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SYNTHETIC ACCESSES TO AZOLYLTHIAZOLES

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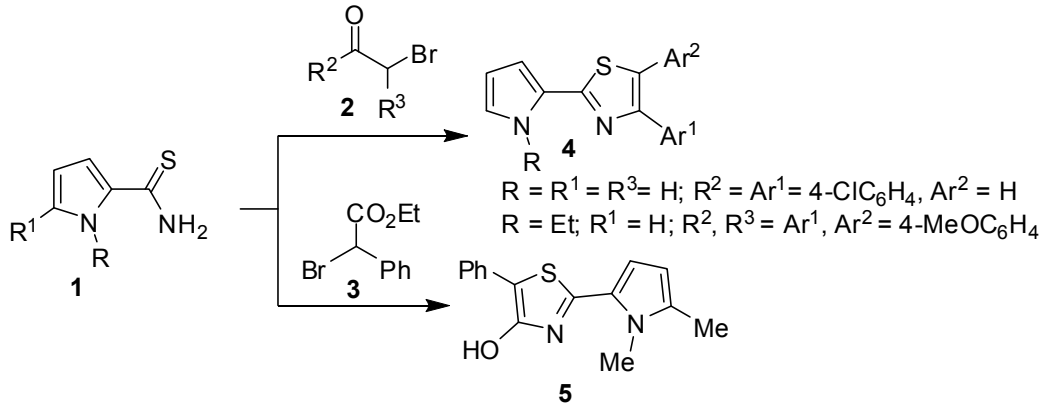
Abstract – Published data over the last years on the methods of synthesis and biological applications of azolylthiazoles are reviewed here for the first time till 2011. The review was classified according to the type of azole ring linked to thiazole.

1. INTRODUCTION

The linking of a thiazole ring with different azoles moieties by one single covalent bond give rise to a class of heterocyclic systems known as azolylthiazoles which have diverse biological activities. Bithiazole derivatives play an important role in the synthesis of polymers possessing magnetic properties,[1] manufacture of high-performance electroluminescent devices such as light-emitting diodes,[2] and medicine, for example, aminoalkyl derivatives of 2,4'-bithiazole-4-carboxylic acid were shown to exhibit antitumor activity.[3] 2',4-Disubstituted 2,4'-bithiazoles represent an important class of natural products which exhibit an intriguing and diversified spectrum of biological acitivities. Bleomycins[4] and tallysomycins[5] are glycopeptide antibiotics which carry a bithiazole amino acid at their C-terminal position. Another field of application of bithiazole derivatives includes synthesis of macrobicyclic cryptands.[6] Despite of this versatile importance and in connection to our previous review articles about azolylthidiazoles[7] and other heterocyclic systems,[8-19] the azolylthiazoles has not previously reviewed. In this review, the azolylthiazoles systems have been classified according to the type of azole nucleus linked to thiazole.

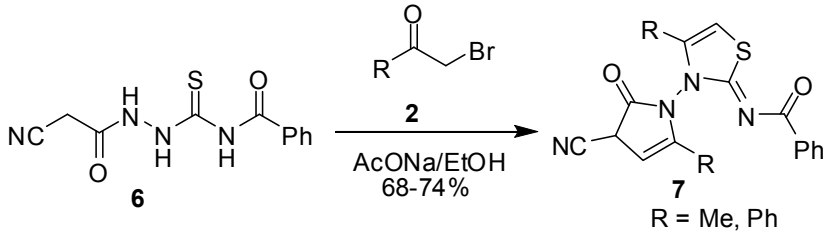
2. PYRROLYLTHIAZOLES

Preparation of pyrrolylthiazoles as agrochemical fungicides has been reported. Thus, pyrrole-2-thioamides **1** were cyclocondensed with phenacylbromides **2** to give 2-(1*H*-pyrrol-2-yl)thiazoles **4** which gave complete control of *Helminthosporium* teres on barley plants when sprayed at 200 ppm and inhibited arachidonate-induced blood platelet aggregation in guinea pigs.[20,21] While 2-(1,5-Dimethylpyrrol-2-yl)-5-phenyl-4-thiazolol **5** was synthesized by cyclocondensation of α-bromo carboxylate **3** with thioamides **1** (Scheme 1).[22]



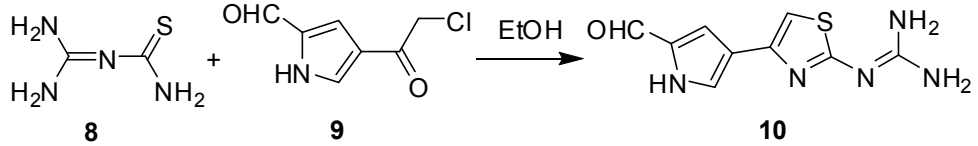
Scheme 1

The reaction of *N*-[2-(2-cyanoacetyl)hydrazinecarbonothioyl]benzamide **6** with phenacyl bromides **2** in boiling ethanol containing a catalytic amount of freshly fused sodium acetate afforded *N*-[3-(3-cyano-5-subst-2-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)-4-methylthiazol-2(3*H*)-ylidene]benzamides **7** (Scheme 2).[23]



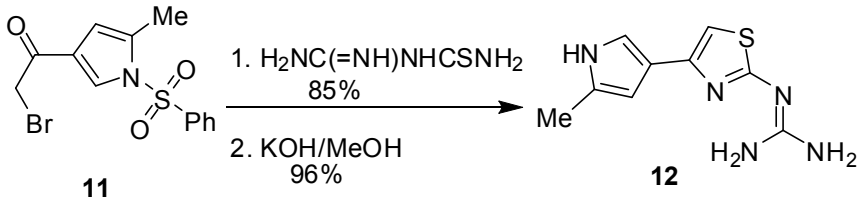
Scheme 2

4-(2-Methyl-1*H*-pyrrol-3-yl)-2-(guanidino)thiazole **10** was prepared, as antiulcer agent, by condensation of (diaminomethy1ene)thiourea **8** with 2-chloro-1-(2-formyl-1*H*-pyrrol-4-y1)ethanone **9** (Scheme 3).[24]



Scheme 3

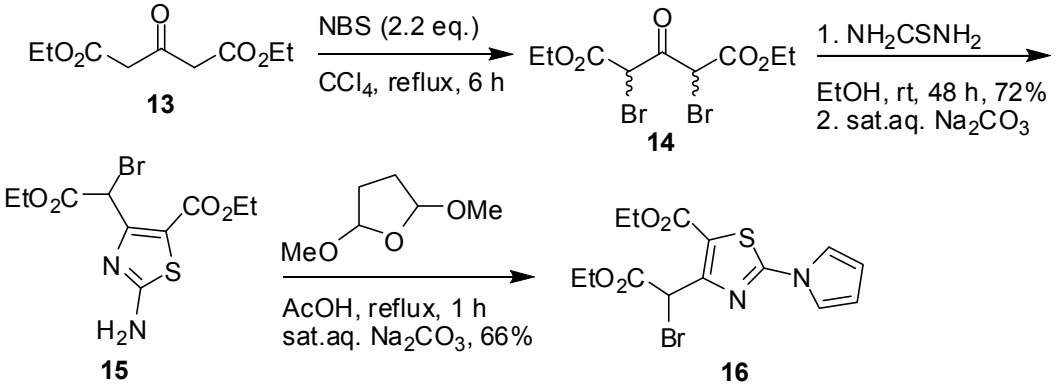
2-Bromo-1-[5-methyl-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]ethanone **11** was cyclocondensed with thioamide in acetone followed by basification by refluxing in methanolic KOH to give 96% 2-[4-(5-methyl-1*H*-pyrrol-3-yl)thiazol-2-yl]guanidine **12** (Scheme 4).[21]



11 **12**

Scheme 4

Diethyl 2,4-dibromo-3-oxoglutarate **14** was synthesized by bromination of diethyl 3-oxoglutarate **13** with of *N*-bromosuccinimide in carbon tetrachloride. The reaction of **14** with thiourea was carried out in ethanol at room temperature for 48 h and subsequent treatment with sodium carbonate furnished ethyl 2-(2-amino-5-ethoxycarbonylthiazol-4-yl)-2-bromoethanoate **15**. Reacting **15** with 2,5-dimethoxy-tetrahydrofuran in acetic acid gave pyrrole derivative **16** (Scheme 5).[25]



13 **14** **15** **16**

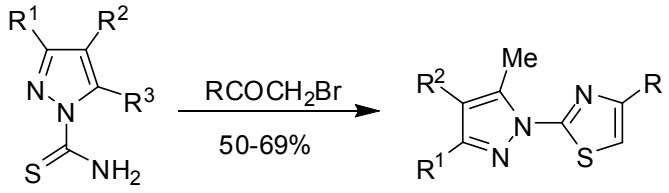
Scheme 5

3. PYRAZOLYLTHIAZOLES

Pyrazolyl-1,3-thiazoles were prepared by different methods such as reaction of 2-bromoketones with carbothioamide or reaction of thiazolylhydrazines with dicarbonyl or 2-ketonitrile compounds.

3.1. Reaction between thiocarboxamides and 2-bromoketones

Pyrazole-1-carbothioamides **17** and phenacylbromides were refluxed in ethanol and acetic acid for 2 h to give 1-(thiazol-2-yl)-1*H*-pyrazoles **18** in good yields (Scheme 6).[26-29]

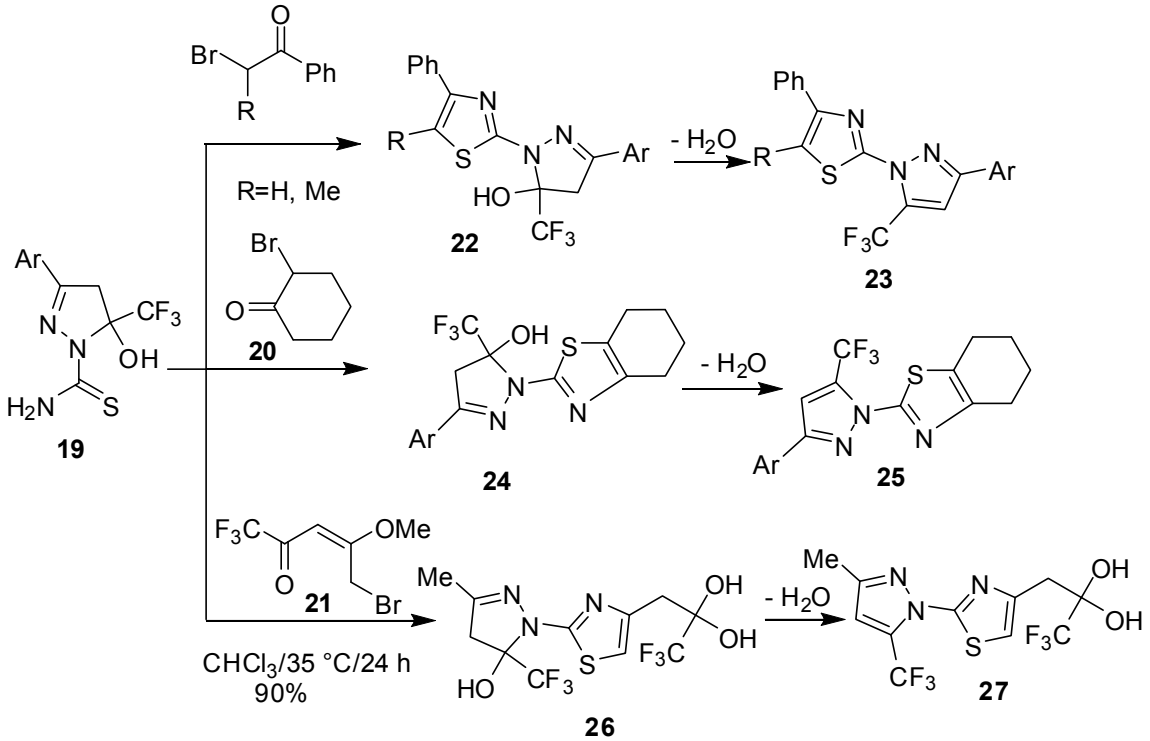


17 **18**

R = Ph, *p*-ClC_6H_4, *p*-BrC_6H_4, p-MeC_6H_4, 3-coumarinyl derv., 3-chromonyl derv., $PhNHCOCH_2$,
R^1 = Me, R^2 = H, PhN:N; R^1 = PhNH, R^2 = H; R^3= NH_2, Me

Scheme 6

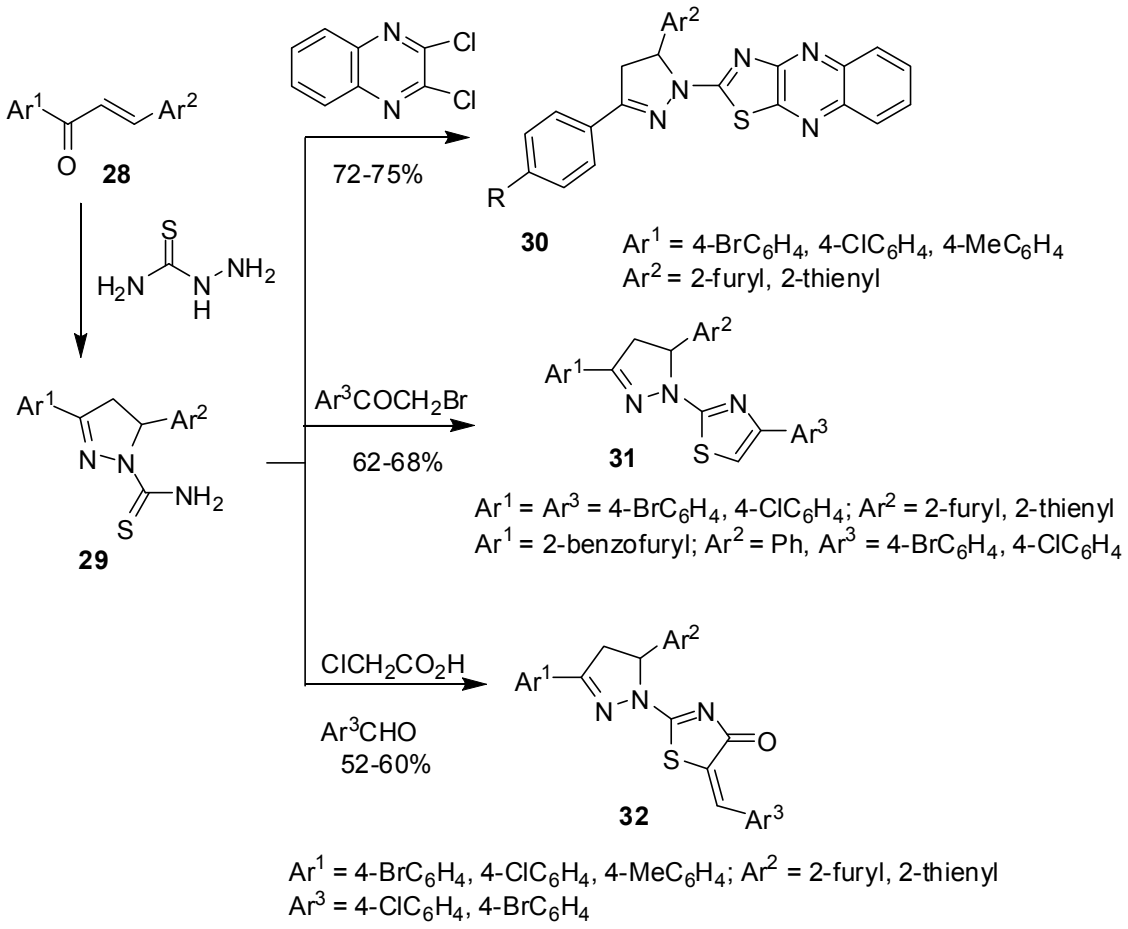
5-Hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-pyrazolethiocarboxyamides **19** were reacted with phenacylbromides, and 2-bromocyclohexanone **20** to give the corresponding pyrazolyl-thiazoles **23** and **25** after dehydration of **22** and **24** respectively (Scheme 7).[30] The reaction of 5-bromo-1,1,1-trifluoro-4-methoxypent-3-en-2-one **21** with 5-hydroxy-3-methyl-5-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide **19** in chloroform under stirring for 24h at 35 °C furnished **27** after removing of water molecule from **26** (Scheme 7).[31]



Scheme 7

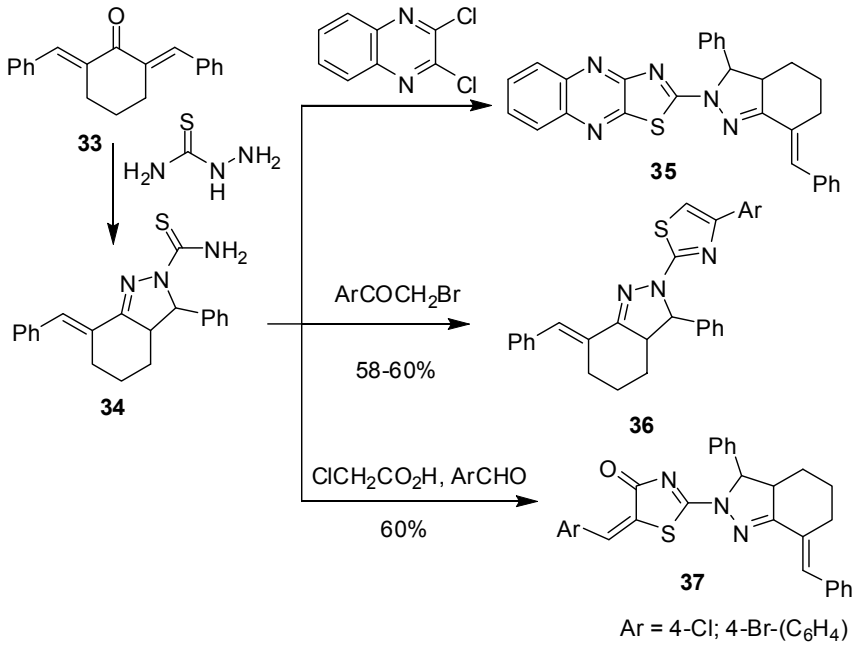
Refluxing the appropriate α,β-unsaturated carbonyl compounds **28** with thiosemicarbazide in presence of NaOH provided the requisite **29** in good overall yields. Reactions of **29** with 2,3-dichloroquinoxaline, substituted phenacyl bromides, and chloroacetic acid and aromatic aldehydes, afforded the corresponding

3,5-diaryl-1-(thiazolo[4,5-*b*]quinoxalin-2-yl)-2-pyrazoline derivatives **30**; 3,5-diaryl-1-(4-aryl-2-thiazolyl)-2-pyrazolines **31**; 3,5-diaryl-1-(5-arylidene-4,5-dihydro-4-oxo-2-thiazolyl)-2-pyrazolines **32** (Scheme 8).[32-35]



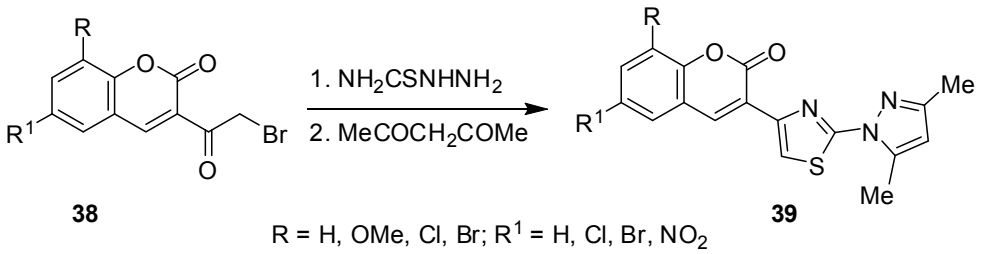
Scheme 8

7-Benzylidene-3,3*a*,4,5,6,7-hexahydro-3-phenyl-2-thiocarbamoyl-2*H*-indazole **34** was synthesized by the reaction of 2,6-bis-benzylidenecyclohexanone **33** with thiosemicarbazide in presence of NaOH. Reaction of **34** with 2,3-dichloroquinoxaline, substituted phenacyl bromides in absolute ethanol, and aromatic aldehydes and chloroacetic acid in presence of a mixture of acetic acid and acetic anhydride gave the corresponding fused 7-benzylidene-3,3a,4,5,6,7-hexahydro-3-phenyl-2-(thiazolo[4,5-*b*]quinoxalin-2-yl)-2*H*-indazole **35**, 2-(4-aryl-2-thiazolyl)-7-benzylidene-3,3a,4,5,6,7-hexahydro-3-phenyl-2*H*-indazole analogues **36** and 2-(5-arylidene-4,5-dihydro-4-oxo-2-thiazolyl)-7-benzylidene-3,3a,4,5,6,7-hexahydro-3-phenyl-2*H*-indazole derivatives **37** (Scheme 9).[33]



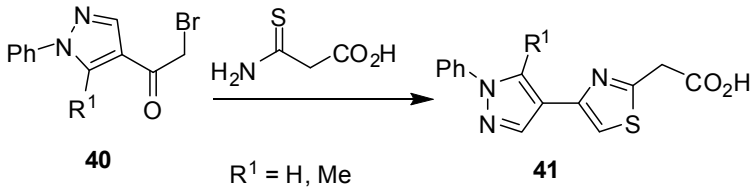
Scheme 9

Reaction of 3-(bromoacetyl)coumarins **38** with thiosemicarbazide and acetylacetone gave 3-[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)thiazol-4-yl]-2*H*-1-benzopyran-2-ones **39** and a in 72-90% yield under solvent free conditions (Scheme 10).[36]



Scheme 10

The antiinflammatoric 1-phenylpyrazolyl-4-heteroarylalkanoic acids **41** have been prepared from pyrazoles **40** and 3-amino-3-thioxopropanoic acid (Scheme 11).[37]

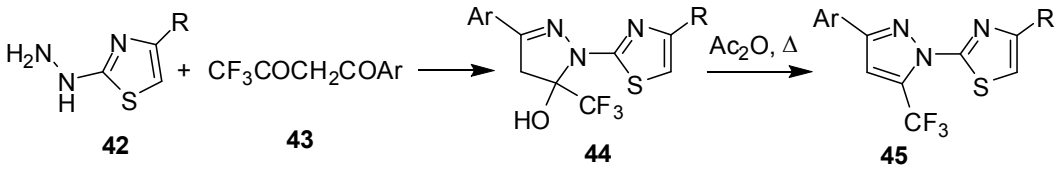


Scheme 11

3.2. Reaction of hydrazines with β-diketones

Regioselectivity of the synthesis of 2-pyrazolinylthiazoles by reacting 2-hydrazinothiazoles with

unsymmetrical β-diketones was reported. 2-Pyrazolinylthiazoles **44** were prepared regioselectively by cyclocondensation of 4-substituted-2-hydrazinothiazoles **42** with 1,3-dicarbonyl compounds **43**. The aromatization of **44** via dehydration to give 2-(3-aryl-5-trifluoromethylpyrazol-l-yl)thiazoles **45** (Scheme 12) required forcing conditions (boiling acetic anhydride).[38]

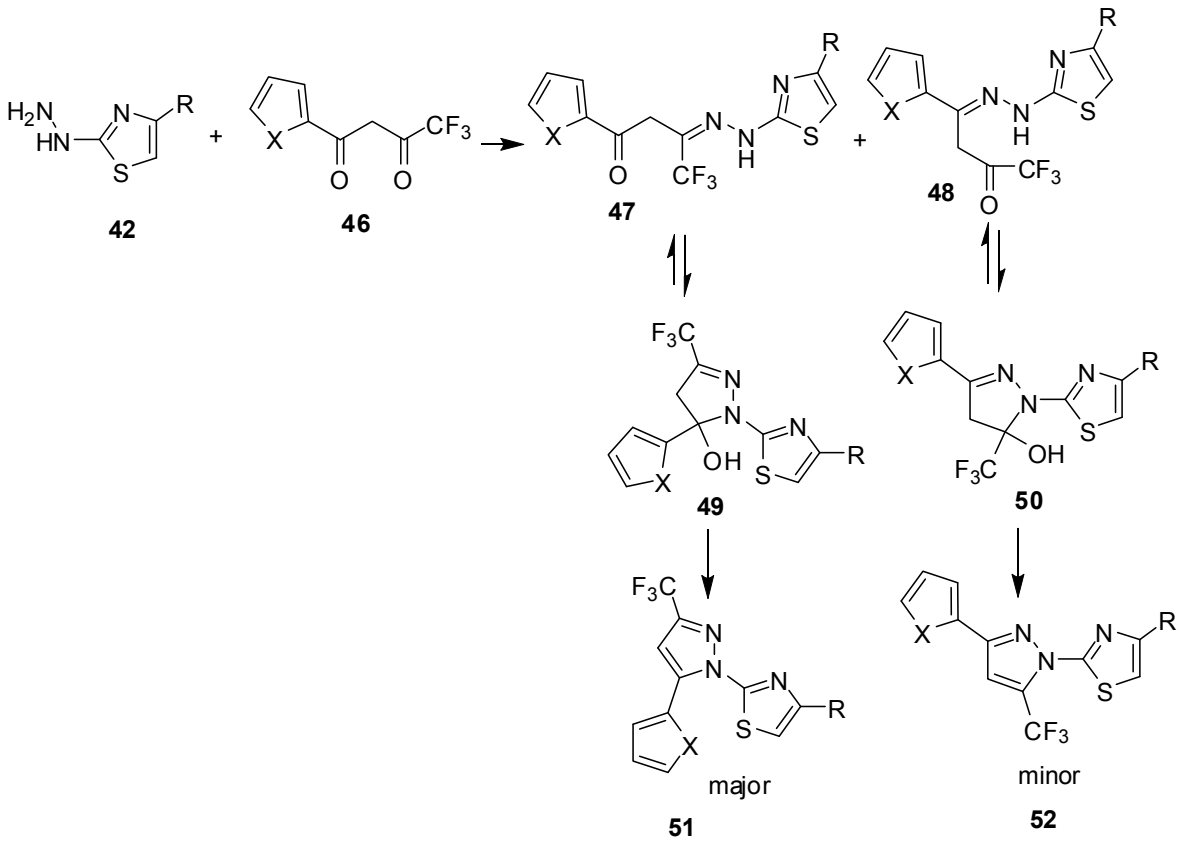


42 **43** **44** **45**

R = CO_2Et, Ar = 2-naphthyl

Scheme 12

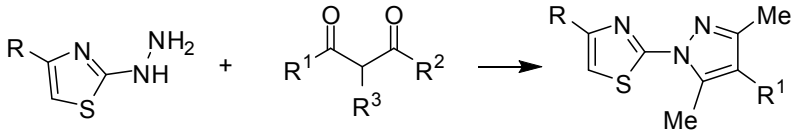
Reaction of 2-hydrazinothiazoles **42** with 1-thienyl- and 1-furyl-1,3-butanediones **46** in methanol in the presence of hydrochloric acid mainly led to a mixture of pyrazoles and pyrazolines **49-52** in strong acidic conditions. Isomeric hydrazones and pyrazolines **47-50** were formed and isolated in these reactions in the absence of hydrochloric acid. It has been shown that the regioselectivity in the reaction of diketones with 2-hydrazinothiazoles is governed by both the concentration of acid and the nature of substituents in the 1,3-diketones. Cyclization of hydrazones is shown to occur under milder conditions than dehydration for pyrazolines **49** and **50** (Scheme 13).[39]



42 **46** **47** **48** **49** **50** **51** **52**

Scheme 13

The pyrazolylthiazoles **54** were prepared by the condensation of appropriate 2-hydrazino-4-arylthiazoles **42** with β-diketones **53** (Scheme 14).[40-44]

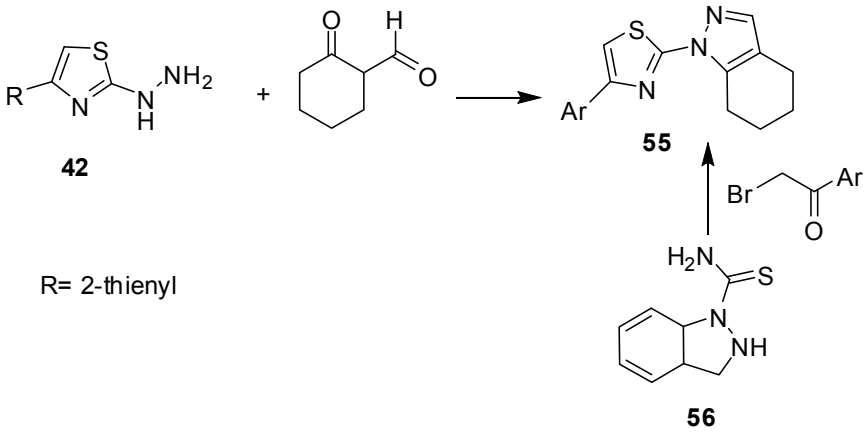


42 **53** **54**

R = 2-thienyl, Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4;
R^1 = R^2 = H, Me; R^1 = Me; R^2 = Ph; R^3 = H, Me, Et, CH_2CO_2Et

Scheme 14

However, treatment of 2-hydrazino-4-(2-thienyl)thiazole **42** with 2-formylcyclohexanone yielded **55** as major product. Which could be obtained exclusively by the reaction of tetrahydroindazolyl-1-thiocarboxamide **56** and phenacyl bromides (Scheme 15).[43]



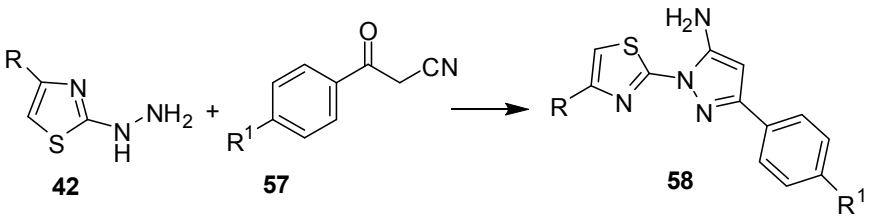
42 **55** **56**

R= 2-thienyl

Scheme 15

3.3. Reaction with β-keto-nitriles

Condensation of 2-hydrazinothiazole **42** and 4-aroylaceteonitriles **57** gave 52-73% pyrazolylthiazoles **58** (Scheme 16).[26]

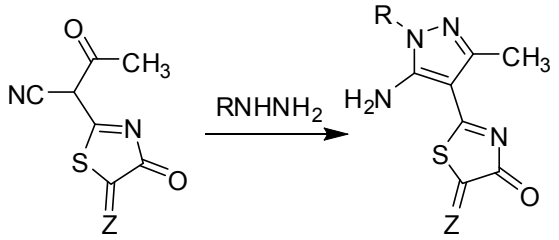


42 **57** **58**

R = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4; R^1 = H, Cl, Br, Me, MeO; R^2 = Me, Ph

Scheme 16

Thiazolinonylpyrazoles **60** were synthesized via the reactions of 2-α-cyanoacetonyl-2-thiazolin-4-one **59** with hydrazine derivatives (Scheme 17).[45]



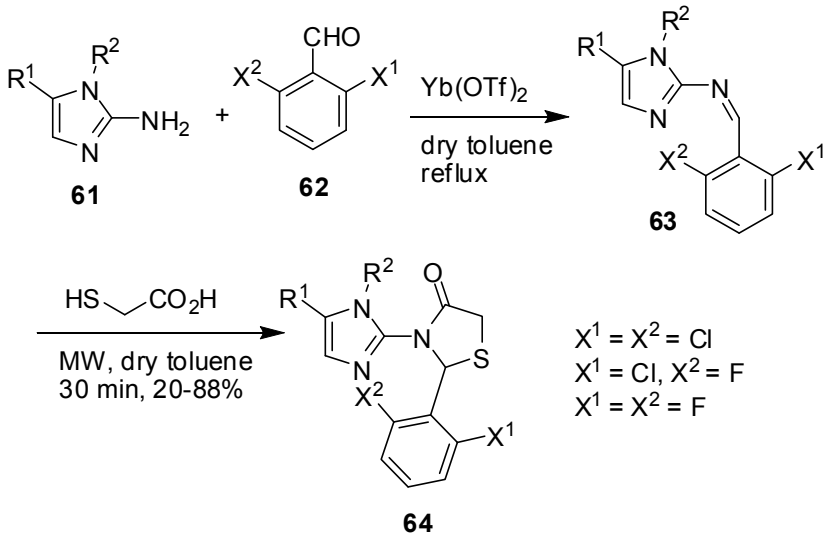
59 **60**

R = H, Ph, Z = NHNHPh, CHPh, (H,H)

Scheme 17

4. IMIDAZOLYLTHIAZOLES

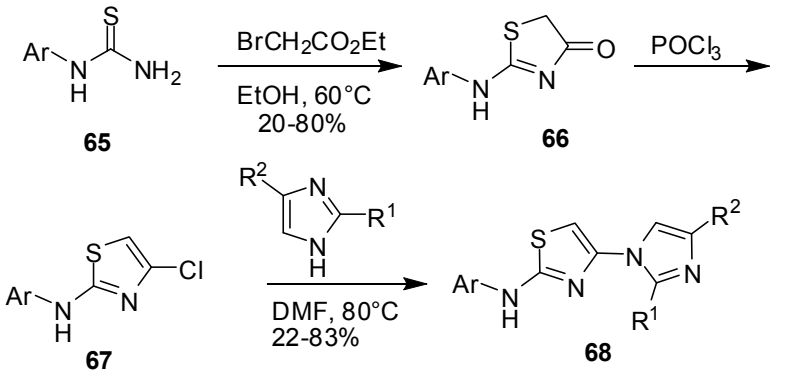
Microwave-assisted synthesis of a novel class of imidazolylthiazolidin-4-ones has reported. Thus, generation of imidazolylthiazolidin-4-ones achieved **64**, in two steps, by reacting a mixture of 5-phenyl-1*H*-imidazol-2-amine **61**, 2,5-disubs. benzaldehyde **62** in dry toluene using 5 mol% of $Yb(OTf)_3$ as catalyst, followed by reaction with mercaptoacetic acid under microwave irradiation (Scheme 18).[46]



61 **62** **63** **64**

Scheme 18

Ring closure of arylthioureas **65** with ethyl bromoacetate followed by chlorination of the resulting 2-phenylaminothiazol-4-ones **66** with phosphorus oxychloride yielded (4-chlorothiazol-2-yl)phenylamines **67** as intermediates. The desired [4-(imidazol-1-yl)-thiazol-2-yl]phenylamines **68** were obtained by nucleophilic aromatic substitution in DMF solution, using the respective imidazoles in excess as reagents and bases which used as potent Colchicine site binding Tubulin inhibitors (Scheme 19).[47]



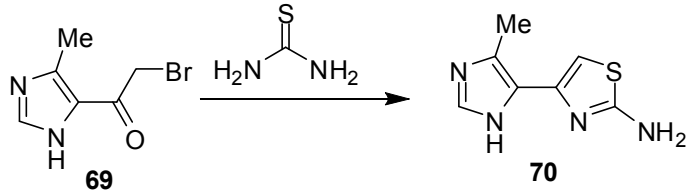
65 **66** **67** **68**

Ar = Ph, 4-BrC_6H_4, 4-$OMeC_6H_4$, 4-MeC_6H_4, 3-BrC_6H_4, 3-$OMeC_6H_4$

$R^1 = R^2 = H$, Me; R^1 = Me, $R^2 = H$

Scheme 19

4-(4-Methyl-5-imidazolyl)thiazole **70** was prepared by reaction of 4-methyl-5-bromoacetylimidazole **69** with thiourea (Scheme 20).[48]

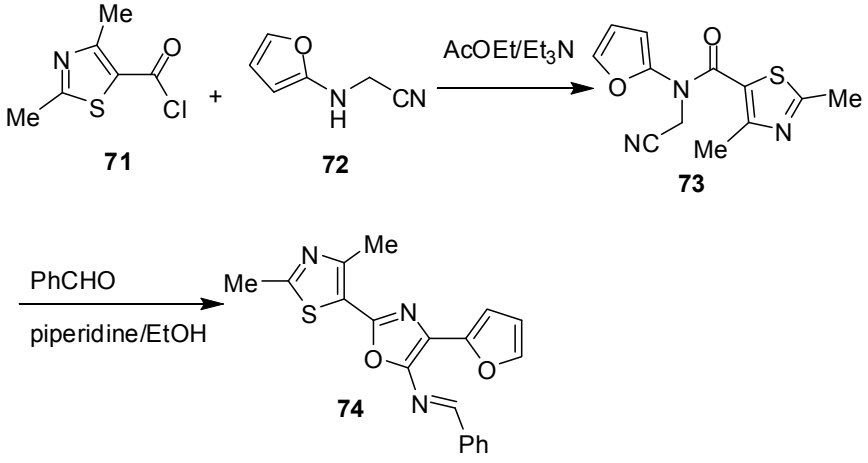


69 **70**

Scheme 20

5. Thiazolyloxazoles

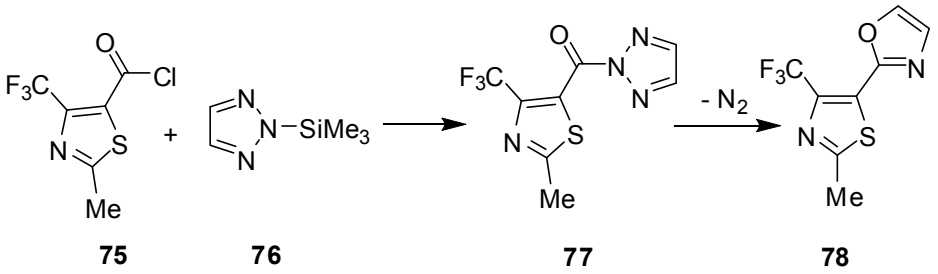
Agrochemical microbicides contain thiazolyloxazoles **74** prepared by treatment of α-furyl-aminoacetonitrile **72** in ethyl acetate/triethylamine with 2,4-dimethylthiazole-5-carboxylic acid chloride **71** at room temperature to give **73** which in ethanol was treated with benzaldehyde in the presence of piperazine at 60 °C for 2 h to afford **74** (Scheme 21).[49]



71 **72** **73** **74**

Scheme 21

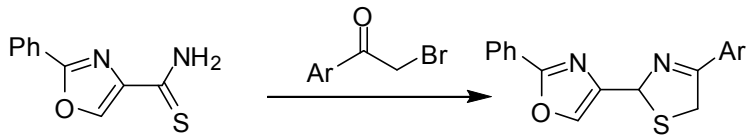
Upon reacting thiazole **75** with 2-trimethylsilyl-1,2,3-triazole **76** in refluxing toluene for three days gave thiazolyl oxazole **78** in a 86% yield by nitrogen elimination rearrangement reaction of the triazole amide **77** (Scheme 22).[50]



75 **76** **77** **78**

Scheme 22

Reaction of 2-aryloxazole-4-carboxylic acid thioamides **79** with different phenacylbromides gave 4-(thiazol-2-yl)oxazoles **80** in high yield (Scheme 23).[51]

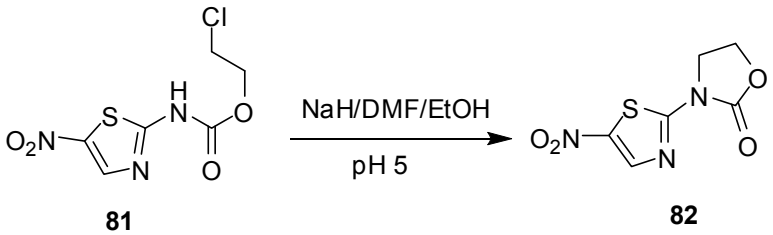


79 **80**

Ar= Ph,4-BrC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4

Scheme 23

3-(5-Nitro-2-thiazolyl)-2-oxazolidinone **82** was obtained by refluxing 2-chloroethyl 5-nitrothiazol-2-ylcarbamate **81** in DMF with sodium hydride and ethanol at pH 5 (Scheme 24).[52-54]

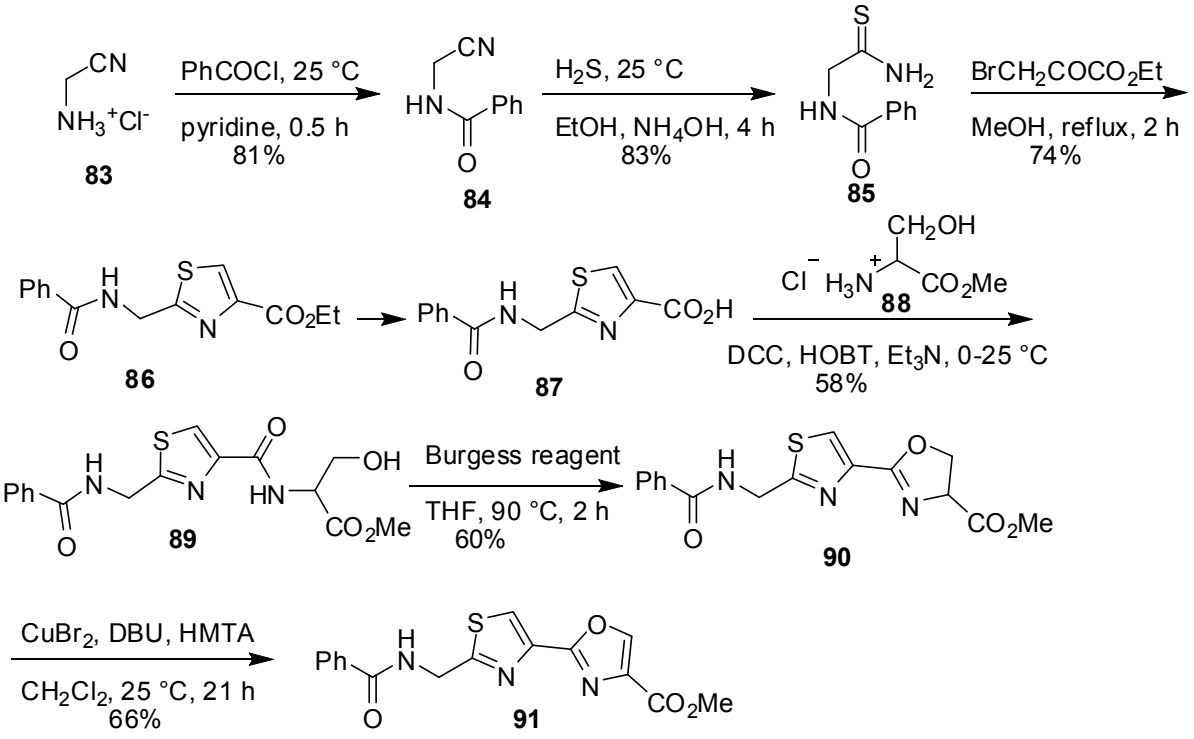


81 **82**

Scheme 24

The synthesis of a directly connected thiazole-oxazole ring system **90** present in Microcin B17 was reported. Aminoacetonitrile hydrochloride **83** was converted to **84** under standard benzoylation conditions. Hydrogen sulfide treatment of an aqueous ethanolic ammonia solution of **84** provided the thioamide **85**, which on condensation with ethyl bromopyruvate in boiling methanol afforded the fully protected thiazole amino acid **86**. Selective hydrolysis of the ester group provided **87**, which the coupling

of **87** with *DL*-serine methyl ester **88** preceded under standard solution to afford 2-(benzamidomethyl)-4-{*N*-[1-(methoxycarbonyl)-2-hydroxyethyl]carbamoyl}thiazole **89** which undergo cyclization using Burgess reagent {methyl *N*-[(triethylammonio)sulfonyl]carbamate}, the aromatization of dihydroxazole **90** was performed using $CuBr_2$-DBU system to afford **91** (Scheme 25).[55]

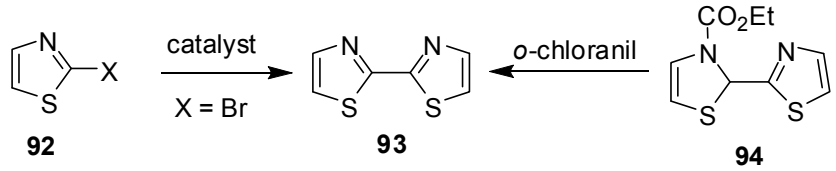


Scheme 25

6. BITHIAZOLES

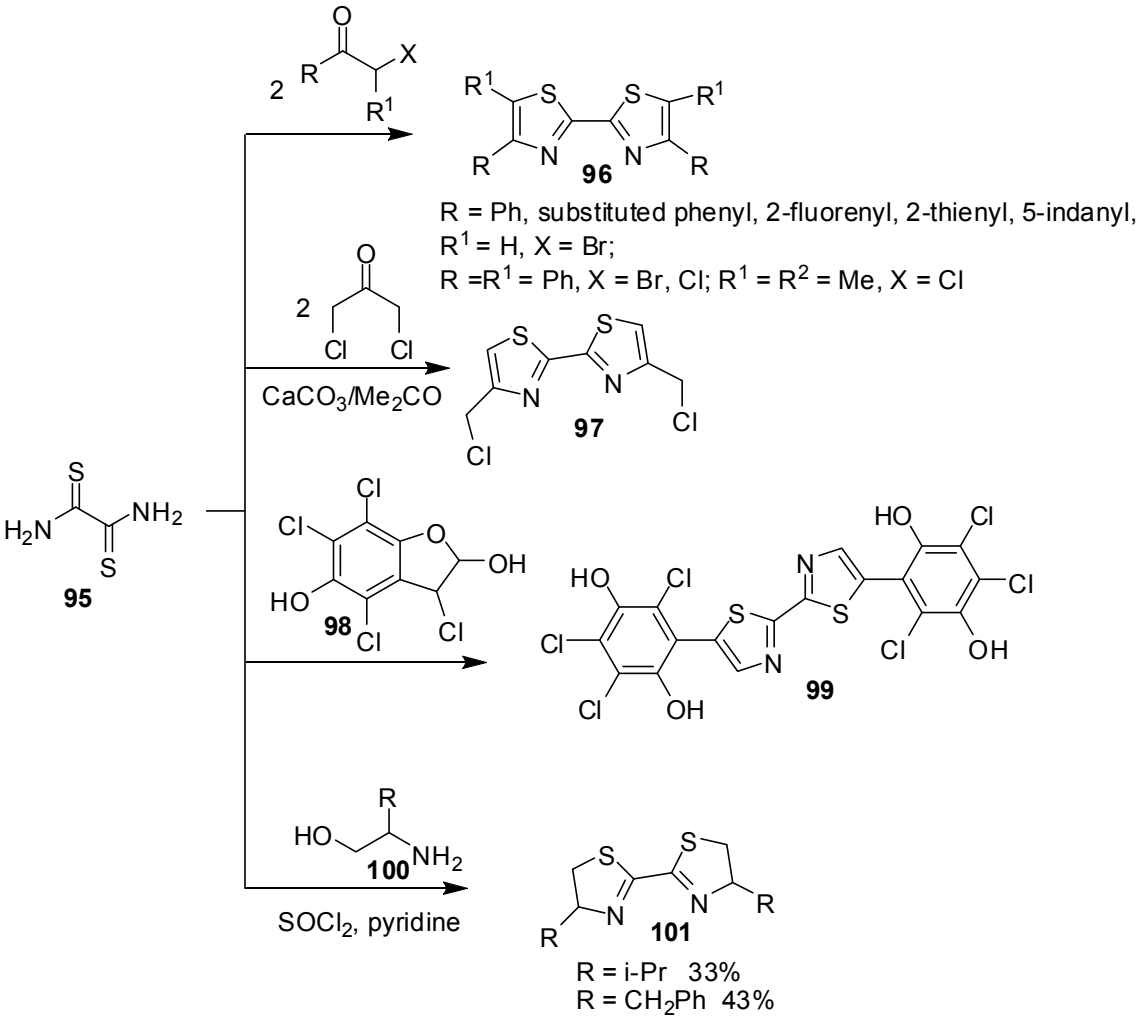
6.1. 2,2'-BITHIAZOLES

2,2'-Bithiazole **93** has been synthesized in good yield via homocoupling of 2-bromothiazole **92** in the presence of a catalyst such as $Pd(OAc)_2$/LiCl (72% yield)[56]; $Pd(OAc)_2$/n-Bu_4NBr/$^iPr_2EtN$ (86% yield)[56]; $Pd(PPh_3)_4$/$Bu_3SnSnBu_3$ (79% yield)[57]; BuLi/CuCl (52% yield)[58] (Scheme 26). Also, 2,2'-bithiazole **93** was prepared by decarboxylation of ethyl 2-(thiazol-2-yl)thiazole-3(2*H*)-carboxylate **94** using *o*-chloranil (Scheme 26).[59]



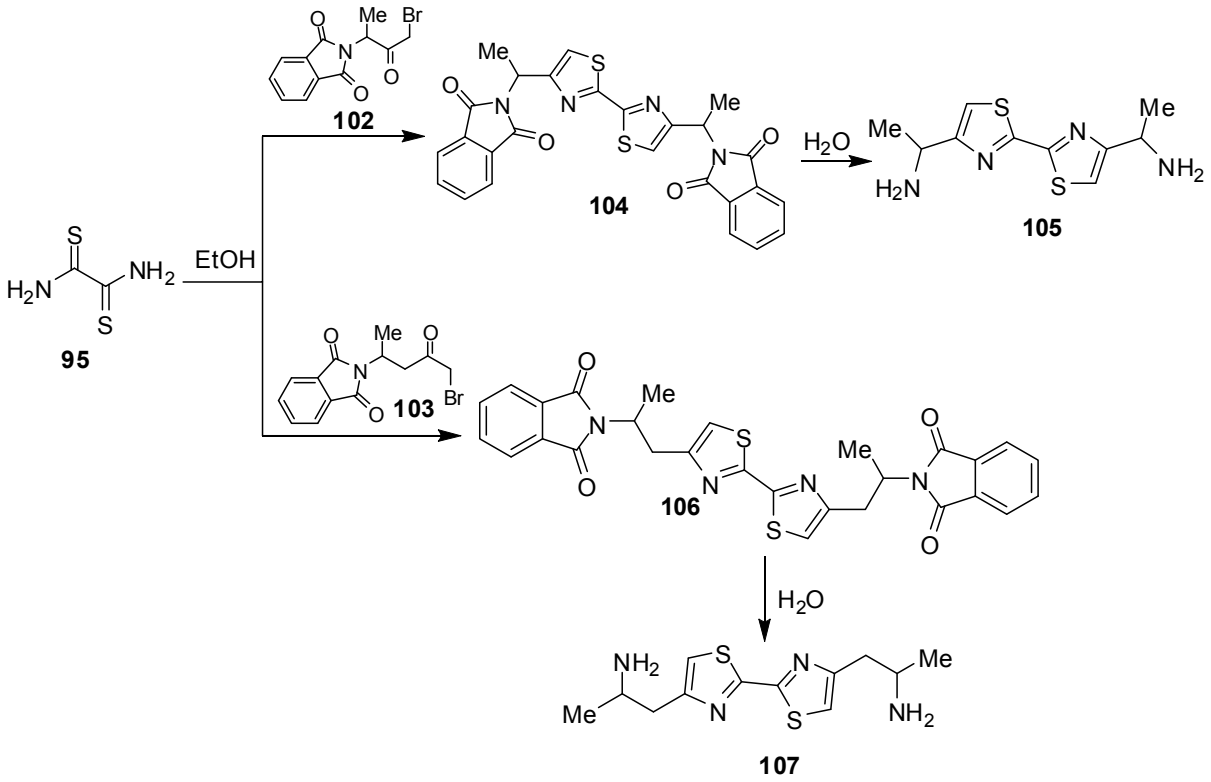
Scheme 26

Bithiazoles **96** were prepared in 80-90% yield by cyclocondensation of 1 mole rubeanic acid **95** with 2 moles appropriate α-bromo ketone.[60-66] 4,4'-Bis(chloromethyl)-2,2'-bi-1,3-thiazole **97** was prepared by condensation of **95** and 1,3-dichloroacetone.[67,68] 5,5'-Bis(2,5-dihydroxy-3,4,6-trichlorophenyl)-2,2'-bithiazole **99** was synthesized from 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[*b*]furan **98** and dithiooxalyl diamide **95**.[69] 2,2'-Bithiazolines **101** were prepared by reaction of 2-amino-alcohol derivatives **100** with ethanebis(thioamide) **95** in two steps (Scheme 27).[64,70]



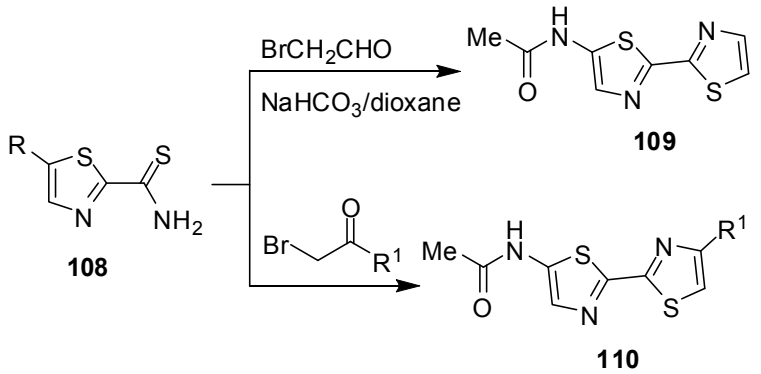
Scheme 27

Condensation of 2-(4-bromo-3-oxobutan-2-yl)isoindoline-1,3-dione **102** and 2-(5-bromo-4-oxopentan-2-yl)isoindoline-1,3-dione **103** with ethanebis(thioamide) **95** in ethanol gave the corresponding 4,4'-bis(1,2-phthalimidoethyl)-2,2'-bithiazole **104** and 4,4'-bis(2-phthalimidopropyl)-2,2'-bithiazole **106** in good yields, hydrolyzed to the di-HCl salts of 4,4'-bis(1-aminoethyl)-2,2'-bithiazole **105** and 4,4'-bis(2-aminopropyl)-2,2'-bithiazole **107** (Scheme 28).[71]



Scheme 28

Refluxing 2-thiocarbamylthiazoles **108** with 2-bromoacetaldehyde in dioxane gave 5-acetyl-2,2'-bithiazole **109**. Condensation of 2-thiocarbamylthiazoles **108** with the appropriate bromoketone by refluxing in glacial AcOH or dioxane and purification gave 5-acetamido-4'-alkyl-2,2'-bithiazoles **110** (Scheme 29).[72,73]

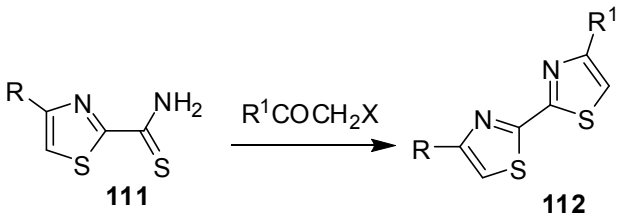


R = MeCONH, NO_2; R^1 = Me, Bu, Am, hexyl, heptyl, Stearoyl,heptadecyl, Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 2,5-$(MeO)_2C_6H_3$

Scheme 29

4-(2-Thienyl)thiazole-2-thiocarboxamide **111** on treatment with a variety of α-tosyloxy ketones afforded 4-substituted 4'-(2-thienyl)-2,2'-bithiazoles **112**.[74] Condensation of **111** with phenacyl bromides gives

4-aryl-4'-(2-thienyl)-2,2'-bithiazoles **112**. Compounds **112** show varying degrees of phototoxicity when tested against mosquito larvae (Scheme 30).[75]

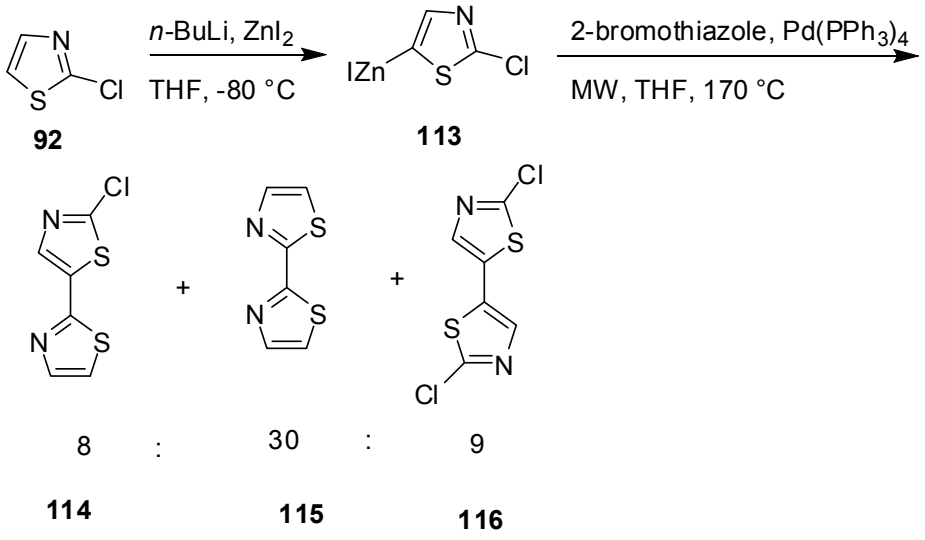


111 **112**

R = R^1 = 2-thienyl; R^1= (un)substituted phenyl, X= OTs, Br

Scheme 30

The organo-zinc intermediate **113** was converted to bithazole **114**, 2,2'-bithiazole **115**, 2,2'-dichloro-5,5'-bithiazole **116** by treatment with 2-bromothiazole, in the presence of $Pd(PPh_3)_4$, and under microwave conditions (Scheme 31).[76]



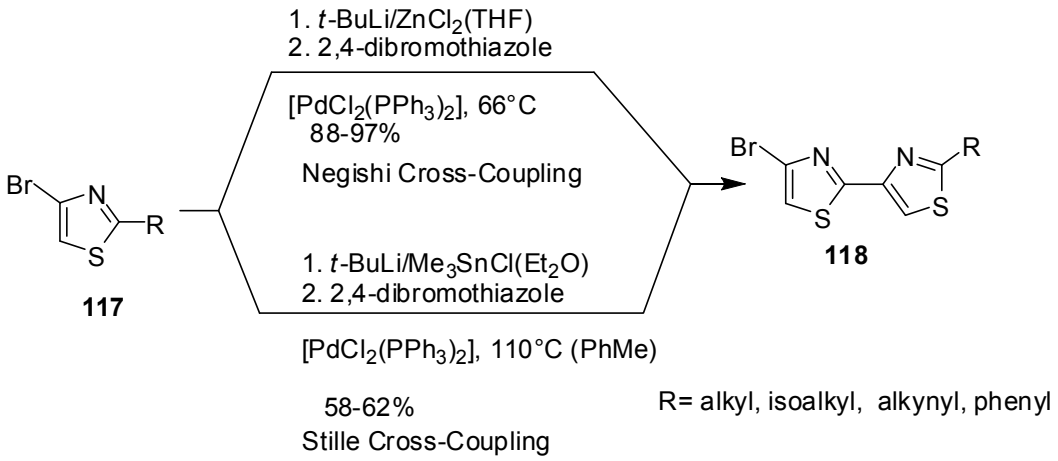
92 **113**

114 **115** **116**

Scheme 31

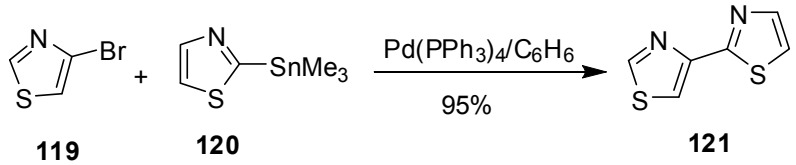
6.2. 2,4'-BITHIAZOLES

2'-Substituted 4-bromo-2,4'-bithiazoles were prepared from 2,4-dibromothiazole by regioselective cross-coupling reactions. Cross-coupling of an organometallic reagent with 2,4-dibromothiazole **117** should occur at the 2-position. Subsequent bromo-lithium exchange generates a carbon nucleophile that can react in a second step with another molecule of compound **117** to the desired product **118**. The Negishi cross-coupling gave high yields of the 2'-alkyl-4-bromo-2,4'-bithiazoles **118** (88-97%). The synthesis of the 2'-phenyl- and 2'-alkynyl-4-bromo-2,4'-bithiazoles **118** required a Stille cross-coupling that did not proceed as smoothly as the Negishi cross-coupling (58-62% yield) (Scheme 32).[77]



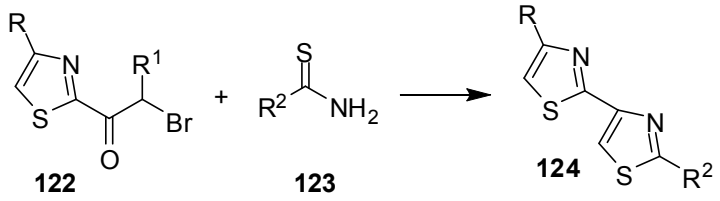
Scheme 32

2,4'-Bithiazoles **121** was prepared in 95% yield by treatment of **119** With 2-(trimethylstannyl)thiazole **120** (Scheme 33).[78]



Scheme 33

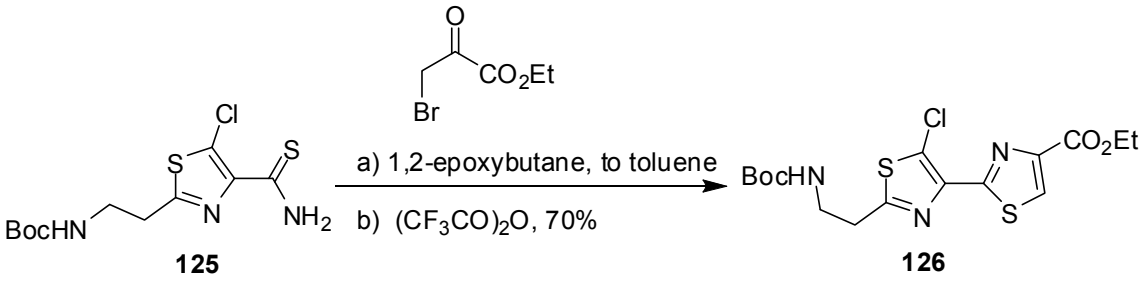
2,4'-Bithiazoles **124** obtained by cyclization of thioacetamides **123** with 2-bromo-1-(4-subst-thiazol-2-yl)-ethanone **122** (Scheme 34).[79-83]



R = Ph, *p*-ClC_6H_4, *p*-MeC_6H_4, CO_2Me; R^1 = H, Me, Et
R^2 = Me, Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, NH_2, PhNH, *p*-MeC_6H_4NH, *p*-ClC_6H_4NH

Scheme 34

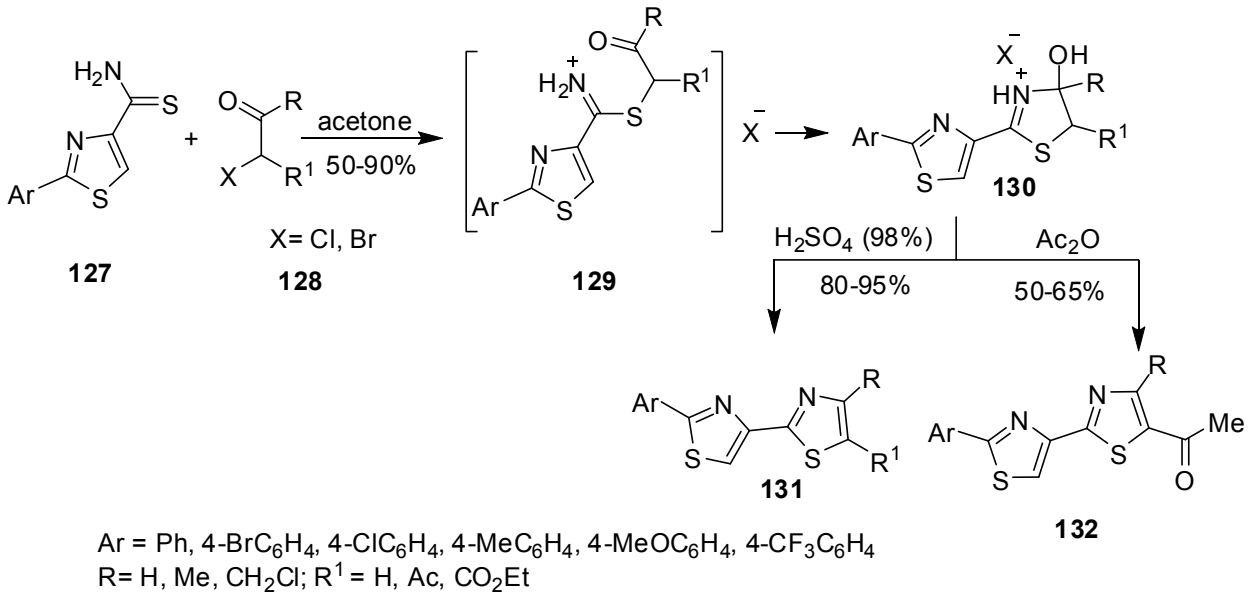
Hantzsch cyclization of **125** with ethyl bromopyruvate was performed in the presence of 1,2-epoxybutane to trap HBr as it evolved during cyclization. The crude hydroxylated intermediate was then dehydrated with trifluoroacetic anhydride in pyridine at –20 °C to afford monochlorobithiazole ethyl ester **126** in 70% yield (Scheme 35).[73]



125 126

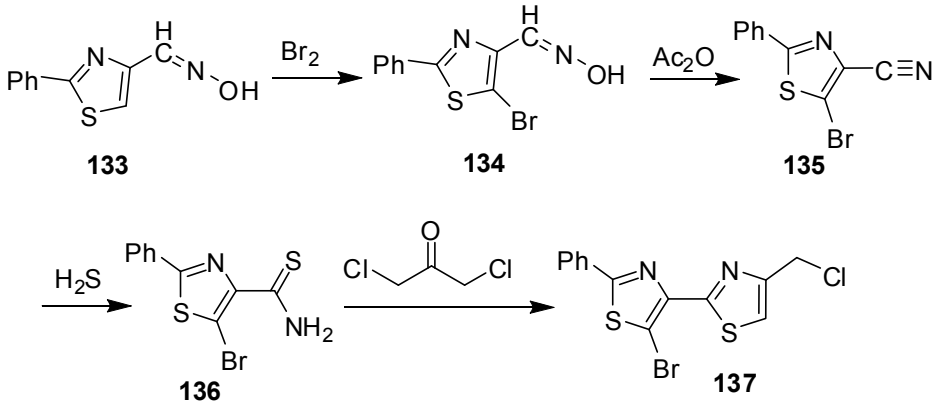
Scheme 35

Bithiazoles **130** were prepared, in 50-90% yield, by reaction of thioamides **127** with α-haloketones **128** in acetone. Treatment of **130** with 98% sulfuric acid gave 2,4-bithiazole **131** in 80-95% yield, while on treatment with acetic anhydride furnished 5-acetylbithiazoles **132** (Scheme 36).[84]



Scheme 36

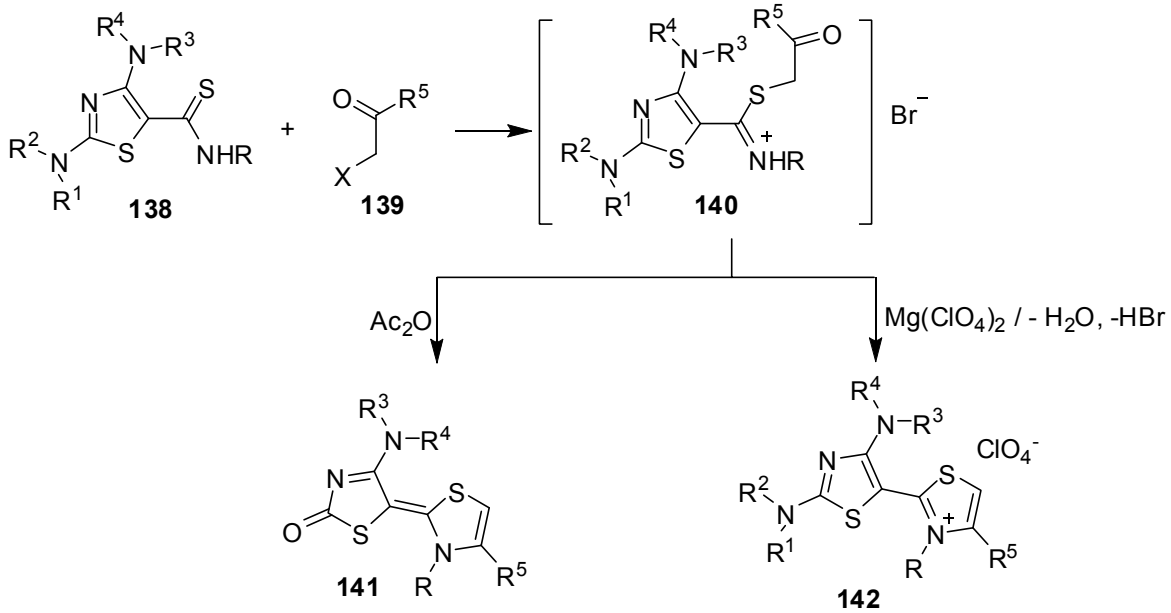
The synthesis of 2'-phenyl-5'-bromo-4-chloromethyl-2,4'-bisthiazole **137** starting from the oxime of 2-phenyl-4-formylthiazole **133** has been reported, thus, bromination of the oxime **133** followed by dehydration afforded 5-bromo-2-phenylthiazole-4-carbonitrile **135**. Thiohydrolysis of the latter gave 5-bromo-2-phenylthiazole-4-carbothioamide **136** which on treatment with 1,3-dichloropropan-2-one led to the target compound **137** (Scheme 37).[85]



Scheme 37

6.3. 2,5'-BITHIAZOLES

The 2,4-diaminothiazole-5-carbothioamides **138** react with halomethyl carbonyl compounds **139** and $Mg(ClO_4)_2$ in Ac_2O, the corresponding 2',4'-bis(dialkylamino)-3,4-diaryl[2,5'-bithiazol]-3-ium perchlorates **141** and **142** were isolated (Scheme 38). These compounds result, obviously, via the primarily formed **140** by a ring-closure reaction between the carbonyl and iminium groups (Scheme 38).[86]



$R^1R^2N = R^3R^4N$ = piperidin-1-yl, morphlin-4-yl
R= 4-$MeOC_6H_4$,4-ClC_6H_4; R^5=4-$NO_2C_6H_4$, 4-ClC_6H_4

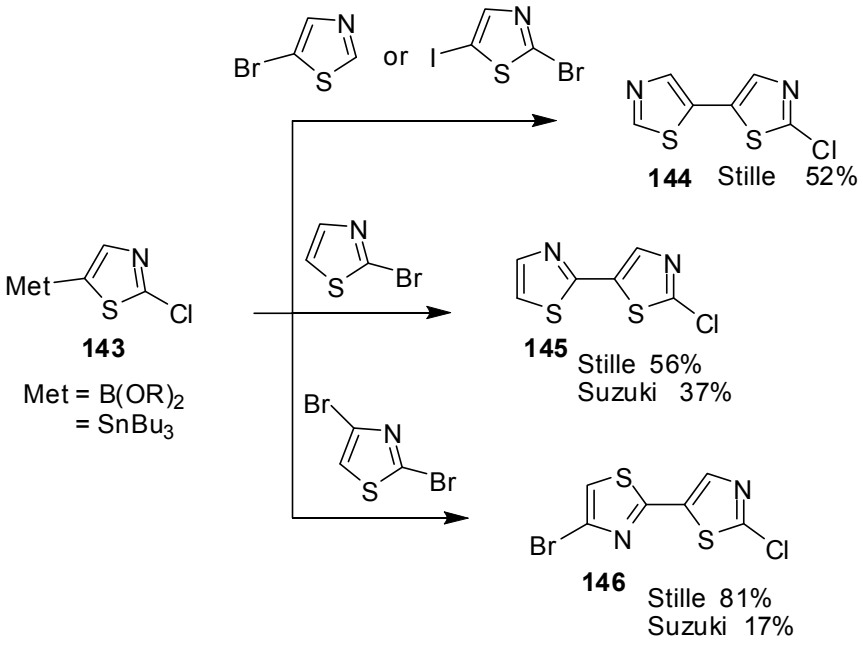
a $R^1R^2N = R^3R^4N$ = piperidin-1-yl; R = 4-$MeOC_6H_4$; R^5 = 4-$NO_2C_6H_4$

b $R^1R^2N = R^3R^4N$ = piperidin-1-yl; R = Ph; R^5= 4-$NO_2C_6H_4$

Scheme 38

Halothiazoles **143** were submitted to the cross-coupling conditions with least-reactive 4-bromothiazole gave 36% of the cross-coupling product **144**. A similar result was obtained when 2-bromo-5-iodothiazole.

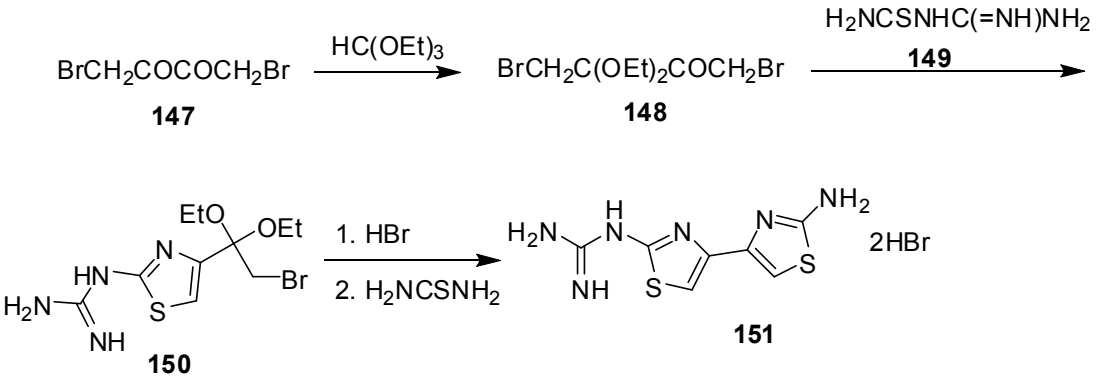
In the reaction with 2-bromothiazole, 2'-chloro-2,5'-bithiazole **145** was obtained. Finally, 2,4-dibromothiazole was cross-coupled to **143** to afford 4-bromo-2'-chloro-2,5'-bithiazole **146** (Scheme 39).[76]



Scheme 39

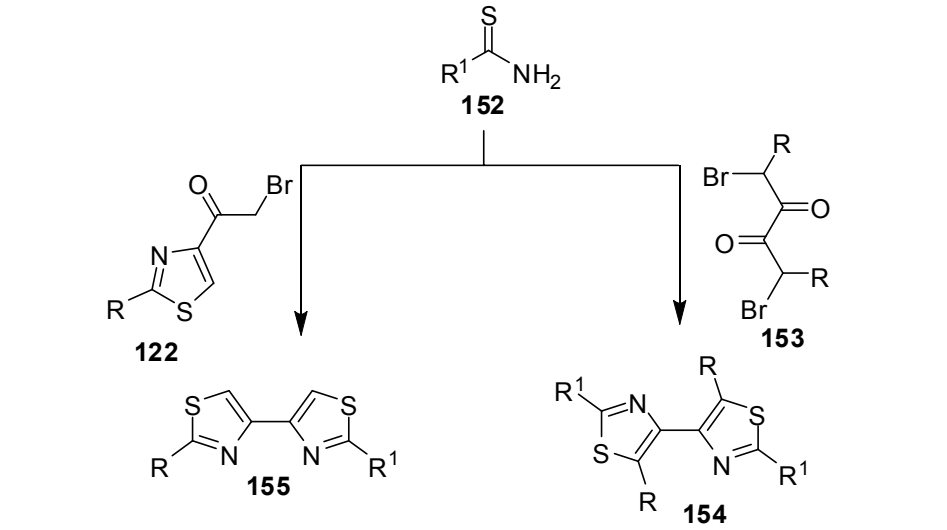
6.4. 4,4'-BITHIAZOLES

1,4-Dibromobutane-2,3-dione **147** was treated with triethyl orthoformate and the resulting 1,4-dibromo-3,3-diethoxybutan-2-one **148** cyclized with thiourea derivative **149** to give 2-guanidino-4-(2-bromo-1,1-diethoxyethyl)thiazole **150**, which was hydrolyzed with HBr followed by cyclization with thiourea to give 1-(2'-amino-4,4'-bithiazol-2-yl)guanidine.2HBr **151** (Scheme 40).[87]



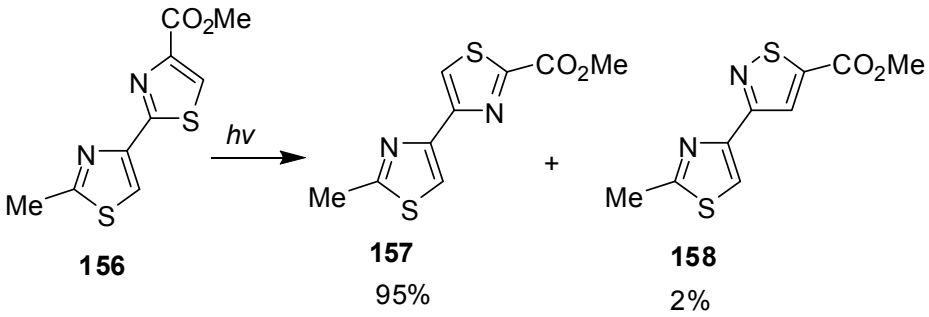
Scheme 40

Heating of the dibromoketones **153** with thioamides **152** gave 2,2'-disubst-5,5'-dimethyl-4,4'-bithiazole-HBr **154** in high yields.[7,36,37] On the other hand, the bithiazoles **155** was prepared by cyclization of the thiazoles **122** with thiocarboxamide **152** (Scheme 41).[80]



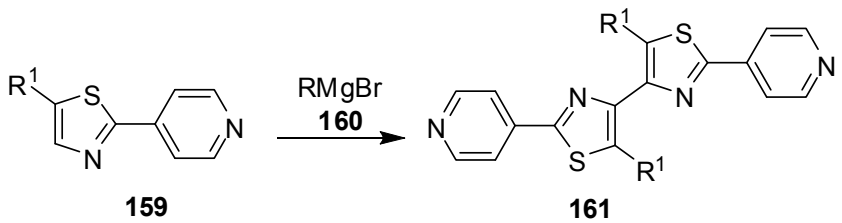
Scheme 41

External irradiation of methyl 2'-methyl-2,4'-bithiazole-4-carboxylate **156** in acetonitrile with a 60 W transilluminator (302 nm) gave 4,4'-bithiazole **157** in 95% yield as determined by HPLC. A more careful examination of the photolysate revealed the presence of another isomer **158** in 2% yield (Scheme 42).[88]



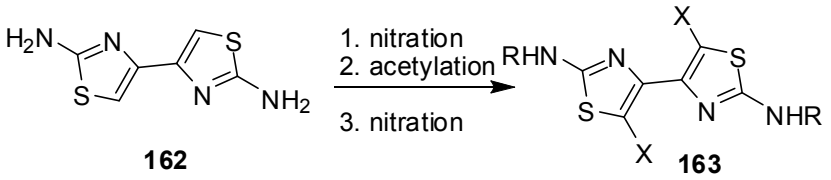
Scheme 42

Al-Azawe in 1988 reported the synthesis of 4,4'-bithiazoles **161** by treatment of pridylthiazoles **159** with Grignard reagents **160** (Scheme 43).[89]



Scheme 43

2,2'-Diamino-4,4'-bithiazole **162** was nitrated or acylated and then nitrated to obtain 2,2'-diamino-5,5'-dinitro-4,4'-bithiazole (**163**, X = NO_2, R= H) and 2,2'-diamino-diacetylamino-4,4'-bithiazole (**163**, X = Ac, R= H) and 2,2'-diacetylamino-5,5'-dinitro-4,4'-bithiazole (**163**, X = NO_2, R= Ac) (Scheme 44).[90]

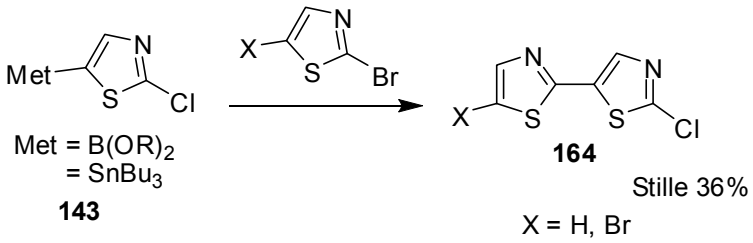


162 **163**

Scheme 44

6.5. 4,5'-BITHIAZOLES

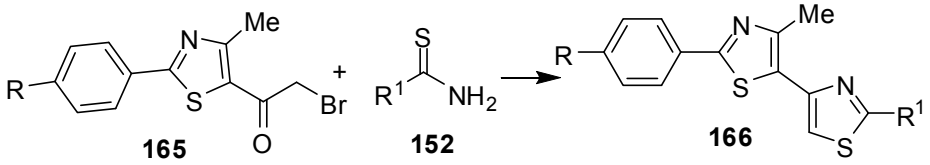
2'-Chloro-4,5'-bithiazoles (**164**, X= H) and 5-bromo-2'-chloro-2,5'-bithiazoles (**164**, X= Br) were obtained by cross-coupling of 2-bromothiazole derivatives with 2-chlorothiazoles **143** (Scheme 45).[76]



143 **164**

Scheme 45

The bithiazoles **166**, which have antiinflammatory activities, were prepared by cyclization of **165** with thioamides **152** (Scheme 46).[91]

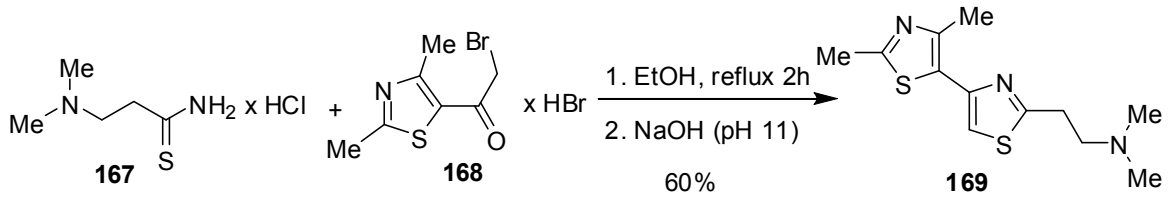


165 **152** **166**

R = H, Cl, OMe; R^1 = Me, Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, PhNH, NH_2, 4-ClC_6H_4NH

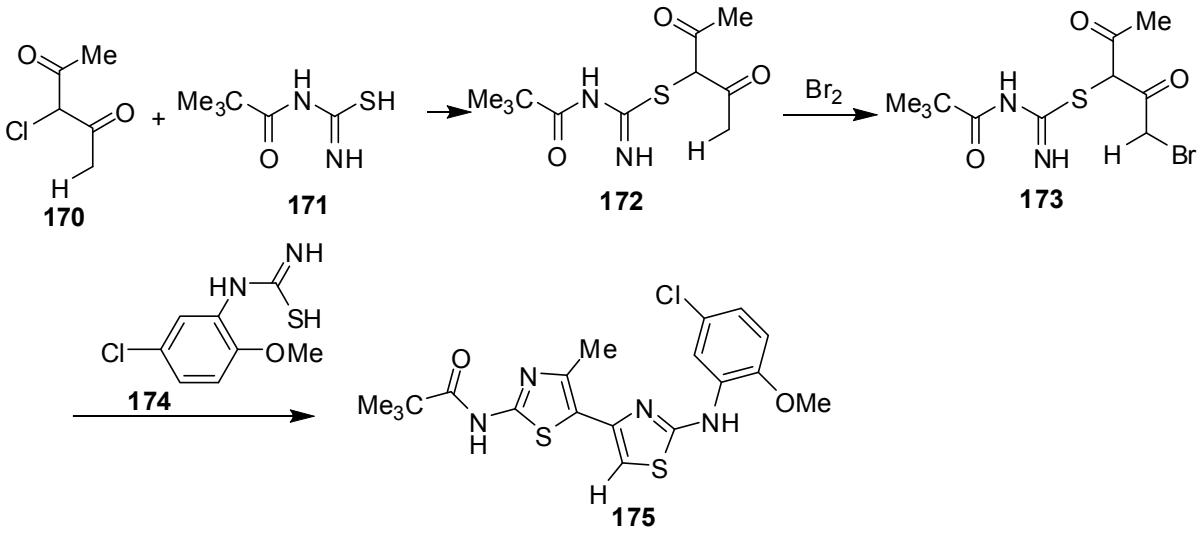
Scheme 46

Heating of 3-dimethylamino(thiopropanamide) hydrochloride **167** and 5-bromoacetyl-2,4-dimethylthiazole hydrobromide **168** in ethanol for 2h followed by basification gave 2-(2",4"-dimethyl-4',5"-bithiazol-2'-yl)-*N*,*N*-dimethylamine **169** in 60% yield (Scheme 47).[83]



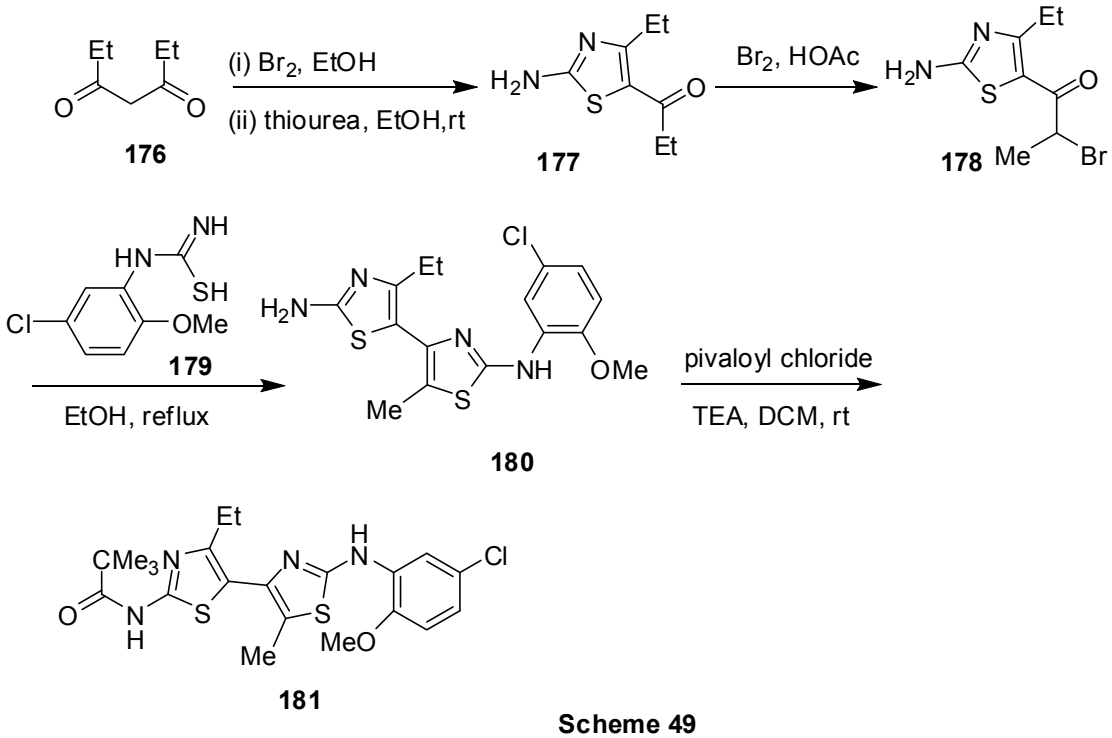
Scheme 47

The preparation of bithiazole **175** was accomplished by condensation of chlorodiketone **170** with *N*-pivaloylcarbamimidothioic acid **171** to give 1-(thiazol-5-yl)ethanone intermediate **172**. α-Bromination of the later to the carbonyl of **173** and subsequent condensation with *N*-(5-chloro-2-methoxyphenyl)carbamimidothioic acid **174** delivers **175** (Scheme 48).[92]



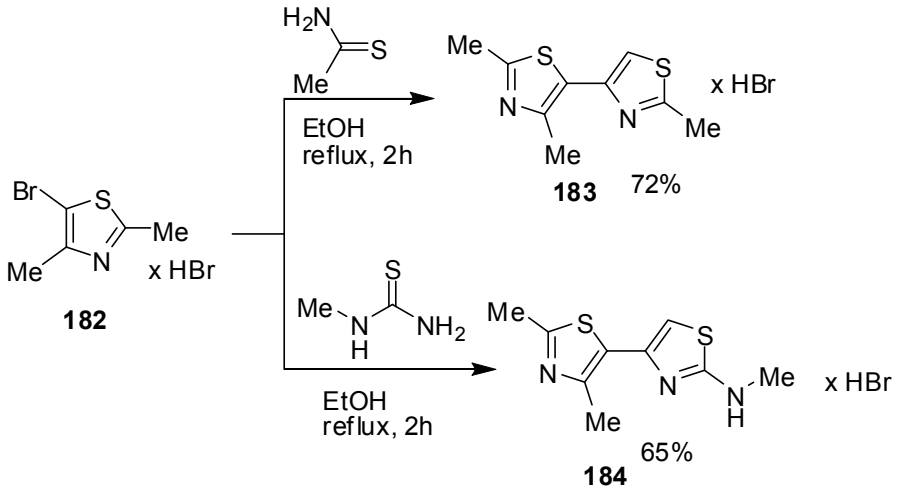
Scheme 48

1-(2-Amino-4-ethylthiazol-5-yl)propan-1-one **177** was prepared in 80% yield by bromination of 3,5-heptanedione **176** in ethanol solution followed by addition of thiourea. Bromination of **177** in acetic acid led to 1-(2-amino-4-ethylthiazol-5-yl)-2-bromopropan-1-one **178** in 86% yield. Reaction of **178** with **179** gave 4-(2-amino-4-ethylthiazol-5-yl)-*N*-(5-chloro-2-methoxyphenyl)-5-methylthiazol-2-amine **180** in 99% yield. *N*-(5-(2-(5-Chloro-2-methoxyphenylamino)-5-methylthiazol-4-yl)-4-ethylthiazol-2-yl)-pivalamide **181** was obtained in 66% yield by reaction of a suspension of **180** in DCM and TEA with pivaloyl chloride (Scheme 49).[92]



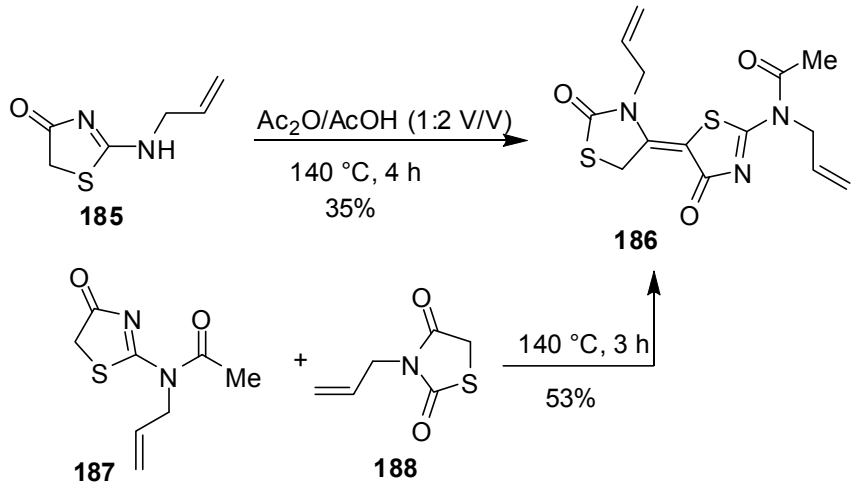
Scheme 49

The reaction of 5-bromo-2,4-dimethylthiazole **182** with thioacetamide and *N*-methylthiourea gave 2,2',4'-trimethyl-4,5'-bithiazole **183** and the corresponding amine **184** respectively (Scheme 50).[93]



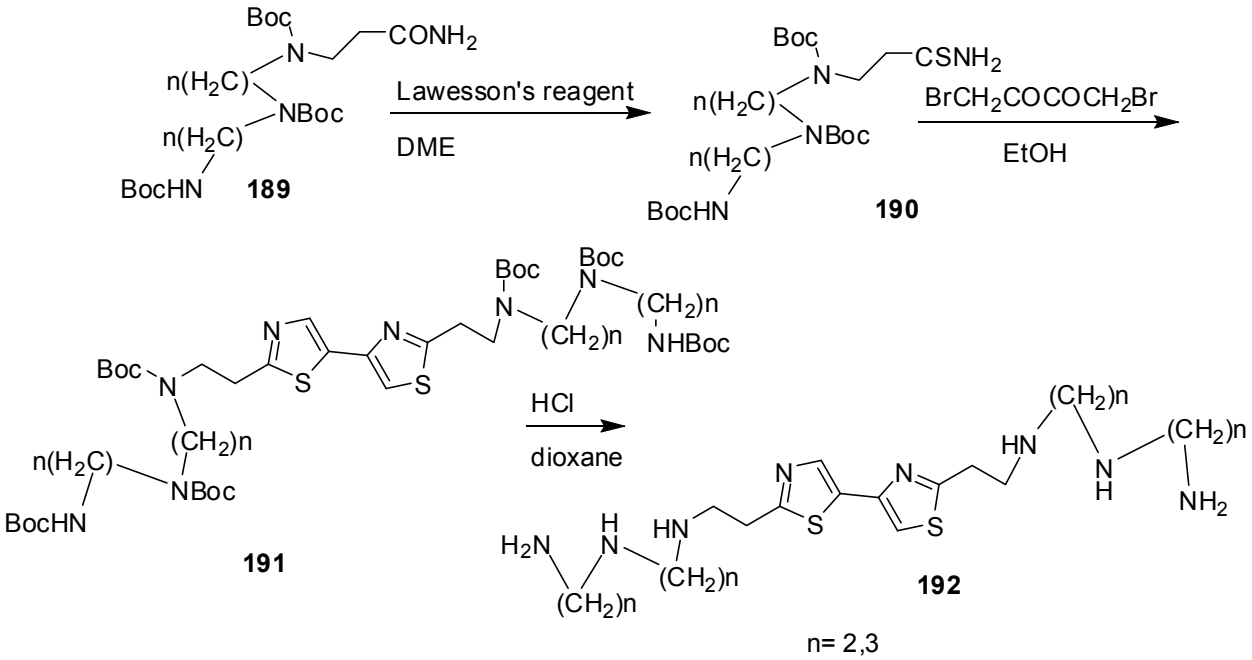
Scheme 50

N-Allyl-*N*-[5-(3-allyl-2-oxothiazolidin-4-ylidene)-4-oxo-4,5-dihydrothiazol-2-yl]acetamide **186** was prepared in 35% yield by heating of 2-(allylamino)thiazol-4(5*H*)-one **185** in a mixture of acetic anhydride and acetic acid (2:1 v/v) at 140 °C. Alternative synthesis of **186** in 53% yield was occurred by reaction of *N*-allyl-*N*-(4-oxo-4,5-dihydrothiazol-2-yl)acetamide **187** with 3-allylthiazolidine-2,4-dione **188** (Scheme 51).[94]



Scheme 51

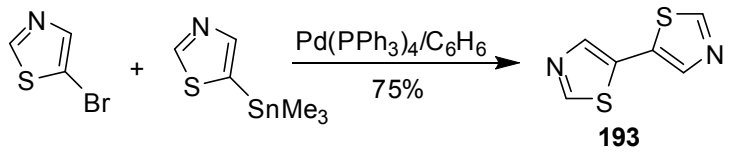
N-[*tert*-Butoxycarbonyl (*Boc*)] protected alkylenediamine-*N*-propionthioamides **190** were obtained by thiation of the amido carbonyl groups in **189** with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) in 70 and 61% yields using dry 1,2-dimethoxyethane (DME) as reaction solvent. When two equimolar amounts of **190** were reacted with 1,4-dibromobutane-2,3-dione at 70 °C for 2 h to provide the corresponding 4,4'-bithiazoles, 2,2'-bis[3,6,9-tri(Boc)-3,6,9-triazanonyl]- and 2,2'-bis[3,7,11-tri(*Boc*)-3,7,11-triazaundecyl]-4,4'-bithiazoles **191** in 73% and 60% yields respectively. Acidic deprotection of the amino groups in **191** afforded the bithiazoles **192** that were useful to inhibit the DNA cleavage (Scheme 52).[95]



Scheme 52

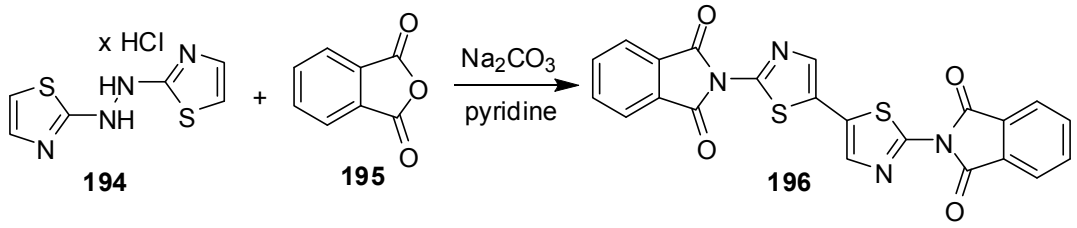
6.6. 5,5'-BITHIAZOLES

5,5'-Bithiazole **193** was prepared in 75% yield by treatment of 5-bromothiazole with 5-(trimethyl-stannyl)thiazole (Scheme 53).[78]



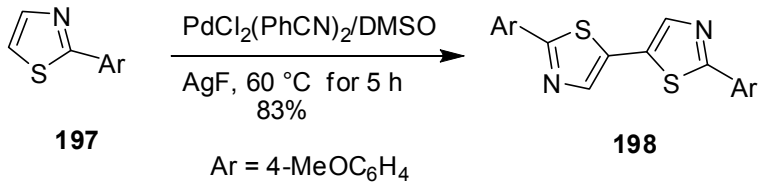
Scheme 53

2,2'-Diphthalimido-5,5'-bithiazole **196** was prepared in 20% yield by reaction 2,2'-hydrazobisthiazole-2HCl **194** with phthalic anhydride **195** (Scheme 54).[96]



Scheme 54

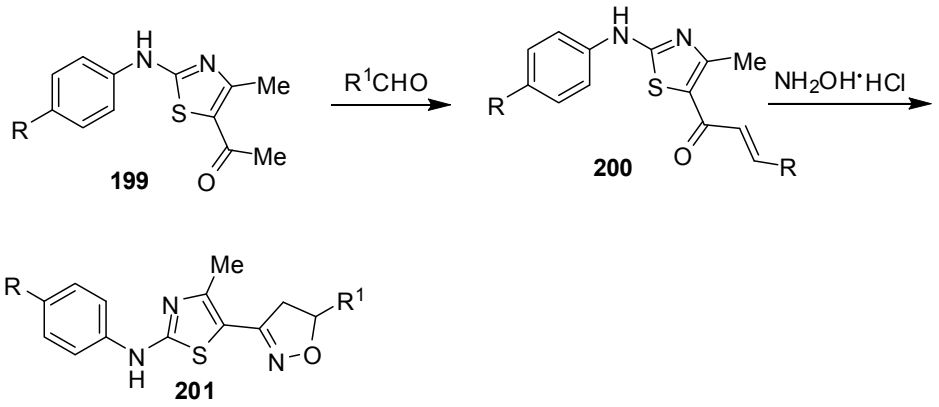
Bithiazole derivatives are prepared by coupling reaction of thiazole derivatives. Thus, a mixture of 2-(4-methoxyphenyl)thiazole **197**, $PdCl_2(PhCN)_2$, and DMSO was treated with AgF at 60 °C for 5 h to give 52,2'-bis(4-methoxyphenyl)-5,5'-bithiazole **198** in 83% yield (Scheme 55).[97]



Scheme 55

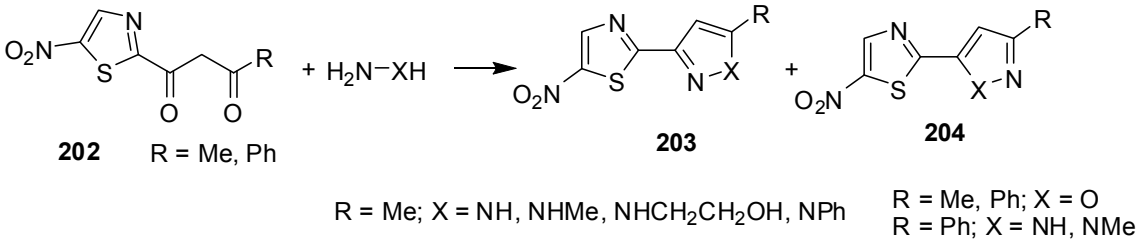
7. THIAZOLYLISOXAZOLES

The product of Claisen Schmidt condensation of 5-acetyl-2-arylamino-4-methylthiazoles **199** reacted with hydroxyl amine to give and thiazolylisoxazolines **201**. Some **201** were screened for fungicidal activity against Penicillium notatum (Scheme 56).[98,99]



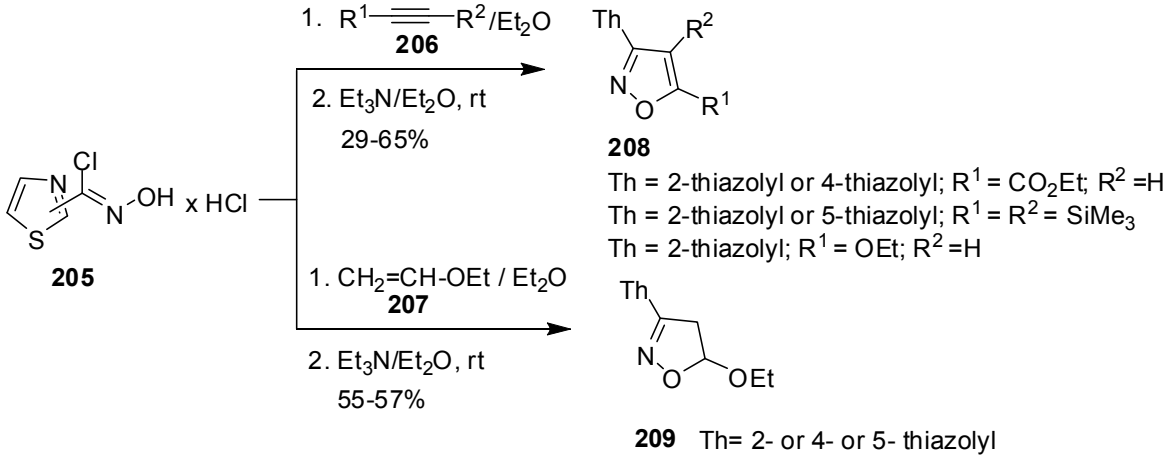
Scheme 56

1,3-Dicarbonyl compounds with a 5-nitro-2-thiazolyl moiety **202** reacted with substituted hydrazines or hydroxylamine to give 26-96% the title pyrazoles (**203**, **204** X = NH) or isoxazoles (**203**, **204** X = O). Some **203** have good antimicrobial activity (Scheme 57).[100]



Scheme 57

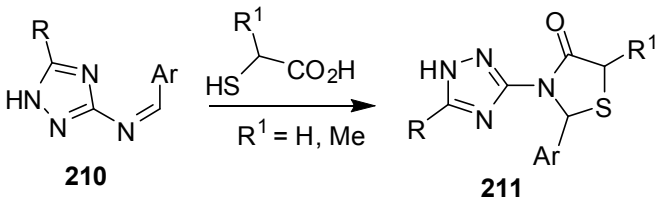
The hydroxamoyl chlorides **205** react with acetylenes **206** and alkene **207** dipolarophiles to give regioselective 3-thiazolylisoxazoles **208** and 3-thiazolylisoxazolines **209** in moderate to good yields (Scheme 58).[101]



Scheme 58

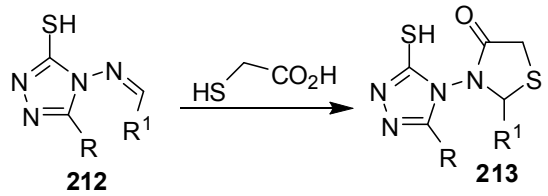
8. TRIAZOLYLTHIAZOLES

3-(1,2,4-Triazol-3-yl)-4-thiazolidinone derivatives **211**, showed antibacterial and antifungal activities, have been synthesized by the reaction of Schiff bases of 3-amino-1,2,4-triazoles **210** with mercaptoacetic acid and 2-mercaptopropionic acid (Scheme 59).[102,103]



Scheme 59

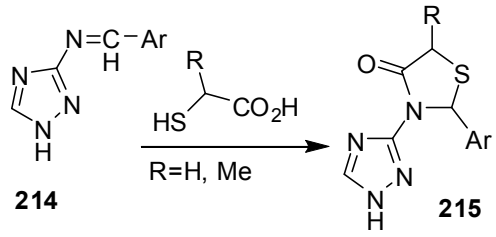
Also, 3-(5'-aryl-3'-mercapto-1',2',4'-triazol-4'-yl)-2-aryl-4-thiazolidinones **213** were prepared by the cyclocondensation of mercaptoacetic acid and anils **212** (Scheme 60).[104]



R = 2-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 2-MeC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 4-HOC$_6$H$_4$
R^1 = 2-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$

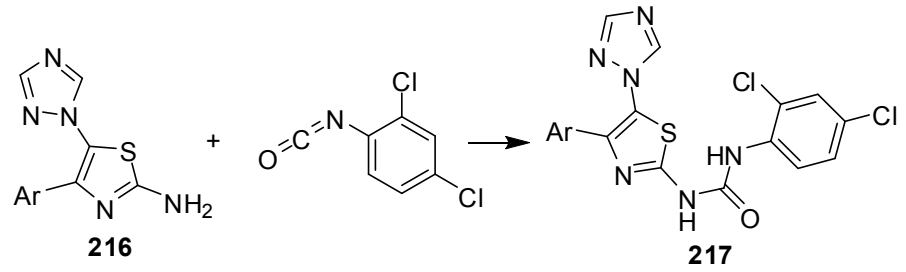
Scheme 60

3-(1,2,4-Triazol-3-yl)-4-thiazolidinone derivatives **215** has been synthesized by the reaction of Schiff bases of 3-amino-1,2,4-triazoles **214** with mercaptoacetic acid and 2-mercaptopropionic acid (Scheme 61).[102]



Scheme 61

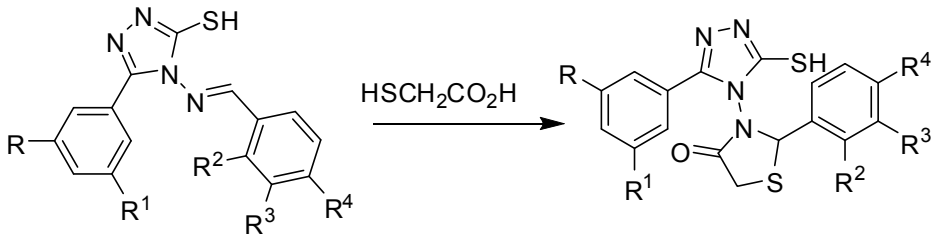
1-(2,4-Dichlorophenyl)-3-[4-aryl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl]urea derivatives **217** were synthesized by the reaction of 2-amino-4-(substituted phenyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazoles **216** with 2,4-dichloro-1-isocyanatobenzene, the structure was confirmed by single crystal X-ray diffraction (Scheme 62).[105]



216 **217**

Scheme 62

3-(5'-Aryl-3'-mercapto-1',2',4'-triazol-4'-yl)-2-aryl-4-thiazolidinones **219**, have insecticidal activities, were prepared by cyclization of **218** with mercaptoacetic acid (Scheme 63).[104,106,107]

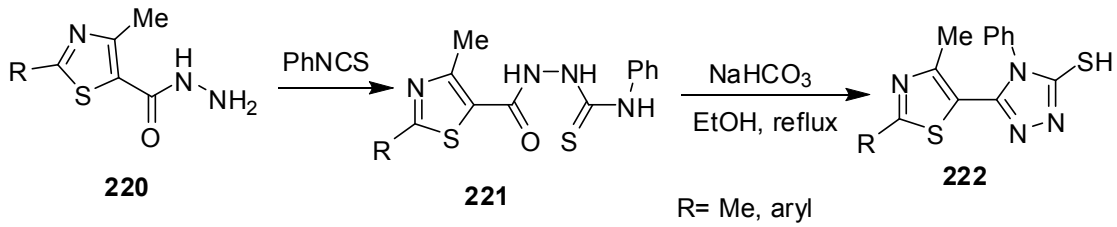


218 **219**

R = H, Me, Cl; R^1 = H, Cl, Me, NO_2, OH; R^2 = H, Cl; R^3 = H, MeO; R^4 = H, MeO, Cl

Scheme 63

Reaction of hydrazide **220** with phenyl isothiocyanate in ethanol and aqueous sodium hydroxide at room temperature gave compound **221**. Refluxing the latter compound with aqueous sodium bicarbonate afforded 4-alkyl(or phenyl)-5-(2,4-dimethyl-5-thiazolyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **222** (Scheme 64).[108,109]

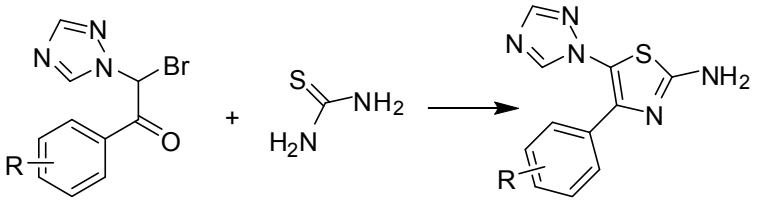


220 **221** **222**

R= Me, aryl

Scheme 64

Compounds **224** were synthesized from the reaction of α-bromo-substituted acetophenones **223** and thiourea by the Hantzsh reaction (Scheme 65).[110]

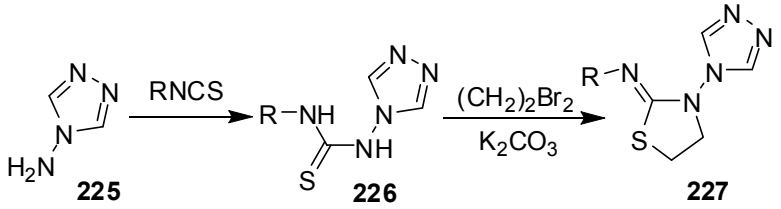


223 **224**

R=H, 4-F, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 4-OMe, 2,4-F_2, 2,4-Cl_2, 2,3,4,Cl_3

Scheme 65

Reaction of 1,2,4-triazol-4-amine **225** with arylisothiocyanates gave thioureas **226** which underwent cyclization with 1,2-dibromoethane in the presence of potassium carbonate to afford 1,2,4-triazol-4-ylthiazolidones **227** (Scheme 66).[111]

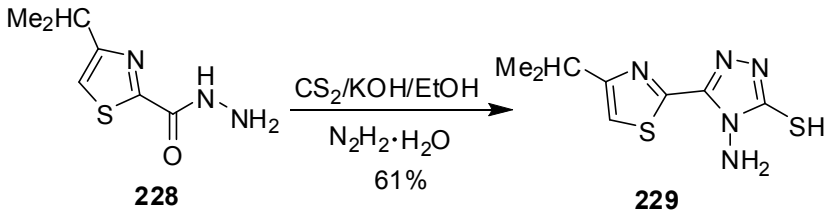


225 **226** **227**

R= 4-EtC_6H_4, 4-ClC_6H_4, 2-$MeOC_6H_4$, 2,4-$Me_2C_6H_3$

Scheme 66

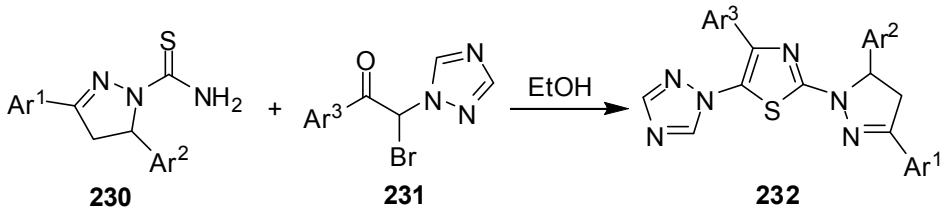
Reacting of 4-isopropylthiazole-2-carbahydrazide **228**, with carbon disulfide under strong basic conditions followed by cyclization with hydrazine hydrate yielded 4-amino-5-(4-isopropyl-1,3-thiazol-2-yl)-4*H*-1,2,4-triazole-3-thiol **229** (Scheme 67).[112]



228 **229**

Scheme 67

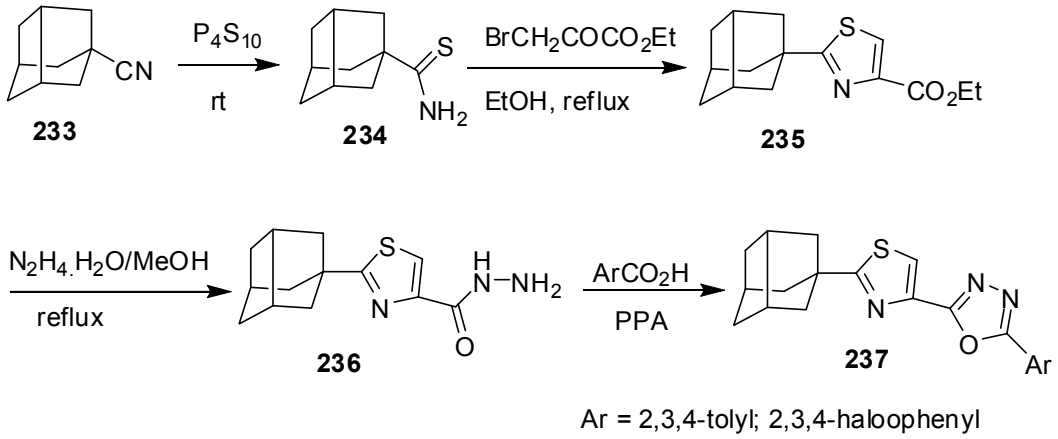
1-(4-Aryl-5-triazolyl-2-thiazolyl)-3,5-diaryl-2-pyrazolines **232** were synthesized by reacting 3,5-diaryl-1-thiocarbamoyl-2-pyrazolines **230** with 2-bromo-1-aryl-2-(1*H*-1,2,4-triazol-1-yl)ethanones **231** in boiling ethanol (Scheme 68).[113]



Scheme 68

9. THIAZOLYLOXADIAZOLES

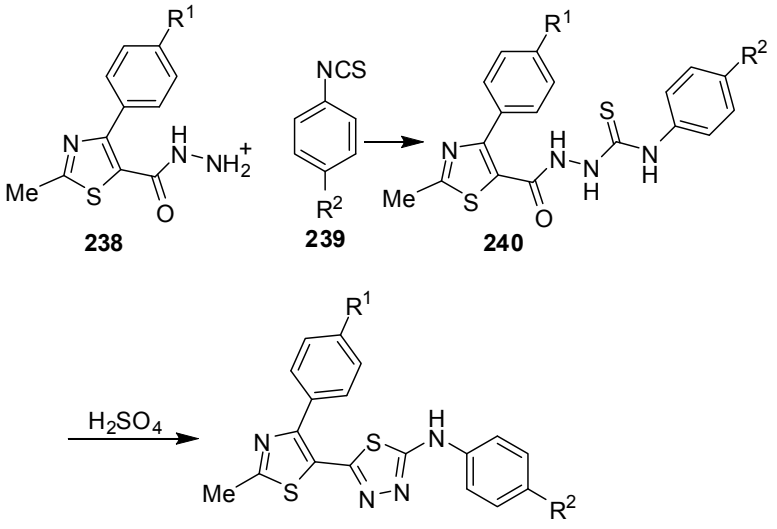
2-(2-Adamant-1-yl-1,3-thiazol-4-yl)-5-aryl-1,3,4-oxadiazoles **237** was synthesized from adamantane-1-nitrile **233** in 4 steps. Adamantan-1-nitrile **233** was converted into thioamide **234** (52%), using P_4S_{10} followed by its treatment with ethyl bromopyruvate to afford **235** (80%). Hydrazinolysis of **235** gave the carbohydrazide-1,3-thiazole **236** in 75% yield. Heating **236** with substituted benzoic acids in the presence of polyphosphoric acid (PPA) furnished 1,3,4-oxadiazole derivatives **237** in 61-66% yields (Scheme 69).[114]



Scheme 69

10. THIAZOLYTHIADIAZOLES

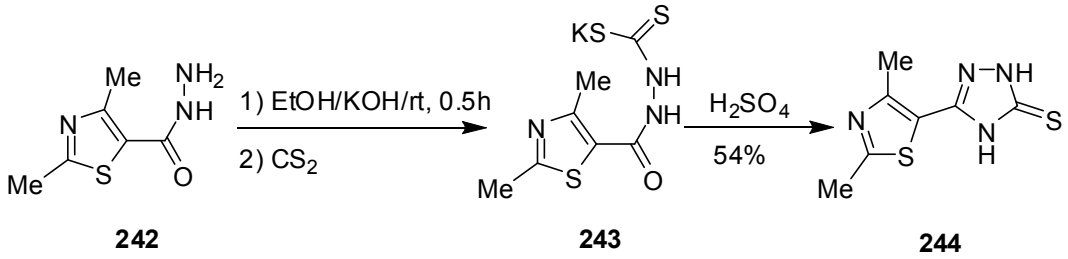
(Thiazolecarbonyl)thiosemicarbazides **238** were prepared and converted to thiadiazoles **241**, which exhibited fungicidal activity, by treatment with sulfuric acid (Scheme 70).[115]



R^1 = H, NO_2; R^2 = H, halo, Me, alkoxy

Scheme 70

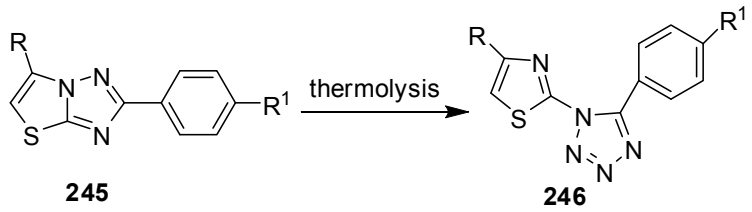
Stirring 2,4-dimethylthiazol-5-carbohydrazide **242** in ethanol and 85% potassium hydroxide for 30 min followed by addition of carbon disulphide gave potassium dithiocarbazate **243** which under ring closure gave 5-(2',4'-dimethylthiazole-5yl)-1,3,4-thiadiazole-2(3*H*)-thione **244** with 54% yield (Scheme 71).[83]



Scheme 71

11. TETRAZOLYLTHIAZOLES

Diarylthiazolotriazoles **246** were prepared by thermolysis of aryltetrazoles **245** (Scheme 72).[116]



R = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 2-BrC_6H_4; R^1 = H, Me, MeO, Cl, NO_2

Scheme 72

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