

Short Review on Synthesis of Thiazolidinone and β -Lactam

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Abstract The review summarizes literature dealing with the synthesis of thiazolidinone and β -lactam. Various methods for synthesis of thiazolidinone and β -lactam are discussed. Like boiling benzene thioglycolic acid was added to (1)a-d using a water separator to give thiazolidinone derivatives (2)a-d. Also Reaction of the Schiff bases of 3 and/or 5 with one mole of thioglycolic acid was proceeded smoothly to afford the corresponding thiazolidinone derivatives 6,7 respectively. The synthesis of a new type of compound, 2-hydrazolyl-5,5-diphenyl-4-thiazolidinone (24), obtained by treatment of thiosemicarbazone with benzyl in basic media. β -lactams were prepared by *N*-Tosyl-3-halo-3-butenylamines underwent efficient Ullmann-type coupling to afford 2-alkylideneazetidines, which could be readily converted to the corresponding β -lactams by oxidation with O₃ to give β -lactams 119. A chiral N-heterocyclic carbene catalyzed the Staudinger reaction of arylalkylketenes with a variety of *N*-tert-butoxycarbonylarylimines to give the corresponding *cis*- β -lactams 124.

Keywords: thiazolidinone, β -lactam, thioglycolic acid, Schiff's bases, synthesis, condensation

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1. Introduction

β -Lactams, being a structural unit found in the most widely used antibiotics [1], have occupied a basic position in medicinal chemistry for almost a century now. With the microbes basic position in medicinal chemistry for almost a century now. With the microbes responding to the traditional antibiotics through β -lactamases, the need for novel antibiotics prevails, making synthesis of newer β -lactams ever more important. In addition to their use as antibiotics, β -lactams are increasingly being used as synthons for other biologically important molecules [2-11]. β -Lactams have been found to act as cholesterol acyl transferase inhibitors [12], thrombin inhibitors [13], human cytomegalovirus protease inhibitors [14], matrix metalloprotease inhibitors [15], cysteine protease [16], and apoptosis inducers [17]. Moreover, thiazolidin-4-ones and their derivatives are an important class of compounds in organic and medicinal chemistry. The thiazolidin-4-one ring system is a core structure in various synthetic pharmaceutical agents, displaying a broad spectrum of biological activities such as, antitubercular [18], antibacterial [19], anti-HIV [20], anti-inflammatory [21], anti-histaminic [22], antifungal [23], anticancer [24] and analgesic [25].

2. Thiazolidinone

2.1. Synthesis from Cycloaddition Reaction of Thioglycolic Acid to Schiff's Bases

Cycloaddition reaction of thioglycolic acid to the Schiff's bases derivatives (1)a-d proceeded successfully. Thus, in boiling benzene thioglycolic acid was added to (1)a-d using a water separator to give thiazolidinone derivatives (2)a-d. Soleiman et al, 2002 [26].

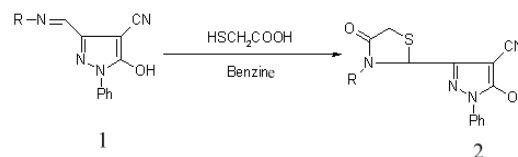


Figure 1. Synthesis from cycloaddition reaction of thioglycolic acid to Schiff's bases

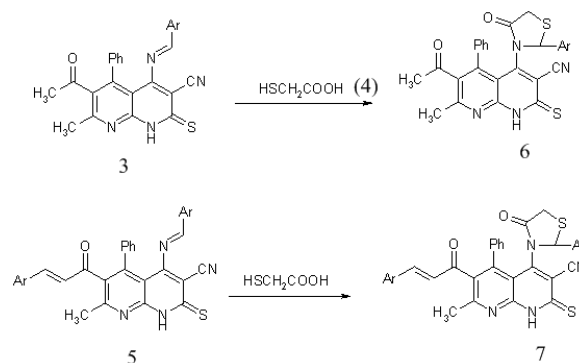


Figure 2. Reaction of the Schiff's bases of 3 and/or 5 with one mole of thioglycolic acid

Reaction of the Schiff bases of 3 and /or5 with one mole of thioglycolic acid was proceeded smoothly to afford the corresponding thiazolidinone derivatives 6,7 respectively. Soleiman H.A. et al, 2002 [26].

It is interesting to mention that along with an efficient strategy for synthesis of new heterocyclic by cyclocondensation, reaction of compound (9) with chloroacetyl chloride produced the new compound (10) which is used for the synthesis of thiazolidinone (13). ELKanzi et al. , 2007 [27].

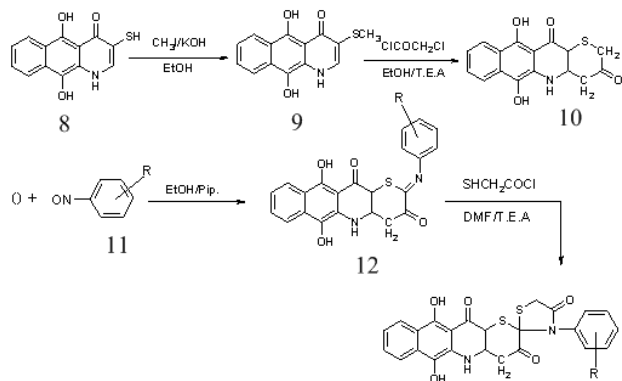


Figure 3. Cycloaddition reaction of thioglycolic acid to Schiff's bases(12) to give thiazolidinone (13)

Cycloaddition reaction of thioglycolic acid to the prepared Schiff's bases (16)a-c in a mixture of ethanol and DMF in the presence of piperidine as catalyst and afforded thiazolidinone derivatives (17)a-c. ELKanzi et al, 2007 [28].

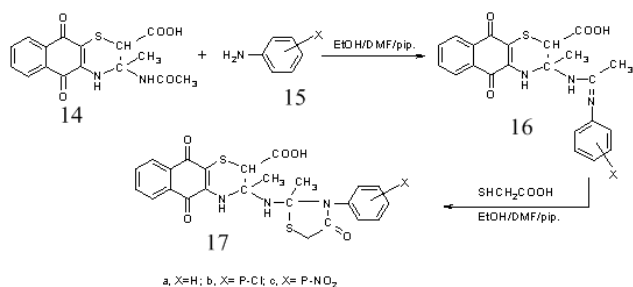


Figure 4. Cycloaddition reaction of thioglycolic acid to the prepared Schiff's bases (16)a-c afforded thiazolidinone derivatives (17)a-c

2.2. Synthesis of Thiazolidinone Derivatives from Aldehydes, Thiosemicarbazides, and Maleic Anhydride

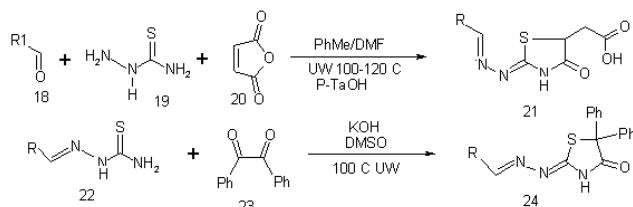


Figure 5. reaction of aldehyde, thiosemicarbazides, and maleic anhydride to give thiazolidinone derivatives (21) and treatment of thiosemicarbazone with benzyl give thiazolidinone derivatives (24)

A tandem method for the synthesis of 2-hydrazolyl-4-thiazolidinones (21) from commercially available materials in a 3-component reaction has been developed. The reaction connects aldehydes, thiosemicarbazides, and maleic anhydride, effectively assisted by microwave irradiation. The synthesis of a new type of compound, 2-

hydrazolyl-5,5-diphenyl-4-thiazolidinone (24), obtained by treatment of thiosemicarbazone with benzyl in basic media is also reported. HOMO/LUMO energies, orbital coefficients, and charge distribution were used to explain the proposed reaction mechanism. Cecilia Saiz et al, 2008 [29].

2.3. Cyclocondensation of Schiff's bases with 2-mercaptopropionic Acid Afforded 4-Thiazolidinone Derivatives

A series of 4-thiazolidinones and 2-azetidinones have been synthesized by condensation of 4,4'-diaminodiphenylsulphone with various aromatic or heterocyclic aldehydes to yield the Schiff's bases. Cyclocondensation of Schiff's bases with 2-mercaptopropionic acid afforded 4-thiazolidinone derivatives, and cyclocondensation of Schiff's bases with chloroacetylchloride in presence of triethylamine afforded 2-azetidinone derivatives.. All these compounds were evaluated for their *in vitro* growth-inhibitory activity against several microbes. Standard ampicillin against *Bacillus subtilis*. Mehta et al, 2006 [30].

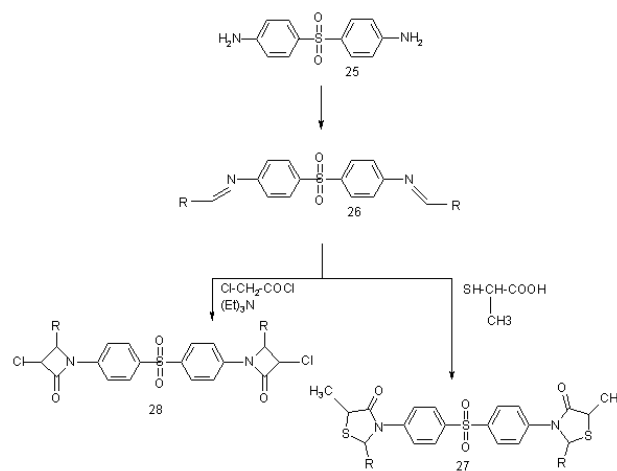


Figure 6. Cyclocondensation of Schiff's bases with 2-mercaptopropionic acid afforded 4-thiazolidinone derivatives (27)

2.4. Synthesis Via Suzuki Coupling Reaction and Knoevenagel Condensation

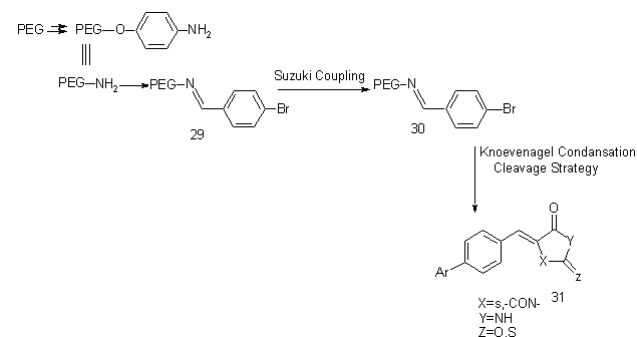


Figure 7. Reaction of Aldehyde to the polyethylene glycol (PEG)-and aniline via an imine linkage follow by Knoevenagel condensation afford thiazolidinone derivatives 31

An efficient method for the soluble polymer-supported synthesis of 5-arylidene thiazolidinones and pyrimidinones using aniline as a traceless linker was described. Aldehyde substrates were attached to the polyethylene glycol (PEG)-

bound aniline via an imine linkage, and after the subsequent PEG-promoted Suzuki coupling reaction for the diversification, Knoevenagel condensation was readily employed as the cleavage strategy. Zhang Liu et al, 2008 [31].

2.5. Reaction of Schiff's bases (35a-i) with Thioglycolic Acid

2-Acetylnaphtho [2,1- b] furan (32), obtained from 2-hydroxy-1-naphthaldehyde was converted into 2-bromoacetylnaphtho[2,1- b]furan 33), which served as an intermediate for the synthesis of title compounds. The compound (33) was treated with thiourea to get 2-(2-aminothiazol-4-yl)naphtho[2,1- b]furan (34), which produced 2-(2-arylideneaminothiazol-4-yl)naphtho[2,1-

b]furans (35 a-i) on reacting with various aromatic aldehydes. Schiff bases (35a-i) yielded 2-[2-(2-aryl-4-thiazolidinone)thiazol-4-yl] naphtho [2,1- b]furans (36 a-i) on treating with thioglycolic acid. Compound (33) was reacted with different aromatic amines to obtain 2-(N-aryl-2-amino) acetylnaphtho [2,1- b]furans (37a-k). Similarly reaction with substituted thiourea furnished 2-(2-N-arylaminothiazol-4-yl)naphtho[2,1- b]furans (38a-k). All the newly synthesized compounds have been characterized by elemental analysis and spectral data, which have been screened for antimicrobial and anthelmintic activities. The selected compounds have been evaluated for antiinflammatory and diuretic activities. Vagdevi et al, 2006 [32].

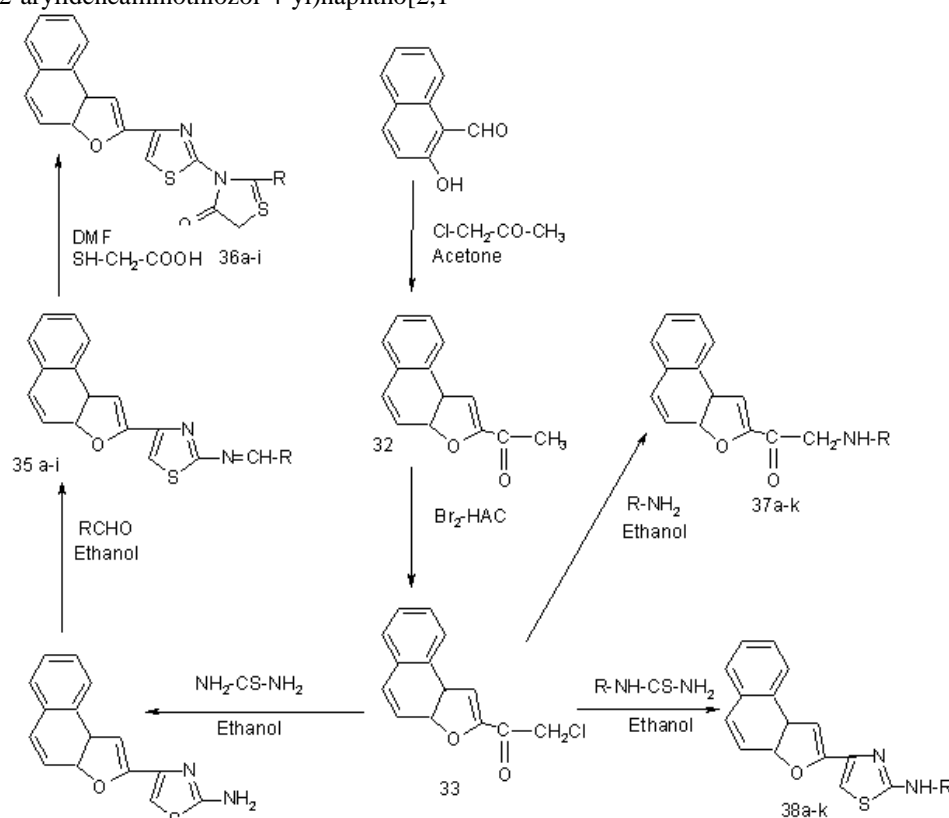


Figure 8. Reaction of Schiff's bases (35a-i) with thioglycolic acid

2.6. Synthesis by Microwave Irradiation of a Mixture of Amine Hydrochloride, Aldehyde and Mercaptoacetic Acid

The preparation of thiazolidin-4-ones by condensation of aromatic aldehydes, amines and mercaptoacetic acid in ethanol. The optimized procedure involved microwave

irradiation of a mixture of amine hydrochloride, aldehyde and mercaptoacetic acid (molar ratio 1:2:3) in the presence of 1.25 equivalents of *N,N*-diisopropylethylamine (DIEA) base in ethanol at 120°C for 30 minutes at atmospheric pressure. Kappe et al, 2004 [33].

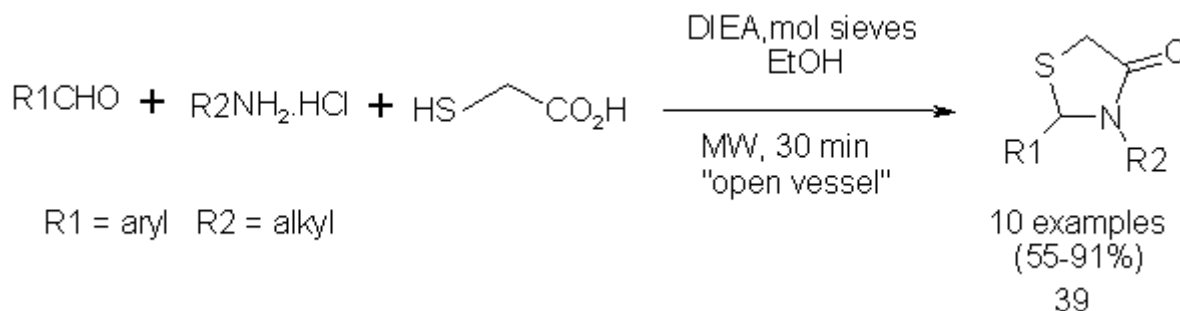


Figure 9. Microwave irradiation of a mixture of amine hydrochloride, aldehyde and mercaptoacetic acid afford thiazolidinone derivatives (39)

2.7. Synthesis from Fluoroussulfonate 42

Synthesis of 2-aryl-substituted 4-thiazolidinone and 4-thiazinanone libraries as drug candidates. Fluoroussulfonate tag 42 was introduced and performed

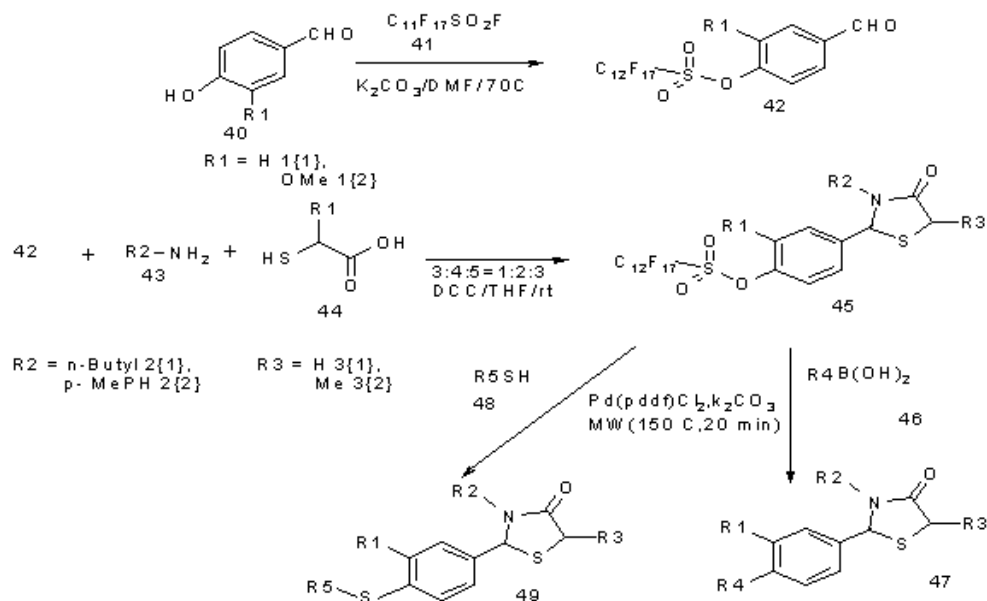


Figure 10. synthesis of 2-aryl-substituted 4-thiazolidinone

2.8. Synthesis from Cyclization of Compound (52a-e) with Thioglycolic Acid Yielded 2-(4-chloro-3-methylphenoxy)-N-(4-oxo-2-arylthiazolidin-3-yl) Acetamide (53 a-e)

2-(4-Chloro-3-methylphenoxy)acetohydrazide (51) derived from ethyl 2-(4-chloro-3-methylphenoxy)acetate (50) was reacted with different aromatic aldehydes

41 functions during the syntheses: as a phase tag for the purification of intermediates 45, and as an activated leaving group for cross-coupling reactions to form the final products of the library Bin Yan et al, 2008 [34].

to yield N-(substituted benzylidene)-2-(4-chloro-3-methylphenoxy)acetamide (52a-e). Cyclization of compound (52a-e) with thioglycolic acid yielded 2-(4-chloro-3-methylphenoxy)-N-(4-oxo-2-arylthiazolidin-3-yl) acetamide (53 a-e). The newly synthesized compounds were characterized on the basis of spectral studies and evaluated for antibacterial and antifungal activities. Neeraj et al, 2009 [35].

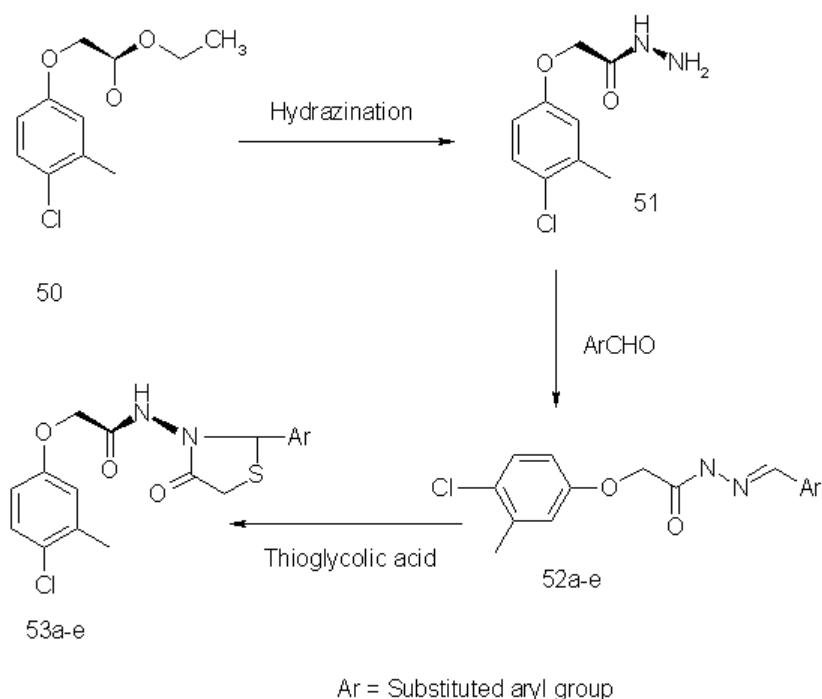


Figure 11. Cyclization of compound (52a-e) with thioglycolic acid yielded 2-(4-chloro-3-methylphenoxy)-N-(4-oxo-2-arylthiazolidin-3-yl) acetamide (53 a-e)

2.9. Synthesis from Nicotinic Acid

Nicotinic acid was refluxed with sulphuric acid and absolute alcohol for 10 h. and the mixture was cooled to

the room temperature and poured on to the crushed ice. The mixture was then made strongly alkaline by the addition of ammonia solution. The resulting mixture was extracted with ether solvent. The ether was then distilled off and the resultant liquid was recovered. (55) Ethyl nicotinate was condensed with hydrazine hydrate by maintaining the reaction temperature of 0°. This resulted in solid nicotinic acid hydrazide. The resultant nicotinic acid hydrazide was recrystallised from warm ethanol. (56) Nicotinic acid hydrazide was refluxed with various aromatic / heterocyclic aldehydes in the presence of sulphuric acid for 6 h. The reaction mixture was then

poured into the crushed ice. The resultant solid was washed with distilled water, dried in vacuum and recrystallised from warm ethanol. (57a-j) To a mixture of compound 57 in dry dioxane, a solution of 2-mercaptopropionic acid in dry dioxane was added and the reaction mixture was refluxed for 24 h. The reaction mixture was then poured into crushed ice. The separated solid was neutralized by sodium bicarbonate to remove excess of 2-mercaptopropionic acid. Solid compound obtained was crystallized from ethanol to give thiazolidinone derivatives (58a-j) Sharma et al, 2009 [36].

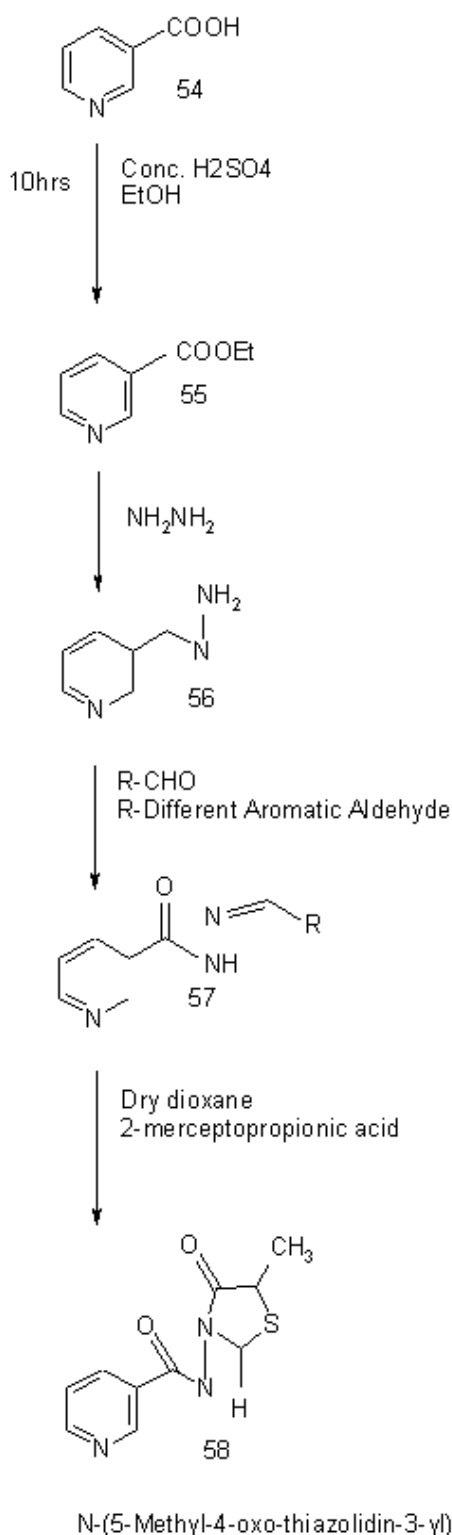


Figure 12. Synthesis of thiazolidinone derivatives 58 from nicotinic acid

2.10. Synthesis from Imines 59a-e and Thioglycolic Acid or Thiolactic Acid

3-aryl-2-(2-pyrrolyl)-4-thiazolidinones, 60a-e and 5-methyl-3-aryl-2-(2-pyrrolyl)-4-thiazolidinones, 61a-e were obtained in good yields by refluxing equimolar amounts of the imines 59a-e and thioglycolic or thiolactic acids in dry benzene. FerayAydogan, et al, 2001 [37].

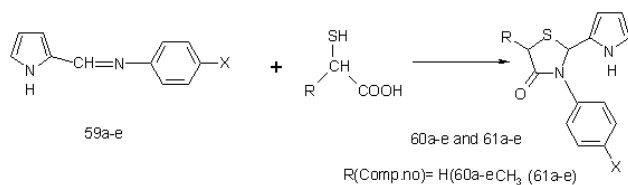


Figure 13. Refluxing equimolar amounts of the imines 59a-e and thioglycolic or thiolactic acids in dry benzene

2.11. Heterocyclisation of Schiff's Bases with Thioglycolic Acid, Thiomalic Acid or Acetic Anhydride Afforded Novel Heterocyclic Derivatives 4-thiazolidinones (66a-c), 5-Carboxymethyl-4-thiazolidinones (67a-c)

4-Methylcoumarinyl- 7-oxyacetic acid hydrazide (62) reacted with arylazopropanes or hydrazono-3-oxobutyrates derivatives to form pyrazole (63a-c) and pyrazolone derivatives (65a-c). Heterocyclisation of Schiff's bases with thioglycolic acid, thiomalic acid or acetic anhydride afforded novel heterocyclic derivatives 4-thiazolidinones (66a-c), 5-carboxymethyl- 4-thiazolidinones (67a-c) and oxadiazoles (68a-c), respectively. Some of the compounds showed promising antioxidant activity *in vitro* and cytotoxic activity against DLA cells and EAC cells. Manojkumar et al, 2009 [38].

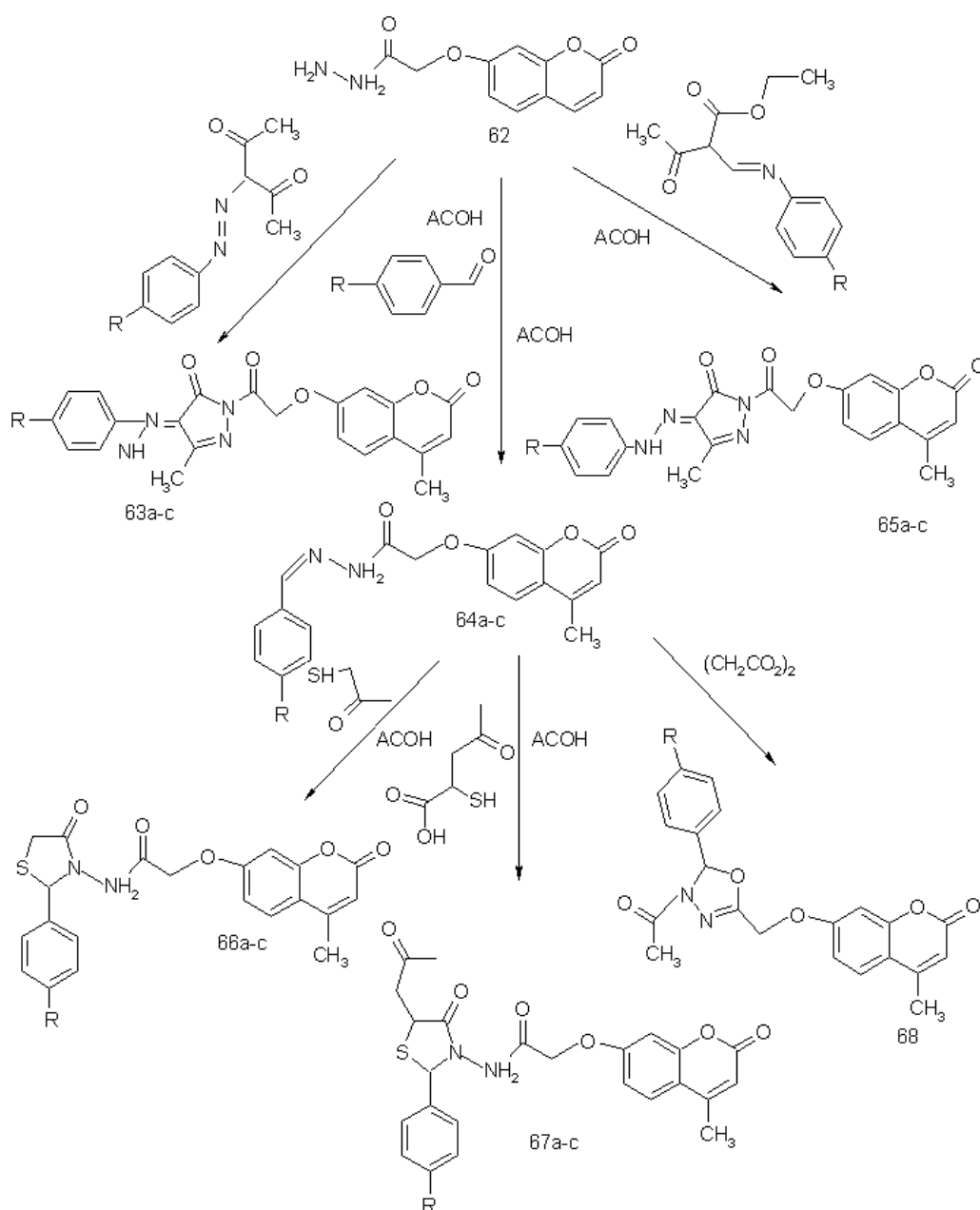


Figure 14. Reaction of Schiff's bases with thioglycolic acid, thiomalic acid or acetic anhydride afforded novel heterocyclic derivatives 4-thiazolidinones (66a-c), 5-carboxymethyl- 4-thiazolidinones (67a-c)

2.12. Cyclocondensation of Schiff's Bases 70a-o with Mercaptoacetic Acid and Mercaptopropionic Acid

Substituted Schiff's bases 70a-o prepared by the treatment of 2-amino-4-(α -methoxyiminocarbomethoxymethyl)-thiazole 69 with different aromatic aldehydes, on cyclocondensation with mercaptoacetic acid and

mercaptopropionic acid in dry benzene furnished desired thiazolidinones of type 71a-o and 72a-j, respectively. The structures of the compounds have been assigned on the basis of elemental analyses and spectral data. The products were evaluated for their *in vitro* growth inhibiting activity against several microbes. Some of the compounds showed significant antitubercular and antifungal activity Parekh et al.2004 [39].

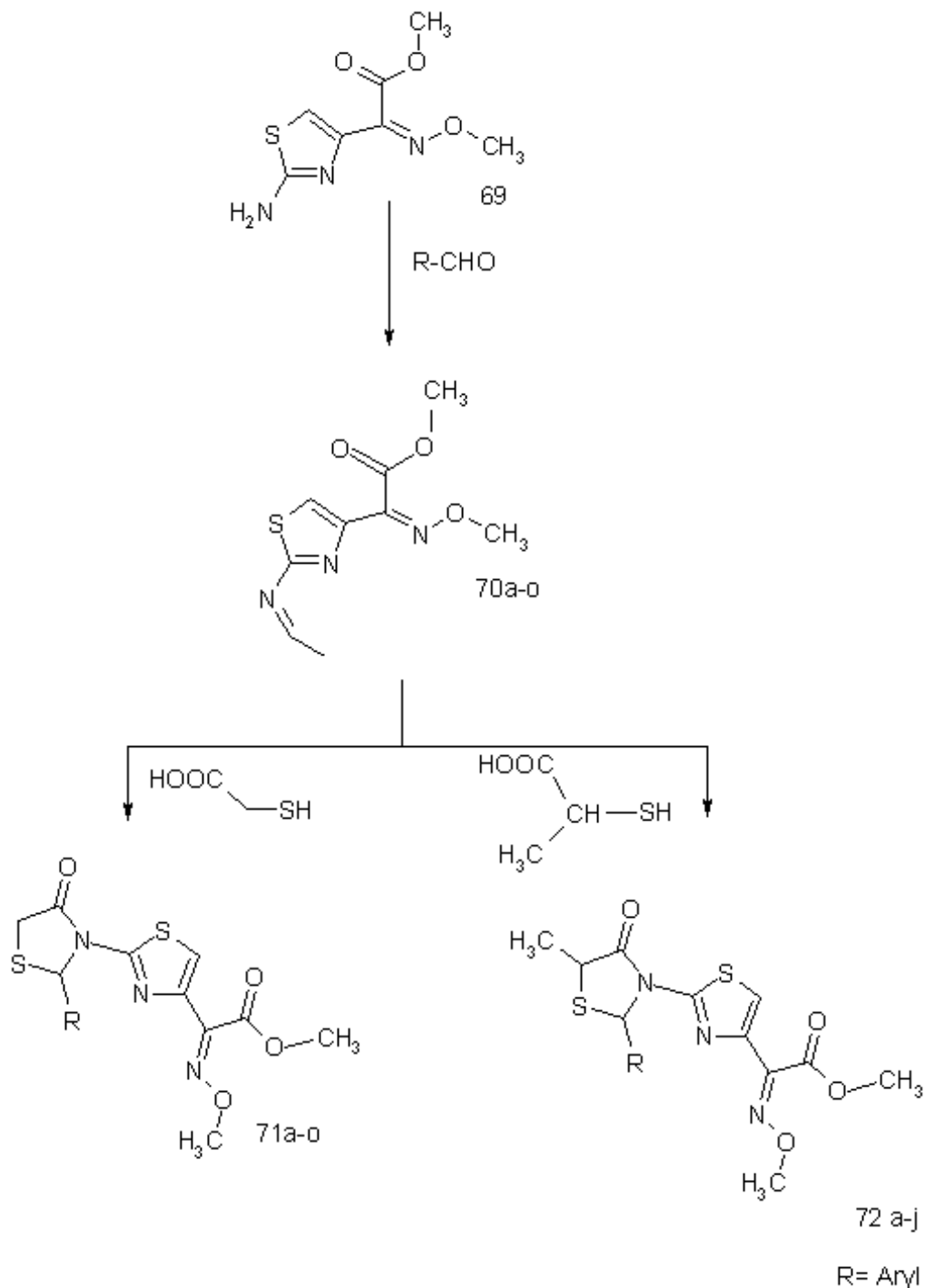


Figure 15. Reaction of Schiff's bases 70a-o with mercaptoacetic acid and mercaptopropionic acid afford thiazolidinone derivatives 71a-o and 72a-o

2.13. Synthesis from 5-Substituted 4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine

5-Substituted 4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine were synthesized by interaction of 4-oxo-2-thioxo-1,2,3,4-

tetrahydropyrimidine-5-sulfonylhydrazide with some aldehydes to give the corresponding Schiff's bases, which after cyclization gave corresponding thiazolidinones. For some of the thiazolidinones, Mannich bases reaction was carried out. Mahmoud et al.2005 [40].

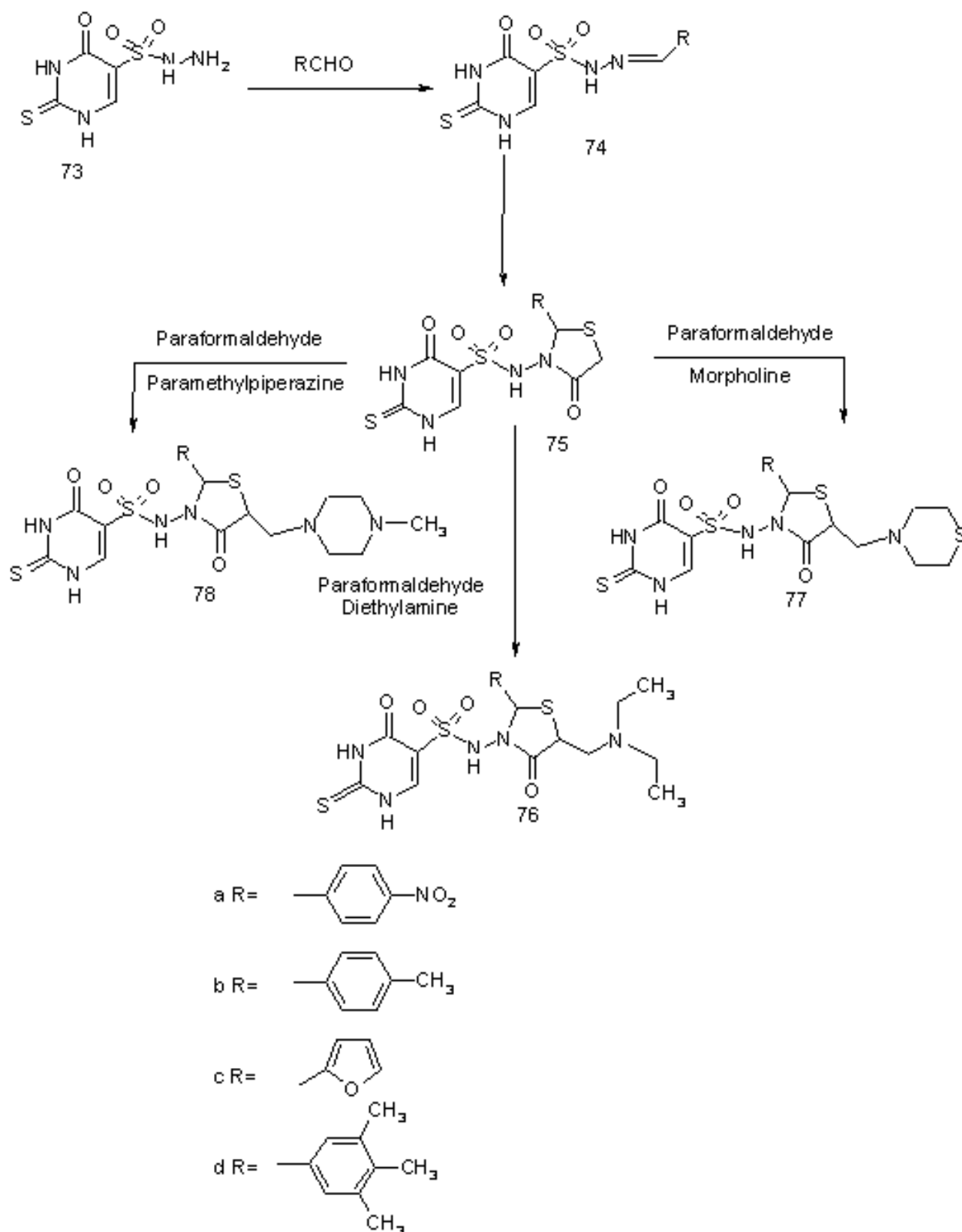


Figure 16. Cyclization of 5-Substituted 4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine afford thiazolidinone derivatives

2.14. Synthesis from 2-chloro-7-methoxy-3-formylquinoline^{24,25}, and 3-amino-4-(phenyldiazenyl) Phenol

The starting compounds 2-chloro-7-methoxy-3-formylquinoline^{24,25}, was condensed with 3-amino-4-(phenyldiazenyl) phenol under microwave irradiation in

one pot to furnish the compound 3-[(1E)-1-aza-2-(2-chloro-7-methoxy-3-quinolyl)-vinyl]-4-(aryldiazenyl) phenol 334 in good yield. Compound, 3-[(1E)-1-aza-2-(2-chloro-7-Methoxy-3-quinolyl)-vinyl]-4-(aryldiazenyl) phenol 79 upon cyclization with chloroacetylchloride and 2-mercapto acetic acid by microwave irradiation technique yields the title compound 80a-s and 81a-s, respectively in good yield Patel et al, 2008 [41].

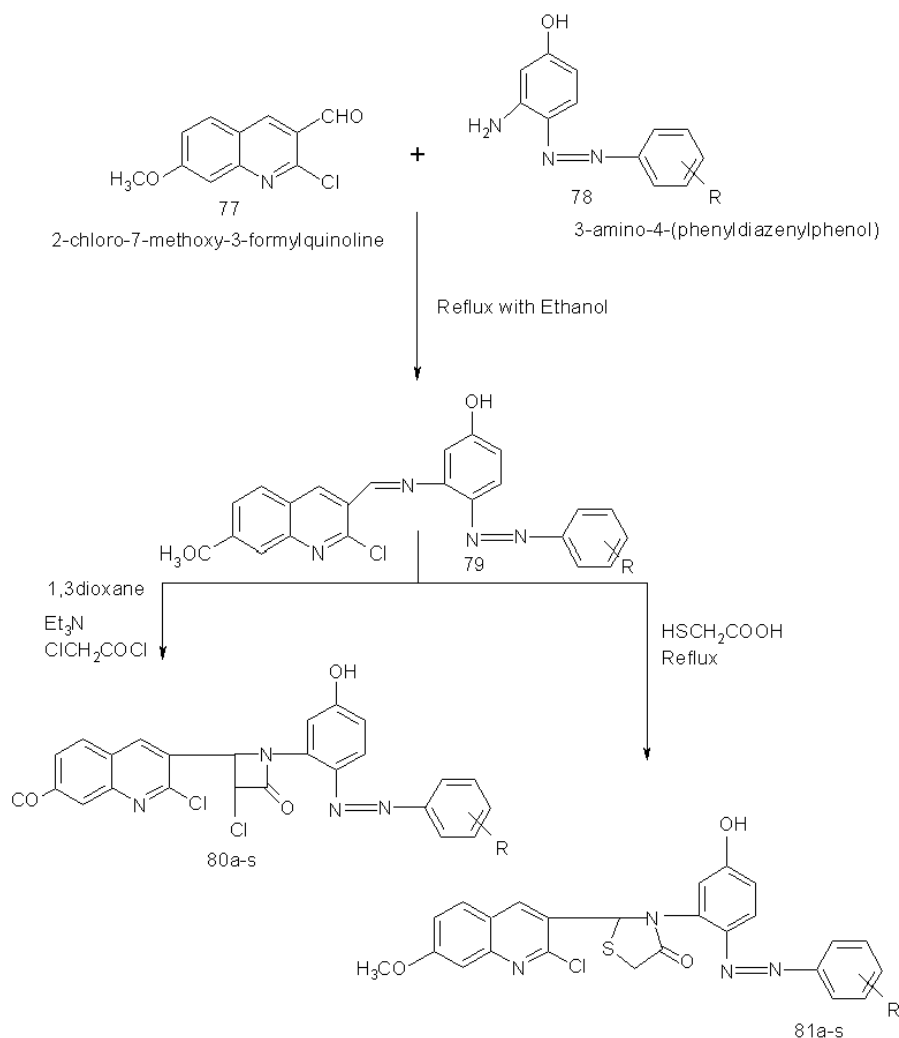
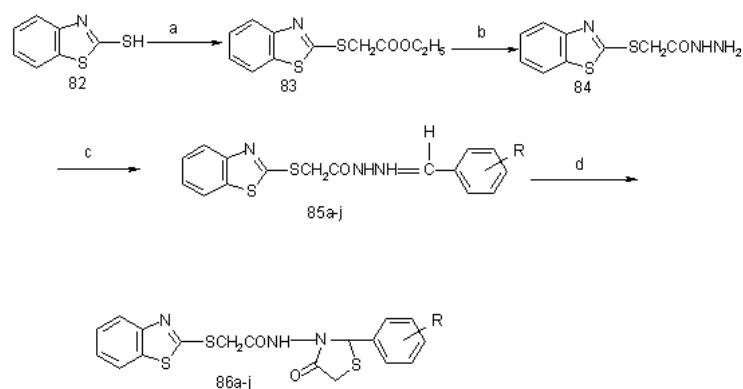


Figure 17. Reaction of 3-[(1E)-1-aza-2-(2-chloro-7-Methoxy-3-quinolyl-vinyl)-4-(aryldiazenyl)phenol 79 with chloroacetylchloride and 2-mercaptoacetic acid by microwave irradiation technique yields 80a-s and 81a-s

2.15. Synthesis from Heterocyclization Reaction of 2-(benzothiazol-2-ylthio)-N'-Benzylideneacetohydrazide 85a-j with SHCH₂COOH

The synthesis of 4-thiazolidinones 86a-j in a good yields from the heterocyclization reaction of 2-

(benzothiazol-2-ylthio)-N'-benzylideneacetohydrazide 85a-j with SHCH₂COOH in DMF in the presence of a catalytic amount of anhydrous ZnCl₂ under microwave irradiation is described and compared with conventional synthesis methods. Some of the new compounds were tested against bacteria (*Gram-ve* and *Gram+ve*) and fungi. Desai et al. 2006 [42].



a) ClCH₂COOC₂H₅; anhydrous K₂CO₃; dry acetone; b) NH₂NH₂; ethanol; c) substituted aromatic aldehyde 2,3 drops of gl. ACOH, ethanol; d) SHCH₂COOH, anhydrous ZnCl₂, DMF.

Figure 18. Reaction of 2-(benzothiazol-2-ylthio)-N'-benzylideneacetohydrazide 85a-j with SHCH₂COOH

2.16. Synthesis from Cyclization of 1-(3-ethyl-4(3H)-quinazolinone-2-ylmercapto-acetyl)-4-alkyl/aryl Thiosemicarbazides (87) with Ethyl 2-bromopropionate

Two regioisomer series, 2-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetyl-hydrazono)-3-alkyl/3-aryl-5-methyl-4-thiazolidinones (88) and 2-arylimino-3-

(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetyl-amino)-5-methyl-4-thiazolidinones (89), were synthesized by the cyclization of 1-(3-ethyl-4(3H)-quinazolinone-2-ylmercapto-acetyl)-4-alkyl/aryl thiosemicarbazides (87) with ethyl 2-bromopropionate in the presence of anhydrous sodium acetate in anhydrous ethanolic medium. Aysel G'URSOY et al, 2005 [43].

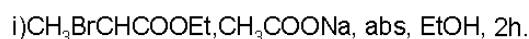
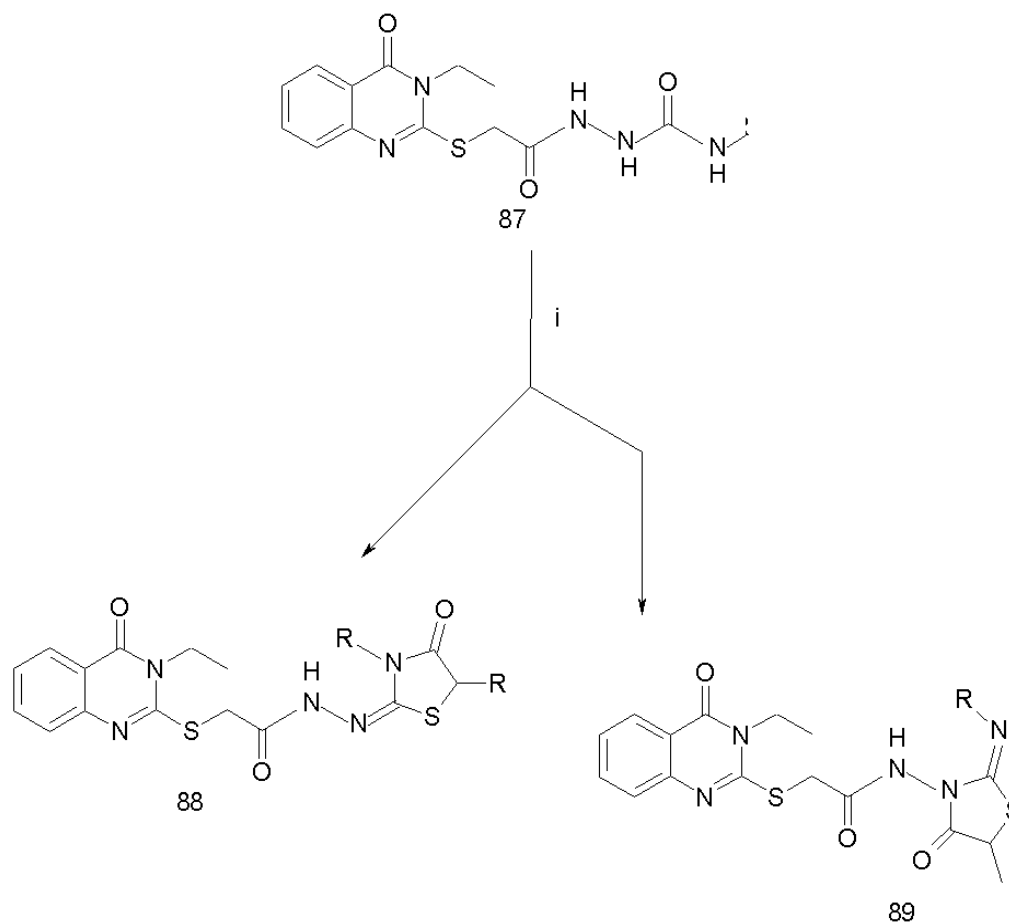


Figure 19. Reaction of 1-(3-ethyl-4(3H)-quinazolinone-2-ylmercapto-acetyl)-4-alkyl/aryl thiosemicarbazides (87) with ethyl 2-bromopropionate to give thiazolidinone 88 and 89

2.17. Synthesis from 4-Carboethoxymethyl-2-[(chloropropionyl-bromobutyryl-chloro(phenyl) acetyl) Amino]thiazoles (91a-c)

4-Carboethoxymethyl-2-[(chloropropionyl-bromobutyryl-chloro(phenyl) acetyl) amino]thiazoles (91a-c) were synthesized by the reaction of 4-carboethoxymethyl-2-aminothiazole (90) with chloropropionyl chloride, bromobutyryl bromide and chlorophenylacetyl chloride, respectively, which were then refluxed with ammonium thiocyanate to obtain 5-substituted 2-[(4-carboethoxymethylthiazol-2-yl)imino]-4-thiazolidinones (92a-c). 92a-c were stirred with formaldehyde and various secondary amines to gain 15 novel compounds with the structure 5-substituted 5-(N,N-disubstituted 2-[(4-carboethoxymethylthiazol-2-yl)imino]-4-thiazolidinone-2-yl)amino]methyl)-2-[(4-carboethoxymethylthiazol-2-yl)imino]-4-thiazolidinones (93a-c).

oxymethylthiazol-2-yl)imino]-4-thiazolidinones (93a-c) Altintas et al, 2005 [44].

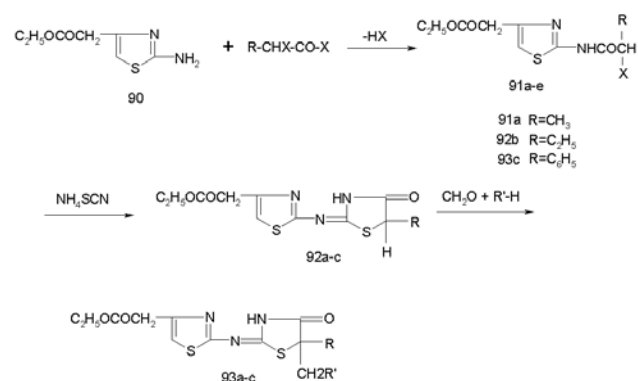


Figure 20. Reaction of 2-[(4-carboethoxymethylthiazol-2-yl)imino]-4-thiazolidinones (92a-c) with formaldehyde and various secondary amines to give 93a-c

2.18. Synthesis from Condensation Reaction of an Aromatic Amine 95, an Aldehyde 94 and a Mercaptoacetic Acid 96

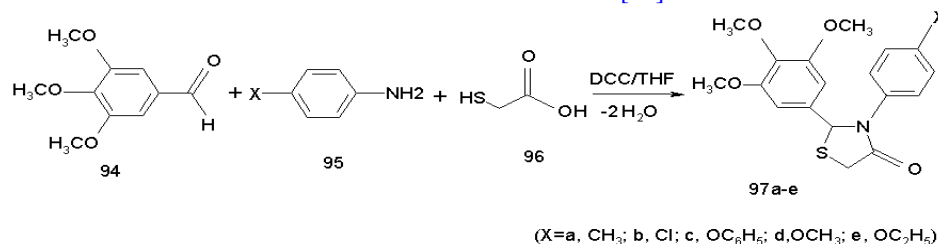


Figure 21. Reaction of an aromatic amine 95, an aldehyde 94 and a mercaptoacetic acid 96 to give thiazolidinone 97a-e

2.19. Synthesis from 1-thia-4-azaspiro[4.5]decan-3-ones 101a-e, 8-tert-butyl-1-thia-4-azaspiro[4.5]decan-3-one and N-Boc-protected 1-thia-4,8-diazaspiro[4.5]decan-3-one 103b

When the monoacids 99a,b were replaced by mercaptosuccinic acid 102c an interference of the additional carboxyl group with DCC was anticipated and therefore, a slightly different strategy was adopted. In this

4-thiazolidinones 97a-e were synthesized by the Katticarbodiimide (DCC) mediated one-pot three component condensation reaction of an aromatic amine 95, an aldehyde 94 and a mercaptoacetic acid 96. Zuhair Turgut et al. 2007 [45].

protocol, the synthesis of 1-thia-4-azaspiro[4.5]decan-3-ones 101a-e, 8-tert-butyl-1-thia-4-azaspiro[4.5]decan-3-one and N-Boc-protected 1-thia-4,8-diazaspiro[4.5]decan-3-one 103b was achieved by refluxing a mixture of amines 98b,c, mercaptosuccinic acid 99c and carbonyl compounds 100a-f in toluene for 10-12 hours.

Removal of the Boc group in 1-thia-4,8-diazaspiro[4.5]decan-3-one 103b with 20% hydrogen chloride/dioxane solution afforded the hydrochloride 104. Tumul Srivastava et al, 2005 [46].

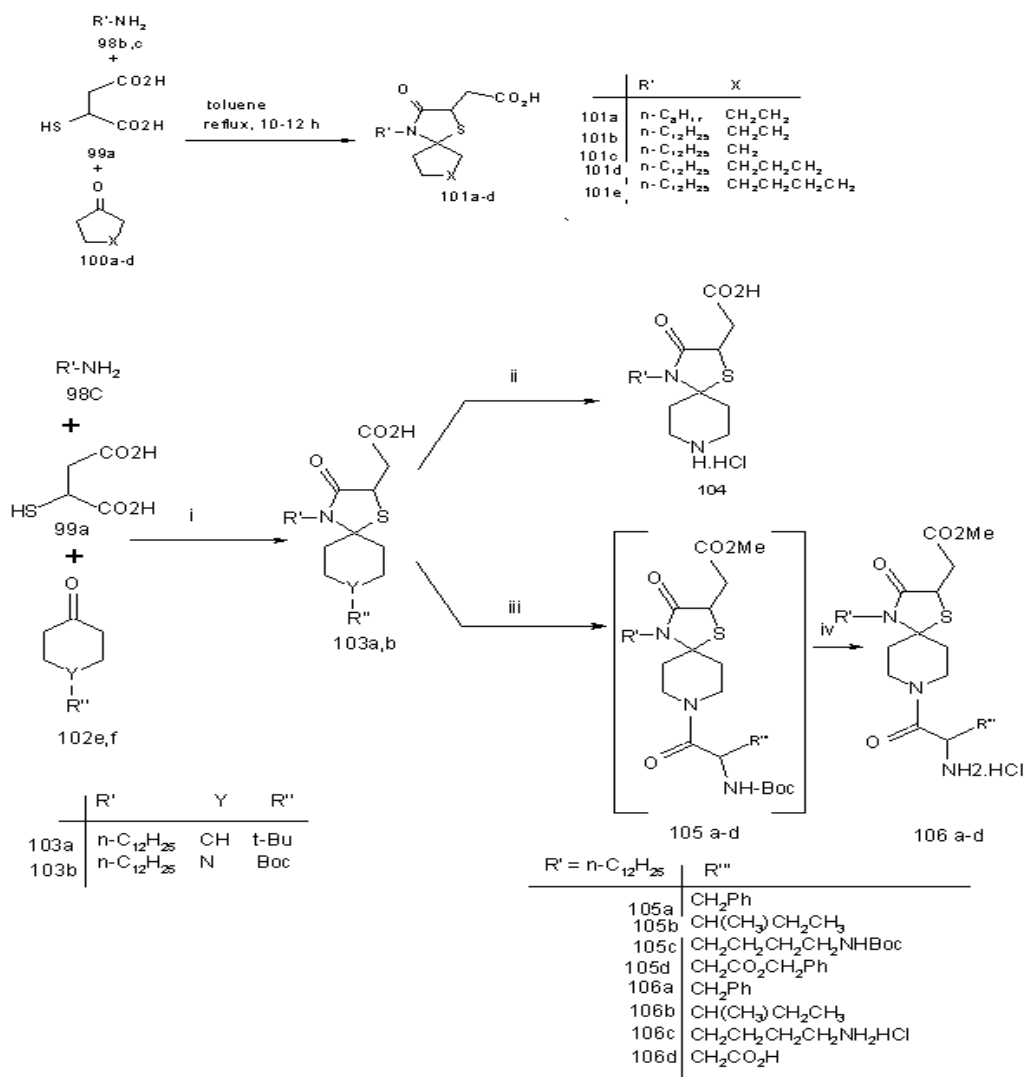


Figure 22. Reaction of amines 98b,c, mercaptosuccinic acid 99c and carbonyl compounds 100a-f

2.20. Synthesis from 4-amino-5- phenyl-3,5-thiaaza-4-pentenoic Acid 107

The 2-phenylimino-1,3-thiazolidin-4-one 108 was obtained by thermal cyclization of 4-amino-5- phenyl-3,5-thiaaza-4-pentenoic acid 107 using DCC as dehydration agent. Treatment of 2-phenylimino-1,3- thiazolidin-4-one 108 with various hydrazonoyl halides 109 (nitrilimines 4 precursor) yielded 6-aryl-9- phenyl- 8-substituted-1,4,6,7,9-thiatetrazaspiro-[4.4]non-7-en-3-ones 110a-l.

2.21. Synthesis from Schiff bases (114a-h)

The 2-Amino-4-(2-naphthalenyl)thiazole 112 was dissolved in ethanol and was reacted with aromatic aldehyde 113 in the presence of piperidine to yield Schiff bases (114a-h). These Schiff bases on cyclo-condensation reaction with chloro acetyl chloride afford 2- azetidinone (115a-h) and with thioglycolic acid afford 4-thiazolidinone (116a-h) Mehta et al, 2006 [47].

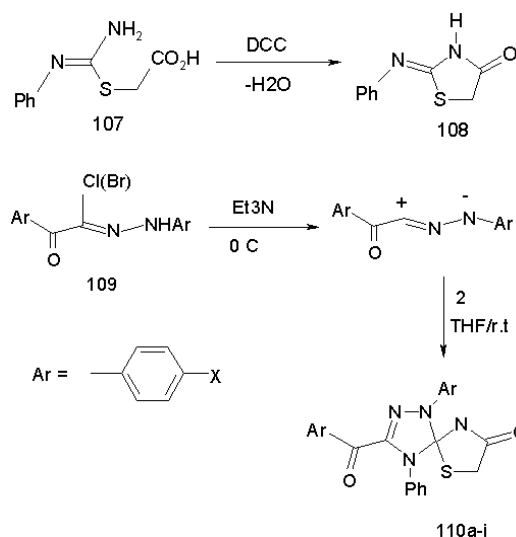


Figure 23. cyclization of 4-amino-5- phenyl-3,5-thiaaza-4-pentenoic acid 107 using DCC as dehydration agent

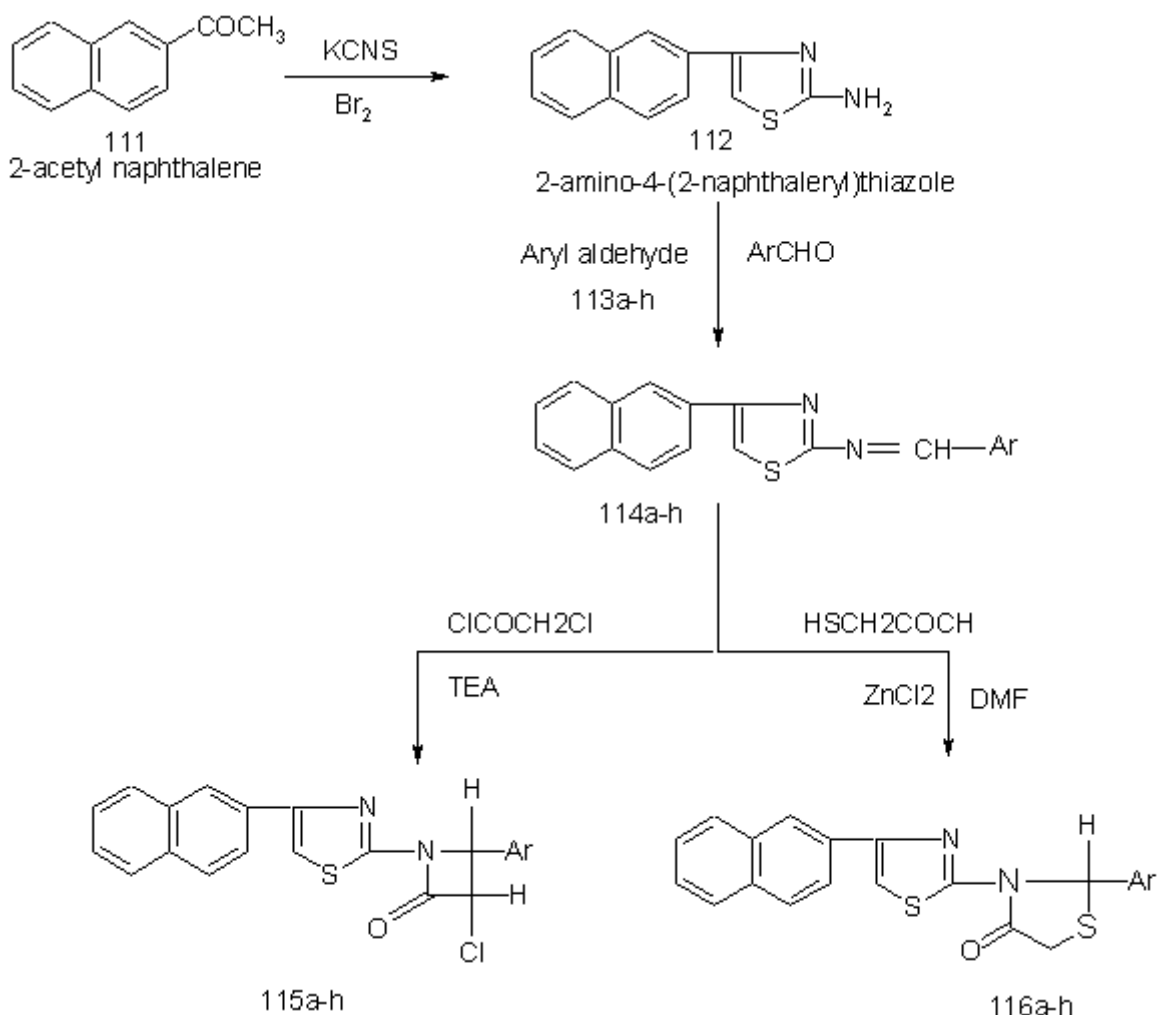


Figure 24. Reaction of Schiff's bases (114a-h) with thioglycolic acid

Where Ar: (a) Phenyl, (b) 4-Methoxy Phenyl (c) 4-Hydroxy Phenyl (d) 2-Hydroxy Phenyl (e) 4-Methyl Phenyl (f) 3,4-Methylenedioxy Phenyl (g) 4-Hydroxy- 3-Methoxy Phenyl (h) 3,4-Diethoxy Phenyl.

3. Synthesis of β -lactam

3.1. Synthesis from α -diazo-acetamides:

Preferential Rh(II) carbenoid intramolecular C-H versus O-H insertion derived from α -diazo-acetamides can be achieved in water by creating a large hydrophobic environment around the reactive carbenoid center using an appropriate combination of the catalyst and amide groups. Candeias *et al*, 2006 [48].

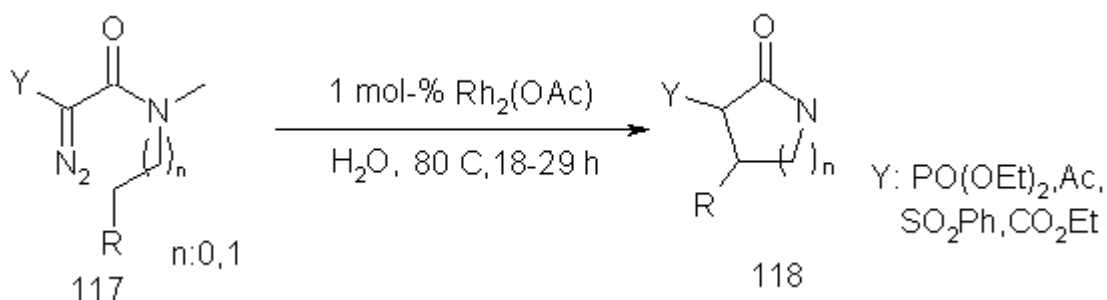


Figure 25. reaction of α -diazo-acetamides with Rh(II) carbenoidintramolecular

N-Tosyl-3-halo-3-butenylamines underwent efficient Ullmann-type coupling to afford 2-alkylideneazetidines, which could be readily converted to the corresponding β -lactams by oxidation with O₃ Lu et al, 2006 [49].

3.2. Synthesis from 2-alkylideneazetidines

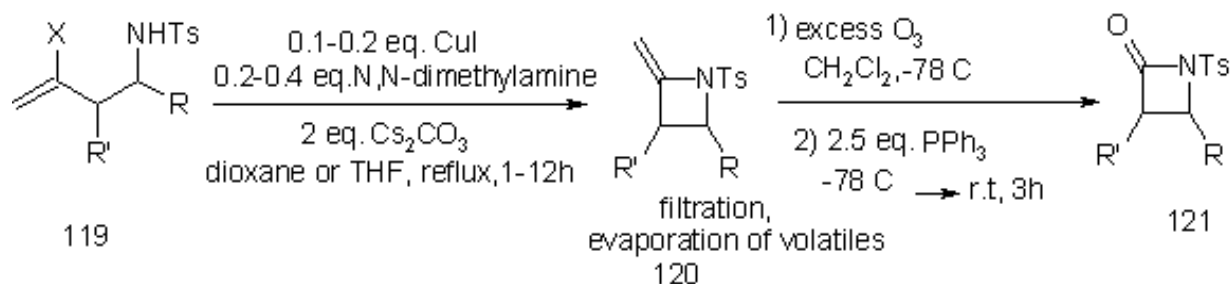


Figure 26. Oxidation of 2-alkylideneazetidines

3.3. Synthesis from Staudinger Reaction of Arylalkylketenes with a Variety of *N*-tert-Butoxycarbonylarylimines

A chiral *N*-heterocyclic carbene catalyzed the Staudinger reaction of arylalkylketenes with a variety of *N*-tert-butoxycarbonylarylimines to give the corresponding *cis*- β -lactams in good yields with good diastereoselectivities and excellent enantioselectivities. Zhang et al, 2008 [50].

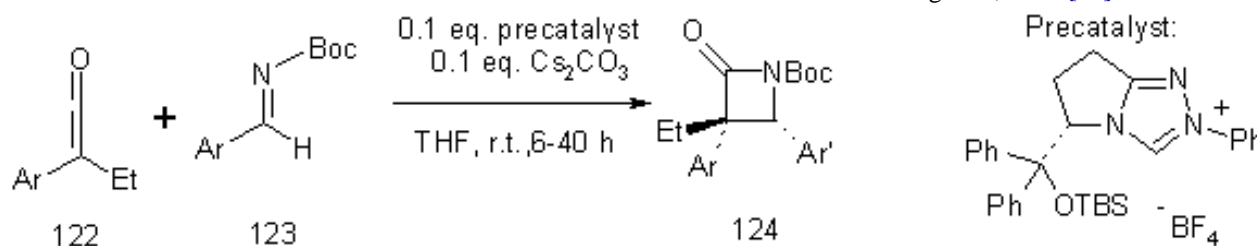


Figure 27. Reaction of arylalkylketenes with a variety of *N*-tert-butoxycarbonylarylimines

3.4. Synthesis from Staudinger Reactions by Using *N*-triflyl Protecting Group for the Imine

A catalytic enantioselective Staudinger reactions is described that preferentially furnish *trans* β -lactams. The use of an *N*-triflyl protecting group for the imine is crucial for the success of the reaction. Lee et al., 2005 [51].

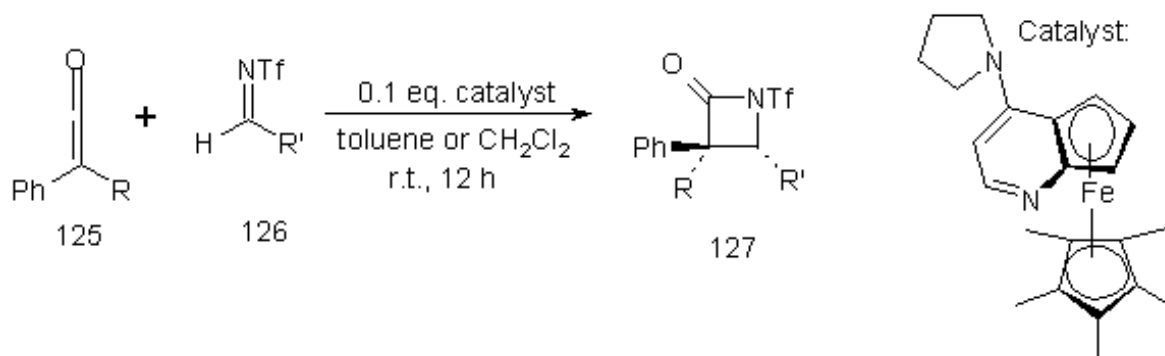


Figure 28. reaction of ketene with imine

3.5. Synthesis from [2 + 2] Cycloaddition of a Ketene with an Imine

The Staudinger synthesis, an overall [2 + 2] cycloaddition of a ketene with an imine, provides a nicely convergent route to biologically and synthetically

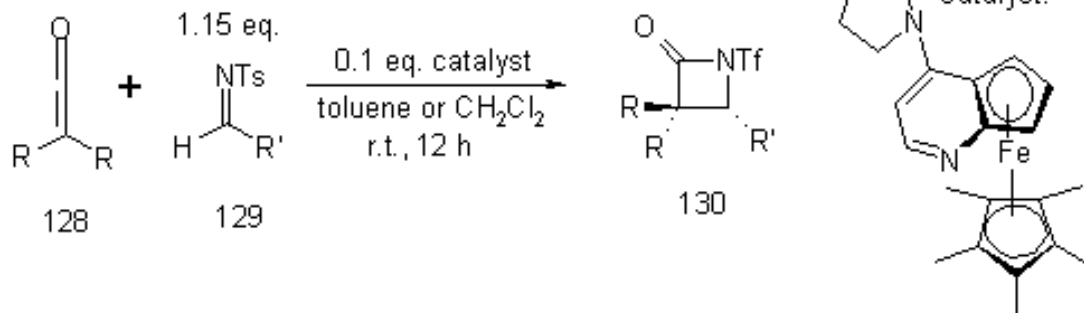


Figure 29. [2 + 2] cycloaddition of ketene with imine

3.6. Synthesis by Microwave Irradiation of Diazoketones

The transformation of diazoketones to ketenes can be realized not only by utilizing photochemical reaction

conditions but also under the action of microwave irradiation. In the presence of imines, the generated ketenes react further to afford β -lactams. Various *trans*-substituted β -lactams derived from amino acids have been prepared. Linder et al, 2001 [53].

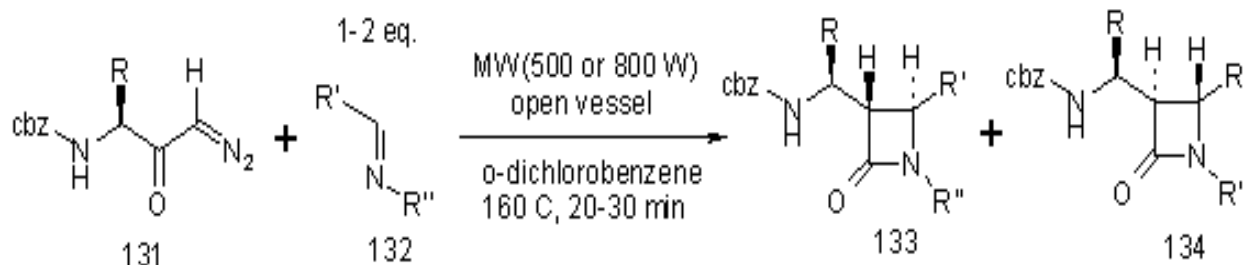


Figure 30. Microwave irradiation of diazoketene

3.7. Synthesis by a Catalyzed Reaction of Ketenes and Imines Using Benzoylquinine

A practical methodology for the catalytic, asymmetric synthesis of β -lactams results from the development of a

catalyzed reaction of ketenes (or their derived zwitterionic enolates) and imines using benzoylquinine as chiral catalyst and proton sponge as the stoichiometric base. Taggi et al, 2002 [54].

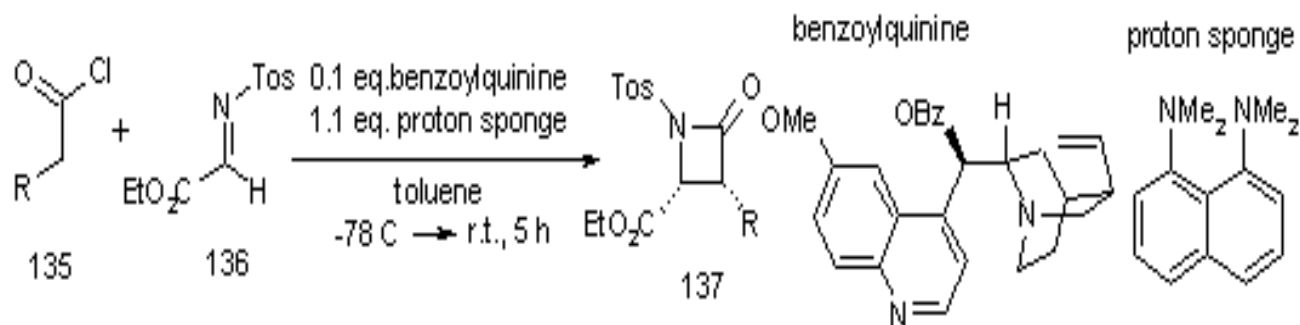


Figure 31. Reaction of ketene and imines using benzoylquinine

3.8. Synthesis from *N*-Propargylnucleobases

Several β -lactam nucleoside chimeras 140 (*cis*) and 141 (*trans*) were synthesized from the corresponding *N*-

propargylnucleobases via Kinugasa reaction in moderate yields. Initial screening for antibacterial activity against ampicillin sensitive *E. coli* showed weak activity for the uracil- β -lactam chimera. Amit Basak et al, 2005 [55].

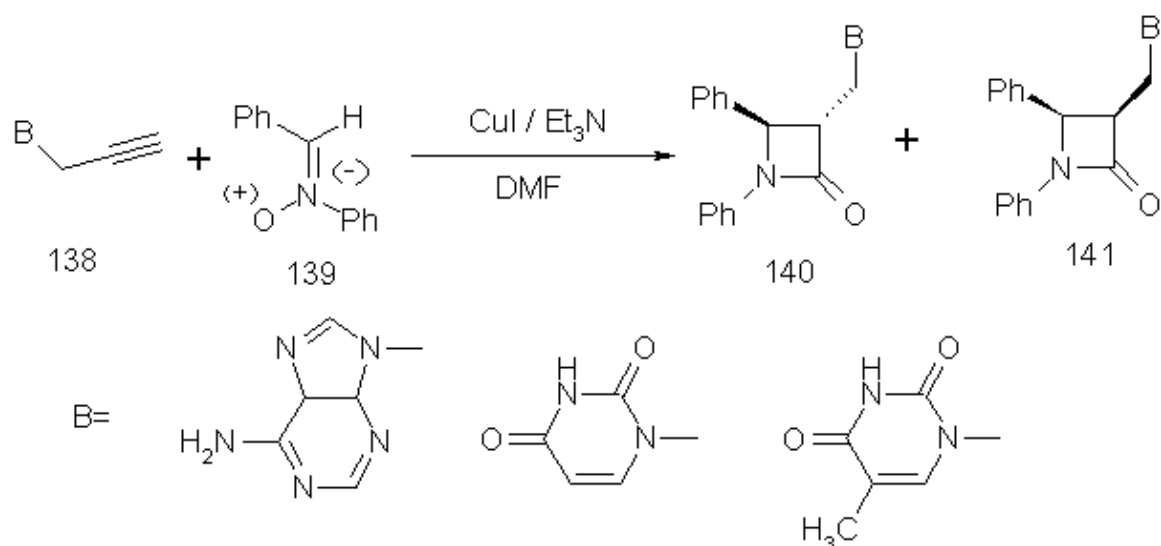


Figure 32. Synthesis from *N*-propargyl nucleobases via Kinugasa reaction

3.9. Synthesis from Cycloaddition of Acetylenes with Nitrones

The group of Fu at MIT has improved a reaction known as the Kinugasa reaction, involving the cycloaddition of acetylenes with nitrones.

By using a copper catalyst and a bisazoferrocene ligand, high yields of the β -lactam product are produced. The process is generally *cis* selective, and is quite versatile, although some yields are only in the 40-60% range Lo et al2002 [56].

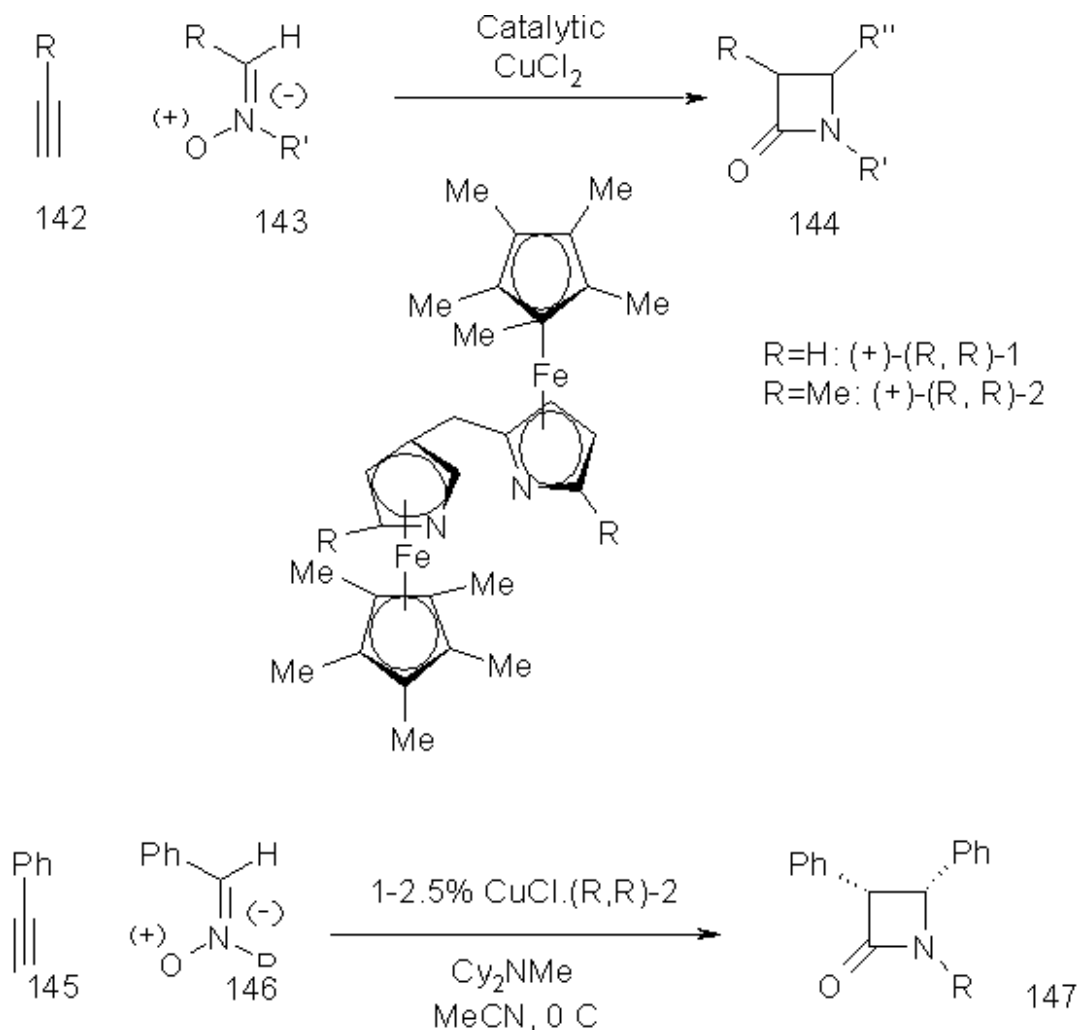


Figure 33. cycloaddition of acetylenes with nitrones

3.10. Synthesis from 2-(2,4-dimethyl-3-phenyl-2*H*-isoxazol-5-ylidene)malonic Acid

2,4-Dimethyl-3-phenylisoxazole anhydrobases were easily prepared from the corresponding 5-chloroisoxazolium trifluoromethanesulfonate and carbon

anions of 1,3-dioxo compounds in the presence of triethylamine. Photorearrangement of 2-(2,4-dimethyl-3-phenyl-2*H*-isoxazol-5-ylidene)malonic acid, diethyl ester gave a 4,5-dihydrofuroazetidione in good yield. Donato et al, 2003 [57].

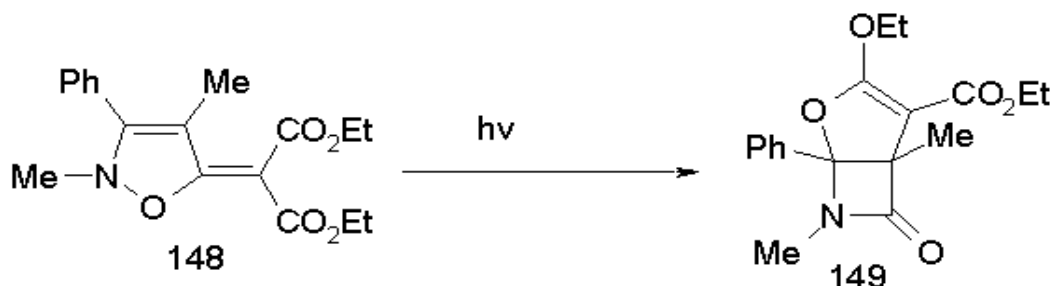


Figure 34. Photorearrangement of 2-(2,4-dimethyl-3-phenyl-2*H*-isoxazol-5-ylidene)malonic acid, diethyl ester

3.11. Synthesis from *N*-Acylimidazoles and Diarylimines

Reaction of *N*-acylimidazoles possessing an electron-withdrawing group in the α position with diarylimines produces β -lactams in high yields Moshe et al, 2006 [58].

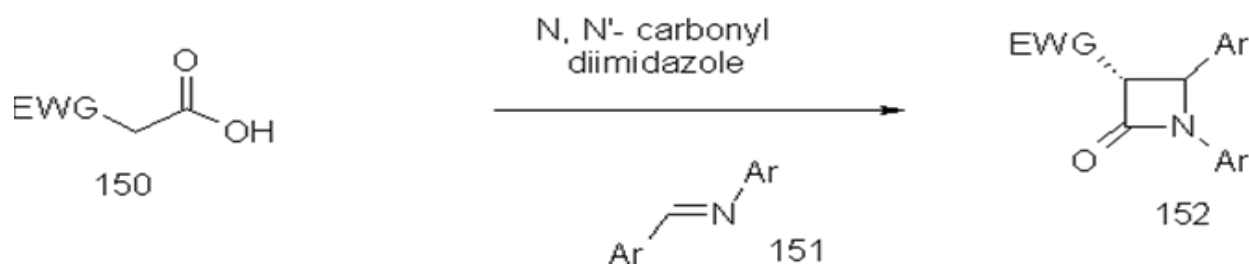


Figure 35. Reaction of *N*-acylimidazoles and diarylimines

3.12. Synthesis from [2 + 2]-Cycloaddition Reaction

A new and effective proteasome inhibitor, β -lactam, has been accessed enantioselectively by multistep synthesis from the readily prepared intermediates and which were joined by a [2 + 2]-cycloaddition reaction to form the

spiro β -lactam stereo selectively. The β -lactam is stable for many days in water at pH 7, in contrast to the natural β -lactones salinosporamide A (153) and omuralide (154). In common with 153 and 154, the β -lactam 155 effectively inhibits the mammalian proteasome Philip et al, 2005 [59].

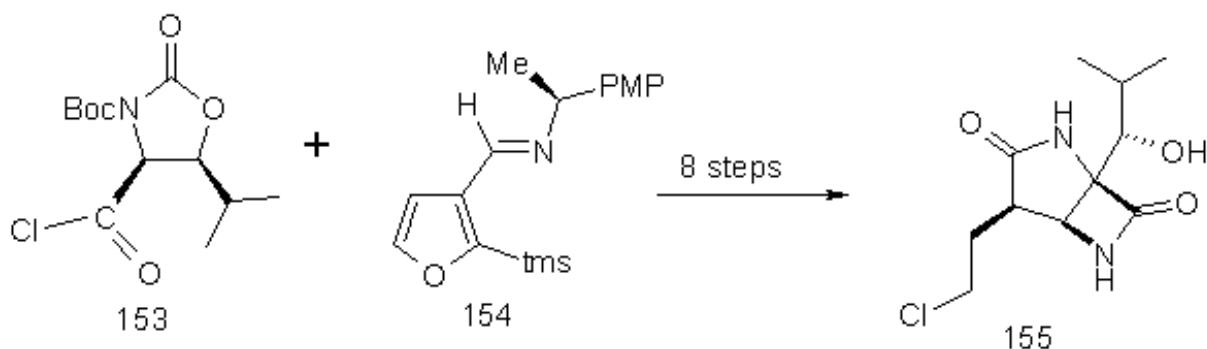


Figure 36. synthesis of β -lactam 155 from [2+2]cycloaddition reaction of 153 and 154

3.13. Synthesis from Substituted Acetic Acids and Alkoxyethylene-*N,N*-dimethyliminium Salts

A number of 2-azetidiones were synthesized in good to excellent yields by a novel reaction between Schiff bases, substituted acetic acids and alkoxyethylene-*N,N*-

dimethyliminium salts, the adduct formed from DMF and *O*-alkylating agents. The advantages of this new method are mild reaction conditions, low cost, avoiding the use of chlorinating agents and easy purification of the products. The best results were obtained when DMF and dimethyl sulfate were used at room temperature. Aliasghar et al, 2009 [60].

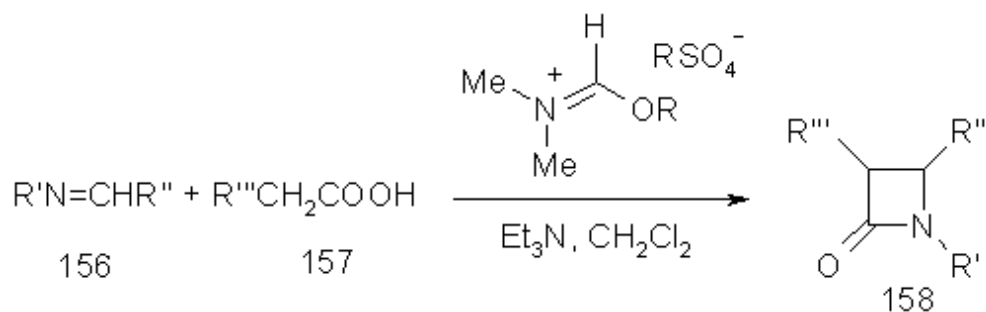


Figure 37. Reaction of substituted acetic acid and alkoxy-methylene-*N,N*-dimethyliminium

3.14. Synthesis from Michael Addition of α -carbamoyl, α -(1-chlorovinyl) ketene-*S,S*-acetals and Subsequent Nucleophilicvinyllic Substitution

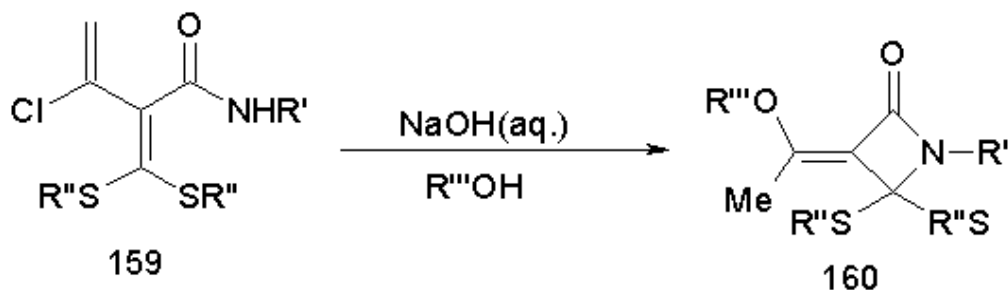


Figure 38. Michael addition of α -carbamoyl, α -(1-chlorovinyl) ketene-*S,S*-acetals and subsequent nucleophilicvinyllic substitution (S_NV) reaction in alcoholic aqueous media

3.15. Synthesis from Alkylol Chloride and Imine Derivatives

Trans-disubstituted β -lactams show increasing utility and prominence in numerous pharmaceutical applications, making their asymmetric synthesis an attractive goal for chemists. We introduce an anionic, nucleophilic catalyst system that provides an efficient, diastereoselective route

to trans-disubstituted β -lactams, a complement to our previously described catalytic methodology for generating the corresponding *cis* diastereomers. This catalytic, “switch mechanism” process allows for flexibility in the stereo selective synthesis of β -lactams, producing either *cis* or *trans* products as desired from the same substrates. Anthony et al, 2005 [62].

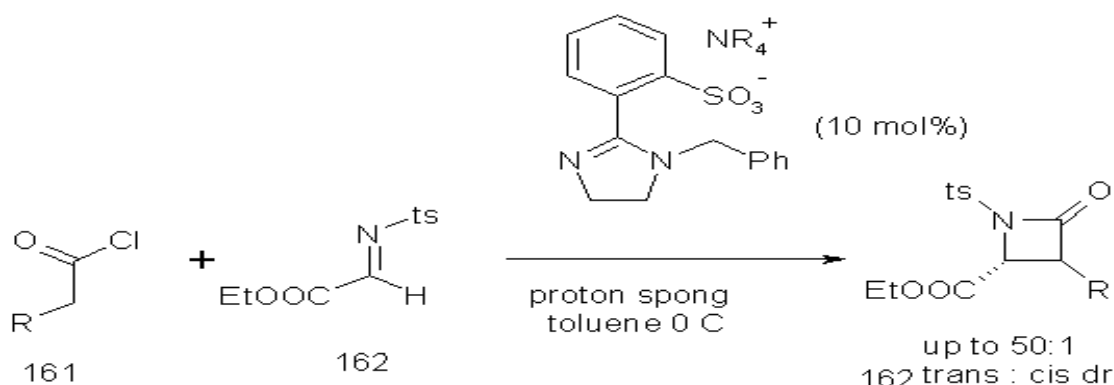


Figure 39. Reaction of alkylol chloride and imine derivatives

3.16. Synthesis from [2+2] Carbonylative Cycloaddition of Chiral Imines to Various Allyl Halides

[2+2] Carbonylative cycloaddition of chiral imines to various allyl halides, under CO pressure, in the presence

of Et_3N , a catalytic amount of $Pd(OAc)_2$ and PPh_3 as ligand, are carried out. Separable diastereomeric mixtures of chiral alkenyl- β -lactams are isolated with good yields and high *Trans* diastereoselections. Absolute configurations are assigned by X-ray measurements and 1H NMR spectroscopy. Luigino et al, 2004 [63].

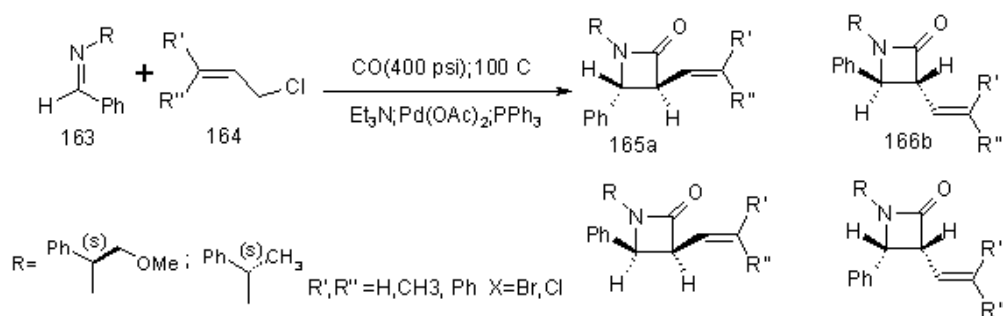


Figure 40. Reaction of imines with alkyl halides

3.17. Synthesis from 1-halo-3-aza-4-alkyl-1,3-dienes

Conrotatory ring closure of 1-halo-3-aza-4-alkyl-1,3-dienes in refluxing toluene gives rise to 3-halo-4-aryl-2-

azetidinones in satisfactory yields. Dehalogenation of the resulting β -lactams by tris(trimethylsilyl)silane furnished 3-unsubstituted azetidinones, valuable intermediates in the synthesis of biologically active compounds. Elisa et al, 2000 [64].

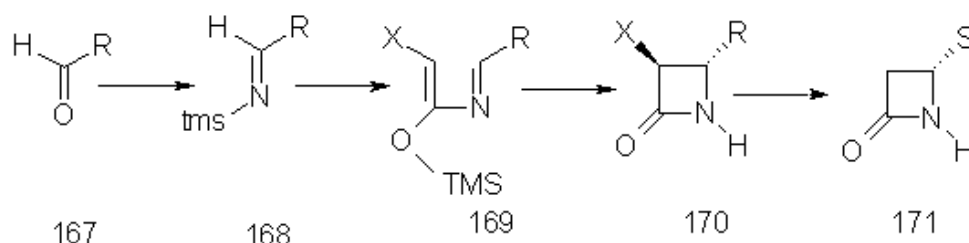


Figure 41. Synthesis from 1-halo-3-aza-4-alkyl-1,3-dienes

3.18. Synthesis from Schiff's Bases and Alkoxy/Aryloxy Acetic Acids

Lawesson's reagent is found to be a unique reagent that provides a convenient route for the synthesis of β -lactams

from Schiff's bases and alkoxy/aryloxy acetic acids. The process involves the formation of a titanium enolate of a mixed anhydride followed by condensation with imine to afford β -lactam. Sharma et al, 2004 [65].

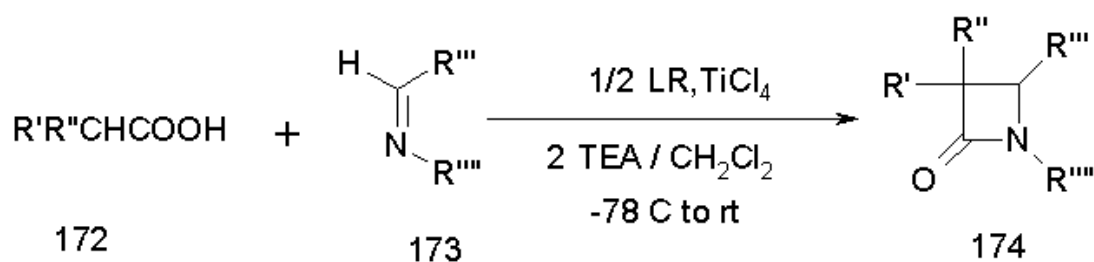
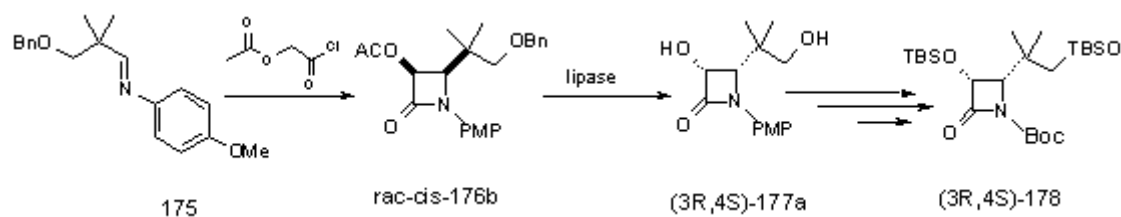


Figure 42. Synthesis from Schiff's bases and alkoxy/aryloxy acetic acids

3.19. Synthesis of Pharmaceutically Important α -hydroxy (or *t*-butyldimethylsilyl protected α -hydroxy)- β -lactams

The synthesis of pharmaceutically important α -hydroxy (or *t*-butyldimethylsilyl protected α -hydroxy)- β -lactams

with functionalized chains in position 4 of the azetidinone ring. A convenient and high-yielding route to these compounds was developed and optimized. Preparation and characterization of several new enantiopure title compounds with various functional groups are discussed. Yan Yang et al, 2007 [66].

Figure 43. Synthesis of pharmaceutically important α -hydroxy (or *t*-butyldimethylsilyl protected α -hydroxy)- β -lactams

3.20. Synthesis of Macrocylic β -lactams

A new approach to N1-C3 bridged macrocylic β -lactams has been developed. Orthogonal functional groups' protection combined with RCM has allowed the construction of the bicyclic systems bearing a β -lactam

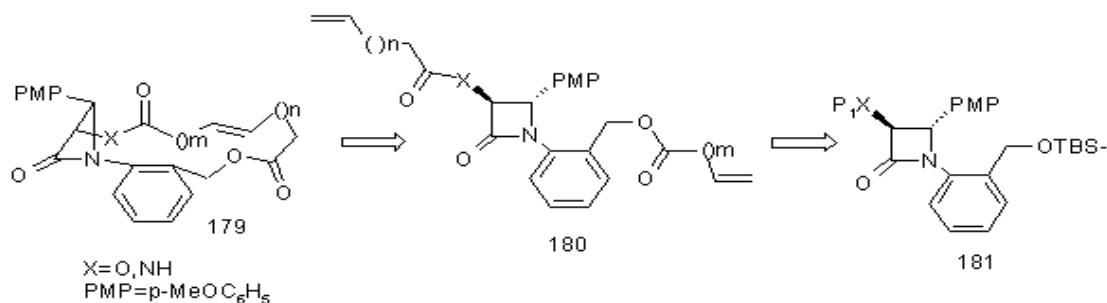


Fig.44. Synthesis of bicyclic systems bearing β -lactam

3.21. Synthesis from 4-*exo-digonal* Cyclization Using Palladium Acetate as the Catalyst

Functionalized *gem*-difluoro β - and γ -lactams were synthesized through a novel intramolecular

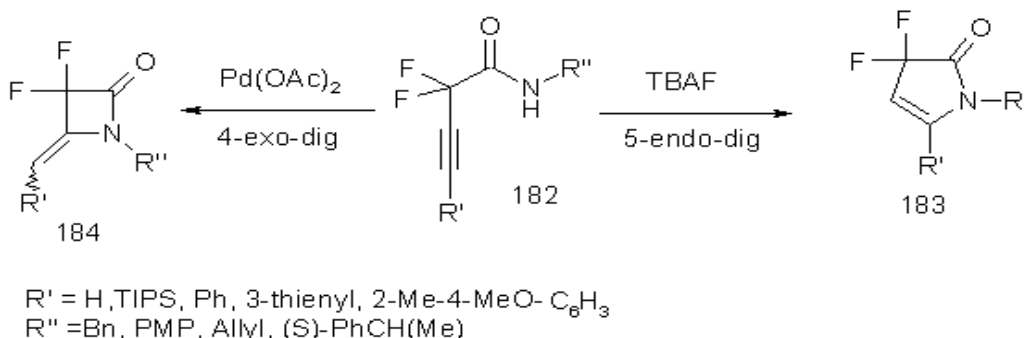


Figure 45. Synthesis from 4-*exo-digonal* cyclization using palladium acetate as the catalyst

3.22. Synthesis from l-serine Using a Zinc-Mediated Coupling Reaction

Synthesis of (-)-tabtoxinine- β -lactam 187, the cause of tobacco wildfire disease, was achieved from l-serine using a zinc-mediated coupling reaction, Sharpless asymmetric dihydroxylation and lactamization of *N*-OBn amide as the key steps Hiromasa Kiyota et al, 2004 [69].

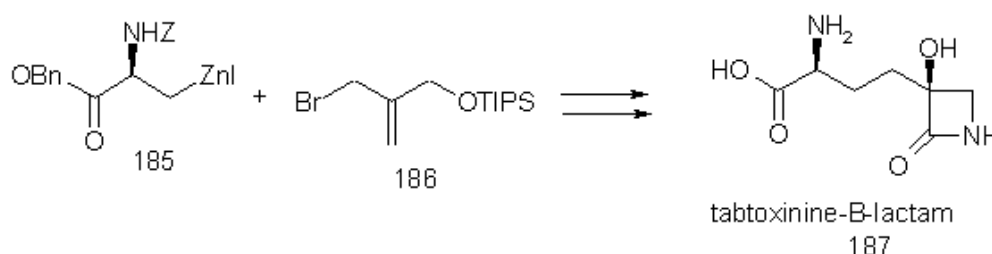


Figure 46. Synthesis from l-serine using a zinc-mediated coupling reaction

3.23. Synthesis by a Palladium-catalyzed [2+2] Carbonylativecycloaddition of Allyl Bromide with Heteroarylidene *N*-alkyl-amines

Novel polyfunctionalized *N*-alkyl- β -lactams were prepared with high stereoselectivity in an efficient manner by a palladium-catalyzed [2+2] carbonylativecycloaddition

of allyl bromide with heteroarylidene *N*-alkyl-amines. The type of alkyl group linked to the nitrogen atom influences the reaction stereoselectivity. Moreover, the C-3 and the C-4 positions of the azetidinone ring can be further stereoselectively functionalized inserting various groups through the generation of a stable azetidylcarbanion and then captured by various electrophiles Luigino Troisi et al, 2008 [70].

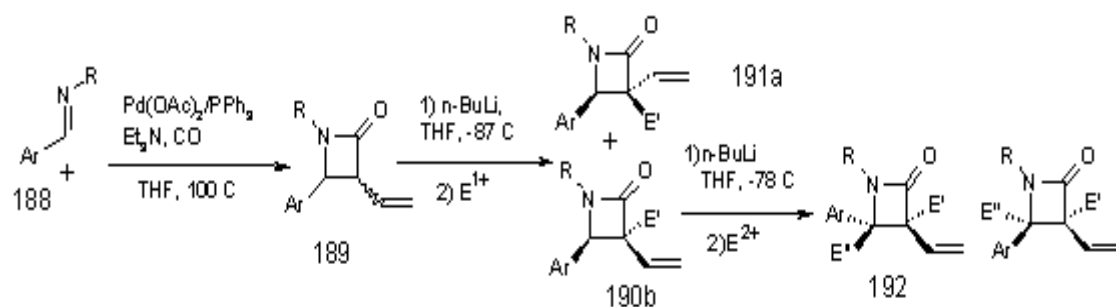


Figure 47. Synthesis by a palladium-catalyzed [2+2] carbonylativecycloaddition of allyl bromide with heteroarylidene*N*-alkyl-amines

3.24. Synthesis from Dimethoxycarbene with Isocyanates

Highly substituted β -lactams have been isolated as the major product of the reaction of dimethoxycarbene with selected isocyanates. This reaction offers the potential for rapid access into a variety of highly functionalized species James et al, 2006 [71].

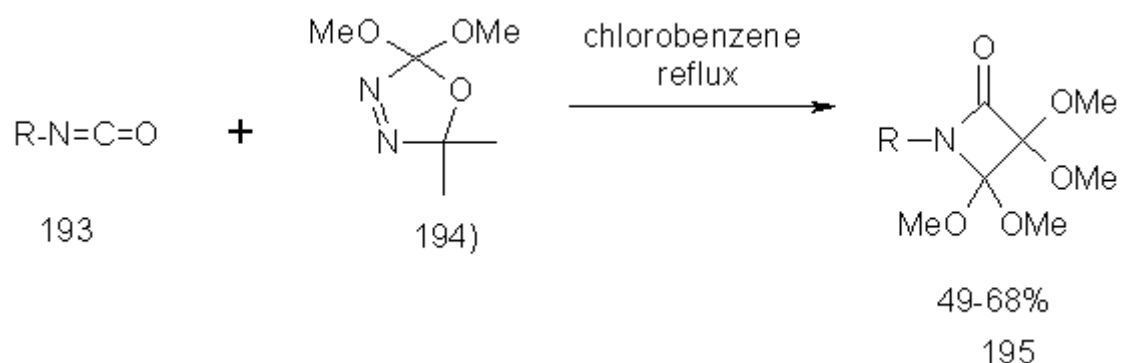


Figure 48. Reaction of dimethoxycarbene with isocyanates

3.25. Synthesis from cyclization of Optically Pure *N*-(*p*-methoxybenzyl)-*N*-(2-chloro) Propionyl Amino Acid Derivatives

The base-promoted cyclization of optically pure *N*-(*p*-methoxybenzyl)-*N*-(2-chloro)propionyl amino acid

derivatives resulted in a diastereo- and enantioselective approach to valuable 1,3,4,4-tetrasubstituted β -lactams. The stereochemical outcome of the reaction is exclusively governed by the configuration of the *N*-(2-chloro)propionyl moiety. Paula Pérez-Faginas et al, 2007 [72].

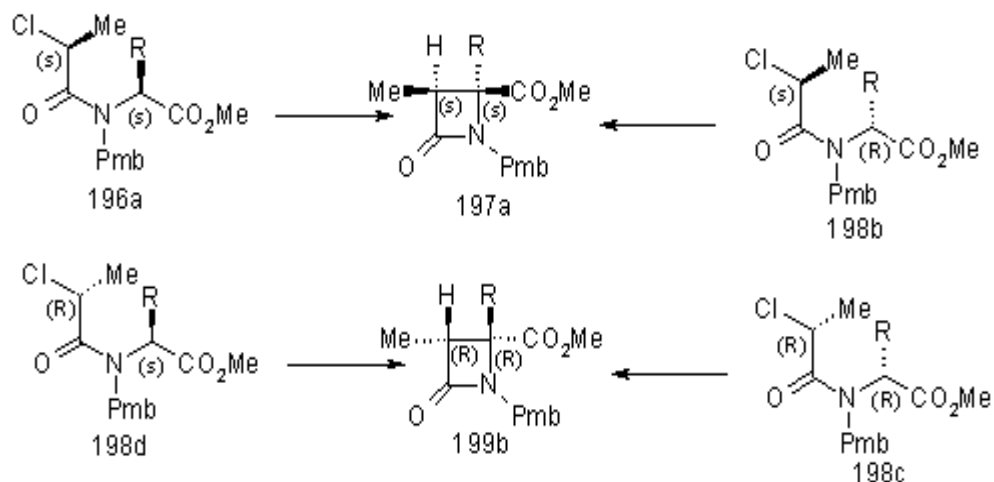


Figure 49. cyclization of optically pure *N*-(*p*-methoxybenzyl)-*N*-(2-chloro)propionyl amino acid derivatives

3.26. Synthesis from reaction of Schiff's Bases with Chloroacetyl Chloride

Further, reaction of the Schiff's bases with one mole of chloroacetyl chloride in ethanol solution in the presence of triethylamine as catalyst leads to the β -Lactam derivatives 201,203. Soleiman et al, 2002 [26].

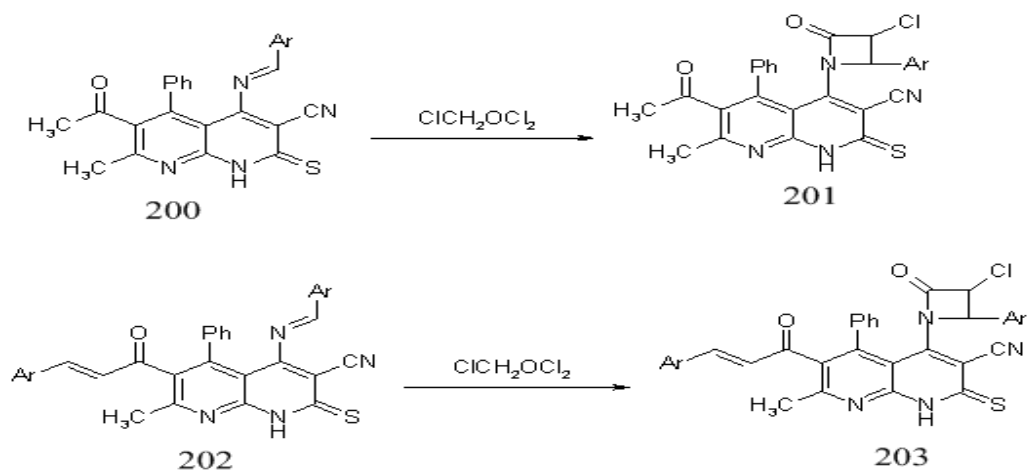


Figure 50. reaction of Schiff's bases with chloroacetyl chloride

3.27. Synthesis from Schiff's Bases 12 with Chloroacetylchloride

It is interesting to mention that along with efficient strategy for synthesis of new heterocyclic by

cyclocondensation, reaction of compound (10) with different nitroso compounds 11 produced the new compound(12) which is used in synthesis of b-lactam (204). ELKanzi et al, 2007 [27].

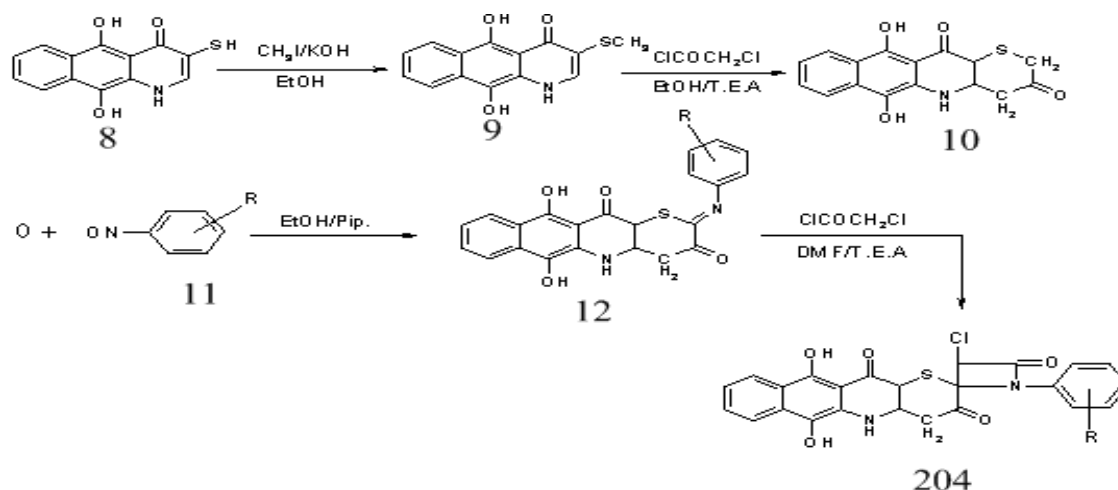


Figure 51. Reaction of Schiff's bases 12 with chloroacetylchloride afford Blactam 204

3.28. Synthesis from Schiff's Bases 16 with Chloroacetylchloride

The reaction of 276 a-c with equimolar ratios of chloroacetylchloride in mixture of ethanol and DMF in the presence of piperidine catalyst afforded lactam derivatives (417). ELKanzi et al, 2007 [28].

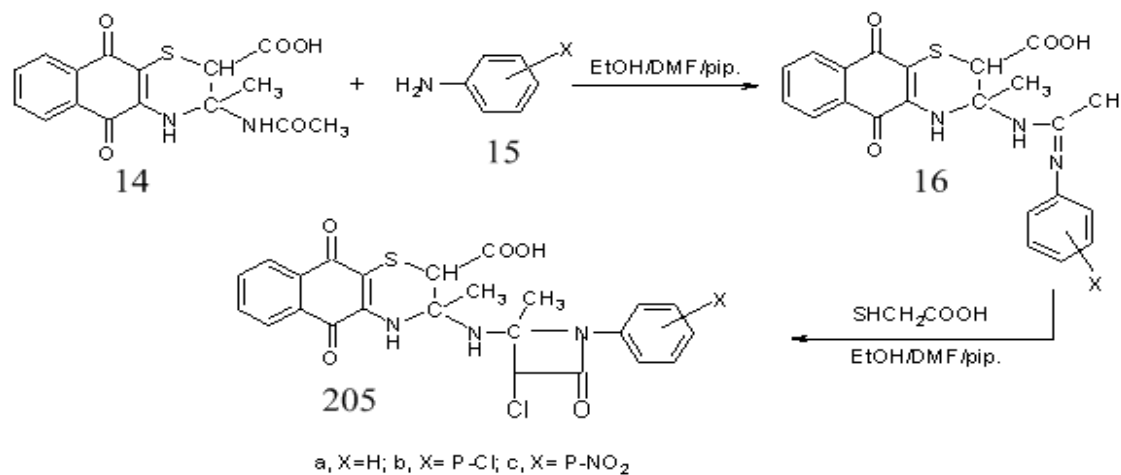


Figure 52. Reaction of Schiff's bases 16 with chloroacetylchloride afford Blactam 205

3.29. Synthesis from Cycloaddition of Compound 206a-d with Chloroketene

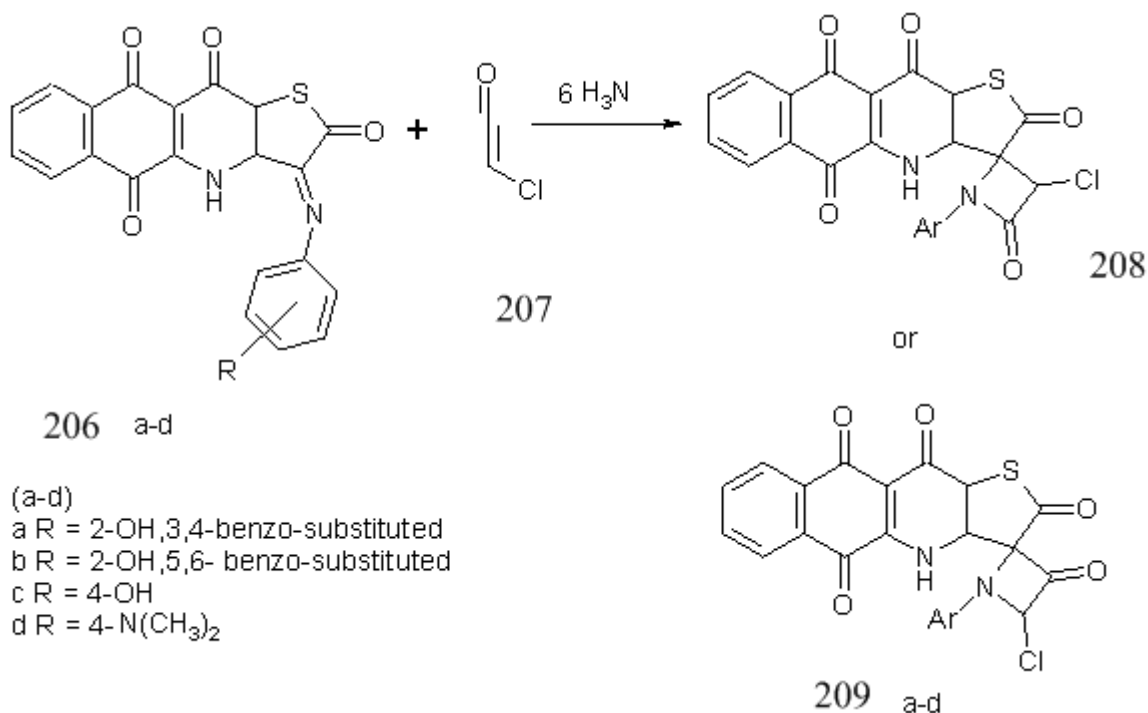


Figure 53. Reaction of compound 206a-d with chloroketene

3.30. Synthesis from Reaction of Cycloheptyl Acid Chloride 210 or Cyclohexyl Acid Chloride 212 with Imine

The spiro β -lactams 211 and 213 were prepared by reaction of either cycloheptyl acid chloride 210 or cyclohexyl acid chloride 212 with imine, respectively (Scheme 92). In a typical procedure, the acid chloride was

added to a stirred, refluxing solution of the imine and triethylamine in toluene. After refluxing the solution overnight and an aqueous work-up, spiro β -lactams 11 and 13 were obtained in moderate yields and trash amount of side products were detected in TLC. The spiro β -lactams 211 and 213 are the expected products of the [2+2] cycloaddition reaction of imine with the cyclic ketenes intermediate. Sun Joo Oh et al., 2007 [74].

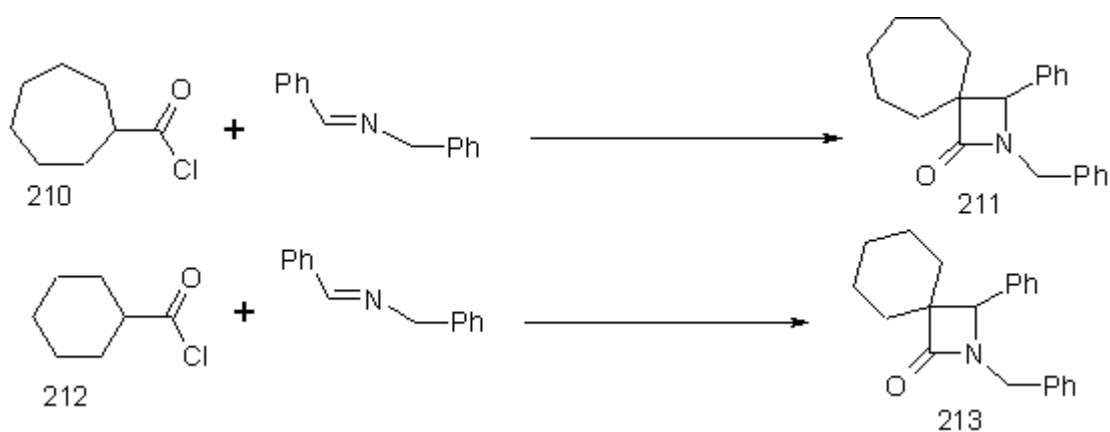


Figure 54. Reaction of cycloheptyl acid chloride 210 or cyclohexyl acid chloride 212 with imines

3.31. Synthesis from Fmoc Aminoacid

For immobilization of the starting material, Fmoc-aminoacid, both Wang resin as well as JandaJel resin were used. Wang resin consists of a basic structure of polystyrene cross-linked with divinylbenzene, and a 4-hydroxybenzyl group as linker. "JandaJel" resin (Toy and

Janda, 1999) is an interesting alternative since polymer matrix is a polystyrene resin cross-linked with 1,4-cis (vinylphenoxy)butane, which increases twice its swelling capacity with respect to common resins. This increase in swelling capacity implies a better contact between reagents and substrate linked to the resin. Then the amino group is deprotected, usually with 30% piperidine in DMF.

The amino group release can be monitored by the Kaiser test (*Kaiser et al, 1970*). The amine linked to solid.

Support is transformed in an imine by condensation with an aldehyde in a 1% v/v AcOH solution. Afterwards, β -lactamic ring formation is carried out by the Staudinger methodology, which involves the reaction of imine linked to the solid support with a ketene, in situ generated from an acid chloride and triethylamine as base. Infrared

spectrum of solid phase product shows a peak at approx. 1770 cm^{-1} , accounting for a β -lactam carbonyl. Finally, resin separation depends on the linker that connects the polymer matrix and the substrate. In the case of using Wang resin, β -lactam is released using a 10% v/v trifluoroacetic acid (TFA) solution in dichloromethane. The acid obtained was methylated with diazomethane. Pablo et al, 2007 [75].

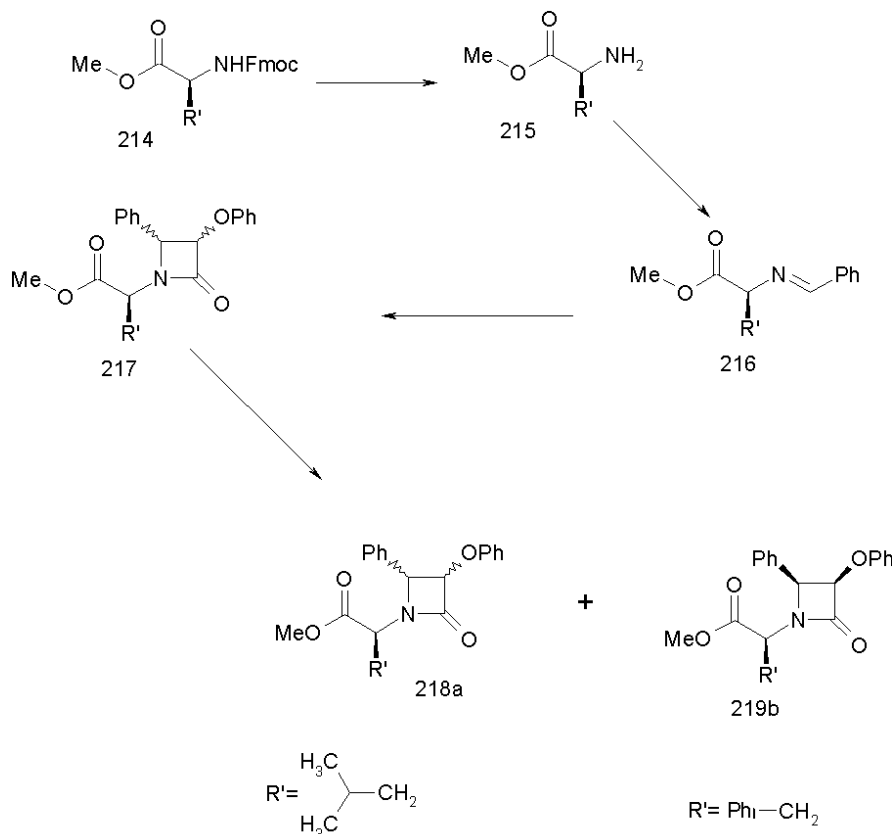


Figure 55. Synthesis from Fmoc-aminoacid

3.32. Synthesis from Imines with Ethyl Bromoacetate

Reaction of various imines with ethyl bromoacetate in the presence of indium metal using anhydrous tetrahydrofuran as the solvent produced the β -lactams 221. Bimal et al, 2000 [76].

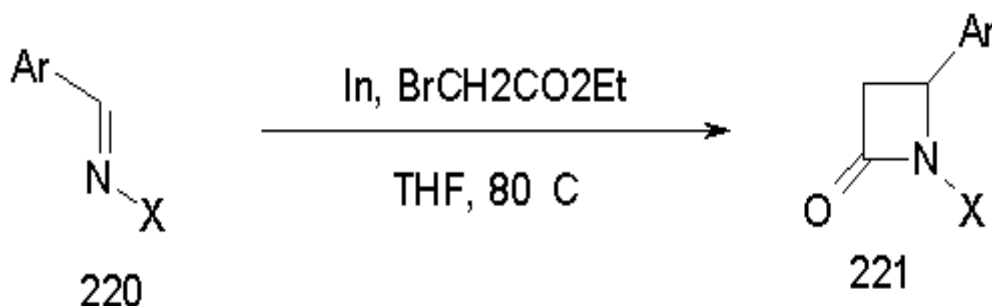


Figure 56. Reaction of imines with bromoacetate in presence of of indium metal using anhydrous tetrahydrofuran as the solvent produced the β -lactams 221

3.33. Synthesis from Phenylacetyl Chloride and BQ(223)

BQ (223a) serves as an excellent shuttle base when added to the solution of phenylacetyl chloride 222c and 224 in toluene at low temperature; a yellow solution of phenylketene was formed along with a white precipitate

over the course of a few minutes. Imino ester 225a was then added to the solution at -78°C , and characteristic ketene color disappeared over the course of 2 h to give *cis*-lactam 226c in 96% ee (65% yield). In this reaction, BQ plays two distinct catalytic roles as a dehydrohalogenation agent and a nucleophilic catalyst. We obtained other β -lactams from a variety of in situ generated Andrew et al, 2000 [77].

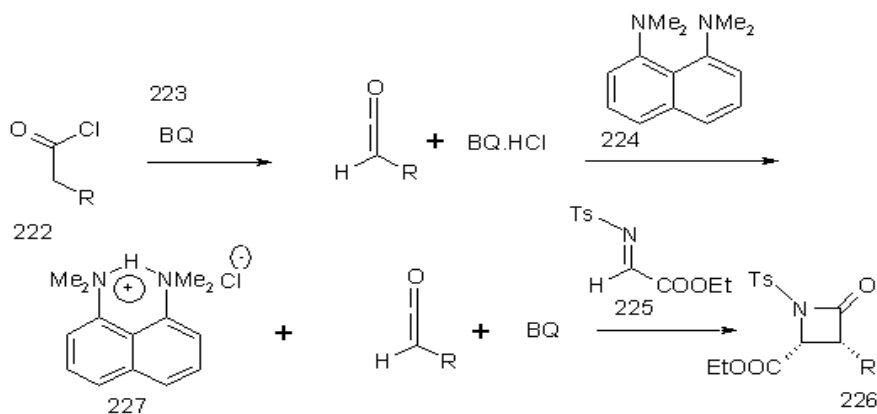


Figure 57. Reaction of phenylacetyl chloride and BQ(223)

3.34. Synthesis from Compounds 228 and (4*R*)-phenyloxazolidylacetyl Chloride 229

Compound 228 (0.35g, 1mmol) was reacted with (4*R*)-phenyloxazolidylacetyl chloride 229(0.38g, 1.58mmol) in the presence of Et₃N in CH₂Cl₂ for 24h to produce the 1,5-benzothiazepine-β-lactam. The triethylamine salt was

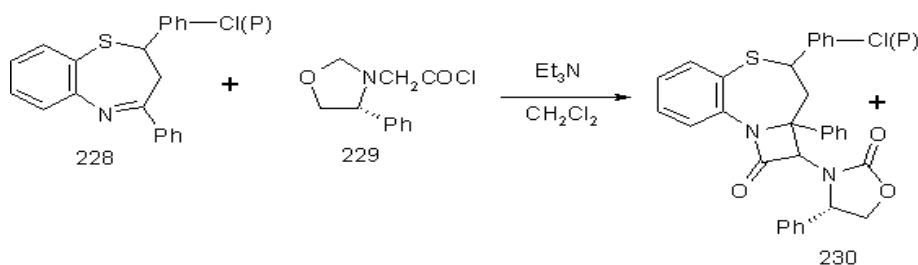


Figure 58. Reaction of compound 228 with (4*R*)-phenyloxazolidylacetyl chloride 229(0.38g, 1.58mmol) in the presence of Et₃N in CH₂Cl₂

3.35. Synthesis from Compound 234a-h with Chloroacetyl Chloride

2-Aminobenzothiazole-6-carboxylic acid 231. This compound, on condensed with chloroacetyl chloride yielded 2-(2-chloroacetylamino) benzothiazole-6-carboxylic acid 232. Compound 232 on amination with hydrazine hydrate afforded 2-(2-hydrazinoacetylamino) benzothiazole-6-carboxylic acid 233. The condensation

removed by filtration, the CH₂Cl₂ solution was evaporated and the residue was purified by column chromatography (ethyl acetate/ petroleum ether = 1:2) to give product 230. The single crystal suitable for X-ray analysis was obtained by slowly evaporating an ethyl acetate-petroleum ether solution in the air. Zhang et al,2002 [78].

reaction of compound 233 with various aromatic aldehydes yielded 2-{2-[*N'*-(arylidene)hydrazino] acetylamino}- benzothiazole-6-carboxylic acids 234a-h. Compounds 234a-h, on reaction with chloroacetyl chloride in the presence of triethylamine underwent dehydrativeannulation to afford 2-{2-[3-chloro-2-(aryl)-4-oxoazetidin-1-ylamino]acetylamino} benzothiazole-6-carboxylic acids 235a-h. These reactions are summarized in. Ameya et al, 2007 [79].

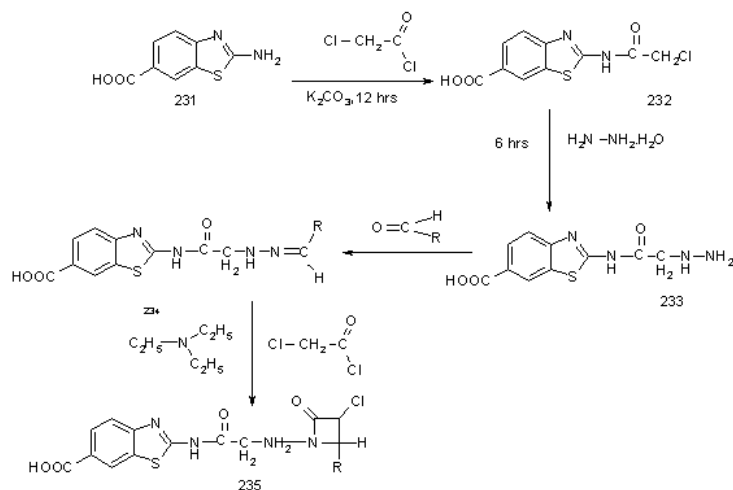


Figure 59. Reaction of compound 234a-h with chloroacetyl chloride

3.36. Synthesis from Reaction of Ketene 236 and Imines 237

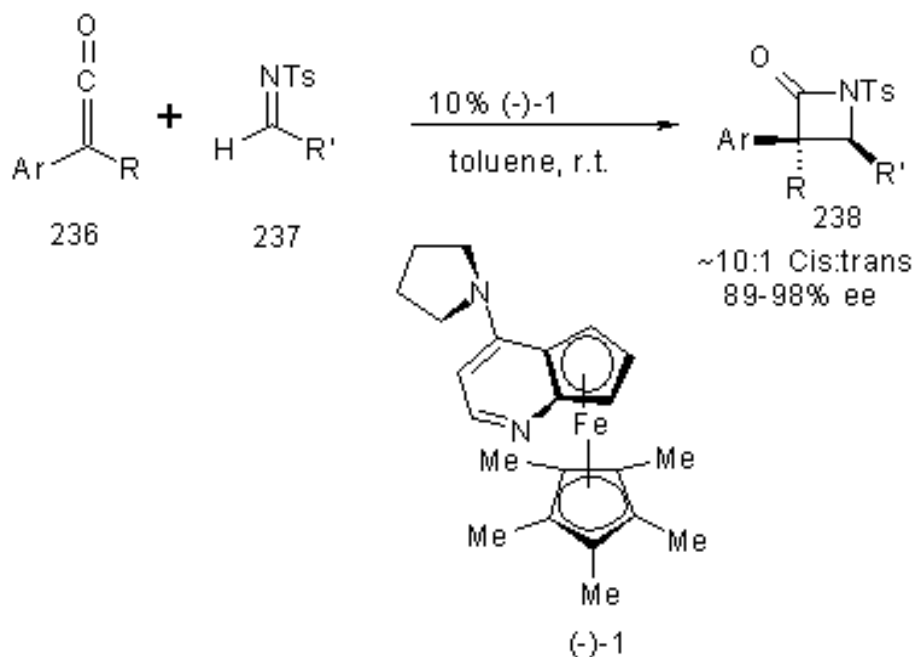


Figure 60. Reaction of ketene and imines afford B-lactam 238

3.37. Synthesis from coupling of Ketenes with *N*-tosyl Imines

While attempting to improve upon the process illustrated in eq 1, we made the exciting discovery that the cis/trans selectivity of Staudinger reactions catalyzed by PPY derivative 1 (PPY) 4-(pyrrolidinopyridine) can be

Only one method has been described for the diastereo- and enantioselective synthesis of R,R-disubstituted β -lactams through a catalytic asymmetric Staudinger reaction; as indicated, this process preferentially affords the cis isomer Elaine et al, 2005 [80].

effectively controlled through the appropriate choice of the *N*-protecting group of the imine. Thus, ketenes couple with *N*-tosyl imines to predominantly generate cis β -lactams, whereas reactions with *N*-triflyl imines preferentially furnish the trans isomers Elaine et al, 2005 [80].

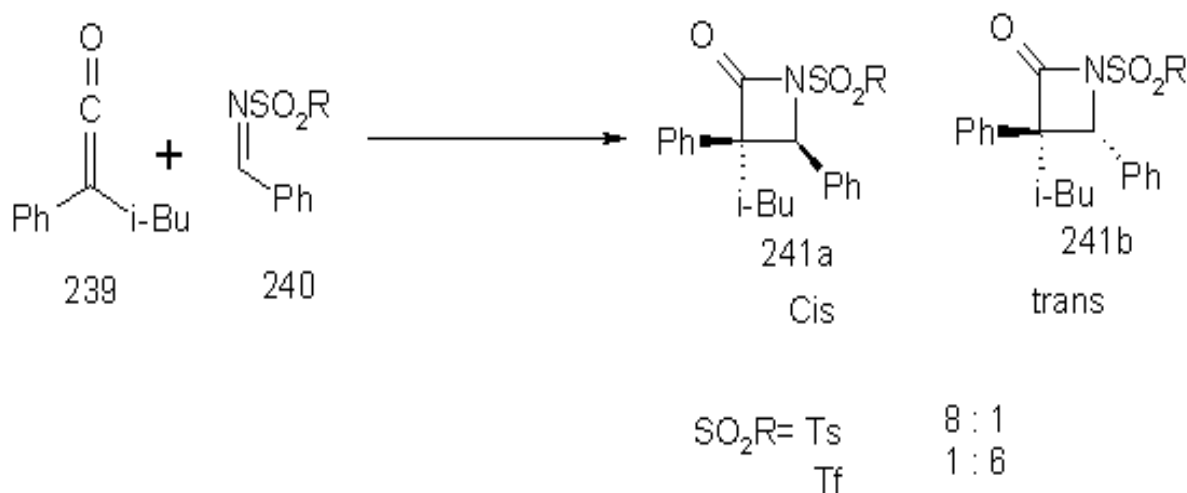


Figure 61. Coupling of ketenes with *N*-tosyl imines

3.38. Synthesis from 3,3-diethoxy-2,2-dimethylpropionic acid ethyl ester 244 with *p*-anisidine 245 gave 3-(4-methoxyphenylimino)-2,2-dimethylpropionic Acid Ethyl Ester 246

Condensation of 3,3-diethoxy-2,2-dimethylpropionic acid ethyl ester 244 with *p*-anisidine 245 gave 3-(4-

methoxyphenylimino)-2,2-dimethylpropionic acid ethyl ester 246, which was used in the following step without purification. Cycloaddition of 246 with the in-situ-generated acetoxyacetyl chloride 253 in the presence of anhydrous triethylamine gave acetyl β -lactam 250 (PMP = *p*-methoxyphenyl) in 53% yield after two steps. Yan et al, 2005 [81].

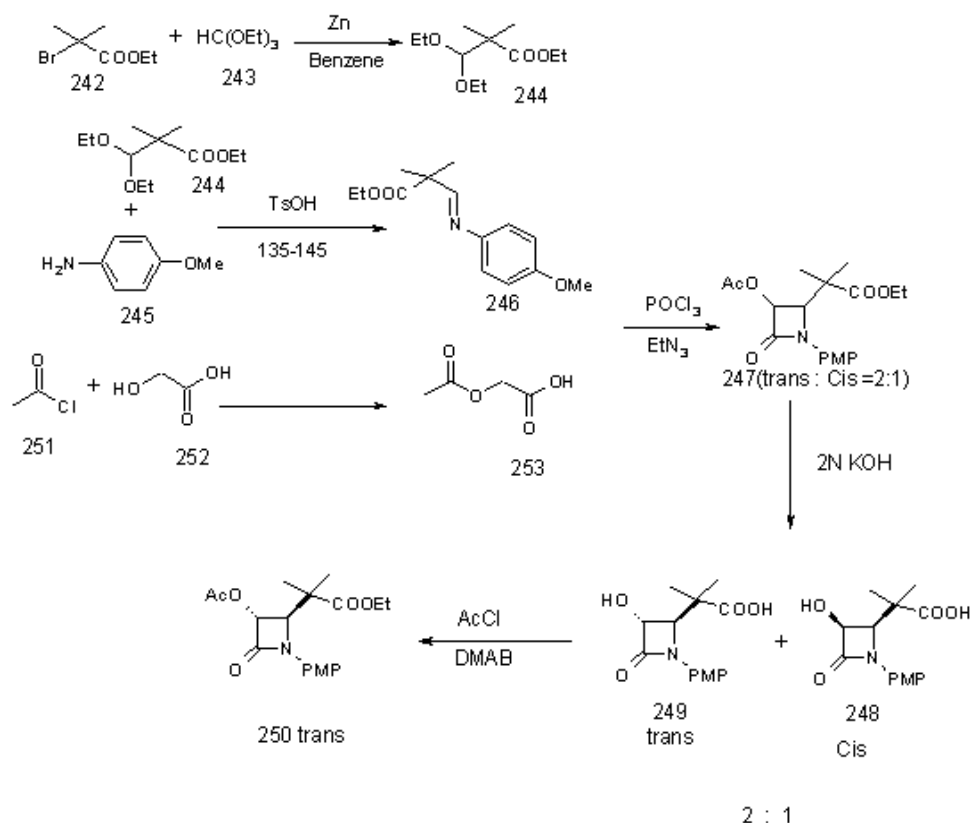


Figure 62. Reaction of 3,3-diethoxy-2,2-dimethylpropionic acid ethyl ester 244 with *p*-anisidine 245 gave 3-(4-methoxyphenylimino)- 2,2-dimethylpropionic acid ethyl ester 246

3.39. Synthesis from Isonicotinamide 254

To establish the feasibility of cyclizing a lithiated benzyl group onto a pyridine ring, the isonicotinamide 254 was made using standard methods and treated with excess LDA 7 at 0°C. A red-brown organolithium was formed, presumably 255. Stirring for 1 h at 0°C and neutral workup yielded a product (258a) resulting from dearomatizing cyclization of 257 into the 3-position of

the pyridine ring and protonation of the resulting enolate 258. Hydrolysis of the unstable amidate 258a on purification by chromatography on silica yielded the stable lactam 259a as a single diastereoisomer. Alkylating the enolate 258 with methyl iodide or acylating with methyl chloroformate gave, after hydrolysis, lactams 260b and 260c, respectively, as single diastereoisomers *Jonathan et al, 2005 [82]*.

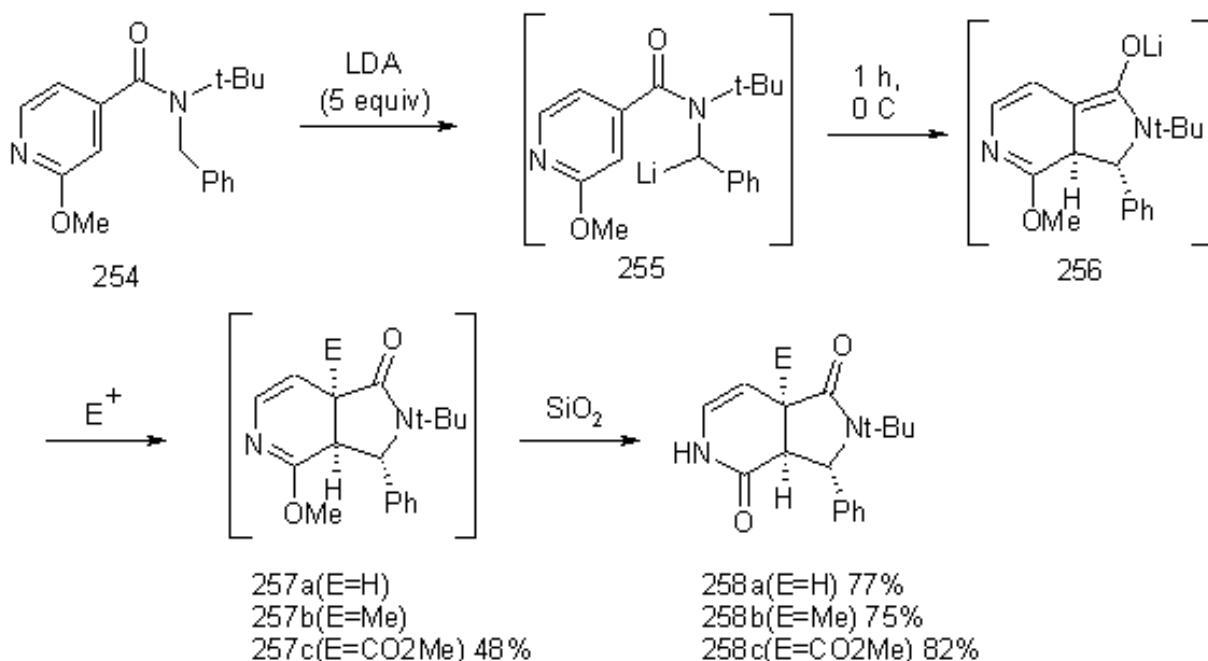


Figure 63. Synthesis from isonicotinamide 254

4. Conclusion

In this review different method for synthesis of thiazolidinone and β -lactam were discussed like a series of 4-thiazolidinones and 2-azetidinones have been synthesized by condensation of 4,4'-diaminodiphenylsulphone with various aromatic or heterocyclic aldehydes to yield the Schiff's bases(26). Cyclocondensation of Schiff's bases with 2-mercaptopropionic acid afforded 4-thiazolidinone derivatives(27), and cyclocondensation of Schiff's bases with chloroacetylchloride in presence of triethylamine afforded 2-azetidinone derivatives(28).. All these compounds were evaluated for their *in vitro* growth-inhibitory activity against several microbes. Standard ampicillin against *Bacillus subtilis*.

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