INVESTIGATION OF THE RADICAL CHEMISTRY OF ORGANIC ISOCYANATES AND IMINES

A thesis presented by Patricia L. Minin to the University of St. Andrews in application for the degree of Doctor of Philosophy.

November 2002

Declarations

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

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Table of contents

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Abbreviations used within text

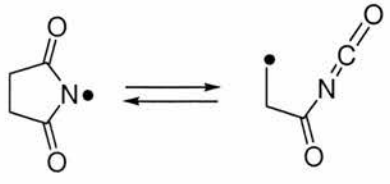
AIBN	2,2'-Azobisisobutyronitrile
aq	Aqueous
Bp	Boiling point in °C at 760 mm pressure, unless otherwise specified
Boc	*t*-Butoxycarbonyl
Bu_3SnH	Tri-*n*-butyltin hydride
°C	Degrees Celsius
ca.	Approximately
Chap	Chapter
DCM	Dichloromethane
dd	Doublet of doublet
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
Ed	Editor
EPHP	Ethylpiperidine hypophosphite
Ether	Diethyl ether
EtOAc	Ethyl acetate
EPR	Electron Paramagnetic Resonance
eq	Equivalent
ESR	Electron Spin Resonance
EtOH	Ethanol

FMO	Frontier Molecular Orbital
g	Gram
GC	Gas Chromatography
GC-MS	Gas Chromatography-Mass Spectrometry
h	Hours
HOMO	Higher occupied molecular orbital
$In^{\cdot}$	Initiator (radical initiator)
IR	Infrared
LUMO	Lower Unoccupied Molecular Orbital
M^{+}	Molecular ion
MeOH	Methanol
mL	Millilitre
mmol	Millimole
mol	Mole
mp	Melting point in ^{0}C
MS	Mass spectrometry
m/z	Mass to charge ratio
NBS	*N*-bromosuccinimide
N.D.	Non defined
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
ppm	Parts per million
quin	quintet
RT	Room Temperature
s	Second

s, d, t, q	Singlet, doublet, triplet, quartet,
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
TTMSS	Tris(trimethylsilyl)silane

Abstract

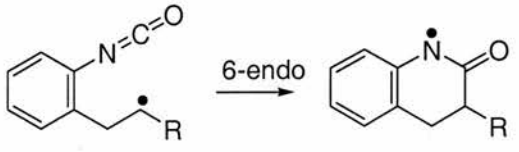
The study of free radical chemistry long lay in the domain of interest of mechanistic and industrial chemists. But in recent years it has become apparent that free radical reactions are very important in synthesis, particularly because they proceed under mild conditions and can be highly selective.[1, 2] This has led to a dramatic increase in the utilization of free radicals in preparative chemistry, especially in the use of radical cyclisation in the synthesis of natural products. In the last decades a lot of examples involving intramolecular addition of free radicals to carbon-carbon multiple bonds have been reported. [3, 4] Some papers dealing with an analogous addition to carbon-heteroatom bonds have appeared as well.[5-7] Unexpectedly, much less attention has been paid to inter- [8-11] and intramolecular [12-18] radical addition to the carbon-nitrogen double bond. In particular, the free radical chemistry of isocyanates has been little studied despite early reviews about the photochemistry[19] and radical addition to isocyanates.[20] Interestingly, ring opening of the succinimidyl radical **1** was reported to be reversible,[21] *i.e.* the ring closure onto isocyanate **2,** was of comparable rate.



1 **2**

This suggested that if the cyclised species could be stabilised by delocalisation, or if it could be trapped by a subsequent rapid rearrangement, construction of heterocyclic

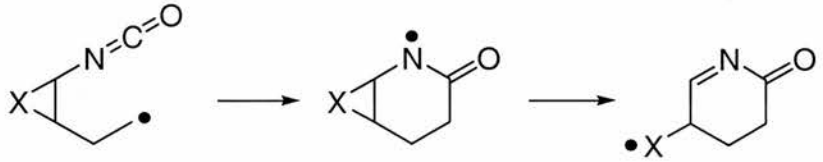
rings could be accomplished. Because of the promise of this equation, we have undertaken a study of radical cyclisation of isocyanates. In the first part, intermolecular addition of alkyl radicals to isocyanates has been investigated. In the second part about the intramolecular addition of isocyanates, two ways of stabilising the cyclised species have been studied. First, by the introduction of an aromatic system **3**, where the unpaired electron in the cyclised radical **4** should be stabilised by resonance.



3 **4**

R = H

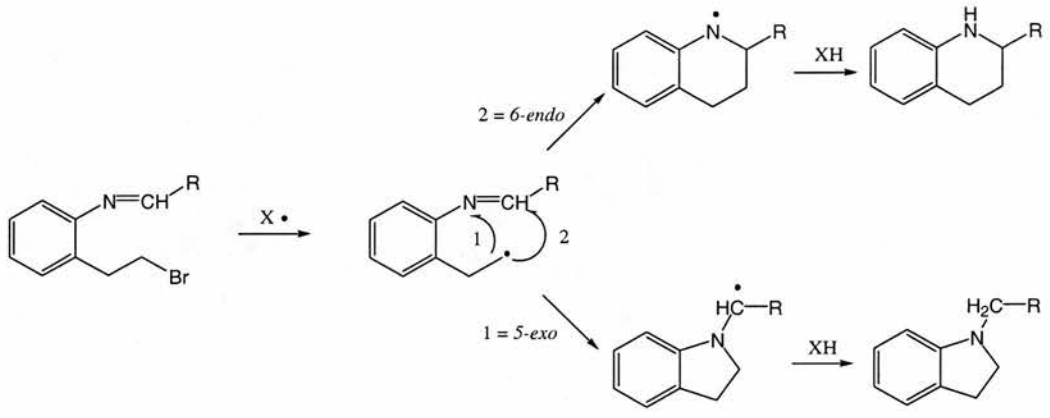
A second approach was to offer the cyclised radical an alternative, more rapid, β-scission which should leave the lactam ring intact. For example, ring closure of the cyclopropyl isocyanate **5** should be followed by rapid cleavage of the 3-membered ring.



5 **6** **7**

X = CH_2, O

In the final part, following the same pathway, an example of intramolecular addition of alkyl radical to an imine has been studied.



The carbon-centered radical could undergo either a *6-endo* or a *5-exo* radical cyclisation respectively onto the C-atom or the N-atom of the imine group.

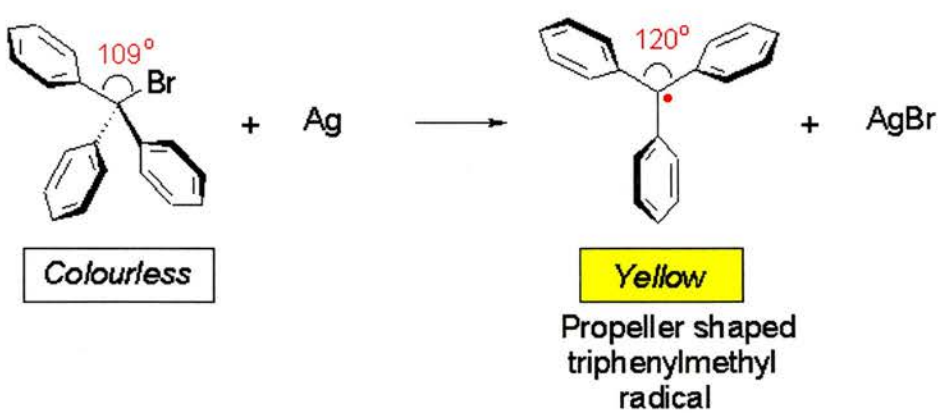
Chapter 1

—

INTRODUCTION

I- Free Radical Methodology

It is now more than 100 years since Moses Gomberg (1866-1947) discovered the first organic free radical. During this time, research has revealed that free radicals are present in the atmosphere, in our bodies and in some very important chemical reactions. In 1900, Moses Gomberg[22] reported his results on the reaction of triphenylmethyl halides with metals. The reactions produced a yellow syrup (in the absence of air) and he attributed this to the formation of the triphenylmethyl radical, $Ph_3C^{\cdot}$. The radical so formed was apparently stable, for it could be kept both in solution and in the dry crystalline state for weeks. The observation of a stable radical was a remarkable achievement, as most radicals exist only momentarily. This can be explained by the presence of three bulky benzene rings (scheme 1). These protect the carbon atom bearing the radical, which slows down radical reactions. Radicals of this type, which do not readily combine at even relatively high concentrations, are now called persistent radicals.

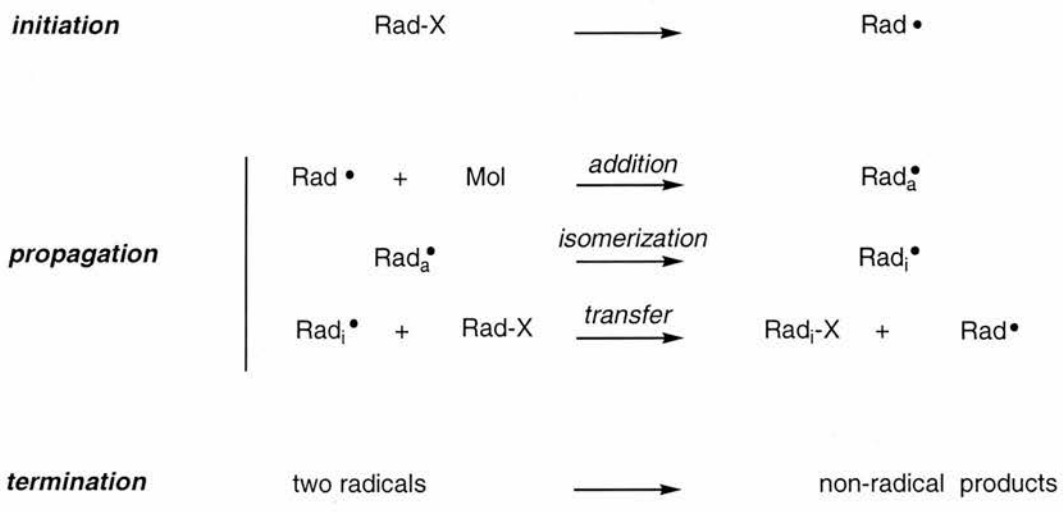


scheme 1

A free radical is an atom or compound, which contains an unpaired electron. All free radicals contain an odd number of electrons and nowadays the term "radical" is often used in place of "free radical". Radical chemistry has advanced tremendously since Moses Gomberg's discovery of the triphenylmethyl radical. However, it is only since the mid 1980s that the synthetic potential of radicals has emerged as a useful tool.[23-26]

Thousands of biological processes are very much dependent on reactions involving free radicals. The use of free radical methodology in organic synthetic procedures,[27-29] has increased since 1980s.[30] Key steps in natural product syntheses have come to depend on radical methodology.[31-34] The use of free radical methods by synthetic organic chemists is due to the mild experimental conditions, the ease with which complex target molecules can be assembled in cascade processes,[35] and the tolerance of a considerable range of functionality in the substrate. In neutral free radical reactions, solvation effects, although they do exist, are less important. Consequently, small radicals are particularly effective in carrying out transformations in hindered situations or in molecules which possess many polar carbon-heteroarom bonds. Carbon-centred radicals are usually inert towards OH and NR_2 groups. Reactions do not have to be carried out under rigorously anhydrous conditions and the protection of alcohols, amines and related functional groups is often unnecessary. In contrast to carbanions, carbon radicals are not subject to β-elimination of OR or NH_2 groups. In contrast to carbocations, carbon radicals are subject neither to capture by β-OR or -NH_2 groups nor migration or elimination of β-H or -CR_3 groups. Also, radical reactions may proceed with high stereo-, chemo- and regio-selectivities under appropriate conditions.

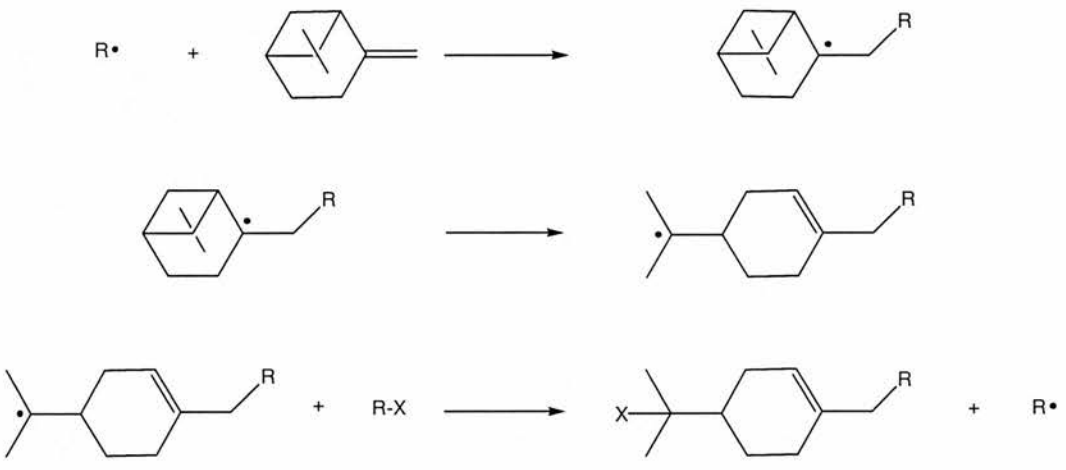
Radical chain mechanisms are very common in radical chemistry, especially in polymerizations and in cascade constructions of complex molecular structures. This mechanism usually involves three stages: initiation, propagation and termination and can be represented as follows (scheme 2):



scheme 2

The *initiation* step consists of creating the first radical of the chain. It may be induced either by photolysis or by action of a radical initiator such as AIBN (azobisisobutyronitrile). The *propagation* steps are a succession of elementary reactions in which the radical produced in one reaction is consumed in the next. The required products are formed in the propagation cycle. The rates of the propagation reactions are all equal to each other and the overall rate is controlled by one step. This propagation step is called the *rate determining step*. If one of these reactions has a rate constant which is too small, the chain propagation will stop. Consequently, the rate constant of each reaction in the propagation process must be high for the yield to be good. The last step, the *termination* involves dimerization, disproportionation,

oxidation or reduction of the radicals involved in the rate-determining step. For example, in some cases the intermediate radical obtained in an addition step can isomerize or rearrange before the transfer step (scheme 3). For example, the addition of R-X to β-pinene gives rise to a compound in which the four-membered ring has opened.

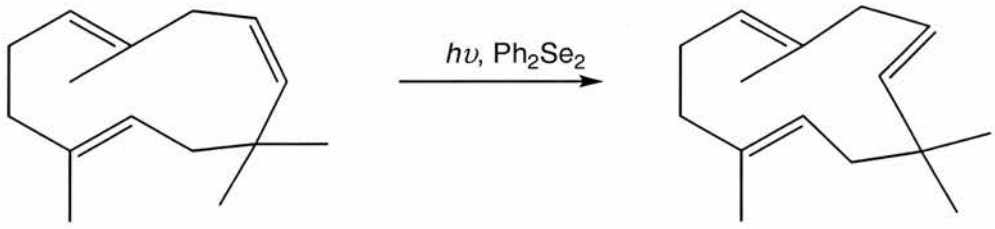


scheme 3

Although free radicals are neutral entities, they do not all behave in a uniform way, and their chemical reactivity is dominated by the nature of the atom containing the unpaired electron.[36] Accordingly they may be endowed with either electrophilic or nucleophilic character and display either hard or soft behaviour. For example, the chemistry of alkoxyl radicals centers around their electrophilic nature, and typical reactions are hydrogen atom abstraction and β-scission (scheme 4).

scheme 4

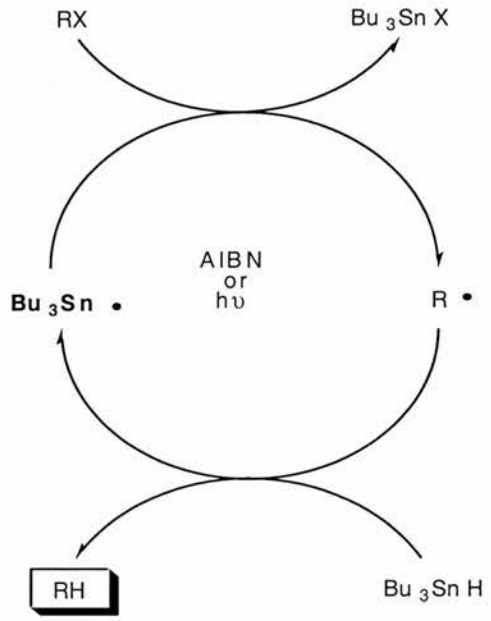
Intermolecular addition of an alkoxyl radical to carbon-carbon double bond is not a favoured process although the intramolecular variant is known. Contrastingly, thiyl radicals are larger and softer. Addition to the carbon-carbon double bond is, however, more favoured than for alkoxyl radicals. However, in diphenyl diselenide isomerization of olefins (scheme 5) both addition and elimination are easily reversible processes.



scheme 5

The electrophilic or nucleophilic character is also influenced by the nature of the groups attached to the radical center containing the unpaired electron. The case of carbon centered radicals is particularly important. The ability to form carbon-carbon bonds is one of the primary tasks in the construction of organic molecules. In the 1980s and 1990s this has been increasingly achieved by the addition of carbon-centered radicals to carbon-carbon multiple bonds.[4, 37]

Tributyltin hydride is the reagent most used in free radical chain methodology, thanks to the pioneer works of Giese (tin hydride mediated radical addition to olefins).[23] An example of the use of tributyltin hydride in a free radical chain sequence is the reductive removal of a halogen atom [38, 39] (scheme 6).

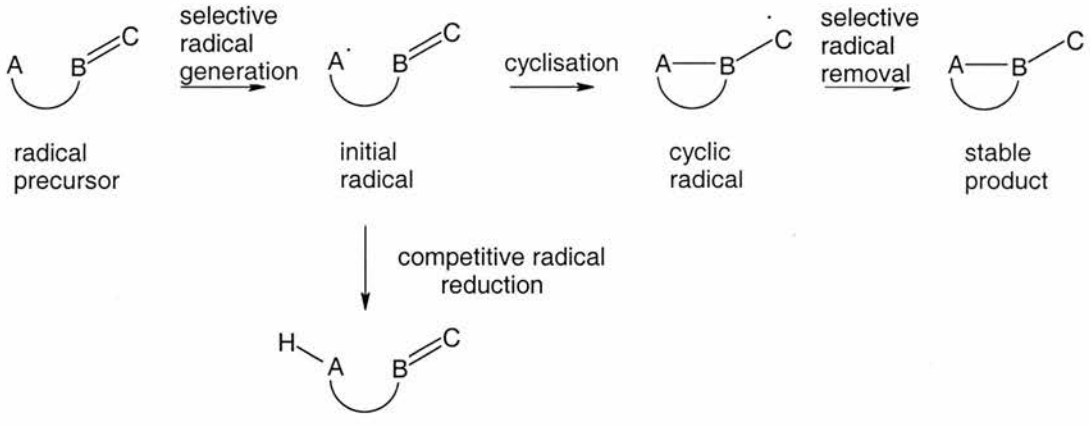


scheme 6

This simple chain reaction is really efficient. The formation of a strong tin-halogen bond and the rapid hydrogen atom abstraction by the alkyl radical from the weak tin-hydrogen bond lead to constant generation of the chain carrying tin-centered radical and hence to long chain lengths.

II- Radical Cyclisation

One of the most important free radical reactions is cyclisation to form rings. This type of reaction has been used to prepare a variety of cyclic natural products. Carbon-centred radicals can undergo intramolecular addition reactions with carbon-carbon multiple bonds. Although they have been recognized only comparatively recently, intramolecular addition reactions of radicals, that is to say radical cyclisation reactions[30] are among the most powerful tools at the disposal of the synthetic chemist. These radical cyclisation reactions have all the advantages of their bimolecular counterparts, such as predictability and functional group tolerances; futhermore, because of the entropic advantages, cyclisation reactions are of much broader scope. In general intramolecular addition is faster than intermolecular addition. The general scheme to conduct a selective radical cyclisation is summarised below (scheme 7).

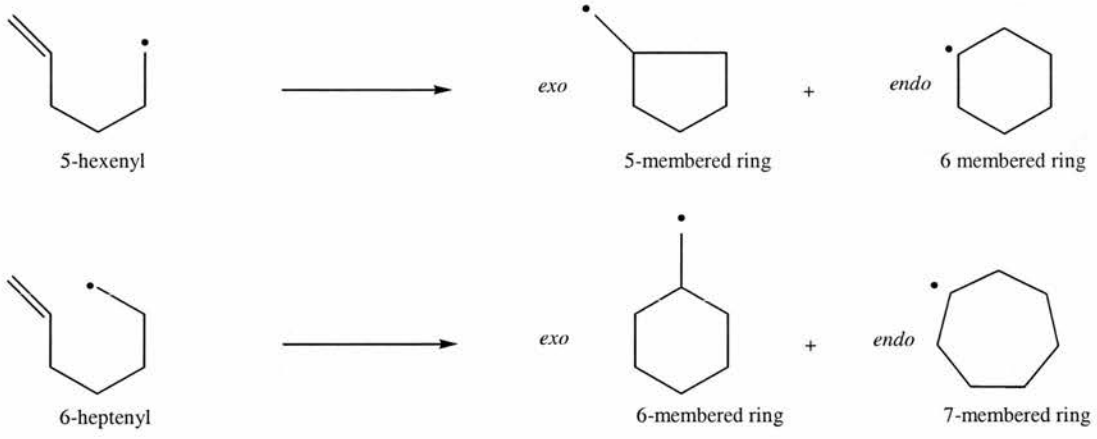


scheme 7

As in an addition reaction, selective radical generation, cyclisation and selective radical removal are necessary. One requirement is that the initial radical must not be

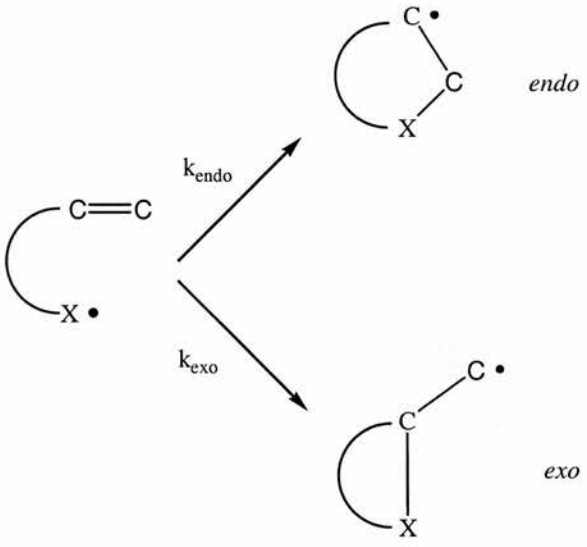
trapped before cyclisation has occurred. Each step must be more rapid than the loss of radicals by (non-selective) radical/radical or radical/solvent reactions. The final radical must be selectively removed in the presence of the initial radical and cyclic radical. It is necessary to reduce competition from bimolecular trapping by reducing the concentration of radical trapping reagent or by using a trap which supplies hydrogen atoms less rapidly, such as $(Me_3Si)_3SiH$. The method chosen must convert the cyclic radical but not the initial radical, to a stable product.

Radical cyclisation reactions are most often applied to the synthesis of 5-membered rings. There are three good reasons for this. The first is that *exo*-cyclisations are usually faster for the formation of 5-membered rings[30] than for any other ring size. The simple 5-hexenyl radical[40-43] cyclizes 20 times faster than does the 6-heptenyl radical (scheme 8).



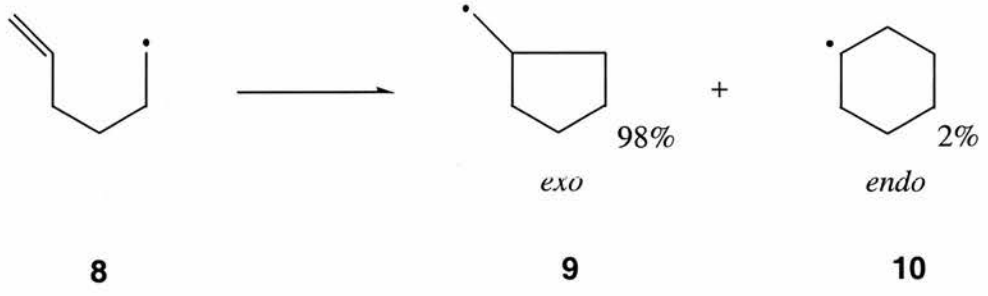
scheme 8

5-Membered ring forming reactions are therefore less subject to competitive formation of reduced, uncyclized by-products. The second reason is that the regioselectivity for 5-*exo* cyclisations is often outstanding.[28, 40-43] Of the two possible cyclisations, *exo* and *endo*, generally the former (*exo*) is preferred (scheme 9).



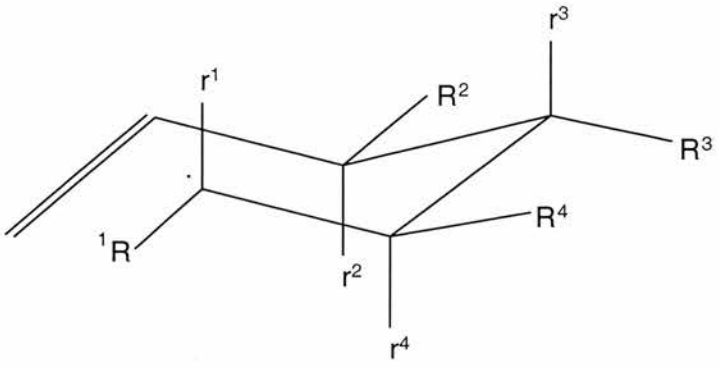
scheme 9

For the parent 5-hexenyl radical, 5-*exo* cyclisation, product **9,** is 50 times faster than 6-*endo* cyclisation, at room temperature (scheme 10).



scheme 10

And the third reason is that radical cyclisations giving 5-membered rings can be highly stereoselective.[40-48] The major product of a 5-*exo* radical cyclisation can generally be predicted by using the Beckwith transition state model[44] (scheme 11).



R = location of substituent in major diastereoisomer

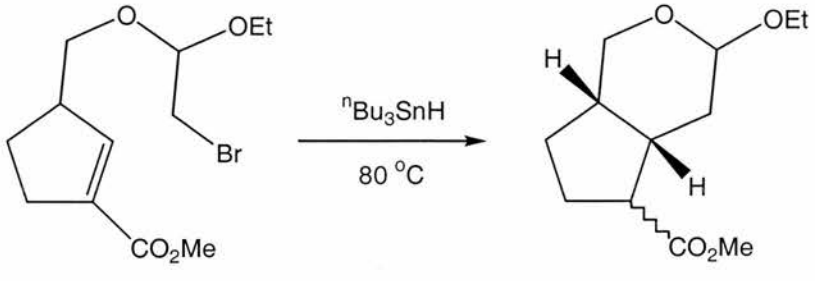
r = location of substituent in minor diastereoisomer

scheme 11

The Beckwith model for stereoselectivity is a good representation of the lowest energy transition state, and it predicts the major product by placing a chain substituent in an equatorial-like orientation. The early transition state of a 5-*exo* radical cyclisation resembling a cyclohexane ring, prefers the chair over the boat form, and prefers that substituents be pseudo-equatorial rather than pseudo-axial.[40-44] Simple model studies show that substitution at C_1 or C_3 of the 5-hexenyl radical gives primarily *cis*-disubstituted cyclopentanes, whereas substitution at C_2 or C_4 gives primarily *trans*-disubstituted cyclopentanes. Stereoselectivity is highest for C_1 and C_4 substituted systems. Theoretical treatments,[40-43] and experimental results, aid in planning highly stereoselective reactions and allow "exceptions" to Beckwith's guidelines to be anticipated.[45-48] Chain length, chain substituents or the nature of the radical are some factors which could determine the regio- and stereoselectivity.

6-Membered ring radical cyclisations are less general than cyclisations leading to 5-membered rings. However, they still have an important place in synthesis. Cyclisation of the 6-heptenyl radical is possible although it is less regio-selective than

cyclisation of the 5-hexenyl radical. The 6-membered ring forming reaction is slower. The rates for 6-*exo* cyclisation at 25°C (k_c=5.10^3 s^{-1}, k_c = rate constant of cyclisation) and 7-*endo* cyclisation (k_c=7.10^2 s^{-1}) are much slower than for the corresponding hex-5-enyl 5-*exo* and 6-*endo* cyclizations.[49] Cyclisation can be accomplished if low concentrations of trapping agents are used or atom transfer cyclisations are utilized. One competing reaction is often reduction of the initial radical by intramolecular 1, 5-hydrogen transfer to form an allyl radical.[50] This problem can be addressed if suitable substituents are located on the chain to block the hydrogen transfer reaction, or if the alkene component is activated. [50, 51] When constructing 6-membered rings by radical cyclisations it is required that the multiple bond acceptor be exocyclic to the forming ring. Thus, with carbon-carbon multiple bond acceptors, an exocyclic ring residue of at least one carbon atom is always produced. When this residue is not required, an alkyne acceptor is often used, and the resulting alkylidene chain is removed by ozonolysis. Cyclisation on a triple bond is always *exo*. It is slower than at a double bond. Since the 1980s, an increasing number of aryl radical cyclisations have been described which provide six-membered rings in high yields via the 6-heptenyl type cyclisation. Stork and co-workers prepared the product **12** in 90% yield [52, 53] (scheme 12).

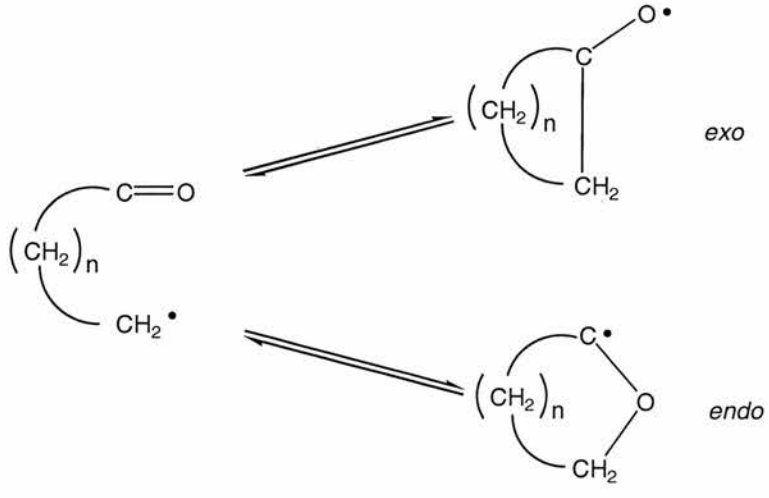


11 **12**

scheme 12

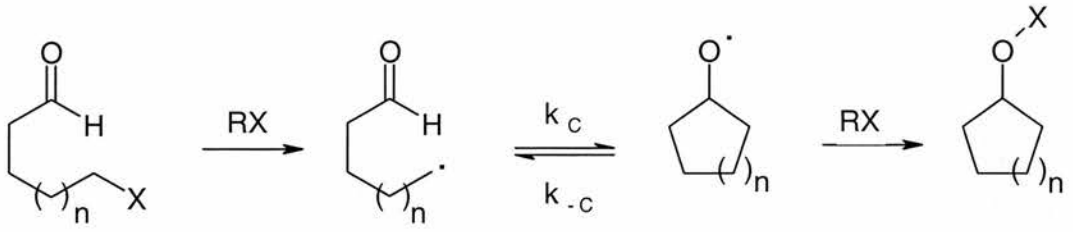
In this example Stork showed that six-membered ring formation was possible when the cyclised radical contained a judicious substituent sited to stabilize the unpaired electron. This system has a high rate constant for cyclisation.

A more direct route to rings that do not possess carbon substituents at the site of cyclisation uses carbon-oxygen multiple bonds. Cyclisation on a carbonyl group is much more frequently observed than the intermolecular addition. Radical cyclisations to carbon-oxygen multiple bonds are considerably different from cyclisations to carbon-carbon or carbon-nitrogen double bonds. Indeed, before the recent discoveries of Fraser-Reid and Tsang,[54-57] cyclisations to carbon-oxygen double bonds were not considered generally useful, and only the reverse reaction (β-fragmentation of the alkoxyl radical) was common. However, a much better understanding of these reactions is beginning to emerge. Radical cyclisation on a carbon-oxygen double bond can take place either on the carbon (*exo*) or on the oxygen (*endo*).



scheme 13

The regioselectivity depends mainly on the size of the ring. For n = 2 cyclisation occurs exclusively on oxygen whereas for n = 1, 3 or 4 reaction is preferentially at carbon (scheme 13). The reverse reaction, β-fragmentation, is usually faster than cyclisation. Therefore to obtain the cyclised alcohol, the equilibrium has to be displaced by trapping the radical with a good hydrogen-donor. As illustrated in the equation below (scheme 14), the cyclisations of radicals to carbonyl groups are best understood in the framework of the Curtin-Hammett principle.[58]



15a, b **13a** n = 1 **14a** **16a, b**

13b n = 2 **14b**

at 80 °C, n = 1, $k_c = 9x10^5\ s^{-1}$ n = 2, $k_c = 1x10^6\ s^{-1}$

$k_{-c} = 5x10^8\ s^{-1}$ $k_{-c} = 1x10^7\ s^{-1}$

$K_{eq} = 0.002$ $K_{eq} = 0.1$

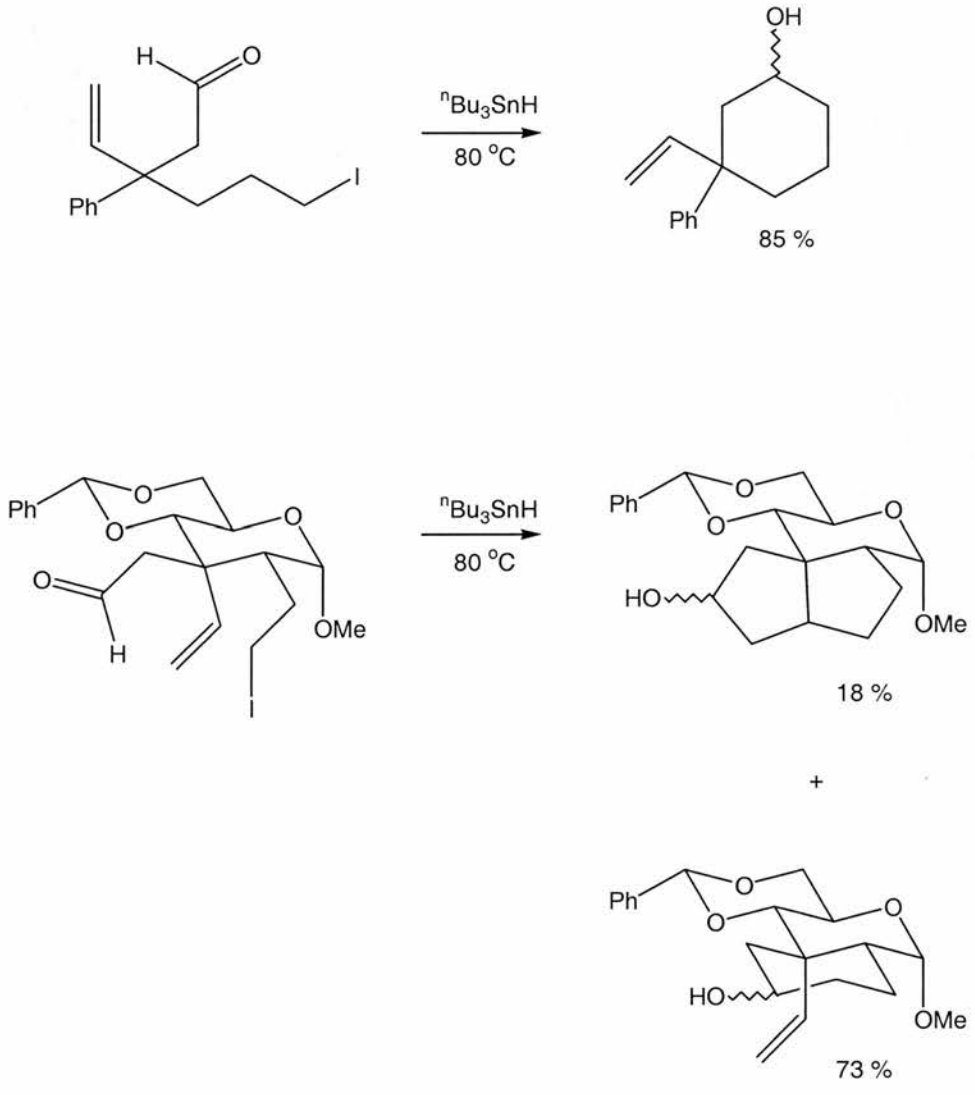
scheme 14

A semi-quantitative analysis[59,60] of these reactions has been greatly facilitated by the recent rate studies of Beckwith and Hay.[7] 5-*Exo* cyclisation (**13a**) and 6-*exo* cyclisation (**13b**) are approximately equal in rate but are more rapid than the cyclization of the hexenyl radical. The high rate of cyclisation and complete absence

of *endo* products indicate the importance of FMO effects on rates: the carbonyl group has a low-lying LUMO with the large orbital coefficient on carbon. Unlike the hexenyl radical, the products of cyclisation **14a** and **14b** can revert to the starting radicals. Indeed, both reverse cyclisations are faster than the forward cyclisations; that is, the starting radicals **13a** and **13b** are favoured at equilibrium. **13a** and **13b** are more stable than **14a** and **14b**. The cyclisation sacrifices a C=O bond, (which is much stronger than the C=C bond that is lost in a hexenyl radical cyclisation), and generates an alkoxyl radical (which is much less stable than the starting carbon radical). Because of the increased strain in the cyclopentane ring relative to cyclohexane, alkoxyl radical **14a** fragments much more rapidly than **14b**. When forming 6-membered rings, it is often possible to trap cyclic radicals **14b** with tin hydride (RX = Bu_3SnH) more rapidly than they revert to **13b**. Even if partial equilibrium occurs, an excellent yield of cyclic product is possible because tin hydride reacts about 100 times more rapidly with **14b** than with **13b**. Therefore, if k_c is not too much smaller than k_{-c}, **14b** will be selectively trapped at equilibrium. In cases where the fragmentation reactions are not prohibitively rapid, it may be possible to conduct cyclisations by selection of appropriate reagents and conditions.[61, 62] This above result demonstrates the importance of the use of organotin hydride in the radical formation of 6-membered rings.

The majority of radical cyclisations are still carried out using organotin hydride[63] as the reducing agent, mainly tri-*n*-butyltin hydride. The reaction conditions are generally to use an excess of tributyltin hydride with a smaller equivalent (5-25 %) of a radical initiator, most commonly (AIBN). The reactions are generally refluxed in benzene or toluene in argon or nitrogen atmospheres for 1-10 hours. Although radical cyclisation reactions are most often applied to the synthesis of 5-membered

rings, the tin hydride method was first applied in natural product synthesis to the construction of 6-membered rings. Fraser-Reid[55, 57] has demonstrated that six-membered rings may be formed efficiently by *exo* mode cyclisation onto aldehydes by the tin hydride method. This mode of cyclisation has been demonstrated to be more rapid than 5-hexenyl type cyclisation.



scheme 15

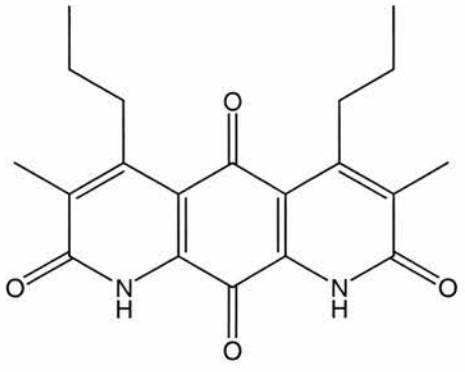
Cyclohexanols have been formed by radical cyclisation from 6-iodohexanols (scheme 15). In these typical experiments the radicals were generated by treating a 0.003M

solution of the iodide in benzene with 1 equivalent of tri-n-butyltin hydride and a catatlytic amount of AIBN under reflux in an argon atmosphere. However, organotin compounds are toxic and the separation of tin residues from the products can be laborious. Organo-silanes such as tris(trimethylsilyl)silane (TTMSS) are good alternatives to tin hydrides despite the cost of use of such compounds.

III- Synthesis of *N*-heterocycles

Because of all the advantages of free-radical chemistry, it was quickly applied for the synthesis of heterocycles. The first applications in natural product synthesis appear and the work of Stork (prostaglandin[34]), Hart (alkaloid synthesis[64]) and Curran (triquinanes[65]) confirmed the unique power of radical reactions.

Due to the rich chemistry and biology of nitrogen-containing compounds, the synthesis of *N*-heterocycles has been a central and important theme in organic chemistry. Many new protocols are being developed to synthesize wide ranges of natural products, which are of interest to organic chemists. Many variants and extensions of the isocyanate-aromatic ring closure appear possible. This homolytic process will provide new routes for the construction of a range of nitrogen-containing heterocycles including tetra- and di-hydroquinolinones, isoquinolinones, other functionalised quinolines and isoquinolines, 1,5-naphthyridines, pyridopyrimidines, benzoquinolines, and related physiologically active molecules. Many derivatives of quinoline, isoquinoline and of quinolinones are biologically active. Derivatives of dihydroquinolin-2-one find wide use as brightening agents and as sensitizing chromophores.[66] They have been incorporated into organic structures and into ligands of transition metal complex fluorescence agents. A good example is the synthesis of diazaquinomycin A. As part of an effort to study the biological activity of bacterial secondary metabolites, Omura's group[67, 68] described the isolation from a *Streptomyces* strain of a compound with antibacterial properties, which they named diazaquinomycin A, compound **17** (scheme 16).

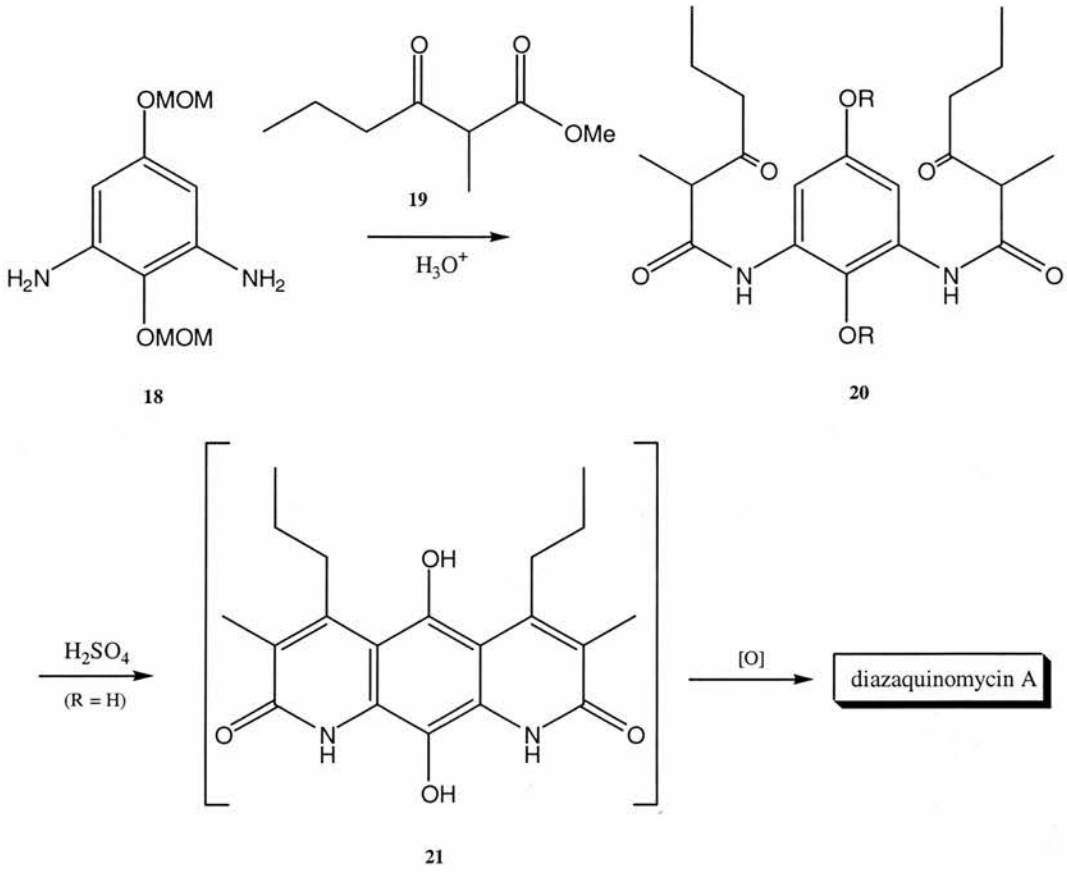


17

scheme 16

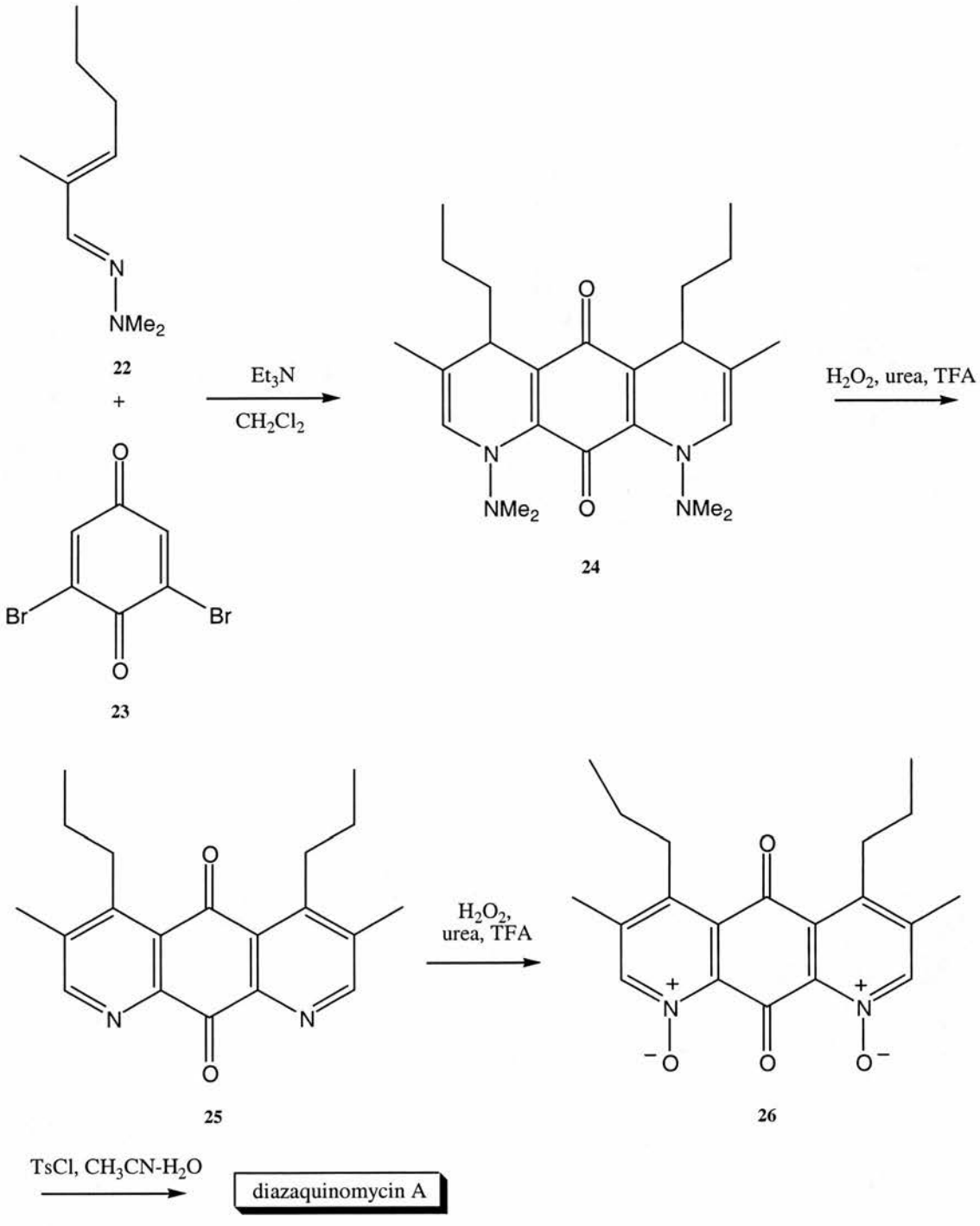
Further research from the same group allowed them to attribute the antibiotic activity to inhibition of thymidylate synthase. This finding made diazaquinomycin A, an attractive lead compound in the field of cancer chemotherapy, although the natural product itself lacked anti-tumour activity because of its poor pharmacokinetic properties.[69] Diazaquinomycin A is a natural antifolate[70] and derivatives are reported to have potent and selective activity towards certain types of solid tumours.[71]

Diazoquinomycin A is also interesting because its 1,8-diazaanthracene-2,7,9,10-tetraone structure is unique, although related natural products, like nibomycin A[72, 73] are known. The only prior total synthesis of diazaquinomycin A was by Kelly and coworkers, and featured a double Knorr cyclisation as the key step[74], scheme 17.



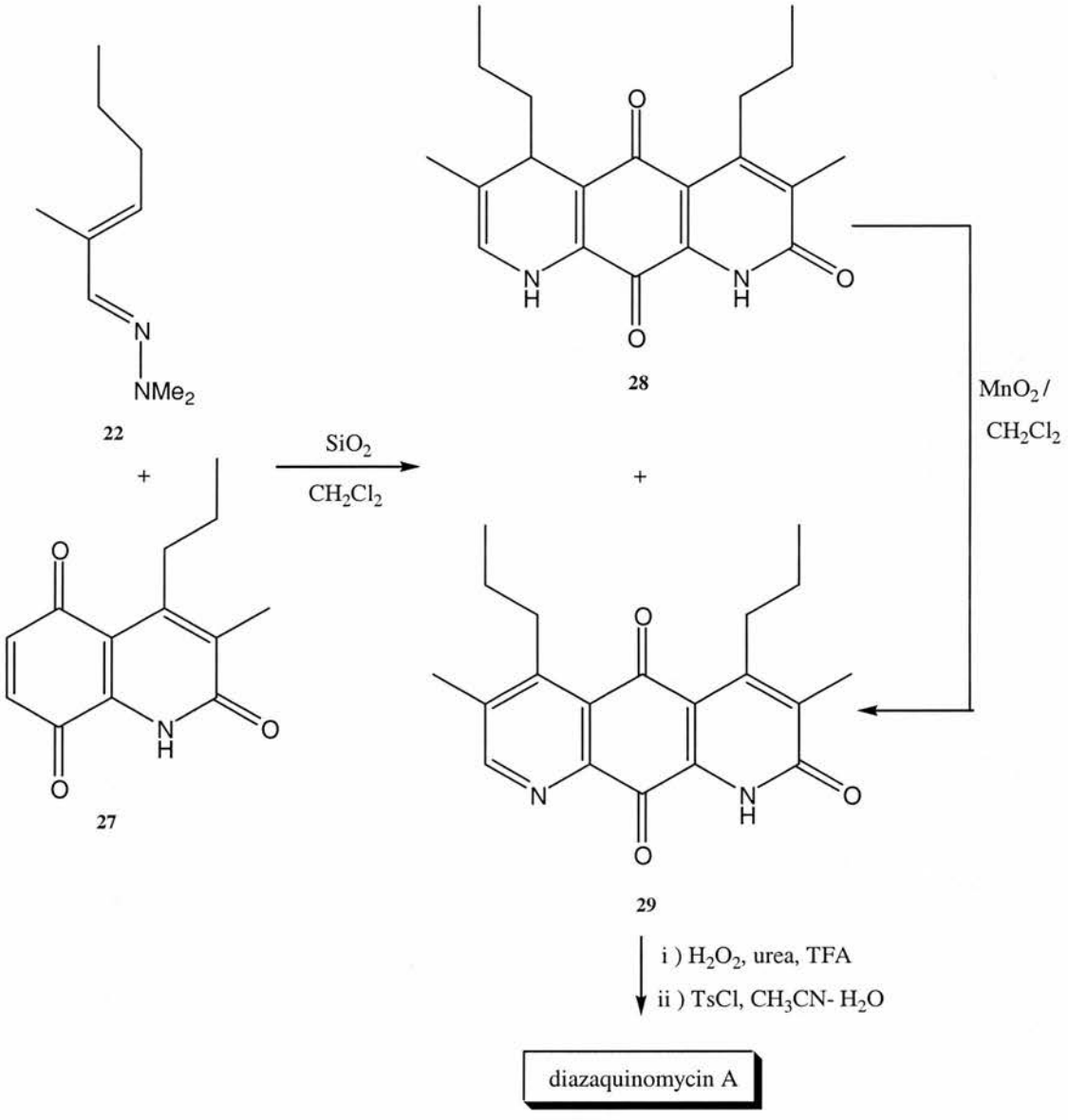
scheme 17

Two concise total syntheses of the diazaanthraquinone unit of diazaquinomycin A have also been reported later by Perez.[75, 76] The first route features a double hetero Diels-Alder reaction between 2,6-dibromobenzoquinone **23** and 2-methyl-2-hexenal dimethylhydrazone **22**, followed by aromatisation by a novel, one-pot *N*-oxidation/elimination procedure with percarbamide in trifluoroacetic acid, and double *N*-oxidation followed by rearrangement to a double lactam system.



Scheme 18

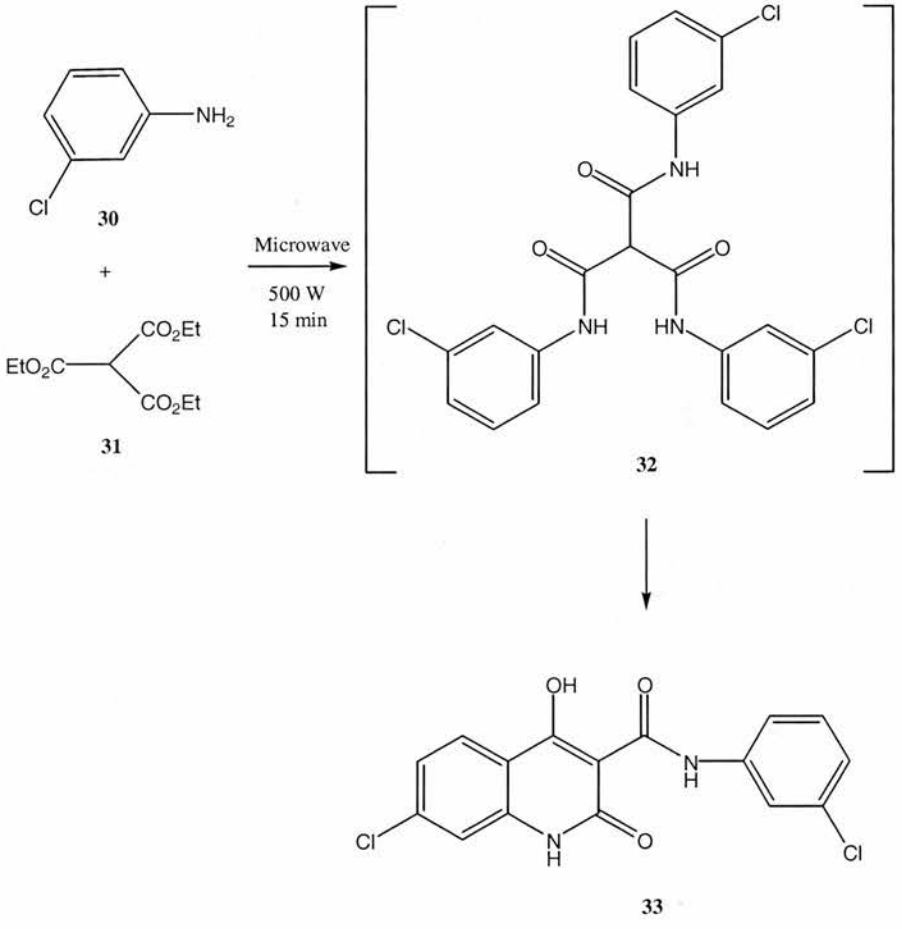
The key step of the second route is a hetero Diels-Alder reaction between 2-methyl-2-hexenal dimethylhydrazone and 3-methyl-4-propyl-1*H*-quinoline-2,5,8-trione.



Scheme 19

A new technique used for the preparation of *N*-heterocycles is microwave irradiation. Microwave irradiation accelerates a variety of synthetic transformations. Microwave-enhanced reactions otherwise normally require many hours at reflux temperatures in a high boiling organic solvent. Lange[77] has reported the synthesis of 4-hydroxy-3-arylquinolin-2-(1*H*)-ones **33** by microwave irradiation under solvent-free conditions. Such quinolinones are potent and selective glycine-site NMDA receptor antagonists

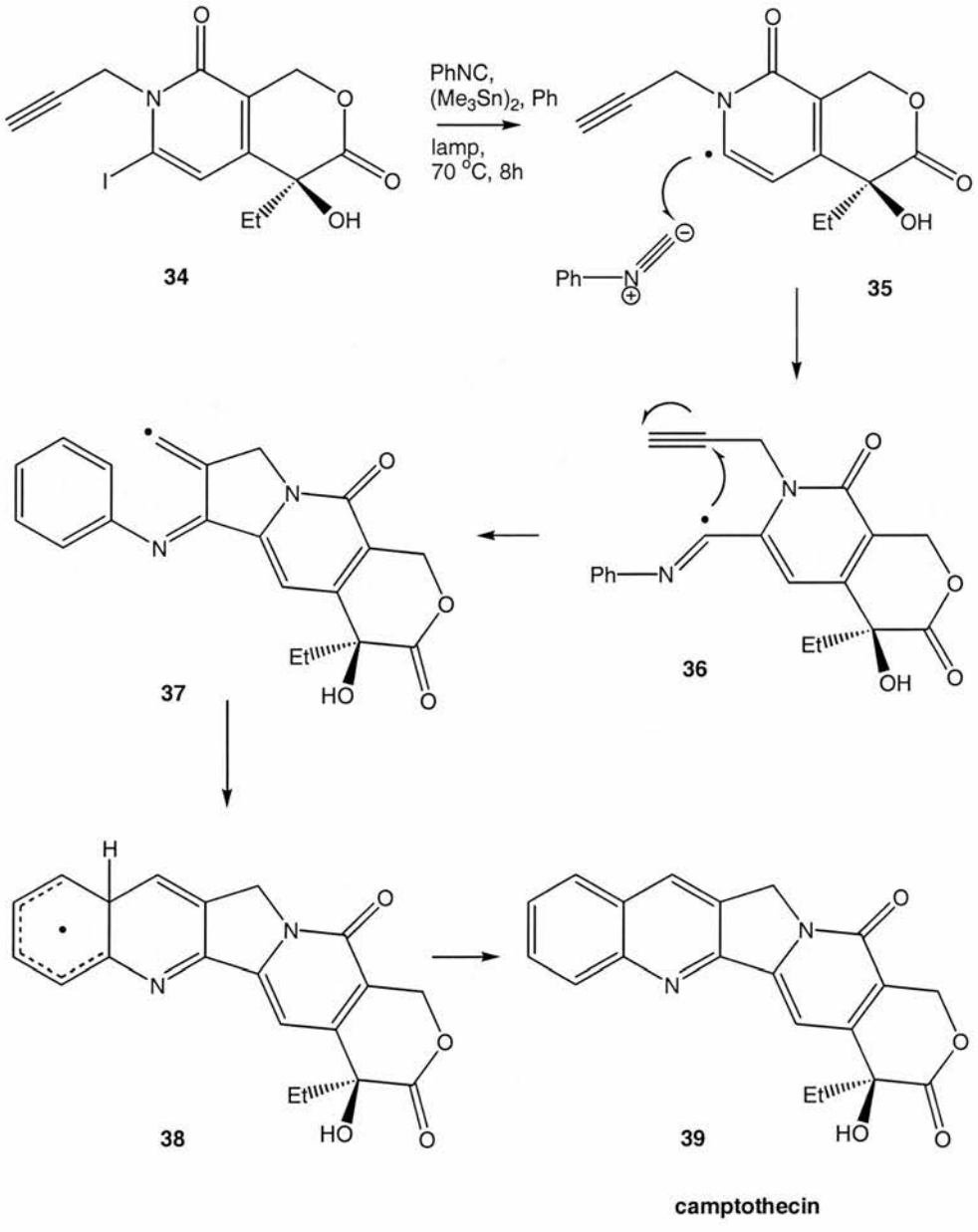
of pharmaceutical interest. The synthetic route chosen by Lange involved the irradiation of a mixture of the aniline **30** and malonic ester **31** derivatives in a microwave oven. Lange has studied the reaction of 3-chloroaniline with triethyl methanetricarboxylate. This reaction gave the formation of 7-chloro-*N*-(3-chlorophenyl)-1,2-dihydro-4-hydroxy-2-oxo-3-quinoline-carboxamide in 31 % yield (scheme 20).



scheme 20

Radical cyclisation for the synthesis of heterocycles is now an established and commonly used methodology. These radical cyclisation methods have several advantages over non-radical protocols. The use of radicals in natural product synthesis allows complex rings systems to be put together without much functional group

protection or problems of racemisation. Radical reactions are increasingly used to facilitate stereoselective cyclisations. These advantages along with the use of one-pot cascade reactions facilitate syntheses, which avoid time-consuming multi-step protocols. Indeed, radical cascade reactions allow the construction of two or more rings in one-pot reactions. One of the most novel radical methodologies has been developed by Curran and co-workers[1, 78] for the synthesis of camptothecin, compound **39**.

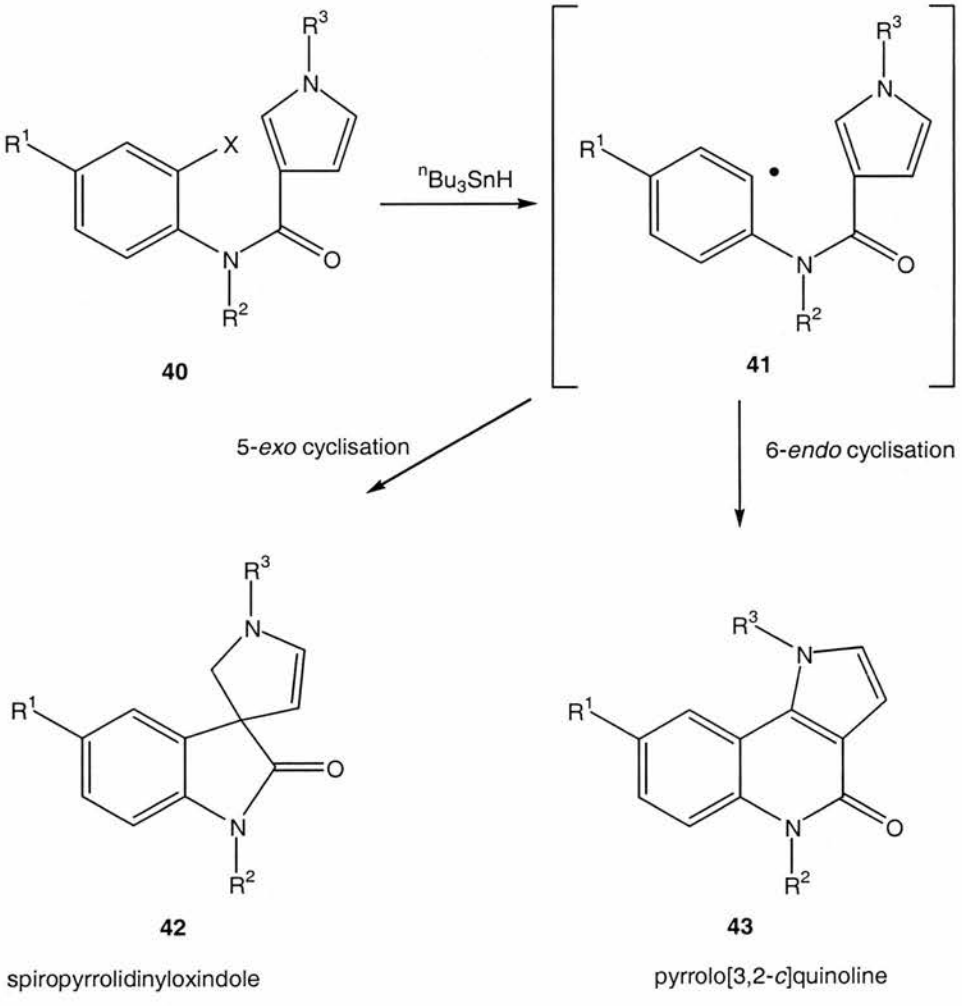


scheme 21

In this cascade reaction (scheme 21) a complex heteroarene system was constructed, as opposed to alicyclic heterocycles. Photolysis of *N*-propargyl-6-iodo-2-pyridone, **34**, in the presence of phenyl isocyanide and hexamethylditin generated the pyridone radical **35**, which underwent bimolecular addition to the reactive isonitrile. The new radical **36** thus generated underwent 5-*exo*-cyclisation onto the pendant alkyne and the intermediate vinyl radical **37** cyclised onto the benzene ring. The intermediate

delocalised radical **38** was oxidised to afford the pentacyclic alkaloid, camptothecin, **39** in 63 % yield.

One of the protocols that have been used is the Bu_3SnH and AIBN mediated oxidative cyclisation of alkyl or aryl radicals onto heteroarenes. In a recent paper Escolano and Jones[79] have reported the intramolecular addition of aryl radicals onto a pyrrole. The cyclisation allows the synthesis of either the spiropyrrolidinyloxindole or the pyrrolo[3,2-*c*]quinoline skeleton, compounds **42** and **43** respectively (scheme 22).



scheme 22

The regiochemistry of cyclisation is governed by the nature of the *N*-substituent on the pyrrole. Pyrroles substituted with an electron-donating group (methyl) on nitrogen

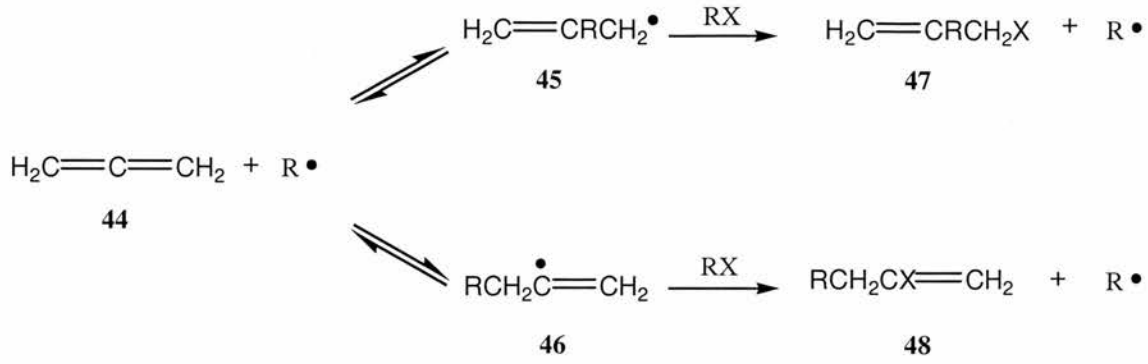
give the pyrrolo[3,2-*c*]quinoline as the major product via a 6-*endo* cyclisation. By way of contrast, an electron-withdrawing group (carbamate) led to formation of the spiropyrrolo dinyloxindole as the major product via a 5-*exo* cyclisation.

IV- Radical addition to X=Y=Z groups

The review will be limited to allene, ketene, azide, isothiocyanate and isocyanate groups. Radical addition to these kinds of system has excited the interest of chemists because of the orientation problem during the addition. Some radicals add to the central atom Y, while others add to one or the other of the two terminal atoms, X or Z.

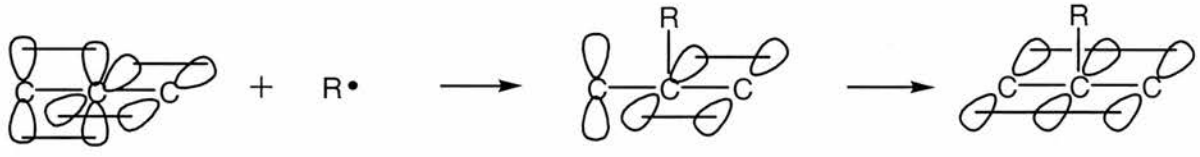
1. Radical addition to allenes

Compounds which contains the C=C=C grouping are known as allenes. Although the earliest authentic syntheses of allenes were reported more than one century ago,[80-82] free-radical reaction of allenes, especially addition to allenes, has been investigated only from 1967.[83] Radical addition to allenes has excited the interest of chemists for two principal reasons. First, the radical addition can occur, either to the central carbon of the allenic bonding system or to one or the other of the two terminal carbons. Second, the initial radical addition to the centre may give allyl-stabilized radicals, but only following a 90° rotation around the carbon-carbon bond. The orientation of the addition depends on both the nature of the attacking radical and the degree and type of substitution of the allenes. It may also be affected by reaction parameters such as temperature, solvent, and initial concentrations. Theoretically adducts may be formed by random terminal and central attack on the allene bond.



scheme 23

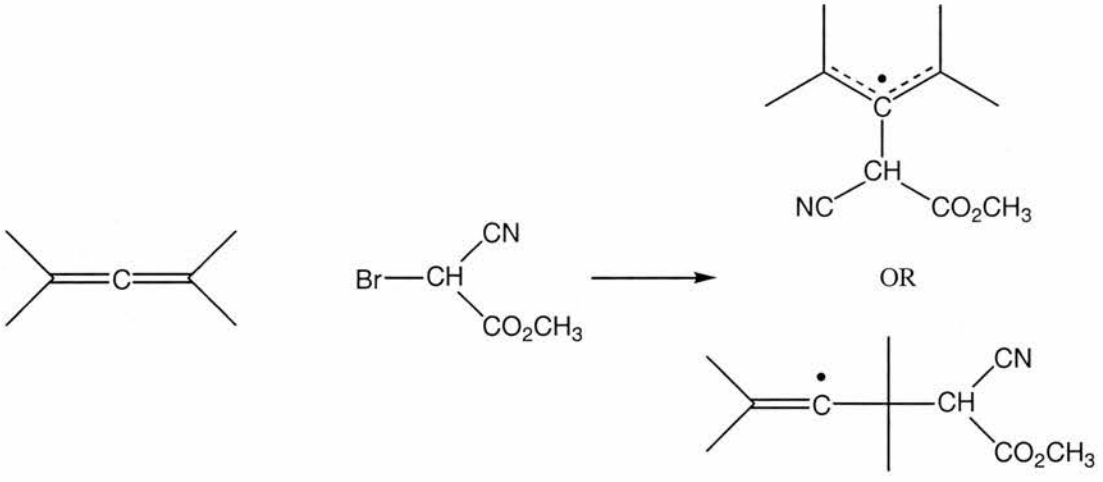
It might be assumed that attack would always take place at the centre carbon to give the more stable allylic intermediate radical **45** (CH_2=CRC$^{\cdot}H_2$), scheme 23. It does imply that the carbon-centred attack achieves irreversible character by allyl radical resonance stabilization, which can be achieved only after the rotation through 90°, scheme 24.



scheme 24

It appears that carbon-centred radicals attack the allene chromophore mainly at the two terminal carbon atoms,[84] whereas there is an increasing tendency for central attack[85-89] by heteroatom-centered radicals, especially along the series HS$^{\cdot}$ < MeCOS$^{\cdot}$ < allyl-S$^{\cdot}$ <PhS$^{\cdot}$ < $Me_3Sn^{\cdot}$ < Br$^{\cdot}$. However, it has been reported that the radical chain addition of bromomalonitrile undergoes addition of the carbon-centred radical

to both the terminal and the central carbon atoms, the extent of attack at the central carbon atom increasing with increasing alkyl substitution on the allene[90], scheme 25.

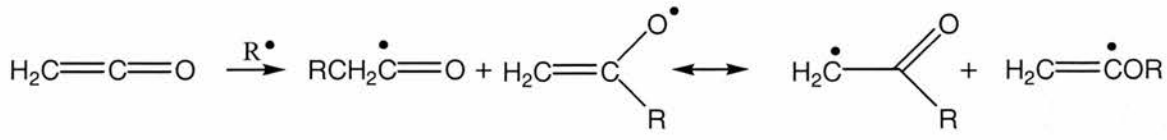


scheme 25

2. Radical addition to ketenes

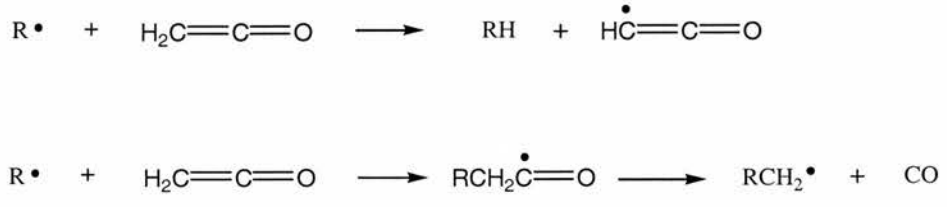
Ketenes are molecules which contain the C=C=O moiety. The free radical chemistry of ketenes has remained *terra incognita*, despite early indications that ketenes are susceptible to radical reactions. In 1905, in the first publications on ketenes, Staudinger[91] reported that diphenylketene reacted with oxygen, which implied a sensitivity to free radicals. Indeed, ketenes are an interesting class of organic molecules that are usually susceptible to be attacked by most reactive intermediates.[92-95] The ionic reactivity of ketenes is known to involve preferential nucleophilic attack at the in-plane LUMO at the carbonyl carbon, whereas preferential elecrophilic attack occurs at the HOMO perpendicular to the molecular plane at the terminal olefinic carbon, and at the oxygen.[92-95] An important question in the reaction of free radicals

with ketenes involves the regiochemistry of the reaction. Attack of radicals on ketenes at the carbonyl carbon, the terminal olefinic carbon, and oxygen would lead to acyl radicals, enolic radicals, and vinyl radicals respectively (scheme 26).



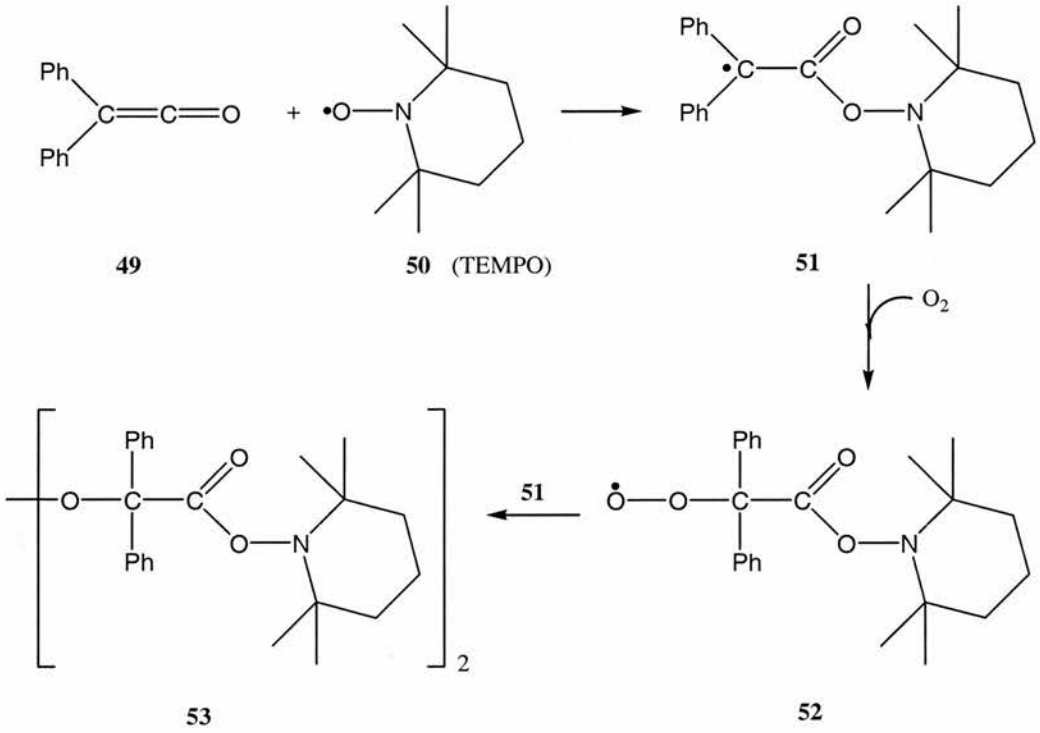
scheme 26

The position of radical attack on ketenes may be expected to be affected by interaction of the radicals with the ketene orbitals. For ketenes the HOMO is perpendicular to the plane of the molecule with large coefficients at the terminal olefinic carbon and oxygen, and the LUMO is in the ketene plane, with large coefficients at the carbonyl carbon and on oxygen. Reported experimental examples of interactions of free radical with ketenes include reactions of R · (R=H [96], t-Bu [97], OH [98], F [99] and Cl [100, 101]) with CH_2=C=O, resulting in either hydrogen abstraction from the ketene or addition to the terminal olefinic carbon forming an acyl radical with subsequent decarbonylation (scheme 27).



scheme 27

These reactions are highly exothermic. So attack at the terminal carbon of ketene is favoured kinetically, even though in the case of CH_3 (H and SiH_3 as well) the attack occurs from both the perpendicular and in-plane directions, corresponding to electrophilic and nucleophilic attack respectively. While for groups containing lone pairs of electrons (OH, F, Cl) the enolic radicals resulting from attack at the carbonyl carbon are predicted to be more stable.[102] Attack at oxygen to give vinyl radicals is less favorable in all cases. In 1999, Huang and co-workers reported an example of addition of nitroxyl radicals to the carbonyl carbon atom of ketene.[103] Thus the reaction of TEMPO **50** with $Ph_2C=C=O$ **49** formed the peroxide **53** (scheme 28).



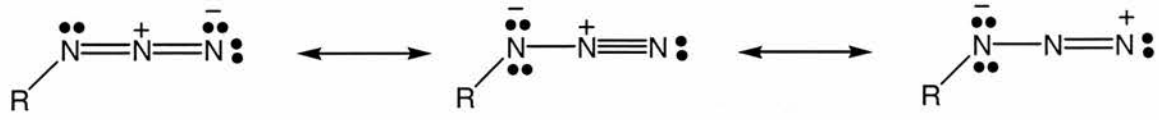
49 **50** (TEMPO) **51**

53 **52**

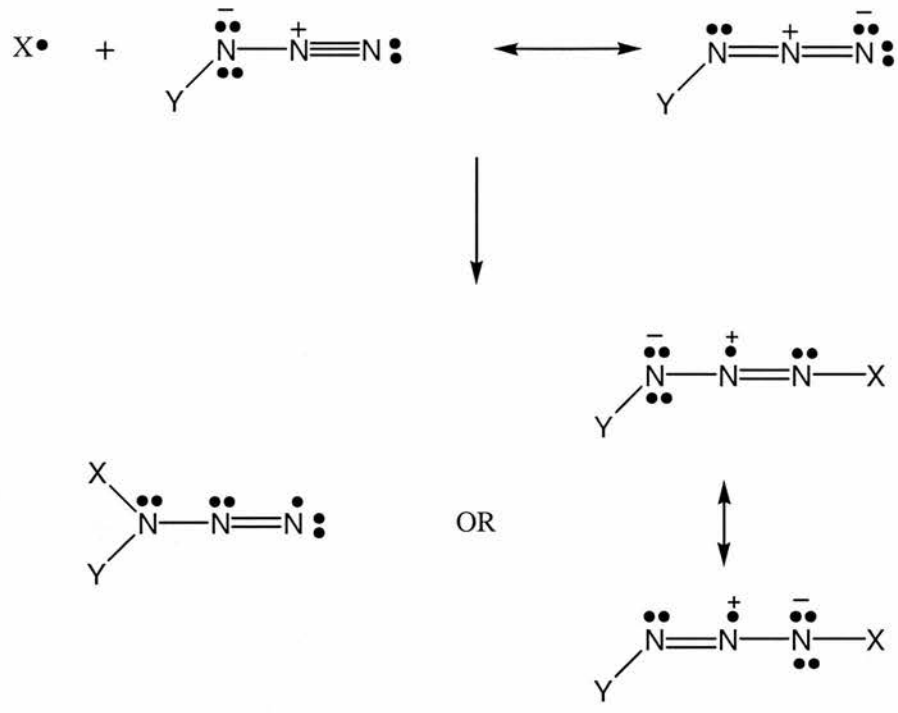
scheme 28

3. Radical addition to azides

It is now generally accepted that azide has a structure in which nitrogen obeys the octet rule and the 'adjacent charge rule'.[104]



The chemistry of azides has attracted the attention of chemists since the discovery of phenylazide by Griess[105] over 100 years ago. Organic azides are versatile nitrogen intermediates whose reactivity and synthetic potential have been investigated under thermal and photochemical conditions.[106-108] On the other hand, radical reactions of organic azides have been far less explored. Relatively little is known about the reactions of free radicals with organic azides. Recent studies have revealed that radical species can add to the N^{α} or N^{γ}-positions of an azide $YN^{\alpha}N^{\beta}N^{\gamma}$ to give an aminyl radical after loss of molecular nitrogen by the initial 1,3-and/or 3,3-triazenyl adduct.[109]



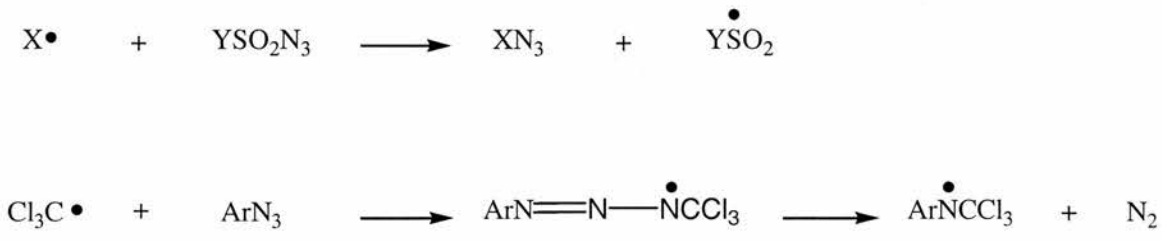
scheme 29

It is sometimes not clear to which end of the azido group addition occurs, because the ultimate products could plausibly arise from either intermediate triazenyl radical[110] (scheme 29). For instance, aryl, acyl and sulfonyl azides undergo induced decomposition when heated in propan-2-ol at 50-80 °C in the presence of diethyl peroxydicarbonate initiator (scheme 30).

scheme 30

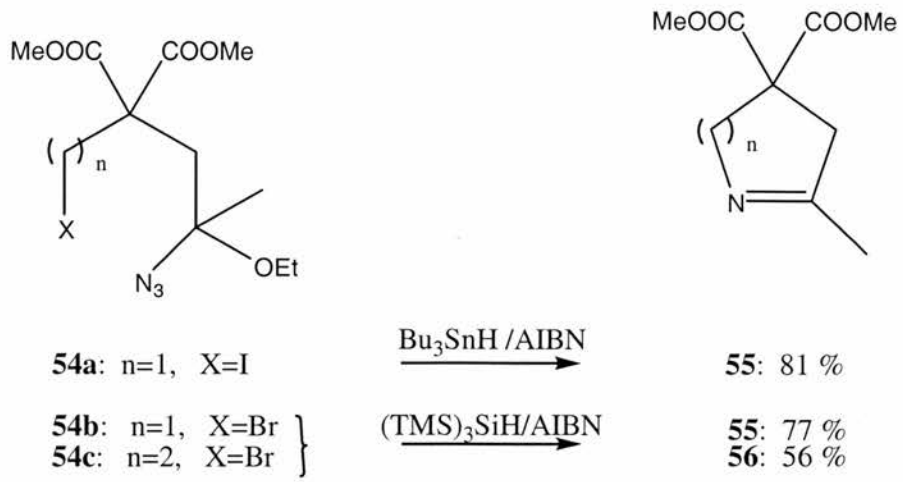
The key step was thought to involve reaction of the radical $Me_2C^{\cdot}OH$ with the azide. Addition of the radical takes place initially at N^{γ} to give a 1,3-triazenyl radical,

followed by intramolecular hydrogen-atom transfer from oxygen to N^{α} with concerted elimination of acetone and molecular nitrogen. However, it seems equally possible that the 3,3-triazenyl radical YN(H)-N=N· is formed initially, by hydrogen atom transfer from oxygen in $Me_2C{\cdot}OH$, followed by loss of nitrogen to give YN·H. Alkyl radicals displace organosulfonyl radicals from sulfonyl azides[111-113] and trichloromethyl radicals induce the decomposition of aryl azides.[114]



scheme 31

Intramolecular additions of carbon-centred radicals, including the aryl,[115] thiocarbonyl,[116] alkyl,[117] and vinyl members,[118] to alkyl and aryl azides have been shown to provide useful synthetic routes to *N*-heterocycles. Indeed, Sunggak in his example of intramolecular addition of an alkyl radical to an azido group showed the efficiency of this method for the creation of *N*-heterocycles. Thus, treatment of the iodo compound **54a** with Bu_3SnH/AIBN afforded the product **55** in 81% isolated yield while treatment of the bromo compounds **54b** and **54c** with $(TMS)_3SiH$/AIBN afforded the products **55** and **56** in 77 % and 56 % isolated yield respectively (scheme 32).

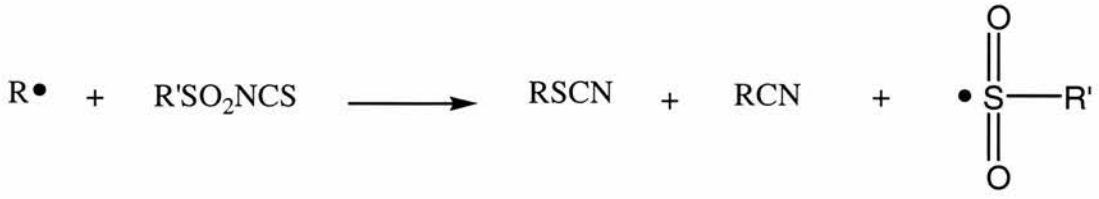


scheme 32

In this approach, the addition of the alkyl radical to the azido group occured in the *exo* mode, followed by the loss of nitrogen to produce an aminyl radical which will be reduced in the next step.

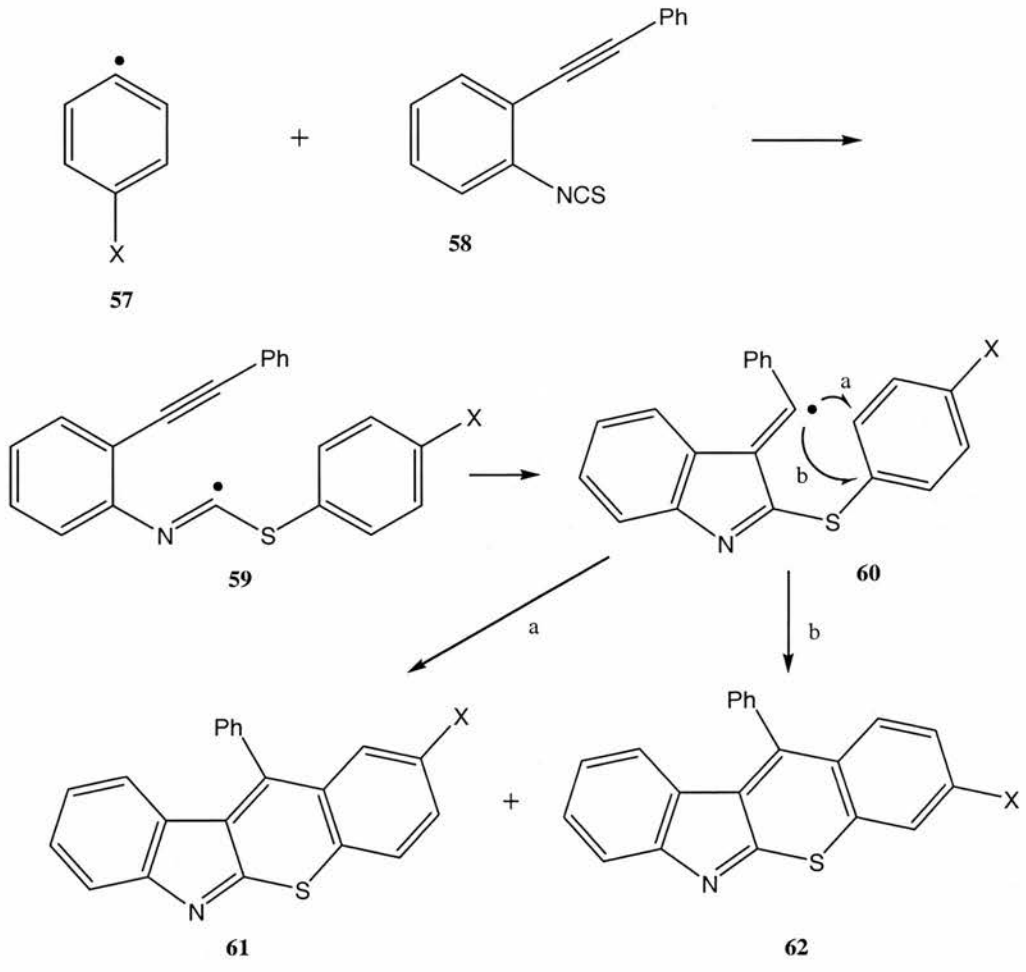
4. Radical addition to isothiocyanates

Isothiocyanates are molecules which contain the N=C=S group. Organic isothiocyanates have recently received increased attention due to their role in many biological systems. Barton's work[119] was the first example of addition of a carbon-centered radical to an isothiocyanate. He showed an example of nitrile transfer to a carbon radical from sulfonyl isothiocyanates. The radical addition can occur either on the sulfur atom or the central carbon atom to give the corresponding nitriles (scheme 33).



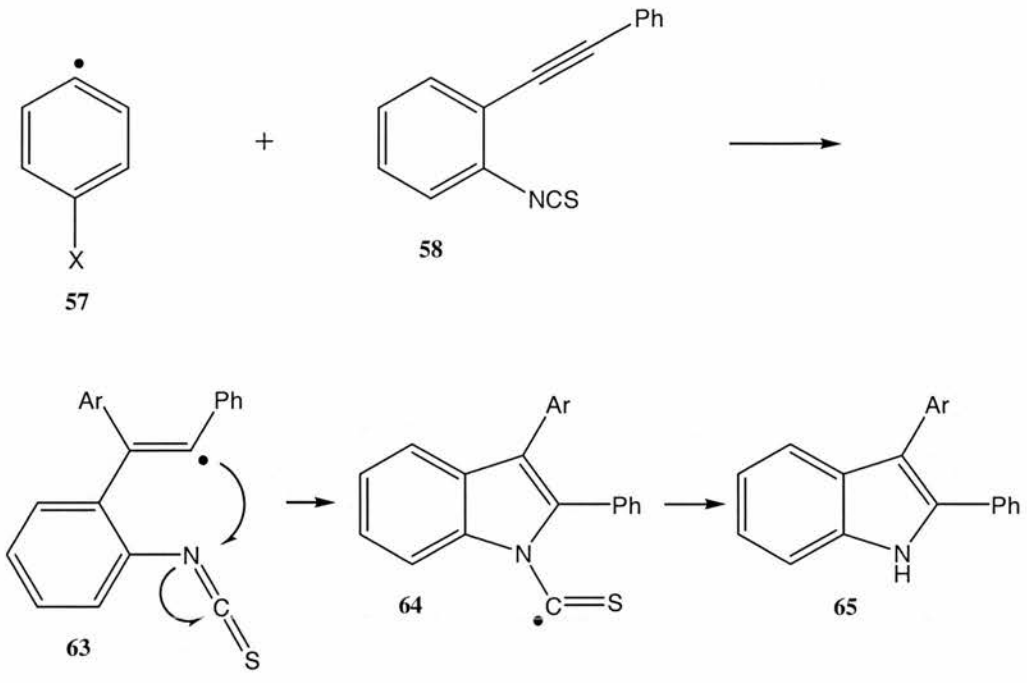
scheme 33

Recently, an example of addition onto the nitrogen atom and onto the sulfur of the isothiocyanate function, has been reported by Benati and co-workers[120] during the cascade radical reaction of 2-(phenylethynyl) phenyl isothiocyanate **58** with a series of aryl radicals **57**. The main products identified came from the addition of the aryl radical to the sulfur atom of the isothiocyanate to give the imidoyl radical **59**.



scheme 34

The formation of either one or the other isomer **61** and **62** depends on the X substituent on the aryl radical. However, during this reaction the radical addition onto the nitrogen atom of the isothiocyanate, also occurred leading to the formation of indoles **65**, identified as by-products of the process. They presumably derived from attack of the aryl radical at the carbon-carbon triple bond, followed by cyclisation of the vinyl radical **63** onto the nitrogen of the isothiocyanate moiety, loss of CS and eventually hydrogen atom abstraction.

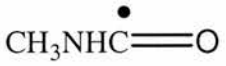


scheme 35

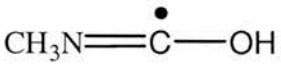
5. Radical addition to isocyanates

Isocyanates are esters of isocyanic acid, and the first member of this class of compound, with the grouping N=C=O, was synthesized by Wurtz in 1848. Shortly thereafter several prominent nineteenth century scientists, such as Hofmann and Curtius, systematically investigated the chemistry of isocyanates. However, the radical chemistry associated with isocyanates has not been studied to any great extent. ESR studies of gamma irradiated crystalline methyl isocyanate at 77K carried out by several investigators,[121-123] showed interesting results. The formation of the $^{\cdot}CH_2NCO$ radical was observed in all these studies. Interestingly, Trofimov and Chkheidze[121] also detected the formation of another radical upon addition of hydrogen atom to the isocyanate group. Three structures of the resulting radical were possible.

66



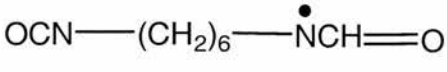
67



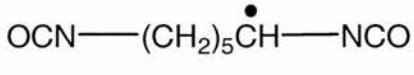
68

scheme 36

Analysis of the ESR spectra indicated that only the radical having structure **67** was formed. Fujiwara [123] also observed the radical $^{\cdot}CH_2NCO$ at 77 K and a similar radical derived from deuterated methyl isocyanate CD_3NCO. In hexamethylene diisocyanate,[121] the ESR spectrum assigned to the hydrogen atom adduct, radical **69,** was detected in addition to the isocyanato radical **70**.



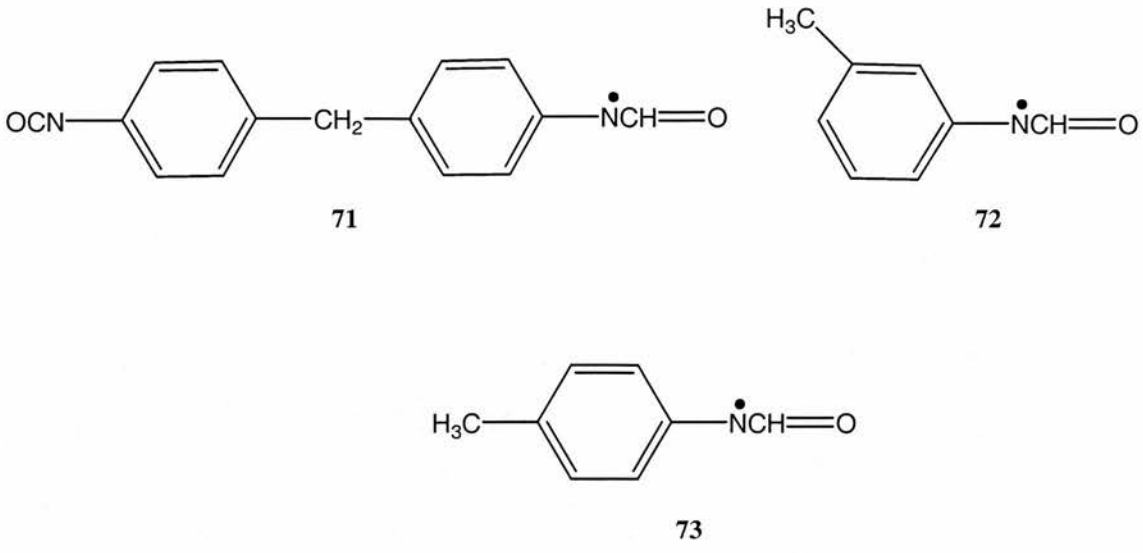
69



70

scheme 37

For aromatic isocyanates, the ESR spectra showed the radicals formed by hydrogen atom addition.[121] The site at which the hydrogen atom attached itself, was determined by the type of aromatic group in the molecule. In phenyl isocyanate the hydrogen atom attacked the phenyl ring, while the hydrogen was bound to the NCO moiety in 4,4'-diisocyanatodiphenylmethane **71**, *m*-tolylisocyanate **72** and *p*-tolylisocyanate **73** (scheme 38).



71 72 73

scheme 38

The presence of an additional reactive functional group on the phenyl ring helps in determining the site of hydrogen atom addition. In *m*-nitrophenylisocyanate, the hydrogen atom added only to the nitro group while in the *ortho* derivative both the isocyanate group and the nitro group were attacked by the hydrogen atom (scheme 39).

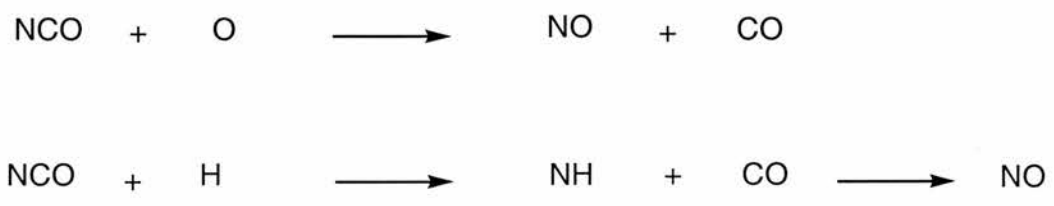
74 75

scheme 39

The radical resulting from the removal of a hydrogen atom from the phenyl ring of *o*-nitrophenylisocyanate was also observed.

V- Radical chemistry of isocyanates and succinimidyl radicals

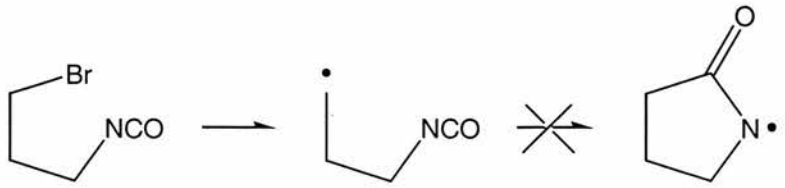
NCO radicals are important intermediates in combustion,[124] in particular, in the conversion of fuel-nitrogen into nitrogen oxides. In this case, NCO radicals are prepared either by the reaction of hydrogen cyanide with oxygen atoms or the reaction of cyanide radicals with hydroxyl radicals or oxygen. The action of O or H on NCO leads directly or indirectly to the formation of NO (scheme 40).



scheme 40

Furthermore, the NCO radical is a key intermediate in NO_x reduction processes.

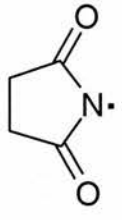
In 1989, Kaushal and co-workers[125] reported studies of the 3-bromopropyl isocyanate compound **76**.



76 **77** **78**

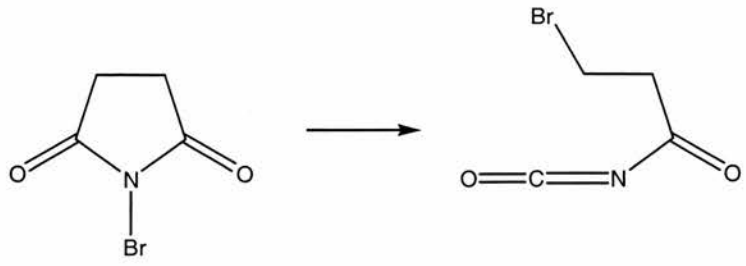
scheme 41

The isocyanatopropyl radical **77** was detectable by ESR spectroscopy for extended periods of time at high temperatures. However no spectroscopic evidence for cyclisation of the former radical was obtained. The cyclised species **78** has not been detected by ESR. Most studies over the past few years have been reported on imidyl radicals, especially the succinimidyl radical **1**, illustrated below.



1

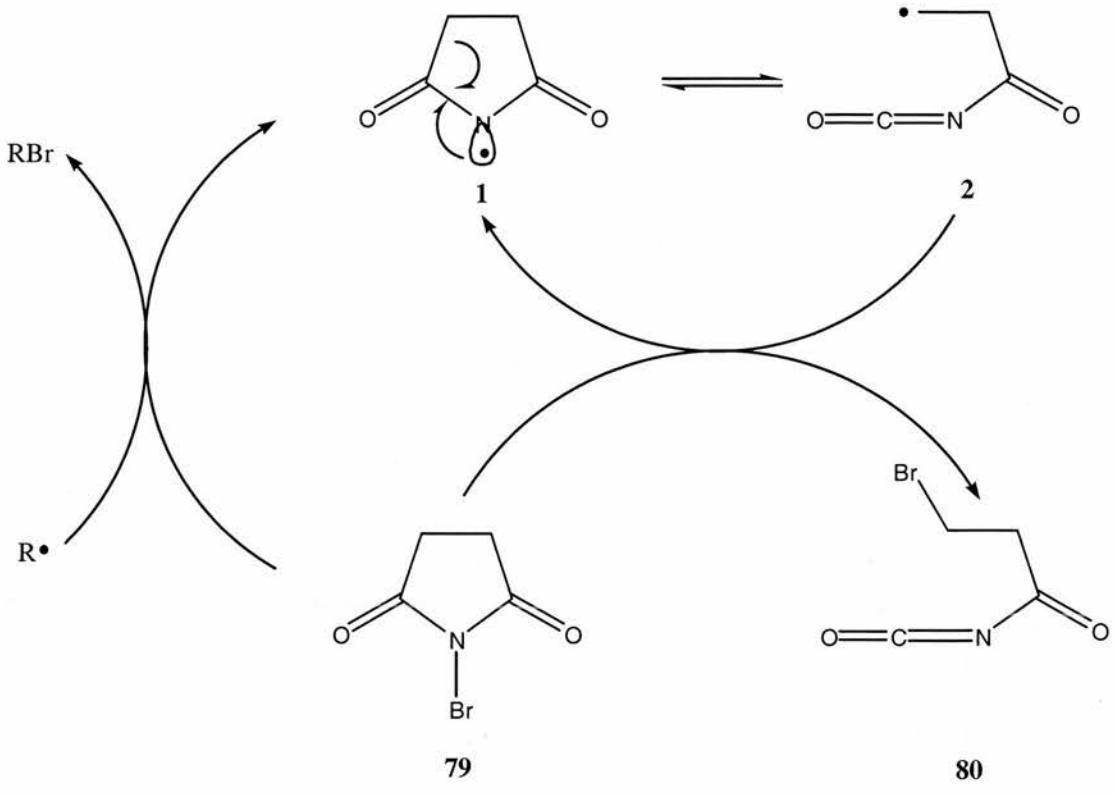
The succinimidyl radical was first proposed as an intermediate in allylic bromination by NBS, (*N*-bromosuccinimide) **79**.



79 **80**

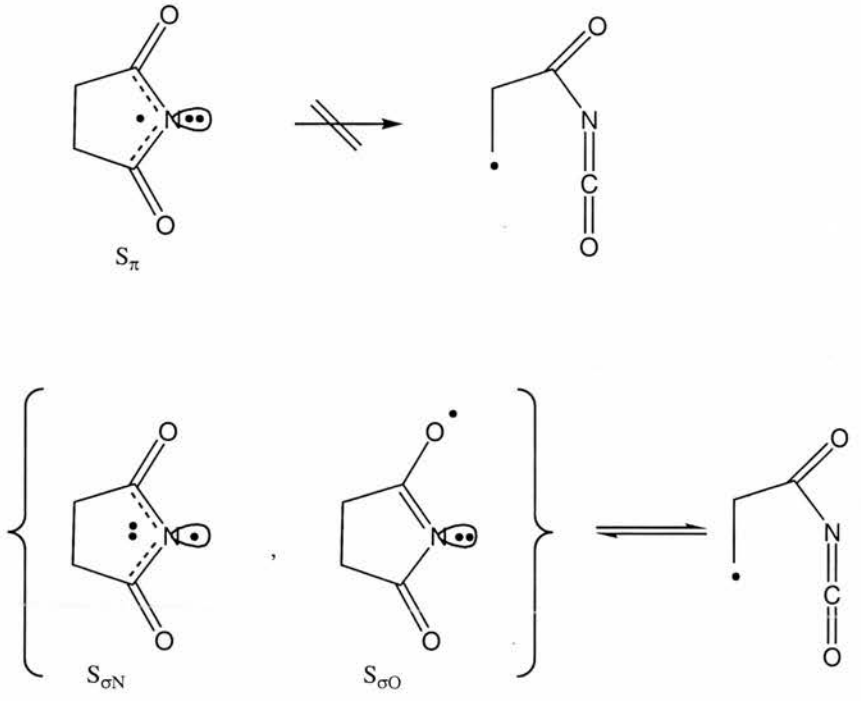
scheme 42

The rearrangement of NBS **79** to 3-bromopropanoyl isocyanate, **80** (scheme 42), was first reported in 1957 by Martin,[126] followed by the work of Johnson[127] in 1958. It was recognized as a radical process. This isomerization involves induced ring opening of the succinimidyl radical to form the 2-(isocyanatocarbonyl) ethyl radical as the key step, (scheme 43).



scheme 43

The rearrangement of the succinimidyl radical and the 2-(isocyanatocarbonyl)ethyl radical is reversible.[128] According to Koenig and Wielesek[129] ground-state succinimidyl and some of its excited states could be described as S_{π} and $S_{\sigma N}$ or $S_{\sigma o}$ respectively (scheme 44).



scheme 44

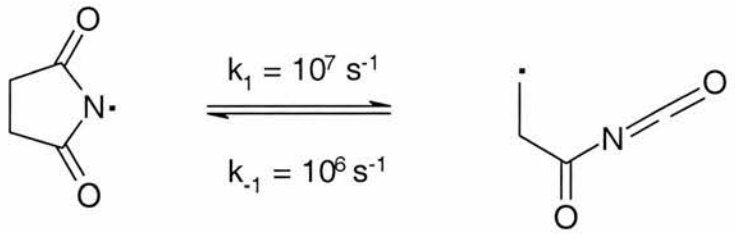
Of the two states of the succinimidyl radical (S_π or S_σ) only the σ excited states had symmetries that correlated with the open-chain 2-(isocyanatocarbonyl) ethyl radical.

Before 1989, no evidence for the cyclisation of 2-(isocyanatocarbonyl) ethyl radical existed because the succinimidyl radical had never been generated from acyclic reagents. Furthermore, no ESR spectrum of the succinimidyl radical in solution has ever been detected. Different attempts under a variety of conditions of solvent and temperature didn't allow Kaushal et al. to observe any ESR spectra of the imidyl radical during UV (ultra-violet) irradiation of the *N*-halogenoimides (chloride or bromide) either alone or in the presence of R_3SnSnR_3 (R = Me or Bu). Note, however, that closure of **2** to **1** amounts to a 5-*exo*/5-*endo* cyclisation at the central C-atom of the isocyanate moiety.

VI- Aims and objectives of the project

The initial aim of this project was the construction of dihydroquinolones by radical cyclisation of organic isocyanates. The cyclisation was to occur by addition to the carbon-oxygen double bond of the isocyanate group. There is a good reason in the choice of this method for synthesizing the dihydroquinolones.

In 1998 Merenyi[21] re-examined the succinimidyl radical **1**. This succinimidyl radical exists in rapid equilibrium[128, 130] with its ring-opened derivative the β-(isocyanatocarbonyl) ethyl radical **2**.

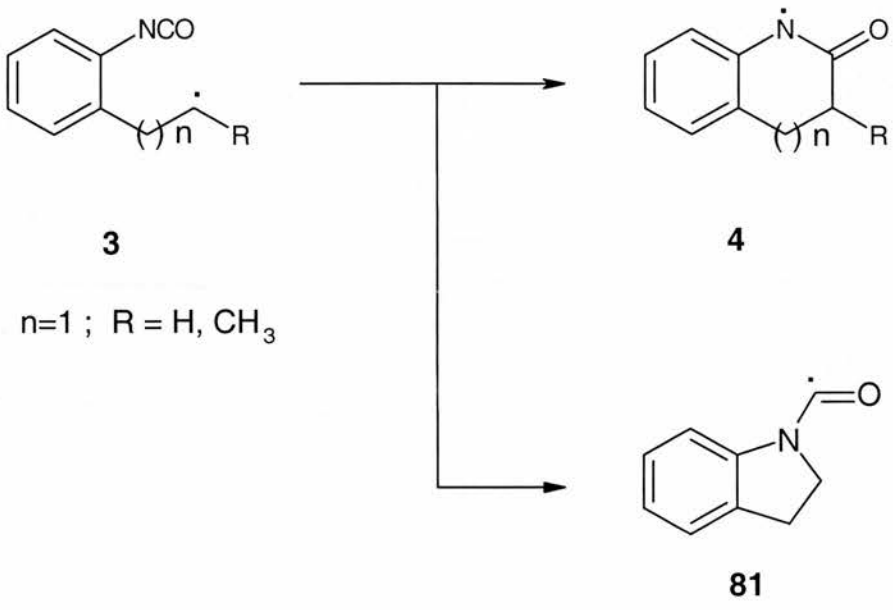


1 **2**

The equilibrium constant K ($K = k_1/k_{-1}$) was found to be 10 with $k_1 = 10^7\ s^{-1}$ and $k_{-1} = 10^6\ s^{-1}$. Halogen abstraction reactions from haloimides by some selected alkyl radicals were also examined. Merenyi found that the 2-cyanoethyl radical abstracted Br from NBS ca. 25 times slower than did the ethyl radical. This showed a strong β-effect and rationalised a relatively slow Br abstraction rate by **2** from NBS. The closure rate of **2** (k_1), was estimated to be ca. 100 times faster in CH_2Cl_2 than in water. This suggested stabilisation of **1** by hydrogen-bonding.

Because the cyclisation is fast, it follows that if the β-scission of the cyclic imidyl could be prevented, this ring closure could become a potentially valuable

homolytic route to lactam structures. Two ways of achieving this are apparent. A first approach is to introduce a provision for resonance stabilisation of the unpaired electron in the cyclised radical.



3

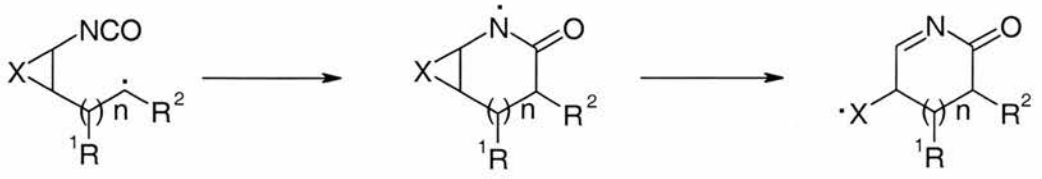
n=1 ; R = H, CH_3

4

81

For instance, the introduction of an aromatic system such as in the 2-alkyl aromatic isocyanates **3** should enable the stabilised radical **4** to be trapped before rupture. It seemed probable that resonance delocalisation of the unpaired electron in **4** would make this cyclisation lower in energy than the alternative 5-*exo* intramolecular addition at the nitrogen yielding aminoacyl radical **81**.

A second way would be to offer the cyclised radical an alternative, more rapid, β-scission which would leave the lactam ring intact.

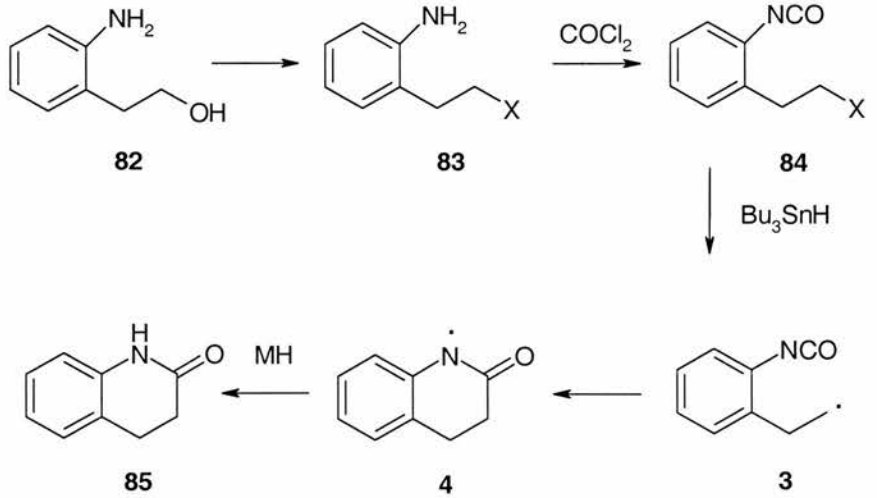


$^1R = R^2 = H$ and $X = CH_2$, O

5 **6** **7**

For example, the cyclopropyl isocyanates **5** should ring close to afford aminyls **6**. The newly formed ring in **6** will be preserved because of the extremely rapid β-scission of the three-membered ring yielding radical **7**.

Preparations of appropriate isocyanates, having substituents suitable for radical generation will be examined. Then the radical cyclisations will be studied under various homolytic experimental conditions. The scope and limitations of aromatic and cyclopropyl isocyanates for the construction of *N*-heterocycles will be explored. For aromatic isocyanates the overall approach is outlined below.

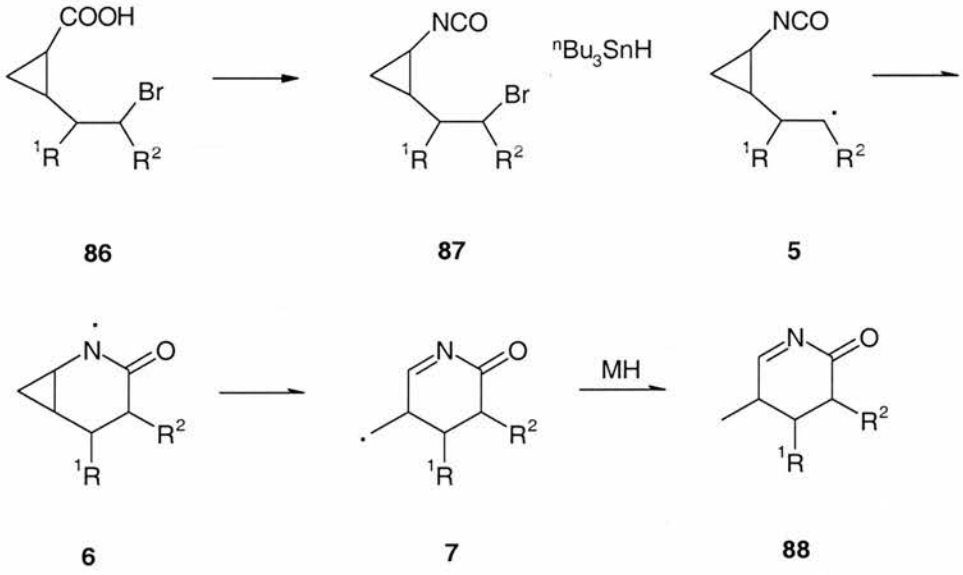


82 **83** **84** **3** **4** **85**

Appropriate radical precursors are the 2-alkyl (or aryl) isocyanates, which can be obtained from the amines **82**. By means of several steps, compound **82** will be prepared and the aromatic isocyanates will be prepared by treatment of the corresponding aromatic amines **83** with phosgene.[131, 132] Radicals will be generated from the halides (or selenides) **84** (X = I, Br, SePh), using radical chain methodology[133] with tributyltin hydride and AIBN as initiator, and in other ways that avoid the use of tin reagents.

Simple reaction of an organic halide with tin hydride involves a controlled chain reaction. The carbon-centered radical **3** will be generated from the organic substrate **84** by atom or group abstraction X, by action of the Bu_3Sn radical. Addition to the C=O double bond will afford the new radical **4**. The cyclised iminyl radical **4** will be trapped by rapid hydrogen transfer with organotin hydride to yield the compound **85**, 3,4-dihydro-quinolin-2-one. Trapping the initial radical **3** with tributyltin hydride before cyclisation could be avoided if low concentrations of the reagent are employed. For particularly slow cyclisations, very low concentrations of Bu_3SnH are often required. This condition could be accomplished by utilizing the catalytic procedures. However, tin reagents are neurotoxic. Tin contamination of compounds for medicinal use is highly undesirable. A solution could be to use Bu_3SnX (X = halogen) and $NaBH_4$ in sub-stoicheometric amounts. However for X = Cl, Br, I, the results are often oils with a poor chromatographic behaviour leading to persistent contamination. The use of silicon alternatives, such as $(Me_3Si)_3SiH$, could be a possibility despite the high cost, other alternative could be polymer-supported reagents[134] or the use of water-soluble or very polar reagents.[134-138]

With regard to the cyclopropyl isocyanates, a first route to yield the isocyanate derivative could again be to start with the corresponding amino compound. However, in a recent paper, Vallgarda[139] described the preparation of this cyclopropyl isocyanate from the corresponding carboxylic acid **86**, by action of ethyl chloroformate and sodium azide.



86 **87** **5**

6 **7** **88**

The cyclopropyl isocyanate will be prepared according to Vallgarda's method. In the same way, the action of tributyltin with the isocyanate **87** will afford the radical **5**, which may cyclize to afford the radical **88**. Subsequently, the cyclized radical **88** will be trapped by rapid hydrogen transfer with organotin hydride to yield a substituted pyridinone.

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Chapter 2

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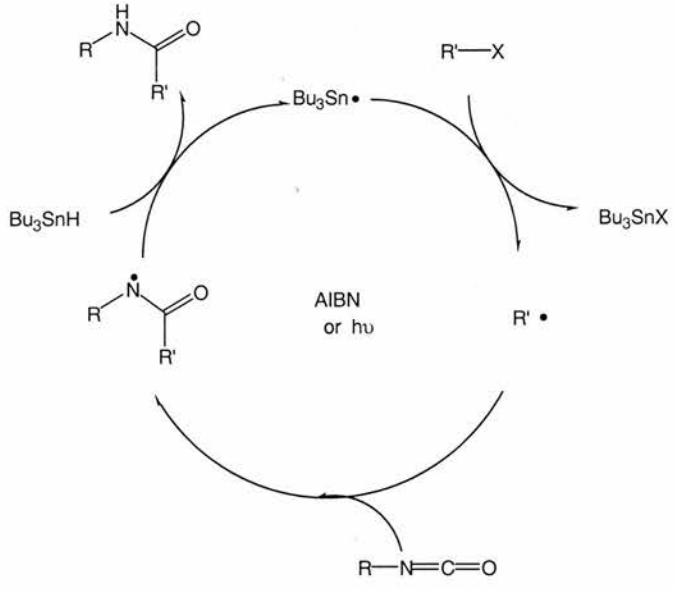
INTERMOLECULAR ADDITION TO ISOCYANATES

I- Introduction

Before investigating intramolecular processes, as a preliminary project, intermolecular addition to organic isocyanates by alkyl radicals was studied. The objectives were to identify the principal products, to gain an understanding of the basic mechanism, and to determine the preferred site of addition of C-centered radicals on the isocyanate moiety.



scheme 45

The general idea is illustrated in the scheme above. The radical reaction would be initiated either by a catalytic amount of AIBN or by photolysis. The initial tributyltin radical would attack the C-halogen bond of the substrate, pick up the halogen from the substrate and an alkyl radical would be released. This alkyl radical could add onto the C-atom of the isocyanate to create an amidyl radical (scheme 45) or onto the N-atom to produce an aminoacyl radical.

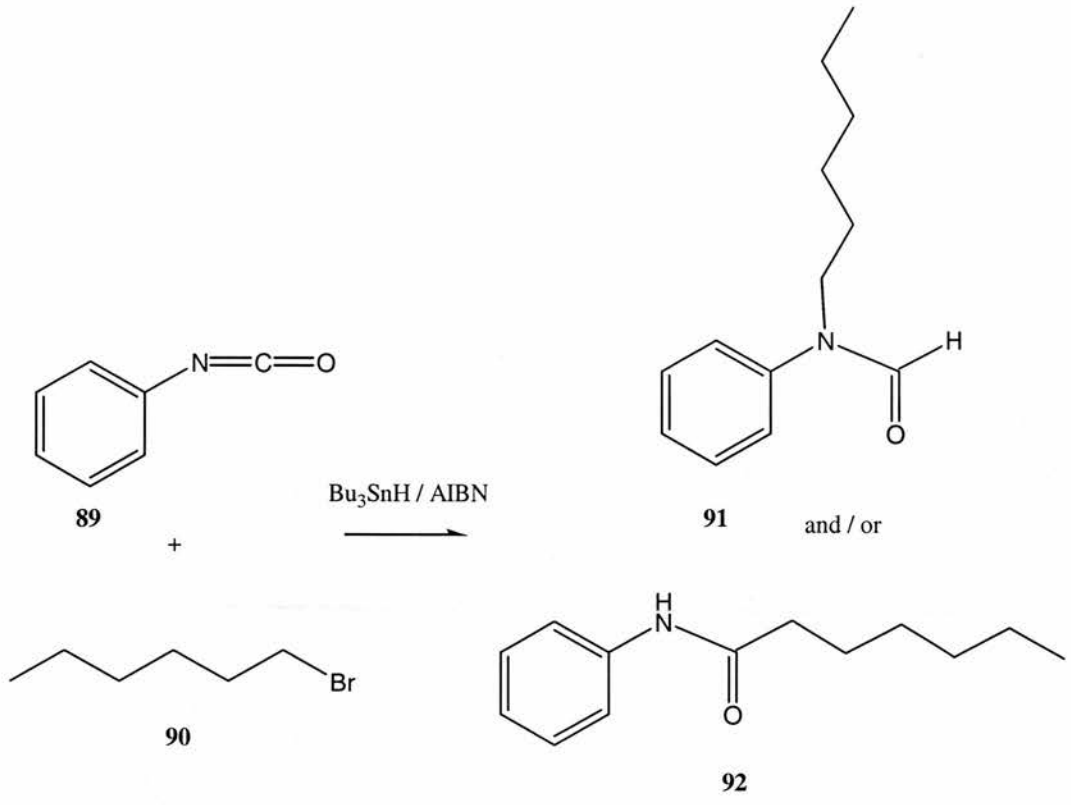
A new tributyltin hydride molecule would donate hydrogen to the amidyl radical to give the expected-product. In this last step a new tin radical would be formed. This new tin radical would be available for the next cycle. This reaction follows a free-radical chain mechanism.

II- Results and discussion

To see if a radical reaction could be induced between an isocyanate and an organic halide, we carried out radical initiated reactions of isocyanates with bromides, both commercially available.

1. Phenyl isocyanate and 1-bromohexane

The first series of experiments was carried out between phenyl isocyanate **89** and 1-bromohexane **90** in the presence of tributyltin hydride as radical reagent (scheme 46).



scheme 46

To establish the best methodology, several experimental conditions were tested for this reaction. All these procedures were analysed by ^{1}H NMR spectroscopy and GC-MS. The different conditions and results of the GC-MS analyses are summarised in the table below. In each case, GC-MS analysis showed solvent, unreacted starting materials and organotin residues, together with the products shown in the following table. The relative amounts of individual components are indicated on a scale from ++++ (major) to + (minor).

Products of homolytic reactions of phenyl isocyanate with 1-bromohexane			
Procedures	**Reactions**	**Products**[g]	**Library fit**[a]
1[b]	PhH, AIBN, UV 4h, RT, no degas	++++ Hexane	
2[c]	PhH, AIBN, UV 5h, RT, degas	++++ *N*-Phenyl formamide	996
3[d]	$PhCH_3$, AIBN, heating 5h, 80 °C, N_2	++++ Aniline	993
4[e]	$PhCH_3$, AIBN, UV 5h, RT, N_2	+++ *N*-Phenyl-hexyl-amine +++ *N*-Phenyl-*N*-hexyl-formamide +++ Pentanoic acid hexyl-phenyl-amide or Heptanoic acid phenyl-butyl-amide ++ Aniline ++++1,3,5-Triphenyl-[1,3,5]triazinane-2,4,6-trione	993
5[f]	PhH, AIBN, UV 7h, RT, slow addition of Bu_3SnH for 1h, tube at 10cm from source.	+Toluene +Hexane ++++Aniline ++++*N*-Phenyl-formamide +++*Tert*-Butyl benzene +++Hexyl-benzene ++Pentanoic acid hexyl-phenyl-amide or Heptanoic acid phenyl-butyl-amide ++*N*-Phenyl-hexyl -amine	993 996
6[f]	$PhCH_3$, AIBN, UV 6h, RT, slow addition of Bu_3SnH for 1h, tube at 20 cm from source.	+++Aniline ++N-Phenyl-hexyl -amine ++++*N*-Hexyl-*N*-phenyl-hydroxylamine	993

[a] 1000 = exact library fit. [b] One unidentified component. [c] Three unidentified components. [d] Three unidentified components. [e] Two unidentified components.

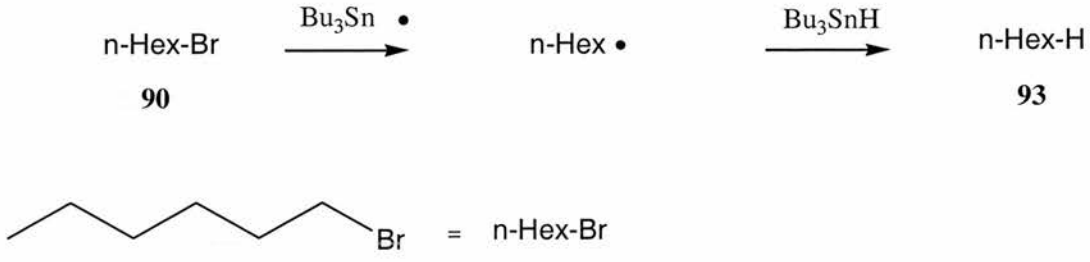
[f] Several traces of unidentified components.

[g] ++++ major product → + minor product.

1. 1. Procedure 1– Photolysis of solution in benzene without degassing

A solution of phenyl isocyanate, 1-bromohexane and tributyltin hydride in benzene was put in a test tube in presence of a catalytic amount of AIBN. The mixture was

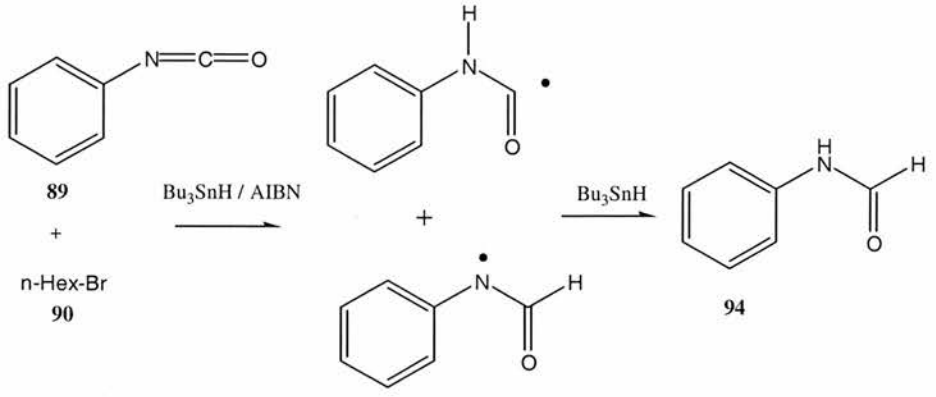
photolysed with an UV lamp for 4 hours. The GC-MS analysis of the solution mixture showed that the major peaks were mainly tin-derived compounds, unreacted phenyl isocyanate together with hexane presumably formed by reaction of hexyl radicals with n-Bu_3SnH as described below in scheme 47.



scheme 47

1. 2. Procedure 2– Photolysis of solution in benzene after degassing

Phenyl isocyanate, 1-bromohexane, tributyltin hydride and AIBN, in catalytic amount, in solution in benzene were degassed for 30 minutes. The solution was photolysed for 5h. The GC-MS analysis of the solution mixture showed the usual tin residues together with a major product with $M^+ = 121$ (C_7H_7NO) which could be *N*-phenyl formamide (fit 996). The formation of *N*-phenyl formamide **94** could be explained as follows.



scheme 48

In this case, phenyl isocyanate was hydrogenated. The hydrogen atom probably originated from the tin hydride. Several traces of unidentified components were also observed.

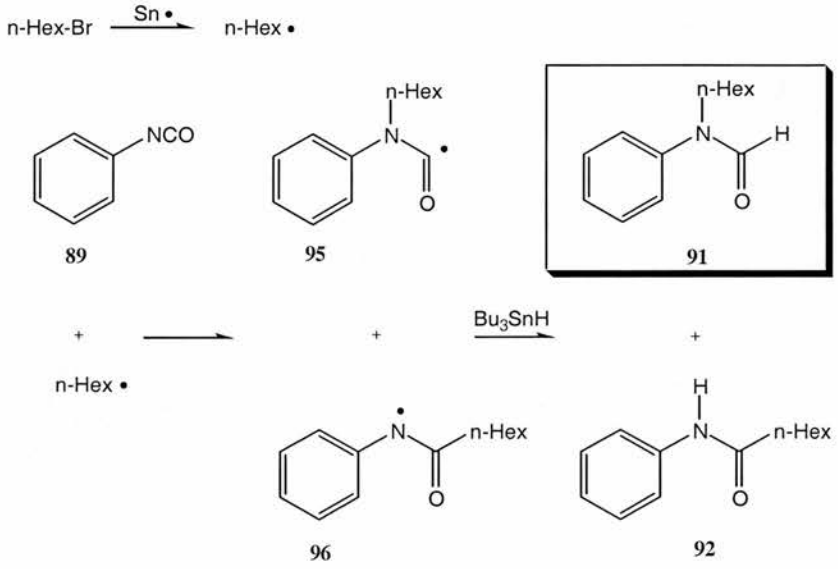
1. 3. Procedure 3 – Solution in toluene, heating with tributyltin hydride

Phenyl isocyanate, 1-bromohexane, AIBN and tributyltin hydride in solution in toluene were mixed in a flask. The solution was heated for 5h under nitrogen at 80° C. For this experiment, the staring materials, tin compounds and aniline were identified. The major product, aniline (fit 993), possibly came from the reduction of phenyl isocyanate with tributyltin hydride. Three products remained unidentified. It is well known that tributyltin hydride can be used as a reducing agent.

1. 4. Procedure 4 – Solution in toluene, photolysis

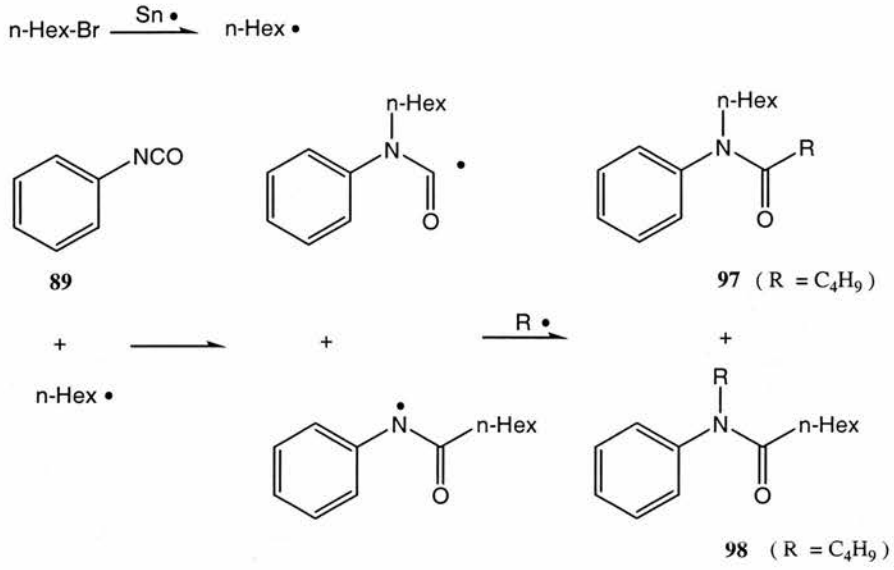
A solution of phenyl isocyanate, 1-bromohexane, AIBN and tributyltin hydride in toluene were photolysed for 5h. The GC-MS showed the presence of the starting materials as well as the presence of aniline, hexyl-phenyl-amine, pentanoic acid

hexyl-phenyl-amide or heptanoic acid phenyl-butyl-amide, *N*-phenyl-*N*-hexyl-formamide (the expected product) and 1,3,5-triphenyl-[1,3,5]triazinane-2,4,6-trione. From the mass spectra, the presence of the mass 119 (M^+- 28) (loss of CO) allowed us to presume that *N*-phenyl-*N*-hexyl-formamide **91** was the only isomer produced during the photolysis. *N*-Phenyl-*N*-hexyl-formamide **91** or heptanoic acid phenylamide **92** could be formed by addition of the hexyl radical either on the nitrogen of the isocyanate moiety or on the isocyanate C-atom respectively (scheme 49).



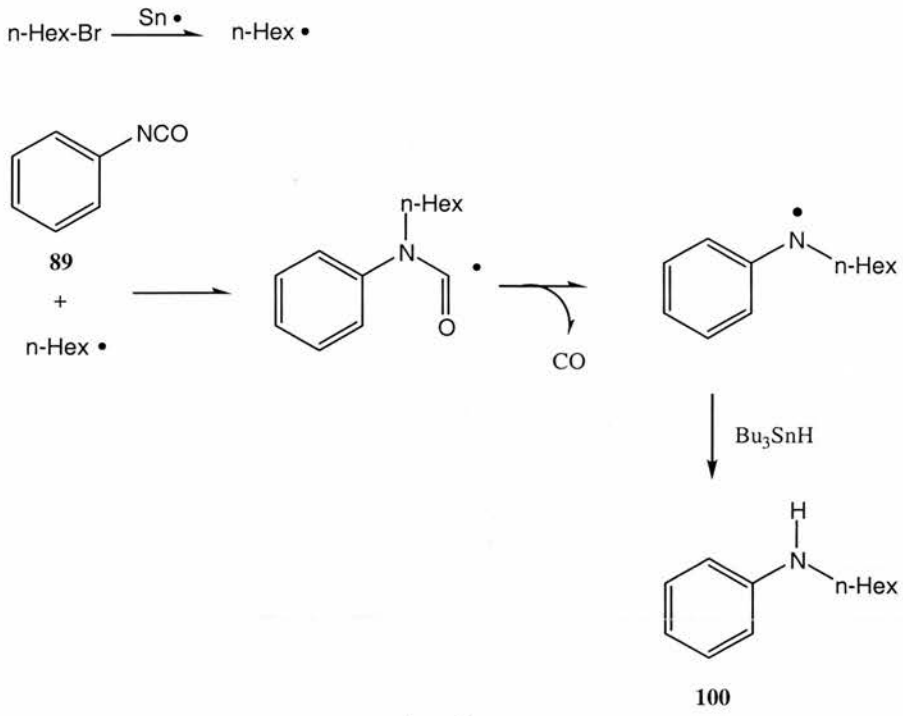
scheme 49

One of the GC-MS peaks with M^+ 261 ($C_{17}H_{27}NO$) might be attributed to pentanoic acid hexyl-phenyl-amide **97** or heptanoic acid phenyl-butyl-amide **98** according to the site of addition of the alkyl radical, either on the C-atom or on the N-atom of the isocyanate moiety. The formation of these compounds could be explained by the following reaction (scheme 50).



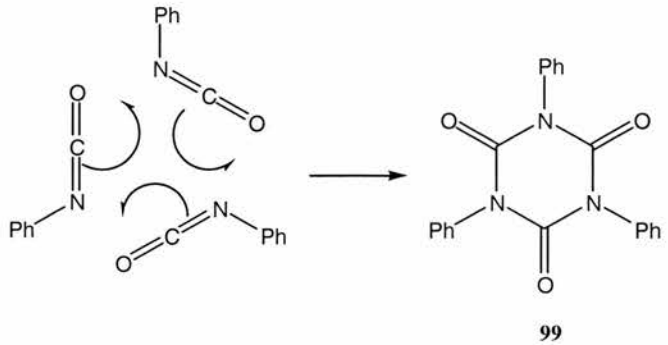
scheme 50

In this particular case, the compounds were formed by addition of the hexyl radical and a butyl radical probably derived from tributyltin hydride. The major fragmentation observed in the GC-MS (M^+- 71) could fit either of the both structures. Hexyl-phenyl-amine was probably formed by hexyl radical addition to the N-atom of the isocyanate followed by loss of CO from the aminoacyl radical (scheme 51).



scheme 51

However, the major product of this reaction was the peak with M^+ 357 ($C_{21}H_{15}N_3O_3$). This peak could be attributed to the cyclic trimer **99**, 1,3,5-triphenyl-[1,3,5]triazinane-2,4,6-trione. On the GC-MS spectrum the presence of two important fragmentations (M^+-119) loss of phenyl isocyanate, PhNCO and (M^+- 238) loss of 2 molecules of phenyl isocyanate were consistent with the structure of the trimer. Its formation could be explained by electrocyclic reaction of three molecules of phenyl isocyanate as illustrated in the scheme 52.



scheme 52

1. 5. Procedure 5 –Slow addition with syringe pump

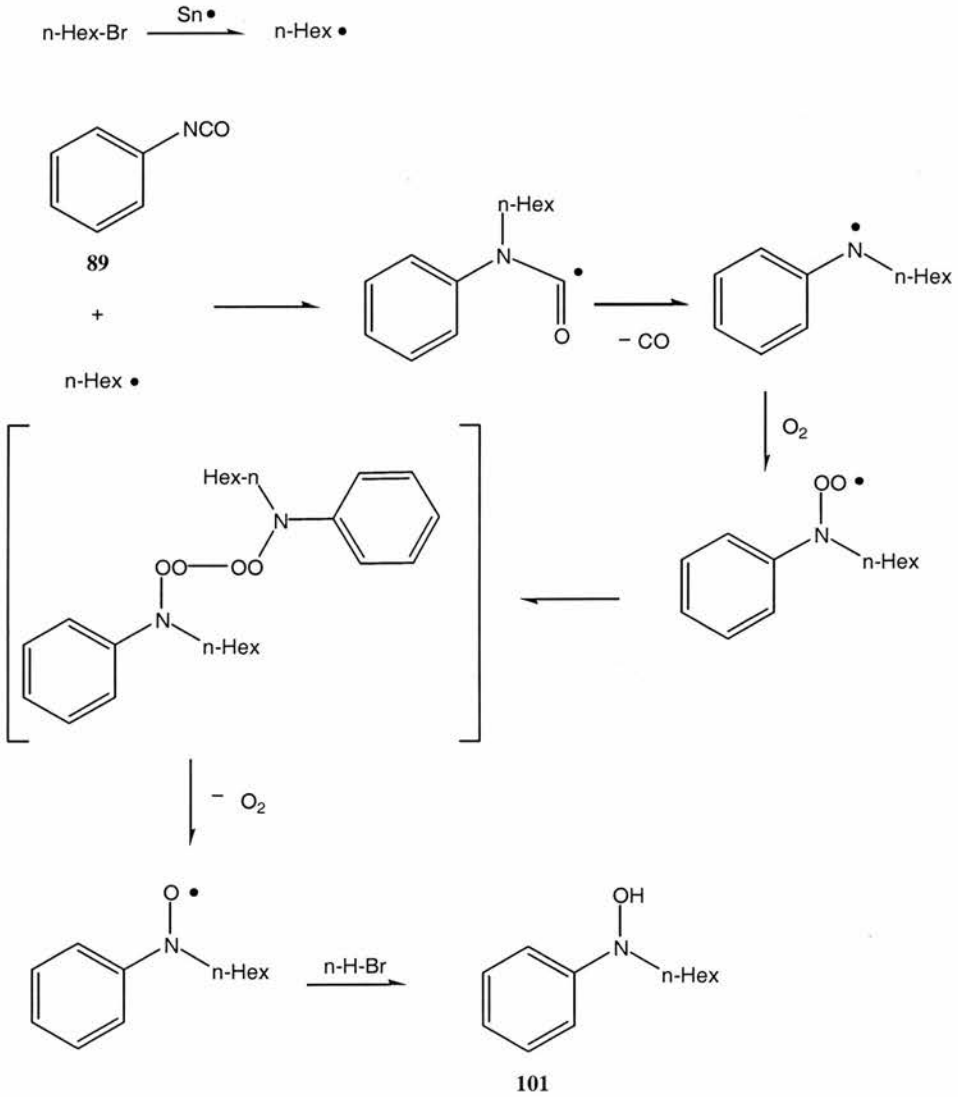
Tributyltin hydride in solution in benzene was slowly added, via the syringe pump, into a solution of phenyl isocyanate, 1-bromohexane, AIBN in benzene. During this time the mixture was photolysed with an UV lamp. The addition lasted for 1h. The photolysis was stopped after an additional 6h. The GC-MS of this reaction showed a complex mixture of compounds including hexane, toluene, aniline, *n*-butylbenzene, hexylbenzene, *N*-phenyl-hexyl-amine and pentanoic acid hexyl-phenyl-amide or heptanoic acid phenyl-butyl-amide. The main product was *N*-phenyl-hexyl-amine, **100**. As mentioned above, the formation of the amine, *N*-phenyl-hexyl-amine could come from the addition of the hexyl radical, followed by elimination of the carbonyl group.

As mentioned above, hexylbenzene came from the reaction between benzene and the hexyl radical, as well as pentanoic acid hexyl-phenyl-amide **97** and heptanoic acid phenyl-butyl-amide **98** was formed by reaction of the hexyl radical and the butyl radical from the tributyltin hydride onto the phenyl isocyanate.

1. 6. Procedure 6 – Slow addition with syringe pump, photolysis at 20cm

Tributyltin hydride in solution in toluene was added, via the syringe pump, into phenyl isocyanate, 1-bromohexane, AIBN (5 %) in toluene. The solution was photolysed for 5h with an UV lamp placed at 20cm from the test tube. The starting materials were recovered after reaction, in presence of tin compounds. Aniline as well as hexyl-phenyl-amine and *N*-hexyl-*N*-phenyl-hydroxylamine have been identified on

the GC-MS chromatogram. The aniline may be formed by reduction of phenyl isocyanate in the presence of *n*-tributyltin hydride. As outlined previously, the formation of the amine, *N*-phenyl-hexyl-amine could come from the addition of the hexyl, followed by elimination of the carbonyl group. The formation of the product with M^+ 193 ($C_{12}H_{19}NO$) could be interpreted in the following way (scheme 53). This GC-MS peak could be attributed to *N*-hexyl-*N*-phenyl-hydroxylamine **101**. Fragmentations due to loss of C_4H_8 (from hexyl chain) (M^+- 56) and OH (M^+- 56- 17) supported this structural assignment.

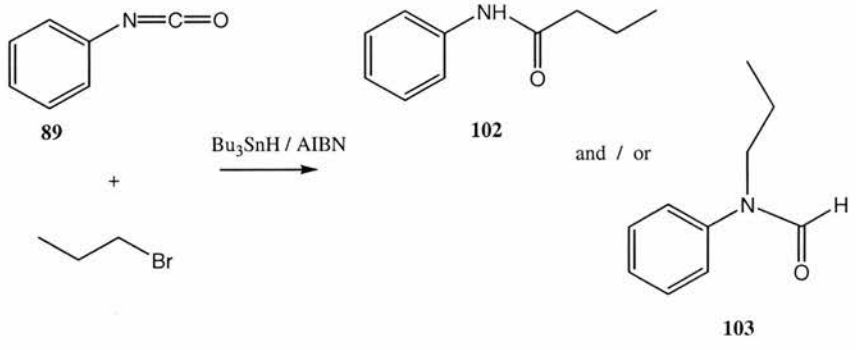


scheme 53

Mostly the same products were obtained for the different conditions. However, in one of the experiments which consisted of photolysing the phenyl isocyanate and 1-bromohexane in presence of AIBN and tributyltin hydride in toluene, the presence of the expected product e.g. *N*-phenyl-*N*-hexyl-formamide **91** was detected. In the majority of the procedures, the hexyl radical added mainly onto the N-atom of the isocyanate group and consequently, the carbonyl group was eliminated to afford *N*-phenyl-hexyl-amine. In this case the alkyl radical added preferentially on the N-atom of the isocyanate moiety.

2. Phenyl isocyanate and 1-bromopropane

The experiment was carried out with the isocyanate and 1-bromopropane which possess a shorter alkyl chain. Thus, a solution of phenyl isocyanate and 1-bromopropane was photolysed in benzene in the presence of tributyltin hydride (scheme 54).

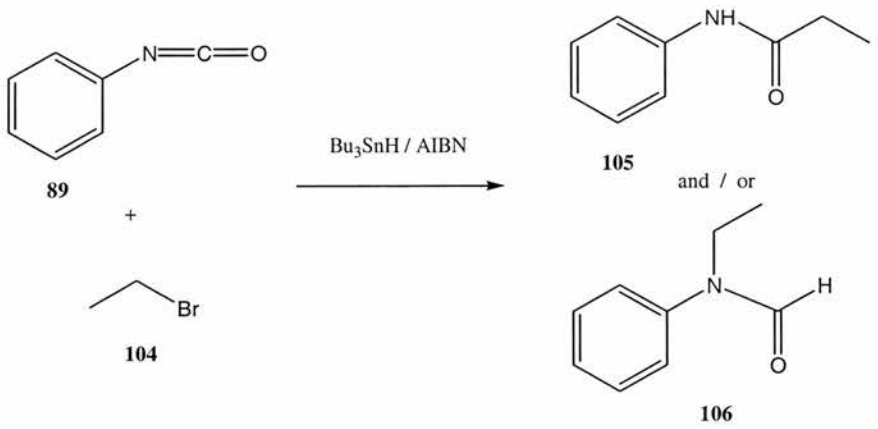


scheme 54

We expected to see the formation of *N*-phenyl-butyramide **103** and *N*-phenyl-*N*-propyl-formamide **102**, which come from the addition of the propyl radical respectively on the C-atom and the N-atom of the isocyanate group. The mixture was checked after 1hour and after 4hours. This experiment was analysed by GC-MS. With the exception of the starting materials, tin compounds and the solvent, the only component identified during the GC-MS analysis was aniline. The conditions chosen didn't allow us to observe any addition of the propyl radical either on the C-atom or the N-atom of the isocyanate moiety.

3. Phenyl isocyanate and 1-bromoethane

The final series of experiments relevant to the intermolecular addition of alkyl radicals onto the isocyanate moiety was carried out with phenyl isocyanate **89** and 1-bromoethane **104**, in the presence of tributyltin hydride.



scheme 55

As outlined in the scheme 55, we expected the products of the intermolecular addition of the ethyl radical onto the isocyanate moiety to be either *N*-phenyl-propionamide

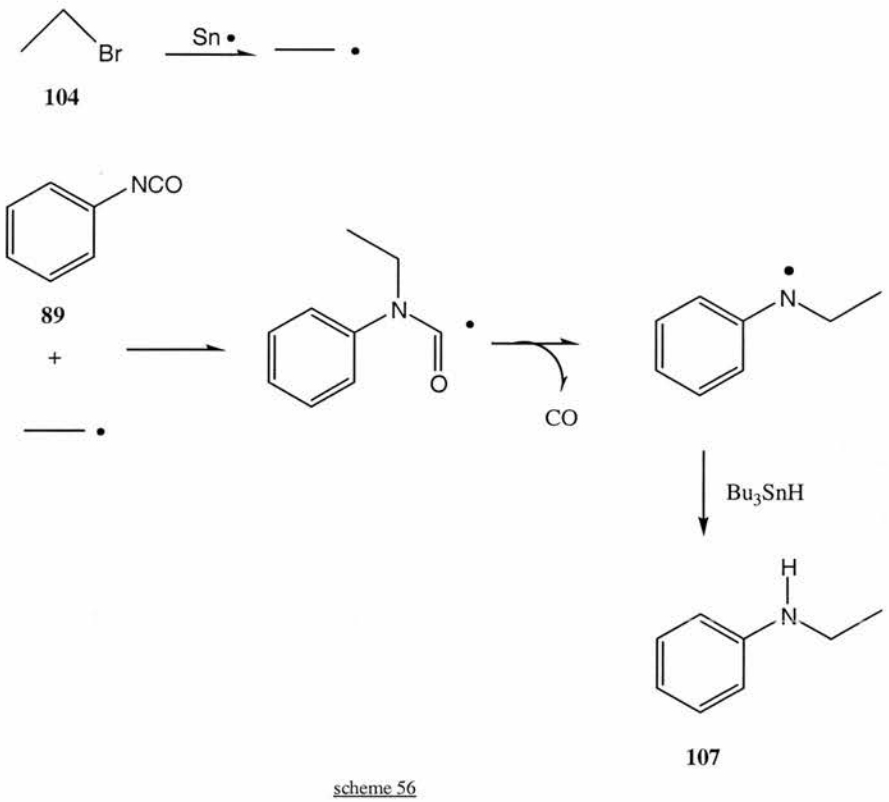
105, which could come from addition of ethyl radical onto the C-atom of the isocyanate group, or *N*-ethyl-*N*-phenyl-formamide **106**, which could come from the addition of the ethyl radical onto the N-atom of the isocyanate moiety. Different procedures were performed. The experiments were analyzed by ^{1}H NMR and GC-MS. The different conditions used and products obtained are summarized in the following table. The tin products, the starting materials and solvent are not mentioned.

Procedures	Reactions	Products[e]	Library fit[a]
1[b]	THF, AIBN, heat 5h, 70 °C, N_2	++Aniline ++++*N*-Phenyl-ethyl-amine	993 998
2	Et_2O (2 mL), UV 5h, RT	++++Aniline	993
3	Et_2O (0.7 mL), UV 3h, 30°C	++++Aniline	993
4	Et_2O (0.7 mL), UV 3h, 33°C	++++Aniline	993
5	Et_2O (0.7 mL), UV 3h, 60°C	++++Aniline	993
6	Et_2O (2 mL), UV 7h, 25 °C	++++Aniline + (1-ethoxyethyl) phenyl amine +*N*-(1-ethoxyethyl)-*N*-phenyl-formamide	993
7	Et_2O (2 mL), UV 7h, 35 °C	++++Aniline +*N*-(1-ethoxyethyl)-*N*-phenyl-formamide	993
8	Et_2O (2 mL), AIBN, UV 7h, 35 °C	++++Aniline + (1-ethoxyethyl) phenyl amine +*N*-(1-ethoxyethyl)-*N*-phenyl-formamide	993
9	Pentane (2 mL), UV 6h, 35 °C	++++Aniline	993
10[c]	Et_2O (400 mL), UV 3h, N_2, 35 °C	++++Aniline +*N*-(1-ethoxyethyl)-*N*-phenyl-formamide	993
11	PhH (2 mL), UV 1h, degas, RT	++++Aniline +1,3,5-triphenyl-[1,3,5]triazinane-2,4,6-trione	993
12[d]	PhH (2 mL), UV 4h, degas, RT	++++Aniline +1,3,5-triphenyl-[1,3,5]triazinane-2,4,6-trione	993

[a] 1000 = exact library fit. [b] One unidentified component. [c] Different procedures were attempted for the removal of tin residues without success, including the use of KF, as described below. [d] two unidentified components.

[e] ++++ major product $\rightarrow$ + minor product

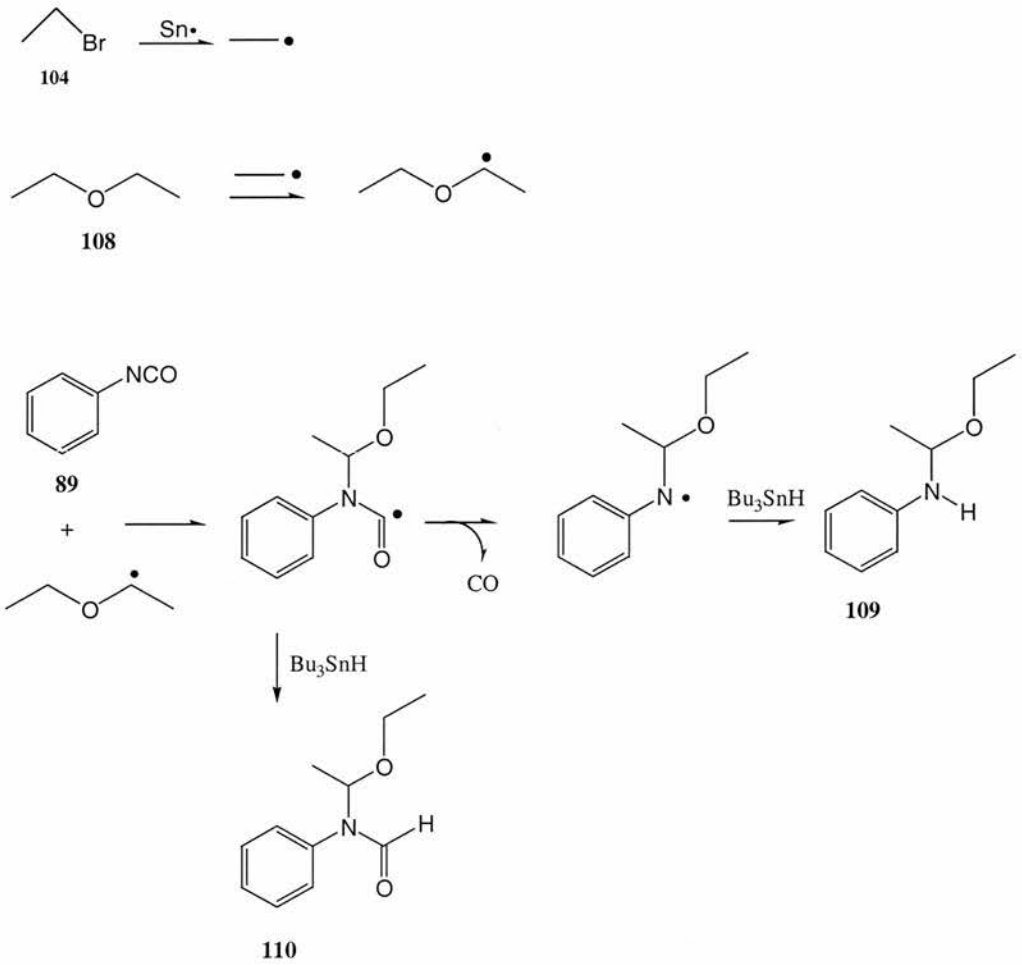
In the first experiment the isocyanate and the bromide were refluxed for 5 hours in dry THF, in the presence of 1.5 equivalent of tributyltin hydride and 0.04 equivalent of AIBN. The GC-MS analysis showed that the major peaks were tin-residues, aniline, and phenyl-ethyl-amine. One of the peaks of the GC-MS spectrum with M^+ 121 ($C_8H_{11}N$) was attributed to *N*-phenyl-ethyl-amine (library fit 998). Two main fragmentations were observed on the mass spectrum, (M^+- 29) (loss of CH_3CH_2) and (M^+- 29 - 27) (loss of CH_3CH_2 and subsequently HCN). As previously, the formation of *N*-phenyl-ethyl-amine **107**, could be explained by addition of the ethyl radical on the nitrogen of the isocyanate moiety followed by elimination of the carbonyl group (scheme 56).



scheme 56

The second experiment consisted in the photolysis for 5h of the isocyanate and the bromide in the presence of tributyltin hydride in ether. The test tube was placed near the lamp. The only product identified was aniline. As outlined in the previous paragraph, aniline likely came from the reduction of the phenyl isocyanate in the presence of tin hydride. In a third group of experiments, phenyl isocyanate and 1-bromoethane in solution in ether were photolysed for 3h in the presence of tributyltin hydride at three different temperatures, 30 °C, 33 °C and 60 °C. The purpose of this series was to study the decarbonylation process, however, aniline was again the only product recovered after reaction. In a fourth series of reactions, phenyl isocyanate and ethyl bromide were photolysed in ether in the presence of tributyltin hydride at 25 °C and 35 °C for several hours. For the first procedure at 25 °C, aniline, (1-ethoxyethyl)-phenyl-amine and *N*-(1-ethoxyethyl)-*N*-phenyl-formamide were identified from the

GC-MS spectra while only aniline and *N*-(1-ethoxyethyl)-*N*-phenyl-formamide were noted on the GC-MS spectrum of the process at 35 °C. On the GC-MS a peak with M^+ 165 ($C_{10}H_{15}NO$) was attributed to (1-ethoxyethyl)-phenyl-amine. The fragmentation (M^+- 45) could be a loss of OCH_2CH_3. Another peak with M^+ 193 ($C_{11}H_{15}NO_2$) could be attributed to *N*-(1-ethoxyethyl)-*N*-phenyl-formamide. The fragmentation (M^+-44) (loss of OCH_2CH_2), (M^+- 44 - 29) (loss of OCH_2CH_2 and subsequently loss of CHO) and (M^+- 73) (loss of $CH_3CH_2OCHCH_3$) were observed on the GC-MS spectrum. (1-Ethoxyethyl)-phenyl-amine **109** and *N*-(1-ethoxyethyl)-*N*-phenyl-formamide **110**, probably come from the reaction between the radical formed from the ether and phenyl isocyanate (scheme 57).



scheme 57

It is likely that the ethoxyethyl radical was formed by ethyl radicals abstracting hydrogen from the solvent **108** at the site adjacent to oxygen. The same experiment was carried out in the presence of AIBN as initiator at 35 °C and the same products e.g., aniline, (1-ethoxyethyl)-phenyl-amine **109** or *N*-(1-ethoxyethyl)-*N*-phenyl-formamide **110**, were obtained. For the ninth procedure which consisted in photolysing a solution of phenyl isocyanate and ethyl bromide in the presence of tin in pentane, the only product detected in the solution mixture was aniline. For the procedure 10 which involved the photolysis of a diluted solution of phenyl isocyanate and ethyl bromide in the presence of tin in ether, the GC-MS spectrum showed the presence of aniline (1-ethoxyethyl)-phenyl-amine **109** or *N*-(1-ethoxyethyl)-*N*-phenyl-formamide **110**. Regarding the last procedures 11 and 12, which consisted of photolysing the phenyl isocyanate and ethyl bromide in solution in benzene in the absence of radical reagent, except the starting material and tin-residues, mainly aniline and the cyclic trimer 1,3,5-triphenyl-[1,3,5]triazinane-2,4,6-trione were observed on the GC-MS spectra. The major product obtained in the overall reactions was aniline.

Independently to the bromide, several products were difficult to identify from only their mass spectra. Product isolation was quite complicated by the presence of non-polar tin-containing material formed as side products in this reaction. Numerous chromatography columns were prepared and eluted with various solvent systems but without success. Each chromatographic fraction was contaminated with tin residues. In addition, the ^{1}H NMR spectra were difficult to analyze because of the presence of tin compounds in the solution. On the NMR spectra the tin-derived resonances obscured the presence of other compounds in the mixtures. Several methods for the

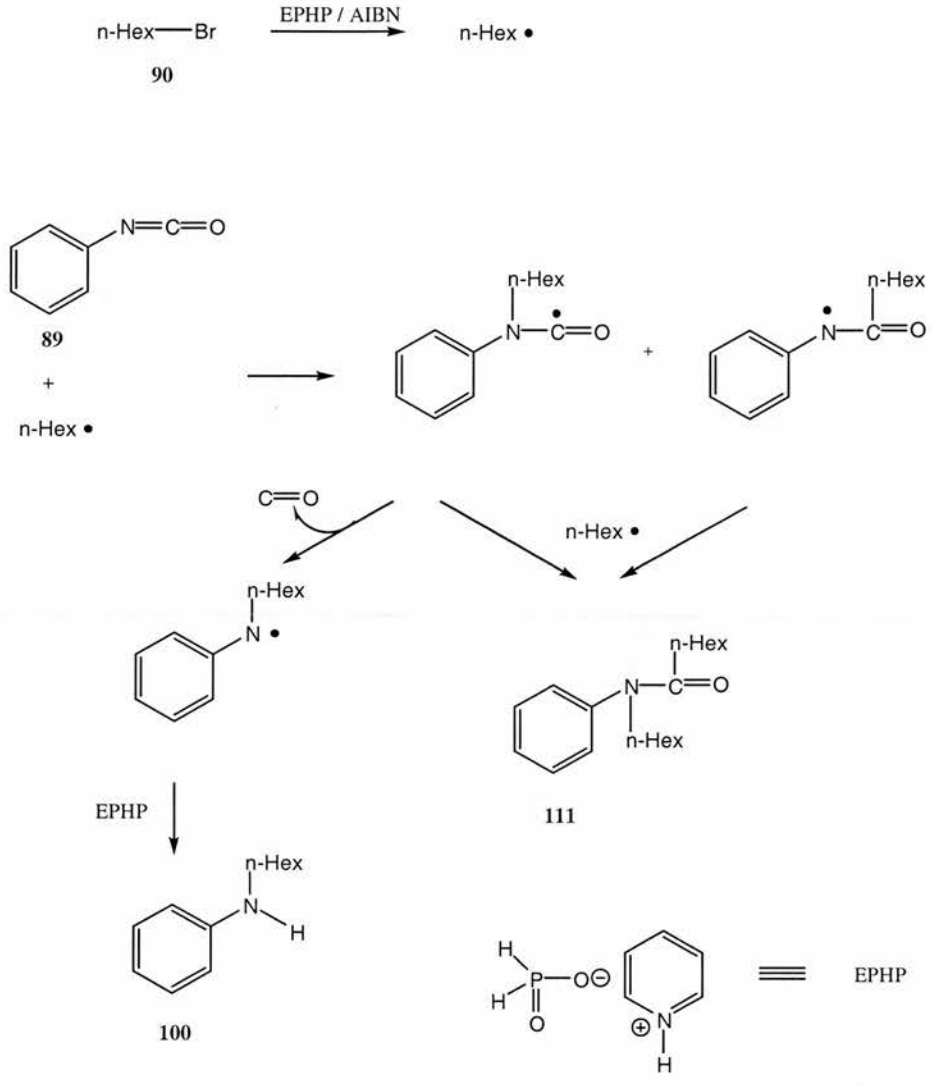
removal of tin residues from reaction mixtures have been described.[1-8] So, several procedures were carried out to remove the tin residues. A simple solution was to wash several times with saturated aqueous solution of potassium fluoride until no more precipitation of the flocculent polymeric tri-*n*-butyltin fluoride was observed. The separate organic phase was then dried and solvent removed in the normal manner. A second method consisted of carrying out the same procedure and subsequently running a column with hexane as eluent, expecting the remaining tin compound to elute first leaving the product still on the column. A third method for removal of tin halides involved adding carbon tetrachloride to the cooled reaction mixture. In this way tri-*n*-butyltin chloride is produced from the hydride. A dilute solution of iodine in ether is then added until a faint coloration persists indicating that cleavage of any hexabutyldistannne to tri-*n*-butyl iodide has occurred. The organic solvent is then removed in *vacuo* and the residue taken up in diethyl ether and washed several times with saturated aqueous solution of potassium fluoride until no more precipitation is noticed. The organic phase is then dried and the solvent removed under vacuum.

All these methods were tried. Despite this, in each case, some tin-derived residues remained in the reaction mixture, preventing a clear reading of the proton NMR spectra. The best solution as this point was to try to use a substitute to palliate the inconvenience encountered during the use of organotin hydride. Water-soluble tin reagents developed by Breslow[1, 9] and Collum[2] as well as the polymer-supported tin reagents of Neumann[10] have gone some way to improve matters although the use of these methods has been limited. Silicon-based radical chain carriers such as tristrimethylsilylsilane[11, 12] (TTMSS) provide an effective alternative to tin reagents although these compounds are often costly. Graham and Murphy[13] have reported the use of phosphorus-centered radicals derived from H_3PO_2 and its salt 1-ethylpiperidine

hypophosphite (EPHP) in radical cyclisations onto various alkene side-chain units of both aryl iodide and aryl bromide substrate. This reagent could be an alternative to the use of tributyltin hydride.

4. Reaction between phenyl isocyanate and 1-bromohexane with EPHP

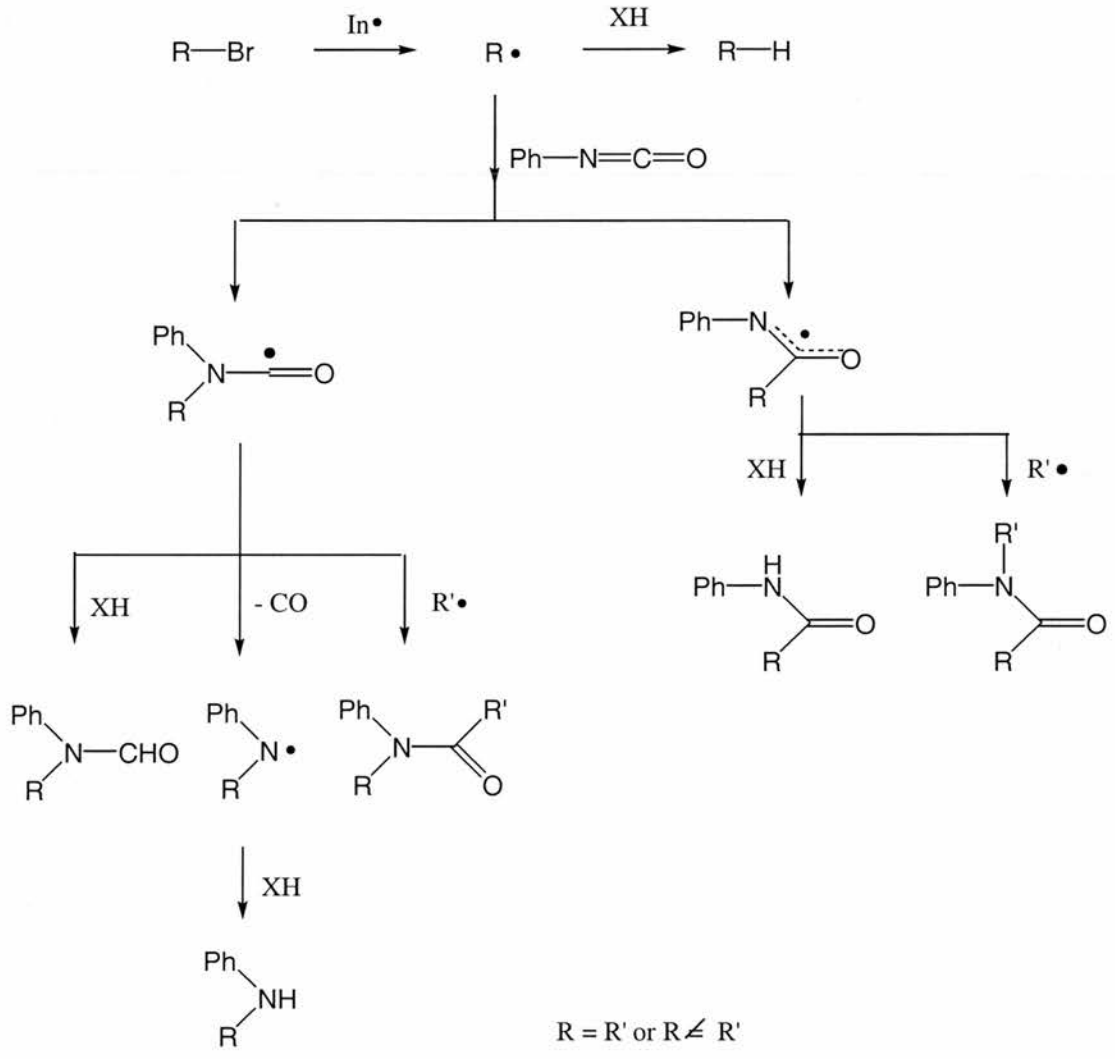
For the reason defined above, the reaction between phenyl isocyanate and 1-bromohexane was repeated using EPHP instead of tributyltin hydride. The procedure used was similar to that reported by Graham and Murphy[13] for the formation of carbon-carbon bonds. The substrates were treated with EPHP in refluxing benzene in the presence of AIBN followed by aqueous work-up (scheme 58).



scheme 58

As the NMR was not conclusive enough, a GC-MS of the mixture was carried out. Except the peaks of the solvent and the starting materials, the main products observed were *N*-n-hexyl-*N*-phenyl-heptanamide and *N*-phenyl-hexyl-amine. *N*-phenyl-hexyl-amine was the major product of the solution mixture. As outlined in the example with the use of tributyltin hydride, this product might come from the addition of a hexyl radical onto the nitrogen of the isocyanate group followed by elimination of the CO moiety. *N*-n-hexyl-*N*-phenyl-heptanamide could come from the addition of two hexyl radicals onto the isocyanate group as shown in scheme 58.

Irrespective of the initiator, conditions and the bromide, the same reactions happened during the intermolecular addition of alkyl radicals onto the isocyanate group. A general mechanism could be drawn, as shown in the scheme 59, to summarize the formation of the products and by-products when phenyl isocyanate and alkyl bromide were put in solution in the presence of tributyltin hydride or other radical reagent.



scheme 59

The alkyl radical formed can add either on the C-atom or the N-atom of the isocyanate group. When it adds on the C-atom, either a hydrogen or another radical

present in the solution can add on the imidyl radical newly formed. Whereas, when the addition occurs on the N-atom of the isocyanate moiety, either another radical present in solution or a hydrogen can add onto the radical newly formed, or the radical can lose the carbonyl and be hydrogenated.

III- Experimental

^{1}H NMR spectra were obtained using Bruker AM 300 MHz, a Bruker Avance 300, and Varian Gemini 2000 spectrometers. The Bruker Avance 300 is fully automated with autosampling robots. All samples were dissolved in deuterated chloroform, unless otherwise stated, using Me_4Si as an internal standard. The chemical shifts δ were given in ppm downfield from Me_4Si. 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). TLC was performed on pre-coated plates of silica gel G-60 F-254 (Merck). Column chromatography was performed using BDH silica gel (40-63 μm) eluting with the given solvent mixture.

1. Reaction between phenyl isocyanate and 1-bromohexane with Bu_3SnH

1. 1. Procedure 1– Photolysis of solution in benzene without degassing

A solution of phenyl isocyanate (0.015 g, 0.12 mmol), 1-bromohexane (0.021 g, 0.12 mmol), AIBN (5 %) and tributyltin hydride (0.037 g, 0.12 mmol) in benzene (0.5 mL)

was photolysed with a 400 W medium pressure UV lamp at ambient temperature. After 4 hours, the solvent was removed under vacuum. A portion of the crude product was anlysed by GC-MS analysis. GC-MS: **Peak 106**, hexane, m/z(%) 86(8), 69(7), 71(9), 57(100), 43(80), 41(71), 39(42), 27(23); **Peak 315**, unidentified, m/z(%) 98(3), 85(10), 71(15), 57(59), 43(100), 41(70), 39(22), 29(68), 27(60). The only product observed was hexane.

1. 2. Procedure 2 – Photolysis of solution in benzene after degassing

A solution of phenyl isocyanate (0.015 g, 0.12 mmol), 1-bromohexane (0.021 g, 0.12 mmol), AIBN (5 %) and tributyltin hydride (0.037 g, 0.12 mmol) in benzene (0.5 mL) was degassed by bubbling N_2 for 30 minutes. The mixture was photolysed with a 400 W medium pressure UV lamp at ambient temperature. After 4 hours, the solvent was removed under vacuum. A sample of the reaction mixture was submitted for analysis by GC-MS. GC-MS: **Peak 244**, C_7H_5NO, unidentified, 119(8), 93(100), 78(5), 66(70), 63(16), 54(11), 52(18), 47(11), 39(50), 28(40), 18(48), 15(5); **Peak 263**, C_7H_7NO, *N*-phenyl-formamide (library fit 996) m/z(%) 121(100), 94(91), 76(3), 61(61), 51(12), 34(23), 28(6); **Peak 469**, unidentified, m/z(%) 162(5), 91(34), 77(5), 65(10), 51(8), 43((12), 32(5), 27(20), 18(100); **Peak 741**, unidentified, m/z(%) 269(22), 213(15), 177(12), 155(18), 121(8), 57(24), 41(60), 29(100), 18(22). The major product identified was *N*-phenyl-formamide.

1. 3. Procedure 3 – Solution in toluene, heating with tributyltin hydride

Phenyl isocyanate (0.25 g, 2 mmol), 1-bromohexane (0.35 g, 2 mmol), AIBN (5 %) and tributyltin hydride (0.64 g, 1.1 eq) in solution in toluene (2 mL) were heated for

5h under a nitrogen atmosphere at 80 °C. Chromatography column, Hexane/EtOAc (1:3). ^{1}H NMR (second fraction) δ_H 0.8-1.0 (m), 1.2-1.5 (m), 1.5-1.8 (m), 3.05 (t, J = 6.8), 3.25 (t, J = 10.2), 4.1-4.2 (m), 4.1-4.4 (m), 6.4-6.7 (m), 6.9-7.1 (ArH, m), 7.1-7.6 (ArH, m). A portion of the second fraction was submitted for analysis by GC-MS. GC-MS: **Peak 247**, m/z(%) unidentified, 137(19), 107(5), 95(2), 93(4), 85(20), 69(7), 65(3), 55(35), 43(88), 29(53), 27(100), 18(20), 15(7); **Peak 270**, aniline, m/z(%) 93(100), 92(10), 78(2), 66(29), 65(10), 39(8), 28(3);**Peak 292**, unidentified, m/z(%) 94(4), 80(3), 77(2), 69(80), 54(36), 41(100), 39(60), 37(8), 27(54), 18(19), 15(25); **Peak 1037**, unidentified, m/z(%) 269(12), 211(6), 177(12), 155(8), 121(9), 57(30), 41(42), 29(60), 18(100). The major product observed was aniline.

1. 4. Procedure 4 – Solution in toluene, photolysis

A solution of phenyl isocyanate (5 μg, 0.04 mmol), 1-bromohexane (6.9 μg, 0.04 mmol), AIBN (5 %) and tributyltin hydride (12.80 μg, 0.04 mmol) in toluene (0.5 mL) was photolysed for 5 h with a 400 W medium pressure UV lamp at ambient temperature. The reaction was carried out under a nitrogen atmosphere. A sample of the reaction mixture was analysied by GC-MS. GC-MS: **Peak 135**, aniline; **Peak 260**, $C_{12}H_{19}N$, m/z(%) 177(11), 163(12), 134(8), 120(7), 106(100), 93(8), 77(10), 65(15), 51(18), 39(28), 29(36), 18(11), 15(15) (probably *N*-phenyl-hexyl-amine); **Peak 355**, unidentified, m/z(%) 220(25), 205(100), 145(13), 115(7), 105(8), 91(7), 67(7), 57(19); **Peak 385**, *N*-phenyl-*N*-hexyl-formamide, m/z(%) 205(9), 177(17), 133(10), 118(24), 106(100), 91(6), 77(15), 57(33), 51(5); **Peak 508**, $C_{17}H_{27}NO$, m/z(%) 261(17), 190(100), 120(44), 106(29), 91(5), 77(11), 55(5), 43(26) (probably pentanoic acid hexyl-phenyl-amide or heptanoic acid phenyl-butyl-amide) **Peak 583**, unidentified, m/z(%) 339(20), 268(100), 198(40), 184(23), 119(10), 105(8), 55(10);

Peak 700, $C_{21}H_{15}N_3O_3$, m/z(%) 357(40), 281(2), 238(5), 207(8), 145(3), 119(100), 91(23), 77(4), 64(8), 51(3) (probably 1,3,5-triphenyl-[1,3,5]triazinane-2,4,6-trione). The major product observed was the cyclic trimer 1,3,5-triphenyl-[1,3,5]triazinane-2,4,6-trione.

1. 5. Procedure 5 –Slow addition with syringe pump

Tributyltin hydride (22 μL, 0.07 mmol) in solution in benzene (2 mL) was slowly added, via the syringe pump, into a solution of phenyl isocyanate (4.56 μL, 0.04 mmol), 1-bromohexane (5. 9μL, 0.04 mmol), AIBN (5 %, 0.33 mg, 0.002 mmol) in benzene (2 mL). During this time the mixture was photolysed with an UV lamp. The addition lasted for 1 h. The photolysis was stopped after an additional 6 h.

GC-MS: **Peak 143**, toluene, m/z(%) 92(80), 91(100), 89(5), 65(23), 63(20) 51(25), 45(15), 39(72), 27(15); **Peak 159**, hexane; **Peak 259**, aniline; **Peak 283**, *N*-phenyl-formamide; **Peak 335**, $C_{10}H_{14}$, m/z(%), 134(20), 115(2), 105(6), 91(100), 77(10), 65(22), 51(12), 39(35), 27(45), 18(7) (probably *n*-butyl benzene); **Peak 528**, hexyl-benzene, m/z(%) 162(17), 133(4), 105(3), 91(100), 77(10), 65(12), 51(8), 43(40), 29(48), 18(11); **Peak 758**, $C_{17}H_{27}NO$, m/z(%) 261(15), 205(14), 177(5), 147(16), 120(16), 93(16), 77(15), 65(8), 57(18), 51(13), 41(42), 29(65), 18(100); **Peak 763**, $C_{12}H_{19}N$, probably *N*-phenyl-hexyl-amine. Traces of several unidentified components were also observed. However the major products observed were aniline and *N*-phenyl-formamide.

1. 6. Procedure 6 – Slow addition with syringe pump, photolysis at 20cm

Tributyltin hydride (12.8 μg, 0.04 mmol) in solution in toluene was added, via the syringe pump, into phenyl isocyanate (5 μg, 0.04 mmol), 1-bromohexane (6.9 μg, 0.04 mmol), AIBN (5 %) in toluene (0.5 mL). The solution was photolysed for 5 h with an UV lamp placed at 15cm from the test tube.

GC-MS: **Peak 225**, aniline; **Peak 603**, $C_{12}H_{19}N$, probably *N*-phenyl-hexyl-amine; **Peak 657**, $C_{12}H_{19}NO$, m/z(%) 193(6), 137(8), 120(13), 93(38), 77(15), 65(20), 57(28), 51(12), 41(55), 29(100), 18(68) (probably *N*-Hexyl-*N*-phenyl-hydroxylamine).

Traces of several unidentified components were also present. Nevertheless the major product observed was *N*-Hexyl-*N*-phenyl-hydroxylamine.

2. Reaction between phenyl isocyanate and 1-bromopropane

Phenyl isocyanate (0.25 g, 2.1 mmoles), 1-bromopropane (0.26 g, 2.1 mmoles), tributyltin hydride (0.6 g, 2.1 mmoles) in solution in benzene (2 mL) were photolysed for 1h. GC-MS: **Peak 151**, aniline. After further 3h of photolysis, GC-MS: **Peak 155**, aniline.

3. Reaction between phenyl isocyanate and 1-bromoethane

3.1. Procedure 1

Phenyl isocyanate (1 g, 8.4 mmol), 1-bromoethane (0.91 g, 8.3 mmol), tributyltin hydride (3.66 g, 12.5 mmol) and AIBN (5%) in solution in THF (30 mL) were heated for 5h under a nitrogen atmosphere at 70 °C. ^{1}H NMR (crude product) δ_H 0.9-1 (m),

1-1.4 (m), 1.4-1.8 (m), 2.2-2.3 (m), 2.35, (s), 2.45 (t, J = 7.3), 3.6 (br), 3.85 (t, J = 7.3), 4.1-4.4 (m), 6.6-6.8 (m), 6.9-7.6 (arH, m), 7.9 (br), 8.1 (s), 8.2 (s), 8.3 (s), 8.4 (s), 8.7 (d, J = 11.0Hz). GC-MS: **Peak 285**, aniline, **Peak 313**, $C_8H_{11}N$, unidentified, m/z(%)121(4), 94(3), 69(100), 54(18); **Peak 504**, *N*-phenyl-ethyl-amine (lib fit 998), m/z(%), 121(100), 93(94), 66(58), 51(11).

3.2. Procedure 2

Phenyl isocyanate (18.4 μL, 0.17 mmol), 1-bromoethane (12.5 μL, 0.17 mmol), tributyltin hydride (50 μL, 0.20 mmol) in solution in ether (1 mL) were photolysed for 5h. GC-MS: **Peak 158**, aniline.

3.3. Procedure 3, 4, 5

Phenyl isocyanate (18.4 μL, 0.17 mmol), 1-bromoethane (12.5 μL, 0.17 mmol), tributyltin hydride (50 μL, 0.20 mmol) in solution in ether (0.7 mL) were photolysed for 3h. The test tube was immerged in an oil bath at 30 °C. GC-MS: **Peak 158**, aniline. The same experiment was repeated at 33 °C and 60 °C. Identical results were obtained.

3.4. Procedure 6

Phenyl isocyanate (18.4 μL, 0.17 mmol), 1-bromoethane (12.5 μL, 0.17 mmol), tributyltin hydride (46 μL, 0.17 mmol) in solution in ether (2 mL) were photolysed for 7h. The test tube was immerged in an oil bath at 25 °C. GC-MS: **Peak 158**, aniline; **Peak 356**, $C_{10}H_{15}NO$, m/z(%) 165(88), 137(5), 120(14), 119(10), 109(5), 106(59),

93(100), 77(17), 69(8), 65(25) (probably (1-ethoxyethyl)-phenyl-amine); **Peak 402**, $C_{11}H_{15}NO_2$, m/z(%) 193(23), 149(35), 120(13), 93(49), 73(100), 65(14), 51(6) (probably *N*-(1-ethoxyethyl)-*N*-phenyl-formamide).

3.5. Procedure 7

Phenyl isocyanate (18.4 μL, 0.17 mmol), 1-bromoethane (12.5 μL, 0.17 mmol), tributyltin hydride (46 μL, 0.17 mmol) in solution in ether (2 mL) were photolysed for 7h. The test tube was immerged in an oil bath at 35 °C. GC-MS: **Peak 163**, aniline; **Peak 405**, $C_{11}H_{15}NO_2$, *N*-(1-ethoxyethyl)-*N*-phenyl-formamide).

3.6. Procedure 8

Phenyl isocyanate (18.4 μL, 0.17 mmol), 1-bromoethane (12.5 μL, 0.17 mmol) and tributyltin hydride (46 μL, 0.17 mmol) in the presence of AIBN (5 %) in solution in 2 mL of ether were photolysed for 7h. The test tube was immerged in an oil bath at 35 °C. GC-MS: **Peak 160**, aniline; **Peak 354**, $C_{10}H_{15}NO$, (1-ethoxyethyl)-phenyl-amine; **Peak 402**, $C_{11}H_{15}NO_2$, propably *N*-(1-ethoxyethyl)-*N*-phenyl-formamide).

3.7. Procedure 9

Phenyl isocyanate (18.4 μL, 0.17 mmol), 1-bromoethane (12.5 μL, 0.17 mmol) and tributyltin hydride (46 μL, 0.17 mmol) in solution in pentane (2 mL) were photolysed for 6h. The test tube was immersed in an oil bath at 35 °C. After reaction, a sample of the reaction mixture was submitted for analysis. GC-MS: **Peak 151**, aniline; **Peak 426**, $C_{11}H_{15}NO_2$, probably *N*-(1-ethoxyethyl)-*N*-phenyl-formamide.

3.8. Procedure 10

Phenyl isocyanate (0.925 mL, 8 mmoles), 1-bromoethane (0.625 mL, 8 mmoles), tributyltin hydride (2 mL, 1.1 eq) in solution in ether (400 mL) were photolysed for 3h. A sample of the solution mixture was submittedfor analysis by proton NMR and GC-MS.

^{1}H NMR (crude product) δ_H 0.70–0.95 (13H, m), 1.20-1.35 (15H, m), 1.35-1.50 (2H, m), 1.50-1.75 (5H, m), 2.25 (2H, s), 3.55 (2H, br), 6.55-6.8 (2H, m), 6.9-7.15 (2H, m), 7.15-7.30 (2H, m). GC-MS: **Peak 172**, aniline, **Peak 405**, $C_{11}H_{15}NO_2$, probably *N*-(1-ethoxyethyl)-*N*-phenyl-formamide. The main product was aniline.

The reaction mixture was worked up for the removal of tin residues.

Tin-removal procedure 1

The reaction mixture was diluted in diethyl ether and washed four times with saturated aqueous solution of potassium fluoride until no more precipitation of the flocculent polymeric tri-*n*-butyltin fluoride was observed. The separate organic phase was then dried and the solvent removed under vacuum. A ^{1}H NMR was performed but is still the same, tin residues were still present in the mixture.

Tin-removal procedure 2

The solution was diluted with ether and washed several times with a saturated aqueous solution of potassium fluoride until no precipitate of tri-*n*-butyltin fluoride appeared in the solution. The separate organic phase was then dried the solvent removed under vacuum and subsequently the mixture was passed through a column and eluted with hexane/EtOAc (1:3). It was expected that any tin compound would

elute first, leaving the product still on the column. Two fractions were recovered but both of them were contaminated with tin residues.

Tin-removal procedure 3

Carbon tetrachloride was added to the cooled reaction mixture. In this way tri-*n*-butyltin chloride is produced from the hydride. A dilute solution of iodine in diethyl ether was added until a faint coloration persists indicating that cleavage of any hexabutyldistannne to tri-*n*-butyl iodide has occurred. The organic solvent was then removed in *vacuo* and the residue taken up in diethyl ether and washed six times with a saturated aqueous solution of potassium fluoride until no more precipitation was noticed. The organic phase was dried and the solvent removed under vacuum. The proton NMR showed that a significant amount of tin residues was still present despite the procedure.

On the GC-MS remained the same appeared trace of different unidentified components because of the reaction between the compounds in the mixture and fluoride or iodine.

3.9. Procedure 11

Phenyl isocyanate (0.25 g, 2.1 mmoles), 1-bromoethane (0.24 g, 2.1 mmoles), tributyltin hydride (0.6 g, 1 eq) in solution in benzene (2 mL) were photolysed for 1 h after being degassed for 15 minutes. A portion of the reaction mixture was analysed by GC-MS. GC-MS: **Peak 143**, aniline, **Peak 666**, $C_{21}H_{15}N_3O_3$, probably 1,3,5-triphenyl-[1,3,5]triazinane-2,4,6-trione.

3.10. Procedure 12

Similar to procedure 11, the solution was degassed for 15 minutes and photolysed for 4h. A sample of the solution mixture was analysed by GC-MS. GC-MS: **Peak 82**, m/z(%), 106(34), 91(100), 77(8), 65(8), 51(8); **Peak 142**, aniline, **Peak 257**, m/z(%) 161(5), 147(21), 132(35), 119(100), 104(49), 91(16), 77(94), 65(5), 51(29); **Peak 673**, $C_{21}H_{15}N_3O_3$, probably 1,3,5-triphenyl-[1,3,5]triazinane-2,4,6-trione.

4. Reaction between phenyl isocyanate and 1-bromohexane with EPHP

Phenyl isocyanate (0.1 g, 0.84 mmol), 1-bromohexane (0.14 g, 0.84 mmol), and EPHP (1.5 g, 10 eq) in solution in benzene (30 mL) were heated for 1 h under a nitrogen atmosphere at 70 °C. AIBN (0.05 g) was added in two portions over 30 minutes and reflux continued for 72 h. On cooling, the reaction was diluted with petroleum ether and washed successively with sodium hydrogen carbonate, aqueous hydrochloric acid (2M), sodium hydrogen carbonate and brine. The organic layer was then dried over magnesium sulfate, filtered and concentrated in *vacuo*. The solution mixture obtained was submitted for analysis by proton NMR and GC-MS. ^{1}H NMR (crude product mixture) δ_H 0.7 (s), 0.8-1 (m), 1.2-1.7 (m), 1.75 (s), 1.9 (s), 2 (s), 2.3-2.4 (m), 2.45 (t, J = 7.0), 3.13 (t, J = 7.0), 3.23 (t, J = 7.0), 3.65 (t, J = 7.0), 6.6 (d, J = 10.5), 6.65 (t, J = 7.7), 6.95 (d, J = 10.5), 7.15 (t, J = 7.7), 7.3 (s), 7.4 (s). GC-MS: Peak **484,** $C_{12}H_{19}N$, probably *N*-phenyl-hexyl-amine; Peak **558**, unidentified, m/z(%) 277(8), 221(100), 204(7), 177(20), 150(23), 106(64), 57(14); Peak **580**, unidentified, m/z(%) 274(100), 193(25), 178(12), 160(15), 149(35), 134(18), 121(19), 96(9), 69(12), Peak **613**, $C_{19}H_{31}NO$, m/z(%) 261(17), 190(100), 120(35), 106(23), 77(6) (probably *N*-n-hexyl-*N*-phenyl-heptanamide).

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Chapter 3

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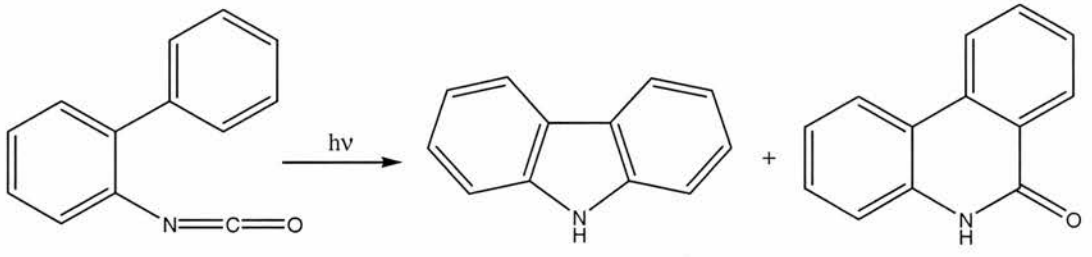
INTRAMOLECULAR ADDITION TO AROMATIC ISOCYANATES

I- Introduction

Aromatic isocyanates are extremely common in the polymer industry, as they are the basic blocks of polyurethanes. The photochemical loss of nitrogen to form the singlet nitrene reaction has been well characterized. Indeed, like organic azides, isocyanates on irradiation represent a potential source of nitrenes. However, not only the dissociation of the RN-CO bond occurs but also the scission of the R-NCO bond. On the other hand, in direct photolysis, the NCO radical seems to abstract hydrogen. During the direct irradiation of methyl isocyanates[1], isocyanic acid is formed.

The ring closure reactions of isocyanates have not been investigated to any significant extent. However, Swenton[2] examined the photochemistry of 2-biphenylisocyanate **112**. The two major products isolated from its direct photolysis in ether (γ A 250 nm) were the corresponding carbazole **113** in 50 % relative yield and the phenanthridone **114** in 33 % relative yield.

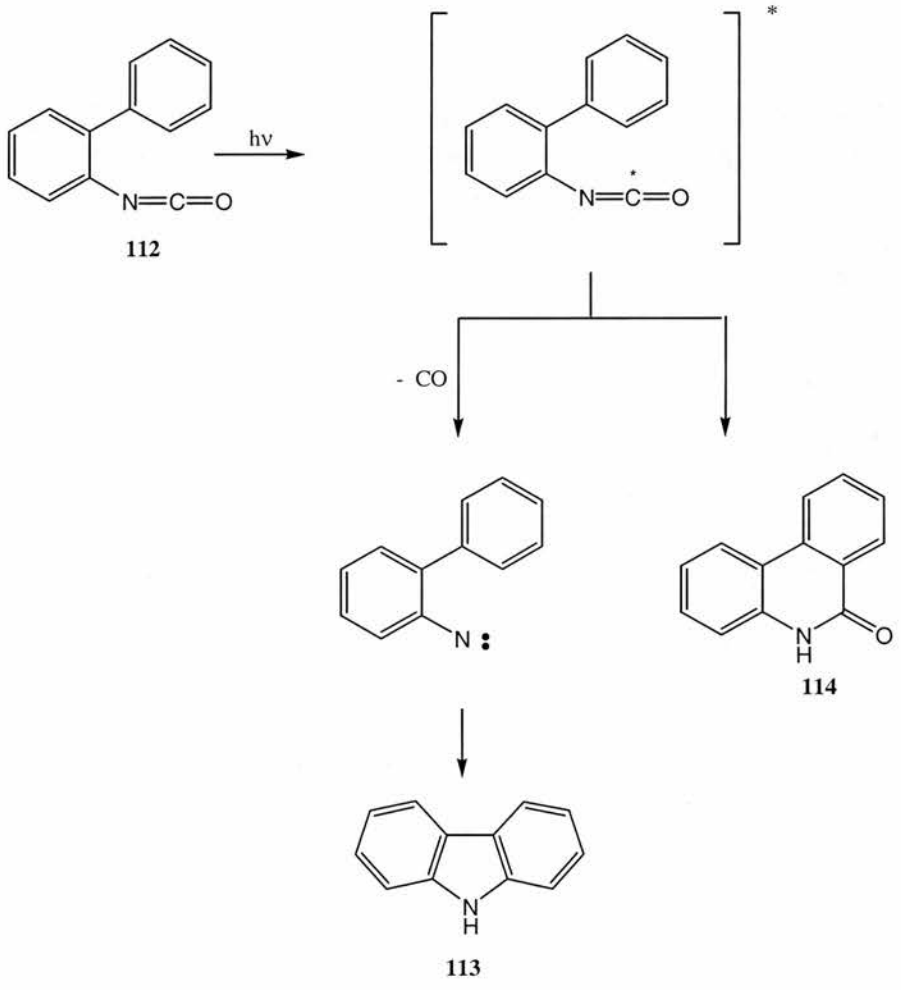


112 **113** **114**

scheme 60

It was not shown that the carbazole **113** was formed from the singlet nitrene, even though the result is consistent with the observed photochemistry of the related 2-

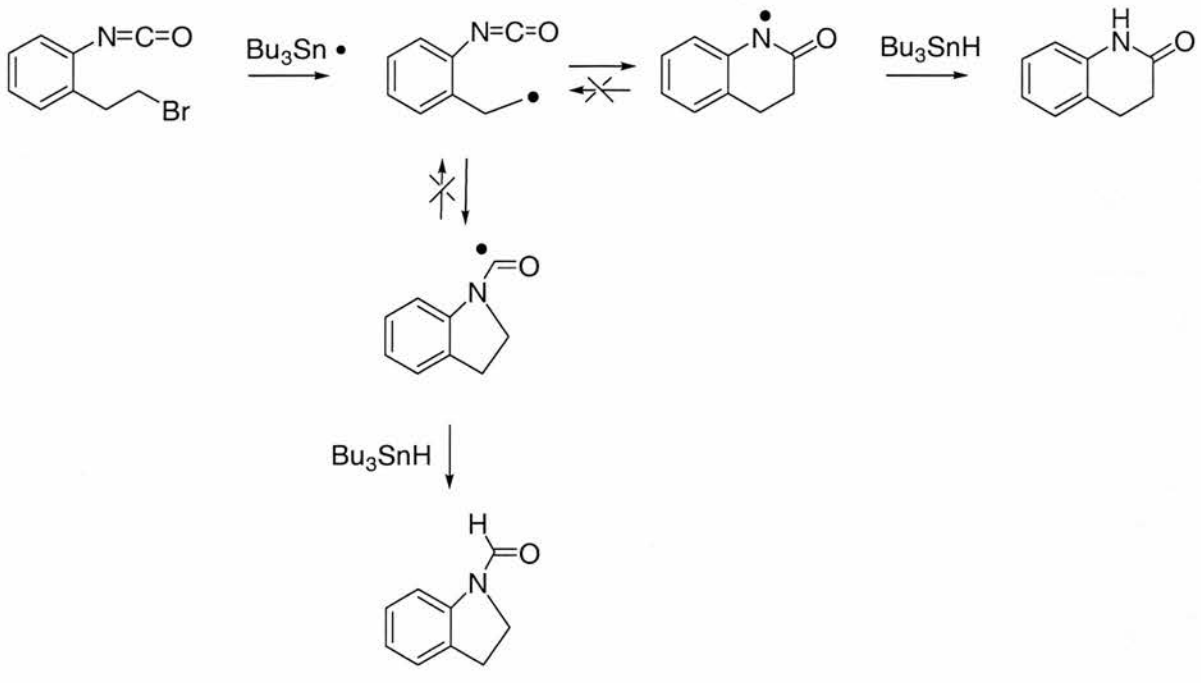
biphenylazide. It was shown that the 2-biphenylisocyanate quenches a variety of ketones. This suggested that the triplet energy is below that of typical ketones and that there is sufficient spin-orbit coupling to allow formation of the compound **114**.



scheme 61

Thus, after our study of intermolecular addition of alkyl radicals to isocyanates, the intramolecular addition of a C-centered radical onto the isocyanate group was next investigated. Following Merenyi's[3, 4] discovery of the fast (reverse) cyclisation in the equilibrium between succinimidyl and its ring-opened derivative the β-(isocyanatocarbonyl) ethyl radical, **2,** our first method for stabilizing ring closure, via

introduction of an aromatic ring, has been studied. The ring closure reaction of the 2-bromoethylphenyl isocyanate has been examined. The idea is illustrated in the scheme below.

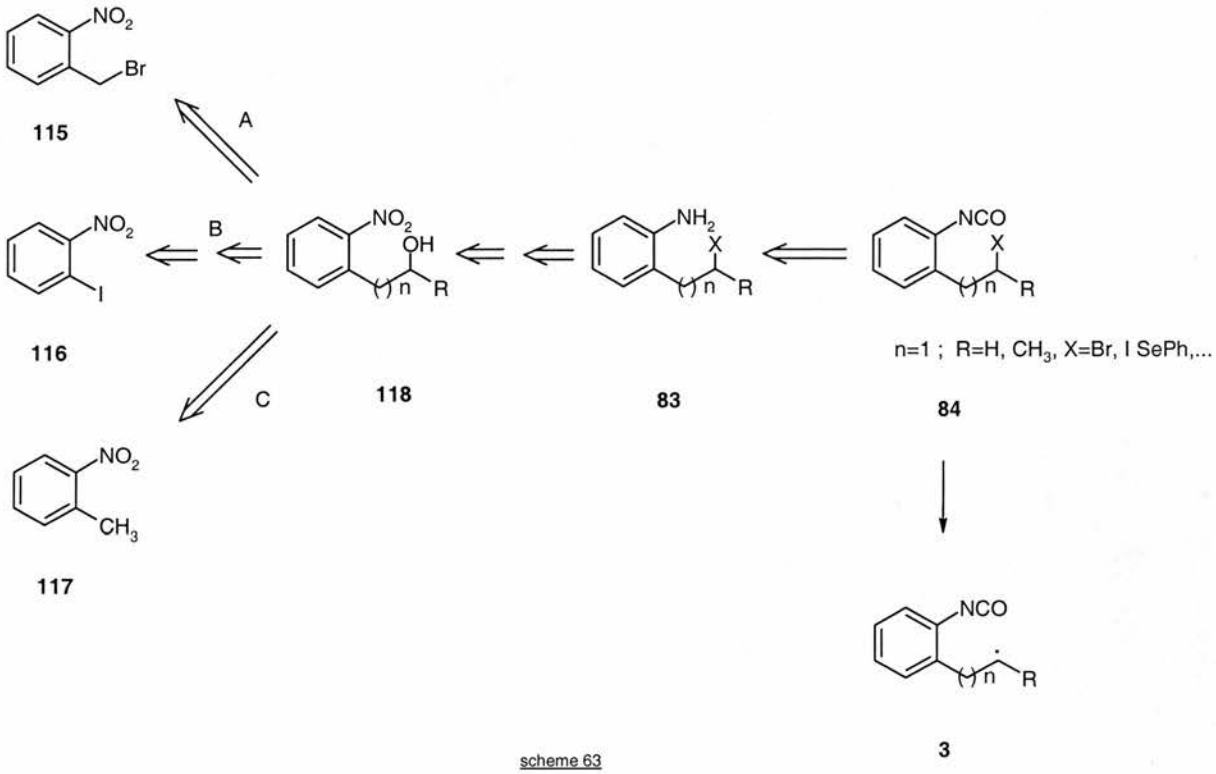


scheme 62

We believed that the alkyl radical formed after abstraction of the bromine would add either on the carbon atom or the nitrogen atom of the isocyanate moiety. We anticipated that the unpaired electron in the quinolinyl radical would be delocalised into the aromatic ring and that this would lead to thermodynamic stabilisation of this species, thus favoring this mode of ring closure. The cyclised radicals thus obtained would pick up hydrogen from tin hydride to afford the corresponding quinolin-2-one and/or *N*-formylindole.

II- Results and discussion

2-Alkyl aromatic isocyanates **84,** are appropriate precursors to generate the radical **3**.



scheme 63

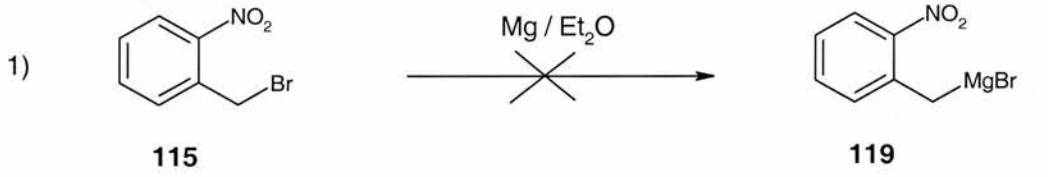
This precursor **84** can potentially be obtained from the 2-aminoaryl halide or selenide **83**. X should be a good leaving group. The most common method for the preparation of isocyanates is by action of phosgene on the corresponding amine. Thus, the precursor **84** could be synthesized according to the scheme outlined above, by reduction of the corresponding nitro compound **118**. Following this option, nitroaryl alcohol **118** might be prepared by different routes A, B or C (n = 1 and R = CH_3 or

H). We attempted to obtain the best experimental conditions for synthesis of **84** and analogues.

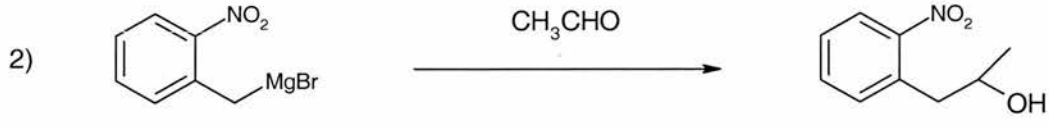
1. Attempts to synthesise 2-nitroaryl alcohol (118)

1.1. Route A: 2-nitroaryl alcohol from 2-nitrobenzyl bromide

With the aim of making the precursor **84** for n = 1 and R = CH_3, the compound **118a** might be obtained directly by the Grignard reaction[5] of 2-nitrobenzyl bromide **115** and acetaldehyde.



115 **119**



119 **118a**

The introduction of iodine in the solution in the first step enabled us to verify that the Grignard reagent **119** wasn't formed. There was no discoloration after the solution was stirred overnight. The halide **115** didn't react with the magnesium. After addition of the aldehyde and work-up of the reaction, the NMR spectrum confirmed that compounds **119** and **118a** were not formed. Unchanged starting material was obtained

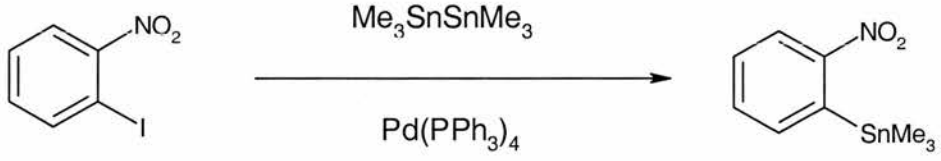
instead. The reason could be that the presence of the 2-nitro group might interfere with the attack of the magnesium on the bromo-compound. Also 2-nitrobenzyl bromide **115** is sterically hindered because of the proximity of the 2-nitro group to the bromine atom.

1.2. Route B: 2-nitroaryl alcohols from 1-iodo-2-nitrobenzene

With the intention of preparing the 2-alkyl aromatic isocyanate **84** for n = 1 and R = H, we attempted a step by step approach from 1-iodo-2-nitrobenzene **116** according to the routes outlined below.

*1.2.1. Preparation of trimethyl (2-nitrophenyl) stannane **120***

The following reaction was tested using a procedure due to Azizian[6, 7] for the *para*- and *meta*-derivatives.

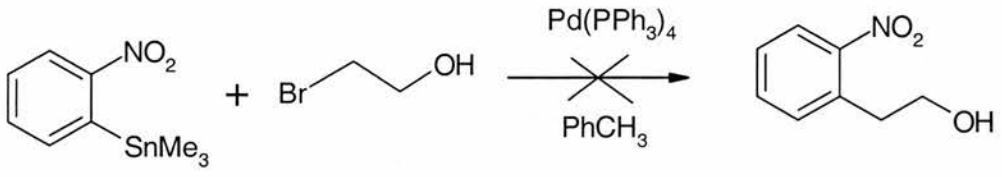


116 **120**

Trimethyl (2-nitrophenyl) stannane **120** was obtained by the action of hexamethylditin on 1-iodo-2-nitrobenzene **116** in the presence of the palladium-based catalyst, tetrakis-(triphenylphosphine) palladium. This reaction yielded 57 % of pure product after distillation at reduced pressure.

*1.2.2. Preparation of 2-(2-nitrophenyl) ethanol **118***

The alcohol **118** was potentially accessible by Stille reaction of the arylstannane with an alkyl halide, by following the procedure described by Devine.[8]



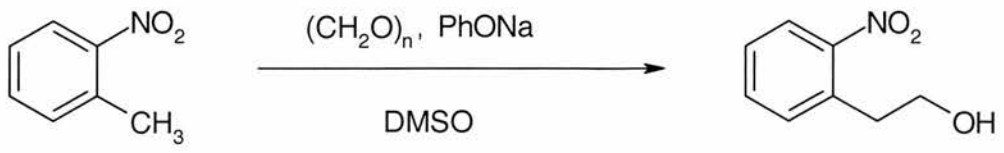
120 **118**

In this particular case, it was the reaction between trimethyl (2-nitrophenyl) stannane **120** and 2-bromoethanol. However, attack of the halide on the stannane derivative failed. After 24h under reflux, TLC indicated no disappearance of the halide. We attempted to continue with the procedure, but the NMR spectrum confirmed these results. The halide didn't react with the starting material.

This result could be attributed to the presence of the nitro and the methyl groups in the starting material. Trimethyl (2-nitrophenyl) stannane **120** is a sterically congested molecule because of the presence of these two groups.

1.3. Route C: 2-nitroaryl alcohol from 2-nitrotoluene

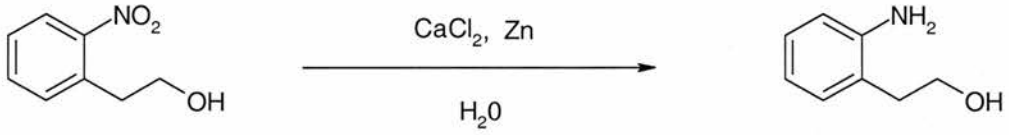
Our next approach to make the nitro precursor of the amino compound **83**, involved another more restrictive method described by Morimoto[9] in his patent.



117 **118**

2-(2-Nitrophenyl) ethanol was obtained by the action of paraformaldehyde on 2-nitrotoluene **117** with sodium phenoxide as base. In the literature the author reported a 91 % yield but the best yield obtained in our work was 37 %. Although this previous procedure was tested several times varying some parameters of the reaction such as doubling the reaction time, the yield remained the same. The alcohol was not formed in very large amount. The yield must be influenced by some other factors.

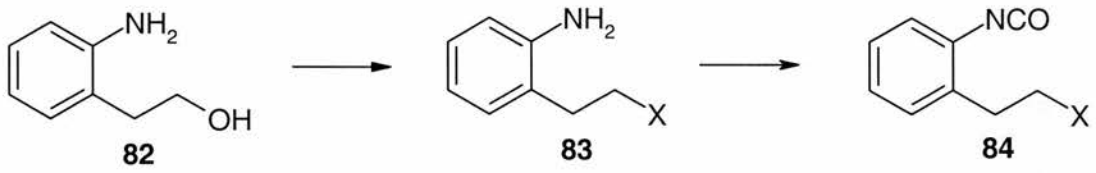
2. Preparation of 2-(2-aminophenyl) ethanol (82)



118 **82**

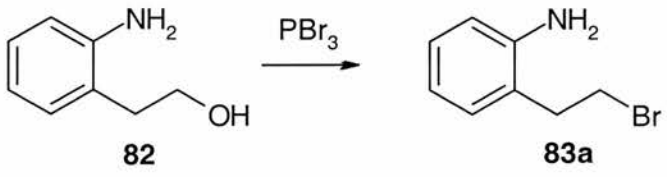
The above procedure was described by Sabetay.[10] 2-(2-Aminophenyl) ethanol **82** was prepared by the reduction of the corresponding nitro compound **118** with calcium chloride and zinc in the aqueous phase. This process yielded 78 % of the pure product in the shape of a yellow oil. The yield increased with the amount of starting material. When the water was removed, a mixture of sodium chloride and oil remained in the bottom of the flask. The more important the amount of oil is, the greater the yield.

3. Preparation of the amine (83) precursor of the isocyanate (84)



Because the amino group is very sensitive in acid and basic condition, several methods were attempted for the conversion of the amino alcohol **82** into a suitable precursor **83** of the aromatic isocyanate **84**, i.e. X = Br, I, SePh...etc.

3.1. Method A: for X = Br with PBr_3, preparation of 2-(2-bromoethyl) phenylamine (83a)

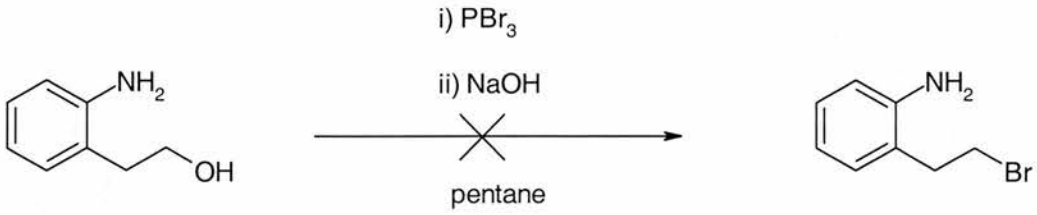


This reaction consists in the preparation of the bromide **83a** (X = Br) by action of phosphorus tribromide. To afford the compound **83a** different procedures were attempted.

3.1.1. Procedure 1

This first procedure was attempted in two different solvents, benzene and pentane.

3.1.1.1. Preparation of 2-(2-bromoethyl) phenylamine **83a** in pentane

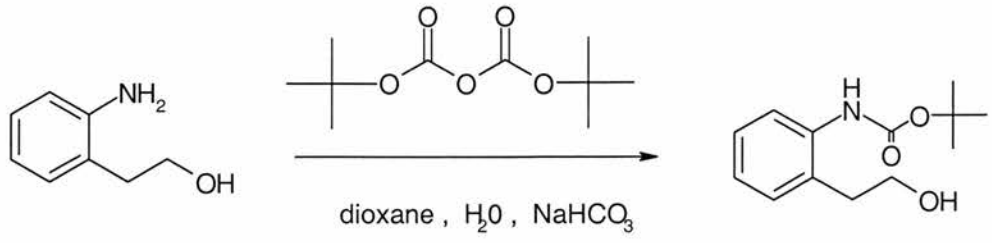


82 **83a**

2-(2-Bromoethyl) aniline **83a** was synthesized by bromination[11] of the corresponding alcohol **82** with phosphorus tribromide in pentane. NaOH was added to release the hydrobromide salt in solution. Some trace of products was obtained after extraction, enough for a NMR spectroscopy. However, the NMR spectrum showed a complex mixture was formed but not the desired product. This method was quite destructive. A problem could be that the amino group underwent some nucleophilic attack producing by-products.

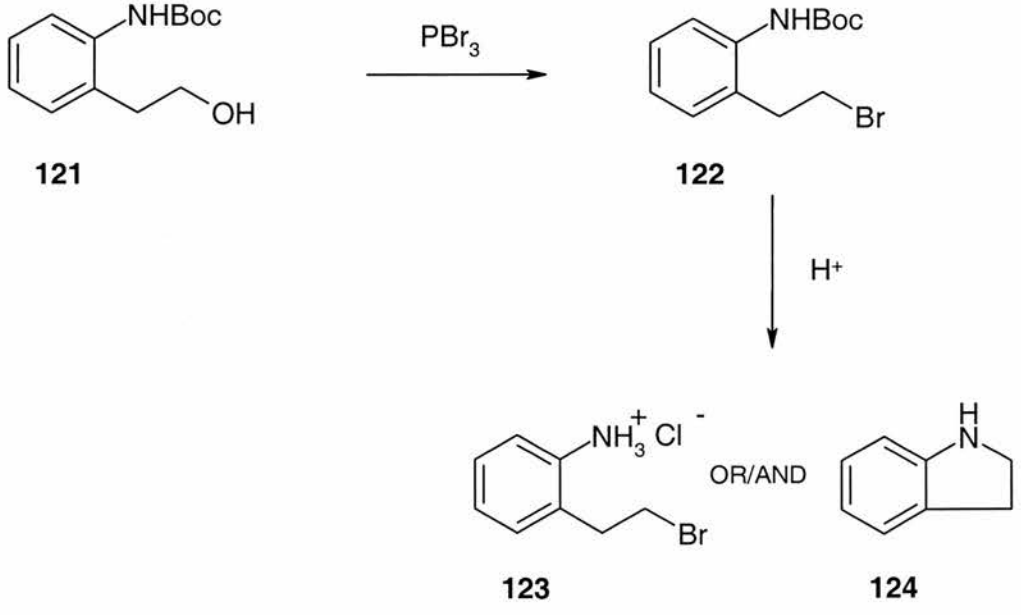
3.1.1.2. Bromination of 2-(2-((*tert*-butyloxycarbonyl) amino) phenyl) ethanol **121**

Since the direct bromination[11] of 2-(2-aminophenyl) ethanol **82**, didn't enable clean product to be obtained from the reaction, we opted to modify the synthetic procedure. To synthesize the bromide **83a** (X = Br) a possible solution was to protect[12] the amino group of the amine **82** with di-*tert*-butyl dicarbonate or *di*-Boc as showed in the scheme below.



82 **121** 72%

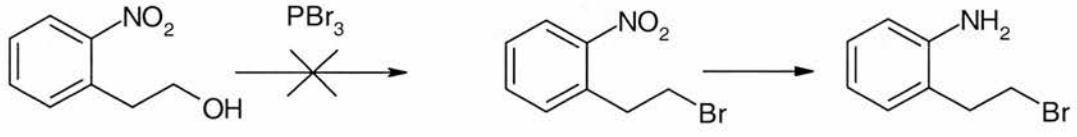
Bromination [13] of the compound **121** was carried out by action of phosphorus tribromide and pyridine in pentane. The NMR and IR spectra showed that the compound **122** was formed. But after deprotection[12] of the amino group with hydrochloric acid, a complex mixture was obtained. The product formed was insoluble in $CDCl_3$, so the NMR was carried out in D_2O. The product could be the salt, compound **123**, or the product of an intramolecular cyclisation, compound **124**. But the NMR spectrum suggested that the product **124** was predominant.



121 **122** **123** **124**

As indicated above, during the deprotection of the amino group, the acid introduced in the flask might react with the amino group to form the hydrochloride salt **123**. Or another possibility, an intramolecular nucleophilic substitution of the bromide by the amino group presumably occurred to give **124**.

3.1.1.3. Bromination of 2-(2-nitrophenyl) ethanol **118**



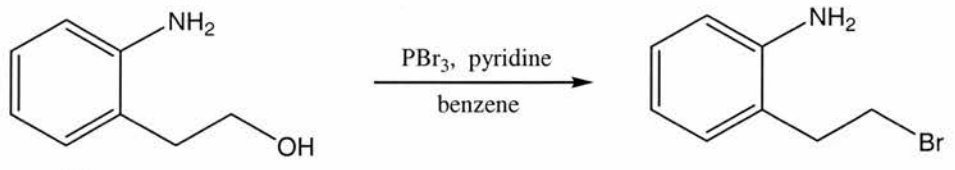
118 **125** **83a**

As the direct bromination with PBr_3 of 2-(2-aminophenyl) ethanol **82** was not successful, another option was chosen. The sequence commenced with the bromination of the corresponding nitro compound and this was to be followed by the reduction of the product to afford the 2-(2-bromoethyl) aniline **82**. The product of bromination might be obtained by action of PBr_3 on the nitro compound **118** in pentane. But the GC-MS showed that the starting material was returned. The bromination didn't produce the expected bromide, **125**. As with the previous procedure, using solely phosphorus tribromide didn't work, we have tried to use phosphorus tribromide in the presence of a basic catalyst such as pyridine.

3.1.2. Procedure 2

We attempted to prepare 2-(2-bromoethyl) aniline **83a** by action of phosphorus tribromide in presence of pyridine in benzene. The same experiments were repeated using this new condition.

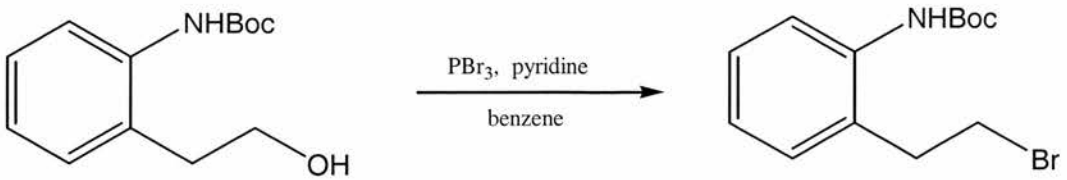
3.1.2.1. Direct bromination of 2-(2-aminophenyl) ethanol **82**



82 **83a**

2-(2-Bromoethyl) aniline **83a** was synthesized by bromination[11] of the corresponding alcohol **82** with phosphorus tribromide in benzene freshly distilled, in presence of pyridine as a base. The reaction was conducted under a nitrogen atmosphere. The product was obtained as an oil, which crystallized the next morning in the flask. However, purification of this crude product wasn't successful. The product decomposed during distillation.

3.1.2.2. Bromination of 2-(2-((*tert*-butyloxycarbonyl) amino) phenyl) ethanol **121**

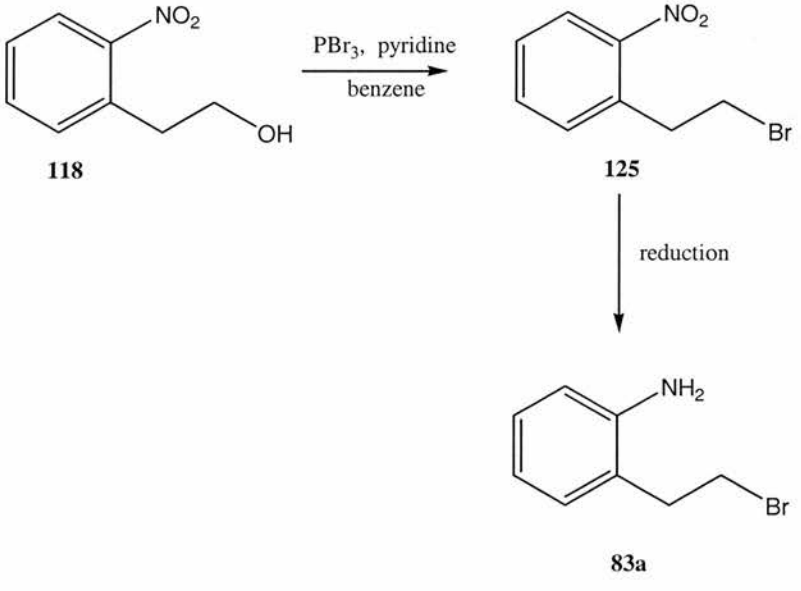


121 **122**

The bromination[13] of protected compound **121** by action of phosphorus tribromide and pyridine in benzene was next examined. The NMR spectra showed that traces of the bromide were present in the mixture obtained but no attempt was made to isolate compound **122** from the complex mixture because the amount of product detected on the spectra was not significant enough to go on with this procedure.

3.1.2.3. Bromination of 2-(2-nitrophenyl) ethanol **118**

With the aim of finding a clean synthetic method, a third option was the bromination of the corresponding nitro compound **118** using the same pathways as previously. 2-(2-Bromoethyl) aniline might be produced followed by reduction of the corresponding nitro compound **125** to afford the expected bromide **83a**.



118 **125** **83a**

scheme 64

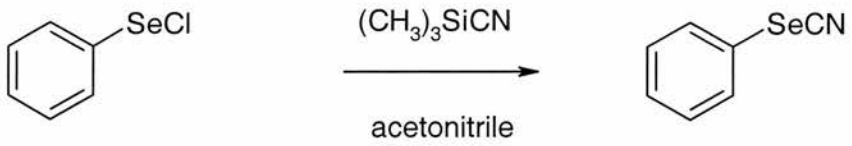
However, as before, the bromination of the nitro compound **118** using PBr_3, in presence of pyridine was not successful.

3.2. Method B: for X = SePh

To avoid nucleophilic cyclisation reactions, and others, we chose as an alternative to replace the bromine by a phenylselenide group. For this method, we attempted to synthesize the selenide **83b** (X = SePh).

3.2.1. Method 1 (reagent = PhSeCN)

The selenide **83b** (X = SePh) might be prepared by action of phenyselenocyanate on the corresponding alcohol. The most useful way for the preparation of phenylselenocyanate was to use of lithium cyanide, but this compound was unavailable, so it was replaced by trimethylsilyl cyanide. According to the method of Clive,[52] phenylselenocyanate **127**, was prepared by nucleophilic substitution of the chloride of phenylselenochloride **126** by cyanide in acetonitrile, yielding 87% of the product.



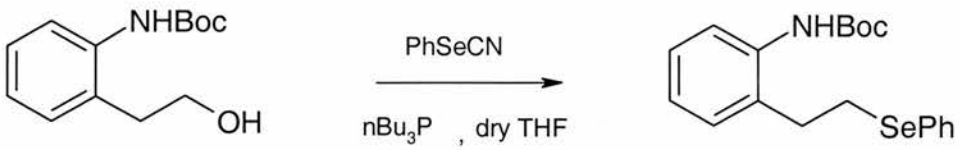
87%

126 **127**

3.2.1.1. Preparation of [1-(phenylseleno) ethyl] 2-(2-((*tert*-butyloxycarbonyl) amino) phenyl) ethanol **128**

Owing to the presence of the amino group, to avoid the formation of an undesirable product, we opted to start from the protected amino compound. The deprotection of the amino group will be required to obtain the corresponding amino compound **83b**.

Following the procedure described by Harpp,[14] compound **128** was obtained by action of phenylselenocyanate on 2-(2-((*tert*-butyloxycarbonyl) amino) phenyl) ethanol **121**, in dry conditions. The reaction was applied directly with the protected amine because, as the above results show, it is a very sensitive functional group.

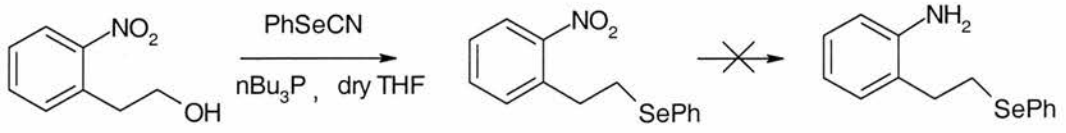


121 **128**

The reaction was stirred at room temperature for two days and followed by TLC. The chromatographic results showed that the product wasn't formed. Also, after chromatography and NMR analysis of each fraction, the Boc group was shown to be absent. This group had been removed during the reaction and lost during the work up.

3.2.1.2. Preparation of [1-(phenylseleno) ethyl] 2-(2-nitrophenyl) ethanol **129**

A second solution was to start the reaction from the nitro compound **118** and then to reduce the product **129**, to produce the selenide **83b**. The procedure was the same as that for the previous reaction, described by Harpp.[14]



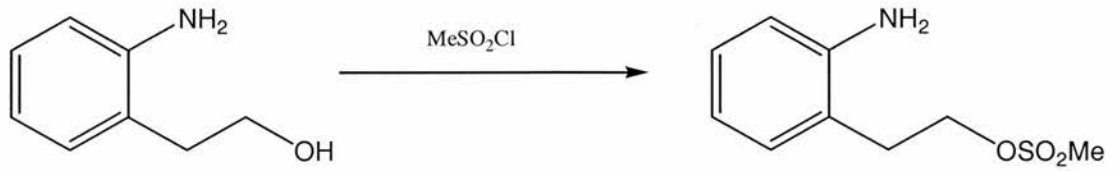
118 **129** **83b**

A complex mixture was obtained after reaction of phenylselenocyanate with the nitro compound **118**. Neither the NMR spectra nor the GC-MS spectra enabled clear conclusions to be drawn. However, since no clean product could be obtained we decided not to proceed with this pathway.

3.2.2.Method 2 (reagent = PhSeNa)

A second way of preparing the selenide compound **83b**, for X = SePh, could be by action of sodium phenylselenide on the corresponding alcohol. One condition required is that amino-alcohol **82** should have a good leaving group. The reaction in question is a nucleophilic substitution between a leaving group and phenylselenide. Thus, in order to prepare the selenide, the alcohol has to be changed to another group such as a halide or a mesylate. As the preparation of the halide has already been attempted, the synthesis of the mesylate was the other option.

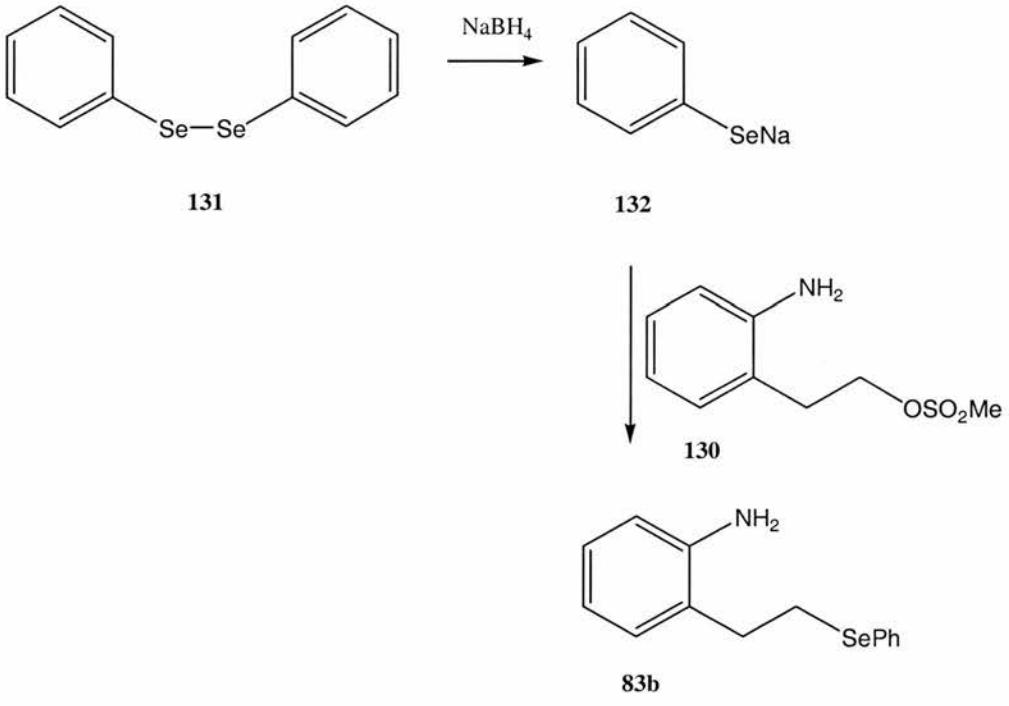
3.2.2.1. Preparation of methanesulfonic acid 2-(2-amino-phenyl) ethyl ester **130**



82 **130**

The mesylate was prepared by addition of methane sulfonyl chloride to 2-(2-aminophenyl) ethanol in the presence of triethylamine in dry dichloromethane, under a nitrogen atmosphere. The mesylate was used without further purification in the following step.

3.2.2.2. Synthesis of 2-[2-aminophenyl] ethyl phenyl selenide **83b**



131 132 130 83b

Preparation of 2-phenylselenoethylamine **83b** was attempted by addition of the methanesulfonic acid 2-(2-amino-phenyl) ethyl ester **130** to a solution of sodium phenylselenide **132,** made in *situ* by treatment of diphenyldiselenide **131** in dry ethanol with sodium borohydride. The NMR spectra didn't show any trace of the selenide compound. The problem could be the purity of the starting material. In this

case the mesylate compound might not have been pure enough to carry out the reaction involving PhSeNa.

3.3. Method C: for X = Br with HBr

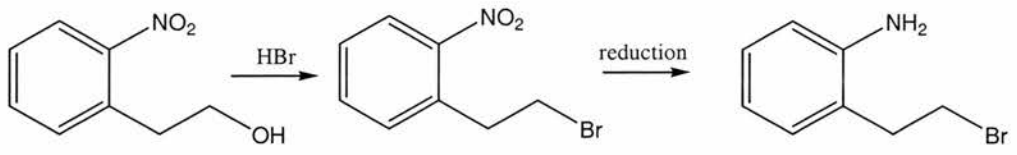
This time we decided to change the reagent of bromination. The bromination of secondary alcohols is commonly carried out using HBr. We could expect that this method would work as well for primary alcohols. We attempted to prepare the bromide by action of hydrobromic acid on the alcohol according to a procedure described by Woodburn.[15] The procedure will be the same for all the examples. The alcohol was dissolved in constant-boiling hydrobromic acid. Either an oil or a crystalline solid was obtained, depending of the starting material.

*3.3.1. Bromination of 2-(2-((*tert*-butyloxycarbonyl) amino) phenyl) ethanol with HBr*

122 **133**

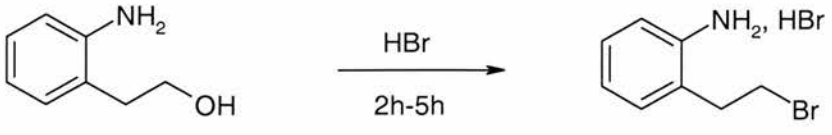
Preparation of the isocyanate is possible directly from the hydrobromide salt,[16] therefore the reaction of HBr with the corresponding alcohol **122** was used to access **133**. However, in the mixture obtained, the expected bromide was not observed.

*3.3.2. Bromination of 2-(2-nitrophenyl) ethanol **118** using HBr*



Following the route outlined in the scheme above (scheme 64), the bromination of the 2-(2-nitrophenyl) ethanol **118** was attempted using HBr. 1-(2-Bromoethyl)-2-nitrobenzene was obtained after refluxing the alcohol for 13 hours in an aqueous solution of HBr (48 %). Using this methodology, 65 % of the bromide **125** was obtained after purification by distillation. The reduction of the nitro compound could be carried out either by action of $Zn/CaCl_2$ or by action of H_2/Pd. The second method is the one usually used for the reduction of the nitro group. For this example the reduction of the nitro compound was carried out using the $Zn/CaCl_2$ aqueous method used previously for the synthesis of the amine **82**. 2-(2-Bromoethyl) aniline was obtained in 38 % yield.

*3.3.3. Hydrobromide of 2-(2-aminophenyl) ethanol **133***



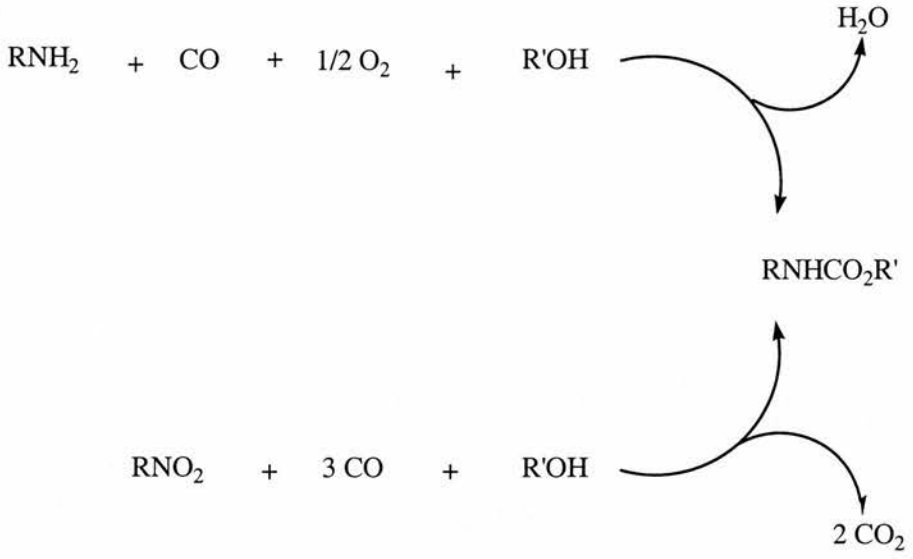
82 **133**

In this experiment the compound **133** was synthesised directly from the amine following Woodburn's procedure. A light-grey solid was obtained in 82 % yield. The NMR spectra allowed us to conclude that the salt of the amine was formed.

4. Synthesis of the isocyanate (84)

4.1. Modern methods

The isocyanate group (N=C=O) is extremely reactive. Presently, isocyanates are usually prepared by reaction of phosgene with an amine. As there are restrictions on the use of very toxic materials such as phosgene because of the formation of gaseous hydrochloric acid during the conversions, sufficiently reactive phosgene analogs have been developed as for example 1,1'-carbonyldiimidazole,[17-20] combination of di-*t*-butyldicarbonate and 4-*N*,*N*-dimethylaminopyridine[21-24] and di-*t*-butyltricarbonate.[25, 26] There has been increasing interest in developing alternative methods for isocyanate production. One such method involves the catalytic production of carbamate esters (by reductive carbonylation of nitro derived compounds, or oxidative carbonylation of amines), dealcoholysis of which gives isocyanates.

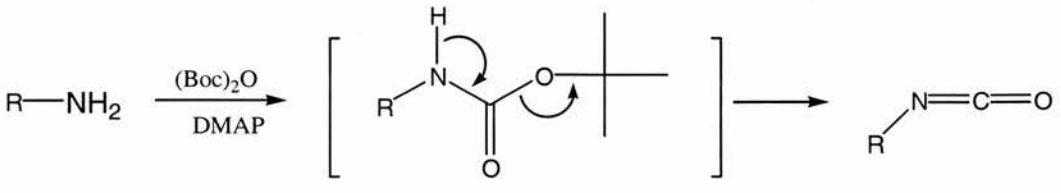


scheme 65

Different routes for the synthesis of isocyanates from carbamate esters are possible.

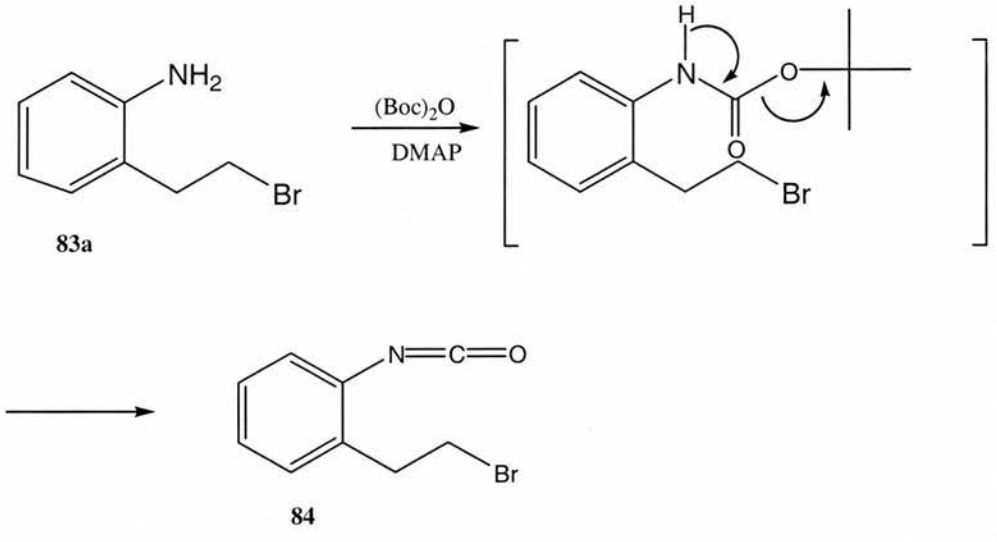
4.1.1. Reaction with DMAP

Another way to prepare isocyanates is by treatment of the carbamate ester with DMAP. Knolker described in 1995 a novel procedure for the synthesis of isocyanates under mild conditions (10min at room temperature) by the DMAP-catalyzed reaction of alkyl- and arylamines with $(Boc)_2O$ (di-tert-butyldicarbonate).[21, 27, 28] The synthetic scheme is outlined below.



scheme 66

The carbamate ester that we decided to use was 2-(2-((*tert*-butyloxycarbonyl) amino) phenyl) ethanol. Thus, the isocyanate could be made from the amine with di-*t*-butyl carbonate and DMAP. Two ways were explored, one starting with the amine and the other one starting with the protected amine already synthesised in a previous experiment (scheme 67).



83a

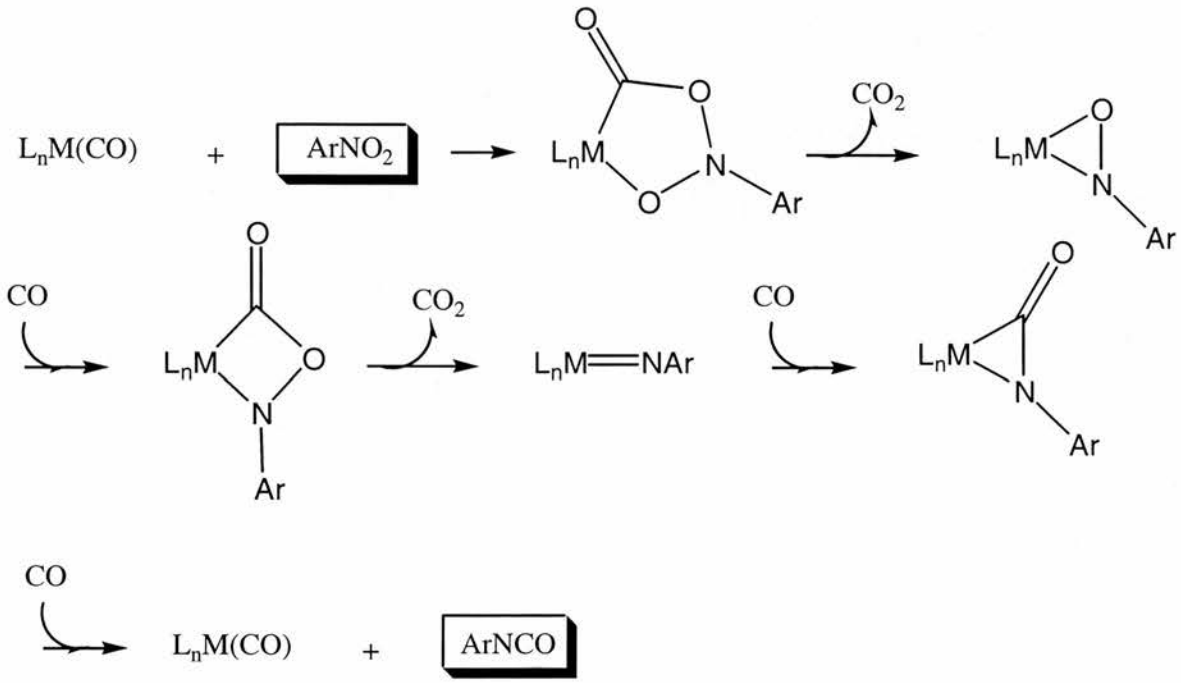
84

Scheme 67

With respect to the first reaction, problems with obtaining the bromide of the amino compound pure enough to go on with following experiments were a hindrance. With regard to the second route, the bromination of the protected amine was not carried out, thus following this pathway was not followed further.

4.1.2. From nitro compounds

Another possiblity could be by carbonylation of the nitro group. Hardy and Bennet[29] reported the first conversion of aromatic nitro compounds to isocyanates by carbon monoxide. This reductive carbonylation is a thermodynamically favorable, highly exothermic process.



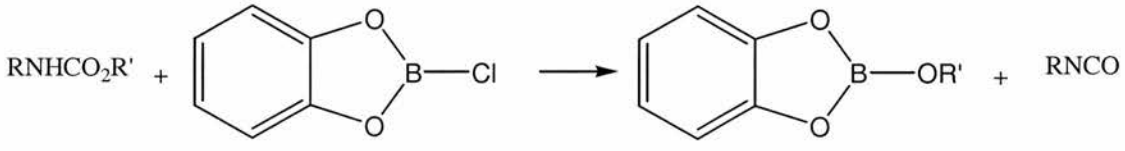
scheme 68

Initially, in the presence of CO and the catalyst[30] (mainly palladium and rhodium), the nitro compound generates a metallacycle (scheme 68). This intermediate undergoes decarboxylation, leaving the nitroso group bound to the metal. The subsequent insertion of CO followed by decarboxylation gives a nitrene species as key intermediate, which can be carbonylated to afford the isocyanate. But as a side-

reaction, the nitrene species can also react with a nitroso compound or another nitrene intermediate, yielding azoxy or azo compounds as by-products.

4.1.3. Reaction with boron trihalide

It has recently been shown that elimination of alcohol from carbamate esters to yield isocyanates can be facilitated using chlorocatecholborane in toluene, in the presence of triethylamine. The way in which the alcohol product is reversibly removed from the reaction solution, in the form of an alkyl catecholborate, is an advantage of this method, compared with routes that employ the thermal decomposition of carbamate esters, in which recombination of the resulting isocyanate with alcohol is possible.

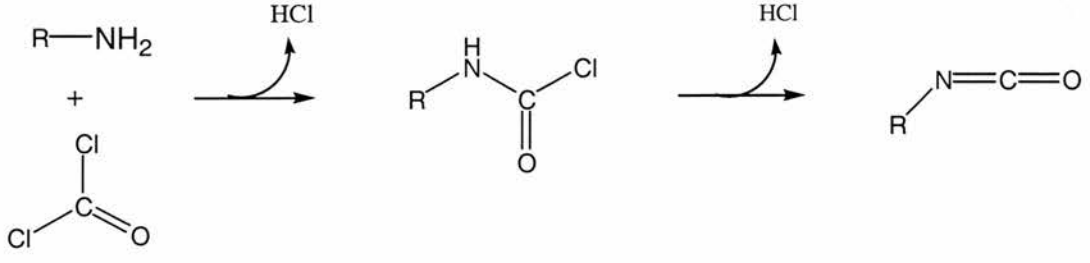


scheme 69

The use of chlorocathecholborane has been demonstrated in this type of reaction. So, simple boron halides BX_3 (X =Cl, Br) may also be active as cheap alternatives. Boron trihalides are known for their strong Lewis acid character, and for their ability to cleave a wide variety of ethers, acetals, and esters under relatively mild conditions. In pursuit of alternative methods of isocyanate production, the conversion of carbamate esters to isocyanates using BCl_3 in the presence of triethylamine could be an option to consider. The reaction is simple in execution and work up occurs under mild conditions.

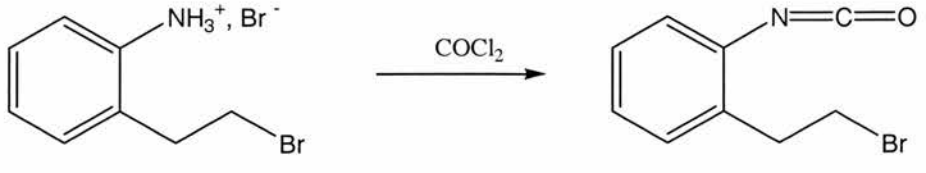
4.2. Conventional method

Regarding our work, for the synthesis of the precursor, 2-(2-bromoethyl) phenyl isocyanate **84**, we decided to use the conventional method. The most common method for the preparation of isocyanates is the phosphogenation of amine or amine salt precursors (scheme 70).



scheme 70

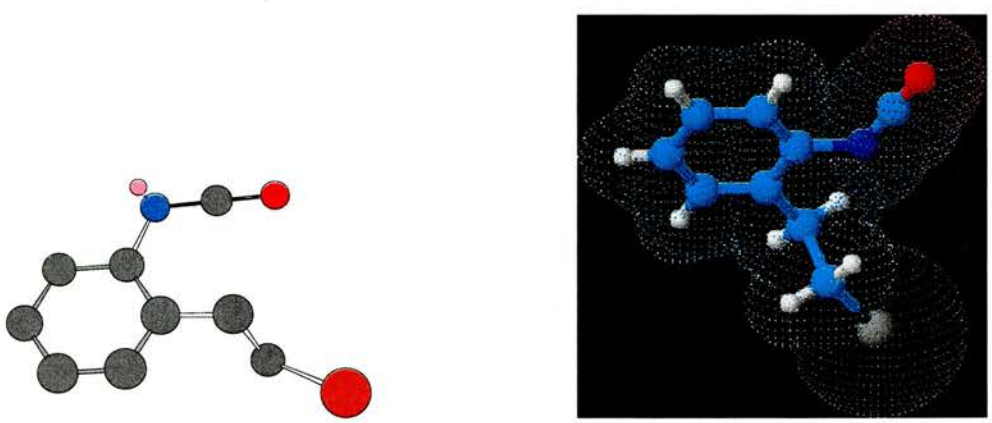
Phosgene reacts with primary amines or their salts to give carbamoyl chlorides which can be readily dehydrohalogenated to isocyanates.[31-33] As this method can be applied to the salt of the amine, the synthesis of isocyanate was attempted by action of phosgene on the hydrobromide salt of 2-(2-bromoethyl) aniline **133**, previously obtained by action of HBr on the corresponding amine.



133 **84**

A first attempt was made by refluxing the hydrobromide salt of the amine in the presence of phosgene in xylene. However, the proton NMR didn't show the presence of the expected 2-(2-bromoethyl) phenyl isocyanate **84** in the mixture obtained. Next, the same experiment was repeated, but in a different solvent. Phosgene was added onto the bromide at reflux in toluene. The proton NMR spectrum showed the presence of the expected adduct, and the presence of the isocyanate moiety was confirmed by IR analysis, which showed the characteristic NCO band at 2217 cm^{-1}. Although the reaction did work, the NMR spectrum showed that benzyl bromide was formed during the reaction. This had presumably arisen from bromination of the toluene solvent during the preparation of 2-(2-bromoethyl) phenyl isocyanate **84.** The product was not isolated from the solvent.

The figure shows a 3D structure of 2-(2-bromoethyl) phenyl isocyanate **84**.

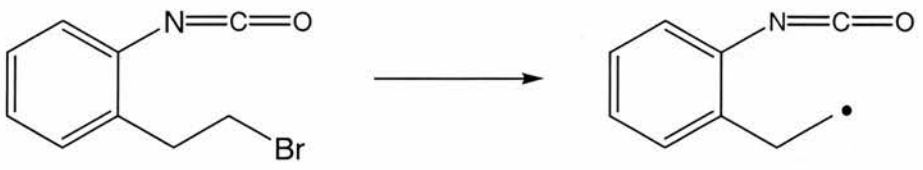


Picture 1

These models showed that ring closure of the 2-(2-bromoethyl) phenyl isocyanate might well be possible.

5. Homolytic reactions of 2-(2-bromoethyl) phenyl isocyanate (84)

5.1 Study of radical generation by ESR spectroscopy

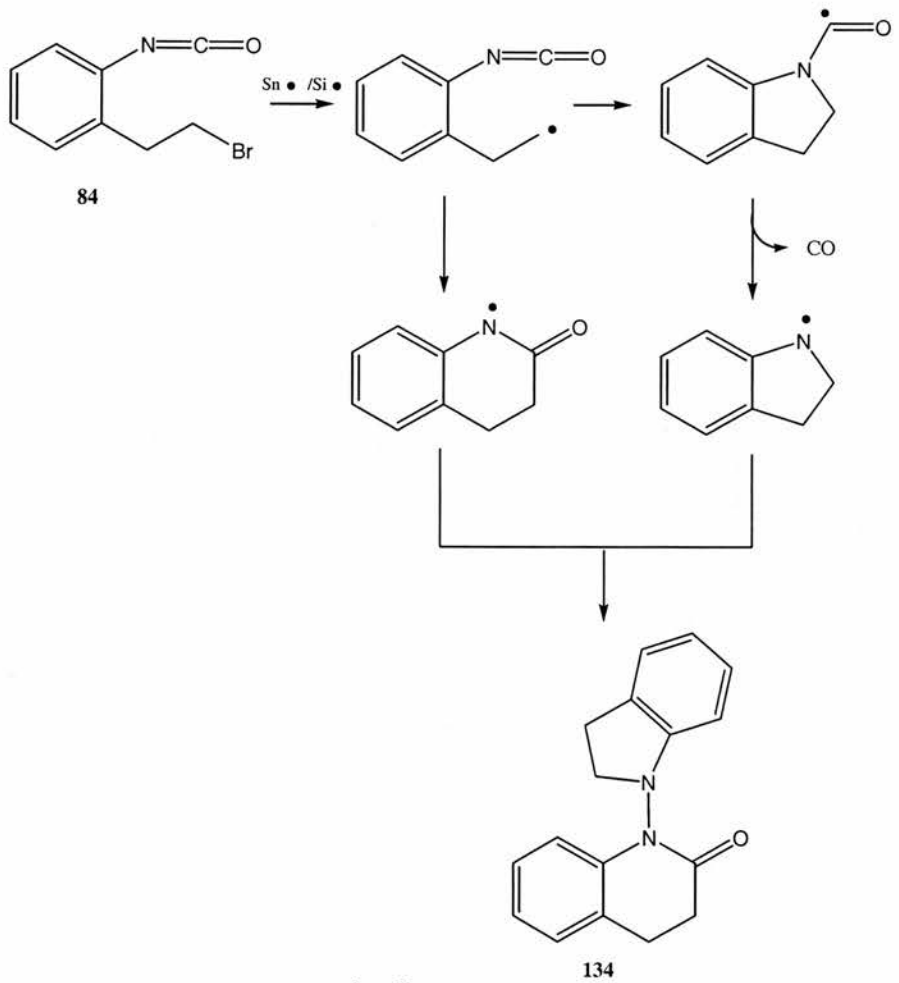


84 **3**

scheme 71

Radical generation from 2-(2-bromoethyl) phenyl isocyanate **84** was examined by ESR spectroscopy. A solution of the isocyanate **84** and hexabutylditin in toluene in a quartz tube was degassed by bubbling nitrogen for 20 min and then photolysed, in the ESR resonant cavity, by light from a 500 W super pressure mercury arc lamp. The ESR spectra were run on a Bruker EMX 10/12 spectrometer operating at 9.5 GHz with 100 KHz modulation. The only radical detected was the benzyl radical. Eventually it was concluded that this must have originated from benzyl bromide. Indeed, the proton NMR spectrum confirmed the presence of traces of benzyl bromide in the solution, δ=4.2 ppm, value which could be attribuate to CH_2 of the benzyl bromide The isocyanate was purified by distillation to remove benzyl bromide present in solution. Despite further purification, and removing of all trace of benzyl bromide, the ESR analysis showed no significant spectra and no signals due to the substituted ethyl radical were obtained.

However, GC-MS analyses of the solutions were obtained after the ESR experiments were carried out. The ESR experiments were carried out in toluene and *tert*-butyl benzene in presence of either hexamethylditin or triethylsilane. Except for the starting materials and the solvent, similar products were identified from reactions with the organotin and the silane. The GC-MS spectra showed the presence of 1-(2,3-dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one, (2,3-dihydroindol-1-yl)-triethylsilanyl-methanone and *N*-[2-(2-bromoethyl)-phenyl]-*N*-hydroxy-formamide or [2-(2-bromoethyl)-phenyl]-carbamic acid. The peak with M+ 264 ($C_{17}H_{16}N_2O$) could be attributed to 1-(2,3-dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one. The fragmentation (M^+- 118) could be the loss of C_8H_9N, i.e. the 2,3-dihydro-1*H*-indole molecule. The second part of the mass spectrum matched with the mass spectrum of what we believed to be 3,4-dihydro-1*H*-quinolin-2-one. 1-(2,3-dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one **134**, presumably came from the radical coupling of 2,3-dihydro-1*H*-indole (indoline) radical (which probably arose from ring closure of 1-ethyl-2-isocyanato-benzene radical followed by loss of the CO group), with the 3,4-dihydro-1*H*-quinolin-2-one radical (scheme 72).

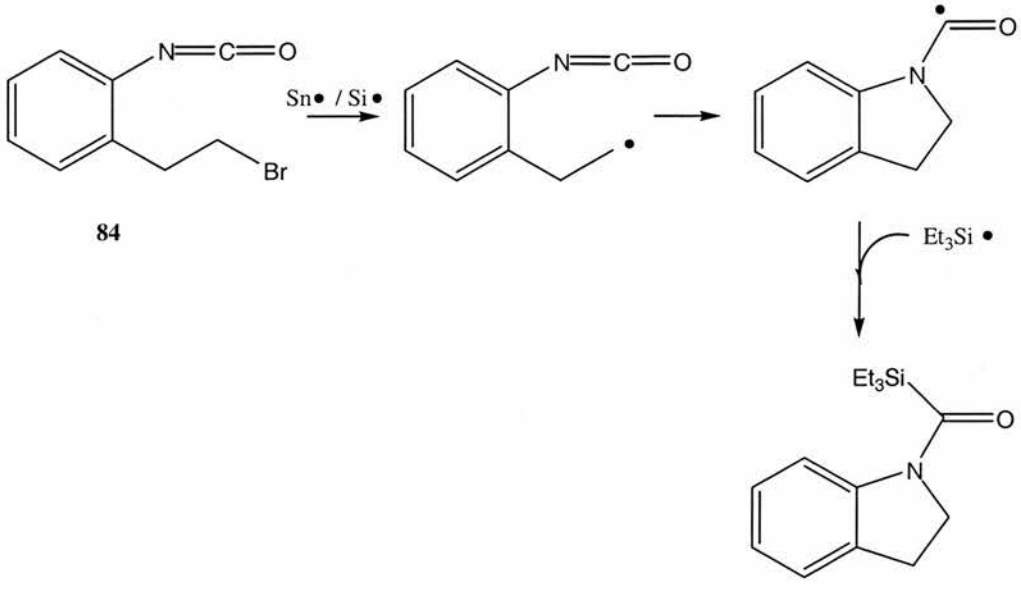


84

134

scheme 72

The peak with M+ 261 ($C_{15}H_{23}NOSi$) could be attributed to (2,3-dihydroindol-1-yl)-triethylsilanyl-methanone. The fragmentation (M^+- 115) could be the loss of $C_6H_{15}Si$, triethylsilyl group. (2,3-Dihydroindol-1-yl)-triethylsilanyl-methanone **135** probably came from coupling between 2,3-dihydroindole-1-carbaldehyde radical and the triethylsilyl radical (scheme 73).



84

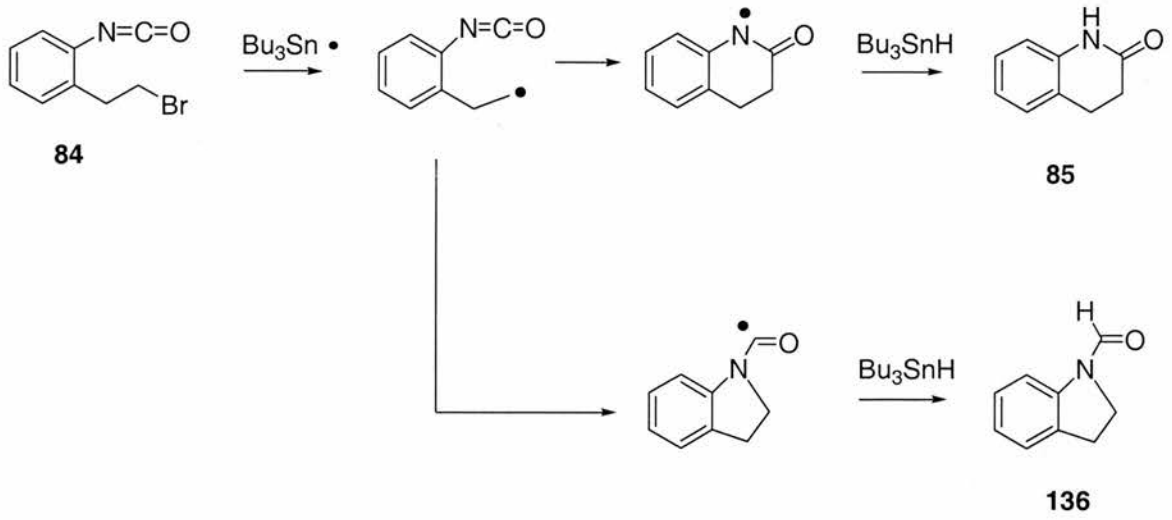
scheme 73

135

N-[2-(2-Bromoethyl)-phenyl]-*N*-hydroxy-formamide might come from oxidation of the reactant. Alternatively, [2-(2-bromoethyl)-phenyl]-carbamic acid might come from partial hydrolysis of the initial isocyanate.

5.2 Radical cyclisation of 2-(2-bromoethyl) phenyl isocyanate (84)

Thc radical cyclisation of the isocyanate **84** has been attempted using different conditions. The radical reaction has been performed using the distilled 2-(2-bromoethyl) phenyl isocyanate. As described in the scheme below, we expected to observe ring closure either in 5-*exo* mode on the N-atom or in the 6-*endo* mode on the C-atom of the isocyanate group.



scheme 74

The reactions were analysed by GC-MS. The results are summarised in the following table. The residues from the radical initiator as well as the starting materials were not mentioned.

Analysis of homolytic reactions of aryl isocyanate (84)			
Entry	**Conditions**	**Products** [i]	**Library fit** [a]
1[b]	Bu_3SnH (slow addition), $PhCH_3$, AIBN, heat 7h, 80 °C, N_2	++++Bromoethyl-benzene ++1-Ethyl-2-isocyanato-benzene ++2,2-Dimethyl-3-phenyl-propionitrile ++++1-Benzyl-2,3-dihydro-1*H*-indole ++2,3-Dihydro-indole-1-carboxylic acid benzyl ester +1-(2,3-Dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one	992
2[c]	Bu_3SnH, PhH, UV 30min, RT, degas	+2-Ethylaniline +1-Ethyl-2-isocyanatobenzene +++2,3-Dihydro-1*H*-indole +1*H*-Indole +++1-Formyl-2,3-dihydro-indole ++1-(2,3-Dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one	996 992 988 926 990

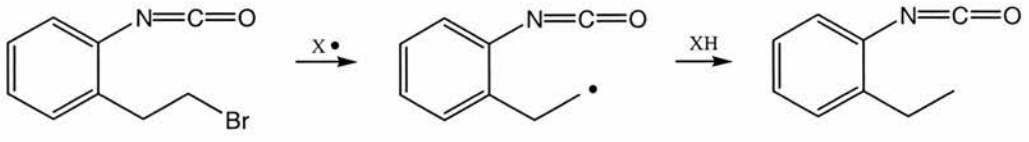
3[d]	Bu_3SnH, PhH, UV 1h, RT, degas	++2-Ethyl-aniline +1-Ethyl-2-isocyanatobenzene +++2,3-Dihydro-1*H*-indole ++++1-Formyl-2,3-dihydro-indole ++++1-(2,3-Dihydro-indol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one +Bis-(2,3-dihydroindol-1-yl)-methanone	996 988 990
4[e]	Bu_3SnH, PhH, UV 2h, RT, degas	++2,3-Dihydro-1*H*-indole ++1-Formyl-2,3-dihydro-indole ++++3,4-Dihydro-1*H*-quinolin-2-one ++++1-(2,3-Dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one ++Bis-(2,3-dihydro-indol-1-yl)-methanone	988 990
5[f]	Bu_3SnH, PhH, UV 3h, RT, degas	+2,3-Dihydro-1*H*-indole ++1-Formyl-2,3-dihydro-indole +++3,4-Dihydro-1*H*-quinolin-2-one ++++1-(2,3-Dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one	988 990
6[g]	EPHP, PhH, AIBN, heat 3 days, 70 °C, N_2	++2,3-Dihydro-1*H*-indole ++++Isomer of 1-bromo-2,3-dihydro-1*H*-indole +1-(2-Bromoethyl)-2-isocyanato-benzene or isomer of 3-bromo-3,4-dihydro-1*H*-quinolin-2-one +Isomer of 1-bromo-1*H*-indole ++++Isomer of 2,2-dibromo-2,3 dihydro-1*H*-indole +++1-Benzyl-2,3-dihydro-1*H*-indole	988
7[h]	TTMSS, C_6D_6, 1,1'-azobis-cyclohexanecarbonitrile, heat 2h30, 103 °C	+1-Ethyl-2-isocyanatobenzene +1-Formyl-2,3-dihydro-indole +++3,4-Dihydro-1*H*-quinolin-2-one ++++1-(2,3-Dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one)	992 990

[a] 1000 = exact library fit. [b] One unidentified component. [c] One unidentified component. [d] No unidentified components. [e] No unidentified components. [f] No unidentified components. [g] One unidentified component. [h] TTMSS and other unidentified components (mostly Si-compounds).

[i] ++++ major product → + minor product.

Almost the same components were identified in the different GC-MS spectra. In the case of procedure 1, the benzyl bromide was a by-product from the preparation of the isocyanate. It was the product of the reaction between toluene with HBr. Bromoethyl-benzene was difficult to separate from the precursor 1-(2-bromoethyl)-2-isocyanatobenzene.

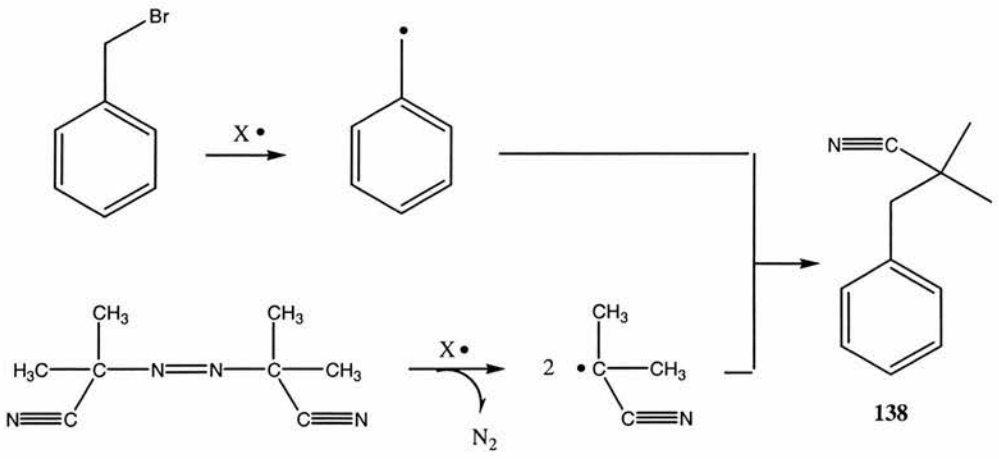
1-Ethyl-2-isocyanato-benzene **137** (library fit 992) was presumably the product of the direct reduction of **2** as described in the following scheme.



84 **137**

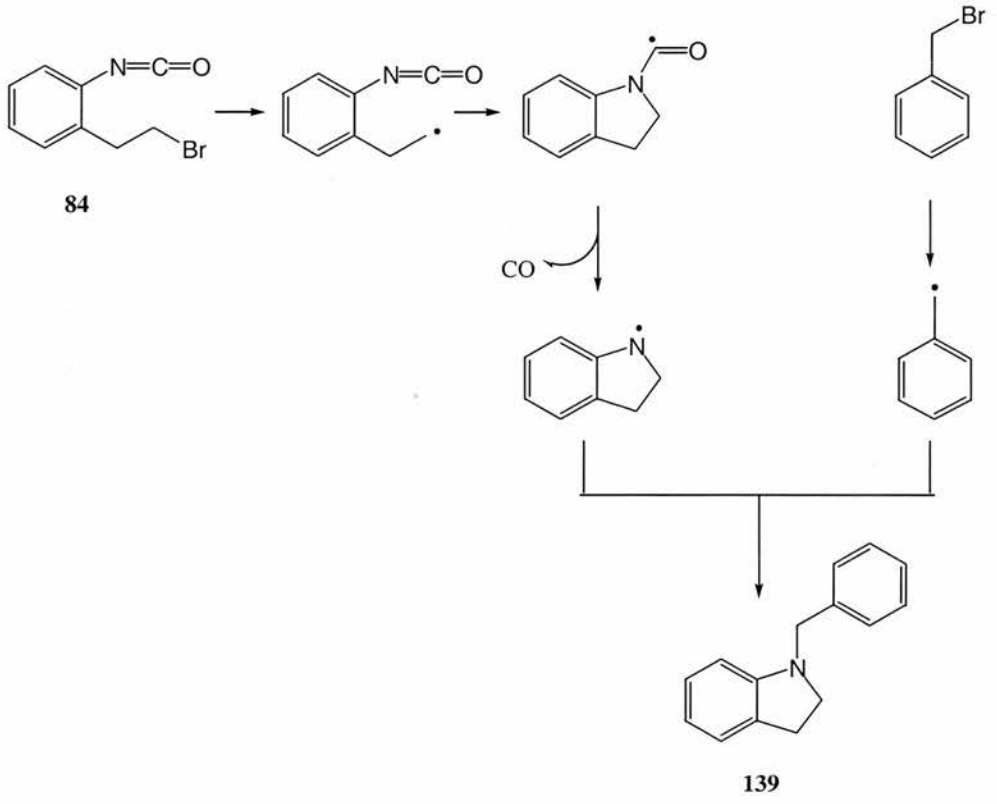
scheme 75

A peak with M^+ 159 ($C_{11}H_{13}N$) was observed on the GC-MS spectra. The fragmentation (M^+- 68) could be the loss of $CNC(CH_3)_2$. This peak could be attributed to 2,2-dimethyl-3-phenylpropionitrile. 2,2-Dimethyl-3-phenylpropionitrile **138** came probably from the reaction between the benzyl radical and the fragment $CNC(CH_3)_2$ of AIBN (scheme 76).



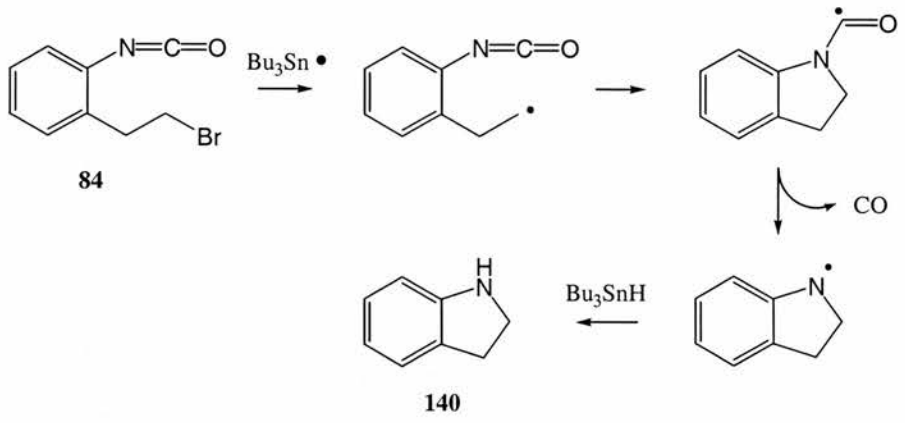
scheme 76

A peak with M+ 209 ($C_{15}H_{15}N$) could be attributed to 1-benzyl-2,3-dihydro-1*H*-indole. The fragmentation (M^+- 77) could be the loss of C_6H_5, a phenyl group. Furthermore a peak with the mass 91 also present, corresponded to the benzyl group. 1-Benzyl-2,3-dihydro-1*H*-indole **139** might come from the reaction between 2,3-dihydro-1*H*-indole and the benzyl radical as shown in the scheme 77.



scheme 77

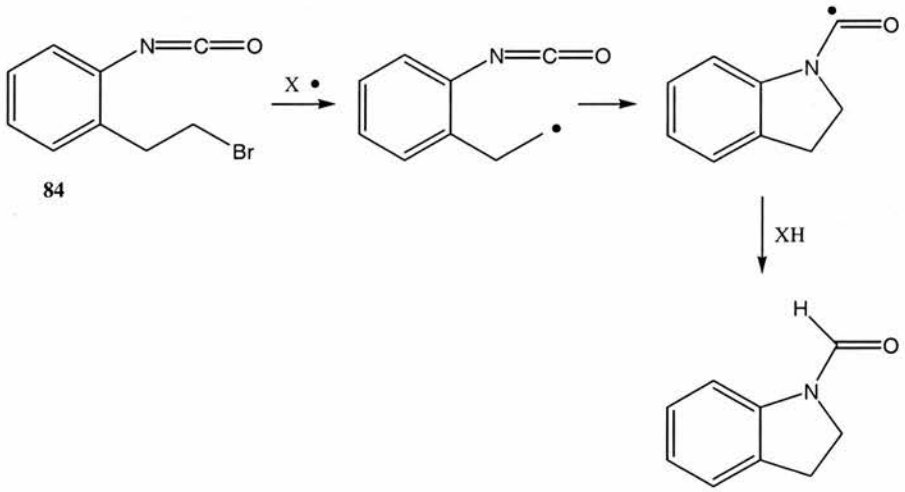
An explanation for the formation of 1-(2,3-dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one **134** has already been mentioned previously in scheme 72. It might come from the radical coupling of 2,3-dihydro-1*H*-indole radical with the 3,4-dihydro-1*H*-quinolin-2-one radical. 2-Ethylaniline (library fit 996) came presumably from 1-ethyl-2-isocyanatobenzene. This product might come from the hydrolysis or the rearrangement of the isocyanate group of 1-ethyl-2-isocyanatobenzene. 2,3-Dihydro-1*H*-indole **140** (library fit 988) has already been seen in different previous examples. It might probably come from the ring closure of 1-ethyl-2-isocyanatobenzene radical followed by loss of the CO group and abstraction of hydrogen (scheme 78).



84 **140**

scheme 78

1*H*-Indole (library fit 926) was presumably the product of oxidation of 2,3-dihydro-1*H*-indole **140**. 1-Formyl-2,3-dihydro-indole **136** (library fit 990) was the expected product of 5-*exo* cyclisation of 1-ethyl-2-isocyanatobenzene onto the N-atom of the isocyanate group (scheme 79).

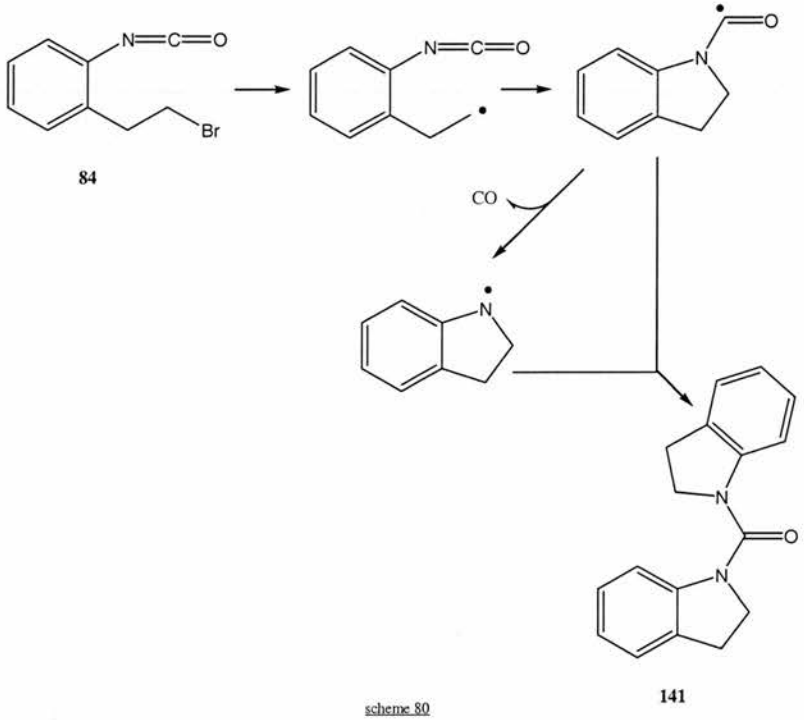


84 **136**

scheme 79

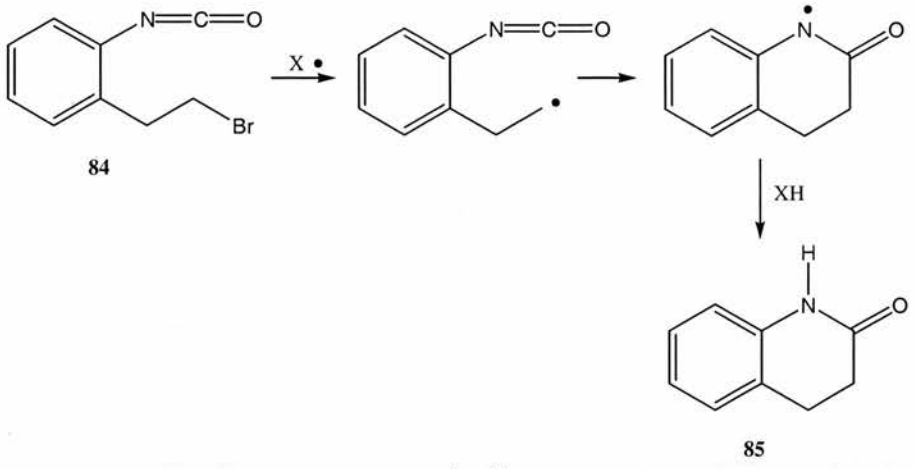
The peak with M^+ 264 ($C_{17}H_{16}N_2O$) could be attributed to bis-(2,3-dihydroindol-1-yl)-methanone. The fragmentation (M^+- 118) could be the loss of C_8H_9N, 2,3-dihydro-1*H*-indole molecule. The second part of the mass spectrum matched with the mass

spectrum of 1-formyl-2,3-dihydro-indole. The formation of bis-(2,3-dihydroindol-1-yl)-methanone **141** could be explained by the reaction of one radical from of 1-formyl-2,3-dihydro-indole with one radical of 2,3-dihydro-1*H*-indole as described in the following scheme.



scheme 80

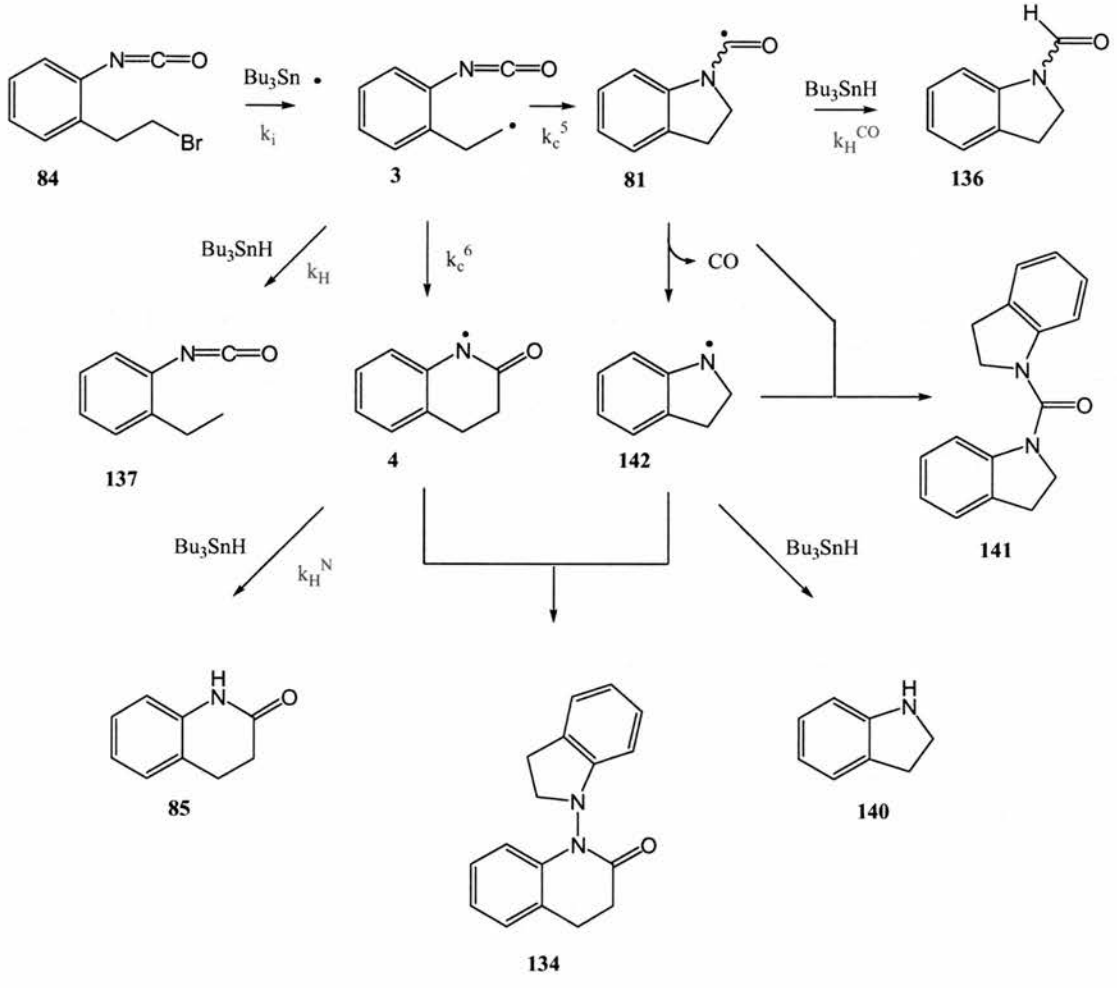
The peak with M^+ 147 (C_9H_9NO) could be attributed to 3,4-dihydro-1*H*-quinolin-2-one. 3,4-Dihydro-1*H*-quinolin-2-one **85** might come from the intramolecular 6-*endo* radical addition of the ethyl radical of 1-ethyl-2-isocyanatobenzene on the C-atom of the isocyanate group followed by abstraction of hydrogen (scheme 81).



84 **85**

scheme 81

For all these different procedures, the results were quite similar. The same products were observed on the GC-MS spectra. A scheme could be drawn to summarize the formation of the main components after reaction (scheme 82).



scheme 82

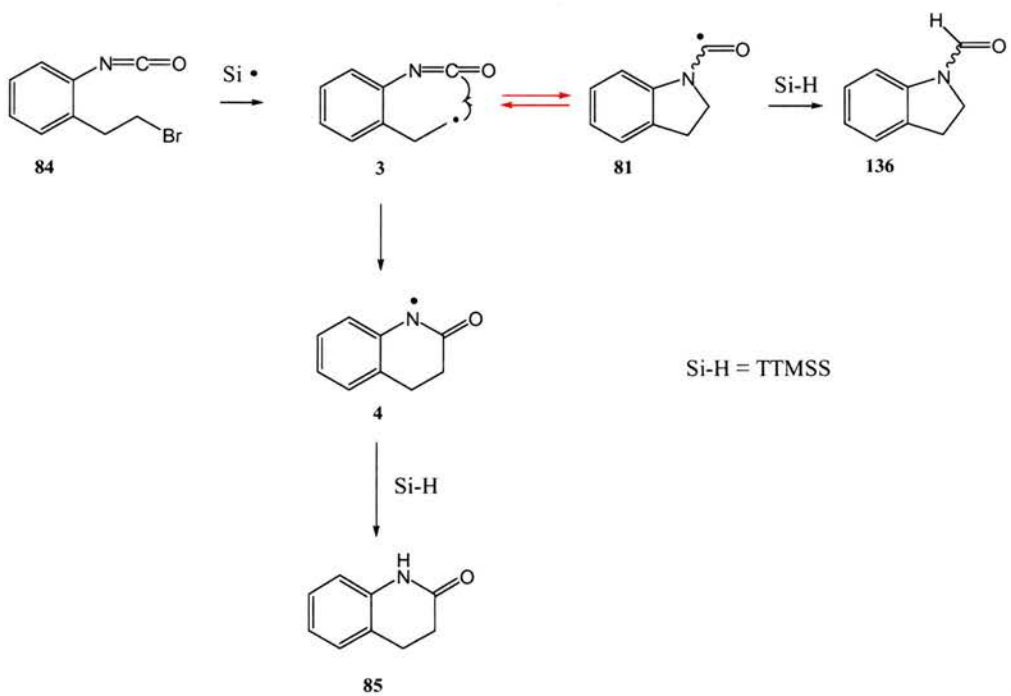
For one of the solutions, which was photolysed in benzene at RT for 3h, column chromatography was performed and the last fraction was analysed by NMR and GC-MS. The results of these analyses showed that the major product formed was 3,4-dihydro-1*H*-quinolin-2-one **85** in 44.1 % yield. 1-Formyl-2,3-dihydro-indole **136** was obtained in 15.7% and 1-ethyl-2-isocyanatobenzene **137** in 3.1% yield. 1-Formyl-2,3-dihydro-indole possesses two rotamers due to hindered rotation of the formyl group. The proton NMR spectrum showed the mixture of the two rotamers in a ratio 3:1. The yields from the photochemical reaction with Bu_3SnH at 30°C showed that 6-*endo*-

cyclisation at the C-atom predominated over 5-*exo*-cyclisation at the N-atom of the isocyanate group by a factor of 2.8. The other components shown in scheme 82 were all very minor. The analysis indicated the presence of a small amount of cross-coupled products 1-(2,3-dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one **134** and bis-(2,3-dihydro-indol-1-yl)-methanone **141** (ratio 1.7:1).

Due to the problem of toxicity of tributyltin hydride, and the problem of contamination with tin residues, and due to the difficulties of removal of tin residues after reaction, the radical reaction of 1-(2-bromoethyl)-2-isocyanatobenzene was also carried out using EPHP in benzene, in the presence of a catalytic amount of AIBN. Regarding this procedure with EPHP, the GC-MS showed the presence of different products of bromination which seemed to correspond of 1-bromo-2,3-dihydro-1*H*-indole or 2-bromo-2,3-dihydro-1*H*-indole, 3-bromo-3,4-dihydro-1*H*-quinolin-2-one, 1-bromo-1*H*-indole or 2-bromo-1*H*-indole and 2,2-dibromo-2,3-dihydro-1*H*-indole. Their formation could be explained by the bromination or dibromination respectively of 2,3-dihydro-1*H*-indole, 3,4-dihydro-1*H*-quinolin-2-one, 1*H*-indole and 2,3-dihydro-1*H*-indole. The bromination agent has not been identified, but it could be that a phosphorus radical was formed and this radical added onto the isocyanate moiety creating either a N-centred radical or a C-centred radical which possibly underwent a intramolecular radical reaction.

The experiment was also attempted using tris(trimethylsilyl)silane instead of the tin reagent. The isocyanate was heated in deuteriobenzene for 2h 30min in presence of 1.2eq of TTMSS and a catalytic amount of 1,1'-azo-di-cyclohexanecarbonitrile at 103 ^{o}C. The reaction was analysed by NMR spectroscopy and GC-MS. Mainly the starting material and the TTMSS were observed on the proton NMR spectrum. However, on the GC-MS spectra 1-ethyl-2-isocyanatobenzene **137**, 1-formyl-2,3-

dihydro-indole **136**, 3,4-dihydro-1*H*-quinolin-2-one **85** and the product of cross-coupling reaction 1-(2,3-dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one **134** were also observed. The reaction was slower, but in this case the cyclisation was much more regioselective, the [**85**]:[**136**] ratio being ca. 59:1. This could be explained if the *5-exo*-cyclisation to **136** were reversible, whereas the *6-endo* process that gives the resonance stabilised radical **4**, was not. The process would be under thermodynamic control at 103 °C. TTMSS is a slower H-atom donor than Bu_3SnH and hence more products build up via the irreversible reaction channel leading to **4** with the TTMSS than with tin hydride.



scheme 83

6. Estimation of the Cyclisation Rate Constants

6.1. With Bu_3SnH

For the mechanism of scheme 82, the cyclisation rate constants have been calculated.

Making the Steady State approximation:

- $d[\mathbf{137}]/dt = k_H[Bu_3SnH][\mathbf{3}]$

  $d[\mathbf{85}]/dt = k_H^N[Bu_3SnH][\mathbf{4}]$

  $d[\mathbf{136}]/dt = k_H^{CO}[Bu_3SnH][\mathbf{81}]$

- $d[\mathbf{3}]/dt = k_i[Bu_3Sn^{\cdot}][\mathbf{84}] - k_H[Bu_3SnH][\mathbf{3}] - k_c^6[\mathbf{3}] - k_c^5[\mathbf{3}] = 0$

- $d[\mathbf{4}]/dT = k_c^6[\mathbf{3}] - k_H^N[Bu_3SnH][\mathbf{4}] = 0$

  $\Rightarrow \quad k_c^6[\mathbf{3}]/[\mathbf{4}] = k_H^N[Bu_3SnH] \quad$ and $\quad [\mathbf{4}]/[\mathbf{3}] = k_c^6 / k_H^N[Bu_3SnH] = [\mathbf{85}]/[\mathbf{137}]$

- $d[\mathbf{81}]/dT = k_c^5[\mathbf{3}] - k_H^{CO}[Bu_3SnH][\mathbf{81}] = 0$

  $\Rightarrow \quad [\mathbf{81}]/[\mathbf{3}] = k_c^5/ k_H^{CO}[Bu_3SnH] = [\mathbf{136}]/[\mathbf{137}]$

$\Rightarrow k_c^6 / k_H^N = [Bu_3SnH]\{ [\mathbf{85}]/[\mathbf{137}] \}$ and $k_c^5 / k_H^{CO} = [Bu_3SnH]\{ [\mathbf{136}]/[\mathbf{137}] \}$

From the experimental data, k_c^6 / k_H^N (30 °C) = 1.6 M and k_c^5 / k_H^{CO} (30 °C) = 0.6 M

If the actual k_H^N and k_H^{CO} values are approximated by the 'normal' k_H for C-centered radicals[34] ($k_H / M^{-1} s^{-1} = 9.1\text{-}3.7/\theta$)[35] then $k_c^6 < 4.2 \times 10^6$ and $k_c^5 < 1.5 \times 10^6\ s^{-1}$. These rate constants are about an order of magnitude greater than k_c^5 for the archetype hex-

5-enyl radical (2.3 x 10^5 s^{-1}). With the tin hydride method the 6-*endo*-cyclisation of 2-(2-bromoethyl) phenyl isocyanate is faster that 5-*exo*-cyclisation.

6.2. With TTMSS

If we follow the same reasoning,

k_c^6 / k_H^N = [TTMSS]{ [**85**]/ [**137**] } and k_c^5 / k_H^{CO} = [TTMSS]{ [**136**]/ [**137**] }

From the experiment, [TTMSS] = 0.212 M and θ = 103 °C = 376 K

If we take the following approximations:

k_H ($RCH_2^{\cdot}$) = 3.8 x 10^5 or log k_H = 8.9 - 4500/θ

k_H ($R_2CH^{\cdot}$) = 1.4 x 10^5 or log k_H = 8.3 - 4300/θ

$\Rightarrow$ k_H (376K) = 6.3 x 10^5

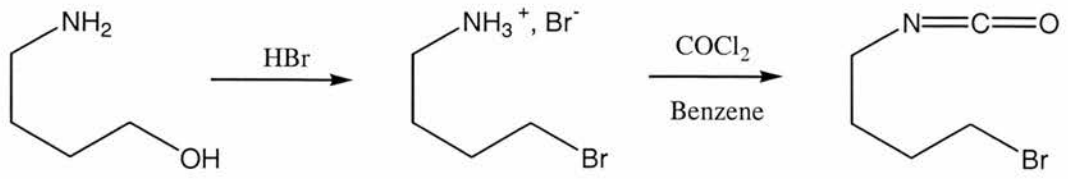
$\Rightarrow$ k_c^6 = 2.4 x 10^6 and k_c^5 = 0.4 x 10^5 at 103 °C

Using TTMSS the 6-*exo*-cyclisation is favoured in comparaison of the 5-*endo*-cyclisation. Nevertheless, the reaction of 2-(2-bromoethyl) phenyl isocyanate **84** is slower using TTMSS than tri-*n*-butyltin hydride.

7. Homolytic reactions of 1-bromo-4-isocyanato-butane

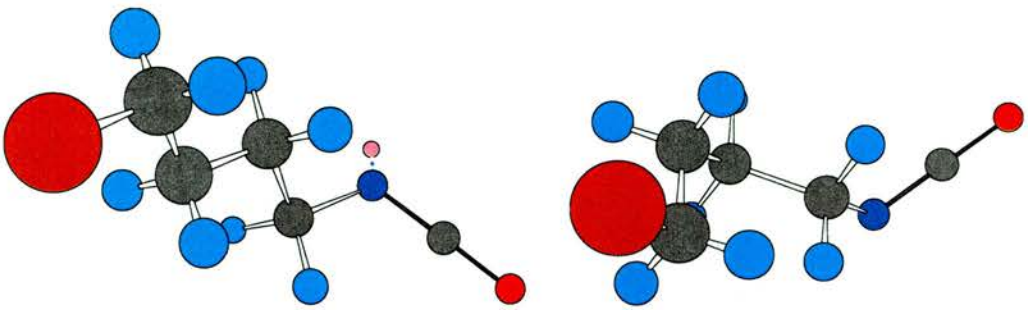
7.1. Synthesis of 1-bromo-4-isocyanato-butane

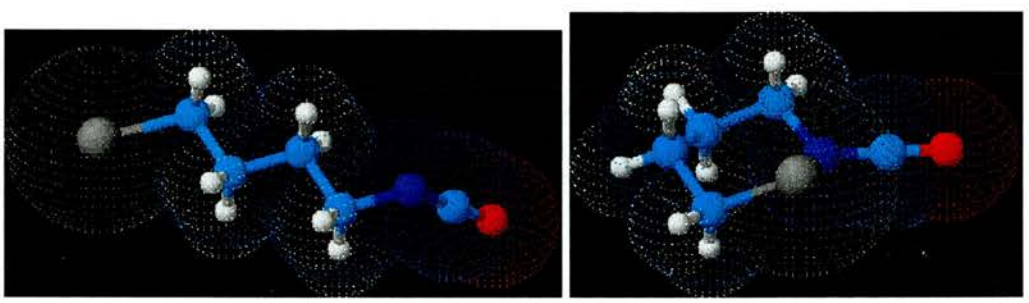
The synthesis of 1-bromo-4-isocyanatobutane was achieved using the same methodology as for the synthesis of 2-(2-bromoethyl) phenyl isocyanate **84.** The route is described below.



143 **144** **145**

The salt of the amine was prepared from commercially available 4-aminobutan-1-ol **143**.[36] By refluxing the alcohol for 3h in aqueous hydrobromic acid (48 %), 4-bromobutylamine, hydrobromide salt **144** was obtained in quantitative amount. Without further purification, the isocyanate was synthesised by adding phosgene (20 % in toluene) into the hydrobromide salt **144** in refluxing benzene, under a nitrogen atmosphere. 1-Bromo-4-isocyanato-butane **145** was obtained in 89 % yield after purification. Despite two distillations, a small amount of benzyl bromide was observed on the NMR spectra ($\delta = 4.2$ ppm, value which could be attribuate to CH_2 of the benzyl bromide). Benzyl bromide presumably came from the interaction between toluene (from the phosgene) and an unidentified bromination reagent. The isocyanate **142** was used without further purification for the next reactions.





Picture 2 Picture 3

The minimal energy conformation has an extended chain (picture 2), however, the conformation from which the molecule cyclised should be the chair (picture 3).

7.2. Radical reactions of 1-bromo-4-isocyanato-butane (145)

The ring closure of the 1-bromo-4-isocyanato-butane **145** was attempted and monitored at different reaction times by GC-MS and NMR spectroscopy. A solution of 1-bromo-4-isocyanato-butane in the presence of tri-n-butyltin hydride in benzene was photolysed at room temperature. The results of these reactions are displayed in the following table. The residues from the radical initiator as well as the starting materials were not mentioned.

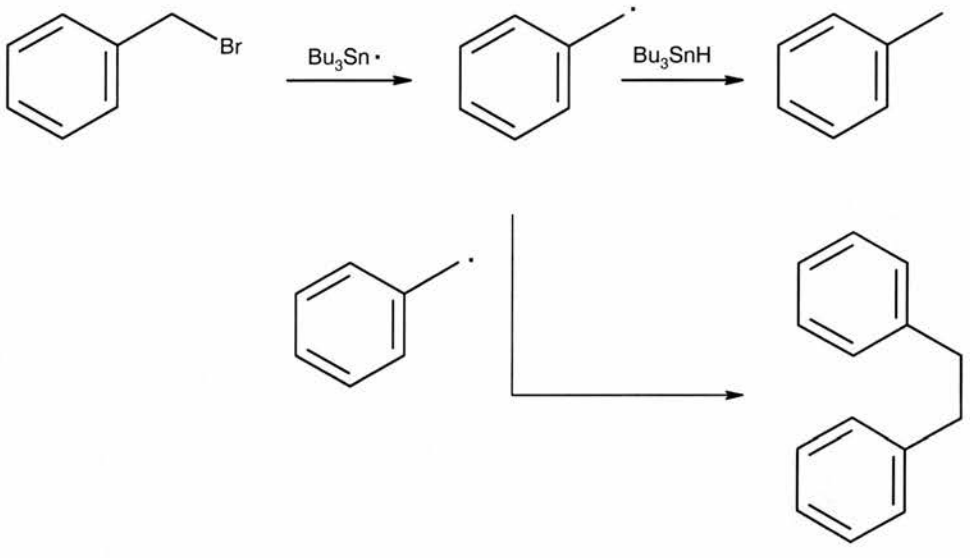
Analysis of homolytic reactions of 1-bromo-4-isocyanato-butane (145)			
Entry	**Conditions**	**Products** [f]	**Library fit** [a]
1[b]	Bu_3SnH, PhH, UV, RT, 2h	++++Toluene +Octane +Butylbenzene ++Piperidin-2-one or 1-formyl-pyrrolidine ++1,2-diphenylethane	995 997 924 937 794 998
2[c]	Bu_3SnH, PhH, UV, RT, 3h	++++1-Isocyanatobutane +++Octane +Butylbenzene ++Pentylbenzene +Piperidin-2-one or 1-formyl-pyrrolidine ++1,2-diphenylethane ++ possibly Di-pyrrolidin-1-yl-methanone or 1-Pyrrolidin-1-yl-piperidin-2-one	947 997 924 998 937 794 998
3[d]	Bu_3SnH, PhH, UV, RT, 5h	++++1-Isocyanatobutane +++Octane +Butylbenzene +Piperidin-2-one or 1-formyl-pyrrolidine +1,2-diphenylethane	947 997 924 937 794 998
4[e]	TTMSS, C_6D_6, 1,1'-azobis-cyclohexanecarbonitrile, heat for 2h30 at 103 °C or for 7h at 83 °C	++++1-Isocyanatobutane ++Piperidin-2-one or 1-formyl-pyrrolidine ++ possibly Di-pyrrolidin-1-yl-methanone or 1-Pyrrolidin-1-yl-piperidin-2-one	947 937 794

[a] 1000 = exact library fit. [b] One unidentified component. [c] One unidentified component. [d] Two unidentified components. [e] Several traces of unidentified components were also present.

[f] ++++ major product → + minor product.

The GC-MS spectra showed the same components were present in the solution mixture after reaction.

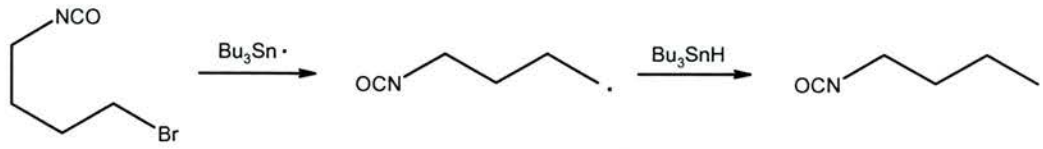
Toluene (library fit 995) was probably formed from the reduction of the benzyl bromide, present in the starting bromide, after abstraction of hydrogen from tin hydride. And 1,2-diphenylethane (or dibenzyl) (library fit 998) presumably came from coupling of 2 benzyl radicals (Scheme 84).



Scheme 84

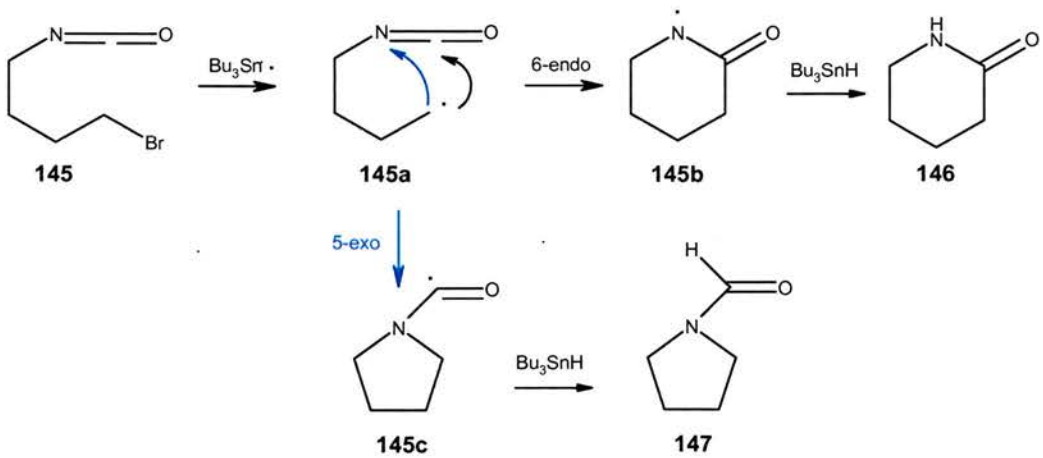
Octane (library fit 997) might come from 1-bromo-4-isocyanato-butane **145**, however, some butyl radicals are usually generated from tributyltin hydride. Butylbenzene (library fit 924) and pentylbenzene (library fit 998) might come from addition of an alkyl radical onto the benzene.

1-Isocyanato-butane (library fit 947) presumably came from the direct reduction of 1-bromo-4-isocyanato-butane (scheme 85).



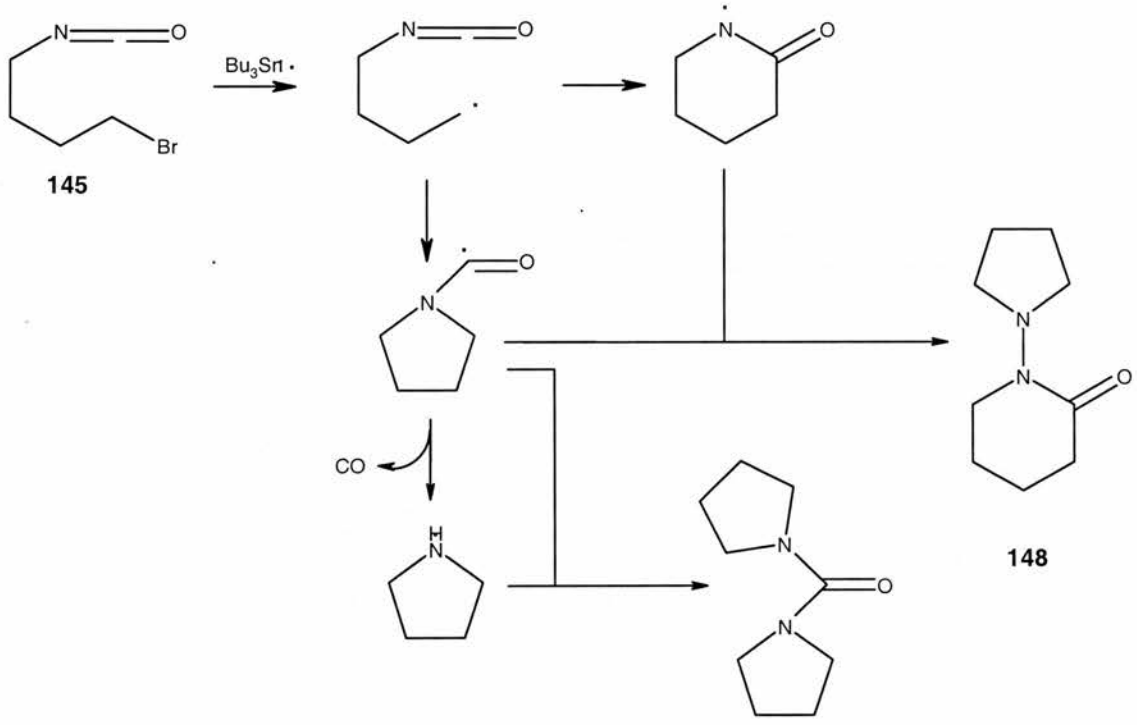
Scheme 85

On the one hand, piperidin-2-one **146** (library fit 937) was presumably the product of the 6-*endo* cyclisation of the alkyl radical onto the C-atom of the isocyanate moiety, and on the other hand, 1-formyl-pyrrolidine **147** (library fit 794) was probably the other product of the 5-*exo* cyclisation. The poorly resolved NMR spectra showed only the product of 6-*endo* cyclisation, and the GC-MS also suggested this was the main product, although the double peak in the GC indicated that some of *exo*-product was probably formed too.



Scheme 86

The peak with M^+ 264 ($C_{17}H_{16}N_2O$) could be attributed to dipyrrolidin-1-yl-methanone **149**. The fragmentation (M^+- 70 - 28) could be loss of C_4H_8N, pyrrolidine molecule and subsequently loss of CO. Dipyrrolidin-1-yl-methanone could be the product of cross coupling of piperidin-2-one and 1-formyl-pyrrolidine. Nevertheless 1-pyrrolidin-1-yl-piperidin-2-one **148** could be also present in the mixture.



145 **148** **149**

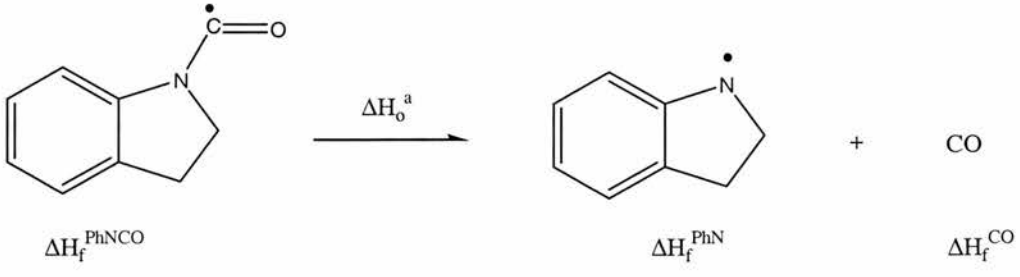
Scheme 87

To minimise all the problems encountered using tri-*n*-butyltin hydride, tris(trimethylsilyl) silane was also tried as reagent in this last experiment. The isocyanate in deuteriobenzene in presence of 1.2eq of TTMSS and a catalytic amount of 1,1'-azobis-cyclohexanecarbonitrile was heated in a first experiment at 103 °C for 2h 30min and in a second experiment at 83 °C for 7h. The reactions were analysed by NMR spectroscopy and GC-MS spectroscopy. The NMR spectra showed mainly

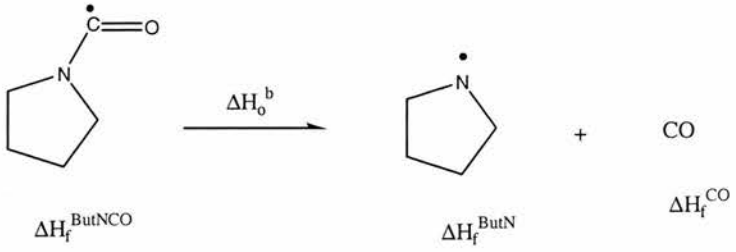
unreacted starting material. On the other hand, on the GC-MS spectra traces of piperidinone **146** and 1-formyl-pyrrolidine **147** were detected with 1-isocyanatobutane which presumably came from the direct reduction of the starting material. The major product observed was 1-isocyanatobutane. Conversion was low in both experiments at 83 °C and 103 °C. However, it appeared that both cyclisation modes were also present in this system despite the slowness of the reaction during the use of TTMSS.

8. Semi-empirical computational study of the loss of the carbonyl group

The energy of loss of CO from 2,3-dihydro-indole-1-carbonyl radical and pyrrolidine-1-carbonyl radical after the alkyl radical added to the N-atom of the isocyanate group, was estimated using AM1 calculations, implemented with the Hyperchem programme package.



scheme 88



scheme 89

As shown in schemes 88 and 89, calculations were performed to examine if the loss of the carbonyl group from 2,3-dihydro-indole-1-carbonyl radical and pyrrolidine-1-carbonyl radical was favourable.

As it is well known, the enthalpy of a reaction is the difference between the enthalpy of formation of the product and the enthalpy of formation of the reactants. For example:

Enthalpy of the above reaction is:

$\Delta H_o = (\Delta H_f^C + \Delta H_f^D) - (\Delta H_f^A + \Delta H_f^B)$

Consequently if $\Delta H_o > 0$ so the reaction is endothermique, what it means it is not favoured thermodynamically. In the reverse, if $\Delta H_o < 0$ so the reaction is exothermique, what it means it is favoured thermodynamically.

AM1 Computed Enthalpies of loss of CO	
2,3-Dihydroindole-1-carbonyl radical	Pyrrolidine-1-carbonyl radical
We considered the following abbreviations:	
• ΔH_f^{PhNCO} = Enthalpy of formation of 2,3-dihydroindole-1-carbonyl radical	• ΔH_f^{ButNCO} = Enthalpy of formation of pyrrolidine-1-carbonyl radical
• ΔH_f^{PhN} = Enthalpy of formation of 2,3-dihydro-1H-indole radical	• ΔH_f^{ButN} = Enthalpy of formation of pyrrolidine radical
• ΔH_f^{CO} = Enthalpy of formation of CO	• ΔH_f^{CO} = Enthalpy of formation of CO
So the enthalpy of decarbonylation was given by the following equations:	
• $\Delta H_o^a = (\Delta H_f^{CO} + \Delta H_f^{PhN}) - \Delta H_f^{PhNCO}$	• $\Delta H_o^a = (\Delta H_f^{CO} + \Delta H_f^{ButN}) - \Delta H_f^{ButNCO}$
Substituting the computed values we obtain :	
$\Delta H_o^a = (-5.69 + 52.148) - 28.073 =$ 18.385 kcal.mol^{-1}	$\Delta H_o^a = (-5.69 + 19.165) - (-12.79) =$ 26.27 kcal.mol^{-1}

In both cases the reaction was substantially endothermic according to the semi-empirical computations. It follows that hydrogen abstraction should be favoured instead of loss of carbonyl group after the 5-exo-cyclisation except possibly at higher temperatures.

9. Computation of the Enthalpies of the cyclisation reactions

Consiering the scheme 82 and the scheme 86, the thermochemistry of the two cyclisation modes was computed using DFT methods implemented the Gaussian 98 programme package.[37]

Enthalpies of cyclisation reactions (kcal mol^{-1}) computed using the ab initio DFT UB3LYP method.[a]		
Cyclisation	**Method/Basis Set**	**Reaction Enthalpy**
3 → 4	UB3LYP/6-31G(d,p)	-4.4
(6-endo)	UB3LYP/6-311+G(d,p)	-13.8
3 → 81	UB3LYP/6-31G(d,p)	+3.6
(5-exo)	UB3LYP/6-311+G(d,p)	-6.4
145a → 145b	UB3LYP/6-31G(d,p)	-5.8
(6-endo)	UB3LYP/6-311+G(d,p)	-2.9
145a → 145c	UB3LYP/6-31G(d,p)	-8.4
(5-exo)	UB3LYP/6-311+G(d,p)	-6.5

[a] All geometries fully optimised at the stated level, energies corrected for zero point vibrations and for vibrational effects to 298 K

Cyclisation of the 2-(2-isocyanatophenyl) ethyl radical **3** takes place in both *6-endo*- and *5-exo*-modes at rates that are comparable to that for the hex-5-enyl radical. The thermodynamically more stable 3,4-dihydro-2-oxo-1*H*-quinolinyl radical **4** was the major product, but the selectivity of ring closure was moderate. Results for the 4-isocyanatobutyl radical **145a** were less clear-cut but both cyclisation modes again appeared to compete.

VI- Experimental

^{1}H, ^{13}C NMR spectra were obtained using Bruker AM 300 MHz, a Bruker Avance 300, and Varian Gemini 2000 spectrometers. The Bruker Avance 300 is fully automated with autosampling robots. All samples were dissolved in deuterated chloroform, unless otherwise stated, using Me_4Si as an internal standard. The chemical shifts δ were given in ppm downfield from Me_4Si. IR spectra were recorded in nujol or neat on a Perkin-Elmer 1710 Infrared Fourier Transform Spectrometer. Frequencies are given in cm^{-1}. Mass spectra and GC-MS spectra were obtained using 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). All melting points were determined in open capillary tubes and are reported uncorrected. TLC was performed on pre-coated plates of silica gel G-60 F-254 (Merck). Elemental analyses were recorded on an Agilent 7500 Series ICP-MS spectrometer that had laser ablation built in capability or on a Carlo Erba CHNS analyser for carbon, hydrogen, nitrogen and sulphur. Column chromatography was performed using BDH silica gel (40-63 μm) eluting with the given solvent mixture.

1. Preparative routes to 2-(2-bromoethyl)-1-isocyanatobenzene and related molecules

Attempted Grignard reaction of 2-nitrobenzyl bromide and acetaldehyde

Dried magnesium turnings (2 g, 9 mmoles) and a small crystal of iodine were added into a dried round bottom flask. The magnesium was heated, and a small amount of a

mixture of diethyl ether/2-nitrobenzyl bromide was added. The solution was allowed to reflux steadily with gentle heating to get the reaction to start. The remaining diethyl ether/2-nitrobenzyl bromide mixture was added slowly. The solution was heated under reflux in a nitrogen atmosphere for 30 minutes. The flask was cooled in an ice/salt bath. The solution was stirred overnight. A solution of acetaldehyde in diethyl ether was added over 30 minutes. The solution was poured onto crushed ice. The basic magnesium bromide was dissolved by the addition of sulfuric acid (15 %). The product was extracted with diethyl ether. The solvent was removed under vacuum. A crystal had taken shape in the product, mp: 48-50 °C (mp: 45-48 °C reported in the Aldrich catalog). The crystal seemed to be 2-nitrobenzyl bromide. A NMR analysis of the remaining solution was made. ^{1}H NMR: δ_H 4.80 (2H, s, CH_2Br), 7.20-7.80 (3H, m, ArylH), 8.10-8.25 (1H, m, ArH). The ^{1}H NMR spectrum is identical to the NMR spectrum of benzyl bromide. The liquid phase seemed to be mainly benzyl bromide. The starting material had been returned and none of the expected alcohol was detected.

Trimethyl-(2-nitrophenyl) stannane

A mixture of hexamethylditin (1.5 g, 4.6 mmoles), 1-iodo-2-nitrobenzene (0.95 g, 3.80 mmoles), tetrakis-(triphenylphosphine) palladium (0.042 g, 0.040 mmol) and toluene (20 mL) was heated under reflux in a nitrogen atmosphere for 5h. The low boiling products were removed under vacuum and then *n*-pentane was added. The solution was filtered, the solvent was evaporated and the residue was distilled. The title compound (0.62 g, 57 %) was obtained as a yellow oil after distillation on the Kugelrohr at 100°C/0.1 mmHg. ^{1}H NMR: δ_H 0.30 (9H, s with Sn satellites, J = 24), 7.25-7.65 (3H, m, ArylH), 8.40-8.60 (1H, m, ArylH). ^{13}C NMR: δ_C 17.1; 22.2;

124.10; 129.50; 133.75; 137.35; 139.30; 152.95. IR: 2852-3383 cm^{-1} (ν_{AR}); 1533 and 1349 cm^{-1} (ν_{NO2}). The mass spectrum showed the base peak at 272 $[M-Me]^+$(^{118}Sn), but there was no molecular ion. The NMR spectrum was consistent with the literature.[7]

Attempted synthesis of 2-(2-nitrophenyl) ethanol by Stille reaction of the arylstannane with an alkyl halide

A mixture of 2-bromoethanol (0.44 g, 3.50 mmoles), stannane trimethyl-(2-nitrophenyl) (1.0 g, 3.5 mmoles) and toluene (20 mL) was heated under a nitrogen atmosphere. The reaction was followed by TLC to monitor the disappearance of the halide. After 24h, the TLC still showed the presence of the halide. The reaction was quenched with aqueous hydrochloric acid and neutralised with sodium hydrogen carbonate solution. The organic layer was then separated and the aqueous layer extracted with toluene. The combined extracts were dried over magnesium sulfate and concentrated to yield the crude product. A sample of the mixture was submitted for analysis by NMR spectroscopy. ^1H NMR: δ_H 0.30 (9H, s with Sn satellites, J_{SnCH3}= 24), 7.25-7.65 (3H, m, ArylH), 8.40-8.60 (1H, m, ArylH). Trimethyl-(-2-nitrophenyl) stannane, the starting material, was recovered. The NMR spectrum confirmed that the reaction hadn't worked.

2-(2-Nitrophenyl) ethanol according to Morimoto's procedure[9]

2-Nitrotoluene (9.2 g, 67.0mmoles), sodium phenoxide (0.06 g, 0.56 mmoles), paraformaldehyde (0.9 g of 95 %) and dimethyl sulphoxide (20 mL) were heated for 1h at 60-67 ^oC. The mixture was poured into water and extracted with diethyl ether. The combined extracts were washed with saturated sodium chloride solution. The

organic phases were dried over magnesium sulfate and diethyl ether was distilled off. 2-(2-Nitrophenyl) ethanol was obtained as a yellow oil (4.3 g, 37 %) by distillation of the crude product on the Kugelrohr at 140°C /0.1mmHg. ^{1}H NMR: δ_H 2.1 (1H, br s, OH), 3.10-3.25 (2H, m, CH_2OH), 3.90-4.10 (2H, m, CH_2), 7.20 (1H, s, ArylH), 7.35-7.45 (1H, m, ArylH), 7.50-7.60 (1H, m, ArylH), 7.90-8.10 (1H, m, ArylH). ^{13}C NMR: δ_C 35.90; 62.55; 124.63; 127.40; 132.60; 132.83; 133.65; 149.65. IR: 3365 cm^{-1} (ν_{OH}); 1525 and 1348 cm^{-1} (ν_{NO2}). The synthesis of the alcohol was first made by Morimoto.[9]

2-(2-Aminophenyl) ethanol[10]

A small amount of 2-(2-nitrophenyl) ethanol (3 g, 18 mmoles) was added dropwise to a flask containing calcium chloride (1.2 g, 12.0 mmoles) and zinc powder (4 g, 180 mmoles) in hot water (25 mL). The mixture was heated under reflux for 30 minutes. The zinc was filtered, washed and sodium carbonate (1.2 g, 12.0 mmoles) was added in the filtrate. The salt was filtered, washed and the water was removed under vacuum. A mixture of sodium chloride and oil was obtained. The crude product was extracted with diethyl ether. The salt was filtered and the solvent was removed under vacuum. The product was obtained by distillation on the Kugelrohr. The title compound (2 g, 78 %) was obtained as a yellow oil; bp: 155 °C at 0.1 mmHg. ^{1}H NMR: δ_H 2.55-2.70 (2H, m, CH_2), 3.25-3.35 (3H, s, NH_2 and OH), 3.70-3.90 (2H, m, CH_2), 6.60-6.80 (2H, m, ArylH), 7.10-7.25 (2H, m, ArylH). ^{13}C NMR: δ_C 34.65; 62.95; 116.20; 119.13; 124.44; 127.50; 130.43; 144.80. IR: 3366 cm^{-1} (ν_{OH}); 2878-2942 ($\nu_{Calkyls}$); 1263 and 1044 cm^{-1} (ν_{C-NH2}). The results were consistent with the literature.[10]

2-(2-Bromoethyl) phenylamine with PBr_3, in pentane

2-(2-Aminophenyl) ethanol (1.0 g, 7.3 mmoles) was dissolved in n-pentane (10 mL). Phosphorus tribromide (1.98 g, 7.30 mmoles) was added dropwise to the above solution at room temperature. A solution of sodium hydroxide (5 ml of 2M) was added to dissolve the salt. The aqueous phase was extracted with n-pentane and the combined organic phases were dried over magnesium sulfate. The solvent was removed under vacuum. The crude product obtained was analysed by NMR spectroscopy. ^{1}H NMR: δ_H 2.00-2.40 (2H, m), 3.00-3.35 (2H, m, NH_2), 3.45-3.65 (2H, m), 6.60-7.25 (4H, m, ArylH). The main product observed by NMR was 2-(2-Bromoethyl) aniline. So the expected bromide was present in the solution mixture in presence of the starting material and other impurities, but the purification by distillation was not a success.

Attempted preparation of 2-(2-bromoethyl) phenylamine with PBr_3, in benzene

A mixture of 2-(2-aminophenyl) ethanol (1.0 g, 7.3 mmoles), phosphorus tribromide (1.98 g, 7.30 mmoles) and distilled pyridine in distilled benzene (10 mL) was stirred at 25 ^{o}C for 21h. The solution was diluted with water and extracted three times with EtOAc. The combined organic phase was successively washed with saturated $NaHCO_3$ solution, H_2O, and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum. The crude product obtained was analysed by NMR spectroscopy. ^{1}H NMR: δ_H 3.25 (2H, t, CH_2, J = 6.9), 3.85 (2H, t, CH_2, J = 6.9),

6.90-7.55 (4H, m, ArylH), 8.40-8.80 (1H, br s, NH). The NMR was consistent with the NMR of 2,3-dihydro-1*H*-indole.[38]

Protection of 2-(2-aminophenyl) ethanol with di-*tert*-butyl dicarbonate

To a stirred solution of 2-(2-aminophenyl) ethanol (1.4 g, 10.0mmoles) at 0 °C in a mixture of dioxane (10 mL), water (5 mL) and saturated aqueous solution of sodium hydrogen carbonate was added di-*tert*-butyl dicarbonate (2.4 g, 11.0 mmol). The reaction mixture was stirred at room temperature for 4h, before water (20 mL) was added. The crystals obtained were filtered under suction and recrystallised from dichloromethane/hexane (1:1) to yield 1.7 g of pure 2-(2-((tert-butyloxycarbonyl) amino) phenyl) ethanol (72 %), mp: 128-130 °C. ^{1}H NMR: δ_H 1.40 (9H, s, *tert*-Bu), 2.75 (2H, t, CH_2, J = 6), 3.85 (2H, t, CH_2OH, J = 6), 6.90-7.30 (3H, m, ArylH), 7.50 (1H, s, NH), 7.60-7.70 (1H, m, ArylH). The C-H-N microanalysis was performed but the numbers obtained was too different from the required numbers.

Bromination of 2-(2-((tert-butyloxycarbonyl) amino) phenyl) ethanol with PBr_3

A mixture of protected 2-(2-aminophenyl) ethanol (0.6 g, 42.0 mmoles) and pyridine (0.2 g, 21.0 mmoles) was dissolved in n-hexane (20 mL). The solution was cooled to -10 °C in an ice/salt bath. Phosphorus tribromide (5.6 g, 21.0 mmoles) was added dropwise to the solution so the temperature remained below 0 °C. The reaction was stirred overnight at ambient temperature. Then the resultant solution was quenched with water (20 mL). The aqueous phase was extracted with ether (3 x 20 mL). The combined organic layers were dried over magnesium sulfate and filtered. The solvent

was removed under vacuum to afford 0.8 g (63 %) of the bromide. ^{1}H NMR: δ_H 1.45 (9H, s, *tert*-Bu), 3.13 (2H, t, CH_2, J = 5.9), 3.53 (2H, t, CH_2Br, J = 5.9), 6.3 (1H, s, NH), 7.00-7.20 (3H, m, ArylH), 7.50-7.70 (1H, m, ArylH).

Deprotection of the amine

The protected amine was treated at room temperature with 3M HCl-EtOAc. After the reaction was completed (30 minutes), the solvent was removed under reduced pressure and the residue was added to dry ether. Then the ether was decanted and the residue further washed with ether several times. 0.7 g of product was obtained, but it was not the product of the deprotection. The NMR analysis of the organic phase was performed. ^{1}H NMR: δ_H 3.50 (2H, t, J= 5.4), 3.70 (2H, t, J_{HH} = 5.4), 3.90-4.00 (1H, m), 7.15-7.20 (3H, m, ArylH), 7.60-7.80 (1H, m, ArylH). The main product of this fraction seemed to be 2,3-dihydroindole. The NMR analysis of the aqueous phase was performed. ^{1}H NMR (D_2O): δ_H 3.00 (2H, t, J = 5.0 Hz), 3.75 (2H, t, J = 5.0), 4.60-4.70 (1H, m), 7.15-7.5 (4H, m, ArylH). The product observed seemed to be hydrobromide of 2-(2-aminophenyl) ethanol.

Attempted bromination of 2-(2-nitrophenyl) ethanol with PBr_3, pyridine

A mixture of 2-(2-nitrophenyl) ethanol (1.0 g, 6.0 mmoles) and pyridine (0.5 g, 6.0 mmoles) was dissolved in n-pentane (15 mL). The solution was cooled to -10°C in an ice/salt bath. Phosphorus tribromide (1.6 g, 6.0 mmoles) was added dropwise to the solution so the temperature remained below 0 °C. The reaction was stirred overnight at ambient temperature. Then the resultant solution was quenched with water (20 mL) and the organic layer was washed with sulfuric acid (0.1 g, 12.6 mmoles). The

aqueous phase was extracted with ether (3 x 20 mL), dried over magnesium sulfate and filtered. The solvent was removed and the crude mixture obtained was analysed by ^{1}H NMR. The NMR didn't show any trace of the expected product.

Preparation of phenylselenocyanate

A solution of phenylselenyl chloride (3.83 g, 0.02 mol) dissolved in acetonitrile (80 mL) was added dropwise to trimethylsilyl cyanide (2.08 g, 0.02 mol) stirring in acetonitrile (20 mL) at room temperature. After addition, the mixture was stirred for 1h, the solvent was evaporated under reduced pressure, and the residue was distilled in the Kugelrohr, at 80 °C/0.1 mmHg. The distillation afforded 3.18 g of a brown oil (87%) which seemed to be the phenylselenocyanate. ^{1}H NMR: δ_H 7.32-7.42 (3H, m, ArylH), 7.58-7.66 (1H, m, ArylH). ^{13}C NMR: δ_C 100.34; 121.79; 129.73; 130.35; 132.72. IR 2340 cm^{-1} (ν_{CN}).

However trace of impurities invalidated the C-H-N microanalysis.

Attempted preparation of [1-(phenylseleno)ethyl] 2-(2-((*tert*-butyloxycarbonyl) amino) phenyl) ethanol

Tri-*n*-butylphosphine (0.99 g, 4.90 mmol) was injected dropwise into a magnetically stirred solution of protected 2-(2-aminophenyl) ethanol (1.00 g, 4.00 mmol) and phenylselenocyanate (0.91 g, 5.00 mmol) in dry THF (15 mL) under a nitrogen atmosphere. After two days, the solvent was evaporated, and the residual oil was chromatographed over silica gel with chloroform/hexane (3:7) to yield a complex mixture but not the expected product of the reaction.

Attempted preparation of [1-(phenylseleno) ethyl] 2-(2-nitrophenyl) ethanol

Tri-*n*-butylphosphine (1.5 g, 7.0 mmoles) was injected dropwise into a magnetically stirred solution of protected 2-(2-nitrophenyl) ethanol (1.0 g, 6.0 mmoles) and phenylselenocyanate (1.4 g, 7.0 mmoles) in dry THF (20 mL) under a nitrogen atmosphere. After two days, the solvent was evaporated, and the residual oil was chromatographed over silica gel with chloroform/hexane (3:7) to yield a mixture of products. However the expected selenide was not observed.

Mesylate of 2-(2-aminophenyl) ethanol

Methane sulfonyl chloride (1.6 g, 0.014 mol) was added over 5 min to a flask containing 2-(2-aminophenyl) ethanol (2 g, 0.014 mol) and triethylamine (1.84 g, 0.018 mol) in dry dichloromethane (20 mL) cooled with an ice-salt bath and under a nitrogen atmosphere. After the solution was stirred further 30 minutes, water was added and the resulting mixture was extracted with dichloromethane. The organic phase was washed with water, and dried over magnesium sulfate. The solvent was evaporated under vacuum. The NMR spectrum showed a trace of the starting material, in addition to the mesylate. ^{1}H NMR: δ_H 2.87 (2H, t, CH_2, J = 5.2), 2.98 (3H, s, CH_3), 3.93 (2H, t, CH_2, J = 5.2), 7.00-7.70 (4H, m, ArylH), 8.40-8.60 (2H, sbr, NH_2). But the presence of the starting material nullified the C-H-N microanalysis.

Attempted generation of 2-phenylselenoethylamine

A solution of sodium benzeneselenolate was prepared by treatment of diphenyldiselenide in dry ethanol with sodium borohydride. The mesylate of 2-(2-

aminophenyl) ethanol was added and the solution was heated under reflux for 2 hours. The solvent was removed, water was added and the solution was washed with hexane. The aqueous layer was basified with potassium carbonate, extracted with dichloromethane and the combined organic fractions were dried over magnesium sulfate. The solvent was removed and the crude product obtained was analysed by NMR spectroscopy. The NMR spectrum showed the presence of several by-products but not the expected selenide.

Mesylate of 2-(2-nitrophenyl) ethanol

Methane sulfonyl chloride (0.7 g, 0.006 mol) was added over 5 minutes in a flask with 2-(2-nitrophenyl) ethanol (1 g, 0.006 mol) and triethylamine (0.82 g, 0.008 mol) in dry dichloromethane (20 mL) cooled with an ice-salt bath and under a nitrogen atmosphere. After the solution was stirred further 30 minutes, water was added and the resulting mixture was extracted with dichloromethane. The organic phase was washed with water, and dried over magnesium sulfate. The solvent was evaporated under vacuum. ^{1}H NMR: δ_H 2.6 (3H, s, CH_3), 3.38 (2H, t, CH_2, J = 7.5), 3.83 (2H, t, CH_2, J = 7.5), 7.10-7.70 (3H, m, ArylH), 7.90-8.00 (1H, m, ArylH). Some impurities were also present.

Attempted generation of 2-phenylselenide compound from the mesylate of 2-(2-nitrophenyl) ethanol

A solution of sodium benzeneselenolate was prepared by treatment of diphenyldiselenide in dry ethanol with sodium borohydride. The mesylate of 2-(2-nitrophenyl) ethanol was added and the solution was heated under reflux for 2 hours.

The solvent was removed, 5 % HCl was added and the solution was washed with hexane. The aqueous layer was basified with potassium carbonate, extracted with dichloromethane and the combined organic fractions were dried over magnesium sulfate. The solvent was removed under vacuum. The NMR spectrum showed the presence of several products but not the expected nitro-compound.

Attempted bromination of 2-(2-((*tert*-butyloxycarbonyl) amino) phenyl) ethanol with HBr

2-(2-((*Tert*-butyloxycarbonyl) amino) phenyl) ethanol (1.5 g, 6.3 mmoles) and concentrated hydrobromic acid (25 mL, 48 % in water) were maintained at gentle reflux for 4h. The cooled mixture was diluted with water, the organic phase was separated, and combined with a dichloromethane extract of the aqueous phase. This solution was washed well with water, dried over magnesium sulfate, and evaporated *in vacuo.* The residue was distilled *in vacuo.* Neither the ^{1}H NMR spectra of the organic phase, nor the ^{1}H NMR of the aqueous phase showed any trace of the expected product of bromination.

Bromination of 2-(2-nitrophenyl) ethanol with HBr

2-(2-Nitrophenyl) ethanol (3.21 g, 21.6 mmol) and concentrated hydrobromic acid (40 ml, 47-49%) were maintained at gentle reflux for 13h. The cooled mixture was diluted with water, the organic phase was separated and combined with a DCM extract of the aqueous phase. The previous solution was washed with water, dried over sodium sulfate, and evaporated in vacuum. The crude expected bromide was purified by distillation in the Kugelrohr at 120°C /0.1mmHg to give a yellow oil (3.21 g, 65 %)

which crystallized on standing; m.p. 25 °C, ^{1}H NMR: δ_H 3.45 (2H, t, CH_2, J = 7.7), 3.65 (2H, t, CH_2, J = 7.7, CH_2Br), 7.20-7.60 (3H, m, ArylH), 7.90-8.10 (1H, m, ArylH). C-H-N microanalysis: found, C 41.77%, H 3.50 %, N 6.09 %; $C_8H_8NO_2Br$ requires C 42.09 %, H 3.32 %, N 6.11 %

Reduction of 2-(2-nitrophenyl) bromoethane

A small amount of 2-(2-nitrophenyl) bromoethane (1 g, 4 mmoles) was added dropwise to a flask containing calcium chloride (0.8 g, 8 mmoles) and zinc powder (8 g, 360 mmoles) in hot water (30 mL). The mixture was heated under reflux for 30 minutes. The zinc was filtered, washed and sodium carbonate (0.8 g, 8 mmol) was added in the filtrate. The salt was filtered, washed and the water was removed under vacuum. A mixture of sodium chloride and oil was obtained. The crude amine was extracted with diethyl ether. The salt was filtered and the solvent was removed under vacuum. 0.3 g (38 %) of 2-(2-bromoethyl) aniline was obtained after distillation in the kugelrohr at 190 °C /0.1 mmHg. ^{1}H NMR: δ_H 2.85 (2H, t, CH_2, J = 6.3), 3.90 (2H, t, CH_2, J = 6.3, CH_2Br), 6.70 (1H, t, ArylH, J = 8.12), 6.78 (1H, d, ArylH, J = 9.4), 7.05 (1H, d, ArylH, J = 9.4), 7.25 (1H, t, ArylH, = 8.1).

Hydrobromide of 2-(2-bromoethyl) phenylamine

2-(2-Aminophenyl) ethanol (0.24 g, 1.75 mmoles) was dissolved in constant-boiling hydrobromic acid (20 ml, 48 % in water) and refluxed for 4h. The crystalline precipitate was filtered, washed with ice-cold hydrobromic acid and dried *in vacuo*. 0.29 g (82 %) of the hydrobromide of 2-(2-bromoethyl) phenylamine was obtained as a light grey solid, mp. 161 °C. ^{1}H NMR (D_2O): δ_H 2.80 (2H, t, CH_2, J = 10.6), 3.75

(2H, t, CH_2, J = 10.6), 4.70 (2H, s, NH_2), 7.20-7.40 (4H, m, ArylH). The C-H-N microanalysis obtained was too different of the C-H-N microanalysis required.

1-(2-Bromoethyl)-2-isocyanatobenzene

To a solution of the hydrobromide of 2-(2-bromoethyl) aniline in toluene (0.6 g, 21 mmoles) was added, at 120 °C over 10 minutes, a solution of phosgene in toluene (5 mL of 20 %). The solvent and excess of phosgene were removed in vacuo to give the title compound (0.4 g, 86 %). ^{1}H NMR δ_H 3.18 (2H, t, CH_2, J = 7.6), 3.58 (2H, t, CH_2Br, J = 7.6), 7.10-7.45 (4H, m, ArylH); ^{13}C NMR, δ_c 31.77; 35.99; 121.59; 124.90; 126.41; 126.74; 128.75; 131.00; 133.22. IR: 2271.64 cm^{-1} (ν_{NCO}). GC-MS: m/z(%), 227/225(20), 182(10), 146(100), 132(6), 57(5); C-H-N microanalysis found, C 47.82 %, H 3.57 %, N 6.20 %; C_9H_8NOBr requires C 47.49 %, H 3.38 %, N 6.98 %.

Ring closure of 1-(2-bromoethyl)-2-isocyanatobenzene

Procedure 1

Tributyltin hydride (0.19 g, 0.5 eq) in solution in toluene (2 mL) was slowly added, via the syringe pump for 1h 30min, into a solution of 1-(2-bromoethyl)-2-isocyanatobenzene (0.3 g, 1.3 mmol) and AIBN (5 %, 0.33 mg, 0.002 mmol) in toluene (25 mL). During this time the mixture was heated at 80 °C and the reaction was carried out under nitrogen. After 7h, the heating was stopped and the GC-MS analysis was carried out. GC-MS: **Peak 272**, unidentified, m/z(%) M^+ 121(4), 94(3), 69(100), 54(19), 52(8); **Peak 303**, C_7H_7Br, m/z(%) M^+ 170/172(5), 91(100), 65(13)

(probably bromoethyl-benzene), **Peak 324**, 1-ethyl-2-isocyanatobenzene (library fit 992), m/z(%) M^+ 147(49), 132(100), 119(26), 104(8), 77(21), 63(7), 51(15); **Peak 397**, $C_{11}H_{13}N$, m/z(%) M^+ 159(15), 119(3), 91(100), 65(7) (probably 2,2-dimethyl-3-phenyl-propionitrile); **Peak 615**, 1-benzyl-2,3-dihydro-1*H*-indole, m/z(%) M^+ 209(100), 132(36), 91(74), 77(6), 65(18), 51(6). The mass spectrum was consistent with the literature.[38] **Peak 734**, $C_{16}H_{15}NO_2$, m/z(%) M^+ 253(13), 209(12), 132(4), 118(10), 91(100), 65(11) (probably 2,3-dihydro-indole-1-carboxylic acid benzyl ester); **Peak 814**, $C_{17}H_{16}N_2O$, m/z(%), M^+ 264(63), 146(100), 128(45), 118(30), 103(5), 91(24), 77(13), 65(9) (probably 1-(2,3-dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one). The major products observed were bromoethyl-benzene and 1-benzyl-2,3-dihydro-1*H*-indole.

Procedure 2

A solution of 1-(2-bromoethyl)-2-isocyanatobenzene (0.07 g, 0.31 mmol) and tributyltin hydride (0.09 g, 0.31 mmol) in solution in benzene (2 mL) was photolysed for 30 minutes. The solution was degassed for 15 minutes before photolysis. The solution was analysed by GC-MS. **Peak 224**, 2-ethyl-aniline (library fit 996), m/z(%) 121(43), 106(100), 77(11), 49(3); **Peak 233**, 1-ethyl-2-isocyanato-benzene (library fit 992), m/z(%) 132(27), 119(100), 106(31), 91(43), 77(11), 65(16), 58(6), 51(12); **Peak 249**, 2,3-dihydro-1*H*-indole (library fit 988), 118(100), 91(21), 65(6), 59(9); **Peak 301**, 1*H*-indole (library fit 926), m/z(%) 117(100), 90(37), 63(14), 58(7); **Peak 346**, N.D., m/z(%) 175(22), 132(100), 117(18), 91(7), 77(8), 69(13); **Peak 369**, 1-formyl-2,3-dihydro-indole (library fit 990), m/z(%) 147(80), 118(100), 91(28), 65(9), 51(5); **Peak 645**, $C_{17}H_{16}N_2O$, probably 1-(2,3-dihydro-indol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one. The major product observed was 2,3-dihydro-1*H*-indole.

Procedure 3

A solution of 1-(2-bromoethyl)-2-isocyanatobenzene (0.1 g, 0.44 mmol) and tributyltin hydride (0.13 g, 0.44 mmol) in solution in benzene (2 mL) was photolysed for 1h. The solution was degassed for 15 minutes before photolysis. The solution was analysed by GC-MS. **Peak 242**, 2-ethyl-aniline; **Peak 251**, 1-ethyl-2-isocyanato-benzene; **Peak 263**, 2,3-dihydro-1*H*-indole; **Peak 398**, 1-formyl-2,3-dihydro-indole; **Peak 690**, $C_{17}H_{16}N_2O$, propably 1-(2,3-dihydro-indol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one; **Peak 710**, $C_{17}H_{16}N_2O$, m/z(%) M^+ 264(65), 147(6), 132(10), 118(100), 91(15), 77(7), 65(3) (propably bis-(2,3-dihydroindol-1-yl)-methanone). The major products observed were 1-formyl-2,3-dihydro-indole and 1-(2,3-dihydro-indol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one.

Procedure 4

A solution of 1-(2-bromoethyl)-2-isocyanatobenzene (0.1 g, 0.44 mmol) and tributyltin hydride (0.13 g, 0.44 mmol) in solution in benzene (2 mL) was photolysed for 2h. The solution was degassed for 15 minutes before photolysis. The solution was analysed by GC-MS, **Peak 271**, 2,3-dihydro-1*H*-indole; **Peak 395**, 1-formyl-2,3-dihydro-indole; **Peak 442**, 3,4-dihydro-1*H*-quinolin-2-one, m/z(%) M^+ 147(100), 128(9), 118(56), 104(15), 92(24), 78(14), 63(5), 59(8); **Peak 688**, $C_{17}H_{16}N_2O$, probably 1-(2,3-dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one; **Peak 708**, $C_{17}H_{16}N_2O$, probably bis-(2,3-dihydro-indol-1-yl)-methanone. The major products observed were 3,4-dihydro-1*H*-quinolin-2-one and 1-(2,3-dihydro-indol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one.

Procedure 5

A solution of 1-(2-bromoethyl)-2-isocyanatobenzene (0.1 g, 0.44 mmol) and tributyltin hydride (0.13 g, 0.44 mmol) in solution in benzene (2 mL) was photolysed in a quartz tube with light from a 400W medium pressure Hg lamp at ambient temperature for 3h. The solution was degassed for 15 minutes before photolysis. The solution was chromatographed on neutral alumina eluting with hexane/ethyl acetate (1:1). Several preliminary fractions containing tin residues were obtained followed a final fraction (0.05 g, *ca.* 77 %). The final fraction was analysed by ^{1}H NMR which showed the presence of 3,4-dihydro-1*H*-quinolin-2-one (44.1 %) δ_H 2.63 (1H, d, J = 7.4), 2.66 (1H, d, J = 5.9), 2.98 (2H, t, J = 7.6), 6.75 (1H, d, J = 7.9), 6.99 (1H, dd, J = 6.9, 8.5), 7.17 (2H, m), 8.02 (1H, b). This spectrum was essentially the same as that reported in the literature.[39], 1-formyl-2,3-dihydro-indole (2 rotamers, ratio 3:1), major isomer (11.8 %): δ_H 3.16 (2H, m), 4.08 (2H, t, $^{3}J_{HH}$ = 8.7), 7.05-7.4(4H, m), 8.94 1H, s), minor isomer (3.9 %): δ_H 3.24 (2H, m), 4.13 (2H, m), 8.53 (1H, s). This spectrum was essentially identical to that reported in the literature.[40] Several resonances due to minor identified components were also present. GC-MS: **Peak 271** (minor) 2,3-dihydro-1*H*-indole, 118(100), 91(21), 65(6), 59(9); **Peak 399**, 1-formyl-2,3-dihydro-indole, m/z(%), 147(80), 118(100), 91(28), 65(9), 51(5); **Peak 430**, 3,4-dihydro-1*H*-quinolin-2-one , m/z(%), 147(100), 128(9), 118(56), 104(15), 92(24), 78(14), 63(5), 59(8); Peak **644** (minor), $C_{17}H_{16}N_2O$, probaly 1-(2,3-dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one, m/z(%), 264(63), 146(100), 128(45), 118(30), 117(15), 103(5), 91(24), 77(13), 65(9). **Peak 659** (minor), $C_{17}H_{16}N_2O$, probably bis-(2,3-dihydro-indol-1-yl)-methanone, 264(65), 147(6), 132(10), 118(100), 91(15), 77(7), 65(3). Ratio of **644:659** was 1.7:1

Procedure 6

1-(2-Bromoethyl)-2-isocyanatobenzene (0.1 g, 0.42 mmol) and EPHP (0.8 g, 7 eq) in solution in benzene (30 mL) were heated for 1h under a nitrogen atmosphere at 70 °C. AIBN (0.03 g, 0.04 eq) was added in two portions over 30 minutes and reflux continued for 3 days. On cooling, the reaction was diluted with petroleum ether and washed successively with sodium hydrogen carbonate, aqueous hydrochloric acid (2M), sodium hydrogen carbonate and brine. The organic layer was then dried over magnesium sulfate, filtered and concentrated in vacuo. GC-MS: **Peak 127**, N.D., m/z(%) M^+ 207(12), 113(27), 98(100), 84(8), 68(4), 55(11); **Peak 345**, 2,3-dihydro-1*H*-indole, 118(100), 91(21), 65(6), 59(9); **Peak 450 and Peak 488**, isomers of 1-bromo-2,3-dihydro-1*H*-indole, m/z(%), 197/199(42), 117(100), 89(15), 59(14); **Peak 509**, 1-(2-bromo-ethyl)-2-isocyanato-benzene or isomer of 3-bromo-3,4-dihydro-1*H*-quinolin-2-one, m/z(%), 225/227(48), 210/212(100), 145(10), 130(45), 117(11), 103(5), 89(16), 78(5), 63(7); **Peak 546**, isomer of 1-bromo-1*H*-indole, m/z(%), 195/197(100), 116(72), 98(6), 89(32), 73(11), 63(15); **Peak 567**, isomer of 2,2-dibromo-2,3 dihydro-1*H*-indole, 279 (45), 277(100), 275(45), 195/197(98), 116(35), 98(6), 89(37), 64(6), 59(33); **Peak 593**, 1-benzyl-2,3-dihydro-1*H*-indole. The major products observed were products of bromination.

Procedure 7

A solution of 1-(2-bromoethyl)-2-isocyanatobenzene (0.04 g, 0.2 mmol), TTMSS (0.05 g, 1.2 eq) in solution in deuteriobenzene (1 mL) was heated for 2h30min at 103 °C, in presence of a catalytic amount of 1,1'-azo-di-cyclohexanecarbonitrile (10%, 4 mg). On cooling, the GC-MS analysis was carried out. The ^{1}H NMR spectrum showed mainly unreacted isocyanate and TTMSS together with 3,4-dihydro-1*H*-

quinolin-2-one (ca. 10 %) and several resonances due to minor unidentified components. GC-MS: **Peak 10.6,** 1-ethyl-2-isocyanatobenzene (5.3 rel. %); **Peak 15.1**, 1-formyl-2,3-dihydro-indole (1.6 rel. %); **Peak 15.6**, 3,4-dihydro-1*H*-quinolin-2-one (93.1 rel. %) **Peak 23.1** $C_{17}H_{16}N_2O$, probably 1-(2,3-dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one. TTMSS and other unidentified components (mostly Si-compounds) were also observed. However the major product observed was 1-(2,3-dihydroindol-1-yl)-3,4-dihydro-1*H*-quinolin-2-one.

2. Homolytic reactions of 1-bromo-4-isocyanatobutane

Preparation of 4-bromobutylamine, hydrobromide salt

4-Aminobutan-1-ol (2 g, 22.4 mmol) was refluxed for 3h in aqueous hydrobromic acid (48 %). On cooling, the solvent was removed under vacuum, to afford 3.49 g (68 % yield) of crude hydrobromide salt. δ_H 1.60-1.71 (2H, m), 1.78-1.83 (2H, m), 2.84-2.90 (2H, m), 3.36-3.40 (2H, m); δ_C = 25.8, 29.2, 33.8, 39.1; ν_{NH3+} = 1500 cm^{-1} and ν_{NH} = 3490 cm^{-1}. M^+ 235(1), 233(2), 231(1), 208(2), 210(4), 212(2), 192(3), 194(5), 196(3), 152/154(100), 135/137(8), 72(94). C-H-N microanalysis: found, C 20.79 %, H 4.24 %, N 6.15 %; $C_4H_{11}NBr_2$ requires C 20.62 %, H 4.76 %, N 6.01 %.

Synthesis of 1-bromo-4-isocyanato-butane

Phosgene (5 mL of solution in toluene, 20 %) was added slowly into a refluxing solution of 4-bromobutylamine, hydrobromide salt (2.15 g, 9.2 mmol) in benzene. The mixture was refluxed until no HCl evolution was noticed. The solvent and remaining phosgene were removed under vacuum. The crude product was distilled at

120°/ 1 mmHg to afford 1.4 g (89 % yield) of 1-bromo-4-isocyanatobutane. δ_H 1.78 (2H, quin. J= 7), 1.98 (2H, quin. J = 7), 3.38 (2H, t, J = 6.4), 3.44 (2H, t, J = 6.7); δ_C = 30.0, 30.1, 34.0, 42.6, 123.2; ν_{NCO} = 2272 cm^{-1}.

Ring c1osure of 1-bromo-4-isocyanato-butane

Procedure 1

A solution of 1-bromo-4-isocyanato-butane (0.1 g, 0.6 mmol) in presence of tri-n-butyltin hydride (0.17 g, 0.6 mmol) in benzene (3 mL) was photolysed at room temperature for 2h. The solution mixture was analysed by GC-MS: **Peak 65**, toluene (library fit 995), m/z(%) M^+ 92(80), 91(100), 65(16), 51(4), 41(2); **Peak 73**, octane (library fit 997), m/z(%) M^+ 114(28), 85(100), 71(32), 57(9), 43(13); **Peak 174**, butylbenzene (library fit 924), m/z(%) M^+ 134(25), 105(8), 91(100), 79(13), 65(16), 51(8), 41(5) **Peak 262** and **Peak 277**, unresolved peaks, mixture of piperidine-2-one (library fit 937) and 1-formyl-pyrrolidine (library fit 794), m/z(%) M^+ 99(100), 70(26), 58(6), 55(38), 42(78); the presence of piperidine-2-one was confirmed by NMR spectroscopy: δ_H 1.70-1.80(4H, m), 2.35-2.40 (2H, t. J= 6.4 Hz), 3.30-3.41 (2H, m), 5.90(1H, br); **Peak 361**, 1,2-diphenylethane (library fit 998), m/z(%) M^+ 182(24), 91(100), 65(4), 51(4), **Peak 527**, unidentified, product with a bromine atom, m/z(%) M^+ 226/228(18), 174/176(65), 154/156(10), 128(20), 114(24), 98(100), 86(13), 70(77), 55(51), 43(52). The major product observed was toluene.

Procedure 2

A solution of 1-bromo-4-isocyanatobutane (0.1 g, 0.6 mmol) in presence of tri-n-butyltin hydride (0.17 g, 0.6 mmol) in benzene (1 mL) was photolysed at room

temperature for 3h. GC-MS analysis: **Peak 63**, 1-isocyanatobutane (library fit 947), m/z(%) M^+ 98(21), 91(21), 70(16), 56(42), 43(100), 41(99); **Peak 69**, octane; **Peak 114**, ND, m/z(%) 128(1), 119(3), 112(11), 99(16), 84(100), 70(26), 57(24), 42(35), (probably $C_8H_{18}N$); **Peak 172**, butyl-benzene; **Peak 218**, pentylbenzene (library fit 998), m/z(%) M^+ 148(23), 105(11), 91(100), 78(8), 65(15), 51(6), 41(10); **Peak 231**, unidentified, m/z(%) M^+ 143(37), 114(100), 98(48), 87(11), 70(89), 56(32), 43(78); **Peak 261 and Peak 292**, unresolved peaks, mixture of piperidine-2-one (library fit 937) and 1-formyl-pyrrolidine (library fit 794), **Peak 361**, 1,2-diphenylethane; **Peak 438**, $C_9H_{16}N_2O$, m/z(%) M^+ 168(32), 155(6), 125(6), 98(67), 70(100), 56(27) (probably di-pyrrolidin-1-yl-methanone or 1-pyrrolidin-1-yl-piperidin-2-one), **Peak 444**, N.D., m/z(%) 170(30), 155(2), 127(9), 114(13), 98(100), 86(17), 70(95), 55(29), 43(51), (probably $C_9H_{18}N_2O$). The major product observed was 1-isocyanatobutane.

Procedure 3

A solution of 1-bromo-4-isocyanatobutane (0.1 g, 0.6 mmol) in presence of tri-n-butyltin hydride (0.17 g, 0.6 mmol) in benzene (3 mL) was photolysed at room temperature for 5h. GC-MS: **Peak 64**,1-isocyanatobutane; **Peak 70**, octane; **Peak 173**, butylbenzene; **Peak 264**, mixture of piperidin-2-one or 1-formyl-pyrrolidine; **Peak 317**, unidentified, m/z(%) M^+ 192(14), 149(7), 135(18), 91(17), 79(27), 57(100), 41(21); **Peak 332**, unidentified, m/z(%) M^+ 190(25), 168(12), 147(100), 117(9), 105(14), 91(37), 77(4), 41(7); **Peak 361**, 1,2-diphenylethane. The major product observed was 1-isocyanatobutane, the product of direct reduction of 1-bromo-4-isocyanatobutane.

Procedure 4 with TTMSS

- With TTMS at 103 °C

A solution of 1-bromo-4-isocyanatobutane (0.04 g, 0.22 mmol), TTMSS (0.07 g, 1.2 eq) in solution in deuteriobenzene (1 mL) was heated for 2h30 min at 103 °C, in presence of a catalytic amount of 1,1'-azobis-cyclohexanecarbonitrile (10 %, 5 mg). The results obtained for this experiment are reported below.

- With TTMS at 83 °C

A solution of 1-bromo-4-isocyanatobutane (0.02 g, 0.11 mmol), TTMSS (0.03 g, 1.2 eq) in solution in deuteriobenzene (1 mL) was heated for 7h at 83 °C, in presence of a catalytic amount of 1,1'-azobis-cyclohexanecarbonitrile (10 %, 3 mg).

NMR spectroscopy and GC-MS analysis were carried out after cool down of the solution. For both experiments the results remained the same. The ^{1}H NMR spectrum showed mainly unreacted starting materials. GC-MS: **Peak 3.46**,1-isocyanatobutane; **Peak 11.12**, possibly piperidin-2-one; **Peak 15.90**, unresolved peak, $C_9H_{16}N_2O$, probably di-pyrrolidin-1-yl-methanone or 1-pyrrolidin-1-yl-piperidin-2-one; **Peak 16.72**, unidentified, m/z(%) M^+ 108(100), 91(100), 65(18), 41(7), (possibly C_7H_8O). The major product observed was 1-isocyanatobutane. GC-MS analysis confirmed that conversion of the bromo-isocyanate was low, but showed a small amount probably of piperidine-2-one **146**.

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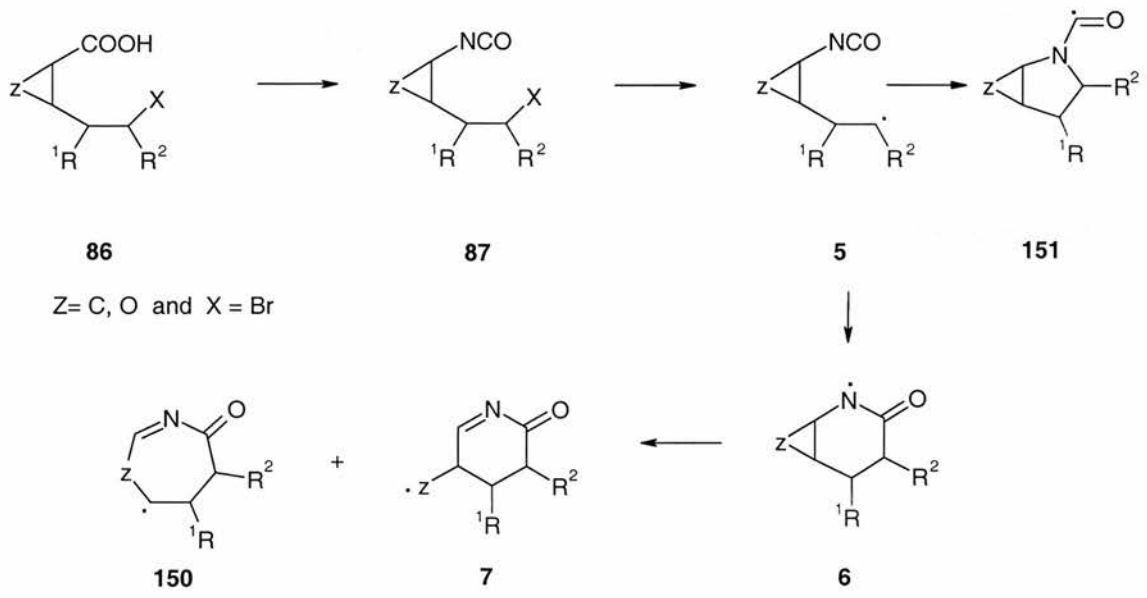
Chapter 4

-

INTRAMOLECULAR ADDITION TO CYCLOPROPYL ISOCYANATES

I- Introduction

The second alternative to prevent reversal of the ring closure onto the isocyanate group, is to introduce another system, such as a three-membered ring, that causes rapid onward rearrangement.



scheme 90

We expected that the tri-*n*-butyltin radical would abstract the bromine atom from compound **87**, the newly formed radical **5** would then add to the carbonyl C-atom of the isocyanate group to produce the acylamino radical **6**. Because of the adjacent, strained, 3-membered ring, radical **6** should rapidly undergo β-scission of either the C-Z bond to produce radical **7**, or the adjacent C-C bond to produce radical **150**, before finally an H-atom would be picked up from the tin hydride. Alternatively, cyclisation might occur at the nitrogen of the isocyanate moiety to form an aminoacyl

radical **151**. Subsequently this radical would abstract a hydrogen atom from the solvent or the tri-*n*-butyl tin hydride.

II- Results and discussion

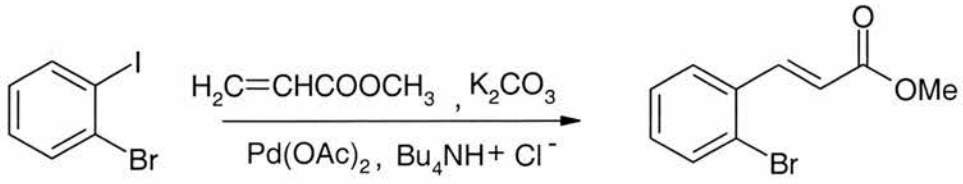
1. Synthesis of *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene (87a)

86a **87a**

For the preparation of the precursor **87a** (R^1 and R^2 forming an aromatic system and Z = CH_2 and X = Br) we followed a synthesis from the literature according to Vallgarda[1] as described below.

1.1. Methyl *trans*-3-(2-bromophenyl) propenoate (153a)

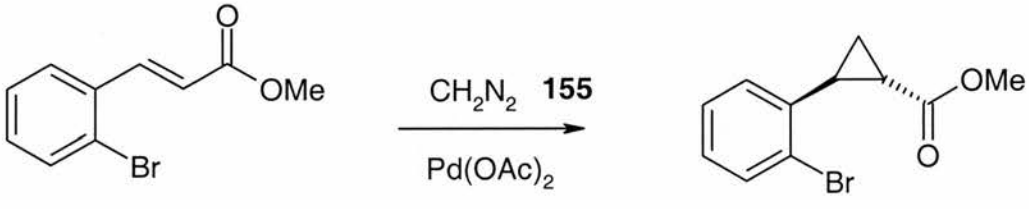
Trans arylated methyl acrylate **153a** was prepared from the corresponding aryl iodide, 2-bromoiodobenzene **152**, by a palladium-catalysed coupling with methyl acrylate under phase transfer conditions with tetra-*n*-butyl ammoniun chloride.



152 **153a** 81%

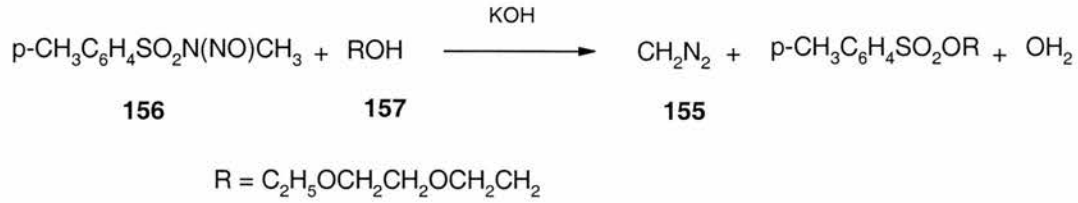
Vinylation of aromatic halides under solid-liquid phase transfer conditions can be greatly accelerated by using potassium carbonate as inorganic base. The ester **153a** was prepared with a yield of 81 %.

1.2. Methyl *trans*-3-(2-bromophenyl)cyclopropane carboxylate (154a)



153a **154a** 98%

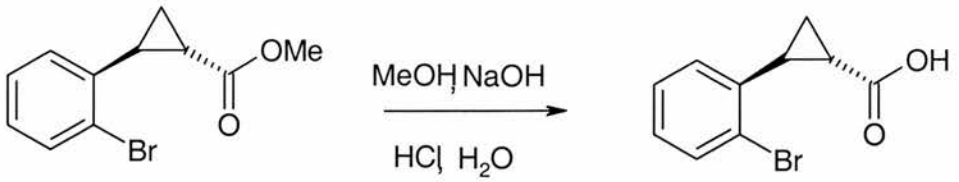
The arylated methyl acrylate derivative **153a** was cyclopropanated with diazomethane **155** in the presence of 0.005 equiv. of palladium(II) acetate. Higher concentrations of the catalyst often lead to precipitation of palladium(0) with accompanying termination of the reaction. We prepared the diazomethane, compound **155**, and distilled it to a flask containing the starting material. The synthesis of the diazomethane was achieved using a procedure described by Deber and Backer.[2]



N-Methyl-*N*-nitroso-*p*-toluenesulfonamide **156**, was added to 2-(2-ethoxyethoxy)-ethanol **157**, in alkaline conditions, to afford the diazomethane. For the efficient preparation of diazomethane, we noticed it was essential to have appropriate fittings. Diazomethane is not only toxic, but also potentially explosive. It is recommended that ground joints and sharp surfaces should be avoided. Thus all glass tubes should be carefully fire-polished, connections should be made with rubber stoppers, and separatory funnels should avoided, as should etched or scratched flasks. At the beginning, we did the reaction with a fitting used in the group before. But the plastic tubes used for the distillation of the diazomethane on to the starting material, seemed to react with the solution and gave it a black coloration. However, when we used the Aldrich distillation kit, the solution with the starting material was the expected yellow colour. The reaction was described above, scheme 3 (maybe it was the solution with a product or the catalyst which reacted with the plastic tube). So, after reaction, the crude product was obtained in 98 % yield after purification on a silica column.

1.3. *Trans*-3-(2-bromophenyl)cyclopropane carboxylic acid (86a)

Alkaline hydrolysis gave the desired *trans*-arylcyclopropane carboxylic acid **86a**.

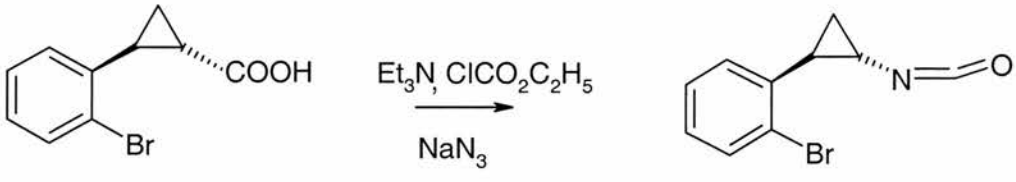


154a **86a** 53%

The resulting ester **154a** was dissolved in methanol and sodium hydroxide, then acidified with hydrochloric acid. The product **86a** was a white powder. The ^{1}H NMR spectrum was in satisfactory agreement with the literature and was consistent with formation of the carboxylic acid.

1.4. *Trans*-1-bromo-(2-isocyanatocyclopropyl) benzene (87a)

The corresponfing 2-(2-bromo-phenyl)-cyclopropylamine was prepared according to Vallgarda's procedure[1]. So the isocyanate derivative was prepared by reaction of the corresponding carboxylic acid **86a** with sodium azide and ethyl chloroformate in anhydrous conditions via a Curtius rearrangment. The reaction scheme is outlined below.



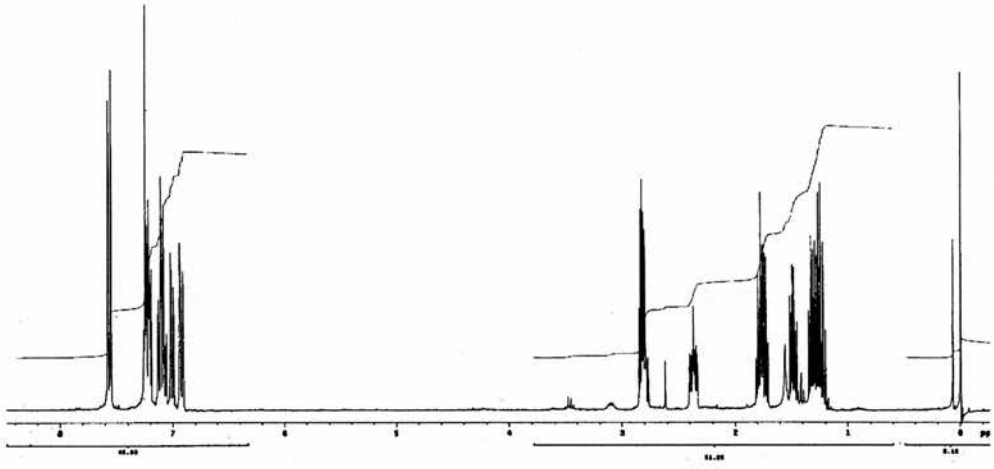
86a **87a**

This route is often used for the synthesis of primary amines by thermal rearrangement of azides of carboxylic acids and is also widely used for the synthesis of isocyanates.

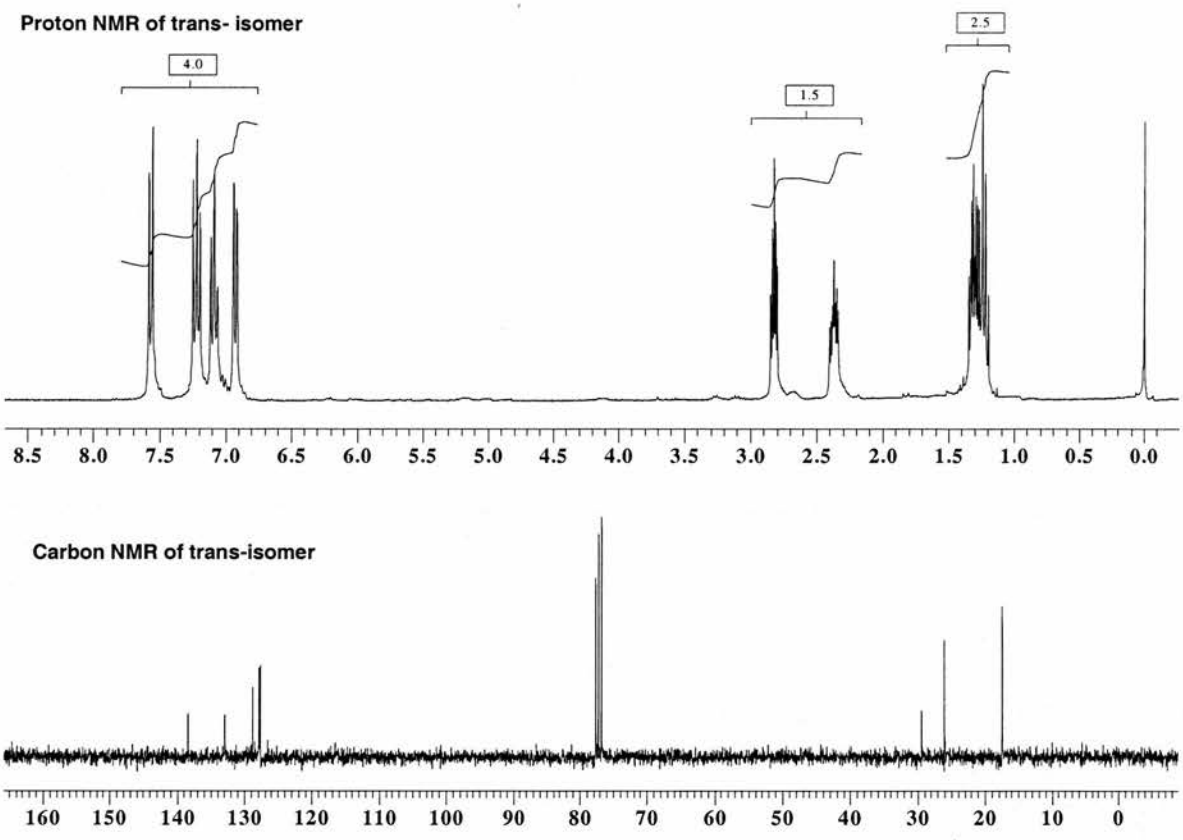
In his synthesis of the corresponding amine, Vallgarda did not isolate the intermediaiate isocyanate. The acid **86a** in presence of ethyl chloroformate and triethylamine was stirred at –10 °C in dry acetone under a nitrogen atmosphere. After 2.5h sodium azide dissolved in water was added and the solution was stirred for a further 2h. The cold mixture was poured into ice-cold water and then worked up. The adduct **87a** was obtained as an oil. The results of the analysis (^{1}H and ^{13}C NMR spectra and IR spectroscopy, ν_{NCO} = 2273 cm $^{-1}$) showed that the isocyanate had been formed. The traces of by-products in the NMR spectra were not significant and the isocyanate was used directly, without further purification, for the following procedure.

The schemes below show the NMR spectra obtained with the *trans*-isomer and the NMR of what we believe to be a mixture of the both *cis* and *trans* isomers (ratio 1.0:3.0), the ratio was measured from the NMR integrals.

^{1}H NMR of *cis* and *trans* isomers

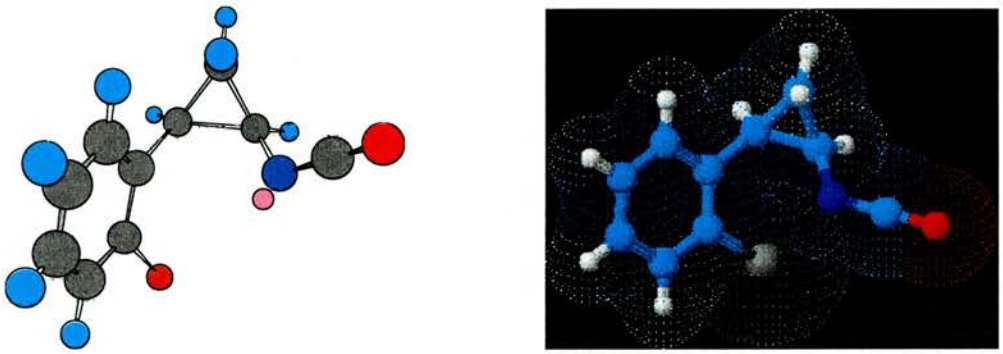


^{1}H and ^{13}C NMR of *trans*-isomer



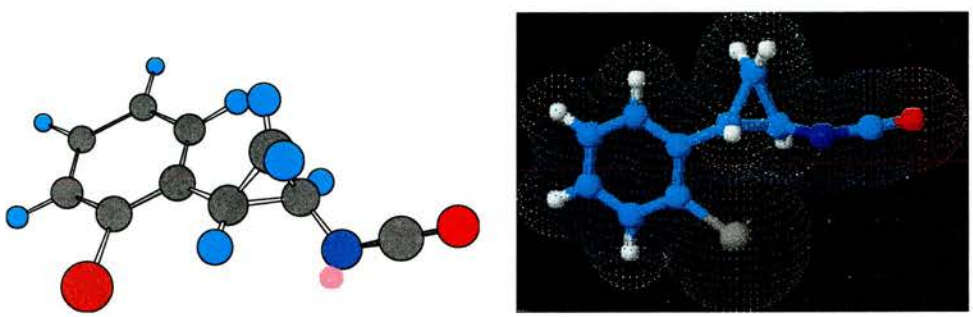
This result, i.e. the *cis/trans* mixture, was obtained only the first time the experiment was attempted. Afterwards the cyclopropanation was repeated many times in similar conditions, but only the *trans*-isomer was obtained.

Cis-isomer:



Picture 4

Trans-isomer:

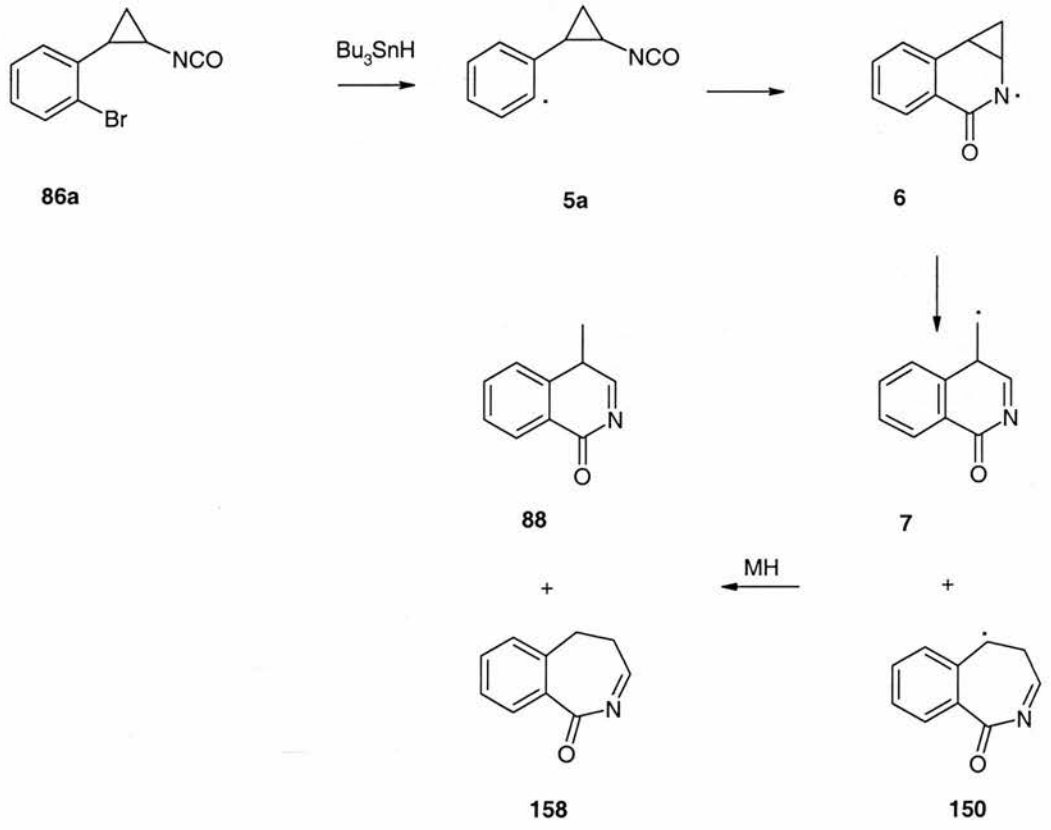


Picture 5

The 3D picture of the both isomers showed that the radical cyclisation could be difficult from the *trans*-isomer. However we expected that the *trans*-isomer would isomerise to give the *cis*-isomer during the reaction, which should facilitate the ring-closure reaction.

1.5. Attempted radical cyclisation of *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene (87a)

The reaction might proceed according to the scheme described below.



scheme 91

The principal aim was to obtain the radical **5a** from the isocyanate, and carry out the radical cyclisation to form the compound **6**. Ring closure of the isocyanate of the *cis/trans* mixture of 3-(2-bromophenyl) cyclopropane **87a** was attempted in the presence of the tin reagent. The different experimental conditions used, as well as the

products obtained, are summarised in the following table. The solvent, starting materials recovered and the tin residues are not mentioned.

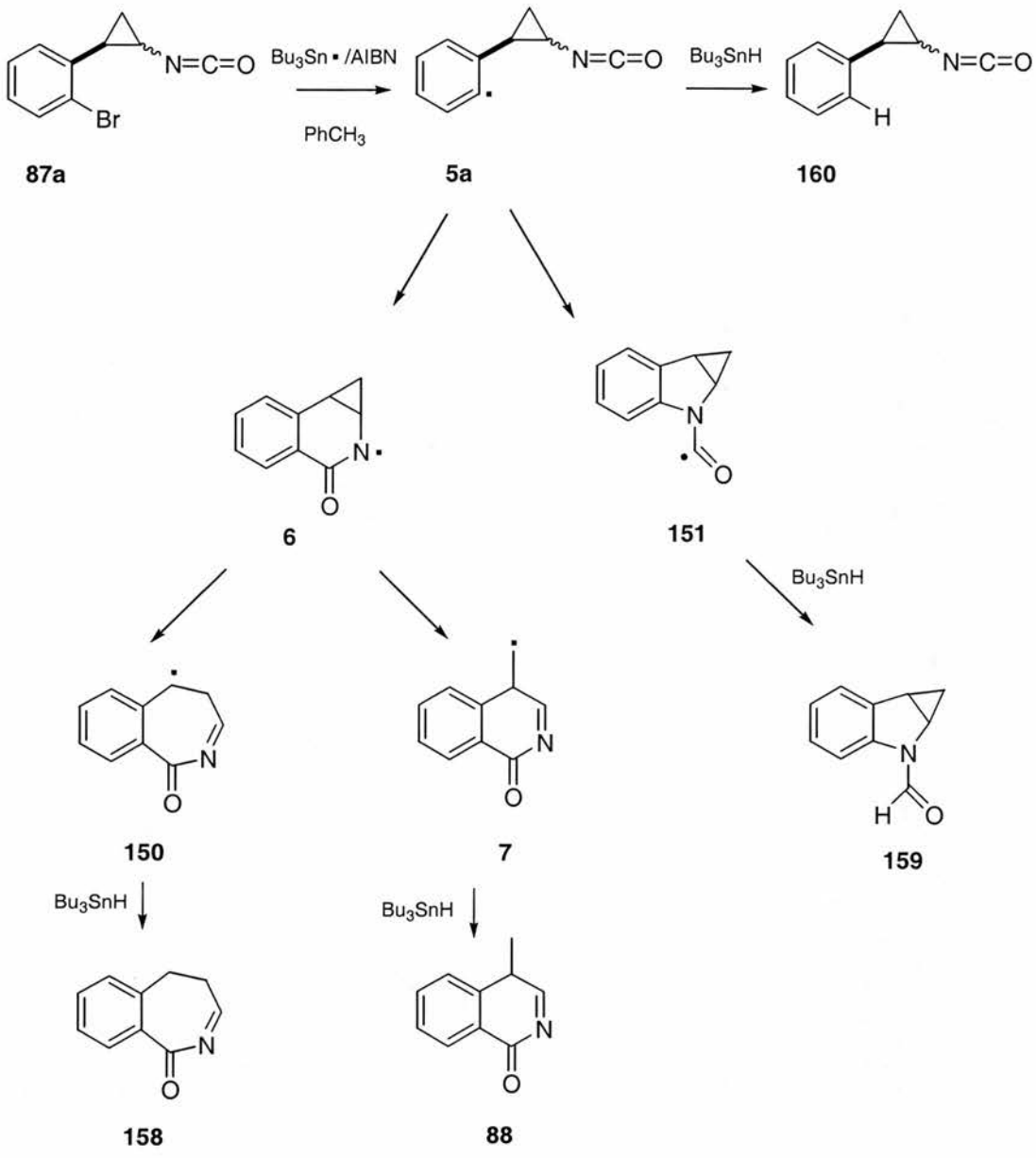
Analysis of homolytic ring closure of *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene (87a)			
Entry	**Conditions**	**Products** [m]	**Library fit** [a]
1[b]	Bu_3SnH, AIBN, $PhCH_3$, UV 2.5h, RT	+++4-Hydroxy-4-methyl-pentan-2-one ++++1,2-Diphenylethane	980 998
2[c]	Bu_3SnH, AIBN, $PhCH_3$, UV 3h, RT	++++1,2-Diphenylethane	998
3[d]	Bu_3SnH, AIBN, $PhCH_3$, UV 4.5h, RT	++4-Hydroxy-4-methyl-pentan-2-one ++Hexylbenzene ++1,2-Diphenylethane ++++*Trans*-(2-Isocyanatocyclopropyl) benzene	980 998 947
4[e]	Bu_3SnH (slow addition), AIBN, $PhCH_3$, UV 3h, RT	++Benzaldehyde +++1,2-Diphenylethane ++++*Trans*-(2-isocyanatocyclopropyl) benzene +4,5-Dihydro-benzo[*c*]azepin-1-one ++*Cis*-3-(2-bromophenyl) cyclopropyl-isocyanate	 998 947
5[f]	$Me_3SnSnMe_3$, AIBN, $PhCH_3$, UV 3h, RT	++++1,2-Diphenylethane	998
6[g]	Bu_3SnH, AIBN, $PhCH_3$, heat 3h, 70 °C	• Any identified components	
7[h]	Bu_3SnH, AIBN, THF, heat 4h, 70 °C, N_2	++++Toluene	
8[i]	Bu_3SnH, heat 5min, 150 °C + UV 30min	++++Isomer of *trans*-(2-isocyanatocyclopropyl) benzene +++*Cis*-3-(2-bromophenyl) cyclopropyl- isocyanate +++2-Phenyl-cyclopropylamine	 963
9[j]	EPHP, AIBN, PhH, heat 3 days, 70 °C, N_2.	• Products of bromination	
10a[k]	TTMSS, 1,1'-azobis-cyclohexanecarbonitrile, C_6D_6, heat 2h, 103 °C	++++*Trans*-(2-isocyanatocyclopropyl) Benzene	947
10b[l]	TTMSS, 1,1'-azobis-cyclohexanecarbonitrile, C_6D_6, heat 7h, 83 °C	++++*Trans*-(2-isocyanatocyclopropyl) Benzene	947

[a] 1000 = exact library fit. [b] Two unidentified components [c] One unidentified components. [d] Two unidentified components. [e] Two unidentified components.

[f] Three unidentified components. [g] Two unidentified components. [h] One unidentified component. [i] Two unidentified components. [j] Several unidentified products of bromination were present. [k, l] Several traces of unidentified components were also present.

[m] ++++ major product $\rightarrow$ + minor product.

Several unidentified products were obtained, including several tin compounds. 4-Hydroxy-4-methyl-pentan-2-one (library fit 980) presumably, came from the decomposition of the starting material. 1,2-Diphenylethane, benzaldehyde and hexylbenzene might come from toluene when used as the solvent.

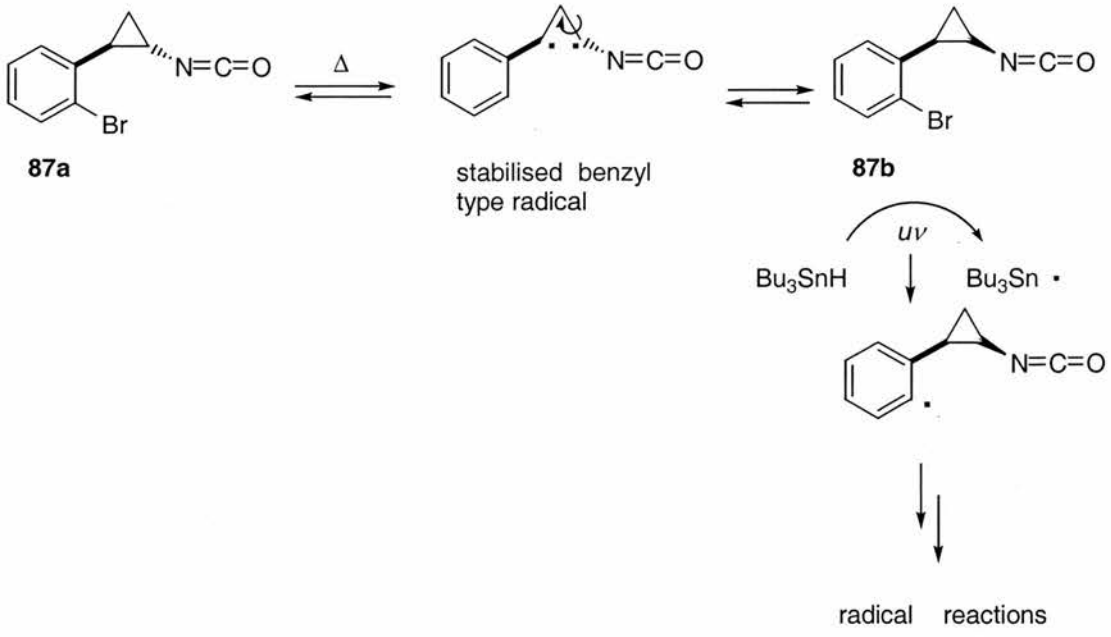


scheme 92

Several compounds isomeric with 4-methyl-4*H*-isoquinolin-1-one **88** are possible, as shown in the scheme above. Despite the procedures didn't show a trace of either 4-methyl-4*H*-isoquinolin-1-one **88** or 1-formyl-1a,6a-Dihydro-1*H*-cyclopropa[*a*]indene **159** as expected (scheme 92), the result led us to think that a radical reaction had occurred. We can't certify that the expected product 4-methyl-4*H*-isoquinolin-1-one **88** of the radical cyclisation on the C-atom of the isocyanate moiety was present in the

product mixture. However in the procedure 4, trace of what was most likely 4,5-dihydro-benzo[*c*]azepin-1-one **158** were observed on the GC-MS spectrum. The mass spectrum was consistent with the seven-membered ring product being formed. In this case we noticed the molecular ion M^+ 91 which only could come from the seven membered ring, 4,5-dihydro-benzo[*c*]azepin-1-one compared with the other isomers. The overall GC-MS result lead us to think that *trans*-(2-Isocyanatocyclopropyl) benzene **160** (library fit 947), which probably came from the reduction of the starting material, was predominant in the solution mixture. One explanation could be the stereochemistry of the isocyanate. The radical cyclisation would ocurr with difficulty on the *trans* compound because of the distance between the bromide and the isocyanate moiety.

In procedure 7, we tried to convert the *trans*-isomer to the *cis*-cyclopropane.[3-5] A quartz tube was heated at 150 °C, and *trans*-3-(2-bromophenyl)-cyclopropyl-isocyanate was poured into the hot tube. After a couple of minutes, tri-*n*-butyltin hydride was added into the isocyanate. The mixture was photolysed for 30 minutes. The procedure was carried out without solvent. We believed that the substrate would undergo a thermal equilibration of *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene with its *cis*-iomer. This reaction apparently should proceed via intermediate formation of a short-lived 1,3-diradical, which is produced by thermal cleavage of one cyclopropane bond. Indeed, Merenyi[6] examined the *trans* to *cis* isomerisation of several systems such as tri- or tetrasubstituted cyclopropanes, from which radicals are formed by bond dissociation.[7-9]



scheme 92

As shown in the scheme above, we hoped that the *trans*-compound **87a** would rearrange via the diradical, which contains stabilised radical centres, to afford an equilibrium mixture of *cis*-and *trans*-isomers. The photolysis initiated the radical reaction and, as for the *trans*-compound, we expected that the isomer mixture would cyclise either on the C-atom or the N-atom of the isocyanate moiety. After reaction, the GC-MS spectra showed that some of the starting material *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene was unreacted as well as some of the tin hydride. The other product recovered could be either *cis*- or *trans*-(2-isocyanatocyclopropyl) benzene or one of the adducts. The MS spectrum alone didn't allow us to reach a definite conclusion. A chromatography column of the product mixture was run. Six fractions were recovered. The first three fractions were tin residues. The last three fractions were mainly unreacted starting material i.e. what we believe to be *cis*-1-bromo-(2-isocyanatocyclopropyl) benzene (despite the mass spectrum being quite similar, the retention time was different to the retention time of the *trans*-1-bromo-(2-

isocyanatocyclopropyl) benzene) and small amounts of 2-phenyl-cyclopropylamine (library fit 963).

A possible solution to this problem was to carry out the reaction using another radical reagent. The radical cyclisation was performed in a first procedure using EPHP instead of the tin reagent. Mostly products of bromination were observed on the GC-MS spectrum after radical reaction.

In a second procedure the radical cyclisation was performed with TTMSS instead of tri-*n*-butyltin hydride, in order to minimise the reaction between the tin reagent and the isocyanate moiety. The procedure was carried out in a NMR tube. The isocyanate in solution in deuteriobenzene in presence of TTMSS and 1,1'-azo-di-cyclohexanecarbonitrile were heated in a first process for 2h at 103 °C and in a second one at 83 °C for 7h. The results were quite similar for both processes. Except unreacted starting materials and TTMSS residues, *trans*-(2-isocyanatocyclopropyl) benzene was the only product indentified on the GC-MS spectra. The proton NMR spectrum showed mainly the presence of the starting material.

We believe therefore that because of the *trans*-geometry, as shown in picture 5, cyclisation was too slow to compete with H-atom abstraction. Once the bromine atom had been abstracted by the Sn- or Si-centred radical, the newly formed aryl-centred radical was too far away from the isocyanate moiety to perform the radical cyclisation. Consequently, the formation of the reduced product was faster that the ring closure reaction.

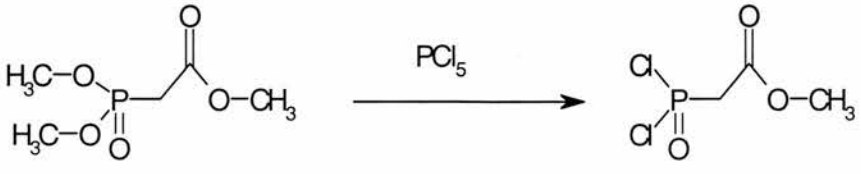
Another option was to find reactions that promoted the formation of the *cis*-compound which we believe possesses a geometry more favorarable for the ring closure reaction.

2. Synthesis of *cis*-1-bromo-(2-isocyanatocyclopropyl) benzene (87b)

2.1. Methyl *cis*-3-(2-bromophenyl) propenoate (153b)

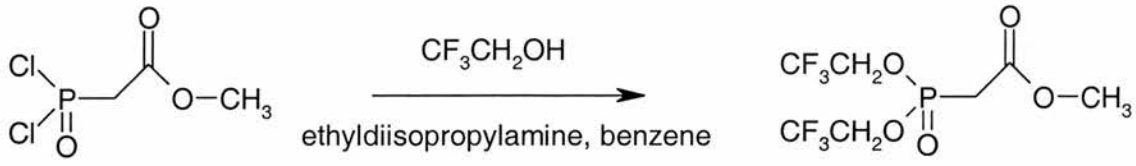
A selective method to prepare the *cis* (or Z) isomer was via the Horner-Emmons reaction.[10] It's a classical method for the preparation of unsaturated esters. Horner-Emmons olefination shows a preference for formation of the more stable E-olefins. It has been found however that Z selectivity may be obtained under certain conditions where elimination of the initial adduct is faster than the adduct equilibration. Unsaturated esters may be prepared from a variety of aromatic, saturated and unsaturated aliphatic aldehydes with high Z stereoselectivity using electrophilic bis(trifluoroethyl) phosphonoesters and/or strongly dissociated bases like $KN(TMS)_2$/18-crown-6. This method represents one of the direct routes from aldehydes to pure Z disubstituted cinnamic esters.

The trifluoroethylphosphonoester **163**[10] was readily prepared from commercially available trimethylphosphonoacetate **161** and trifluoroethanol in a two step reaction as show below.



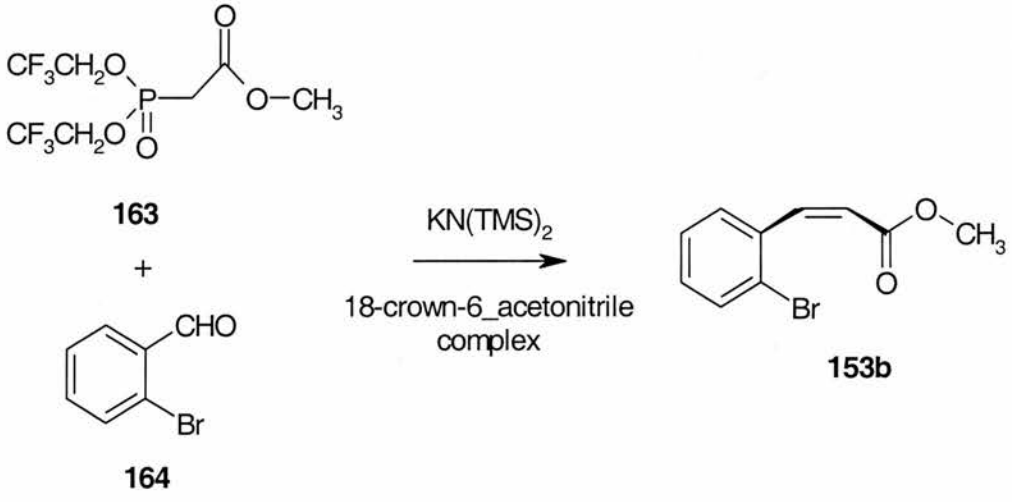
161 **162**

In a first step the dichlorophosphonoacetate **162** was formed by action of phosphorus pentachloride on trimethylphosphonoacetate **161**. The dichloride was obtained in a 99 % yield after removal of the unreacted phosphorus pentachloride.



162 **163**

In a second step the action of trifluoroethanol with the newly formed dichloride in the presence of ethyldiisopropyamine, afforded the trifluorophosphonoacetate **163** in a 28 % yield after chromatography.

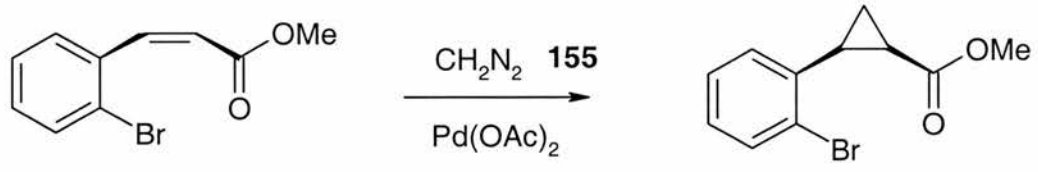


The reaction of the aldehyde **164** and the substitued **163** with the optimal base system $KN(TMS)_2$/18-crown-6-acetonitrile[11] should be quite effective at producing the *cis*-3-(2-bromophenyl) propanoate. The reaction summarised above was conducted at -78 ^{o}C in THF. Only 13% of a mixture of *cis*-and *trans*-isomers was obtained. Some of

the *trans*-isomer appeared in solution after chromatography, 2.5:1.0 (*cis:trans,* 13 % yield). Isomer ratios were measured by integration of resolved signals in the 300 MHz ^{1}H NMR.

The *cis/trans* mixture obtained was using without further purification in the next steps following the procedure described by Vallgarda,[1] as previously for only the *trans*-isomer.

2.2. Methyl *cis*-3-(2-bromophenyl)cyclopropane carboxylate (154b)

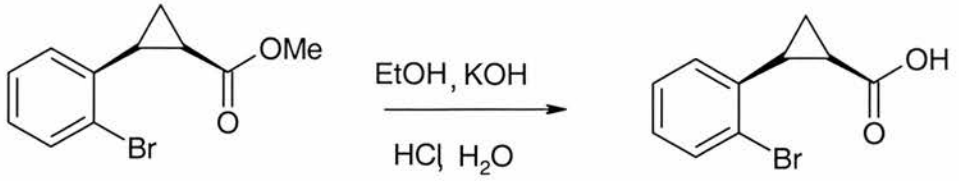


153b **154b**

The arylated methyl acrylate derivative **153b** was cyclopropanated with diazomethane **155** in the presence of 0.005 equiv. of palladium(II) acetate. The diazomethane, compound **155**, was prepared[2] and distilled in to a flask containing the *cis*-isomer. The cyclopropyl product was obtained in a 94%yield. The *trans*-isomer was present in a ratio 1.0:2.5 (*trans*:*cis*).

2.3. *Cis*-3-(2-bromophenyl)cyclopropane carboxylic acid (86b)

Alkaline hydrolysis gave the desired *cis*-arylcyclopropane carboxylic acid **86b**.

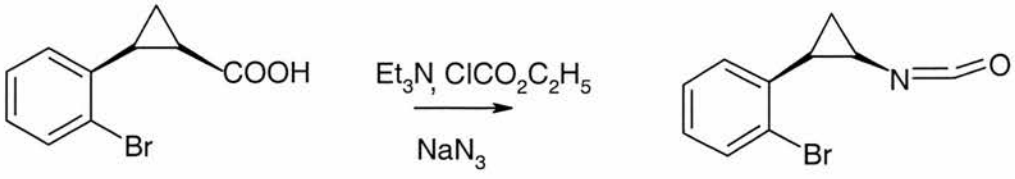


154b **86b**

The ester **154b** was dissolved in ethanol and potassium hydroxide, then acidified with hydrochloric acid. The acid **86b** was obtained in 98 % yield after removal of the solvent. The ^{1}H NMR spectrum was consistent with formation of the carboxylic acid. The *trans*-isomer was also observed on the NMR spectrum. The ratio was quite impossible to estimate because of the almost identical chemical shifts of both isomers.

2.4. *Cis*-1-bromo-(2-isocyanatocyclopropyl) benzene (87b)

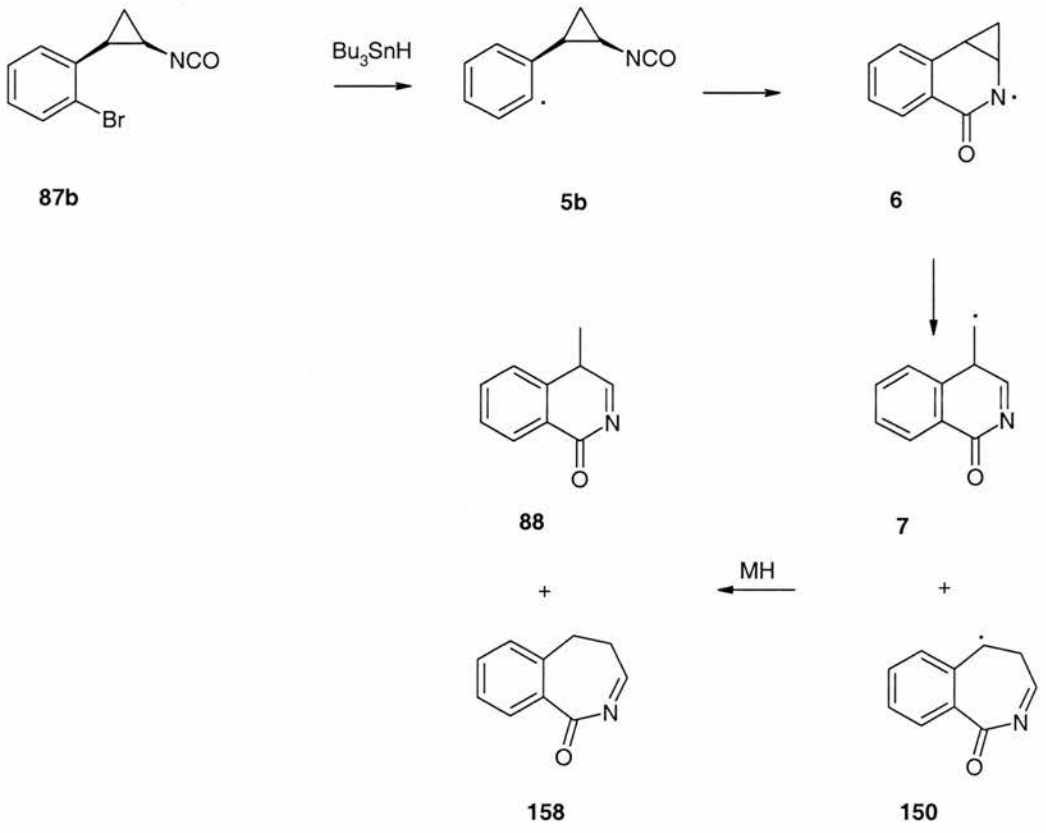
Following the same pathway,[1] the isocyanate derivative was prepared by reaction of the corresponding carboxylic acid **86b** with sodium azide and ethyl chloroformate in anhydrous conditions.



86b **87b**

98 % of the product **87b** was obtained as a yellow oil. The results of the analysis (^{1}H NMR and IR spectra) showed that the isocyanate has been formed, ν_{NCO} = 2272 cm^{-1}. Some trace of trans-isomer was also present in the NMR spectra (*cis*:*trans*, ratio 2.5:1). No purification of the compound was attempted because of the small amount of product we were working with. The isocyanate was used directly, without further purification, for the radical cyclisation.

2.5. Attempted radical cyclisation of the isocyanate of *cis*-3-(2-bromophenyl) cyclopropane (87b)



scheme 93

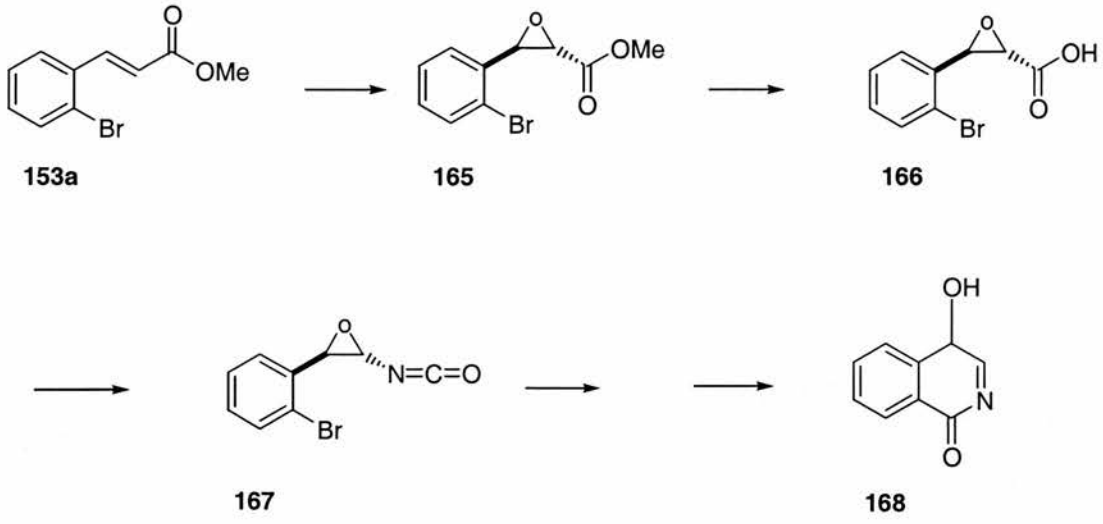
As described in the scheme above, the objective remained the same. The radical cyclisation was attempted from the *cis*-isocyanate **4b** in presence of the *trans*-isomer (in the ratio *cis:trans*, 2.5:1.0). The mixture was reacted with tributyltin hydride. After photolysing the solution for 3h in deuteriobenzene, the crude product mixture was analysed by GC-MS spectroscopy. The GC-MS didn't show a trace of adduct, however several traces of unidentified components were observed.

The ring closure of the isocyanate was also attempted using TTMSS. The procedure was carried out in a NMR tube, the isocyanate in solution in deuteriobenzene, was heated at 103 °C for 2h in presence of TTMSS and 1,1'-azobis-cyclohexanecarbonitrile. While the NMR spectra show principally unreacted starting

material, we could observe on the GC-MS spectra the presence of *trans*-(2-isocyanatocyclopropyl) benzene and *trans*-3-(2-bromophenyl) cyclopropyl-isocyanate in the solution mixture beside the *cis*-3-(2-bromophenyl) cyclopropyl-isocyanate. The ratio of the two isomers was estimated from the area of the both compounds on the GC-MS spectrum. The initial *cis*:*trans* ratio of 2.5:1 dropped to 1:5. During the reaction the thermodynamically stable isomer was favoured. At 103 °C at the thermal isomerisation of the *cis*-isomer into the *trans*-isomer evidently took place rapidly. As a result, after reaction, the same products were obtained from the *cis*-isomer.

3. Synthesis of (2-bromophenyl)-3-isocyanato-oxirane (167)

Following the same idea, to prevent reversal of ring closure onto the isocyanate group, an epoxide ring could be introduced and undergo a rapid onward rearrangement. The general pathway is illustrated in the following scheme. The model considered was for Z = O and X= Br.



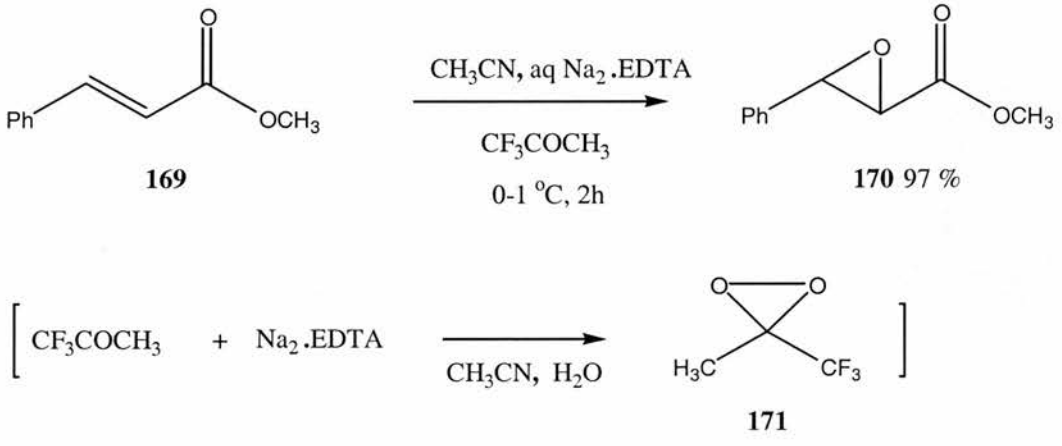
scheme 94

The scope of reaction used was quite similar to that of the cyclopropyl case, according to the procedure described by Vallgarda, except for the first steps. The isocyanate would be made from the acid in a Curtius rearrangement.

scheme 95

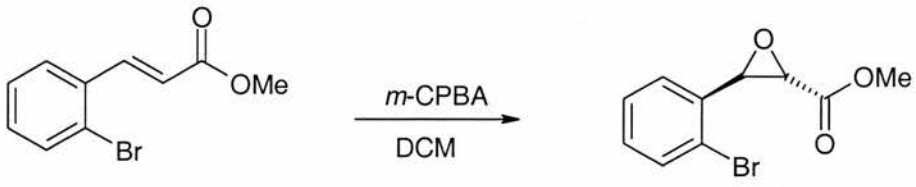
3.1. Formation of methyl 3-(2-bromophenyl)-2-oxiranecarboxylate (165)

The epoxidation of olefins is a particularly useful reaction from the synthetic point of view as two carbons atoms are oxygenated in a single step, and high chemo-, regio, and diastereoselectivities are often obtained. Peroxides[12, 13] and peracids[14] are classical epoxidising reagents. Some metal peroxides and hydroperoxides,[14-19] dioxiranes, N-sulfonyloxaziridines[20-23] and perfluoro-*cis*-2,3-dialkyloxaziridines[24] are more recent epoxidizing agents which have emerged for their effectiveness, versatility, and selectivity. The common feature of these latter agents is that the active oxygen is part of a three-membered ring. Yang and co-workers[25] reported an example of epoxidation that uses methyl (trifluoromethyl) dioxirane **171**, generated *in situ*. The epoxide **170** was obtained in 97 % yield after 2h of reaction.



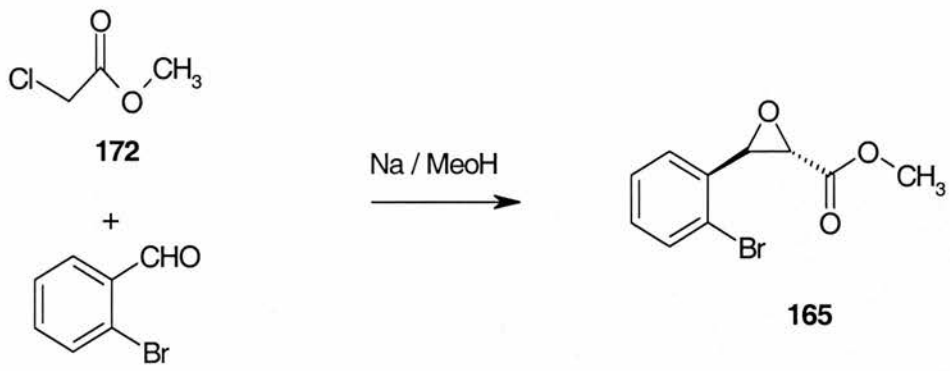
scheme 96

To prepare methyl-3-(2-bromophenyl)-2-oxirancarboxylate, the first method we chose was to use the commercially available m-chloro-perbenzoic acid (*m*-CPBA), following the procedure described by Honig.[26]



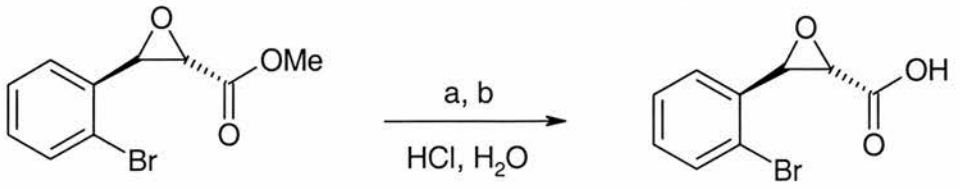
153a **165**

The solution was refluxed in dichloromethane for 48h. At the end of the reaction the product was obtained with a 24 % yield after purification by column chromatography. Because of the poor yield obtained another method of making the epoxide was investigated.



Methyl 3-(2-bromophenyl)-2-oxiranecarboxylate **165** was made by following a method described by Wunsch.[27] This 16h process involved the reaction of 2-bromobenzaldehyde **164** and methyl chloroacetate **172** with NaOMe. The ester **165** was obtained in 82 % yield.

3.2. Formation of 3-(2-bromophenyl)-2-oxiranecarboxylic acid (166)



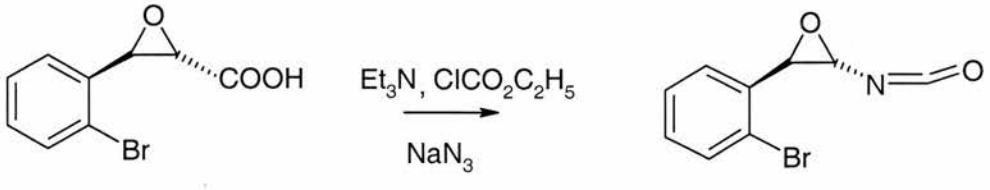
165 **166**

a : NaOH, MeOH

b : KOH, EtOH

First the method reported by Vallgarda[1] using NaOH/MeOH was performed to make the 3-(2-Bromophenyl)-2-oxiranecarboxylic acid. The acid was obtained with a 50 % yield. To improve the modest yield obtained with the previous procedure, the same reaction was carried out in the presence of KOH/EtOH instead of NaOH/MeOH as described by Wunsch.[27] 3-(2-Bromophenyl)-2-oxiranecarboxylic acid was obtained in a 98 % yield.

3.3. Preparation of (2-bromophenyl)-3-isocyanato-oxirane (167)

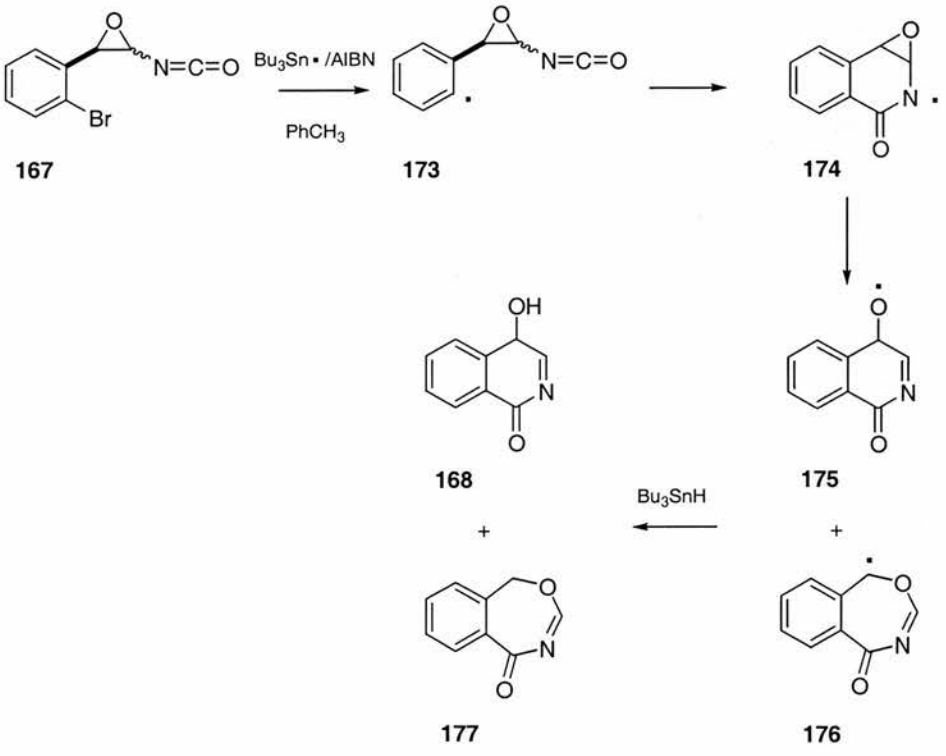


166 **167**

Following the same pathway as for the synthesis of *trans*-3-(2-bromophenyl)-cyclopropyl isocyanate, (2-bromophenyl)-3-isocyanato-oxirane was made by the procedure described by Vallgarda.[1] The NMR and the IR spectra (ν_{NCO} = 2260 cm^{-1}) allowed us to conclude that the isocyanate was prepared in 83 % yield. The product was used without further purification for the next step.

3.4. Homolytic ring closure of (2-bromophenyl)-3-isocyanato-oxirane

We could expect that the epoxy-isocyanate would cyclise following the pathways described below.



167 173 174 168 175 177 176

scheme 97

Ring closure of the isocyanate was attempted in presence of tri-*n*-butyltin hydride in C_6D_6. The crude product was sent for GC-MS spectroscopy. Only the corresponding 3-phenyloxiranylamine was observed with traces of several unidentified components on the GC-MS chromatogram.

The ring closure of the isocyanate was attempted using TTMSS. The procedure was carried out in an NMR tube, the isocyanate in solution in D_6-benzene, was heated in presence of TTMSS and 1,1'-azobis-cyclohexanecarbonitrile. The procedure was carried out at 103 °C and at 83 °C for 2h and 7h respectively. For both procedures, the NMR spectra showed principally the presence of unreacted starting materials. On the GC-MS spectra, we noticed the presence of unreacted starting materials, of TTMSS residues as well as the presence of 3-(2-bromophenyl)-oxiranylamine, and 4-hydroxy-4*H*-isoquinolin-1-one.

In these TTMSS mediated reactions although mainly the reduced product was obtained, the presence of a peak with M^+ 161 was detected. From the fragmentation (M^+ - 17) (loss of OH) observed on the GC-MS, this could be the 4-hydroxy-4*H*-isoquinolin-1-one **168**. This component was minor compared with the reduced-product.

VI- Experimental

^1H, ^{13}C, ^{31}P, ^{19}F NMR spectra were obtained using Bruker AM 300 MHz, a Bruker Avance 300, and Varian Gemini 2000 spectrometers. The Bruker Avance 300 is fully automated with autosampling robots. All samples were dissolved in deuterated

chloroform, unless otherwise stated, using Me_4Si as an internal standard. The chemical shifts δ were given in ppm downfield from Me_4Si. IR spectra were recorded in nujol or neat on a Perkin-Elmer 1710 Infrared Fourier Transform Spectrometer. Frequencies are given in cm^{-1}. Mass spectra and GC-MS spectra were obtained using 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). All melting points were determined in open capillary tubes and are reported uncorrected. TLC was performed on pre-coated plates of silica gel G-60 F-254 (Merck). Elemental annalysis are recorded on an Agilent 7500 Series ICP-MS spectrometer that has laser ablation built in capability or on a Carlo Erba CHNS analyser for carbon hydrogen nitrogen sulphur. Column chromatography was performed using BDH silica gel (40-63 μm) eluting with the given solvent mixture.

1. Preparative routes to the isocyanate of *trans*-3-(2-bromophenyl) cyclopropane (4a) and related molecules

Preparation of methyl *trans*-3-(2-bromophenyl) propenoate[1]

A mixture of 2-bromoiodobenzene (7.0 g, 24.7 mmoles), methyl acrylate (2.8 mL, 31.9 mmol), palladium acetate (0.1 g, 0.5 mmol), tetrabutylammonium chloride (6.9 g, 24.7 mmoles), and finely ground potassium carbonate (8.6 g, 62.0 mmoles) in DMF (26 mL) was stirred at 50 °C for 19h. Petroleum ether (150 mL) and brine (40 mL) were added and the mixture was filtered under suction. The filtrate was collected, and the aqueous layer was extracted with petroleum ether (3 x 30 mL). The combined

organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was purified on a silica column (ether/hexane, 1:3) to afford 4.9 g of pure methyl *trans*-2-(2-bromophenyl) propenoate as a clear yellow oil (81 %). ^{1}H NMR: δ_H 3.85 (3H, s, Me), 6.43 (1H, d, CHCOOR, J = 16.0), 7.25-7.40 (2H, m, ArylH), , 7.65-7.75 (2H, m, ArylH), 8.83 (1H, d, CHAr, J = 16.0), ^{13}C NMR : δ_C 51.79 ; 120.58 ; 125.24 ; 127.63 ; 127.67 , 131.14 ; 133.34 ; 134.37 ; 143.07 ; 166.70. The results were consistent with the literature.[1]

Preparation of methyl *trans*-3-(2-bromophenyl) cyclopropane carboxylate[1]

In a distillation flask was placed a solution of potassium hydroxide (3 g) dissolved in water (5 mL), monoethyl ether of diethylene glycol (13 mL) and ether (5 mL). There was placed in the droping funnel a solution of *p*-tolylsulfonylmethylnitrosamide in ether (70 mL). The distillation flask was heated in a water bath at 75-80 °C, the stirrer was started, and the nitrosamide solution was added at a regular rate during 25-30 minutes. As soon as all the nitrosamide solution has been added, additional ether (60 mL) was placed in the dropping funnel and added at the previous rate until the distillate was colourless. The resulting ether solution of diazomethane was continously distilled into a stirred, cooled (-10 °C) solution of methyl *trans*-3 (-2-bromophenyl) propenoate (1.0 g, 5.6 mmoles) and palladium acetate (0.006 g, 0.003 mmol) in dichloromethane/ether (1:2, 75 mL). The reaction was quenched by addition of 2 mL of acetic acid after 2h. The resulting mixture was washed with saturated aqueous sodium hydrogen carbonate (3 x 5 mL), dried over magnesium sulfate, filtered, and concentrated. The crude product was purified on a silica column eluted with ether/hexane (1:1) to afford 2.0 g of the pure methyl *trans*-2-(2-bromophenyl)

cyclopropane carboxylate (98 %). ^{1}H NMR : δ_H1.35-1.40 (1H, m, CH), 1.60-1.70 (1H, m, CH), 1.80-1.70 (1H, m, CH), 2.70-2.80 (1H, m, CH), 3.80 (3H, s, Me), 7.00-7.20 (2H, m, ArylH), , 7.25-7.35 (1H, m, ArylH), 7.60-7.65 (1H, m, ArylH). ^{13}C NMR: δ_C 15.81; 22.89; 27.03; 51.98; 126.23; 127.35; 127.53; 128.19; 132.61; 138.93; 173.72.

Preparation of *trans*-3-(2-bromophenyl) cyclopropane carboxylic acid [1]

Methyl *trans*-3-(-2-bromophenyl)cyclopropenoate (1 g, 5.2 mmoles) was dissolved in methanol (10m L), and 2M aqueous sodium hydroxide (5 mL) was added. The solution was stirred at room temperature for 2h. The methanol was evaporated, and the remaining solution was diluted with water (15 mL), washed with ether (20 mL), acidified with 5M aqueous hydrochloric acid, and extracted with ether (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford pure *trans*-3-(-2-bromophenyl)cyclopropanecarboxylic acid (0.5 g, 53 %). ^{1}H NMR: δ_H1.25-1.40 (1H, m, CH), 1.50-1.65 (1H, m, CH), 1.65-1.80 (1H, m, CH), 2.60-2.80 (1H, m, CH), 6.90-7.10 (2H, m, ArylH), 7.15-7.20 (1H, m, ArylH), 7.40-7.60 (1H, m, ArylH).

Preparation of *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene [1]

A mixture of *trans*-3-(-2-bromophenyl)cyclopropanecarboxylic acid (0.5 g, 2.1 mmoles), triethylamine (0.3 g, 2.9 mmoles), and ethyl chloroformate (0.3 g, 3.1 mmoles) in dry acetone (20 mL) was stirred at -10 °C. A solution of sodium azide (0.2 g, 3.6 mmol) in H_2O (10 mL) was added after 2.5h. The stirring was discontinued after an additional 30 minutes. The resulting suspension was poured into cold H_2O (22

mL) and was extracted with toluene. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to about 50 % of the volume to remove remaining traces of H_2O. The resulting solution was heated (90 °C bath temperature) until the evolution of nitrogen ceased, and the solution was concentrated to give the resulting isocyanate in oil. The NMR spectra showed that the isocyanate has been obtained in a mixture of the *trans* and *cis* isomers. ^{1}H NMR: δ_H1.20-1.38 (4H, m, *cis* + *trans*), 1.40-1.58 (0.5H, m, *cis*), 1.65-1.80 (0.5H, m, *cis*), 2.30-2.40 (1H, m, *trans*), 2.80-2.90 (2H, m, *cis* + *trans*), 6.90-7.10 (4H, m, ArylH, *cis* + *trans*), 7.15-7.20 (2H, m, ArylH, *cis* + *trans*), 7.40-7.60 (2H, m, ArylH, *cis* + *trans*). ^{1}H NMR (*trans*-isomer): δ_H 1.20-1.38 (2H, m), 2.30-2.40 (1H, m), 2.80-2.90 (1H, m), 6.95 (1H, d, ArylH, J = 8.8), 7.10 (1H, t, ArylH, J = 8.1), 7.20 (1H, t, ArylH, J = 8.1), 7.55 (2H, d, ArylH, J = 8.8). δ_C (*trans*-isomer) 17.46, 26.04, 29.41, 126.53, 127.63, 127.85, 128.75, 132.90, 138.40, 179.50 ν_{NCO} = 2273 cm^{-1}. MS, m/z (%), $[m-1]^+$ 238/236(2), 208/210(8), 182/184(6), 158(100), 130(28), 115(29), 103(23), 89(7), 77(7), 63(8), 51(16). C-H-N microanalysis found, C 50.35 %, H 3.36 %, N 5.78 % $C_{10}H_8BrNO$ requires C 50.45 %, H 3.39 %, N 5.88 %.

Homolytic reactions of *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene

Procedure 1

Trans-1-bromo-(2-isocyanatocyclopropyl) benzene (10 mg, 0.04 mmol) and tributyltin hydride (11 mg, 0.04 mmol) in solution in toluene (5 mL) were photolysed for 2.5h in the presence of 10 % of AIBN. GC-MS: **Peak 3.70**, 4-hydroxy-4-methylpentan-2-one (library fit 980), m/z(%) M^+ 101(17), 59(49), 38(100); **Peak**

5.71, N.D., m/z(%) M^+ 121(4), 94(3), 69(100), 54(19); **Peak 10.09**, N.D., product which contains bromine, m/z(%) M^+ 208/210(9), 196/198(21), 160/162(32), 130/132(34), 115(100), 103/105(26), 89(13), 77(34), 70(53), 63(14), 51(19); **Peak 10.5**, diphenylethane (library fit 998), m/z(%) M^+ 182(24), 91(100), 65(4), 51(4). The major product observed was 1,2-diphenylethane.

Procedure 2

Trans-1-bromo-(2-isocyanatocyclopropyl) benzene (10 mg, 0.04 mmol) and tributyltin hydride (11 mg, 0.04 mmol) in solution in toluene (5 mL) were photolysed for 3h in presence of 10 % of AIBN. GC-MS: **Peak 3.96**, N.D., m/z(%) M^+ 112(29), 83(100), 67(20), 55(95); **Peak 10.08**, 1,2-diphenylethane. The only product observed was 1,2-diphenylethane.

Procedure 3

Trans-1-bromo-(2-isocyanatocyclopropyl) benzene (10 mg, 0.04 mmol) and tributyltin hydride (11 mg, 0.04 mmol) in solution in toluene (5 mL) were photolysed for 4.5h in presence of 10 % of AIBN. GC-MS: **Peak 53**, 4-hydroxy-4-methyl-pentan-2-one; **Peak 66**, N.D., m/z(%) M^+ 100(4), 87(18), 75(6), 57(100), 45(41); **Peak 145**, hexylbenzene, m/z %) M^+ 148(18), 105(12), 91(100), 77(7), 65(16), 51(7); **Peak 185**, 1,2-diphenylethane; **Peak 208**, *trans*-(2-isocyanatocyclopropyl) benzene (library fit 947), m/z(%) M^+ 159(78), 130(100), 117(19), 115(26), 104(27), 89(6), 77(19), 63(8), 51(16); **Peak 408**, N.D., m/z(%) M^+ 238(20), 230(6), 195(7), 147(100), 122(7), 109(16), 91(53), 82(14), 67(22), 57(10). The major product of the reaction was *trans*-(2-isocyanatocyclopropyl) benzene.

Procedure 4

Tributyltin hydride (11 mg, 0.04 mmol) was added slowly into a solution of 10 mg (0.04 mmol) of *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene in toluene (5 mL) in presence of 10 % of AIBN. The solution was photolysed for 3h. GC-MS: **Peak 53**, 4-hydroxy-4-methylpentan-2-one; **Peak 79**, benzaldehyde, m/z(%) M^+ 106(100), 105(99), 77(85), 5(29); **Peak 93**, N.D., m/z(%) M^+ 381(5), 145(52), 130(100), 116(23), 100(27), 86(23), 72(25), 58(97); **Peak 193**, $C_{10}H_9NO$, M^+ 159(13), 115(2), 91(100), 65(11), 51(3) (probably 4,5-dihydro-benzo[*c*]azepin-1-one); **Peak 200**, 1,2-diphenylethane; **Peak 215**, *trans*-(2-isocyanatocyclopropyl) benzene; **Peak 416**, N.D., m/z(%) M^+ 299/301(7), 274/276(8), 220(23), 130(8), 117(100), 103(5), 90(38), 77(7), 62(5), 51(4); **Peak 520**, *cis*-1-bromo-(2-isocyanatocyclopropyl) benzene. The major product of the reaction was *trans*-(2-isocyanatocyclopropyl) benzene.

Procedure 5

Trans-1-bromo-(2-isocyanatocyclopropyl) benzene (10 mg, 0.04 mmol) and hexamethylditin (12.4 mg, 0.04 mmol) in solution in toluene (5 mL) were photolysed for 3h in presence of 10 % of AIBN. GC-MS: **Peak 4.01**, N.D., m/z(%) M^+ 185(32), 174(2), 165(18), 155(15), 146(7), 135(10), 120(7), 111(20), 91(100), 83(15), 69(17), 55(16); **Peak 10.34**, N.D., m/z(%) M^+ 256(14), 241(17), 211(13), 165(97), 150(13), 135(32), 120(15), 91(100), 65(27), 51(8); **Peak 14.25**, 1,2-diphenylethane; **Peak 16.57**, N.D., m/z(%) M^+ 259(10), 161(25), 144(20), 130(19), 117(100), 107(18), 91(80), 77(35), 65(22), 51(23). The only identified product was 1,2-diphenylethane.

Procedure 6

A solution of *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene (10 mg, 0.04 mmol) and tributyltin hydride (11 mg, 0.04 mmol) in toluene (5 mL) in the presence of 10 % of AIBN was heated for 3h at 70 °C. Except for the tin residues (such as tributyltin bromide) only two unidentified components containing bromine were observed on the GC-MS spectrum. GC-MS: **Peak 336**, N.D., m/z(%) M^+ 251(13), 236(13), 172(27), 130(7), 116(57), 103(13), 89(8), 77(12), 69(100), 42(29); **Peak 355**, N.D., m/z (%) M^+ 270(6), 213(14), 189(36), 161(18), 144(30), 116(100), 89(13), (6), 63(11).

Procedure 7

A solution of *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene (0.50 g, 2 mmol) and tributyltin hydride (0.78 g, 27 mmol) in dry THF (25 mL) in presence of 10 % of AIBN was heated for 4h at 70 °C. The reaction was carried out under a nitrogen atmosphere. GC-MS: **Peak 154**, toluene, m/z(%) M^+ 92(80), 91(100), 65(16), 51(4), 41(2); **Peak 306**, N.D., m/z(%) 121(4), 94(3), 69(100), 54(19); **Peak 535**, *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene.

Procedure 8

A tube was heated in an oil bath at 150 °C. When the temperature was reached, 100 mg (100 mg, 0.42 mmol) of *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene was added in to the tube. After 5 minutes, tributyltin hydride (147 mg, 0.50 mmol) was added into the isocyanate compound. The mixture was photolysed for 15 minutes. A GC-MS was performed showing only tri-*n*-butyltin bromide, in presence of 10 % of AIBN. The mixture was photolysed for a further 15 minutes. The GC-MS remained

the same. So a chromatography column of the mixture was performed (hexane/EtOAc, 1:3). Fraction 1 and fraction 2 showed that only tin residues were present. GC-MS: *fraction 3,* **Peak 525**, *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene; **Peak 535**, isomer of *trans*-(2-isocyanatocyclopropyl) benzene, m/z(%) M^+ 159(5), 149(100), 132(14), 115(21), 104(9), 77(8), 56(5); *fraction 4*, **Peak 267,** 2-phenyl-cyclopropylamine (library fit 963), m/z (%) $[m-1]^+$ 132(100), 115(40), 104(14), 91(20), 77(18), 63(8), 56(39); **Peak 457**, N.D.(isomer of peak 267), m/z (%) M^+ 132(31), 116(100), 103(14), 91(15), 77(22), 70(16), 63(7), 56(13); **Peak 522,** *cis*-1-bromo-(2-isocyanatocyclopropyl) benzene; **Peak 549,** *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene; **Peak 658,** N.D., m/z(%) M^+ 208/210(9), 196(21), 160(32), 130(34), 115(100), 103(26), 89(13), 77(34), 70(53), 63(14), 51(19); *fraction 5*, **Peak 540,** *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene.

Procedure 9, EPHP reagent

Trans-1-bromo-(2-isocyanatocyclopropyl) benzene (0.50 g, 2 mmol) and EPHP (10 eq) in solution in benzene (30 mL) were heated for 1h under a nitrogen atmosphere at 70 °C. AIBN (0.04 eq) was added in two portions over 30 minutes and reflux continued for 3 days. On cooling, the reaction was diluted with petroleum ether and washed successively with sodium hydrogen carbonate, aqueous hydrochloric acid (2M), sodium hydrogen carbonate and brine. The organic layer was then dried over magnesium sulfate, filtered and concentrated in vacuo. Several traces of unidentified components were present. Mainly products of bromination were observed.

Procedure 10, TTMSS reagent

-With TTMSS at 103 °C

Trans-1-bromo-(2-isocyanatocyclopropyl) benzene (60 mg, 0.25 mmol) and tris(trimethylsilyl)silane (75 mg, 0.30 mmol) in solution in deuteriobenzene (1 mL) were heated for 2h at 103 °C (oil bath) in presence of 10 % of 1,1'-azo-di-cyclohexanecarbonitrile (0.006 g). On the ^{1}H NMR spectrum, mainly the starting material and several resonances due to minor unidentified components were present. GC-MS: **Peak 12.91**, *trans*-(2-isocyanatocyclopropyl) benzene; **Peak 15.72**, *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene.

-With TTMSS at 83 °C

Trans-1-bromo-(2-isocyanatocyclopropyl) benzene (20 mg, 0.08 mmol) and tris(trimethylsilyl)silane (25 mg, 0.10 mmol) in solution in deuterobenzene (1 mL) were heated for 7h at 83 °C (oil bath) in presence of 10 % of 1,1'-azo-di-cyclohexanecarbonitrile (0.002 g). The result was the same as the previous experiment. GC-MS: **Peak 12.98**, *trans*-(2-isocyanatocyclopropyl) benzene; **Peak 15.67**, *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene. Several traces of unidentified components were also observed.

2. Preparative routes to *cis*-1-bromo-(2-isocyanatocyclopropyl) benzene (4) and related molecules

Synthesis of dichlorophosphonoacetate[10]

Trimethyl phosphonoacetate (3.64 g, 0.02 mole) was cooled to 0 °C and stirred while PCl_5 (10.54 g, 0.05 mole) was added. An exothermic reaction took place and MeCl

was evolved. The mixture was stirred at 25 °C for 1h and then at 75 °C for 3h. Distillation removed the by-product $POCl_3$ (bp 40 °C, 20 mm) and excess PCl_5, and yielded the dichloro phosphonoacetate in 99 % yield. ^{31}P: 34.26; ^{1}H NMR: δ_H 3.7 (1H, s), 3.8 (1H, s), 3.9 (3H, s)

Synthesis of bis(trifluoroethyl) phosphonoacetate[10]

Dichloro phosphonoacetate (9.3 g, 49 mmoles) was dissolved in 100 mL benzene and treated at 0 °C with a solution of trifluoroethanol (8.15 g, 81 mmoles) and ethyl diisopropylamine (10.85 g, 81 mmoles) in 50 mL of benzene. After stirring for 1h at 25 °C, the solvent was evaporated and the residue was filtered through a 4 inch plug of silica gel with 7:3 ethyl acetate:petroleum ether to remove contaminating (MeO)(TFEO)$POCH_2COOMe$ and afforded the bis(trifluroethyl) phosphonoester in 28 % yield. ^{31}P: 24.36; ^{19}F: -75.78 (t, $^{3}J_{FH}$ = 9.7 Hz); ^{1}H NMR: δ_H 3.1 (1H, s), 3.2 (1H, s), 3.8 (3H, s), 4.35 (4H, q, $^{3}J_{HF}$ = 9.7 Hz)

Synthesis of 18-crown-6-acetonitrile complex[11]

To 18-crown-6 (10 g, 0.027 mole) in an Erlenmeyer flask was added 32.50 mL of acetonitrile. The resulting slurry was heated on a hot plate to effect solution. A magnetic stirring bar was added and the neck was equipped with a $CaSO_4$ drying tube. The solution was stirred vigorously as it was allowed to cool to room temperature, and fine white crystals of crown-acetonitrile complex were deposited. The flask was finally cooled in an ice-acetone bath to precipitate as much complex as possible. The solid was then collected by rapid filtration. The 18-crown-6-acetonitrile complex[11] was obtained pure in 100 % yield. ^{1}H NMR: δ_H 2.00 (6H, s), 3.7 (18H, s).

Preparation of methyl *cis*-3-(2-bromophenyl) propenoate

A solution of bis(trifluoroethyl) phosphonoacetate previously synthesised (1.92 g, 7 mmoles), 18-crown-6 acetonitrile complex (11.62 g, 5 eq) in 25 mL anhydrous THF was cooled to –78 °C under nitrogen and treated with $KN(TMS)_2$ (1.34 g, 1e q, 0.6M in toluene). 2-Bromobenzaldehyde (1.24 g, 7 mmoles) was then added and the resulting mixture was stirred for 30 min at –78 °C. Saturated NH_4Cl was added and the product was extracted into ether (3 x 30 mL). The organic phases were dried under magnesium sulfate and evaporated. Flash chromatography was performed (7:3 EtOAc:petroleum ether) and the product was eluted at the same time as the aldehyde. The solution was treated with sodium bisulfite for the removal of the bromo-benzaldehyde and a second column was then performed with the same conditions to afford 0.2 g (13 %) of *cis/trans* mixture of methyl-2-(2-bromophenyl) propenoate. ^1H NMR of the *cis* isomer: δ_H 3.75 (3H, s, Me), 6.05 (1H, d, J = 13.2), 6.95 (1H, d, J = 13.2), 7.2-8 (4H, m). *Trans*-isomer was observed in the NMR spectrum in 1.0:2.5 ratio (*trans*:*cis*). The ratio was estimated from the integrals of the NMR spectrum.

Preparation of methyl *cis*-3-(2-bromophenyl) cyclopropane carboxylate

In a distillation flask was placed a solution of potassium hydroxide (2 g) dissolved in water (4 mL), monoethyl ether of diethylene glycol (12 mL) and ether (4 mL). There was placed in the droping funnel a solution of *p*-tolylsulfonylmethylnitrosamide (7.2 g) in ether (42 mL). The distillation flask was heated in a water bath at 75-80 °C, the stirrer was started, and the nitrosamide solution was added at a regular rate during 25-30 minutes. As soon as all the nitrosamide solution has been added, additional ether

(60 mL) was placed in the dropping funnel and added at the previous rate until the distillate was colourless. The resulting ether solution of diazomethane was continously distilled into a stirred, cooled (-10 °C) solution of the *cis/trans* mixture of methyl-2-(-2-bromophenyl) propenoate (200 mg, 0.8 mmol) and palladium acetate (0.089 mg, 0.0004 mmol) in dichloromethane/ether (1:2, 75 mL). The reaction was quenched by addition of a 1 mL of acetic acid after 2h. The resulting mixture was washed with saturated aqueous sodium hydrogen carbonate (3 x 5 mL), dried over magnesium sulfate, filtered, and concentrated to afford 0.2 g of crude product. The crude product was purified on a silica column eluted with ether/hexane (2:1) to afford 0.06 g (30 %) of the *cis/trans* mixture of methyl-2-(2-bromophenyl) cyclopropane carboxylate. The trans-isomer was still present. The *cis/trans* mixture of methyl-2-(2-bromophenyl) cyclopropane carboxylate was used without further purification for the next step. ^{1}H NMR of the *cis* isomer: δ_H1.35-1.40 (1H, m, CH), 1.60-1.70 (1H, m, CH), 1.80-1.70 (1H, m, CH), 2.70-2.80 (1H, m, CH), 3.80 (3H, s, Me), 7.00-7.20 (2H, m, ArylH), 7.25-7.35 (1H, m, ArylH), 7.60-7.65 (1H, m, ArylH). Trans-isomer was observed in a ratio 1.0:2.5 (*trans:cis*).

Preparation of *cis*-3-(2-bromophenyl) cyclopropanecarboxylic acid

The *cis/trans* mixture of methyl-2-(-2-bromophenyl)cyclopropenoate (0.06 g, 0.24 mmol) was dissolved in ethanol (10 mL), and 2M aqueous potassium hydroxide (5 mL) was added. The solution was stirred at room temperature for 2h. The ethanol was evaporated, and the remaining solution was diluted with water (5 mL), washed with ether (20 mL), acidified with 5M aqueous hydrochloric acid, and extracted with ether (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford the the *cis/trans* mixture of methyl-2-(-2-

bromophenyl)cyclopropanecarboxylic acid (0.057 g, 98 %). ^{1}H NMR (acetone) *cis* + *trans*: δ_H1.07-1.12 (2H, m, CH), 1.40-1.55 (2H, m, CH), 1.75-1.81 (1H, m, CH), 2.03-2.07 (1H, m, CH), 7.09-7.86 (8H, m, ArylH). The ratio was quite impossible to estimate because of the almost identical chemical shifts of both isomers.

Preparation of *cis*-1-bromo-(2-isocyanatocyclopropyl) benzene

A mixture of 2-(-2-bromophenyl)cyclopropanecarboxylic acid (0.55 g, 0.24 mmol, *cis/trans* mixture), triethylamine (0.03 g, 1.4 eq), and ethyl chloroformate (0.04 g, 1.5 eq) in dry acetone (10 mL) was stirred at -10 °C. A solution of sodium azide (0.03 g, 1.7 eq) in H_2O (0.1 mL) was added after 2.5h. The stirring was discontinued after an additional 30 minutes. The resulting suspension was poured into cold H_2O (5 mL) and was extracted with toluene. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to about 50% of the volume to remove remaining traces of H_2O. The resulting solution was heated (90 °C bath temperature) until the evolution of nitrogen ceased, and the solution was concentrated to give 0.055 g (98 % yield) of the resulting isocyanate, *cis/trans* mixture of 1-bromo-(2-isocyanatocyclopropyl) benzene. *Cis*-isomer: ν_{NCO} = 2272 cm^{-1}. ^{1}H NMR (benzene): δ_H 1.20-1.40 (2H, m, CH), 1.50-1.65 (0.5H, m, CH), 1.65-1.80 (0.5H, m, CH), 2.60-2.80 (1H, m, CH), 6.90-7.10 (2H, m, ArylH), 7.15-7.20 (1H, m, ArylH), 7.40-7.60 (1H, m, ArylH). Trans-isomer was observed in a ratio 1.0:2.5 (*trans:cis*).

Homolytic reactions of 1-bromo-(2-isocyanatocyclopropyl) benzene (cis/trans mixture in a ratio 2.5:1.0)

Tin hydride method

Cis/trans-1-bromo-(2-isocyanatocyclopropyl) benzene (40 mg, 0.2 mmol) and tributyltin hydride (50 mg, 0.2 mmol) in solution in d-benzene (1 mL) in a quartz tube were photolysed for 3h. The GC-MS didn't show any trace of the adduct. Several peaks of unidentified components were observed.

TTMSS method

Cis/trans-1-bromo-(2-isocyanatocyclopropyl) benzene (20 mg, 0.08 mmol) and tris(trimethylsilyl)silane (25 mg, 0.10 mmol) in solution in d-benzene (1 mL) were heated for 2h at 103 °C (oil bath) in presence of 10 % of 1,1'-azo-di-cyclohexanecarbonitrile (0.002 g). The NMR spectrum showed mainly the presence of the *cis*-1-bromo-(2-isocyanatocyclopropyl) benzene. GC-MS: **Peak 12.89**, *trans*-(2-isocyanatocyclopropyl) benzene; **Peak 15.50**, *cis*-1-bromo-(2-isocyanatocyclopropyl) benzene, **Peak 15.65**, *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene (*Cis*:*trans*, ratio 1:5). Several traces of unidentified components were also observed.

3. Synthesis of 2-(2-bromophenyl)-3-isocyanato-oxirane

Preparation of methyl 3-(2-bromophenyl)-2-oxiranecarboxylate[27]

Method 1

A solution of methyl *trans*-3-(2-bromophenyl)propenoate (2.5 g, 10.37 mmoles) in dichloromethane was treated with *m*-CPBA (2.15 g, 12.45 mmoles) and refluxed for

48h. The reaction mixture was cooled with ice, filtered, and the filtrate was extracted with saturated $NaHSO_3$, aq $NaHCO_3$ and brine. The resulting organic layers were dried over anhydrous sodium sulfate and evaporated in vacuo. The product was purified by column chromatography to afford 24 % of the methyl 3-(2-bromophenyl)-2-oxiranecarboxylate (spectra as below).

Method 2

2-Bromobenzaldehyde (9.25 g, 50 mmoles) and methyl chloroacetate (6.6 mL, 75 mmoles) were added dropwise at the same time to 1.8 g (78.5 mmoles) of Na in 75 mL of dry methanol. The solution was stirred for 1 hour at –10 °C, then for 16h at RT. 60 mL of 0.3 N HCl was added, and the solution was extracted with dichloromethane. The organic phases were then dried over magnesium sulfate and the solvent evaporated under reduce pressure. The product was purified by fractional distillation (bp. = 112-120 °C) to afford 10.5 g (82 %) of the epoxide. Methyl 3-(2-bromophenyl)-2-oxiranecarboxylate[27] was obtained as a clear oil which crystallised on standing. ^{1}H NMR: δ_H 3.29 (1H, s, CH), 3.76 (3H, s, CH_3), 4.27 (1H, s, CH), 7.08-7.24 (3H, m, ArylH), 7.41-7.43 (1H, m, ArylH). MS m/z(%) M^+ 256/258(43), 225/227(20), 197/199(100), 169/171(29), 89(9). C-H-N microanalysis found, C 46.26 %, H 3.59 %, $C_{10}H_9BrO_3$ requires C 46.72 %, H 3.53 %.

Preparation of methyl 3-(2-bromophenyl)-2-oxiranecarboxylic acid[27]

Method 1

Methyl-3-(2-bromophenyl)-2-oxirancarboxylate (2.3 g, 9 mmoles) was dissolved in methanol (30 mL), and 2M aqueous sodium hydroxide (15 mL) was added. The solution was stirred at room temperature for 2h. The methanol was evaporated, and

the remaining solution was diluted with water (15 mL), washed with ether (20 mL), acidified with 5M aqueous hydrochloric acid, and extracted with ether (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford pure methyl-3-(2-bromophenyl)-2-oxirancarboxylic acid (1.1 g, 50 %). The details of the analysis are outlined below. The results were identical for both procedures.

Method 2

Methyl-3-(2-bromophenyl)-2-oxirancarboxylate (2.1 g, 8.2 mmoles) was dissolved in ethanol (20 mL), and 2M aqueous potassium hydroxide (15 mL) was added. The solution was stirred at room temperature for 2h. The methanol was evaporated, and the remaining solution was diluted with water (15 mL), washed with ether (20 mL), acidified with 5M aqueous hydrochloric acid, and extracted with ether (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford pure methyl-3-(2-bromophenyl)-2-oxirancarboxylic acid (1.96 g, 98 %), mp 108 °C. ^{1}H NMR: δ_H 3.42 (1H, s, CH), 4.45 (1H, s, CH), 5.45 (1H, br, OH), 7.21-7.41 (3H, m, ArylH), 7.56-7.65 (1H, m, ArylH). ^{13}C NMR, δ_c 55.94, 58.52, 123.11, 126.71, 128.16, 130.63, 132.93, 134.69, 173.10. MS. m/z(%) $[m+1]^+$ 243/245(76), 225/227(31), 197/199(100), 185(140), 168(28), 119(7), 57(20). C-H-N microanalysis: found, C 44.48 %, H 2.68 %, $C_9H_7BrO_3$ requires C 44.47 %, H 2.90 %.

Preparation of 2-(2-bromophenyl)-3-isocyanato-oxirane

A mixture of methyl-3-(2-bromophenyl)-2-oxirancarboxylic acid (1.0 g, 4.0 mmoles), triethylamine (0.5 g, 5.0 mmoles), and ethyl chloroformate (0.6 g, 5.5 mmoles) in dry acetone (30 mL) was stirred at -10 °C. A solution of sodium azide (0.45 g, 6.9

mmoles) in H_2O (2 mL) was added after 2.5h. The stirring was discontinued after an additional 30 minutes. The resulting suspension was poured into cold H_2O (12 mL) and was extracted with toluene. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to about 50 % of the volume to remove remaining traces of H_2O. The resulting solution was heated (90 °C bath temperature) until the evolution of nitrogen ceased, and the solution was concentrated to give the resulting isocyanate in 83 % yield. ^1H NMR: δ_H 3.08 (1H, s, CH), 4.46 (1H, s, CH), 6.60-6.83 (1H, m, ArylH), 7.01-7.29 (2H, m, ArylH), 7.71-7.77 (1H, m, ArylH). ν_{NCO} = 2260 cm^{-1}. MS, m/z(%) M^+ 239/241(100), 195/197(3), 183/185(60), 153/155(18), 132(15), 115(20), 89(25), 75(20), 50(15).

Homolytic reactions of 2-(2-bromophenyl)-3-isocyanato-oxirane

Tin hydride method

2-(2-Bromo-phenyl)-3-isocyanato-oxirane (50 mg, 0.21 mmol) and tributyltin hydride (60 mg, 0.21 mmol) in solution in d-benzene (0.5 mL) were photolysed for 3h. The GC-MS showed no trace of the adduct. Only the product of reduction was identified. Several traces of unindentified components were observed. GC-MS, **Peak 373**, 3-phenyl-oxiranylamine, m/z(%) M^+ 135(100), 118(17), 107(68), 91(67), 79(49), 65(16), 51(14).

TTMSS method

2-(2-Bromo-phenyl)-3-isocyanato-oxirane (40 mg, 0.17 mmol) and tris(trimethylsilyl)silane (50 mg, 0.20 mmol) in solution in d-benzene (1 mL) were heated for 2h at 103 °C (bath oil) in presence of 10 % of 1,1'-azo-di-cyclohexanecarbonitrile (0.004 gr). The same procedure was repeated at 83 °C for 7h. The result was quite identical. The 1H NMR spectrum showed mainly the unreacted starting materials. GC-MS, **Peak 17.04**, 3-(2-bromo-phenyl)-oxiranylamine, m/z(%) M^+ 213/215(100), 185/187(80), 171/173(17), 157/159(19), 134(3), 118(38), 89(90), 63(23), 29(18); **Peak 18.4**, $C_9H_7NO_2$, m/z(%) M^+ 161(100), 144(3), 117(15), 105(70), 91(4), 77(36), 51(13), 29(2) (probably 4-hydroxy-4*H*-isoquinolin-1-one); **Peak 20.61**, 2-(2-Bromo-phenyl)-3-isocyanato-oxirane. Several minor unidentified components were also present.

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Chapter 5

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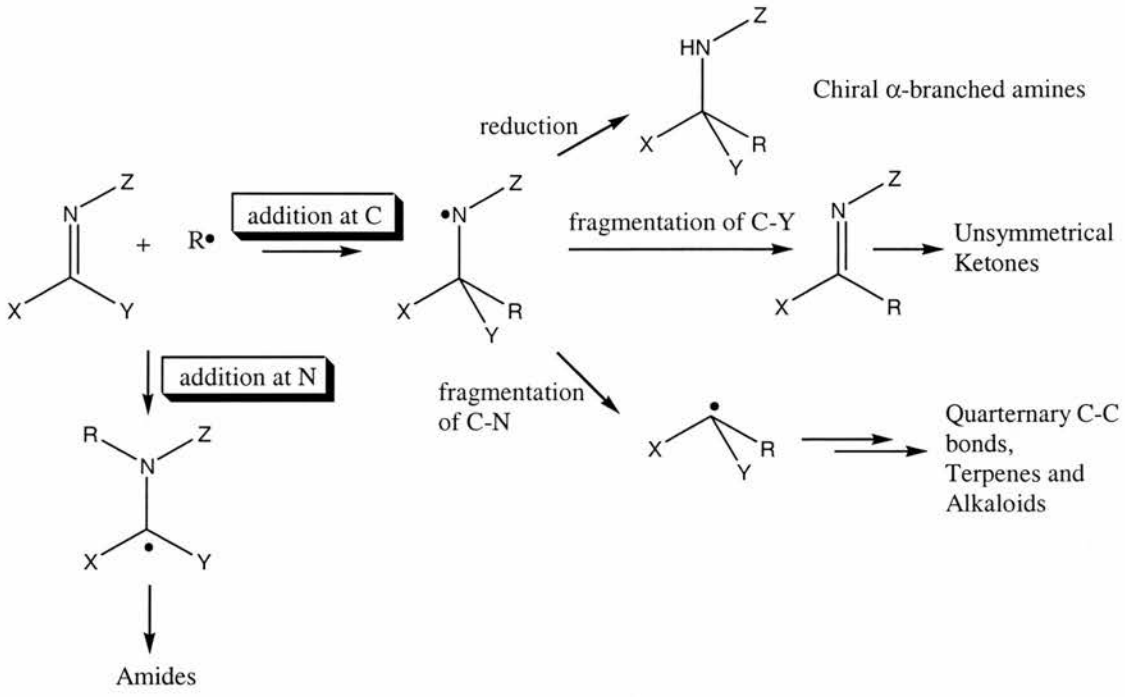
INTRAMOLECULAR ADDITION TO AROMATIC IMINES

I- Introduction

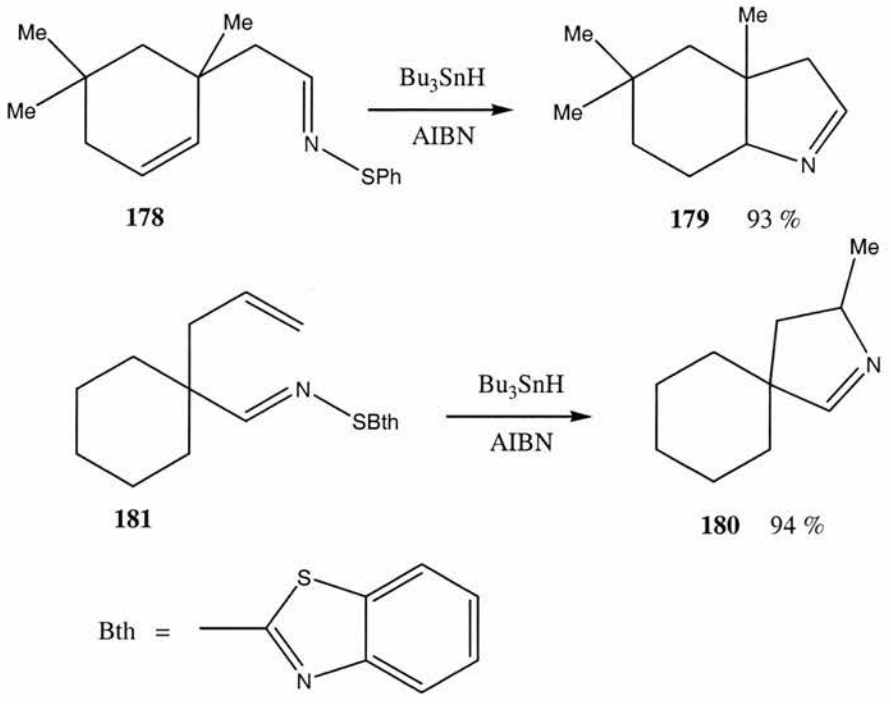
Synthesis using radical cyclisation onto multiple bonds containing heteroatoms has been of increasing interest in recent years.[1-3] Although radical cyclisations of alkyl radicals onto C=C and C=O bonds have been studied extensively,[3-11] radical cyclisations to C=N bonds received relatively little attention.

Imines, and related compounds, have been used as electrophiles for ionic bond constructions (e.g. in Mannich reactions) for many years, but the ongoing demand for more efficient, mild and general synthetic methodology makes radical addition to imine derivatives an increasingly attractive alternative. Although industrially important radical additions to alkenes have long attracted research effort, radical addition to imines and related compounds began to emerge as a useful synthetic process only since the 1980s.[12-16] This is rather surprising in retrospect, given that these functional groups can exhibit up to three orders of magnitude higher radical addition rates relative to analogous alkene acceptors. Furthermore, a useful functional group remains available for subsequent synthetic elaboration, either via fragmentation and further radical chemistry, or by traditional transformations of closed-shell products. In contrast to alkenes, the Lewis basic nitrogen of imines offers an inherent site within the acceptor for Lewis acid complexation, which has ramifications for rate enhancement and stereochemical control. Synthetic applications of radical addition to C=N are summarized in the scheme 98.



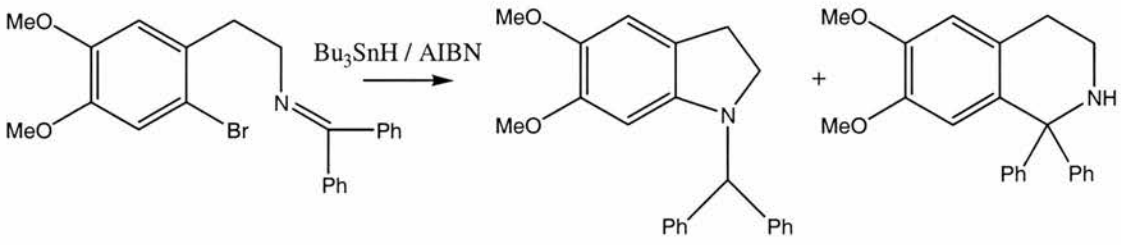
scheme 98

Radical additions to C=N bonds can occur either to the N-atom or the C-terminus of the imine moiety. The most common application is reductive radical addition to the CN double bonds to obtain amines. Radical addition to the C-terminus leads to N-centred radicals that are prone to fragmentation by β-elimination if weak bonds are appropriately located. Fragmentation can be encouraged by the presence of ring strain or groups that afford stable free radicals upon homolysis. The fragmentation can occur either by cleavage of a weak C-X bond to the C-terminus of the original CN bond, cleavage of a C-C bond at the C-terminus aided by relief of ring strain, or by fragmentation of a bond within the group linked to the N-terminus of C=N. Examples of fragmentations of N-linked groups have been reported by Boivin and co-workers.[17, 18] Cyclisations of the imines below afforded the bicyclic products shown in excellent yields.



scheme 99

Addition to the N-terminus of the C=N bond is not so common. A stabilising 3-electron interaction of the forming aminyl radical with non-bonding electrons on either oxygen or nitrogen is generally invoked. In contrast to oxime ethers or hydrazones, this radical α-effect is not possible in the case of imines. In the cases of addition at nitrogen known to date,[19, 20] additional stabilising groups, such as benzylic groups, conformational restriction, severe steric hindrance, or polar effects are present to further promote attack at nitrogen. Takano and co-workers [21] reported that in the ketimines **182** derived from acetophenone and benzophenone, the free-radical centre added exclusively to the nitrogen terminus of the azamethine bond in a 5-*exo* fashion to give the indoline **183** in 59 % yield.



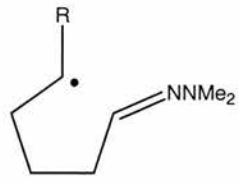
182 **183** 59 % **184** 0 %

scheme 100

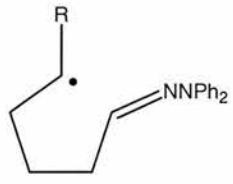
Usually this pathway is kinetically disfavoured as mentioned above, but the extra steric hindrance present in the molecule led to exclusive formation of the indoline **183** at the expense of the isoquinoline **184**. The fine-tuning of the substituents allowed control of the competition between the 5-*exo* and the 6-*endo*-cyclisation mode.

Among the various CN-containing functional groups, oxime ethers and hydrazones are by far the most commonly used radical acceptors. 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. More importantly, imines have slower radical addition rates. Selected rate constants[22] for intramolecular radical addition reactions are compiled in the schemes below.

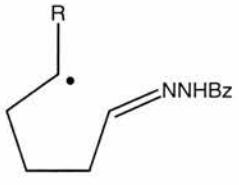
Hydrazones (*5-exo*) :



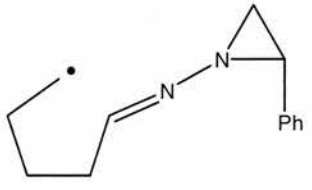
$k = 2.4 \times 10^7\ s^{-1}$



$k = 1.6 \times 10^8\ s^{-1}$



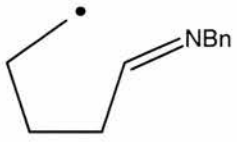
$k = 1.6 \times 10^8\ s^{-1}$



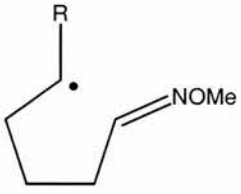
$k = 2.5 \times 10^8\ s^{-1}$

Oxime Ethers (*5-exo*) :

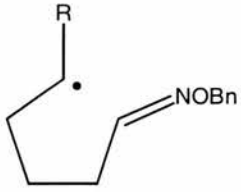
Imine (*5-exo*) :



$k = 6.0 \times 10^6\ s^{-1}$

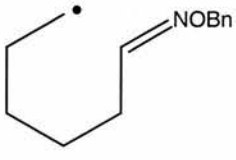


$k = 2.4 \times 10^7\ s^{-1}$

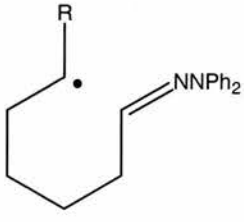


$k = 3.3 \times 10^7\ s^{-1}$

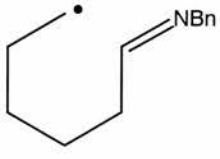
***6-exo* Cyclisations :**



$k = 2.4 \times 10^6\ s^{-1}$



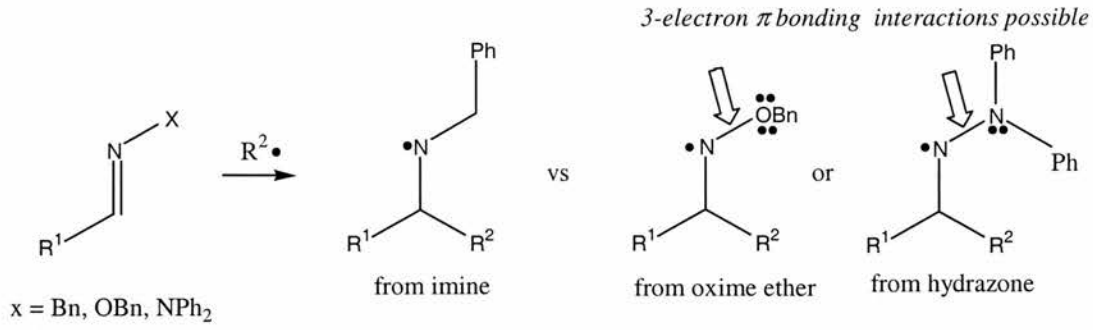
$k = 1.9 \times 10^6\ s^{-1}$



$k = 6.7 \times 10^5\ s^{-1}$

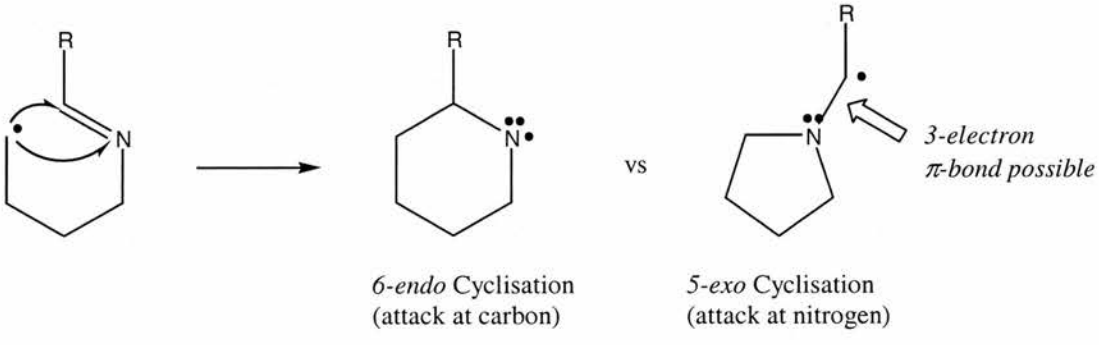
scheme 101

All data were obtained at 80 °C with tin-mediated conditions.[22] R is a primary alkyl chain containing an alternative radical acceptor (data obtained via competition study). The rate differences have been rationalised by considering semi-empirical calculations (MOPAC) of electron densities on the CN carbon, which are in the order hydrazone > oxime ether > imine.[23, 24] Also, imines lack the potential for a stabilising three-electron bond in the adduct aminyl radical as shown in scheme 102.



scheme 102

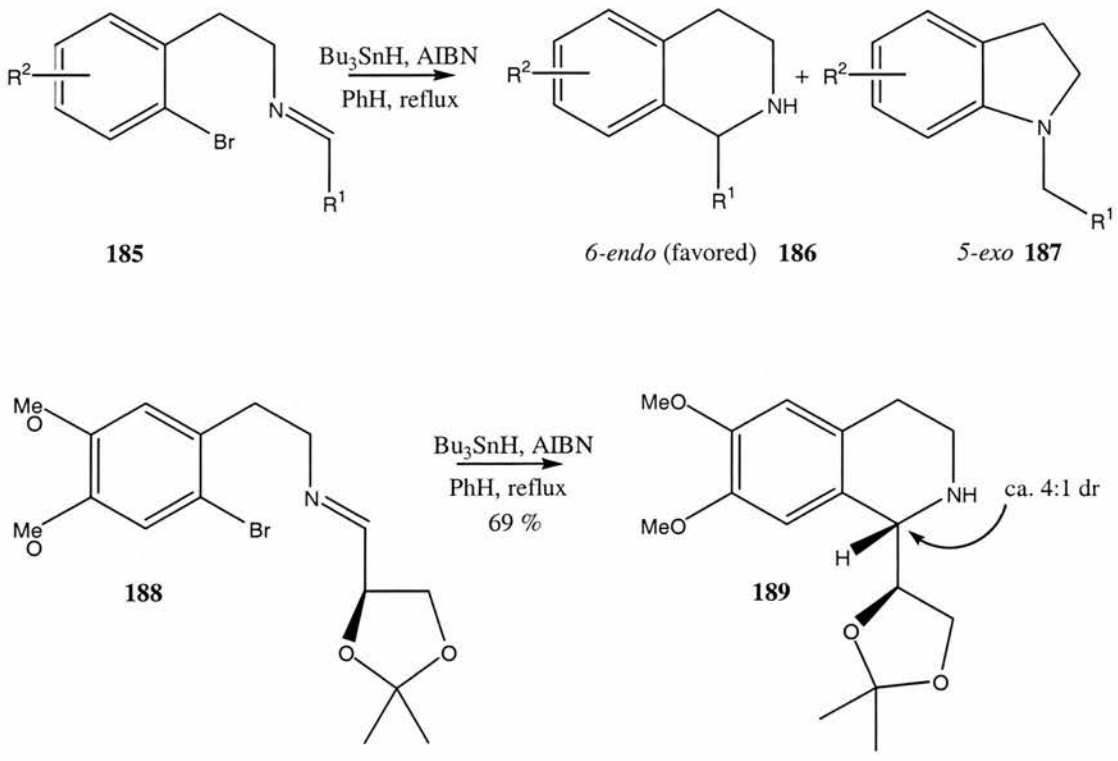
This developing interaction could affect the stabilisation of the transition-state. Regarding the regioselectivity, attack at carbon of the CN double bond is almost exclusively observed, except in unusual cases. Radical addition to the CN double bond could occur with attack at nitrogen to give an α-amino radical, which should be stabilised by the adjacent nitrogen atom (scheme 103).



scheme 103

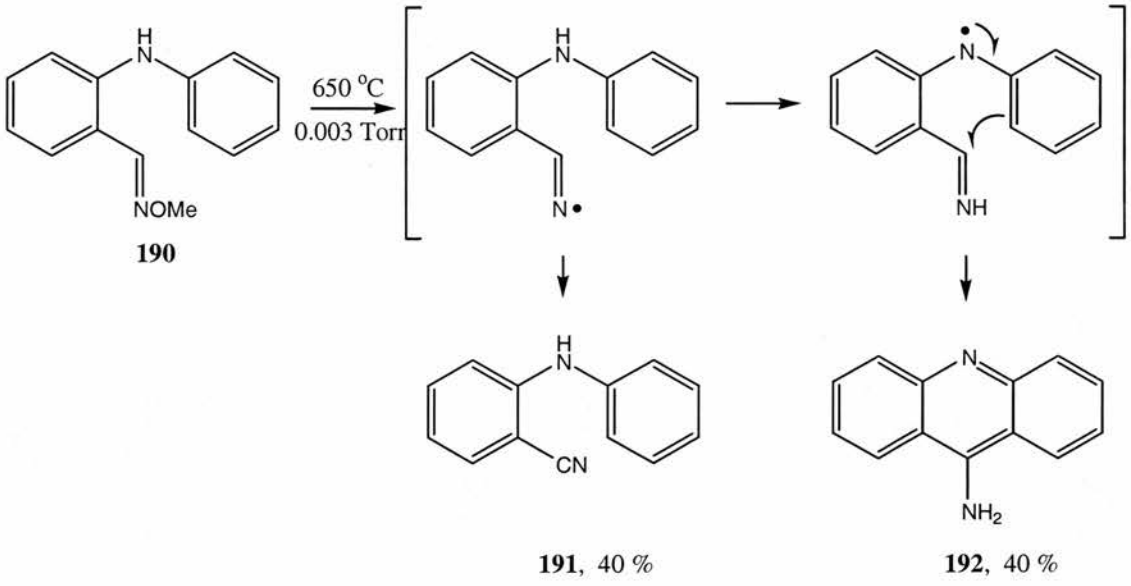
The competition between 5-*exo* and 6-*endo* cyclizations has been used to examine this issue. Favoured attack at carbon is illustrated nicely by Warkentin's competition studies with aryl radical cyclizations,[20] wherein 6-*endo* attack at carbon was preferred over 5-*exo* attack at nitrogen. This is in contrast with the radical cyclizations of alkenes wherein 5-*exo* cyclization rates are higher. Warkentin's calculations on

aldimines exhibit higher LUMO coefficients on carbon, consistent with the kinetically preferred attack at this site. Ryu and Komatsu showed that there was virtually no thermodynamic preference for 6-*endo* cyclization, so attack at the C-terminus of CN bonds appears kinetically favoured.[25] The reversibility of alkyl radical additions to CN double bonds appears to be dependent on the nature of the adduct radical. Kinetic data[23, 24] and (UHF/3-21G) MO calculations[25] suggest that 5-*exo* and 6-*exo* cyclisations of both imines and oxime ethers are essentially irreversible. Accounts of radical additions to simple aldimine functional groups appeared in 1975. The reaction has been put forward as a proposed mechanistic step in various unusual reactions.[26-28] The first synthetic use of an imine as a radical acceptor, was reported by Takano et al.[19] in 1990 as a key step in their synthesis of cryptostyline alkaloids, isolated from the *Orchidaceae*. Warkentin subsequently contributed detailed studies of related reactions to access tetrahydroisoquinoline structures[20] (scheme 104).



scheme 104

In the above-mentioned example, 6-*endo*-trig cyclisation of an aryl radical onto an aldimine acceptor was favoured. This was rationalised by considering the larger calculated LUMO coefficients on carbon and the smaller C-N=C bond angle relative to the corresponding alkene leading to better orbital overlap of the aryl radical with the C=N LUMO. Substrate-induced diastereocontrol was observed using a glyceraldehyde-derived imine, which led to a 4:1 diastereomeric mixture. McNab and collaborators reported that flash vacuum pyrolysis of oxime ethers gave iminyl radicals which underwent various secondary processes including addition to the C=N bond,[29] scheme 105.



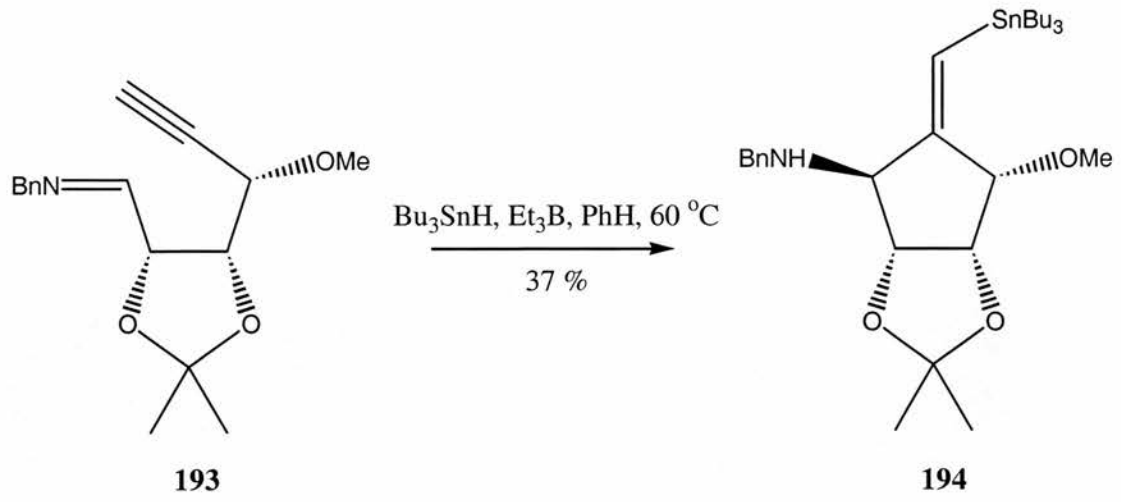
190

191, 40 %

192, 40 %

scheme 105

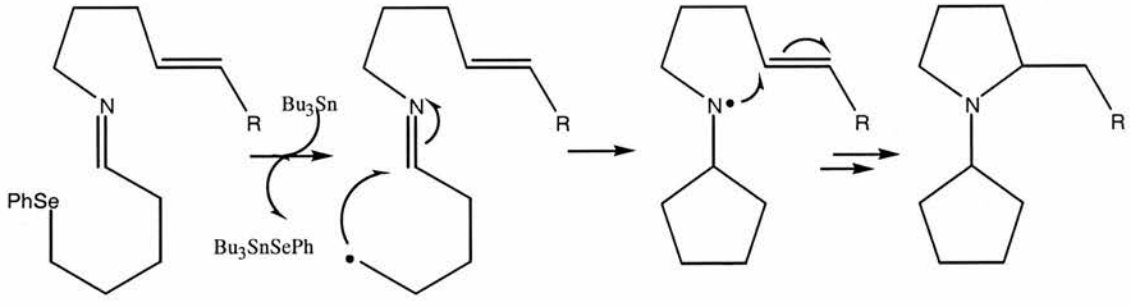
Formation of **192**, from aldoxime **190,** was attributed to tandem reactions involving N-O homolysis, radical translocation, and 6-*exo* cyclisation onto the C=N bond. However, no examples have been reported regarding flash vacuum pyrolysis of imines. Radical cyclisation onto C=N bonds can be initiated by intermolecular radical addition to alkenes or alkynes. For instance, Marco-Contelles has studied addition/cyclisation processes with alkynyl imine derivatives from carbohydrate precursors,[30] (scheme 106).



193 **194**

scheme 106

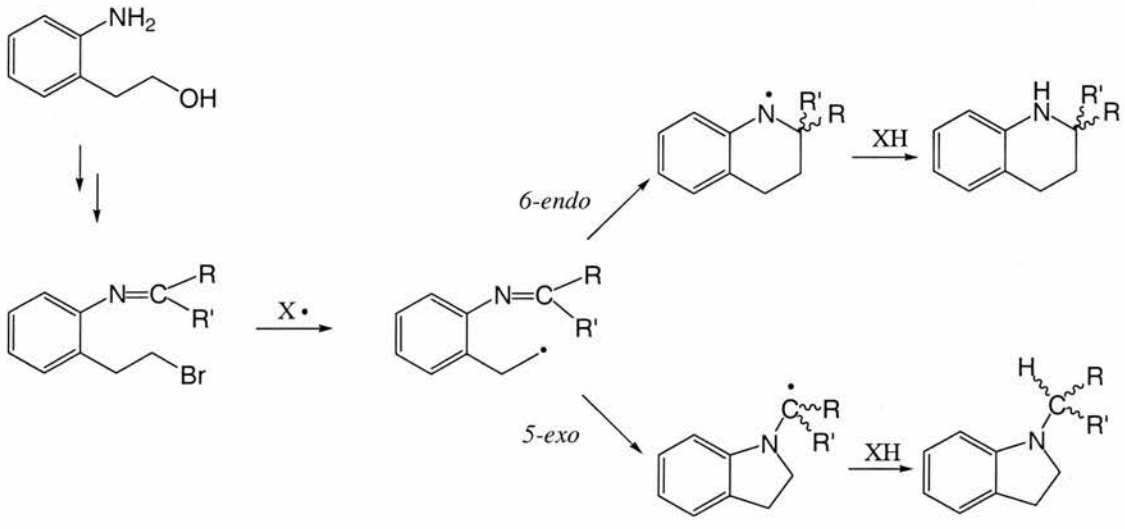
Stannyl addition and cyclisation of imines **193** furnished the corresponding cyclic vinylstannanes **194** with a modest 37 % yield. Cyclisation onto the carbon atom of imines generated intermediate aminyl radicals. Bowman[16, 31] reported a tandem radical cyclisation onto imines which provided a new synthetic route to bicyclic nitrogen-heterocycles, (scheme 107).



scheme 107

The imines were formed in situ by condensation of the respective aldehydes or ketones with the amines and reacted with tributyltin hydride to give the tandem-cyclised pyrrolidines in reasonable yields.

A new pathway for performing radical cyclisations from imines was chosen for study, and is outlined in scheme 108.



scheme 108

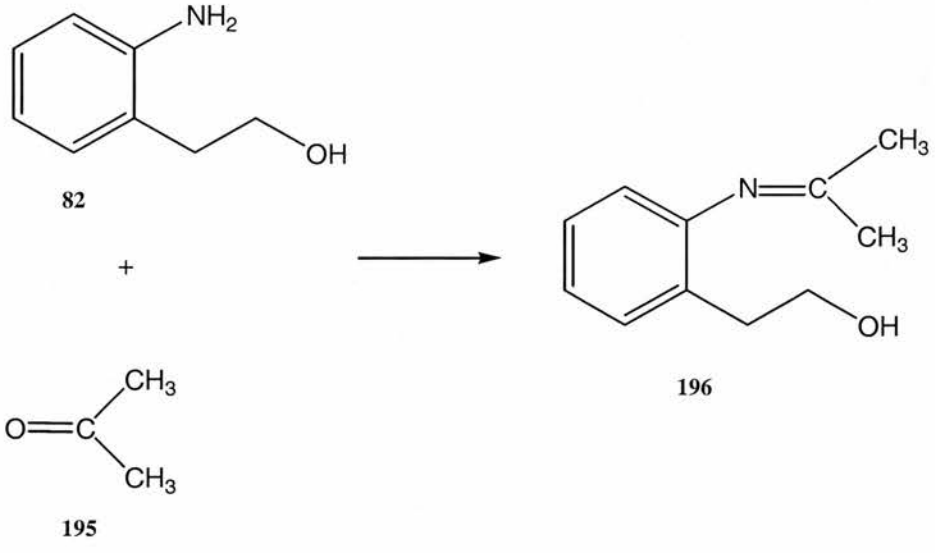
The methodology involves a multi-step synthesis followed by an intramolecular alkyl radical addition on the C=N bond as the final step. The alkyl radical could undergo either a *6-endo* or a *5-exo* radical cyclisation onto the C-atom or the N-atom respectively of the imine group. The imine precursor is to be formed by condensation of the respective aldehyde or ketone with the aromatic amino alcohol using a Dean-Stark water separator. The second step consists in introducing a good leaving group, instead of the alcohol, to facilitate the radical cyclisation.

II- Results and discussion

1. Formation of the imine

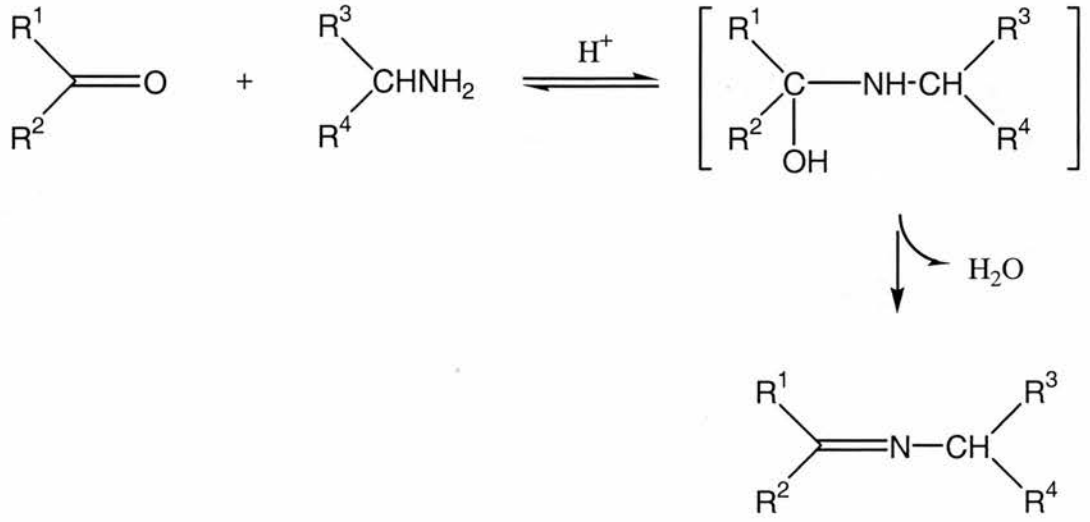
1.1. Synthesis of 2-(2-isopropylideneaminophenyl) ethanol (196)

A common method used in the preparation of ketimines was to reflux an equimolar amount of the ketone and the corresponding amine in toluene using a Dean-Stark apparatus to remove the water formed during the reaction. Cope, Hancock, and co-workers[32-35] have prepared a number of condensation products of ketones with alkanolamine by azeotroping the water of reaction with benzene.



In our case, we were interested in preparing the ketimine **196**. Although the procedure was performed by refluxing the amine **82** and acetone **195** in the presence

of an azeotroping reagent, toluene, after 3 days, the starting material was recovered. However some ketimines may be prepared from ketones and amines with acidic catalysts (scheme 109).



scheme 109

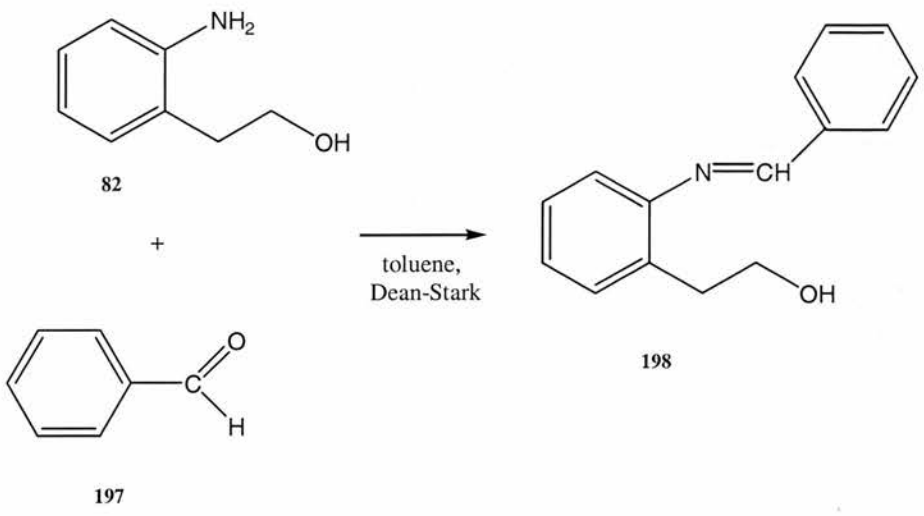
The reaction was, therefore, next carried out by condensing imine **82** and acetone in presence of either *p*-TsOH[36] or $ZnCl_2$. A modest 23.5 % yield of ketimine was obtained after distillation using zinc chloride. With *p*-TsOH, the amount obtained was not significant.

The probleme was to choose acetone as the ketone. Because of the low boiling point of the acetone, it was removed by distillation during the Dean-Stark procedure.

1.2. Synthesis 2-[2-(benzylidene-amino) phenyl] ethanol (198)

The general procedure to prepare an imine is by refluxing an equimolar mixture of the corresponding primary amine and the carbonyl compound with an azeotroping

agent,[37, 38] such as benzene, toluene or xylene, or in presence of molecular sieves to remove the water of reaction. Occasionally an acidic catalyst such as p-TsOH[39] could be used.



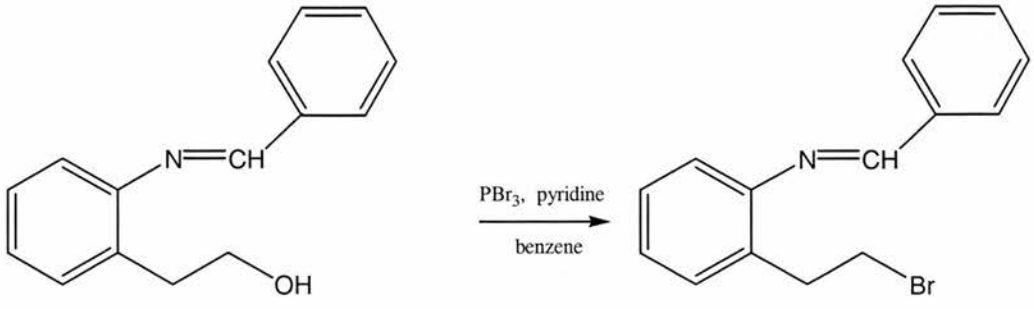
In this study, the imine precursor **198** was synthesised by refluxing an equimolar mixture of 2-(2-aminophenyl) ethanol **82** and benzaldehyde **197** in a Dean-Stark apparatus for removal of the water formed by azeotropic distillation.[37] The imine was obtained in 97 % yield after distillation.

2. Introduction of a leaving group, X = Br, I

Bromination of aliphatic alcohol has been widely investigated and various reagents are convenient. The most commonly used reagents for the conversion of alcohols to bromides involves HBr[40], PBr_3[41] and Ph_3PBr_2;[42] although they have limited selectivity. Some of the recent methods involve more selective phosphorus-[43] and sulfur-based[44] reagents, as well as the use of bromotrimethylsilane,[45]

chlorotrimethylsilane/lithium bromide and hexamethyldisilane/pyridinium bromide perbromide,[46] or polymer supported reagents.[47-52] However, the choice depends strongly on the structure of the organic molecule and the functional groups present. Several procedures were therefore attempted.

2.1. Bromination with PBr_3

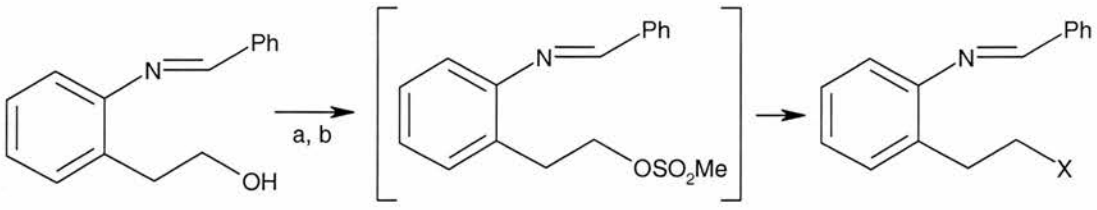


198 **199**

An attempt to prepare the bromide from the imine was carried out using PBr_3.[53] The procedure consisted of the addition of phosphorus tribromide to the imine, in the presence of pyridine, in benzene. The reaction was not successful. The C=N bond was presumably hydrolysed during the reaction and the aldehyde and the imine were recovered at the end of the procedure.

2.2 Bromination with LiBr and iodation with NaI

Another method to replace an alcohol with a halide proceeds via the corresponding mesylate.



198 **201** **199**, X = Br

200, X = I

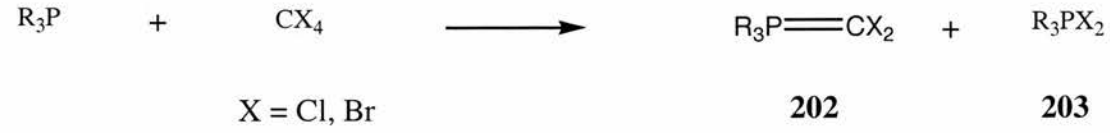
a- i) $MeSO_2Cl$; ii) LiBr
b- i) $MeSO_2Cl$; ii) NaI

The same procedure was employed but with two different solvents because of the problem of solubility of the sodium iodide in THF. The procedure[54] for making the mesylate involved adding methane sulfonyl chloride to a solution containing the imine and triethylamine in THF/acetone at 0 °C. The product was not isolated but used without further purification for the next step. Lithium bromide or sodium iodide dissolved in the solvent was then added into the mixture after 2h.

No procedure allowed us to obsverve the iodide on the NMR spectra. The procedure carried on with LiBr in acetone gave rise to the bromide after reaction. But it was impossible to isolate the product. The procedure performed with LiBr in THF gave similar result to the reaction with NaI. The benzaldehyde was recovered after reaction. The imine might hydrolyse during the synthetic steps. The GC-MS of the solution confirmed these results. The presence of benzaldehyde and 2,3-dihydro-1*H*-indole were observed on the GC-MS spectrum.

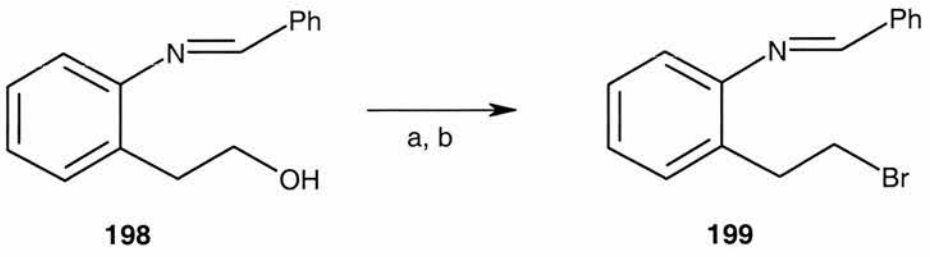
2.3. Bromination with CBr_4

A method was carried out to attempt the bromination of the imine in mild conditions, using CBr_4. The formation of ylid and triphenylphosphine dihalide from the interaction of triphenylphosphine with carbon tetrahalides was first reported by Rabinowitz[55] and Ramirez.[56]



scheme 110

An ionic mechanism involving nucleophilic displacement on halogen has been invoked.[57] R_3PX_2, **203**, allows the conversion of alcohols to alkyl halides to proceed without complication of elimination or rearrangement.[42, 58]



198 **199**

a- CBr_4, PPh_3
b- CBr_4, trioctylphosphine

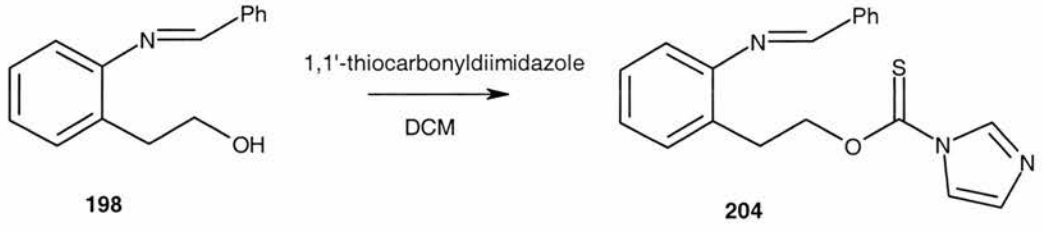
The bromination was carried out with carbon tetrabromide in the presence of either triphenylphosphine or trioctylphosphine. A first attempt at synthesis of the bromide

was carried out using CBr_4-Ph_3P[59] in dichloromethane at ice bath temperature. The reaction was run in the presence of 1.25 eq of CBr_4 and 1.25 eq of Ph_3P. The NMR analysis of the solution at the end of the reaction showed that a complex mixture was obtained and the product expected was not present. The GC-MS of the mixture showed the presence of tribromomethane and (2,2-dibromovinyl) benzene (or isomer).

Hooz[60] showed that by using tri-*n*-octylphosphine (TOP) and primary alcohols the conversion was of the order of 90-100 %. So the preparation of the bromide was performed by adding 2 equivalents of TOP to a solution of the alcohol and carbon tetrabromide in anhydrous ether. The NMR showed the presence of the expected bromide. In addition, the GC-MS showed the presence of benzaldehyde and 2,3-dihydro-1*H*-indole.

Tribromomethane presumably came from carbon tetrabromide and (2,2-dibromovinyl) benzene might come from the reaction between the ylide $Ph_3P{=}CBr_2$ and benzaldehyde to give the corresponding dibromide.

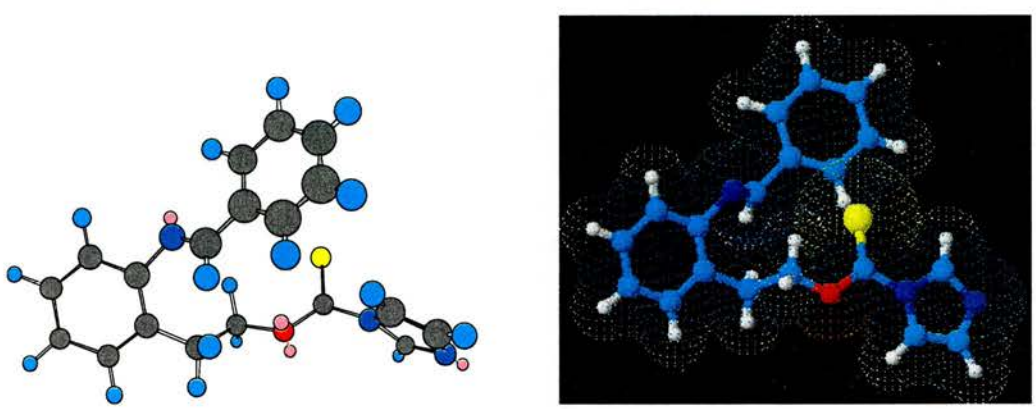
3. Formation of the thiocarbonylimidazolide



198 **204**

To synthesise the thicarbonylimidazolide **204**, a first procedure consisted in refluxing a mixture of the imine **198** and *N,N'*-thiocarbonyldiimidazole in dry tetrahydrofuran for 2 hours.[61] The proton NMR showed that the imine was hydrolysed during the

reaction. Although the procedure was carried out by refluxing the imine and *N,N'*-thiocarbonyldiimidazole in dry dichloromethane for 2 hours[62] the NMR showed that a complex mixture was also obtained containing benzaldehyde. The GC-MS showed that benzaldehyde and 2,3-dihydro-1*H*-indole were present in the mixture after reaction, as well as a trace of the adduct. The reaction with thiocarbonyldiimidazole in dichloromethane at RT gave rise finally to conversion to a compound whose ^{1}H NMR spectrum and low resolution mass spectrum were consistent with imidazole-1-carbothioic acid *O*-{2-[2-(benzylidene-amino) phenyl] ethyl} ester, compound **204**. The thicarbonylimidazolide was obtained in a relatively modest yield (38 %) after purification by column chromatography.

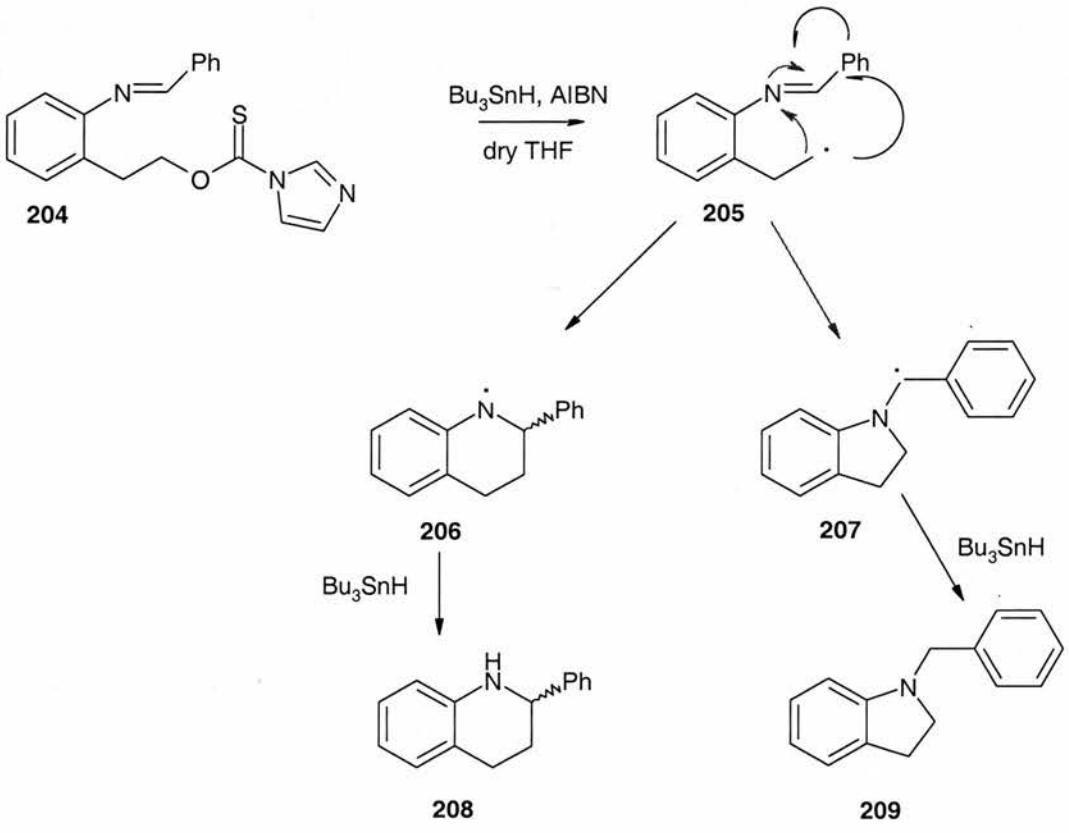


Picture 4

These models showed that ring closure of the imidazolide might well be possible.

4. Attempted radical cyclisations

The intermolecular addition of the imine was performed using tri-*n*-butyltin hydride as reagent in dry THF.[62]



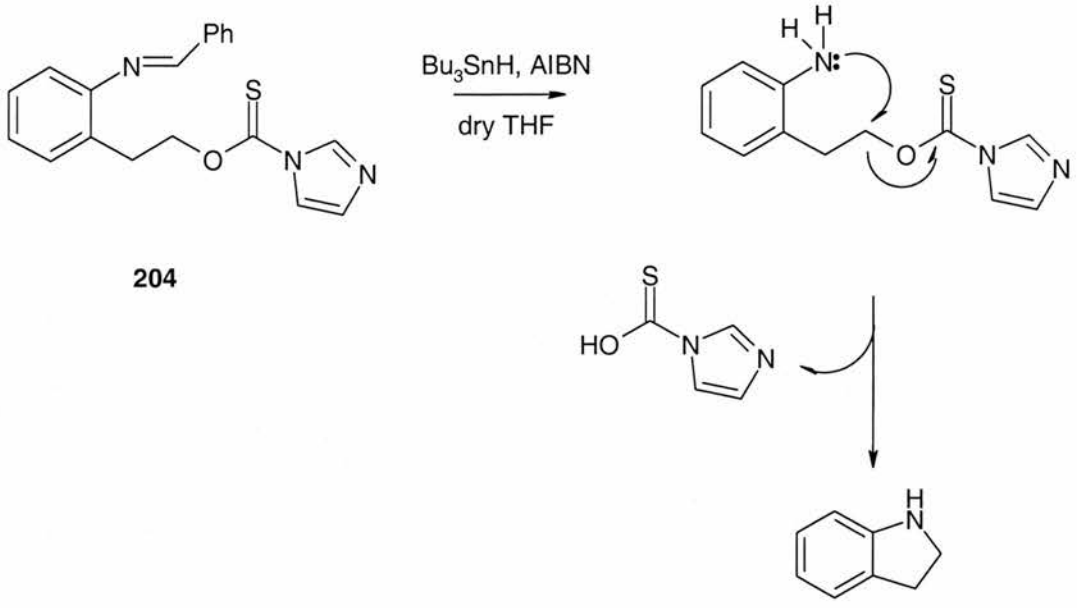
scheme 111

Two procedures were examined. In the first one the radical cyclisation was performed by refluxing the imine and tri-*n*-butyltin hydride in the presence of AIBN in dry THF. The second one involved the slow addition of AIBN using a syringe pump to the solution at reflux, containing the imine and the tin compound.

The GC-MS was relatively the same for both procedures. With the exception of the solvent or the starting material, benzyl alcohol, 2,3-dihydro-1*H*-indole **210** and

2-phenyl-1,2,3,4-tetrahydroquinoline **208** or 1-benzyl-2,3-dihydro-1*H*-indole **209** were the only products observed on the GC-MS spectra.

As described in scheme 111, 1-benzyl-2,3-dihydro-1*H*-indole **209** presumably came from 5-*exo*-cyclisation of the radical onto the nitrogen-atom of the imine moiety to form the amino radical which then abstracted a hydrogen from the tin hydride. Similarly, 2-phenyl-1,2,3,4-tetrahydroquinoline **208** probably came from 6-*endo*-cyclisation of the C-centred radical onto the C-atom of the imine group followed by abstraction of hydrogen from tin hydride. From the mass spectra, the presence of the mass 132 (M^+- 77) (loss of C_6H_5, a phenyl group) and the presence of the mass 118 (M^+- 91) (loss of C_7H_7, a benzyl group) allowed us to presume that 1-benzyl-2,3-dihydro-1*H*-indole **209** could be the only isomer present in the solution mixture after reaction. The fragmentation pattern was a good fit for 1-benzyl-2,3-dihydro-1*H*-indole **209**[63] but did not agree with that reported for 2-phenyl-1,2,3,4-tetrahydroquinoline **208**.[64] Formation of dihydroindole **210** could probably be attributed to hydrolysis of the imine to afford the corresponding aromatic amine that then underwent intramolecular nucleophilic substitution of the thioester group (scheme 112).



204

210

scheme 112

This mechanism was supported by the detection of benzyl alcohol that is the expected partner from the hydrolysis of the thiocarbonylimidazolide **204**.

So regarding to the imidazole-1-carbothioic acid *O*-{2-[2-(benzylidene-amino) phenyl] ethyl} ester, the radical cyclisation presumabably occurred on the N-centered atom of the imine moiety. The mass spectrum was consistent[63] with 1-benzyl-2,3-dihydro-1*H*-indole **209** being formed. 5-*Exo* appeared to be the predominant mode of cyclisation for this system.

III-Experimental

^{1}H, ^{13}C NMR spectra were obtained using Bruker AM 300 MHz, a Bruker Avance 300, and Varian Gemini 2000 spectrometers. The Bruker Avance 300 is fully

automated with autosampling robots. All samples were dissolved in deuterated chloroform, unless otherwise stated, using Me_4Si as an internal standard. The chemical shifts δ were given in ppm downfield from Me_4Si. IR spectra were recorded in nujol or neat on a Perkin-Elmer 1710 Infrared Fourier Transform Spectrometer. Frequencies are given in cm^{-1}. Mass spectra and GC-MS spectra were obtained using 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). All melting points were determined in open capillary tubes and are reported uncorrected. TLC was performed on pre-coated plates of silica gel G-60 F-254 (Merck). Elemental analysis were recorded on an Agilent 7500 Series ICP-MS spectrometer that had laser ablation built in capability or on a Carlo Erba CHNS analyser for carbon hydrogen nitrogen and sulphur. Column chromatography was performed using BDH silica gel (40-63 μm) eluting with the given solvent mixture.

1. Preparation of 2-(2-isopropylideneaminophenyl) ethanol

1.1. Procedure 1

A mixture of the primary amine (0.5 g, 3.6 mmoles) and acetone (0.46 g, 2 eq) was refluxed in toluene (30 mL) using a Dean-Stark apparatus in order to remove the water formed by azeotropic distillation. The reaction was carried out for 24 hours. The solvent was removed under vacuum. The proton NMR showed that the amine and the acetone were recovered after reaction.

1.2. Procedure 2

An equimolar mixture of the primary amine (0.5 g, 3.6 mmoles) and acetone (0.23 g, 1 eq) was refluxed in toluene (30 mL) using a Dean-Stark apparatus in order to remove the water formed by azeotropic distillation. The reaction was carried out for 5 days in presence of *p*-TsOH. The solvent was removed under vacuum. Although the proton NMR showed that the amine (65 %) was recovered after reaction, 35% of ketimine* was present in the mixture. ^{1}H NMR δ_H 1.80* (3H, s, CH_3), 2.18* (3H, s, CH_3), 2.70* (2H, t, CH_2, J = 6.3), 2.73 (2H, t, CH_2, J = 6.3), 3.77* (2H, t, CH_2, J = 6.3), 3.82 (2H, t, CH_2, J = 6.3), 6.50-6.75 (3H, m, ArylH), 6.90-7.15 (5H, m, ArylH).

1.3. Procedure 3

The aromatic amine (0.5 g, 3.6 mmoles) was refluxed in acetone (30 mL) using molecular sieves in order to remove the water formed by azeotropic distillation. The reaction was carried out for 2.5 days. The solvent was removed under vacuum. The proton NMR showed that 60 % of the amine had reacted. Leaving the reaction for longer had no additional effect.

1.3. Procedure 4

A mixture of the aromatic amine (1.6 g, 12 mmoles) and acetone (1.04.g, 1.5 eq) was refluxed in toluene (30 mL) using a Dean-Stark apparatus in order to remove the water formed by azeotropic distillation. The reaction was carried out for 5 days in the presence of $ZnCl_2$. The solvent was removed under vacuum. The proton NMR showed the presence of the imine in the mixture. After distillation 0.5 g (23.5 %) of 2-(2-isopropylideneaminophenyl) ethanol was obtained but some amine was also present besides the adduct. ^{1}H NMR: δ_H 1.80 (3H, s, CH_3), 2.18 (3H, s, CH_3), 2.70

(2H, t, CH_2, J = 6.3), 3.77 (2H, t, CH_2, J = 6.3), 6.65-6.80 (2H, m, ArylH), 6.90-7.15 (2H, m, ArylH). 80 % of the ketimine was present in the solution mixture obtained.

2. Preparation of 2-[2-(benzylideneamino) phenyl] ethanol

An equimolar mixture of the primary amine (4 g, 29 mmoles) and benzaldehyde (3.08 g, 1 eq) was refluxed in toluene (50 mL) in a Dean-Stark apparatus in order to remove the water formed by azeotropic distillation. The reaction was carried out for 24 hours. The solvent was removed under vacuum. Distillation of the oil obtained was performed to give 2-[2-(benzylideneamino) phenyl] ethanol in 97 % yield. ^{1}H NMR : δ_H 2.4 (1H, s, OH), 3.10 (2H, t, CH_2, J = 7.1), 3.95 (2H, t, CH_2, J = 7.1), 7.00-7.30 (4H, m, ArylH), 7.40-7.60 (3H, m, ArylH), 7.80-8.00 (2H, m, ArylH), 8.4 (1H, s, CH). C-H-N microanalysis: found, C 79.86 %, H 6.82 %, N 6.16 %; $C_{15}H_{15}NO$ requires C 79.97 %, H 6.71 %, N 6.22 %.

The following reactions were performed using 2-[2-(benzylideneamino) phenyl] ethanol.

3. Bromination of the imine with PBr_3, in the presence of pyridine

A mixture of phosphorus tribromide (0.49 g, 0.0018 mol), distilled pyridine (0.11 g, 0.0013 mol) and 2-[2-(benzylideneamino) phenyl] ethanol (1 g, 0.0045 mol) in 10 mL of distilled benzene was stirred at 25 °C for 21h. The solution was diluted with water

and washed three times with EtOAc. The combined EtOAc layers were successively washed with saturated $NaHCO_3$ solution, H_2O, and brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum to afford the product. The crude bromide obtained was analysed by NMR spectroscopy. 2-[2-(Benzylideneamino) phenyl] ethanol and benzaldehyde were recovered after reaction.

4. Halogenation of the imine with LiBr/NaI

4.1. In THF

Methane sulfonyl chloride (0.3 g, 0.0024 mol) was added into a solution of 2-[2-(benzylideneamino) phenyl] ethanol (0.5 g, 0.002 mol), and triethylamine (0.3 g, 0.003 mol) in 10 mL of dry THF at 0 °C. After 1h, 0.52 g (0.006 mole) of lithium bromide dissolved in THF or 0.9 g (0.006 mole) of NaI (insoluble in THF) was added to the solution mixture. The stirring was discontinued after a further 16h. The solution was diluted with water (25 mL) and dichloromethane (25 mL) was then added. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product obtained was analysed by NMR spectroscopy. The product consisted of a complex mixture containing the benzaldehyde and the amine. 2-[2-(Benzylideneamino) phenyl] ethanol was presumably hydrolysed during the reaction. With LiBr: GC-MS: **Peak 100**, benzaldehyde, m/z(%) 106(100), 105(99), 77(85), 5(29); with NaI: GC-MS: **Peak 104**, benzaldehyde; **Peak 191**, 2,3-dihydro-1*H*-indole, m/z (%) 119(100), 91(26), 68(11), 63(13), 59(6), 51(7).

4.2. In acetone

Methane sulfonyl chloride (0.3 g, 0.0024 mol) was added to a solution of 2-[2-(benzylideneamino) phenyl] ethanol (0.5 g, 0.002 mole), and triethylamine (0.3 g, 0.003 mole) in 20 mL of dry acetone at 0 °C. After 1h, of lithium bromide (0.52 g, 0.006 mol) or NaI (0.9 g, 0.006 mol) dissolved in acetone was added to the solution mixture. The stirring was discontinued after a further 30 minutes. Water was then added and the solution was extracted with ether. The combined organic layers were washed with water, dried over magnesium sulfate and concentrated. The crude bromide obtained was analysed by NMR spectroscopy. ^{1}H NMR (product of bromination with LiBr): δ_H 3.13 (2H, t, CH_2, J = 8.6), 3.93 (2H, t, CH_2, J = 8.6), 7.00-7.25 (3H, m, ArylH), 7.35-7.60 (6H, m, ArylH), 7.75 (1H, s, CH). However small amount of the amine and benzaldedehyde were also detected on the NMR spectrum.

5. Bromination of the imine with CBr_4

5.1. In the presence of PPh_3

Triphenylphosphine (1.2 g, 4.5 mmoles) was added slowly into 2-[2-(benzylideneamino) phenyl] ethanol (1 g, 0.0045 mol) and carbon tetrabromide (2.24 g, 6.7 mmoles) in dry DCM. The solution was cooled with an ice-salt bath during the addition. The reaction was carried out under nitrogen. The reaction was stirred for further 15min. A white precipitate of phosphine oxide was formed during the reaction. Pentane was added and the mixture was filtered and the filter cake washed with pentane. The combined filtrate and washings were concentrated in vacuo and an extract of the residue was examined by GC-MS: **Peak 69**, tribromomethane, m/z(%) 256(6), 252/254(18), 250(6), 175(50), 173(100), 171(50), 91/93(22), 79/81(26); **Peak**

126, (2,2-dibromovinyl)benzene, m/z (%) 264(14), 262(28), 260(14), 181/183(12), 102(100), 79/81(5), 74(28), 63(18), 50(37); **Peak 127**, benzaldehyde.

5.2. In the presence of tri-n-octylphosphine

Tri-*n*-octylphosphine (2.5 g, 0.0067 mol) was added to a magnetically-stirred solution of the alcohol (1 g, 0.0045 mol) and carbon tetrabromide (2.24 g, 0.0067 mol) in 20 mL anhydrous ether. An immediate exothermic reaction took place. The mixture was cooled in an ice-salt bath. After complete addition of the phosphine, the solution was stirred for a further 1h. A white precipitate of phosphine oxide appeared in the solution during the stirring. The solution was filtered. The solid was washed with diethyl ether ether. The solvent was removed under reduce pressure. The residue was chromatographed on silica gel (hexane:ether, 1:1) and distilled via Kugelrohr. A sample of the distillate was submitted for analysis by GC-MS. GC-MS: **Peak 89**, benzaldehyde; **Peak 183**, 2,3-dihydro-1*H*-indole.

6. Preparation of imidazole-1-carbothioic acid *O*-{2-[2-(benzylideneamino) phenyl] ethyl} ester

6.1. Synthesis of the imidazolide in THF

2-[2-(Benzylideneamino) phenyl] ethanol (0.5 g, 0.0022 mol) was dissolved in dry tetrahydrofuran (10 mL) containing *N,N'*-thiocarbonyldiimidazole (0.86 g, 1.2 eq) and the mixture was heated under reflux for 2h under nitrogen atmosphere. The reaction mixture was evaporated to dryness. The NMR showed that 2-[2-(benzylideneamino) phenyl] ethanol was hydrolysed during the reaction and that benzaldehyde and the amine remained.

6.2. Synthesis of the imidazolide in DCM

6.2.1. Method 1

2-[2-(Benzylideneamino) phenyl] ethanol (0.5 g, 0.002 mol) and *N,N'*-thiocarbonyldiimidazole (0.86 g, 2.4 eq) were heated under reflux in dry dichloromethane (30 mL) for 1 hour. The reaction was carried out under nitrogen. After cooling, the reaction mixture was evaporated to dryness to afford a viscous orange oil. A sample of this oil was analysed by GC-MS. GC-MS: **Peak 86**, benzaldehyde; **Peak 182**, 2,3-dihydro-1*H*-indole; **Peak 665**, imidazole-1-carbothioic acid *O*-{2-[2-(benzylideneamino) phenyl] ethyl} ester, m/z(%) 335(13), 294(11), 207(11), 162(8), 117(13), 91(100), 65(12). The expected thiocarbonylimidazolide was present in the solution mixture with benzaldehyde and 2,3-dihydro-1*H*-indole after reaction.

6.2.2. Method 2

The alcohol (1 g, 0.004 mol) and *N,N'*-thiocarbonyldiimidazole (0.85 g, 1.2 eq) were stirred at room temperature overnight in dry dichloromethane (30 mL). The reaction was carried out under nitrogen. The solvent was evaporated under reduced pressure. 0.51 g (38 %) of the expected imidazolide was obtained after column chromatography (EtOAc). ^{1}H NMR, δ_H 3.00 (2H, t, J = 8.7), 3.35 (2H, t, J = 8.7), 6.65-6.75 (7H, m, ArH), 6.95-7.15 (5H, m, ArH), 7.25 (1H, s). Mass spectrum, m/z(%) M^+ 335(13), 294(11), 207(11), 162(8), 117(13), 91(100), 65(12).

7. Radical cyclisation of the imine

7.1. Procedure 1

The imidazolide (0.21 g, 0.62 mmol) was refluxed at 65 °C in dry THF in presence of tri-*n*-butyltin hydride (0.2 g, 1.2 eq) and AIBN (0.042 mmol) under a nitrogen atmosphere for 4h. The solvent was evaporated and the crude product was analysed by proton NMR. ^{1}H NMR, δ_H 0.9-1.0 (m), 1.1-1.4 (m), 1.4-1.7 (m), 2.9-3.1 (m), 3.25 (t, J = 8.6), 3.6 (t, J = 8.6), 3.7-3.8 (m), 3.93 (t, J = 8.6), 4.7(s), 5.8(s), 6.35 (t, J = 8.6), 6.6-6.8(m), 6.9-7.1 (m, ArH), 7.2-7.6 (m, ArH), 7.7 (s), 7.85 (d, J = 8.6), 8.0 (d, J = 8.6), 8.4 (s), 10.0 (s). Except the tin compounds present in majority, several others peaks were observed on the NMR spectrum, showing that there were different components present in the mixture. It was difficult to assign the different peaks observed.

7.2. Procedure 2

AIBN (0.008 g) dissolved in dry THF (2 mL) was added slowly for 1h into a solution of the imidazolide (0.51 g, 1.5 mmoles), and tri-*n*-butyltin hydride (1.63 g, 5.6 mmoles) in dry THF. The solution was refluxed at 65 °C under a nitrogen atmosphere for 5h. The solvent was removed under reduced pressure and a GC-MS analysis of the mixture was performed. GC-MS: **Peak 171**, benzyl alcohol, m/z(%) M^+ 108(94), 91 (15), 79(100), 77(58), 65(8), 51(28); **Peak 262**, 2,3-dihydro-1*H*-indole; **Peak 479**, 1-benzyl-2,3-dihydro-1*H*-indole, m/z(%) M^+ 209(100), 132(36), 91(74), 77(6), 65(18), 51(6). This mass spectrum was essentially consistent with that reported in the literature.[63] Column chromatography of the mixture was carried out (hexane/EtOAc, 1:3). Both fractions obtained were contaminated with tin residues. ^{1}H NMR, (fraction 1), δ_H 0.90-1.00 (m), 1.20-1.40 (m), 1.40-1.60 (m), 1.60-1.70 (m), 1.80 (s), 2.00 (s),

2.90-3.10 (14H, m), 3.33 (4H, t, J = 8.6), 3.55 (4H, t, J = 8.6), 3.93 (2H, t, J = 7.7), 4.70 (1H, s), 5.80 (1H, s), 6.35 (1H, d, J = 9.4), 6.60-6.80 (7H, m), 6.90-7.20 (13H, m), 7.20-7.40 (14H, m), 7.40-7.70 (4H, m), 7.85 (3H, d, J = 9.4), 8.40 (1H, s), 10.00 (1H, s).

^{1}H NMR, (fraction 2), δ_H 0.9-1.0 (m), 1.1-1.4 (m), 1.5-1.7 (m), 2 (s), 2.8 (t, J = 7.8), 3.0-3.2 (m), 3.9 (t, J = 7.8), 4.0-4.2 (m), 4.3-4.5 (m), 6.6-6.8 (m), 6.9-7.3 (m, ArH), 7.3-7.6 (m, ArH), 7.7 (d, J = 8.6), 7.9 (s), 8.1 (d, J = 8.6), 8.6 (s). As mentioned above, each fraction was contaminated with tin residues. The different components were not separated by column chromatography. Each fraction corresponded at a mixture of different unidentified components.

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Chapter 6

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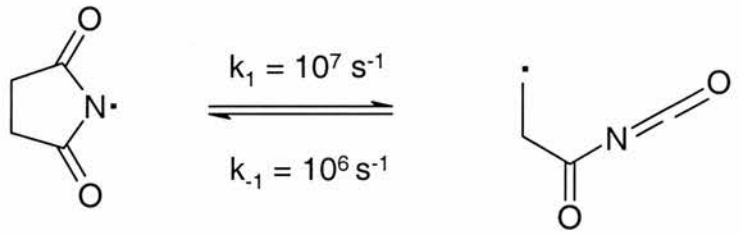
SUMMARY & CONCLUSIONS

Several reviews highlighting the importance of radical reactions in total syntheses have appeared and demonstrate their synthetic potential in term of predictability, generality and variability.

Merenyi has demonstrated that the succinimidyl radical, **1,** exists in rapid equilibrium with its ring-opened derivative the β-(isocyanatocarbonyl) ethyl radical, **2.**



1 **2**

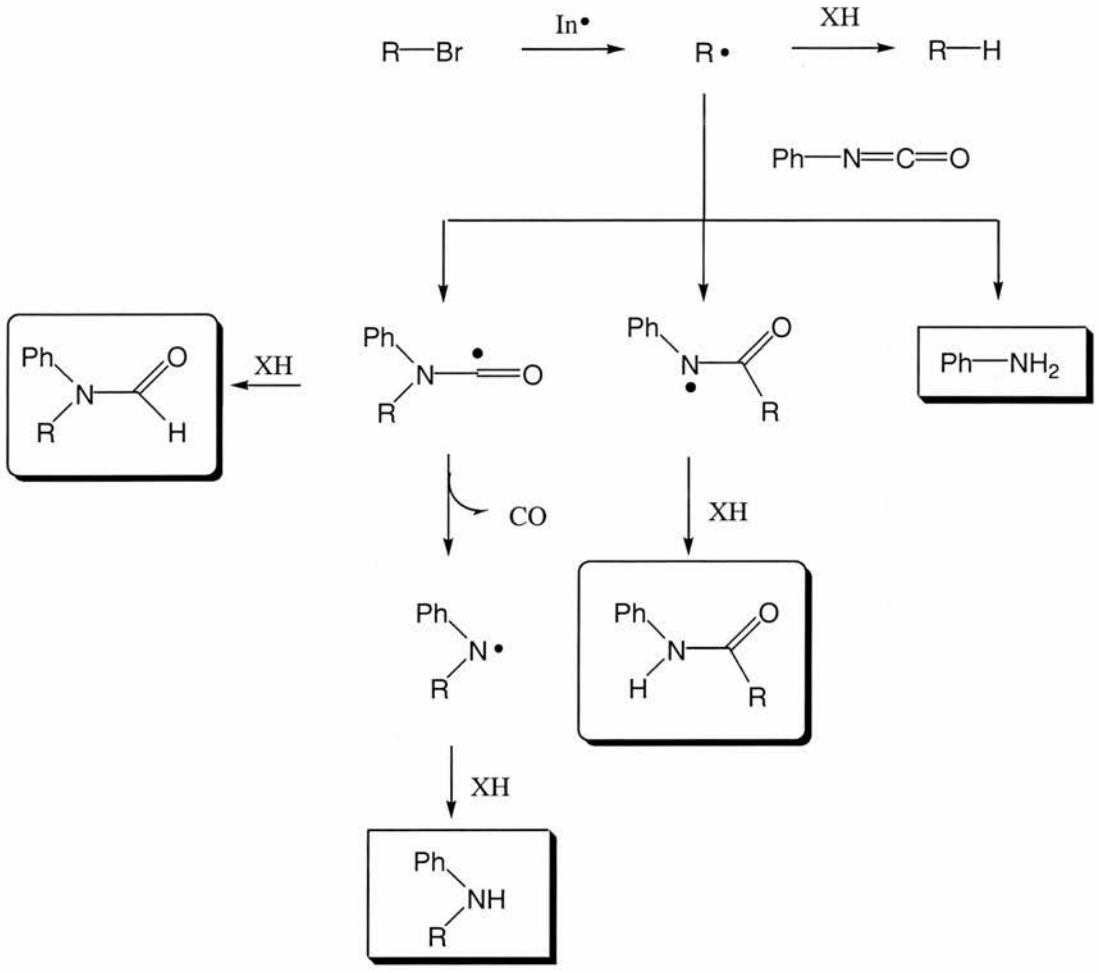
Thus, if the ring-closed radical **1** could be stabilised, a new way for the construction of N-heterocycles, including dihydroquinolones, could be possible, by cyclisation of organic isocyanates. The cyclisation should occur by intramolecular radical addition to the carbon-oxygen double bond of the isocyanate group. To test if this reaction could be a viable process, the ring closures of several types of organic isocyanates have been investigated during the course of this project.

1. Intermolecular addition to aromatic isocyanates

The first study carried out was concerned with intermolecular addition of C-centred radicals to isocyanates. The reaction between phenyl isocyanate and several alkyl bromides, both commercially available, was carried out in the presence either tri-*n*-butyltin hydride or EPHP in different solvents. The main products obtained are summarised in the following table.

Alkyl radical addition to phenyl isocyanate		
Isocyanate	**Bromide**	**Major product of the overall experiments**
Phenyl isocyanate	1-Bromohexane	• Hexyl phenyl amine (major) • *N*-phenyl-*N*-hexyl-formamide
	1-Bromopropane	• Aniline
	1-Bromoethane	• Ethyl phenyl amine • Aniline (major)

From these examples of intermolecular addition, alkyl radical addition onto the isocyanate moiety was found to occur mainly on the N-atom of the isocyanate group, with subsequent loss of the CO group. Phenyl alkyl amines and aniline were the main products observed on the GC-MS spectra. However, the adduct was detected after the photolysis of phenyl isocyanate with 1-bromohexane in presence of AIBN and tributyltin hydride in toluene. This compound is the product of the addition of the alkyl radical onto the N-atom of the isocyanate group. Nevertheless, ethyl phenyl amine was the main product of the radical reaction between phenyl isocyanate and an alkyl bromide.

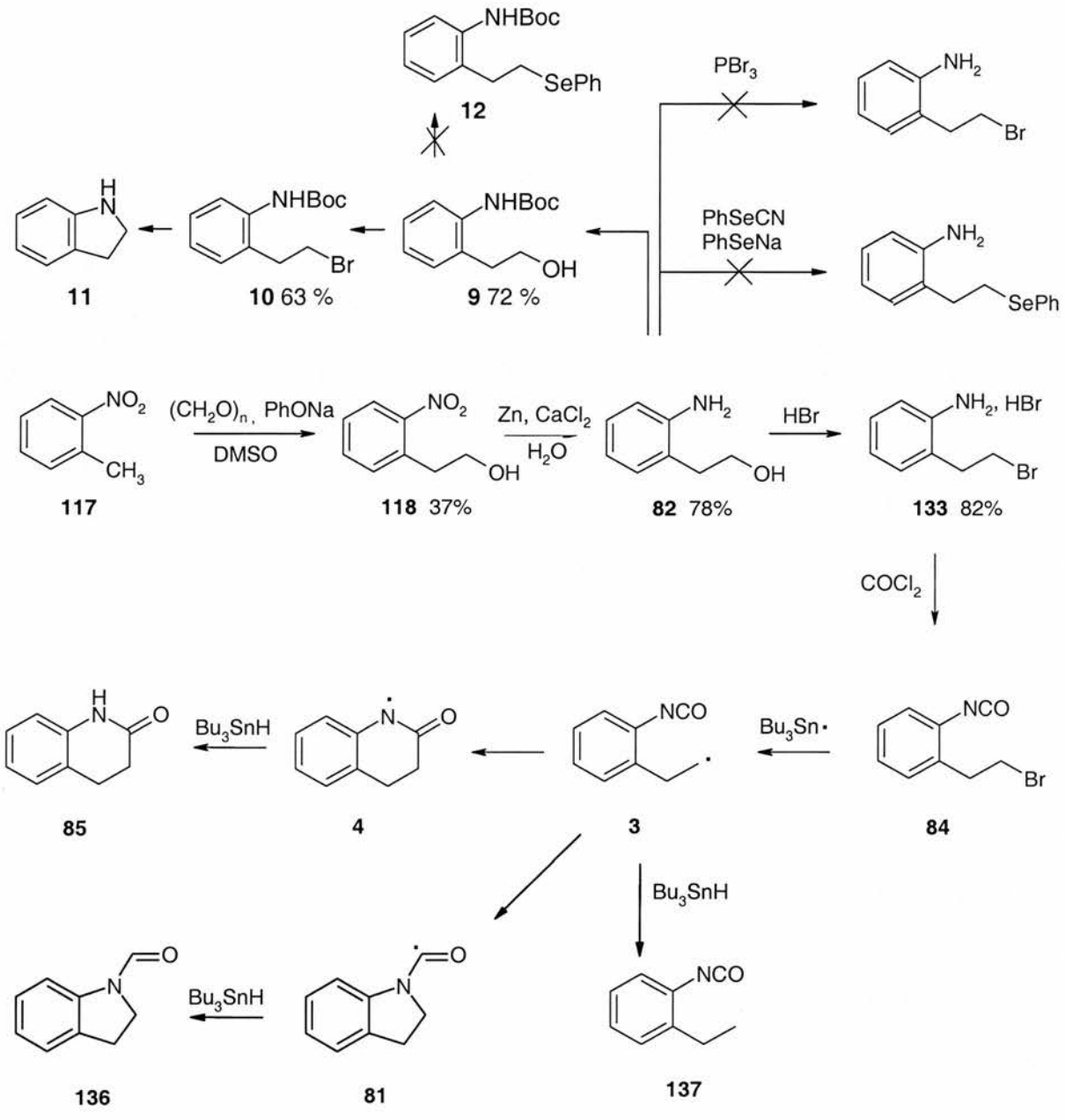


scheme 113

The above scheme summarises the different processes that probably occurred during the radical reaction.

2. Intramolecular addition to aromatic isocyanates

For study of intramolecular addition to an aromatic isocyanate, radical precursors were synthesised following the pathways outlined below.

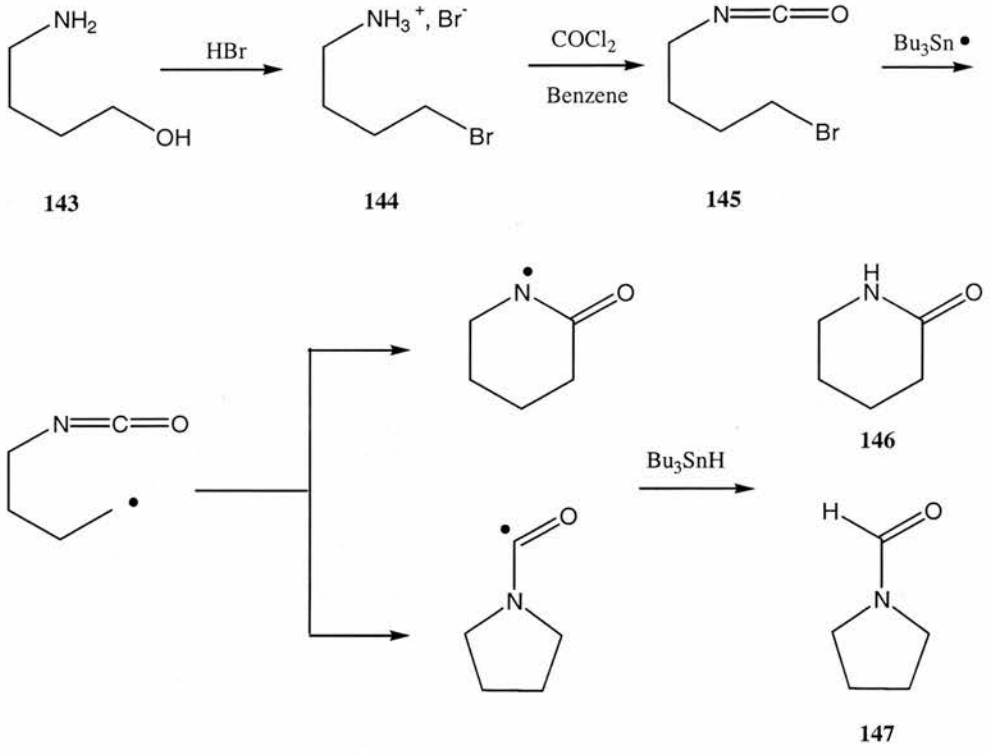


scheme 114

2-Aryl isocyanates were obtained from the key nitro-intermediate **118.** By means of mild reduction, compound **118** was converted to alcohol **82.** Various attempts to make the corresponding bromo-amine or phenyl selenide as radical precursors were unsuccessful. Furthermore, the isolation of dihydroindole from several of these

reactions indicated that the bromo-amine underwent cyclisation by an intramolecular nucleophilic substitution and hence would not be suitable as an isocyanate precursor. The crucial breakthrough was the discovery that the hydrobromide salt **133** could be made in good yield by treating **82** with aq HBr. The resulting salt was protected from intramolecular nucleophilic ring closure and was directly converted to the isocyanate by treatment with phosgene.

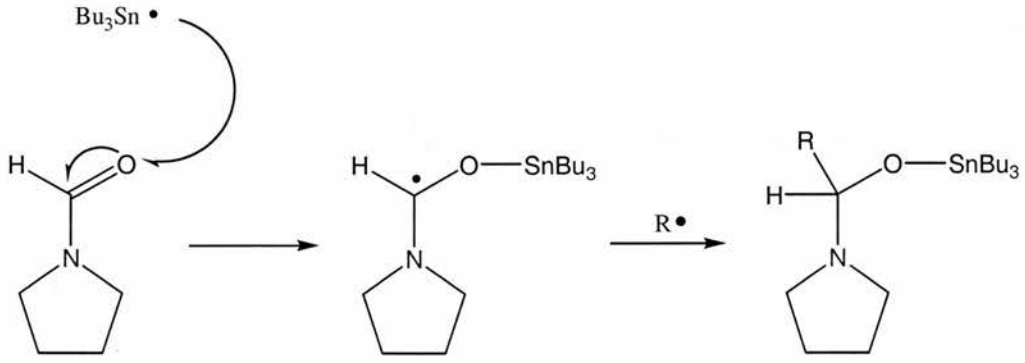
Radicals were generated from the bromo-isocyanate **84** using radical chain methodology with either tributyltin hydride, EPHP or TTMSS both in the presence or absence of thermal initiators such as AIBN or 1,1'-azo-di-cyclohexanecarbonitrile. The carbon-centred radical **3** was generated from the organic substrate **84** by atom or group abstraction of Br, by action of the Bu_3Sn radical. Addition to the C=O double bond of the isocyanate moiety afforded the new radical **4**. The cyclised imidyl radical **4** was trapped by rapid hydrogen transfer with the hydride to yield dihydroquinolin-2-one **85**. The results of these analyses showed that the major product formed was 3,4-dihydro-1*H*-quinolin-2-one **85** in 44.1 % yield. 2,3-Dihydroindole-1-carbaldehyde **136** and 1-ethyl-2-isocyanato-benzene **137** were also present in 15.7 % and 3.1 % yield respectively. In this example the ring closure occurred mainly on the C-atom of the isocyanate moiety. This could be rationalised by the fact that the N-centred radical obtained on 6-*endo*-cyclisation, was stabilised by delocalisation of the unpaired electron into the aromatic ring. Thus, the lactam ring remained intact and led to 3,4-dihydro-1*H*-quinolin-2-one **85** formation, after hydrogen abstraction**.** We wanted to examine the regioselectivity of ring closure in the absence of the aromatic system, therefore, we studied the radical cyclisation of 1-bromo-4-isocyanato-butane.



scheme 115

1-Bromo-4-isocyanato-butane was made according to the above scheme from the commercially available 4-aminobutan-1-ol **143**. After making the salt by reaction with aqueous HBr, the isocyanate was prepared by action with phosgene on the hydrobromide salt. The ring closure onto the isocyanate was attempted by photolysing the compound **145** in presence of tri-*n*-butyltin hydride in benzene or by heating in presence of TTMSS and 1,1'-azo-di-cyclohexanecarbonitrile. The GC-MS analysis of the product mixtures showed that the both modes of cyclisation occurred. There were two broad peaks present on the GC-MS chromatogram, which could be attributed to piperidin-2-one **146** and pyrrolidine-1-carbaldehyde **147.** However, the NMR spectrum as well as the GC-MS data suggested the product of 6-*endo* cyclisation **146** was the main product. The disappearance of pyrrolidine-1-

carbaldehyde **147** from the system might be explained by a secondary reaction, which could occur between the compound **147** and tin radical present in solution as shown in the scheme below.



R = H or any radical present in solution

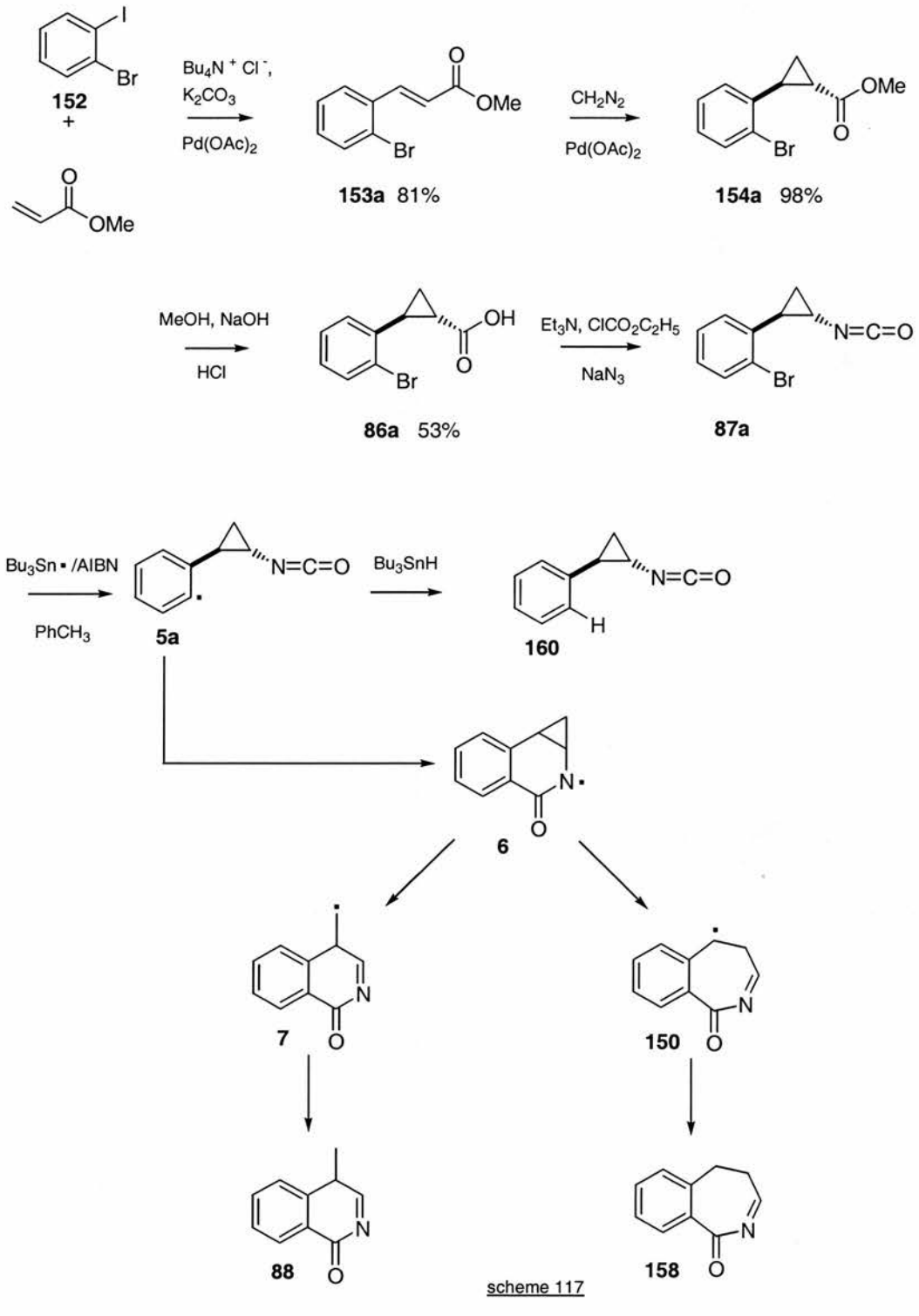
Scheme 116

Consequently, the new product formed would be hidden as a tin-residue and impossible to detect either on the NMR or on the GC-MS spectra.

Both cyclisation modes were evidently operative in the ring-closure reaction of 1-bromo-4-isocyanato-butane, but in view of the incomplete and defective character of the reactions, conclusions about the regioselectivity would be unsafe.

3. Intramolecular addition to cyclopropyl isocyanates

With regard to the cyclopropyl isocyanates, we successfully prepared the carboxylic acid **3** and then the corresponding isocyanate **4** to examine the radical cyclisation. The preparation of *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene was performed following a pathway described by Vallgarda for the corresponding cyclopropyl amine.

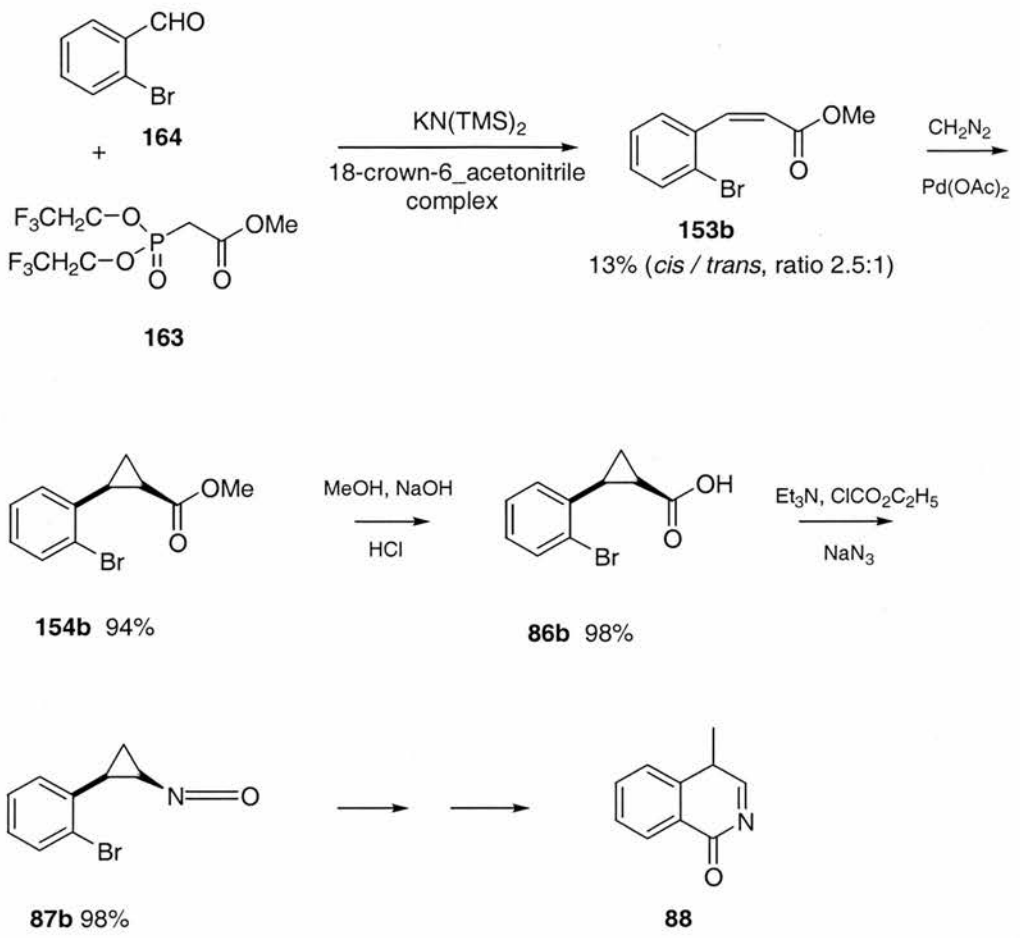


scheme 117

The *trans*-ester, prepared from 1-iodo-2-bromobenzene and methyl acrylate, was cyclopropanated with diazomethane. After hydrolysis to the corresponding acid, the

isocyanate was made by action of sodium azide and ethyl chloroformate on the acid. We encountered some difficulties in keeping this compound for several days. After 2 weeks we noticed extensive decomposition of the isocyanate.

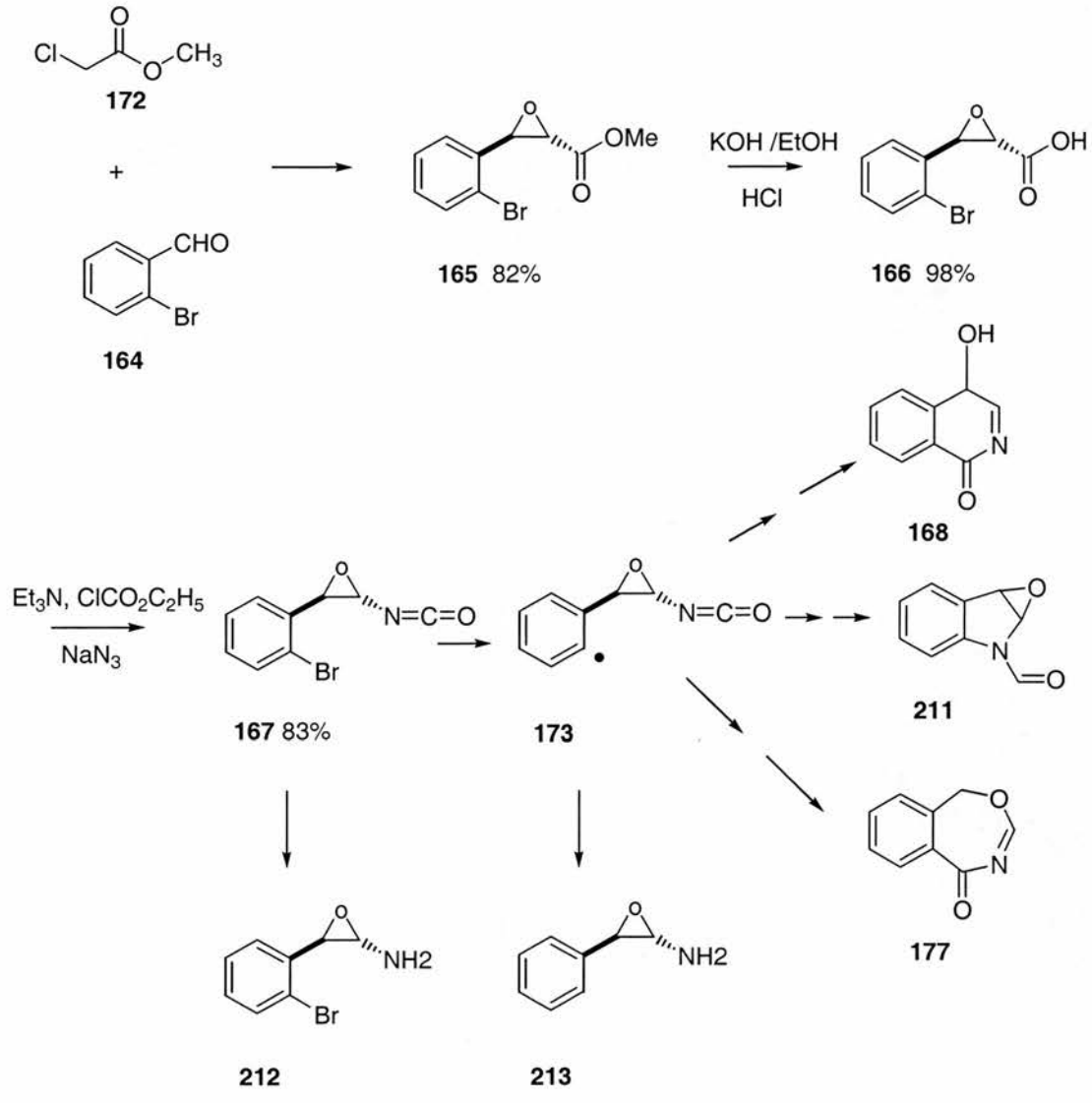
In the same way, the action of tributyltin hydride with *trans*-1-bromo-(2-isocyanatocyclopropyl) benzene **4** afforded the radical **13**, which either cyclized by addition to the C-atom or to the N-atom of the isocyanate moiety, or abstracted an hydrogen atom from the tin hydride. The cyclized radicals were expected to undergo rapid ring fission in one or other mode and then be trapped by rapid hydrogen abstraction from organotin hydride to yield 4-methyl-4*H*-isoquinolin-1-one or an isomer. The radical reaction was attempted using tri-n-butyltin hydride, EPHP and TTMSS. According to the mass spectrum the seven-membered ring **158** seemed to be the isomer obtained. However, the results showed that t*rans*-(2-isocyanatocyclopropyl) benzene was the main product obtained. The problem seemed to be the *trans*-stereochemistry of the isocyanate. Consequently, the synthesis of *cis*-1-bromo-(2-isocyanatocyclopropyl) benzene was carried out.



scheme 118

Except for the synthesis of the *cis*-3-(2-bromophenyl) propanoate, which was made by reaction of 1-bromobenzaldehyde with trifluoroethylphosphonoacetate, the synthesis of the *cis*-1-bromo-(2-isocyanatocyclopropyl) benzene followed the same route as that for the *trans*-isomer. The radical reaction was attempted using the tin hydride method and TTMSS, but the GC-MS analysis didn't show the expected adduct. The main product observed was t*rans*-(2-isocyanatocyclopropyl) benzene. This result could be explained by the fact that a *cis* to *trans*-isomerisation occurred during the radical process. The isomerisation was initiated either thermally or photochemically to give the more stable *trans*-isomer.

The radical cyclisation was also attempted with (2-bromophenyl)-3-isocyanato-oxirane **167**. The synthetic pathway followed is outlined below.



scheme 119

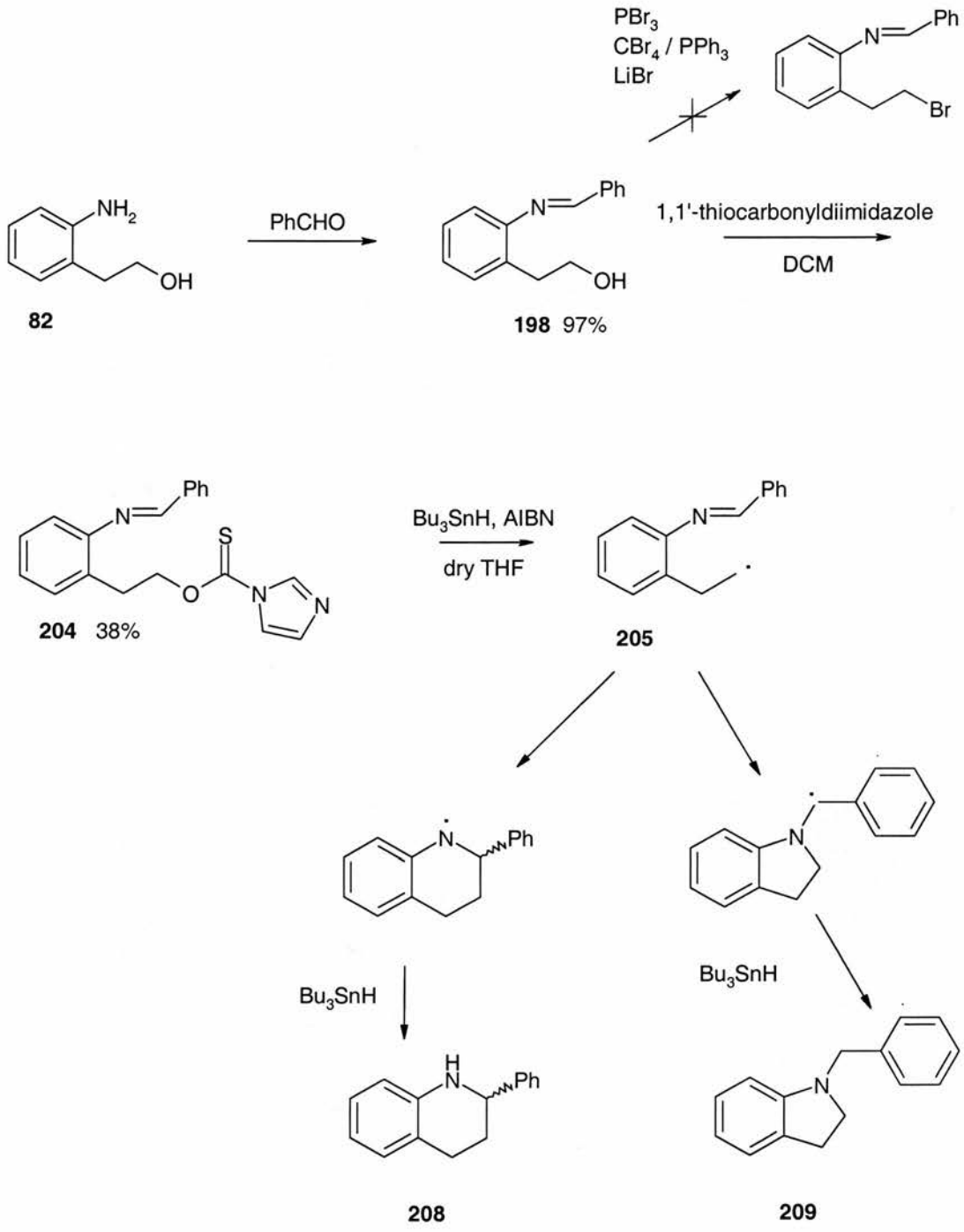
Methyl-3-(2-bromophenyl)-2-oxirancarboxylate **165** was made according to Wunsch's procedure, by the reaction of 2-bromobenzaldehyde **164** and methyl chloroacetate **172** in the presence of NaOMe. Once the ester had been made, the isocyanate was reached by following Vallarga's procedure.

A potential problem was preferential reaction of the organotin hydride with the isocyanate moiety. This evidently was not serious with the 2-(2-bromoethyl) phenyl isocyanate **84**, but could have been a problem with the bromo-arylcyclopropyl- and epoxy-isocyanates. As previously, the ring closure reaction was attempted using the tin hydride and TTMSS methods. The GC-MS showed that mainly the corresponding amines 3-(2-bromo-phenyl)-oxiranylamine **212** and 3-phenyloxiranylamine **213** were obtained. Nevertheless 4-hydroxy-4*H*-isoquinolin-1-one was noticed, but it was in small quantity.

We believed that the cyclopropyl precursor would offer the cyclised radical an alternative, more rapid, β-scission which would leave the lactam ring intact. However, the results obtained did not enable us to reach a clear conclusion, except that H-donation to the aromatic radical was rapid and cyclisation was not able to compete effectively. Investigation of the epoxy-compounds was started at the end of research project. Time to examine all the different conditions was not available and a lot of work remains to be done.

4. Intramolecular addition to imines

A new synthetic route in which imines were precursors of ring closure processes instead of isocyanates was also investigated during this study.

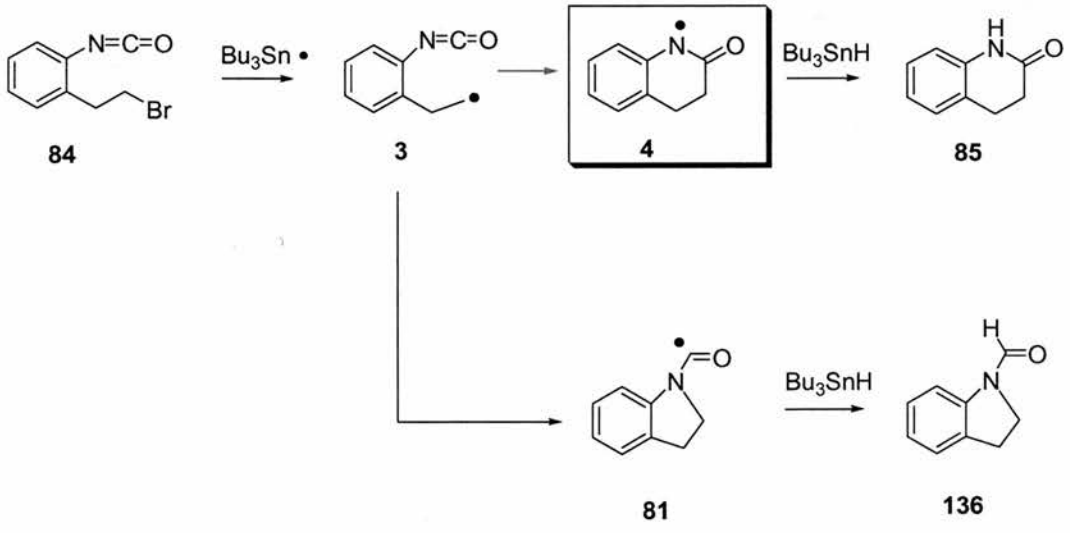


scheme 120

The imine was synthesised by condensation of the amine **82** with benzaldehyde in a Dean-Stark apparatus. None of the bromination methods were successful because of hydrolysis of the imine moiety. The thiocarbonylimidazolide **204** was therefore made

by stirring the imine with 1,1'-thiocarbonyldiimidazole in DCM at room temperature. The ring closure of the imidazolide was then attempted using the tin hydride method in THF. The product **209** of the cyclisation onto the N-atom of the imine moiety was the only one observed on the GC-MS spectra. 5-*Exo*-cyclisation appeared to be the predominant mode of cyclisation for this system.

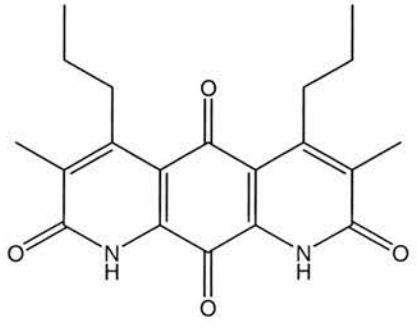
In the overall project, the best results were obtained with 2-(2-bromoethyl) phenyl isocyanate **84**. Cyclisation of the 2-(2-isocyanatophenyl) ethyl radical **3** took place in both *6-endo-* and *5-exo*-modes at rates that were comparable to that for the hex-5-enyl radical. The thermodynamically more stable 3,4-dihydro-2-oxo-1*H*-quinolinyl radical was the major product. These results could be explained by the fact that once the radical **4** was formed, it had a better radical stabilisation due to resonance. Consequently, its formation was favoured in comparison to radical **81**.



scheme 74

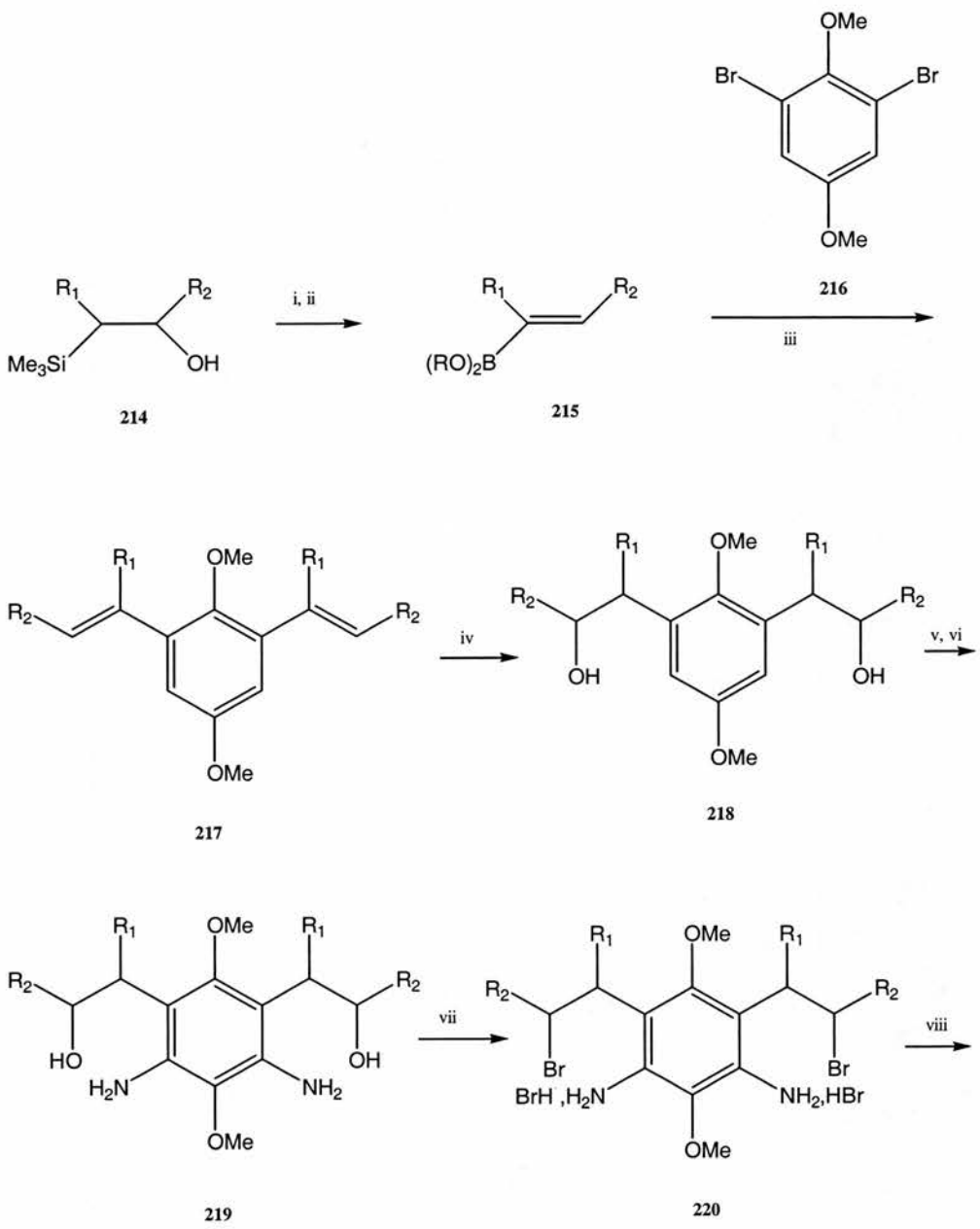
The selectivity of ring closure was moderate when Bu_3SnH was used to mediate the reactions but improved considerably with TTMSS.

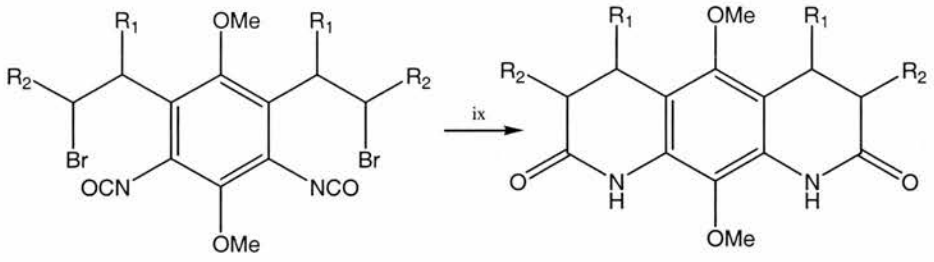
This homolytic process could provide new routes for the construction of a range of nitrogen-containing heterocycles. Many derivatives of quinoline, isoquinoline and of quinolinones are physiologically active and this proposed methodology could be a new approach for their synthesis. An extensive range of biological and medicinal roles has been reported for members of each heterocyclic class, for example, quinolinones have antibacterial activity, quinoline and isoquinoline derivatives have been used as leucotriene receptors and DNA gyrase inhibitors. From this project could emerge a new synthetic route to diazaquinomycin A, in which the key step could be a double homolytic cyclisation of a bis-isocyanate.



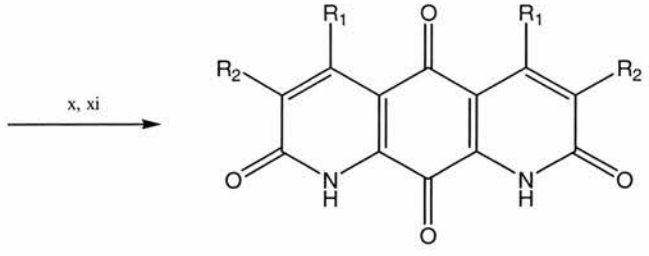
Diazoquinomycin A

Because of the better regioselectivity, TTMSS could be the radical reagent of choice rather than the tin hydride, if suitable conditions are found to lead this reaction to completion. The reaction scheme could be as follows.


OMe
Br
Br
OMe
216
R1
R2
Me3Si
OH
i, ii
214
R1
R2
(RO)2B
215
iii
R1
OMe
R1
R2
R2
OMe
217
iv
R1
OMe
R1
R2
R2
OH
OH
OMe
218
v, vi
R1
OMe
R1
R2
R2
HO
OH
H2N
NH2
OMe
219
vii
R1
OMe
R1
R2
R2
Br
Br
BrH ,H2N
NH2,HBr
OMe
220
viii



221 222



223

i) H^+ ; ii) BBr_3-DCM-catechol ; iii) $Pd(pph_3)_4$; iv) BH_3,THF/H_2O_2, NaOH ;

v) aq HNO_3 ; vi) Zn/$CaCl_2$, H_2O ; vii) aq HBr viii) $COCl_2$;

ix) TTMSS-AIBN-PhH ; x) KOBu-t (or Pd) ; xi) BBr_3-DCM, then Fremy's salt-HSO_4NBu_4

Several routes to the leading intermediate **217** are possible. However, the one selected from trimethylvinylsilane via **214** and Suzuki coupling of boronic ester **215** with aromatic dibromide **216** may be chosen to facilitate introduction of a good range of functinal groups R^1 and R^2, for the synthesis of diazaquinomycin derivatives. Hydroboration of **217** will afford bis-alcohol **218**, which may be converted to the corresponding aromatic amine **219** by aromatic nitration with aqueous nitric acid followed by reduction of the nitro group with zinc and calcium chloride in aqueous conditions. Compound **219** contains four electron-releasing substituents and hence dinitration should take place under mild conditions. Subsequent bromination with aq HBr (48 %) will afford the hydromide salt **220**, which will be converted to bis-

isocyanate **221** with phosgene. Treatment of **221** with TTMSS will lead to a double cyclisation and production of diazaanthracene derivative **222**. The latter can be aromatised either by reaction with base, or by treatment with Pd metal. The final oxidation to introduce the quinone structure can be accomplished with Fremy's salt or with ceric ammonium nitrate.

Control of stereochemistry in the first steps is not important because of radical production in the last but one step and the final aromatisation. Bis-phenylselenide **219** may be chosen instead of the bromide for introduction of the nitro and amine groups. Obviously, if this is unsuccesful, other protection of the hydroxyl groups of compound **218** will be arranged. This route should enable a wide range of tetrahydrodiazaanthraquinones **223** to be made such as diazaquinomycin A (for R_1 = Pr and R_2 = Me). By choosing different aromatics in place of **216**, further structural analogues are within reach.