METALLIC ACETATE OXIDATIONS OF SUBSTITUTED HYDRAZONES OF ACETOACETANILIDES AND THEIR CONVERSION TO β-LACTAMS

by

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November 1993

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 work.

Signed: Carol Downey Date: November 1993

CAROL DOWNEY

Per Ardua Ad Astra

To Janet

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Abstract

In recent years, the ability to prepare 4-substituted β-lactams (2-azetidinones) has become a major synthetic objective. Monocyclic β-lactams bearing a heteroatom at C4 are of particular interest, especially as potential precursors of novel bicyclic β-lactams. The introduction of 4-alkyl groups into monobactams results in an increase in activity against Gram-negative bacteria and enhanced β-lactamase stability.

Among a variety of methods for construction of the β-lactam ring, formation of the N-C4 bond is known to be a biomimetic process. Chemical syntheses of the 2-azetidinone ring by N-C4 lactamisation mostly involve nucleophilic attack by N at C4, with displacement of a good leaving group, or intramolecular dehydration of β-hydroxy amide derivatives by application of the Mitsunobu reaction. Base-induced N-C4 cyclisation of azoacetates derived from p-nitrophenylhydrazones of acetoacetanilides was envisaged as a potential route to novel 4-azo-4-methyl-β-lactams.

Lead (IV) acetate oxidation of acetoacetanilide p-nitrophenylhydrazones gave, in most cases, the expected azoacetates. With α-unsubstituted substrates, the usual intramolecular acetoxylation was not observed using acetic acid as solvent, and Z-azoalkenes were formed exclusively. α-Methyl derivatives afforded diastereomeric azoacetates in a stereoselective manner consistent with a Cram-type mechanism, as determined by X-ray crystallographic analysis.

Mercury (II) acetate oxidation of α-unsubstituted acetoacetanilide p-nitrophenylhydrazones furnished the corresponding azoalkenes as mixtures of E- and Z-isomers. The configuration of each olefin was established through ^{1}H NMR studies.

Metallic acetate oxidation of toluene-p-sulfonylhydrazones derived from acetoacetanilides was perceived as a possible new synthesis of 4-methyl-2-azetidinones involving N-C4 cyclisation of a carbenic intermediate. Mercury (II) acetate oxidation of α-unsubstituted substrates resulted in the unexpected formation of acetylenic amides.

A system of model compounds was examined in order to gain insight into the reactivity of the acetoacetanilide-derived azoacetates and the conditions which might be employed to induce N-C4 dehydroacetoxylation. ^{1}H NMR was used to determine the stereochemistry of model 3,4-dimethyl-2-azetidinones, where the trans-β-lactam was formed in preference to the cis-isomer.

A variety of bases were identified which enable the conversion of acetoacetanilide-derived azoacetates to novel 4-azo-4-methyl-2-azetidinones. The transformation is believed to involve an unstable intermediate azoalcohol in some cases. The monocyclic β-lactams prepared are important since they possess both an alkyl group and a heteroatom substituent in the 4-position.

Acknowledgements

Firstly, I must thank my supervisor, Dr. Paraic James, for his help and guidance during my postgraduate years. I would like to thank the academic and technical staff, and all the postgraduate students in the School of Chemical Sciences. Thanks also to Dr. Conor Long and colleagues for determination of the X-ray crystal structure and to Donncha Ó Cróinín for his advice about computers.

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Thanks to Debbie for many enjoyable Sunday nights, to Orlaigh and Rose for their encouragement, and to Michael for lending me his computer.

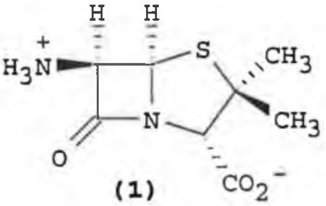
List of Abbreviations

Ac:	$COCH_3$
tBOC:	$OCOC(CH_3)_3$
b.p.:	boiling point
iBu:	$CH_2CH(CH_3)_2$
nBu:	$(CH_2)_3CH_3$
tBu:	$C(CH_3)_3$
Bz:	$CH_2C_6H_5$
Cbz:	$OCOCH_2C_6H_5$
DMF:	dimethylformamide
DMSO:	dimethylsulfoxide
e.s.r.:	electron spin resonance
Et:	C_2H_5
hal:	halogen
hrs.:	hours
IR:	infra-red
Me:	CH_3
MP:	melting point
NMR:	nuclear magnetic resonance
NOE:	nuclear Overhauser effect
Ph:	C_6H_5
Phth:	phthalimido
ppm:	parts per million
iPr:	$CH(CH_3)_2$
r.t.:	room temperature
TBDMS:	t-butyldimethylsilyl
TEA:	triethylamine
THF:	tetrahydrofuran
TLC:	thin layer chromatography
TMS:	trimethylsilyl
UV:	ultra-violet
Δ:	heat
δ:	chemical shift

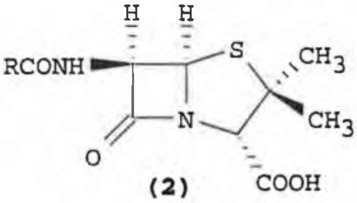
Chapter 1

1.1 The Development of β-Lactam Antibiotics[1-4]

The era of β-lactam antibiotics, the most important class of drugs against infectious bacterial diseases, began in 1929, with the discovery, by Alexander Fleming, that a metabolite of the fungus Penicillium notatum possessed antibiotic activity against the pathogen Staphylococcus aureus. The isolation and testing of this penicillin in animals was not achieved until 1940, and the first human trials took place in 1941. Structural elucidation was not completed until the mid-1940s, showing the active compounds to be acyl derivatives of 6-aminopenicillanic acid (6-APA) (1), which was itself synthesised in 1950 by enzymatic hydrolysis of benzylpenicillin (2: R = $PhCH_2$).



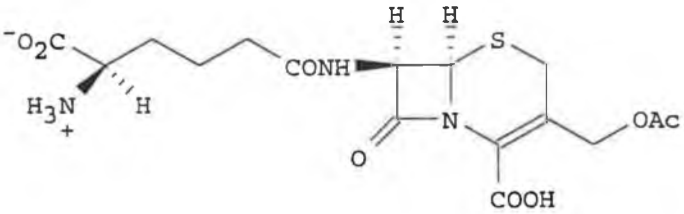
(1)



(2)

Subsequently, a hectic search began for semi-synthetic benzylpenicillin analogues, prepared by acylation of 6-APA with various acylating agents. The result was numerous semi-synthetic penicillins (2), some superior to benzylpenicillin. The first broad-spectrum penicillin, ampicillin (2: R = C_6H_5-$CH(NH_2)$-), which is active against a whole range of bacterial strains unaffected by benzylpenicillin, was introduced in 1961.

In 1948, certain strains of the fungus Cephalosporium filamentous were also found to produce metabolites with antibiotic properties. One of these, cephalosporin C (3), was isolated, and by the end of the 1950s, the parent compound, 7-aminocephalosporanic acid (7-ACA) (4), was synthesised. Derivatisation again yielded a range of therapeutically-important semi-synthetic cephalosporins.



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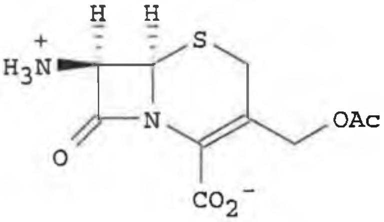
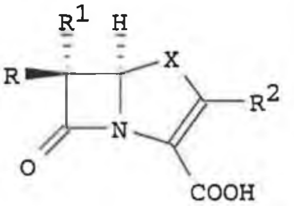


(4)

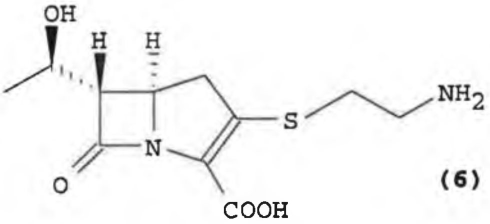
Soon, strains of pathogens resistant to existing penicillins and cephalosporins began to emerge at an alarming rate. This problem was approached not only by the semi-synthesis of new penicillins and cephalosporins, but also by the development of non-classical structures.

In 1975, a new β-lactam skeleton, hitherto not found in nature, was announced. This type of compound, a penem (5: X = S), can be regarded as a hybrid between penicillins and cephalosporins.



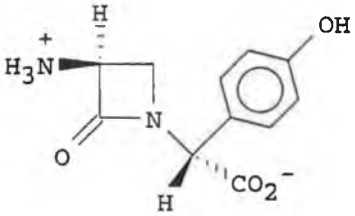
(5)

Suitable substitution produced chemically-stable, antibiotically-active derivatives. The analogous carbapenems (5: X = CH_2), in particular thienamycin (6), proved to be highly active, broad-spectrum antibiotics.



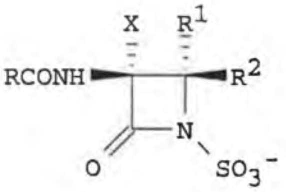
(6)

Monocyclic β-lactam antibiotics were first described in the mid-1970s. Their main clinical use to date has been in the treatment of patients who are allergic to the bicyclic penicillins and cephalosporins. The nocardicins, derivatives of 3-aminonocardicinic acid (3-ANA) (7), were the first examples of this class of β-lactams to exhibit high antibacterial activity.



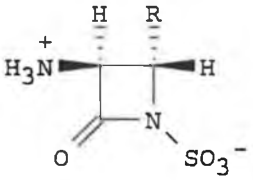
(7)

In 1981, the most important group of monocyclic β-lactam antibiotics, the monobactams (8) (monocyclic bacterially-produced β-lactams), were isolated. Here, the usual ionisable carboxylate group is replaced by the sulfonate moiety.



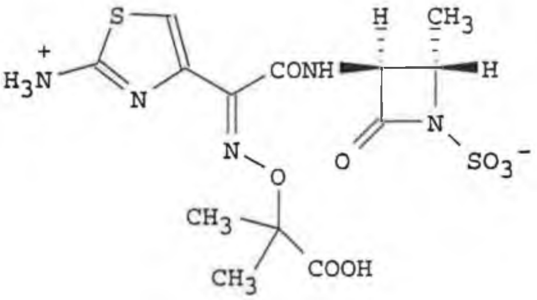
(8)

Natural monobactams occur mainly as the 3-methoxy derivatives (8: X = OCH_3), which are only weakly active as antibacterial agents. In order to improve activity, variation of the skeleton and 3-acylamido side-chain was necessary. For this purpose, the parent compound, 3-aminomonobactamic acid (3-AMA) (9: R = H), had to be synthesised.



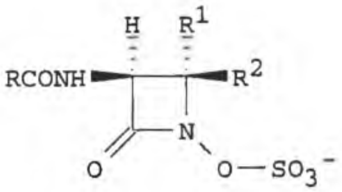
(9)

A stereospecific total synthesis of monobactams, including the 4-methylated derivative (9: R = CH_3), was published by Squibb[5]. Structural variation of the 3-amino group led to the discovery of aztreonam (10)[6], which is highly active against Gram-negative bacteria.



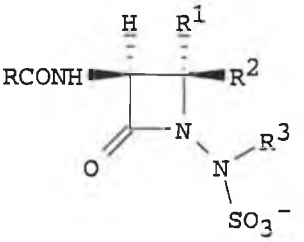
(10)

Because the antibacterial properties of monobactams rivalled those of traditional penicillins and cephalosporins, during the past decade there has been a high level of interest in replacing the N-1 sulfonate with new N-1 substituents that impart activity on the β-lactam nucleus. In monobactams, the ionisable group is positioned one atom closer to the β-lactam ring than in penicillins, cephalosporins and nocardicins. Obvious synthetic targets were, therefore, analogues of monobactams incorporating one spacer atom between the ring and the anionic centre. The monosulfactams (11) were synthesised[7,8] and shown to have significant antibiotic properties.



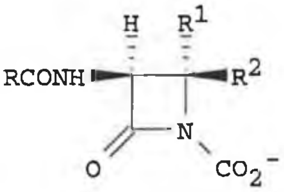
(11)

The corresponding nitrogen-linked species (12) did not exhibit any interesting biological activity[9].



(12)

Logical structural analogues of the monobactams and monosulfactams are the corresponding carboxylates (13) and (14).



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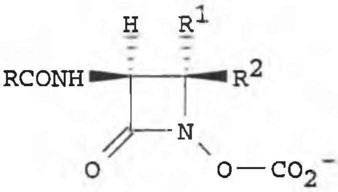
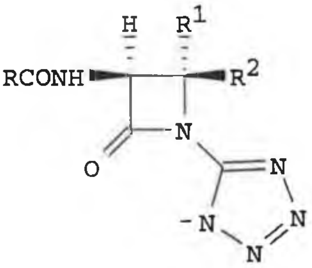


(14)

However, these species are unstable and prone to decarboxylation[10]. The tetrazole moiety possesses comparable electron-withdrawing power and acidity to a carboxylic acid. Chemists at Merck, Sharp and Dohme[11] have reported synthesis of N-(tetrazol-5-yl)-β-lactams (15), which are strongly active against a variety of bacteria[12,13].



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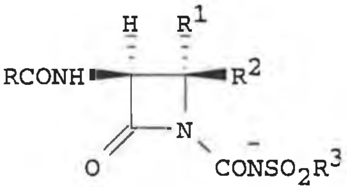
Research by the Squibb group produced the monocarbams (16) and monophosphams (17)[14].



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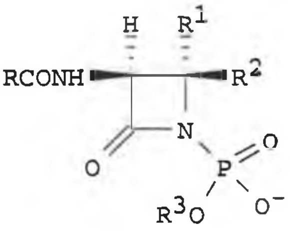
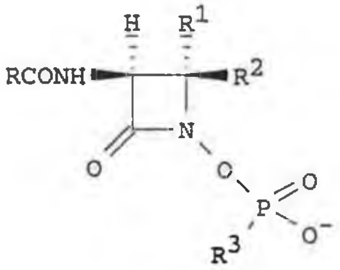


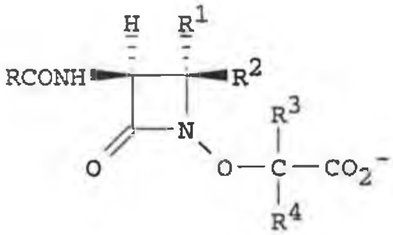
(17)

Both these and the related monophosphatams (18) have good antibacterial properties[15].



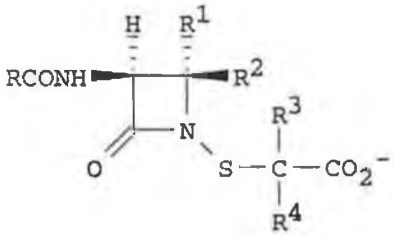
(18)

Investigation of the effect of moving the ionisable group one atom further away from the β-lactam nitrogen than in classical antibiotics led to the development of the surprisingly potent oxamazins (19)[16-19].



(19)

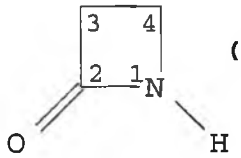
Replacing the oxygen of oxamazins with a sulphur atom produced the thiamazins (20)[20], which were strangely devoid of biological activity[21].



(20)

1.2 Mode of Action of ß-Lactam Antibiotics[1,2,22,23]

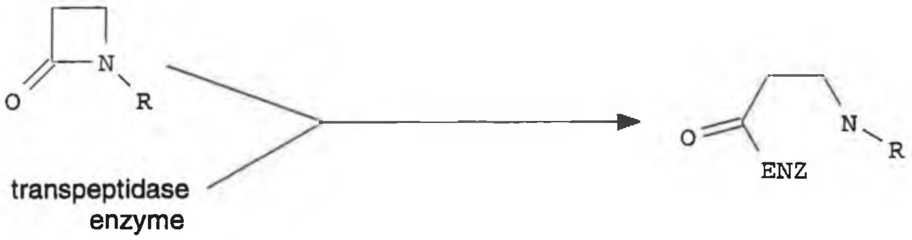
Because of the structural diversity of all the β-lactam antibiotics, the minimum structural unit necessary for antibacterial activity has been revised several times over decades. The evidence to date suggests that the essential pharmacophore for antibiotic activity is a reactive β-lactam (or azetidin-2-one) ring (21) with an ionisable acidic group located near the azetidinyl nitrogen[21].



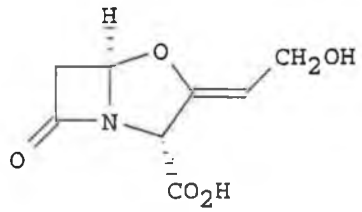
(21)

Incorporation of an amide linkage into the four-membered azetidin-2-one ring results in angle strain and inhibition of amide resonance, exemplified by unusually long C-N bonds and very short C=O distances. Typical β-lactam carbonyl absorptions are seen at 1730-1790 cm^{-1} in the infra-red. Consequently, β-lactams are more susceptible than normal amides to nucleophilic attack at the carbonyl group. This ability to act as an acylating agent is largely responsible for the antibacterial properties of β-lactams.

β-Lactam antibiotics selectively and irreversibly inhibit transpeptidase enzymes necessary for the synthesis of peptidoglycan, the stabilising framework of the bacterial cell wall. These enzymes become acylated, via cleavage of the β-lactam ring, and are thereby inactivated.

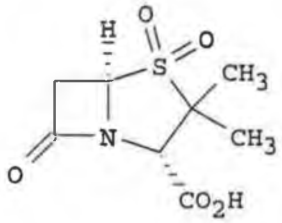


Many bacteria, however, produce penicillinase (β-lactamase) enzymes, which are effective antagonists of antibiotics, since they catalyse hydrolytic cleavage of the β-lactam ring before reaching the transpeptidases. The first success in the strategy of neutralising penicillinases came in 1976, with the isolation of clavulanic acid (22)[24].



(22)

Other newly-developed inhibitors include sulbactam (23) and olivanic acid (24).



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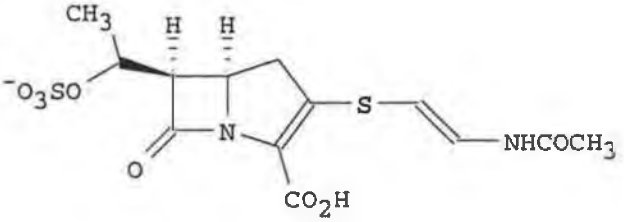
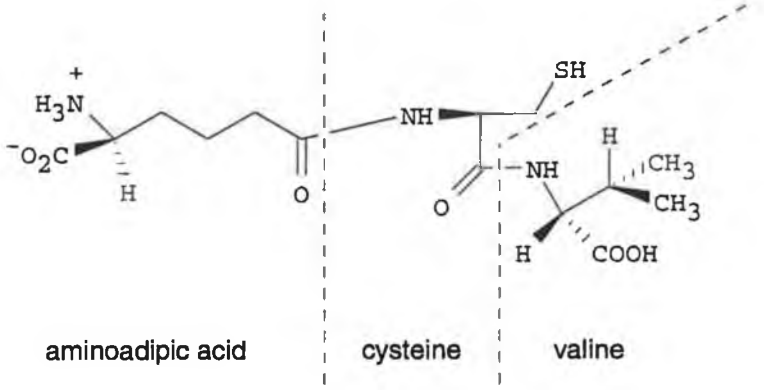


(24)

Although these inhibitors themselves show slight antibacterial activity, their most important attribute is that they improve the effectiveness of β-lactam antibiotics by inhibiting penicillinases. They are usually prescribed in combination with the active drug.

1.3 Methods for Construction of the β-Lactam Ring

It is now universally accepted that, in nature, penicillin and cephalosporin antibiotics are derived from three amino acids (L-α-aminoadipic acid, L-cysteine and L-valine) via the so-called Arnstein tripeptide, δ-(L-α-aminoadipoyl)-L-cysteinyl-D-valine (LLD-ACV) (25)[25].



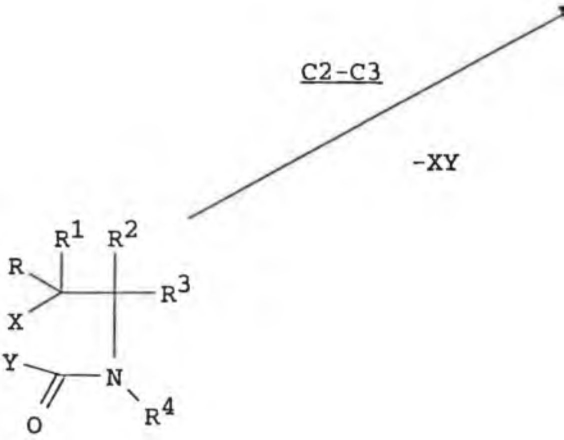
(25)

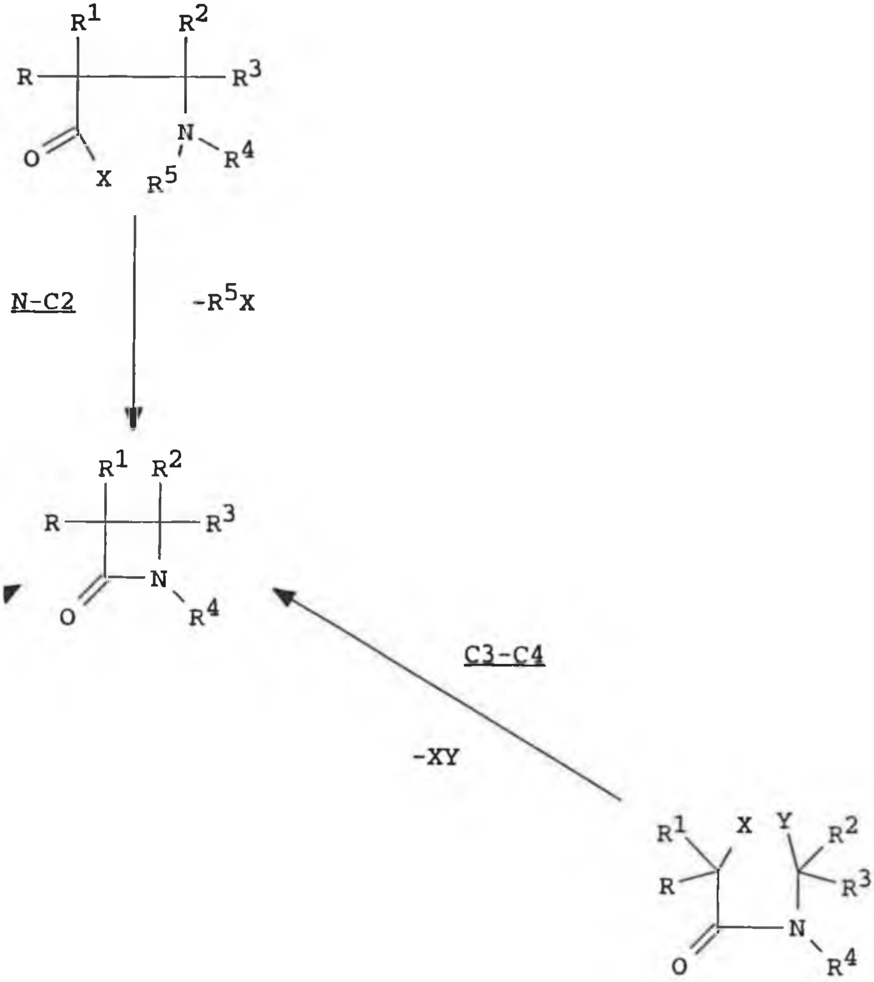
Furthermore, it is believed that, during the enzyme-catalysed bicyclisation process, the β-lactam ring is the first to form, by N-C4 bond closure[26].

Chemical synthesis of the β-lactam ring has been approached from every conceivable angle. A wealth of literature exists describing formation of the 2-azetidinone ring via closure of the N-C2[27], C2-C3[28] and C3-C4[29] bonds (Scheme 1), [2+2] cycloaddition reactions[30-35] (Scheme 2), ring expansions[36] and contractions[37], and transformations of azetidines[38].

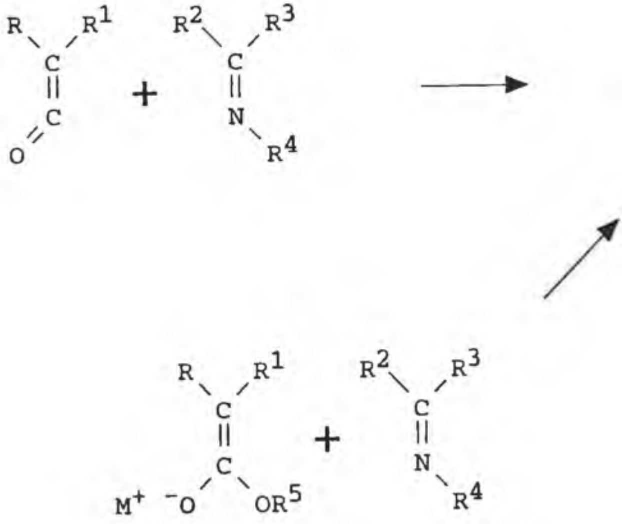
Construction of the β-lactam ring by N-C4 bond formation is especially appealing because of its biosynthetic analogy. These cyclisations almost invariably involve intramolecular alkylation through nucleophilic attack by N1 at C4, with displacement of a suitable leaving group, or application of the Mitsunobu reaction.

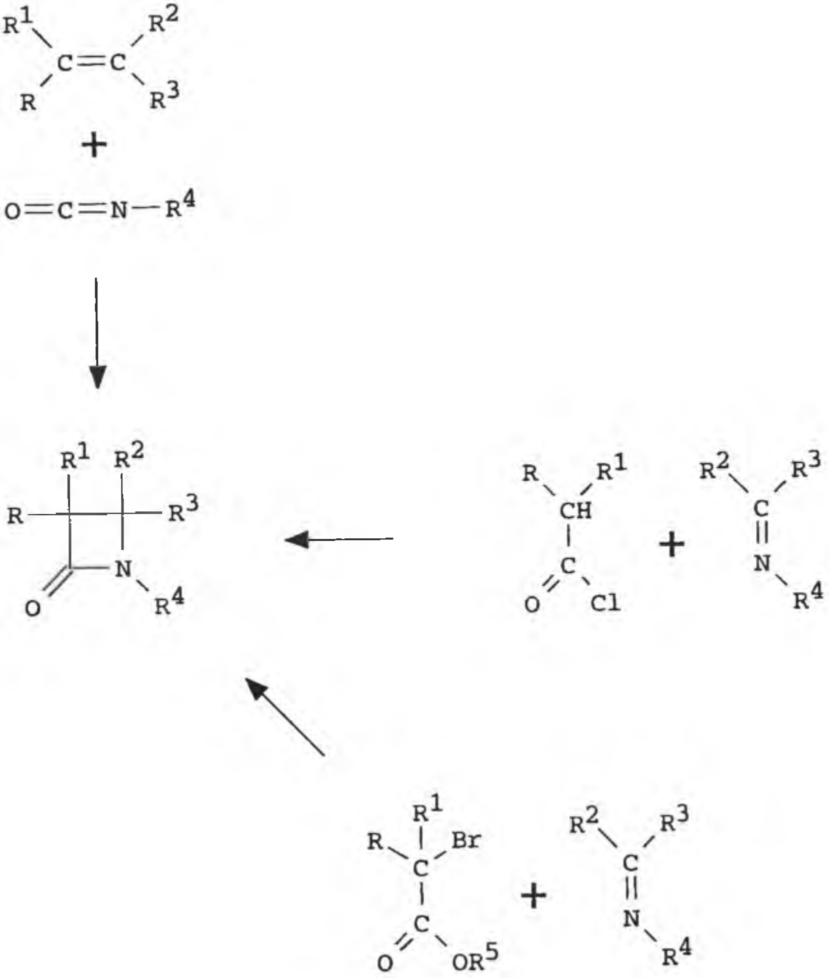
Scheme 1




N-C2
-R5X
C3-C4
-XY

Scheme 2




R1
R2
R
R3
O=C=N—R4
R
OR5
Br
Cl
N
O

1.3.1 Cyclisation of 3-Halopropionamides

The synthesis of β-lactams from β-haloamides by treatment with strong base was developed by Knunyants in the late 1950s[39,40]. Subsequently, the cyclisation of β-bromopropionanilide (26) in the presence of various bases (NaNH$_2$, NaH/DMSO and tBuOK/DMSO) was evaluated by Manhas and Jeng[41].

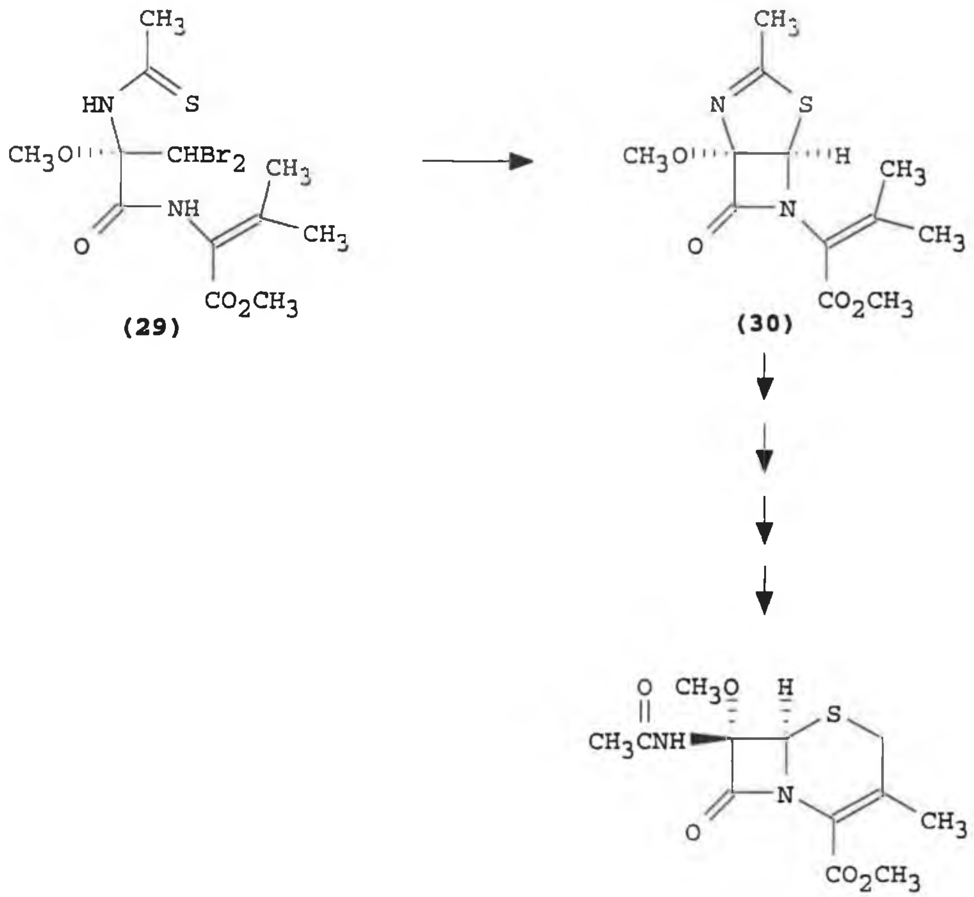
(26) (27)

The best yield (95%) of β-lactam (27) was obtained using NaH/DMSO (dimsyl anion). Surprisingly, no competitive acrylamide (28) formation was reported.

(28)

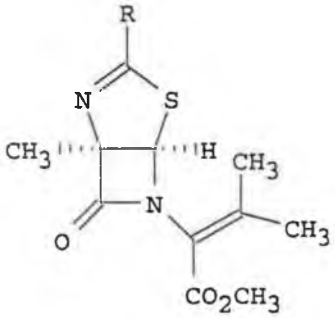
Such dehydrohalogenation is a significant side reaction in the N-C4 base-catalysed cyclisation of β-haloamides, which are not disubstituted in the α-position[42]. Wasserman and colleagues[43], in their initial studies on the cyclisation of β-halopropionamides using NaH in DMF/CH$_2$Cl$_2$, found that β-elimination predominated. However, by varying the experimental conditions (i.e. dilution, rate of addition of amide to base and choice of halide), these workers claim to have minimised acrylamide formation and developed an efficient general method for the preparation of 3-unsubstituted azetidin-2-ones.

Base-induced N-C4 cyclisation of β-haloamides has been applied to the synthesis of several biologically important β-lactams. Kishi and associates[44], hoping to achieve total synthesis of the 3-deacetoxy-7-methoxycephalosporin derivative (31), utilised NaH in THF to effect the double cyclisation of the thioamide (29) to the β-lactam thiazoline derivative (30).



(29) **(30)** **(31)**

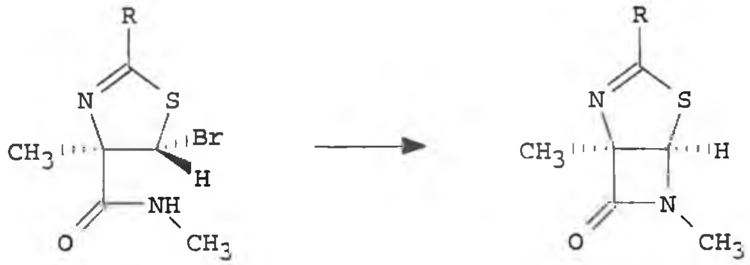
While investigating routes to the 3-methyl-β-lactam (32), these workers examined cyclisation of the isomeric bromides (33) and (34) with KH in THF[45].



(32)

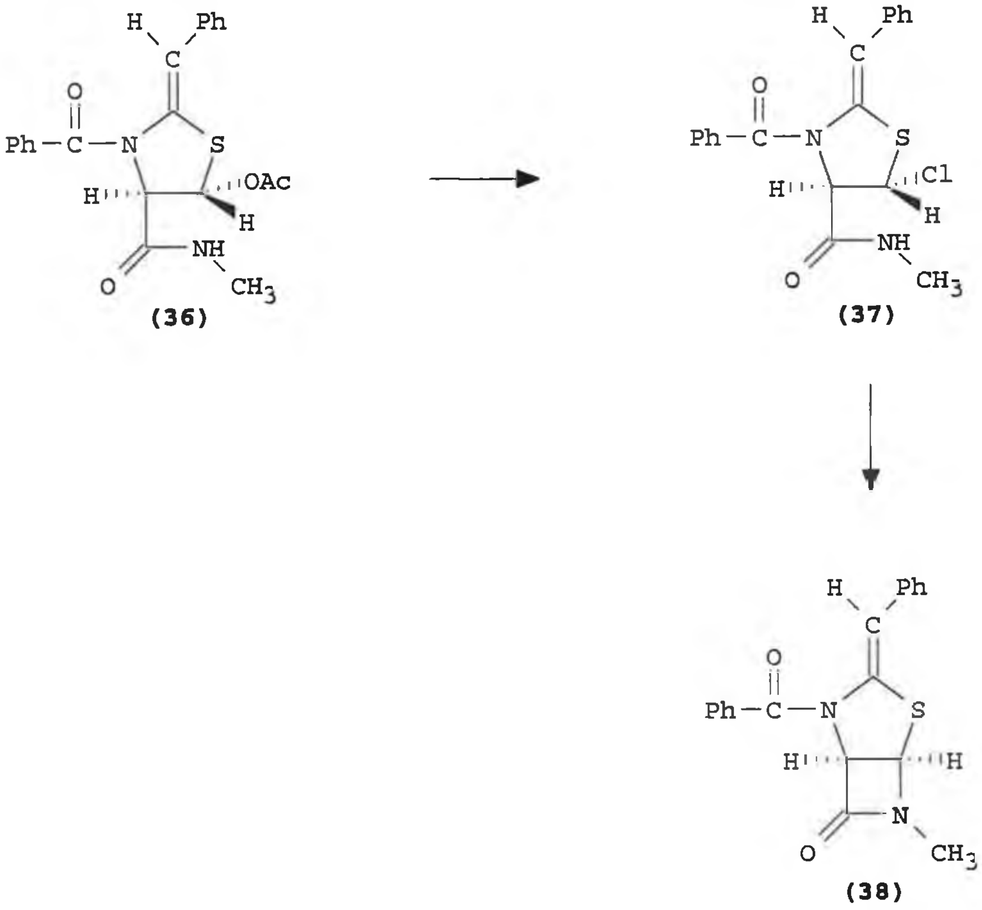
R = p-CH_3O-C_6H_4

The bromide (33) gave the β-lactam (35) in high yield, whereas the epimer (34) was recovered unchanged, supporting the contention that cyclisation proceeds through an S_N2 process.

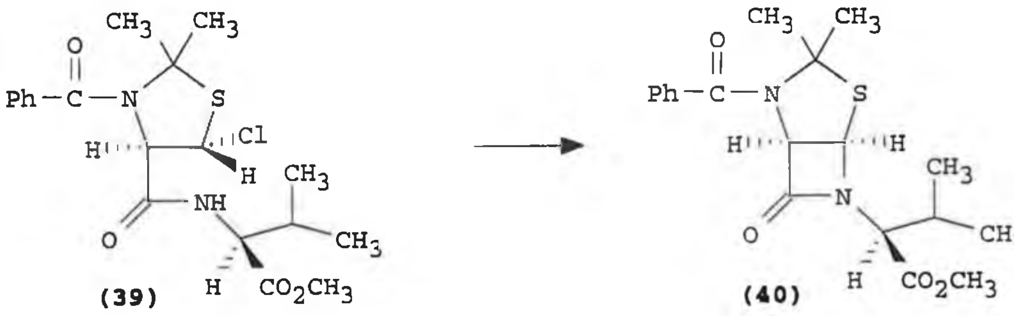


(33) **(35)**

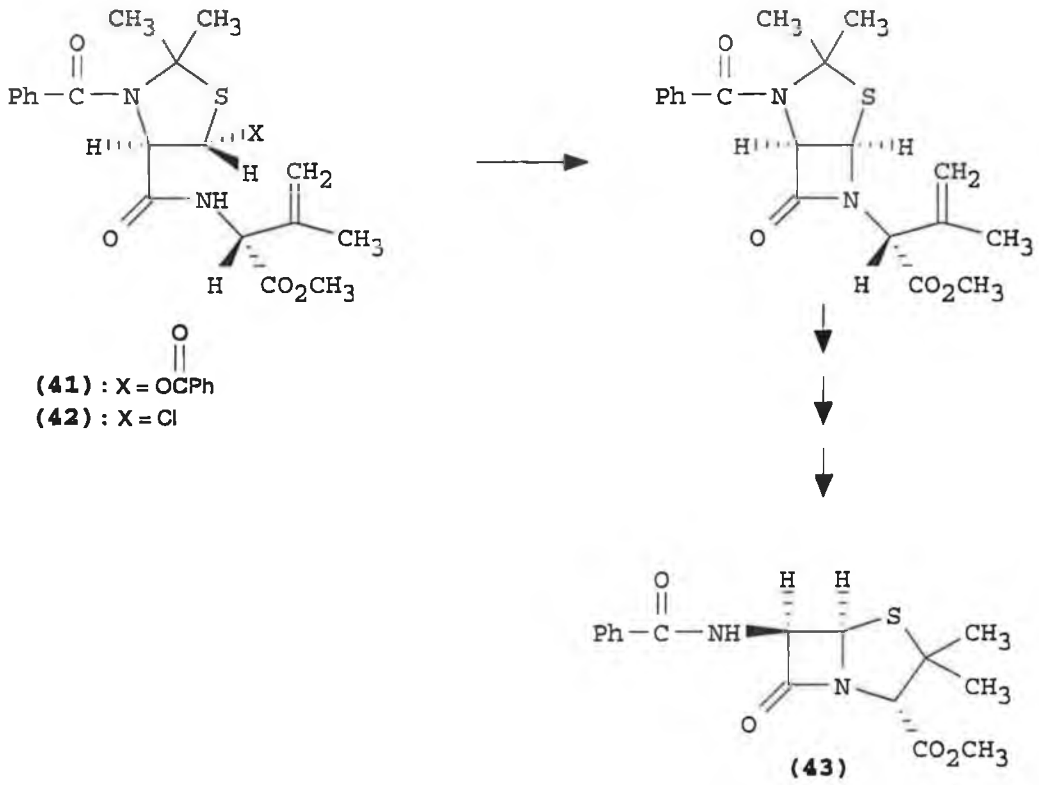
Of particular interest is the reported cyclisation of the acetate (36) to the β-lactam (38). This was accomplished by reaction with HCl gas, affording the chloride (37), which lactamised in the presence of KH[42,45].



Similarly, Baldwin's group[46] achieved ring closure of the chlorothiazolidine (39) to the β-lactam (40), in 81% yield, using NaH as base.



These investigators proceeded to develop a stereospecific synthesis of the penicillin methyl ester (43)[47], in which cyclisation of the benzoate (41) was realised by conversion to the chloride (42), and treatment with NaH in CH_2Cl_2/DMF.



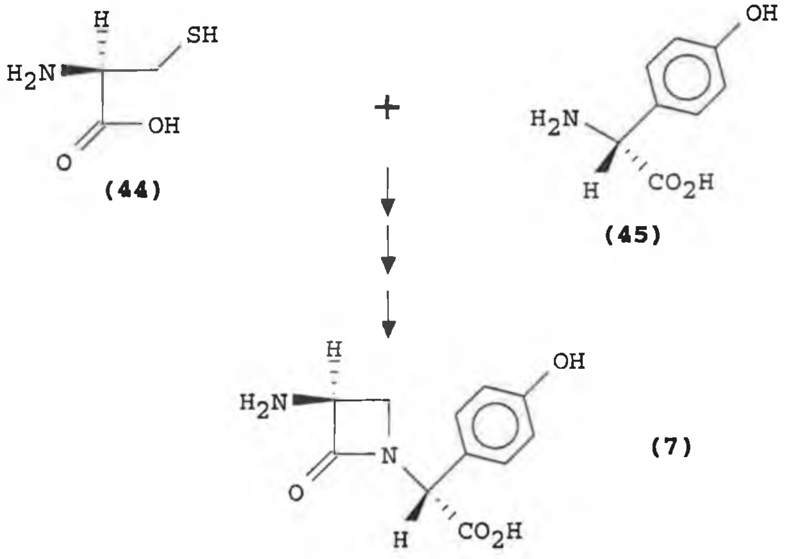
(41) : $X = O\overset{O}{\overset{\|}{C}}Ph$

(42) : X = Cl

(43)

A shorter stereocontrolled synthesis of the penam system was later described by this group[48], again involving transformation of a benzoate to a chloride, and β-lactam ring closure with NaH.

Koppel and colleagues[49] applied Baldwin's methodology to the chirally-specific total synthesis of 3-ANA (7) from L-cysteine (44) and D-p-hydroxyphenylglycine (45).

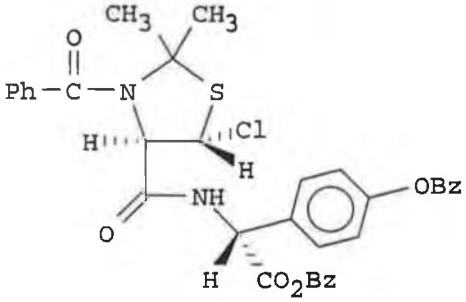


(44)

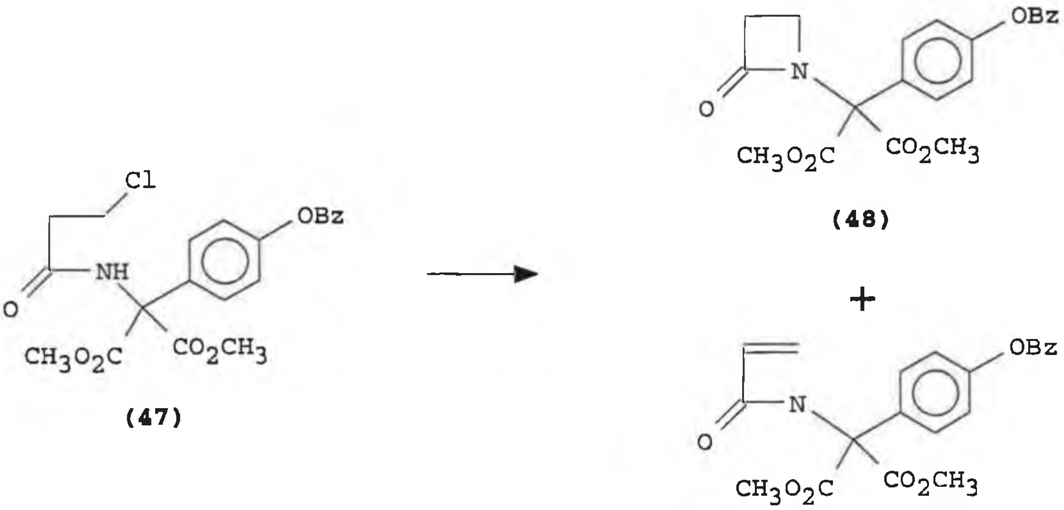
(45)

(7)

The β-lactam ring was constructed by base-catalysed closure (NaH in CH_2Cl_2/DMF) of the chloro- precursor (46).


(46)

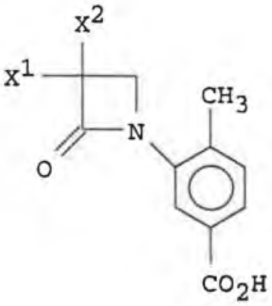
Wasserman et al. used base-induced cyclisation of a β-haloamide in their synthesis of 3-ANA[50,51]. The 3-chloropropionamide (47), as a dilute solution in CH_2Cl_2/DMF, was added to a suspension of NaH, in the same solvent mixture, to produce the β-lactam (48) in 76% yield. A small amount (approximately 5%) of the α,β-unsaturated amide (49) was also formed. As indicated by their studies on minimisation of dehydrohalogenation[43], a substantially larger amount of the elimination product was obtained with more concentrated reaction mixtures.


(47)

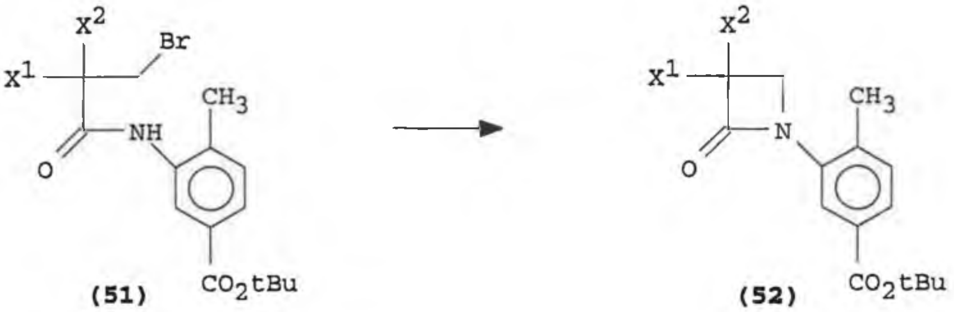
(48)

(49)

In a search for new β-lactamase inhibitors, N-aryl-3-halo- and -3,3-dihalo-2-azetidinones (50) were prepared by Wakselman and associates[52].


(50) : X^1, X^2 = H, Br or F

The substituted 3-bromopropionanilides (51) were cyclised using the Wasserman procedure[51], with NaH as base in dilute CH_2Cl_2/DMF solution. As expected, the yield of β-lactam was lower than in the case of the 2,3-dibromopropionanilide (51d), which has an acidic α-hydrogen atom. Cleavage of the t-butoxy protecting group in the β-lactam products (52) gave the free acids (50).



(51) **(52)**

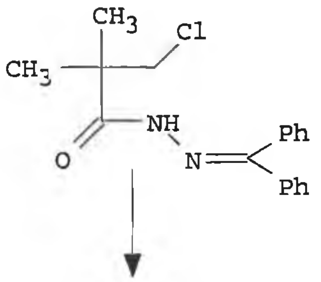
a: X^1, X^2 = F, Br
b: X^1, X^2 = F, F
c: X^1, X^2 = Br, Br
d: X^1, X^2 = H, Br

In order to investigate acyloxylation at the 4-position of 2-azetidinones, Easton and co-workers[53] synthesised a series of β-lactams (54) using Wasserman's methodology. Thus, the substituted propionamides (53) were lactamised, using NaH in dilute CH_2Cl_2/DMF, to afford the azetidin-2-ones (54).

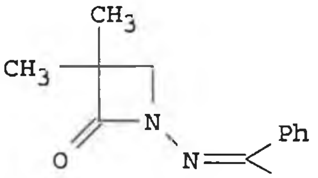
(53) **(54)**

R, R^1 = H, CH_3, Ph
R^2 = tBu, Ph, 4-CH_3O-C_6H_4
X = Cl, Br, I

Taylor et al.[54] showed that treatment of the 3-chloro-2,2-dimethylpropionylhydrazone (55) with NaH in THF resulted in a good yield of the 3,3-dimethyl-β-lactam (56) and a minor amount of the zwitterion (57).



(55)



(56)

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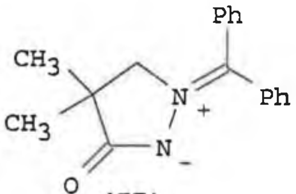
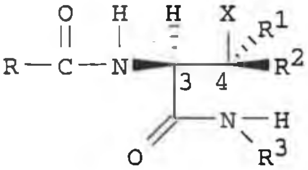


(57)

An added attraction of the N-C4 bond closure approach is the potential to use chiral α-amino acid amides, and other modified amides, with β-leaving groups, as starting materials. Conceptually, the base-induced cyclisation of amides such as (58) is straightforward, but experimentally this lactamisation is problematic for several reasons.

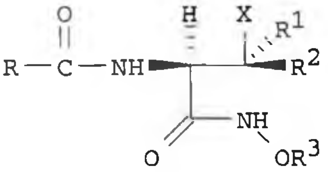


(58)

X = leaving group

Because the acidities of the requisite N-H, the C3-H and the C3 amide N-H are similar, on treatment with the required strong base, detrimental proton transfers can occur, and subsequent reactions result in little of the desired cyclisation to the β-lactam product (60) (Scheme 3). Therefore, additional protective steps must be incorporated to avoid competitive elimination and racemisation, especially when C3 is monosubstituted by an amide group, as seen in many β-lactam antibiotics. In the aforementioned synthesis of 3-ANA[49], Koppel and associates overcame these problems by incorporating C3 and C4 into a five-membered ring (46) before effecting β-lactam ring closure. In addition, base-induced N-C4 cyclisations are often limited by the need for multi-step incorporation of a suitable β-leaving group, as seen in Baldwin's synthesis of the penicillin methyl ester (43)[47].

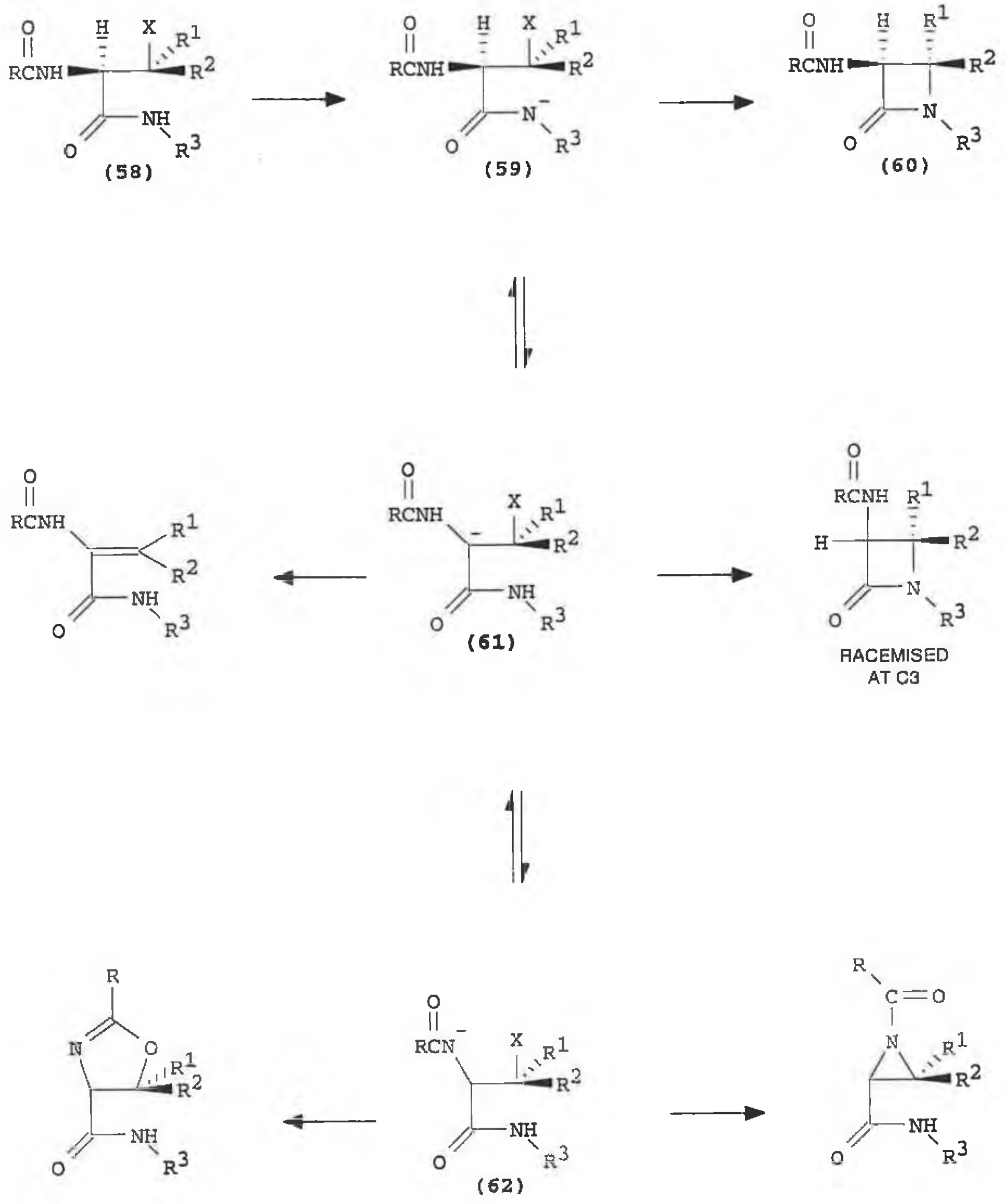
Seeking a direct method for the N-C4 cyclisation of amides of the type (58), without the need for elaborate prior manipulations, Miller and co-workers addressed the problem of differentiating the pK values at the three potentially ionisable positions [(59), (61), (62)], and postulated that the required selective N-H ionisation to (59) could be achieved by heteroatom activation, using hydroxamate derivatives of β-halo-carboxylic acids (63).



(63) : X = Cl, Br

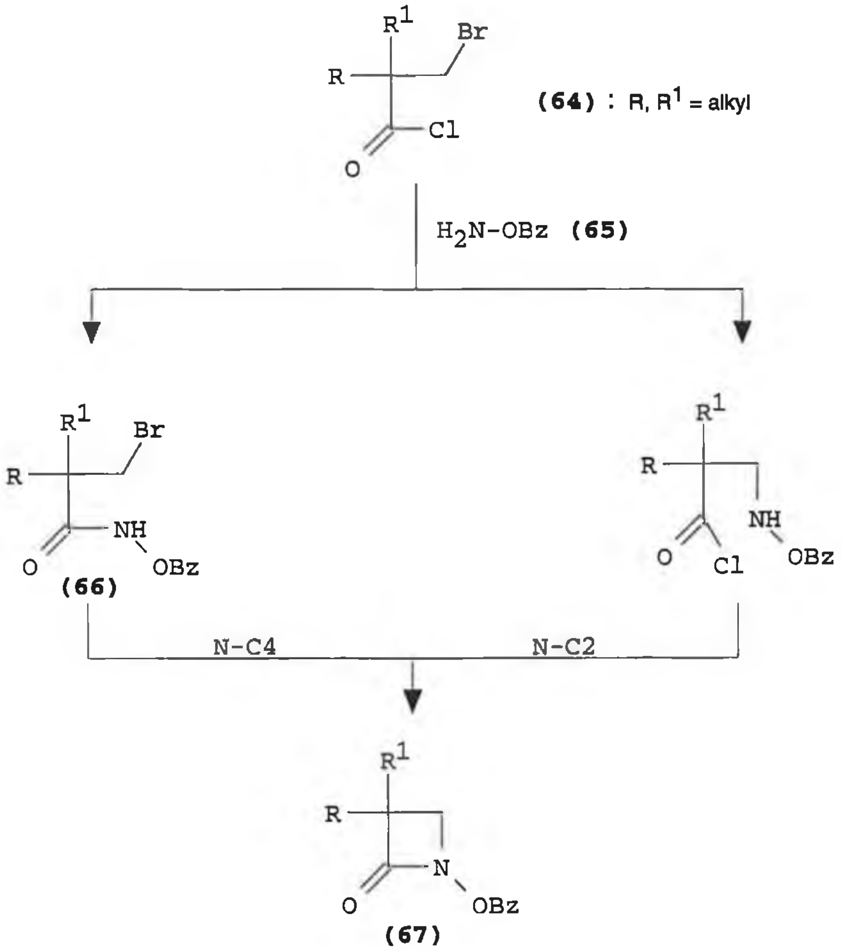
It should be noted that the reaction of the β-bromo acid chloride (64) with O-benzylhydroxylamine (65), in the presence of pyridine, affording the N-benzyloxy-2-azetidinone (67) had been reported previously by Nicolaus and colleagues[55]. This reaction could occur by

Scheme 3



N-C4 cyclisation[56] of an intermediate β-bromohydroxamate (66) or alternatively by initial N-alkylation followed by N-C2 ring closure[57] (Scheme 4).

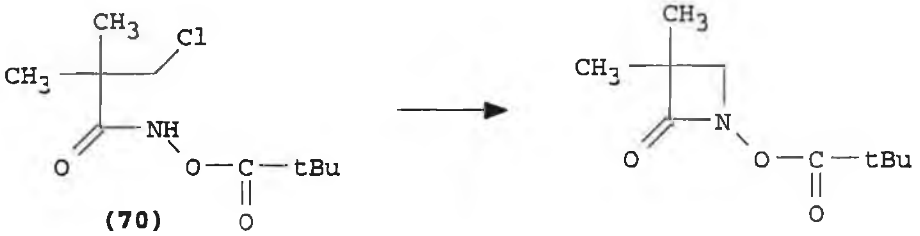
Scheme 4



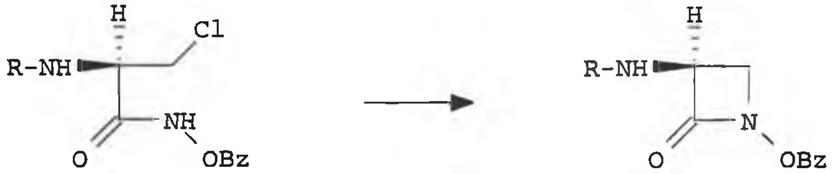
In either case, the potential of achieving selective ionisation by heteroatom activation in substrates such as (63) was probably not recognised.

Miller's group set about testing their theory by initially studying cyclisation of the model compound (68), containing only one ionisable position. Reaction with NaH in DMF at 20°C produced the N-hydroxy-β-lactam derivative (69) in 94% yield[58].

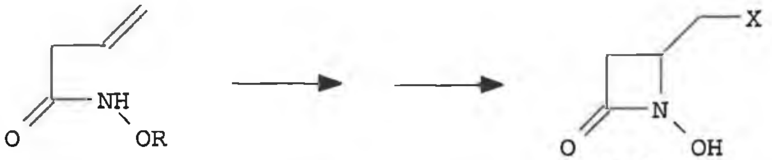
Interestingly, cyclisation of the corresponding O-acylhydroxamate (70) could be achieved using a weak base (Li_2CO_3 in DMF at 20°C).

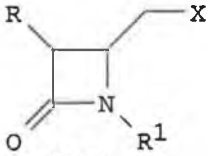

(70)

To assess differentiation of the hydroxamate anion and other potential anions within the β-lactam precursor, synthesis of chiral models was attempted[58,59]. The β-chloro-L-alanine derivatives (71) and (72) were reacted with NaH in CH_2Cl_2/DMF (1:1) at 50°C, and provided azetidin-2-ones (73) and (74) in high yields. No products arising from competing reactions were observed.

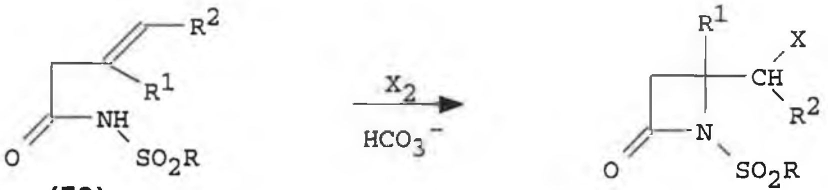

(71) : R = Cbz
(72) : R = tBoc
(73) : R = Cbz
(74) : R = tBoc

Miller's success in exploiting the acidity of O-substituted hydroxamates to facilitate selective cyclisation to β-lactams prompted his investigation of the oxidative cyclisation of β,γ-unsaturated hydroxamates (75) to 4-(halomethyl)-N-hydroxy-2-azetidinones (76)[60]. The related 4-(halomethyl)-2-azetidinones (77) are useful intermediates in the synthesis of bicyclic and functionalised monocyclic β-lactams.


(75)
(76)


(77)

Miller was encouraged by Ganem's observation[61] that the lowered pK of the carboxamide group in β,γ-unsaturated N-sulfonylated amides (78) promoted halogen-induced oxidative cyclisation to β-lactams (79).



(78) **(79)**

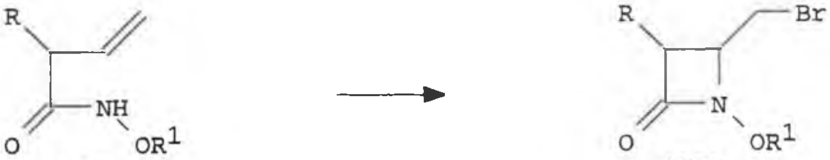
R = OCH_3, OC_2H_5, OCH_2CCl_3, p-CH_3-C_6H_4
R^1, R^2 = H, CH_3
X = Br, I

Oxidative cyclisation of the O-acylhydroxamates (80) was attempted by Miller[60], using Ganem's procedure (Br_2, K_2CO_3, H_2O/CH_2Cl_2), and although the O-acetyl derivative (80a) furnished the desired β-lactam (81a) in 73% yield, several other hydroxamates (80b-d) afforded mixtures containing little or no β-lactam products. However, treatment of all hydroxamates (80a-d) with Br_2/K_2CO_3 in 5-10% aqueous acetonitrile promoted efficient cyclisation to the β-lactams (81a-d) in 75-90% yields. Catalytic hydrogenation of the N-benzyloxy-2-azetidinone (81d) gave the target N-hydroxy-β-lactam (76: X = Br).

(80) **(81)**

a: R = CH_3
b: R = iPr
c: R = tBu
d: R = OBz

Since the most effective β-lactam antibiotics contain alkyl, substituted alkyl or substituted amino groups in the 3-position of the 2-azetidinone ring, Miller and Rajendra[62] extended their study to the oxidative cyclisation of α-substituted β,γ-unsaturated hydroxamates (82), using bromine and K_2CO_3 in aqueous CH_3CN.

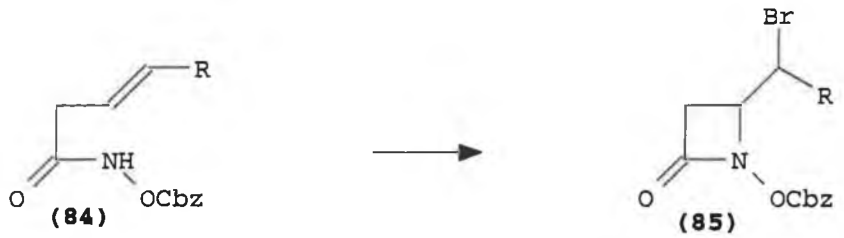


(82) **(83)**

a: R = Bz; R^1 = Cbz
b: R = CH_3; R^1 = Cbz
c: R = CbzNH; R^1 = Cbz
d: R = CbzNH; R^1 = Ac

Miller discovered that substrates containing α-alkyl groups (82a,b) formed 3,4-trans-β-lactams (83a,b) preferentially, whereas those with protected α-amino substituents (82c,d) gave predominantly cis products (83c,d). The stereoselectivity observed is significant since many biologically active α-alkylated bicyclic β-lactams are trans-substituted, and most α-amino-substituted bicyclic β-lactams are cis-substituted.

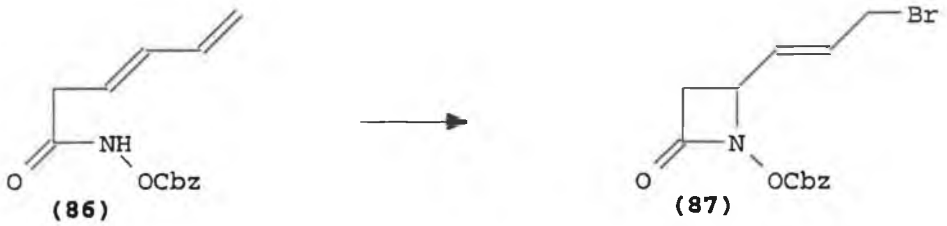
These investigators proceeded to consider the effect of γ-substitution on the oxidative cyclisation of γ-substituted O-acyl-vinylacetohydroxamates (84)[63].



(84) **(85)**

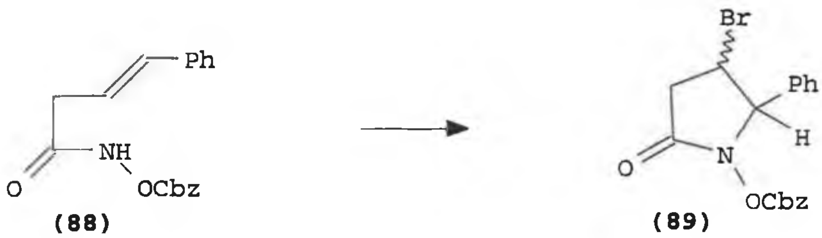
a: R = Et
b: R = CH_2CO_2Me

Treatment of the β,γ-unsaturated hydroxamate (84a) with bromine under the usual conditions provided the β-lactam (85a) in 53% yield. The analogous substrate (84b) cyclised quantitatively to the 2-azetidinone (85b). Surprisingly, the 3,5-hexadienohydroxamate (86) gave only the β-lactam product (87), apparently via a 1,4-addition process.



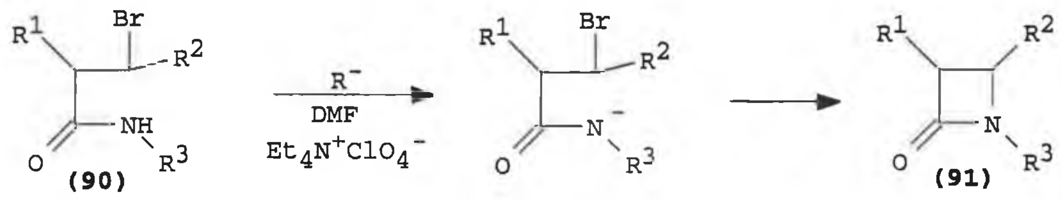
(86) **(87)**

However, the styrylacetohydroxamate (88) afforded only the γ-lactam (89) under the standard cyclisation conditions.



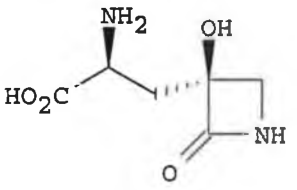
(88) **(89)**

Both β-bromopropionamides and β-bromopropionohydroxamates have been used as β-lactam precursors in a novel N-C4 electrocyclisation by Moracci and colleagues[64]. Cathodic reduction of a probase (ethyl 2-bromo-2-methylpropanoate or diethyl bromomalonate) yielded an electrogenerated base, R^-, which reacted with the substrates (90), to produce a nitrogen anion. Intramolecular nucleophilic substitution afforded the β-lactams (91) in poor to very high yields.

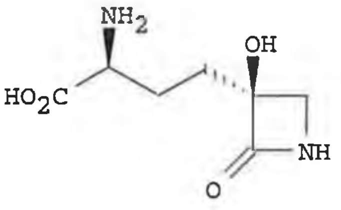


R = probase
R^1 = H, Phth
R^2 = H, CH_3
R^3 = Bz, OBz, p-CH_3O-C_6H_4

Baldwin and associates[65] report the cyclisation of hydroxamate derivatives to 3-methylene-2-azetidinones in their synthetic studies towards the β-lactam (92), a lower homologue of tabtoxinine-β-lactam (93), which is a potent inhibitor of glutamine synthetase.

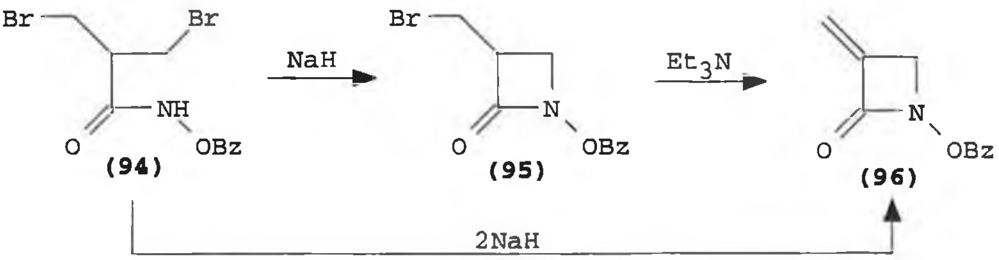


(92)

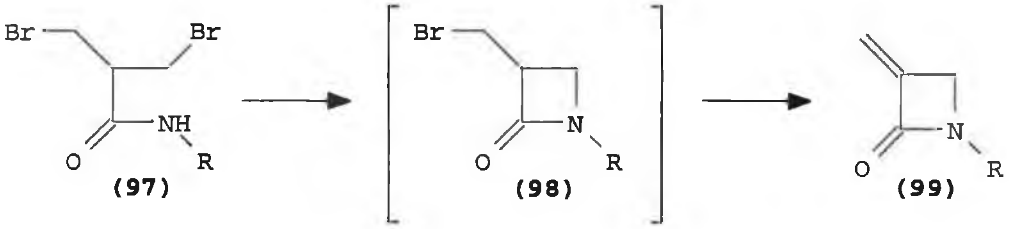


(93)

Thus, treatment of the β-bromohydroxamate (94) with 1 equivalent of NaH in THF gave the 3-(bromomethyl)-2-azetidinone (95). Dehydrobromination with triethylamine furnished the 3-methylene-2-azetidinone (96). Alternatively, the β-lactam (96) could be obtained directly from the hydroxamate (94) by reaction with 2 equivalents of NaH.

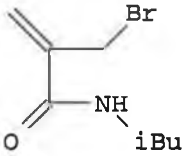


Fletcher and Kay[66] employed phase-transfer catalysis in their synthesis of 3-methylene-β-lactams. The 3-bromo-2-bromomethylpropionanilides (97: R = aryl) were cyclised to the N-aryl-2-azetidinones (99: R = aryl) in high yields, using an excess of 40% NaOH/CCl_4 containing a trace of pentyltriethylammonium bromide.



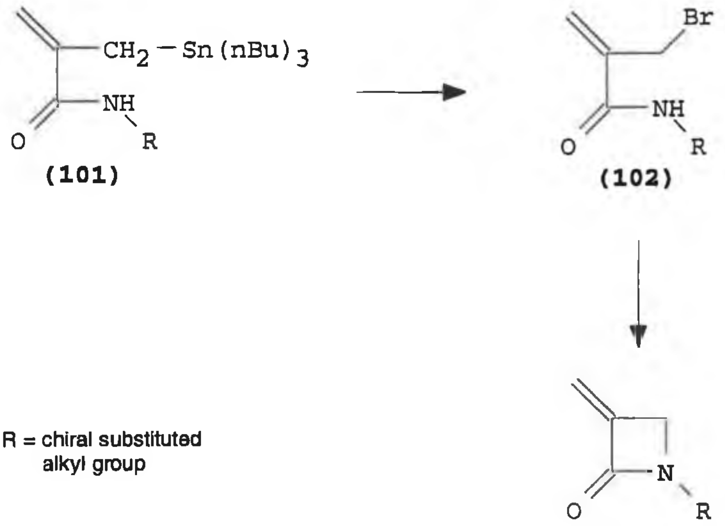
(97) (98) (99)

In the cyclisation of the N-phenylamide (97: R = Ph), the intermediate 3-bromomethyl-β-lactam (98: R = Ph) could be isolated, and further reacted to the 3-methylene-2-azetidinone (99: R = Ph). By contrast, in the lactamisation of the analogous N-isobutylamide (97: R = iBu), the bromomethylacrylamide (100) could be isolated after a reduced reaction time, and converted, under the same phase-transfer conditions, to the 3-methylene-β-lactam (99: R = iBu).



(100)

An alternative route to 3-methylene-β-lactams is described by Tanaka and colleagues[67]. The N-monosubstituted 2-[(tributylstannyl)-methyl]propenamides (101) were brominated, using dioxane dibromide in dry THF, to afford the corresponding 2-(bromomethyl)-propenamides (102). Treatment with NaH or tBuOK in THF at -78°C provided the 3-methylene-2-azetidinones (103) in good yields.



(101) (102) (103)

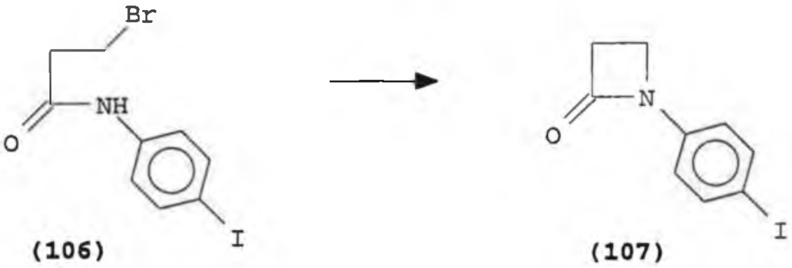
R = chiral substituted alkyl group

In the phase-transfer-catalysed cyclisation of α-unsubstituted β-bromopropionamides (104) to β-lactams, Yamazaki and co-workers[68,69] demonstrated that high dilution was necessary to avoid dehydrohalogenation to acrylamides. Thus, addition of a solution of the amides (104) in CH_2Cl_2, CH_2Cl_2:CH_3CN (19:1), or THF, to a suspension of pulverised KOH and tetrabutylammonium bromide, in the same solvent, produced the β-lactams (105) in high yields, without any by-product acrylamides.


(104) (105)

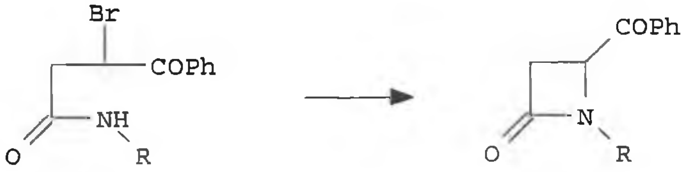
R = alkyl, aryl

More recently, the efficacy of several structurally varied phase-transfer catalysts was evaluated in the base-catalysed cyclisation of 3-bromo-N-(4-iodophenyl)propionamide (106) to 1-(4-iodophenyl)-2-azetidinone (107) in CH_2Cl_2:CH_3CN (19:1) using pulverised KOH as base[70].


(106) (107)

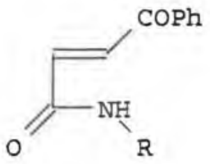
18-Crown-6 proved to be the best catalyst for this reaction and hence was employed in the preparation of a series of 1-aryl-2-azetidinones (105: R = e.g. Ph, 4-Cl-C_6H_4) by the base-catalysed cyclisation of the appropriate N-aryl-3-bromopropionamides (104).

Yamazaki's group extended their phase-transfer procedure to the synthesis of 4-benzoyl-2-azetidinones (109)[69]. The 3-benzoyl-3-bromopropionanilides (108) were cyclodehydrohalogenated (KOH, CH_2Cl_2:CH_3CN (19:1), tetrabutylammonium bromide), affording the β-lactams (109) in moderate yields.


(108) (109)

R = Ph, 4-Cl-C_6H_4, 4-CH_3-C_6H_4, 4-CH_3O-C_6H_4

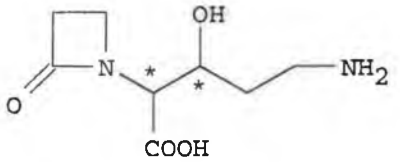
Abdulla and Williams[71] had previously cyclised anilides of the type (108) to the corresponding β-lactams using an anion exchange resin. Again, no 1,2-elimination to 2-benzoylacrylanilides (110) was reported.



(110)

R = Ph, 4-Cl-C_6H_4, 4-CH_3-C_6H_4, 3-CF_3-C_6H_4

Beecham chemists[72] recently outlined research leading to the discovery of the absolute stereochemistry of proclavaminic acid (111), an intracellular β-lactam involved in the biosynthesis of clavulanic acid (22).



(111)

Attempting to synthesise all four possible stereoisomers of (111), Baggaley and associates initially examined preparation of each of the two enantiomers of dehydroxy-proclavaminic acid (114), via cyclisation of the two enantiomeric 3-bromopropionamides (112). Using Yamazaki's methodology[69], a dilute solution of amide (112) in CH_2Cl_2:CH_3CN (19:1) was added slowly to a suspension of pulverised KOH and tetrabutylammonium bromide in the same solvent mixture. Each of the protected amino acid β-lactams (113) obtained was catalytically reduced, affording the 2-azetidinones (114).

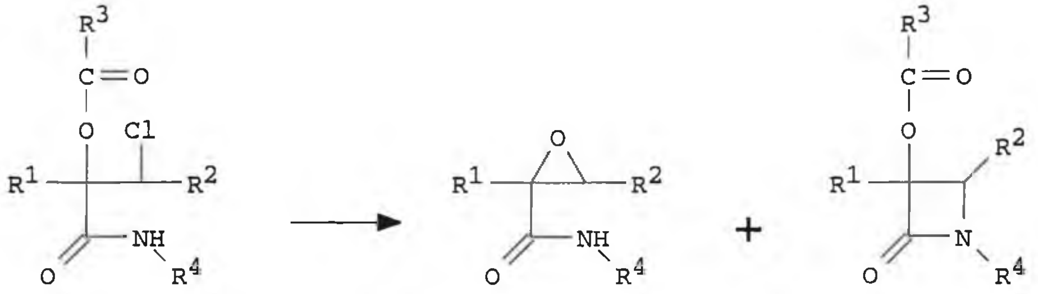
(112)

(113) : R = Bz; R^1 = Cbz

(114) : R = R^1 = H

Unfortunately, analysis revealed that considerable racemisation had occurred during the base-induced cyclisation.

Sebti and Foucaud[73] studied lactamisation of the 2-acyloxy-3-chloropropionamides (115) using powdered KOH as a base in THF, in the absence of phase-transfer catalyst, and obtained either the oxiranes (116) quantitatively, or a mixture of oxirane and β-lactam (117).

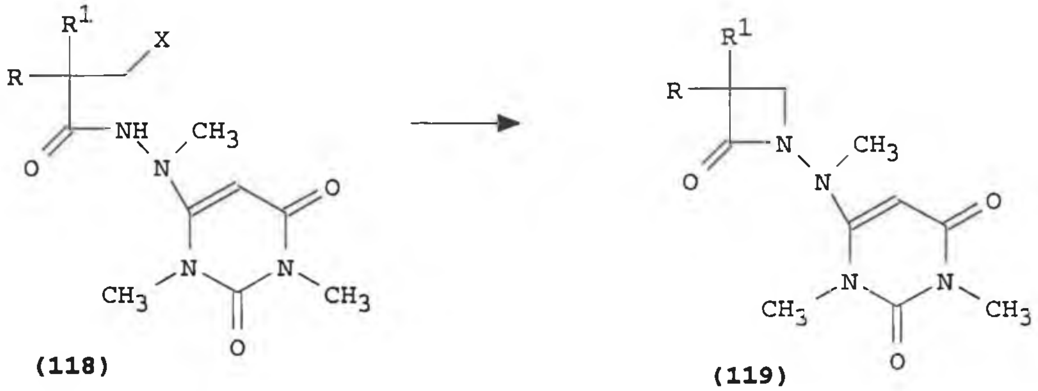


(115) (116) (117)

$R^1 = CH_3, CH_2Cl$
$R^2 = H, CH_3$
$R^3 = CH_3, n\text{-}C_3H_7, Ph, PhCH{=}CH$
$R^4 = i\text{-}C_3H_7, t\text{-}C_4H_9$

These investigators found that the desired 3-acyloxy-2-azetidinones (117) could be synthesised in high yields by treatment of the amides (115) with caesium fluoride in THF, in the presence of benzyltriethylammonium chloride. Some amides (115) were heated at 85-90°C with CsF, in the absence of solvent and catalyst, and furnished the corresponding β-lactams (117) in good yields, suggesting that reaction can take place on the surface of the alkali metal fluoride.

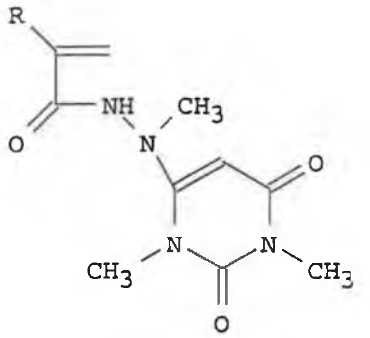
Phase-transfer conditions (powdered KOH in CH_2Cl_2 containing benzyltriethylammonium chloride) were utilised in the cyclisation of the N-haloacylhydrazinouracils (118a) and (118b) to the novel β-lactams (119a) and (119b)[74].



(118) (119)

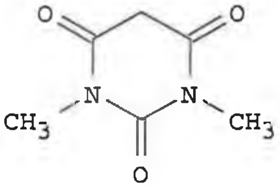
a: $R = CH_3$; $R^1 = Br$; $X = Br$
b: $R = CH_3$; $R^1 = CH_3$; $X = Cl$
c: $R = H$; $R^1 = H$; $X = Br$
d: $R = Br$; $R^1 = H$; $X = Br$

In the case of the corresponding uracil substrates (118c) and (118d), β-elimination occurred preferentially, affording the α,β-unsaturated hydrazides (120a) and (120b) respectively, in addition to 1,3-dimethylbarbituric acid (121), formed by alkaline hydrolysis of the hydrazides. Trace amounts of the target β-lactams (119c) and (119d) were also produced.



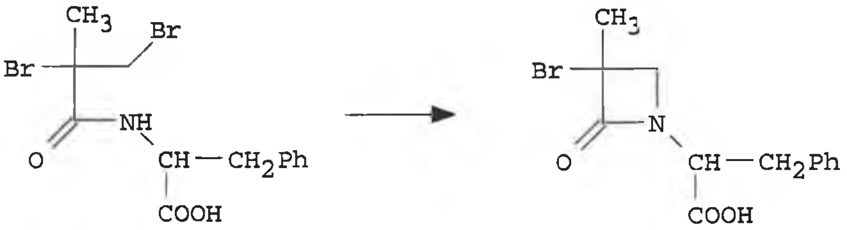
(120)

a: R = H
b: R = Br



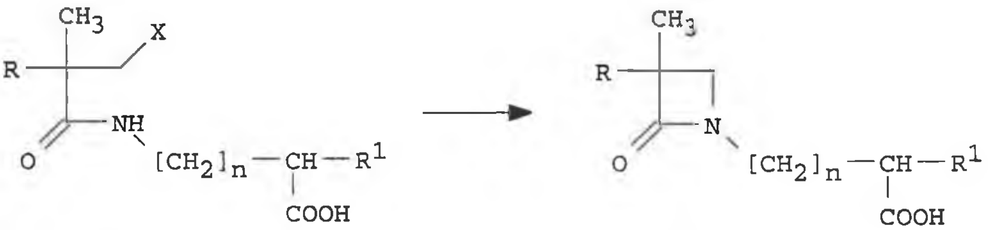
(121)

Okawara and colleagues[75] claimed that cyclisation of N-(α,β-dibromo-α-methylpropionyl)-(S)-phenylalanine (122) to the β-lactam (123) could only be achieved in aqueous NaOH/CH_2Cl_2 mixtures in the presence of a phase-transfer catalyst (e.g. benzyltriethylammonium chloride). The reaction was reported not to proceed in the absence of catalyst.



(122) **(123)**

Irwin and Timoney[76] examined intramolecular N-alkylation of the related amides (124) to produce the corresponding β-lactams (125), and found that the cyclisation proceeded in aqueous 1.25M NaOH. The presence or absence of catalyst and/or solvent did not affect the reaction rate.

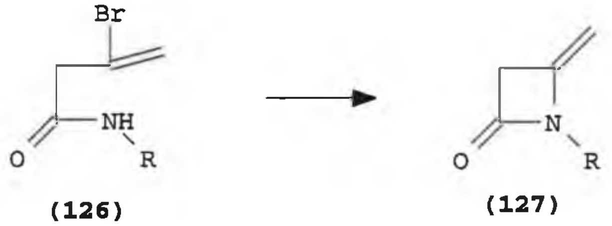


(124) **(125)**

X = Br, Cl
R = Br, CH_3
R^1 = H, iPr, CH_2-indole
n = 0,1

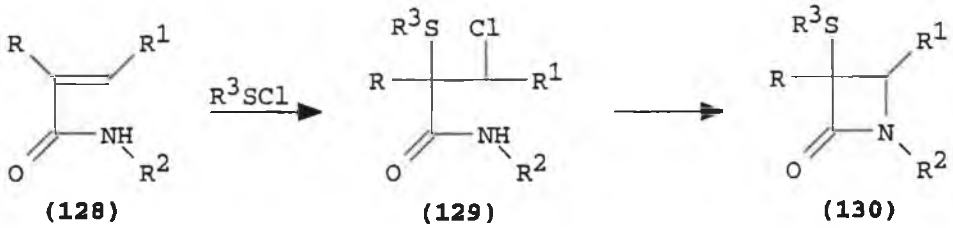
These workers concluded that a phase-transfer process was not involved. Not surprisingly, the method is limited to the cyclisation of α-disubstituted N-(3-halogenoacyl)amino acids (124).

An innovative copper-mediated N-C4 ring closure was used in the synthesis of novel 4-methylene-2-azetidinones by Joyeau and colleagues[77]. A variety of N-alkyl- and N-aryl-3-bromo-3-butenamides (126), when treated with copper powder in DMF at 130-135°C, gave the 4-methylene-β-lactams (127) in 12-85% yields.



R = Bz, OBz, aryl, CH_2CO_2-alkyl

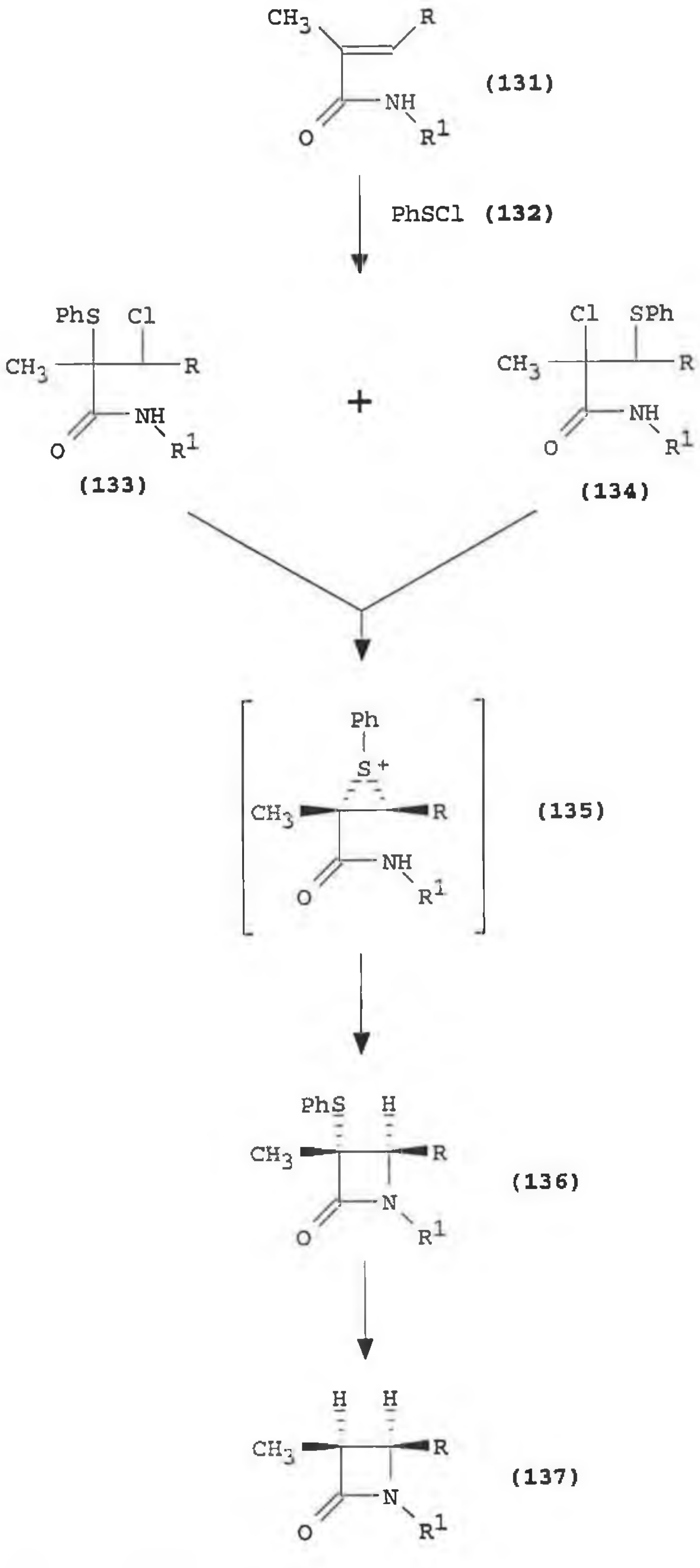
Seeking an improved method of β-lactam ring construction via N-C4 bond closure of β-halopropionamides, Kametani and associates[78] examined addition of sulfenyl halides to α,β-unsaturated amides (128), with an end to generating β-haloamides of the type (129). These researchers anticipated that subsequent intramolecular substitution, giving the β-lactams (130), would be facilitated by a neighbouring group effect.



However, reaction of the substituted acrylamides (131) with benzenesulfenyl chloride (132) produced a mixture of two adducts (133) and (134). Interestingly, treatment of the mixture of regioisomers with KOH under phase-transfer conditions afforded the β-lactams (136), as single stereoisomers. This outcome was rationalised by the formation of an episulfonium ion intermediate (135). Removal of the benzenesulfenyl group, using Raney nickel, furnished the 3-methyl-2-azetidinones (137) (Scheme 5).

Kametani's group later applied this novel "sulfeno-cycloamination" process to the synthesis of key intermediates of monobactam and nocardicin derivatives[79].

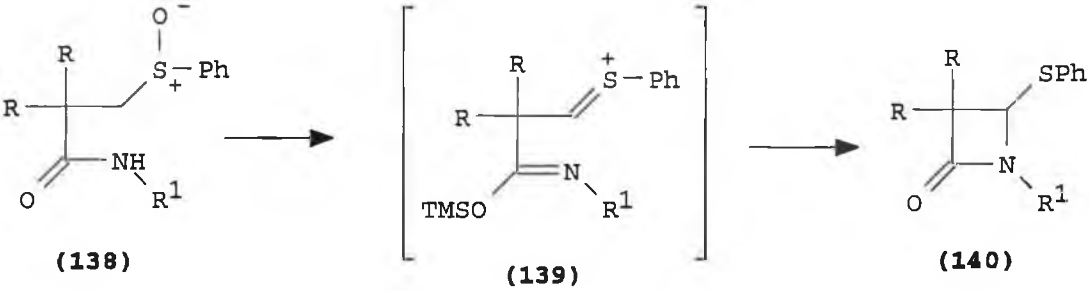
Scheme 5



R = H, CH_3
R^1 = Ph, Bz, p-CH_3O-C_6H_4, p-NO_2-C_6H_4

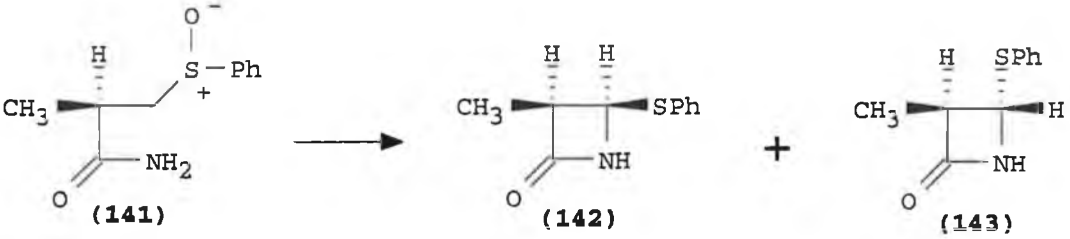
1.3.2 The Pummerer Rearrangement

In recent years, successful N-C4 ring closures to β-lactams via a Pummerer rearrangement of sulfoxides have been described. Kaneko[80] reported that when N-(phenylmethoxy)-2,2-dimethyl-3-(phenylsulfinyl)propionamide (138a) was treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and Et_3N in CH_2Cl_2, the 3,3-dimethyl-4-phenylthio-2-azetidinone (140a) was obtained in 51% yield, via a sulfonium ion intermediate (139a). Similarly, (138b) and (138c) were converted to the corresponding β-lactams (140b) and (140c).

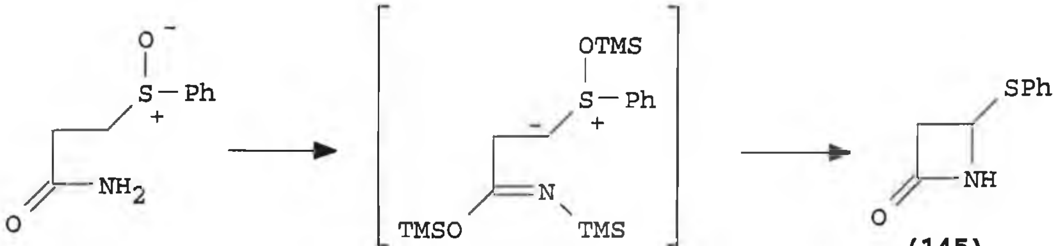


a: R = CH_3; R^1 = OBz
b: R = H; R^1 = OBz
c: R = R^1 = H

Interestingly, reaction of the amide (141), as a 1:1 mixture of diastereomers, with TMSOTf/Et_3N furnished a mixture of β-lactams (142) and (143) (cis:trans 2.7:1)[80].

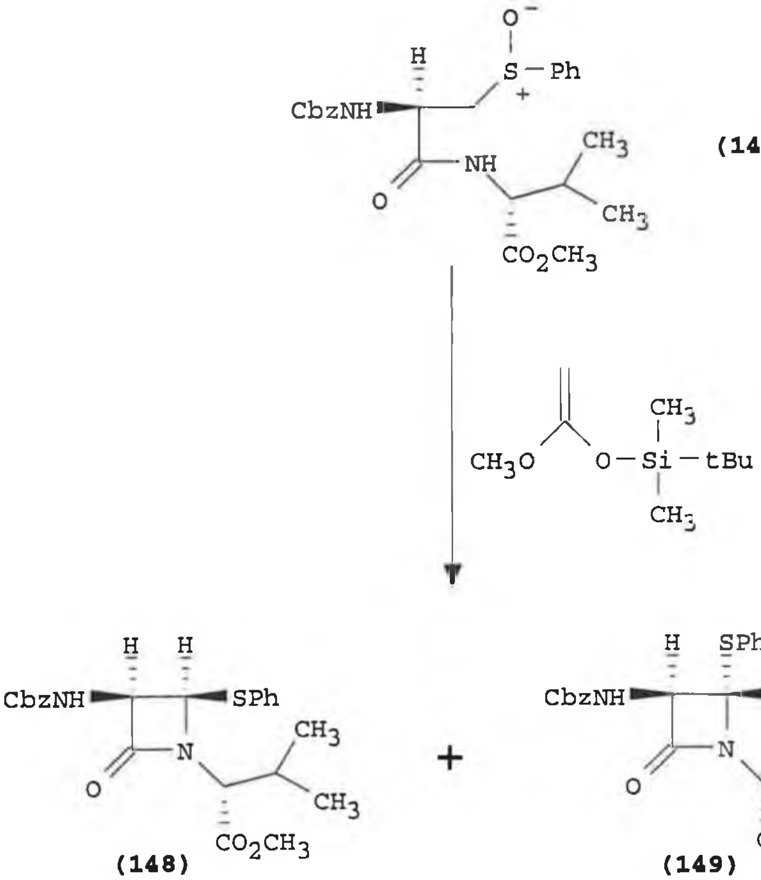


Stereoselectivity was again observed by Kaneko[81] in the application of this methodology to the synthesis of the 2-azetidinones (145), which are key intermediates for the synthesis of several bicyclic β-lactams. The (+)-sulfoxide (144) was reacted with TMSOTf and di-isopropylethylamine to afford the β-lactam (4S)-(145) in 76% yield and 67% enantiomeric excess. The corresponding (–)-sulfoxide (144) gave the 2-azetidinone (4R)-(145) in similar yield and optical purity.



(144) (145)

Treatment of the Arnstein tripeptide analogue (146), as a 37:63 mixture of diastereomers, with ketene methyl t-butyldimethylsilyl acetal (147) furnished the cis-β-lactam (148) in 40% yield, and the trans-β-lactam (149) in 15% yield[25]. To examine the stereoselectivity of this transformation, the mixture of amides (146) was separated chromatographically. Reaction of the more polar isomer (146a) with the acetal (147) gave the cis-β-lactam (148) predominantly, whereas the less polar isomer (146b) was converted preferentially to the trans-2-azetidinone (149).

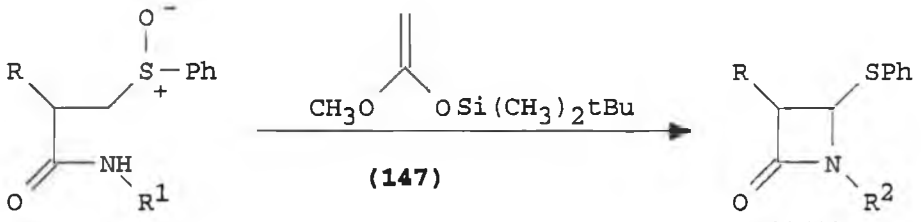


(146)

(147)

(148) (149)

Kita and colleagues extended this methodology to the preparation of a series of 4-phenylthio-2-azetidinones (151)[82]. N-Substituted and N-unsubstituted β-amido sulfoxides (150) were treated with 1-(dimethyl-t-butylsiloxy)-1-methoxyethylene (147) to produce the β-lactams (151) in high yields.

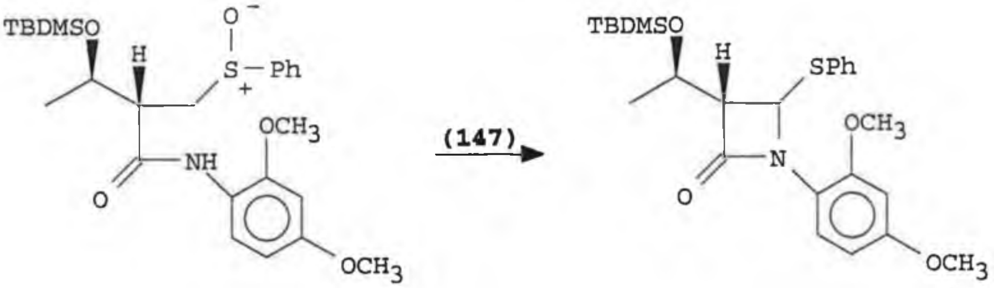


(150) (151)

R = H, CH_3, C_2H_5
R^1 = H, Bz, $CH(CH_3)Ph$, $CHPh_2$
R^2 = $SiMe_2tBu$, Bz, $CH(CH_3)Ph$, $CHPh_2$

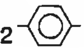
When an alkyl substituent (R) was present in the α-position of the starting amide (150), a cis-stereoselectivity was generally observed.

Subsequently, these researchers described a stereoselective synthesis of a chiral thienamycin intermediate[83], in which the optically active β-amido sulfoxide (152) was cyclised by reaction with the O-silylated ketene acetal (147), affording the 4-phenylthio-2-azetidinone (153) in 65% yield (4R:4S 4:1).

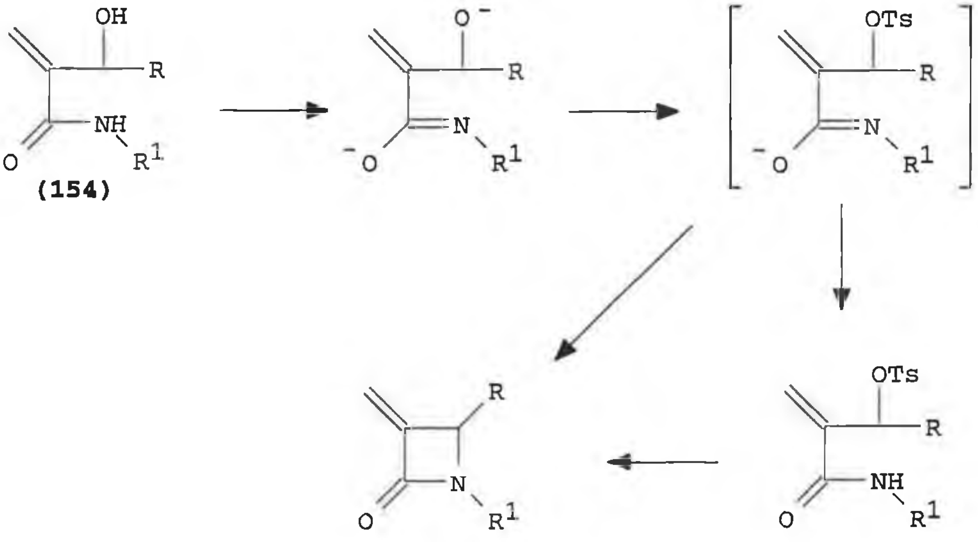


(152) (153)

1.3.3 Cyclisation of Mesylates and Tosylates

X = Ms = SO_2CH_3
X = Ts = SO_2  CH_3

Propionamides bearing a mesylate or tosylate group in the β-position can be cyclised to β-lactams by treatment with base. In 1981, Barrett and associates[84] reported the novel one-step reaction of the substituted acrylamides (154) with two equivalents of n-butyl lithium, followed by toluene-4-sulfonyl chloride, which produced the 3-methylene-2-azetidinones (156) in good yields. In some cases, the intermediate tosylates (155) were isolated, and cyclised under the influence of NaH in THF.



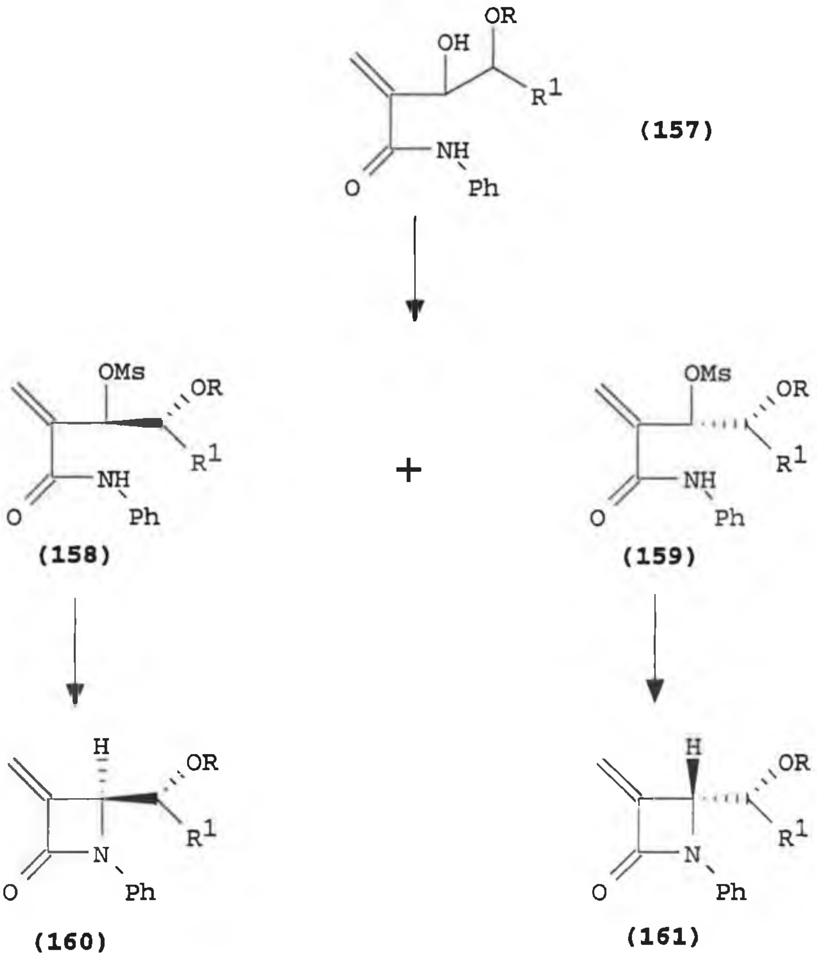
(154)

(156)

(155)

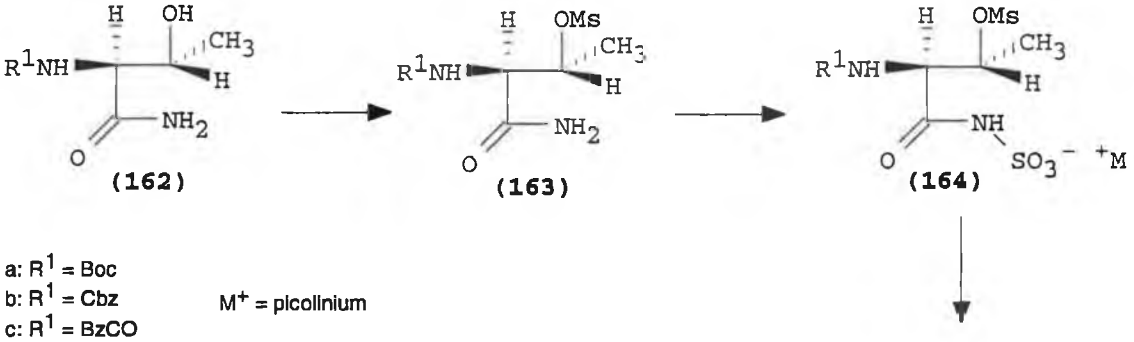
R = H, CH_3, C_2H_5, n-C_3H_7, n-C_7H_{15}
R^1 = cyclohexyl, Bz

A stereospecific synthesis of 3-methylene-2-azetidinones has more recently been described[85], which involves the N-C4 cyclisation of mesylate intermediates. The diastereomeric α-methylene-β-hydroxyamides (157), which could not be resolved, were reacted with methanesulfonyl chloride. The resultant mesylates (158) and (159), separable by column chromatography, were individually lactamised, using NaH in THF, to afford the β-lactams (160) and (161) respectively.



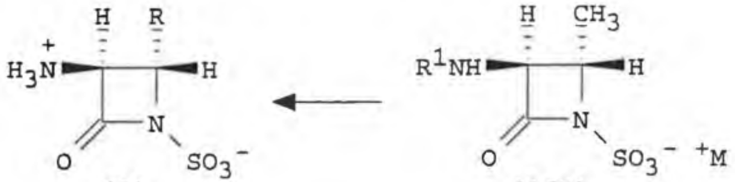
R = TBDMS
R^1 = alkyl

In the stereospecific total synthesis of 4-alkylated monobactams developed by Squibb chemists[5], the β-hydroxyamides (162), derived from L-threonine, were firstly mesylated and subsequently sulfonated, using 2-picoline–sulfur trioxide complex, to give the acylsulfamates (164). Noteworthy is the selective sulfonation of the primary amide of mesylate (163c) in the presence of a secondary amide group. Cyclisation was achieved by refluxing in a mixture of 1,2-dichloroethane and water containing potassium bicarbonate. Initial attempts to effect ring closure to the β-lactams (165) using potassium carbonate in refluxing acetone or acetonitrile gave highly variable results. Deprotection of the α-amino function of azetidin-2-ones (165) afforded (3S,4S)-trans-3-amino-4-methylmonobactamic acid (9: R = CH_3), a suitable starting material for the synthesis of active monobactams e.g. aztreonam (10)[1,6].



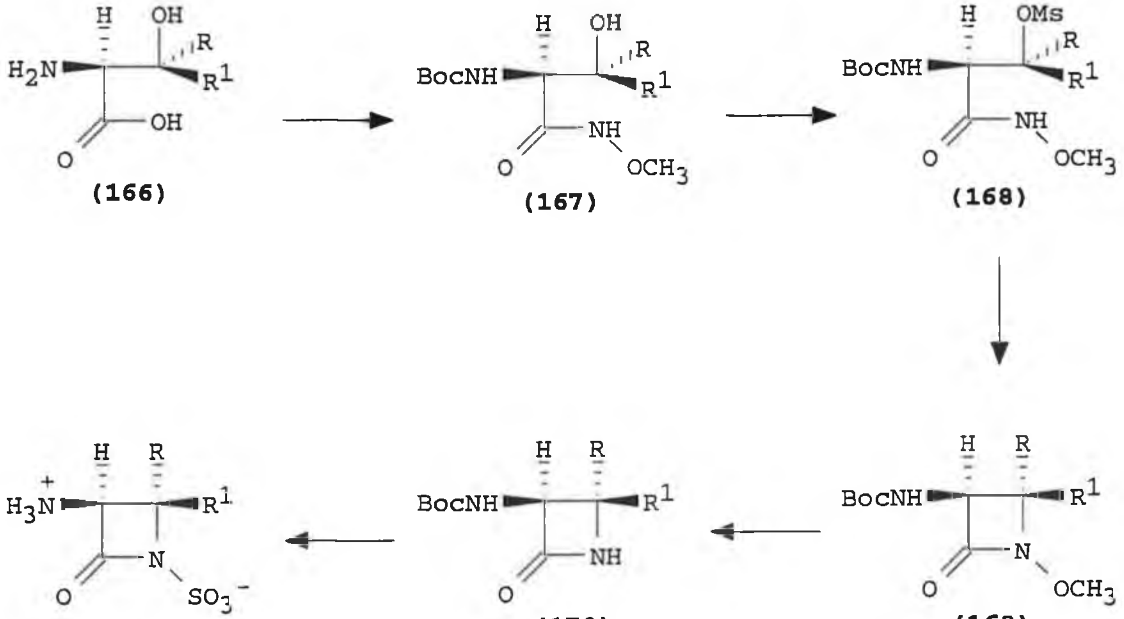
a: R^1 = Boc
b: R^1 = Cbz
c: R^1 = BzCO

M^+ = picolinium



(9) (165)

An additional route to monobactams from L-α-amino-β-hydroxy acids was described by these workers[86]. The L-amino acids serine (166a), allo-threonine (166b), and again threonine (166c), were used as starting materials. Protection of the α-amino group as the t-butoxycarbonyl derivative, and coupling with O-methylhydroxylamine produced the hydroxamates (167) in good yields. Conversion to the mesylates (168), followed by treatment with potassium carbonate in refluxing acetone, afforded the N-methoxy-2-azetidinones (169). Reductive cleavage of the N-O bond furnished the N-unsubstituted β-lactams (170). Sulfonation and finally deprotection of the α-amino function gave the target zwitterions (171). These procedures have been used to prepare the 3-AMA derivative (171c) on a multikilogram scale.

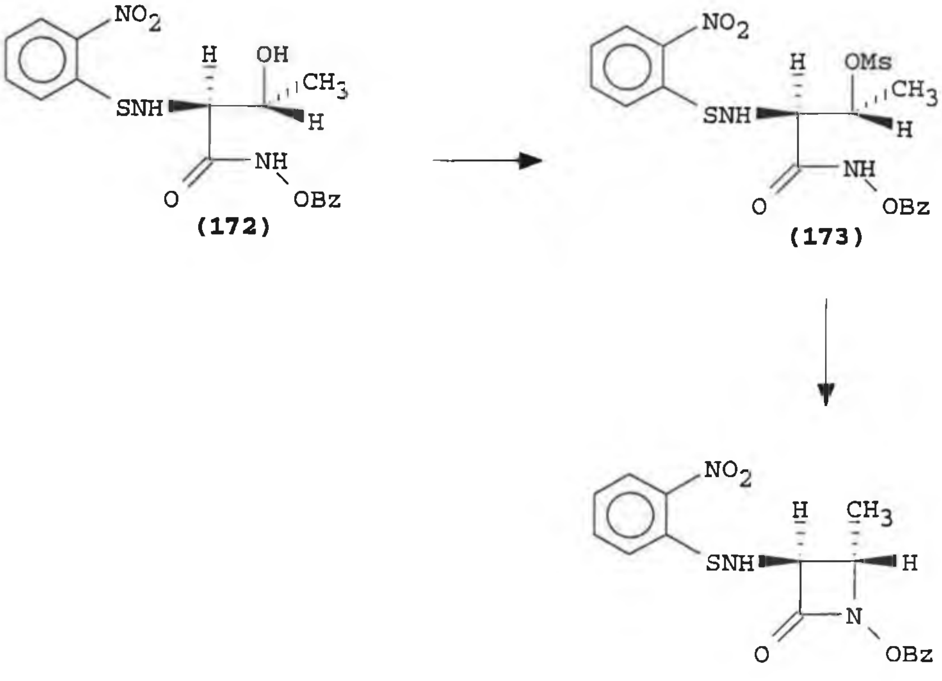


(166) (167) (168) (169) (170) (171)

a: $R = R^1 = H$
b: $R = H$; $R^1 = CH_3$
c: $R = CH_3$; $R^1 = H$

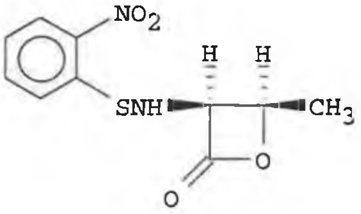
These two methods for the preparation of 4-alkylated monobactams are discussed in a later publication[87], where the structure-activity relationships of 4-alkylated monobactams are examined. Of particular relevance is the finding that the presence of 4-alkyl (especially methyl) groups in monobactams increases activity against Gram-negative bacteria, and enhances β-lactamase stability.

Gordon and co-workers[7] applied the methodology developed by Floyd et al.[86] to the synthesis of monosulfactams. Thus, the L-threonine-derived hydroxamate (172) was treated with methanesulfonyl chloride in pyridine to afford the mesylate (173), which was directly cyclised to the β-lactam (174) using K_2CO_3 in refluxing acetone.



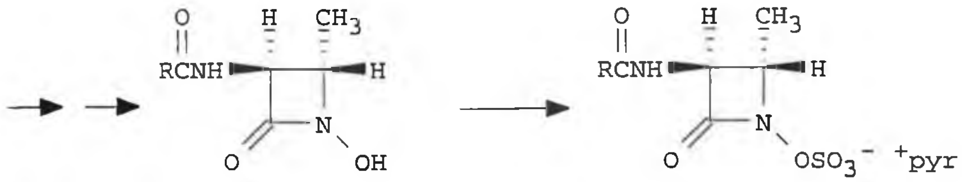
(172) **(173)** **(174)**

It should be noted that the β-lactone (175), formed by competitive N-mesylation, was also isolated in significant yield. However, no N-mesylation/β-lactone formation was observed in this system when N-Cbz or N-Boc protection was employed.



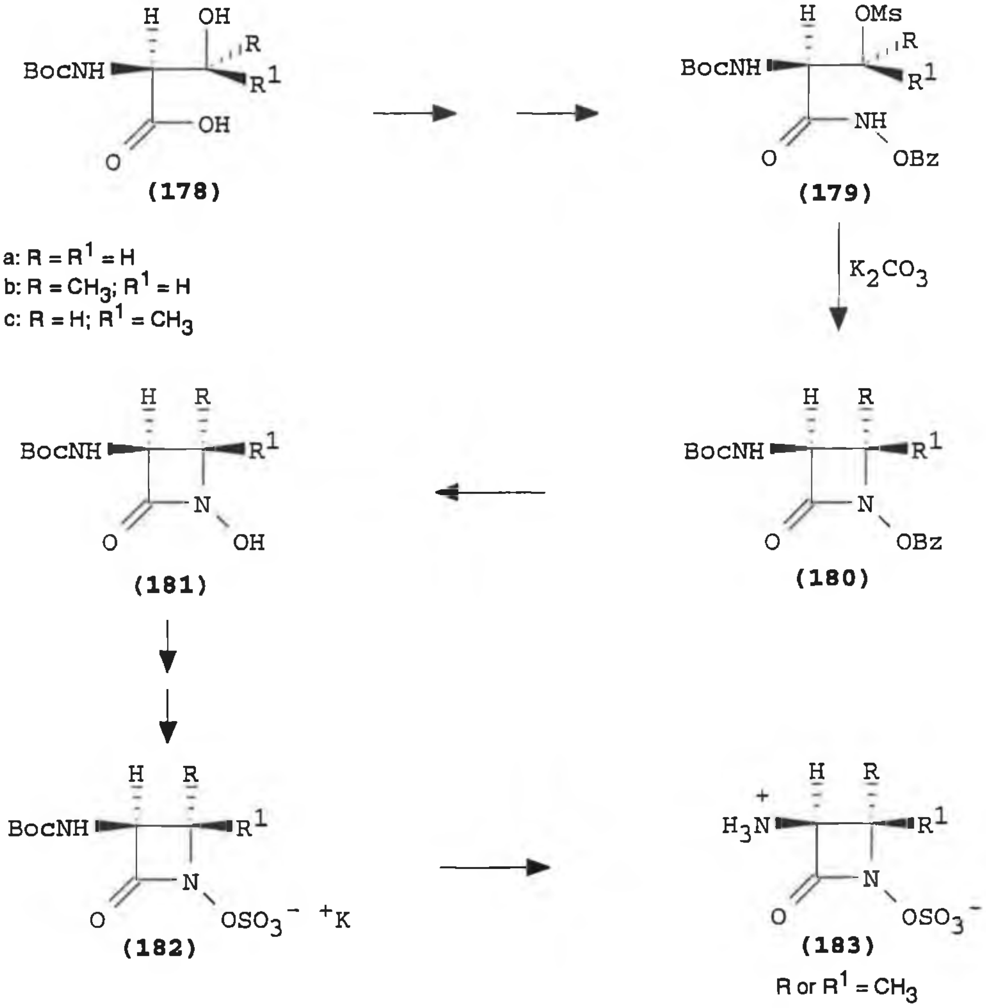
(175)

The N-benzyloxy-2-azetidinone (174) was converted to N-hydroxy-β-lactams of the type (176), which were sulfated to produce L-threonine-derived monosulfactams (177), displaying potent antimicrobial activity.

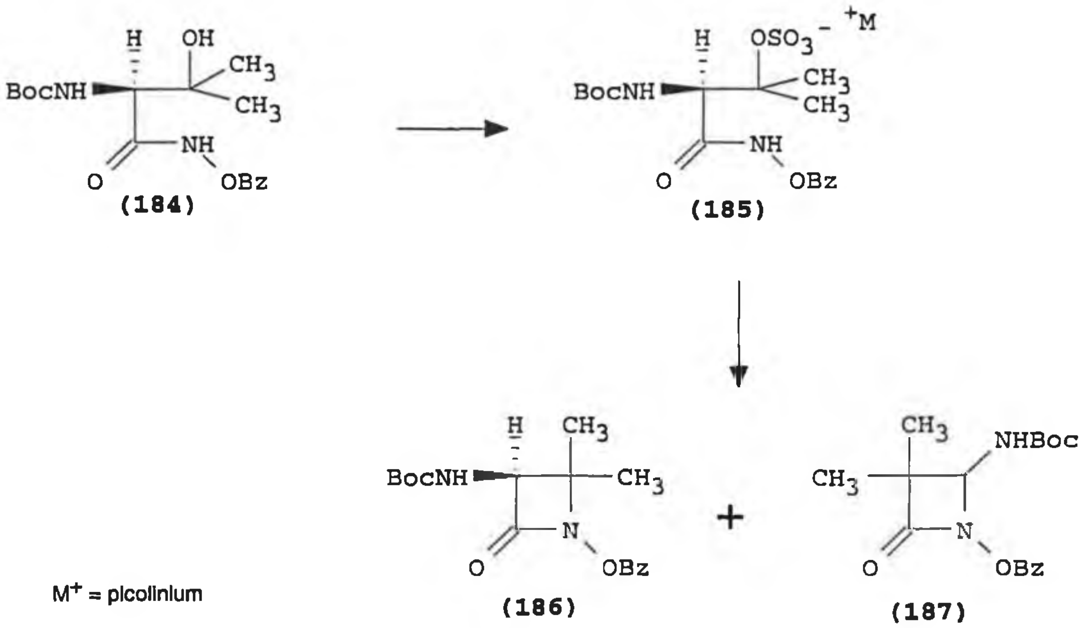


(174) **(176)** **(177)**

Taking a lead from Gordon et al.[7], Slusarchyk and colleagues[15] investigated the synthesis of related monosulfactams. The requisite N-hydroxy-2-azetidinones (181) were prepared by lactamisation of the mesylates (179), obtained from the Boc-derivatives of L-serine (178a), L-threonine (178b) and L-allo-threonine (178c), through the intermediacy of the N-benzyloxy-2-azetidinones (180). Sulfonation and deprotection of the β-lactams (181b) and (181c) proceeded smoothly, affording the target monosulfactam zwitterions (183b) and (183c) respectively. However, attempted deprotection of the 4-unsubstituted β-lactam (182a) resulted in decomposition.



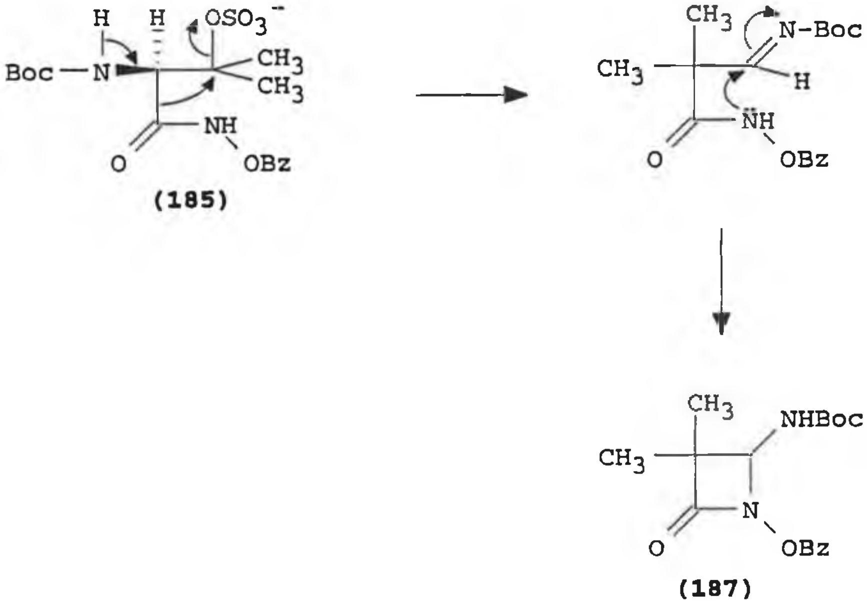
Slusarchyk and Godfrey[88] have described the synthesis of 4,4-dimethyl substituted monosulfactams, which were prepared using an interesting variation of the mesylate methodology. The (S)-hydroxamate (184), obtained from 3-hydroxyvaline, could not be transformed to the β-lactam (186) via mesylate displacement, since mesylation of the tertiary alcohol group was non-selective, due to steric hindrance. The authors found, however, that sulfonation of the hydroxamate (184), using 2-picoline·SO_3 complex, gave the sulfate (185) cleanly, which could be cyclised directly, with $KOH/K_2B_4O_7$, to afford the 4,4-dimethyl-N-benzyloxy-2-azetidinone (186), in 58% isolated yield, with retention of stereochemistry.



M⁺ = picolinium

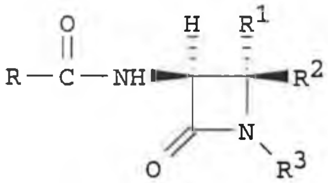
Unfortunately, substantial amounts of the isomeric β-lactam (187) were also formed, as a racemic mixture, by a 1,2-acyl migration-cyclisation process[89] (Scheme 6).

Scheme 6



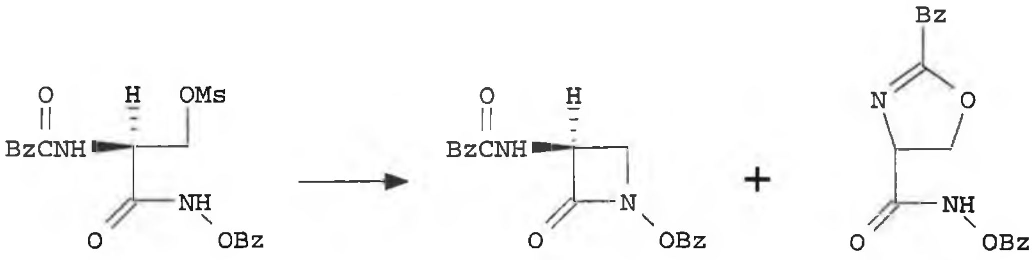
Despite the competitive formation of the rearrangement product (187), the availability of the 4,4-dimethylated intermediate (186), using the above route, allowed the preparation of a variety of potent antibiotics.

Krook and Miller[90], seeking an efficient route to the key monocyclic β-lactam intermediates (60),



(60) : R^3 = H, OH

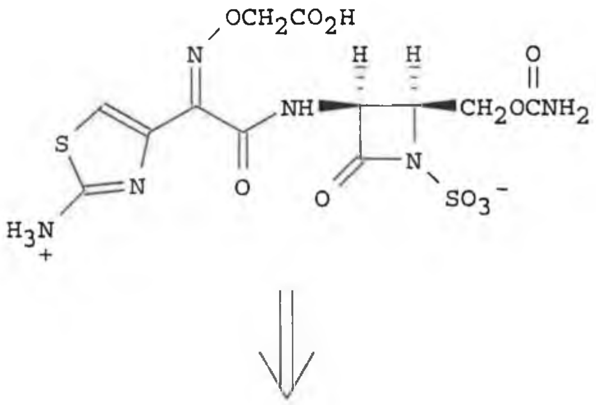
examined cyclisation of the mesylate (188) of (phenylacetyl)serine O-benzylhydroxamate, where simple acyl-protection of the α-amino function is employed. Initial attempts to effect ring closure to the 2-azetidinone (189) using, for example, $KHCO_3/CH_3CHCl_2/\Delta$, were hindered by the competitive formation of undesired products, such as the oxazoline (190).



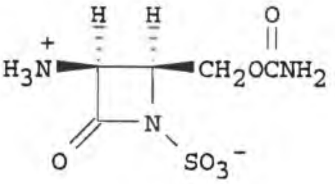
(188) **(189)** **(190)**

The required lactamisation was achieved, avoiding by-product generation, using one equivalent of potassium t-butoxide in DMF at –23°C. Under these conditions, the 4-unsubstituted β-lactam (189) was obtained in 75% recrystallised yield.

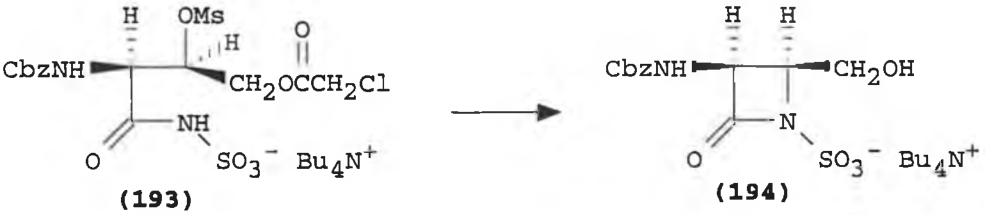
Chemists at Hoffmann-La Roche[91], involved in the commercial development of the antibiotic carumonam (191), have reported a practical synthesis of the chiral zwitterionic intermediate (192), in which formation of the β-lactam ring was accomplished by N-C4 cyclisation of a mesylate precursor.



(191)

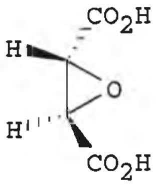

(192)

The mesylate (193), ultimately derived from L-ascorbic acid, was cyclised stereospecifically, with concomitant hydrolysis of the chloroacetyl protecting group, using Floyd's two-phase system[5] consisting of 1,2-dichloroethane and aqueous potassium bicarbonate, furnishing the 4-hydroxymethyl-2-azetidinone (194) in 87% yield.

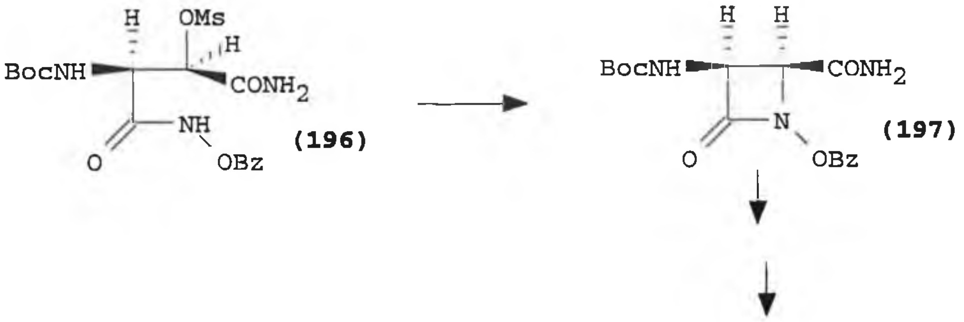

(193) **(194)**

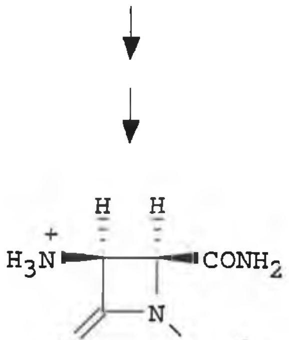
An improved process for the preparation of the monobactam (194) was later published[92], where either calcium L-threonate (derived from L-ascorbic acid) or L-(+)-tartaric acid was used as a starting material. Closure of the β-lactam ring was effected using the earlier procedure.

Kishimoto and colleagues[93] have also described synthesis of the 4-hydroxymethyl-2-azetidinone (194), but starting from (2R,3R)-epoxysuccinic acid (195).


(195)

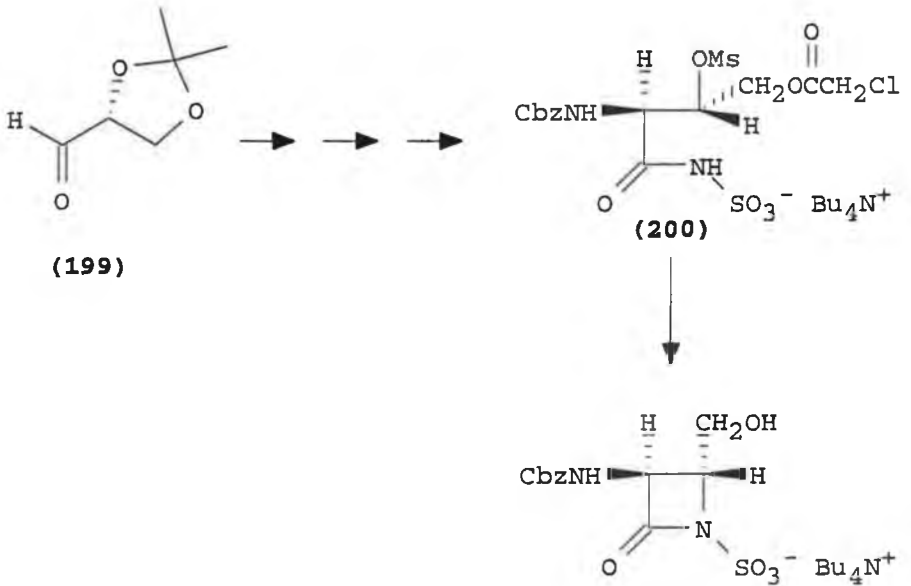
Again, the two-phase cyclisation methodology[5] was used to achieve β-lactam ring formation. In addition, these authors reported that the mesylate (196), obtained from the epoxide (195), on treatment with K_2CO_3 in hot acetone, afforded the N-benzyloxy-2-azetidinone (197) in 91% yield. This β-lactam was converted to the zwitterion (198), a precursor of an antibiotic structurally-related to, and having antibacterial activity comparable to carumonam (191).


(196) **(197)**



(198)

Herranz and co-workers[94] have recently detailed synthesis of the trans epimer of the 4-hydroxymethyl-2-azetidinone (194). The mesylate (200), derived from 2,3-O-isopropylidene-D-glyceraldehyde (199), was transformed to the β-lactam (201) in 95% yield, by refluxing in the two-phase 1,2-dichloroethane/aqueous $KHCO_3$ system.

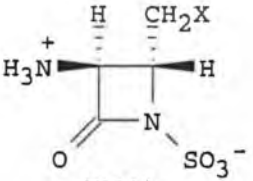


(199) (200) (201)

Initial attempts to prepare the β-lactam (201) by cyclisation of the mesylate (202), where the primary alcohol function is protected by tritylation, gave only the butenamide (203), and none of the β-lactamic compound.

(202) (203)

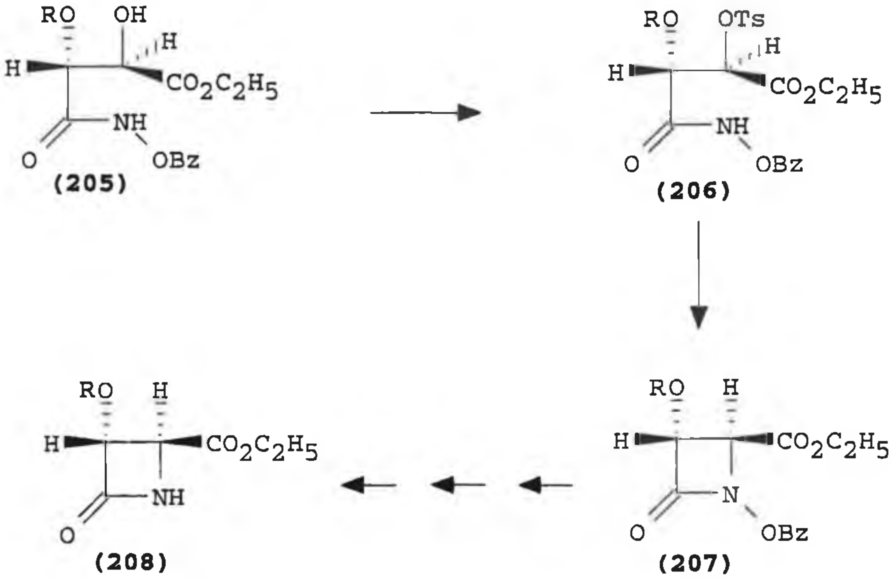
The 2-azetidinone (201) was used to prepare a range of 3,4-trans-4-(substituted methyl)monobactams of the type (204).



(204)

X = e.g. OMs, I

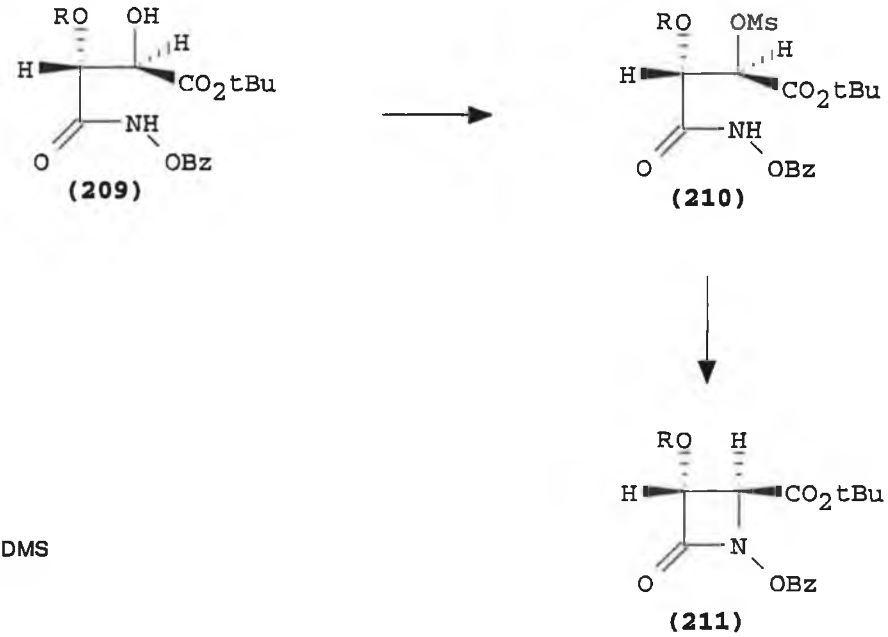
The use of L-tartaric acid as a chiral building block for the synthesis of 2-azetidinones with non-classical substitution at C3 and C4 has been reported by Gateau-Olesker et al.[95]. Cyclisation of the β-hydroxyhydroxamates (205) to the β-lactams (207) by, for example, mesylation followed by treatment with K_2CO_3 in acetone proved inefficient. Ring closure could only be achieved effectively via tosylation. The sulfonate esters (206), obtained in 80% yields, were lactamised using K_2CO_3/acetone, furnishing the azetidin-2-ones (207) in almost quantitative yields. Further manipulations provided the target 3,4-disubstituted chiral β-lactams (208).



(205) **(206)** **(207)** **(208)**

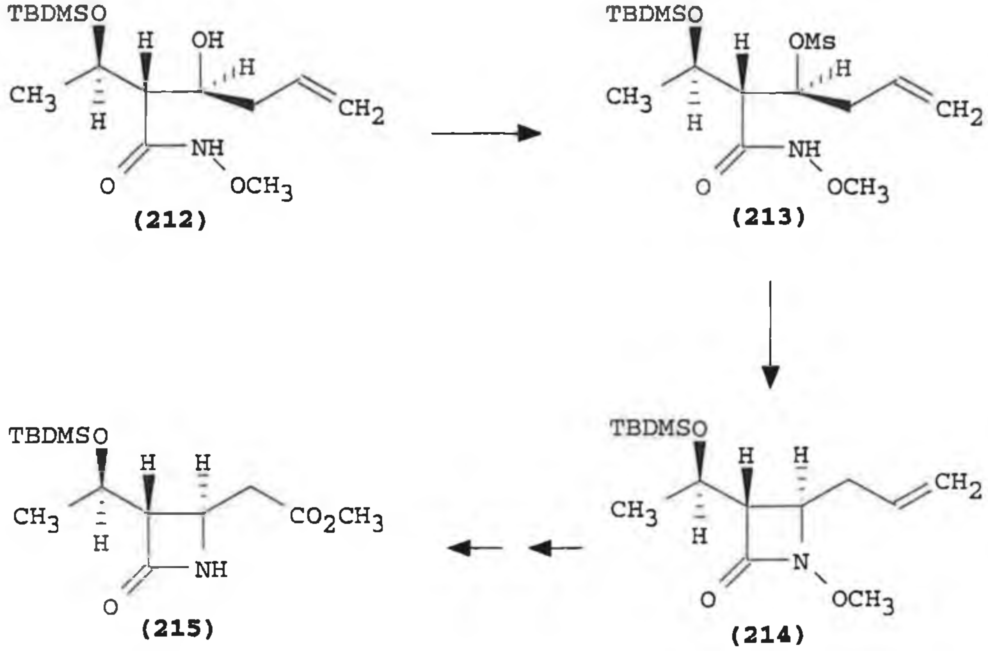
R = CH_3, Bz

L-Tartaric acid has also been used as a starting material by Kolasa and Miller in their synthesis of optically active substituted 3-hydroxy-4-alkoxycarbonyl-2-azetidinones (211)[96,97]. Contrary to the findings of Gateau-Olesker and associates[95], lactamisation was readily accomplished via a mesylate intermediate. Thus, the α-silyloxy-β-hydroxyhydroxamate (209) was converted to the corresponding mesylate (210), in 95% yield. Treatment with triethylamine in ethanol afforded the desired β-lactam (211) quantitatively.

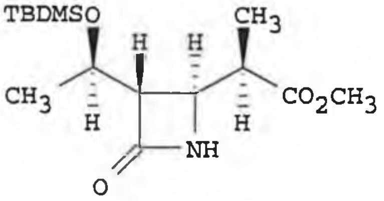


R = TBDMS

Mesylate displacement was again operative in an enantioselective synthesis of the versatile thienamycin precursor (215) by Evans and Sjogren[98]. The β-hydroxyhydroxamate (212) was reacted with methanesulfonyl chloride in pyridine to produce the mesyloxy compound (213), which was directly cyclised using Floyd's methodology (K_2CO_3/acetone/reflux) to give the N-methoxy-2-azetidinone (214) in 94% overall yield from (212). Further transformations provided the thienamycin precursor (215).

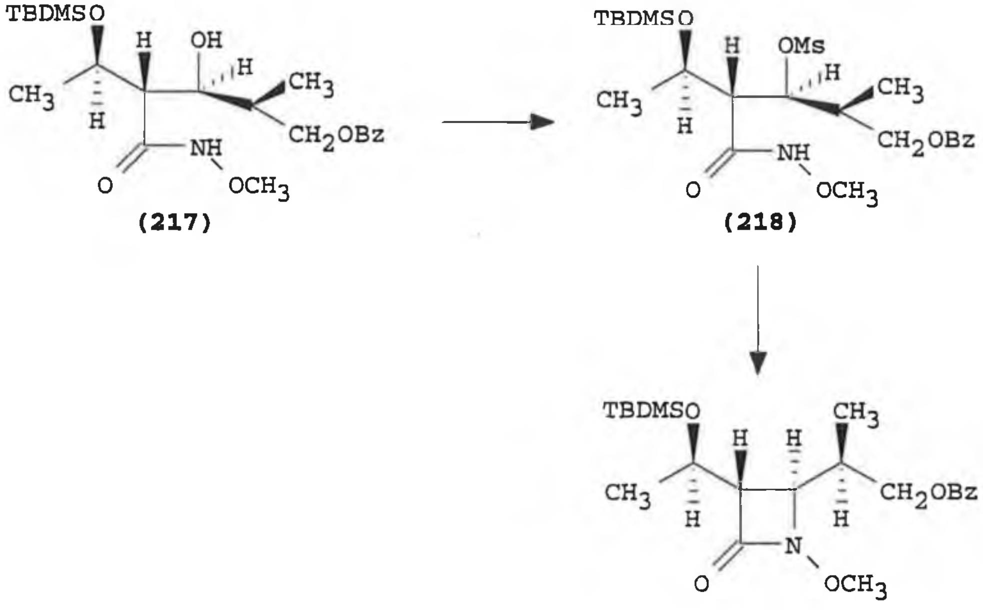


Shirai and Nakai have recently reported a novel synthetic approach to the related carbapenem precursor (216)[99].



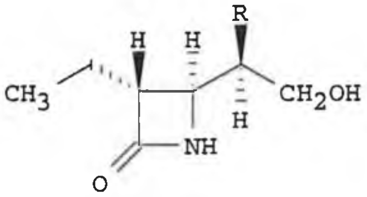
(216)

Mesylation of the hydroxamate (217) afforded the cyclisation substrate (218). Treatment with potassium carbonate in methanol at ambient temperature furnished the β-lactam (219), which was subsequently converted to the intended carbapenem intermediate (216).



(217) **(218)** **(219)**

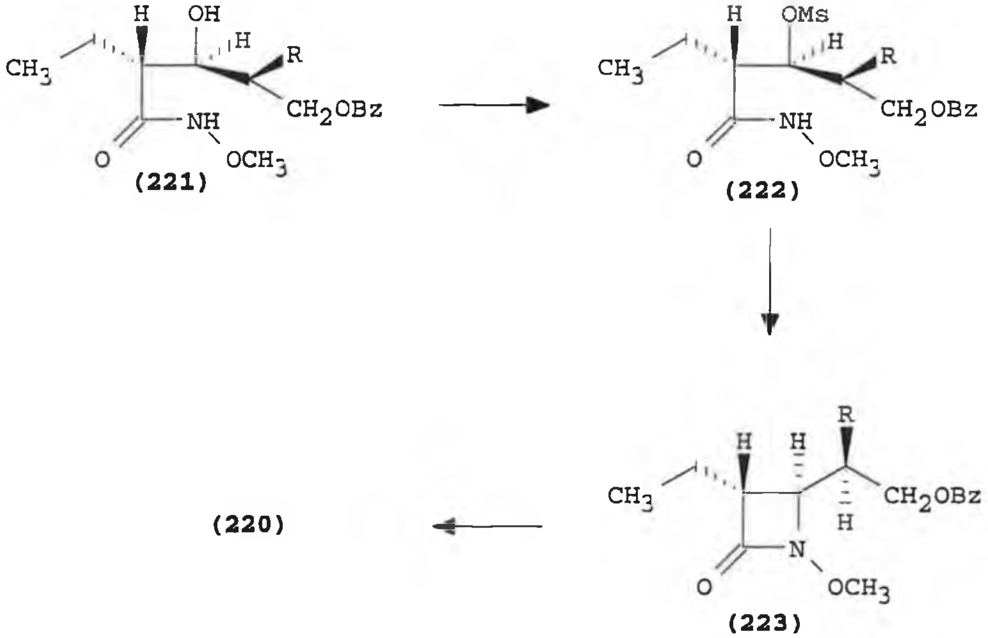
A stereoselective synthesis of the key carbapenem building blocks (220a) and (220b) has been devised by Gennari and Cozzi[100].



a: R = H
b: R = CH_3

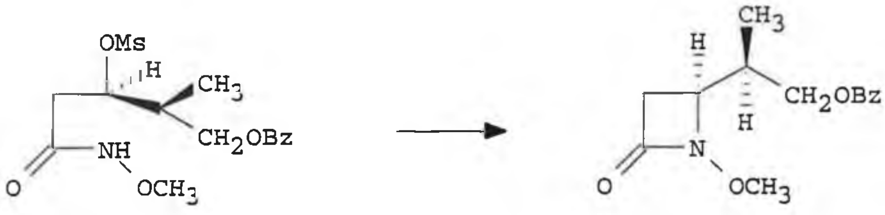
(220)

The β-hydroxyhydroxamate (221a) was transformed to the analogous β-mesyloxy compound (222a) and directly cyclised, under the influence of K_2CO_3 in refluxing acetone, to afford the N-methoxy-β-lactam (223a) as a 8:1 trans:cis mixture, in 70% overall yield from the hydroxamate (221a). Similarly, the homologous hydroxamate (221b) was converted to the β-lactam (223b). Dissolving metal reduction cleanly effected cleavage of both the N-O and O-Bz bonds, furnishing the target azetidin-2-ones (220a) and (220b).

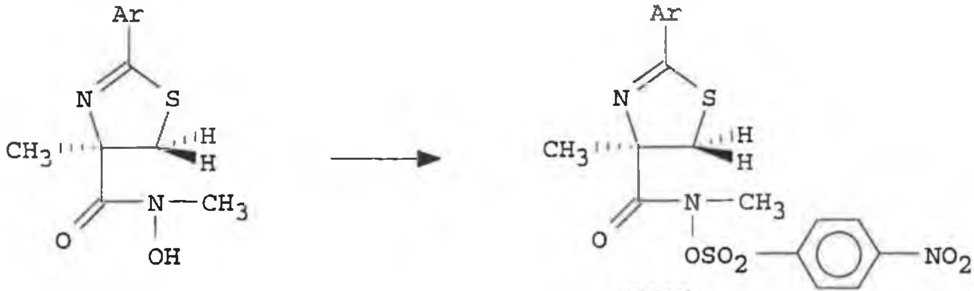

(221) **(222)** **(223)** **(220)**

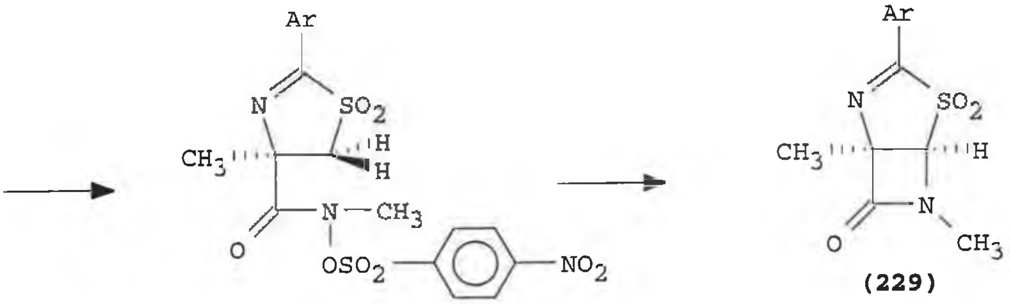
a: R = H
b: R = CH_3

These investigators have also utilised the K_2CO_3/acetone system to effect cyclisation of the α-unsubstituted-β-mesyloxyhydroxamate (224) to the β-lactam (225)[101].


(224) **(225)**

Finally, and somewhat unusually, the β-lactam ring has also been constructed via C4-N cyclisation[102]. In this case, the β-lactam precursor was designed so that the amide nitrogen, bearing a sulfonate leaving group, would undergo nucleophilic attack by an anionic β-carbon atom, under the influence of base. The hydroxamic acid (226) was reacted with p-nitrobenzenesulfonyl chloride to give the sulfonate (227). Oxidation with m-chloroperbenzoic acid provided the sulfone (228), which was treated with potassium t-butoxide in THF to afford the bicyclic β-lactam (229) in moderate yield.


(226) **(227)**



(228)

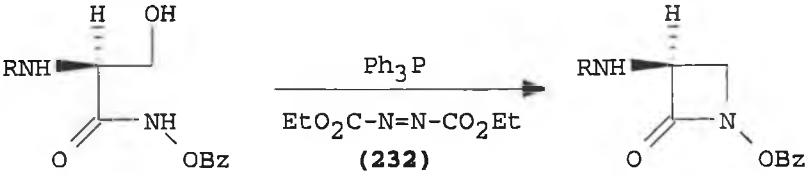
(229)

Ar = p-CH_3O-C_6H_4

1.3.4 The Mitsunobu Reaction

Chiral α-amino acid derivatives are especially attractive starting materials for the synthesis of β-lactams. As previously indicated, β-halo-α-amino acid amides and hydroxamates can be cyclised directly to β-lactams, under the influence of base. However, chiral β-hydroxy-α-amino acids are much more readily accessible than their β-halo counterparts, but, methods for the lactamisation of substrates with β-hydroxy groups have required conversion of the alcohol function to a suitable leaving group, e.g. mesylate, prior to N-C4 bond closure. Miller and colleagues, aware of these restrictions, sought to develop an efficient direct method for the cyclisation of β-hydroxylated β-lactam precursors, and found that the required intramolecular dehydration could be achieved by applying the Mitsunobu reaction[103-105].

The first use of this methodology in construction of the β-lactam ring was reported in 1979[58]. The protected L-serine hydroxamates (230) and (231) were treated with one equivalent each of triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) (232) in THF to afford the corresponding (3S)-1-benzyloxy-3-(protected amino)-2-azetidinones (73) and (74), in good yields, following chromatographic purification and recrystallisation.



(230) : R = Cbz
(231) : R = tBoc

(73) : R = Cbz
(74) : R = tBoc

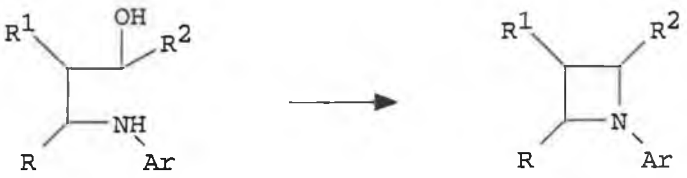
No undesired elimination product was detected, and the reaction proceeded with retention of chirality at C3. More recently, Fujita and co-workers have used this method to prepare the β-lactam (73) in 77% yield[106].

In order to test whether this cyclisation procedure would allow stereochemical control at both C3 and C4 of the eventual β-lactam, Miller and associates[59] investigated cyclisation of the protected L-threonine hydroxamate (233a) and L-allo-threonine hydroxamates (233b) and (233c). Reaction with TPP/DEAD in THF furnished the corresponding 4-methyl-2-azetidinones (234), as single diastereomers, in good yields, after chromatography. No products arising from racemisation and/or elimination were detected, and the β-lactams (234) were formed by clean inversion of configuration at the β-position during ring closure.

(233) **(234)**

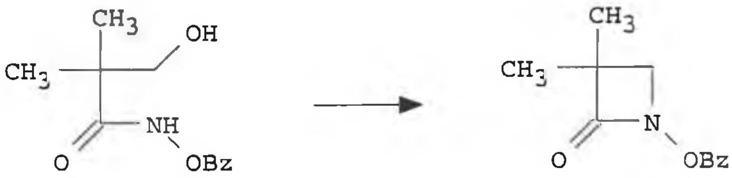
a: R = Boc; $R^1 = CH_3$; $R^2 = H$
b: R = Cbz; $R^1 = H$; $R^2 = CH_3$
c: R = Boc; $R^1 = H$; $R^2 = CH_3$

Although NMR analysis of crude reaction mixtures obtained using this strategy indicated that essentially quantitative conversion to the desired β-lactams had occurred, isolated yields were invariably lower, owing to difficulties in the chromatographic separation of the β-lactamic compounds from the by-product diethyl hydrazodicarboxylate (H_2DEAD). To circumvent this, Miller's group searched for an alternative procedure, avoiding the use of DEAD. Combinations of TPP and a halogen source had previously been used extensively to convert alcohols to halides[107,108] and even 1-(arylamino)-3-alkanols (235) to N-arylazetidines (236)[109].



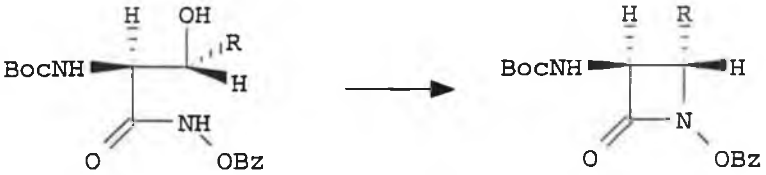
(235) **(236)**

Accordingly, Miller et al.[59] examined the reaction of the model compound O-benzyl-2,2-dimethyl-3-hydroxypropanohydroxamate (237) with equimolar amounts of TPP and carbon tetrachloride in CH_3CN, in the presence of triethylamine (to preform the hydroxamate nitrogen anion). Under these conditions, N-(benzyloxy)-3,3-dimethyl-2-azetidinone (69) was isolated in 94% yield.



(237) **(69)**

These modified Mitsunobu conditions (TPP/CCl_4/Et_3N) were then applied to the cyclisation of the serine and threonine hydroxamates (231) and (233a).

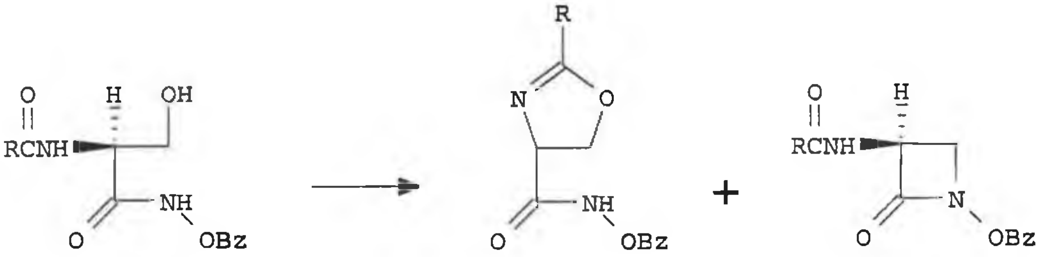


(231) : R = H
(233a) : R = CH$_3$

(74) : R = H
(234a) : R = CH$_3$

Ring closure proceeded smoothly, affording the β-lactams (74) and (234a) in improved isolated yields, again with retention of configuration at C3 and clean inversion at C4. The 1-(benzyloxy)-2-azetidinone (74), prepared as described above, was subsequently used as a key intermediate in the synthesis of protected forms of 3-ANA^{110}.

Hoping to extend the generality of this process to the synthesis of 3-acylamino-β-lactams, Miller and colleagues studied the cyclisation of the L-serine O-benzylhydroxamates (238a) and (238b), using the TPP/CCl$_4$/Et$_3$N system. In each case, the major product was an oxazoline (239), and not the expected β-lactam (240).

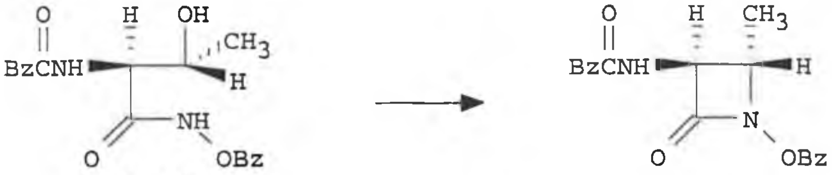


(238)
a: R = Ph
b: R = Bz

(239)

(240)

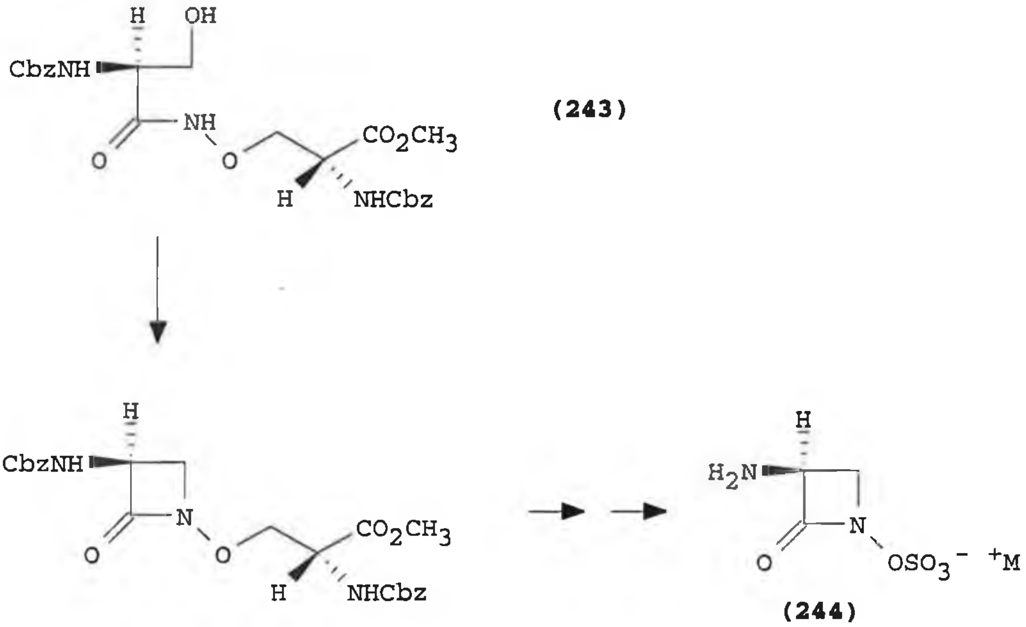
Repeating the cyclisation of the phenylacetyl derivative (238b), but using TPP/DEAD as the mediator, minimised detrimental oxazoline formation. Fortunately, the target β-lactam (240b) was readily separated chromatographically from H$_2$DEAD. Later, Gordon an co-workers^{7} employed Miller's route (TPP/DEAD) to the β-lactam (240b), and similarly cyclised the L-threonine hydroxamate (241) to the β-lactam (242), in their preparation of the first synthetic monosulfactams.



(241)

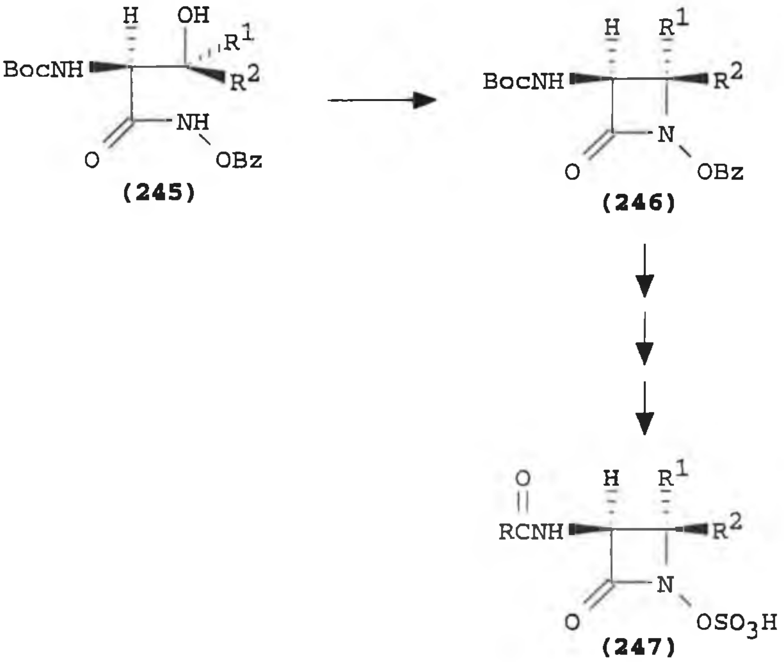
(242)

Application of the Mitsunobu reaction has also provided access to the unsubstituted monosulfactam nucleus (244)^{7,15}. Here, the key β-lactam ring closure was achieved by treatment of the hydroxamate (243) with TPP and DEAD.


(243)

(244)

Yoshida and colleagues[111] have conducted an extensive study of the synthesis and biological activity of 4-substituted monosulfactams. The 2-azetidinones (246), prepared in good yields by cyclodehydration of the appropriate hydroxamates (245), under the influence of excess TPP/CCl_4/Et_3N, were further modified to give monosulfactams of the type (247).

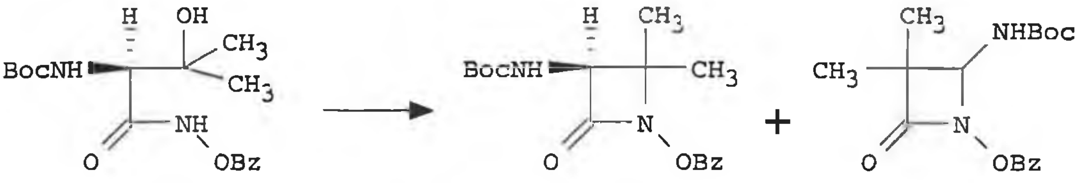

(245)

(246)

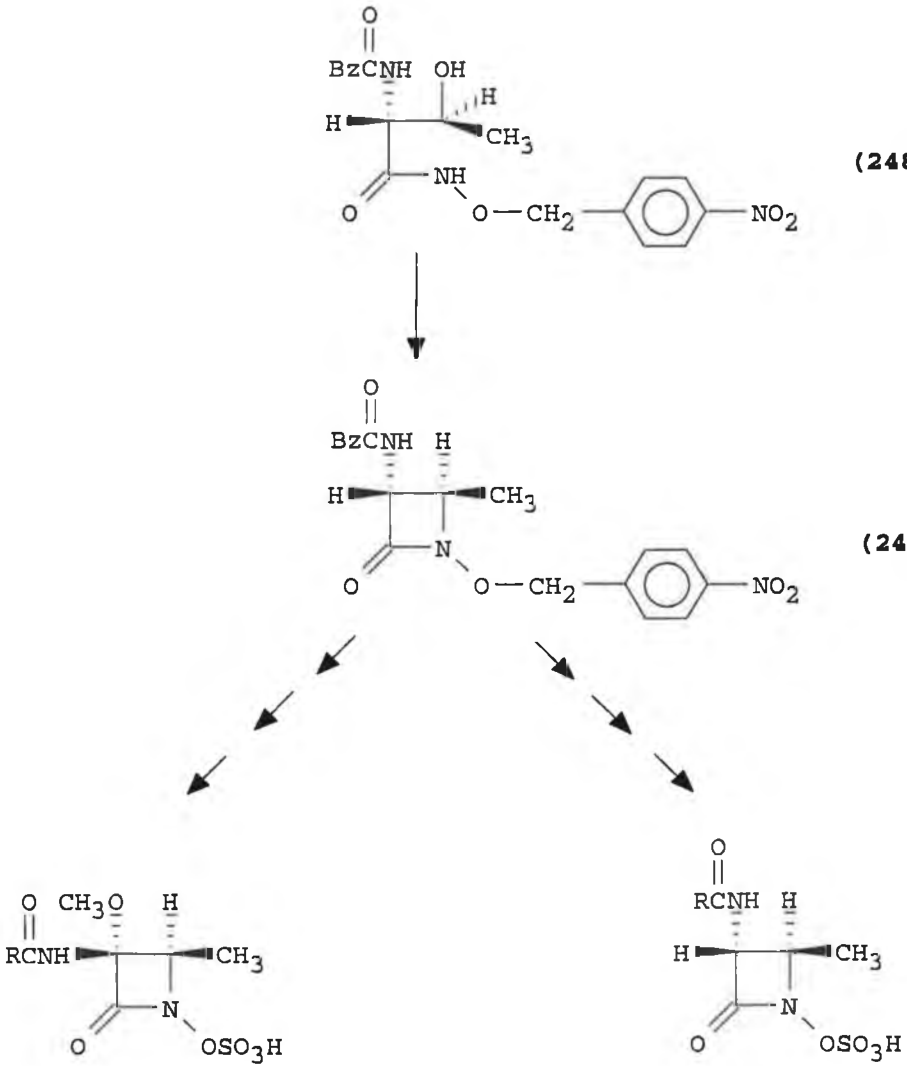
(247)

R^1, R^2 = H, CH_3, C_2H_5, $CH(CH_3)_2$, Ph

It should be noted that although cyclisation of the tertiary hydroxyamino acid hydroxamate (184) was reported to afford the 4,4-dimethyl-2-azetidinone (186) in 64% yield, Squibb chemists[88,89] later revealed that ring closure of the substrate (184) using TPP/CCl_4/Et_3N produced a 1:1 mixture of the desired β-lactam (186) and the isomeric rearrangement product (187).

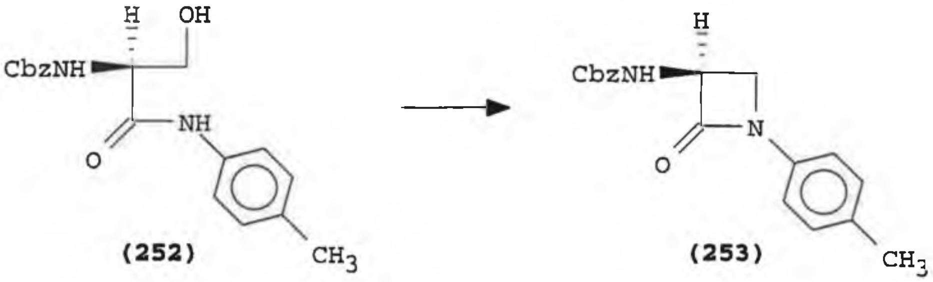


Yoshida's group also reacted the N-phenylacetyl-D-threonine hydroxamate (248) with TPP/CCl_4/Et_3N, and obtained the 4-methyl-2-azetidinone (249), in 89% yield. This β-lactam was used to prepare the monosulfactams (250) and (251).

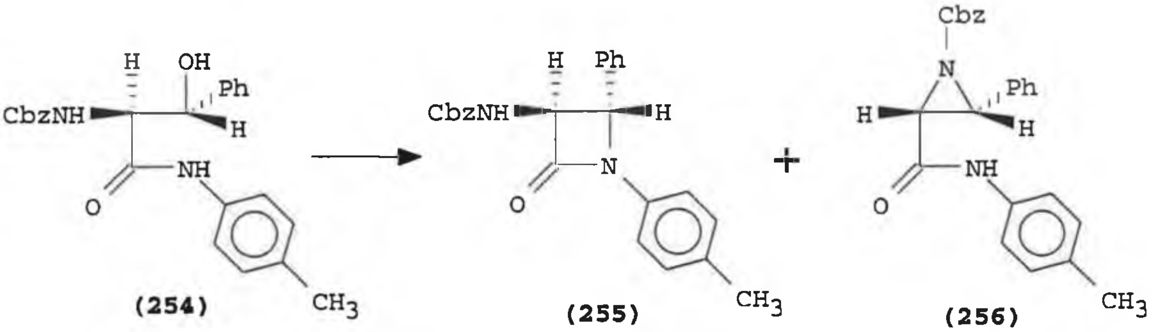


These researchers examined the influence of the C4-substituents on the antibacterial effectiveness of the above monosulfactams, (247), (250) and (251), and concluded that, in particular, the 4-methylated species exhibited excellent activity versus Gram-negative bacteria, echoing Cimarusti's findings[87] in the study of 4-alkylated monobactams.

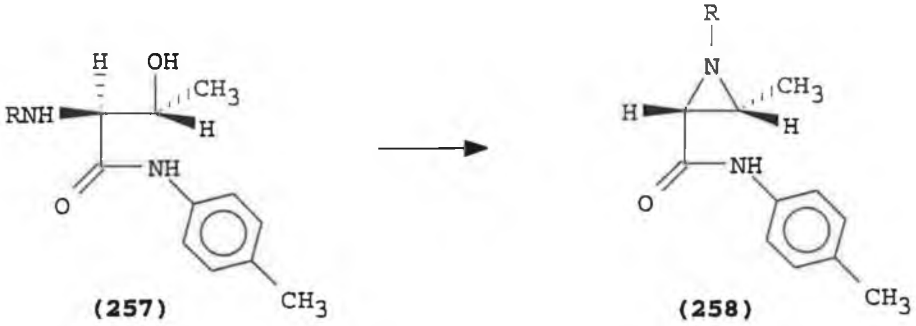
Independently from Miller, Bose and colleagues were also involved in the early adaptation of the Mitsunobu reaction to the synthesis of β-lactams, but using β-hydroxy-α-amino acid amides, not hydroxamates, as substrates[112,113]. Treatment of the p-toluidide (252) of N-carbobenzyloxy-L-serine with TPP/DEAD in THF was reported to produce the N-aryl-2-azetidinone (253) in 53% yield, with retention of chirality.



However, reaction of the analogous phenylserine derivative (254) with TPP/DEAD gave the β-lactam (255) and the aziridine (256) in approximately equal amounts.

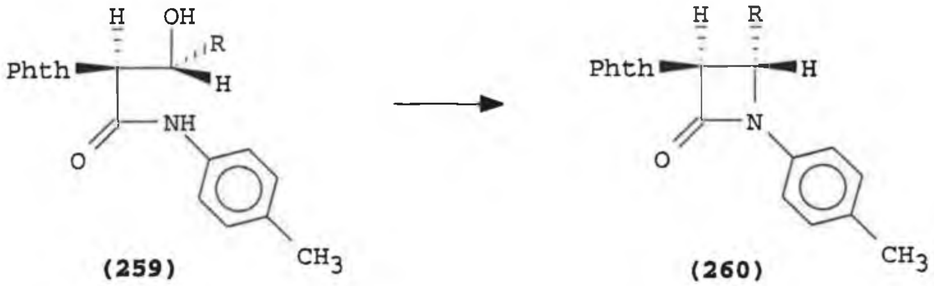


In addition, the L-threonine p-toluidides (257), under the TPP/DEAD reaction conditions, furnished the aziridines (258). No β-lactams were formed.



a: R = Cbz
b: R = Boc

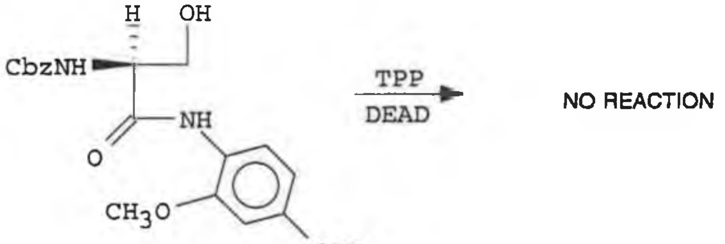
Aziridine formation was prevented by protection of the α-amino group as the phthalimido derivative. Thus, the alternatively protected p-toluidides (259) cyclised smoothly to the corresponding azetidin-2-ones (260), under the influence of TPP and DEAD.



(259) (260)

R = H, CH_3, Ph

In stark contrast to the facile lactamisation of the N-Cbz-L-serine p-toluidide (252), the related 2',4'-dimethoxybenzamide (261) reportedly failed to undergo any reaction with TPP/DEAD.



(261)

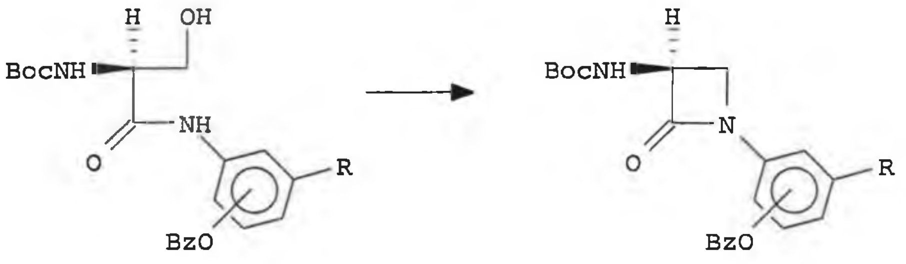
Furthermore, this anilide, and also the substrates (257a) and (262), when reacted with DEAD and either tributylphosphine [$P(nBu)_3$] or triethylphosphite [$P(OEt)_3$], formed the acrylamides (263).

(263)

(261) : R = Cbz; R^1 = H; R^2 = R^3 = OCH_3
(257a) : R = Cbz; R^1 = CH_3; R^2 = H; R^3 = CH_3
(262) : R = Boc; R^1 = H; R^2 = H; R^3 = OCH_3

These workers also examined the effect of varying the phosphorus and hydrazine reagents on the cyclodehydration of the N-Cbz-L-serine p-toluidide (252).

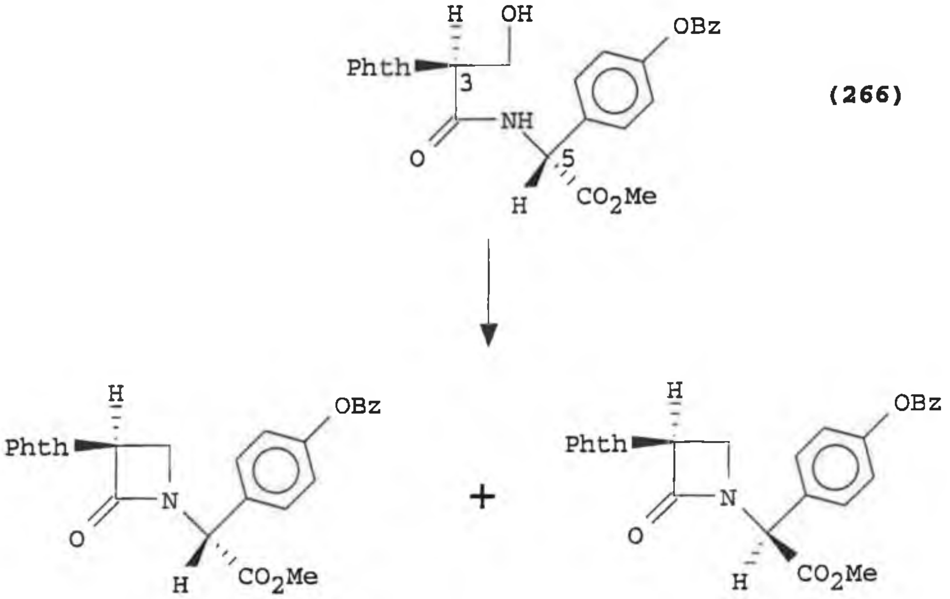
Recently, Costerousse et al.[114] have reported the Mitsunobu-type cyclisation of L-serine-derived benzyloxyphenylamides (264). Treatment with TPP/DEAD afforded the substituted N-(hydroxyphenyl)-2-azetidinones (265), in good yields. Secondary products, present in variable amounts, were acrylamides and aziridines.



(264) (265)

R = H, CF_3

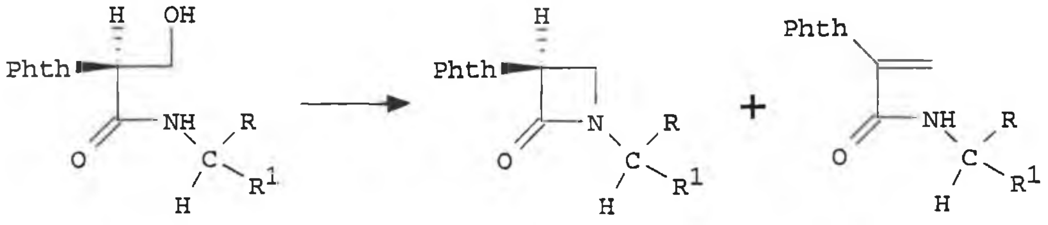
Townsend and Nguyen[115] have applied the Mitsunobu reaction to the synthesis of 3-ANA derivatives. The optically active dipeptide (266), derived from N-phthaloyl-L-serine, was treated with 2.5 equivalents each of TPP and DEAD to produce a 2:1 mixture of the β-lactams (267) and (268).



(266)

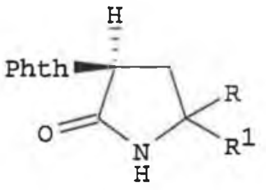
(267) (268)

This cyclisation was reported to proceed cleanly, yielding the β-lactamic species to the exclusion of acrylamide or γ-lactam products, arising from anion formation at C3 or C5 respectively. This remarkable selectivity prompted Miller and Mattingly to examine more closely the reaction of substituted serylamides of the type (269) with TPP/DEAD[116]. In general, mixtures of the desired β-lactam (270) and the 1,2-elimination product (271) were obtained.



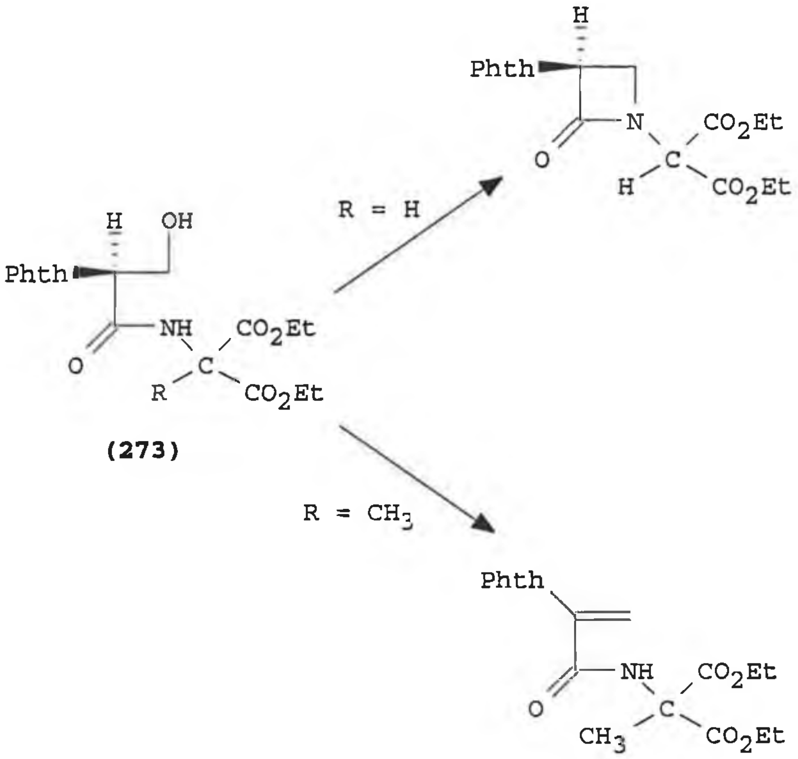
(269) (270) (271)

Intriguingly, the trend that emerged indicated that increased acidity of the α'-CH bond of the amide (269) increased the relative amount of β-lactam (270) formed, and, that the TPP/DEAD mediated reaction was not proceeding through the straightforward pathway where the most acidic position becomes alkylated, which would lead to the formation of γ-lactams (272).



(272)

In fact, the presence of an acidic proton on the carbon attached to the amide nitrogen was shown to be necessary for successful β-lactam ring closure of the serylaminomalonates (273). Under Mitsunobu conditions, substrate (273a) furnished the β-lactam (274) in 82% yield, whereas the C-methylated analogue (273b) gave predominantly the dehydropeptide (275).



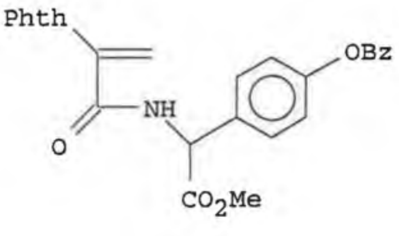
(274)

(273)

(275)

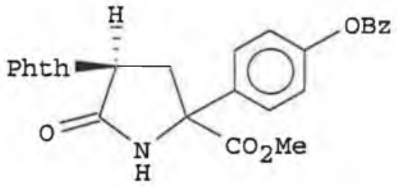
a: $R = H$
b: $R = CH_3$

In a more detailed study of the preparation of 3-ANA derivatives, Townsend and colleagues conceded that, under their original cyclisation conditions (2.5 equivalents of TPP/DEAD), 7% of the dehydroalanylpeptide (276) was formed alongside the β-lactams (267) and (268)[117,118].



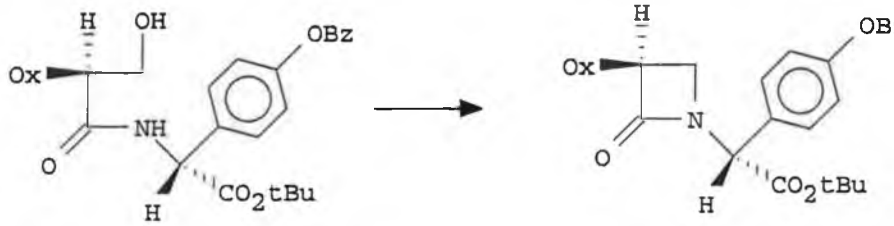
(276)

The replacement of TPP by triethylphosphite (2.5 equivalents) reduced the rate of ring closure, but gave a more favourable ratio (6.8 : 1) of the desired β-lactam (267) and its epimer (268). In this case, the γ-lactam (277) was formed as a by-product.



(277)

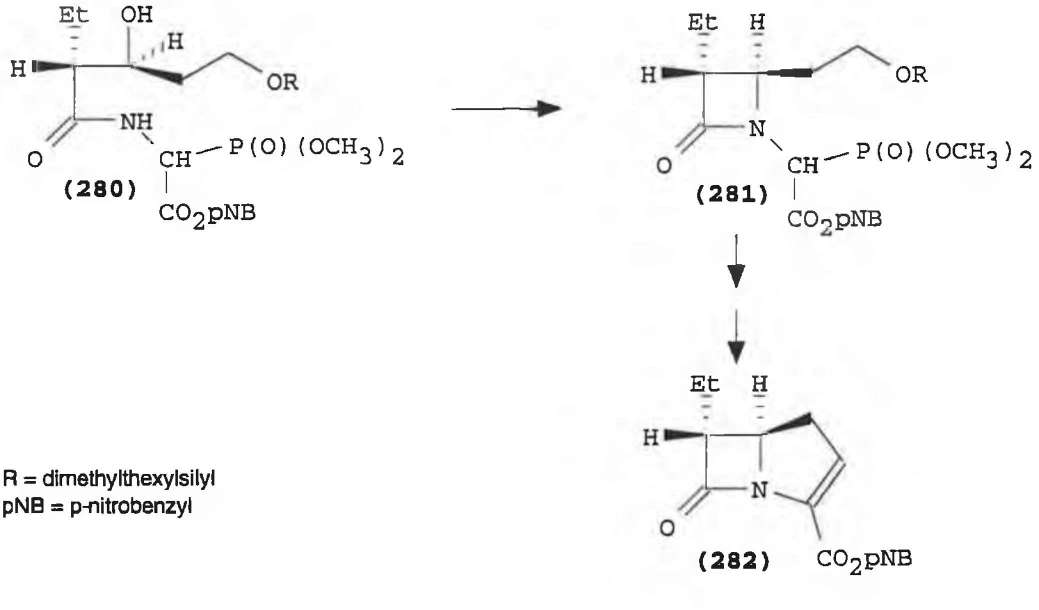
By using only equimolar amounts of $P(OEt)_3$/DEAD, the reaction was optimised, and a >50:1 mixture of the 3-ANA derivatives (267) and (268) could be obtained, accompanied only by <3% of the γ-lactam (277). These modified Mitsunobu conditions were later used in the total synthesis of nocardicins A and G, where cyclisation of the amide (278) furnished the 2-azetidinone (279), as a single diastereomer, in 83% yield[119].



(278) **(279)**

Ox = 4,5-diphenyl-4-oxazolin-2-one

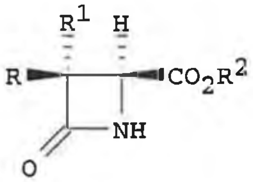
Recently, cyclisation of the β-hydroxyamide (280), using TPP and di-(t-butyl)-azodicarboxylate, has been described[120]. The monocyclic β-lactam (281), which could only be isolated in 66% yield, owing to difficulties in the chromatographic removal of the by-product triphenylphosphine oxide, was further transformed to the carbapenem nucleus (282).



(280) **(281)** **(282)**

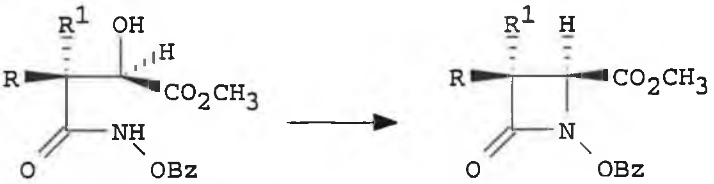
R = dimethylthexylsilyl
pNB = p-nitrobenzyl

Returning our attention to the early Mitsunobu cyclisation of hydroxamate substrates, Miller and associates[121] extended the scope of this reaction to the synthesis of optically pure 3-substituted 4-(alkoxycarbonyl)-2-azetidinones (283), which are versatile intermediates for the preparation of a variety of bicyclic β-lactams.



(283)

The hydroxamates (284), derived from malic acid, were reacted with TPP/DEAD to afford the 1-(benzyloxy)-3-ethyl-4(S)-carbomethoxy-2-azetidinones (285), as single diastereomers, in 75% yields.



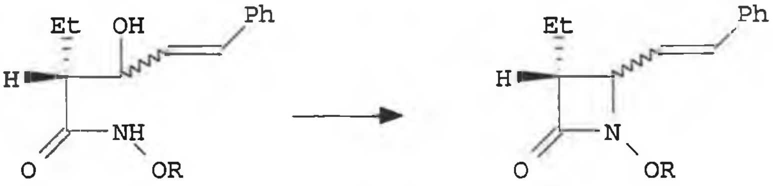
(284) **(285)**

a: R = H; R^1 = Et
b: R = Et; R^1 = H

Similarly, Gennari and colleagues have reported that treatment of the O-benzylhydroxamate (286), present as a 6:4 mixture of <u>anti</u> and <u>syn</u> isomers, with an equivalent amount of TPP/DEAD, resulted in the formation of the epimeric β-lactams (287) (cis:trans 6:4), in 80% yield[122].

(286) **(287)**

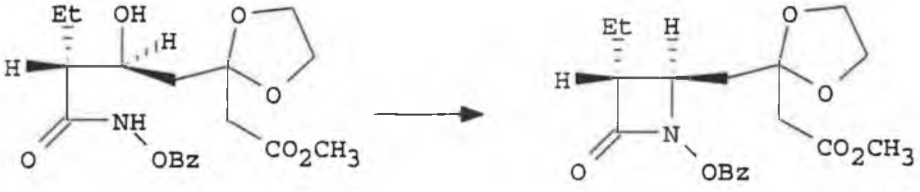
These researchers also described cyclisation of the hydroxamates (288), using the same reagents, to the cis- and trans-β-lactams (289), separable by chromatography.



(288) **(289)**

R = CH_3, Bz

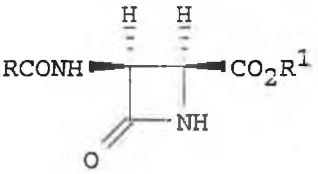
While investigating routes to carbapenem precursors, Jung and Miller[123] employed the TPP/DEAD combination to effect ring closure of the β-hydroxyhydroxamate (290) to the trans-substituted monocyclic β-lactam (291), which was obtained in 73% yield.



(290) (291)

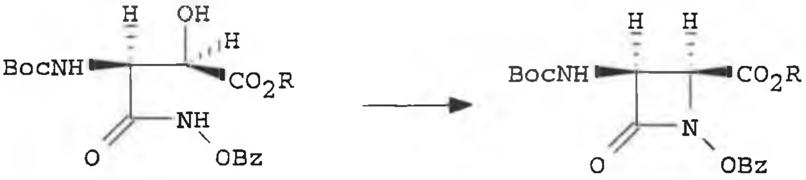
Unfortunately, complete chromatographic removal of H_2DEAD from the β-lactam product (291) was difficult. Alternatively, this 2-azetidinone could be prepared cleanly from the hydroxamate (290) via a mesylate intermediate, which was cyclised with K_2CO_3 in methanol. Later, Hsiao, Ashburn and Miller found that the use of diisopropyl azodicarboxylate (DIAD) instead of DEAD in the Mitsunobu cyclisation gave the desired β-lactam (291) in at least 93% e.e.[124].

The utility of the Mitsunobu reaction was further demonstrated by the synthesis of chiral 4-(alkoxycarbonyl)-2-azetidinones (292), bearing protected amino substituents at C3 of the β-lactam ring[125].



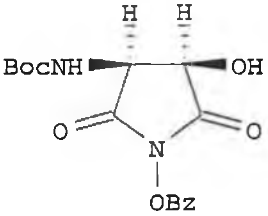
(292)

Treatment of the β-hydroxyaspartyl-α-hydroxamate (293a) with the standard TPP/DEAD mixture provided the N-(benzyloxy)-cis-2-azetidinone (294a) in 78% recrystallised yield. However, reaction of the corresponding methyl ester (293b) with TPP and DIAD gave the desired β-lactam (294b) in only 58% yield, since this hydroxamate was prone to competitive cyclisation to the succinimide (295).



a: R = Et
b: R = Me

(293) (294)



(295)

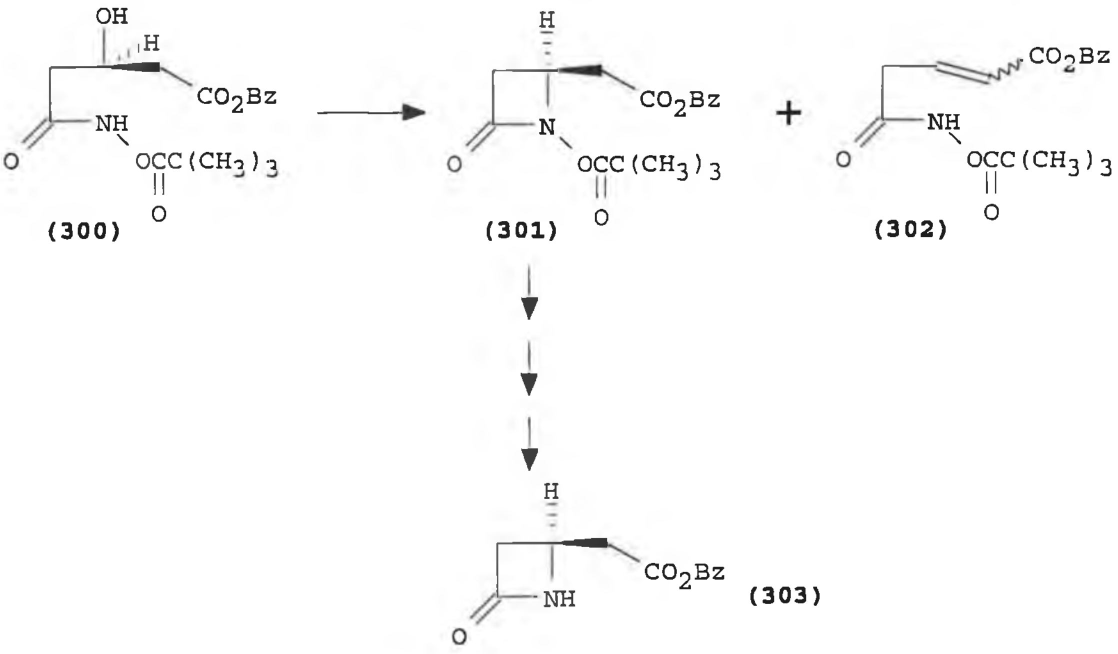
Interestingly, the isomeric methyl ester substrate (296), under the influence of TPP/DEAD, was reported to undergo lactamisation to the trans-2-azetidinone (297), in 67% yield, without detrimental imide formation.

(296) (297)

TPP/DEAD–mediated cyclisation of the O-benzylhydroxamate (298), where the α-amino group is protected as the Ox-derivative, furnished the cis-β-lactam (299) in 69% yield[123].

(298) (299)

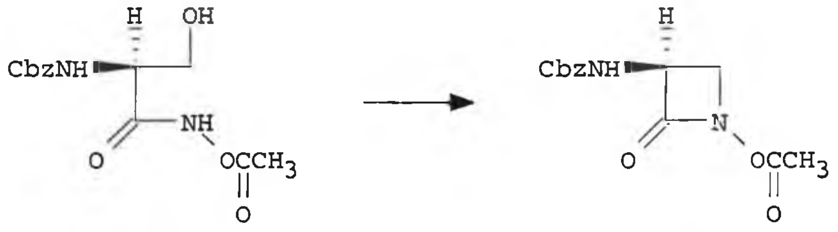
The Mitsunobu reaction has also been applied to the ring closure of O-acylhydroxamates. Aiming to prepare 4-[[(benzyloxy)carbonyl]methyl]-2-azetidinone (303), a suitable nucleus for elaboration to the basic carbapenem framework, Morrison and Miller[126] attempted cyclodehydration of benzyl O-pivaloyl-β-hydroxyglutarohydroxamate (300) using the TPP/DEAD system. Under these conditions, the β,γ-unsaturated hydroxamates (302) were produced in 78% yield, and the desired N-(pivaloyloxy)-2-azetidinone (301) was obtained in only 22% yield.



(300) (301) (302) (303)

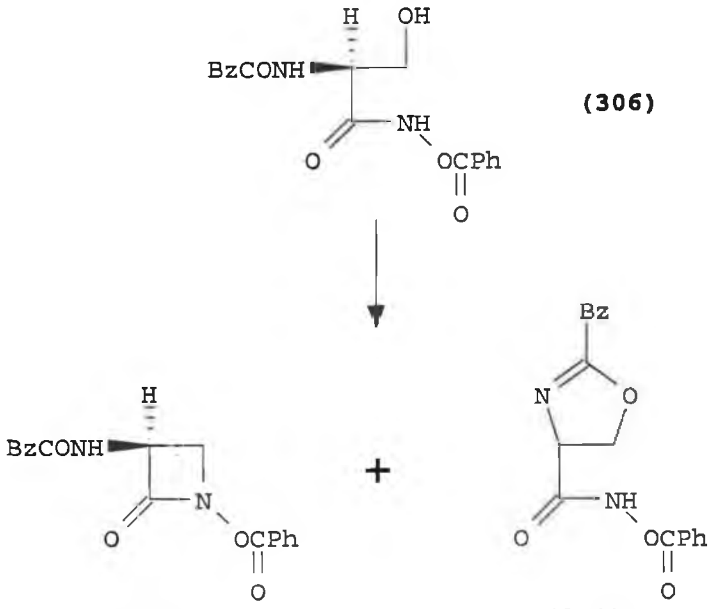
Replacing TPP by triphenylphosphite [$(PhO)_3P$] increased the required reaction time, but afforded only the β-lactam (301), in 70% yield, which was subsequently converted to the target carbapenem precursor (303).

A practical synthesis of intermediates useful for the preparation of a variety of monocyclic β-lactam antibiotics, such as monosulfactams, has been described, based on the N-C4 bond closure of substituted α-amino-β-hydroxy-O-acylhydroxamates[8]. The carbamate-protected L-serine hydroxamate (304) cyclised smoothly, on reaction with TPP/CCl_4/Et_3N, giving the N-acetoxy-2-azetidinone (305) in 66% yield.



(304) (305)

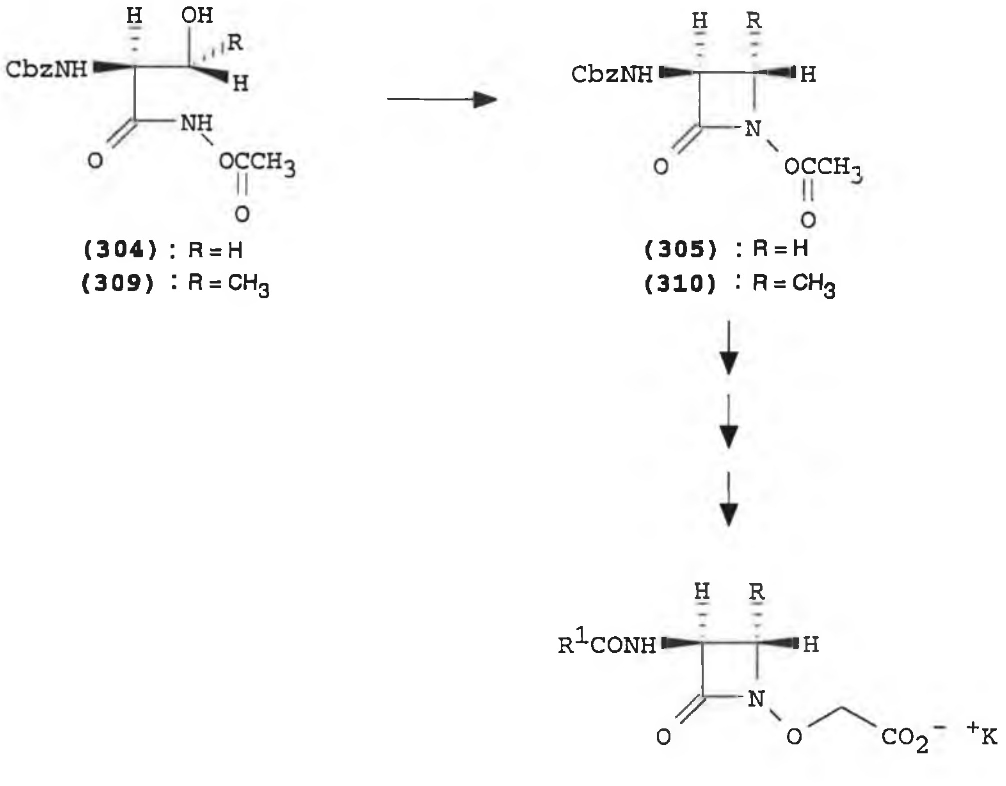
In contrast, the amide-protected hydroxamate (306), when treated with TPP and DIAD, afforded a 1:5 mixture of the corresponding β-lactam (307) and the oxazoline (308).



(306)

(307) (308)

Woulfe and Miller[17] later employed TPP/DEAD to effect cyclisation of the O-acylhydroxamate (304) and the analogous L-threonine-derived substrate (309) to the N-acetoxy-2-azetidinones (305) and (310) respectively, in their synthesis of oxamazins of the type (311), which possess significant activity against Gram-negative bacteria.

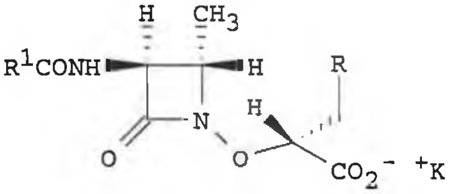


(304) : R = H
(309) : R = CH_3

(305) : R = H
(310) : R = CH_3

(311) : R = H, CH_3

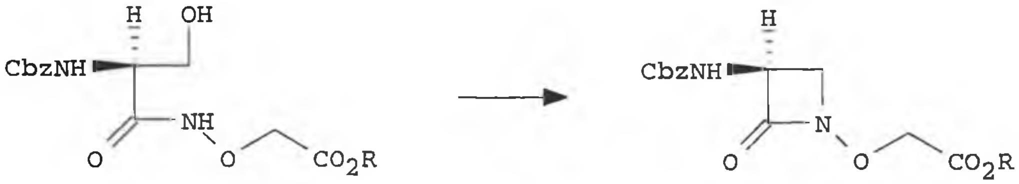
Subsequently, the β-lactam (310) was used to prepare the oxamazins (312), bearing substituents on the oxyacetic acid moiety[19].



(312)

R = H, OAc

In addition, Woulfe and Miller reported that treatment of the serine O-alkyl hydroxamates (313) with TPP/CCl_4/Et_3N provided the protected oxamazin nucleus (314) directly, in good yields[19].

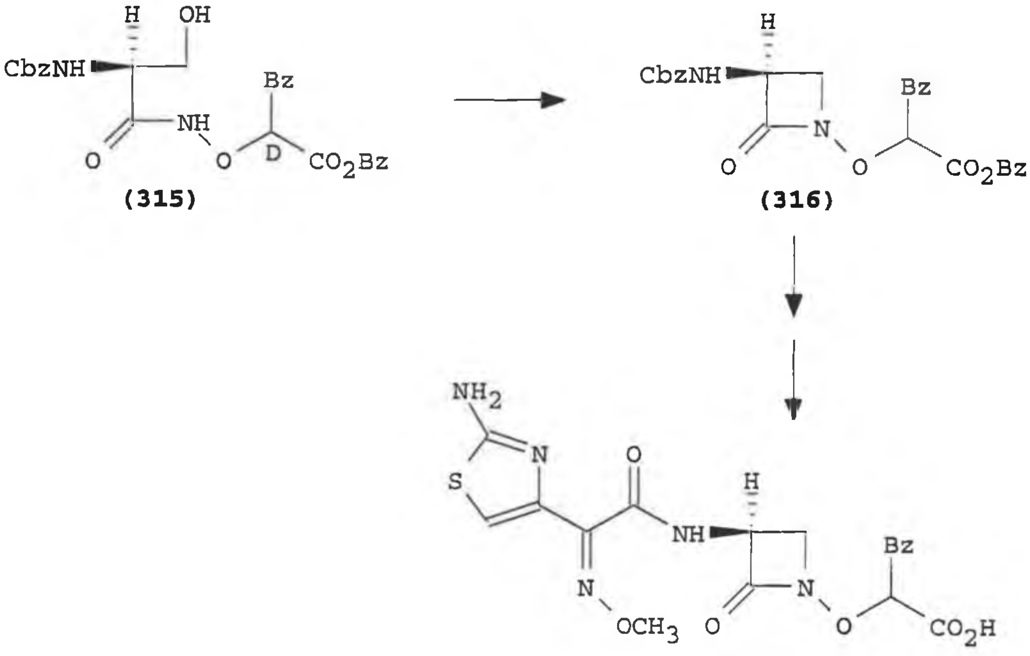


(313)

(314)

R = CH_3, Bz, CH_2CCl_3

Roche chemists, Atherton and Lambert, used TPP in combination with dimethyl azodicarboxylate (DMAD) in CH_2Cl_2 to achieve ring closure of the β-hydroxyhydroxamate (315) to the chiral β-lactam (316), which was obtained in 79% yield[16]. Further reactions afforded the oxamazin (317).

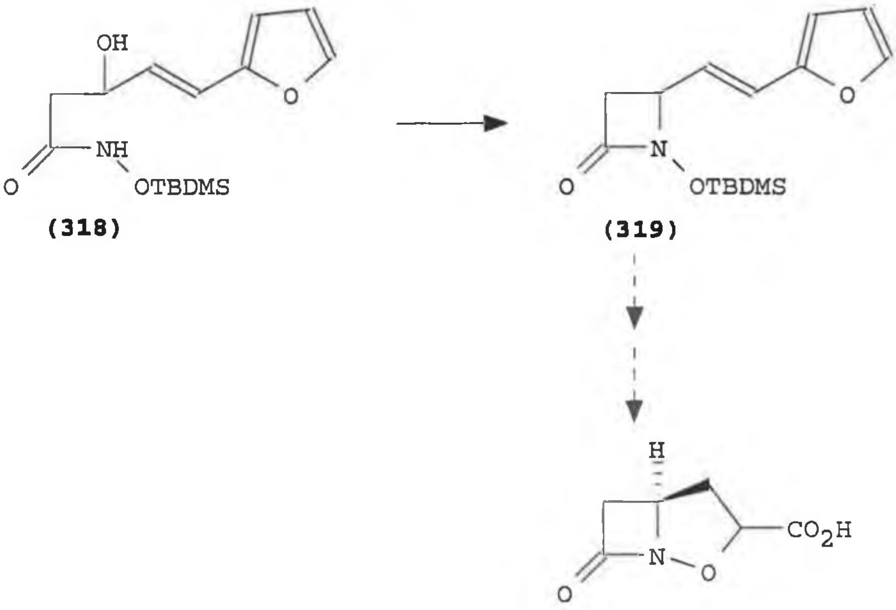


(315)

(316)

(317)

In an effort to synthesise the "cyclo-oxamazin" (320), which would be expected to possess particular reactivity due to a combination of heteroatom activation and bicyclic structure, Zercher and Miller[127] found that cyclisation of the hydroxamate substrate (318) to the monocyclic β-lactam (319) proceeded in a 75% yield, using TPP/DMAD in THF.

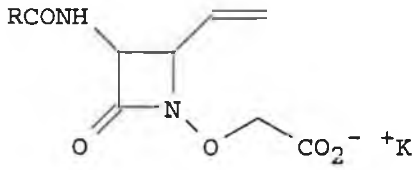


(318)

(319)

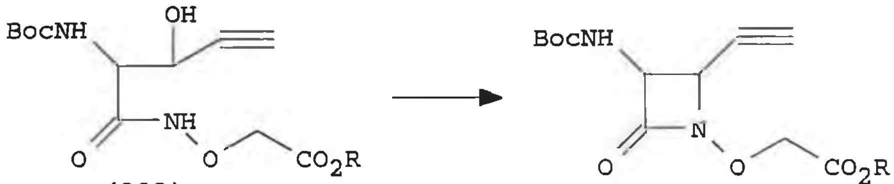
(320)

A synthetic approach to the 4-vinyl-substituted oxamazin (321), a useful starting material for the preparation of other oxamazin derivatives, has recently been described[128].



(321)

Here, the protected hydroxamate (322), as a 1:1 mixture of diastereomers, on treatment with an equimolar amount of TPP/DEAD, afforded the 4-ethynyl-2-azetidinone (323), in 79% yield, as cis and trans isomers in a ratio of 1:1.



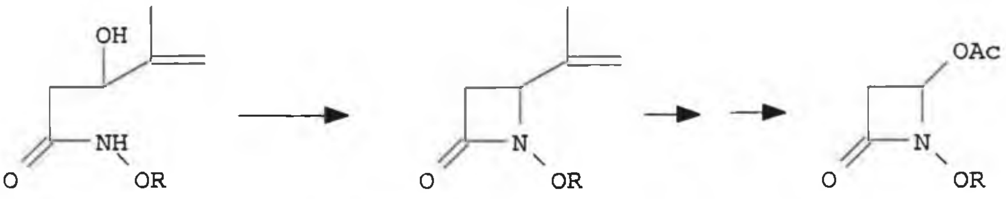
(322) **(323)**

R = —$(CH_2)_2$TMS

Curiously, the use of the TPP/CCl_4/Et_3N system to effect this cyclodehydration failed to give the desired product. The 4-allyl-β-lactam (325) has also been prepared by Mitsunobu-type cyclisation (TPP/DEAD) of the hydroxamate substrate (324)[129].

(324) **(325)**

In a general synthesis of 4-acetoxy-1-oxyazetidin-2-ones (328), Sheppard and Miller[130] have detailed ring closure of the α-(unsubstituted)-β-hydroxyhydroxamates (326) to the 4-isopropenyl-2-azetidinones (327).

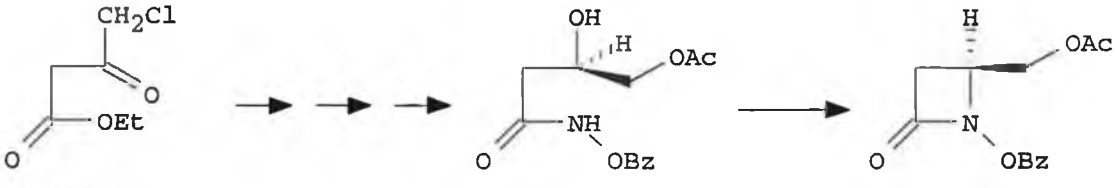


(326) **(327)** **(328)**

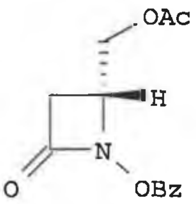
a: R = Bz
b: R = CH_2CO_2Bz
c: R = $COC(CH_3)_3$

The conventional Mitsunobu reagents, TPP and DEAD, were employed for the cyclisation of (326a) and (326b), but in the case of (326c), the TPP/CCl_4/Et_3N combination was preferred, since, owing to the lability of the O-pivaloyl group, the β-lactam (327c) was unstable to lengthy chromatographic purification.

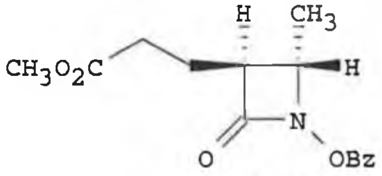
Kajiwara and colleagues[131] utilised TPP/DEAD to achieve cyclisation of the hydroxamate (330), ultimately derived from ethyl 4-chloroacetoacetate (329), to (S)-N-(benzyloxy)-4-acetoxymethyl-2-azetidinone (331).

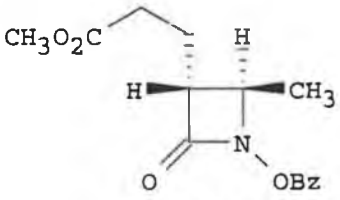

(329) **(330)** **(331)**

The same procedure was adopted to prepare the corresponding (R)-azetidin-2-one (332), using natural L-malic acid as a chiral building block.

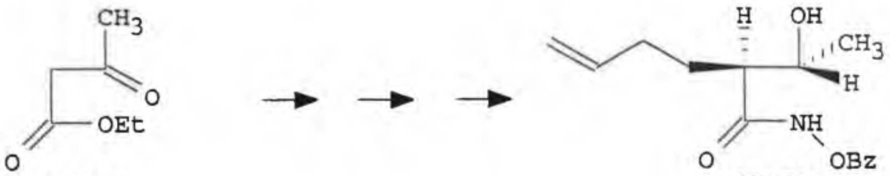

(332)

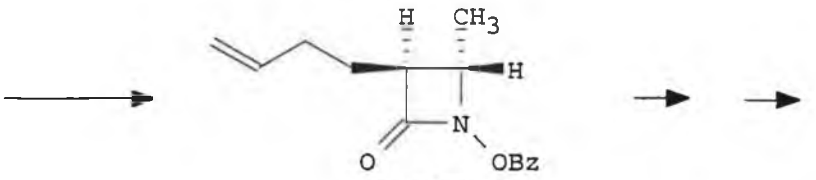
Ethyl acetoacetate (335) was used as a starting material in the enantiospecific syntheses of both (3S),(4S)- and (3R),(4R)-1-benzyloxy-3-methoxycarbonylethyl-4-methylazetidin-2-one (333) and (334) respectively[132].


(333)

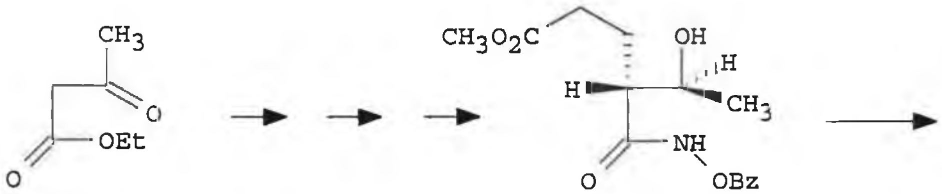

(334)

Treatment of the hydroxamate (336) with 1.2 equivalents of TPP/DEAD in THF furnished (3S),(4S)-1-benzyloxy-3-(3-butenyl)-4-methyl-2-azetidinone (337) in 67% yield, which was converted to the target β-lactam (333).

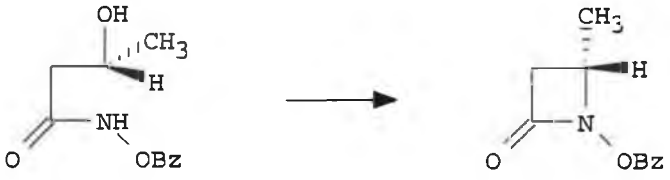

(335) **(336)**


(337) (333)

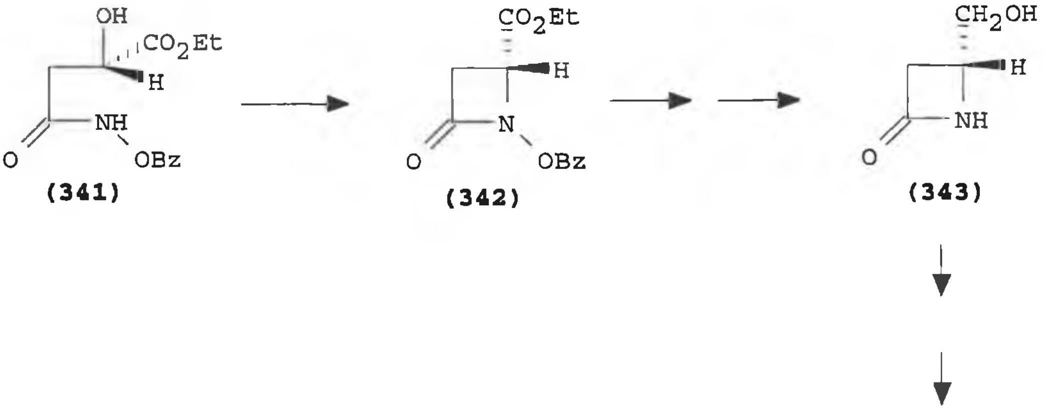
Under the same conditions, ring closure of the hydroxamate (338) afforded the desired β-lactam (334) directly, in 72% yield.

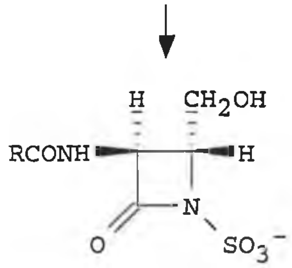

(335) (338) (334)

The 3-unsubstituted analogue of the β-lactam (333) had previously been prepared by Nagao and associates[133]. Reaction of N-benzyloxy-3(R)-hydroxybutyramide (339) with TPP and DEAD produced optically pure 1-benzyloxy-4(S)-methyl-2-azetidinone (340) in 84% yield.


(339) (340)

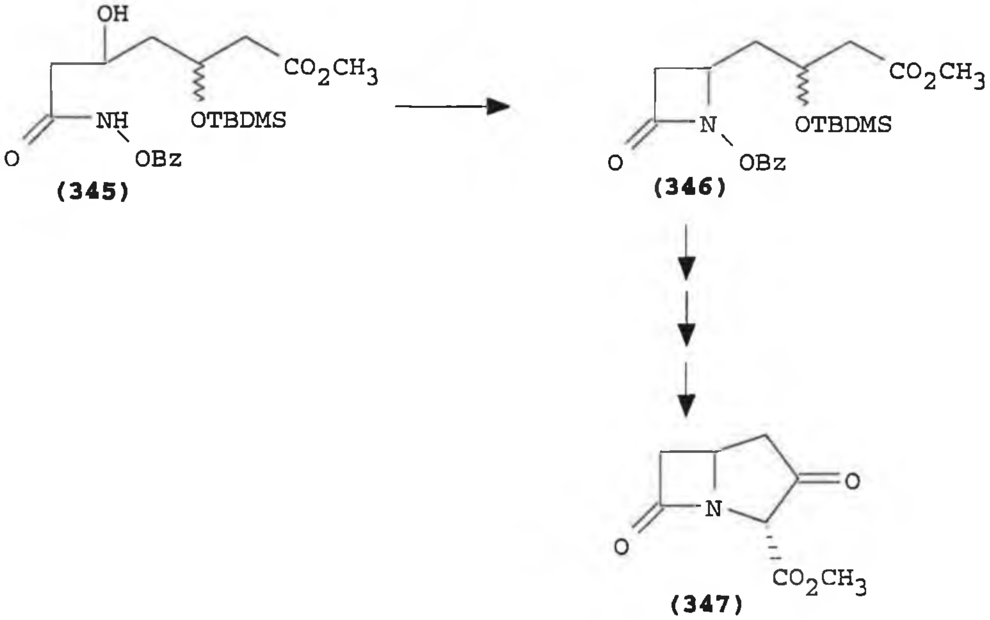
A synthetic route to 4-hydroxymethyl-2-azetidinones has been described by Shibuya et al.[134]. The hydroxamate (341), derived from L-malic acid, on treatment with an equivalent amount of TPP/DEAD, gave (4R)-1-benzyloxy-4-ethoxycarbonyl-2-azetidinone (342), in good yield. Subsequent deprotection and sodium borohydride reduction furnished (4R)-4-hydroxymethyl-2-azetidinone (343). This β-lactam was converted to monobactams of the type (344), which were, unfortunately, biologically inactive.


(341) (342) (343)



(344)

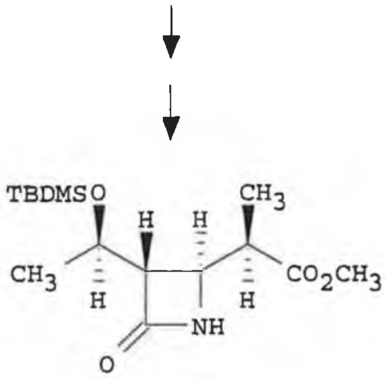
The Mitsunobu reaction has recently provided access to the carbapenam (347). Under the influence of TPP and DEAD, the β-hydroxyhydroxamate (345) cyclised to the intermediate monocyclic β-lactam (346)[135].



(345) (346) (347)

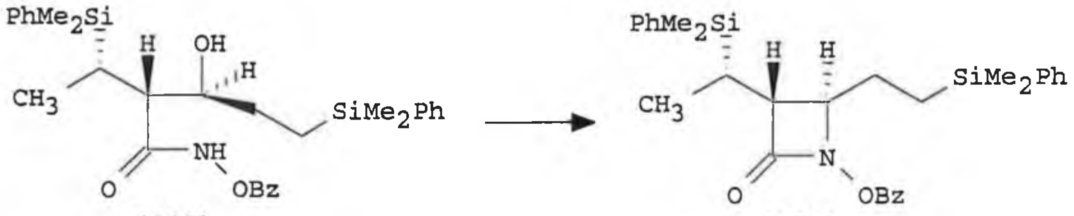
Japanese chemists, Shirai and Nakai, who previously employed the mesylation/base treatment cyclisation procedure to prepare the carbapenem precursor (216)[99], have since reported an alternative approach, involving Mitsunobu chemistry[136]. Here, the hydroxamate (348), when subjected to N-C4 bond closure conditions (TPP/DMAD in THF), was converted to the N-methoxyazetidin-2-one (225), in 92% yield. Notably, the use of DEAD in place of DMAD resulted in only 46% yield of the desired β-lactam (225).

(348) (225)



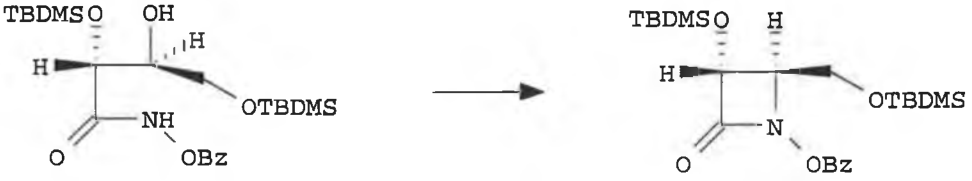
(216)

In a formal synthesis of racemic thienamycin, Fleming and Kilburn have described the use of TPP/DEAD to mediate cyclisation of the O-benzylhydroxamate (349) to the corresponding β-lactam (350)[137].



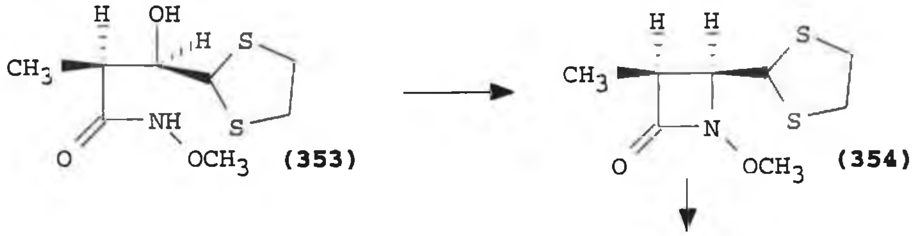
(349) (350)

The TPP/CCl_4/Et_3N combination proved effective in promoting lactamisation of the L-threonic acid hydroxamate (351), yielding the protected trans-3-hydroxy-4-hydroxymethyl-2-azetidinone (352)[91].

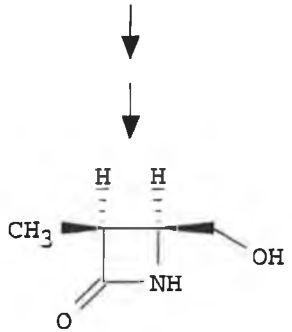


(351) (352)

cis-3-Methyl-4-hydroxymethyl-2-azetidinone (355) has been prepared, in >98% e.e., by Gennari and colleagues[138]. Following unsuccessful attempts to cyclise the α-methyl-β-hydroxyhydroxamate (353) to the key β-lactamic intermediate (354) via the mesylate derivative, these researchers found that the desired ring closure could be achieved using 1.5 equivalents of TPP/DEAD in THF.

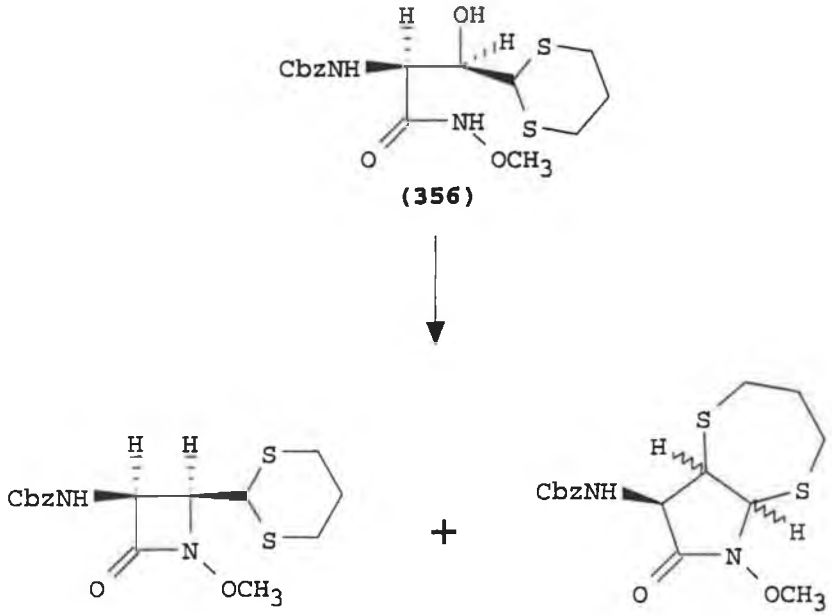


(353) (354)



(355)

Unexpectedly, treatment of the analogous hydroxamate substrate (356) with excess TPP/DEAD resulted in the formation of equal amounts of the target β-lactam (357) and the pyrrolidinone (358).

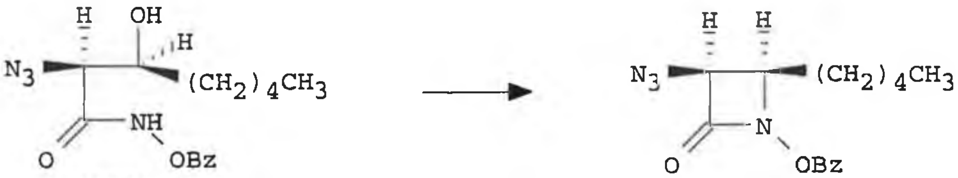


(356)

(357) (358)

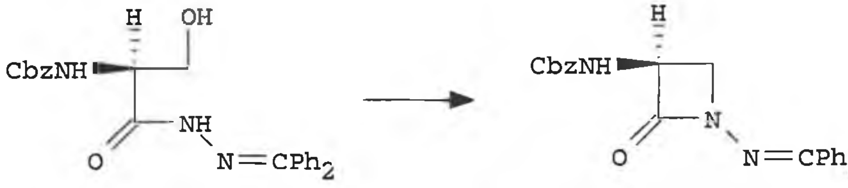
Variation of the experimental conditions, solvent and phosphine reagent failed to improve the yield of the cis-substituted 3-amino-2-azetidinone (357).

The cis-3-azido-β-lactam (360) has recently been isolated as a single diastereomer, in 70% yield, from the reaction of the α-azido-β-hydroxyhydroxamate (359) with TPP/DEAD in THF[139].



(359) (360)

The Mitsunobu reaction has also been invoked to effect cyclisation of hydrazide substrates to β-lactams. Bose and co-workers, during their initial exploration of Mitsunobu-type cyclodehydration of β-lactam precursors, reported that N-Cbz-L-serine-2-(diphenylmethylene)hydrazide (361), obtained from the reaction of N-Cbz-L-serine with benzophenone hydrazone, when treated with TPP and DEAD, afforded the N-aza-β-lactam (362), but only in 30% yield[112,113].



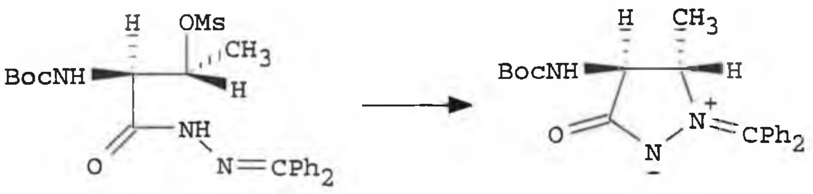
(361) (362)

Later, Curran et al.[9], applying this methodology to the synthesis of novel N-azamonobactams (12) found that ring closure of the alternatively-protected L-serine hydrazide (363a), and the corresponding L-threonine derivative (363b), using equimolar amounts of TPP/DEAD, gave good yields of the β-lactams (364a) and (364b) respectively.

(363) (364)

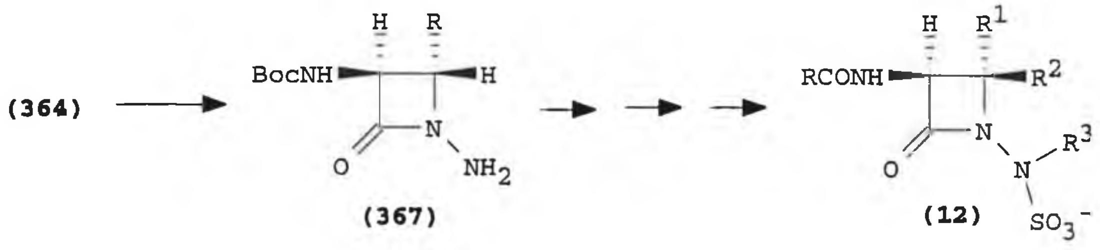
a: R = H
b: R = CH_3

Noteworthy is the fact that when the hydrazide (363b) was converted to the mesylate derivative (365), and refluxed in acetone containing K_2CO_3, the pyrazolidinium ylide (366) was isolated as the main product.



(365) (366)

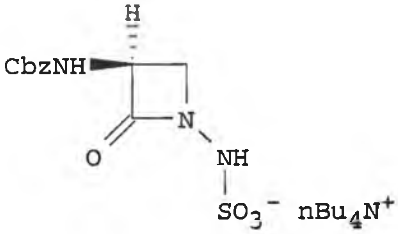
Catalytic hydrogenation of the β-lactams (364) produced the N-amino compounds (367), which were modified to afford the target N-azamonobactams (12).



(364) (367) (12)

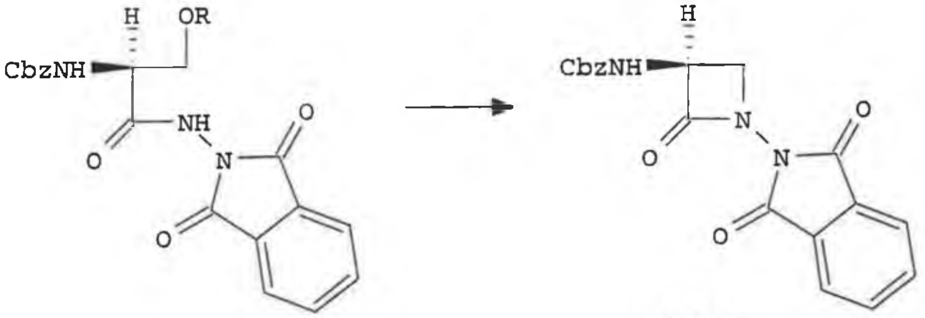
R = H, CH3

Iwagami and Yasuda[140] have detailed synthesis of the N-azamonobactam (368).



(368)

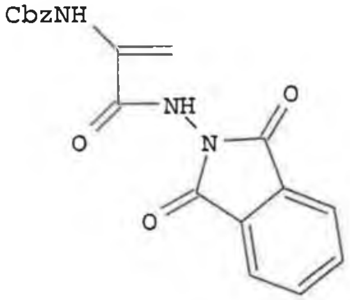
The key step in the preparation of this compound involved cyclisation of α-N-carbobenzoxy-N-phthalyl-L-serine carboxamide (369a) to the N-phthalyl-β-lactam (370).



(369) (370)

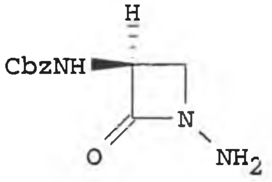
a: R = H
b: R = Ms

These researchers firstly examined ring closure of the O-mesyl derivative (369b) using K_2CO_3 in refluxing acetone, but discovered that the dehydro amino acid amide (371) was formed preferentially under these conditions.



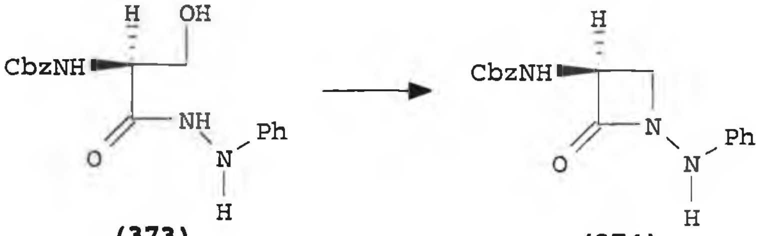
(371)

However, by utilising the more direct Mitsunobu approach (TPP/DEAD), the requisite β-lactam (370) was obtained in 75% yield from the amino acid hydrazide (369a). Removal of the phthaloyl group furnished (S)-3-carbobenzoxyamino-1-amino-2-azetidinone (372), which was sulfonated to provide the objective N-azamonobactam (368).



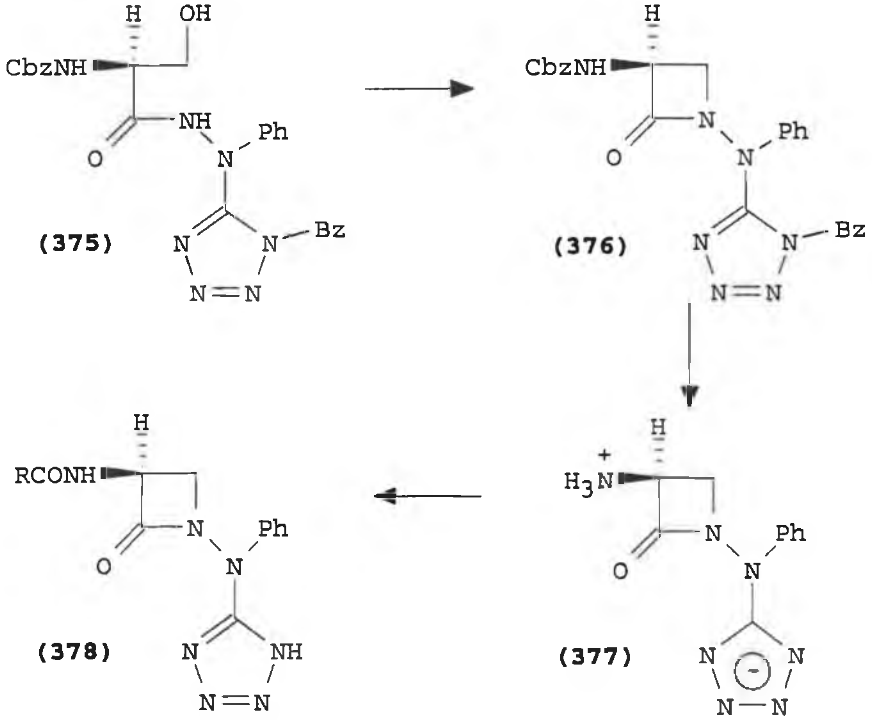
(372)

In their synthesis of 3(S)-acylamino-1-[(phenyl)(1H-tetrazol-5-yl)amino]-2-azetidinones (378), Atherton and Lambert[141] began by considering lactamisation of the model hydrazide (373), prepared from N-Cbz-L-serine and phenylhydrazine. Under the influence of TPP and DMAD in CH_2Cl_2, the β-lactam (374) was produced in 50% yield.



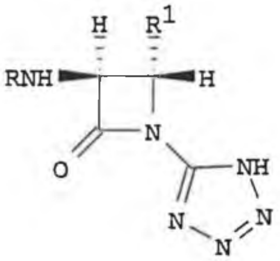
(373) **(374)**

The same modified Mitsunobu conditions were then employed to convert the substituted serylhydrazide (375) to the fully protected β-lactam (376). Hydrogenolytic deprotection gave the parent zwitterion (377), which could be acylated, affording the target species (378).



(375) **(376)** **(377)** **(378)**

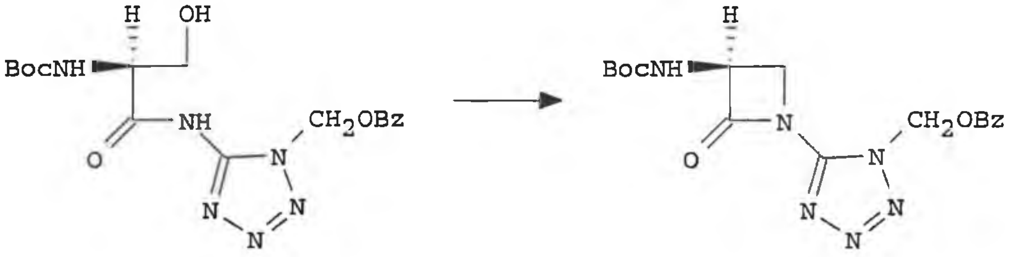
Chemists at Merck, Sharp and Dohme have reported synthesis of N-(tetrazol-5-yl)-azetidin-2-ones of the type (379) which displayed moderate to potent bioactivity versus a variety of bacteria[11].



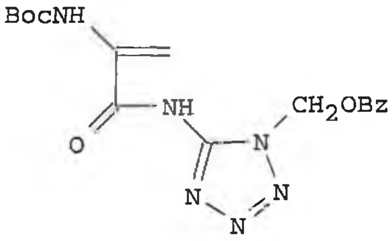
(379)

$R^1 = H, CH_3$

Initial attempts to cyclise the L-serine-derived substrate (380) to the corresponding β-lactam (381) via the mesylation/base treatment sequence gave primarily the elimination product (382).

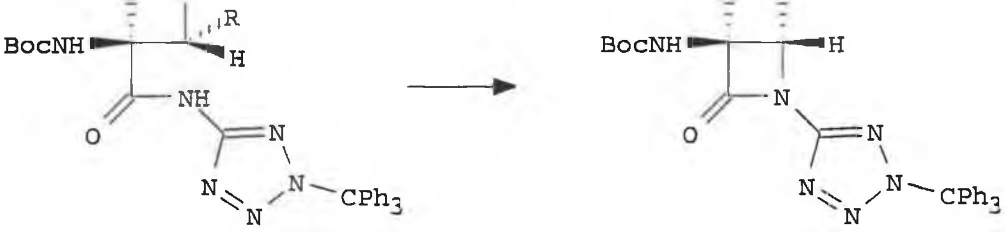


(380) **(381)**



(382)

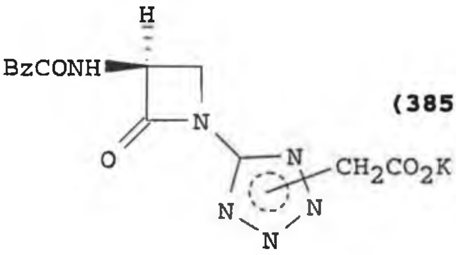
Alternatively, direct cyclodehydration of the 3-hydroxypropionamide (380) with TPP/DIAD furnished the β-lactam (381) cleanly, in 71% yield. The related L-serine- and L-threonine-derived precursors (383a) and (383b) were lactamised similarly, affording the 2-azetidinones (384a) and (384b) respectively.



(383) **(384)**

a: R = H
b: $R = CH_3$

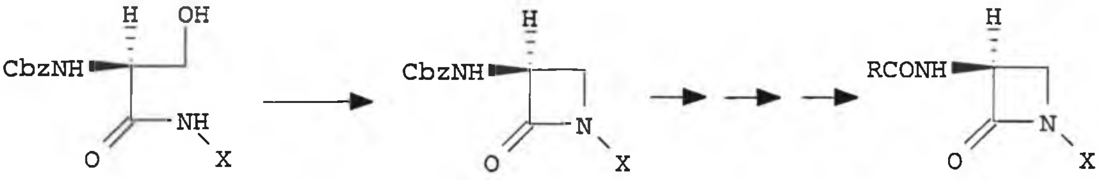
In a subsequent publication[142], these researchers employed the same cyclisation procedure to prepare the N-(carboxymethyltetrazol-5-yl)-β-lactams (385a) and (385b), which had limited activity.



(385)

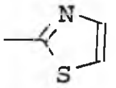
a: N-1-isomer
b: N-2-isomer

Yoshida and colleagues[12] have conducted a comprehensive study of the synthesis and antibacterial potency of a range of N-1-heterocyclic β-lactams (387), prepared by means of the TPP/DEAD-mediated N-C4 cyclisation of serylamides (386).

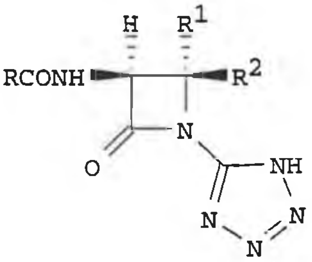


(386) **(387)**

X = aromatic cycle, e.g.



In addition, these investigators described synthesis of substituted 3-amino-4-methyl-1-(1H-tetrazol-5-yl)-2-azetidinones of the type (388).

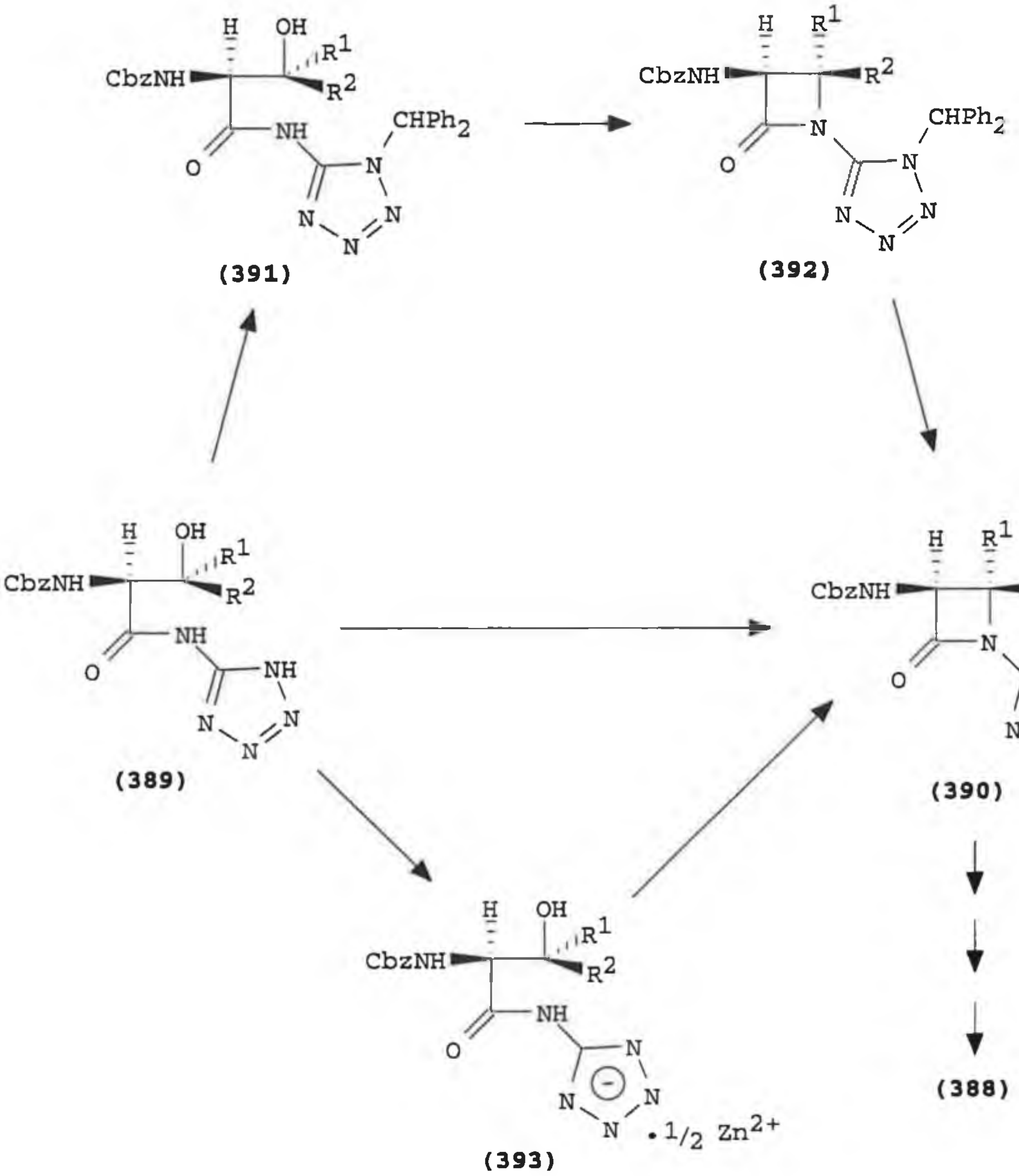


(388)

a: $R^1 = CH_3$; $R^2 = H$
b: $R^1 = H$; $R^2 = CH_3$

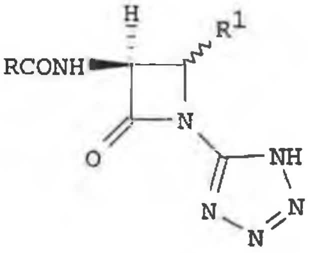
Direct ring closure of the β-hydroxyamides (389a) and (389b), originating from L-threonine and L-allothreonine respectively, using the standard TPP/DEAD combination, gave only low yields of the desired β-lactams (390). A more efficient conversion was made possible by firstly protecting the tetrazolyl nitrogen via quantitative regiospecific N-1-alkylation with diphenyldiazomethane. The resultant compounds (391) were then cyclised as above, furnishing the intermediate β-lactams (392), in 70% yields. Finally, deprotection produced the N-(tetrazol-5-yl)-2-azetidinones (390). Preferably, the protection/deprotection sequence could be cleverly avoided by converting the substituted amide substrates (389) to their zinc salts (393), which were cyclised directly, again using TPP and DEAD, in high yields. These strategies are depicted in Scheme 7. Completion of the synthesis afforded the target β-lactams (388).

Scheme 7



a: $R^1 = CH_3$; $R^2 = H$
b: $R^1 = H$; $R^2 = CH_3$

Yoshida's group subsequently utilised the methodology outlined above in the preparation of N-(tetrazol-5-yl)azetidin-2-ones (394), bearing various functional moieties at the C4-position of the β-lactam ring, many of which exhibited strong antibacterial activity[13].



(394)

R^1 = substituted methyl

The impressive array of β-lactamic compounds that have been synthesised from β-hydroxy carboxylic acid derivatives, by application of the Mitsunobu reaction and its various modifications, substantiates Miller's contention that

> "....essentially any chiral β-lactam could be made by simply choosing the appropriate chiral starting β-hydroxy acid"[3].

Chapter 2

2.1 Lead Tetraacetate Oxidation of p-Nitrophenylhydrazones of Acetoacetanilides

2.1.1 Introduction

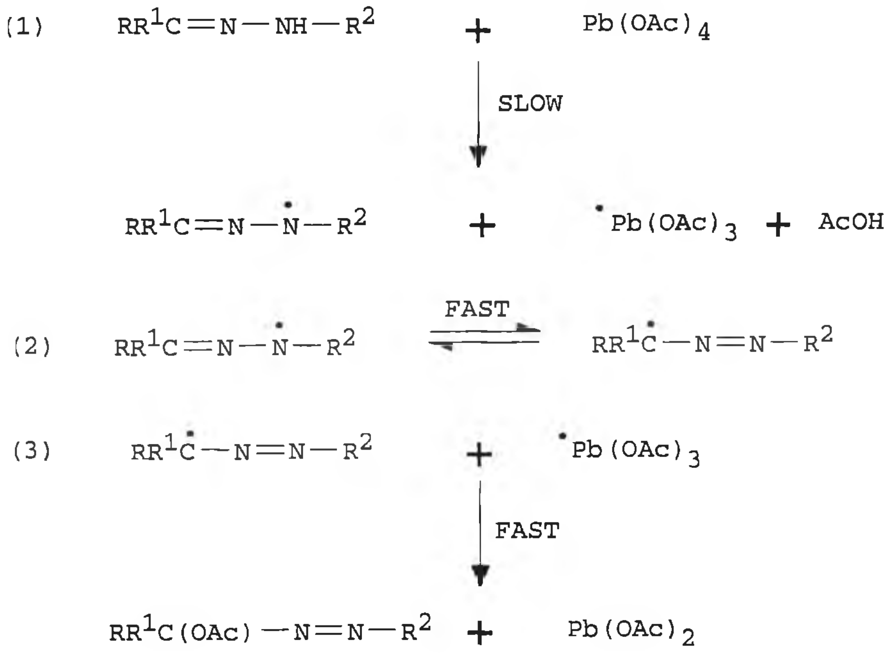
Lead tetraacetate (LTA), $Pb(OAc)_4$, has been widely used as an oxidant throughout organic and natural chemistry. The LTA oxidation of hydrazones can give a variety of products, depending on the nature of the substrate and the reaction conditions[143,144]. Monosubstituted ketohydrazones (395) react rapidly with LTA to give good yields of α-acetoxylated azo compounds of the type (396), which have been termed "azoacetates".


(395)

(396)

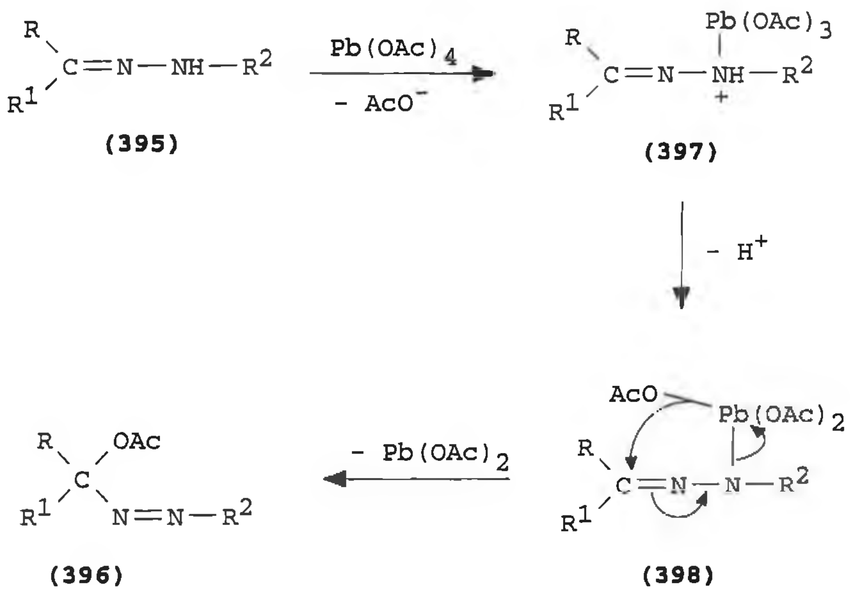
Iffland and colleagues[145] first reported this transformation in 1961, and suggested a free-radical mechanism involving abstraction of the hydrazino hydrogen atom by an acetate radical, followed by attack at the carbon atom by $^{\bullet}Pb(OAc)_3$, as depicted in Scheme 8. However, subsequent e.s.r. studies of reactions of the hydrazones (395) with LTA failed to detect the presence of radicals[146]. Kinetic data indicated a polar mechanism.

Scheme 8

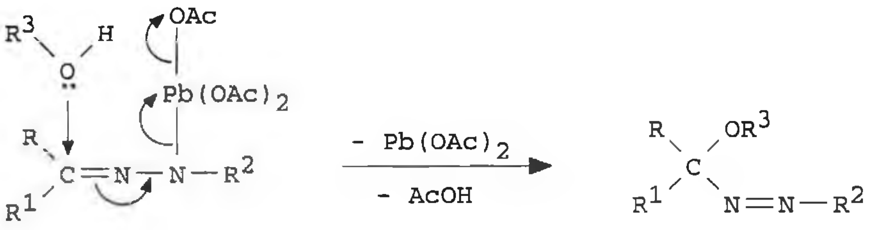


Norman and associates[146] formulated an ionic mechanism to explain azoacetate formation, where a rate-determining displacement of an acetate anion from LTA by the NH-nitrogen yields an ammonium species (397). This highly reactive N-metallo intermediate undergoes deprotonation and an intramolecular redox, with an acetoxy migration to the methine carbon, giving the azoacetate product (396) (Scheme 9).

Scheme 9

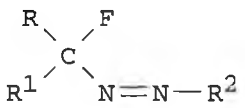


Considerable experimental evidence supports the intramolecular nature of this acetoxylation process. Norman's group[146] found that when the LTA oxidation was conducted in the presence of alcohol, mixtures of azoacetates and azoethers (399) were obtained, the latter arising from intermolecular displacement on the lead intermediate (398) by an alcohol molecule.



(398) (399)

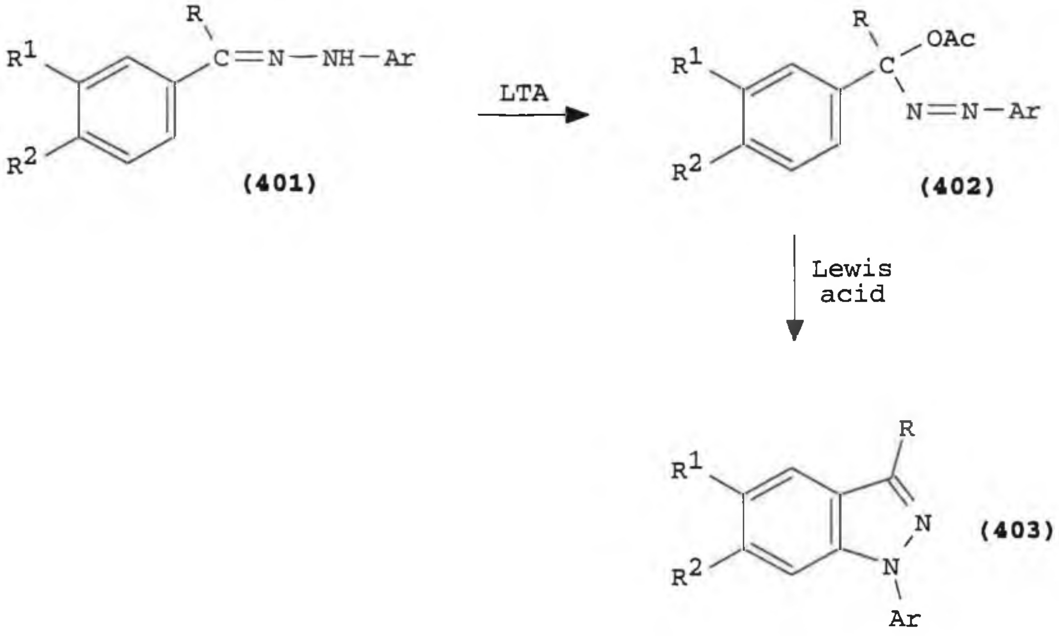
Acetoxylation was favoured with respect to alkoxylation, even in solutions containing large excesses of alcohol. Bornstein and Skarlos[147] found that treatment of monosubstituted ketohydrazones with lead (IV) diacetate difluoride in chloroform resulted in the formation of azoacetates and azofluorides (400).



(400)

The observed preference for azoacetate formation in such systems is again consistent with an intramolecular mechanism. More conclusively, Butler and associates[148] have shown that azoacetate formation occurs readily in solvents such as CH_2Cl_2/Et_3N, where external acetic acid is not available.

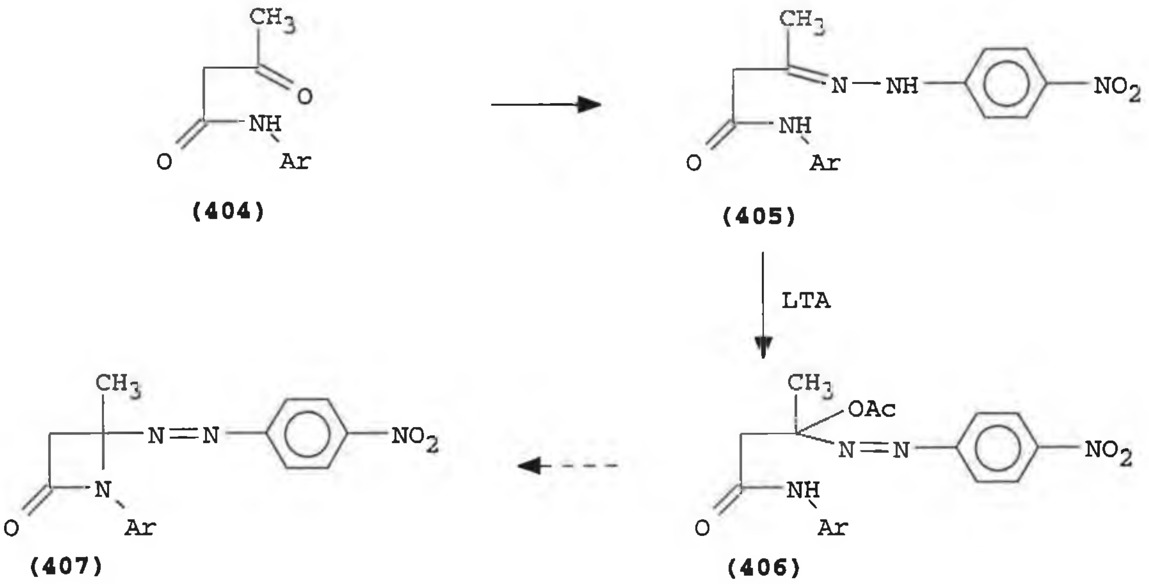
Since azoacetates are useful synthetic intermediates, a wide range of ketone hydrazones has been oxidised with LTA[143]. Azoacetates have been cyclised to heterocyclic systems. On treatment with Lewis acids, azoacetates (402), prepared from ketone arylhydrazones (401), readily lose their acetate group and undergo ring closure, affording indazoles of the type (403).



This methodology has been applied to the synthesis of 1-arylindazoles[149], 3-substituted-1-arylindazoles[150,151], pyridylindazoles[151] and thienopyrazoles[151].

2.1.2 Results and Discussion

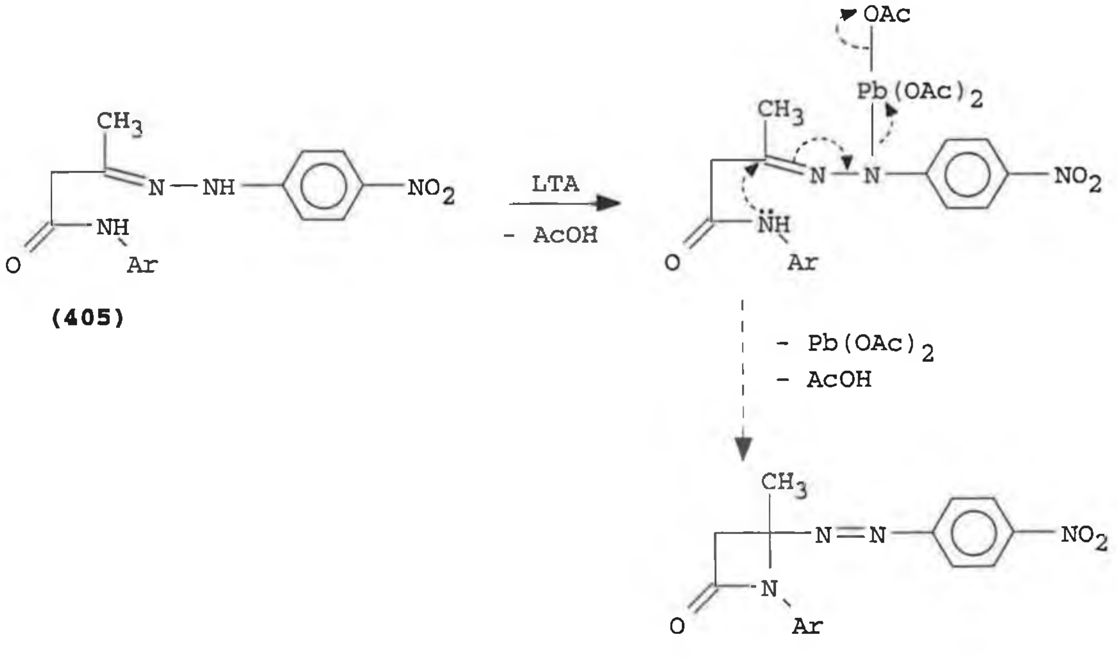
On oxidation with LTA, the p-nitrophenylhydrazones (405), derived from acetoacetanilides (404), were expected to provide azoacetates of the type (406), which could potentially be cyclised, by N-C4 bond closure, to novel 4-azo-2-azetidinones (407).



(404) (405) (406) (407)

a: Ar = Ph
b: Ar = p-Cl-C_6H_4

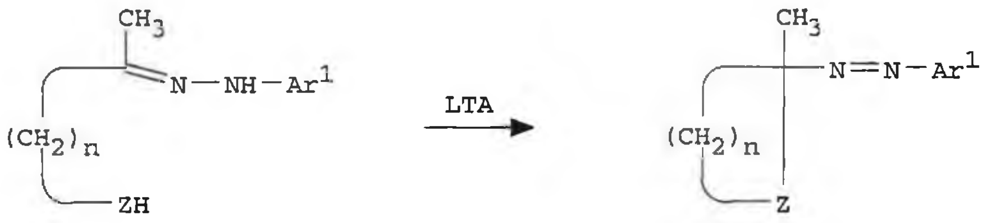
There was also a possibility that, when treated with LTA, the hydrazones (405) would undergo an oxidative cyclisation, giving the 4-azo-β-lactams (407) directly.



(405) (407)

a: Ar = Ph
b: Ar = p-Cl-C_6H_4

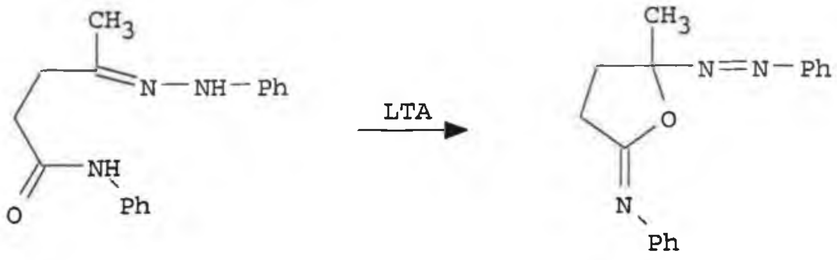
Oxidative cyclisation of ketohydrazones with LTA has been shown to occur when there is a nucleophilic function within the ketone residue capable of displacing the Pb salt from the N-lead triacetate intermediate. However, this type of cyclisation has only been successful in the formation of 5- and 6-membered rings (408)[143,152].



(408)

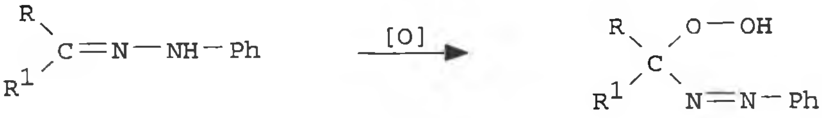
n = 2; Z = COO
n = 3; Z = COO
n = 3; Z = O

Also, in the case of levulinanilide phenylhydrazone (409), it is claimed[152] that ring closure to the amide oxygen, rather than the nitrogen atom, occurred, affording the iminolactone (410).



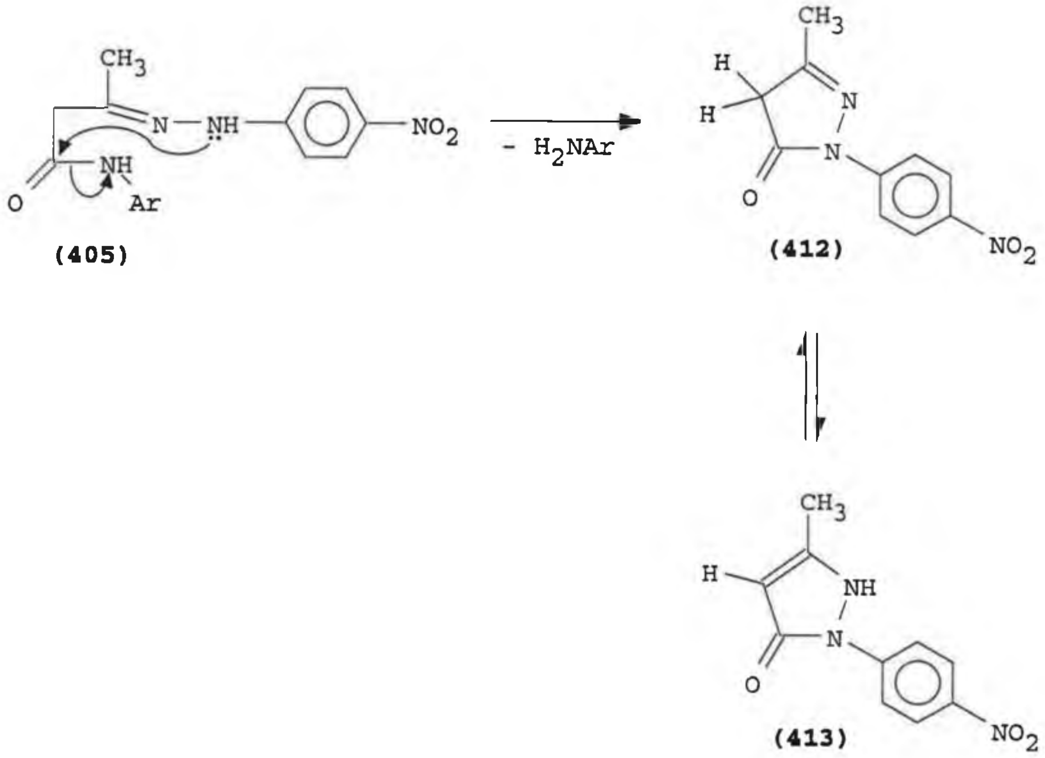
(409) (410)

Acetoacetanilide (N-phenyl-3-oxobutanamide) (404a) and p-chloroacetoacetanilide (404b) were selected as starting materials because of their commercial availability and low cost. It was decided to use the p-nitrophenylhydrazone derivatives (405) rather than the unsubstituted phenylhydrazones, since, in general, the latter species are unstable, being prone to atmospheric oxidation to the corresponding azohydroperoxides (411)[153,154].



(411)

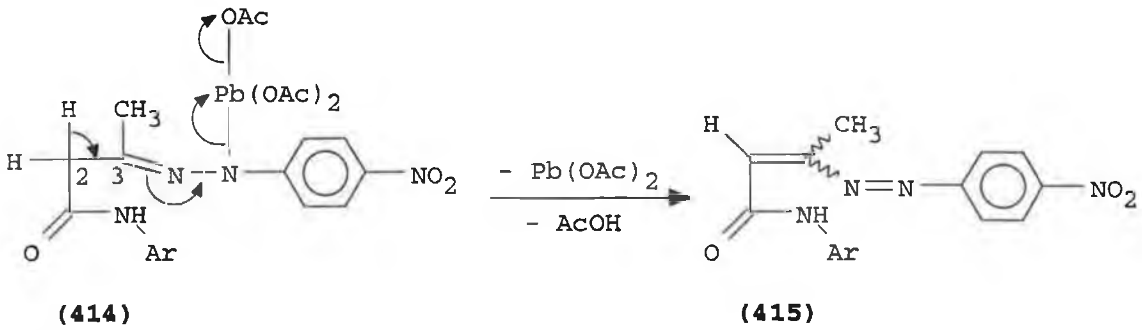
Synthesis of the requisite p-nitrophenylhydrazones (405) proved to be non-trivial because these compounds readily cyclise (e.g. on heating in AcOH) to 1-(4-nitrophenyl)-3-methyl-2-pyrazolin-5-one (412)[155].



(405) (412) (413)

It should be noted that in DMSO solution, the pyrazolin-5-one tautomerises to (413), exhibiting a vinylic peak at 5.42 ppm in the ^{1}H NMR spectrum. This detrimental cyclisation was avoided and the desired hydrazones (405) were prepared in high yields under careful conditions (AcOH, r.t., 20 minutes).

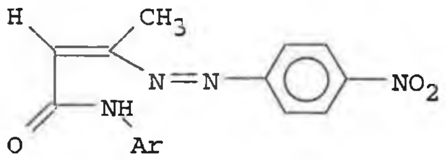
LTA oxidation of the hydrazones (405) in CH_2Cl_2 proceeded as expected, providing the azoacetates (406) as single products, in good yields. No cyclic products arising from oxidative ring closure were formed. However, when the oxidation of hydrazone (405a) was repeated, but using acetic acid as solvent, a product was obtained which was not the azoacetate (406a). Analysis indicated that an azoacrylamide of the type (415a) had been formed, apparently via a 1,4-elimination from the N-metallo intermediate (414a).



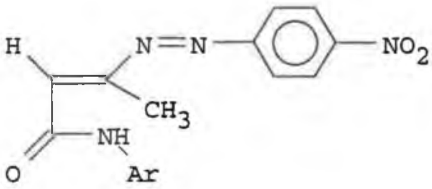
(414) (415)

a: Ar = Ph
b: Ar = 4-Cl-C_6H_4

One would expect rotation about the C2-C3 bond of the Pb-intermediate (414a) to be unrestricted, and that this species would collapse affording a mixture of the Z-isomer (416a) and the E-isomer (417a).



(416)

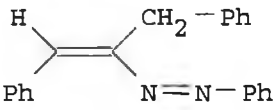


(417)

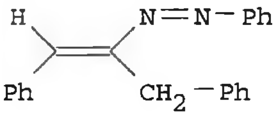
a: Ar = Ph
b: Ar = 4-Cl-C_6H_4

Surprisingly, only one of these azoalkenes had been produced. In a similar fashion, hydrazone (405b) also gave a single azoacrylamide (415b) when oxidised with LTA in AcOH.

In order to determine which of the azoalkenes (416) and (417) had been formed, the chemical shift of the vinylic proton of each isomer was estimated with the aid of tabulated spectral data[156] (Figure 1). Compound (418) was used as a model of the Z-isomer (416). The chemical shift of the olefinic proton of this model compound was calculated to be 7.07 ppm. Similarly, compound (419) was used as a model of the E-isomer (417). The vinylic proton here would be expected to appear at 7.45 ppm. Moreover, the olefinic proton of Z-1,3-diphenyl-2-(phenylazo)propene (420) is reportedly seen at 6.76 ppm, while that of the corresponding E-isomer (421) appears at 8.17 ppm[157].



(420)



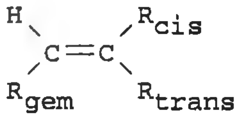
(421)

Since the NMR spectra of the azoacrylamide products (415a) and (415b) both contain a peak at 6.58 ppm, it was assumed that the Z-azoalkene (416) had been formed in each case. This stereochemical assignment is later shown to be correct.

The formation of these unusual oxidation products prompted two important questions. Why does the expected intramolecular acetoxylation not occur when AcOH is used as solvent? Why is the Z-isomer, which is not the thermodynamic product, formed exclusively?

Figure 1: **Estimation of the chemical shifts of the vinylic protons in azoalkenes (416) and (417)**

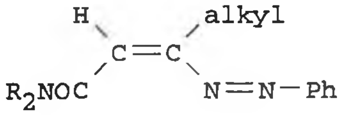
For alkenes of the type



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

$$\delta_{C=CH} = 5.25 + Z_{gem} + Z_{cis} + Z_{trans}$$

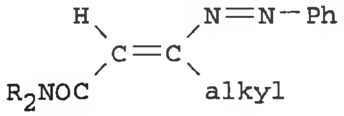
Z-isomer:



(418)

$$\delta_{C=CH} = 5.25 + 1.37 + (-0.22) + 0.67$$
$$= 7.07$$

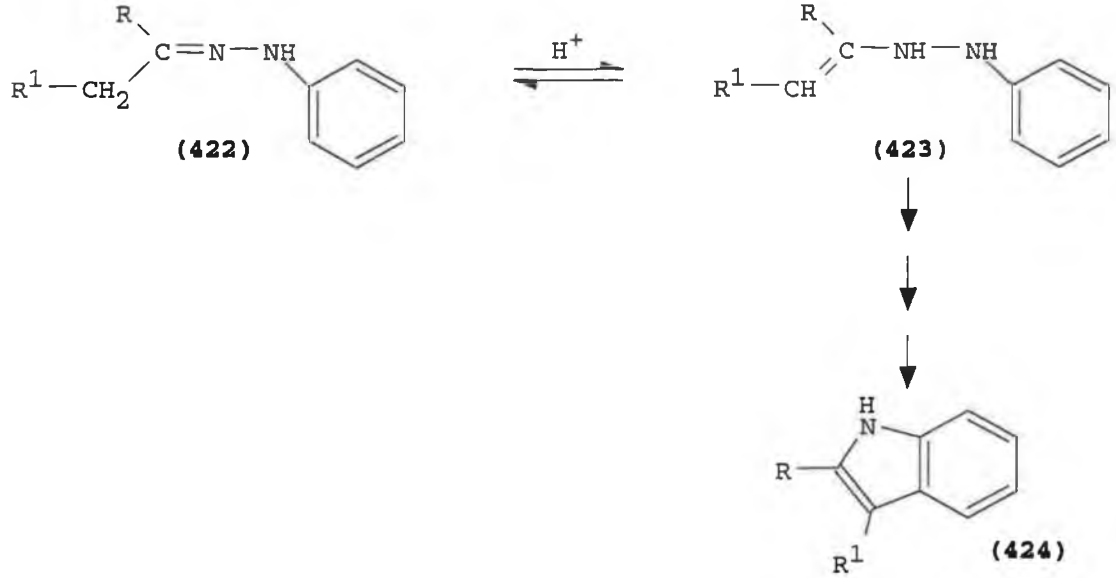
E-isomer:



(419)

$$\delta_{C=CH} = 5.25 + 1.37 + 1.11 + (-0.28)$$
$$= 7.45$$

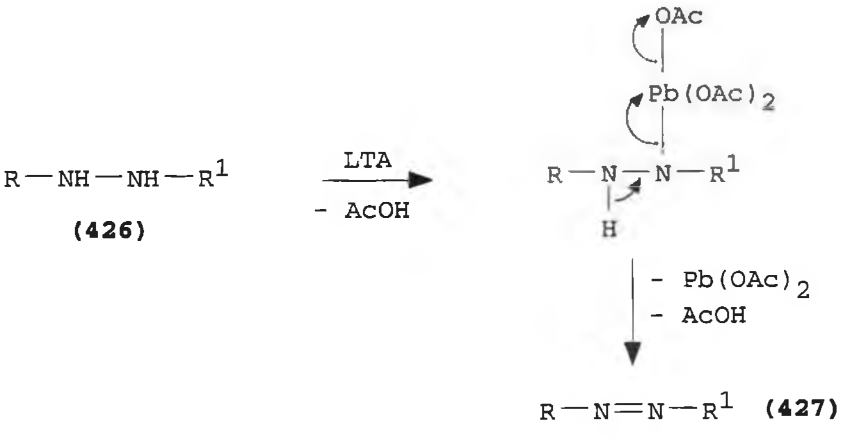
In the Fischer indole synthesis, the first step in the conversion of an arylhydrazone (422) to an indole (424) is considered to be tautomerism of the hydrazone (422) to the enehydrazine (423)[158].


(422) (423) (424)

This cyclisation reaction is known to proceed readily in acetic acid solution, in the absence of other acidic species[154,158,159], indicating that this solvent is capable of catalysing the rearrangement of hydrazones (422) to enehydrazines (423). It follows, therefore, that in AcOH, the acetoacetanilide hydrazones (405) may be present in equilibrium with the enehydrazine tautomers (425).

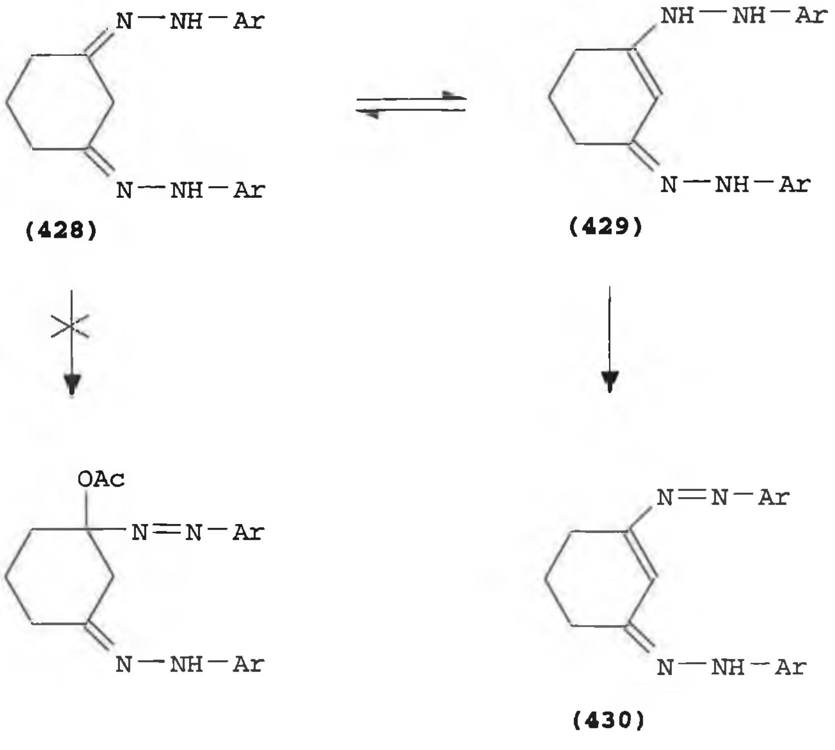

(405) (425)

Now, the –NH–NH– unit has a low oxidation threshold[144], and 1,2-disubstituted hydrazines (426) are readily dehydrogenated with LTA, giving the corresponding azo compounds (427)[144,160].


(426) (427)

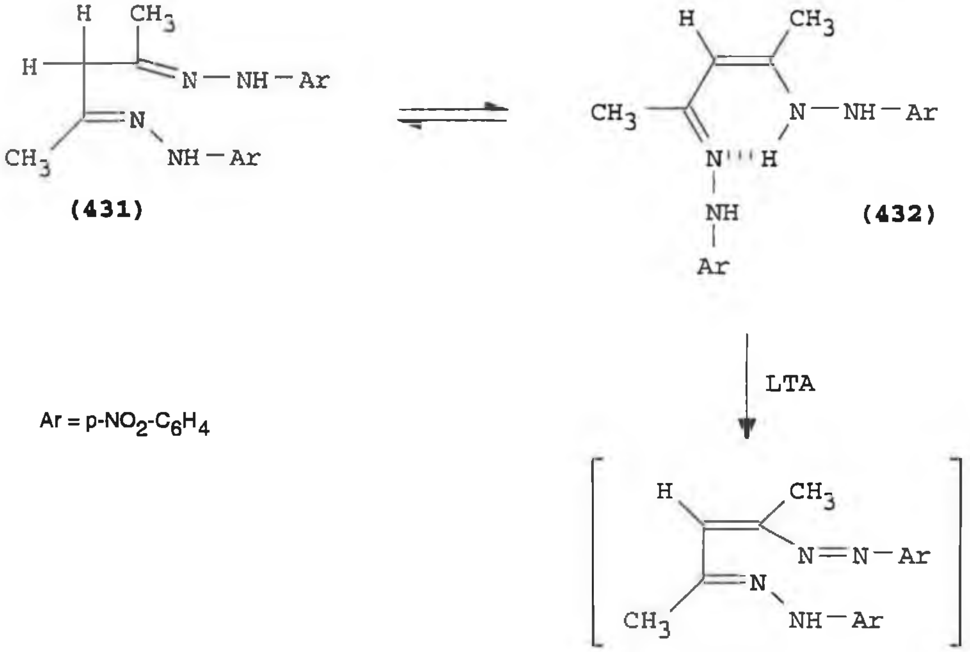
In the case of the LTA oxidation of the hydrazones (405) in AcOH, it is proposed that an equilibrium concentration of the enehydrazines (425) is present, and that the latter species, being highly reactive, are preferentially oxidised, generating the azoacrylamides (415). As the reaction proceeds, the concentration of hydrazone gradually decreases through constant re-equilibration, with the result that the azoacrylamides (415) are formed as the sole oxidation products. In a study of tautomerism in phenylhydrazones, O'Connor[161] found no detectable concentration of the enehydrazine tautomer in solutions of phenylhydrazones in neutral non-polar organic solvents, which explains why only the expected acetoxylation occurs when this oxidation is conducted in CH_2Cl_2.

This type of hydrazone–enehydrazine tautomerism, with the resultant formation of azoalkenes instead of azoacetates, has previously been described. When cyclohexane-1,3-dione bis-(4-nitrophenylhydrazone) (428) was treated with LTA in AcOH, the azo-olefin (430) was obtained in 87% yield, this product arising from an initial tautomerism to the enehydrazine (429)[162].



Ar = p-NO_2-C_6H_4

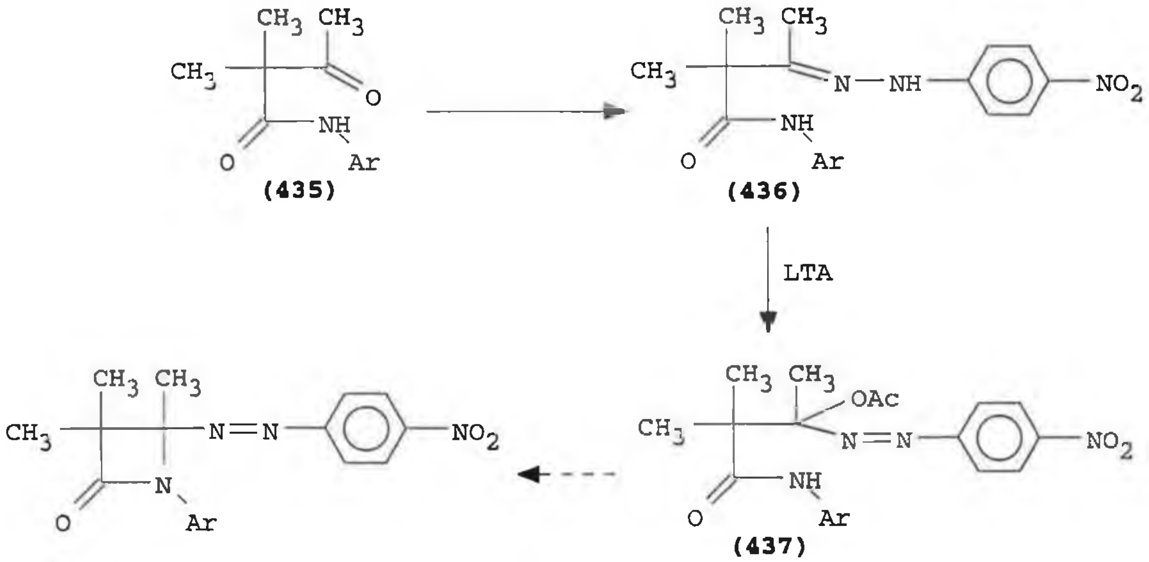
Furthermore, when pentane-2,4-dione bis-(4-nitrophenylhydrazone) (431) was oxidised with LTA, reaction again occurred via the enehydrazine form (432), giving an azoalkene (433), which reacted further by cyclisation. Most importantly, it is claimed that the intermediate azo-olefin (433) has the Z-configuration as a result of stabilising intramolecular hydrogen-bonding in the enehydrazine precursor (432)[162].


(431) (432) (433)

Ar = p-NO_2-C_6H_4

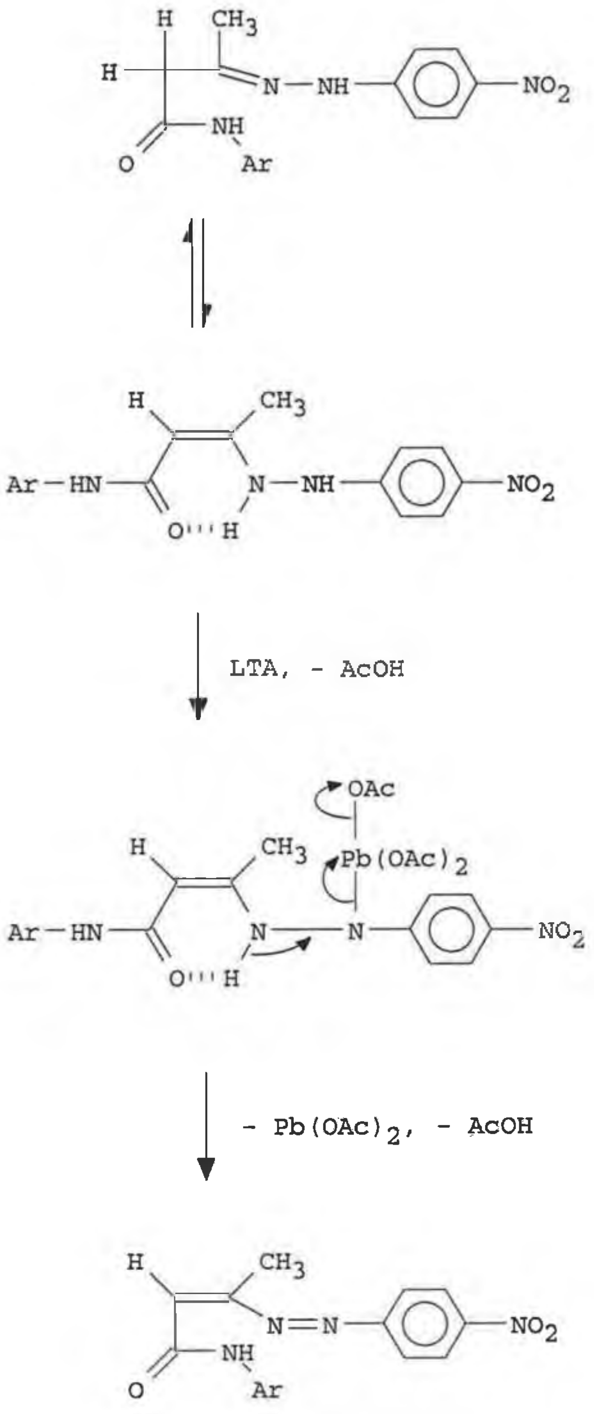
Therefore, it is proposed that a similar stabilisation may be operative in the case of the acetoacetanilide hydrazones (405), and that once tautomerism to the enehydrazines (425) occurs, intramolecular H-bonding between the enolisable NH proton and the amide carbonyl fixes these species in the Z-form (434), thus conferring stereoselectivity on the oxidation reaction (Scheme 10).

The reactions of the p-nitrophenylhydrazones (436), derived from α,α-dimethylated acetoacetanilides (N-phenyl-2,2-dimethyl-3-oxobutanamides) (435), which do not possess an enolisable methylene proton, were examined. These were expected to afford azoacetates of the type (437) on oxidation with LTA, even when acetic acid was used as solvent.


(435) (436) (437)

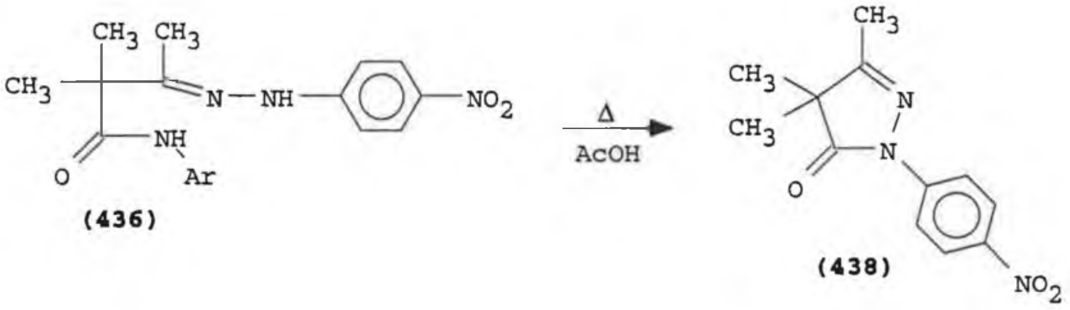
a: Ar = Ph
b: Ar = 4-Cl-C_6H_4

Scheme 10



The azoacetates (437) were considered to be more promising candidates for N-C4 cyclisation to the novel 4-azo-2-azetidinones than their unsubstituted counterparts (406), since the latter species, under cyclisation conditions, would be susceptible to competing side-reactions, such as 1,2-elimination leading to acrylamides, that often plague attempted lactamisations[43,140].

Acetoacetanilide (404a) and p-chloroacetoacetanilide (404b) were each C-dimethylated, using an excess of methyl iodide and K_2CO_3 in acetone, affording the α,α-dimethylacetoacetanilides (435a) and (435b) respectively, in good yields. The p-nitrophenylhydrazones (436) were prepared under mild conditions, since again, heating in AcOH caused cyclisation of these compounds, giving 1-(4-nitrophenyl)-3,4,4-trimethyl-2-pyrazolin-5-one (438).



(436)

(438)

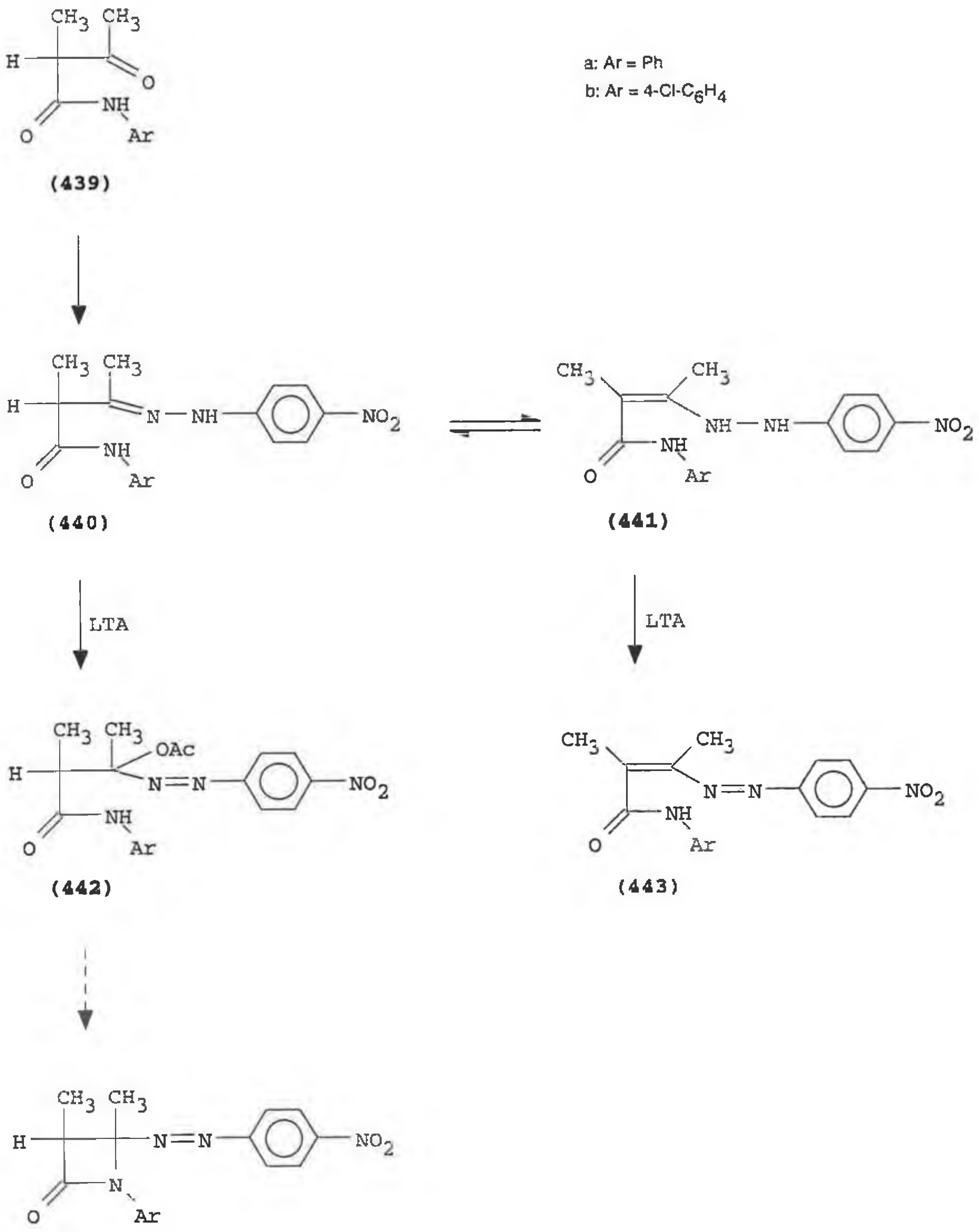
a: Ar = Ph
b: Ar = 4-Cl-C_6H_4

LTA oxidation of the hydrazones (436) in CH_2Cl_2 proceeded as expected, furnishing the azoacetates (437). When the oxidation reactions were repeated in AcOH, the predicted intramolecular acetoxylation occurred here also, and no unusual transformations were observed.

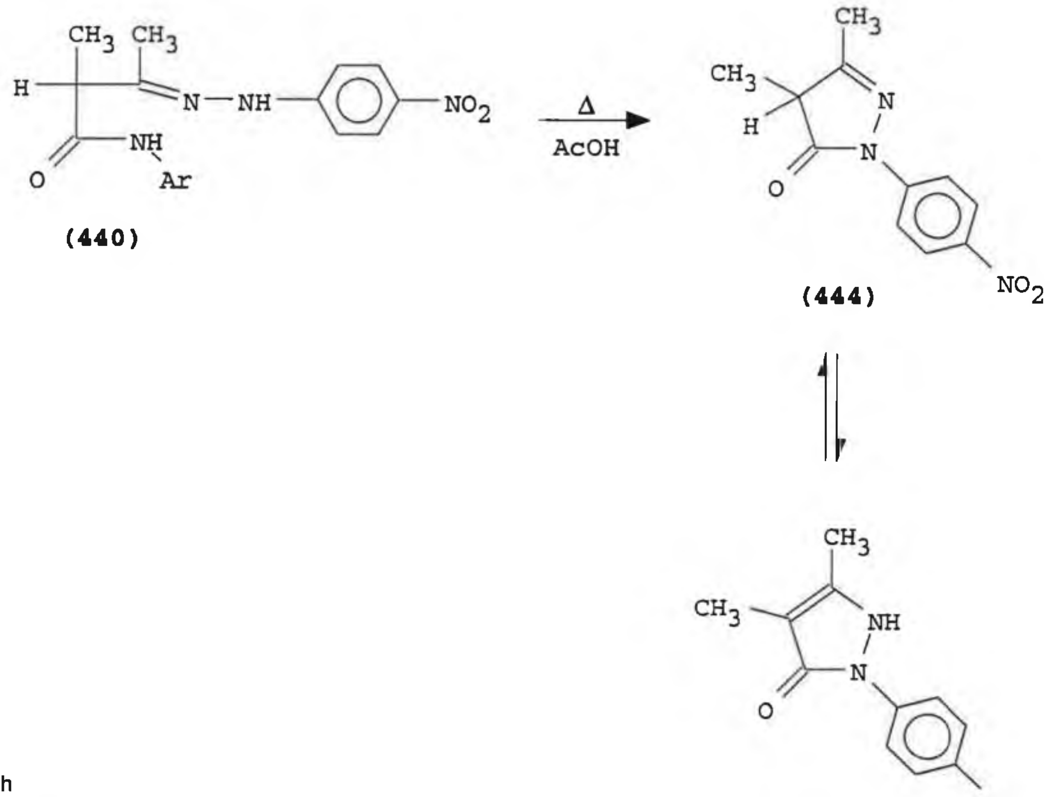
Finally, the p-nitrophenylhydrazones (440), obtained from α-methylacetoacetanilides (439) were studied. These species were of interest because on oxidation with LTA in AcOH, two possible products could be formed: – (i) the azoacetates (442) and (ii) the azoalkenes (443) (Scheme 11).

Acetoacetanilide and p-chloroacetoacetanilide were each C-monomethylated using a method based on that described by Kettrup and Grote[163] for the synthesis of 2-alkyl- and 2-allyl-acetoacetarylamides. The α-methylated β-ketoanilides (439) were then coupled with p-nitrophenylhydrazine to provide the oxidation substrates (440). Heating in AcOH again resulted in cyclisation of the hydrazones (440), affording 1-(4-nitrophenyl)-3,4-dimethyl-2-pyrazolin-5-one (444).

Scheme 11



a: Ar = Ph
b: Ar = 4-Cl-C_6H_4



(440)

(444)

(445)

a: Ar = Ph
b: Ar = 4-Cl-C_6H_4

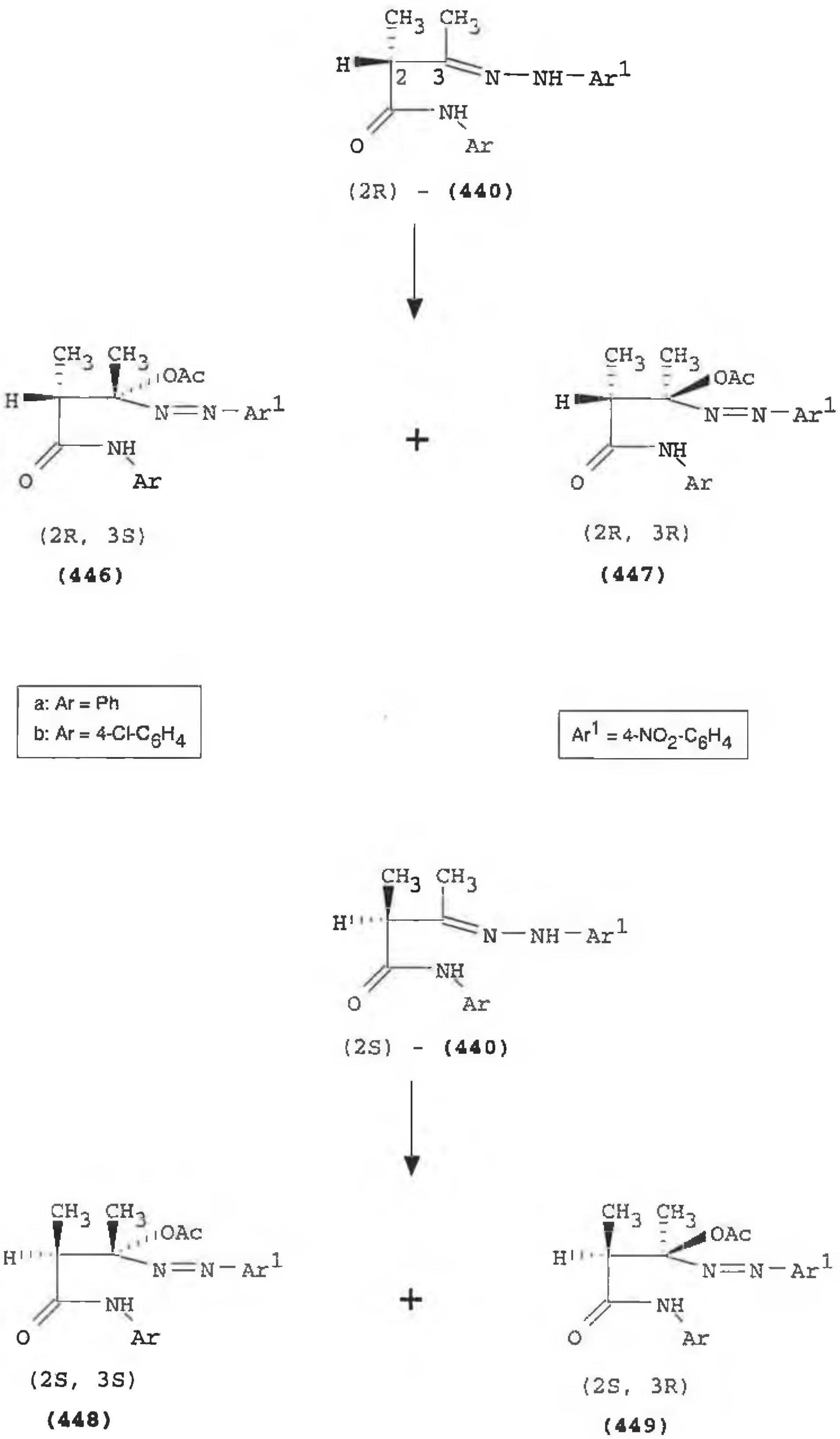
The cyclic product (444) tautomerises to the enone (445) in DMSO solution, giving a ^1H NMR spectrum containing an uncoupled 4-methyl singlet, and lacking a methine C<u>H</u> signal.

LTA oxidation of the hydrazones (440) in CH_2Cl_2 was expected to provide some interesting results, since they contain a chiral carbon, and intramolecular acetoxylation would result in the creation of a second asymmetric centre, giving diastereomeric azoacetate products (Scheme 12). However, according to Cram's rule[164,165], the four isomers (446)-(449) should not be formed in equal amounts.

Cram's rule allows prediction of the stereochemical direction of asymmetric induction in reactions of acyclic systems in which a new chiral centre is created adjacent to an old. Thus, in certain addition reactions, Cram's rule states that the predominant diastereomer will be that formed by approach of the entering group from the least hindered side of the double bond, when the rotational conformation of the C-C bond is such that the double bond is flanked by the two least bulky groups attached to the adjacent asymmetric centre.

if a Cram-type mechanism is observed for the introduction of the acetate group in the oxidation of the hydrazones (440), in each case the azoacetate (446) and its enantiomer (449) would be obtained as the major products, and their epimers (447) and (448) in lesser amounts (Scheme 13).

Scheme 12


(2R) - **(440)**

(2R, 3S) **(446)**

(2R, 3R) **(447)**

a: Ar = Ph
b: Ar = 4-Cl-C_6H_4

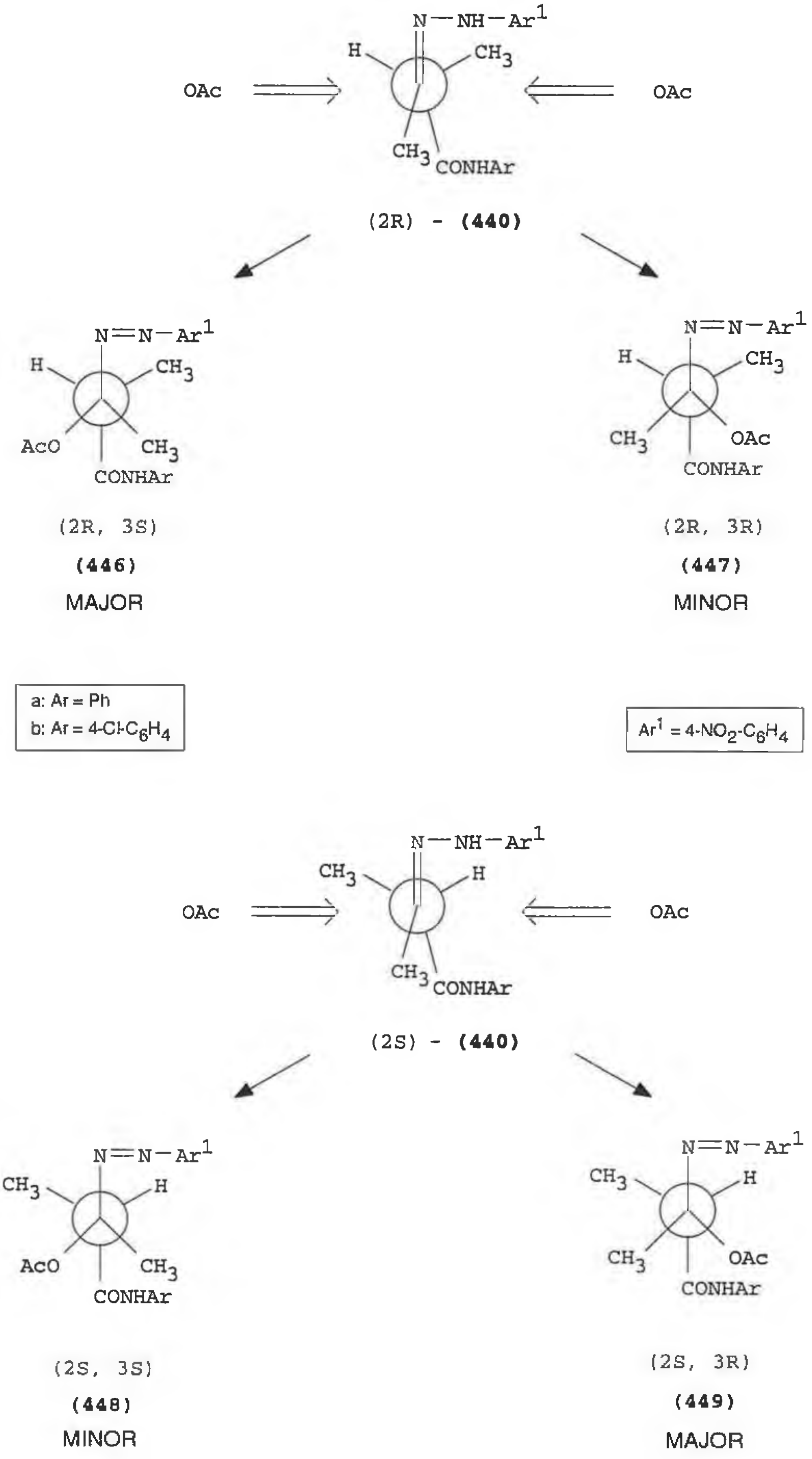
Ar^1 = 4-NO_2-C_6H_4

(2S) - **(440)**

(2S, 3S) **(448)**

(2S, 3R) **(449)**

Scheme 13


OAc
N—NH—Ar^1
H
CH$_3$
CH$_3$
CONHAr
OAc
(2R) - (440)
N=N—Ar^1
H
CH$_3$
AcO
CH$_3$
CONHAr
(2R, 3S)
(446)
MAJOR
N=N—Ar^1
H
CH$_3$
CH$_3$
OAc
CONHAr
(2R, 3R)
(447)
MINOR
a: Ar = Ph
b: Ar = 4-Cl-C$_6$H$_4$
Ar^1 = 4-NO$_2$-C$_6$H$_4$
OAc
N—NH—Ar^1
CH$_3$
H
CH$_3$
CONHAr
OAc
(2S) - (440)
N=N—Ar^1
CH$_3$
H
AcO
CH$_3$
CONHAr
(2S, 3S)
(448)
MINOR
N=N—Ar^1
CH$_3$
H
CH$_3$
OAc
CONHAr
(2S, 3R)
(449)
MAJOR

Hydrazone (440a) was reacted with LTA in CH_2Cl_2 to afford the azoacetate (442a) in 74% yield. ^1H NMR spectra (Figures 2 and 3) of this crude product indicated that, indeed, an unequal (3:1) mixture of diastereomers had been formed. Similarly, oxidation of the analogous hydrazone (440b) in CH_2Cl_2 gave a 78% yield of crude azoacetate (442b). The 400 MHz proton NMR spectrum (Figure 4) of this material showed that a 2.7 : 1 mixture of the major and minor isomers was present. It should be noted that expansion of the region around 1.85 ppm allowed partial resolution of the apparent singlet (unresolved at 270 MHz), revealing a major and a minor peak (Figure 5). Also, enlargement of the peaks near 3.20 ppm showed the methine proton of each component of the mixture clearly, as two quartets.

Obviously, a substantial degree of stereoselectivity had been achieved in these oxidative acetoxylation reactions, but had the azoacetates (446) and (449) been formed preferentially, in accordance with Cram's rule?

Fractional crystallisation of the crude azoacetate (442b) provided the dominant isomers in 34% yield (from hydrazone (440b)). Further recrystallisation from dilute ethanol solution gave crystals suitable for X-ray crystallographic analysis. Reflections were collected using graphite monochromated Mo radiation. The structure was solved by direct methods (SHELX86[166]), and refined by full matrix least squares (SHELX76[167]). The structure was refined to an R value of 8.66% with a weighted R value of 9.57% for 1557 reflections. The crystals were found to be monoclinic with refined unit cell parameters $a = 9.312$, $b = 10.649$, $c = 21.313$ Å, $\alpha = 90$, $\beta = 99.77$, $\gamma = 90^o$ and space group $P2_1/n$ with $Z = 4$. The unit cell is shown in Figure 6. The crystal structure is drawn in Figure 7, with hydrogen atoms omitted for clarity. The final positional parameters for all atoms other than hydrogen are listed in Table 1, bond lengths in Table 2 and bond angles in Table 3. The Fo and Fc tables are given in the Appendix.

The crystal structure clearly shows that the major isomers produced in the oxidation were the (2R,3S)- and (2S,3R)-azoacetates (446b) and (449b) respectively, proving that introduction of the acetate group had occurred selectively in the manner predicted by Cram's rule. The ^1H NMR spectrum of the pure dominant isomers (446b) and (449b) is shown in Figure 8.

Figure 2: 270 MHz ^{1}H NMR spectrum of azoacetate (442a) 0.50 - 10.70 ppm

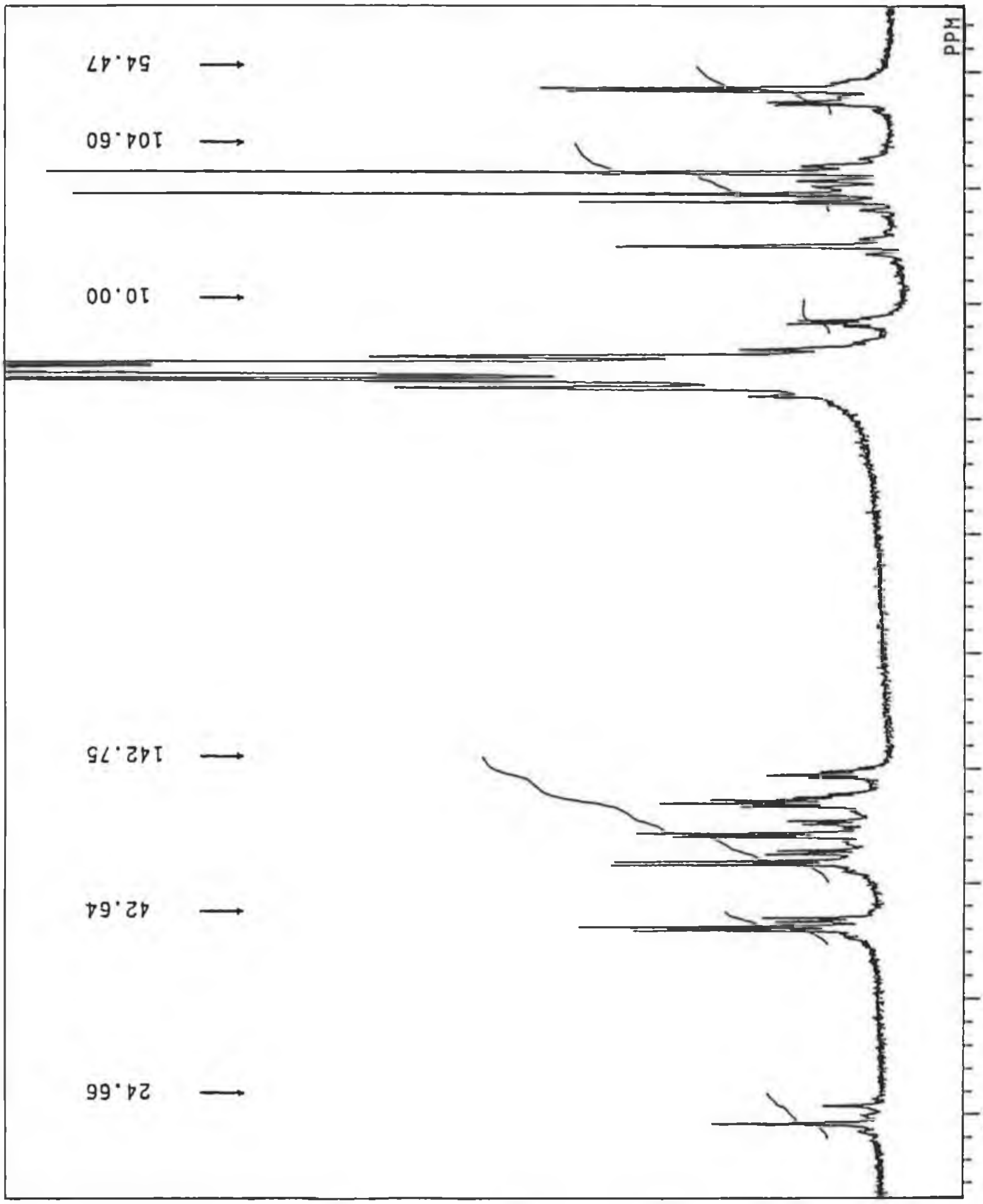


Figure 3: 270 MHz ^{1}H NMR spectrum of azoacetate (442a) 0.60 - 3.40 ppm and 6.70 - 10.50 ppm

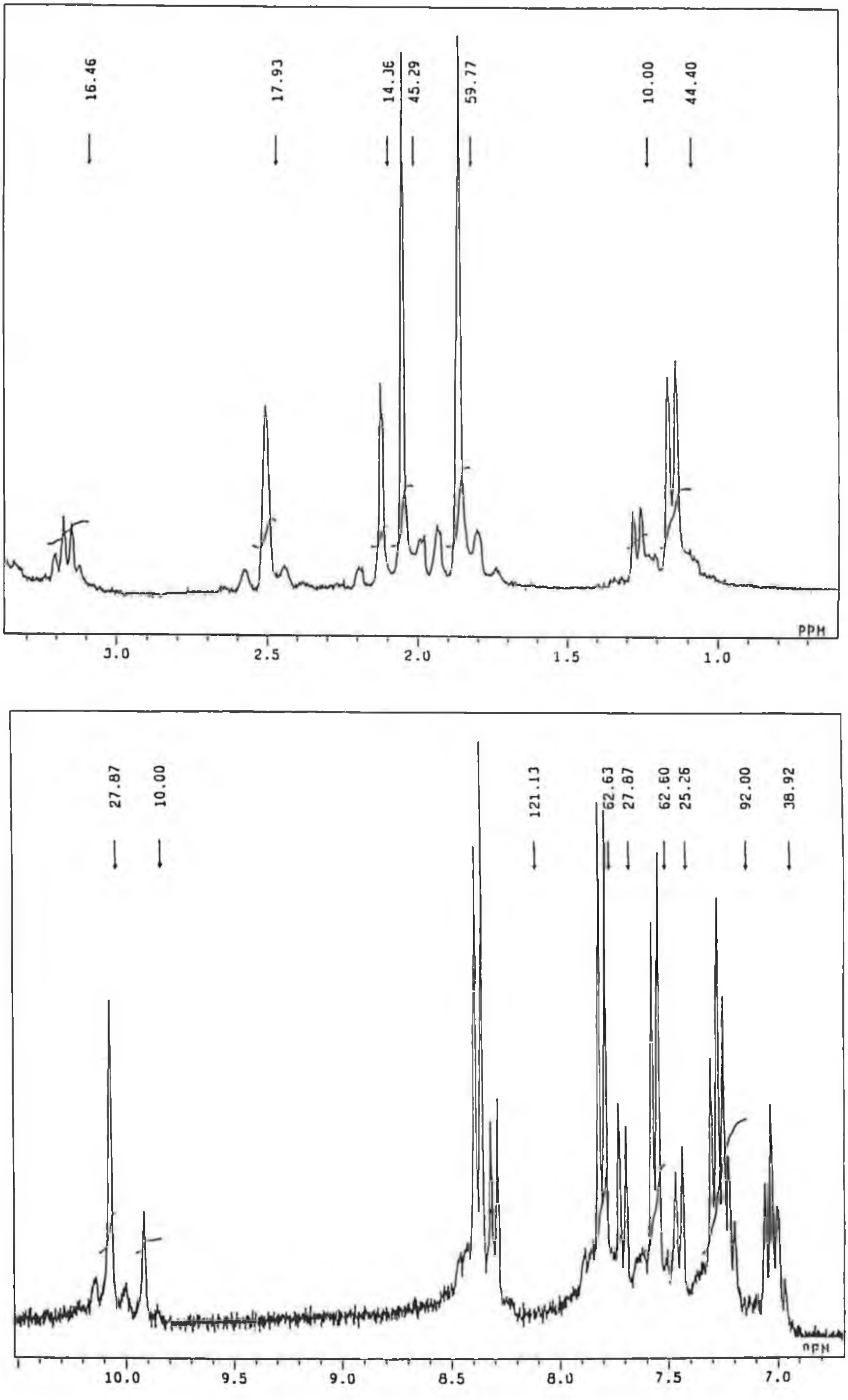


Figure 4: 400 MHz ^{1}H NMR spectrum of azoacetate (442b) 0.00 - 11.00 ppm

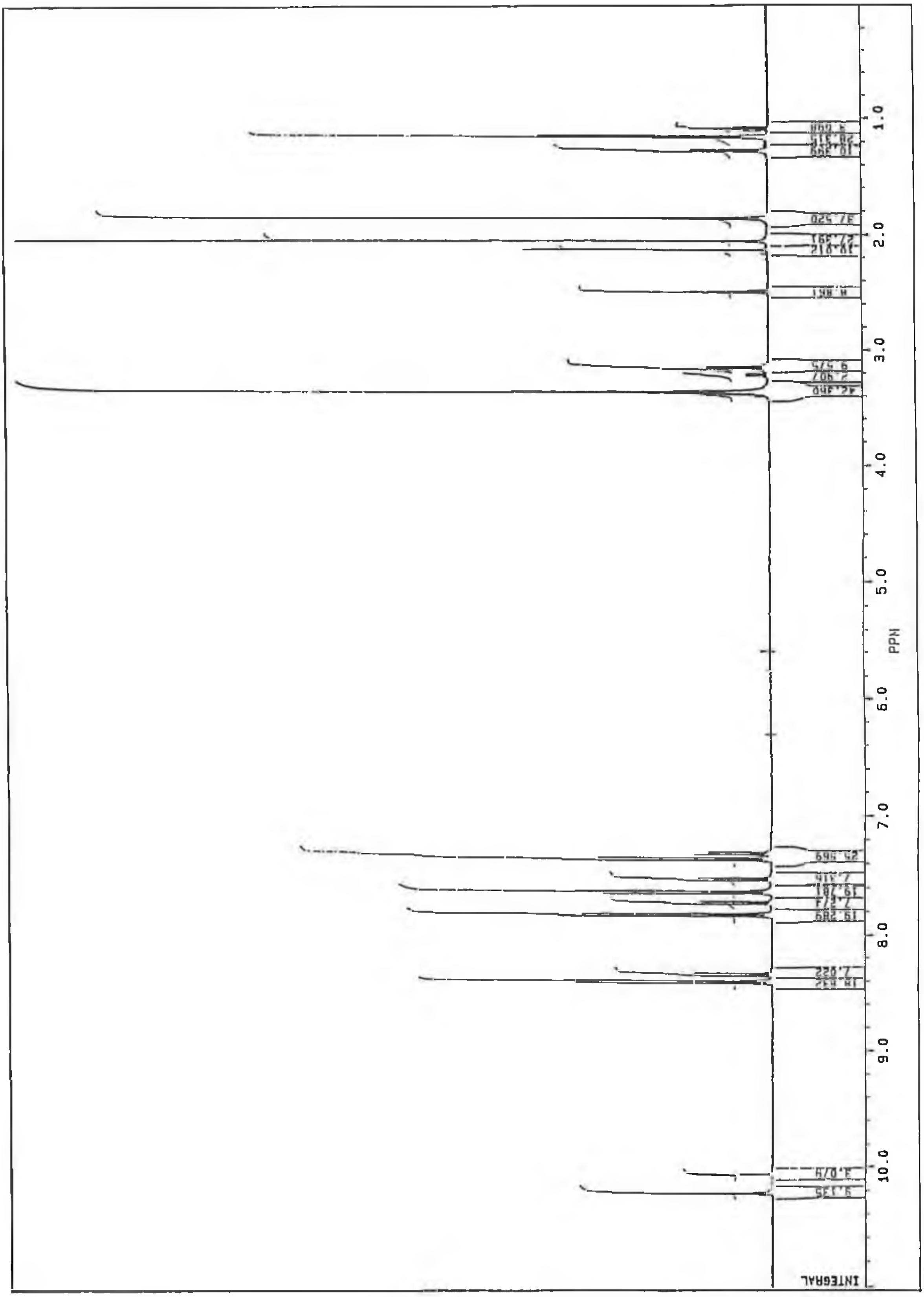


Figure 5: 400 MHz ^{1}H NMR spectrum of azoacetate (442b) 1.70 - 3.30 ppm

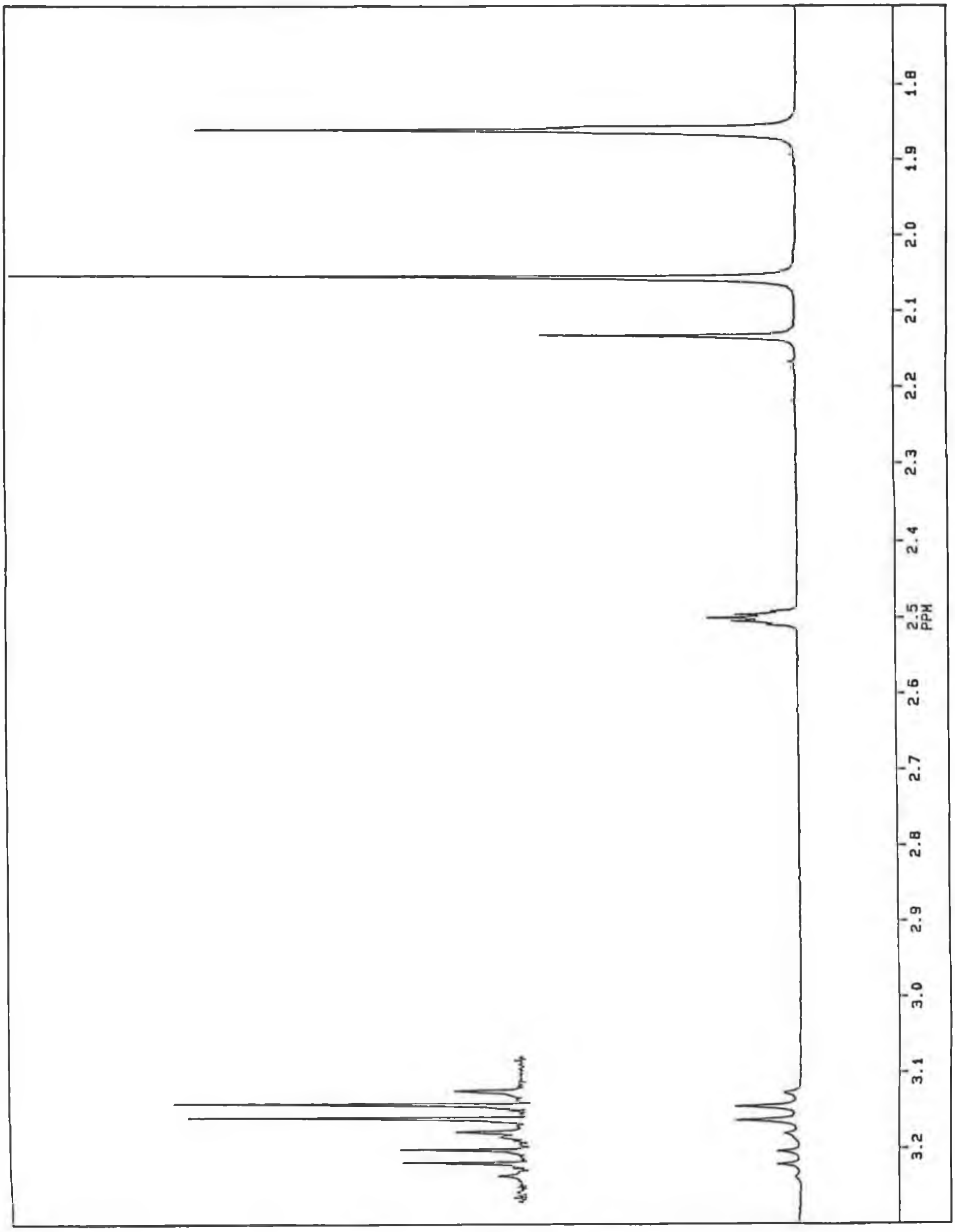


Figure 6: **Unit cell for major isomers of azoacetate (442b)**

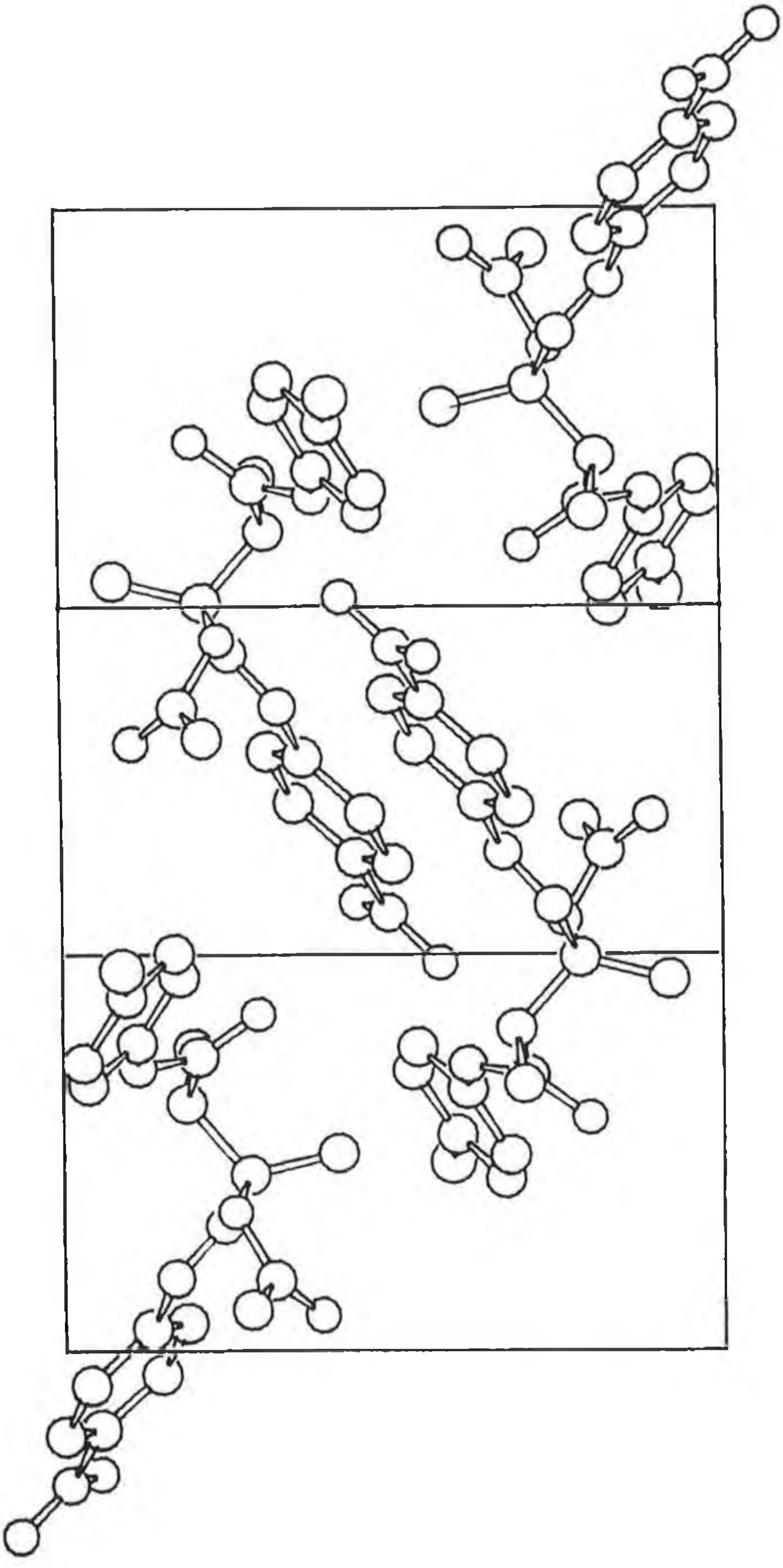


Figure 7: **X-ray crystal structure of the major isomers of azoacetate (442b)**

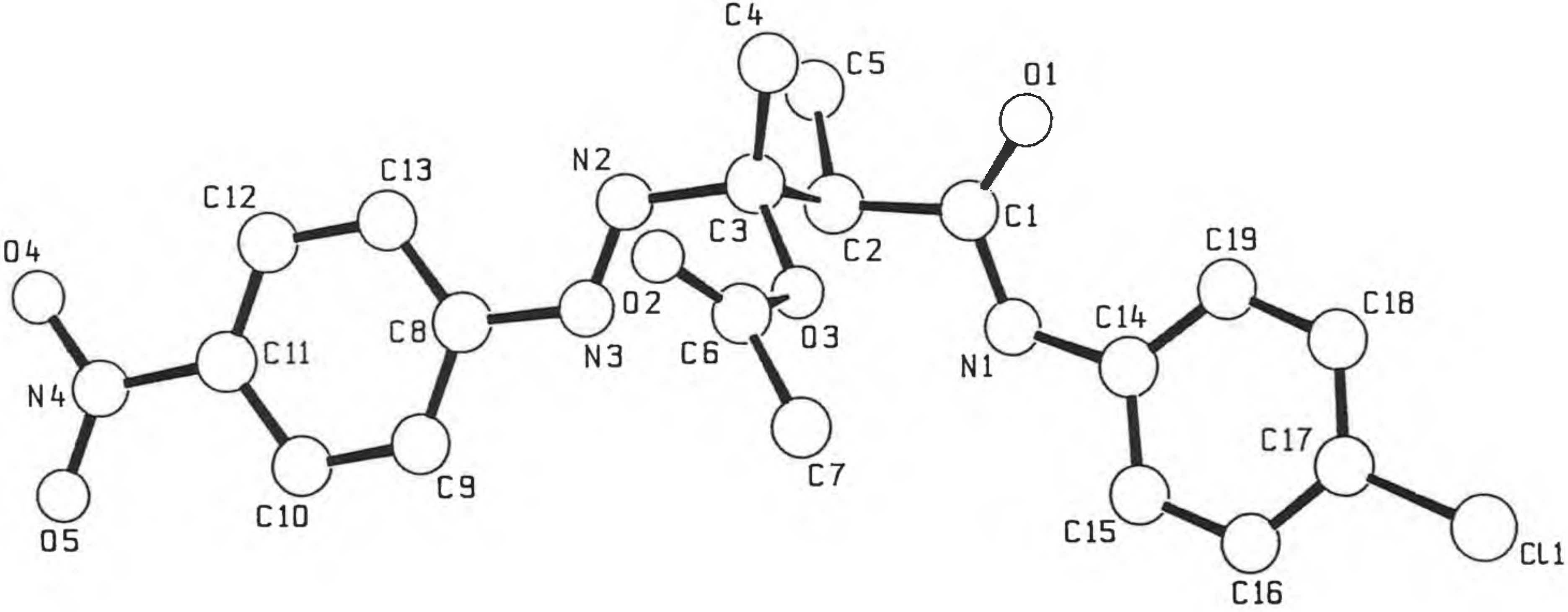


Table 1 : **Non-hydrogen atomic co-ordinates, with standard deviations in parentheses, for major isomers of azoacetate (442b)**

	X	Y	Z
Cl1	0.7253 (4)	0.0908 (3)	0.1253 (1)
C1	1.0089 (9)	0.2059 (9)	-0.1438 (4)
C2	1.0214 (8)	0.1875 (9)	-0.2137 (4)
C3	0.9185 (8)	0.2834 (9)	-0.2551 (4)
C4	0.9630 (11)	0.4183 (9)	-0.2500 (5)
C5	1.1804 (10)	0.1983 (12)	-0.2244 (5)
C6	0.6642 (10)	0.3209 (10)	-0.2617 (4)
C7	0.5329 (12)	0.2837 (15)	-0.2307 (7)
C8	0.8154 (9)	0.1318 (9)	-0.4077 (4)
C9	0.7188 (11)	0.0379 (10)	-0.4307 (4)
C10	0.7076 (11)	-0.0032 (10)	-0.4917 (5)
C11	0.7964 (11)	0.0525 (10)	-0.5305 (4)
C12	0.8928 (11)	0.1456 (10)	-0.5092 (4)
C13	0.9030 (10)	0.1859 (10)	-0.4462 (5)
C14	0.8886 (8)	0.1136 (8)	-0.0606 (4)
C15	0.7708 (10)	0.0388 (11)	-0.0545 (5)
C16	0.7207 (12)	0.0308 (11)	0.0030 (5)
C17	0.7900 (12)	0.0978 (10)	0.0534 (4)
C18	0.9095 (12)	0.1695 (10)	0.0496 (5)
C19	0.9589 (10)	0.1775 (9)	-0.0087 (4)
N1	0.9357 (7)	0.1126 (6)	-0.1205 (3)
N2	0.9138 (8)	0.2432 (7)	-0.3222 (3)
N3	0.8187 (8)	0.1693 (7)	-0.3421 (3)
N4	0.7821 (12)	0.0037 (10)	-0.5967 (4)
O1	1.0610 (8)	0.2970 (7)	-0.1138 (3)
O2	0.6584 (7)	0.3920 (7)	-0.3054 (4)
O3	0.7816 (6)	0.2604 (5)	-0.2329 (3)
O4	0.8676 (9)	0.0512 (9)	-0.6282 (4)
O5	0.6918 (13)	-0.0733 (8)	-0.6149 (4)

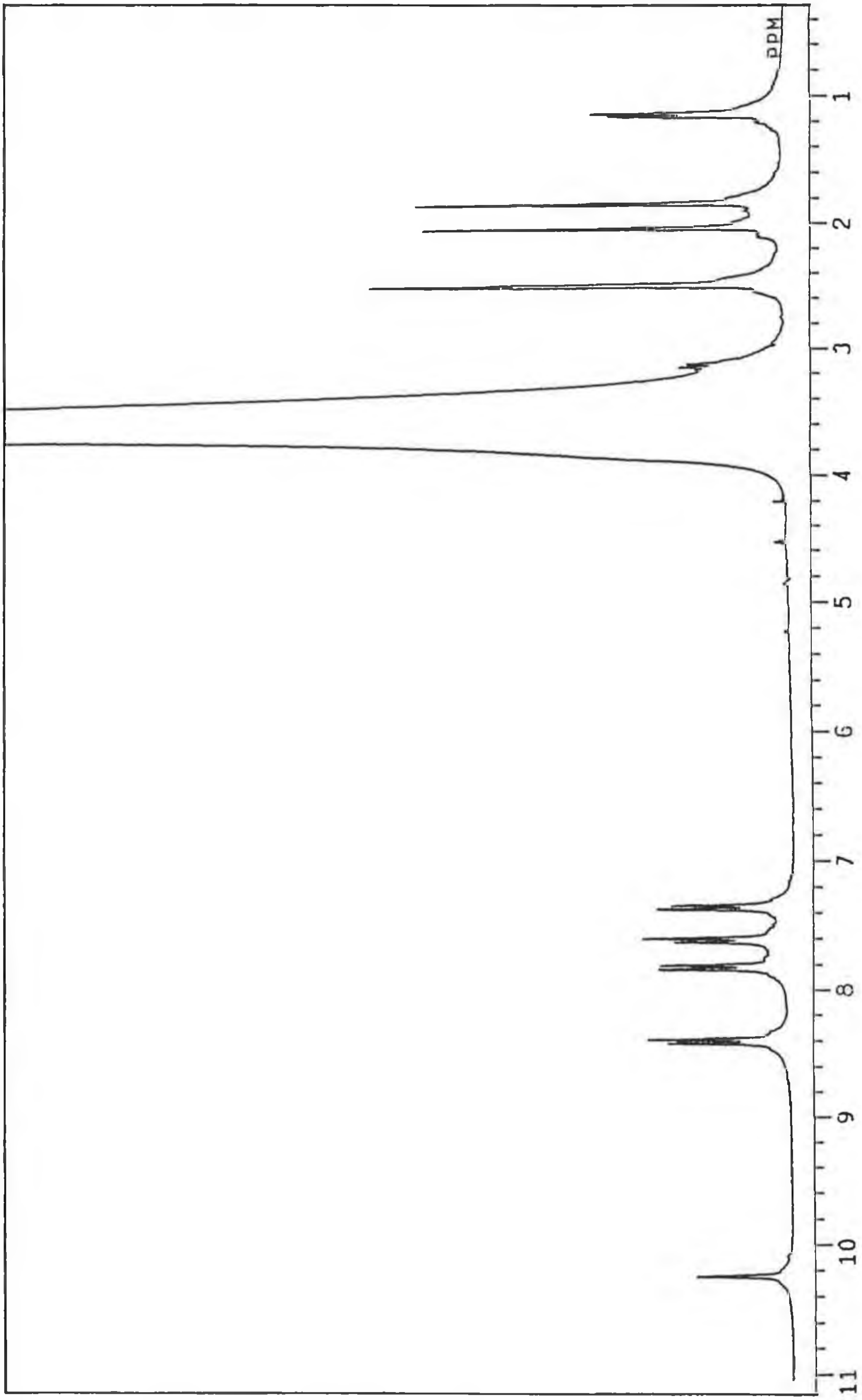
Table 2 : **Interatomic distances (Å), with standard deviations in parentheses, for major isomers of azoacetate (442b)**

Cl1 - C17	1.740 (9)
C1 - C2	1.525 (11)
C1 - N1	1.347 (10)
C1 - O1	1.217 (10)
C2 - C3	1.566 (12)
C2 - C5	1.541 (11)
C3 - C4	1.495 (13)
C3 - N2	1.486 (10)
C3 - O3	1.454 (9)
C6 - C7	1.537 (13)
C6 - O2	1.194 (10)
C6 - O3	1.326 (10)
C8 - C9	1.378 (13)
C8 - C13	1.377 (12)
C8 - N3	1.449 (10)
C9 - C10	1.359 (12)
C10 - C11	1.396 (13)
C11 - C12	1.362 (14)
C11 - N4	1.489 (12)
C12 - C13	1.398 (13)
C14 - C15	1.379 (12)
C14 - C19	1.367 (12)
C14 - N1	1.419 (9)
C15 - C16	1.386 (13)
C16 - C17	1.359 (14)
C17 - C18	1.363 (14)
C18 - C19	1.399 (12)
N2 - N3	1.207 (9)
N4 - O4	1.234 (12)
N4 - O5	1.192 (12)

Table 3 : **Bond angles, with standard deviations in parentheses, for major isomers of azoacetate (442b)**

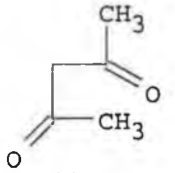
Angle	Degrees (^{O})	Angle	Degrees (^{O})
C2 - C1 - N1	113.2 (8)	C10 - C11 - N4	116.5 (10)
C2 - C1 - O1	121.8 (8)	C12 - C11 - N4	121.1 (10)
N1 - C1 - O1	125. 1 (7)	C11 - C12 - C13	118.5 (9)
C1 - C2 - C3	109.0 (7)	C8 - C13 - C12	119.5 (10)
C1 - C2 - C5	111.7 (7)	C15 - C14 - C19	119.4 (8)
C3 - C2 - C5	112.3 (7)	C15 - C14 - N1	116.9 (8)
C2 - C3 - C4	116.8 (7)	C19 - C14 - N1	123.6 (7)
C2 - C3 - N2	105.7 (7)	C14 - C15 - C16	120.7 (10)
C2 - C3 - O3	101.2 (6)	C15 - C16 - C17	118.7 (10)
C4 - C3 - N2	108.0 (7)	Cl1 - C17 - C16	119.0 (9)
C4 - C3 - O3	112.7 (7)	Cl1 - C17 - C18	119.0 (9)
N2 - C3 - O3	112.4 (6)	C16 - C17 - C18	122.0 (9)
C7 - C6 - O2	124.4 (9)	C17 - C18 - C19	118.8 (10)
C7 - C6 - O3	109.2 (9)	C14 - C19 - C18	120.2 (9)
O2 - C6 - O3	126.4 (8)	C1 - N1 - C14	125.5 (7)
C9 - C8 - C13	120.5 (8)	C3 - N2 - N3	115.3 (7)
C9 - C8 - N3	116.7 (8)	C8 - N3 - N2	114.5 (7)
C13 - C8 - N3	122.7 (9)	C11 - N4 - O4	114.3 (11)
C8 - C9 - C10	120.9 (9)	C11 - N4 - O5	119.5 (10)
C9 - C10 - C11	118.1 (10)	O4 - N4 - O5	126.2 (11)
C10 - C11 - C12	122.4 (9)	C3 - O3 - C6	117.9 (6)

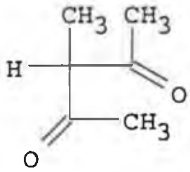
Figure 8: 270 MHz ^{1}H NMR spectrum of azoacetates (446b) and (449b) 0.30 - 11.20 ppm



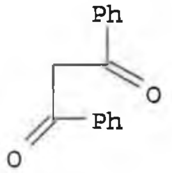
LTA oxidation of the hydrazones (440) was then examined in AcOH. Here, the azoacetates (442) were again produced in good yields, and no azoalkenes (443) were detected. These results were surprising since the hydrazones (440) contain an enolisable methine proton and might therefore be expected to tautomerise (at least to some extent) to the enehydrazines (441) in acetic acid solution, and yield the azoalkenes (443) on treatment with LTA. Particularly curious is the fact that α-unsubstituted β-ketoanilide hydrazones (405) had been oxidised exclusively to the azoalkenes (416), while, under the same conditions, the analogous α-methylated species (440) afforded azoacetates (442) as the sole oxidation products.

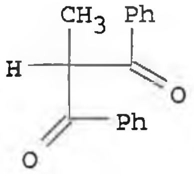
Apparently, the electron-releasing ability of the appended α-CH_3 is sufficiently powerful to destroy the lability of the enolisable methine proton, and destabilise the enehydrazine tautomer with respect to the hydrazone form. Indeed, inductive effects such as this have been reported. Burdett and Rogers[168], in their study of keto-enol tautomerism in β-dicarbonyl compounds, found that alkyl substitution in the α-position resulted on a large reduction in the enol content of such compounds. For example, the enol content of pentane-2,4-dione (450) was determined to be 81%, whereas its α-methylated counterpart (451) contained only 30% enol tautomer.


(450)


(451)

Moreover, Allen and Dwek[169], report the enol content of 1,3-diphenylpropane-1,3-dione (452) to be 100%, while in 2-methyl-1,3-diphenylpropane-1,3-dione (453), the percentage enol is zero.


(452)


(453)

In addition, although α-unsubstituted acetoacetanilides are known to form metal chelate complexes, through reaction of the metal atom with the C3 oxygen of the acyl group in its enol form[170], Kettrup and Grote[163] found that α-monoalkylated acetoacetanilides were unable to form metal chelates, since they exist only in the keto form.

The ^1H NMR spectrum of the crude azoacetate (442b) produced in the LTA/AcOH oxidation of hydrazone (440b) indicated that, again, an approximately 3:1 mixture of diastereomers had been formed, the major products being (446b) and (449b), in keeping with

Cram's rule. Removal of the dominant isomers by fractional crystallisation gave (447b) and (448b) in about 92% d.e.. ^{1}H NMR spectra of these minor isomers are given in Figures 9 and 10.

The reactions of the acetoacetanilide p-nitrophenylhydrazones discussed above are summarised in Scheme 14.

Figure 9: 270 MHz ^{1}H NMR spectrum of azoacetates (447b) and (448b) 0.70 - 10.50 ppm

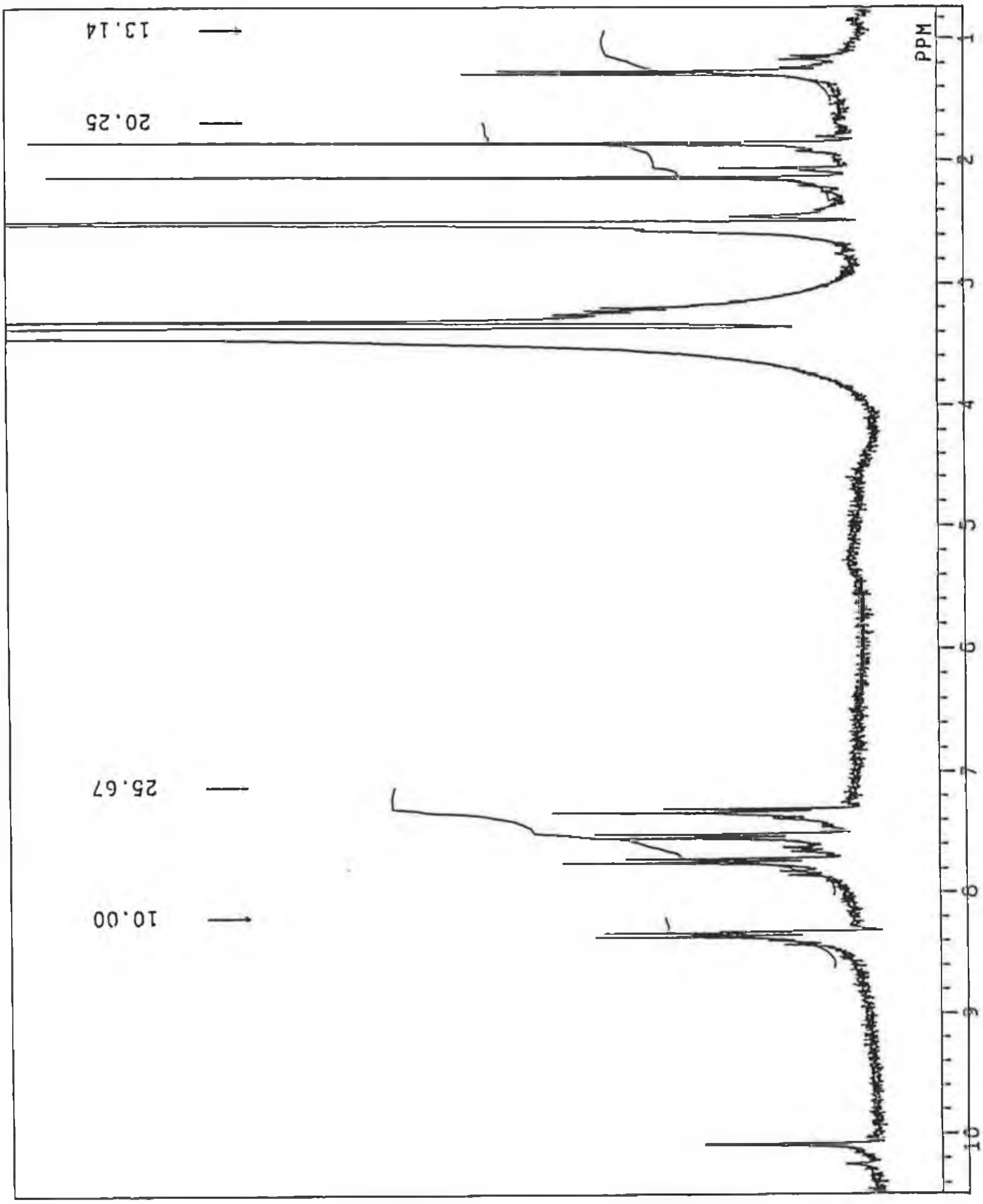
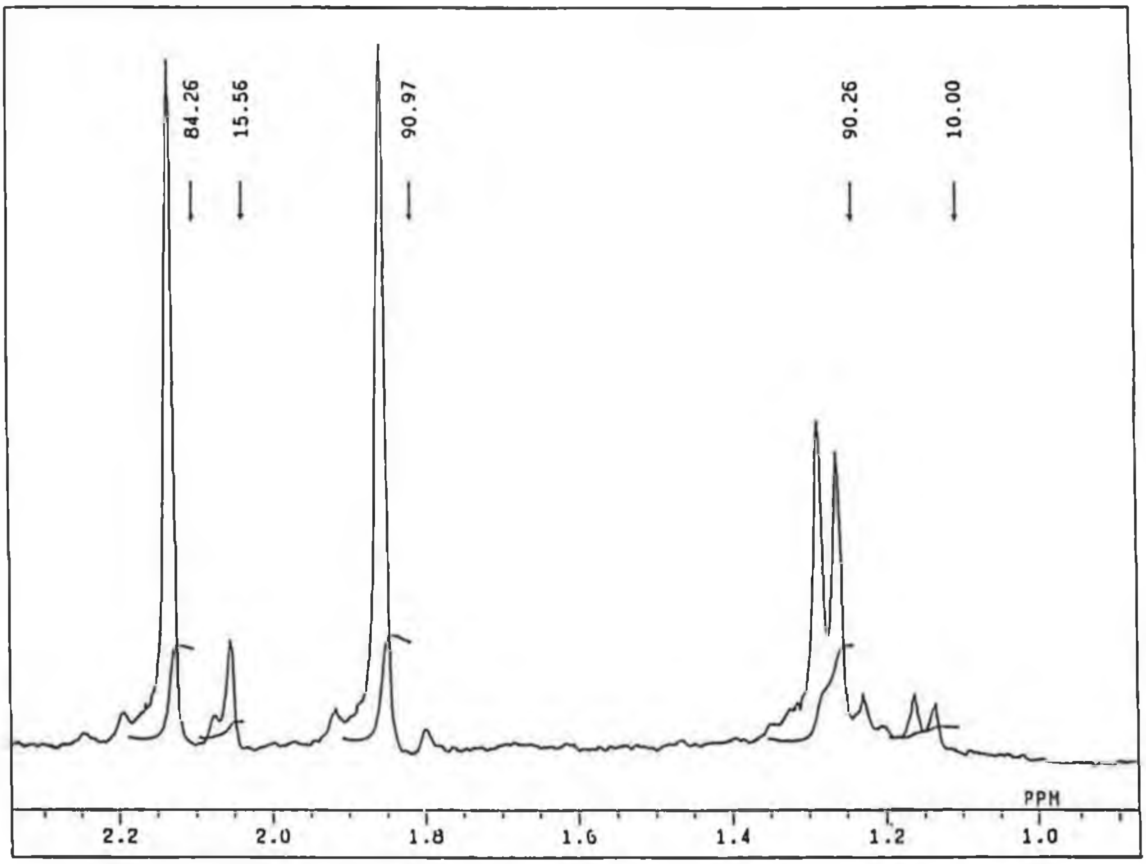
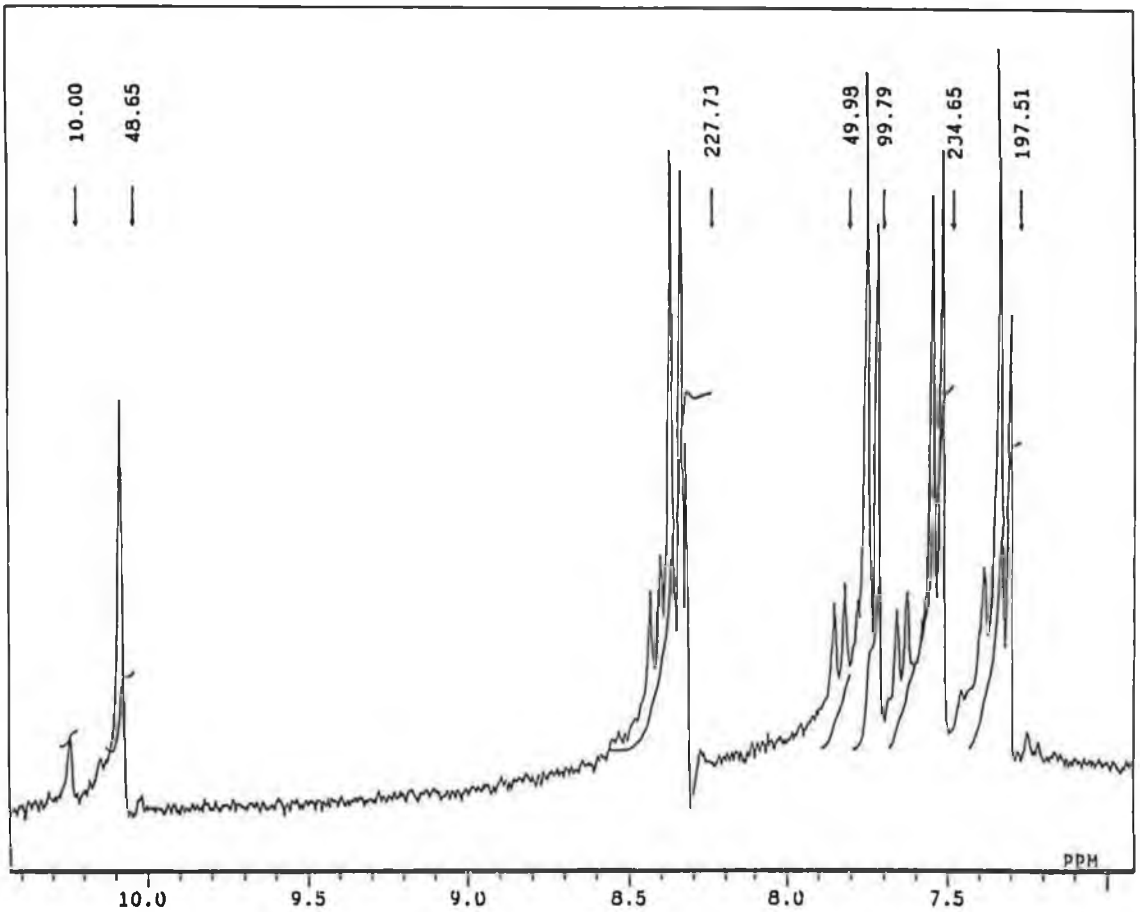
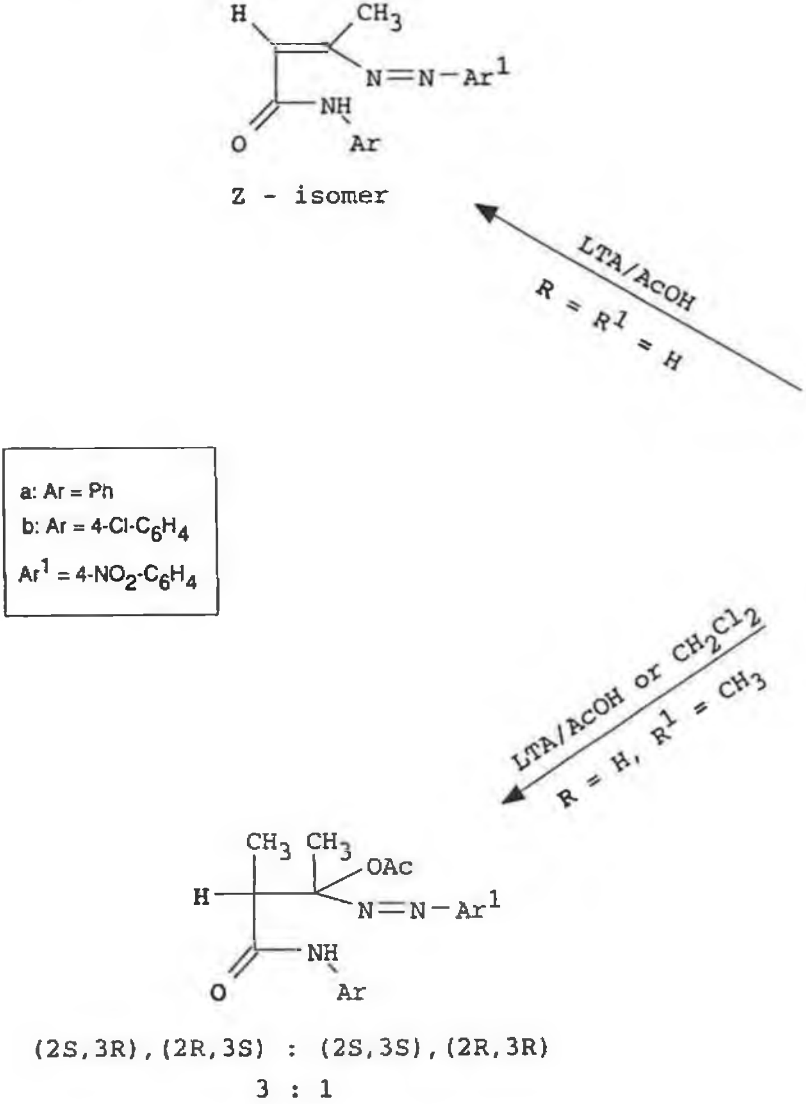


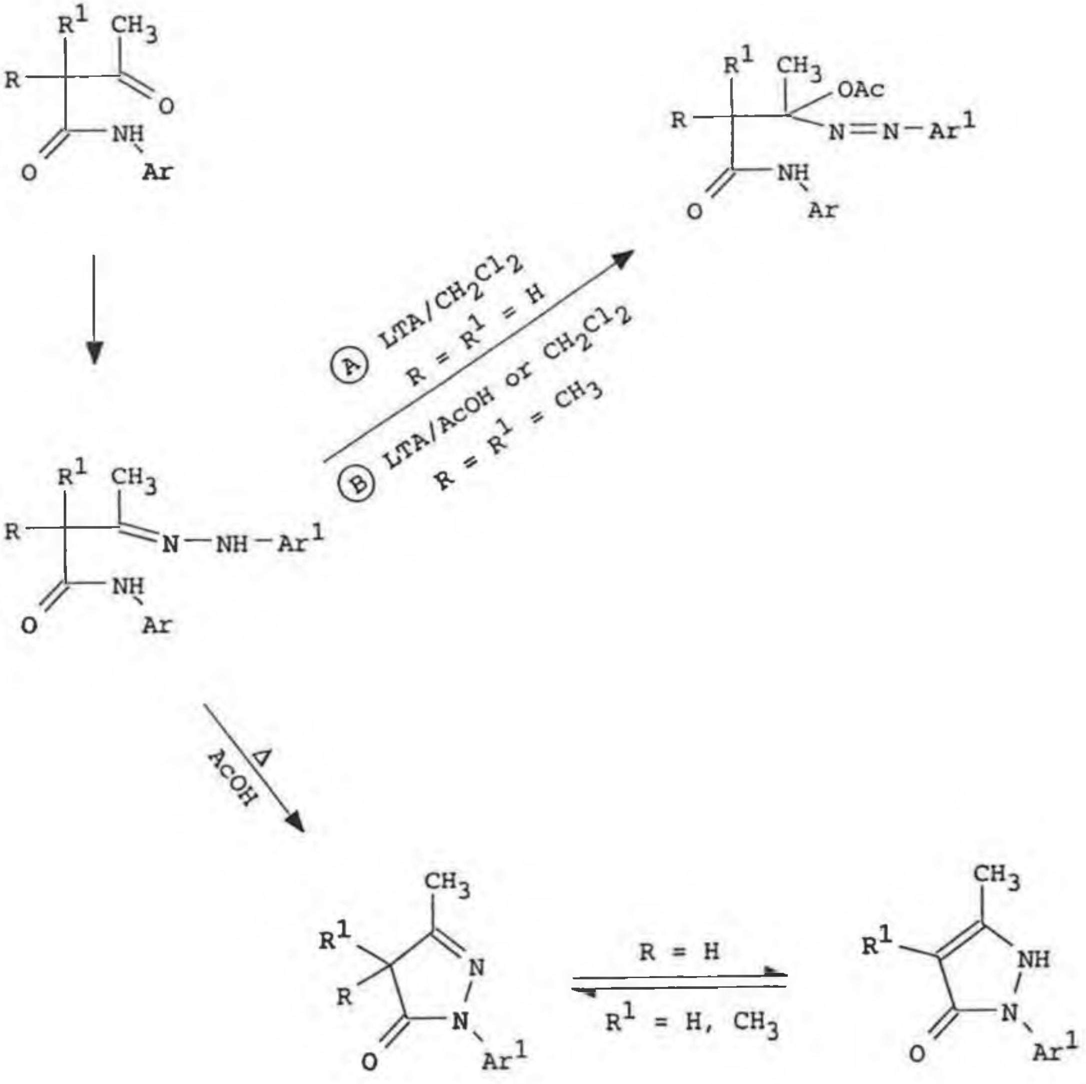
Figure 10: 270 MHz ^{1}H NMR spectra of azoacetates (447b) and (448b) 0.90 - 2.35 ppm and 7.00 - 10.40 ppm





Scheme 14


H
CH$_3$
N=N−Ar^1
NH
O
Ar
Z - isomer
LTA/AcOH
R = R^1 = H
a: Ar = Ph
b: Ar = 4-Cl-C$_6$H$_4$
Ar^1 = 4-NO$_2$-C$_6$H$_4$
LTA/AcOH or CH$_2$Cl$_2$
R = H, R^1 = CH$_3$
CH$_3$
CH$_3$
OAc
H
N=N−Ar^1
NH
O
Ar
(2S,3R),(2R,3S) : (2S,3S),(2R,3R)
3 : 1


R1
CH3
R
O
NH
Ar
Ⓐ LTA/CH2Cl2
R = R1 = H
Ⓑ LTA/AcOH or CH2Cl2
R = R1 = CH3
OAc
N=N-Ar1
N-NH-Ar1
Δ
AcOH
N
Ar1
R = H
R1 = H, CH3
NH

2.1.3 Experimental

Melting points were determined in open capillary tubes with a Gallenkamp melting point apparatus, and are uncorrected. IR spectra were recorded for KBr discs or nujol mulls with a Perkin-Elmer 983-G spectrometer. NMR spectra (^{1}H and ^{13}C) were measured for solutions in $CDCl_3$ or DMSO-d_6 with Perkin-Elmer R12B 60 MHz, JEOL GX-FT 270 MHz and Bruker AC-F 400 MHz spectrometers, and referenced to tetramethylsilane or residual solvent H. Elemental analyses were performed in the Microanalytical Laboratory, University College Dublin. Common reagent grade chemicals were purchased from Aldrich Chemical Company, and were used as received. LTA was washed with dry diethyl ether, under suction, before use.

(i) Synthesis of acetoacetanilide p-nitrophenylhydrazone (405a)

7.66g (50 mmoles) p-nitrophenylhydrazine was dissolved in 100mls AcOH at room temperature. 8.86g (50 mmoles) acetoacetanilide was added with good stirring. A yellow solid precipitated almost immediately. After stirring for 20 minutes, the product was filtered (14.62g; 94%). MP 182-183^{o}C (EtOH). IR (nujol mull) 3315, 3236, 1643 cm^{-1}. ^{1}H NMR (270 MHz; DMSO-d$_6$) δ 2.04 (s, 3H), 3.43 (s, 2H), 7.04-7.33 (m, 5H), 7.62 (d, 2H, J = 8.8 Hz), 8.09 (d, 2H, J = 8.1 Hz), 9.94 (s, 1H), 10.14 (s, 1H).

(ii) Synthesis of p-chloroacetoacetanilide p-nitrophenylhydrazone (405b)

This hydrazone was prepared in a 90% yield using the procedure described above. MP 190-191^{o}C (EtOH). IR (KBr) 3305, 3232, 1644 cm^{-1}. ^{1}H NMR (270 MHz; DMSO-d$_6$) δ 2.02 (s, 3H), 3.41 (s, 2H), 7.19 (d, 2H), 7.37 (d, 2H), 7.64 (d, 2H), 8.10 (d, 2H), 9.95 (s, 1H), 10.28 (s, 1H).

(iii) Preparation of 1-(4-nitrophenyl)-3-methyl-2-pyrazolin-5-one (412)

(a) From hydrazone (405a)

3.12g (10 mmoles) hydrazone (405a) was refluxed in 70mls AcOH for 15 minutes. On cooling, the beige product crystallised from solution (2.02g; 92%). MP 210-211^{o}C (AcOH) (lit.[155] 205-210^{o}C). IR (KBr) 1622 cm^{-1}. ^{1}H NMR (270 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%.

(b) From hydrazone (405b)

Similar treatment of this hydrazone gave the pyrazolin-5-one (412) in 84% yield.

(iv) Oxidation of hydrazone (405a) with LTA in CH_2Cl_2

1.00g (3.2 mmoles) of hydrazone (405a) was suspended in 30mls CH_2Cl_2 and 1.73g (4 mmoles; 120 mole%) LTA was added. After stirring at room temperature for 2 hours, the white precipitate of $Pb(OAc)_2$ was removed by filtration. The filtrate was washed with $NaHCO_3$ solution, dried over Na_2SO_4, and the solvent removed under reduced pressure to give an orange/red oil. Crystallisation from diethyl ether/petroleum ether (40-60^{o}) gave the mustard-coloured azoacetate (406a) (0.89g; 75%). An analytical sample was obtained by recrystallisation from ethanol. MP 116-118^{o}C. IR (KBr) 3325, 1720, 1681 cm^{-1}. ^{1}H NMR (270 MHz; DMSO-d$_6$) δ 1.78 (s, 3H), 2.12 (s, 3H), 3.15 (q, 2H), 7.05 (t, 1H), 7.30 (t, 2H), 7.58 (d, 2H, J = 8.8 Hz), 7.82 (d, 2H, J = 9.2 Hz), 8.40 (d, 2H, J = 8.8 Hz), 10.01 (s, 1H). ^{13}C NMR (67.5 MHz; CDCl$_3$) 21.7, 23.2, 44.9, 101.2, 119.8, 123.2, 124.5, 124.6, 128.9, 137.6, 148.8, 154.1, 166.3, 170.0 ppm. $C_{18}H_{18}N_4O_5$ requires C, 58.37; H, 4.90; N, 15.13%. Found C, 58.47; H, 5.13; N, 15.28%.

(v) Oxidation of hydrazone (405b) with LTA in CH_2Cl_2

This hydrazone was oxidised as described for hydrazone (405a), except here removal of the solvent gave the azoacetate product (406b) directly as a solid, in 91% yield. Recrystallisation from ethanol afforded an analytical sample. MP 149-150°C. IR (KBr) 3325, 1725, 1681 cm^{-1}. ^1H NMR (270 MHz; DMSO-d_6) δ 1.78 (s, 3H), 2.12 (s, 3H), 3.15 (q, 2H), 7.35 (d, 2H, J = 7.3 Hz), 7.61 (d, 2H, J = 8.1 Hz), 7.82 (d, 2H, J = 8.1 Hz), 8.40 (d, 2H, J = 7.3 Hz), 10.21 (s, 1H). ^{13}C NMR (67.5 MHz; DMSO-d_6) 21.9, 23.2, 43.8, 101.2, 121.3, 123.5, 125.5, 127.4, 129.0, 138.2, 149.0, 154.4, 166.6, 169.5 ppm. $C_{18}H_{17}N_4O_5Cl$ requires C, 53.40; H, 4.23; N, 13.84%. Found C, 53.24; H, 4.07; N, 13.81%.

(vi) Oxidation of hydrazone (405a) with LTA in AcOH

3.41g (7.7 mmoles; 120 mole%) LTA was added to a suspension of 2.00g (6.4 mmoles) hydrazone (405a) in 40mls AcOH. The resultant red solution was stirred at room temperature for 1 hour. Dropwise addition of water precipitated the red azoalkene product (416a) (1.28g; 64%). MP 141-142°C (EtOH). IR (nujol mull) 3297, 1639 cm^{-1}. ^1H NMR (270 MHz; $CDCl_3$) δ 2.18 (s, 3H), 6.58 (s, 1H), 7.12 (t, 1H), 7.34 (t, 2H), 7.57 (d, 2H, J = 8.1 Hz), 7.92 (d, 2H, J = 8.8 Hz), 8.41 (d, 2H, J = 8.8 Hz), 9.91 (s, 1H). ^{13}C NMR (67.5 MHz; $CDCl_3$) 16.9, 119.5, 123.6, 124.6, 125.2, 129.3, 132.6, 138.1, 149.5, 155.6, 155.8, 162.7 ppm. Calculated for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06%. Found C, 62.13; H, 4.59; N, 18.20%.

(vii) Oxidation of hydrazone (405b) with LTA in AcOH

This hydrazone was oxidised as outlined in (vi) and gave the azoalkene (416b) in 63% yield. MP 158-159°C (EtOH). IR (KBr) 3283, 1642 cm^{-1}. ^1H NMR (270 MHz; $CDCl_3$) δ 2.20 (s, 3H), 6.58 (s, 1H), 7.30 (d, 2H, J = 8.8 Hz), 7.52 (d, 2H, J = 8.8 Hz), 7.91 (d, 2H, J = 9.2 Hz), 8.44 (d, 2H, J = 9.2 Hz), 9.95 (s, 1H). $C_{16}H_{13}N_4O_3Cl$ requires C, 55.74; H, 3.80; N, 16.26%. Found C, 55.98; H, 3.66; N, 16.38%.

(viii) Synthesis of α,α-dimethylacetoacetanilide (435a)

22.15g (0.125 moles) acetoacetanilide was refluxed with 34.55g (0.25 moles; 200 mole%) anhydrous K_2CO_3 and 106.45g (0.75 moles; 600 mole%) CH_3I in 250mls acetone for 8 hours. TLC (100% $CHCl_3$) indicated incomplete reaction, so a further 17.74g (0.125 moles; 100 mole%) CH_3I was added. Reflux was continued for 1.5 hours. The reaction mixture was poured into 500g ice/water with vigorous stirring. A yellow oil formed which was separated and crystallised from benzene/petroleum ether (40-60^o). 21.30g (83%) of N-phenyl-2,2-dimethyl-3-oxobutanamide (435a) was obtained as white crystals. An analytical sample was prepared by recrystallisation from aqueous ethanol. MP 87-88^{o}C (lit.[171] 87.5-88^{o}C). IR (KBr) 3286, 1708, 1651 cm^{-1}. ^{1}H NMR (270 MHz; DMSO-d_6) δ 1.37 (s, 6H), 2.15 (s, 3H), 7.06-7.61 (m, 5H), 9.44 (s, 1H). ^{13}C NMR (67.5 MHz; DMSO-d_6) 22.1, 26.0, 56.5, 120.6, 123.8, 128.7, 138.9, 171.9, 207.5 ppm. $C_{12}H_{15}NO_2$ requires C, 70.22; H, 7.37; N, 6.83%. Found C, 70.44; H, 7.52; N, 6.90%.

(ix) Synthesis of α,α-dimethyl-p-chloroacetoacetanilide (435b)

p-Chloroacetoacetanilide was dimethylated as described in (viii). N-(4-Chlorophenyl)-2,2-dimethyl-3-oxobutanamide (435b) was obtained in 78% yield. Recrystallisation from aqueous ethanol provided an analytical sample. MP 88-89^{o}C. IR (KBr) 3233, 1710, 1662 cm^{-1}. ^{1}H NMR (270 MHz; DMSO-d_6) δ 1.38 (s, 6H), 2.16 (s, 3H), 7.37 (d, 2H, J = 8.8 Hz), 7.65 (d, 2H, J = 8.8 Hz), 9.60 (s, 1H). ^{13}C NMR (67.5 MHz; DMSO-d_6) 22.2, 26.0, 56.7, 122.3, 127.7, 128.7, 138.0, 172.2, 207.7 ppm. Calculated for $C_{12}H_{14}NO_2Cl$: C, 60.13; H, 5.89; N, 5.85%. Found C, 59.84; H, 6.03; N, 5.83%.

(x) Preparation of α,α-dimethylacetoacetanilide p-nitrophenylhydrazone (436a)

This hydrazone was prepared using the procedure outlined in (i), except here, the product did not precipitate from solution until 15 minutes after mixing of the reactants. The hydrazone (436a) was obtained in 89% yield. MP 180-181^{o}C (EtOH). IR (KBr) 3329, 1684 cm^{-1}. ^{1}H NMR (60 MHz; DMSO-d_6) δ 1.30 (s, 6H), 1.80 (s, 3H), 6.90-8.20 (m, 9H), 9.15 (bs, 1H), 9.80 (bs, 1H).

(xi) Preparation of α,α-dimethyl-p-chloroacetoacetanilide p-nitrophenylhydrazone (436b)

The same methodology was used to prepare the hydrazone (436b) in 92% yield. MP 194-198^{o}C. IR (KBr) 3316, 1665 cm^{-1}.

(xii) Preparation of 1-(4-nitrophenyl)-3,4,4-trimethyl-2-pyrazolin-5-one (438)

(a) From hydrazone (436a)

0.34g (1 mmole) hydrazone (436a) was refluxed in 20mls AcOH for 30 minutes. The resultant solution was cooled and dropwise addition of water precipitated the product as a beige solid (0.145g; 59%). MP 129-130^{o}C. IR (KBr) 1719 cm^{-1}. ^{1}H NMR (270 MHz; DMSO-d_6) δ 1.28 (s, 6H), 2.13 (s, 3H), 8.10 (d, 2H, J = 9.2 Hz), 8.29 (d, 2H, J = 8.8 Hz). ^{13}C NMR (67.5 MHz; DMSO-d_6) 13.4, 20.8, 50.3, 117.7, 125.2, 143.2, 143.4, 167.3, 177.5 ppm. $C_{12}H_{13}N_3O_3$ requires C, 58.29; H, 5.30; N, 17.00%. Found C, 58.33; H, 5.41; N, 16.91%.

(b) From hydrazone (436b)

Cyclisation of hydrazone (436b) was achieved as described in (a), giving the pyrazolin-5-one (438) in a 39% yield.

(xiii) Oxidation of hydrazone (436a) with LTA in CH_2Cl_2

0.51g (1.5 mmoles) of hydrazone (436a) was dissolved in 20mls CH_2Cl_2 and treated with 0.80g (1.8 mmoles; 120 mole%) LTA. After stirring at room temperature for 1 hour, the reaction mixture was worked-up as described in (iv). Removal of the solvent gave the azoacetate (437a) as a yellow solid (0.48g; 80%). Recrystallisation from ethanol provided orange crystals. MP 160-161^{o}C. IR (KBr) 3383, 1731, 1667 cm^{-1}. ^{1}H NMR (270 MHz; DMSO-d_6) δ 1.31 (s, 3H), 1.40 (s, 3H), 1.88 (s, 3H), 2.19 (s, 3H), 7.07 (t, 1H), 7.30 (t, 2H), 7.57 (d, 2H, J = 7.5 Hz), 7.76 (d, 2H, J = 8.8 Hz), 8.37 (d, 2H, J = 8.8 Hz), 9.08 (s, 1H). ^{13}C NMR (67.5 MHz; DMSO-d_6) 17.0, 20.4, 21.3, 50.7, 103.5, 120.9, 123.0, 123.5, 124.7, 128.1, 138.3, 148.2, 153.6, 168.5, 170.6 ppm. Calculated for $C_{20}H_{22}N_4O_5$: C, 60.29; H, 5.57; N, 14.07%. Found C, 60.25; H, 5.74; N, 14.00%.

(xiv) Oxidation of hydrazone (436b) with LTA in CH_2Cl_2

Oxidation of this hydrazone was carried out as reported in (iv). Evaporation of the solvent yielded the azoacetate (437b) (61%). An analytical sample was prepared by recrystallisation from chloroform/petroleum ether (40-60^{o}). MP 202-204^{o}C. IR (KBr) 3383, 1727, 1668 cm^{-1}.

(xv) Oxidation of hydrazone (436a) with LTA in AcOH

The reaction was performed as outlined in (vi). Addition of water to the orange solution precipitated the azoacetate (437a) in 98% yield.

(xvi) Oxidation of hydrazone (436b) with LTA in AcOH

7.97g (18 mmoles; 120 mole%) LTA was added to a suspension of 5.62g (15 mmoles) of hydrazone (436b) in 150mls AcOH. After stirring at room temperature for 1 hour, the orange solid that had precipitated was collected (4.20g; 65%). The product was analytically identical to the azoacetate (437b) obtained from the oxidation in CH_2Cl_2.

(xvii) Synthesis of α-methylacetoacetanilide (439a)

8.86g (50 mmoles) acetoacetanilide, 6.92g (50 mmoles; 100 mole%) anhydrous K_2CO_3 and 10.66g (75 mmoles; 150 mole%) CH_3I were refluxed in 75mls acetone for 4.5 hours. The reaction mixture was cooled and poured into 150g ice/water, with vigorous stirring, to precipitate

N-phenyl-2-methyl-3-oxobutanamide (439a) as a white solid (6.98g; 73%). Recrystallisation from aqueous ethanol provided analytically pure material. MP 138-139°C (lit.[172] 137-139°C (water)). IR (KBr) 3233, 1717, 1639 cm^{-1}. ^1H NMR (60 MHz; $CDCl_3$) δ 1.55 (d, 3H), 2.30 (s, 3H), 3.55 (q, 1H), 6.90-7.70 (m, 5H), 8.40 (bs, 1H). ^{13}C NMR (67.5 MHz; DMSO-d_6) 13.5, 28.7, 55.1, 119.9, 124.2, 129.3, 139.3, 169.4, 205.2 ppm. $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N, 7.33%. Found C, 68.94; H, 6.93; N, 7.31%.

(xviii) Synthesis of α-methyl-p-chloroacetoacetanilide (439b)

Monomethylation of p-chloroacetoacetanilide, using the procedure outlined in (xvii), gave crude N-(4-chlorophenyl)-2-methyl-3-oxobutanamide (439b) in 85% yield. Recrystallisation from aqueous ethanol afforded colourless crystals. MP 129-130°C. IR (KBr) 3237, 1715, 1649 cm^{-1}. ^1H NMR (60 MHz; DMSO-d_6) δ 1.25 (d, 3H), 2.10 (s, 3H), 3.60 (q, 1H), 7.25 (d, 2H), 7.60 (d, 2H), 10.30 (bs, 1H). ^{13}C NMR (67.5 MHz; DMSO-d_6) 13.2, 28.4, 54.8, 121.2, 127.5, 128.9, 138.0, 169.3, 204.9 ppm. Calculated for $C_{11}H_{12}NO_2Cl$: C, 58.54; H, 5.36; N, 6.21%. Found C, 58.77; H, 5.43; N, 6.17%.

(xix) Preparation of α-methylacetoacetanilide p-nitrophenylhydrazone (440a)

This hydrazone was prepared as described in (i), in an 88% yield. MP 212-213°C. IR (KBr) 3306, 3244, 1644 cm^{-1}. ^1H NMR (60 MHz; DMSO-d_6) δ 1.35 (d, 3H), 2.00 (s, 3H), 3.55 (q, 1H), 6.90-7.40 (m, 5H), 7.60 (d, 2H), 8.05 (d, 2H), 9.90 (s, 1H), 10.00 (s, 1H).

(xx) Preparation of α-methyl-p-chloroacetoacetanilide p-nitrophenylhydrazone (440b)

A 94% yield of this hydrazone was obtained using the procedure outlined in (i). MP 219-220°C. IR (KBr) 3301, 3230, 1649 cm^{-1}. ^1H NMR (60 MHz; DMSO-d_6) δ 1.25 (d, 3H), 1.85 (s, 3H), 3.40 (q, 1H), 6.90-7.35 (m, 4H), 7.50 (d, 2H), 7.95 (d, 2H), 9.70 (s, 1H), 10.00 (s, 1H).

(xxi) Synthesis of 1-(4-nitrophenyl)-3,4-dimethyl-2-pyrazolin-5-one (444)

(a) From hydrazone (440a)

This pyrazolin-5-one was prepared in 86% yield by the method described in (iii). MP 225-227°C (AcOH). IR (KBr) 1638 cm^{-1}. ^1H NMR (270 MHz; DMSO-d_6) δ 1.75 (s, 3H), 2.11 (s, 3H), 8.00 (d, 2H, J = 8.8 Hz), 8.28 (d, 2H, J = 9.5 Hz). ^{13}C NMR (67.5 MHz; DMSO-d_6) 6.7, 11.9, 12.6, 117.6, 118.1, 125.2, 143.0, 143.4, 150.9 ppm.

(b) From hydrazone (440b)

This hydrazone was cyclised similarly, affording the pyrazolin-5-one (444) in 84% yield.

(xxii) LTA oxidation of hydrazone (440a) in CH_2Cl_2

Hydrazone (440a) was oxidised as outlined in (iv) to give azoacetate (442a) in 74% yield. This crude mixture of isomers was analysed. IR (KBr) 3349, 1721, 1684 cm^{-1}. ^1H NMR (270 MHz; DMSO-d_6) (note: peaks for minor isomers denoted by *) δ 1.15 (d, 3H), 1.26* (d), 1.86 (s), 2.05 (s, 3H), 2.12* (s), 3.16 (q, 1H), 7.05-7.32 (m), 7.47* (d, J = 8.1 Hz), 7.57 (d, 2H, J = 8.1 Hz), 7.72* (d, J = 9.2 Hz), 7.82 (d, 2H, J = 8.8 Hz), 8.31* (d, J = 8.8 Hz), 8.39 (d, 2H, J = 9.2 Hz), 9.92* (s), 10.07 (s, 1H). The ratio of major : minor isomers was calculated by integration and found to be 3:1.

(xxiii) LTA oxidation of hydrazone (440b) in CH_2Cl_2

This hydrazone was oxidised in a similar fashion, yielding 78% of the azoacetate (442b). IR (KBr) 3356, 1721, 1685 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6) (note: minor peaks denoted by *) δ 1.156 (d, 3H, J = 7.0 Hz), 1.278* (d, J = 6.9 Hz), 1.859* (s), 1.864 (s, 3H), 2.058 (s, 3H), 2.135* (s), 3.153 (q, 1H, J = 7.0 Hz), 3.212* (q, J = 7.0 Hz), 7.313* (d, J = 8.9 Hz), 7.362 (d, 2H, J = 8.9 Hz), 7.528* (d, J = 8.9 Hz), 7.636 (d, 2H, J = 8.9 Hz), 7.727* (d, J = 9.0 Hz), 7.828 (d, 2H, J = 9.0 Hz), 8.342* (d, J = 9.0 Hz), 8.406 (d, 2H, J = 9.0 Hz), 10.059* (s), 10.218 (s, 1H). Purification of the crude mixture of isomers was monitored by TLC, using 1:1 ethyl acetate: petroleum ether (40-60°) as mobile phase, which allowed separation of the major and minor components. Fractional crystallisation from CH_2Cl_2/petroleum ether (40-60°) gave the dominant diastereomers in pure form (34%). MP 185-186°C. IR (KBr) 3366, 1727, 1690 cm^{-1}. Recrystallisation from an excess of ethanol afforded large orange crystals. ^1H NMR (270 MHz; DMSO-d_6) (note: signal for methine proton at 3.2 ppm obscured by solvent peak) δ 1.14 (d, 3H), 1.84 (s, 3H), 2.04 (s, 3H), 7.35 (d, 2H, J = 7.3 Hz), 7.61 (d, 2H, J = 7.3 Hz), 7.82 (d, 2H, J = 7.3 Hz), 8.40 (d, 2H, J = 7.3 Hz), 10.24 (s, 1H). ^{13}C NMR (67.5 MHz; DMSO-d_6) 12.1, 18.1, 21.8, 47.4, 103.0, 121.7, 123.6, 125.5, 127.8, 129.1, 138.0, 149.0, 154.4, 169.4, 170.3 ppm. X-ray crystallographic analysis showed that the major azoacetate isomers were (2R, 3S) - (446b) and (2S, 3R) - (449b).

(xxiv) LTA oxidation of hydrazone (440a) in AcOH

This oxidation was performed as described in (vi). The azoacetate (442a) was obtained in 78% yield, as a mixture of isomers. IR (KBr) 3347, 1721, 1684 cm^{-1}. ^1H NMR (60 MHz; DMSO-d_6) (note: peaks for minor isomers denoted by *) δ 1.05 (d, 3H), 1.20* (d), 1.80 (s), 1.90 (s, 3H), 2.00* (s), 3.10 (q, 1H), 6.70-8.40 (m), 9.65* (s), 9.80 (s, 1H).

(xxv) LTA oxidation of hydrazone (440b) in AcOH

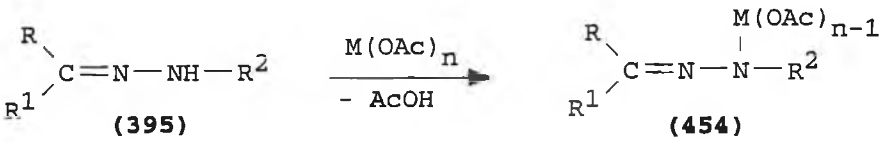
Hydrazone (440b) was oxidised using the procedure outlined in (vi), and gave the crude azoacetate (442b) in 83% yield. IR (KBr) 3355, 1721, 1685 cm^{-1}. ^{1}H NMR (270 MHz; DMSO-d$_6$) (note: minor isomer peaks denoted by *) δ 1.13 (d, 3H), 1.23* (d), 1.83 (s), 2.02 (s, 3H), 2.09* (s), 3.13 (q, 1H), 7.25-7.33 (m), 7.47* (d, J = 8.1 Hz), 7.57 (d, 2H, J = 8.1 Hz), 7.70* (d, J = 8.1 Hz), 7.79 (d, 2H, J = 8.1 Hz), 8.30* (d, J = 8.1 Hz), 8.36 (d, 2H, J = 8.8 Hz), 10.09* (s), 10.23 (s, 1H). Fractional crystallisation from CH_2Cl_2/petroleum ether (40-60^{o}) removed the major diastereomers, affording material concentrated in the minor isomers. ^{1}H NMR (270 MHz; DMSO-d$_6$) (note: impurity peaks due to major diastereomers denoted by *) δ 1.15* (d), 1.27 (d, 3H), 1.85 (s), 2.05* (s), 2.13 (s, 3H), 7.30-7.38 (m), 7.52 (d, 2H, J = 8.8 Hz), 7.63* (d), 7.72 (d, 2H, J = 8.8 Hz), 7.83* (d), 8.31-8.42 (m), 10.07 (s, 1H), 10.24* (s). (Note: methine signal at 3.2 ppm obscured by solvent peak).

2.2 Mercuric Acetate Oxidation of p-Nitrophenylhydrazones of Acetoacetanilides[144]

2.2.1 Introduction

Mercury (II) acetate and lead (IV) acetate constitute a pair of comparable isoelectronic oxidising agents, of which mercuric acetate, $Hg(OAc)_2$, has the weaker oxidising power[173]. $Hg(OAc)_2$, as an oxidising agent, often closely parallels LTA in its mode of action and can give analogous results. Nonetheless, in many cases, the reactions of mercuric acetate with hydrazones differ dramatically from those of LTA.

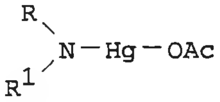
The oxidation reactions of $Hg(OAc)_2$ and LTA with ketone hydrazones (395) may be related by the key N-metallo intermediates (454).



(395) (454)

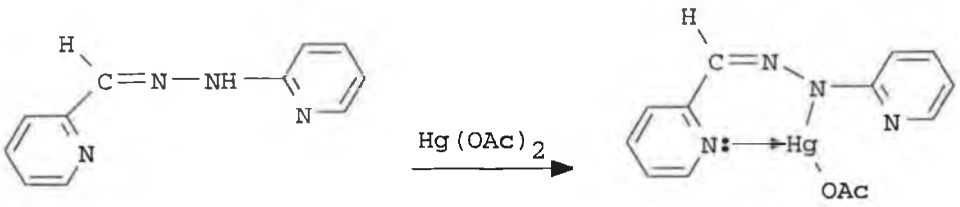
a: M = Pb; n = 4
b: M = Hg; n = 2

Unlike the Pb-intermediates (454a), which are highly reactive, Hg-intermediates (454b) are relatively stable. Compounds containing Hg(II)-N bonds are well-known, and, in $Hg(OAc)_2$ oxidations, some organomercury intermediates (455) containing the moiety N-Hg-OAc have been isolated.



(455)

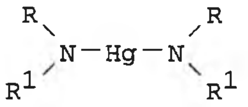
For example, in the reaction of hydrazone (456) with $Hg(OAc)_2$, the intermediate (457) was isolated in quantitative yield at ambient temperatures[174].



(456) (457)

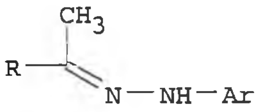
Compound (457) is probably stabilised by co-ordination of the metal by the pyridine nitrogen.

Also, with Hg(II)-N intermediates, there is time for the best external nucleophile to become involved, often attacking the Hg(II), which stays in this oxidation state. Selective attack on the metal by the parent nitrogen compound may occur, giving stable products of the type (458).



(458)

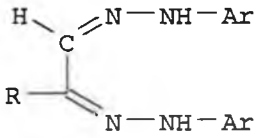
The reactions of ketone p-nitrophenylhydrazones (459) with mercuric acetate in hot acetic acid have been studied by Butler and Morris[175].



(459)

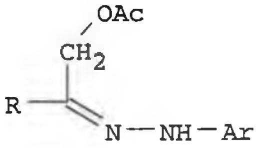
R = alkyl, aryl
Ar = 4-NO_2-C_6H_4

The main products obtained were the 1,2-bis-hydrazones (460) of the corresponding 1,2-dicarbonyl compounds, arising from a hydrazino-transfer to the methyl group.



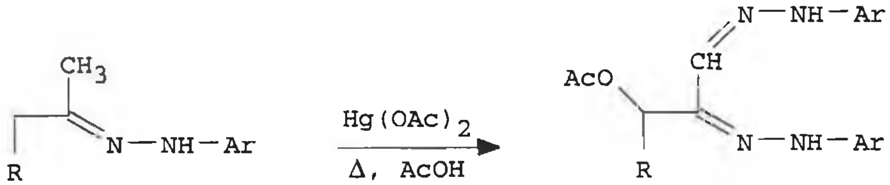
(460)

In some cases, the osazones (460) were accompanied by the α-acetoxy derivatives (461).



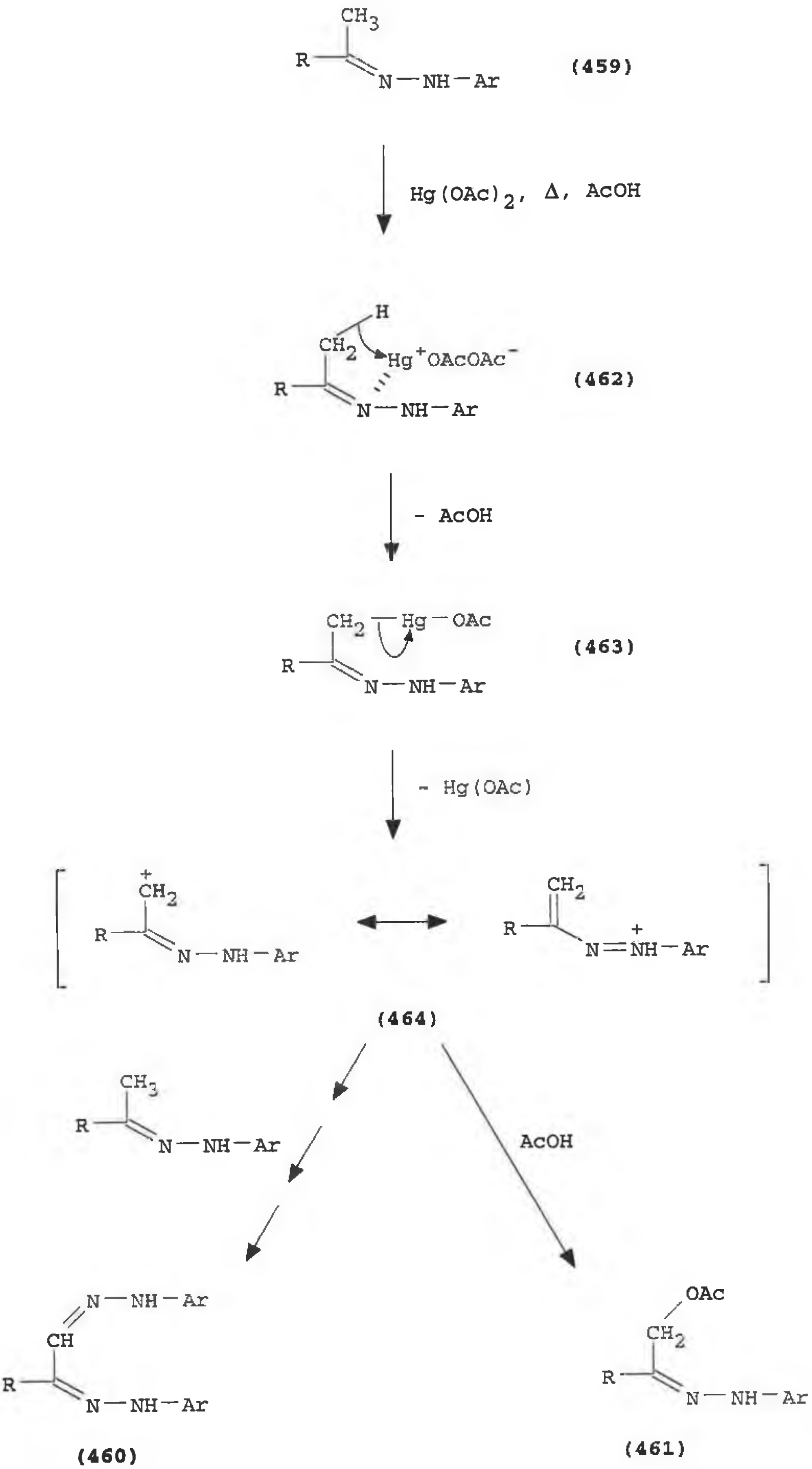
(461)

These researchers proposed that initial complexation at the methine imino nitrogen predominates, giving the N-mercuri intermediates (462). An electrophilic mercury migration to the adjacent methyl group then occurs, affording species (463). Loss of HgOAc generates a relatively stable aza-allylic cation (464). Nucleophilic attack by unreacted hydrazone leads ultimately to the formation of the osazones (460). Alternatively, attack on the cation (464) by solvent AcOH furnishes the α-acetoxy-hydrazones (461) (Scheme 15). Interestingly, hydrazones (465), bearing a methyl group and a methylene group on the hydrazone methine carbon, underwent the hydrazino-transfer to the methyl group accompanied by an acetoxylation of the methylene group, yielding products (466).



R = Me, Ph
Ar = 4-NO_2-C_6H_4

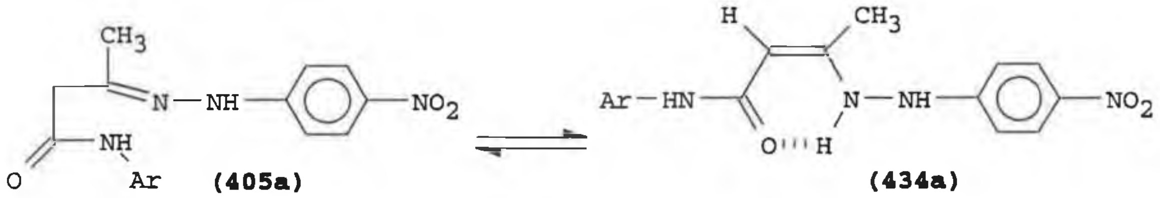
Scheme 15



2.2.2 Results and Discussion

The reactions of p-nitrophenylhydrazones of acetoacetanilides with mercuric acetate were studied because, with this oxidant, the possibility of azoacetate formation does not exist.

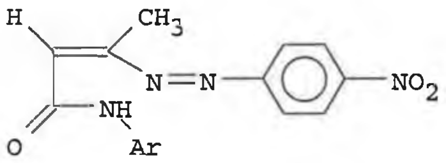
Firstly, oxidation of acetoacetanilide p-nitrophenylhydrazone (405a) with $Hg(OAc)_2$ in AcOH was investigated. In this solvent, hydrazone (405a) is believed to be in equilibrium with the enehydrazine (434a), which should be fixed in the Z-configuration by intramolecular H-bonding.



(405a) **(434a)**

Ar = Ph

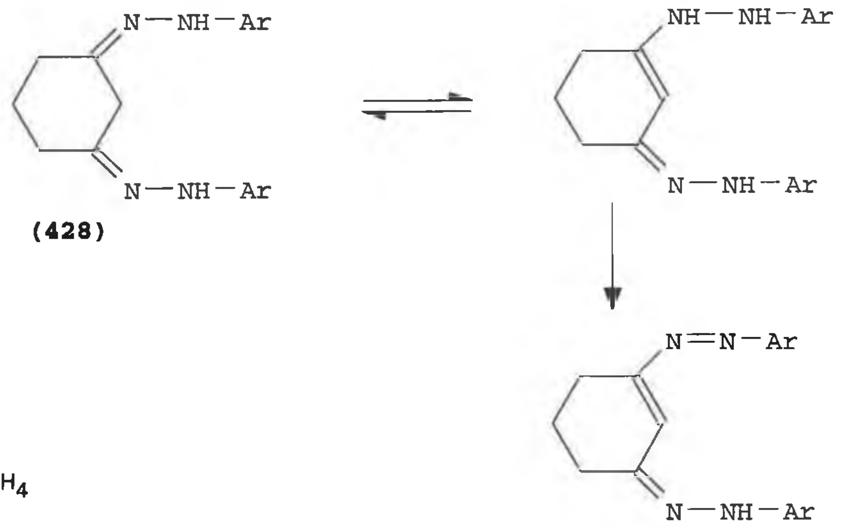
It was expected, then, that $Hg(OAc)_2$, like $Pb(OAc)_4$, would readily dehydrogenate the reactive enehydrazine tautomer (434a) present in the system, affording the Z-azoalkene (416a) as the sole oxidation product.



(416a)

Ar = Ph

Indeed, the azoalkene (430), prepared by the LTA oxidation of cyclohexane-1,3-dione bis-(4-nitrophenylhydrazone) (428) in AcOH, was also obtained when $Hg(OAc)_2$ was used as the oxidant[162].



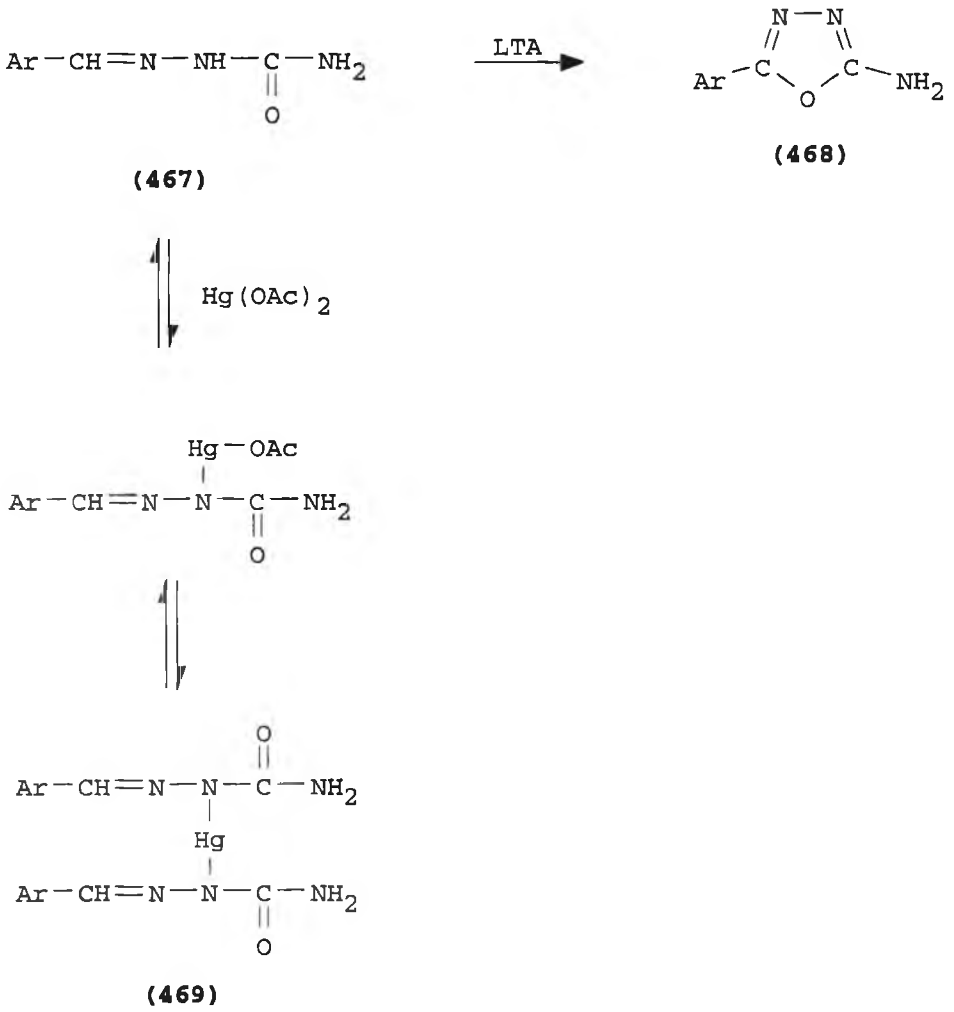
(428)

(430)

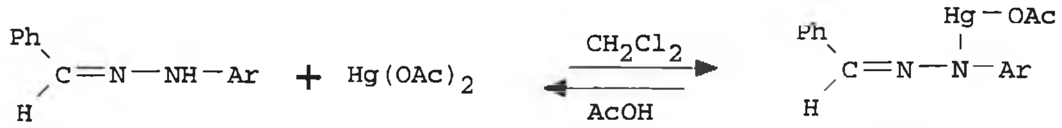
Ar = $4\text{-}NO_2\text{-}C_6H_4$

However, when hydrazone (405a) was treated with 1.2 equivalents of $Hg(OAc)_2$ in cold acetic acid for 24 hours, monitoring by TLC indicated that mainly starting hydrazone was present. Unfortunately, the conditions (Δ, AcOH, 3.5 hours) used by Butler and Morris[175] to effect reaction of the analogous hydrazones (465) with mercuric acetate could not be applied here, since hydrazone (405a) cyclises to 1-(4-nitrophenyl)-3-methyl-2-pyrazolin-5-one (412) on heating in AcOH.

The failure of mercuric acetate to oxidise hydrazone (405a) is not very surprising since, in many cases, $Hg(OAc)_2$ has been found to be an insufficiently strong oxidising agent with hydrazone systems to bring about dehydrogenations or oxidative cyclisations which are readily obtained with LTA[176]. For instance, aldehyde semicarbazones (467), although readily cyclised to oxadiazoles (468) on brief treatment with LTA at room temperature[177], were relatively inert to mercuric acetate, and gave bis(hydrazono)mercuri derivatives (469) in an equilibrium, which lay strongly on the semicarbazone side in acetic acid[178].



Also, the organomercury intermediate (471), isolated from the reaction of benzaldehyde p-nitrophenylhydrazone (470) with $Hg(OAc)_2$ in CH_2Cl_2, rapidly exchanged a proton when dissolved in AcOH, giving the parent hydrazone (470) and mercuric acetate[179].

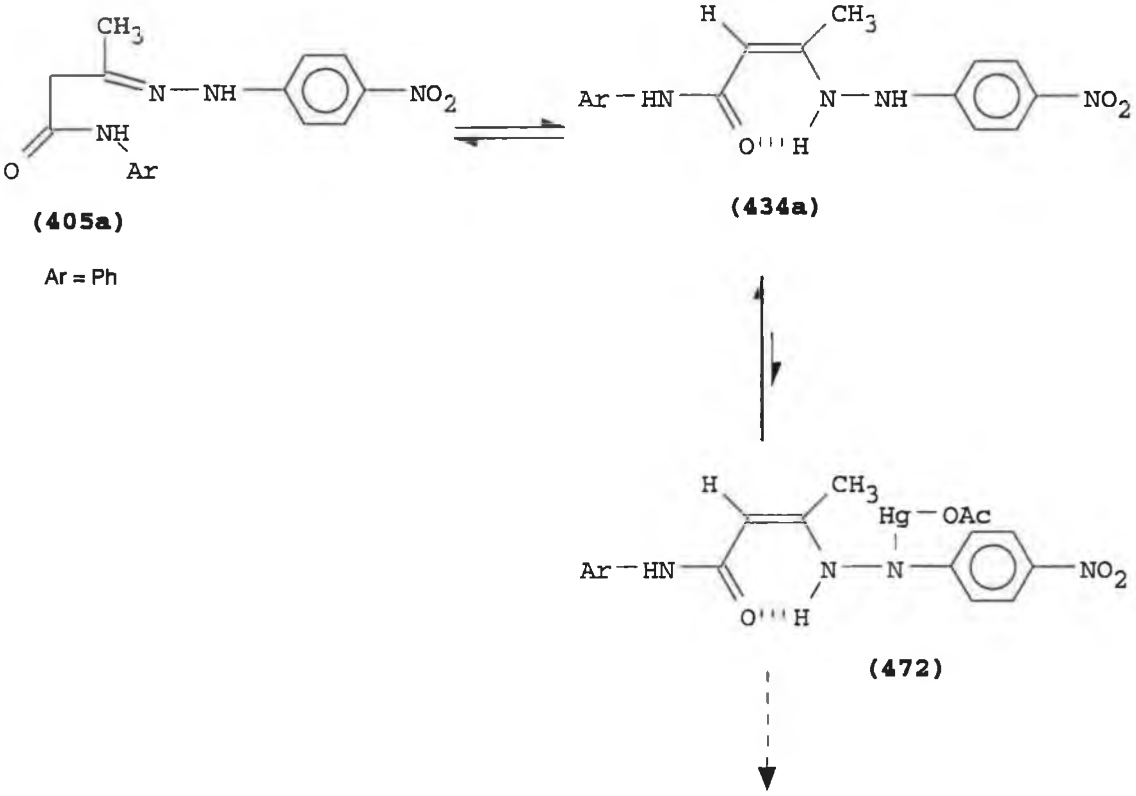


(470) (471)

Ar = 4-NO_2-C_6H_4

It is suggested, therefore, that when hydrazone (405a) is treated with $Hg(OAc)_2$ in AcOH, the N-metallo intermediate (472) may indeed be formed, but that proton exchange, regenerating the substrate, is preferred to possible fragmentation paths (Scheme 16).

Scheme 16



(405a)

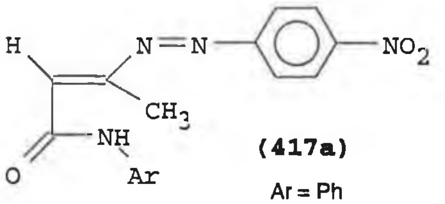
Ar = Ph

(434a)

(472)

PRODUCTS

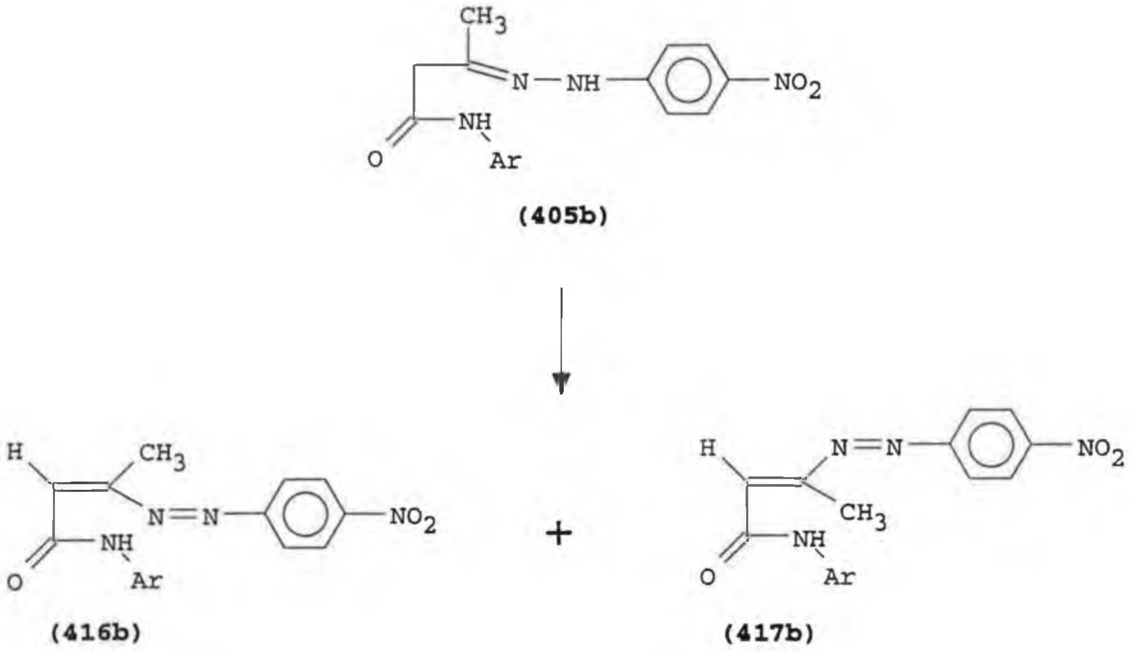
Treatment of the hydrazone (405a) with $Hg(OAc)_2$ in CH_2Cl_2 at room temperature for 24 hours again had little effect. However, using this solvent, heat could be applied without causing any adverse cyclisation, and, after refluxing for 4.5 hours, all of the starting hydrazone (405a) had been consumed. Here, two products were formed, in approximately equal amounts, one of which proved to be the Z-azoalkene (416a), which had also been produced in the LTA/AcOH oxidation of hydrazone (405a). Analysis of the second product indicated that it had a structure very similar to that of the Z-azoalkene (416a), and its ^1H NMR spectrum, containing a vinylic peak at 7.28 ppm, showed that it was, in fact, the E-azoalkene (417a).



(417a)

Ar = Ph

Similarly, oxidation of the hydrazone (405b) with mercuric acetate in refluxing CH_2Cl_2 gave the Z-azoalkene (416b) and the E-azoalkene (417b) in crude yields of 47% and 36% respectively.



(405b)

(416b)

(417b)

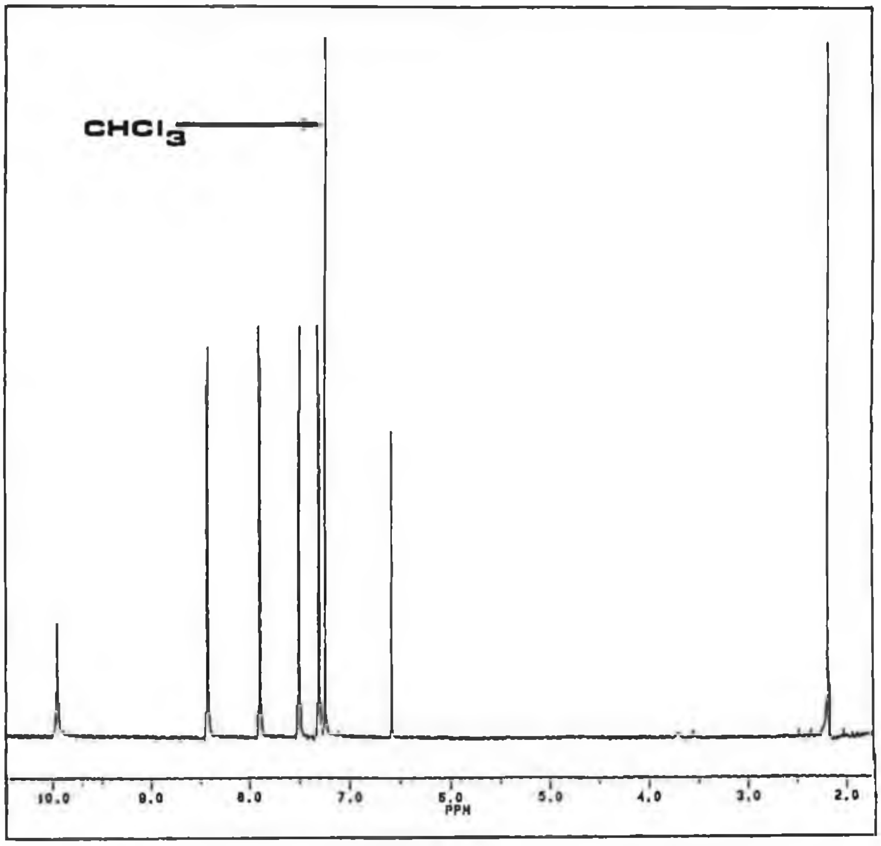
Ar = 4-Cl-C_6H_4

Now that samples of both isomeric azoalkenes were available, NOE difference experiments were carried out to unequivocally establish the conformation of each vinylic compound. The 400 MHz ^1H NMR spectrum of the Z-azoalkene (416b) was recorded (Figure 11a). The methyl signal at 2.18 ppm was irradiated and an NOE difference spectrum obtained (Figure 11b). A 10% increase in the intensity of the vinylic peak at 6.58 ppm was observed, indicating spatial proximity of this proton and the methyl group. The 400 MHz ^1H NMR spectrum of the E-azoalkene (417b) and the corresponding NOE difference spectrum are shown in Figure 12. Here, saturation of the methyl resonance did not cause enhancement of the vinyl singlet. These results confirm that the earlier assignment of configuration, based of the chemical shift of each olefinic proton, is correct.

Mechanistically, it is proposed that formation of the azo-olefins (416) and (417) occurs via an initial mercuration of the hydrazone substrates (405). A 1,4-elimination from the organomercury intermediates (473) then generates the olefinic products (Scheme 17).

Figure 11: (a) 400 MHz ^1H NMR spectrum of Z-azoalkene (416b)
(b) Corresponding NOE difference spectrum

(a)



(b)

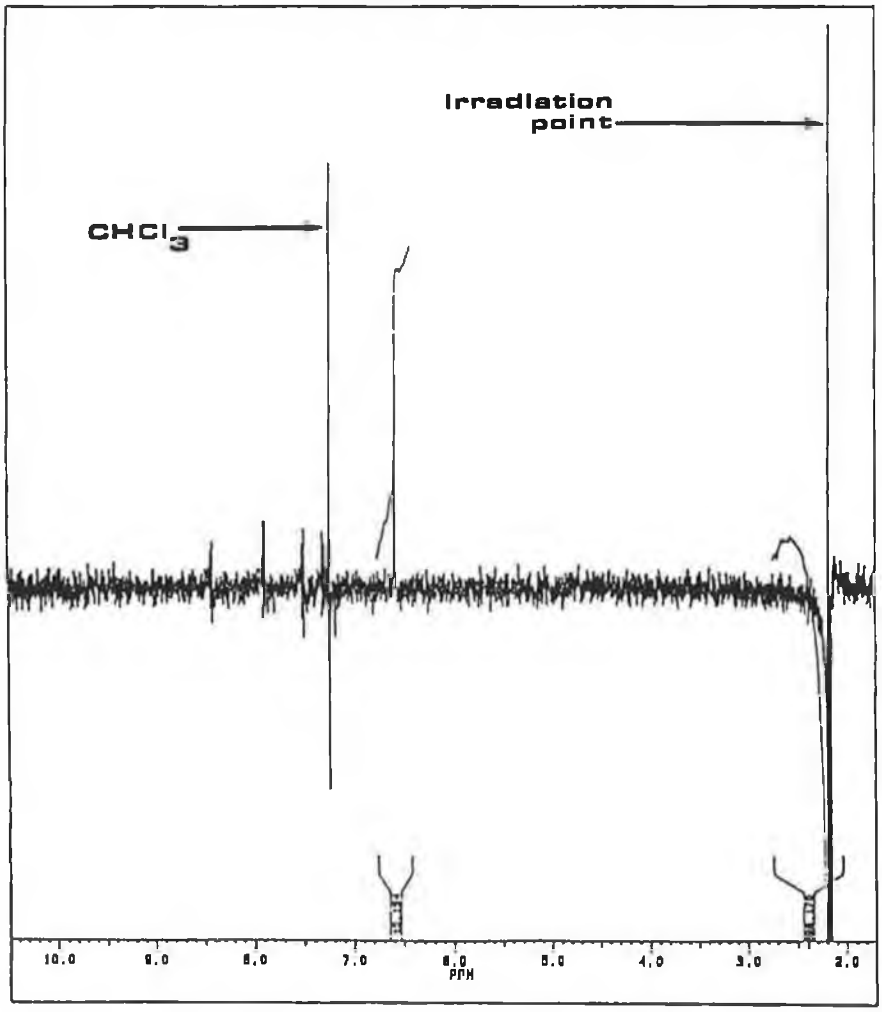
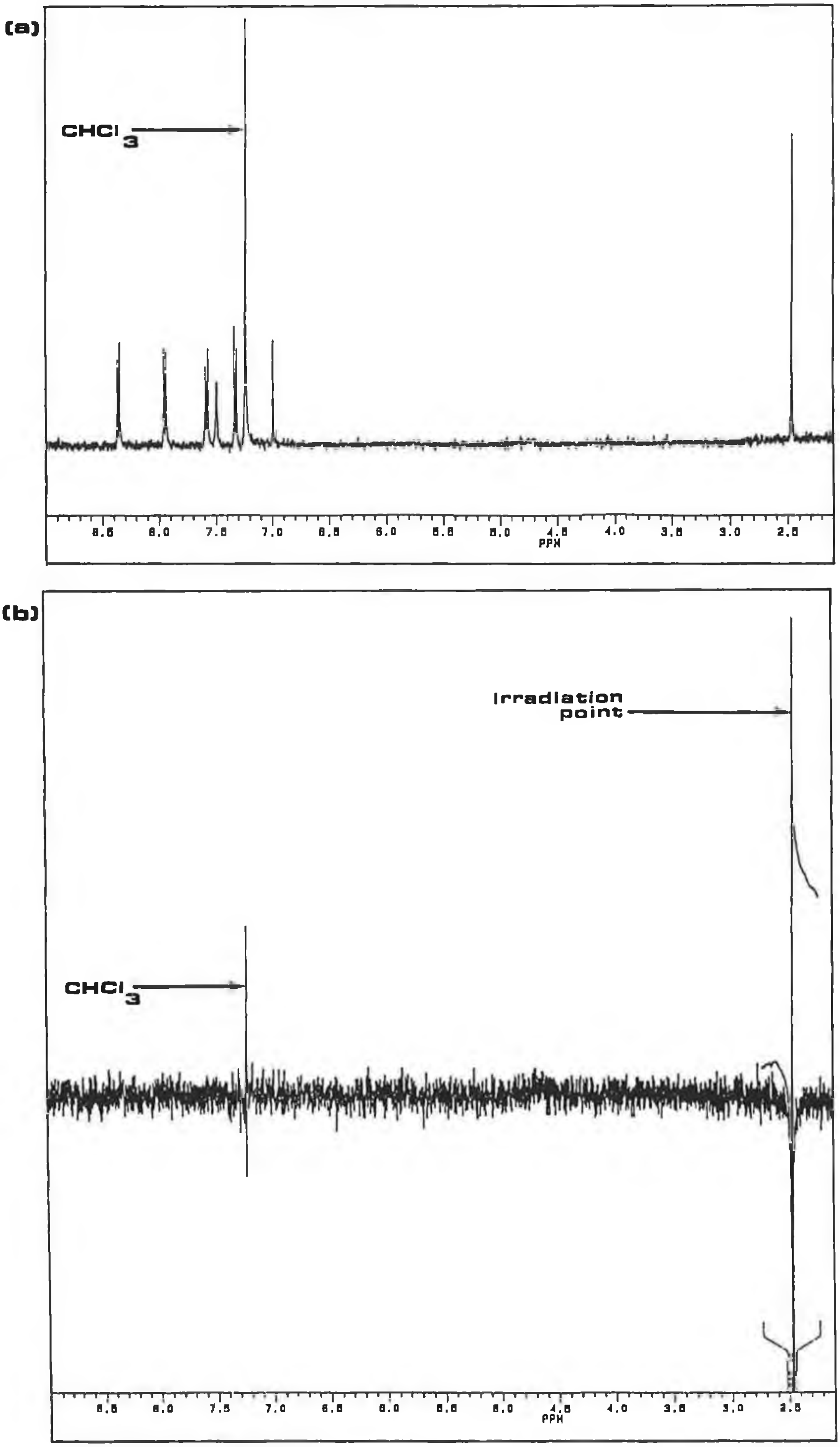
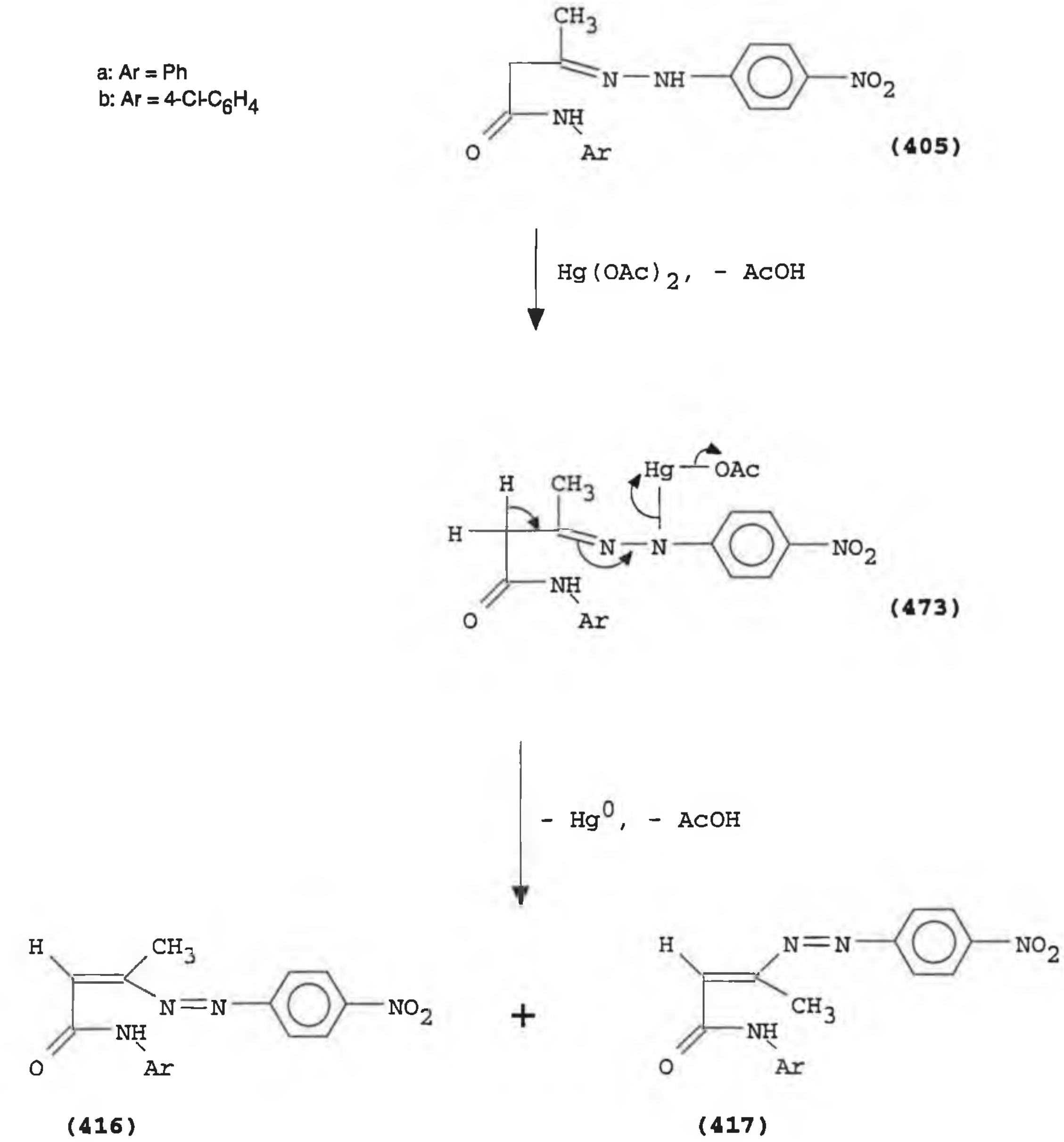


Figure 12: (a) 400 MHz ^{1}H NMR spectrum of E-azoalkene (417b)
(b) Corresponding NOE difference spectrum

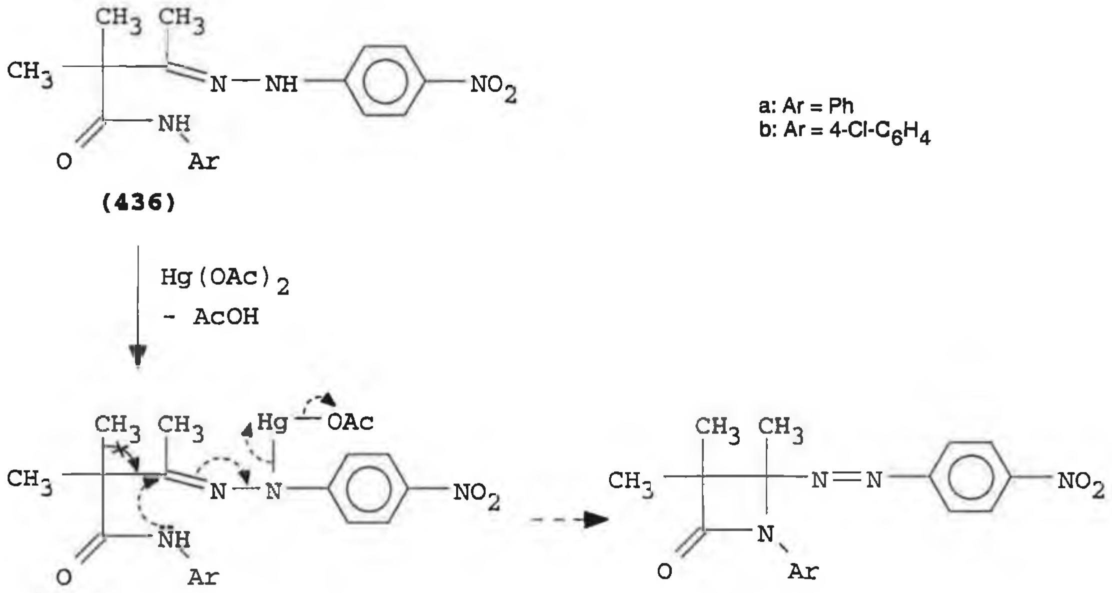


Scheme 17



In this system, the N-metallo intermediate is not subject to any restrictive intramolecular H-bonding, so equal amounts of the E- and Z-isomers are formed.

Finally, the reaction of α,α-dimethylacetoacetanilide p-nitrophenylhydrazone (436a) with $Hg(OAc)_2$ in CH_2Cl_2 was studied. Since this substrate lacks a labile α-proton, the pathway leading to azoalkene formation was effectively blocked, and there was a possibility that oxidative cyclisation involving the amide nitrogen, affording the 4-azo-β-lactam (474a), might occur.



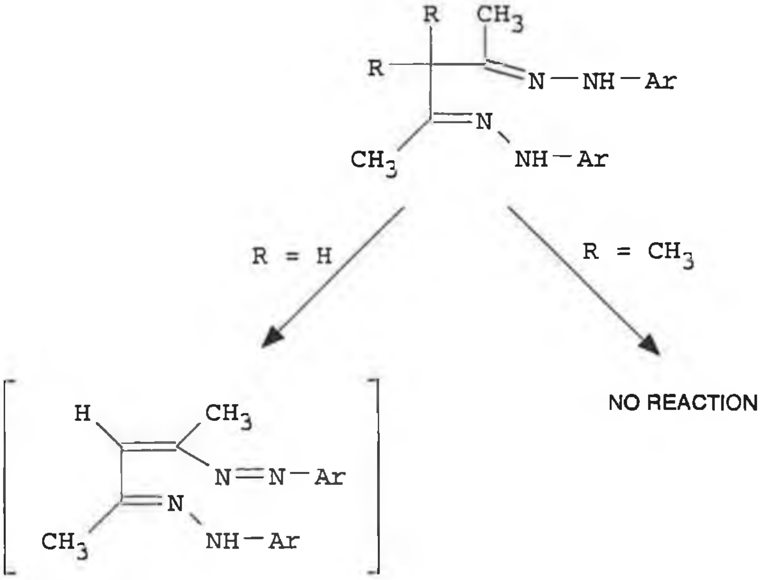
(436)

(474)

a: Ar = Ph
b: Ar = 4-Cl-C_6H_4

However, even after refluxing for 24 hours, no reaction was observed, and the starting hydrazone (436a) was recovered.

A similar contrast in the reactivity of unsubstituted and dimethylated substrates has been reported by Butler and James[162]. Whereas pentane-2,4-dione bis-(4-nitrophenylhydrazone) (431) was readily oxidised by mercuric acetate, furnishing the azo-olefin (433), the analogous 3,3-disubstituted hydrazone (475) failed to react with this oxidant unless forcing conditions were employed, causing decomposition.



(431) : R = H
(475) : R = CH_3

(433)

Ar = 4-NO_2-C_6H_4

2.2.3 Experimental

Melting points were determined in open capillary tubes with a Gallenkamp melting point apparatus. IR spectra were recorded for KBr discs with a Perkin-Elmer 983-G spectrometer. NMR spectra (^{1}H and ^{13}C) were measured for solutions in $CDCl_3$ or DMSO-d_6 with Perkin-Elmer R12B 60 MHz, JEOL GX-FT 270 MHz and Bruker AC-F 400 MHz spectrometers, and referenced to tetramethylsilane or residual solvent H. Elemental analyses were performed in the Microanalytical Laboratory, University College Dublin. Common reagent grade chemicals were purchased from Aldrich Chemical Company, and were used as received.

(i) Reaction of hydrazone (405a) with $Hg(OAc)_2$ in AcOH

0.96g (3 mmoles; 120 mole%) $Hg(OAc)_2$ was added to a mixture of 0.78g (2.5 mmoles) hydrazone (405a) in 20mls AcOH. After stirring at room temperature for 24 hours, TLC analysis (ethyl acetate: petroleum ether (40-60°) 70:30) indicated that the mixture contained mainly the starting hydrazone (405a).

(ii) Reaction of hydrazone (405a) with $Hg(OAc)_2$ in CH_2Cl_2 at room temperature

To a suspension of 1.56g (5 mmoles) hydrazone (405a) in 150mls CH_2Cl_2 was added 1.91g (6 mmoles; 120 mole%) $Hg(OAc)_2$. The mixture was stirred for 24 hours, without the application of heat. TLC (70:30 petroleum ether (40-60°): ethyl acetate) showed that mostly hydrazone (405a) remained.

(iii) Oxidation of hydrazone (405a) with $Hg(OAc)_2$ in refluxing CH_2Cl_2

1.56g (5 mmoles) of hydrazone (405a) was suspended in 150mls CH_2Cl_2 and 1.91g (6 mmoles; 120 mole%) $Hg(OAc)_2$ was added. The yellow insoluble mixture was refluxed for 4.5 hours. A dark red solution containing some light brown solid and elemental Hg was obtained. TLC (70:30 petroleum ether (40-60°): ethyl acetate) showed that no hydrazone (405a) remained, and that the Z-azoalkene (416a) and the E-azoalkene (417a) had been formed in approximately equal amounts. The reaction mixture was filtered while hot through a bed of Celite to remove Hg^0. A red filtrate was obtained. The residue/Celite was washed with an excess of hot CH_2Cl_2. The washings and the red filtrate were combined, washed with aqueous $NaHCO_3$ and dried over Na_2SO_4. Removal of the solvent gave a reddish solid. This was heated to boiling in ethanol and filtered hot to give crude E-azoalkene (417a) as a beige solid (0.54g; 35%). On standing, the ethanol filtrate yielded red crystals of the Z-azoalkene (416a) (0.14g; 9%). This material was identical to the product obtained in the LTA oxidation of hydrazone (405a) in AcOH. The ethanol mother liquor was then subjected to column chromatography on neutral alumina. Elution with 70:30 petroleum ether (40-60°): ethyl acetate provided a small amount of analytically pure E-azoalkene (417a) as rusty-orange crystals. MP 173-175°C. IR (KBr) 3265, 1644 cm^{-1}. ^1H NMR (270 MHz; DMSO-d_6) δ 2.40 (s, 3H), 7.11 (t, 1H), 7.28 (s, 1H), 7.36 (t, 2H), 7.72 (d, 2H, J = 7.7 Hz), 7.99 (d, 2H, J = 8.4 Hz), 8.41 (d, 2H, J = 8.4 Hz), 10.30 (s, 1H). ^{13}C NMR (67.5 MHz; DMSO-d_6) 10.1, 118.7, 122.5, 123.0, 124.2, 127.9, 133.8, 138.0, 147.9, 154.2, 160.0, 162.4 ppm. Calculated for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06%. Found C, 62.32; H, 4.55; N, 18.35%.

(iv) Oxidation of hydrazone (405b) with $Hg(OAc)_2$ in refluxing CH_2Cl_2

This hydrazone was treated in a similar manner. On removal of the CH_2Cl_2, an orange-red solid containing approximately equal amounts of the Z-azoalkene (416b) and the E-azoalkene (417b) was obtained. This was slurried in cold ethyl acetate and filtered to give crude E-azoalkene (417b) as a beige solid (0.56g; 36%). Removal of the ethyl acetate under reduced pressure afforded crude Z-azoalkene (416b) (0.81g; 47%). Crystallisation of this red solid from ethanol provided a pure sample, which was identical to the product obtained in the LTA/AcOH oxidation of hydrazone (405b). An analytical sample of the E-azoalkene (417b) was prepared by recrystallisation from $CHCl_3$. MP 190-191^{o}C. IR (KBr) 3368, 1678 cm^{-1}. ^{1}H NMR (270 MHz; DMSO-d_6) δ 2.39 (s, 3H), 7.27 (s, 1H), 7.42 (d, 2H, J = 8.8 Hz), 7.75 (d, 2H, J = 8.8 Hz), 8.01 (d, 2H, J = 8.8 Hz), 8.43 (d, 2H, J = 9.2 Hz), 10.77 (s, 1H). $C_{16}H_{13}N_4O_3Cl$ requires C, 55.74; H, 3.80; N, 16.26%. Found C, 55.05; H, 3.76; N, 15.60%.

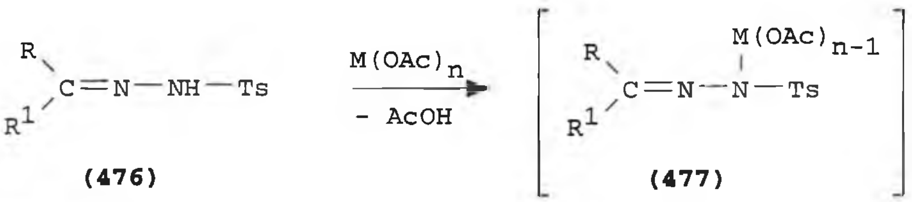
(v) Reaction of hydrazone (436a) with $Hg(OAc)_2$ in refluxing CH_2Cl_2

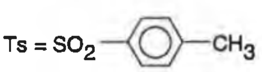
0.34g (1 mmole) of hydrazone (436a) was dissolved in 30mls CH_2Cl_2. 0.41g (1.3 mmoles; 130 mole%) $Hg(OAc)_2$ was added, and the mixture refluxed for 24 hours. TLC (70:30 ethyl acetate: petroleum ether (40-60^{o})) indicated that no reaction had occurred. The mixture was filtered and the filtrate evaporated to give a yellow solid (0.38g). After purification, analysis showed that this material was unreacted hydrazone (436a).

2.3 Oxidation of p-Toluenesulfonylhydrazones of Acetoacetanilides with Lead Tetraacetate and Mercuric Acetate

2.3.1 Introduction

p-Toluenesulfonylhydrazones (tosylhydrazones) (476) react with lead (IV) acetate and mercury (II) acetate to give N-metallo derivatives (477) which can fragment to afford a variety of products, depending on the reaction conditions employed and the nature of the substituents, R and R^1.

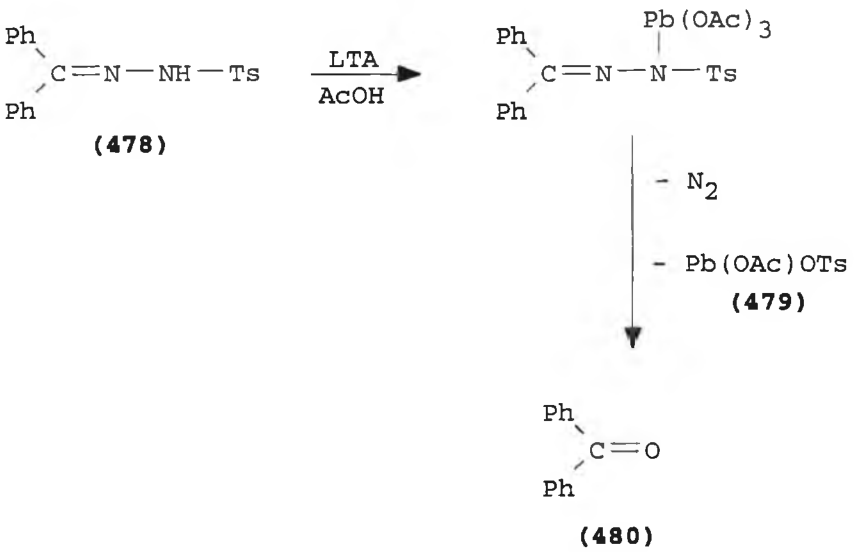




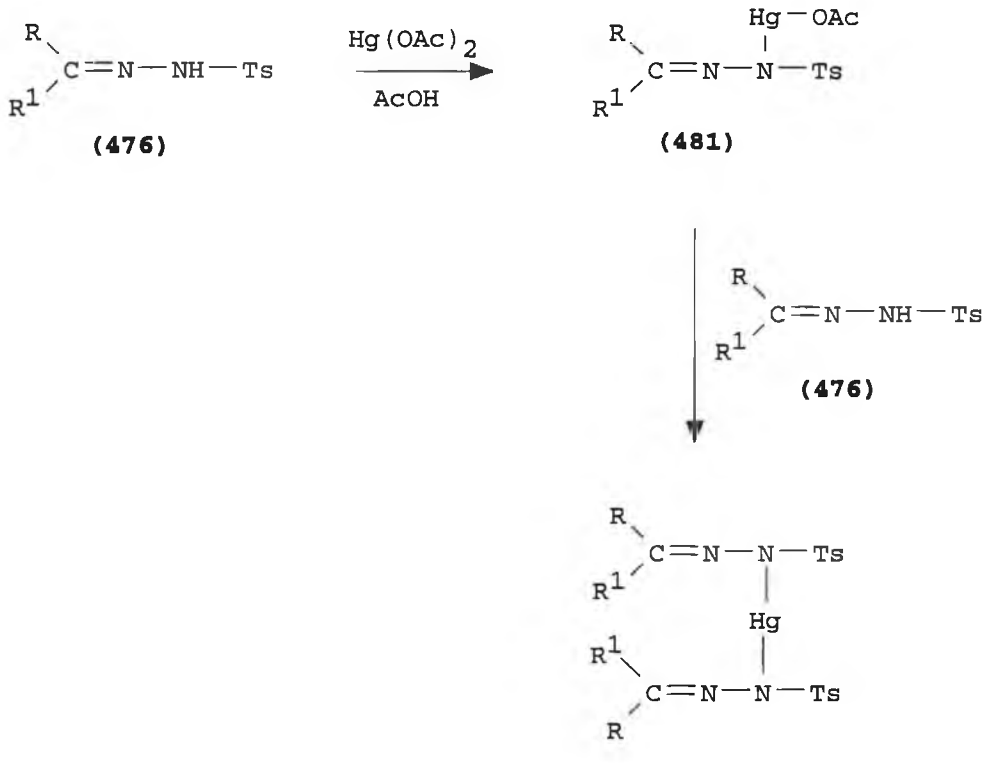
M = Hg; n = 2
M = Pb; n = 4

Tosylhydrazones (476) often yield the same products when oxidised with either $Pb(OAc)_4$ or $Hg(OAc)_2$ because of the high reactivity and leaving ability of the tosyl group. However, in many cases, different results are obtained with each oxidant, reflecting the relative lability of the N-metal bond (N-Pb >> N-Hg) in the derivatives (477).

Ketones are easily regenerated from their tosylhydrazones by treatment with LTA[180]. When benzophenone toluene-p-sulfonylhydrazone (478) was reacted with LTA in acetic acid at ambient temperature, immediate and brisk evolution of nitrogen was observed, with concomitant separation of lead acetate toluene-p-sulfonate (479). The parent ketone, benzophenone (480), was recovered in 88% yield[173].

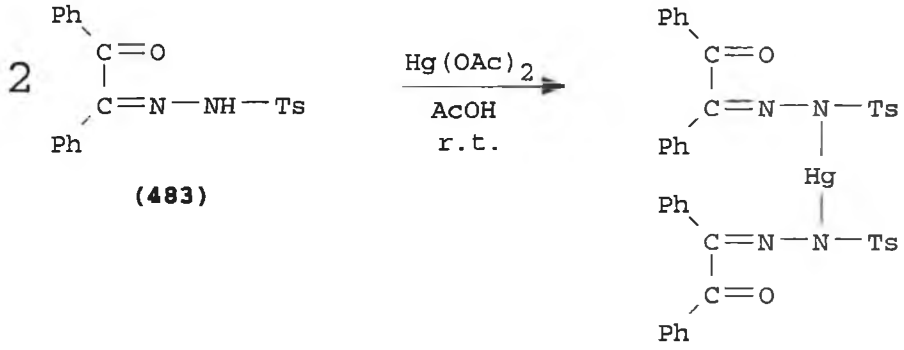


In contrast, treatment of tosylhydrazones (476) with the weaker oxidising agent $Hg(OAc)_2$ in AcOH gives the comparatively stable N-metallo intermediates (481), which can react intermolecularly, without a change in the oxidation state of the metal, to afford isolable bis-hydrazono-mercury compounds (482).



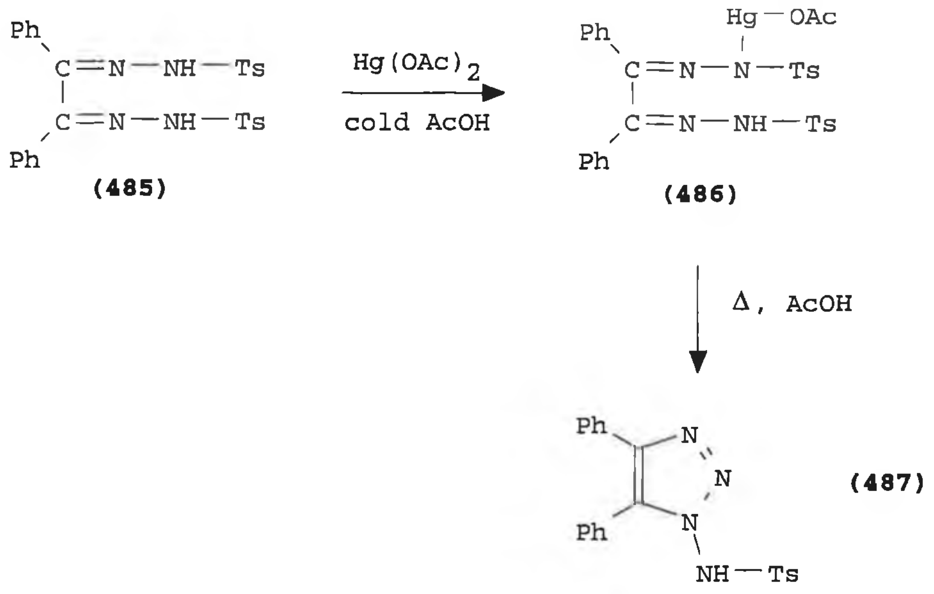
(476) **(481)** **(476)** **(482)**

Butler and colleagues[173,181] have reported that reaction of benzil mono(toluene-p-sulfonylhydrazone) (483) with mercuric acetate in cold acetic acid gave bis(benzil toluene-p-sulfonylhydrazono)mercury (484) in quantitative yield.

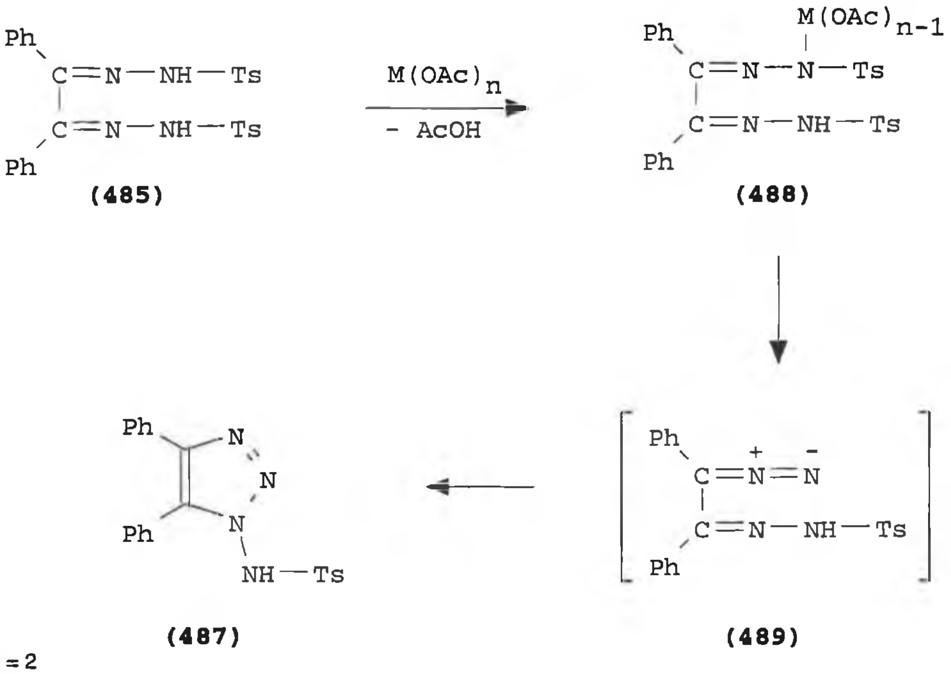


(483) **(484)**

In some cases, tosylhydrazono-mercury acetate intermediates of the type (481) have been intercepted. When benzil bis(toluene-p-sulfonyl)hydrazone (485) was treated with $Hg(OAc)_2$ in AcOH at ambient temperature, the unstable N-acetoxymercurio-N-toluene-p-sulfonylhydrazonobenzil toluene-p-sulfonylhydrazone (486) was isolated in 80% yield. Separate heating of the mercurio-intermediate (486) in acetic acid resulted in cyclisation to N-(4,5-diphenyl-1,2,3-triazol-1-yl)toluene-p-sulfonamide (487)[173,181].

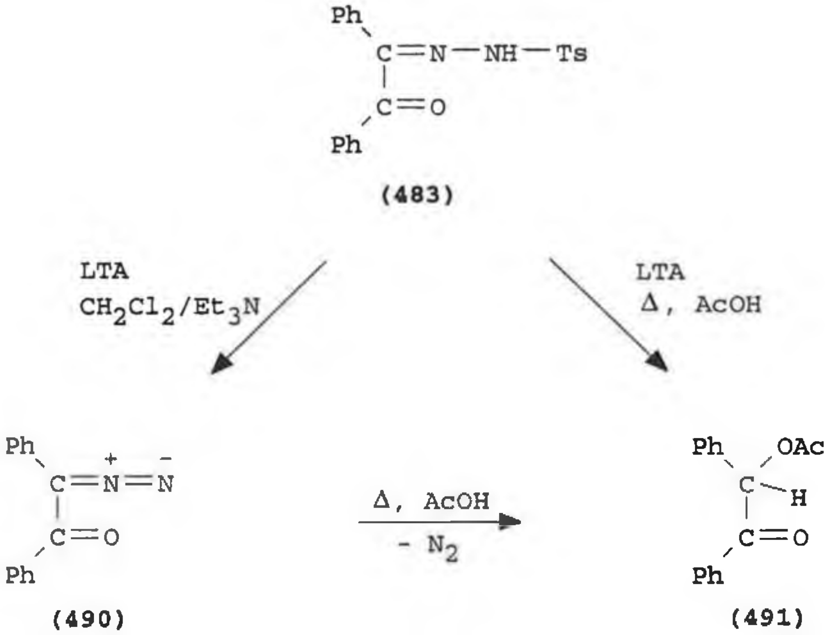


The triazolylsulfonamide (487) could also be obtained directly from the 1,2-bis(hydrazone) (485) by either refluxing with $Hg(OAc)_2$ in AcOH, or heating at 60°C with LTA in AcOH. In each of these reactions, formation of the triazole (487) is believed to involve a fragmentation of the N-metallo intermediate (488), in which the metal is reduced and the diazo-compound (489) is generated. Rapid internal cyclisation of the diazo species (489) then gives the 1,2,3-triazole derivative (487).



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

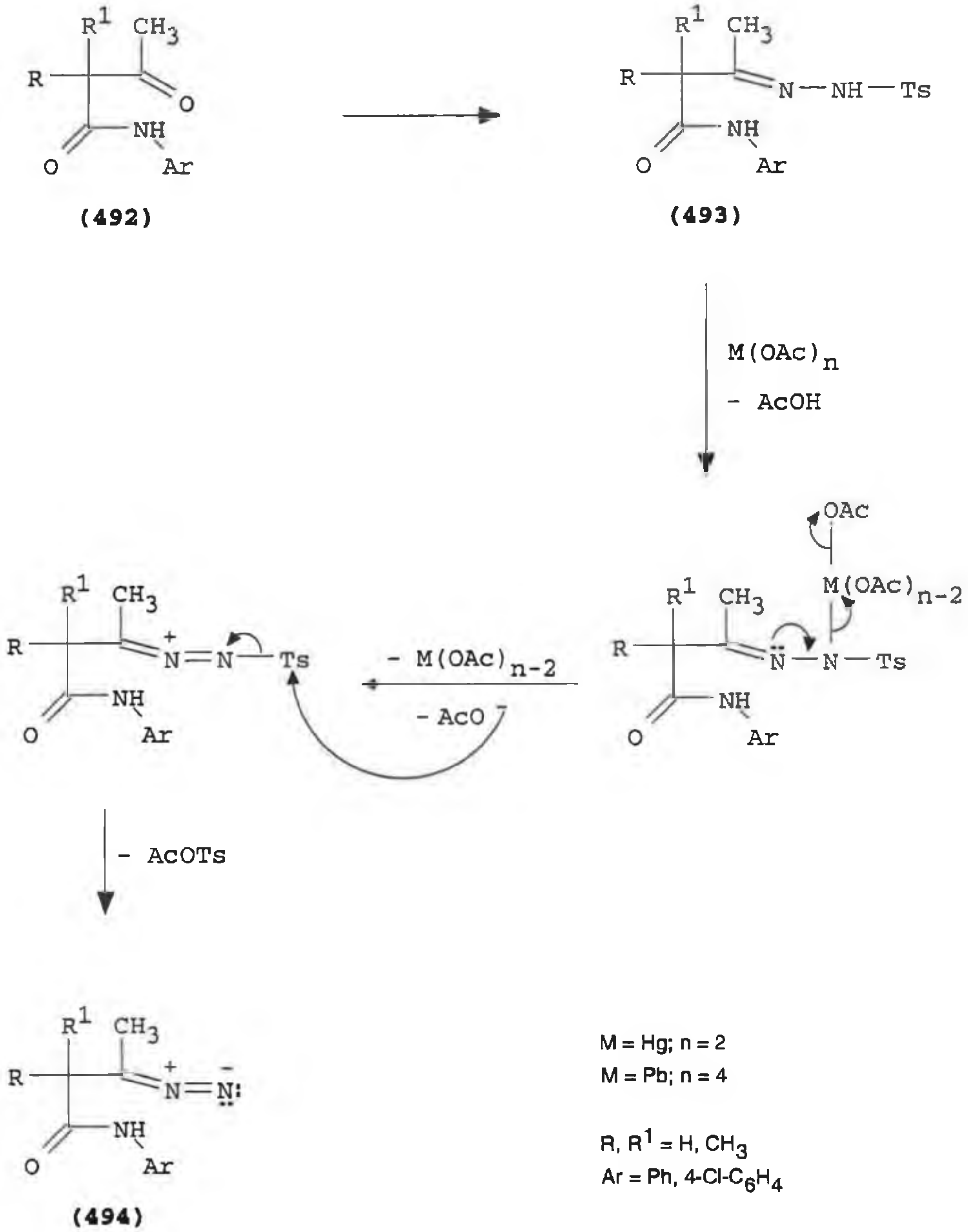
The diazo-compound (490) has been isolated from the reaction of benzil mono(toluene-p-sulfonyl)hydrazone (483) with lead tetraacetate in dichloromethane containing triethylamine. Subsequent warming of the diazo-derivative (490) in acetic acid afforded O-acetylbenzoin (491), which was also obtained directly from the tosylhydrazone (483) by treatment with LTA in AcOH at 60°C[173,181].



2.3.2 Results and Discussion

Oxidation of the toluene-p-sulfonylhydrazones (493), derived from acetoacetanilides (492), with either $Pb(OAc)_4$ or $Hg(OAc)_2$ could give rise to diazo-compounds of the type (494) (Scheme 18).

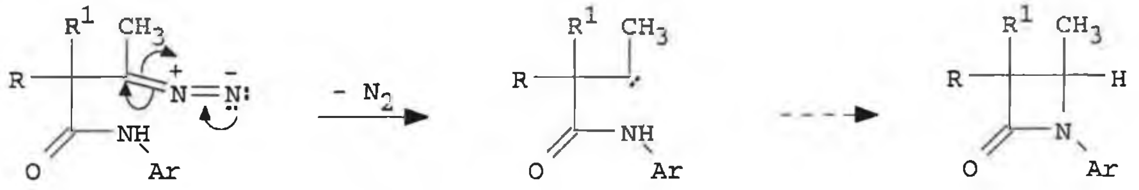
Scheme 18



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

R, R^1 = H, CH_3
Ar = Ph, 4-Cl-C_6H_4

Diazoalkanes, in general, are known precursors of carbenes[182,183]. Carbenes are highly reactive, neutral, bivalent carbon intermediates, which can add to or insert into a variety of bonds, both inter- and intra-molecularly. Indeed, several examples of carbenic insertion into N-H bonds have been reported[184-187]. Loss of molecular nitrogen from the acetoacetanilide-derived diazoalkanes (494) would give carbenes (495), and subsequent intramolecular insertion into the amide N-H bond would furnish the β-lactams (496).



(494) **(495)** **(496)**

R, R^1 = H, CH_3
Ar = Ph, 4-Cl-C_6H_4

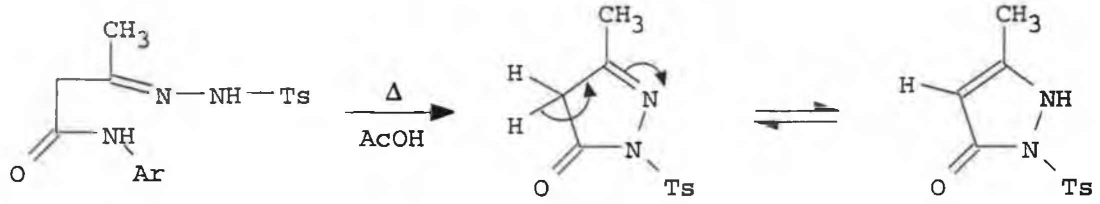
Although C3-C4 β-lactam ring closure via intramolecular carbenic insertion into C-H bonds has been achieved[29,188-190], to our knowledge, no report of N-C4 lactamisation of a β-carbenic amide has appeared. Thus, metallic acetate oxidation of the tosylhydrazones (493) could provide a novel route to β-lactams of the type (496).

Reaction of the acetoacetanilides (404) with one molar equivalent of p-toluenesulfonhydrazide in acetic acid afforded the tosylhydrazones (497) in excellent yields.

(404) **(497)**

a: Ar = Ph
b: Ar = 4-Cl-C_6H_4

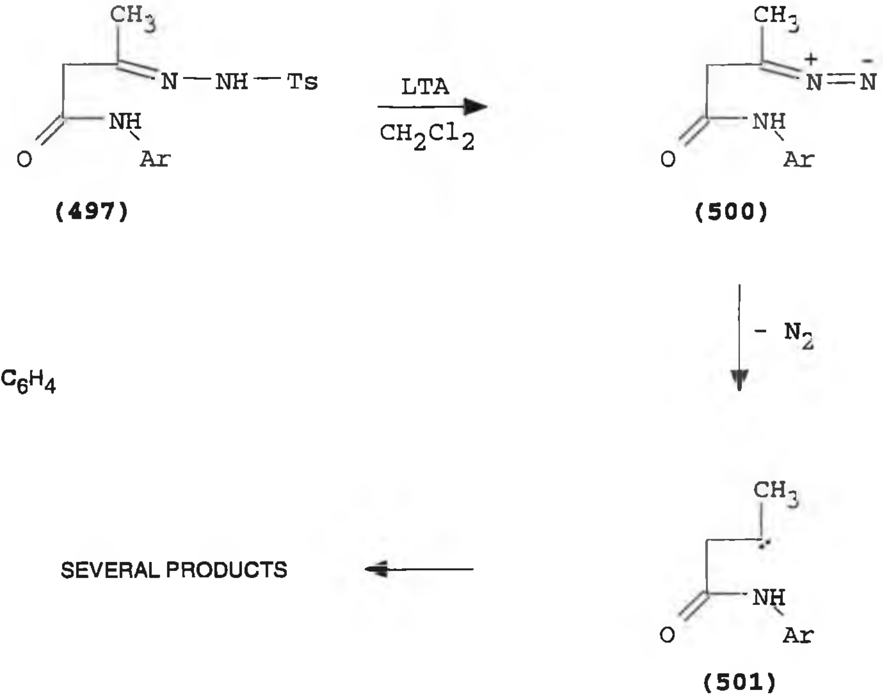
The hydrazones (497) were each cyclised to 1-(4-toluenesulfonyl)-3-methyl-2-pyrazolin-5-one (498) by careful heating in AcOH. Excessive heating resulted in decomposition. The cyclic product (498) tautomerises to (499) in DMSO solution, giving a ^1H NMR spectrum with a vinylic peak at 5.02 ppm.



(497) **(498)** **(499)**

a: Ar = Ph
b: Ar = 4-Cl-C_6H_4

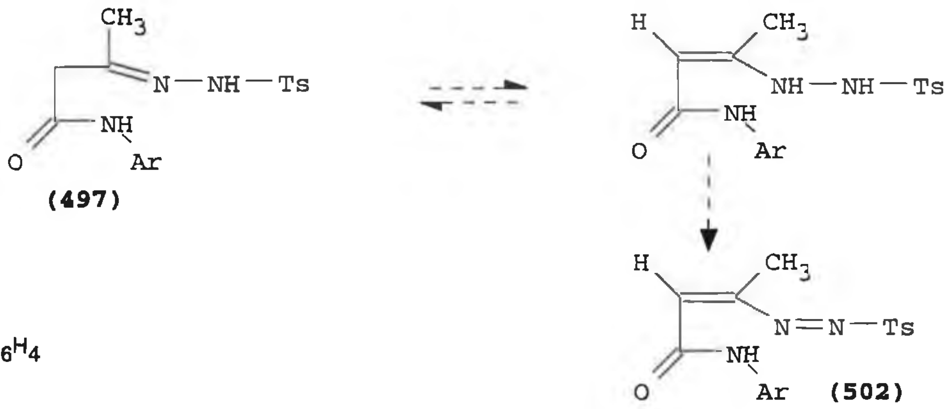
In contrast to the clean reactions observed when the analogous p-nitrophenylhydrazones (405) were oxidised with $Pb(OAc)_4$ in dichloromethane, affording azoacetates (406), treatment of the tosylhydrazones (497) with LTA in CH_2Cl_2 gave, in each case, a mixture containing at least six products, none of which could be separated and isolated. In both reactions, gas evolution was evident, suggesting loss of molecular nitrogen from intermediate diazo-compounds (500), and the generation of carbenes (501). The unstable carbenic species (501) could undergo a variety of addition and insertion reactions, as well as rearrangements, and such indiscriminate reactions would account for the formation of numerous products.



(497) **(500)** **(501)**

a: Ar = Ph
b: Ar = 4-Cl-C_6H_4

As previously discussed, p-nitrophenylhydrazones (405) derived from α,α-unsubstituted acetoacetanilides (404) are believed to tautomerise to enehydrazines in acetic acid solution, the latter being oxidised by LTA to the corresponding Z-azoalkenes (416). Thus, the tosylhydrazones (497) might be expected to afford tosylazoalkenes of the type (502) when treated with LTA in AcOH.



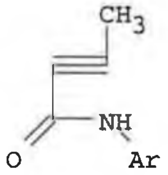
(497) **(502)**

a: Ar = Ph
b: Ar = 4-Cl-C_6H_4

Tosylazoalkenic compounds have been proposed as intermediates in many reactions[191-193]. Although some such azo-olefins have been isolated and characterised[194], these labile species are mostly generated *in situ* and reacted further.

Treatment of acetoacetanilide tosylhydrazone (497a) with 1.2 equivalents of $Pb(OAc)_4$ in acetic acid resulted in the development of a strong red colouration, characteristic of diazo-compounds[173,181]. Once the colour faded and effervescence ceased, a white precipitate which had formed was collected. Analysis revealed that this was lead acetate toluene-p-sulfonate (479), a known[173] by-product of LTA oxidation of tosylhydrazones. Unfortunately, examination of the filtrate showed that, again, a complex mixture of several products had been obtained.

Reaction of the hydrazone (497a) with mercuric acetate in acetic acid resulted in oxidation, as evidenced by the separation of metallic mercury, but failed to yield any isolable products. However, when treated with 1.2 equivalents of $Hg(OAc)_2$ in CH_2Cl_2 for 24 hours at ambient temperature, TLC analysis indicated that, in addition to material which remained baseline (100% CH_2Cl_2), a single non-polar product (503a) had been formed. The IR spectrum of this compound, which was separated by column chromatography, showed a sharp band at 2235 cm^{-1}, initially suggesting that perhaps the diazoalkane (500a) had been isolated. Similarly, oxidation of hydrazone (497b) with $Hg(OAc)_2$ in CH_2Cl_2 afforded, after chromatography, a product (503b) displaying a sharp absorption at 2237 cm^{-1} in the IR spectrum. Further analysis revealed that compound (503b) was, in fact, N-(4-chlorophenyl)but-2-ynamide, giving rise to a C≡C stretch near 2200 cm^{-1}.

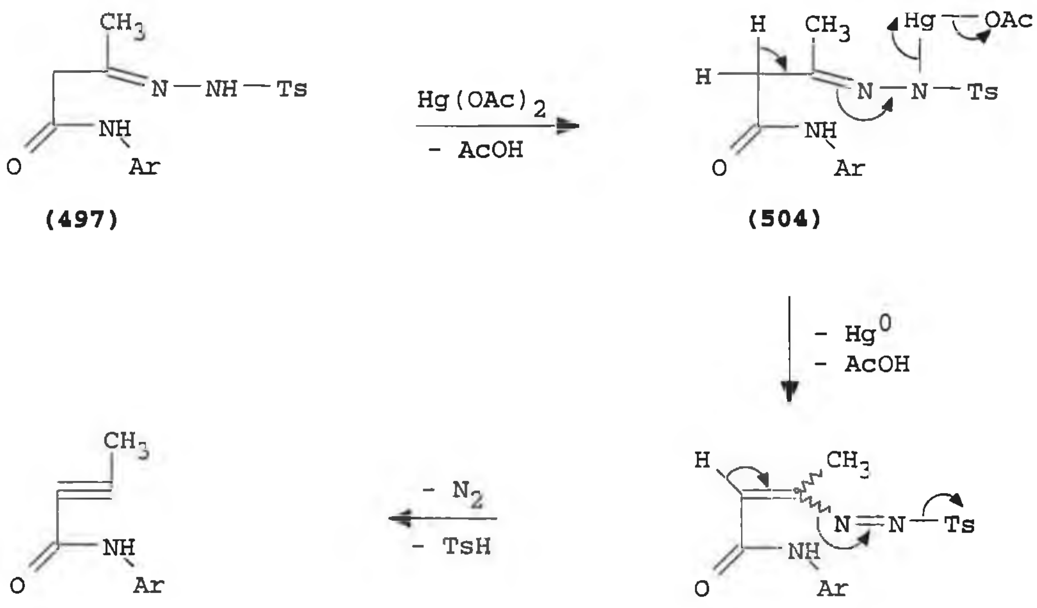


(503)

a: Ar = Ph
b: Ar = 4-Cl-C_6H_4

Formation of the acetylenic amides (503) is proposed to occur via initial metalation of the starting hydrazones (497), 1,4-elimination of elemental Hg and AcOH from the N-mercuri species (504) to afford the tosylazoalkenes (505), and finally loss of molecular nitrogen and toluene-p-sulfinic acid from the labile intermediates (505) (Scheme 19).

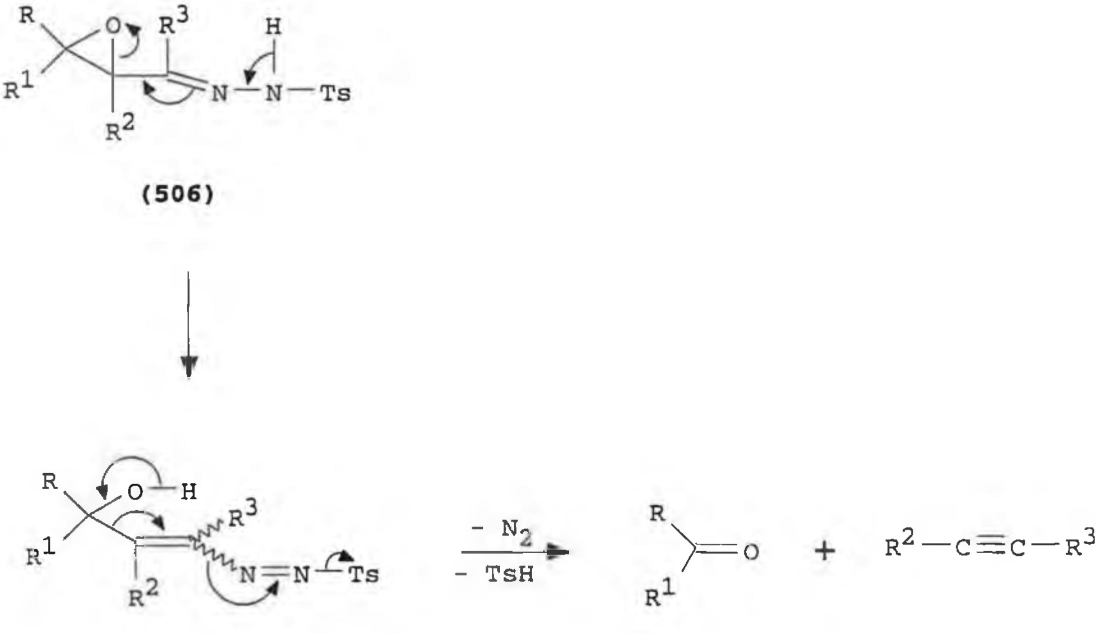
Scheme 19



(497) (504) (503) (505)

a: Ar = Ph
b: Ar = 4-Cl-C_6H_4

From a mechanistic viewpoint, formation of the 2-butynamides (503) can be likened to the classic Eschenmoser-Tanabe reaction[191,192,195,196], where α,β-epoxytosylhydrazones (506) undergo fragmentation, with elimination of nitrogen and toluene-p-sulfinic acid from intermediate tosylazoalkenes (507), to give carbonyl compounds (508) and alkynes (509).

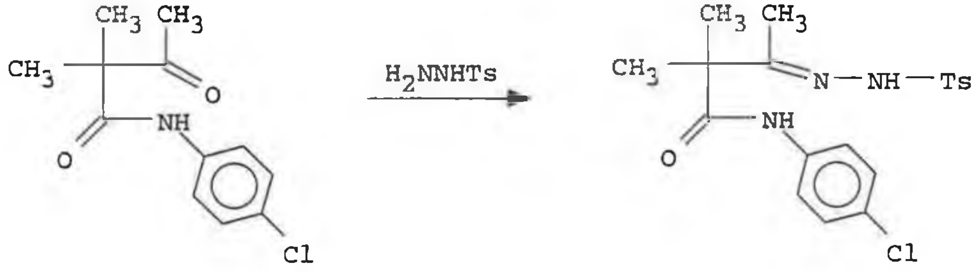


(506) (507) (508) (509)

It may be noted that Gilbert and Blackburn[197] have reported the isolation of acetylenic amides similar to those encountered here.

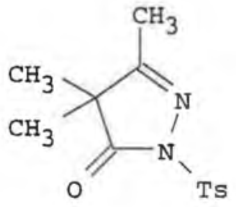
Since generation of the 2-butynamides (503) involves loss of both methylene protons of each starting hydrazone (497), we were interested to see what products, if any, could be isolated when this degradative pathway was effectively blocked. Thus, oxidation of the α,α-dimethyl-p-chloroacetoacetanilide p-toluenesulfonylhydrazone (510) with mercuric acetate in dichloromethane was investigated.

The tosylhydrazone (510) was prepared in good yield by condensing N-(4-chlorophenyl)-2,2-dimethyl-3-oxobutanamide (435b) with toluene-p-sulfonhydrazide in acetic acid.



(435b) (510)

A brief reaction time was found to be essential here, since prolonged stirring in AcOH, even at ambient temperature, resulted in cyclisation of the product hydrazone (510), and the isolation of 1-(4-toluenesulfonyl)-3,4,4-trimethyl-2-pyrazolin-5-one (511) In 87% crude yield.

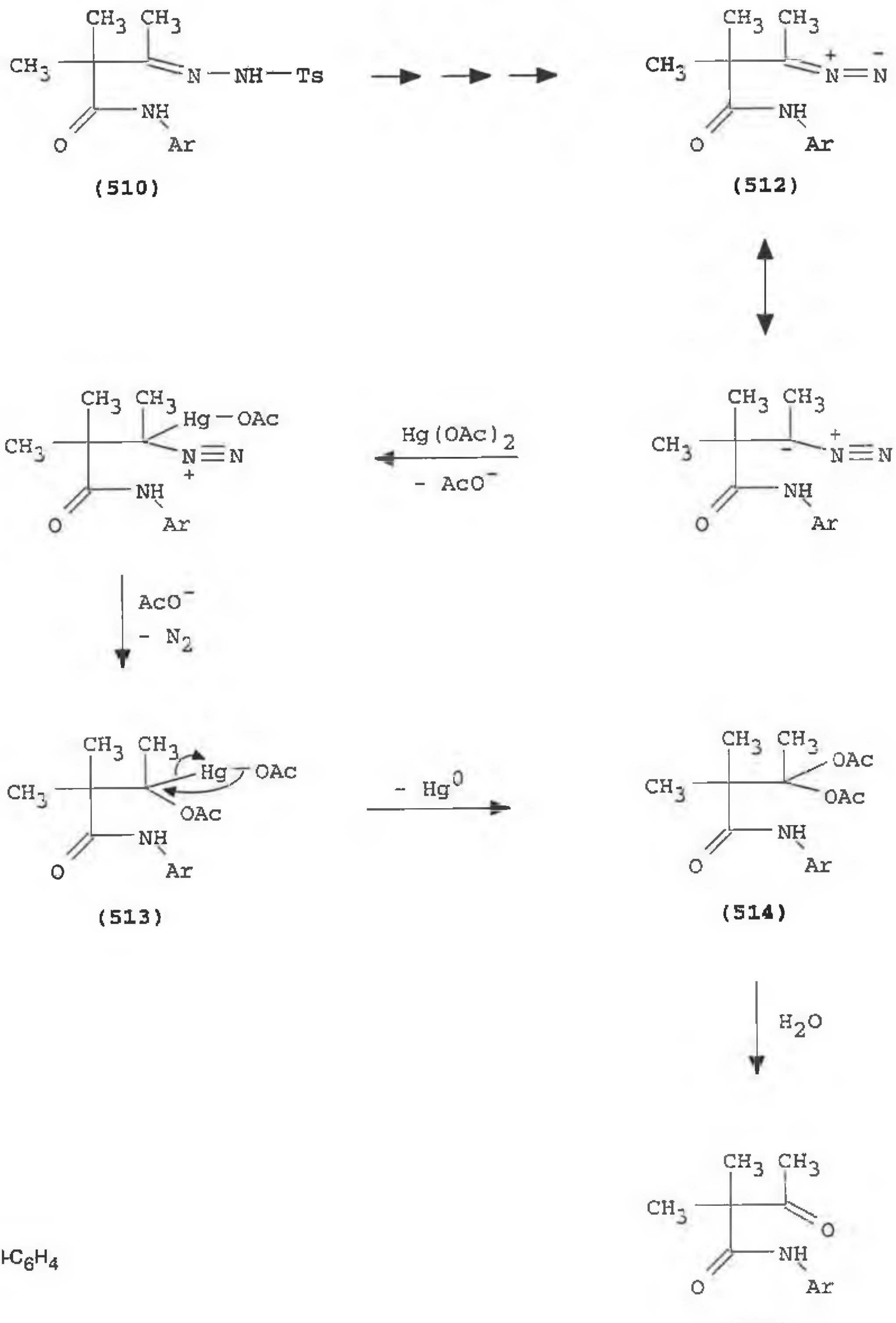


(511)

Reaction of the tosylhydrazone (510) with $Hg(OAc)_2$ in CH_2Cl_2 gave a mixture containing two products which moved from the baseline on TLC. The least polar of these was separated on a silica gel column and identified as the parent acetoacetanilide (435b).

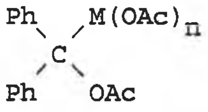
Whereas the regeneration of ketones from their tosylhydrazones with lead (IV) acetate is well-known[173,180], such a reaction with mercury (II) acetate as oxidant is unusual. Production of the acetoacetanilide (435b) is believed to involve initial oxidation of the hydrazone (510) to the diazoalkane (512). Subsequent attack on a second molecule of $Hg(OAc)_2$ would give, with loss of molecular nitrogen, the mercury-containing intermediate (513). A 1,2-acetoxy migration with elimination of elemental mercury would then furnish the unstable gem-diacetoxy compound (514), which, on hydrolysis, would yield the original carbonyl compound (435b) (Scheme 20).

Scheme 20



Ar = 4-Cl-C_6H_4

Indeed, a mechanism of this type, involving the analogous Pb-intermediate (515), has been invoked to explain the recovery of benzophenone (480) from its unsubstituted hydrazone on treatment with 2 equivalents of LTA[198].



(515) : M = Pb; n = 3
(516) : M = Hg; n = 1

Moreover, oxidation of benzophenone hydrazone with mercuric acetate has been reported[144,176] to give the Hg(II)-species (516), which reverts to the parent ketone (480) on standing.

2.3.3 Experimental

Common reagent grade chemicals were purchased from Aldrich Chemical Company, and were used as received. LTA was washed with dry diethyl ether under suction before use.

Melting points were determined in open capillary tubes with a Gallenkamp melting point apparatus, and are uncorrected. IR spectra were recorded for KBr discs and nujol mulls with a Perkin-Elmer 983-G spectrometer. ^1H and ^{13}C NMR spectra were measured for solutions in $CDCl_3$, DMSO-d_6 or 10% DMSO-d_6 in $CDCl_3$ with Perkin-Elmer R12B 60 MHz and JEOL GX-FT 270 MHz spectrometers, and referenced to tetramethylsilane or residual solvent H. Elemental analyses were performed in the Microanalytical Laboratory, University College Dublin.

(i) Synthesis of acetoacetanilide p-toluenesulfonylhydrazone (497a)

8.86g (50 mmoles) acetoacetanilide (404a) was added to a solution of 9.31g (50 mmoles) p-toluenesulfonhydrazide in 150mls acetic acid at ambient temperature, with good stirring. A white solid precipitated almost immediately. After stirring for 15 minutes, the tosylhydrazone (497a) was filtered (15.72g; 91%). MP 136-138°C. IR (nujol mull) 3283, 3209, 1660 cm^{-1}. ^{1}H NMR (60 MHz; 9:1 $CDCl_3$:DMSO-d_6) δ 2.00 (s, 3H), 2.35 (s, 3H), 3.30 (s, 2H), 6.90-8.00 (m, 9H), 9.45 (bs, 1H), 9.90 (bs, 1H).

(ii) Synthesis of p-chloroacetoacetanilide p-toluenesulfonylhydrazone (497b)

p-Chloroacetoacetanilide (404b) was condensed with p-toluenesulfonhydrazide as described in (i) to afford the tosylhydrazone (497b) as a white solid in 90% yield. MP 155-156°C. IR (KBr) 3337, 1674 cm^{-1}. ^{1}H NMR (270 MHz; DMSO-d_6) δ 1.88 (s, 3H), 2.33 (s, 3H), 3.24 (s, 2H), 7.27 (d, 2H, J = 6.6 Hz), 7.36 (d, 2H, J = 6.6 Hz), 7.59 (d, 2H, J = 7.3 Hz), 7.71 (d, 2H, J = 6.6 Hz), 10.18 (s, 1H), 10.24 (s, 1H).

(iii) Preparation of 1-(4-toluenesulfonyl)-3-methyl-2-pyrazolin-5-one (498)

(a) From hydrazone (497a)

A mixture of 3.45g (10 mmoles) hydrazone (497a) in 60mls AcOH was heated at 90-95°C for 15 minutes. The resultant pale yellow solution was diluted with water. On standing, the cyclic product (498) precipitated from solution as white crystals (1.29g; 51%). MP 153-154.5°C. IR (KBr) 1626 cm^{-1}. ^{1}H NMR (270 MHz; DMSO-d_6) δ 2.02 (s, 3H), 2.34 (s, 3H), 5.02 (s, 1H), 7.40 (d, 2H, J = 7.7 Hz), 7.75 (d, 2H, J = 8.1 Hz). $C_{11}H_{12}N_2O_3S$ requires C, 52.36; H, 4.79; N, 11.11%. Found C, 52.65; H, 4.74; N, 11.22%.

(b) From hydrazone (497b)

Tosylhydrazone (497b) was cyclised in a similar manner, furnishing the pyrazolin-5-one (498) in 60% yield.

(iv) Oxidation of hydrazone (497a) with LTA in CH_2Cl_2

To a mixture of 1.73g (5 mmoles) hydrazone (497a) in 40mls CH_2Cl_2 was added 2.66g (6 mmoles; 120 mole%) LTA with stirring. Almost immediately, nitrogen evolution was observed. After stirring for 1 hour at 20°C, the mixture was filtered. The orange filtrate was washed with sodium bicarbonate solution and water, and dried over Na_2SO_4. Evaporation of the solvent afforded a red oil. TLC analysis (70:30 dichloromethane: petroleum ether (40-60°)) indicated that at least six products had been formed.

(v) Oxidation of hydrazone (497b) with LTA in CH_2Cl_2

Hydrazone (497b) was oxidised similarly with LTA in dichloromethane, but here over a 24 hour period. Again, TLC analysis revealed the presence of at least six products.

(vi) Oxidation of hydrazone (497a) with LTA in AcOH

2.66g (6 mmoles; 120 mole%) LTA was added to a mixture of 1.73g (5 mmoles) hydrazone (497a) in 40mls acetic acid at room temperature. A red colour developed quickly, then faded, and effervescence was observed. After 1 hour, the mixture was filtered to give a white solid, which was washed with acetic acid and dried. This proved to be lead acetate toluene-p-sulfonate (479) (0.42g; 19%). IR (KBr) 1521, 1411, 1210, 1139, 1123, 1037, 1011, 813, 678, 658 cm^{-1}. ^1H NMR (270 MHz; DMSO-d_6) δ 1.73 (s, 3H), 2.29 (s, 3H), 7.13 (d, 2H, J = 8.1 Hz), 7.50 (d, 2H, J = 8.1 Hz) [lit.[173] ^1H NMR (DMSO-d_6) δ 1.74 (3H), 2.28 (3H), 7.12 and 7.52 (dd, 4H, J = 9 Hz)]. ^{13}C NMR (67.5 MHz; DMSO-d_6) 20.5, 27.2, 125.3, 127.9, 137.6, 145.1, 178.6 ppm. $C_9H_{10}O_5PbS$ requires C, 24.71; H, 2.30%. Found C, 24.45; H, 2.27%. TLC analysis of the orange filtrate showed that multiple products had been formed.

(vii) Oxidation of hydrazone (497a) with $Hg(OAc)_2$ in AcOH

To a mixture of 1.73g (5 mmoles) hydrazone (497a) in 50mls acetic acid was added 1.91g (6 mmoles; 120 mole%) $Hg(OAc)_2$. After stirring at 20°C for 24 hours, a reddish-brown solution containing Hg^0 was obtained. The mixture was filtered through a bed of Celite. TLC analysis of the filtrate indicated the presence of 5 products, the most intensely UV-absorbing of these remaining on the baseline.

(viii) Oxidation of hydrazone (497a) with $Hg(OAc)_2$ in CH_2Cl_2

2.29g (7.2 mmoles; 120 mole%) $Hg(OAc)_2$ was added to 2.07g (6 mmoles) hydrazone (497a) in 100mls CH_2Cl_2, and the mixture stirred for 24 hours at ambient temperature. TLC analysis (100% CH_2Cl_2) of the resultant dark red solution revealed the presence of a single non-polar product plus baseline material. The mixture was filtered through Celite to remove Hg^0. The filtrate was washed with $NaHCO_3$ solution, then water, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue applied to a silica gel column. Elution with 100% CH_2Cl_2 provided N-phenyl-2-butynamide (503a) as a pale yellow oil, which was crystallised from diethyl ether/petroleum ether (40-60°) (30mg; 3%). IR (KBr) 3252, 2235, 1633 cm^{-1}.

(ix) Oxidation of hydrazone (497b) with $Hg(OAc)_2$ in CH_2Cl_2

Hydrazone (497b) was reacted with $Hg(OAc)_2$ in dichloromethane as described in (viii). Column chromatography on silica gel, eluting with 100% CH_2Cl_2, afforded N-(4-chlorophenyl)but-2-ynamide (503b) as a pale yellow solid (6%). Recrystallisation from benzene/petroleum ether (40-60^o) gave an analytical sample. MP 138-139^{o}C. IR (KBr) 3261, 2237, 1638 cm^{-1}. ^{1}H NMR (60 MHz; DMSO-d$_6$) δ 1.90 (s, 3H), 7.25 (d, 2H), 7.55 (d, 2H), 10.55 (bs, 1H). $C_{10}H_8NOCl$ requires C, 62.03; H, 4.16; N, 7.24%. Found C, 62.32; H, 4.22; N, 7.22%.

(x) Synthesis of α,α-dimethyl-p-chloroacetoacetanilide p-toluenesulfonylhydrazone (510)

2.40g (10 mmoles) N-(4-chlorophenyl)-2,2-dimethyl-3-oxobutanamide (435b) was dissolved in 25mls acetic acid and added to a solution of 1.85g (10 mmoles) p-toluenesulfonhydrazide in an equal volume of the same solvent. After stirring at room temperature for approximately 15 minutes, a white solid precipitated from solution. The suspension was stirred for a further 15 minutes. Hydrazone (510) was collected by filtration, washed with water and dried (3.03g; 74%). Crystallisation from ethanol afforded white crystals. MP 171-172^{o}C. IR (KBr) 3353, 3209, 1662 cm^{-1}. ^{1}H NMR (60 MHz; DMSO-d$_6$) δ 1.10 (s, 6H), 1.60 (s, 3H), 2.20 (s, 3H), 6.90-7.70 (m, 8H), 9.05 (bs, 1H), 9.90 (bs, 1H).

(xi) Preparation of 1-(4-toluenesulfonyl)-3,4,4-trimethyl-2-pyrazolin-5-one (511)

The acetoacetanilide (435b) and p-toluenesulfonhydrazide were reacted as described in (x), but here stirring was continued for 48 hours. Addition of water to the resulting solution precipitated crude 1-(4-toluenesulfonyl)-3,4,4-trimethyl-2-pyrazolin-5-one (511) (87%). Recrystallisation from ethanol gave analytical material. MP 144-145^{o}C. IR (KBr) 1740 cm^{-1}. ^{1}H NMR (60 MHz; CDCl$_3$) δ 1.15 (s, 6H), 2.00 (s, 3H), 2.45 (s, 3H), 7.35 (d, 2H), 7.90 (d, 2H).

(xii) Oxidation of hydrazone (510) with $Hg(OAc)_2$ in CH_2Cl_2

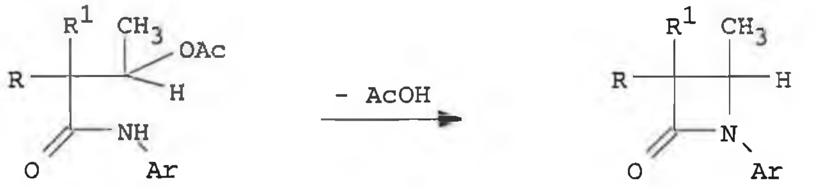
0.82g (2 mmoles) hydrazone (510) was dissolved in 30mls CH_2Cl_2 and 0.76g (2.4 mmoles; 120 mole%) $Hg(OAc)_2$ was added. The mixture was stirred for 24 hours at ambient temperature, then filtered through a bed of Celite. The filtrate was washed with sodium bicarbonate solution and water, and dried over Na_2SO_4. TLC analysis (70:30 petroleum ether (40-60^o): ethyl acetate) showed that, in addition to material that remained on the baseline, two products had been formed. The residue obtained on evaporation of the solvent was applied to a silica gel column. Elution with 70:30 petroleum ether (40-60^o): ethyl acetate allowed separation of the least polar component, which was shown by analysis to be N-(4-chlorophenyl)-2,2-dimethyl-3-oxobutanamide (435b) (0.144g; 30%).

Chapter 3

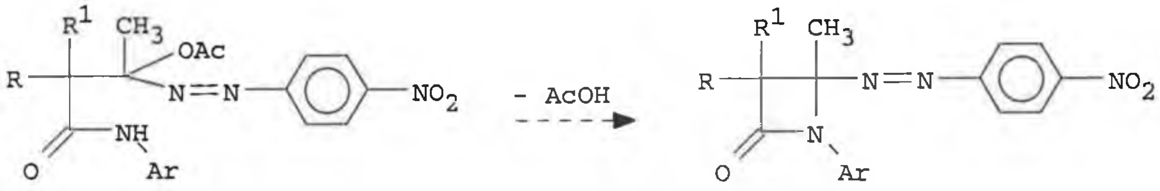
3.1 The Model System

3.1.1 Introduction

Before attempting N-C4 cyclisation of the acetoacetanilide-derived azoacetates (518), a system of model compounds bearing a proton in place of the arylazo- substituent was studied. It was hoped that investigation of the reactions of the key acetate compounds (517) would provide insight into the cyclisation conditions necessary to induce lactamisation of the azoacetates (518).



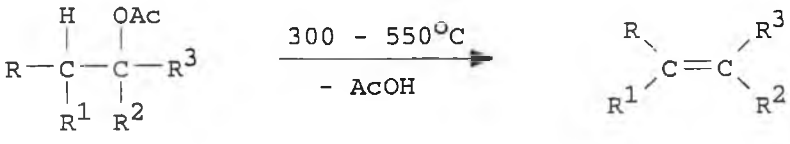
(517) (496)



(518)

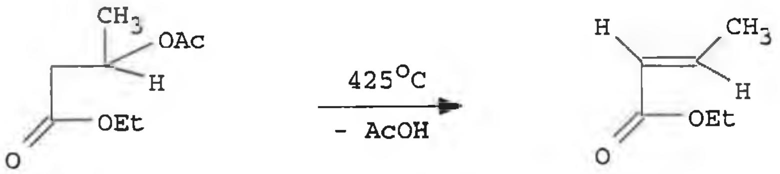
R = R^1 = H, CH_3
R = H; R^1 = CH_3
Ar = Ph, 4-Cl-C_6H_4

With substrates of the type (519), where there is an acetoxy group β to a carbon bearing a hydrogen atom, elimination of acetic acid (dehydroacetoxylation) can be effected by pyrolysis.



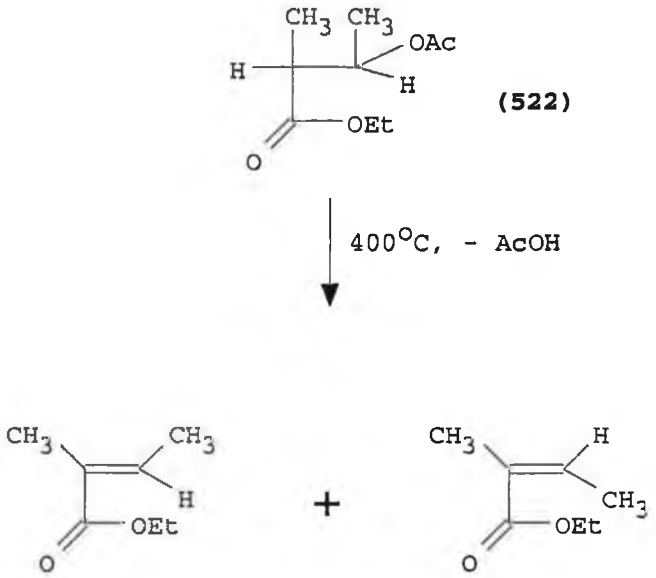
(519)

Bailey and King[199] have reported the isolation of ethyl crotonate (521) as the sole product from the pyrolysis of ethyl β-acetoxy-n-butyrate (520).



(520) (521)

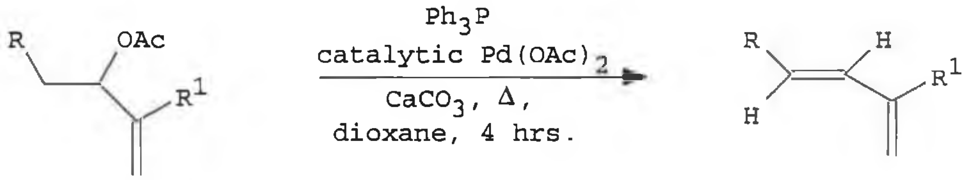
Similar thermal decomposition of the analogous α-methylated compound (522) gave ethyl tiglate (523) and a small amount of ethyl angelate (524)[199].



(522)

(523) (524)

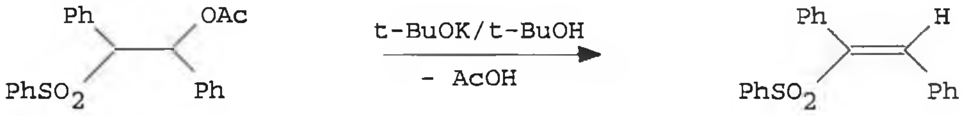
Allylic acetates can be dehydroacetoxylated using metal catalysts. Stereospecific palladium-catalysed elimination of AcOH from the allylic acetates (525) gives the E-1,3-disubstituted 1,3-dienes (526) in high yields[200].



(525) (526)

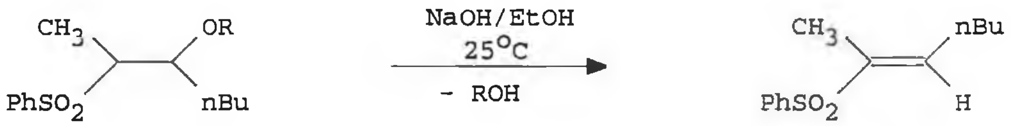
R, R^1 = alkyl

Numerous bases have been employed to induce loss of acetic acid. When 1-acetoxy-2-(phenylsulfonyl)-1,2-diphenylethane (527) was treated with 1 equivalent of t-BuOK in t-BuOH, the vinyl sulfone (528) was produced in 94% yield[201].



(527) (528)

Julia et al.[202] found that reaction of the erythro β-acetoxy sulfone (529a) with NaOH in ethanol at 25°C afforded the E-vinyl sulfone (530).

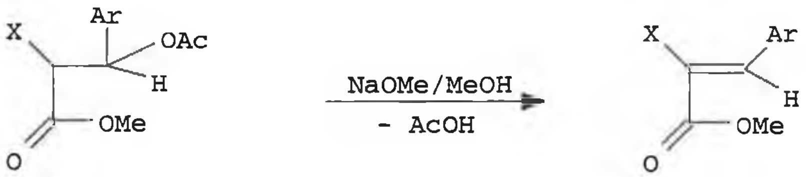


(529) **(530)**

a: R = Ac
b: R = Ts

Interestingly, the corresponding tosylate (529b) also underwent elimination to (530) in the presence of NaOH/EtOH at ambient temperature.

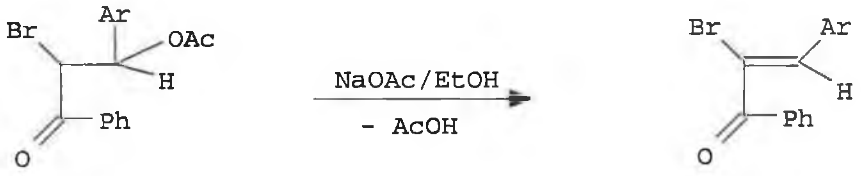
Methanolic sodium methoxide-induced dehydroacetoxylation of the methyl 3-acetoxy-3-aryl-2-halogenopropanoates (531) gives exclusively the Z-olefins (532)[203].



(531) **(532)**

X = Br, Cl
Ar = 4-CH_3O-C_6H_4, 4-CH_3-C_6H_4, Ph, 4-Cl-C_6H_4, 4-NO_2-C_6H_4

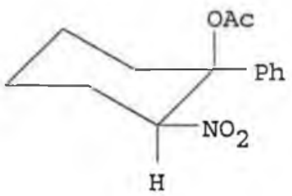
The 3-phenyl species (531: Ar = Ph) also eliminated AcOH when treated with an excess of triethylamine in methanol[204]. Sodium acetate in ethanol has been used to dehydroacetoxylate 2-bromo-3-acetoxy-3-(4-nitrophenyl)-1-phenylpropanone (533), affording the olefin (534) in 97.4% yield[205].



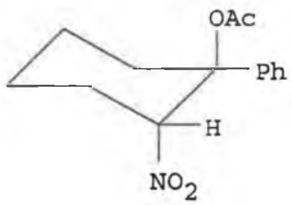
(533) **(534)**

Ar = 4-NO_2-C_6H_4

Bordwell and colleagues[206] have reported cis- and trans-elimination of AcOH from the stereoisomeric 1-acetoxy-2-nitro-1-phenylcyclohexanes (535) and (536) on treatment with piperidine in chloroform-ethanol solution.

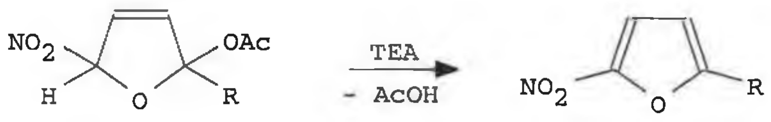


(535)



(536)

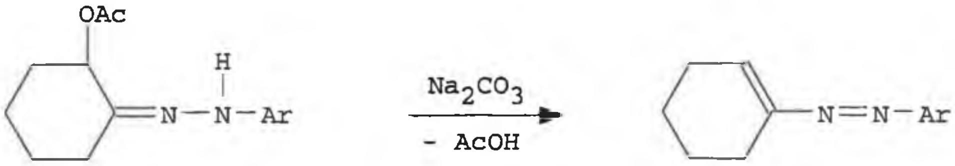
1,4-Elimination of acetic acid from 2-acetoxy-5-nitro-2,5-dihydrofurfural diacetate (537a) and methyl 2-acetoxy-5-nitro-2,5-dihydro-2-furancarboxylate (537b) can be effected by reaction with triethylamine in acetone or methanol[207].



(537) **(538)**

a: $R = CH(OAc)_2$
b: $R = CO_2CH_3$

This aromatising dehydroacetoxylation to the nitrofurans (538) also occurred when substrates (537) were chromatographed on silica gel. Finally, the azoalkenes (540) have been prepared in good yields by treatment of ethereal solutions of the arylhydrazones (539) with aqueous sodium carbonate at room temperature[208].

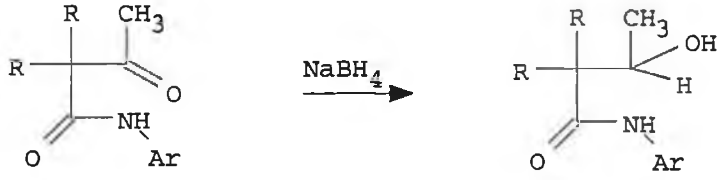


(539) **(540)**

Ar = Ph, $4\text{-}CH_3\text{-}C_6H_4$, $4\text{-}CH_3O\text{-}C_6H_4$

3.1.2 Results and Discussion

Sodium borohydride reduction of the acetoacetanilides (404) and (435) gave the 3-hydroxybutyranilides (541) and (542) respectively, in high yields.

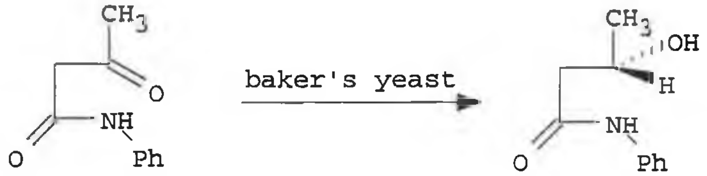


(404) : R = H
(435) : R = CH_3

(541) : R = H
(542) : R = CH_3

a: Ar = Ph
b: Ar = 4-Cl-C_6H_4

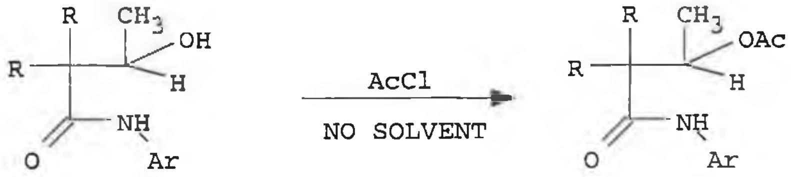
As a point of interest, acetoacetanilide (404a) can be reduced enantioselectively with Baker's yeast, affording (S)-(+)-N-phenyl-3-hydroxybutanamide (543)[209,210].



(404a)

(543)

The target acetates (544) and (545) were prepared cleanly, in almost quantitative yields, by treating the alcohols (541) and (542) respectively with an excess of acetyl chloride, in the absence of solvent.

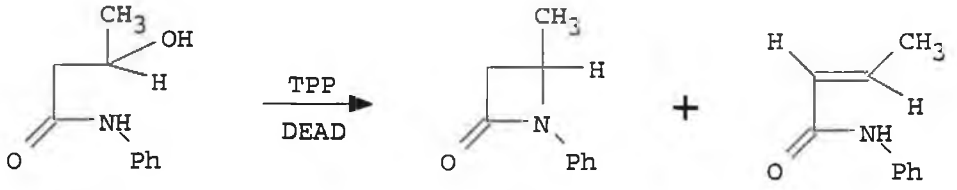


(541) : R = H
(542) : R = CH_3

(544) : R = H
(545) : R = CH_3

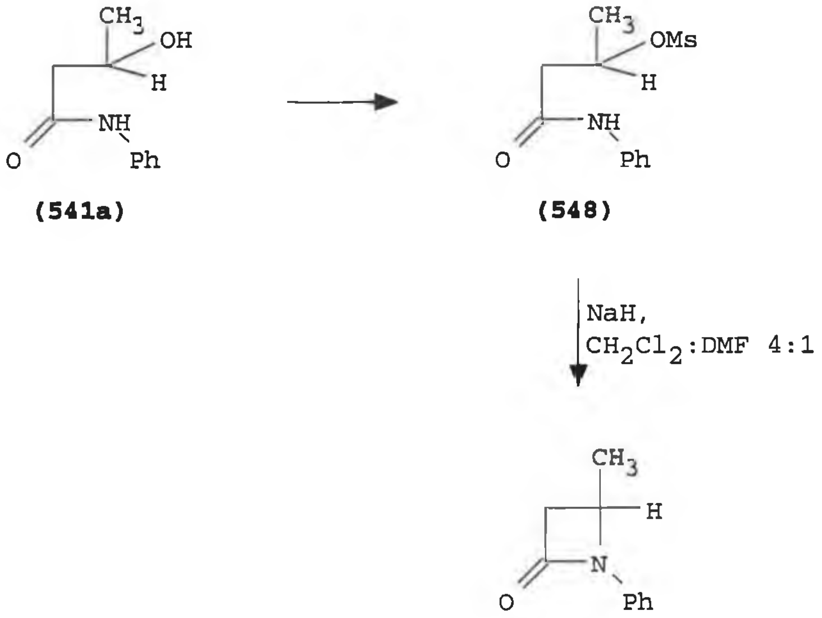
a: Ar = Ph
b: Ar = 4-Cl-C_6H_4

Direct N-C4 cyclisation of N-phenyl-3-hydroxybutanamide (541a) to the model β-lactam (546) has already been reported. Applying the Mitsunobu reaction[105], Bose and colleagues[113] found that dehydration of the alcohol (541a) with TPP/DEAD in THF gave N-phenyl-4-methyl-2-azetidinone (546) in 41% yield, after chromatography. However, under these conditions, the β-elimination product crotonanilide (547) was also formed, in 21% yield.



(541a) **(546)** **(547)**

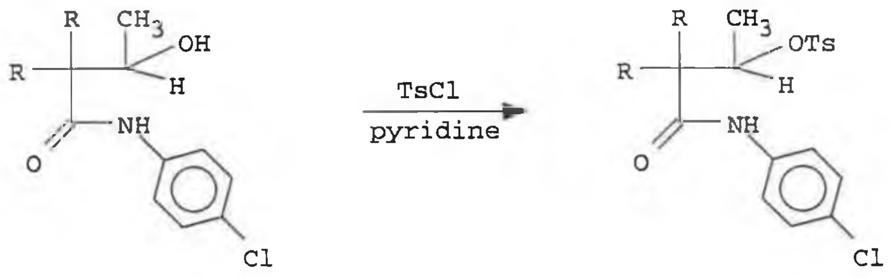
In a cleaner synthesis of the model β-lactam (546), Japanese chemists[210] used the methodology of Wasserman et al.[43] to effect ring closure of the mesylate derivative (548). N-Phenyl-4-methyl-2-azetidinone (546) was obtained in 82% overall yield from the alcohol (541a), and very little (<5%) competing β-elimination was observed.



(541a) **(548)**

(546)

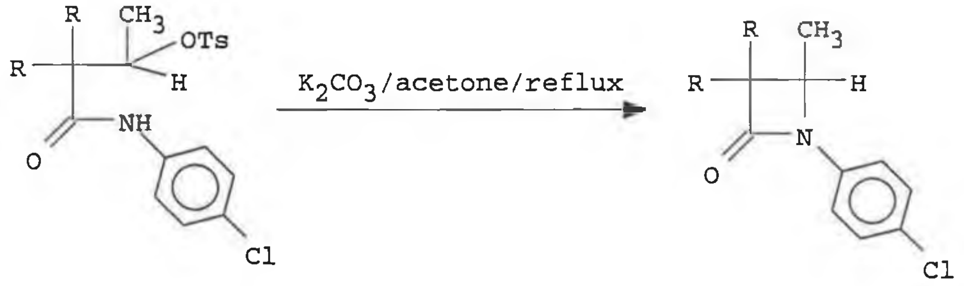
Adopting a similar approach, the model alcohols (541b) and (542b) were converted to the corresponding tosylates (549) and (550) by reaction with p-toluenesulfonyl chloride in dry pyridine.



(541b) : R = H
(542b) : R = CH_3

(549) : R = H
(550) : R = CH_3

The tosylates (549) and (550) were lactamised using the procedure developed by Floyd and associates[86]. Thus, treatment of the esters (549) and (550) with an excess of K_2CO_3 in refluxing acetone[95] furnished the target 2-azetidinones (551) and (552) in good yields.

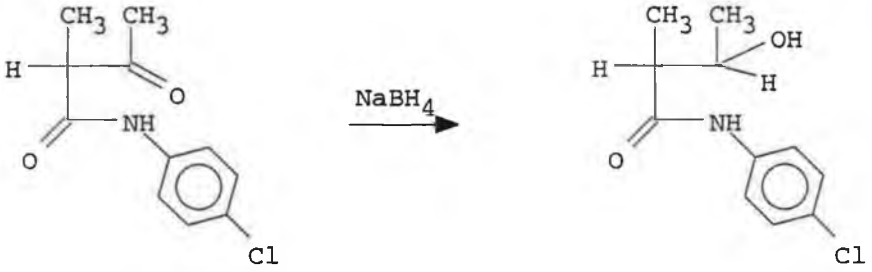


(549) : R = H
(550) : R = CH_3

(551) : R = H
(552) : R = CH_3

When the above sequence of reactions was repeated using N-(4-chlorophenyl)-2-methyl-3-oxobutanamide (439b) as starting material, some interesting and unexpected results were obtained. $NaBH_4$ reduction of the acetoacetanilide (439b), which contains an asymmetric carbon, should lead to the formation of four diastereomeric alcohols (553)-(556) (Scheme 21). Furthermore, Cram's rule[164,165] predicts that the alcohols (553) and (556) will be produced in preference to their epimers (554) and (555) (Scheme 22).

Reaction of the acetoacetanilide (439b) with $NaBH_4$ in THF gave N-(4-chlorophenyl)-2-methyl-3-hydroxybutanamide (557), as an unequal mixture of diastereomers, in 92% yield.



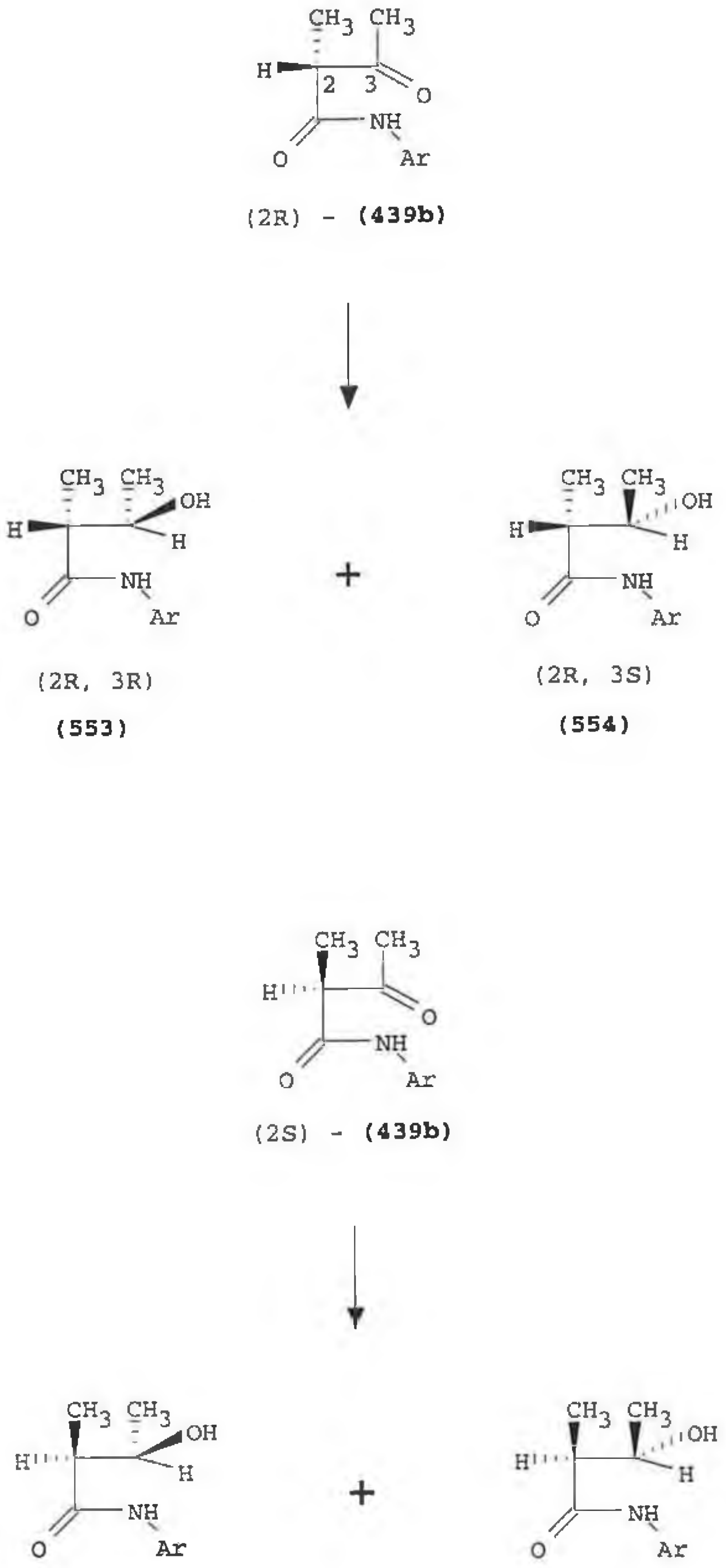
(439b)

(557)

An accurate estimate of the composition of the mixture could not be made by examination of the ^1H NMR spectrum (Figure 13a), since none of the peaks corresponding to the major component were sufficiently resolved from those of the minor component. Unfortunately, the diastereomeric pairs could not be separated chromatographically. However, by repeatedly recrystallising the crude mixture, a single pair of isomers (557(i)) was isolated in 18% yield (Figure 13b).

Scheme 21

Ar = 4-Cl-C_6H_4



(2R) - **(439b)**

(2R, 3R) **(553)**

(2R, 3S) **(554)**

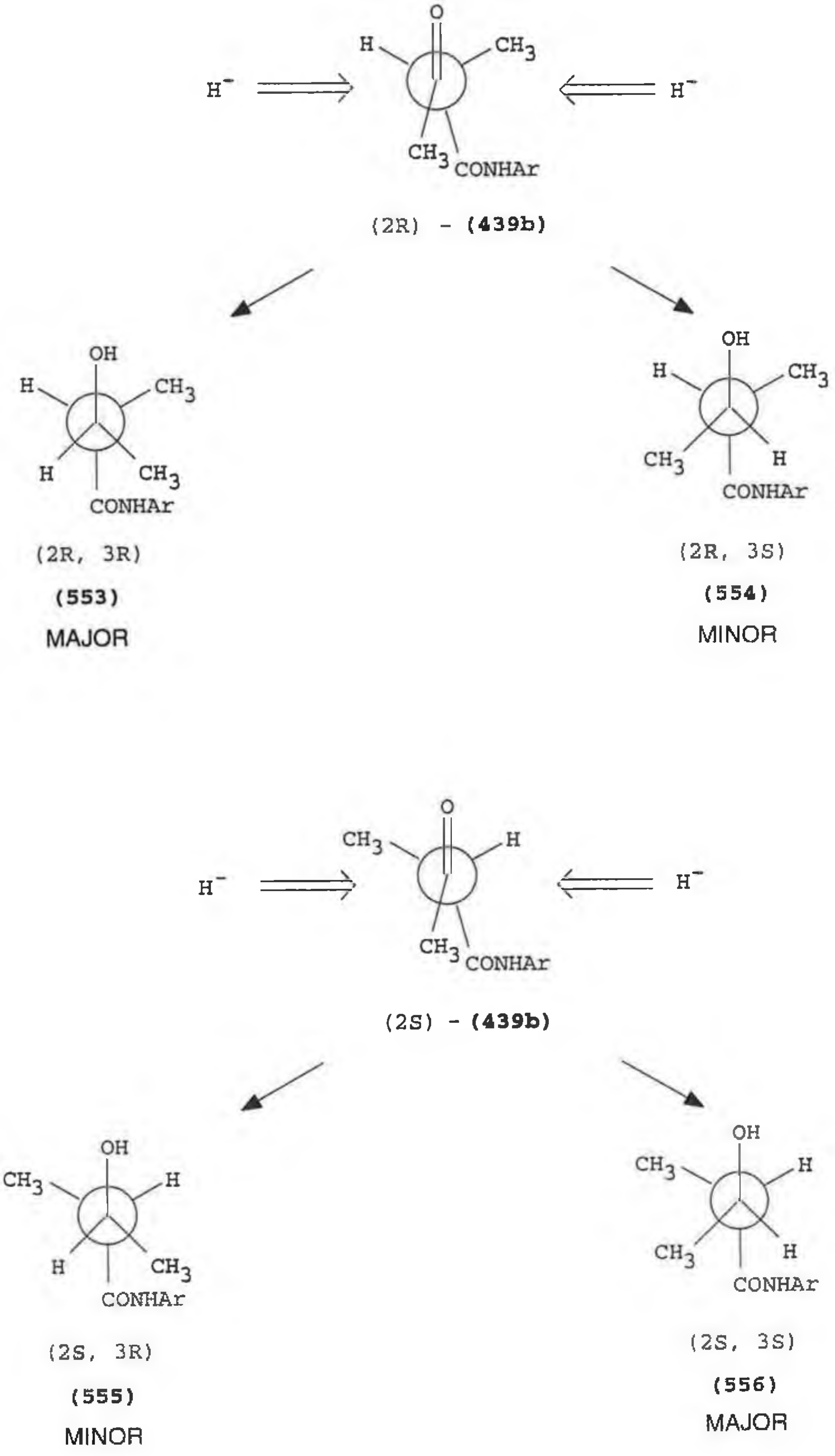
(2S) - **(439b)**

(2S, 3R) **(555)**

(2S, 3S) **(556)**

Scheme 22

Ar = 4-Cl-C_6H_4



(2R) - **(439b)**

(2R, 3R)

(553)

MAJOR

(2R, 3S)

(554)

MINOR

(2S) - **(439b)**

(2S, 3R)

(555)

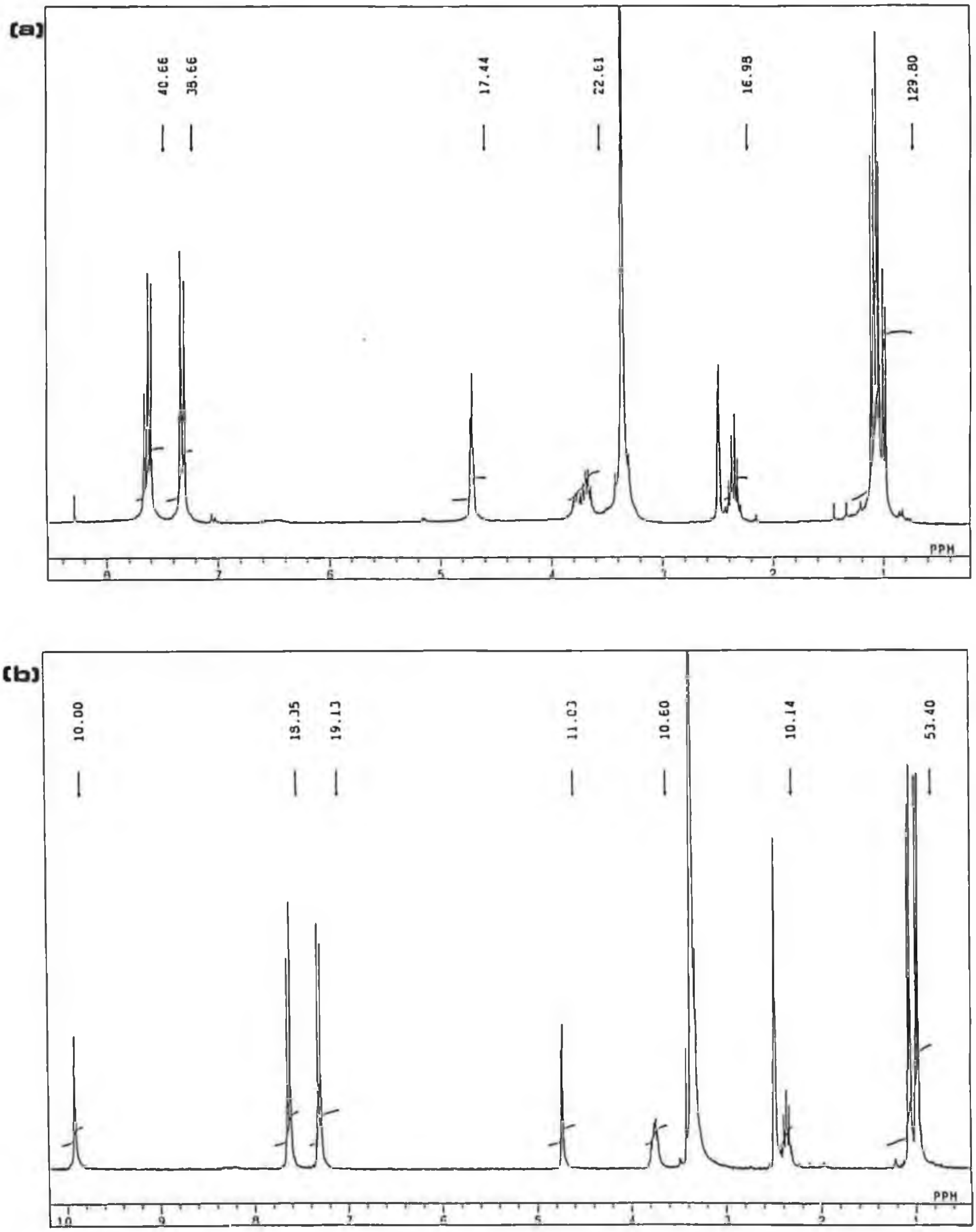
MINOR

(2S, 3S)

(556)

MAJOR

Figure 13: (a) ^{1}H NMR spectrum of diastereomeric mixture of alcohols (557)
(b) ^{1}H NMR spectrum of one pair of enantiomers (557(i))

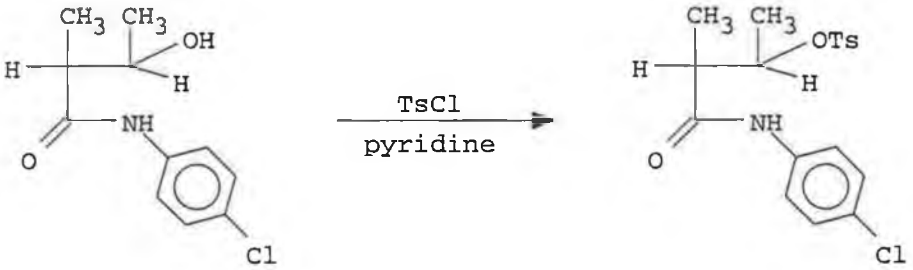


Acetylation of the crude alcohol (557) gave a mixture of diastereomeric acetates (558).

(557) (558)

The acetate singlets in the ^{1}H NMR spectrum of the derivative (558) (Figure 14a) were well-resolved (1.89 and 2.01 ppm) and showed that the major and minor isomers were present in a ratio of 1.8 : 1, indicating that a considerable degree of stereoselectivity had been achieved in the reduction step. A single pair of enantiomers (558(i)) was prepared by reacting the alcohol (557(i)) with acetyl chloride. Comparison of the ^{1}H NMR spectrum of acetate (558(i)) (Figure 14b) with that of the crude acetate (558) demonstrated that the isomeric pair (558(i)) corresponded to the minor component of the mixture (558).

The alcohol (557(i)), now known to comprise the minor isomers, was treated with p-toluenesulfonyl chloride to afford the tosylate (559(i)), a single pair of enantiomers, in 84% yield. Similarly, the mixture of diastereomeric alcohols (557) was converted to the crude tosylate (559).

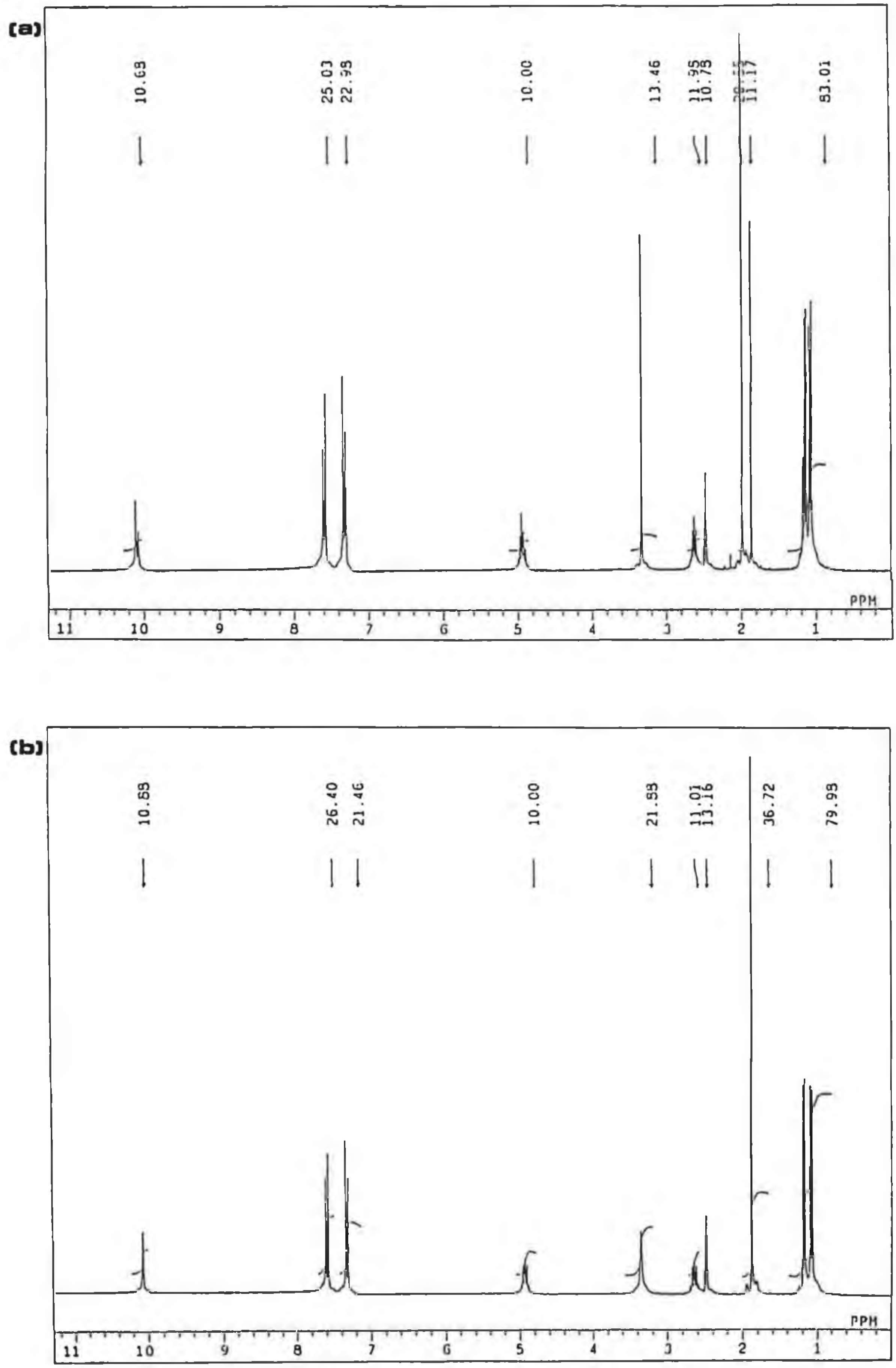


(557) (559)

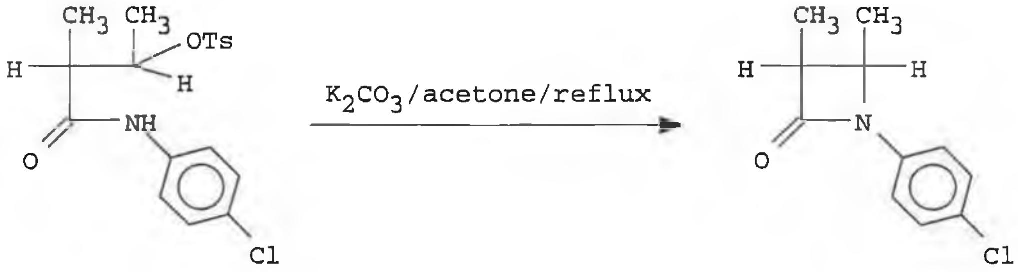
The major and minor components of tosylate (559) were separable by chromatography, and a sample of the predominant (less polar) enantiomers (559(ii)) was isolated on a silica column.

The minor tosylate (559(i)) was refluxed with K_2CO_3 in acetone to give the corresponding β-lactam (560(i)). The stereochemistry of this azetidin-2-one was assigned on the basis of its ^{1}H NMR data. Coupling constants for the interaction between vicinal protons in trans-β-lactams are normally in the range 1.5 - 2.5 Hz, whereas J values for the coupling of C3- and C4-protons in cis-β-lactams are typically between 4.5 and 6.5 Hz[53,138,211]. For the minor β-lactam (560(i)), $J_{3,4}$ was found to be 5.9 Hz, implying that this product comprised the cis-isomers (3R,4S)-(560) and (3S,4R)-(560). N-C4 ring closure of the major tosylate (559(ii))

Figure 14: (a) ^{1}H NMR spectrum of diastereomeric mixture of acetates (558)
(b) ^{1}H NMR spectrum of one pair of enantiomers (558(I))



afforded the β-lactam (560(ii)), which exhibited a C3-H/C4-H coupling constant of 2.2 Hz, demonstrating the trans stereochemistry of this 2-azetidinone. When the mixture of diastereomeric tosylates (559) was cyclised, β-lactam (560) was obtained, in 94% yield.



(559) **(560)**

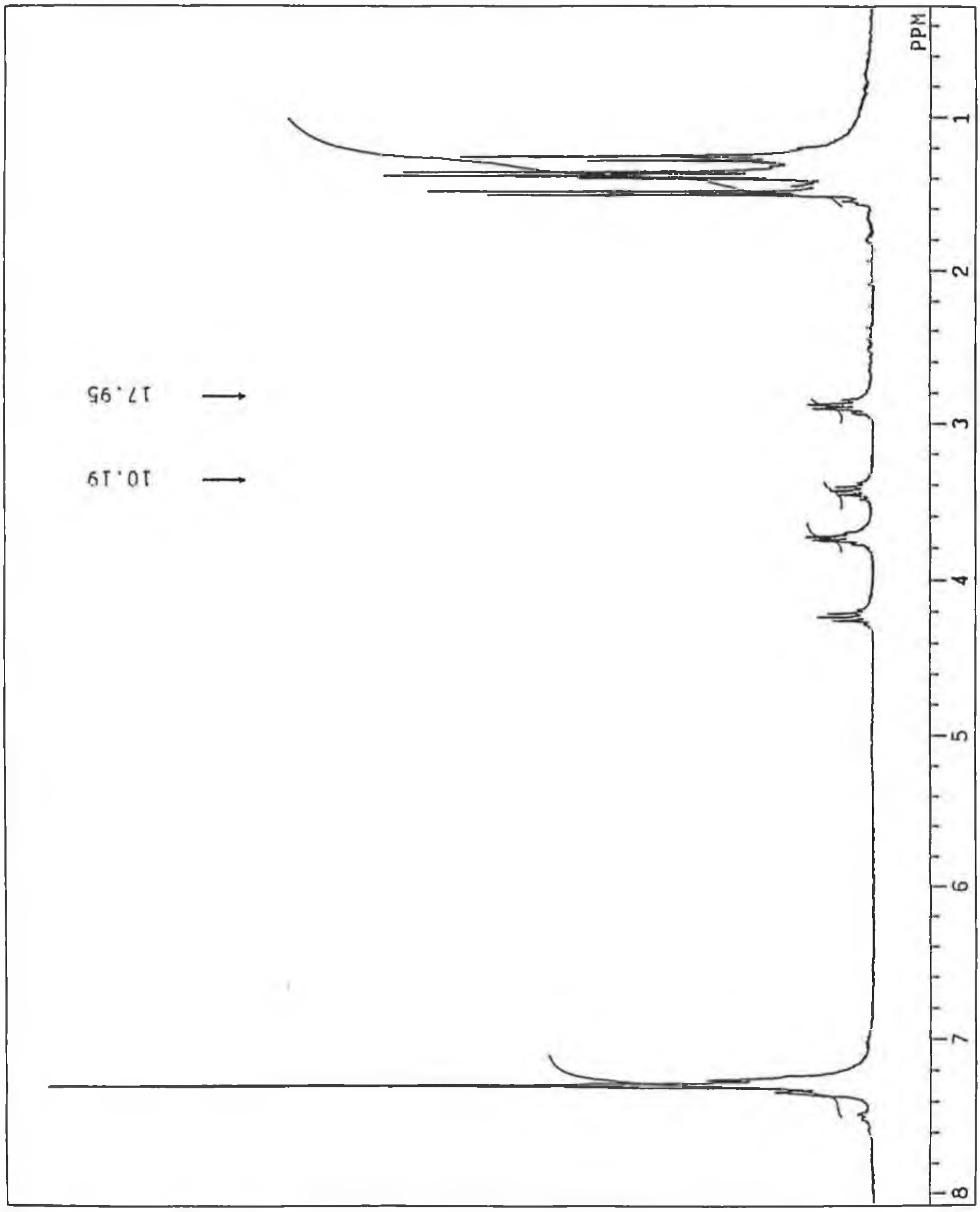
The crude material (560) contained the trans- and cis-isomers in a ratio of 1.8 : 1, as evidenced by its ^{1}H NMR spectrum (Figure 15).

It had now been established that the trans-β-lactams (3R,4R)-(560) and (3S,4S)-(560) were the predominant products of the synthetic sequence. Was this the expected result had the initial reduction occurred selectively in the manner predicted by Cram's rule?

Remembering that N-C4 cyclisation of tosylates occurs with complete inversion of configuration at C3 of the substrate[95], the trans-isomers (3R,4R)-(560) and (3S,4S)-(560) are necessarily derived from the alcohols (2R,3S)-(554) and (2S,3R)-(555), respectively (Scheme 23). However, according to Cram's rule, the alcohols (2R,3R)-(553) and (2S,3S)-(556) should have been formed preferentially in the reaction of the acetoacetanilide (439b) with $NaBH_4$. Likewise, the cis-β-lactams (3R,4S)-(560) and (3S,4R)-(560) originate from the alcohols (2R,3R)-(553) and (2S,3S)-(556), respectively (Scheme 24). Theoretically, their epimers (2R,3S)-(554) and (2S,3R)-(555) should have been the minor products of the reduction. Obviously, a simple Cram-type mechanism was not operative in the sodium borohydride reduction of N-(4-chlorophenyl)-2-methyl-3-oxobutanamide (439b).

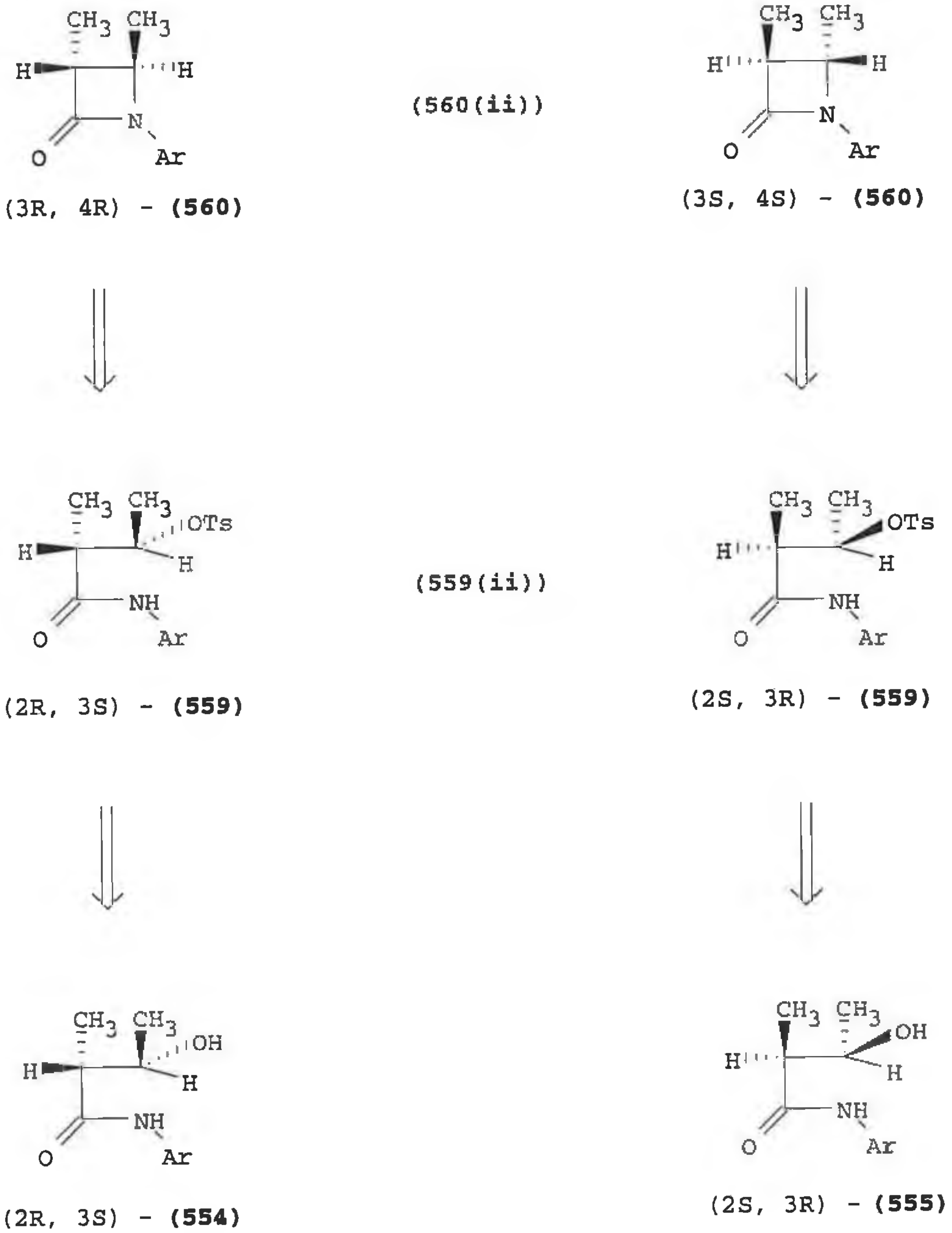
The "open-chain" Cram model (A) is useful for predicting the steric direction of 1,2-asymmetric induction in reactions of carbonyl compounds having an adjacent chiral carbon atom only when the α-carbon carries no polar substituent or group capable of complexing with the reagent involved in creating the new asymmetric centre. When the chiral carbon in the starting material bears a group such as OH or NH_2, which can chelate the cationic part of the reagent, the conformation of the carbonyl compound in the transition state is no longer determined solely by steric factors, and the "cyclic" or "chelate Cram" model (B)[164,212] must be applied to predict the stereochemical outcome of the reaction. In these instances, the predominant product is that formed by approach of the incoming group from the least-hindered side of the intermediate chelate ring.

Figure 15: ^{1}H NMR spectrum of mixture of trans- and cis-β-lactams (560)



Scheme 23

Ar = 4-Cl-C_6H_4



(3R, 4R) - **(560)**

(560(ii))

(3S, 4S) - **(560)**

(2R, 3S) - **(559)**

(559(ii))

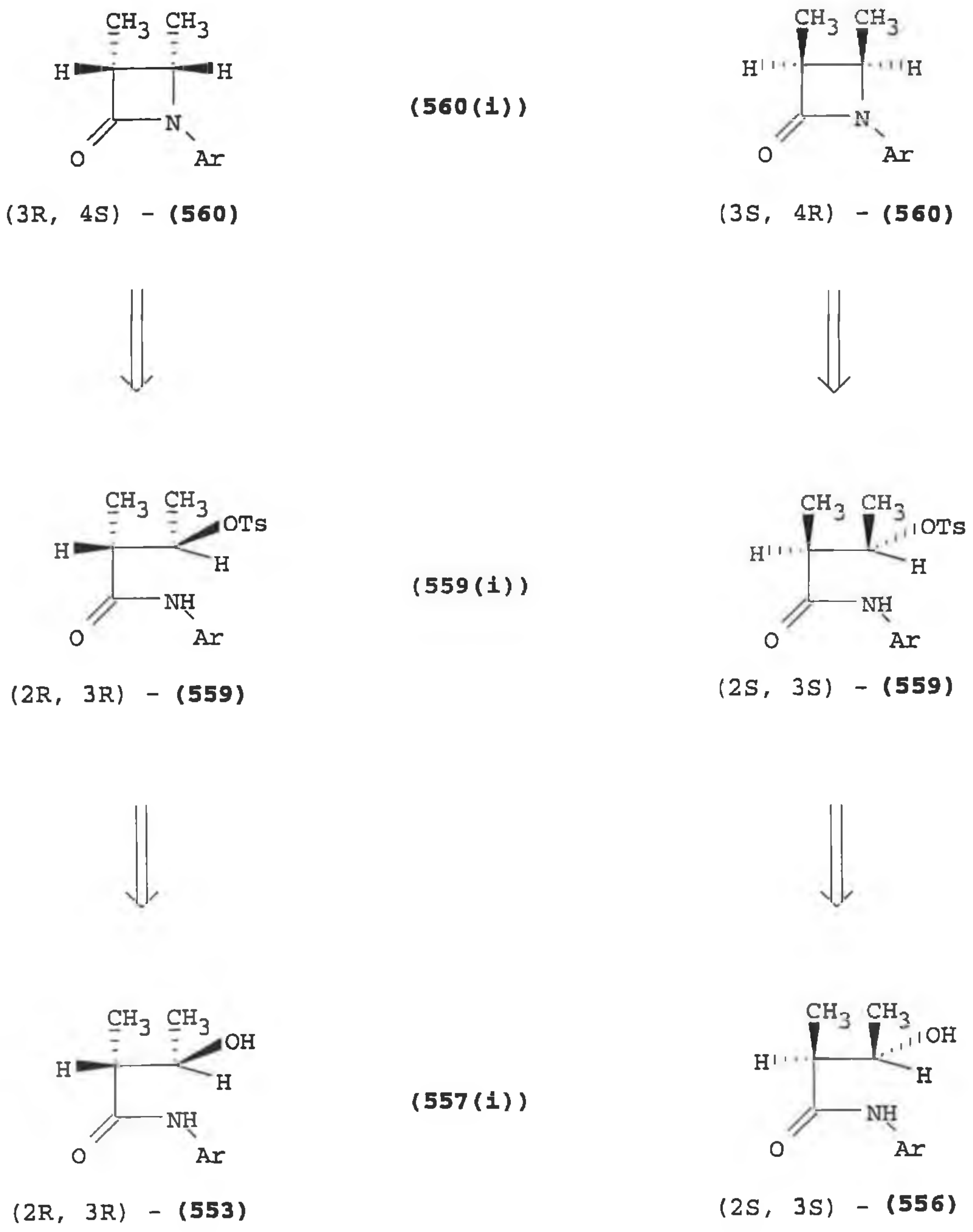
(2S, 3R) - **(559)**

(2R, 3S) - **(554)**

(2S, 3R) - **(555)**

Scheme 24

Ar = 4-Cl-C_6H_4


(3R, 4S) - **(560)**

(560(i))

(3S, 4R) - **(560)**

(2R, 3R) - **(559)**

(559(i))

(2S, 3S) - **(559)**

(2R, 3R) - **(553)**

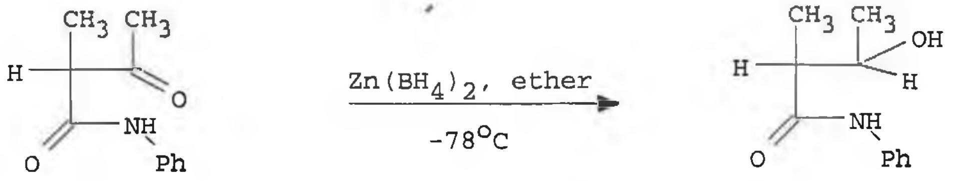
(557(i))

(2S, 3S) - **(556)**

If the polar group attached to the original asymmetric centre is also the medium-sized substituent, models (A) and (B) predict the same result. However, if the co-ordinating moiety corresponds to the smallest or largest substituent, in terms of effective bulk, then the "open-chain" model (A) and the "chelate Cram" model (B) predict opposite stereoselectivities.

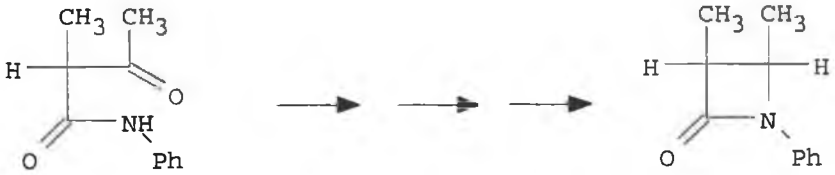
In the case of the acetoacetanilide (439b), the largest substituent at C2, the amide group, is capable of serving as a ligand. It is proposed therefore, that, in the reaction with $NaBH_4$, the amide and ketone carbonyls initially chelate the sodium cation, forming the complex (561). Attack by the hydride anion then occurs preferentially from the side of the 6-membered chelate bearing the smallest group, the proton (Scheme 25). Thus, the alcohols (2R,3S)-(554) and (2S,3R)-(555) are the major products of the reduction, with (2R,3R)-(553) and (2S,3S)-(556) being formed in lesser amounts.

It should be noted that N-phenyl-2-methyl-3-oxobutanamide (439a) has been reduced, using zinc borohydride in ether at –78°C, to the corresponding alcohol (562) with excellent stereoselectivity, in quantitative yield[213].



(439a) **(562)**

The product ratio, determined by ^1H NMR after acetylation, showed that the (2R,3S)- and (2S,3R)-isomers had been formed in 96%d.e.. Also, Sakaki and Kaneko[210] have reported synthesis of the cis- and trans-isomers of N-phenyl-3,4-dimethyl-2-azetidinone (563) from the acetoacetanilide (439a) by $NaBH_4$ reduction, followed by mesylation, and finally cyclisation using Wasserman's procedure[43].



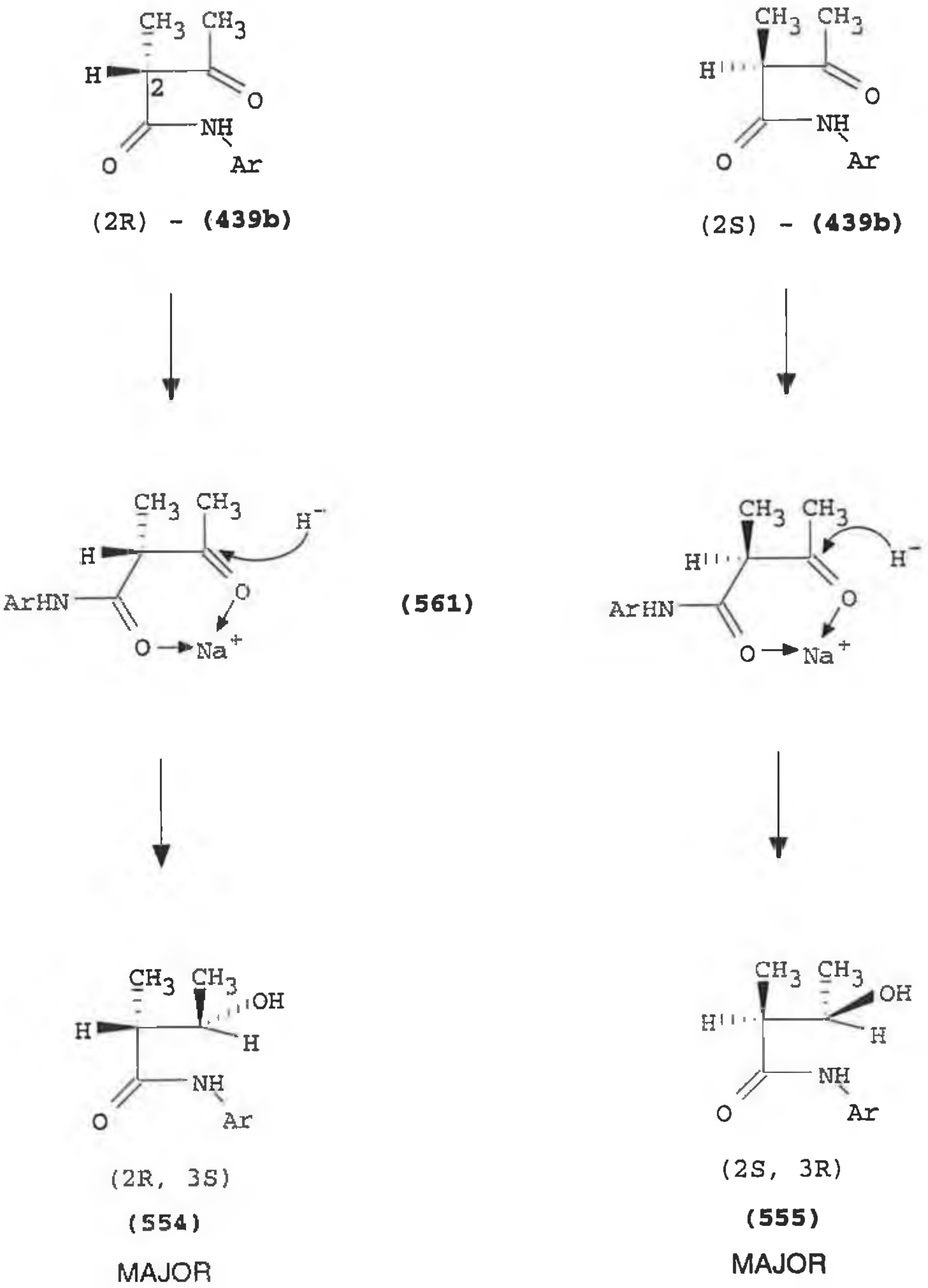
(439a) **(563)**

A 1.6 : 1 mixture of trans:cis β-lactams (563) was obtained, but the authors offer no explanation to account for the selectivity observed.

The reactions yielding the acetoacetanilide-derived model compounds are summarised in Scheme 26.

Scheme 25

Ar = 4-Cl-C_6H_4



(2R) - **(439b)**

(2S) - **(439b)**

(561)

(2R, 3S)

(554)

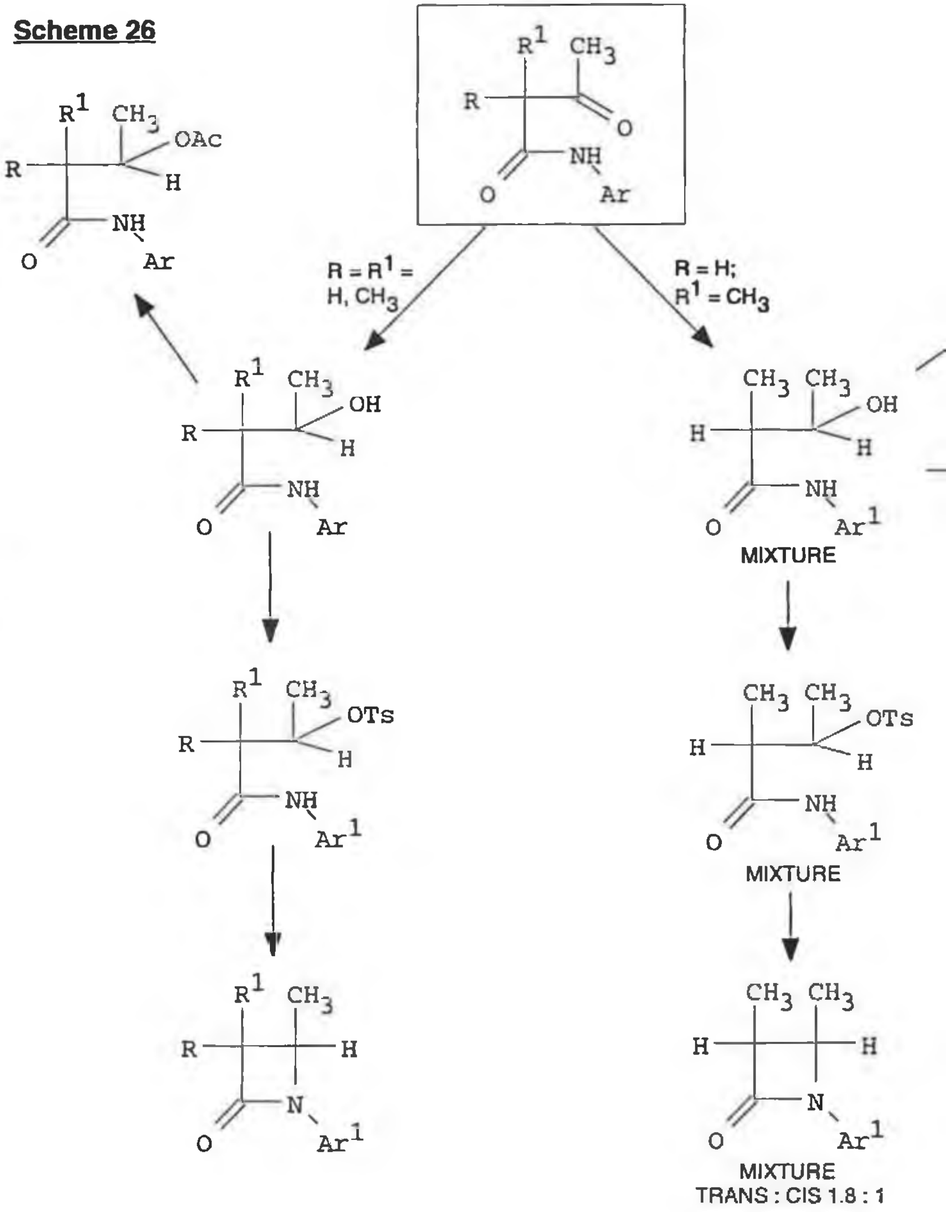
MAJOR

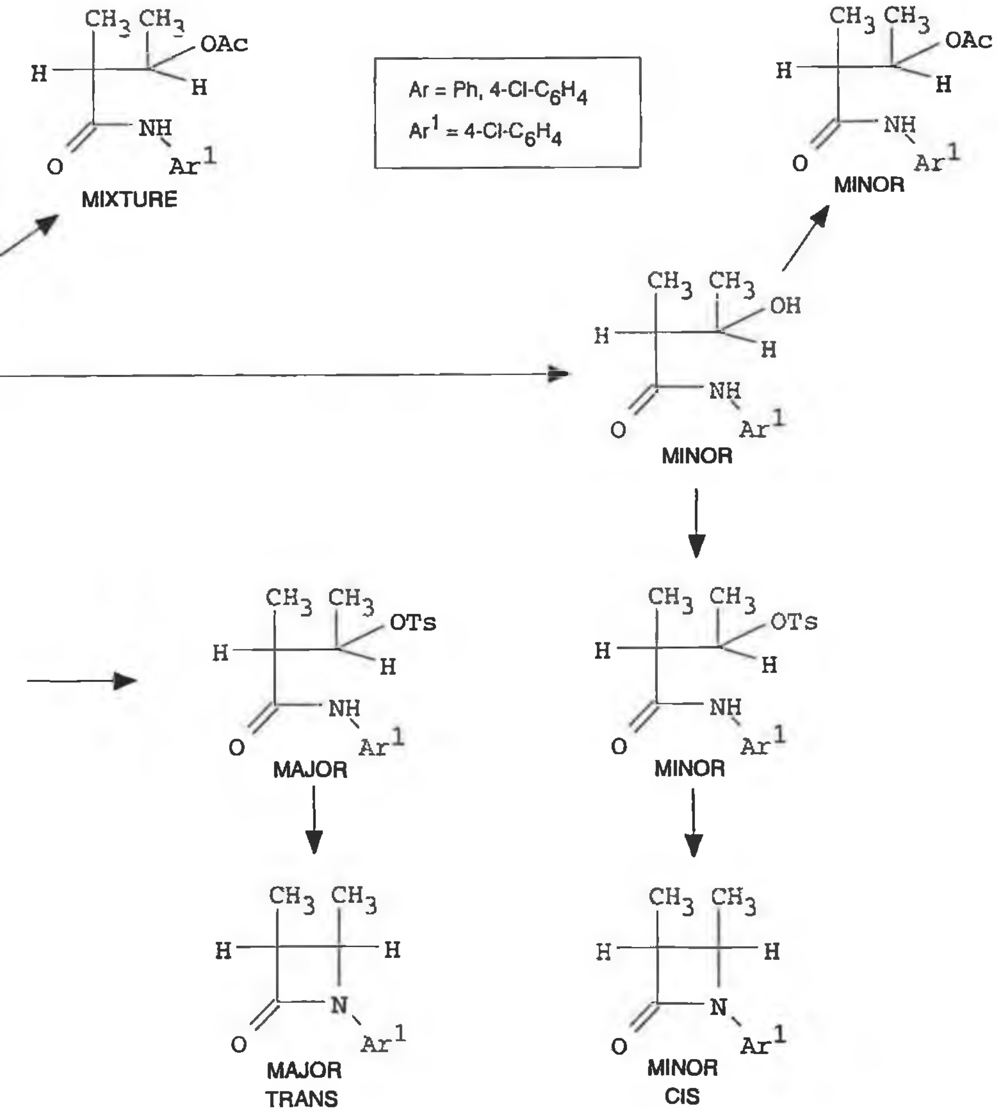
(2S, 3R)

(555)

MAJOR

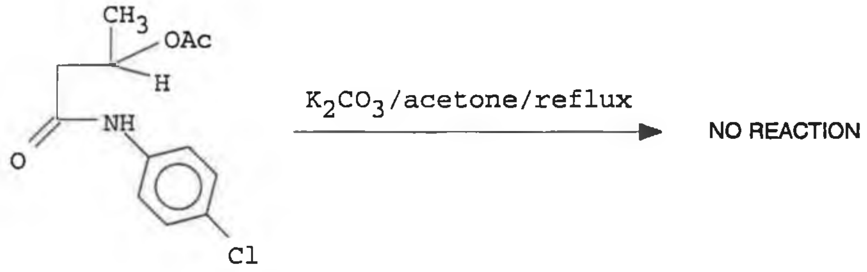
Scheme 26





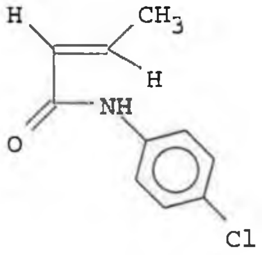
Ar = Ph, 4-Cl-C_6H_4
Ar^1 = 4-Cl-C_6H_4
MIXTURE
MINOR
MINOR
MAJOR
MINOR
MAJOR TRANS
MINOR CIS

N-C4 cyclisation of N-(4-chlorophenyl)-3-acetoxybutanamide (544b) was attempted using the method which had been successful for lactamisation of the model tosylates. However, after refluxing with K_2CO_3 in acetone for 2.5 hours, TLC analysis indicated that no reaction had occurred, and the starting acetate (544b) was recovered unchanged.



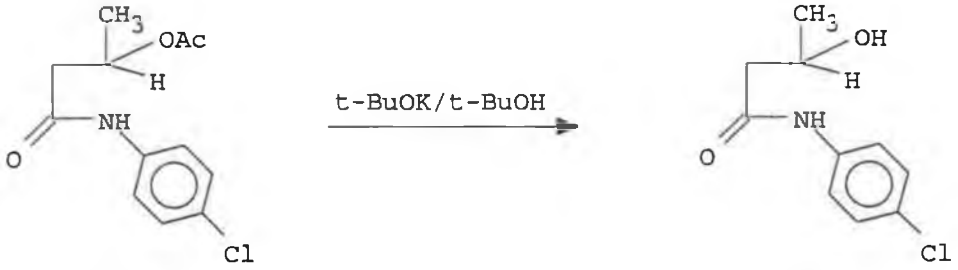
(544b)

Reaction of the model acetate (544b) with the more powerful base, sodium hydride, was then examined. Treatment of (544b) with 1.5 equivalents of NaH in refluxing THF gave a mixture comprising two major products, neither of which was the corresponding β-lactam (551). The less polar component was isolated and identified by its physical and spectral properties as trans-N-(4-chlorophenyl)but-2-enamide (564), identical in all respects to material prepared independently from trans-crotonic acid.



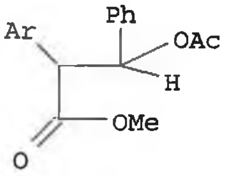
(564)

When the acetate (544b) was reacted with an excess of potassium t-butoxide in t-butanol at room temperature, cleavage of the acetate group occurred, furnishing N-(4-chlorophenyl)-3-hydroxybutanamide (541b) in 81% yield.



(544b) **(541b)**

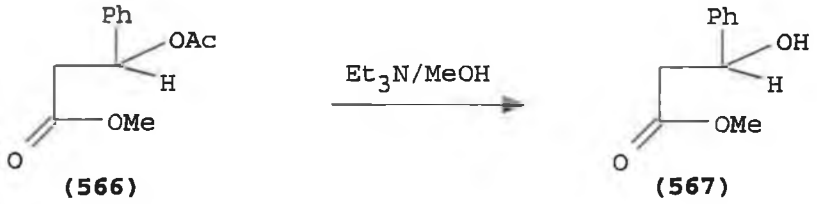
Neither the β-lactam (551) nor the acrylamide (564) were detected in the crude reaction mixture. Indeed, Garay and Cabaleiro[214] have reported that in the dehydroacetoxylation of methyl 3-acetoxy-2-aryl-3-phenylpropanoates (565) with methanolic sodium methoxide, the elimination was accompanied by saponification of the acetate.



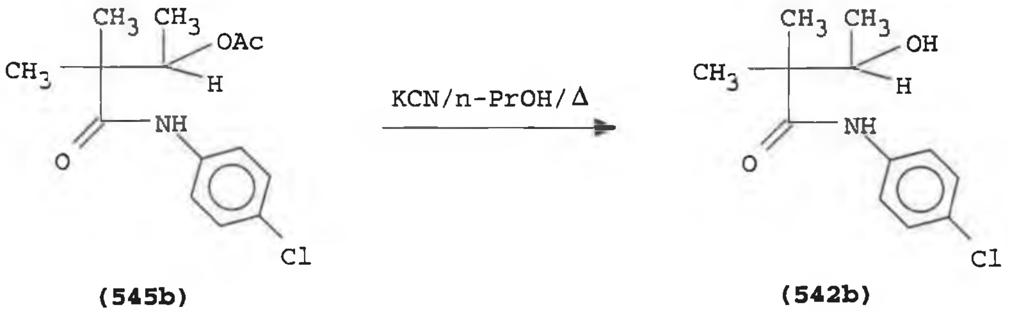
(565)

Ar = 4-CH_3O-C_6H_4, Ph, 4-NO_2-C_6H_4, 3-Cl-C_6H_4

Also, these authors found that reaction of methyl 3-acetoxy-3-phenylpropanoate (566) with triethylamine in methanol led exclusively to loss of the acetyl group, with formation of methyl 3-hydroxy-3-phenylpropanoate (567)[215].



Treatment of N-(4-chlorophenyl)-2,2-dimethyl-3-acetoxybutanamide (545b) with potassium cyanide in refluxing n-propanol afforded only the parent alcohol (542b).



Potassium cyanide is known to be an effective transesterification catalyst[216].

Although no direct method for effecting N-C4 cyclisation of acetates of the type (517) was identified, procedures for regenerating the parent alcohols, which can be readily transformed to the corresponding β-lactams, were found. If similar treatment of the azoacetates (518) also resulted in cleavage of the acetate group, then a potential route to the target 4-azo-β-lactams was available.

3.1.3 Experimental

Common reagent grade chemicals were purchased from Aldrich Chemical Company, and used without further purification. Where necessary, solvents were dried using standard procedures. Sodium hydride (80% in mineral oil) was washed with dry petroleum ether (40-60^{o}), under suction, before use.

Melting points were determined in open capillary tubes with a Gallenkamp melting point apparatus, and are uncorrected. IR spectra were recorded for KBr discs, nujol mulls or neat oils with a Perkin-Elmer 983-G spectrometer. ^{1}H and ^{13}C NMR spectra were measured for solutions in $CDCl_3$, DMSO-d_6 or 10% DMSO-d_6 in $CDCl_3$ with Perkin-Elmer R12B 60 MHz and JEOL GX-FT 270 MHz spectrometers, and referenced to tetramethylsilane or residual solvent H. Elemental analyses were performed in the Microanalytical Laboratory, University College Dublin.

(i) Synthesis of N-phenyl-3-hydroxybutanamide (541a)

To a solution of 35.44g (200 mmoles) acetoacetanilide (404a) in 200mls ethanol was added 2.44g (64 mmoles) $NaBH_4$, in portions, with cooling. After stirring at room temperature for 3 hours, 100mls dilute HCl was added slowly, to give a solution. On removal of the ethanol under reduced pressure, a white suspension was obtained. Diethyl ether was added to dissolve the product. A second ether extract was prepared. The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent gave the alcohol (541a) as white crystals (28.07g; 78%). Recrystallisation from $CHCl_3$ afforded an analytical sample. MP 107-108°C (lit.[113] 109°C). IR (nujol mull) 3280, 1673, 1661 cm^{-1}. ^1H NMR (270 MHz; DMSO-d_6) δ 1.14 (d, 3H, J = 6.2 Hz), 2.39 (m, 2H), 4.10 (m, 1H), 4.76 (s, 1H), 7.31 (m, 5H), 9.87 (s, 1H).

(ii) Synthesis of N-(4-chlorophenyl)-3-hydroxybutanamide (541b)

p-Chloroacetoacetanilide (404b) was reduced according to the procedure outlined in (i), but using THF instead of ethanol as solvent. The alcohol (541b) was obtained in 71% yield, and was recrystallised from benzene. MP 121-122°C. IR (nujol mull) 3278, 1671, 1655 cm^{-1}. ^1H NMR (60 MHz; $CDCl_3$: DMSO-d_6 9:1) δ 1.20 (d, 3H), 2.40 (d, 2H), 4.15 (m, 2H), 7.25 (d, 2H), 7.60 (d, 2H), 9.70 (bs, 1H).

(iii) Synthesis of N-phenyl-2,2-dimethyl-3-hydroxybutanamide (542a)

α,α-Dimethylacetoacetanilide (435a) was reduced with $NaBH_4$ in THF as described in (ii). Quenching with water and evaporation of the THF led to separation of the product as an oil, which solidified on standing. The alcohol (542a) was obtained as a white solid (82%). MP 92-93°C. IR (KBr) 3390, 3268, 1649 cm^{-1}. ^1H NMR (60 MHz; DMSO-d_6) δ 0.95 (m, 9H), 3.65 (m, 1H), 5.10 (bs, 1H), 7.15 (m, 5H), 9.10 (bs, 1H).

(iv) Synthesis of N-(4-chlorophenyl)-2,2-dimethyl-3-hydroxybutanamide (542b)

Reduction of the acetoacetanilide (435b) with $NaBH_4$/THF as outlined in (iii) gave the 3-hydroxybutyranilide (542b) in 94% yield. Recrystallisation from aqueous ethanol afforded white crystals. MP 104-105°C. IR (KBr) 3381, 3254, 1647 cm^{-1}. ^1H NMR (270 MHz; $CDCl_3$) δ 1.17 (s, 3H), 1.22 (d, 3H, J = 6.2 Hz), 1.31 (s, 3H), 3.16 (d, 1H, J = 4.0 Hz), 3.82 (m, 1H), 7.24 (d, 2H, J = 8.8 Hz), 7.45 (d, 2H, J = 8.8 Hz), 8.80 (s, 1H). ^{13}C NMR (67.5 MHz; $CDCl_3$) 18.6, 21.3, 24.4, 46.9, 73.6, 121.2, 121.6, 128.7, 136.6, 175.4 ppm.

(v) Preparation of N-phenyl-3-acetoxybutanamide (544a)

30mls (33.12g; 422 mmoles; 5.3 equivalents) acetyl chloride was added slowly to 14.34g (80 mmoles) alcohol (541a) with good stirring. After approximately 5 minutes, a clear solution formed. Stirring was continued for a further 15 minutes. Removal of excess AcCl under reduced pressure gave an oil. This was dissolved in a small volume of AcOH and added dropwise to 60mls water, with vigorous stirring. The acetate (544a) precipitated as a white solid (17.00g; 96%). MP 97-98^{o}C. IR (nujol mull) 3252, 1721, 1657 cm^{-1}. ^{1}H NMR (270 MHz; $CDCl_3$) δ 1.31 (d, 3H, J = 6.6 Hz), 1.99 (s, 3H), 2.51 (dd, 1H, J = 5.1, 14.7 Hz), 2.64 (dd, 1H, J = 6.6, 14.7 Hz), 5.28 (m, 1H), 7.02 - 7.47 (m, 5H), 7.82 (bs, 1H). ^{13}C NMR (67.5 MHz; $CDCl_3$) 20.1, 21.4, 44.3, 68.4, 120.1, 124.6, 129.1, 137.9, 168.0, 170.7 ppm.

(vi) Preparation of N-(4-chlorophenyl)-3-acetoxybutanamide (544b)

The alcohol (541b) was acetylated using the procedure outlined in (v). The acetate (544b) was obtained as an oil, which crystallised on standing (94%). Recrystallisation from benzene/petroleum ether (40-60^{o}) provided an analytical sample. MP 85-86^{o}C. IR (nujol mull) 3336, 1718, 1686 cm^{-1}. ^{1}H NMR (270 MHz; $CDCl_3$) δ 1.36 (d, 3H, J = 6.4 Hz), 2.05 (s, 3H), 2.56 (dd, 1H, J = 5.5, 14.7 Hz), 2.68 (dd, 1H, J = 7.0, 14.7 Hz), 5.31 (m, 1H), 7.27 (d, 2H, J = 8.8 Hz), 7.46 (d, 2H, J = 8.8 Hz), 7.83 (s, 1H). ^{13}C NMR (67.5 MHz; $CDCl_3$) 20.1, 21.3, 44.2, 68.2, 121.2, 129.0, 129.4, 136.3, 167.9, 170.7 ppm.

(vii) Preparation of N-phenyl-2,2-dimethyl-3-acetoxybutanamide (545a)

Acetylation of the alcohol (542a) as described in (v) gave the acetate (545a) as an oil. On standing, a white solid formed (91%). MP 48-50^{o}C. IR (KBr) 3385, 1720, 1665 cm^{-1}. ^{1}H NMR (60 MHz; $CDCl_3$) δ 1.25 (m, 9H), 2.10 (s, 3H), 5.10 (q, 1H), 7.30 (m, 5H), 7.70 (bs, 1H).

(viii) Preparation of N-(4-chlorophenyl)-2,2-dimethyl-3-acetoxybutanamide (545b)

The procedure given in (v) was used to acetylate alcohol (542b) except, here, a longer reaction time was required (30 minutes). Again, the acetate was obtained as an oil. IR (neat) 3357, 1731, 1662 cm^{-1}. The oil solidified on standing (92% yield) and was recrystallised from aqueous ethanol. MP 93-95^{o}C. ^{1}H NMR (60 MHz; DMSO-d_6) δ 0.95 (m, 9H), 1.80 (s, 3H), 5.05 (q, 1H), 7.15 (d, 2H), 7.50 (d, 2H), 9.15 (bs, 1H).

(ix) Synthesis of N-(4-chlorophenyl)-3-tosyloxybutanamide (549)

0.54g (2.5 mmoles) alcohol (541b) was dissolved in 5mls dry pyridine and cooled to <5^{o}C. 1.24g (6.5 mmoles; 260 mole%) p-toluenesulfonyl chloride was added in portions. After 48 hours at <10°C, the mixture was poured into 30g ice/water with good agitation. The white solid that precipitated was filtered, washed successively with dilute HCl and water, and dried at the pump. 0.71g of tosylate (549) was obtained (77%). Recrystallisation from aqueous ethanol gave white crystals. MP 120-124°C (dec.). IR (nujol mull) 3349, 1681 cm^{-1}. ^1H NMR (270 MHz; $CDCl_3$) δ 1.42 (d, 3H, J = 8.1 Hz), 2.40 (s, 3H), 2.69 (m, 2H), 5.06 (m, 1H), 7.23 - 7.76 (m, 9H).

(x) <u>Synthesis of N-(4-chlorophenyl)-2,2-dimethyl-3-tosyloxybutanamide (550)</u>

Tosylate (550) was prepared in 80% yield from the alcohol (542b) using the method described in (ix). MP 111-113°C. IR (KBr) 3424, 1673 cm^{-1}. ^1H NMR (60 MHz; DMSO-d_6) δ 1.10 (m, 9H), 2.20 (s, 3H), 4.95 (m, 1H), 7.35 (m, 8H), 9.20 (bs, 1H).

(xi) <u>Preparation of N-(4-chlorophenyl)-4-methyl-2-azetidinone (551)</u>

To a refluxing mixture of 3.00g (22 mmoles; 22 equivalents) anhydrous K_2CO_3 in 20mls acetone was added a solution of 0.370g (1 mmole) tosylate (549) in 2mls acetone. After refluxing for 3.5 hours, TLC (100% ethyl acetate) indicated complete reaction and the formation of a single product. The mixture was cooled and filtered through a bed of Celite. The solids were washed with 20mls ethyl acetate. The acetone filtrate and ethyl acetate wash were combined and concentrated *in vacuo*. The residue was rediluted with 20mls ethyl acetate. After washing sequentially with 5ml-portions of 1M HCl, saturated $NaHCO_3$ solution and brine, the organic phase was dried over $MgSO_4$. Evaporation of the solvent gave an oil which solidified on standing. The β-lactam (551) was obtained as a white solid (0.155g; 79%). MP 71-73°C. IR (neat oil) 1746 cm^{-1}. ^1H NMR (270 MHz; $CDCl_3$) δ 1.50 (d, 3H, J = 6.6 Hz), 2.69 (dd, 1H, J = 2.6, 15.0 Hz), 3.26 (dd, 1H, J = 5.5, 15.0 Hz), 4.15 (m, 1H), 7.30 (s, 4H).

(xii) <u>Preparation of N-(4-chlorophenyl)-3,3,4-trimethyl-2-azetidinone (552)</u>

A solution of 1.98g (5 mmoles) tosylate (550) in 15mls acetone was added to a refluxing mixture of 2.07g (15 mmoles; 300 mole%) anhydrous K_2CO_3 in 90mls acetone, and reflux was continued for 6 hours. On cooling, the mixture was filtered through Celite. The solids were washed with 100mls ethyl acetate. The combined filtrates were evaporated to give β-lactam (552) as a white solid (0.81g; 72%). Recrystallisation from aqueous ethanol afforded an analytical sample. MP 81.5-82°C. IR (KBr) 1743 cm^{-1}. ^1H NMR (60 MHz; $CDCl_3$) δ 1.25 (m, 9H), 3.75 (q, 1H), 7.20 (s, 4H). $C_{12}H_{14}NOCl$ requires C, 64.43; H, 6.31; N, 6.26%. Found C, 64.47; H, 6.29; N, 6.18%.

(xiii) Synthesis of N-(4-chlorophenyl)-2-methyl-3-hydroxybutanamide

(a) As a mixture of diastereomers (557)

0.35g (9.3 mmoles) $NaBH_4$ was added in portions to a solution of 6.77g (30 mmoles) of the acetoacetanilide (439b) in 120mls THF, with cooling. After stirring at room temperature for 45 minutes, 30mls of 3M HCl was added to give a solution. The THF was evaporated under reduced pressure, and the product, which had separated as an oil, was extracted into ethyl acetate. The organic layer was dried over $MgSO_4$. Removal of the solvent gave the alcohol (557) as an oil. On standing overnight, a white solid formed (6.27g; 92%). ^1H NMR (270 MHz; DMSO-d_6) δ 1.06 (m, 6H), 2.36 (m, 1H), 3.73 (m, 1H), 4.72 (m, 1H), 7.32 (m, 2H), 7.64 (m, 2H), 9.91 (2 x s, 1H).

(b) As a single pair of enantiomers (557(i))

The acetoacetanilide (439b) was reduced as described in (a). The crude product obtained was recrystallised several times from ethyl acetate to provide a single pair of enantiomers (557(i)) as white crystals (1.26g; 18%). MP 171-172^{o}C. IR (KBr) 3315, 1664 cm^{-1}. ^1H NMR (270 MHz; DMSO-d_6) δ 1.00 (d, 3H, J = 7.3 Hz), 1.08 (d, 3H, J = 5.9 Hz), 2.38 (m, 1H), 3.77 (m, 1H), 4.75 (d, 1H, J = 5.1 Hz), 7.32 (d, 2H, J = 8.8 Hz), 7.65 (d, 2H, J = 8.8 Hz), 9.93 (s, 1H).

(xiv) Preparation of N-(4-chlorophenyl)-2-methyl-3-acetoxybutanamide

(a) As a diastereomeric mixture (558)

2.1mls (2.32g; 30 mmoles; 600 mole%) acetyl chloride was added to 1.14g (5 mmoles) of crude alcohol (557) with stirring. The solution which resulted was stirred at room temperature for 18 hours. Excess AcCl was evaporated. The residue was dissolved in 2mls AcOH and added dropwise to 20mls H_2O with good agitation. The acetate (558) precipitated as a white solid (1.24g; 92%). ^1H NMR (270 MHz; DMSO-d_6) (note: peaks for minor isomers denoted by *) δ 1.14 (m), 1.89* (s), 2.01 (s), 2.63 (m), 4.96 (m), 7.35 (m), 7.61 (m), 10.10* (s), 10.13 (s). The ratio of major : minor isomers was calculated by integration and found to be 1.8 : 1.

(b) As a single enantiomeric pair (558(i))

The alcohol (557(i)) was acetylated in a similar manner and gave the acetate (558(i)) in 69% yield. MP 105-106^{o}C. IR (KBr) 3253, 1734, 1657 cm^{-1}. ^1H NMR (270 MHz; DMSO-d_6) δ 1.09 (d, 3H, J = 7.0 Hz), 1.19 (d, 3H, J = 6.2 Hz), 1.89 (s, 3H), 2.66 (m, 1H), 4.95 (m, 1H), 7.34 (d, 2H, J = 8.8 Hz), 7.61 (d, 2H, J = 9.2 Hz), 10.09 (s, 1H).

(xv) Preparation of N-(4-chlorophenyl)-2-methyl-3-tosyloxybutanamide

(a) The minor enantiomers (559(i))

The minor alcohol (557(i)) was reacted with p-toluenesulfonyl chloride using the procedure outlined in (ix). The tosylate (559(i)) was obtained as a white solid in 84% yield. MP 110-111^{o}C. IR (KBr) 3362, 1689 cm^{-1}. ^{1}H NMR (270 MHz; DMSO-d$_6$) δ 1.02 (d, 3H, J = 7.3 Hz), 1.34 (d, 3H, J = 6.6 Hz), 2.30 (s, 3H), 2.67 (m, 1H), 4.79 (m, 1H), 7.20 (d, 2H, J = 8.1 Hz), 7.31 (d, 2H, J = 8.8 Hz), 7.44 (d, 2H, J = 8.8 Hz), 7.60 (d, 2H, J = 8.1 Hz), 10.04 (s, 1H).

(b) As a mixture of diastereomers (559)

The crude alcohol (557) was tosylated as described in (ix). The tosylate (559) was isolated in 62% yield. TLC (90:10 CHCl$_3$: petroleum ether (40-60^{o})) showed that the product contained 2 components. The Rf of the more polar constituent of the mixture matched that of the minor tosylate isomers (559(i)).

(c) The major enantiomers (559(ii))

Some of the crude tosylate (559) was chromatographed on a silica gel column, eluting with 90:10 CHCl$_3$: petroleum ether (40-60^{o}), to provide a sample of the less polar major tosylate enantiomers (559(ii)). MP 138-140^{o}C. IR (KBr) 3373, 1691 cm^{-1}. ^{1}H NMR (270 MHz; DMSO-d$_6$) δ 0.98 (d, 3H, J = 7.3 Hz), 1.22 (d, 3H, J = 6.6 Hz), 2.35 (s, 3H), 2.66 (m, 1H), 4.66 (m, 1H), 7.33 (d, 2H, J = 8.8 Hz), 7.40 (d, 2H, J = 8.1 Hz), 7.53 (d, 2H, J = 8.8 Hz), 7.77 (d, 2H, J = 8.1 Hz), 10.13 (s, 1H).

(xvi) Synthesis of N-(4-chlorophenyl)-3,4-dimethyl-2-azetidinone

(a) The minor enantiomers (560(i))

0.38g (1 mmole) of tosylate (559(i)) was lactamised using the method outlined in (xii), except here, a reflux time of 9 hours was necessary for complete reaction. The β-lactam (560(i)), comprising the minor enantiomers, was isolated as a white solid (0.17g; 81%). MP 76-78^{o}C. IR (KBr) 1729 cm^{-1}. ^{1}H NMR (270 MHz; CDCl$_3$) δ 1.27 (d, 3H, J = 7.3 Hz), 1.40 (d, 3H, J = 6.6 Hz), 3.44 (dq, 1H, J = 5.9, 7.3 Hz), 4.24 (dq, 1H, J = 5.9, 6.6 Hz), 7.28 (d, 2H, J = 8.8 Hz), 7.33 (d, 2H, J = 8.8 Hz). ^{13}C NMR (67.5 MHz; DMSO-d$_6$) 8.7, 13.6, 46.7, 50.8, 118.5, 127.3, 129.5, 136.7, 168.8 ppm. $C_{11}H_{12}NOCl$ requires C, 63.01; H, 5.77; N, 6.68%. Found C, 62.94; H, 5.76; N, 6.40%. The J value for the coupling of the C3- and C4-protons indicated that this minor β-lactam contained the cis-isomers (3R,4S)-(560) and (3S,4R)-(560).

(b) The major enantiomers (560(ii))

Ring closure of the tosylate (559(ii)) as described in (a) gave β-lactam (560(ii)), the major enantiomers, in 81% yield. Recrystallisation from ethanol/petroleum ether (40-60^{o}) afforded white crystals. MP 82-84^{o}C. IR (KBr) 1731 cm^{-1}. ^{1}H NMR (270 MHz; CDCl$_3$) δ 1.38 (d, 3H, J =

7.3 Hz), 1.50 (d, 3H, J = 5.9 Hz), 2.90 (dq, 1H, J = 2.2, 7.3 Hz), 3.74 (dq, 1H, J = 2.2, 5.9 Hz), 7.31 (s, 4H). $C_{11}H_{12}NOCl$ requires C, 63.01; H, 5.77; N, 6.68%. Found C, 63.24; H, 5.80; N, 6.44%. Here, $J_{3,4}$ was 2.2 Hz, implying that the trans-isomers (3R,4R)-(560) and (3S,4S)-(560) were present.

(c) As a mixture of diastereomers (560)

The crude tosylate (559) was cyclised in a similar manner, affording an oil which solidified on standing at 0°C. The β-lactam (560), a mixture of diastereomers, was obtained as a white solid, in 94% yield. ^1H NMR (270 MHz; $CDCl_3$) (note: peaks corresponding to the minor isomers denoted by *) δ 1.27* (d, J = 7.3 Hz), 1.38 (m), 1.50 (d, 3H, J = 5.9 Hz), 2.89 (dq, 1H, J = 2.2, 7.3 Hz), 3.44* (dq, J = 5.9, 7.3 Hz), 3.74 (dq, 1H, J = 2.2, 5.9 Hz), 4.24* (dq, J = 5.9, 6.6 Hz), 7.31 (m). By integrating the C3-H multiplets at 2.89 and 3.44 ppm, it was found that the crude product (560) contained the trans- and cis-isomers in a ratio of 1.8 : 1.

(xvii) Reaction of N-(4-chlorophenyl)-3-acetoxybutanamide (544b) with K_2CO_3 in refluxing acetone

0.64g (2.5 mmoles) acetate (544b) and 0.50g (3.6 mmoles; 1.45 equivalents) anhydrous K_2CO_3 were refluxed in 30mls acetone. After 2.5 hours, TLC (50:50 ethyl acetate: petroleum ether (40-60°)) showed that only starting material was present. The mixture was cooled and filtered through a bed of Celite. Removal of the solvent gave a white solid which was analytically identical to the starting material. 0.55g (86%) of the acetate (544b) was recovered.

(xviii) Reaction of N-(4-chlorophenyl)-3-acetoxybutanamide (544b) with NaH in refluxing THF

2.56g (10 mmoles) acetate (544b) and 0.35g (14.7 mmoles; 147 mole%) NaH were refluxed in 60mls dry THF for 3 hours. TLC (70:30 ethyl acetate: petroleum ether (40-60°)) indicated that no starting acetate remained, and that two major products had been formed, neither of which had an Rf matching that of the β-lactam (551). On cooling, the mixture was filtered through Celite, and the filtrate evaporated to dryness. 1.64g of a tacky yellow solid was obtained. The crude product was slurried in a small volume of acetone and filtered to give a white solid (0.43g). TLC showed that this was the least polar component of the mixture in pure form. Analysis revealed that trans-N-(4-chlorophenyl)but-2-enamide (564) had been isolated (22%). MP 172-173°C (ethanol). IR (KBr) 3283, 3253, 1667, 1634 cm^{-1}. ^1H NMR (270 MHz; DMSO-d_6) δ 1.86 (dd, 3H, J = 1.5, 7.3 Hz), 6.10 (dd, 1H, J = 1.5, 15.4 Hz), 6.81 (m, 1H), 7.35 (d, 2H, J = 9.5 Hz), 7.67 (d, 2H, J = 8.8 Hz), 10.06 (s, 1H). $C_{10}H_{10}NOCl$ requires C, 61.39; H, 5.15; N, 7.16%. Found C, 61.21; H, 5.17; N, 7.12%.

(xix) Synthesis of trans-N-(4-chlorophenyl)but-2-enamide (564)

(a) Preparation of trans-crotonoyl chloride

36mls (58.7g; 0.49 moles; 1.4 equivalents) thionyl chloride was added dropwise to a refluxing solution of 30.13g (0.35 moles) trans-crotonic acid in 30mls dry diethyl ether over a period of 2 hours. The solution was heated at reflux for a further 1 hour. The solvent and excess $SOCl_2$ were removed by distillation. trans-Crotonoyl chloride was then distilled at atmospheric pressure. The fraction of b.p. 100-120^{o}C was collected. 19.80g (54%) of a pale yellow liquid was obtained. IR (neat) 1755 cm^{-1}.

(b) Reaction with p-chloroaniline

A solution of 7.02g (55 mmoles; 110 mole%) p-chloroaniline in 150mls dry diethyl ether was added during 1 hour to 5.23g (50 mmoles) trans-crotonoyl chloride in 50mls dry diethyl ether, at reflux. After 30 minutes, the mixture was cooled and filtered. The solid obtained was washed successively with dilute HCl and water, and dried at the pump. 6.12g (63%) trans-N-(4-chlorophenyl)but-2-enamide was collected. Recrystallisation from ethanol afforded material which was analytically identical to the product isolated in (xviii) above.

(xx) Reaction of N-(4-chlorophenyl)-3-acetoxybutanamide (544b) with t-BuOK in t-BuOH

0.77g (3 mmoles) acetate (544b) and 3.37g (30 mmoles; 10 equivalents) potassium t-butoxide were stirred in 40mls t-butanol at room temperature for 1 hour. TLC (60:40 ethyl acetate: petroleum ether (40-60^{o})) showed that only the corresponding alcohol (541b) was present. The mixture was poured into 60mls of water, with stirring, to give a solution. The organic layer extracted with diethyl ether was dried over $MgSO_4$ and evaporated to dryness under reduced pressure. N-(4-Chlorophenyl)-3-hydroxybutanamide was obtained as a white solid (0.52g; 81%).

(xxi) Reaction of N-(4-chlorophenyl)-2,2-dimethyl-3-acetoxybutanamide (545b) with KCN in refluxing n-propanol

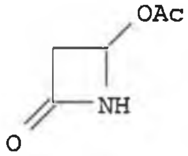
0.57g (2 mmoles) acetate (545b) and 0.20g (3 mmoles; 150 mole%) KCN were refluxed in 30mls n-propanol for 1 hour. TLC (100% CH_2Cl_2) indicated that complete conversion to the alcohol (542b) had occurred. The solvent was evaporated and the residue partitioned between dichloromethane and water. The organic layer was separated and dried over Na_2SO_4. Removal of the solvent gave N-(4-chlorophenyl)-2,2-dimethyl-3-hydroxybutanamide (542b) (0.37g; 77%).

3.2 N-C4 Cyclisation of Acetoacetanilide-Derived Azoacetates

3.2.1 Introduction

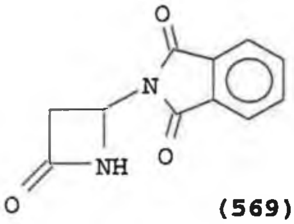
The synthesis of novel β-lactams has continued to attract widespread interest for many years. Monocyclic β-lactams with a heteroatom substituent at the 4-position are especially important, in particular as precursors of new ring systems with improved biological properties.

In the field of β-lactam chemistry, one of the most versatile synthons to date has been 4-acetoxy-2-azetidinone (568).

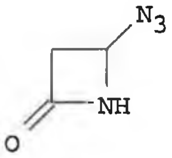


(568)

Displacement by heteronucleophiles of the acetate group in 4-acetoxy-2-azetidinone (568) affords rapid access to a range of functionalised substrates[217]. The reactions of 4-acetoxy-2-azetidinone (568) with several nitrogen nucleophiles have been examined. 4-Phthalimido-2-azetidinone (569) and 4-azido-2-azetidinone (570) have been prepared in good yields[217].

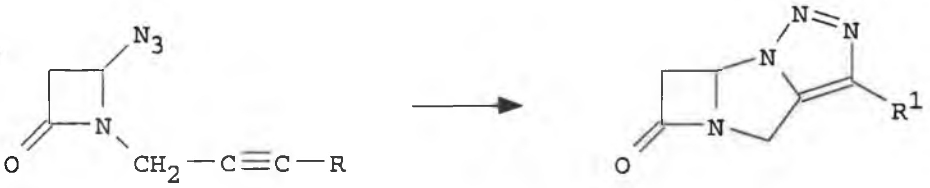


(569)



(570)

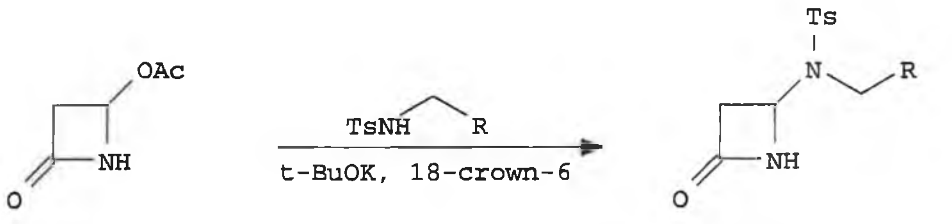
The 4-azido-2-azetidinones (571) were employed as key intermediates in the synthesis of unnatural tricyclic β-lactams (572), which proved to be antibacterially inactive, but possessed weak β-lactamase inhibitory properties[218].



(571) **(572)**

R = H, CHO, CO_2CH_3
R^1 = H, CHO, CH_2OH, CO_2CH_3

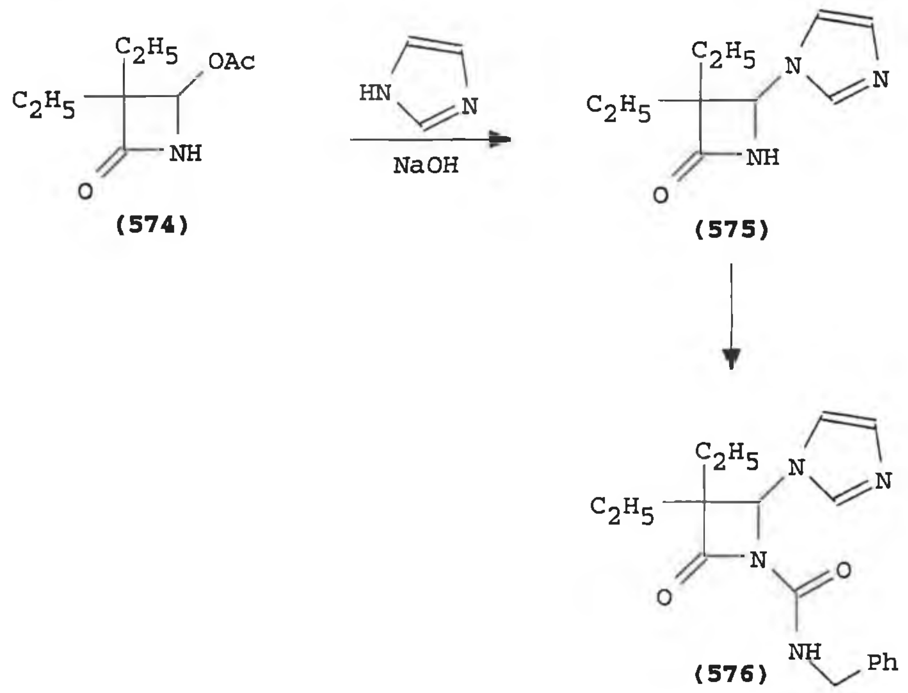
In an effort to prepare possible precursors of 1-azapenam and 1-azacepham systems, Campbell and Connarty[219] have displaced acetate from 4-acetoxy-2-azetidinone (568) using N-tosylamino nucleophiles to afford a range of substituted 4-amino-β-lactams (573).



(568) (573)

R = e.g. CO_2CH_2Ph, CN, $CH(OCH_3)_2$, $CH{=}CH_2$, $CH_2CO_2CH_2Ph$

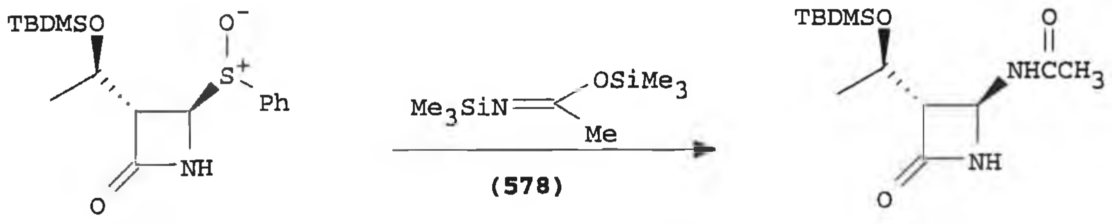
A recent report describes the reaction of 3,3-diethyl-4-acetoxy-2-azetidinone (574) with imidazole in the presence of sodium hydroxide giving 4-(1-imidazolyl)-3,3-diethyl-2-azetidinone (575) in 54% yield[220].



(574) (575) (576)

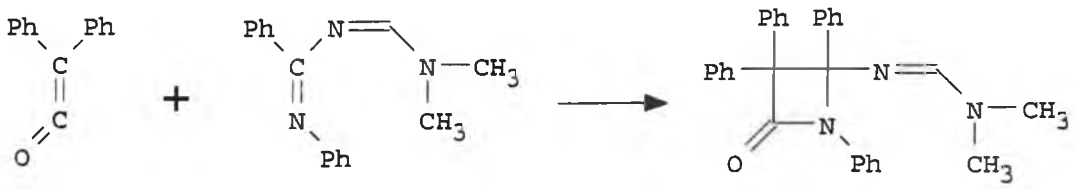
The β-lactam (575) was converted to 4-(1-imidazolyl)-1-[(benzylamino)carbonyl]-3,3-diethyl-2-azetidinone (576), which was evaluated as an orally active inhibitor of human leukocyte elastase.

Treatment of 3-(1-t-butyldimethylsiloxy)ethyl-4-phenylsulfinylazetidin-2-one (577) with the silylated aza-nucleophile (578) furnished the 4-amido-2-azetidinone (579) bearing a protected form of the α-(1-hydroxy)ethyl side chain found in thienamycin[221].



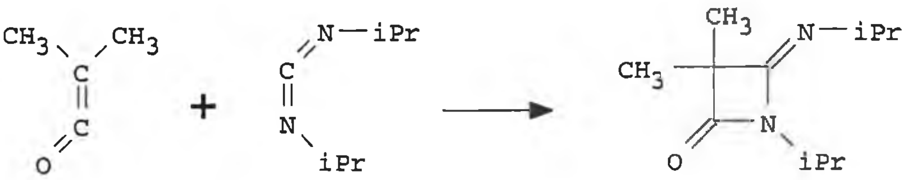
(577) (578) (579)

A variety of β-lactams with nitrogen substituents at C4 have been produced by [2+2]-cycloaddition reactions. Luthardt and Würthwein[30] have prepared the azetidin-2-one (581) in 74% yield from diphenylketene and 1,2-diphenyl-4-dimethylamino-1,3-diazabutadiene (580).



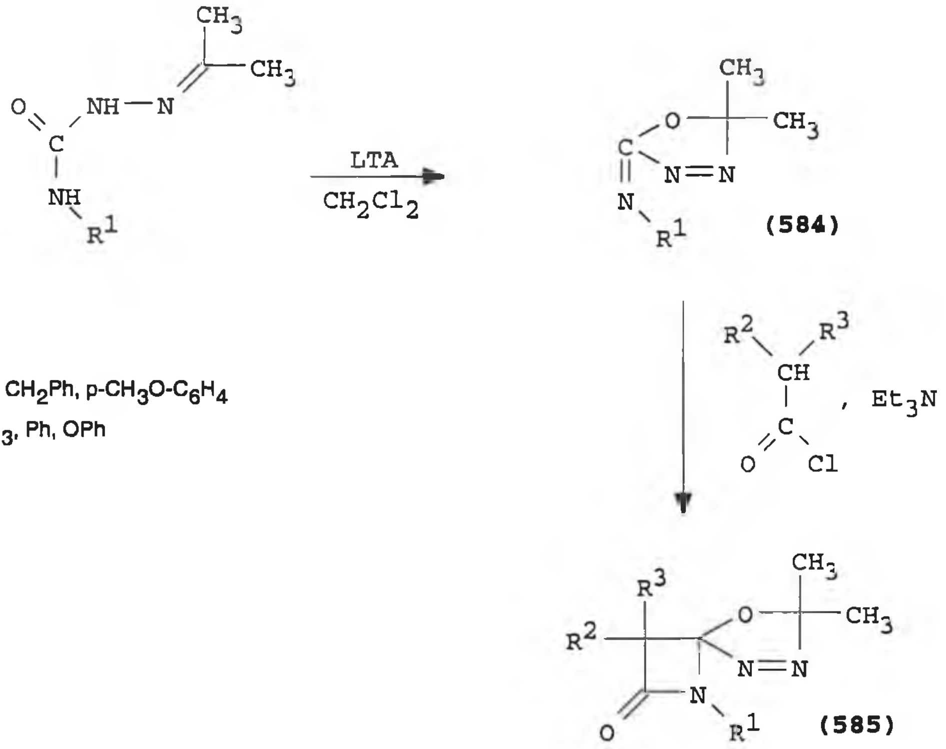
(580) **(581)**

Cycloaddition of dimethylketene with diisopropylcarbodiimide (582) has afforded the 3,3-dimethyl-4-imino-2-azetidinone (583)[222].



(582) **(583)**

Treatment of 2-imino-Δ^3-1,3,4-oxadiazolines (584), prepared by oxidative cyclisation of 4-substituted semicarbazones of acetone[223], with acid chlorides in the presence of triethylamine has recently provided nine members of the 1,7,8-triaza-5-oxa-2-oxospiro[3,4]oct-7-ene family (585)[224].

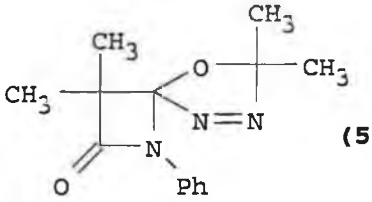


(584)

(585)

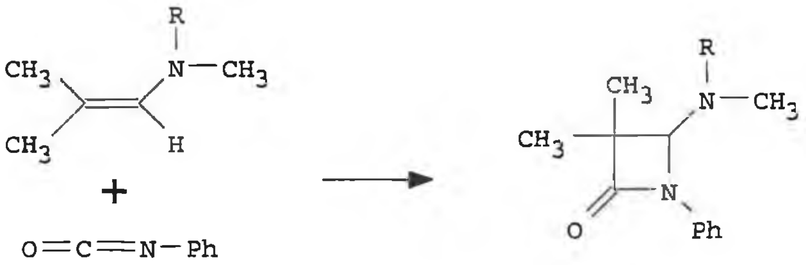
R^1 = e.g. CH_3, Ph, CH_2Ph, p-CH_3O-C_6H_4
R^2, R^3 = H, Cl, CH_3, Ph, OPh

Perhaps the most relevant β-lactam produced, in this context, is the 3,3-dimethyl-N-phenyl-2-azetidinone (586).



(586)

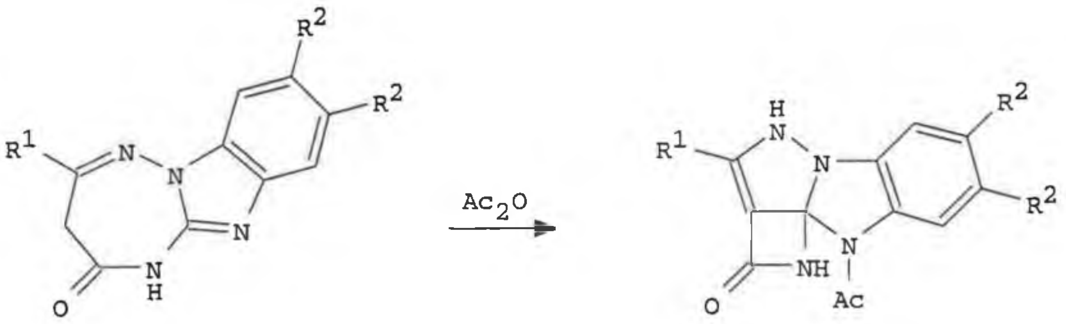
The cycloaddition of enamines with isocyanates provides an alternative route to 4-amino-β-lactams. Perelman and Mizsak[225] have described the reaction of N,N-dimethylisobutenylamine with phenyl isocyanate giving 1-phenyl-3,3-dimethyl-4-dimethylamino-2-azetidinone (587) in 95% crude yield.



(587) : R = CH_3
(588) : R = Ph

1-Phenyl-3,3-dimethyl-4-(N-methylanilino)-2-azetidinone (588) was prepared in a similar manner.

Finally, some uncommon fused tetracyclic β-lactams (590) have been isolated from the ring contraction of triazepinones (589) in acetic anhydride[37].

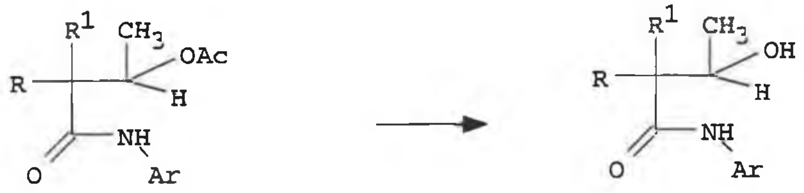


(589) **(590)**

$R^1 = CH_3, CH_2CH_2CH_3$
$R^2 = H, CH_3$

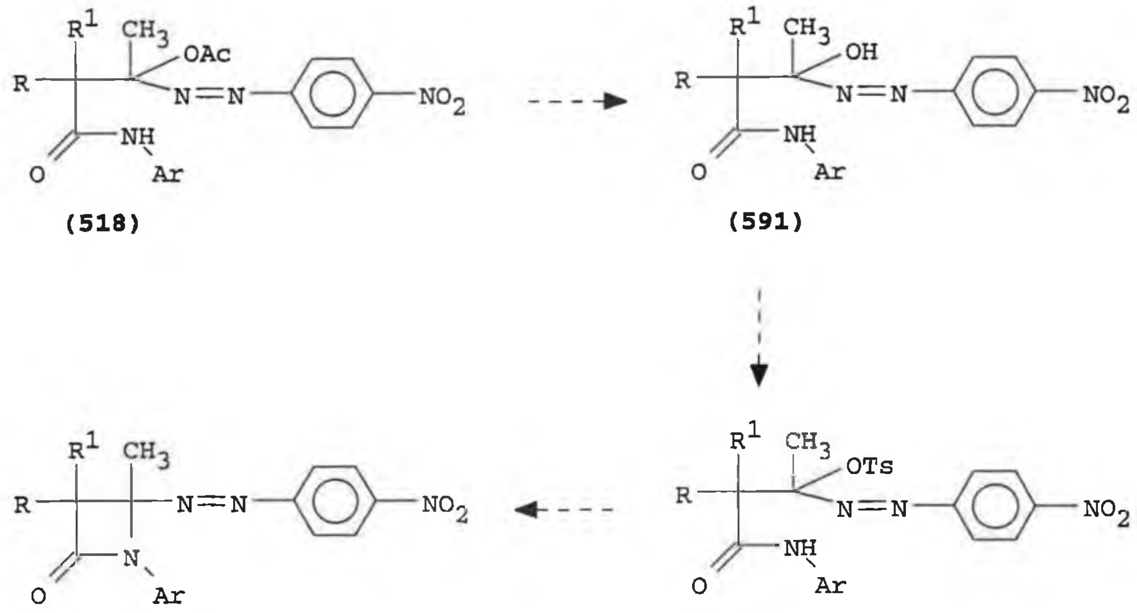
3.2.2 Results and Discussion

Having established conditions under which deacetylation of model acetate compounds (517) could be effected, it was hoped that similar treatment of the acetoacetanilide-derived azoacetates (518) might result in the isolation of azoalcohols (591) which could be converted, perhaps via the corresponding tosylates (592), to 4-azo-β-lactams (593).



(517)

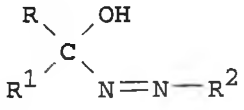
R = R^1 = H, CH_3
Ar = 4-Cl-C_6H_4



(518) (591) (593) (592)

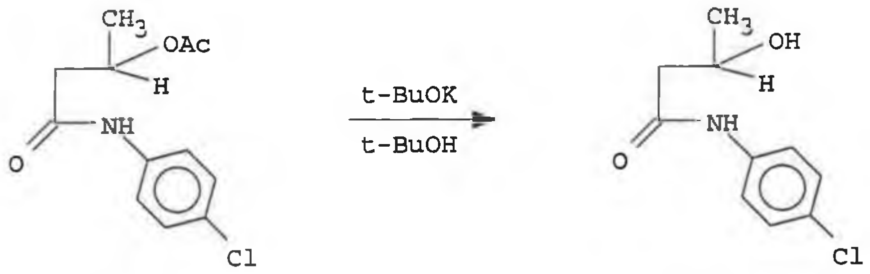
R = R^1 = H, CH_3
R = H; R^1 = CH_3
Ar = Ph, 4-Cl-C_6H_4

Although azocarbinols (594) are generally rather unstable species, several examples of this class of compound have been isolated and characterised[226,227].

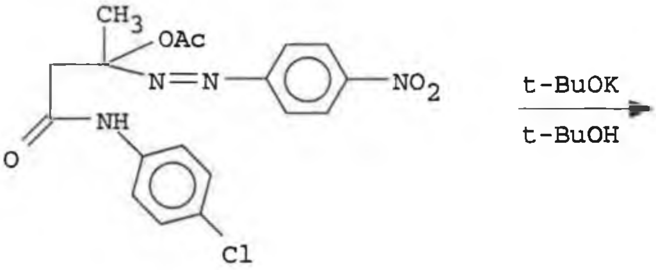


(594)

Treatment of the azoacetate (406b) with potassium t-butoxide in t-butanol, under conditions which had resulted in clean deacetylation of the corresponding model acetate (544b), gave a complex mixture of products, none of which could be separated.

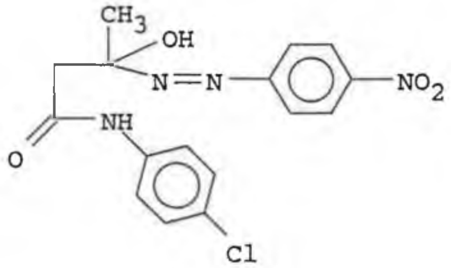


(544b) **(541b)**



(406b)

Similarly, refluxing this azoacetate (406b) with either K_2CO_3 in acetone or KCN in n-propanol afforded numerous products. However, when the azoacetate (406b) was reacted for 20 minutes with KCN in ethanol at 50°C, TLC analysis indicated that one major product had been formed. The IR spectrum of the crude product, an orange oil, lacked an ester carbonyl stretch and exhibited a broad band at 3309 cm^{-1}, suggesting that the azoalcohol (595) had been isolated.

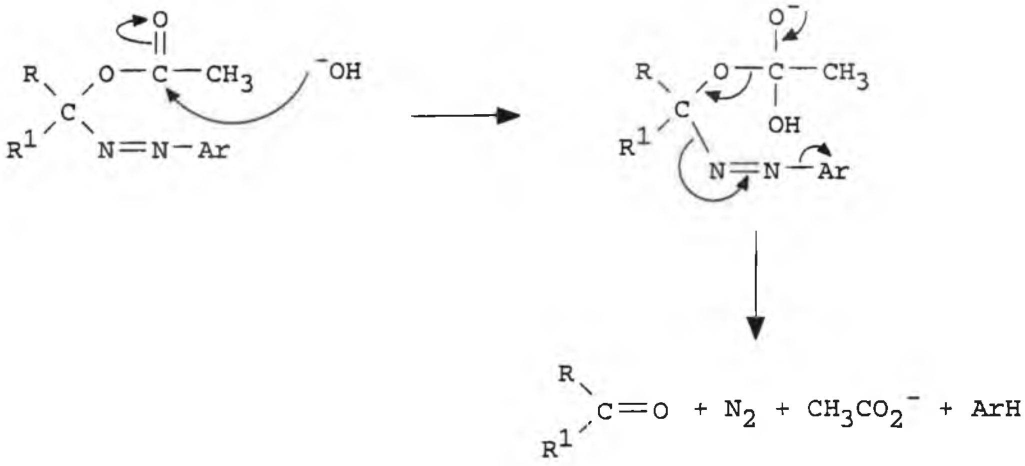


(595)

Attempted chromatographic purification of the oil resulted in decomposition. Moreover, the crude product degraded on standing for 48 hours at ambient temperature. p-Chloroaceto-acetanilide (404b) was isolated from the mixture of decomposition products.

Norman and colleagues[228], in their study of the reactions of azoacetates with base, found that, in some cases, the parent ketone was formed. With hydroxide ion as base, they proposed a mechanism whereby the ketone is produced directly by elimination, following initial attack at the acetate carbonyl (Scheme 27).

Scheme 27



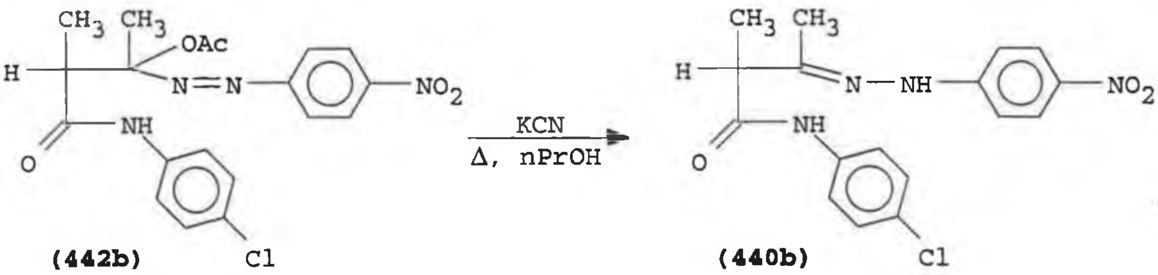
The existence, of an intermediate azocarbinol was not considered here. Nonetheless, azocarbinols have been shown to yield the corresponding ketones on decomposition. Yeung and Warkentin[229] have reported that t-butylazodiphenylcarbinol (596) degrades giving benzophenone (480).

(596) **(480)**

Therefore, since KCN is known to be an effective transesterification catalyst[216], it is believed that the unstable product isolated from the reaction of the azoacetate (406b) with KCN in ethanol was, in fact, the azoalcohol (595).

Attempted tosylation of the suspected azoalcohol (595) failed, probably for steric reasons.

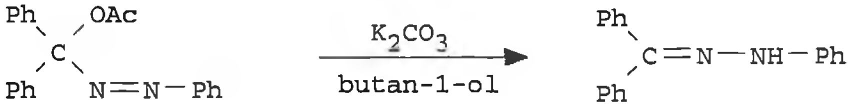
Treatment of the monomethylated azoacetate (442b) ((2R,3S)- and (2S,3R)-isomers) with potassium carbonate in refluxing acetone again gave several inseparable products. However, when this azoacetate was reacted with KCN in hot n-propanol, the parent hydrazone (440b) was isolated from the product mixture in 11% yield.



(442b) **(440b)**

Formation of the hydrazone (440b) was somewhat surprising since this implied that the azoacetate (442b) had undergone reduction. In the absence of any obvious reducing agent, how had this transformation occurred?

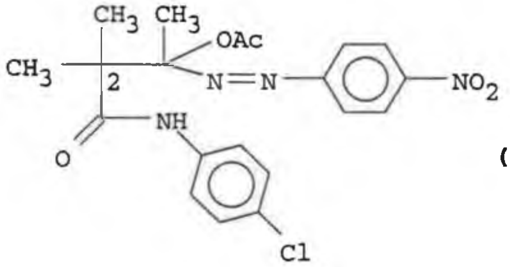
Norman's group[228] have noted that azoacetates, as a class, are easily reduced. Indeed, these workers report several examples where treatment of azoacetates under various basic conditions afforded the corresponding hydrazones in yields of up to 90%. In particular, α-phenyl-α-phenylazobenzyl acetate (597), when refluxed in butan-1-ol containing suspended potassium carbonate, gave benzophenone phenylhydrazone (598).



(597) **(598)**

To explain this reduction, the authors suggest a mechanism involving hydride-transfer, where attack by the basic anion on a solvent molecule results in its oxidation with release of a hydride ion, which then attacks the azoacetate substrate. In support of this mechanism, methyl ethyl ketone was isolated, as its 2,4-dinitrophenylhydrazone, from the product mixture obtained when the azoacetate (597) was reacted in refluxing butan-2-ol. A hydride-transfer of this type might account for the reductive deacetoxylation observed when the azoacetate (442b) was treated with KCN in hot n-propanol (Scheme 28).

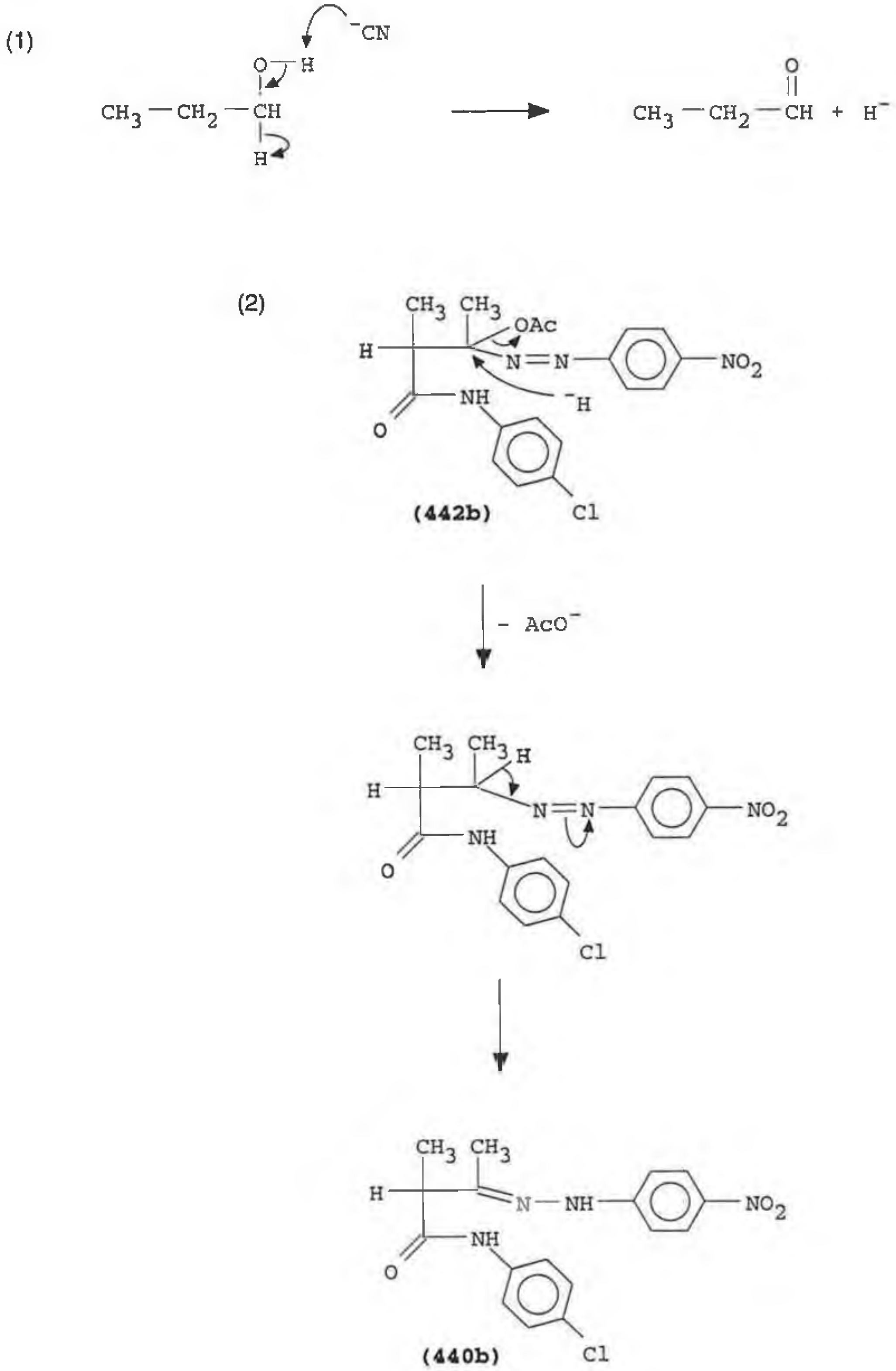
The reactions of the dimethylated azoacetate (437b) with different bases were then examined. Since this substrate possesses no labile proton in the 2-position, it was hoped that the number of possible reactions would be limited and that a cleaner product mixture could be obtained.



(437b)

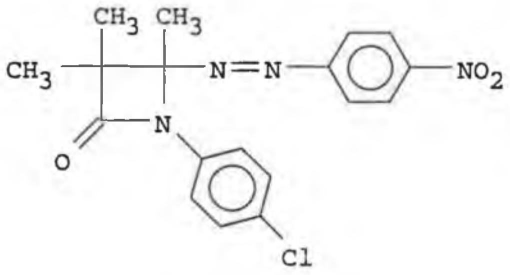
When N-(4-chlorophenyl)-2,2-dimethyl-3-acetoxy-3-(4-nitrophenylazo)butanamide (437b) was refluxed for 30 minutes with 1.5 equivalents of KCN in n-propanol, TLC analysis showed that no starting material remained and that two major products, one polar and one non-polar, had been formed. The less polar of these was separated and purified. The IR spectrum of this product lacked an amide N-H stretch and displayed a strong carbonyl absorption at 1749 cm^{-1}, typical of monocyclic β-lactam compounds. Further analysis confirmed that N-(4-chlorophenyl)-3,3,4-trimethyl-4-(4-nitrophenylazo)-2-azetidinone (474b) had been produced.

Scheme 28



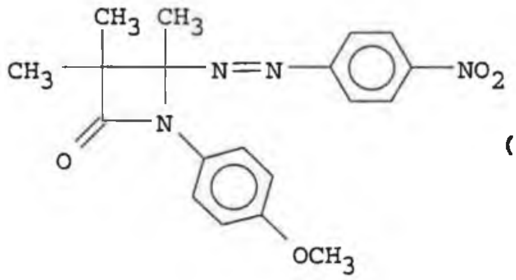
(442b)

(440b)



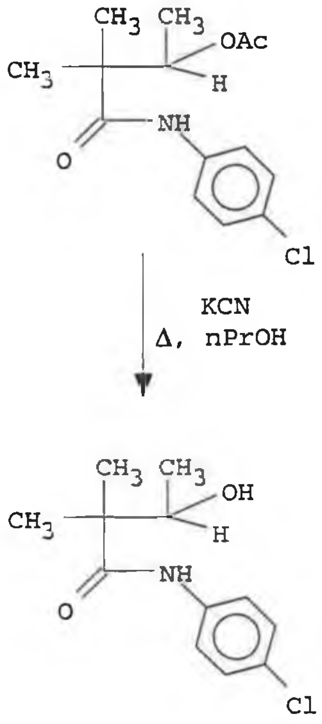
(474b)

The ^1H and ^{13}C NMR spectra of the 4-azo-β-lactam (474b) are shown in Figure 16. Although crystals of this novel β-lactam suitable for X-ray crystallographic analysis could not be obtained, the structure of the analogous N-(4-methoxyphenyl)-2-azetidinone (599) has recently been determined (Figure 17)[230].



(599)

As we have already seen, treatment of the model acetate (545b) with KCN in hot n-propanol afforded the corresponding alcohol (542b) in 77% yield.



(545b)

(542b)

Did lactamisation of the analogous azoacetate (437b) proceed directly, or was an intermediate azoalcohol (600) involved?

Figure 16: ^1H and ^{13}C NMR spectra of the 4-azo-β-lactam (474b)

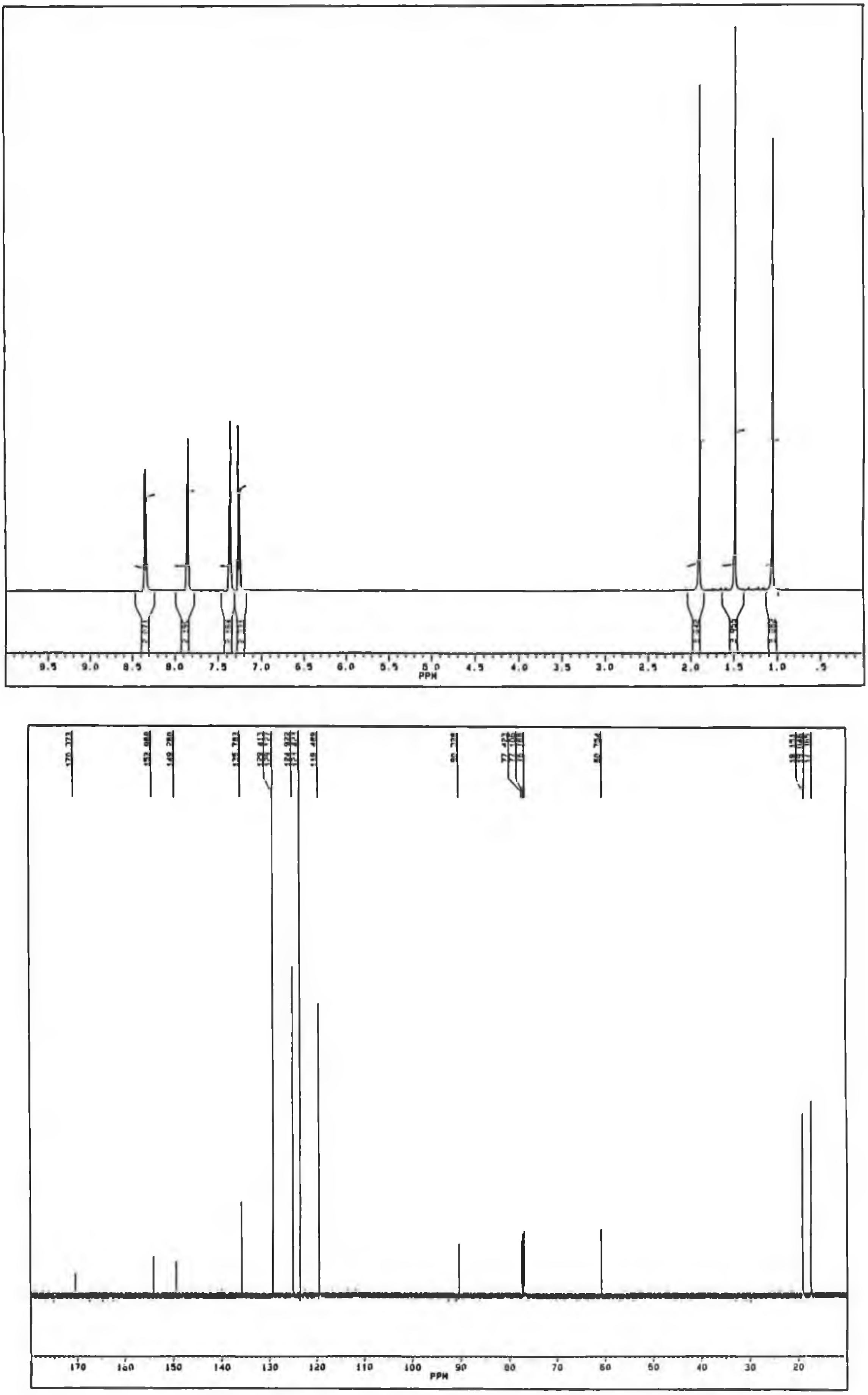
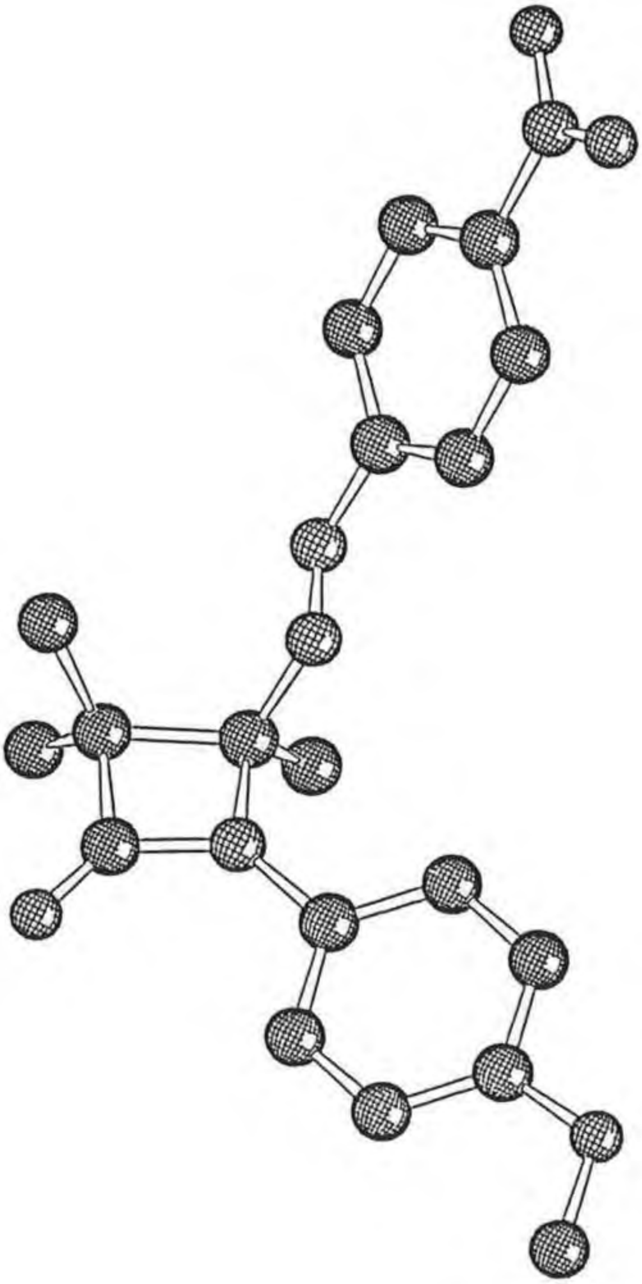
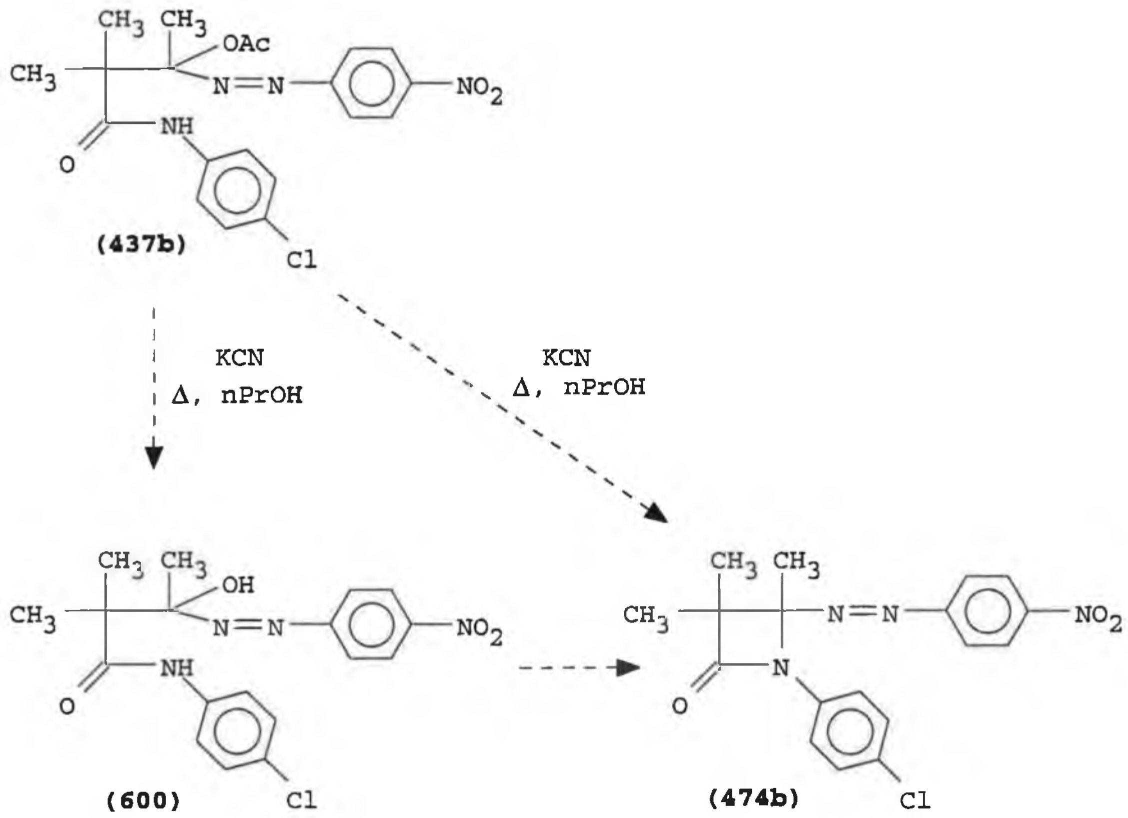


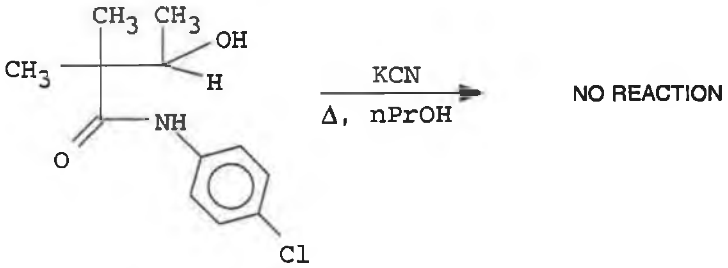
Figure 17: X-ray crystal structure of the 4-azo-β-lactam (599)





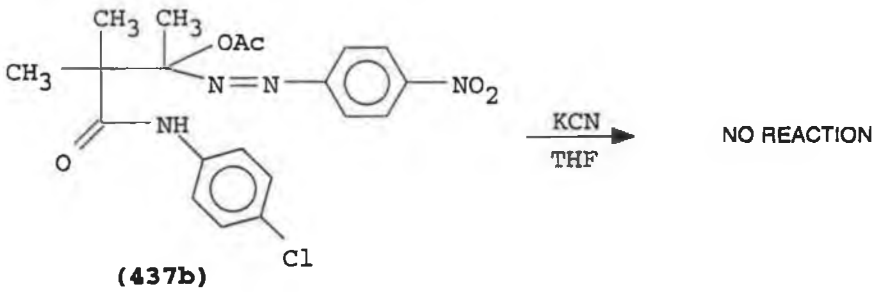
(437b) (600) (474b)

When the model alcohol (542b) was refluxed with KCN in n-propanol, no reaction was observed.



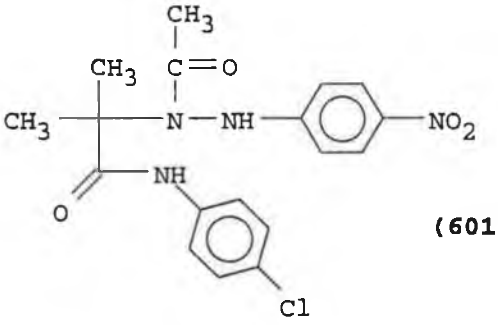
(542b)

This suggested that KCN could not effect dehydration of an azoalcohol, and that a single-step N-C4 cyclisation giving the β-lactam (474b) had occurred. If a direct lactamisation was operative, then treatment of the azoacetate (437b) with KCN in a non-alcoholic solvent should also furnish the 4-azo-β-lactam (474b). However, after heating the azoacetate (437b) with KCN in THF for 80 minutes, TLC analysis showed that only starting material was present.



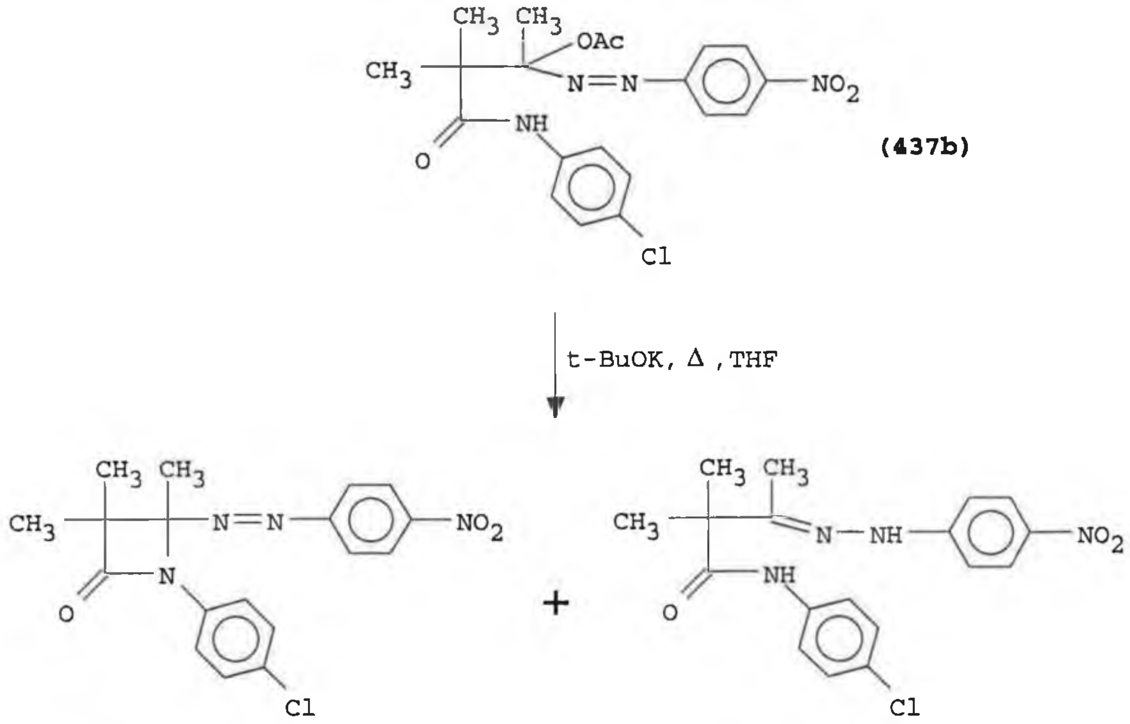
(437b)

Recently, the second, more polar product from the reaction of the azoacetate (437b) with KCN in hot n-propanol has been identified as the hydrazide (601)^{231}.


(601)

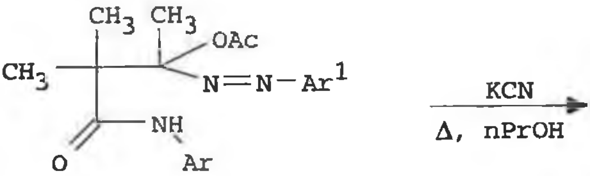
This compound is believed to be derived from an intermediate azoalcohol (600). It is proposed, then, that formation of both the 4-azo-β-lactam (474b) and the hydrazide (601) occurs via initial deacetylation of the azoacetate (437b) affording the azoalcohol (600). Subsequent abstraction of the alcoholic hydrogen by the azo group gives the oxaziridine (602), which undergoes either (a) N-C4 cyclisation furnishing the β-lactam (474b) or (b) rearrangement yielding the hydrazide (601) (Scheme 29).

N-(4-Chlorophenyl)-3,3,4-trimethyl-4-(4-nitrophenylazo)-2-azetidinone (474b) was again produced when the azoacetate (437b) was refluxed with t-BuOK in n-propanol, K_2CO_3 in acetone and t-BuOK in THF. In the last case, the parent hydrazone (436b) was also isolated from the product mixture.


(437b)

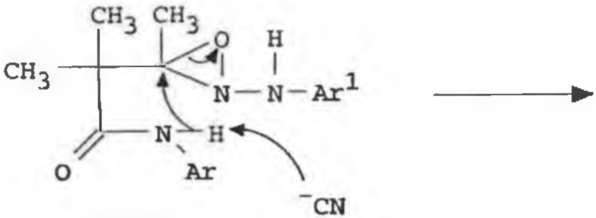
(474b) **(436b)**

Scheme 29



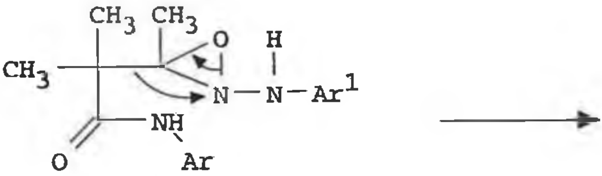
(437b)

(a) β-lactam formation

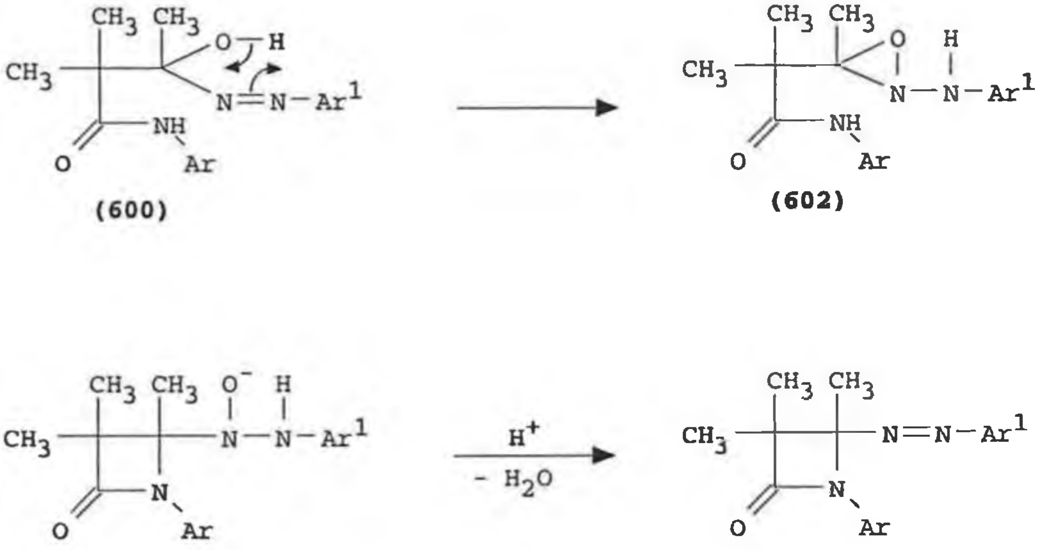


(602)

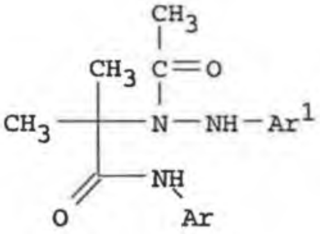
(b) hydrazide formation



(602)



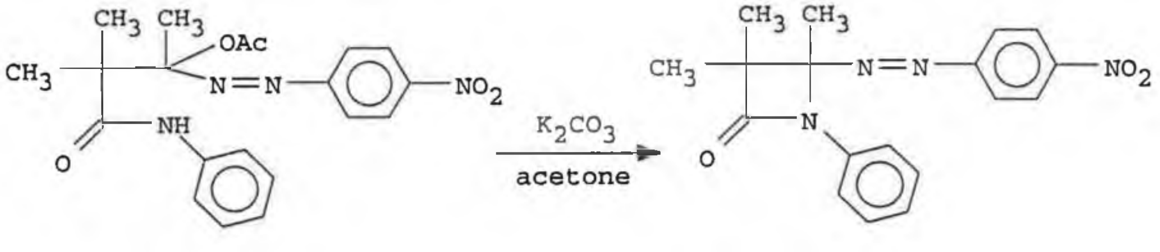
(600) **(602)** **(474b)**



(601)

$Ar = 4\text{-}Cl\text{-}C_6H_4$
$Ar^1 = 4\text{-}NO_2\text{-}C_6H_4$

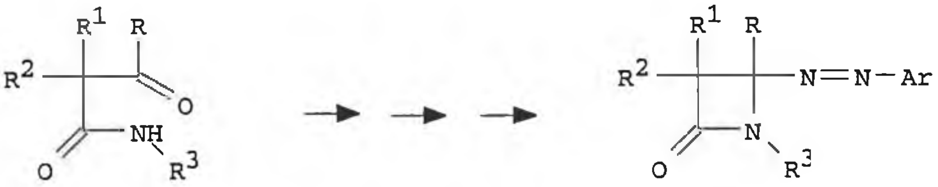
Finally, the analogous N-phenyl-4-azo-β-lactam (474a) was prepared in 28% yield by heating N-phenyl-2,2-dimethyl-3-acetoxy-3-(4-nitrophenylazo)butanamide (437a) with K_2CO_3 in acetone for 22 hours.



(437a) **(474a)**

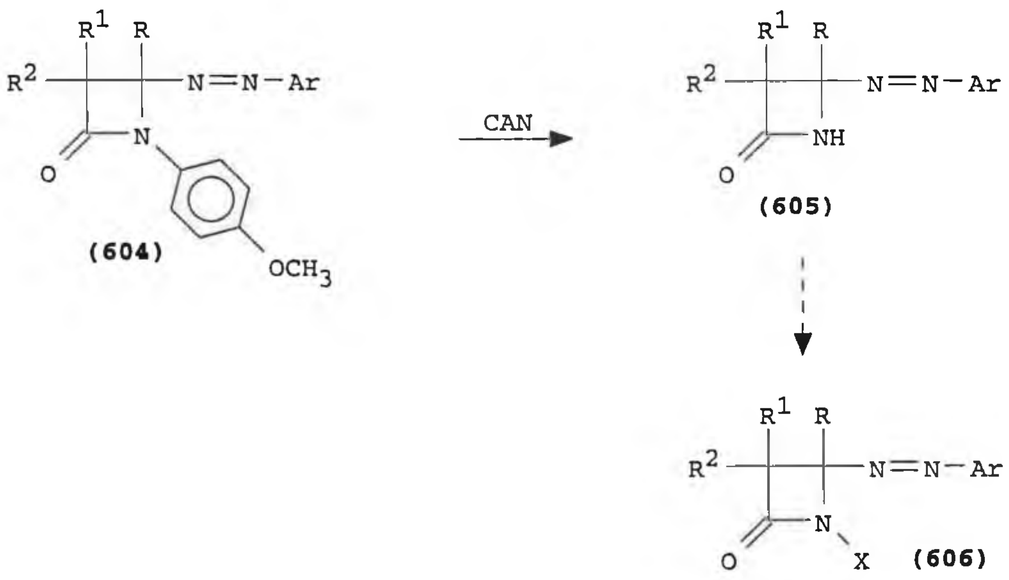
The reactions affording the novel 4-azo-β-lactams are summarised in Table 4.

The methodology developed for the synthesis of the novel 4-azo-β-lactams (474) could be extended to the preparation of a range of analogous 2-azetidinones (603) bearing a variety of different substituents.



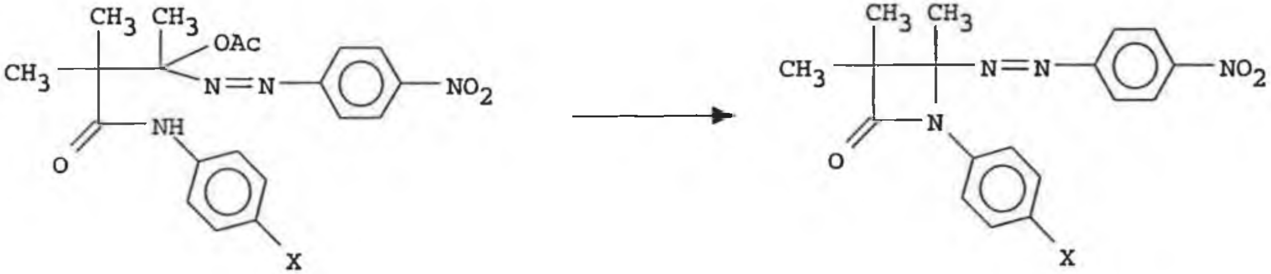
(603)

N-(4-Methoxyphenyl)-4-azo-2-azetidinones (604), including the 3,3,4-trimethylated species (599) described above, could be converted to the corresponding N-unsubstituted β-lactams (605) by treatment with ceric ammonium nitrate (CAN), an established deblocking procedure[232]. Thus, an array of N-substituted 4-azo-β-lactams (606) might be prepared.



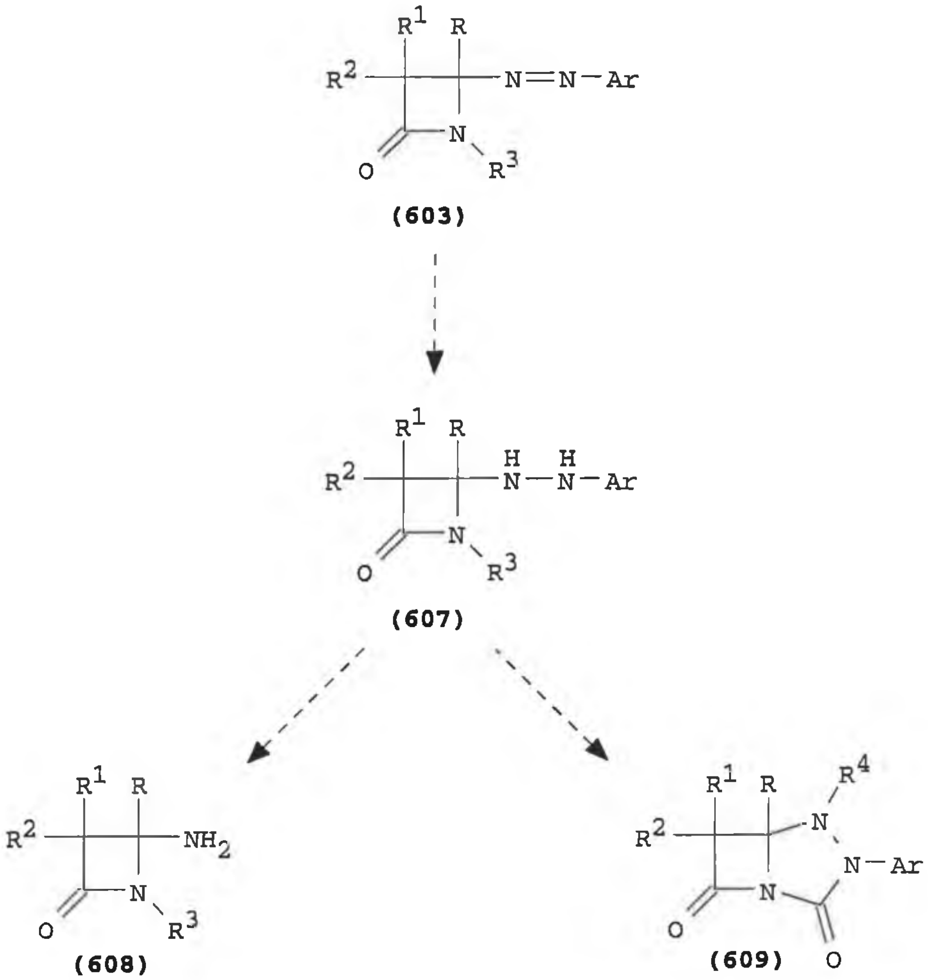
(604) **(605)** **(606)**

Table 4: **Reactions yielding 4-azo-β-lactams**

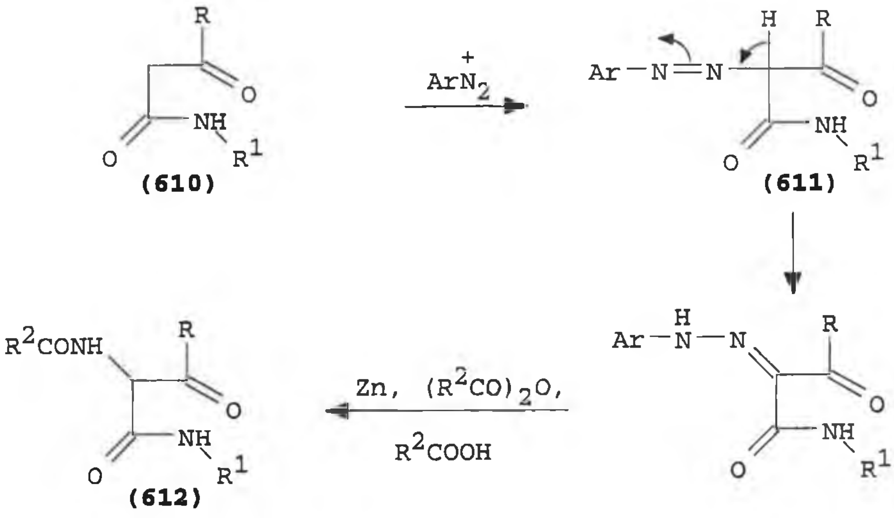


X	Reaction Conditions	Isolated Products (% yield)
Cl	KCN/Propan-1-ol, 30 minutes reflux	β-Lactam (40)
Cl	t-BuOK/Propan-1-ol, 1 hour reflux	β-Lactam (27)
Cl	K_2CO_3/Acetone, 22 hours reflux	β-Lactam (49)
Cl	t-BuOK/THF, 2 hours reflux	β-Lactam (5) Hydrazone (9)
H	K_2CO_3/Acetone, 22 hours reflux	β-Lactam (28)

Hydrogenation of 4-azo-2-azetidinones (603) should result in the production of 4-hydrazino-2-azetidinones (607), which could be further reduced to afford 4-amino-β-lactams of the type (608). An attractive alternative would be the possible transformation of the 4-hydrazino-2-azetidinones (607) to bicyclic β-lactams, e.g. (609).



α-(Arylazo)-β-ketoamides (611), prepared by the diazotisation of α-unsubstituted β-ketoamides (610)[170], could be converted, by reductive acylation, to the α-amido derivatives (612)[233].



Such α-amido-β-ketoamides (612) might be used as substrates in the synthesis of 4-azo-2-azetidinones (613) bearing the 3-amido substituent present in many biologically-active β-lactams.

(612) **(613)**

Possible elaborations of the work described in this thesis are currently under investigation.

3.2.3 Experimental

Melting points were measured in open capillary tubes with a Gallenkamp melting point apparatus. IR spectra were recorded for KBr discs or neat oils using a Perkin-Elmer 983-G spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured for solutions in $CDCl_3$ with a Bruker AC-F 400 MHz spectrometer and referenced to tetramethylsilane or residual solvent H. Elemental analyses were performed in the Microanalytical Laboratory, University College Dublin. Common reagent grade chemicals were purchased from Aldrich Chemical Company, and were used as received.

(i) Reaction of N-(4-chlorophenyl)-3-acetoxy-3-(4-nitrophenylazo)butanamide (406b) with t-BuOK in t-BuOH

0.81g (2 mmoles) azoacetate (406b) and 2.25g (20 mmoles; 10 equivalents) potassium t-butoxide were stirred in 30mls t-butanol at ambient temperature for 1 hour. TLC analysis (70:30 ethyl acetate: petroleum ether (40-60^{o})) revealed that a mixture of several products had been formed.

(ii) Reaction of azoacetate (406b) with K_2CO_3 in refluxing acetone

The azoacetate (406b) (0.81g; 2 mmoles) and anhydrous K_2CO_3 (0.33g; 2.4 mmoles; 120 mole%) were refluxed in 35mls acetone. After 2.5 hours, TLC (60:40 CCl_4: ethyl acetate) indicated the presence of numerous products.

(iii) Reaction of azoacetate (406b) with KCN in hot n-propanol

0.81g (2 mmoles) azoacetate (406b) was heated under reflux in 60mls n-propanol with 0.20g (3 mmoles; 150 mole%) potassium cyanide for 1 hour. A complex mixture of products was obtained (TLC 70:30 ethyl acetate: petroleum ether (40-60^{o})).

(iv) Reaction of azoacetate (406b) with KCN in ethanol

0.50g (1.24 mmoles) azoacetate (406b) was dissolved in 50mls ethanol at 50^{o}C and 0.10g (1.54 mmoles; 1.24 equivalents) KCN was added. After 20 minutes at 50^{o}C, the red mixture was cooled and filtered, under suction, through a bed of silica gel. The filtrate was evaporated to dryness and an orange oil was obtained. TLC (70:30 CH_2Cl_2: ethyl acetate) indicated the presence of one major product. IR (neat) 3309, 1660 cm^{-1}. On standing at room temperature for 48 hours, the oil became dark red in colour and TLC analysis showed that decomposition had occurred. The mixture was applied to a silica gel column. Elution with 70:30 CH_2Cl_2: EtOAc allowed the separation of one of the degradation products in pure form. Analysis revealed that this was p-chloroacetoacetanilide (404b).

(v) Attempted synthesis of N-(4-chlorophenyl)-3-tosyloxy-3-(4-nitrophenylazo)-butanamide

A solution of 0.50g (1.4 mmoles) of the suspected azoalcohol (595) in 5mls dry pyridine was cooled to 0-5^{o}C and 0.62g (3.3 mmoles; 240 mole%) p-toluenesulfonyl chloride was added. After 24 hours at <10^{o}C, TLC (70:30 CH_2Cl_2: petroleum ether (40-60^{o}C)) showed that no reaction had occurred.

(vi) Reaction of N-(4-chlorophenyl)-2-methyl-3-acetoxy-3-(4-nitrophenylazo)butanamide (442b) with K_2CO_3 in refluxing acetone

0.21g (0.5 mmoles) azoacetate (442b) and 0.083g (0.6 mmoles; 120 mole%) anhydrous potassium carbonate were refluxed in 25mls acetone for 2 hours. TLC (100% CH_2Cl_2) indicated that mostly starting material remained. The mixture was heated for a further 22 hours, at which time TLC analysis revealed the presence of several products.

(vii) Reaction of azoacetate (442b) with KCN in hot n-propanol

To a mixture of the (2R,3S)- and (2S,3R)-isomers of the azoacetate (442b) (0.50g; 1.2 mmoles) in 50mls refluxing n-propanol was added 0.12g (1.8 mmoles; 1.5 equivalents) KCN. After 1.5 hours, none of the starting azoacetate remained and at least seven products had been formed (TLC 100% CH_2Cl_2). The n-propanol was evaporated and the residue obtained was partitioned between chloroform and water. An interfacial solid formed. This was collected and identified as the parent hydrazone (440b) (0.021g; 5%). The organic layer was separated and concentrated to give a red residue. Addition of a small volume of $CHCl_3$ resulted in the separation of a yellow solid which again proved to be the hydrazone (440b) (0.025g; 6%).

(viii) Reaction of N-(4-chlorophenyl)-2,2-dimethyl-3-acetoxy-3-(4-nitrophenylazo)-butanamide (437b) with KCN in refluxing n-propanol

1.73g (4 mmoles) azoacetate (437b) was dissolved in 120mls boiling n-propanol and 0.39g (6 mmoles; 150 mole%) KCN was added. After 30 minutes at reflux, TLC (100% $CHCl_3$) indicated that the reaction was complete and that two major products, one polar and one non-polar, had been formed. The solvent was removed *in vacuo* to give a red oil which was dissolved in $CHCl_3$ and washed with water. The organic layer was separated and dried over Na_2SO_4. The residue obtained on evaporation of the solvent was chromatographed on a silica gel column, eluting with 100% $CHCl_3$. The less polar major component of the mixture was separated and identified as N-(4-chlorophenyl)-3,3,4-trimethyl-4-(4-nitrophenylazo)-2-azetidinone (474b) (0.60g; 40%). Recrystallisation from benzene/petroleum ether (40-60^o) provided orange crystals. MP 150-151^{o}C. IR (KBr) 1749 cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.055 (s, 3H), 1.485 (s, 3H), 1.896 (s, 3H), 7.254 (d, 2H, J = 7.4 Hz), 7.361 (d, 2H, J = 7.5 Hz), 7.852 (d, 2H, J = 8.5 Hz), 8.345 (d, 2H, J = 7.5 Hz). ^{13}C NMR (100 MHz; $CDCl_3$) 17.4, 19.0, 19.2, 60.8, 90.3, 119.5, 123.4, 124.9, 129.1, 129.4, 135.8, 149.3, 154.0, 170.4 ppm. $C_{18}H_{17}N_4O_3Cl$ requires C, 57.99; H, 4.60; N, 15.03%. Found C, 58.02; H, 4.55; N, 14.92%.

(ix) Reaction of N-(4-chlorophenyl)-2,2-dimethyl-3-hydroxybutanamide (542b) with KCN in refluxing n-propanol

0.48g (2 mmoles) model alcohol (542b) and 0.20g (3 mmoles; 150 mole%) KCN were refluxed in 30mls n-propanol for 1 hour. TLC (100% CH_2Cl_2) showed that only starting material was present.

(x) Reaction of azoacetate (437b) with KCN in hot THF

The azoacetate (437b) (0.65g; 1.5 mmoles) and potassium cyanide (0.15g; 2.3 mmoles; 150 mole%) were heated under reflux in 50mls THF for 80 minutes. No reaction was observed (TLC 100% CH_2Cl_2).

(xi) Reaction of azoacetate (437b) with t-BuOK in refluxing n-propanol

0.65g (1.5 mmoles) azoacetate (437b) and 0.20g (1.8 mmoles; 120 mole%) t-BuOK were refluxed in 45mls n-propanol for 1 hour. The reaction was worked-up as described in (viii). Chromatographic separation afforded the β-lactam (474b) (0.152g; 27%).

(xii) Reaction of azoacetate (437b) with K_2CO_3 in refluxing acetone

Anhydrous potassium carbonate (0.50g; 3.6 mmoles; 120 mole%) was added to the azoacetate (437b) (1.30g; 3 mmoles) in 50mls hot acetone. The mixture was refluxed for 22 hours, at which time TLC (100% $CHCl_3$) indicated that the reaction was complete. Insoluble material was removed by filtration. The filtrate was evaporated to dryness and the residue applied to a silica gel column. Elution with 100% $CHCl_3$ gave the β-lactam (474b) (0.55g; 49%).

(xiii) Reaction of azoacetate (437b) with t-BuOK in hot THF

1.30g (3 mmoles) azoacetate (437b) was refluxed with 0.40g (3.6 mmoles; 120 mole%) t-BuOK in 60mls THF for 2 hours. The mixture was filtered. The residue obtained on evaporation of the filtrate was taken up in chloroform and washed with water. The organic layer was dried over Na_2SO_4 and concentrated. Column chromatography (silica gel; 100% $CHCl_3$) allowed separation of the β-lactam (474b) (56mg; 5%) and the parent hydrazone (436b) (96mg; 9%).

(xiv) Synthesis of N-phenyl-3,3,4-trimethyl-4-(4-nitrophenylazo)-2-azetidinone (474a)

The azoacetate (437a) was lactamised by treatment with K_2CO_3 in hot acetone, using the method outlined in (xii). The β-lactam (474a) was obtained as a yellow solid in 28% yield. MP 94-96^oC. IR (KBr) 1745 cm^{-1} (split C=O). ^1H NMR (400 MHz; $CDCl_3$) δ 1.061 (s, 3H), 1.481 (s, 3H), 1.900 (s, 3H), 7.113 (t, 1H, J = 7.2 Hz), 7.307 (t, 2H, J = 7.9 Hz), 7.415 (d, 2H, J = 7.9 Hz), 7.861 (d, 2H, J = 8.8 Hz), 8.352 (d, 2H, J = 8.8 Hz). ^{13}C NMR (100 MHz; $CDCl_3$) 17.4, 19.1, 19.2, 60.5, 90.2, 118.3, 123.4, 124.4, 124.9, 129.1, 137.2, 149.2, 154.1, 170.5 ppm. $C_{18}H_{18}N_4O_3$ requires C, 63.89; H, 5.36; N, 16.56%. Found C, 64.03; H, 5.41; N, 16.63%.

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Appendix

Appendix: Observed and calculated structure factors for major isomers of azoacetate (442b)

H	K	L	FO	FC
2	0	0	115	-98
4	0	0	51	46
6	0	0	16	-14
8	0	0	16	-16
1	1	0	90	84
2	1	0	100	92
3	1	0	37	-35
4	1	0	27	24
5	1	0	18	-17
7	1	0	10	9
8	1	0	27	-30
0	2	0	19	-24
1	2	0	124	121
2	2	0	170	-158
3	2	0	9	7
4	2	0	24	23
5	2	0	33	29
7	2	0	18	-18
9	2	0	12	-12
1	3	0	104	-115
2	3	0	36	38
3	3	0	36	33
4	3	0	15	16
5	3	0	15	-17
8	3	0	15	16
1	4	0	43	49
2	4	0	11	-10
3	4	0	53	-51
4	4	0	28	28
6	4	0	11	-12
1	5	0	14	16
3	5	0	15	16
5	5	0	22	21
7	5	0	9	9
0	6	0	12	-11
2	6	0	10	11

H	K	L	FO	FC
3	6	0	11	-10
4	6	0	9	-6
6	6	0	9	9
1	7	0	13	12
3	7	0	15	-16
6	7	0	9	-9
7	7	0	10	-10
0	8	0	9	-8
1	8	0	15	14
2	8	0	12	-13
6	8	0	12	-9
2	9	0	10	9
0	10	0	11	10
2	12	0	8	-3
-11	0	1	9	-10
-3	0	1	132	110
-1	0	1	94	79
1	0	1	22	25
3	0	1	10	-9
-10	1	1	9	-9
-8	1	1	8	6
-7	1	1	19	-19
-6	1	1	15	-14
-3	1	1	40	37
-2	1	1	48	49
-1	1	1	98	97
0	1	1	9	-9
1	1	1	102	89
3	1	1	31	-25
4	1	1	40	37
5	1	1	35	31
6	1	1	17	-17
7	1	1	28	-28
9	1	1	12	11
-6	2	1	7	5
-5	2	1	14	-13

H	K	L	FO	FC
-4	2	1	54	-49
-3	2	1	6	-7
-2	2	1	43	43
-1	2	1	92	-92
0	2	1	33	-37
1	2	1	43	47
2	2	1	17	-13
3	2	1	24	-22
4	2	1	59	53
5	2	1	10	-9
7	2	1	10	-11
-7	3	1	15	15
-5	3	1	29	-27
-3	3	1	50	44
-2	3	1	39	-35
-1	3	1	74	-80
0	3	1	37	-42
1	3	1	24	27
2	3	1	47	42
3	3	1	45	41
4	3	1	30	-26
5	3	1	25	27
-7	4	1	11	-13
-6	4	1	8	-8
-5	4	1	39	36
-4	4	1	17	-15
-3	4	1	21	-22
-2	4	1	24	25
-1	4	1	6	-5
0	4	1	31	-31
1	4	1	23	-25
2	4	1	11	-10
3	4	1	18	18
4	4	1	9	-7
5	4	1	13	-12
6	4	1	28	-27

H	K	L	FO	FC
7	4	1	14	15
-7	5	1	9	-10
-6	5	1	10	8
-4	5	1	14	15
-3	5	1	23	23
0	5	1	43	-47
1	5	1	18	19
2	5	1	46	45
3	5	1	19	-20
4	5	1	18	-17
5	5	1	13	-12
6	5	1	20	20
-6	6	1	8	9
-5	6	1	13	-12
-4	6	1	10	8
0	6	1	7	-7
2	6	1	19	-21
3	6	1	33	27
4	6	1	16	13
5	6	1	18	16
6	6	1	9	8
8	6	1	9	11
-7	7	1	10	8
-5	7	1	11	8
-4	7	1	7	-8
-2	7	1	16	16
-1	7	1	12	12
1	7	1	18	-21
2	7	1	7	7
3	7	1	8	6
4	7	1	13	-13
7	7	1	11	9
-1	8	1	9	10
0	8	1	14	14
1	8	1	13	-12
2	8	1	15	-14

H	K	L	FO	FC
3	8	1	15	-14
5	8	1	9	-7
7	8	1	8	-3
-3	9	1	11	-12
0	9	1	8	8
1	9	1	11	-13
4	9	1	10	-12
1	10	1	12	13
3	10	1	8	-7
2	12	1	8	5
-12	0	2	11	-14
-10	0	2	16	15
-6	0	2	38	-35
-4	0	2	41	-36
-2	0	2	92	-72
0	0	2	11	11
2	0	2	72	-70
4	0	2	29	26
6	0	2	26	-26
8	0	2	11	13
-8	1	2	9	-11
-7	1	2	10	-11
-5	1	2	34	-33
-4	1	2	18	17
-3	1	2	79	73
-2	1	2	24	26
-1	1	2	44	37
0	1	2	27	-30
1	1	2	19	18
2	1	2	174	153
3	1	2	25	-20
4	1	2	14	13
5	1	2	12	-10
7	1	2	7	-4
8	1	2	22	22
-9	2	2	9	10

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
-8	2	2	11	-11	-2	4	2	39	-39	4	8	2	8	-8	-3	2	3	15	17	6	4	3	10	-10
-7	2	2	12	-14	-1	4	2	41	44	8	8	2	8	-2	-2	2	3	21	-23	9	4	3	10	-8
-6	2	2	15	15	0	4	2	16	-16	-2	9	2	8	-7	0	2	3	42	47	-7	5	3	21	22
-5	2	2	9	-7	1	4	2	37	41	2	9	2	18	-15	1	2	3	11	8	-6	5	3	10	-13
-4	2	2	46	43	2	4	2	9	-9	3	9	2	11	-11	2	2	3	62	56	-5	5	3	10	-10
-3	2	2	27	-24	3	4	2	102	-95	-3	10	2	8	7	3	2	3	24	-24	-4	5	3	8	8
-1	2	2	96	-97	4	4	2	60	55	0	11	2	7	9	4	2	3	64	-56	-3	5	3	10	9
0	2	2	135	159	7	4	2	18	-18	2	11	2	11	7	5	2	3	10	-7	-2	5	3	15	-17
1	2	2	143	146	-7	5	2	10	-8	3	11	2	9	6	6	2	3	12	11	-1	5	3	16	-16
2	2	2	200	-179	-6	5	2	11	12	-7	0	3	17	-18	7	2	3	13	13	0	5	3	26	30
3	2	2	50	44	-3	5	2	37	-33	-5	0	3	30	-27	-8	3	3	20	22	1	5	3	30	-32
4	2	2	37	32	-2	5	2	26	29	-3	0	3	22	-17	-7	3	3	13	-13	2	5	3	7	-6
5	2	2	8	9	0	5	2	7	8	-1	0	3	139	-120	-6	3	3	17	-16	3	5	3	40	38
6	2	2	19	-17	1	5	2	18	-21	1	0	3	85	86	-5	3	3	20	23	-6	6	3	10	-10
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