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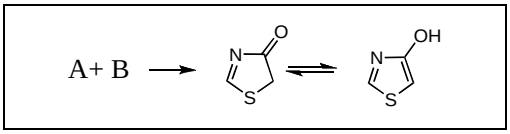

This review article includes a recent development in the chemistry of 4-thiazolidinones. Structure, basicity, synthetic aspects, reactions, and applications were also reported.

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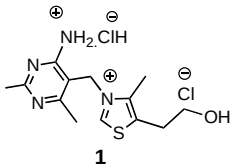
Contents

1. Introduction and Scope

The Chemistry of 4-thiazolidinones has been covered by several reviews [1a-1d], however, no collected data regarding the title compounds is available at the present time. Therefore, in this article, our aim will be devoted to give a broad general review of the structures, syntheses, reactions, and applications of these important classes of compounds through surveying the relevant individual articles recently reported in the literature.

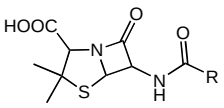
In recent years, interests of researchers have been focused on the heterocyclic systems which contain various heteroatoms such as nitrogen, sulphur and oxygen, because of their biological importance.

An example of such moieties is the thiazole moiety, which is present not only in the skeleton of vitamin B_1 (Thiamine) **1** and Penicillins **2** but also in the structures of various drugs.



1

Vitamine B_1

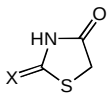


2

[R= $C_6H_5CH_2$-(penicillin G), $C_6H_5CH(NH_2)$-(ampicillin), $C_6H_5OCH_2$-(penicillin V)]

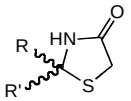
Thiazolidinones are derivatives of thiazolidines which belong to an important group of heterocyclic compounds. Thiazolidinones, with a carbonyl group at position 2,4 or 5, have been subjected to extensive study in the recent years.

4-Thiazolidinones **3** and **4** are the most extensively investigated class of compounds. 4-Thiazolidinone derivatives have been demonstrated to act as antibacterial [2-7] and antiprotozoal [2b], antifungal [8-11], anticonvulsant [12-15], anticancer [16,17], antituberculosis [18-20], antitumour [21] and antiparasitic [22a], herbicidal agents [22b], anti-inflammatory [22c], analgesic [22d], and antipsychotic agents [22e].



3

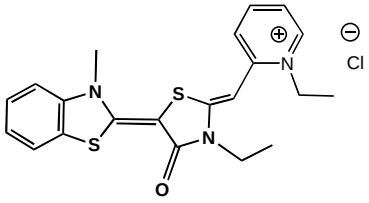
[X = O, S, NR, N-N=CRR']



4

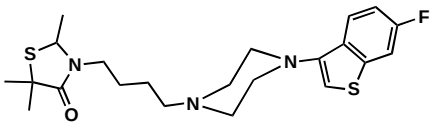
[R, R' = H, alkyl]

4-Thiazolidinones have been reported as novel inhibitors of the bacterial enzyme Mur **B** which was a precursor during the biosynthesis of peptidologycan [23], non-nucleoside inhibitors of HIV-RT [24,25], HIV-1 integrase inhibitors [26] and anti-histaminic agents [27]. For example, compounds **MKT 077**(**5**) and **HP-236** (**6**) have been registered as antitumour and antipsychotic agents while compound **7** and **8** have antimycobacterial activity. Also 2-aryl-3-aminoalkyl-thiazolidin-4-one derivative **9** possessed not only potent Ca^{2+} antagonistic activity but also Ca^{2+} overload inhibition and antioxidant activity [28]. Thiazolidinones derivatives **CP-060 (9)** and its analogues being antidiabetic drugs are used for the treatment of diabetes [29].



5

[MKT 077]



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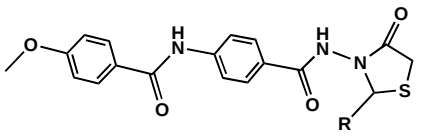
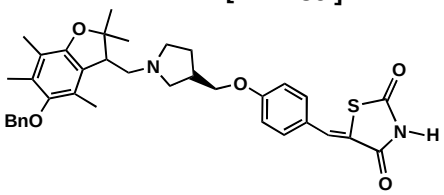
[HP-236]



7

[R = CH_3, -$CH_2CH{=}CH_2$, -C_6H_5]



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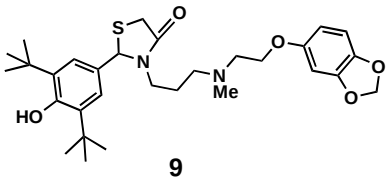
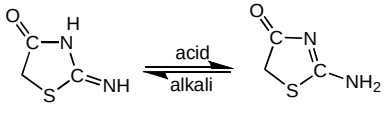


9

[CP-060]

1.1 Structure and Basicity

Some of the reported 4-thiazolidinones showed envelope or half-chair conformation with different configurations [30-33]. Their structural and conformational features are essential to correlate with their biological activity and their basicity [34]. The most significant rearrangement within the heterocyclic ring was observed for 2-imino-4-thiazolidinone (**3**) in the case of imino-amino tautomerism [35]. Disappearance of the acidic properties of the NH_{cyclic} group of the thiazolidine ring in aqueous solution indicates the strong tendency for rearrangement of this compound into its tautomeric amine form **B**. Furthermore, Ramsh *et al*. [36] studied the ultraviolet spectra of 2-amino-Δ^2-thiazolin-4-one (**3**) and some model compounds and determined their basicity. They also found that compound **3** exists in the amino form in water solution and determined the tautomeric equilibrium constant, K_t = amino form/imino form ~ 10^3.



(A) **3** (B)

It is known that the basicity strengths of the "aza" and "imino" nitrogens are higher than that of the exocyclic amino nitrogen, and basicity could be a relevant parameter for explaining these present results. The "aza" nitrogen appears to be a more efficient nucleophile than amino nitrogen toward an sp^2 aromatic carbon. The imino nitrogen appears also to be a very efficient nucleophilic center [37]. Despite the fact that 2-iminothiazolidin-4-one (**3**) has four nucleophilic reaction centers, *viz*., the two nitrogens (imino and amido), oxygen and C_5 atoms, its aminomethylation usually takes place only at the ring nitrogen atom [38,39] or, if it is substituted, at the exocylic nitrogen atom [40,41].

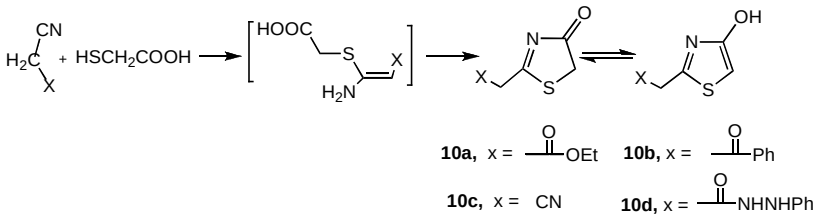
2. Synthetic Aspects: An Overview

Several methods for the preparation of 4-thiazolidinone derivatives and reactions have been reported in the literature, and the following routes have been employed.

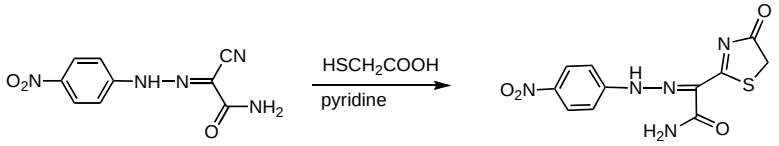
2.1 From Thioglycolic Acid

2.1.1 Nitriles

The thiazole derivatives **10** [42,43] was formed by heating activated nitriles with thioglycolic acid in glacial acetic acid at the reflux temperature.



Also, thioglycolic acid reacts with azocyanoacetamide derivative **11** in pyridine solution to yield 4-thiazolinone derivative **12** [44].

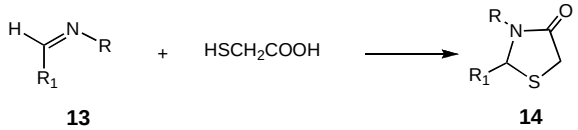


11 **12**

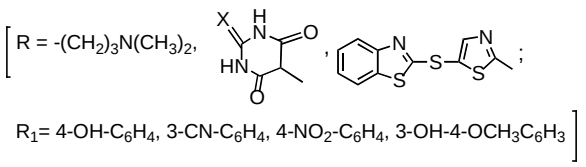
2.1.2 Imines

4-Thiazolidinone derivatives **14** were obtained by refluxing equimolecular amounts of aldimines **13** and thioglycolic acid in dry benzene [45-50], or in anhydrous $ZnCl_2$ [51].

Also, cyclo-addition reaction of equimolecular ratio of thioglycolic acid and 4-aryl-iminoazole derivatives **15** in boiling benzene using water separator for five days afforded the spiro-4-azolo thiazolidinone derivatives **16** [52,53].



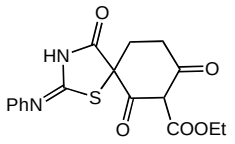
13 **14**



Furthermore, novel route to the synthesis of spiro thiazolidinones **17** using Michael addition reaction followed by Dieckmann condensation or Calisen type condensation reaction was described [54]. Also, *p*-bis(4-thiazolidinon-3-yl)phenylene **18** was synthesized by cyclo-addition of bis Schiff bases of *p*-phenylenediamine with thioglycolic acid [55].

2.1.3 Amines and Aldehydes

Ternary condensation of substituted aldehydes with an equimolecular amount of amines in the presence of an excess of mercaptoacetic acid in refluxing toluene yielded 4-thiazolidinone derivatives **19** [56-60]. Also, 2-(aryl)-3-furan-2-ylmethylthiazolidine-4-ones were synthesized by reacting the appropriate amine, aldehyde and mercapto-acetic acid in the presence of dicyclohexylcarbodiimide (DCC) at room temperature. They were used as selective HIV-RT inhibitors.



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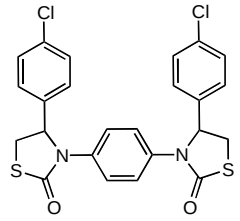

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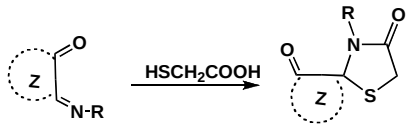
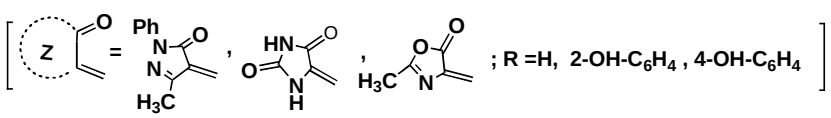
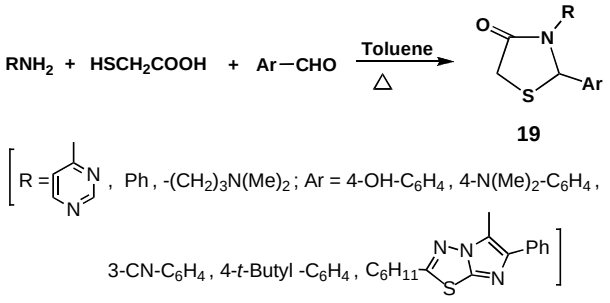
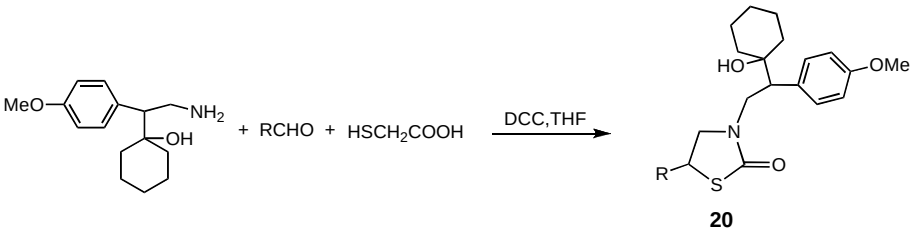


15 **16**

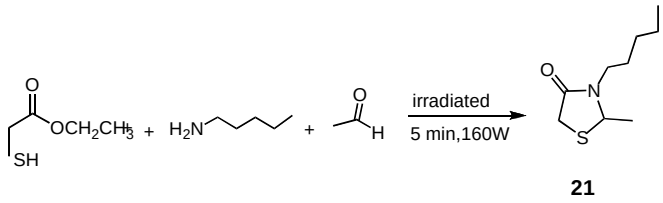




Condensation of the synthon 1-[2-amino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol with aromatic and hetero-cyclic aldehydes and thioglycolic acid using DCC gave compound **20**. It is used as antimicrobials [61].

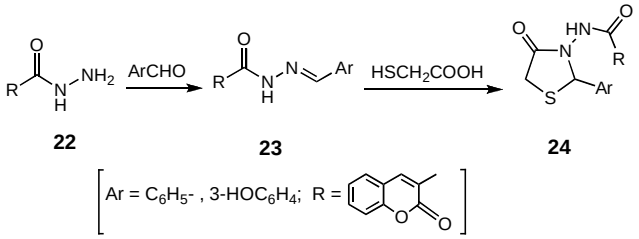


Thiazolidinone **21** resulted in good yield under microwave heating of a mixture from *n*-pentylamine, acetaldehyde and ethyl thioglycolate without solvent [62].



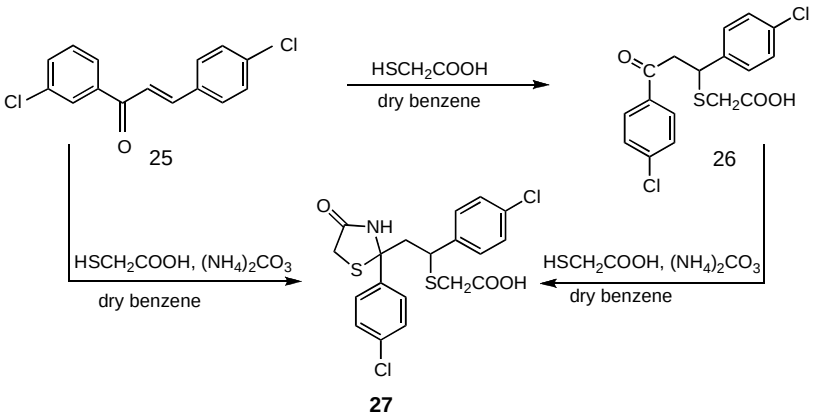
2.1.4 Acid Hydrazides

Reaction of hydrazide **22** with the appropriate aromatic aldehydes gave the arylidenehydrazinocarbonyl **23**, which on condensation with thioglycolic acid in dry benzene gave thiazolidinone derivatives **24** [63-66].

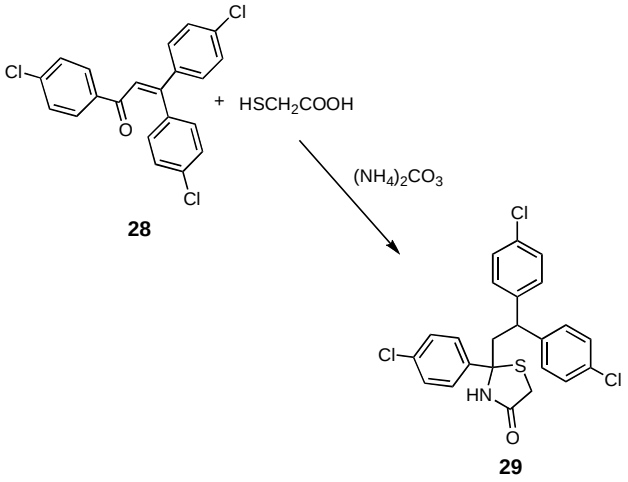


2.1.5 α,β-Unsaturated Systems

Synthesis of 2-[2-carboxymethylthio-2-(4-chloro-phenyl) ethyl]-2-(4-chlorophenyl)-4-thiazolidinone **27** [67] was reported either by , a) refluxing a mixture of chalcone **25**, thioglycolic acid and ammonium carbonate in dry benzene or b) by formation of the thioether **26** firstly *via* refluxing the chalcone **25** and thioglycolic acid in dry benzene. Then condensation of thioether **26** with thioglycolic acid and ammonium carbonate furnished **27**.

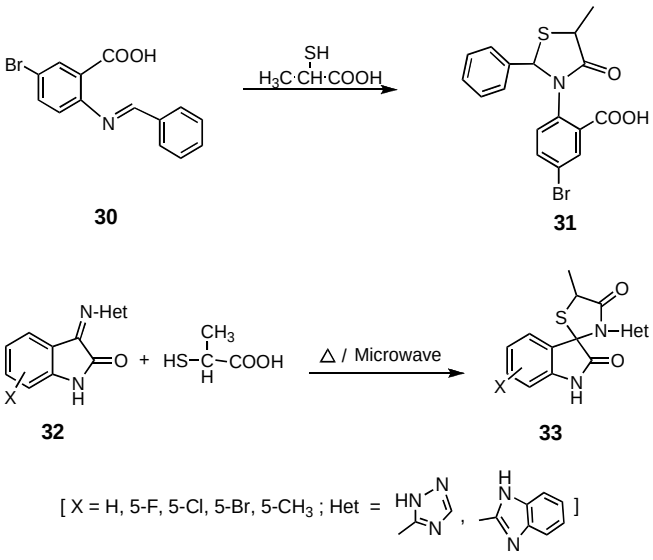


Also, thiazolidinone derivative **29** was prepared from 4,4'-dichlorochalcone *via* heterocyclization of the intermediate tris(4-chlorophenyl)propenone (**28**) with thioglycolic acid in the presence of ammonium carbonate [68].



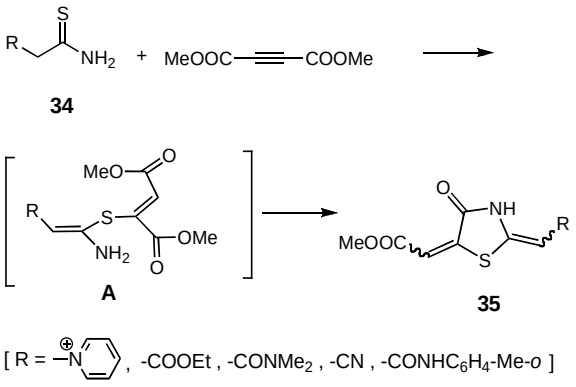
2.2 From Thiolactic Acid

Cyclo-condensation of the Schiff base **30** with thiolactic acid at high temperature furnished 2-substituted-3-(4-bromo-2-carboxyphenyl)-5-methyl-4-thiazolidinone **31** [69-70]. The spiro compound **33** can be achieved *via* cyclo-addition of the ketimine **32** with thiolactic acid under microwave heating [71].



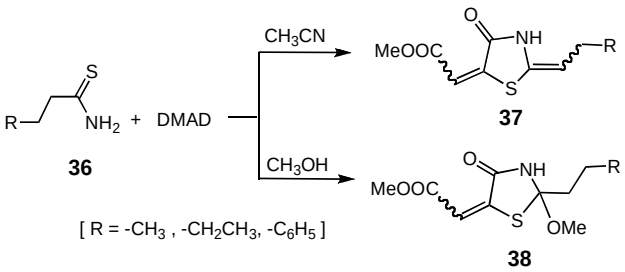
2.3 From Dimethyl Acetylenedicarboxylate

Reaction of thioamides **34** with dimethyl acetylenedicarboxylate (DMAD) have been shown to occur *via* the α-situated ester group followed by cyclization leading to a five-membered thiazolidinone ring **35** [72-74].

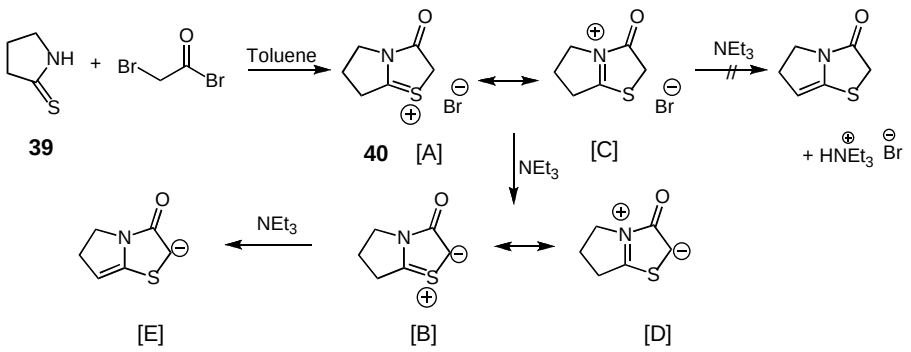


Also, thioamides of alkyl carboxylic acids **36** reacted with DMAD to afford 2,5-dimethylene thiazolidin-4-one **37** or 2-methoxy-2-alkylsubstituded thiazolidinone **38** depending on the solvent in which the reaction is carried out (Scheme **1**) [75].

Scheme 1

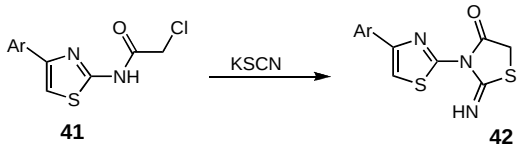


Moreover, the thioamide of pyrrolidine-2-thione (**39**) was reacted with 2-bromoacetyl bromide gave thio-isomunchone [1,3-thiazolium-4-oiates] (**40**) [76]. Furthermore, using this procedure thiazole[3,2-*a*]indole-3-one was obtained as the sole reaction product [77].



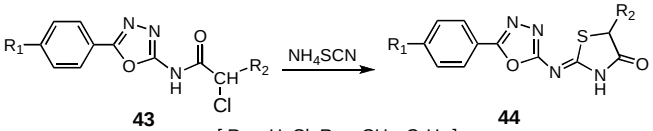
2.4 From Thiocyanates

2-Chloroacetamido-4-arylthiazoles **41** was treated with potassium thiocyanate in refluxing acetone to afford the related 2-imino-3-(4-arylthiazol-2-yl)thiazolidin-4-ones **42** [78].



[Ar = C_6H_5 , *P*-ClC_6H_4 , *P*-$NO_2C_6H_4$, 2,4-$(Cl)_2$-5-F-C_6H_2]

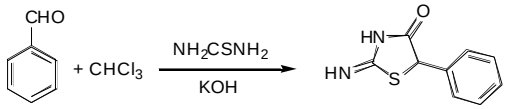
Moreover, 5-aryl-2-(α-chloro-α-phenylacetyl)amino-1,3,4-oxadiazole **43** when heated with ammonium thiocyanate gave 5-aryl-2-(5-aryl-1,3,4–oxadiazol-2-yl]imino)-4-thiazolidinones **44** [79] and it's analogues [80].



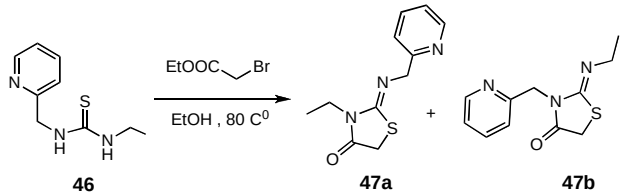
[R_1 = H, Cl; R_2 = CH_3, C_6H_5]

2.5 From Thiourea

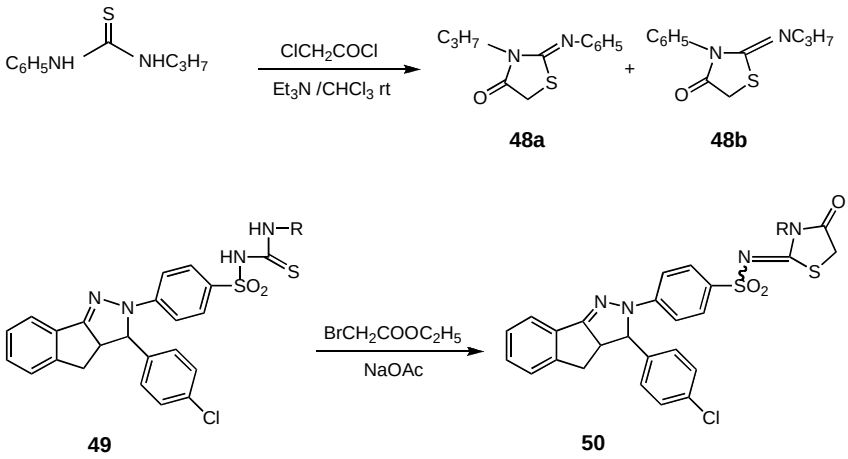
Ternary condensation of benzaldhyde, chloroform and thiourea under Reeve's conditions (MeOH, KOH, 50 °C) afforded the 2-imino-4-thiazolidinone derivative **45** [81].



Furthermore, the reaction of unsymmetrical thiourea **46** with ethyl bromoacetate in the presence of 2 equivalents of sodium acetate in ethanol afforded a (1:1) mixture of regioisomeric iminothiazolidinone **47a** and **47b**. But in absence of sodium acetate, it afforded regioselective 2-ethylimino-3-pyridin 2-ylmethyl-thiazolidin-4-one (**47b**) only [82].

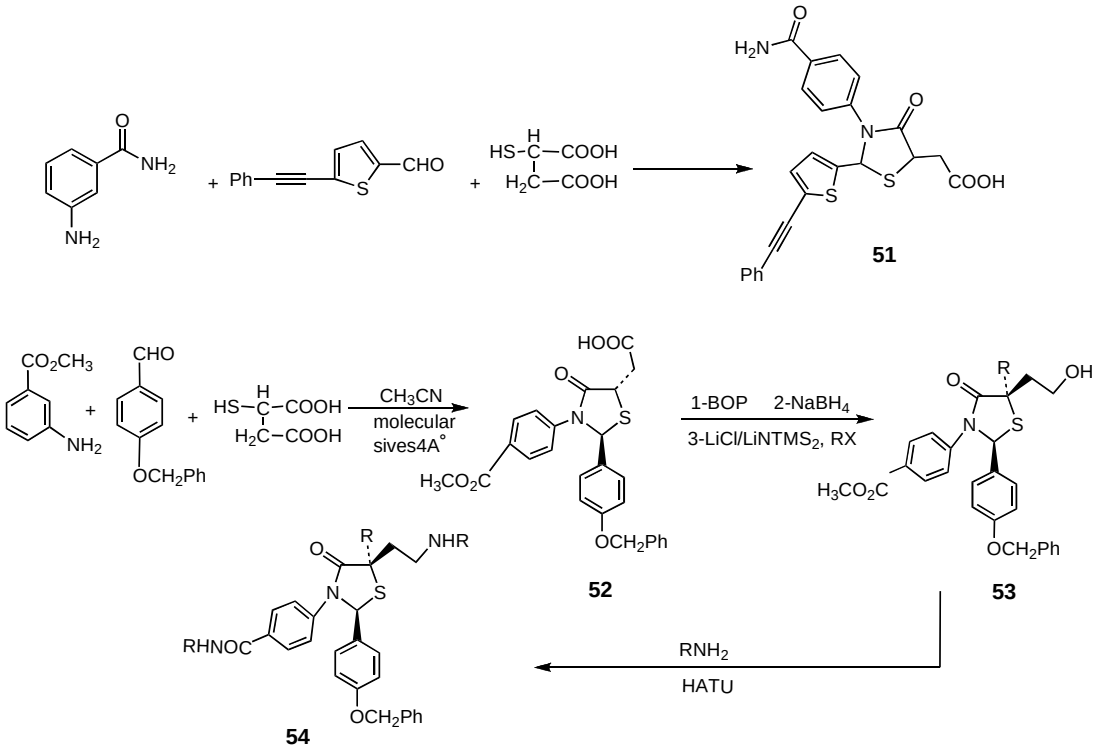


Condensation of *N*-propyl-*N*'-phenylthiourea with chloroacetyl chloride in presence of triethylamine in chloroform at room temperature gave compound **48** [83]**.** The reaction gave a mixture of two isomers arylimino **48a** and propylimino **48b** in about 1:2 ratio, respectively. Besides, cyclization of benzene-sulfonylthioureas [sulfonylthioureido derivatives] **49** with ethyl bromoacetate in the presence of anhydrous sodium acetate afforded the corresponding thiazolidin-4-ones **50** [84].



2.6 From Mercaptosuccinic Acid

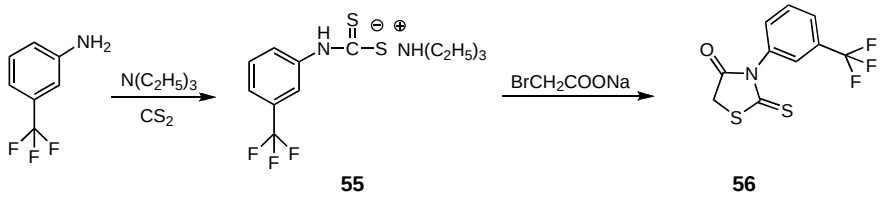
Thiazolidinone derivative **51** was prepared by reaction of 3-aminobenzamide, 5- (phenylethynyl)-2-thiophene carboxaldehyde and mercaptosuccinic acid [85]. Also, compound **52** was prepared by condensation of methyl-3-aminobenzoate, 4-benzyloxybenzaldehyde and mercaptosuccinic acid [86].



[BOP=benzotriazol-1-yloxytris(dimethylamino)phosphoniumhexafluorophosphate; $LiNTMS_2$=Lithium hexamethyldisilazide; DIEA= diisopropylethylamine]

2.7 From Dithiocarbamate

2-Thioxo-3-(3-trifluoromethylphenyl)-4-thiazolidinone **56** was prepared by the reaction of dithiocarbamate **55** with ^{14}C labeled sodium bromoacetate at room temperature [87].

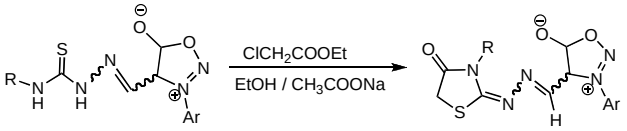


55 **56**

2.8 From Thiosemicarbazide and Thiosemicarbazone Derivatives

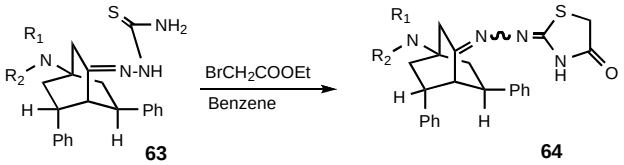
Electrophilic substitution on 2-hydroxypyrazine by ethyl chloroacetate under reflux afforded ethyl (pyrazin-2-yl-oxy) acetate (**57**). Which on amination with hydrazine hydrate afforded 2-(pyrazine-2-yl)acetohydrazide (**58**). Reaction of **58** with alkyl/aryl isothiocyanate in ethanol gave compounds **59**. Condensation of **59** with chloroacetic acid in boiling ethanol containing sodium acetate led to the formation of 4-thiazolidinone derivatives **60** [88].

Treatment of 3-aryl-4-formylsydnone thiosemicarbazones derivatives **61** with ethyl chloroacetate afforded thiazolidinone derivatives **62** [89]. Also, the influence of the free thioamido group of compound **63** was examined by cyclization with α–halocarbonyl reagents to give 1,3-thiazolidone derivatives **64** [90]. Furthermore, thiocarbamoyl derivative **65** was reacted with ethyl chloroacetate in absolute ethanol and fused sodium acetate to afford compound **66** [91].



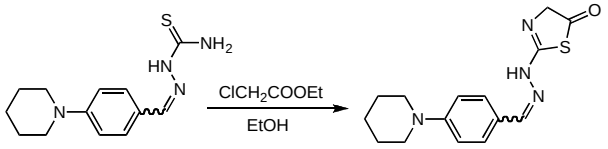
61 **62**

[R = H , Ph ; Ar = C_6H_5 , *P*-$CH_3C_6H_4$, *P*-$CH_3OC_6H_4$, *P*-$C_2H_5OC_6H_4$]

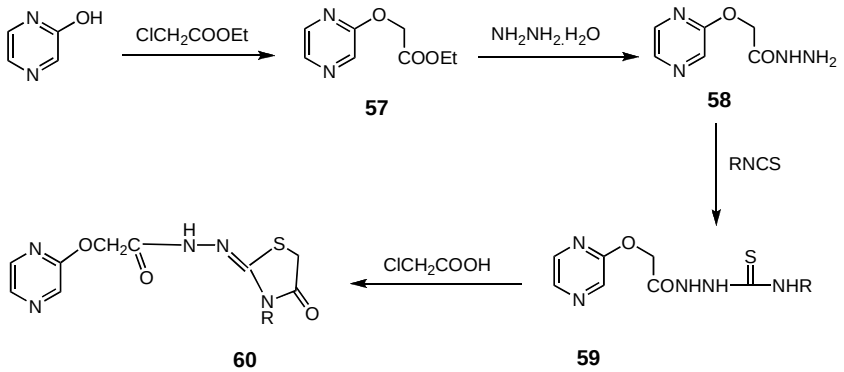


63 **64**

[R_1R_2 = -$(CH_2)_2O(CH_2)_2$- , -$(CH_2)_4$-]

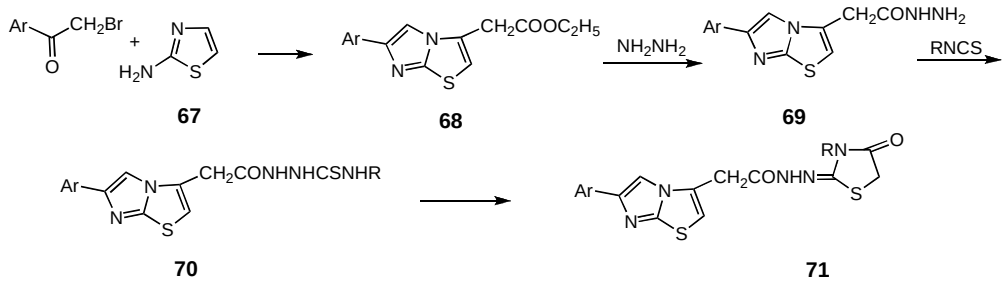


65 **66**



57 **58** **59** **60**

[R = 4-chloro-2-nitrophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, n-butyl, *t*-butyl]



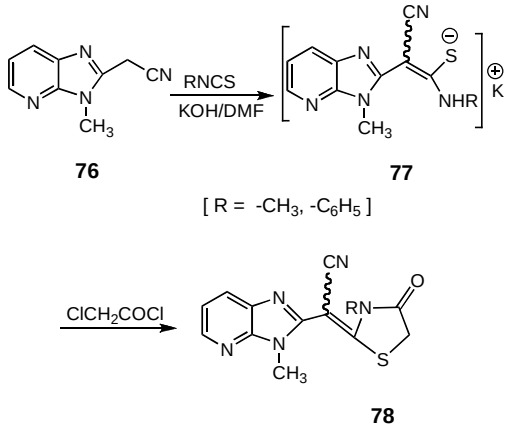
The target compound **71** was prepared from 6-arylimidazo[2,1-*b*]thiazole-3-acetic acid hydrazide (**69**) as outlined in the above Scheme. Compound **69**, when reacted with alkyl isothiocyanates gave **70**. Its treatment with ethyl bromoacetate, yielded 3-alkyl-2-(((6-phenylimidazo[2,1-*b*]thiazol-3-yl)-acetyl)-hydrazono)-4-thiazolidinones (**71**) [92] and was evaluated for antifungal activity [92,93].

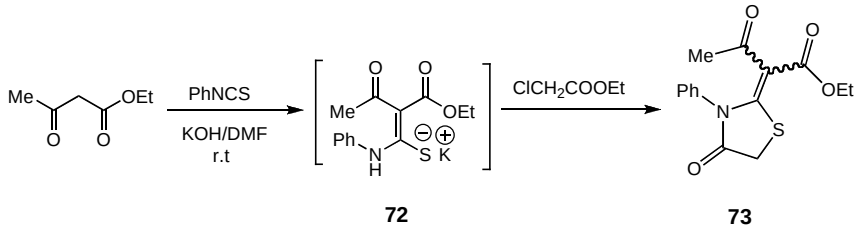
2.9 From Active Methylene Compounds

The reaction of ethyl acetoacetate with phenyl isothiocyanate in dry dimethyl formamide (DMF) at room temperature yields the non-isolable intermediate **72**. The cyclization of the intermediate **72** with ethyl chloroacetate affords the 4-thiazolidinone derivative **73** [94].

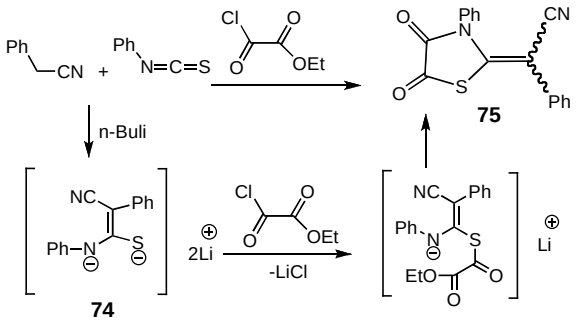
Also, the reaction of the dianion of benzyl cyanide **74** generated by *n*-butyllithium, with *N*-phenyl isothiocyanate with ethyl-2-chloro-2-oxoacetate afforded compound **75** (Scheme **2**) [95].

Furthermore, the reaction of cyanomethyl derivative **76** with isothiocyanates in basic DMF gave the non-isolable potassium salt **77**; its reaction with chloroacetyl chloride gave compound **78** [96].



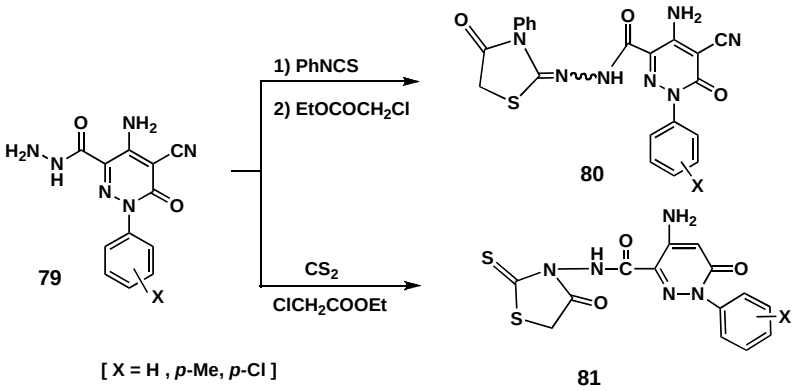


Scheme 2



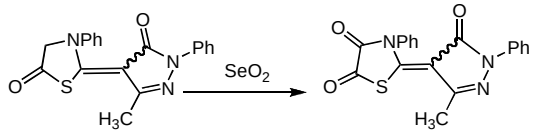
2.10 From Hydrazide Derivatives

Reactions of the pyridazine derivatives **79** with phenyl isothiocyanate followed by heterocyclization with ethyl chloroacetate gave thiazolidinone derivatives **80** [97]. Also, reactions of the pyridazine derivatives **79** with carbon disulfide (CS_2), followed by heterocyclization with ethyl chloroacetate, gave compound **81** [98].



2.11 From Oxidation of 5-Thiazolidinone Derivative

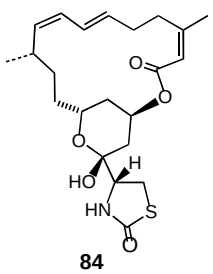
El-desoky *et al*. reported the oxidation of 2-(3-methyl-5-oxo-1-phenyl-1,5-dihydro pyrazol-4-yl-idene)-3-phenylthiazolidin-5-one (**82**) with selenium dioxide (SeO_2) to afford the corresponding thiazolidin-4,5-dione **83** [99].



82 **83**

2.12 From a Specimen of Chromodoris sp

Latrunculin A (**84**) was isolated from a specimen of chromodoris sp. Collected from Indonesian water, and also **84** was determined in organic extract of the Red Sea sponge [100].



84
(Latrunculin A)

2.13 From Thiolactam Derivative

Reaction of piperidine-2-thione with α-bromoesters gave the nitrogen bridgehead compounds **85** [101].

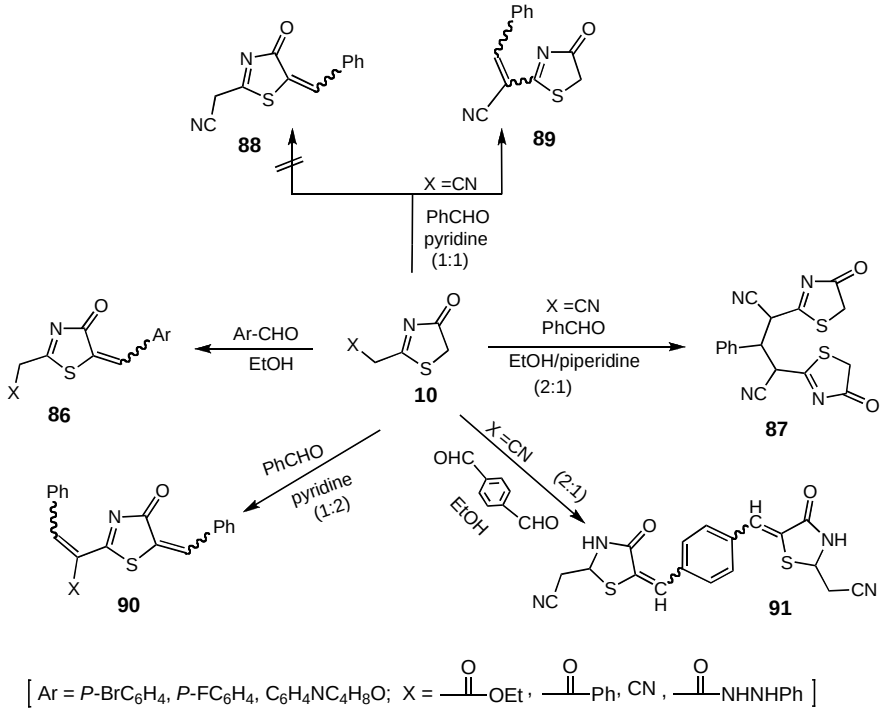
85

[R^1 = Me, n-Pr, n-Bu: R^2 = OMe, OEt: DBU = methyl phenidate derivatives]

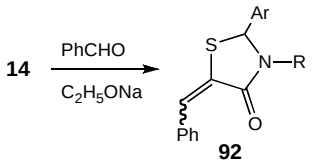
3. Reactions of 4-Rhiazolidinones

3.1 Reactions with Electrophiles

Condensation of the thiazolidinone **10** with aldehydes in ethanol piperidine solution furnished the thiazolidinone derivatives **86** [103,104]. Besides, treatment of **10** with benzaldehyde in refluxing pyridine afforded the α-benzylidene derivative **89**. On the other hand, repeating this reaction in the presence of ethanol/piperidine yielded the bis benzylidene derivatives **87** [42]. Also, the reaction of **10** with benzaldehyde (1:2 molar ratio) in pyridine afforded thiazolidinone derivative **90** [44]. Condensation 2-cyanomethyl-4-thiazolinone **10** with terphthaladehyde (2:1 molar ratio) in ethanol afforded 1,4-bis(2-cyanomethyl-4,5-dihydro-5-methylidens-4-thiazolonon-5-yl)benzene **91**.



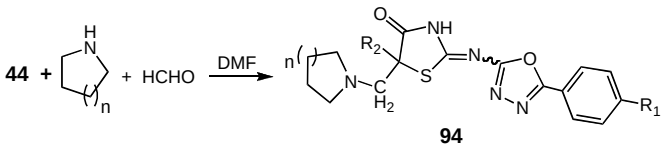
Also, compounds **14** when subjected to Claisen Schmidt condensation with benzaldehyde in the presence of sodium ethoxide gave 5-benzylidne derivative **92** [45].

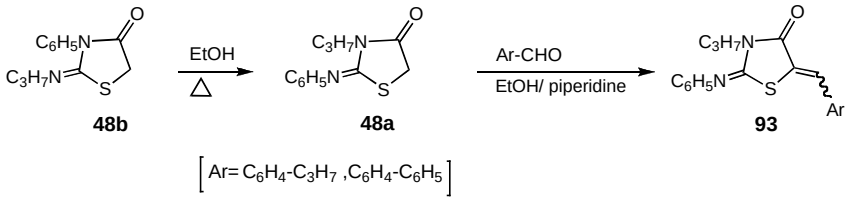


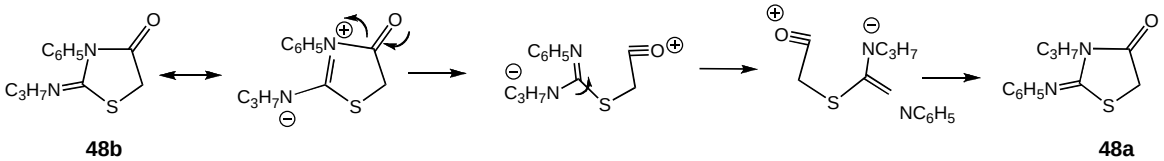
5-Arylidine-2-imino-4-thiazolidinones (**93**) were synthesized as novel anti-inflammatory agents by condensation under basic conditions of compound **48a** and appropriate aldehydes in refluxing ethanol [83]. Rearrangement of **48b** into **48a** is illustrated in the following scheme.

3.2 Mannich Reaction

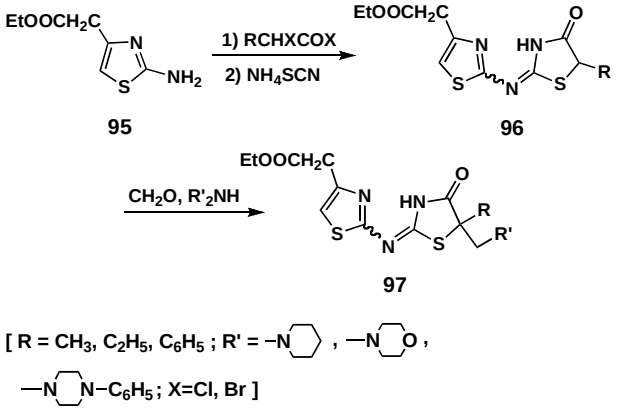
Compound **44** was heated under reflux after the addition of 37% formaldehyde and piperidine (or pyrrolidine) (1:1) to give 5-phenylmethyl-5-piperidino (or pyrrolidino) methyl-2-(5-aryl-1,3,4-oxadiazol-2-yl)imino)-4-thiazolidinones **94** [79], respectively.



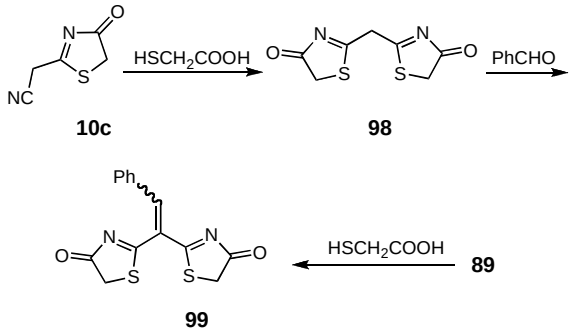




The product of 4-carboxyethyl-2-aminothiazole **95** with α-halo compounds, was refluxed with ammonium thiocyanate to obtain 5-substituted 4-thiazolidinone derivatives **96** which were stirred with formaldehyde and various secondary amines to give 2,5-disubstituted-4-thiazolidinoes **97** [95].

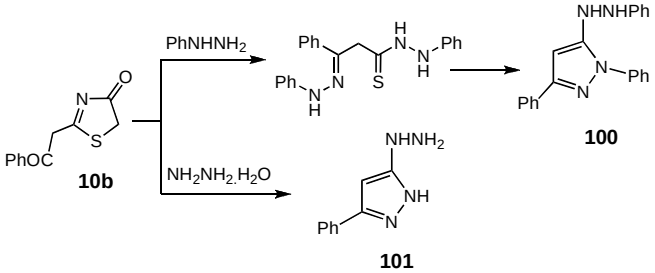


Treatment of compound **10** with thioglycolic acid in refluxing pyridine furnished bis thiazol derivatives **98**. When the latter compound was treated with benzaldehyde gave compound **99** which can also be obtained from compound **89** when treated with thioglycolic acid [42].



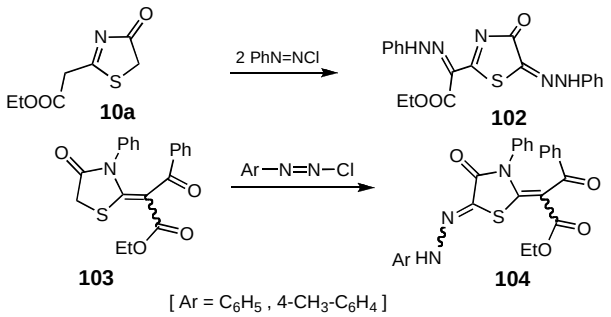
3.3 Ring Cleavage Reactions

When compound **10** reacted with phenyl hydrazine and hydrazine hydrate in absence of a solvent, the phenyl-hydrazinopyrazole derivative **100** and hydrazinopyrazole **101** were formed [43].



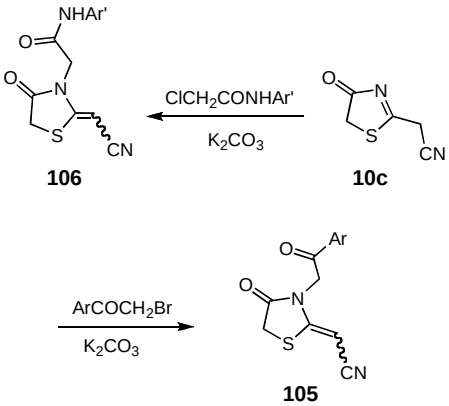
3.4 Electrophilic Coupling Reaction

The formation of 4-arylazo-2-(2-arylazo-ethyl acetate)-4-thiazolidinone **102** was achieved by treatment of compound **10a** with benzenediazonium chloride (1:2 molar ratio) [44]. Also, the active methylene group of the thiazolidinone **103** was coupled with different diazonium salts to give the corresponding arylazo derivatives **104** [105].



3.5 Reaction with Halo Compounds

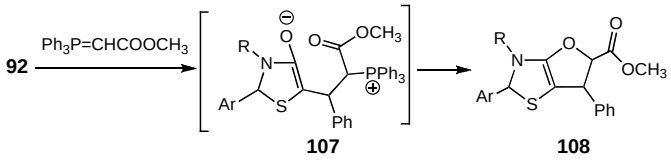
The alkylation of the compound **10c** with 2-bromo-acetophenones or chloroacetic acid anilides in the presence of potassium carbonate was found to proceed smoothly at the nitrogen atom resulting in 3-(2-aryl-oxoethyl)-2-methylidene-thiazolidin-4-ones **105** and *N*-aryl-[2-methylidene-4-oxo-3-thiazolidinyl]acetamides **106** respectively [106].



3.6 Reaction with Organometallic Compounds (Wittig Reagent)

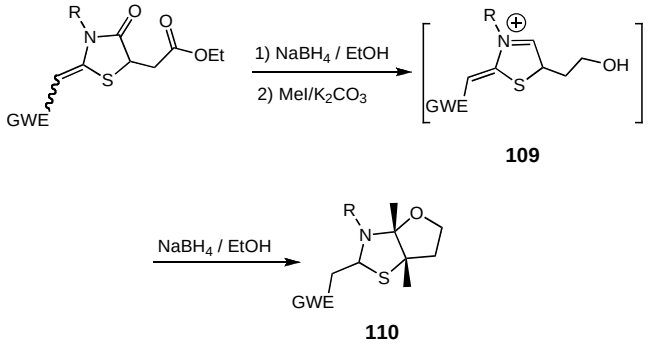
Furothiazolidines **108** were obtained by refluxing compound **92** with methoxycarbonyl methylidinetri-

phenylphosphorane in ethyl acetate containing triethylamine [45]. The dipolar intermediate **107** formed from the initial attack of the carbanion center in the Wittig reagent on the active exocyclic electrophilic carbon atom of α,β-unsaturated system in **92** undergoes O-alkylation with triphenyl phosphine elimination to give 5-methoxycarbonyl-3-alkyl-6-phenyl-2-aryl-dihydrofuro[2,3-*d*]thiazolidine **108**.



[R = $CH_3(CH_2)_6CH_2$-; Ar = 4-OHC_6H_4, 3-CNC_6H_4, 4-$NO_2C_6H_4$]

Heterocyclization of (*Z*)-5-(2-hydroxyethyl)-3-methyl-4-oxothiazolidines **109**, bearing electron withdrawing groups conjugated to an exocyclic double bond at C(2)-position, under reductive conditions afforded, *cis*-tetrahydrofuro[2,3-*d*]thiazole derivatives **110** [46].

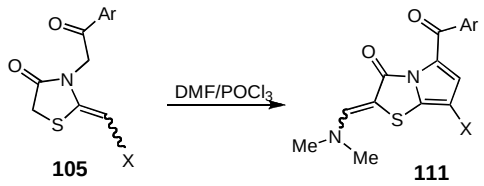


[EWG = COPh , COOEt , $CONH(CH_2)_2Ph$, CN ; R = H , Me]

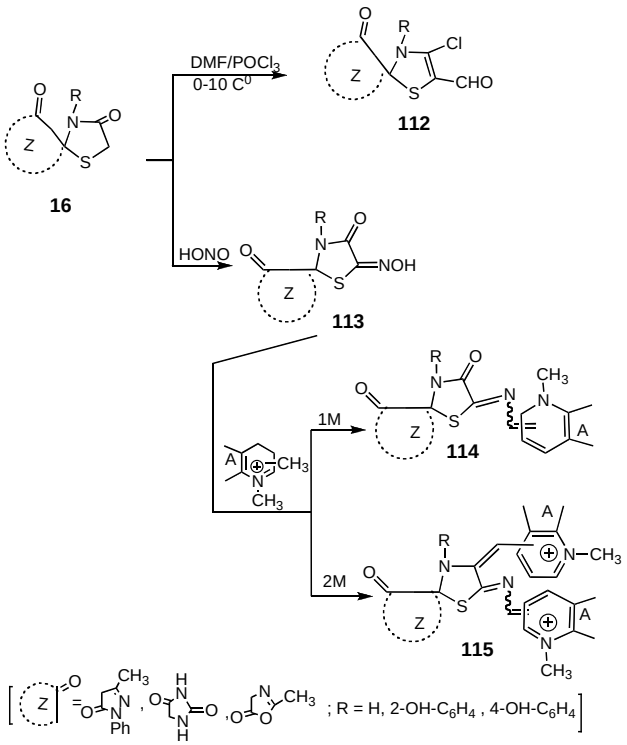
3.7 Reactions with Phosphorous Oxychloride Dimethyl Formamide Complex

The formylation of the thiazolones **105** with excess of phosphorous oxychloride in dimethylformamide ($POCl_3$/DMF) accomplished the preparation of oxopyrrolo[2,1-*b*]thiazole system. The pyrrole ring closure is accompanied with the methylene group transformation into its (dimethylamino)methylidene derivatives yielded 3-oxopyrrolo[2,1-*b*]thiazole derivative **111** [106]. Also, treatment of compound **16** with $POCl_3$/DMF at room temperature afforded the corresponding spiro compounds **112** [52] (Scheme **4**).

Scheme 4



[Ar = H , 4-ClC_6H_4 , 4-Br-C_6H_4 , 4-O_2N-C_6H_4, ; X = COOEt , COOMe , CN]



[Z = , , ; R = H, 2-OH-C_6H_4 , 4-OH-C_6H_4]

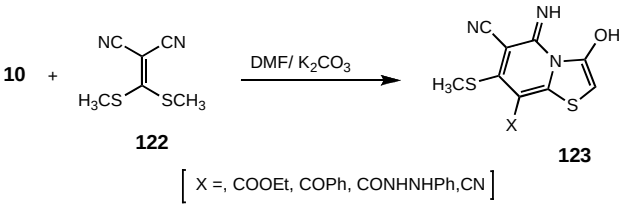
3.8 Reactions with Nitrous Acid

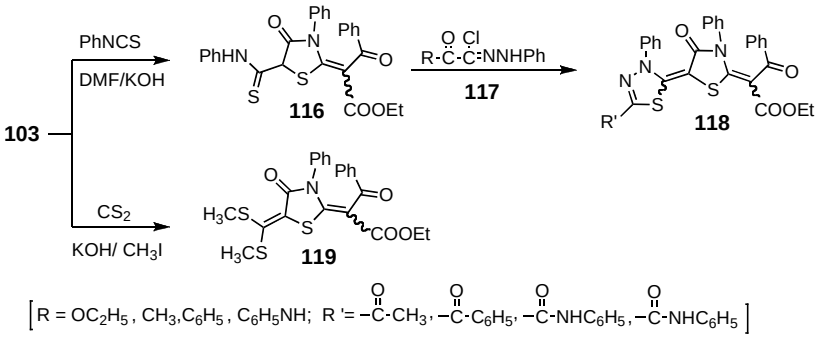
Reaction of spiro-4-azolo-thiazolidinone derivatives **16** with nitrous acid afforded the corresponding 2-oxime-spiro-4-azolo-thiazolidinone derivatives **113**. These newly synthesized oximes **113** were considered as a key intermediate in the synthesis of aza mero cyanine dyes **114** and aza penta methine cyanine dyes, **115** respectively. Thus, reaction of 1 mmol of 2-oxime spiro-4-azolo thiazolidinone derivatives **113** with 1 or 2 mmol of 2(4)-methyl heterocyclic quaternary salts in the presence of basic catalyst afforded the corresponding spiro-4-azolo thiazolidinone-4-[2(4)] aza-mero cyanine dyes **114** and 4,5 [2(4)]-azapenta methane cyanine dyes **115**, respectively [52] (Scheme **4**).

3.9 Reactions with Phenyl Esothiocyanate and Carbon Disulfide

Thioanilide **116** was obtained by treatment of compound **103** with phenyl isothiocyanate in the presence of potassium hydroxide which converted to 2,3-dihydro-1,3,4-thiadiazoles **118**, *via* it's reaction with the appropriate hydrazonoyl halides **117**. Also, methyl carbodithioate **119** was prepared *via* reaction of **103** with carbon disulfide in dimethyl formamide and potassium hydroxide followed by iodomethane [105].

K_2CO_3 to yield the 7-methyl sulfanyl thiazolo- [3,2-a]pyridine derivative **123** [107].

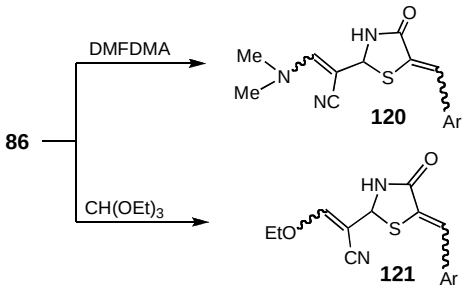




3.10 Reaction with Dimethylformamide dimethylacetal and Triethyl orthoformate

Condensation of compound **86** with dimethylformamide dimethylacetal (DMF-DMA) and triethyl orthoformate $HC(OEt)_3$, yielded *N*,*N*-dimethylamino derivative **120** and ethoxymethylene derivatives **121,** respectively (Scheme **5**) [104].

Scheme 5

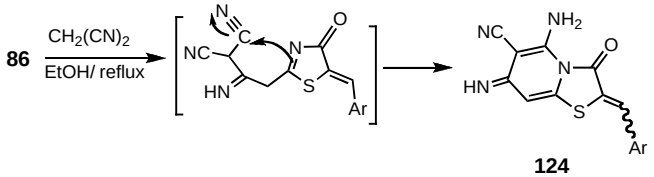


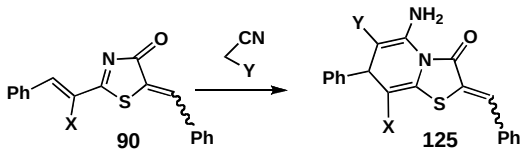
3.11 Reaction with Different Arylidenes

[Bis(methylsulfanyl)methylidene]malononitrile(**122**) reacts with 1,3-thiazol-4-(5*H*)one derivative **10** in refluxing DMF containing the equivalent amount of

3.12 Reaction with Nitrile Containing Active Methylene Compounds

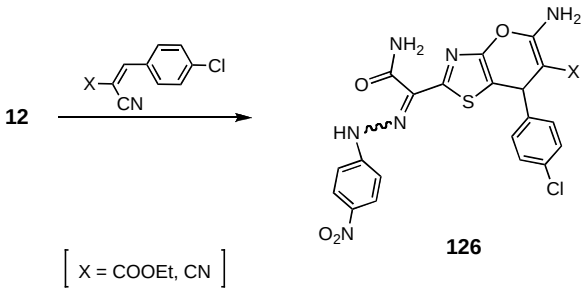
Lamphon *et al.* reported the cyclo-condensation of compound **86** with malononitrile in ethanol and triethyl-amine under reflux to furnish the novel thiazolo[3,2-*a*]-pyridine derivative **124** [104]. Furthermore, refluxing compound **90** in ethanol containing catalytic amount of piperidine with active methylene compounds, *viz.* malononitrile, cyanoacetamide, ethyl cyanoacetate, benzoyl-cyanomethane and cyanoacetanilide gave the corresponding thiazolo[3,2-*a*]-1,4-dihydropyridines **125** [44].



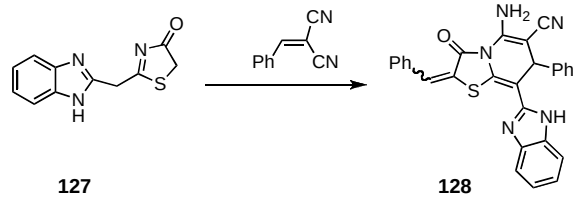


3.13 Reaction with Different Arylidenes

4-Thiazolidinone derivative **12** could be condensed with 4-chlorobenzylidene cyanoacetate or 4-chlorobenzylidene malononitrile to yield the corresponding compounds **126** [44].

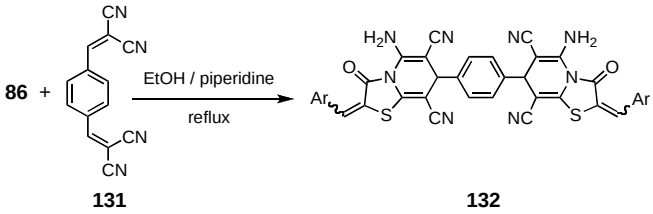


Also, benzimidazolylthiazolo[3,2-*a*]pyridines **128** were prepared by reaction of 2-(4-oxo-4,5-dihydro-thiazol–2-yl)methyl)-1*H*-benzimidazole (**127**) with benzylidene malononitrile in (1:2) molar ratio. Compounds **128** were reported as antimicrobial, anti-HIV and anti cancer agents [108].



1,4-Bis(5-amino-7-(4-florobenzyl)-2-methylidene[3,2-*a*]pyridine-6,8-dicarbonitrile-2-yl)benzene **130** was achieved when a solution of compound **129** and 4-florobenzylidine malononitrile (1:2 molar ratio) was heated under reflux in absolute ethanol and in the presence of catalytic amount of piperidine. The reaction proceeds *via* Michael addition followed by intramolecular cyclization at the cyano group [109].

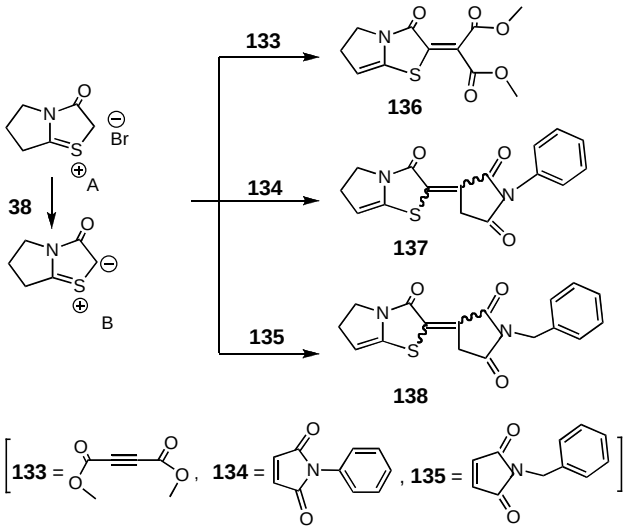
Moreover, reaction of compound **86** with bisbenzylidene derivative **131** in EtOH in the presence of triethylamine gave 1,4-bis[5-amino-2-arylmethylidene-2,3-dihydro-7H-3-oxothiazolo[3,2-*a*]pyridine-6,8-carbonitrile-7-yl) benzene derivatives **132** [95].

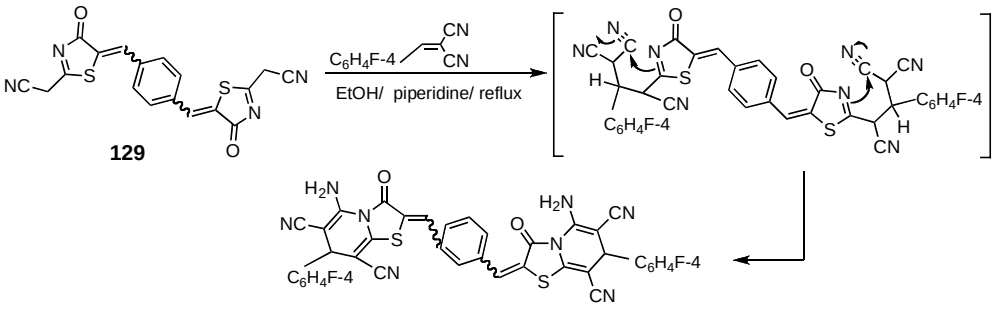


[Ar = *4*-BrC_6H_4, *4*-FC_6H_4,2-$C_6H_4NC_4H_8O$]

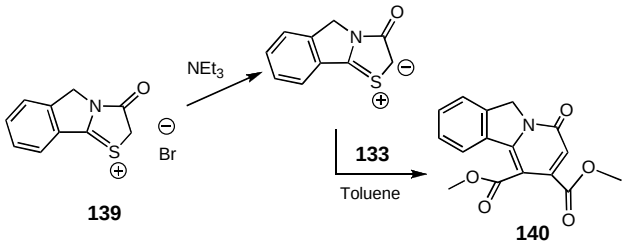
3.14 Reaction with Dipolarophiles

The Intramolecular 1,3-dipolar cycloaddition of fused thioisomunchones (**38**) with systematically three different dipolarophiles **133, 134 and 135** [75] was achieved to give the corresponding thioisomunchone derivatives **136**, **137**, and **138**.





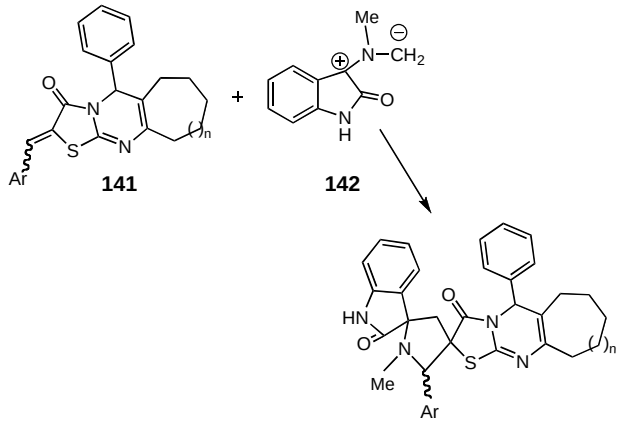
While, compound **139** when reacted with dipolarophile **133** gave compound **140** *via* Intramolecular 1,3-dipolarcyclo addition followed by desulfurization of the adduct [110].



139 **140**

3.15 Reaction with Azomethine Ylide

Cycloalkano[*d*]thiazolo[3,2-*a*]pyrimidine-3-one derivatives **141** reacted as dipolarophiles with azomethine ylide **142** [generated *in situ* from isatine and sarcosine] to give cyclo adducts dispiro-oxindolecycloalkano[*d*]pyrimidino-[2,3-*b*]thiazolepyrrolidines(**143**) [111a].



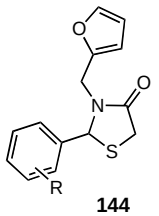
141 **142** **143**

[n = 1,2 ; Ar = C_6H_5 , 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4]

4 Applications and Uses of 4-Thiazolidinones

4.1 Biological Applications

The thiazole ring has been incorporated into a wide range of known biologically active compounds, either as a substitutuent group or as a replacement of another ring. A preliminary biological evaluation of some of the 4-thiazolidinone series has shown a promising pharmacological activity as selective HIV-RT Inhibitors. Where the HIV-1 RT inhibitory activity of 2,3-diaryl-thiazolidin-4-ones **144** has been analyzed and a detailed structure-activity relationship study has been made also to correlate the derived physicochemical properties with the HIV-RT inhibitory activity.

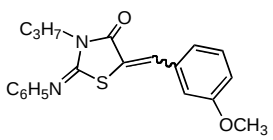


144

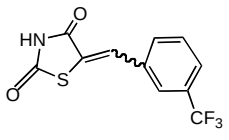
[R = 2,6-$(Cl)_2C_6H_3$, 2,6-$(F)_2C_6H_3$, 2,6-$(OCH_3)_2C_6H_3$, 2,6-$(CH_3)_2C_6H_3$]

The results indicate that changes at C-2 of thiazolidinone moiety, may lead to a reduction in HIV-RT inhibitory reactivity [23], and also these compounds have antibacterial and PBP (penicillin binding proteins) inhibiting activities [111b].

Compound **145** and **146** show *in vitro* antiproliferative activity against human colon cancer [111c].



145



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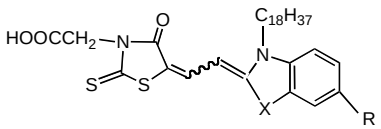
4.2 Industrial Applications

Of late, a large [number] of complexes of 5-(4-derivatives phenyldiazo)-3-phenyl-2-thioxo-4-thiazolidinone [112] and rhodanine azosulphadrugs [113], have been prepared and characterized by magnetic and spectral studies. These compounds have a donor ability toward metal ions, which makes them suitable as ligands in coordination compounds. Also 2-thioxo-4-thiazolidinone and its derivatives have wide industrial applications as vulcanizing agents of synthetic latex-base rubbers, extreme-pressure lubricants, antioxidants, and brightening additives in silver electroplating [114], and are used for formation of J-aggregates of mixed merocyanine dyes in Langmuir-Blodgett films **147** [115]**.**



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[X = O, S; R = H, CH_3]

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