2-Amino-4-thiazolidinones: synthesis and reactions

M.A. Metwallya*, Abdelbasset A. Farahatb,c and Bakr F. Abdel-Wahabd

aDepartment of Chemistry, Faculty of Science, Mansoura University, P.O. Box 23, Mansoura, Egypt; bDepartment of Chemistry, Georgia State University, Atlanta, GA 30303, USA; cDepartment of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt; dDepartment of Chemistry, Faculty of Science & Arts, King Abdulaziz University, Khulais, Saudi Arabia

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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 thiazolodihydropyrazoles, thiazolotriazines, 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), cardiotonic (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.
(Scheme 1) (11–15).

\[
\begin{array}{c}
\text{H}_2\text{N} \quad \text{NH}_2 + \text{Cl} \quad \text{CO}_2\text{Et} \quad \xrightarrow{95\% \text{EtOH}} \quad \text{N} \quad \text{S} \quad \text{NH}_2 \quad \text{HCl} \quad \xrightarrow{92\%} \quad \text{AcONa, water} \quad \text{N} \quad \text{S} \quad \text{NH}_2 \quad 84\% \\
\end{array}
\]

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).

\[
\begin{array}{c}
\text{Ph} \quad \text{Cl} \quad \text{CO}_2\text{Et} + \text{H}_2\text{N} \quad \text{NH}_2 \quad \xrightarrow{\text{anhd. AcONa}} \quad \text{EtOH} \quad \text{N} \quad \text{S} \quad \text{NH}_2 \quad \text{Ph} \quad 55–65\%
\end{array}
\]

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).

\[
\begin{array}{c}
\text{Ar} = [2,4-(\text{OEt})_2; 3,4-\text{Me}_2; 4-\text{Cl}-3-\text{MeO}; 3,5-(\text{MeO})_2; 4-\text{NHCOMe},3-\text{MeO}]\text{phenyl}
\end{array}
\]

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).

\[
\begin{array}{c}
\text{X} = \text{O}, \text{S}
\end{array}
\]

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

2-[(2-Amino-4,5-dihydro-4-oxothiazol-5-yl)methyl]isothiourea 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-thiazolidones 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-thiazolidones.

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

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).


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).

Reaction of $\alpha$-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-Phenylbenz[d]oxazol-5-amine 31 was converted to 2-amino-5-((2-phenylbenz[d]oxazol-5-yl)methyl)thiazol-4(5H)-one 32, upon treatment with methyl acrylate followed by reaction with thiourea (Scheme 16) (30).


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(5H)-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(5H)-one.](image)

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.](image)

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

![Scheme 21. Synthesis of aminothiazolidinone.](image)

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.](image)

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

![Scheme 23. Synthesis of thiazole derivative.](image)
2-Alkyl/arylimino-5-carbethoxythiazolidin-4-ones 49 have been synthesized by the interaction of thiocarbamides 48 with diethyl bromomalonate (Scheme 24) (38).

\[
\begin{align*}
R \quad \text{NH} \quad \text{NH}_2 + \text{BrCO}_2\text{Et} & \xrightarrow{\text{NH}_2\text{OH} / \text{H}_2\text{O}} \text{R} \quad \text{N} \quad \text{S} \quad \text{CO}_2\text{Et} \\
48 & \rightarrow 49 \\
R = \text{H, Me, Ph, 4-MeC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 2-\text{MeOC}_6\text{H}_4
\end{align*}
\]


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

\[
\begin{align*}
\text{ArCl} \quad \text{OEt} & \xrightarrow{\text{thiourea}} \text{Ar} \quad \text{H}_2\text{N} \quad \text{S} \quad \text{O} \\
50 & \rightarrow 51 \\
\text{Ar} = \{2,4-\text{diethoxy}; 3,4-\text{dimethoxy}; 3-\text{ethoxy},4-\text{hydroxy}; 3-\text{chloro},4-\text{hydroxy,5-}
\text{methoxy}\}\text{phenyl}
\end{align*}
\]

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]isoindoline-1,3-dione 53. Hydrolysis of 53 in the presence of hydrobromic acid gave 2-amino-5-(aminomethyl)thiazol-4(5H)-one 54 (Scheme 26) (21).

\[
\begin{align*}
\text{Phthalic anhydride} \quad \text{H}_2\text{N} \quad \text{CO}_2\text{H} & \xrightarrow{1. \text{P}, \text{Br}_2} \text{Phthalamide} \quad \text{H}_2\text{N} \quad \text{CO}_2\text{H} \\
52 & \xrightarrow{2. \text{HBr/\text{H}_2\text{O}}} \text{Phthalimide} \quad \text{H}_2\text{N} \quad \text{CO}_2\text{H} \\
& \xrightarrow{3. \text{thiourea, AcOH}} \text{Aminothiazolidine} \quad \text{H}_2\text{N} \quad \text{CO}_2\text{H} \\
52 & \rightarrow 53 \\
\text{HBr, H}_2\text{O, BuOH} & \rightarrow \text{C}_6\text{H}_6 \quad 76\% \\
\text{H}_2\text{N} \quad \text{S} \quad \text{NH}_2 & \xrightarrow{54} \text{NH}_2 \quad \text{S} \quad \text{NH}_2 \\
\end{align*}
\]


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).

\[
\begin{align*}
\text{S-(1-phenylpyrrolidin-2-on-3-yl)isothiuronium salts} \quad \text{NH}_2 \quad \text{S} \quad \text{NH}_2 & \xrightarrow{\text{weak base}} \text{Thiazolidine} \quad \text{NH}_2 \quad \text{S} \quad \text{NH}_2 \\
55 & \rightarrow 57 \\
\text{R}_1 = \text{NO}_2, \text{MeO; R}_2, \text{R}_3 = \text{H, Me}
\end{align*}
\]

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(5H)-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(5H)-one.]

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

![Scheme 29. Synthesis of 2-aminothiazol-4(5H)-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 NH₃ 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-aroylmethyl-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 \( \text{72} \), its methyl ester \( \text{73} \) 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(4H)-ylidene)acetate \( \text{74} \) (Scheme 37) \((52, 53)\).

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

2.5. From anhydrides or imides

Maleic anhydrides \( \text{75} \) reacted with thiourea to give 1,3-thiazolidine \( \text{76} \) (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\text{-amino-4-oxothiazol-5}(4H)\text{-ylidene})\text{acetic acid} \(78\) (Scheme 39) \((54)\).

Scheme 39. Synthesis of \((E)-2\text{-}(2\text{-amino-4-oxothiazol-5}(4H)\text{-ylidene})\text{acetic acid.}\)

\[
\begin{align*}
\text{Br} & \quad \text{R} \\
\text{O} & \quad \text{O} \\
| & \quad | \\
\text{H}2\text{N} & \quad \text{S} \\
\text{O} & \quad \text{CO2H}
\end{align*}
\]

\(41\% \text{ R} = \text{Br} \quad 10\% \text{ R} = \text{H}\)

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

Scheme 40. Synthesis of \(2-(2\text{-amino-4-oxo-4,5-dihydrothiazol-5-yl})\text{-N-O-tolylacetamide.}\)

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

Scheme 41. Synthesis of \(N\)-ethyl-\(\alpha\)-(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.

\[
\begin{align*}
\text{R} & \quad \text{R1} \quad \text{R2} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{N} \\
\text{R} & \quad \text{R1} \quad \text{R2}
\end{align*}
\]

\(\text{R} = \text{Et, Ph}; \text{R1} = \text{R2} = \text{H}, \text{R}1 = \text{H}, \text{R}2 = \text{Ph}, \text{R}1 = \text{R2} = \text{Ph}\)

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 cyanocarboxyln 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-methylepoxysuccinic 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(5H)-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 tautomeration 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 isothiourea derivatives

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

Scheme 49. Synthesis of 2-thiazoline.

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

Scheme 50. Synthesis of E-5-arylidenethiazolin-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).

\[
\begin{align*}
\text{MeS} & \quad \text{ArNH}_2 \\
99 & \quad \text{ArNH}_2 \\
\text{NH}_2 & \quad \text{ArNH}_2 \\
100 & \quad \text{ArNH}_2 \\
101 & \quad \text{ArNH}_2 \\
\end{align*}
\]

\( R = 2\text{-Cl}, 4\text{-Cl}, 2\text{-MeO}, 3\text{-MeO}, 4\text{-MeO}; \)
\( \text{Ar} = \text{H}, 4\text{-MeC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, \text{PhCH}_2, 4\text{-MeC}_6\text{H}_4\text{CH}_2, 4\text{-MeOC}_6\text{H}_4\text{CH}_2; \text{X} = \text{CH}_2, \text{O} \)

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

2.10. Miscellaneous methods

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

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{ArNH}_2 \\
103 & \quad \text{ArNH}_2 \\
\end{align*}
\]

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).

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{ArNH}_2 \\
104 & \quad \text{ArNH}_2 \\
\end{align*}
\]

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(4H)-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-(5-methyl-2-pyridyl)ethoxy)aniline 111 was reacted with methyl acrylate and thiourea to give aminothiazolidinone 112 (Scheme 57) (7).

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(5H)-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(sulfanediyl))diacetic acid 119, respectively (Scheme 63) (75).

\[
\text{BaCl}_2 \xrightarrow{\text{NaOH}} \text{BaS} \quad 95.2\%
\]

\[
\text{ClCH}_2\text{CO}_2\text{H} \xrightarrow{\text{NaOH}} \text{CO}_2\text{H} \quad 84\%
\]

\[
\text{ClCH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{NaOH}} \text{CO}_2\text{H} \quad 96\%
\]

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).

\[
\text{H}_2\text{N} \xrightarrow{\text{H}_2\text{SO}_4/\text{H}_2\text{O}} \text{SH} \quad 34\%
\]

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).

\[
\begin{align*}
\text{N} \xrightarrow{\text{Cl}\text{COOMe}} \text{N} \\
\text{NaOH/\text{H}_2\text{O}} & \quad 122
\end{align*}
\]

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).

\[
\text{H}_2\text{N} \begin{array}{c}
\text{S} \\
\text{N} \\
\text{O} \\
\text{H}_2\text{N}
\end{array} \text{CO}_2\text{H} \xrightarrow{\text{Ac}_2\text{O}} \text{Me} \begin{array}{c}
\text{N} \\
\text{S} \\
\text{O} \\
\text{HN}
\end{array} \text{CO}_2\text{H}
\]

\( \text{R} = \text{H, Me, Ph} \)

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).

\[
\text{H}_2\text{N} \begin{array}{c}
\text{S} \\
\text{O} \\
\text{N} \\
\text{H}_2\text{N}
\end{array} \text{CO}_2\text{H} \xrightarrow{\text{Ac}_2\text{O}} \text{H}_3\text{C} \begin{array}{c}
\text{O} \\
\text{HN} \\
\text{S} \\
\text{O}
\end{array} \text{N} \begin{array}{c}
\text{H}_2\text{N}
\end{array} \text{CO}_2\text{H}
\]

\( \text{R} = \text{H, Cl, Me, MeO, NO}_2 \)

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).

\[
\text{R} = \text{Ac, R}_1 = \text{Ph, p-MeNC}_6\text{H}_4; \text{p-EtNC}_6\text{H}_4; \text{p-[(ClCH}_2\text{CH}_2)]NC}_6\text{H}_4; \\
\text{R} = \text{Bz, R}_1 = \text{Ph, p-O}_2\text{NC}_6\text{H}_4; \text{p-O}_2\text{NC}_6\text{H}_4; \text{p-Me}_2\text{NC}_6\text{H}_4; \text{p-[(ClCH}_2\text{CH}_2)]NC}_6\text{H}_4, \text{2-furyl}
\]

Scheme 68. Acylation of pseudothiohydantoin.
4.4. **Alkylation**

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

![Scheme 69](image)

Scheme 69. Alkylation of 2 with acetone.

Methylation of 2-aminothiazol-4(5H)-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](image)

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

4.5. **Bromination**

Bromination of 2-alkyl/arylimino-5-carbethoxythiazolidin-4-ones 49 afforded 5-bromo derivatives 133, which reacted with thiocarbamides to give 2-alkyl/arylimino-5-carbethoxy-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](image)

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](image)

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(5H)-one 2 with formalin (Scheme 73) (96).

\[
\begin{align*}
\text{2} & \quad \text{HCHO/MeOH} \quad \text{137} \\
\end{align*}
\]

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

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

\[
\begin{align*}
\text{138} & \quad \text{HCHO} \quad \text{139} \\
R = \text{H, Cl, NO}_{2}, \text{OMe, Br, F} \\
\end{align*}
\]

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

\[
\begin{align*}
\text{2} & \quad \text{ArCHO} \quad \text{ACOH/MeONa} \quad \text{MW, 10 min, 170°C} \quad \text{63–91%} \\
\text{140} & \quad \text{Ar} \quad \text{NH}_2 \\
\end{align*}
\]

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).

\[
\begin{align*}
\text{2C'} & \quad \text{CHO} \quad \text{MeO} \quad \text{OMe} \\
\text{141} & \quad \text{OMe} \quad \text{OMe} \\
\end{align*}
\]

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 cardiotonic Knoevenagel product 143 in 70% yield (Scheme 78) (7).

Scheme 78. Formation of Knoevenagel product 143.

(5Z)-5-(3,5-Di-tert-butyl-4-hydroxybenzylidene)-2-aminothiazol-4(5H)-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(5H)-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(5H)-one 146 by condensation of 2-aminothiazol-4(5H)-one 2 with picolinaldehyde (Scheme 81).

\[ \text{N}S\text{NH}_2 + \text{CHO} \rightarrow \text{N}S\text{NH}_2 \text{CHO} \]

1) Na\(_2\)CO\(_3\), glycine 2) H\(_2\)O 90%

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 thiazolodihydropyrazole 148 and thiazolotetrahydropyrimidone 149, respectively (Scheme 82) (102).

\[ \text{R} = \text{Ph}, 4-\text{ClC}_6\text{H}_4, 3,4,5-(\text{MeO})_3\text{C}_6\text{H}_2 \]

Scheme 82. Formation of thiazolodihydropyrazole and thiazolotetrahydropyrimidone.

Substituted 1,5-naphthyridine thiazolinones 151 reported to have antiproliferative and anticancer 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).

\[ \text{NC} + \text{AcONa/AcOH} \rightarrow \text{NC} \text{AcONa/AcOH} \]

23%

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).
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).

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).

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

(5\(E\))-5-((1\(H\)-Pyrrolo[2,3-\(b\])pyridin-3-yl)methylene)-2-aminothiazol-4(5\(H\))-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).

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 (5\(Z\))-5-(4-(4-(trifluoromethyl)-2-nitrophenoxy)-3-methoxybenzylidene)-2-aminothiazol-4(5\(H\))-one 165 (Scheme 90) (107).

Thiazolinone 3,4-disubstituted quinolines as CDK1 inhibitors for treating cancer was reported. 6-((15\(E\))-(2-Amino-4-oxothiazol-5(4\(H\))-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-dioxa-8-azaspiro[4.5]dec-8-yl)benzaldehyde 168 and pseudothiohydantoin 2 afforded (Z)-5-(4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)benzylidene)-2-aminothiazol-4(5H)-one 169 in 94% yield as potent and selective human β3 agonists (Scheme 92) (108, 109).

Scheme 92. Reaction of 2 with 4-(1,4-dioxa-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 thiosatin) 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-amino-thiazolidin-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-cyclohexanediol gave 5,5′-(1,4-cyclohexanediylidene)bis[2-imino-4-thiazolidinone] 178 (Scheme 97) (112).

Scheme 97. Condensation of 2 with 1,4-cyclohexanediol.

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


(E)-2-benzylidene-3,5-dioxo-7-phenyl-3,5-dihydro-2H-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-benzylidene-thiazol-4(5H)-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).

\[
\text{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).

\[
\text{Scheme 101. Formation of thiazolotriazines.}
\]

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

\[
\text{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).

\[
\text{Scheme 103. Formation of thiazolotriazinones.}
\]

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-idoaniline (Scheme 104) (118).
The aminomethylation of arylidene 2-aminothiazolidin-4-ones 138 by aqueous formaldehyde and aniline afforded thiazolotriazines 191 (Scheme 105) (118).

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

Thiazolidone 2 reacted with phenylisothiocyanate to give 2-imino-5-phenylaminothiocarboxamido-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).
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).

\[
\text{PhNCS} + \overset{\text{MeCN, reflux, 3h}}{\text{2}} \rightarrow \overset{55\%}{\text{197}}
\]

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).

\[
\begin{align*}
\text{NH}_2 \text{S} \text{O} \text{R}_1 & \text{H}_2\text{N} \text{O} \text{Ph} \text{NCO} \quad \text{toluene} \\
\text{NH}_2 \text{S} \text{O} \text{R}_1 & \text{N} \text{H} \text{R}_2 \text{H}_2\text{N} \text{O} \text{Ph} \text{NCO} \quad \text{THF/H}_2\text{O}
\end{align*}
\]

\[\text{R}_1=\text{H, R}_2=\text{Me}; \text{R}_1=\text{H, R}_2=\text{CO}_2\text{Et}; \text{R}_1=\text{Me, R}_2=\text{CO}_2\text{Et}\]

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-carbethoxy-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).

\[
\begin{align*}
\text{H}_2\text{N} \text{S} \text{O} \text{R}_1 & \text{Br}_2/\text{AcOH} \\
\text{R}_1\text{NHNNH}_2 & \text{R}_1\text{NHNH}_2 \\
\text{CO}_2\text{Et} & \text{CO}_2\text{Et}
\end{align*}
\]

\[\text{R}=\text{H, Me, Ph, 4-MeC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 2-\text{MeOC}_6\text{H}_4\]

Scheme 110. Reaction with hydrazines and bromine.

Pyrazolinothiazolidin-2-ones 206 were prepared from rhodamine benzylidene 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(5H)-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. Thioxoaplysinsin derivative 209 was prepared
Scheme 111. Formation of Pyrazolinothiazolidin-2-ones.

by reaction of \( N \)-substituted thiohydantoin 208, Bredereck’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) \((126)\).
Thiazolo[3,2-α]pyrimidine 212 was prepared in one-pot reaction from 2-imino-4-thiazolidinone 2 and malononitrile (Scheme 114) (116).

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{S} & \quad \text{NH}_2 \\
\text{HN} & \quad \text{O} \\
\text{CN} & \quad \text{CN}
\end{align*}
\]

Scheme 114. Reaction of 2 with malononitrile.

Dispiro[thiazolidine-2,2′-[1,3]diazetidine-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).

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{O} & \quad \text{N} \\
\text{S} & \quad \text{NH}_2 \\
\text{HN} & \quad \text{O} \\
\text{CO}_2\text{H} & \quad \text{CO}_2\text{H}
\end{align*}
\]

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).

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{S} \\
\text{N} & \quad \text{O} \\
\text{NH}_2 & \quad \text{O} \\
\text{HC} & \quad \text{CH}_2
\end{align*}
\]

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

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References


