

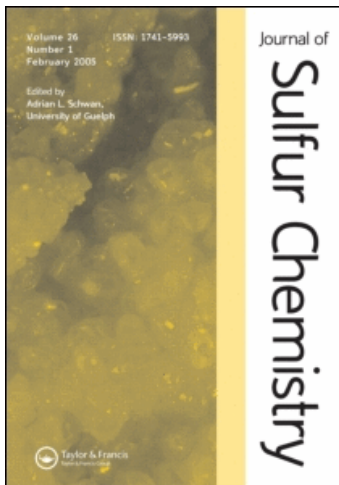
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2-Amino-4-thiazolidinones: synthesis and reactions

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REVIEW ARTICLE

2-Amino-4-thiazolidinones: synthesis and reactions

M.A. Metwally^{a*}, Abdelbasset A. Farahat^{b,c} and Bakr F. Abdel-Wahab^d

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Methods for the synthesis of 2-amino-4-thiazolidinones and their chemical properties are reviewed for the first time. 2-Amino-4-thiazolidinones are synthetically versatile substrates, as they can be used for the synthesis of a large variety of biologically active compounds, such as thiazolidihydropyrazoles, thiazolo-triazines, and thiazolotetrahydropyrimidones, and as a raw material for drug synthesis. The high reactivity of amino and active methylene groups next to the carbonyl of the thiazolidin ring represents useful targets for many organic reactions.

Keywords: thiazolidine; 5-ones; synthesis; reactions; applications

1. Introduction

Amino-4-thiazolidinones, or their tautomeric forms, named pseudothiohydantoin have encountered a prominent place in heterocyclic chemistry, due to the high practical value of these compounds, and the broad spectrum of their biological activities. For example, 2,4-dioxothiazolidine derivatives are useful as hypoglycemics and hypolipidemic agents (1), and as intermediates in the synthesis of antidiabetic drugs (2). Other compounds derived from 2-amino-4-thiazolidinones are used as anticancer agents (3, 4), antiproliferative (5), antiinflammatory (6), cardiotoxic (7), tuberculostatic (8, 9) and as dual 5-lipoxygenase and cyclooxygenase inhibitors with antiinflammatory activity (10). Despite this versatile importance, 2-amino-4-thiazolidinones have not been previously reviewed. The main purpose of this review is to present a survey of the chemistry of 2-amino-4-thiazolidinones and provide useful and up-to-date data for medicinal chemists.

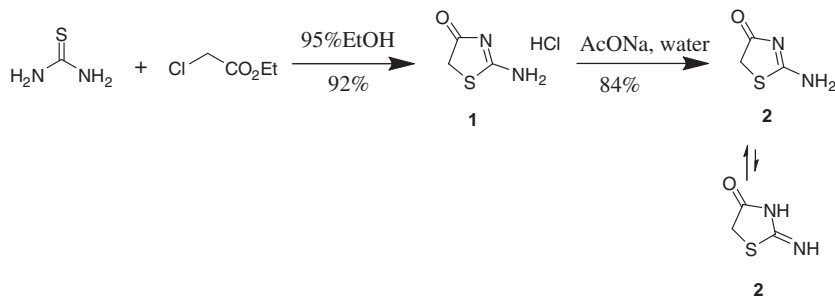
2. Synthesis of 2-amino-4-thiazolidinones

2.1. From α -halo carboxylic acid derivatives

2-Imino-4-thiazolidone HCl **1** was synthesized from ethyl chloroacetate and thiourea in 95% ethanol, neutralization in sodium acetate solution under reflux gave 2-imino-4-thiazolidone **2**

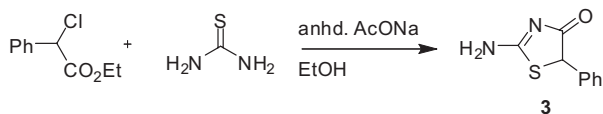
*Corresponding author. Email: mamegs@mans.edu.eg

(Scheme 1) (11–15).



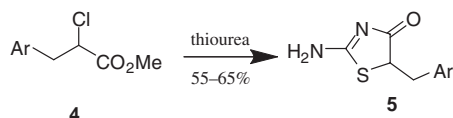
Scheme 1. Synthesis of 2-imino-4-thiazolidone.

5-Phenyl-2-amino-4-thiazolinone **3** has been synthesized from ethyl 2-chloro-2-phenylacetate, thiourea, and anhydrous sodium acetate in ethanol (Scheme 2) (16).



Scheme 2. Route to 5-Phenyl-2-amino-4-thiazolinone.

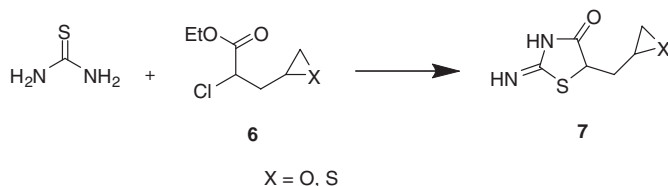
Treatment of 2-chloroesters **4** with thiourea afforded 2-aminothiazolidin-4-ones **5** (Scheme 3) (17, 18).



Ar=[2,4-(OEt)₂; 3,4-Me₂; 4-Cl-3-MeO; 3,5-(MeO)₂; 4-NHCOMe,3-MeO]phenyl

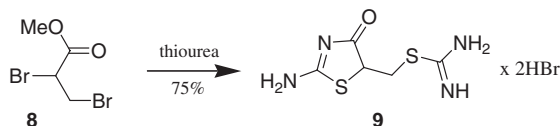
Scheme 3. Synthesis of 2-aminothiazolidin-4-ones.

Oxiranyl- and thiiranyl-substituted 2-imino-thiazolidine-4-ones **7** (Scheme 4) were prepared by refluxing thiourea with ethyl 2-chloro-3-(oxiran-2-yl)propanoate (**6**, X=O) or ethyl 2-chloro-3-(thiiran-2-yl)propanoate (**6**, X=S) (19).



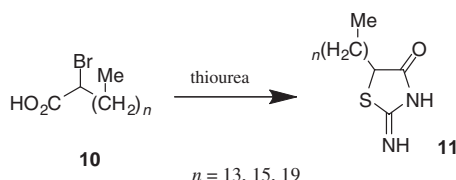
Scheme 4. Synthesis of substituted 2-imino-thiazolidine-4-ones.

2-[(2-Amino-4,5-dihydro-4-oxothiazol-5-yl)methyl]isothiurea **9** was obtained upon treatment of methyl 2,3-dibromopropanoate **8** with thiourea (Scheme 5) (19).



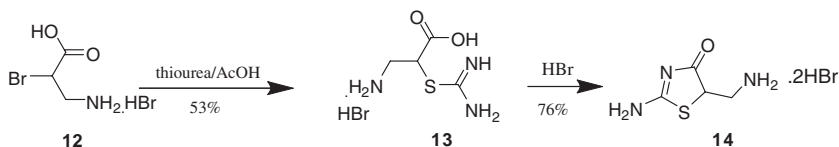
Scheme 5. Synthesis of isothiourea.

Long-chain-substituted 2-imino-4-thiazolidinones and 2,4-thiazolidinediones **11** were prepared in about 80% yield by condensation of α -bromo-carboxylic acids **10** with thiourea (Scheme 6) (20).



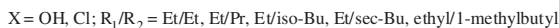
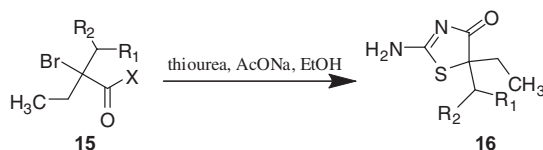
Scheme 6. Synthesis of 2-imino(oxa)-4-thiazolidinones.

Reaction of 2-bromo-3-aminopropionic acid **12** with thiourea in AcOH gave 53% thiourea derivative **13**, which upon treatment with HBr gave 76% thiazoline derivative **14** (Scheme 7) (21).



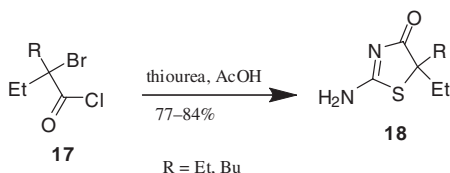
Scheme 7. Synthesis of thiazoline derivative.

5,5-Dialkyl-2-imino-4-thiazolidinones **16** were prepared by condensing thiourea with dialkyl-substituted bromoacetic acids or the acid chlorides **15** (Scheme 8) (22).



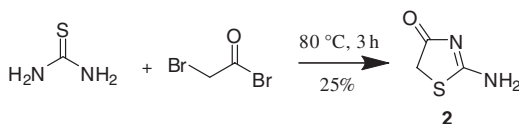
Scheme 8. Synthesis of 5,5-dialkyl-2-imino-4-thiazolidinones.

5,5-Disubstituted-2-imino-4-thiazolidinones **18** were prepared by refluxing of α -bromoacid chlorides **17** with thiourea in glacial acetic acid (Scheme 9) (23).



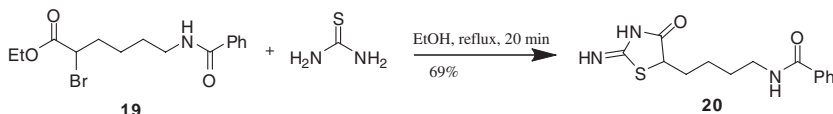
Scheme 9. Synthesis of 5,5-disubstituted-2-imino-4-thiazolidinones.

Reaction of α -bromo acetyl bromide and thiourea afforded 2-amino-4-thiazolidinone **2** in 25% yield (Scheme 10) (24).



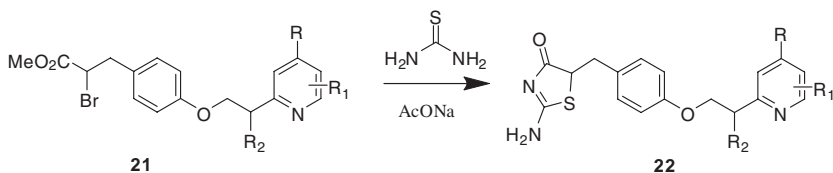
Scheme 10. Route to 2-amino-4-thiazolidinone **2**.

Refluxing ethyl 6-(benzamido)-2-bromohexanoate **19** with thiourea in ethanol gave the iminothiazolidinone **20** (Scheme 11) (25).



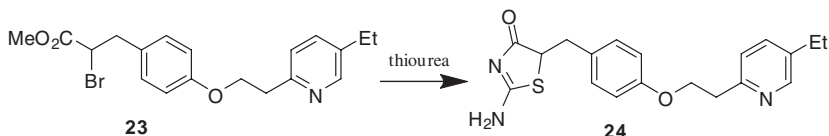
Scheme 11. Synthesis of iminothiazolidinone.

The synthesis of 5-[4-(pyridylalkoxy)benzyl]-2,4-thiazolidinediones **22**, which have hypoglycemic and hypolipidemic activities, was described. Thus treatment of α -bromoesters **21** with thiourea in the presence of sodium acetate afforded 2-amino-4-thiazolidinones **22** (Scheme 12) (26).



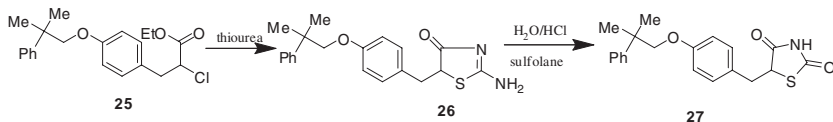
Scheme 12. Synthesis of 2-amino-4-thiazolidinones.

α -Bromoester **23** underwent cyclocondensation with thiourea to give the imino compound **24** (Scheme 13) (27).



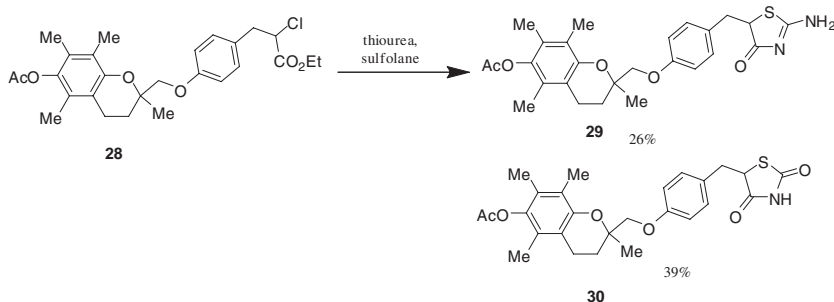
Scheme 13. Synthesis of imino compound.

Ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate **25** was condensed with thiourea followed by hydrolysis using HCl to give 5-[4-(2-methyl-2-phenylpropoxy)benzyl]thiazolidine-2,4-dione **27** which possess hypoglycemic and hypolipidemic activities (Scheme 14) (28).



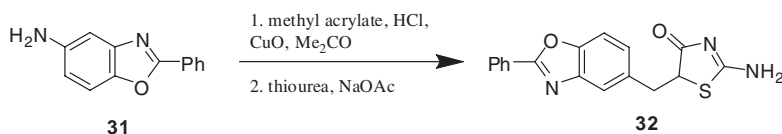
Scheme 14. Synthesis of (AL-321).

Reaction of α -haloester **28** with thiourea in the presence of sulfolane afforded 2-((4-((2-amino-4-oxo-4,5-dihydrothiazol-5-yl)methyl)phenoxy)methyl)-2,5,7,8-tetramethylchroman-6-yl acetate **29** and 2-((4-((2,4-dioxothiazolidin-5-yl)methyl)phenoxy)methyl)-2,5,7,8-tetramethylchroman-6-yl acetate **30** in 26% and 39% yields, respectively (Scheme 15) (29).



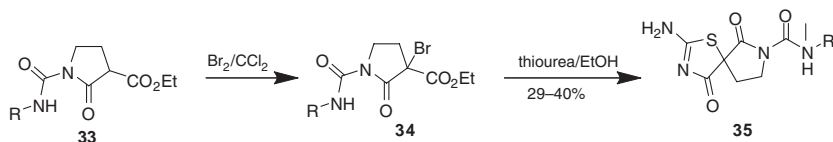
Scheme 15. Synthesis of tetramethylchroman-6-yl acetates.

2-Phenylbenzo[*d*]oxazol-5-amine **31** was converted to 2-amino-5-((2-phenylbenzo[*d*]oxazol-5-yl)methyl)thiazol-4(5*H*)-one **32**, upon treatment with methyl acrylate followed by reaction with thiourea (Scheme 16) (30).



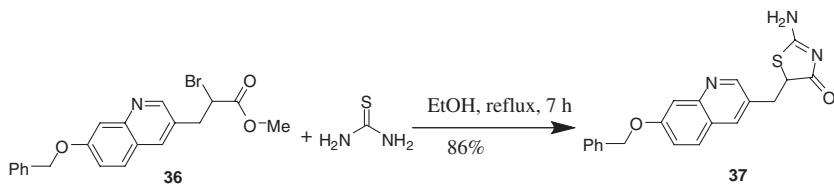
Scheme 16. Synthesis of thiazol-4(5*H*)-one.

1-Carbaniloyl-2-oxo-3-pyrrolidinecarboxylates **33** were brominated to give **34**. These underwent substitution and cyclization reactions with thiourea to give spiro[pyrrolidinethiazolidine] **35** in 29–40% yields (Scheme 17) (31).



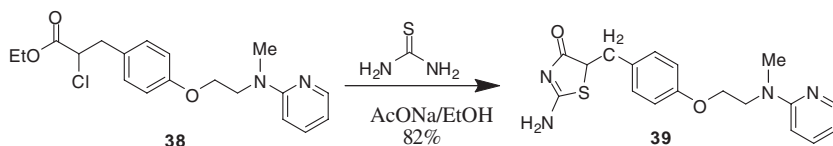
Scheme 17. Synthesis of spiro[pyrrolidinethiazolidine].

Methyl 3-(7-(benzyloxy)quinolin-3-yl)-2-bromopropanoate **36** was cyclocondensed with thiourea in the presence of AcONa in ethanol under reflux for 7 h to give 86% 2-imino-5-[(7-benzyloxy-3-quinolyl)methyl]thiazolidin-4-one **37** which has an antihyperglycemic effect (Scheme 18) (32).



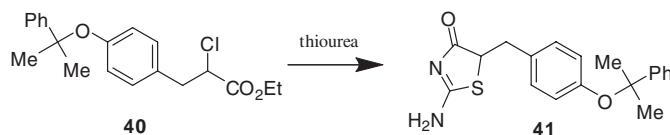
Scheme 18. Synthesis of thiazolidin-4-one.

2-Aminothiazol-4(5*H*)-one **39** was prepared in 82% by reaction of α -chloro-ester **38** with thiourea in ethanol in the presence of sodium acetate (Scheme 19) (33).



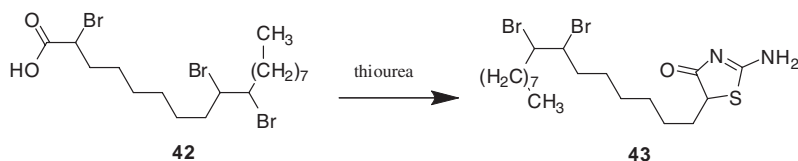
Scheme 19. Synthesis of 2-aminothiazol-4(5*H*)-one.

Thiazolidin-4-one **41** of hypoglycemic and hypolipidemic properties was prepared by treatment of ethyl 2-chloro-3-(4-(2-phenylpropan-2-yloxy)phenyl)propanoate **40** with thiourea (Scheme 20) (34).



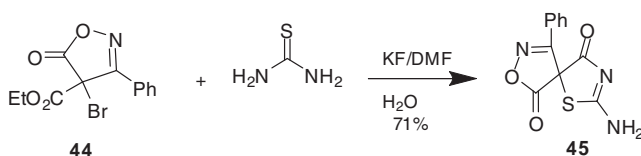
Scheme 20. Synthesis of thiazolidin-4-one.

Reaction between 2,9,10-tribromostearic acid **42** and thiourea afforded amino thiazolidinone **43** (Scheme 21) (35).



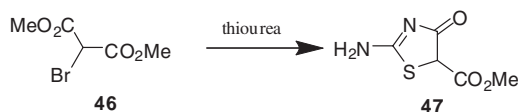
Scheme 21. Synthesis of aminothiazolidinone.

Reaction of ethyl 4-bromo-5-oxo-3-phenyl-4,5-dihydroisoxazole-4-carboxylate **44** with thiourea afforded 2-amino-9-phenyl-7-oxa-1-thia-3,8-diazaspiro[4.4]nona-2,8-diene-4,6-dione **45** (Scheme 22) (36).



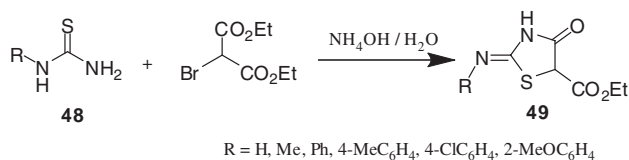
Scheme 22. Synthesis of 3,8-diazaspiro[4.4]nona-2,8-diene-4,6-dione.

α -Bromocarbonyl compound **46** reacted with thiourea to give thiazole derivative **47** (Scheme 23) (37).



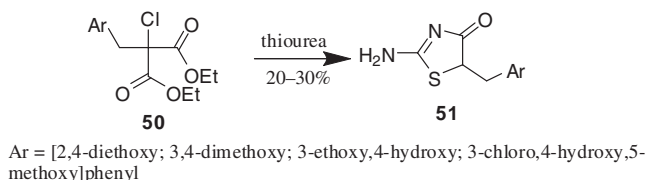
Scheme 23. Synthesis of thiazole derivative.

2-Alkyl/arylimino-5-carbomethoxythiazolidin-4-ones **49** have been synthesized by the interaction of thiocarbamides **48** with diethyl bromomalonate (Scheme 24) (38).



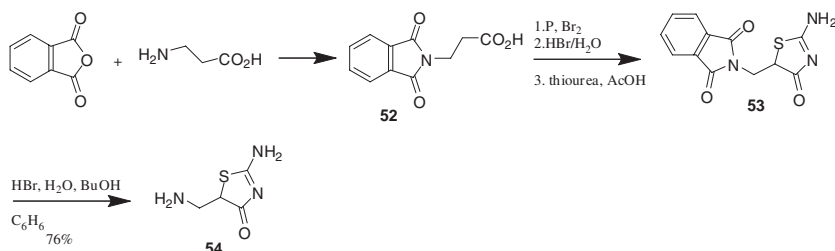
Scheme 24. Synthesis of 2-substituted imino-5-carbomethoxythiazolidin-4-ones.

Condensation of diethyl 2-chloro-2-arylmethylmalonates **50** with thiourea afforded 2-aminothiazolidin-4-one derivatives **51** (Scheme 25) (17).



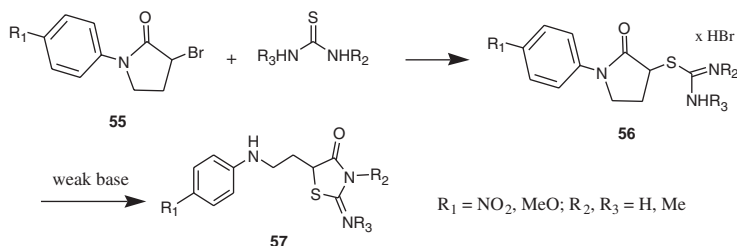
Scheme 25. Synthesis of 2-aminothiazolidin-4-one derivatives.

Phthalic anhydride was allowed to react with 3-aminopropanoic acid to give 3-(1,3-dioxoisindolin-2-yl)propanoic acid **52**, which upon bromination followed by reaction with thiourea afforded 2-[(2-amino-4-oxo-4,5-dihydrothiazol-5-yl)methyl]isindoline-1,3-dione **53**. Hydrolysis of **53** in the presence of hydrobromic acid gave 2-amino-5-(aminomethyl)thiazol-4(5*H*)-one **54** (Scheme 26) (21).



Scheme 26. Synthesis of 2-amino-5-(aminomethyl)thiazol-4(5*H*)-one.

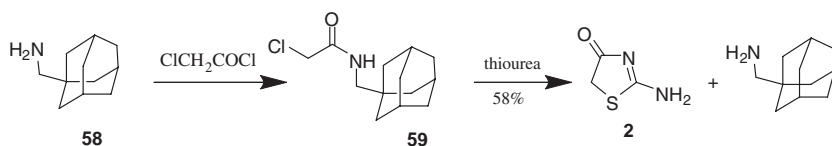
Substituted *S*-(1-phenylpyrrolidin-2-on-3-yl)isothiuronium salts **56** in weakly basic media underwent intramolecular recyclization reaction in which the γ -lactam cycle is split and a thiazolidine cycle **57** is formed (Scheme 27) (39–41).



Scheme 27. Synthesis of thiazolidine.

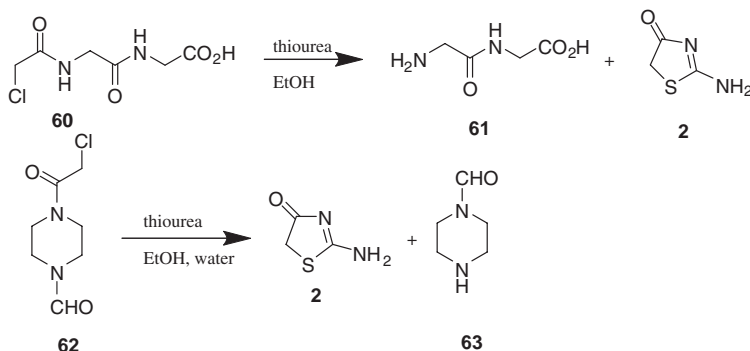
2.2. From chloroacetamides

Method for the removal of chloroacetyl groups is used for the preparation of 2-imino-4-thiazolidinone. Thus, 1-adamantyl methyl amine **58** was acylated with chloroacetyl chloride to give the corresponding amide **59**, which was then treated with thiourea to give 2-aminothiazol-4(5*H*)-one **2** in addition to the recovering of the starting material as a by-product (Scheme 28) (42).



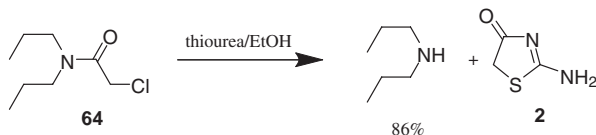
Scheme 28. Pathway to 2-aminothiazol-4(5*H*)-one.

2-(2-(2-Chloroacetamido)acetamido)acetic acid **60** was treated with thiourea to give a mixture of 2-(2-aminoacetamido)acetic acid **61** and 2-aminothiazol-4(5*H*)-one **2**. While 4-(2-chloroacetyl)piperazine-1-carbaldehyde **62** gave a mixture of piperazine-1-carbaldehyde **63** and 2-aminothiazol-4(5*H*)-one **2** (Scheme 29) (43).



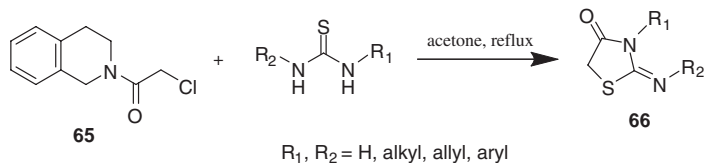
Scheme 29. Synthesis of 2-aminothiazol-4(5*H*)-one.

Condensation of 2-chloro-*N,N*-dipropylacetamide **64** with thiourea in ethanol gave 2-amino-4-thiazolidinone **2** as a side product (Scheme 30) (44, 45).



Scheme 30. Synthesis of amino-4-thiazolidinone.

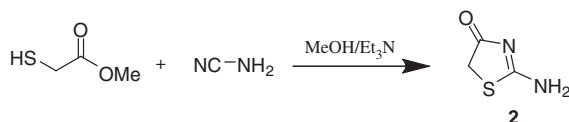
2-Imino-4-thiazolidinones **66** were prepared by reaction of thiourea derivatives with *N*-(2-chloroacetyl)tetrahydroisoquinoline **65** (Scheme 31) (46).



Scheme 31. Synthesis of 2-imino-4-thiazolidinones.

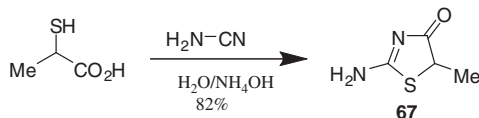
2.3. From cyanamide

Cyclocondensation of methyl 2-mercaptoacetate with cyanamide in methanol containing triethylamine afforded 2-amino-4-thiazolidinone **2** (Scheme 32) (47).



Scheme 32. Synthesis of 2-amino-4-thiazolidinone.

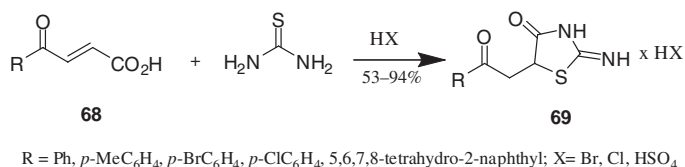
Heating thiolactic acid with cyanamide in water/ammonium hydroxide gave NH_3 gas and a precipitate of 82% 2-imino-4-oxo-5-methylthiazolidine **67** (Scheme 33) (48).



Scheme 33. Synthesis of 2-imino-4-oxo-5-methylthiazolidine.

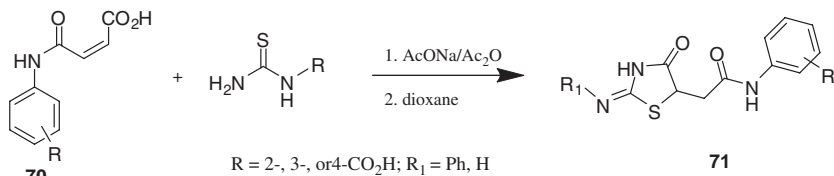
2.4. From α,β -unsaturated carboxylic acids

Single-stage synthesis of 5-arylmethyl-2-iminothiazolidin-4-ones **69** was achieved by reaction between β -aroylacrylic acids and thiourea. Thus, hydrochlorides, hydrobromides, and sulfates of **69** were prepared in good yields by cyclocondensation of β -aroylacrylic acids **68** with thiourea in the presence of the appropriate HX (Scheme 34) (49).



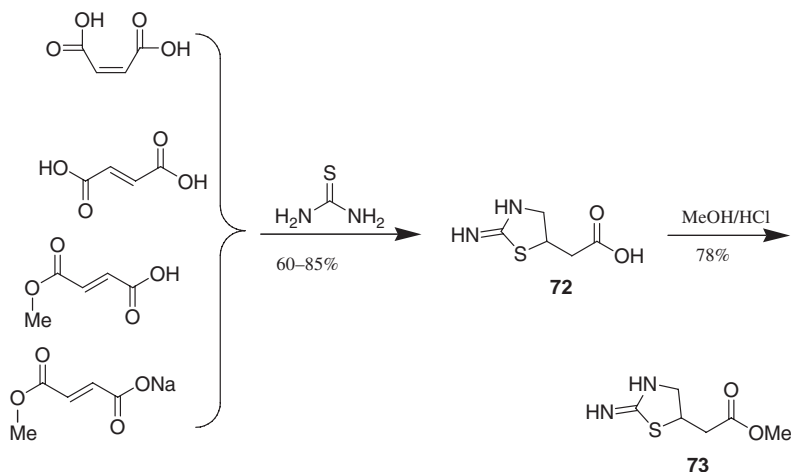
Scheme 34. Synthesis of sulfates.

N-(maleoylamino)benzoic acids **70** were treated with thiourea derivatives to give thiazolidines **71** (Scheme 35) (50).



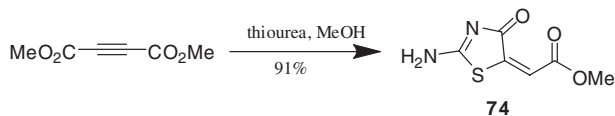
Scheme 35. Synthesis of thiazolidines.

Reactions of thiourea with, maleic acid, fumaric acid, methyl hydrogen fumarate, or its sodium salt give 2-imino-2,3,4,5-tetrahydro-1,3-thiazol-5-acetic acid **72**, its methyl ester **73** was prepared by heating in methanol in the presence of concentrated HCl (Scheme 36) (51).



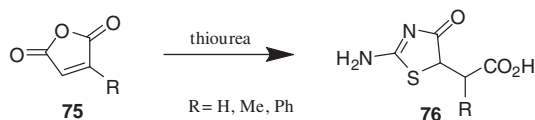
Scheme 36. Synthesis of methyl 1,3-thiazol-5-acetic acid ester.

Dimethyl acetylene-dicarboxylic esters (DMADCs) have been treated with thiourea to give (*E*)-methyl 2-(2-amino-4-oxothiazol-5(4*H*)-ylidene)acetate **74** (Scheme 37) (52, 53).

Scheme 37. Synthesis of (*E*)-methyl 2-(2-amino-4-oxothiazol-5(4*H*)-ylidene)acetate.

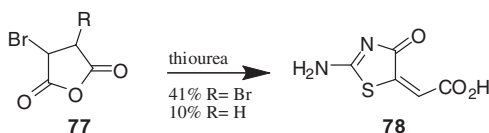
2.5. From anhydrides or imides

Maleic anhydrides **75** reacted with thiourea to give 1,3-thiazolidine **76** (Scheme 38) (51).



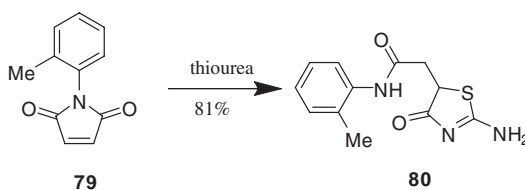
Scheme 38. Synthesis of 1,3-thiazolidine.

Reaction of 2,3-dibromosuccinic anhydride or bromomaleic anhydride **77** and thiourea gave (*E*)-2-(2-amino-4-oxothiazol-5(4*H*)-ylidene)acetic acid **78** (Scheme 39) (54).



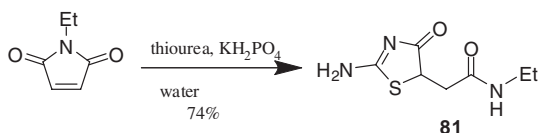
Scheme 39. Synthesis of (*E*)-2-(2-amino-4-oxothiazol-5(4*H*)-ylidene)acetic acid.

1-*o*-Tolyl-1*H*-pyrrole-2,5-dione **79** was reacted with thiourea to give 2-(2-amino-4-oxo-4,5-dihydrothiazol-5-yl)-*N*-*o*-tolylacetamide **80** in good yield (Scheme 40) (51).



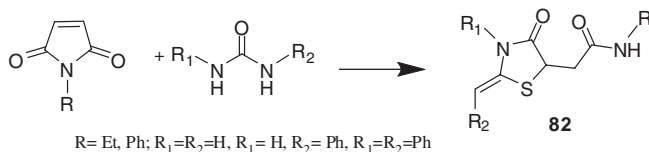
Scheme 40. Synthesis of 2-(2-amino-4-oxo-4,5-dihydrothiazol-5-yl)-*N*-*o*-tolylacetamide.

When a buffer solution of *N*-ethylmaleimide and thiourea was left for 2 days at room temperature, *N*-ethyl- α -(2-imino-4-oxothiazolidin-5-yl)acetamide **81** was obtained (Scheme 41) (55).



Scheme 41. Synthesis of *N*-ethyl- α -(2-imino-4-oxothiazolidin-5-yl)acetamide.

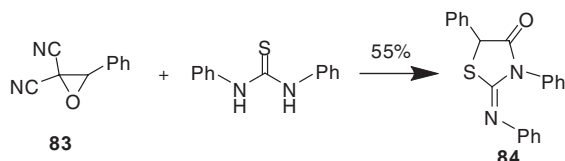
N-substituted maleimides were condensed with thiourea derivatives to give 4-thiazolidone derivatives **82** in 46–71% yields (Scheme 42) (56).



Scheme 42. Synthesis of 4-thiazolidone derivatives.

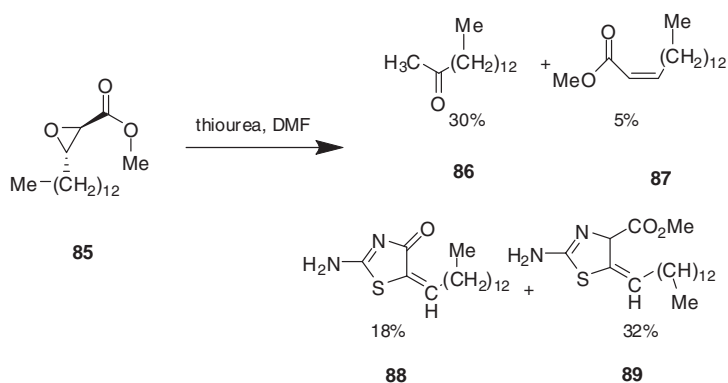
2.6. From epoxides

The nucleophilic ring opening of gem-dicyano epoxides by *N*-substituted or *N,N'*-disubstituted thioureas leads to 2-imino-4-thiazolidinones, via postulated cyanocarbonyl intermediates. Thus, reaction of 2,2-dicyano-3-phenyloxirane **83** and diphenylthiourea gave 55% diphenylthiazolidinone **84** (Scheme 43) (57).



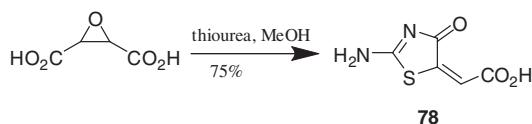
Scheme 43. Synthesis of diphenylthiazolidinone.

Methyl *E*-2,3-epoxyhexadecanoate **85** reacted with thiourea to give aminotridecylthiazolinecarboxylate **88** and tridecylmethylenethiazolinone **89** along with *Z*- and *E*-**86** and **87** (Scheme 44) (58).



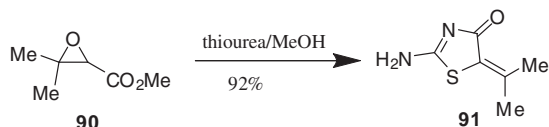
Scheme 44. Synthesis of thiazolinecarboxylate and thiazolinone.

The reaction of *Z*-methyleneepoxysuccinic acid with thiourea gave 2-imino-4-oxothiazolidine **78** (Scheme 45) (59).



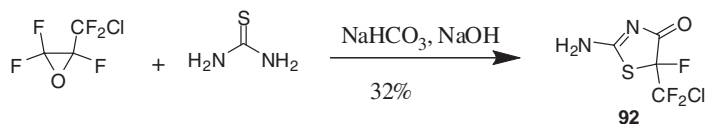
Scheme 45. Synthesis of 2-imino-4-oxothiazolidine.

Ethylene oxide **90** and thiourea in MeOH, kept for 2 weeks at 30 °C, gave 2-amino-4-keto-5-isopropylidene-2-thiazoline **91** in 92% yield (Scheme 46) (60).



Scheme 46. Synthesis of 2-amino-4-keto-5-isopropylidene-2-thiazoline.

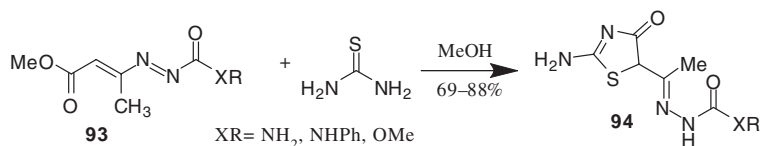
Reactions of 3-chloropentafluoropropene-1,2-oxide with thiourea gave 2-amino-5-(chlorodifluoromethyl)-5-fluorothiazol-4(5*H*)-one **92** (Scheme 47) (61).



Scheme 47. Synthesis of 5-fluorothiazol-4(5H)-one.

2.7. From azoalkenes

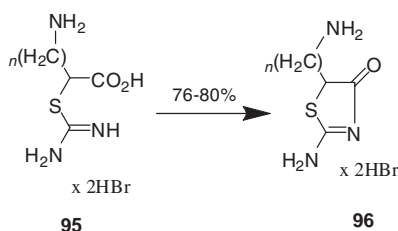
Thiourea easily reacted under very mild conditions with some conjugated azoalkenes **93** in a one-pot reaction to give 39–88% of substituted thiazolinones **94** that frequently exhibited hydrazono-hydrazino tautomerism in the chain at position 5 of the ring. The chemical structure was confirmed by x-ray diffraction (Scheme 48) (62).



Scheme 48. Synthesis of substituted thiazolinones.

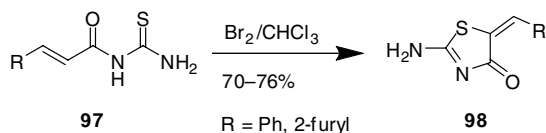
2.8. From isothioureia derivatives

2-Amino-4-oxo-5-aminomethyl(ethyl)thiazolines, which have radioprotective activity, were synthesized. 2-Amino-4-oxo-5-aminomethyl-2-thiazoline dihydrobromide (**96**, $n = 0$) and 2-amino-4-oxo-5-aminoethyl-2-thiazoline dihydrobromide (**96**, $n = 1$) were prepared by cyclization of *S*-(1-carboxy-2-aminoethyl)isothioureia (**95**, $n = 0$) and *S*-(1-carboxy-3-aminopropyl)isothioureia (**95**, $n = 1$), respectively (Scheme 49) (63).



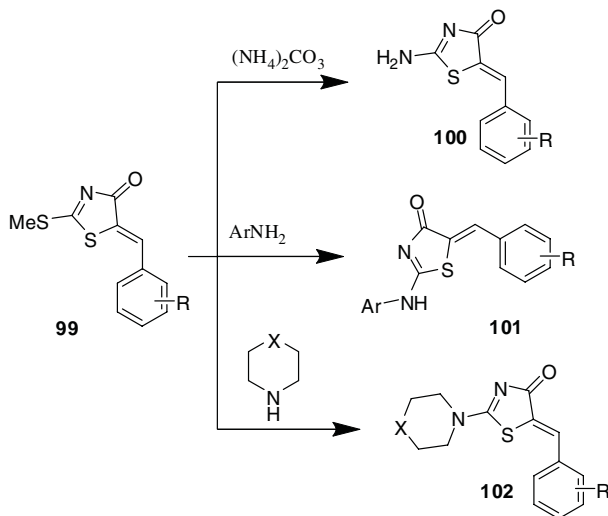
Scheme 49. Synthesis of 2-thiazoline.

Synthesis of 2-substituted *E*-5-arylidenthiazolin-4-ones **98** from α,β -unsaturated acyl isothiocyanates was reported. Thus, propenylthioureas **97** were oxidized with bromine in chloroform to *E*-5-arylidenthiazolin-4-ones **98** (Scheme 50) (64).

Scheme 50. Synthesis of *E*-5-arylidenthiazolin-4-ones.

2.9. From 2-(alkylthio)-2-thiazolin-4-ones

Reactions of *E*-5-(arylmethylene)-2-(alkylthio)-2-thiazolin-4-ones **99** with ammonium carbonate were reported to give **100** while reaction with aromatic primary amine and secondary amines afforded **101** and **102** (Scheme 51) (65).



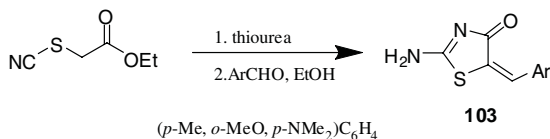
R = 2-Cl, 4-Cl, 2-MeO, 3-MeO, 4-MeO;

Ar = H, 4-MeC₆H₄, 4-MeOC₆H₄, PhCH₂, 4-MeC₆H₄CH₂, 4-MeOC₆H₄CH₂; X = CH₂, O

Scheme 51. Synthesis of *E*-5-(arylmethylene)-2-thiazolin-4-ones.

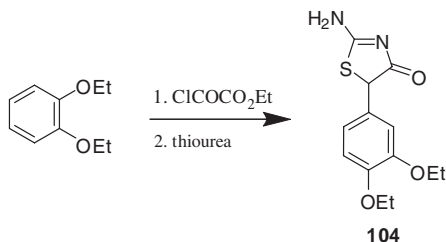
2.10. Miscellaneous methods

Reaction of ethyl thiocynoacetate with aromatic aldehydes in the presence of thioureas afforded *E*-5-arylidene-2-imino-4-thiazolidinones **103** (Scheme 52) (66).



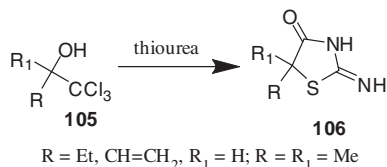
Scheme 52. Synthesis of *E*-5-arylidene-2-imino-4-thiazolidinones.

2-Iminothiazolidin-4-one **104** derivative was prepared in two steps. 1,2-Diethoxybenzene was condensed with ethyl (chlorocarbonyl)formate followed by thiourea (Scheme 53) (67).



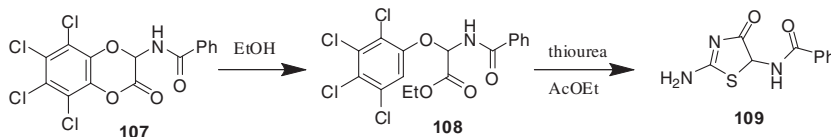
Scheme 53. Synthesis of 2-iminothiazolidin-4-one.

The reaction of ethyl-, vinyl-(trichloromethyl)carbinols **105** with aqueous thiourea was reported. Thus, **105** and alkaline thiourea gave 27–66% of the corresponding 2-imino-4-thiazolidinones **106** (Scheme 54) (68).



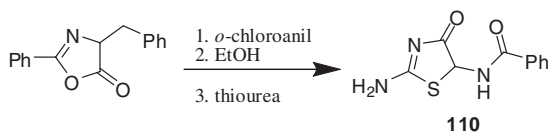
Scheme 54. Synthesis of 2-imino-4-thiazolidinones.

Tetrachlorobenzodioxinone **107** reacted with ethanol to give ethyl 2-benzamido-2-(2,3,4,5-tetrachlorophenoxy)acetate **108** and reacted with thiourea to give *N*-(2-amino-4-oxo-4,5-dihydrothiazol-5-yl)benzamide **109** (Scheme 55) (69).



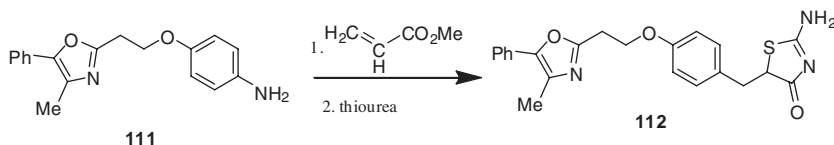
Scheme 55. Synthesis of 4,5-dihydrothiazol-5-yl)benzamide.

N-(2-amino-4-oxo-4,5-dihydrothiazol-5-yl)benzamide **110** was prepared by reaction of 4-benzyl-2-phenyloxazol-5(4*H*)-one with chloroanil followed by thiourea (Scheme 56) (69).



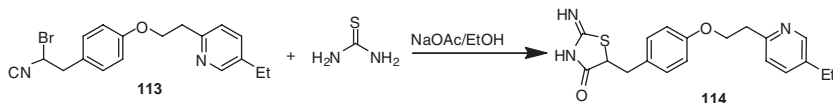
Scheme 56. Synthesis of *N*-(4,5-dihydrothiazol-5-yl)benzamide.

5-(4-Hydroxybenzyl)-2,4-dioxothiazolidine derivatives, which are useful as hypoglycemic and hypolipidemic agents, were prepared. Thus 4-(2-(4-methyl-5-phenyloxazol-2-yl)ethoxy)aniline **111** was reacted with methyl acrylate and thiourea to give aminothiazolidinone **112** (Scheme 57) (1).



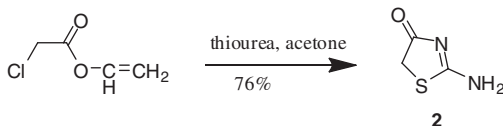
Scheme 57. Synthesis of aminothiazolidinone.

2-Bromo-3-[4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl]propionitrile **113** was refluxed for 6 h with thiourea and sodium acetate in ethanol to give 59% yield of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2-imino-4-thiazolidinone **114** (Scheme 58) (70).



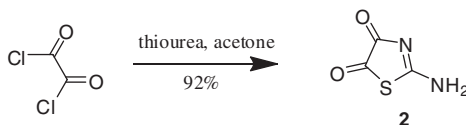
Scheme 58. Synthesis of 2-imino-4-thiazolidinone.

Vinyl 2-chloroacetate underwent nucleophilic displacement with thiourea to give 2-aminothiazol-4(5*H*)-one **2** (Scheme 59) (71).



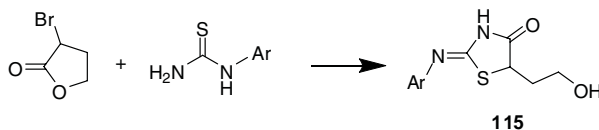
Scheme 59. Reaction of vinyl 2-chloroacetate with thiourea.

The reaction of thiourea with oxalyl chloride permits the preparation of 2-aminothiazolidin-4-one **2** (Scheme 60) (72).



Scheme 60. Reaction of thiourea with oxalyl chloride.

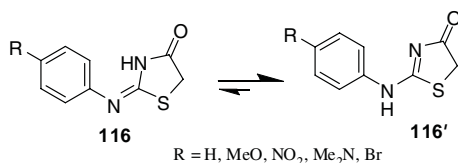
The synthesis of substituted 5-(2-hydroxyethyl)-2-phenylimino-1,3-thiazolidin-4-ones **115** is described, starting from phenylthioureas and 3-bromotetrahydrofuran-2-one under mild conditions (Scheme 61) (73).



Scheme 61. Synthesis of 1,3-thiazolidin-4-ones.

3. Imino-amino tautomerism

Ramsh *et al.* (74) reported that 2-imino-4-thiazolinone and its 2-aryl derivatives **116** exist in the crystal state as the amino tautomers (Scheme 62).

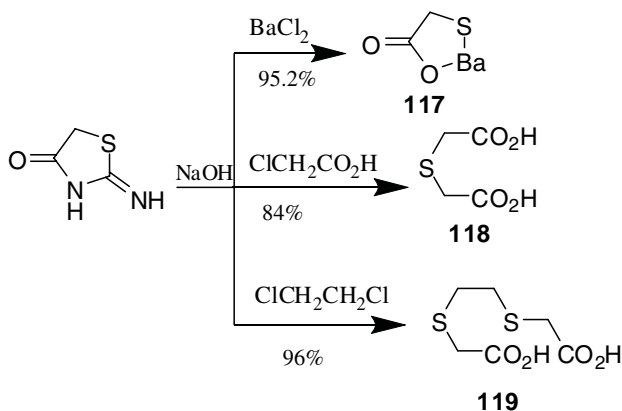


Scheme 62. Tautomerization of 2-imino-4-thiazolinone.

4. Reactions

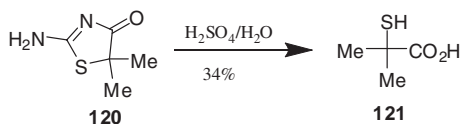
4.1. Ring cleavage

2-Imino-4-thiazolidinone **2** was cleaved with aqueous sodium hydroxide. Treatment of the product with barium chloride, chloroacetic acid, or 1,2-dichloroethane gave barium 2-sulfidoacetate **117**, 2,2'-thiodiacetic acid **118**, and 2,2'-(ethane-1,2-diylbis(sulfanediy))diacetic acid **119**, respectively (Scheme 63) (75).



Scheme 63. Reactivity of **2** towards barium chloride, chloroacetic acid, and 1,2-dichloroethane.

2-Amino-5,5-dimethylthiazol-4(5*H*)-one **120** underwent ring cleavage when heated with aqueous sulfuric acid to give 2-mercapto-2-methylpropanoic acid **121** (Scheme 64) (76).



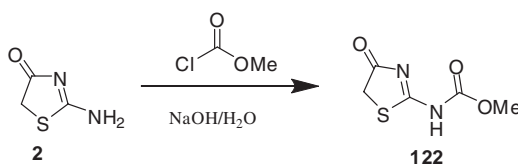
Scheme 64. Hydrolysis of 2-amino-5,5-dimethylthiazol-4(5*H*)-one.

4.2. Hydrolysis

2-Amino-5-ethylidenethiazol-4(5*H*)-ones underwent acid hydrolysis to give thiazolidin-2,4-dione which showed diverse biological activities (1, 11, 68, 77–88).

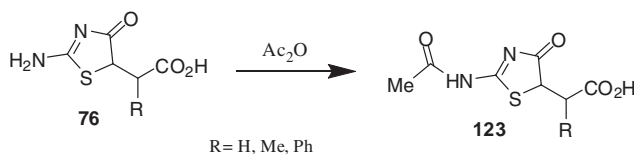
4.3. Acylation

Thiazolidinone **2** was acylated with methyl chloroformate to yield methyl 4,5-dihydro-4-oxothiazol-2-ylcarbamate **122** (Scheme 65) (89).



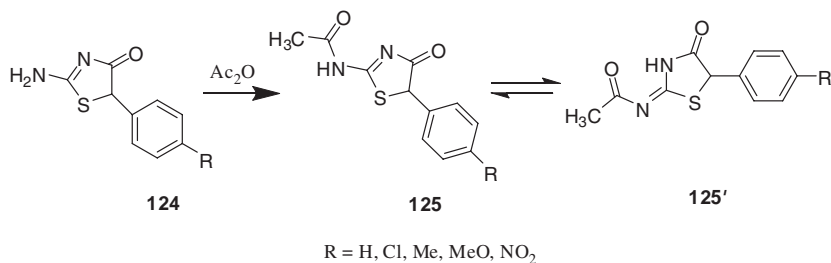
Scheme 65. Reaction of **2** with methyl chloroformate.

Acetylation of 2-aminothiazolidin-4-one **76** with acetic anhydride gave *N*-acetyl derivative **123** (Scheme 66) (90).



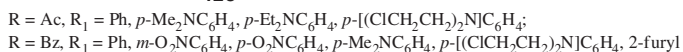
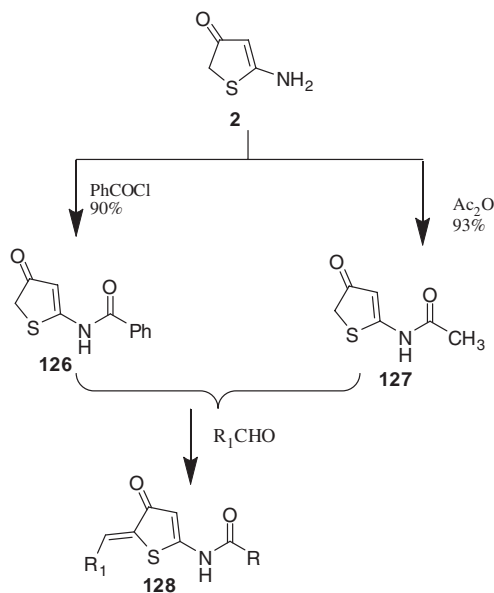
Scheme 66. Acetylation of 2-aminothiazolidin-4-one.

Acetyliminothiazolidinones **125** were prepared in high yields by acetylation of **124**, which exist in tautomeric equilibrium with 2-amino-4-hydroxythiazolines **125** (Scheme 67) (91).



Scheme 67. Formation of 2-amino-4-hydroxythiazolines.

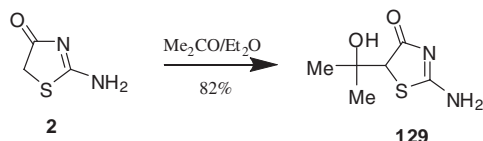
Acetylation or benzoylation of pseudothiohydantoin gave **126** and **127**. The reaction of **127** with the corresponding aldehyde gave **128** that had tuberculostatic activity (Scheme 68) (8, 9).



Scheme 68. Acylation of pseudothiohydantoin.

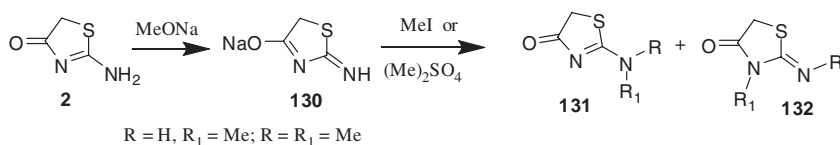
4.4. Alkylation

2-Amino-5-(2-hydroxypropan-2-yl)thiazol-4(5*H*)-one **129** was prepared in 82% yield by alkylation of 2-amino-4-thiazolidinone **2** with acetone (Scheme 69) (92).



Scheme 69. Alkylation of **2** with acetone.

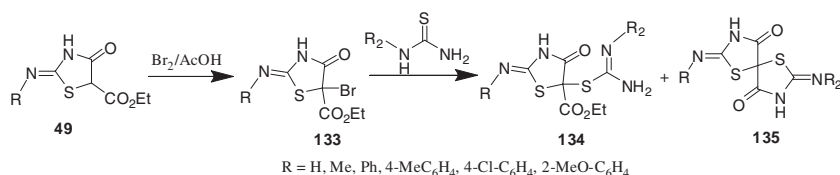
Methylation of 2-aminothiazol-4(5*H*)-one has been reported. Treatment of 2-amino-4-thiazolidinone **2** with sodium methoxide gave **130** which underwent alkylation with methyl iodide or dimethyl sulfate to give a mixture of **131** and **132** (Scheme 70) (93).



Scheme 70. Methylation of 2-amino-4-thiazolidinone **2**.

4.5. Bromination

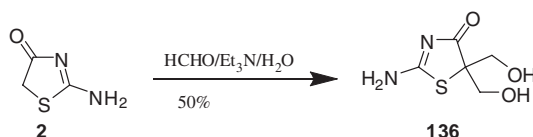
Bromination of 2-alkyl/arylimino-5-carbomethoxythiazolidin-4-ones **49** afforded 5-bromo derivatives **133**, which reacted with thiocarbamides to give 2-alkyl/arylimino-5-carbomethoxy-5-isothiocarbamidothiazolidin-4-ones **134** and 2,7-dialkyl/arylimino-3,8-diaza-1,6-dithiaspiro[4.4]nonane-4,9-diones **135** (Scheme 71) (94).



Scheme 71. Bromination of **49**.

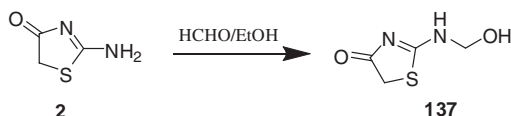
4.6. Reaction with formalin

2-Amino-5,5-bis(hydroxymethyl)-4-thiazolinone **136** was synthesized in 50% yield by treating pseudothiohydantoin **2** with formalin in the presence of catalytic amount of triethylamine (Scheme 72) (95).



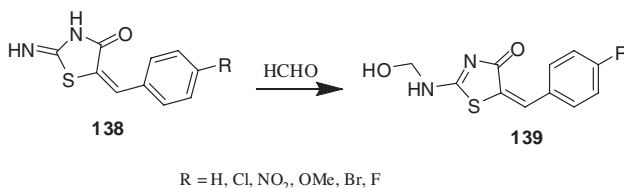
Scheme 72. Formation of 2-Amino-5,5-bis(hydroxymethyl)-4-thiazolinone.

2-[(Hydroxymethyl)amino]-4-thiazolinone **137** was prepared by reaction of 2-aminothiazol-4(5*H*)-one **2** with formalin (Scheme 73) (96).



Scheme 73. Formation of 2-[(Hydroxymethyl)amino]-4-thiazolinone **137**.

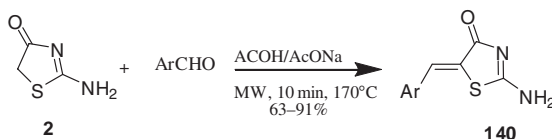
The hydroxymethylation of 2-imino-5-arylidene-thiazolidin-4-ones **138** has been reported to give (*E*)-5-arylidene-2-(hydroxymethylamino)thiazol-4(5*H*)-ones **139** (Scheme 74) (97, 98).



Scheme 74. Formation of (*E*)-5-arylidene-2-(hydroxymethylamino)thiazol-4(5*H*)-ones.

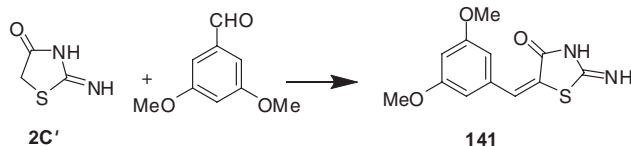
4.7. Knoevenagel condensation

5-Arylidene-2-imino-4-thiazolidinone derivatives **140** were synthesized, in 10 min with 63–91% yields, by the cross-aldol condensation of aromatic aldehydes with 2-amino-4-thiazolidinone **2** in sodium acetate/acetic acid under microwave irradiation (Scheme 75) (99).



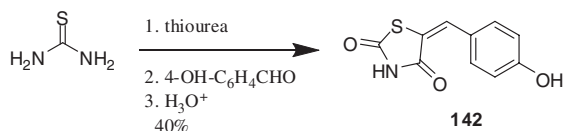
Scheme 75. Formation of 5-Arylidene-2-imino-4-thiazolidinone derivatives.

5-[(3,5-Dimethoxyphenyl)methylene]-2-imino-4-thiazolidinone **141** as an anti-inflammatory agent was synthesized from 3,5-dimethoxybenzaldehyde and **2'** via Knoevenagel condensation (Scheme 76) (6).

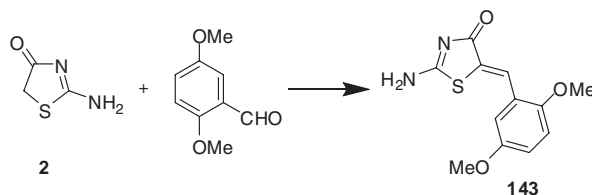


Scheme 76. Formation of 5-[(3,5-dimethoxyphenyl)methylene]-2-imino-4-thiazolidinone.

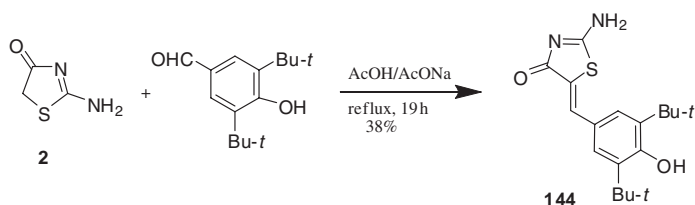
5-[(4-Hydroxy)-benzylidene]thiazolidine-2,4-dione **142** (an intermediate in synthesis of antidiabetic agents) was prepared from thiourea in four steps with overall yield of 40% (Scheme 77) (2).

Scheme 77. Formation of 5-[(4-Hydroxy)-benzylidene]thiazolidine-2,4-dione **142**.

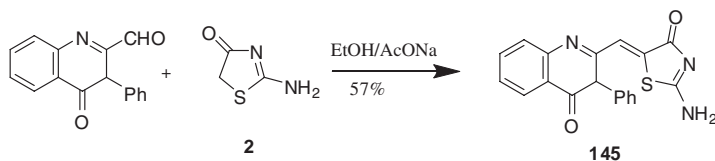
Treatment of 2-amino-4-thiazolidinone **2** with 2,5-dimethoxybenzaldehyde afforded the potential cardiotoxic Knoevenagel product **143** in 70% yield (Scheme 78) (7).

Scheme 78. Formation of Knoevenagel product **143**.

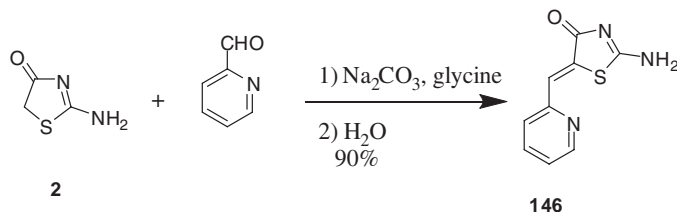
(5*Z*)-5-(3,5-Di-*tert*-butyl-4-hydroxybenzylidene)-2-aminothiazol-4(5*H*)-one **144** was prepared by Knoevenagel condensation of 2-amino-4-thiazolidinone **2** with 2,6-di-*tert*-butyl-4-formylphenol (Scheme 79) (100).

Scheme 79. Reaction of **2** with 2,6-di-*tert*-butyl-4-formylphenol.

Quinazolin-4(3)-ones bearing different 2-amino-4-thiazolidinone as potential antiinflammatory agent were reported. Thus the Knoevenagel condensation of 2-amino-4-thiazolidinone **2** with 3,4-dihydro-4-oxo-3-phenylquinoline-2-carbaldehyde led to (*Z*)-2-amino-5-((4-oxo-3-phenyl-3,4-dihydroquinolin-2-yl)methylene)thiazol-4(5*H*)-one **145** (Scheme 80) (101).

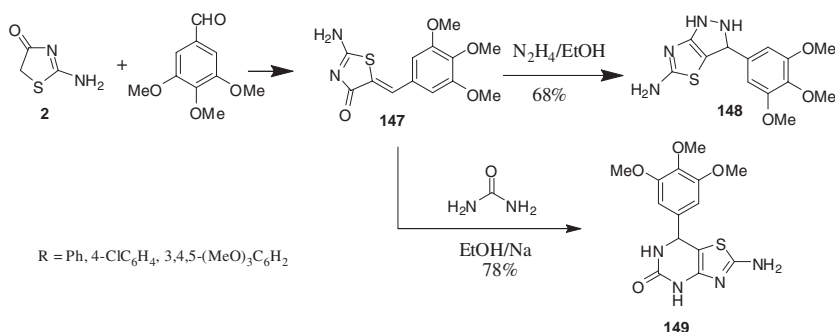
Scheme 80. Reaction of **2** with 3,4-dihydro-4-oxo-3-phenylquinoline-2-carbaldehyde.

Chowdhry *et al.* (102) reported the synthesis of bidentate ligand (*Z*)-2-amino-5-(pyridin-2-ylmethylene)thiazol-4(5*H*)-one **146** by condensation of 2-aminothiazol-4(5*H*)-one **2** with picolinaldehyde (Scheme 81).



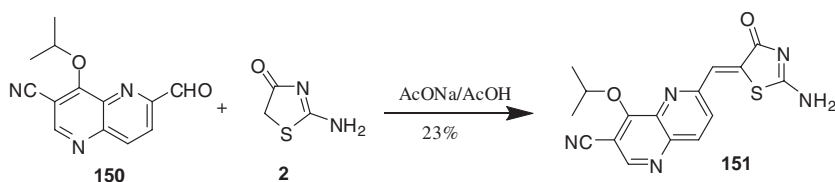
Scheme 81. Reaction of **2** with picolinaldehyde.

The arylidene derivatives **147** were also prepared through reaction of **2** with aromatic aldehydes. **147** Reacted with hydrazine hydrate and urea to give thiazolidihydropyrazole **148** and thiazolotetrahydropyrimidone **149**, respectively (Scheme 82) (102).



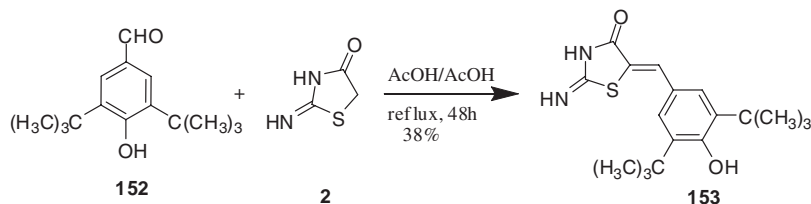
Scheme 82. Formation of thiazolidihydropyrazole and thiazolotetrahydropyrimidone.

Substituted 1,5-naphthyridine thiazolinones **151** reported to have antiproliferative and anti-cancer activities. 6-Formyl-4-isopropoxy-1,5-naphthyridine-3-carbonitrile **150** was condensed with 2-amino-4-thiazolidinone **2** to afford the Knoevenagel product **151** in 23% yield (Scheme 83) (5).

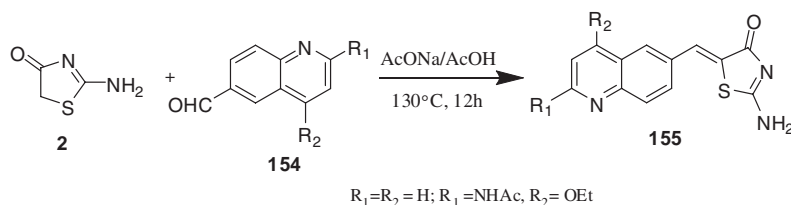


Scheme 83. Formation of 1,5-naphthyridine thiazolinones.

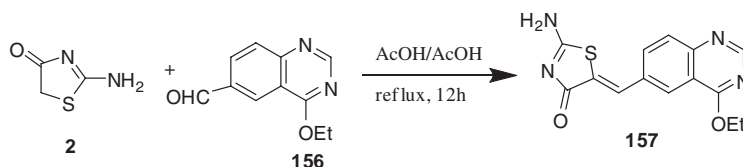
(*Z*)-5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-methylene]-2-imino-4-thiazolidinone **153** is useful as dual 5-lipoxygenase and cyclooxygenase inhibitors with antiinflammatory activity, and was prepared in 38% yield by reaction of 2-imino-4-thiazolidinone **2** with 3,5-di-tert-butyl-4-hydroxybenzaldehyde **152** (Scheme 84) (10).

Scheme 84. Reaction of **2** with 3,5-di-tert-butyl-4-hydroxybenzaldehyde.

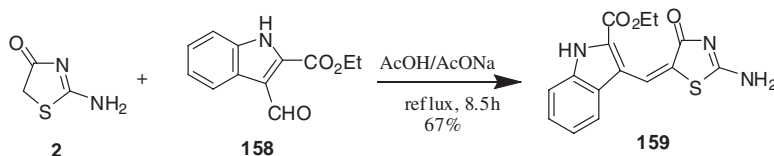
Quinolinyl-methylene-thiazolinones have been reported as potent and selective cyclin-dependent kinase 1 (CDK1) inhibitors. Thus, the Knoevenagel condensation of 2-amino-4-thiazolidinone **2** with quinoline-6-carbaldehyde derivatives **154** led (*Z*)-2-amino-5-((2,4-dialkylquinolin-6-yl)methylene)thiazol-4(*5H*)-one **155** (Scheme 85) (103, 104).

Scheme 85. Reaction of **2** with quinoline-6-carbaldehyde derivatives.

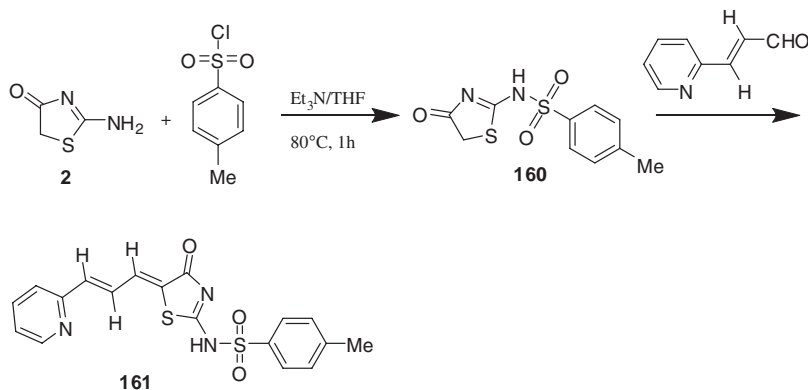
Quinazolinylmethylene thiazolinones as CDK1 inhibitors were prepared. Thus, the Knoevenagel condensation of 2-amino-4-thiazolidinone **2** with 4-ethoxyquinazolin-6-carbaldehyde **156** afforded stereo-selectively, (*5Z*)-2-amino-5-((4-ethoxyquinazolin-6-yl)methylene)thiazol-4(*5H*)-one **157** (Scheme 86) (105).

Scheme 86. Reaction of **2** with 4-ethoxyquinazolin-6-carbaldehyde.

Stereoselective synthesis of ethyl 3-[(9*E*)-(2-amino-4-oxothiazol-5(*4H*)-ylidene)methyl]-1*H*-indole-2-carboxylate **159** was achieved in 67% yield by condensation of ethyl 3-formyl-1*H*-indole-2-carboxylate **158** with 2-amino-4-thiazolidinone **2** under Knoevenagel conditions (Scheme 87) (106).

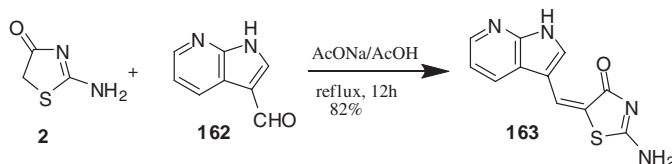
Scheme 87. Reaction of ethyl 3-formyl-1*H*-indole-2-carboxylate.

Thiazolone-based sulfonamides were prepared as inhibitors of nonstructural protein 5B polymerase. Thus, 4-methylbenzene-1-sulfonyl chloride was condensed with 2-amino-4-thiazolidinone **2** to afford sulfonamide **160**, that condensed with (*E*)-3-(pyridin-2-yl)acrylaldehyde under the Knoevenagel condition to give compound **161** (Scheme 88) (14).



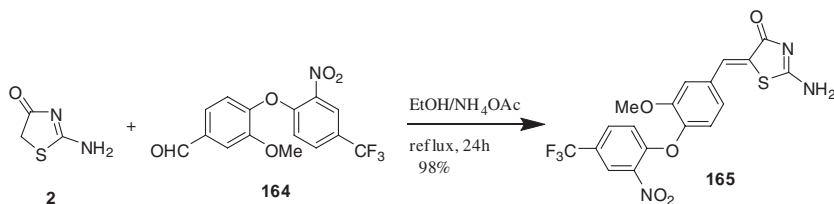
Scheme 88. Reaction of **2** with 4-methylbenzene-1-sulfonyl chloride.

(*5E*)-5-((1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)methylene)-2-aminothiazol-4(*5H*)-one **163** was prepared in 82% yield as anti-cancer agent by the Knoevenagel condensation of 2-amino-4-thiazolidinone **2** with 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde **162** (Scheme 89) (3).



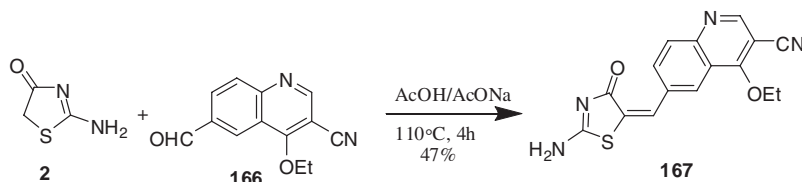
Scheme 89. Reaction of **2** with 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde.

Heterocyclic arylidene aryl ether compounds are useful for treating diseases or disorders mediated through modulation of estrogen-related alpha receptors. The Knoevenagel condensation of 2-amino-4-thiazolidinone **2** with 4-(4-(trifluoromethyl)-2-nitrophenoxy)-3-methoxybenzaldehyde **164** afforded (*5Z*)-5-(4-(4-(trifluoromethyl)-2-nitrophenoxy)-3-methoxybenzylidene)-2-aminothiazol-4(*5H*)-one **165** (Scheme 90) (107).



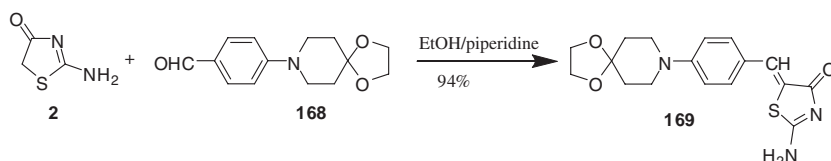
Scheme 90. Reaction of **2** with 4-(4-(trifluoromethyl)-2-nitrophenoxy)-3-methoxybenzaldehyde.

Thiazolinone 3,4-disubstituted quinolines as CDK1 inhibitors for treating cancer was reported. 6-((15*E*)-(2-Amino-4-oxothiazol-5(*4H*)-ylidene)methyl)-4-ethoxyquinoline-3-carbonitrile **167** was prepared by reaction of 2-amino-4-thiazolidinone **2** with 4-ethoxy-6-formylquinoline-3-carbonitrile **166** (Scheme 91) (4).



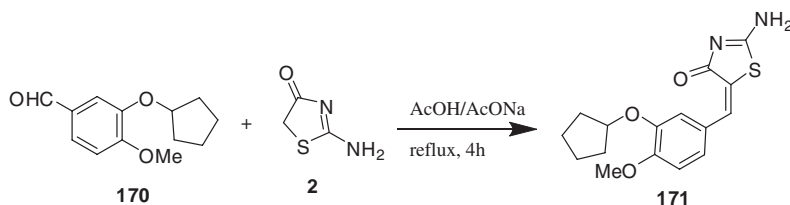
Scheme 91. Reaction of **2** with 4-ethoxy-6-formylquinoline-3-carbonitrile.

The Knoevenagel condensation between 4-(1,4-dioxo-8-azaspiro[4.5]dec-8-yl)benzaldehyde **168** and pseudothiohydantoin **2** afforded (Z)-5-(4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)benzylidene)-2-aminothiazol-4(5H)-one **169** in 94% yield as potent and selective human β_3 agonists (Scheme 92) (108, 109).



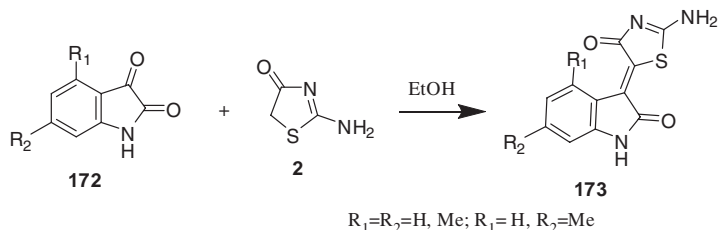
Scheme 92. Reaction of **2** with 4-(1,4-dioxo-8-azaspiro[4.5]dec-8-yl)benzaldehyde.

Synthesis and *in vitro* activity of rhodanine-based phosphodiesterase-4 (PDE4) inhibitors has been described. Knoevenagel condensation of 2-imino-4-thiazolidinone **2** with 3-(cyclopentyloxy)-4-methoxybenzaldehyde **170** in sodium acetate/acetic acid under refluxing conditions for 4 h afforded 5-(3-(cyclopentyloxy)-4-methoxybenzylidene)-2-aminothiazol-4(5H)-one **171** (Scheme 93) (110).



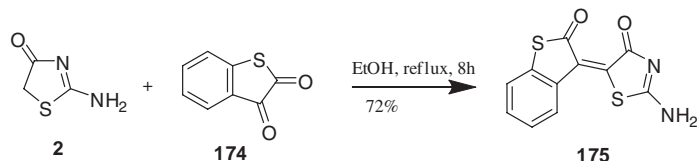
Scheme 93. Reaction of **2** with 3-(cyclopentyloxy)-4-methoxybenzaldehyde.

Condensation of isatin derivatives **172** with 2-aminothiazol-4(5H)-one **2** in refluxing ethanol afforded isatylidene derivatives **173** in good yields, and showed promising antibacterial activity (Scheme 94) (111, 112).

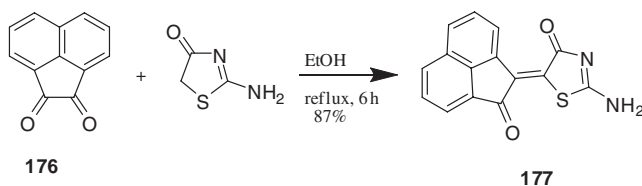


Scheme 94. Reaction of **2** with isatin derivatives.

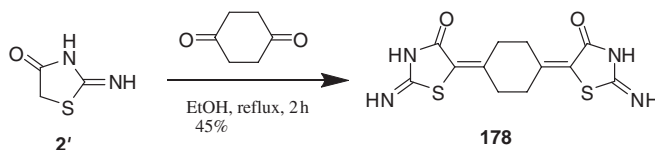
A facile synthesis of thiazolidinone **175** was described by the Knoevenagel-type condensation of benzo[*b*]thiophene-2,3-dione **174** (commonly known as thioisatin) with 2-amino-4-thiazolidinone **2** (Scheme 95) (113).

Scheme 95. Condensation of **2** with benzo[*b*]thiophene-2,3-dione.

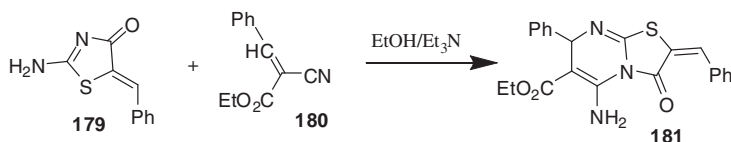
The synthesis of acenaphthylidene derivative **177** involved the Knoevenagel-type condensation of 2-aminothiazolidin-4-one **2** with acenaphthylene-1,2-dione **176** (Scheme 96) (114).

Scheme 96. Condensation of **2** with acenaphthylene-1,2-dione.

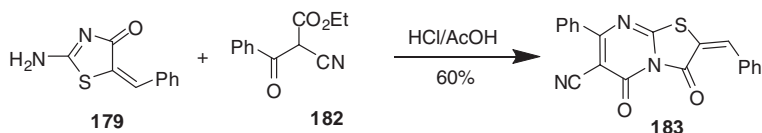
Condensation of 2-imino-4-thiazolidinone **2** with 1,4-cyclohexanedione gave 5,5'-(1,4-cyclohexanediyldene)bis[2-imino-4-thiazolidinone] **178** (Scheme 97) (112).

Scheme 97. Condensation of **2** with 1,4-cyclohexanedione.

(*E*)-ethyl 5-amino-2-benzylidene-3-oxo-7-phenyl-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate **181** was obtained by reaction of (5*Z*)-2-amino-5-benzylidenethiazol-4(5*H*)-one **179** with ethyl 2-cyano-3-phenylacrylate **180** (Scheme 98) (115).

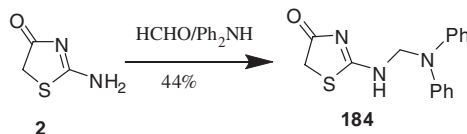
Scheme 98. Formation of thiazolo[3,2-*a*]pyrimidine derivatives.

(*E*)-2-benzylidene-3,5-dioxo-7-phenyl-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile **183** was prepared by reaction of ethyl 2-cyano-3-oxo-3-phenylpropanoate **182** with 2-amino-5-benzylidenethiazol-4(5*H*)-one **179** in a mixture of acetic and hydrochloric acid (Scheme 99) (116).

Scheme 99. Reaction between **179** and ethyl 2-cyano-3-oxo-3-phenylpropanoate.

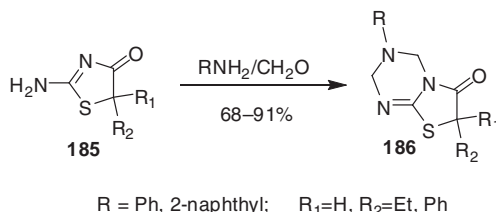
4.8. Mannich reactions

The Mannich reaction of aminothiazolidinone **2** with aqueous formaldehyde and diphenylamine gave 44% 2-((diphenylamino)methylamino)thiazol-4(5*H*)-one **184** (Scheme 100) (117).



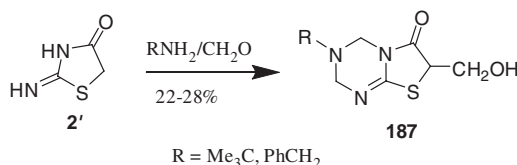
Scheme 100. Formation of 2-((diphenylamino)methylamino)thiazol-4(5*H*)-one.

The aminomethylation of 2-iminothiazolidin-4-ones by aqueous formaldehyde and primary amines was studied. Thiazolotriazines **186** were prepared in 68–91% yields by the aminomethylation of iminothiazolidinones **185** with primary amines and aqueous formaldehyde (Scheme 101) (118).



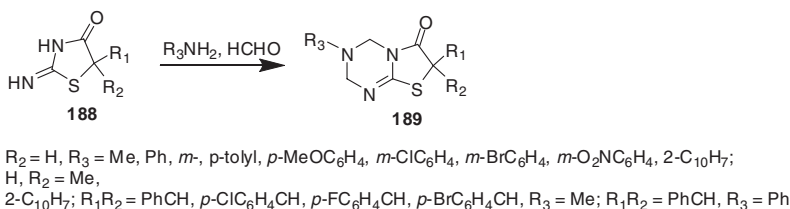
Scheme 101. Formation of thiazolotriazines.

Similarly, iminothiazolidinone **2** gave 22 and 28% thiazolotriazines **187** with *t*-butylamine and benzylamine (Scheme 102) (118).



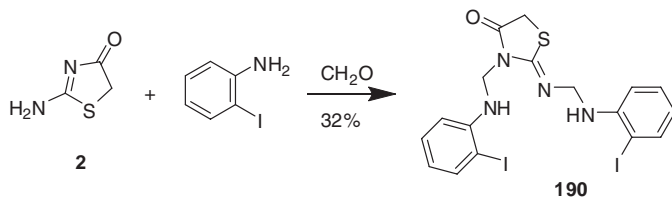
Scheme 102. Mannich reaction with *t*-butylamine and benzylamine.

Thiazolotriazinones **189** were prepared in 42–90% yields by Mannich reactions of **188** with formaldehyde and primary amines (Scheme 103) (119).



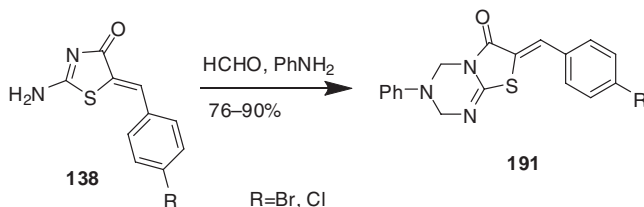
Scheme 103. Formation of thiazolotriazinones.

Additionally (Z)-3-((2-iodophenylamino)methyl)-2-((2-iodophenylamino)methylamino)thiazolidin-4-one **190** was obtained in 32% yield through the aminomethylation of **2** with 2-iodoaniline (Scheme 104) (118).



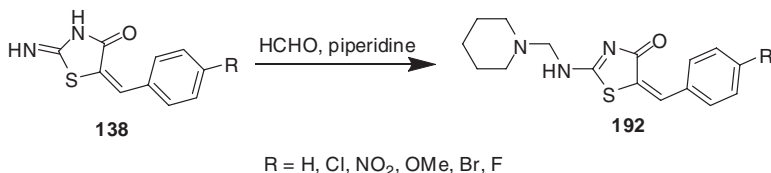
Scheme 104. Mannich reaction with 2-iodoaniline.

The aminomethylation of arylidene 2-aminothiazolidin-4-ones **138** by aqueous formaldehyde and aniline afforded thiazolotriazines **191** (Scheme 105) (118).



Scheme 105. Synthesis of thiazolotriazines.

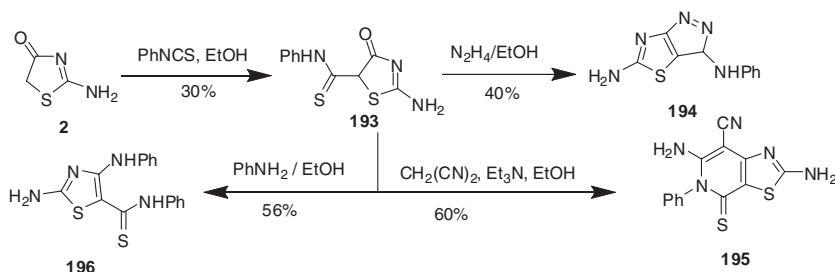
The aminomethylation of 2-imino-5-arylidene-thiazolidin-4-ones **138** have been reported to give (*E*)-5-benzylidene-2-(piperidin-1-ylmethylamino)thiazol-4(5*H*)-ones **192** (Scheme 106) (96, 97).



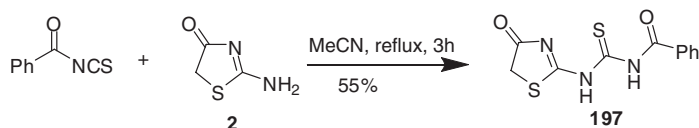
Scheme 106. Aminomethylation of 2-imino-5-arylidene-thiazolidin-4-ones.

4.9. Reaction with phenylisocyanate derivatives

Thiazolidone **2** reacted with phenylisothiocyanate to give 2-imino-5-phenylaminothiocarbonyl-4-thiazolidone **193** which was converted to a thiazolopyrazole **194**, a thiazolopyridine **195**, and a (phenylamino)thiazoleamine **196** by reaction with hydrazine hydrate, malononitrile, and aniline (Scheme 107) (120).

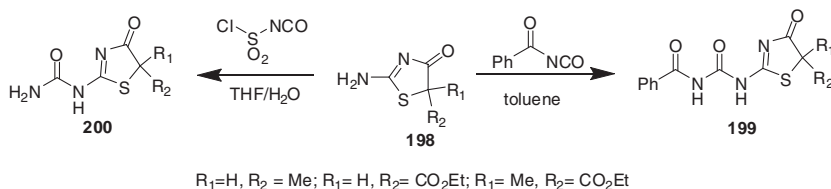
Scheme 107. Reaction of **2** with phenylisothiocyanate.

2-Amino-4-thiazolidinone **2** was reacted with benzoyl isothiocyanate in refluxing acetonitrile to give *N*-(4-oxo-4,5-dihydrothiazol-2-ylcarbamothioyl)benzamide **197** with 55% yield (Scheme 108) (121).



Scheme 108. Reaction of **2** with benzoyl isothiocyanate.

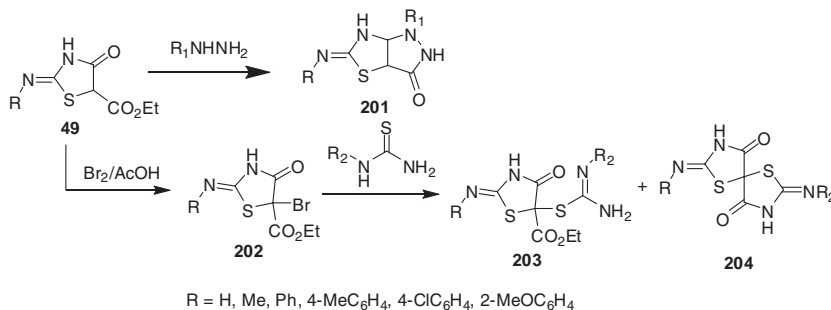
2-Aminothiazolidinone **198** reacted with benzoyl isocyanate and sulfurisocyanatidic chloride to give thiazolyl ureas **199** and thioureas **200**, respectively (Scheme 109) (122).



Scheme 109. Formation of thiazolyl ureas and thioureas.

4.10. Reaction with hydrazines

The reaction of **49** with hydrazines afforded 2-arylimino-2,3,4,5-tetrahydropyrazolo[3,4-*d*]-thiazol-6(*H*)-ones **201**. Bromination of **49** afforded 5-bromo derivatives **202**, which upon reaction with thiocarbamides gave 2-alkyl/arylimino-5-carbomethoxy-5-isothiocarbamidothiazolidin-4-ones **203** and 2,7-dialkyl/arylimino-3,8-diaza-1,6-dithiaspiro[4.4]nonane-4,9-diones **204** (Scheme 110) (38).

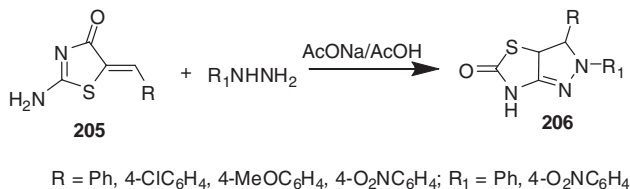


Scheme 110. Reaction with hydrazines and bromine.

Pyrazolinothiazolidin-2-ones **206** were prepared from rhodamine benzyldene derivatives **205** by condensation with phenylhydrazines, some of them showed antifungal activity (Scheme 111) (123).

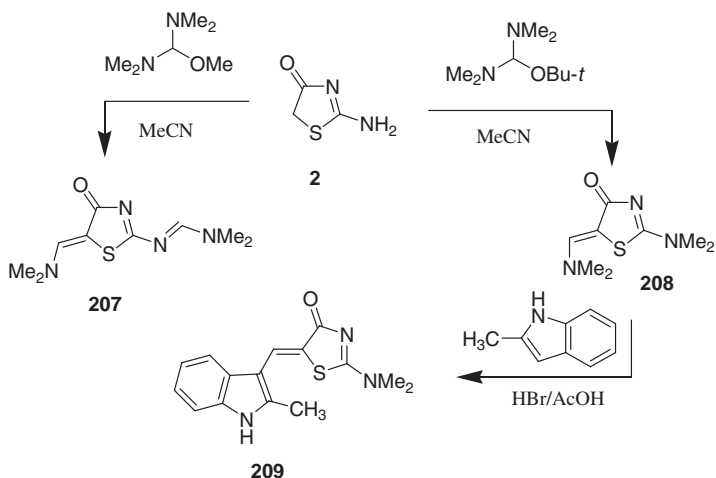
4.11. Formation of enaminones

The enaminones of 2-aminothiazol-4(5*H*)-ones **207** and **208** were prepared by reaction of **2** with methoxy-*N,N,N',N'*-tetramethylmethanediamine or *t*-butoxy-*N,N,N',N'*-tetramethylmethanediamine in acetonitrile. Thiooxaplysinopsin derivative **209** was prepared



Scheme 111. Formation of Pyrazolinothiazolidin-2-ones.

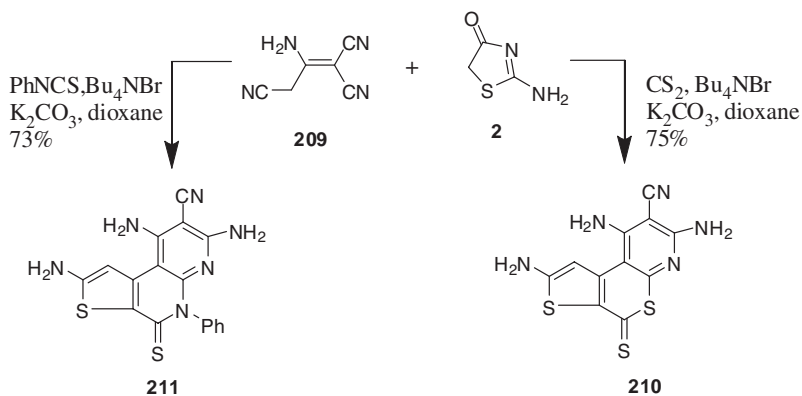
by reaction of *N*-substituted thiohydantoin **208**, Brederick's reagent, and 2-methylindole (Scheme 112) (124, 125).



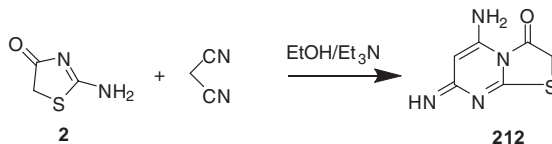
Scheme 112. Formation of enaminones.

4.12. Different reactions

Ketoketene thioacetals, which were formed by treatment of 2-amino-1-propene-1,1,3-tricarbonitrile **210** with carbondisulphide or with phenylisothiocyanate, were allowed to react with 2-aminothiazol-4(5*H*)-one **2** under phase transfer catalytic (PTC) conditions to afford thiopyrano[2,3-*b*]pyridine or pyrido[2,3-*b*]pyridine derivatives **211** and **212**, respectively (Scheme 113) (126).

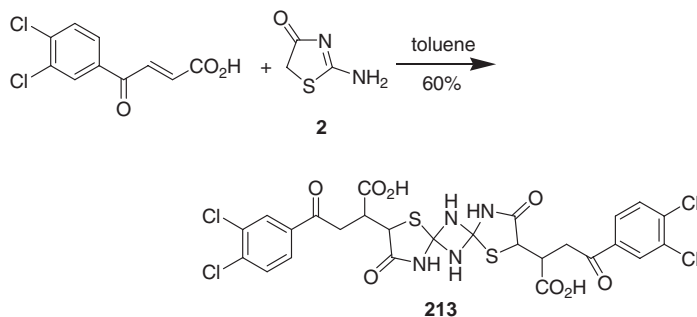
Scheme 113. Synthesis of pyrido[2,3-*b*]pyridine.

Thiazolo[3,2-*a*]pyrimidine **212** was prepared in one-pot reaction from 2-imino-4-thiazolidinone **2** and malononitrile (Scheme 114) (116).



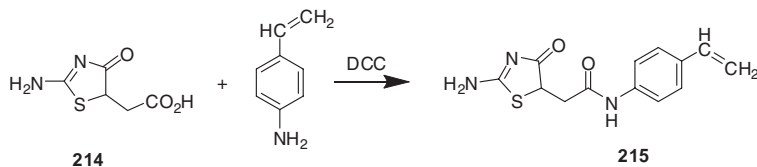
Scheme 114. Reaction of **2** with malononitrile.

Dispiro[thiazolidine-2,2'-[1,3]diazetidone-4',2''-thiazolidine]-5,5''-diacetic acid **213** was prepared in 60% yield by reaction of 3,4-dichlorocinnamic acid with pseudothiohydantoin **2** (Scheme 115) (127).



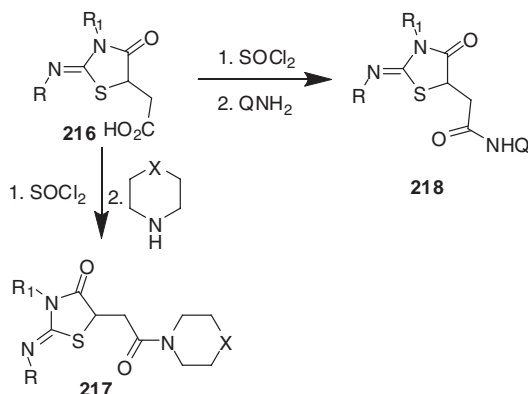
Scheme 115. Formation of dispiro compound.

The reaction of 2-amino-4-oxothiazolidine-5-acetic acid **214** with *p*-aminostyrene in the presence of dicyclohexylcarbodiimide (DCC) gave a new monomer **215** which was obtained conveniently under mild conditions (Scheme 116) (77).



Scheme 116. Reaction with *p*-aminostyrene.

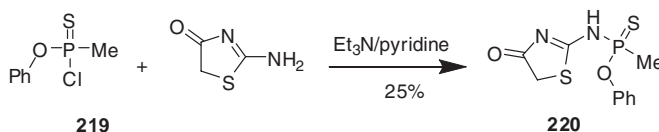
Thiazolidineacetic acids **216** which was amidated by first making the acid chloride then amination by morpholine, piperidine, aniline, phenylhydrazine, or prop-2-en-1-amine gave the corresponding amides **217** and **218**, respectively (Scheme 117) (128, 129).



R = H, Ph, allyl, R₁ = H; R = Ph, R₁ = Et, Bu, cyclohexyl, Ph;
 R = R₁ = Me₂CH, cyclohexyl; R = PhCH₂, R₁ = Me
 Q = Ph, PhNH, or CH₂:CHCH₂; X = CH, O

Scheme 117. Formation of amides.

Thiophosphorylation of thiazolidinone was achieved. Thiazolidine **220** was prepared in 25% yield by condensing **2** with *o*-phenyl methylphosphonochloridothioate **219** (Scheme 118) (126).



Scheme 118. Synthesis of thiazolidine.

Acknowledgements

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