OXIDATION, CYCLISATION AND REARRANGEMENTS OF HYDRAZONE DERIVATIVES OF β-KETOESTERS

by

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A Thesis presented to Dublin City University
for the degree of Doctor of Philosophy.

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February 1997

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of Ph.D is entirely my own work and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my own work.

Signed Pat O'Malley Date February 1997

Patrick O' Malley.

To my Parents

Fay and Kathleen

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CHAPTER THREE

ABSTRACT

The oxidation of the *para*-nitrophenylhydrazones, derived from the β-ketoester ethyl acetoacetate and its derivatives, using lead tetraacetate (LTA) and mercuric acetate (MA) were studied.

The oxidation products isolated were the azoacetate and, in some cases, the azoalkene. The product formed was found to depend, to a large extent, on the choice of solvent. Oxidation of the hydrazone in acidic medium resulted in azoacetate formation while azoalkene was formed in neutral medium. Azoacetate formation could be ensured, irrespective of solvent used, by replacing the labile hydrogens on the carbon *alpha* to the ester group, with methyl groups. Initial studies involving replacement of the hazardous metallic oxidising agents by iodobenzene diacetate (IBA) have proved successful. We report the first use of IBA as a route to obtaining azoacetates.

A number of azoacetates isolated were further reacted with base in alcoholic medium, in the presence of a catalyst. Among the products isolated was a tertiary amide which was conclusively identified using X-ray crystallography. The mechanism by which this tertiary amide was arrived at was studied in some detail. The possibility of an intermediate azocarbinol was addressed and results indicate this may not be the case. Further studies involving addition reactions and cross-over experiments indicate a concerted one step carbon to nitrogen acetyl migration followed by rearrangement. This novel rearrangement was extended to a number of azoacetate derivatives, and NMR temperature dependent studies were carried out on the resulting rearranged species which exhibited characteristic resonances for amides and nitrogen inversion.

A selection of these tertiary amides were considered as possible aza-β-lactam precursors. While there is a proliferation of literature on β-lactams these cyclic dinitrogen analogues have received little attention. In a number of cases, the tertiary amides isolated, were successfully cyclised to novel aza-β-lactams, which may prove to be active antibacterical agents.
The work has been reported as a preliminary communication (see appendix).

Acknowledgements

I wish to express my sincere gratitude to Dr. Paraic James for his encouragement and guidance during my postgraduate study. Thanks to Dr. Conor Long for assistance with the X-ray data analysis. Also to the technical staff for their help.

Thanks to the staff at Athlone R.T.C for providing me with a lecture timetable to accommodate my postgraduate pursuits. Thanks to Ann, Martina and Trish for well-earned refreshments in Sean's bar!

I would like to acknowledge all postgraduates, past and present, for making my stay at D.C.U so enjoyable (and difficult to end!). A special mention for the P. James research group, Carol, Joe, Declan, James, Ciaran, Donal and the *inmates* of AG07 and AG12. To the Thursday night *socalites* including Cormac, Peter (Classen), Teresa, Fiona, Rachel and Paddy invariably ending up at the *Turks head* (*Turks not dead*!).

A special thanks to Maria for her patience and affection for my computer, and me!! Thanks to Joe and Orla, Don and Mairead, John (Fogo) and Tony for providing welcome distractions!

Finally a sincere thanks to my Parents and Gerry, Grace, Ann and Christine for their endless support and encouragement.

CHAPTER ONE

Chapter 1

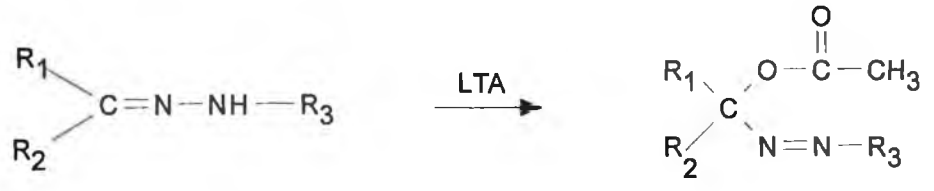
1.1 INTRODUCTION

1.1.1 Lead tetraacetate

Lead tetraacetate (LTA ; $Pb(OAc)_4$) has been used as an oxidant in organic chemistry for almost fifty years. It is a very versatile reagent with comprehensive reviews on its reactions with 1,2-glycols, sugars, sterols and hydrazones as well as some general reviews[1].

The LTA oxidation of hydrazones gives a variety of products, depending on the nature of the substrate and reaction conditions. The reaction of LTA with ketohydrazones (1) was found to form an azo compound with the acetoxyl group on the same carbon. These compounds are called azoacetates[2] (2).

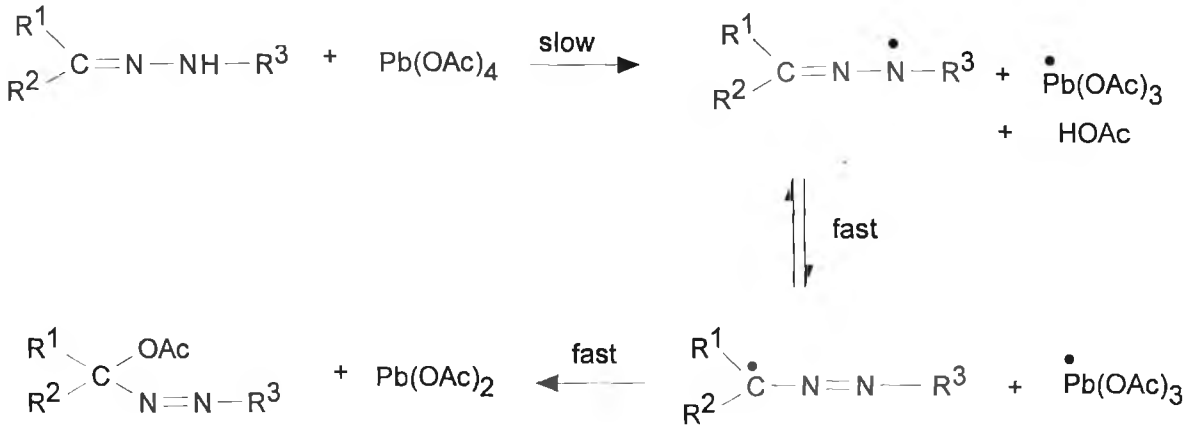
Scheme 1.1



(1) (2)

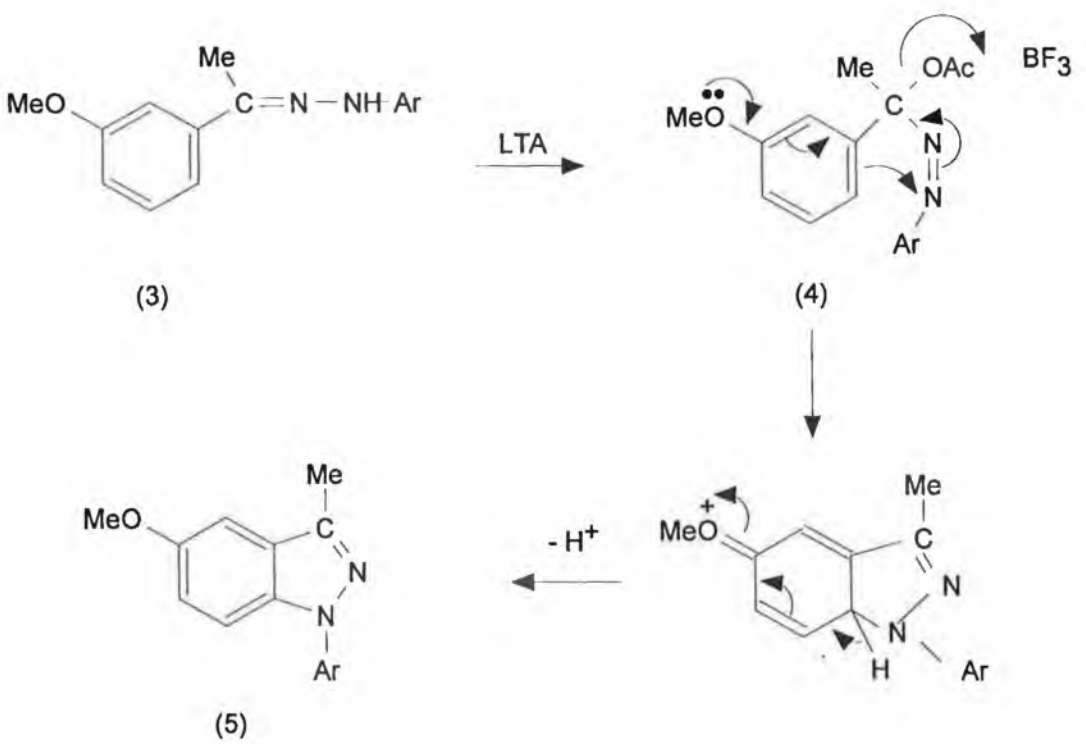
The reaction is usually carried out in dichloromethane at 0-10°C, owing to its ability to dissolve the reactants and easy removal once the reaction is complete. Cavill *et al.*[3] studied the oxidation of phenol and its derivatives. The acetoxycyclohexadienone products isolated were explained via a free radical mechanism. This proposal for azoacetate formation of ketone hydrazones is generalised as follows[2,3,4] (Scheme 1.2).

Scheme 1.2



When arylhydrazones of aromatic ketones are used, the resulting azoacetates lend themselves to possible cyclisation with a Lewis acid forming indazoles[5]. The yield of indazole varies widely depending on the structure of the azoacetate, the nature of the Lewis acid, and the reaction temperature[6]. For example, the arylhydrazone (3) is first treated with LTA in CH_2Cl_2 to give the azoacetate (4) and cyclisation to 5-methoxyindazole (5) is then induced as follows[5] (Scheme 1.3).

Scheme 1.3

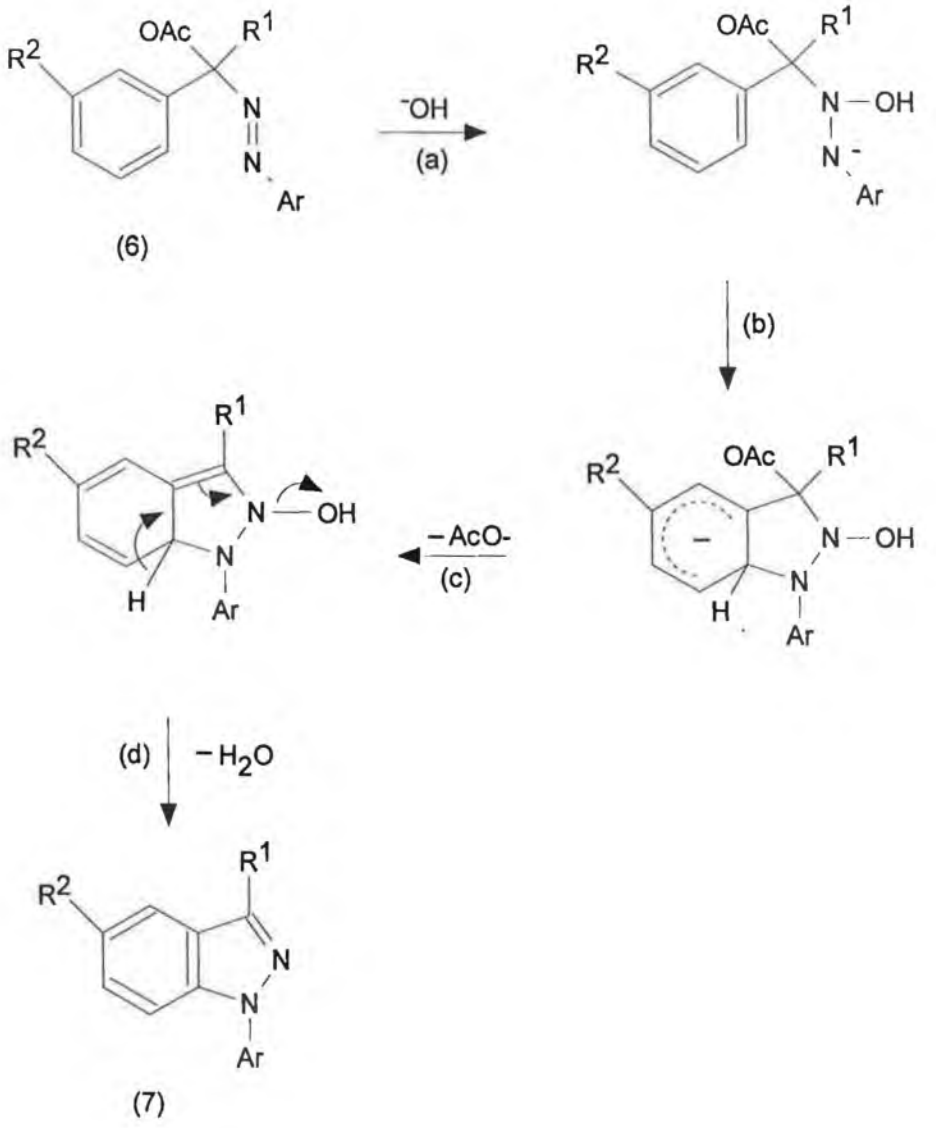


The Lewis acids used are boron trifluoride ether complex or aluminium trichloride. The yield of indazole varies from 50% to 90% depending on the type of substituted azoacetate[1,6,7].

A similar cyclisation product is formed under base catalysed conditions[8]. However this reaction is more restricted occurring only for compounds with a *p*-nitro group on the aryl moiety. For example the azoacetate of benzophenone *p*-nitrophenylhydrazone (R^1=Ph ; R^2=H) (6) gave 1-*p*-nitrophenyl-3-phenylindazole (7) in 72% yield under basic conditions compared to 95% by acid catalysis[5,8].

The proposed mechanism is as follows (Scheme 1.4).

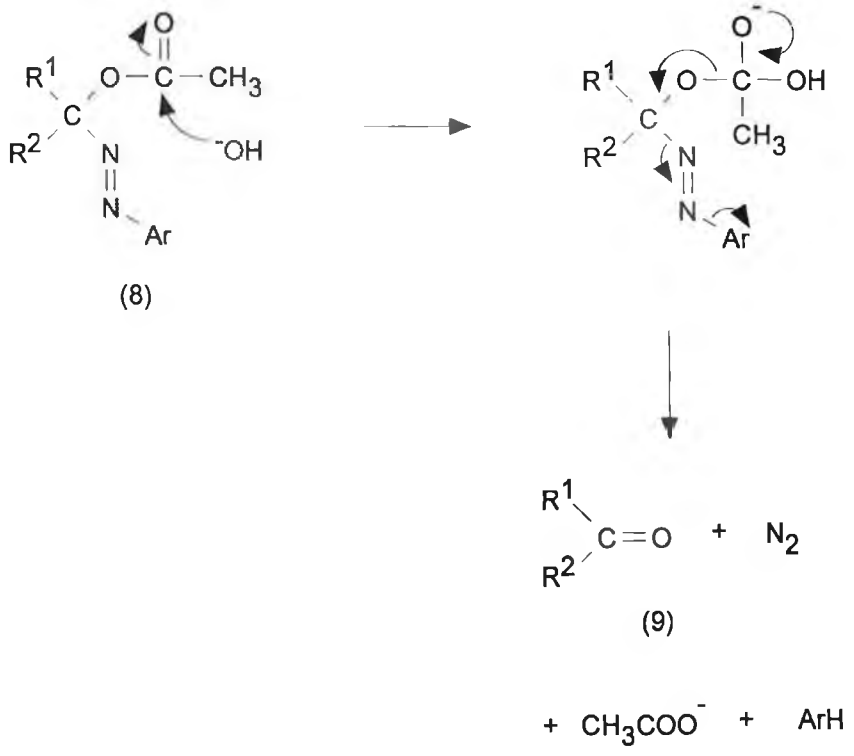
Scheme 1.4



The base catalysed cyclisation shown, occurs for R^2=H;NO_2 suggesting that steps (b) and (c) are concerted.

However, when the arylazo-moiety (Ar) does not contain a *para*-nitro group (8), a competing reaction leads to the aromatic ketone (9), arrived at as follows:

Scheme 1.5



The formation of the azoacetate (8) is found to be favoured in strongly basic conditions. However while the ketone (9) has been isolated, as shown above, the hydrazone from which the azoacetate originated has also been detected in less basic conditions. For example, the azoacetate of benzophenone phenylhydrazone reverts to the hydrazone in 49% yield, upon heating in either butan-1-ol or butan-2-ol in the presence of potassium carbonate. As the hydrazone has not been isolated when *t*-butyl alcohol is used as the solvent, it is concluded that hydrazone formation is a result of hydride transfer, made possible by the alcohol solvents. The resulting reduced version of the solvent butan-2-ol *i.e* ethylmethylketone has been detected in the reaction mixture[8].

The mechanism by which LTA reacts with ketone arylhydrazones has been investigated based on the Hammett equation, and an alternative to a free radical mechanism[2] has been proposed[6]. In the free radical mechanism, the rate determining step is the formation of (10) as follows:

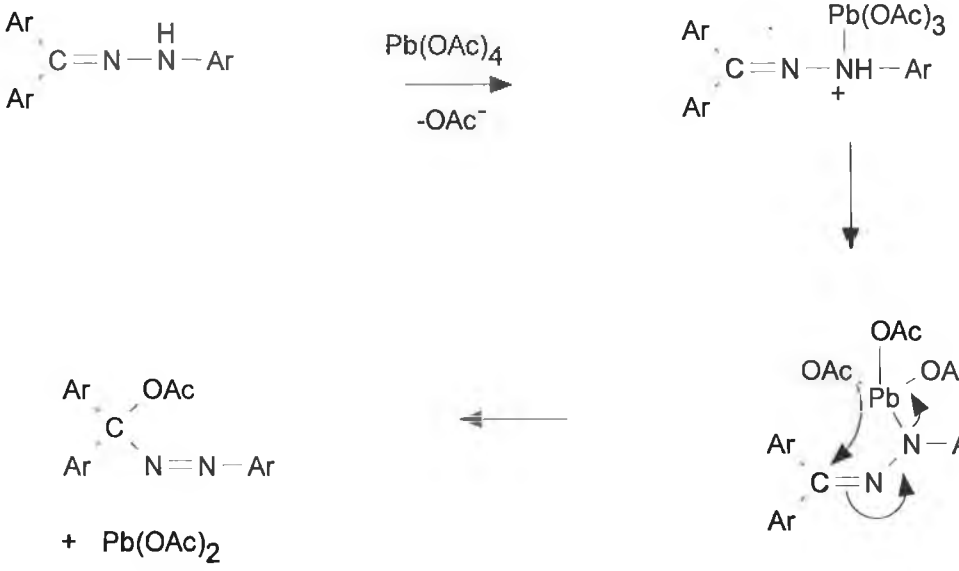
Scheme 1.6

(10i) (10ii)

Here the nitro group should stabilize the developing radical and hence have a less marked deactivating influence than is actually observed.

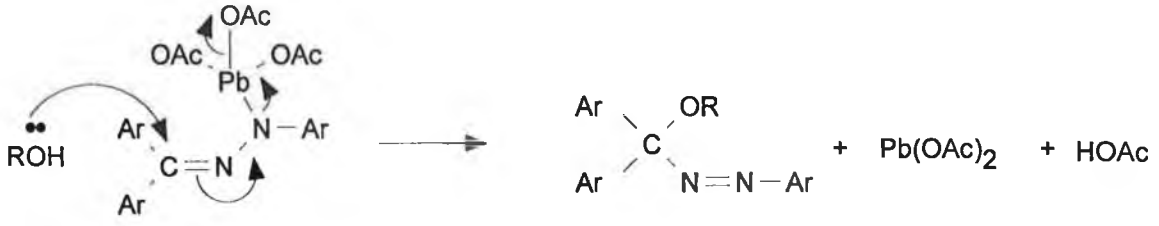
Benzophenone phenylhydrazone and the *p*-nitrophenyl derivative are oxidised using LTA in alcohol when the corresponding azoacetates were formed. The oxidation rate was found to depend on the polar effects of substituents both on the ketone and more notably on the arylhydrazine moieties. More consistent with rates studied is the view that the rate determining step of the oxidation involves the displacement of the acetate anion of the LTA by the N-H nitrogen involving an ionic mechanism. This is followed by the uptake of an acetoxy at the ketonic carbon occurring intramolecularly within an intermediate lead derivative[9].
This is illustrated in scheme 1.7.

Scheme 1.7



This mechanism involving a lead triacetate intermediate is further extended to explain the formation of azoethers (11) which are isolated in some oxidations when carried out in an alcoholic medium *i.e* Scheme 1.8.

Scheme 1.8



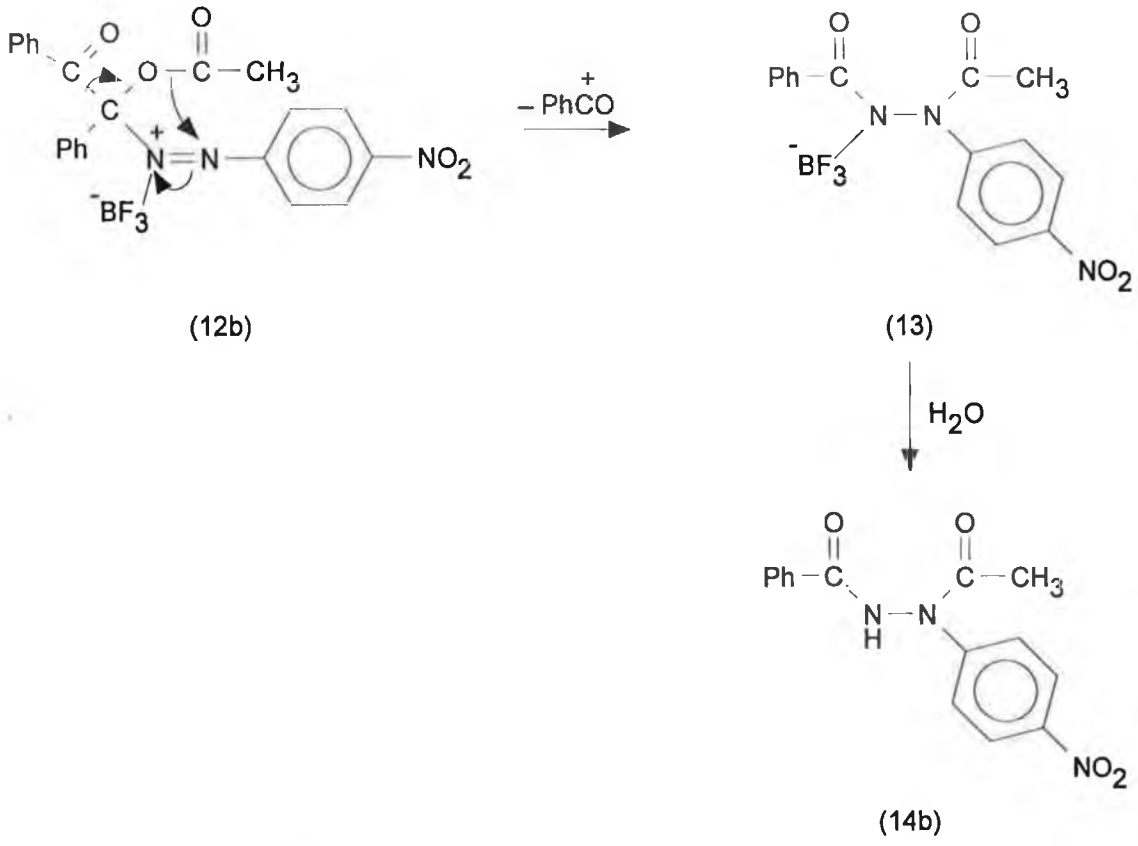
(11)

The azoether (11) is a result of intermolecular displacement of the lead salt and it is not formed from the azoacetate. The acetoxylation is seen as intramolecular as opposed to intermolecular, based on the ratio of azoether to azoacetate. For example, when the compound, benzophenone-*p*-nitrophenylhydrazone is oxidised by LTA with ethanol as solvent, the ratio of azoether to azoacetate was found to be 3:1. An intermolecular mechanism

would favour ethoxylation, thus a greater excess of azoether would be anticipated (14:1), which is not observed[9,10].

The azoacetates derived from benzil phenylhydrazone and *p*-nitrophenylhydrazone undergo other reactions in preference to cyclisation when treated with boron trifluoride[11].
Consider for example the azoacetate of benzil-*p*-nitrophenylhydrazone (12b), which reacts as follows (Scheme 1.9), when treated with BF_3-ether complex, yielding N-acetyl-N`-benzoyl-*p*-nitrophenylhydrazine (14b):

Scheme 1.9



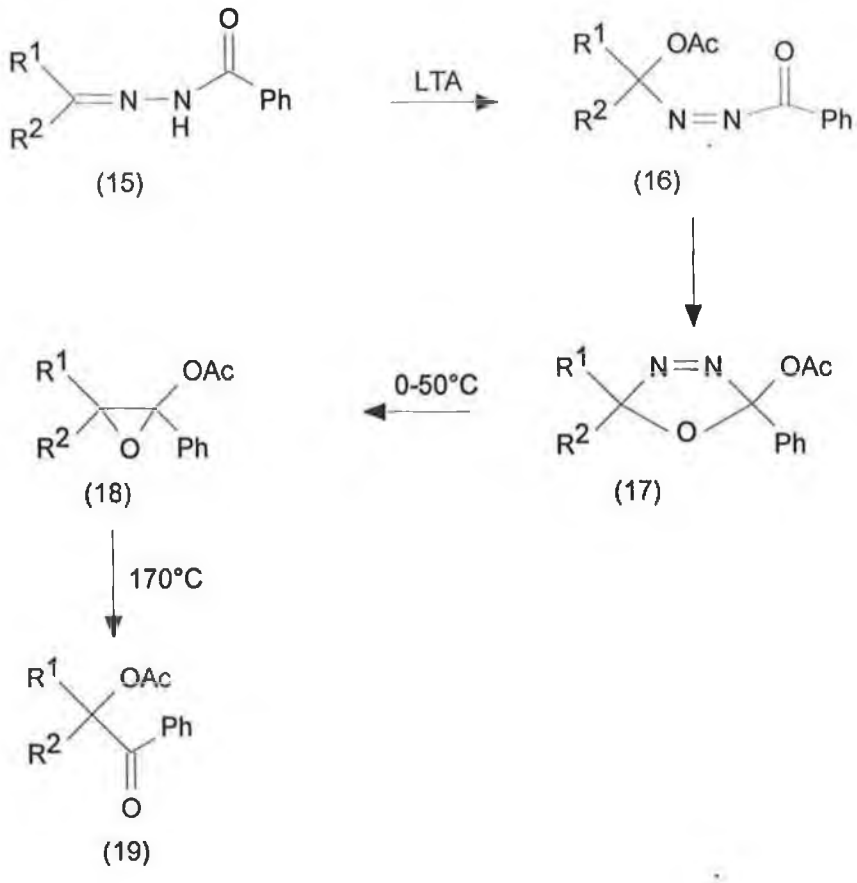
(12b) (13) (14b)

[a=Ph : b=*p*-NO_2Ph]

Acid catalysed removal of the acetate is not possible since the *p*-nitrophenyl substituent would not stabilise the resulting cation.

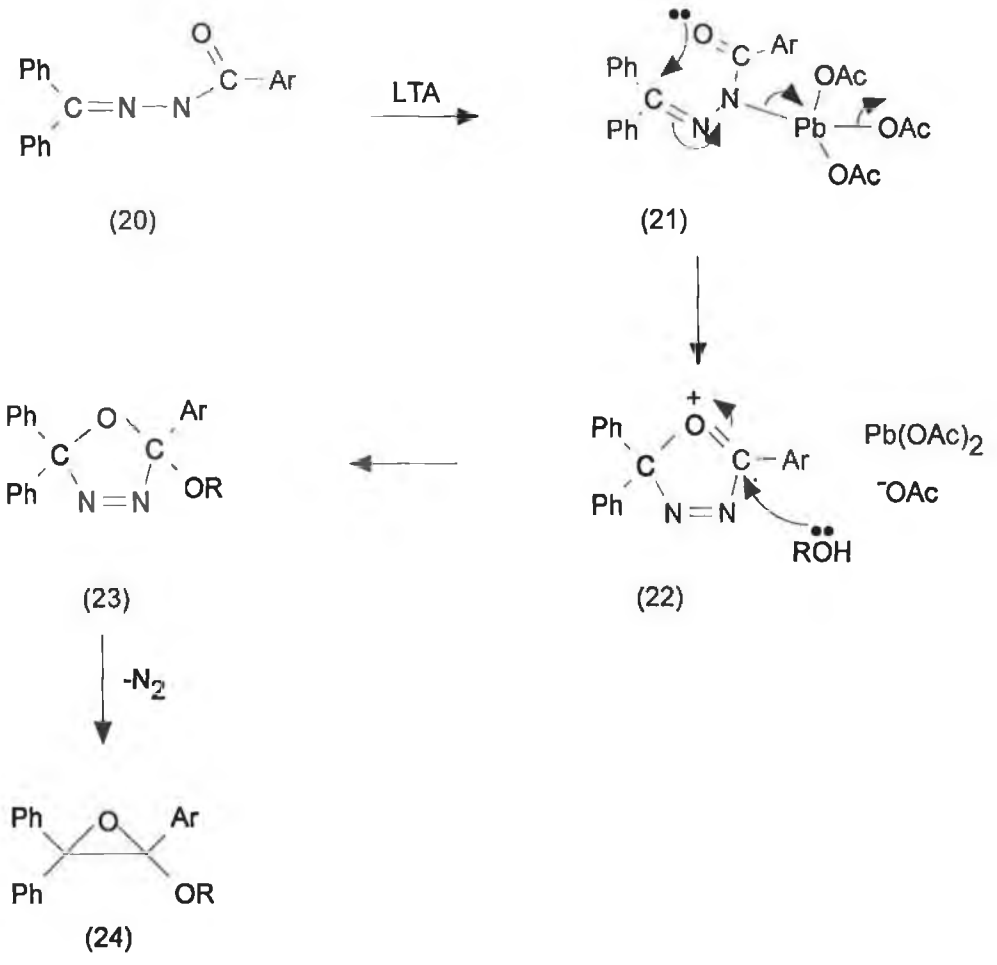
The azoacetates (16) obtained from ketocarbonylhydrazones (15) are found to be very reactive[12,13] and many may react further to produce 1,3,4-oxadiazolines (17). Gentle heating of these materials results in the loss of nitrogen with the formation of an epoxide (18), which on further heating yields an α-ketoacetate (19) as shown in scheme 1.10[14].

Scheme 1.10



Thus, for example, benzophenone-*p*-nitrobenzoylhydrazone (20) gives rise to an epoxide (24) as follows (Scheme 1.11):

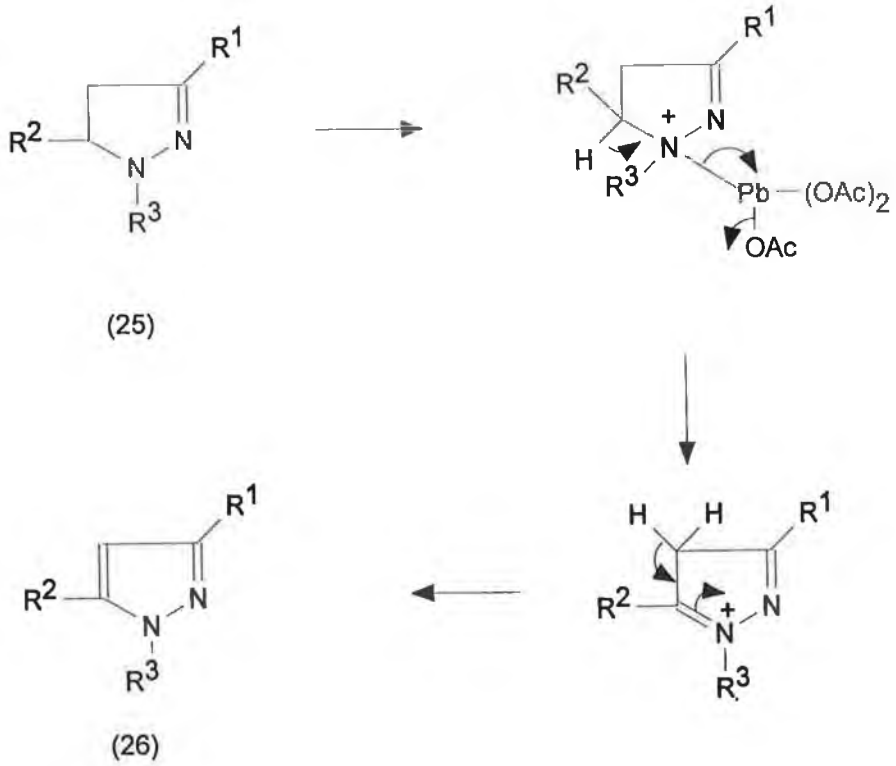
Scheme 1.11



This epoxide formation is compatible with the suggestion that the first step in the reaction of hydrazones with LTA is the formation of the bond between the nitrogen of the N-H group and the lead atom[11].

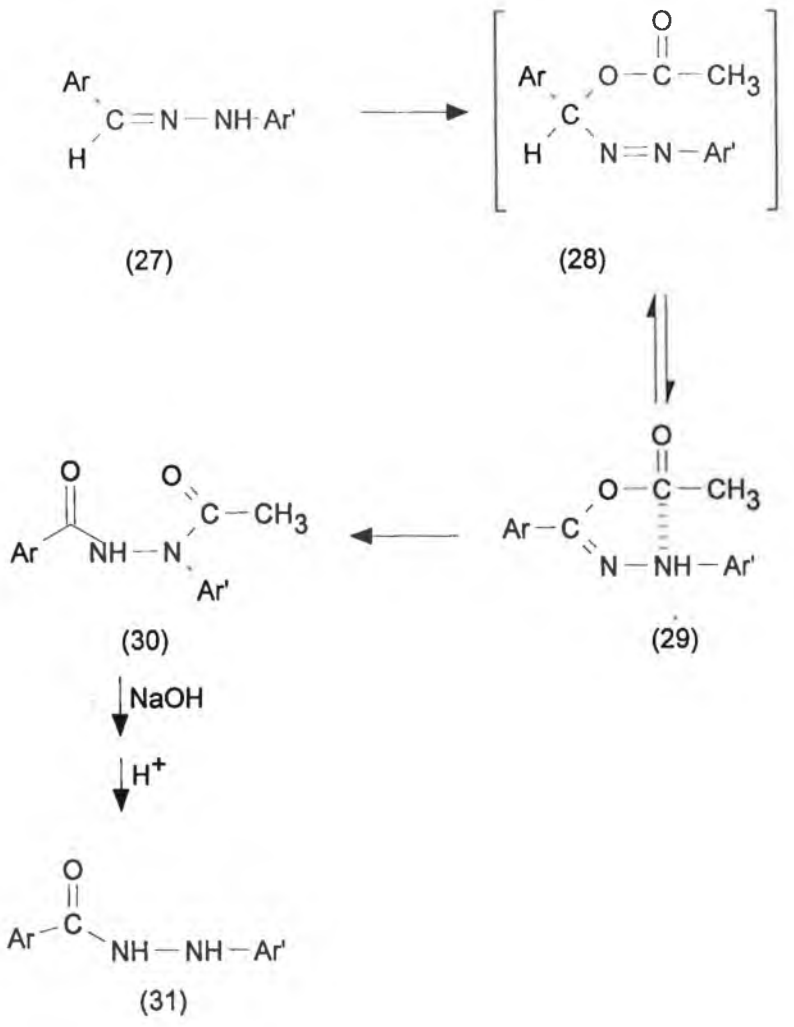
The nitrogen to lead bond is also evident in the conversion of 2-pyrazolines (25) into the corresponding pyrazoles (26), an oxidation effected by LTA as follows[11] (Scheme 1.12).

Scheme 1.12



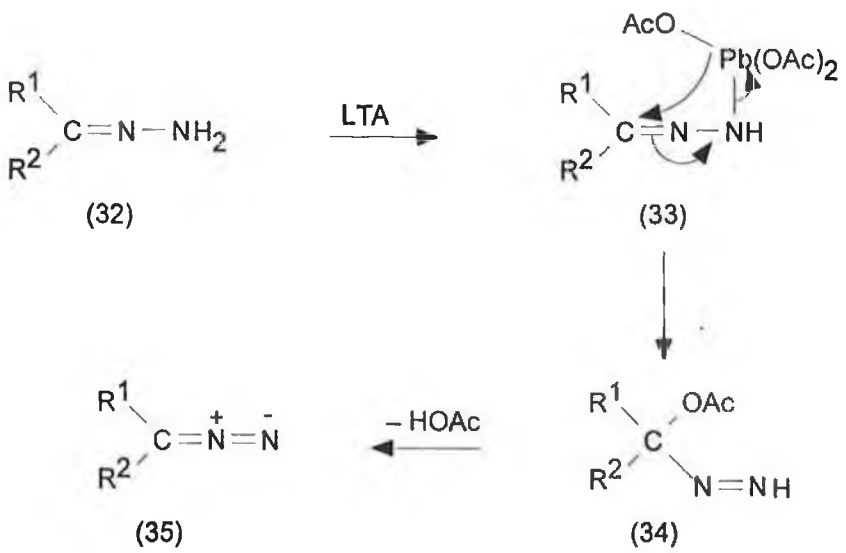
When one of the hydrazonyl carbon substituents is replaced by a hydrogen atom, *i.e* an aldehyde hydrazone (27), there is a substantial change in the nature of the products upon reaction with LTA[12,16,17] (Scheme 1.13). The formation of N-acetylhydrazide (30) is observed as opposed to the azoacetate (28). When these N-acetylhydrazides (30) are stirred in a 10% solution of sodium hydroxide, at room temperature for short periods, the acetyl group is removed, and acidification of the solution causes the hydrazides (31) to separate. (However when the aryl groups are nitro substituted, deacetylation does not occur).

Scheme 1.13



The following scheme (1.14) illustrates the reaction of LTA with unsubstituted hydrazones, which yields diazoalkenes (35) as intermediates.

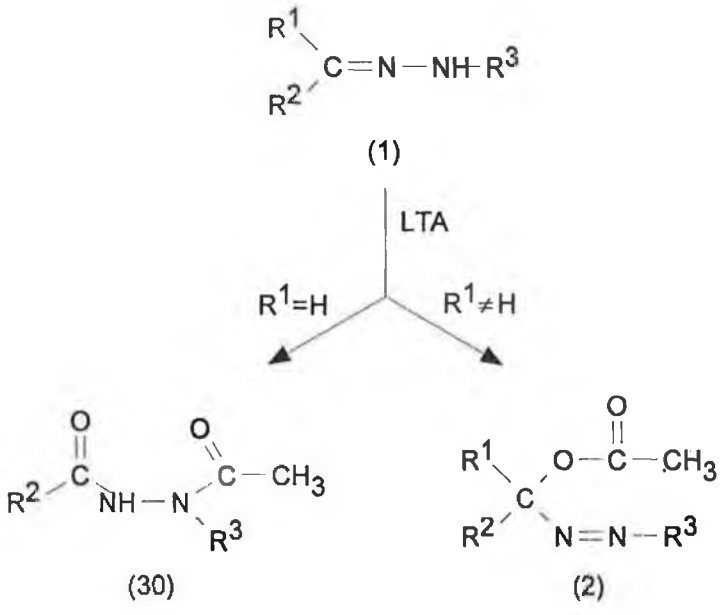
Scheme 1.14



Further reaction of the intermediates yields as usual products, the monoacetoxylalkanes (36) or diacetoxylalkanes (37)[1]:

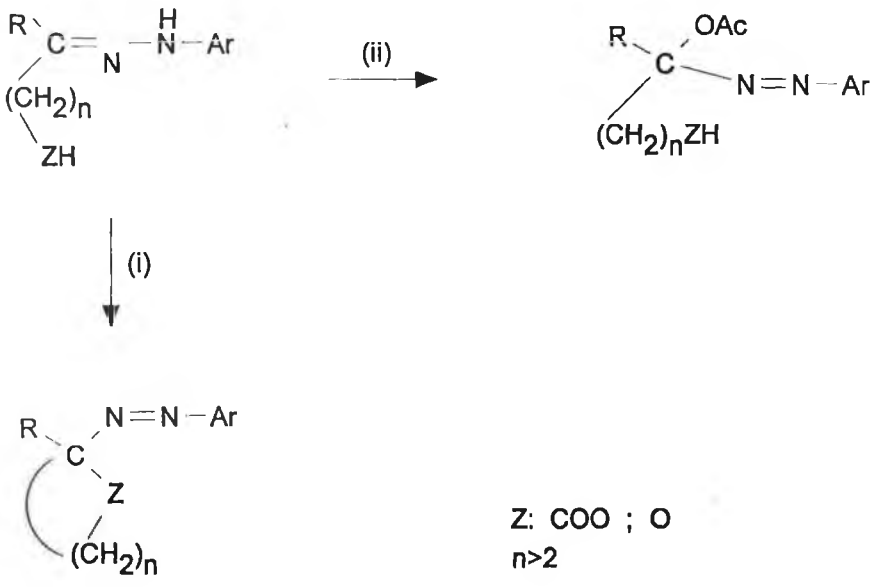
In general, the reactions of LTA with substituted hydrazones follow the pattern outlined in scheme 1.15. Ketohydrazones (1) yield azoacetates (2) while aldehyde hydrazones (27) yield N-acyl-N'-acetylhydrazines (30)[18].

Scheme 1.15



In the lead tetraacetate oxidation of ketone hydrazones containing a suitable cyclisation site on the ketone substituents, oxidative cyclisation (i) and azoacetate formation (ii) are competitive processes thus (Scheme 1.16).

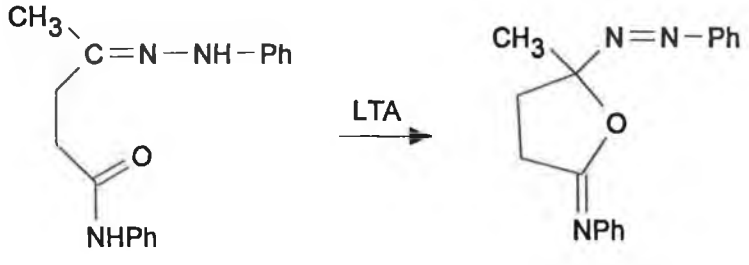
Scheme 1.16



In general, cyclisation is the major reaction accompanied by low yields of azoacetate when there is a suitable site available at the fourth or fifth atom from the methine carbon[1].

Consider, for example[19], oxidation of the phenylhydrazone of levulinanilide (38) by LTA yielding the iminolactone (39) (Scheme 1.17).

Scheme 1.17



(38) (39)

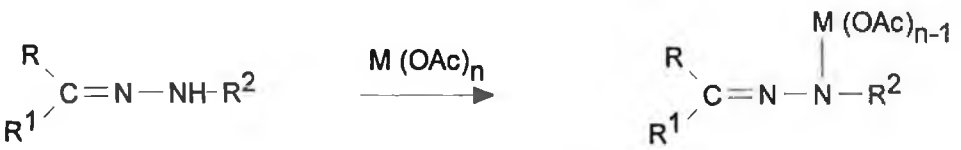
1.1.2 Mercuric acetate as an oxidising agent

Mecury(II) acetate, $Hg(OAc)_2$, (MA) often closely parallels lead (IV) acetate as an oxidising agent. However in many cases the reactions of MA with hydrazones differ dramatically from those of LTA. One influencing factor is the much weaker oxidising power[20] of MA.

One notable difference is the reaction of MA with some *p*-nitrophenylhydrazones. This results in mercuriation of the N-phenyl ring at the *ortho* position as opposed to proton displacement from the hydrazone N-H site. This formation of a metal-carbon bond instead of a metal-nitrogen bond is rare[10].

Generally, the oxidation reactions of $Hg(OAc)_2$ and LTA with ketone hydrazones tend to share the common N-metallo intermediates (40):

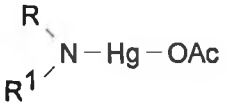
Scheme 1.18



(40)

M=Pb ; n=4
M=Hg ; n=2

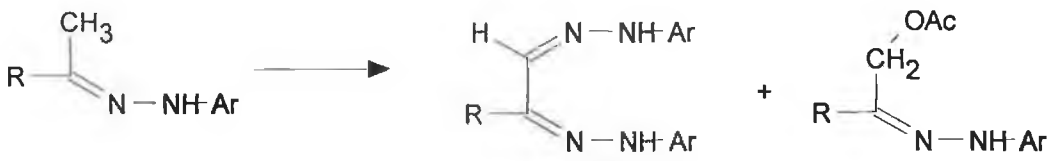
While the lead intermediates are highly reactive, the analogous mercury intermediates are relatively stable. This has led to the isolation of some organomercury intermediates (41) containing the N-Hg-OAc moiety[10].



(41)

The reactions of ketone *p*-nitrophenylhydrazones (42) with mercuric acetate in acetic acid have been studied by Butler and Morris[21].

Scheme 1.19



(42) (43) (44)

The main products obtained were the 1,2-bishydrazones (43) arising from a hydrazino-transfer to the methyl group. In some cases intermolecular attack by AcOH led to the α-acetoxy derivatives (44).

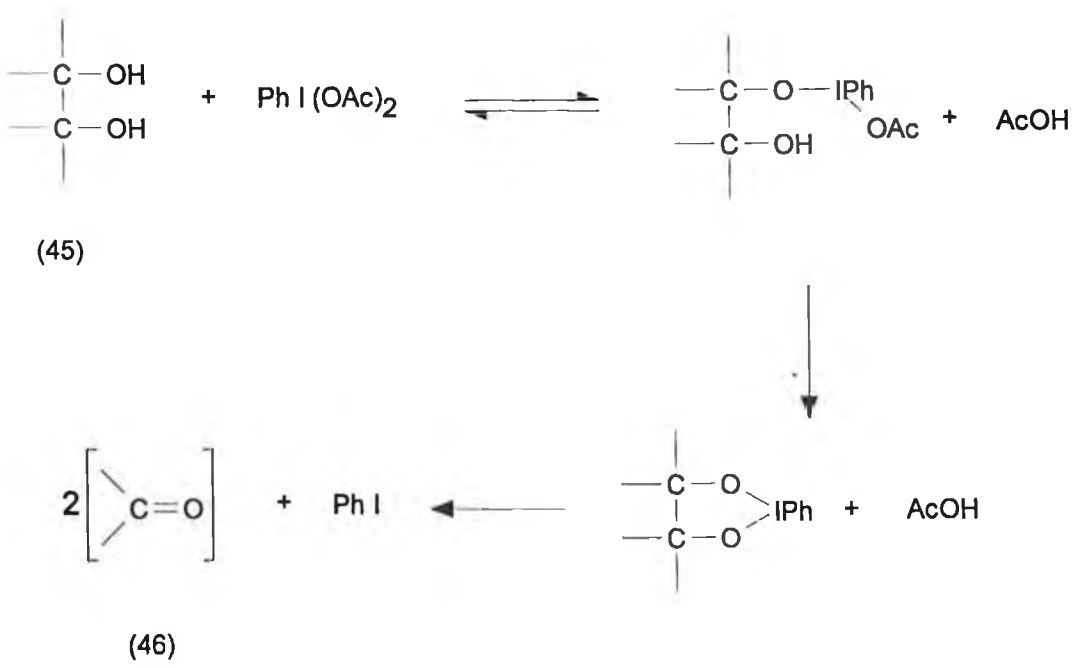
1.1.3 Iodobenzene diacetate as an alternative oxidising agent

In order to consider a less hazardous replacement for the metallic oxidising agents, already discussed above, some of the similarities and reactions of iodobenzene diacetate (IBA) are considered.

Iodobenzene diacetate, also known as aryliodine(III)dicarboxylate (AID) or phenyliodine(III)diacetate (PID), among others, can be prepared by the reaction of iodobenzene with peracetic acid when the product is collected as a white crystalline material on cooling[22]. The electronic structure and bonding associated with IBA has received extensive investigation by Ramsden[23], Varvoglis *et al.*[24] and earlier studies by Alcock *et al.*[25].
Similarities are indicated by some of the following reactions.

One of the best known reactions of IBA is the cleavage of glycols (45) to carbonyl compounds (46)[26,27,28] . As in the case of LTA[29], a free radical mechanism has been eliminated following studies of the oxidation of methylphenylsulphide to the sulphone for example[30]. The mechanism (Scheme 1.20) is similar to that for LTA, however the rate is about 100 times slower for IBA.

Scheme 1.20



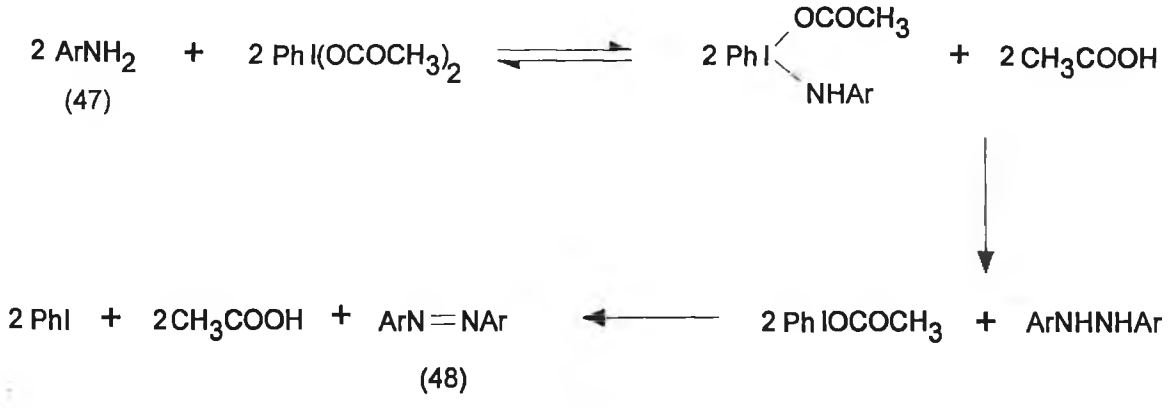
(45)

(46)

The cleavage reactions of vicinal diols by both LTA and IBA are also observed for covalent derivatives of these diols[31].

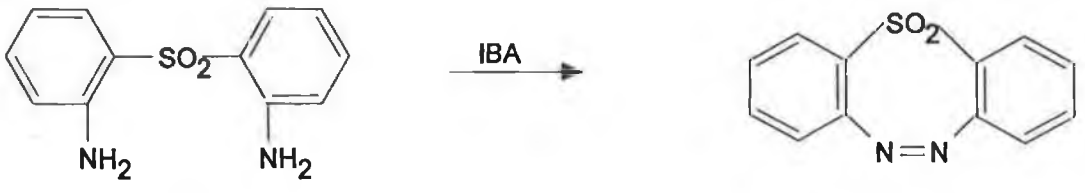
Iodobenzene diacetate effects oxidation of primary aromatic amines[32,33,34] in benzene or acetic acid solutions. Substituted aromatic amines (47) form the corresponding azo compounds (48). A mechanism was proposed similiar to that postulated for the glycol fission above[27,28], as follows:

Scheme 1.21



In a similiar fashion Szmant[35,36,37] found that IBA oxidises the di-(*o*-aminophenyl)sulphone (49) to the cyclic azo compound (50) as shown (Scheme 1.22)

Scheme 1.22



(49) (50)

LTA is a useful methylating agent. Likewise, IBA in hot acetic acid was found to be equally good for this purpose. For example, a 20% yield of 1,3,5-trinitro-2,4-dimethylbenzene was obtained from 1,3,5-trinitrobenzene and the diacetate. A free radical mechanism was proposed[34] to account for the product as follows.

Scheme 1.23

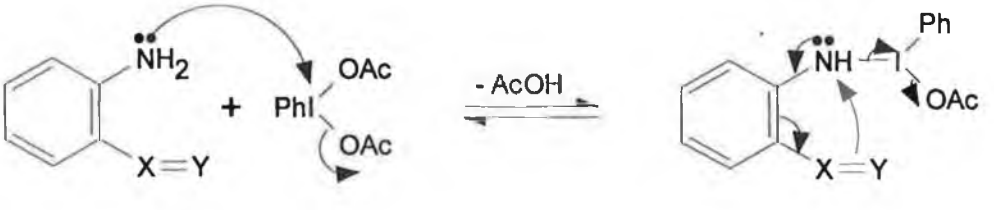
$$C_6H_5I(OCOCH_3)_2 \longrightarrow C_6H_5I + 2(OCOCH_3)^{\bullet}$$

$$2(OCOCH_3)^{\bullet} \longrightarrow 2CH_3^{\bullet} + 2CO_2$$

$$2CH_3^{\bullet} + ArH \longrightarrow ArCH_3 + CH_4$$

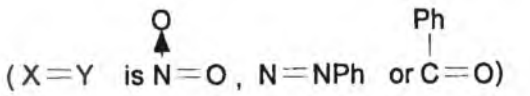
IBA is known to cause oxidative cyclisation of *ortho* substituted anilines (51). For example, when the *ortho* substituent is a nitro group, a furoxan results. Initially the reaction was postulated as an attack of the diacetate on the ketimine tautomer of the substituted aniline followed by intramolecular cyclisation[34,28]. However this has been superceded by a general mechanistic scheme (1.24) based on kinetic studies[38].

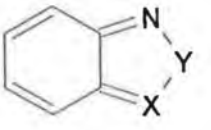
Scheme 1.24



(51) (52)

- PhI
- AcOH



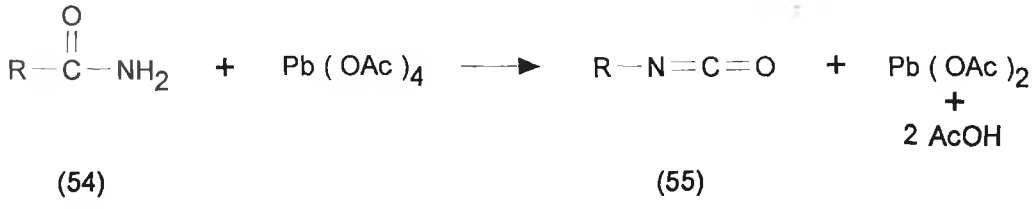


(53)

A nucleophilic displacement at iodine leads to the formation of intermediate (52), which by neighbouring group participation is oxidatively cyclised to (53). Oxidative cyclisations at oxygen have been reported by Bennett *et al.*[39].

Further similarities between IBA and LTA are indicated by the following type of reaction. LTA transforms carboxamides to acylamines[40,41,42] with the formation of an intermediate isocyanate. Similiarly Baumgarten[43] has reported an oxidative rearrangement of simple amides (54) using LTA that yields products (55) similiar to those obtained from the Hofmann rearrangement as follows:

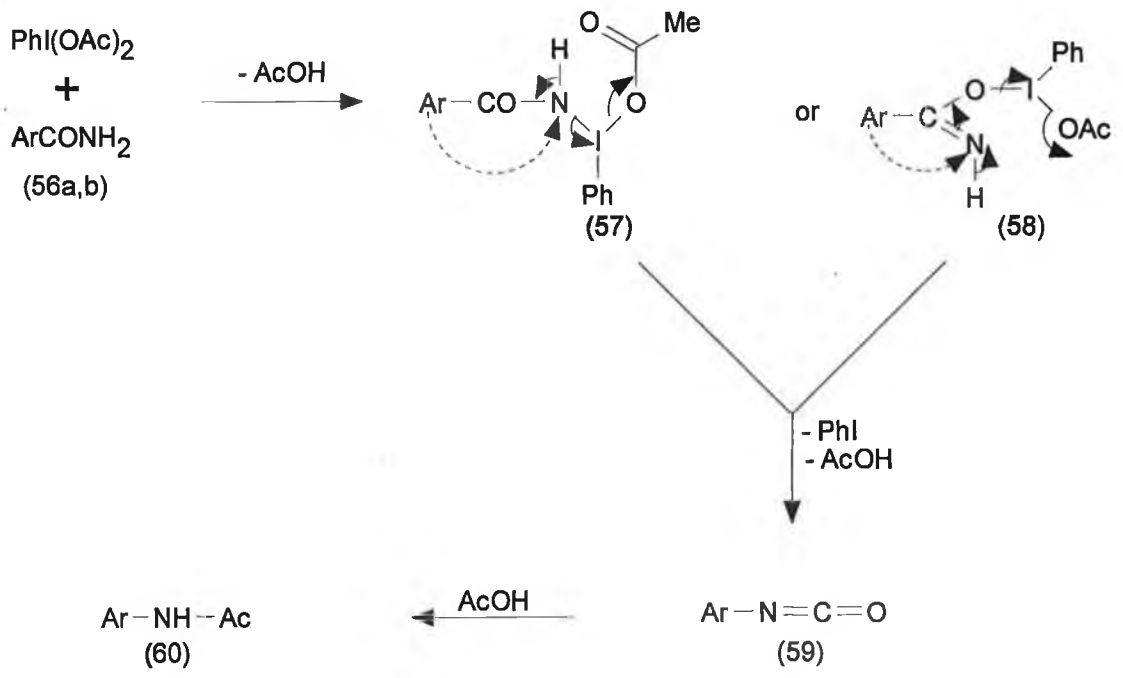
Scheme 1.25



(54) (55)

Attempts to follow the kinetics of these reactions failed because high temperatures were required to follow the conversions. However the amides entered into smooth reactions with IBA. In view of the similarities between LTA and IBA, a thorough investigation of the kinetics of the oxidation of benzamides (56a) and substituted benzamides (56b) by IBA was possible resulting in the following proposed mechanism[38,44] (Scheme 1.26).

cheme 1.26

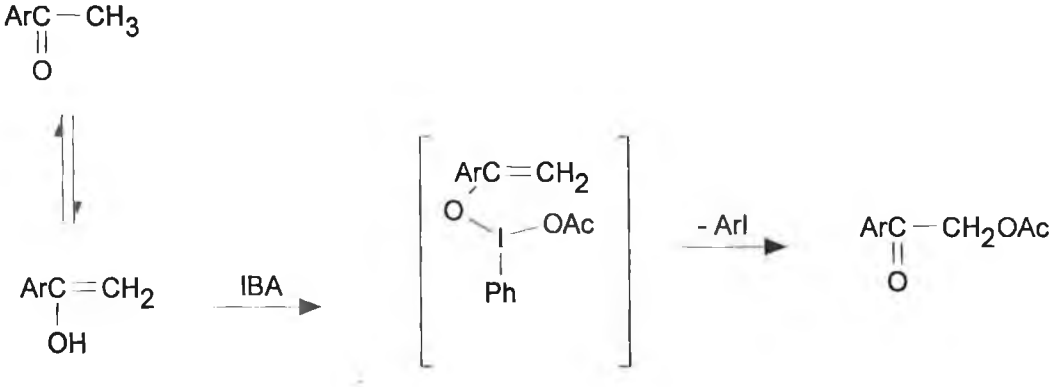


It was found that electron donors in the benzene ring (Ar) accelerate the reaction whereas electron acceptors retard them. The mechanism involves the formation of an iodine(III)-amide complex (57) or (58), which rearranges in a concerted manner into the isocyanate (59). (Compound (58) arises as the amide may undergo initial oxygen substitution as opposed to substitution on the nitrogen). In acetic acid solvent, the isocyanide is converted to the acylamine (60) *via* the amine formed by hydrolysis. This reaction lends a further insight into the mode of action of IBA.

The dehydrogenating properties of IBA are further improved by opting for the bis(trifluoroacetoxy)iodobenzene derivative[32]. For example, the reagent bis(trifluoroacetoxy)iodobenzene is found to bring about the conversion of carboxylic acid amides to amines under extremely mild conditions without isolating the intermediate isocyanate[45,46].

One of the earliest reactions of IBA was the addition of two acetoxy groups to an ethylenic double bond[38]. This acetoxylation reaction was extended to several β–diketones and acetophenones[47]. The reactions proceed in Ac_2O-AcOH system or in aqueous AcOH with H_2SO_4 as a catalyst. The reactions occur *via* the enolic form of the ketones, with intermediate formation of an O-phenyliodinated species (61) as in the following scheme (1.27).

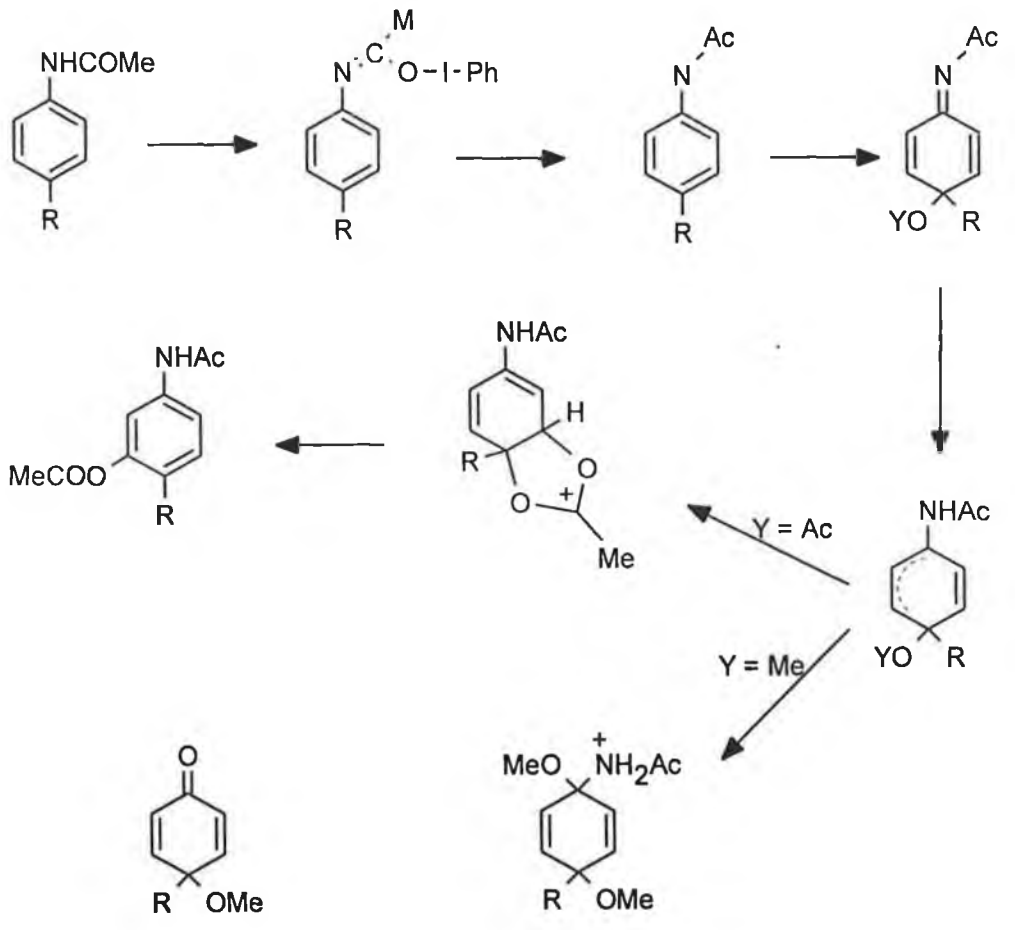
Scheme 1.27



(61)

Further examples of acetoxylation with IBA have been reported. For example, the reaction of IBA with substituted acetanilide yields 3-acetoxy-derivatives. The suggestion that the reaction is an electrophilic displacement involving direct transfer of the acetoxy cation from phenylacetoxyiodonium ion to the substrate[48], has proved unsatisfactory. Johnson *et al.*[49,50] found the effects of substituents were quite clearly defined, with electron withdrawing groups accelerating the reaction, while electron donating groups inhibit the reaction. The mechanism of this reaction has been elucidated and the acetoxy-group actually enters the aromatic ring as a nucleophile[38], as summarised in scheme 1.28.

Scheme 1.28

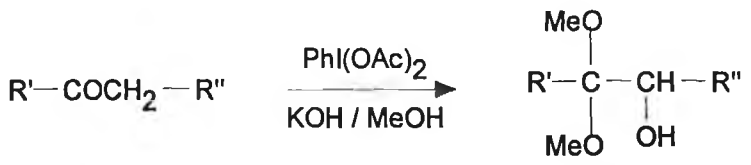


Oxidation has extended to oxidative coupling reactions[51] and intramolecular cyclisation[52]. The oxidative cyclisation of oxalyldiacetone was effected by IBA while LTA gave a rearrangement product[53].

IBA has been reported to effect acetoxylation of both acetone and methyl ethyl ketone, with an increase in rate with decreasing polarity of the solvent medium[54].

IBA has been used recently in the synthesis of heterocyclic compounds[55]. First consider the conversion of enolizable ketones (62) to α-hydroxydimethylacetals (63) by IBA in methanolic potassium hydroxide.

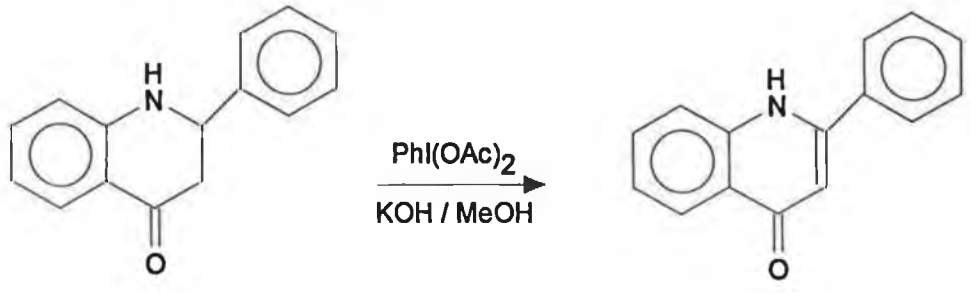
Scheme 1.29



(62) (63)

This system has also been used to oxidise quinones (Scheme 1.30), for example the conversion of 2-aryl-1,2,3,4-tetrahydro-4-quinolones (64) to 2-aryl-4-quinolones (65) as follows[56]:

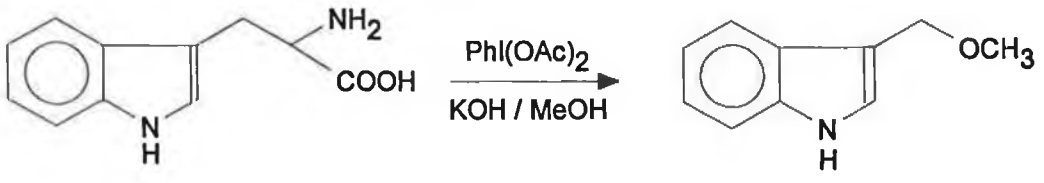
Scheme 1.30



(64) (65)

IBA is capable of a novel and specific cleavage reaction for L-tryptophan (66), again using the basic conditions shown[57]:

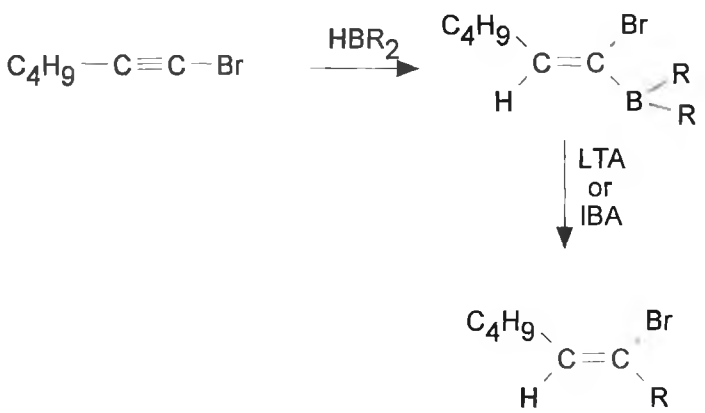
Scheme 1.31



(66)

Both LTA and IBA have allowed for the stereoselective synthesis of 1-halo-1-alkenyldialkylboranes from the corresponding alkynes[58]. The reaction involves migration of an alkyl group from the boron atom to the alkenyl carbon atom (Scheme1.32).

Scheme 1.32



R = cyclohexyl or
1,2-dimethylpropyl.

Stereospecific bromoalkenes could be obtained by controlling reaction conditions such as temperature and solvent.

IBA and cyanamide operate as a useful reagent, with low steric demands, providing cyanonitrene adducts of β-lactams previously derived from cyanogen azide[59,60].
Acyloxylation of α-pinene has been effected by the three oxidising agents, LTA, MA, and IBA, with an evident reduced rate of reaction for the latter two reagents[61].

The preceding reactions indicate some overlap between the three oxidising agents. This propelled us to consider initial studies using IBA *in lieu* of the more hazardous metallic agents, LTA and MA.

CHAPTER 1

RESULTS AND DISCUSSION

CHAPTER 1

1.2 Results and discussion.

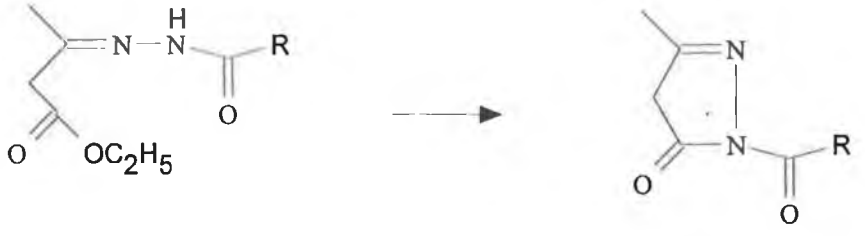
In order to study the oxidising abilities of the three main reagents previously discussed, their effect on hydrazone compounds is compared. LTA oxidises ketone hydrazones to form azoacetates. If there is a suitable cyclisation site available on the ketone substituent, oxidative cyclisation may occur.
The hydrazones derived from ethyl acetoacetate were considered suitable candidates for azoacetate formation to occur, depending on the choice of oxidising agent. Cyclisation of the azoacetate may occur readily or the azoacetate may prove a useful synthon to effect ring closure at a later stage, as the β-ketoester backbone has a relatively good leaving group. Thus the choice of this β-ketoester allows for a study of comparative oxidising abilities, and may also provide interesting synthons for further work,
The hydrazones of the β-ketocarbonyl compound ethyl acetoacetate (67) and its derivatives were synthesised as follows.

1.2.1 *p*-nitrophenylhydrazone synthesis

Synthesis of the *p*-nitrophenylhydrazone of ethyl acetoacetate (68) proved to be non-trivial. The compound most readily isolated was the corresponding 5-membered pyrazole (69), obtained *via* cyclisation of the hydrazone in acidic conditions (Scheme 1.35).

These pyrazoles are well established compounds and some are found to possess promising antiviral activity. Many pyrazole derivatives possess antiviral activity, with 3,5-dimethylpyrazoles having specific antidiabetic properties[62]. Their synthesis involved condensation of substituted aroylhydrazines (42) with ethyl acetoacetate in dioxane to form ethylbutyrate-2-substituted-aroylhydrazones (70). Cyclisation was effected by refluxing (70) in *o*-dichlorobenzene forming (71), as follows:

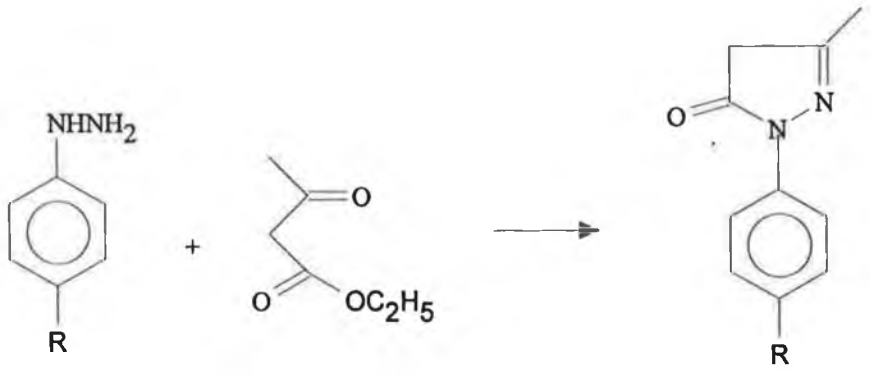
Scheme 1.33



(70) (71)

Similarly 1-aryl-3-methyl-2-pyrazoline-5-ones (73) are synthesised by the reaction of arylhydrazine (72) with ethylacetoacetate (67):

Scheme 1.34



(72) (67) (73)

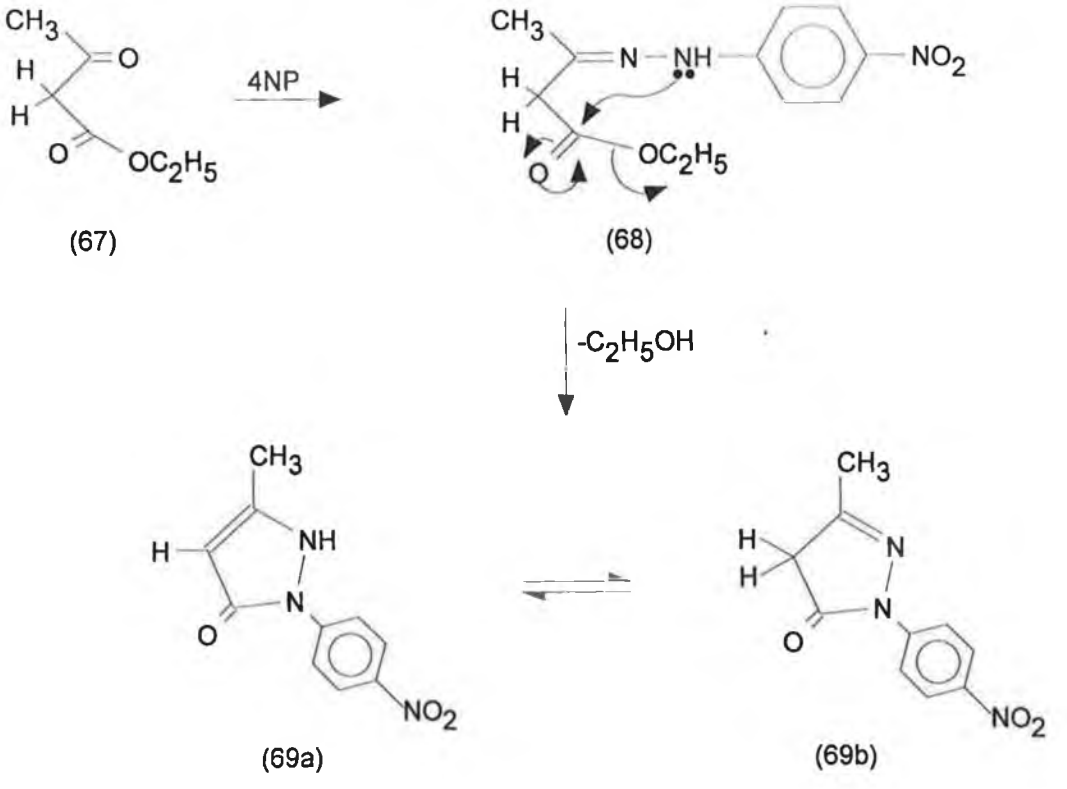
Cyclisation of the hydrazone to the corresponding pyrazolone has been studied by Pavlov *et al.*[63]. It is found to depend upon the nature of the group (R) attached to the phenyl of the substituted phenylhydrazine (72). Thus, for example, ethyl acetoacetate trinitrophenylhydrazone cyclises less readily than ethyl acetoacetate-*p*-nitrophenylhydrazone.

The coupling reaction of ethyl acetoacetate with 4-nitrophenylhydrazine (4NP) was accomplished by stirring a 1.1 mole equivalent of the β-ketoester (67) to the hydrazine, (previously dissolved in glacial acetic acid), when the resulting hydrazone (68) was collected as a yellow precipitate.(Scheme 1.35).

It was found the hydrazone readily cyclised to 1-(*p*-nitrophenyl)-3-methyl-2-pyrazolin-5-one (69) when allowed to stay in solution for 30 minutes at room temperature.

In order to ensure isolation of ethyl acetoacetate *p*-nitrophenylhydrazone (68) as a precipitate, dilute acetic acid was used to suspend the 4NP, before reaction with the ester. In cases where the hydrazone was slow to precipitate from solution, the acetic acid was further diluted by adding water dropwise, thus encouraging precipitation. This ensured against contamination by the cyclised product (69) (Scheme 1.35).

Scheme 1.35



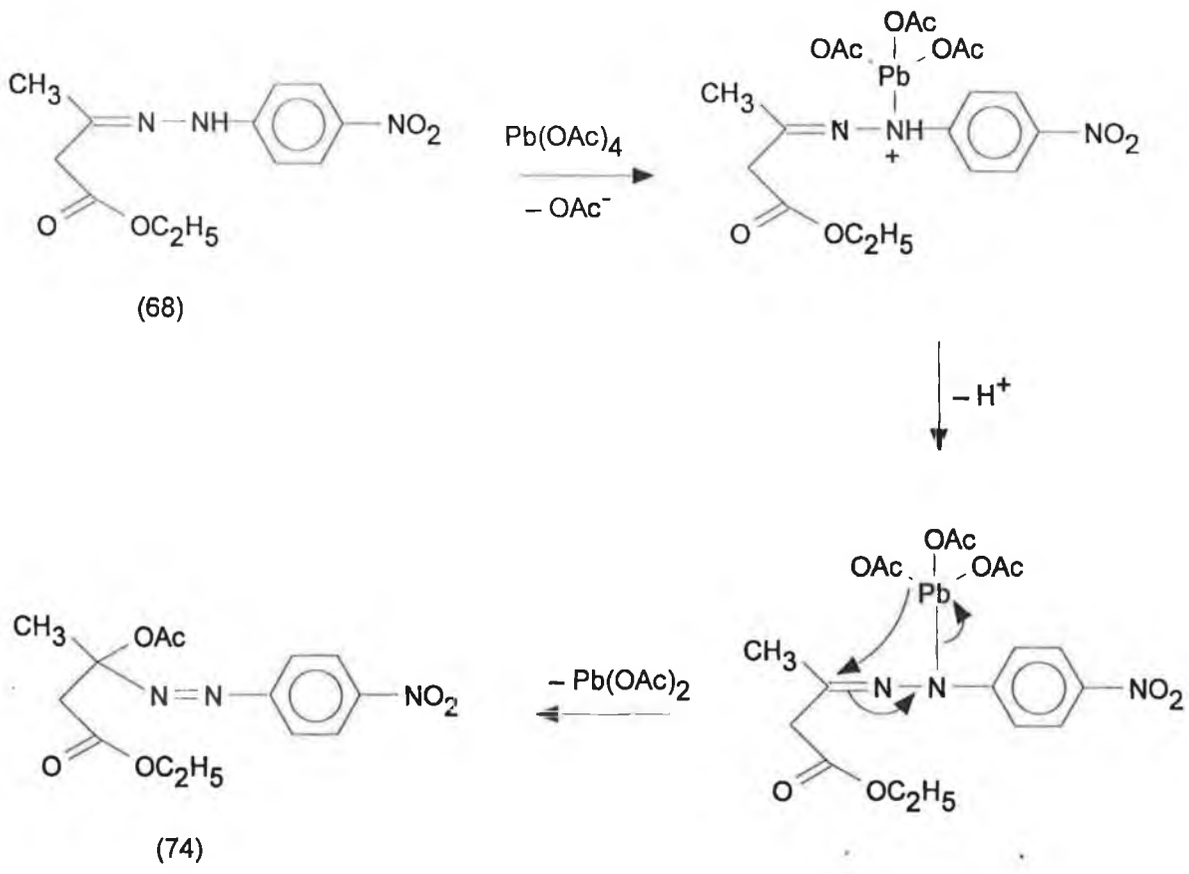
The cyclised product alone was isolated by heating the reaction mixture for five minutes. Tautomerism of the pyrazole results in structures (69a) and (69b). ^{1}H NMR analysis indicated its existence as the enone form (69a) in DMSO, with the vinylic peak at 5.4 ppm.

1.2.2 Oxidation reaction with LTA

LTA oxidation of the hydrazone (68) in CH_2Cl_2 gave the azoacetate (74) in good yield as a deep red oil. (Its existence as an oil persisted following chromatography and attempted crystallisation).

Based on the previous reports, the following mechanism is proposed (Scheme 1.36).

Scheme 1.36



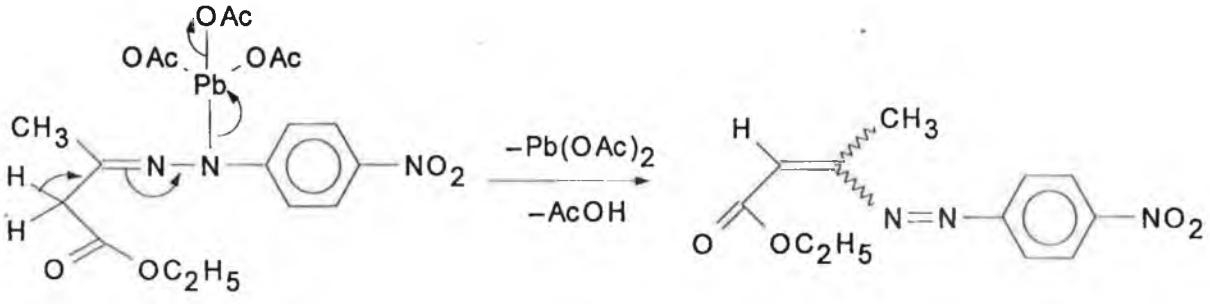
(68)

(74)

While cyclic products arising from oxidative ring closure[1] have been reported, none were obtained in this instance. Those that were successful in cyclising formed 5- and 6-membered rings[19] owing to the carbon backbone, $(CH_2)_n$, with n>1. However this is not possible in the case of ethyl acetoacetate (67), where, n=1.

When the oxidation of the hydrazone (68) was repeated using acetic acid as solvent the compound isolated was not the azoacetate (74), as in the case of CH_2Cl_2 solvent, but an azoalkene (76) resulting from loss of a proton from the α-carbon to the imine bond, assisting loss of the N-metallo intermediate as follows:

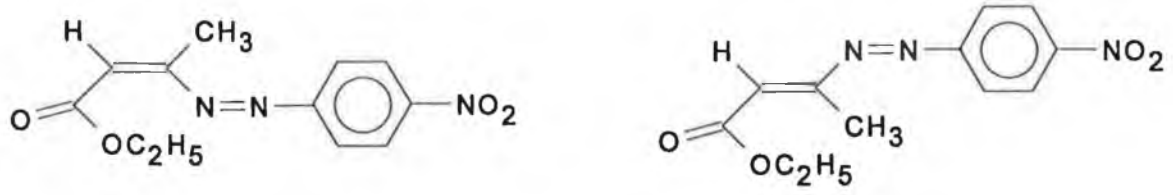
Scheme 1.37



(76)

Rotation about the C2-C3 single bond of the lead intermediate is unrestricted, consequently one would expect formation of two isomers, the Z-isomer (76i) and the E-isomer (76ii):

Scheme 1.38



(76i) (76ii)

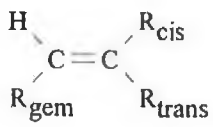
NMR analysis of the product isolated allows us to determine which of the azoalkenes (76i) or (76ii) has been formed.

The chemical shift of the olefinic proton for each isomer was calculated with the aid of tabulated spectral data[64]. Compound (X) was used as a model for the Z-isomer (76i). The olefinic proton of this isomer has been calculated to occur at 6·50 ppm. Similarily using compound (Y) as a model for (76ii), the olefinic proton of the E-isomer is calculated to occur at 6·88 ppm (Figure 1.1).

Analysis of the ^{1}H NMR of the azoalkene isolated shows the occurrence of the olefinic proton at 6·4 ppm, thus indicating the existence of (76) as the Z-isomer (76i) (Figure 1.1).

Figure 1.1 : Estimation of the chemical shifts of the vinylic protons in azoalkenes (76i) and (76ii)

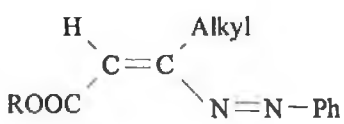
For alkenes of the type:



the chemical shift of the vinylic proton can be calculated using the formula:

$$\delta_{C=CH} = 5{\cdot}25 + Z_{gem} + Z_{cis} + Z_{trans}$$

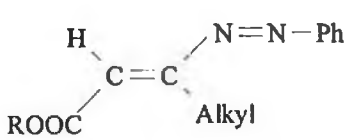
Z-isomer:



$$\delta_{C=CH} = 5{\cdot}25 + 0{\cdot}8 + (-0{\cdot}22) + 0{\cdot}67$$

$$= \underline{6{\cdot}5 \text{ ppm}}$$

E-isomer:



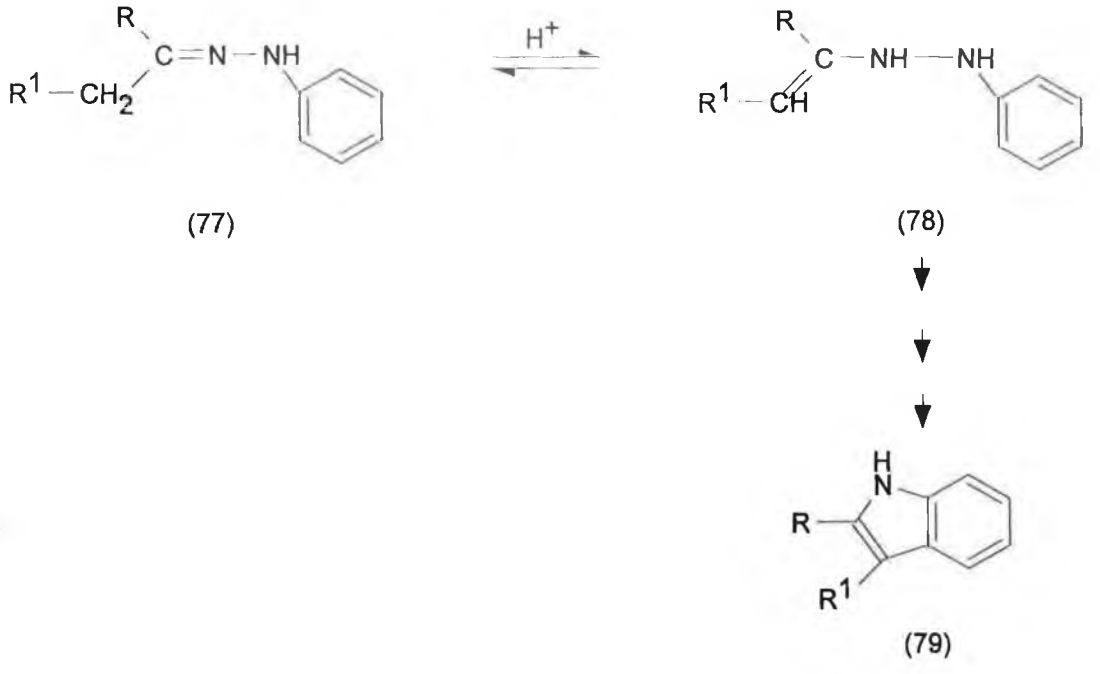
$$\delta_{C=CH} = 5{\cdot}25 + 0{\cdot}8 + 1{\cdot}11 + (-0{\cdot}28)$$

$$= \underline{6{\cdot}88 \text{ ppm}}$$

In order to consider isolation of an azoalkene by LTA oxidation in specifically acidic conditions, first consider the equilibrium that hydrazones may establish in acidic conditions.

In the Fischer indole synthesis[65] involving conversion of an aryl hydrazone (77) to an indole (79), the first step is considered to be tautomerism of the hydrazone (77) to the enehydrazine (78):

Scheme 1.39

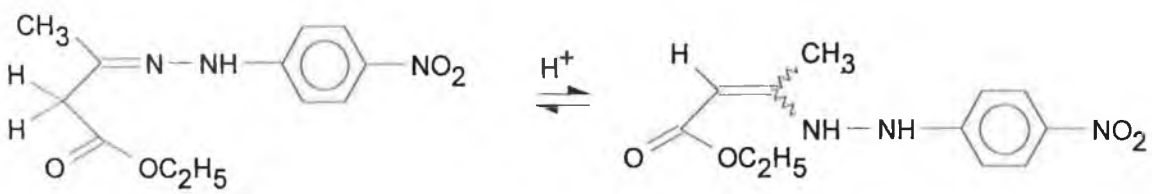


(77) (78) (79)

This cyclisation proceeds readily in acetic acid solution indicating the ability of the solvent to catalyse tautomerism between the hydrazone (77) and the enehydrazine (78).

Likewise, in acetic acid, this equilibrium may be estabilished between the hydrazone, ethyl acetoacetate *p*-nitrophenylhydrazone (68), and the corresponding enehydrazine (75) (Scheme 1.40).

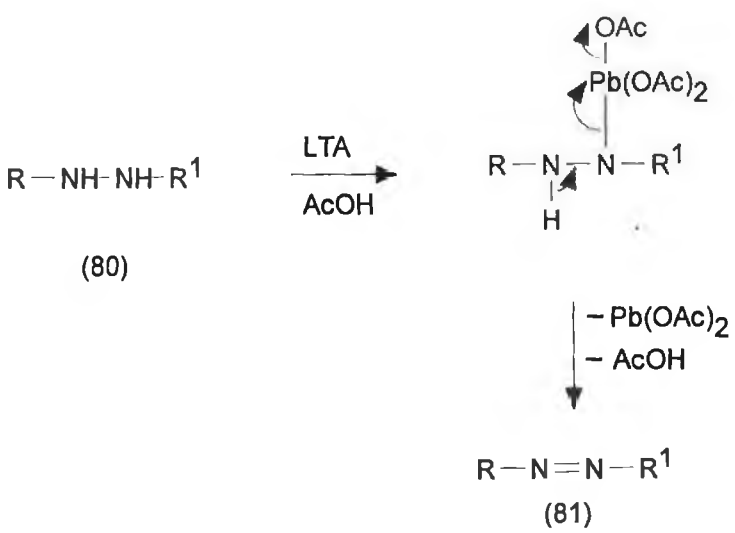
Scheme 1.40



(68) (75)

It has been reported[66,67] that the -NH-NH- unit of type (80) has a low oxidation threshold, thus in the presence of LTA dehydrogenation readily yields the azo compound (81) as follows:

Scheme 1.41



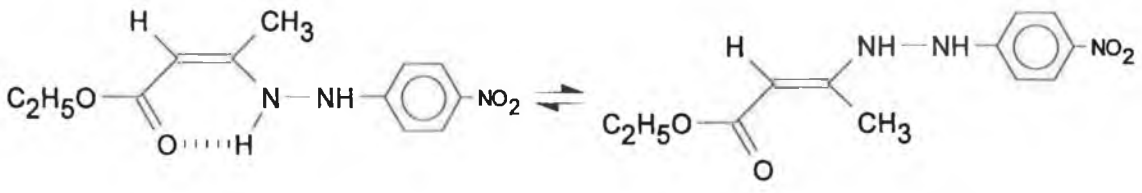
(80) (81)

In this instance, it is proposed that, while the hydrazone-enehydrazine equilibrium (68⇔75) is established in acidic conditions, the latter species is preferentially oxidised, generating the azoalkene (76). As the enehydrazine (75) is transformed, the amount of hydrazone (68) is depleted as the reaction proceeds and hydrazone-enehydrazine equilibrium is constantly re-established. Thus azoalkene (76) is the sole product isolated *via* enehydrazine as depicted in scheme 1.43.

O Connor[68] reports no obvious tautomerism to enehydrazine for solutions of phenylhydrazones in neutral solution. This is in keeping with isolation of the azoacetate (74) (Scheme 1.36) in CH_2Cl_2, in the absence of tautomerism.

In order to explain the existence of the azoalkene in the Z-isomeric form, (76i), as established by spectral details, (Figure 1.1), it is necessary to consider the probable structure of the preceeding enehydrazine (75) as outlined in scheme 1.42.

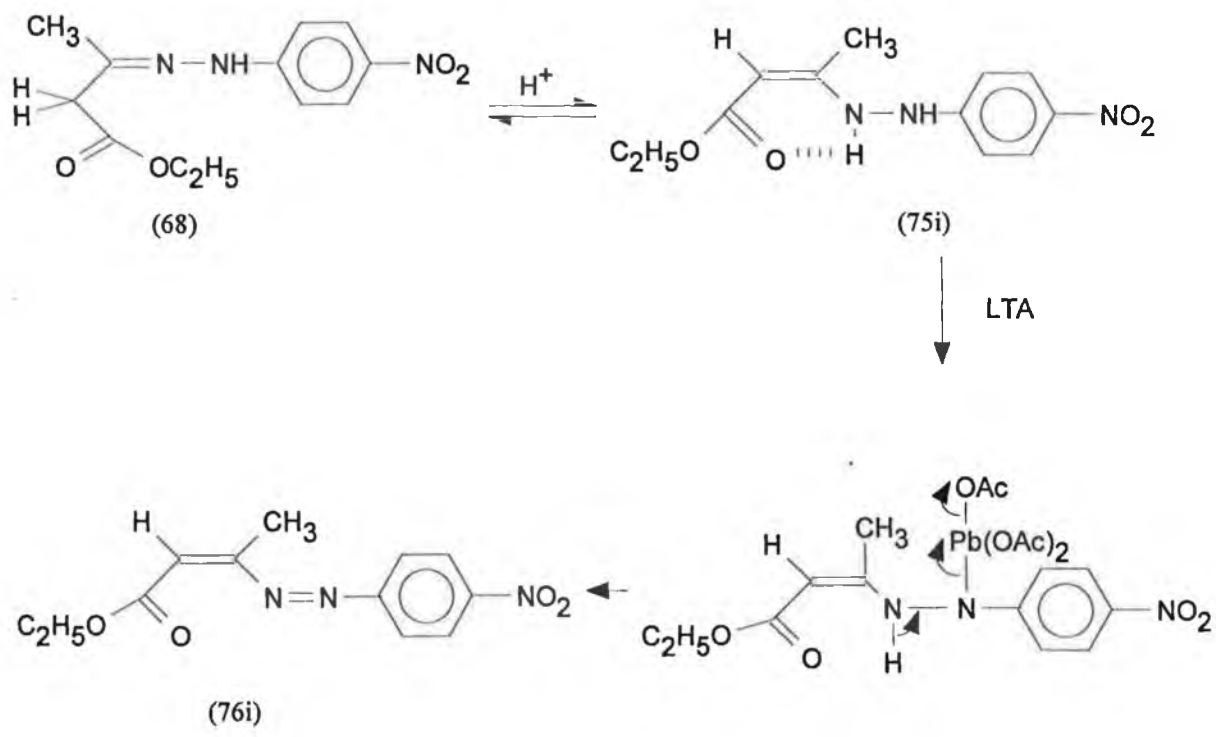
Scheme 1.42



Z-isomer (75i) E-isomer (75ii)

While considering the Z-isomer (75i) and the E-isomer (75ii), the stabilization conferred on the former, by intramolecular H-bonding, points to the existence of the ene-hydrazine (75) as the Z-isomer (75i). Consequently this imposes stereoselectivity on the following oxidation step thus ensuring formation of the azoalkene (76) in the Z-form (76i) (Scheme 1.43).

SCHEME 1.43



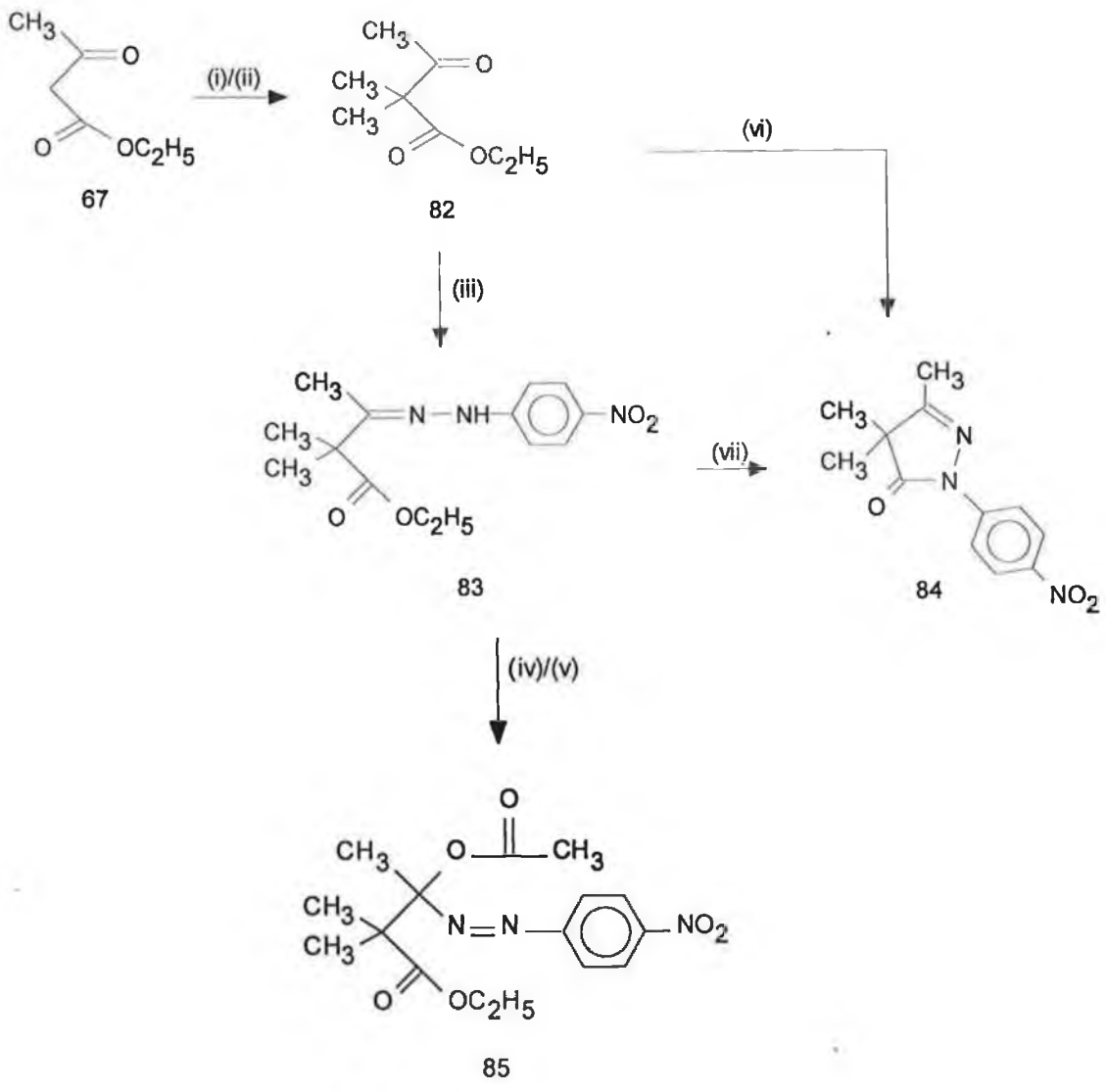
(68) (75i) (76i)

In order to consider oxidation by LTA where there is no enolisable proton, the *p*-nitrophenylhydrazone of α,α-dimethylethyl acetoacetate (83) was investigated.

Dimethylation[69,70] was achieved by heating ethyl acetoacetate with a three-fold excess of potassium carbonate and a six-fold excess of iodomethane in acetone for 56-60 hours when the product (82) was isolated in 90% yield. α,α-dimethylethyl acetoacetate (82) was also obtained when sodium hydride was used as base, in DMSO. While the latter preparation reduced the reaction time, the product was difficult to isolate, necessitating distillation, which resulted in a poor yield. The *p*-nitrophenylhydrazone of α,α–dimethylethyl acetoacetate was prepared as for (68), using dilute acetic acid as solvent which afforded the hydrazone (83) as a yellow precipitate within minutes.

Cyclisation of the hydrazone (83) was effected by stirring in acetic acid for 1hr and monitoring by t.l.c, or by simply heating (83) in acetic acid when 1-(4-nitrophenyl)-3,4,4-trimethyl-2-pyrazolin-5-one (84) formed in a matter of minutes. Oxidation of (83) yielded the azoacetate (85) when either AcOH or CH_2Cl_2 were used as solvents. This was anticipitated having removed the labile α-protons. The above reactions are summarised in scheme 1.44.

Scheme 1.44



67 82 83 84 85

(i)CH_3I / K_2CO_3 / Acetone

(ii)CH_3I / NaH / DMSO

(iii) 4NP / AcOH:H_2O ; R.Temp

(iv) LTA / CH_2Cl_2

(v) LTA / AcOH

(vi) 4NP / AcOH / Heat

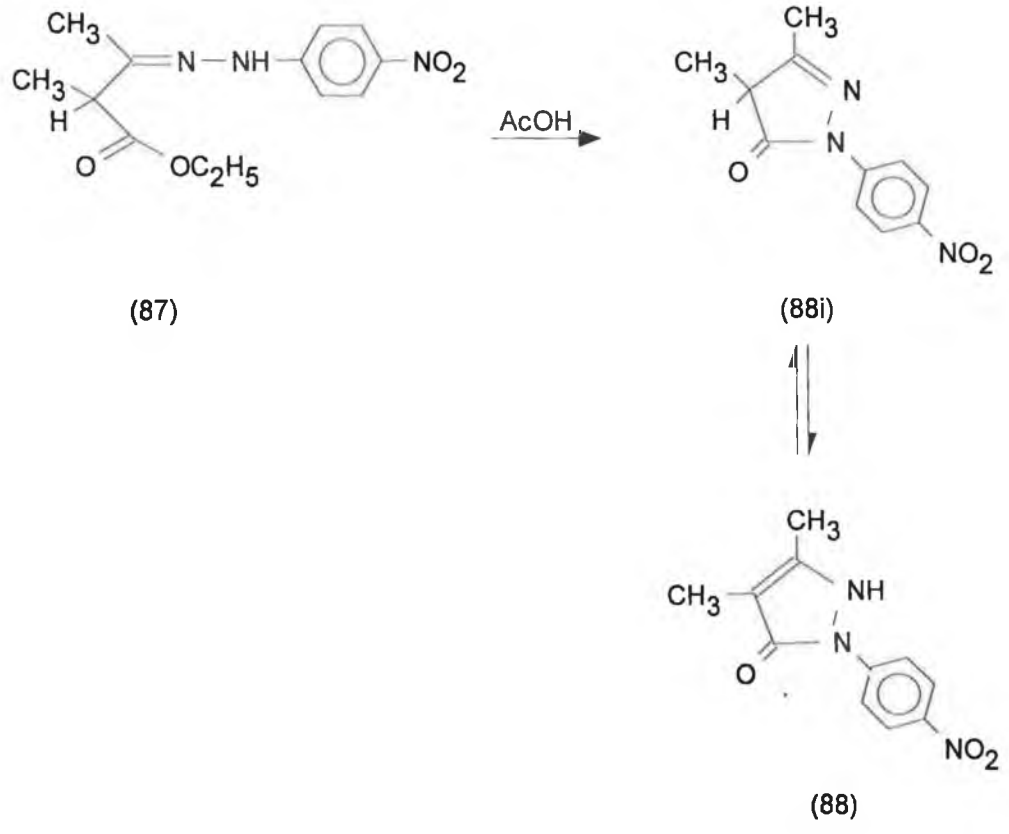
(vii) AcOH / Heat

Finally a further derivative of ethyl acetoacetate, α-methylethyl acetoacetate *p*-nitrophenylhydrazone (87) allowed for an interesting study with LTA. The hydrazone (87) was isolated as a yellow precipitate from the reaction of 4NP with the β-ketoester, α-methylethyl acetoacetate (86) in dilute AcOH, within minutes.

Cyclisation was effected by heating the hydrazone reaction when 1-(*p*-nitrophenyl)-3,4-dimethylpyrazolin-5-one (88) was isolated (Scheme 1.45).

Tautomerism is possible between (88) and (88i) however the ^{1}H NMR spectrum (DMSO) indicates its existence as (88) evident from an uncoupled 4-methyl singlet and absence of a methine signal. The IR spectrum shows an NH absorbtion band at 3,120 cm^{-1} complimenting the proposal that (88) was the favoured isomer. Studies have been carried out by DeRuiter *et al.*[71] on tautomerism of similiar pyrazolinones and results support (88) as the major tautomer.

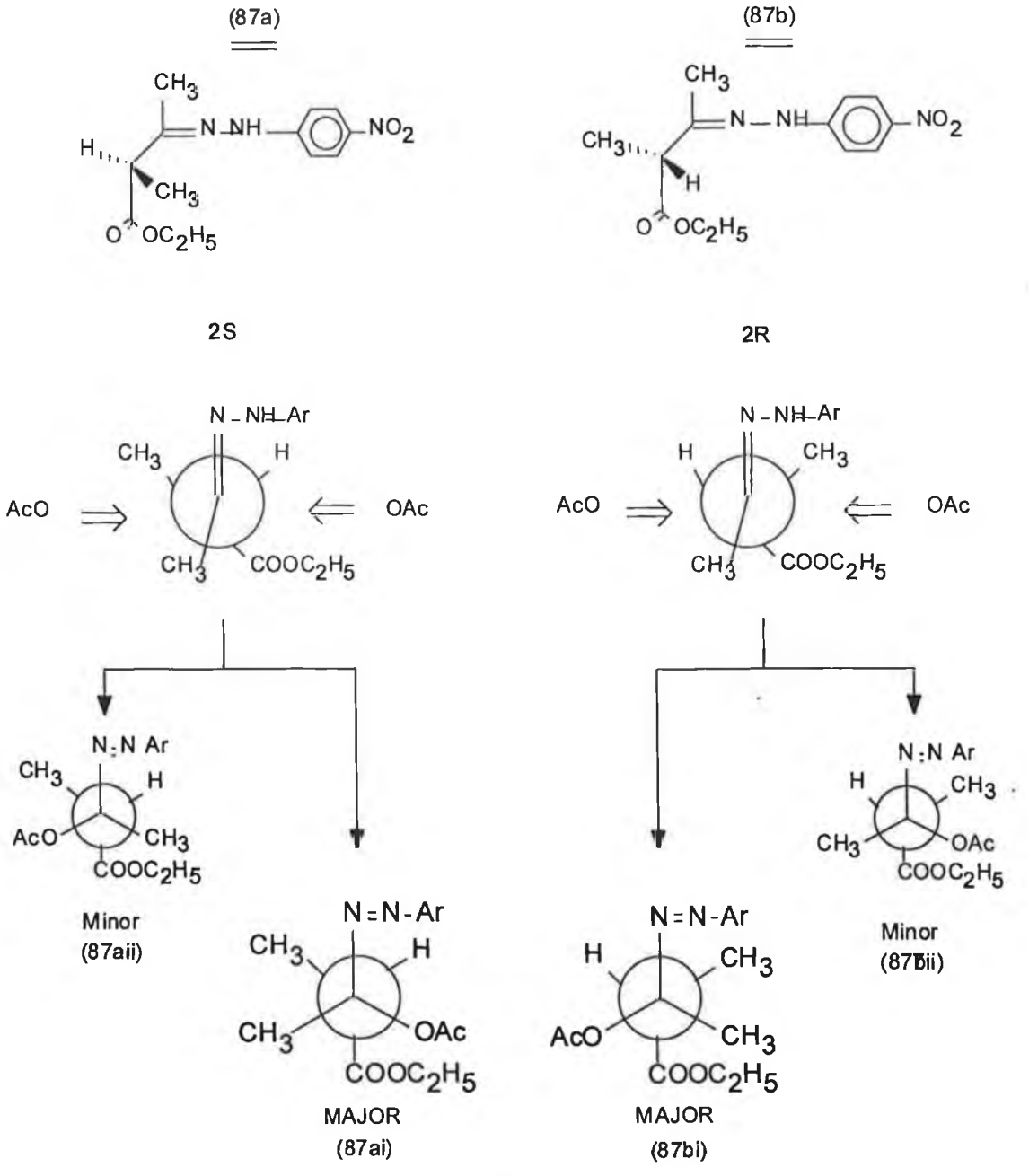
Scheme 1.45



(87) (88i) (88)

Hydrazone (87) was reacted with LTA in CH_2Cl_2 affording the azoacetate (89) as a red oil in 90% yield. Here the intramolecular acetylation results in the creation of a second asymmetric centre adjacent to the chiral carbon already present at the methylation site. Thus the azoacetate exists as diastereomers and this is indicated by the shadow peaks evident in the ^1H NMR spectrum. The hydrazone (87) can be envisaged in its two possible forms (87a) and (87b) as follows(Figure 1.2):

Figure 1.2

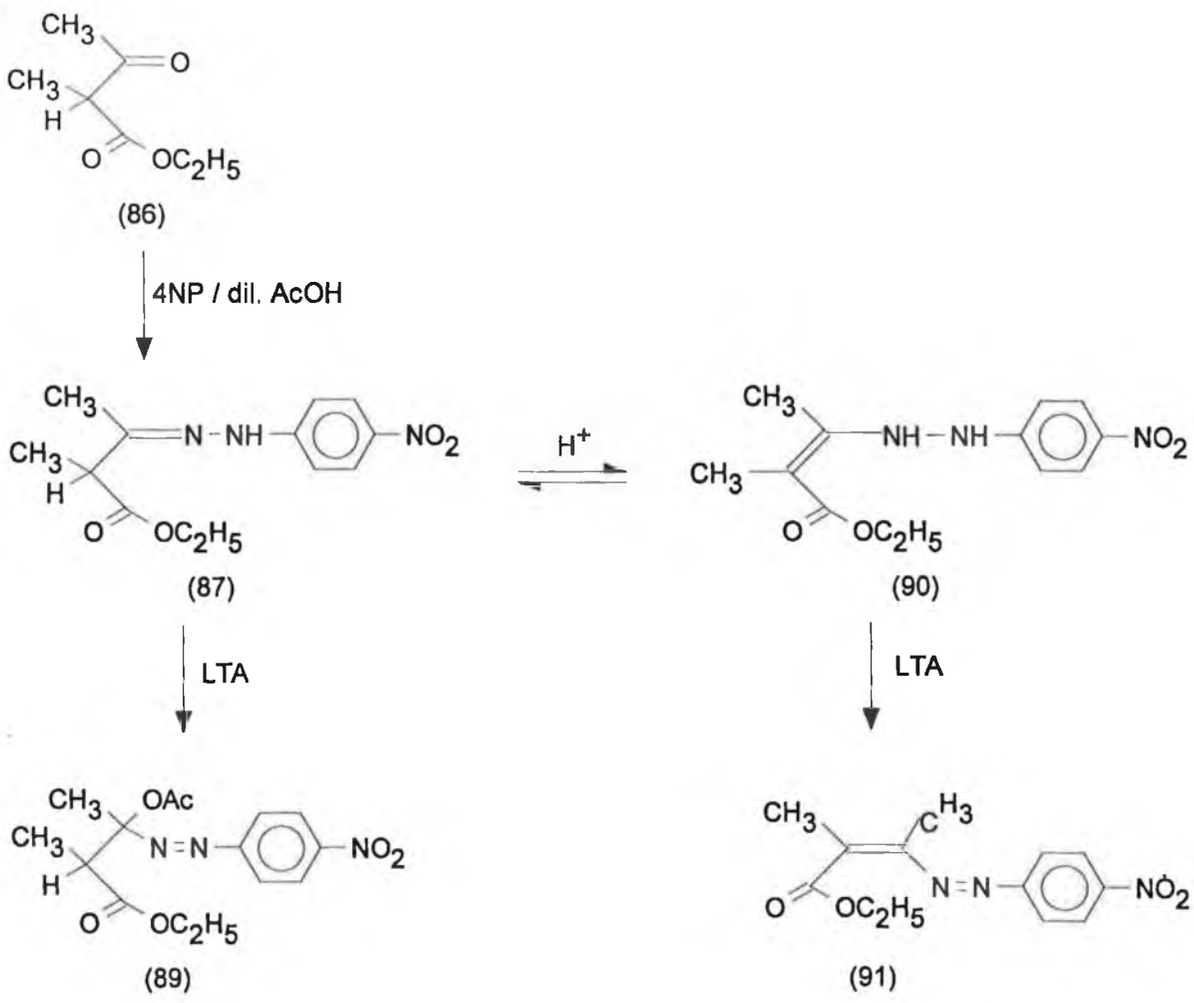


While attack by the azo group on both (87a) and (87b) gives rise to diasteromers, the major product in each case will result from attack at the least hindered side[72]. Thus the expected products are the major isomers *i.e* the enantiomers (87ai) and (87bi).

This is indicated by the twin set of peaks visible on the ^1H NMR. Possible separation of the diastereoisomers by crystallisation was hindered by the existence of the azoacetate as an oil.

The azoacetate (89) had resulted from acetoxylation of the hydrazone (87) in the presence of CH_2Cl_2. The reaction was then undertaken in acidic conditions. Thus the hydrazone (87), was dissolved in AcOH to which 1.2 equivalents of LTA were added. As for the non-methylated hydrazone (68), it is probable tautomerism between the hydrazone (87) and the ene-hydrazine (90) could be initiated in acidic conditions affording the azoalkene (91) exclusively or accompanied with azoacetate (89) as shown in scheme 1.46:

Scheme 1.46



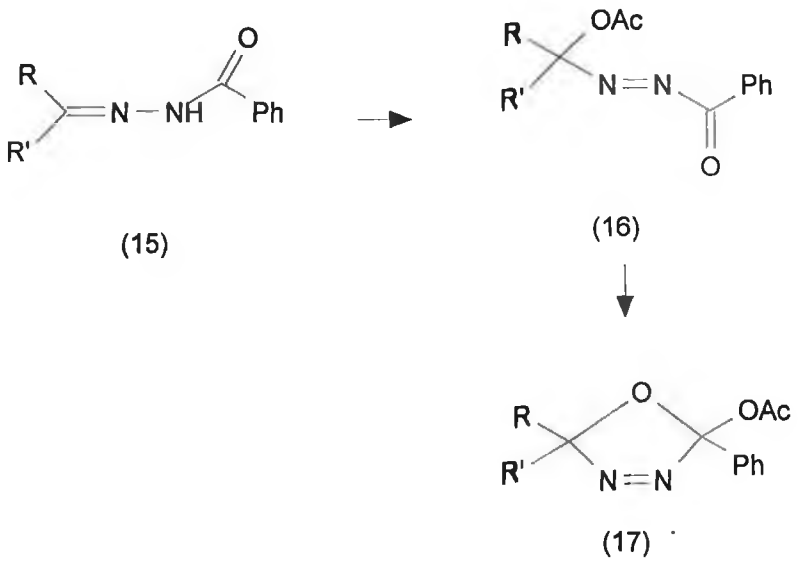
However the sole product isolated was the azoacetate (89) with no traces of azoalkene (91). Thus the electron-releasing ability of lone methyl group at the α-position is capable of reducing the lability of the enolisable methine proton.

Burdett and Rogers[73] have reported similiar effects following studies involving α-methylation of the parent ester, ethyl acetoacetate. Here, they report a large reduction in the percentage enol content observed when an alkyl group was introduced at the α position. When this effect is applied to (87), tautomerism to the ene-hydrazine (90) is discouraged, thus explaining the absence of the oxidation product (91) (Scheme 1.46).

1.2.2.1 Ketocarbonylhydrazones

The azoacetates (16) derived from ketocarbonyl hydrazones (15) are found to be very reactive and their isolation is usually difficult owing to the formation of 5-membered oxadiazolines (17) which may proceed to epoxide formation[13,14].

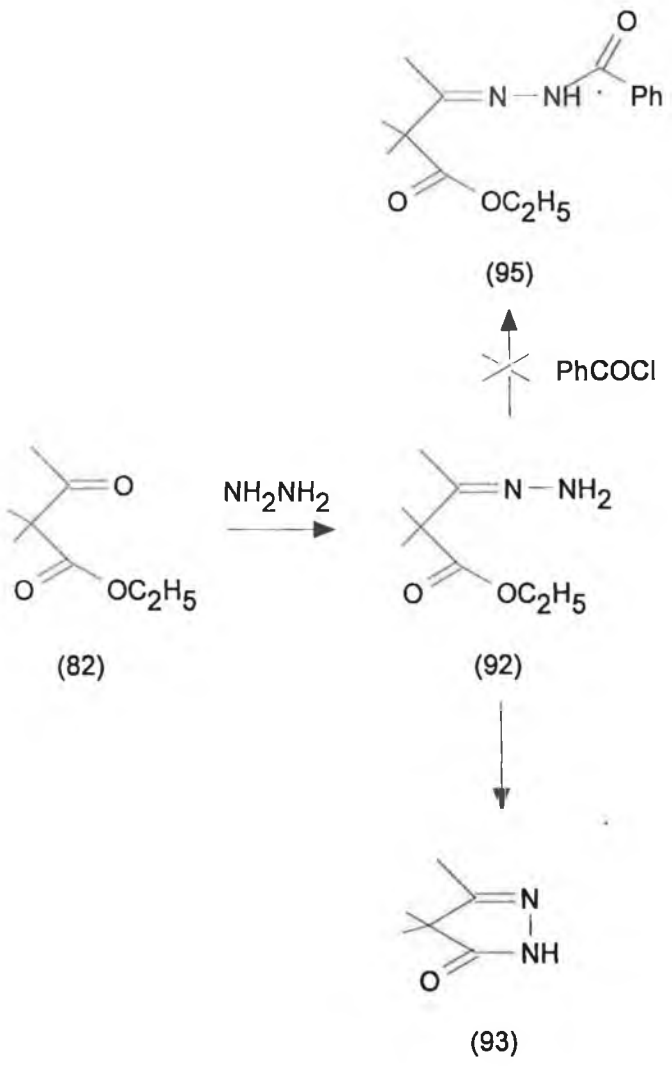
Scheme 1.47



Such a benzoyl hydrazone has being studied to examine the possibility of isolating the acyclic azoacetate which would prove a useful synthon for further work. Synthesis of the benzoyl hydrazone of α,α–dimethylethyl acetoacetate did not prove trivial.

The first approach involved the condensation of anhydrous hydrazine with the β-ketoester (82) followed by reaction of the resulting hydrazone (92) with benzoyl chloride (Scheme 1.48). However, the proven ability of the hydrazone to cyclise became evident allowing for the isolation of the pyrazol-5-one (93) before reaction with benzoylchloride was possible.

Scheme 1.48

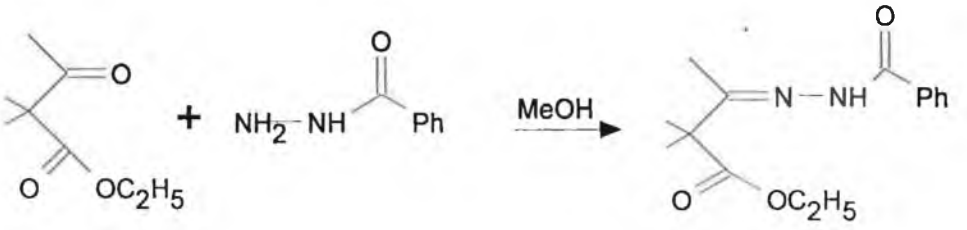


In order to eliminate such ring closure, condensation of α,α–dimethylethyl acetoacetate with benzoyl hydrazine was considered.

Condensation between the β-ketoester (82) and benzoyl hydrazine (94) (Scheme 1.49) did not occur in acetic acid or acetic acid:water dilutions. Similarly El-Sayed *et al.*[74] report difficulties with the condensation of N-phenyl, N-benzoyl hydrazine and ethyl acetoacetate. Their reaction required a temperature of 140°C in the presence of phosphorous pentoxide.

The most suitable conditions for the condensation of (82) with (94), were found to be gentle heating of the hydrazide and the β-ketoester overnight in methanol (Scheme 1.49) when the product (95) was isolated as a white precipitate in 60% yield.

Scheme 1.49



(82) (94) (95)

Initial attempts at oxidising (95) with LTA yielded a tar-like substance with no evidence of the azoacetate. Reports by Hogale *et al.*[62] indicate the use of such aroyl hydrazones for the isolation of substituted pyrazolones and related compounds. Likewise the easy cyclisation of benzoyl hydrazones to form oxdiazolines has been reported[13,14].

The above reaction was carried out in CH_2Cl_2 at ambient temperature, however none of the required azoacetate was evident. Further investigation would involve varying the temperature and oxidising agents to provide more temperate conditions.

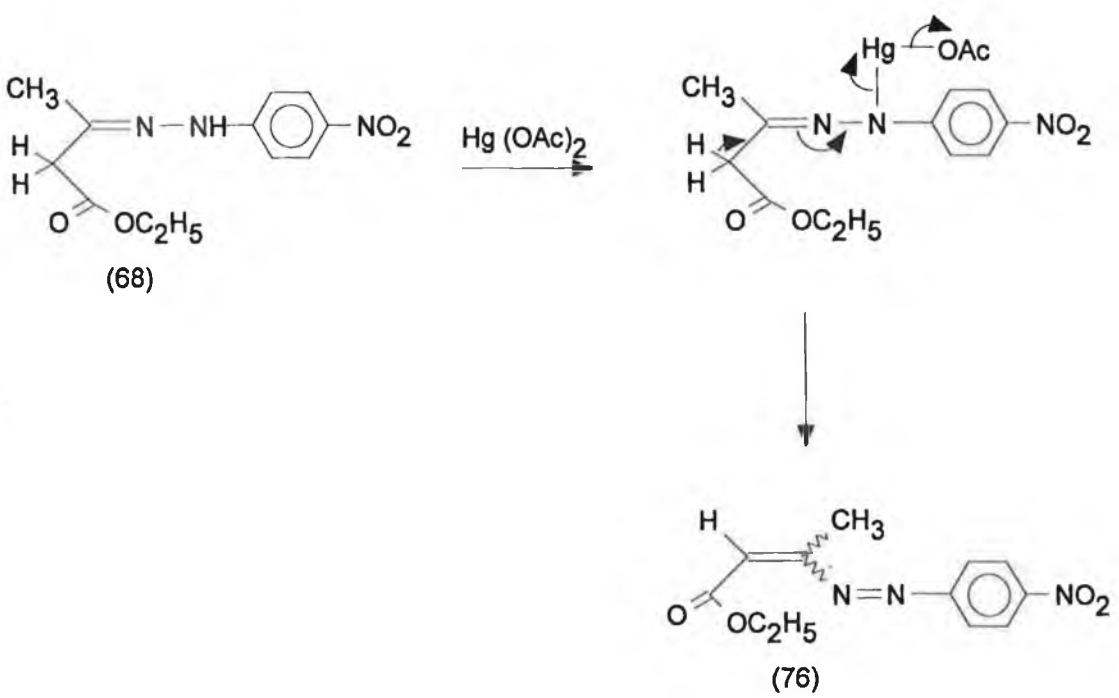
1.2.3 Mecuric Acetate oxidation of p-Nitrophenylhydrazones of β–Ketoesters.

In order to extend the range of oxidising agents, Mecury(II) acetate (MA), $Hg(OAc)_2$, was considered.

Oxidation of ethyl acetoacetate *p*-nitrophenylhydrazone (68) with MA in CH_2Cl_2 was investigated. While the same reaction was complete within minutes for LTA, this reaction required 7 hrs for an appreciable amount of product to be isolated. NMR analysis indicated azoalkene (76) formation, however the signals at 6.4ppm and 6.9ppm indicate the presence of both the Z-form and the E-form respectively (as outlined in Figure 1.1). Chomatography and recrystallation of the crude product yielded approximately equal amounts.

This can be explained by considering the mechanism proposed in scheme 1.50.

Scheme 1.50



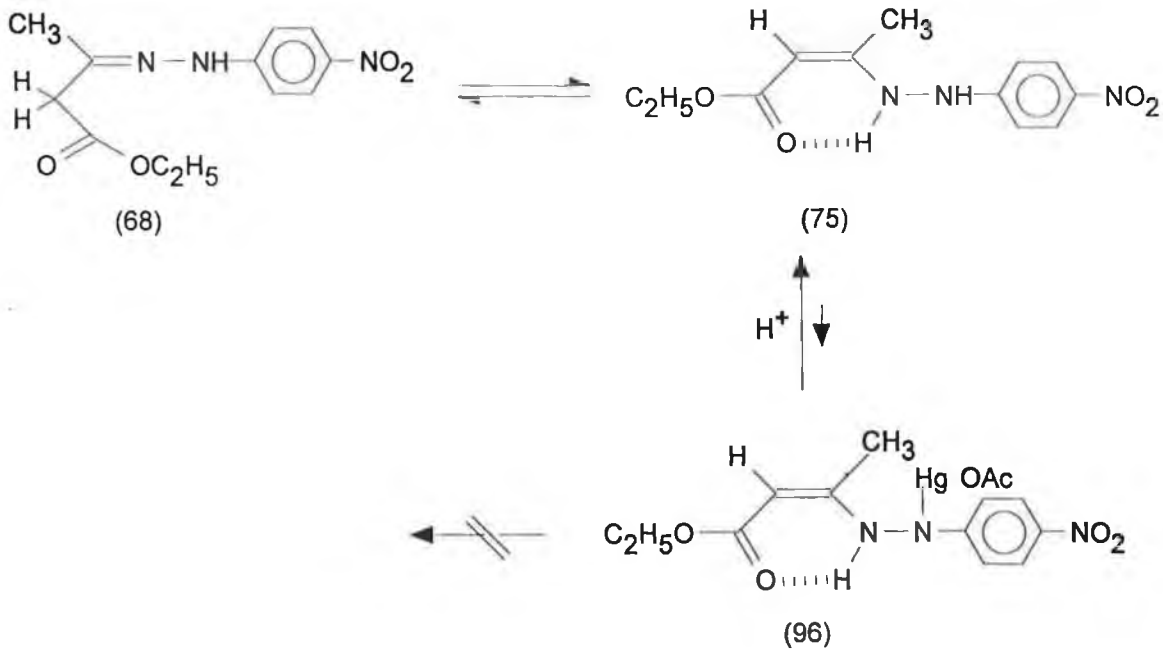
Here, as in the case of LTA, an N-metallo-intermediate is formed. However intramolecular acetoxylation does not occur for this weaker oxidising agent, instead formation of the N-metallo-intermediate is followed by a 1,4-elimination resulting in the azoalkene, which was subsequently isolated.

In this system, the intermediate is not restricted to intramolecular H-bonding, thus eliminating preference for a particular isomer of the resulting azoalkene (76). Hence both E- and Z-isomers are observed.

The reaction was repeated using AcOH as solvent. After stirring at room temperature for a number of hours, most of the starting material was recovered as hydrazone (68) or cyclised to the corresponding pyrazolin-5-one (69). However a small amount of inorganic material was also isolated. It was not possible to encourage reaction by applying heat as the hydrazone has proved its ability to cyclise rapidily under these conditions.

As already described, the acid conditions provide tautomerism between the hydrazone (68) and the enehydrazine (75) (Scheme 1.40), with the latter more susceptible to oxidation. This allows for the formation of the N-metallo intermediate (96) (Scheme 1.51), but proton exchange in acid conditions shifts the equilibrium back to (75), thus yielding starting material as the main product.

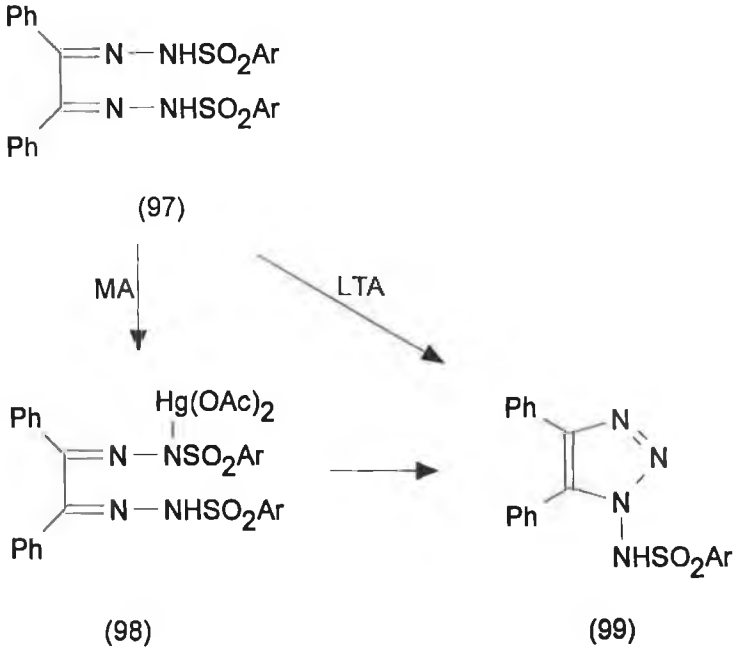
Scheme 1.51



The inorganic nature of the minor product isolated suggests that a small amount of the organometallic intermediate (96) has been isolated. This is quite plausible as there has been frequent detection of organomecury intermediates[20], unlike those of LTA.

The following reaction[66] outlined in scheme 1.52 represents one of the few cases where treatment of a substrate (97) with either of the reagents MA or LTA gives the cyclised product (99). However use of the reagent MA allows for the isolation of the N-metallo intermediate (98).

Scheme 1.52



The existence of the N-metallo intermediate for MA is also encountered in the oxidations of pyridine 2-carbaldehyde 2-pyridylhydrazone. Oxidations with a series of similar hydrazones using LTA yielded the fused 1,2,3-triazolium systems[10].

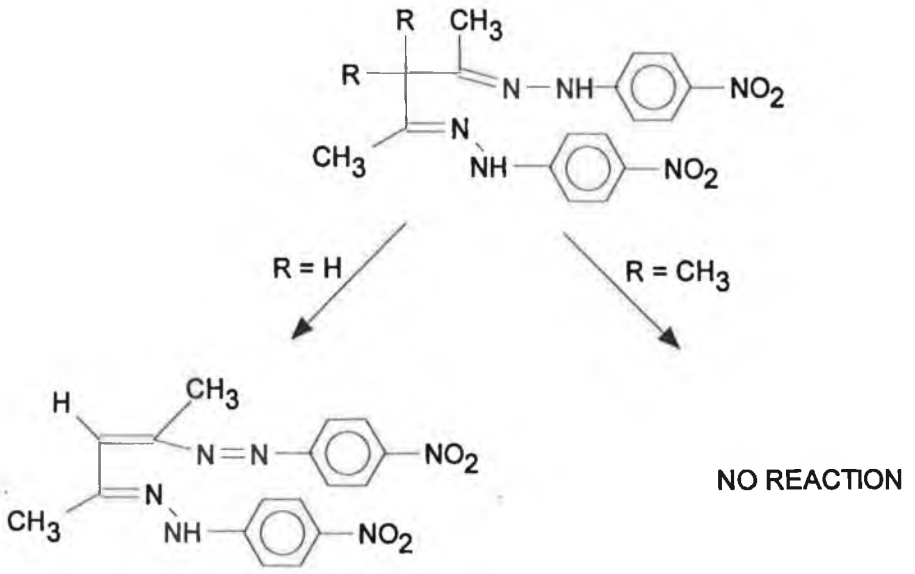
Monomethylation at the α-carbon of the β-ketoester had already proved sufficiently powerful in removing the lability of the enolisable proton, hence eliminating azoalkene formation. Thus the reaction of (87) with LTA, provided the azoacetate (89) alone.

Likewise the dimethylethyl acetoacetate *p*-nitrophenylhydrazone (83) has been investigated with LTA whereby azoalkene formation has not been possible thus providing azoacetate (85) as the sole product.

When (83) was stirred with MA in either CH_2Cl_2 or AcOH for several hours, no reaction was observed. The starting material was evident in both cases, thus highlighting the weaker oxidising ability of this reagent compared to LTA.

A similar contrast in the reactivity of unsubsituted and dimethylated substrates has been reported by Butler and James[75]. They found methylation eliminated the possibility of azoalkene formation. Thus for example, pentane-2,4-dione bis-(4-nitrophenylhydrazone) was readily oxidised to the azo-olefin by both $Hg(OAc)_2$ and $Pb(OAc)_4$ and proceeded to a pyrazole compound. The 3,3-disubstituted hydrazone formed the azoacetate in the presence of $Pb(OAc)_4$. However this derivative failed to react with $Hg(OAc)_2$ at room temperature, and the severe conditions resulting from reflux, merely caused decomposition.

Scheme 1.53



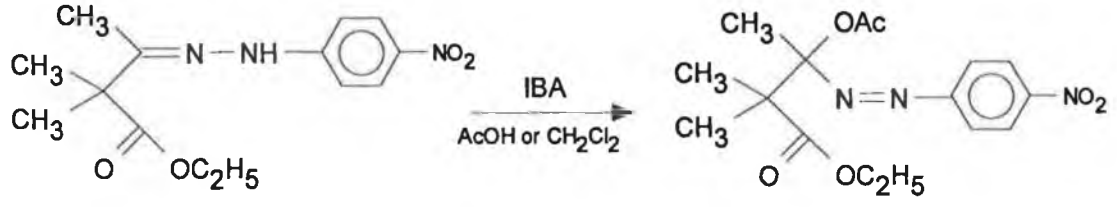
1.2.4 Iodobenzene diacetate as an alternative oxidising agent

While LTA has proved a useful oxidising agent, it has a number of drawbacks. It is a cumulative poison. It is readily absorbed through the skin from solutions with a threshold limit of 0.1-0.2mg / Litre[66]. This toxicity leads to severe handling and waste disposal problems, which also extend to MA. It is therefore desirable, on both environmental and health grounds, to replace these heavy metal reagents. The replacement sought had to be less hazardous, while mimicking the reactions of LTA.

Some of the reactions of IBA have been reviewed and notable similarities with LTA have become evident. These many similarities between IBA and LTA propelled us to consider the use of IBA instead of LTA, as an oxidising agent for hydrazones.

Oxidation of α,α-dimethylethyl acetoacetate *p*-nitrophenylhydrazone (83) has been conducted as follows (Scheme 1.54). When IBA was added to the hydrazone (83) in acetic acid, and the reaction monitored by t.l.c, the formation of the azoacetate (85) was observed. The product was isolated in 80%. The azoacetate was again isolated when the reaction was carried out in dichloromethane.

Scheme 1.54



(83) (85)

This represents the first report for the formation of azoacetates from hydrazones, using IBA.

The noticeable difference in using IBA as opposed to LTA, was the reaction time. While the oxidation is complete within minutes using LTA, there is a slow accumulation of azoacetate with IBA. The weaker oxidising ability of IBA has been noted . However the latter reagent gave a product that was much easier to isolate[76] with the noticeable absence of hazardous inorganic by products.

Consequently, initial studies are promising for the use of IBA as an acetoxylating agent *in lieu* of LTA. Extended use of IBA may render the more hazardous LTA redundant in many cases.

In summary, the *p*-nitrophenyl hydrazones of ethyl acetoacetate and its derivatives have been synthesised and isolated. Their ability to readily cyclise to the corresponding 5-membered pyrazoles has been observed. Thus the acidity of the solvent, to ensure isolation of the hydrazone before continuing to cyclise, was paramount.

The cyclisation products, the pyrazoles, have also been isolated and characterised. A number of hydrazones have been acetoxylated to the azoacetates using the oxidising agents, LTA and, more notably, IBA. The oxidising ability of MA has also been studied.

The study also demonstrates that when there is an enolizable proton present on the hydrazone, the oxidation product may be an azoalkene. It is discovered, azoalkene formation is predetermined by an acid medium, which tautomerises the hydrazone. Thus azoacetate formation is ensured by choosing a neutral solvent during oxidation. A number of azoacetates have been isolated which will now prove useful synthons for further study.

1.3 EXPERIMENTAL

Common reagent grade chemicals were purchased from Aldrich Chemical Company. LTA was washed with petroleum ether (40-60°C) /diethyl ether under suction immediately before use. The NaH used was an 80% suspension in oil, and was washed as for LTA.

Melting points were determined in open capillary tubes with a Gallenkamp melting point apparatus and are uncorrected.

NMR spectra were measured for solutions in $CDCl_3$ or DMSO-d_6 with Perkin-Elmer R12B 60MHz or Bruker AC-F 400MHz spectrometers, and referenced to tetramethylsilane.

IR spectra were recorded for KBr discs or nujol mulls on a Perkin-Elmer 983-G spectrometer or a Nicolet 205 FT-IR.

Thin layer chromatography (t.l.c) was carried out using silica gel t.l.c plates containing a fluorescent indicator (Riedel de Haen, δ_c cards SiF, layer thickness 0.2mm). Riedel de Haen silica gel (0.032 - 0.063mm) was used for column chromatography.

Mass spectra were recorded on a VG12 250 Mass spectrometer.

Elemental analyses were performed in the Microanalytical Laboratory, University College Dublin.

CHAPTER 1

EXPERIMENTAL PROCEDURES

(i) Preparation of ethyl acetoacetate *p*-nitrophenylhydrazone (68)

1g (7.7 mmoles) of ethyl acetoacetate was added to a solution of 4NP (*p*-nitrophenyl hydrazine) dissolved in a mixture of acetic acid (25mls) and water (5mls). The solution was stirred for 5 minutes. The product was collected as a yellow precipitate and washed with a little water followed by pet-ether (40:60) (yield: 1.8g; 95%).

MP 110-111°C.

IR 3314, 1720 cm^{-1}.

^1H NMR (60 MHz;DMSO-d_6) δ 1.1 (t, 3H), 1.9 (s, 3H), 3.2 (s, 2H), 4.0 (q, 2H), 7.0 (d, 2H), 7.9 (d, 2H), 9.8, (s, 1H).

(ii) Synthesis of 1-(*p*-nitrophenyl)-3-methyl-2-pyrazoline-5-one (69)

1g (3.77 mmoles) of hydrazone (68) was heated under reflux in AcOH (15mls) for 5 minutes. On cooling a beige product crystallised from solution (yield: 0.74g; 90%).

MP 210-211°C.

IR 1620 cm^{-1}.

^1H NMR (400 MHz;DMSO-d_6) δ 2.14 (s, 3H), 5.42 (s, 1H), 8.05 (d, 2H, J=8.8 Hz), 8.30 (d, 2H, J=8.8 Hz).

$C_{10}H_9N_3O_3$ requires C, 54.79; H, 4.14; N, 19.17%,

Found C, 54.67; H, 4.12; N, 19.14%.

(iii) Oxidation of hydrazone (68) with LTA in CH_2Cl_2

1g (3.7 mmoles) of hydrazone (68) was dissolved in CH_2Cl_2 (20mls) to which 2.0g (4.5 mmoles; 1.2 equiv) LTA was added. The solution was stirred for 40 minutes when t.l.c monitoring indicated completion. The reaction was washed with a saturated $NaHCO_3$ solution. The lead salts were filtered through a short silica column and the water layer extracted with CH_2Cl_2 (25mlsx3). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure yielding the azoacetate (74) as a red-brown oil (yield:1g; 90%). The oil persisted following recrystallisation (EtOH) and chromatography (EA:PE; 30:70).

IR 1741 cm^{-1} (broad).

^1H NMR (60 MHz;$CDCl_3$) δ 1.25 (t, 3H), 1.75 (s, 3H), 2.25 (s, 3H), 3.2 (d, 2H), 4.15 (q, 2H), 7.8 (d, 2H), 8.3 (d, 2H).

$C_{14}H_{17}N_3O_6$ requires C, 52.1; H, 5.3; N, 13.0%,
found C, 52.1; H, 5.3; N, 12.96%.

(iv) Oxidation of hydrazone (68) with LTA in acetic acid

2g (4.5 mmoles; 1.2 equiv) of LTA was added to 1g (3.77 mmoles) of hydrazone (68) dissolved in AcOH (30mls). The resultant deep red solution was stirred at room temperature for 30 minutes and then added to water (50mls) which caused the product to precipitate as a red solid. It was purified by extracting into diethyl ether. The ether layers were washed with $NaHCO_3$ solution, dried over $MgSO_4$ and the solvent evaporated under reduced pressure yielding the azoalkene (76), as a red precipitate (yield: 0.57g; 60%).

MP 76-78°C.

IR 3100, 1709, 1625 cm^{-1}.

^1H NMR (60 MHz;DMSO-d_6) δ 1.3 (t, 3H), 2.1 (s, 3H), 4.3 (q, 2H), 6.4 (s, 1H), 7.9 (d, 2H), 8.3 (d, 2H).

$C_{12}H_{13}N_3O_6$ requires C, 54.75; H, 5.0; N, 15.96%,
found C, 54.58; H, 5.12; N, 15.49%.

(v) Preparation of monomethylethyl acetoacetate-
-*p*-nitrophenylhydrazone (87)

[Note: This hydrazone was prepared from commercially available monomethylethyl acetoacetate (86)].The preparation was similar to that of (68), with the hydrazone (87) collected as a fine yellow powder in 85% yield.

MP 102-104 °C.

IR 3331, 1716, 1595 cm^{-1}.

^1H NMR (60 MHz;$CDCl_3$) δ 1.3 (t, 3H), 1.4 (d, 3H), 2.0 (s, 3H), 3.5 (q, 1H), 4.2 (q, 2H), 7.1 (d, 2H), 7.7 (s, 1H), 8.1 (d, 2H).

(vi) Synthesis of 1-(4-nitrophenyl)-3,4-dimethyl-2-pyrazolin-5-one (88)

This pyrazolin-5-one was prepared by the method described in **(ii)** to yield the product (88) as a fine yellow powder in 78%.

MP 237-238 °C.

IR 3120, 1638 cm^{-1}.

^1H NMR (60 MHz;DMSO-d_6) δ 1.7 (s, 3H), 2.0 (s, 3H), 7.9 (d, 2H), 8.1 (d, 2H).

$C_{11}H_{11}N_3O_3$ requires C, 56.65; H, 4.22; N, 18.02%,
found C, 56.55; H, 4.51; N, 18.01%.

(vii) Oxidation of hydrazone (87) with LTA in CH_2Cl_2

1g (3.58 mmoles) of hydrazone (87) was suspended in of CH_2Cl_2 (30mls) to which 1.75 g (3.94 mmoles; 1.1equiv) of LTA were added. After 15 minutes stirring at room temperature, $NaHCO_3$ solution (20mls) were added. The lead salts were removed by filtration and the aqueous layer extracted into diethyl ether. The combined organic layers were further purified by passing through a short silica column and the ether removed under reduced pressure yielding a sticky red oil (yield: 0.98g; 82%).

The product (89) appeared as one major spot on t.l.c with a partially superimposed minor spot, (which proved inseparable by flash chromatography (EA:PE; 70:30). The appearance of two almost indistinguishable products by t.l.c is attributed to a mixture of

diastereoisomers, also indicated by the presence of shadow peaks in the ^1H NMR spectrum.

^1H NMR (60 MHz;$CDCl_3$) δ 1.05 (t, 3H), 1.15 (d, 3H), 1.7 (s, 3H), 1.95 (s, 3H) 3.1 (q, 1H) 4.0 (q, 2H), 7.6 (d, 2H), 8.15 (d, 2H).

(viii) Oxidation of hydrazone (87) with LTA in AcOH

1g (3.58 mmoles) of hydrazone (87) was dissolved in AcOH (25 mls). 1.75g (3.94 mmoles; 1.1 equiv) of LTA were added to the red solution and stirred for 20 minutes. The reaction mixture was added to H_20 (30mls) and the organic layer extracted into diethyl ether. The combined ether extracts were washed with saturated $NaHCO_3$ solution to remove any acetic acid, separated, dried over $MgSO_4$ and the solvent removed under reduced pressure to yield the azoacetate (89) as a red oil in 85% yield.

^1H NMR (60 MHz;$CDCl_3$) δ 1.1 (t, 3H), 1.20 (d, 3H), 1.75 (s, 3H), 2.0 (s, 3H) 3.15 (q, 1H) 4.05 (q, 2H), 7.65 (d, 2H), 8.2 (d, 2H).

(ix) Synthesis of dimethylethyl acetoacetate (82)

Method (a):

Monomethylethyl acetoacetate (86) (10g; 69 mmoles) was added to acetone (60mls) containing 28.8g (21 mmoles;3 equiv) of anhydrous potassium carbonate and 59g (42 mmoles; 4 equiv) of methyl iodide. The solution was heated under reflux gently for 42 hours when t.l.c monitoring indicated the reaction was complete (note: A further 15g (7mmoles;1 equiv) of methyliodide was added at intervals during the reaction). Water (100mls) was added and the organic layer extracted into diethyl ether. The organic extracts were then dried over $MgSO_4$ and evaporated under reduced pressure to yield the product as a pale yellow liquid (8.7g, 80%).

^1H NMR (270MHz;$CDCl_3$) δ 1.2 (t, 3H), 1.3 (s, 6H), 2.1 (s, 3H), 4.1 (q, 2H).

Method (b):

Sodium hydride (NaH; 80% suspension) (1.65g; 54.36 mmoles; 1.3equiv) was washed with pet-ether and added to DMSO (50mls) carefully over 30

minutes forming a grey sludge. The ester (86) (6.1g; 42 mmoles) was added slowly and stirred for 2 hours. 12g of methyl iodide (84 mmoles; 2.0 equiv) was then added slowly turning the green solution to brown with a temperature rise to 40°C. The reaction was stirred at room temperature for 6 hours and then slowly added to water (100mls) with stirring. The organic material was extracted into diethyl ether and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a pungent yellow liquid. Purification by distilling over a short column (under vacuum ;119-120°C) yielded the dimethylated β-ketoester (82) (4g ; 25 mmoles; 60%).

(x) Preparation of dimethylethyl acetoacetate *p*-nitrophenylhydrazone (83)

This hydrazone (83) was prepared as described in **(i)** in an 85% yield.

MP 132-133°C

IR 3320, 1707, 1603 cm^{-1}.

^1H NMR (60 MHz;DMSO-d_6) δ 1.25 (t, 3H), 1.9 (s, 3H), 4.2 (q, 2H), 7.1 (d, 2H), 7.55 (s, 1H), 8.15 (d, 2H).

(xi) Preparation of 1-(4-nitrophenyl)-3,4,4-trimethyl-2-pyrazolin-5-one (84)

1g (3.41 mmoles) of hydrazone (83) was heated under reflux in AcOH (25mls) for 20 minutes. The solution was then allowed to cool when dropwise addition of water precipitated the product as a pale orange powder (yield:0.65g; 77%).

MP 130-131°C.

IR 1718 cm^{-1}.

^1H NMR (60 MHz;DMSO-d_6) δ 1.15 (s, 6H), 2.0 (s, 3H), 7.9 (d, 2H), 8.0 (s, 1H), 8.1 (d, 2H).

$C_{12}H_{13}N_3O_3$ requires C, 54.29; H, 5.26; N, 17.0%,

found C, 54.26; H, 5.25; N, 17.03%.

(xii) Oxidation of hydrazone (83) with LTA in CH_2Cl_2

The hydrazone (83) was converted to the azoacetate (85) as a crude product in 95% yield using the procedure described in **(iii)**. An oil persisted following purification by chromatography (EA:PE; 3:7) and attempted crystallisation.

IR 2987, 1745, 1729, 1612 cm^{-1}.

^1H NMR (60 MHz;$CDCl_3$) δ 1.25 (t, 3H), 1.3 (s, 6H), 2.0 (s, 3H), 2.1 (s, 3H), 4.1 (q, 2H), 7.7 (d, 2H), 8.2 (d, 2H).

$C_{16}H_{21}N_3O_6$ requires C, 54.70; H, 6.03; N, 11.96%,

Found C, 54.44; H, 6.31; N, 11.62%.

(xiii) Oxidation of hydrazone (83) with LTA in AcOH.

The reaction was performed as outlined in **(viii)** providing the azoacetate (85) as a red oil in 90% yield.

IR 2972, 1750, 1730, 1610 cm^{-1}.

^1H NMR (60 MHz;$CDCl_3$) δ 1.3 (t, 3H), 1.35 (s, 6H), 2.2 (s, 3H), 2.25 (s, 3H), 4.1 (q, 2H), 7.75 (d, 2H), 8.25 (d, 2H).

(xiv) Oxidation of hydrazone (68) with $Hg(OAc)_2$ in AcOH.

1g (3.8 mmoles) of (68) was dissolved in AcOH (40mls) to which 1.45g (4.5 mmoles; 1.2 equiv) MA were added. The reaction was followed by t.l.c. (EA:PE; 2:8) which indicated traces of starting material (68), cyclised pyrazolinone (69) and baseline product, after 10 hours. The reaction was extracted into ethyl acetate:diethyl ether (50:50), washed with a saturated $NaHCO_3$ solution and the organic layers dried over $MgSO_4$ and the volume reduced when the hydrazone (68) and pyrazolinone (69) were precipitated from solution as a mixture. Crude separation indicated approximate amounts of (68) and (69) in 14% and 60% yields respectfully. The remaining solution was evaporated to dryness and passed through a short silica column when a black inorganic powder remained, insoluble in $CHCl_3$ or DMSO.

MP 286-289°C.

IR 1623,1584 cm^{-1}.

(xv) Oxidation of hydrazone (68) with $Hg(OAc)_2$ in CH_2Cl_2

1g (3.8 mmoles) of hydrazone (46) was suspended in CH_2Cl_2 (50mls) to which 1.45g (4.5 mmoles; 1.2 equiv) $Hg(OAc)_2$ were added. The reaction was stirred for 7 hours when t.l.c analysis indicated only traces of starting material. $NaHCO_3$ solution (20mls) was added and the reaction filtered. The red filtrate was evaporated to yield 0.7g of a sticky powder. This was redissolved in diethyl ether:ethylacetate (80:20). Pet-ether was added dropwise which caused precipitation of a red powder which proved to be the azoalkene in the *Z*-form (76i) (yield: 0.4g; 40%).

The remaining solution was chromatographed on a silica gel column, eluting with ethyl acetate:pet-ether (60:40), which yielded a pale red powder, identified as the *E*-isomer (76ii) (yield 0.34g ;34%).

IR 1709, 1602 cm^{-1}.

^1H NMR (60 MHz;$CDCl_3$) δ 1.2 (s, 3H), 1.35 (t, 3H), 2.35 (s, 3H), 4.25 (q, 2H), 6.95 (s, 1H) 7.9 (d, 2H), 8.25 (d, 2H).

(xvi) Oxidation of hydrazone (83) with IBA in AcOH

Dimethylethyl acetoacetate *p*-nitrophenylhydrazone (2g; 6.8 mmoles) was dissolved in glacial acetic acid (30mls). 1.1 equiv IBA was added (2.4g; 7.5 mmoles). Monitoring by t.l.c indicated completion of the reaction after 2 hrs. The reaction mixture was then added to water (50mls) and extracted into diethyl ether (30mls x 3). The combined ether layers were washed with a saturated $NaHCO_3$ solution, extracted, dried over $MgSO_4$ (anhydrous), and evaporated to dryness under reduced pressure resulting in a sticky solid.

This crude product provided the azoacetate in 80% yield following chromatography using diethylether:ethyl acetate (95:5) as eluent. Chomatography allowed for the isolation of a mixture of two fast-running (relative large R_f values: 0.8-0.9) compounds. Analysis of this mixture inferred small amounts of unreacted iodobenzene diacetate, and iodobenzene.

IR 2990, 1740, 1725, 1605 cm^{-1}.

^1H NMR (60 MHz;$CDCl_3$) δ 1.2 (t, 3H), 1.3 (s, 6H), 1.8 (s, 3H), 2.1 (s, 3H) 3.9 (q, 2H), 7.7 (d, 2H), 8.2 (d, 2H) (Major product).

(xvii) Oxidation of hydrazone (83) with IBA in CH_2Cl_2

The procedure was as in **(xvi)**. However, in this case, the reaction mixture was not added to water upon completion. It was washed with a saturated solution of $NaHCO_3$, extracted and chomatographed as in **(xvi)**. This provided small amounts of iodobenzene diacetate and iodobenzene, separated from the azoacetate (85), which was isolated in 75% yield.

^1H NMR (60 MHz;$CDCl_3$) δ 1.2 (t, 3H), 1.3 (s, 6H), 1.7 (s, 3H), 2.0 (s, 3H), 3.8 (q, 2H), 7.65 (d, 2H), 8.2 (d, 2H) (Major product).

CHAPTER TWO

CHAPTER TWO

Introduction

2.1 Review of Carbon to Nitrogen Migration 1,2 Shifts

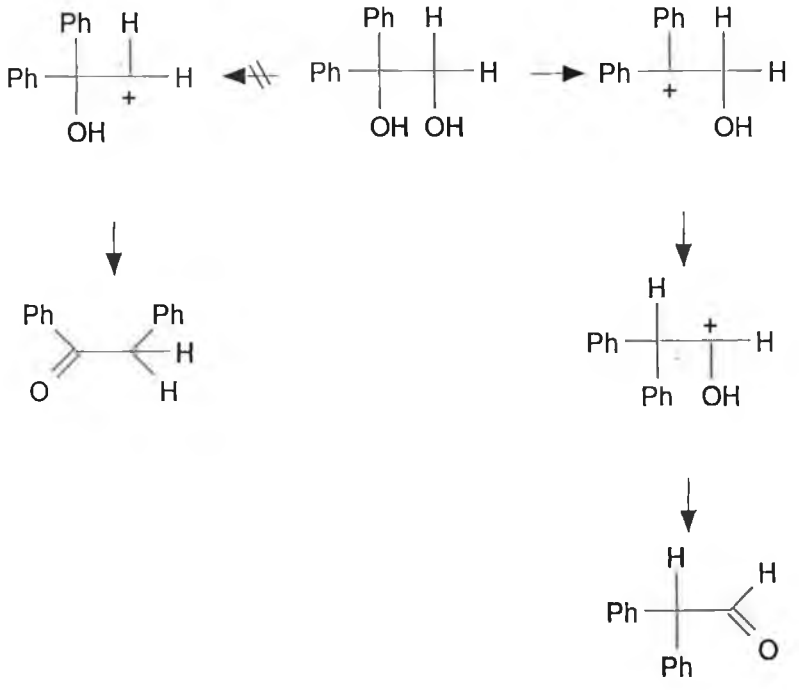
2.1.1 General review

Many rearrangements involve migration of an atom or group from one atom to another. There are many types, depending on how many electrons the migrating species carries with it. For example migration with an electron pair (nucleophilic), migration with one electron (free radical) and migration without electrons (electrophilic)[77].

Most nucleophilic 1,2 shifts are intramolecular. In some rearrangements there can be two or more potential migrating groups, however, the group which migrates is dictated by the geometry of the molecule. In cases where geometry is not restrictive the choice of migrating group is largely determined by which group is in the right place in the most stable conformation of the molecule. Such rearrangements allow for the study of relative migratory aptitude[77].

Thus for example, in the pinacol rearrangement the following two options are available but only one proceeds yielding (102) as the sole product[77] (Scheme 2.1).

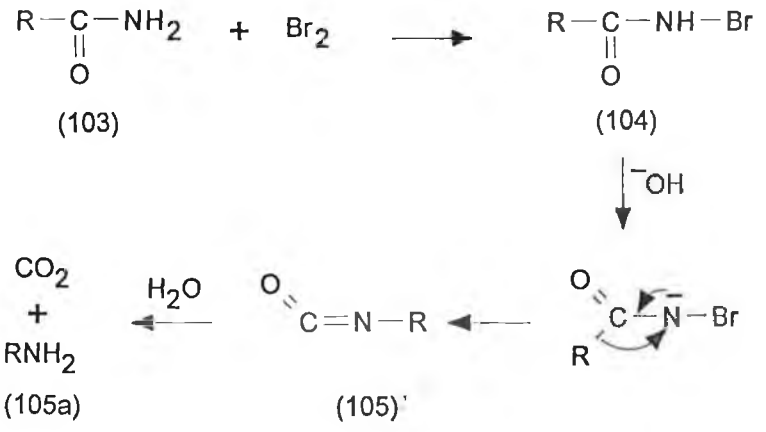
Scheme 2.1



The carbocation stability is enhanced by groups in the order
Aryl > Alkyl > Hydrogen, thus determining which carbon loses the hydroxy group.

Some typical carbon to nitrogen migrations are illustrated by the following[77]. The Hofmann rearrangement (Scheme 2.2) involves treatment of an unsubstituted amide (103) with bromine and sodium hydroxide to give a primary amine(105a)which has one carbon less than the starting amide.

Scheme 2.2

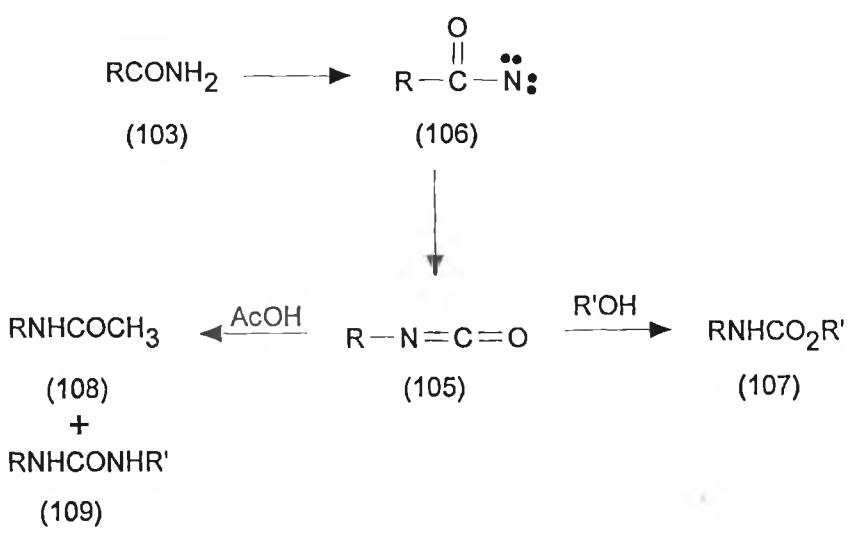


The actual product of the reaction is the isocyanate (105), but this compound is rarely isolated, as it usually hydrolyses under the reaction conditions to the amine (105a). Rearrangement proceeds with complete retention of configuration about the chiral centre of the migrating group as illustrated by α-phenyl propionamide. Therefore the chiral carbon of the R group (Scheme 2.2) does not break away from the carbonyl group until it has started to attach itself to the nitrogen, *i.e* intramolecular rearrangement is favoured over intermolecular rearrangement[78].

Baumgarten and Staklis[43] reported the oxidative rearrangement of simple amides using LTA that yielded products similar to those obtained from the Hofmann rearrangement. Under suitable conditions the amide could be converted into the corresponding isocyanate or derivatives there of (Scheme 2.3).

The isocyanate was isolated in neutral solvents such as DMF, however in different solvents the isocyanate reacts further. For example[41] when the reaction is conducted in *t*-butanol, *t*-butylcarbamates (107) are formed, while in benzene-acetic acid solvent, a mixture of acylamine (108) and dialkylurea (109) are formed. In neat acetic acid, dialkylurea formation is suppresed[40]. Consider for example[42], when pentamide was heated with LTA in benzene-acetic acid, the products N-butylacetamide (108;R:C_4H_9) and N,N'-dibutylurea (109;R:C_4H_9) were identified. A rearrangement involving a nitrene intermediate (106) was suggested[40,41], as follows:

Scheme 2.3



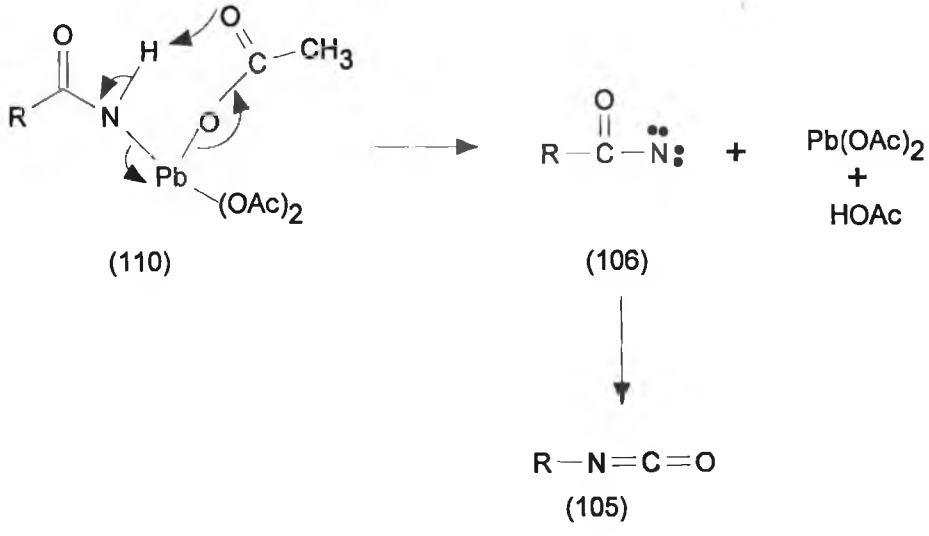
Acott *et al.*[41] extended the reaction of LTA with primary amides to alkylcarbamates in the hope of isolating the proposed nitrene, however its absence prompted the suggestion of an oxidative rearrangement of a tetravalent lead-amide complex[41]. Such a lead-amide complex (110) was seen to exist in equilibrium with the reactants[42] as follows:

Scheme 2.4

(110)

This decomposition may involve intramolecular proton transfer through a six membered cyclic transition state[42] (Scheme 2.5).

Scheme 2.5

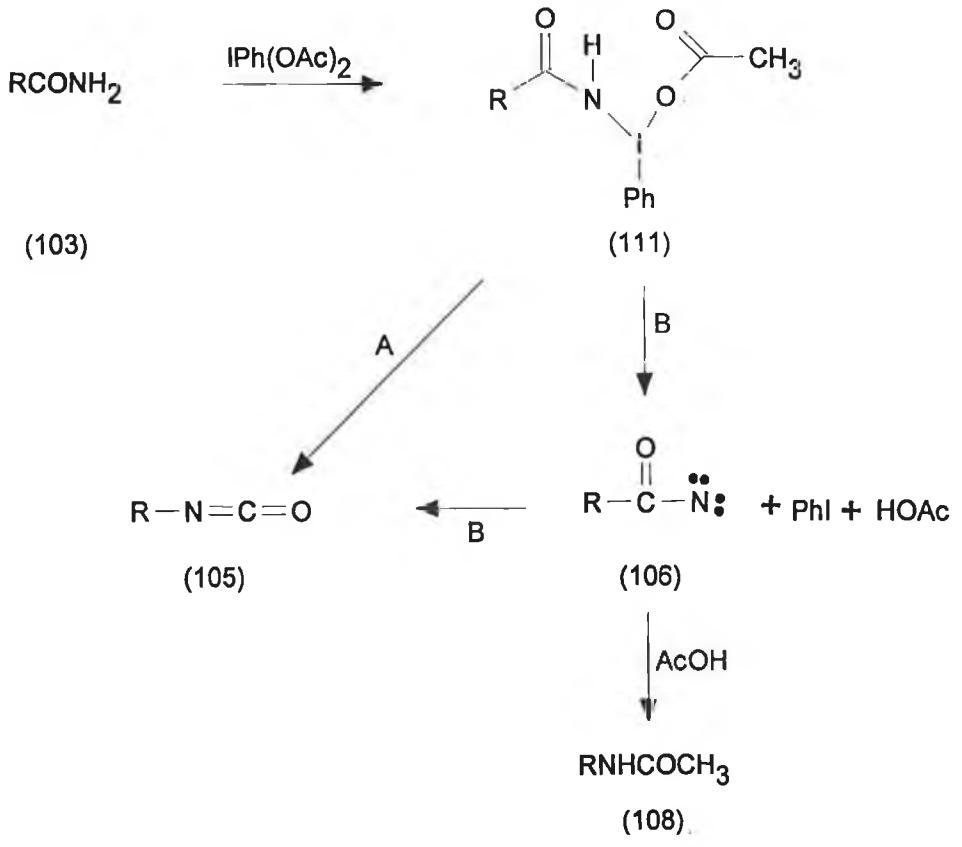


(110) (106) (105)

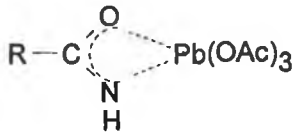
Despite the evidence in support of this mechanism, the authors were unable to obtain unambigious proof for the existence of the nitrene intermediate[42]. The favoured mechanism is the concerted oxidative rearrangement of the lead-amide complex (110) to the isocyanate (105) substantiated by the following observations.

Swaminathan et *al.*[44] reports the ability of IBA to effect a similar conversion of primary amides to acylamines in acetic acid (Scheme 2.6). The proposed mechanism includes an iodine-amide complex (111) which rearranges to the isocyanate and proceeds to the acylamine (108) in acetic acid.

Scheme 2.6



Following kinetic studies, the concerted one-step rearrangement (A) is favoured over the 2-step route (B), the latter incorporating nitrene formation. Baumgarten[79] suggests amide conversion to the isocyanate effected by LTA involving the lead-amide complex (110), may involve a resonance intermediate in which the lead is partially bonded to both the nitrogen and the oxygen as follows:



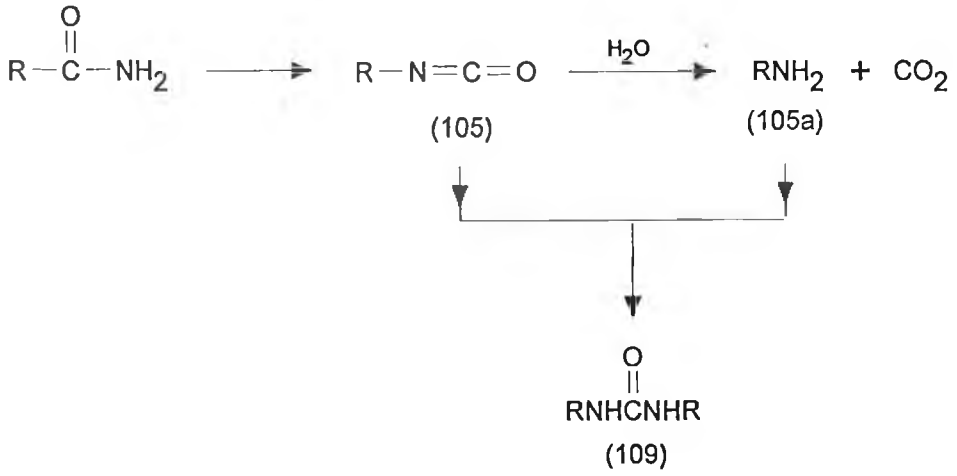
Baumgarten[79] established that the reaction involving LTA proceeds with retention of configuration by conversion of *trans*-2-phenylcyclopropane carboxamide (112) into *tert*-butyl N-(*trans*-2-phenylcyclopropyl) carbamate (113).

Scheme 2.7

(112) (113)

The use of 1,1-bis(trifluroacetoxy) iodobenzene (PIFA) is found to bring about the conversion of carboxylic acid amides to amines[80] without the necessity of trapping or isolating the intermediate isocyanate (Scheme 2.8). The isocyanate (105) can react with the amine produced to form the symmetrical urea (109), also reported for rearrangement effected by IBA or LTA, as follows:

Scheme 2.8



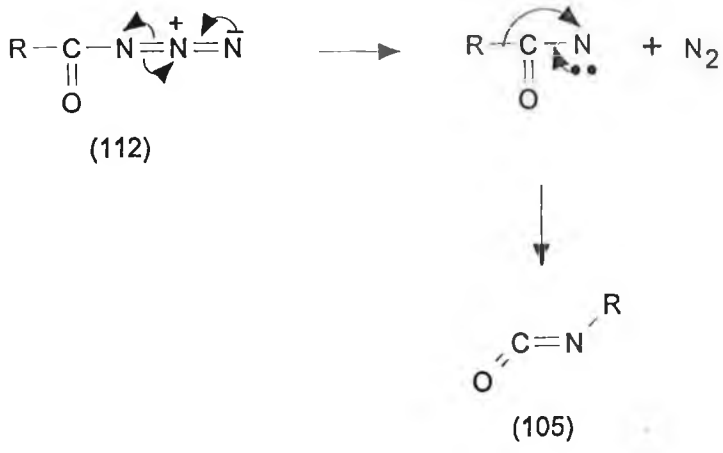
However PIFA provides conditions which are sufficiently acidic to eliminate urea formation, while catalysing isocyanate hydrolysis[46].

Kinetic studies as reported by Boutin *et al.*[46] indicate that the rate for various migrating groups is quantitatively similar to that observed in similar reactions such as the Lossen rearrangement, the Hofmann rearrangement and the Baeyer-Villiger reaction.

The rearrangement of amides to amines proceeds with retention of stereochemical configuration at the migrating carbon[45].

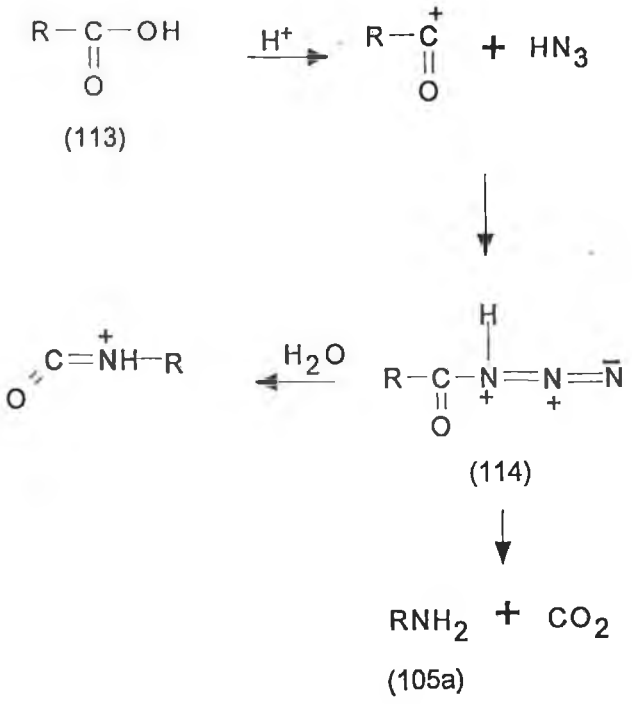
The Curtius rearrangement (Scheme 2.9) involves the pyrolysis of acylazides (112) to yield isocyanates (105) involving a migration from C to N.

Scheme 2.9



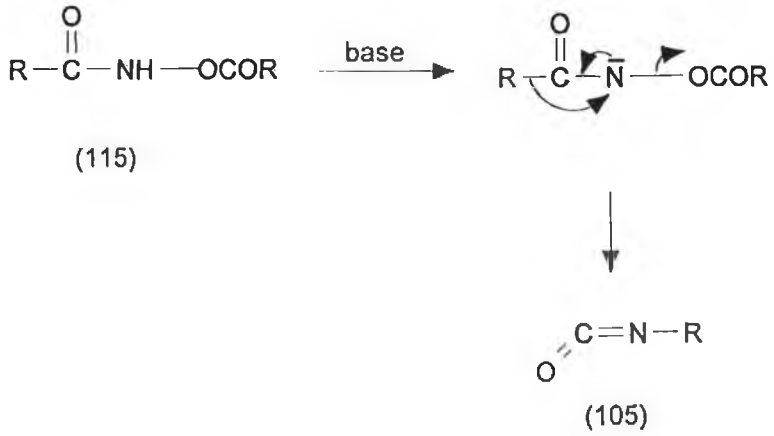
Similarily the Schmidt reaction (Scheme 2.10) involves the inversion of carboxylic acid (113) to amine(105a). The reaction is similar to the Curtius rearrangement except that it is the protonated azide (114) that undergoes the rearrangement.

Scheme 2.10



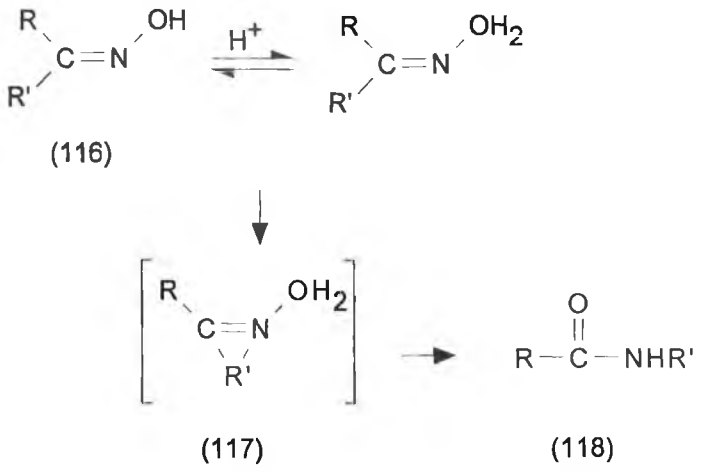
In a similar manner the Lossen rearrangement (Scheme 2.11) also yields isocyanates (105) resulting from the O-acyl derivatives of hydroxamic acids (115).

Scheme 2.11



Carbon to nitrogen migration is also illustrated by the Beckmann rearrangement (Scheme 2.12). When the oximes (116) are treated with PCl_5 or a number of other reagents they rearrange to substituted amides (118).

Scheme 2.12

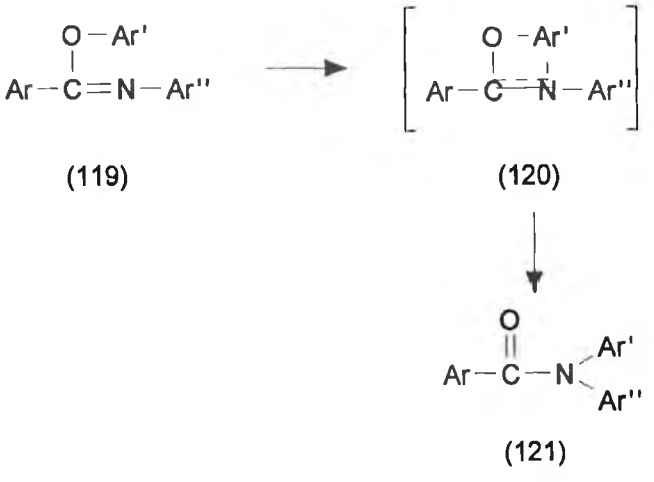


(116) (117) (118)

The group that migrates is generally the one anti as illustrated by the pseudo three-membered transition state (117).

When the carbon of an amine contains an aryloxy group (119) a ketone results with the carbon to nitrogen double bond being reduced to a single bond (121). This, the Chapman reaction[81,82] (Scheme 2.13), is essentially an intramolecular nucleophilic displacement on an aromatic ring involving carbon to nitrogen migration. The reaction is brought about thermally, while higher temperatures are required for rearrangement of alkyl imidates which are found to be intermolecular.

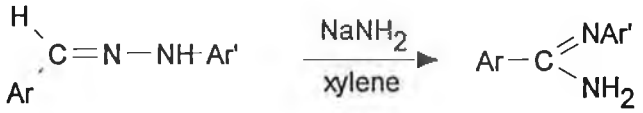
Scheme 2.13



(119) (120) (121)

Likewise it has been found that the phenylhydrazones of aromatic aldehydes are converted to amidines when treated with either sodium amide or phenyllithium in boiling xylene as follows.

Scheme 2.14

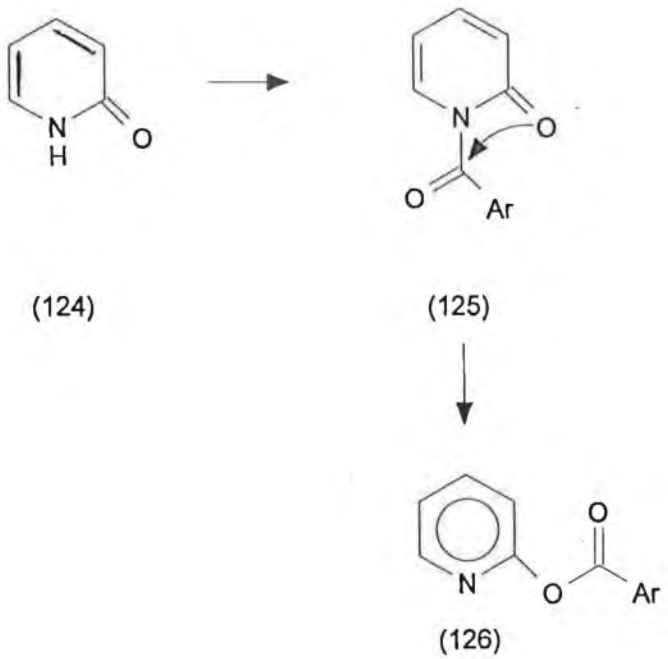


(122) (112)

Cross over experiments show this reaction, the Robev rearrangement[82] (Scheme 2.14), to have intermolecular characteristics and a radical mechanism is proposed.

An aroyl migration is proposed by Curtin and Miller[83] as they speculate the O-acylation of 2-pyridone (124) may proceed via an N- to O- rearrangement (Scheme 2.15).

Scheme 2.15



(124) (125)

(126)

2.1.2 AZOACETATES

We have seen in chapter one that azoacetates result from the oxidation of a variety of hydrazones by LTA or IBA. It was found that the choice of solvent and the substitution pattern of the hydrazone were deciding factors for azoacetate formation.

Consider the findings of Gladstone *et al.*[8] when they studied a variety of azoacetates in acidic and basic medium. Thus, for example, the aryl hydrazones of aromatic ketones have been converted into azoacetates by LTA which undergo cyclisation in the presence of Lewis acids to 1-arylindazoles. The yield of indazole varies widely, depending on the structure of the azoacetate, the nature of the Lewis acid and the temperature of the reaction[5].

The azoacetates derived from the oxidation of benzil phenylhydrazone and *p*-nitrophenylhydrazone with LTA react quite differently when treated with boron trifluoride compared with the azoacetates obtained from aromatic ketone hydrazones, as reported by Gladstone *et al.* [11,12].

It was reported the azoacetate (12a) derived from benzil monophenylhydrazone, gives mainly N,N'-dibenzoylphenylhydrazine (14a) when treated with boron trifluoride[11] *via* a rearrangement as illustrated in scheme 1.9a.

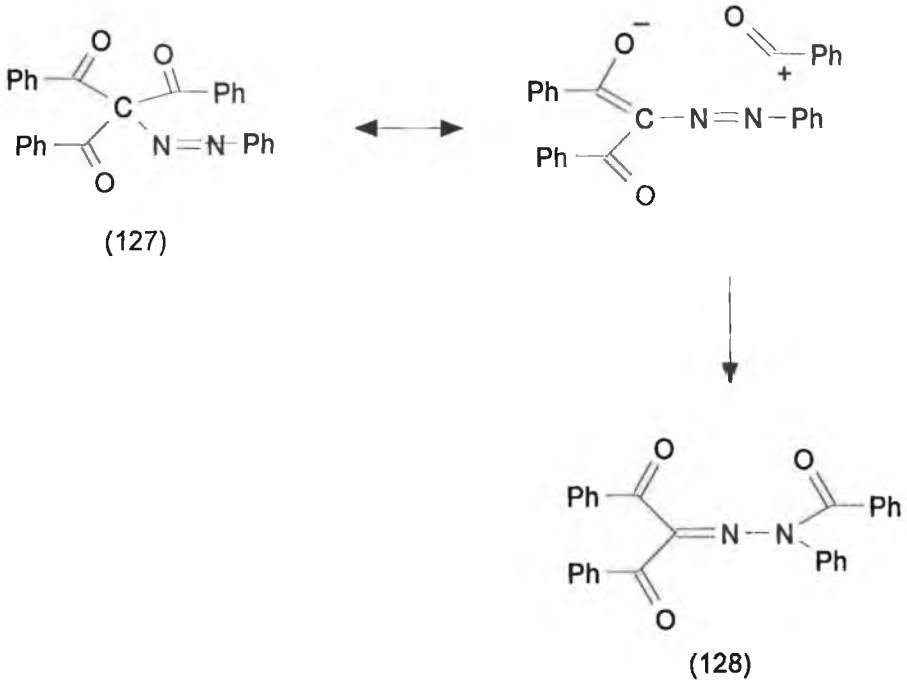
Scheme 1.9a

(12a) (14a)

The Lewis acid encourages removal of the acetoxyl group followed by migration of the benzoyl group, without its bonding pair, to the azo group. (The aqueous conditions assist formation of the second benzoyl group).

Rearrangement involving benzoyl cation migration has been reported by Curtin *et al.*[129] when they considered the thermal rearrangement of phenylazotribenzoylmethane (127) to diphenylketone benzoylphenylhydrazone (128) (Scheme 2.16).

Scheme 2.16



(127)

(128)

However the mono-*p*-nitrophenylhydrazone azoacetate (12b), derived from benzil, behaved differently to that of the phenyl derivative (12a). In this case, acid catalysed removal of the azoacetate, as proposed for the phenyl derivative does not occur. Instead the azoacetate (12b) gave N-acetyl-N'-benzoyl-*p*-nitrophenylhydrazone (14b) as the major product involving acetyl migration and loss of a benzoyl group (Scheme 1.9b).

Scheme 1.9b

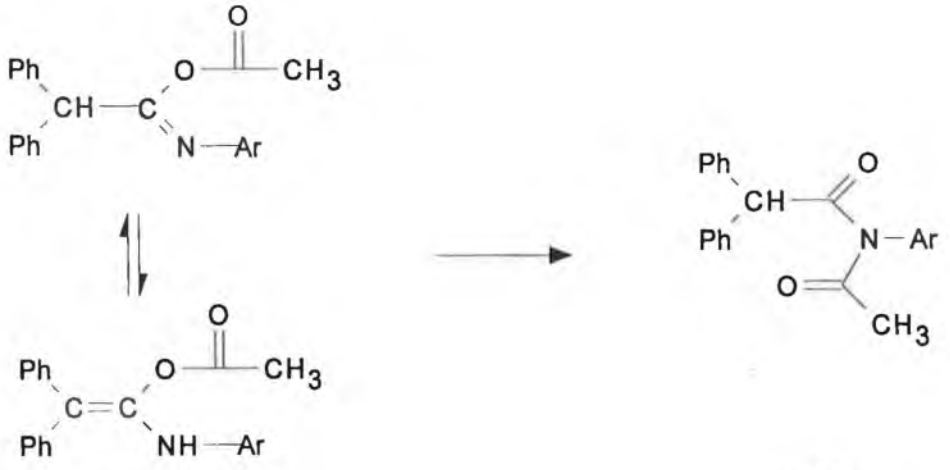
(12b)

(14b)

Support for this proposal was also based on the finding that benzoin *p*-nitrophenylhydrazone reacts with LTA with more ease. A parallel mechanism accounts for the same rearrangement product isolated, accompanied by benzaldehyde[11]. The reaction illustrates removal of an acetyl group from oxygen to nitrogen.

Rearrangements of this nature have been reported by Stephens and Munk[85]. Consider, for example, the intramolecular oxygen to nitrogen acyl migration (Scheme 2.17) for the conversion of (129) to (130) with the possibility of a four-membered transition state.

Scheme 2.17

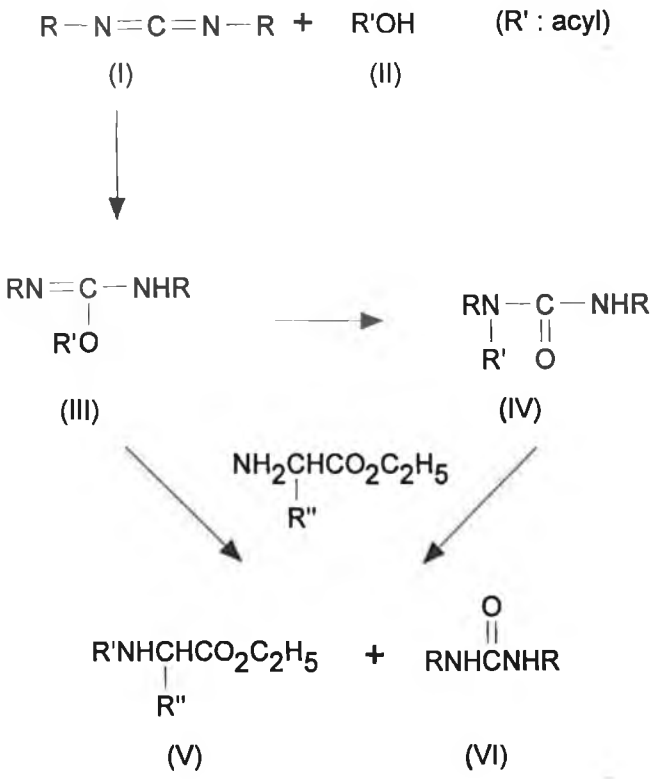


(129) (130)

Closely related examples of this type of rearrangement are: (i) The reaction of carbodiimide with carboxylic acid to form acylurea[86,87] as follows (Scheme 2.18).

Dicyclohexylcarbodiimide (I : R=Ph) was reacted with a number of N-acylamino acids in the presence of glycine ethyl ester. The products proved to be mixtures of peptide esters (V) and acylureas of type (IV).

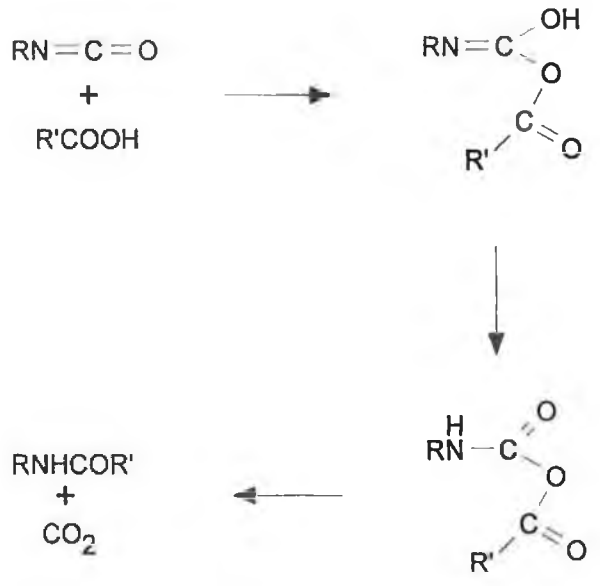
Scheme 2.18



The conversion of (III) to (IV), involving oxygen to nitrogen acyl migration provides a relatively stable acylurea with little tendency to undergo conversion to (V) under mild conditions.

(ii) Naegeli *et al.*[88] report a similar migration (Scheme 2.19) involving the reaction of an isocyanate with a carboxylic acid to give an amide and carbon dioxide.

Scheme 2.19



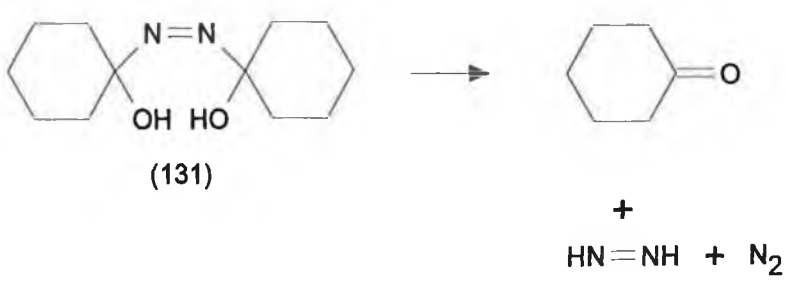
(iii) Hodgkins *et al.*[89] reported the reaction of isothiocyanate and thiobenzoic acid (Scheme 2.20) to give benzamide (II) and carbon disulphide which may form through (I), involving C to N migration.

Scheme 2.20

2.1.3 AZOCARBINOLS

Oxygen to nitrogen migration is evident in the title compounds. α-hydroxyalkyl azo compounds also called α-hydroxyalkyl diazenes or azocarbinols were first reported by Schmitz *et al.*[90] and subsequently by Hunig and Cramer[99]. Since then several other compounds of this series including cyclic and acyclic members have been reported. Most of these compounds are relatively unstable decomposing so rapidly as to preclude convenient purification and isolation[91]. Rearrangement of this rare combination of an azo group and an α-hydroxyalkyl group involves oxygen to nitrogen migration. Consider the semiaminal of diimide, 1,1-dihydroxyazocyclohexane (131) which decomposes rapidly at room temperature[91] to form the products as shown in scheme 2.21.

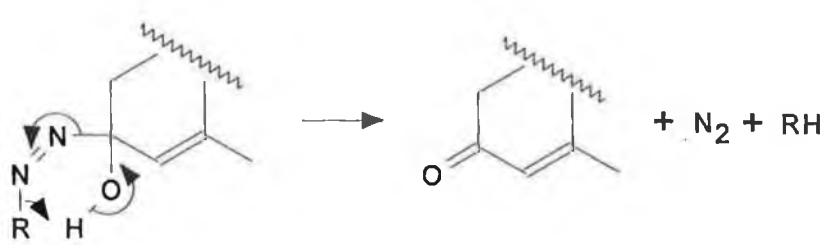
Scheme 2.21



(131)

Similarly for the steroid based azocarbinol (azoalcohol) (132), the following rearrangement occurs[92]:

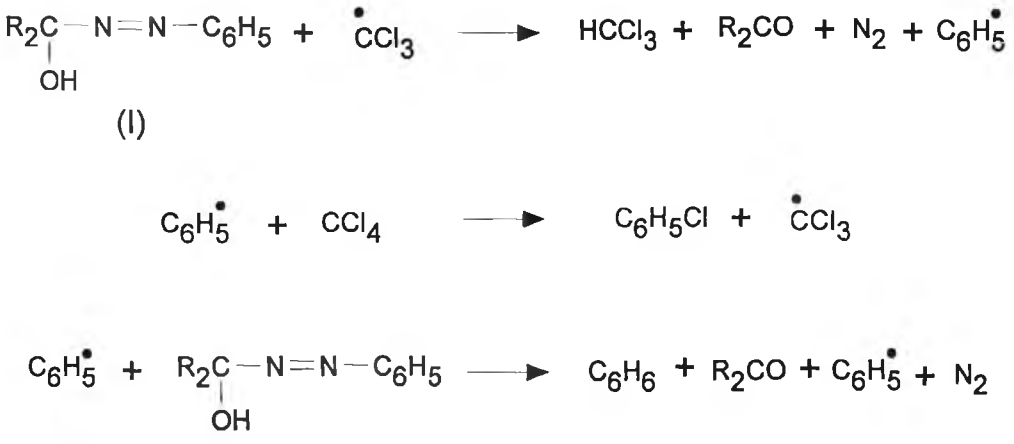
Scheme 2.22



(132)

Scheme 2.23 illustrates azocarbinols of type (I: R = Me;Ph) which decompose smoothly[93,94] in solution at temperatures between 24°C and 80°C. The products formed were indicative of a radical mechanism due to their decomposition in carbon tetrachloride.

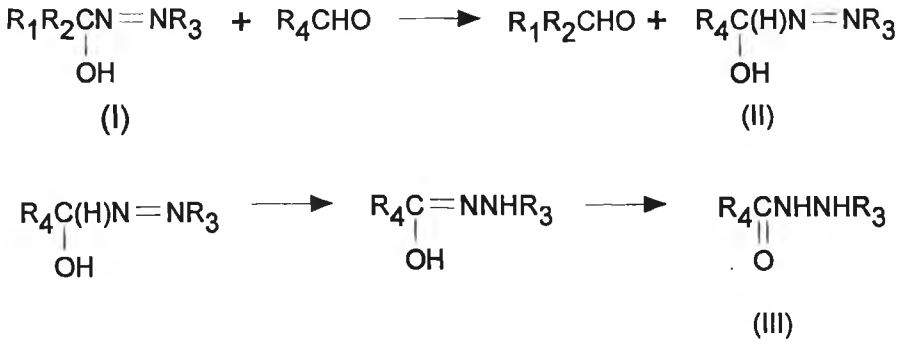
Scheme 2.23



The stabilization afforded at the transition state from the heats of formation of N_2 and a carbonyl group (R_2CO) is sufficient to permit a variety of radicals, such as carbon tetrachloride, as illustrated above, to abstract hydroxyl hydrogen[95].

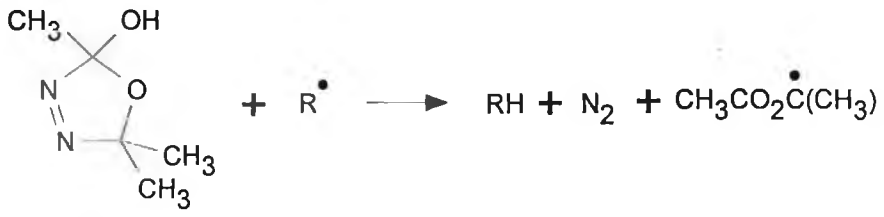
Alternative non-chain mechanisms for the decomposition of azocarbinols were considered particulary worthy of attention in view of reports by Buttner *et al.*[96]. Here they report that azocarbinols of type (I) (Scheme 2.24) react with ketones to form new azocarbinols (II) and with aldehydes to form hydrazides (III) via azocarbinols[93], as shown:

Scheme 2.24



Knittel *et al.*[97] report decomposition of 2-hydroxy-2,5,5-trimethyl-1,3,4-oxadiazoline (132) involving liberation of N_2 and formation of isopropylacetate involving radical abstraction of hydroxyl hydrogen as follows.

Scheme 2.25

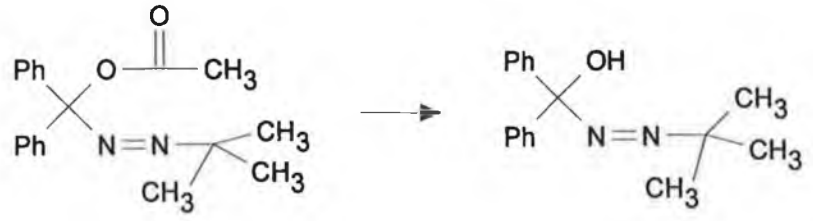


(132)

The regiochemistry of the addition of (132) to unsymmetric unsaturated systems is that predicted by a radical chain mechanism, thus further supporting the decomposition illustrated in scheme 2.23.

Treatment of the azoacetate (133) with methyllithium followed by acidification provides the azocarbinol (134), *t*-butylazodiphenylcarbinol[88].

Scheme 2.26



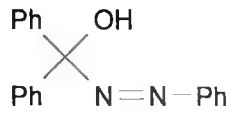
(133) (134)

The azocarbinol (134) is found to decompose spontaneously in carbon tetrachloride at room temperature yielding benzophenone, *t*-butylchloride and chloroform. A study of rate constants indicates a behaviour which would be inconsistent with rate determining unimolecular homolysis of (133), but points to a radical chain process, the rate of which can depend strongly on the concentrations of adventitious initiators, inhibitors or chain transfer reagents.

One such initiator for the decomposition of (133) may be oxygen as a

degassed sample in CCl_4 decomposed more slowly than in the corresponding undegassed sample. When solutions of (133) in benzene, were considered, the most reasonable chain mechanism was the attack of *t*-butyl radicals at the hydroxy hydrogen, as benzophenone and isobutane were the only readily detectable products.

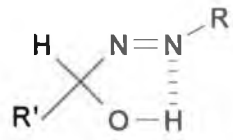
Likewise phenylazodiphenylmethanol (135) is reported to decompose in solution by processes involving phenyl radicals, (thus pointing to their use for radical chain hydrophenylation) [93].



(135)

These reactions highlight the ease with which azocarbinols tend to decompose.

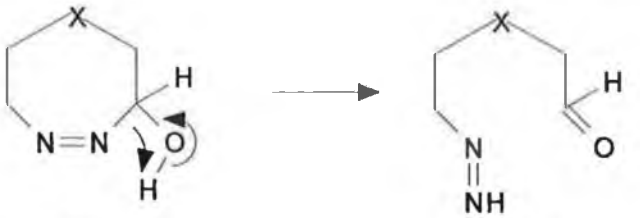
Intramolecular hydrogen bonding is evident in these compounds[93]. Consider, for example, *t*-butyl-α-hydroxylalkyl diazene (136) [R:$C(CH_3)_3$; R':alkyl] existing as a yellow liquid with an OH band visible at 3370-3390 cm^{-1} on the infra-red spectrum, which remains when the sample is diluted, indicating intramolecular hydrogen bonding[98]:



(136)

Complete removal of the alcoholic proton[99] has been proposed as illustrated for conversion of (137) to (138) :

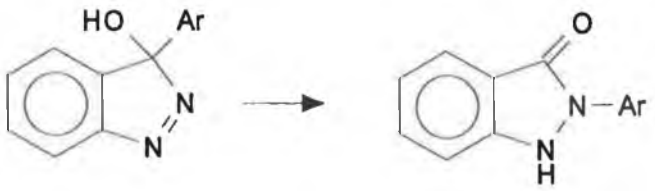
Scheme 2.27



(137) (138)

Rearrangement involving aryl migration of cyclic azocarbinols has been reported. Consider, for example[100], the base treatment of (139) yielding the indazolinone (140).

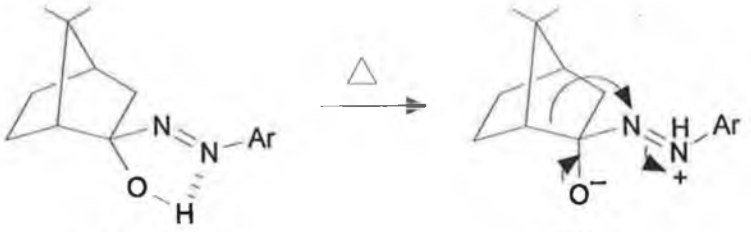
Scheme 2.28



(139) (140)

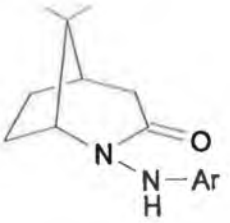
Similarly carbon to nitrogen rearrangement of the α-azoalcohol (141) yields the N-substituted bridged bicyclic lactam[100] (143):

Scheme 2.29



(141)

(142)



(143)

CHAPTER 2

RESULTS AND DISCUSSION

CHAPTER 2

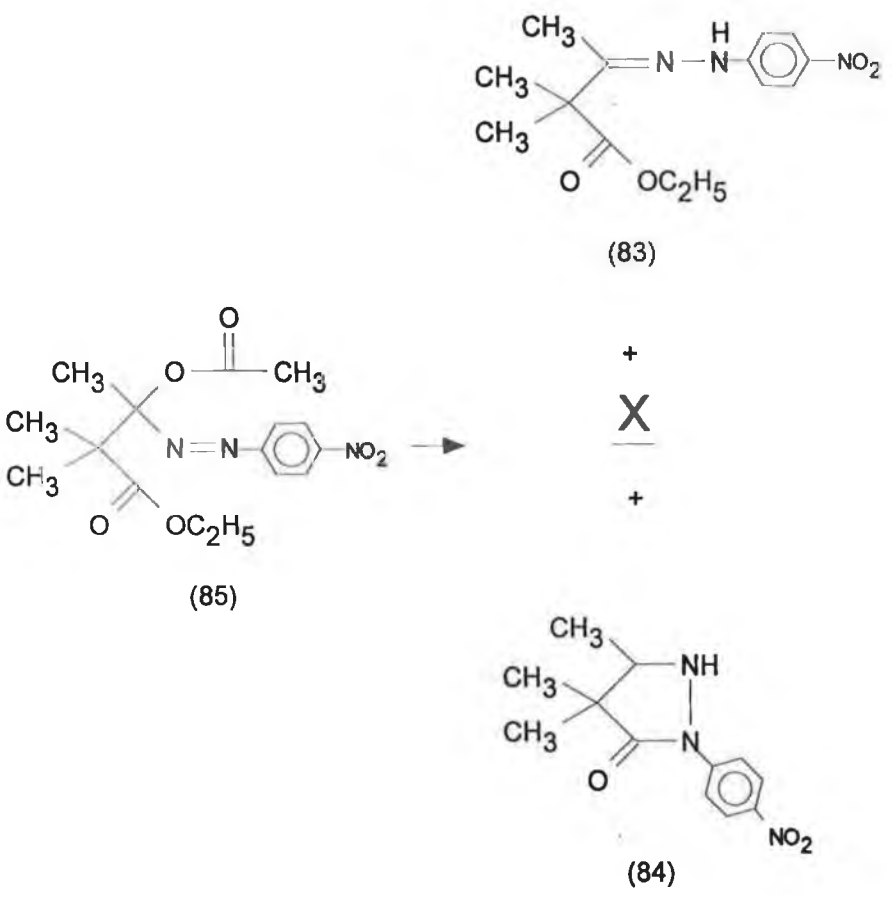
2.2 RESULTS AND DISCUSSION

2.2.1 Azoacetate reaction with base

The reaction of azoacetates of aromatic ketone arylhydrazones with base has been studied by Gladstone *et al.* yielding a variety of products[5]. Typically products included the indazole, the parent ketone and the parent hydrazone.

We have studied the reaction of the azoacetate (85) derived from dimethylethyl acetotacetate-*p*-nitrophenylhydrazone under basic conditions. Thus upon heating a sample of (85) in ethanol using potassium cyanide as base the following products were isolated. Some starting hydrazone (83) was recovered probably involving hydride transfer as suggested by Gladstone *et al.*[8]. The corresponding cyclic pyrazole (84) was also isolated *via* cyclisation of the hydrazone (Chapter One). A third compound (X) was collected which aroused most interest (Scheme 2.30).

Scheme 2.30



(83)

(85)

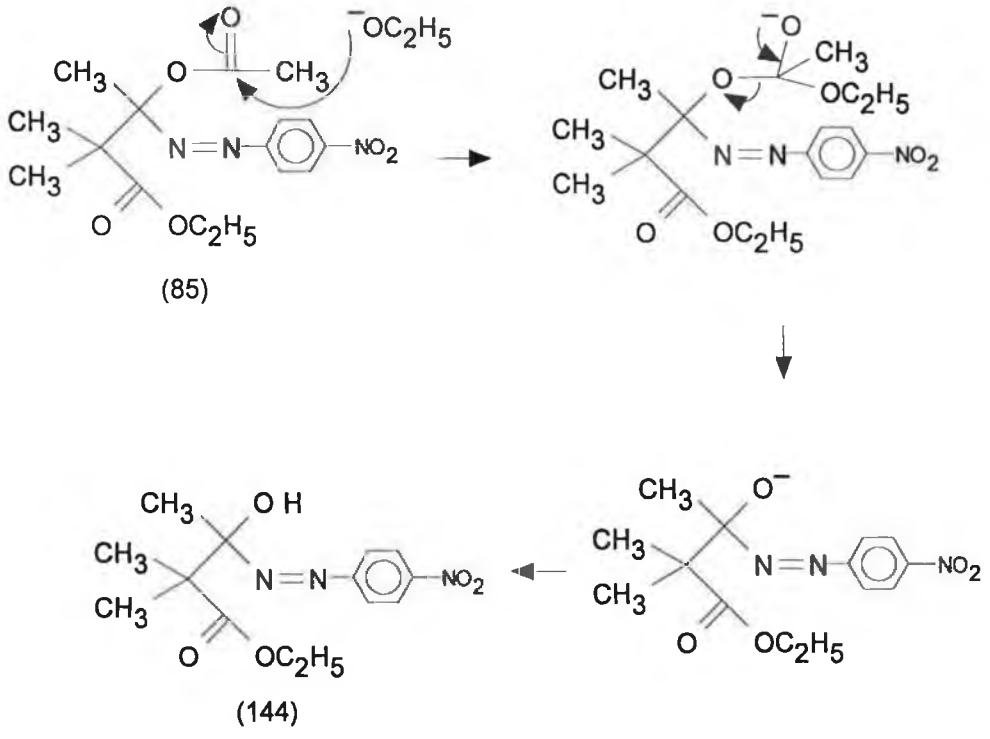
(84)

Initially CHN analysis of this compound isolated suggested the formation of an azoalcohol, with figures which correspond to the loss of an acetyl group from the azoacetate. If the reaction proceeded *via* a transesterification, then azoalcohol formation is quite a plausable structure.

Such a proposal is supported by the documented use of potassium cyanide as a catalyst for transesterification reactions[102,103].

Some transesterification may also occur at the ester group, however, the same functional group will persist when ethanol is used as solvent (Scheme 2.31).

Scheme 2.31



However, while this mechanism points to an azocarbinol (144) (azoalcohol) as a probable candidate for compound (X), there was no obvious band on the infra-red spectrum to indicate the presence of an hydroxy group and the aromatic region of the ^1H NMR spectrum did not indicate a neighbouring azo group effect on aryl hydrogens.

Isolation of the azoalcohol (144) was considered unlikely given their reported instability.

2.2.2 NMR temperature study

The ^1H NMR spectrum of compound (X) was a very interesting one, giving rise to a temperature dependent study.

The spectrum of the compound at room temperature indicated broad peaks in the aromatic region (Figure 2.1). As the temperature was increased the aromatic region provided sharper peaks. (Figure 2.2).

Figure 2.1

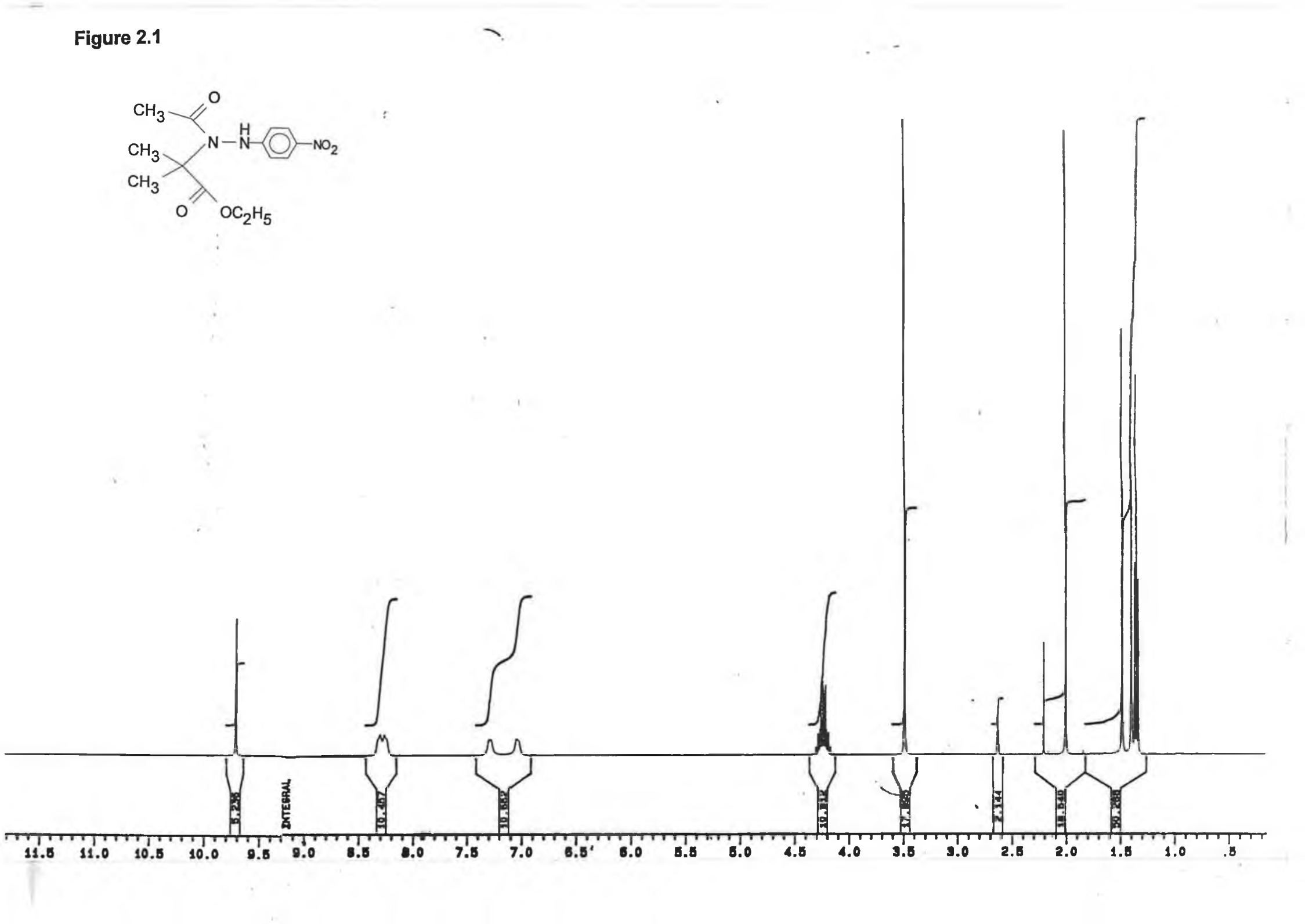
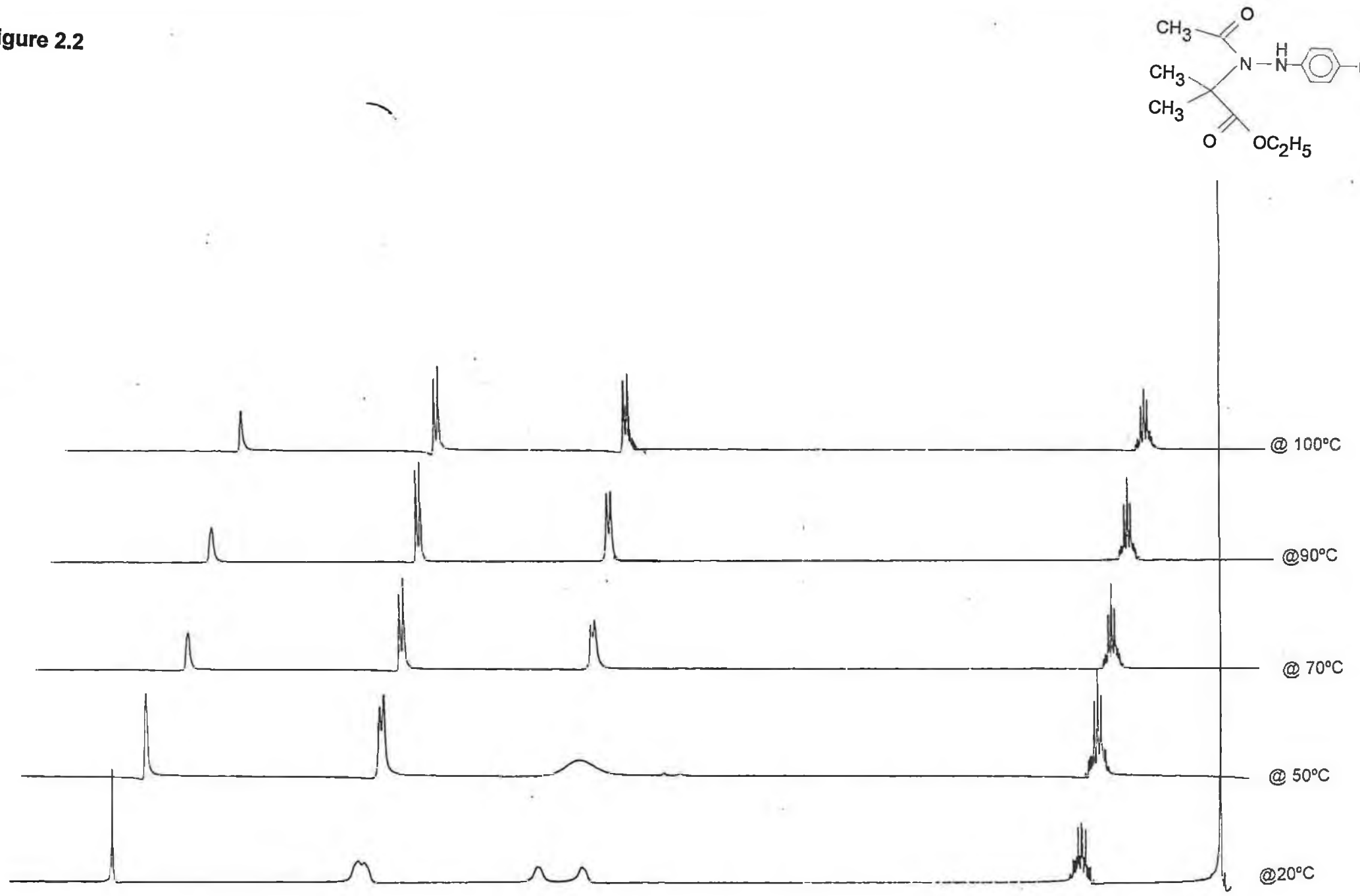

CH3
O
N
H
N
NO2
CH3
CH3
O
OC2H5
INTEGRAL
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5

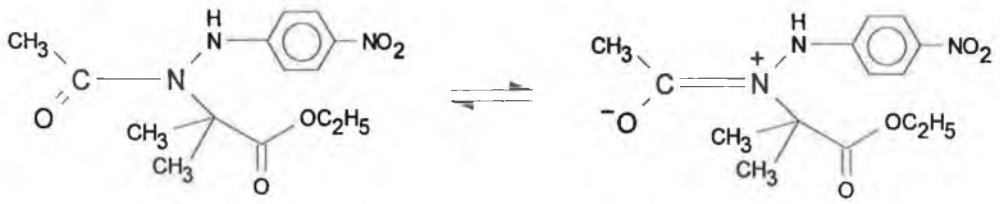
Figure 2.2



This is characteristic of amide resonance[104]. The tertiary amide, (hydrazide), (145) has been proposed.

The spectrum can be explained by, considering the resonance structures, (145a) and (145b) (Scheme 2.32).

Scheme 2.32



(145a) (145b)

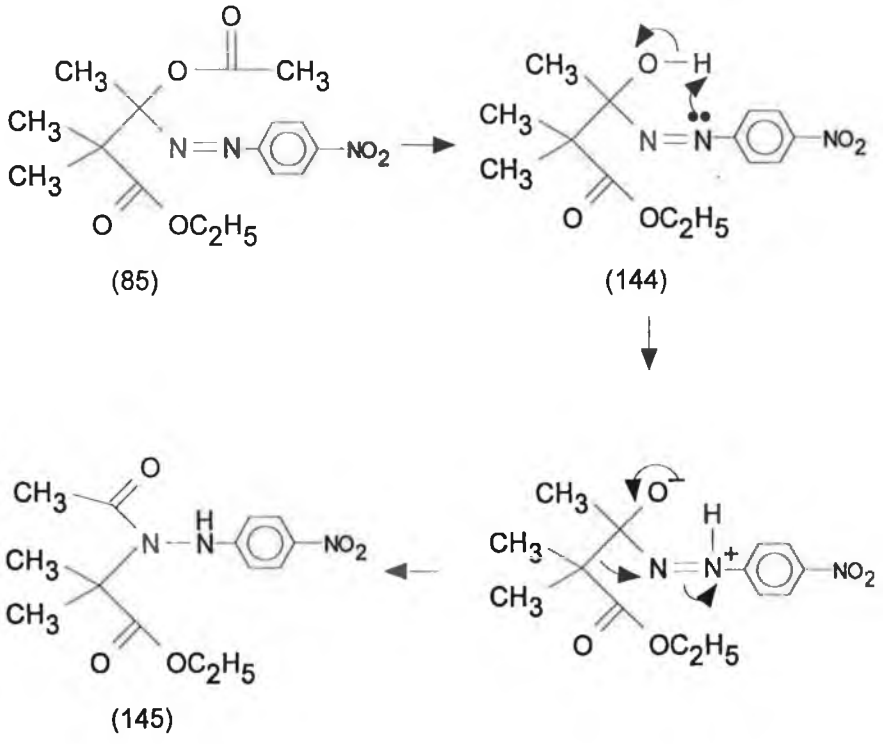
At room temperature the compound is found to exist with partial double bond character (145b). This in turn leads to hindered rotation about the amide bond and consequently the aromatic protons are seen to exist in different environments, indicated by the broadening effect.

As the sample is heated the aromatic region becomes sharper. Finally at high temperatures the tendency towards (145a) allows free rotation about the C-N bond.

The aromatic protons are seen in one time averaged environment. The two methyl groups are seen as two singlets at room temperature. As the temperature is increased they become closer decreasing from 34.9 Hz at 20°C to 13.1 Hz at 120°C.

The tertiary amide (145) may be arrived at *via* rearrangement of the azocarbinol (144) proposed earlier (Scheme 2.31), as follows (Scheme 2.33).

Scheme 2.33

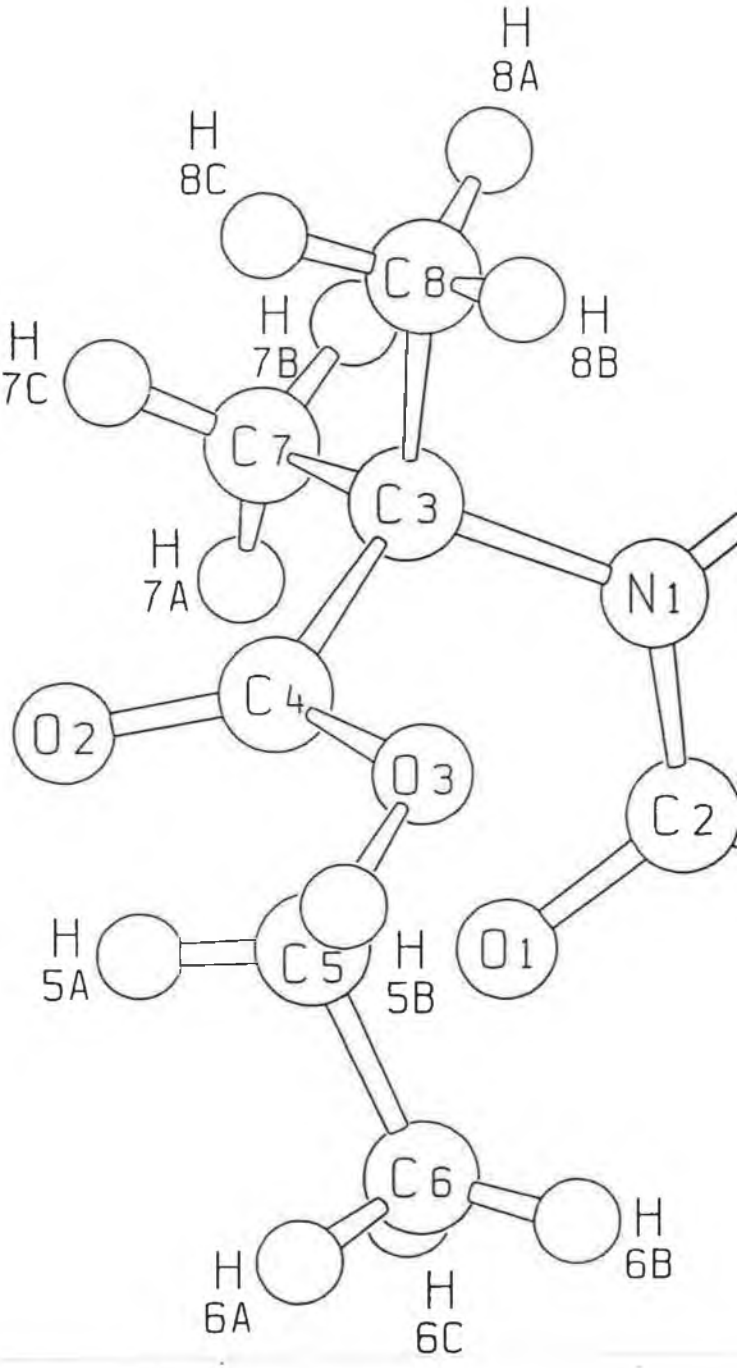


(85) (144) (145)

A similar type of rearrangement has been illustrated in the introduction to this chapter (See Scheme 2.28) involving carbon to nitrogen migration of an aryl group[100]. Conclusive evidence of the tertiary amide structure is provided by the X-ray crystal structure data . A diagram showing the structure as determined by X-ray analysis is shown [Figure 2.3], and with the hydrogen atoms omitted [Figure 2.4].

The atomic coordinates are given in Table 2.1, bond lengths in Table 2.2 and bond angles in Table 2.3.

Figure 2.3


H
8A
H
8C
C 8
H
7B
H
8B
H
7C
C 7
C 3
H
7A
N 1
C 4
O 2
O 3
C 2
H
5A
C 5
H
5B
O 1
C 6
H
6B
H
6A
H
6C

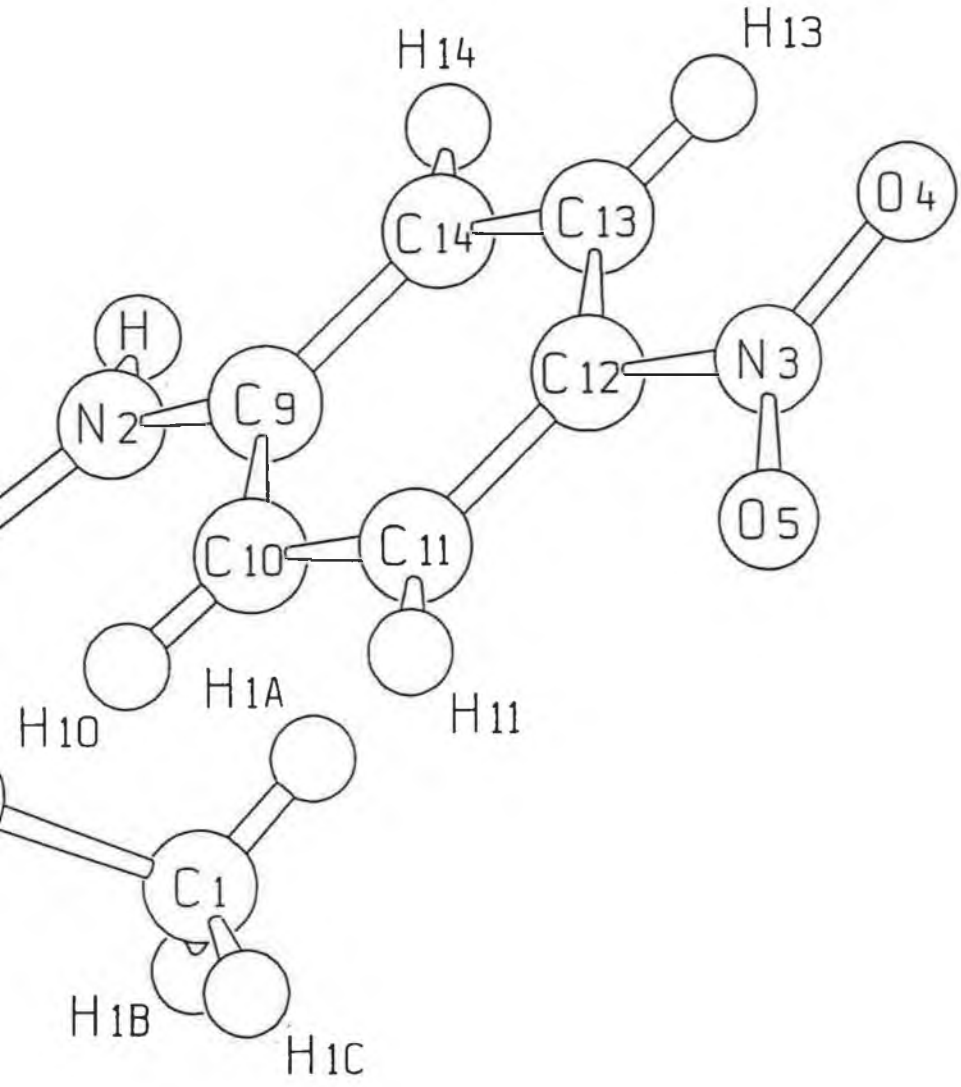

H14
H13
O4
C14
C13
H
C12
N3
N2
C9
O5
C10
C11
H1A
H10
H11
C1
H1B
H1C

Figure 2.4

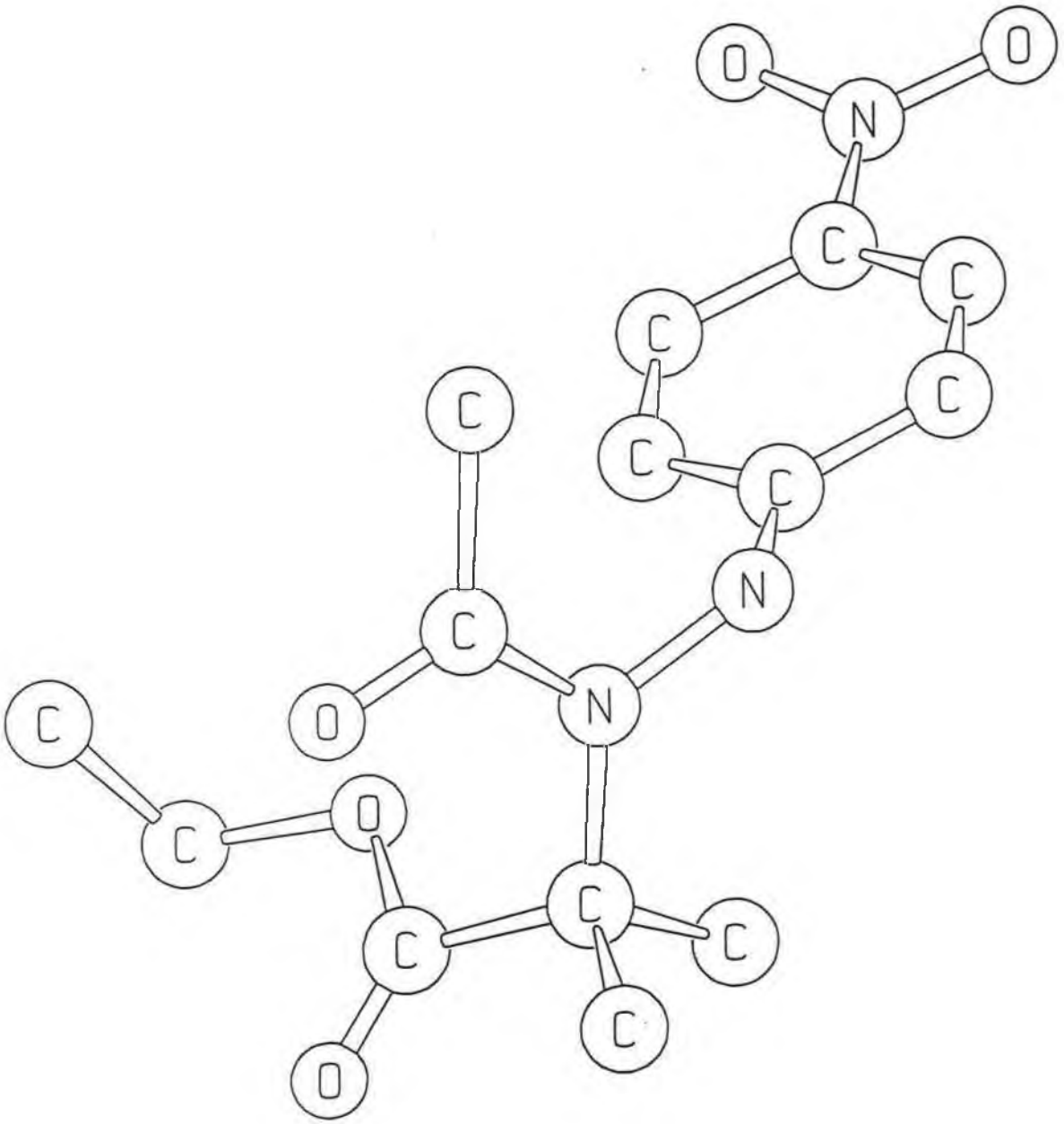


Table 2.1

Atomic Co-ordinates for (145)

	X	Y	Z
C (10)	-15 (8)	1764 (8)	6974 (7)
C (12)	1188 (10)	1936 (8)	5411 (8)
N (3)	1264 (100	1912 (8)	4226 (7)
C (13)	2233 (9)	2133 (9)	5992 (7)
N (1)	-82 (7)	1886 (6)	9258 (6)
C (9)	1034 (9)	2016 (8)	7573 (7)
C (14)	2174 (9)	2193 (8)	7082 (7)
O (1)	-1816 (6)	2507 (6)	10062 (6)
O (5)	277 (8)	1841 (9)	3724 (6)
O (3)	-1979 (6)	527 (6)	8651 (6)
N (2)	967 97)	2125 (6)	8666 (5)
O (4)	2305 (8)	1974 (8)	3805 (5)
C (11)	41 (9)	1741 (9)	5881 (7)
O (2)	-2134 (8)	-88 (7)	10343 (6)
C (7)	147 (11)	862 (10)	10950 (7)
C (3)	-229 (10)	790 (9)	9775 (7)
C (6)	-4033 (13)	1084 (12)	8285 (13)
C (4)	-1604 (10)	388 (9)	9646 (10)
C (8)	599 (12)	-59 (9)	9212 (10)
C (5)	-3258 (12)	137 (15)	8443 (13)
C (2)	-900 (10)	2685 (10)	9470 (8)
C (1)	-742 (12)	3799 (9)	8934 (11)

Table 2.2

Bond Lengths [Å] for (145)

BOND	Length [Å]
C (10)-C (11)	1.367 (11)
C (10)-C (9)	1.380 (11)
C (12)-C (13)	1.350 (12)
C (12)-C (11)	1.376 (12)
C (12)-N (3)	1.484 (12)
N (3)-O (5)	1.225 (10)
N (3)-O (4)	1.228 (10)
C (13)-C (14)	1.366 (11)
N (1)-C (2)	1.357 (12)
N (1)-N (2)	1.3720 (9)
N (1)-C (3)	1.5310 (3)
C (9)-C (14)	1.377 (12)
C (9)-N (2)	1.375 (11)
O (1)-C (2)	1.244 (11)
O (3)-C (4)	1.317 (12)
O (3)-C (5)	1.468 (13)
O (2)-C (4)	1.198 (12)
C (7)-C (3)	1.525 (12)
C (3)-C (4)	1.556 (14)
C (3)-C (8)	1.553 (13)
C (6)-C (5)	1.4600 (2)
C (2)-C (1)	1.564 (14)

Table 2.3

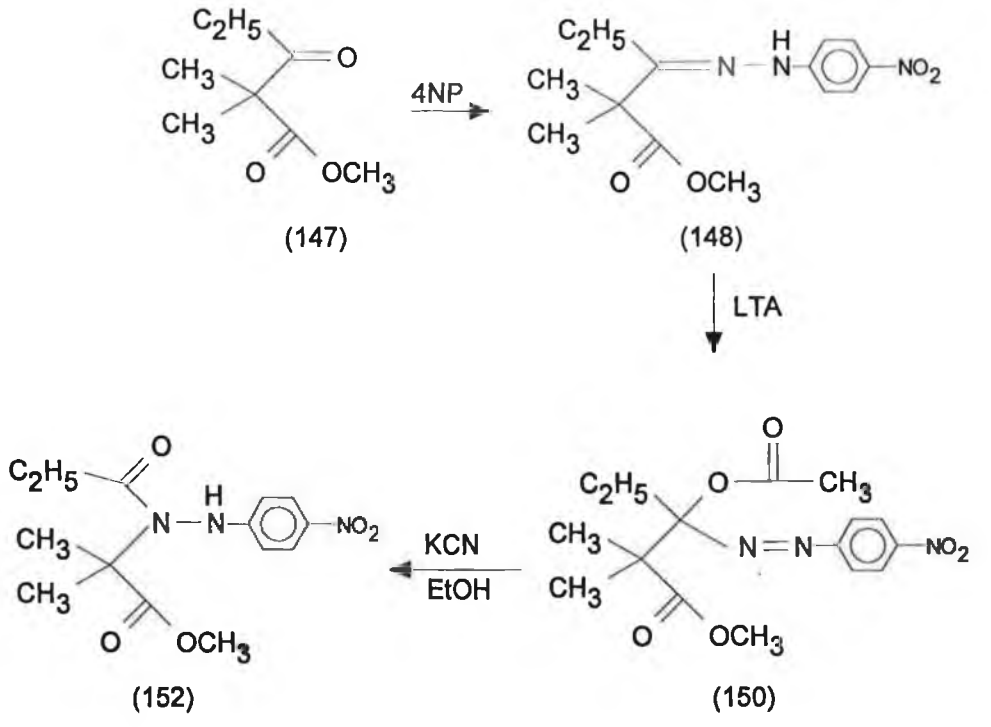
Bond Angles for (145)

BOND	ANGLE
C (11)-C (10)-C (9)	120.8 (10)
C (13)-C (12)-C (11)	122.20 (9)
C (13)-C (12)-N (30	119.7 (10)
C (11)-C (12)-N (3)	118.1 (10)
O (5)-N (3)-O (4)	123.90 (9)
O (5)-N (3)-C (12)	117.8 (100
O (4)-N (3)-C (12)	118.4 (10)
C (14)-C (13)-C (12)	120.6 0(9)
C (2)-N (1)-N (2)	117.60(8)
C (2)-N (1)-C (3)	121.40 (8)
N (2)-N (1)-C (3)	120.60 (7)
C (14)-C (9)-N (2)	118.20 (9)
C (14)-C (9)-C (10)	120.40 (9)
N (2)-C (9)-C (10)	121.40 (9)
C (13)-C (14)-C (9)	118.4 (100
C (4)-O (3)-C (5)	113.8 (10)
C (9)-N (2)-N (1)	123.80 (8)
C (10-C (11)-C (12)	117.4 (10)
C (7)-C (3)-N (1)	109.00 (8)
C (7)-C (3)-C (4)	111.40 (9)
N (1)-C (3)-C (4)	110.20 (8)
C (7)-C (3)-C (8)	109.20 (9)
N (1)-C(3)-C (8)	111.80 (8)
C (4)-C (3)-C (8)	105.20 (9)
O (2)-C (4)-O (3)	127.6 (10)
O (2)-C (4)-C (3)	122.0 (11)
O (3)-C (4)-C (3)	109.8 (10)
O (3)-C (5)-C (6)	105.9 (13)
O (1)-C (2)-N (1)	119.0 (11)
O (1)-C (2)-C (1)	120.1 (11)
N (1)-C 92)-C (1)	120.80 (9)

In order to extend this rearrangement to similar azoacetates, the β-ketoester methyl propionyl acetate (146), was considered as a starting material for the proposed rearrangement (Scheme 2.34).

Thus the β-ketoester (146) was dimethylated by heating in acetone with potassium carbonate as base and methyl iodide as alkylating agent. Condensation of the resulting ester (147) with 4NP in a weak solution of acetic acid provided 2,2-dimethyl methylethylketone-*p*-nitrophenylhydrazone (148). The hydrazone was oxidised using LTA in CH_2Cl_2 when the azoacetate (150) was isolated as a red oil.

Scheme 2.34



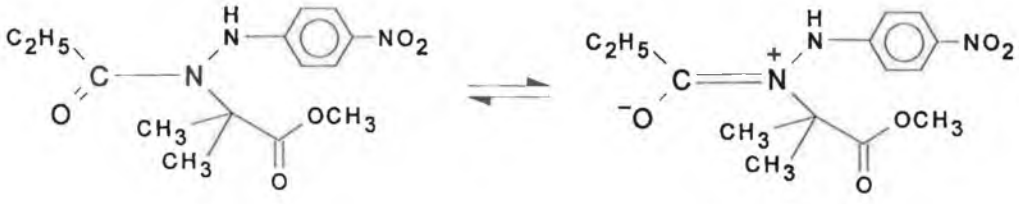
(147) (148) (150) (152)

The azoacetate (150), was dissolved in ethanol to which 1.3 equivalents of KCN were added. Following heating under reflux for 24 hrs, work-up of the reaction, as for (85), provided a mixture of hydrazone (148), cyclic hydrazone (149), and the tertiary amide (151). The reaction was worked up as for (145). Pet-ether was added to a reduced volume of the reaction mixture. This initiated precipitation of the tertiary amide as a pale cream precipitate (Scheme 2.34).

2.2.3 NMR Temperature study

The ^1H NMR indicates the resonance structures (152a) and (152b) for the amide (152), similar to that observed for the preceding tertiary amide (145).

Scheme 2.35



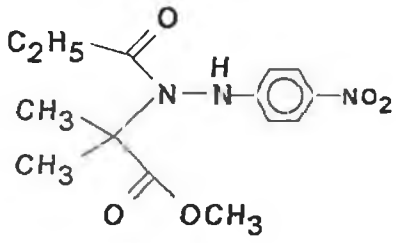
(152a) (152b)

Increasing the temperature causes sharpening of the aromatic region to one average set of peaks owning to the increased C-N single bond character and fast inversion about the tertiary nitrogen [Figures 2.5 and 2.6].

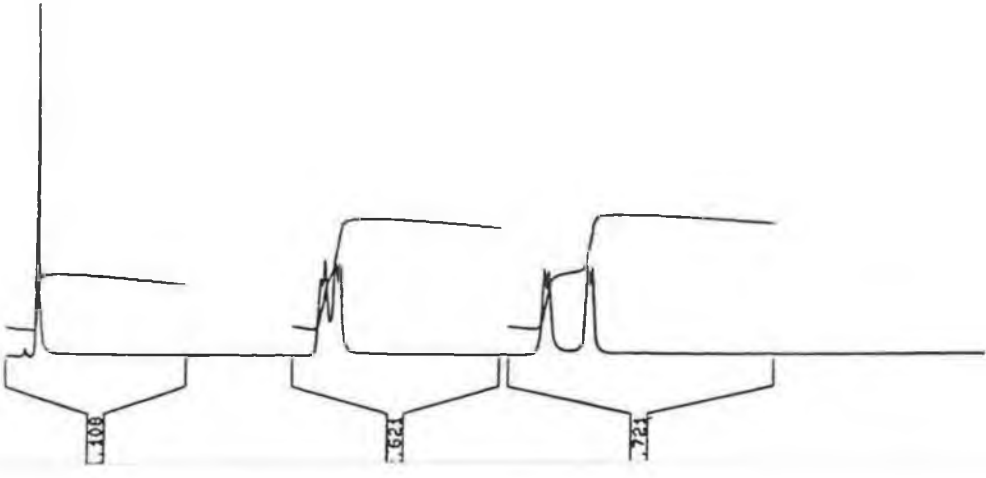
The ethyl group attached to the keto carbon gives rise to two multiplets at 2.0 ppm and 2.4 ppm as well as the expected triplet for the terminal methyl of this ethyl group. Absence of the typical triplet-quartet coupling for such a simple group can be explained as follows. The methylene carbon of this ethyl group is a prochiral carbon, therefore the two protons associated with it are non-equivalent. This gives rise to a multiplet for each proton, as observed at 2.0 ppm and 2.4 ppm, because they are split by one another and also by the terminal methyl group [Figure 2.7].

This is further investigated by considering Figure 2.8. Here the sample has been irradiated at the frequency of the methyl group. The methylene protons are now reduced to two simple doublets, due to each methylene proton splitting one another.

Figure 2.5



@ 20°C



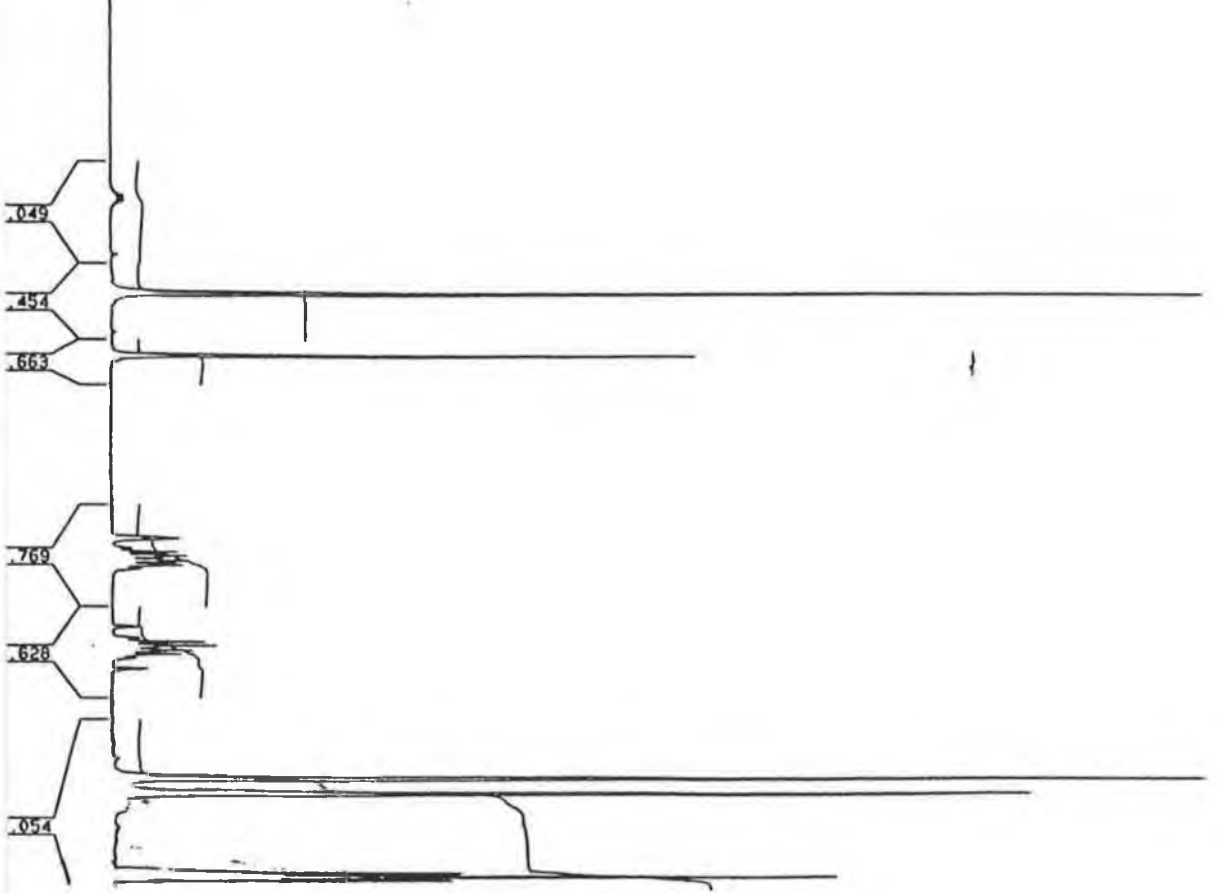
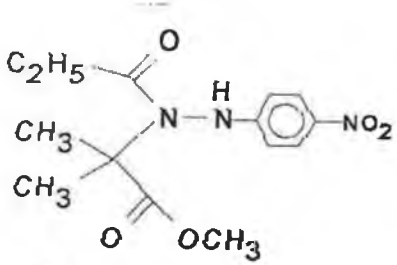
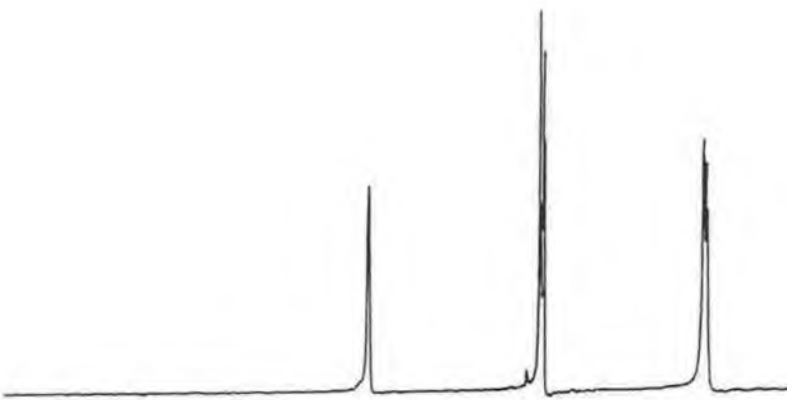

.049
.454
.663
.769
.628
.054

Figure 2.6



@ 60°C



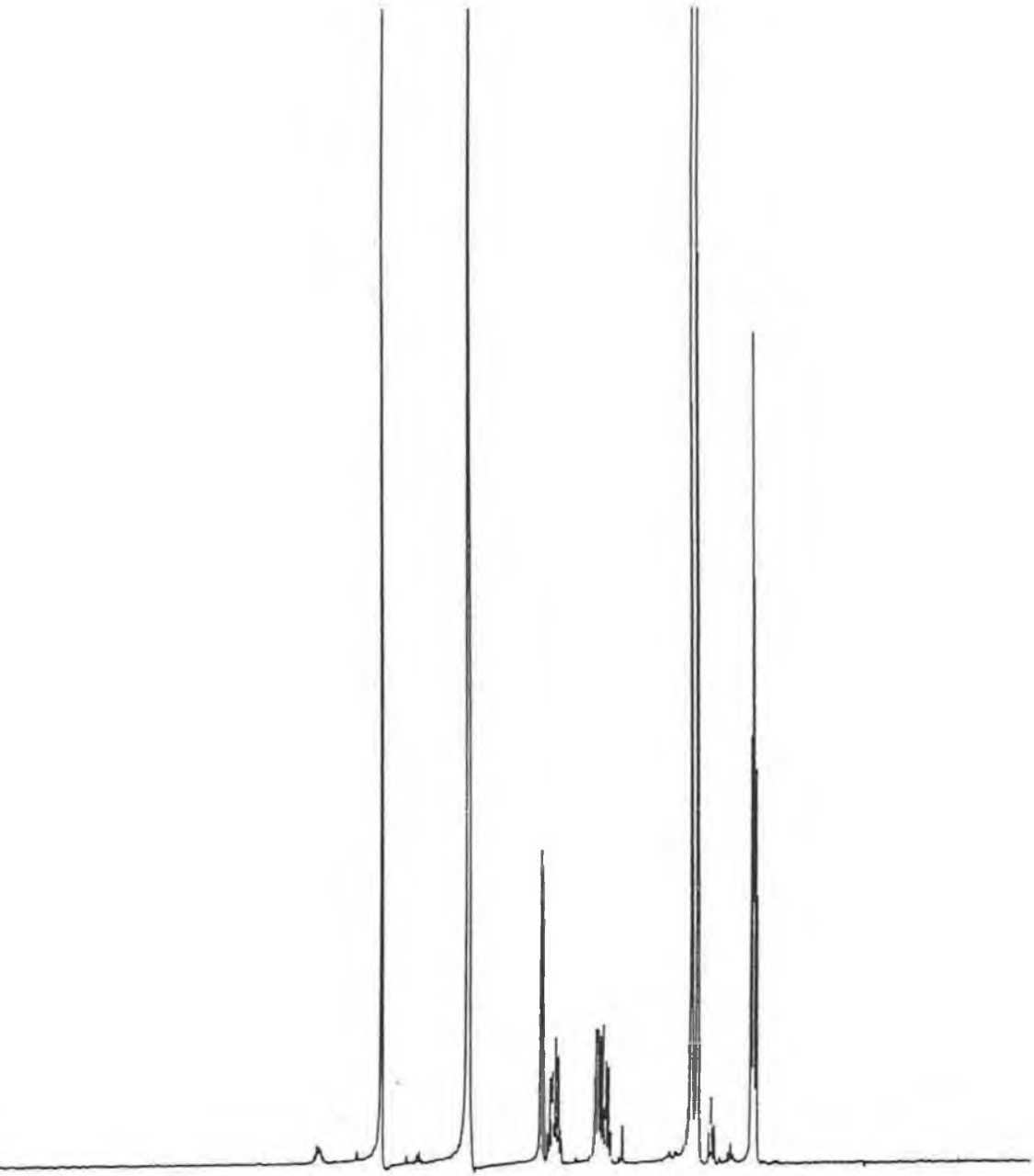


Figure 2.7

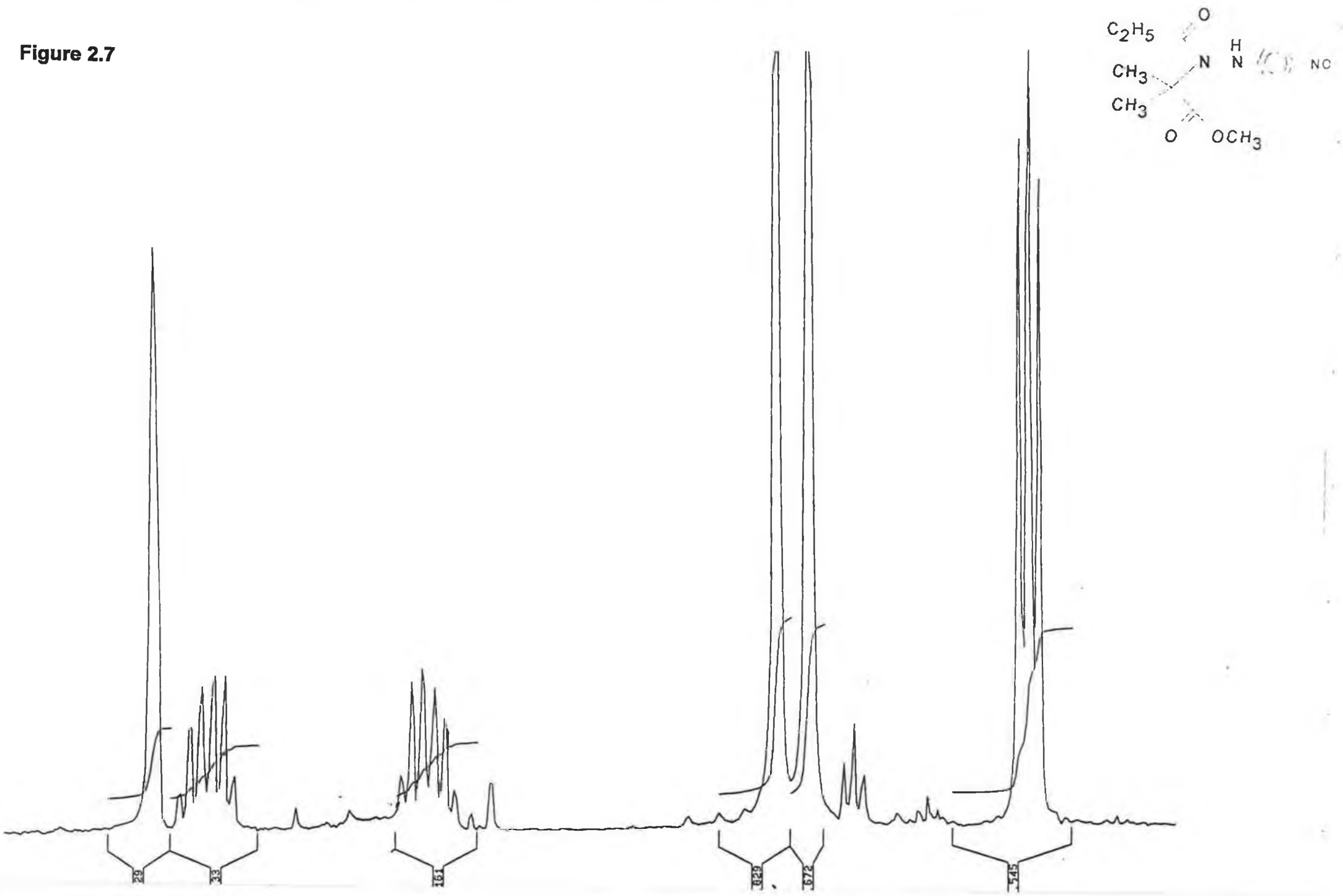
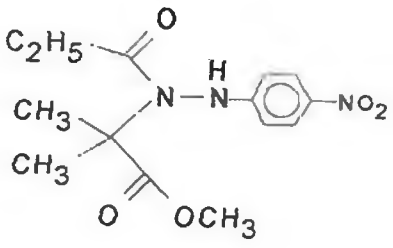
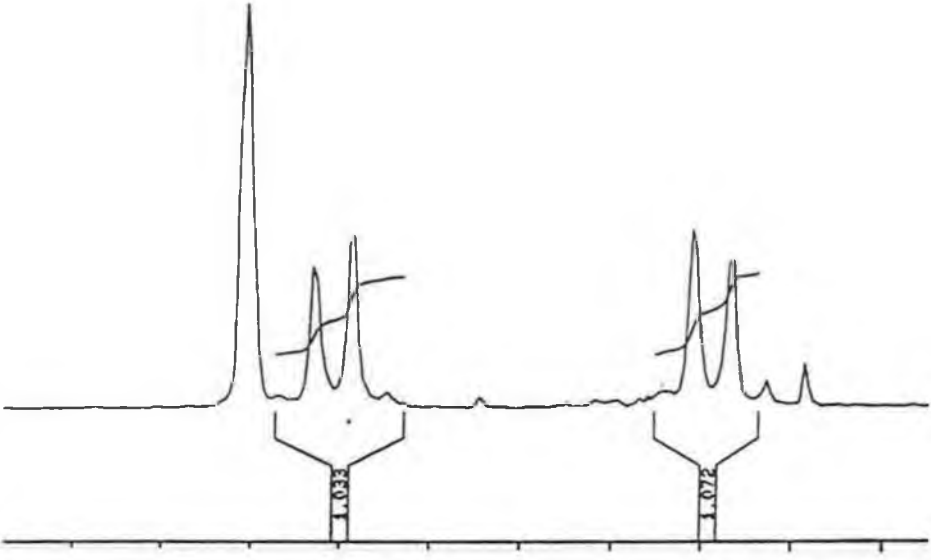
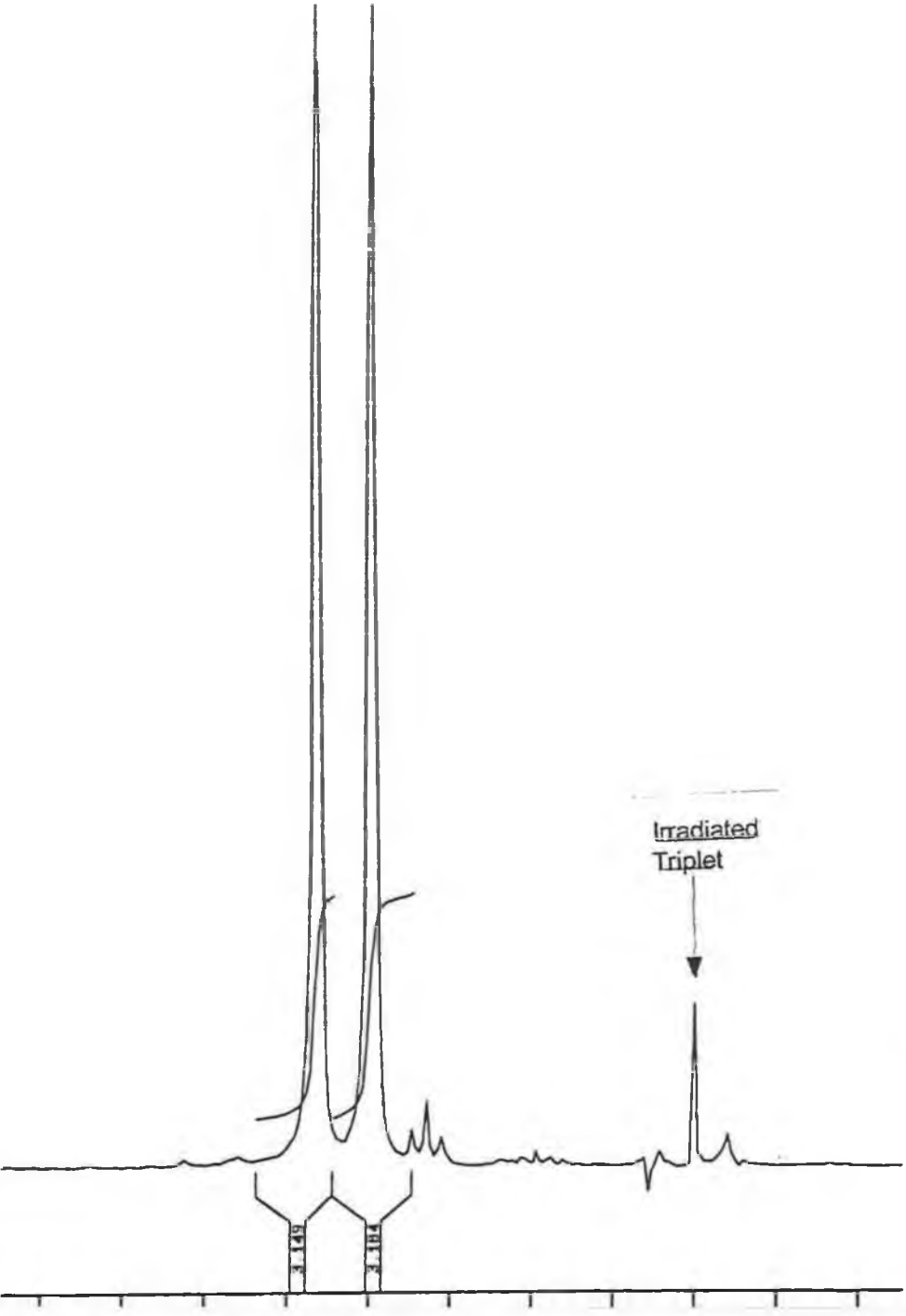


Figure 2.8






Irradiated
Triplet
3.149
3.184

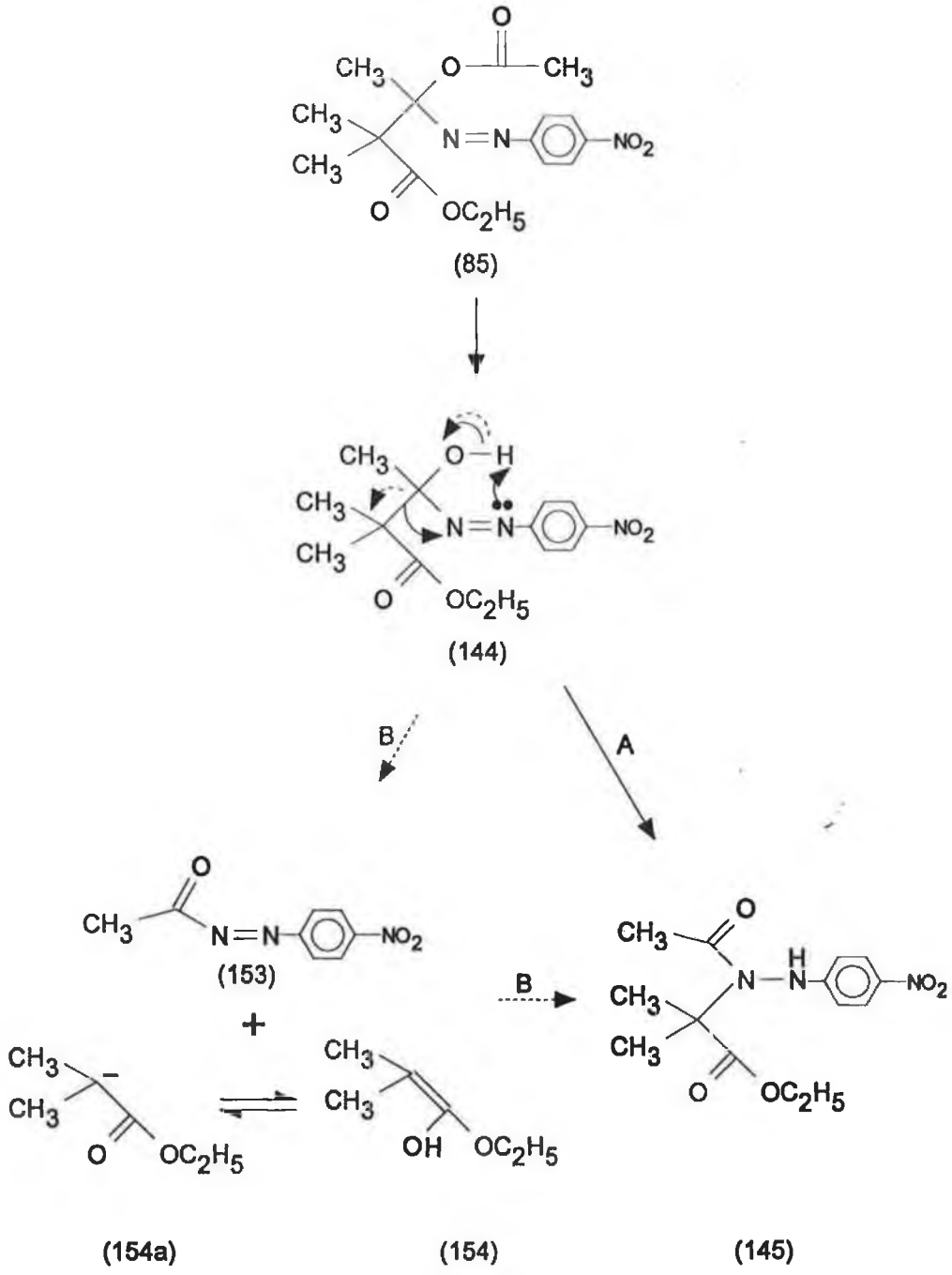
2.2.4 MECHANISM OF REACTION

To investigate the reaction mechanism by which the tertiary amide is isolated from the azoacetate, the following studies were undertaken.

The reaction of the azoacetate (85) under basic conditions was carried out in both ethanol and propanol. The tertiary amide (145) was isolated in both cases, in yields of 35% and 32% respectively. No tertiary amide resulting from attack by propanol at the ester group of the azoacetate (85) was observed. However, when the reaction was carried out with acetone as solvent instead of alcohol, the starting material was recovered in 80% yield. The only other products were the hydrazone (83) and the cyclic pyrazole (84). The lack of amide when there is no alcohol solvent further points to a transesterification reaction, generating the azoalcohol. The reaction was repeated using potassium carbonate as base *in lieu* of potassium cyanide with ethanol as solvent. The amide (145) was again isolated, though yields were now reduced to 10%. Thus the catalytic effect of KCN for transesterification reactions, as reported by K. Mori *et al*[102], appear to be further underlined.

While considering the reaction from azoacetate (85) to tertiary amide (145), carbon to nitrogen rearrangement may proceed *via* a concerted mechanism (route A) or by a two step addition mechanism involving an intermediate (154), with subsequent nucleophilic addition to the azo functionality (153) (route B) (Scheme 2.36).

Scheme 2.36



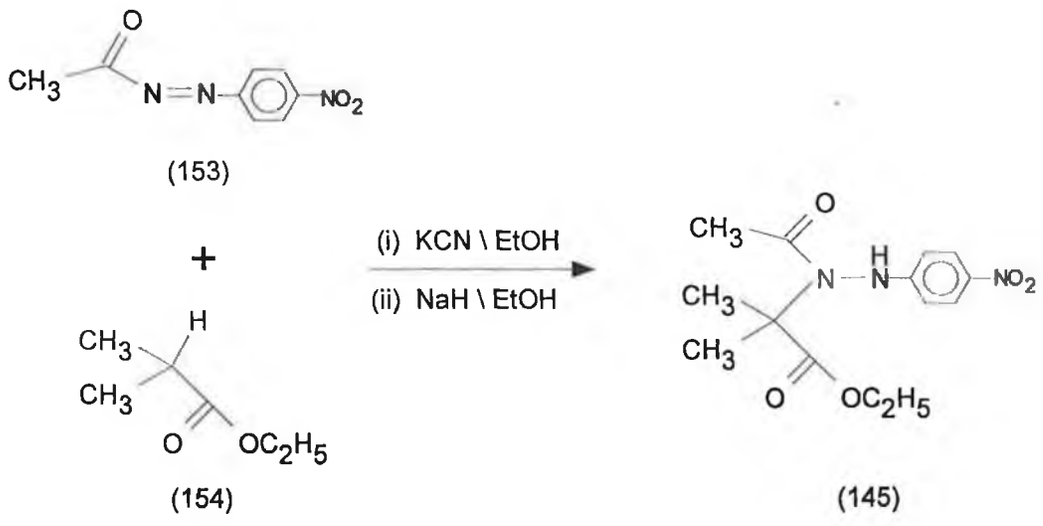
In order to explore the possibility of an addition reaction (route B), two possible approaches (i) an addition reaction and

(ii) a cross-over experiment were considered.

2.2.5 (i) ADDITION REACTION

Arrival at the tertiary amide (145), via an addition mechanism (Scheme 2.37) would involve reaction of ethyl isobutryate (154) with the azo compound (153) as follows:

Scheme 2.37



In order to consider such an addition reaction, the azo compound (153), must first be synthesised.

Acetylation of *p*-nitrophenylhydrazine was attempted using acetyl chloride[106] with a view to subsequently oxidising to the required azo compound (153). While reaction of *p*-nitrophenylhydrazine with acetyl chloride was complete within minutes, a number of products were present due to the indiscriminate acetylation by the reagent[108,109].

However when *p*-nitrophenylhydrazine was suspended in acetic acid, and heat applied with the gradual introduction of 1.5 equivalents of acetic anhydride, the product 2-acetyl-*p*-nitrophenylhydrazine (155) alone, was isolated from solution as a pale brown solid.

Following isolation of (155), oxidation to provide the hydrazone (153), required for the addition reaction (Scheme 2.37), was investigated.

Initial attempts at oxidising (155) to the corresponding hydrazone (153) proved non-trivial. Initially N-bromosuccinimide (NBS) was choosen as oxidising agent (Scheme 2.38).

Thus NBS was stirred with the hydrazine (155) suspended in CH_2Cl_2, from which a clear red solution resulted. One major product was evident with a large R_f value on t.l.c. However the presence of a number of other

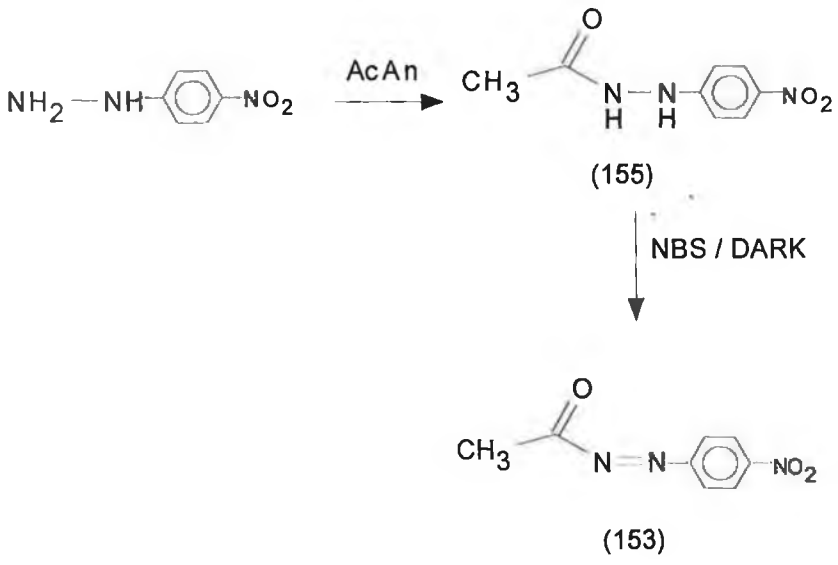
products, as indicated by t.l.c, precluded convienent isolation and identification.
Oxidation using potassium permanganate was investigated. The hydrazone was dissolved in EtOH while the oxidising reagent was added as an aqueous solution. A number of products were present after a short time indicated by t.l.c monitoring. The medium for the reaction consisted of EtOH and H_20 which may have further complicated the reaction, as hydrolysis or esterification of the required product may occur[110]. The reaction was repeated using LTA and again with lead oxide as oxidising agents, however the number of products present after a short time did not indicate a feasible route.

Little work in this area of acetylated azo compounds was evident from a literature review. While reference to benzoylphenyl hydrazone was made by Chatt *et al.*[112], the synthesis was not referred to. Barton *et al.*[114] refer to the superior oxidising ability of benzeneselenic anhydride with a similar family of compounds.

However all the reactions undertaken in an attempt to oxidise (155) to (153) had, in common, the presence of a fast running intense spot as indicated by t.l.c monitoring. Thus it was suspected the problem rested with the instability of the required product (153), as opposed to the oxidising agent. Indeed Milne *et al.*[110] report the instability of the oxidation product from the reaction of NBS with N-acetyl-α-amino acid phenylhydrazides. They report the azo product was successfully isolated when the reaction was conducted in the dark and at low temperatures.

This approach was applied to the hydrazine (155). Oxidation was effected using N-bromosuccinimide with trace amounts of pyridine in the absence of light. Under these conditions the azo compound (153) was successfully isolated as a red crystalline material (Scheme 2.38).

Scheme 2.38



(155)

(153)

Investigation of an addition reaction (Scheme 2.37) as a possible route to the tertiary amide (145) was now pursued, as the starting material (153) had been synthesised and isolated.

Ethyl isobutyrate (154) underwent heating at reflux with 2-acetyl-*p*-nitrophenylhydrazone (153) in ethanol for 24 hours in the presence of 1.3 equivalents of potassium cyanide. Initially gentle heat was applied and the reaction was protected from light, in order to enhance the life time of the azo compound (153).

The reaction was evaporated to dryness, washed with water and extracted into diethylether:ethyl acetate (80:20). The organic extracts were combined, dried over magnesium sulphate, filtered and evaporated to a reduced volume.

However, no tertiary amide precipitated nor was there any evident from t.l.c analysis. Following work-up of the reaction, the main products isolated were the hydrazone (153) and its reduced form, N-acetyl-*p*-nitrophenylhydrazine (155).

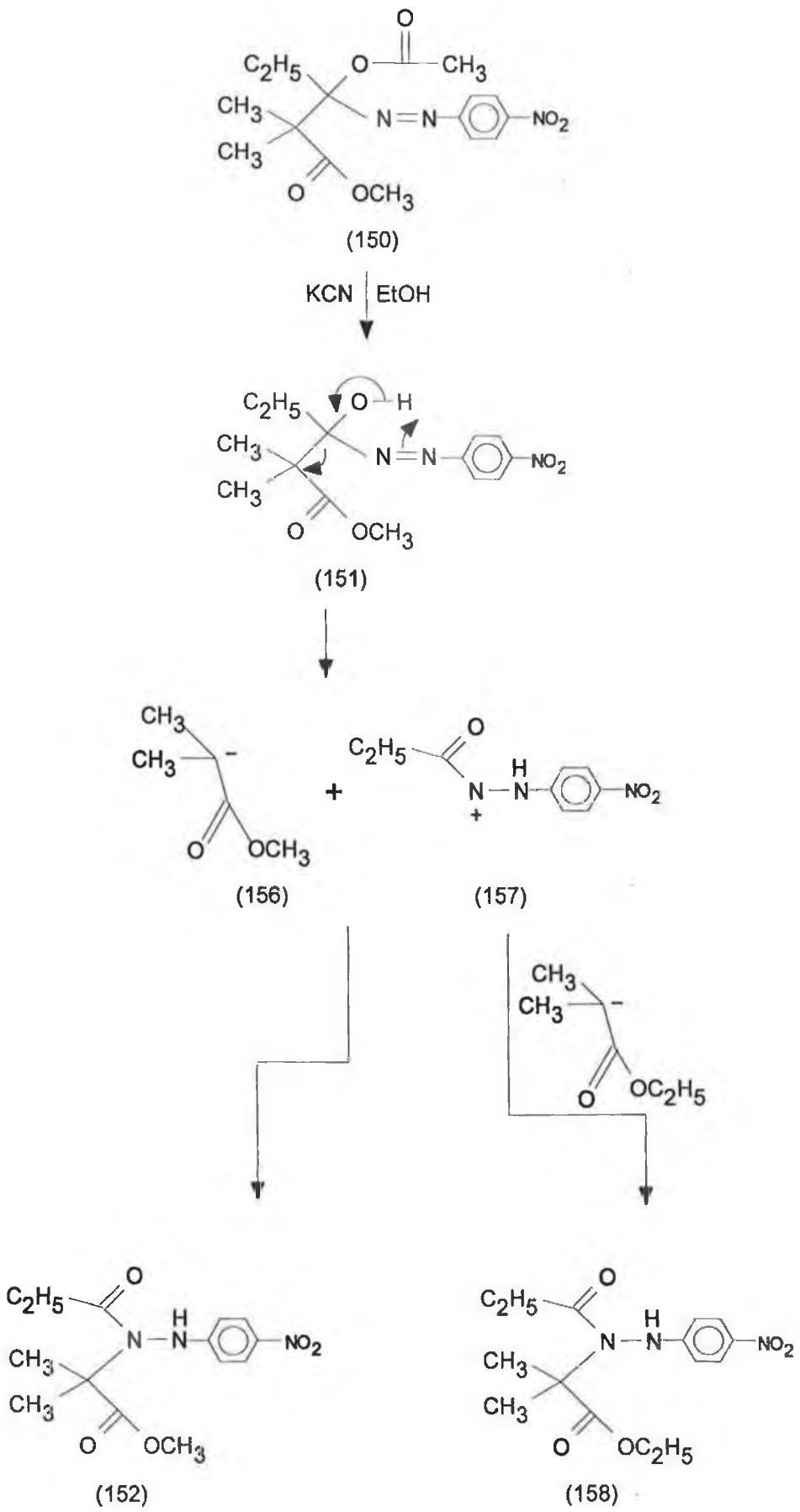
The reaction was repeated using sodium hydride as base in order to encourage the formation of the ethyl isobutyrate anion and thus improve the possibility of an addition reaction. However following such conditions, the product (145), *via* this proposed addition mechanism, was not detected.

Thus arrival at the tertiary amide *via* an addition mechanism as outlined by route (B) (Scheme 2.36), is improbable.

2.2.6 (ii) Crossover experiment

In order to further consider the idea of an addition mechanism, the following crossover experiment (Scheme 2.39) was considered:

Scheme 2.39



The azoacetate (150) of methylpropionylacetate-*p*-nitrophenylhydrazone was heated in KCN/EtOH which has allowed for isolation of the rearrangement product (152) (Scheme 2.34). If the rearrangement proceeds via a carbon to nitrogen migration involving two steps, then addition of a competing anion (154) should allow for a quantity of (158) procured by this competitive route. Thus a mixture of tertiary amides (152) and (158) would be anticipated (Scheme 2.39). This cross-over type experiment further investigates if the base induced rearrangement of azoacetate to tertiary amide occurs via a two step addition mechanism.

The azoacetate (150) was heated at 80°C in the EtOH/KCN system for 24 hrs in the presence of a large excess of ethyl isobutyrate (154). Following work-up of the reaction, the product which readily precipitated proved to be the tertiary amide (152). Tertiary amide (158) due to the proposed competing reaction was not detected.

Consequently, results from both the addition reaction and the crossover experiment suggest a two step mechanism is not involved. This points to the one-step concerted mechanism as outlined by route (A) (Scheme 2.36).

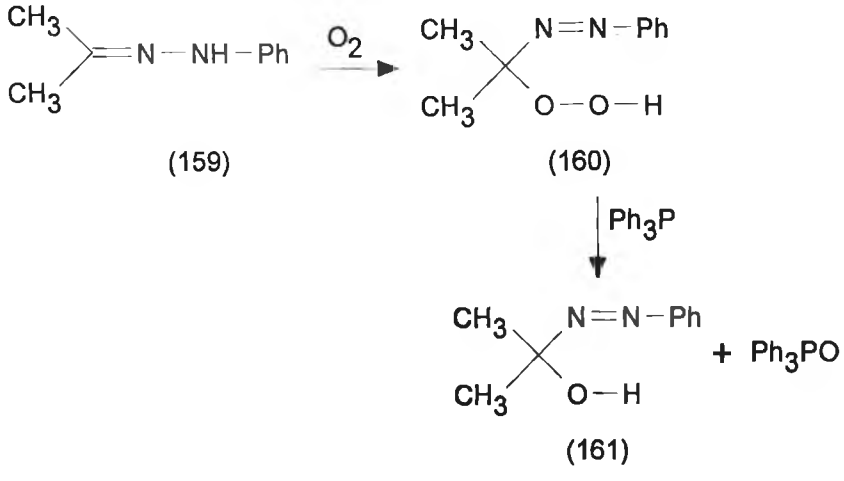
Another approach in addressing the mechanism, involved conversion of the azoacetate of dimethylethyl acetoacetate (85) to the corresponding tertiary amide (145) using a five-fold excess of KCN as base. The amide (145) was isolated as before, in a 35% yield. Therefore increasing the amount of base has little effect on the product yield, as anticipated for a one step concerted mechanism.

2.2.7 AZOCARBINOL FORMATION

The rearrangement from azoacetate to tertiary amide incorporates an azocarbinol intermediate, as seen in Scheme 2.31. It was decided to consider isolation of this proposed azocarbinol intermediate (144) and subject it to the basic conditions as a route to the tertiary amide (145).

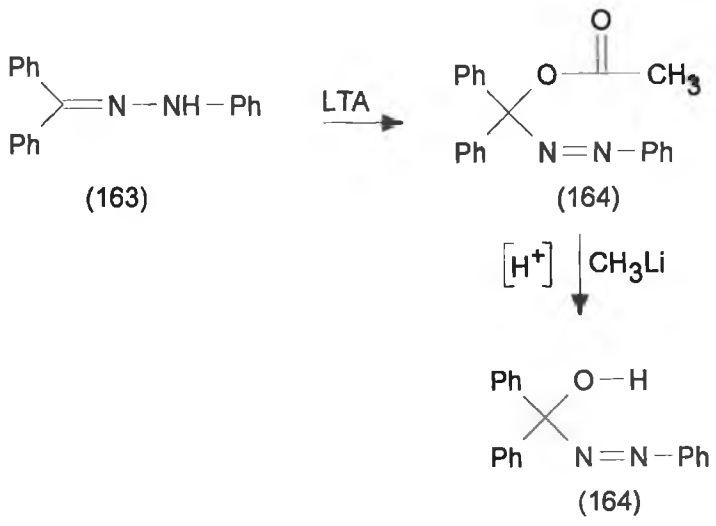
Azocarbinols have been previously synthesised by oxidation of the hydrazone followed by reduction of the peroxide to the azoalcohol[93] using triphenyl phosphine as illustrated by Scheme 2.40.

Scheme 2.40



Oxidation of the hydrazone can also be effected by LTA followed by reduction of the resulting azoacetate with methyllithium in acidic conditions[93] forming the azocarbinol (Scheme 2.41).

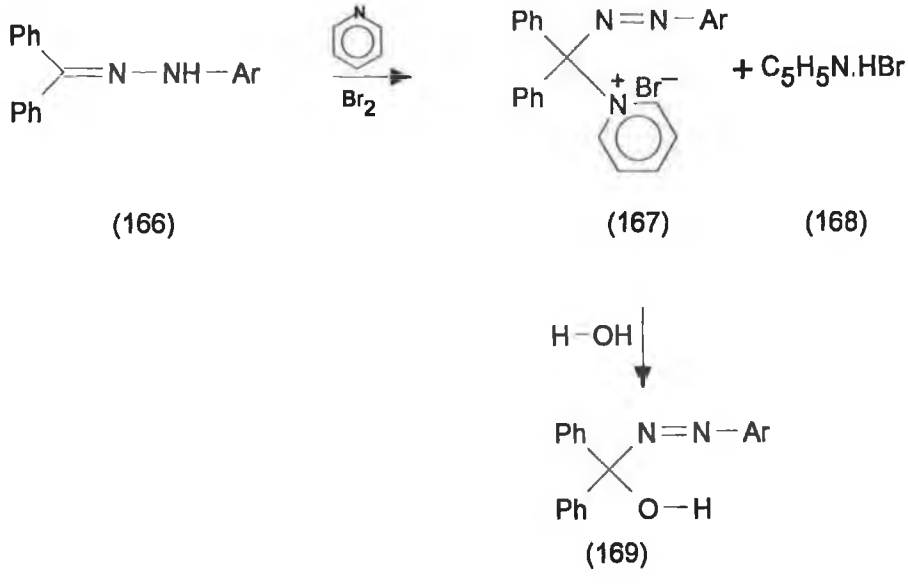
Scheme 2.41



(163) (164) (164)

Alternatively azocarbinols have been synthesised *via* hydrolysis of pyridinium bromide salts[111,113].

Scheme 2.42



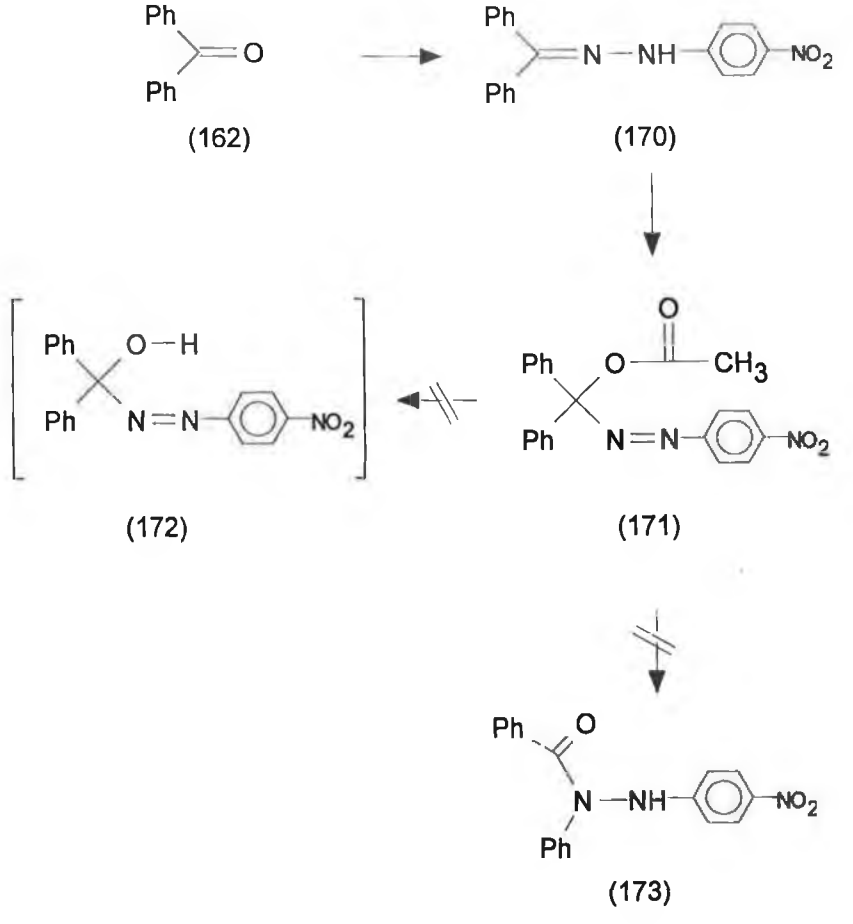
(166) (167) (168) (169)

For example Schantl *et al.*[111] report the *p*-chlorophenylhydrazone of benzophenone was converted to the corresponding azocarbinol *via* the pyridinium bromide salt, depicted above (Scheme 2.42).

Schantl *et al.*[111] have reported the conversion of *p*-nitrophenyl hydrazone of benzophenone to the corresponding azocarbinol. Therefore this hydrazone was considered as a compound which may undergo conversion to the azocarbinol, both by the route reported by Schantl *et al.*[111] and *via* the KCN\EtOH system under investigation in this chapter.

Rearrangement of the azoacetate of benzophenone *p*-nitrophenylhydrazone, using the KCN/EtOH system, was first considered (Scheme 2.43).

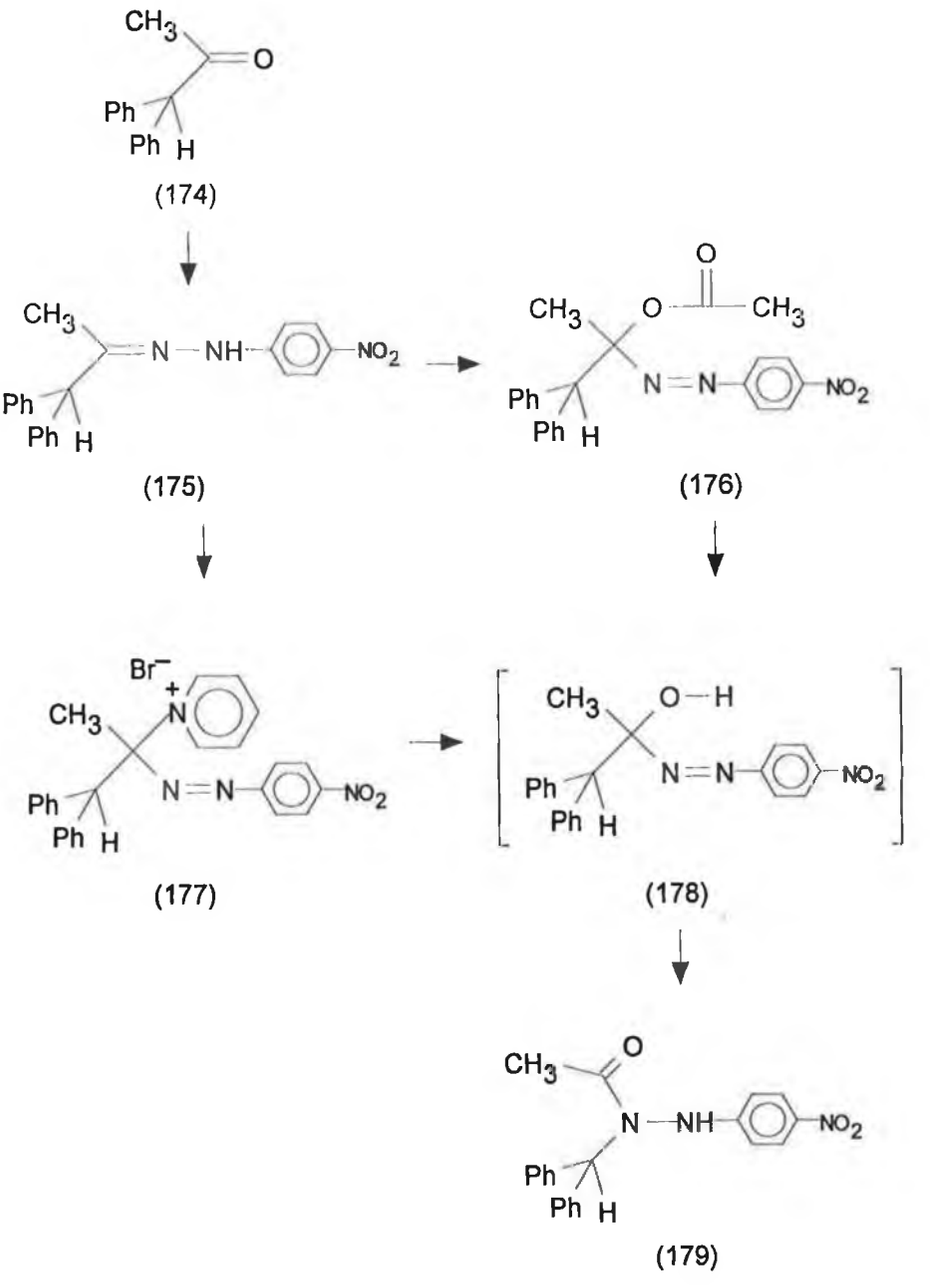
Scheme 2.43



The *p*-nitrophenyl hydrazone of benzophenone (170) was synthesised and its oxidation lead to isolation of the corresponding azoacetate (171). However, when azoacetate (171) was heated under reflux in ethanol in the presence of potassium cyanide, none of the anticipated rearrangement product, 2-benzoyl-2-phenyl-*p*-nitrophenylhydrazine (173), was detected. Therefore the method reported by Schantl *et al.*[111], in order to obtain azocarbinol (172), was not pursued, for this particular hydrazone.

1,1-diphenyl acetone (174) was then considered as an alternative candidate which may undergo rearrangement by both routes (Scheme 2.44), *i.e* formation of the azocarbinol from the hydrazone (175) or from the azoacetate (176).

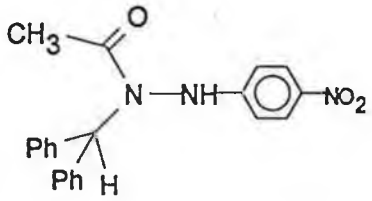
Scheme 2.44



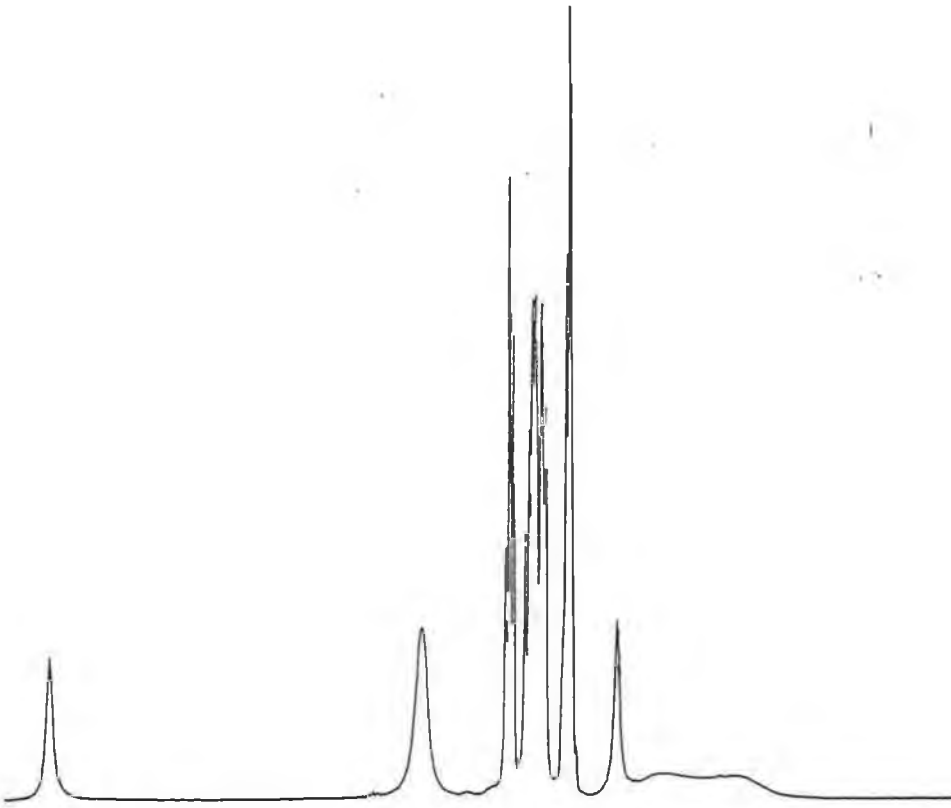
The *p*-nitrophenylhydrazone (175) of 1,1-diphenyl acetone was synthesised and following oxidation, the azoacetate (176) was isolated. The azoacetate rearranged in the KCN/EtOH system to give the corresponding hydrazide (179).

A ^{1}H NMR temperature study of the hydrazide (179), indicates typical amide characteristics [Figures 2.9, 2.10 and 2.11 overleaf] previously observed [See Figures 2.1, 2.2].

Figure 2.9



@ 20°C



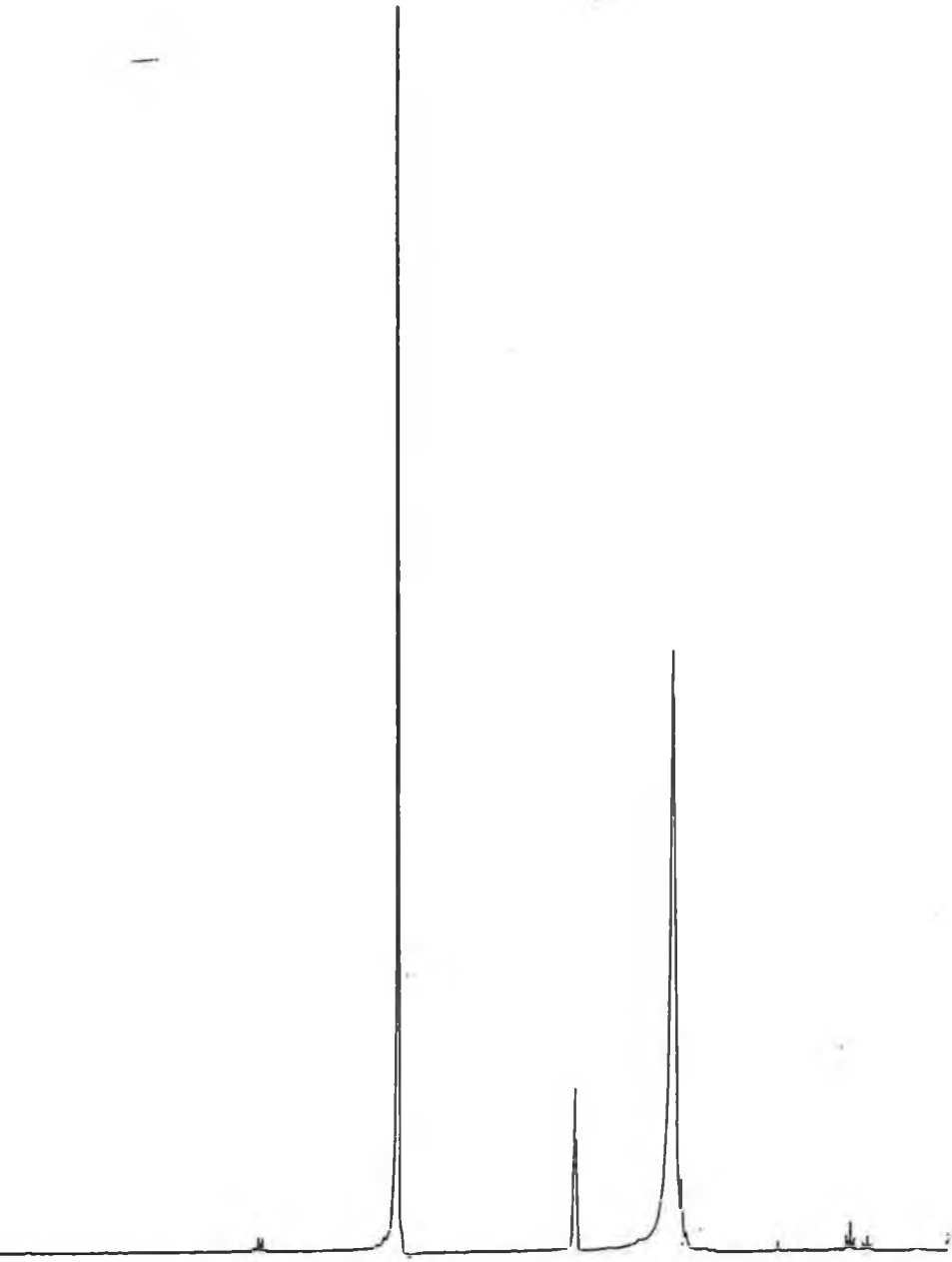
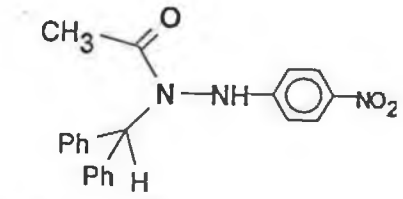
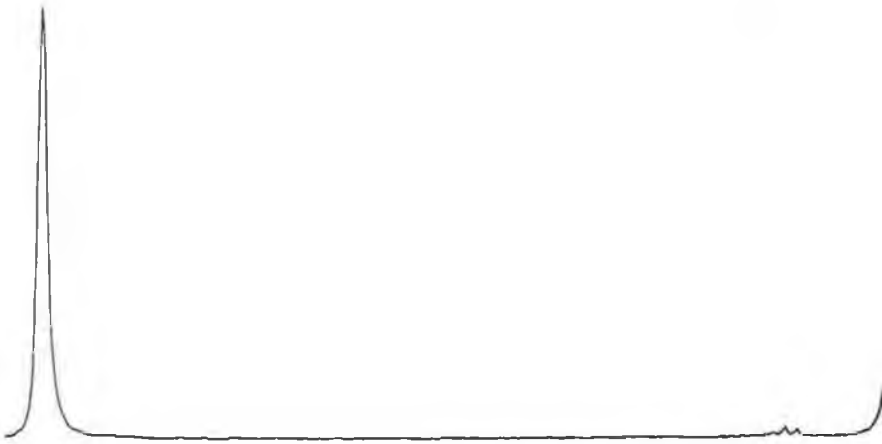


Figure 2.10



@ 40°C



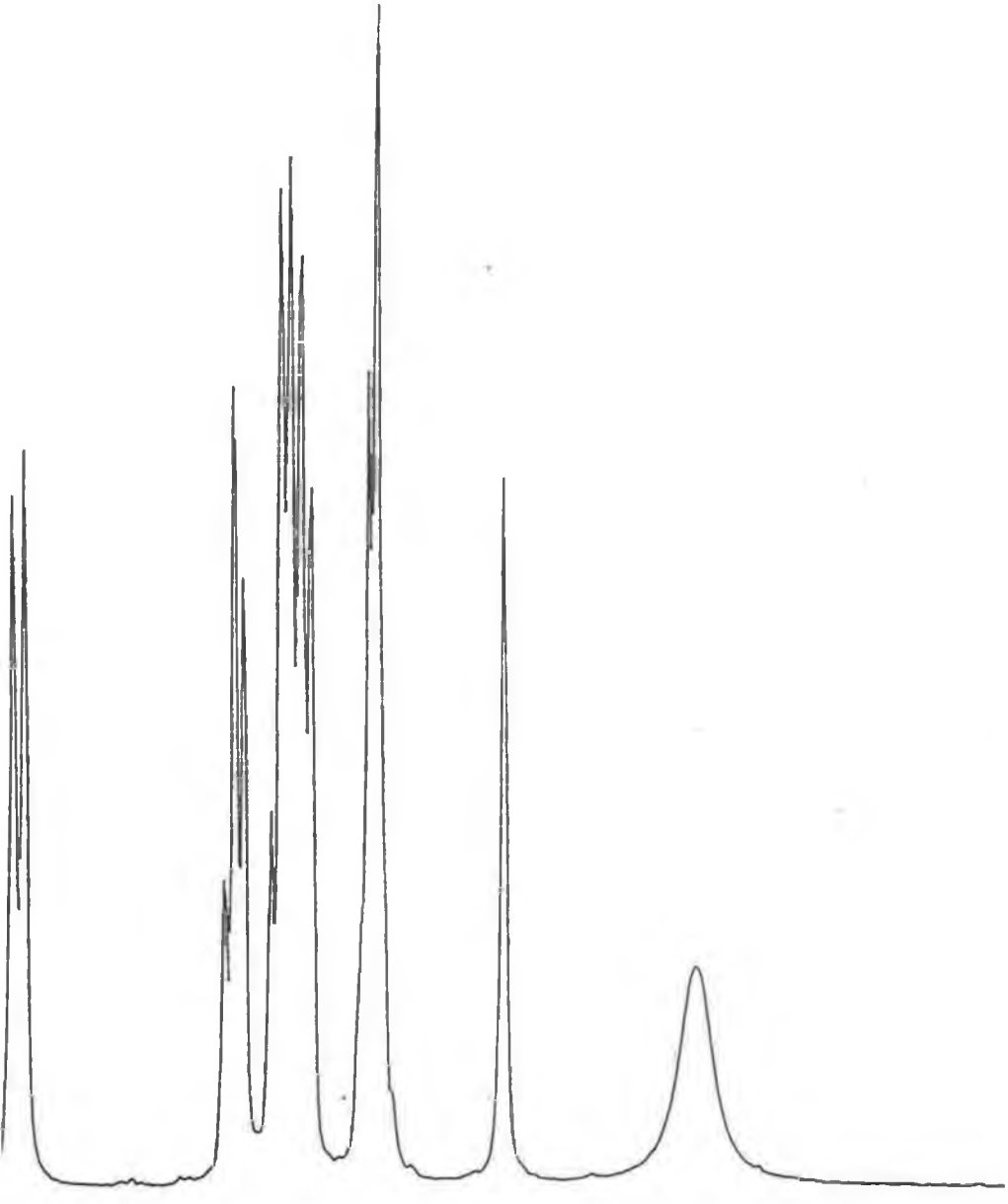
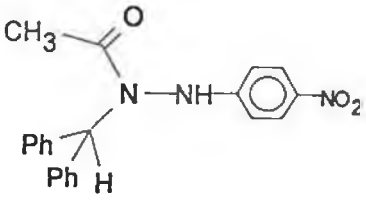
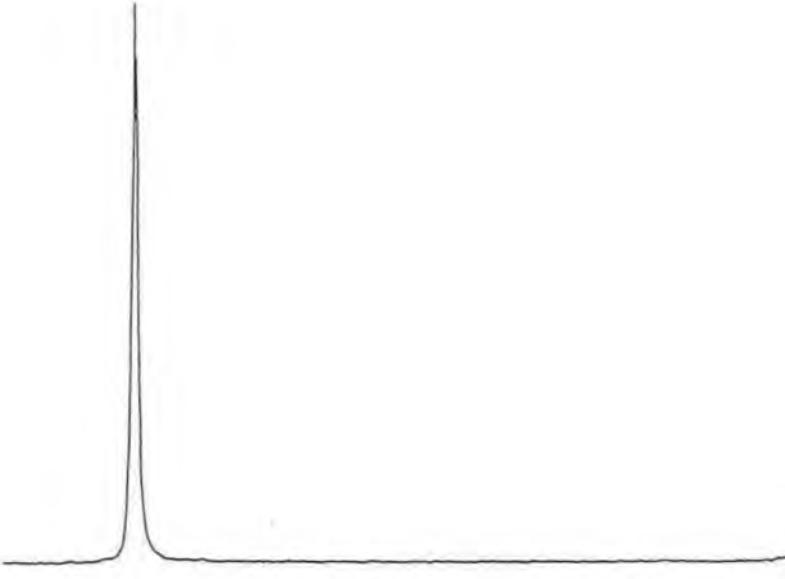
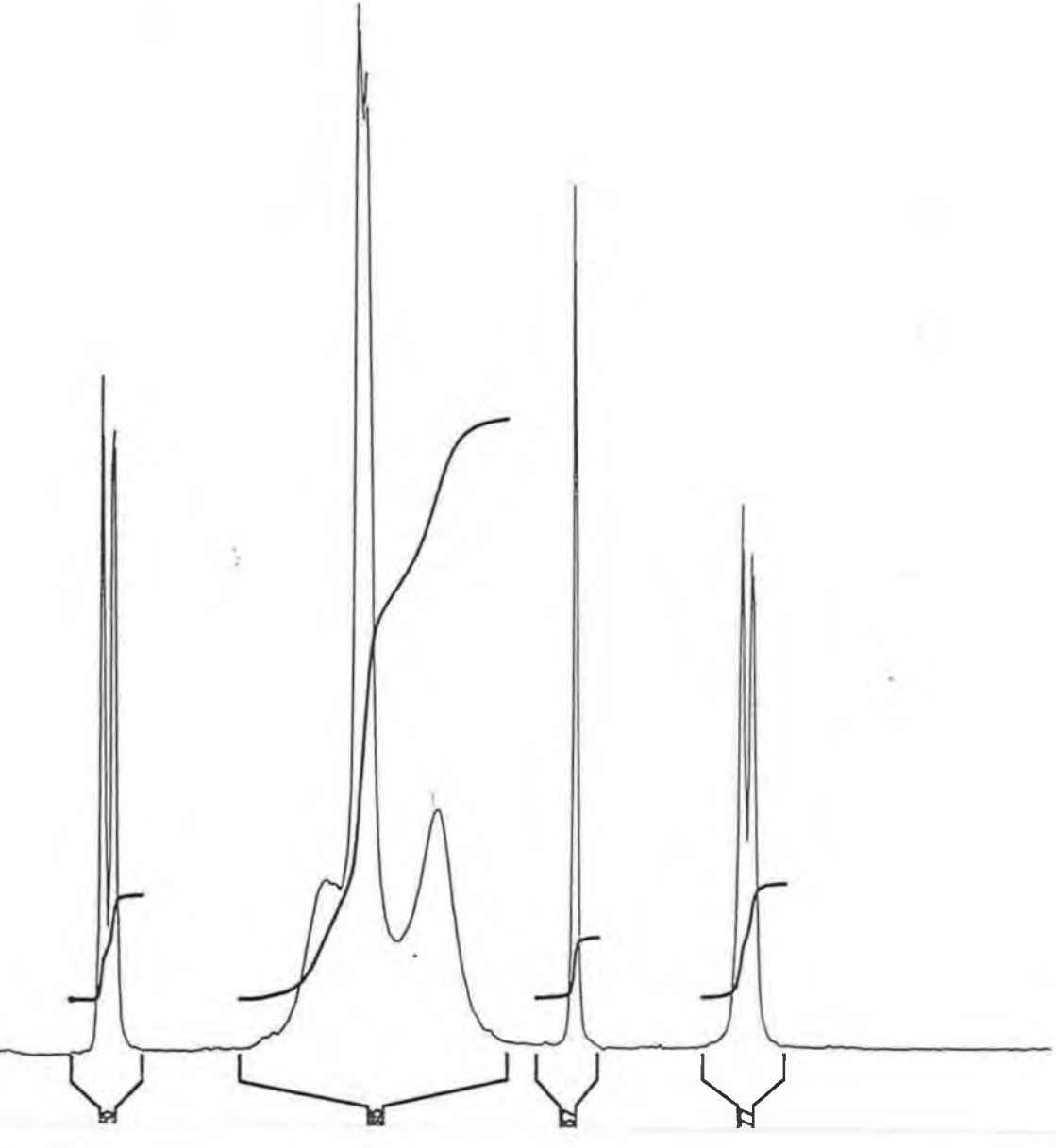


Figure 2.11



@ 60°C



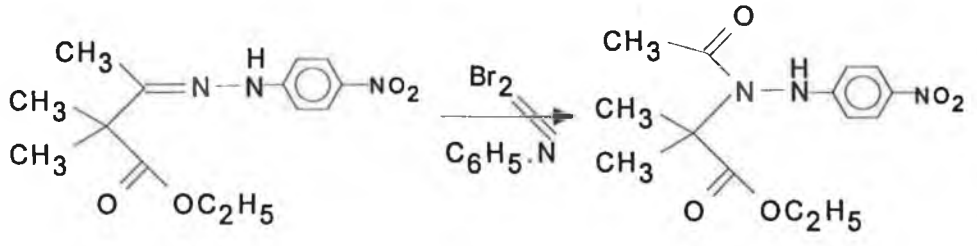


The hydrazone (175) of 1,1-diphenylacetone was then reacted with pyridinium bromide, using the procedure described by Schantl *et al.*[111] as an alternative route to the proposed azocarbinol (178). If this azocarbinol can be isolated and exposed to the KCN/EtOH system, then subsequent formation of the tertiary amide would prove the existence of the azocarbinol as an intermediate.

Thus the hydrazone was reacted with bromine in pyridine in order to effect salt formation. A solution of aqueous $NaHCO_3$ was then added in an attempt to isolate the azocarbinol. However none of the required product was evident. The basic conditions may cause any probable azocarbinol present to rearrange to the corresponding tertiary amide (179). Following work up of the reaction neither azocarbinol nor tertiary amide were present. The hydrazone (175) was evident in large quantities.

This reaction, involving the pyridinium bromide salt followed by base, in order to form azocarbinol, was then considered for the *p*-nitrophenylhydrazone of 2,2-dimethylethyl acetoacetate (Scheme 2.45). Again, if the azocarbinol (144) was not isolatable the reaction may proceed to the tertiary amide (145), as proposed for 1,1-diphenylacetone-*p*-nitrophenylhydrazone (175).

Scheme 2.45



(83) (145)

The procedure was followed as reported by Schantl *et al.*[111]. However adding ether in order to effect precipitation of the pyridinium bromide salt of the hydrazone (83) was not sucessful. Addition of base to the reaction at this stage did not provide the azocarbinol.

The reaction was repeated a number of times, isolating samples at different stages and times. None of these samples provided azocarbinol (144) or rearranged tertiary amide (145), either before or following addition of aqueous $NaHCO_3$.

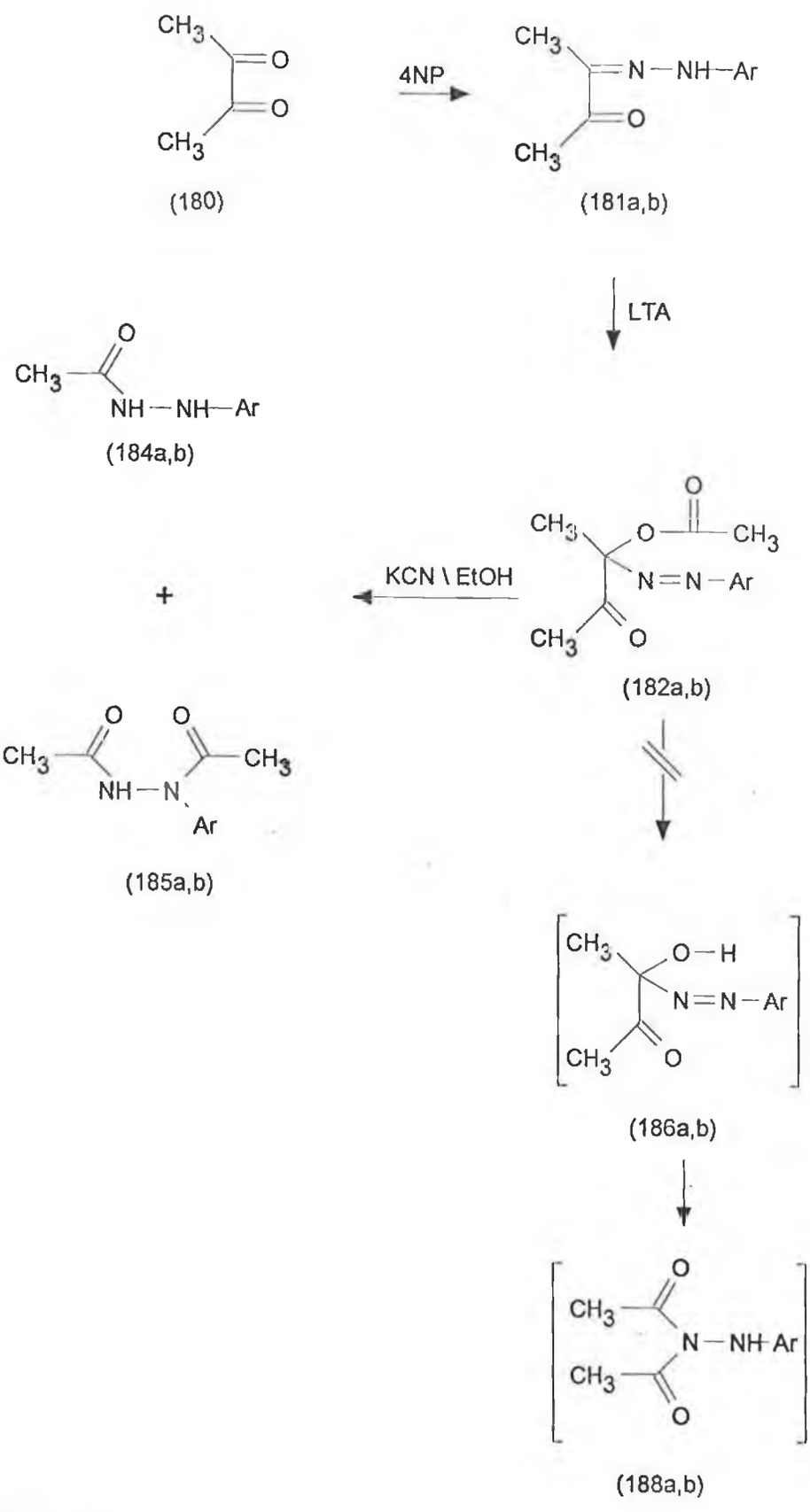
2.2.8 BUTANE-2.3-DIONE REARRANGEMENTS

The basic conditions to which the preceeding azoacetates were exposed caused a number of these compounds to rearrange to the corresponding tertiary amides. We now wish to extend this rearrangement to more azoacetate derivatives with the intent of addressing the mechanism and limitations involved. One such limitation is the migrating ability of groups attached to the azoacetate. In order to consider groups *alpha* to the imine carbon of the respective hydrazone with good migrating ability, the reactions involving the diketone, butane-2,3-dione (180) (Scheme 2.46) were investigated.

The mono-*p*-nitrophenylhydrazone (181b) formation was ensured by the slow addition of a solution of 4NP to an excess of the diketone, reducing the possibility of formation of the dihydrazone. The hydrazone was oxidised to the azoacetate (182b) by LTA. The azoacetate was heated under reflux with potassium cyanide in ethanol overnight, the reaction conditions known to induce rearrangement. A pale brown solid was precipitated from the reaction which was identified as 2-acetyl-*p*-nitrophenylhydrazone (184b) with obvious NH peaks at 9.3ppm and 9.9ppm (IR: 3290; 3260 cm^{-1}).

When the reaction was repeated in ethanol opting for the milder base, potassium carbonate, a second product was evident with an R_f value similar to the former product isolated. Following chromatography the new product was collected as a solid. Spectral details indicated the formation of 1,2-diacetyl-*p*-nitrophenylhydrazine (185b). In this case, the proposed 2,2-diacetyl-*p*-nitrophenylhydrazine (188b), *via* the tentative mechanism involving azocarbinol (186b) rearrangement, was not isolated (Scheme 2.46).

Scheme 2.46



a : Ar = Ph

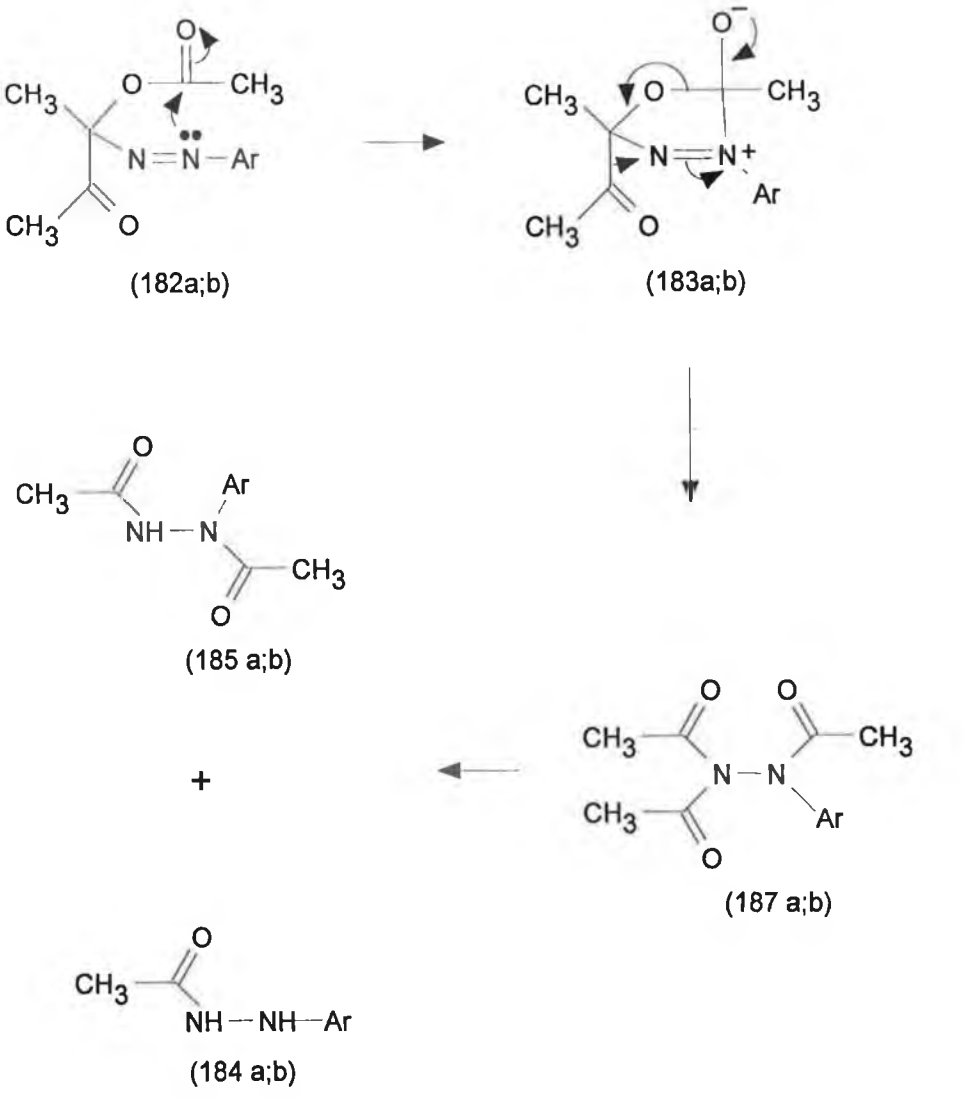
b : Ar = *p*-NO_2-Ph

This reaction further illuminates the possible mechanism by which azoacetates rearrange to the corresponding tertiary amides in the basic conditions provided by the KCN/EtOH system.

As the solvent used was EtOH, the acetyl group acquired by the nitrogen, bearing the *p*-nitrophenyl group, could not originate from the solvent. The acetoxy group of the azoacetate is a more intrinsic part of the rearrangement than originally anticipated.

It is not replaced *via* a transterification reaction, but migrates, and following rearrangement, provides the acetyl group which the products bear, as follows (Scheme 2.47).

Scheme 2.47

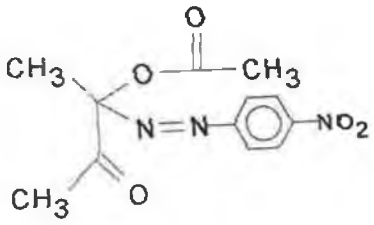


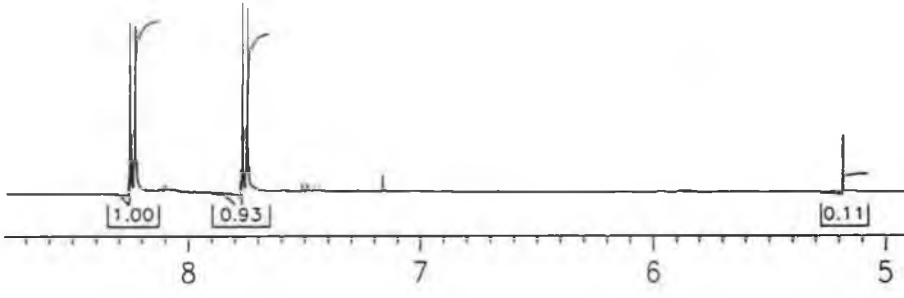
Thus the reaction is seen to proceed *via* a carbon to nitrogen acetyl migration. The mechanism involves a triacetylhydrazine species (187) which undergoes deacetylation to provide the products (184, 185) isolated.

The reaction was repeated using the KCN/EtOH system when t.l.c analysis indicated the presence of both products (184b) and (185b) after 30 mins with gentle reflux. Following work-up of the reaction, these products were initially isolated as a mixture.

Analysis of the ^{1}H spectrum of this mixture indicated the presence of (184b) and (185b) in 37% and 63% yields respectively. [Figures 2.12 and 2.13 overleaf].

Figure 2.12





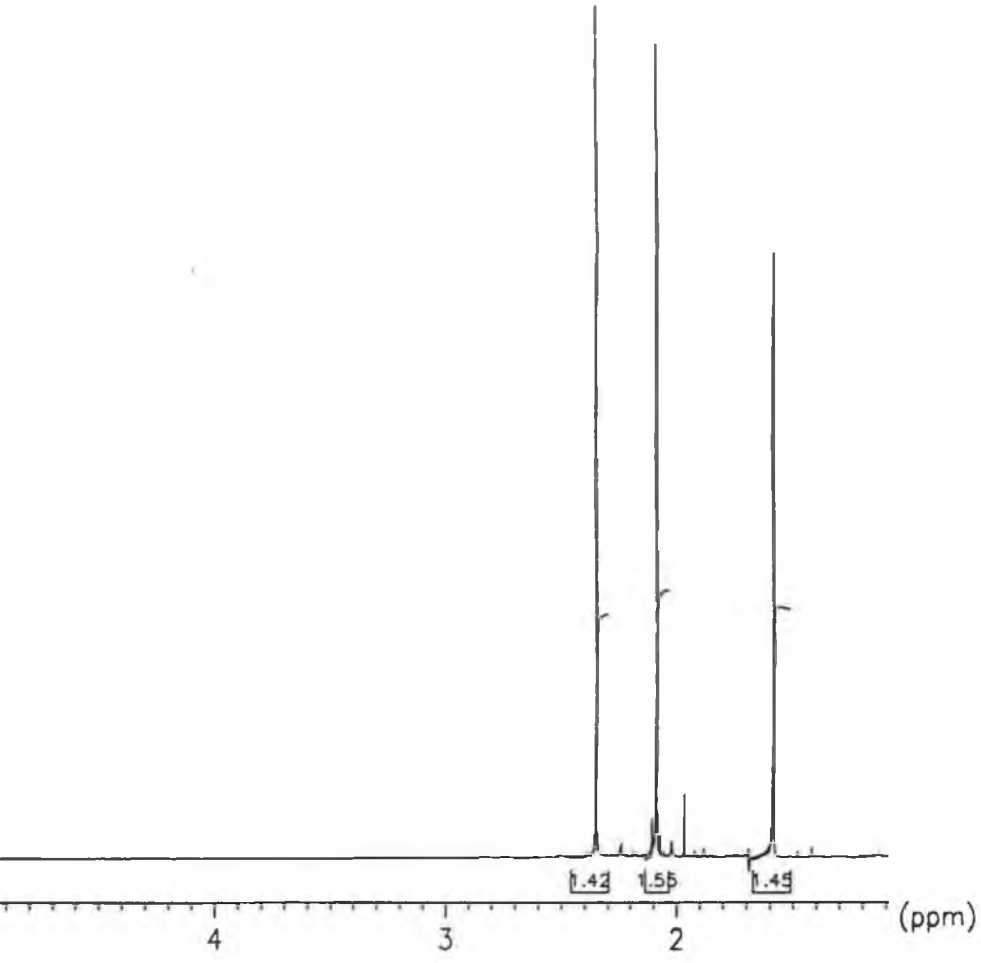
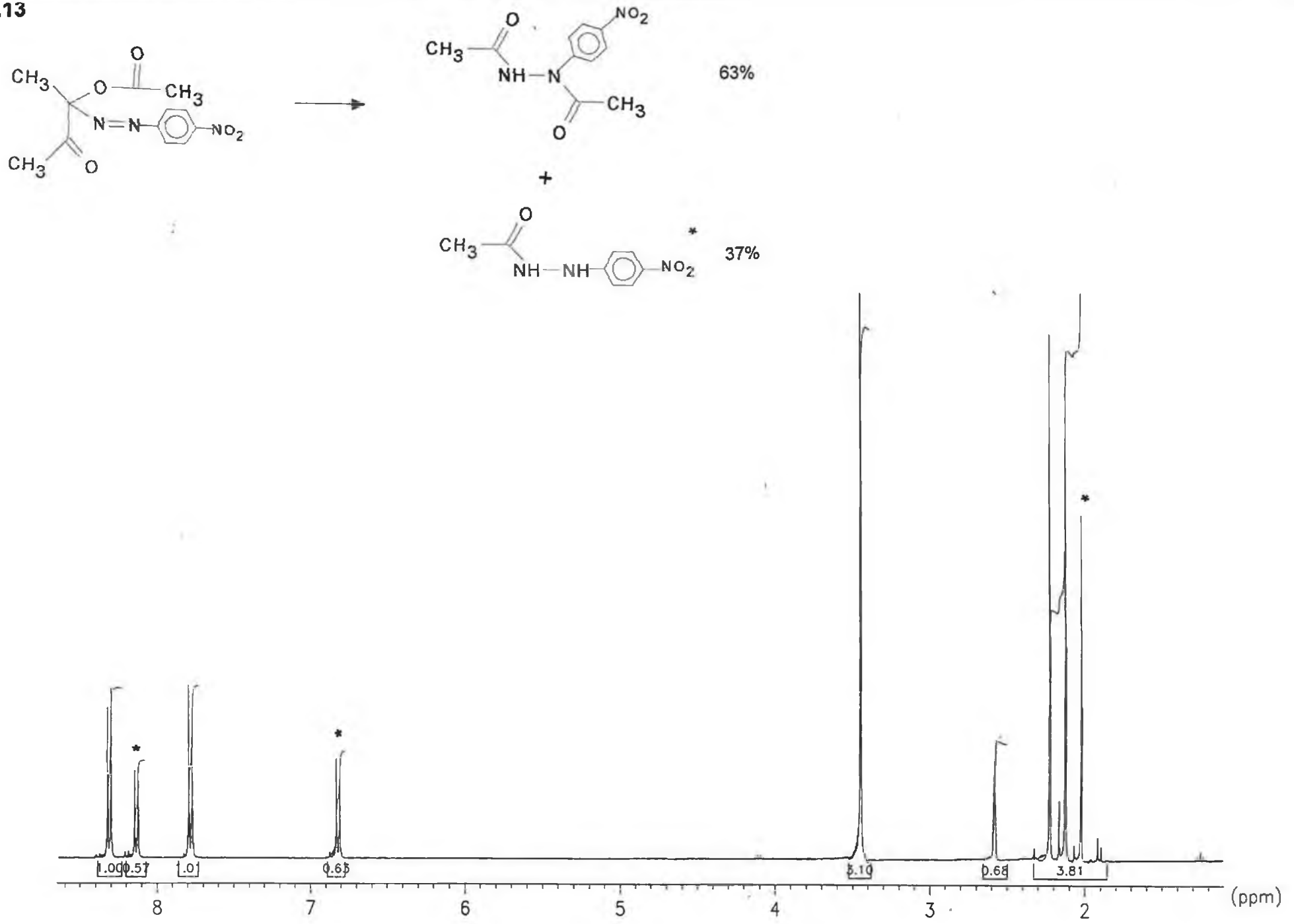

1.42
1.55
1.45
4
3
2
(ppm)

Figure 2.13


CH3
O
CH3
O
N=N
NO2
CH3
O
NO2
CH3
O
NH–N
CH3
O
63%
+
CH3
O
NH–NH
NO2
*
37%
*
*
1.00
0.57
1.01
0.63
5.10
0.68
3.81
8
7
6
5
4
3
2
(ppm)

Following chromatography of the reaction mixture none of the proposed triacetylated intermediate (187b) was detected. The absence of this triacetyl species can be attributed to its ready deacetylation in basic ethanol.

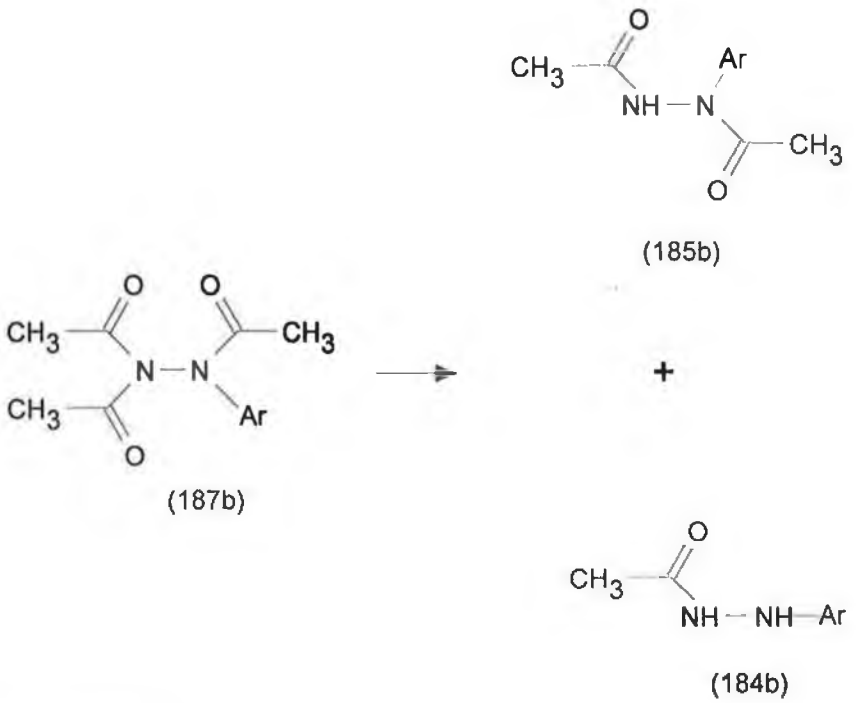
The proposed mechanism (Scheme 2.47 ; Ar:*p*-NO_2Ph) above, involves deacetylation of triacetyl-*p*-nitrophenylhydrazone (187b). Formation to 2,2-diacetyl-*p*-nitrophenylhydrazone (188b), as well as the acetylated species (184b) and (185b) isolated, may well be anticipated. The absence of the diacetyl compound (188b) was addressed by considering the independent acetylation of *p*-nitrophenylhydrazone.

When *p*-nitrophenylhydrazone was acetylated using excess acetic anhydride in acetic acid, 2-acetyl-*p*-nitrophenylhydrazone, 1,2-diacetyl-*p*-nitrophenylhydrazone, 1,2,2-triacetyl-*p*-nitrophenylhydrazone and mixtures thereof were isolated. However 2,2-diacetyl-*p*-nitrophenylhydrazone (188b) eluded synthesis each time.

Egg *et al.*[108] report similar findings. They refer to the readily isolated 1-acyl-2-arylhydrazines and 1,2-diacyl-arylhydrazines[109]. They established a system to provide 2,2-diacetyl-phenylhydrazines. Likewise substituted phenylhydrazines gave rise to 2,2-diacetyl derivatives. However when the phenyl substituent was a *p*-nitro group, the anticipated 2,2-diacetyl derivative was not isolated, thus further highlighting the elusive nature of this acetyl derivative (188b).

Scheme 2.47 proposes formation of (184) and (185) *via* a deacetylation of the triacetylated hydrazine intermediate (186). This was further investigated as follows. The compound, 1,2,2-triacetyl-*p*-nitrophenylhydrazine (187b) was independently synthesised by heating *p*-nitrophenylhydrazine with an excess of acetic anhydride in acetic acid followed by precipitation of the product as a solid by the dropwise addition of water. When (187b) was stirred in hot ethanol in the presence of 1.2 equivalents of KCN, its instability was highlighed by its disappearance within minutes. The reaction was quenched after fifteen minutes, when 2-acetyl-*p*-nitrophenylhydrazine (184b) and 1,2-diacetyl-p-nitrophenylhydrazine (185b) were evident by t.l.c analysis (Scheme 2.48).

Scheme 2.48



[b: Ar =*p*-NO_2Ph]

Analysis of the ^{1}H NMR spectrum of this mixture indicated the presence of (184b) and (185b) in 42% and 58% yields respectively. [Figures 2.14 and 2.15 overleaf].

Figure 2.14

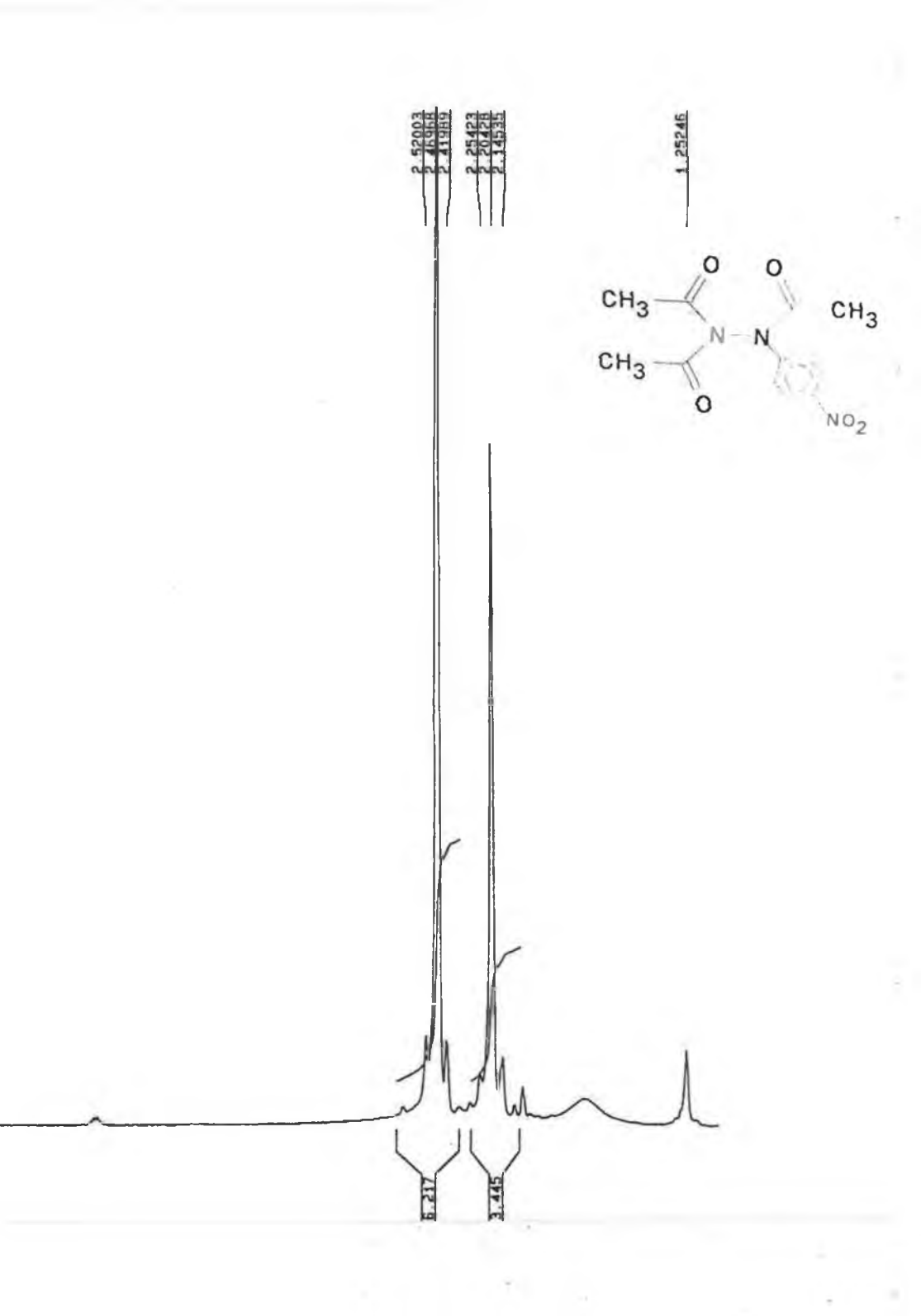
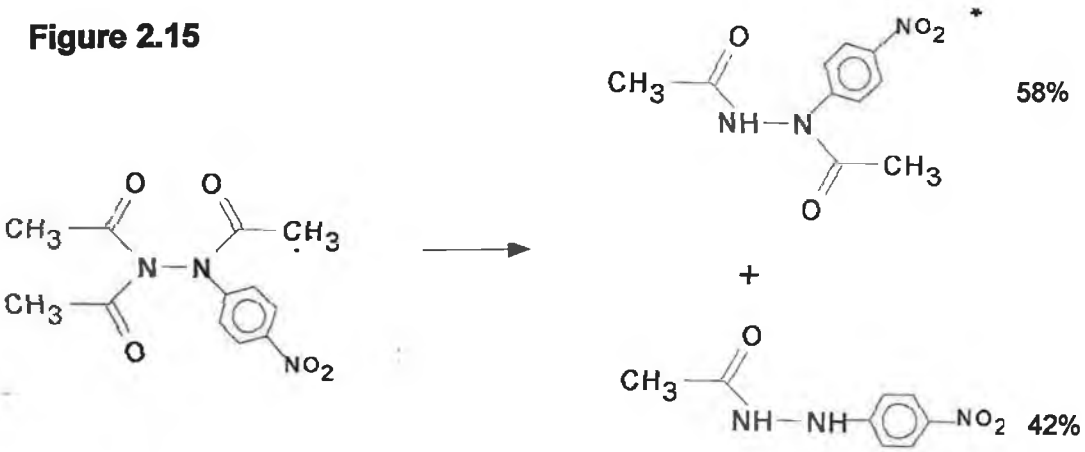
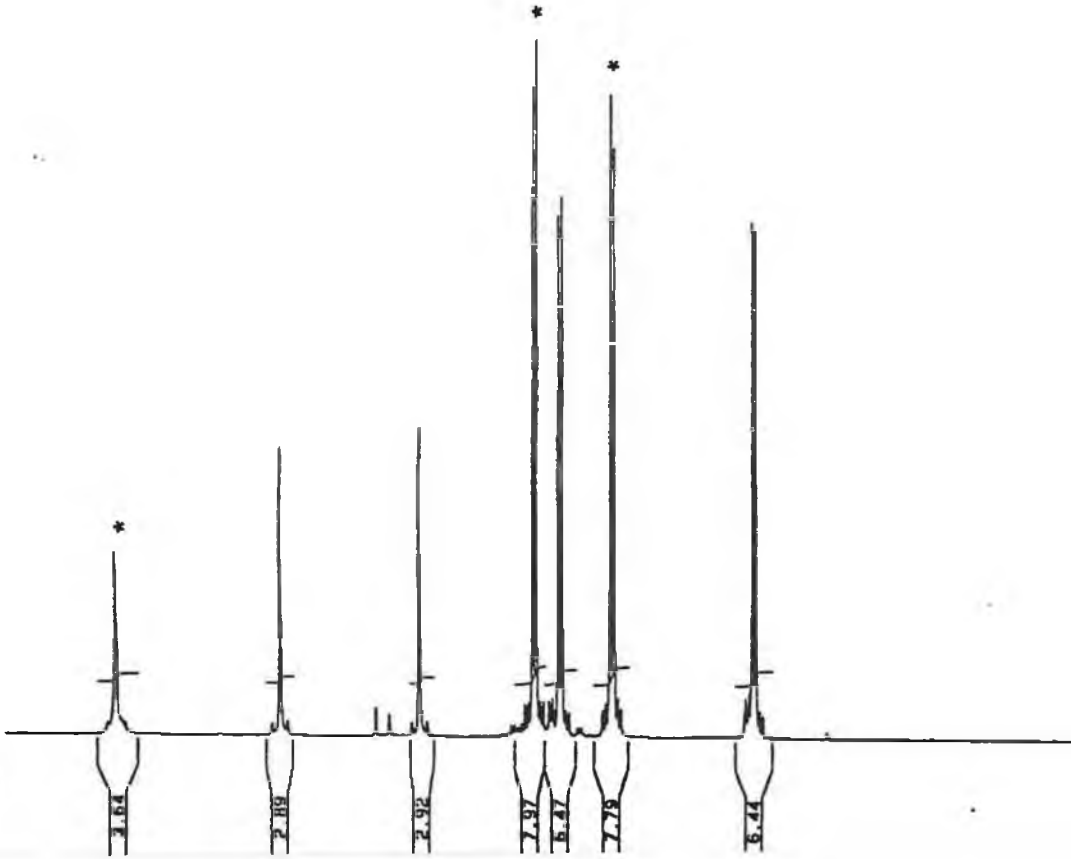
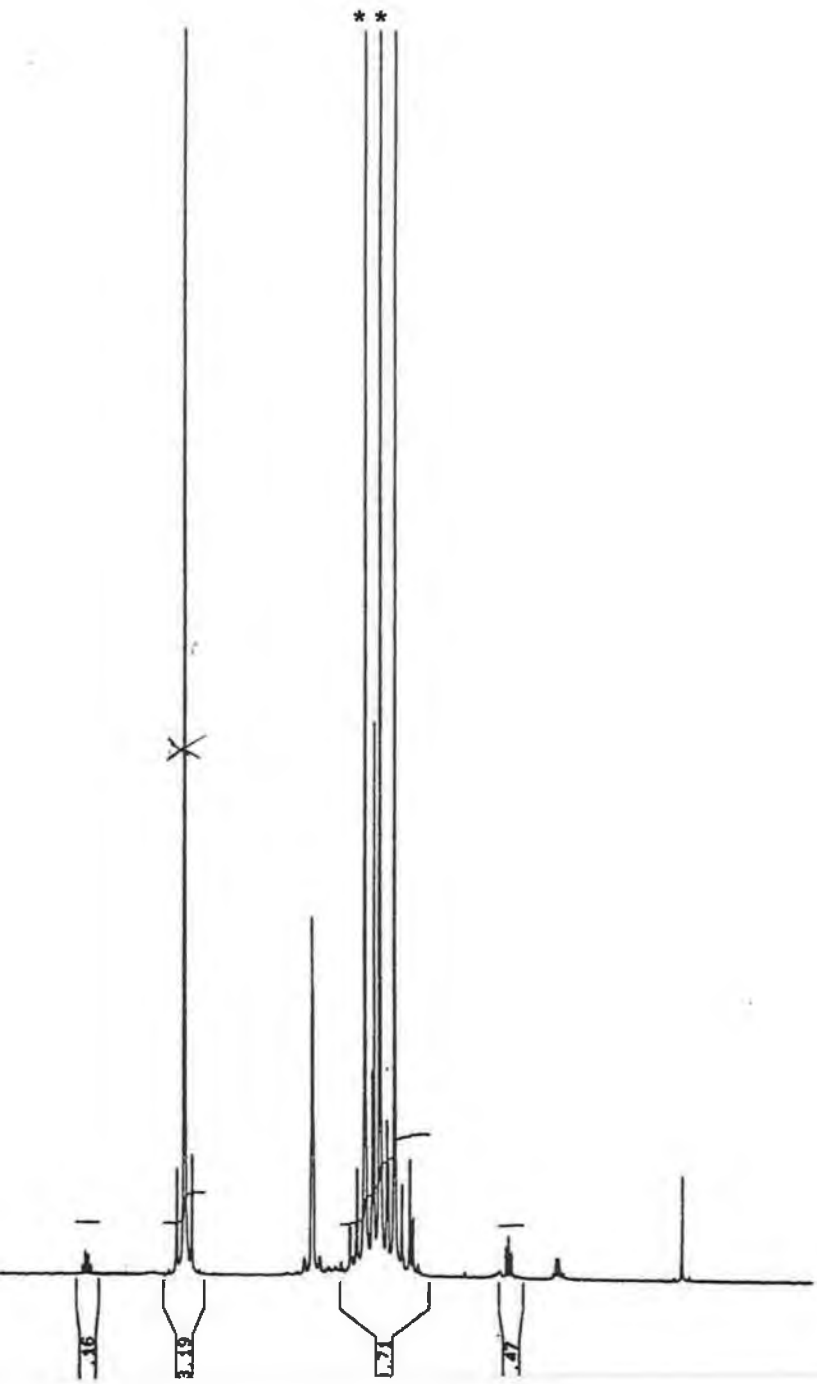

2.52003
2.41989
2.25423
2.14531
1.25246
6.217
3.445

Figure 2.15


O
O
CH3
CH3
N
N
CH3
O
NO2
O
CH3
NH
N
CH3
O
NO2
*
58%
+
O
CH3
NH
NH
NO2
42%


*
*
*
3.64
2.89
2.92
7.97
6.47
7.79
6.44


* *
.16
3.19
1.71
.47

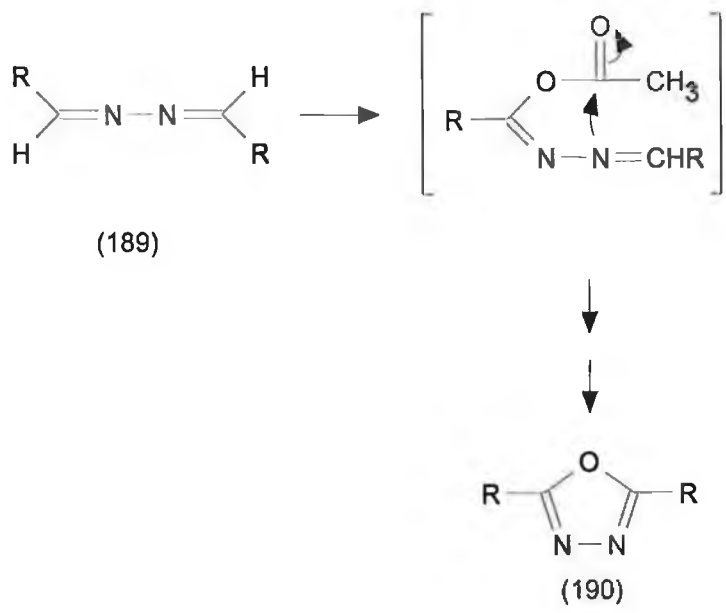
Thus the azoacetate of butane-2,3-dione-*p*-nitrophenylhydrazone (182b) rearranges involving a carbon to nitrogen acetyl migration to form the triacetylated species (187b) as an intermediate. It further deacetylates to form the 2-acetyl derivative (184b) and the 1,2-diacetyl derivative (185b) as the products, which were present in 37% and 63% yields respectively.

This is further supported as the triacetylated species (187b) has been independently synthesised. When a sample is exposed to the reaction conditions known to effect rearrangement, it undergoes deacetylation yielding the products (184b) and (185b), present in 42% and 58% yields respectively, which are quantitatively comparable to the products isolated from azoacetate rearrangement above.

The aryl-*p*-nitrophenyl moiety may effect the stability of the proposed intermediate (187), and its subsequent isolation. Therefore, in order to overcome this, the reactions of butane-2,3-dione monophenylhydrazone (Scheme 2.46: Ar=Ph) were considered thus. Following hydrazone (181a) and azoacetate synthesis (182a), the rearrangement was conducted in the KCN/EtOH system. In this case a greater quantity of the 1,2-diacetylated phenylhydrazine (185a) was isolated than the analogous 1,2-diacetylated-*p*-nitrophenylhydrazine (185b), most likely due to absence of the destabilizing nitro group. 2-Acetyl-phenylhydrazine (184a) was also isolated as for (184b). However, as for the *p*-nitro derivative, none of the proposed intermediate 1,2,2-triacetylphenylhydrazone (187a) was detected. Its absence can also be attributed to the ready deacetylation observed for the *p*-nitrophenyl derivative of the tiacetylated intermediate (187b) (Scheme 2.48).

Acetyl migrations of this nature have been reported previously[12,66]. For example, both aromatic and aliphatic aldazides (189) yield 1,3,4-oxadiazolines (190) on treatment with LTA as follows (Scheme 2.49).

Scheme 2.49



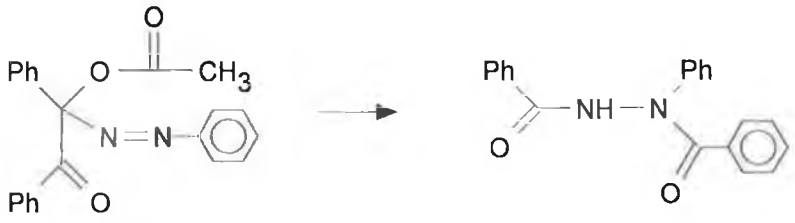
(189)

(190)

2.2.9 Benzil (Benzoin) rearrangements

Gladstone and Norman[11] report azoacetates derived from benzil and benzoin arylhydrazones rearrange in the presence of a Lewis acid (Scheme 1.9a). Thus the azoacetate (12a) of benzil monophenylhydrazone is converted to N,N'-dibenzoylphenylhydrazone (14a), involving a deacetoxylation followed by a benzoyl migration.

Scheme 1.9a



(12a) (14a)

The corresponding azoacetate (12b) of benzil mono-*p*-nitrophenylhydrazone is converted to 2-benzoyl-1-acetyl-*p*-nitrophenylhydrazine (14b) involving acetyl migration followed by debenzoylation.

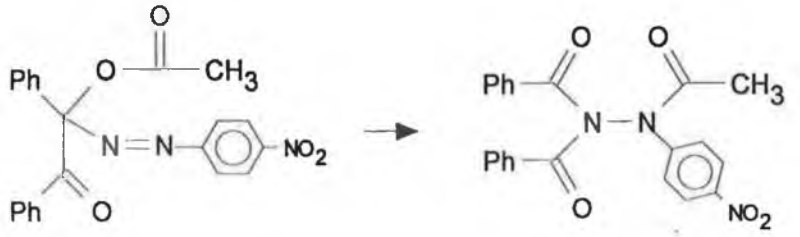
Scheme 1.9b

(12b) (14b)

It was decided to consider the type of reaction these azoacetates (12a) and (12b) may undergo under the basic conditions being studied as a further insight into the reaction. Thus in order to isolate the azoacetate (12b) the *p*-nitrophenyl hydrazone of benzil was first synthesized as follows. An excess of benzil was condensed with 4NP in acetic acid, when the hydrazone (192b) was collected as a yellow solid. Oxidation by LTA resulted in formation of the

azoacetate (12b). When this was heated in ethanol in the presence of potassium cyanide the anticipitated acetyl migration to the N-aryl moiety followed by rearrangement would result in formation of 2,2-dibenzoyl-acetyl-*p*-nitrophenylhydrazine (193b) (Scheme 2.50).

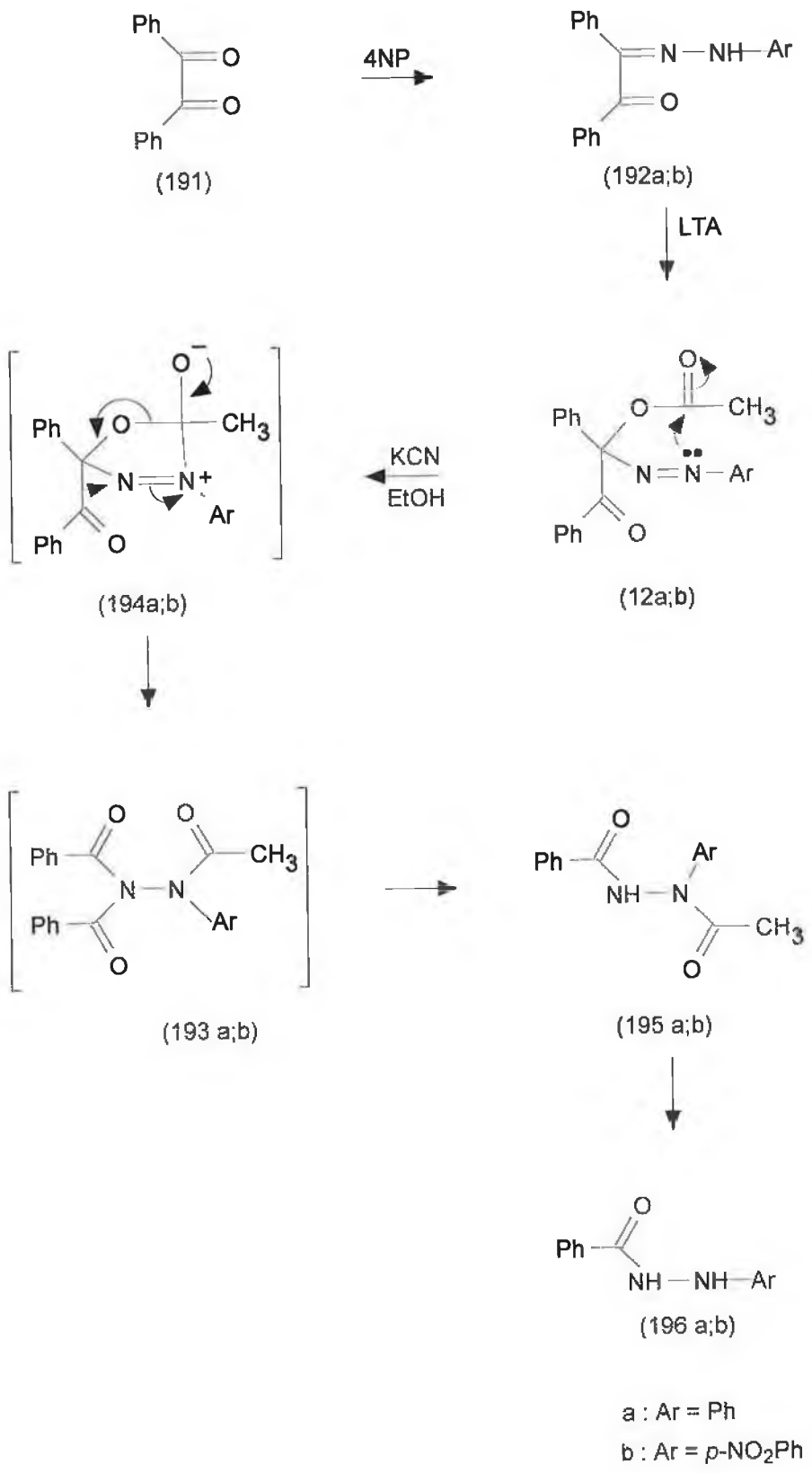
Scheme 2.50



(12b) (193b)

However the product isolated was 2-benzoyl-*p*-nitrophenylhydrazine (196b) (Scheme 2.51: Ar=*p*-NO_2Ph).

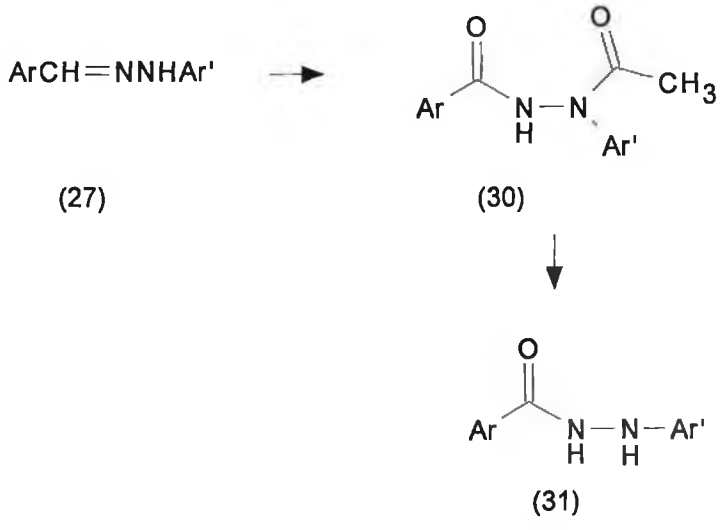
Scheme 2.51


Ph
O
O
Ph
(191)
4NP
Ph
N — NH — Ar
O
Ph
(192a;b)
LTA
O
CH3
Ph
O
N
N
Ar
Ph
O
(194a;b)
KCN
EtOH
O
Ph
O
CH3
N
N
Ar
Ph
O
(12a;b)
O
O
Ph
CH3
N
N
Ar
Ph
O
(193 a;b)
O
Ph
NH
N
Ar
CH3
O
(195 a;b)
O
Ph
NH — NH — Ar
(196 a;b)
a : Ar = Ph
b : Ar = p-NO2Ph

This is explained by considering loss of a benzoyl group from the intermediate (193b) to provide 2-benzoyl-acetyl-*p*-nitrophenylhydrazine (195b) which was destabilised by the *p*-nitro group, thus precluding isolation. Therefore loss of the acetyl group from this compound (195b) resulted in the product, 2-benzoyl-*p*-nitrophenylhydrazone (196b), isolated. The reaction was repeated using benzil monophenylhydrazone azoacetate (12a) (Scheme 2.51: Ar=Ph). This azocetate was synthesised as for (12b). Rearrangement of (12a) by the basic conditions employed, resulted in isolation of 2-benzoyl-1-acetyl-phenylhydrazine (195a), due to absence of the destabilising *p*-nitrophenyl group on (193). The compound was further deacetylated by continued reflux in KCN/EtOH forming 2-benzoylphenylhydrazine (196a).

Indeed Butler *et al.* [12,17] report the oxidation of a range of arylidene arylhydrazones (27) with LTA which lead to the formation of N-acetylhydrazides (30) (Scheme 1.13).

Scheme 1.13



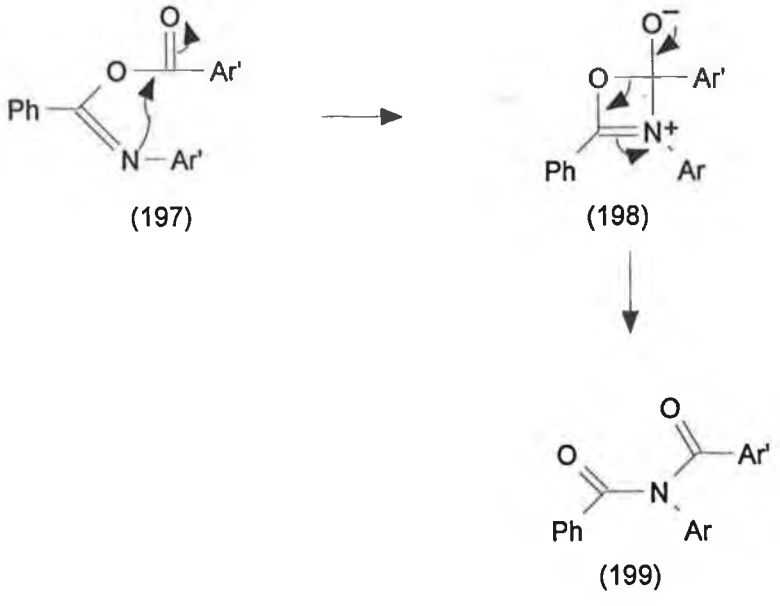
This highlights the facile deacetylation of 2-benzoyl-1-acetylphenylhydrazine (194a) to 2-benzoylphenylhydrazine (195a).

Synthesis of the proposed intermediate 2,2-dibenzoylacetylphenylhydrazine (193a) was considered, as follows. 2-Benzoyl-1-acetylphenylhydrazine (195a) has been isolated *via* the proposed rearrangement (Scheme 2.51). However initial attempts at benzoylation of this compound by reflux with benzoyl chloride, in order to provide the intermediate (193a), have proved unsuccessful.

Acetyl migration followed by rearrangement, as proposed for butane-2,4-dione azoacetate derivatives appears very plausible considering the mechanism (Scheme 2.47) is extended to the reactions of benzil (Scheme 2.51) which satisfactorily explains the products (195) and (196).

References have been made to similar intramolecular acetyl migrations, in the introduction to this chapter. Furthermore, this type of rearrangement has been proposed by Curtin and Miller[83] involving 1,3-acyl migration (Scheme 2.52) as follows.

Scheme 2.52

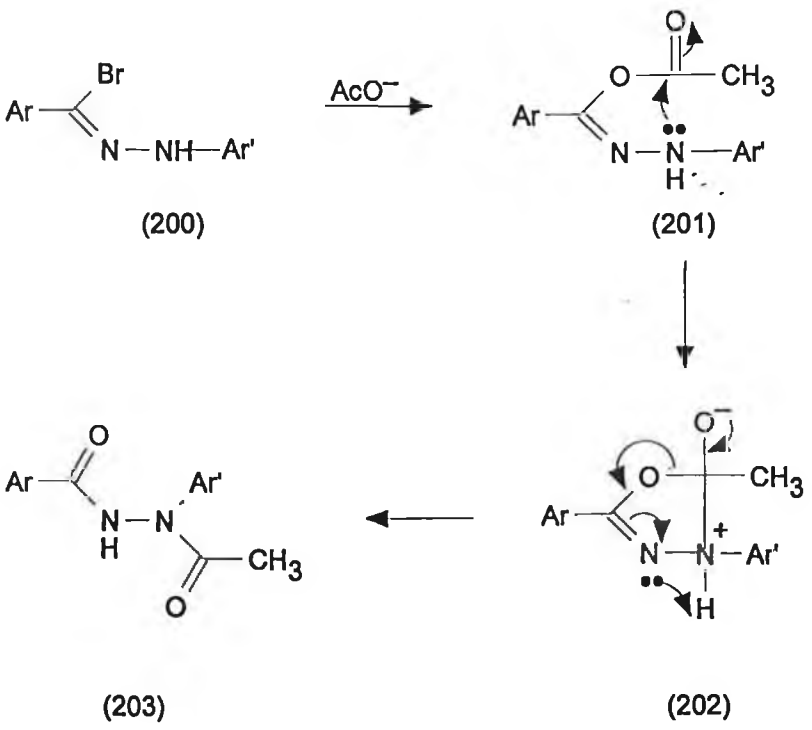


(197) (198) (199)

Good first order behaviour and insensitivity to acid suggests rearrangement is intramolecular.

A related rearrangement to that proposed in this chapter is that reported by Burgess *et al.* [115] and Barnish *et al.*[116]. They report the reaction of acetate ion on the bromo derivative (200) was found to yield the hydrazine (203):

Scheme 2.53

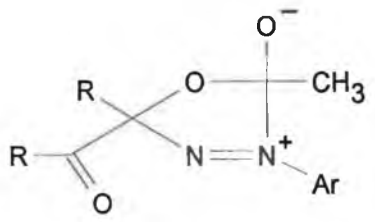


(200) (201)

(203) (202)

Formation of the α-acetoxyl compound (201) is proposed which then undergoes oxygen to nitrogen acetyl migration. The intermediate (202) has a cyclic five-membered transition state. A similar transition state is the one proposed for butane-2,3-dione and benzil rearrangements (Consider Structure A).

Structure A



Structure A	R	Ar	
183a 183b	Me Me	Ph p-NO_2-Ph	Scheme 2.47
194a 194b	Ph Ph	Ph p-NO_2-Ph	Scheme 2.51

Consider such a transition state in the generalised form (204) and rearrangement to (205):

Scheme 2.54

(204) (205)

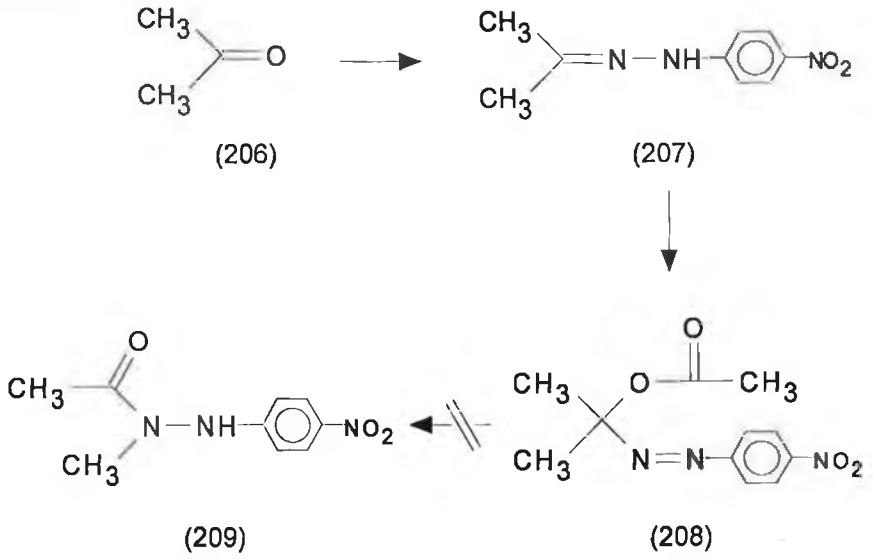
Cross-over experiments and addition reactions do not support a two step mechanism. Likewise the absence of any intermediates to suggest same, leads to the more favoured idea of a concerted one step reaction.

It is evident that while the acetyl group migrates there will be an inevitable build-up of negative charge on the quaternary carbon and consequently on the migrating group (R' ;204) . It was decided to consider a number of compounds with various migrating groups (R') to further explore this theory.

2.2.10 Migrating group variation

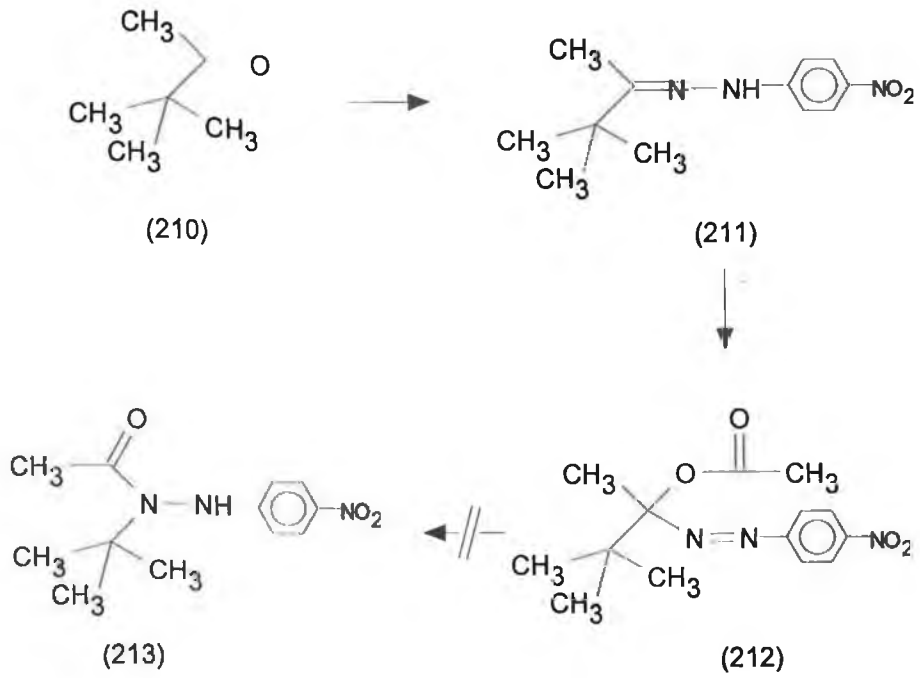
The first such compound to be considered was acetone-*p*-nitrophenylhydrazone (207). The hydrazone was readily synthesised and oxidised to the corresponding azoacetate (208) (Scheme 2.55). However attempts to induce rearrangement to the tertiary amide (209) shown were unsuccessful.

Scheme 2.55



Following this, pinacolone (1,1,1-trimethylacetone), was considered (Scheme 2.56). This ketone (210) required some time to condense with 4NP, to form the hydrazone (211). Oxidation provided the azoacetate (212), but no rearrangement product (213) was detected upon reaction with the KCN/EtOH system.

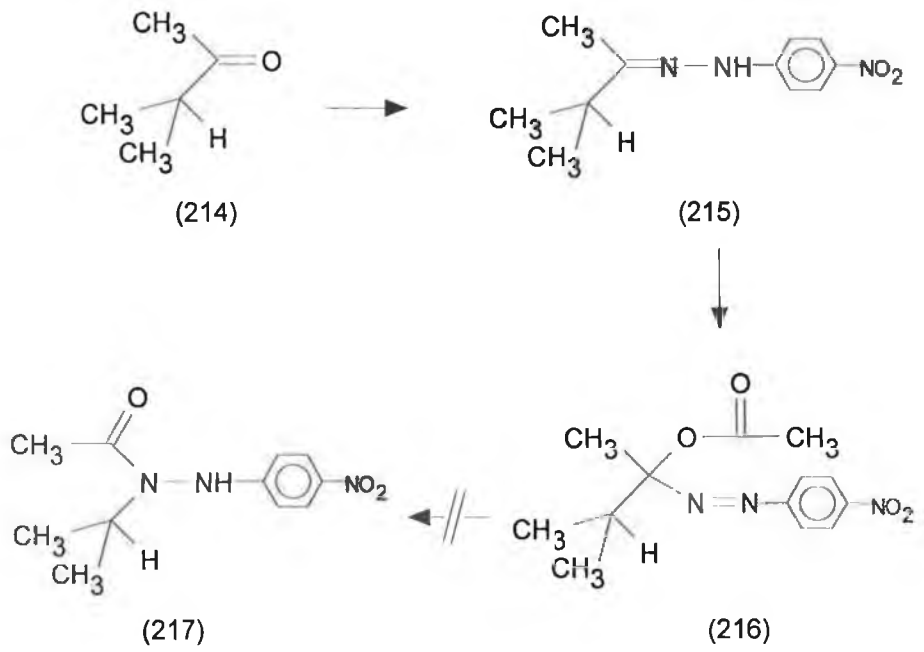
Scheme 2.56



This rearrangement involving pinacolone gave rise to a number of compounds within minutes. This may be attributed to the unstable nature of the azoacetate of pinacolone *p*-nitrophenylhydrazone, which was found to decompose upon standing for a few hours.

Similarly, the compound methylisopropyl ketone (MIPK) (214) was considered. The respective hydrazone (215) and azoacetate (216) were isolated (Scheme 2.57). Reaction of the latter (216) under basic conditions did not result in isolation of any of the proposed tertiary amide (217).

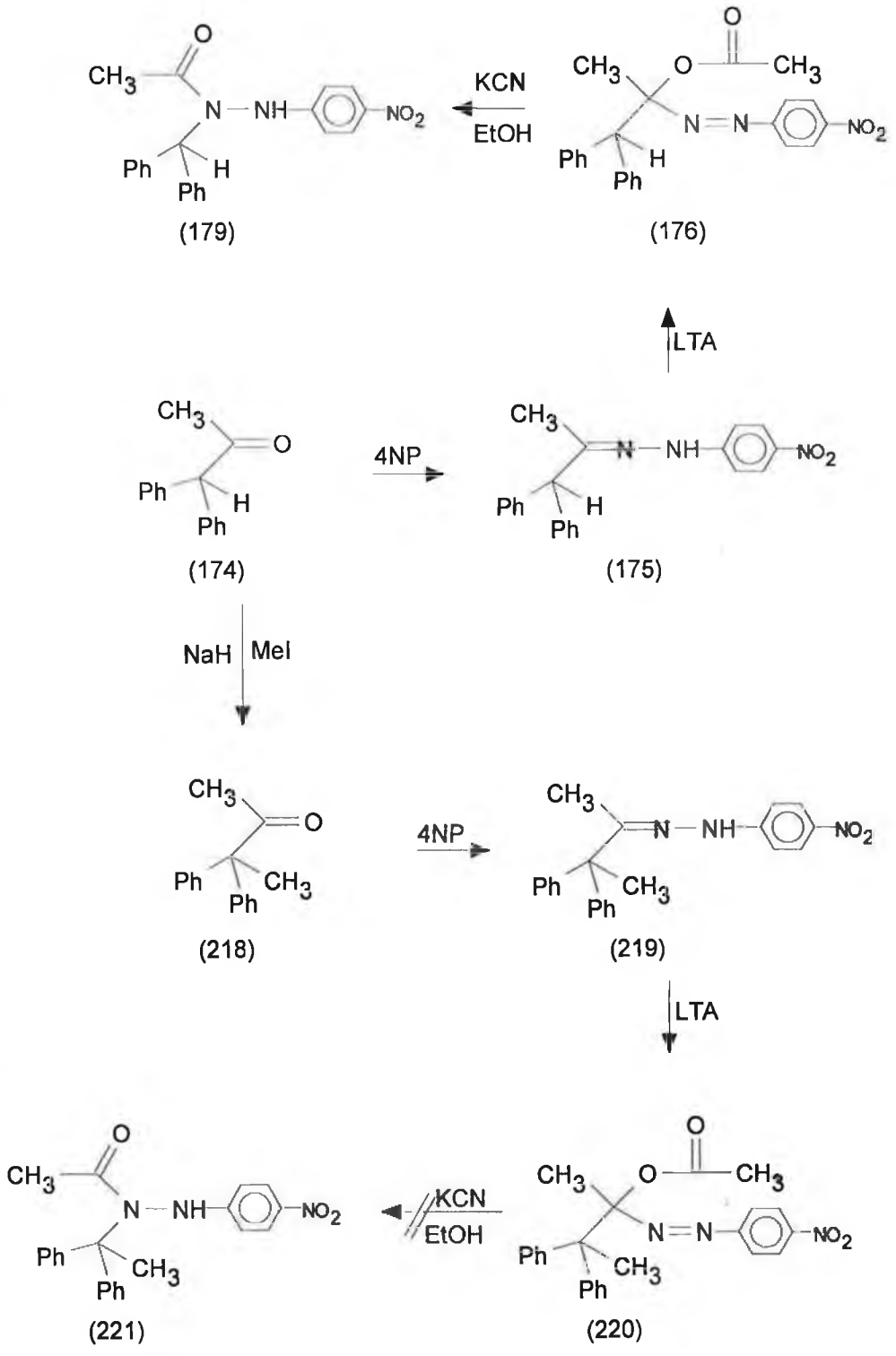
Scheme 2.57



While all the above compounds formed the respective azoacetate, none of the rearranged species were detected upon reaction with KCN/EtOH. In all cases, the unchanged azoacetate was the major product with varying quantities of the hydrazone. The absence of the respective tertiary amides can be explained by considering the inability of the group attached to the imine carbon to stabilise a negative charge. In the three cases shown, the prominence of methyl groups have a destabilising effect on the carbanion centre of the respective intermediate transition state. Thus the presence of methyl groups is strongly associated with an inability to rearrange, due to their inability to stabilize the build-up of negative charge.

Consider the successful rearrangement of the azoacetate of 1,1-diphenylacetone *p*-nitrophenylhydrazone (176) (Scheme 2.44). Tertiary amide formation *via* azocarbinol originally proposed, as illustrated for dimethylethyl acetoacetate (Scheme 2.31), has now been superceded by acetyl migration. However, introduction of a methyl group on 1,1-diphenyl-*p*-nitrophenylhydrazone has a pronounced effect on the preceding reaction, as follows (Scheme 2.58).

Scheme 2.58



(179) (176) (174) (175) (218) (219) (221) (220)

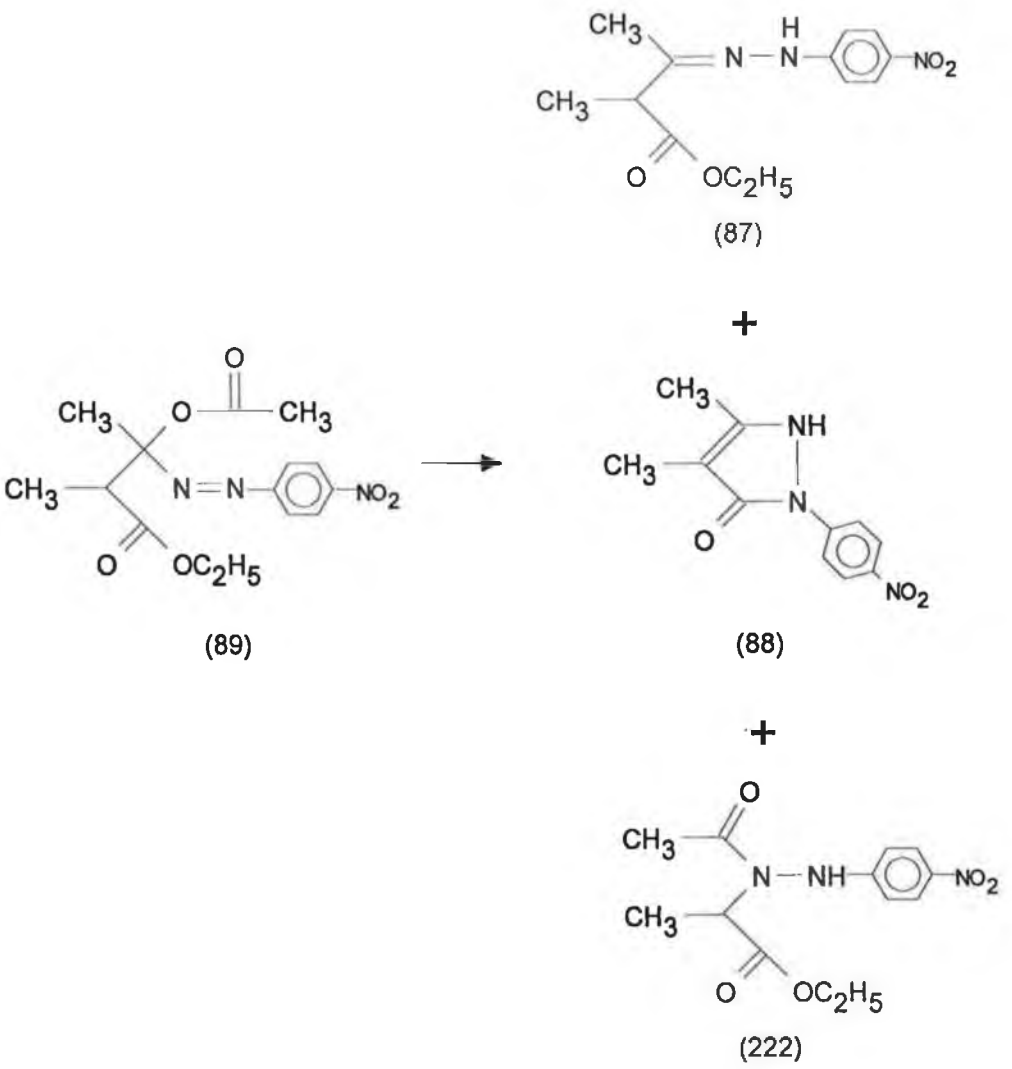
Methylation of 1,1-diphenylacetone (174) was effected by heating the ketone in THF with NaH as base and CH_3I as methylating agent when 1,1-diphenyl-1-methyl acetone (218) was isolated in 72% yield. Oxidation of the corresponding hydrazone (219) with LTA provided the azoacetate (220).

However attempts to convert this azoacetate using KCN/EtOH to the corresponding hydrazide (221) resulted in starting material (220) mainly, accompanied by hydrazone (219) (Scheme 2.58).

Thus the electron donating effect of the alkyl group is quite pronounced in the proposed rearrangement. While such alkyl groups are present on the original dimethylethyl acetoacetate *p*-nitrophenylhydrazone azoacetate, the ester group which is an integral part of the migrating group, proves its ability to delocalise the build-up of negative charge thus enhancing rearrangement.

The azoacetate of α-methylethyl acetoacetate *p*-nitrophenylhydrazone was also exposed to KCN in EtOH (Scheme 2.59). Following heating at reflux overnight, the hydrazone (87) was present along with the cyclised analogue (88). The rearranged tertiary amide (222) was isolated in 35% yield. Again the ester group proves to be sufficient in delocalising the partial build-up of negative charge thus providing a stable migrating group.

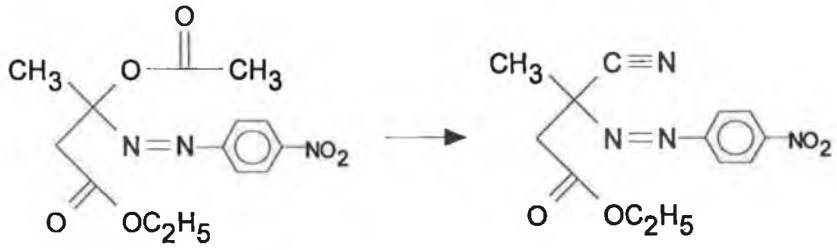
Scheme 2.59



The reaction of ethyl acetoacetate *p*-nitrophenylhydrazone azoacetate (74) was then considered (Scheme 2.60). When it was stirred in hot EtOH with 1.3 equiv of KCN the disappearance of starting material was noted after 4 hrs, by t.l.c analysis. Following work-up there was no obvious accumulation of precipitate, whose presence was normally characteristic of all the previously rearranged tertiary amides isolated. The reaction mixture was chromatographed, and the main fractions yielded hydrazone (68) and cyclised hydrazone (69). However the fraction preceeding the above compounds provided a small quantity of white solid.

The ^{1}H NMR spectrum indicated the presence of the backbone of the β-ketoester (67). However the terminal methyl and the methine groups *alpha* to the keto carbon were both shifted slightly downfield compared to the corresponding hydrazone (68) and azoacetate (74). The presence of a disubstituted phenyl group was evident, however it did not exhibit the characteristic broadening effect of the previous examples of tertiary amides. Likewise the ^{1}H NMR spectrum indicated a neighbouring azo group effect, compounded by the absence of any NH peak. The mass spectrum proved the compound was a nitrile (223). This was confirmed by CHN analysis.

Scheme 2.60



(74) (223)

Thus absence of methyl groups on the position *alpha* to the chiral carbon of the azoacetate reduces steric hindrance about this carbon. This allows nucleophilic attack on the cyano group, which replaces the acetoxy group, of (74) providing the nitrile (223).

Replacement of one or two of the methine protons *alpha* to the chiral carbon provides sufficient steric hindrance to eliminate cyanide attack, thus favouring rearrangement to the tertiary amide. This has been evident for the azoacetates of monomethylethyl acetoacetate *p*-nitrophenylhydrazone (89) and dimethylethyl acetoacetate *p*-nitrophenylhydrazone (85).

2.2.11 Further variation at the α-carbon of the β-keto-ester

In order to further consider the effect of substituents at the methylene carbon of the azoacetate (74), the introduction of phenyl groups at this position were considered *i.e* replacement of the dimethyl substituents on the α-carbon of ethyl acetoacetate with diphenyl substituents provides another derivative worthy of consideration.

2.2.12 Arylation

The synthesis of ethyl α,α-diphenylacetoacetate was reviewed. Barton *et al.*[117] have reported the use of pentavalent organobismuth reagents for the phenylation of phenols. Thus 2-naphthol is phenylated to 1-phenyl-2-naphthol or 2-naphthylphenylether depending on the conditions used. Further studies involving phenylation of enols and of enolate anions of ketones, β-ketones and keto esters have been studied[118].
It was found 1,3-dicarbonyl compounds could be phenylated or perphenylated with organobismuth reagents. The choice of organobismuth reagent dictates whether O- or C- phenylated products will be obtained. Ethyl acetoacetate and triphenylbismuth carbonate gave ethyl α-phenyl acetoacetate in 59% yield. When an excess of the reagent was used the perphenylated compound, ethyl α,α-diphenyl acetoacetate was obtained in 55% yield accompanied by ethyl diphenylacetate (21%)[119].

Rossi *et al.*[120] reports the isolation of arylacetone and 1,1-diarylacetone, which represents double arylation, upon reacting arylhalides with acetone in the presence of liquid ammonia and sodium metal. The use of phenyl halides with alkali amides has been employed by Leake *et al.*[121] to effect the phenylation of ketones. Methylethyl ketone and methyl-*n*-propyl ketone have been phenylated to give 3-phenyl-2-butanone and 3-phenyl-2-pentanone in yields of 75% and 65% respectively. Apparently both ketones were phenylated exclusively at their methylene carbon atoms, thus making application of this procedure quite attractive. Phenylation of acetophenone was reported to provide some of the diphenylated compound, phenyl benzhydryl ketone, among its products.
Leake *et al.*[122] extended this work to include phenylation of a number of esters. The diphenylated species was isolated in all cases reported. Reaction of ethyl acetate gave ethyl diphenylacetate in 14%, for example.

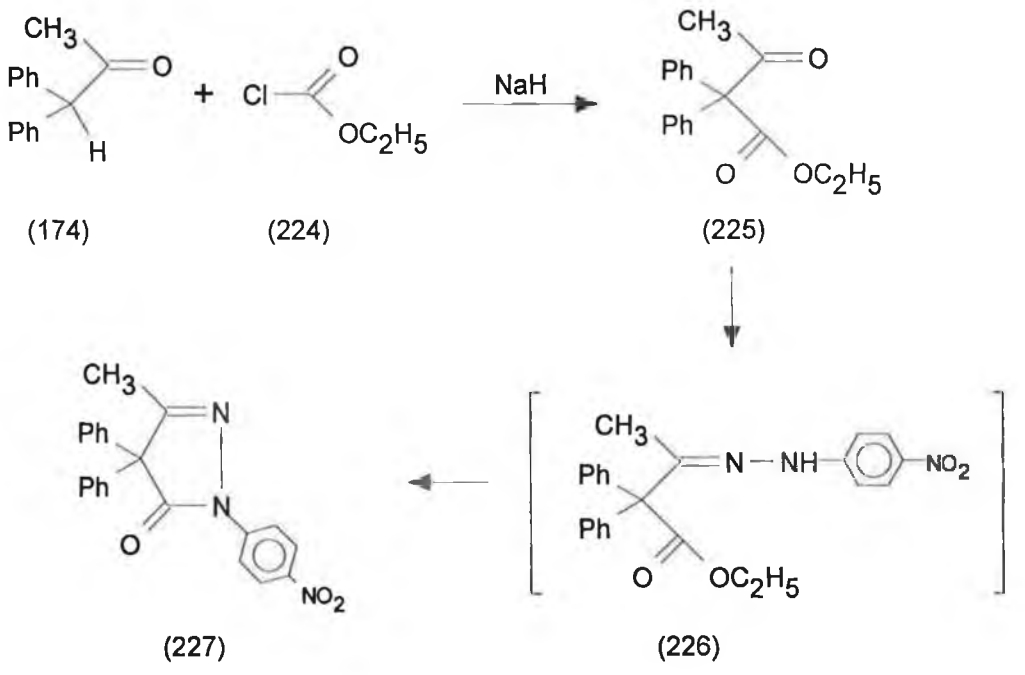
Phenylation of malonic esters with bromobenzene and sodium amide resulted in monophenylation at the methylene carbon of the esters. Indeed Citterio[123] reports aromatic substitution of malonic acid derivatives by manganese (III) acetate. While Canonne *et al.*[124] addresses arylation of ethyl acetoacetate using Gringard reagent, they report substitution at the keto carbon, the ester carbon and mixtures thereof.

The preparation with the most appeal was the synthesis of α-aryl-β-ketoesters as described by Wong and Ali[125]. The procedure involves the formation of the anion of a phenylacetone by the action of sodium hydride in THF. The homogeneous solution of the carbanion is then allowed to react with ethylchloroformate for carbethoxylation. The procedure was reported for the synthesis of ethyl α-phenylacetoacetate. However this approach was modified in the hope of obtaining ethyl α,α-diphenylacetoacetate.

Thus 1,1-diphenylacetone (174) was allowed to react with ethyl chloroformate (224) in the presence of sodium hydride (Scheme 2.61). The required disubstituted β-ketoester (225) was obtained and further purified by distillation, yielding the product. The ester was then reacted with 4NP to provide the corresponding hydrazone (226). 4NP required a number of hours to condense with the disubstituted β-ketoester due to the steric hindrance imposed by the two phenyl groups. Similar difficulties were noted by Newkome *et al.*[130] for highly hindered ketones.

However the product isolated was the cyclised hydrazone (227) instead of the anticipated hydrazone (226). Any attempts to precipitate possible (226) after a short reaction time, by the dropwise addition of water, resulted in the formation of an oil. Likewise, varying the solvent system and the reaction time did not provide any (226).

Scheme 2.61



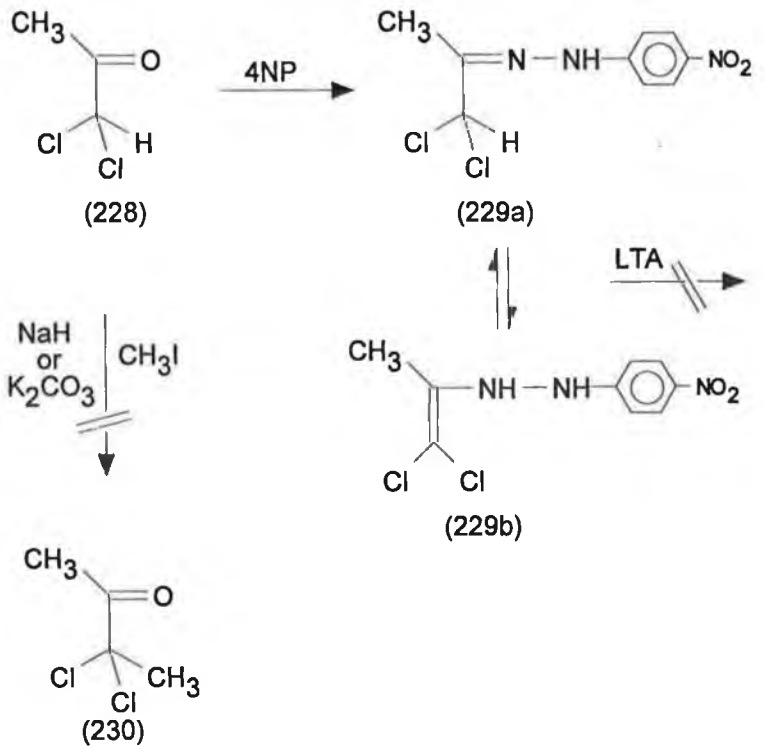
Attempts to cleave open the cyclised hydrazone (227), with the possibility of providing (226), by stirring in weakly acidified ethanol proved unsuccessful. Consequently further consideration of this hydrazone was abandoned.

2.2.13 Chlorination

As already seen, the azoacetate species that rearrange to the corresponding tertiary amide tend to have migrating groups capable of stabilizing the partial build up of negative charge. In order to facilitate this probable distribution of charge upon rearrangement, a compound containing electron withdrawing groups on the migrating species, was considered.

The compound 1,1-dichloroacetone (228) was choosen as starting material. Condensation with 4NP was effected in the usual manner when the hydrazone (229) was collected. However oxidation with LTA did not provide the azoacetate. The ^1H NMR spectrum of the hydrazone illustrated the existence of tautomerism, as represented by structures (229a) and (229b) (Scheme 2.62). This eliminated trivial oxidation by LTA. Replacement of the labile proton of the ketone (228), was considered by methylating 1,1-dichlorophenylacetone. However alkylation of the ketone using either NaH or K_2CO_3 as base, and CH_3I as methylating agent, did not provide any of the methylated species (230).

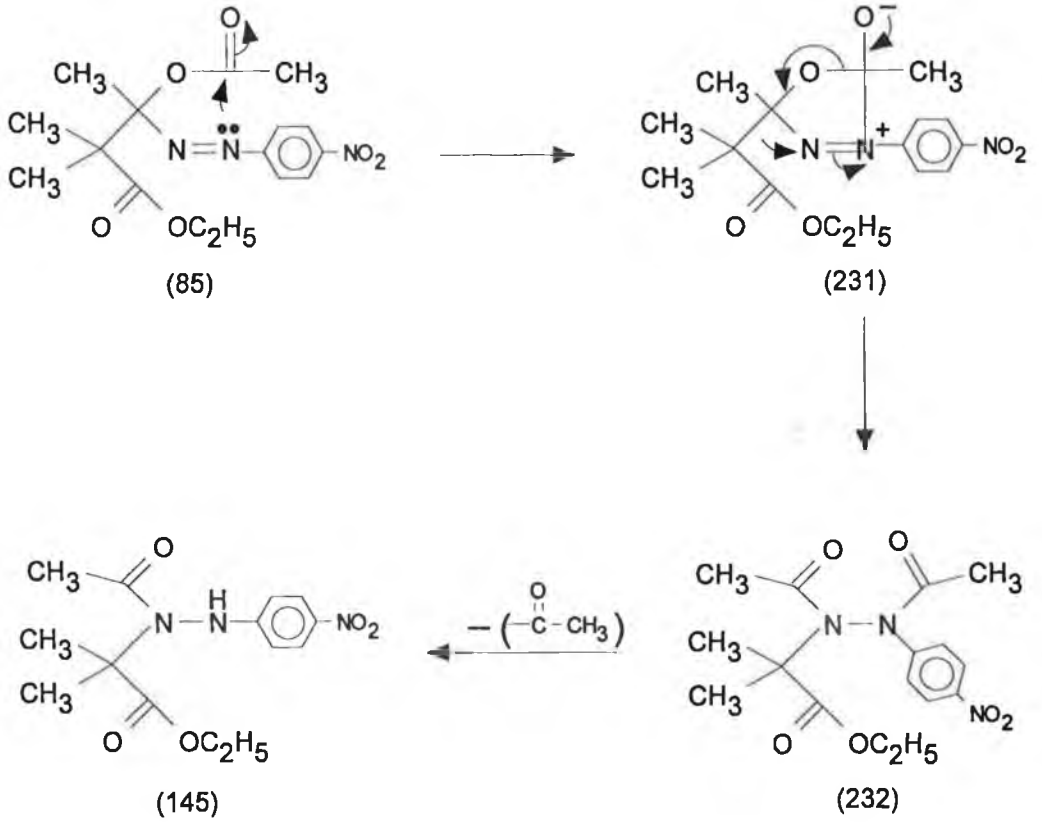
Scheme 2.62



Further investigation may involve arrival at (230) by chlorination[126] of methylethyl ketone using sulphuryl chloride[127,128]. (However their product is referred to in terms of G.C analysis as opposed to isolation).

Considering the groups that have afforded rearranged products, it appears that a build up of negative charge on the migrating group is a prerequisite. The concept of general rearrangement *via* azocarbinol formation is unlikely as isolation or synthesis has proved unsuccessful. The reactions of benzil and butane-2,4-dione are best explained by the mechanism involving intramolecular acetyl migration accompanied by rearrangement, with subsequent deacetylation.
Thus the rearrangement of the azoacetate of ethyl α,α-dimethylacetoacetate *p*-nitrophenylhydrazone to the tertiary amide is envisaged (Scheme 2.63) as follows.

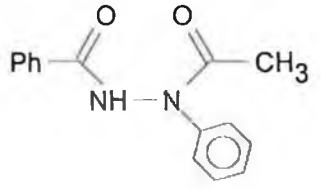
Scheme 2.63



Scheme 2.63 includes the diacetylated hydrazine (232) as an intermediate.

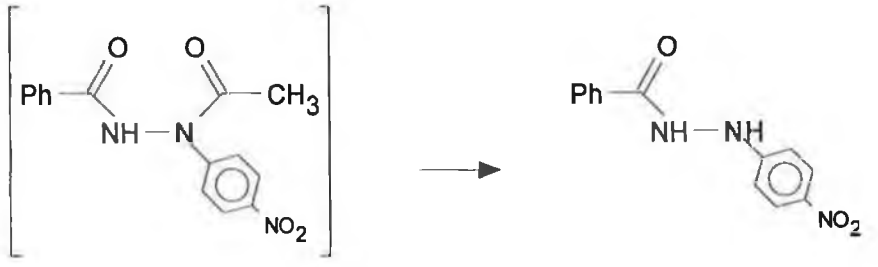
While it has not been isolated from the reaction mixture, its absence can be attributed to the destabilising effect of the *p*-nitrophenyl group. Here, the compound is made susceptible to attack by the ethanol solvent in the presence of potassium cyanide causing deacetylation to form the tertiary amide (145), as identified. This effect has been evident when studying the rearrangement reactions of benzil derivatives. In that case, the diacetylated compound (195a) was isolatable, (See 1) while the corresponding *p*-nitrophenyl derivative (195b) was not isolated due to the destabilising effect of the *p*-nitro group. It was readily deacetylated to form (196b) (See 2).

1



(195a)

2

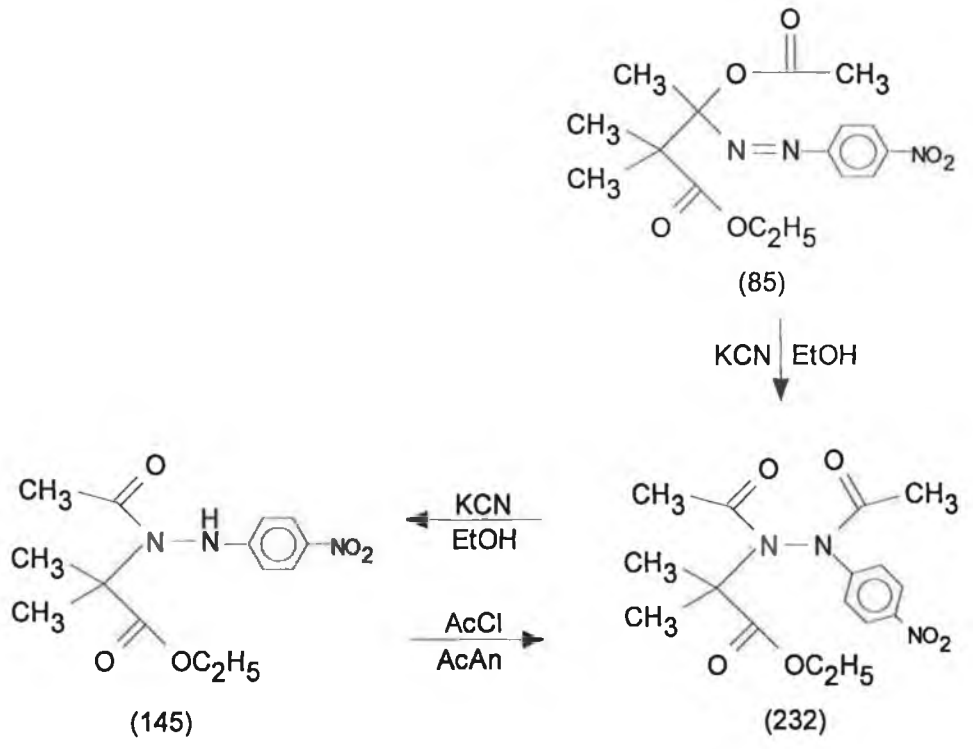


(195b) (196b)

Finally, in order to conclude that the base induced rearrangement from azoacetate (85) to tertiary amide (145) (Scheme 2.63) occurs involving acetyl migration, with the diacetylated species (232) as the penultimate step, independent synthesis of this hydrazide (232) was attempted. The tertiary amide (145), previously isolated from the rearrangement of the azoacetate (85), was dissolved in acetic anhydride and refluxed for 4 hours in order to effect acetylation to (232). Monitoring by t.l.c indicated the slow appearance of a product. Acetyl chloride was added to the reaction and it was allowed to reflux overnight.

Acetylation still proved difficult under these severe conditions as the starting material was evident in appreciable quantities after 24 hrs. Following chromatography of the reaction mixture the required diacetylated compound (232) was isolated, as a pale yellow powder, in 30% yield.

Scheme 2.64



A sample of (232) was stirred in ethanol and heat was applied, but no reaction was observed.

However, upon adding 1.2 equivalents of potassium cyanide to the reaction, the diacetylated compound disappeared quite rapidly with the formation of the monoacetylated derivative (Scheme 2.64), *i.e.* the tertiary amide (145), as the sole product. Hence rearrangement of the azoacetate (85) to the tertiary amide (145) *via* intramolecular acetylation would provide the diacetylated hydrazine (232). The instability of this compound in the EtOH/KCN system has been observed when it is found to readily deacetylate to the tertiary amide (145), which was subsequently isolated.

Stability of this original mono acetylated tertiary amide (145) isolated, was then addressed. It was allowed to stir in ethanol with a large excess of potassium cyanide heating under reflux, with the possibility of effecting

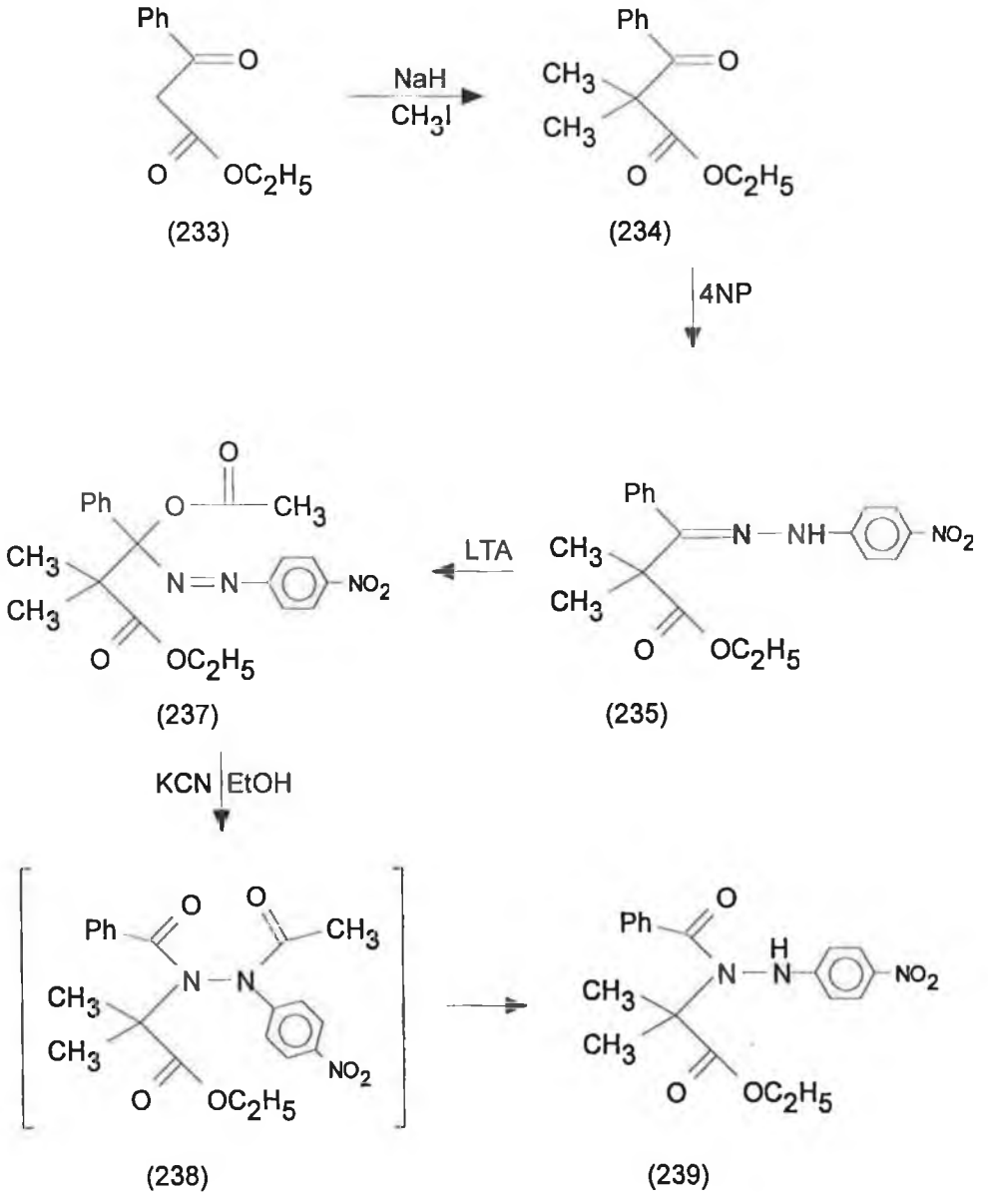
deacetylation. However after a number of days the starting material was recovered unchanged, highlighting its stability.

2.2.14 Variation at the terminal group of the β-keto-ester

Substituents at the methylene carbon *alpha* to the keto carbon of the β-ketoester (67) have been investigated. These included the dimethyl (82) and the diphenyl (225) substituents. Slight variation of the ester group involved consideration of the reactions of methyl propionyl acetate (146) (Scheme 2.34).

In order to vary the terminal methyl group of ethyl acetoacetate (67), a phenyl group was considered, thus the β-ketoester, ethylbenzoylacetate (233) was used as starting material. Following dimethylation, the ester (234) was condensed with 4NP. The resulting hydrazone (235), isolated as a red oil, was oxidised using LTA to the azoacetate (237). When azoacetate (237) was dissolved in hot ethanol, to which potassium cyanide was added, acetyl migration and rearrangement, and subsequent deacetylation of the proposed intermediate (238), gave the anticipated tertiary amide (239) as outlined in Scheme 2.65.

Scheme 2.65



Again, the ester group proved itself to be an efficient migrating group. The azoacetate with a phenyl group attached to the chiral carbon rearranges to give a nitrogen bearing a benzoyl group (239). Rearrangement incorporates (238) as an intermediate, which is deacetylated yielding the product isolated. This is perfectly analogous to α,α-dimethylethyl acetoacetate which provided the tertiary amide (145) with a nitrogen bearing an acetyl group.

2.1.15 Conclusion

The rearrangement of azoacetate aryl hydrazones in basic conditions provides the corresponding tertiary amides (hydrazides). Rearrangment is dictated by the ability of the migrating group to sustain a build-up of negative charge.
Likely intermediates have been synthesised in order to address the mechanism of the reaction. Bringing such reagents together in an addition type mechanism was investigated. The absence of rearranged product (hydrazide) by this independent route indicates that the rearrangement does not proceed *via* an addition mechanism. Likewise cross-over experiment results suggest the alternative more favoured concerted one step mechanism.

Rearrangement involving an azocarbinol (azoalcohol) as an intermediate was suspected. The inability to isolate the azocarbinol could be attributed to their unstable nature. Thus rearrangement incorporating the azocarbinol warranted further investigation. An alternative route to azocarbinol formation was explored, however it did not allow for isolation of the azocarbinol. The basic conditions involved should convert any azocarbinol formed to the corresponding tertiary amide. Therefore absence of both azocarbinol and tertiary amide indicated that the rearrangement does not proceed *via* a mechanism with azocarbinol as an intermediate.

The rearrangement was found to occur for derivatives of butane-2,3-dione. The acetylated products isolated are best explained *via* a rearrangement involving acetyl migration. Similarly this mechanism readily encompasses the acetyl derivatives isolated from the rearrangement of benzil derivatives, studied. All rearrangements observed involve carbon to nitrogen acetyl migration accompanied by rearrangement. This is followed by deacetylation to a varying extent, depending on the stability of the resulting compound. In most cases the reaction proceeded to form the tertiary amide.

Further evidence for this mechanism involved the independent synthesis of the proposed intermediate. When such a species was exposed to the basic conditions known to induce rearrangement, the products isolated and the ratio in which they were formed compared favourably to the tertiary amides already isolated.

A number of analogous rearrangements from the literature further substantiate this novel rearrangement. Some such mechanisms reported, are also found to incorporate a transition state comparable to that proposed in this work.

CHAPTER 2

EXPERIMENTAL PROCEDURES

CHAPTER 2

EXPERIMENTAL

(i) Preparation of N-acetyl-N'-*p*-nitrophenylhydrazine (155)

1g (6.5 mmoles) of 4NP was dissolved in the minimum of hot acetic acid. 1g (9.8 mmoles;1.5 equiv) of acetic anhydride was added and the solution heated under gentle reflux for 1 hr. On cooling the product was collected as a pale brown powder.

MP 204-206°C.

IR 3220, 3280, 1650 cm^{-1}.

^1H NMR (60 MHz;DMSO-d_6) δ 1.9 (s, 3H), 6.7 (d, 2H), 7.9 (d, 2H), 8.8 (s, 1H), 9.8 (s, 1H).

(ii) Preparation of 2-acetyl-*p*-nitrophenyl azo compound (153)

The following reaction was protected from light until the product was isolated. 1g (5 mmoles) of the hydrazine (155) was suspended in CH_2Cl_2 to which 2-3 drops of pyridine were added. 1.82g (10 mmoles; 2 equiv) of NBS were added. The reaction was allowed to stir, at ambient temperature, for 40 minutes. It was then added to H_2O (100mls) and extracted into dichloromethane (40mlsx3). The combined extracts were dried over magnesium sulphate. Following the addition of methylcyclohexane (30mls), the solution was evaporated to a small volume. The product precipitated from solution as a red crystalline solid.

IR 1750, 1610, 1590 cm^{-1}.

^1H NMR (60 MHz;$CDCl_3$) δ 2.5 (s, 3H), 8.0 (d, 2H), 8.4 (d, 2H).

$C_{12}H_{13}N_3O_6$ requires C, 54.75; H, 5.0; N, 15.96%,

found C, 54.58 H, 5.12 N, 15.49%.

(iii) Preparation of tertiary amide of 2,2-dimethylethyl acetoacetate (145)

1g (2.8 mmoles) of the azoacetate was dissolved in EtOH (30mls). 0.24g (3.7 mmoles; 1.3 equiv) of KCN were added. Following heating under reflux for 24 hrs the reaction was evaporated to dryness and H_2O (100mls) added. The reaction was extracted into ethyl acetate:diethyl ether (15:85) and these combined extracts were dried over $MgSO_4$. Upon evaporation to a reduced volume, a pale brown precipitate became evident. Thus the product was collected in a 35% yield following filtration and pet-ether wash.

MP 172-174°C.

IR 3286, 1737, 1646, 1593 cm^{-1}.

^1H NMR (400 MHz;DMSO-d_6) δ 1.2 (t, 3H), 1.3 (s, 3H), 1.4 (s, 3H), 1.9 (s, 3H), 4.1 (q, 2H), 7.1 (d, 2H), 8.2 (d, 2H), 9.6 (s, 1H).

$C_{13}H_{19}N_3O_4$ requires C,54.36; H,6.14; N, 13.5%,

found C,54.53; H, 6.29; N, 13.51%.

(iv) Preparation of 1,1-diphenylacetone *p*-nitrophenylhydrazone (175)

1g (4.7 mmoles) of 1,1-diphenylacetone was added to 0.73g (4.7 mmoles; 1 equiv) of 4NP suspended in a weak solution of acetic acid. The solution was stirred overnight when a yellow crystalline precipitate was collected in 90% yield.

IR 3326, 1591 cm^{-1}.

^1H NMR (400 MHz;DMSO-d_6) δ 1.9 (s, 3H), 5.1 (s, 1H), 6.8 (d, 2H), 7.2 (m, 10H), 7.6 (s, 1H), 8.0 (d, 2H).

(v) Preparation of azoacetate of 1,1-diphenylacetone *p*-nitrophenylhydrazone (176)

1g of hydrazone (175) was suspended in CH_2Cl_2 (30mls) to which 1.67g (3.7 mmoles; 1.3 equiv) of LTA was added and the solution stirred for 20 mins. A saturated solution of $NaHCO_3$ (20mls) was added. The resulting lead salts were filtered, the filtrate extracted into CH_2Cl_2 and the organic extracts dried over $MgSO_4$. The volume was reduced by rotary evaporation when the product was collected as a red-brown oil.

IR 1745, 1608, 1593 cm^{-1}.

^1H NMR (400 MHz;DMSO-d_6) δ 2.1 (s, 3H), 2.5 (s, 3H), 4.6 (s, 1H), 7.45 (m, 4H), 7.75 (m, 4H), 8.45 (d, 2H).

(vi) Preparation of 1,1-diphenylacetone-tertiary amide (179).

1g (2.5 mmoles) of azoacetate was dissolved in hot EtOH (40mls) to which 1.43g (3.2 mmoles; 1.3 equiv) KCN were added. The solution was allowed to reflux gently overnight, and then evaporated to dryness. Water was added (50mls) to the reaction which was then extracted into ethyl acetate:diethylether (20:80). The combined extracts were dried over $MgSO_4$ and the solution reduced to a small volume, by evaporation, from which the product precipitated as a powder.

IR 3240, 1646, 1595 cm^{-1}.

^1H NMR (400 MHz;DMSO-d_6) δ 2.1 (s, 3H), 6.2 (d, 2H), 6.5 (s, 1H), 7.2 (m, 10H), 7.8 (d, 2H), 9.4, (s, 1H).

(vii) Preparation of pinacolone *p*-nitrophenylhydrazone (211)

1g (10 mmoles) of pinacolone was added to 1.53g (10 mmoles; 1 equiv) of 4NP suspended in weak acetic acid. The product was formed, in a 90% yield, as a yellow precipitate within seconds.

^1H NMR (400 MHz;$CDCl_3$) δ 0.8 (s, 9H), 1.9 (s, 3H), 7.2 (d, 2H), 7.7 (s,1H), 8.0 (d, 2H).

(viii) Preparation of azoacetate of pinacolone-*p*-nitrophenylhydrazone (212).

The procedure was the same as in preparation **(v)** . A red oil was obtained.

^1H NMR (400 MHz;$CDCl_3$) δ 0.9 (s, 9H), 1.7 (s, 3H), 1.9 (s, 3H), 7.6 (d, 2H), 8.1 (d, 2H).

(ix)Preparation of methyl isopropylketone *p*-nitrophenylhydrazone (215).

The procedure was repeated as in preparation **(vii)**, when the product was again collected as a yellow precipitate within seconds in a 92% yield.

IR 3310, 1595, 1495 cm^{-1}.

^1H NMR (400 MHz;DMSO-d_6) δ 1.1 (d, 3H), 1.15 (d, 3H), 1.9 (s, 3H), 2.6 (m, 1H), 7.0 (d, 2H), 7.6 (s, 1H), 8.1 (d, 2H).

(x) Preparation of azoacetate of methylisopropylketone *p*-nitrophenylhydrazone (216)

The procedure used was as in preparation **(v)**. The product was isolated as an oil in 75% yield.

^1H NMR (400 MHz;$CDCl_3$) δ 1.0 (d, 3H), 1.1, (d, 2H), 1.8, (s, 3H), 2.1 (s, 3H), 2.2 (m, 1 H), 7.7 (d, 2H), 8.3 (d, 2H).

(xi) Preparation of 1,1-diphenyl-1-methylacetone (218).

5g (24 mmoles) of 1,1-diphenylacetone was added to dry THF (50mls). 0.69g (28 mmoles; 1.2 equiv) of NaH was added slowly with stirring. This grey suspension was stirred at room temperature until effervescence subsided (2hrs). 10.1g of CH_3I (71 mmoles; 3 equiv) was added slowly as the exothemeric reaction caused a temperature increase to 40°C. The reaction

was allowed to stir overnight at ambient temperature. The reaction mixture was then neutralised by the slow addition of aqueous HCl resulting in a pale yellow solution. The product was extracted into diethyl ether, the organic extracts dried over $MgSO_4$, when the volume was reduced by rotary evaporation to provide the methylated product as a pale yellow liquid, in 72% yield.

^{1}H NMR (400 MHz;$CDCl_3$) δ 1.9, (s, 3H), 2.1 (s, 3H), 7.6 (m, 10H).

(xii) Preparation of 1,1-diphenylmethylacetone-*p*-nitrophenylhydrazone (219)

1g (4 mmoles) of ketone (218) was added to AcOH (20mls) containing 0.61g of 4NP (4 mmoles; 0.9 equiv). The hydrazone precipitated from solution, after 30 mins, as a yellow solid.

IR 1330, 1600, 1497 cm^{-1}.

^{1}H NMR (400 MHz;$CDCl_3$) δ 1.6, (s, 3H), 1.7 (s, 3H), 7.0 (m, 12H), 7.8 (d, 2H), 9.8 (s, 1H).

(xiii) Preparation of azoacetate of 1,1-diphenyl-1-methylacetone-*p*-nitrophenylhydrazone (220)

1.9g (5.3 mmoles) of the hydrazone (219) was suspended in CH_2Cl_2 (30mls). Addition of 3g (6.9 mmoles;1.3 equiv) of LTA resulted in the usual formation of a clear red solution. The product was isolated, as in preparation **(v)**, in 92% yield.

IR 1752, 1675, 1635, 1515 cm^{-1}.

^{1}H NMR (400 MHz;$CDCl_3$) δ 2.1, (s, 3H), 2.5 (s, 3H), 4.6 (s, 1H), 7.5 (m, 10H), 8.4 (d, 2H).

(xiv) Preparation of acetone *p*-nitrophenylhydrazone (202)

1g (6.5 mmoles) of 4NP was added to a solution of acetone. An immediate precipitate was collected which proved to be the hydrazone in 95% yield.

^{1}H NMR (400 MHz;DMSO-d_6) δ 1.9 (s, 3H), 2.1 (s, 3H), 7.0 (d, 2H), 7.4 (s, 1H), 8.2 (d, 2H).

(xv) Preparation of acetone-*p*-nitro-phenylhydrazone azoacetate (208).

Preparation as described in preparation **(v)**. An oil was obtained.

^{1}H NMR (400 MHz;$CDCl_3$) δ 1.7 (s, 6H), 2.2 (s, 3H), 7.8 (d, 2H), 8.3 (d, H).

(xvi) Preparation of 1.1-dichloroacetone *p*-nitro-phenylhydrazone (229)

1g (7.8 mmoles) of 1,1-dichloroacetone was added to 1.1g (7 mmoles; 0.9 equiv.) of 4NP suspended in AcOH. A red precipitate was collected within minutes.

^{1}H NMR (400 MHz $CDCl_3$) δ 2.1 (s, 3H), 2.3 (s, 3H), 7.1 (s, 1H), 7.4 (d, 2H), 7.6 (d, 2H), 8.2 (d, 2H), 8.3 (d, 2H), 9.5 (s,1H), 10.6 (s, 2H), 11.4, (s, 1H).

(xvii) Preparation of nitrile (223).

3g (9.2 mmoles) of azoacetate was placed in hot EtOH (50mls) with 0.78g (12 mmoles; 1.3 equiv) of KCN. The reaction was heated under reflux for 4hrs, when t.l.c monitoring indicated completion. It was then evaporated to dryness. Chromatography of the resulting viscous mass, using ethyl acetate:pet-ether (25:75) as eluent, yielded (223) in 15% yield.

MP 180-182°C.

IR 3346, 1675, 1614, 1596, cm^{-1}.

^{1}HNMR (60 MHz;DMSO-d_6) δ 1.4 (t, 3H), 2.4 (s, 3H), 4.3 (q, 2H), 5.5 (s, 1H), 7.8 (d, 2H) 8.4 (d, 2H).

Mass Spec. $M^{+\cdot}$ 290, 244.

(xviii) Preparation of monomethylethyl acetoacetate-tertiary amide (222)

Procedure as described in preparation **(iii)**. The product was collected as a yellow solid following chromatography.

^{1}H NMR (400 MHz;DMSO-d_6) δ 1.2 (t, 3H), 1.3 (d, 2H), 2.1 (s, 3H), 4.1 (q, 2H), 5.3 (q, 1H), 6.8 (d, 2H), 7.3 (s, 1H), 8.1 (d, 2H).

(xix) Preparation of 2,2-diphenylethyl acetoacetate (225)

5g (24 mmoles) of diphenylacetone was added to a solution containing 1.15g (47.6 mmoles; 2 equiv) of NaH in THF (50mls). The solution was stirred for 30 mins until effervesence subsided. 2.6g (24 mmoles; 1equiv) of ethyl chloroformate was slowly added over an ice-bath, as this exothermic reaction caused a temperature rise to 15°C. The reaction which was monitored by t.l.c, was deemed complete after 90 minutes. It was then neutralized with cold aqueous HCl. The mixture was extracted into ether which was dried

over $MgSO_4$ and evaporated to yield the product as a yellow viscous liquid in 80% yield.

^1H NMR (400 MHz;$CDCl_3$) δ 1.1 (t, 3H), 2.0 (s, 3H), 4.1 (q, 2H), 7.2 (m, 9H), 7.7 (d,1H).

(xx) Preparation of 4.4-diphenyl-5-methylpyrazol-3-one (227)

1g (3.5 mmoles) of the β-ketoester (225) was added to to 0.49g (3.2 mmoles; 0.9 equiv) of 4NP in glacial acetic acid. The reaction was allowed to stir at ambient temperature. After 1hr, t.l.c monitoring indicated a lot of starting material. Water was added dropwise in order to effect precipitation of the straight chain hydrazone (226) or the corresponding cyclic hydrazone (227), however this only resulted in an oil formation. Consequently the reaction was left stirring overnight when the cyclic product was collected as a yellow precipitate.

MP 136-138°C.

^1H NMR (400 MHz;DMSO-d_6) δ 2.0 (s, 3H), 6.9 (d, 2H), 7.2 (m, 5H), 7.4 (m, 5H), 7.8 (s,1H), 8.0 (d, 2H).

(xxi) Preparation of 3,3-dimethylethyl benzoylacetate (234).

Method (a) :

5g (26 mmoles) of ethyl benzoylacetate was added to acetone (50mls) containing 14.3g (104 mmoles; 4 equiv) potassium carbonate and 22g (156 mmoles; 6 equiv) of methyl iodide. After 50hrs, a further 2 equivs of K_2CO_3 and 2 equivs of CH_3I were added. The reaction required 4 days gentle reflux for completion using a large excess of CH_3I. It was then added to H_20 (100mls) and following extraction into diethyl ether, dried over $MgSO_4$ and evaporated yielding a yellow viscous liquid in 80% yield.

^1H NMR (400 MHz;$CDCl_3$) δ 0.9 (t, 3H), 1.5 (s, 6H), 4.0 (q, 2H), 7.3 (m, 3H), 7.7 (d, 2H).

Method (b) :

5grams (26 mmoles) of ethyl benzoylacetate was slowly added to 1.56g (65 mmoles; 2.5equiv) of NaH suspended in THF (40mls). The grey suspension was stirred for 30 mins when 11.1g (78 mmoles; 3equiv) of CH_3I were added slowly causing a temperature increase to 40°C. The reaction was heated gently overnight. The product was isolated and identified, as for 'Method (a)', in 70% yield.

(xxii) Preparation of 3.3-dimethylethyl benzoylacetate-*p*-nitrophenylhydrazone (235)

1g (4.5 mmoles) of the ketone (29) was added to an acetic acid solution containing 0.63g (4 mmoles; 0.9equiv) of 4NP. The reaction was monitored by t.l.c which indicated the simultaneous formation of two products after 10 minutes. The addition of water in order to effect precipitation caused oil formation. Following further addition of acetic acid the reaction was stirred overnight at room temperature. 0.8g of yellow precipitate was then collected which yielded the required product as the second fraction following chromatography of this precipitate using E.A:P.E (60:40) as eluent. The yield of hydrazone was 15%.

IR 3306, 1722, 1602 cm^{-1}.

^1H NMR (400 MHz;DMSO-d_6) δ 1.2 (t, 3H), 1.4 (s, 6H), 4.1 (q, 2H), 6.9 (d, 2H), 7.0 (d, 2H), 7.3 (s, 1H), 7.4 (m, 3H), 8.0 (d, 2H).

(xxiii) Preparation of 5-phenyl-4,4-dimethylpyrazol-3-one (236)

This compound was obtained following chromatography of the above reaction **(xxii)**. It was the first fraction collected in 85% yield.

IR 1701, 1595 cm^{-1}.

^1H NMR (400 MHz;DMSO-d_6) δ 1.5 (s, 6H), 7.5 (m, 3H), 7.9 (d, 2H), 8.3 (s, 4H).

(xxiv) Preparation of methyl propionyl acetate tertiary amide (152)

The procedure used was the same as preparation **(iii)**. However the product did not readily precipitate from the final reaction mixture. This mixture was chromatographed using ethyl acetate:pet-ether (20:80) as eluent. The product was collected in a 25% yield as a pale brown solid.

IR 3350, 3290, 1750, 1650, 1595 cm^{-1}.

^1H NMR (400MHz;DMSO-d_6) δ 0.9 (t, 3H), 1.4 (s, 3H), 1.5 (s, 3H), 2.0 (m, 1H), 2.5 (m, 1H), 3.7 (s, 3H), 7.0 (d, 1H), 7.2 (d, 1H), 8.2 (m, 2H), 9.5 (s, 1H).

(xxv) Preparation of butane 2,3-dione-*p*-nitrophenylhydrazone (181a)

0.9g (5.8 mmoles) 4NP dissolved in AcOH (15mls), was added slowly to a solution containing 1g (11.6mmol; 2 equiv) of butan-2,4-dione in AcOH

(15mls). The product was collected as a yellow precipitate in 90% yield when addition of the 4NP solution was complete.

MP 158-160°C.

IR 3420, 1729, 1689, 1587 cm^{-1}.

^1H NMR (400 MHz;DMSO-d_6) δ 2.0 (s, 3H), 2.4 (s, 3H), 7.4 (d, 2H), 8.2 (d, 2H), 10.6 (s, 1H).

(xxvi) Preparation of the azoacetate (182b) of butan-2.3-dione-*p*-nitrophenylhydrazone.

1g (4.5 mmoles) of hydrazone (181b) formed an insoluble suspension in glacial acetic acid (25 mls). 8g (18 mmoles; 2equiv) of L.T.A. was added. The reaction was stirred overnight and any insoluble precipitate was filtered. Any remaining lead salts were further precipitated and filtered as a white sticky solid following addition of water to the reaction. The H_2O-AcOH solution was then extracted into diethyl ether. The combined diethyl ether layers were washed with aqueous $NaHCO_3$, further extracted, dried over $MgSO_4$ and evaporated to a small volume from which any unreacted hydrazone (181b) precipitated out as a yellow solid. Following filtration of this hydrazone, the solution was evapourated to dryness yielding the azoacetate (182b) in 30% yield as a red oil.

^1H NMR (400 MHz;$CDCl_3$) δ 1.7 (s, 3H), 2.2 (s, 3H), 2.5 (s, 3H), 7.85 (d, 2H), 8.3 (d, 2H).

(xxvii) Preparation of 2-acetyl-*p*-nitrophenylhydrazone (184b)

0.9g (13.9 mmoles; 1.3 equiv) of KCN was added to 3g (10.7 mmoles) of the azoacetate (182b) in a hot solution of EtOH. The solution was heated gently and monitoring by t.l.c indicated completion after 5hrs. The reaction was evaporated to dryness. Water (50mls) was added and this mixture was extracted into diethyl ether:ethyl acetate (80:20) (3x50mls). The combined extracts were dried over $MgSO_4$, filtered, and evapourated to a small volume from which the product precipitated as an orange brown solid in 50% yield.

MP 205-206°C.

IR 3290, 3260, 1645, 1593 cm^{-1}.

^1H NMR (400 MHz;DMSO-d_6) δ 1.9 (s, 3H), 6.8 (d, 2H), 8.1 (d, 2H), 9.0 (s, 1H), 9.9 (s, 1H).

^{13}C (400 MHz;DMSO-d_6) δ 169.09, 154.9, 137.9, 125.9, 110.5, 20.5.

(xxviii)

(a) Preparation of 1.2-diacetyl-*p*-nitrophenylhydrazine (185b)

The reaction was repeated as for **(xxvii)**. However the KCN was replaced by K_2CO_3. The reaction was quenched after 2 hours and, following work-up, the product which readily precipitated was 1,2-diacetyl-*p*-nitrophenylhydrazine.

^{1}H NMR (400 MHz;DMSO-d_6) δ 2.1 (s, 3H), 2.2 (s, 3H), 7.75 (d, 2H), 8.25 (d, 2H), 11.1 (s, 1H).

(xxviii)

(b) 2-acetyl-*p*-nitrophenylhydrazine (184b): 1.2-diacetyl-*p*-nitrophenylhydrazine (185b) mixture.

The reaction was again repeated as for **(xxvii)**. However in this instance the reaction was quenched following gentle heat after 30 minutes when t.l.c monitoring indicated the presence of both 2-acetyl-*p*-nitrophenylhydrazine and 1,2-diacetyl-*p*-nitrophenylhydrazine. Following isolation of this mixture as a precipitate, ^{1}H NMR analysis indicated 2-acetyl-*p*-nitrophenylhydrazine* (184b) and 1,2-diacetyl-*p*-nitrophenylhydrazine (185b) in 37% and 63% distribution respectively.

^{1}H NMR (400 MHz;DMSO-d_6) δ 2.0 (s, 3H)*, 2.1 (s, 3H), 2.2 (s, 3H), 6.8 (d, 2H)*, 7.75 (d, 2H), 8.15 (d, 2H)*, 8.3 (d, 2H).
[Note: NH region omitted;See Figure 2.13].

(xxix) Preparation of benzophenone-*p*-nitrophenylhydrazone (170)

The procedure was followed as described in preparation **(vii)** when the product was collected in 90% yield.

^{1}H NMR (400MHz; DMSO-d_6) δ 6.9 (d, 2H), 7.1-8.0 (m, 11H), 8.2 (d, 2H), 8.5, (s, 1H).

(xxx) Preparation of azoacetate (171) of benzophenone-*p*-nitrophenylhydrazone

The procedure was followed as described in **(v)** when the azoacetate was collected in 85% yield.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.4-8.2 (m, 13H), 8.3 (d, 2H).

(xxxi) Preparation of triacetyl-*p*-nitrophenylhydrazine (187b)

2g of 4NP was dissolved in AcOH (30mls) to which pyridine (5mls) and excess acetic anhydride were added. The reaction was heated under gentle

reflux for 60 hours when t.l.c indicated the disappearance of the monoacetyl and diacetyl derivatives and formation of the triacetylated derivative (highest R_f value). The reaction was allowed to cool, added to H_2O (50mls), extracted into ethyl acetate, dried over $MgSO_4$, filtered, and removal of the solvent under reduced pressure yielded the product (187b) as a brown solid in a 60% yield. The product was recrystallised from ethanol.

^{1}H NMR (400 MHz;DMSO-d_6) δ 2.1 (s, 3H), 2.5 (s, 6H), 7.5 (d, 2H), 8.3 (d, 2H).

(xxxii) Triacetyl-*p*-nitrophenylhydrazine (187b) deacetylation

The title compound (1g; 3.6 mmoles) was added to of EtOH (30mls) containing 2 equiv of KCN and the reaction mixture heated for 20 minutes when t.l.c indicated disappearance of the starting material. The reaction was worked up as for **(xxvii)**, and the product which was isolated proved to be a mixture of 2-acetyl-*p*-nitrophenylhydrazine* (184b) and 1,2-diacetyl-p-nitrophenylhydrazine (185b) in 42% and 58% distribution respectively.

^{1}H NMR (400 MHz;DMSO-d_6) δ 1.95 (s, 3H), 2.05 (s, 3H)*, 2.1 (s, 3H)*, 6.7 (d, 2H), 7.7 (d, 2H) *, 8.05 (d, 2H), 8.2 (d, 2H)*, 9.0 (s, 1H), 9.95 (s,1H), 11.1 (s, 1H)*.

(xxxiii) Preparation of benzil mono-*p*-nitrophenylhydrazone (192b)

1g (4.7 mmoles) of benzil was disolved in EtOH (25mls) containing 1ml of AcOH. 0.68g of 4NP (0.95 equiv; 4.5 mmoles) was suspended in a mixture of EtOH (15mls) and AcOH (10mls) and this solution was added dropwise to the former, when the product formed within 10 minutes of stirring at room temperature. The solution was filtered and the product, which was washed with pet-ether, collected as bright orange crystals in 60% yield.

MP 191-192°C.

IR 3260, 1627 cm^{-1}.

^{1}H NMR (400 MHz;DMSO-d_6) δ 7.2 (d, 2H), 7.3-7.9 (m, 10H), 8.1 (d, 2H), 10.8 (s, 1H).

(xxxiv) Preparation of benzil mono-*p*-nitrophenylhydrazone azoacetate (12b).

2g (5.8 mmoles) of the hydrazone (12b) were suspended in CH_2Cl_2 with a few drops of EtOH to help dissolve. 3.1g of LTA (1.2 equiv; 6.9 mmoles) was added and the solution stirred for 3hrs when t.l.c indicated disappearance of

starting material. A dilute solution of $NaHCO_3$ was added, the mixture filtered to remove lead salts, and the filtrate extracted into CH_2Cl_2 (3x25mls). When these combined extracts were dried over $MgSO_4$, filtered, and the solvent removed by evaporation under reduced pressure, the resulting sticky solid proved to be the azoacetate in 74% yield.

^1H NMR (400 MHz;DMSO-d_6) δ 2.2 (s, 3H), 7.1-8.0 (m, 14H), 8.1 (d, 2H), 10.8 (s, 1H).

(xxxv) Preparation of 2-benzoyl-*p*-nitrophenylhydrazine (196b).

1g (2.5 mmoles) of benzil mono-*p*-nitrophenylhydrazone azoacetate (12b) was heated in EtOH containing 1.2 equiv (3 mmoles; 0.19g) KCN and the reaction worked up after 2hrs as in preparation **(xxvii)** when the title compound was collected in 70% yield as a pale brown solid.

MP 189-191°C.

IR 1630, 1605, 1514, 1329 cm^{-1}.

^1H NMR (400 MHz;DMSO-d_6) δ 6.65 (s, 1H), 6.9 (d, 2H), 7.6 (m, 3H), 7.9 (m, 2H), 7.95 (s, 1H), 8.2 (d, 2H).

(xxxvi) Preparation of benzil monophenylhydrazone (192a)

The procedure was followed as for (192b) when the hydrazone was collected as bright yellow crystals after agitating the reaction for 1hr.

MP 121-122°C.

IR 3284, 1636 cm^{-1}.

^1H NMR (400 MHz;DMSO-d_6) δ 7.1-7.7 (m, 15H), 8.05 (s, 1H), 8.25 (s, 2H).

(xxxvii) Preparation of benzil monophenylhydrazone azoacetate(12a)

The procedure was followed as in preparation **(xxxiv)** which rendered the azoacetate (12a) as a dark brown sticky solid in 46% yield.

IR 1750, 1690 cm^{-1}.

^1H NMR (400 MHz;DMSO-d_6) δ 2.0 (s, 1H), 7.0-8.0 (m, 15H).

(xxxviii) Preparation of 2-benzoyl-1-acetyl-phenylhydrazine (195a)

The rearrangement of benzil monophenylhydrazone azoacetate(12a) was induced as for (12b). The reaction was worked up as described in **(xxvii)** after 30 minutes when column chromatography, using ethyl acetate:pet-ether (30:70) as eluent, of the resulting brown viscous oil provided N'-benzoyl N-acetyl phenylhydrazine as the major product in 45% yield.

IR 3264, 1688, 1650, 1596 cm^{-1}.

^{1}H NMR (400 MHz;DMSO-d_6) δ 2.0 (s, 3H), 7.0-8.0 (m, 10H),
9.0 (s, 1H), 9.5 (s, 1H).

(xxxix) Preparation of 2-benzoylphenylhydrazine (196a)

When the rearranged product, 2-benzoyl-1-acetyl-phenylhydrazine (195a) was heated under reflux for 3hrs and the reaction worked up as for preparation **(xxxvii),** deacetylation was found to occur yielding 2-benzoyl phenylhydrazine (196a) as a pale cream precipitate.

^{1}H NMR (400 MHz;DMSO-d_6) δ 6.4 (s, 1H), 6.9 (m, 3H), 7.25 (m, 2H),
7.6 (m, 3H), 7.9 (m, 2H), 8.0 (s, 1H).

(xxxx) Preparation of diacetylated tertiary amide (232)

0.45g of the tertiary amide (145) was dissolved in acetic anhydride (20mls) to which acetyl chloride was added (10mls initially increased to 40mls over reaction time). The reaction was heated for 48hrs, then allowed to cool, and added to H_2O (80mls). The reaction mixture was then extracted into ethyl acetate (40mlsx3), dried over $MgSO_4$, filtered and evaporated to dryness. The resulting solid was chromatographed with ethyl acetate:pet-ether (50:50) which separated the product from the starting material as a pale yellow powder in a 30% yield (150mgs).

MP 88-90°C.

^{1}H NMR (400MHz;DMSO-d_6) δ 1.3 (m, 9H), 2.2 (s, 3H), 2.6 (s, 3H),
4.2 (q, 2H), 7.6 (d, 2H), 8.3 (d, 2H).

^{13}C (400MHz DMSO-d_6) δ 172.2, 171.7

(xxxxi) Deacetylation of (232)

When 0.1g (0.28 mmoles) of the diacetylated compound (232) was heated in ethanol for 2 hrs no reaction was observed. However upon addition of 2 equivs of KCN (0.38 mmoles) and further heating for 30 minutes, the tertiary amide (145) was the sole product isolated.

^{1}H NMR (400 MHz;DMSO-d_6) δ 1.2 (t, 3H), 1.35 (s, 3H), 1.4 (s, 3H),
2.0 (s, 3H), 4.0 (q, 2H), 7.2 (d, 2H),
8.2 (d, 2H), 9.9 (s, 1H).

CHAPTER THREE

CHAPTER 3

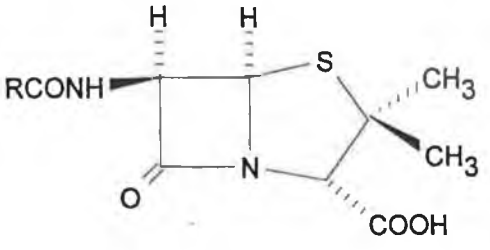
INTRODUCTION

3.1 AZA-β-LACTAMS REVIEW

In 1929 Fleming first reported his findings on the selective antibacterial activity of penicillin which created the ongoing interest in the β-lactam ring.

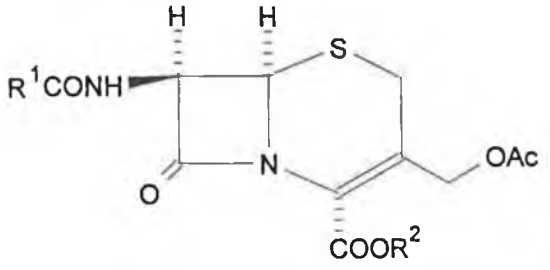
Since then thousands of compounds have been made by varying substituents on the monobactam and bicyclic system[133,134,135,136].

The active compounds of the fungus penicillium were found to be acyl derivatives of 6-aminopenicillanic acid such as benzylpenicillin (R: CH_2Ph) (240) :



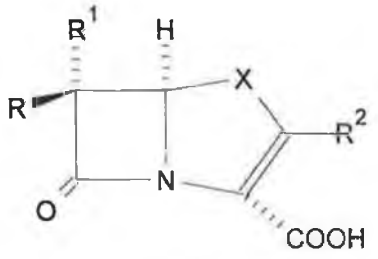
(240)

Following isolation of penicillins in the 1940's, their facile conversion lead to compounds of type (241) the cephalosporins, which were found to have greater biological activity[134,135].



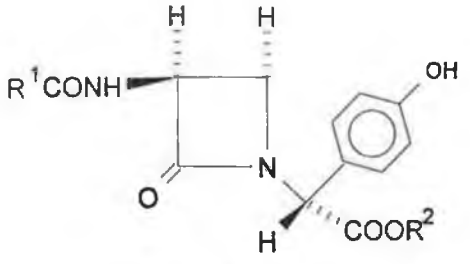
(241)

In 1975 a new β-lactam skeleton, a hybrid of (240) and (241), the penem (242; X=S), was isolated:



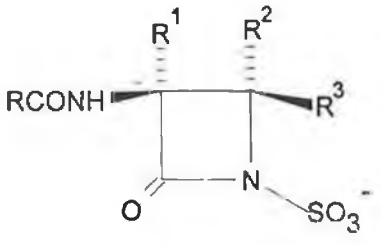
(242)

Monocyclic β-lactams, the norcardicins (243), were first described in the mid 1970's.



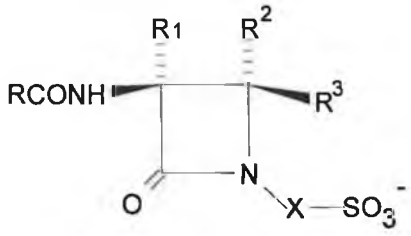
(243)

These were improved upon when the ionisable carboxylate group was replaced by a sulfonate moiety providing the monobactams[137] (244):



(244)

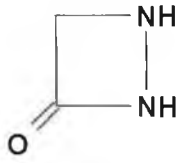
However in order to parallel the essential unit of active bicyclic systems, the ionisable group should be one atom further from the azetidinyl nitrogen thus (245):



(245)

It was found while X=O an active agent was formed, but when X=N there was no interesting biological activity[138]. However when the second nitrogen is incorporated into the ring structure then a whole new family of compounds, analogous to the β-lactams, the aza-β-lactams or the 1,2-diazetidin-3-ones are produced which also exhibit biological activity.

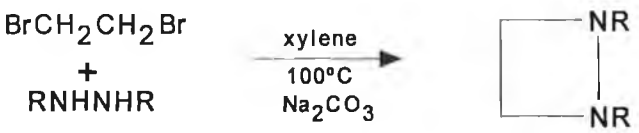
A typical example having minimum substitution is, the 1,2-diazetidin-3-one ring system (246)[139].



(246)

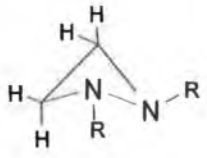
As a general insight into the structure of 4-membered dinitrogen compounds, 1,2-dialkyl -1,2,-diazetidines (247) have been prepared by the direct reaction of 1,2-dibromoethane and the corresponding 1,2-dialkylhydrazine in hot xylene in the presence of anhydrous sodium carbonate[140].

Scheme 3.1



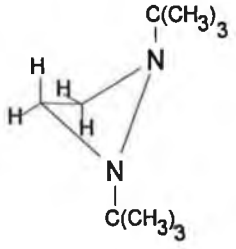
(247)

Examination of the coupling constants revealed a highly puckered structure as follows:



(247)

Examination of the coupling constants and chemical shifts for 1,2-di-*t*-butyl-1,2-diazetidine (248) suggests it may have a somewhat different conformation.



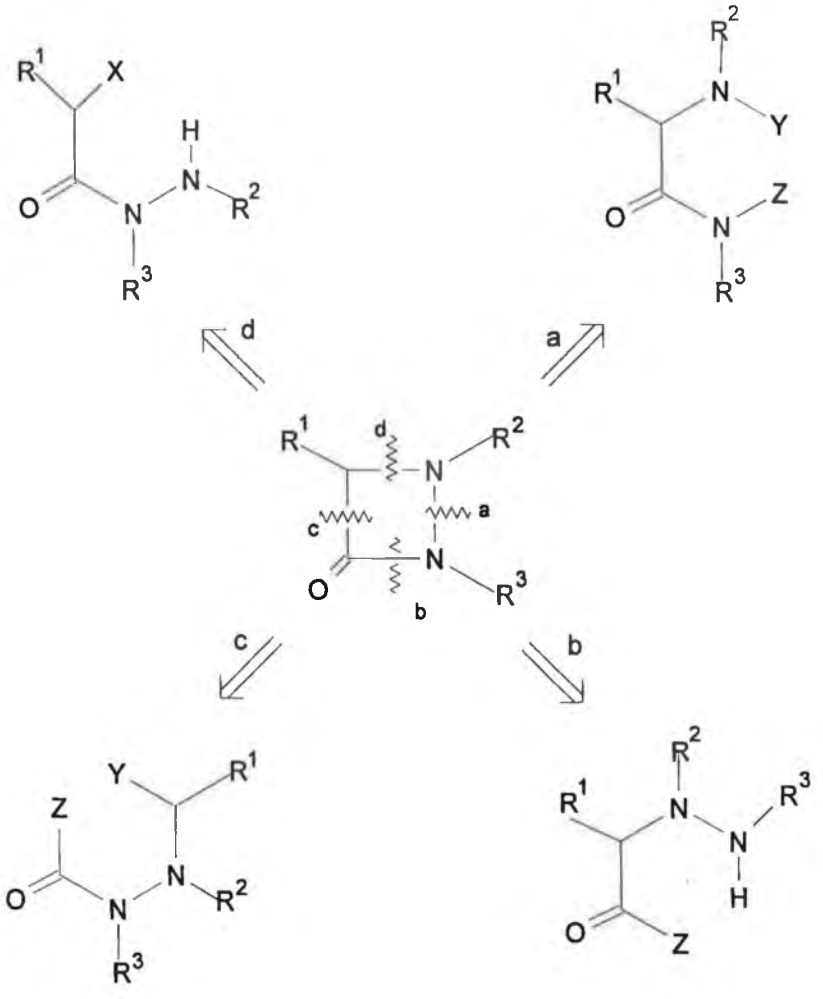
(248)

Chemical synthesis of the β-lactam ring has been approached from every possible route, for example, N-C2, C2-C3, C3-C4, and N-C4 ring closures[136]. Bond formation involving N-C4 ring closure was considered especially appealing because this is the route which biosynthetic pathways assume[141].

The cyclisations usually involve intramolecular alkylation through nucleophilic attack by N1 at C4 with displacement of a suitable leaving group. As we shall see, some of these approaches have been applied to the synthesis of aza-β-lactams.

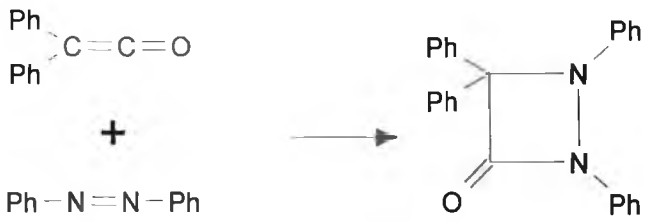
First consider retrosynthetic analysis of the cyclic dinitrogen system which illustrates the following possible starting materials (Scheme 3.2).

Scheme 3.2



The first preparation[142] of the 1,2 diazetidin-3-one ring system was in 1912 from the cycloaddition of azobenzene (249) and diphenylketene to give the tetraphenyl 1,2-diazetidin-3-one (250) (Scheme 3.3).

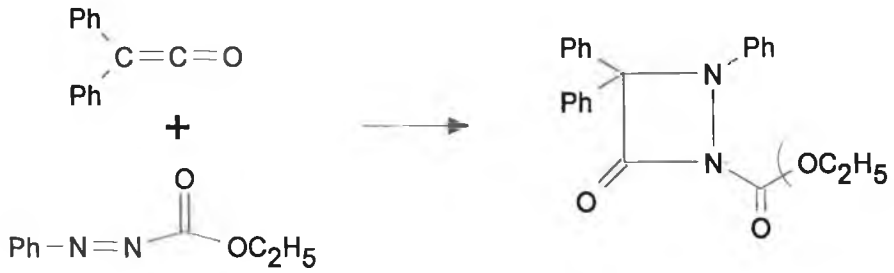
Scheme 3.3



(249) (250)

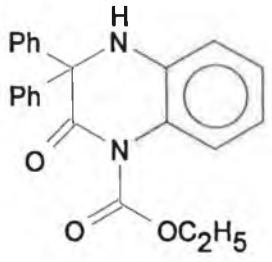
Ingold and Weaver[143] used a similar [2+2] cycloaddition using azo-esters instead of azobenzene as the former have greater additive power.

Scheme 3.4



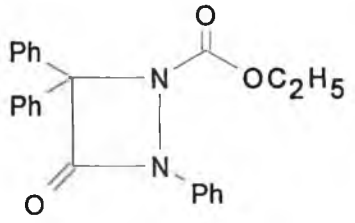
(251) (252)

Hence the aza-lactam (252) was formed by the addition of diphenylketene to ethyl phenylazocarboxylate (251). This 4-membered ring is capable of undergoing an *ortho*-semidine rearrangement when boiled with mineral acids[143] to yield the isomer (253):



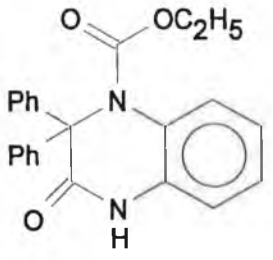
(253)

In 1963 Bird[144] revised structures (252) and (253). In order to establish the orientation of (252) it was synthesised from chlorodiphenylacetylchloride and ethyl N'-phenylhydrazine-N-carboxylate.
The alternative orientation (254), ethyl-2,4,4-triphenyl 1,2-diazetidin-3-one-1-carboxylate was confirmed by the high frequency carbonyl band at 1790 cm^{-1}.



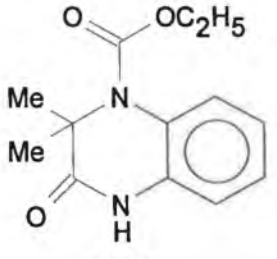
(254)

The structure of the isomer (253) was also revised. When (254) was treated with hydrochloric acid in ethanol, assuming an *ortho*-semidine rearrangement, as postulated by Ingold *et al.*[143], the expected isomer would be (255).



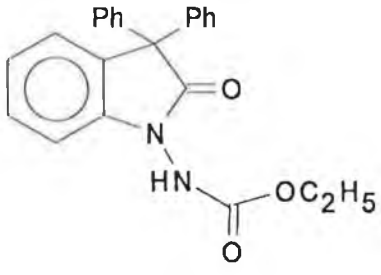
(255)

However Bird independently prepared the analogous methyl compound (256) with carbonyl bands at 1710 and 1670 cm^{-1} differing from the isomerization product (255) which had such bands at 1740 and 1700 cm^{-1}.



(256)

This evidence lead to the reformulation of the isomer of (254) to be neither the aza-β-lactam (253) nor the six membered heterocycle (255) but instead the five-membered (257).

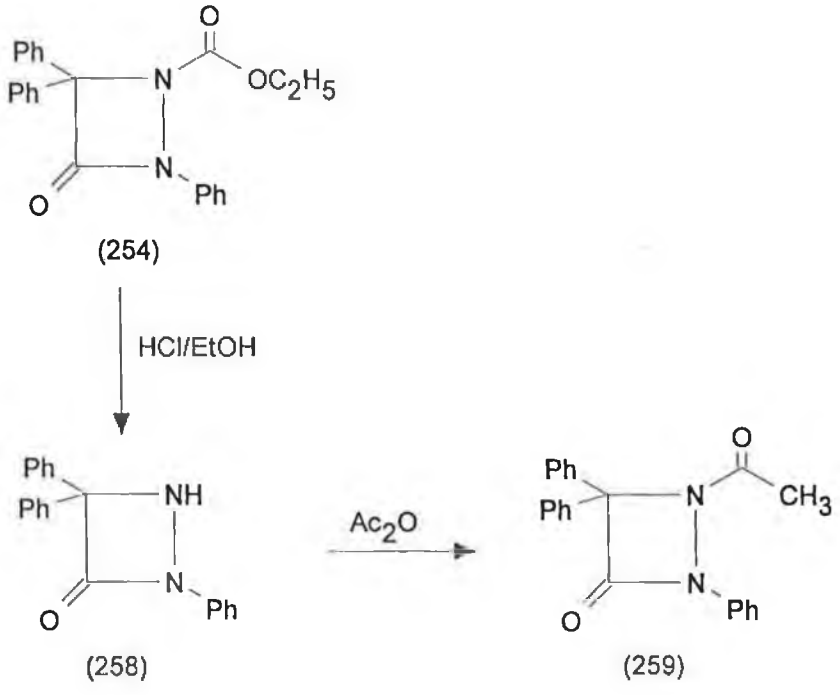


(257)

This was confirmed by subsequent transformations.

Further derivatives of the aza-β-lactam were obtained[144] from reactions of (254) (Scheme 3.5). Acid catalysed removal of the ethoxy group provides (258) and subsequent acetylation allowed for isolation of the acetyl derivative (259).

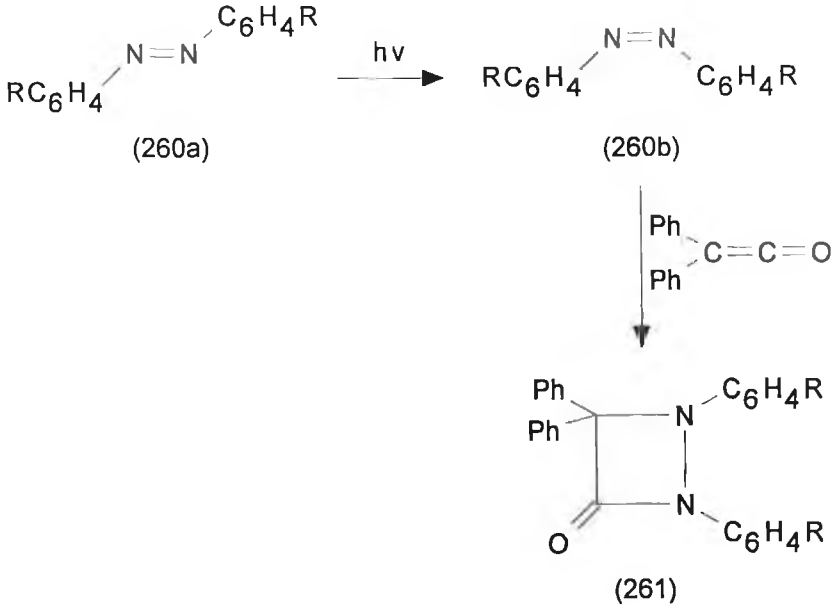
Scheme 3.5



(254) (258) (259)

The initial route to the aza-β-lactam involved [2+2] cycloaddition[142]. Cook and Jones[145] further studied the photolytic reaction of diphenylketene with azobenzene. They found the *cis* azobenzene reacts rapidly at room temperature while the *trans* isomer requires temperatures of 125-130°C to react, and then only slowly. Thus reaction of substituted azobenzenes (260) with diphenylketene was irradiated first to ensure the *cis* form (260b) which readily provided the corresponding diazetidinone (261) (Scheme 3.6) upon reaction with diphenylketene.

Scheme 3.6

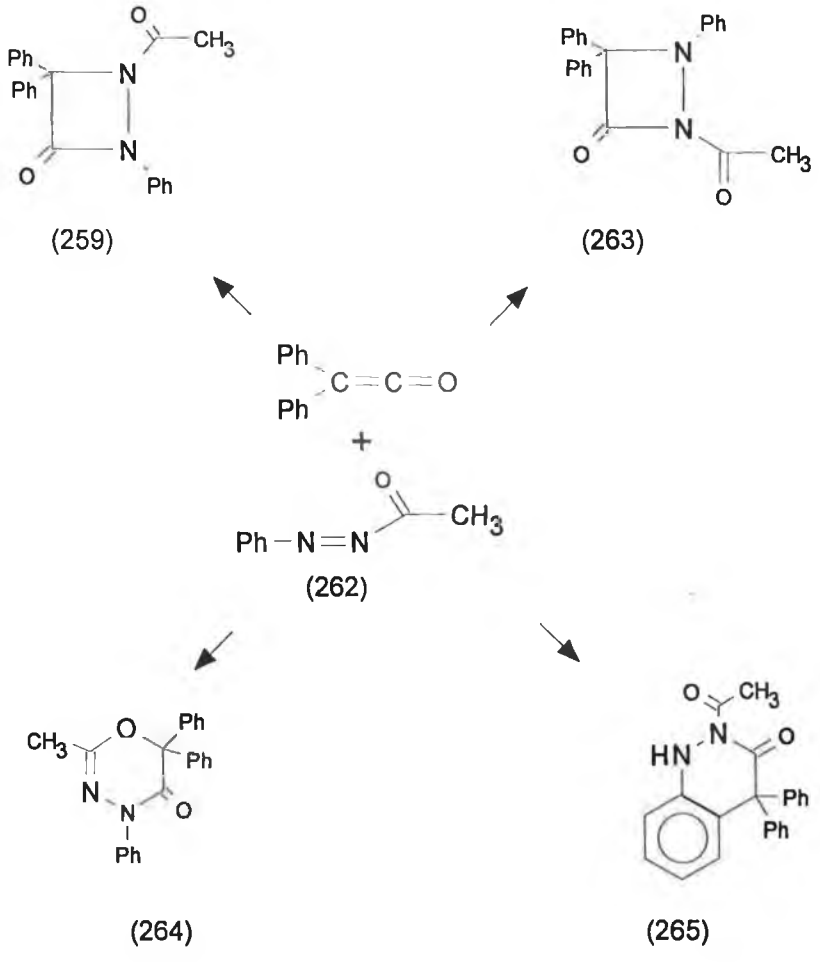


Ethyl phenylazoformate is the only azo compound of those investigated by Kerber *et al.*[146] that gave cycloaddition with diphenylketene in the absence of irradiation. However the slow nature of the reaction suggests *trans* to *cis* conversion occurs before reaction proceeds. The unreactivity of the *trans* azo group can be attributed to steric problems with one of the ketene phenyl groups upon orthogonal approach of the azo group.

Sommer[147,148] reported similar addition reactions providing 1,2-diazetidin-3-ones. *Trans*-azobenzenes react with diphenylketene very slowly to give 1,2-diazetidinones.

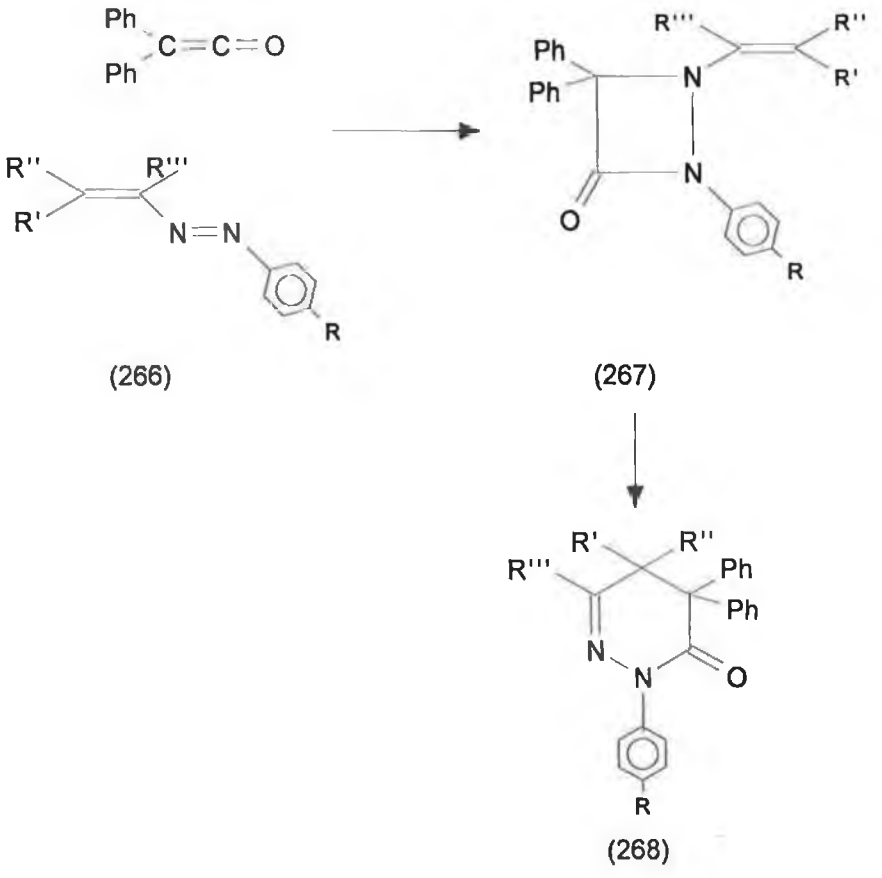
Arylazocarbonyl compounds (262) on the other hand react exothermically with diphenylketene to give [2+2] cycloadducts (259) and (263), and [4+2] cycloadducts (264) and (265) (Scheme 3.7).

Scheme 3.7



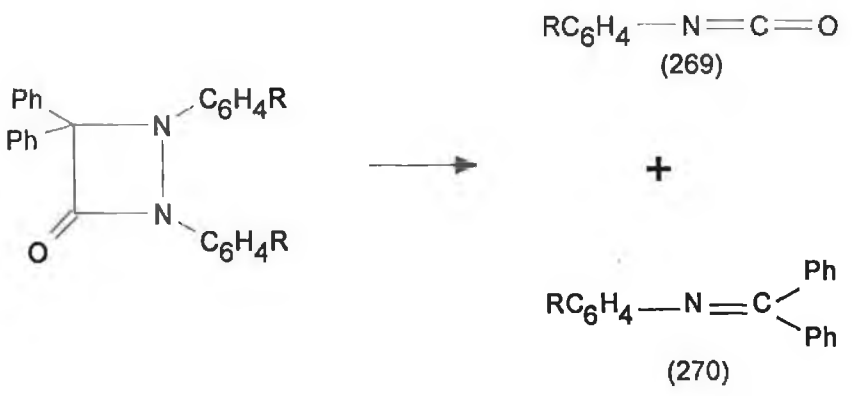
Arylazoalkenes (266) are also capable of forming [2+2] and [4+2] cycloadducts to provide N-vinyl-1,2-diazetidinone (267) and 4,5-dihydro-2H-pyrazinone (268) derivatives respectively (Scheme 3.8).

SCHEME 3.8



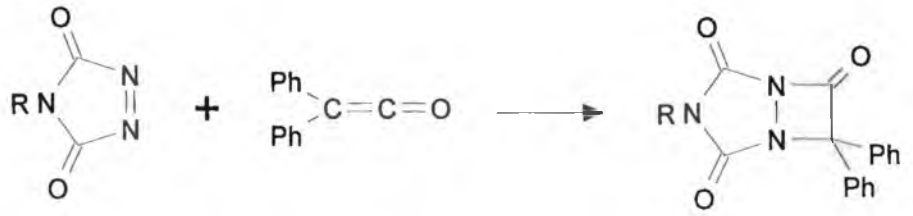
In order to further study the [2+2] cycloaddition approach to form the cyclic dinitrogen unit, the reverse reaction (Scheme 3.9) was investigated by Hall and Kellogg[149]. They isolated the isocyanate (269) and ketimines (270) as products from the thermal decomposition of tetraphenyl 1,2-diazetidinones (261):

Scheme 3.9



An additional example of the reaction of an azo compound with diphenylketene is as follows[150]. [2+2] Cycloaddition is observed for 4-substituted-1,2,4-triazoline-3,5-diones (271) with diphenylketene (Scheme 3.10). The bicyclic system (271) is formed.

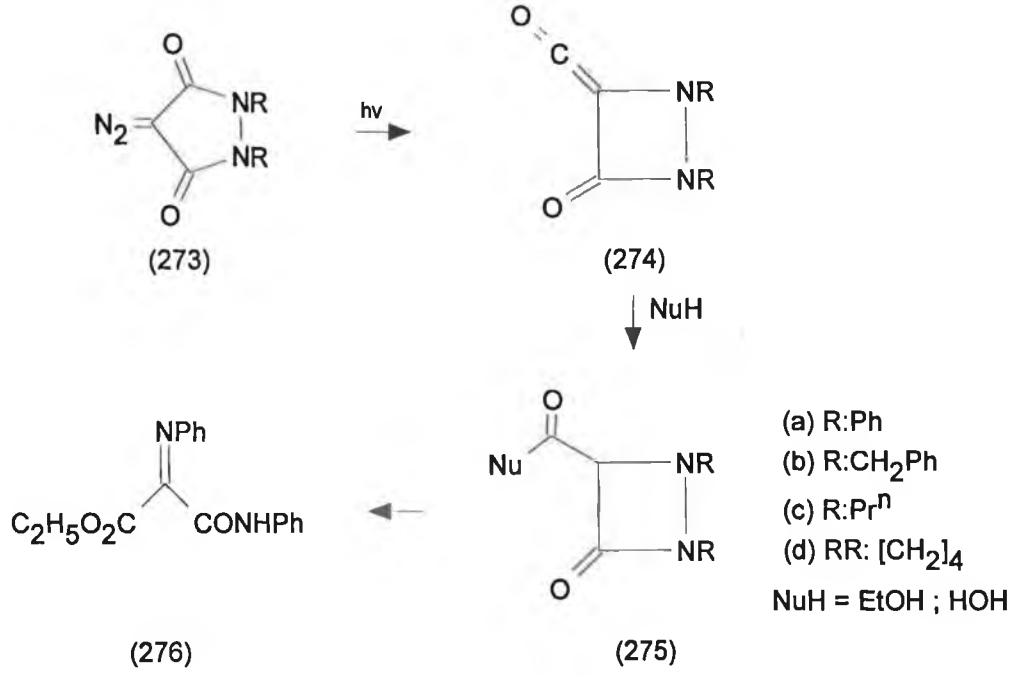
Scheme 3.10



(271) (272)

A concise route for aza-β-lactam formation involves the photochemical ring contraction[151,152] of 4-diazopyrazolidine-3,5-diones (273) and subsequent trapping of the intermediate ketenes (274) with nucleophiles (Scheme 3.11).

Scheme 3.11



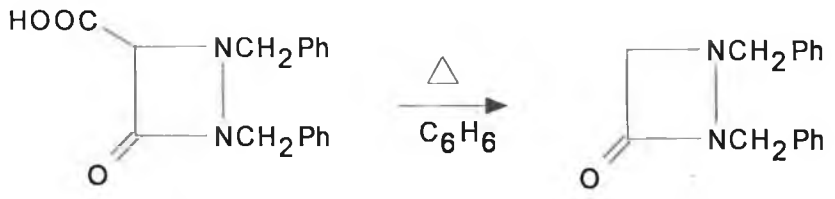
(273) (274) (275) (276)

The reaction involves the migration of the nitrogen to the electron deficient carbene centre. Irradiation of (273a) in diethyl ether and ethanol provided a small quantity of azo-benzene and a major product which was not (275a) but identified as (276)[153]. This compound probably arises by photochemical

homolytic cleavage of the N-N bond in (275a). In the case of (273b) it is found the reaction stops at (275) possibly due to replacement of the aryl substituents by 1,2 dialkyl substituents. Likewise, (273c) and (273d) yielded (275) as bicyclic aza-β-lactams, however the yields were reduced.

The chemistry of these aza-lactams has been briefly investigated in the dibenzyl series[151]. For example, (277) is decarbonylated by heating in benzene to give (278) (Scheme 3.12).

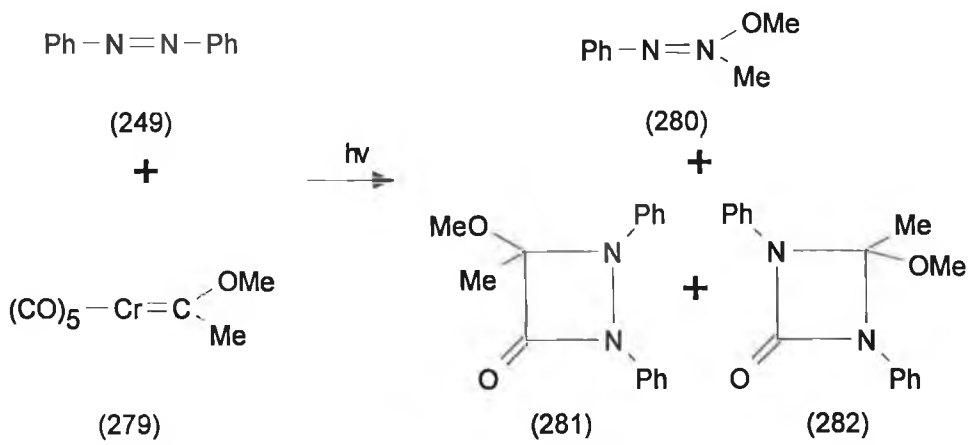
Scheme 3.12



(277) (278)

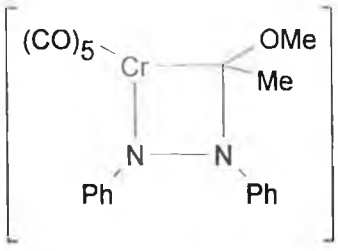
The photolysis approach to aza-β-lactams was conducted by Hegedus *et al.*[154] as follows (Scheme 3.13). Sunlight irradiation of a pet-ether solution of azobenzene (249) and methylmethoxycarbene pentacarbonyl-chromium (279) at 300°C produces an iminoester (280) as the main product and a minor product (10%) consisting of 1:1 mixture of the two diazetidinones (281) and (282).

Scheme 3.13



The product distribution of this reaction was remarkably sensitive to reaction conditions. Irradiation at lower temperatures (0°C), in sunlight lead to a decrease in (280) and an increase in (281) and (282). A similar trend was evident when artificial light was used instead of sunlight. Unsymmetrically substituted azobenzenes also underwent this reaction. In contrast to electron-rich azobenzenes, the electron-deficient *p*-nitrobenzene was relatively inert towards the chromium complex (279).

A suggested mechanism for the reaction has been the photocycloaddition of the azobenzene to the chromium carbene complex to produce a diazametallacyclobutane (283).

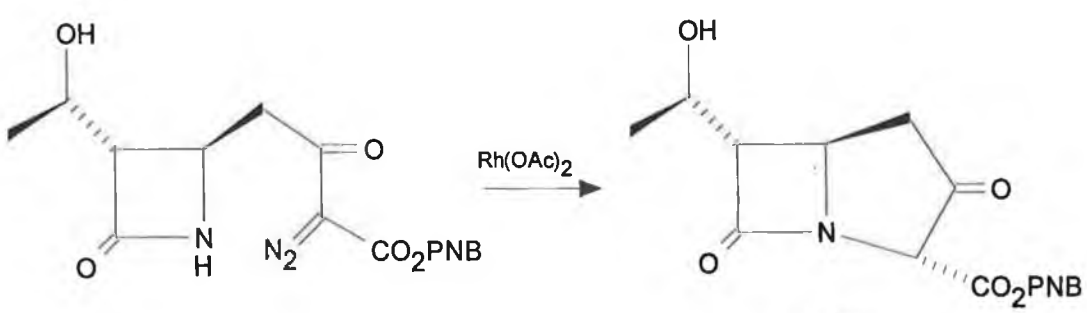


(283)

With high light intensity, CO insertion and reductive elimination to form the cyclic compounds is favoured.

The use of rhodium (II) acetate to effect ring closure has been precedented in β-lactam chemistry. Consider for example the step by step process for the synthesis of thienamycin as reported by Melillo *et al.*[155]. The final stages involves the use of catalytic amounts of rhodium (II) acetate, resulting in selective NH insertion of the carbenoid intermediate (284) to provide the bicyclic structure (285), preceding thienamycin formation, as follows:

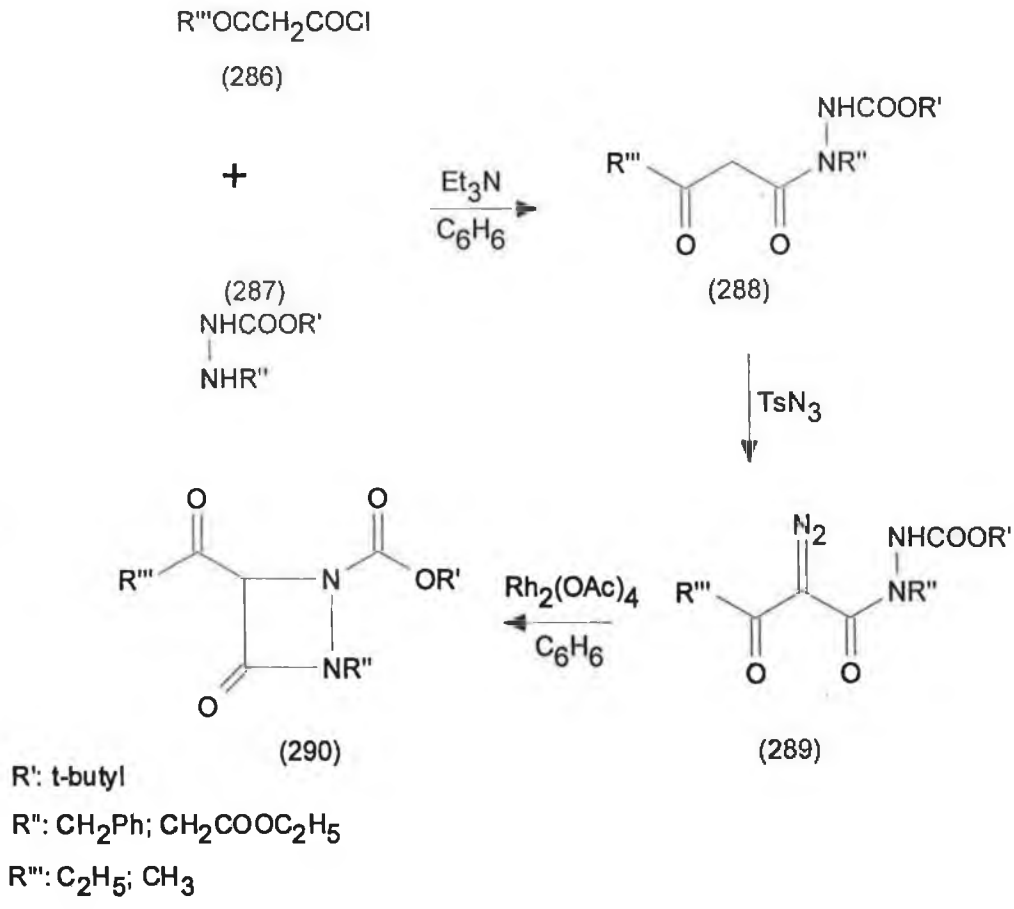
Scheme 3.14



(284) (285)

Synthesis of aza-β-lactams by rhodium carbenoid mediated cyclisation has been investigated by Moody *et al.*[153]. Acylation of (287) with ethylmalonyl chloride (286 ; R'''=Et), yields a diacyl hydrazine (288). Diazotization to (289) is followed by cyclisation to the aza-lactam (290), by treatment with a catalytic amount of rhodium (II) acetate in refluxing benzene.

Scheme 3.15



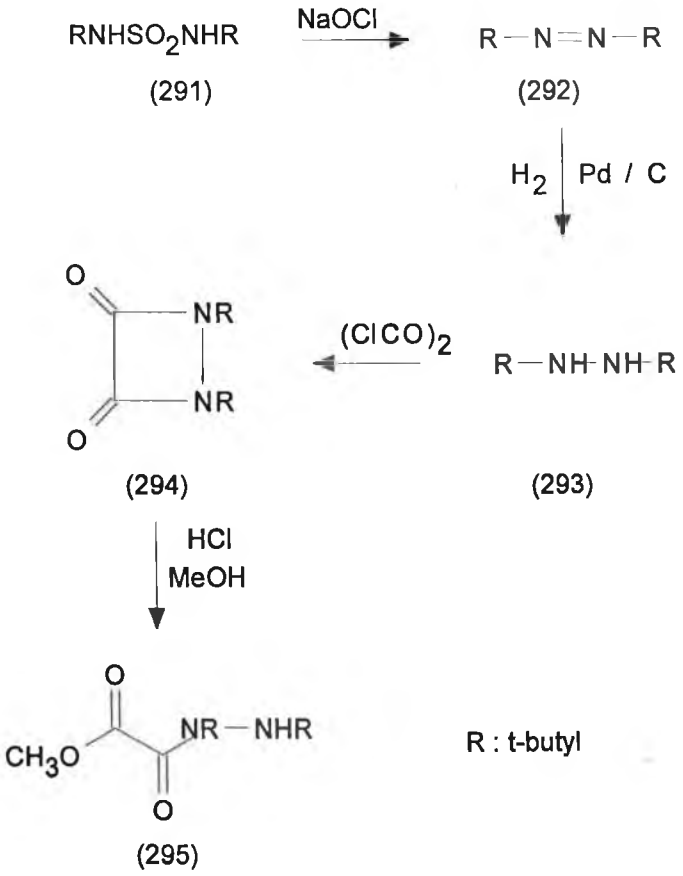
R': t-butyl

R'': CH_2Ph; $CH_2COOC_2H_5$

R''': C_2H_5; CH_3

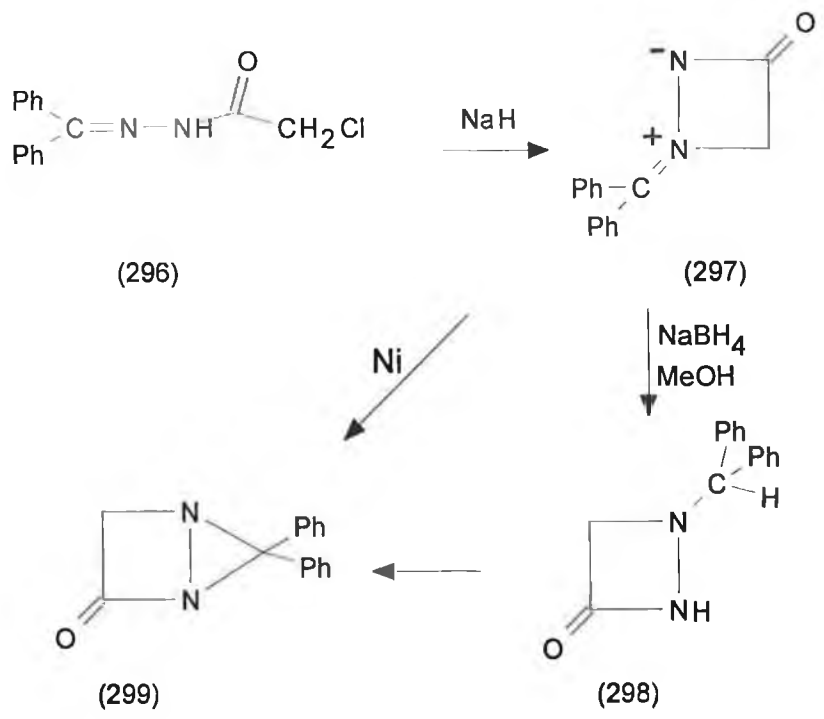
In 1967 Stowell[156] presented the synthesis of an aza-lactam, di-*t*-butyl-1,2-diazetidinedione, as follows (Scheme 3.16). The reaction of N,N'-di-*t*-butylsulfamide (291) with aqueous alkaline sodium hypochlorite yields an azo compound (292) which is hydrogenated to N,N'-di-*t*-butylhydrazine (293). This hydrazine reacted with oxalyl chloride affording the yellow crystalline di-*t*-butyl-1,2-diazetidinedione (294). Cleavage of (294), by stirring in a methanol solution containing a trace of hydrochloric acid, formed (295).

Scheme 3.16



An alternative approach to the diazetidinone ring system was developed by Taylor *et al.*[157] as follows (Scheme 3.17). Treatment of benzophenone chloroacetylhydrazone (296) with sodium hydride or potassium *t*-butoxide gave a colourless crystalline solid, the cyclic azomethine imide, 1-(diphenylmethylene)-3-oxo-1,2-diazetidinium inner salt (297). Reduction of (297) with sodium borohydride in methanol gave a dihydrocompound (298), a typical diazetidinone which does not have an azo compound as a starting material, and proves a useful synthon for further reaction[158].

Scheme 3.17

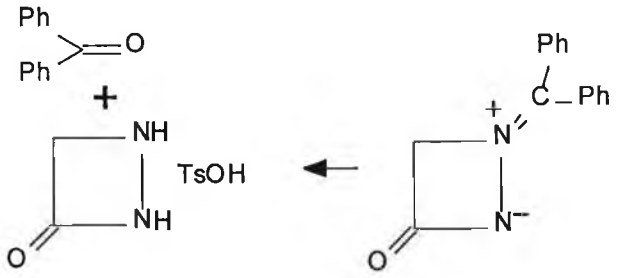


Catalytic reduction[159] of the azomethine imide (297) with deactivated Raney nickel gave 2,2-diphenyl-4-imidazolidinone (299).

Certain structural features appear to be critical[160] for a successful intramolecular dehydrohalogenation of the hydrazides (296) to give the azomethine ylides (297). The presence of steric bulk at the imine carbon is of critical importance. The direct intramolecular nucleophilic displacement of halide by the imine nitrogen is consistent with all experimental observations. These 1-(diarylmethylene)-3-oxodiazetinium ylides are remarkably stable thermally and can be recovered unchanged after refluxing for 24 hours in ethanol or toluene.

Investigation of the chemical reactivity of compound (297) found it to be stable to mild bases such as sodium bicarbonate or triethylamine, however, it was much more sensitive to acids. Selective cleavage of the iminium bond with retention of the labile β-lactam group could be achieved by treatment of (297) with 1 equivalent of water. Reaction of (297) with *p*-toluene sulphonic acid monohydrate in CH_2Cl_2 resulted in precipitation of 3-oxo-1,2-diazetidinium tosylate (300) (Scheme 3.18).

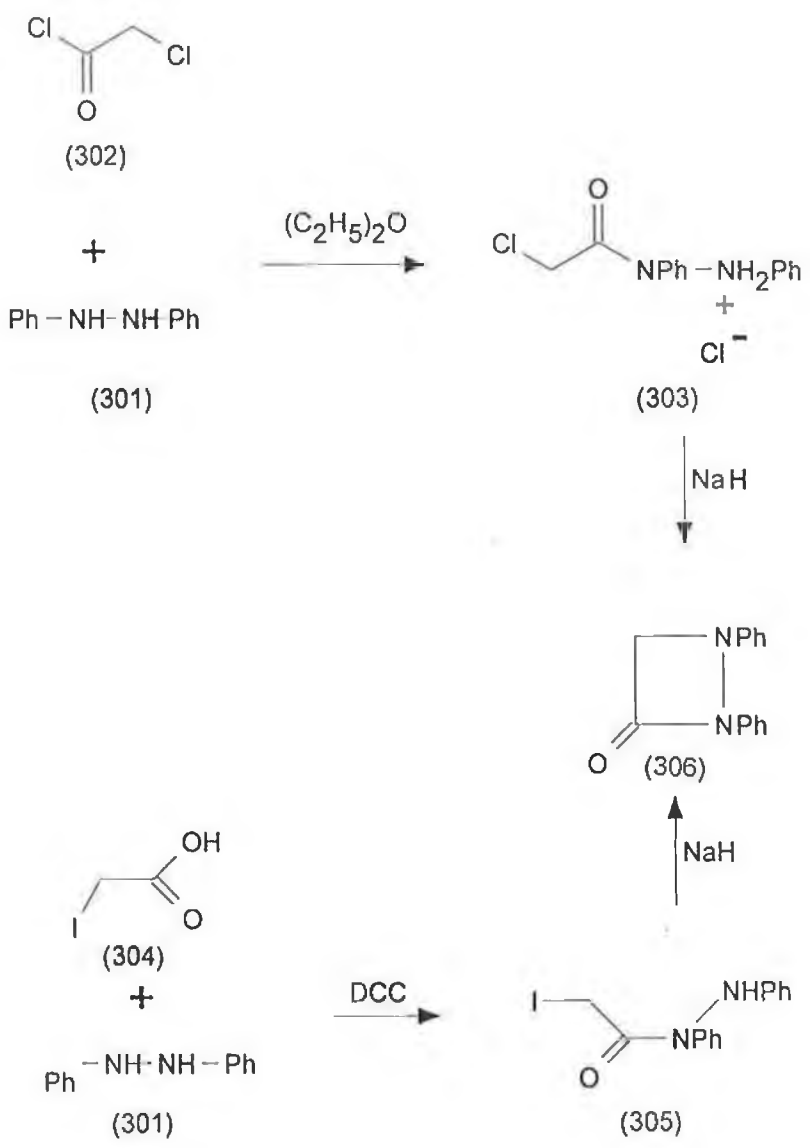
Scheme 3.18



(300) (297)

Another route to 1,2-diazetidin-3-ones involves the intramolecular alkylation of an α-haloacylhydrazine precursor[161] as follows (Scheme 3.19). Stirring 1,2-diphenylhydrazine (301) with chloracetylchloride (302) in ether at 0°C forms the salt (303). This is then converted to the aza-β-lactam (306) with 2 equivalents of base.

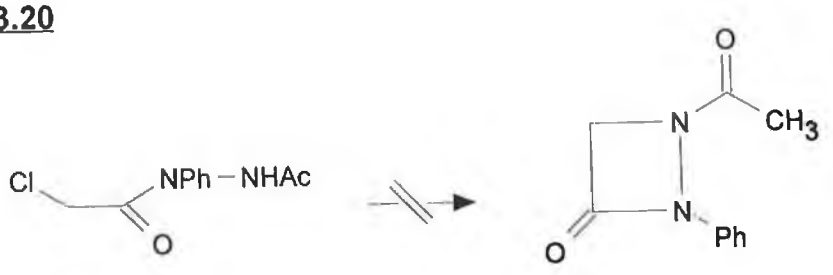
Scheme 3.19



A similar route to arrive at (306) consists of the dicyclohexylcarbodimide (DCC) coupling of (301) with iodoacetic acid (304) to give (305), which when treated with base cyclises to (306).

This latter approach was used to prepare 1-acetyl-2-phenyl-1,2-diazetidinone (308) which was unobtainable by attempted cyclisation of the precursor (307) (Scheme 3.20).

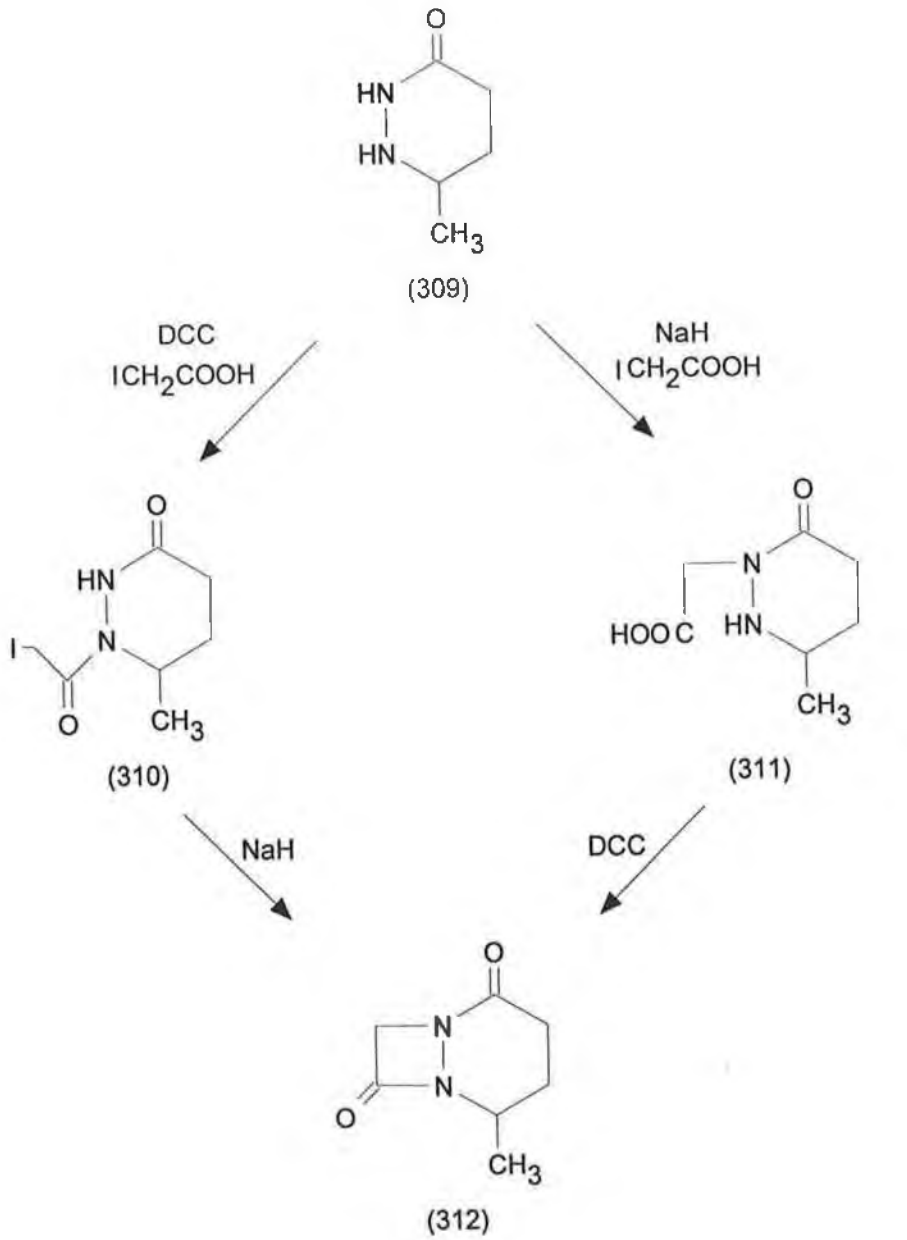
Scheme 3.20



(307) (308)

The latter strategies were successfully applied to the preparation of bicyclic diazetidinones (312) as follows[161] :

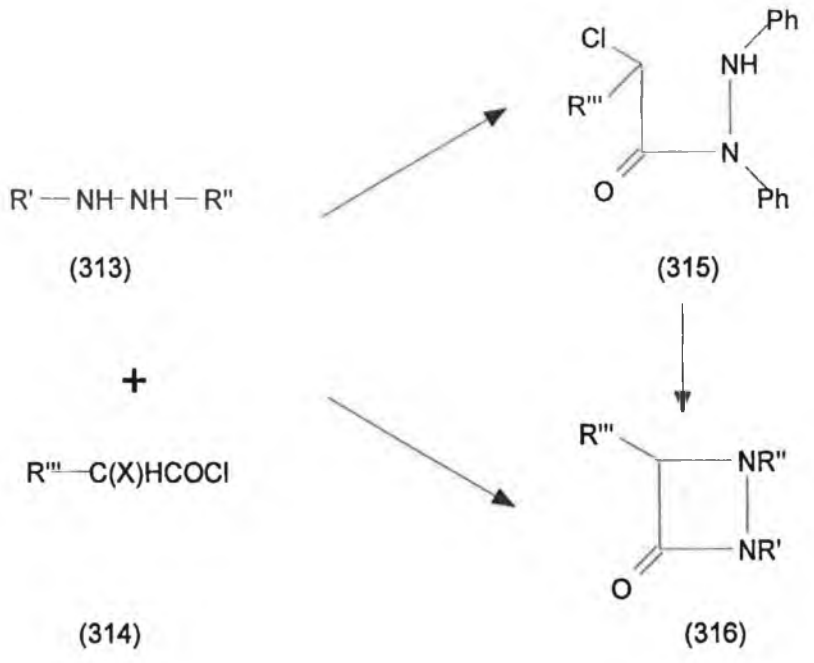
Scheme 3.21



A similar approach was used by Okawara[162]. Reaction of 1,2-disubstituted hydrazines (313) with α-halogenacyl halides (314) in 5% NaOH-CH_2Cl_2 in the presence of a phase transfer catalyst, benzyltriethyl ammonium chloride (BTEAC), gave the 1,2-diazetidin-3-ones (316) (Scheme 3.22).

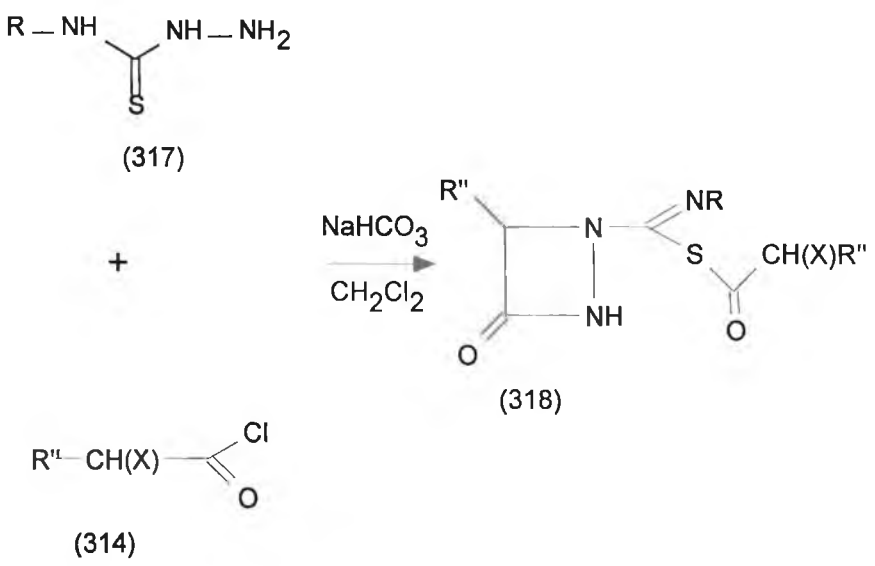
Reaction of (313; R'=R''=Ph) with (314; X=Cl), in the absence of BTEAC or in saturated $NaHCO_3$-CH_2Cl_2 afforded the N-halogenacyl intermediate (315) which readily afforded (316) when treated with the catalyst system.

Scheme 3.22



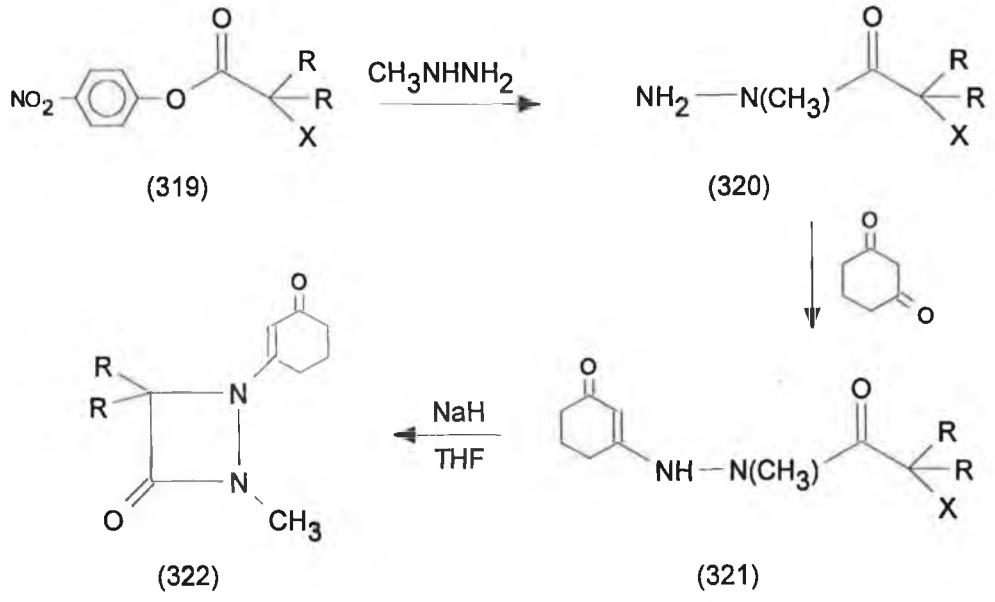
In a similar manner reaction of the 4-substituted thiosemicarbazide (317) with (314) in saturated $NaHCO_3$-CH_2Cl_2 gave 1-substituted-1,2-diazetidin-3-ones (318) in 52-84% yields.

Scheme 3.23



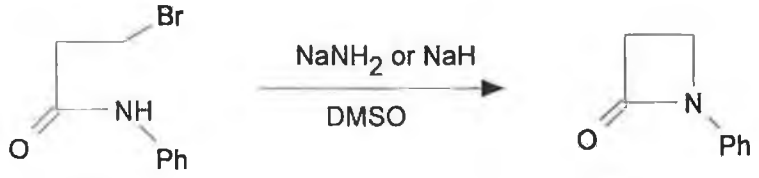
The following Scheme 3.24 outlines a route established by Taylor *et al.*[163] to 4,4-disubstituted diazetidinones. Reaction of a series of 4-nitrophenylesters (319) of 2-haloalkanoic acids with methylhydrazine gave the hydrazides (320). Addition of cyclohexane-1,3-dione under Dean-Stark conditions led smoothly to the enaminones (321).

Scheme 3.24



Ring closure of (321) to (322) was achieved by heating with sodium hydride in THF. This choice of base to effect ring closure is precedented in β-lactam chemistry[136]. Consider for example[164] the β-haloamide, β-bromopropionanilide (323), which is cyclised to (324) in the presence of various strong bases ($NaNH_2$ or NaH in DMSO).

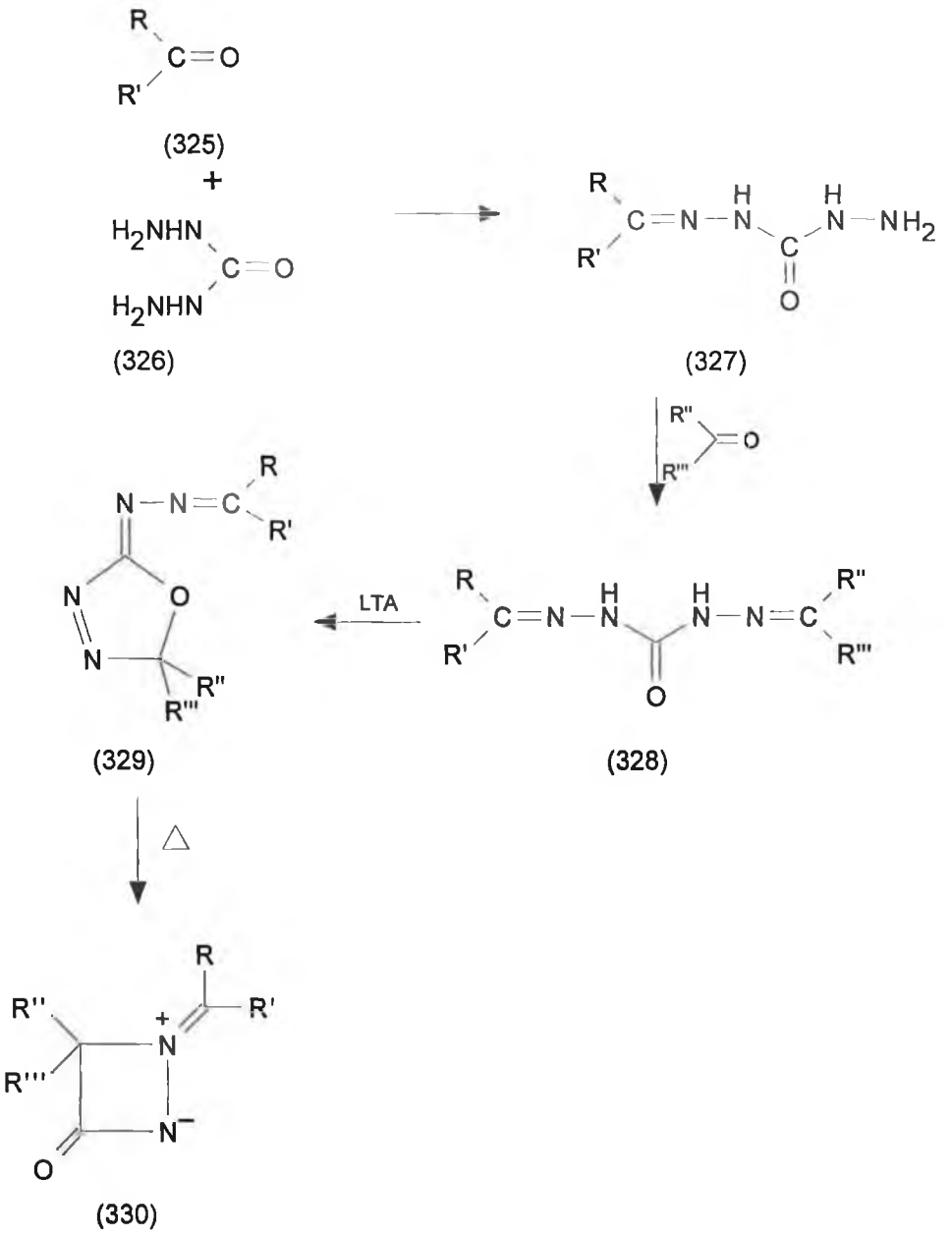
Scheme 3.25



(323) (324

Warkentin *et al.*[165] reported a new synthesis of 4,4-disubstituted cyclic azomethine imines (Scheme 3.26) which provides further variation on the methods described by Taylor *et al.*[166-171] particularly with regard to 4,4-disubstituted systems[163].

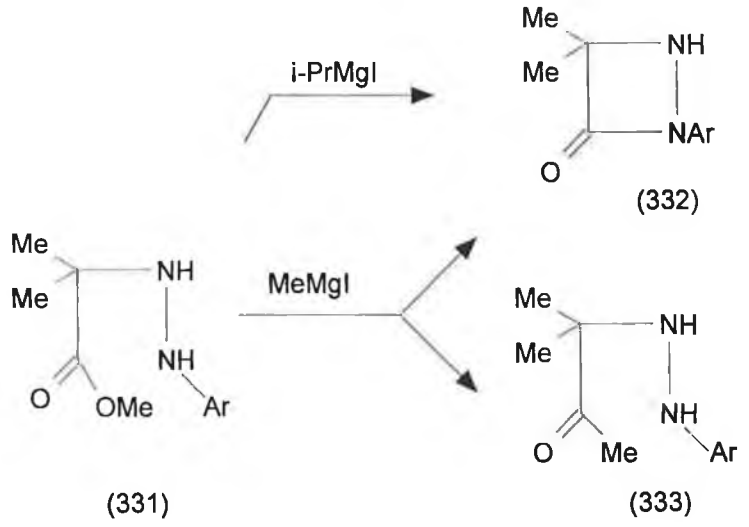
Scheme 3.26



This scheme illustrates the sequence of reactions by which carbonyl compounds (325) and carbohydrazide (326) are converted to 2-hydrazono-3-1,3,4-oxadiazolines (329) and 3-oxo-1,2-diazetidinium hydroxide inner salts (330).

Grignard induced cyclisation[172] of α-arylhydrazine-esters affords the aza-β-lactams as follows involving N-C2 cyclisation :

Scheme 3.27

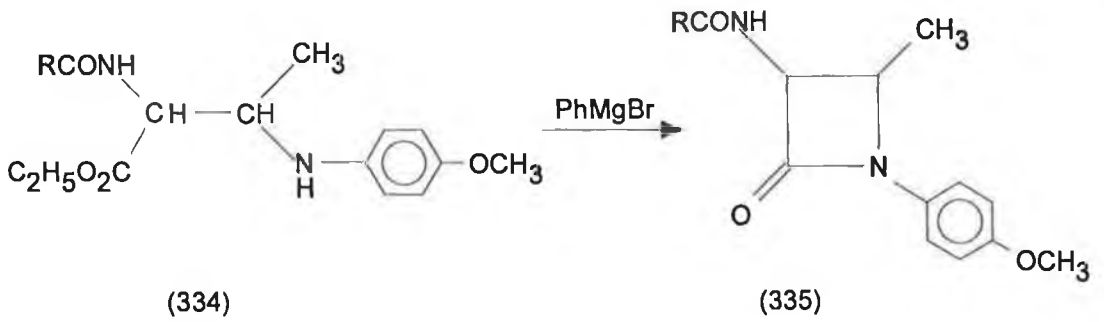


(331) (332) (333)

Reaction of the esters (331) with methyl magnesium iodide gave two products, the aza-β-lactam (332) and the ketone (333), in a ratio of 4:1 respectively. The sterically more demanding isopropylmagnesium iodide fully supressed ketone formation.

Fernandez-Resa *et al.*[173] describes the use of Grignard reagents to effect β-lactam formation. For example, when the acetylamino derivative (334) was treated with phenylmagnesium bromide in anhydrous THF, the β-lactam (335) was isolated.

Scheme 3.28



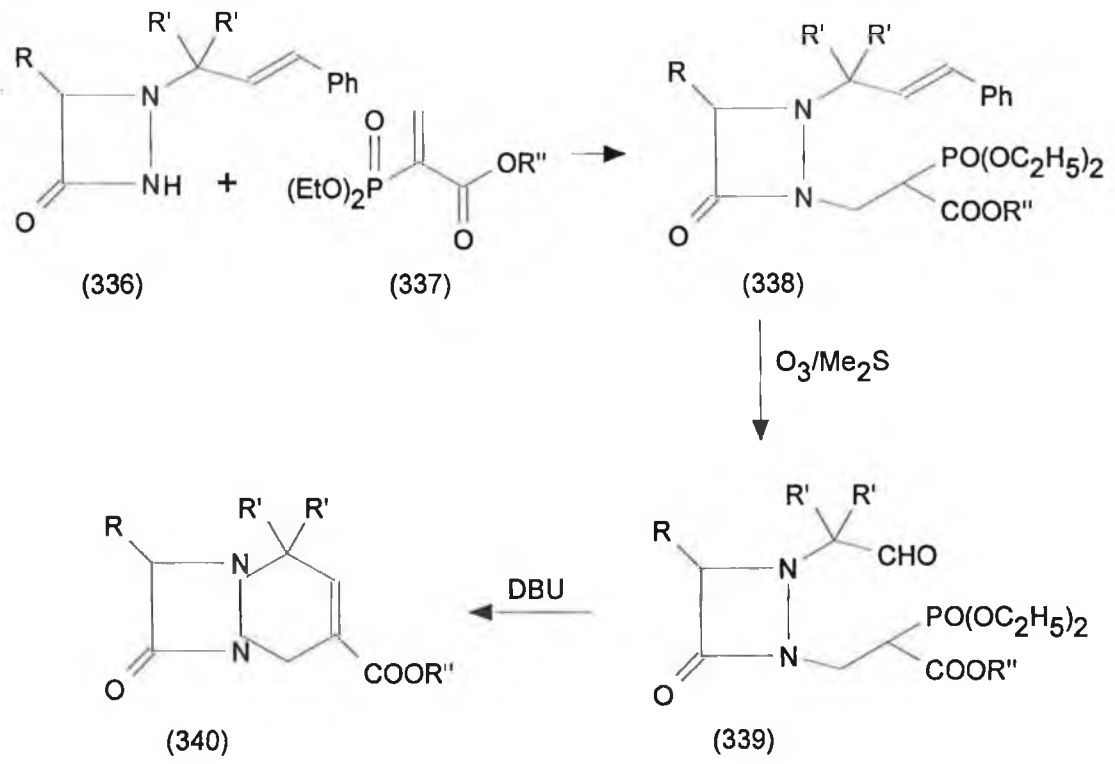
(334) (335)

In order to fully benefit from the aza-lactam ring, investigations towards active β-lactam analogues i.e. bicyclic systems, has earned a lot of interest.

For example, Taylor *et al.*[169] report the synthesis of (340) as follows (Scheme 3.29). Condensation of (336) with the vinyl phosphonate (337) took place in 93% yield simply by stirring the reactants together overnight. The aza-lactam (338) was converted to the aldehyde (339) by ozonolysis, which was subsequently cyclised using DBU to the bicyclic system (340).

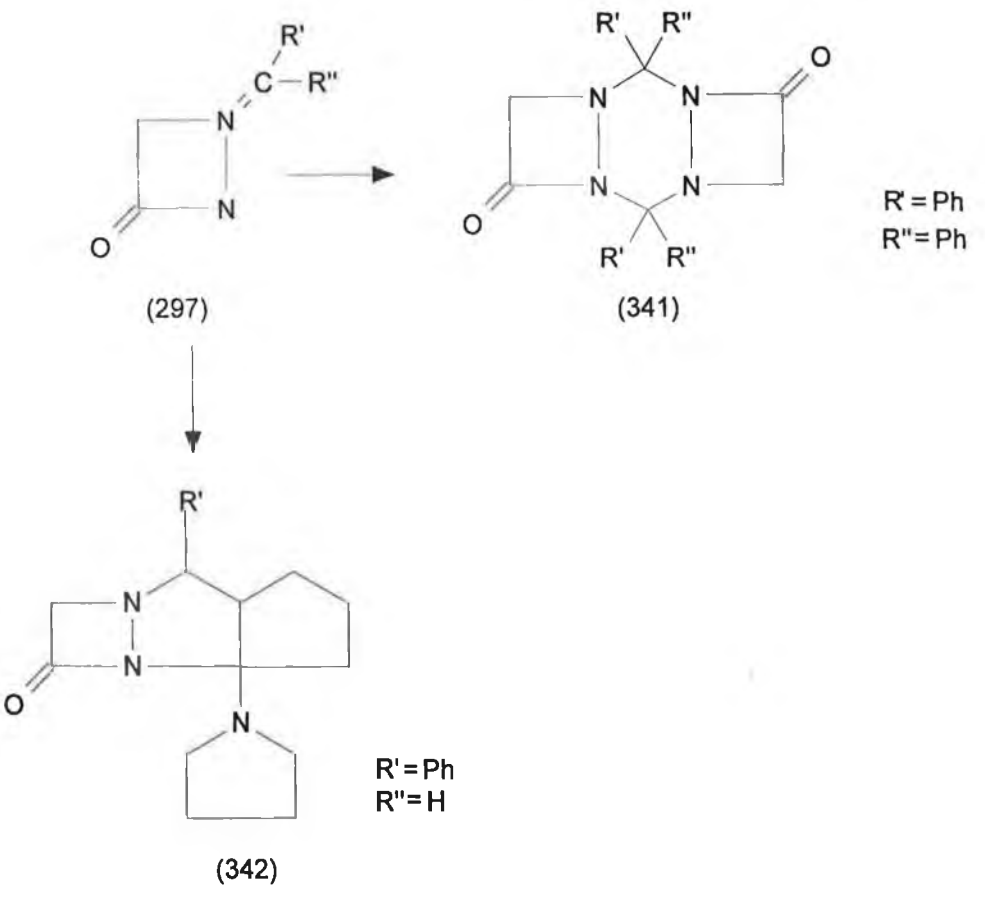
The reaction also reflects the nucleophilicity of the N-2 of the aza-β-lactam (336), as no base was required for the initial condensation step. The analogous β-lactam reaction requires more severe conditions[174].

Scheme 3.29



Further examples of bicyclic formation[170] include the conversion of (297;R'=Ph,R''=Ph) into the bicyclic system (341) (Scheme 3.30). Alternatively, reaction of the azomethine ylide (297;R'=H;R''=Ph) at 20°C with 1-pyrrolidinocyclopentene to affords excellent yields of the adduct (342), a highly strained aza-anologue of β-lactam antibiotics[167].

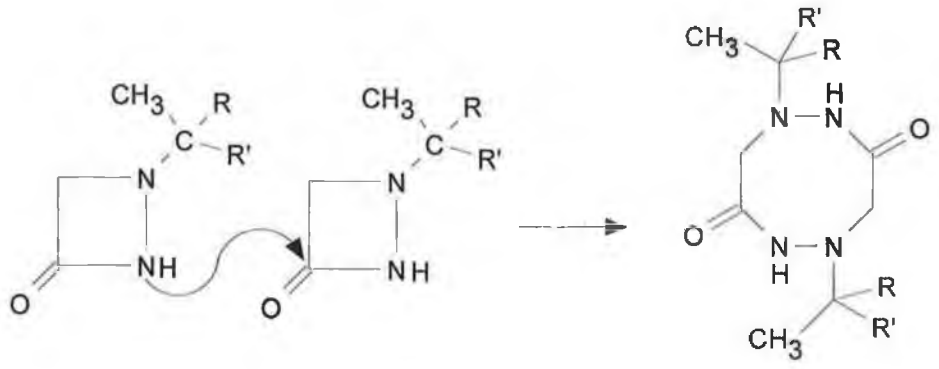
Scheme 3.30



There is a tendency for azetidin-2-ones (β-lactams), with no substituents on the nitrogen, to readily polymerise under basic conditions in the presence of a catalytic amount of acylating agent. This sensivity is also shared by aza-β-lactams apparently as a result of their instability in the absence of an effective electrophilic trapping agent.

Thus compounds of type (343) which were isolated as gums, underwent irreversible transformation to dimers (344) upon standing[171].

Scheme 3.31



(343) (344)

This transformation of an eight membered ring *via* a six membered intermediate is precedented in β-lactam chemistry during the synthesis of homaline[175].

CHAPTER 3

RESULTS AND DISCUSSION

CHAPTER 3

3.2 Results & Discussion

Aza-β-Lactams: A Novel Synthesis.

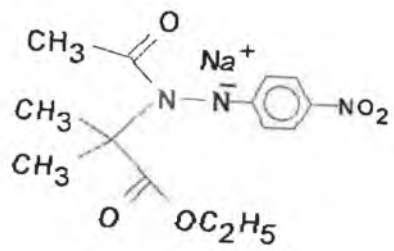
As previously discussed the β-lactams and, more recently, the aza-β-lactams have both warranted thorough investigation since the discovery of their biological activity.
From our earlier work on the rearrangement of azoacetates derived from β-ketoesters, an interesting new route to the aza-lactam was identified.

If ring closure for the hydrazide (145) could be effected, a new route to aza-β-lactams would be established. While extensive research has been dedicated to the area of β-lactams, aza-β-lactams studies are relatively fewer. Some of these compounds are reported to possess biological activity, therefore it is desirable to have the potential to extend this list.

As an initial attempt to effect ring closure, the hydrazide (145) was heated under reflux in the presence of NaH in THF overnight. While this system of base is reported to effect ring closure in β-lactam chemistry[176], the red solution which resulted, yielded a yellow precipitate at first which proved to be starting material.

However, following removal of the starting material, a red salt was then isolated whose ^{1}H NMR spectrum suggested the formation of the monosodium salt (347) (Scheme 3.32) of the hydrazide (145) [Figure 3.1a].
Addition of a few drops of acetic acid to the ^{1}H NMR sample changed the spectrum as shown [Figure 3.1b].

Figure 3.1a



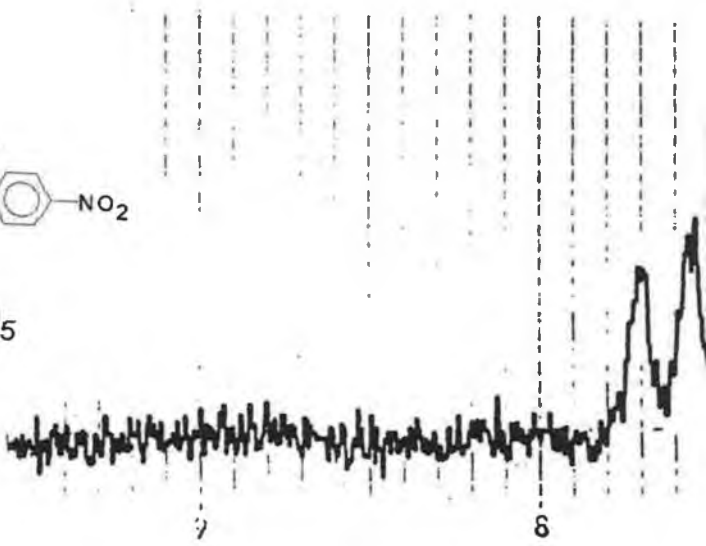
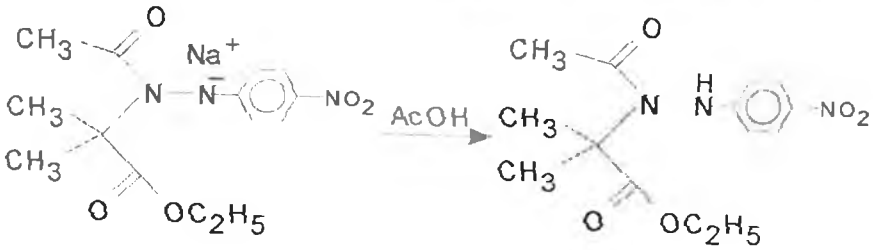
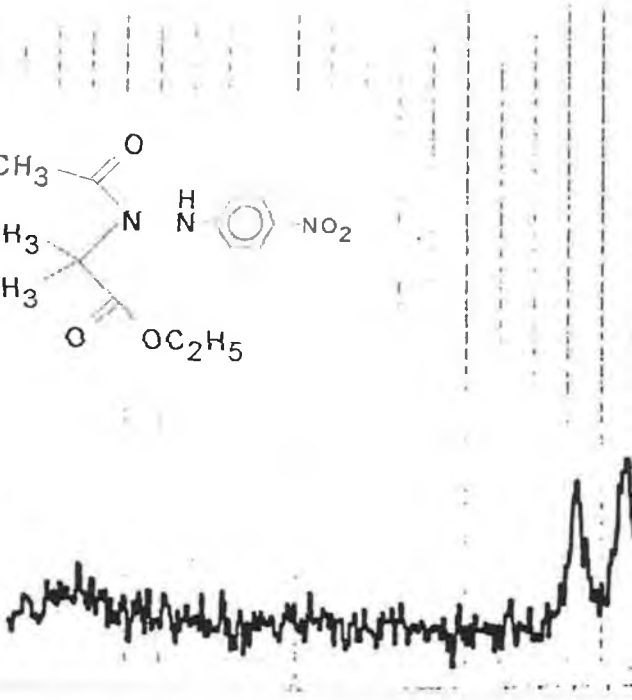
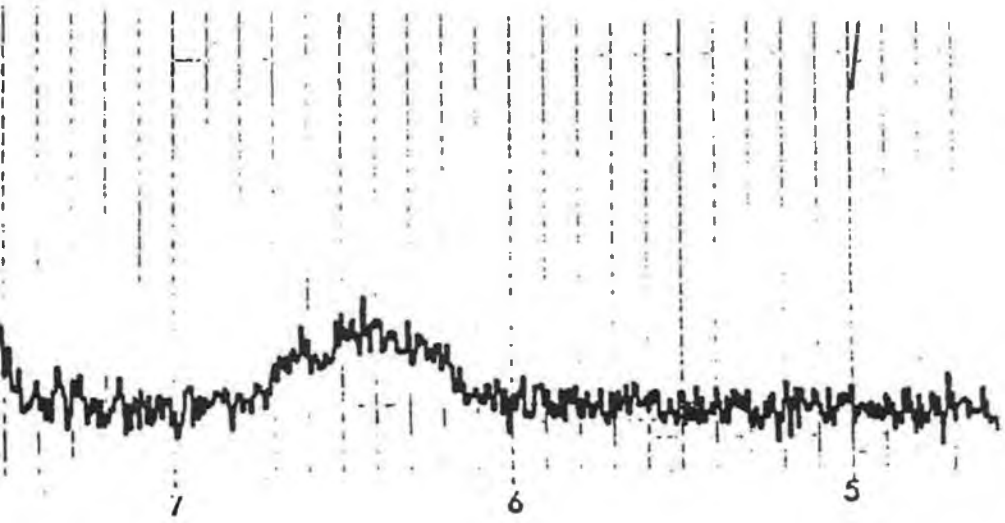
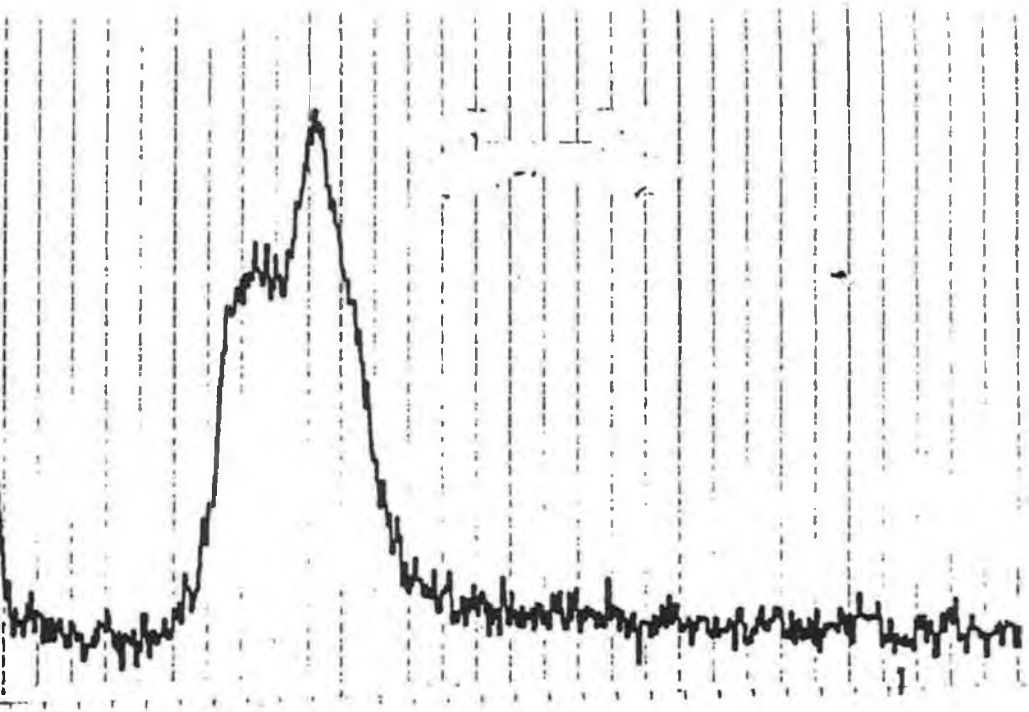


Figure 3.1b






7
6
5



The broadening of the ^1H NMR spectrum of the sodium derivative (347) was attributed to the nitrogen sodium bonding i.e:

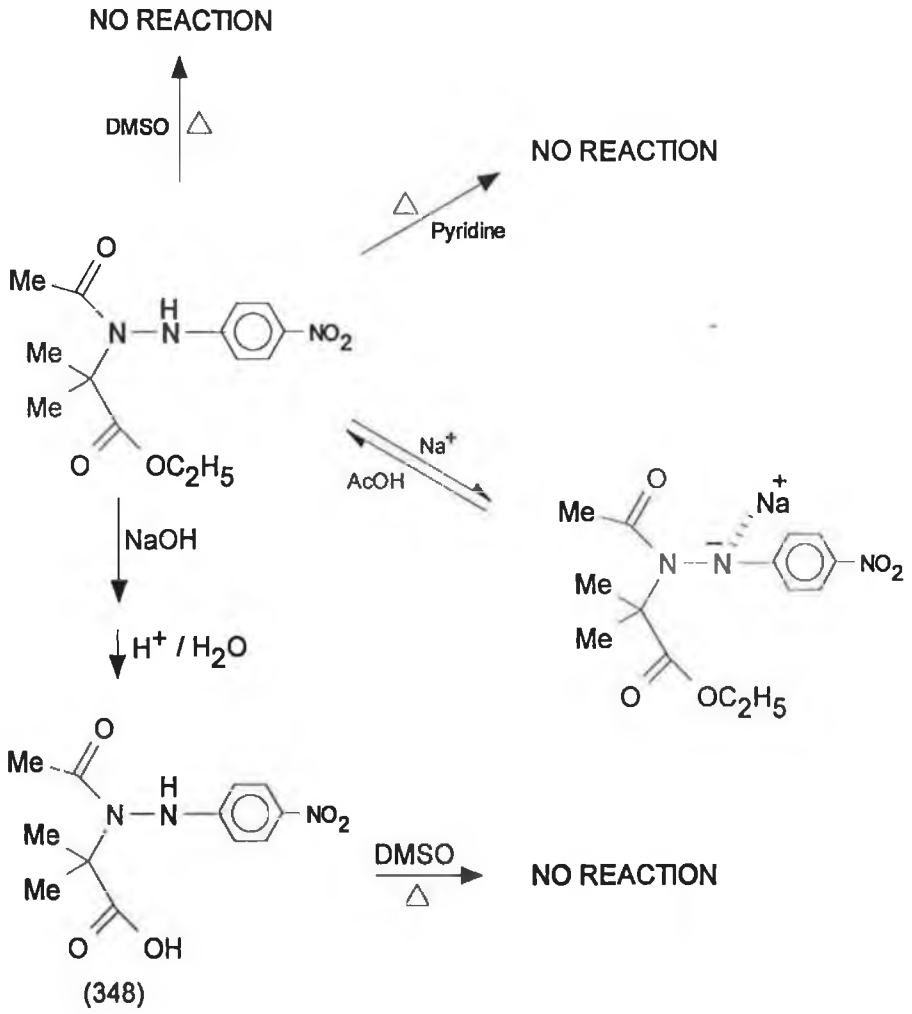
The spectrum was converted back to the sharp peaks characteristic of N-H, by the addition of a few drops of acid, thus indicating that the sodium salt had indeed been isolated. The spectum of acetic acid is superimposed on this region which leads to the distortion seen [Figure 3.1b].

When the monosodium salt (347) was heated gently with water or acetic acid the hydrazide (145) was recovered. Likewise (347) reverted to (145) when allowed to stand at room temperature for 2-3 days.

Possible ring closure of (145) by heating in pyridine was investigated but no reaction was observed. It was decided to replace the ethoxy group with an hydroxy group which may prove to be a better leaving group hence enhancing ring closure.

Saponification of (145) was effected by heating under reflux in a 3M NaOH solution followed by acidification with HCl. The resulting yellow precipitate was extracted into ethyl acetate from which the carboxylic acid (348) was obtained in 90% yield (Scheme 3.32).

SCHEME 3.32



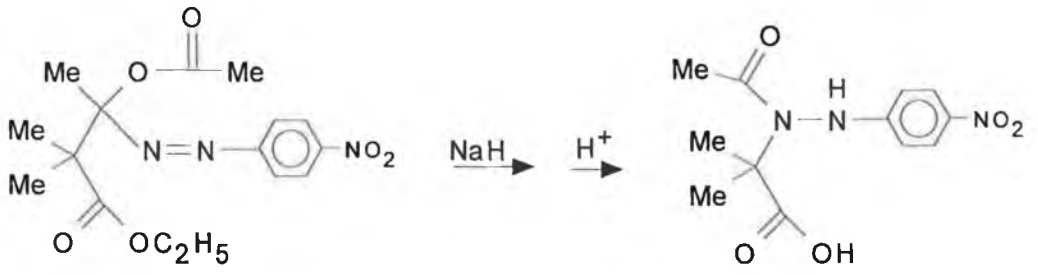
(348)

Following the report[139] of ring closure of 3-aminopropanoic acid in DMSO at 150°C, the acid (348) was heated in DMSO in the hope of effecting cyclisation. However, after 3 hrs at high temperatures, no reaction was evident. The hydrazide (145) also failed to cyclise when heated for a several hours in DMSO.

The carboxylic acid (348) has been arrived at in a two-step process from the azoacetate (85) of α,α-dimethylethyl acetoacetate *p*-nitrophenylhydrazone .

It was investigated to see if it would be more expeditious to form (348) from (85) in one step. Thus the azoacetate (85) was heated under gentle reflux in a 3M solution of NaOH overnight. The resulting clear red solution was acidified and extracted into ethyl acetate from which a very small quantity of (348) was eventually isolated (Scheme 3.33).

Scheme 3.33

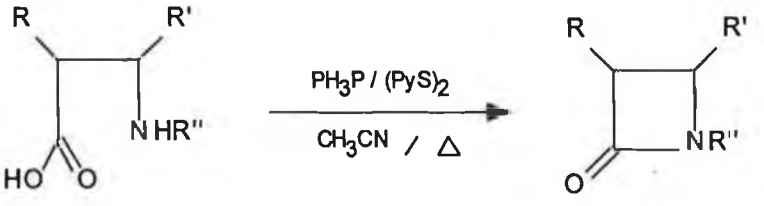


(85) (348)

Therefore, while saponification of the azoacetate (85) forms the hydrazide (348), with the sodium salt of the hydrazide as a possible intermediate, it is not an efficient route over the favoured two-step approach.

According to Kobayashi *et al.*[177] the β-amino acid ester (349) may be dehydrated to (350) by heating in acetonitrile in the presence of triphenylphosphine (Ph_3P) and dipyridyldisulphide $(PyS)_2$, with the choice of acetonitrile[178] as solvent, having a noticable effect in providing yields of 84%.

Scheme 3.34

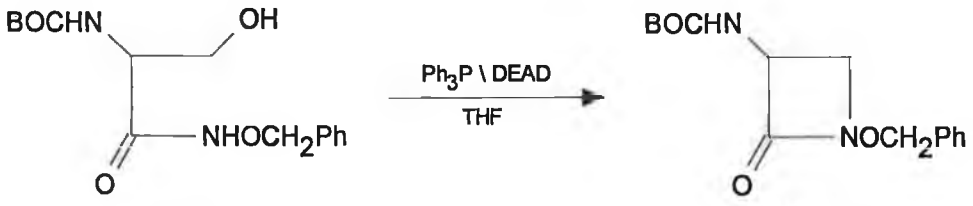


(349) (350)

In an analogous manner, a sample of the acid (348) was dissolved in acetonitrile to which triphenylphosphine and dipyridyldisulphide were added. The reaction was heated under reflux. After 6 hrs, t.l.c monitoring indicated a lot of starting material. However, a second major product was evident. The reaction mixture was chromatographed which allowed for removal of unreacted (348), as anticipated. The ^1H NMR spectrum of the second product isolated, suggested the presence of both dipyridyl disulphide and its reduced form.

A similar type of ring closure had been accomplished by Mattingly and Miller[179] applied to another β-lactam precursor (351), using triphenylphosphine and diethylazodicarboxylate (DEAD)[180], in THF as shown.

Scheme 3.35

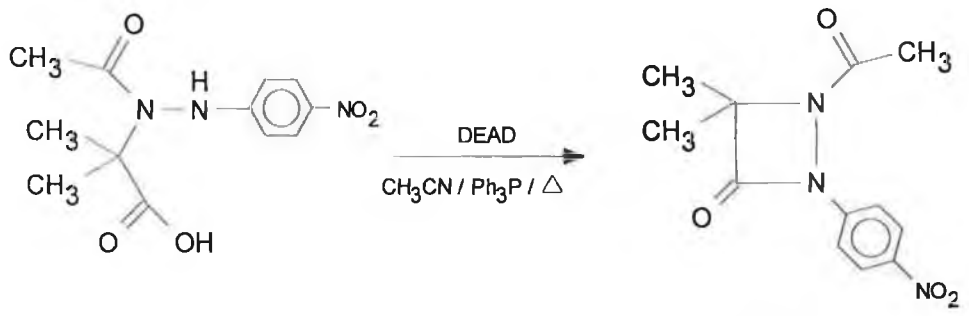


(351) (352)

Likewise Miller[176], describes a mild facile N-C4 bond closure of a hydroxamic acid of type (351) to the related substituted N-hydroxy-2-azetidinone (352) upon treatment with Ph_3P/DEAD.

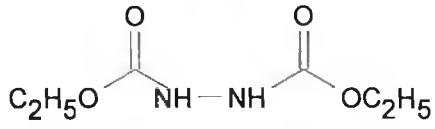
In an attempt to parallel these ring closures, compound (348a) was dissolved in acetonitrile to which 1.3 equivs of DEAD and 1.3 equivs of Ph_3P were added (Scheme 3.36). The reaction was heated under gentle reflux overnight when t.l.c monitoring indicated the disappearance of (348). Following chromatography or the reaction mixture, the 4-membered aza-β-lactam N-acetyl N'-p-nitrophenyl-4,4-dimethyl diazetidin-3-one (353) was successfully isolated as yellow needles contaminated with 1,2-dicarbethoxyhydrazine (354), the side product resulting from reduction of DEAD.

Scheme 3.36



(348) (353)

+



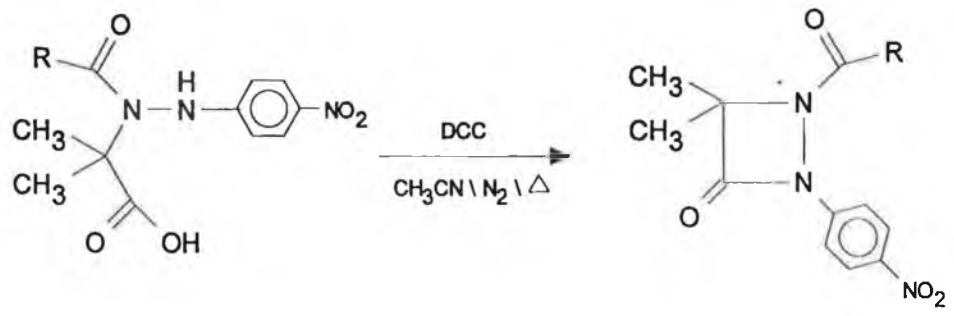
(354)

Repeated recrystallisation of (353), followed by further chromatography yielded the product, 80% pure, by ^1H NMR analysis. Purification by chromatography proved very difficult as the required product (353) and the contaminant (354) had the same R_f values in varying eluent systems. Attempts to oxidise the hydrazine (354) back to DEAD, which had a different R_f value, thus simplifing purification, were considered. An aqueous solution of $KMnO_4$ (excess) was added to a sample of the impure aza-β-lactam (353) dissolved in ether/dichloromethane. The MnO_2 precipitate was filtered and, following extraction, the organic layer was chromatographed yielding the aza-β-lactam with a trace of 1,2-dicarbethoxyhydrazine (354). Therefore, the hydrazide (145) was sucessfully cyclised *via* the acid derivative (348), and the resulting novel aza-β-lactam (353) characterised. In order to extend this new route to other hydrazide candidates, the choice of oxidising agent had to be reconsidered, so that product isolation would be less arduous.

Taylor *et al.*[161] have formed aza-β-lactams via haloacylhydrazines. The dehydrative condensation step was effected by dicyclohexylcarbodiimide (DCC). Thus the carboxylic acid (348) was placed in dry CH_3CN, to which a six-fold equivalent of DCC was added. The reaction was heated gently under reflux overnight under a nitrogen atmosphere. These were found to be the optimum conditions. The copious quantities of white precipitate filtered from

the reaction proved to be dicyclohexylcarbourea (DCU). Chromatography of the remaining orange oil yielded the aza-β-lactam, N-acetyl-N'-(*p*-nitrophenyl)-4,4-dimethyl-diazetidin-3-one (353), in a 40% yield (Scheme 3.37) [See Figure 3.2].

Scheme 3.37



(348 a; b)

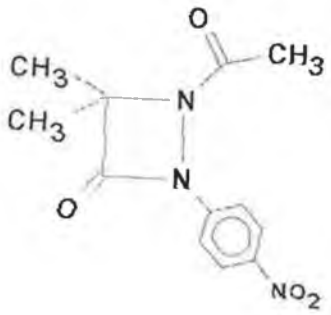
(353 a; b)

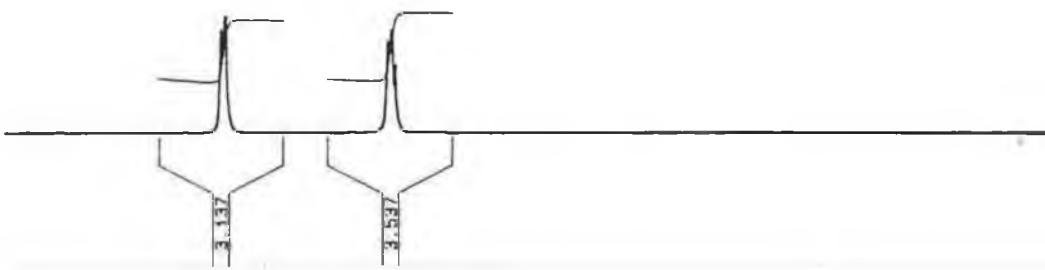
a:Me

b:Et

Following the successful isolation of this aza-β-lactam, the hydrazide (152) resulting from methyl propionyl acetate (146) was considered as a candidate which may be cyclised. Thus (152) initially underwent base hydrolysis to form the corresponding carboxylic acid (348b). This acid (348b) was successfully cyclised using the conditions as for (348a) to provide another aza-β-lactam (353b) by this route (Scheme 3.37).
[See Figures 3.2, 3.3, 3.4].

Figure 3.2





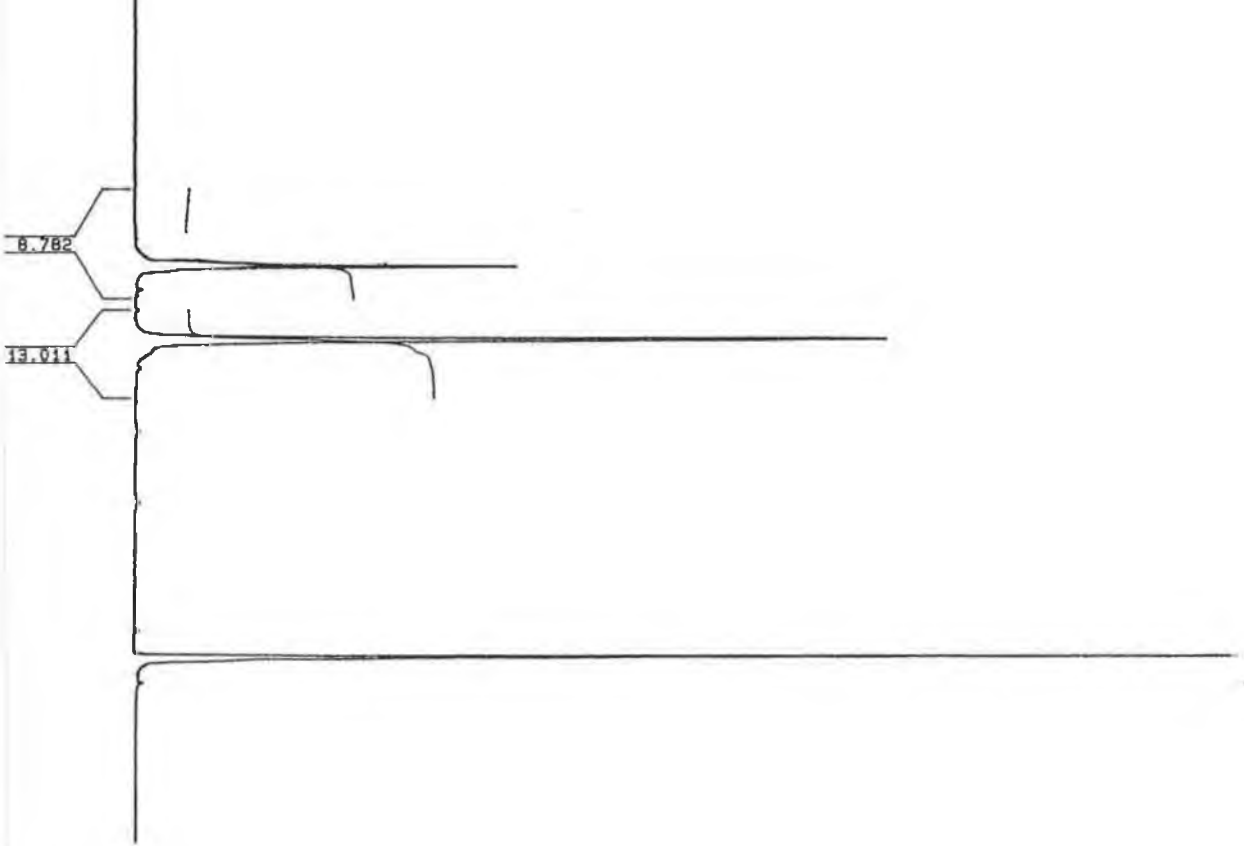
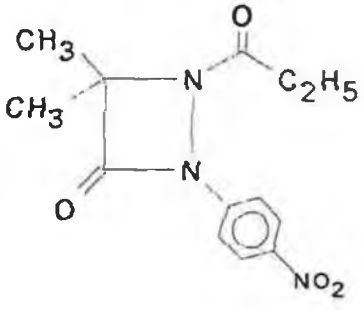
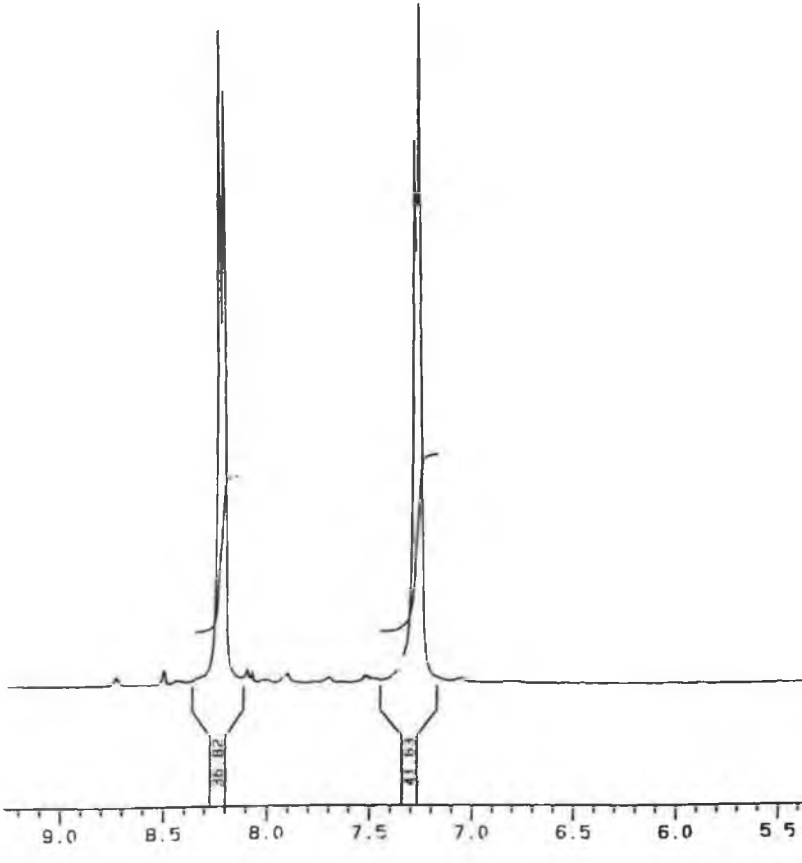

8.782
13.011

Figure 3.3





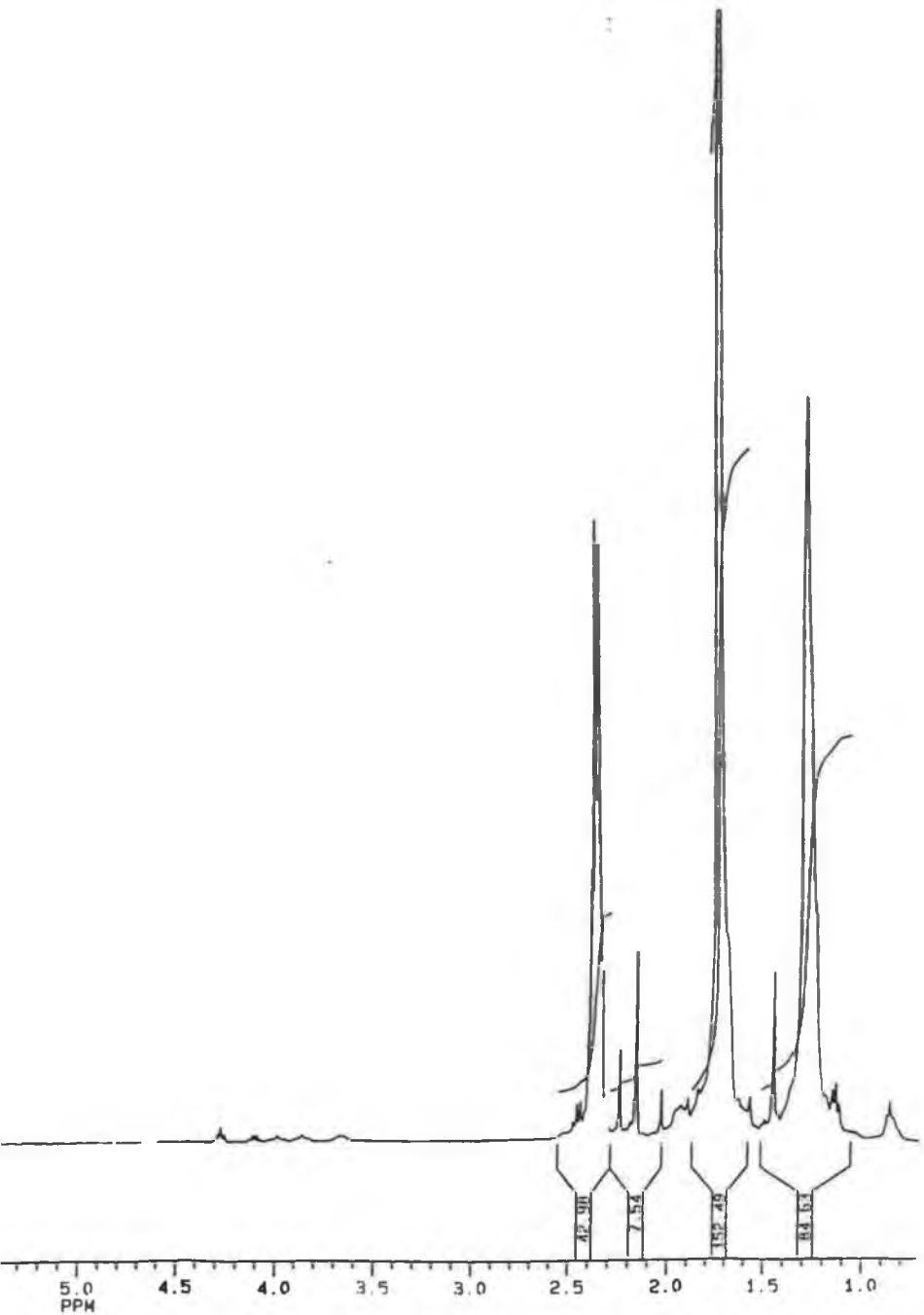
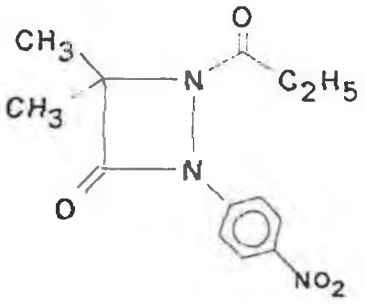
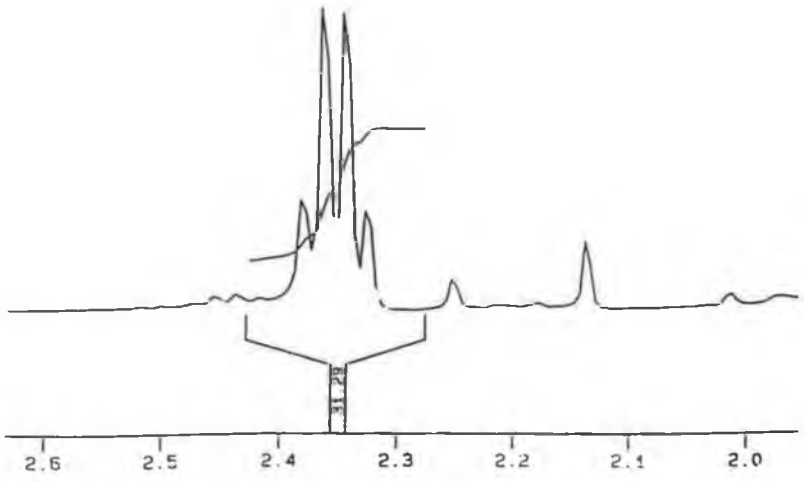
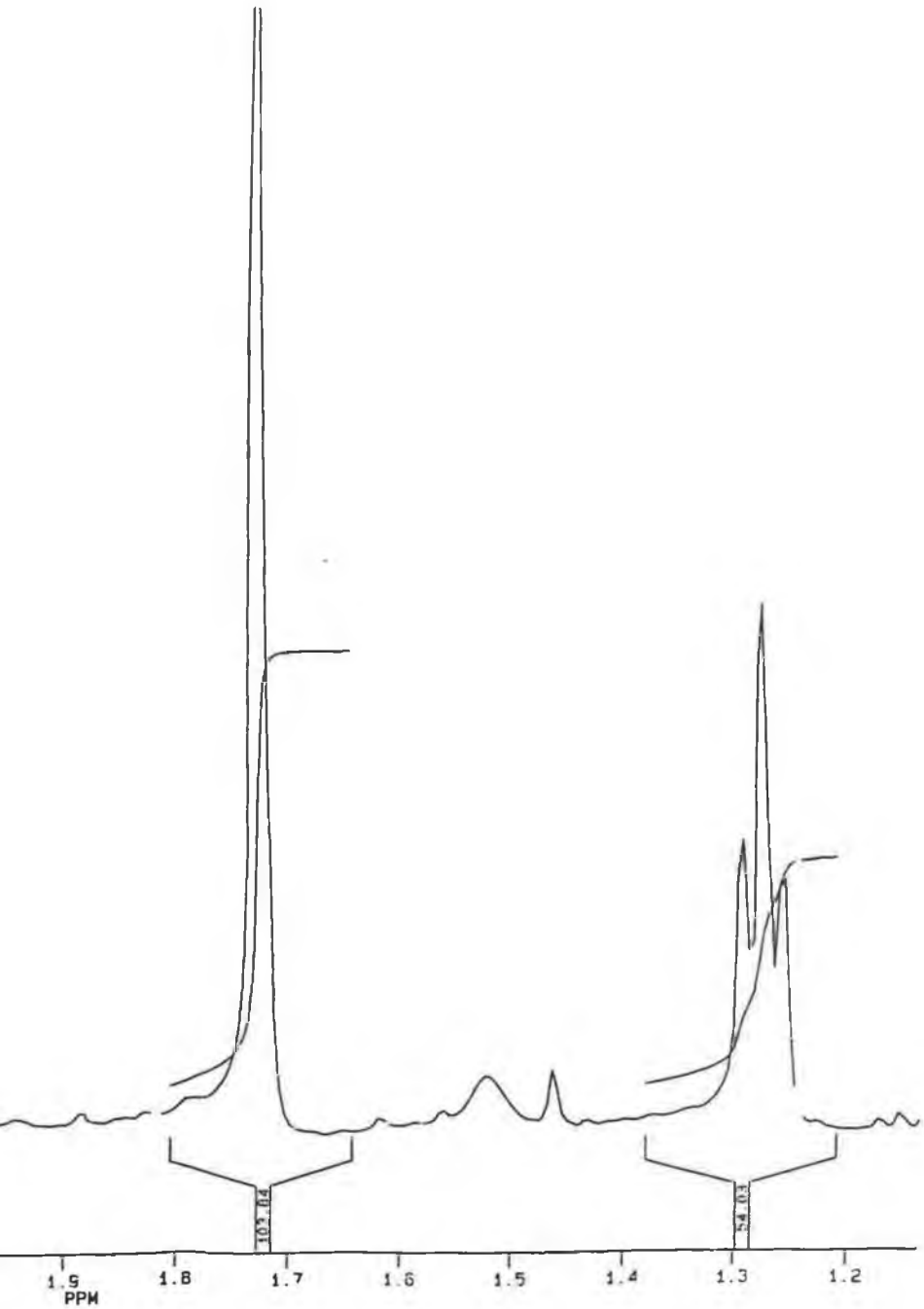

42.98
7.54
152.49
84.63
5.0
PPM
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

Figure 3.4



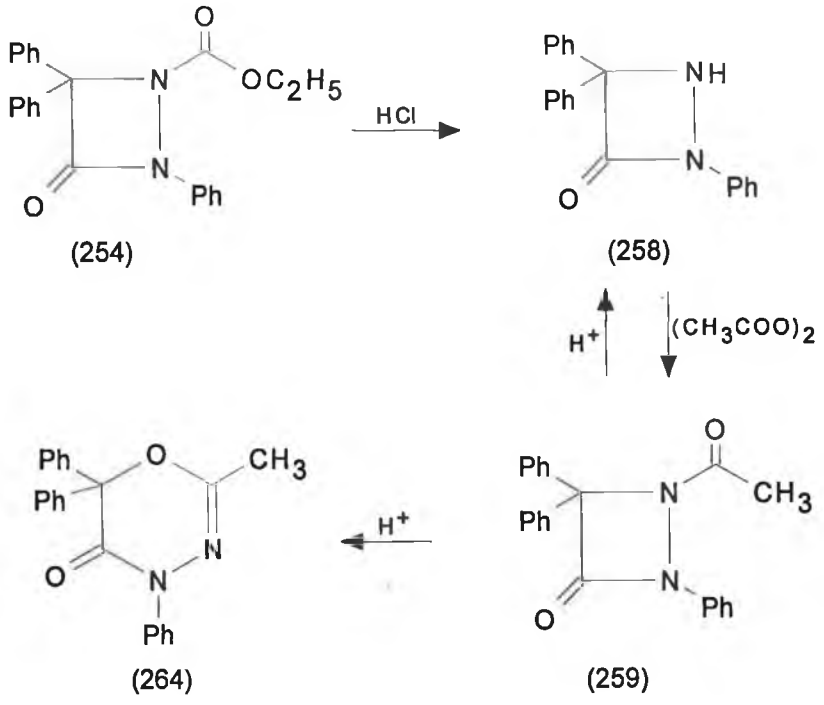



103.04
54.03
1.9
PPM
1.8
1.7
1.6
1.5
1.4
1.3
1.2

In summary, a new, six step route has been developed to convert a simple β-ketoester into a unique aza-β-lactam (353) . It was decided to investigate the possibility of obtaining an aza-β-lactam which would be more amenable to derivitisation.

Bird[181] found acid treatment of the aza-β-lactam (254) cleaved the ester group to give (258) which was acetylated with acetic anhydride to form (259). Acid treatment of (259) reverted to (258) and some of (264).

Scheme 3.4b

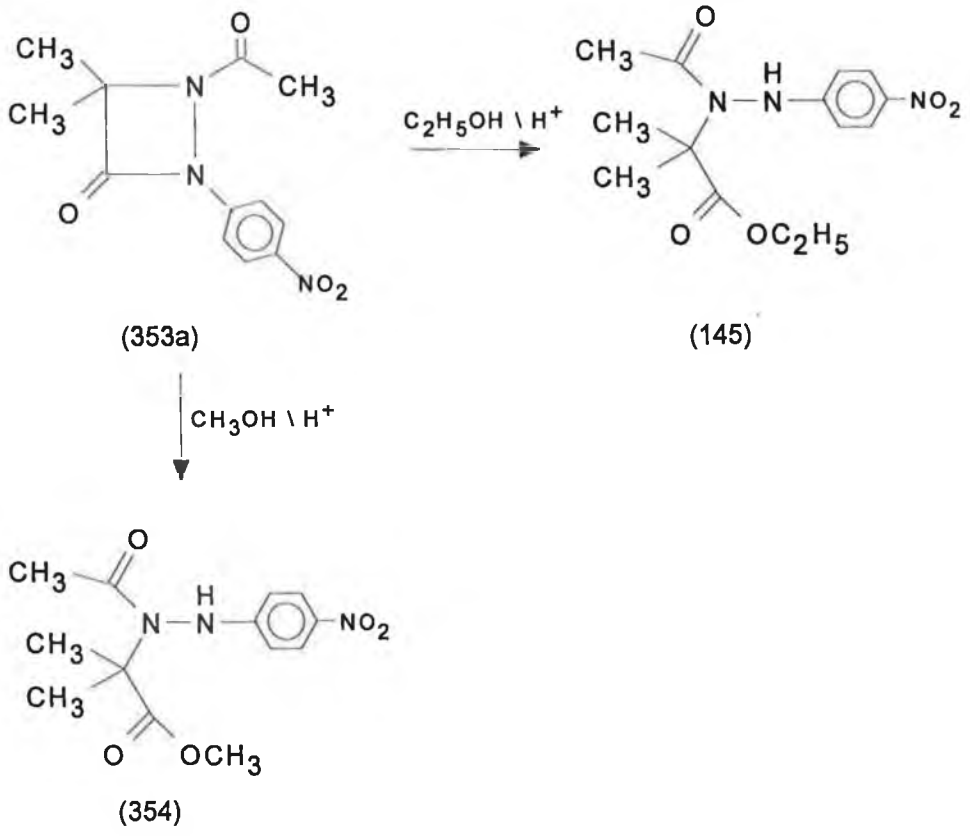


(254) (258) (264) (259)

It was investigated to see if the acetyl group at the N1 position of N,1-acetyl, N,2-(*p*-nitrophenyl)-4,4-dimethyl-diazetidin-3-one (353a) isolated, could be cleaved. Thus (353a) was heated in acidified ethanol and monitored by t.l.c, which indicated no immediate reaction. The reaction was allowed to proceed overnight when a large quantity of starting material was still present. Traces of hydrazide (145) were identified. This was due to the ethanol which had suceeded in cleaving small amounts of the aza-β-lactam, at the N2-C3 bond (Scheme 3.38).

A sample of the aza-β-lactam (353a) was stirred in a methanol solution containing sodium hydride. The sodium methoxide proved capable of cleaving the ring at the N2-C3 bond in a methanolysis type reaction forming (354), which was isolated as yellow needles in 70% yield (Scheme 3.38).

Scheme 3.38



(353a) (145)

(354)

In conclusion, the β-ketoester, α,α-dimethylethyl acetoacetate has been converted to the hydrazone. This hydrazone was oxidised to the azoacetate. The oxidation step is dictated by the choice of solvent and oxidising agent (Chapter I).

The azoacetate undergoes a carbon to nitrogen migration in the presence of potassium cyanide in ethanol to provide the corresponding hydrazide (Chapter II).

Following the use of a variety of dehydrating and condensing agents, two such hydrazides have been sucessfully cyclised to the corresponding aza-β-lactam ring (Chapter III). These compounds or similar derivatives may prove to have antibacterial properties, as further studies in this area are conducted.

CHAPTER THREE

EXPERIMENTAL

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EXPERIMENTAL

(i) Preparation of carboxylic acid (348a).

The tertiary amide (145) (0.5g;1.6mmoles) was added to a 2.5 molar solution of sodium hydroxide (3.9g dissolved in 40mls H_2O). The solution underwent gentle reflux for 4 hours until a clear red solution was obtained. The pH was then adjusted to 7-8 with conc. HCl. A yellow precipitate which formed was extracted into ethyl acetate, dried over $MgSO_4$, filtered and evaporated to dryness yielding the product as a yellow powder (0.45g; 90%).

MP 215-216°C.

IR 3347, 1710, 1619,1599 cm^{-1}.

'H NMR (400 MHz;DMSO-d_6) δ 1.2 (s, 3H), 1.3 (s,3H), 1.9 (s, 9H), 6.9 (d,1H), 7.1 (d,1H), 8.2 (d, 2H), 9.5 (s,1H).

$C_{12}H_{15}N_3O_5$ requires C 51.24, H 5.4, N 14.94%,

found C 51.12, H 5.5, N 14.71%.

(ii) Preparation of carboxylic acid (348b)

The preparation was repeated as in **(i)**. The tertiary amide (152) was used as starting material. The carboxylic acid (348b) was isolated in 85% yield.

IR 3450, 3450, 1750, 1700, 1630 cm^{-1}.

'H NMR (400 MHz; DMSO-d_6) δ 1.0 (t, 3H), 1.43 (s, 3H), 1.44 (s, 3H), 2.1 (m, 1H), 2.5 (m, 1H), 7.1 (d, 2H), 8.3 (d, 2H), 9.6 (s, 1H).

(iii) Preparation of monosodium salt (347)

0.5g (1.6mmoles) of the tertiary amide (145) was dissolved in THF (10mls). 0.04g of NaH (pet-ether washed) (1.1equiv; 1.7 mmoles) were added slowly and stirred at room temperature for 1 hour when the product was collected as a red precipitate (0.32g; 60%).

MP 236-238°C.

IR 3430 (broad) 1720, 1610, 1600 cm^{-1}.

'H NMR (60 MHz; DMSO-d_6) δ 1.2 (t, 3H), 1.3 (s, 3H), 1.7 (s, 3H), 4.1 (q, 2H), 6.5 (broad singlet), 7.6 (d, 2H).

(iv) Preparation of aza-β-lactam (353a-crude)

The carboxylic acid (348) (0.5g; 1.8 mmoles) was suspended in CH_3CN (30mls) to which 1.3 equiv (0.40g; 23 mmoles) of diethylazodicarboxylate (DEAD) and 1.3 equiv (0.60g; 2.2 mmoles) Ph_3P were added. The reaction was allowed to reflux overnight. The solution was evaporated to dryness under vacuum and chromatographed with dichlomethane:diethyl ether (50:50) eluent system. The hydrazine (354) was collected as white needles and the aza-β-lactam was the second product isolated as pale yellow needles (80% purity).

The aza-β-lactam was dissolved in CH_2Cl_2 to which 3 equiv of aqueous $KMnO_4$ was added. The solution was stirred for 4 hours, the MnO_2 brown precipitate removed by filtration and the organic layer extracted into ethyl acetate. The resulting orange oil was columned, (EA:PE;40:60), yielding the aza-β-lactam (353a).

IR 1790, 1694, 1623 cm^{-1}

'H NMR (60 MHz; $CDCl_3$) δ 1.3 (s, trace) 1.8 (s, 6H), 2.2 (s, 3H), 4.2 (q, trace), 7.3 (d, 2H), 8.2 (d, 2H).

(v) Preparation of 1-acetyl, 2-(*p*-nitrophenyl)-4,4-dimethyldiazetidin-3one (353a).

A 0.05M solution of (145) was made up in acetonitrile (0.85g/60mls). 6 equiv (3.7g; 18 mmoles) of dicyclohexylcarbodimide (DCC) was added by heating the wax-like substance. The reaction was heated under gentle reflux overnight under a nitrogen atmosphere. Evaporation of the solvent rendered an orange oil with yellow needles. Chromatography [PE:CH_2Cl_2; 80:20] yielded dicyclohexylcarbourea (DCU) as the first product and the required aza-β-lactam as the 2nd main product. It was purified by recrystallisation from ethyl acetate:pet-ether (20:80) yielding the product as pale yellow needles in 45% yield.

MP112-114°C.

IR 1796, 1696, 1627, cm^{-1}.

'H (400 MHz;$CDCl_3$) δ 1.7 (s, 6H) 2.2 (s, 3H), 7.3 (d, 2H), 8.2 (d, 2H).

$C_{12}H_{13}N_3O_4$ requires C 54.75, H, 4.94, N 15.96%,

found C 54.38, H 4.93, N 15.84%.

Preparation of 1.2-(*p*-nitrophenyl)-4.4-dimethyl diazetidin-3-one (353b)

The procedure was similar to that described in **(v)**, using the carboxylic acid (348b) which provided the product in 40% yield.

IR 1790, 1690, 1610 cm^{-1}.

'H (400 MHz;$CDCl_3$) δ 1.3 (t, 3H), 1.7 (s, 6H), 2.4 (q, 2H), 7.3 (d, 2H), 8.2 (d, 2H).

Preparation of hydrazide (355).

0.5g (1.9mmoles) of the aza-β-lactam (353a) was dissolved in methanol (10mls) to which 0.05g (2.1mmoles;1.1equiv) of NaH was added. Following 15 minutes stirring at room temperature the reaction was evaporated under reduced pressure to remove the methanol. The resulting red oil was dissolved in ethyl acetate when addition of pet-ether caused the product to precipitate overnight, as yellow needles, in 70% yield.

IR 3303, 1740, 1650 cm^{-1}.

'H NMR (400 MHz;$CDCl_3$) δ 1 .4 (s, 3H), 1.5 (s, 3H), 2.0 (s, 3H), 3.9 (s, 3H), 7.0 (d, 3H), 8.2 (d, 2H).

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Appendix

Azoacetates as Synthons for the Azetidinone and Diazetidinone Ring Systems

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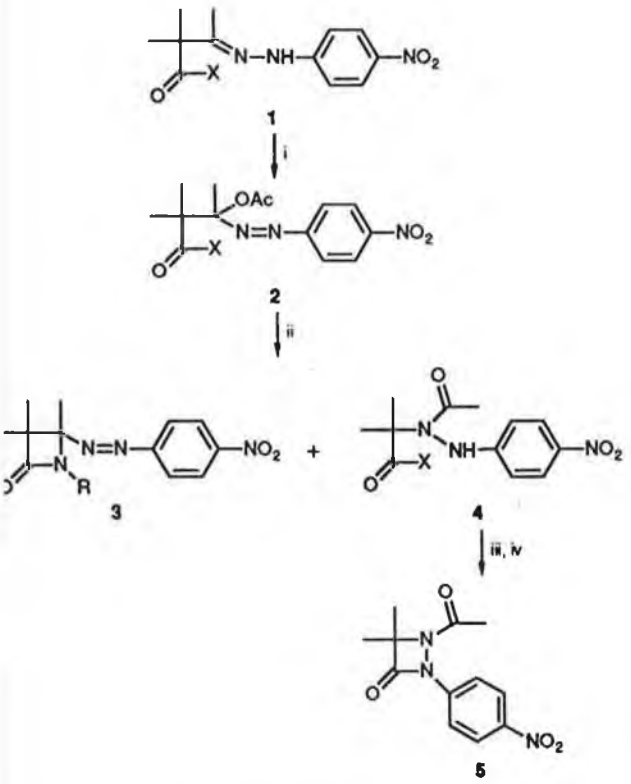
The azoacetates derived from aryl hydrazones of α,α-disubstituted-β-ketoamides are readily transformed into azetidinones or diazetidinones.

Aryl hydrazones ($R^1R^2C{=}N{-}NH{-}Ar$) of ketones are in general readily transformed to azoacetates [$R^1R^2C(OAc){-}N{=}N{-}Ar$] on treatment with lead tetraacetate (LTA), iodobenzene diacetate or thallium triacetate in solvents such as acetic acid and methylene chloride.[1,2] Azoacetates **2** are easily obtained by oxidation of aryl hydrazones **1** derived from β-keto compounds. Acyclic azoacetates have received relatively little attention as substrates for cyclisation to heterocycles with the exception of their transformation to five-membered heterocycles *e.g.* imidazoles and pyrazoles.[3]



a; X = NH-phenyl
b; X = NH-*p*-chlorophenyl
c; X = OEt
d; X = NH_2
e; R = phenyl
f; R = *p*-chlorophenyl
g; R = acetyl
h; X = OH

cheme 1 *Reagents*: i, lead tetraacetate, methylene chloride; ii, base, :etone or alcohol; iii, NaOH, H_2O; iv, DCC, MeCN

We now report an important contribution to the chemistry f azoacetates **2** which results in their cyclisation to four- ıembered rings **3** or **5** (see Table 1). Azoacetates **2a–d** are ɔrmed in high yield from the corresponding hydrazones **1a–d** nd LTA in methylene chloride (>80%). Azoacetates of :,α-dimethylated-β-ketoamides **2a,b** cyclise to the azetidin-2-one ring **3e,f**, a β-lactam with unusual substitution. Acetylation of the primary amide **2d** allows cyclisation after base treatment to the lactam **3g**. When the reaction of **2a,b** with base is carried out in alcohol the β-lactam is accompanied by an unusual rearrangement product **4a,b**. The azoacetate **2c** derived from β-ketoester hydrazone **1c** gives an improved yield of the rearrangement product **4c**. The rearrangement is thought to follow deacetylation of the azoacetate. On hydrolysis, **4a–c** give the carboxylic acid **4h** which is readily cyclised to the 1,2-diazetidin-3-one **5**, and represents a new route to this ring system (see Scheme 1).[4] In previous reports on base treatment of azoacetates the products are five-membered rings together with parent ketone and hydrazone.[5]

The generality of the reactions described and their extension to more appropriately substituted structural types is under investigation.

Table 1

	Reagent	Product [yield (%)]
2a	K_2CO_3, acetone	**3e** (28)
2b	K_2CO_3, acetone	**3f** (50)
2a	KCN, propanol	**3e** (44), **4a** (13)
2b	KCN, propanol	**3f** (34), **4b** (44)
2b	KCN, ethanol	**3f** (48), **4b** (25)
2c	KCN, ethanol	**4c** (30)
4a	H^+, H_2O	**4h** (55)
4c	NaOH, H_2O	**4h** (80)
4h	DCC, MeCN[a]	**5** (45)

[a] DCC = 1,3-dicyclohexylcarbodiimide.

Received, 12th December 1991; Com. 1/06238G

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