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REVIEW

VERSATILE 2-AMINO-4-SUBSTITUTED-1,3-THIAZOLES: SYNTHESIS AND REACTIONS

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Syntheses and reactions of 2-amino-4-substituted-1,3-thiazoles are reviewed in a formal way. The title compounds are most easily accessible by various approaches, and even waste-free solid-state procedures have been developed. The substitution in 4-position has synthetic reasons and therefore most interest accumulates around these derivatives of 2-aminothiazole. The high reactivity of both the amino group and the positions 3 and 5 of the 1,3-thiazole ring are used for numerous syntheses in a comprehensive way. The reactions are subdivided in groups that cover reactions at the amino substituent without touching the thiazole ring, reactions which involve both nitrogens in the formal amidine system to give thiazolo-pyrimidinones and -imidazoles as well as more involved polycondensed N,S-heterocycles with multiple possibilities for substituents, and substitution reactions at the 5-position of the thiazole ring. Most of the imaginable reaction types have been successfully applied and used, as many of the synthesized compounds exhibit interesting biological activity in various fields.

Keywords: Addition; 2-Aminothiazole; Biological activity; Condensation; Cyclization; Enone; Heterocycle; Mannich base; Substitution; Synthetic use

INTRODUCTION AND SCOPE

2-Aminothiazoles and their derivatives have long been used as precursors for the synthesis of biologically active molecules. Because of the wide spectrum of activity shown by the thiazole moiety, numerous thiazoles substituted with different groups at various positions have been prepared. Despite this importance, 2-aminothiazoles have not been previously reviewed. In recent years, several new methods for the preparation of 2-aminothiazole derivatives and reactions have been reported, including waste-free techniques. 2-Amino-4-substituted-1,3-thiazoles, in the presence of various reagents, undergo different types of reactions to yield other heterocyclic compounds, *e.g.*, thiazolo[3,2-*a*]pyrimidine-5-ones, thiazolo[3,2-*a*]-pyrimidine-7-ones, imidazo[2,1-*b*]thiazoles, thiazolo[3,2-*a*]benzimidazoles, *etc.* Consequently we were interested in surveying the synthetic utility of 2-amino-4-substituted-thiazoles.

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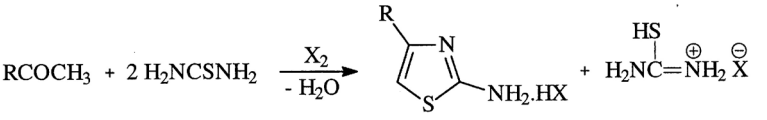
SYNTHESIS OF 2-AMINO-4-SUBSTITUTED-1,3-THIAZOLES

From Ketones

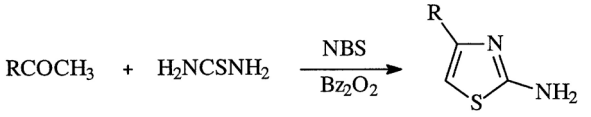
Using Halogen and Thiourea

Methyl ketones of the type **1** react directly with one mole of halogen and two moles of thiourea to give 2-aminothiazoles (**2**) in excellent yield [1, 2] (R = phenyl, substituted phenyl, β-naphthyl, 2-thienyl, methyl, t-butyl; X = Br, I).



Using NBS and Thiourea

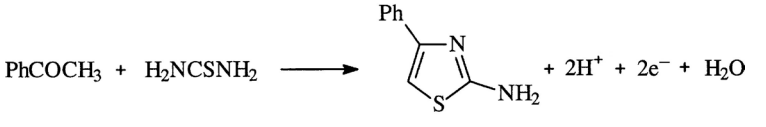
Methyl ketones **1** react with thiourea in the presence of *N*-bromosuccinimide (NBS) using benzoyl peroxide as radical initiator to furnish 2-aminothiazoles (**3**) [3, 4].



R = (un)substituted-3-coumarinyl,
(un)substituted phenyl

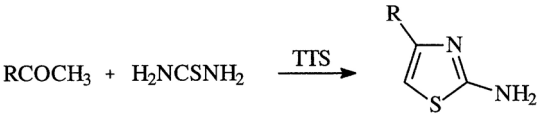
Using Oxidizing Agents and Thiourea

An oxidative process can accomplish the formation of 2-aminothiazoles from a ketone and thiourea. Thus, mixtures of thiourea and acetophenone have been treated with various oxidizing agents, namely sulfuryl chloride, chlorosulfonic acid, thionyl chloride, sulfur monochloride, sulfur trioxide, sulfuric acid, nitric acid and sulfur. In each case a considerable quantity of 2-amino-4-phenylthiazole (**4**) was obtained [5].



Ketones **1** on oxidation with thallium(III)-*p*-tosylsulfonate (TTS) in refluxing acetonitrile or dioxane followed by additional refluxing of the reaction mixture with thiourea yielded

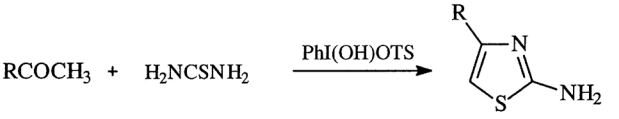
the 2-amino-4-substituted-thiazoles as *p*-toluenesulfonates. Basification with aqueous potassium carbonate then provided **3** as free bases in good yields [6].



1 **3**

R = Ph, 4-BrC$_6$H$_4$, 2-thienyl

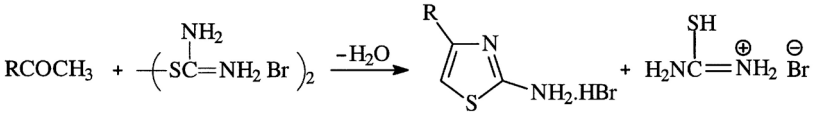
A facile synthesis for **3** (R = 2-furyl) through a very simple and eco-friendly methodology has been reported. Stirring 2-acetylfuran **1** (R = 2-furyl) with [hydroxyl-(tosyloxy)-iodo]benzene (HTIB) in dichloromethane at room temperature provided 2-tosyl oxy-acetylfuran, which underwent smooth transformation with thiourea, affording **3** (R = 2-furyl) in excellent yield [7].



1 **3**

Using Formamidine Disulfide Dihydrobromide

Ketones **1** have also been reacted with formamidine disulfide dihydrobromide to give the corresponding 2-amino-4-substituted-thiazoles (**2**) [8]. The reaction may be formulated as follows:

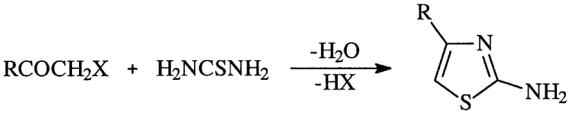


1 **2**

R = Ph, 3-O$_2$N.C$_6$H$_4$, Me

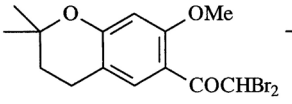
From α-Haloketones

Thiazoles are generally synthesized by the Hantzsch thiazole synthesis from α-haloketones and thioureas (or thioamides) [9, 10]. The syntheses of numerous 2-amino-4-substituted-thiazoles **3** have been reported [11–18] and involve the reaction of α-halogeno-ketones (**5**) with thiourea in polar solvents or better with quantitative yield in the solid-state [19] (R = 3-coumarinyl, 3-indolyl, 2-thienyl, pyridyl, quinolyl, 2-benzothiazolyl, phenyl, substituted phenyl, methyl, 4-antipyrinyl).



5 **3**

Instead of the expected 2-amino-4-(2,2-dimethyl-7-methoxychroman-6-yl)-5-bromothiazole (**8**), the product obtained by the condensation of 6-dibromoacetyl-2,2-dimethyl-7-methoxychroman (**6**) with thiourea was 2-amino-4-(2,2-dimethyl-7-methoxychroman-6-yl) thiazole (**9**), which could be also obtained by the condensation of 6-bromoacetyl-2,2-dimethyl-7-methoxychroman (**7**) with thiourea [20].



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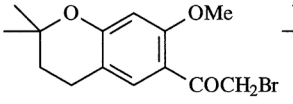

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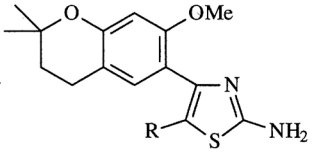
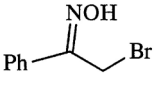


8, R = Br

9, R = H

From α-Haloketone Derivatives

Both bromoacetophenone oxime (**10**) and 2-bromo-1-phenylethylidenemalononitrile (**11**) react with thiourea to give 2-amino-4-phenylthiazole (**4**). In both reactions, ring closure is accompanied by the elimination of hydroxylamine [21] and malononitrile [22], respectively.



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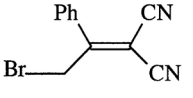
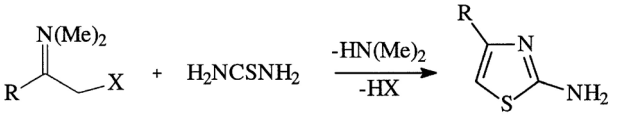


11

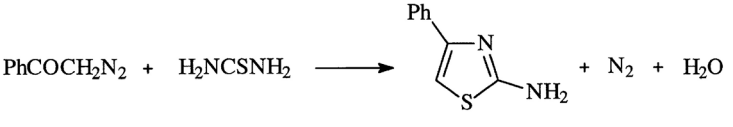
Halo-methyl ketimines **12** (X = Br, Cl) have condensed with thiourea in methanol to afford 2-aminothiazoles **3** (R = t-Bu., Ph, 4-MeC_6H_4) whereas the *N*-isopropyl moiety has been lost during the condensation of the halo-ketimines [23].



12 **3**

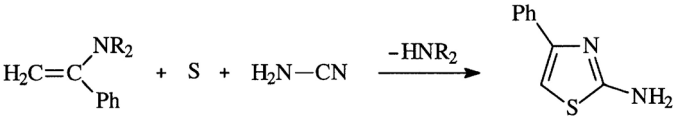
Miscellaneous Methods

Diazoacetophenone has been reacted with thiourea to furnish 2-amino-4-phenylthiazole (**4**). The transformation was completed either by heating an intimate mixture of the reactants on a steam bath, or by refluxing an alcoholic solution of the reaction components [24].



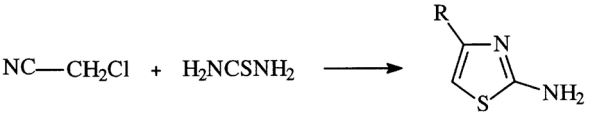
4

Enamines of the type **13** react with sulfur and cyanamide at room temperature without catalyst [25] to give the corresponding 2-amino-4-phenylthiazole (**4**).



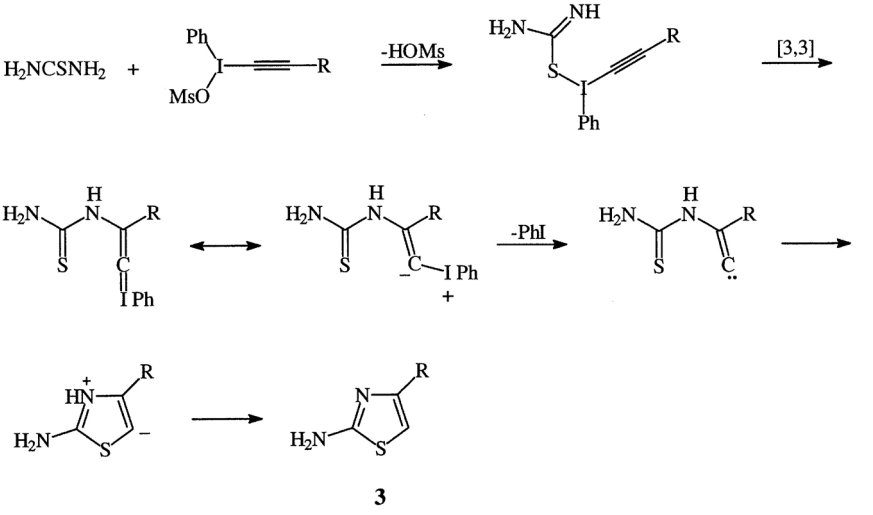
13 **4**

The condensation of thiourea and halogeno-nitriles to form salts of 2,4-diaminothiazole is a general reaction, which is, however, limited by the lack of reactivity of the halogens in some substituted nitriles. For example, chloroacetonitrile interacts with thiourea in cold ethanol [26] to give the hydrochloride of **3** (R = NH_2).



3

The formation of 2-aminothiazoles **3** (R = Bu, Ph) in a single reaction step from alkynyl(phenyl)iodonium mesylates and thiourea can be rationalized mechanistically by a thiophilic attack of the hypervalent iodine atom on the sulfur atom of the thiocarbonyl group [27].



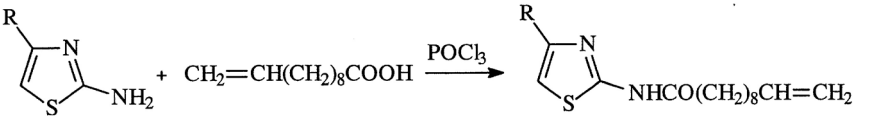
3

REACTIONS AND CHEMISTRY INVOLVING THE AMINO GROUP

Acylation Reactions

Acylation by Acid

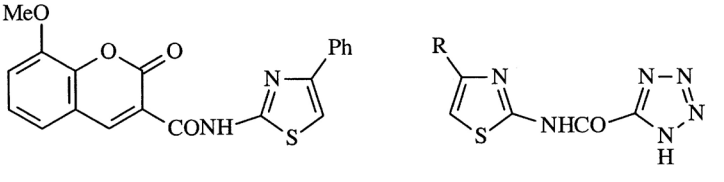
2-Aminothiazoles (**3**) have been condensed with undecenoic acid in the presence of phosphorous oxychloride to afford the corresponding acid amides **14** [28] (R = Me, Ph, 4-$MeOC_6H_4$, 4-Cl-C_6H_4).



3 **14**

Coumarin carboxamide (**15**) [29] has been prepared from the corresponding coumarin carboxylic acid and 2-amino-4-phenylthiazole and has been tested for anti-fungal and antibacterial activity.

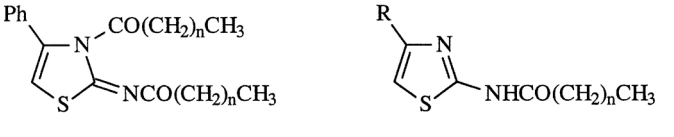
Tetrazoles **16** have been prepared by the treatment of 2-aminothiazoles with a suspension of dipotassium-1*H*-tetrazole-5-carboxylate in acetonitrile containing pyridine. The compound **16** (R = 4-MeC_6H_4) gave 89% inhibition of anti-passive cutaneous anaphylaxis in rats at 20 mg kg^{-1} orally [30].



15 **16**

Acylation by Acid Anhydride

Depending on the reaction conditions, 2-aminothiazoles undergo acylation by acid anhydrides (*e.g.* acetic, propionic and butyric anhydride) to give the corresponding 3-acyl-2-acylimino-2,3-dihydrothiazoles (**17**, n = 1–3) [31] or *N*-(-2-thiazolyl)amides (**18**, R = Ph, substituted phenyl, β-naphthyl, 2-thienyl, n = 1; R = Ph, n = 2, 3) [2, 31].



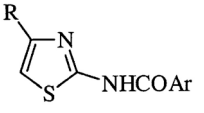
17 **18**

Acylation by Acid Chloride

2-Aminothiazoles have been acylated with aroyl or heteroaroyl acid chlorides in dry pyridine or dry benzene to give the corresponding 2-(*N*-acylamino)thiazoles (**19**, R = Me, Et, Ph, substituted phenyl; Ar = Ph, substituted phenyl, Ph-CH=CH, 5-NO_2-2-furyl) [32–35].

Compound **19** (R = Ph; Ar = 4-$(Et_2O)_2POCH_2C_6H_4$) is useful for the treatment of hyperlipidemia, cataract and diabetes [36]. Compound **19** (R = Ph; Ar = CH_2OCH_3) has also been scanned in the rat PCA (passive cutaneous anaphylaxis) assay by oral administration [37].

The compounds **20** (R = Me; R^1 = H, Cl, Me, NO_2) have been prepared by the reaction of phenoxyacetyl chlorides with 2-aminothiazoles [38].



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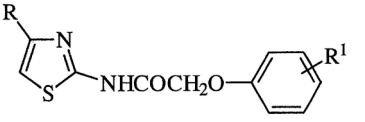
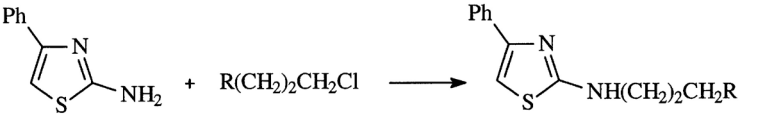


20

Alkylation

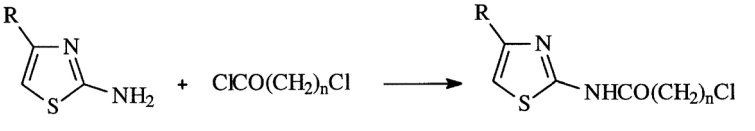
2-(3-Aryloxy/arylpropyl)aminothiazoles (**21**, R = 2-thienylcarbonyl, PhCO, 4-PhC_6H_4) have been synthesized from the appropriate 3-aroyl/arylpropyl chlorides and 2-amino-4-phenylthiazole [39].



21

Reaction with Chloroacyl Chlorides

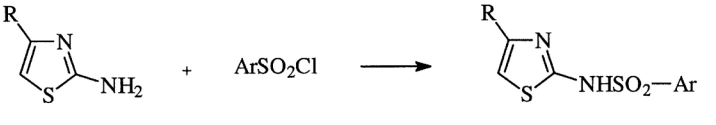
2-Aminothiazoles have been treated with chloroacyl chlorides to give the corresponding 2-(chloroacylamino)-4-substituted-thiazoles (**22**, R = Me, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-HOC_6H_4, 4-ClC_6H_4; n = 1–3) [40–43].



22

Reaction with Aryl Sulfonyl Chlorides

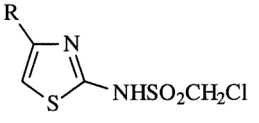
Reaction of 2-aminothiazoles (**3**) with the appropriate sulfonyl chlorides in pyridine has furnished a series of 2-sulfonamido-thiazoles (**23**, R = Me, Ph, substituted phenyl; Ar = Ph, substituted phenyl, 4-acetylamino-1-naphthyl, 2-arylnaphth[1,2-*d*]oxazol-5-yl) [44–46]. The compounds **23** were evaluated as inhibitors of rat kidney kynurenine 3-hydroxylase using L-[3-^{3}H]kynurenine as substrate [47].



3 **23**

Reaction of 2-aminothiazoles with chloromethanesulfonyl chloride has yielded the corresponding *N*-2-thiazolyl chloromethanesulfonamides (**24**, R = Me, Ph, 2,4-$(Cl)_2C_6H_3$) [48].

Sulfanilamidothiazoles **25** (R = Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$, 2,5-$(MeO)_2C_6H_3$, 2,4-$(Cl)_2$-C_6H_3, 2-naphthyl; X = NH_2) have been prepared by acylation of 2-aminothiazoles with 4-(*N*-acetylaminobenzenesulfonyl chloride followed by deacetylation by heating in aqueous NaOH [49] or 80% CH_3COOH [50]. *p*-(*p*-Tosyloxy)benzenesulfonyl chloride was condensed with 2-aminothiazoles in pyridine and the tosyl group then removed by hydrolysis to give a series of *N*-2-thiazolyl-1-phenol-4-sulfonamides (**25**, R = Me, Ph; X = OH) [51].



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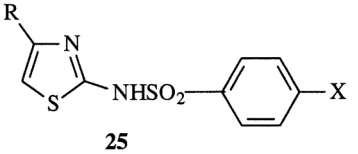
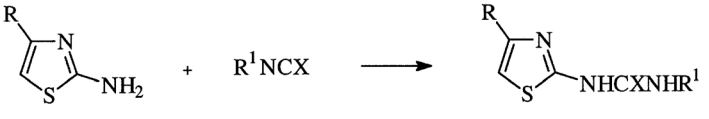


25

Reaction with Isocyanates and Isothiocyanates

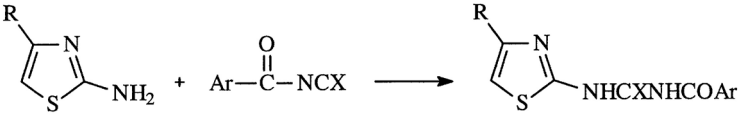
The reaction of 2-aminothiazoles with aryl or alkyl isocyanates [52–55] has given *N*-aryl/alkyl-*N*′-(2-thiazolyl)ureas (**26**, R = Ph, 2-pyridyl; R^1 = Bu, cyclohexyl, Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 3,5-$(MeO)_2C_6H_3$, PhCH=CH; X = O). Also, a number of *N*-substituted-*N*′-(4-aryl-2-thiazolyl) thiocarbamides (**26**, R = Ph, substituted phenyl; R^1 = Et, $PhCH_2$, Ph, substituted phenyl, tetra-*O*-acetyl-β-D-glucopyranosyl; X = S) have been synthesized by the reaction of 2-aminothiazoles **3** with alkyl or aryl isothiocyanates [56–60].



3 **26**

A series of aroylureas (**27**) have been prepared by the reaction of 2-aminothiazoles with aroyl isocyanates and were tested for insecticidal, fungicidal and herbicidal activities. Compound **27** (R = CF_3; Ar = 2-BrC_6H_4) was the most potent insecticide [61].

Benzoyl isothiocyanate reacts with 2-aminothiazoles to yield the corresponding *N*-(2-thiazolyl)-*N*′-benzoylthioureas **28** (R = Me, Ph; Ar = Ph) [62].



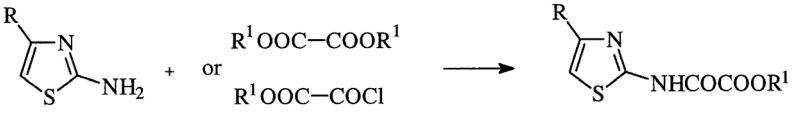
27, X = O

28, X = S

Reaction with Oxalates and Oxalyl Chlorides

Thiazolyloxamates of structure **29** (R = Ph, substituted phenyl, biphenyl, cyclohexyl-, phenyl, naphthyl, 2-pyridylmethyl, pentyl; R^1 = lower alkyl, $PhCH_2$) have been prepared from 2-aminothiazoles by the reaction with alkyl oxalyl chlorides [63–65]. An improved procedure to prepare thiazolyloxamates **29** (R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-HO -C_6H_4,

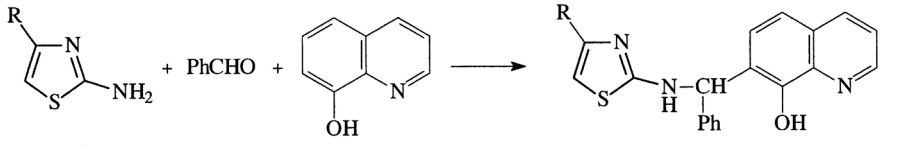
2-pyridyl; R^1 = Me, Et, t-Bu) is the reaction of 2-aminothiazoles with dialkyl oxalates in the presence of sodium alkoxides at room temperature [66]. Compounds **29** have been examined for their antiallergic activity in the rat passive cutaneous-anaphylaxis assay and the reactivity order based on the substituents in the *p*-position of the phenyl ring [65].



29

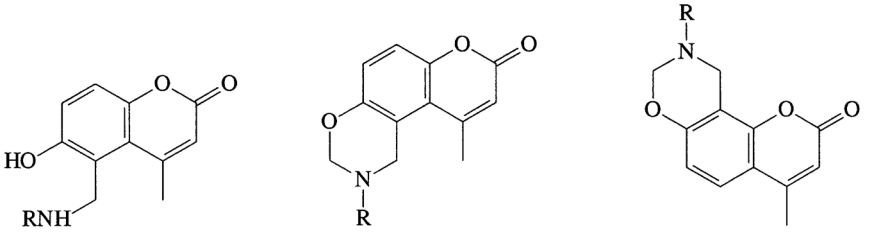
Mannich Reaction

Biologically active 7-substituted-8-hydroxyquinoline derivatives have been prepared by the Mannich reaction of 8-hydroxyquinoline with aromatic amines and aldehyde. Several workers have extended this reaction to different heterocyclic amines. Thus, 2-aminothiazoles have been condensed with benzaldehyde and 8-hydroxyquinoline to give a series of Mannich bases, **30** (R = Ph, substituted phenyl, α-$C_{10}H_7$, β-$C_{10}H_7$) [67].



30

2-Amino-4-phenylthiazole reacts with 6-hydroxy-4-methyl-chromen-2-one and formaldehyde in ethanol to afford the expected Mannich product 6-hydroxy-4-methyl-5-[(4-phenyl-2-thiazolylamine)methyl]-chromen-2-one (**31**) [68]. However, the reaction of 2-amino-4-phenylthiazole with 6- or 7-hydroxy-4-methyl-chromen-2-one and formaldehyde in acetic acid furnishes the corresponding chromeno[1,3]oxazinone **32** or **33** [68].

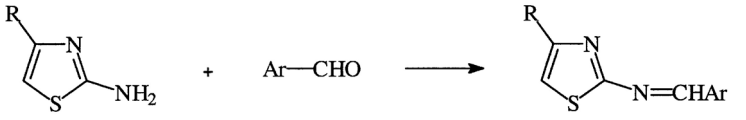


31 **32** **33**

R = 4-phenyl-2-thiazolyl

Reaction with Aldehydes

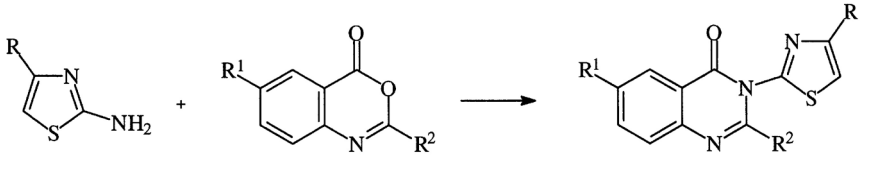
2-Aminothiazoles undergo condensation with aromatic or heterocyclic aldehydes [69–76] to give the corresponding Schiff's bases **34** (R = Me, t-Bu, Ph, substituted phenyl; Ar = Ph, substituted phenyl, 2-hydroxy-1-naphthyl, 2-thienyl, 6-substituted-3-chromonyl).



34

Reaction with 3,1-Benzoxazin-4-ones

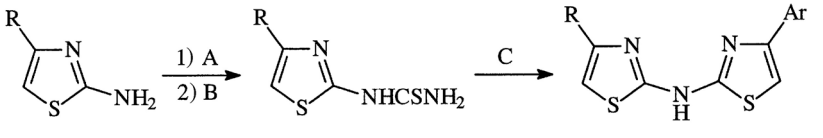
Condensation of 2-aminothiazoles with substituted benzoxazin-4-ones in dry pyridine has given the corresponding thiazolylquinazolones (**35**, R = Ph, substituted phenyl, Et, Me_2CHCH_2, thienyl; R^1 = H, Br; R^2 = Me, Ph) [77–80]. The antimicrobial activities of these compounds against various microbes were determined [78].



35

Reaction with Ammonium Thiocyanate

N-(4-Aryl-2-thiazolyl)thioureas (**36**, R = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4) have been synthesized by the reaction of 2-aminothiazoles with ammonium thiocyanate and benzoyl chloride in dry acetone, followed by hydrolysis of the resulting *N*-(4-aryl-2-thiazolyl)-*N′*-benzoyl-thioureas with 10% NaOH [81, 82]. Condensation of **36** with phenacyl bromides proceeded in ethanol to give the dithiazol-2-ylamines **37** (R = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4; Ar = Ph, substituted phenyl) [83].



36 **37**

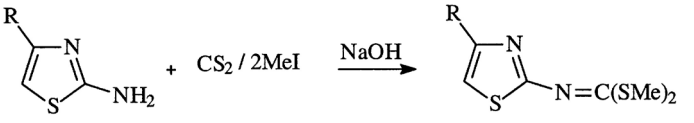
A = NH_4SCN, PhCOCl in acetone

B = 10% NaOH

C = $ArCOCH_2Br$

Reaction with CS_2/2MeI

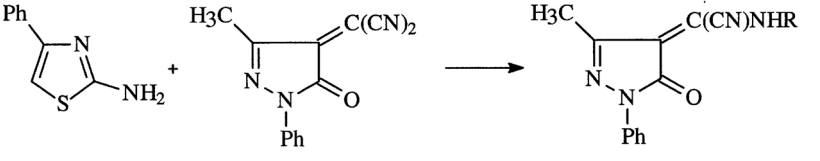
The reaction of 2-amino-4-arylthiazoles with carbon disulfide and methyl iodide in the presence of concentrated aqueous NaOH gave the corresponding dimethyl-*N*-(4-aryl-2-thiazolyl)dithiocarbonimidates (**38**, R = Ph, substituted phenyl) [83, 84].



38

Reaction with α,β-Unsaturated Compounds

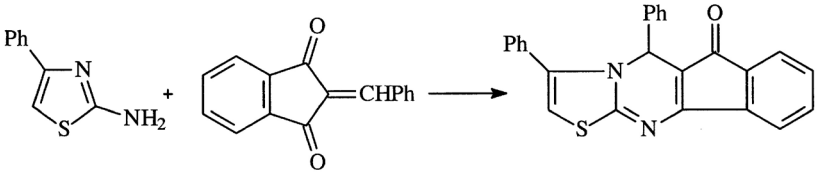
2-Amino-4-phenylthiazole has been condensed with 4-(dicyanomethylene)-3-methyl-1-phenyl-2-pyrazolin-5-one (**39**) to afford the thiazole **40** [85].



39 **40**

R = 4-phenyl-2-thiazolyl

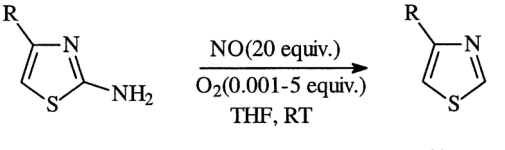
Tetracycle **41** has been prepared by the condensation of 2-amino-4-phenylthiazole with 2-benzylidene-indan-1,3-dione [86].



41

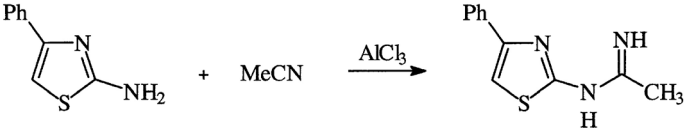
Miscellaneous Reactions

2-Aminothiazoles have been readily deaminated using nitric oxide (NO) in the presence of a catalytic amount of oxygen [87] to afford the corresponding thiazoles (**42**, R = Me, Ph).



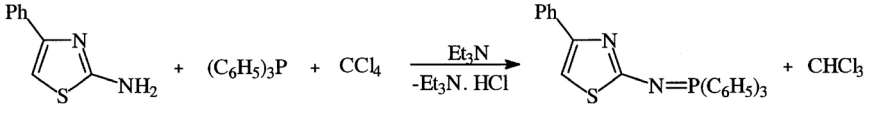
42

N-(4-Phenyl-2-thiazolyl)acetamide (**43**) has been obtained from the reaction of 2-amino-4-phenyl-thiazole with acetonitrile in the presence of anhydrous aluminium chloride [88].



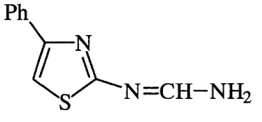
43

N-α-(4-Phenyl-2-thiazolyl)triphenylphosphinimine (**44**) has been prepared by the reaction of 2-amino-4-phenylthiazole with triphenylphosphine in the presence of triethylamine and carbon tetrachloride [89].



44

N,*N*′-Bis(4-phenyl-2-thiazolyl)formamidine (**46**) was formed as a result of the interaction between 2-amino-4-phenylthiazole with s-triazine. The intermediate **45** postulated for this reaction type was identified in an interception reaction by means of secondary amines. As a prototype, the reaction of piperidine with the intermediate product **45** to form 4-phenyl-2-piperidinoformamidoylthiazole (**47**) was cited [90].



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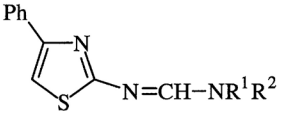
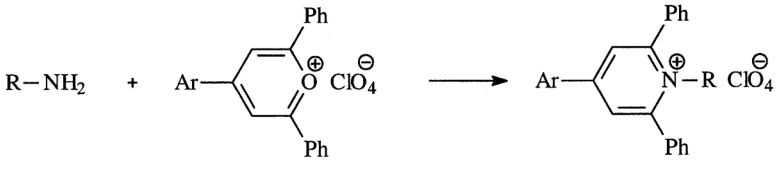


46, R^1 = H; R^2 = 4-phenyl-2-thiazolyl

47, R^1R^2 =$(CH_2)_5$

In the presence of an appropriate acid-binding agent (*e.g.* piperidine acetate or sodium acetate), 2-amino-4-phenylthiazole reacts with 2,4,6,-triarylpyrylium salts **48** via pyrylium ring transformation, yielding 2,4,6-triaryl-1-(4-phenyl-2-thiazolyl)pyridinium perchlorates (**49**) [91].



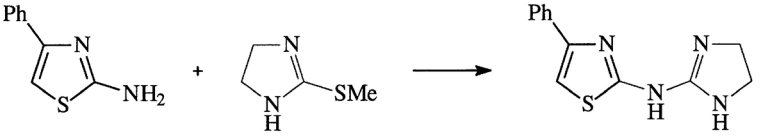
48

49

R = 4-phenyl-2-thiazolyl;

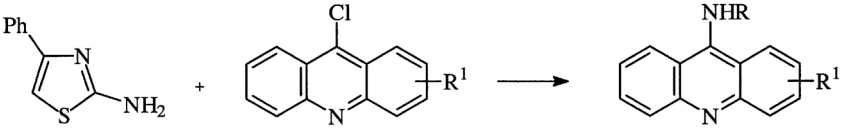
Ar = Ph, 4-ClC_6H_4

Imidazoline **50** was prepared by the reaction of 2-methylthio-2-imidazoline with 2-amino-4-phenylthiazole, and showed bactericidal activity [92].



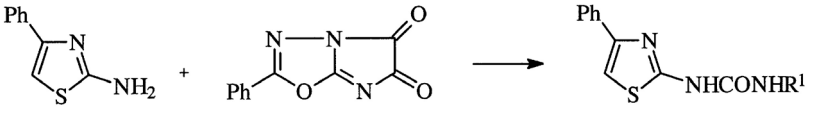
50

9-(4-Phenyl-2-thiazolylamino)acridine derivatives **52** (R = 4-phenyl-2-thiazolyl; R^1 = H, 3-Cl, 1-Me, 3-Me) have been prepared as fungicides by treating 2-amino-4-phenylthiazole with the corresponding 9-chloroacridines (**51**) [93].



51 **52**

2-Amino-4-phenylthiazole reacts as a nucleophile with 2-phenylimidazo[2,1-*b*]-oxadiazole-5,6-dione (**53**) to give the urea derivative **54** (R^1 = 5-phenyl-1,3,4-oxadiazol-2-yl) [94].



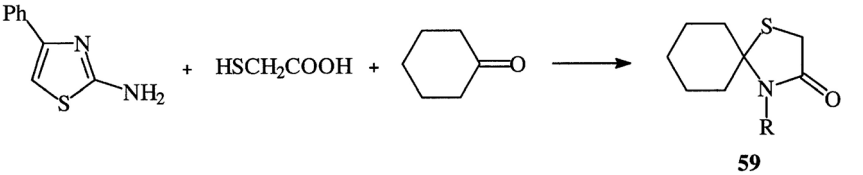
53 **54**

2-Aminothiazoles (**3**) have been shown to react with 2-phenyl-2-oxazolin-5-one (**55**) to give the corresponding hippurylaminothiazoles (**57**). Ethoxymethylene-2-oxazolin-5-one (**56**), however, reacts with 2-aminothiazoles to give the corresponding 4-(2-thiazolylamino-methylene)-2-oxazolin-5-ones (**58**) [95].

55, Z = CH_2 **57** **58**

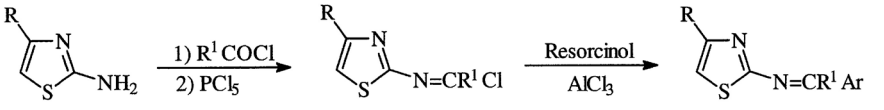
56, Z = C=CHOEt R = Ph, 4-HOC_6H_4

4-(4-Phenyl-2-thiazolyl)-1-thia-4-azaspiro[4.5]decan-3-one (**59**, R = 4-phenylthiazol-2-yl) has been prepared by refluxing equivalent quantities of a mixture of cyclohexanone, mercaptoacetic acid and 2-amino-4-phenylthiazole in either benzene or toluene [96].



59

N-(4-Aryl-2-thiazolyl)-2,2-diarylazomethines (**61**) have been prepared by condensing the appropriate imido chlorides (**60**) with resorcinol in the presence of anhydrous aluminium chloride. The imido chlorides (**60**) were obtained from 2-aminothiazoles by acylation and chlorination of the so-produced amides with PCl_5 [97].



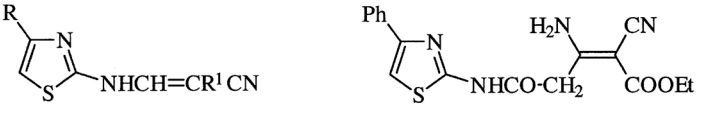
60 **61**

R = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$

R^1 = Ph, 2,4$(Cl)_2C_6H_3$; Ar = 2,4$(HO)_2C_6H_3$

2-Aminothiazoles were treated with EtO−CH=CR_1CN in ethoxide-ethanol to give 2-thiazolyl-aminopropenenitriles (**62**, R = alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkyl- sulfonyl, cycloalkyl; R^1 = CN, 1*H*-tetrazol-5-yl) [98].

2-Amino-4-phenylthiazole has been treated with diethyl-3-amino-2-cyano-2-pentendioate to yield the corresponding amide derivative **63** [99].



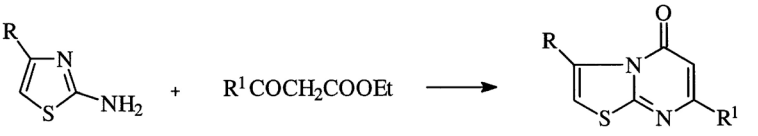
62 **63**

CYCLIZATION REACTIONS

Reaction with β-Ketoester, DEMM, 2-Acetylbutyrolactone

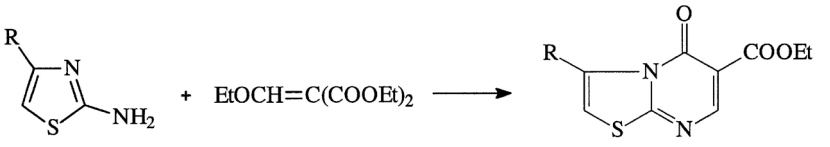
Formation of Thiazolo[3,2-a]pyrimidin-5-ones

The condensation products 3,7-disubstituted-thiazolo[3,2-*a*]pyrimidin-5-ones (**64**, R = Me, Ph, *p*-MeC_6H_4, *p*-ClC_6H_4; R^1 = Me, Ph) were obtained from the reaction of 2-aminothiazoles with the corresponding β-ketoester [100–102]. The compounds **64** (R^1 = CH=CHR^2 where R^2 = substituted and unsubstituted pyridyl; R = Me, Ph) have been prepared [103].



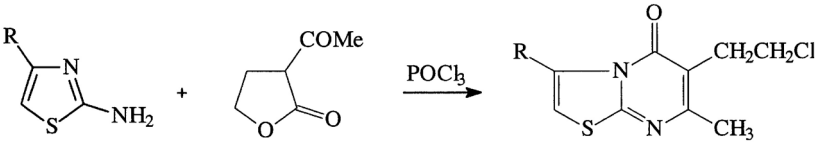
64

2-Aminothiazoles react with diethyl ethoxymethylenemalonate (DEMM) to furnish the corresponding 3-substituted-6-carbethoxythiazolo[3,2-*a*]pyrimidin-5-ones (**65**, R = Me, Ph, 4-ClC_6H_4) [100, 101].



65

The reaction of 2-aminothiazoles with 2-acetylbutyrolactone and $POCl_3$ gave 6-chloro-ethyl-7-methyl-thiazolo[3,2-*a*]pyrimidin-5-ones (**66**, R = Ph optionally substituted by C_{1-2} halo, C_{1-4} alkyl, C_{1-4}-alkoxy and CF_3) [104].

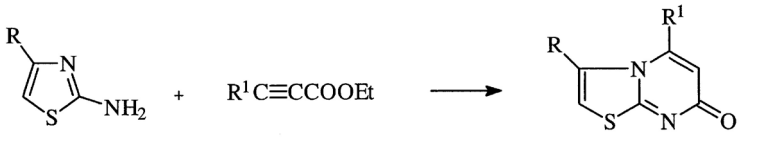


66

Reaction with Ethyl Propiolates, Methyl Acrylate

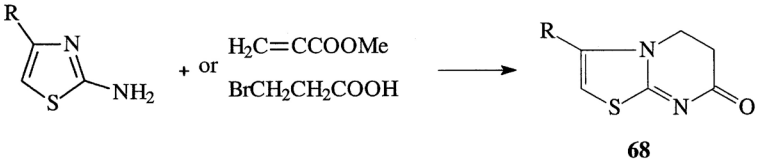
Formation of Thiazolo[3,2-a]pyrimidin-7-ones

2-Aminothiazoles were reacted with 3-substituted propiolic acid esters to give the corresponding 3,5-disubstituted thiazolo[3,2-*a*]pyrimidin-7-ones (**67**, R = Me, Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$; R^1 = H, Me, Ph, CH_2Cl, COOEt) [105–107].



67

2-Aminothiazoles also react with methyl acrylate in the presence of hydroquinone or with bromopropionic acid to give 5,6-dihydrothiazolo[3,2-*a*]pyrimidin-7-ones (**68**) [108].



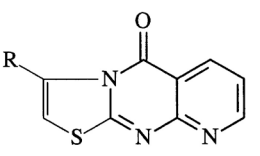
68

R = Me, Ph

Reaction with Chloronicotinic Acids

2-Aminothiazoles react with 2-chloronicotinic acid to furnish 3-aryl-5*H*-pyrido[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-ones (**69**, R = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4) [109],

while the reaction of 2-aminothiazoles with 2-chloropyridine-3-carbonyl chloride affords 9-aryl-5-oxo-5*H*-pyrido[3′, 2′:5, 6]pyrimido[2,1-*b*]thiazoles (**70**, R = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4) [110].



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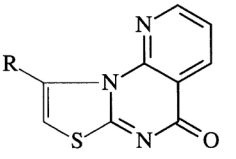
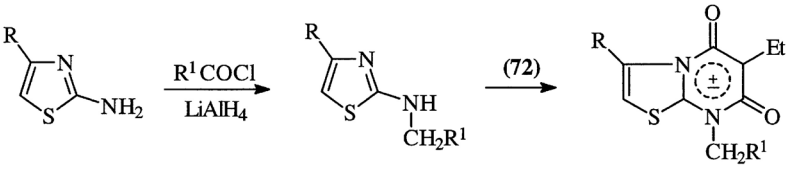


70

Formation of Thiazolo Pyrimidindiones

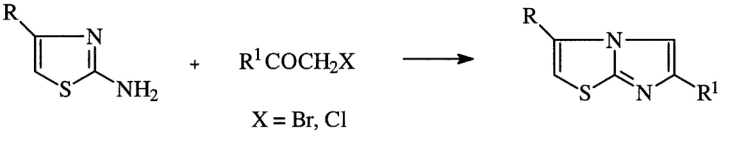
Mesoionic thiazolo[3,2-*a*]pyrimidin-5,7-diones (**73**, R = Me, Ph; R^1 = Me, cyclopropyl) have been prepared simply by the thermal condensation of 2-alkylamino-4-phenylthiazole (**71**) with bis(2,4,6-trichlorophenyl)ethyl malonate (**72**) [111].



71 **73**

Reaction with α-Halocarbonyl Compounds

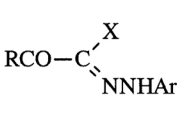
2-Aminothiazoles react with α-halocarbonyl compounds, *e.g.* (un)substituted phenacyl bromides [112, 113], *N,N*-disubstituted chloroacetamides [114], 2-bromoacetyl chromones [115], 3-bromo-2-oxo-propionic acid ethyl ester [116], to give the corresponding 3,6-di-substituted-imidazo[2,1-*b*]thiazoles (**74**, R = Ph, substituted phenyl, β-naphthyl, Me; R^1 = Ph, substituted phenyl, Et_2NCl, EtHNCl, MeHNCl, $C_6H_{10}NCl$, substituted-6-chromonyl, COOEt).



74

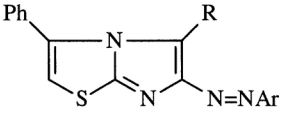
When equivalent amounts of 2-amino-4-phenylthiazole and **75** were refluxed in ethanol in the presence of triethylamine, the product 6-arylazo-3,5-disubstitutedimidazo[2,1-*b*]thiazoles (**76**, R = Me, Ph, substituted phenyl, heteroaryl; Ar = Ph, substituted phenyl) were obtained

in good yield [117–119]. The similar reaction of the chlorides **75** (R = OEt) with 2-amino-4-phenylthiazole yielded the products **77** [117].



75

X = Cl, Br



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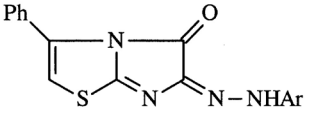
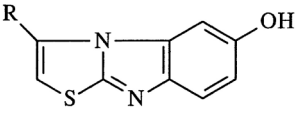


77

Reaction with *p*-Benzoquinone

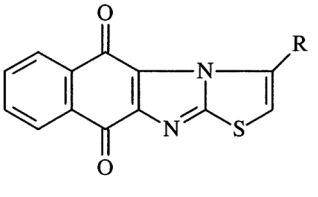
6-Hydroxy-3-substituted thiazolo[3,2-*a*]benzimidazoles (**78**, R = Me, Ph, 4-MeC_6H_4, 4-Br-C_6H_4, 4-HOC_6H_4, 2-thienyl, 2-naphthyl) have been synthesized by condensation of substituted 2-aminothiazoles with *p*-benzoquinone in acetic acid. A study of the absorption spectra of the synthesized compounds in ethanol at different pH shows a bathochromic shifting of the absorption maxima in both acidic and alkaline media [120].



78

Reaction with 2,3-Dichloronaphthoquinone and 2,3-Dichloroquinazoline

Thiazoloquinones (**79**, R = Me, Et, Ph) have been obtained in 40–50% yield by refluxing 2-aminothiazoles with 2,3-dichloronaphthoquinone in ethanol [121]. 2,3-Dichloroquinazoline also reacts with 2-amino-4-phenylthiazole to give **80** [122].



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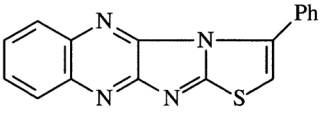
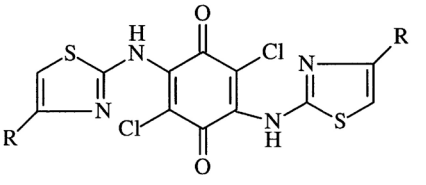


80

Reaction with Chloranil

2-Aminothiazoles react with chloranil in glacial acetic acid at room temperature to give the corresponding 2,5-dichloro-3,6-bis(2-thiazolylamino)-1,4-benzoquinone **81** (R = Me, Ph, 4-

MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4) [123, 124]. However, a mixture of **82** (Z-form) and **83** (E-form) was obtained by heating 2-aminothiazoles with chloranil in ethanolic medium [123].



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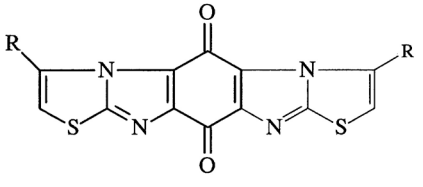

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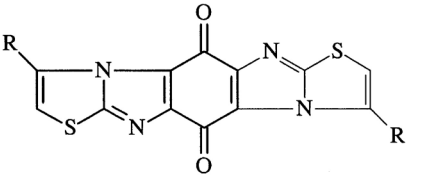
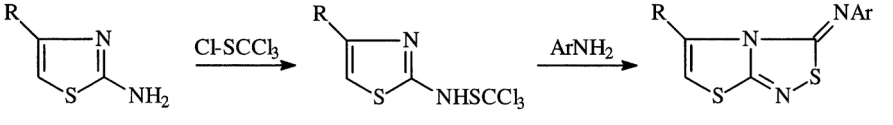


83

Reaction with Cl-$SCCl_3$ and Aromatic Amines

The reaction of 2-aminothiazoles (**3**) with perchloromethyl mercaptan at room temperature gave the corresponding 2-thiazolyl trichloromethane sulfenamides (**84**), which on treatment with aromatic amines afforded 3,5-disubstituted-3*H*-thiazolo[2,3-*c*][1,2,4]thiadiazoles (**85**, R = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 2,4-$(Cl)_2C_6H_3$; Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$) [125].

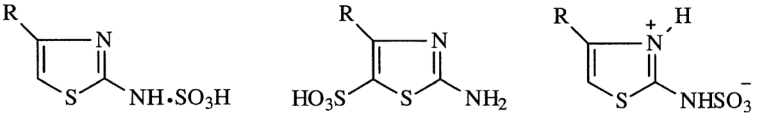


3 **84** **85**

ELECTROPHILIC SUBSTITUTION REACTIONS

Sulfonation

Hurd and Kharasch [126] found that, at low temperatures, fuming sulfuric acid converted 2-aminothiazoles into 2-thiazolylsulfamic acids (**86**, R = Me, Ph). At higher temperatures the sulfamic acid was converted into an isomeric amino sulfonic acid (**87**, R = Me) [126]. The high stabilities displayed by the 2-thiazolylsulfamic acids suggest that the 2-thiazolylsulfamic acids are better represented by the dipolar ion **88**.



86 **87** **88**

Halogenation

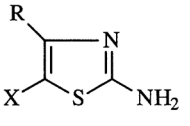
2-Aminothiazoles gave the monohalo-derivatives 2-amino-5-halothiazoles **89** (R = Me, Ph; X = Br, Cl) when subjected to halogenation conditions [127, 128].

Formylation

Formylation of 2-amino-4-phenylthiazole by $POCl_3$–DMF (Vilsmeier–Haack formylation) yields the corresponding 5-formylthiazole **90** [129, 130] through electrophilic attack at C-5.

Chlorosulfonation

2-Amino-4-phenylthiazole on acetylation followed by chlorosulfonation of the resultant 2-acetylamino-4-phenylthiazole under controlled conditions gave 2-acetylamino-4-phenylthiazole-5-sulfonyl chloride (**91**) [131].



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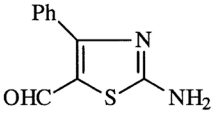

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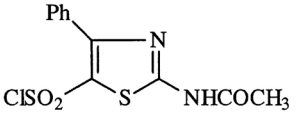
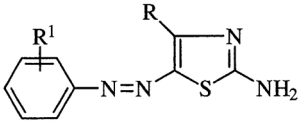


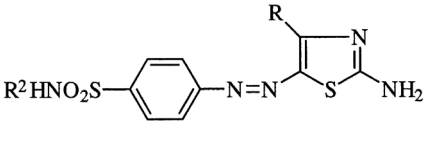
91

Coupling with Diazonium Salts

2-Aminothiazoles (**3**) undergo coupling reactions when treated with aromatic diazonium salts [132–134] or diazotized sulfanilamides [135, 136] to give the corresponding 2-amino-5-aryl-azothiazoles **92** [R = Me, Ph, 4-ClC_6H_4; R^1 = H, Me, OMe, 4-Cl, 4-phenoxy, 4-(4-chlorophenoxy)] or **93** (R = Ph, substituted phenyl; R^2 = H, guanidino, 2-thiazolyl, 2-pyrimidyl and other heterocycles) respectively.



92

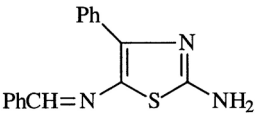


93

OTHER SUBSTITUTION REACTIONS

2-Amino-4-phenylthiazole undergoes nitrosation at the 5-position when treated with isoamylnitrile to give the corresponding 5-nitroso derivative. Subsequent reduction with zinc and acetic acid followed by condensation with benzaldehyde produced 2-amino-4-phenyl-5-benzalaminothiazole (**94**) [137].

2-Amino-4-phenylthiazole reacts with rhodanamine (*S*-cyanothiohydroxylamine) at the 5-position to produce the corresponding 2-amino-4-phenyl-5-rhodanothiazole (4-phenyl-5-thiocyanatothiazole-2-amine, **95**) [138].



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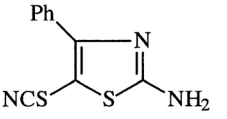
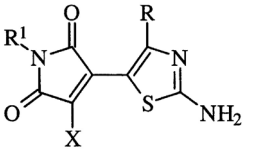


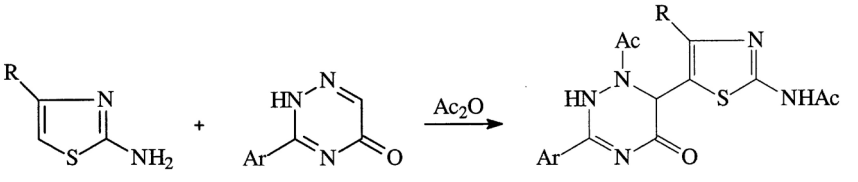
95

The maleimides **96** (R^1 = H, aliphatic or aromatic group; X = CN, C_{1-6} alkylsulfonyl, SO_2Ph; R = halo, C_{1-4} alkyl, phenyl, substituted phenyl, 2-furyl, 2-thienyl) were prepared by the reaction of 2-chloromaleimides with 2-aminothiazoles [139].



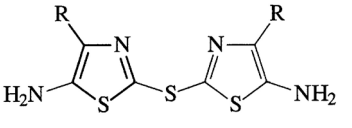
96

2-Aminothiazoles react in acetic anhydride with compounds **97**, yielding 1-acetyl-3-aryl-6-(2-acetylamino-5-thiazolyl)-1,6-dihydro-1,2,4-triazin-5-(2*H*)-ones (**98**) [140]. (R = Ph; Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4).



97 **98**

The synthesis of bis(2-amino-5-thiazolyl)sulfides (**99**) has been achieved by reacting the appropriate 4-substituted-2-aminothiazole with thiourea and elemental iodide at room temperature in the presence of sodium hydroxide (R = CH_3, $CH_3CHCOOEt$, C_2H_5, $C_2H_5CHCOOEt$) [141].



99

CONCLUSION

2-Amino-4-substituted-1,3-thiazoles are easily available and offer countless modifications by numerous reaction modes in various positions due to their high reactivity. This has been comprehensively documented. Apart from the synthetic interest, the known and expected biological or medicinal activities of the numerous derivatives deserve particular mention. The field is far from being exhausted in all of its subdivisions and many new developments and uses await

exploration. In fact, more recent work used some of the title compounds for reactions both at the amino function and at C-5 of the 1,3-thiazole moiety and new azo dyes with favourable dyeing properties have already been synthesized [142, 143].

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