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Review Article

NEW SCHIFF'S BASES AS ROUTE FOR SYNTHESIS OF NEW SPIRO AND ISOLATED β LACTAMS.

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Abstract:

Compound 5 react with different aromatic nitroso compound to give new Schiff's bases 7a-c. The activity of azamethine center in compound 7a-c renders it available to react with chloroacetyl chloride to give new Isolated βlactams 8a-c. The synthesis some new Schiff's bases through the condensation of both compound 8 and or 12 with different aromatic aldehyde in the presence of piperidine catalyst afforded the corresponding Schiff bases compounds 10a-c, 14a-c, [21]. These newly synthesised Schiff's bases compounds used for the synthesis of new isolated βlactam. Thus compound 10a-c, 14a-c react with chloroacetylchloride and or mercaptoacetic acid in the presence of triethylamine to give isolated β -Lactams 11a-c, 15a-c respectively.

Key words: Schiff's bases, βlactams, chloroacetyl chloride, aromatic aldehyde,nitroso compounds.

Introduction

Schiff,s bases and beta lactam have been possess Antiviral[1], anticancer[2], antifungal[3-8], pesticidal[9], anti-inflammatory[10], and cholesterol absorption inhibitors[11,12],Also antibacterial[13-18]there for the activity of the carbonyl group in compound**1** render it to react with different aromatic amine to give new Schiff's bases**3a-c[19]**. The activity of the azamethine center in compound **3a-c** is more available than the activity of the NH group toward the addition process of chloroacetyl chloride, and this mentioned phenomena is due to the presence of π electron, which makes the foundation of the δ positive and δ negative charge on the carbon and nitrogen atom, respectively, more easy than the presence of this phenomena on the NH group in which the bonding between nitrogen and hydrogen wheather strong according to the nature of this bonding which leads to decreasing of the mobility desire of the hydrogen atom of this pH group[**19]**. Thus compound **3a-c** reacted with chloroacetyl chloride to give spiro βlactam[**19**]**3a-c** .

Also Compound **5** react with different aromatic nitroso compound to give new Schiff bases **7a-c**.

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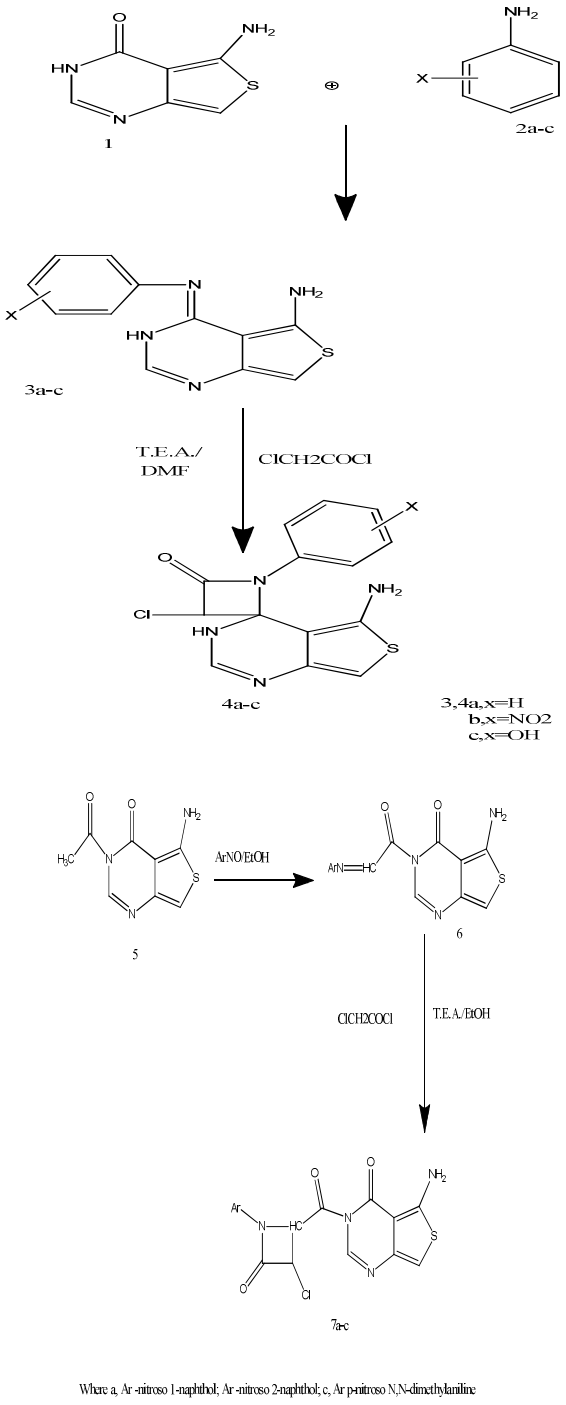
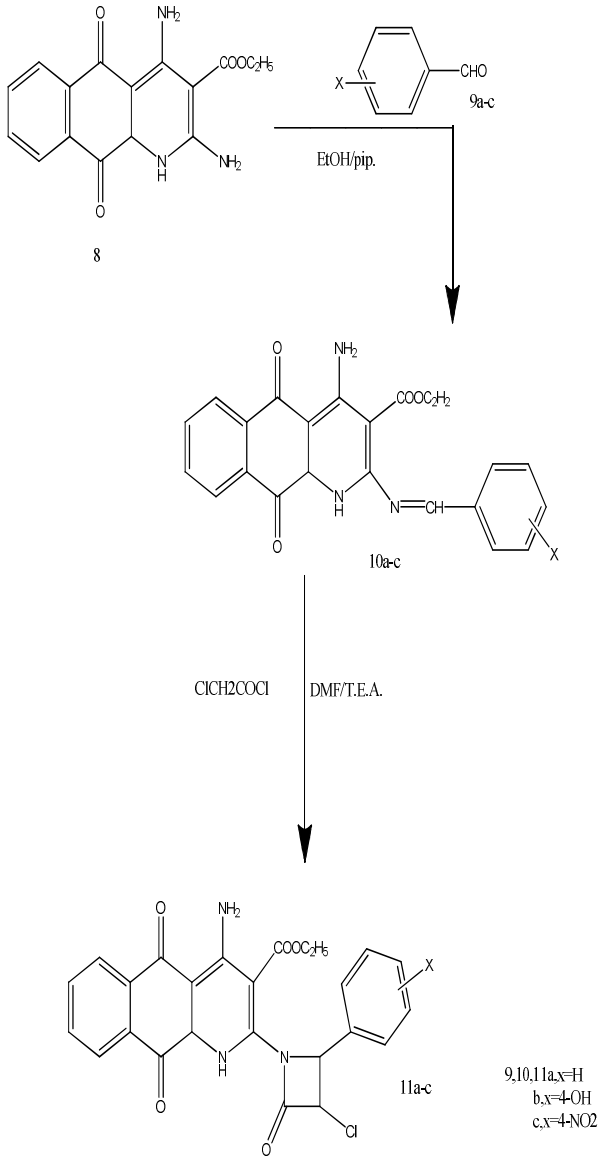
The activity of azamethine center in compound **7a-c** render it available to react with chloroacetyl chloride to give new Isolated βlactams **8a-c.[20]** .

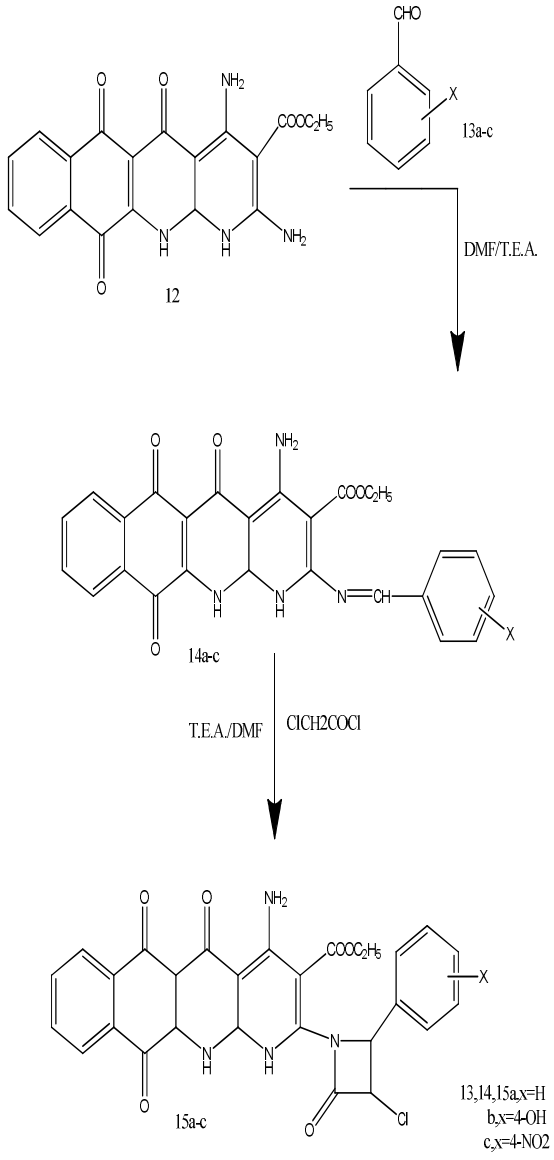


Scheme 1

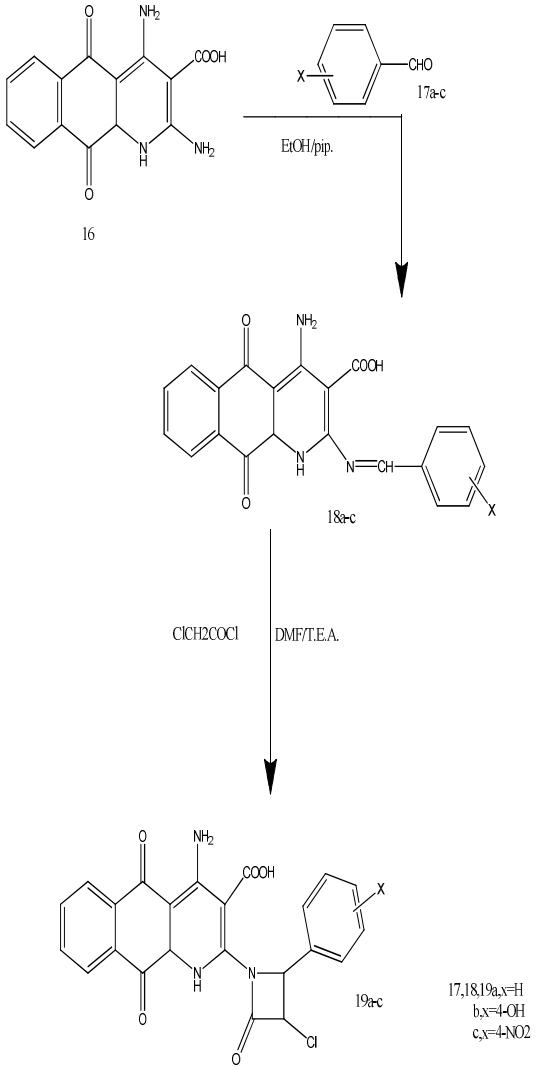
The synthesis some new Schiff's bases through the condensation of both compound **8** and or **12** with different aromatic aldehyde in the presence of piperidine catalyst afforded the corresponding Schiff bases compounds **10a-c**, **14a-c,[21]**. These newly synthesised Schiff bases compounds used for the synthesis of new isolated β-Lactam. Thus compound **10a-c**, **14a-c** react with chloroacetylchloride and or mercaptoacetic acid in the presence of triethylamine to give isolated β -Lactams **11a-c**, **15a-c** respectively. Compounds **8,12** undergo basic hydrolysis by boiling with concentrated sodium hydroxide solution acidified by concentrated hydrochloric acid to give compound **16**,**20** which have carboxylic group. Thus compounds **16**,**20** reacts with different aromatic aldehyde to give Schiff bases **18a-c**, **22a-c**, respectively which undergo cycloaddition reaction with chloroacetyl chloride in the presence of triethylamine to give β -Lactams **19a-c**, **23a-c** respectively**[21].**



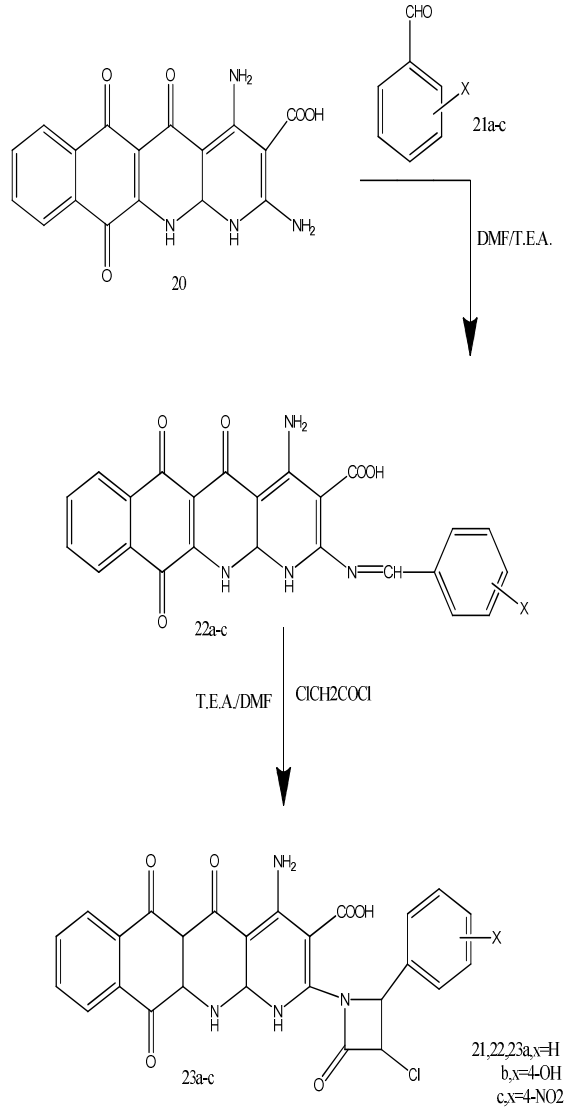
Scheme 2



Scheme 3

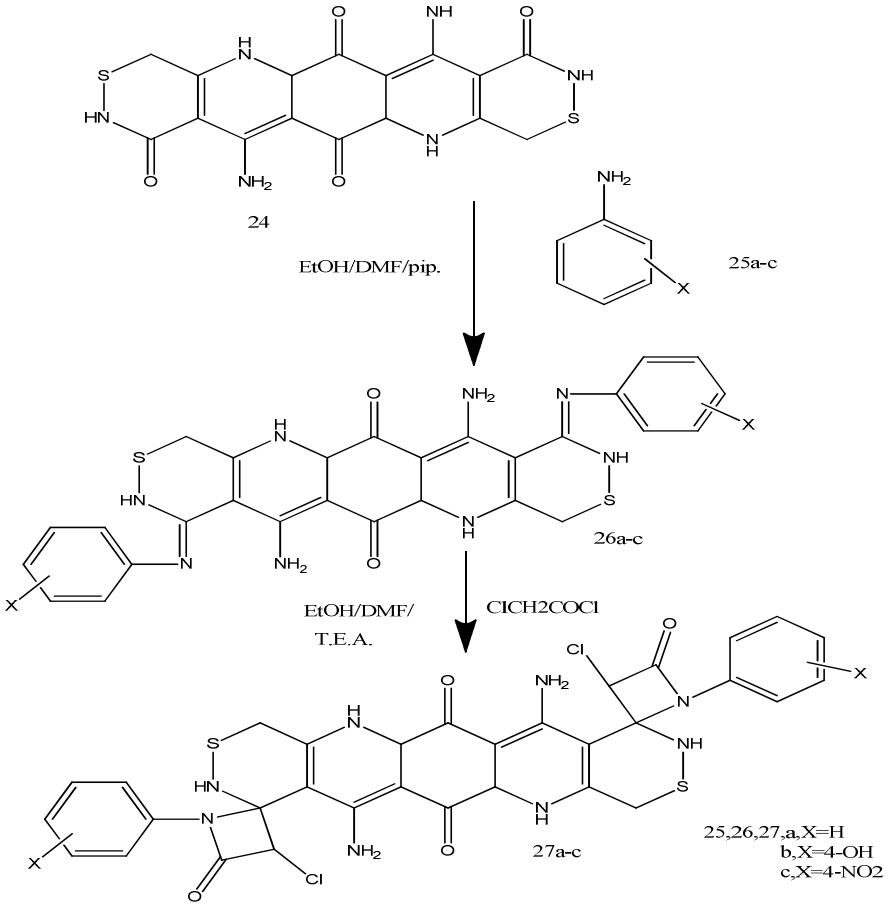


Scheme 4



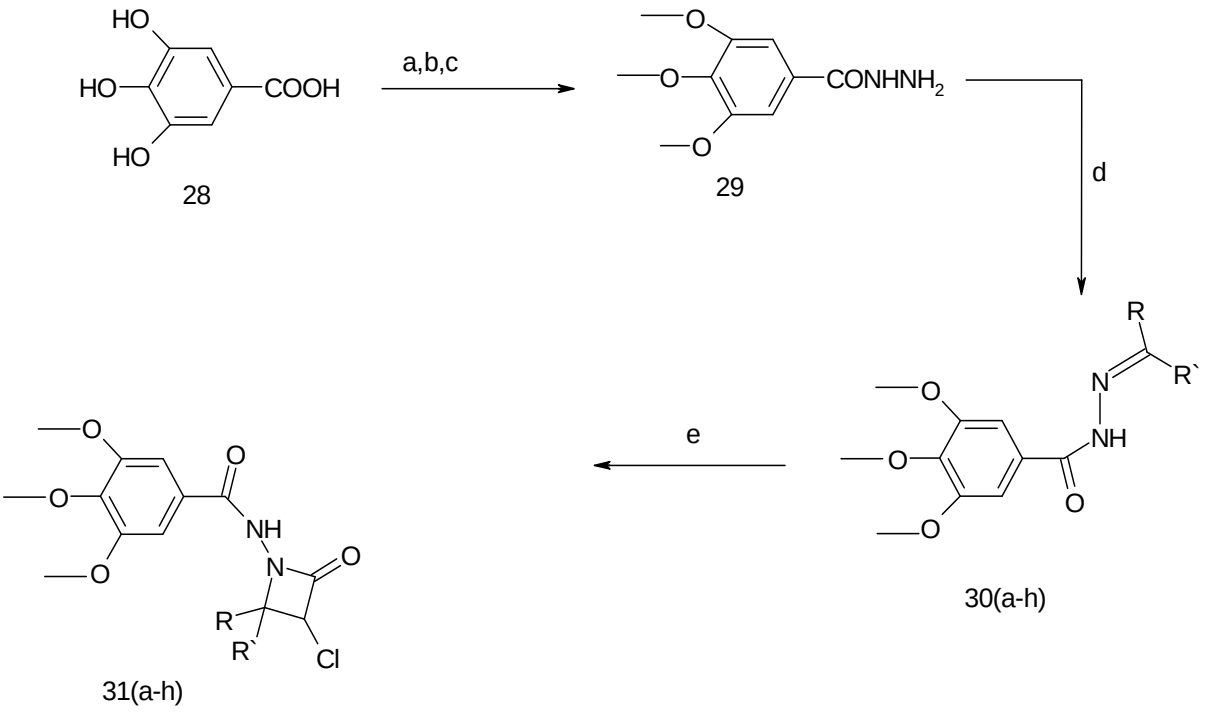
Scheme 5

The activity of the two carbonyl group in compound 24 render it to react with different aromatic amine25a-c in the presence of a mixture of ethanol (20 ml) and DMF (10 ml) as solvent at (0.5 ml) piperidine catalyst to give new Schiff bases 26a-c. The activity of azamethine centre in compound 26a-c is more available than the activity of the NH group toward the addition process of chloroacetyl chloride, and this mentioned phenomena is due to the presence of the π electron, which makes the foundation of the δ positive and δ negative charge on the carbon and nitrogen atom, respectively, more easy than the presence of this phe-nomena on the NH group in which the bonding between nitrogen and hydrogen wheather strong according to the nature of this bonding which leads to decreasing of the mobility desire of the hydrogen atom of this NH group [19]. Thus compound 26a-c reacted with chloroacetyl chloride to give spiro β-Lactams27a-c [23].



Scheme 6

The natural gallic acid **28** was selected as starting materials, which were routinely transferred to the corresponding 3,4,5-trimethoxybenzohydrazide **29** *via* sequence steps including *O*-alkylation, esterification and hydrazinolysis reaction. The synthesized benzoates were treated with hydrazine hydrate in EtOH to afford the hydrazides **29**. The following condensation reaction between hydrazides **29** and various aldehyde or ketone led to the important substrates, substituted benzoylhydrazone **30a-h**. Then the various benzoylhydrazone derivatives **30a-h** were treated with ketenes, generated *in-situ* from 2-chloroacetyl chloride in the presence of triethylamine to give desired multi-substitutedmonocyclic β-lactams derivatives **31a-h**. All the target compounds**31a-h** gave satisfactory chemical analyses. The ketene-imine heterocyclization reaction is most probably initiated by a nucleophilic attack of the iminohydrazone nitrogen to the carbonyl carbon of *in-situ* generatedketene leading to an intermediate, with subsequentintramolecular reaction leading to the formation of target compounds. In the above-described experimental conditions, the heterocyclization reaction reached completion with a moderate yields and shorter time for target β--lactams derivedfrom gallic acid. The obtained novel β-lactams derivatives were screened for insecticidal activity. The commercial insecticidespirodiclofen was tested as a reference compoundunder the same conditions as the synthesized β—lactams derivatives[**24].**

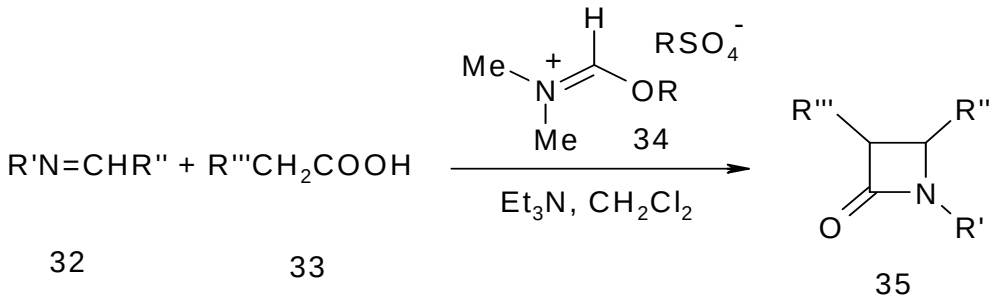


30,31	substituent	
a	R=H,R`=Ph	R=H,R`=4-Cl-Ph
|	R=H,R`=2,4-Cl2Ph	R=H,R`=Pr
|	R=H,R`=4-CF3-Ph	R=H,R`=Furan
h	R=H,R`=4-F-Ph	R=H,R`= Cyclohexyle

Synthetic route for azetidinones derivatives. Reagents and conditions: a. Me2SO4, NaOH, then HCl; b. EtOH, Conc. H2SO4; c. 5 equiv. NH2NH2· H2O, reflux for 5-7 h; d. 1.1 equiv. Ketone/aldehyde, EtOH, reflux for 6-8 h; e. 1.2 equiv. ClCH2COCl, CHCl3, Et3N, r.t. to 40 oC for 2-5 h

Scheme 7

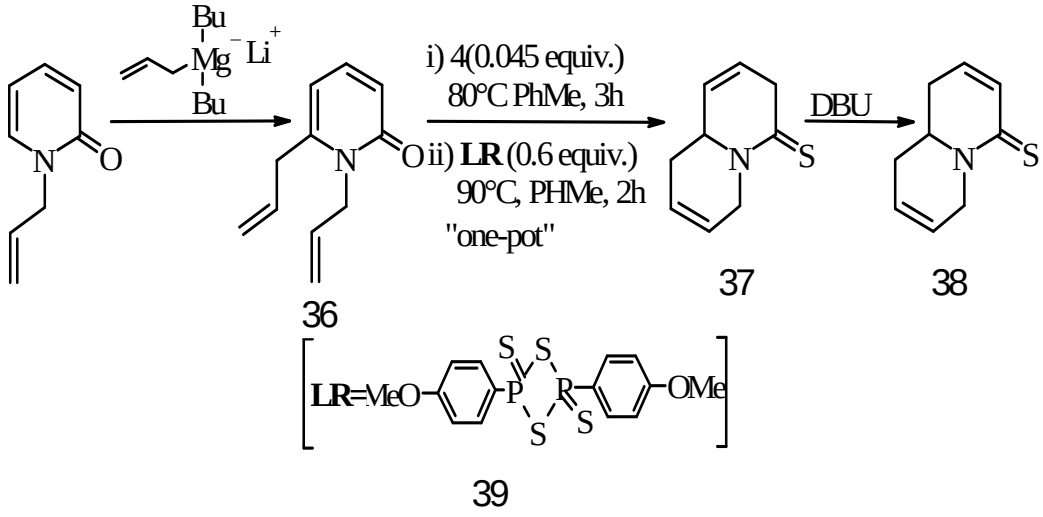
A number of 2-azetidinones were synthesized in good to excellent yields by a novel reaction between Schiff bases, substituted acetic acids and alkoxymethylene-*N*,*N*-dimethyliminium salts, the adduct formed from DMF and O-alkylating agents. The advantages of this new method are mild reaction conditions, 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 [**25].**



Scheme 8

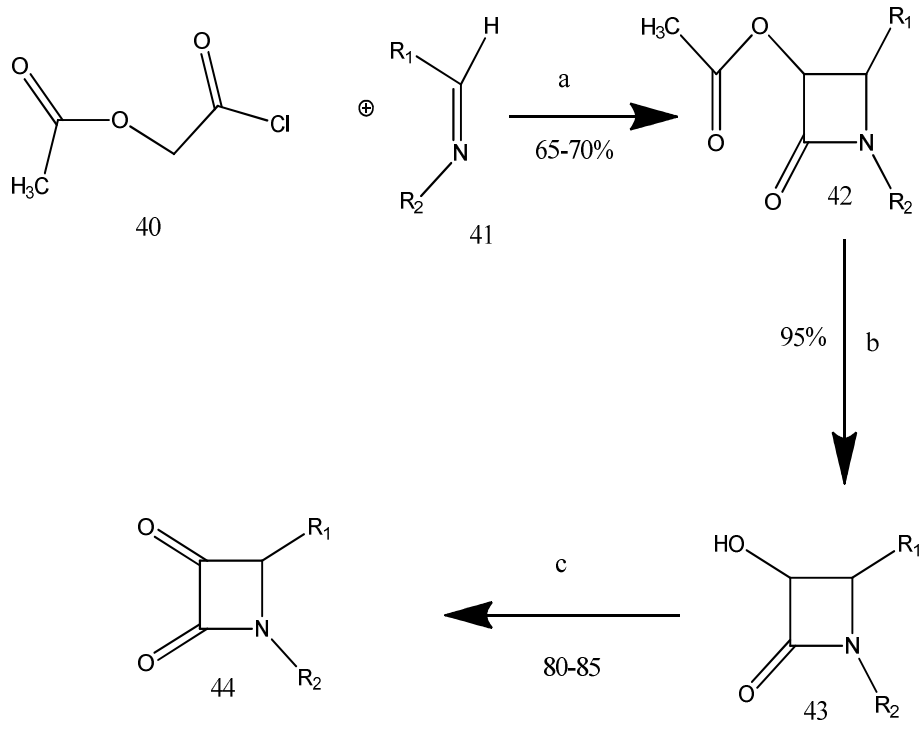
The α,β-unsaturated δ-thiolactams have been recognized as good Michael acceptor, where, they form C-C bonds in reactions with C-nucleophiles: alkyl lithium, alkyl magnesium, lithium enolate and with aliphatic nitro compounds in the presence of a base catalyst. Also, he reported that, it is easy synthetic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

RCM/thionation/isomerization applied successfully to N,6-diallylic β,γ-unsaturated lactam **(36)** providing unsaturated thiolactams **(37)** and **(38)** **[26]**possessing bicyclic quinolizidine in high yields in the following (Scheme9)[**26]**.



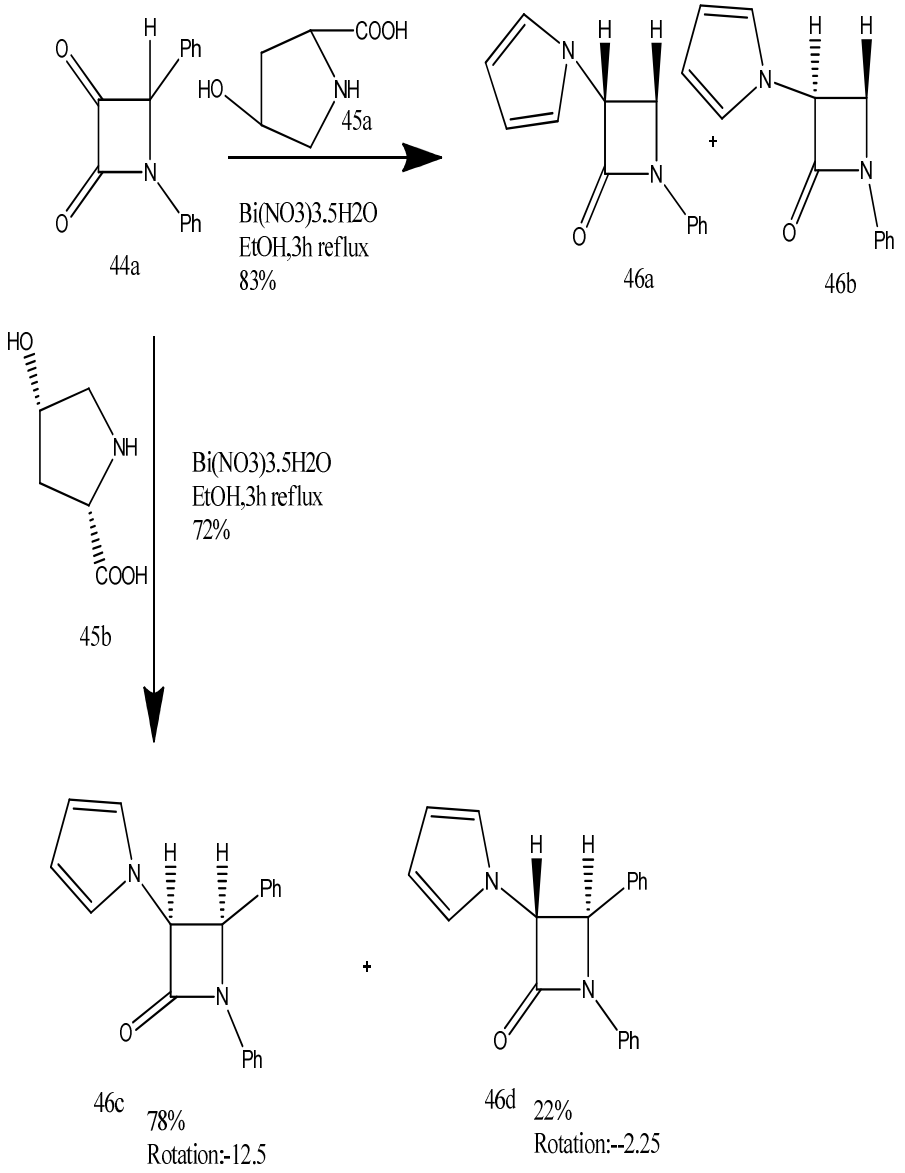
Scheme 9

The new pathway for the synthesis of new β-lactams that have a pyrrole ring at the C-3 position of the Staudinger cycloaddition reaction ofacetoxyacetyl chloride **40** with imine **41** gave 3-acetoxy-β-lactams in 65-70% yield, which oncareful hydrolysis with aqueous NaOH in THF**[27]** gave the corresponding 3-hydroxy-β-lactams **43** in **Scheme 10.** almost quantitative yield. Oxidation of hydroxylgroup was carried out by a known procedure using phosphorous pentoxide and dimethylsulfoxide[**28]** to give the desired α-keto-β-lactams **44a-d** in 80-85% yield (**Scheme 10)**



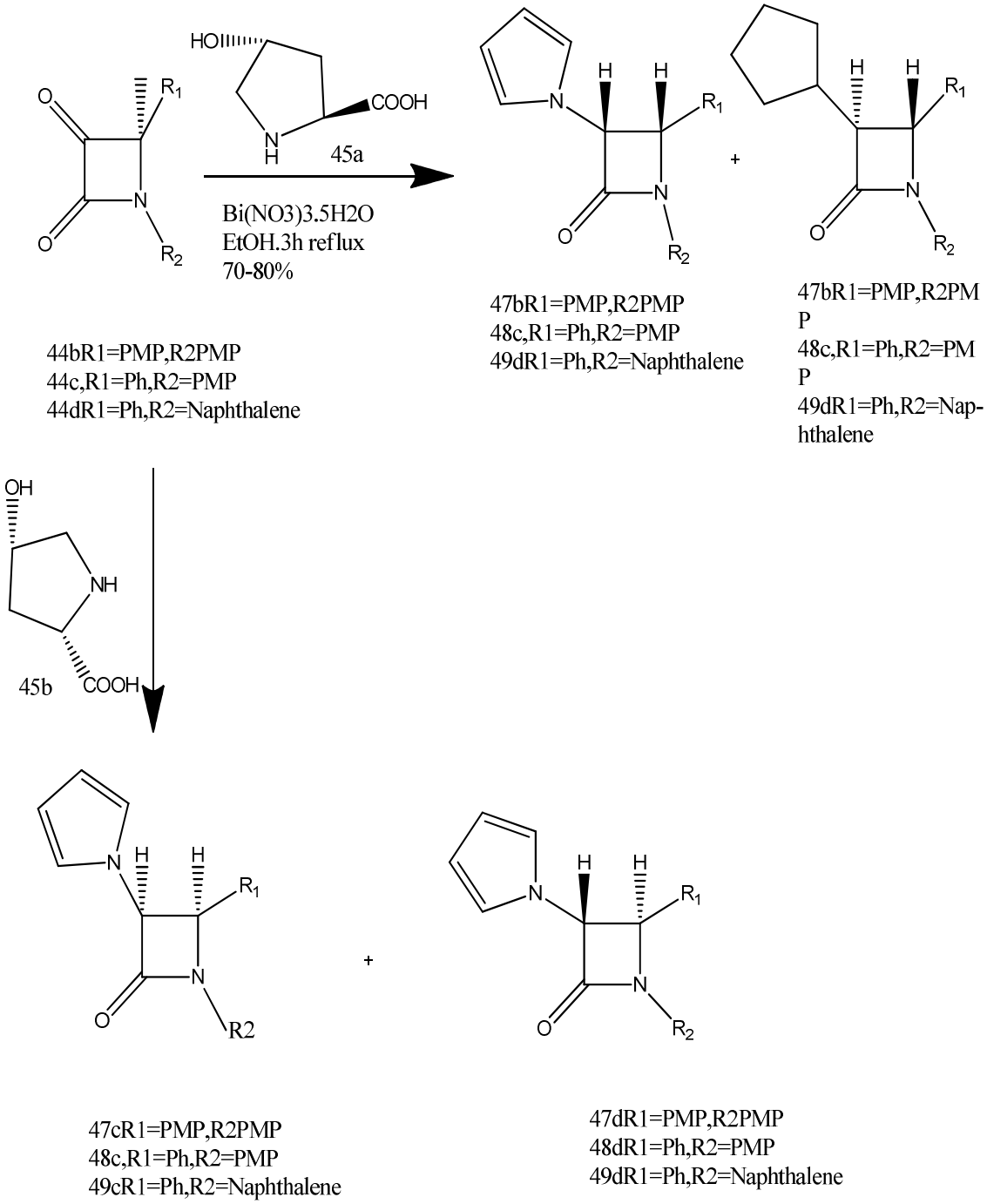
Scheme10.
Synthesis of α-keto-β-lactams **44a-d**

Initially racemic α-keto-β-lactam **44a** was reacted with *trans*-4-hydroxy L-proline **45a** in the presence of catalytic bismuth nitrate in ethanol at room temperature. But, no product formation was observed. We tried the reaction without bismuth nitrate in dilute reaction condition but there was no change in TLC and staring materials were recovered. Then reaction mixture was refluxed for 3 h while a dramatic change was observed (**Scheme 11**). The TLC of reaction mixture indicated formation of two new spots. showed the presence of two diastereomers. These two diastereomers were separated by flash column chromatography to give pure *cis*-β-lactams **46a** (78%) and *trans*-β-lactams **46b** (22%)with pyrrole substituent at C-3 position. These two products were optically active. Higher diastereoselectivity for *cis*-β-lactam **46a** with pyrrole substituent at C-3 position was observed. We performed the same experiment with *cis*-4-hydroxy D-proline (**45b**) in the presence of a catalytic amount of bismuthnitrate in ethanol to obtain diastereomers **46c** (78%) as *cis* isomer and **46d** (22%) as *trans*isomer (**Scheme 11**). The spectral and analytical data for **46c** and **46d** had close similarity with **46a** and **46b** except optical rotations. The absolute stereochemistry for β-lactam carbon C-3 and C-4 for **46a, 46b, 46c** and **46d** were



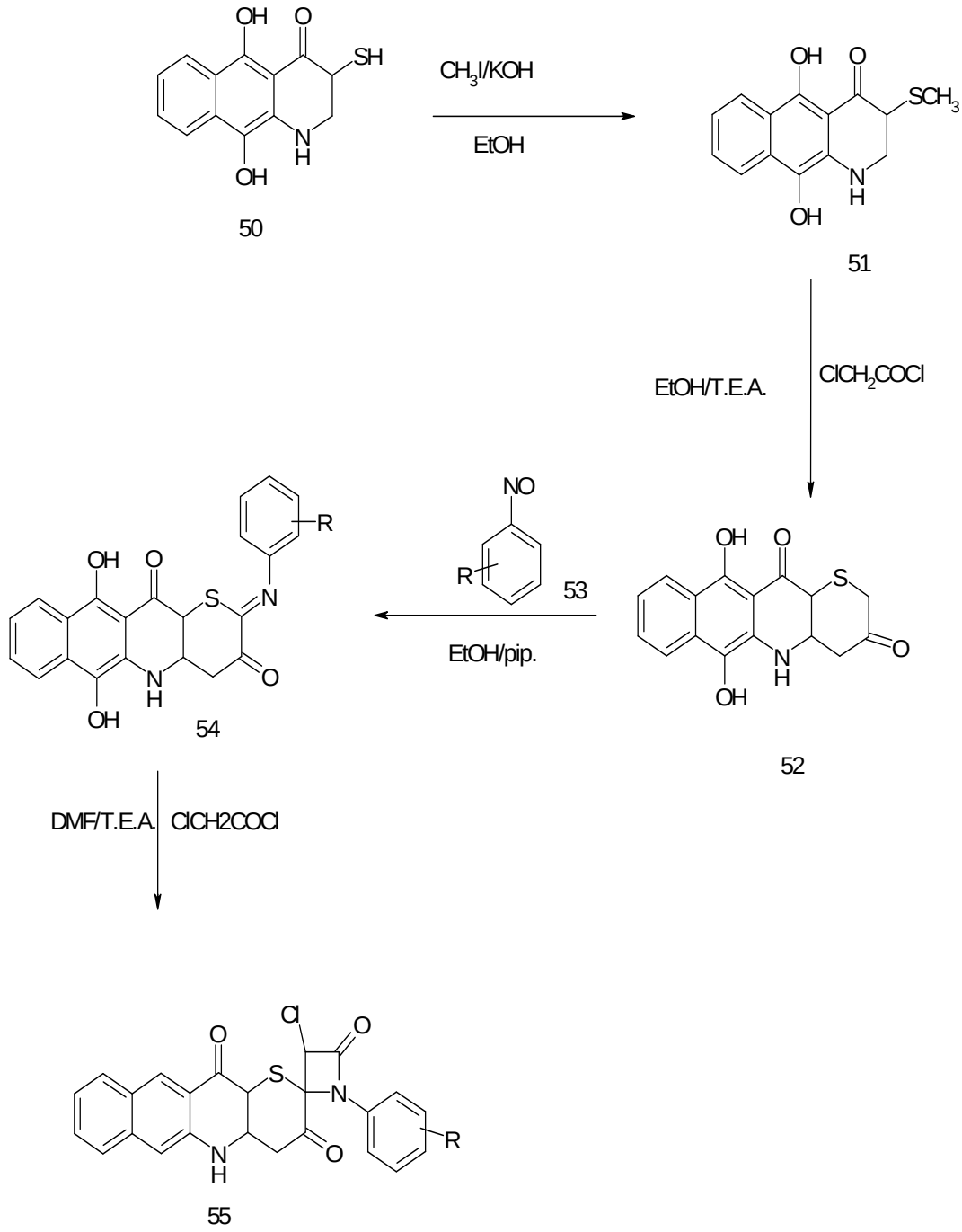
Scheme11 Synthesis of α-keto-β-lactams**46a-d**

The amino and the carboxyl group in **45a-b**are ideally located to undergo a condensationreaction to the highly reactive keto group of theα-keto-β-lactam **44a** in the presence of bismuthnitrate [**29]** Severalracemic α-keto-β-lactams **44b-d** were synthesized and reacted with *trans*-4-hydroxy L-proline (**45a**) and *cis*-4-hydroxy D-proline (**45b**) in the presence of catalytic bismuth nitrate to give *cis* isomers**47a**, **48a**, **47c** and **47d** as major isomers along with*trans* isomers **47b**, **48b**, **47d** and **48d** as minor isomers also successfullysynthesized racemic α-keto-β-lactams with *N*substitued polyaromatic naphthalene **44d** andanthracene **44e**. Synthesis of their optically pure 3-pyrrole substituted β-lactams **49a-d** are inprogress.**(Scheme12)**



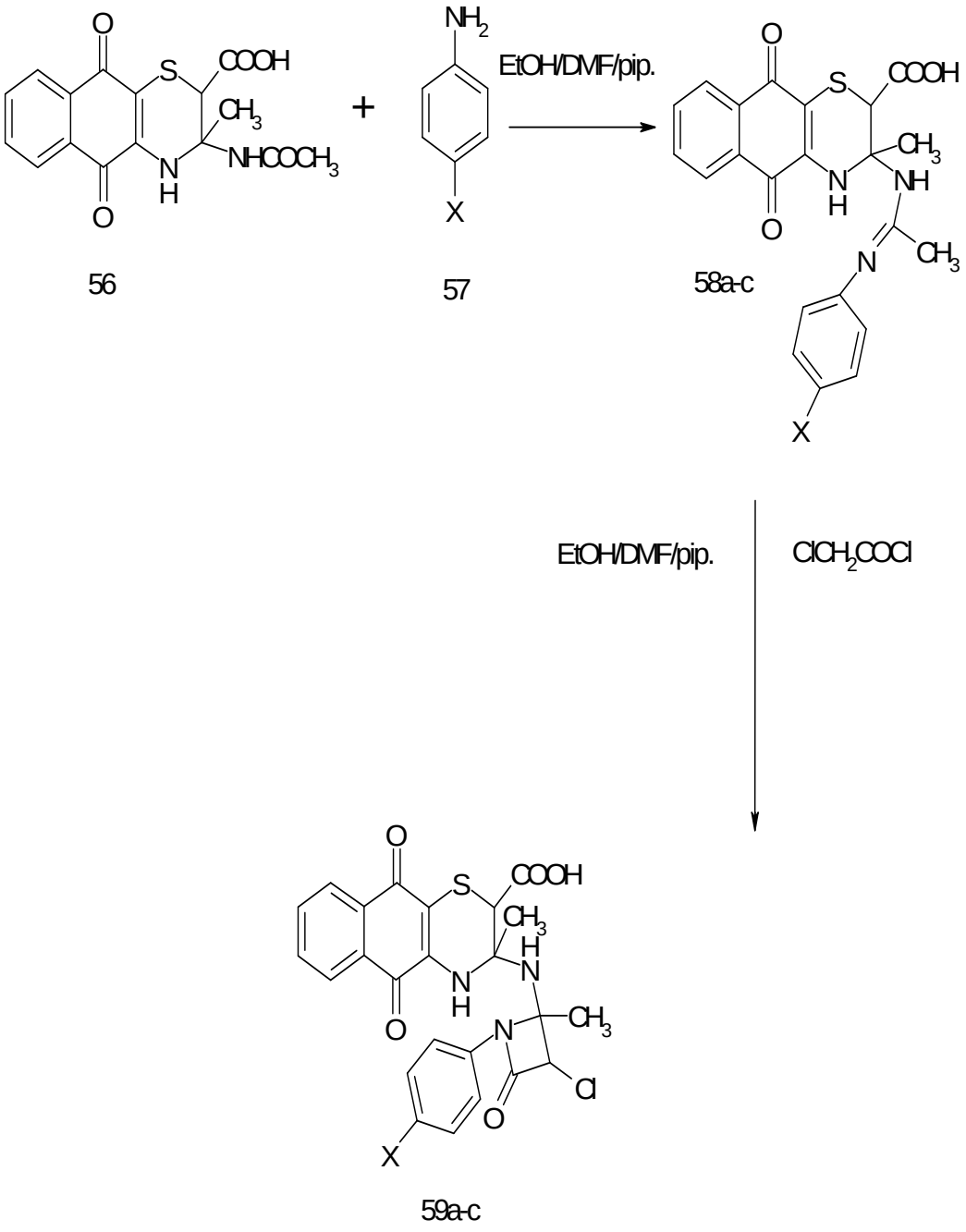
Scheme12 Synthesis of α-keto-β-lactams **47a-d** to **49a-d**

The synthesis of new heterocyclic by cyclocondensation , reaction of compound **50** with chloroacetyle choloride produced the new compound **51** which is used in synthesis of b-lactam **55** ,**[30].**



Scheme 13

The reaction of **58 a-c** with equimolar ratios of chloroacetylchloride in mixture of ethanol and DMF in the presence of piperidine catalyst afforded lactam derivatives **59a-c**. **[31].**



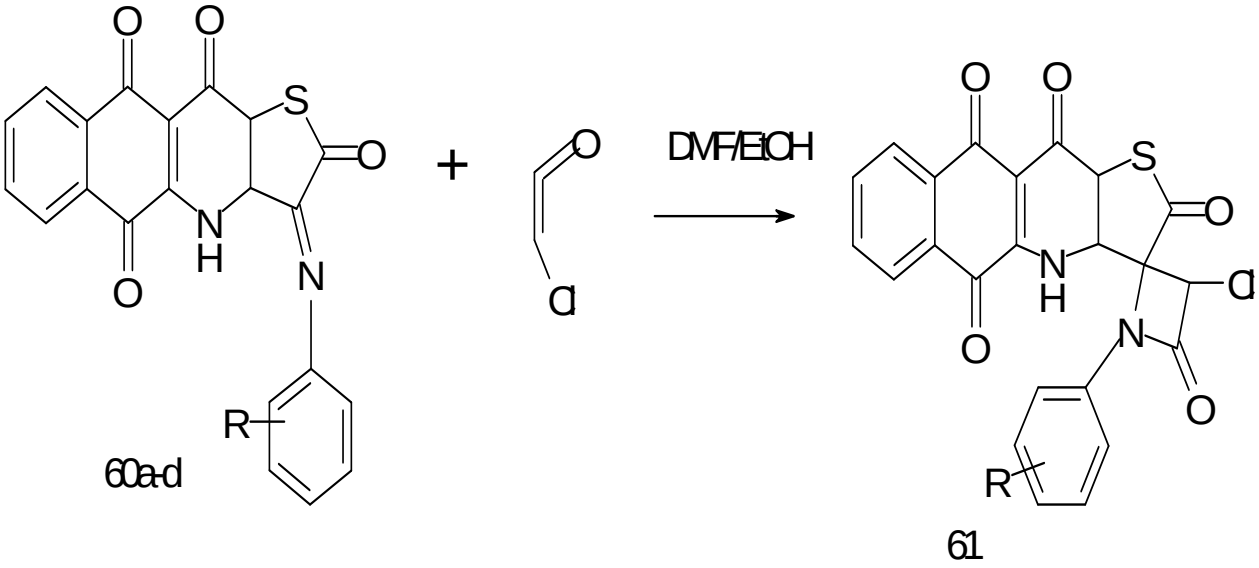
56 57 58a-c

59a-c

58,59, a,x=H,b,x=p-Cl,c,x=p-NO2

Scheme 14

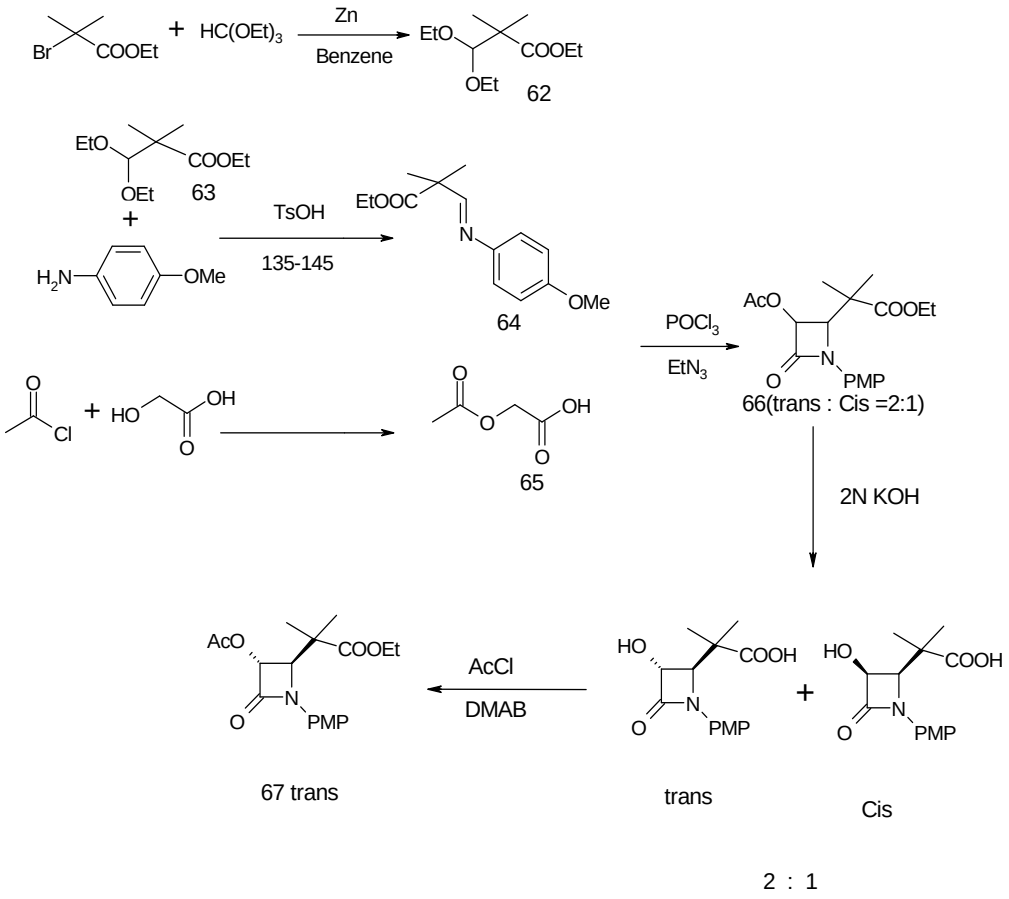
Compound **60a-d** underwent cycloaddition with chloroketone to give spiro lactam .The cycloaddition proceeded smoothly in dimethylformamide in the presence of triethyl amin catalyst to afford **61 a-d**, **[32].**



60,61, a,R=2-OH,3,4Benz substituted
b,R=2-OH,5,6Benz substituted
c,R=4-OH
d,R=4N(CH3)2

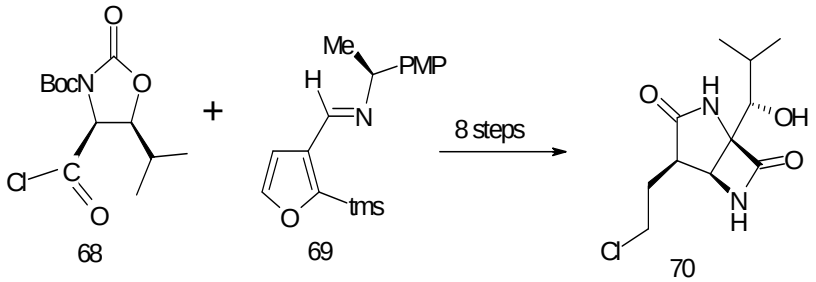
Scheme 15

Condensation of 3, 3-diethoxy-2,2-dimethylpropionic acid ethyl ester with *p*-anisidine gave 3-(4-methoxyphenylimino)- 2,2-dimethylpropionic acid ethyl ester , which was used in the following step without purification. Cycloaddition of 5 with the in-situ-generated acetoxyacetyl chloride in the presence of anhydrous triethylamine gave acetyl β-lactam (PMP = *p*-methoxyphenyl) in 53% yield after two steps, **[33].**



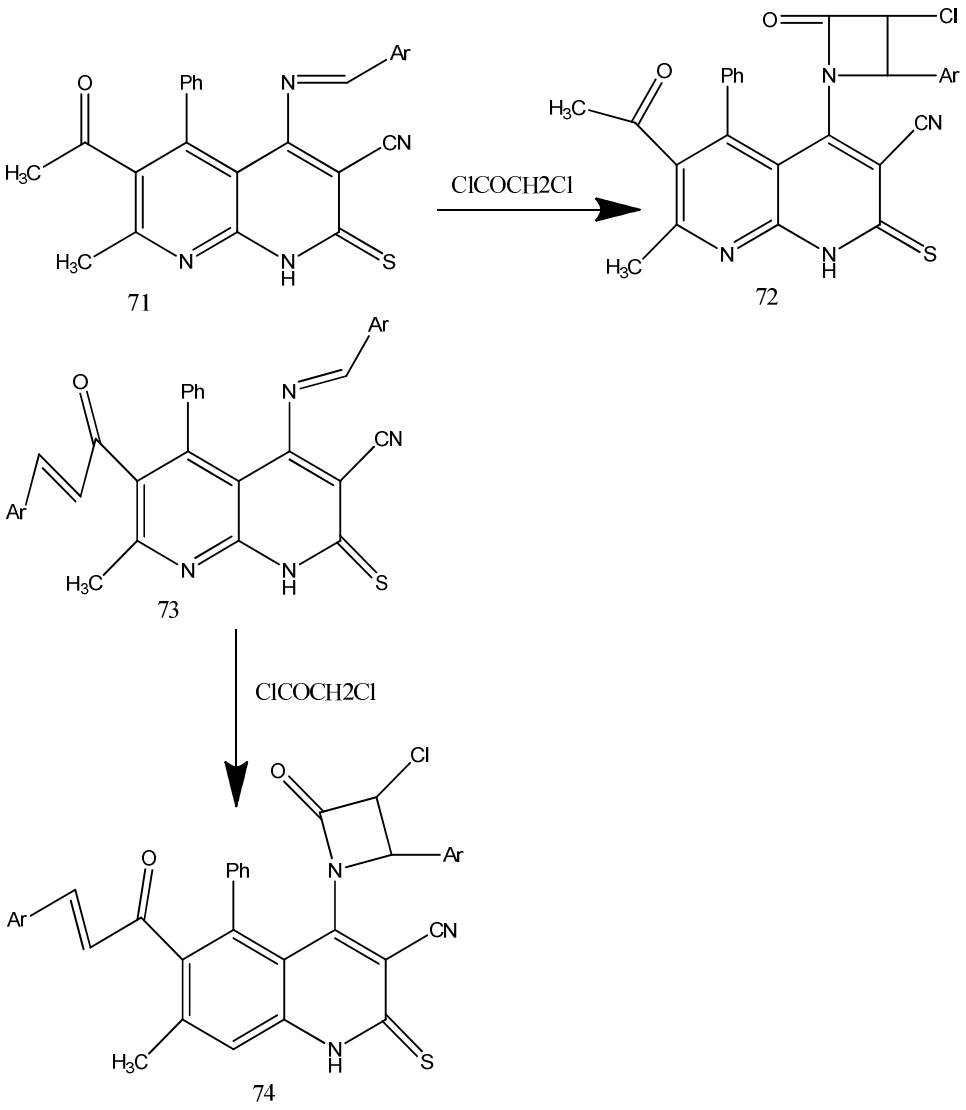
Scheme 16

A new and effective proteasome inhibitor, β-lactam **70**, 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 **70** stereoselectively. The intermediate was converted to **70** in seven steps and 30% overall yield. The β-lactam **70** is stable for many days in water at pH 7, in contrast to the natural β-lactones salinosporamide A **68** and omuralide **69**. In common with **68** and **69**, the β-lactam **70** effectively inhibits the mammalian proteasome **,[34].**



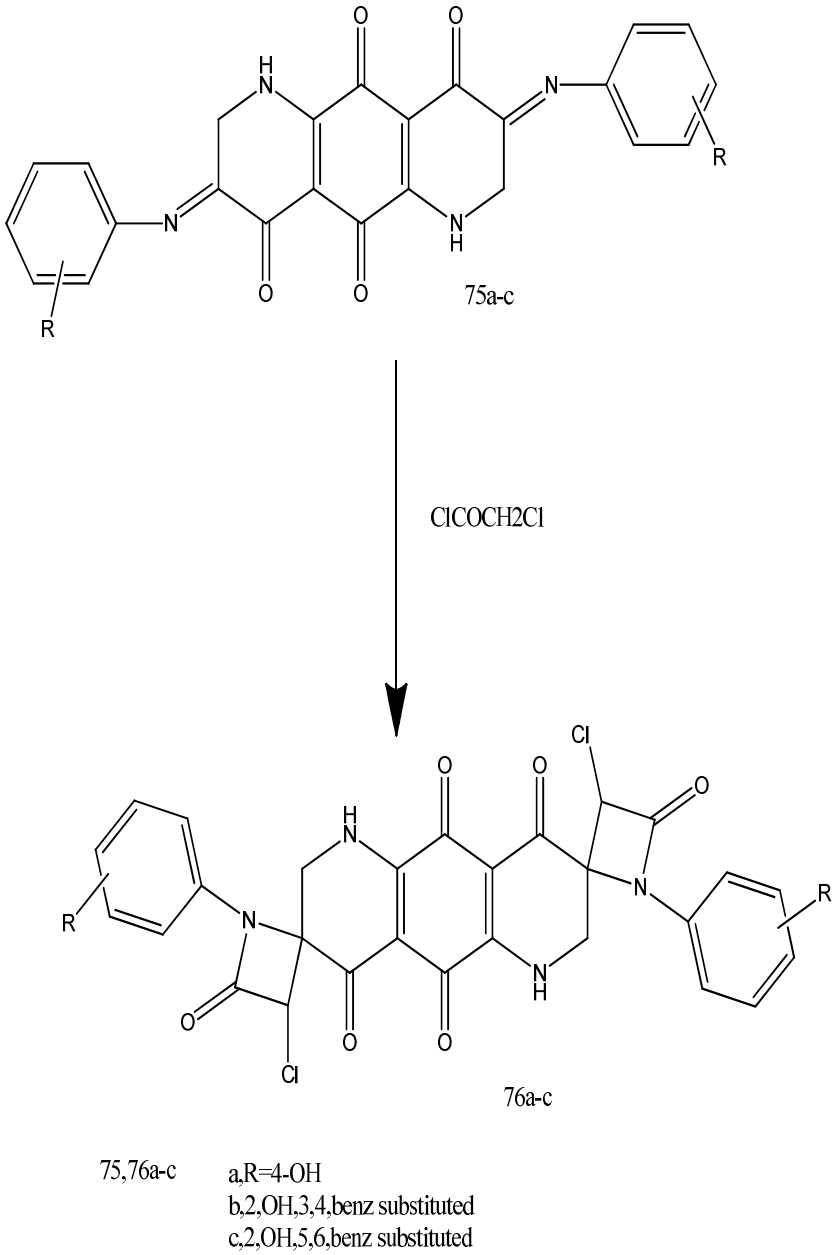
Scheme 17

Further, reaction of the Schiffs bases with one mole of chloroacetyl chloride in ethanol solution in the presence of triethylamine as catalyst leads to the β-Lactam derivatives **72**,**74**, **[35] .**



Scheme 18

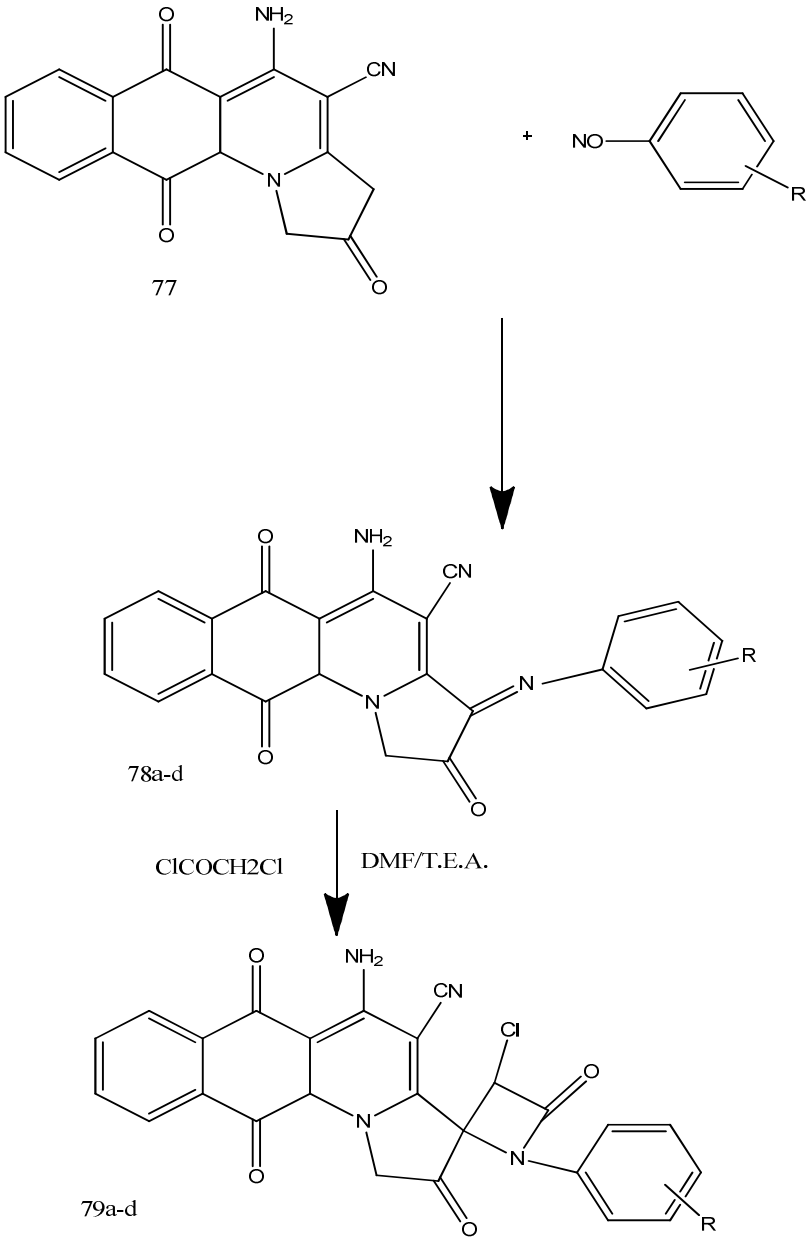
The reaction of **75a-c** with bimolecular ratio of monochloro- acetyl chloride in the presence of triethylamine as catalyst and dioxin as solvent afforded the corresponding 4,9 – dioxo- spiro - 3,3 – bis β-Lactams piperidino (2,3 g)- 1,2,3,4,5,6,7,8,9 –octaahydroquinolino quinine **76a-c ,[36].**



75,76a-c a,R=4-OH
b,2,OH,3,4,benz substituted
c,2,OH,5,6,benz substituted

Scheme 19

The synthesis of the desired spiro compounds started with the compound **78 a-d** and **81 a-d** which were prepared by the condensation of nitroso compound such as nitrosophenol, p-nitroso-N- dimethylaniline , nitroso – naphthol and – nitroso—naphthol with compounds **77** and **80** in ethanol using piperidine as catalyst .Compounds **78** and **81** under went cycloaddition with chlororoacetyl chloride to give **79a-d** and **82 a-d** . The cycloadditionn proceeded smoothly in dimethyl formamide in the presence of triethylamine as catalyst to afford,**[37].**



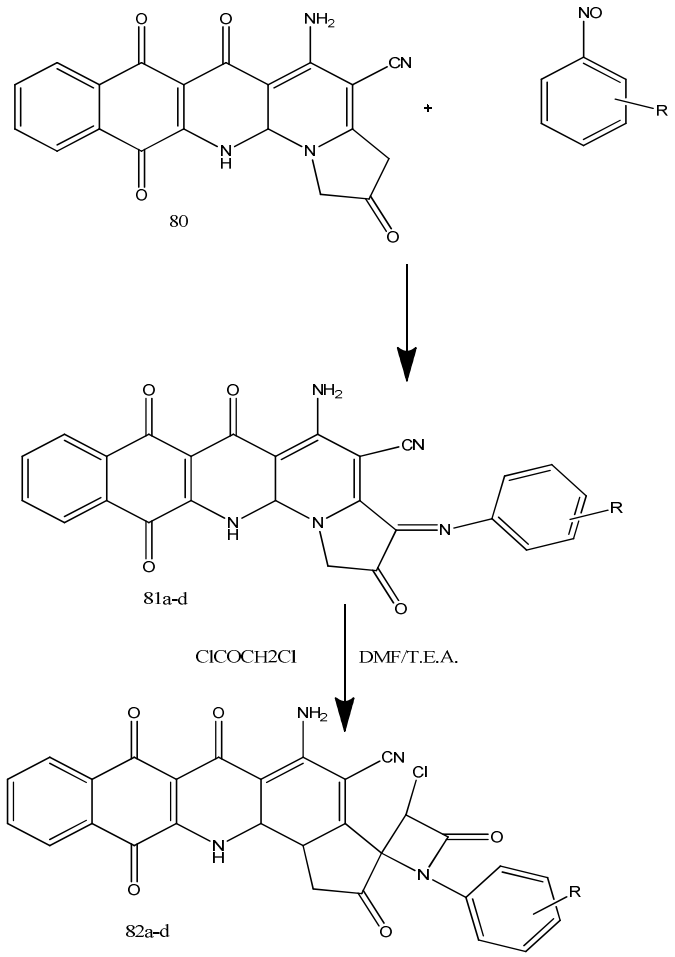
78,79a,R=4-OH

b,R=4N(CH3)2

c,2-OH,3,4,benzsubstituent

d,2,OH,5,6benzsubstituent

Scheme 20



81,82 a,R=4-OH

b,R=4N(CH3)2

c,2-OH,3,4,benzsubstituent

d,2,OH,5,6benzsubstituent

Scheme 21

Conclusion:

In this review we synthesis lactams via The reaction of **58 a-c** with equimolar ratios of chloroacetylchloride in mixture of ethanol and DMF in the presence of piperidine catalyst afforded lactam derivatives **59a-c**. **[31].** Compound **60a-d** underwent cycloaddition with chloroketone to give spiro lactam .The cycloaddition proceeded smoothly in dimethylformamide in the presence of triethyl amin catalyst to afford **61 a-d**,**[32].**

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Transparency declarations
The author: none to declare.

Contributions
N.A.A. Elkanzi Draw structure and wrote the manuscript.

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