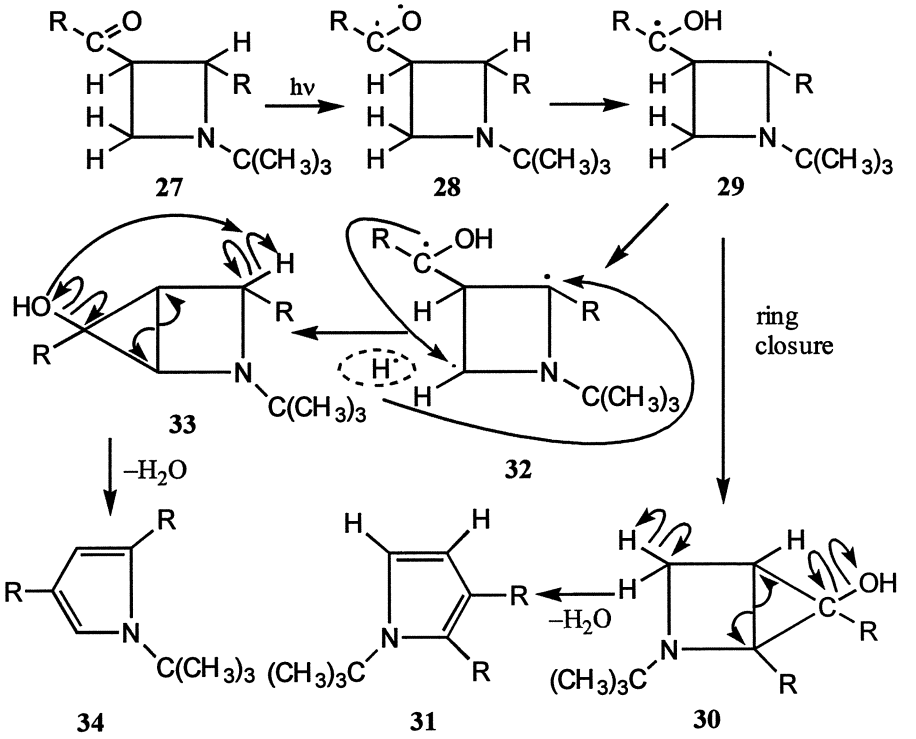
Azetidine ketones **27** undergo photochemical rearrangement resulting in ring expansion to pyrroles **31** and **34** (scheme-12)[11]. The reaction proceeds to involve intramolecular hydrogen shift with the generation of 1,3-biradical intermediate **29** which undergoes ring closure to form bicyclic unstable compounds **30** and **33** which, in turn, finally lead to the formation of pyrroles **31** and **34**, respectively with the loss of water molecules.

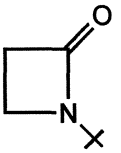


Scheme-12

1.2 Azetidinones (β-Lactams)

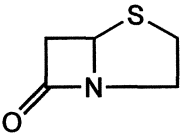
1.2.1 General

Azetidinones[13,14] are the carbonyl derivatives of azetidines containing carbonyl group at the position-2. These are also known as 2-azetidinones or more commonly β-lactams **35**. Azetidinone or β-lactam chemistry is of great importance because of the use of β-lactam derivatives as antibacterial agents[15,16].

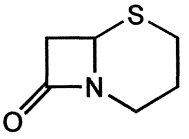


35

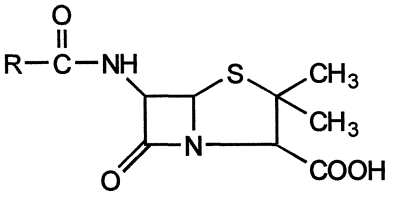
The discovery of penicillin structure that contains β-lactam system led extensive investigations to obtain β-lactam antibiotics with a wider spectrum of activities and greater resistance to enzymatic cleavage. β-Lactam antibiotics contain two basic structural units; penam **36** and cepham **37** (both contain β-lactam unit), and include two powerful antibiotics; penicillins **38** and cephalosporins **39**.



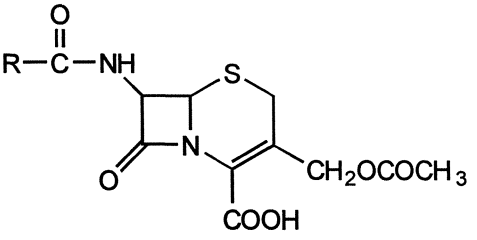
36



37



38



39

Infrared absorption spectrum of monocyclic β-lactams (absorption at 1735–1765 cm^{-1} as compared to that of unstrained amides at 1660 cm^{-1}) reflects the behaviour of carbonyl group as an ester linkage which accounts for its higher reactivity in the ring (making carbonyl carbon more electrophilic than in acyclic amides). In penicillin **38** and cephalosporin **39**, the fusion of β-lactam ring with heterocyclic ring has the effect of shifting the amide carbonyl absorption to 1770–1780 cm^{-1} suggesting increased electrophilicity and, in turn, more reactivity of carbonyl group. The increased reactivity of carbonyl group which has been considered to be associated with the antibiotic activity in penicillin **38** and cephalosporin **39** is

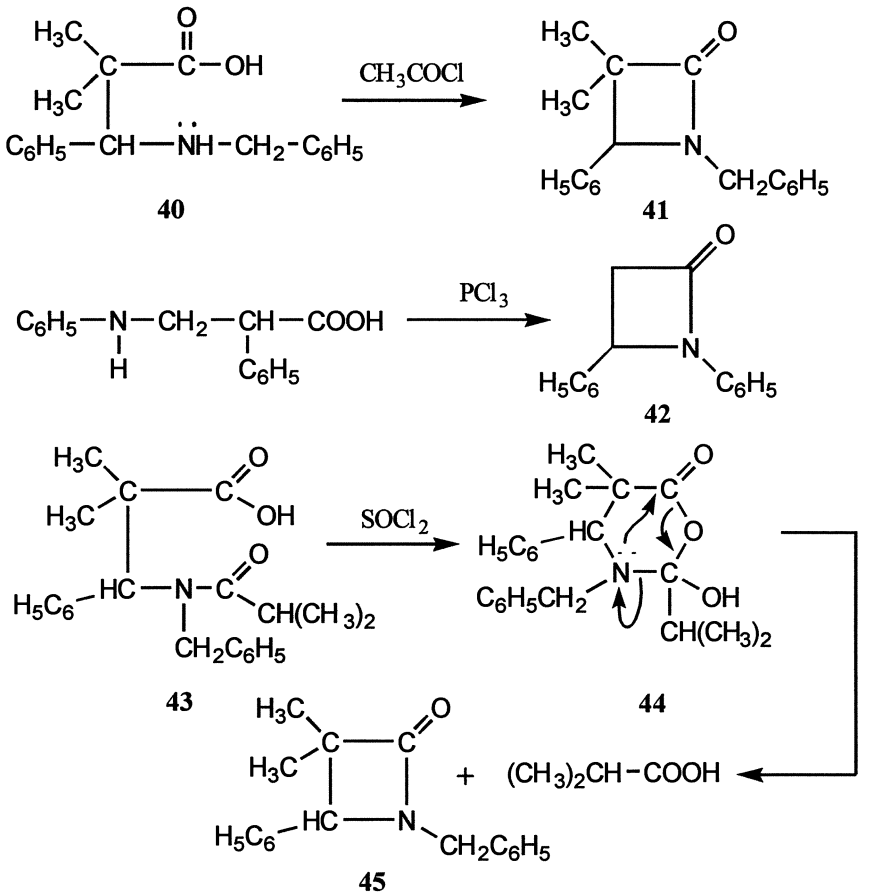
attributed to the fact that the ring fusion does not allow the amide nitrogen (bridgehead nitrogen) to achieve the planarity, since sp^2-hybridized nitrogen imposes greatly increased angle strain on the system.

1.2.2 Synthesis

1.2.2.1 Cyclization Reactions

1.2.2.1.1 Intramolecular Cyclization of β-Amino Acids

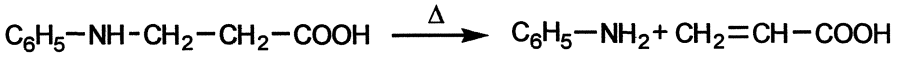
Intramolecular cyclization of β-amino acids in the presence of certain reagents including acyl chloride, phosphorus trichloride and thionyl chloride provides β-lactams (scheme-13)[17,20-25]. However, β-aminopropionic acids are not cyclized to



40 41 42 43 44 45

Scheme-13

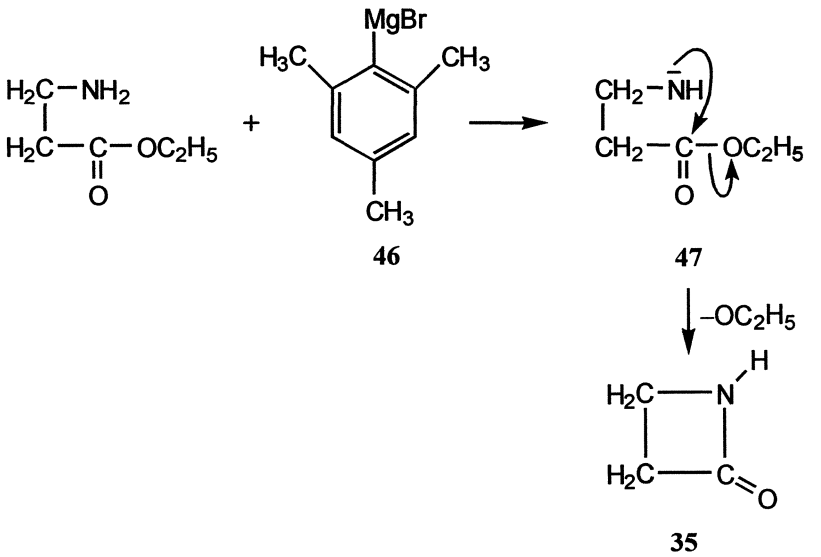
β-lactams on heating, but undergo elimination reaction providing amines and acids (scheme-14).



Scheme-14

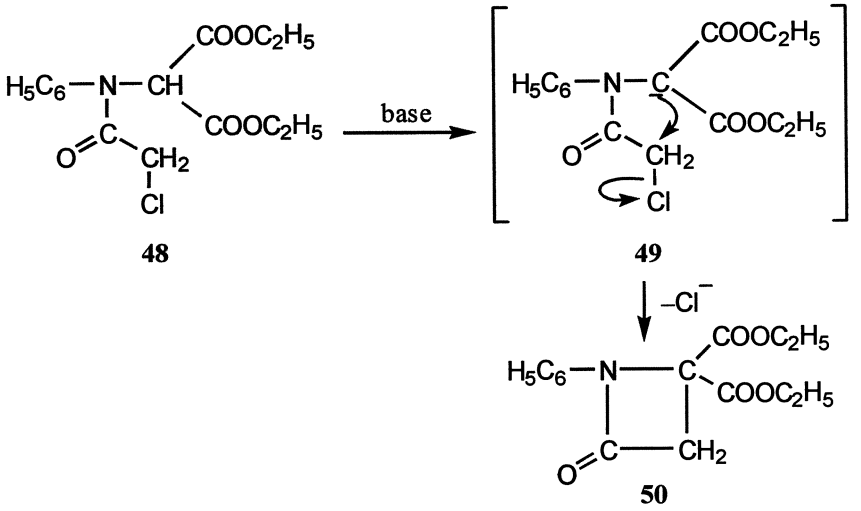
1.2.2.1.2 Cyclization of Amino Esters

The reaction of β-amino esters with Grignard reagents **46** leads to the formation of azetidinones (β-lactams) **35** via the formation of N-anion **47** (scheme-15)[21-23]. Further reaction of mesityl magnesium bromide **46** with β-lactam at carbonyl site is prevented due to its steric nature.



Scheme-15

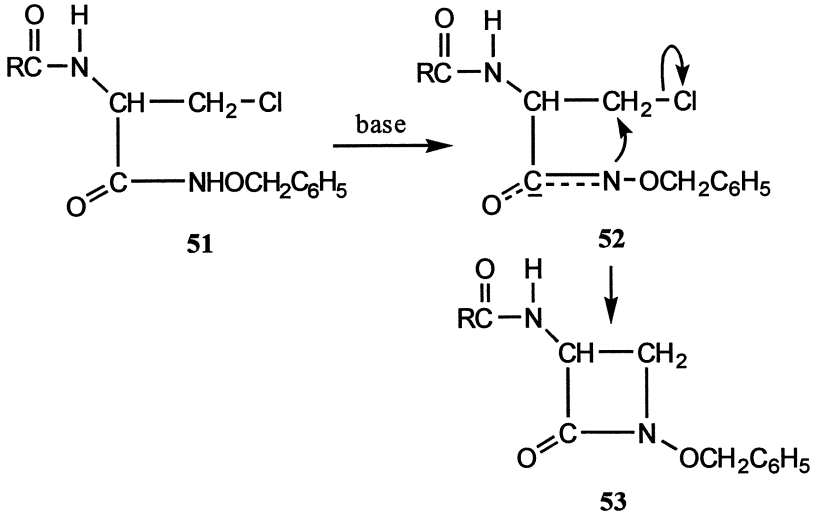
N-Substituted diethylmalonates **48** undergo base catalyzed ring closure to yield β-lactams (scheme-16)[21-24].



Scheme-16

1.2.2.1.3 Cyclization of β-Halo Amides

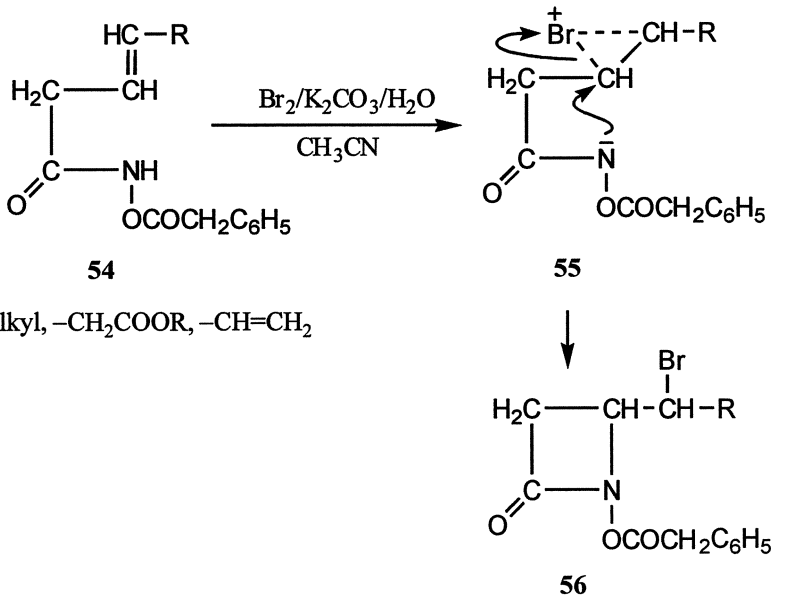
N-Substituted β-halo amides **51** are cyclized in the presence of a base to β-lactams **53** via an intermediate **52** (scheme-17)[26-28].



Scheme-17

1.2.2.1.4 Cyclization of β,γ-Unsaturated Hydroxamates

The bromine induced cyclization of O-acyl-β,γ-hydroxamates **54** provides β-lactams **56** via the formation of bromonium ion intermediate **55** (shceme-18). The presence of a phenyl group at the γ-position fails to provide β-lactams because the regioselectivity of opening of the bromonium ion intermediate **55** is reversed due to the formation of stabilized benzylic carbonium ion[29].



54 **55**

R = alkyl, $-CH_2COOR$, $-CH{=}CH_2$

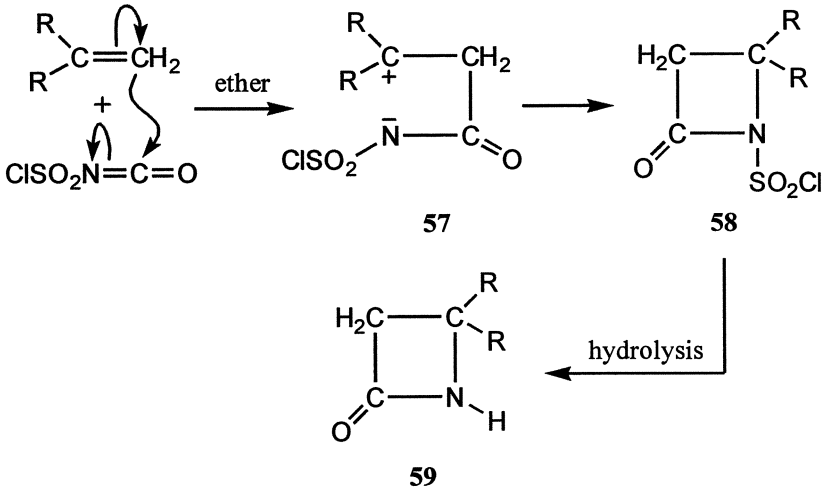
56

Scheme-18

1.2.2.2 Cycloaddition Reactions

1.2.2.2.1 Cycloaddition of Olefins to Isocyanates

The reaction of nucleophilic olefins with isocyanates provides β-lactams involving [2 + 2] cycloadditions. Chlorosulfonyl isocyanate reacts with olefins to form the corresponding chlorosulfonyl β-lactams **58**. The chlorosulfonyl group can be easily removed from the cycloadducts by hydrolysis to provide N-unsubstituted β-lactams **59** (scheme-19)[30]. The reaction proceeds with the formation of dipolar intermediate **57** involving electrophilic attack at the olefinic site by an isocyanate group. The resulting intermediate **57** readily collapses to yield β-lactam **59**.

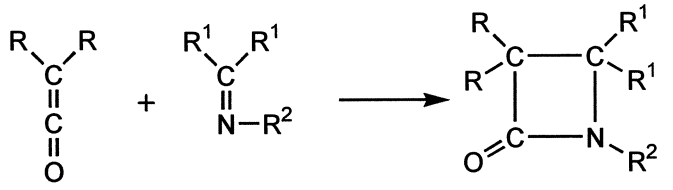


57 58 59

Scheme-19

1.2.2.2.2 Cycloaddition of Imines with Ketenes

The cycloaddition of ketoketenes **60** with imines **61** also results in the formation of β-lactams **62** (scheme-20)[31-35].



60 **61** **62**

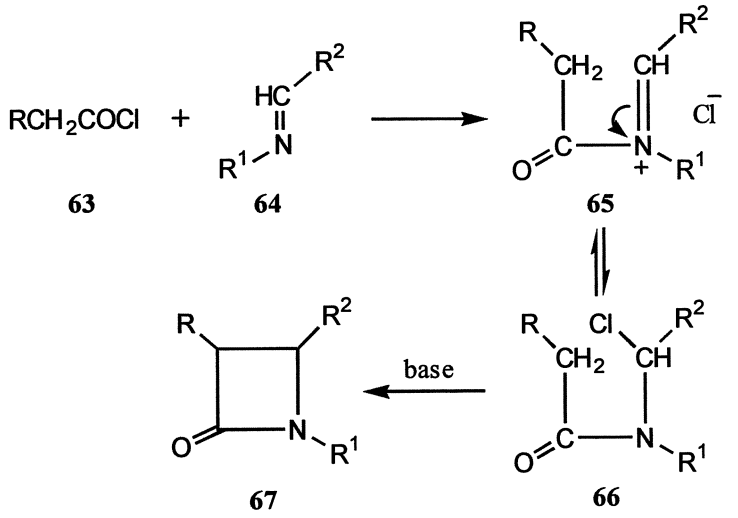
Scheme-20

1.2.2.2.3 Cycloaddition of Imines with Acid Chlorides

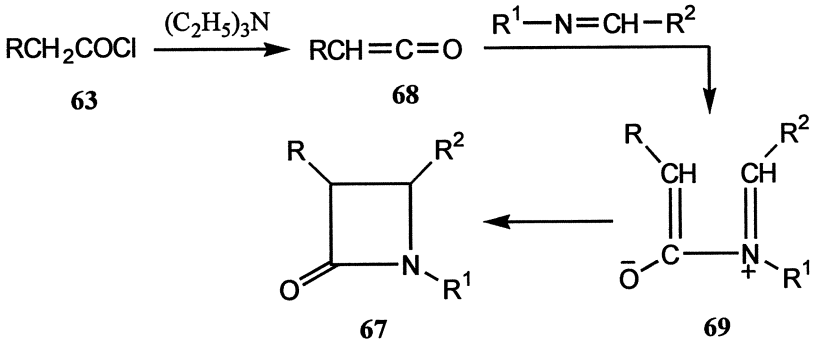
The reaction of acid chlorides with imines in the presence of a base provides β-lactams (scheme-21)[34-40].

The reaction mechanism involves direct acylation of imine with acid chloride giving N-acylium chloride **65** which is in equilibrium with chloramide **66**. The reaction of **65** or **66** with a base gives β-lactams **67**. However, an alternative

mechanism has also been proposed involving prior formation of a ketene **68** by the reaction of acid chloride **63** with a base and subsequent cycloaddition with imine via zwitterionic intermediate **69** (scheme-22)[40].

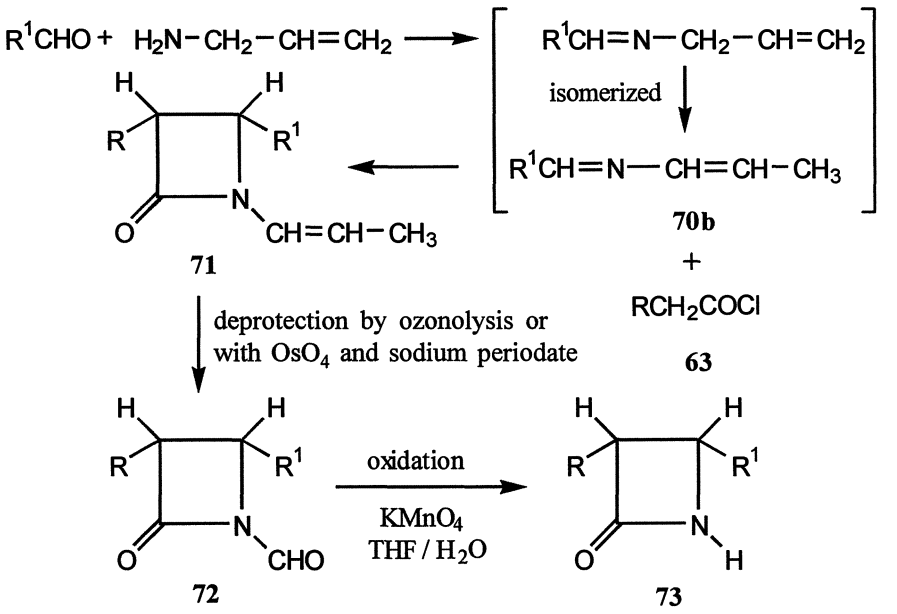


Scheme-21



Scheme-22

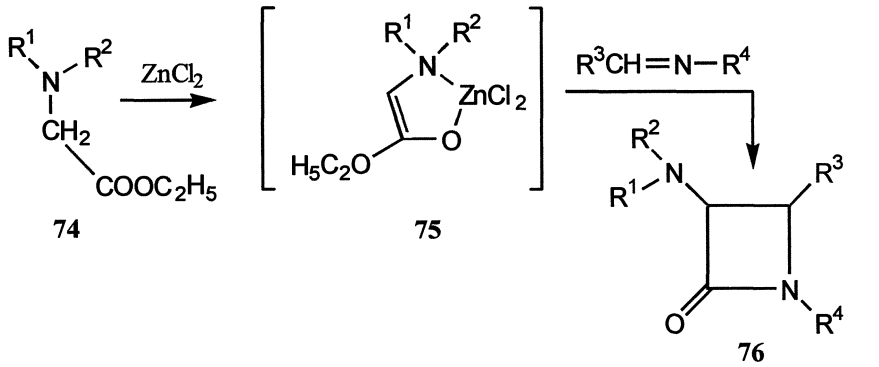
2-Aza-1,3-dienes **70**, obtained by the reaction of aldehydes with allylamine, also undergo [2 + 2] cycloaddition with acid chlorides yielding N-1-propenyl-β-lactams **71**. N-Propenyl group can be removed by ozonolysis followed by the oxidation of resulting N-formyl lactam **72** with potassium permanganate. It provides a convenient route for the preparation of N-unsubstituted β-lactams **73** (scheme-23)[41].



Scheme-23

1.2.2.2.4 Cycloaddition of Imines with α-Amino Esters

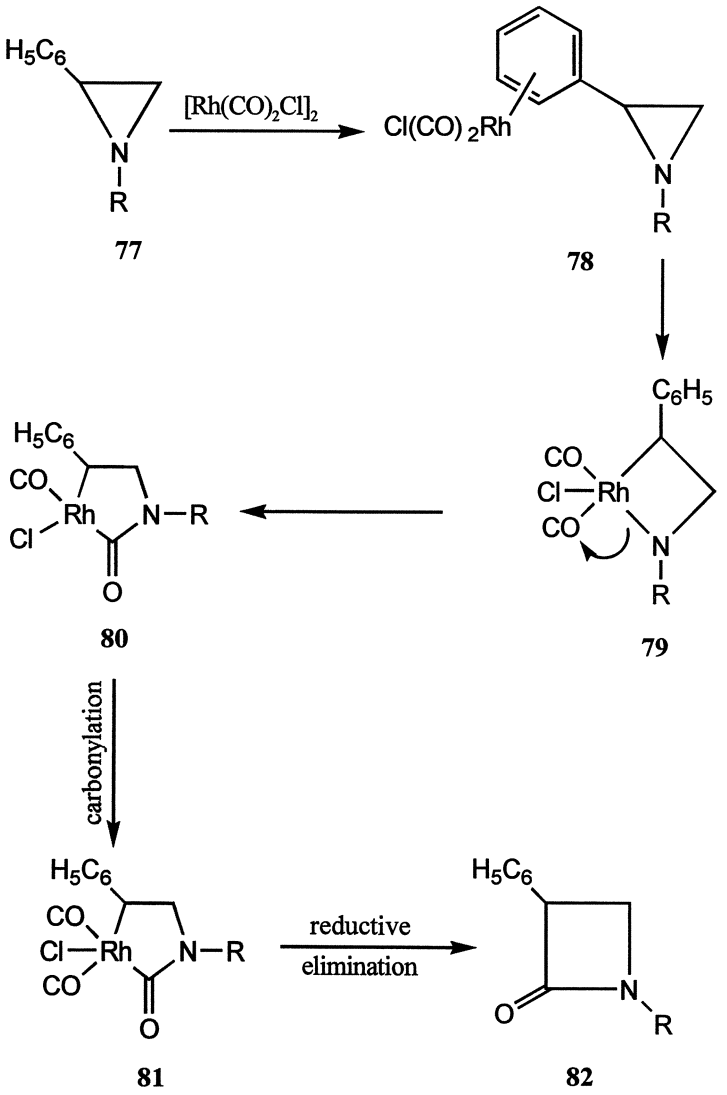
The reaction of α-amino esters **74** with imines in the presence of zinc chloride affords stereoselective β-lactams **76** involving the formation of zinc enolates **75** (scheme-24)[42,43]. The nature of the solvent and the substituents present on an imine affect the reaction stereochemically.



Scheme-24

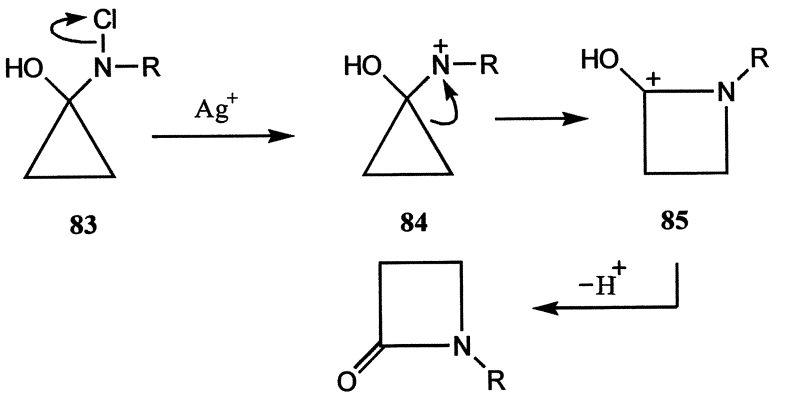
1.2.2.3 Ring Expansion Reactions

Rhodium (I) catalyzed carbonylation of aziridines results in the ring expansion to β-lactams with the insertion of CO into the more substituted C–N bond (scheme-25)[44-47]. The process is stereospecific and enantiospecific and proceeds with the retention of configuration. However, the ring expansion using nickel carbonyl occurs with the insertion of CO into the less substituted C–N bond[48].



Scheme-25

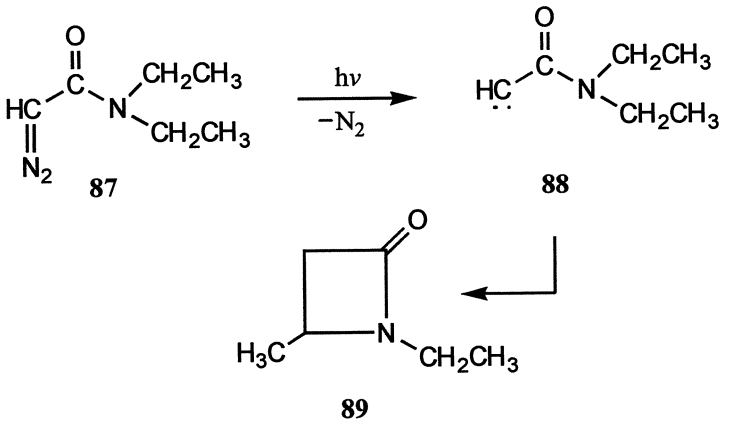
Cyclopropanes also undergo ring expansion reaction with the formation of β-lactams **86** (scheme-26).



Scheme-26

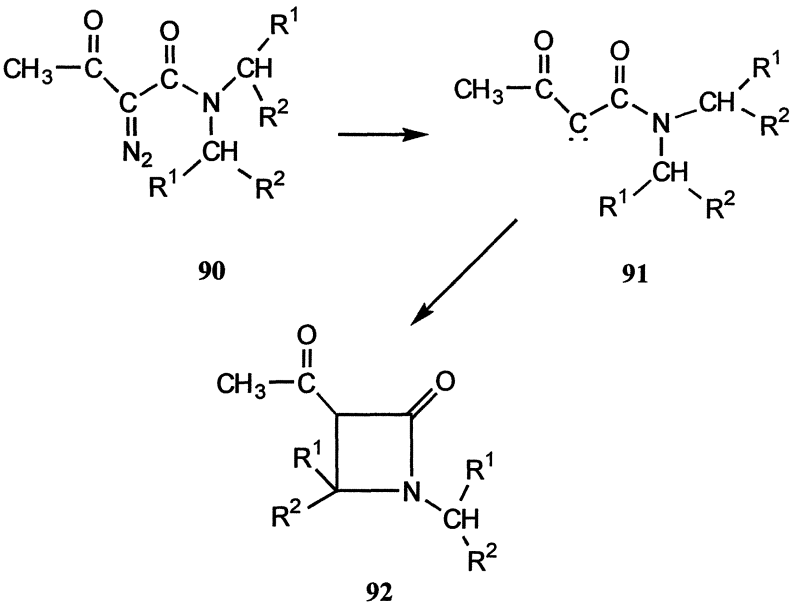
1.2.2.4 Methylene Insertion Reactions

The photolysis of N,N-disubstituted diazoacetamides **87** proceeds with the insertion of methylene group in the carbon–carbon bond affording β-lactams **89** (scheme-27)[49,50].



Scheme-27

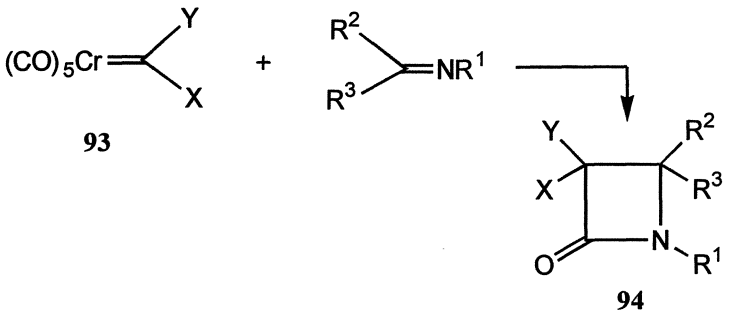
Rhodium (II) acetate catalyzed decomposition of diazoacetoactamides **90** with bulky N-substituents also involves methylene insertion in the carbon–carbon bond providing β-lactams (scheme-28)[51].



90 **91** **92**

Scheme-28

β-Lactams **94** are also obtained by the photolysis of chromiumcarbene complexes **93** in the presence of imines involving methylene group insertion (scheme-29)[52].

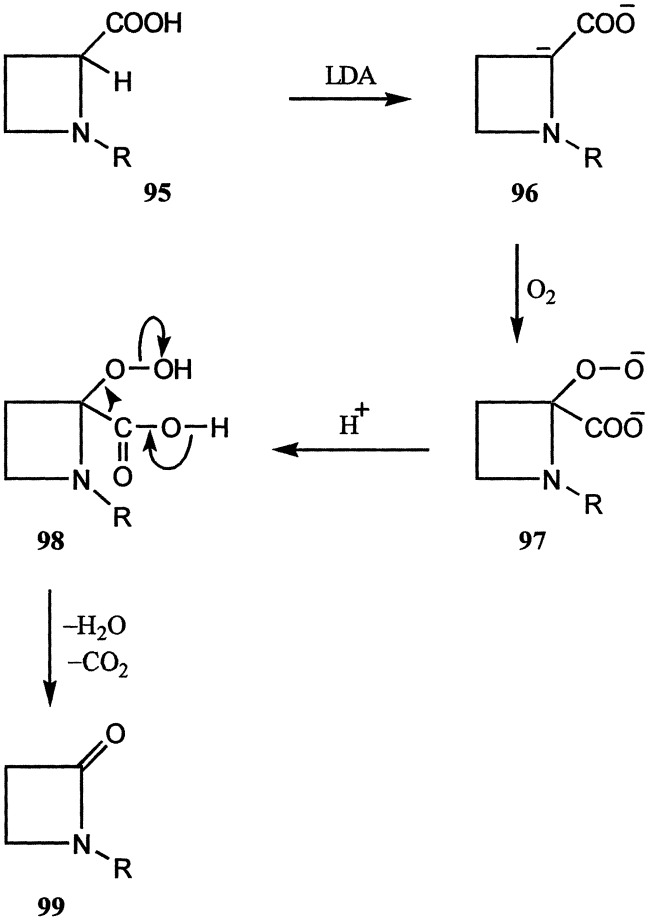


93 **94**

Scheme-29

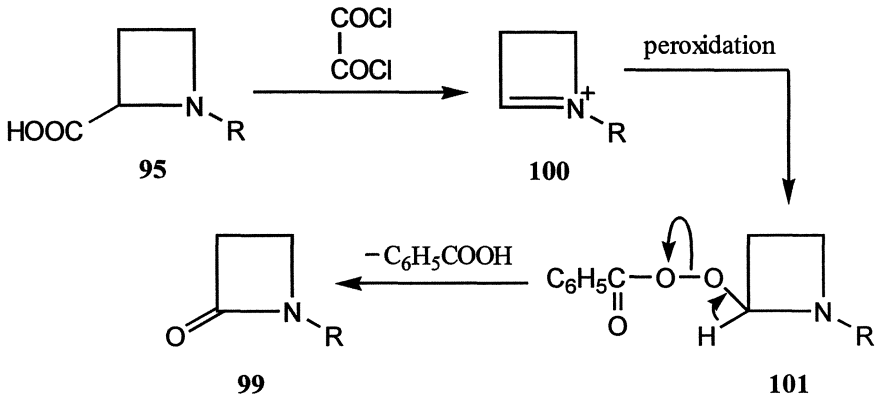
1.2.2.5 From Substituted Azetidines

The reaction of N-substituted azetidine-2-carboxylic acids **95** with lithium diisopropylamide results in the formation of β-lactams involving oxidative decarboxylation of the resulting dicarbanion intermediate **96** (scheme-30)[53].



Scheme-30

Alternatively, decarboxylation of azetidine-2-carboxylic acids with oxalyl chloride followed by peroxidation with *m*-chloroperbenzoic acid provides β-lactams **99** (scheme-31).

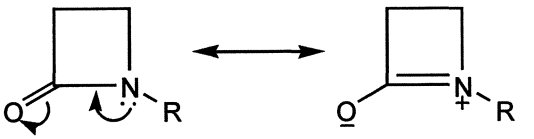


Scheme-31

1.2.3 Reactions

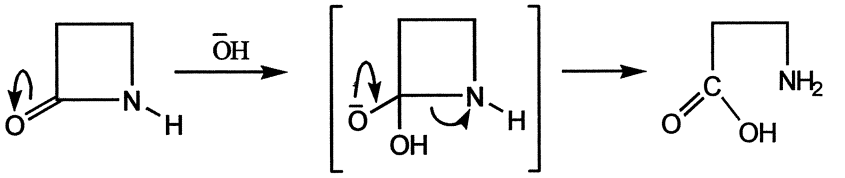
1.2.3.1 Ring Opening Reactions

β-Lactams are considerably more reactive than the acyclic amides and the larger ring lactams because of the ring strain. The additional ring strain in the resonating form **102a** compared to in the form **102b** makes the carbonyl group of β-lactam more like an ester carbonyl group. The resonating form **102a** makes the β-lactam carbonyl more electrophilic than an acyclic amide and thus carbonyl group in β-

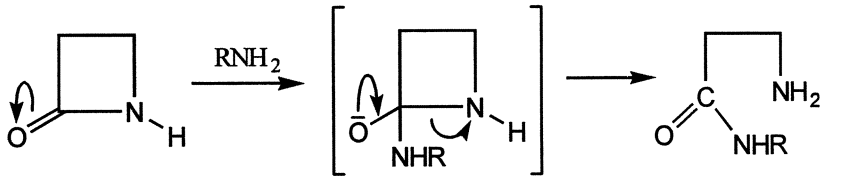


102a **102b**

lactams is more susceptible towards the nucleophilic attack. The ring strain after the addition of nucleophile facilitates the cleavage of ring (acyl–nitrogen bond fission). β-Lactams undergo ring opening reaction in the presence of a base providing β-amino acids (scheme-32). Similarly, the reaction of β-lactams with amines involves the nucleophilic attack at the carbonyl carbon and proceeds with the cleavage of ring providing β-amino amides **103** (scheme-33).



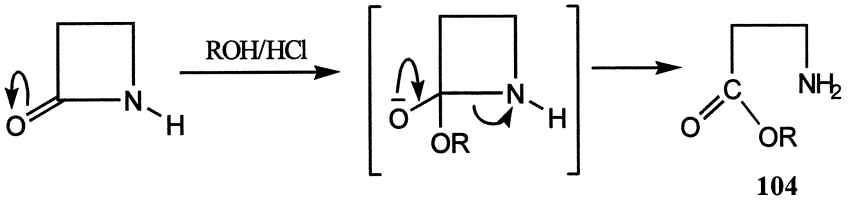
Scheme-32



103

Scheme-33

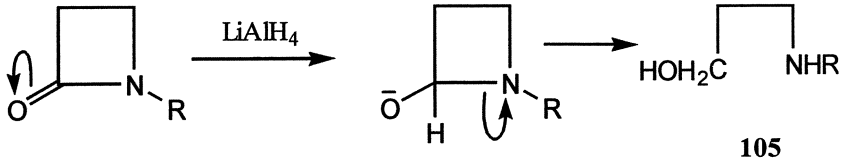
The acylating property of β-lactams is believed to be related to the antibacterial function of penicillins. The reaction of alcoholic hydrochloric acid with β-lactams also causes ring cleavage providing β-amino esters **104** (scheme-34).



104

Scheme-34

The reduction of β-lactams with lithium aluminium hydride results in the cleavage of ring yielding γ-amino alcohols **105** (scheme-35).

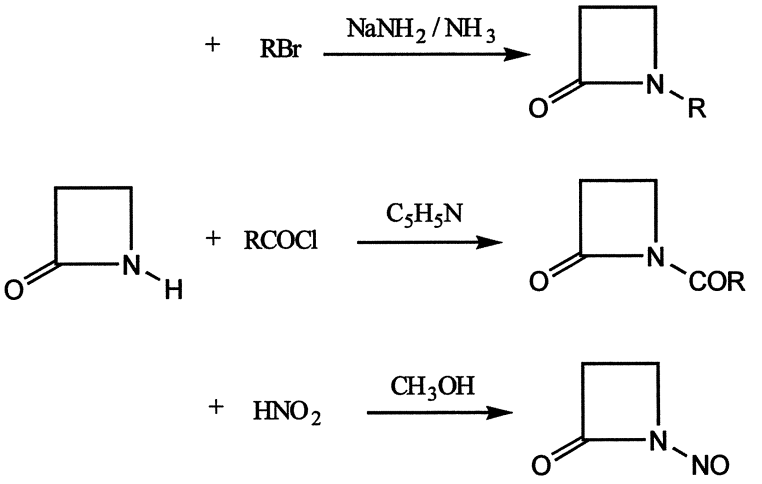


105

Scheme-35

1.2.3.2 Functionalization at Nitrogen

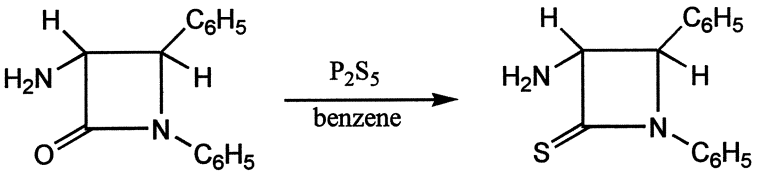
The nitrogen atom in N-unsubstituted β-lactams can be substituted by electrophiles in the absence of nucleophiles which can cause ring cleavage (scheme-36).



Scheme-36

1.2.3.3 Reaction with Phosphorus Pentasulfide

The reaction of β-lactams with phosphorus pentasulfide results in the formation of thiolactams **107** (scheme-37)[54].

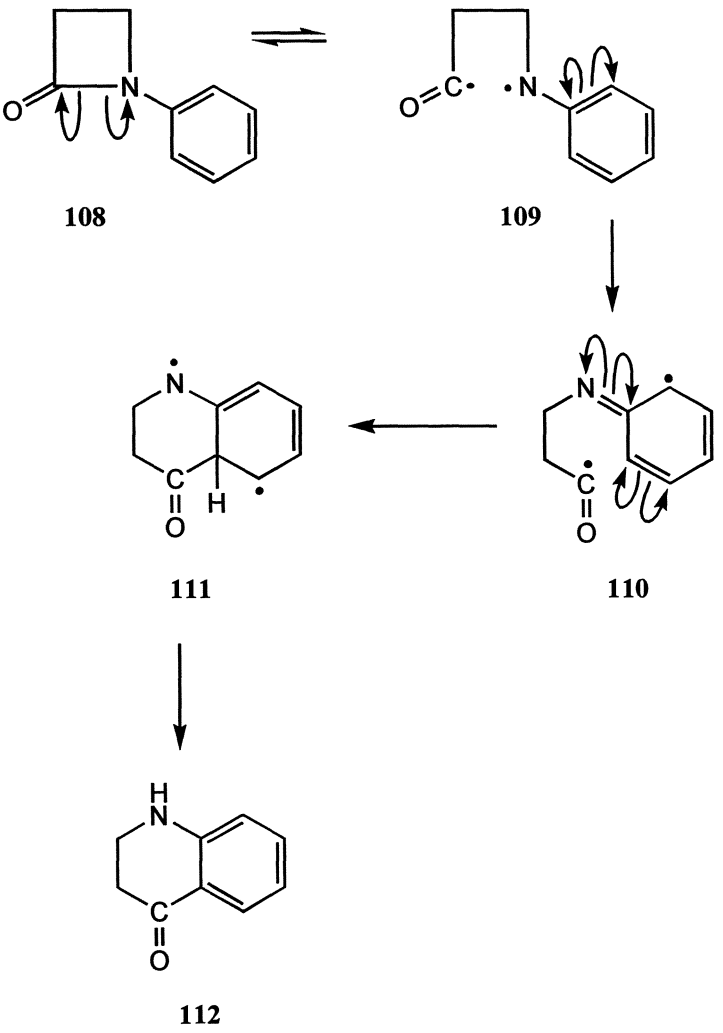


106 **107**

Scheme-37

1.2.3.4 Photochemical Reactions

Photolysis of N-phenyl-β-lactam **108** proceeds with the cleavage of C–N bond of the β-lactam ring via free radical mechanism (scheme-38)[55].



108 **109** **110** **111** **112**

Scheme-38