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SYNTHESIS OF β-LACTAM AND THEIR REACTIVITY

N.A.A. El-Kanzi*[(a,b)]

a- *Chemistry Department, Faculty of Science, Aswan University, Aswan, Egypt.*
b- Chemistry Department, Faculty of Science, Al Jouf University, Sakaka, Al Jouf
E-mail:nadiaelkanzi88@yahoo.com

Abstract: The review summarizes literature dealing with the synthesis of, β-lactam and reactivity of β-lactam.

Key words:, β-lactam, reactivity of β-lactam, synthesis.

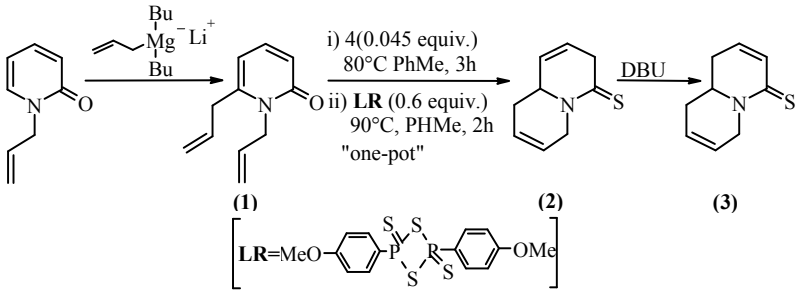
Contents:

Introduction

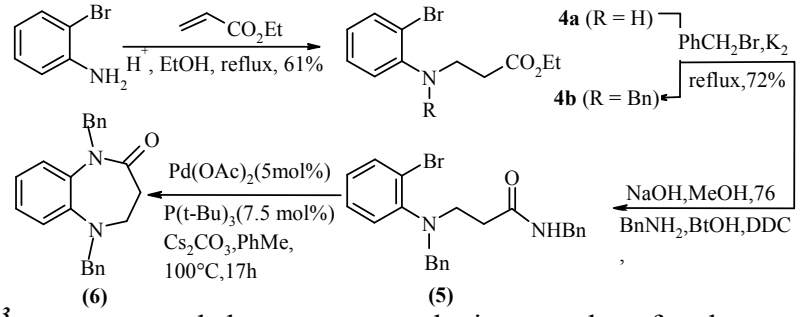
I- Synthesis of β-lactam

Jacek G. 2009[1] was reported that, α,β-unsaturated δ-thiolactams have been recognized as good Michael acceptor, where, they form C-C bonds in reactions with C-nucleophiles: alkyl lithium, alkyl magnesium, lithium enolate and with aliphatic nitro compounds in the presence of a base catalyst. Also, he reported that, it is easy synthetic approach to mono- and bicyclic derivatives of 5,6-dihydro-1H-pyridine-2-thiones by ring closing metathesis (RCM) and thionation using Lawesson's reagent followed by isomerization of 3,6-dihydro-isomers. RCM/thionation/isomerization applied successfully to N,6-diallylic β,γ-unsaturated lactam **(1)**

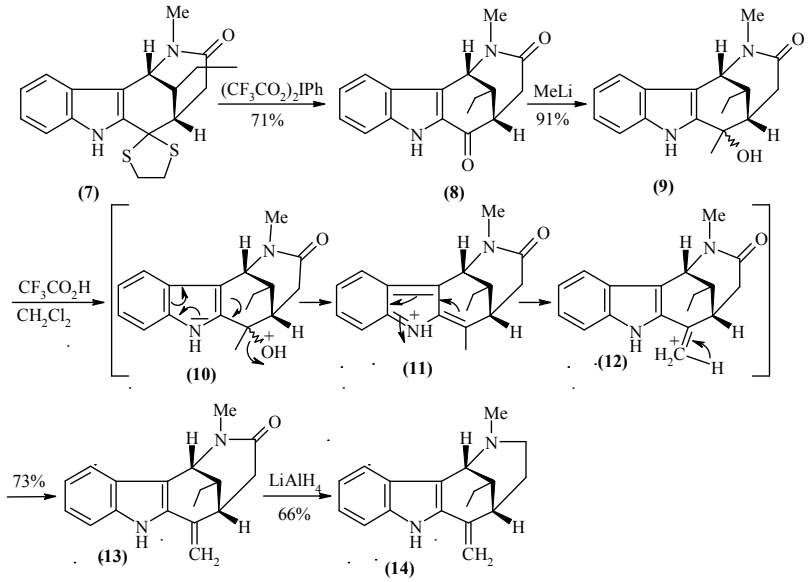
providing unsaturated thiolactams **(2)** and **(3)** possessing bicyclic quinolizidine in high yields in the following Scheme.



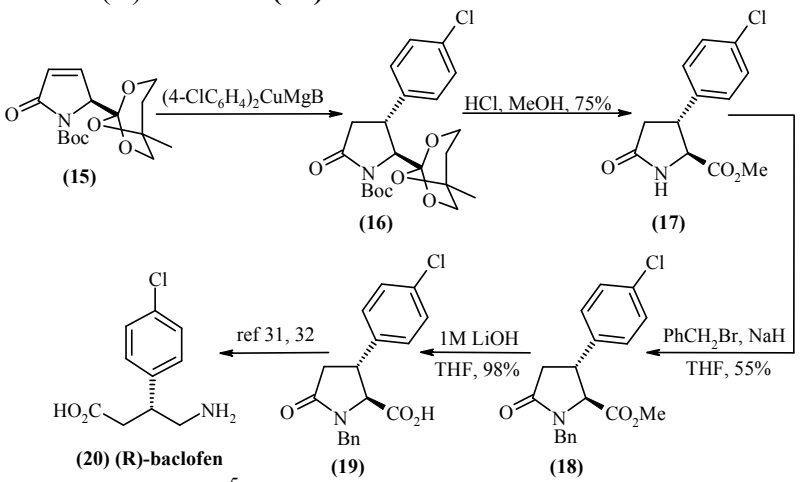
Emma L. Cropper et al.[2] were reported that, Pd-catalysed C-N bond forming reactions between N-nucleophiles and aryl halides attracted a tremendous amount of attention and are becoming increasingly common in industrial processes. Also, pd-catalysed protocol was applied to synthesis of 1,5-benzo-diazin-2-one **(6)** according to the following Scheme. Where compound **(4)** was prepared by an aza-Michael reaction between 2-bromoaniline and ethyl acetate, followed by N-benzoylation to form the benzylamide **(5)** via standard procedures, followed by cyclization to form **(6)**



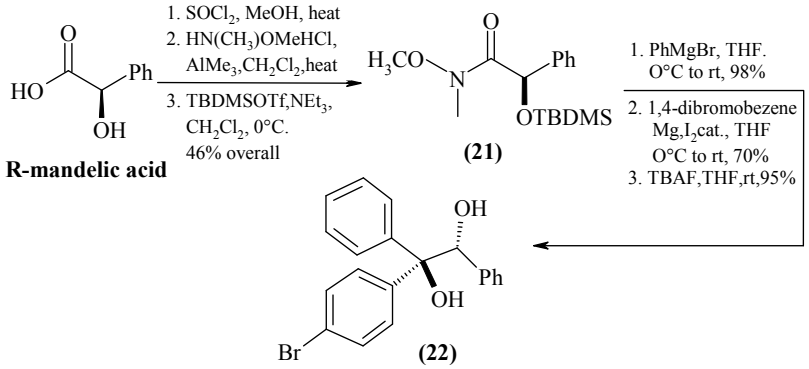
Suleyman *et al.*[3] were reported that, a new synthetic procedure for the total synthesis of the alkaloide (±)-epiddasycarpidone by an acid ctalysed ring closure of racemic cis-3-ethyl-4-oxo-2,3,4,9-tetrahydro-carbazole derivatives. This leading to synthesize (±)-uleine **(14)** where, the uleine group starts either from 2(4-piperi-dinylmethyl)-indole, 3(2-iperidinylmethyl)indole, or with Fischer indolization of 2-azabicyclo[3.3.1]nonane. (±)-uleine can be accomplished by removing of the protecting group in compound **(7)** by treatment with [bis(trifluoroacetoxy)iodo]-benzene in acetonitrile : water (9:1) to give compound **(8)**, which can be converted into compound **(13)**. By treatment compound **(8)** with methyllithium can be transformed into alcohol **(9)**. The dehydration of **(9)** with trifluoroacetic acid transformed into **(13)**. The reduction of compound **(13)** with $LiAlH_4$ in tetrahydrofuran led to the alkaloid (±)-uleine **(14)**



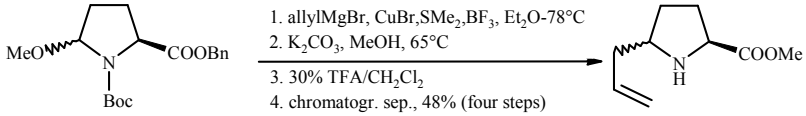
***Makoto Oba et al.*, 2009**[4] have reported that, (R)-baclofen can be synthesized by the treatment of Michael acceptor **(15)** with Grignard-cuparates containing phenyl and 4-chlorophenyl groups to produce the 1,4-adducts **(16)** in 68% yield, which (R)-baclofen is known as a muscle relaxer and an antipastic and the preparation of (R) baclofen can be achieved by methanolysis of **(16)** followed by LiOH-promoted hydrolysis of methyl ester yielded pyroglutamic acid **(19)**. The acid **(19)** can be converted to (R)-baclofen **(20)** as described.



Johannes C. Vogel et al., 2008[5] have been reported that, 1,2,2-Triphenyl-1,2-diol can be prepared from R-mandelic acid with phenylmagnesium bromide and 4-bromophenylmagnesium bromide followed by TBAF deprotection of the resultant secondary alcohol to give **(22)**.

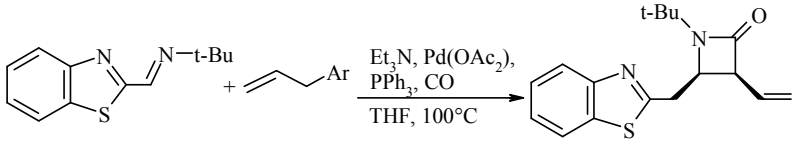


Giordano Lesma et al., 2008[6] have been reported the allyl-proline derivative **(24)** was obtained through a stereoselective allylation on precursor **(23)** using allylmagnisium bromide with CuBr:Me_2S complex in the presence of BF_3 etherate at - 78°C according to slight modifications of a reported protocol, the 5-allyl-N-Boc-proline ester. After trans esterification in refluxing methanol with an excess of K_2CO_3 the Boc group was removed with 30% TFA in CH_2Cl_2.



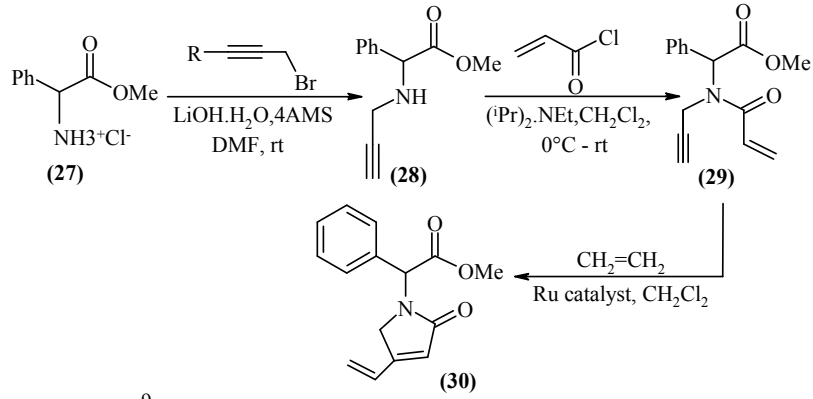
(23) **(24)**

Luigino Troisi et al., 2008[7] have been reported that, N-alkyl-4-aryl-3-vinyl-2-azetidinones, (E)-arylidenalkyl amines, **(26)** have been synthetized following a palladium-catalyzed [2+2] cycloaddition with allyl bromide under Copressure (300-400psi), in THF and $Pd(OAc)_2/PPh_3$ as the catalyst system, in the presence of triethylamine.



(25) **(26)**

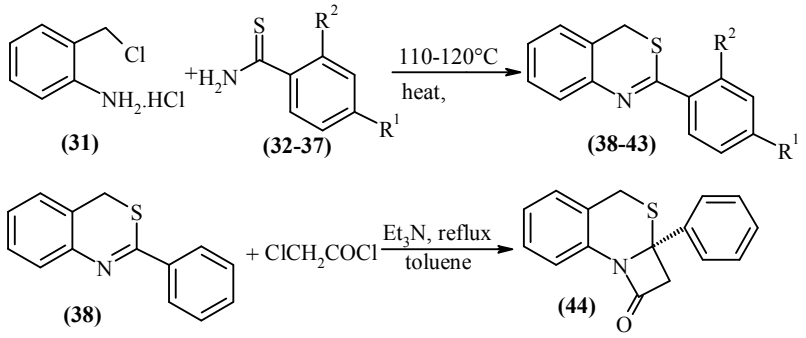
Qian Yuan et al., 2008[8] said that, the ringe-closing enyne **(29)** metathesis reaction of alkyl 2-(N-alkyl acrylamido)ester using the first generation Grubbs' catalyst afforded five-membered lactams bearing a 1,3-diene in high isolated yields. In the reaction process, the presence of ethylene gas is essential. The reaction of **(29)** with ethylene in the presence of Ru catalyst in methylen chloride formed 4-vinyl α,β-unsaturated γ-lactam **(30)**.



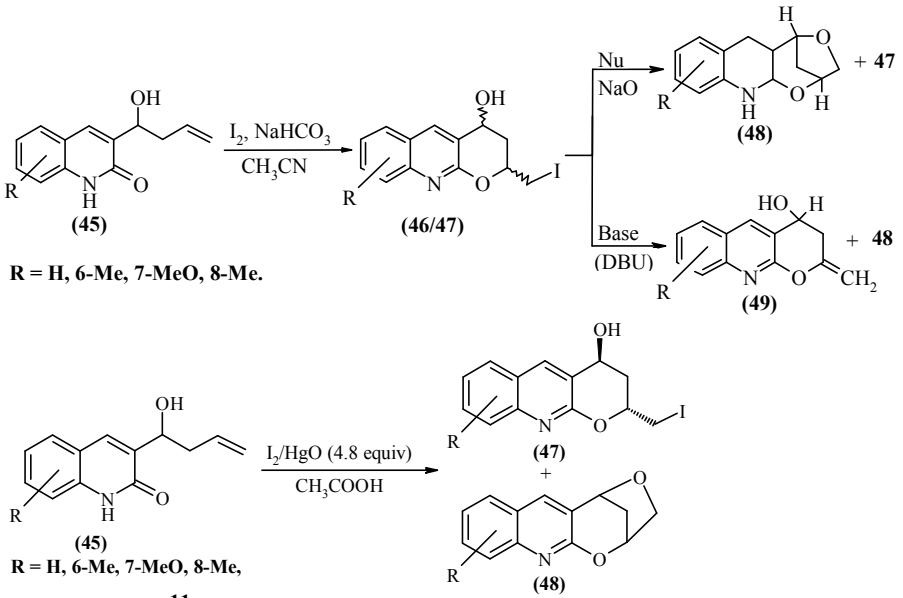
(27) **(28)** **(29)** **(30)**

Peter Cosomos et al., 2008[9] showed that with the starting 2-aminobenzyl chloride hydrochloride **(31)**, which can be obtained by treatment of 2-aminobenzyl alcohol with thionyl chloride, fusion of **(31)** with thiobenzamides **(32-37)** [**32**, $R^1 = R^2 = H$; **33**, $R^1 = Cl$, $R^2 = H$; **34**, $R^1 = CH_3$, R^2 H;

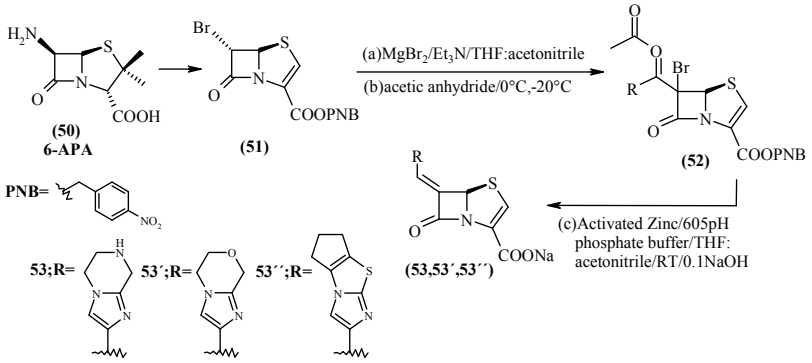
35, R^1 = H, R^2 = Cl; **36**, R^1 = H, R^2 = CH_3; **37**, R^1 = H, R^2 = OCH_2CH_3] provided the key intermediate 4H-3,1-benzothazine derivatives **(38-43)** [**38**, R^1 = R^2 =H; **39**, R^1 = Cl, R^2 = H; **40**, R^1 = CH_3, R^2 H; **41**, R^1 = H, R^2 = Cl; **42**, R^1 = H, R^2 = CH_3; **43**, R^1 = H, R^2 = OCH_2CH_3] the reaction of **(38)** with chloroacetylchloride in dichloromethane in the presence of triethyl-amine as catalyst. When the reaction was carried out in refluxing benzene, azeto[2,1-a][3,1]benzothiazin-1-one **(44)** can be synthesized.



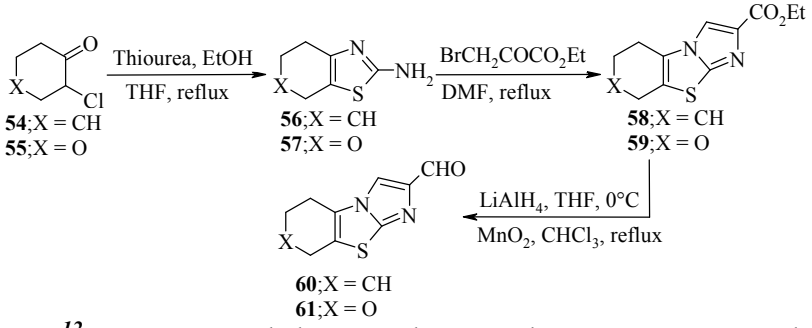
Bahawana Singh et al., 2008[10] have been synthesized the diastere-omeric 2,4-disubstituted pyrano [2,3-b]quinolines **(46/47)**, via intra-molecular cyclization of 3-homo-allyl-2-quinolines **(45)** with iodine and sodium bicarbonate in THF with either base or nucleophiles afforded tetracyclic pyranoquinolines **(48)**. Thus, the variations in reaction times that alter the trans/cis ratios provide evidence for the intramolecular electrophilic/ nucleophilic cyclization to produce **(48)**.



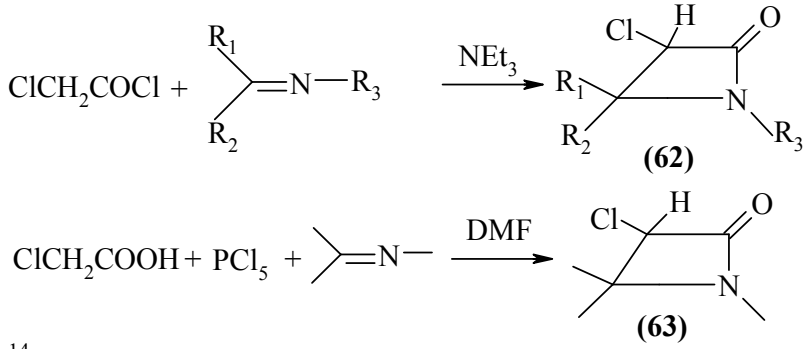
Aranapakam et al ., 2008[11] report that 6,5-fused bicyclic heterocyclic or 5,5,5-fused tricyclic heterocyclic are effective broad-spectrum β-lactamase inhibitors. Compounds **(53,53′,53′′)** were synthesized on the bases of both modeling experiments and mechanistic and were found to be potent both in vitro and in vivo, The tricyclic heterocyclic heterocyclic bearing 6-methylidine penem carboxylic acid sodium salt 12a-g were prepared by a novel two-step aldolcondensation and reductive elimination procedures.



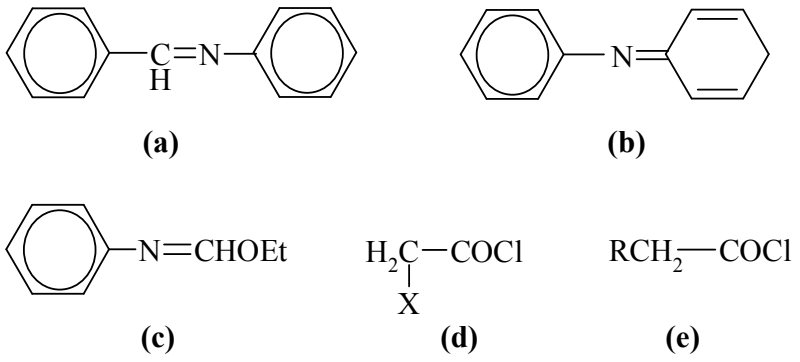
Also, the aldehydes intermediates **(60** and **61)** can be synthesized as follows;



Ferando et al., 1970[12] were reported that α-Halogenated **(62)** were prepared by interaction of monochloroacetyl-chloride with Schiff bases derived from aliphatic or aromatic amines in the presence of NEt_3. However, ***Ziegeler et al., 1986***[13] were report that single isomer of diaryl-3-halo-2-azetidinone **(63)** had been prepared by the addition of haloacetic acid and phosphoryl chloride, in DMF, to imine .

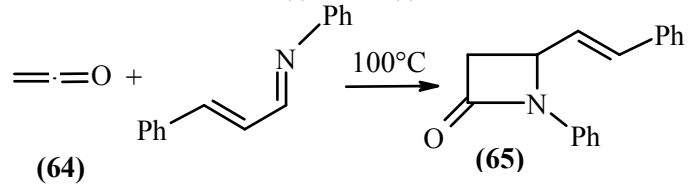


Bose et al., 1972[14] have reported that three types of Schiff bases (a, b and c) and two types of acid chlorides (d and e) were prepared from the point of view of preparation of.

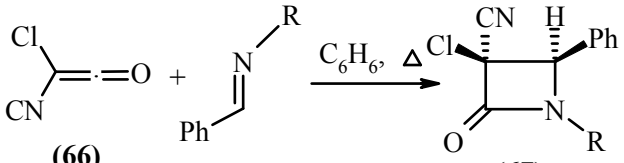


The acid chlorides possessing a nitrogen, oxygen, sulphur or chlorine atoms in the α-position (group **d**) and an alkyl or aryl group in this position (group e) reacted with Schiff bases **(a)** to give. The class **(d)** type of acid chlorides reacted wiyh Schiff bases **(b)** and **(c)** but the class **(e)** failed to react. The acid chlorides of class **(e)** gave only trans- with Schiff bases (a) whereas both geometric isomers were obtained from **(a)** and acid chlorides of class **(d)**.

Katagiri et al., 1983[15] and Moore et al., 1985[16] were reported that ketenes for example, ketene **(64)** and ketene **(66)** react with imines, formimidates, and thioformimidates to give 3-cyano-2-azetidinones with trans stereochemistry at $C_{(3)}$ and $C_{(4)}$.

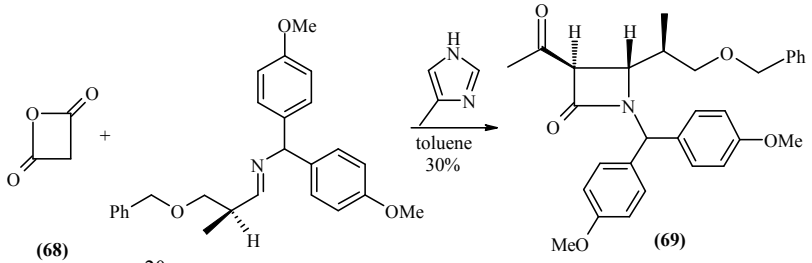


(64) **(65)**



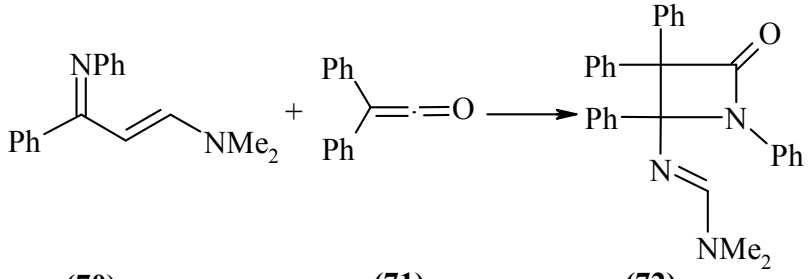
(66) **(67)**

Soto et al., 1983[17], Kawabata et al., 1988[18], Ito et al., 1989[19] have reported that the reaction of diketene **(68)** with imine gave β-Lactam **(69)**.



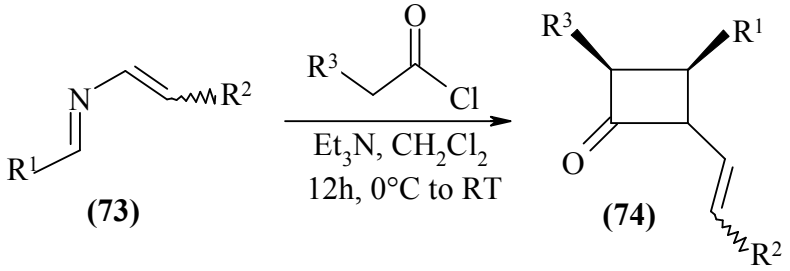
(68) **(69)**

Mazumdar et al., 1986[20] have reported that 1,3-diaza-1,3-dienes **(70)** react with diketene **(71)** to give β-Lactam **(72)**.



(70) **(71)** **(72)**

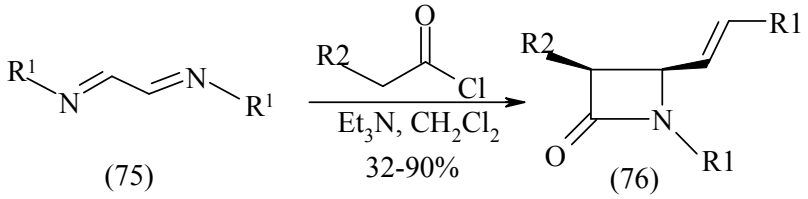
The majority of synthesis of β-Lactams via the Staudinger reaction are produced from acid chlorides or other ketene precursors. ***Bari et al., 1992***[21] and ***Bachi et al., 1993*** [22]were reported that various imino substrates have been used including dithio carbonate imins, 2-aza-1,3-dienes **(73)** react with acid chloride to give β-Lactams **(74) [*Georg et., 1988[23], 1990[24]* and *1993*[25]]**.



(73) **(74)**

R^1 = Ph, PhCH=CH, PhCH=CMe, Ph_2C=CH; R^2 = H, Me;
R^3 = PhO,Phth

Lasarte et al., 1989[26] was reported that the reaction of acid chloride with α,β unsaturated imines give β-Lactam, also ***Alcaide et al., 1992***[27] report that 1,4-diaza-1,3-dienes **(75)** react with acid chloride to give β-Lactam **(76)** ***Alcaide et al., 1992***[27].

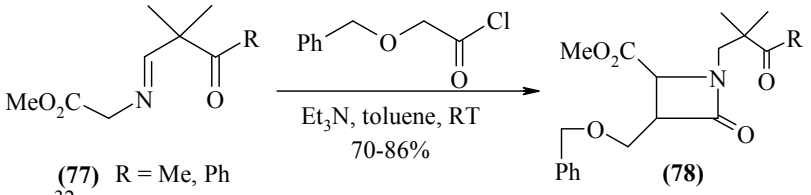


(75) (76)

R1 = PMP or CH(PMP)2;
R2 = Ph,Me,PhS, PhCH2O, PhO, Et, Pri, Cl, Phth,Br,Vinyl.

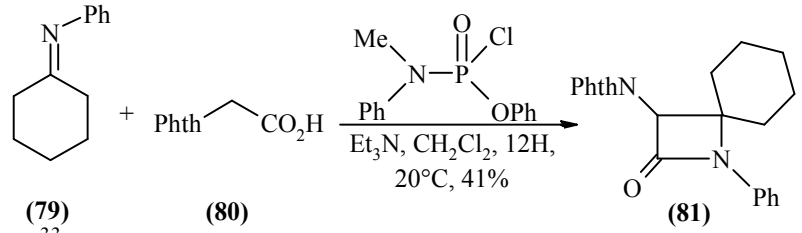
Also hydrazones and α-fluoro aldimines react with acid chloride to give β-Lactam ***Sharma et al., 1990***[28] and ***Yoshioka et al., 1984***[29].

Lunch et al., 1989 [30]and ***Alcaide et al., 1993***[31] have reported that 1,2-iminoketones, for example, **(77)** react with acid chloride to give β-Lactam **(78)**.



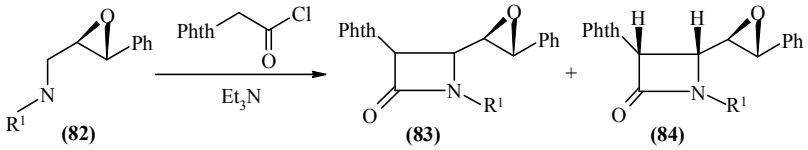
(77) R = Me, Ph **(78)**

Shridhar et al., 1984[32] have reported that the ketimines, for example, (**79)** react with **(80)** to give β-Lactam **(81)**.



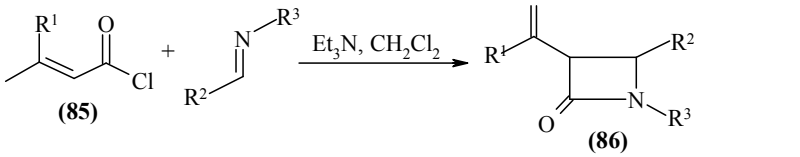
(79) **(80)** **(81)**

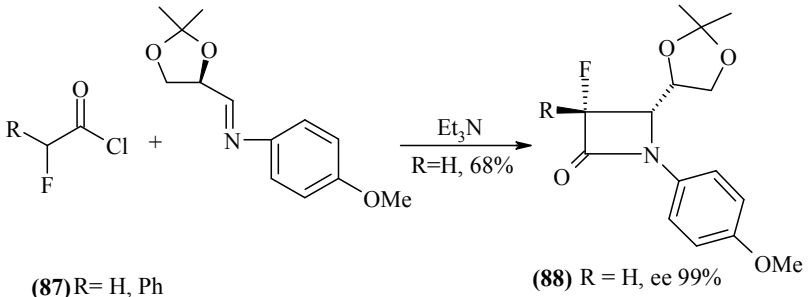
Evans et al., 1988[33] was reported that imines derived from chiral α,β-epoxyaldehydes, for example, **(82)**, have been shown to be good chiral glyoxal imine synthons in ketene-imine cycloaddition reaction. This process, which proceeds with high levels of reaction diastereo-selection, affords enantiomerically pure cis-substituted 3-amino-4-alkyl-2-azetidinones **(83, 84)**.



(82) **(83)** **(84)**

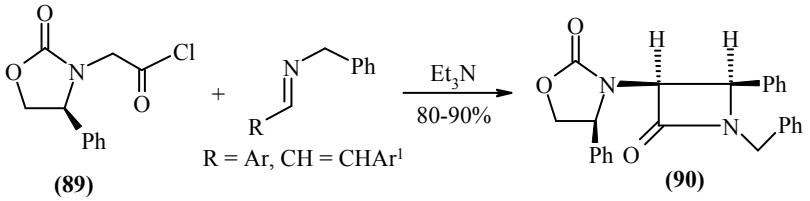
Herdewijn et al., 1983[34], ***Ghosez et al., 1991***[35] and ***Vander Steen et al., 1991***[36] had been reported that several types of ketene precursors have been used, including carboxylic acid chlorides, also α,β-unsaturate acid chlorides **(85)** ***Manhas et al., 1990***[37], α-fluoro acid chlorides **(87)** ***Welch et al., 1993***[38], α-sulfenylated acid chlorides ***Palomo et al., 1991***[39], and other α- or β-functionalized carboxylic acid chlorides, ***Ghosez et al., 1991*** [35]and ***Van der Steen et al., 1991***[36].



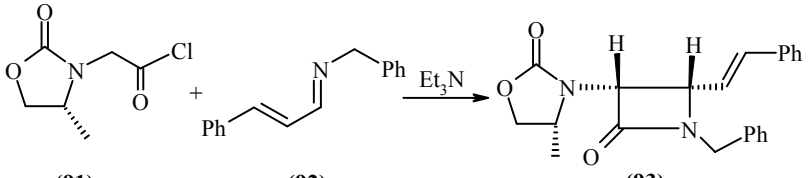


(87) R= H, Ph **(88)** R = H, ee 99%

Evants et al., 1985[40] was reported that use of phenyl-oxazolidinylacetylchloride **(89)** has been successful as a homochiral ketene synthon, which reacts with N-benzyl imines to give β-Lactams **(90)** with exceptional levels of asymmetric induction.



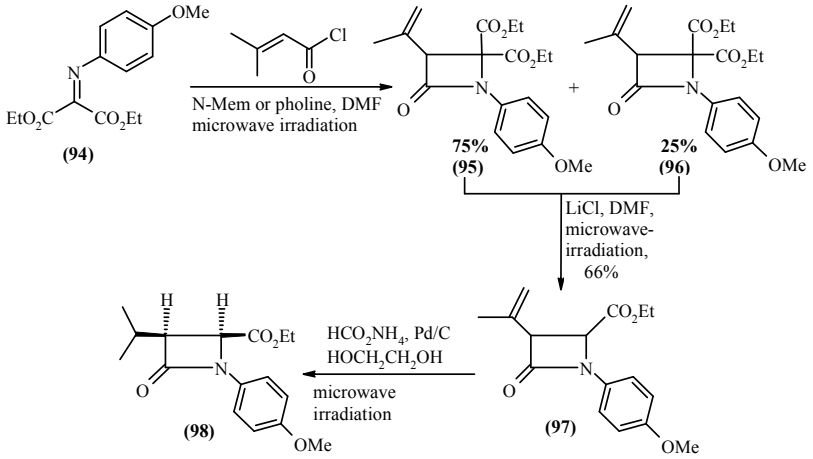
This process had been utilized for the synthesis of cis-3(R)-hydroxyl-4(S)-phenyl-1-(4-methoxyphenyl)-2-azetidine, which is a suitable precursor to the taxol side chain, ***Holton et al., 1993***[41] and the synthesis of a conformational analog of deoxy-boyvardin via β-Lactam **(93)** ***Boger et al., 1991***[42].



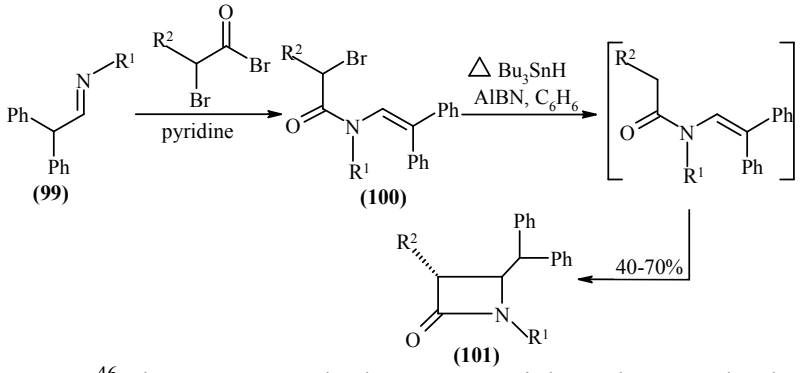
Hegedus et al., 1991[43] was reported that the stereo-selectivity of the reaction of benzylideneamines and cinnamaldimines had been compared with ketenes. The ketenes include those generated by the reaction of optically active oxazolidinone acid chlorides with triethylamine and complexe ketenes, generated by photolysis of optically active oxazolidine, and oxazilidinone, chromium carbine complexes in the presence of Et_3N. The absolute stereochemistry is determined primarily by the structure of the chiral auxiliary. The relative cis-trans stereochemistry is determine primarily by the structure of imine and the free or bound character of the ketene.

Banilk et al., 1993[44] was reported that a simplified and stereo-controlled synthesis of β-Lactams **(98)** starting from an oxomalonate imine has been achieved in open vessels under microwave

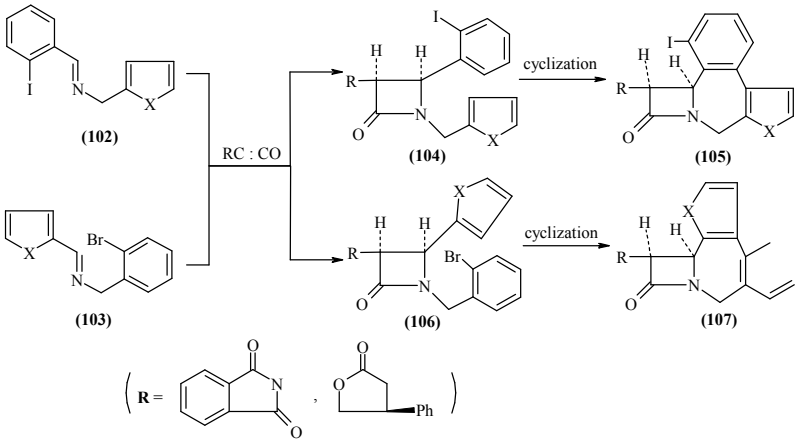
irradiation in an unmodified domestic microwave oven. Also isomerization of alkenyl groups and reduction of the carbon-carbon double bond occurs efficiently under microwave irradiation.



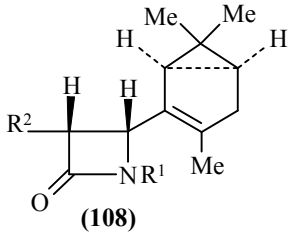
Fremont et al., 1991[45] was reported that diphenyl-acetalimines **(99)** react with α-bromoacylbromides in the presence of pyridine to afford enamides **(100)** which undergo free radical cyclization to form β-Lactams **(101)**.



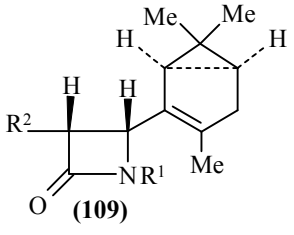
Matthew et al., 1995[46] have reported that sequential and cascade ketene-imine [2+2] cycloaddition-palladium ctalyzed cyclization reactions occure in good yield. Racemic an homochiral examples incorporating of aromatic and heteroaromatic rings are reported. Thus, imines **(102)** and **(103)** underwent cycloaddition with ketenes RC: C: O (R = OCH_2PH, R^1, R^2), to give lactams **(104)** and **(105)**. The β-Lactams were then cyclized to give polycycles **(106)** (Z = CH) and **(107)** respectively.



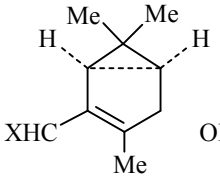
Jayaraman et al., 1996[47] was reported that the diastereo-selection in the synthesis of β-Lactams **(108)** and **(109)** [R^1 = PMP, $PhCH_2$, furfuryl, (R)-PhMeCH, (S)-PhMeCh, R^2 = PhThN, PhO, $PhCH_2$, MeO, ACO, N_3] via ketene-imine cyclo-addition (staudinger reaction) using different chiral auxiliaries has been examined. While sterically demanding imines derived from bicyclic aldehyde **(110)** (X = O) with a β-chiral center provided excellent selectivity, use of imines derived from bicyclic aldehyde **(111)** with a β chiral center was not effective. Improvement of stereoselectivity was also sought using imines **(112)** [X = NCHMePh-(R), -(S)] derived from chiral amines, (S)- and (R)-$PhMeCHNH_2$, and chiral aldehyde **(110)** (X = O). The bicyclic terpenoid skeleton of the chiral auxiliary in **(110)** (X = O) was dissociation by ruthenium tetroxide to give multiply functionalized β-Lactams **(112)** in good yield.



(108)



(109)



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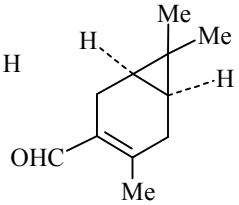
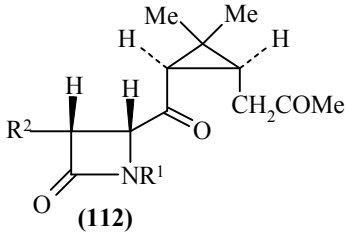
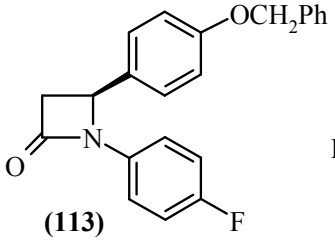


(111)

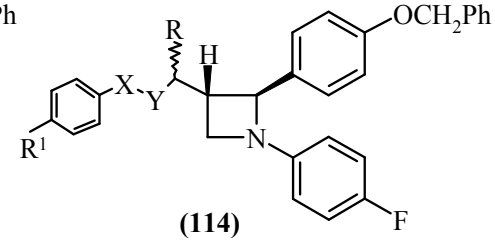


(112)

Shankar et al., 1996[48]was reported that the asymmetric induction by several chiral alcs. In the reaction of their bromo-acetates with imines in the presence of activated Zn (Reformatsky reaction) was studied. (-)-trans-2-phenylcyclo-hexanol and (-)-phenylmethanol gave β-Lactam **(113)** in > 99% ee via cyclization of the diastereoisomeric β-aminoester intermediates. The resulting chiral 3-unsubstituted azetidin-2-one **(113)** was converted to 3-substituted products **(114)** (R = OH, R^1 = F, X = O, Y = CH_2; R = R^1 = H, XY = CH = CH, $COCH_2$).

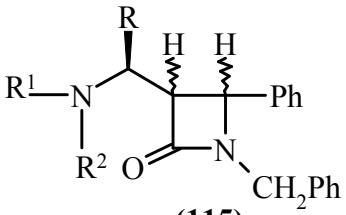


(113)



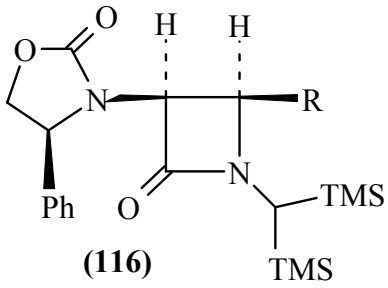
(114)

Joachim et al., 1996[49] was reported that the photochemical rearrangement of diazoketones (derived from suitably protected α-amino acids) in the presence of imines led to the diastereoselective formation of aminoalkyl substituted β-Lactams **(115)** (R = Me, Bu-i, Pr-i, Bu-S, CH_2Ph; R^1 = Boc, Cbz; R^2 = H; rlR_2N = Phthaloyl). Two diastereo-isomeric trans-substituted ring systems were formed with selectivity up to 93:7 and yields up to 90%.



(115)

Claudio et al., 1996[50] was reported that the reaction of a chiral oxazolidineacetyl chloride with α-bis(trimethylsilyl) methyl imines gave exclusively cis and trans β-Lactams **(116)** [R = Me, Et, Pr, $(CH_2)_2Ph$, CH_2Ph, Pr-i, CH_2OCH_2-Ph, $(CH_2)_2CO_2Bu$-t] with good to excellent diastereomeric selectivities and complete asymmetric induction at C_3. **(116)**[R = Me] was deprotected in a multistep process to give **(117)** [R = Me].



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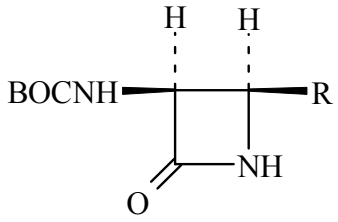
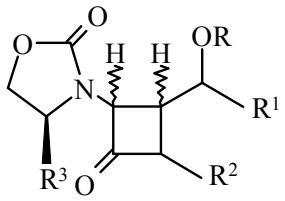
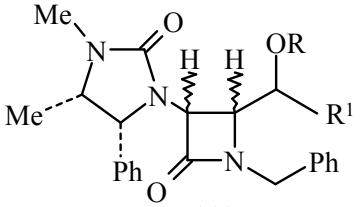


(117)

Claudio et al., 1996 [50]have reported that the cis-azetidin-2-ones **(118)** [R = $SiMe_2CMe_3$; R^1 = Me, Ph; R^2 = benzyl, (R), (S)-$PhCH(CH_3)$; R^3 = Ph, $(CH_3)_2CH$, $(CH_3)_3C$] and **(119)** (R =$SiMe_2CMe_3$; R^1 = Me, Ph) were stereoselectively prepared from the corresponding enantiomerically pure oxazolidinyl- or imidazolidinylacetyl chlorides and imines of lactalehyde or mandel-aldehyde. The absolute configuration of C_3 and C_4 positions of the azetidinones was mainly dictated by the intermediate ketene formed from the chiral acetyl chlorides. E.G., β-Lactam **(120)** (R = $SiMe_2CMe_3$) was formed in 56%yield as the major cis-diastereomer by stereo-selective cycloaddition of (S)-acetylchloride **(121)** and (S)-$PhCH_2N$-CHCH-(Me)$OSiMe_2CMe_3$.



(118)



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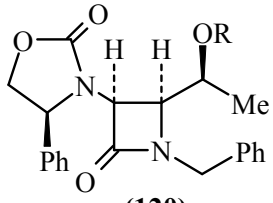
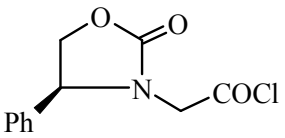


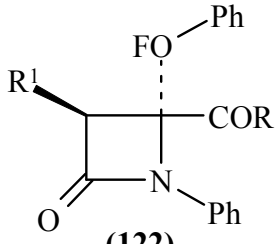
(120)



(121)

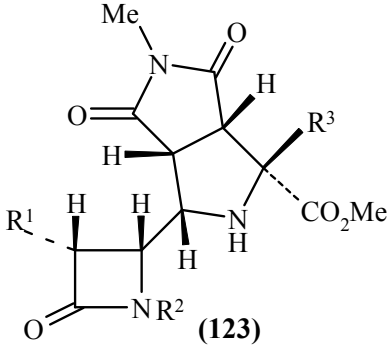
Krystyna et al., 1998[51] was reported that the reaction of phenylimines derived from β-phenyl-α,β-diketopropanoate, β-phenyl-α,β-diketopropanoic morpholide or α,β-diketo-propanoic morpholide with ketenes in the presence of Et_3N yielded mixtures of diastereomeric azetidinones such as **(122)** (R = EtO , morpholino; R^1 = Ph, PhO, Cl, phathalimido) as the major isomers. The

reaction of **(122)** (R = morpholino; R^1 = Ph) with $NaBH_4$ involved the reductun of the benzoyl moiety to afford the corresponding monohydroxy derivative.

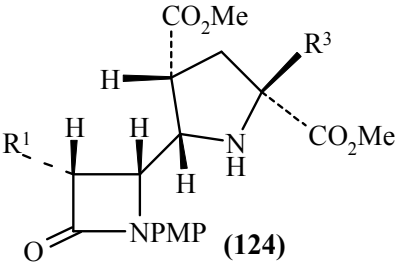


(122)

Ronald et al., 1999[52] was reported that the synthesis of novel 4-(5'-pyrrolidinyl)-β-Lactams e.g. **(123)** [R^1 = Et, OCH_2Ph, phathal-imido, R^2 = PMP, R^3 = Me; R^1 = OCH_2Ph, phathalimido, R^2 = Pme, R^3 = Me; R^1 = CMe_3, R^2 = PMP, R^3 = Me; R^1 = OCH_2Ph, R^2 = allyl, $CH_2CH(OMe)_2$, R^3 = Me; PMP = C_6H_4OMe-4] and **(124)** (R^1 = Et, R^3 = Me; R^1 = phathlimido, R^3 = Me, H), from imines derived from 4-formyl-β-Lactams and α-amino esters via cascade imine-azo-methineylide-1,3-dipolar cycloaddition reactions is described. These cascades are endo-specific, exhibit facial stereoselectivity and occur in good to excellent yields.



(123)

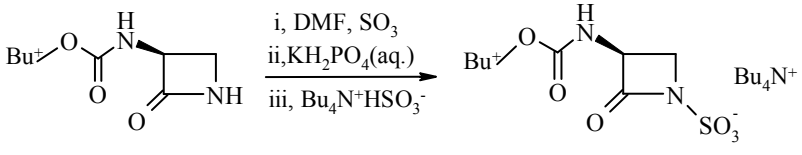


(124)

II- Reactivity of β-Lactams:

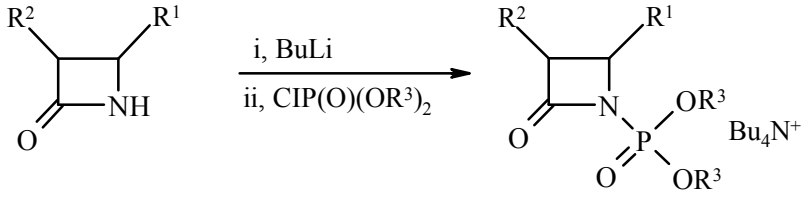
1- Electrophilic attack at nitrogen:

Cimarusti et al., 1983[53] reported that the reaction of the β-Lactams with sulfur trioxide complexes to give Lactam-type structures.



(125) (126)

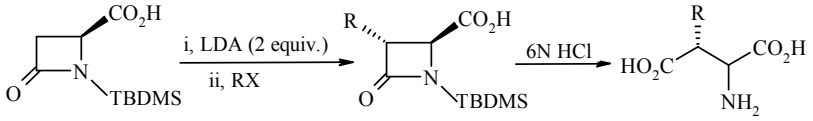
The preparation of organophosphorous substituted β-Lactams **(128)** had been suggested by ***Koster et al., 1983***[54] and ***Just et al., 1983***[55].



(127) (128)

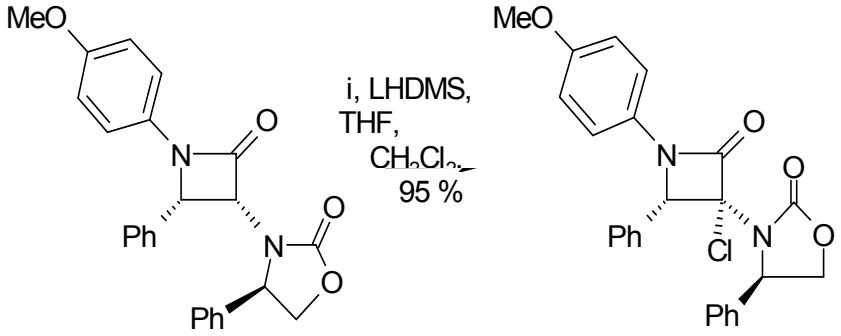
2) Electrophilic attack at carbon:

electrophilic reagent. The 3-position is activated by the carbonyl function, which makes it. The presence of a carboxyl group at $C_{(4)}$ does not interfere as the dilithium salt alkylated at $C_{(3)}$ with excellent stereocontrol, giving the trans-disubstituted lactam **(129)** ***Baldwion et al., 1990***[56]. Hydrolysis of leads to unprotected β-alkyl aspartates **(130)** ***Hanessian et al., 1992***[57].



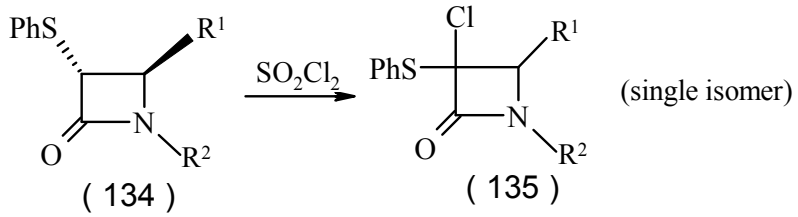
(129) (130) (131)

The reaction of such amide enolates with alkyl halides or aldehydes has been proven to be very useful when the 3-position carried an additional heteroatom, for example, nitrogen, like conversion of **(132)** to **(133)** ***Holton et al.,1993***[58].

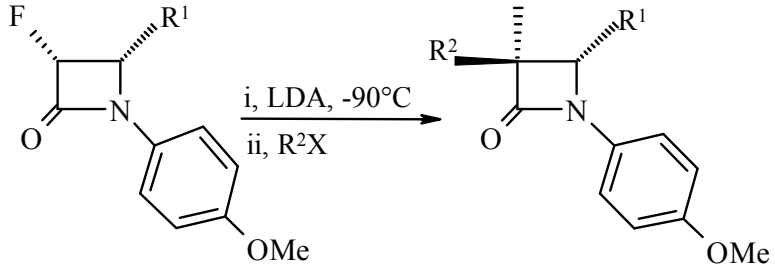


(132) (133)

Van der veen et al., 1989[59] report that sulfur like conversion of **(134)** to **(135)** and fluoro like conversion of **(136)** to **(137)** ***Welch et al., 1993***[60].



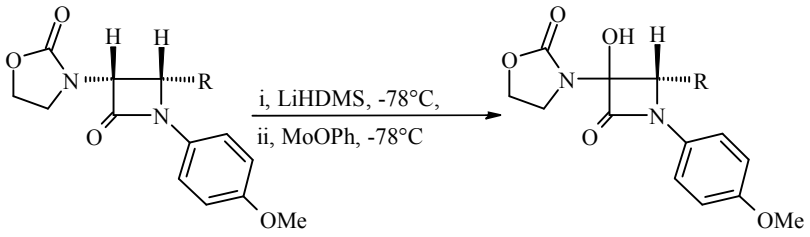
(134) (135)



(136) (137)

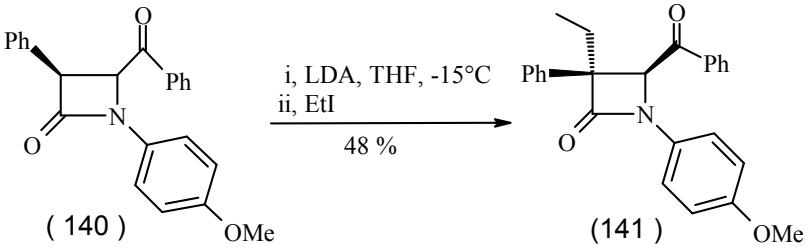
azidation with tosylazide via the enolate is an elegant approach to 3-amino-β-Lactams

3-Hydroxylations of 2-azetidinones have been executed using the MoOPh reagent like conversion of **(138)** to **(139)** ***Palomo et al., 1993***[61],

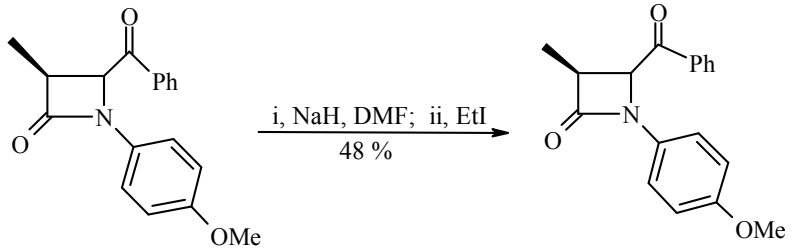


(138) (139)

When electron-withdrawing groups, for example, benzoyl, are present at $C_{(4)}$ the $C_{(3)}$ alkylation of **(140)** via the enolate can be performed with LDA/THF, but the benzoyl oxygen of **(142)** was alkylated when NaH/DMF is used, clearly underlying the importance of anion stabilizing substituents, either at $C_{(3)}$ or $C_{(4)}$ and the base solvent pair***Alcaide et al., 1987*** [62]



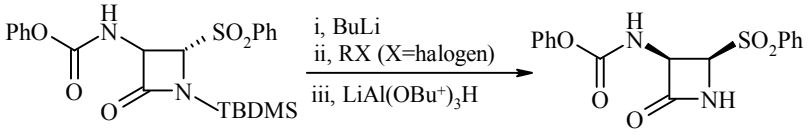
(140) (141)



(142) (143)

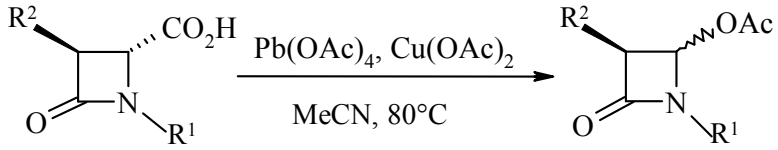
Reactions at $C_{(4)}$ of β-Lactams require the presence of activating group. A method for the

synthesis of chiral azetidinones **(144)** with a C-C bond at $C_{(4)}$ consists of the stereoselective alkylation-reduction of a silylated 4-phenyl-sulfonyl azetidinone **(145)** ***Deeter et al., 1993***[63].



(144) (145)

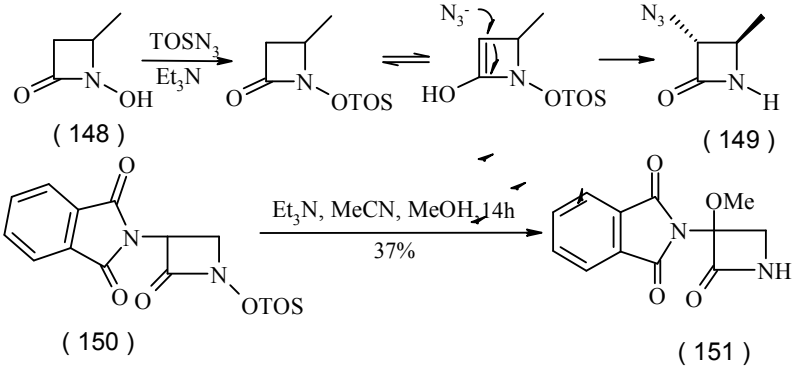
The oxidative decarboxylation of 2-azetidinone-4-car-boxylic acids **(146)** to give 4-acetoxy-2-azetidinones **(147)** via reaction with lead(IV) acetate is a frequently used procedure in β-Lactam chemistry ***Fritz et al., 1986***[64]



(146) (147)

3) Nucleophilic attack at carbon:

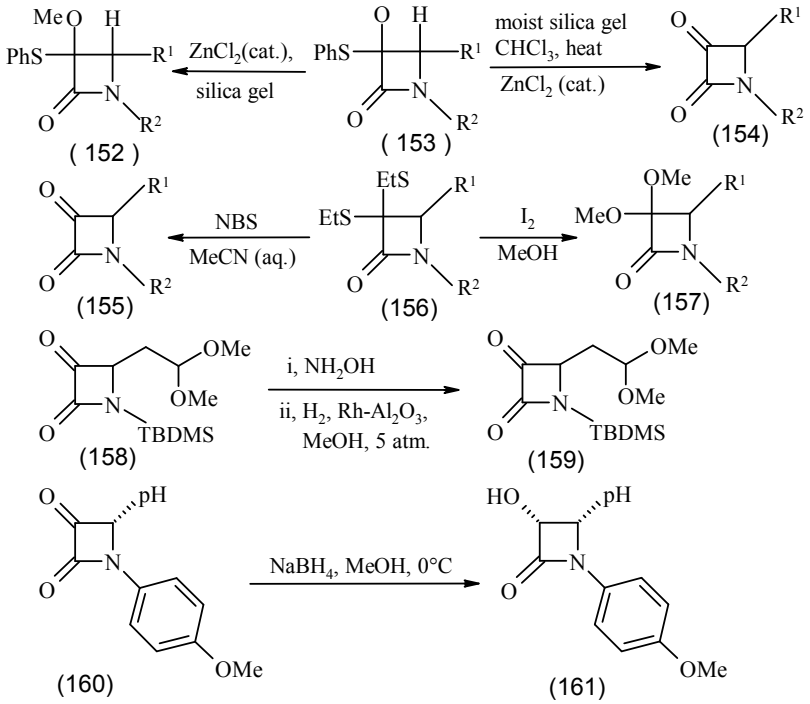
The α-azidation of 1-hydroxy-2-azetidinones, for example, **(148)** with arenesulfonyl azides in the presence of triethylamine afforded 3-azetidinones **(149)** via O-tosaylation and S_N^2-type displacement of the tosyloxy group ***Gasparski et al., 1992***[65]***, Teng et al., 1993*** [66]and ***Klich et al., 1993***[67]. However, the S_N^2-type displacement of 1-tosyloxy-2-azetidinones, for example, **(150)**, with methanol occurs only in low to moderate yield but supports the proposed mechanism.



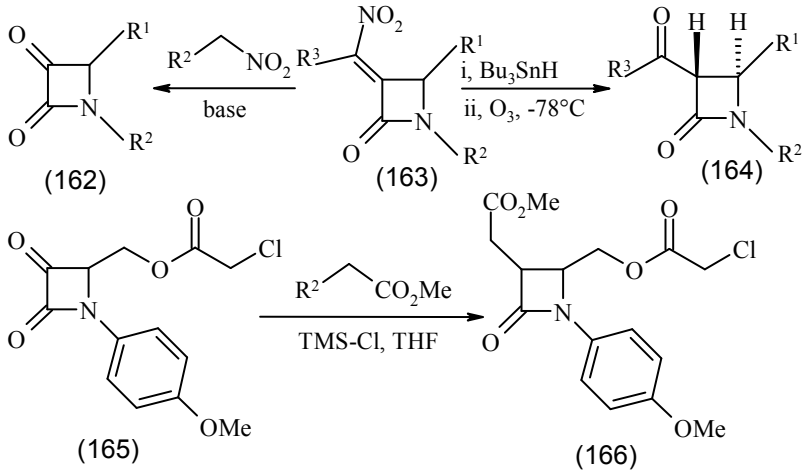
(148) (149)

(150) (151)

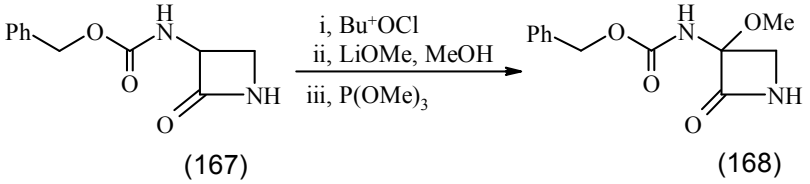
It had been shown that 3-chloro-3-(phenylsulfenyl)-2-azetidines **(153)** undergo stereospecific methanolysis in the the presence of zinc chloride/silica gel to afford methoxylated β-lactams **(152)**, while hydrolysis under similar conditions leads to azetidine-2,3-diones **(154)** ***Van der Veen et al., 1989***[59]. Hydrolysis of 3,3-di(ethylthio)-2-azetidinones **(156)** with NBS in aqueous acetonitrile, or with dimethylsulfide, dibromide, furnishes azetidine-2,3-diones **(155)**, while 3,3-dimethoxy-2-azetidinones **(157)** are formed by iodine induced methanolysis **[*Cossio et al., 1985*[68]*, 1988*[69] and ***Palomo et al., 1990***[70]**]**. Such azetidine **(158)** are readily attacked by nucleophiles at the 3-position. Oximation and subsequent reduction is a route to 3-amino-2-azetidinones **(159)** ***Kametani et al., 1985***[71]. ***Holton et al., 1993***[72] was report that cis-3(3)-hydroxy-4(S)-phenyl-β-lactam **(161)**was synthesized by reaction of 160 in presence of methanol and NaBH.



Azetidine-2,3-diones **(163)** undergo a base-induced alkenation reaction with nitroalkanes affording nitroalkenes **(164)** which, are reduced and then oxidized to give 3-acyl-2-azetidinones **(165) [*Palomo et al., 1990*[73]]**. The same substrates suffer alkenation reactions with Reformatesky type reagents affording 3-methylene-2-azetidinones, for example, **(166)** ***Palomo et al., 1990***[74].

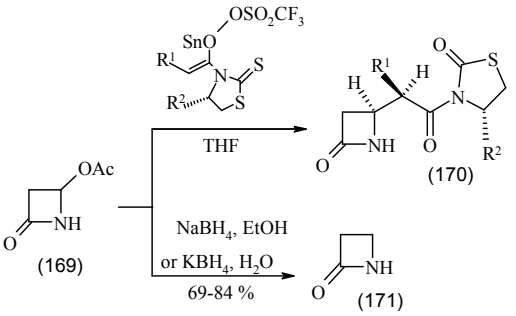


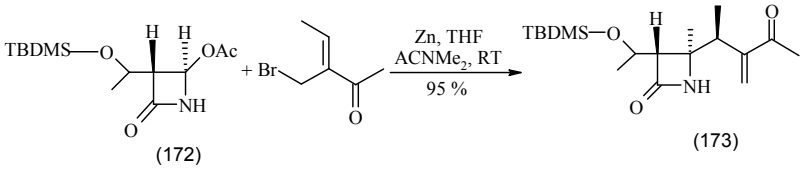
It had been shown that 3-amino-2-azetidinones **(167)** carrying an electron-withdrawing substituent at 3-amino substituent were methoxylated at the 3-position by oxidation to the 3-imino-2-azetidinone and subsequent nucleophilic addition of lithium methoxide ***Nishiada et al., 1984***[75].



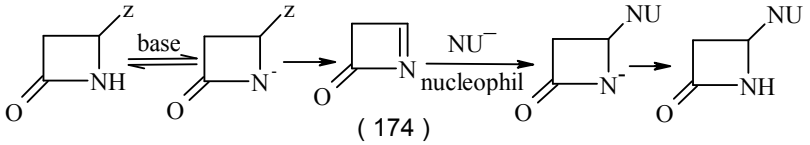
The classical functionalized of 4-acetoxy-2-azeti-dinones, for example, **(169)** at the 4-position

Davies et al., 1984[76] had been exploited several times with a variety of reagents, including a Barier-type allylation using a Pb/Al bimetal redox system ***Tanaka et al., 1988***[77], diethylmethylmalonate ***Miura et al., 1993***[78], tin(II) enolates ***Shirai et al., 1987***[79] and ***Nagao et al., 1992***[80,81,82], thiols ***Barret et al., 1990***[83], organozinc reagents ***Mori et al., 1993***[84], and sodium or potassium borohydride***Ogilvie et al., 1988***[85]



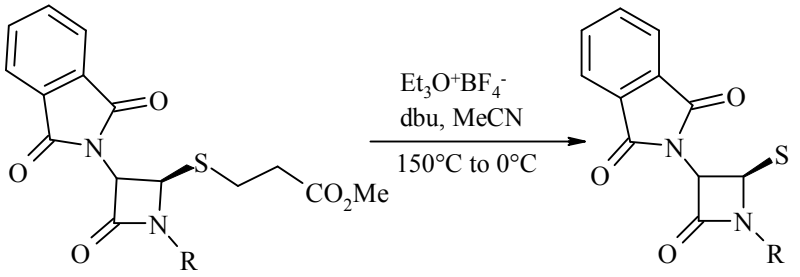


The mechanism of these substitution reactions been investigated and it was shown that the reactions occur by an ElcB elimination-addition pathway in which a 1-azetin-4-one **(174)** acts as intermediate ***Fedor et al., 1984***[86]***, Rao et al., 1990***[87] and ***Gu et al., 1990***[88], for N-substituted derivatives, substitution at the 4-position involves either elimination- addition via 4-azetinone intermediate **(174)** or direct displacement by S_N2 or S_N1 mechanisms ***Rao et al., 1990***[87]. The intermediacy of 1-azetin-4-one in solution had been demonstrated via polymer-bound 2-azetidinones ***Gavia et al., 1990***[89].



(174)

The conversion of 4-sulfenylated-2-azetidinones into 4-fluoroazetidinones **(176)** or 4-chloro-2-azetidinones occurs by reaction with triethyloxonium tetrafluoroborate or chlorine, respectively ***Brennan et al., 1986***[90] and ***Endo et al., 1987***[91].

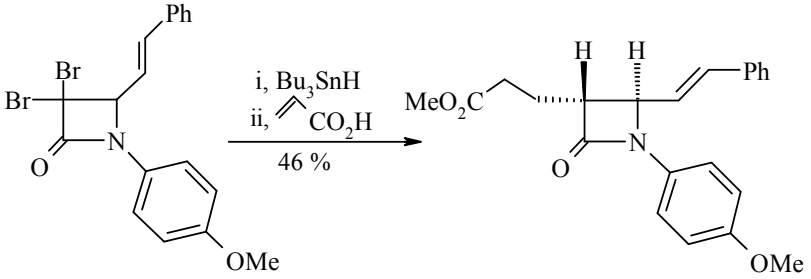


(175) (176)

4) Radicals and photochemical conversion:

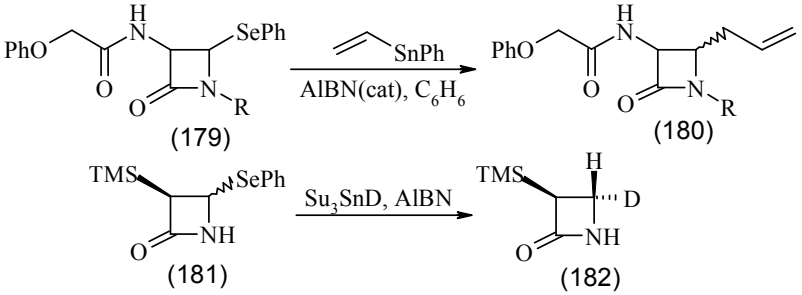
Manhas et al., 1983[92]was reported that dehalogenation of 3,3-dibromo-2-azetidinones occurs readily with tributyltin hydride the intermediate radicals add across methyl acrylate to give

highly functionalized β-Lactams **(178)** ***Sacripante et al., 1987***[93].



(177) (178)

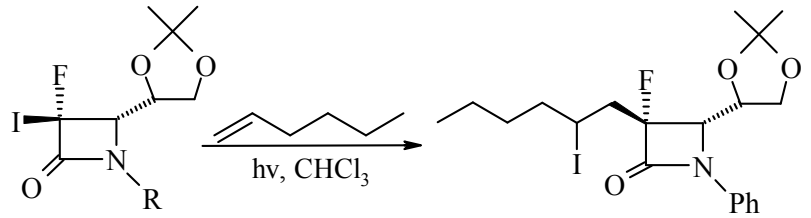
. Stereospecific synthesis of chiral $C_{(4)}$ deuterated β-lactams **(182)** has been worked out in this way ***Basak et al., 1993***[94]. The reaction of 4-(t-butylthio)-β-lactams with tributyltin hydride affords 4-thiol-β-lactams. ***Wagle et al., 1988***[95].



(179) (180)

(181) (182)

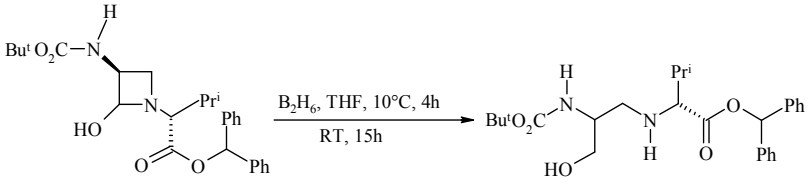
The iodine atom transfer addition reaction of 3-fluoro-3-iodo-β-lactams **(183)** under photolytic conditions is a convenient stereoselective method for the functionalization of β-lactams at the position.



(183) (184)

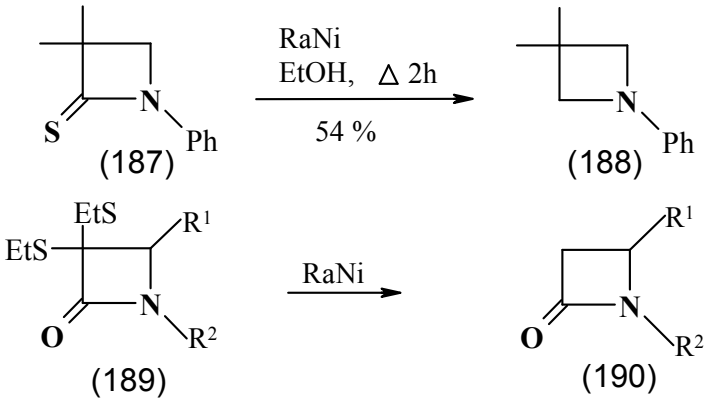
5) Reduction:

The reduction of β-lactams **(185)** by diborane gives access to γ-amino alcohols **(186)** ***Sammes et al., 1984***[96]**,** while the microwave mediated catalytic transfer hydrogenation by means of ammonium format and pd/c has realized **[*Bose et al., 1993***[97,98]**]**.

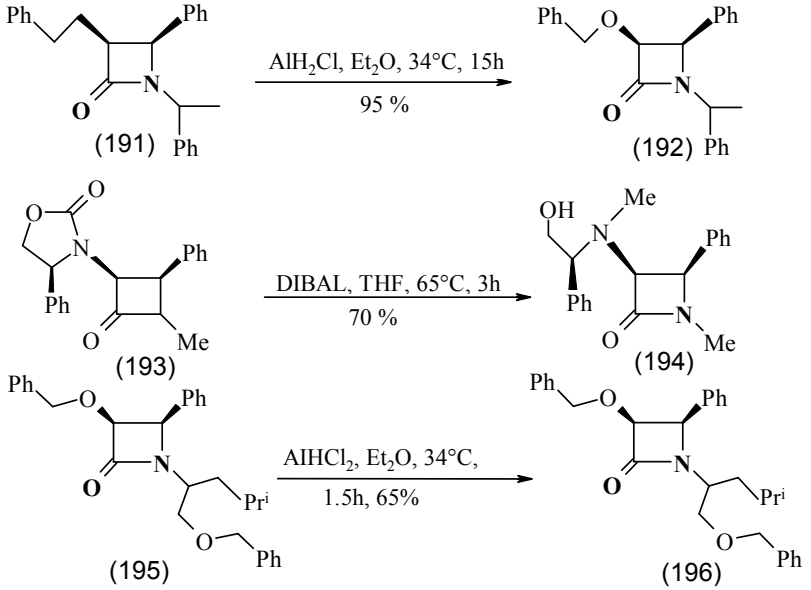


(185) (186)

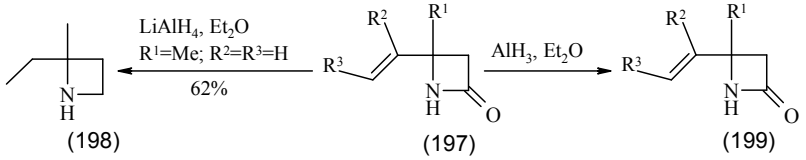
Raney nickel reduces 2-azetidinethiones, for example, **(187)**, in ethanol to afford azetidines, for example **(188)** ***Verkoyen et al., 1985***[99]**.** Derivatives with 4-phenyl substitutions give only complex reaction mixtures, where as 3,3-disulfe-nylated β-lactams **(189)** are readily desulfurized by raney nickel **[*Cossio et al., 1987***[100]**].**



Highly selective reductions of β-lactams to the corresponding azetidines were successfully performed by using diisobutyl aluminum hydride ***Sagami et al., 1985***[101] and ***Ojima et al., 1991***[102]**,** monochloro-hydralane, and dichloroalane as reducing agents ***Yamashita et al., 1983***[103]**,** ***Ojima et al., 1985***[104]**,** ***1987***[105]**,*****1991***[102]**.** Enantiomerically pure azetidines for example, **(194)** and **(196)** are readily synthesized without loss of enantiomeric purity ***Ojima et al., 1991***[102]**.**

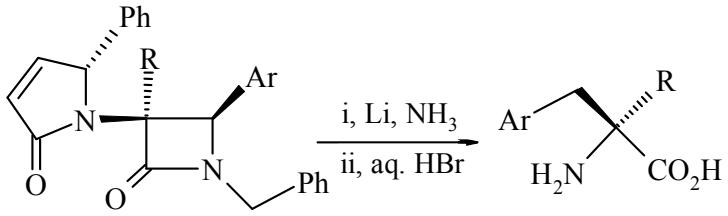


Aluminum hydride reduces 4-(1-alkenyl)azetidin-2-ones **(197)** to give 2-(1-alkenyl)azetidines **(199)** but the reduction of the same substrates with lithium aluminum hydride also reduces the alkene moiety to afford 2,2-disuubstituted azetidines **(198)** ***Hassner et al., 1986***[106]**, *****1987***[107].



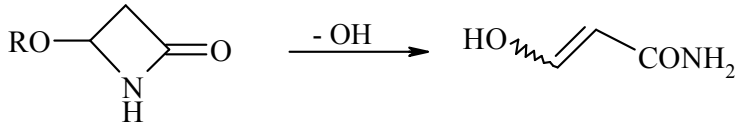
6) Ring opening:

The hydrolysis of chiral β-lactams **(200)**, after reductive removal of the N-benzyl substituent, in acid medium provides α-alkylated α-amino acids **(201)** in a stereospecific way ***Ojima et al., 1988***[108,109]**, *****1990***[110]**.**



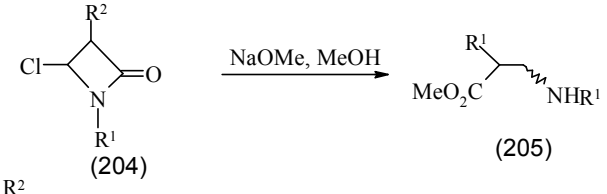
(200) (201)

Nucleophilic attack upon the β-lactam ring normally occurs at the carbonyl carbon atom and leads to opening of the ring ***Van Elburg 1985***[111]. When the ring contains a leaving group at the 4-position, nucleophilic displacement can also occur for exempl by substitutions of 4-acetoxy-2-azetidinones and related sudstrates. Such 4-acetoxy- and 4-aryloxy-2-azeti-dinones **(202)** undergo ring opening by aqueous alkaline solution to give 3-hydroxyacylamide or α-formyl-carbox-amides ***Fedor al., 1984***[112].

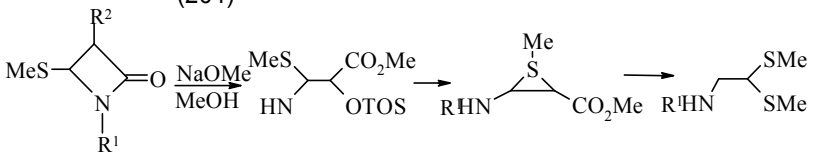


(202) R = AC, Ph (203)

Similarly, the ring opening of 4-chloro-β-Lactams **(204)** with sodium methoxide affords enamino esters **(205)** ***Rao et al., 1990***[87]. In contrast to the 4-chloro derivatives, the 4-(methylthio)-3-(tosyloxy) and 3-azidoazetidinones **(206)** in the presence of triethylamine undergo elimination of tosylate and azide in competition with loss of methanethiol. The methylthio group rearranges from $C_{(4)}$ to $C_{(3)}$ to afford enamino esters **(209)** ***Rao et al., 1990***[87].

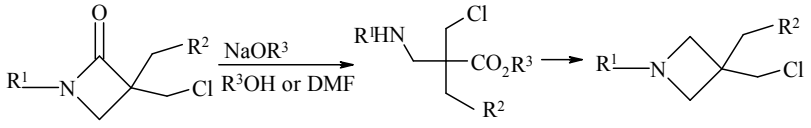


(204) (205)



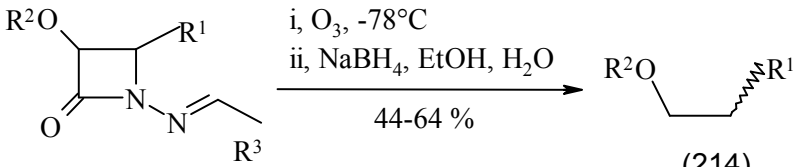
(206) (207) (208) (209)

Alkoxides with 3-(chloromethyl)-2-azetidinones **(210)** give ring opening to β-amino esters **(211)** which undergo ring closure to azetidine-3-carboxylic esters **(212)**.



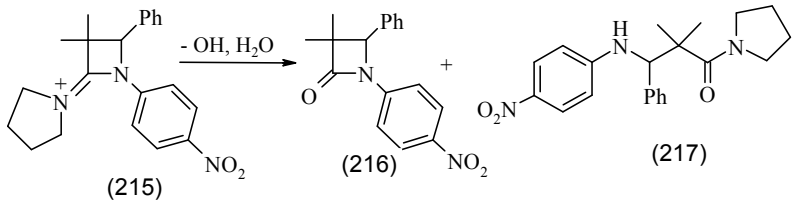
(210) (211) (212)

Fragmentation of β-Lactams **(213)** by ozonolysis, followed by reduction with sodium borohydride provides vinyl ethers **(214)** via intermediate N-nitroso-β-Lactams ***Alcaide et al., 1993***[113].



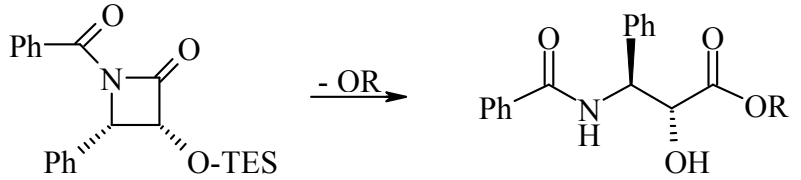
(213) (214)

The hydrolysis of 2-azetideneammonium salts **(215)** in sodium hydroxide and in carbonate buffers yields 2-azetidinones and β-amino carboxylic amides by competitive endo and exocyclic C-N bond cleavage, the product ratio being pH and buffer dependent ***Page et al., 1987***[114]***, 1988***[115]***, 1990***[116]**.** The rate law for hydrolysis shows a third order term that is first order is substrate, hydroxide, and carbonate ions. It is interpreted as kinetically equivalent to general acid catalyzed breakdown of the ionized tetrahedral intermediate and as evidence for non facial C-N bond cleavage in the four-membere ring.



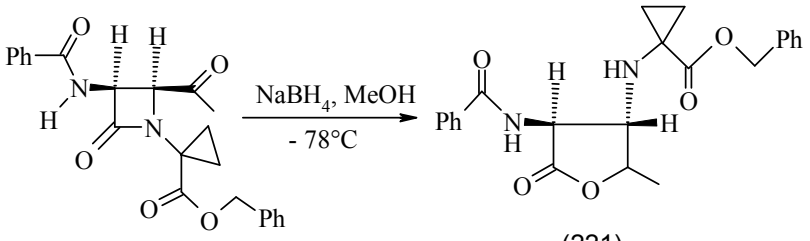
(215) (216) (217)

The ring opening of 3-oxygenated-4-phenyl-β-Lactams, for example, β-Lactam **(218)** by alkoxides has found an important application in the synthesis of tazol and related substances, delivering the correct stereochemistry of tazol side chain ***Holton et al., 1990***[117]***, 1991***[118]***, Ojima et al., 1991***[119]***, 1992***[120]***, 1993***[121]***, Endo et al., 1993***[122]**,** and ***Holton et al., 1994***[123]**.**



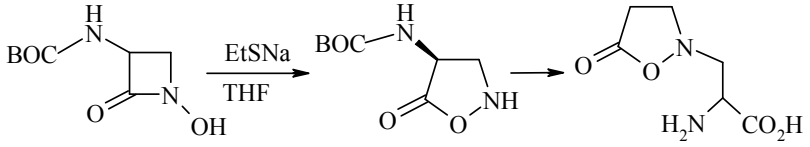
(218) (219)

Intermolecular ring opening, via an in situ generated alkoxide from reduction of an acetyl moiety by hydride, furnishes ring expansion to lactone **(221**
) ***Farouz-Grant et al., 1993***[124]**.**



(220) (221)

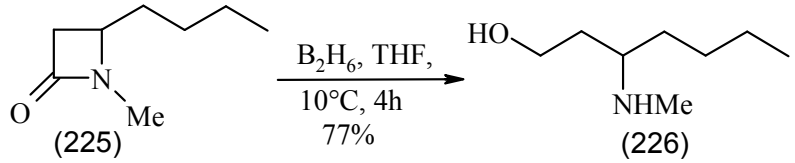
The ring expansion of β-Lactam **(222)** by thiolate to give isoxazolidinone **(223)** was utilized as a key step in the synthesis of 2- alanyl-3-isoxazolin-5-one **(224)** ***Baldwin et al., 1985***[125].



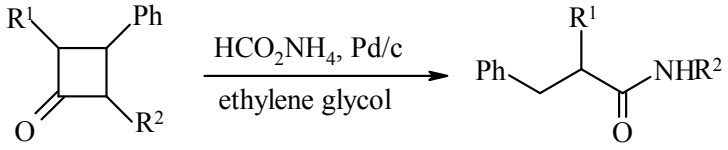
(222) (223) (224)

Ring opining of β-lactams, for example, **(225)**, by diborane ***Sammes et al., 1984***[96], lithium aluminium hydride, lithium triethylborohydrie and dissobutylaluminum hydride have been described ***Ojima et al., 1991***[102] and **Bartholomew *et al., 1991***[126].

However, these reducing agents are better known for the conversion of β-lactams into azetidines. A high temperature catalytic transfer hydrogenation of β-lactams by means of ammonium format and Pd/c in ethylene glycol to afford carboxylic amides **(228)** has been realized in an a domestic microwave oven ***Bose et al., 1993***[98].



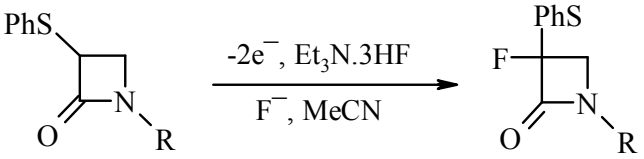
(225) (226)



(227) (228)

7- Electrochemical transformations:

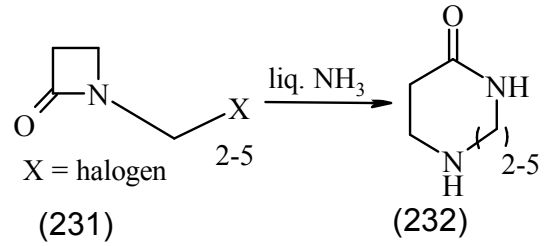
The anodic fluorination of 3-(phenylthio)-2-azetidines **(229)** is a useful method for the synthesis of 3-fluorinated β-lactams **(230)** ***Narizuka et al., 1993***[127]**.**



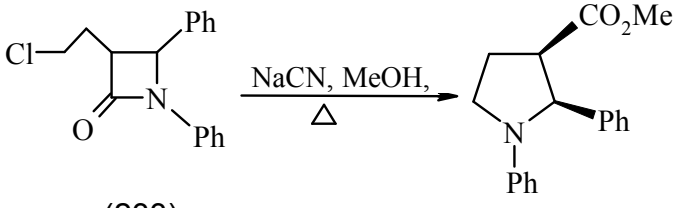
(229) (230)

8- Conversions into other heterocyclic:

Ring expansion of β-Lactams, bearing a ω̃-haloalkyl substituent at the nitrogen atom, occurs with liquid ammonia to heterocycles **(232)** ***Crombie et al., 1983***[128]**, *1986***[129] A related ring expansion to pyrrolidine occurs with 3-(2-chloroethyl)-2-azetidinones **(234)** ***Bose et al., 1986***[130]**.**

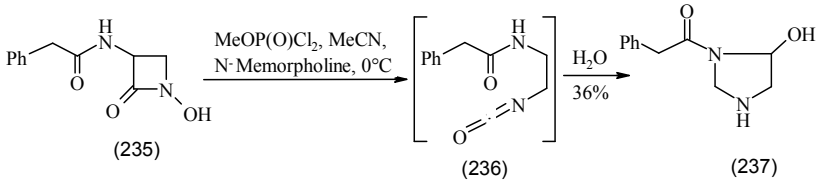


(231) (232)



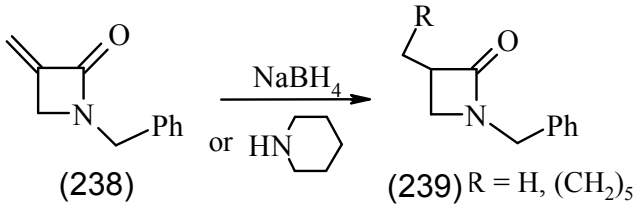
(233) (234)

Ring expansion of 1-hydroxyazetidine-2-ones produces 2-imdazolidinones **(237)** via activation with $MeOPOCl_2$ ***Krook et al., 1985***[131,132].

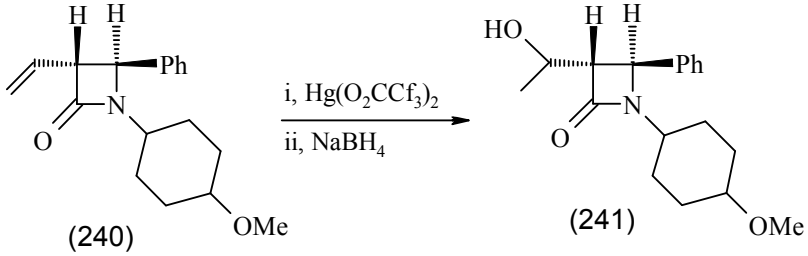


9- Reactivity of substituents attached to ring carbon atoms:

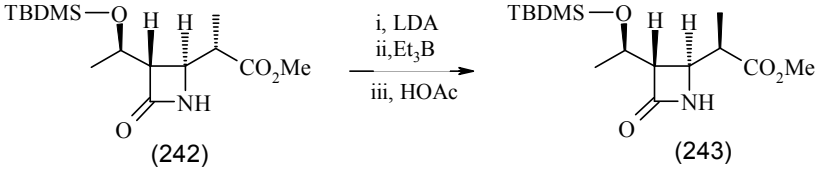
Michael addition of sodium borohydride or pipridine across 3-methyleneazetidin-2-one **(238)** affords the adducts **(239)** ***Mori et al., 1985***[133]. It has been shown that 4-(iodomethyl)azetidin-2-one undergoes nuclieophilic substitution by sodium azide in DMF to give the azide compound ***Knapp et al., 1988***[134].



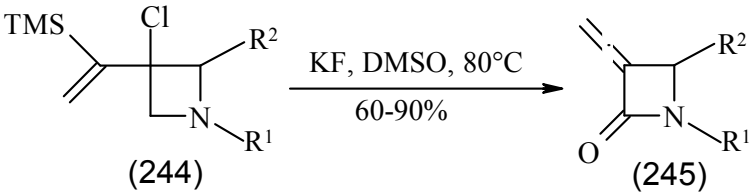
The 3-vinyl substituent of β-lactam **(240)** was converted into a 1-hydroxyethyl group by oxymercuration and reductive demercuration ***Bose et al., 1993***[98]. The 1-hydroxyethyl substituent was readily oxidized by the Jones reagent and was further transformed to a hydromethyl substituent by silylation, ozonolysis, oxalylchloride treatment, and hydride reduction ***Ruediger et al., 1991***[135].



Triethylborane mediated epimerization of the α-methyl diastereomer **(242)** proceeds with high stereo selectivity ***Bender et al., 1992***[136]. Enzyme-catalyzed hydrolyses of carboxlic ester groups, localized in the $C_{(2)}$ side chain, have been performed ***Schirmeister et al., 1993***[137]. Ozonolysis of 4-(1-alkenyl) substituents is a convenient rout towards 4-acyl-β-lactams ***Palomo et al., 1989***[138].

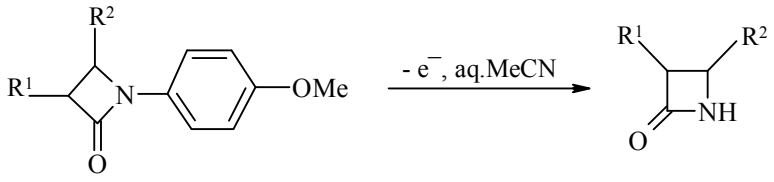


. The production of 3-ethylidine-2-azetidinones **(245)** is possible from fluoride-mediated desilylation and concomitant chloride elimination ***Buynak et al., 1987***[139].



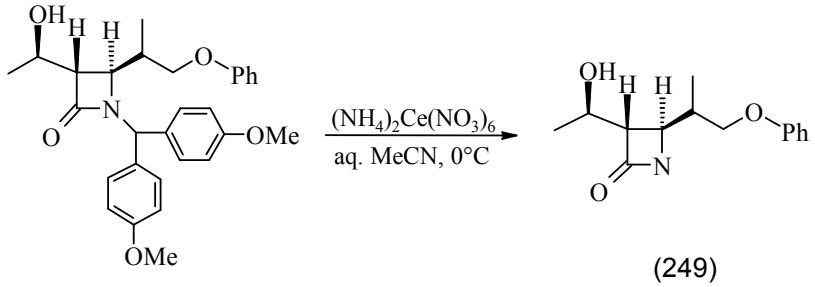
10-Reactivity of substituents attached to the ring nitrogen atom:

, while the 4-methoxyphenyl protective group is conveniently removed by ammonium nitrate ***Hanessian et al., 1985***[140]



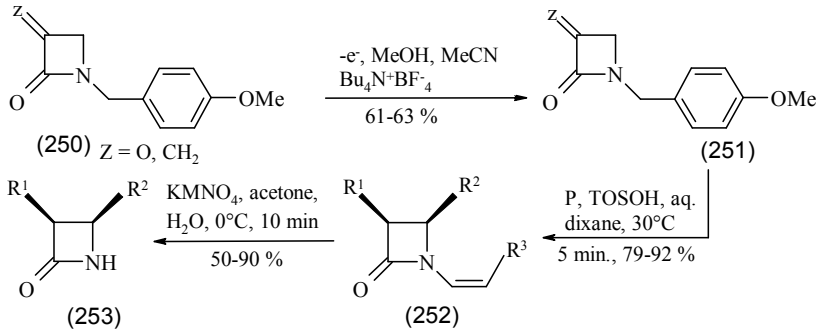
(246) (247)

The oxidative removal of the di-(p-anisyl)methyl group is readily accomplished using ceric ammonium nitrate ***Kawabata et al., 1986***[141]***, 1988***[142]**,** or peroxodisulfate salts ***Terajima et al., 1990***[143]**.**



(248) (249)

It has been shown that N-phenacyl protected 2-azetidinones were converted in N-unsubstituted 2-azetidinones by oxidation with $KMnO_4$ or via α-bromination and subsequent mercury assisted hydrolysis ***Cossio et al., 1985***[144]**.**



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