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Recent advances in β-lactam chemistry

Rajneesh Kaur,[1] Divya Tripathi,[1] Kuldeep Singh,[1] Raman Singh[1]*

Department of Chemistry, MMEC, Maharishi Markandeshwar (Deemed to be University), Mullana, Haryana – 133207, India

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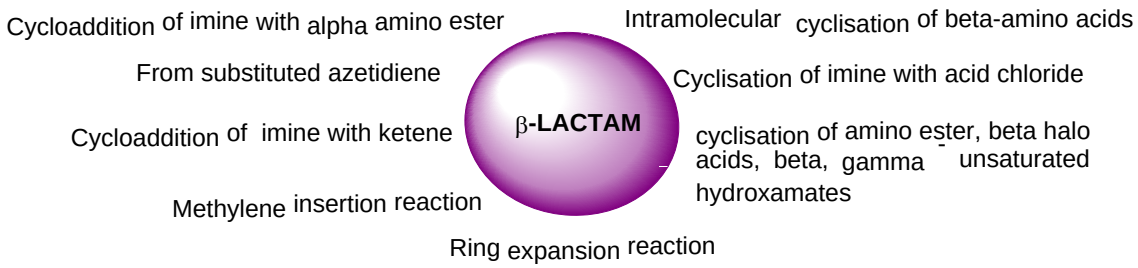
ABSTRACT



Beta-lactams are one of the essential heterocycles which have saved humans from deadly infections. Over the years many methods have been developed. This review classifies various methods based on reagents and reactions. It has been concluded that Ketene–Imine Staudinger Reaction is the method of choice.

Keywords: Beta-lactam, Antibacterial, azomethine linkage, antibacterial activity, antibacterial resistance

INTRODUCTION

Heterocyclic compounds or Heterocycles are cyclic organic molecules with atleast one. hetero atom other than carbon and hydrogen.[1] Any class of organic molecule in which three or more atom joined to form a cyclic structure containing one or more heteroatom are classified as heterocyclic compound. The cyclic part in heterocycles indicates at least one ring is present in the structure and prefix hetero represents presence of at least one atom other than carbon in the ring.

Heterocyclic compounds plays a vital role in human life. They have various biological activities and also used in production of different type of materials. Presence of hetero atoms such as nitrogen, oxygen and sulfur, shows many biological activities like antibacterial,[2–8] anti-tubercular,[9–11] anti-inflammatory,[12] anti-HIV,[13] analgesic, anti-diabetic,[14] anti-cancer and anticonvulsant etc (Figure -1).[15–17] They also participate in important biochemical processes and are the constituents of main substances like DNA and RNA in living cells.

The Heterocyclic compound may be aromatic and non aromatic. The aromatic heterocycles are classified into five membered ring and six membered ring. The nomenclature of six memberd aromatic heterocyclic ring that contain nitrogen generally end with “ine”. But note that very important heterocyclic system purine which is bicyclic system with both six memberd and five membered nitrogen cotaining heterocyclic ring. Five membered aromatic heterocycles that contain nitrogen is generally end with “ole”.

Six membered aromatic heterocycles are pyridine, quinoline, isoquinoline pyridazine, pyrimidine etc. Non-aromatic heterocycles are pyrrolidine, piperidine, morpholine, tetrahydofuran, dioxane, tetrahydopyran.[18–25]

The important five membered heterocycles are pyrrole, furan and thiophene.[26] The main reason for the study of five membered ring is its biological role. Pyrrole is structural part of haeme, the blood respiratory pigment and chlorophyll; green photosynthesis pigment which is important for plants. Thiophene occur in plants. Furan is widely occur in secondary plant metabolites.[26–31]

Small ring heterocycles includes four membered and three membered ring system. Most of the systems are nonaromatic. The bond angle strain is large in small ring heterocycles. The ring strain in small membered is due to the bond angle deviation. Due to the presence of unsaturation in the small ring, increase in angle strain.

Corresponding Author: Dr. Raman Singh, Department of Chemistry, Maharishi Markandeshwar (Deemed to be University) Mullana, Haryana – 133207, India
Tel: +91-805-993-0802
Email: raman@orgsyn.in

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Strateties to incorporation of heterocyclic system in desired molecule involves two main methodologies:[18,32–35] (i) Directly substituting a heterocyclic moiety; (ii) constructution of heterocyclic ring system from substituted acyclic precursor.

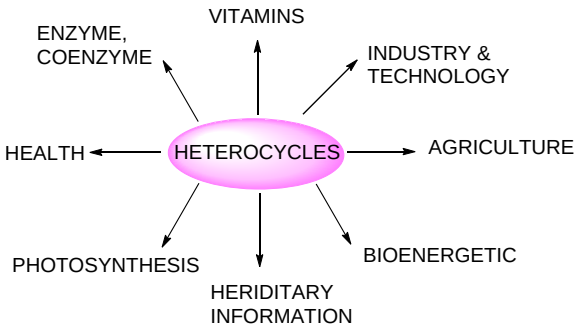


Figure 1 Application of heterocycles

BETA-LACTAM

β-Lactam are carbonyl derivative of azetidines which contain carbonyl group at position-2.[1] Thus, β-lactam is also called 2-azetidines. β-lactams not fused with any other ring system are grouped as monobactams. The chemistry of β-lactam is of great importance, mainly because of its presence in antibacterial agents and other bioactive molecules.[36]

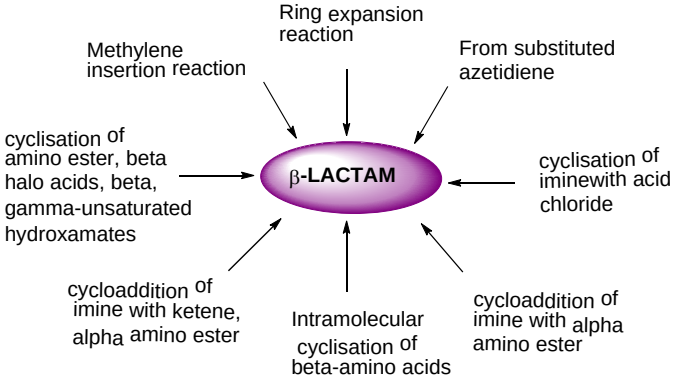
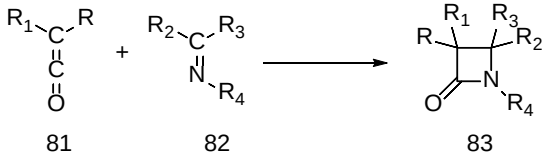


Figure 2: Various methods for preparation of beta-lactam

METHODS OF PREPARATION OF BETA-LACTAMS

CYCLOADDITION OF IMINE WITH KETENE:

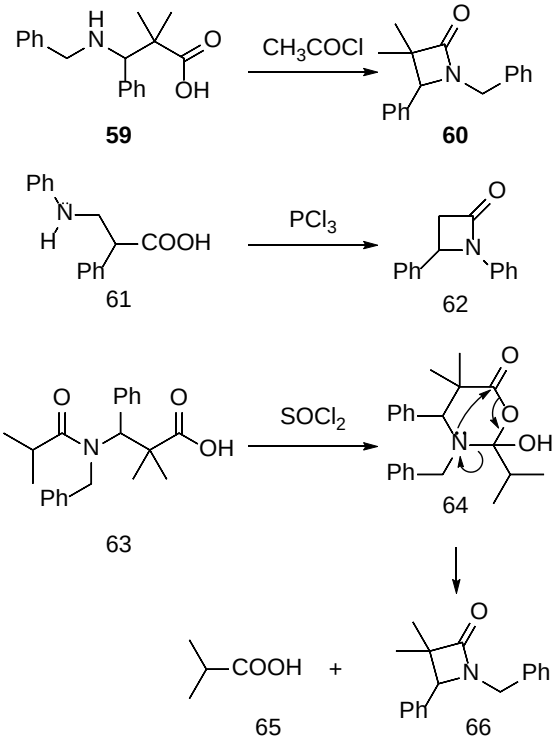
Cycloaddition of ketoketene with imine is the most general and useful method for the synthesis of β-lactams and their derivatives (Scheme – 1).[37–41] The centuary old reaction is popularly known as the Ketene−Imine Staudinger Reaction.[42–44]



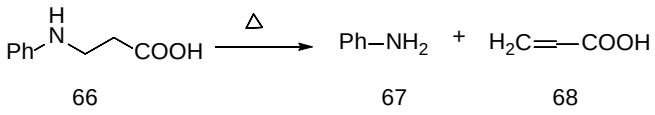
Scheme 1: Ketene−Imine Staudinger Reaction

INTRAMOLECULAR CYCLISATION OF BETA AMINO ACIDS:

Intramolecular cyclisation reactions of β-aryl-β-amino acids produce a great diversity of cyclic derivatives with numerous biological and therapeutic properties.[45] Intramolecular cyclisation of beta amino acids in presence of acyl chloride, phosphorus trichloride or thionyl chloride give β-lactam (Scheme - 2). β-aminopropanoic acid does not cyclised to give beta lactam, but gives elimination reaction to yield amine and acid (Scheme- 3).[46–48]



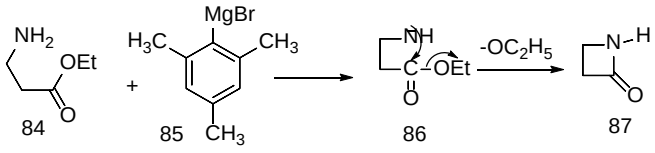
Scheme 2



Scheme 3

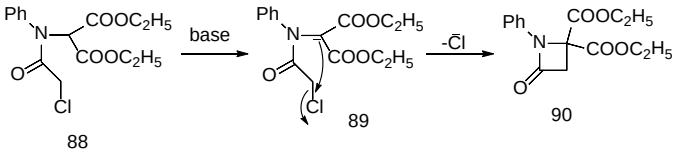
CYCLISATION OF AMINO ESTER-

The reaction of beta amino ester with Grignard reagent give beta lactam via the formation of *N*-anion. The reaction of mesityl magnesium bromide with beta lactam at carbonyl site prevented due to steric nature (Scheme-4).[48,49]



Scheme 4

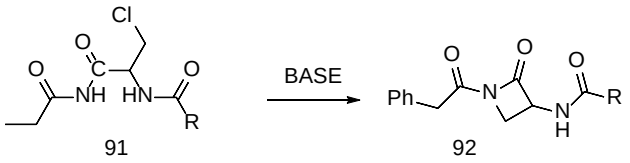
N-substituted diethyl malonate is catalysed by base to give β-lactam(scheme-5).[50]



Scheme 5

CYCLISATION OF BETA-HALO ACIDS

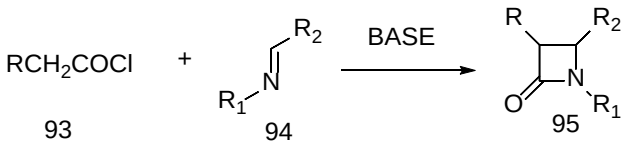
The reaction of beta amino acids with CH_2X at alpha carbon in presence of base gives beta lactam (Scheme-13).[51,52]



Scheme 6

CYCLOADDITION OF IMINE WITH ACID CHLORIDE

The reaction of acid chloride in presence of base gives beta lactam (Scheme-7).[40,41,53,54] The reaction mechanism involves direct acylation of imine with acid chloride giving N-acylium chloride which is in equilibrium with chloramide.[55]

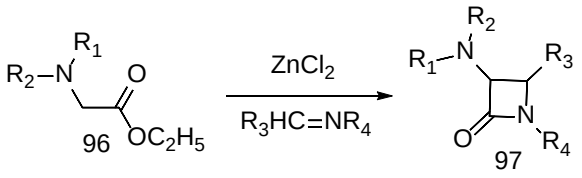


Scheme 7

The reaction has been extended to hydrazones, cyclic imines and other azomethine containing systems.[56–59]

CYCLOADDITION OF IMINE WITH ALPHA AMINO ESTER

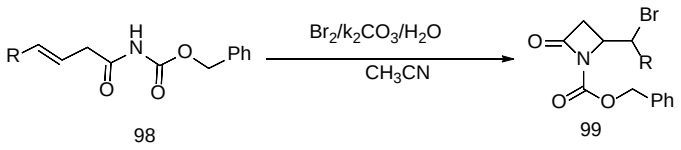
The reaction of imine with alpha amino ester in the presence of zinc chloride gives sterioselective β-lactum involving the formation of zinc enolates. The nature of solvent and substituent present on an imine affect the reaction steriochemically (scheme-8).[60,61]



Scheme 8

CYCLISATION OF β, γ- UNSATURATED HYDROXAMATES-

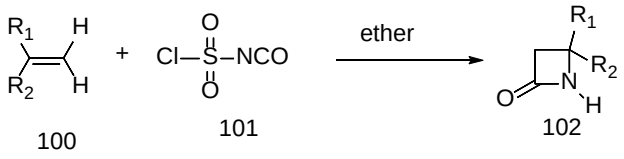
The reaction is induced by bromine. Cyclization of o-acyl-β, γ hydroxymates give β-lactam by the formation of bromonium ion intermediate. The cyclisation in the presence of phenyl group at γ position fail to give β-lactam because due to the formation of stablised benzylic carbonium ion the regioselectivity of opening of brominium ion is reversed.(scheme-9).[62]



Scheme 9

CYCLOADDITION OF OLEFINS TO ISOCYANATES:-

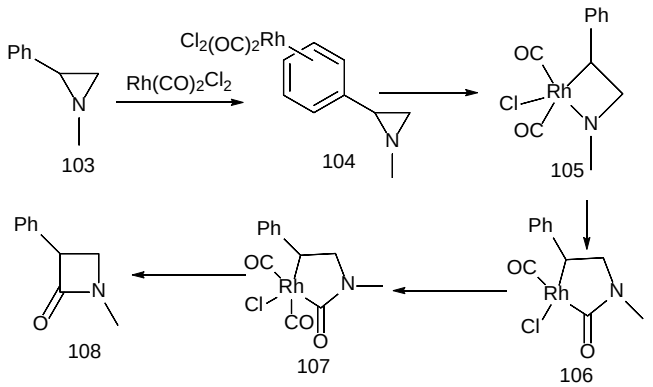
The reaction provides β-lactam by [2+2] cycloaddition of nucleophilic olefins and isocyanates. In these raction chlorosuphonyl β-lactam is formed. It is formed by the reaction of chlorosulphonyl isocynate and olefins. The N-unsubstituted β-lactam is formed by the easily removal of chlorosulphonyl group during workup (scheme-10).[63]



Scheme 10

RING EXPANSION REACTION:-

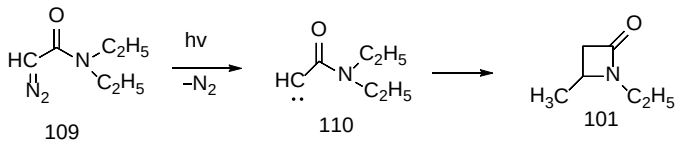
In these reaction the rhodium(1) catalyst is used. Rhodium (1) catalyzed carbonylation of aziridine give β-lactam through the expansion in the ring with the insertion of CO into the more substituted C-N bond.[64] The reaction is proceed by retention in configuration and the process is stereospecific and enantiospecific. In case of using nickel carbonyl as a catalyst the reaction is occur with the insertion of carbonyl into the less substituted C-N bond(scheme-11).[65–67]



Scheme 11

METHYLENE INSERTION REACTION-

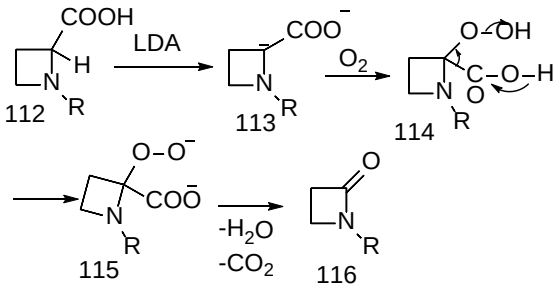
The reaction proceeds with the insertion of methylene group in the carbon-carbon bond formed β-lactam. This reaction is photochemical reaction(scheme-12).[68,69]



Scheme 12

FROM SUBSTITUTED AZETIDINE:

The reaction N-substituted azetidiene-2-carboxylic acids in the presence of lithium diisopropylamide give β-lactam(scheme-13).[70]



Scheme 13

CONCLUTIONS

Beta-lactams are one of the essential heterocycles which have saved humans from deadly infections. Over the years many methods have been developed. This review classify various methods based on reagents and reactions. It has been concluded that Ketene−Imine Staudinger Reaction is the method of choice.

ACKNOWLEDGMENTS

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