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Recent progress in the synthesis and chemistry of azetidinones

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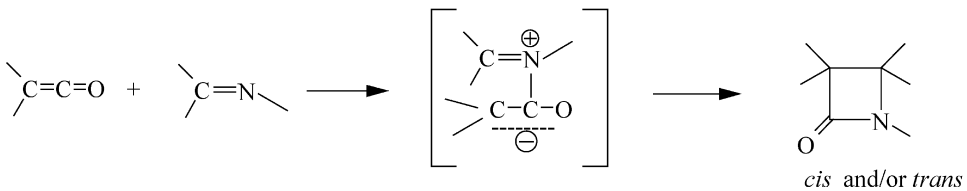
1. Introduction

Natural and synthetic azetidinone derivatives occupy a central place among medicinally important compounds due to their diverse and interesting antibiotic activities.[1–9] Even though they have a long history of development starting from the discovery of Penicillin in 1928 the quest for new synthetic methods and refinement of those already known remains appealing, as does the research into the application of these methods in synthesising novel biologically active azetidinone derivatives. Recent years have seen a resurgence of interest in the development of stereo- and enantioselective methodologies. The utility of azetidinones as synthons for various biologically active compounds, as well as their recognition as cholesterol absorption inhibitors[10–14] and enzyme inhibitors,[15–16] has given impetus to these studies.[17–21] In the late 1990s, several groups reported novel methodologies for the synthesis of azetidinones and new azetidinones of potential biological activities by applying known methods[22–38] and the 31st issue of Vol. 56 of *Tetrahedron* in 2000 was completely devoted to β-lactam chemistry. Since then a plethora of work has appeared in the literature. It would therefore be useful to review the work done in this area more frequently.

This article aims to review the work reported on the synthesis of azetidinones during the last three years. The synthetic methods are described under four headings—Staudinger reaction and related methods (cycloaddition), cyclisation (amino acids, amino esters, etc.) and other methods, chemical transformations in azetidinone ring-containing compounds and, finally, the synthesis of 3-azetidinones.

2. Staudinger reaction and related methods

Staudinger's ketene–imine reaction is the most common method for the synthesis of azetidinones[39] and it has been reviewed recently by Palomo et al.[35] The reaction is carried out thermally or photochemically using acid chlorides in the presence of triethylamine or α-diazoketones as ketene precursors. The previous decade has also seen the use of microwave radiation in synthesising azetidinones.[40–41]



cis and/or *trans*

Keywords: azetidinones; Staudinger reactions; asymmetric synthesis; aminoacid cyclization; antibiotics; antifungals; cholesterol absorption inhibitors; enzyme inhibitors.

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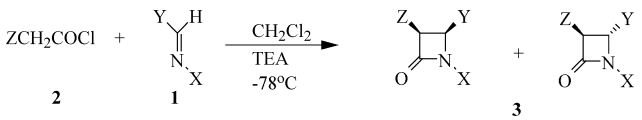


Z = OAc, OPh; Y = Ph; X = naphthyl, anthracenyl, Ph

Scheme 1.

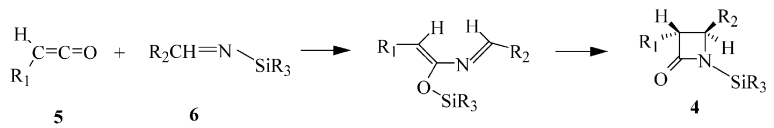
Although commonly described as a [2+2] cycloaddition, it is generally accepted that the reaction is in fact stepwise. The first step of the reaction involves a nucleophilic attack of an imino nitrogen on the sp-hybridised carbon of a ketene to form a zwitterionic intermediate, which cyclises to form the azetidinone ring. The stereochemistry of the resulting azetidinone can be *cis*, *trans* or a mixture of both isomers.

This reaction is still being investigated extensively, both from the synthetic and mechanistic points of view, to achieve stereo- and enantiocontrol and to explain the stereochemical outcome. The substituents present in the imines or the acid chlorides, the nature of bases/solvents, the reaction conditions and even the order of addition of the reagents have been found to affect the formation of the azetidinone ring. Some computer-assisted theoretical calculations have been published to explain the stereoselectivity of the reaction.[42–44]

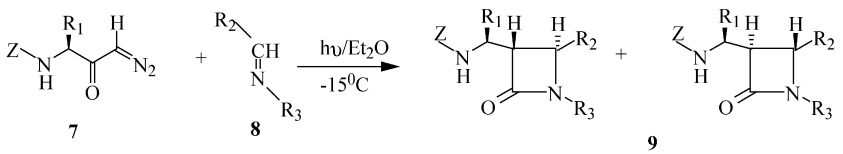
Banick and Becker have reported for the first time the reaction of the polycyclic aromatic imines **1** with acid chlorides **2** under normal Staudinger conditions, leading to the formation of the *trans*-azetidinones **3** (Scheme 1).[45] The authors have hinted at a possible role of bulky substituents on the nitrogen atom of the imines in determining the stereochemistry of the products. The synthesis of the novel azetidinones **4** with *trans* stereochemistry using the Staudinger reaction has been reported by Panunzio and co-workers,[46] who isolated O-silylated intermediates in the reaction of the ketenes **5** with *N*-silylimines **6** (Scheme 2) confirming the stepwise nature of the reaction and explaining the *trans* stereochemistry of the products. In order to explain the origin of the stereocontrol in this reaction, Arrieta and co-workers have employed a range of computational methods.[47] They found that the energy of activation of isomerisation of the starting *N*-silylimines was lower than that of the formation of the C–N bond, a fact that explains the stereochemistry observed in the reaction.

Podlech and co-workers have reported highly stereoselective photochemical reactions of the diazoketones **7**,[48] derived from suitably protected amino acids (Ala, Val and Tle), with the imines **8**, leading to *trans*-arranged 4-aryl/cinnamoyl-substituted azetidinones **9** (Scheme 3). The stereoselectivities have been observed to depend on the steric demand of the amino acid side-chains.

Cycloadditions of ketenes, generated in situ from

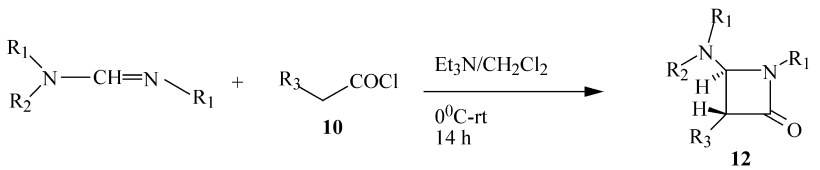


Scheme 2.



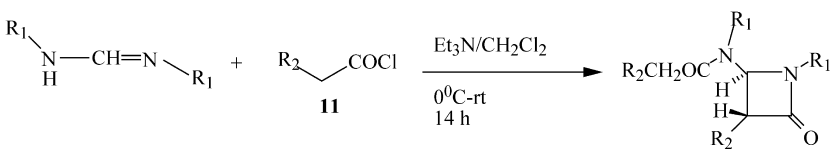
R_1 = Me,*i* Pr,*t* Bu; R_2 = Ar; R_3 = Bn,*t* -Bu, Allyl

Scheme 3.



R_1 = Ph, 4-ClC_6H_4, 3-MeC_6H_4, 4-MeOC_6H_4; R_2 = PhCO, 4-$NO_2C_6H_4$CO, Ts; R_3 = PhO, PhthN

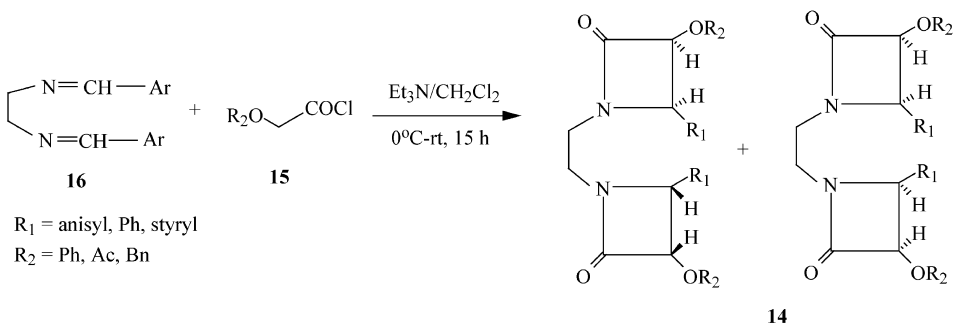
(a)



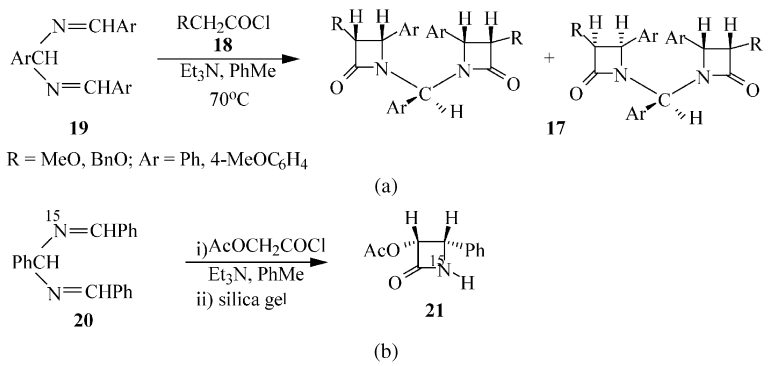
R_1 = Ph, 4-ClC_6H_4, 3-MeC_6H_4, 4-MeOC_6H_4; R_2 = PhO, PhthN

(b)

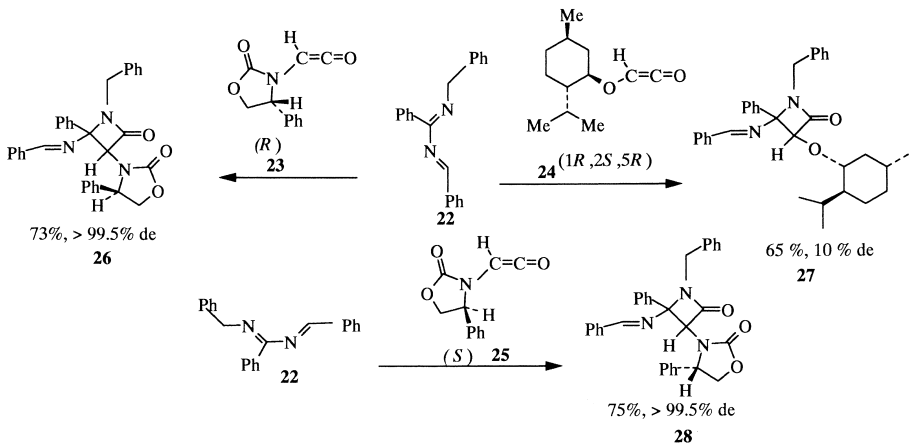
Scheme 4.



Scheme 5.



Scheme 6.



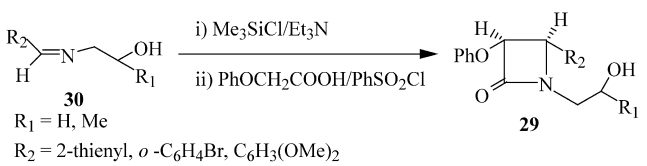
Scheme 7.

phenoxyacetyl chloride **10** or phthalimidoacetyl chloride **11** and triethylamine, to the C=N bond of amidines, leading to the formation of *trans*-4-acylamino- and 4-sulfonamido-2-azetidinones **12**, **13** (Scheme 4a and b) have been reported by Bhawal and his group.[49]

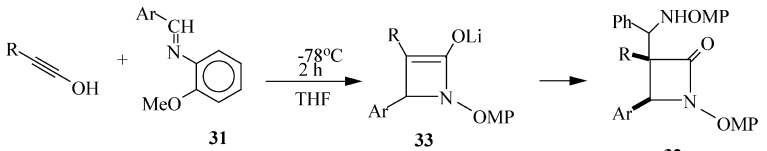
The same group has reported the synthesis of bis-azetidinones **14** linked with an ethylene bridge and possessing *cis* stereochemistry, using the same methodology, but with different ketenes **15** and bis-imines **16** (Scheme 5).[50] *Cis*-bis-azetidinones **17** have also been reported by Bose and co-workers by the cycloaddition of ketenes, obtained from the acid chlorides **18**, to the C=N bond of the bis-imines **19** (Scheme 6a). The use of ^{15}N-labelled imines **20** in this reaction affords the ^{15}N-labelled 2-azetidinones such as **21** (Scheme 6b).[51]

Abbiati and Rossi have reported [2+2] cycloaddition reactions of 1-benzyl-2,4-diphenyl-1,3-diazabuta-1,3-diene **22** with the chiral ketenes **23**–**25**, leading to the azetidinones **26**–**28** (Scheme 7).[52]

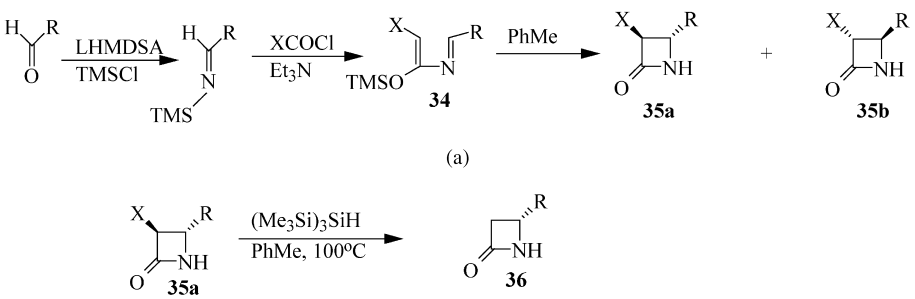
Synthesis of *cis*-*N*-2-hydroxyethyl-2-azetidinones **29** (Scheme 8) has been reported by Sharma and Bhaduri,[53] who used phenoxyacetic acid in the presence



Scheme 8.



Scheme 9.



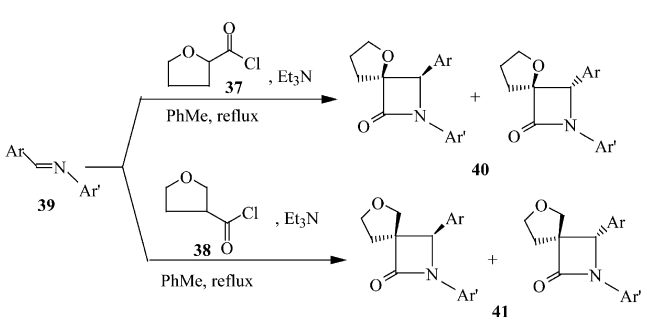
Scheme 10.

of benzenesulfonyl chloride. The protection of the hydroxy group in the imines **30** is a necessity for the reaction to proceed and it has been achieved by using trimethylsilyl chloride.

Cycloaddition of lithium ynolates to *N*-sulfonyl imines was reported by Shindo and co-workers.[54] Unactivated imines such as *N*-4-methoxyphenyl imines are however, much less reactive in this reaction. The group has improved the method by introducing a methoxy group *ortho* to the imino group in **31**. The co-ordination of the methoxy group with lithium activates the imine and yields the 2-azetidinones **32** as a single isomer as a result of a 2:1 molar reaction of the imine with the ynolate via **33** (Scheme 9).

Panunzio and co-workers have explored the utilisation of 2-aza-1,3-dienes **34** for the formation of the azetidinone ring.[55,56] Their group has reported a *trans*-stereoselective synthesis of 3-halo-4-arylazetidin-2-ones **35a** and **35b** through conrotatory ring closure of 1-halo-3-aza-4-alkyl-1,3-dienes **34** in refluxing toluene (Scheme 10a).[57] They have also achieved a useful modification of the azetidinones **35** so obtained, by dehalogenation using tris(trimethylsilyl)-silane, giving rise to the azetidinones **36** (Scheme 10b).

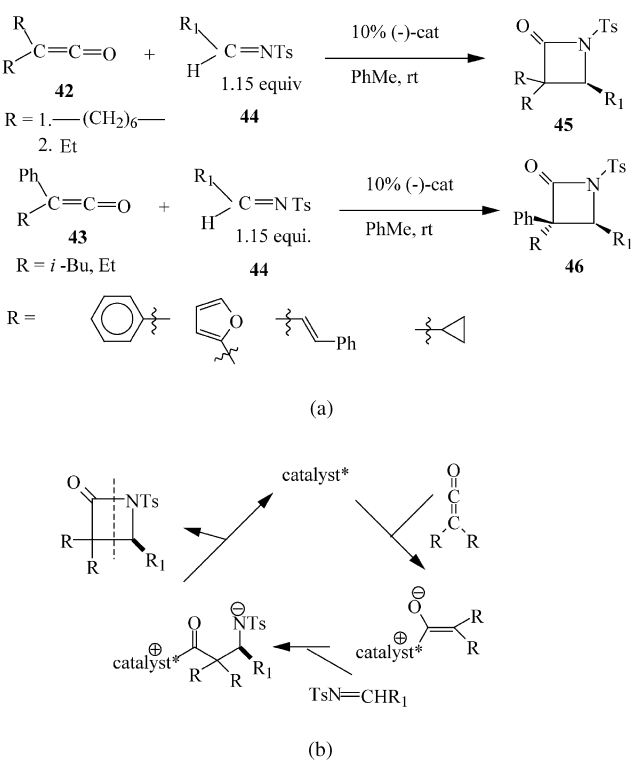
Gonzalez and co-workers have used a tetrahydrofuran-derived cyclic ketene for the first time in a Staudinger reaction.[58] The reaction of 2- or 3-tetrahydrofuroyl chloride **37** or **38** with the several imines **39**, containing a range of



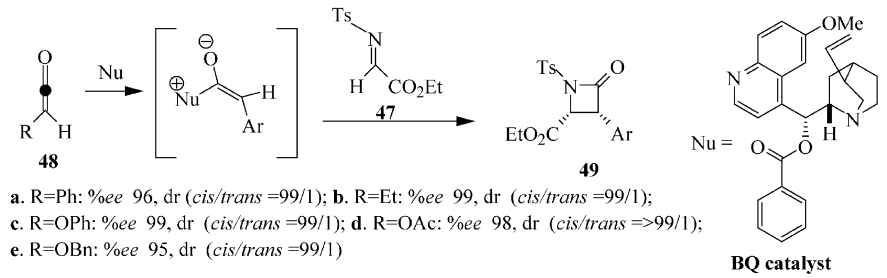
40. **a**.Ar=Ar'=4-MeOC$_6$H$_4$; **b**. Ar=Ph, Ar'=4-MeOC$_6$H$_4$; **c**.Ar=Ar'=Ph; **d**. Ar=2-furyl, Ar'=4-MeOC$_6$H$_4$; **e**. Ar=3-pyridyl, Ar'=4-MeOC$_6$H$_4$; **f**. PhCH=CH, Ar'=4-MeOC$_6$H$_4$; **g**. Ar=Ph, Ar'=Me; **h**. Ar=Ph, Ar'=PhCH$_2$; **i**. Ar=Ph, Ar'=4-NO$_2$C$_6$H$_4$; **j**. Ar=4-NO$_2$C$_6$H$_4$,Ar'=Ph; **k**. Ar=4-NO$_2$C$_6$H$_4$, Ar'=Me; **l**. Ar=Ar'=4-NO$_2$C$_6$H$_4$; **m**. Ar=4-NO$_2$C$_6$H$_4$, Ar'=4-MeOC$_6$H$_4$

41. **a**. Ar=Ar'=4-MeOC$_6$H$_4$; **b**. Ar=Ph, Ar'=4-MeOC$_6$H$_4$; **c**. Ar=Ar'=Ph**d**. Ar=4-NO$_2$C$_6$H$_4$,Ar'=Ph

Scheme 11.



Scheme 12.



a. R=Ph: %*ee* 96, dr (*cis/trans* =99/1); **b**. R=Et: %*ee* 99, dr (*cis/trans* =99/1);
c. R=OPh: %*ee* 99, dr (*cis/trans* =99/1); **d**. R=OAc: %*ee* 98, dr (*cis/trans* =>99/1);
e. R=OBn: %*ee* 95, dr (*cis/trans* =99/1)

Scheme 13.

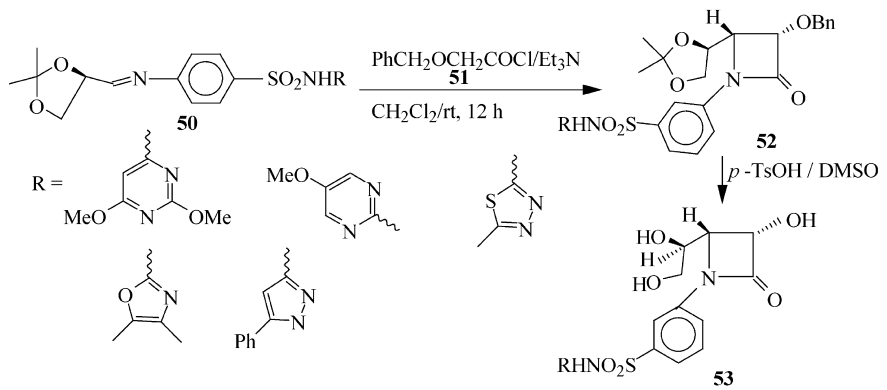
aromatic substituents on both nitrogen and azomethine carbon, leads to the formation of the spiroazetidinones **40** and **41** (Scheme 11), respectively.

Fu and co-workers have reported a highly enantioselective Staudinger reaction of various symmetrical ketenes **42** and unsymmetrical ketenes **43** with the imines **44**, derived from aromatic, α,β-unsaturated and aliphatic aldehydes, in the presence of a 4-(pyrrolidino)pyridine derivative as a chiral catalyst (Scheme 12a).[59] The yields of the products **45** and **46** are in the range of 76–98% while the ee is 82–98%. The communication also presents a tentative mechanism for the reaction which is shown in Scheme 12b.

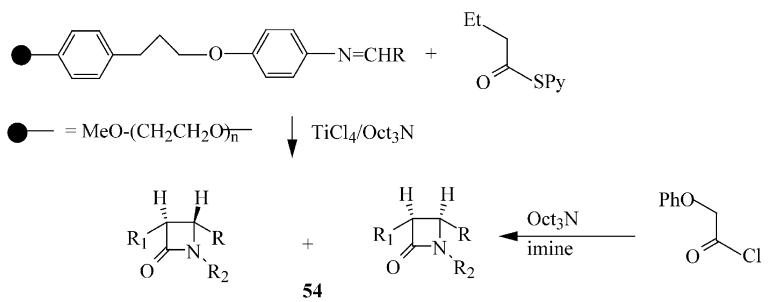
Lectka and co-workers have reported the catalytic asymmetric reaction of the imine **47** with various ketenes **48** to produce the azetidinones **49** (Scheme 13) diastereoselectively and enantioselectively, employing chiral nucleophilic amine as a catalyst.[60a] They have studied the role of some bifunctional amines and optically active cinchona alkaloid derivatives as potential diastereoselective and enantioselective catalysts in the reaction and have reported a detailed investigation of the mechanism of the β-lactam-forming reaction with a proton sponge as the stoichiometric base, including kinetics and isotopic labeling.[60b] This report also presents stereochemical models based on molecular mechanics calculations, which account for the observed stereochemical sense of induction in the reactions and provide a guide for the design of other catalytic systems.

A stereospecific Staudinger reaction has also been reported by Hassan and Soliman.[61] Chiral aldimines **50**, obtained from D-(*R*)-glyceraldehyde acetonide and some biologically important heterocyclic amines, have been reacted with benzoyloxyacetyl chloride **51** in the presence of Et_3N to give optically pure *cis*-3-benzyloxy-2-azetidinones **52** (Scheme 14). The latter compounds yield 3-hydroxy-2-azetidinones **53** having an *N*-sulfonamido drug side chain on hydrolysis.

Chiral aldimines, obtained from the condensation of



Scheme 14.



R = Ph, 2-thienyl, (*E*)-PhCH=CH, Et, Ph, CO_2Et
R_1 = R_1 = PhO, Et
R_2 = -$C_6H_4O(CH_2)_3C_6H_4O$-

Scheme 15.

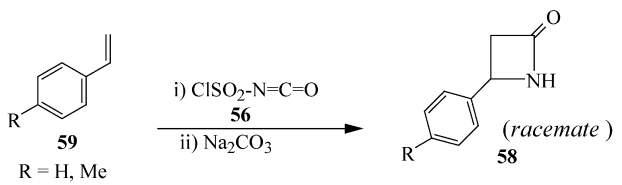
Scheme 16.

(*S*)-glyceraldehyde acetonide with amines, are reported to undergo cycloaddition in a highly stereoselective manner to give a series of (1′*R*,3*R*,4*R*)-*N*-substituted-3-(1′-hydroxyethyl)-4-acetoxy-2-azetidinones, key intermediates for the synthesis of carbapenems.[62]

Enolate/imine condensations and the [2+2] cycloaddition reactions carried out by Cozzi and co-workers over a soluble polymer support have led to the formation of 2-azetidinones **54** (Scheme 15). They have reported the development of a modified poly(ethyleneglycol) (PEG) for the synthesis. The monomethyl ether of PEG (MeOPEG) with an average MW of 5000 was used as the support, a 4-(3-propyl)phenyl residue as the spacer and a 4-oxyphenylamino group as the moiety with the reactive functionality.[63]

Several other authors have applied the Staudinger ketene–imine cycloaddition to synthesise 2-azetidinones with a broad range of substituents including various heterocycles. These azetidinones have been screened for different biological activities such as antibacterial,[64–68] antifungal,[64–68] anticancer[69] and antitubercular.[70] The principal logic in designing these compounds is to incorporate the azetidinone ring in a well-known biologically active moiety.

Lee and co-workers have used alkene and isocyanate instead of ketene and imine[71] and they reacted the *E*-vinyl sulfide **55** with *N*-chlorosulfonyl isocyanate **56** to give a 2.5:1 diastereomeric mixture of phenylthioazetidinones **57** (Scheme 16). The facial selectivity in the cycloaddition is explained by the conformational preference of the allylic groups in the transition structure. Fulop and Forro have likewise synthesised the *racemic* 4-aryl-2-azetidinones **58** (Scheme 17) by reacting the same isocyanate with styrene and 4-methylstyrene **59**.[72]

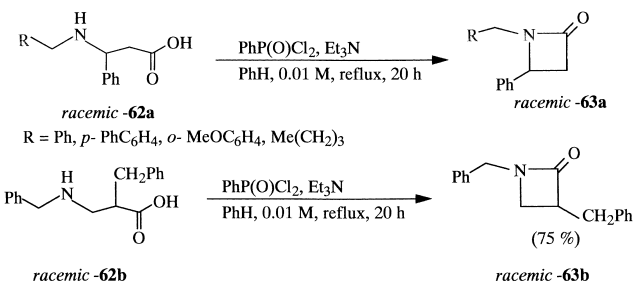


Scheme 17.

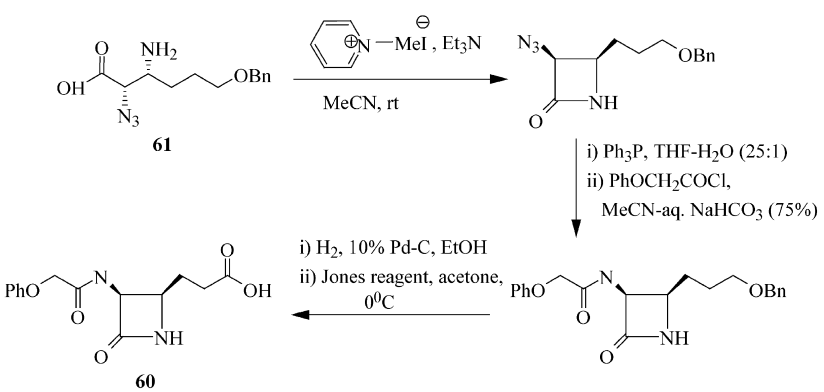
3. Cyclisation and other methods

β-Amino acid cyclisation has been utilized by Lee and co-workers to synthesise the *cis*-(3*S*,4*R*)-azetidinone **60** as a precursor for the antibiotic, loracarbef (Scheme 18).[73] The required α-azido-β-amino acid **61** was synthesised by asymmetric aminohydroxylation of the α,β-unsaturated ester followed by the introduction of azide.

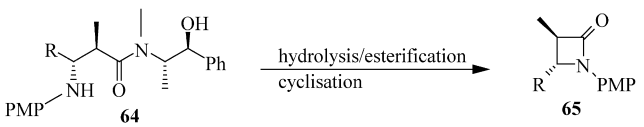
Escalante and co-workers have reported the cyclisation of the β-amino acids **62a** and **62b** activated by $PhP(O)Cl_2$.[74] The effects of substituents, concentration of substrates, solvent and temperature on the yield of the products have been studied. 3-(*N*-substituted amino)-3-phenylpropanoic acid **62a** and racemic-*N*,α-dibenzyl-β-alanine **62b** lead to the synthesis of 2-azetidinones **63a** and **63b**, respectively, in optimum yield when a 0.01 M benzene solution of the substrate is refluxed for 20 h (Scheme 19). A base-promoted cyclisation of β-amino acid amides **64** to azetidinones **65** (Scheme 20) has been reported by Vicario and co-workers.[75]



Scheme 19.



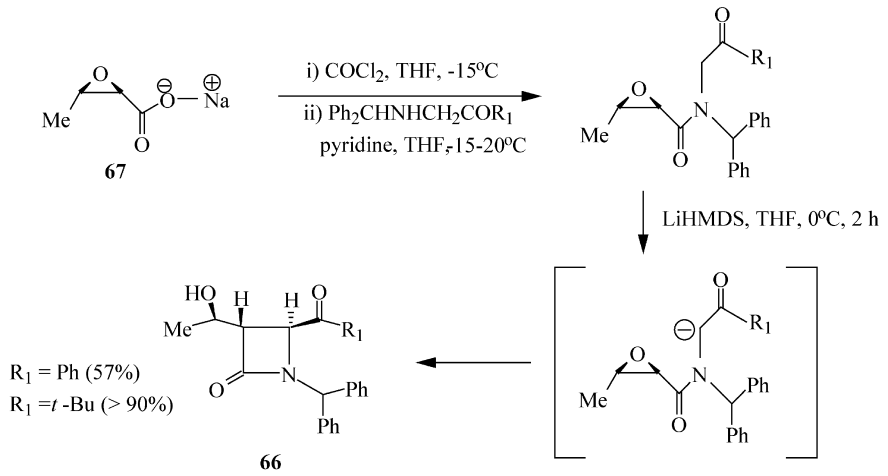
Scheme 18.



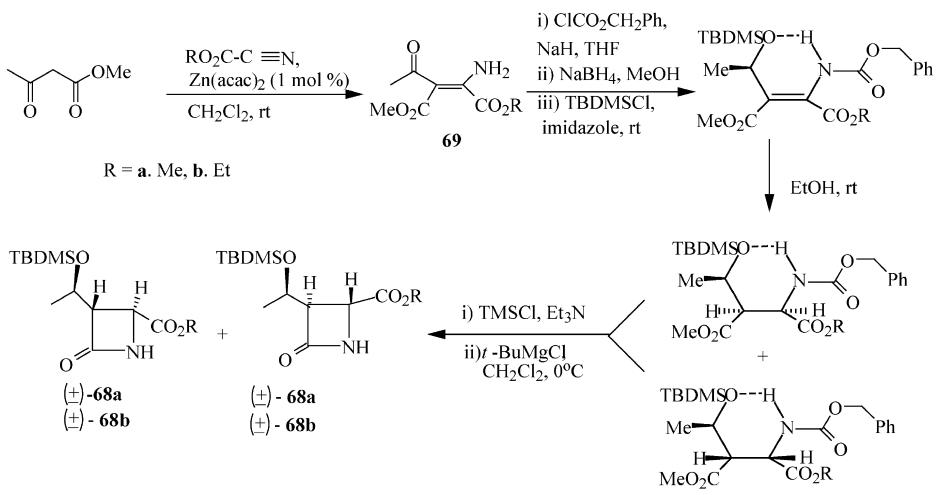
Scheme 20.

Marchand–Brynaert and co-workers have reported the preparation of (3*S*,4*S*)-1-benzhydryl-3-[(5*R*)-1′-hydroxyethyl]-4-acyl-2-azetidinones **66** (Scheme 21) from the (2*R*,3*R*)-*cis*-2,3-epoxybutanoate **67** which in turn was synthesised from L-threonine according to known procedures. Treatment of the epoxybutanoate with aminoketones lead to the formation of the *N*-(phenyl)- and *N*-(pivaloylmethyl)-derivatives of the former. Under basic conditions (the best being LiHMDS), they afford the azetidinones **66** as a result of C-alkylation.[76] Two side products are, however, also formed in this reaction as a result of O-alkylation.

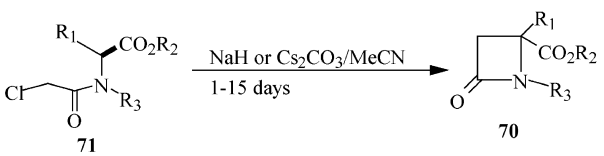
A new simple route (Scheme 22) for the synthesis of *racemic* 2-azetidinones **68**, structurally related to the



Scheme 21.

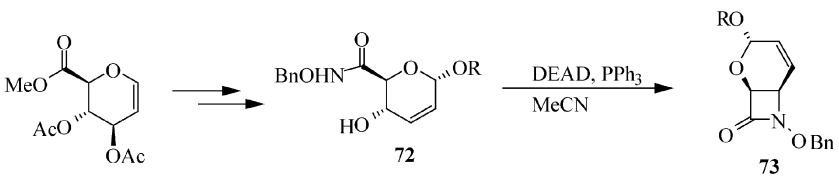


Scheme 22.



a. $R_1 = CH_2Ph$, $R_2 = t$-Bu, R_3 = Bzl; **b**. $R_1 = CH_2Ph$, R_2 = Me, R_3 = Bzl; **c**. $R_1 = CH_2Ph$, $R_2 = t$-Bu, R_3 = pmb
d. $R_1 = CH_2Ph$, R_2 = Me, R_3 = Pmb; **e**. $R_1 = CH_2Ph$, R_2 = Bzl, R_3 = Pmb; **f**. R_1 = H, $R_2 = t$-Bu, R_3 = Pmb;
g. R_1 = H, R_2 = Me, R_3 = Pmb; **h**. R_1 = Me, $R_2 = t$-Bu, R_3 = Bzl; **i**. $R_1 = R_2$ = Me, R_3 = Bzl; **j**. $R_1 = CH_2CHMe_2$,
$R_2 = t$-Bu, R_3 = Pmb; **k**. $R_1 = CH_2CHMe_2$, R_2 = Me, R_3 = Pmb; **l**. $R_1 = (CH_2)_2CO_2Bu^t$, R_2 = Me, R_3 = Pmb;
m. $R_1 = (CH_2)_3NHZ$, R_2 = Bzl, R_3 = Pmb
Bzl = benzyl; Pmb = (p-methoxybenzyl)

Scheme 23.



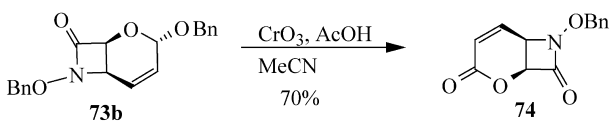
Scheme 24.

antibiotic, thienamycin, has been reported by De Risi and co-workers.[77] β-Enaminoketoesters **69**, obtained by zinc acetylacetonate-catalysed reaction of methyl acetoacetate with alkyl cyanoformates, has been transformed into the β-enaminoesters by reduction of both the C=O and C=C groups. The β-enaminoesters react with trimethylsilyl chloride in triethylamine to give an intermediate which, on treatment with *t*-BuMgCl, leads to the formation of the 2-azetidinones **68**.

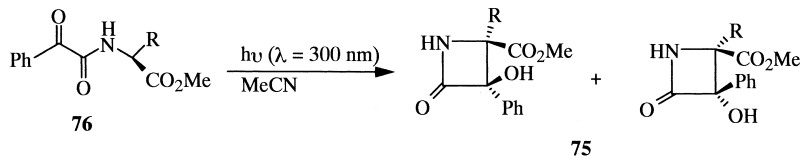
A versatile route (Scheme 23) for the synthesis of an unusual class of 2-azetidinones containing a quaternary carbon at position-4 of the azetidinone ring, the 4-alkyl-4-carboxy-2-azetidinones **70** has been reported by Gonzalez–Muniz and co-workers.[78] This route involves the intramolecular alkylation of *N*-benzyl-*N*-chloroacetylamino acid derivatives **71**.

Durham and Miller have used a carbohydrate template in the glucuronic acid glycosides **72** to prepare novel fused bicyclic azetidinones **73** (Scheme 24).[79] Their strategy involves N1–C4 bond closure of β-hydroxyhydroxamates. Treatment of the azetidinone **73b** with chromium trioxide gives the azetidinone **74** (Scheme 25).

The formation of 3-hydroxy-2-azetidinones **75** in a reversible photocyclisation of phenylglyoxamides **76**



Scheme 25.



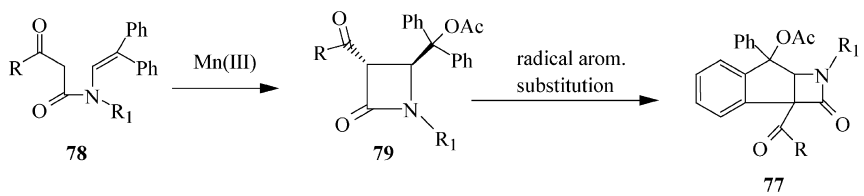
Scheme 26.

(Scheme 26) of enantiomerically pure α-amino acid methyl esters has been reported by Griesbeck and Heckroth.[80] α-Amino acids taken were glycine, alanine, phenylalanine, valine, leucine, isoleucine, t-leucine, aspartic acid, glutamic acid, threonine, proline, thiaproline and sarcosine. In many cases they have isolated the azetidinones in moderate to high diastereoselectivity, with the *cis* isomer as the major component. The presence of a catalytic amount of hydrochloric acid in the reaction mixture stabilises the azetidinones, but reduces and inverts the diastereomeric ratios.

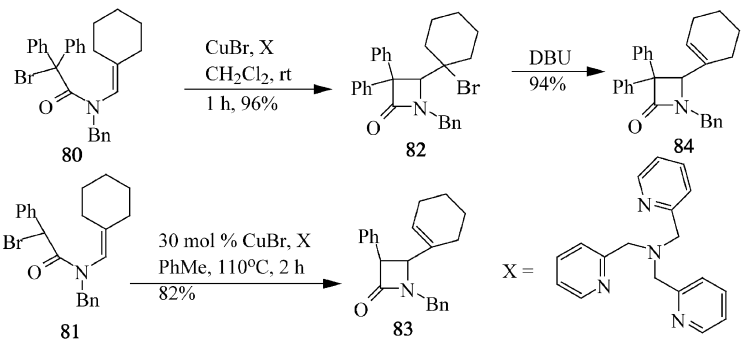
A novel synthesis of fused tricyclic hydrindene-azetidinone compounds **77** from 2-acyl-*N*-(2,2-diphenyl-1-ethyl)-*N*-alkylacetamides **78** (Scheme 27) has been reported by Cerreti and co-workers.[81] The substrates undergo a 4-*exo*-*trig* radical cyclisation, followed by ring closure of the azetidinone **79** via a radical aromatic substitution in the presence of Mn(III) to afford the product.

Copper-mediated atom transfer radical cyclisations of the *N*,*N*-disubstituted bromodiphenylacetamide **80** and the *N*,*N*-disubstituted bromophenylacetamide **81** leading to the formation of the 2-azetidinones **82** and **83** (Scheme 28), respectively, have been reported by the groups of Clark[82] and Bryans.[83] Treatment of the azetidinone **82** with DBU affords the azetidinone **84** in 94% yield.

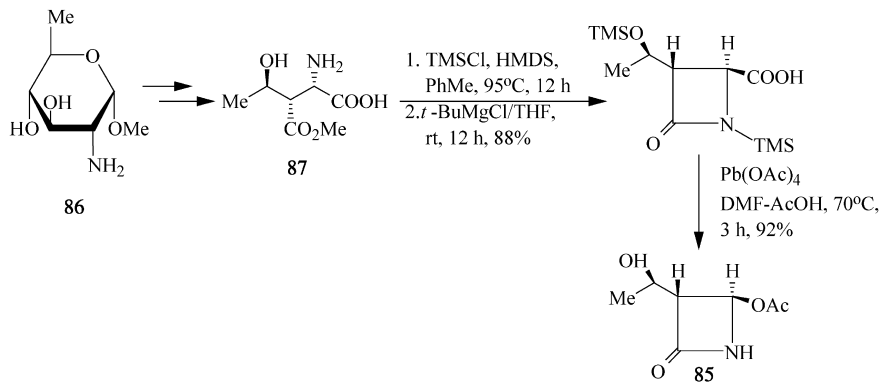
A synthesis of (+)-4-acetoxy-3-hydroxyethyl-2-azetidinone **85**, which is a key intermediate for the synthesis of the carbapenem antibiotic, (+)-thienamycin, has been reported by Tatsuta and co-workers.[84] A commercially available starting material, 2-amino-2,6-dideoxy-α-D-glucopyranoside **86** leads to the formation of a hydroxy acid **87** through



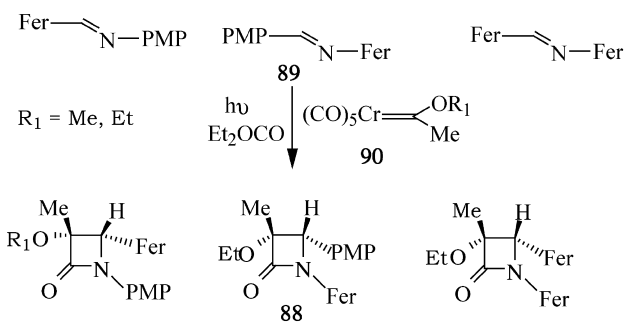
Scheme 27.



Scheme 28.



Scheme 29.



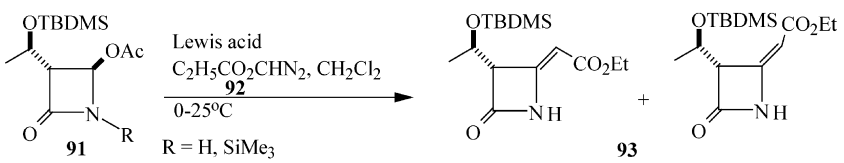
Scheme 30.

a skeletal rearrangement and stereoselective epimerisation. The latter acid has been transformed to **85** as shown in Scheme 29.

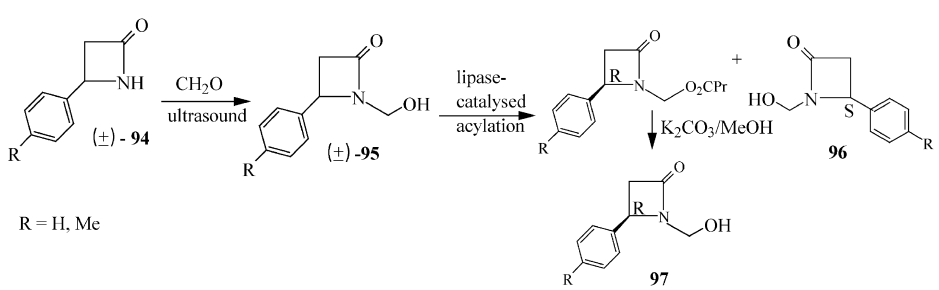
Novel ferrocene-substituted 2-azetidinones **88** have been prepared by a photochemical reaction of the ferrocene-containing imines **89** with chromium carbonyl-carbene complexes **90** (Scheme 30).[85]

4. Chemical transformations of azetidinone derivatives

Several novel compounds containing an azetidinone ring



Scheme 31.



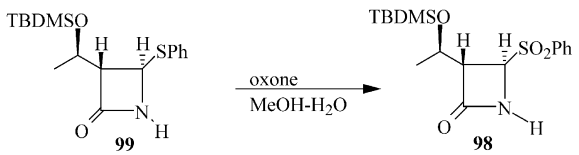
Scheme 32.

have been synthesised by the transformation of a compound already having this ring.

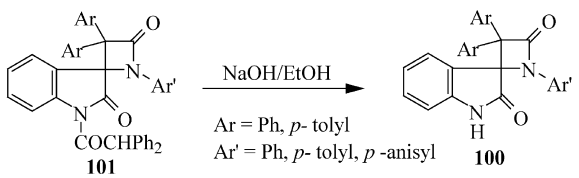
Cainelli and co-workers have treated (3*R*,4*R*,1′*R*)-3-[1-(*t*-butyldimethylsilyloxy)ethyl]-4-acetoxy-2-azetidinones **91** with ethyl diazoacetate **92** in the presence of a Lewis acid such as $TiCl_4$, TiF_4, $AlCl_3$ or $SnCl_4$ to synthesise the novel (3*S*,1′*R*)-3-[1-(*t*-butyldimethylsilyloxy)ethyl]-4-(1-ethoxycarbonylmethylidene)-2-azetidinone **93** as an *E* and/or *Z* isomer (Scheme 31).[86]

Fulop and Furo treated 4-aryl-2-azetidinones **94** with formaldehyde under sonication to form the *N*-hydroxymethyl-2-azetidinones **95** (Scheme 32).[72] They resolved the *racemate* by enzyme-catalysed acylation to obtain azetidinones **96** and **97**.

Lee and co-workers have reported the synthesis of the (−)-4-phenylsulfonyl-2-azetidinone **98** by sulfur oxidation of the sulfide in the azetidinone **99** (Scheme 33).[71]



Scheme 33.



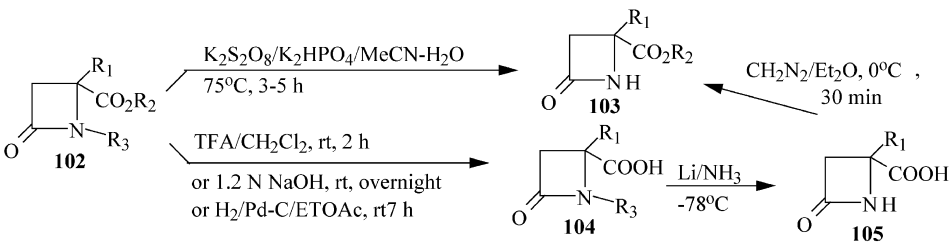
Scheme 34.

The synthesis of some novel spiroazetidinones **100** containing an indolinone ring has been reported by Singh.[87] The spiroazetidinones **101** undergo selective N-decarbonylation in ethanolic sodium hydroxide to give the products (Scheme 34). The spiroazetidinones **101** are known to have significant anticonvulsant activity.[24] Gonzalez–Muniz have reported selective C- and N-deprotections in 4-alkyl-4-carboxy-2-azetidinones **102**, leading to the formation of the N-unsubstituted azetidinones **103**–**105** (Scheme 35).[78] An oxidative N-dearylation in the spiro-azetidinones **106** using ceric ammonium nitrate, followed by treatment with a SO_3–pyridine complex, leads to the synthesis of the spiro-*N*-sulfonylazetidinone derivatives **107** (Scheme 36).[58]

Oxidative degradation of the azetidinones **108** bearing electron-rich groups such as *p*-methoxyphenyl, furyl and thienyl has led to the synthesis of the 4-carboxy derivatives **109**, which have been further transformed into an acetoxy group **110** in a Kolbe reaction of the type II (Scheme 37a). The compounds containing a cinnamyl group **111** have been reported to undergo ozonolysis, giving rise to the 4-formyl-substituted azetidinones **112** and **113** (Scheme 37b).[48]

Synthesis of *cis*-3-phenoxyacetamido-4-alkoxyazetidinones **114** from a dirhodium tetraacetate-catalysed reaction of the azetidinones **115** containing a diazo group has been reported by Wolfe and co-workers.[88] The azetidinones **115**, formed by a diazo transfer in the azetidinones **116**, have been shown to undergo an electrocyclic ring opening, leading to the formation of a thietanone and the 3-acylaminoazetinones. The latter react with various alcohols in the presence of Rh_2OAc_4 to give the products (Scheme 38).

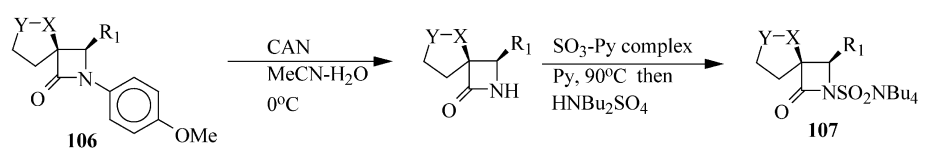
Ceric and co-workers have reported the formation of *trans*-3-amino-4-oxo-azetidin-2-sulfonic acid **117** as a result of regioselective epimerisation (Scheme 39) of its *cis* isomer **118**.[89] Both *cis* and *trans* isomers have been converted to the



104a. R_1 = CH_2Ph; R_3 = Bzl; **b**. R_1 = CH_2Ph, R_3 = Pmb; **c**. R_1 = H, R_3 = Pmb; **d**. R_1 = Me, R_3 = Bzl; **e**. R_1 = CH_2CHMe_2, R_3 = Pmb

105a. R_1 = CH_2Ph, R_2 = Bu*t*; **b**. R_1 = CH_2Ph, R_2 = Me

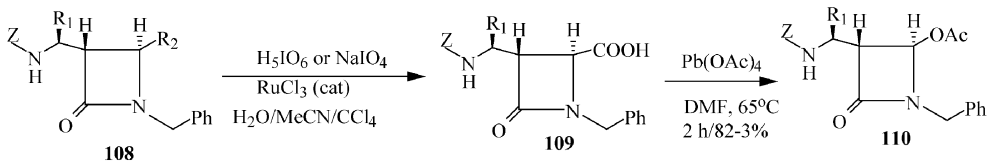
Scheme 35.



X = O, Y = CH_2
X = CH_2, Y = O

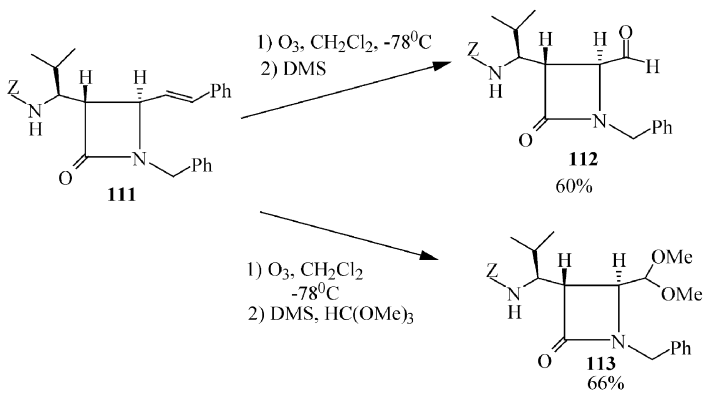
a. R_1 = Ph, X = O, Y = CH_2
b. R_1 = Ph-CH=CH, X = O, Y = CH_2
c. R_1 = Ph, X = CH_2, Y = O

Scheme 36.



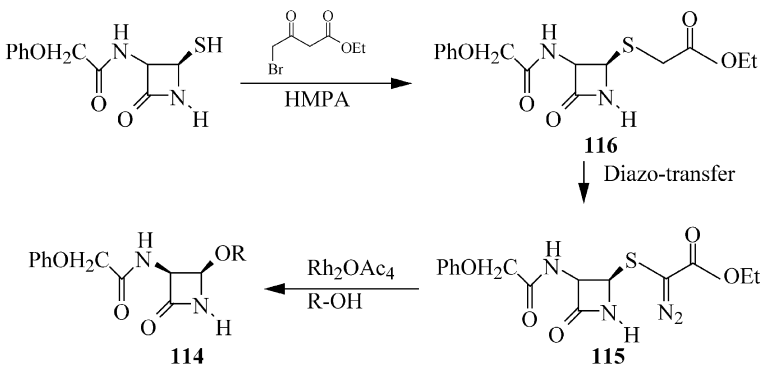
a. R_1 = Me, R_2 = 4-$MeOC_6H_4$; **b**. R_1 = Me, R_2 = 2-furyl; **c**. R_1 = Me, R_2 = 2-thienyl; **d**. R_1 = *i*-Pr, R_2 = 2-furyl; **e**. R_1 = *i*-Pr, R_2 = 2-thienyl;

(a)



(b)

Scheme 37.



Scheme 38.

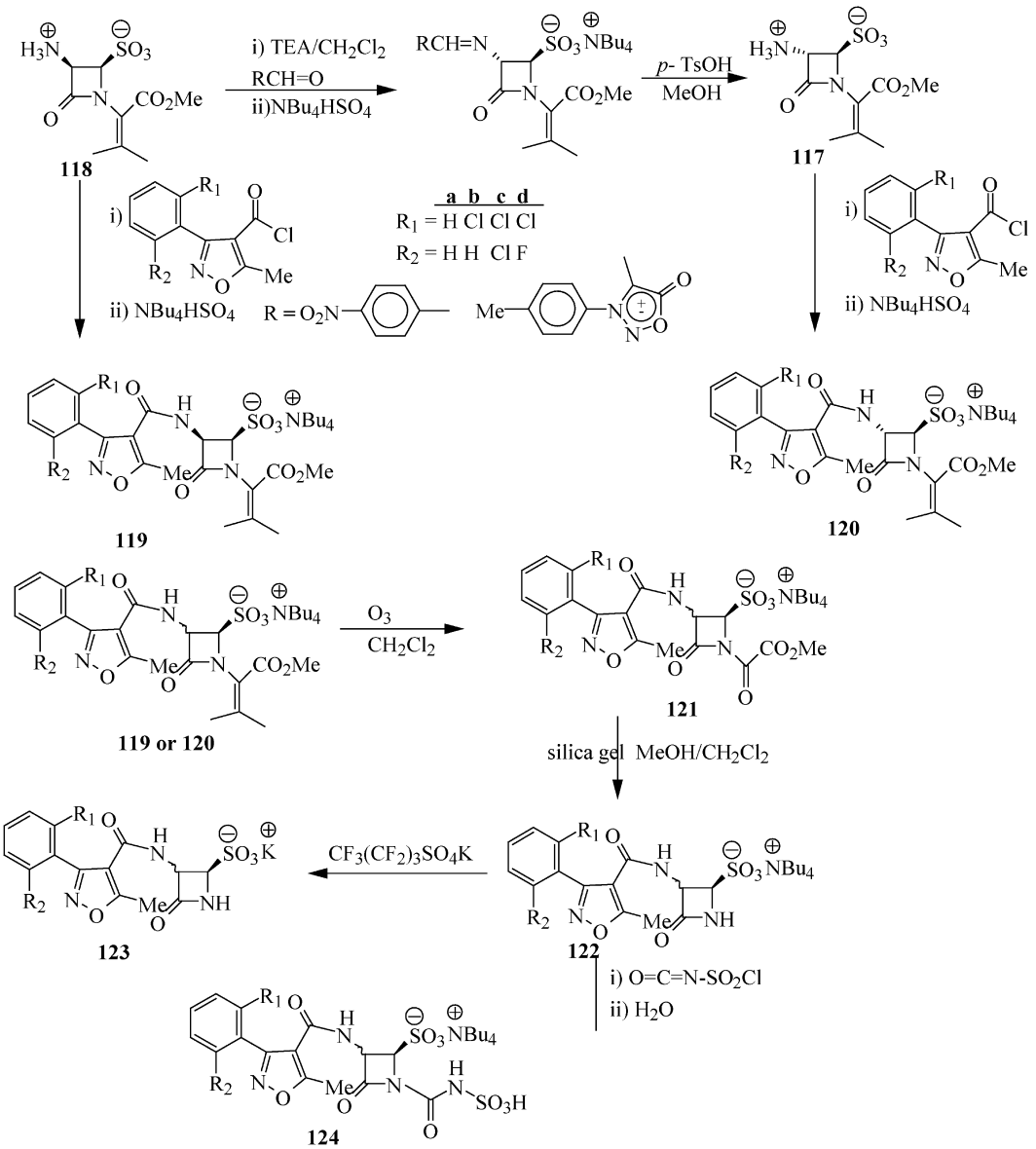
monocyclic azetidinones **119**–**124** by simple methods (Scheme 39).

Kilburn and his group have published the synthesis of the novel fused tricyclic azetidinones **125** and **126** by radical cyclisation in the suitably substituted azetidinones **127** and **128** (Schemes 40 and 41).[90] They first synthesised the 4-methylenecyclopropyl azetidinone **129** by coupling of azetidinone **130** with lithium bis(methylenecyclopropyl)-cuprate (Scheme 42). The former compound has been subjected to various reactions giving the new azetidinone derivatives (**127**, **128** and **131**–**133** (Scheme 42). The azetidinones **127** and **128** bearing a 1-propyne substituent on nitrogen have afforded the tricyclic azetidinones **125** and **126**, respectively, via a 7-*endo* cyclisation on treatment with Bu_3SnH/AIBN. Azetidinone **136** has been synthesised from the azetidinone **135** and **134** by the method used for the synthesis of azetidinone **129** and has been transformed to a fused tricyclic azetidinone **137** (Scheme 43).

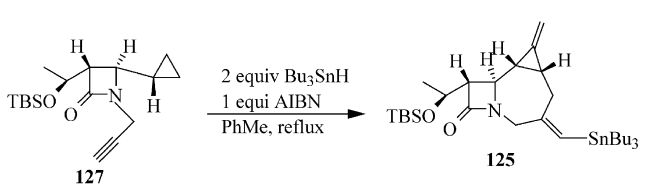
Clamente and co-workers have transformed the azetidinones **138** to **139** in a few simple steps (Scheme 44). These compounds have been found to exhibit the inhibitory potency and selectivity for the enzyme, human leukocyte elastase (HLE).[91]

A general and efficient synthesis of different types of 2-azetidinones **140** bearing a quinone moiety at the N-1, C-3 and C-4 positions has been reported by Alcaide and his group. The azetidinones **141**, synthesised by the Staudinger method, have been treated with CAN in acetonitrile–water (3:1) at 25°C to afford the products **140** (Scheme 45).[92] It is noteworthy that the stereochemistry of the starting azetidinone is transferred to the product.

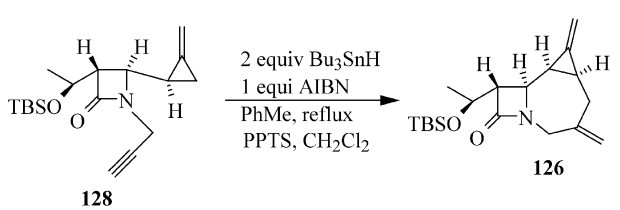
The 2-azetidinones **142** with 3-(3′-arylpropenyl) substituents have been synthesised by Rosenblum and his group employing a palladium-catalysed arylation of the azetidinone **143** (Scheme 46).[93] The unsaturated



Scheme 39.



Scheme 40.

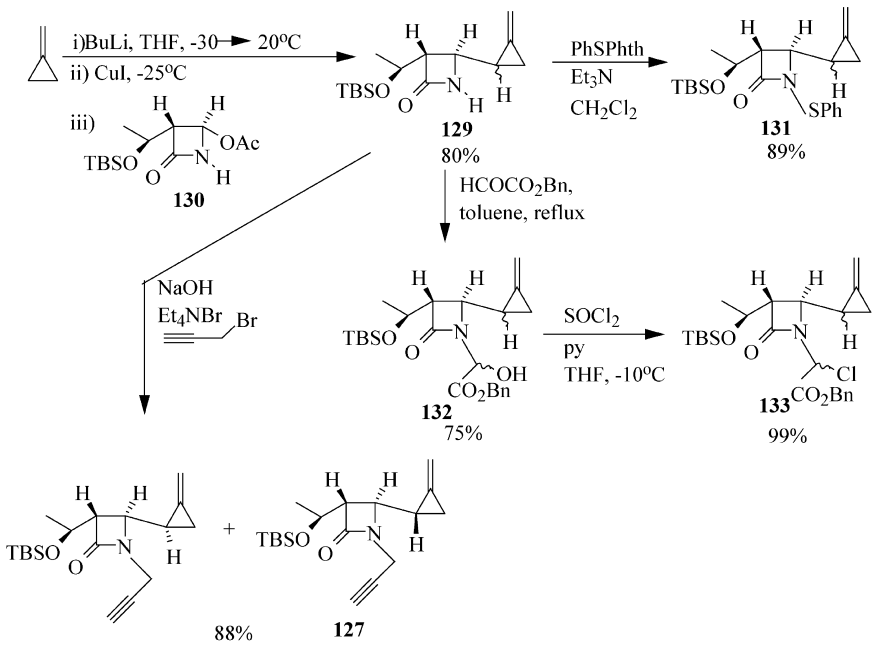


Scheme 41.

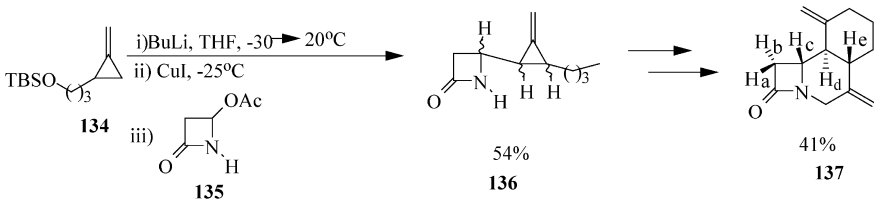
azetidinones have been transformed to their saturated analogues **144** by catalytic hydrogenation. The authors have reported their cholesterol absorption inhibitory activity.

A base-catalysed isomerisation of the azetidinones **145** with *cis* geometry to the azetidinones **146** with *trans* geometry has been reported by Alcaide and co-workers[94] Azetidinones **146**, on Wittig reaction, yield the azetidinones **147** (Scheme 47). This group has also reported a thermally induced isomerisaton of the azetidinones **148** with *cis* geometry to the azetidinones **149** with *trans* geometry (Scheme 48).[95]

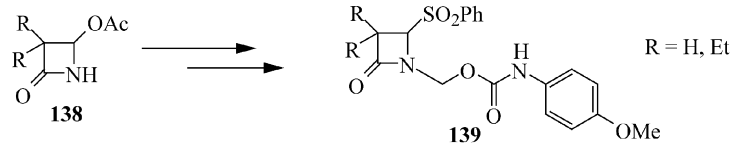
Alcaide and co-workers have done commendable work in the area specifically employing 4-oxoazetidin-2-carbaldehydes.[96–98] The latter derivatives, synthesised both in the *racemic* and optically active forms using standard methodology, have been subjected to various reactions, such as



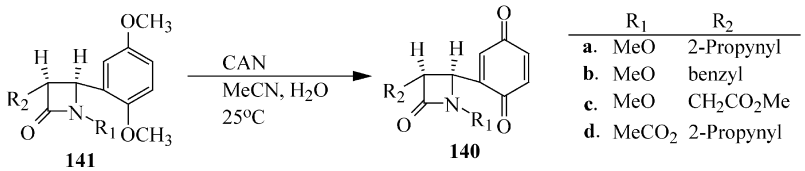
Scheme 42.



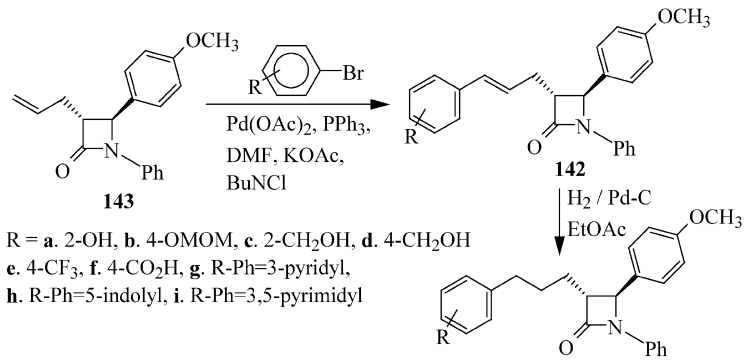
Scheme 43.



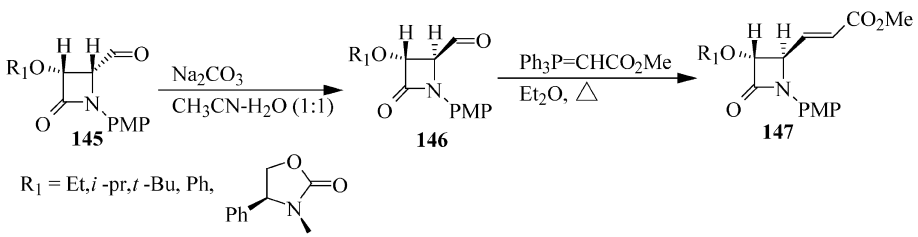
Scheme 44.



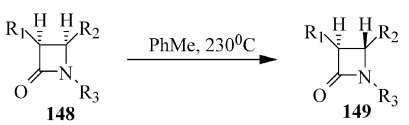
Scheme 45.



Scheme 46.

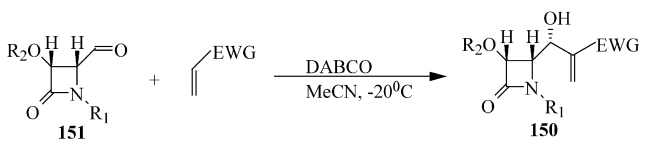


Scheme 47.



a. R_1=MeO, R_2=3-furyl, R_3=3-butenyl; **b**. R_1=MeO, R_2=3-furyl, R_3=allyl;
c. R_1=MeO, R_2=3-furyl, R_3=benzyl; **d**. R_1=PhO, R_2=2-furyl, R_3=propargyl
e.R_1=PhO, R_2=2-furyl, R_3=3-butenyl; **f**. R_1=PhO, R_2=PMP, R_3=$PhCH_2$;
g. R_1=MeO, R_2=3-thienyl, R_3=allyl

Scheme 48.

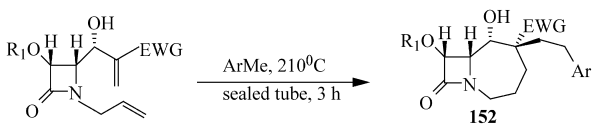


R_1 = 2-propenyl, 3-butenyl, 2-propynyl, 3-butynyl, 4-pentynyl, 5-hexynyl
R_2 = Ph, Me; EWG = COMe, CN, CO_2Me

Scheme 49.

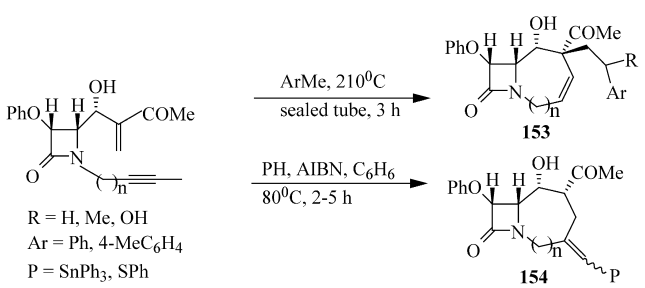
cycloadditions, cyclisations, rearrangements and isomerisation, leading to a wide variety of monocyclic and fused bi- and tricyclic compounds. These reactions have been reviewed by Alcaide and Almendros.[99]

The Baylis–Hillman adducts **150** have been synthesised, almost as single diastereomers, by a DABCO-promoted reaction of various activated vinyl systems with the appropriate 4-oxoazetidine-2-carbaldehydes **151** in acetonitrile at −20°C (Scheme 49).[100] The former compounds, on heating in toluene, *p*-xylene or mesitylene in a sealed tube at 210°C, have led to the synthesis of bicyclic products in single stereoisomeric forms (**152**–**154**) (Schemes 50 and 51).



R_1 = Ph, Me; R_2 = Ph, 4-MeC_6H_4, 3,5-diMeC_6H_4; EWG = COMe, CO_2Me, CN

Scheme 50.



Scheme 51.

The formation of the products has been explained in terms of a competition between a tandem radical Michael addition/*endo* cyclisation and a tandem radical addition/Michael addition, depending on the electronic nature of radical promoter.

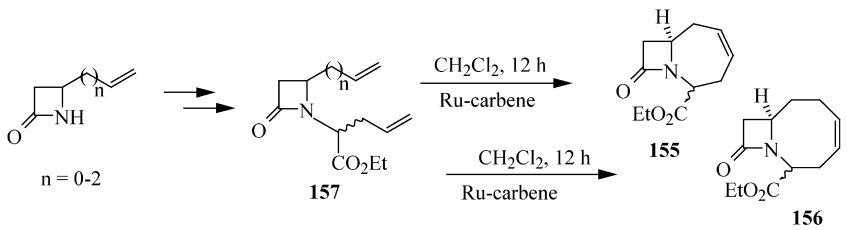
Barrett and co-workers have reported a method for the synthesis of the novel fused bicyclic azetidinone carboxylic esters **155** and **156** from 4-alkenyl-2-azetidinones **157** via an Ireland–Claisen rearrangement and subsequent metathesis employing molybdenum carbene or ruthenium carbene catalysts (Scheme 52).[101] The azetidinones **158** and **159** have been synthesised using the same method from the azetidinones **160** and **161** (Schemes 53 and 54), respectively. A fused bicyclic azetidinone **162** with a diene function in the other ring, synthesised by this methodology, has been transformed to a fused tetracyclic azetidinone **163** (Scheme 55).

Mori and Kozawa are actively engaged in developing new methods for the construction of the carbapenem skeleton.[102–103] A new method involving a palladium-catalysed C–N bond-forming reaction (Scheme 56) in the azetidinones **164** leading to the synthesis of the carbapenem **165** with a carboxy group on C-3 of the five-membered ring has been reported by these workers.[104] An access to the carbacephem skeleton has been reported by Avenoza and co-workers by an asymmetric hetero Diels–Alder reaction of the benzylimine derived from the enantiomer of Garner's aldehyde with Danishefsky's diene.[105]

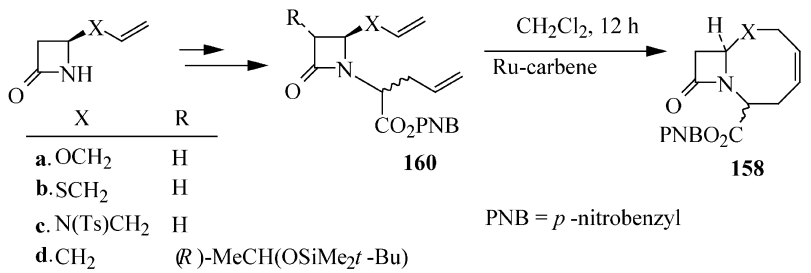
The azomethine ylide strategy is of general utility for the synthesis of a wide range of bicyclic azetidinones. Oxazolidinones serve as a source of β-lactam-based azomethine ylides. A comprehensive mechanistic evaluation of this strategy and alternative pathways for azomethine ylide generation have been discussed by Brown et al.[106,107]

5. Synthesis of 3-azetidinones

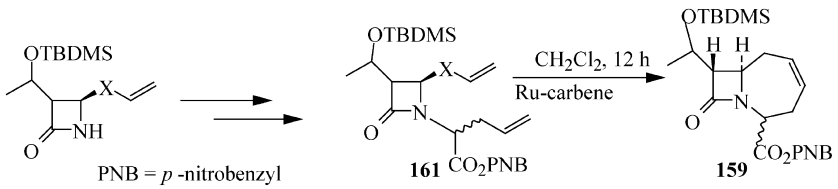
Little attention has been paid so far to azetidin-3-ones, probably because they are not found in the nature. Recently, 3,3-dihydroxyazetidine, the hydrate of azetidin-3-one, has been isolated from *Bacillus cereus* and has been found to act as a growth-promoting factor for several stains of Bifidobacteriua.[108] The important methods for the synthesis of azetidin-3-ones involve cyclisation of α-amino-α′-diazoketones[109] or α-amino-α′,β′-epoxyketones,[110] oxidation of 3-azetidinols[111] and ozonisation of 3-alkylidene-1-substituted azetidines.[112]



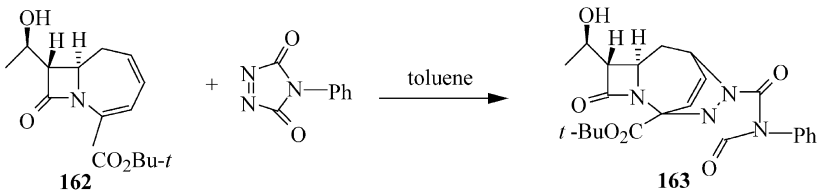
Scheme 52.



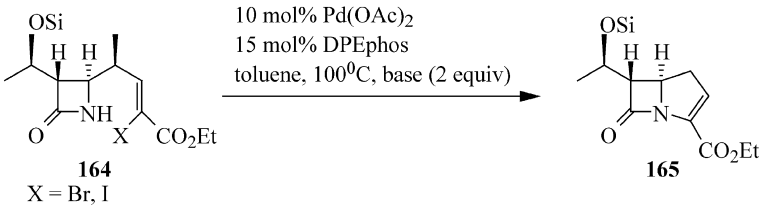
Scheme 53.



Scheme 54.



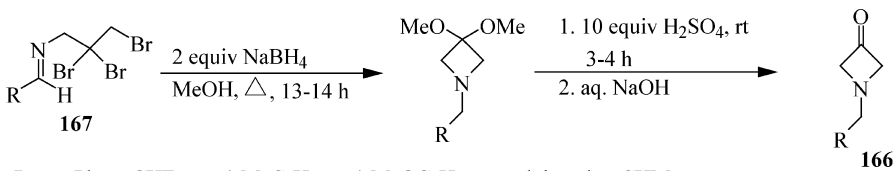
Scheme 55.



Scheme 56.

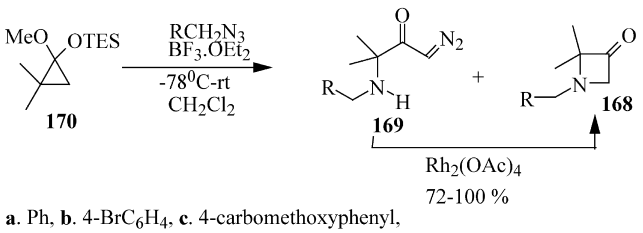
Kimpe and co-workers have reported an easy entry to the 2,4-unsubstituted azetidin-3-ones **166**, starting from the *N*-(alkylidene)-, or *N*-(arylidene)-2,2,3-tribromopropylamines **167**.[113] Cyclization of the latter derivatives with excess sodium borohydride in methanol under reflux, followed by treatment with concentrated sulfuric acid, afforded the products **166** (Scheme 57).

Desai and Aube have reported a facile route to the 3-azetidinones **168** through cyclisation of the



R = **a**. Ph, **b**. $CHEt_2$, **c**. 4-MeC_6H_4, **d**. 4-$MeOC_6H_4$, **e**. cyclohexyl, **f**. $CHMe_2$

Scheme 57.



a. Ph, **b**. 4-BrC_6H_4, **c**. 4-carbomethoxyphenyl, **d**. 2-naphthyl, **e**. 9-anthracenyl, **f**.*n*-hexyl

Scheme 58.

α-amino-α′-diazomethylketones **169**.[114] The latter compounds have been synthesised via ring opening of the substituted cyclopropanone **170** with alkyl azides. Treatment of the α-amino-α′-diazomethylketones with dirhodium tetraacetate affords the products **168** in good yield (72–100%) (Scheme 58).

6. Concluding remarks

The antibiotic activity of azetidinone ring-containing compounds, their effectiveness in cholesterol absorption and enzyme inhibitions and their applications as synthons for various biologically important compounds make them appealing targets for medicinal synthetic chemists. The Staudinger reaction still occupies a central place among the synthetic methods for azetidinone synthesis. Efforts are in hard to achieve stereocontrol in the reaction. Many authors are now able to carry out stereo- and enantioselective reactions employing different conditions and reagents, e.g. chiral imines, ketenes and catalysts. Attempts have been made to define the mechanistic pathway in many cases and computer-assisted calculations have been used in some areas. It may be readily anticipated that more reports will be forthcoming in this area. Cyclisation of azetidinone-tethered compounds remains the principle strategy for the synthesis of bi- and tricyclic compounds containing the azetidinone ring. 3-Azetidinones are likely to attract increasing attention in the near future.

I would like to apologise to those scientists whose work may not have appeared in this review due to oversight.

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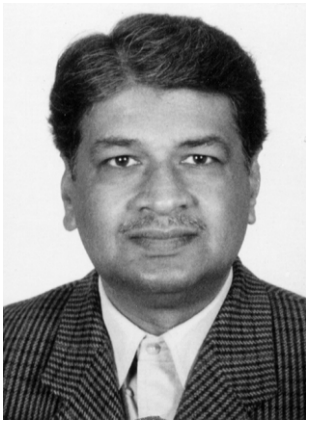
Biographical sketch



Girija S. Singh was born in 1957 in Sasaram (Bihar), India. He received his BSc and MSc degrees from the Gorakhpur University, India, in 1977 and 1979, respectively. He received his PhD degree from the Banaras Hindu University (BHU), India, completing his doctoral thesis on the reactions of diazoalkanes and diazoketones with imines, amines and hydrazones in October, 1984 as junior research fellow (1981–82) and senior research fellow (1983–85) of the Council of Scientific and Industrial Research (CSIR), N. Delhi. He was then awarded a post-doctoral fellowship of the CSIR for one year and worked with Professor S. N. Pandeya in the same university on synthesis and anticonvulsant activities of thiadiazoles and azetidinones. Before joining Professor Pandeya again in 1989 as a research associate of the University Grants Commission, N. Delhi, he worked as a research associate of the Ministry of Environment and Forest, India, with Professor U. K. Choudhary in the Ganga Laboratory, BHU (1987–88). He joined the research group of Professor T. Ibata at Osaka University, Japan in 1992 and worked on the reactions of ketocarbenoids and metal-catalyzed oxidations as a post-doctoral research student sponsored by the Ministry of Education, Science and Culture, Japan. He returned to the Chemistry Department of BHU in July 1994 as a senior research associate (Pool Officer) where he taught organic photochemistry and molecular rearrangements to MSc Students, and did independent research. He joined as a lecturer in the University of Zambia in 1996, and then in the University of Botswana in 1998 where he is currently working as a senior lecturer. His research interests include the development of new methodologies for the synthesis of biologically important heterocycles, specially using diazo compounds, metal-catalyzed oxidations and organic chemistry education.