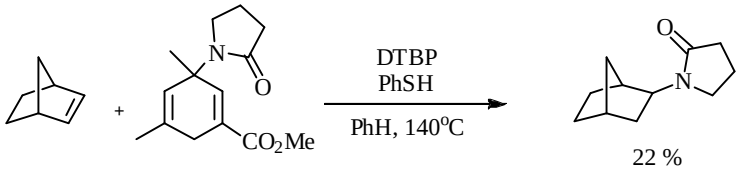


126 **127** **128** **129** **130**

Scheme 50

Rearomatization of **127** releases *t*-butyldimethylsilyl radicals which can propagate the chain by halogen abstraction from an aryl halide to give the desired aryl radical **129**. Intramolecular addition onto a double bond and subsequent bisallylic H-abstraction from more **126**, produced the dihydrobenzofuran **130**, the only by-product being methylated resorcin diether **128**.

Recently, Studer and co-workers have introduced N-functionalized cyclohexadienes as a good alternative in the generation of aminyl and amidyl radicals.[111] These cyclohexadienes can be used as an efficient reagent for the transition metal free hydroamination of unactivated olefins (Scheme 51).



Scheme 51

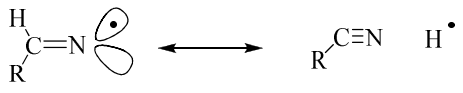
4.0 Iminyl Radicals.

In the last decade radical reactions have been conclusively accepted as a powerful tool in organic synthesis, and the excellent control for regio- and stereo-selectivity achieved in radical chemistry has allowed an extraordinary growth in the design of novel, exciting radical-based synthetic strategies.

Among the diverse radical species, iminyl radicals were almost entirely ignored by organic chemist until the eighties, however by now they have been definitely established as very interesting, versatile intermediates, capable of being employed in many synthetically useful transformations.[112]

Iminyl radicals are of significant interest in synthetic radical chemistry due to their ability to perform cyclizations onto aromatic rings and double bonds, constituting an attractive strategy for the synthesis of nitrogen heterocycles.

For EPR spectroscopic studies, alkyliminyl radicals have been generated by thermal rearrangements of oxime thiocarbamates[113] and by H-atom abstraction from imines.[114] Both alkyl- and aryl-iminyls have *g*-factors of about 2.0033, *a*(N) values close to 10 G and *a*(β-H) values of about 80 G. This evidence indicates that iminyls are σ-type species with their unpaired electrons in orbitals on the N-atoms in the nodal plane of the C=N π-system as shown in **131**. The large *a*(β-H) values show that monoalkyliminyls are subject to hyperconjugation **132** (Figure 6).



131 **132**

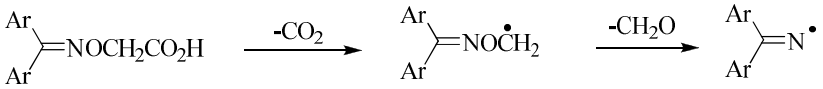
Figure 6

The structure **131** precludes substantial delocalization of the unpaired electron into the ring π-system of aryliminyls. Consequently, substituent effects on the reactivity of iminyls are weak-inductive and steric; strong effects from ring substituents of aryliminyls are not expected to come into play. These factors also imply that N-X bonds in R_2C=N-X compounds will be weak compared to N-X bonds in other N-containing compounds.

During the past several years, an increasing number of research groups, have developed ingenious methodologies for the generation and cyclisation of iminyl radicals and it has been recognized as a powerful method for construction of nitrogen heterocycles.

4.1 Generation of Iminyl Radicals.

Early attempts to generate iminyl radicals relied on harsh conditions and this limited their synthetic application. Forrester and co-workers[115] demonstrated that iminyl radicals could be obtained from imino-oxyacetic acid on boiling in the presence of persulfate.

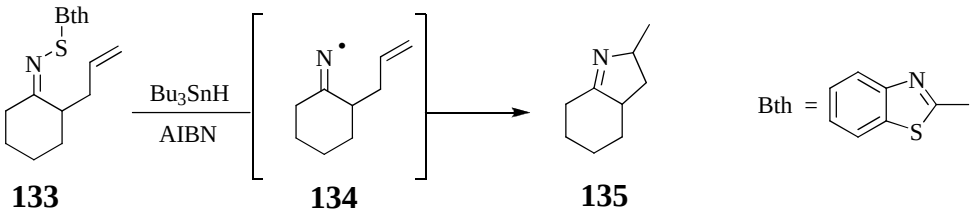


Scheme 52

It was not until the early 1990's, when Zard and co-workers conducted their intensive investigation into the chemistry of iminyl radicals, that methods of generating iminyl radicals under mild conditions became available.

4.1.1 Synthetic methods using tributyltin hydride.

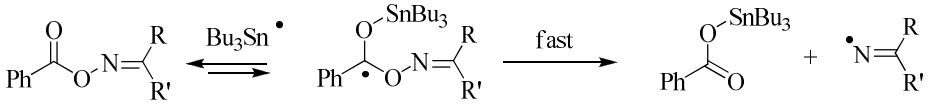
The original methodology employed by Zard and co-workers[116] for producing iminyl radicals was tin based. The precursor **133** was prepared via the condensation reaction of benzathiazolylsulfenamide with 2-allyl-cyclohexanone. On slow addition of tributylstannane in the presence of a small quantity of AIBN the precursor was found to give the iminyl radical **134** which cyclised to give the desired pyrrolenine derivative **135** in good yield (Scheme 53).



133 **134** **135**

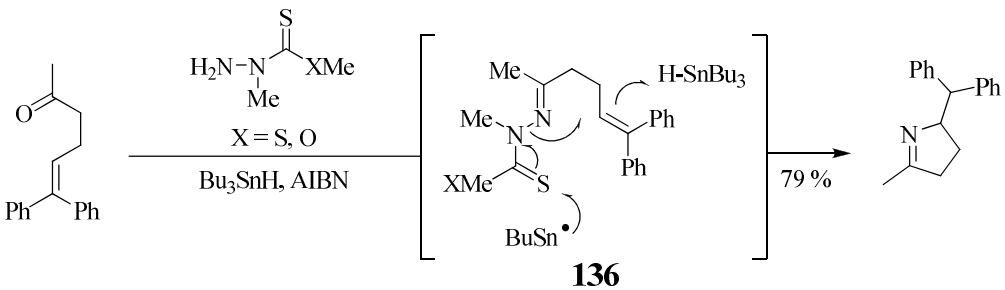
Scheme 53

The synthesis of the sulphenylimine precursor is not straightforward, especially when hindered or heavily functionalised substrates are involved. Zard et al.[117] sought another type of precursor which would lead to an iminyl upon exposure to stannyl radicals, the benzoates of oximes. Benzoates of oximes are trivial to synthesise and under the same conditions used for the sulfenimides, addition of tributylstannane to various oxime benzoates led smoothly to the products expected for iminyl radicals (Scheme 54).



Scheme 54

A more recent and general route to nitrogen centred radicals, which takes advantage of the weakness of the nitrogen-nitrogen bond in hydrazones as well as the radicophilicity of the thiocarbonyl group, was introduced by Zard.[118] Derivatives such as **136** would be expected to react with stannyl radicals in the manner outlined in Scheme 55 to give the iminyl radical. The hydrazone precursors are prepared by a simple condensation reaction. Because of the presence of the thiocarbonyl group, such derivatives turn out to be much more reactive towards tin radicals than the corresponding oxime benzoates.

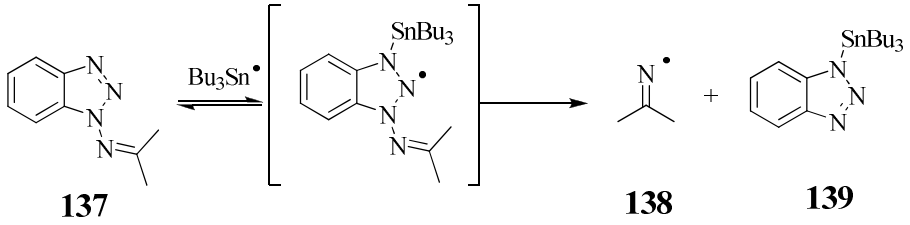


136

Scheme 55

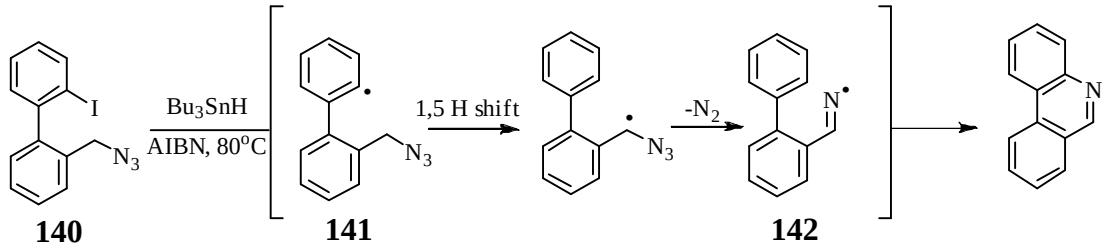
Klaim[119] described N-benzotriazolylimines **137** as suitable precursors for the generation of iminyl radicals and disclose a new radical chain process involving attack of a

stannyl radical on a nitrogen atom. N-benzotriazolylimines have several attractive features: first, their preparation from the corresponding carbonyl derivatives is an easy process, and moreover, these compounds incorporate a relatively weak N-N bond. Treatment of N-benzotriazolylimines **137** with Bu_3SnH in benzene containing a catalytic amount of AIBN leads to the formation of the corresponding iminyl radical **138** and N-(tributylstannyl)benzotriazole **139** (Scheme 56).



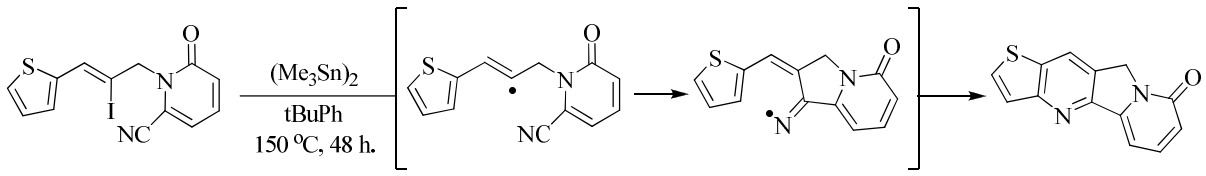
Scheme 56

Spagnolo and co-workers[120] have reported very recently the generation of iminyl radicals making use of the radical chemistry of azides. The radical reaction of tributyltinhydride with the iodo azide **140** provides an excellent access to iminyl radical **142** through 1,5-hydrogen transfer reaction of initially formed aryl radical **141** followed by β-elimination of dinitrogen (Scheme 57).



Scheme 57

An interesting methodology for the formation of iminyl radicals involves the cyclisation of a carbon centred radical onto a nitrile. This process has been investigated extensively by Bowman et al.[121] and has proved to be an effective source of iminyl radicals in the synthesis of polycyclic nitrogen heterocycles (Scheme 58).

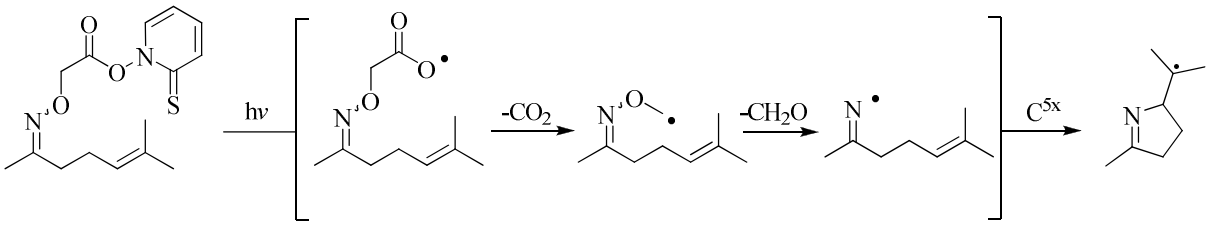


Scheme 58

4.1.2 Tin free synthetic methods.

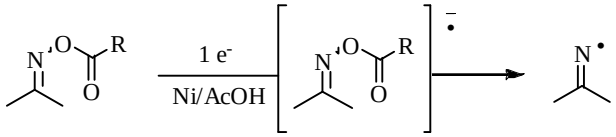
Due to the problems of tin hydride previously described, great effort has gone into developing tin free methodologies for the generation of iminyl radicals. Thermal and photochemical methods have been used in the generation of iminyl radicals from a wide variety of oxime derivatives.[122]

Zard and co-workers, connoisseurs of the problems related to the use of tin, were anxious to develop a tin free methodology. They examined the chemistry of Forrester,[115] and attempted to replace the harsh oxidising conditions described above, with much milder Barton chemistry. The Barton decarboxylation reaction provided a photochemical route to iminyl radicals[123] (Scheme 59).



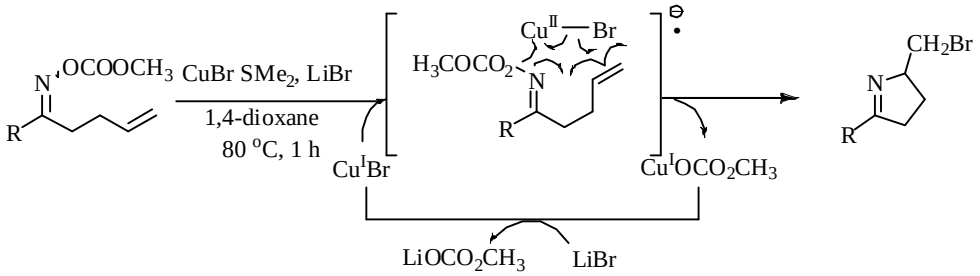
Scheme 59

A second tin-free methodology employing nickel powder as a single electron reducing agent was described by Zard.[124] The origin of the iminyl radical based on the weak oxime N-O bond. It was postulated that a mild reducing agent would break the N-O bond, resulting in formation of the iminyl radical (Scheme 60).



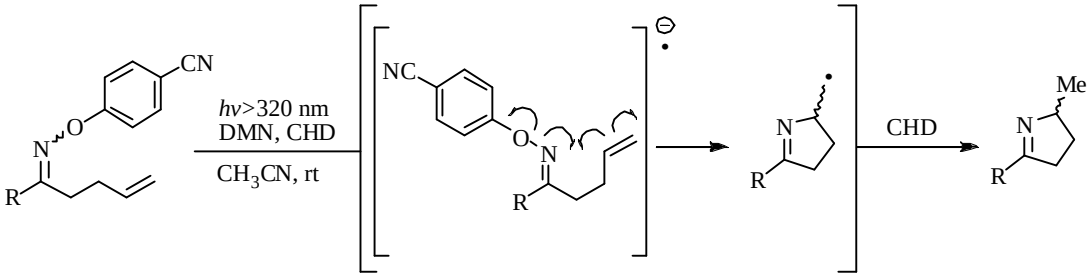
Scheme 60

The reaction however, requires a large excess of nickel powder. Narasaka and co-workers[125] conducted such a transformation in a catalytic manner. Copper(I) complexes were found to work as redox catalysts. When *O*-methoxycarbonyloxime of γ,δ-unsaturated ketones, 5 mol % of CuBr SMe_2 and LiBr in 1,4-dioxane was heated at 80 °C several bromomethyl dihydropyrroles were obtained in good yields (Scheme 61).



Scheme 61

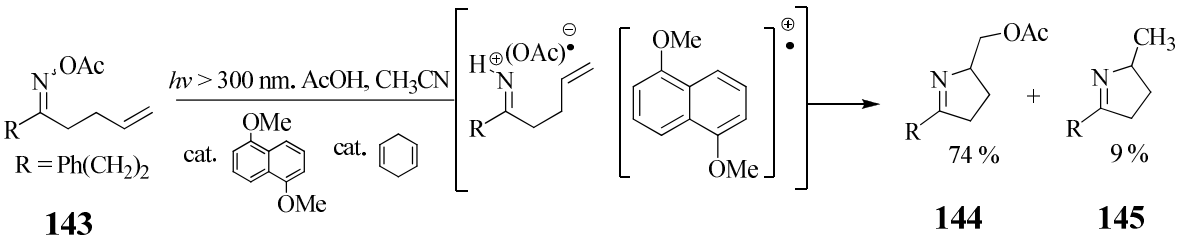
Narasaka and coworkers[126] have done extensive research into the generation of iminyl radicals by electron transfer to oxime derivatives. They introduced a photo-induced electron-transfer process to the radical cyclization of oximes (Scheme 62).



Scheme 62

Photo irradiation of a mixture of γ,δ-unsaturated *O*-(*p*-cyano-phenyl)oxime in the presence of 1,5-dimethoxynaphthalene and a radical trap afforded the synthesis of dihydropyrroles in good yields. In this reaction, the excited 1,5-dimethoxynaphthalene was used as a one-electron reductant. To make the electron transfer efficient, a *p*-cyanophenyl group was introduced as a substituent of the oxime oxygen.

Narasaka et al.[127] replaced the cyanophenyl group by a small substituent in the sense of atom economy and for the availability of the starting material. They reported the photochemical cyclization of γ,δ-unsaturated oximes having acetyl groups on their oxime oxygen (Scheme 63).

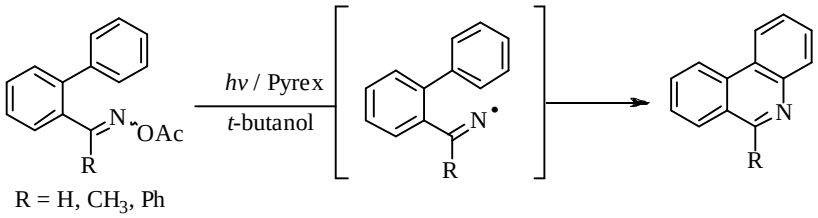


Scheme 63

The photochemical radical cyclization was examined under UV irradiation in the presence of 1,5-dimethoxynaphthalene as a sensitizer in acetonitrile. Although acetyloxime **143** does not act as a good electron acceptor, the presence of acetic acid accelerates the electron transfer, in which the protonated *O*-acetyl, generated in equilibrium, might work as a good electron acceptor.

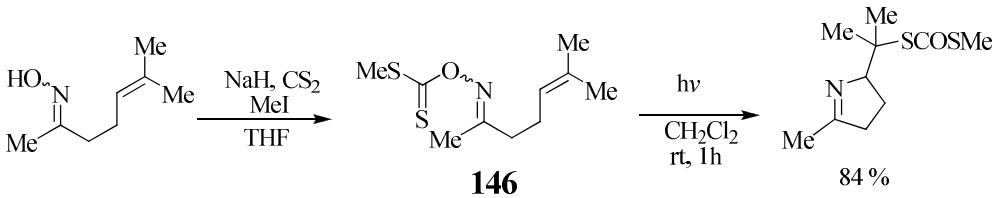
Next, Narasaka[127] examined the cyclization of aryl ketone oximes instead of alkyl ketone oximes and observed that the reaction proceeded in the absence of AcOH and the presence of excess of 1,4-cyclohexadiene and 1,5-dimethoxynaphthalene. These results indicated that the cyclization of phenyl ketone oximes does not proceed by the electron transfer process. *O*-Alkyloximes are cleaved homolytically by photoexcitation.

Rodriguez and co-workers[128] have recently reported the iminyl radical cyclization by UV irradiation of acetyloximes in the synthesis of six-membered nitrogen heterocyclic rings (Scheme 64).



Scheme 64

Concerning photochemical radical reaction of oximes, Zard et al.[129] reported an efficient radical chain cyclization of *O*-(methylthio)thiocarbonyloxime **146** initiated by homolytic cleavage of an N-O bond by photo irradiation (Scheme 65).

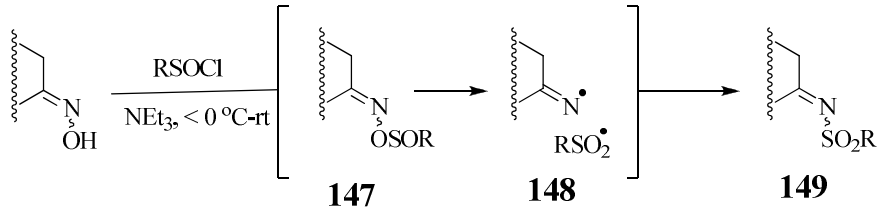


146

Scheme 65

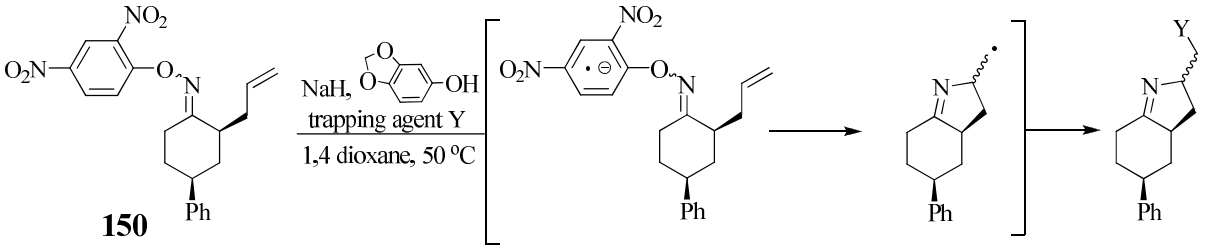
Weinreb and co-workers[130] have developed a new, mild, methodology for the generation of iminyl and amidyl radicals, based on the treatment of oximes with 2,4-dimethylbenzenesulfinyl chloride. Using a series of mechanistic experiments, it was determined that the process involves the initial formation of the sulfinite ester **147** which

upon warming, undergoes a spontaneous homolysis to an iminyl/sulfinyl 'caged' radical pair **148**. Subsequent recombination of this pair was found to afford the product **149** (Scheme 66).



Scheme 66

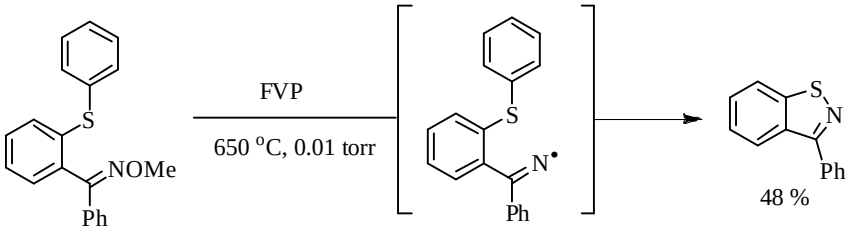
Thermal methods are usually advantageous in synthetic procedures because they are simpler, experimentally convenient and because they readily lend themselves to scale up. A few precursors suitable for thermal release of iminyls are known. For instance, *O*-2,4-dinitrophenyloximes **150** were introduced by Narasaka et al.[131] as intermediates suitable for thermal release of iminyl radicals in the presence of NaH and 3,4-methylenedioxyphenol (Scheme 67).



Scheme 67

The reaction was initiated by one electron reduction of the oxime with NaH and 3,4-methylenedioxyphenol to form an anion radical species. Subsequently, radical cyclisation proceed to form the alkyl radical, which was trapped with a radical trapping reagent.

McNab et al.[132] introduced a gas-phase generation of iminyl radical by flash vacuum pyrolysis (FVP) of oxime ethers at 650 °C and 0.001 Torr., affording the synthesis of several nitrogen heterocycles in moderate yields (Scheme 68).

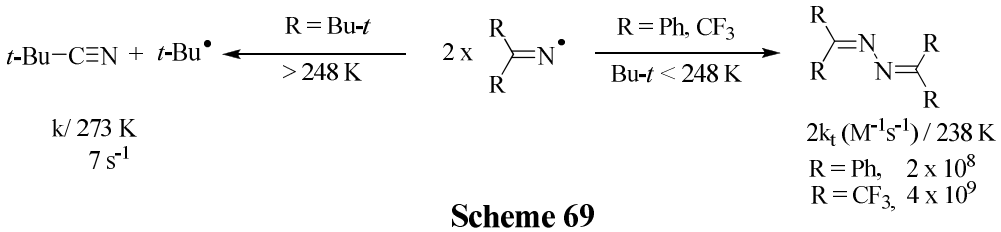


Scheme 68

4.2 Synthetic applications of iminyl radicals.

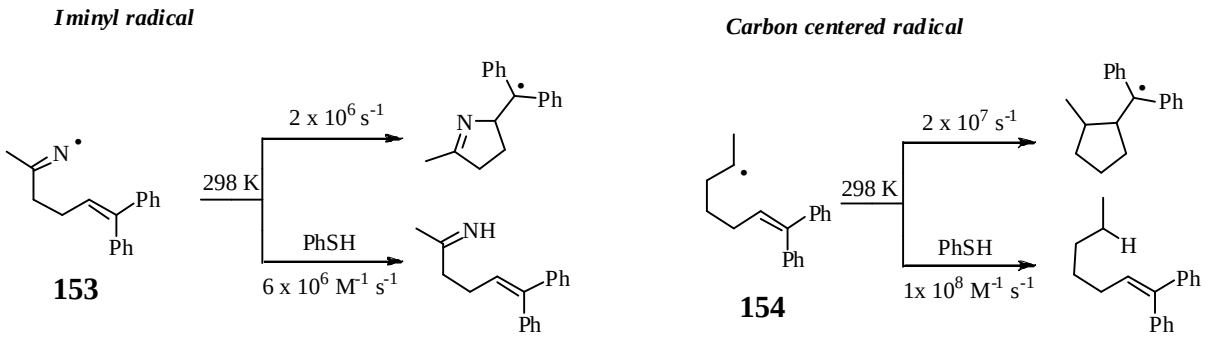
Iminyl radicals are exceptionally useful intermediates, capable of mediating a lot of synthetically interesting transformations. A great deal of work has been done on their intramolecular capture by an olefin moiety: this is a particularly efficient synthetic method for nitrogen heterocycles, especially relevant to the field of alkaloids. However, other interesting behaviours have been reported, *e.g.* addition to aromatic rings and fragmentation to nitriles with concomitant opening of strained rings: the latter is a particularly useful process that can be incorporated in synthetically useful radical cascade reaction, as will be demonstrated later.

In the absence of other reaction channels, iminyl radicals terminate by N-N coupling to give azines. The large magnitudes of the rate constant of these dimerization reactions, for small to moderately sized species,[133] indicate their coupling is diffusion controlled, just like the terminations of simple alkyl radicals. As expected, steric hindrance drastically reduced $2k_t$ for di-*t*-butyliminyl which undergoes slow dimerization ($2k_t = 4 \times 10^2$ M^{-1} s^{-1} at 238 K) at temperature below 248 K, but β-scission above this (Scheme 69). β-Scission reactions yielding nitriles are not important at T < 420 K for aryliminyls or for iminyls with primary-alkyl substituents (Scheme 69).



Scheme 69

The addition reactions of iminyl radicals were investigated by Newcomb and co-workers[134] using laser flash photolysis. 5-*Exo*-ring closure is very important from a synthetic perspective, so they measured the rate constant for the 5-*exo* cyclisation of 6,6-diphenylhex-5-en-2-iminyl **153** by LFP. The measurement showed it to be a factor of 10 slower than the C centered analog **154**. The rate constant for H-abstraction from thiophenol by a model was also determined for iminyl **153** and proved to be about a factor of 16 slower than the C-centered analog **154** (Scheme 70).

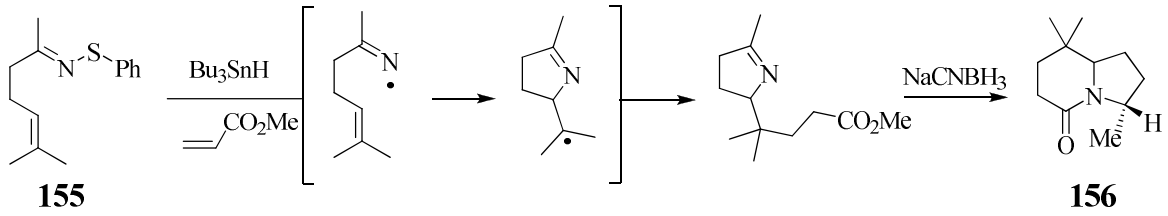


Scheme 70

In a preparative sequence, ring closure is often in competition with H-abstraction by the iminyl intermediate. The fact that H-abstraction by iminyl is also comparatively slow is crucial for the success of many heterocycle syntheses.

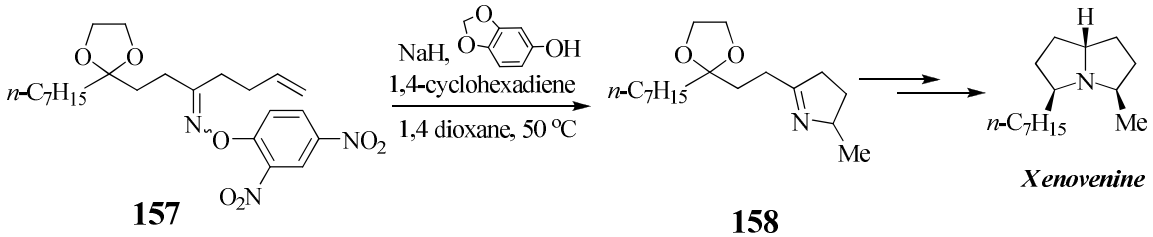
The synthetic potential of iminyl radicals has been investigated intensively during the last decade. The most studied reactions of iminyl radicals are cyclisations onto double-bonds. It constitutes an attractive strategy for constructing nitrogen heterocycles.

The cyclisation reactions of iminyl radicals have been applied to the preparation of the skeleton of indolizidine alkaloids by Zard and co-workers. The iminyl radical, formed on treatment of the sulphenylimine **155** with tributyltin hydride could undergo a 5-*exo* cyclisation followed by addition to the electrophilic alkene. Reduction with sodium cyanoborohydride was followed by spontaneous cyclisation to give the lactam **156** (Scheme 71).



Scheme 71

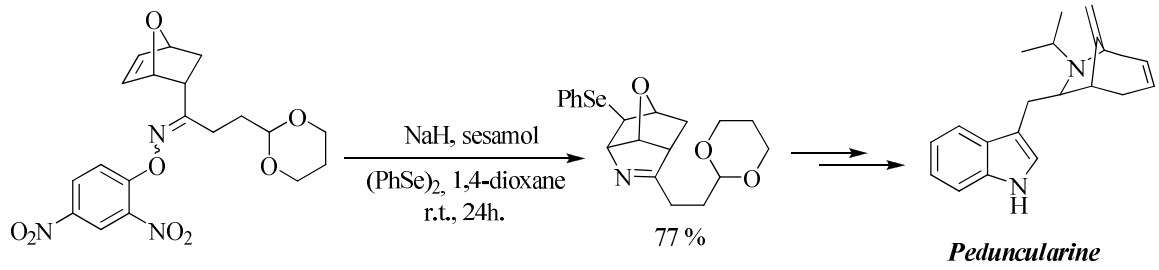
Narasaka and co-workers[131] applied the iminyl radical cyclisation reaction onto a double bond in the synthesis of the dialkylpyrrolizidine alkaloid *xenovenine*. The key step is the construction of the dihydropyrrole **158** *via* a 5-*exo* ring closure. The precursor 2,4-dinitrophenyloxime **157** was treated with NaH and 3,4-methylenedioxyphenol in the presence of 1,4-cyclohexadiene as a H donor (Scheme 72).



157 **158**

Scheme 72

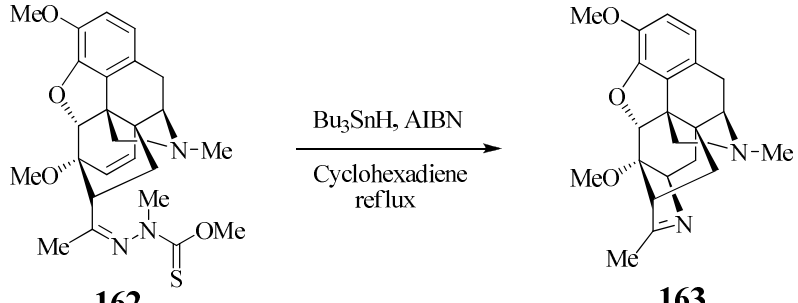
Very recently the same group has reported the total synthesis of the natural product *peduncularine*. This alkaloid consists of an unusual 6-azabicyclo[3.2.1]octane core with a 3-indolylmethyl group **161**. Narasaka et al.[135] proposed the radical cyclisation of oximes as a key step to construct the 6-azabicyclo[3.2.1]octane framework. *O*-(2,4-dinitrophenyl)oxime **159** was treated with NaH and 3,4-methylenedioxyphenol in the presence of diphenyl selenide at 50 °C for 2 h. The expected tricyclic imine *exo*-**160** possessing a phenylseleno group was obtained in 77 % yield (Scheme 73).



159 **160** **161**

Scheme 73

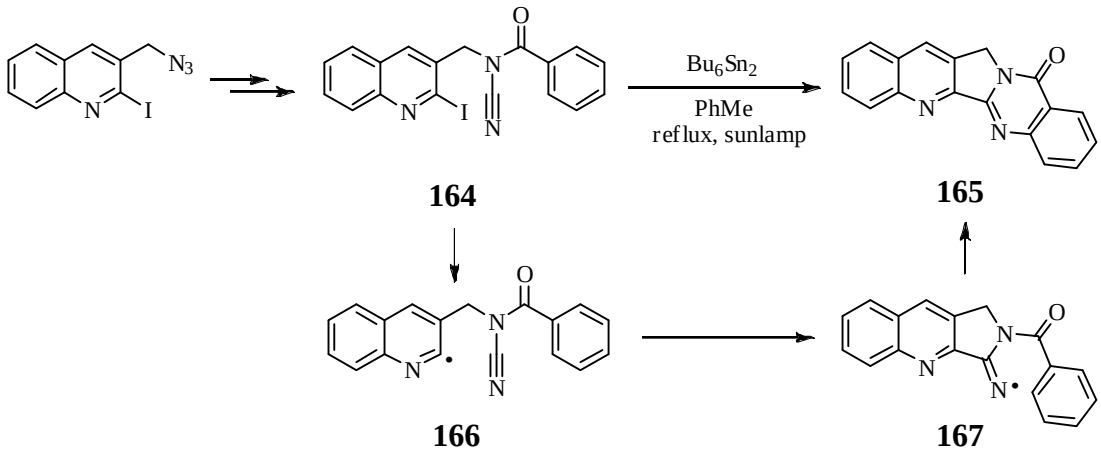
The ability of iminyl radicals to ring close onto double bonds was proved in the synthesis of the complex heptacyclic compound **163** carried out by Zard and co-workers.[118] Treatment of the corresponding thiocarbazone precursor **162** with Bu_3SnH generated the nitrogen centered radical which underwent 5-*exo* addition affording the desired polycyclic structure in very high yield (Scheme 74).



162 **163**

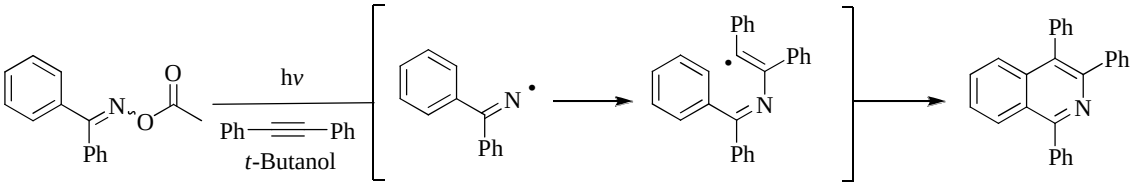
Scheme 74

A very elegant synthetic application of iminyl radical has been used by Malacria et al.[136] in the total synthesis of the anticancer alkaloid *luotonin A* **165**. They proposed a cascade radical cyclisation process to build the pyrroloquinazoline moiety **165** from N-acylcyanamide radical precursor **164**. In this case, the iminyl radical was generated by the cyclisation of the aryl radical onto the triple bond of the cyanamide **166** in a 5-*exo* process. The iminyl intermediate **167** undergoes homolytic aromatic substitution *via* 6-*endo* cyclisation onto the phenyl ring followed by rearomatization (Scheme 75).



Scheme 75

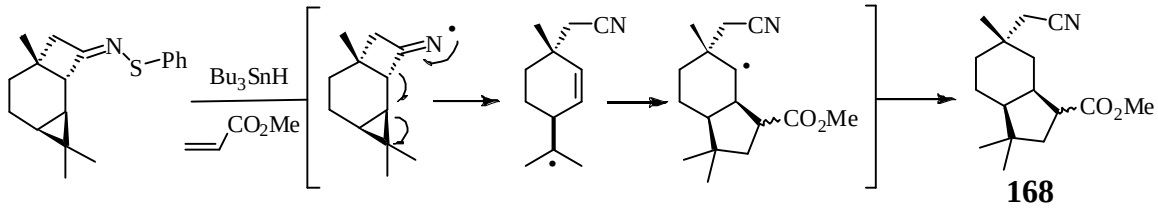
Although 5-*exo* cyclisation between an iminyl radical and an olefin has been proved to be an excellent strategy to construct five-membered nitrogen heterocyles, the synthesis of six-membered heterocyclic rings has been hardly described. Forrester[115] and recently Rodriguez and co-workers[128] have reported an efficient photochemical approach for the unusual generation of six-membered azaheterocycles (Scheme 76).



Scheme 76

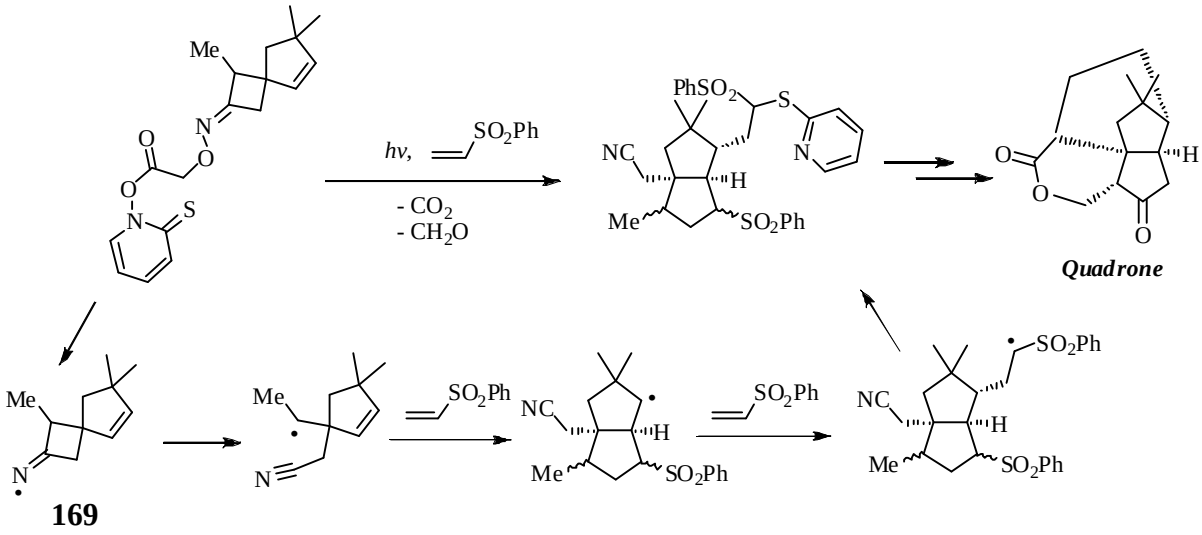
Other important potential applications of iminyl radicals involve ring-opening reactions of strained rings such as cyclobutane and cyclopropane to give steroids and terpenes. In the absence of a radical trap the process leads to formation of a nitrile through scission of the intermediate cyclobutyliminyl radical to give the more stable carbon-centered radical. Scheme 77 shows an elegant route to bicyclic compound **168** involving a cascade of ring-opening reactions followed by a ring-closure reaction. The level of control is high since

the configuration of the carbon bearing the ester group can be corrected (via the enolate) in almost quantitative yield on treatment with base. The starting material was readily prepared from Δ-carene, and its configuration dictates that of the end product.



Scheme 77

The ring opening tendency of iminyl radicals has also been applied to the preparation of terpenes and alkaloids. In the total synthesis of Quadrone, Zard and co-workers demonstrated how the carbon skeleton of Quadrone could be assembled in a one-pot synthesis starting from the iminyl radical **169** derived from a Barton decarboxylation (Scheme 78).



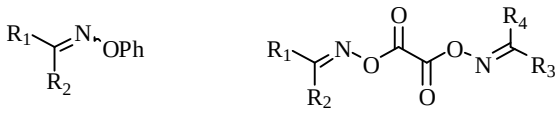
Scheme 78

It can be seen from these examples that iminyl radicals are of significant interest in synthetic radical chemistry due to their ability to perform cyclisations onto double bonds and aromatic rings and fragmentation reactions to give nitrile products. Therefore, research into the development of new precursors and new applications is ongoing.

5.0 Aims and Objectives.

It is clear from the material covered in this introduction that free radicals are a powerful tool for synthetic organic chemistry and have been used to prepare an impressive range of complex organic molecules. However, it is also clear that the dependence on tin hydride and other metal based chemistry is holding back its application to general synthesis.

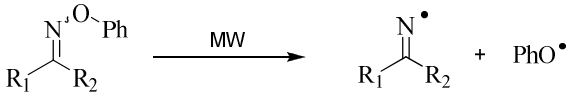
This research project had a number of aims and objectives, of which, the primary was the development of two new "clean" sources of iminyl radicals avoiding the use of tin hydride. The precursors investigated were phenyl oxime ethers **170** and dioxime oxalates **171** (Figure 7)**.**



170 **171**

Figure 7

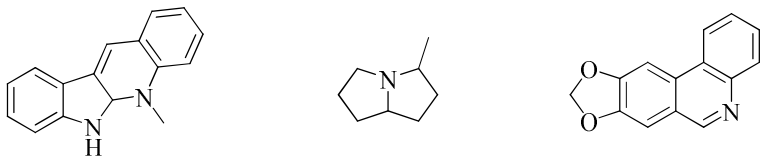
Phenyl oxime ethers **170** were the first iminyl radical precursors extensively studied during this project. The main objective was to develop an efficient and relievable thermal methodology for generation of iminyl radicals **172** *via* microwave irradiation of *O*-phenyl oximes (Scheme 79).



170 **172** **173**

Scheme 79

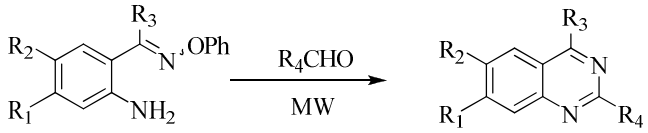
The study of the cyclisation properties of iminyl radicals onto different groups promoted by microwaves became our next goal. A wide range of phenyl oxime ethers with a variety of acceptor side-chains would be prepared and studies towards the synthesis of biologically active heterocycles such as neocryptolepine **174**, pyrrolizidine **175** and trisphaeridine **176** were planned (Figure 8).



174 **175** **176**

Figure 8

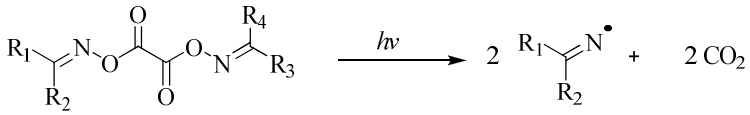
Another aim of the project was to observe cyclisation of iminyl radicals onto imines. Imines were expected to aid cyclisation and also to introduce another nitrogen atom into the cyclised species. In particular, our ambition was to develop an efficient, reliable and high yielding procedure for the synthesis of quinazolines **178**.



177 **178**

Scheme 80

Finally, the last aim of the project was to find an efficient, versatile, synthetic route to dioxime oxalates **171**. Once the precursor molecules had been prepared it was hoped to test them as photochemical sources of free radicals. The dioxime oxalate was designed to act as a photochemical precursor for two molecules of iminyl radical **172** in a clean and atom-efficient mode on account of the fact that the only by-product would be CO_2 (Scheme 81).

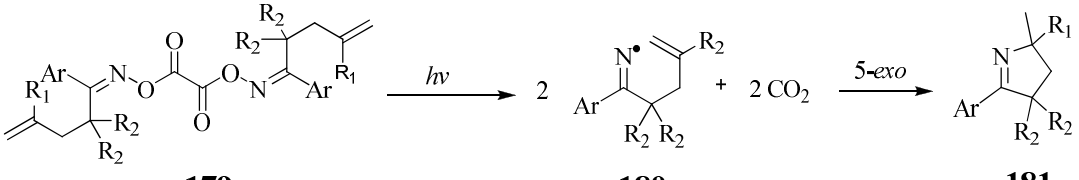


171 **172**

Scheme 81

It was also an aim of this project to monitor the photochemistry of these systems and to characterise the radicals using ESR spectroscopy. These ESR studies would serve to validate proposed mechanisms and might also provide some useful kinetic data for iminyl radical cyclisations.

The third main objective was to design and prepare dioxime oxalates which had a proximate radical acceptor such as double bond and phenyl group for ring closure of the iminyl radical. It was hoped in this way to prepare several dihydropyrroles (Scheme 82).



179 **180** **181**

Scheme 82

6.0 References.

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Chapter 2

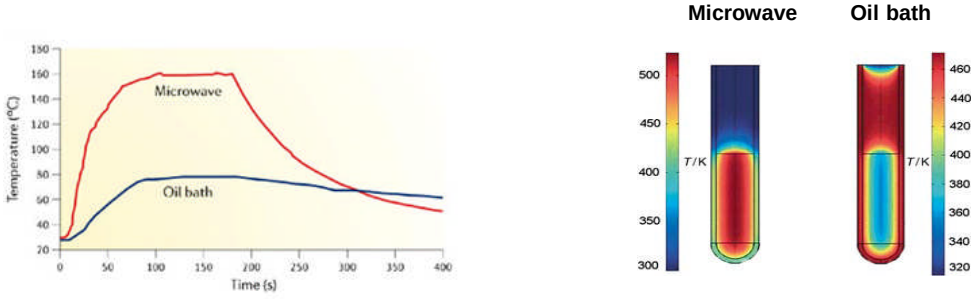
Microwave Assisted Generation of Iminyl Radicals; Syntheses of *N*-Heterocycles

1.0 Introduction

1.1 Microwave Chemistry.

High-speed syntheses with microwaves have attracted a considerable amount of attention in recent years.[1] Microwave-assisted heating under controlled conditions is an invaluable technology for medicinal chemistry and drug discovery applications because it often dramatically reduces reaction times, typically from days or hours to minutes or even seconds. Many reaction parameters, such as reaction temperature and time, variations in solvents, additives and catalysts, or the molar ratios of the substrates, can be evaluated in a few hours to optimize the desired chemistry.

Traditionally, organic reactions are heated using an external heat source, and therefore heat is transferred by conductance. This is a comparatively slow and inefficient method for transferring energy into the system because it depends on the thermal conductivity of the various materials that must be penetrated, and results in the temperature of the reaction vessel being higher than that of the reaction mixture. By contrast, microwave irradiation produces efficient internal heating by direct coupling of microwave energy with polar molecules that are present in the reaction mixture. In Figure 1A can be observed the difference in temperature profiles for a 5-ml sample of ethanol heated under single-mode, sealed vessel microwave irradiation and an open-vessel-oil-bath conditions for 3 minutes. Using sealed-vessel microwave irradiation, a significantly higher temperature can rapidly be reached, compared with the oil-bath experiment, which was carried out under standard open-vessel reflux conditions. Figure 1B represents the inverted temperature gradients in microwave versus oil-bath heating. Temperature profiles 1 minute after heating by microwave irradiation compared with treatment in an oil-bath. Microwave irradiation raises the temperature of the whole volume simultaneously whereas in the oil-heated tube the reaction mixture in contact with the vessel wall is heated first (Figure 1).[2]



A **Figure 1** **B**

1.1.1 Microwave theory.

Microwave assisted organic syntheses (MAOS) are mainly based on the efficient heating of materials by "microwave dielectric heating" effects.[3] Microwave dielectric heating is dependent on the ability of a specific material to absorb microwave energy and convert it to heat. Microwave irradiation triggers heating by two main mechanisms: dipolar polarization and ionic conduction. Whereas the dipoles in the reaction mixture are involved in the dipolar polarization effect, the charged particles in a sample are affected by ionic conduction. When irradiated at microwave frequencies, the dipoles or ions of the sample align in the applied electric field. As the applied field oscillates, the dipole or ion field attempts to realign itself with the alternating electric field and, in the process, energy is lost in the form of heat through molecular friction and dielectric loss. The amount of heat generated by this process is directly related to the capacity of the matrix to align itself with the frequency of the applied field. If the dipole does not have enough time to realign, or reorients too quickly with the applied field, no heating occurs. The allocated frequency of 2.45 GHz used in the commercial systems lies between these two extremes, and gives the molecular dipole time to align in the field but not to follow the alternating field precisely. Under such conditions, rapid heating will be observed, particularly if a sealed vessel system is used (Figure 2).[4]

Figure 2

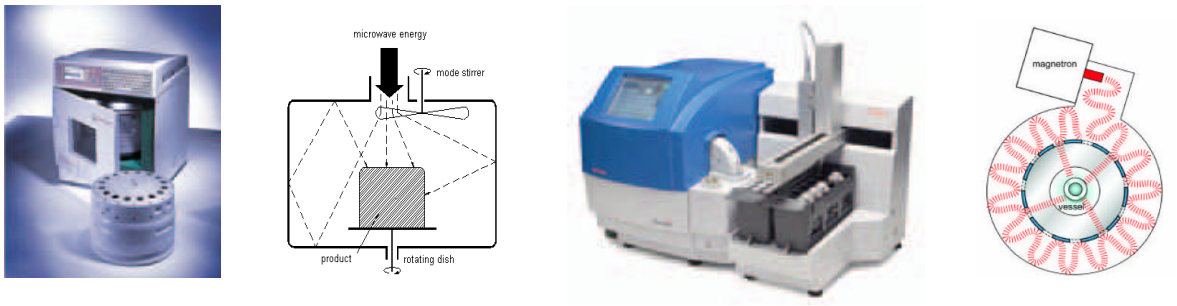
The ability of a specific substance to convert electromagnetic energy into heat at a given frequency and temperature is determined by the so-called loss factor tanδ. This loss factor is expressed as the quotient $\tan\delta=\varepsilon''/\varepsilon'$, where ε'' is the dielectric loss, which is indicative of the efficiency with which electromagnetic radiation is converted into heat, and ε' is the dielectric constant describing the ability of molecules to be polarized by the electric field. A reaction medium with a high tanδ value is required for efficient absorption and, consequently, for rapid heating. It has to be emphasized that a low tanδ values does not preclude a particular solvent from being used in a microwave-heated reaction. Since either the substrates or some of the reagents are likely to be polar, the overall dielectric properties of the reaction medium will in most cases allow sufficient heating by microwaves. Furthermore,

polar additives such as ionic liquids, for example, can be added to otherwise low-absorbing reaction mixtures to increase the absorbance level of the medium.

1.1.2 Equipment.

Although many of the early experiments in microwave-assisted organic syntheses were carried out in domestic ovens, the current trend is to use dedicated instruments for chemical syntheses.

Two different philosophies with respect to microwave reactor design are currently emerging: multimode and monomode. In the multimode instruments (Figure 3A) the microwaves that enter the cavity are reflected by the walls and the load over the typically large cavity. In the smaller monomode cavities (Figure 3B), the electromagnetic irradiation is directed through an accurately designed rectangular or circular wave guide onto the reaction vessel mounted at a fixed distance from the radiation source, thus creating a standing wave.[5]



A **B**

Figure 3

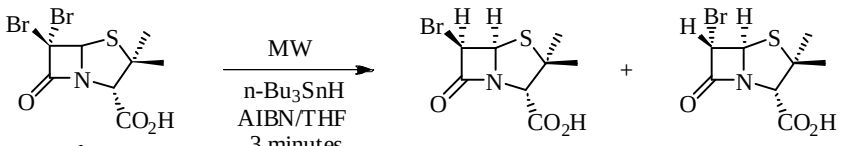
The key difference between the two types of reactor systems is that whereas in multimode cavities several reaction vessels can be irradiated simultaneously in multi-vessel rotors, in monomode systems only one vessel can be irradiated at a time.

Microwave chemistry has an edge over conventional heating methods for conducting chemical reactions, and it will soon emerge as the preferred technology for performing chemical synthesis relating to lead development in pharmaceutical and biotechnology companies. Moreover, the use of microwave chemistry for industrial production holds promise, since research has already been initiated to scale up microwave chemistry reactions from milligrams to kilograms.

1.2 Microwave Assisted Free Radical Reactions.

The new instrument innovations allow careful control of time, temperature, and pressure profiles, paving the way to reproducible protocol development and scale up. MAOS not only reduces chemical reaction times significantly, but it is also known to reduce side reactions, increase yields and improve reproducibility. Therefore, many academic and industrial research groups use MAOS as a technology for rapid reaction optimization, for the efficient syntheses of new chemical entities, or for discovering and probing new chemical reactivity. MAOS has been extensively used in a great number of different types of chemical transformations, such as, organometallic reactions, alkylations, oxidations, reductions, pericyclic reactions, additions etc.

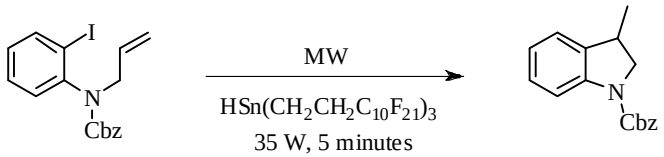
However, surprisingly, only a few reports have appeared concerning microwave–induced free radical reactions. The first example was reported by Bose and coworkers[6] in the early nineties. They carried out stereoselective dehalogenation of α-halo-β-lactams by a free-radical reaction in dry tetrahydrofuran with tributyltin hydride in the presence of AIBN. 6,6-Dibromopenicillanic acid **1** was converted to the *cis*-6-β-bromo compound **2** with minor amounts of the *trans*-6-α-bromo isomer **3** in about 3 minutes of heating at low energy in a commercial microwave oven (Scheme 1).



1 **2** **3**

Scheme 1

Hallberg et al.[7] reported radical-mediated cyclisations utilizing benzotrifluoride as a solvent under microwave irradiation. In the presence of AIBN as a radical initiator, the aryl iodide **4** smoothly underwent microwave–mediated cyclisation to the corresponding indole derivative **5** in high yield. With these highly fluorous tin reagents, the advantage of microwave irradiation, along with reducing reaction times, may be the rapid coalescence of the organic and fluorous phases to form a homogeneous solution (Scheme 2).

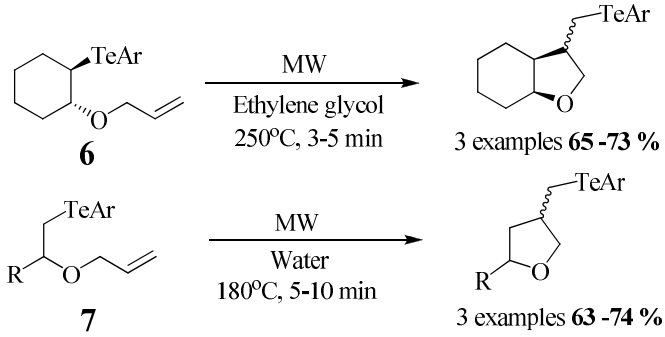


4 **5**

Scheme 2

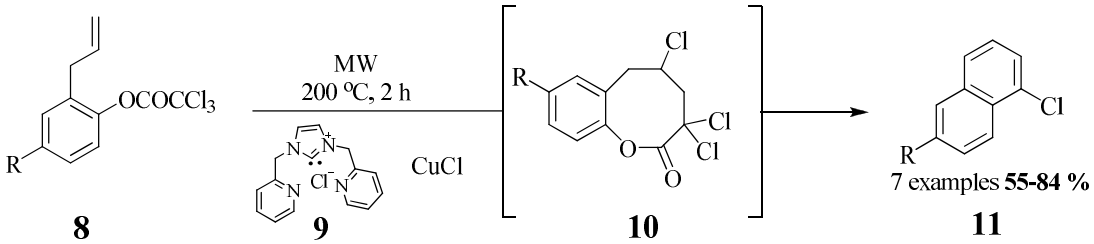
The effect of microwave irradiation on atom- or group-transfer reactions has been studied by several groups. In such processes, a carbon-centred radical is initially produced by homolytic cleavage of a C-X bond where X is commonly halogen or a chalcogen derivative. Following some type of radical transformation (for example, intra- or inter-molecular addition), the heteroatom is transferred from the radical precursor to give the group- or atom-transfer product with generation of the initially formed carbon-centred radical. In contrast with products of reductive radical transformations, the functional group of the radical precursor is retained in the group-transfer product and is thus available for further synthetic manipulations.

Engman and coworkers[8] reported on rapid radical group-transfer cyclization of organotellurium compounds **6** and **7**. They found that primary and secondary alkyl aryl tellurides underwent rapid (3-10 min) group transfer cyclisation to afford tetrahydrofuran derivatives in good yields when heated in a microwave cavity at 250 °C in ethylene glycol or at 180 °C in water (Scheme 3).



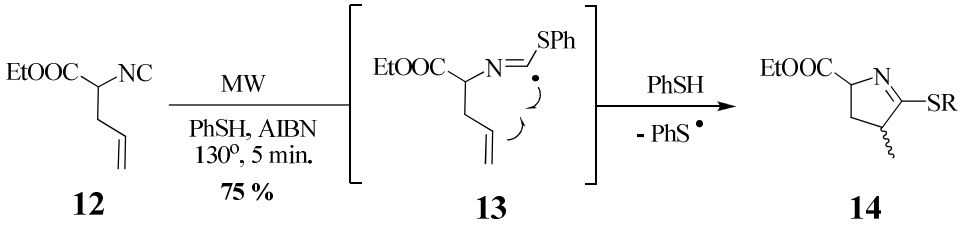
Scheme 3

Very recently an example of atom-transfer radical cyclisation induced by microwave irradiation has been reported by Quayle and coworkers.[9] They described that a catalyst system comprising the ligand **9** in conjunction with a suitable source of Cu(I), promoted a regiospecific benzannulation reaction of 2-allylphenyl trichloroacetate **8** to chloronaphthalene **11**. This reaction proceeded under microwave irradiation for two hours at 200 °C in dichloroethane via the intermediacy of lactone **10**, the result of an initial 8-*endo-trig* atom transfer radical cyclisation (Scheme 4).



Scheme 4

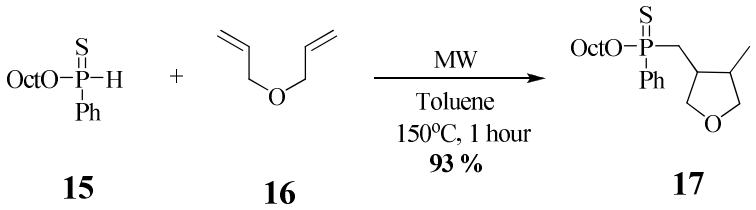
Kilburn et al.[10] described how flash-heating by microwave irradiation promoted rapid thiol-mediated radical cyclisation of alkenyl and alkynyl isonitriles to give highly functionalised pyrrolines. The usefulness of this technique was exemplified by comparison with traditional thermal heating techniques. In a typical reaction a thiyl radical added to an alkenyl isocyanide **12**, generating the thioimidoyl radical **13**, which underwent 5-*exo* cyclisation and subsequent hydrogen abstraction to afford *cis* and *trans*-pyrroline **14** (Scheme 5).



12 **13** **14**

Scheme 5

Phosphorus hydrides have acquired relevance in recent years as replacements of tributyltin hydride in radical reductions. Parsons and coworkers[11] investigated whether radical reactions of hydrides with particularly weak P-H bonds could be initiated simply by heating without any initiator. They found that phosphinothioate **15**, heated under reflux with diallyl ether **16** in cyclohexane gave the tetrahydrofuran **17** in only 39 % yield after 60 hours. On the other hand, microwave irradiation of phosphinothioate **15** and diallyl ether **16** in a sealed tube in dioxane at 150 °C for 1 hour, afforded tetrahydrofuran **17** in 93 % yield. The yield of **17** obtained by the use of microwave irradiation is considerably higher than by the use of conventional heating, and the reaction time is considerably shorter (Scheme 6).

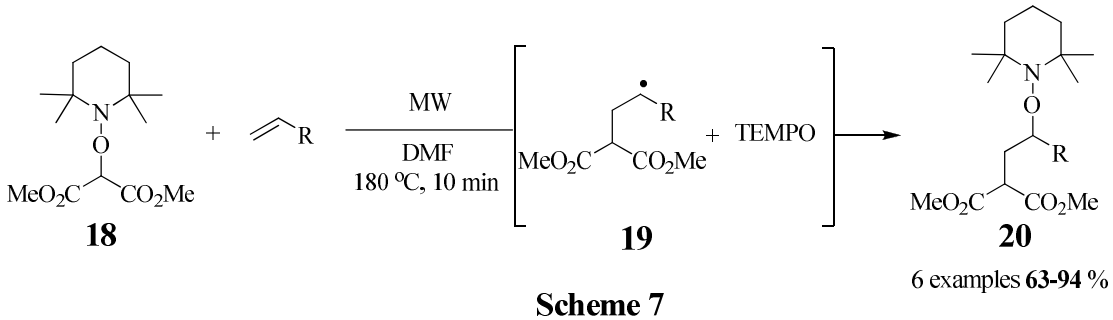


15 **16** **17**

Scheme 6

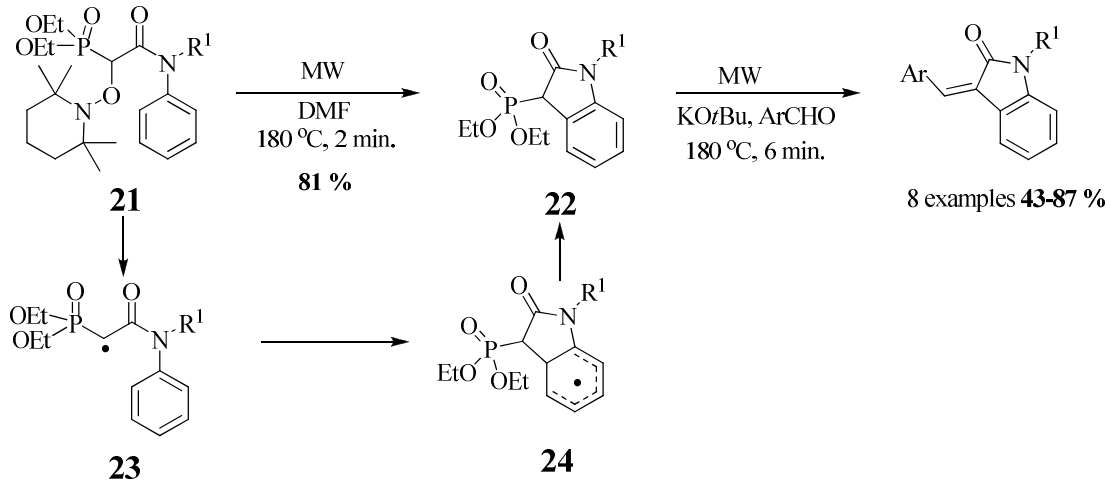
Studer and Wetter[12] have described radical carboaminoxylations of various non-activated alkenes and difficult radical cyclisations. The thermally reversible homolysis of alkoxyamines **18** generates the persistent radical 2,2,6,6-tetramethylpiperidinyl-1-ol (TEMPO) and a stabilized transient malonyl radical **19**, which subsequently reacts with an alkene to afford the corresponding carboaminoxylation product **20**. Under conventional conditions (DMF, sealed tube, 135 °C) these radical addition processes take up to 3 days.

Using sealed-vessel microwave heating at 180 °C for 10 minutes higher yields were obtained (Scheme 7).



Scheme 7

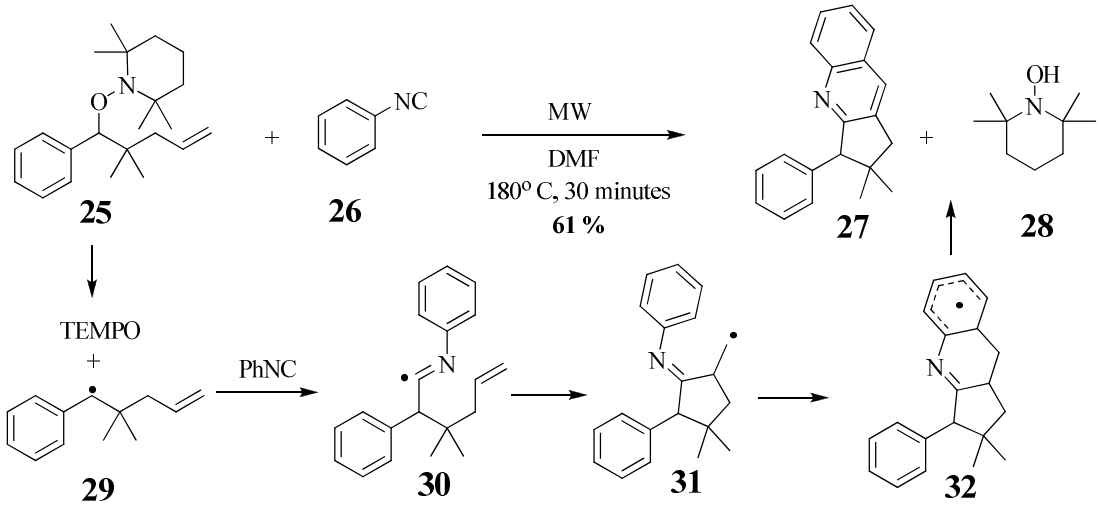
The same group disclosed a related free radical process, namely an efficient one-pot sequence comprising a homolytic aromatic substitution followed by an ionic Horner-Wadsworth-Emmons olefination, for the production of a small library of α,β-unsaturated oxindoles.[13] Suitable TEMPO-derived alkoxyamine precursors **21** were exposed to microwave irradiation in DMF for 2 minutes to generate and oxindole intermediate **22** via an intramolecular homolytic aromatic substitution (Scheme 8).



Scheme 8

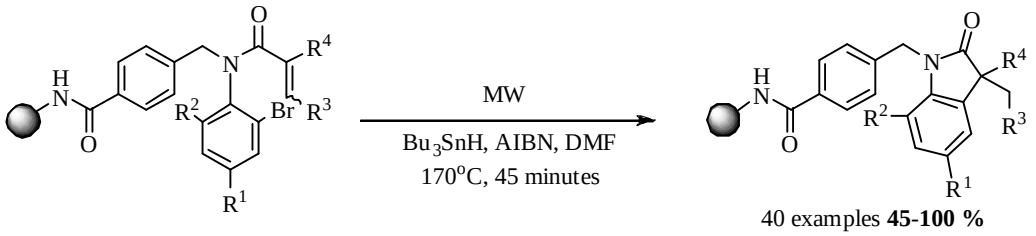
A recent example in the use of alkoxyamines as clean sources for the generation of C-centred radicals via microwave irradiation was described by Studer et al[14] in their syntheses of quinolines by a tandem radical process. Carbon centred radical **29** generated via thermal C-O bond homolysis will react either with TEMPO to reform starting material **25** or with phenyl isonitrile **26** to afford the corresponding imidoyl radical **30**. Radical **30** can further react in a 5-*exo* type cyclisation to give the primary alkyl radical **31** which can undergo homolytic aromatic substitution to provide imine **32** which readily oxidizes during workup to the corresponding quinoline. The heterocycles were obtained in moderate to good yield.

Upon using microwave-induced heating, the reaction time can be shortened from 3 days to 30 minutes (Scheme 9).



Scheme 9

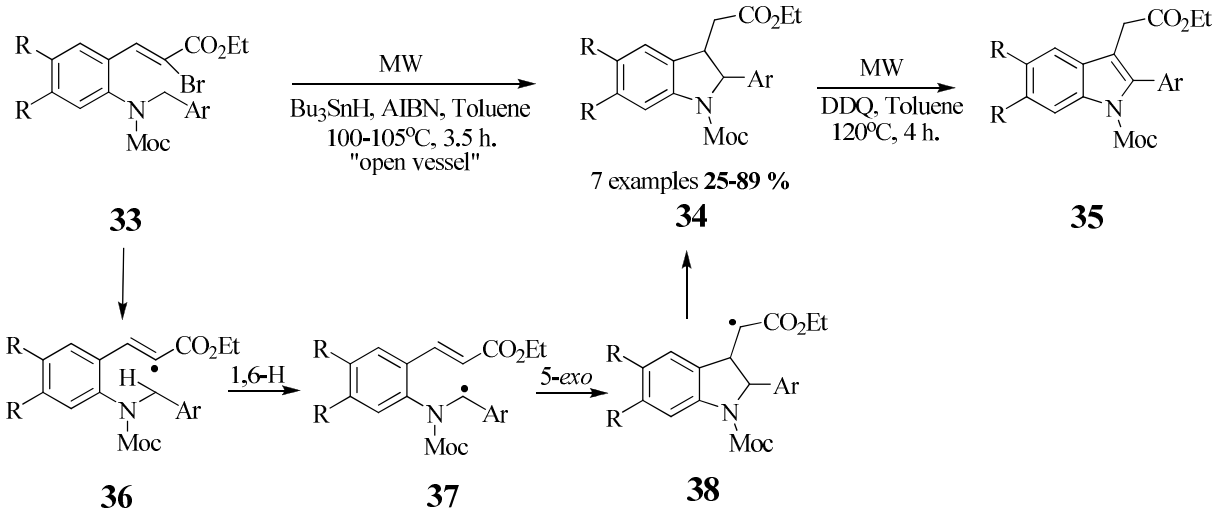
Kusumoto and co-workers[15] have recently described a solid-phase synthesis of indol-2-ones based on a radical cyclisation. Medicinal chemists in the pharmaceutical industry now routinely utilize solid-phase organic synthesis (SPOS) to prepare libraries of small organic molecules for screening. The advantages of this methodology have been well described in the recent literature.[16] Excess reagents can be used to drive reactions to completion, impurities and excess reagents can be removed by simple washing of the solid-phase, and enormous numbers of compounds can be created using the mix and split technique. In this example, N,N-dimethylformamide was found to be the best solvent for the radical cyclisation. Interestingly, the radical-induced cyclisation with tributyltin hydride and AIBN did not proceed at all under conventional thermal conditions. However the radical cyclisation could be performed utilizing a single mode microwave reactor (Scheme 10).



Scheme 10

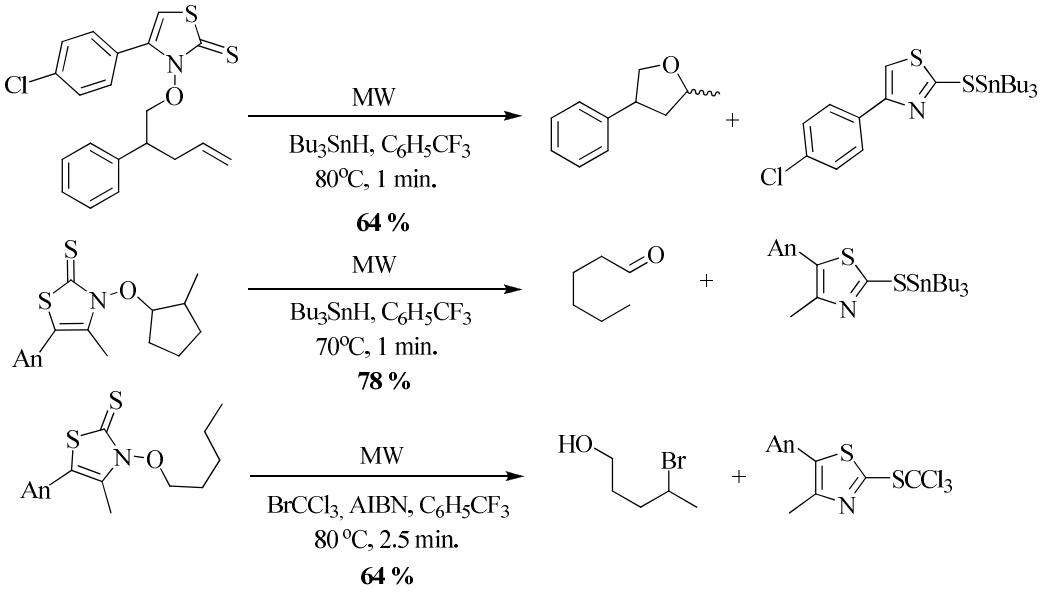
In a very recent report Reiser's group[17] has described the synthesis of 2-arylindoles **35** via tandem radical cyclisations of the corresponding acrylates **33** and subsequent oxidation. In the first step of the synthesis, acrylates are transformed to 2-arylindolines **34** by a

tributyltin hydride mediated radical cyclization involving a 1,6-H transfer followed by a 5-*exo* ring closure under open vessel microwave conditions (Scheme 11).



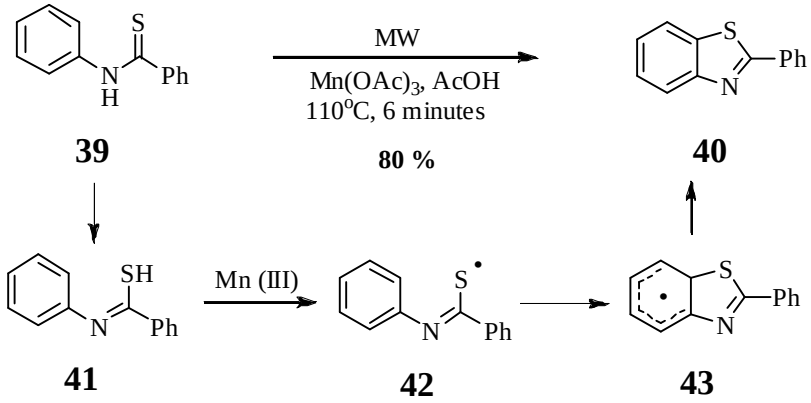
Scheme 11

Not only carbon-centred radicals have been reported to be generated via microwave irradiation. Hartung and co-workers[18] published a comprehensive study in the microwave generation of alkoxyl radicals from *N*-(alkoxy)thiazole-2(3*H*)-thiones and their use in the synthesis of disubstituted tetrahydrofurans by intramolecular additions, formation of carbonyl compounds via β-fragmentation and C-H activation of aliphatic subunits by δ-selective hydrogen atom transfer (Scheme 12).



Scheme 12

Zou and coworkers[19] reported the thiyl radical cyclisation of substituted thioformanilides in the presence of manganese (III) triacetate as an electron oxidant. When the solution of **39** and $Mn(OAc)_3$ $2H_2O$ in acetic acid was irradiated with microwaves the reaction was completed in 6 minutes with an excellent yield. Phenylthioformanilide **39** could exist as thioimidol **41**; the later reacted with $Mn(OAc)_3$ to produce thiyl radical **42**, while Mn(III) was reduced to Mn(II) at the same time. Then, homolytic aromatic substitution gave a cyclohexadienyl radical which re-aromatized to yield 2-phenylbenzo[*d*]thiazole **40** (Scheme 13).



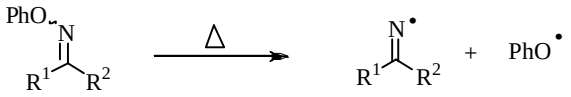
Scheme 13

It is clear from the examples described above that microwave technology reduces reaction times and increases yields and reproducibility in radical processes. The mild and neutral conditions associated with radical chemistry and the ability of radicals to perform intramolecular cyclisations, together with the virtues of MAOS make the combination of both an extremely useful tool for organic and medicinal chemists. Surprisingly, no nitrogen centred radical precursors for microwave irradiations have been reported. More concretely, no iminyl radical precursors under microwave conditions have been described in the literature. Ring closures of iminyl radicals constitute a particularly promising method in the syntheses of nitrogen heterocycles as has been described earlier. Nitrogen-containing compounds are part of the basis of life and are one of the main classes of pharmacologically active agents. One of the main goals of synthetic organic chemists is to find new and advanced methods for their preparations. It is, therefore highly desirable to develop new sources of iminyl radicals promoted by microwave irradiation which could afford the syntheses of aza-heterocycles in a “clean”, fast and high yielded manner.

.

1.3 *O*-Phenyl oxime ethers as sources of iminyl radicals.

Quite recently it was reported by Walton and co-workers[20] that *O*-phenyl oxime ethers **44** are a new class of nonazo and nonperoxide free-radical initiators that release iminyl **45** and phenoxyl radicals **46** at relatively low temperatures (scheme 14).

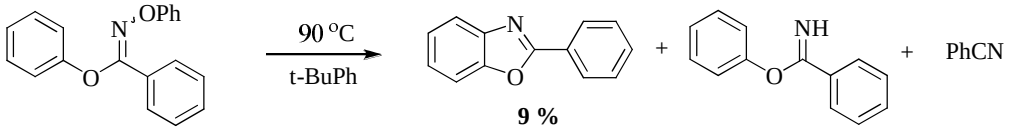


44 **45** **46**

Scheme 14

From detailed studies of the thermal dissociations of a representative set of these compounds the N-O bond dissociation energies were determined to be only 35 kcal mol^{-1} for R^1 = Me and R^2 = Ph. Thus, the N-O bonds of these compounds are actually weaker than the O-O bonds of dialkyl peroxides.

O-Phenyl oxime ethers are easily to prepare from aldehydes or ketones simply by condensing them with the commercially available *O*-phenylhydroxylamine hydrochloride in anhydrous pyridine at room temperature. They anticipated, therefore, that it would be possible to devise convenient thermal procedures for preparing dihydropyrroles and other heterocycles from conversion of unsaturated ketones to the corresponding *O*-phenyl oxime ethers. Thermal release of the unsaturated iminyl radicals would be followed by their ring closure. In conventional, sealed tube type thermolyses of *O*-phenyl oxime ethers derived from hexenone and related ketones, reaction times had to be long, products were not cleanly formed at higher temperatures, and yields were disappointingly low. Similarly, thermal decomposition of phenyl *N*-phenoxybenzimidate **47** in a sealed tube was still incomplete after 26 h at 90 °C and the ring-closed oxazole **48** was accompanied by significant amounts of phenyl benzimidate and benzonitrile (Scheme 15).



47 **48**

Scheme 15

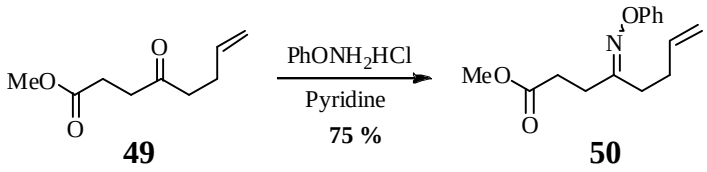
It was, therefore, desirable to develop a new thermal methodology which could improve yields, reproducibility and decrease reaction times.

2.0 Results and Discussion.

It was postulated that thermolyses of *O*-phenyl oxime ethers might give cleaner product mixtures and the reaction times would be considerably shortened if microwave irradiation were to be employed. Iminyl radical generation and cyclisation, for a representative range of functionalized *O*-phenyl oxime ethers, were therefore investigated using microwave irradiation.

2.1 Discovery and Optimization.

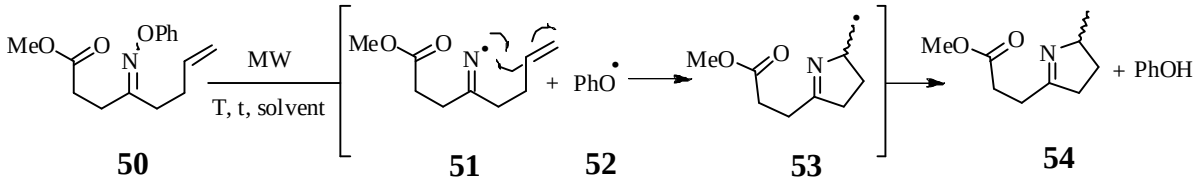
Compound **50** was chosen for detailed study to enable optimum reaction conditions to be established. The *O*-phenyl oxime ether **50** was prepared in 75 % yield as a mixture of E and Z isomers by stirring methyl 4-oxooct-7-enoate **49** with *O*-phenylhydroxylamine hydrochloride in pyridine at room temperature. The fact that two isomers were present did not matter because both released the same iminyl radical on scission of their N-O bonds (Scheme 16).



49 **50**

Scheme 16

We anticipated that under microwave irradiation the main initial reaction would be scission of the N-O bond yielding butenyl-iminyl **51** with the phenoxyl radical **52** in equal proportions. Scission of the weak N-O bond is favoured because of the resonance stabilisation of the released phenoxyl radical. 5-*Exo*-ring closure of the iminyl radicals was expected to produce 3,4-dihydro[2*H*]pyrrolomethyl radicals **53** that would yield the corresponding substituted dihydropyrrole **54** on hydrogen abstraction from the solvent. Similarly, the phenoxyl radicals would give phenol as the main co-product (Scheme 17).



50 **51** **52** **53** **54**

Scheme 17

Solutions of oxime ether **50** in toluene as the H-atom donor were irradiated in a Biotage Initiator microwave reactor (nominally 300 MHz). The loss factor of toluene is low (tanδ = 0.04), so the ionic liquid 1-ethyl-3-methyl-1H-imidazol-3-ium hexafluorophosphate (emimPF_6, IL) was included to increase the microwave absorbance level of the medium.[21] The presence of this IL allowed the solution to be heated to 180 °C without any decomposition of the ionic liquid. In the absence of emimPF_6, 110 °C was the highest temperature achievable in toluene. Other hydrogen donor solvents, such as isopropanol or 1,4-cyclohexadiene, presented the handicap of their low boiling point and the high levels of pressure to which the microwave vessels were exposed under microwave irradiation. The effect of different concentrations, temperatures and reaction times on the yield of dihydropyrrole **54** was monitored by NMR spectroscopy, and the results are shown in Table 1 (Table 1).

Run	phenyl oxime (mmol)	T (^oC)	time (min)	Yields 54 (mol%)[b]
1	0.2	120	10	**25**
2	0.2	140	10	**55**
3	0.2	160	10	**75**
4	0.2	180	10	**72**[c]
5	0.2	160	5	**66**
6	0.2	160	15	**99**
7	0.2	160	20	**96**
8	0.3	160	15	**78**
9	0.4	160	15	**67**
10	0.5	160	15	**59**

Table1. [a] Optimization of dihydropyrrole yield from microwave irradiation of **50.** Reactions in PhMe (1.5 mL) containing emimPF_6 (0.05g) with CH_2Br as internal standard. [b] Yields in mol % determined by ^1H NMR. [c] Amount of emimPF_6 was 0.075 g.

Entries **1-4** showed that a temperature of 160 °C was necessary to achieve complete conversion and high yields but that at higher temperatures side reactions/degradative process set in. Entries **3** and **5-7** showed that at 160 °C best yields were obtained with an irradiation time of 15 minutes. However, for larger amounts of precursor **50**, entries **8-10**, yields fell off in 15 minute reactions.

The NMR spectrum of the total reaction mixture from entry **6** showed essentially quantitative formation of dihydropyrrole **54** together with an equal quantity of phenol. This

supported the mechanism shown in Scheme 17 and indicated that microwave irradiation could be applied in an efficient method for use with *O*-phenyl oximes.

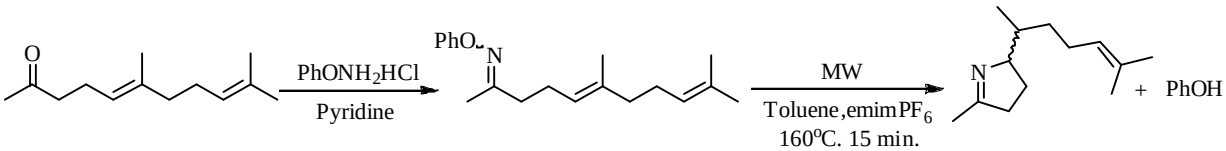
2.2 Iminyl radical addition onto alkenes.

Intramolecular radical addition to alkenes is very versatile and efficient reaction that leads to cyclic products. Cyclisations are generally faster than comparable intermolecular additions, and iminyl radicals can add to alkenes (intramolecularly) to form cyclic products containing a new carbon-nitrogen bond. These reactions are particularly useful for the formation of five- and six-membered rings. The additions are regioselective and radical addition usually occurs so as to form the smallest ring in an *exo* cyclisation process.

2.2.1 Syntheses of dihydropyrroles via 5-*exo* cyclisations.

Numerous biologically active alkaloids contain dihydropyrroles or related rings.[22] Microwave thermolyses of *O*-phenyl oxime ethers appeared capable of converting ketones with but-3-enyl type substituents into dihydropyrroles in two steps. The scope of this pathway was probed by preparing a set of precursor oxime ethers and subsequent microwave irradiation under the optimal conditions.

Oxime ether **56** was prepared from the corresponding commercially available ketone **55** by stirring at room temperature with one equivalent of *O*-phenylhydroxylamine HCl in pyridine. The precursor **56** was isolated via column chromatography as red oil in 71 % yield. A solution of the oxime ether in toluene was irradiated under microwave conditions during 15 minutes at 160°C affording the dihydropyrrole **57**. The NMR spectrum of the total reaction mixture showed basically the presence of dihydropyrrole **57** and phenol. 5-Methyl-2-(6-methylhept-5-en-2-yl)-3,4-dihydro-2H-pyrrole **57** was isolated in a 70 % yield after column chromatography (Scheme 18).

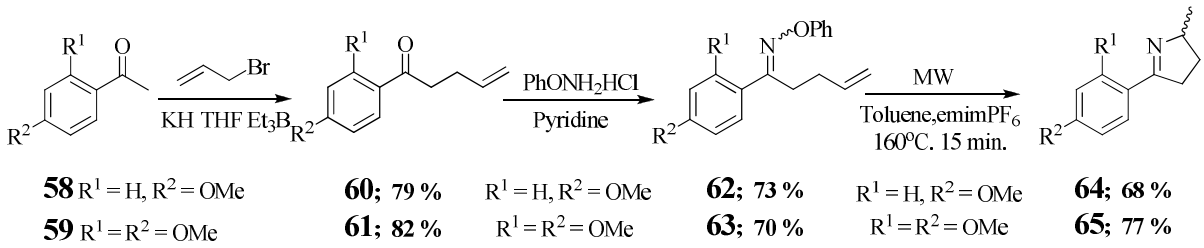


55 **71 %** **56** **70 %** **57**

Scheme 18

The aryl-butenyl ketones **60** and **61**, were prepared by alkylation of 4-methoxyacetophenone, and the 2,4-dimethoxy analogue respectively with allyl bromide. The first attempt was carried out in THF with 1.2 equivalents of NaH and 1.2 equivalents of allyl

bromide. A disappointing 34 % yield of the isolated unsaturated ketone **58** was obtained after reaction of starting materials during 24 hours at room temperature. In order to improve the yield of the process, the reaction was carried out in DMF at 60 °C for 24 hours. The unsaturated ketone was isolated in 68 % yield in a clear improvement in the efficiency of the alkylation. Nevertheless, a third methodology was tested. 4-Methoxyacetophenone was stirred at room temperature for 4 hours in the presence of 1.2 equ. of KH, 1.2 equ. of Et_3B and 1.2 equ. of allyl bromide. After workup the unsaturated ketone **60** was isolated by column chromatography in an excellent 79 % yield. Reaction of 2,4-dimethoxyacetophenone with allyl bromide in the same reaction conditions gave 82 % of the unsaturated ketone **61**. Subsequent condensation with *O*-phenylhydroxylamine HCl in pyridine yielded the oxime ethers **62** and **63** in 73 % and 70 % respectively, which were submitted to microwave irradiation. After being irradiated in the optimal conditions 5-(4-methoxyphenyl)-2-methyl-3,4-dihydro-2*H*-pyrrole **64** was isolated in 68 % yield and the 2,4-dimethoxy analogue **65** in 77 % yield following generation and intramolecular cyclisation of the iminyl radical onto the alkene group (Scheme 19).



Scheme 19

2.2.2 Potential syntheses of pyrrolizidine and indolizidine alkaloids.

Azabicyclic skeletons are important frameworks in natural products. For instance, pyrrolizidine[23] and indolizidines are present in many natural products (Figure 4).

(+)-Hyacinthacine A₂ ***Indolizidine 239CD***

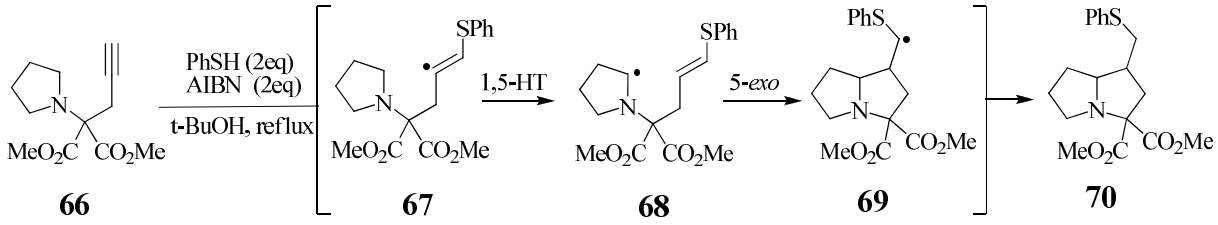
Figure 4

Polyhydroxylated pyrrolidine and pyrrolizidine alkaloids are a class of naturally occurring compounds, primarily isolated from plants throughout the world, that have attracted considerable attention owing to their significant biological activity.[24] Many of these alkaloids exhibit diverse biological activities, including powerful glycosidase inhibitory

properties and antiviral and antiretroviral activities, and are, therefore, potential chemotherapeutic drug targets for HIV and cancer therapy.[25]

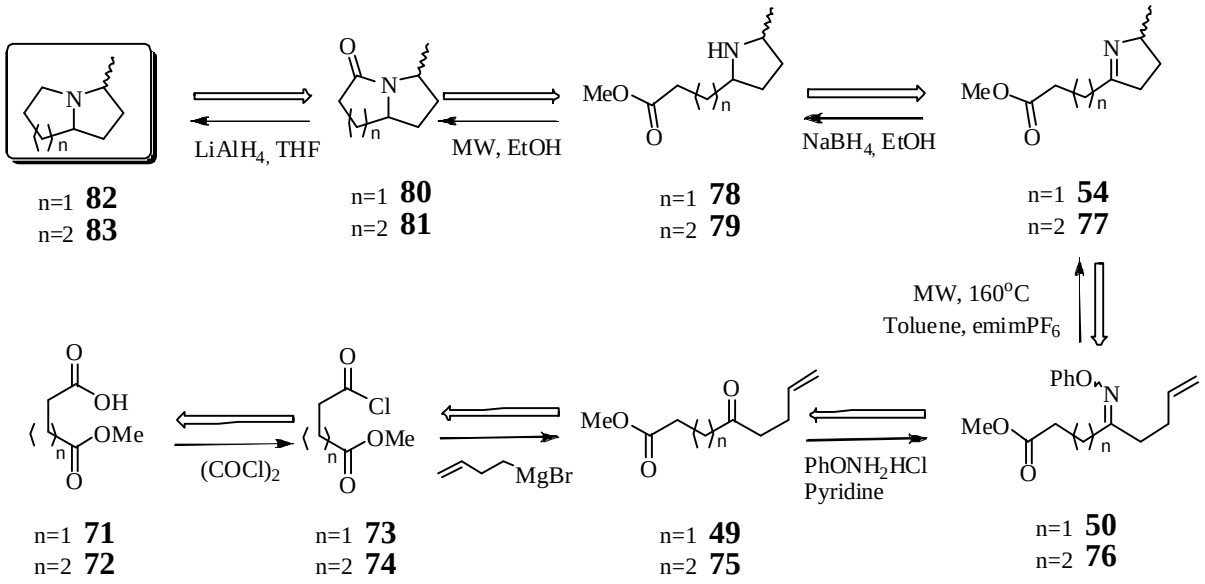
Many strategies have been developed to achieve the formation of the bicyclic skeleton; most of them involve the nitrogen atom in the cyclization step. Strategies involving activation of the position α to the nitrogen atom are known and involve mainly iminium and acyliminium ion chemistry. Several radical approaches to bicyclic alkaloid skeletons have been developed in the last 20 years, but most of them rely on the use of toxic tin derivatives.

Recently, Renaud and co-workers[26] have reported the synthesis of pyrrolizidines and indolizidines avoiding the use of *n*-Bu_3SnH. The reaction involved a radical cascade initiated by addition of a thiyl radical onto the alkyne moiety leading to **67** followed by an intramolecular 1,5-hydrogen transfer, a 5-*exo* cyclisation of **68**, and finally a reduction of the cyclised radical **69** by thiophenol (Scheme 20).



Scheme 20

It has been shown that using our thermal methodology, oxime ethers **50** could be converted in high yield in the corresponding dihydropyrroles **54**. It was assumed therefore that the process would be successful for the oxime ether analogue **76** which would be converted to the dihydropyrrole **77**. We postulated that these two intermediates might constitute the key compounds in the syntheses of 3-methylhexahydro-1H-pyrrolizidine **82** and 3-methyloctahydroindolizidine **83.** Selective reduction of the imine bond in the dihydropyrrole rings would yield pyrrolidinyl esters **78** and **79**. Subsequent intramolecular nucleophilic substitution and reduction with $LiAlH_4$ should yield the desired pyrrolizidine **82** and indolizidine **83** (Scheme 21).

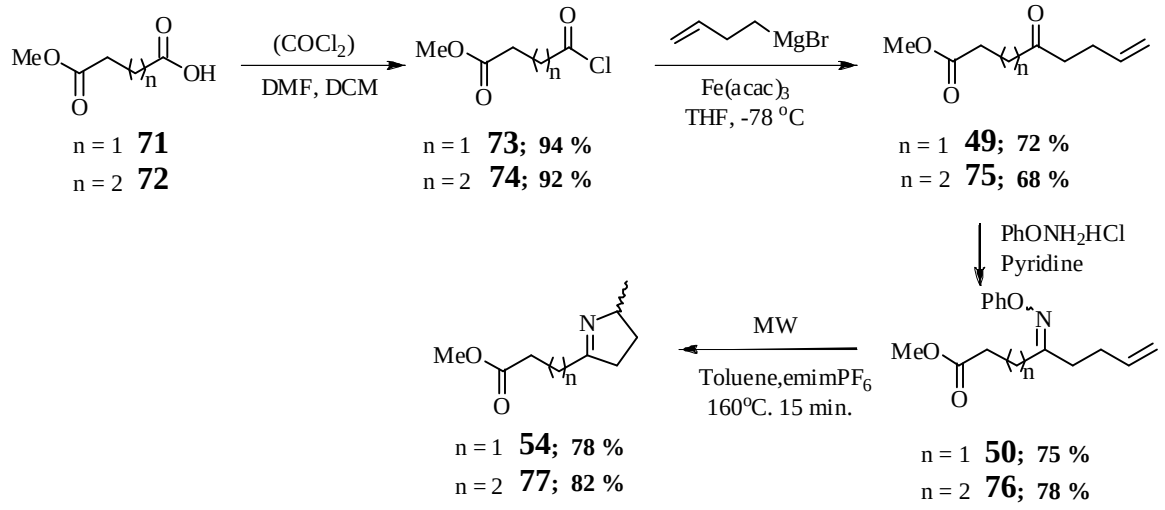


n=1 **82** n=2 **83**; n=1 **80** n=2 **81**; n=1 **78** n=2 **79**; n=1 **54** n=2 **77**

n=1 **71** n=2 **72**; n=1 **73** n=2 **74**; n=1 **49** n=2 **75**; n=1 **50** n=2 **76**

Scheme 21

Our synthetic process started with the preparation of the acid chlorides **73** and **74**. Reaction of mono-methyl succinate and mono-methyl glutarate with oxalyl chloride and a catalytic amount of *N*,*N*-dimethylformamide afforded **73** and **74** respectively in excellent yields. Subsequent addition of but-3-enylmagnesium bromide in the presence of a catalytic amount of $Fe(acac)_3$ gave the unsaturated ketones **49** and **75** which were converted to the oxime ethers **50** and **76**, by condensation with *O*-phenylhydroxylamine HCl, in 75% and 78% yield respectively. These precursors were submitted to microwave irradiation in the optimal conditions and methyl 3-(2-methyl-3,4-dihydro-2*H*-pyrrol-5-yl)propanoate **54** and the analogue 3-(2-methyl-3,4-dihydro-2*H*-pyrrol-5-yl)butanoate **77** were isolated in 78 % and 82 % yield respectively (Scheme 22).

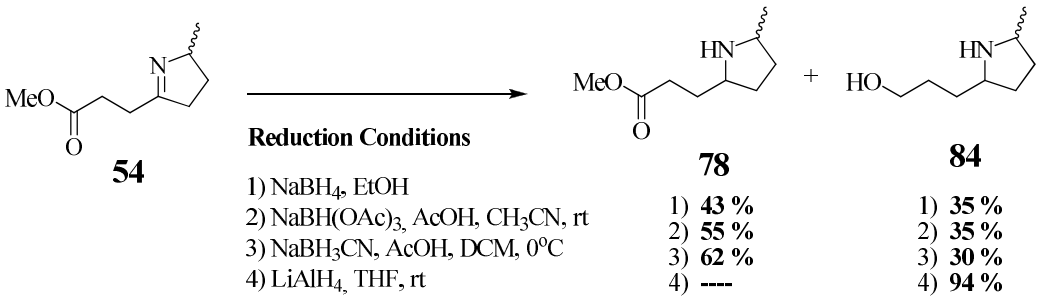


n = 1 **71** n = 2 **72**; n = 1 **73; 94 %** n = 2 **74; 92 %**; n = 1 **49; 72 %** n = 2 **75; 68 %**

n = 1 **54; 78 %** n = 2 **77; 82 %**; n = 1 **50; 75 %** n = 2 **76; 78 %**

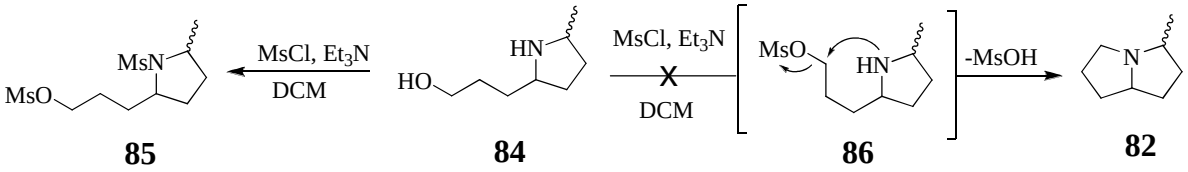
Scheme 22

The next step in our proposed approach was the selective reduction of the imine bond in the dihydropyrrole rings to yield pyrrolidine esters. Several attempts to reduce selectively the cyclic imine **54** were carried out. In practise reaction with $NaBH_4$, $NaBH_3CN$, and $NaBH(OAc)_3$ in several conditions all gave mixtures of **78** and alcohol **84** from the unexpected reduction of both the ester and imine groups. To overcome this problem dihydropyrrole **54** was treated with $LiAlH_4$ in THF for complete reduction of the imine and ester to cleanly give pyrrolidine **84** (Scheme 23).



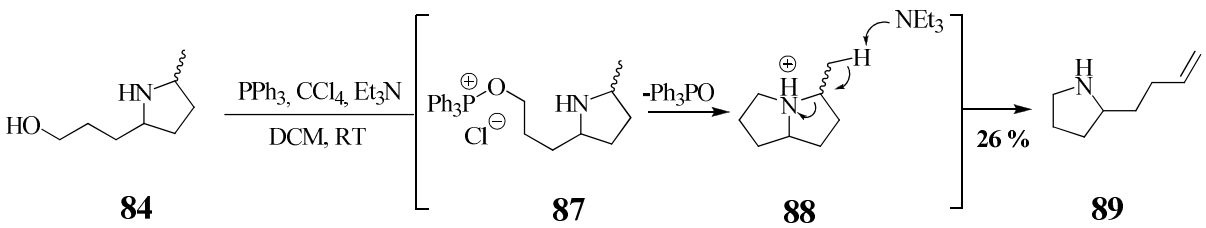
Scheme 23

Ring closure of 3-(5-methylpyrrolidin-2-yl)propan-1-ol **84** was first attempted via the mesylate.[27] However, it was found that treatment of **84** with $MeSO_2Cl/Et_3N$ in DCM did not afford the pyrrolizidine **82** via a S_N2 displacement of the mesylate formed in situ. The reaction led to the dimesylate pyrrolidine **85** from conversion of both the alcohol and the amine (Scheme 24).



Scheme 24

An alternative, Appel's hydroxyl activation protocol, which has worked for other pyrrolizidine derivatives,[28] was therefore tried. Surprisingly, however, when amine **84** was treated with PPh_3, CCl_4 and Et_3N in DCM, the main isolated product was found to be 2-(but-3-enyl)pyrrolidine. A mechanistic rationale of this result is shown in Scheme 25.

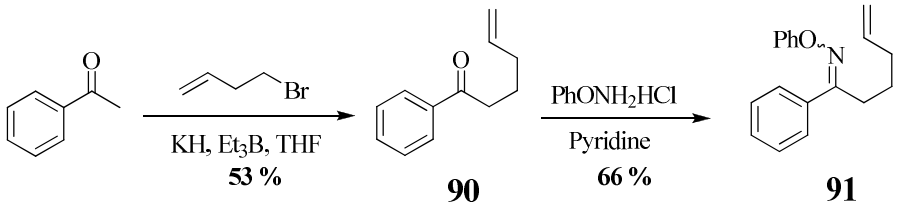


Scheme 25

The alcohol side-chain is likely to react with the phosphonium chloride to yield alkoxy-triphenylphosphonium intermediate **87**.[29] Intramolecular nucleophilic displacement of the phosphonium group will generate pyrrolizidinyl-ammonium ion **88**. This intermediate will be susceptible to Hofmann type eliminations, promoted by the triethylamine base. In keeping with the Hofmann rule, one of the methyl H-atoms will be selectively removed by the base, rather than any of the secondary ring β-H atoms, to yield the least stable alkene **89**.

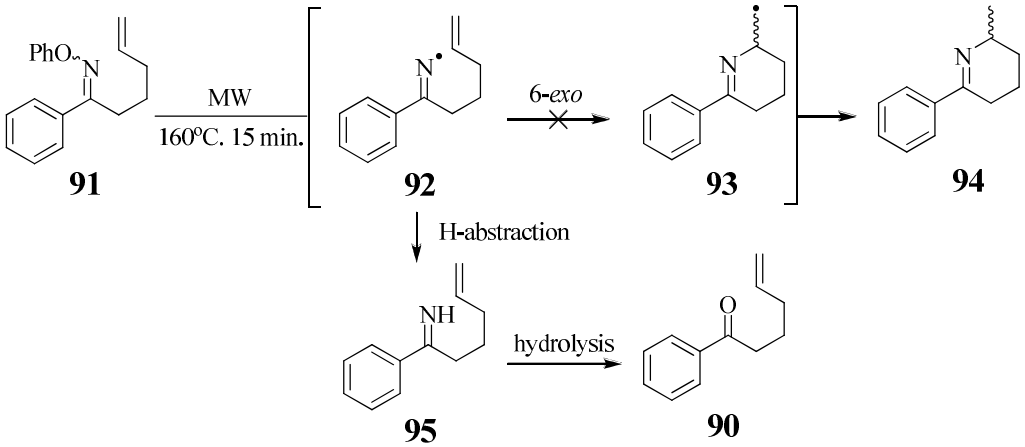
2.2.3 Potential syntheses of tetrahydropyridines via 6-*exo* cyclisations.

In principle, tetrahydropyridines might be obtained from 6-*exo* ring closures of hexenyl-imines. To test this process, 1-phenylhex-5-en-1-one **90** was prepared by alkylation of acetophenone with 4-bromobut-1-ene using KH as base in the presence of Et_3B in THF. The ketone was isolated in a useful 53 % yield. The condensation with *O*-phenylhydroxylamine HCl in pyridine afforded the desired oxime ether intermediate **91** in 66 % yield (Scheme 26).



Scheme 26

This *O*-phenyl oxime ether of 1-phenylhex-5-en-1-one was examined as a model compound for this process. Microwave irradiation of this precursor in toluene, followed by the usual workup, gave phenol, 1-phenylhex-5-en-1-one **90** and 1-phenylhex-5-en-1-imine **95**, together with several minor compounds. The ketone was almost certainly produced from in situ hydrolysis of the corresponding imine. The main reaction was therefore simply H-atom abstraction by the iminyl radical from the solvent and 6-*exo*-cyclisation was too slow to complete (Scheme 27).



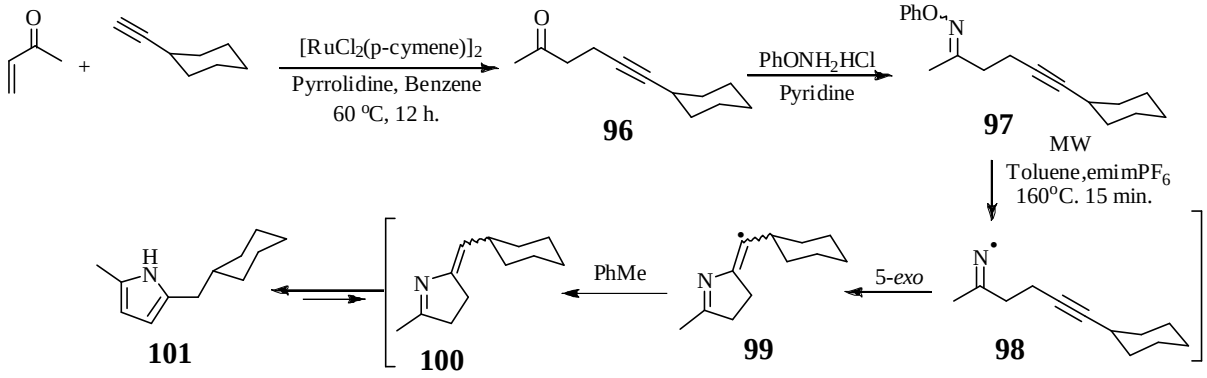
Scheme 27

2.3 Iminyl radical addition to alkynes.

Iminyl radical cyclisation onto triple bonds has been scarcely investigated.[30] Cyclisation proceeds by the *exo* pathway to give the smaller ring. Intramolecular additions onto alkynes are slower than for alkenes because a less stable vinyl radical is generated.

2.3.1 Syntheses of cyclohexylmethyl-5-methyl-1*H*-pyrrole via 5-*exo* cyclisation.

The *O*-phenyl oxime of cyclohexylhex-5-yn-2-one **96** was chosen as a precursor to probe the effectiveness of the alkyne group as an acceptor for iminyl radical cyclisations. Compound **96** was prepared by ruthenium catalyzed conjugate addition of ethynyl cyclohexane to methyl vinyl ketone using the method of Kim and co-workers,[31] followed by standard *O*-phenyl oxime conversion. Microwave irradiation of **97** in toluene at 160 °C for 15 minutes gave pyrrole **101** in 72 % yield. Vinyl radical **99** formed by 5-*exo* ring closure of the iminyl radical, was expected to rapidly abstract an H-atom from the solvent to produce **100**. However, under the microwave conditions, it appears that two 1,3-proton migrations converted **100** to **101**, the aromaticity of this product ensuring this was a rapid and complete rearrangement (Scheme 28).

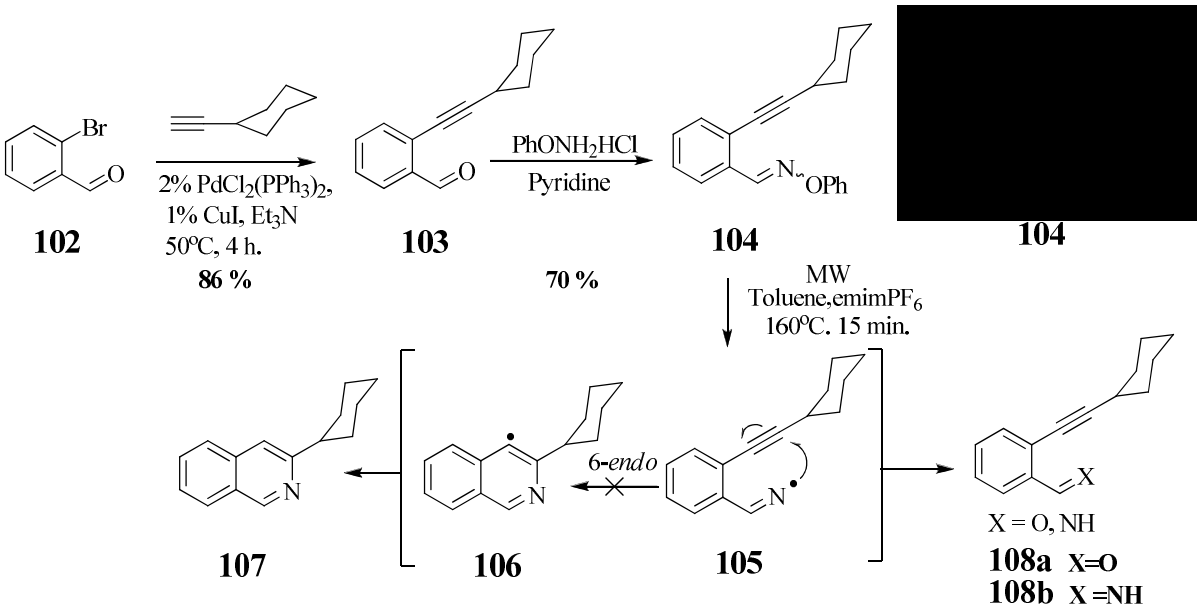


Scheme 28

2.3.2 Potential syntheses of 3-Cyclohexylisoquinoline.

O-Phenyl oxime ether **104**, with an alkynylaryl skeleton, was prepared by Sonogashira Pd-catalyzed coupling[32] of 2-bromobenzaldehyde with ethynylcyclohexane to yield 2-(cyclohexylethynyl)benzaldehyde **103** followed by condensation with *O*-phenylhydroxylamine hydrochloride. It was postulated that microwave irradiation of **104** in toluene would release iminyl radical **105**. The architecture of **105** may favour ring closure

onto the triple bond in the 6-*endo trig* mode giving the aryl radical **106**. Hydrogen abstraction from the toluene solvent should then furnish isoquinoline **107**. Disappointingly, microwave irradiation of **104** in toluene led to a complex mixture of products including the imine **108a**, its hydrolysis product **108b**, and trace amounts of the corresponding nitrile. In this case neither 6-*endo* nor 5-*exo* ring closure was fast enough to compete successfully with H-atom abstraction from solvent, and other side reactions. It may be due to the distance between the iminyl radical and the alkyne acceptor, as can be appreciated in the geometrical optimization of phenyl oxime ether **104** with MM2 (Scheme 29).

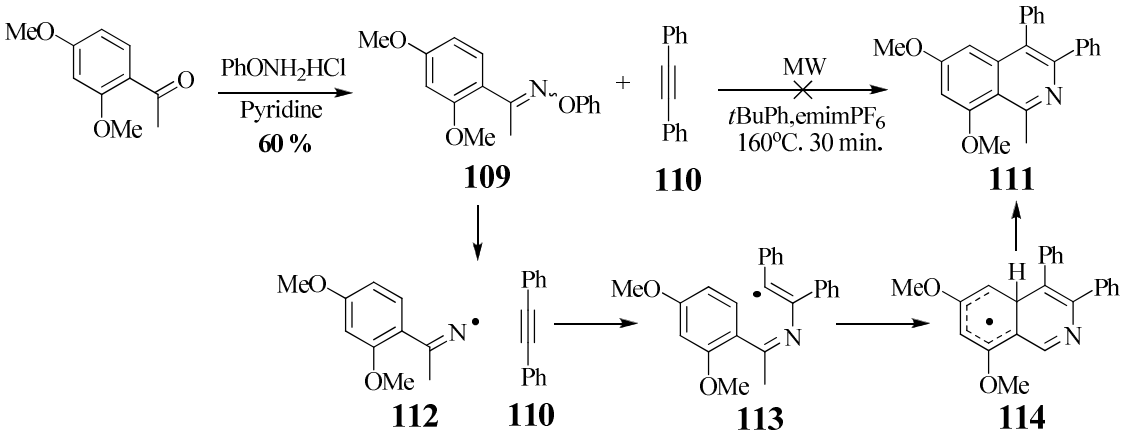


Scheme 29

2.3.3 Potential intermolecular addition onto alkynes.

It was also postulated that iminyl radicals generated using our thermal methodology could undergo intermolecular addition to alkynes. Tri-substituted quinoline **111** could be prepared by microwave irradiation of oxime ether **109** in the presence of ten equivalents of diphenyl acetylene **110** in the optimal reaction conditions (Scheme 30). The big excess of the radical acceptor was used because the intermolecular addition process would be much slower than intramolecular cyclisation. The iminyl radical would undergo addition to the triple bond affording the highly reactive vinyl radical **113**. This vinyl radical might yield an homolytic aromatic substitution onto the phenyl ring generating cyclohexadienyl radical **114**. After an oxidative process, quinoline **111** should be formed. Disappointingly, none of the desired

product could be isolated. The NMR spectrum of the total reaction mixture showed an intractable mixture of products. It may be due to a polymerization process.



Scheme 30

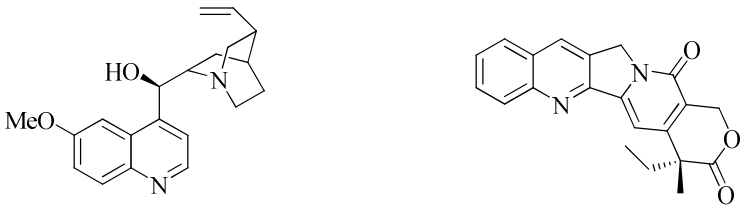
2.4 Iminyl radical addition onto phenyl rings.

Addition of iminyl radical onto phenyl groups constitutes an attractive strategy for the synthesis of a wide range of nitrogen heterocycles. There are no kinetic data of the intramolecular iminyl radical cyclisation onto aromatic rings, but it is supposed to be a bit slower than addition to an alkene. This is because of the greater stability of the aromatic π system which is destroyed on addition of a radical. After addition of an iminyl radical, a cyclohexadienyl radical would be formed. These cyclohexadienyl radicals may react to regenerate the aromatic ring by expulsion of the initial radical or by formally losing a hydrogen atom. The cyclohexadienyl radical is believed not to simply lose a hydrogen atom because the C-H bond is relatively strong. The hydrogen atom may be abstracted by another radical or, alternatively, the radical could be oxidized to form a cation which could then lose a proton. Non-H-atom donor solvents were therefore required to facilitate this oxidative process.[33]

2.4.1 Syntheses of quinolines via 6-*endo* intramolecular cyclisations.

The quinoline ring system is an important target in synthetic chemistry. It is found in a large number of natural products, many of which have important biological activities (e.g., quinine, camptothecin).[34] Quinolines are integral to a large number of synthetic drug substances with activities including antimalarial, antiinflammatory, antineoplastic, antifungal, antiseptic, antiinfective, and analgesic properties.[35] They also find application in agrochemicals and effect chemicals such as dyestuffs and corrosion inhibitors.[36] The

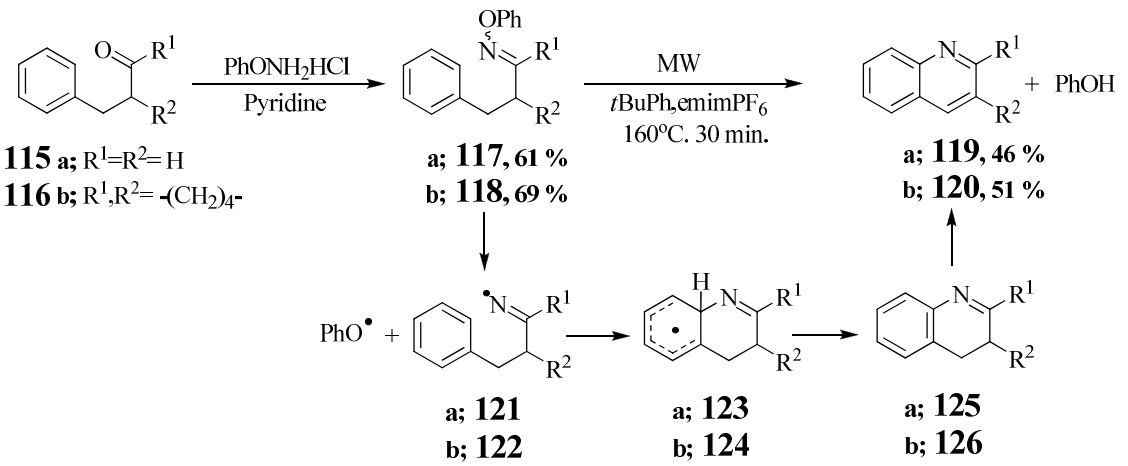
development of new methods for their synthesis is therefore an area of considerable ongoing interest.[37]



Quinine ***Camptothecin***

Figure 5

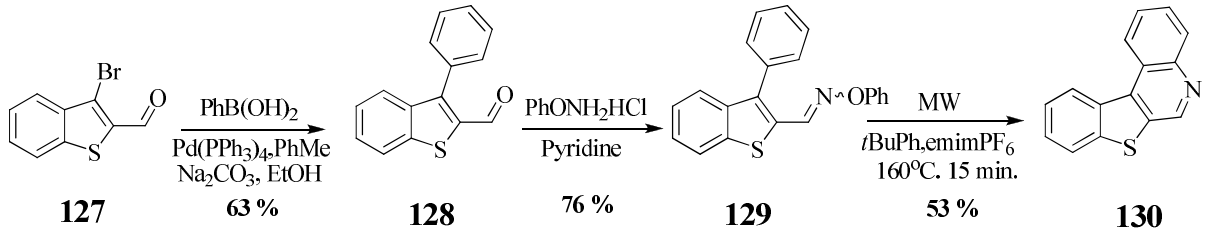
Quinolines were therefore interesting heterocyclics which could be achieved via our microwave induced iminyl radical cyclisation methodology. The efficiency of this process was tested in the preparation of six-membered rings from 6-*endo* cyclisation of appropriate precursors. 3-Phenyl oxime ethers **117** and **118** were easily prepared from the corresponding commercial carbonyl compounds **115** and **116**. When subjected to microwave irradiation in *tert*-butylbenzene as non-H-atom donor solvent and including emimPF_6, **117** gave a 46 % yield of the quinoline **119** and similarly **118** afforded tetrahydroacridine **120** in 51% yield. For these and subsequent cyclisations onto aromatic acceptors an irradiation time of 30 minutes was adopted to ensure complete reaction. 6-*Endo* cyclisation of the initial iminyl radical **121** and **122**, will produce cyclohexadienyl radicals **123** and **124**. Loss of an H-atom will restore aromaticity to the benzo rings with the production of dihydroquinolines **125** and **126**. The cyclohexadienyl H-atoms could be abstracted by phenoxyl radicals or other radicals in the system, or possibly by electron transfer from **123**/**124** yielding the corresponding cyclohexadienyl cations which then lose a proton. The latter seems unlikely in *t*-BuPh solvent and in the absence of a good electron acceptor molecule. However, in both dihydroquinolines, a further in situ dehydrogenation took place so that only the fully aromatic quinolines **119** and **120** could be isolated after the microwave irradiation (Scheme 31).



Scheme 31

The NMR spectrum of the total reaction mixture showed in both cases the presence of the corresponding imine and its hydrolyzed carbonyl compound which proved the competition between the homolytic aromatic substitution and the H-atom abstraction. Especially important was the presence of the nitrile derivative from **121** via β fragmentation of the iminyl radical in the syntheses on the quinoline **119**.

The possibility of preparing tetracyclic quinolines by using benzothiophene as the support for the iminyl radical and acceptor was also examined. Thus, precursor **129** was prepared from 3-bromobenzothiophene-2-carbaldehyde **128**. The sequence started with the Suzuki coupling of **127** with phenyl boronic acid in the presence of 0.2 % $Pd(PPh_3)_4$ and Na_2CO_3.[38] 3-Phenylbenzo[*b*]thiphene-2-carbaldehyde was isolated in 63 % yield. Subsequent condensation with *O*-phenylhydroxylamine HCl gave oxime ether **129** in 76 % yield. On irradiation with microwaves benzo[*b*]thieno[2,3-c]quinoline **130** was isolated in a 53 % yield (Scheme 32).



Scheme 32

2.4.2 Syntheses of phenanthridines via 6-*endo* intramolecular cyclisations.

The phenanthridine framework lies at the heart of a number of natural products including the *amaryllidaceae* alkaloids such as the *norchelerythrine*[39] and *trisphaeridine*, and the *papaveraceae* benzophenanthridine alkaloids such as the tubulin polymerization inhibitor *chelidonine*[40]. These, and the closely related class of phenanthridones, are known to exhibit diverse biological activities, and thus present excellent targets for natural product scaffold-based libraries (Figure 6).

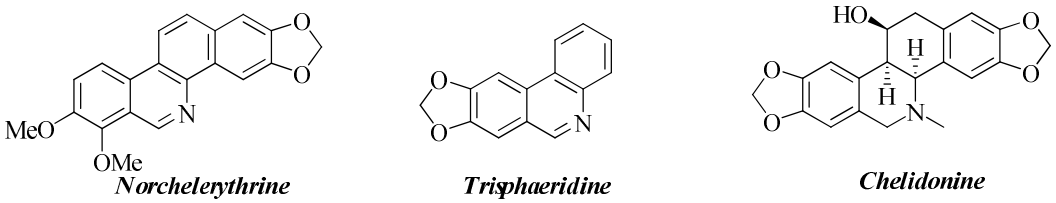
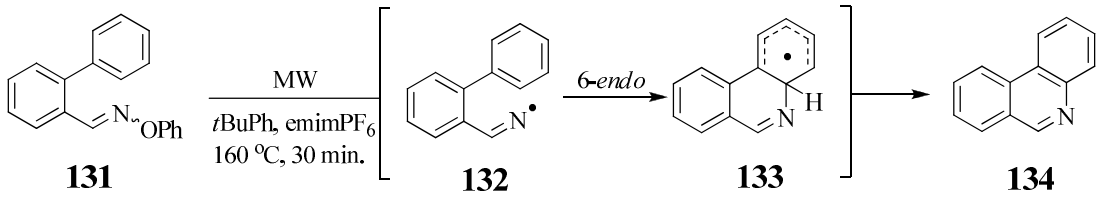


Figure 6. Natural products containing a phenantridine core structure.

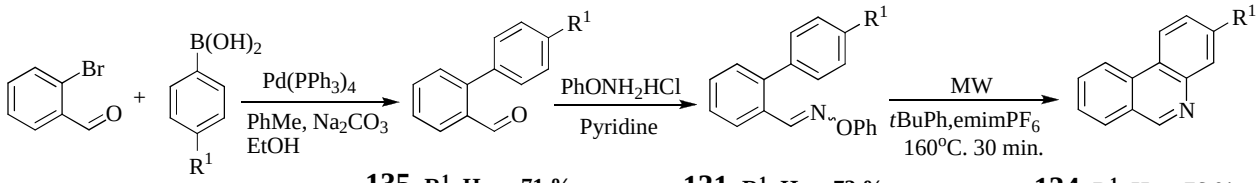
It was postulated that our radical methodology could be applied for the syntheses of several phenanthridines. In this case a phenyl ring, rather than benzothiophene, was used to support a second aromatic acceptor next to the oxime ether group, i.e. situated *ortho* to each other. In these systems the derived iminyl radicals are ideally placed for intramolecular addition to the ring of the adjacent acceptor. An iminyl radical mediated route to derivatives of phenanthridines is shown in Scheme 33.



Scheme 33

Microwave irradiation of oxime ether **131** under the optimal conditions induced N-O bond scission releasing iminyl radical **132**. Homolytic aromatic substitution onto the phenyl ring gave cyclohexadienyl radical **133**. In the absence of H-atom donor solvent this cyclohexadienyl radical oxidised yielding the azaheterocyclic phenanthridine **134**.

To assess the scope of this cyclisation, a set of 2-formylbiphenyls **135-138** were prepared by Pd-catalyzed coupling of 2-bromobenzaldehyde with various aromatic boronic acids in yields ranging from 62 % to 71 %. They were converted to the corresponding *O*-phenyl oximes by treatment with *O*-phenylhydroxylamine hydrochloride. Individual precursors in *t*-BuPh, with emimPF_6 as ionic liquid, were then irradiated with microwaves for 30 minutes. Using this methodology gave the parent phenanthridine **134** which was isolated in 76 % yield along with phenol. The reaction was equally successful for precursors containing electron-withdrawing substituents (Br, CN), which yielded **142** and **143**, and for precursor containing an electron-releasing substituent (OMe), which gave the 3-methoxy derivative **144**. The 3-bromo- and 3-cyanophenanthridines are convenient for further functional group transformations (Scheme 34).



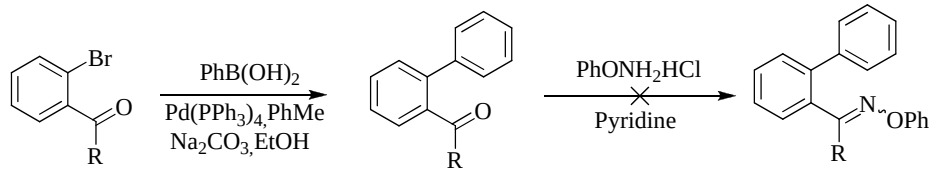
135; **R¹=H** 71 %
136; **R¹=Br** 69 %
137; **R¹=CN** 62 %
138; **R¹=OMe** 63 %

131; **R¹=H** 72 %
139; **R¹=Br** 78 %
140; **R¹=CN** 74 %
141; **R¹=OMe** 70 %

134; **R¹=H** 76 %
142; **R¹=Br** 73 %
143; **R¹=CN** 66 %
144; **R¹=OMe** 62 %

Scheme 34

Syntheses of oxime ethers **149** and **150** were also examined by following a similar synthetic route. Disappointingly, the condensation reaction of *O*-$PhONH_2HCl$ in pyridine with 1-(2-bromophenyl)ethanone and 2-bromophenyl(phenyl)methanone did not work at room temperature for 24 hours. The condensation was also carried out at room temperature for 48 hours and at 50 °C for four hours but none of the oxime ethers **149, 150** was formed. This unsuccessful reactivity may be due to steric hindrance between the phenyl group in the *ortho* position, the methyl or the phenyl group from the respective ketones and the phenyl hydroxylamine (Scheme 35).



145; **R = Me**
146; **R = Ph**

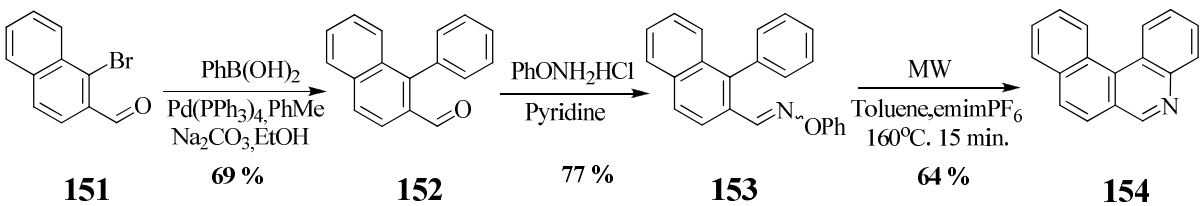
147; **R = Me 63 %**
148; **R = Ph 58 %**

149; **R = Me**
150; **R = Ph**

Scheme 35

2.4.2.1 Syntheses of benzo[*k*]phenanthridines.

Because of the biological significance of benzo-fused phenanthridine alkaloids,[41] we decided to check if our methodology could be applied to the synthesis of benzo[*k*]-phenanthridines. These compounds have recently been made by an anionic/aryne cyclisation and in situ oxidation sequence starting from 2-bromonaphthyl-2-fluorophenylamine.[42] Our three-step preparative method is based on the naphthalene-containing precursor **152**, which was made by a Suzuki coupling from 1-bromo-2-naphthaldehyde **151** and phenylboronic acid. Condensation with *O*-$PhONH_2HCl$ in pyridine afforded the oxime ether precursor. Microwave irradiation of **153** under the standard conditions in *t*-BuPh enabled **154** to be isolated in 64 % yield (Scheme 36).



151

69 %

152

77 %

153

64 %

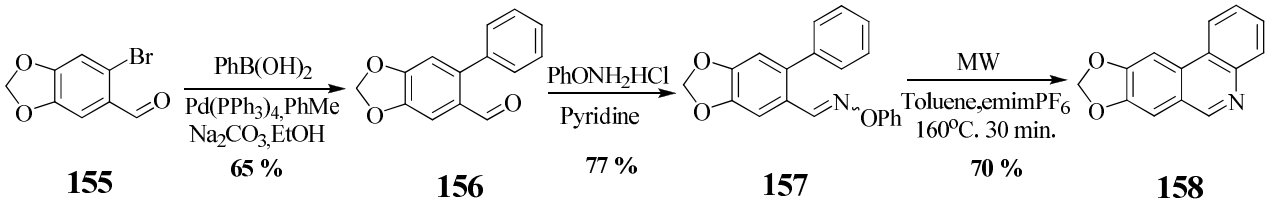
154

Scheme 36

2.4.2.2 Syntheses of Trisphaeridine alkaloid.

The *Amaryllidaceae* alkaloids are a group of natural products having in most cases a phenanthridine-type structure. Trisphaeridine is one example of this group of alkaloids that has been isolated from a few plants of the *Amaryllidaceae* family.

In a similar way to that described above for the syntheses of substituted phenanthridines, the natural product trisphaeridine **158** was prepared in three steps starting from the commercial 6-bromopiperonal **155**, via the corresponding formyl **156** and oxime ether **157** derivatives. A 70 % yield of **158** was obtained from microwave irradiation of **157** in *t*-BuPh (Scheme 37).



Scheme 37

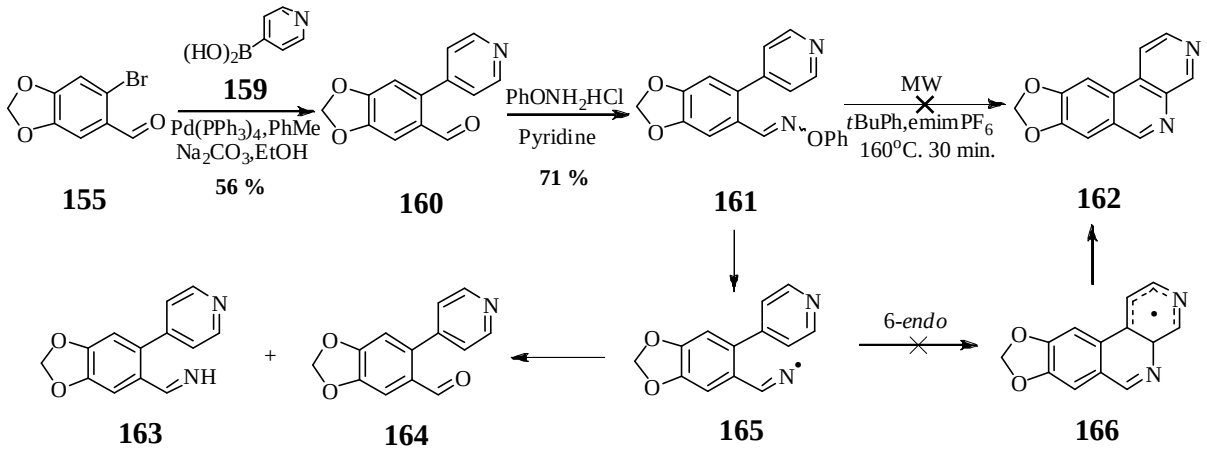
Previous syntheses have been accomplished via tributyltin hydride induced cyclisation of *N*-(2-bromobenzyl)aniline,[43] via the internal Pd-catalyzed aryl-aryl coupling reaction of MOM protected halo amides, followed by reduction with $LiAlH_4$ and treatment with hydrochloric acid,[44] and by Pd[0]-mediated Ullmann cross-coupling of 1-bromo-2-nitrobenzene with 6-bromopiperonal.[45]

2.4.3 Syntheses of benzonaphthyridines via 6-*endo* intramolecular cyclisations.

Benzonaphthyridine derivatives are of special interest in drug discovery because they have been extensively studied as potential agents to modulate the activity of the central nervous system. Benzonaphthyridine analogs are also known as antagonists of 5-HT4 receptors,[46] antitumor agents,[47] potential antimalarials,[48] R-adrenoreceptor blockers,[49] PKC inhibitors,[50] and cancer cell growth inhibitors.[51]

A simple extension of the method employed in the syntheses of trisphaeridine appeared to offer a route to benzo[*c*][1,7]naphthiridine derivatives **162**. The sequence started with Pd-catalyzed coupling of 6-bromopiperonal, with pyridin-4-ylboronic acid **159** to give formyl derivative **160**, which was then transformed to the *O*-phenyl oxime ether **161** in good

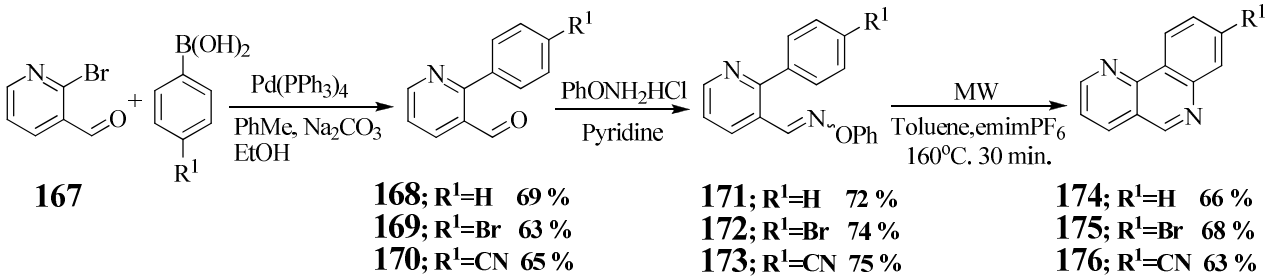
yield. However, when the latter was subjected to microwave irradiation, none of the desired benzonaphthiridine **162** was formed. Instead, a mixture of imine **163** and its hydrolysis product **164** was obtained. This result suggested that ring closure of intermediate iminyl radical **165** onto the pyridine ring was slower than cyclisation onto the phenyl ring and unable to compete with H-atom abstraction from other reaction components (Scheme 38) .



Scheme 38

Reports of ring closure of C-centred radicals onto pyridine rings are comparatively rare,[52] and the reaction is usually low yielding in comparison with ring closure onto pyridinium salts.[53-55] Iminyl radicals are expected to be electrophilic in comparison with C-centred radicals, and therefore their even slower cyclisation onto pyridine, due to an unfavourable polar effect with the ring N-atom, makes reasonable sense.

The methodology was, however, readily adapted for preparations of benzo[*h*][1,6]naphthiridines by using pyridine as the basal support for the aromatic acceptor and iminyl radical. 2-Bromonicotinaldehyde **167** underwent Suzuki couplings with phenyl boronic acids to afford 2-aryl-3-formyl-pyridine derivatives **168**-**170**, which were smoothly converted to the corresponding oxime ethers **171**-**173**. On irradiation of **171** with microwaves in the usual way a very satisfactory yield of benzo[*h*][1,6]naphthiridine **174** was obtained. The results from the precursors with CN and Br substituents showed that benzo[*h*][1,6]naphthiridine containing useful functionality in the 8-position **175** and **176**, could easily be accessed (Scheme 39).



167

168; R^1=H 69 %
169; R^1=Br 63 %
170; R^1=CN 65 %

171; R^1=H 72 %
172; R^1=Br 74 %
173; R^1=CN 75 %

174; R^1=H 66 %
175; R^1=Br 68 %
176; R^1=CN 63 %

Scheme 39

Figure 7 shows the X-Ray crystal structure of the phenyl oxime ether **171**. The *E* configuration of **171** is presumably the most stable configuration, minimizing the interaction between the different aryl rings.

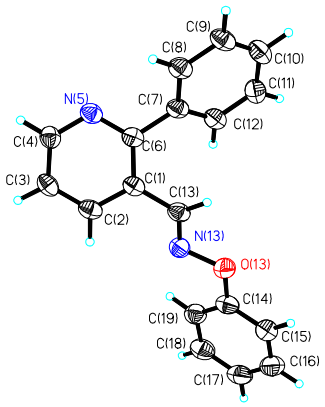


Figure 7. X-ray structure of O-phenyl oxime ether **171**.

A few benzo[*h*]naphthyridine derivatives have been reported in the literature,[56] but interestingly none appear to be commercially available.

2.5 Iminyl radical addition onto indoles.

Intramolecular addition of iminyl radicals onto phenyl groups proved to be a very efficient method in the syntheses of aza-heteropolycyclic compounds. Fully aromatic products are obtained after the oxidation of the initially formed cyclohexadienyl radical. In this context, cyclisations of aryl and alkyl radicals upon heteroaromatic substrates such as azoles,[57] indoles[58] or pyridines[59] have become increasingly important for the synthesis of otherwise quite inaccessible substituted heterocycles. However, similar processes involving iminyl radicals, which have a high synthetic potential due to their intrinsic functionalization, have scarcely been investigated.[60]

Knowing that indoles are privileged and highly interesting heterocyclic rings in medicinal chemistry, it was decided to study the iminyl radical addition onto indoles, as a source of indolopyridines, a highly interesting core in the pharmaceutical industry.

2.5.1 Syntheses of indolopyridines via 6-*endo* intramolecular cyclisations.

In recent years pyrido[2,3-*b*]indoles (α-carbolines) have received renewed interest due to their biological activity as antiviral and antitumor agents that function by the formation of intercalation complexes with DNA or the inhibition of topoisomerase II.[61] Anxiolytic, antiinflammatory, and CNS stimulating activity has also been reported.[62] Some natural products contain this tricyclic core as grossularines and neocryptolepine (Figure 8). 3 R-Carbolines have also been detected in the products from the pyrolysis of protein containing food products and cigarette smoke.[63]

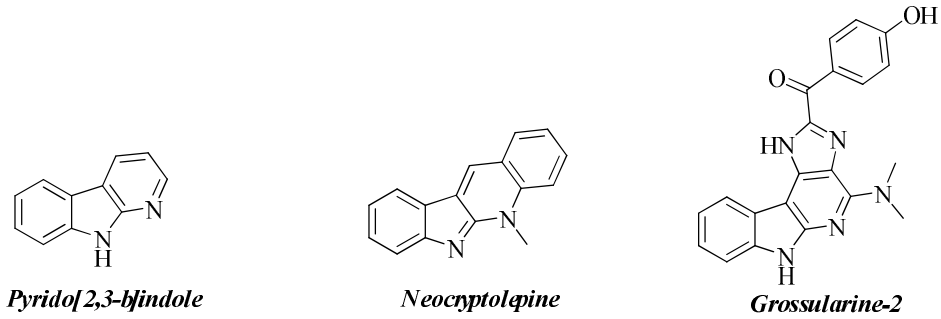
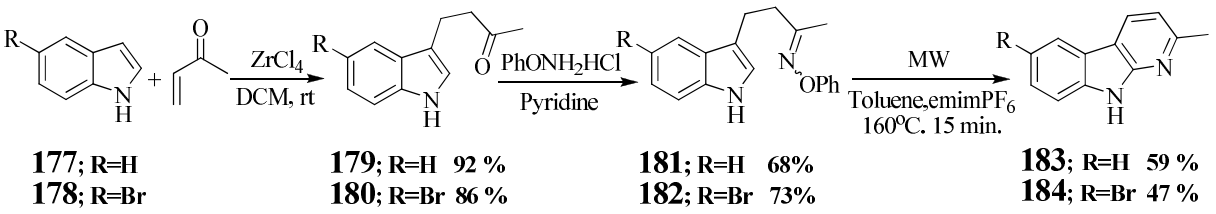


Figure 8. Pyrido[2,3-*b*]indole and related natural products.

Our proposed pathway for the syntheses of indolopyridines making use of the iminyl radical methodology described in this chapter, started with the syntheses of 4-(1H-indol-3-yl)butan-2-one **179** and its analogue 4-(5-bromo-1*H*-indol-3-yl)butan-2-one **180** by $ZrCl_4$ induced Michael addition of the corresponding indole **177** and **178** respectively with the vinyl ketone shown. Subsequent condensation with *O*-phenylhydroxylamine HCl, afforded the desired oxime ether precursors **181** and **182**. Interestingly, microwave irradiation of these oxime ethers in *t*BuPh in the optimal conditions yielded indolopyridine derivatives **183** and **184** in which both the acceptor ring and the pyridyl ring has become aromatic (Scheme 40). 6-*Endo* cyclisation was probably favoured in these example, because it generated resonance stabilized benzyl type radicals, unlike the alternative 5-*exo* mode which would involve formation of a strained spiro-C-atom.



177; **R=H**
178; **R=Br**

179; **R=H 92 %**
180; **R=Br 86 %**

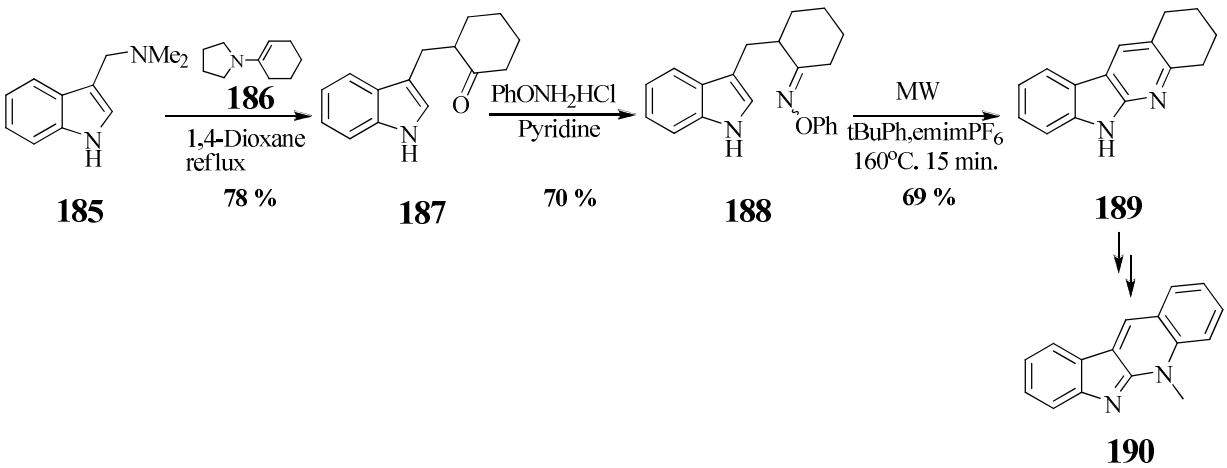
181; **R=H 68%**
182; **R=Br 73%**

183; **R=H 59 %**
184; **R=Br 47 %**

Scheme 40

2.5.2 Formal syntheses of neocryptolepine.

An analogous sequence was designed for the preparation of the natural product neocryptolepine. Neocryptolepine is the minor alkaloid of the African plant *Cryptolepis Sanguinolenta* and it has proved to posess in vitro antimalarial activity and reduced cytotoxicity compared with related natural products such as cryptolepine.[64] The indoloketone **187** was obtained in 78 % yield from reaction of gramine **185** with 1-cyclohexenylpyrrolidine **186** in 1,4-dioxane at reflux temperature for 5 hours. Conversion to the corresponding *O*-phenyl oxime ether **188** was accomplished in 70 % yield. Microwave irradiation of **188** in *t*-BuPh afforded tetrahydroindolo[2,3-*b*]quinoline **189** in 69 % yield (Scheme 41). As with several previous products of these microwave-mediated reactions, a second in situ dehydrogenation step rendered the newly formed pyridine ring aromatic. Tetrahydroindolo[2,3-*b*]quinoline **189** is a known compound and has previously been converted to neocryptolepine in two steps by dehydrogenation/aromatization with DDQ followed by methylation with methyl sulphate.[65] Thus, overall, the sequence represents a formal synthesis of neocryptolepine **190** in five steps from gramine.



185

78 %

187

70 %

188

69 %

189

190

Scheme 41

3.0 Conclusions.

It has been shown that *O*-phenyl oximes are excellent precursors for a variety of iminyl radicals. The oximes are easily made in one step from carbonyl compounds and can be stored indefinitely. Their microwave-assisted reactions have several advantages over existing methods for N-heterocycle preparations. Reactions are rapid (≤ 30 minutes), require no acids, bases, or toxic metals, and are comparatively mild and high-yielding. Unlike many other radical-mediated synthetic methods, no initiator is needed and hence no by-products from initiator fragments contaminate the system. Comparatively few microwave-assisted synthetic methods, based around radical intermediates, are known.

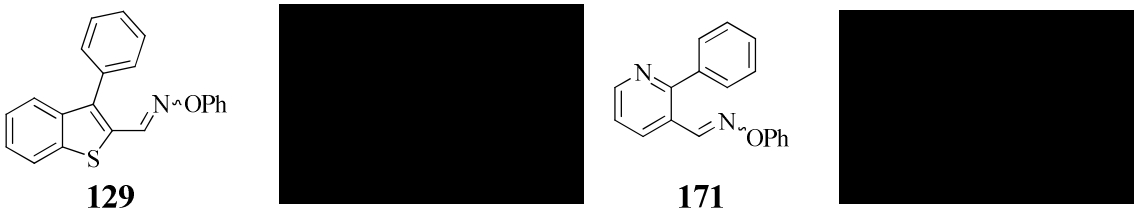
Dihydropyrroles can be made in good yields from *O*-phenyl oximes containing pent-4-ene acceptors. However, the analogous process with a hex-5-enyl acceptor did not yield a dihydropyridine, probably because the 6-*exo-trig* iminyl radical ring closure was too slow to compete with H-atom abstraction. Reduction of dihydropyrrole **54** gave 2-(5-methylpyrrolidin-2-yl)ethanol **84**, which seemed suitable for conversion to a pyrrolizidine. In practice, treatment of **84** under Appel type conditions yielded only 2-(but-3-enyl)pyrrolidine **89**. It is probable that this results from base attack on the 5-methyl group of the pyrrolizidinyl-ammonium ion intermediate in a Hofmann elimination. If this explanation is correct, similar eliminations can be expected for other 5-alkyl-substituted analogues.

Intramolecular addition of iminyl radical **98** onto alkynes afforded 2-cyclohexylmethyl-5-methyl-1*H*-pyrrole **101** in good yield after rearomatization of the dihydropyrrole **100**. The intramolecular addition of iminyl radical onto an alkyne in the alkynylaryl skeleton **105** to yield isoquinoline **107** was also studied. Disappointingly, only the reduced imine and its hydrolyzed product could be isolated. Intermolecular addition onto an alkyne was also attempted but none of the desired addition product was found.

Suitably substituted iminyl radicals ring closed readily onto aromatic acceptors, thus enabling several N-heterocyclic systems to be accessed. The favoured mode of cyclisation was 6-*endo* in this case because this generated resonance-stabilized cyclohexadienyl (or analogous) radicals. Quinoline was made from 3-phenylpropanone via the *O*-phenyl oxime; a process with obvious further scope. Syntheses of phenanthridines starting from 2-formylbiphenyls were particularly efficient and this approach enabled the natural product trisphaeridine to be made. Starting from 2-phenylnicotinaldehyde, and derivatives, ring closures of the derived iminyl radicals onto the phenyl rings yielded

benzo[*h*][1,6]naphthyridines. Similarly, ring closure onto a phenyl ring from benzothiophene based iminyl yielded benzo[*b*]thieno[2,3-*c*]quinoline, It was found that the analogous iminyl ring closure onto pyridine rings did not compete with other reactions of the iminyl radical.

It was evident that iminyl ring closure onto a phenyl ring occurs readily, although the lower yield of benzo[*b*]thieno[2,3-*c*]quinoline compared with phenanthridines and benzo[h][1,6]naphthyridines may indicate it was slightly more difficult with the architecture of oxime ether **129** because of the larger bond angles of the adjacent iminyl and phenyl groups on the 5-membered ring as compared with a six-membered ring.



129 **171**

Figure 9. Geometry optimization of *O*-phenyl oximes **129** and **171** with MM2.

However, iminyl radical closure onto indoles enabled indolopyridines to be prepared. This latter route was exploited in a short formal synthesis of neocryptolepine starting from 2-((1H-indol-3-yl)methyl)cyclohexanone.

It is clear that microwave-assisted reactions of *O*-phenyl oximes are very promising as fast, clean and flexible routes to many biologically active compounds.

4.0 Experimental.

Instrumentation and General Techniques.

1. NMR Spectroscopy:

^{1}H-NMR: Routine spectra were obtained at 400 MHz on a Bruker Avance II 400 MHz or a Bruker Avance 300 MHz.

^{13}C-NMR: Spectra were obtained on a 75 MHz Bruker Avance 300.

Both the ^{1}H-NMR and ^{13}C-NMR spectra were obtained from solutions in $CDCl_3$ unless otherwise stated. All spectra were referenced to internal tetramethylsilane and the chemical shifts for all NMR spectra are expressed in parts per millions to high frequency of the reference.

2. Infrared spectroscopy.

The IR spectra were obtained on a Perkin Elmer FT-IR Paragon 1000 spectrometer. Solid were run as nujol mulls and liquids were run as thin films on NaCl plates.

3. Mass Spectroscopy.

Low resolution and high-resolution (HR) mass spectral analysis (EI and CI) were recorded using a VG AUTOSPEC mass spectrometer or a Micromass GCT (Time-ofFlight), high performance, orthogonal acceleration spectrometer coupled to an Agilent Technologies 6890N GC system. Electrospray mass spectrometry (ESMS) was recorded on a high performance orthogonal acceleration reflecting TOF mass spectrometer, coupled to a Waters 2975 HPLC.

4. GC/MS.

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).

5. Melting points.

Routine melting points were carried out on a Gallenkamp melting point apparatus. All melting points are uncorrected.

6. Chromatography.

TLC was carried out using either Polygram silica plates (0.2 mm with 254 nm fluorescent dye) or Fluka alumina plates (0.2 mm with 254 nm fluorescent dye). The components were observed under ultraviolet light (254 nm/ 365 nm) and stained with ninhydrin (1-2 5 in EtOH) or $KMnO_4$ aqueous solution. Column chromatography was performed using silica gel (40-63 μm, Fluorochem).

7. Reagents and solvents.

Diethyl ether and THF were freshly distilled from sodium benzophenone ketyl. Dry pyridine was freshly dried over CaH_2. Other organic compounds were used as received, without further drying. Organic solutions were dried by standing over anhydrous magnesium sulphate. Solvents were evaporated under reduced pressure on a rotary evaporator. Nitrogen gas was dried (NaOH, $CaCl_2$, 4 Å molecular sieve) prior to use.

8. UV Photolysis.

Ultra violet irradiation was carried out in quartz apparatus using 400 W medium pressure Hg lamp.

9. X-Ray crystallography.

Data were collected on a Bruker SMART diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The structures were solved by direc methods and refined using full-matrix least squares methods. Atomic coordinates and bond lengths and angles are listed in the Appendix and the structures are shown in the discussion.

10. ESR spectroscopy.

ESR spectra were obtained with a Bruker EMS 10/12 spectometer operating at 9.5 GHz with 100 KHz modulation. Irradiation of samples was carried out in a resonant cavity by unfiltered light from a 500 W super pressure Hg arc.

Methyl 4-oxooct-7-enoate 49.

3-Butenylmagnesium bromide (0.5 M in THF 59.9 mL, 34.8 mmol) was added dropwise to a stirred solution of methyl 4-chloro-4-oxobutanoate (4.5 g, 29.0 mmol) and iron (III) acetylacetonate (0.3 g, 0.87 mmol) at -78˚C under nitrogen. After complete addition and stirring for 15 min at that temperature, the reaction was quenched with NH_4Cl solution (20 mL) and extracted with diethyl ether (3 x 20 mL).The combined organic layers were dried over $MgSO_4$, the solvent was evaporated and the residue was purified by flash chromatography on silica (hexane/EtOAc 10/1) providing the title compound as an orange oil (3.8 g, 77 %). ^{1}H NMR (400MHz, $CDCl_3$), δ_H; 2.35 (2H, q, J = 7.1 Hz, CH_2), 2.5-2.6 (4H, m, CH_2), 2.72 (2H, t, J = 6.5 Hz, CH_2), 3.65 (3H, s, CH_3), 5.01 (2H, m, CH_2), 5.31 (1H,m, CH); ^{13}C NMR ($CDCl_3$) δ_C; 27.7, 31.3, 37.1, 41.8 (CH_2), 51.8 (CH_3), 115.3 (CH_2), 137.0 (CH), 173.3, 208.1(C)); IR 3054, 1738, 1703, 1616 cm^{-1}.

Methyl 4-(phenoxyimino)oct-7-enoate 50.

O-Phenylhydroxylamine hydrochloride (1 g, 6.41 mmol) was dissolved in anhydrous pyridine (20.0 mL) under N_2 at room temperature, and methyl 4-oxooct-7-enoate (1.1 g, 6.41 mmol) was added in one portion. The resulting solution was stirred at room temperature overnight, and the progress of the reaction was monitored by TLC (EtOAc/hexane, 1:2). Upon completion, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (3 × 10 mL), and the combined organic phases were washed several times with saturated, aqueous $CuSO_4$ solution to remove any traces of pyridine. The solution was then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc/hexane) giving the named product as a red oil (146 mg, 75 %); two isomers (2:3) ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.34-2.84 (8H, m, CH_2), 3.73/3.74 (3H, s, CH_3), 5.12 (2H, m, CH_2), 5.89 (1H, m, CH), 6.99-7.41 (5H, m, CH); ^{13}C NMR δ_C; 24.7/29.0, 29.7/29.8, 29.9/30.1, 30.3/34.0 (CH_2), 51.7/51.9 (CH_3), 114.4/114.7 (CH)x2, 115.8 (CH_2), 121.8/122.0 (CH), 129.2/129.3 (CH)x2, 137.1/137.2 (CH), 159.3/159.4, 161.8/162.2, 173.3/173.3 (C); IR 3075, 1736, 1590, 1488 cm^{-1}; HRMS (CI$^+$) calcd for $C_{15}H_{20}NO_3$; 262.1443. Found: 262.1447.

Methyl 3-(2-methyl-3,4-dihydro-2*H*-pyrrol-5-yl)propanoate 54.

Methyl 4-(phenoxyimino)oct-7-enoate (500 mg, 1.91 mmol) was dissolved in toluene (12 mL, 0.15 M) in a microwave vessel (10-20 mL) and emimPF_4 (490 mg, 1.91 mmol) was added. The vessel was sealed and subjected to microwave irradiation for 15 min at 160 °C in a Biotage Initiator system. After cooling, the ionic liquid was filtered off and the toluene was removed under reduced pressure. The residue was purified by flash column chromatography (5 % EtOAc/hexane) affording **54** as a yellow oil (252 mg, 78 %); ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.14 (3H, d, J = 6.7 Hz, CH_3), 1.32 (1H, m, CH_2), 2.01 (1H, m, CH_2), 2.33-2.68 (6H, m, CH_2), 3.61 (3H, s, CH_3), 3.98 (1H, m, CH); ^{13}C NMR δ_C; 22.0 (CH_3), 28.5 (CH_2), 30.5 (CH_2×2), 37.9 (CH_2), 51.7 (CH_3), 67.8 (CH), 173.6, 175.0 (C); IR 1735, 1644 cm^{-1}; HRMS (CI$^+$) calcd for $C_9H_{16}NO_2$; 170.1181. Found: 170.1186.

Procedure A. General procedure for preparation of *O*-phenyl oximes.

O-Phenylhydroxylamine hydrochloride (100 mg, 0.75 mmol) was dissolved in anhydrous pyridine (8.0 mL) under N_2 at room temperature, and the carbonyl compound (0.75 mmol) was added in one portion. The resulting solution was stirred at room temperature overnight, and the progress of the reaction was monitored by TLC (EtOAc/hexane, 1:2). Upon completion, the reaction mixture was poured into water (8 mL) and extracted with EtOAc (3 × 10 mL), and the combined organic phases were washed several times with saturated, aqueous $CuSO_4$ solution to remove any traces of pyridine. The solution was then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc/hexane).

(5E)-6,10-Dimethylundeca-5,9-dien-2-one *O*-phenyl oxime 56.

From 6,10-dimethylundeca-5,9-dien-2-one (145 mg, 0.75 mmol), following procedure A. Red oil (151 mg, 71%); two isomers; ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.50-1.78 (12H, m, CH_3), 2.08 (4H, m, CH_2), 2.32 (4H, m, CH_2), 5.12 (1H, m, CH), 5.19 (1H, m, CH), 6.98 (1H, J = 7.3 Hz, CH), 7.21 (2H, m, CH), 7.31 (2H, m, CH); ^{13}C NMR δ_C; 11.3/14.1, 20.4, 23.1 (CH_3), 24.2/24.3 (CH_2), 25.3 (CH_3), 26.7, 30.0/30.2, 40.0 (CH_2), 115.0 (CH×2), 122.0, 123.1, 124.3, 129.8 (CH×2), 131.3, 136.5, 159.8, 161.5/161.8 (C) ; IR 2965, 1590, 1488 cm^{-1}; HRMS (CI$^+$) calcd for $C_{19}H_{28}NO$: 286.2171. Found: 286.2177.

Procedure B. General procedure for microwave-induced reactions of *O*-phenyl oximes.

The *O*-phenyl oxime (100 mg) and emimPF_4 (1 equiv.) were dissolved in toluene (0.15 M) in a microwave vessel (2-5 mL). The vessel was sealed and subjected to microwave irradiation for 15 min at 160 °C in a Biotage Initiator system. After cooling the ionic liquid was filtered off and the toluene was removed under reduced pressure. The residue was purified by flash column chromatography (5 % EtOAc/hexane).

5-Methyl-2-(6-methylhept-5-en-2-yl)-3,4-dihydro-2*H*-pyrrole 57.

From (5*E*)-6,10-dimethylundeca-5,9-dien-2-one *O*-phenyl oxime (100 mg, 0.35 mmol), following procedure B. Yellow oil (47 mg, 70 %); ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 0.71/0.89 (3H, d, J = 6.8 Hz, CH_3), 1.09 (1H, m, CH), 1.32-1.54 (2H, m, CH_2), 1.53 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.78-1.92 (2H, m, CH_2), 1.95 (3H, s, CH_3), 2.05 (2H, m, CH_2), 2.36 (2H, m, CH_2), 3.80 (1H, m, CH), 5.04 (1H, m, CH); ^{13}C NMR δ_C; 14.6/16.3, 17.7, 19.7 (CH_3), 24.5 (CH_2), 25.7 (CH_3), 25.8/26.2, 32.9/34.3 (CH_2), 37.1/37.8 (CH), 39.1/39.2 (CH_2), 77.3/77.9, 124.8/124.9 (CH), 131.4, 174.0 (C); IR 2964, 1652 cm^{-1}; HRMS (CI^+) calcd for $C_{13}H_{24}N$; 194.1909. Found: 194.1909.

1-(4-methoxyphenyl)pent-4-en-1-one 60.[65]

A solution of 1-(4-methoxyphenyl)ethanone (1 g, 6.7 mmol) in dry THF (5 mL) was added dropwise over 10 min to a suspension of potassium hydride (0.32 g, 8 mmol,) in dry THF (30 mL) at 0 °C under N_2. The yellow suspension was stirred at 23 °C for 30 min and BEt_3 (8 ml 0.1 M. in THF, 8 mmol) was added dropwise at 15 °C over 15 min. After stirring the resulting clear solution at 23°C for 15 min, allyl bromide (1.23 g, 10 mmol,) was added dropwise over 10 min and the resulting suspension was stirred for 4 h at 23 °C and quenched with a 1:1 mixture of 30 % NaOH and 30 % H_2O_2 (15 mL) at 0°C over 15 min. The reaction mixture was then diluted with H_2O (30 mL), the layers were separated and the organic layer diluted with Et_2O (80 mL) and washed with water (2 x 30 mL). The combined water layers were extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The isolated product was purified by column chromatography (AcOEt/hexane 1:30) to afford the named product as a

colourless oil (0.9 g, 79 %). ^{1}H NMR (400MHz,$CDCl_3$), δ_H; 2.46-2.54 (2H, m, CH_2), 3.06-3.11 (2H, m, CH_2), 4.99-5.13 (2H, m, CH_2), 5.84-5.98 (1H, m, CH), 7.43-7.59 (3H, m, CH), 7.97 (2H, d, *J*= 7.2 Hz, CH); ^{13}C NMR δ_C; 28.2 (CH_2), 37.8 (CH_2), 115.2 (CH_2), 127.9 (CH)x2, 128.4 (CH)x2, 132.9 (CH), 136.8 (C), 137.1 (CH), 199.1 (C). IR 3067, 2977, 2855, 1820, 1687 cm^{-1}.

1-(2,4-Dimethoxyphenyl)pent-4-en-1-one 61.

A solution of 1-(1,4-dimethoxyphenyl)ethanone (2 g, 11 mmol) in dry THF (10 mL) was added dropwise over 10 min to a suspension of potassium hydride (0.53 g, 13 mmol) in dry THF (25 mL) at 0°C under N_2. The yellow suspension was stirred at 23°C for 30 min and BEt_3 (1M solution in THF, 13 mL, 13 mmol) was added dropwise at 15°C over 15 min. After stirring the solution at 23 °C for 15 min, allyl bromide (1.99 g, 16.5 mmol) was added dropwise over 10 min and the resulting suspension was stirred for 4 h at 23 °C and quenched with a 1:1 mixture of 30 % NaOH and 30 % H_2O_2 (15 mL) at 0 °C over 15 min. The reaction mixture was then diluted with H_2O (20 mL), the layers were separated and the organic layer diluted with Et_2O (75 mL) and washed with water (2 × 30 mL). The combined water layers were extracted with DCM (2 × 30 mL) and the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The isolated product was purified by column chromatography (AcOEt/hexane 5%) to afford 1-(2,4-dimethoxyphenyl)pent-4-en-1-one as a colourless oil (1.86 g, 77 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.35 (2H, q, *J* = 7.2 Hz, CH_2), 2.97 (2H, t, *J* = 7.2 Hz, CH_2), 3.77 (3H, s, CH_3), 3.81 (3H, s, CH_3), 4.95 (2H, m, CH_2), 5.84 (1H, m , CH), 6.37 (1H, d, *J* = 2.3 Hz, CH), 6.44 (1H, dd, *J* = 8.7, 2.3 Hz, CH), 7.73 (1H, d, *J* = 8.7 Hz, CH); ^{13}C NMR δ_C; 28.7, 43.0 (CH_2), 55.7 (CH_3)x2, 98.5, 105.2 (CH), 114.7 (CH_2), 121.4 (C), 133.0, 138.3 (CH), 160.8, 164.4, 199.6 (C); IR 2942, 1664, 1575 cm^{-1}.

1-(4-Methoxyphenyl)-4-en-1-one *O*-phenyl oxime 62.

From 1-(4-methoxyphenyl)pent-4-en-1-one (142 mg, 0.75 mmol), following procedure A. Red oil (153.8 g, 73 %); two isomers (3:1). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.25 (2H, m, CH_2), 2.66/2.89 (2H, t, *J* = 8.2 Hz, CH_2), 3.70 (3H, s, CH_3), 4.93 (2H, m, CH_2), 5.78 (1H, m , CH), 6.77-6.96 (3H, m, CH), 7.05-7.27 (4H, m, CH), 7.37/7.60 (2H, d, *J* = 8.8 Hz, CH); ^{13}C NMR δ_C; 25.5/29.7, 29.8/33.6 (CH_2), 54.4 (CH_3), 112.5/112.9 (CH×2), 113.7/113.7 (CH×2),

114.3/114.4 (CH_2), 120.8/120.9 (CH), 126.3 (C), 127.1/128.1 (CH×2), 128.2/128.8 (CH×2), 136.2 (CH), 158.5/158.6, 158.8/159.5, 159.1/159.8 (C); IR 3018, 1594, 1490 cm^{-1}; HRMS (CI^+) calcd for $C_{18}H_{20}NO_2$; 282.1494. Found: 282.1497.

1-(2,4-Dimethoxyphenyl)pent-4-en-1-one *O*-phenyl oxime 63.

From 1-(2,4-dimethoxyphenyl)pent-4-en-1-one (165 mg, 0.75 mmol), following procedure A. Red oil (163 mg, 70 %); Two isomers (3:1). ^1H NMR (400 MHz, $CDCl_3$), δ_H; 2.22 (2H, m, CH_2), 2.66/2.91 (2H, t, J = 8.0, CH_2), 3.68/3.75 (3H, s, CH_3), 3.76/3.78 (3H, s, CH_3), 4.90 (2H, m, CH_2), 5.76 (1H, m, CH), 6.43 (2H, m, CH), 6.85-7.26 (6H, m, CH); ^{13}C NMR δ_C; 29.5/30.9, 30.6/35.0 (CH_2), 56.0 (CH_3×2), 99.2, 104.7 (CH), 115.4 (CH×2), 115.5 (CH_2), 118.4 (C), 122.1-122.3 (CH), 129.5/129.6 (CH×2), 130.1/131.7 (CH), 138.1/138.3 (CH), 159.2, 160.0, 162.4, 163.7 (C); IR 3075, 1640, 1594, 1489 cm^{-1}; HRMS (ES^+) calcd for $C_{19}H_{21}NO_3Na$: 334.1419. Found: 334.1411.

5-(4-Methoxyphenyl)-2-methyl-3,4-dihydro-2*H*-pyrrole 64.

From 1-(4-methoxyphenyl)-4-en-1-one *O*-phenyl oxime (100 mg, 0.355 mmol), following procedure B. Red oil (45 mg, 68 %). ^1H NMR (400 MHz, $CDCl_3$), δ_H; 1.28 (3H, d, J = 6.8, CH_3), 1.46 (1H, m, CH_2), 2.15 (1H, m, CH_2), 2.78 (1H, m, CH_2), 2.96 (1H, m, CH_2), 3.78 (3H, s, CH_3), 4.20 (1H, m, CH), 6.83 (2H, d, J = 8.8 Hz, CH), 7.71 (2H, d, J = 8.8 Hz, CH); ^{13}C NMR δ_C; 22.2 (CH_3), 30.7, 35.2 (CH_2), 55.6 (CH_3), 68.2 (CH), 113.8 (CH×2), 127.4 (C), 129.3 (CH×2), 161.2, 171.1 (C); IR 3268, 2923, 1684 cm^{-1}; HRMS (CI^+) calcd for $C_{12}H_{16}NO$; 190.1232. Found 190.1238.

5-(2,4-Dimethoxyphenyl)-2-methyl-3,4-dihydro-2*H*-pyrrole 65.

From 1-(2,4-dimethoxyphenyl)pent-4-en-1-one *O*-phenyl oxime (100 mg, 321 mmol), following procedure B. Red oil (54 mg, 77 %); ^1H NMR (400 MHz, $CDCl_3$), δ_H; 1.28 (3H, d, J = 6.7 Hz, CH_3), 1.44 (1H, m, CH_2), 2.12 (1H, m, CH_2), 2.88 (1H, m, CH_2), 3.04 (1H, m, CH_2), 3.77 (3H, s, CH_3), 3.78 (3H, s, CH_3), 4.12 (1H, m, CH), 6.43 (2H, m , CH), 7.68 (1H, d, J = 8.5, CH); ^{13}C NMR δ_C; 21.9 (CH_3), 30.1, 38.1 (CH_2), 55.5 (CH_3×2), 66.4 (CH), 98.6, 105.1 (CH), 116.6 (C), 131.7 (CH), 159.0, 165.8, 172.3 (C); IR 3018, 2964, 1609 cm^{-1}; HRMS (CI^+) calcd for $C_{13}H_{18}NO_2$; 220.1338. Found: 220.1337.

Methyl 4-chloro-4-oxobutanoate 73.

A solution of mono-methyl succinate (2 g, 15 mmol) in DCM (25 mL) and a catalytic amount of DMF (4 drops) was stirred at room temperature. Oxalyl chloride (3.85 g, 30 mmol) was added dropwise at 0 °C. The mixture was stirred for 4 h at room temperature. The solvent was removed under reduced pressure affording the methyl 4-chloro-4-oxobutanoate as a yellow paste (2.15 g, 94 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.62 (2H, t, J = 6.4 Hz, CH_2), 3.16 (2H, t, J = 6.4 Hz, CH_2), 3.65 (3H, s, CH_3).

Methyl 5-chloro-5-oxopentanoate 74.

A solution of mono-methyl glutarate (2 g, 14 mmol) in DCM (25 mL) and catalytic amount of DMF (4 drops) was stirred at rt. Oxalyl chloride (3.45 g, 28 mmol) was added dropwise at 0 °C. The mixture was stirred for 4 h at rt. The solvent was removed under reduced pressure affording the methyl 5-chloro-5-oxopentanoate as a yellow paste (1.93 g, 92 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.95 (2H, qt, J = 7.2 Hz, CH_2), 2.34 (2H, t, J = 7.2 Hz, CH_2), 2.94 (2H, t, J = 7.2 Hz, CH_2), 3.64 (3H, s, CH_3).

Methyl 5-oxonon-8-enoate 75.[66]

3-Butenylmagnesium bromide (0.5 M in THF, 69.6 mL, 34.8 mmol) was added dropwise to a stirred solution of methyl 5-chloro-5-oxopentanoate (3.0 g, 18.3 mmol) and iron (III) acetylacetonate (0.3g, 0.87 mmol) at -78˚C under nitrogen. After complete addition stirring was continued for 15 min at that temperature, the reaction was quenched with NH_4Cl solution (20 mL) and extracted with diethyl ether (3 x 20mL). The combined organic layers were dried over $MgSO_4$, the solvent was evaporated and the residue was purified by flash chromatography on silica (hexane/EtOAc 10/1) providing the title compound as an orange oil (3.8 g, 77%). ^{1}H NMR (400MHz, $CDCl_3$), δ_H; 1.82 (2H, qt, J = 7.2 Hz, CH_2), 2.26 (4H, m, CH_2), 2.42 (4H, m, CH_2), 3.60 (3H, s, CH_3), 4.94 (2H, m, CH_2), 5.74 (1H, m, CH); ^{13}C NMR ($CDCl_3$) δ_C; 18.8, 27.8, 33.0, 41.6, 41.8 (CH_2), 51.7 (CH_3), 115.5 (CH_2), 137.0 (CH), 173.9, 209.3 (C); IR 3050, 1736, 1703 cm^{-1}

Methyl 5-(phenoxyimino)non-8-enoate 76.

From methyl 5-oxonon-8-enoate (138 mg, 0.75 mmol), following procedure A. Red oil (161 mg, 78 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.91-2.66 (10H, m, CH_2), 3.71 (3H, s, CH_3), 5.10 (2H, m, CH_2), 5.88 (1H, m, CH), 7.00 (1H, t, J = 7.3 Hz, CH), 7.20 (2H, m, CH), 7.33 (2H, m, CH); ^{13}C NMR δ_C; 21.2/21.2, 28.2/28.4, 30.0/30.2, 33.3, 33.6 (CH_2), 51.5 (CH_3), 114.6 (CH×2), 115.4 (CH_2), 121.8 (CH), 129.2 (CH ×2), 137.2/137.4 (CH), 159.4, 163.0, 173.5/173.7 (C); IR 2951, 1736, 1590, 1488 cm^{-1}; HRMS (CI$^+$) calcd for $C_{16}H_{22}NO_3$; 276.1600. Found: 276.1600.

Methyl 4-(2-methyl-3,4-dihydro-2*H*-pyrrol-5-yl)butanoate 77.

From methyl 5-(phenoxyimino)non-8-enoate (100 mg, 0.363 mmol), following procedure B. Yellow oil (55 mg, 82 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.17 (3H, d, J = 6.8 Hz, CH_3), 1.30 (1H, m, CH_2), 1.87 (2H, m, CH_2), 2.01 (1H, m , CH_2), 2.25-2.52 (6H, m, CH_2), 3.59 (3H, s, CH_3), 3.96 (1H, m, CH); ^{13}C NMR δ_C; 21.6 (CH_2), 22.1 (CH_3), 30.5, 32.9, 33.5, 37.4 (CH_2), 51.5 (CH_3), 67.6 (CH), 173.9, 176.7 (C); IR 1734, 1644 cm^{-1}; HRMS (CI$^+$) calcd for $C_{10}H_{18}NO_2$; 184.1338. Found: 184.1340.

Methyl 3-(5-methylpyrrolidin-2-yl)propanoate 78.
Method A.

$NaBH_4$ (24 mg, 0.65 mmol) was added in one portion to a stirred solution of 3-(2-methyl-3,4-dihydro-2*H*-pyrrol-5-yl)propanate (100 mg, 0.59 mmol) in EtOH (10 mL). The suspension was stirred for 3 hours at room temperature and after that was poured into water (10 mL) and extracted with DCM (3 x 10 mL). The combination of the organic layers was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The NMR spectrum of the reaction crude showed a mixture of **78** 43 % and **84** 35 %.

Method B.

To a stirred solution of 3-(2-methyl-3,4-dihydro-2*H*-pyrrol-5-yl)propanate (100 mg, 0.59 mmol) in CH_3CN (10 mL) was added dropwise a solution of sodium triacetoxyborohydride (420 mg, 1.95 mmol) and acetic acid (39 mg, 0.65 mmol) in CH_3CN (5 mL). The mixture was allowed to stir for 3 h at rt and the suspension was poured onto aqueous saturated

$NaHCO_3$ (10 mL) and extracted with DCM (3 x 10 mL). The organic layer was dried over $MgSO_4$ filtered and concentrated in vacuo. The NMR spectrum of the crude reaction showed a mixture of **78** 55 % and **84** 35 %.

Method C.

To a stirred solution of 3-(2-methyl-3,4-dihydro-2*H*-pyrrol-5-yl)propanate (100 mg, 0.59 mmol) and acetic acid (35 mg, 0.59 mmol) in DCM (10 mL) at 0 °C, was added portionwise $NaCNBH_3$ (37 mg, 0.59 mmol). After stirring for 2 h at 0 °C the reaction was poured onto saturated $NaHCO_3$ (10 mL) and extracted with DCM (3x10 mL). The organic layer was dried over $MgSO_4$ filtered and concentrated in vacuo. The NMR spectrum of the reaction crude showed a mixture of **78** 62 % and **84** 30 %.

3-(5-methylpyrrolidin-2-yl)propan-1-ol 84.

A solution of methyl 3-(2-methyl-3,4-dihydro-2*H*-pyrrol-5-yl)propanate (200 mg, 1.18 mmol) in dry ether (3 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (134 mg, 3.5 mmol) in dry ether (10 mL) at 0°C under N_2. The suspension was stirred for 3 h. at room temperature at which time the mixture was cooled to 0°C and water (2 mL) was added dropwise carefully. The mixture was allowed to warm to rt and ether (10 mL) was added. The suspension was filtered through celite and the solution was dried over $MgSO_4$ and concentrated in vacuo to give a clear oil (160 mg, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.05/1.09 (3H, d, J = 6.3 Hz, CH_3), 1.11-1.97 (8H, m, CH_2), 3.06 (2H, m, CH), 3.53 (2H, m, CH_2); ^{13}C NMR δ_C; 28.4/29.2 CH_3, 29.2/29.5, 30.4/31.8, 32.2/32.9, 33.8/33.9 (CH_2), 52.3/53.6, 57.1/58.6 (CH), 60.8/61.0 (CH_2); IR 3282, 2929, 1453 cm^{-1}.

3-(5-Methyl-1-(methylsulfonyl)pyrrolidin-2-yl)propyl methanesulfonate 85.

To a solution of amino alcohol 3-(5-methylpyrrolidin-2-yl)propan-1-ol (70 mg, 0.25 mmol) in dry dichloromethane (5 mL) was added MsCl (34 mg, 0. 3 mmol) at -10 °C followed by dropwise addition of Et_3N (38 mg, 0.38 mmol). After being stirred for 1 h at -10 °C, the cooling bath was removed and stirring was continued for a further 2 h. The solvent was evaporated at reduced pressure, and the residue was directly purified by column chromatography (55:30:15) dichloromethane-methanol-35% NH_4OH). None of the desired cyclised product was isolated instead 3-(5-methyl-1-(methylsulfonyl)pyrrolidin-2-yl)propyl

methanesulfonate was found. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.22/1.26 (3H, d, J = 6.2 Hz, CH_3), 1.50-2.06 (9H, m, CH_2, CH), 2.73/2.84 (3H, s, CH_3), 2.95 (3H, s, CH_3), 3.65 (1H, m, CH), 4.18 (2H, m, CH_2); ^{13}C NMR δ_C; 18.9 (CH_3), 28.5, 30.8, 31.9, 33.0 (CH_2), 37.3, 40.8 (CH_3), 50.3, 55.2 (CH), 70.7 (CH_2).

2-(But-3-enyl)pyrrolidine 89.[67]

To a solution of 3-(5-methylpyrrolidin-2-yl)propan-1-ol (80 mg, 0.55 mmol) in dry DMF (2 mL) were successively added PPh_3 (228 mg, 1.1 mmol), CCl_4 (167 mg, 1.1 mmol) and Et_3N (111 mg, 1.1 mmol). After stirring overnight at room temperature the solution was poured into water (3 mL) and extracted with diethyl ether (3 x 5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography DCM/MeOH/28% aqueous NH_3 (200/9/1) affording a colourless oil (18 mg, 26 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.18 (1H, m, NH), 1.43-1.96 (6H, m, CH_2), 2.32 (2H, m, CH_2), 2.73-3.34 (3H, m, CH_2, CH), 4.90 (2H, m, CH_2), 5.78 (1H, m, CH); ^{13}C NMR δ_C; 25.6, 31.6, 32.0, 36.0, 46.8 (CH_2), 59.0 (CH), 114.8 (CH_2), 139.2 (CH).

1-Phenylhex-5-en-1-one 90.[68]

A solution of acetophenone (2 g, 16.6 mmol) in dry THF (10 mL) was added dropwise over 10 min to a suspension of potassium hydride (0.80 g, 19.92 mmol,) in dry THF (40 mL) at 0 $^{\circ}$C under N_2. The yellow suspension was stirred at 23 °C for 30 min and BEt_3 (19.92 mL, 0.1 M in THF, 19.92 mmol) was added dropwise at 15 °C over 15 min. After stirring the resulting clear solution at 23°C for 15 min, 4-bromobut-1-ene (2.7 g, 19.92 mmol,) was added dropwise over 10 min and the resulting suspension was stirred for 4 h at 23 °C and quenched with a 1:1 mixture of 30% NaOH and 30% H_2O_2 (25 mL) at 0°C over 15 min. The reaction mixture was then diluted with H_2O (40 mL), the layers were separated and the organic layer diluted with Et_2O (80 mL) and washed with water (2 x 30 mL). The combined water layers were extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The isolated product was purified by column chromatography (AcOEt/hexane 1:30) to afford the named product as a colourless oil (1.53 g, 53 % yield). ^{1}H NMR (400MHz,$CDCl_3$), δ_H; 1.78-1.88 (2H, m, CH_2), 2.10-2.17 (2H, m, CH_2), 2.95 (2H, t, J = 7.3 Hz, CH_2), 4.49-5.08 (2H, m, CH_2), 5.73-5.86 (1H, m, CH), 7.41-7.56 (3H, m, CH), 7.91-7.98 (2H, m, CH); ^{13}C NMR δ_C; 23.1,

33.0, 37.6, 115.3 (CH_2), 128.0 (CHx2), 128.5 (CHx2), 132.9, 137.0 (CH), 138.0, 200.2 (C); IR 3067, 1820 cm^{-1}

1-Phenylhex-5-en-1-one *O*-phenyl oxime 91.

From 1-phenylhex-5-en-1-one (130 mg, 0.75 mmol), following procedure A. Red oil (145 mg, 73 %); two isomers (3:1). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.51-1.80 (2H, m, CH_2), 2.03-2.21 (2H, m, CH_2), 2.62/2.68 (2H, m, CH_2), 4.94-5.03 (2H, m, CH_2), 5.80 (1H, m, CH), 6.87-7.40 (8H, m, CH), 7.64-7.88 (2H, m, CH); ^{13}C NMR δ_C; 25.9, 26.7, 33.7, 114.7(CHx2), 115.4 (CH_2), 122.3 (CH), 126.8 (CHx2), 128.2 (CHx2), 129.3 (CHx2), 129.8, 138.0 (CH), 139.0, 156.6, 157.0 (C); IR 3018, 1590, 1490 cm^{-1}; HRMS (ES^+) calcd for $C_{18}H_{19}NONa$; 288.1364. Found: 288.1360.

6-Cyclohexylhex-5-yn-2-one 96.

To a stirred solution of $[RuCl_2(p\text{-cymene})]_2$ (30.6 mg, 0.05 mmol) in benzene (4 mL) was added pyrrolidine (14.2 mg, 0.2 mmol), and the mixture was stirred for 10 min at rt followed by the addition of ethynylcyclohexane (108.4 mg, 1.0 mmol) and methyl vinyl ketone (210 mg, 3.0 mmol). After the reaction mixture was stirred for 12 h at 60 °C, 6-cyclohexylhex-5-yn-2-one (142 mg, 80%) was isolated by column chromatography on silica gel (EtOAc/hexane 1:3). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.59 (2H, m, CH_2), 1.68 (2H, m, CH_2), 2.10 (3H, s, CH_3), 2.22 (1H, m, CH), 2.35 (2H, m, CH_2), 2.56 (2H, t, J = 7.3 Hz, CH_2); ^{13}C NMR δ_C; 13.8 (CH_2), 25.0 (CH_2)x2, 26.0 (CH), 29.0 (CH), 30.0 (CH_3), 33.0 (CH_2x2), 43.2 (CH_2), 78.3, 85.4, 207.7 (C); IR 2929, 2853, 2232, 1717 cm^{-1}; HRMS (CI^+) calcd for $C_{12}H_{17}O$; 177.1279. Found: 177.1277.

6-Cyclohexylhex-5-yn-2-one *O*-phenyl oxime 97.

From 6-cyclohexylhex-5-yn-2-one (133 mg, 0.75 mmol), following procedure A. Red oil (153 mg, 76 %); two isomers (7:3). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.11-1.73 (10H, m, CH_2), 1.97/1.98 (3H, s, CH_3), 2.23 (1H, m, CH), 2.39/2.59 (2H, t, J = 7.1 Hz, CH_2), 2.41 (2H, m, CH_2), 6.89 (1H, t, J = 7.2 Hz, CH), 7.09 (2H, m, CH), 7.19 (2H, m, CH); ^{13}C NMR δ_C; 15.0/20.5 (CH_3), 15.5/16.3 (CH_2), 24.9/25.0, 25.9 (CH_2), 29.1 (CH), 29.7 (CH_2), 33.0 (CH_2×2), 35.6 (CH), 81.5, 85.8 (C), 114.9 (CH×2), 121.9 (CH), 129.3 (CH×2), 160.3 (C),

163.6 (C); IR 3063, 2929, 1590, 1489 cm^{-1}; HRMS (CI^+) calcd for $C_{18}H_{24}NO$; 270.1858. Found: 270.1852.

2-(Cyclohexylmethyl)-5-methyl-1*H*-pyrrole 101.

From 6-cyclohexylhex-5-ynone *O*-phenyl oxime (100 mg, 0.371 mmol), following procedure B. Orange oil **(**47 mg, 72 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 0.75-1.71 (11H, m, CH_2, CH), 2.16 (3H, s, CH_3), 2.33 (2H, d, J = 7.1 Hz, CH_2), 5.70 (2H, m, CH), 7.45 (1H, s, NH); ^{13}C NMR δ_C; 12.0 (CH_3), 25.3 (CH_2×2), 25.4, (CH_2), 32.2 (CH_2×2), 34.9 (CH_2), 37.8, 104.6, 104.8 (CH), 124.6, 129.0 (C); IR 3370, 2921, 1595, 1448 cm^{-1}; HRMS (CI^+) calcd for $C_{12}H_{20}N$; 178.1596. Found: 178.1601.

2-(Cyclohexylethynyl)benzaldehyde 103.[69]

To a solution of 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and ethynylcyclohexane (1.29 g, 12.0 mmol) in Et_3N (40 mL) was added $PdCl_2(PPh_3)_2$ (140 mg, 2 mol %). The mixture was stirred for 5 min and CuI (20 mg, 1 mol %) was added. The resulting mixture was then heated under a nitrogen atmosphere at 50 °C for 4 h. The reaction was monitored by TLC to establish completion. The reaction mixture was allowed to cool to room temperature, and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using 20:1 hexanes/EtOAc to afford (1.88 g, 86 %) of the compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.34-1.45 (3H, m, CH_2), 1.52-1.63 (3H, m, CH_2), 1.71-1.78 (2H, m, CH_2), 1.87-1.92 (2H, m, CH_2), 2.68 (1H, m, CH), 7.34-7.39 (1H, m, CH), 7.48-7.54 (1H, m, CH), 7.88 (1H, m, CH), 10.56 (1H, s, CH); ^{13}C NMR δ_C; 24.9 (CH_2)x2, 25.9 (CH_2), 29.9 (CH), 32.5 (CH_2)x2, 76.3, 102.2, 126.9 (C), 127.9, 128.1 (CH), 133.3 (C), 133.7, 136.0 (CH), 192.3 (C).

2-(Cyclohexylethynyl)benzaldehyde *O*-phenyl oxime 104.

From 2-(cyclohexylethynyl)benzaldehyde (159 mg, 0.75 mmol), following procedure A. Brown solid (179 mg, 79 %); mp 59-61°C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.18-1.80 (10H, m, CH_2), 2.56 (1H, m, CH), 6.94 (1H, tt, J = 6.94, 1.58 Hz, CH), 7.21 (6H, m, CH), 7.38 (1H, m, CH), 7.91 (1H, d, J = 6.75 Hz, CH), 8.82 (1H, s, CH); ^{13}C NMR δ_C; 23.9 (CH_2×2), 24.8

(CH_2), 28.8 (CH), 31.5 (CH_2×2), 76.4 (C), 99.8 (C), 113.8 (CH×2), 121.3 (CH), 123.7 (C), 124.5 (CH), 126.7 (CH), 128.8 (CH×2), 129.0 (CH), 131.2 (C), 131.6 (CH), 149.5 (CH), 158.4 (C); IR 3063, 2929, 2226, 1591, 1490 cm^{-1}; HRMS (ES^+) calcd for $C_{21}H_{21}NONa$; 326.1521. Found: 326.1511.

1-(2,4-Dimethoxyphenyl)ethanone *O*-phenyl oxime 109.

From 1-(2,4-dimethoxyphenyl)ethanone (135 mg, 0.75 mmol), following procedure A. Purple oil, (148 mg, 73%). Two isomers 9:1. ^{1}H NMR (300MHz, $CDCl_3$) 2.20, 2.30 (3H, s, CH_3), 3.67, 3.73 (3H, s, CH_3), 6.14 (1H, s, CH), 6.42 (1H, m, CH), 6.90 (1H, t, *J*=6.88, CH), 7.04-7.30 (5H, m, CH); δ_C; 15.7, 20.4, 54.3, 54.8 (CH_3), 97.8, 103.6, 113.8 (CH), 118.4 (C), 120.9, 128.1, 129.7 (CH), 158.0, 158.6, 159.1, 161.2 (C)); IR 1594 cm^{-1}; HRMS (CI^+) calcd for $C_{16}H_{18}NO_3$; 272.1291. Found 272.1287.

3-Phenylpropanal *O*-phenyl oxime 117.

From 3-phenylpropanal (100 mg, 0.75 mmol), following procedure A. Red oil (102 mg, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.56/2.79 (2H, m, CH_2), 2.58/2.71 (2H, m, CH_2), 6.88-7.27 (10H, m, CH), 7.22/7.68 (1H, t, *J* = 5.9, CH); ^{13}C NMR δ_C; 26.6/30.2, 31.1/31.6 (CH_2), 113.3/113.7 (CH×2), 121.0/121.2, 125.3/125.4 (CH), 127.3/127.4 (CH×2), 127.6 (CH×2), 128.2 (CH×2), 139.5 (C), 152.4/152.8 (CH), 158.2 (C); IR 3062, 1594, 1486 cm^{-1}; HRMS (CI^+) calcd for $C_{15}H_{16}NO$; 226.1232. Found: 226.1240.

2-Benzylcyclohexanone *O*-phenyl oxime 118.

From 2-benzylcyclohexanone (141 mg, 0.75 mmol), following procedure A. Yellow solid (144 mg, 69 %); mp 79-81 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.16-3.79 (11H, m, CH, CH_2), 6.95 (1H, t, *J* = 7.3 Hz, CH), 6.97-7.24 (9H, m, CH); ^{13}C NMR δ_C; 24.2, 25.3, 26.4, 32.4, 37.3 (CH_2), 44.1 (CH), 114.5 (CH×2), 121.6, 126.0 (CH), 128.3 (CH×2), 129.2 (CH×2), 129.2 (CH×2), 140.6, 159.6, 165.4 (C); IR 3420, 1590, 1488 cm^{-1}; HRMS (CI^+) calcd for $C_{19}H_{22}NO$; 280.1701. Found: 280.1701.

Procedure C. General procedure for microwave-induced reactions of *O*-phenyl oximes with a phenyl ring as a radical acceptor.

The *O*-phenyl oxime (100 mg) and emimPF_4 (1 equiv.) were dissolved in *t*-butylbenzene (0.15 M) in a microwave vessel (2-5 mL). The vessel was sealed and subjected to microwave irradiation for 30 min at 160 °C in a Biotage Initiator system. After cooling the ionic liquid was filtered off and the toluene was removed under reduced pressure. The residue was purified by flash column chromatography (5 % EtOAc/hexane)

Quinoline 119.[70]

From 3-phenylpropanal *O*-phenyl oxime (100 mg, 0.444 mmol), following procedure C. Clear oil (26 mg, 46 %). ^{1}H NMR (400MHz,$CDCl_3$), δ_H; 7.40 (1H, dd, *J* = 8.4, 4.2 Hz, CH), 7.57 (1H, dt, *J* = 8.4, 1.1 Hz, CH), 7.68 (1H, dt, *J* = 7.2, 1.4 Hz, CH), 7.76 (1H, d, *J* = 8.1 Hz, CH), 8.06 (1H, *J* = 8.2 Hz, CH), 8.20 (1H, d, *J* = 8.1 Hz, CH), 8.95 (1H, dd, *J* = 4.2, 1.5 Hz, CH); ^{13}C NMR δ_C; 121.0, 126.4, 127.7 (CH), 128.2 (C), 129.3, 129.4, 135.9 (CH), 148.3 (C), 150.3 (CH); IR 3063, 1500 cm^{-1}.

1,2,3,4-Tetrahydroacridine 120.[45]

From 2-benzylcyclohexanone *O*-phenyl oxime (100 mg, 0.358 mmol), following procedure C. Yellow solid (33 mg, 51 %); mp 53-55 °C. ^{1}H NMR (400MHz,$CDCl_3$), δ_H; 1.88 (2H, m, CH_2), 1.96 (2H, m, CH_2), 2.94 (2H, t, *J* = 6.5 Hz, CH_2), 3.12 (2H, t, *J* = 6.5 Hz, CH_2), 7.41 (1H, t, *J* = 8.1 Hz, CH), 7.59 (1H, dt, *J* = 8.4, 1.4, CH), 7.67 (1H, d, *J* = 8.1 Hz, CH), 7.77 (1H, s, CH), 7.98 (1H, d, *J* = 7.8 Hz, CH); ^{13}C NMR δ_C; 23.0, 23.3, 29.3, 33.6 (CH_2), 125.7, 127.0 (CH), 127.3 (C), 128.3, 128.6 (CH), 131.1 (C), 135.2, 146.6, 159.3 (C); IR 2935, 2858, 1623, 1491, 1437 cm^{-1}.

Procedure D. General procedure for Suzuki coupling.

The bromo-compound (3 mmol) and the boronic acid (3 mmol) were dissolved in toluene (40 mL), and sodium carbonate (6 mmol, 2 M) was added. To this reaction mixture was added ethanol (2 mL) followed by tetrakis(triphenylphosphine)-palladium (2 %). The reaction mixture was refluxed overnight under N_2 and then diluted with water, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined

organic extracts were washed with water (3 × 30 mL) and brine (1 × 30 mL) dried over $MgSO_4$ and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/EtOAc).

3-Phenylbenzo[*b*]thiophene-2-carbaldehyde 128.[71]

From 3-bromobenzo[b]thiophene-2-carbaldehyde (723 mg, 3 mmol), following procedure D. Green oil, (450 mg, 63 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.26 (1H, ddd, *J* = 8.2, 7.1, 1.1 Hz, CH), 7.35-7.45 (6H, m, CH), 7.65 (1H, d, *J* = 7.9 Hz, CH), 7.78 (1H, d, *J* = 7.7 Hz, CH), 9.80 (1H, s, CH); ^{13}C NMR δ_C; 122.2, 124.1, 124.4, 127.3 (CH), 127.7 (CH×2), 128.0 (CH), 129.4 (CH×2), 131.2, 137.8, 138.2, 140.8, 146.6 (C), 184.9 (CH); IR 3019, 1662 cm^{-1}; HRMS (CI$^+$) calcd for $C_{15}H_{11}OS$; 239.0531. Found: 239.0528.

3-Phenylbenzo[*b*]thiophene-2-carbaldehyde *O*-phenyl oxime 129.

From 3-Phenylbenzo[*b*]thiophene-2-carbaldehyde (178 mg, 0.75 mmol), following procedure A. Brown solid, (187 mg, 76 %); mp 81-83 °C; two isomers (1:1). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 6.98 (1H, m, CH), 7.16 (1H, m, CH), 7.22-7.49 (10H, m, CH), 7.55/7.58 (1H, d, *J* = 8.1 Hz, CH), 7.78/7.85 (1H, d, *J* = 7.9 Hz, CH), 7.83/8.44 (1H, s, CH); ^{13}C NMR δ_C; 113.3/113.7 (CH×2), 121.2/121.4, 121.8, 122.7, 123.3/123.7, 125.5/127.7, 127.4/127.5 (CH), 127.7/127.8 (CH×2), 128.3/128.3 (CH×2), 129.1/129.5 (CH×2), 129.8, 132.4/132.7, 136.6/138.2, 138.7/141.0, 140.4/141.6 (C), 141.9/145.7 (CH), 157.8/158.1 (C); IR 3059, 1590, 1489 cm^{-1}; HRMS (ES$^+$) calcd for $C_{21}H_{15}NONaS$; 352.0772. Found: 352.0778.

[1]Benzothieno[2,3-*c*]quinoline 130.[72]

From 3-phenylbenzo[*b*]thiophene-2-carbaldehyde *O*-phenyl oxime (100 mg, 0.3 mmol), following procedure C. Brown solid, (38 mg, 53 %), mp 129-131 °C [lit. 118-119 ^{o}C][72]**.** ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.59 (2H, m, CH), 7.71 (2H, m, CH), 8.01 (1H, m, CH), 8.26 (1H, m, CH), 8.84 (2H, m, CH), 9.30 (1H, s, CH); ^{13}C NMR δ_C; 121.9, 122.8, 124.4 (CH), 124.5 (C), 125.1 (CH), 126.6 (CH×2), 126.9, 129.7 (CH), 131.6, 132.3, 134.2, 140.5, 141.5 (C), 145.2 (CH); IR 3018, 1502 cm^{-1}; HRMS (CI$^+$) calcd for $C_{15}H_{10}NS$; 236.0534. Found: 236.0538.

Biphenyl-2-carbaldehyde *O*-phenyl oxime 131.

From biphenyl-2-carbaldehyde (136 mg, 0.75 mmol), following procedure A. Red oil (147 mg, 72 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 6.95 (1H, t, *J* = 7.4, CH), 7.10-7.42 (12H, m, CH), 8.05 (1H, dd, *J* = 7.8, 1.4 Hz, CH), 8.31 (1H, s, CH); ^{13}C NMR δ_C; 114.4 (CH×2), 122.3, 126.7 (CH), 127.7 (CH×2), 128.5 (CH×2), 129.0 (C), 129.4 (CH×2), 129.8 (CH×2), 130.3, 130.4 (CH), 139.4, 142.8 (C), 150.8 (CH), 159.4 (C) ; IR 3061, 1590, 1489 cm^{-1}; HRMS (ES^+) calcd for $C_{19}H_{16}NO$; 274.1232. Found: 274.1244.

Phenanthridine 134.[75]

From biphenyl-2-carbaldehyde *O*-phenyl oxime (100 mg, 0.366 mmol), following procedure C. Yellow solid (50 mg, 76 %), mp 105-107. ^{1}H NMR (400MHz,$CDCl_3$), δ_H; 7.65 (3H, m, CH), 7.80 (1H, t, *J* = 7.7 Hz, CH), 7.98 (1H, d, *J* = 8.1 Hz, CH), 8.13 (1H, dd, *J* = 8.1, 1.5 Hz, CH), 8.53 (1H, t, *J* = 8.9 Hz, CH), 9.22 (1H, s, CH); ^{13}C NMR δ_C; 121.9, 122.3 (CH), 124.2, 128.4 (C), 127.2, 127.6, 128.8, 128.9, 130.0, 131.2 (CH), 132.7, 144.3 (C); IR 3370, 2921, 1595, 1448 cm^{-1}; HRMS (CI^+) calcd for $C_{13}H_{10}N$ 180.0813 found 180.0820.

Biphenyl-2-carbaldehyde 135.[73]

From 2-bromobenzaldehyde (555 mg, 3 mmol) and phenylboronic acid (366, 3 mmol), following procedure D. Clear oil (400 mg, 73 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.36-7.40 (2H, m, CH), 7.43-7.52 (5H, m, CH), 7.64 (1H, td, *J* = 7.5, 1.4 Hz, CH), 8.03 (1H, dd, *J* = 7.7, 1.1, CH), 9.98 (1H, s, CH); ^{13}C NMR δ_C; 127.5, 127.8, 128.1, 128.4 (CH), 130.1 (CH×2), 130.8 (C), 133.6 (CH×2), 133.7 (CH), 137.7, 146.0 (C), 192.5 (CH); IR 3020, 1691, 1596 cm^{-1}.

4'-Bromobiphenyl-2-carbaldehyde 136.

From 2-bromobenzaldehyde (555 mg, 3 mmol) and 4-bromophenylboronic acid (600 mg, 3 mmol), following procedure D. White solid (536 mg, 69 %); mp 67-69 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H ; 7.17 (2H, d, *J* = 8.5 Hz, CH), 7.32 (1H, dd, *J* = 7.7, 1.2 Hz, CH), 7.43 (1 H, tt, *J* = 7.5, 1.0 Hz, CH), 7.52 (2H, d, *J* = 8.5 Hz, CH), 7.56 (1H, td, *J* = 7.5, 1.5 Hz, CH), 7.94 (1H, dd, *J* = 7.7, 1.2 Hz, CH), 9.88 (1H, s, CH); ^{13}C NMR δ_C; 122.6 (C), 128.0, 128.2, 130.6 (CH), 131.6 (CH)x2, 131.7(CH)x2 (CH), 133.6 (C), 133.7 (CH), 136.7, 144.5 (C),

191.8 (CH); IR 3019,1692, 1599 cm^{-1}; HRMS (CI^+) calcd for $C_{13}H_{10}Obr$; 260.9915. Found: 260.9915.

2'-Formylbiphenyl-4-carbonitrile 137.

From 2-bromobenzaldehyde (555 mg, 3 mmol) and 4-cyanophenylboronic acid (441 mg, 3 mmol), following procedure D. Yellow solid (385 mg, 62 %); 83-85 °C. ^1H NMR (400 MHz, $CDCl_3$), δ_H; 7.33 (1H, dd, *J* = 7.5, 1.0 Hz, CH), 7.42 (2H, d, *J* = 8.6 Hz, CH), 7.49 (1H, t, *J* = 7.5 Hz, CH), 7.61 (1H, td, *J* = 7.6, 1.5 Hz, CH), 7.68 (2H, d, *J* = 8.2 Hz, CH), 7.95 (1H, dd, *J* = 7.7, 1.3 Hz, CH), 9.86 (1H, s, CH); ^{13}C NMR δ_C; 112.1, 118.6 (C), 128.6, 128.9, 130.6 (CH), 130.7 (CH×2), 132.2 (CH×2), 133.6 (C), 133.9 (CH), 142.8, 143.4 (C), 191.5 (CH); IR 3020, 2229, 1699, 1581 cm^{-1}; HRMS (CI^+) calcd for $C_{14}H_{10}NO$; 208.0762. Found: 208.0765.

4'-Methoxybiphenyl-2-carbaldehyde 138.[74]

From 2-bromobenzaldehyde (555 mg, 3 mmol) and 4-methoxyphenylboronic acid (456 mg, 3 mmol), following procedure D. Brown solid, (400 mg, 63 %); mp 46-46 °C. ^1H NMR (400 MHz, $CDCl_3$), δ_H; 3.78 (3H, s, CH_3), 6.91 (2H, d, *J* = 8.7 Hz, CH), 7.21 (2H, d, *J* = 8.7 Hz, CH), 7.32-7.39 (2H, m, CH), 7.52 (1H, td, *J* = 7.6, 1.5 Hz, CH), 7.91 (1H, dd, *J* = 7.7, 1.5, CH), 9.91 (1H, s, CH); ^{13}C NMR δ_C; 55.5 (CH_3), 114.0 (CH×2), 127.4, 127.6 (CH), 130.0 (C), 130.8 (CH), 131.3 (CH×2), 133.5 (CH), 133.7, 145.7, 159.7 (C), 193.1 (CH); IR 3020,1690, 1595 cm^{-1}; HRMS (CI^+) calcd for $C_{14}H_{13}O_2$; 213.0916. Found: 213.0916.

4'-Bromobiphenyl-2-carbaldehyde *O*-phenyl oxime 139.

From 4'-bromobiphenyl-2-carbaldehyde (195 mg, 0.75 mmol), following procedure A. Brown solid (205 mg, 78 %); mp 80-82 °C. ^1H NMR (400 MHz, $CDCl_3$), δ_H; 6.93 (1H, t, *J* = 7.24 Hz, CH), 7.11 (4H, m, CH), 7.22 (3H, m, CH), 7.35 (2H, m, CH), 7.48 (2H, d, *J* = 8.6 Hz, CH), 8.00 (1H, d, *J* = 7.4 Hz, CH), 8.24 (1H, s, CH); ^{13}C NMR δ_C; 113.4 (CH×2), 121.0 (C), 121.3, 125.9, 127.0 (CH), 128.0 (C), 128.3 (CH×2), 129.1, 129.3 (CH), 130.3 (CH×2), 130.6 (CH×2), 137.2, 140.3 (C), 149.3 (CH), 158.3 (C); IR 3016, 1591, 1499 cm^{-1}; HRMS (ES^+) calcd for $C_{19}H_{15}NOBr$; 352.0337. Found: 352.0324.

2'-((Phenoxyimino)methyl)biphenyl-4-carbonitrile 140.

From 2'-formylbiphenyl-4-carbonitrile (155 mg, 0.75 mmol), following procedure A. Yellow solid, (165 mg, 74 %); mp 88-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 6.93 (1H, t, J = 7.3Hz, CH), 7.10 (2H, d, J = 8.4 Hz, CH), 7.18-7.25 (3H, m, CH), 7.34 (2H, d, J = 8.4 Hz, CH), 7.39 (2H, m, CH), 7.63 (2H, d, J = 8.4 Hz, CH), 8.01 (1H, d, J = 7.5 Hz, CH), 8.18 (1H, s, CH); ^{13}C NMR δ_C; 111.8 (C), 114.5 (CH×2), 118.7 (C), 122.7, 127.4, 128.9 (CH), 129.1 (C), 129.5 (CH×2), 130.2 (CH), 130.5 (CH×2), 130.6 (CH), 132.3 (CH×2), 140.6, 144.3 (C), 149.8 (CH), 159.3 (C); IR 3020, 1591, 1489 cm^{-1}; HRMS (CI^+) calcd for $C_{20}H_{15}N_2O$; 299.1184. Found: 299.1176.

4'-Methoxybiphenyl-2-carbaldehyde *O*-phenyl oxime 141.

From 4'-methoxybiphenyl-2-carbaldehyde (159 mg, 0.75 mmol), following procedure A. Brown solid, (159 mg, 70 %); mp 85-87 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 3.76 (3H, s, CH_3), 6.87-6.97 (3H, m, CH), 7.12-7.38 (9H, m, CH), 8.00 (1H, d, J = 7.5 Hz, CH), 8.31 (1H, s, CH); ^{13}C NMR δ_C; 55.4 (CH_3), 113.9 (CH×2), 114.4 (CH×2), 122.3, 126.8, 127.4 (CH), 129.1 (C), 129.4 (CH×2), 130.3, 130.5 (CH), 131.0 (CH×2), 131.7, 142.6 (C), 151.2 (CH), 159.4, 159.5 (C); IR 3065, 1592, 1478 cm^{-1}; HRMS (CI^+) calcd for $C_{20}H_{18}NO_2$; 304.1338. Found: 304.1338.

3-Bromophenanthridine 142.[76]

From 4'-bromobiphenyl-2-carbaldehyde *O*-phenyl oxime (100 mg, 0.284 mmol), following procedure C. Yellow solid, **(**53 mg, 73 %); mp 110-112 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.68 (2H, m, CH), 7.81 (1H, t, J = 7.7 Hz, CH), 7.98 (1H, d, J = 8.0 Hz, CH), 8.28 (1H, d, J = 1.9 Hz, CH), 8.35 (1H, d, J = 8.8 Hz, CH), 8.48 (1H, d, J = 8.8 Hz, CH), 9.20 (1H, s, CH); ^{13}C NMR δ_C; 121.9 (CH), 122.5 (C), 123.7 (CH), 126.4, 127.5 (C) 127.9, 129.0, 130.3, 131.6 (CH), 132.3 (C) 132.6 (CH), 146.3 (C), 154.7 (CH) ; IR 3019, 1595, 1476 cm^{-1}; HRMS (CI^+) calcd for $C_{13}H_9NBr$; 257.9918. Found: 257.9921.

Phenanthridine-3-carbonitrile 143.

From 2'-((phenoxyimino)methyl)biphenyl-4-carbonitrile (100 mg, 0.335 mmol), following procedure C. Yellow solid, (45 mg, 66 %); mp 117-119 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H;

7.75-7.83 (2H, m, CH), 7.90 (1H, t, *J* = 7.8 Hz, CH), 8.06 (1H, d, *J* = 7.7 Hz, CH), 8.46 (1H, d, *J* = 1.6 Hz, 1H), 8.58 (2H, d, *J* = 8.9 Hz, 2H), 9.31 (1H, s, CH); ^{13}C NMR δ_C; 112.0, 118.6 (C), 122.5, 123.7 (CH), 127.0, 127.4 (C), 128.7, 129.2, 129.4 (CH), 131.5 (C), 132.0, 135.1 (CH), 143.7 (C), 155.5 (CH); IR 3020, 2232, 1593, 1480 cm^{-1}; HRMS (ES$^+$) calcd for $C_{14}H_9N_2$; 205.0766. Found: 205.0764.

3-Methoxyphenanthridine 144.[77]

From 4'-methoxybiphenyl-2-carbaldehyde *O*-phenyl oxime (100 mg, 0.330 mmol), following procedure C. Brown solid, (43 mg, 62 %); mp 81-83 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 3.91 (3H, s, CH_3), 7.25 (1H, dd, *J* = 9.1, 2.7 Hz, CH), 7.53 (1H, d, *J* = 2.7 Hz, CH), 7.56 (1H, t, *J* = 7.6 Hz, CH), 7.76 (1H, t, *J* = 7.7 Hz), 7.95 (1H, d, *J* = 8.0 Hz, CH), 8.40 (1H, d, *J* = 9.0 Hz, CH), 8.44 (1H, d, *J* = 8.2 Hz, CH), 9.2 (1H, s, CH); ^{13}C NMR δ_C; 54.8 (CH_3), 108.9, 117.1, 120.4, 122.4 (CH), 124.6 (C×2), 125.4, 127.8, 130.2 (CH), 131.8, 145.2 9(C), 153.2 (CH), 159.4 (C); IR 3018, 1619, 1471 cm^{-1}; HRMS (CI$^+$) calcd for $C_{14}H_{12}NO$; 210.0919. Found: 210.0917.

1-(Biphenyl-2-yl)ethanone 147.[78]

From 1-(2-bromophenyl)ethanone (597 mg, 3 mmol) and phenylboronic acid (366 mg, 3 mmol), following procedure D. Clear oil, (370 mg, 63 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.03 (3H, s, CH_3), 7.35-7.47 (7H, m, CH), 7.53 (1H, dt, *J* = 7.5, 1.4 Hz, 1H), 7.58 (1H, dd, *J* = 7.5, 1.2 Hz, CH); ^{13}C NMR δ_C; 30.8 (CH_3), 127.5 (CH), 127.9 (CHx2), 128.7 (CHx2), 128.9 (CHx2), 130.3, 130.7 (CH), 140.4, 140.6, 140.8, 204.7 (C); IR 3060, 1688, 1594 cm^{-1}.

Biphenyl-2-yl(phenyl)methanone 148.[79]

From (2-bromophenyl)(phenyl)methanone (783 mg, 3 mmol) and phenylboronic acid (366 mg, 3 mmol), following procedure D. White crystals, (433 mg, 56 %), mp 85-87 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.00/7.18 (7H, m, CH), 7.48-7.25 (5H, m, CH), 7.57-7.52 (2H, m, CH); ^{13}C NMR δ_C; 127.2, 127.4 (CH), 128.1 (CHx2), 128.3 (CHx2), 128.8 (CH), 129.0 (CHx2), 130.0 (CHx2), 130.1, 130.4, 132.9 (CH), 137.5, 139.0, 140.2, 141.2, 199.3 (C); IR 3060, 1665, 1598 cm^{-1}.

1-Phenyl-2-naphthaldehyde 152.[80]

From 1-bromo-2-naphthaldehyde (705 mg, 3 mmol) and phenyl boronic acid (366 mg, 3 mmol), following procedure D. Light yellow oil, (487 mg, 70 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.27-7.35 (3H, m, CH), 7.40-7.45 (3H, m, CH), 7.51-7.56 (2H, m, CH), 7.81 (1H, d, *J* = 3.5 Hz, CH), 7.83 (1H, d, *J* = 3.8 Hz, CH), 7.97 (1H, d, *J* = 8.6 Hz, CH), 9.80 (1H, s, CH); ^{13}C NMR δ_C; 122.2, 126.9, 127.7 (CH), 128.3 (CH)x2, 128.3 (CH), 128.4 (CH)x2, 128.8 (CH), 131.0 (CH)x2, 131.2, 132.5, 135.2, 136.1, 146.6, 193.1 (C); IR 3020, 1684 cm^{-1}.

1-Phenyl-2-naphthaldehyde *O*-phenyl oxime 153.

From 1-phenyl-2-naphthaldehyde (174 mg, 0.75 mmol), following procedure A. Brown solid, (186 mg, 77 %); mp 97-99 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 6.93 (1H, t, *J* = 7.2 Hz, CH), 7.12-7.33 (7H, m, CH), 7.42 (5H, m, CH), 7.79 (2H, m, CH), 8.15 (1H, d, *J* = 8.8 Hz, CH), 8.17 (1H, s, CH); ^{13}C NMR δ_C; 114.6 (CH×2), 122.3, 122.6, 126.6 (CH), 127.0 (C), 127.1, 127.2, 128.0, 128.2, 128.3 (CH), 128.5 (CH×2), 129.4 (CH×2), 130.8 (CH×2), 132.8, 134.4, 137.0, 141.5 (C), 151.0 (CH), 159.5 (C); IR 3017, 1592, 1489 cm^{-1}; HRMS (CI^{+}) calcd for $C_{23}H_{18}NO$; 324.1388. Found: 324.1383.

Benzo[*k*]phenanthridine 154.[42]

From 1-phenyl-2-naphthaldehyde *O*-phenyl oxime (100 mg, 0.31 mmol), following procedure C. Brown solid (45 mg, 64 %); mp 108-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.66-7.77 (4H, m, CH), 7.89 (1H, d, *J* = 8.4 Hz, CH), 7.96 (1H, d, *J* = 8.4 Hz, CH), 8.02 (1H, d, *J* = 7.0 Hz, CH), 8.26 (1H, d, *J* = 8.1, 1.6 Hz, CH), 9.05 (1H, d, *J* = 8.5 Hz, CH), 9.15 (1H, d, *J* = 8.0 Hz, CH), 9.29 (1H, s, CH); ^{13}C NMR δ_C; 119.0, 124.1 (CH), 124.2 (C), 125.8, 125.9, 126.0 (CH), 126.5 (C), 127.1, 127.2 (CH), 127.4 (C), 127.8, 128.0, (CH), 128.0, (C), 129.2 (CH), 134.2, 145.7 (C), 151.6 (CH); IR 2923, 1579, 1451, 1381 cm^{-1}.

6-Phenylbenzo [d] [1,3]dioxole-5-carbaldehyde 156.

From 6-bromopiperonal (687 mg, 3 mmol) and phenylboronic acid (366 mg, 3 mmol) following procedure D. Clear oil (413 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 6.00 (s, 2H, CH_2), 6.78 (s, 1H, CH), 7.27 (m, 2H, CH), 7.36 (m, 3H, CH), 7.40 (s, 1H, CH), 9.67 (s,

1H, CH); ^{13}C NMR δ_C; 102.4 (CH_2), 106.6, 110.5, 128.2, 128.4, 130.1 (CH), 137.4, 143.8, 147.8, 152.3, 127.8 (C), 190.6 (CH); IR 3058, 2907, 1677 cm^{-1}; HRMS (CI^+) calcd for $C_{14}H_{11}O_3$; 227.0708. Found 227.0704.

6-Phenylbenzo[*d*][1,3]dioxole-5-carbaldehyde *O*-phenyl oxime 157.

From 6-phenylbenzo [d] [1,3]dioxole-5-carbaldehyde (169 mg, 0.75 mmol), following procedure A. Yellow solid, (183 mg, 77%); mp 115-117 °C. ^{1}H NMR (400 MHz,$CDCl_3$), δ_H; 5.99 (2H, s, CH_2), 6.74 (1H, s, CH), 6.94 (1H, t, *J* = 7.2 Hz, CH), 7.13 (2H, m, CH), 7.20-7.28 (4H, m, CH), 7.31-7.41 (3H, m, CH), 7.51 (1H, s, CH), 8.18 (1H, s, CH); ^{13}C NMR δ_C; 101.8 (CH_2), 105.7, 110.3 (CH), 114.5 (CH×2), 122.2 (CH), 123.0 (C), 127.7 (CH), 128.5 (CH×2), 129.4 (CH×2), 129.9 (CH×2), 138.5, 139.2, 147.5, 149.6 (C), 150.6 (CH), 159.5 (C); IR 3062, 2908, 1591, 1475 cm^{-1}; HRMS (CI^+) calcd for $C_{20}H_{16}NO_3$: 318.1130. Found: 318.1128.

[1,3]Dioxolo[4,5-*j*]phenanthridine. Trisphaeridine 158.[42]

From 6-phenylbenzo[*d*][1,3]dioxole-5-carbaldehyde *O*-phenyl oxime (100 mg, 0.315 mmol), following procedure C. Brown solid (49 mg, 70 %); mp 144-146 °C [lit. 138-140 ^oC][42]. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 6.00 (2H, s, CH_2), 7.33 (1H, s, CH), 7.62 (1H, td, *J* = 7.5, 1.5, CH), 7.62 (1H, td, *J* = 7.5, 1.2 Hz, CH), 7.91 (1H, s, CH), 8.13 (1H, dd, *J* = 7.4, 1.2 Hz, CH), 8.37 (1H, dd, *J* = 8.4, 1.2 Hz, CH), 9.08 (1H, s, CH); ^{13}C NMR δ_C; 99.9 (CH), 101.9 (CH_2), 105.5, 122.0 (CH), 123.0, 124.3 (C), 126.7, 128.0, 130.0 (CH), 130.3, 144.0, 148.2, 151.5 (C), 151.7 (CH); IR 2904, 1620, 1580, 1498, 1464 cm^{-1}; HRMS (CI^+) calcd for $C_{14}H_{10}NO_2$; 224.0712. Found: 224.0712.

6-(Pyridin-4-yl)benzo[d][1,3]dioxole-5-carbaldehyde 160.

From 6-bromopiperonal (687 mg, 3 mmol) and pyridin-4-ylboronic acid (369 mg, 3 mmol) following procedure D. Yellow oil, (394 mg, 58%). ^{1}H NMR (400MHz,$CDCl_3$), δ_H; 6.04 (s, 2H, CH_2), 6.74 (s, 1H, CH), 7.20 (d, *J* = 5.3 Hz, 2H, CH), 7.38 (s, 1H, CH), 8.61 (m, 2H, CH), 9.64 (s, 1H, CH); ^{13}C NMR δ_C; 102.5 (CH_2), 106.7, 109.8, 124.8 x 2 (CH), 128.7, 140.2, 145.5, 148.7 (C), 149.8 x 2 (CH), 152.4 (C), 189.5 (CH); IR 3019**,** 2917, 1677; HRMS (ES^+) calcd for $C_{13}H_{10}NO_3$; 228.0661. Found 228.0651.

6-(Pyridine-4-yl)benzo[*d*][1,3]dioxole-5-carbaldehyde *O*-phenyl oxime 161.

From 6-(pyridin-3-yl)benzo[d][1,3]dioxole-5-carbaldehyde (170 mg, 0.75 mmol), following procedure A. Yellow solid, (169 mg, 71 %); mp 133-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 5.97 (2H, s, CH_2), 6.69 (1H, s, CH), 6.93 (1H, t, *J* = 7.3 Hz, CH), 7.07-7.27 (6H, m, CH), 7.50 (1H, s, CH), 8.13 (1H, s, CH), 8.61 (2H, m, CH); ^{13}C NMR δ_C; 101.9 (CH_2), 106.0 (CH), 109.6 (CH), 114.5 (CH×2), 122.4 (CH×2), 123.1 (C), 124.7 (CH), 129.4 (CH×2), 135.0, 147.0, 148.5 (C), 149.5 (CH), 149.9 (C), 150.0 (CH×2), 159.2 (C); IR 3020, 1593, 1482 cm^{-1}; HRMS (CI^+) calcd for $C_{19}H_{15}N_2O_3$; 319.10.83. Found: 319.1082.

2-Phenylnicotinaldehyde 168.

From 2-bromonicotinaldehyde (558 mg, 3 mmol) and phenylboronic acid (366 mg, 3 mmol) following procedure D. Yellow oil, (378 mg, 69 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.35 (1H, dd, *J* = 7.9, 4.7 Hz, CH), 7.46-7.40 (3H, m, CH), 7.53-7.49 (2H, m, CH), 8.22 (1H, dd, *J* = 7.8, 1.9 Hz, CH), 8.79 (1H, dd, *J* = 4.8, 1.8 Hz, CH), 9.98 (1H, s, CH); ^{13}C NMR δ_C; 122.5 (CH), 128.6 (CH×2), 129.5 (C), 129.6 (CH), 130.4 (CH×2), 135.9 (CH), 137.0 (C), 153.3 (CH), 162.2 (C), 191.5 (CH). IR 3020, 1699, 1583 cm^{-1}; HRMS (CI^+) calcd for $C_{12}H_{10}NO$; 184.0762. Found: 184.0761

2-(4-Bromophenyl)nicotinaldehyde 169.

From 2-bromonicotinaldehyde (558 mg, 3 mmol) and 4-bromophenylboronic acid (600 mg, 3 mmol), following procedure D. White solid, (510 mg, 65 %); mp 84-86 °C. ^{1}H NMR (400MHz,$CDCl_3$), δ_H; 7.33 (1H, m, CH), 7.35 (2H, d, *J* = 8.6 Hz, CH), 7.53 (2H, d, *J* = 8.6 Hz, CH), 8.16 (1H, dd, *J* = 7.9, 1.8 Hz, CH), 8.74 (1H, dd, *J* = 4.7, 1.7 Hz, CH), 9.91 (1H, s, CH); ^{13}C NMR δ_C; 121.8 (CH), 123.3, 128.5 (C), 130.7 (CH×2), 130.8 (CH×2), 134.9 (C), 135.0, 152.4 (CH), 160.0 (C), 190.1 (CH); IR 3019, 1696, 1580 cm^{-1}; HRMS (CI^+) calcd for $C_{12}H_9NOBr$; 261.9868. Found: 261.9870.

4-(3-Formylpyridin-2-yl)benzonitrile 170.

From 2-bromonicotinaldehyde (558 mg, 3 mmol) and 4-cyanophenylboronic acid (441 mg, 3 mmol), following procedure D. White solid, (565 mg, 63 %); mp 138-140 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.46 (1H, t, *J* = 8.0, CH), 7.65 (2H, d, *J* = 8.5 Hz, CH), 7.76 (2H, d, *J* = 8.5

Hz, CH), 8.27 (1H, dd, *J* = 7.9, 1.8 Hz, CH), 8.84 (1H, dd, *J* = 4.7, 1.7 Hz, CH), 9.97 (1H, s, CH); ^{13}C NMR δ_C; 113.5, 118.3 (C), 123.6 (CH), 129.8 (C), 131.0 (CH×2), 132.4 (CH×2), 136.4 (CH), 141.5 (C), 153.8 (CH), 160.0 (C), 190.8 (CH); IR 3020, 2233**,** 1699, 1581 cm^{-1}; HRMS (CI$^+$) calcd for $C_{13}H_9N_2O$; 209.0715. Found: 209.0712.

2-Phenylnicotinaldehyde *O*-phenyl oxime 171.

From 2-phenylnicotinaldehyde (137 mg, 0.75 mmol), following procedure A. Brown solid, (147 mg, 72 %); mp 78-80 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 6.95 (1H, t, *J* = 7.1 Hz, CH), 7.14 (2H, m, CH), 7.20-7.27 (3H, m, CH), 7.33-7.49 (5H, m, CH), 8.30 (1H, dd, *J* = 7.9, 1.7 Hz, CH), 8.35 (1H, s, CH), 8.64 (1H, dd, *J* = 4.7, 1.6 Hz, CH); ^{13}C NMR δ_C; 113.5 (CH×2), 121.3, 121.5 (CH), 124.2 (C), 127.5 (CH×2), 127.9 (CH), 128.3 (CH×2), 128.7 (CH×2), 133.8 (CH), 137.3 (C), 148.5, 150.0 (CH), 157.8, 158.2 (C); IR 3060, 1591, 1489 cm^{-1}; HRMS (CI$^+$) calcd for $C_{18}H_{15}N_2O$; 275.1184. Found: 275.1188.

2-(4-Bromophenyl)nicotinaldehyde *O*-phenyl oxime 172.

From 2-(4-bromophenyl)nicotinaldehyde (196 mg, 0.75 mmol), following procedure A. Brown solid, (198 mg, 75 %); mp 90-91 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 6.95 (1H, t, *J* = 7.3 Hz, CH), 7.13 (2H, m, CH), 7.24 (3H, m, CH), 7.35 (2H, d, *J* = 8.6 Hz, CH), 7.54 (2H, d, *J* = 8.6 Hz, CH), 8.28 (1H, dd, *J* = 8.01, 1.7 Hz, CH), 8.31 (1H, s, CH), 8.63 (1H, dd, *J* = 4.7, 1.7 Hz, CH); ^{13}C NMR δ_C; 114.5 (CH×2), 122.7 (CH×2), 123.7, 125.3 (C), 129.5 (CH×2), 131.4 (CH×x2), 131.8 (CH×2), 135.1 (CH), 137.3 (C), 149.2, 151.1 (CH), 157.6, 159.2 (C); IR 3018, 1592, 1490 cm^{-1}; HRMS (CI$^+$) calcd for $C_{18}H_{14}N_2OBr$; 353.0289. Found: 353.0283.

4-(3-((Phenoxyimino)methyl)pyridine-2-yl)benzonitrile 173.

From 4-(3-((phenoxyimino)methyl)pyridine-2-yl)benzonitrile (156 mg, 0.75 mmol), following procedure A. Brown solid, (166 mg, 74 %); mp 100-102 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 6.99 (1H, t, *J* = 7.3 Hz, CH), 7.14 (2H, m, CH), 7.27 (2H, m, CH), 7.35 (1H, dd, *J* = 7.87, 4.77 Hz, CH), 7.62 (2H, d, *J* = 8.38 Hz, CH), 7.73 (2H, d, *J* = 8.38 Hz, CH), 8.30 (1H, s, CH), 8.35 (1H, dd, *J* = 8.03, 1.7 Hz, CH), 8.70 (1H, dd, *J* = 4.68, 1.73 Hz); ^{13}C NMR δ_C; 112.9 (C), 114.4 (CH×2), 118.5 (C),122.9, 123.4 (CH), 127.7 (C), 129.5 (CH×2), 130.5

(CH×2), 132.4 (CH×2), 135.4 (CH), 142.9 (C), 148.5, 151.2 (CH), 156.6, 159.1 (C); IR 3018, 2230, 1591, 1489, 1427 cm^{-1}; HRMS (CI^+) calcd for $C_{19}H_{14}N_3O$; 300.1136. Found: 300.1137.

Benzo[*h*][1,6]naphthyridine 174.[81]

From 2-phenylnicotinaldehyde *O*-phenyl oxime (100 mg, 0.364 mmol), following procedure C. Brown solid, (43 mg, 66 %); mp 95-97 °C. ^1H NMR (400 MHz, $CDCl_3$), δ_H; 7.60 (1H, dd, *J* = 8.0, 4.4 Hz, CH), 7.72 (1H, t, *J* = 7.6 Hz, 7.81 (1H, t, *J* = 7.6 Hz, CH), 8.20 (1H, d, *J* = 8.3 Hz, CH), 8.31 (1H, dd, *J* = 8.0, 1.8 Hz, CH), 9.10 (1H, d, *J* = 8.0 Hz, CH), 9.14 (1H, dd, *J* = 4.4, 1.8 Hz, CH), 9.27 (1H, s, CH); ^{13}C NMR δ_C; 120.3 (C), 120.7 (CH), 125.1 (C), 127.6, 127.8, 129.2, 129.4, 140.8 (CH), 146.2, 147.4 (C), 151.6, 152.4 (CH); IR 1589, 1440 cm^{-1}; HRMS (CI^+) calcd for $C_{12}H_9N_2$; 181.0766. Found: 181.0761.

8-Bromobenzo[*h*][1,6]naphthyridine 175.

From 2-(4-bromophenyl)nicotinaldehyde *O*-phenyl oxime (100 mg, 0.283 mmol), following procedure C. Brown solid, (46 mg, 63 %); mp111-113 °C. ^1H NMR (400 MHz, $CDCl_3$), δ_H; 7.60 (1H, dd, *J* = 8.1, 4.5 Hz, CH), 7.79 (1H, dd, *J* = 8.8, 2.2 Hz, CH), 8.28 (1H, dd, *J* = 8.1, 1.8 Hz, CH), 8.31 (1H, d, *J* = 2.0 Hz, CH), 8.94 (1H, d, *J* = 8.7 Hz, CH), 9.11 (1H, dd, *J* = 4.5, 1.7 Hz, CH), 9.23 (1H, s, CH); ^{13}C NMR δ_C; 120.9 (C), 123.1 (CH), 124.2, 124.5 (C), 125.3, 131.0, 131.9, 136.2 (CH), 147.4, 148.3 (C), 153.7, 153.9 (CH); IR 1585, 1440, cm^{-1}; HRMS (CI^+) calcd for $C_{12}H_8N_2Br$; 258.9871. Found 258.9870.

Benzo[*h*][1,6]naphthyridine-8-carbonitrile 176.

From 4-(3-((phenoxyimino)methyl)pyridine-2-yl)benzonitrile (100 mg, 0.334 mmol), following procedure C. Brown solid, (47 mg, 68 %); mp 116-118 °C. ^1H NMR (400 MHz, $CDCl_3$), δ_H; 7.30 (1H, dd, *J* = 8.1, 4.4 Hz, CH), 7.88 (1H, dd, *J* = 8.51, 1.7 Hz,), 8.35 (1H, dd, *J* = 8.1, 1.8 Hz, CH), 8.48 (1H, d, *J* = 1.4, CH), 9.17-9.20 (2H, m, CH), 9.34 (1H, s, CH); ^{13}C NMR δ_C; 112.7, 117.5, 120.9 (C), 123.2, 124.3 (CH), 127.5 (C), 128.2, 133.6, 135.3 (CH), 144.8, 146.7 (C), 153.0, 153.5 (CH); IR 2228, 1586, 1440 cm^{-1}; HRMS (CI^+) calcd for $C_{13}H_8N_3$; 206.0718. Found: 206.0728.

4-(1*H*-indol-3-yl)butan-2-one 179.[82]

To a mixture of indole (1.0 g, 8.5 mmol), buten-3-en-2-one (0.59 g, 8.5 mmol) in DCM (25 mL), at room temperature was added $ZrCl_4$ (45 mg, 0.2 mmol) and the reaction mixture was stirred for 30 min. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water (20 mL) and extracted with DCM (3 × 20 mL). The organic phase was washed twice with saturated brine solution and dried over $MgSO_4$. The solvent was evaporated and the residue chromatographed on silica gel to give the product as a white solid (1.41 g, 89% yield); mp 70-72 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.18 (3H, s, CH_3), 2.88 (2H, t, J = 7.3 Hz, CH_2), 3.10 (2H, t, J = 7.3 Hz, CH_2), 6.99 (1H, m, CH), 7.15- 7.28 (2H, m, CH), 7.37 (1H, d, J = 8.2 Hz, CH), 7.63 (1H, d, J = 7.8 Hz, CH), 8.09 (1H, s, NH); ^{13}C NMR δ_C; 19.4 (CH_2), 29.9 (CH_3), 44.0 (CH_2), 111.1 (CH), 115.0 (C), 118.6, 119.2, 121.5, 122.0 (CH), 127.0, 136.2, 208.9 (C); IR 3479, 1712, 1457 cm^{-1}.

4-(5-Bromo-1*H*-indol-3-yl)butan-2-one 180.[82]

To a mixture of 5-bromo-1*H*-indole (2.0 g, 17 mmol), but-3-en-2-one (1.18 g, 17 mmol) in DCM (40 mL), at rt was added $ZrCl_4$ (90 mg, 0.4 mmol) and the reaction mixture was stirred for 30 min. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water (30 mL) and extracted with DCM (3 × 20 mL). The organic phase was washed twice with saturated brine solution and dried over $MgSO_4$. The solvent was evaporated and the residue chromatographed on silica gel to give the product as a white solid (3.7 g, 82 %); mp 71-73 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.17 (3H, s, CH_3), 2.84 (2H, t, J = 7.3 Hz, CH_2), 3.01 (2H, t, J = 7.3 Hz, CH_2), 7.00 (1H, m, CH), 7.22-7.30 (2H, m, CH), 7.63 (1H, m, CH), 8.11 (1H, s, NH) ; ^{13}C NMR δ_C; 19.0 (CH_2), 30.1 (CH_3), 43.9 (CH_2), 112.5 (CH), 112.6, 114.9 (C), 121.3, 122.8, 124.8 (CH), 128.9, 134.9, 208.5 (C); IR 3475, 1711, 1459 cm^{-1}.

4-(1*H*-indol-3-yl)butan-2-one *O*-phenyl oxime 181.

From 4-(1*H*-indol-3-yl)butan-2-one (140 mg, 0.75 mmol), following procedure A. Yellow solid, (141 mg, 68 %); mp 48-50 °C; two isomers (1:3). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.88/1.99 (3H, s, CH_3), 2.65/2.83 (2H, m, CH_2), 2.97/3.00 (2H, m, CH_2), 6.88-6.93 (2H, m, CH), 7.02-7.14 (4H, m, CH), 7.17-7.26 (3H, m, CH), 7.58/7.54 (1H, d, J = 7.9 Hz, CH), 7.79 (1H, s, NH); ^{13}C NMR δ_C; 15.0/20.4 (CH_3), 21.6/22.0 (CH_2), 36.5/36.7 (CH_2), 111.3 (CH),

114.7 (CH×2), 115.4 (C), 118.8, 119.4, 121.3/121.5, 121.8/121.9, 122.1/122.2 (CH), 127.4 (C), 129.3 (CH×2), 136,6, 159.7, 161.5/162.3 (C); IR 3421, 1589, 1489 cm^{-1}; HRMS (CI^+) calcd for $C_{18}H_{19}N_2O$; 279.1497. Found: 279.1496.

4-(5-Bromo-1H-indol-3-yl)butan-2-one *O*-phenyl oxime 182.

From 4-(5-bromo-1H-indol-3-yl)butan-2-one (199 mg, 0.75 mmol), following procedure A. Brown solid, (190 mg, 71 %); mp 50-52 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.84/1.96 (3H, s, CH_3), 2.58/2.76 (2H, t, *J*= 7.4 Hz, CH_2), 2.89 (2H, m, CH_2), 6.80/6.93 (2H, m, CH), 6.99-7.21 (6H, m, CH), , 7.63/7.69 (1H, d, *J*= 1.9 Hz, CH), 7.83 (1H, s, NH); ^{13}C NMR δ_C; 14.0/19.2 (CH_3), 20.3/20.6, 29.4/35.2 (CH_2), 111.5 (C), 111.6 (CH), 113.6 (CHx2), 113.8 (C), 120.3, 120.8, 121.5, 121.7, 123.8 (CH), 128.0 (C), 128.2 (CHx2), 133.8, 161.1, 160.8 (C); IR 3430, 1589, 1489 cm^{-1}; HRMS (CI^+) calcd for $C_{11}H_{27}N_2O_2Br$; 379.0419. Found: 379.0418.

2-Methyl-9*H*-pyrido[2,3-*b*]indole 183.[83]

From 4-(1*H*-indol-3-yl)butan-2-one *O*-phenyl oxime (100 mg, 0.359), following procedure C. Brown solid, (39 mg, 59 %); mp 219-220°C**.** ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.67 (3H, s, CH_3), 7.00 (1H, d, *J* = 7.8 Hz, CH), 7.18 (1H, m, CH), 7.43 (2H, m, CH), 7.95 (1H, d, *J* = 7.7 Hz, CH), 8.17 (1H, d, *J* = 7.8 Hz, CH), 9.42 (1H, s, NH); ^{13}C NMR δ_C; 24.2 (CH_3), 111.3, 115.3 (CH), 115.5 (C), 120.4, 120.7 (CH), 120.8 (C), 126.6, 129.4 (CH), 139.5, 143.8, 146.3 (C); IR 1602, 1456, 1417 cm^{-1}; HRMS (CI^+) calcd for $C_{12}H_{11}N_2$; 183.0922. Found: 183.0928.

6-Bromo-2-methyl-9*H*-pyrido[2,3-*b*]indole 184.

From 4-(5-Bromo-1H-indol-3-yl)butan-2-one *O*-phenyl oxime (100 mg, 0.280 mmol), following procedure C. White solid, (34 mg, 47 %); mp 233-235 °C**.** ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.64 (3H, s, CH_3), 7.16 (1H, d, *J* = 7.9 Hz, CH), 7.48 (1H, d, *J* = 8.4 Hz, CH), 7.57 (1H, dd, *J* = 8.6, 1.9 Hz, CH), 8.40 (1H, d, *J* = 1.8 Hz, CH), 8.47 (1H, d, *J* = 7.8 Hz, CH), 11.8 (1H, s, NH); ^{13}C NMR δ_C; 25.0 (CH_3), 113.5, 115.5 (CH), 122.7 (C), 123.7 (CH), 127.3 (C), 128.6, 129.7 (CH), 137.2, 145.9, 152.0, 156.1 (C); IR 3128, 2931, 1607, 1455 cm^{-1}.

2-((1*H*-Indol-3-yl)methyl)cyclohexanone 187.

A solution of gramine (2 g, 11.5 mmol) and 1-(1-(cyclohexen-1-yl)pyrrolidine (1.74 g, 11.5 mmol) in dioxane (20 mL) was heated under reflux for 24 h. The mixture was poured into water (25 mL) and stirred for 30 minutes. The emulsion was extracted with DCM (3 x 15 ml). The organic layer was dried over $MgSO_4$ and concentrated in vacuo and the residual oil was subjected to column chromatography over silica gel (5% EtOAc/hexane) to yield a brown solid, (2.03 g, 78 %); 48-50 °C. ^{1}H NMR (400MHz,$CDCl_3$), δ_H; 1.44 (1H, m, CH_2), 1.54-1.78 (2H, m, CH_2), 1.83 (1H, m, CH_2), 2.04-2.19 (2H, m, CH_2), 2.37 (1H, m, CH_2), 2.48 (1H, m, CH_2), 2.68 (2H, m, CH, CH_2), 3.36 (1H, m, CH_2), 7.03 (1H, d, *J* = 2.3 Hz, CH), 7.14 (1H, t, *J* = 7.3 Hz, CH), 7.22 (1H, t, *J* = 7.4 Hz, CH), 7.38 (1H, d, *J* = 8.0 Hz, CH), 7.59 (1H, d, *J* = 7.8 Hz, CH), 8.06 (1H, s, NH); ^{13}C NMR δ_C; 24.7, 25.0, 28.1, 33.9, 42.3 (CH_2), 51.5, 111.2 (CH), 114.1 (C), 118.8, 119.2, 121.9, 122.6 (CH), 127.7, 136.2, 213.6 (C); IR 3412, 3055, 2936, 1702, 1456 cm^{-1}; HRMS (CI^+) calcd for $C_{15}H_{17}NO$; 227.1310. Found: 227.1314.

2-((1*H*-Indol-3-yl)methyl)cyclohexanone *O*-phenyl oxime 188.

From 2-((1*H*-Indol-3-yl)methyl)cyclohexanone (170 mg, 0.75 mmol), following procedure A. Brown gum, (167 mg, 70 %); two isomers (4:1). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.34-3.98 (11H, m, CH_2, CH), 6.86-7.30 (9H, m, CH), 7.55/7.70 (1H, d, *J* = 7.8 Hz, CH), 7.80/7.86 (1H, s, NH); ^{13}C NMR δ_C; 24.0, 25.3, 26.5, 26.5, 32.8 (CH_2), 43.2, 111.1 (CH), 113.8 (C), 114.5 (CH×2), 119.0, 119.3, 121.5, 121.9, 122.5 (CH), 129.3 (CH×2), 127.8, 136.3, 159.8, 165.9 (C); IR 3421, 2933, 1590, 1488 cm^{-1}; HRMS (CI^+) calcd for $C_{21}H_{22}N_2O$; 318.1731. Found: 318.1745.

6*H*-1,2,3,4-Tetrahydroindolo[2,3-*b*]quinoline 189.[84]

From 2-((1*H*-Indol-3-yl)methyl)cyclohexanone *O*-phenyl oxime (100 mg, 0.314 mmol), following procedure C. Brown solid, (48 mg, 69 %); mp 220-221 °C**.** ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 1.79-1.98 (4H, m, CH_2), 2.90 (2H, t, *J* = 6.11 Hz, CH_2), 3.10 (2H, t, *J* = 6.5 Hz, CH_2), 7.16 (1H, t, *J* = 7.4 Hz, CH), 7.36 (1H, t, *J* = 7.5 Hz, CH), 7.43 (1H, d, *J* = 8.1 Hz, CH), 7.91 (1H, d, *J* = 7.7 Hz, CH), 7.96 (1H, s, CH), 10.20 (1H, s, NH) ; ^{13}C NMR δ_C; 22.2, 22.2, 28.0, 31.7 (CH_2), 110.2 (CH), 113.9 (C), 118.8, 119.6 (CH), 120.1, 122.8 (C), 125.4,

128.5 (CH), 137.9. 149.4, 152.5 (C); IR 3128, 2931, 1609, 1458 cm^{-1}; HRMS (CI^{+}) calcd for $C_{15}H_{15}N_2$; 223.1235. Found: 223.1231.

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Chapter 3

Addition of Iminyl Radicals onto Imines; Syntheses of Quinazolines Promoted by Microwaves

1.0 Introduction.

1.1 Quinazolines.

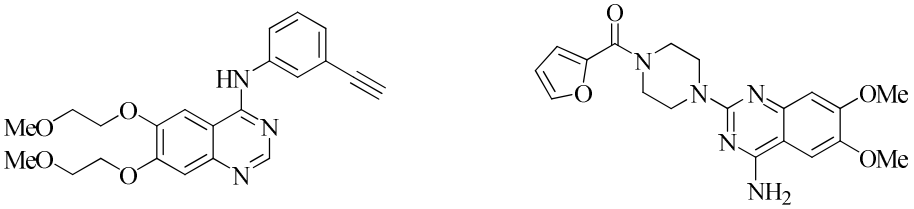
Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide.[1] In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. 4(3*H*)-Quinazolinones **1** and related quinazolines **2** are classes of fused heterocycles that are of considerable interest (Figure 1).

1 **2**

Figure 1

For quinazolines, an increase in potency over other Tyrosine Kinase inhibitors of 4-5 orders of magnitude has been demonstrated for the inhibition of isolated epidermal growth factor receptor (EGFR) Tyrosine Kinase and 3-4 orders of magnitude for the inhibition of cellular phosphorylation.[2] They have shown remarkable activity as antitubercular,[3] antiviral,[4] and anticancer agents.[5] These have been used as DNA ligands[6] and also have shown binding to benzodiazepines and adenosine receptors,[7] as well as being proved to be potent antibacterial agents.[8]

The growing medicinal importance of these heterocycles is demonstrated in Figure 2, where two top-selling drugs, Erlotinib and Prazosin are represented. Erlotinib[9] is a drug used to treat non-small cell lung cancer, pancreatic cancer and several other types of tumors. It specifically targets the epidermal growth factor receptor (EGFR) tyrosine kinase, which is highly expressed and occasionally mutated in various forms of cancer. The other drug, Prazosin,[10] belongs to the class of alpha-adrenergic blockers. It is selective for the alpha-1-receptors on vascular smooth muscle and reduces blood pressure.



Erlotinib ***Prazosin***

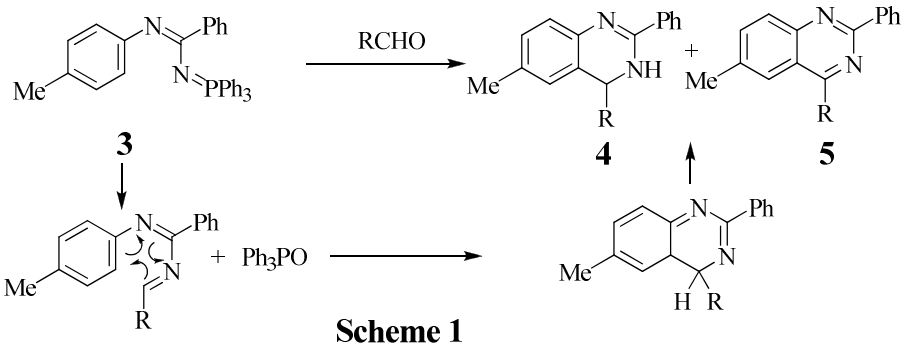
Figure 2

The quinazolines represent a useful natural product scaffold with demonstrated activities against numerous disorders. The transferable nature of their properties provides a strong rationale for the development of synthetic methods for their preparation.

1.2 Syntheses of quinazolines.

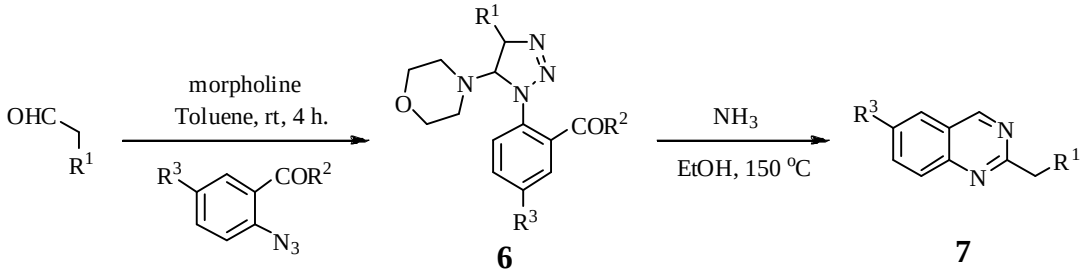
Studies on quinazoline compounds and quinazoline natural products have a long history, however, remarkable progress in synthetic methodology applicable to syntheses of quinazoline alkaloids and related molecules has been attained during the last decade. These efforts have led to several reviews emphasising the synthesis[11] and biological evaluation of quinazolines.

The utilization of aza-Wittig methods for the synthesis of heterocyclic natural products is spreading out to a variety of nitrogen heterocycles from simple alkaloids to complex functionalized natural products.[12] Rossi et al.[13] have utilized the tandem aza-Wittig/6π-electrocyclization principle for synthesis of quinazoline rings **4** and **5** starting from N-imidoyl iminophosphorane **3** (Scheme 1).



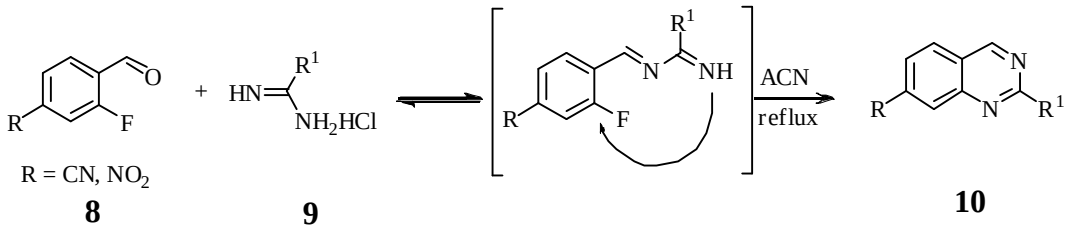
Scheme 1

Erba et al.[14] employed a three-component reaction to form 2-alkylquinazolines from the reaction of amidines with ammonia. In the first step, an aldehyde was reacted with morpholine and, subsequently, with an aryl azide to afford the triazolines **6**. On exposure to a saturated ethanolic solution of ammonia in a sealed vessel at 150 °C, the triazolines were converted into the desired quinazolines **7** (Scheme 2).



Scheme 2

A condensation methodology of cyano- and nitro-activated *o*-fluorobenzaldehydes **8** with amidines **9** to give a variety of quinazoline derivatives **10** has been introduced by Kotsuki and co-workers.[15] This method involves tandem imine formation with the aldehyde function and an intramolecular nucleophilic aromatic substitution at the fluorine-substituted carbon centre (Scheme 3).



Scheme 3

Recently, there has been a renewal of interest in 4-arylamino-quinazolines, owing to reports of their high biological activity as potential antitumour agents.[16] In May 2003, the US Food and Drug Administration (FDA) approved the first epidermal growth factor receptor inhibitor, Iressa, for the treatment of lung cancer, further highlighting the importance of the 4-anilinoquinazolines in medicine (Figure 3).

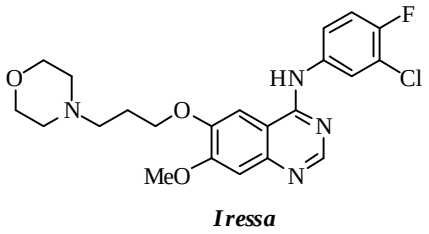
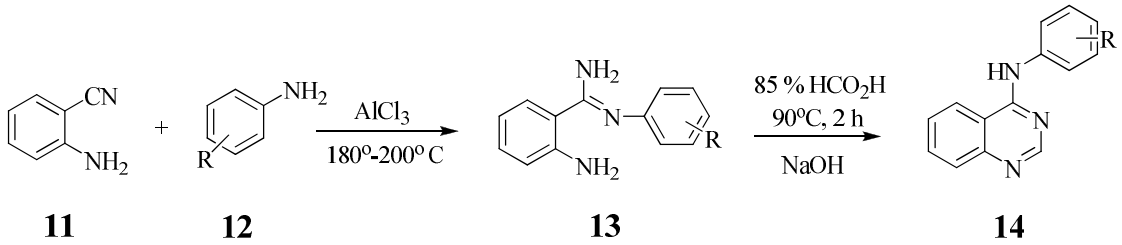


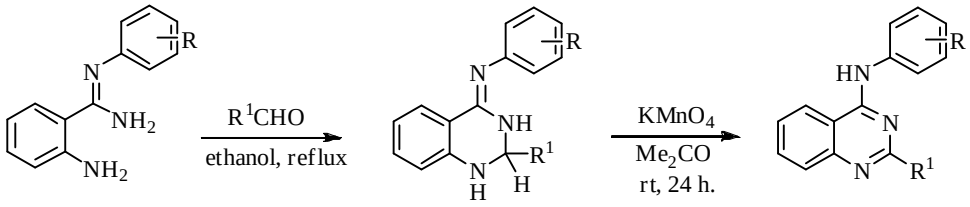
Figure 3

Szczepankiewicz et al.[17] have extensively studied the synthesis of 4-arylamino-quinazolines. Amidines **13** are readily synthesised from the reaction of 2-aminobenzonitrile **11** with aniline **12** and anhydrous aluminium chloride. The 2-amino-N-arylbenzamines **13** furnished the 4-aryl-aminoquinazolines **14** in good yields when heated with 85 % formic acid (Scheme 4).



Scheme 4

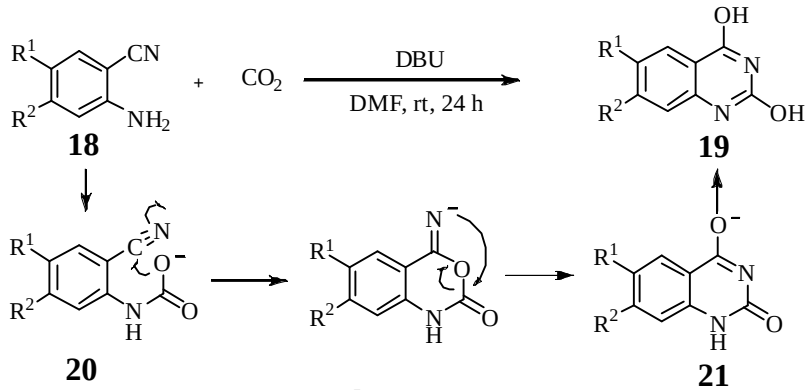
This reaction can only be applied to the synthesis of 2-unsubstituted 4-arylamino-quinazolines. Szczepankiewicz's group[18] modified its procedure so that the 2-amino-N-arylbenzamide **15** employed could be reacted with benzaldehyde or its ring-substituted derivatives to afford the 2-aryl-4-arylimino-(1*H*)-2,3-dihydroquinazolines **16**. Treatment of these dihydroquinazoline derivatives with potassium permanganate afforded the corresponding aromatic quinazolines **17** (Scheme 5).



15 **16** **17**

Scheme 5

2,4-Dihydroxyquinazolines have also been subjects of interest. Mizuno and coworkers[19] developed a synthesis of quinazolines **19** using 2-aminobenzonitrile and carbon dioxide in the presence of DBU under mild conditions. Carbon dioxide reacts with 2-aminobenzonitriles **18** in the presence of a suitable base to generate the carbamate salt **20**. This is followed by nucleophilic cyclisation with attack of the carbamate oxygen on the nitrile functionality. A rearrangement then occurs to afford the intermediate **21**, which is protonated to yield the desired 2,4-dihydroxyquinazolines **19** (Scheme 6).



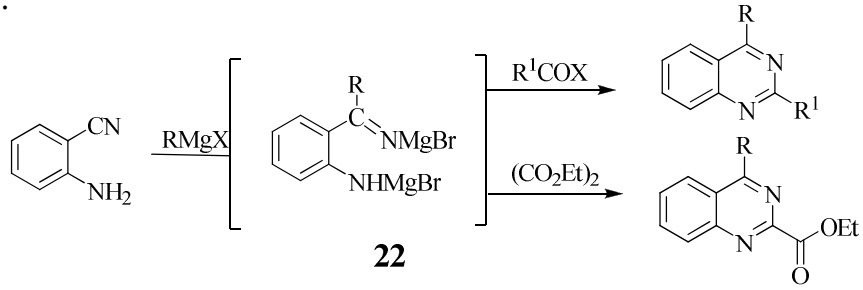
18 **19**

20 **21**

Scheme 6

The research of Bergman et al.[20] demonstrated that 2-aminobenzonitrile reacted with Grignard reagents and the resulting intermediate **22** was useful in accessing a variety of important quinazoline derivatives. Cyclisation of the intermediate **22** after reaction with acid

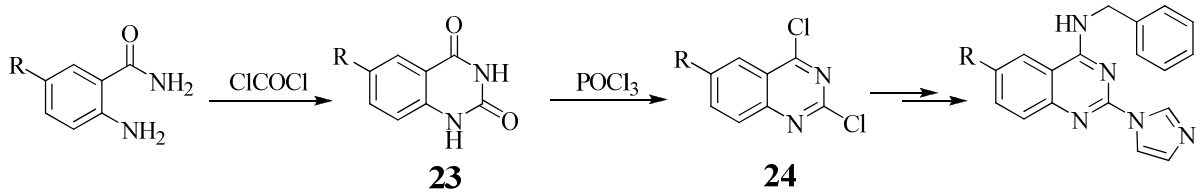
chlorides and anhydrides produced the respective quinazolines in moderate to good yields (Scheme 7).



22

Scheme 7

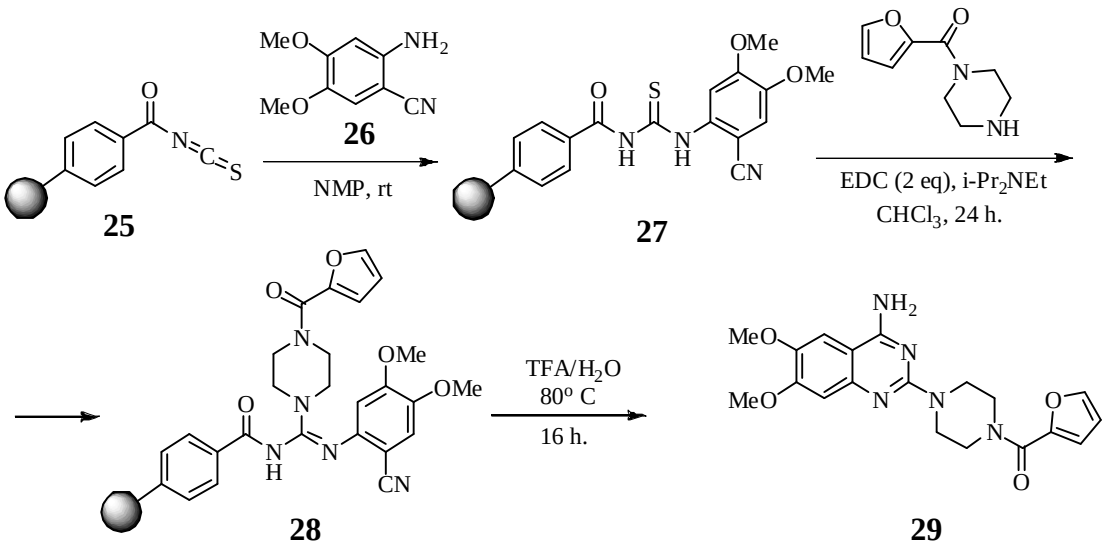
Other quinazolines, which constitute key intermediates in syntheses of numerous biologically active compounds, are the 2,4-dichloroquinazolines. Lee et al.[21] exploited the differential reactivity of 2,4-dichloroquinazoline derivatives **24** as part of their structure-activity relationship studies of phosphodiesterase inhibitors. The 6-substituted quinazoline-2,4-diones **23** were readily prepared from the anthranilamides by treatment with phosgene. The substituted 2,4-dichloroquinazoline was prepared in excellent yield by refluxing the 6-substituted quinazoline-2,4-dione **23** in phosphorus oxychloride (Scheme 8).



23 **24**

Scheme 8

The widespread acceptance and use of high throughput screening technologies for the purpose of drug discovery and development has created an unprecedented demand for small molecules. Combinatorial chemistry, especially on solid support, plays an important role in increasing the efficiency of organic syntheses. Wilson et al.[22] developed a solid-supported method for the formation of the 2,4-diaminoquinazoline ring system. The α-1 antagonist Prazosin **29** was synthesised in good yield and purity. The reaction of 2-amino-4,5-dimethoxybenzonitrile **26** dissolved in N-methylpyrrolidinone with the acyl isothiocyanate resin **25** produced the intermediate **27**. This was followed by the addition of the appropriate amine, in this case, 1-(2-furoyl)-piperazine, in the presence of EDC to furnish the resin-bound guanidine **28**. The optimal ring closure and cleavage conditions yielded Prazosin **29** in 70 % yield (Scheme 9).

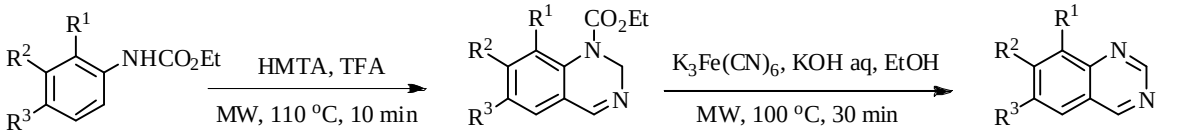


Scheme 9

1.3 Microwave-assisted syntheses of quinazolines.

Although the area of microwave-assisted chemistry is 20 years old, the technique has only recently received widespread global acceptance. This is a consequence of the recent availability of commercial microwave systems, specially designed for synthesis, which offer improved opportunities for reproducibility, rapid synthesis, rapid reaction optimisations and the potential discovery of new chemistries. The beneficial effects of microwave irradiation are finding an increased role in process chemistry, especially in cases when usual methods require forcing conditions or prolonged reaction times. The various opportunities offered by microwave technology are particularly attractive for the synthesis of aromatic quinazolines implied in drug discovery strategies, where fast high yielding protocols and the avoidance or facilitation of purification are highly desirable.

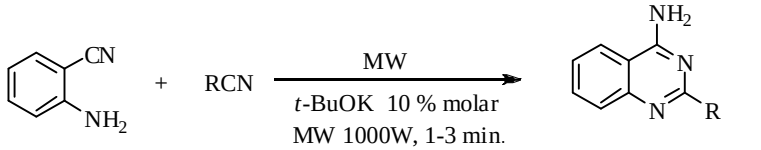
Examples of syntheses, particularly microwave-assisted syntheses, of the nude quinazoline core are very rare in the literature. A recent report of Chilin and co-workers[23] described a rapid and efficient protocol based on the use of cycles of microwave irradiation under pressure in a monomode reactor. In this work the entire pyrimidine ring is built from simple anilines after *N*-protection of ethyl carbamates. Reaction of the aniline with hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA), followed by treatment with potassium ferricyanide in aqueous ethanolic potassium hydroxide afforded the quinazoline system in good yields (Scheme 10).



10 examples 55-95 %

Scheme 10

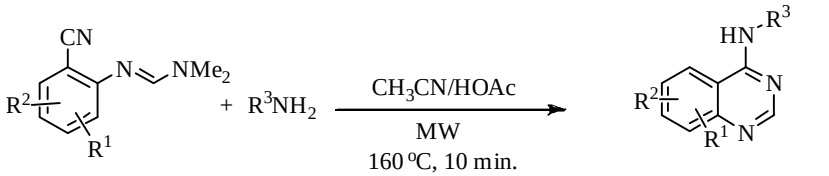
The use of 4-aminoquinazolines[24] substituted in position 2 of the pyrimidine moiety as fungicides, anti-inflammatory, anti-cancer, anti-microbial and anti-hypertensive agents can explain the recent interest of research groups for microwave-assisted synthesis of these rings. Seijas and co-workers[25] described the rapid and efficient synthesis of 4-amino-2-arylquinazolines. In this process, cyano-aromatic compounds reacted with anthranilonitrile in the presence of catalytic amounts of base. The reactions were performed at 1000 W in a domestic microwave oven and require only a very short heating time 1-3 minutes (Scheme 11).



10 examples 73-93 %

Scheme 11

Han et al.[26] have developed a high-yielding and straightforward method for the synthesis of 4-aminoquinazoline derivatives using microwave irradiation in their search for novel compounds with pharmaceutical value and expanding application of formamidines in organic synthesis. Reaction of N-(2-cyanophenyl)-*N*,*N*-dimethylformamidine derivatives and amines in acetonitrile with a catalytic amount of acetic acid under microwave conditions afforded 4-aminoquinazolines in very high yield (Scheme 12).

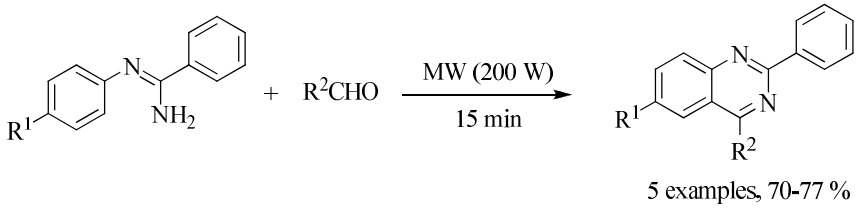


20 examples 70-96 %

Scheme 12

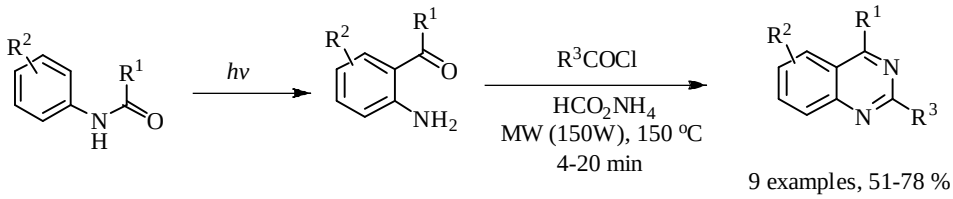
Recently, Mahajan et al.[27] developed a solvent-free and catalyst free approach towards the selective synthesis of quinazolines and benzo[g]quinazolines. Using a domestic microwave oven, the authors reported the solvent-free condensation of N-arylamidines with

various aldehydes in the absence of any Lewis acid catalyst. The desired quinazolines were exclusively formed in excellent yields after 15 minutes of irradiation (Scheme 13).



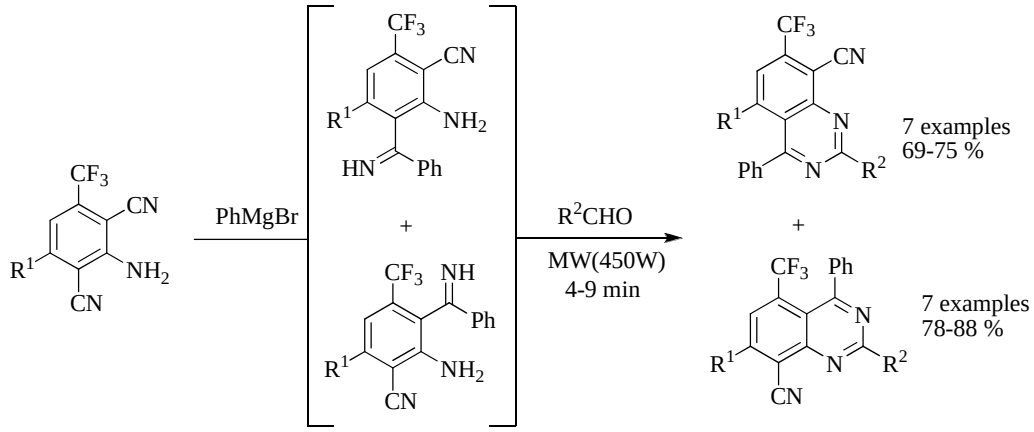
Scheme 13

The most recent convenient synthetic approach to 2,4-disubstituted quinazolines was published by Taddei and co-workers.[28] 2,4-Dialkyl or aryl quinazolines were prepared in three steps starting from easily available anilides. A photochemically induced Fries rearrangement of the anilides gave several *ortho*-aminoacylbenzene derivatives that were acylated at the NH_2. These acylamides underwent rapid cyclization to 2,4-disubstituted quinazolines in the presence of ammonium formate under microwave heating (Scheme 14).



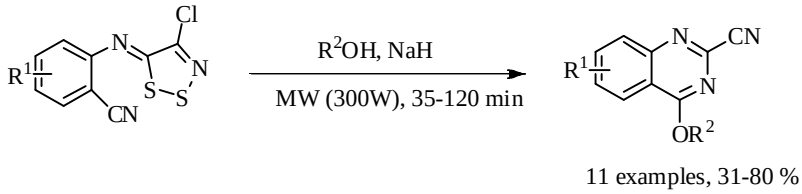
Scheme 14

Studying the regioselective addition of Grignard reagents to 2,6-dicyanoanilines, Narsaiah and co-workers[29] described the microwave-assisted cyclization of the intermediate imines to provide in good yields novel 2,4-disubstituted quinazolines with various groups on the benzenic part of the aromatic core.



Scheme 15

Studying possible extension of the scale of microwave assisted processes, Besson et al.[30] described ten years ago the expeditious route to 4-alkoxyquinazoline-2-carbonitrile using a focussed microwave reactor. After preliminary investigation, this group studied the conversion of *N*-arylimino-4-chloro-5H-1,2,3-dithiazoles into quinazolines in the presence of sodium alkoxide in the corresponding alcohol (Scheme 16).

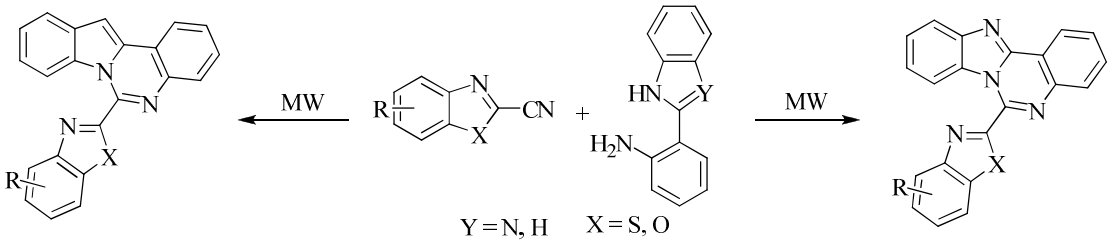


11 examples, 31-80 %

Scheme 16

Microwave irradiation of the solutions in open vessels in monomode systems with focused irradiation and continuous temperature control gave, faster, cleaner and higher yielding reactions compared with the conventional conditions. These experiments could be safely scaled up to multigram quantities in a large reactor.

In the search for new bioactive heterocycles, inspired by various marine natural alkaloids, the rapid synthesis of various derivatives of indolo[1,2-c]quinazolines and benzimidazo[1,2-c]quinazolines have been described. The products were obtained by condensation of appropriate diamines with benzothiazole-2-carbonitrile substituted on the benzenic part. In this study, the use of graphite as a thermal accelerator enabled ready access to the desired product (Scheme 17).[31]



8 examples 54-68 %

Y = N, H X = S, O

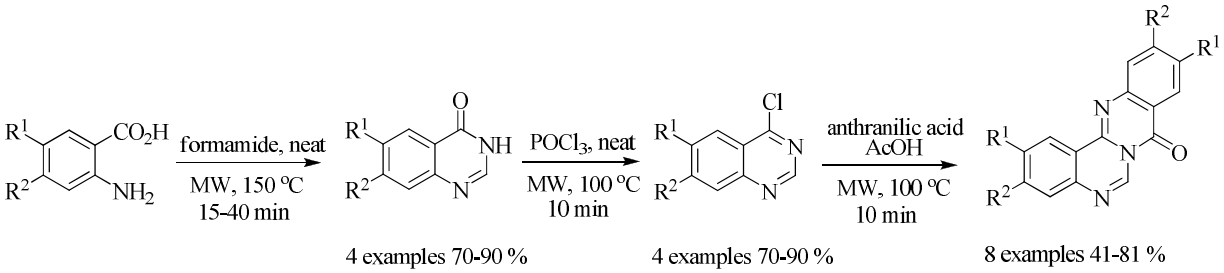
MW: graphite (10 %), 150 °C, 150W, 30-240 min

8 examples 58-73 %

Scheme 17

Another multistep protocol that initially involves the formation of quinazolines has been described by Besson and co-workers[32] in the context of synthesizing 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones via double Niementowski condensation reaction. In the first step of the sequence, an anthranilic acid was condensed with formamide under open-vessel microwave conditions. Subsequent chlorination with excess $POCl_3$, again under open-

vessel conditions, produced the anticipated 4-chloro-quinazoline derivatives, which were subsequently condensed with anthranilic acids in acetic acid to produce the tetracyclic 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones (Scheme 18).



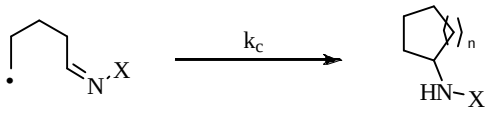
Scheme 18

The examples described above demonstrate that microwave-assisted syntheses can allow easy and rapid access to various aromatic heterocyclic compounds, which may have interesting pharmaceutical potential.

1.4 Radical addition onto imine derivatives.

The addition of free radicals to alkenes has been thoroughly investigated and many synthetic strategies employ this methodology. However, radical addition to imines and related compounds has only emerged as a useful synthetic process since the 1980's. Friestad has compiled a recent review on addition reactions to imines and related compounds.[33]

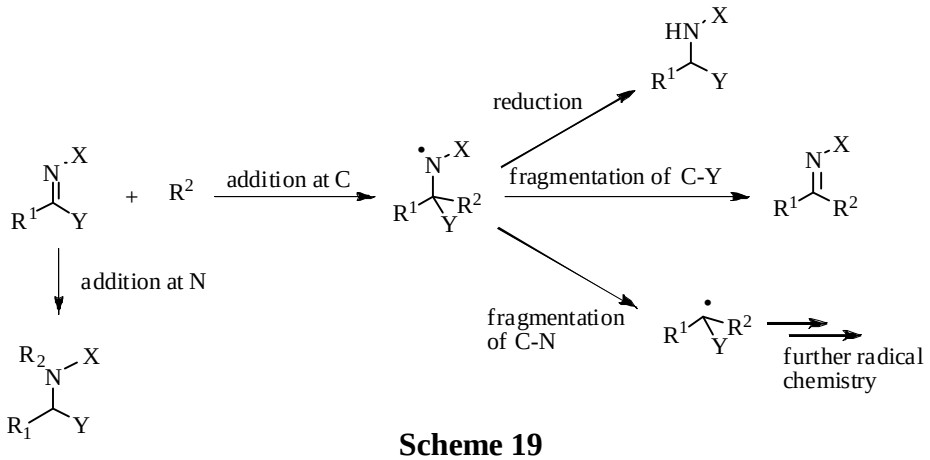
Oxime ethers and hydrazones are by far the most commonly used radical receptors among the various C=N-containing functional groups. Imines can be used, but they are more difficult to handle since they are more prone to hydrolysis and tautomerization than the oximes and hydrazones. Furthermore, imines have slower radical addition rates as Figure 4 shows. Nevertheless, the efficiency of C=N bonds as radical traps can be anticipated based on the kinetic data.[34]



	n = 1	n = 2
X = Bn	$6.2 \times 10^6\ s^{-1}$	$6.7 \times 10^5\ s^{-1}$
X = OBn	$4.2 \times 10^7\ s^{-1}$	$2.9 \times 10^6\ s^{-1}$
X = NMe_2	$7.6 \times 10^7\ s^{-1}$	$3.1 \times 10^6\ s^{-1}$

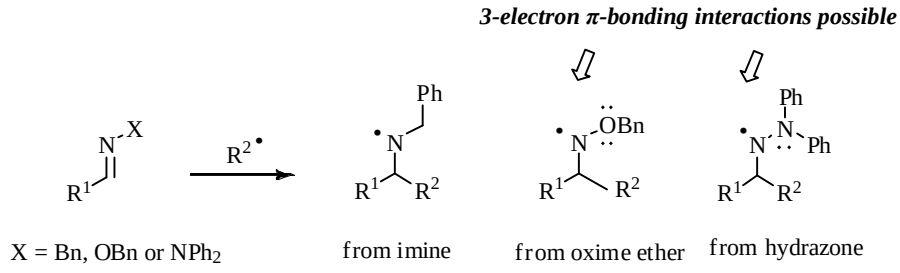
Figure 4. Kinetic data for ring closure of alkyl radicals. Data obtained at 80 °C.

Since an amino group is one of the most important functional groups in organic chemistry, radical reactions using C=N bonds as radical traps have attracted a great deal of attention. Synthetic applications of radical additions to C=N bonds are summarized in Scheme 19. By far the most common application is reductive addition to obtain amines. Moreover, specialized functional groups have been developed as radical acceptors for tandem processes involving addition followed by fragmentation of bonds at either the N-terminus or C-terminus of the original C=N bond.



Scheme 19

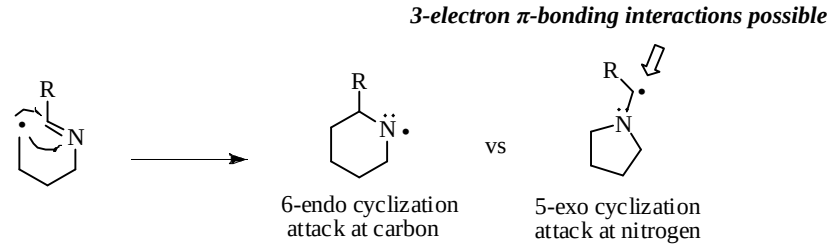
Attack at carbon of the C=N bond is almost exclusively observed, especially in oxime ethers and hydrazones where the stabilizing three-electron π-bond in the adduct aminyl radical could effect stabilization on the transition state (Scheme 20).



Scheme 20

On the other hand, the regioselectivity of radical addition onto imines has been subject to study during recent years. One might envision that radical addition to the C=N bond could occur with attack at nitrogen to give a α-amino radical, which should be stabilized by the adjacent nitrogen (Scheme 21). The competition between *5-exo* and *6-endo* cyclization of

alkyl, aryl and acyl radicals onto imines has been deeply studied to examine this issue, as will be shown later.

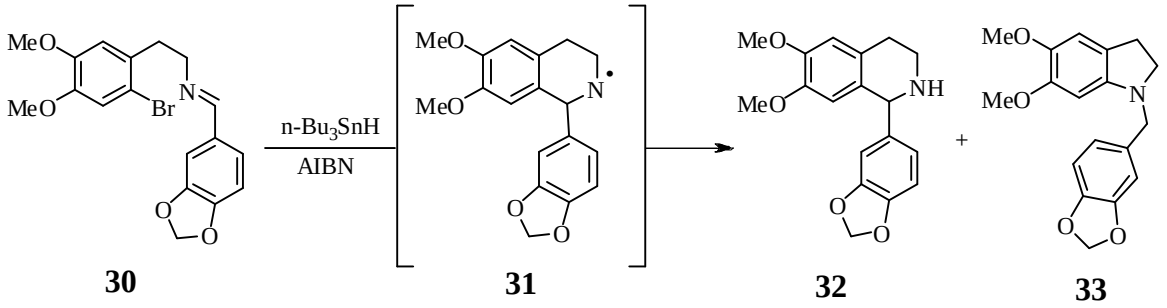


Scheme 21

1.4.1 Imines as radical acceptors.

As expected from the kinetic data and the stabilizing factors shown above, imines are less effective as radical traps than oxime ethers or hydrazones.

An early example of an intramolecular addition onto an imine bond was reported by Takano and co-workers[35] as a key step in their synthesis of the Cryptostyline alkaloids. Cyclisation of the aryl bromide **30** gave the isoquinoline skeleton **32** as a major product from a 6-*endo* addition to form the aminyl radical **31** from addition to the carbon centre of the imine bond. The alternative pathway, the *5-exo* cyclization, was the minor route and afforded the dihydroindole **33** in 10 % yield (Scheme 22).

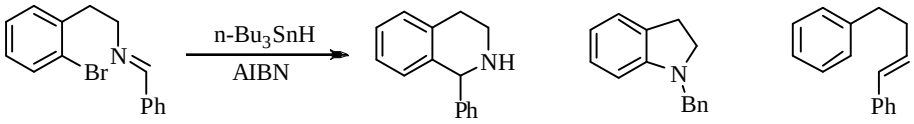


30 **31** **32** **33**

Scheme 22

Warkentin and coworkers[36] have also studied this pattern of reactivity. They reported a large *6-endo* preference for the cyclisation of an aryl radical onto an aldimine receptor. Cyclization of the bromide **34** is a typical example, and afforded a 70 % yield of **35** accompanied by lesser amounts of the *5-exo* product **36** and the reduced starting material **37** (Scheme 23). The formation of the corresponding C-C single bond is favoured over the corresponding C-N bond by approximately, 10 kcal/mol.[37] In addition the geometry inherent in the imine functional group, with a C-C=N angle of approximately 119° is more suited to

endo addition than, for instance, the alkene with a larger angle of approximately 125°,[38] where the *5-exo* is favoured.



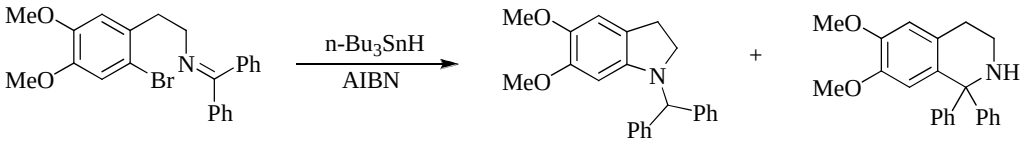
70 % 15 % 14 %

34 **35** **36** **37**

Scheme 23

Despite numerous examples of radical additions to C=N bonds, there have only been a few cases where addition occurs at the nitrogen. A stabilizing 3-electron interaction of the forming aminyl radical with non-bonding electrons on either oxygen or nitrogen is generally invoked to explain the facility of radical addition to oxime ethers and hydrazones. In the case of imines, this 'radical α-effect' is not possible, thus it is surprising that addition does not often occur at nitrogen, given the stabilization available through interaction of the adduct α-aminyl radical with the non-bonding electron pair on nitrogen. In the cases of additions at nitrogen known to date, additional stabilizing groups, conformational restriction, severe steric hindrance, or polar effects are present to further promote attack at nitrogen.

In an early example Takano et al.[35] showed that in the ketimine derived from acetophenone and benzophenone the free radical centre added exclusively to the nitrogen of the azomethine in a 5-*exo* fashion. Generally this pathway is disfavoured, but the extra steric hindrance, together with the resonance stabilizing effect of the two phenyl rings **38**, led to the exclusive formation of the indole **39** (Scheme 24).



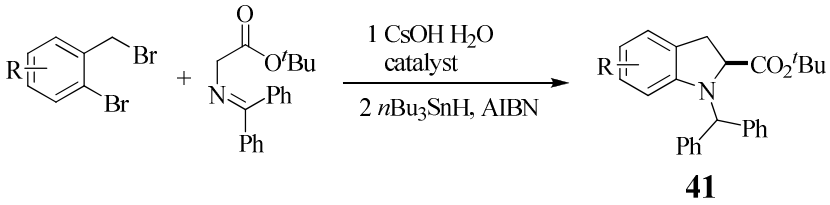
59 % 0 %

38 **39** **40**

Scheme 24

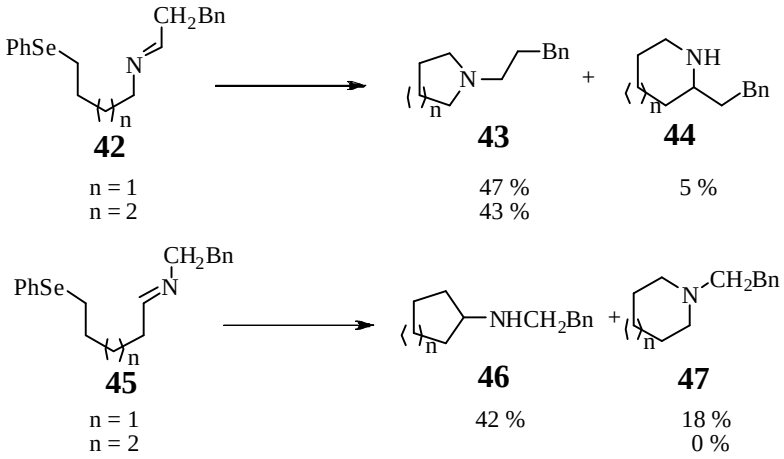
More recently, Johnston and coworkers[39] reinvestigated aryl radical additions to azomethine with the expectation that use of a C-N π-bond would provide a base-free aryl amination method expected to be relatively insensitive to electronic effects. They applied the

aryl radical cyclization via the 5-*exo* mode onto imines in the enantioselective synthesis of indoline α-amino acids **41** (Scheme 25).



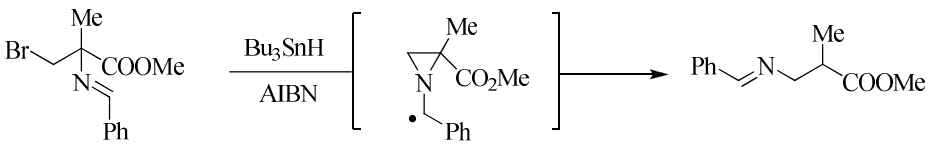
Scheme 25

Bowman et al.[40] investigated the cyclization of various primary radicals generated from phenyl selenides onto diverse imines. Representative examples included the cyclization of **42** (n = 1) to give the *5-exo* product **43** in 47 % yield and the *6-endo* heterocycle **44** in 5 % yield. In the case of **42** (n = 2), the only product arose from *6-exo* cyclization to give **44** in 43 % yield. Reversal of the regiochemistry of the imine bond led to the investigation of **45**. In the case for n = 1 the major *5-exo* cyclization product **46** was formed in 42 % yield compared to 18 % for the *6-endo* product. With the longer chain (n = 2) none of **47** was formed (Scheme 26).



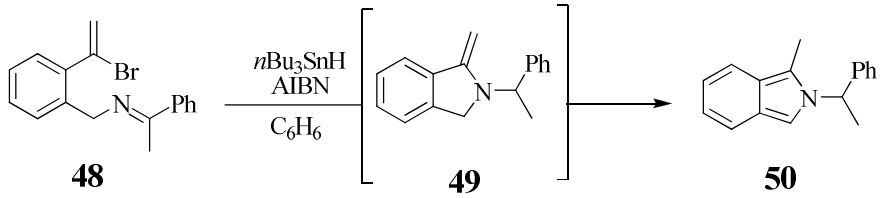
Scheme 26

Frey and coworkers[41] proved the feasibility of a radical mechanism involving the 3-*exo* cyclisation of a primary radical to the N=C bond followed by ring opening to the most stable radical by performing the reaction under tin hydride conditions (Scheme 27).



Scheme 27

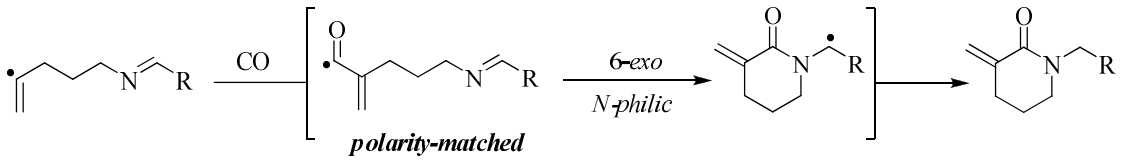
Recently Johnston et al.[42] have introduced the first examples of free radical-mediated vinyl amination by non-conventional vinyl radical addition to azomethine nitrogen (Scheme 28).



Scheme 28

The addition of vinyl radicals to the nitrogen of an azamethine provides a pH-neutral method for directed, regioselective enamine formation. Furthermore, the vinyl radical intermediate may be formed either directly or as part of a tandem series of bond-forming events.

Other interesting radical cyclisations onto imines have been extensively investigated by Ryu and co-workers.[43] They described the regioselective addition of acyl radicals onto the azomethine nitrogen. Cyclizations occur with high regioselectivity favouring the N-philic mode for the synthesis of 4-, 5-, 6-, 7-, and 8-membered rings. The radical cyclization was accomplished by using a tin hydride mediated carbonylation system using azaenyne as the substrate, which led to α-stannylmethylenes (Scheme 20).



Scheme 29

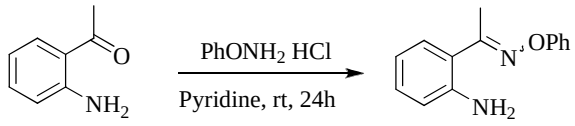
By adding carbon monoxide to the reaction, they envisioned that in situ conversion of the "polarity-mismatched" vinyl radical/imine combination to a "polarity-matched" α,β-unsaturated acyl radical/imine combination would result in efficient cyclization leading to the α-amino radical of α-methylene-substituted δ-lactams.

It has been proved, with the examples described above, that the additions of alkyl, aryl, vinyl and acyl radicals onto imines, constitute synthetically useful processes in the syntheses of azaheterocycles. On the other hand, addition of iminyl radicals onto imines, has not been reported so far. It could constitute an attractive approach for the synthesis of heterocycles, such as quinazolines or benzopyrazoles.

2.0 Results and discussion.

As has been shown in the previous chapter, microwave promoted thermolyses of *O*-phenyl oxime ethers release iminyl radicals together with phenoxyl radicals. Microwave irradiations of suitable *O*-phenyl oxime ethers with radical acceptors such as double and triple bonds and phenyl groups constitute remarkable methods for the synthesis of a wide range of nitrogen heterocycles.

We reasoned that other heterocyles could probably be made by using *O*-phenyl oximes containing different types of radical acceptor in their side-chain. In particular, by use of imine functionality in the side chain, di-aza-heterocycles might be accessible under mild, neutral conditions with all the convenience and rapidity of a microwave-assisted process. The *O*-phenyl oxime of 2-aminoacetophenone **52** can be made in high yield by treatment of the ketone **51** with commercially available *O*-phenylhydroxylamine hydrochloride (Scheme 30).

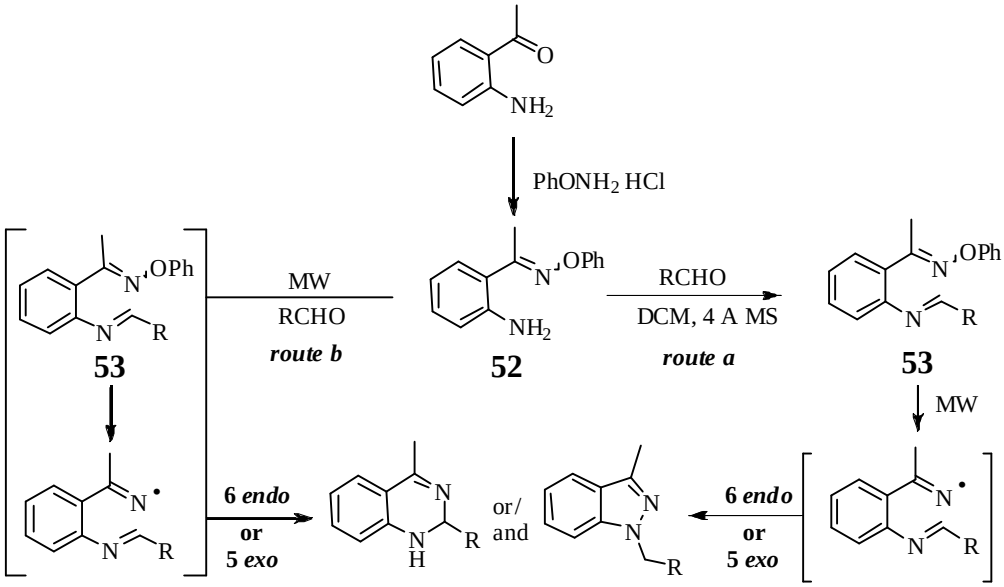


51 **52**

Scheme 30

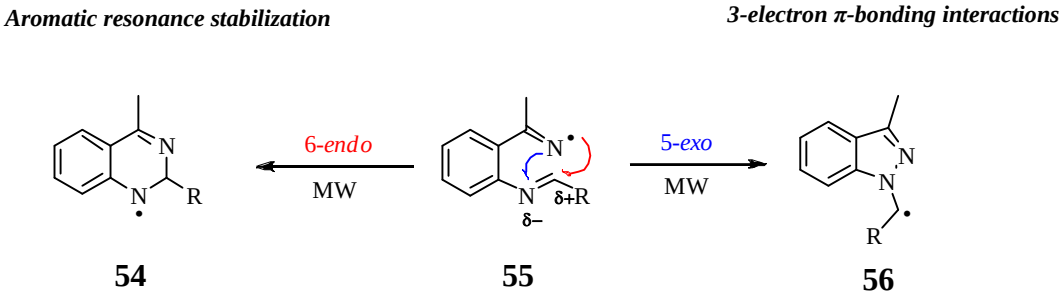
Imines **53** could be made by condensation of aniline **52** with aldehydes in the conventional way (***route a***, Scheme 31). Stirring both starting materials in DCM in the presence of a drying agent at room temperature should afford the desired imine. As was described earlier, the fact that imines are difficult to handle, due to their trend to hydrolysis and tautomerization, makes azomethines the least commonly used radical acceptor among the various C=N-containing functional groups. To overcome this problem, it was conjectured that the imine forming condensation would also be promoted by microwaves.

It is widely reported that microwave irradiation assists imine formation.[44] This procedure has been established as a standard method in the syntheses of secondary amines, via microwave induced reductive amination.[45] There was a possibility therefore of assimilating imine formation with radical generation thus enabling the whole sequence to be combined in one pot (***route b***, Scheme 31).



Scheme 31

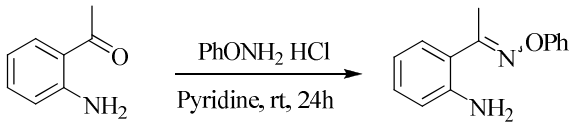
The regioselectivity is another potential problem associated with the imines. The competition between the 5-*exo* and 6-*endo* radical ring closure onto C=N has been extensively investigated.[38] Thus, this type of radical cyclization has limited use because of poor selectivities associated with 5-*exo* versus 6-*endo* cyclisations. It was assumed, however, that the architecture of iminyl radical **55** favours ring closure onto N=C bond in the 6-*endo-trig* mode because the resultant aminyl radical **54** will be strongly resonance stabilised. Furthermore, the combination of the nucleophilic iminyl radical and the nitrogen atom of imines is polarity-mismatched. The combination of these two effects may lead to regiospecific 6-*endo* cyclisation, as against the 5-*exo* mode, despite the possible 3-electron π-bonding interaction **56** (Scheme 32).



Scheme 32

2.1 Optimization.

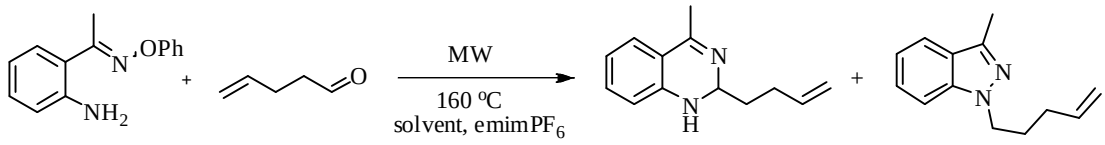
The *O*-phenyl oxime ether **52** was prepared in 76 % yield as a mixture of E and Z isomers by stirring 2-aminoacetophenone **51** with *O*-phenylhydroxylamine hydrochloride in pyridine at room temperature. The fact that two isomers were present did not matter because both released the same iminyl radical on scission of their N-O bonds (Scheme 33).



51 **52**

Scheme 33

One equivalent of pent-4-enal **57** and oxime ether **52** were irradiated under microwave conditions to test the outcome of this novel annulation sequence and the regioselectivity of the process (Scheme 34).



52 **57** **58** **59**

Scheme 34

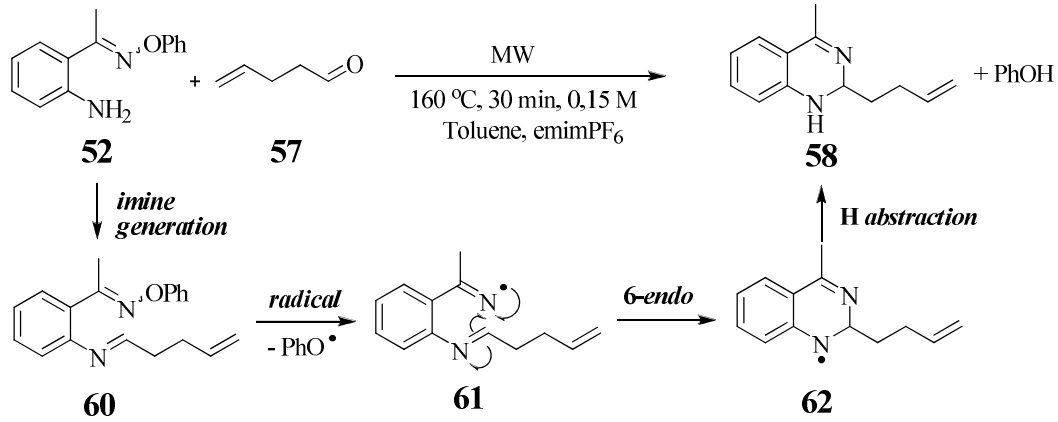
The reaction was carried out in various solvents, with and without 1-ethyl-3-methyl-1H-imidazol-3-ium hexafluorophosphate (emimPF_6) as ionic liquid, and with different concentrations of **52** and reaction times. It was expected, from previous results (**Chapter 2**) that the optimal temperature for scission of the N-O bond and subsequent release of iminyl radical would be 160 °C. The percentages of the cyclised species were monitored by NMR spectroscopy (Table 1).

Run	Solvent	Time(min)	Concentration(M)	IL	Yields 58 / 59 (mol%)
1	Toluene	15	0.15	emimPF_6	**68 / 0**
2	Toluene	20	0.15	emimPF_6	**74 / 0**
3	Toluene	25	0.15	emimPF_6	**90 / 0**
4	Toluene	30	0.15	emimPF_6	**94 / 0**
5	Toluene	35	0.15	emimPF_6	**88 / 0**
6	Toluene	30	0.20	emimPF_6	**81 / 0**
7	Isopropanol	30	0.15	none	**91 / 0**
8	^{t}BuOH	30	0.15	none	**83 / 0**

Table1. Microwave-assited reactions of pent-4-enal with **52** at 160 °C.

From the results of these experiments it was possible to draw a number of conclusions regarding the mechanism, regioselectivity and optimum conditions of the process.

It was proved, that microwave irradiation of the phenyl oxime ether **52** and aldehyde **57** in the best reaction conditions, afforded dihydroquinazoline **58** in an excellent yield. The one-pot protocol proceeded by the syntheses of the imine intermediate **60**, subsequent generation of iminyl radical **61** and cyclization onto the imine, providing the aminyl radical **62**. Hydrogen abstraction from toluene gave essentially quantitative production of dihydroquinazoline **58** with an equal amount of phenol. The latter is formed by H-abstraction from solvent by the phenoxyl radicals and is easily separated (Scheme 35).



Scheme 35

If H-atom abstraction from solvent by the iminyl radical generated from **52** before imine formation had been important, then **63a** or its hydrolysis product **63b** should have been formed (Figure 5). Similarly, if H-atom abstraction from solvent by radical **61** had been faster than ring closure then **64a**, or its hydrolysis product **64b**, should have been detected. In practise none of **63a,b** or **64a,b** was observed. Imine production from **52** and an aldehyde takes place via a series of equilibria involving hemiaminal formation, water loss and various protonation/deprotonation steps. The absence of **63a,b** shows that the equilibria must be fast in comparison with radical generation. Evidently, the imine intermediate is rapidly trapped by the cyclisation step but the fast imine formation equilibria ensure a constant supply until reactant depletion sets in.

63 a X = NH
63 b X = O

64 a X = NH
64 b X = O

Figure 5

At the same time, the plain fact that none of the benzopyrazole **59** had been detected, confirmed the regiospecific character of the reaction. Iminyl radical **61** cyclised in a 6-*endo* mode onto the C of the C=N giving aminyl radical **62** regiospecifically. It may be due to the strong resonance stabilisation effect and the "polarity-mismatch" between iminyl radical and the N of the imine, as it was discussed earlier.

Kinetic data for this particular type of ring closure are not available. However, the known rate constant for 6-*endo trig* cyclisation of C-centred radicals onto C=N bonds,[46] and for iminyl radical onto C=C bonds,[47] suggest **61** → **62** would be a fast process at 160 °C with a rate constant at least equal to that of a C-centred radical onto C=C bond and probably greater because of the resonance stabilisation on **62**. This is consistent with the absence of compounds **64a,b** (figure 5) in the product mixture.

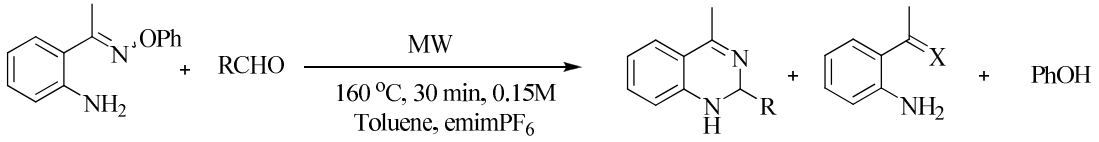
Finally from the results described in Table 1, the optimal reaction conditions can be defined. The solvent played a basic role in the radical process. The use of a poor hydrogen donor solvent such as toluene or isopropanol allowed the iminyl radical, enough life-time to cyclise. Both solvents proved to give good yields, however, isopropanol had the inconvenience of its low boiling point and the microwave vial was exposed to high levels of pressure. The ionic liquid emimPF_6 was used together with toluene, due to the poor microwave absorption properties of this solvent. Entries 1-5 show that at 160 °C the reaction needed an irradiation time of 30 minutes to achieve complete conversion but that at longer times side reactions/degradative processes set in. However, for larger concentrations of precursor **52** in toluene (entry 6) the yield fell off in 30 minute reactions.

The NMR spectrum of the total reaction mixture from entry 4 showed essentially quantitative formation of dihydroquinazoline **58**. This supported the mechanism shown in Scheme 35 and indicated that this methodology could be applied as an efficient syntheses of dihydroquinazolines.

2.2 Reaction with aldehydes.

2.2.1 Syntheses of 4-methyl 2-substituted dihydroquinazolines.

To assess the scope of the annulation, oxime ether **52** was reacted with a range of commercially available aldehydes under the optimal conditions established above, i. e. 0.15 M toluene solution with microwave irradiation at 160 °C for 30 min in the presence of emimPF_6 as ionic liquid (Scheme 36).



52

63a X= NH
63b X = O

Scheme 36

Reactions with aliphatic aldehydes delivered the corresponding dihydroquinazolines in very high yields and none of the starting materials were found. Neither imine **63a**, or its hydrolysis product **63b** was observed. The four steps involved in this process, imine formation, iminyl radical generation, 6-*endo* radical cyclisation onto C=N and H-atom abstraction from the solvent, proved to be extremely efficient (Table 2).

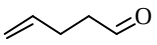
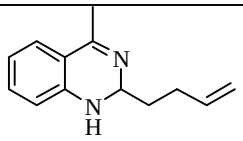
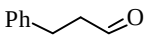
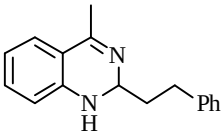
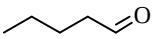
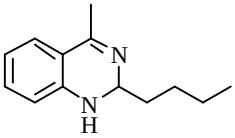
Run	Aliphatic Aldehyde	Dihydroquinazoline	Yields (mol%)
1	 **57**	 **58**	**94**
2	 **65**	 **66**	**92**
3	 **67**	 **68**	**91**

Table 2. Syntheses of dihydroquinazolines via microwave assisted reaction of **52** and commercial aliphatic aldehydes. Isolated yields. Reactions in PhMe, 0.15 M., emimPF_6,160 °C, 30 minutes.

Reactions of oxime ether **52** with aromatic aldehydes were next examined under the same conditions. Microwave irradiation of **52** with benzaldehyde **69** gave a 72 % yield of the corresponding dihydroquinazoline **70**. The ^{1}H NMR spectrum of the total product mixture showed dihydroquinazoline **70** and quantitative production of phenol, but also benzaldehyde **69**, imine **63a** and its hydrolysis ketone **63b.** Two more reactions were carried out with aromatic aldehydes and oxime ether **52**. 4-Methoxybenzaldehyde **71** and thiophene-2-carbaldehyde **73** gave dihydroquinazolines **72** and **74** in 51 % and 46 % yield respectively. Both yields were determined by ^{1}H NMR because none of the desired compounds could be isolated. In both cases the crude ^{1}H NMR showed a complex mixture of species, wherein the

aldehyde starting materials **71** and **73** were present as well as imine **63a** and ketone **63b.** However, phenol was formed quantitatively as was expected (Table 3).

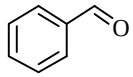
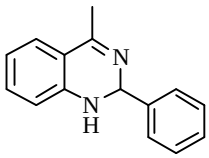
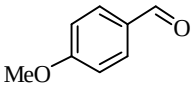
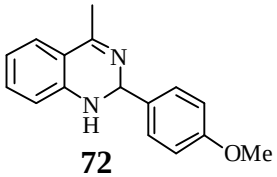
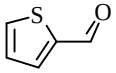
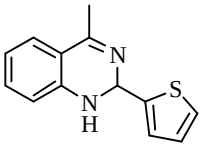
Run	Aromatic Aldehyde	Quinazolines	Yields
1	 **69**	 **70**	**72 %[a]**
2	 **71**	 **72**	**51 %[b]**
3	 **73**	 **74**	**46 %[b]**

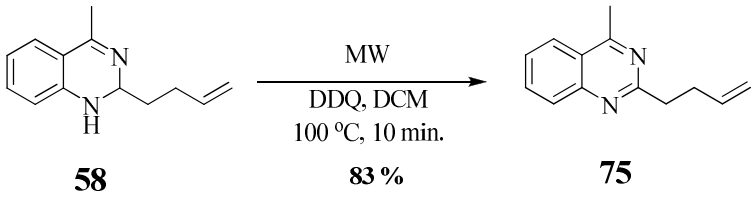
Table 3. Syntheses of dihydroquinazolines via microwave assisted reaction of **52** and commercial aromatic aldehydes. [a] Isolated yields. [b] Determined by ^{1}H NMR of crude reaction mixture. Reactions in PhMe, 0.15 M, emimPF_6, 160 ^{o}C, 30 minutes.

It can be concluded from these results that for aromatic aldehydes, the reactions tended to be incomplete and lower yields were obtained. Furthermore, the presence of unreacted aldehyde starting material**,** inferred that the first step of the sequence, the imine formation, was not completed. It may be due to a steric hindrance effect with the phenyl oxime ether group. Moreover, the fact that, imine **63a** and ketone **63b** were present as well in the reaction mixture, together with a quantitative amount of phenol**,** suggested that the generation of the iminyl radical was successful but the transformation of aniline **52** to the imine intermediate was not completed.

Imine formation plays a key role in the success of the entire sequence since the iminyl radical cyclisation onto imines had proved to be very efficient. Therefore, an improvement in the imine forming condensation should imply an increase in the efficiency of the entire process and hence an increase in the dihydroquinazoline yields.

It was observed as well that dihydroquinazolines tended to slowly oxidise to the corresponding quinazolines over a period of days when stored in air at room temperature. Thus, it was desirable to find an effective oxidation protocol which could yield quinazolines

in high yields and in short reaction times. Microwave irradiation of dihydroquinazoline **58** in DCM and in the presence of the oxidizing agent DDQ gave the desired quinazoline **75** in good yield after irradiating for 10 minutes at 100 °C (Scheme 37).



58 **75**

Scheme 37

The oxidation of dihydroquinazoline **58** was also studied by continuously bubbling oxygen through a solution of **58** in $CDCl_3$ at 50 °C. The course of the oxidation was monitored by ^1H NMR spectroscopy over time (Table 4).

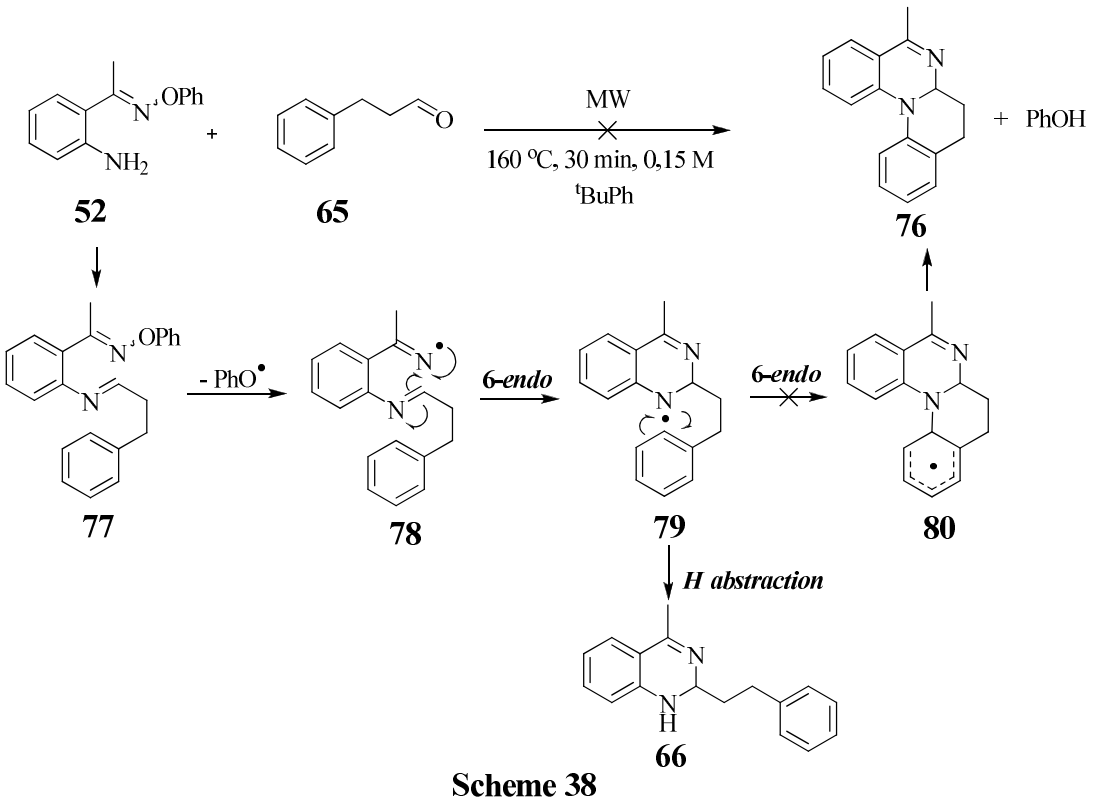
Run	Time	Yield 75 (mol%)
1	4 h.	**28 %**
2	8 h.	**32 %**
3	24 h.	**42 %**
4	48 h.	**88 %**

Table 4. Oxidation of dihydroquinazoline **58** in $CDCl_3$ at 50 °C by continuous oxygen bubbling.

The oxidation to quinazoline **75** was slower than expected. It took 48 hours to get an 88 % conversion from the starting dihydroquinazoline **58**. Furthermore side-processes set in and various unidentified side-products were present in the total reaction mixture.

2.2.2 Potential tandem reaction.

It was postulated that on microwave irradiation of 3-phenylpropenal **65** with oxime ether **52** in a non hydrogen donor solvent, *t*-butyl benzene instead of toluene, intermediate aminyl radical **79** could undergo homolytic aromatic substitution onto the phenyl ring. Cyclohexadienyl radical **80** would be formed, and hence a 5-methyl-7,8-dihydro-6a*H*-quinolino[1,2-a]quinazoline **76** would result after losing one H-atom and gaining aromaticity (Scheme 38)**.** However, none of this product was detected and evidently H-atom abstraction by radical **79** is too fast for the homolytic aromatic substitution to complete. Instead dihydroquinazoline **66** was obtained in 86 % yield. Nevertheless, the result was not surprising because neutral aminyl radicals are not very reactive and it is known that their additions to olefins are often reversible.[48]



Scheme 38

2.2.3 Syntheses of 2-substituted-4-methylquinazolines.

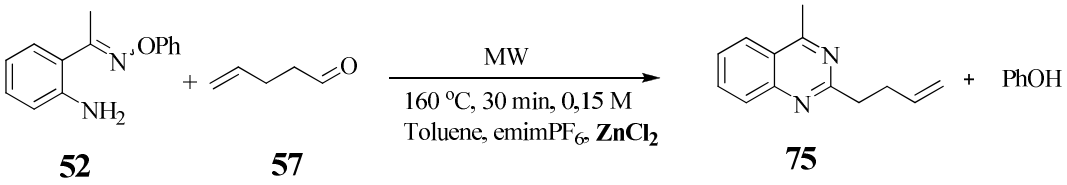
As was described above, the efficiency of the imine formation constituted a critical parameter for the success of the multi-step process and hence of dihydroquinazoline formation.

It was shown that reaction of oxime ether **52** with less reactive aldehydes, such as 4-methoxybenzaldehyde **71** and thiophene-2-carbaldehyde **73**, did not give clean reactions but disappointing dihydroquinazoline yields.

Imine formation takes place via a series of equilibria involving hemiaminal formation, water loss and various protonation/deprotonation steps. The dehydration step is acid catalysed and the rates of individual steps depend on pH.[49] It is known that imine formation via microwave irradiation is promoted by inclusion of zinc chloride.[50] It was hoped, therefore, that addition of $ZnCl_2$, as a promoter would improve the product yields when less reactive carbonyl compounds were employed.

Pent-4-enal **57** was reacted with oxime ether **52** in the presence of $ZnCl_2$ using the optimal reaction conditions. An excellent product yield was obtained, but the surprising

outcome was that the quinazoline **75** rather than the dihydroquinazoline, was formed under these circumstances (Scheme 39).



52 **57** **75**

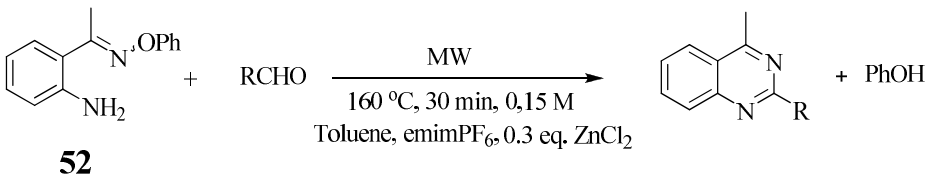
Scheme 39

Reactions with 0.1, 0.3 and 0.5 equivalents of $ZnCl_2$ indicated that 0.3 equivalents was the optimal amount and this was adopted as standard in subsequent preparations (Table 5).

Run	$ZnCl_2$ (equiv.)	Yield 75 (mol%)*
1	0.1	**74 %**
2	0.3	**91 %**
3	0.5	**88 %**

Table 5. Microwave-assited reactions of pent-4-enal with **52** in the presence of $ZnCl_2$ in PhMe, 0.15 M and $emimPF_6$ at 160 °C. NMR yields.*

To assess the scope of this new process, oxime ether **52** was reacted with a range of aldehydes under the optimal reaction conditions and in the presence of 0.3 equivalents of $ZnCl_2$ (Scheme 40).



52

Scheme 40

High yields of quinazolines **75** and **82** were obtained from **52** with the aliphatic aldehydes pent-4-enal and cyclohexanecarbaldehyde respectively (Table 6).

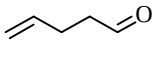
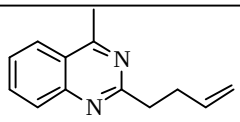
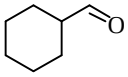
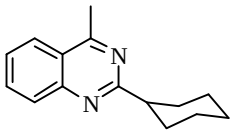
Run	Aliphatic Aldehyde	Quinazolines	Yields
1	 **57**	 **75**	**91 %**
2	 **81**	 **82**	**80 %**

Table 6. Syntheses of quinazolines via microwave assisted reaction of **52** and commercial alifatic aldehydes. Isolated yields. Reactions in PhMe, 0.15 M, 0.3 equ. $ZnCl_2$, emimPF_6, 160 ^oC, 30 minutes.

Aromatic aldehydes with electron-withdrawing substituents in the 4-position, i.e. 4-bromo- and 4-nitro-benzaldehyde, gave **84** and **86** also in high yields. Somewhat lower, but still useful, yields of quinazolines were obtained on starting with aromatic aldehydes containing electron donating substituents, e.g. **88** and **90**. The low yield of the latter may be due to the high steric hindrance in the formation of the imine intermediate (Table 7).

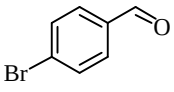
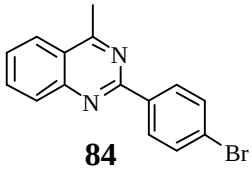
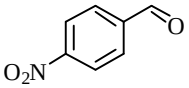
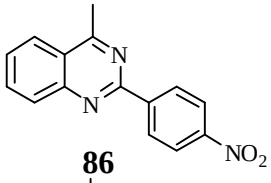
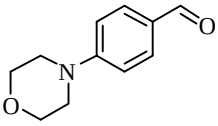
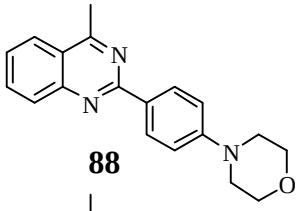
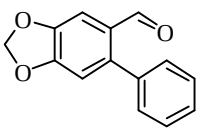
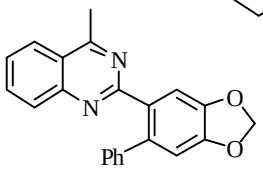
Run	Aromatic Aldehyde	Quinazoline	Yields
1	 **83**	 **84**	**85 %**
2	 **85**	 **86**	**90 %**
3	 **87**	 **88**	**77 %**
4	 **89**	 **90**	**58 %**

Table 7. Syntheses of quinazolines via microwave assisted reaction of **52** and aromatic aldehydes. Isolated yields. Reactions in PhMe, 0.15 M, 0.3 equ. $ZnCl_2$, emimPF_6, 160 ^oC, 30 minutes.

Similarly, the annulations worked well with heterocyclic aldehydes including pyridine-2-carbaldehyde and furfural (Table 8).

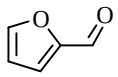
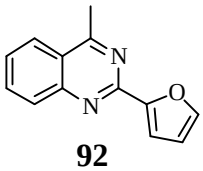
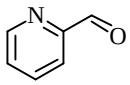
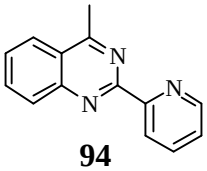
Run	Ar. Heterocyclic Aldehyde	Quinazoline	Yields
1	 **91**	 **92**	**76 %**
2	 **93**	 **94**	**71 %**

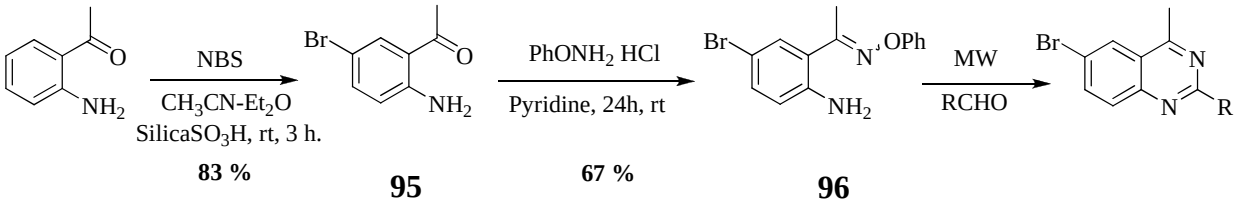
Table 8. Syntheses of quinazolines via microwave assisted reaction of **52** and heteocyclic aromatic aldehydes. Isolated yields. Reactions in PhMe, 0.15 M, emimPF_6, 160 ^{o}C, 30 minutes.

From these results, it can be concluded that oxime ether **52** is a very good precursor for the syntheses of quinazolines. Excellent yields were obtained in reactions with aliphatic aldehydes, where none of the starting material was shown in the ^{1}H NMR of the total reaction mixture, and quantitative conversion to the quinazoline and phenol was observed. Also, good yields were achieved for aromatic aldehydes with electron-withdrawing and electron-releasing groups in the 4-position. The slightly better yields for aromatic aldehydes with electron-withdrawing groups may due to an increase in the electrophilic character of the carbonyl group, which would support the nucleophilic addition of the aniline **52**. The use of heterocyclic aldehydes led to syntheses of interesting compounds such as 4-methy-2-(pyridine-2-yl)quinazoline **94** and 2-(furan-2-yl)-4-methylquinazoline **92** in good yields.

The efficiency of the reaction was also investigated for a small set of *O*-phenyl oxime ethers having different functionality in the amino-aryl ring.

2.2.4 Syntheses of 6-bromo-4-methyl phenylquinazoline.

5-Bromo-2-aminoactophenone **95** was obtained regioselectively in 83 % yield by treatment of 2-aminoacetophenone with NBS in the presence of sulfonic-acid-functionalised silica as a heterogeneous catalyst.[51] Reaction of **95** with *O*-phenyl hydroxylamine hydrochloride in pyridine at room temperature yielded the desired brominated oxime ether **96** in 67 % yield (Scheme 41).



Scheme 41

Microwave irradiation of the oxime ether **96** and benzaldehyde, using the optimal reaction conditions, afforded the 6-bromo substituted quinazoline **97** in an excellent yield (Table 9).

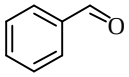
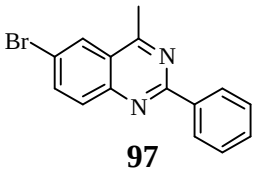
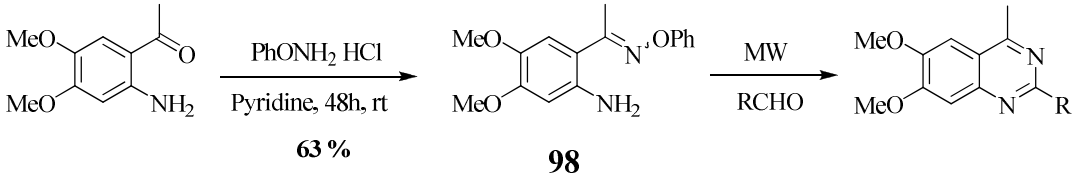
Run	Aldehyde	Quinazoline	Yields
1	 **69**	 **97**	**89 %**

Table 9. Syntheses of 6-bromo-4-methyl-2-phenylquinazoline via microwave assisted reaction of **96** and benzaldehyde. Isolated yields. Reactions in PhMe, 0.15 M, $emimPF_6$, 160 ^oC, 30 minutes.

2.2.5 Syntheses of 2-substituted 6,7-dimethoxy-4-methyl quinazolines.

The 1-(2-amino-4,5-dimethoxyphenyl)ethanone *O*-phenyl oxime **98** was obtained from reaction of the commercially available 4,5-dimethoxy-2-acetophenone with phenyl hydroxylamine hydrochloride in pyridine. The reaction mixture was stirred for 24 hour at room temperature, but a disappointing 46 % yield was obtained. The reaction was carried out as well at 50 °C for 3 hours, but numerous of by-products were formed, probably from scission of the N-O bond. The best result of the condensation was achieved by stirring the starting materials for 48 h at room temperature in pyridine. The reaction gave the desired oxime ether **98** in a satisfactory yield of 63 % (Scheme 42).



Scheme 42

The slowness of this reaction may be due to the presence of three good electron-releasing groups in the acetophenone ring. This electron-donating effect could have decreased the electrophilic character of the ketone, and hence its reactivity towards *O*-phenyl hydroxylamine.

Microwave irradiation of the oxime ether **98** with 4-bromo- and 4-nitro-benzaldehyde gave quinazolines **99** and **100** in high yields 80 % and 91 % respectively (Table 10).

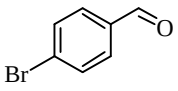
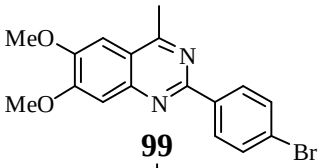
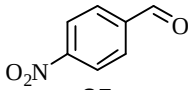
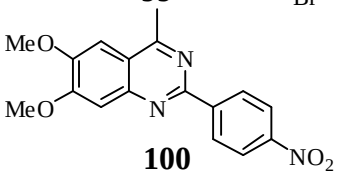
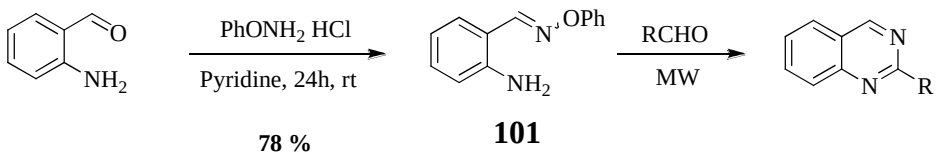
Run	Aldehyde	Quinazoline	Yields
1	 **83**	 **99**	**80 %**
2	 **85**	 **100**	**91 %**

Table 10. Syntheses of 2 substituted 6,7-dimethoxy-4-methylquinazolines via microwave assisted reaction of **98** and aromatic aldehydes. Isolated yields. Reactions in PhMe, 0.15 M, 0.3 equ $ZnCl_2$, $emimPF_6$, 160 ^oC, 30 minutes.

2.2.6 Syntheses of 2- substituted quinazolines.

To probe the sensitivity of the reaction to substituents at the fourth position of the quinazoline, *O*-phenyl oxime ether **101** was prepared in good yield from the condensation of 2-aminobenzaldehyde and *O*-phenyl hydroxylamine hydrochloride in pyridine. The reaction gave the desired precursor **101** in 78 % yield (Scheme 43).



Scheme 43

The unsubstitued oxime ether **101** reacted well with aliphatic, aromatic and heterocyclic aldehydes, giving good yields of 2-subtitued quinazolines (Table 11).

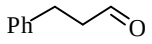
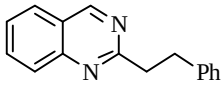
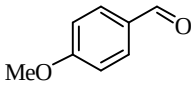
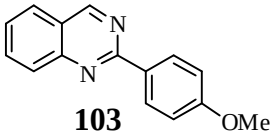
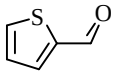
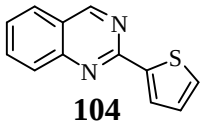
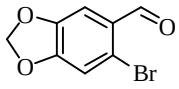
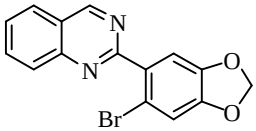
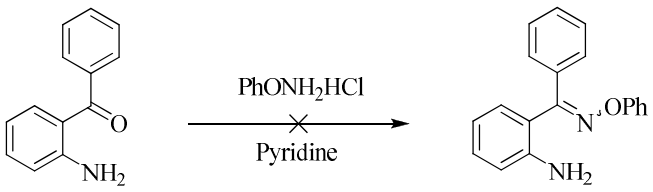
Run	Aldehyde	Quinazoline	Yields
1	 **65**	 **102**	**82 %**
2	 **71**	 **103**	**71 %**
3	 **73**	 **104**	**78 %**
4	 **105**	 **106**	**71 %**

Table 11. Syntheses of 2 substituted quinazolines via microwave assisted reaction of **101** and aldehydes. Isolated yields. Reactions in PhMe, 0.15 M, 0.3 equ $ZnCl_2$ emimPF_6, 160 ^oC, 30 minutes.

The interesting building block **106** is of special interest. Reaction of 6-bromo piperonal **105** with the oxime ether **101** gave the quinazoline **106** with an excellent level of conversion. The 71 % yield was obtained, despite the presence of a large Br group and a good electron-donating substituent, the dioxole, in the aromatic aldehyde. Both factors could have inhibited the first step of the sequence, the imine formation, by steric hindrance and electronic effects respectively. The result proved that this formation was very efficient.

It was also a possibility to place a phenyl substituent in the 4-position of the quinazolines. In this case, 2-aminobenzophenone **107** would be reacted with *O*-phenyl hydroxylamine hydrochloride in pyridine to yield the oxime ether **108**. The reaction was carried out at room temperature for 24 hour, 48 hours and 72 hours. Unfortunately only a minimal conversion to the desired product was achieved in all of them. The condensation was also carried out at 50 °C for four hours but none of the oxime ether **108** was formed. This unsuccessful reactivity may be due to steric hindrance between one of the phenyl groups of the 2-aminobenzophenone and the phenyl hydroxylamine (Scheme 44).

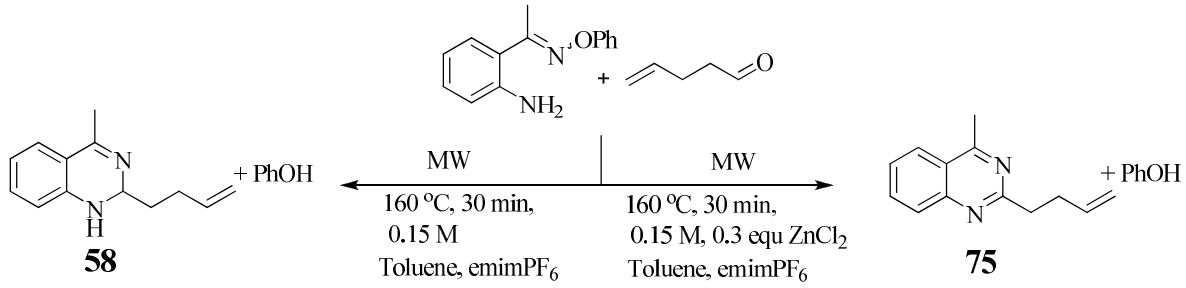


107 **108**

Scheme 44

2.2.7 Mechanism.

As has been described above, the inclusion of $ZnCl_2$ in the reaction entailed a change in the final product. Excellent yields in the syntheses of quinazolines were achieved instead of dihydroquinazolines in the presence of $ZnCl_2$. It was, therefore, possible that the presence of the Lewis acid had caused a change in the mechanism of the process (Scheme 45).



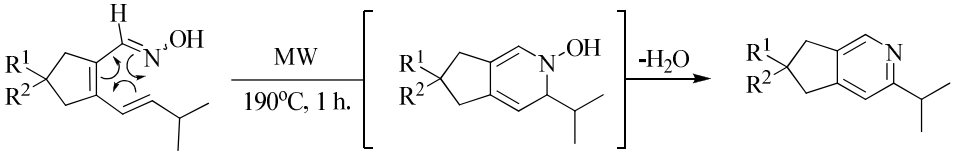
58 **75**

Scheme 45

However, it is known from earlier results described in the previous chapter that the precursor *O*-phenyl oximes are completely dissociated to radicals in < 30 min under the microwave conditions. To compete, any alternative mechanism would have to be faster than this.

2.2.7.1 Electrocyclic approach.

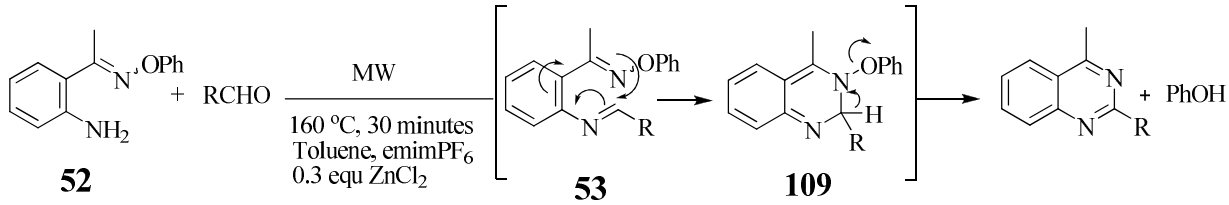
Electrocyclic ring closures could be an alternative to the radical proposed mechanism. Recently Trost and coworkers[52] have described the syntheses of substituted pyridine rings via 6π-electrocyclization and subsequent elimination of water under microwave irradiation (Scheme 46).



Scheme 46

There was, therefore, a possibility that electrocyclic ring closure could take place in the formation of the quinazolines. Imines **53** might electrocyclise to give the dihydroquinazoline intermediate **109** followed by the elimination of PhOH. The quinazoline and phenol would be the final products in this sequence (Scheme 47). However, it is unlikely

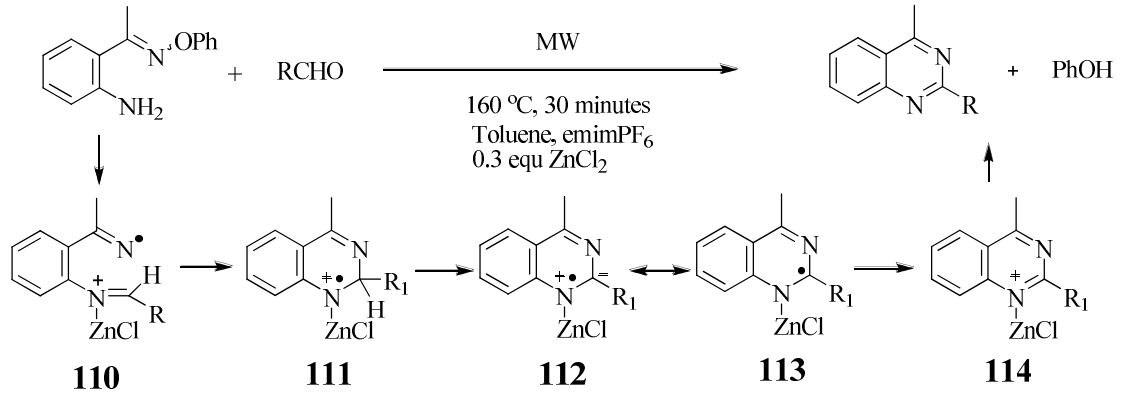
both these steps could be fast enough to compete with the radical process. Furthermore, none of the quinazoline was observed in the absence of $ZnCl_2$, therefore, the Lewis acid must play an important role in the mechanism.



Scheme 47

2.2.7.2 Iminium salt approach.

A different mechanism that could explain the formation of quinazoline in the presence of $ZnCl_2$ is outlined in Scheme 48. Possibly the zinc bonds to the imine prior to cyclisation i.e. **110** and the subsequent ring closure gives amminium radical cation **111** in a process akin to an iminium salt cyclisation. The adjacent cation would considerably lower the pK_a of the H-atom at position 2 of the heterocycle **111**. Proton loss would then yield **112** in a process reminiscent of the Minisci reaction.[53] Stabilised intermediate **113** might tranfer an electron to the starting oxime ether to give **114** or be converted to **114** on exposure to oxygen during work-up. When the $ZnCl_2$ is not present, the C-H at position 2 is not acidic, and hence aromatisation to a quinazoline does not occur.[54]

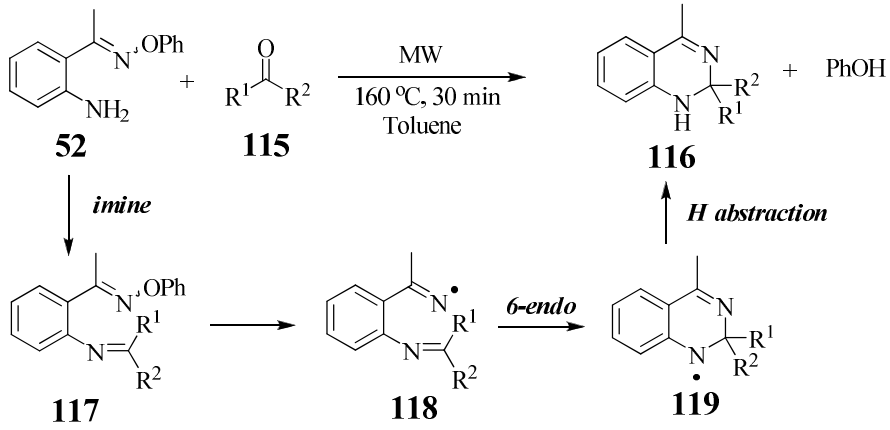


Scheme 48

2.3 Reaction with ketones.

2.3.1 Syntheses of 2-disubstituted 4-methyl-dihydroquinazolines.

It was postulated that stable 2-disubstituted dihydroquinazolines could also be prepared by reaction of the oxime ether **52** with ketones as is outlined in Scheme 49.



Scheme 49

This approach is similar to the one described for the aldehydes, the formation of the imine intermediate **117** being the first step of the sequence. Subsequently, iminyl radical **118** would be generated by N-O bond scission and cyclisation onto the imine would yield the aminyl radical **119**. Hydrogen abstraction from toluene may give the 2-di-substituted dihydroquinazoline **116** with an equal amount of phenol. The absence of an H-atom at the 2-position of the dihydroquinazoline prevents oxidation to quinazolines.

To assess the scope and limitations of this annulation, reactions of oxime ether **52** with several commercially available ketones were carried out in toluene, emimPF_6 as ionic liquid, with and without $ZnCl_2$ under microwave irradiation for 30 minutes at 160 °C (Table 12).

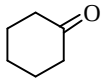
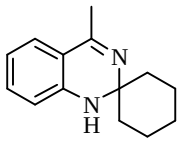
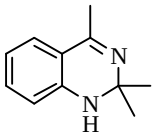
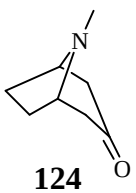
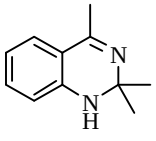
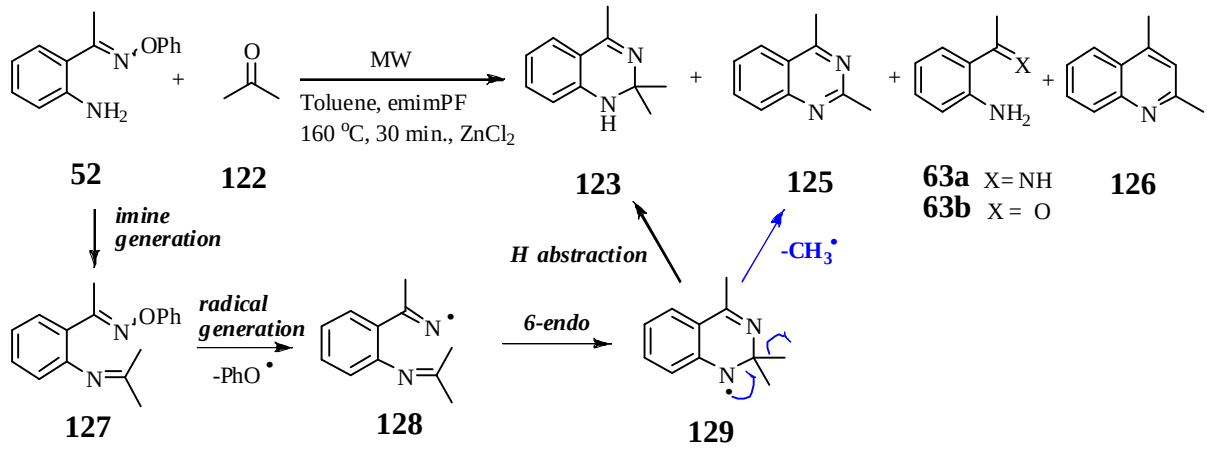
Run	Ketones	Conditions	Quinazolines	Yields
1	 **120**	0.1 M, Toluene emimPF_6, 160°C, 30 min.	 **121**	**78 %**[a]
2		0.1 M, Toluene emimPF_6, 0.3 eq. $ZnCl_2$ 160°C, 30 min.		**82 %**[a]
3	 **122**	0.1 M, Toluene emimPF_6, 160°C, 30 min.	 **123**	**36 %**[b]
4		0.1 M, Toluene emimPF_6, 0.3 eq. $ZnCl_2$ 160°C, 30 min.		**45 %**[a]
5	 **124**	0.1 M, Toluene emimPF_6, 160°C, 30 min.	 **123**	**20 %**[b]
6		0.1 M, Toluene emimPF_6, 0.3 eq. $ZnCl_2$ 160°C, 30 min.		**21 %**[a]

Table 12. Syntheses of dihydroquinazolines via microwave assisted reaction of **52** and ketones. [a] Isolated yields. [b] Determined by ^{1}H NMR of crude reaction mixture.

A promising result was achieved by reaction of oxime ether **52** with cyclohexanone **120** (entries 1 and 2). Microwave irradiation of the mentioned starting materials in toluene afforded excellent yields of the spirodihydroquinazoline **121**, with and without $ZnCl_2$.

When the reaction was carried out with acetone the dihydroquinazoline **123** yield dropped dramatically to 36 % and 45 % in the absence and presence of $ZnCl_2$ respectively (entries 3 and 4). The total reaction mixture of the Lewis acid mediated process was studied by NMR and GC/MS. The ^1H NMR showed a complex mixture of products difficult to identify. The GC/MS of the reaction mixture showed phenol, imine **63a**, ketone **63b** and six additional major peaks. The first eluted component had M^+ = 158 and its spectrum matched the library spectrum of 2,4-dimethylquinazoline **125** (91% confidence level). The second eluted component (M^+ = 174) was probably dihydroquinazoline **123** (Scheme 50). The quantitative formation of phenol was also of note. Its presence confirmed the generation of the phenoxyl radical and hence strengthened the radical mechanism approach described in Scheme 48. If the 6π-electrocyclization had taken place, anisole should have been formed in the elimination step, by analogy with the step shown in Scheme 47. No anisole was detected by GC/MS.



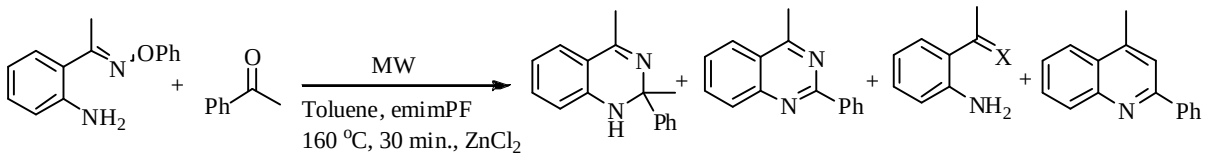
Scheme 50

The expected product **123** was presumably formed by H-atom abstraction by aminyl radical **129** from the solvent. The elimination of a methyl radical would provide a plausible explanation to the experimental finding of **125**. Interestingly, the mass spectrum of the third eluted component (M^+ = 157) matched the library spectrum of 2,4-dimethylquinoline **126** (94 % confidence level). The fourth component remained unidentified but the final two longer

retention time components had mass spectra identical to those of **135** and **136** (Figure 6 see below for an explanation of the formation of the quinoline derivatives).

Reaction of oxime ether **52** with the alkaloid tropinone **124** was also studied. Unfortunately none of the desired product was formed according to the NMR and GC/MS data. Moreover, it is possible that tropinone was not stable in the reaction conditions and may have decomposed to various fragments. The fact, that 2,2,4-trimethyl-1,2-dihydroquinazoline **123** was isolated in 21 % yield, may tell us that acetone was formed during the process and it could have reacted with oxime ether **52** as described in Scheme 50.

Acetophenone was the last ketone studied in this annulation process. Microwave irradiation in the usual conditions gave again a complex mixture of compounds difficult to interpret by NMR spectroscopy (Scheme 51). The GC/MS showed the presence of unreacted starting material **130**, phenol, imine **63a**, ketone **63b**, together with six additional major components and several minor ones. The first and second of these (M^+ = 221 and 220 respectively) were probably dihydroquinazoline **131** and quinazoline **132**. The mass spectrum of the third component (M^+ = 219) matched the library spectrum of 2-phenyl-4-methylquinoline **133** at the 95 % confidence level. There were two additional longer retention time components (M^+ = 234, 235 respectively) which we identify as quinoline **136** and quinazoline **135** derivatives respectively (Figure 6).

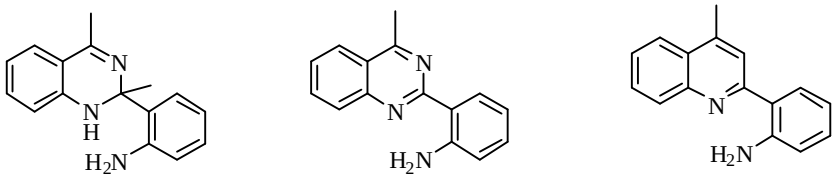


52 **130** **131** **132** **63a** X = NH **63b** X = O **133**

Scheme 51

The presence of **130**, the imine **63a** and its hydrolysis product **63b** in the crude reaction mixture confirmed that the annulation reaction, and more concretely the imine formation, was not very efficient. This may be due to the high sensitivity of the imine condensation to steric hindrance effects.

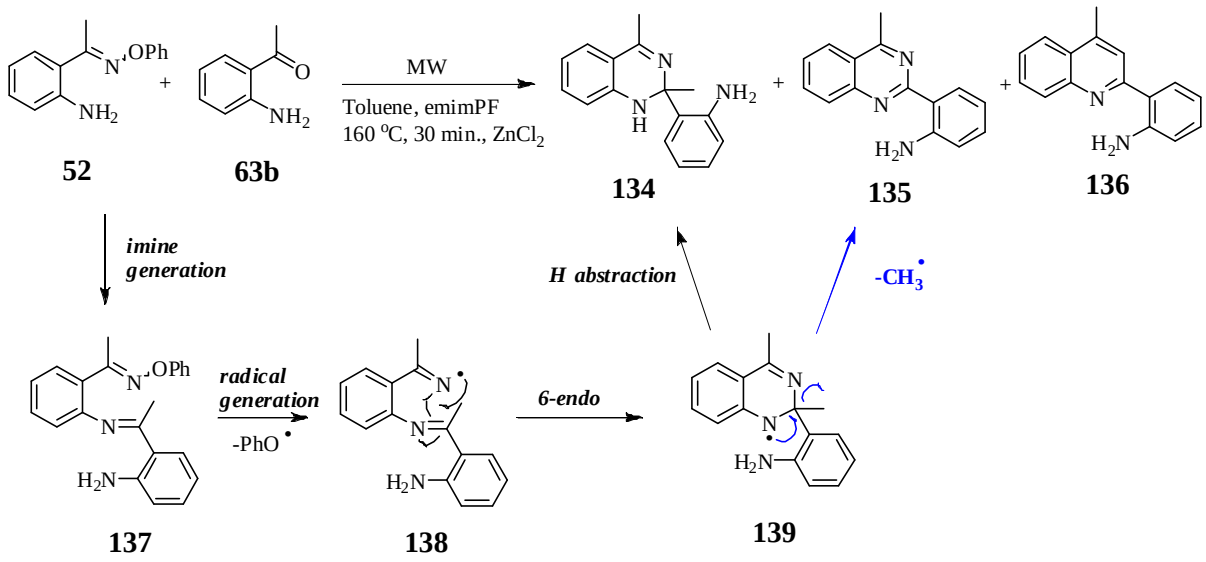
Interestingly, in all the reactions of **52** with the different ketones, three comon peaks were found in the GC/MS spectra, independently of which ketone was used. We identified these peaks as quinazolines **134** and **135** and quinoline **136** (Figure 6).



134 **135** **136**

Figure 6

To explain the formation of these compounds, it was conjectured that aniline **52** could react with the ketone **63b** the hydrolyzed product of the imine **63a**, to give the imine **137**. Subsequent generation of the iminyl radical and 6-*endo* cyclisation onto the imine, could give aminyl radical **139**. Dihydroquinazoline **134** would be obtained by hydrogen abstraction from the solvent. The related quinazoline **135** was presumably formed by elimination of a methyl radical (Scheme 52).



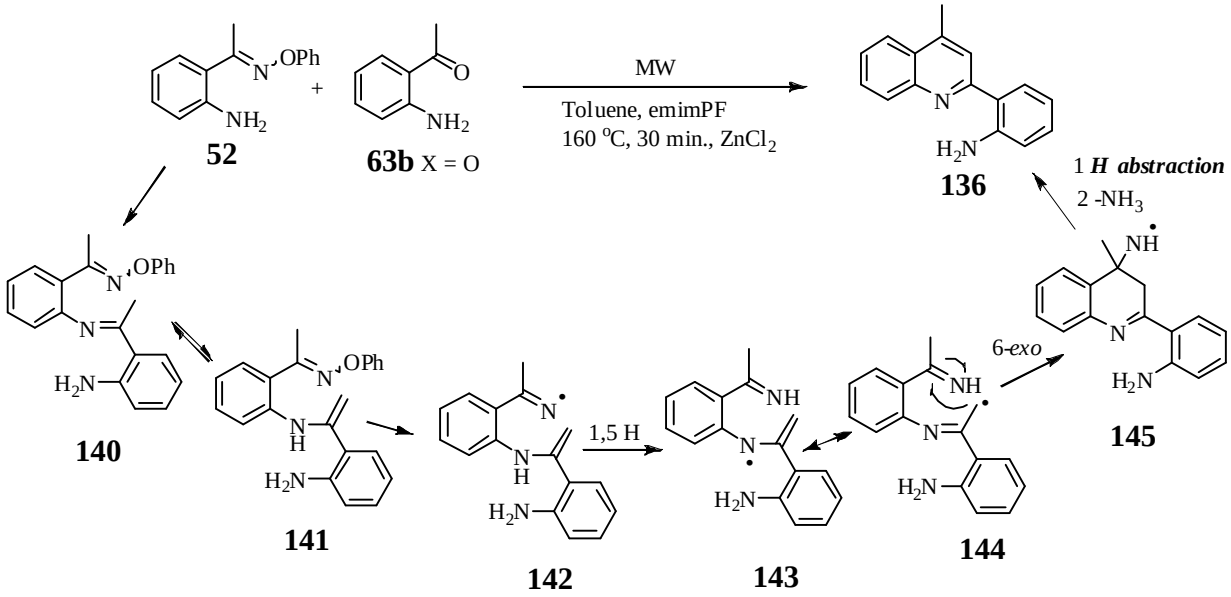
52 **63b** **134** **135** **136**

137 **138** **139**

Scheme 52

The most intriguing aspect of this reaction was the apparent formation of products containing the *quinoline* ring, i.e. **126**, **133** and **136**. A tentative mechanism to account for

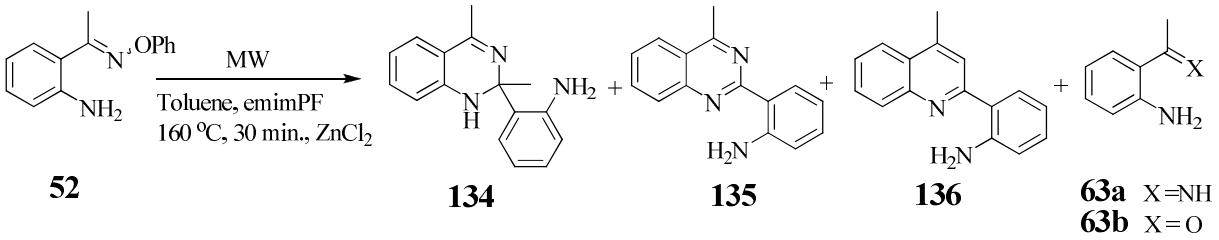
this is outlined in Scheme 53 for the case of **136**. The imine **140** may tautomerize to the enamine intermediate **141**. Generation of the iminyl radical could be followed by a favoured [1,5] hydrogen shift giving the aza-allyl radical **143**. This radical is in resonance with **144** which may undergo 6-*exo* intramolecular addition onto the newly formed imine **144** giving aminyl radical **145**. Hydrogen abstraction from the solvent and subsequent elimination of ammonia could then yield 2-(4-methylquinolin-2-yl)aniline **136**.



Scheme 53

The presence of quinolines **126** and **133** in the reactions of oxime ether **52** with acetone **122** and acetophenone **130** respectively, induced us to think that a mechanism analogous to that described in Scheme 53 could have also taken place with the corresponding ketones, in competition with the 6-*endo* cyclisations.

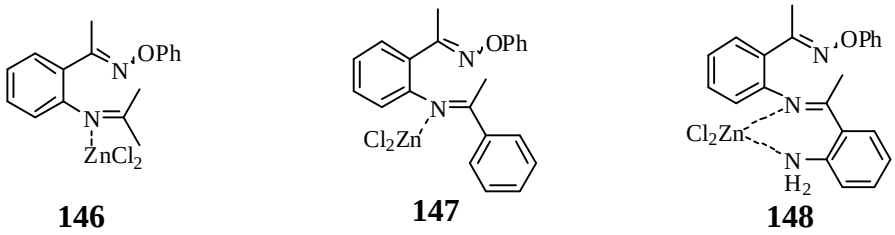
To confirm that quinazoline **135** and quinoline **136** were formed as described in Scheme 52, oxime ether **52** was reacted on its own, without any ketone being present, under the usual reaction conditions in toluene with ionic liquid and $ZnCl_2$ (Scheme 54). The 2-(4-methylquinazolin-2-yl)aniline **135** was isolated in 41 % yield, dihydroquinazoline **134** could not be isolated but a minor peak in the GC/MS with the correct mass confirmed that it was formed. The driving force for the elimination of a methyl radical, as described in Scheme 52, may be the high level of aromatic resonance of the final product **135**. The quinoline **138** was also isolated in 18 % yield and its identity confirmed from its NMR spectra.



52 **134** **135** **136** **63a** X=NH **63b** X=O

Scheme 54

It was interesting that oxime ether **52** reacted with the ketone **63b**, being a side product of the reaction, instead of reacting with one equivalent of the corresponding ketone acetone or acetophenone. A tentative explanation was that the amine group in the imine intermediate as well as imine might interact with the $ZnCl_2$ present in the reaction medium i.e. **148** favoured against intermediates **146** and **147** from acetone and acetophenone respectively (Figure 7).



146 **147** **148**

Figure 7

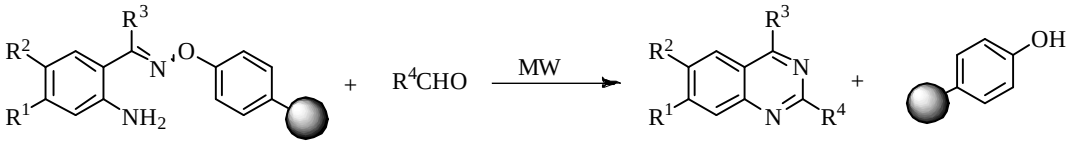
It was clear from the results described above, that reaction of oxime ether **52** with ketones, did not constitute an efficient method for the syntheses of 2-disubstituted quinazolines. The reactions generally gave complex mixtures of numerous compounds. It was also shown that when reactions were carried out with more sterically demanding ketones, such as acetophenone, the complexity of the total reaction mixture increased due to the poor efficiency of imine formation.

3.0 Conclusions.

The results show that 2-(aminoaryl)alkanone *O*-phenyl oximes are excellent precursors for quinazoline derivatives. They react in one pot, with aliphatic aldehydes, in microwave-assisted reactions yielding dihydroquinazolines. When more sterically demanding aldehydes were used the yield dropped dramatically.

The precursor *O*-phenyloximes are easily made in one step from the corresponding carbonyl and *O*-phenyl hydroxylamine in good yields and can be stored indefinitely. Nevertheless, it was found that electronic and steric hindrance effects played an important role in the success of the condensation reaction.

An interesting possibility would be the use a solid supported *O*-phenyl hydroxylamine HCl. The use of solid-supported syntheses in combinatorial chemistry and drug discovery is having a profound effect on the way synthetic chemistry is carried out due to the inherent advantages it offers. In this case the use of solid supported *O*-phenyl hydroxylamine HCl would have a dramatic impact in the purification process because the phenol could be removed by a simple filtration (Scheme 55).



Scheme 55

If $ZnCl_2$ is included in the mixture, quinazolines are obtained instead of dihydroquinazolines. The process is of wide scope and works well with alkyl, aryl and heterocyclic types of aldehydes. The reaction has all the advantages associated with microwave chemistry. The process is rapid, high yielding, reproducible, neutral and comparatively mild. The methodology was successful in the syntheses of quinazolines with high steric demand, such as, 4-methyl-2-(6-phenylbenzo[*d*][1,3]dioxol-5-yl)quinazoline **90** and 2-(6-bromobenzo[d][1,3]dioxol-5-yl)quinazoline **106** (Figure 8).

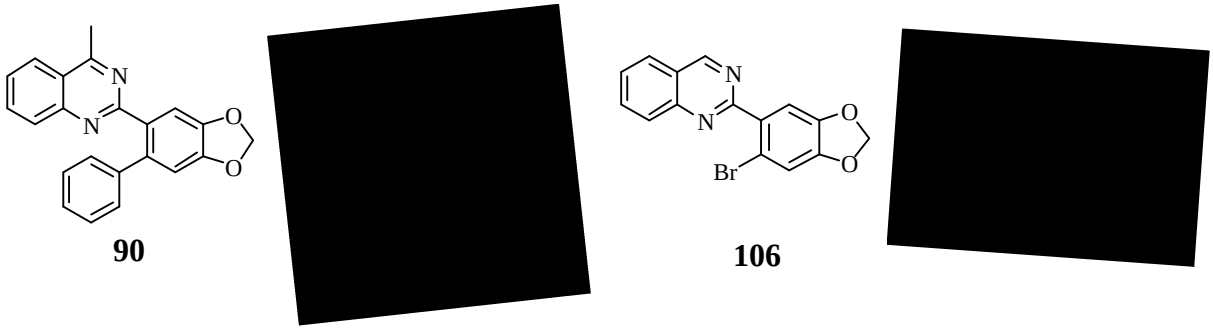


Figure 8. Geometry optimization of quinazolines **90** and **106** with MM2.

Interesting and useful quinazoline building blocks were prepared in excellent yields and short reaction times with a variety of substituents convenient for further functional group transformation, such as, palladium coupling or reduction of nitro groups to amines. Quinazolines with heterocycles as substituents were also achieved in good yields. Quinazoline derivatives exhibit interesting pharmacological properties related to the planarity of the system. Consequently, these compounds present a DNA-chain intercalating ability. Quinazolines like 4-methyl-2-(pyridine-2-yl)quinazoline, which resembles the adenine structure, may have this ability.

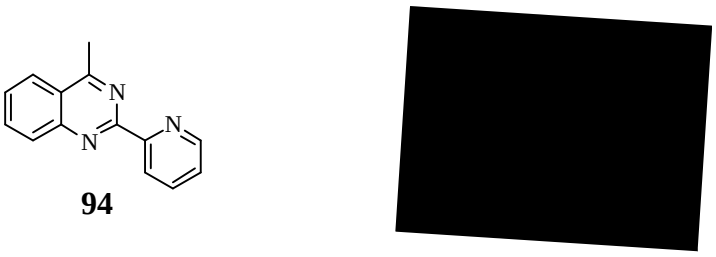


Figure 9. Geometry optimization of quinazoline **94** with MM2.

On the other hand, although this methodology is extremely effective for the preparation of quinazolines from aldehydes it does not appear to be a suitable method in the preparation of dihydroquinazolines from ketones. Apart from the reaction with cyclohexanone, complex mixtures of several compounds were obtained in the reaction of 1-(2-aminophenyl)ethanone *O*-phenyl oxime with ketones.

4.0 Experimental.

1-(2-aminophenyl)ethanone *O*-phenyl oxime 52.

O-Phenyl hydroxylamine hydrochloride (2.15 g, 15 mmoles) was dissolved in anhydrous pyridine (40 mL) under N_2 at room temperature, and 1-(2-aminophenyl)ethanone (2.0 g, 15 mmoles) was added in one portion. The resulting solution was stirred at room temperature overnight, and the progress of the reaction was monitored by TLC (EtOAc/ hexane, 1:2). Upon completion, the reaction mixture was poured into water (40 mL) and extracted with EtOAc (3 x 30 mL), and the combined organic phases were washed several times with saturated, aqueous $CuSO_4$ solution to remove any traces of pyridine. The solution was then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc/hexane) affording a dark orange oil (2.54 g, 76 %). NMR (400 MHz, $CDCl_3$), δ_H; 2.56 (3H, s, CH_3), 5.72 (2H, s, NH_2), 6.80 (2H, m, CH), 7.10 (1H, tt, J = 7.2, 1.1 Hz, CH), 7.22 (1H, t, J = 7.7 Hz, CH), 7.28 (2H, m, CH), 7.39 (2H, t, J = 7.2 Hz, CH), 7.49 (1H, dd, J = 7.7, 1.4 Hz, CH); ^{13}C NMR δ_C; 14.1 (CH_3), 114.8, 118.8, 117.0 (CH), 117.6 (C), 122.3, 129.4, 129.5, 130.3 (CH), 146.2, 159.4, 160.4 (C); IR3474, 3345, 1613, 1593 cm^{-1}; HRMS calcd for $C_{14}H_{15}N_2O$ (MH^+) 227.1183, found 227.1184.

Typical procedure for 4-methyldihydroquinazoline preparations 2-(but-3-enyl)-4-methyl-1,2-dihydroquinazoline 58.

Pent-4-enal (37.0 mg, 0.44 mmol) was added to a solution of 1-(2-aminophenyl)ethanone *O*-phenyl oxime (100 mg, 0.44 mmol) in toluene (0.15 M) and emimPF_4 (100 mg, 0.46 mmol) in a microwave vessel (2-5 cm^3). The vessel was sealed and subjected to microwave irradiation for 30 min at 160 °C in a Biotage Initiator system (nominally 300MHz). After cooling the ionic liquid was filtered off and the toluene was removed under reduced pressure. The residue was purified by flash column chromatography (25 % EtOAc/hexane) affording the desired product as a yellow oil (83.1 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.84 (2H, m, CH_2), 2.20 (2H, m, CH_2), 2.23 (3H, s, CH_3), 3.90 (1H, s, NH), 4.77 (1H, t, J = 5.8 Hz, CH), 4.92 (1H, m, CH_2), 5.01 (1H, dq, J = 17.0, 1.8 Hz, CH_2), 5.80 (1H, m, CH), 6.45 (1H, dd, J = 8.0, 0.8 Hz, CH), 6.63 (1H, td, J = 7.6, 1.1 Hz, CH), 7.1 (1H, m, CH), 7.21 (1H, dd, J = 7.7, 1.3 Hz, CH); ^{13}C NMR δ_C; 21.0 (CH_3), 28.11, 34.5 (CH_2), 67.9, (CH), 112.9 (CH), 114.1 (CH_2), 117.0 (CH), 117.5 (C), 125.3, 131.7 (CH), 137.6 (CH), 144.7, 161.9 (C); IR 3302, 1611 cm^{-1}; HRMS calcd for $C_{13}H_{17}N_2$ (MH^+) 201.1392, found 201.1390.

4-Methyl-2-phenethyl-1,2-dihydroquinazoline 66.

From 3-phenyl propanal (58.9 mg, 0.44 mmol), as described for **58**.Yellow oil (101.7 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.06 (2H, m, CH_2), 2.23 (3H, s, CH_3), 2.75 (2H, m, CH_2), 3.80 (1H, s, NH), 4.78 (1H, t, *J* = 5.6 Hz, CH), 6.36 (1H, d, *J* = 8.0 Hz, CH), 6.61 (1H, t, *J* = 7.9 Hz, CH), 7.12 (7H, m, CH); ^{13}C NMR δ_C; 21.6 (CH_3), 30.2, 37.1 (CH_2), 67.7 (CH), 113.0, 116.9 (CH), 117.6 (C),121.9, 124.9, 127.4, 127.4, 131.5 (CH), 140.7, 144.6 162.3 (C); IR 3395, 1585 cm^{-1}; HRMS calcd for $C_{17}H_{19}N_2$ (MH^+) 251.1548, found 251.1551.

2-*n*-Butyl-4-methyl-1,2-dihydroquinazoline 68.

From pentanal (37.8 mg, 0.44 mmol), as described for **58**.Yellow oil (80.0 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 0.86 (3H, t, *J* = 7.1 Hz, CH_3), 1.33 (4H, m, CH_2), 1.75 (2H, m, CH_2), 2.24 (3H, s, CH_3), 3.86 (1H, s, NH), 4.71 (1H, t, *J* = 6.0 Hz, CH), 6.46 (1H, dd, *J* = 8.0, 0.8 Hz, CH), 6.62 (1H, td, *J* = 7.4, 1.1 Hz, CH), 7.10 (1H, m, CH), 7.21, (1H, dd, *J* = 7.7 Hz, 1.3 Hz, CH); ^{13}C NMR δ_C; 13.9, 22.4 (CH_3), 23.1, 27.3, 36.5 (CH_2), 69.1 (CH), 114.0, 117.9 (CH), 118.9 (C), 126.3, 132.5 (CH), 146.2, 162.8 (C); IR3467, 1573 cm^{-1}; HRMS calcd for $C_{13}H_{19}N_2$ 203.1548 (MH^+), found 203.1556.

4-Methyl-2-phenyl-1,2-dihydroquinazoline 70.

From benzaldehyde (46.6 mg, 0.44 mmol), as described for **58**.Yellow oil (70.7 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.15 (3H, s, CH_3), 4.05 (1H, s, NH), 5.77 (1H, m, CH), 6.48 (1H, dd, *J* = 8.0, 0.9 Hz, CH), 6.68 (1H, td, *J* =7.5, 1.1 Hz, CH), 7.14 (1H, m, CH), 7.24-7.34 (5H, m, CH), 7.46 (1H, m, CH); ^{13}C NMR δ_C; 21.5 (CH_3), 71.5 (C) 113.1, 117.5 (CH), 116.8 (C), 125.5, 126.1, 127.3, 127.6, 131.7 (CH), 134.1, 145.7, 162.1 (C); IR 3347, 1571 cm^{-1}; [NB: MS analysis, with several different insertion methods, showed **7d** converted to the corresponding quinazoline (MH^+ = 221.1087; calcd. for $C_{15}H_{13}N_2$ 221.1079) during spectral collection.]

Typical Procedure of Oxidation of Dihydroquinazolines to Quinazolines . 2-(But-3-enyl)-4-methylquinazoline 75.

A solution of 2-(But-3-enyl)-4-methyl-1,2-dihydroquinazoline **58** (50 mg, 0.25 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (68 mg, 0.30 mmol) in DCM (4 mL) was placed in a microwave vial and was irradiated for 10 minutes at 100 °C. The solvent was removed

under reduced pressure. The residue was purified by column chromatography (5 % EtOAc/hexane) giving the desired product as a brown oil (49 mg, 83 %).

Dihydroquinazoline oxidation by oxygen bubbling: 2-(But-3-enyl)-4-methylquinazoline 75.

A solution of 2-(but-3-enyl)-4-methyl-1,2-dihydroquinazoline **58** (25 mg, 0.12 mmol) in $CDCl_3$ (1 cm^3) was placed in a standard NMR tube and oxygen was continuously bubbled for 48 h. at 50 °C. The conversion to quinazoline **75** was monitored by ^1H NMR spectroscopy at 4 h., 8 h., 24 h. 48 h (yields in Table 4). Conversion of **58** was complete in 48 h giving **75** (88 %) together with additional unidentified by-products.

Typical Procedure for $ZnCl_2$ Promoted Quinazoline Preparations: 2-(But-3-enyl)-4-methylquinazoline 75.

Pent-4-enal (36.9 mg, 0.44 mmol) was added to a solution of 1-(2-aminophenyl)ethanone *O*-phenyl oxime (100 mg, 0.44 mmol) in toluene (0.15 M), containing anhydrous $ZnCl_2$ (17 mg, 0.13 mmol) and $emimPF_4$ (100 mg, 0.46 mmol) in a microwave vessel (2-5 cm^3). The vessel was sealed and subjected to microwave irradiation for 30 min at 160 °C in a Biotage Initiator system. After cooling, the ionic liquid was filtered off and the toluene was removed under reduced pressure. The residue was purified by flash column chromatography (5 % EtOAc/hexane) affording the desired product as a yellow oil (79.0 mg, 91 %). ^1H NMR (400 MHz, $CDCl_3$), δ_H; 2.60 (2H, q, J = 8.0 Hz, CH_2), 2.87 (3H, s, CH_3), 3.09 (2H, m, CH_2), 4.92-5.01 (2H, m, CH_2), 5.88 (1H, m, CH), 7.48 (1H, ddd, J = 8.2,6.9, 1.2 Hz, CH), 7.76 (1H, ddd, J = 8.4, 6.9, 1.4 Hz, CH), 7.88 (1H, d, J = 8.3 Hz, CH), 7.98 (1H, d, J = 8.3 Hz, CH); ^{13}C NMR δ_C; 22.0 (CH_3), 38.8 (CH_2), 39.3 (CH_2), 115.2 (CH_2), 122.5 (C), 125.0, 126.7, 128.5, 133.6 (CH), 137.9 (CH), 149.9, 166.1, 168.1 (C); IR 1617, 1561 cm^{-1}; HRMS calcd for $C_{13}H_{15}N_2$ (MH^+) 199.1235, found 199.1234

2-Cyclohexyl-4-methylquinazoline 82.

From cyclohexanecarbaldehyde (49 mg, 0.44 mg), as described for **75**.Yellow solid (79.9 mg, 80%); mp 46-48 °C. ^1H NMR (400 MHz, $CDCl_3$), δ_H; 1.35-1.73 (8H, m, CH_2), 1.99 (2H, m, CH_2), 2.86 (3H, s, CH_3), 2.93 (1H, m, CH), 7.47 (1H, ddd, J = 8.2, 6.9, 1.2 Hz, CH), 7.75 (1H, ddd, J = 8.3, 6.8, 1.3 Hz, CH), 7.90 (1H, d, J = 8.3 Hz, CH), 7.97 (1H, m, CH); ^{13}C NMR δ_C; 21.7 (CH_3), 26.0, 26.3, 31.9 (CH_2), 47.8 (CH), 122.8 (C), 125.1, 126.4, 128.5,

133.3 (CH), 150.1, 168.1, 170.0 (C); IR 1615, 1560 cm^{-1}; HRMS calcd for $C_{15}H_{19}N_2$ (MH^+) 227.1548, found 227.1544.

2-(4-Bromophenyl)-4-methylquinazoline 84.

From 4-bromobenzaldehyde (80 mg, 0.44 mmol), as described for **75**.Yellow solid (112.3 mg, 85 %); mp 82-85 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.93 (3H, s, CH_3) 7.50 (1H, td, *J* = 7.7, 1.1 Hz, CH), 7.56 (2H, dt, *J* = 8.7, 1.9 Hz, CH), 7.78 (1H, td, *J* = 7.7, 1.4 Hz, CH), 7.98 (1H, d, *J* = 8.9 Hz, CH), 8.01 (1H, d, *J* = 8.9 Hz, CH), 8.42 (2H, dt, *J* = 8.7, 1.9 Hz, CH); ^{13}C NMR δ_C; 21.0 (CH_3), 122.0 (C), 124.0 (CH), 124.1 (C), 126.1, 128.2, 129.1, 130.7, 132.6 (CH), 136.2, 149.2, 158.1, 167.3 (C); IR 1616, 1572 cm^{-1}; HRMS calcd for $C_{15}H_{12}N_2{}^{79}Br$ (MH^+) 299.0184, found 299.0189.

4-Methyl-2-(4-nitrophenyl)quinazoline 86.[55]

From 4-nitrobenzaldehyde (66.4 mg, 0.44 mmol), as described for **75**.Yellow solid (105.4 mg, 90%); mp 168-179 °C. ^{1}H NMR (400 MHz,$CDCl_3$), δ_H; 2.96 (3H, s, CH_3), 7.58 (1H, ddd, *J* = 8.2, 7.6, 1.2 Hz, CH), 7.84 (1H, ddd, *J* = 8.5, 7.0, 1.4 Hz, CH), 8.02 (1H, d, *J* = 7.8 Hz, CH), 8.04 (1H, d, *J* =7.8 Hz, CH), 8.26 (2H, d, *J* =9.0 Hz, CH), 8.72 (2H, dt, *J* = 9.0. 2.0 Hz, CH); ^{13}C NMR δ_C; 21.5 (CH_3), 122.3 (C), 122.6, 124.3, 126.9, 128.4, 128.3, 133.0 (CH), 143.0, 148.1, 149.2, 156.8, 167.8 (C); IR 1597, 1569, 1548, 1340 cm^{-1}; HRMS calcd for $C_{15}H_{12}N_3O_2$ (MH^+) 266.0930, found 266.0936.

4-(4-(4-Methylquinazolin-2-yl)phenyl)morpholine 88.

From 4-morpholinobenzaldehyde (84.0 mg, 0.44 mmol) as described for **75**.Yellow solid (103.8 mg, 77 %); mp 135-137 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.91 (3H, s, CH_3), 3.22 (4H, t, *J* = 4.9 Hz, CH_2), 3.82 (4H, t, *J* = 4.9 Hz, CH_2), 6.94 (2H, d, *J* = 8.9 Hz, CH), 7.45 (1H, td, *J* = 7.5, 1.2 Hz, CH), 7.75 (1H, td, *J* = 7.5, 1.2 Hz, CH), 7.96 (2H, m, CH), 8.48 (2H, d, *J* = 8.9 Hz, CH); ^{13}C NMR δ_C; 22.4 (CH_3), 48.3, 67.1 (CH_2), 114.9 (CH), 122.8 (C), 124.9, 126.5 (CH), 128.8 (C), 129.0 (CH), 129.2 (C), 130.0, 133.0 (CH), 152.8, 160.0, 168.1 (C); IR 1603, 1572 cm^{-1}; HRMS calcd for $C_{19}H_{20}N_3O$ (MH^+) 306.1606, found 306.1602.

4-Methyl-2-(6-phenylbenzo[*d*][1,3]dioxol-5-yl)quinazoline 90.

From 6-phenylbenzo[d][1,3]dioxole-5-carbaldehyde (99.4 mg, 0.44 mmol) as described for **75**.Yellow solid (85.6 mg, 58 %); mp 215-217 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.63 (3H, s, CH_3), 6.01 (2H, s, CH_2), 6.89 (1H, s, CH), 7.07 (5H, m, CH), 7.41 (1H, s, CH), 7.48 (1H, ddd, J = 8.3, 6.7, 1.5 Hz, CH), 7.73 (1H, m, CH), 7.77 (1H, m, CH), 7.92 (1H, d, J = 8.3 Hz, CH) ; ^{13}C NMR δ_C; 20.6 (CH_3), 100.4 (CH_2), 109.8, 110.0 (CH), 121.1 (C), 123.8, 125.2, 126.0, 126.9, 127.8, 128.2, 132.6 (CH), 136.0, 140.9, 141.7, 146.0, 147.5, 158.9, 161.7, 167.7 (C); IR 1612, 1550 cm^{-1}; HRMS calcd for $C_{22}H_{16}N_2O_2Na$ (MNa^+) 363.1110, found 363.1101

2-(Furan-2-yl)-4-methylquinazoline 92.

From fural-2-carbalehyde (42.3 mg, 0.44 mmol), as described for **75**. Brown solid (65.2 mg, 76%); mp 106-108. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.91 (3H, s, CH_3), 6.53 (1H, dd, J = 3.4, 1.8 Hz, CH), 7.38 (1H, dd, J = 3.4, 0.8 Hz, CH), 7.49 (1H, ddd, J = 8.2, 7.0, 1.2 Hz, CH), 7.60 (1H, m, CH), 7.77 (1H, ddd, J = 8.4, 6.9, 1.2 Hz, CH), 7.99 (2H, m, CH); ^{13}C NMR δ_C; 20.6 (CH_3), 111.0, 112.7 (CH), 121.6 (C), 124.2, 126.0, 128.1, 132.7, 144.1 (CH), 147.8, 149.2, 164.2, 167.7 (C); IR 1589, 1547 cm^{-1}; HRMS calcd for $C_{13}H_{11}N_2O$ (MH^+) 211.0871, found 211.0874.

4-Methyl-2-(pyridine-2-yl)quinazoline 94.

From picolinaldehyde (47.0 mg, 0.44 mmol) as described for **75**.Yellow solid (69.3 mg, 71%); mp 108-110 °C. ^{1}H NMR (400 MHz, DMSO), δ_H; 3.01 (3H, s, CH_3), 7.59 (1H, m, CH), 7.78 (1H, ddd, J = 8.2, 6.9, 1.2 Hz, CH), 8.05 (2H, m, CH), 8.14 (1H, m, CH), 8.35 (1H, d, J = 8.2 Hz, CH), 8.58 (1H, d, J = 7.7 Hz, CH), 8.82 (1H, d, J = 4.3 Hz, CH); ^{13}C NMR δ_C; 22.2 (CH_3), 119.6 (C), 123.4, 124.3, 125.5, 126.2, 128.6, 129.3 (CH), 130.7 (C), 134.91 (CH), 149.9 (C), 150.1 (CH) 158.7, 169.7 (C); IR 1616, 1569, 1549 cm^{-1}; HRMS calcd for $C_{14}H_{12}N_3$ (MH^+) 222.1031, found 222.1029.

1-(2-amino-5-bromophenyl)ethanone 95.

A mixture of 2-aminoacetophenone (1g, 7.4 mmol) and sulfonic-acid-functionalized-acid (100 mg) in CH_3CN-Et_2O (1:3) (25 mL) NBS was added (7.4 mmol). The mixture was stirred at room temperature and the reaction was followed by TLC. After 3 hour the reaction was completed and the mixture was filtered. The filtrate was concentrated and the residue was subjected to column cromatography on silica gel (EtOAc/hexane) to obtained pure product as

a brown solid (1.31g, 83 %); mp 81-84 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.60 (3H, s, CH_3), 6.59 (1H, d, J = 8.8 Hz, CH), 7.36 (1H, dd, J = 8.8, 2.3 Hz, CH), 7.87 (1H, d, J = 2.3 Hz, CH); ^{13}C NMR δ_C; 27.8 (CH_3), 106.6 (C), 119.1, 134.4, 137.4 (CH), 149.4, 199.8 (C).

1-(2-Amino-5-bromophenyl)ethanone *O*-phenyl oxime 96.

O-Phenyl hydroxylamine hydrochloride (0.68 g, 4.69 mmoles) was dissolved in anhydrous pyridine (20 mL) under N_2 at room temperature, and 1-(2-amino-5-bromophenyl)ethanone (1 g, 4.69 mmoles) was added in one portion. The resulting solution was stirred at room temperature overnight, and the progress of the reaction was monitored by TLC (EtOAc/ hexane, 1:2). Upon completion, the reaction mixture was poured into water (40 mL) and extracted with EtOAc (3 x 30 mL), and the combined organic phases were washed several time with saturated, aqueous $CuSO_4$ solution to remove any traces of pyridine. The solution was then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc/hexane) affording a yellow solid (955 mg, 67 %); mp 50-52 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.39 (3H, s, CH_3), 5.54 (2H, s, NH_2), 6.55 (1H, d, J = 8.7 Hz, CH), 6.98 (1H, tt, J = 7.3, 1.1 Hz, CH), 7.15 (3H, m, CH), 7.27 (2H, t, J = 7.4 Hz, CH), 7.45 (1H, d, J = 2.3 Hz, CH); ^{13}C NMR δ_C; 14.1 (CH_3), 108.5 (C), 115.2, 118.6 (CH), 119.6 (C), 122.8, 129.5, 131.6, 132.7 (CH), 145.5, 159.3 (C); IR 3475, 3341, 1611, 1593 cm^{-1}; HRMS calcd for $C_{14}H_{14}N_2O^{79}Br$ (MH^+) 305.0289, found 305.0292.

6-Bromo-4-methyl-2-phenylquinazoline 97.

Benzaldehyde (34.9 mg, 0.33 mmol) was added to a solution of 1-(2-amino-5-bromophenyl)ethanone *O*-phenyl oxime (100 mg, 0.33 mmol) in toluene (0.15 M), containing anhydrous $ZnCl_2$ (13 mg, 0.10 mmol) and $emimPF_4$ (100 mg, 0.46 mmol) in a microwave vessel (2-5 cm^3). The vessel was sealed and subjected to microwave irradiation for 30 min at 160 °C in a Biotage Initiator system. After cooling, the ionic liquid was filtered off and the toluene was removed under reduced pressure. The residue was purified by flash column chromatography (5 % EtOAc/hexane) affording the desired product as a yellow solid (87.2 mg, 89 %); mp 88-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.91 (3H, s, CH_3), 7.43 (3H, m, CH), 7.84 (2H, m, CH), 8.14 (1H, dd, J =1.8, 0.8 Hz, CH), 8.50 (2H, m, CH); ^{13}C NMR δ_C; 21.3 (CH_3), 119.6, 122.8 (C), 126.3, 127.0, 127.6, 129.6, 130.0, 135.9 (CH), 136.8, 148.0, 159.4, 166.2 (C); IR 1616, 1565 cm^{-1}; HRMS calcd for $C_{15}H_{12}N_2{}^{79}Br$ (MH^+) 299.0184, found 299.0189.

1-(2-Amino-4,5-dimethoxyphenyl)ethanone *O*-phenyl oxime 98.

O-Phenyl hydroxylamine hydrochloride (0.74 g, 5.1 mmoles) was dissolved in anhydrous pyridine (20 mL) under N_2 at room temperature, and 1-(2-amino-4,5-dimethoxyphenyl)ethanone (1 g, 5.1 mmoles) was added in one portion. The resulting solution was stirred at room temperature for 48 h, and the progress of the reaction was monitored by TLC (EtOAc/ hexane, 1:2). Upon completion, the reaction mixture was poured into water (40 mL) and extracted with EtOAc (3 x 30 mL), and the combined organic phases were washed several times with saturated, aqueous $CuSO_4$ solution to remove any traces of pyridine. The solution was then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc/hexane) affording a brown solid (0.92, 63 %); mp 51-53 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.40 (3H, s, CH_3), 3.76 (3H, s, CH_3), 3.78 (3H, s, CH_3), 5.43 (2H, s, NH_2), 6.18 (1H, s, CH), 6.85 (1H, s, CH), 6.95 (1H, tt, J = 7.3, 1.1 Hz, CH), 7.15 (2H, t, J = 8.1 Hz, CH), 7.25 (2H, t, J = 8.1 Hz, CH); ^{13}C NMR δ_C; 13.9, 56.2, 57.6, 100.8, 109.4, 113.4, 114.7, 122.1, 129.3, 141.0, 141.98, 151.4, 159.4, 160.2; IR 3398, 3265, 1592, 1515 cm^{-1}; HRMS calcd for $C_{16}H_{19}N_2O_3$ (MH^+) 287.1396, found 287.1409.

6,7-Dimethoxy-4-methyl-2-(4-bromophenyl)quinazoline 99.

4-Bromobenzaldehyde (63.9 mg, 0.35 mmol) was added to a solution of 1-(2-amino-4,5-dimethoxyphenyl)ethanone *O*-phenyl oxime (100 mg, 0.35 mmol) in toluene (0.15 M), containing anhydrous $ZnCl_2$ (13 mg, 0.10 mmol) and emimPF_4 (100 mg, 0.46 mmol) in a microwave vessel (2-5 mL). The vessel was sealed and subjected to microwave irradiation for 30 min at 160 °C in a Biotage Initiator system. After cooling, the ionic liquid was filtered off and the toluene was removed under reduced pressure. The residue was purified by flash column chromatography (5 % EtOAc/hexane) affording the desired product as a yellow solid (102.5 mg, 80%); mp 180-182 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.90 (3H, s, CH_3), 4.01 (3H, s, CH_3), 4.05 (3H, s, CH_3), 7.16 (1H, s, CH), 7.57 (1H, s, CH), 7.61 (2H, d, J = 8.6 Hz, CH), 8.44 (2H, d, J = 8.4 Hz, CH); IR 1619, 1551 cm^{-1}; HRMS calcd for $C_{17}H_{16}N_2O_2$ ^{79}Br (MH^+) 359.0395, found 359.0388.

6,7-Dimethoxy-4-methyl-2-(4-nitrophenyl)quinazoline 100.

From 4-nitrobenzaldehyde (52.8 mg, 0.35 mmol), as described for **99**. Yellow solid (105.6 mg, 91%); mp 201-203. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.90 (3H, s, CH_3), 4.01 (3H, s, CH_3), 4.04 (3H, s, CH_3), 7.17 (1H, s, CH), 7.39 (1H, s, CH), 8.27 (2H, d, J = 9.0 Hz, CH), 8.70 (2H, d, J = 9.0 Hz, CH); ^{13}C NMR δ_C; 22.3, 56.3, 56.6 (CH_3), 102.4, 107.3(CH), 118.8 (C), 123.7, 129.2 (CH), 147.7, 148.3, 148.9, 150.1, 150.7, 156.1, 165.3 (C); IR 1625, 1572, 1516, 1349 cm^{-1}; HRMS calcd for $C_{17}H_{16}N_3O_4$ (MH^+) 326.1141, found 326.1143.

2-Aminobenzaldehyde *O*-phenyl oxime 101.

O-Phenyl hydroxylamine hydrochloride (1.25 g, 8.3 mmoles) was dissolved in anhydrous pyridine (25 mL) under N_2 at room temperature, and 2-aminobenzaldehyde (1 g, 8.3 mmoles) was added in one portion. The resulting solution was stirred at room temperature overnight, and the progress of the reaction was monitored by TLC (EtOAc/ hexane, 1:2). Upon completion, the reaction mixture was poured into water (40 mL) and extracted with EtOAc (3 x 30 mL), and the combined organic phases were washed several times with saturated, aqueous $CuSO_4$ solution to remove any traces of pyridine. The solution was then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc/hexane) affording a yellow solid (1.36g, 78%); mp 45-47 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 5.49 (2H, s, NH_2), 6.68 (2H, m, CH), 6.97 (1H, tt, J = 7.2, 1.1 Hz, CH), 7.13 (4H, m, CH), 7.27 (2H, m, CH), 8.4 (1H, s, CH); ^{13}C NMR δ_C; 113.5 (C), 114.4, 115.8, 117.0, 122.3, 129.5, 131.2, 133.0 (CH), 146.9 (C), 155.0 (CH), 159.5 (C); IR 3467, 3325, 1618, 1593 cm^{-1}; HRMS calcd for $C_{13}H_{13}N_2O$ (MH^+) 213.1028, found 213.1025.

2-Phenethylquinazoline 102.[56]

3-Phenylpropanal (63.2 mg, 0.47 mmol) was added to a solution of 2-aminobenzaldehyde *O*-phenyl oxime (100 mg, 0.47mmol) in toluene (0.15 M), containing anhydrous $ZnCl_2$ (18 mg, 0.14 mmol) and $emimPF_4$ (100 mg, 0.46 mmol) in a microwave vessel (2-5 cm^3). The vessel was sealed and subjected to microwave irradiation for 30 min at 160 °C in a Biotage Initiator system. After cooling, the ionic liquid was filtered off and the toluene was removed under reduced pressure. The residue was purified by flash column chromatography (5 % EtOAc/hexane) affording the desired product as a yellow oil (90.2 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 3.19 (2H, m, CH_2), 3.38 (2H, m, CH_2), 7.19 (5H, m, CH), 7.54 (1H, ddd, J = 8.1, 7.0, 1.2 Hz, CH), 7.83 (2H, m, CH), 7.92 (1H, d, J = 8.4 Hz, CH), 9.30 (1H, s, CH);

^{13}C NMR δ_C; 33.8, 41.3 (CH_2), 122.1 (C), 124.9, 126.0, 126.8, 127.3, 127.4, 133.2, (CH), 140.7 149.3, (C), 159.6 (CH), 165.7 (C); IR 1619, 1585 cm^{-1}; HRMS calcd for $C_{16}H_{15}N_2$ (MH^+) 235.1235, found 235.1230.

2-(4-Methoxyphenyl)quinazoline 103.[57]

From 4-methoxybenzaldehyde (63.9 mg, 0.47 mmol) as described for **102**.Yellow solid (78.9 mg, 71%); mp 81-83 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 3.83 (3H, s, CH_3), 6.97 (2H, d, *J* = 9.0 Hz, CH), 7.50 (1H, ddd, *J* = 8.2, 7.0, 1.2 Hz, CH), 7.81 (2H, m, CH), 7.97, (1H, d, *J* = 8.3 Hz, CH), 8.50 (2H, d, *J* = 9.0 Hz, CH), 9.35 (1H, d, *J* = 0.7 Hz, CH); ^{13}C NMR δ_C; 54.3 (CH_3), 113.1 (CH), 123.4 (C), 125.8, 126.1, 127.4, 129.2, 133.0, 159.4 (CH), 142.7, 150.8, 161.8, 167.4 (C); IR 1606, 1588 cm^{-1}; HRMS calcd for $C_{15}H_{13}N_2O$ (MH^+) 237.1028, found 237.1031.

2-(Thiophen-2-yl)quinazoline 104.

From thiophene-2-carbaldehyde (52.6 mg, 0.47 mmol), as described for **102**. Yellow solid (78.0 mg, 78%); mp 64-66 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.12 (1H, dd, *J* = 5.1, 3.8 Hz, CH), 7.44 (1H, dd, *J* = 5.0, 1.1 Hz, CH), 7.50 (1H, ddd, *J* = 8.1, 6.8, 1.0 Hz, CH), 7.81 (1H, m, CH), 7.83 (1H, m, CH) 7.94 (1H, d, *J* =8.9 Hz, CH), 8.08 (1H, dd, *J* = 3.7, 1.2 Hz, CH), 9.28 (1H, s, CH); ^{13}C NMR δ_C; 122.3 (C), 126.0, 126.3, 127.2, 127.4, 128.2, 129.0, 133.4 (CH), 140.8, 149.7, 157.0 (C), 159.8 (CH); IR 1617, 1586 cm^{-1}; HRMS calc for $C_{12}H_9N_2S$ (MH^+) 213.0486, found 213.0483.

2-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)quinazoline 106.

From 6-bromopiperonal (106 mg, 0.47 mmol), as described for **102**. Yellow solid (110.0 mg, 71%); mp 170-172 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 6.00 (2H, s, CH_2), 6.99 (1H, s, CH), 7.13 (1H, d, *J* = 8.2 Hz, CH), 7.22 (1H, td, *J* = 7.6, 1.1 Hz, CH), 7.53 (1H, m, CH), 7.61 (1H, dd, *J* = 7.8, 1.3 Hz, CH), 7.75 (1H, s, CH), 8.70 (1H, s, CH); ^{13}C NMR δ_C; 102.9 (CH_2), 108.7, 112.9 (CH), 117.2 (C), 119.1 (CH), 120.3 (C), 126.0 (CH), 128.1 (C), 133.3, 133.9 (CH), 148.2, 152.0, 154.3 (C), 161.3 (CH), 174.4 (C); IR 1618, 1589 cm^{-1}; HRMS calcd for $C_{15}H_{10}N_2O_2{}^{79}Br$ (MH^+) 328.9926, found 328.9926.

4'-Methyl-1'*H*-spiro[cyclohexane-1,2'-quinazoline] 121.

From cyclohexanone (43.1 mg, 0.44 mmol), as described for **58** and **75**. Brown oil (73.2 mg, 78 %) and (77.2 mg, 82 %) respectively. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 1.22-1.83 (10H, m, CH_2), 2.26 (3H, s, CH_3), 4.16 (1H, s, NH), 6.47 (1H, dd, *J* = 8.0, 0.6 Hz, CH), 6.60 (1H, td, *J* = 7.5, 1.0 Hz, CH), 7.11 (1H, m, CH), 7.21 (1H, dd, *J* = 7.7, 1.3 Hz, CH); ^{13}C NMR δ_C 20.8 (CH_2), 21.2 (CH_3), 24.1, 28.7, 35.8 (CH_2), 68.4 (C), 113.3, 116.7, 125.6, 131.6 (CH), 122.7, 143.1, 162.6 (C) one C not obs.; IR 3350, 1631 cm^{-1}; HRMS calcd for $C_{14}H_{19}N_2$ (MH^+) 215.1546, found 215.1544.

2,2,4-trimethyl-1,2-dihydroquinazoline 123.

From acetone (25.5 mg, 0.44 mmol), as described for **75**. Brown oil (34.6 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.39 (6H, s, CH_3), 2.24 (3H, s, CH_3), 3.83 (1H, s, NH), 6.42 (1H, dd, *J* = 8.0, 0.8 Hz, CH), 6.60 (1H, td, *J* = 7.6, 1.1 Hz, CH), 7.09 (1H, td, *J* = 7.6, 1.4 Hz, CH), 7.22 (1H, dd, *J* = 7.7, 1.3 Hz, CH); ^{13}C NMR δ_C; 21.5 (CH_3), 28.4 2x(CH_3), 67.8 (C), 112.9, 116.6, 125.1, 131.6 (CH), 116.8, 144.5, 161.0 (C); IR 3348, 1627 cm^{-1}; HRMS calcd for $C_{11}H_{15}N_2$ (MH^+) 175.1235, found 175.1235.

2-(4-methylquinazolin-2-yl)aniline 135.

A solution of 1-(2-aminophenyl)ethanone *O*-phenyl oxime (100 mg, 0.44 mmol) in toluene (0.15 M), containing anhydrous $ZnCl_2$ (17 mg, 0.13 mmol) and emimPF_4 (100 mg, 0.46 mmol) was placed in a microwave vessel (2-5 cm^3). The vessel was sealed and subjected to microwave irradiation for 30 min at 160 °C in a Biotage Initiator system. After cooling, the ionic liquid was filtered off and the toluene was removed under reduced pressure. The residue was purified by flash column chromatography (5 % EtOAc/hexane) affording a yellow solid (20 mg, 41 %); mp 162-165 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.92 (3H, s, CH_3), 6.47 (2H, s, NH_2), 6.73 (2H, m, CH), 7.17 (1H, m, CH), 7.47 (1H, m, CH), 7.75 (1H, m, CH), 7.90 (1H, d, *J* = 8.3 Hz, CH), 7.99 (1H, d, *J* = 7.7 Hz, CH), 8.59 (1H, dd, *J* = 8.0, 1.7 Hz, CH); ^{13}C NMR δ_C; 21.1 (CH_3), 115.9, 116.0 (CH), 118.3, 121.0 (C), 124.0, 125.5, 127.5, 130.3, 130.5, 132.4 (CH), 138.4, 148.0, 162.6 weak, 166.3 (C) weak); IR 3451, 3320, 1613, 1256 cm^{-1}; HRMS calcd for $C_{15}H_{14}N_3$ (MH^+) 236.1181, found 236.1188.

2-(4-methylquinolin-2-yl)aniline 136.[58]

As described for **137**. Yellow solid (10 mg, 19 %); mp 77-79 °C [lit. 78-79 °C][58]. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.73 (3H, s, CH_3), 6.14 (2H, s, NH_2), 7.19 (1H, t, *J* = 8.0 Hz, CH), 7.52 (1H, t, *J* = 8.0 Hz, CH), 7.65(3H, m, CH), 7.96 (1H, d, *J* = 8.0 Hz, CH), 8.03 (1H, d, *J* = 8.0 Hz, CH) ; ^{13}C NMR δ_C; 19.1 (CH_3), 117.3, 117.4 (CH), 121.1 (C), 121.8, 123.6 (CH), 125.9 (C), 126.5, 129.3, 129.4, 129.8, 130.1 (CH), 144.7, 146.7, 147.4, 158.9 (C).

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Chapter 4

Dioxime Oxalates as Iminyl Radical Precursors.

A Preparative and ESR Study.

1.0 Introduction

The importance of free radicals in organic synthesis and the necessity for the development of clean free radical precursors has been discussed in Chapter 1. Apart from peroxides and azo-compounds, the range of molecules suitable for direct photolysis is quite limited. The photolytic dissociation of these suitable molecules could be followed very efficiently using ESR spectroscopy. Furthermore, the determination of radical concentrations and therefore the assessment of kinetic data in radical process can be performed using ESR spectroscopy.

1.1 Electron Spin Resonance Spectroscopy (ESR).

Electron spin resonance spectroscopy (ESR), also known as electron paramagnetic resonance (EPR), is related to the study of species containing one or more unpaired electrons and therefore can be applied to the study of free radicals. The technique was first developed in 1945 and since then has found many applications in physics, chemistry and biology. The technique is extremely sensitive and can be used to detect radicals down to concentrations of 10^{-9} M.[1]

The principles of ESR are closely related to those of NMR spectroscopy. Just like the proton in NMR spectroscopy, the electron spin in ESR has an associated magnetic moment. Consequently, the electron will have two distinct energy levels in an applied magnetic field and will undergo transitions between spin states if energy of the correct frequency is applied.

ESR records the magnetic resonance spectrum of unpaired electrons. The ESR spectrum of a paramagnetic compound in an external magnetic field B can be described using a Hamiltonian operator (Eqn 1).

$$\mathbf{H = H_{EZ} + H_{NZ} + H_{EN} + H_Q} \qquad \text{Eqn 1}$$

$\mathbf{H_{EZ}}$ is the electronic Zeeman operator, which represents the interaction between the electron spin S and the external field **B**. Unpaired electrons have a non-classical intrinsic angular momentum called spin. The spin is characterised by the quantum number M_s = (+/-) 1/2, that gives two spin states differing in M_s.

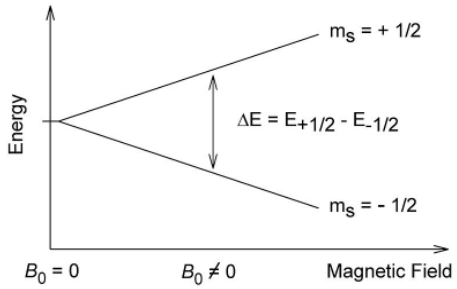
M_s = + 1/2: spin up **(↑)** or α

M_s = - 1/2 : spin down **(↓)** or β

The magnetic moment μ is derived from the spin state using the equation $\mu = -g\beta M_s$, where M_s is the electron spin, β is the Bohr magneton ($eh/4\pi m$ = 9.2733E-24 JT^{-1}), where e and m are the charge and the mass of the electron and h = 6.624E-27 is the Planck constant), and g is a dimensionless number whose value for a free electron is 2.0023. The interaction of this magnetic moment and the applied magnetic field can therefore be described by (Eqn 2).

$$\mathbf{H}_{EZ} = -\pi\mathbf{B} = g\beta M_s\mathbf{B} \qquad \text{Eqn 2}$$

In the absence of a magnetic field the two spin states are degenerate, i.e. they have the same energy. When the magnetic field B, is applied it interacts with the magnetic moment and the spin states are no longer degenerate. This is known as the Zeeman effect and the difference in energy between the levels is given by the equation $\Delta E = g\beta B$. If electromagnetic radiation of a frequency equivalent 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 can occur. In a field of 3400 Gauss, the Larmor frequency of a free electron will be 9.2 GHz, therefore ESR spectra are recorded in the microwave region of the electro-magnetic spectrum.



The spin state of a free electron is influenced by its local atomic environment, which in turn affects the g-factor of the electron and its magnetic moment. In a magnetic field the unpaired electron possesses, in addition to its spin angular momentum, a small amount of extra orbital angular momentum. It is the interaction between these, called spin-orbit coupling, which results in electrons having a different effective magnetic moment from that of the free electron. Since the equation for energy required for resonance is dependent on the magnetic moment, this implies that radicals of differing g-factors will resonate at different field strengths.

The nuclear Zeeman operator, $\mathbf{H}_{NZ}$ represents the interaction between the nuclear spin and the external magnetic field $\mathbf{B_0}$. This value is very small and is often negligible as the nuclear magneton is approximately 1836 times smaller than the Bohr magneton. As a result

the Zeeman energy is very much smaller than its electronic counterpart and can often be ignored.

The term $\mathbf{H}_{EN}$ describes the interaction between the electron spin and the 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 moment 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 paramagnetic compounds contain one magnetic nucleus in close proximity to the free electron, the unpaired electron will experience a local magnetic field arising from the magnetic nucleus. For example, the proton spin has two possible orientations which are parallel and antiparallel to the electron. There are four possible transitions but since the nuclear spin quantum number (M_I) cannot change during a transition, only two transitions are allowed. For this reason the hydrogen atom will therefore give an ESR spectrum of two lines of equal intensity. The separation between the two lines is known as the hyperfine splitting and in general can be used to deduce structural information about a free radical. As a general rule the spectrum will contain $(2nI+1)$ lines where I is the spin quantum number of the nucleus and n is the number of equivalent nuclei present.

$\mathbf{H_Q}$ 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 within the nucleus is not spherical. This does not occur in the organic molecules described in this thesis and can be ignored here.

The net result of eliminating these operations from the Hamiltonian operator given in (Eqn 1), gives a simplified equation for the spectrum observed using ESR in solution (Eqn 3).

$$H = g\beta\mathbf{B_o}S_z + \alpha S_z I_z \qquad \text{Eqn 3}$$

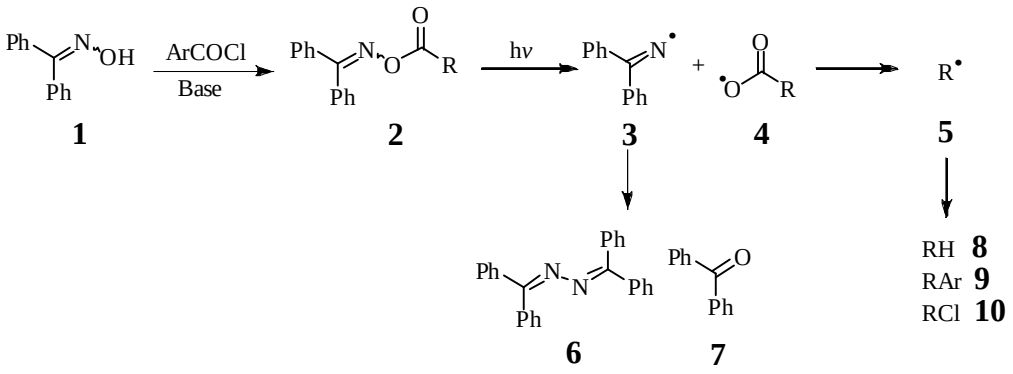
In solids the radicals are fixed and can be orientated in any direction with respect to the applied magnetic field. This means that the α- and g- values take on a number of different values. However in solution phase ESR, molecular tumbling averages the values of α and g resulting in simplified spectra.

As was mentioned earlier, a deep understanding of the kinetics of radical cyclization is necessary for the planning and understanding of radical reactions. ESR has been applied to the study of both dissociation and cyclisation kinetics and has provided valuable information for planning synthetic strategies.

1.2 Oxime Derivatives as Photochemical Radical Precursors.

1.2.1 Oxime esters as iminyl and alkyl radicals precursors.

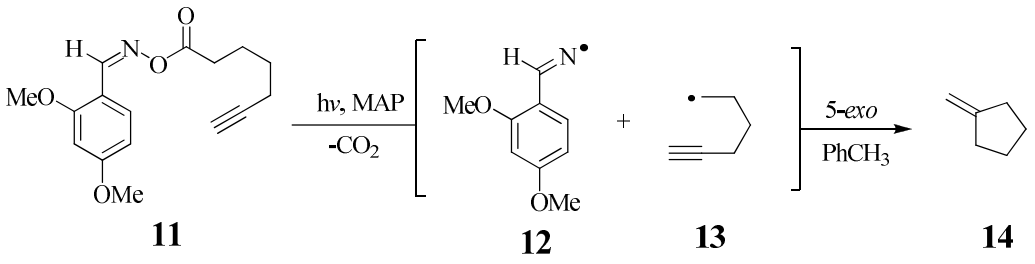
In the 1980's Hasebe and co-workers[2-4] demonstrated that benzophenone oxime esters **2** could readily be photolysed to generate alkyl radicals **5** together with the diphenyl iminyl radical **3** (Scheme 1).



Scheme 1

The photolysis reactions were carried out in benzene or carbon tetrachloride. The diphenyliminyl radical either dimerised to give the benzophenone azine **6** or else abstracted hydrogen to give an imine which was subsequently hydrolysed to the corresponding ketone **7**. The radical R$^{\cdot}$(**5**) could then undergo classic free radical chemistry to give alkanes **8**, alkyl aromatics **9** and alkyl chlorides **10**.[5]

The homolytic chemistry of oxime esters was further investigated by Walton and co-workers.[6,7] It was determined that the efficiency of oxime ester photolysis could be improved through the incorporation of methoxy substituents into the aromatic ring and through the use of photosensitisers. Oxime ester **11** was used in the preparation of cyclopentane ring **14** in good yield (Scheme 2).

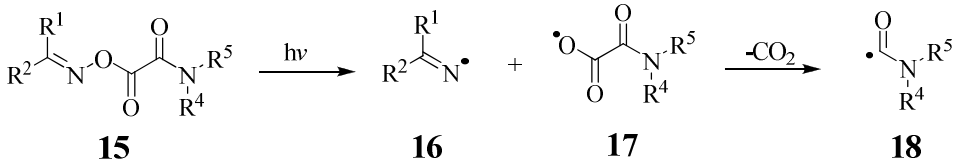


Scheme 2

The oxime ester **11** on photolysis, cleaves at the N-O bond giving the iminyl and the acyloxyl radical which rapidly loses CO_2 to give the alkyl radical **13**. This can then undergo a 5-*exo* mode cyclisation, followed by hydrogen-atom abstraction from the solvent to give methylenecyclopentane **14** in 77% yield.

1.2.2 Oxime oxalate amides as precursors of iminyl and carbamoyl radicals.

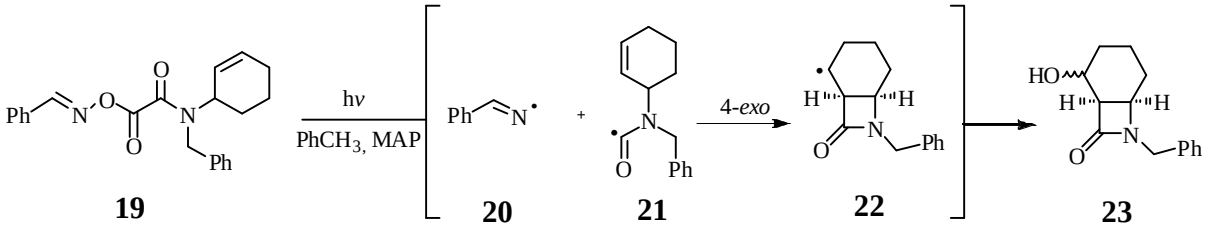
It was apparent from the work of Hasebe[2-5] and Walton[6,7] that the oxime functionality was a suitable radical precursor for iminyl and alkyl radicals. Walton's group proposed to study oxime oxalate amides as a precursor of iminyl and carbamoyl radicals. The oxime oxalate amide still incorporates the weak N-O oxime bond and should function as a radical precursor. The resulting acyloxyl radical **17** would then lose CO_2 to give the carbamoyl radical **18** (Scheme 3).[8]



15 **16** **17** **18**

Scheme 3

This methodology was applied in the synthesis of the β-lactam **23** from the corresponding oxime oxalate amide **19**. Upon irradiation of **19** in the presence of photosensitizer in toluene iminyl radical **20** was produced as co-intermediate with the aminoacyl **21**. This aminoacyl radical underwent 4-*exo* ring closure to afford the secondary radical **22**. Interestingly, however, the product isolated was the hydroxylated compound **23** probably by reaction of **22** with dissolved dioxygen in toluene (Scheme 4).



19 **20** **21** **22** **23**

Scheme 4

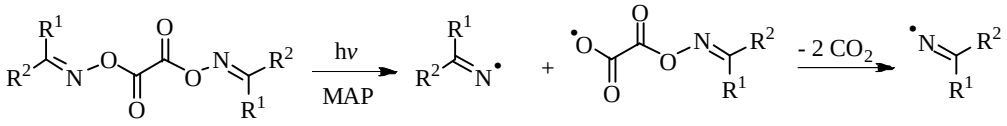
1.2.3 Dioxime oxalates as iminyl radicals precursor.

As has been described in the introduction, new preparative methods that are more environmentally friendly, and that allow access to new range of N-heterocycles, are emerging from N-centered radical reactions. Of the available radical types, iminyls rank high because a wide variety can be generated that react rapidly in C-N bond forming processes.

It has been shown from the work of Walton et al.[6-8] that oxime esters and oxime oxalate amides are useful sources of iminyl and alkyl radicals and iminyl and carbamoyl radicals respectively.

It seemed possible therefore, that dioxime oxalates **24** could function as particularly clean and atom-efficient sources of iminyl radicals, the only by-product being CO_2. Dioxime oxalates are readily prepared through the condensation of oxalyl chloride with two molecules of oxime. These molecules contain the weak N-O bond and should work as radical precursors.

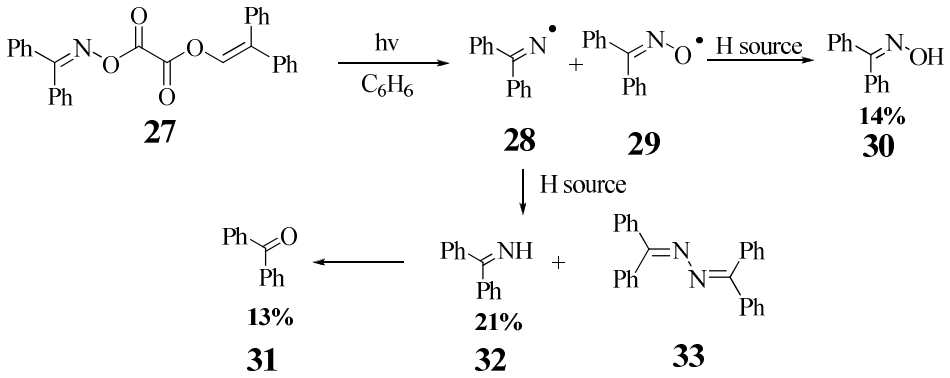
Photolysis of dioxime oxalate **24** in the presence of photosensitizer MAP would give rise to scission of the N-O bond yielding iminyl radical **25** and acyloxyl radical **26**. This acyloxyl radical **26** would then lose two molecules of CO_2 to give a second equivalent of the iminyl radical **25** (Scheme 5).



24 **25** **26** **25**

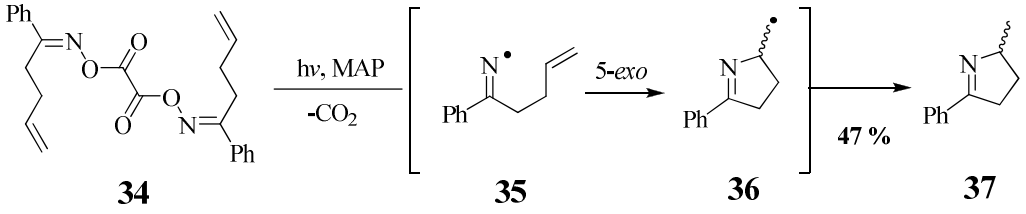
Scheme 5

The only previous attempt to generate radicals from dioxime oxalates was briefly mentioned by Forrester et al.[9] in the late 70's. They found that the dioxime oxalate **27** derived from the benzophenone oxime, on photolysis, underwent homolytic fission of the oxime N-O bond to give two moles of the iminyl radical **28** and two moles of CO_2. End-product analysis revealed the expected imine **32** and benzophenone **31** derived from hydrolysis of the imine. Traces of diazine **33** were also found probably from the dimerization of the iminyl radical. The oxime **30** was also isolated suggesting that some homolysis of the O-C bond also occurred generating iminoxyl radical which can abstract hydrogen to yield oxime **30** (Scheme 6).



Scheme 6

This "clean" source for generating iminyls was further investigated by Walton and co-workers.[10] Several iminyl radicals have been successfully generated from dioxime oxalates and, most significantly, the dioxime oxalate from 5-phenylpent-4-ene-1-al **34** gave an unsaturated iminyl radical **35** that cyclised via the 5-*exo* mode affording dihydropyrrole **36** in 47 % yield (Scheme 7).



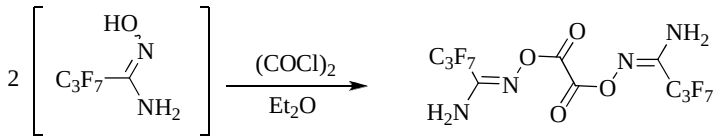
Scheme 7

2.0 Results and Discussion

It was postulated therefore that dioxime oxalates constituted useful precursors for the clean and atom-efficient generation of iminyl radicals by sensitised UV photolysis as the source of iminyl radical. Photochemical dissociations of the dioxime oxalates could be followed by ESR spectroscopy and kinetic data may be determined. Iminyl radical generation and cyclisation, for a representative range of dioxime oxalates, were investigated using UV irradiation.

2.1 Preparation of dioxime oxalates.

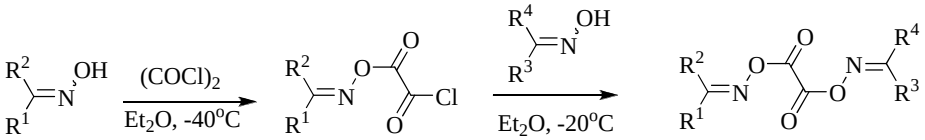
The first synthesis of a dioxime oxalate was by Brown et al.[11] who prepared symmetric dioxime oxalate derivative **39** from oxalyl chloride and perfluorobutyramidoxime **38** in dry diethyl ether (Scheme 8).



38 **39**

Scheme 8

Jochims et al.[12] reported the preparation of six asymmetric dioxime oxalates in very good yields. The treatment of oxalyl chloride with one equivalent of an oxime led to the intermediate *O*-(chlorooxalyl)oximes **40** at low temperature in dry diethyl ether. Compounds **40,** tended to be unstable and moisture-sensitive. A second equivalent of oxime reacted with *O*-(chlorooxalyl)oxime to afford the dioxime oxalates **41** (Scheme 9).



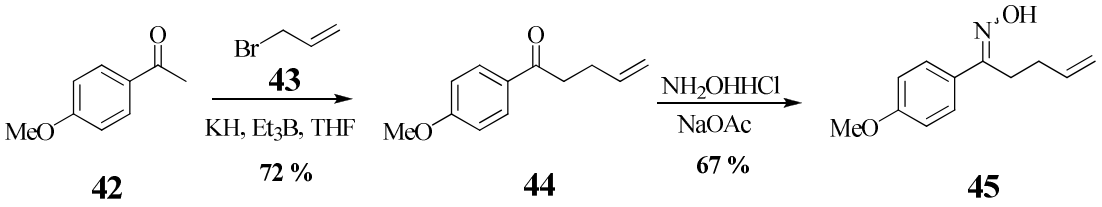
40 **41**

Scheme 9

This method was used in the preparation of both symmetrical and asymmetrical dioxime oxalates with a radical acceptor in a suitable position. The efficiency of the photolytic generation of iminyl radical from dioxime oxalates was studied by ESR spectroscopy. Purification was usually impracticable because most of the dioxime oxalates were oils that hydrolyzed rapidly on exposure to air and during chromatography (SiO_2 or Al_2O_3) to give the oxime and ketone. However, by using fresh oxalyl chloride, and by careful control of the reactant quantities, almost pure dioxime oxalate could be made quantitatively and used immediately without further purification.

The symmetrical dioxime oxalate **46**, with an alkene in a suitable position for 5-*exo* cyclisation of the iminyl radical, was prepared in three steps from 4-methoxyacetophenone. Reaction of the ketone **42** with KH in the presence of Et_3B generated the enolate, which underwent nucleophilic substitution onto allyl bromide **43**, affording the γ,δ-unsaturated

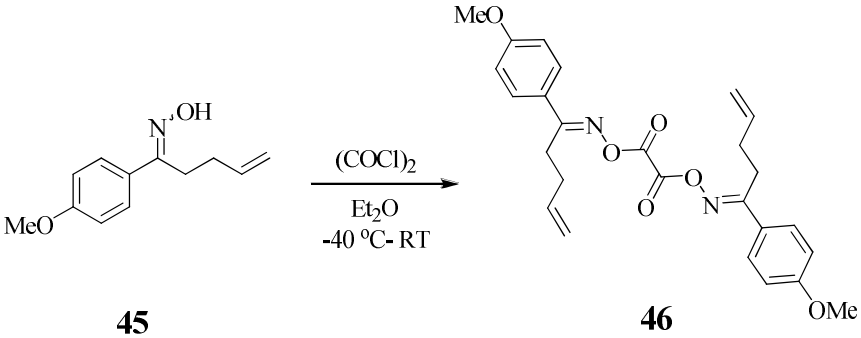
ketone **44** in good yield. Condensation with hydroxylamine hydrochloride in ethanol and in the presence of sodium acetate afforded the unsaturated oxime **45** in 67 % yield (Scheme 10).



42 **44** **45**

Scheme 10

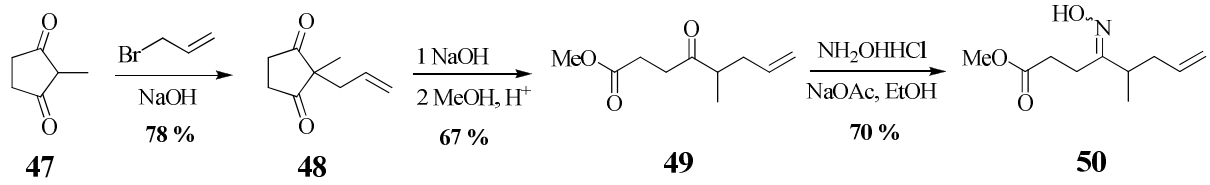
Two equivalents of oxime **45** in diethyl ether were added dropwise to a stirred solution of oxalyl chloride in Et_2O at -40 °C and the mixture was stirred for 3 hours before allowing it to warm up to room temperature. Dioxime oxalate **46** was a purple oil which decomposed rapidly. Purification by flash chromatography in silica and alumina was tried but the compounds did not survive these processes. Nevertheless, the crude reaction showed a quantitative formation of dioxime oxalate **46** as a mixture of E/Z stereoisomers (Scheme 11).



45 **46**

Scheme 11

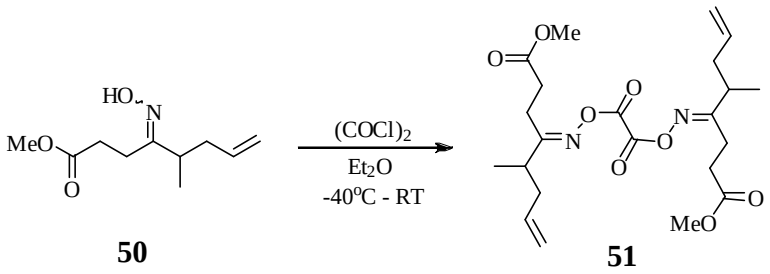
Dioxime oxalate **51** was also chosen as a model to study the structure of radical intermediates using ESR spectroscopy. In this case no aryl groups were present in the radical precursor. Instead an alkyl chain with an ester group was present for further functional group transformations. The keto-ester **49**, needed for making a suitable dioxime oxalate precursor **51**, was prepared by allylation of 2-methylcyclopentane-1,3-dione **47** by reaction with allyl bromide in the presence of NaOH. The allylated cycloalkanone **48** was ring opened and esterified yielding **49**, which was converted in the corresponding oxime **50** by reaction with hydroxylamine hydrochloride in standard conditions (Scheme 12).



47 **48** **49** **50**

Scheme 12

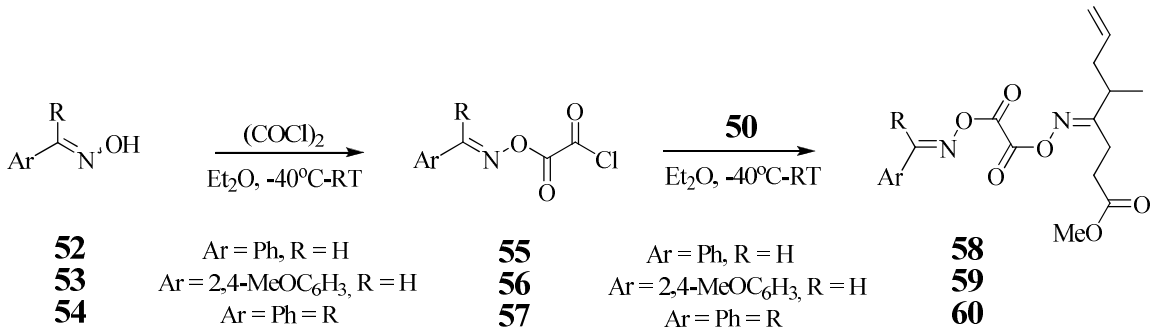
A symmetrical dioxime oxalate **51** was first prepared by reaction of two equivalents of the unsaturated oxime **50** with oxalyl chloride. The reaction was carried out under an inert atmosphere and -25 °C for 3 hours. After that time the solvent was removed under reduced pressure affording a red oil, which hydrolyzed readily to the oxime **50**. No further purification could be carried out with these types of dioxime oxalates. The crude NMR showed a mixture of stereoisomers of **51** and almost nothing of the starting oxime **50**, which made them suitable for ESR spectroscopy (Scheme 13).



50 **51**

Scheme 13

Asymmetric dioxime oxalates were also prepared, with one half containing an aromatic oxime. They were prepared by reacting the oxime from benzaldehyde **52**, 2,4-dimethoxybenzaldehyde **53** and benzophenone **54** with one equivalent of oxalyl chloride in diethyl ether at -20 °C for 2 hours, giving the oxoacetyl chloride intermediates as a moisture sensitive powder **55-57**. Without further purification, they were reacted with γ,δ-unsaturated oxime **50** under the same reaction conditions for another 2 hours to afford a set of asymmetric dioxime oxalates **58-60** containing an aryl group. These dioxime oxalates were obtained as moisture-sensitive purple oils which hydrolyzed very easily to the corresponding starting material (Scheme 14).



52 Ar = Ph, R = H
53 Ar = 2,4-$MeOC_6H_3$, R = H
54 Ar = Ph = R

55 Ar = Ph, R = H
56 Ar = 2,4-$MeOC_6H_3$, R = H
57 Ar = Ph = R

58
59
60

Scheme 14

Following the successful preparation of these dioxime oxalates and the development of a general route to their preparation, it was decided to investigate the photochemistry of these compounds via ESR spectroscopy.

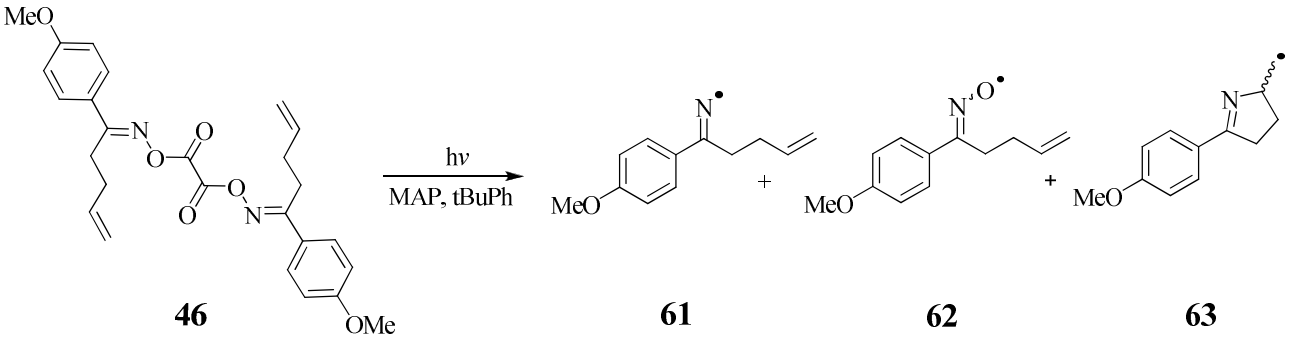
2.2 ESR Spectroscopy of dioxime oxalates.

In this project, ESR was used to determine the structures of radical intermediates and hence to validate the mechanism of their photodissociation. The spectrometer used for these studies was a Bruker EMX 10/12 operating at 9.5 GHz with 100 kHz modulation. Samples were photolysed in the resonance cavity by unfiltered light from a 500 W super pressure Hg lamp.

Samples were prepared by taking 20 mg of the starting dioxime oxalate and dissolving in *t*-butylbenzene (ca. 500 μL). To this was then added two molar equiv. of the photosensitizer, *para*-methoxyacetophenone (MAP). The sample was deaerated under N_2 and then sealed in a 4 mm quartz ESR tube.

2.2.1 EPR spectroscopy of symmetric dioxime oxalates.

The photochemistry of the symmetrical dioxime oxalate **46** was first examined. As explained above, iminyl radical **61** was expected from the photodissociation of the weak N-O bond of the dioxime **46**, together with the corresponding carbon-centred radical **63**, resulting from 5-*exo* cyclisation of the iminyl radical (Scheme 15). It was also a possibility, according with the results obtained by Forrester and co-workers, that iminoxyl radical **62** could be detected by a possible, but improbable, C-O bond scission.



Scheme 15

Spectra were obtained over a range of temperatures. Figure 1 represents the spectrum obtained at 240 K.

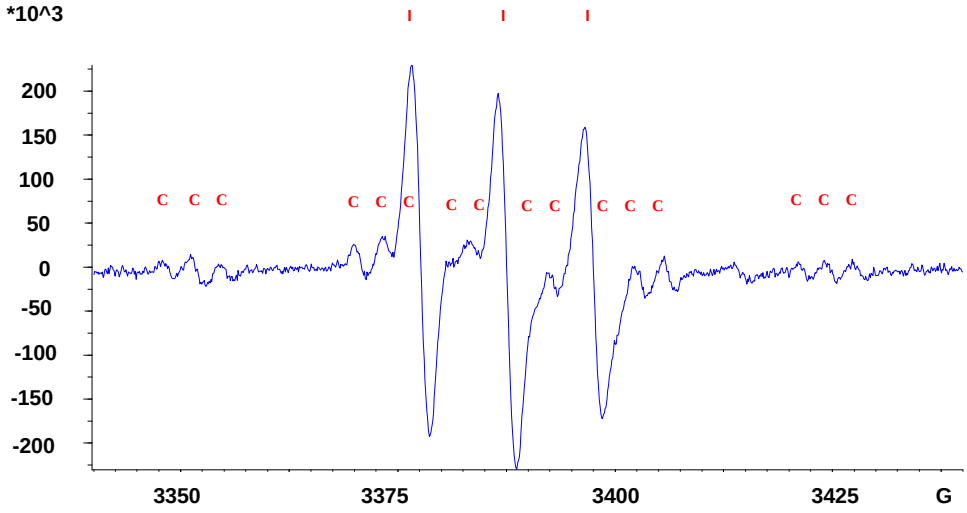


Figure 1. 9.4 GHz ESR spectrum obtained on photolysis of the solution of **46** and MAP in *tert*-butylbenzene at 240 K, I; iminyl radical **61**, C; carbon centered radical **63**.

The spectrum clearly shows a 1:1:1 triplet with an *a*(N) value of 10.1 G (marked **I**) which is typical of an iminyl radical, **61**. At this temperature a second radical species was observed which is shown also in Figure 1. The EPR parameters were *a*(N) = 3.65 G, a(2H) = 21.9 G, *a*(1H) = 28,2 G and g = 2.0025 (marked **C**).

The 21.9 G hfs are typical of α-hydrogens of carbon centred radicals and this together with the g-factor, showed this to be a carbon-centred radical. It was attributed to the 2-azacyclopentylmethyl radical **63** formed by 5-*exo* cyclisation of iminyl radical **61** onto the double bond. Figure 2 shows the simulation of the iminyl radical **61** and carbon-centred radical **63**.

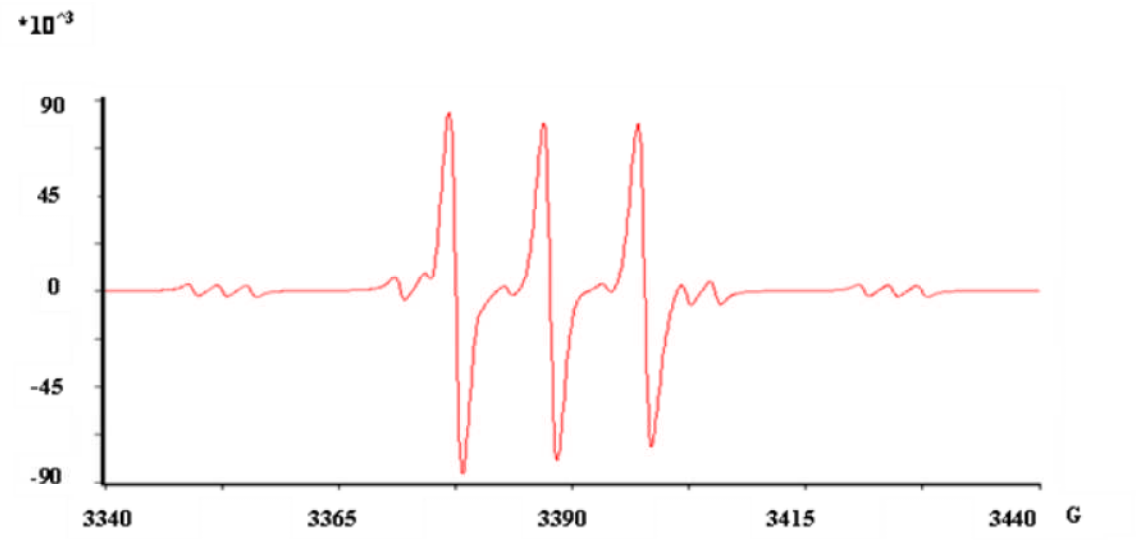
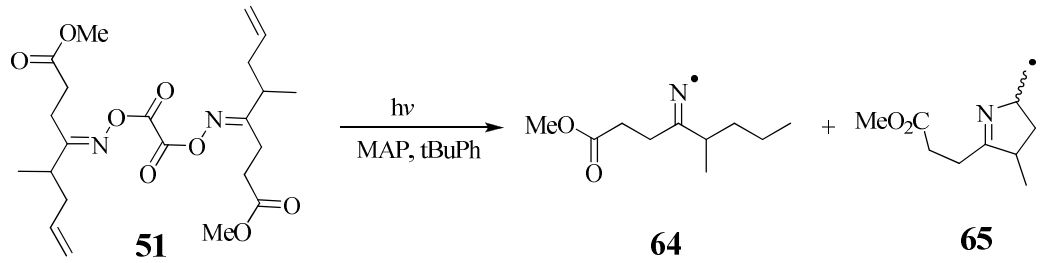


Figure 2. Simulation of iminyl radical **61** and carbon centered radical **63**.

If the slightest trace of starting oxime was present, the iminyl radical spectrum was accompanied by that of the iminoxyl radical **62**. However, iminoxyls was not observed when completely pure dioxime oxalate **46** was employed. It was believed therefore, that the iminoxyl spectra result from H-atom abstraction, probably by MAP triplet states, from traces of oxime impurities and are not due to UV induced scission of the O-C bond in dioxime oxalates. Iminoxyl radicals are persistent and have much longer lifetimes than iminyls so their concentration can build up to levels detectable by ESR spectroscopy even when only minute traces of oxime **45** are present. The observation of iminoxyl by Forrester et al.[9] was probably due to the same cause.

The ESR spectra established that iminyls are cleanly released from dioxime oxalates containing aryl groups, on photolysis. It also showed that 5-*exo* radical cyclisation occurred efficiently and the characteristic signals of carbon centred radicals were observed.

The photodissociation of symmetric dioxime oxalates without any aryl group were also examined by ESR spectroscopy. A sample of precursor **51** was prepared in the standard way and photolysed with light from the 500 W UV lamp in the presence of two equivalents of MAP. Iminyl radical **64** was expected to be formed by homolysis of the N-O bond and subsequent cyclisation onto the double-bond should afford carbon-centred radical **65**. Both radicals could potentially be detected under UV photolysis by ESR spectroscopy (Scheme 16).



51 **64** **65**

Scheme 16

Figure 3 shows the spectrum obtained on photolysis of the dioxime oxalate **51** in the presence of MAP at 240K. Neither the characteristic signals of the iminyl radicals, nor the signals of the carbon-centred radicals could be detected.

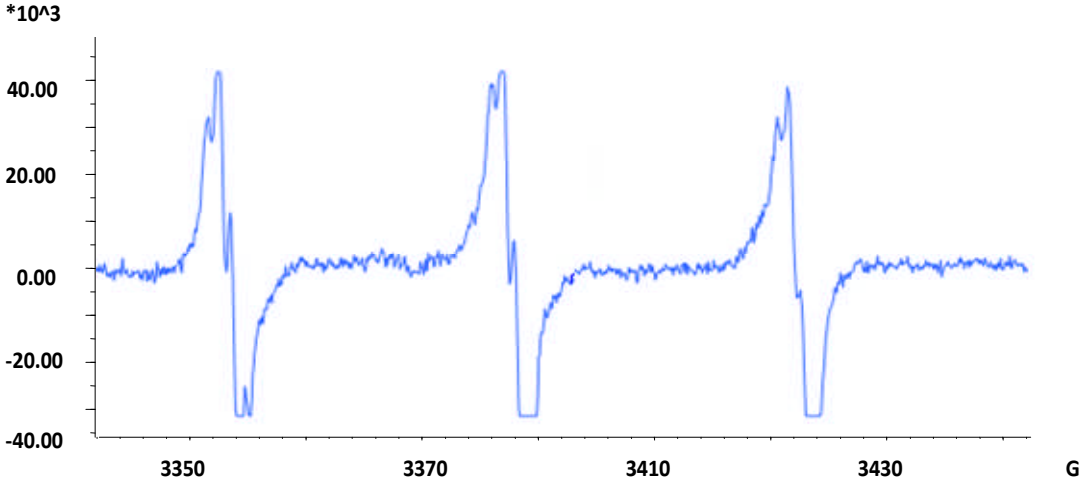
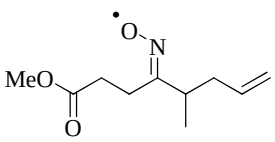


Figure 3. 9.4 GHz ESR spectrum obtained on photolysis of the solution of **51** and MAP in *tert*-butylbenzene at 240 K.

On the other hand the signal corresponding to the iminoxyl radical **66**, which is a stable and long-lived radical dominated the spectrum (Figure 4). The EPR parameters were a(N) = 30.5, a(3H) = 1.3G. and g = 2.0070 at 240 K.



66

Figure 4

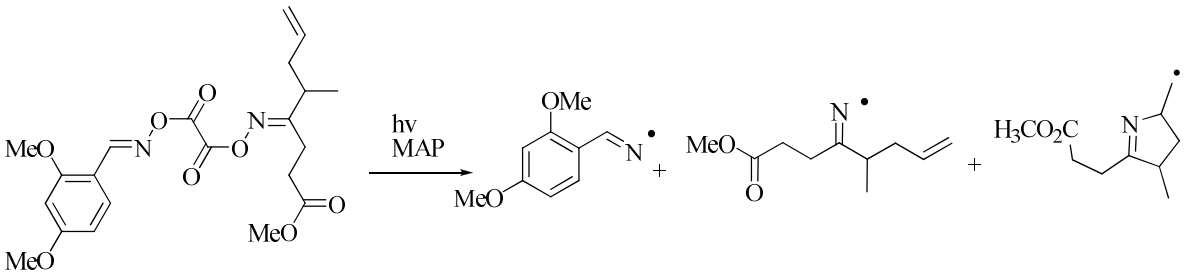
It is possible that the iminoxyl radicals result from the C-O bond homolysis of the dioxime oxalate but this seems improbable. It has been shown above that iminyl radicals were generated efficiently from dioxime oxalate **46**, which contained an aryl group close to the C=N bond. Moreover, Walton and co-workers[10] found for the dioxime oxalate **35** that the N-O and C-O bond lengths are 1.442 Å and 1.361 Å respectively. The longer N-O bond compared to N-O bonds in oximes suggests it may be weak and will probably break more readily than the C-O bond. Furthermore carbon dioxide is a more favourable by-product resulting from N-O bond homolysis, than carbon monoxide resulting from the cleavage of the C-O bond.

It was therefore believed, that the radiation was insufficient to afford the homolysis of the C-O bond and therefore that the iminoxyl radicals resulted from H-atom abstraction from residual oximes in the EPR samples.

2.2.1 EPR spectroscopy of asymmetric dioxime oxalates.

Considering that the homolysis of the N-O bond in symmetric dioxime oxalates without aryl group did not work, it seemed possible that transfer of energy from the excited state of MAP was inefficient with this kind of precursor. It was decided to study the photosensitised decomposition of asymmetric dioxime oxalates containing an aromatic moiety. Increasing the chromophoric activity of the radical precursors may promote homolysis of the N-O bond. Furthermore, the transmission of energy from the photosensitiser to the dioxime oxalates may also be more effective.

Dioxime oxalate **59** from the corresponding 2,4-dimethoxybenzaldehyde oxime **53** was firstly investigated by ESR spectroscopy at several temperatures. The samples were prepared in *tert*-butylbenzene in the standard way and photolysed with light from 500W UV lamp in the presence of two equivalents of MAP. In this case, three different radicals were expected to be detected by ESR spectroscopy. The benzyl iminyl radical **67** corresponding to the aromatic part of the dioxime oxalates **59**, the γ-δ-unsaturated iminyl radical **64** and the carbon-centred radical **65** formed after 5-*exo* iminyl radical cyclisation onto the double-bond (Scheme 17).



Scheme 17

Figure 5 shows the spectrum obtained on photolysis of the dioxime oxalate **59** in the presence of MAP at 255 K. The 1:1:1 triplets (marked **I**) at either extreme of the spectrum, are due to aryl iminyl radical **67**. A second radical species is observed in the spectrum which may be the carbon centred radical **65** (marked **C**), resulting from 5-*exo* cyclisation. Apparently, the signal of γ,δ-unsaturated iminyl radical **64** characterised by a 1:1:1 triplet with an *a*(N) value of 10.1G did not appear, which would mean that the intramolecular ring closure onto the double bond was very fast. The EPR parameters were: aryl iminyl radical (I) *g* = 2.0034, *a*(H) = 81.2, *a*(N) = 10.1G; cyclised radical (C) *g* = 2.0025, *a*(2H) = 21.7 G, *a*(1H) = 28.8 G and *a*(N) = 3.5 G at 255 K.

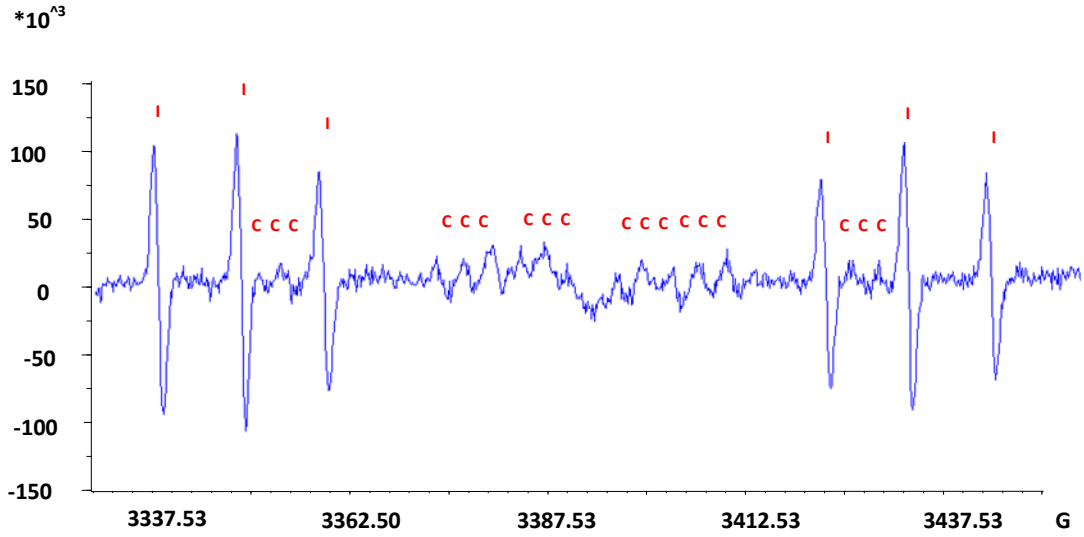


Figure 5. 9.4 GHz ESR spectrum obtained on photolysis of the solution of **59** and MAP in tert-butylbenzene at 255 K; I; iminyl radical **67**, C; carbon centred radical **65**.

Figure 6 represents the simulated ESR of iminyl radical **67** and carbon-centred radical **65**. The 21.7 G hfs observed is typical of α-hydrogens of carbon-centered radicals and this, together with the *g*-factor, indicates this to be a carbon-centred radical. The spectrum was run at lower temperature to try to identify the γ,δ-unsaturated iminyl radical but the signals

broadened owing to inefficient tumbling and to the presence of solid in the sample. Also, the spectrum was run at higher temperatures but the peaks decreased in intensity.

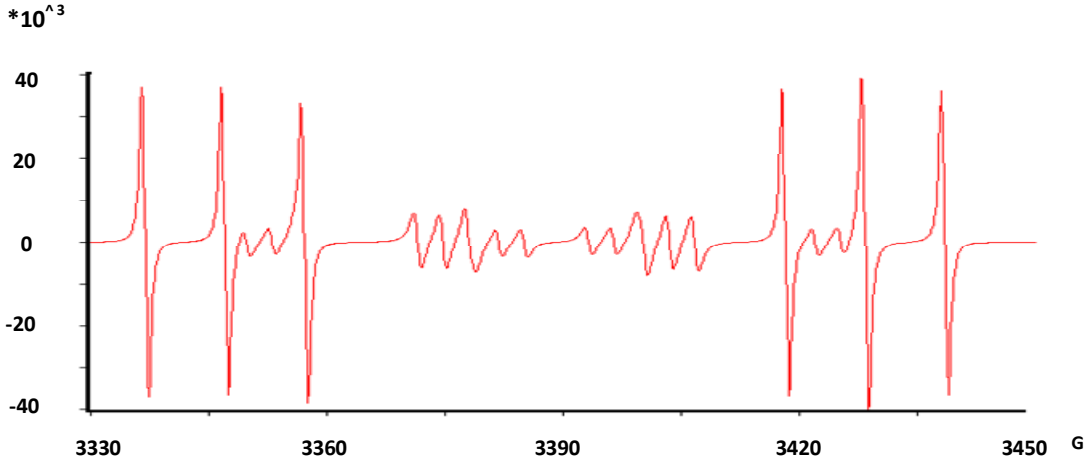
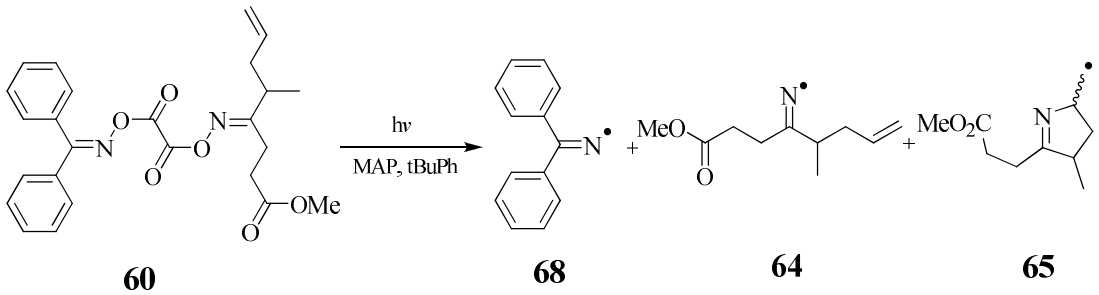


Figure 6. Simulation of iminyl radical **67** and carbon-centred radical **65**.

Another asymmetric dioxime oxalate studied was **60** from the corresponding benzophenone oxime which was UV photolysed under usual conditions. Benzophenone iminyl radical **68**, γ,δ-unsaturated iminyl radical **63** and carbon-centred radical **64** from the 5-*exo* cyclisation were expected (Scheme 18).



60 **68** **64** **65**

Scheme 18

Figure 7 shows the spectrum obtained on photolysis of the dioxime oxalate **60** in the presence of MAP at 250K. The main feature is clearly a nitrogen-centred radical as a 1:1:1 triplet with an *a*(N) = 10.1G which is typical of an iminyl radical (marked **I**). Presumably, these signals belong to benzophenone iminyl radical **68**. The γ,δ-unsaturated iminyl radical **64** may be under the signal of the radical **68**. On the other hand, the signals of the carbon-centred radical of **65** (marked **C**) resulting of the 5-*exo* cyclisation could be observed, which confirmed the proposed route. The EPR parameters were: benzophenone iminyl radical (I) *g*

= 2.0033, *a*(N) = 10.1G.; cyclised radical (C) *g* = 2.0025; *a*(2H) = 21.8; *a*(H) = 27.5; *a*(N) = 3.1 G.

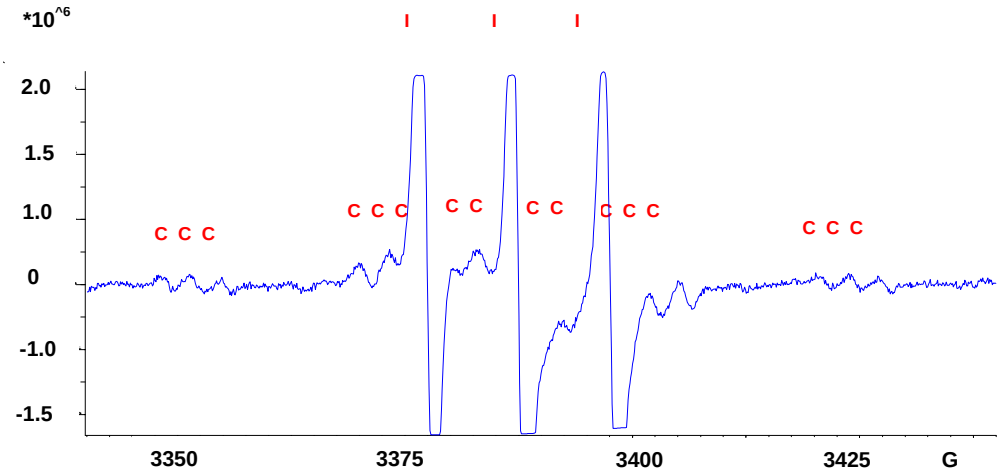


Figure 7. 9.4 GHz ESR spectrum obtained on photolysis of the solution of **60** and MAP in tert-butylbenzene at 255 K, I; iminyl radical **68**, C; carbon centered radical **65**.

It can be concluded that iminyl radical generation takes place much more readily, when the dioxime oxalate contains an aromatic ring attached to the C=N moiety of the dioxime oxalate. The presence of an aryl ring appeared to enhance energy pick-up by the dioxime oxalate from the MAP excited state. Although iminoxyl radicals were detected in several cases, it was believed that they were due to traces of starting oxime and not to UV induced scission of the O-C bonds in dioxime oxalates.

The identification of several dihydropyrrolo-methyl radicals also confirmed that unsaturated iminyl radicals underwent 5-*exo* mode cyclisation rather than the disfavoured 6-*endo*-cyclisation. The observation of these iminyl and carbon-centred radicals gives a good indication of the potential for dioxime oxalates to serve as iminyl radical precursor and their success in forming cyclised species.

2.3 Kinetic study for iminyl radical cyclisation using ESR spectroscopy.

Knowledge of the rate constants of iminyl radical reactions would be useful for synthetic design, but kinetic studies of iminyl radical reactions have been limited. Newcomb and co-workers[13] reported the rate of ring closure for the 2-methyl-6,6-diphenyl-5-hexeniminyl radical and found it to be in the order of 2 x 10^6 s^{-1} at 298 K. Apart from this

work, kinetic studies of iminyl radicals have been confined to self-trapping[14] and β-fragmentation.[15]

2.3.1 1-(4-Methoxyphenyl)pent-4-en-1-iminyl radical.

The absorption intensity of ESR signals generated by transient free radicals is directly proportional to the radical concentration. However, measurements of these parameters are relatively difficult as the reactive radicals exist in very low concentrations and are often very difficult to detect.

In order to gain kinetic data using ESR, it was necessary to record measurements when both of the transient radicals could be distinguished on the same spectrum (Figure 8).

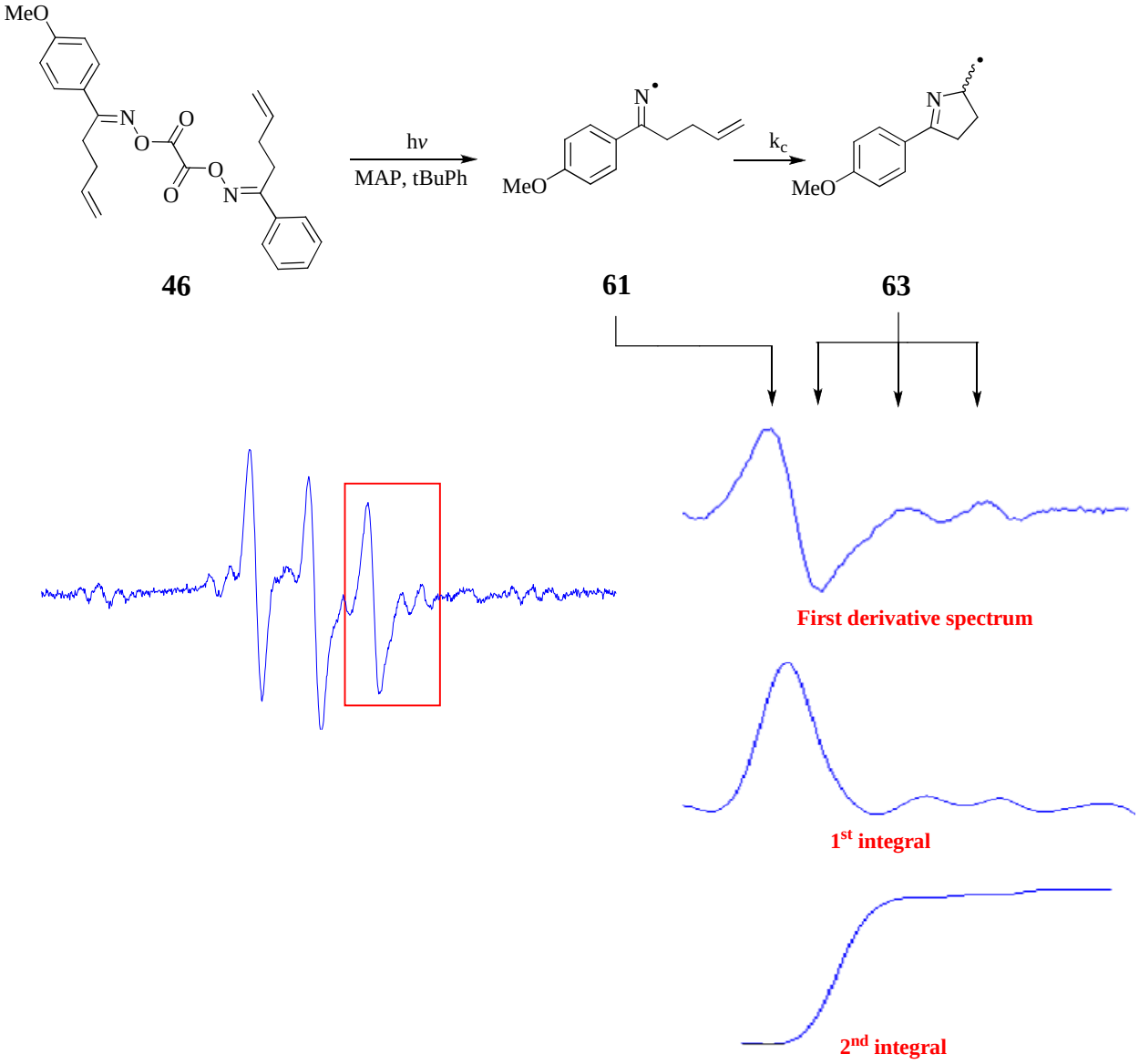


Figure 8. 9.4 GHz ESR spectrum obtained on photolysis of the solution of **46** and MAP in *tert*-butylbenzene at 245 K.

Using the appropriate computer software, it is possible to select a small portion of the ESR differential spectrum on which a double integration can be easily performed. Hence the area underneath the selected peaks can be determined. For example, the ESR spectra acquired on photolysis of dioxime oxalate **46** at 245 K showed peaks that were generated by both the iminyl radical **61** and the dihydropyrrolo-methyl radicals **63**. The first integral of the first derivative ESR spectrum was obtained by using Bruker WinEPR software which gave a profile with a distorted baseline. Fortunately the software is provided with a baseline correction facility, which allows the baseline to be reset in such manner that the second integral can be obtained giving a step diagram similar to that used in NMR (Figure 8).

In order to obtain the actual concentration of a transient radical, comparison of the double integral value with that obtained from a standard solution containing a stable radical of known concentration was necessary. A standard solution of 2,2-diphenyl-1-picrylhydrazyl (DPPH) in toluene having a known concentration of 10^{-4} M was prepared and 250 μL aliquot was placed in a quartz ESR tube before being thoroughly degassed with N_2. The sample was inserted into the resonant cavity, and the ESR spectra acquired using identical parameters to those used with the dioxime oxalates (Figure 9).

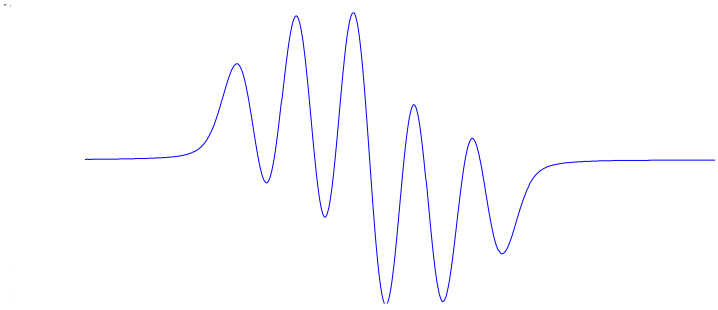


Figure 9. 9.4 GHz ESR spectrum obtained on photolysis of the solution of DPPH in toluene.

The photolysis of dioxime oxalate **46** was therefore investigated by ESR spectroscopy in order to determinate kinetic information. The ESR samples were prepared by taking 70 mg of the starting dioxime oxalate **46**, 2 mol equiv of MAP and dissolving them in *tert*-butylbenzene (3.5 cm^3). The solution was stirred until homogeneous and this allowed the preparation of seven identical samples, each of 500 μL. The degassed sample was placed in the resonance cavity and ESR spectra were obtained in a range of temperatures. The temperature had a direct effect on radical cyclisation and the spectrum varied significantly.

Figure 10 shows the ESR spectrum obtained on photolysis of **46** at 245 K and 280 K. As the temperature was increased the intensity of the iminyl radical **61** **I** began to diminish and the signals of the cyclised species **63** **C** to increase.

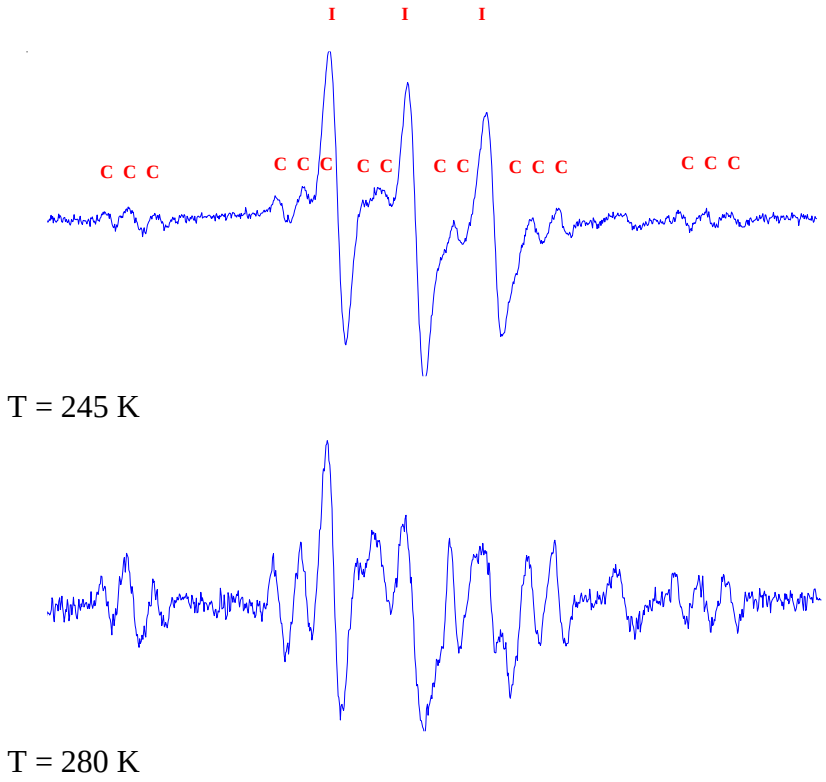
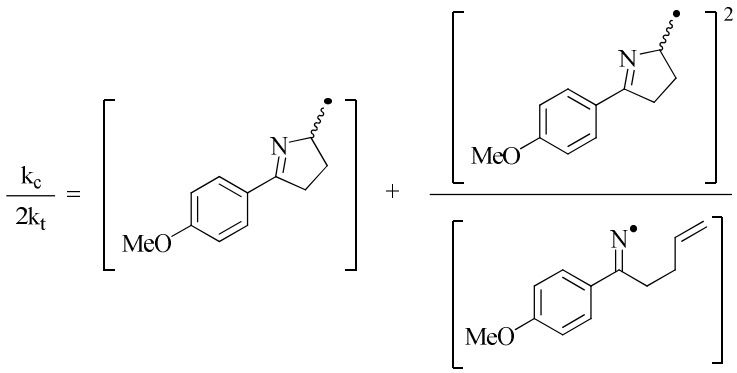


Figure 10. 9.4 GHz ESR spectra obtained on photolysis of a solution of **46** and MAP in *tert*-butylbenzene at 245 K and 280 K. I; iminyl **61**, C; cyclised radical **63**.

The concentration of the two transient radicals **61** and **63** at each temperature, were determined by direct comparison of doubly integrated spectral lines to a standard DPPH spectrum. The derived values for the transient radical concentrations were placed into the steady state equation to give a value for $\log k_c/2k_t$ at each temperature. Eqn 4 shows the steady state equation derived for the photolysis of dioxime oxalate **46**.



Equation 4

The steady state equation was derived with the assumption that the termination rates of the iminyl **61** and the cyclised radical **63** are diffusion controlled so that $2k_t$ is the same for each species and is about the same as that of other small radicals such as *t*-butyl.

Data for the diffusion-controlled rate constants of *t*-butyl radicals ($2k_t$) have previously been determined for many solvents by Fischer and co-workers.[16] These data allowed the calculated $2k_t$ values to be corrected for solvent viscosity and provided the values used in determining the Arrhenius parameters of k_c. Table 1 shows the kinetic ESR data obtained for dioxime oxalate **46**.

T/K	[63]	[61]	Log$k_c/2k_t$	$10^3/T$	Log $2k_t$	k_c/s^{-1}
245	2,04E-08	8,66E-09	-7,17	4,06	9,08	8,20E+01
248	2,07E-08	4,54E-09	-6,94	4,01	9,12	1,52E+02
250	1,94E-08	4,35E-09	-6,98	3,98	9,15	1,50E+02
252	2,56E-08	5,89E-09	-6,86	3,95	9,18	2,06E+02
255	2,26E-08	6,07E-09	-6,97	3,90	9,22	1,76E+02
258	1,94E-08	3,92E-09	-6,94	3,85	9,25	2,07E+02
260	2,14E-08	5,25E-09	-6,96	3,82	9,28	2,06E+02
265	1,89E-08	2,81E-09	-6,84	3,75	9,33	3,15E+02
270	2,29E-08	3,02E-09	-6,71	3,68	9,39	4,79E+02
272	1,57E-08	1,09E-09	-6,62	3,65	9,41	6,18E+02
275	2,05E-08	1,87E-09	-6,61	3,61	9,44	6,70E+02
280	1,28E-08	6,16E-10	-6,56	3,55	9,48	8,47E+02

Table 1. Kinetic ESR data for **46** (70 mg), in *t*-BuPh (3.5 mL) with 2 eq MAP.

The variation in the rate of a chemical reaction with temperature can be represented using the Arrhenius equation. By plotting the calculated values of log k_c against $10^3/T$ for the data of Table 1, and implementing a line of best fit (Figure 11), it was possible to obtain the associated gradient and intercept of this line, which are related to the values of the activation energy (E_c) and the pre-exponential factor (A_c) for **46** (Equation 5)

$$\ln k_c = \ln A_c - \frac{E_c}{RT}$$

Equation 5

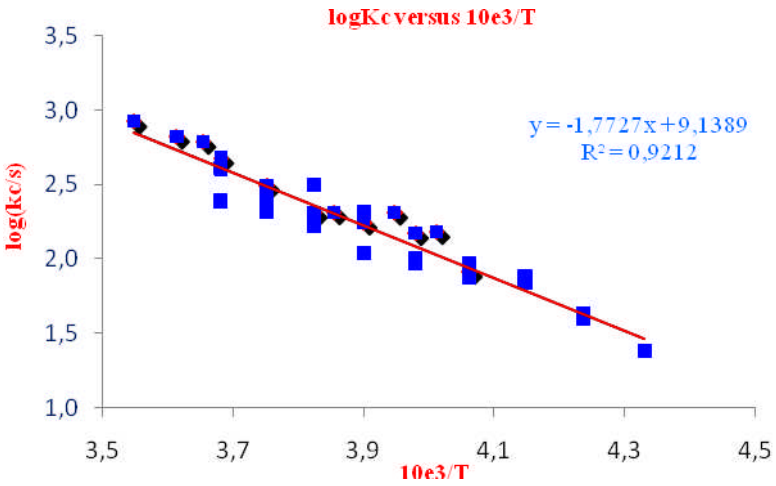


Figure 11. Plot of log k_c against 10^3/T.

For iminyl radical the accessible temperature range was small and the error limits on individual rate constants was large. Because of the long extrapolations required, reliable pre-exponential factors could not be derived. Instead, it is well established[17] that the log(A) values of *5-exo* cyclizations are close to 10.0 s^{-1}, and therefore this value was used for evaluations of the activation energies.

Radical	k_c/s^{-1} (300 K)	Log A_c/s^{-1}	E_c/ kcal mol^{-1}
61 ⟶ **63**	2 E+03	10.0	9.1

Table 2

The rate constant of 2.0 x 10^3 s^{-1} at 300 K for ring closure of the iminyl radical **61** would appear to be a reasonable figure for the 5-*exo* cyclisation. As was mentioned earlier, Newcomb and co-workers determined the rate of ring closure for the iminyl radical **69**[13]. They found k_c for this iminyl radical to be three orders of magnitude larger than the one found for **61**. The difference between these rate constants may be due to the presence of the two terminal phenyl rings in the alkene radical acceptor. The tertiary radical **70** would be strongly delocalised which would favour the cyclisation process. Table 3 illustrates some rate constants determined for ring closure reactions. It can be seen that, the rates of carbon ring closure onto alkenes with two phenyl rings **73** to give tertiary radical **74** are around 2 orders of magnitude faster than those onto the simple carbon double bond **71**[18] to give the primary radical **72**. This is in agreement with the kinetic data obtained for **61**.

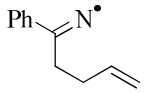
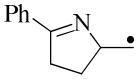
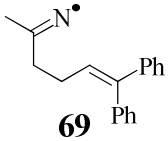
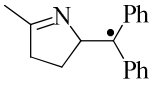
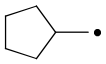
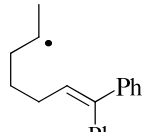
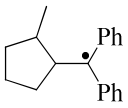
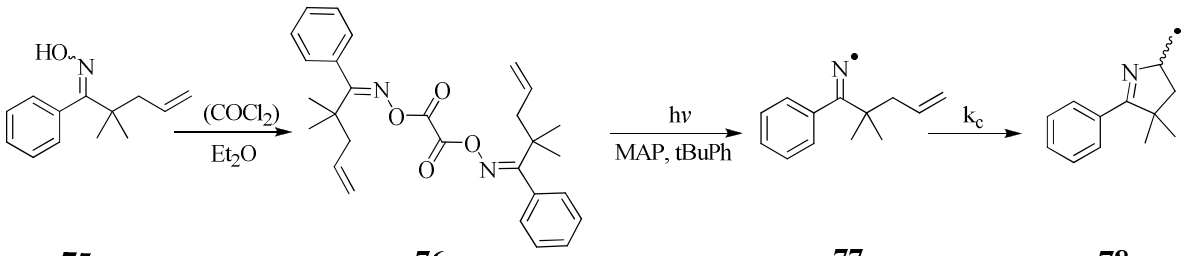
Radical	Cyclised Radical	k_c (s^{-1})
 **61**	 **63**	2×10^3
 **69**	 **70**	2×10^6
 **71**	 **72**	2×10^5
 **73**	 **74**	2×10^7

Table 3. Rate constants of cyclisation for iminyl and carbon-centered radicals at 300 K.

2.3.2 Kinetic study of 2,2-Dimethyl-1-phenylpent-4-en-1-iminyl radical.

The kinetics of cyclisation of iminyl radical **77** were also studied by ESR spectroscopy from 237 K to 285 K. In this case, the unsaturated nitrogen-centered radical **77** contained two geminal methyl groups (Scheme 19).



75 **76** **77** **78**

Scheme 19

An acceleration of the cyclisation was expected due to the replacement of hydrogen atoms with alkyl groups. Decreasing the natural tetrahedral angle by introducing two germinal methyl groups which repel each other, greatly favours the 5-membered ring formation by the so called Thorpe-Ingold effect, by compressing the two reactive centres close together.[19]

The ESR samples were prepared by taking 70 mg of the starting dioxime oxalate **76**, 2 mol equiv of MAP and dissolving them in *tert*-butylbenzene (3.5 cm^3). The solution was stirred until homogeneous and this allowed the preparation of seven identical samples, each of 500 μL. The degassed sample was placed in the resonant cavity and was cooled to 237 K. Once the temperature had reached thermal equilibrium the cavity was photolysed with light from 500 W UV lamp and the ESR spectrum was recorded. The cavity temperature was then increased and a fresh sample was placed in the resonant cavity. This was also photolysed and the spectrum recorded. The process was repeated, increasing temperature until 285 K.

T/ K	**[78]**	**[77]**	**Log$K_c/2k_t$**	**$10^3/T$**	**Log $2k_t$**	**K_c/s^{-1}**
237	5,38E-09	5,74E-08	-8,23	4,20	8,96	5,3
242	8,04E-09	4,77E-08	-8,03	4,11	9,03	10,2
245	6,43E-09	4,28E-08	-8,13	4,06	9,08	8,9
248	5,42E-09	3,90E-08	-8,21	4,01	9,12	8,2
252	1,01E-08	2,67E-08	-7,85	3,95	9,18	21,0
258	6,32E-09	2,08E-08	-8,08	3,85	9,25	14,8
262	1,10E-08	3,34E-08	-7,83	3,79	9,30	29,2
267	9,46E-09	2,42E-08	-7,88	3,72	9,36	29,9
272	1,26E-08	1,68E-08	-7,66	3,65	9,41	56,6
275	9,63E-09	1,60E-08	-7,81	3,61	9,44	42,3
280	1,35E-08	1,69E-08	-7,62	3,55	9,48	73,9
285	1,05E-08	1,45E-08	-7,74	3,48	9,53	60,8

Table 4. Kinetic ESR data for **76** (70 mg), in *t*-BuPh (3.5 mL) with 2 eq MAP.

By plotting the calculated values of log k_c against $10^3/T$, and implementing a line of best fit, it was possible to obtain the activation energy (E_c) and the pre-exponential factor (A_c) for **76** (Figure 12 and Table 5).

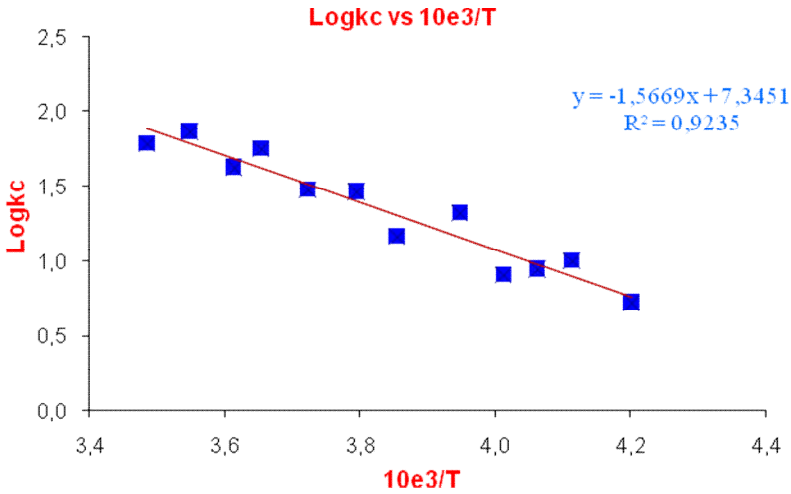


Figure 12. Plot of log k_c against 10^3/T.

Radical	k_c/s^{-1} (300 K)	Log A_c/s^{-1}	E_c/ kcal mol^{-1}
77 ⟶ **78**	3 E+02	10.0	10.6

Table 5

The Thorpe-Ingold effect proved to be efficient in the cyclisation of carbon-centred radical **79**[18] increasing by one order of magnitude the rate constant with respect to the parent species **71**. Surprisingly, the measured rate constant for iminyl radical **77** turned out to be one order of magnitude less than the related iminyl radical **61**. Therefore, no support was forthcoming for gem-dimethyl enhancement of aryliminyl cyclization (Table 6).

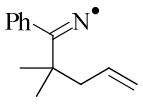
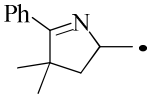
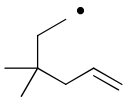
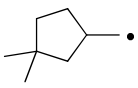
Radical	Cyclised Radical	k_c (s^{-1})
 **77**	 **78**	3 x 10^2
 **79**	 **80**	5 x 10^6

Table 6. Rate constants of cyclisation for iminyl and carbon-centered radicals at 300 K.

This unexpected result may be due to the steric interaction between the phenyl ring and the two geminal dimethyl groups that may cause a loss of planarity in the system and therefore an increase of energy. Figure 13 represents the crystal structure of the 2,2-dimethyl-1-phenylpent-4-en-1-one oxime **75.** It shows that the torsion angle of C(6)-C(1)-C(7)-N(7) is 87.4 ° probably due to the presence of the two methyl groups. Thus, it was probable that the same interaction had taken place in the iminyl radical **77.**

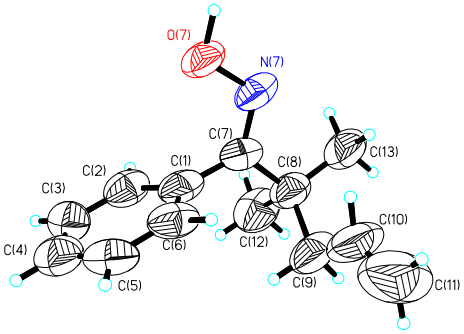


Figure 13. X-Ray structure of the oxime **75**.

It seemed possible that this surprisingly low rate constant might be a result of slow decay of radical **77**. Steric shielding of the iminyl radical centre might impede dimerisation giving **77** some persistence and thus lowering $2k_t$. To check on this possibility, a sample of dioxime oxalate **76** and MAP in *t*-BuPh was studied by ESR spectroscopy with and without UV irradiation. The radical decayed rapidly with second-order kinetics when the light was cut off (Figure 14) and hence **77** was not persistent and the normal $2k_t$ applied.

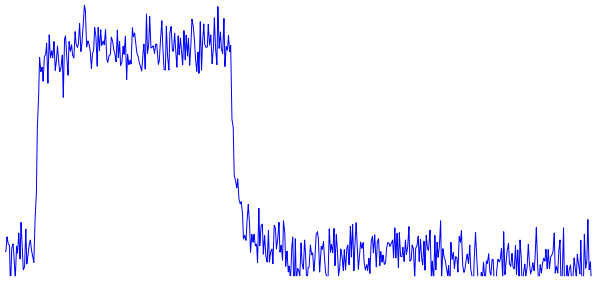
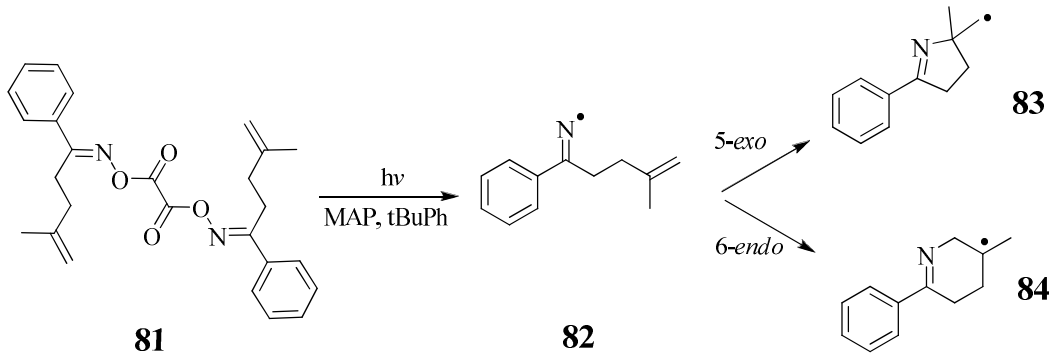


Figure 14. 9.4 GHz ESR signal decay for iminyl radical **77**.

2.3.3 Kinetic study of 4-methyl-1-phenylpent-4-en-1 iminyl radical.

Dioxime oxalate **81** was used as the precursor in the study of the 5-*exo* cyclisation of iminyl radical **82**. In this occasion, the unsaturated iminyl radical had a methyl group in the 4-position, which may slow down the 5-*exo* cyclisation to give **83**. It was possible therefore, that formation of carbon-centered radical **84** could happen by a 6-*endo* ring closure (Scheme 20).



Scheme 20

ESR was used to determine the structures of radical intermediates and hence to validate the mechanism of the photodissociation. Figure 15 shows the spectrum obtained on photolysis of the dioxime oxalate **81** in the presence of MAP at 275 K. The 1:1:1 triplet (marked **I**) has a *a*(N) value of 10.1 G which is typical of an iminyl radical **82**. A second radical species with a triplet of triplet structure was observed in the spectrum which may be attributed the carbon centred radical **83** (marked **C**).

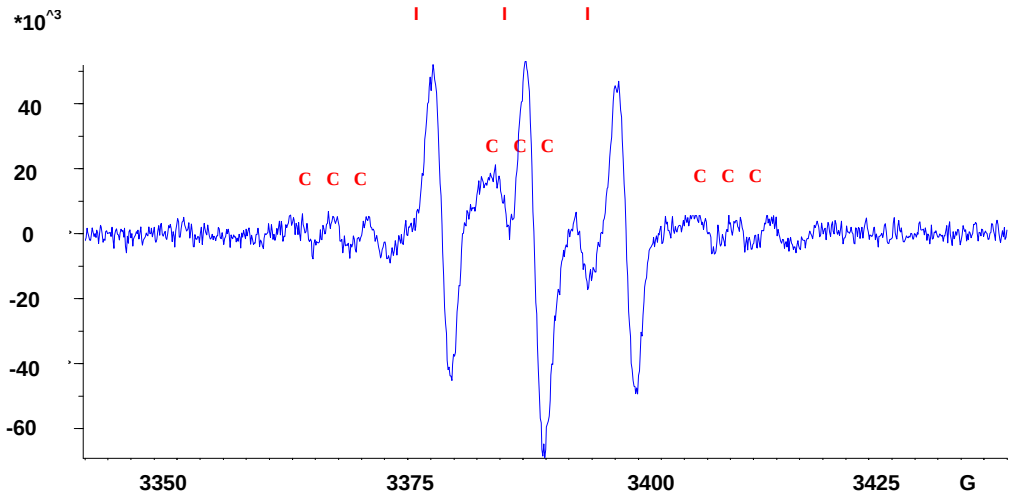


Figure 15. 9.4 GHz ESR spectrum obtained on photolysis of the solution of **81** and MAP in *tert*-butylbenzene at 275 k, I; iminyl radical **82** and C; carbon centred radical **83**.

The parameters of this intermediate are *a*(2H) = 21.8 G and *a*(N) = 4.3 G corresponding with the carbon centered radical **83** resulting from 5-*exo* cyclisation. None of the cyclised radical **84** was found in the spectrum which confirms that the 5-*exo* mode was faster than the 6-*endo* one.

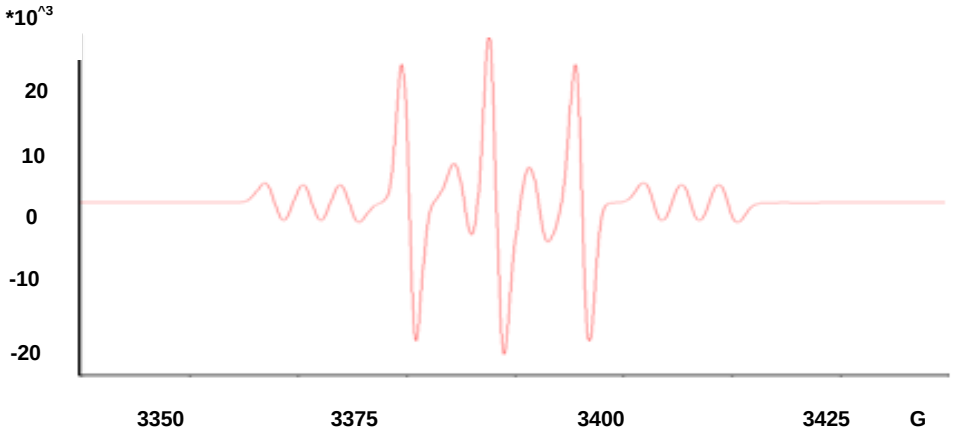


Figure 16. Simulation of iminyl radical **82** and carbon centred radical **83**.

To determinate kinetic data of the cyclisation process, ESR samples were prepared as usual by taking 70 mg of the starting dioxime oxalate **81**, 2 mol equiv of MAP and dissolving them in *tert*-butylbenzene (3.5 cm^3). The solution was stirred until homogeneous and this allowed the preparation of seven identical samples, each of 500 μL. Once the samples were degassed, they were photolysed with light from 500 W UV lamp and ESR spectra were recorded at several temperatures. Table 7 shows the kinetic ESR data obtained for dioxime oxalate **81**.

T/ K	[83]	[82]	$Log k_c/2k_t$	$10^3/T$	$Log\ 2k_t$	k_c/s^{-1}
270	1,18E-08	5,41E-08	-7,84	3,68	1,54	35,0
275	1,61E-08	5,73E-08	-7,68	3,61	1,75	56,6
280	1,11E-08	2,21E-08	-7,78	3,55	1,71	51,2
282	1,35E-08	2,85E-08	-7,70	3,52	1,80	63,5
285	1,50E-08	2,55E-08	-7,62	3,48	1,90	80,0
290	1,57E-08	2,46E-08	-7,59	3,42	1,98	95,6
295	1,31E-08	1,54E-08	-7,61	3,37	1,99	98,5
297	1,74E-08	1,85E-08	-7,47	3,34	2,15	141,9
300	1,85E-08	2,13E-08	-7,46	3,31	2,18	152,0
302	1,75E-08	1,76E-08	-7,46	3,29	2,20	157,9
305	1,38E-08	1,36E-08	-7,55	3,25	2,12	132,6
310	1,64E-08	1,18E-08	-7,41	3,20	2,30	200,8

Table 7. Kinetic ESR data for **81** (70 mg), in *t*-BuPh (3.5 mL) with 2 eq MAP.

By plotting the calculated values of log k_c against 10^3/T, and implementing a line of best fit, it was possible to obtain the activation energy (E_c) and the pre-exponential factor (A_c) for **81** (Figure 17 and Table 8).

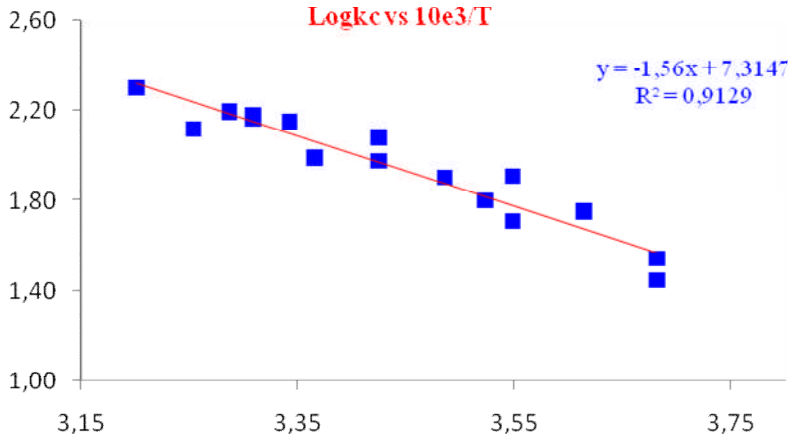


Figure 17. Plot of log K_c against 10^3/T.

Radical	k_c/s^{-1} (300 K)	Log A_c/s^{-1}	E_a/ kcal mol^{-1}
82 ⟶ **83**	1.6 E+02	10.0	10.71

Table 8

The rate constant for the cyclisation of iminyl radical **82** was found to be one order smaller than that of iminyl radical **61**. It was therefore clear, that the simple presence of a methyl group in the 4-position hinders the 5-*exo* approach. (Table 9).

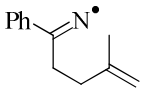
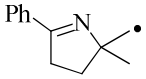
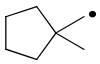
Radical	Cyclised Radical	k_c (s^{-1})
 **82**	 **83**	2×10^2
 **85**	 **86**	5×10^3
 **85**	 **87**	9×10^3

Table 9. Rate constants of cyclisation for iminyl and carbon-centered radicals at 300 K.

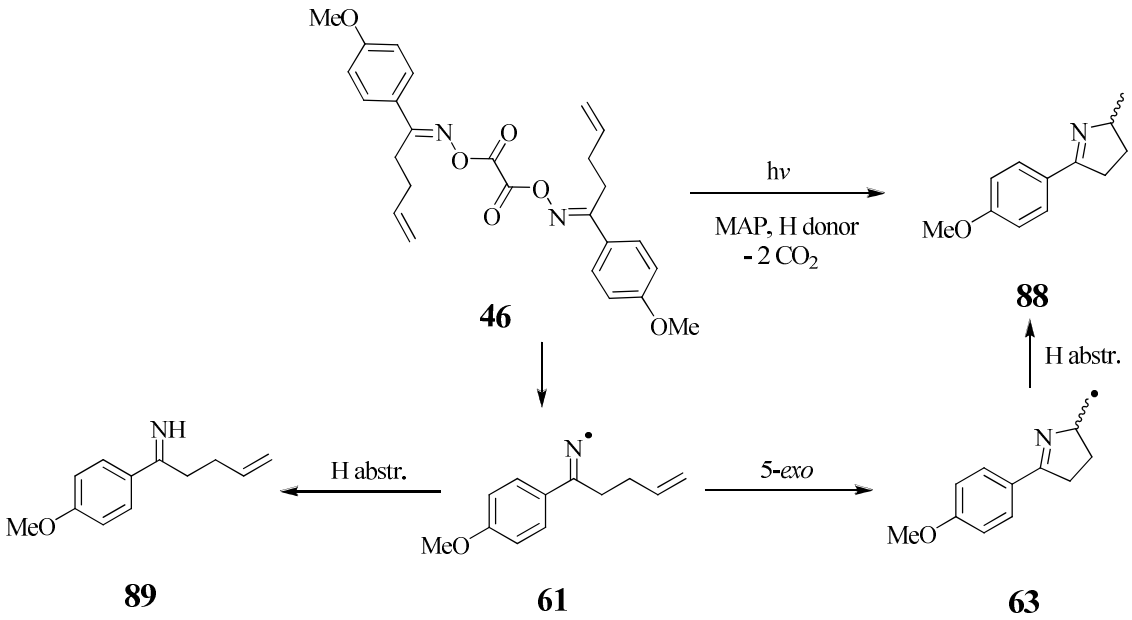
The kinetic data for the related carbon centred radical **84**[21] shows the influence of the methyl on the rate constant being two orders of magnitude smaller than related **71**. Interestingly, 6-*endo* cyclisation in **84** is slightly faster than the 5-*exo* one, in contrast to the iminyl radical **82** which undergoes preferably 5-*exo* mode ring closure to give the primary radical **83**, according with ESR study

2.4 Preparative scale photolysis study.

The successful detection by ESR spectroscopy of iminyl radicals and carbon-centred radicals resulting from 5-*exo* cyclisation, led us to investigate the application of the dioxime oxalate route to iminyl radical cyclisation as a synthetic method for dihydropyrrole derivatives and other aza-heterocycles.

2.4.1 Iminyl radical addition onto alkenes. Syntheses of dihydropyrroles.

As has been described earlier, when dioxime oxalate **46** was UV irradiated in the presence of photosesitizer MAP the weak N-O bond of the dioxime oxalate should break first yielding iminyl radical **61** and acyloxyl radicals. Rapid dissociation of the latter would release a second iminyl radical along with two CO_2 molecules. The iminyl radical **61** could then undergo ring closure in the favoured 5-*exo*-*trig* mode to afford dihydropyrrolomethyl radicals **63** that abstracted an H-atom from the solvent with production of the 3,4-dihydro-2H-pyrrole **88**. Alternatively, iminyl **61** could directly abstract an H-atom from solvent with production of imine **89**. The latter may hydrolyze to the corresponding ketone (Scheme 21).



Scheme 21

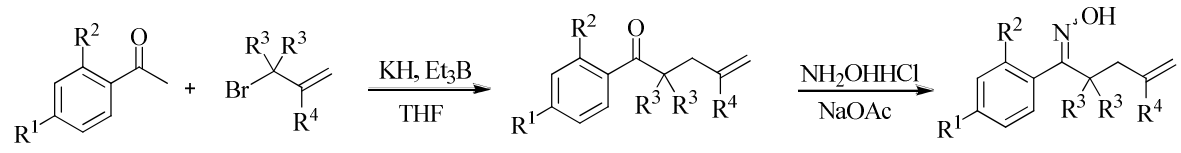
To find the optimum conditions, dioxime oxalate **46** was reacted under various reaction conditions and the product yields monitored by NMR. The dioxime oxalate was dissolved in various solvents (25 mL) along with MAP and the solutions were photolyzed in quartz tubes with light from a 400 W medium pressure Hg lamp (Table 10).

Run	solvent	*T* (°C)	time (h)	Yields 88	Yields 89
1	Toluene	rt	4	**60**	**17**
2	Toluene	rt	6	**63**	**12**
3	Toluene	50	4	**27**	**10**
4	Isopropanol	rt	6	**11**	**78**
5	Cyclo-1,4-hexadiene	rt	6	**15**	**63**
6	Cyclohexane	rt	6	**45**	**17**

Table 10. Optimization of dihydropyrrole yield from sensitized photolyses of **46**. Yields in mol % determined by ^{1}H NMR with CH_2Br as internal standar.

The results indicated that isopropanol and cyclohexa-1,4-diene were too efficient as H-atom donors, such that cyclisation could not compete with reduction of the iminyl radical to imine. Toluene and cyclohexane were both satisfactory in this respect. The poor yield in the experiment carried out in toluene at 50 °C suggested the dioxime oxalate degraded too rapidly at this temperature and starting oxime was the main product present in the reaction mixture. The best combination was UV irradiation of dioxime oxalate **46** for 4 hours in toluene at rt with 2 equiv of MAP.

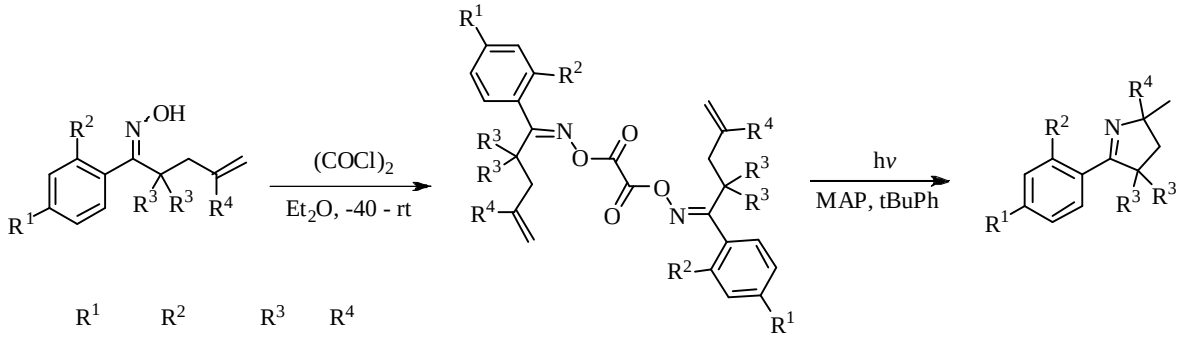
To test the efficiency of this process for preparative purposes a set of dioxime oxalates was prepared in three step syntheses as described earlier. Alkylation of several substituted acetophenones with alkyl bromides gave a set of γ,δ-unsaturated ketones in good yields. Reaction with hydroxylamine hydrochloride afforded unsaturated oximes (Scheme 22).



	R^1	R^2	R^3	R^4		
a	H	MeO	H	H	**a** **44**; 72 %	**a** **45**; 67 %
b	H	H	Me	H	**b** **90**; 68 %	**b** **75**; 59 %
c	H	H	H	Me	**c** **91**; 70 %	**c** **93**; 64 %
d	MeO	MeO	H	H	**d** **92**; 77 %	**d** **94**; 71 %

Scheme 22

Two equivalents of the unsaturated oximes in diethyl ether were reacted with oxalyl chloride in Et_2O at -40 °C and the mixtures were stirred for 3 hours before allowing them to warm up to room temperature. Dioxime oxalates were unstable purple oils which were used without further purification. The optimum conditions developed in the photolysis of **46** were applied to reactions of the rest of the set (Scheme 23).



		R^1	R^2	R^3	R^4
a	**45**	H	MeO	H	H
b	**75**	H	H	Me	H
c	**93**	H	H	H	Me
d	**94**	MeO	MeO	H	H

a **46; quant.**
b **76; quant.**
c **81; quant.**
d **95; quant.**

a **88; 61 %**
b **96; 47 %***
c **97; 38 %***
d **98; 67 %**

Scheme 23

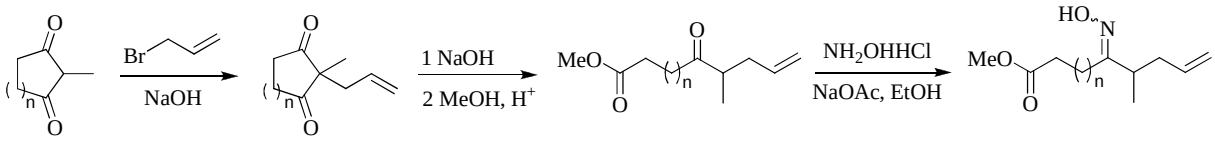
Dihydropyrrole **88** and **98** were isolated in a 61 % and 67 % respectively. The NMR spectrum of the crude reaction mixtures showed in both cases the presence of a vinyl group probably due to early hydrogen abstraction from the corresponding iminyl radical. More important was the presence of the imine derivative when dioxime oxalate **76** was UV irradiated in the optimal conditions. The NMR yield* of **96,** 47 %, was lower than **88** and **98** in agreement with the rate constant calculated previously for this 5-*exo* cyclisation, no support was found from gem-dimethyl enhancement of aryliminyl cyclisation. Hydrogen-atom abstraction from the solvent worked much more efficiently. Disappointingly, none of the desired dihydropyrrole **96** could be isolated.

The lower NMR yield* for the dihydropyrrole **97** after photolysis of the dioxime oxalate **81** in the optimal conditions, was also in agreement with the kinetic data for the 4-methyl-1-phenylpent-4-en-1 iminyl radical. The NMR spectrum of the total reaction mixture showed a complex mixture of compounds, including the unsaturated imine/ketone as the main product. It was clear for this result that ring closure was not fast enough to compete with the reduction of the iminyl radical to imine by hydrogen-atom abstraction from solvent. It was also possible that 6-*endo* cyclisation could have taken place together with 5-*exo* ring closure and iminyl reduction. None of the desired dihydropyrrole **97** was isolated.

2.4.2 Potential synthesis of pyrrolizidines and indolizidines.

It was a possibility to make use of this methodology in the synthesis of dihydropyrroles of type **104** and **105** (Scheme 26). These dihydropyrroles were interesting because they can serve as precursors for biologically active pyrrolizidines and indolizidines.

The keto-esters **49** and **101** needed for the making suitable dioxime oxalate precursors were prepared by allylation of 2-methylcycloalkane-1,3-diones **47** and **99**. The allylated cycloalkanones **48** and **100** were ring opened and esterified yielding **49** and **98** in 67 % and 60 % respectively, which were converted to the corresponding oximes **50** and **102** in the standard way in a 70 % and 73 % yield (Scheme 24).



n=1; **47**
n=2; **99**

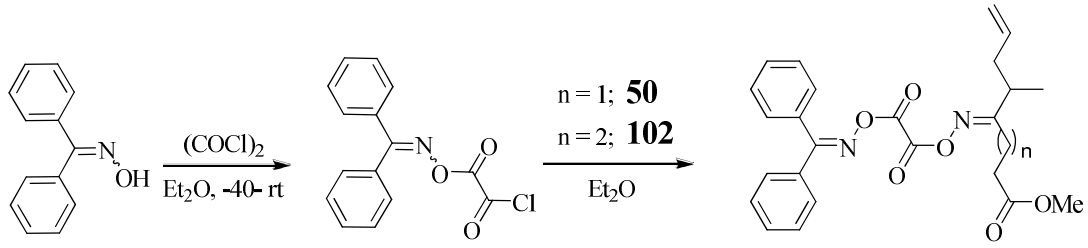
n = 1; **48**; **78 %**
n = 2; **100**; **73 %**

n = 1; **49**; **67 %**
n = 2; **101** **60 %**

n = 1; **50**; **70 %**
n = 2; **102**; **73 %**

Scheme 24

Knowing from ESR spectroscopy that iminyl radical generation was much less efficient in the symmetrical dioxime oxalate containing no aryl groups, it was decided to prepare unsymmetrical dioxime oxalates, with one half containing an aromatic oxime. ESR spectroscopy proved that these unsymmetrical dioxime oxalates were efficient iminyl radical precursors under photolytic conditions. Therefore, dioxime oxalates **60** and **103** were prepared by reaction of one equivalent of the benzophenone oxime **54** with oxalyl chloride affording **57** in 96 % yield. Reaction with a second equivalent of the oxime ester **50** and **102** gave the dioxime oxalates **60** and **103** as moisture-sensitive purple oils (Scheme 25).



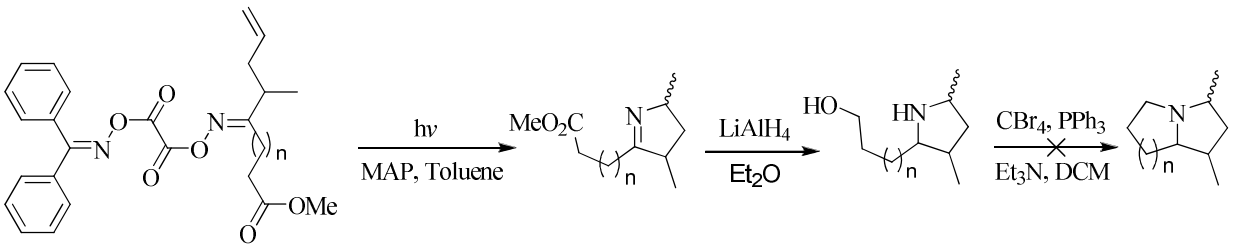
54; **71 %**

57; **96 %**

n = 1; **60**; **quant.**
n = 2; **103**; **quant.**

Scheme 25

Due to the instability of these dioxime oxalates, radical precursors **60** and **103** were photolysed without further purification. The radical precursors were dissolved in 25 mL of toluene and they were photolyzed for 4 hour in the presence of two equivalents of photosensitizer MAP. The NMR spectra of the crude reaction mixtures showed the presence of dihydropyrroles **104** and **105** as mixtures of diastereoisomers (1:1). After purification by column chromatography dihydropyrroles **104** and **105** were isolated in 61 % and 58 % yield (Scheme 26).

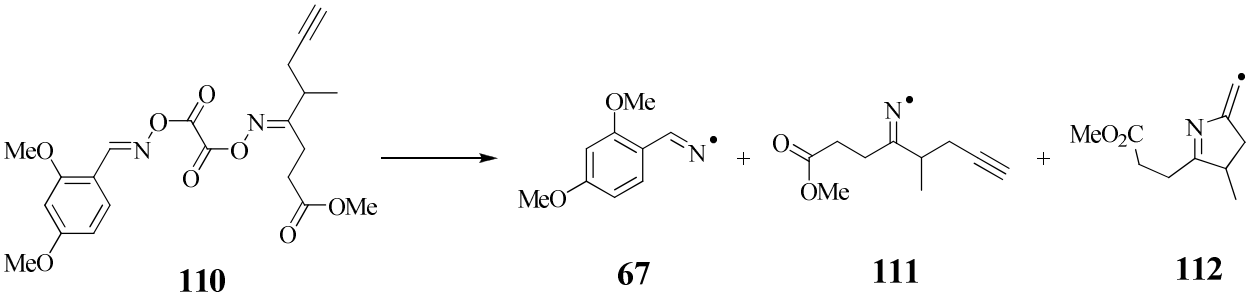


Scheme 26

We investigated methods for converting ester-containing dihydropyrroles **104** and **105** into a pyrrolizidine **108** and indolizidine **109** derivatives by means of an intramolecular nucleophilic substitution. Complete reduction of the imine and ester were therefore carried out with $LiAlH_4$ giving pyrrolidines **106** and **107** as mixtures of stereoisomers. An Appel type method, which has worked for other pyrrolizidine and indolizidine derivates, was tried. However when the amines were treated with PPh_3, CCl_4 and Et_3N in DCM only intractable mixtures were obtained.

2.4.3 Iminyl radical addition onto alkynes.

The potential addition of an iminyl radical onto an alkyne group was also studied. Photolytic dissociation of dioxime oxalate **110** was studied by ESR spectroscopy. The samples were prepared in *tert*-butylbenzene in the standard way and photolysed with light from 500W UV lamp in the presence of two equivalents of MAP. In this case, two different radicals were expected to be detected by ESR spectroscopy, the aryl iminyl radical **67**, corresponding to the aromatic part of the dioxime oxalates **110** and the γ,δ-unsaturated iminyl radical **111.** Vinyl radical **112** may be formed by 5-*exo* cyclisation but, being an extremely reactive intermediate, and it was not expected to be detected by ESR (Scheme 27).



Scheme 27

Figure 18 shows the spectrum obtained on photolysis of the dioxime oxalate **110** in the presence of MAP at 220 K. Two different radicals are observed. The triplets marked (I) at either extreme of the spectrum are due to aryl iminyl radical **67** characterised by g = 2.0033, a(H) = 81.2, a(N) = 10.16 G. A second radical is observable in the spectrum (Im), having the same g = 2.0033 as the radical **67** and the same splitting of a(N) = 10.16 G. This suggests that the second radical is the γ,δ-unsaturated iminyl radical **111**. On the other hand, the vinyl radical **112** does not appear in the EPR spectrum due to its great reactivity.

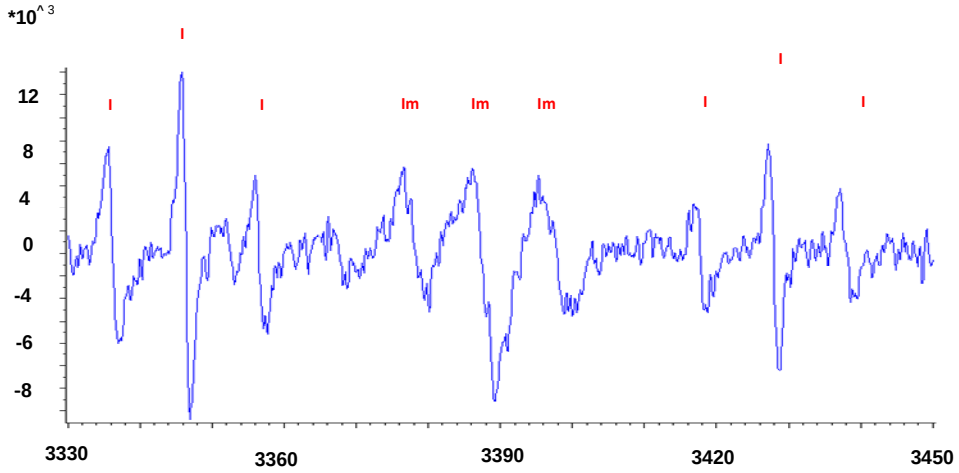


Figure 18. 9.4 GHz ESR spectrum obtained on photolysis of the solution of **110** and MAP in *tert*-butylbenzene at 220 K, I; benzyl radical, IM; unsaturated iminyl radical **111**.

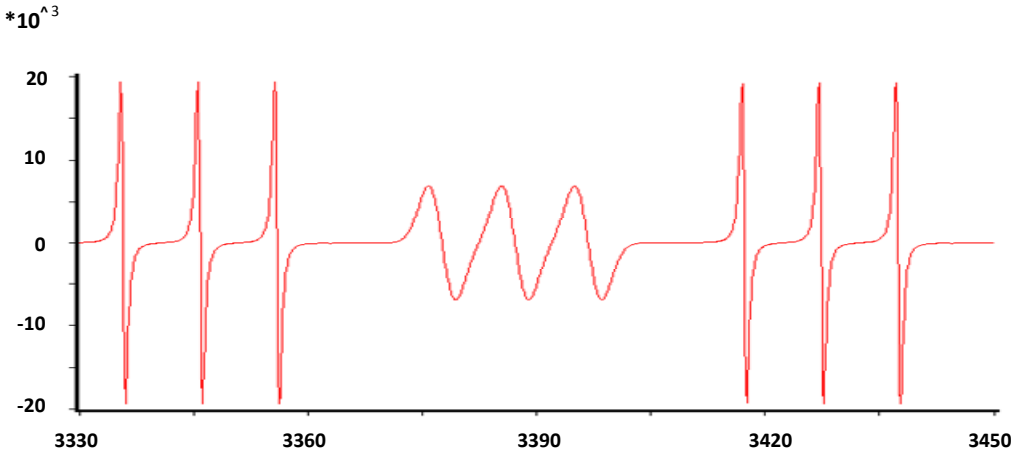
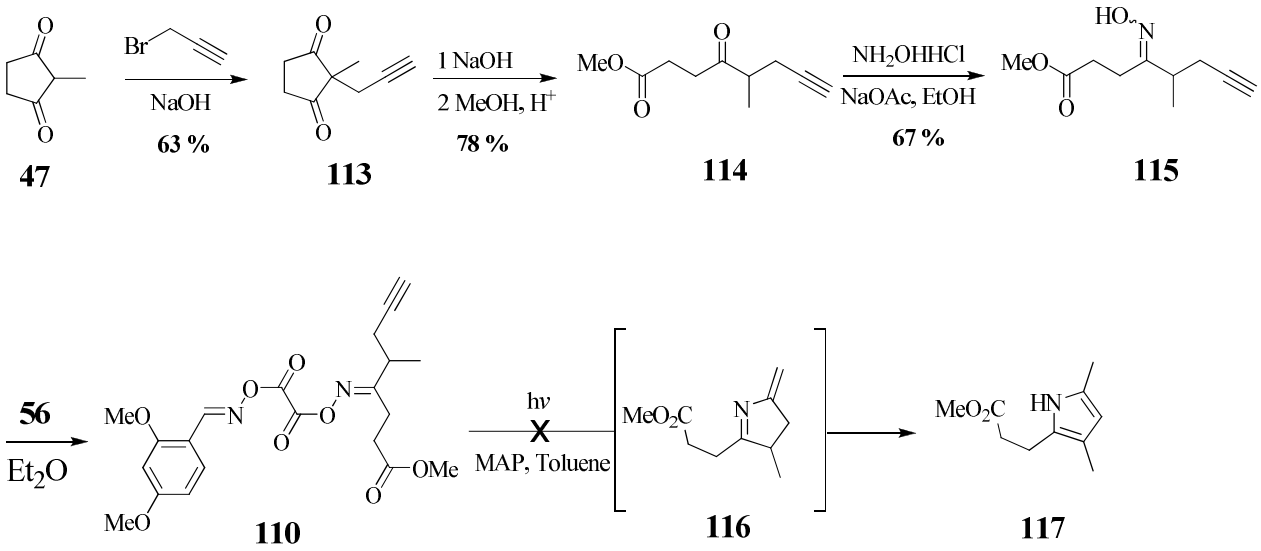


Figure 19. Simulation of the aryl iminyl radical **67** and γ,δ unsaturated iminyl radical **111**.

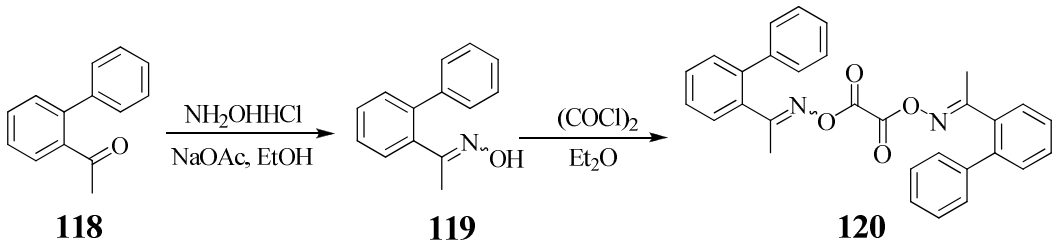
Dioxime oxalate **110** was prepared by a pathway analogous to the one described above. In this case cyclodiketone **47** was reacted with propargyl bromide instead of allyl bromide. Ring opening and esterification was followed by condensation of the keto-ester **114** with hydroxylamine hydrochloride affording the oxime intermediate **115**. Reaction of **115** with 2-(2,4-dimethoxybenzylideneaminooxy)-2-oxoacetyl chloride **56** gave a mixture of stereoisomers of dioxime oxalate **110** as a moisture-sensitive purple oil. A solution of **110** in toluene (400 mL) and in the presence of 2 equi. of MAP was UV photolysed for 4 hours, giving a complex mixture of products. The NMR spectrum of the total reaction mixture showed neither dihydropyrrole **116**, nor pyrrole **117** from a possible aromatic rearrangement (Scheme 28). Instead the reduced imine and its hydrolysed ketone were present in the mixture.



Scheme 28

2.4.4 Iminyl radical addition onto phenyl rings. Synthesis of phenanthridines.

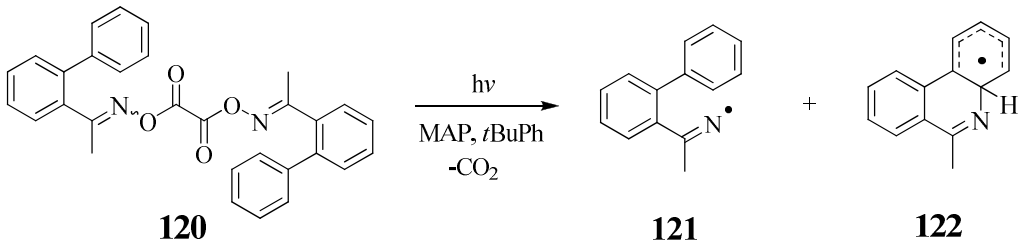
Judging by literature precedent,[20] iminyl radicals can also ring close onto aromatic acceptors, in appropriate circumstances. To broaden the scope of our methodology we prepared dioxime oxalate **120** as outlined in Scheme 29. Condensation of 1-(biphenyl-2-yl)ethanone **118** with hydroxylamine HCl in standard conditions gave the oxime **119** in good yield. This oxime was reacted with oxalyl chloride to give the symmetrical dioxime oxalate **120** as a white powder.



118 **119** **120**

Scheme 29

Photolytic dissociation of dioxime **120** was studied by ESR spectroscopy. The samples were prepared in *tert*-butylbenzene in the standard way and photolysed with light from 500W UV lamp in the presence of two equivalents of MAP. In this case, it was expected that the iminyl radicals released on photolysis **121** would undergo 6-*endo* cyclisation onto the phenyl acceptor because this would yield the resonance stabilized cyclohexadienyl type radical **122** (Scheme 30).



120 **121** **122**

Scheme 30

Figure 20 shows the spectrum obtained on photolysis of the dioxime oxalate **120** in the presence of MAP at 240 K. The triplet marked (**I**) is due to iminyl radical **121** characterised by g = 2.0033, a(N) = 10.14 G. None of the cyclohexadienyl radical was detected.

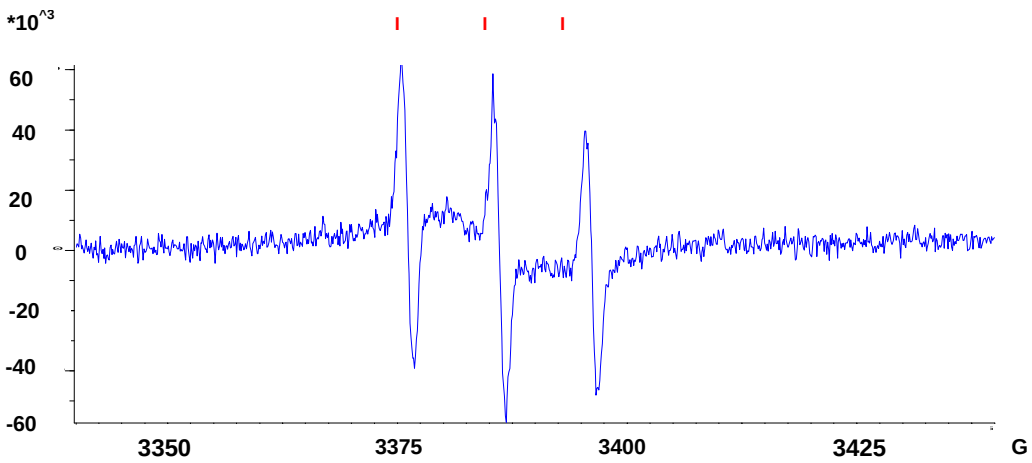
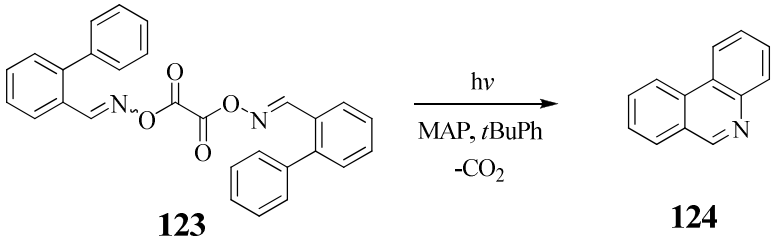


Figure 20. 9.4 GHz ESR spectrum obtained on photolysis of the solution of **120** and MAP in *tert*-butylbenzene at 245 K, I; iminyl radical **121**.

To prove the efficiency of this methodology in the synthesis of phenanthridines, photolysis of dioxime oxalate **123** was chosen as a model to find the best reaction conditions.



Scheme 31

The radical precursor was photolyzed at rt in several different solvents and under various conditions as shown in Table 11.

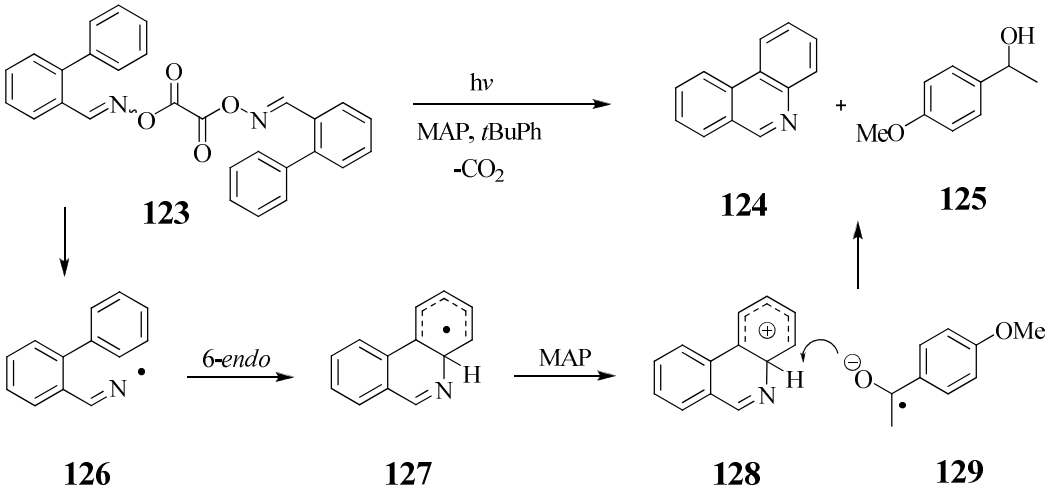
Run	solvent	MAP	time (h)	Yields 124
1	CH_3CN	None	2	**42**
2	CH_3CN	None	4	**66**
3	CH_3CN	2	2	**76**
4	CH_3CN	2	4	**71**
5	*t*-BuPh	2	2	**69**
6	*t*-BuOH	2	2	**34**

Table 11. Optimization of phenantridine **124** yield from sensitized photolyses of **123.** Yields in mol % determined by ^1H NMR with CH_2Br as internal standar.

Heterocycle formation proceeded satisfactorily in the absence of photosensitizer (entries 1 and 2) but a better yield was obtained by inclusion of 2 equiv. of MAP (entry 3). Comparison of entries 3 and 4 indicated that 2 h irradiation was more efficient than 4 h irradiation. Entry 6 shows that *tert*-butanol was not satisfactory as a solvent probably due to the poor solubility of the starting dioxime oxalate. Although a good yield was obtained in *t*-BuPh (entry 5), acetonitrile was more convenient to use, so the conditions of entry 3 were adopted as standard.

Photolytic dissociation of the N-O bond afforded iminyl radical **126** which underwent homolytic aromatic substitution onto the phenyl ring giving cyclohexadienyl radical **127**. The latter is too thermodynamically stabilized to abstract H-atoms from the solvent, and so it should re-aromatize and afford phenanthridine **124**. The mechanism of the final oxidation may involve electron transfer from the cyclohexadienyl radical **127** to MAP yielding the

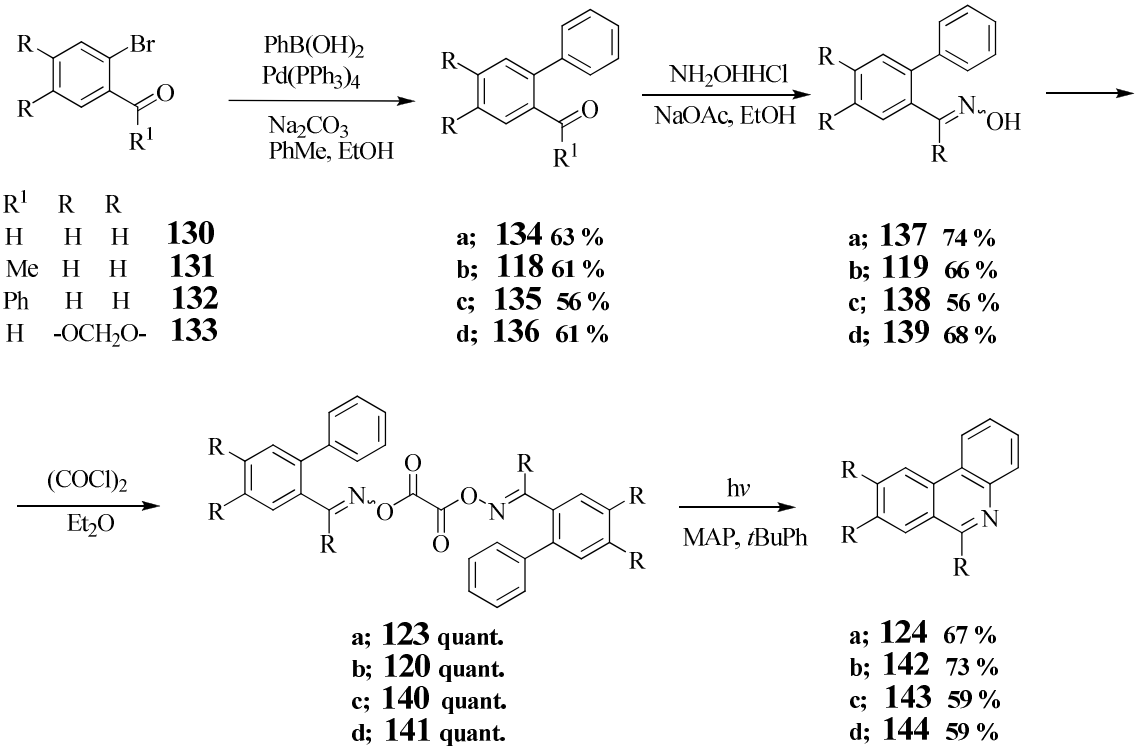
corresponding delocalized cation **128**, together with MAP$^{-\bullet}$ **129** radical anion. Proton transfer from **128** to MAP$^{-\bullet}$ would then yield the phenanthridine **124** together with MAPH$^{\bullet}$, which would pick up hydrogen in solution to give 1-(4-methoxyphenyl)ethanol **125**. This alcohol was detected by NMR and MS in several reactions (Scheme 32).



123 **124** **125** **126** **127** **128** **129**

Scheme 32

The best reaction conditions were applied in the synthesis of substituted phenanthridines in a four-step synthesis from the aromatic carbonyl compounds **130-133** (Scheme 33).



	R^1	R	R	
a;	H	H	H	**130**
b;	Me	H	H	**131**
c;	Ph	H	H	**132**
d;	H	-OCH$_2$O-		**133**

a;	**134**	**63 %**
b;	**118**	**61 %**
c;	**135**	**56 %**
d;	**136**	**61 %**

a;	**137**	**74 %**
b;	**119**	**66 %**
c;	**138**	**56 %**
d;	**139**	**68 %**

a;	**123**	**quant.**
b;	**120**	**quant.**
c;	**140**	**quant.**
d;	**141**	**quant.**

a;	**124**	**67 %**
b;	**142**	**73 %**
c;	**143**	**59 %**
d;	**144**	**59 %**

Scheme 33

The biphenyl derivatives **118**, **134-136** were obtained in good yields by Suzuki coupling with phenyl boronic acid. The oximes were obtained by the standard method and converted to symmetrical dioxime oxalates **120**, **123**, **140** and **141** essentially quantitatively. Photolytic irradiation of these precursor for 2 hours in CH_3CN with 2 equiv. of MAP gave the substituted phenanthridines.

Photolysis of **123** afforded phenathridine **124** in 67 % yield. The reaction was tolerant of Me and Ph substituents on the iminyl radical giving 6-substituted phenanthridines **142** in 73 % yield and **143** in a significantly lower 59 % yield. The poor solubility of the dioxime oxalate **140** in the different solvents may be the reason of this poorer yield. In a similar vein, the plant alkaloid trisphaeridine **144** was prepared in four steps from commercial 6-bromopiperonal. A 59 % yield of **144** was obtained from UV irradiation of **141** in acetonitrile.

3.0 Conclusions.

It was demonstrated that dioxime oxalates can be used as clean efficient precursors for iminyl radicals. Homolytic cleavage of the N-O oxime bond occurs on photolysis, releasing two molecules of CO_2 and two iminyl radicals.

A versatile, efficient route to dioxime oxalates was developed and was found to work well for symmetric and unsymmetric varieties. These compounds are moisture-sensitive and hydrolyzed steadily to oximes during several attempts at purification by different methods.

ESR spectroscopy was used to demonstrate that dioxime oxalates dissociate on photolysis to give iminyl radicals in the presence of photosensitizer MAP. It was shown that symmetrical dioxime oxalates containing aryl groups released iminyl radicals very efficiently. On the other hand, when symmetrical dioxime oxalates containing no aryl rings were studied by ESR spectroscopy, no iminyl radicals were detected. To overcome this problem, unsymmetrical dioxime oxalates with one half containing an aromatic oxime were examined and proved to be efficient precursors of iminyl radicals.

Although iminoxyl radicals were detected in some cases the overall pattern of results indicates these are formed by H-abstraction from traces of oximes remaining in the dioxime oxalates.

In the study of suitable dioxime oxalates with an alkene side-chain, it was also possible to detect dihydropyrrolomethyl radicals. It was confirmed therefore, that 5-*exo* cyclisation was preferred over 6-*endo* cyclisation in accord with expectation.

By measuring the radical concentrations at a range of temperatures it was possible to determine the rate of the 5-*exo* iminyl radical cyclisation onto various alkenes with several substituents. The rates for ring closure were fast enough for preparative work and a number of attempts were made to prepare and isolate the cyclised product.

Photolysis of dioxime oxalates containing alkenyl groups yielded iminyl radicals that ring closed to 3,4-dihydro-2H-pyrroles in toluene solutions. Several of these dihydropyrroles were prepared in useful yields. The major products in all cases were the dihydropyrroles and the imine from reduction of the iminyl radical by hydrogen-atom abstraction from the solvent. The later was especially important when the cyclisation was slower, in agreement with the kinetic data obtained by ESR spectroscopy. Dihydropyrroles **91** and **92** were interesting because they could serve as precursors for biologically active pyrrolizidines and indolizides. Disappointingly, reduction with $LiAlH_4$ and intramolecular nucleophilic substitution under Appel reaction conditions gave an intractable mixture of product and none of the desired products could be isolated.

It was also found that addition onto an alkyne group was not fast enough to compete with reduction of the iminyl radical to imine.

Photolysis of symmetrical dioxime oxalates containing phenyl rings as the radical acceptors were also studied by ESR. The reaction was carried out on a preparative scale in the presence of MAP and a non hydrogen donor solvent. It was shown that iminyl radicals also ring closed onto the phenyl groups. In these conditions the intermediate cyclohexadienyl type radicals aromatized. This oxidation process may involve electron transfer from the cyclohexadienyl radical to the MAP. This approach provides a useful and atom efficient method of making phenanthridines. Natural product Trisphaeridine **144** was also prepared following this methodology.

4.0 Experimental

1-(4-Methoxyphenyl)pent-4-en-1-one 44.[21]

A solution of 1-(4-methoxyphenyl)ethanone (2 g, 13 mmol) in dry THF (5 mL) was added dropwise over 10 min to a suspension of potassium hydride (0.54 g, 13 mmol) in dry THF (25 mL) at 0°C under N_2. The yellow suspension was stirred at 23°C for 30 min and BEt_3 1M solution in THF (13 mL, 13 mmol) was added dropwise at 15°C over 15 min. After stirring the solution at 23 °C for 15 min, allyl bromide (1.99 g, 19.5 mmol) was added dropwise over 10 min and the resulting suspension was stirred for 4 h at 23 °C and quenched with 1:1 mixture of 30% NaOH and 30% H_2O_2 (15 mL) at 0 °C over 15 min. The reaction mixture was then diluted with H_2O (20 mL), the layers were separated and the organic layer diluted with Et_2O (75 mL) and washed with water (2 × 30 mL). The combined water layers were extracted with DCM (2 × 30 mL) and the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The isolated product was purified by column chromatography (AcOEt/hexane 5%) to afford 1-(4-methoxyphenyl)pent-4-en-1-one as a colourless oil 1.78 g, 72 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 3.38 (2H, q, J = 7.7 Hz, CH_2), 2.91 (2H, t, J = 7.3 Hz, CH_2), 3.76 (3H, s, CH_3), 4.92 (2H, m, CH_2), 5.79 (1H, m, CH), 6.82 (2H, d, J = 9.8 Hz, CH), 7.85 (2H, d, J = 9.8 Hz, CH); ^{13}C NMR δ_C; 28.7, 37.7 (CH_2), 55.7 (CH_3), 114.0 (CHx2), 115.4 (CH_2), 130.0 (C), 130.4 (CH)x2, 137.6 (CH), 163.5, 198.2 (C); IR 3058, 1667, 1593 cm^{-1}.

1-(4-Methoxyphenyl)pent-4-en-1-one oxime 45.

A suspension of 1-(4-methoxyphenyl)pent-4-en-1-one (2g, 10.4 mmol), hydroxylamine hydrochloride (1.46 g, 20 mmol) and sodium acetate (1.64 g, 20 mmol) in EtOH (40 mL) was heated under reflux for 4 h. The reaction was monitored by TLC (EtOAc/hexane 1:2) and on completion the mixture was poured into water (30 mL) and extracted with DCM (3 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane 10%) to afford the desired product as a white solid 1.42 g, 67 %; mp 57-59 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.22 (2H, q, J = 8.0 Hz, CH_2), 2.78 (2H, t, J = 8.0 Hz, CH_2), 3.67 (3H, s, CH_3), 4.92 (2H, m, CH_2), 5.75 (1H, m, CH), 6.79 (2H, d, J = 9.8 Hz, CH), 7.43 (2H, d, J = 9.8 Hz, CH), 9.94 (1H, s, OH); ^{13}C NMR δ_C; 25.8, 30.4 (CH_2), 55.3 (CH_3), 114.2 (CHx2), 115.0 (CH_2), 127.6 (CHx2), 128.0 (C), 137.7 (CH), 158.6, 160.8 (C); IR 3267, 3078, 3015, 2937, 1644, 931 cm^{-1}.

1-(4-Methoxyphenyl)pent-4-en-1-one dioxime oxalate 46.

A solution of 1-(4-methoxyphenyl)pent-4-en-1-one oxime (1g, 4.87 mmol) in Et_2O (20 mL) was added dropwise to a stirred solution of oxalyl chloride (309 mg, 2.43 mmol) in dry Et_2O (10 mL) at -40°C. After stirring for 1 hour at -20°C the suspension was warmed up to room temperature and stirred for another two hours. After reaction completion, the solvent was evaporated under reduced pressure to give a purple oil, in a quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.23 (4H, m, CH_2), 2.88 (4H, m, CH_2), 3.74 (6H, s, CH_3), 4.94 (4H, m, CH_2), 5.68 (2H, m, CH), 6.82 (4H, d, J = 8.6 Hz, CH), 7.55 (4H, d, J = 8.6 Hz, CH); ^{13}C NMR δ_C; 27.5, 30.9 (CH_2), 55.5 (CH_3), 114.2 (CH×2), 116.2 (CH_2), 125.0 (C), 129.1 (CH×2), 136.2 (CH), 160.9 (C), 162.2 (C), 166.5 (C); IR 3077, 3003, 2934, 1768, 1723, 1663, 917 cm^{-1}.

2-Allyl-2-methylcyclopentane-1,3-dione 48.[22]

Allyl bromide (3 g, 26 mmol), and Bu_4NI (50 mg, 0.13 mmol) was added to a solution of 2-methyl-1,3-cyclopentanedione (1.45 g, 13 mmol) in 1M aqueous NaOH (13 mL, 13 mmol). The mixture was stirred vigorously at 50 °C for 24 h. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated. Vacuum distillation of the crude material gave the title compound as a colourless oil 1.54 g, 78 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 0.95 (3H, s, CH_3), 2.19 (2H, d, J = 7.5 Hz, CH_2), 2.47-2.70 (4H, m, CH_2), 4.91 (2H, m, CH_2), 5.44 (1H, m, CH); ^{13}C NMR δ_C; 18.6 (CH_3), 35.3 (CH_2×2), 40.0 (CH_2), 56.6 (C), 119.7 (CH_2), 131.5 (CH), 216.2 (C×2) ; IR 3079, 2979, 1764, 1725, 1641cm^{-1}.

Methyl 5-methyl-4-oxooct-7-enoate 49.

2-Allyl-2-methyl cyclopentane-1,3-dione (2 g, 13.1 mmol) was added to a stirred solution of NaOH (1.1 g, 26.2 mmol) in H_2O (25 mL) and stirred at room temperature overnight. The reaction mixture was washed with Et_2O (3 × 20 mL), acidified with 5M H_2SO_4, and extracted with Et_2O (4 × 20 ml). The combined extracts of the acidified reaction mixture were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in MeOH (50 mL) in the presence of catalytic amount of H_2SO_4 (0.5 mL) and stirred at reflux temperature for 4 h. The solution was added to H_2O (40 mL) and stirred for 10 min. The mixture was extracted with DCM (3 × 20 mL). The combined extracts were washed with

H_2O (3 × 20 mL), saturated aqueous $NaHCO_3$ (3 × 30 mL) and H_2O (3 × 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Distillation of the residue on a Kugelrohr (124°C, 0.10 mmHg) afforded the desired product as a yellow oil 1.63, g 67 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.12 (3H, d, J = 7.03 Hz, CH_3), 2.12 (1H, m , CH_2), 2.41 (1H, m, CH_2), 2.54-2.85 (5H, m, CH, CH_2), 3.69 (3H, s, CH_3), 5.05 (2H, m, CH_2), 5.73 (1H, m, CH); ^{13}C NMR δ_C; 16.0 (CH_3), 27.8, 35.8, 37.2 (CH_2), 45.8 (CH), 51.8 (CH_3), 116.8 (CH_2), 135.8 (CH), 173.2, 212.1 (C); IR 2972, 1739, 1711, 1437 cm^{-1}.

Methyl 4-(hydroxyimino)-5-methyloct-7-enoate 50.

Sodium acetate (0.89 g, 10.9 mmol) was added to a stirred solution of methyl 5-methyl-4-oxooct-7-enoate (1 g, 5.4 mmol) in ethanol (20 mL) and hydroxylamine hydrochloride (0.65 g, 10.9 mmol). The mixture was stirred for 5 h at reflux temperature. The solution was poured into H_2O (25 mL) and extracted with DCM (3 × 15 mL). The combined extracts were dried over $MgSO_4$. The solvent was evaporated to dryness to give the crude oxime as a light yellow oil which was distilled on a Kugelrohr (188°C, 0.10 mmHg) to give the product as a colourless oil 0.76 g, 70 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.07/1.09 (3H, d, J = 7.0 Hz, CH_3), 2.13 (1H, m, CH_2), 2.31 (1H, m, CH_2), 2.41-2.69 (5H, m, CH, CH_2), 3.68/3.69 (3H, s, CH_3), 5.02 (2H, m, CH_2), 5.71 (1H, m, CH); ^{13}C NMR δ_C; 16.7/17.8 (CH_3), 22.8/25.2, 30.2/30.3 (CH_2), 31.5/39.5 (CH), 37.8/38.5 (CH_2), 52.1/52.1 (CH_3), 116.7/117.1 (CH_2), 136.3/136.5 (CH), 162.5/163.1, 173.8/174.0 (C); IR 3445, 2994, 2968, 1740, 1641, 1498, 924 cm^{-1}.

Methyl 5-methyl-4-oxooct-7-enoate dioxime oxalate 51.

A solution of methyl 4-(hydroxyimino)-5-methyloct-7-enoate (1 g, 4.97 mmol) in Et_2O (20 mL) was added dropwise to a stirred solution of oxalyl chloride (315 mg, 2.48 mmol) in dry Et_2O (10 mL) at -40°C. After stirring for 1 h at -20°C the suspension was warmed up to room temperature and stirred for another two h. After reaction completion, the solvent was evaporated under reduced pressure to give a pink oil, in a quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.08/1.12 (6H, m, CH_3), 2.08-3.40 (14H, m, CH, CH_2), 3.63/3.65 (6H, s, CH_3), 5.01 (4H, m, CH_2), 5.66 (2H, m, CH); ^{13}C NMR δ_C; 13.9/14.1 (CH_3), 16.6/17.3, 23.7/25.7 (CH_2), 29.1/30.2 (CH), 37.6/37.9 (CH_2), 52.1/52.2 (CH_3), 117.6 (CH_2), 134.7/135.0 (CH), 162.7/163.1, 172.4/172.8, 173.3/174.4 (C); IR 3079, 2978, 2965, 1781, 1734, 1641, 916 cm^{-1}.

Benzaldehyde oxime 52.[23]

From benzaldehyde (2 g, 18.9 mmol) as described for **45**. White solid 1.71 g, 75 % yield; mp 34-36 °C [lit. 35 °C].[24] ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.38 (3H, m, CH), 7.57 (2H, m, CH), 8.18 (1H, s, CH), 8.90 (1H, s, OH); ^{13}C NMR δ_C; 127.5 (CH×2), 129.3 (CH×2), 130.6 (CH), 132.3 (C), 150.8 (CH); IR 3313, 1694, 952 cm^{-1}.

2,5-Dimethoxybenzaldehyde oxime 53.[25]

From 2,4-dimethoxybenzaldehyde (2 g, 12.8 mmol) as described for **45**. White solid 1.62 g, 70 %; mp 104-105°C [lit. 103-105 °C].[25] ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 3.81 (3H, s, CH_3), 3.83 (3H, s, CH_3), 6.47 (2H, m, CH), 7.53 (1H, d, J = 8.7 Hz, CH), 8.36 (1H, s, CH); ^{13}C NMR δ_C; 55.8, 55.9 (CH_3), 99.0, 105.7 (CH), 114.1 (C), 129.4, 147.0 (CH), 159.3, 162.7 (C); IR 3320, 1695, 956 cm^{-1}.

Benzophenone oxime 54.[26]

From benzophenone (2 g, 10.1 mmol) as described for **45.** White solid, 1.41 g, 71 %; mp 143-145 °C [lit. 143-145 °C].[26] ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.19-7.57 (10H, m, CH), 9.33 (1H, s, OH); ^{13}C NMR δ_C; 128.3 (CH×2), 128.6 (CH×2), 128.7 (CH×2), 129.6 (CH), 129.7 (CH×2), 129.9 (CH), 133.2, 136.5, 158.4 (C); IR 3235, 2923, 1456, 919 cm^{-1}.

2-(Benzylideneaminooxy)-2-oxoacetyl chloride 55.[27]

A solution of benzaldehyde oxime (1 g, 8.3 mmol) in Et_2O (15 mL) was added dropwise to a stirred solution of oxalyl chloride (1.05 g, 8.3 mmol) in dry Et_2O (10 mL) at -40°C. After stirring for 1 h at -20°C, the solvent was evaporated to leave a colourless, temperature sensitive, white powder 1.71 g, 98 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.37-7.51 (3H, m, CH), 7.67 (2H, m, CH), 8.45 (1H, s, CH); ^{13}C NMR δ_C; 129.4 (C), 129.6 (CH×2), 132.6 (CH×2), 133.2 (CH), 159.6 (CH), 172.1, 173.0 (C); IR 2921, 1792, 1767, 1609, 974 cm^{-1}.

2-(2,4-Dimethoxybenzylideneaminooxy)-2-oxoacetyl chloride 56.

A solution of 2,5-dimethoxybenzaldehyde oxime (1 g, 5.5 mmol) in Et_2O (15 mL) was added dropwise to a stirred solution of oxalyl chloride (0.70 g, 5.5 mmol) in dry Et_2O (10 mL) at -

40°C. After stirring for 1 h at -20°C, the solvent was evaporated to leave a colourless, temperature sensitive, white powder 1.38 g, 93 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 3.86 (6H, s, CH_3), 6.45 (1H, d, J = 2.3 Hz, CH), 6.54 (1H, dd, J = 8.7, 2.3 Hz, CH), 7.86 (1H, d, J = 8.7 Hz, CH), 8.83 (1H, s, CH); ^{13}C NMR δ_C; 56.0 (CH_3×2), 98.5, 106.6 (CH), 109.8 (C), 129.3, 155.4 (CH), 161.0, 165.4, 172.1, 172.3 (C); IR 2926, 1791, 1760, 1604, 974 cm^{-1}.

2-(Diphenylmethylleneaminooxy)-2-oxoacetyl chloride 57.

A solution of benzophenone oxime (1 g, 5.0 mmol) in Et_2O (15 mL) was added dropwise to a stirred solution of oxalyl chloride (0.64 g, 5.0 mmol) in dry Et_2O (10 mL) at -40°C. After stirring for 1 h at -20°C, the solvent was evaporated to leave a colourless, temperature sensitive, white powder 1.37 g, 96 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.23-7.60 (10H, m, CH); ^{13}C NMR δ_C; 128.8 (CH×2), 129.1 (CH×2), 129.4 (CH×2), 129.8 (CH×2), 131.0 (CH), 131.4 (C), 132.3 (CH), 133.8 (C), 155.1 (C), 168.6 (C×2); IR 2928, 1766, 1763, 1606, 950 cm^{-1}.

Methyl 4,5-dioxo-8-(pent-4-en-2-yl)-1-phenyl-3,6-dioxa-2,7-diazaundeca-1,7-dien-11-oate 58.

A solution of methyl 4-(hydroxyimino)-5-methyloct-7-enoate (1 g, 4.9 mmol) in Et_2O (20 mL) was added dropwise to a stirred solution of 2-(benzylideneaminooxy)-2-oxoacetyl chloride (1.03 g, 4.9 mmol) in dry Et_2O (20 mL) at -40°C. After stirring for 1 h at -20°C the suspension was warmed up to room temperature and stirred for another two hours. After reaction completion, the solvent was evaporated under reduced pressure to give a pink oil, in a quantitative yield, as a mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.07 (3H, m, CH_3), 2.06-2.81 (6H, m, CH_2), 3.42 (1H, m, CH), 3.76 (3H, m, CH_3), 5.06 (2H, m, CH_2), 5.73 (1H, m, CH), 7.32-7.81 (5H, m, CH), 8.51 (1H, s, CH); ^{13}C NMR δ_C; 17.0/17.1 (CH_3), 24.5/24.4, 29.7/29.8 (CH_2), 34.2/39.9 (CH), 38.6/38.7 (CH_2), 53.0 (CH_3), 110.7 (C), 117.8 (CH_2), 129.9 (CH×2), 133.6 (CH×2), 134.5, 135.4, 159.2 (CH), 164.9, 165.0, 172.7, 173.3 (C); IR 2976, 1779, 1752 1740, 1642, 914 cm^{-1}.

Methyl 1-(2,4-dimethoxyphenyl)-4,5-dioxo-8-(peny-4-en-2-yl)3,6-dioxa-2,7-diazaundeca-1,7-dien-11-oate 59.

A solution of methyl 4-(hydroxyimino)-5-methyloct-7-enoate (1 g, 4.9 mmol) in Et_2O (20 mL) was added dropwise to a stirred solution of 2-(2,4-dimethoxybenzylideneaminooxy)-2-oxoacetyl chloride (1.32 g, 4.9 mmol) in dry Et_2O (20 mL) at -40°C. After stirring for 1 h at -20°C the suspension was warmed up to room temperature and stirred for another 2h. After reaction completion, the solvent was evaporated under reduced pressure to give a purple oil, in a quantitative yield as a mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.15 (3H, m, CH_3), 2.05-2.80 (6H, m ,CH_2), 3.46 (1H, m, CH), 3.69 (3H, m, CH_3), 3.85 (6H, s, CH_3), 5.03 (2H, m, CH_2), 5.71 (1H, m, CH), 6.42-6.55 (2H, m, CH), 7.82-7.84 (1H, m, CH), 8.77/8.79 (1H, s, CH); ^{13}C NMR δ_C; 16.9/17.7 (CH_3), 24.2/25.9, 29.3/30.7 (CH_2), 34.5/39.9 (CH), 37.9/38.0 (CH_2), 52.2/52.4, 55.9, 56.1 (CH_3), 98.5, 106.4 (CH), 110.6 (C), 117.9 (CH_2), 129.3, 135.2/135.4, 153.8/154.3 (CH), 160.7, 160.8, 164.9, 165.0, 172.7, 173.3 (C); IR 2975, 1790, 1761, 1758, 1601, 916 cm^{-1}.

Methyl 4,5-dioxo-8-(pent-4-en-2-yl)-1,1-diphenyl-3,6-dioxa-2,7-diazaundeca-1,7-dien-11-oate 60.

A solution of methyl 4-(hydroxyimino)-5-methyloct-7-enoate (1 g, 4.9 mmol) in Et_2O (20 mL) was added dropwise to a stirred solution of 2-(diphenylmethylleneaminooxy)-2-oxoacetyl chloride (1.40 g, 4.9 mmol) in dry Et_2O (20 mL) at -40°C. After stirring for 1 h at -20°C the suspension was warmed up to room temperature and stirred for another 2 h. After reaction completion, the solvent was evaporated under reduced pressure to give a purple oil, in a quantitative yield as a mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.03 (3H, m, CH_3), 1.93-2.71 (6H, m, CH_2), 3.28-3.31 (1H, m, CH), 3.50-3.64 (3H, m, CH_3), 4.94 (2H, m, CH_2), 5.60 (1H, m, CH), 7.06-7.64 (10H, m, CH); ^{13}C NMR δ_C; 17.0/17.7 (CH_3), 24.2/25.7, 29.3/30.5 (CH_2), 34.3/39.8 (CH), 37.9/38.1 (CH_2), 52.2/52.5 (CH_3), 118.0 (CH_2), 128.7 (CH×2), 128.9 (CH×2), 129.4 (CH), 129.5 (CH×2), 130.7 (CH), 131.6 (C), 131.9 (CH×2), 134.2 (C), 135.1 (CH), 158.5, 160.2, 166.4, 172.6, 173.2 (C) ; IR 2977, 1791, 1756, 1734, 1641, 916 cm^{-1}.

2,2-Dimethyl-1-phenylpent-4-en-1-one oxime 75.

A suspension of 2,2-dimethyl-1-phenylpent-4-en-1-one (2 g, 10.6 mmol), hydroxylamine hydrochloride (1.47 g, 21.2 mmol) and sodium acetate (1.73 g, 21.2 mmol) in EtOH (40 mL) was heated under reflux condition for 4 h. After reaction conclusion, followed by TLC (EtOAc/hexane 1:2), the reaction mixture was poured into water (30 mL) and extracted with DCM (3 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane 10%) to afford the desired product white solid 1.27 g, 59 %; mp 108-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.03 (6H, s, CH_3), 2.11 (2H, d, J = 7.0 Hz, CH_2), 4.96 (2H, m, CH_2), 5.73 (1H, m, CH), 7.05 (2H, m, CH), 7.34 (3H, m, CH), 9.14 (1H, s, OH); ^{13}C NMR δ_C; 25.0 (CH_3x2), 39.3 (C), 43.7, 117.2 (CH_2), 126.7 (CHx2), 126.9 (CH), 127.0 (CHx2), 132.5 (C), 133.4 (CH), 164.2 (C); IR 3258, 3062, 2974, 2965, 1640, 952 cm^{-1}.

2,2-Dimethyl-1-phenylpent-4-en-1-one dioxime oxalate 76.

A solution of methyl 2,2-dimethyl-1-phenylpent-4-en-1-one oxime (1 g, 4.3 mmol) in Et_2O (20 mL) was added dropwise to a stirred solution of oxalyl chloride (272.5 mg, 2.15 mmol) in dry Et_2O (10 mL) at -40°C. After stirring for 1 h at -20°C the suspension was warmed up to room temperature and stirred for another 2 h. After reaction completion, the solvent was evaporated under reduced pressure to give a white solid 1.5 g, 76 % yield, as a mixture of isomers. The compound was unstable to high temperatures. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.13 (12H, s, CH_3), 2.22 (4H, d, J = 7.2 Hz, CH_2), 5.04 (4H, m, CH_2), 5.78 (2H, m, CH), 6.91-7.05 (4H, m, CH), 7.28-7.43 (6H, m, CH); ^{13}C NMR δ_C; 25.9 (CH_2), 41.9 (C), 44.2 (CH_3×2), 118.6 (CH_2), 126.7 (CH×2), 128.2 (CH×2), 128.8 (CH), 131.7 (C), 133.8 (CH), 163.3, 173.8 (C) ; IR 3060, 2970, 1763, 1752, 1675, 914 cm^{-1}. HRMS (ES) calcd for $C_{28}H_{32}N_2O_4Na$; 483.2260. Found: 483.2267.

4-Methyl-1-phenylpent-4-en-1-one dioxime oxalate 81.

A solution of 4-methyl-1-phenylpent-4-en-1-one oxime (1 g, 5.74 mmol) in Et_2O (20 mL) was added dropwise to a stirred solution of oxalyl chloride (364.5 mg, 2.87 mmol) in dry Et_2O (20 mL) at -40°C. After stirring for 1 h at -20°C the suspension was warmed up to room temperature and stirred for another 2 h. After reaction completion, the solvent was evaporated under reduced pressure to give a purple oil, in a quantitative yield as a mixture of isomers. ^{1}H

NMR (400 MHz, $CDCl_3$), δ_H; 1.66-1.70 (6H, s, CH_3), 2.15 (4H, m, CH_2), 2.94-2.96 (4H, m, CH_2), 4.60 (2H, m, CH_2), 4.66 (2H, m, CH_2), 7.28-7.44 (6H, m, CH), 7.54-7.61 (4H, m, CH); ^{13}C NMR δ_C; 22.2 (CH_3), 26.9, 34.4, 111.1 (CH_2), 127.3 (CH×2), 128.9 (CH×2), 131.2 (CH), 133.0, 144.1, 157.1, 167.8 (C); IR 3000, 2991, 1786, 1760, 1653, 909 cm^{-1}.

5-(4-Methoxyphenyl)-2-methyl-3,4-dihydro-2*H*-pyrrole 88.

A solution of the 1-(4-methoxyphenyl)pent-4-en-1-one dioxime oxalate (400 mg, 0.86 mmol) and *p*-methoxyacetophenone (256 mg, 1.71 mmol) in toluene (25 mL) placed in a quartz flask, was photolysed for 4h. at room temperature by light from a 400 W UV lamp. After this time the toluene was evaporated to dryness to give a yellow oil. The oil was purified by column chromatography (10% EtOAc/hexane) red oil, 198.2 mg, 61 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.28 (3H, d, J = 6.8, CH_3), 1.46 (1H, m, CH_2), 2.15 (1H, m, CH_2), 2.78 (1H, m, CH_2), 2.96 (1H, m, CH_2), 3.78 (3H, s, CH_3), 4.20 (1H, m, CH), 6.83 (2H, d, J = 8.8 Hz, CH), 7.71 (2H, d, J = 8.8 Hz, CH); ^{13}C NMR δ_C; 22.2 (CH_3), 30.7, 35.2 (CH_2), 55.6 (CH_3), 68.2 (CH), 113.8 (CH×2), 127.4 (C), 129.3 (CH×2), 161.2, 171.1 (C); IR 3268, 2923, 1684 cm^{-1}. HRMS (CI^+) calcd for $C_{12}H_{16}NO$; 190.1232. Found 190.1238.

2,2-Dimethyl-1-phenylpent-4-en-1-one 90.

A mixture of isobutyrophenone (2 g, 13.6 mmol), allyl bromide (1.76 g, 14.4 mmol) and potassium *t*-butoxide (1.7 g, 15 mmol) in *t*-butyl alcohol (20 mL) was heated at reflux for 3h under a nitrogen atmosphere. After cooling the reaction mixture was poured into water (25 mL) and extracted with diethyl ether (3 ×15 mL). The solvent was removed under reduced pressure and the residue was distilled on a Kugelrohr (131°C, 0.4 mmHg) to give the title ketone as a colourless oil 1.73 g, 68 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.23 (6H, s, CH_3), 2.40 (2H, d, J = 7.3 Hz, CH_2), 4.93 (2H, m, CH_2), 5.65 (1H, m, CH), 7.34 (3H, m, CH), 7.57 (2H, m, CH); ^{13}C NMR δ_C; 24.8 (2xCH_3), 45.0 (CH_2), 49.7 (C), 115.5 (CH_2), 126.4 (2x CH), 127.2 (2xCH), 131.5 (CH), 136.0 (C), 138.1 (CH), 206 (C); IR 2976, 1676, 1597 cm^{-1}

4-Methyl-1-phenylpent-4-en-1-one 91.

A solution of acetophenone (2 g, 16 mmol) in dry THF (5 mL) was added dropwise over 10 min to a suspension of potassium hydride (0.64 g, 17 mmol) in dry THF (25 mL) at 0°C under N_2. The yellow suspension was stirred at 23°C for 30 min and BEt_3 1M solution in

THF (17 mL, 17 mmol) was added dropwise at 15°C over 15 min. After stirring the solution at 23 °C for 15 min, 3-bromo-2-methyl-prop-1-ene (3.21 g, 24 mmol) was added dropwise over 10 min and the resulting suspension was stirred for 4 h at 23 °C and quenched with a 1:1 mixture of 30% NaOH and 30% H_2O_2 (15 mL) at 0 °C over 15 min. The reaction mixture was then diluted with H_2O (20 mL), the layers were separated and the organic layer diluted with Et_2O (75 mL) and washed with water (2 × 30 mL). The combined water layers were extracted with DCM (2 × 30 mL) and the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The isolated product was purified by column chromatography (AcOEt/hexane 5%) to afford the named product as a colourless oil, 2.14 g, 77 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.71 (3H, s, CH_3), 2.37 (2H, t, J = 6.3 Hz, CH_2), 3.04 (2H, t, J = 7.5 Hz, CH_2), 4.66 (1H, s, CH_2), 4.67 (1H, s, CH_2), 7.38 (2H, m, CH), 7.47 (1H, m, CH), 7.89 (2H, m, CH); ^{13}C NMR δ_C; 23.1 (CH_3), 31.9, 37.2, 110.5 (CH_2), 128.0 (CHx2), 128.6 (CHx2), 133.0 (CH), 137.0, 144.7, 199.7 (C); IR 2970, 1674, 1590 cm^{-1}.

1-(2,4-Dimethoxyphenyl)pent-4-en-1-one 92.

A solution of 1-(1,4-dimethoxyphenyl)ethanone (2 g, 11 mmol) in dry THF (5 mL) was added dropwise over 10 min to a suspension of potassium hydride (0.53 g, 13 mmol) in dry THF (25 mL) at 0°C under N_2. The yellow suspension was stirred at 23°C for 30 min and BEt_3 1M solution in THF (13 mL, 13 mmol) was added dropwise at 15°C over 15 min. After stirring the solution at 23 °C for 15 min, allyl bromide (1.99 g, 16.5 mmol) was added dropwise over 10 min and the resulting suspension was stirred for 4 h at 23 °C and quenched with a 1:1 mixture of 30% NaOH and 30% H_2O_2 (15 mL) at 0 °C over 15 min. The reaction mixture was then diluted with H_2O (20 mL), the layers were separated and the organic layer diluted with Et_2O (75 mL) and washed with water (2 × 30 mL). The combined water layers were extracted with DCM (2 × 30 mL) and the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The isolated product was purified by column chromatography (AcOEt/hexane 5%) to afford the named product as a colourless oil, 1.86 g, 77 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.35 (2H, t, J = 7.2 Hz, CH_2), 2.97 (2H, t, J = 7.2 Hz, CH_2), 3.77 (3H, s, CH_3), 3.81 (3H, s, CH_3), 4.95 (2H, m, CH_2), 5.84 (1H, m , CH), 6.37 (1H, d, J = 2.3 Hz, CH), 6.44 (1H, dd, J = 8.7, 2.3 Hz, CH), 7.73 (1H, d, J = 8.7 Hz, CH); ^{13}C NMR δ_C; 28.7, 43.0 (CH_2), 55.7 (CH_3x2), 98.5, 105.2 (CH), 114.7 (CH_2), 121.4 (C), 133.0, 138.3 (CH), 160.8, 164.4, 199.6 (C); IR 2942, 1664, 1575 cm^{-1}.

4-Methyl-1-phenylpent-4-en-1-one oxime 93.

A suspension of 4-methyl-1-phenylpent-4-en-1-one (2 g, 11.5 mmol), hydroxylamine hydrochloride (1.59 g, 23 mmol) and sodium acetate (1.88 g, 23 mmol) in EtOH (40 mL) was heated under reflux condition for 4 h. After reaction conclusion, followed by TLC (EtOAc/hexane 1:2), the reaction mixture was poured into water (30 mL) and extracted with DCM (3 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane 10%) to afford the desired product white solid 1.39 g, 64%; mp 68-70 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.68 (3H, s, CH_3), 2.18 (2H, t, J = 7.7 Hz, CH_2), 2.88 (2H, t, J = 8.2 Hz, CH_2), 4.65 (1H, s, CH_2), 4.67 (1H, s, CH_2), 7.30 (3H, m, CH), 7.51 (2H, m, CH), 9.63 (1H, s, OH); ^{13}C NMR δ_C; 21.4 (CH_3), 23.9, 32.8, 109.4 (CH_2), 125.3 (CHx2), 127.6 (CHx2), 128.2 (CH), 134.6, 144.0, 158.3 (C); IR 3255, 3076, 3018, 2972, 1649, 930 cm^{-1}.

1-(2,4-Dimethoxyphenyl)pent-4-en-1-one oxime 94.

A suspension of 1-(2,4-dimethoxyphenyl)pent-4-en-1-one (1 g, 4.5 mmol), hydroxylamine hydrochloride (0.62 g, 9 mmol) and sodium acetate (0.73 g, 9 mmol) in EtOH (25 mL) was heated under reflux condition for 4 h. After reaction conclusion, followed by TLC (EtOAc/hexane 1:2), the reaction mixture was poured into water (20 mL) and extracted with DCM (3 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane 10%) to afford the desired product white solid 0.75 g, 71 %; mp 77-79 °C; two isomers 7:3. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.14 (2H, m, CH_2), 2.52/2.76 (2H, m, CH_2), 3.71 (3H, s, CH_3), 3.73 (3H, s, CH_3), 4.88 (2H, m, CH_2), 5.72 (1H, m, CH), 6.35-6.46 (2H, m, CH), 6.98/7.10 (1H, d, J = 8.8 Hz, CH); ^{13}C NMR δ_C; 28.2/30.9, 30.3/34.9 (CH_2), 55.8/56.0 (CH_3x2), 99.2/99.3, 104.6/104.8 (CH), 115.1/115.6 (CH_2), 118.9 (C), 130.2/131.2, 138.0/138.6 (CH), 157.5/158.9, 160.1, 161.7/161.9 (C); IR 3257, 3079, 3015, 2939, 1639, 1610, 927 cm^{-1}.

1-(2,4-Dimethoxyphenyl)pent-4-en-1-one dioxime oxalate 95.

A solution of 1-(2,4-dimethoxyphenyl)pent-4-en-1-one oxime (700 mg, 2.97 mmol) in Et_2O (20 mL) was added dropwise to a stirred solution of oxalyl chloride (189 mg, 1.48 mmol) in dry Et_2O (20 mL) at -40°C. After stirring for 1 h at -20°C the suspension was warmed up to room temperature and stirred for another 2 h. After reaction completion, the solvent was evaporated under reduced pressure to give a purple oil, in a quantitative yield as a mixture of

isomers. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.06-2.70 (8H, m, CH_2), 3.71-3.81 (12H, m , CH_3), 4.97 (4H, m, CH_2), 5.77 (2H, m, CH), 6.43 (2H, m, CH), 7.51 (2H, m , CH), 8.16 (2H, m, CH); ^{13}C NMR δ_C; 27.8/29.6, 34.4/34.5 (CH_2), 55.8 (CH_3×2), 98.6/98.7, 103.7/104.6 (CH), 115.7 (CH_2), 120.7/129.6 (CH), 121.4, 149.1, 156.3, 161.9, 169.9, 174.6 (C); IR cm^{-1} 2934, 1768, 1705, 1605, 1512, 926 cm^{-1}.

5-(2,4-Dimethoxyphenyl)-2-methyl-3,4-dihydro-2*H*-pyrrole 98.

A solution of 1-(2,4-dimethoxyphenyl)pent-4-en-1-one dioxime oxalate (400 mg, 0.76 mmol) and *p*-methoxyacetophenone (228 mg, 1.52 mmol) in toluene (25 mL) placed in a quartz flask was photolysed for 4h. at room temperature by light from a 400 W UV lamp. After this time the toluene was evaporated to dryness to give a yellow oil. The oil was purified by column chromatography (10% EtOAc/hexane), red oil 222 mg, 67 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.28 (3H, d, J = 6.7 Hz, CH_3), 1.44 (1H, m, CH_2), 2.12 (1H, m, CH_2), 2.88 (1H, m, CH_2), 3.04 (1H, m, CH_2), 3.77 (3H, s, CH_3), 3.78 (3H, s, CH_3), 4.12 (1H, m, CH), 6.43 (2H, m , CH), 7.68 (1H, d, J = 8.5, CH); ^{13}C NMR δ_C; 21.9 (CH_3), 30.1, 38.1 (CH_2), 55.5 (CH_3×2), 66.4 (CH), 98.6, 105.1 (CH), 116.6 (C), 131.7 (CH), 159.0, 165.8, 172.3 (C); IR 3018, 2964, 1609 cm^{-1} HRMS (CI^{+}) calcd for $C_{13}H_{18}NO_2$; 220.1338. Found: 220.1337.

2-Allyl-2-methylcyclohexane-1,3-dione 100.[22]

Allyl bromide (3 g, 26 mmol), and Bu_4NI (50 mg, 0.13 mmol) were added to a solution of 2-methylcyclohexane-1,3-dione (1.64 g, 13 mmol) in 1 M. aqueous NaOH (13 mL, 13 mmol). The mixture was stirred vigorously at 50 °C for 24 h. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated. Vacuum distillation of the crude material gave the title compound as a colourless oil 1.57 g, 73%. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.22 (3H, s, CH_3), 1.78-2.07 (2H, m, CH_2), 2.52 (2H, dt, J = 7.0, 1.0 Hz, CH_2), 2.55-2.72 (4H, m, CH_2), 5.04 (2H, m, CH_2), 5.56 (1H, m, CH); ^{13}C NMR δ_C; 17.5 (CH_2), 19.3 (CH_3), 38.1 (CH_2×2), 41.2 (CH_2), 65.1 (C), 119.1 (CH_2), 132.2 (CH), 209.8 (C×2); IR 3079, 2967, 1724, 1693, 1454 cm^{-1}.

Methyl 6-methyl-5-oxonon-8-enoate 101.

2-Allyl-2-methylcyclohexane-1,3-dione (2 g, 12.0 mmol) was added to a stirred solution of NaOH (0.98 g, 24.0 mmol) in H_2O (25 mL) and stirred at room temperature overnight. The reaction mixture was washed with Et_2O (3 × 20 mL), acidified with 5 M H_2SO_4, and extracted with Et_2O (4 × 20 ml). The combined extracts of the acidified reaction mixture were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in MeOH (50 mL) in the presence of catalytic amount of H_2SO_4 (0.5 mL) and stirred at reflux temperature for 4 h. The solution was added to H_2O (40 mL) and stirred for 10 minutes. The mixture was extracted with DCM (3 × 20 mL). The combined extracts were washed with H_2O (3 × 20 mL), saturated aqueous $NaHCO_3$ (3 × 30 mL) and H_2O (3 × 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Distillation of the residue on a Kugelrohr (120°C, 0.10 mmHg) afforded the desired product as a yellow oil, 1.42 g, 60 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.08 (3H, d, J = 7.0 Hz, CH_3), 1.89 (2H, qt, J = 7.1 Hz, CH_2), 2.09 (1H, m, CH_2), 2.28-2.67 (6H, m, CH, CH_2), 3.67 (3H, s, CH_3), 5.04 (2H, m, CH_2), 5.72 (1H, m, CH); ^{13}C NMR δ_C; 16.0 (CH_3), 18.6, 32.9, 37.0, 39.9 (CH_2), 45.8 (CH), 51.4 (CH_3), 116.8 (CH_2), 135.5 (CH), 173.9, 213.0 (C) ; IR 2970, 1739, 1710, 1437 cm^{-1}

Methyl 5-(hydroxyimino)-6-methylnon-8-enoate 102.

Sodium acetate (0.82 g, 10.0 mmol) was added to a stirred solution of methyl 6-methyl-5-oxonon-8-enoate (1 g, 5.0 mmol) in ethanol (20 mL) and hydroxylamine hydrochloride (0.69 g, 10.0 mmol). The mixture was stirred for 5 h at reflux temperature. The solution was poured into H_2O (25 mL) and extracted with DCM (3 × 15 mL). The combined extracts were dried over $MgSO_4$. The solvent was evaporated to dryness to give the crude oxime as a light yellow oil which was distilled on a Kugelrohr (182°C, 0.10 mmHg) to give the product as a colourless oil 0.77 g, 70 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.06/1.10 (3H, d, J = 6.7 Hz, CH_3), 1.79-2.54 (9H, m, CH, CH_2), 3.67/3.68 (3H, s, CH_3), 5.04 (2H, m, CH_2), 5.73 (1H, m, CH), 9.32 (1H, s, OH); ^{13}C NMR δ_C; 16.7/17.9 (CH_3), 21.5/21.6, 26.6/29.9 (CH_2), 31.7/39.0 (CH), 33.8/34.4, 37.8/38.8 (CH_2), 52.0 (CH_3), 116.7/117.0 (CH_2), 136.6/136.7 (CH), 163.1/163.7, 174.2 (C); IR 3325, 2972, 2930, 1739, 1641, 1498, 928 cm^{-1}.

Methyl 4,5-dioxo-8-(pent-4-en-2-yl)-1,1-diphenyl-3,6-dioxa-2,7-diazadodeca-1,7-dien-12-oate 103.

A solution of methyl 5-(hydroxyimino)-6-methylnon-8-enoate (1 g, 4.7 mmol) in Et_2O (20 mL) was added dropwise to a stirred solution of 2-(diphenylmethyleneaminooxy)-2-oxoacetyl chloride (1.34 g, 4.7 mmol) in dry Et_2O (20 mL) at -40°C. After stirring for 1 h at -20°C the suspension was warmed up to room temperature and stirred for another 2 h. After reaction completion, the solvent was evaporated under reduced pressure to give a purple oil, in a quantitative yield as a mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.04/1.13 (3H, d, J = 6.9 Hz, CH_3), 2.05-3.26 (9H, m, CH, CH_2), 3.61/3.68 (3H, s, CH_3), 4.98 (2H, m, CH_2), 5.63 (1H, m, CH), 7.33-7.61 (10H, m, CH); ^{13}C NMR δ_C; 16.9/17.7 (CH_3), 20.7/21.2, 24.3/25.7, 29.3/30.4, 31.3/33.3 (CH_2), 34.2/39.8 (CH), 52.2/52.3 (CH_3), 117.7/117.8 (CH_2), 128.8 (CH×2), 128.9 (CH×2), 129.4 (CH×2), 129.5 (CH×2), 130.6/130.7, 131.9, 135.1/135.4 (CH), 131.7, 134.2, 135.0, 158.5, 160.1, 166.4, 173.2 (C); IR 2977, 1791, 1755, 1734, 1641, 912 cm^{-1}.

Methyl 3-(2,4-dimethyl-3,4-dihydro-2*H*-pyrrol-5-yl)propanoate 104.

A solution of methyl 4,5-dioxo-8-(pent-4-en-2-yl)-1,1-diphenyl-3,6-dioxa-2,7-diazaundeca-1,7-dien-11-oate (400 mg, 0.88 mmol) and *p*-methoxyacetophenone (264 mg, 1.76 mmol) in toluene (25 mL) placed in a quartz flask was photolysed for 4h at room temperature by light from a 400 W UV lamp. After this time the toluene was evaporated to dryness to give a yellow oil. The oil was purified by column chromatography (10% EtOAc/hexane), the named compound was isolated as a yellow oil, 0.98 g, 61 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.03/1.09 (3H, d, J = 7.2 Hz, CH_3), 1.10/1.19 (3H, d, J = 7.2 Hz, CH_3), 1.61 (1H, t, J = 6.7 Hz, CH_2), 2.22-2.84 (6H, m, CH, CH_2), 3.60 (3H, s, CH_3), 3.77/4.01 (1H, m, CH); ^{13}C NMR δ_C; 16.4/17.1, 20.7/21.9 (CH_3), 24.9/25.1, 28.7/29.4, 38.5/39.2 (CH_2), 43.4/44.5 (CH), 50.6 (CH_3), 64.3/64.7 (CH), 172.8, 177.2 (C); IR 1764, 1646 cm^{-1}.

Methyl 4-(2,4-dimethyl-3,4-dihydro-2*H*-pyrrol-5-yl)butanoate 105.

A solution of methyl methyl-4,5-dioxo-8-(pent-4-en-2-yl)-1,1-diphenyl-3,6-dioxa-2,7-diazadodeca-1,7-dien-12-oate (400 mg, 0.86 mmol) and *p*-methoxyacetophenone (258 mg, 1.72 mmol) in toluene (25 mL) placed in a quartz flask was photolysed for 4h at room temperature by light from a 400 W UV lamp. After this time the toluene was evaporated to dryness to give a yellow oil. The oil was purified by column chromatography (10%

EtOAc/hexane), the named compound was isolated as a yellow oil, 0.94 g, 56 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.01/1.08 (3H, d, J = 7.1 Hz, CH_3), 1.11/1.21 (3H, d, J = 7.1 Hz, CH_3), 1.59 (1H, m, CH_2), 1.86 (2H, m, CH_2), 2.18-2.35 (5H, m, CH_2), 2.71 (1H, m, CH), 3.60 (3H, s, CH_3), 3.75/4.01 (1H, m, CH); ^{13}C NMR δ_C; 16.4/17.1 (CH_3), 20.48 (CH_2), 20.9/21.8 (CH_3), 29.3/29.4, 32.5/32.6, 38.4/39.1 (CH_2), 42.9/44.0 (CH), 50.5 (CH_3), 64.1/64.5 (CH), 172.8, 178.2/178.3 (C).; IR,1764, 1645 cm^{-1}.

2-4 Dimethoxybenzaldehyde-*O*-(*O*-5-methyl-4-oxooct-7-ynoic acid methyl ester) dioxime oxalate 110.

A solution of methyl 4-(hydroxyimino)-5-methyl-oct-7-ynoic acid methyl ester (1g, 5.0 mmol) in Et_2O (20 mL) was added dropwise to a stirred solution of 2-(2,4-dimethoxybenzylideneaminooxy)-2-oxoacetyl chloride (1.37 g, 5.0 mmol) in dry Et_2O (20 mL) at -40°C. After stirring for 1 h at -20°C the suspension was warmed up to room temperature and stirred for another 2 h. After reaction completion, the solvent was evaporated under reduced pressure to give a purple oil, in a quantitative yield as a mixture of isomers. ^{1}H NMR δ_H; 1.24 (3H, d, *J* = 7.1 Hz, CH_3), 1.99 (1H, t, *J* = 2.7 Hz, CH), 2.31-3.10 (7H, m, CH, CH_2), 3.67 (3H, s, CH_3), 3.86 (6H, s, CH_3), 6.40 (1H, s, CH), 6.55 (1H, d, *J* = 8.8 Hz, CH), 7.88 (1H, d, *J* = 8.8 Hz, CH), 8.86 (1H, s, CH); ^{13}C NMR δ_C; 16.7 (CH_3), 22.3, 28.1, 36.2 (CH_2), 45.3 (CH), 52.1, 56.4, 56.4 (CH_3), 69.5 (CH), 82.0 (C), 98.2, 105.6 (CH), 110.8 (C), 129.1, 154.9 (CH), 160.7, 160.9, 166.3, 166.5, 166.8, 173.59 (C); IR 3288, 2953, 1782, 1738, 1706 cm^{-1}.

2-Methyl-2-prop-2-ynylcyclopentane-1,3-dione 113.[28]

Propargyl bromide (5.35 g, 45 mmol) was added to a solution of NaOH (1.8 g, 45 mmol) and 2-methylcyclopentane-1,3-dione (5 g, 45 mmol) in H_2O (40 mL) The mixture was stirred at 60 ºC for 10 h and then extracted with CH_2Cl_2 (5 x 20mL). The combined extracts were concentrated under reduced pressure. The residue was dissolved in MeOH (15 mL) and stirred with water (10 mL) and concentrated H_2SO_4 (1 mL) at reflux temperature for 3 h.. The MeOH was removed under reduced pressure and the remaining mixture was extracted with CH_2Cl_2 (5 x 20 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (3 x 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Distillation of the residue on a Kugelrohr (124 ºC, 0.1 mm Hg) afforded the product as a yellow oil, 4.18 g, 63

%. ^{1}H NMR δ_H; 1.14 (3H, s, CH_3), 1.99 (1H, t, J= 2.7 Hz, CH), 2.60-2.70 (4H, m, CH_2), 2.77 (2H, d, J = 2.6 Hz, CH_2).

Methyl 5-methyl-4-oxooct-7-ynoate 114.

2-Methyl-2-prop-2-ynylcyclopentane-1,3-dione (2 g, 13.3 mmol) was added to a stirred solution of NaOH (1.2 g, 26.6 mmol) in H_2O (25 mL) and stirred at room temperature overnight. The reaction mixture was washed with EtO_2 (3 × 20 mL), acidified with 5M H_2SO_4, and extracted with Et_2O (4 × 20 ml). The combined extracts of the acidified reaction mixture were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in MeOH (50 mL) in the presence of catalytic amount of H_2SO_4 (0.5 mL) and stirred at reflux temperature for 4 h. The solution was added to H_2O (40 mL) and stirred for 10 min. The mixture was extracted with DCM (3 × 20 mL). The combined extracts were washed with H_2O (3 × 20 mL), saturated aqueous $NaHCO_3$ (3 × 30 mL) and H_2O (3 × 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Distillation of the residue on a Kugelrohr (133°C, 0.10 mmHg) afforded the desired product as a yellow oil, 1.88 g, 78 %. ^{1}H NMR δ_H; 1.24 (3H, m, CH_3), 1.98 (1H, t, J = 2.7 Hz, CH), 2.34 (1H, m, CH_2), 2.48 (1H, m, CH_2), 2.60-2.85 (5H, m, CH_2, CH), 3.67 (3H, s, CH_3).

Methyl 4-(hydroxyimino)-5-methyloct-7-ynoate 115.

Sodium acetate (0.90 g, 11 mmol) was added to a stirred solution of 5-methyl-4-oxooct-7-ynoic acid methyl ester (1 g, 5.5 mmol) in ethanol (20 mL) and hydroxylamine hydrochloride (0.76 g, 11 mmol). The mixture was stirred for 4 h at reflux temperature. The solution was poured into H_2O (25 mL) and extracted with DCM (3 × 15 mL). The combined extracts were dried over $MgSO_4$. The solvent was evaporated to dryness to give the crude oxime as a light yellow oil which was distilled on a Kugelrohr (203 °C, 0.10 mmHg) to give the product as a colourless oil and a mixture of isomers, 1.45 g, 67 %. ^{1}H NMR δ_H; 1.14 (3H, m, CH_3), 1.94 (1H, t, J = 2.3 Hz, CH), 2.33-2.40 (2H, m, CH_2), 2.62-2.89 (4H, m, CH_2), 3.31 (1H, m, CH), 3.67 (3H, s, CH_3); ^{13}C NMR δ_C; 16.7/17.9 (CH_3), 22.6/23.5, 24.3/25.8, 30.6 (CH_2), 31.7/38.9 (CH), 51.6 (CH_3), 70.4 (CH), 82.4, 161.5/162.1, 173.6/173.9 (C); IR, 3285, 1737, 1709 cm^{-1}.

1-(Biphenyl-2-yl)ethanone 118.[29]

1-(2-bromophenyl)ethanone (1g, 5 mmol) and phenylboronic acid (0.61g, 5 mmol) were dissolved in toluene (40 mL), and sodium carbonate (1.05 g, 10 mmol, 2M) was added. To this reaction mixture was added ethanol (2 mL) followed by tetrakis(triphenylphosphine)-palladium (0.11 g, 2 %). The reaction mixture was refluxed overnight under N_2 and then diluted with water, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with water (3 × 30 mL) and brine (1 × 30 mL) dried over $MgSO_4$ and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/EtOAc 5%) to yield a colourless oil, 0.59 g, 61 %. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 2.03 (3H, s, CH_3), 7.35-7.47 (7H, m, CH), 7.53 (1H, dt, J = 7.5, 1.4 Hz, 1H), 7.58 (1H, dd, J = 7.5, 1.2 Hz, CH); ^{13}C NMR δ_C; 30.8 (CH_3), 127.5 (CH), 127.9 (CHx2), 128.7 (CHx2), 128.9 (CHx2), 130.3, 130.7 (CH), 140.4, 140.6, 140.8, 204.7 (C); IR 3060, 1688, 1594 cm^{-1}.

1-(Biphenyl-2-yl)ethanone oxime 119.

A suspension of 1-(biphenyl-2-yl)ethanone (1g, 5.1 mmol), hydroxylamine hydrochloride (0.71 g, 10.2 mmol) and sodium acetate (0.84 g, 10.2 mmol) in EtOH (40 mL) was heated under reflux condition for 4 h. After the conclusion of the reaction as indicated by TLC (EtOAc/hexane 1:2), the reaction mixture was poured into water (30 mL) and extracted with DCM (3 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The solid residue was recrystalised (EtOAc/hexane) to give a white crystal, 0.71 g, 66 %; mp 35-37 °C; two isomers 9:1. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 1.58/1.63 (3H, s, CH_3), 7.16-7.40 (9H, m, CH); ^{13}C NMR δ_C; 16.2 (CH_3), 127.4, 127.5 (CH), 128.6 (CHx2), 129.0 (CHx2), 129.1, 129.3, 130.4 (CH), 136.8, 140.7, 141.1, 159.2 (C).; IR cm^{-1} 3228, 1595, 921 cm^{-1}.

1-(Biphenyl-2-yl)ethanone dioxime oxalate 120.

A solution of 1-(biphenyl-2-yl)ethanone oxime (0.7 g, 3.31 mmol) in Et_2O (20 mL) was added dropwise to a stirred solution of oxalyl chloride (210.5 mg, 1.65 mmol) in dry Et_2O (10 mL) at -40°C. After stirring for 1 h at -20°C the suspension was warmed up to room temperature and stirred for another 2 h. After completion of the reaction, the solvent was evaporated under reduced pressure to give a white solid, in a quantitative yield. ^{1}H NMR

(400 MHz, $CDCl_3$), δ_H; 1.74 (6H, s, CH_3), 7.12-7.53 (18H, m, CH) ; ^{13}C NMR δ_C; 17.4 (CH_3), 126.5, 126.8 (CH), 127.7 (CH×2), 127.8 (CH×2), 128.5, 129.3, 129.4 (CH), 133.0, 139.0, 139.8, 168.3 (C); IR 3054, 2986, 1787, 1764, 1684, 909 cm^{-1}.

Biphenyl-2-carbaldehyde dioxime oxalate 123.

A solution of biphenyl-2-carbaldehyde oxime (1.0 g, 5.07 mmol) in Et_2O (20 mL) was added dropwise to a stirred solution of oxalyl chloride (322 mg, 2.53 mmol) in dry Et_2O (10 mL) at -40°C. After stirring for 1 h at -20°C the suspension was warmed up to room temperature and stirred for another 2 h. After reaction completion, the solvent was evaporated under reduced pressure to give a white solid, in a quantitative yield. ^1H NMR (400 MHz, $CDCl_3$), δ_H; 7.17/7.24 (4H, m, CH), 7.31-7.41 (10H, m, CH), 7.49 (2H, td, *J* = 7.5, 1.5 Hz, CH), 8.02 (2H, d, *J* = 7.8 Hz, CH), 8.40 (2H, s, CH); ^{13}C NMR δ_C; 126.8 (C), 127.5 (CH), 127.9 (CH), 128.2 (CH), 128.7 (CH×2), 129.7 (CH×2), 130.5, 132.0 (CH), 138.6, 144.0 (C), 157.5 (CH), 163.7 (C); IR 2980, 1768, 1734, 1610, 914 cm^{-1}.

Phenanthridine 124.[30]

A solution of biphenyl-2-carbaldehyde dioxime oxalate (250 mg, 0.55 mmol) and *p*-methoxyacetophenone (165.2 mg, 1.11 mmol) in CH_3CN (25 mL) was photolysed for 4h. at room temperature placed in a quarzt flask by light from a 400 W UV lamp. After this time the CH_3CN was evaporated to dryness to give a yellow oil. The oil was purified by column chromatography (10% EtOAc/hexane), the named compound was isolated as a yellow crystal, 130 mg, 67 %; mp 105-107 °C. ^1H NMR (400 MHz, $CDCl_3$), δ_H; 7.62-4.65 (2H, m, CH), 7.71-7.75 (2H, m, CH), 8.08 (1H, d, *J* = 8.1, CH), 8.22 (1H, d, *J* = 8.2 Hz, CH), 8.61 (1H, dd, *J* = 8.1, 1.2 Hz, CH), 8.65 (1H, d, *J* = 8.3, CH), 9.32 (1H, s, CH); ^{13}C NMR δ_C; 121.7, 122.1 (CH), 123.9, 126.9 (C), 127.3 (CH), 128.4 (CH×2), 128.6, 130.0, 130.8 (CH), 132.3, 144.3 (C), 153.4 (CH).

Biphenyl-2-carbaldehyde 134.[31]

From 2- bromobenzaldehyde (1g, 5.5 mmol), as described for **118**. Clear oil, 0.62 g, 63 %. ^1H NMR (400 MHz, CDCl3), δ_H; 7.36-7.40 (2H, m, CH), 7.43-7.52 (5H, m, CH), 7.64 (1H, td, *J* = 7.5, 1.4 Hz, CH), 8.03 (1H, dd, *J* = 7.7, 1.1, CH), 9.98 (1H, s, CH); 13C NMR δ_C; 127.5,

127.8, 128.1, 128.4 (CH), 130.1 (CHx2), 130.8 (C), 133.6 (CHx2), 133.7 (CH), 137.7, 146.0 (C), 192.5 (CH); IR 3020, 1691, 1596 cm-1.

Biphenyl-2-yl(phenyl)methanone 135.[32]

From (2-bromophenyl)(phenyl)methanone (1g, 3.84 mmol), as described for **118**. White crystals 0.55 g, 56 %; mp 85-87 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.00/7.18 (7H, m, CH), 7.48-7.25 (5H, m, CH), 7.57-7.52 (2H, m, CH); ^{13}C NMR δ_C; 127.2, 127.4 (CH), 128.1 (CHx2), 128.3 (CHx2), 128.8 (CH), 129.0 (CHx2), 130.0 (CHx2), 130.1, 130.4, 132.9 (CH), 137.5, 139.0, 140.2, 141.2, 199.3 (C); IR 3060, 1665, 1598 cm^{-1}.

6-Phenylbenzo[*d*][1,3]dioxole-5-carbaldehyde 136.

From 6-bromopiperonal (1 g, 4.38 mmol), as described for **118**. White solid 0.60 g, 61 %; mp 80-82 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 6.00 (2H, s, CH_2), 6.78 (1H, s, CH), 7.27 (2H, m, CH), 7.36 (3H, m, CH), 7.40 (1H, s, CH), 9.67 (1H, s, CH); ^{13}C NMR δ_C; 102.4 (CH_2), 106.6, 110.5 (CH), 127.8 (C), 128.2 (CH), 128.4 (CH×2), 130.1 (CH×2), 137.4, 143.8, 147.8, 152.3 (C), 190.6 (CH); IR 3058, 2907, 1677 cm^{-1}; HRMS (CI^+) calcd for $C_{14}H_{11}O_3$; 227.0708. Found 227.0704.

Biphenyl-2-carbaldehyde oxime 137.

From biphenyl-2-carbaldehyde (1 g, 5.5 mmol), as described for **119**. Yellow solid 1.08 g, 74 %; mp 108-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.21-7.42 (8H, m, CH), 7.84 (1H, d, J = 7.6 Hz, CH), 8.04 (1H, s, CH); ^{13}C NMR δ_C; 126.1, 127.6, 127.7 (CH), 128.4 (CHx2), 129.7 (CHx2), 129.8, 130.3 (CH), 136.0, 139.5, 145.2 (C), 149.8 (CH); IR 3313, 1616, 931 cm^{-1}.

Biphenyl-2-yl(phenyl)methanone oxime 138.

From biphenyl-2-yl(phenyl)methanone (1.0 g, 3.87 mmol), as described for **119**.Yellow solid 0.59 g, 56 %; mp 102-104 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 6.96-7.50 (14H, m, CH), 9.41 (1H, s, OH); ^{13}C NMR δ_C; 127.1, 127.2, 127.3, 127.9/128.0 (CHx2), 128.2/128.3 (CHx2), 128.5 (CHx2), 129.2 (CH), 129.4 (CHx2), 129.6, 130.1 (CH), 132.2/132.8, 135.6/136.2, 140.6, 141.3, 158.0/158.8 (C) ; IR 3231, 1593, 921 cm^{-1}.

6-Phenylbenzo[*d*][1,3]dioxole-5-carbaldehyde oxime 139.

From 6-phenylbenzo[*d*][1,3]dioxole-5-carbaldehyde (1 g, 4.42 mmol), as described for **119**. Yellow solid 0.69 g, 68 %; 140-142 °C; mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H;

6.05 (2H, s, CH_2), 6.81 (1H, s, CH), 7.30 (2H, m, CH), 7.43 (3H, m, CH), 7.62 (1H, s, CH), 8.02 (1H, s, CH); ^{13}C NMR δ_C; 101.9 (CH_2), 105.7, 110.4 (CH), 124.0 (C), 128.1 (CH), 128.8 (CHx2), 130.2 (CHx2), 138.1, 139.7, 147.8, 149.5 (C), 149.9 (CH); IR 3238, 1613, 943 cm^{-1}.

Biphenyl-2-yl(phenyl)methanone dioxime oxalate 140.

From biphenyl-2-yl(phenyl)methanone oxime (400 mg, 1.46 mmol), as described for **120**. White solid quantitative yield; mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 6.81-7.58 (28, m, CH); ^{13}C NMR δ_C 126.1, 126.6 (CH), 127.2 (CH×2), 127.3 (CH×2), 127.5, 127.6 (CH), 128.1 (CH×2), 128.2 (CH×2), 129.0 (CH), 129.7, 130.2 (C), 130.5 (CH), 132.8, 138.8, 140.3, 165.1 (C); IR 3059, 1790, 1764, 1653, 919 cm^{-1}.

6-Phenylbenzo[*d*][1,3]dioxole-5-carbaldehyde dioxime oxalate 141.

From 6-phenylbenzo[*d*][1,3]dioxole-5-carbaldehyde oxime (500 mg, 2.1 mmol) as described for **120**. White solid quantitative yield; mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 5.96/6.00 (4H, s, CH_2), 6.71/6.75 (2H, s, CH), 7.13-7.22 (4H, m, CH), 7.28-7.42 (8H, m, CH), 7.91/8.25 (2H, s, CH); ^{13}C NMR δ_C; 101.6/102.1 (CH_2), 105.2/106.1, 110.0/110.2 (CH), 121.8 (C), 127.5 (CH), 128.4/128.6 (CH×2), 129.7/129.8 (CH×2), 139.2, 142.4, 149.0, 149.4 (C), 149.6/150.5 (CH), 168.2 (C); IR 2980, 1768, 1734, 1610, 917 cm^{-1}.

6-Methylphenanthridine 142.[33]

From 1-(biphenyl-2-yl)ethanone dioxime oxalate (100 mg, 0.2 mmol), as described for **124**. Yellow crystals 59 mg, 73 %; mp 81-83 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 3.02 (3H, s, CH_3), 7.57-7.76 (3H, m, CH), 7.79-7.85 (1H, m, CH), 8.11 (1H, dd, J = 8.1, 1.1 Hz, CH), 8.19 (1H, d, J = 8.2 Hz, CH), 8.51 (1H, d, J = 8.1 Hz, CH), 8.59 (1H, d, J = 8.1 Hz, CH); ^{13}C NMR δ_C; 23.3 (CH_3), 122.0, 122.3 (CH), 123.8, 125.9 (C), 126.3, 126.5, 127.3, 128.6, 129.4, 130.5 (CH), 132.5, 143.7, 158.9 (C).

6-Phenylphenanthridine 143.[34]

From biphenyl-2-yl(phenyl)methanone dioxime oxalate (100 mg, 0.17 mmol), as described for **124**. Yellow crystals 50 mg, 59 %; mp 104-106 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 7.50-7.80 (8H, m, CH), 7.88 (1H, ddd, J = 8.3, 7.0, 1.3 Hz, CH), 8.11 (1H, dd, J = 8.3, 1.3 Hz, CH), 8.26 (1H, dd, J = 8.0, 1.6 Hz, CH), 8.64 (1H, d, J = 8.0 Hz, CH), 8.72 (1H, d, J =

8.3 Hz, CH); ^{13}C NMR δ_C; 121.9, 122.2 (CH), 123.7, 125.2 (C), 126.9, 127.1, 128.4, 128.7, 128.8, 128.9 (CH), 129.7 (CH×2), 130.2 (CH), 130.5 (CH×2), 133.4, 139.8, 143.8, 161.4 (C).

[1,3]Dioxolo[4,5-*j*]phenanthridine (**trisphaeridine**) **144.**[35]

From 6-phenylbenzo[*d*][1,3]dioxole-5-carbaldehyde dioxime oxalate (100 mg, 0.186 mmol), as described for **124**. Yellow solid 49 mg, 59 %; mp 144-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ_H; 6.00 (2H, s, CH_2), 7.33 (1H, s, CH), 7.62 (1H, td, *J* = 7.5, 1.5, CH), 7.62 (1H, td, *J* = 7.5, 1.2 Hz, CH), 7.91 (1H, s, CH), 8.13 (1H, dd, *J* = 7.4, 1.2 Hz, CH), 8.37 (1H, dd, *J* = 8.4, 1.2 Hz, CH), 9.08 (1H, s, CH); ^{13}C NMR δ_C; 99.9 (CH), 101.9 (CH_2), 105.5, 122.0 (CH), 123.0, 124.3 (C), 126.7, 128.0, 130.0 (CH), 130.3, 144.0, 148.2, 151.5 (C), 151.7 (CH); IR 2904, 1620, 1580, 1498, 1464 cm^{-1}; HRMS (CI^+) calcd for $C_{14}H_{10}NO_2$; 224.0712. Found: 224.0712.

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Appendix 1

X Ray Data

X Ray data of 2-phenylnicotinaldehyde *O*-phenyl oxime.

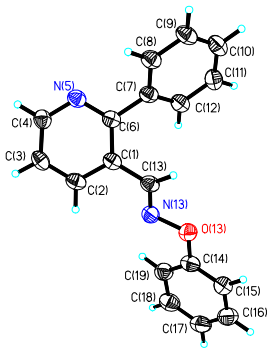

Table 1. Crystal data and structure refinement for 171 (Chapter 2).

Identification code	**171**	
Empirical formula	C18 H14 N2 O	
Formula weight	274.31	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 10.049(6) Å	α = 90°.
	b = 7.401(4) Å	β = 90°.
	c = 38.972(9) Å	γ = 90°.
Volume	2899(2) $Å^3$	
Z	8	
Density (calculated)	1.257 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	1152	
Crystal size	0.1500 x 0.0500 x 0.0500 mm^3	
Theta range for data collection	2.09 to 25.50°.	
Index ranges	-12<=h<=11, -8<=k<=8, -47<=l<=43	
Reflections collected	24359	
Independent reflections	2681 [R(int) = 0.1742]	
Completeness to theta = 25.00°	99.6 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.9666	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2681 / 0 / 191	
Goodness-of-fit on F^2	1.287	
Final R indices [I>2sigma(I)]	R1 = 0.0961, wR2 = 0.2553	
R indices (all data)	R1 = 0.1091, wR2 = 0.2616	
Largest diff. peak and hole	0.282 and -0.301 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and U(eq) for 171 (Chapter 2).

	x	y	z	U(eq)
C(1)	7507(3)	1014(4)	767(1)	33(1)
C(2)	8652(3)	1426(4)	580(1)	39(1)
C(3)	8542(3)	2101(4)	253(1)	38(1)
C(4)	7282(3)	2332(4)	121(1)	37(1)
N(5)	6166(2)	1951(3)	291(1)	36(1)
C(6)	6264(3)	1320(4)	611(1)	34(1)
C(7)	4982(3)	955(4)	789(1)	35(1)
C(8)	3939(3)	200(4)	602(1)	39(1)
C(9)	2732(3)	-152(4)	761(1)	42(1)
C(10)	2543(3)	268(5)	1101(1)	43(1)
C(11)	3568(3)	1035(4)	1287(1)	43(1)
C(12)	4788(3)	1376(4)	1132(1)	38(1)
C(13)	7621(3)	227(4)	1112(1)	36(1)
N(13)	8604(3)	718(4)	1299(1)	38(1)
O(13)	8558(2)	-255(3)	1612(1)	43(1)
C(14)	9578(3)	235(5)	1833(1)	41(1)
C(15)	9721(3)	-876(5)	2114(1)	47(1)
C(16)	10711(4)	-535(6)	2350(1)	54(1)
C(17)	11556(4)	909(6)	2305(1)	51(1)
C(18)	11399(3)	2036(5)	2025(1)	49(1)
C(19)	10402(3)	1721(5)	1787(1)	43(1)

Table 3. Bond lengths [Å] and angles [°] for 171 (Chapter 2) .

C(1)-C(2)	1.396(4)	C(11)-C(12)	1.392(4)
C(1)-C(6)	1.409(4)	C(11)-H(11A)	0.95
C(1)-C(13)	1.469(4)	C(12)-H(12A)	0.95
C(2)-C(3)	1.373(4)	C(13)-N(13)	1.280(4)
C(2)-H(2A)	0.95	C(13)-H(13A)	0.95
C(3)-C(4)	1.377(4)	N(13)-O(13)	1.418(3)
C(3)-H(3A)	0.95	O(13)-C(14)	1.386(4)
C(4)-N(5)	1.332(4)	C(14)-C(15)	1.376(5)
C(4)-H(4A)	0.95	C(14)-C(19)	1.388(5)
N(5)-C(6)	1.335(4)	C(15)-C(16)	1.378(5)
C(6)-C(7)	1.488(4)	C(15)-H(15A)	0.95
C(7)-C(12)	1.385(4)	C(16)-C(17)	1.376(6)
C(7)-C(8)	1.394(4)	C(16)-H(16A)	0.95
C(8)-C(9)	1.386(4)	C(17)-C(18)	1.382(5)
C(8)-H(8A)	0.95	C(17)-H(17A)	0.95
C(9)-C(10)	1.374(5)	C(18)-C(19)	1.387(5)
C(9)-H(9A)	0.95	C(18)-H(18A)	0.95
C(10)-C(11)	1.382(5)	C(19)-H(19A)	0.95
C(10)-H(10A)	0.95		

C(2)-C(1)-C(6)	118.0(3)	C(10)-C(11)-H(11A)	120
C(2)-C(1)-C(13)	120.0(3)	C(12)-C(11)-H(11A)	120
C(6)-C(1)-C(13)	121.9(3)	C(7)-C(12)-C(11)	120.2(3)
C(3)-C(2)-C(1)	119.8(3)	C(7)-C(12)-H(12A)	119.9
C(3)-C(2)-H(2A)	120.1	C(11)-C(12)-H(12A)	119.9
C(1)-C(2)-H(2A)	120.1	N(13)-C(13)-C(1)	117.9(3)
C(2)-C(3)-C(4)	117.8(3)	N(13)-C(13)-H(13A)	121.1
C(2)-C(3)-H(3A)	121.1	C(1)-C(13)-H(13A)	121.1
C(4)-C(3)-H(3A)	121.1	C(13)-N(13)-O(13)	108.7(2)
N(5)-C(4)-C(3)	124.2(3)	C(14)-O(13)-N(13)	112.1(2)
N(5)-C(4)-H(4A)	117.9	C(15)-C(14)-O(13)	114.5(3)
C(3)-C(4)-H(4A)	117.9	C(15)-C(14)-C(19)	120.9(3)
C(4)-N(5)-C(6)	118.4(3)	O(13)-C(14)-C(19)	124.6(3)
N(5)-C(6)-C(1)	121.7(3)	C(14)-C(15)-C(16)	119.8(4)
N(5)-C(6)-C(7)	115.8(3)	C(14)-C(15)-H(15A)	120.1
C(1)-C(6)-C(7)	122.5(3)	C(16)-C(15)-H(15A)	120.1
C(12)-C(7)-C(8)	119.3(3)	C(17)-C(16)-C(15)	120.3(4)
C(12)-C(7)-C(6)	122.0(3)	C(17)-C(16)-H(16A)	119.9
C(8)-C(7)-C(6)	118.7(3)	C(15)-C(16)-H(16A)	119.9
C(9)-C(8)-C(7)	120.0(3)	C(16)-C(17)-C(18)	119.8(3)
C(9)-C(8)-H(8A)	120	C(16)-C(17)-H(17A)	120.1
C(7)-C(8)-H(8A)	120	C(18)-C(17)-H(17A)	120.1
C(10)-C(9)-C(8)	120.6(3)	C(17)-C(18)-C(19)	120.7(4)
C(10)-C(9)-H(9A)	119.7	C(17)-C(18)-H(18A)	119.7
C(8)-C(9)-H(9A)	119.7	C(19)-C(18)-H(18A)	119.7
C(9)-C(10)-C(11)	119.8(3)	C(18)-C(19)-C(14)	118.5(3)
C(9)-C(10)-H(10A)	120.1	C(18)-C(19)-H(19A)	120.7
C(11)-C(10)-H(10A)	120.1	C(14)-C(19)-H(19A)	120.7
C(10)-C(11)-C(12)	120.1(3)		

Table 4. Torsion angles [°] for 171 (Chapter 2).

C(6)-C(1)-C(2)-C(3)	-0.3(5)	C(9)-C(10)-C(11)-C(12)	-0.2(5)
C(13)-C(1)-C(2)-C(3)	177.6(3)	C(8)-C(7)-C(12)-C(11)	0.4(5)
C(1)-C(2)-C(3)-C(4)	-0.4(5)	C(6)-C(7)-C(12)-C(11)	179.1(3)
C(2)-C(3)-C(4)-N(5)	0.3(5)	C(10)-C(11)-C(12)-C(7)	0.3(5)
C(3)-C(4)-N(5)-C(6)	0.7(5)	C(2)-C(1)-C(13)-N(13)	33.9(4)
C(4)-N(5)-C(6)-C(1)	-1.5(4)	C(6)-C(1)-C(13)-N(13)	-148.2(3)
C(4)-N(5)-C(6)-C(7)	178.8(3)	C(1)-C(13)-N(13)-O(13)	-177.4(2)
C(2)-C(1)-C(6)-N(5)	1.3(5)	C(13)-N(13)-O(13)-C(14)	-178.6(3)
C(13)-C(1)-C(6)-N(5)	-176.6(3)	N(13)-O(13)-C(14)-C(15)	-169.3(3)
C(2)-C(1)-C(6)-C(7)	-179.0(3)	N(13)-O(13)-C(14)-C(19)	11.4(4)
C(13)-C(1)-C(6)-C(7)	3.1(5)	O(13)-C(14)-C(15)-C(16)	179.4(3)
N(5)-C(6)-C(7)-C(12)	-139.6(3)	C(19)-C(14)-C(15)-C(16)	-1.3(5)

C(1)-C(6)-C(7)-C(12)	40.8(4)	C(14)-C(15)-C(16)-C(17)	0.0(6)
N(5)-C(6)-C(7)-C(8)	39.2(4)	C(15)-C(16)-C(17)-C(18)	0.8(6)
C(1)-C(6)-C(7)-C(8)	-140.5(3)	C(16)-C(17)-C(18)-C(19)	-0.3(5)
C(12)-C(7)-C(8)-C(9)	-1.1(5)	C(17)-C(18)-C(19)-C(14)	-1.0(5)
C(6)-C(7)-C(8)-C(9)	-179.9(3)	C(15)-C(14)-C(19)-C(18)	1.8(5)
C(7)-C(8)-C(9)-C(10)	1.2(5)	O(13)-C(14)-C(19)-C(18)	-179.0(3)
C(8)-C(9)-C(10)-C(11)	-0.5(5)		

X Ray data of 2,2-Dimethyl-1-phenylpent-4-en-1-one oxime.

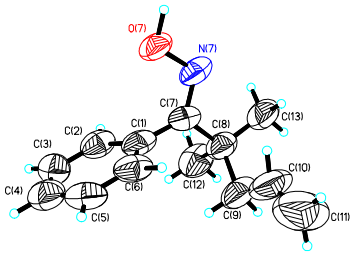

Table 1. Crystal data and structure refinement for 75 (Chapter 4).

Identification code	**75**	
Empirical formula	C13 H17 N O	
Formula weight	203.28	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 7.699(7) Å	α= 90°.
	b = 6.489(6) Å	β= 90°.
	c = 24.188(13) Å	γ = 90°.
Volume	1194.1(17) $Å^3$	
Z	4	
Density (calculated)	1.131 Mg/m^3	
Absorption coefficient	0.071 mm^{-1}	
F(000)	440	
Crystal size	0.3000 x 0.1000 x 0.0100 mm^3	
Theta range for data collection	2.68 to 25.30°.	
Index ranges	-7<=h<=9, -7<=k<=7, -29<=l<=18	
Reflections collected	6348	
Independent reflections	2118 [R(int) = 0.1303]	
Completeness to theta = 25.00°	98.1 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.9884	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2118 / 0 / 137	
Goodness-of-fit on F^2	1.152	
Final R indices [I>2sigma(I)]	R1 = 0.1500, wR2 = 0.3699	
R indices (all data)	R1 = 0.2611, wR2 = 0.4610	
Largest diff. peak and hole	0.412 and -0.515 $e.Å^{-3}$	

Table 2. Crystal data and structure refinement for 74 (Chapter 4).

	x	y	z	U(eq)
C(1)	699(9)	4076(11)	6140(3)	73(2)
C(2)	1163(9)	6090(10)	5975(3)	76(2)
C(3)	2439(10)	7239(12)	6313(4)	86(2)
C(4)	3262(11)	6513(13)	6801(4)	93(2)
C(5)	2865(11)	4549(14)	6976(3)	91(2)
C(6)	1623(10)	3332(10)	6646(3)	77(2)
C(7)	-655(8)	2866(10)	5803(3)	66(2)
N(7)	-355(6)	1520(8)	5417(2)	73(2)
O(7)	1496(5)	1450(6)	5388(2)	77(2)
C(8)	-2603(9)	3142(10)	5869(3)	75(2)
C(9)	-2769(10)	2718(13)	6491(3)	95(2)
C(10)	-2423(13)	585(15)	6665(4)	121(3)
C(11)	-2760(20)	-390(20)	7032(5)	207(7)
C(12)	-3124(10)	5401(11)	5738(4)	99(3)
C(13)	-3762(9)	1715(12)	5482(4)	97(3)

Table 3. Bond lengths [Å] and angles [°] for 75 (Chapter 4).

C(1)-C(2)	1.396(4)	C(11)-C(12)	1.392(4)
C(1)-C(6)	1.409(4)	C(11)-H(11A)	0.95
C(1)-C(13)	1.469(4)	C(12)-H(12A)	0.95
C(2)-C(3)	1.373(4)	C(13)-N(13)	1.280(4)
C(2)-H(2A)	0.95	C(13)-H(13A)	0.95
C(3)-C(4)	1.377(4)	N(13)-O(13)	1.418(3)
C(3)-H(3A)	0.95	O(13)-C(14)	1.386(4)
C(4)-N(5)	1.332(4)	C(14)-C(15)	1.376(5)
C(4)-H(4A)	0.95	C(14)-C(19)	1.388(5)
N(5)-C(6)	1.335(4)	C(15)-C(16)	1.378(5)
C(6)-C(7)	1.488(4)	C(15)-H(15A)	0.95
C(7)-C(12)	1.385(4)	C(16)-C(17)	1.376(6)
C(7)-C(8)	1.394(4)	C(16)-H(16A)	0.95
C(8)-C(9)	1.386(4)	C(17)-C(18)	1.382(5)
C(8)-H(8A)	0.95	C(17)-H(17A)	0.95
C(9)-C(10)	1.374(5)	C(18)-C(19)	1.387(5)
C(9)-H(9A)	0.95	C(18)-H(18A)	0.95
C(10)-C(11)	1.382(5)	C(19)-H(19A)	0.95
C(10)-H(10A)	0.95		

C(2)-C(1)-C(6)	118.0(3)	C(10)-C(11)-H(11A)	120
C(2)-C(1)-C(13)	120.0(3)	C(12)-C(11)-H(11A)	120
C(6)-C(1)-C(13)	121.9(3)	C(7)-C(12)-C(11)	120.2(3)
C(3)-C(2)-C(1)	119.8(3)	C(7)-C(12)-H(12A)	119.9
C(3)-C(2)-H(2A)	120.1	C(11)-C(12)-H(12A)	119.9

C(1)-C(2)-H(2A)	120.1	N(13)-C(13)-C(1)	117.9(3)
C(2)-C(3)-C(4)	117.8(3)	N(13)-C(13)-H(13A)	121.1
C(2)-C(3)-H(3A)	121.1	C(1)-C(13)-H(13A)	121.1
C(4)-C(3)-H(3A)	121.1	C(13)-N(13)-O(13)	108.7(2)
N(5)-C(4)-C(3)	124.2(3)	C(14)-O(13)-N(13)	112.1(2)
N(5)-C(4)-H(4A)	117.9	C(15)-C(14)-O(13)	114.5(3)
C(3)-C(4)-H(4A)	117.9	C(15)-C(14)-C(19)	120.9(3)
C(4)-N(5)-C(6)	118.4(3)	O(13)-C(14)-C(19)	124.6(3)
N(5)-C(6)-C(1)	121.7(3)	C(14)-C(15)-C(16)	119.8(4)
N(5)-C(6)-C(7)	115.8(3)	C(14)-C(15)-H(15A)	120.1
C(1)-C(6)-C(7)	122.5(3)	C(16)-C(15)-H(15A)	120.1
C(12)-C(7)-C(8)	119.3(3)	C(17)-C(16)-C(15)	120.3(4)
C(12)-C(7)-C(6)	122.0(3)	C(17)-C(16)-H(16A)	119.9
C(8)-C(7)-C(6)	118.7(3)	C(15)-C(16)-H(16A)	119.9
C(9)-C(8)-C(7)	120.0(3)	C(16)-C(17)-C(18)	119.8(3)
C(9)-C(8)-H(8A)	120	C(16)-C(17)-H(17A)	120.1
C(7)-C(8)-H(8A)	120	C(18)-C(17)-H(17A)	120.1
C(10)-C(9)-C(8)	120.6(3)	C(17)-C(18)-C(19)	120.7(4)
C(10)-C(9)-H(9A)	119.7	C(17)-C(18)-H(18A)	119.7
C(8)-C(9)-H(9A)	119.7	C(19)-C(18)-H(18A)	119.7
C(9)-C(10)-C(11)	119.8(3)	C(18)-C(19)-C(14)	118.5(3)
C(9)-C(10)-H(10A)	120.1	C(18)-C(19)-H(19A)	120.7
C(11)-C(10)-H(10A)	120.1	C(14)-C(19)-H(19A)	120.7
C(10)-C(11)-C(12)	120.1(3)		

Table 4. Torsion angles [°] for 75 (Chapter 4).

C(6)-C(1)-C(2)-C(3)	-1.5(9)	C(1)-C(7)-N(7)-O(7)	0.0(8)
C(7)-C(1)-C(2)-C(3)	178.6(6)	C(8)-C(7)-N(7)-O(7)	178.5(5)
C(1)-C(2)-C(3)-C(4)	-0.5(11)	N(7)-C(7)-C(8)-C(13)	2.1(8)
C(2)-C(3)-C(4)-C(5)	1.1(11)	C(1)-C(7)-C(8)-C(13)	-179.4(6)
C(3)-C(4)-C(5)-C(6)	0.3(11)	N(7)-C(7)-C(8)-C(12)	-119.0(7)
C(4)-C(5)-C(6)-C(1)	-2.3(10)	C(1)-C(7)-C(8)-C(12)	59.5(8)
C(2)-C(1)-C(6)-C(5)	2.8(9)	N(7)-C(7)-C(8)-C(9)	124.2(6)
C(7)-C(1)-C(6)-C(5)	-177.2(6)	C(1)-C(7)-C(8)-C(9)	-57.2(8)
C(6)-C(1)-C(7)-N(7)	-87.4(8)	C(13)-C(8)-C(9)-C(10)	55.0(9)
C(2)-C(1)-C(7)-N(7)	92.6(8)	C(12)-C(8)-C(9)-C(10)	176.2(7)
C(6)-C(1)-C(7)-C(8)	94.2(7)	C(7)-C(8)-C(9)-C(10)	-66.8(8)
C(2)-C(1)-C(7)-C(8)	-85.8(7)	C(8)-C(9)-C(10)-C(11)	-160.9(15)

Appendix 2

Publications

1. Microwave-assisted preparations of dihydropyrroles from alkenone *O*-phenyl oximes. Fernando Portela-Cubillo, Jackie S. Scott and John C. Walton, *Chem. Commun.*, 2007, 4041.

2. Microwave-assisted syntheses of *N*-heterocycles using alkenone-, alkynone- and aryl-carbonyl *O*-phenyl oximes: formal synthesis of neocryptolepine. Fernando Portela-Cubillo, Jackie S. Scott and John C. Walton, *J. Org. Chem.*, **73**, 2008, 5558.

3. 2-(Aminoaryl)alkanone *O*-Phenyl Oximes: Versatile Reagents for Syntheses of Quinazolines. Fernando Portela-Cubillo, Jackie S. Scott and John C. Walton, *Chem. Commun.*, 2008, 2935.

4. From dioxime oxalates to dihydropyrroles and phenanthridines via iminyl radicals. Fernando Portela-Cubillo, Eoin M. Scanlan, Jackie S. Scott and John C. Walton, *Chem. Commun.*, 2008, 4189.

5. Dioxime oxalates; new iminyl radical precursors for synthesis of heterocycles. Fernando Portela-Cubillo, James Lymer, Eoin M. Scanlan, Jackie S. Scott and John C. Walton, *Tetrahedron*, 2008, **64**, 11908.

6. Cyclohexadiene. John C. Walton and Fernando Portela-Cubillo, *Electronic Encyclopedia of Reagents for Organic Synthesis (e-EROS)*; L. A. Paquette (Ed.-in-Chief); J. Wiley & Sons, 2008.

7. Thermal rearrangement of indolooxime esters to pyridoindoles. Fernando Portela-Cubillo, Brian A. Surgenor, R. Alan Aitken and John C. Walton, *J. Org. Chem.*, 2008, **73**, 8124.