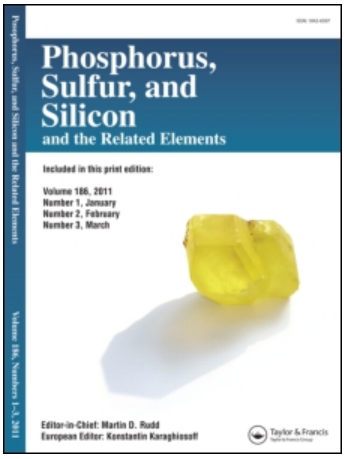

Phosphorus, Sulfur, and Silicon and the Related Elements

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Recent Trends in Chemistry of Thiazolopyridines

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Recent Trends in Chemistry of Thiazolopyridines

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The aim of this review article is to present the syntheses, reactions, and applications of thiazolopyridines.

Keywords Thiazolo[3,2-a]pyridine; thiazolo[3,4-a]pyridine; thiazolo[4,5-b]pyridine; thiazolo[4,5-c]pyridine; thiazolo[5,4-b]pyridine; thiazolo[5,4-c]pyridine

INTRODUCTION

There are six isomeric thiazolopyridine systems reported in the literature. Depending on the fusion of the thiazole moiety to the pyridine ring, thiazolopyridines can be classified into the following classes (see Scheme 1): Thiazolo[3,2-a]pyridine (**I**), thiazolo[3,4-a]pyridine (**II**), thiazolo[5,4-b]pyridine (**III**), thiazolo[5,4-c]pyridine (**IV**), thiazolo[4,5-c]pyridine (**V**), and thiazolo[4,5-b]pyridine (**VI**).

The present review article deals with these six systems and their chemically and biologically active derivatives.

THIAZOLO[3,2-a]PYRIDINES

Synthesis and Reactions of Thiazolo[3,2-a]pyridines

Synthesis from Multicomponent Reactions

7H-thiazolo[3,2-a]pyridine-3(2*H*)-ones (**4**) were obtained in high yields from benzylidenemalononitrile (**1**, Ar=C_6H_5) and thiocarbamoy-

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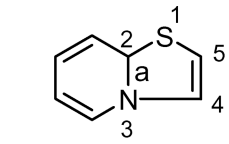
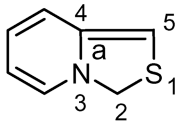


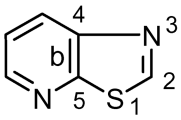
Thiazolo[3,2-*a*]pyridine

(I)



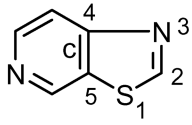
Thiazolo[3,4-*a*]pyridine

(II)



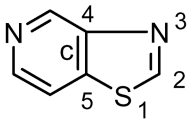
Thiazolo[5,4-*b*]pyridine

(III)



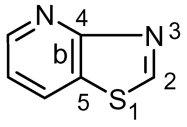
Thiazolo[5,4-*c*]pyridine

(IV)



Thiazolo[4,5-*c*]pyridine

(V)



Thiazolo[4,5-*b*]pyridine

(VI)

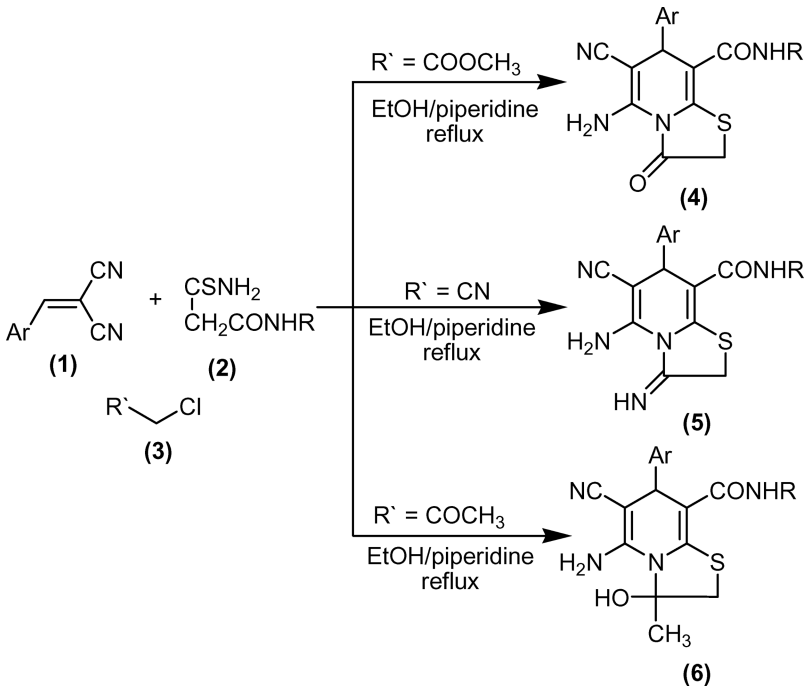
SCHEME 1

lacetamides (**2**) in the presence of an equimolar amount of piperidine and methyl chloroacetate (**3**; R′=$COOCH_3$) after a brief heating at 30–40°C. The use of chloroacetonitrile (**3**; R′=CN) instead of methyl chloroacetate gave the corresponding thiazolo[3,2-a]pyridine-3-imines (**5**), while chloroacetone (**3**; R′=$COCH_3$) as an alkylating agent afforded 3-hydroxy-2,3-dihydro-7H-thiazolo[3,2-a]pyridines (**6**) in 83–91% yields[1] (Scheme 2).

Ternary condensation of aromatic aldehydes, malononitrile, and thioglycolic acid (2:2:1 molar ratio) in absolute ethanol in the presence of a catalytic amount of piperidine yielded 5-amino-2-arylmethylidene-7-aryl-6,8-dicyano-3-oxo-2,3-dihydro-7H-thiazolo[3,2-a]pyridines (**7**) in good yields[2,3] (Scheme 3).

A reaction mechanism[2] is proposed for the formation of the thiazolopyridines (**7**) and is illustrated in Scheme 4.

Reactions of thiazolo[3,2-a]pyridines (7) with some electrophilic and nucleophilic reagents. El-Maghraby and colleagues[2] reported the reactivity of thiazolopyridines (**7**), which contains chalcone and

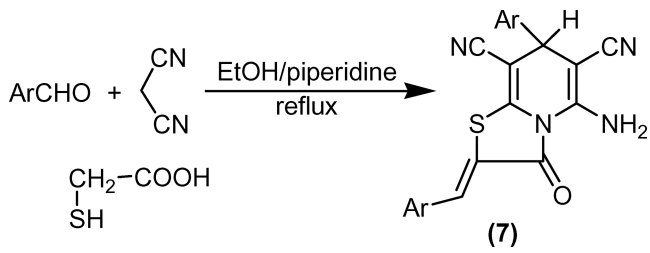


SCHEME 2

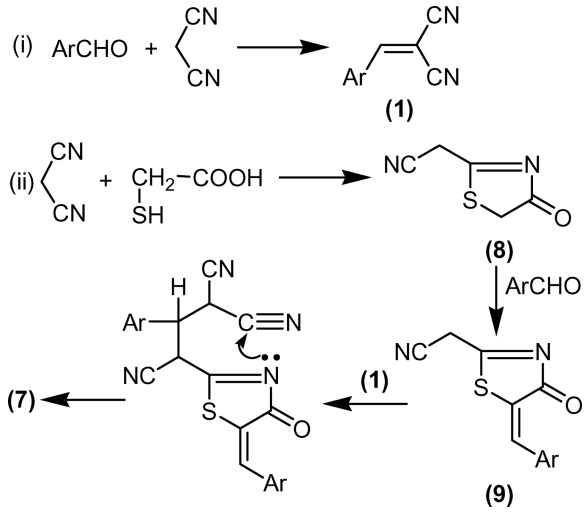
o-aminonitrile moieties, towards some electrophilic and nucleophilic reagents.

1. With Acetic anhydride

Compound **7** (Ar=C_6H_4F-4) was refluxed with acetic anhydride to yield thiazolo[2′,3′:1,6]pyrido[2,3-d]pyrimidine (**11**), through a Dimroth rearrangement of an initial cyclization product (**10**) under the applied reaction conditions[2] (Scheme 5).



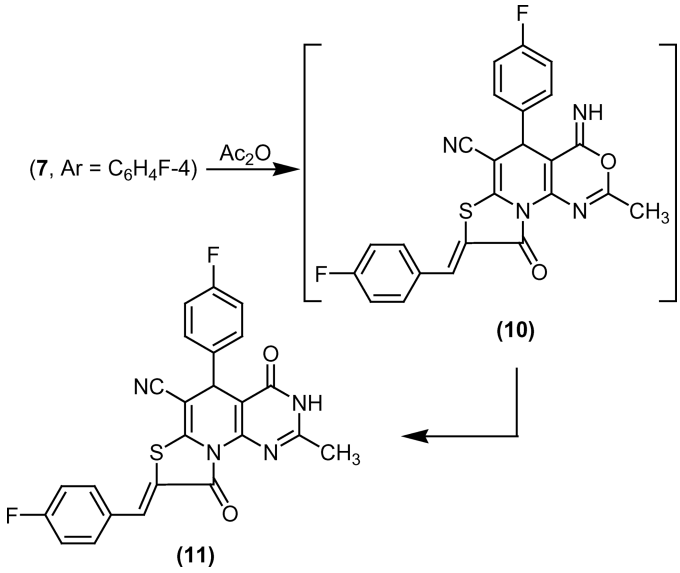
SCHEME 3



SCHEME 4

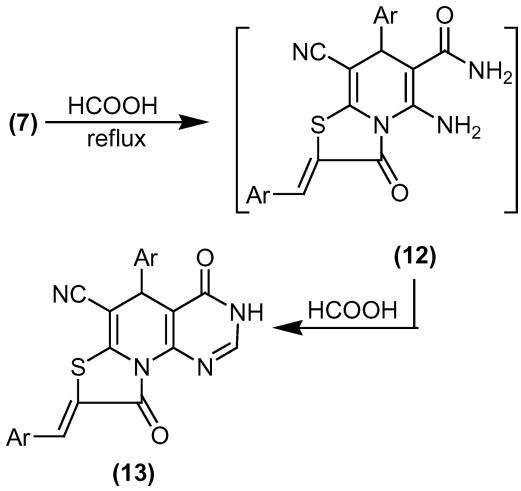
2. With formic acid

Thiazolo[2′,3′:6,1]pyrido[2,3-d]pyrimidines (**13**) were obtained by the refluxing of compounds (**7**) in formic acid, via intermediate amide formation (**12**), which resulted from the partial hydrolysis of cyano



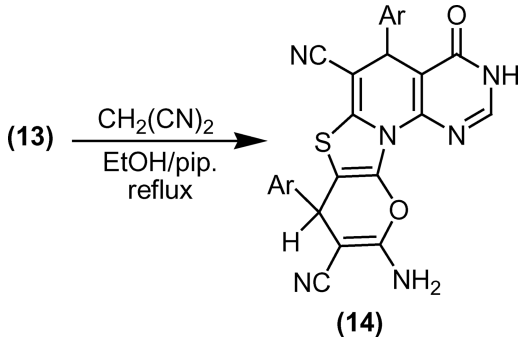
SCHEME 5

functionally present at the position six of (**7**) and was followed by intramolecular cyclization[2] with formic acid (Scheme 6).



SCHEME 6

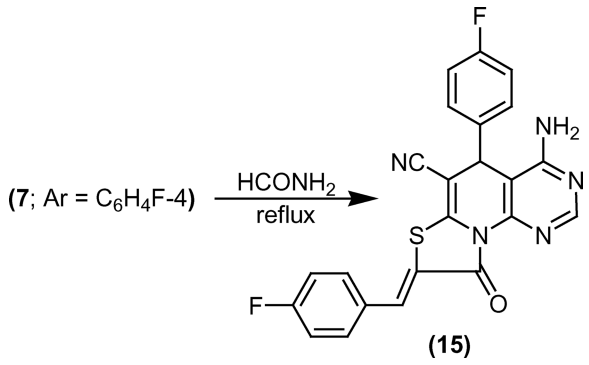
When the α,β-unsaturated ketone (**13**) was treated with malononitrile in ethanol containing a catalytic amount of piperidine the pyrano[2′,3′:4,5]thiazolo[3′,2′:6,1]pyrido[2,3-a]pyrimidine, (**14**) was obtained[3] (Scheme 7).



SCHEME 7

3. With formamide

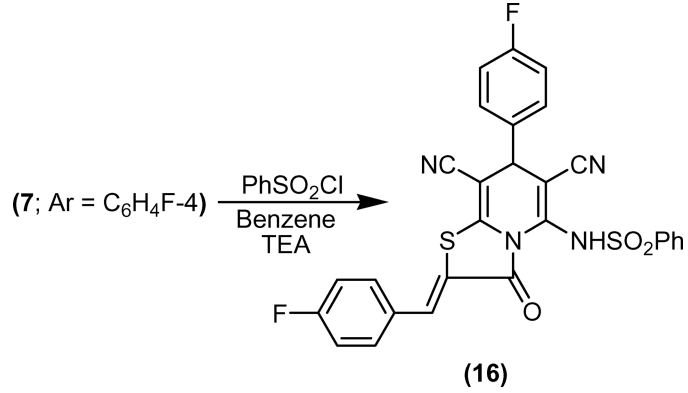
The heating of **7** (Ar=C_6H_4F-4) with formamide yielded the corresponding thiazolopyridopyrimidine (**15**)[2] (Scheme 8).



SCHEME 8

4. With benzene sulfonyl chloride

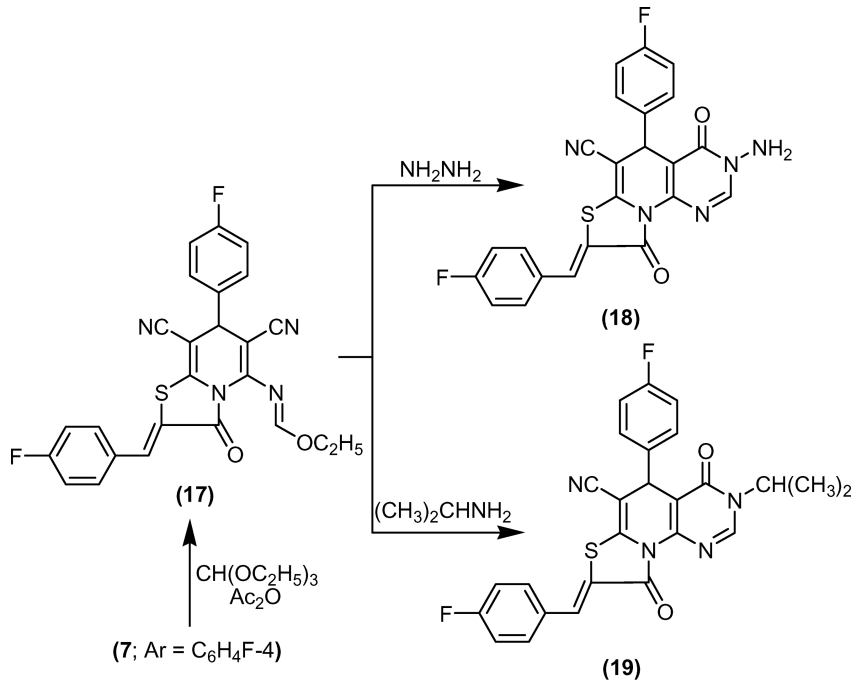
The treatment of **7** (Ar=C_6H_4F-4) with benzene sulfonyl chloride in benzene furnished the novel sulfonamide derivative (**16**)[3] (Scheme 9).



SCHEME 9

5. With triethyl orthoformate

Ethoxymethylene derivative (**17**) was obtained by refluxing **7** (Ar=C_6H_4F-4) with triethyl orthoformate as electrophile in the presence of acetic anhydride.[2] The treatment of (**17**) with hydrazine hydrate in ethanol at r.t. furnished the novel thiazolopyridopyrimidine derivative (**18**) in good yield.[2] Also, compound (**17**) under-went aminolysis and cyclization by refluxing with isopropyl-amine in absolute ethanol to give (**19**)[2] (Scheme 10).



SCHEME 10

6. With malononitrile

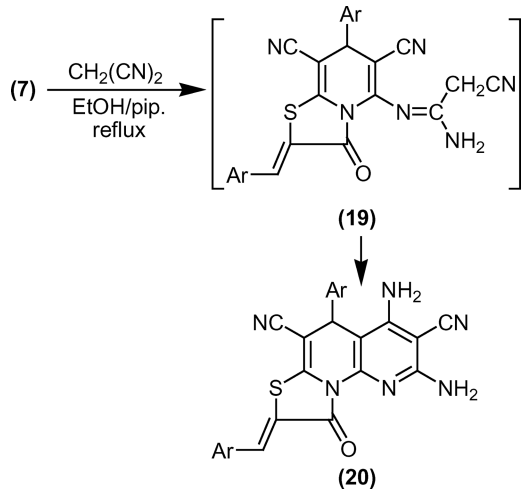
Compounds (**7**) were allowed to react with malononitrile in ethanol in the presence of pipridine under reflux to give thiazolo[3,2-a]naphthyridines (**20**)[3] (Scheme 11).

Hypoglycemic agent (**23**) was readily synthesized from aminoethanethiol (**22**) and keto acid (**21**) in one step via cyclocondensation[4] in an excellent yield (85%) (Scheme 12).

Synthesis from Thiazole Derivatives

Cyclocondensation of 2-cyanomethyl-5-[4-morpholin-4-yl)-benzylidenyl]-4,5-dihydro-4-thiazolinone (**24**) with malononitrilele in ethanol in the presence of triethylamine under reflux furnished the novel thiazolo[3,2-a]pyridine derivative (**25**)[5] (Scheme 13). The formation of thiazolopyridine (**25**) is assumed to proceed via the addition of the active methylene in malononitrile to the cyano function group in (**24**) followed by intramolecular cyclization[5] at the cyano group and tautomerization to furnish (**25**) (Scheme 13).

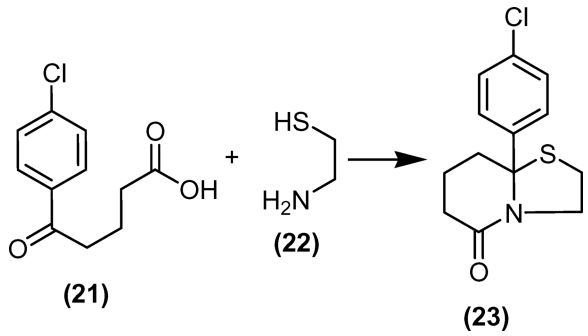
Elgemeie and Sayed[6] reported the synthesis of thiazolo[3,2-a]-pyridines (**29**) by the condensation of cyanoacetic acid



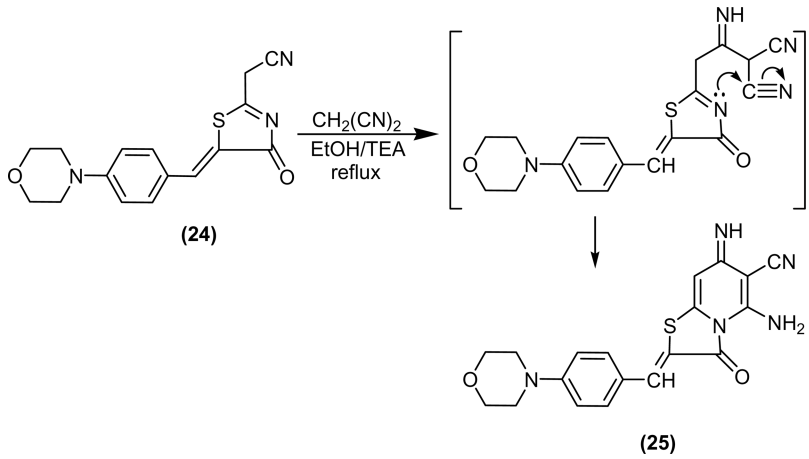
SCHEME 11

2-(arylsulfonyl)hydrazides (**26**) with thioglycolic acid to give (**27**), followed by cyclization with heteroarylidenemalononitriles (**28**) (Scheme 14).

1,4-bis[5-amino-7-aryl-2-methylidene-2,3-dihydro-7H-3-oxothiazolo [3,2-a]pyridine-6,8-dicarbonitrile-2-yl]benzene derivatives (**32**)[7] were achieved when a solution of 1,4-bis(2-cyanomethyl-4,5-dihydro-5-methylidene-4-thiazolinone-5-yl)-benzene (**30**) and arylidenemalononitrile (**1**) (in a 1:2 molar ratio) was heated under reflux in absolute ethanol in the presence of a catalytic amount of piperidine via a



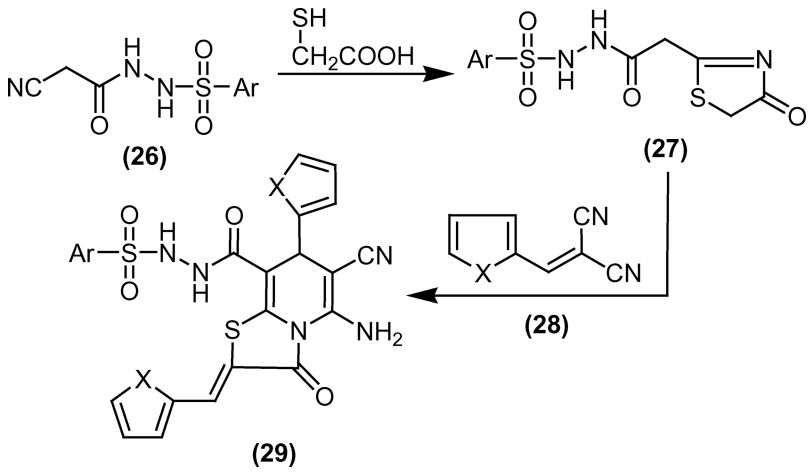
SCHEME 12



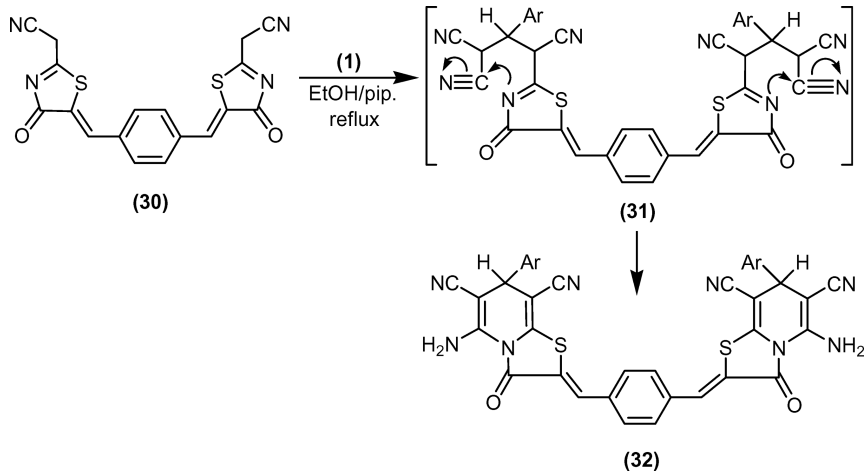
SCHEME 13

Michael adduct (**31**) followed by intramolecular cyclization at the cyano group (Scheme 15).

Also, the reaction of the benzylidene derivative (**33**) with an excess of 5-arylmethylidene-2-cyanomethyl-4,5-dihydro-4-thiazolinones (**9**) in absolute ethanol in the presence of triethylamine gave 1,4-bis[5-amino-2-arylmethylidene-2,3-dihydro-7H-3-oxo-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile-7-yl]benzene derivatives (**34**)[7] (Scheme 16).



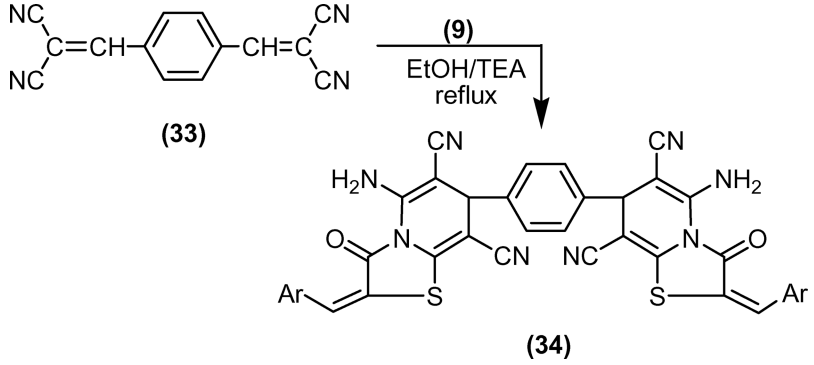
SCHEME 14



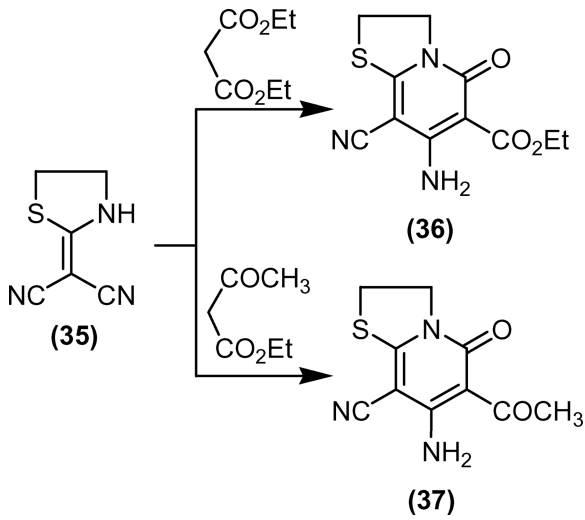
SCHEME 15

Cyclic ketene acetal (**35**) reacted with diethyl malonate and ethyl acetoacetate to give thiazolo[3,2-a]pyridines (**36**) and (**37**),[8] respectively (Scheme 17).

2-methylenethiazolidinones (**38**) reacted smoothly with methyl propiolate (**39**) in boiling absolute ethanol to give 8-substituted-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-5-ones (**40**) in high yields. In a similar manner, compounds (**38**) reacted readily with dimethyl acetylenedicarboxylate (**41**) to furnish thiazolo[3,2-a]pyridines (**42**). Compounds (**38**) also reacted with methyl acrylate (**43**) in boiling ethanol to yield thiazolo[3,2-a]pyridines[9] (**44**) (Scheme 18).

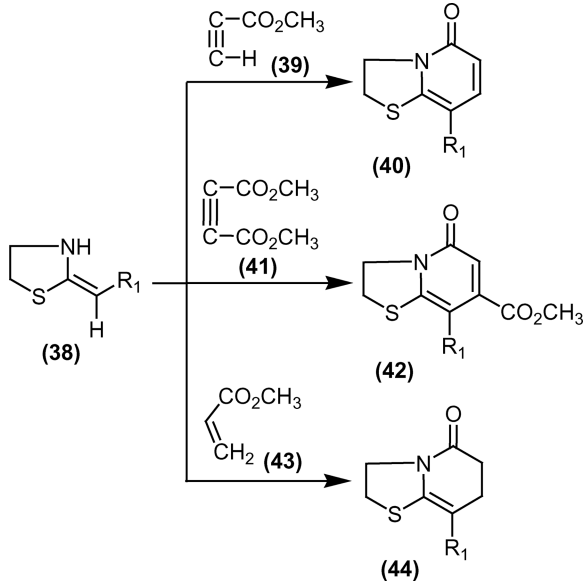


SCHEME 16

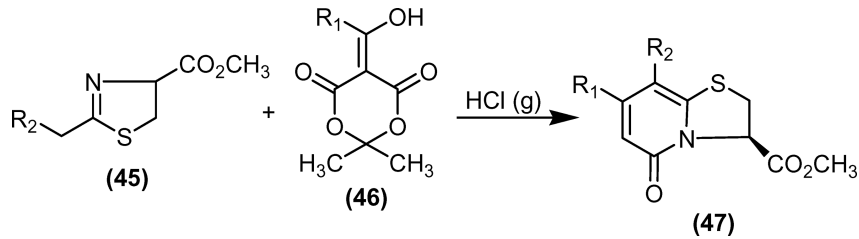


SCHEME 17

When 2-alkyl-Δ^2-thiazoline (**45**) and Meldrum's acid derivatives (**46**) were treated with HCl (g) in benzene, the thiazolo[3,2-a]pyridine-3-carboxylic acid derivatives (**47**) were obtained[10,11] (Scheme 19).



SCHEME 18



SCHEME 19

The above reaction products in Scheme 19 were assumed according to the following mechanism[10] (Scheme 20):

The dimerization of 2-alkenylthiazolines (**48**) with trifluoroacetic anhydride in chloroform at r.t. furnished the novel 2-(5,7-diaryl-2,3,6,7-tetrahydro-5*H*-[1,3]thiazolo[3,2-a]pyridine-6-ylidene)-3-(2,2,2-trifluoroacetyl)-4,5-dihydro-1,3-thiazoles (**49**)[12] (Scheme 21).

The formation of the thiazolopyridines (**49**) could be explained through the following reaction mechanism (Scheme 22):[12]

Reaction of compound **49** (Ar=C_6H_5) with sodium borohydride in ethanol gave the novel thiazolopyridine derivative (**50**)[12] (Scheme 23).

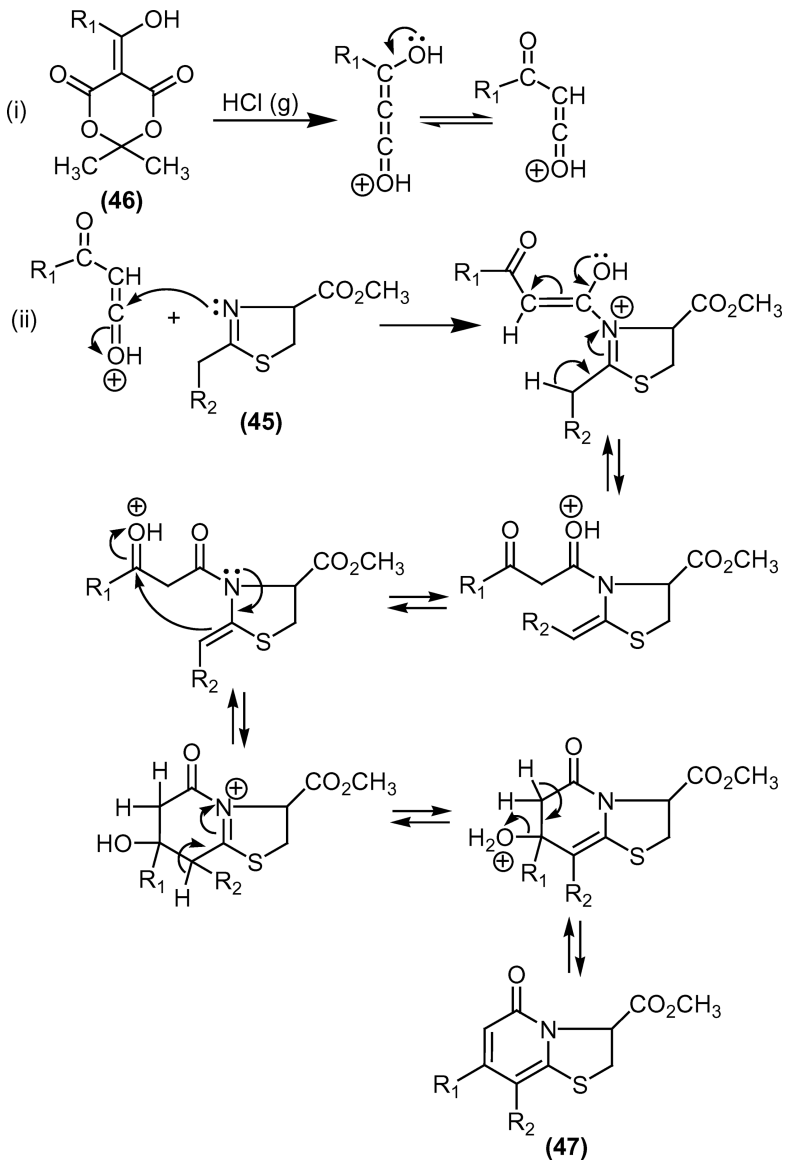
[Bis(methylsulfanyl)methylidene]malononitrile (**52**) reacted with 1,3-thiazol-4(5*H*)-one derivative (**51**) in refluxing dimethylformamide containing the equivalent amount of potassium carbonate to yield the 7-methylsulfanylthiazolo-[3,2-a]pyridine derivative (**53**)[13] (Scheme 24).

The benzimidazolylthiazolo[3,2-a]pyridines (**55**)[14] were prepared by reaction of 2-[(4-oxo-4,5-dihydrothiazol-2-yl)methyl]-1*H*-benzimidazole (**54**) with arylidenemalononitrile (**1**) in 1:2 molar ratio (Scheme 25). Compounds (**55**) were screened as antimicrobial, anti-HIV, and anti-cancer agents.[14]

By the reaction of 4-methylthiazole derivative (**56**) with ethoxymethylenemalononitrile (**57**) in the presence of potassium carbonate, the corresponding thiazolo[3,2-a]-pyridine derivative (**58**)[15] was obtained (Scheme 26).

The treatment of *tert*-butyl-2-(3-dicyano-2-aryl allylidene)-thiazolidene-3-carboxylates (**59**) with trifluoroacetic acid at r.t. led to the formation of thiazolo-[3,2-a]pyridines (**60**).[16] These heterobicycles were formed by the proton-catalyzed intramolecular addition of the intermediately formed NH-group of the thiazolidine to one of the nitrile functions[16] (Scheme 27).

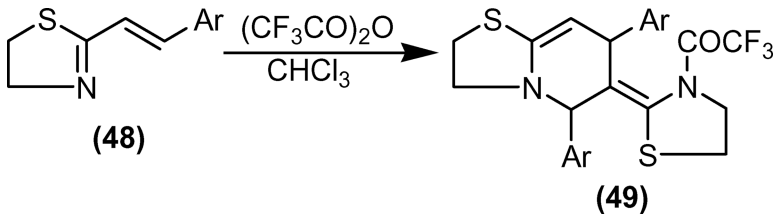
Moderate-to-high yields of *tert*-butyl substituted thiazolo[3,2-a]pyridines (**63**) were obtained by the addition of 2-lithiothiazole (**62**) to *tert*-butylcyclobutene-1,2-diones (**61**) followed by an acetic anhydride



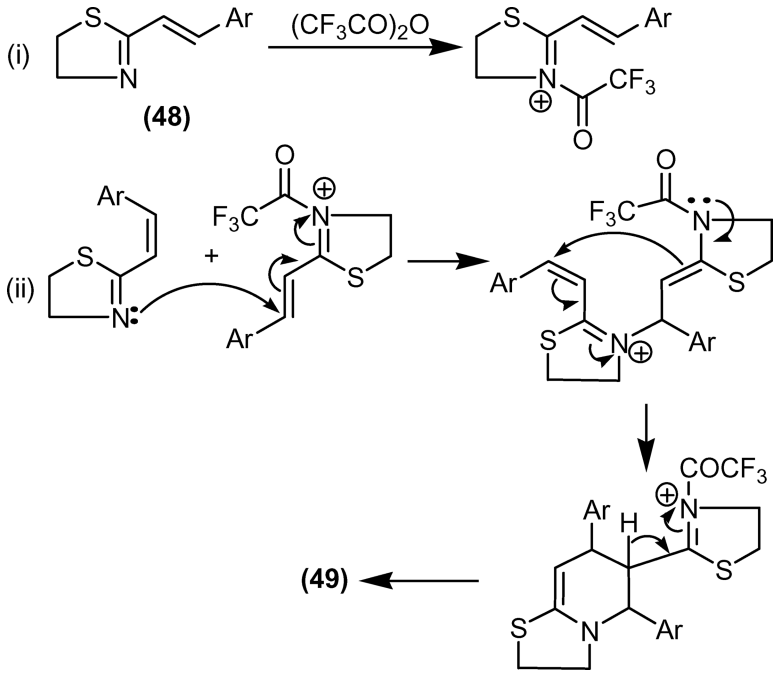
SCHEME 20

quench and the thermolysis of the crude reactions products[17] (Scheme 28).

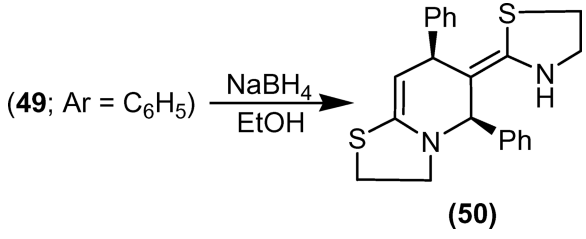
Cleavage of the *tert*-butyl substituent in compounds (**63**) was proceeded by refluxing in acetic acid and gave products (**64**) via protonation



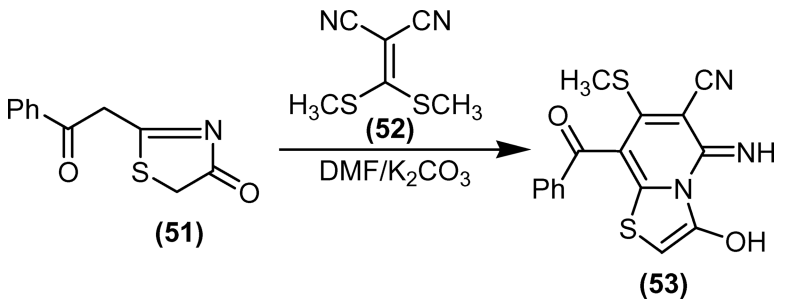
SCHEME 21



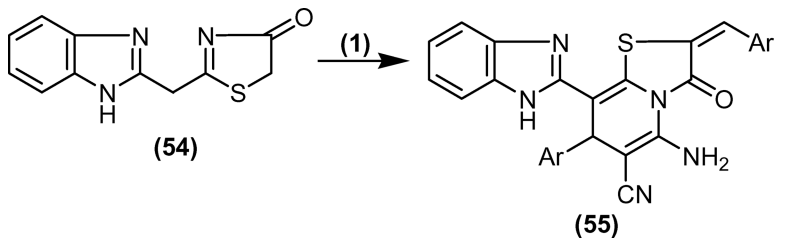
SCHEME 22



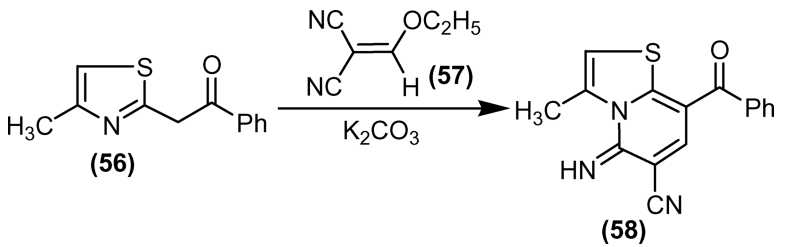
SCHEME 23



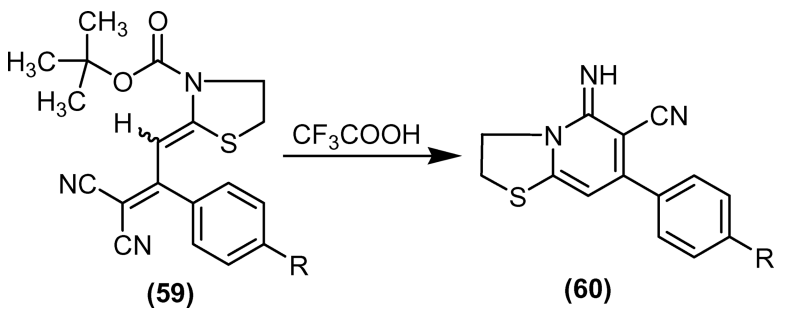
SCHEME 24



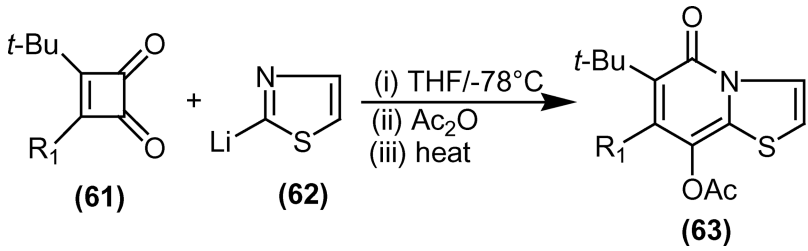
SCHEME 25



SCHEME 26

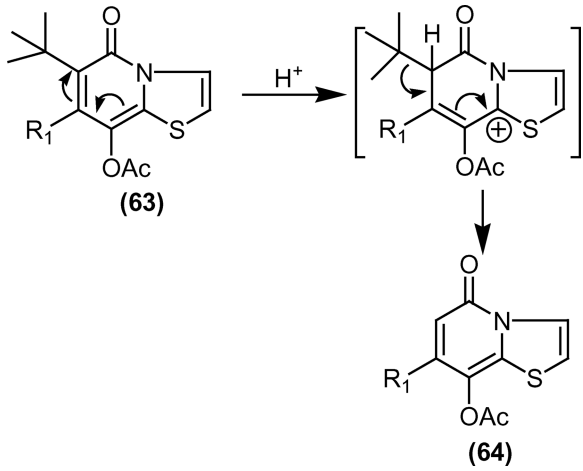


SCHEME 27



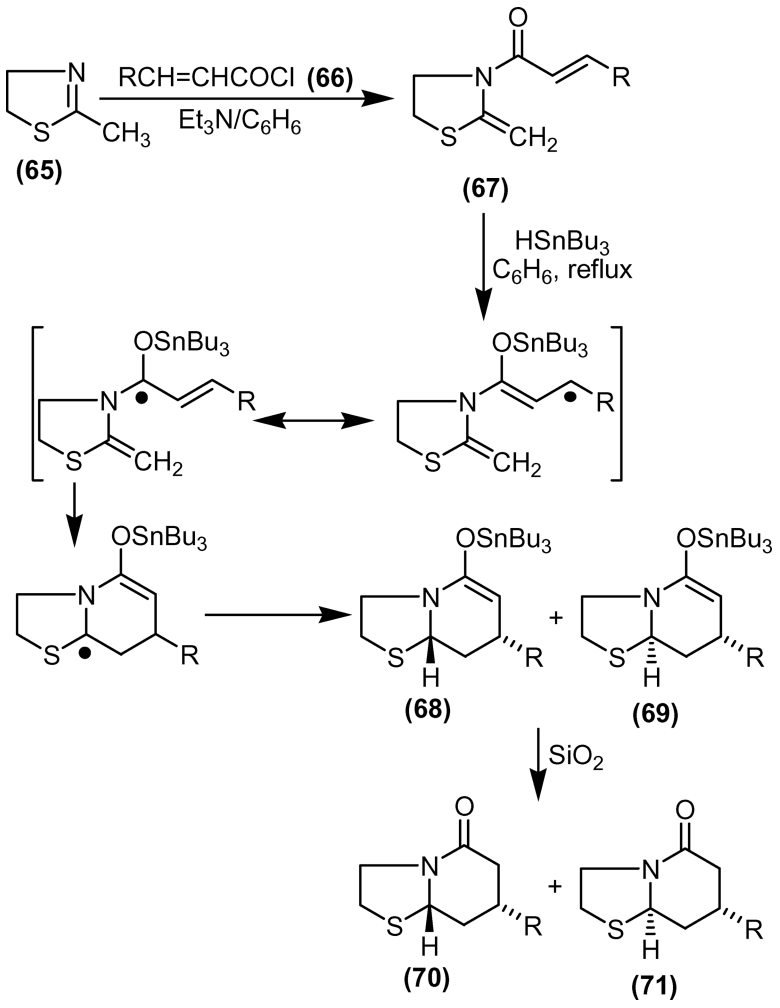
SCHEME 28

at the *tert*-butyl bearing carbon atom, which must be a consequence of considerable stabilization of the charge by delocalizing into the adjacent heterocyclic ring[17] (Scheme 29).



SCHEME 29

3-alkenoyl-2-methylene-1,3-thiazolidinones (**67**) were obtained by the acylation of 2-methyl-4,5-dihydrothiazole (**65**) with α,β-unsaturated acid chlorides (**66**) in the presence of excess triethylamine at r.t. The crude compounds (**67**), when heated under reflux in benzene with stoichiometric amounts of $HSnBu_3$, gave bicycles (**68**) and (**69**) in the form of tin (IV) enolates, which hydrolyzed during chromatography to thiazolo[3,2-a]pyridines (**70**) and (**71**)[18] (Scheme 30).

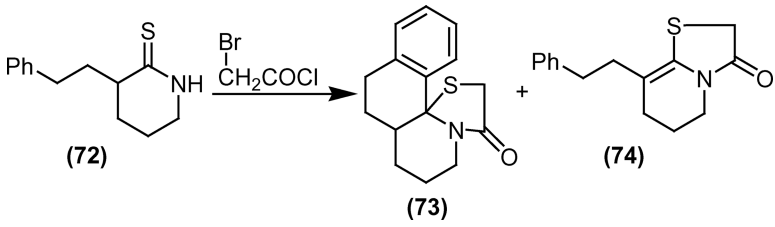


SCHEME 30

Synthesis from Pyridine Derivatives

The treatment of 3-phenethylpiperidine-2-thione (**72**) with bromoacetyl chloride afforded a 2:1 mixture of N,S-ketal (**73**) and thiazolo[3,2-a]pyridine (**74**)[19] (Scheme 31).

Also, the treatment of thiolactams (**75**) with bromoacetyl chloride and triethylamine yielded thiazolo[3,2-a]pyridines (**77**),[20] via the elimination of the proton alpha to thiocarbonyl ylide dipoles (**76**) (Scheme 32).

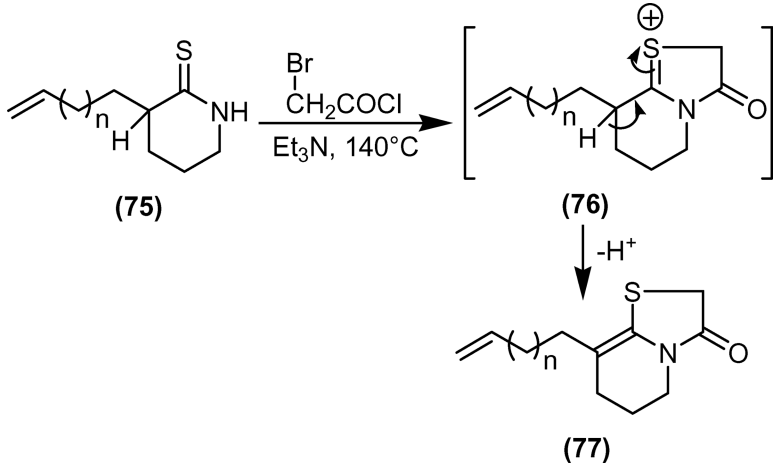


SCHEME 31

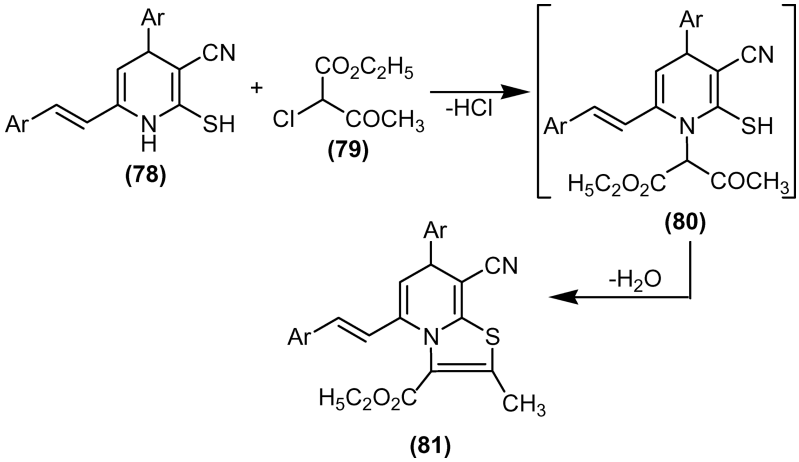
Compounds (**78**) reacted with ethyl α-chloroacetoacetate (**79**) in glacial acetic acid to give the thiazolo[3,2-a]-pyridines (**81**) via initial dehydrochlorination to yield the condensation intermediate (**80**), which then could be cyclized through enolization and loss of a water molecule under the applied reaction condition to furnish the final isolable (**81**)[21] (Scheme 33).

When 5-cyano-2,4-dioxo-6-methoxycarbonyl methylthio-tetrahydropyridine (**82**) was treated with acetic acid and hydrochloric acid, the cyclized thiazolo[3,2-a]pyridine derivative (**83**)[22,23] was obtained in a 75% yield (Scheme 34).

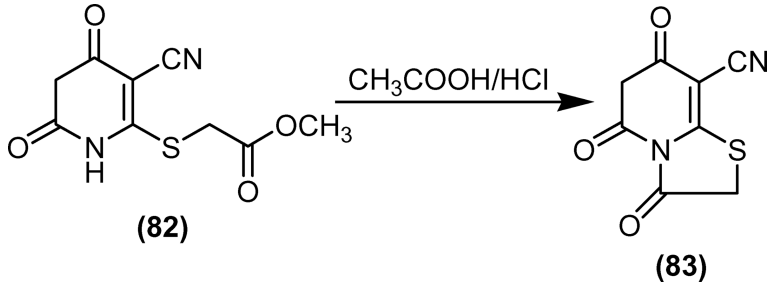
The treatment of thiolactam (**84**) with diethyl bromomalonate (**85**) in dichloromethane at r.t. yielded thioimide (**86**), which on refluxing in the presence of potassium carbonate, afforded ethyl 3-oxo-8-phenyl-2,3,6,7-tetrahydro-5*H*-[1,3]thiazolo[3,2-a]pyridine-2-carboxylate (**87**)[24] (Scheme 35).



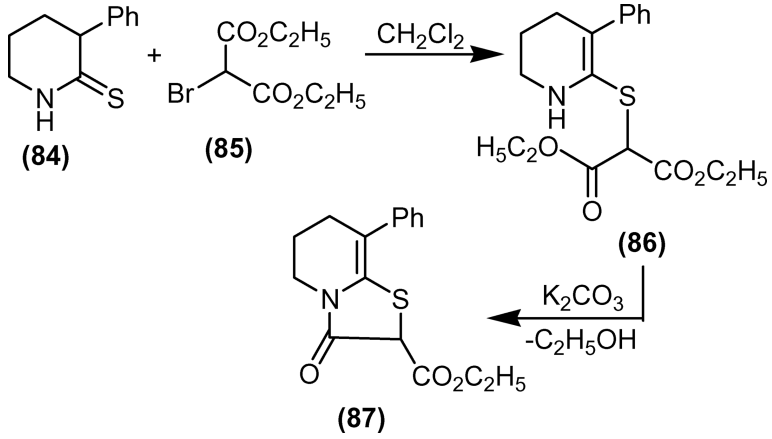
SCHEME 32



SCHEME 33

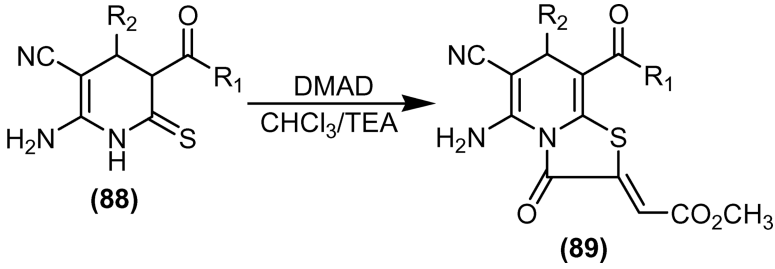


SCHEME 34



SCHEME 35

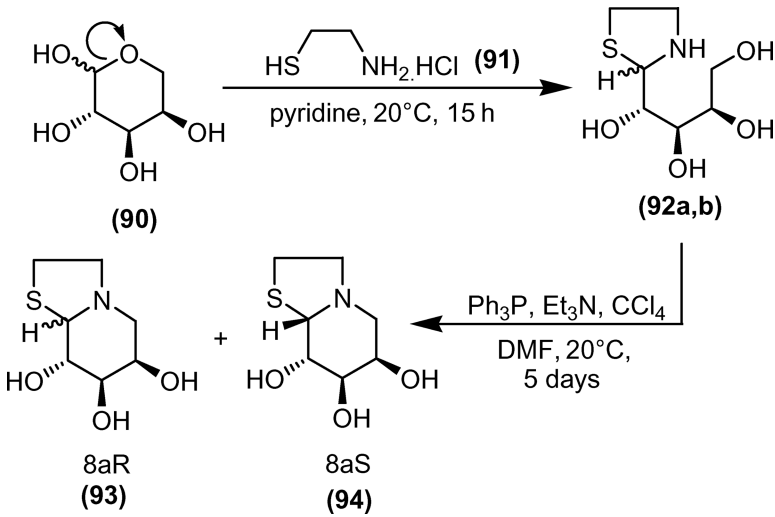
The reaction of pyridinethiones (**88**) with dimethyl acetylenedicarboxylate (DMAD) in chloroform in the presence of triethylamine affords thiazolo[3,2-a]pyridines (**89**)[25] in good yields (Scheme 36).



SCHEME 36

Synthesis from Ring Transformations

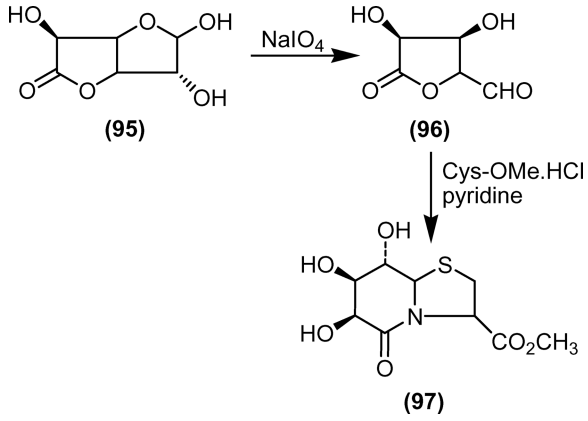
The reaction of D-(−)-arabinose (**90**) with 2-aminoethanethiol hydrochloride (**91**) in pyridine overnight gave an inseparable mixture of epimeric thiazolidines (**92a**,**b**), which cyclized using triphenylphosphine and triethylamine in dimethylformamide at 20°C for 5 days to give a 1:1 mixture of the 8aR (**93**) and 8aS (**94**) epimers[26] (Scheme 37).



SCHEME 37

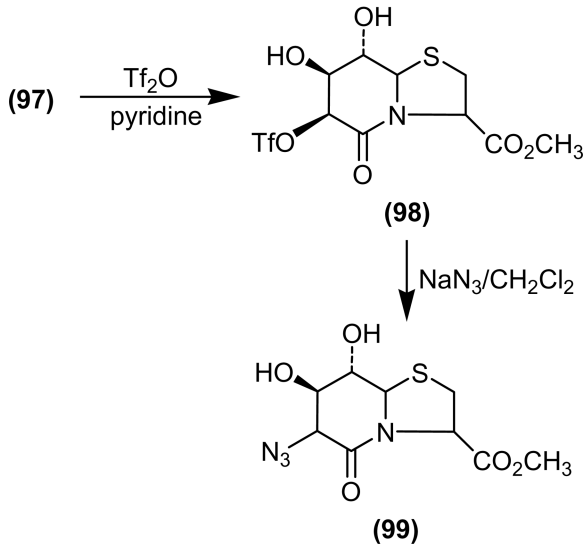
Periodate cleavage[27] of D-glucurono-3,6-lactone (**95**) yielded D-arabinurono-2,5-lactone (**96**), which combined with L-cysteine methyl

ester hydrochloride to give the methyl (3*R*, 6*S*, 7*R*, 8*S*, *8aS*)-6,7,8-trihydroxy-5-oxohexahydro-5*H*-[1,3]-thiazolo[3,2-a]pyridine-3-carboxylate (**97**) (Scheme 38).



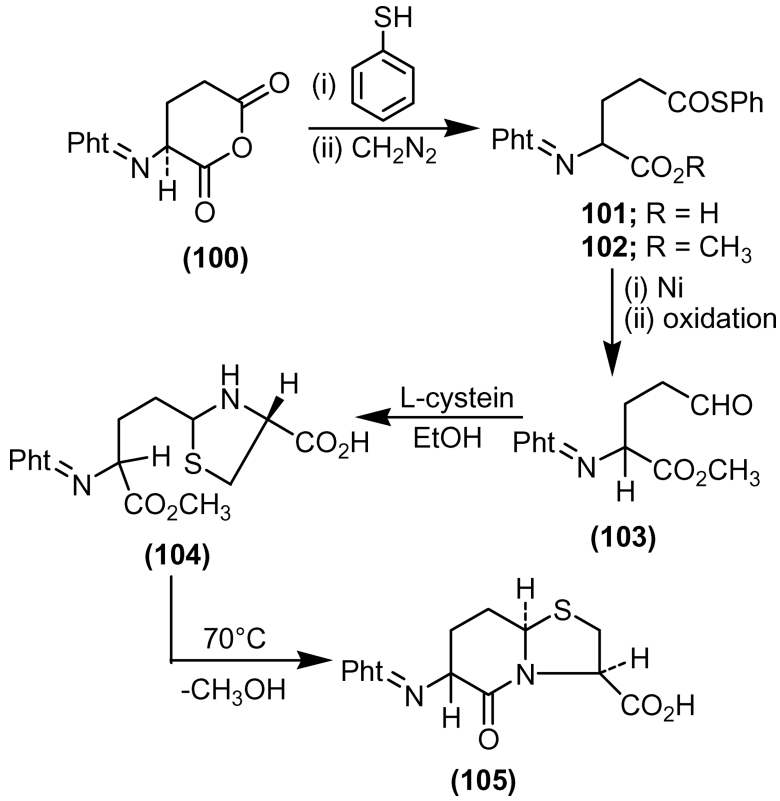
SCHEME 38

The treatment of (**97**) with triflic anhydride in pyridine furnished triflate (**98**). The triflate is displayed with an inversion of the configuration by an azido group in dichloromethane to yield (**99**)[27](Scheme 39).



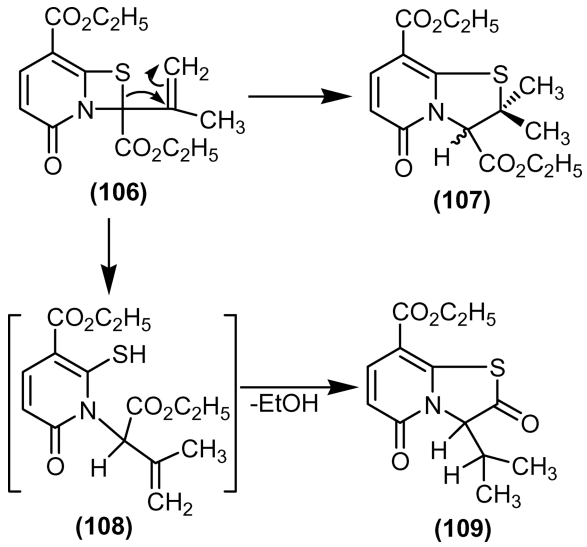
SCHEME 39

Phthaloyl-L-glutamic anhydride (**100**) was treated with thiophenol to give the half thioester (**101**), which then converted to the methyl ester (**102**) by treatment with diazomethane. A raney-nickel reduction of (**102**) followed by oxidation afforded the aldehyde (**103**). An overnight reaction of L-cystiene with compound (**103**) in aqueous ethanolic solution at r.t. gave compound (**104**), which was heated overnight at 70°C to give the thiazolo[3,2-a]-pyridine derivative (**105**)[28] (Scheme 40).



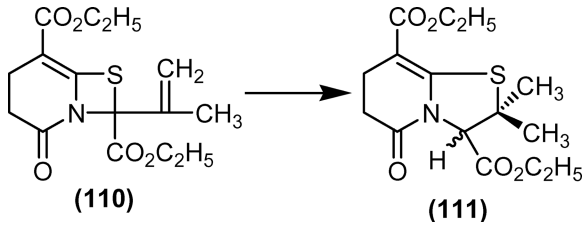
SCHEME 40

A hydrogenative rearrangement[29] of thiazetidine (**106**) at r.t. and pressure using an Adams catalyst and either ethyl acetate or ethanol as a solvent gave the thiazolo-[3,2-a]pyridine derivative (**107**) in addition to the thiolactone (**109**). The thiolactone (**109**) resulted from hydrogenolysis of the sulfur carbon bond of the thiazetidine to give an intermediate such as (**108**), which, on thiolactonisation and reduction of the olefin, would yield the thiolactone (**109**) (Scheme 41).



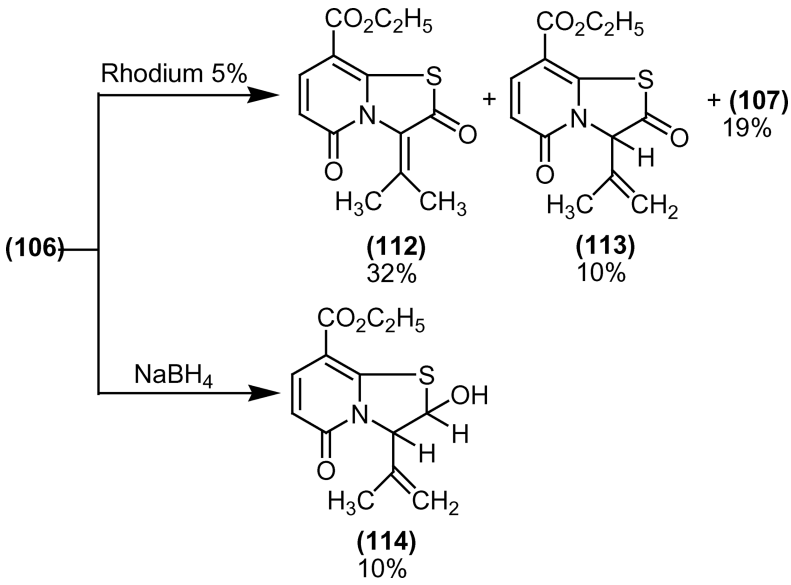
SCHEME 41

Also, the dihydropyridone-thiazetidine (**110**) was hydrogenated using an Adams catalyst to give the correspo-nding diethyl 6,7-dihydro-2, 2-dimethyl-5-oxo-5H-thiazolo-[3,2-a]pyridine-3,8-dicarboxylate (**111**)[29] in a 60% yield (Scheme 42).



SCHEME 42

Hydrogenolysis of (**106**) using 5% rhodium on alumina as a catalyst furnished the isopropylidene thiolactone (**112**) in a 32% yield and (**113**) in a 10% yield in addition to 19% of the thiazolidine (**107**) (Scheme 43). The thiolactol (**114**) was achieved by the hydrogenation of (**106**) with sodium borohydride in aqueous tetrahydro-furan[29] (Scheme 43).

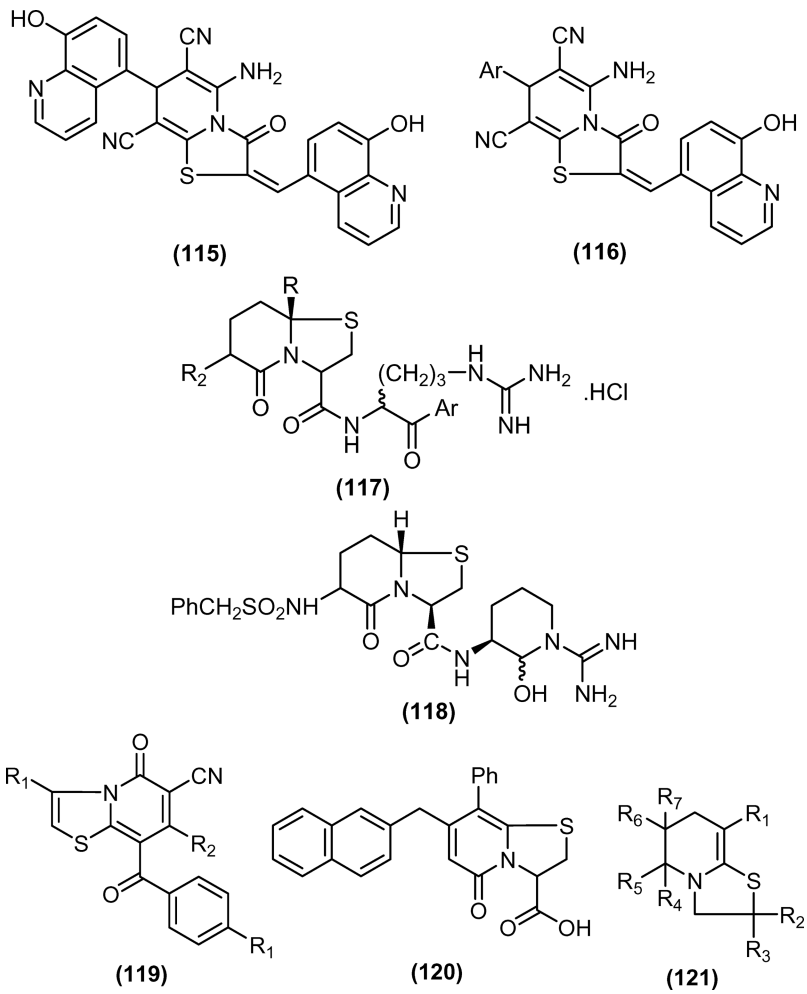


SCHEME 43

Applications of Thiazolo[3,2-a]pyridines

5-amino-2,3-dihydro-7*H*-(8′-hydroxyquinolin-5′-yl)-2-(8″-hydroxyquinolin-5″-ylmethylidene)-3-oxothiazolo[3,2-a]-pyridine-6,8-dicarbonitrile (**115**) and 7-arylsubstituted-5-amino-2,3-dihydro-7*H*-2-(8′-hydroxyquinolin-5′ylmethylide-ne)-3-oxo-thiazolo[3,2-a]pyridine-6,8-dicarbonitriles (**116**) have antifungal activity.[30] Guanidinothiazolo[3,2-a]pyridines (**117**) have been evaluated as thrombin inhibitors,[31] and thiazolo[3,2-a]pyridine(**118**) have been shown to have serine protease inhibitor activity.[32] Thiazolo[3,2-a]pyridines (**119**) have a broad spectrum of potent anticancer activity and are useful for chemotherapy of various cancers, such as leukemia, lung cancer, and melanoma.[33] Almqvist and colleagues[34] synthesized a certain thiazolo[3,2-a]pyridine derivative (**120**) to treat and prevent bacterial infections. In 1993, Suzuki, Nakayama, Saijo and colleagues[35] and Suzuki, Nakayama, Hasegawa and colleagues[36] synthesized some new thiazolo[3,2-a]pyridines (**121**) as drugs for liver diseases. Moreover, several substituted thiazolo [3,2-a]pyridines were reported to act as antirhino-viral,[37] antihypertensive,[38] and anticancer[39] agents (Scheme 44).

Chen and Wang[40] prepared some thiazolo[3,2-a]pyridines (**122**) and (**123**) which were suitable as disperse dyes for polyester fibers (Scheme 45).

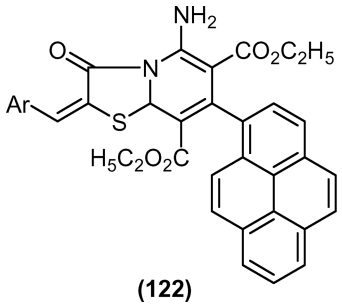


SCHEME 44

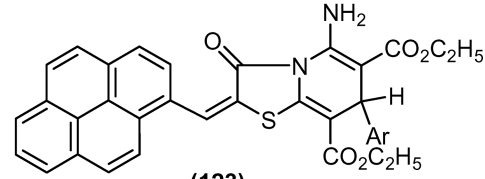
THIAZOLO[3,4-a]PYRIDINES

Synthesis of Thiazolo[3,4-a]pyridines

The reaction of pyridine (**124**) with chloromethyl(trimethyl-silyl)methyl sulfide (**125**) followed by treatment with cesium fluoride in acetonitrile at r.t. gave the thia-zolo[3,4-a]pyridine (**126**)[41,42] in a high yield (Scheme 46).



(122)



(123)

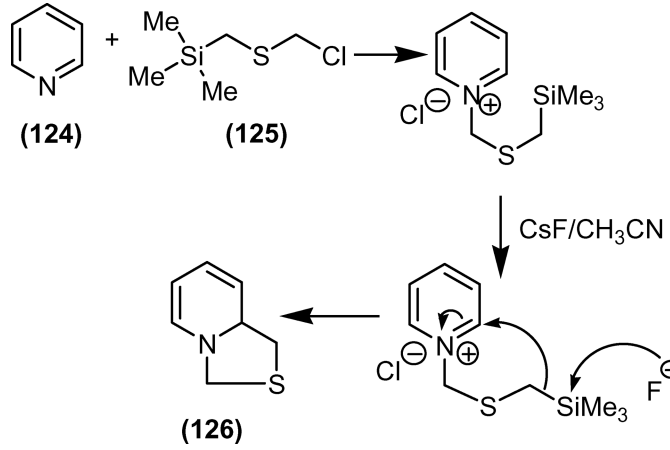
SCHEME 45

Thiazolo[3,4-a]pyridine derivative (**128**) was achieved by the treatment of piperidylmethanol (**127**) with thionyl chloride[43] (Scheme 47). Compound (**128**) have sympatho-mimetic activity.

2-piperidinemethanol (**129**) was condensed with isothio-cyanates (**130**) to give thiourea derivatives (**131**), which were cyclized to yield thiazolo[3,4-a]pyridines (**132**)[44] (Scheme 48).

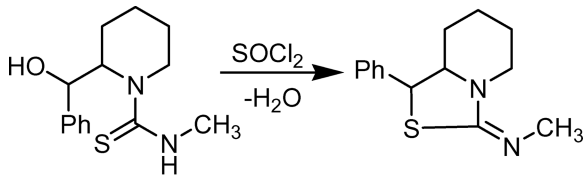
Applications of Thiazolo[3,4-a]pyridines

Numerous studies have been reported for thiazolo[3,4-a]-pyridines (**133**), which show antiasthmatic and antiinflammatory activity[45–47]. Herbicide activity for several deriveatives of thiazolo[3,4-a]pyridine has been reported (Scheme 49).[48]



(124) (125) (126)

SCHEME 46



(127) **(128)**

SCHEME 47

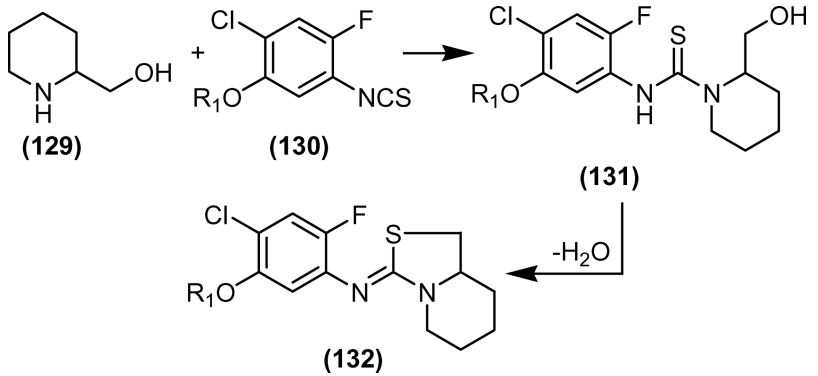
THIAZOLO[5,4-b]PYRIDINES

Synthesis from Thiazole Derivatives

The condensation of 5-amino-2-thioamidothiazole (**134**) with ethyl acetoacetate followed by thermal cyclization of the intermediate *N*-(2-carbethoxyisopropylidene) derivative (**135**) afforded the corresponding 7-hydroxy-5-methyl-2-thiocarba-moylthiazolo[5,4-b]pyridine (**136**) in a 75% yield[49] (Scheme 50).

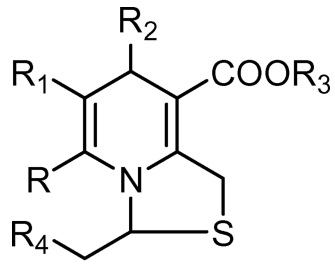
The reaction of compound (**136**) with paraformaldehyde and diethylamine in ethanol at the reflux temperature for several hours gave 6-diethylaminomethyl-7-hydroxy-5-methyl-2-thiocarbamoylthiazolo[5,4-b]pyridine (**137**).[49] Upon heating the Mannich base (**137**) at its decomposition temperature, it loses an amine molecule by self-conden-sation to give the dimeric product bis(7-hydroxy-5-methyl-2-thiocarbamoylthiazolo[5,4-b]pyridine-6-yl)methane (**138**)[49] (Scheme 51).

Chlorination of a Mannich base (**137**) with phosphorus oxychloride yielded the corresponding 7-chloro derivative (**139**).[49] The subsequent



(129) **(130)** **(131)** **(132)**

SCHEME 48



(133)

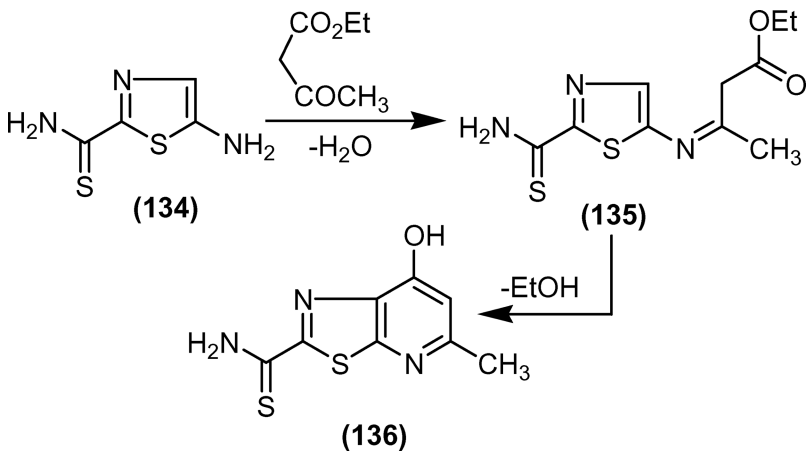
SCHEME 49

condensation of (**139**) with aromatic amine afforded the amino derivatives (**140**)[49] (Scheme 52).

Synthesis from Pyridine Derivatives

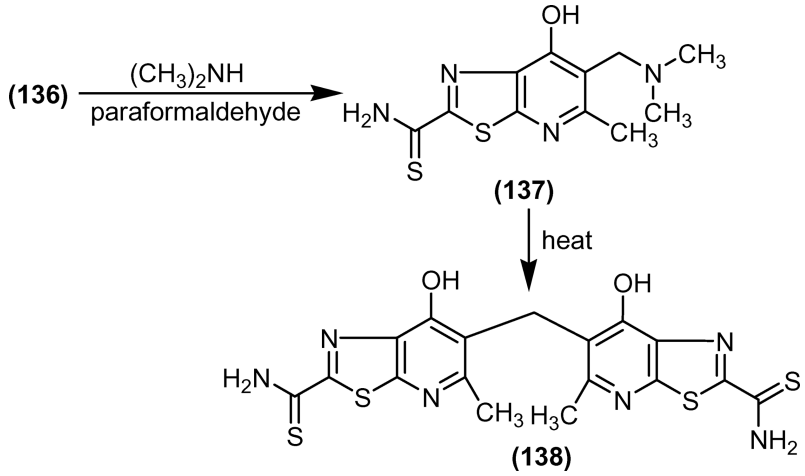
Intramolecular oxidative cyclization[50] of N-(3-pyridyl)-N′-ethylthiourea (**141**) with sulphuryl chloride in toluene afforded the corresponding bicyclic derivative of thiazolo-[5,4-b]pyridine (**142**) in a good yield (Scheme 53).

5-amino-2-chloropyridine (**143**) was converted to 5-amino-6-chlorothiazolo[5,4-b]pyridine (**144**) by the treatment with sodium thiocyanate in the presence of bromine in acetic acid[51] (Scheme 54).

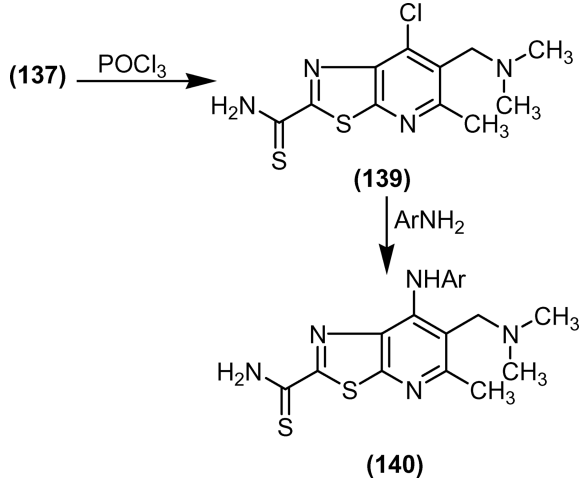


(134) **(135)** **(136)**

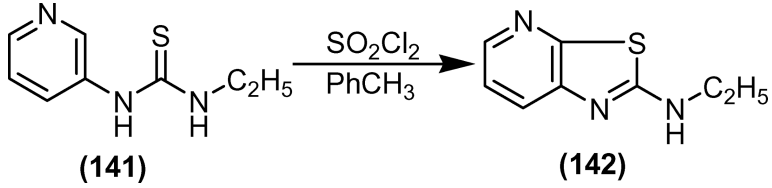
SCHEME 50



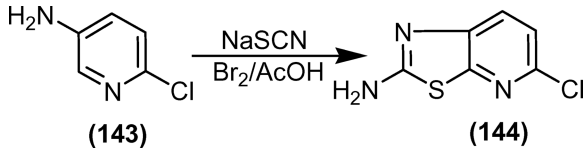
SCHEME 51



SCHEME 52



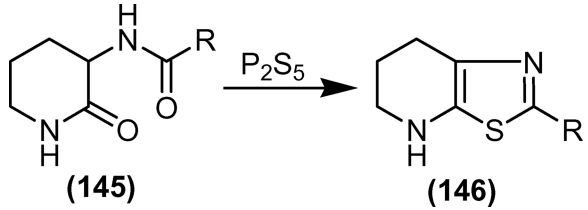
SCHEME 53



(143) (144)

SCHEME 54

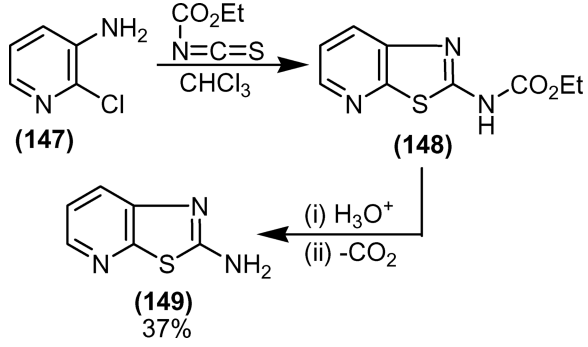
The treatment of diamides (**145**) with phosphorus pentasulfide was reported to give a convenient method to prepare 4,5,6,7-tetrahydrothiazolo[5,4-b]pyridines (**146**)[52] (Scheme 55).



(145) (146)

SCHEME 55

The cyclization of 3-amino-2-chloropyridine (**147**) by refluxing in chloroform with ethoxycarbonyl isothiocyanate gave (**148**), which was hydrolyzed-decarboxylated to give 2-aminothiazolo[5,4-b]pyridine (**149**)[53] (Scheme 56).



(147) (148) (149) 37%

SCHEME 56

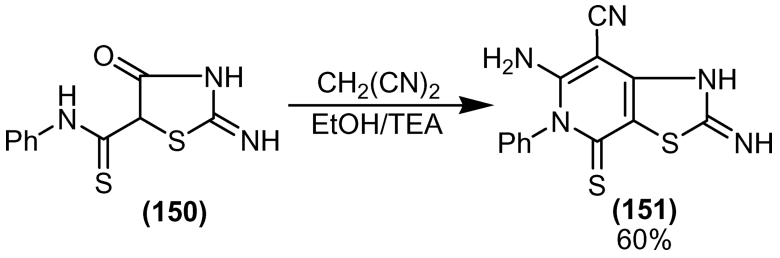
Applications of Thiazolo[5,4-b]pyridines

Several thiazolo[5,4-b]pyridines were evaluated as anti-bacetrials,[54–58] antibiotic,[59,60] antiviral,[61] bronchospasmolytics,[62] leukotriene anti-agonists,[63] antiulcer agents[64,65] and as azo dyes.[66]

THIAZOLO[5,4-c]PYRIDINES

Synthesis from Thiazole Derivatives

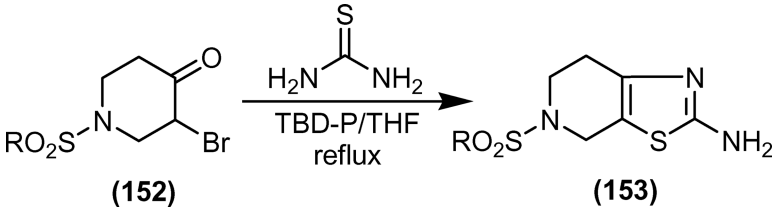
The reaction of 2-imino-5-phenyl aminothiocarboxa-mido-4-thiazolidene (**150**) with malononitrile in the presence of triethyl-amine gave the thiazolo[5,4-c]pyridine derivative(**151**) through condensation, followed by intra-molecular cyclization[67] (Scheme 57).



SCHEME 57

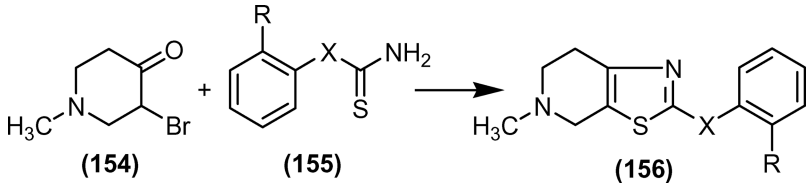
Synthesis from Pyridine Derivatives

The direct treatment of α-bromo piperidones (**152**) with thiourea in the presence of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD-P) as a base in refluxing tetrahydrofuran affected cyclodehydration to give 2-aminothiazolo[5,4-c]pyridine derivatives (**153**) in high yields[68] (Scheme 58).



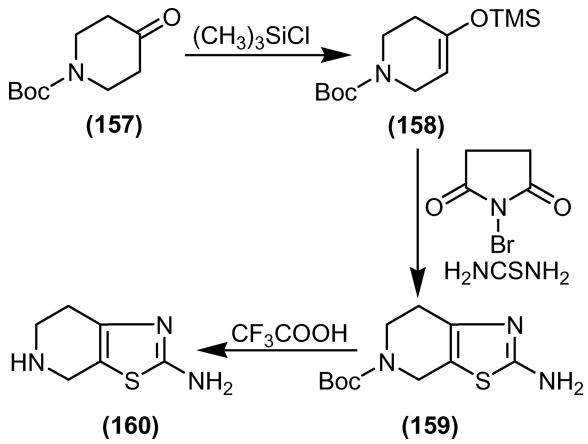
SCHEME 58

Tetrahydrothiazolo[5,4-c]pyridines (**156**) were prepared from thioamides (**155**) by condensation with 3-bromo-1-methyl-4-piperidone (**154**) in 2-propanol under reflux in good yields, which were used for the treatment of constipation[69] (Scheme 59).



SCHEME 59

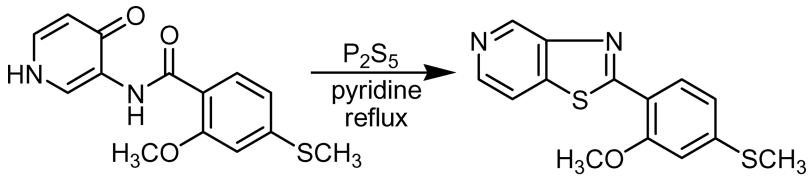
The interaction of N-(*tert*-butoxycarbonyl)piperidine (**157**) with trimethyl silyl chloride followed by cyclocondensation with thiourea in the presence of *N*-bromosuccinimide yielded the thiazolo[5,4-c]pyridine derivative (**158**). Removal of the *tert*-butoxycarbonyl protecting group from (138) by trifluoroacetic acid gave antifungal agent (**159**)[70] (Scheme 60).



SCHEME 60

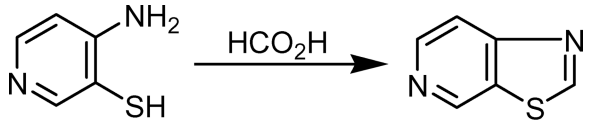
The heating of 3-(2-methoxy-4-methylthiobenzoyl)amino-pyrid-4-one(**161**) with phosphorous pentasulfide in xylene in the presence of pyridine furnished the thiazolo[4,5-c]-pyridine derivative (162) (Scheme 61), which was evaluated as an inotropic agent[71].

Thiazolo[5,4-c]pyridine(**164**) was prepared by the cyclization of 4-amino-3-pyridinethiol (**163**) with formic acid[72] (Scheme 62).



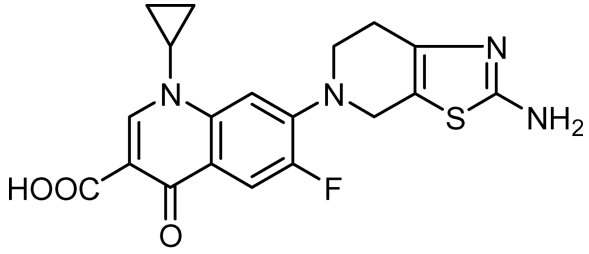
(161) **(162)**

SCHEME 61

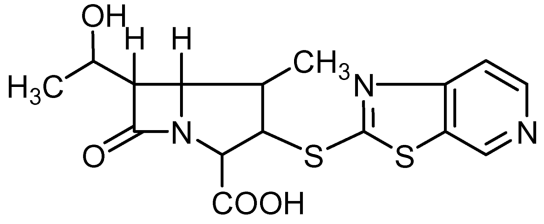


(163) **(164)**

SCHEME 62



(165)



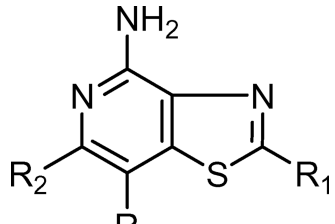
(166)

SCHEME 63

Applications of Thiazolo[5,4-c]pyridines

Antibacterial activity for thiazolo[5,4-c]pyridine derive-atives (**165**)[73] and (**166**)[74] has been reported (Scheme 63).

The compounds (**167**)[75] are useful in the treatment of viral and neoplastics diseases.

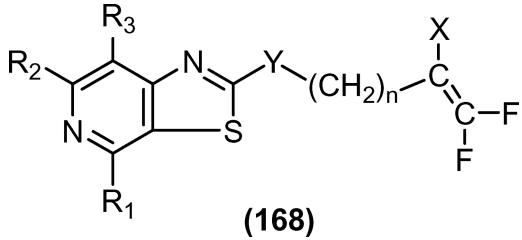


(167)

SCHEME 64

In addition, derivatives of thiazolo[5,4-c]pyridine were used as antitumor agents,[76] fundic relaxants,[77] ulcer inhibitors,[78] inhibitors of the activated blood coagulation factor X,[79] and for treatment or prevention of diabetes.[80]

Fluorinated thiazolo[5,4-c]pyridines (**168**) (Scheme 65) are useful to control nematodes and arachnids and for treating, controlling and protecting warm-blooded animals, fish, and humans against infestation by helminths, arachnids, and arthropod endo- and ectoparasites.[81]



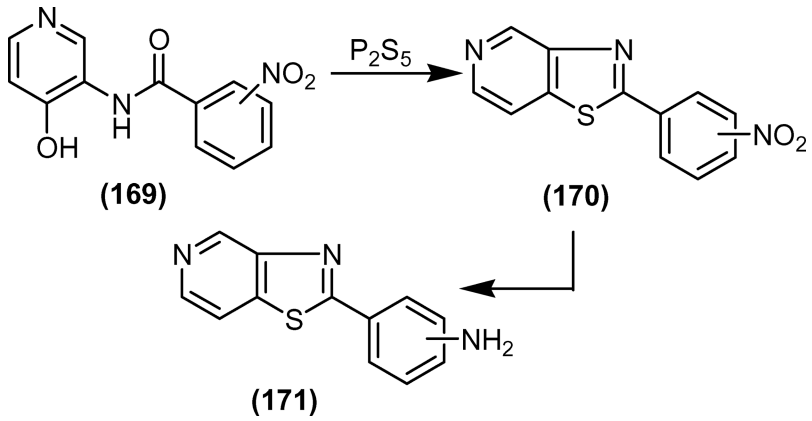
(168)

SCHEME 65

THIAZOLO[4,5-C]PYRIDINES

Synthesis of Thiazolo[4,5-c]pyridines

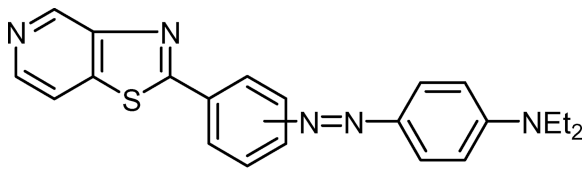
Compounds (**169**) were cyclized in the presence of phosphorus pentasulfide to give thiazolo[4,5-c]pyridine derivatives (**170**) which could be hydrogenated to yield dye intermediates (**171**)[82] (Scheme 66). The heteroaromatic amines (**171**) were suitable precursors for the synthesis of disperse dyes.[82]



SCHEME 66

Applications of Thiazolo[4,5-c]pyridines

Antibacterial,[83,84] antifungal,[85] anticoagulant[86] and antiglaucoma[87] activity of thiazolo[4,5-c]pyridines have been observed in the literature. Thiazolo[4,5-c]pyridines (**172**) (Scheme 67) were synthesized as disperse and cationic azo dyes[88].



(172)

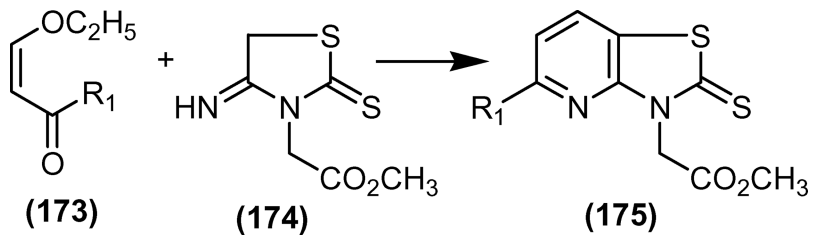
SCHEME 67

THIAZOLO[4,5-b]PYRIDINES

Synthesis of Thiazolo[4,5-b]pyridines

Synthesis of thiazolo[4,5-b]pyridines from thiazole derivatives

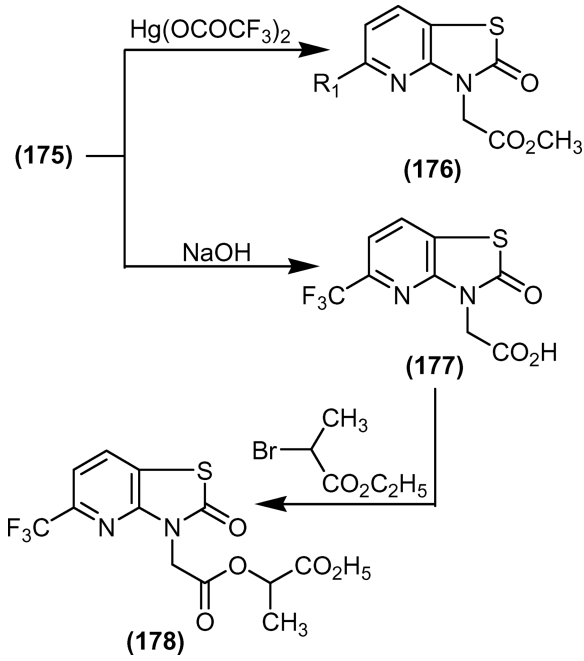
The synthesis of 2-thioxothiazolo[4,5-b]pyridine-3(2*H*)- acetate derivatives (**175**)[89] entailed a novel condensation reaction of the β-ethoxyenones (**173**) with methyl 4-imino- 2-thioxo-3-thiazolidineacetate(**174**) in the presence of a catalytic amount of piperidine (Scheme 68). Compounds (**175**) were screened as herbicidal agents.[89]



SCHEME 68

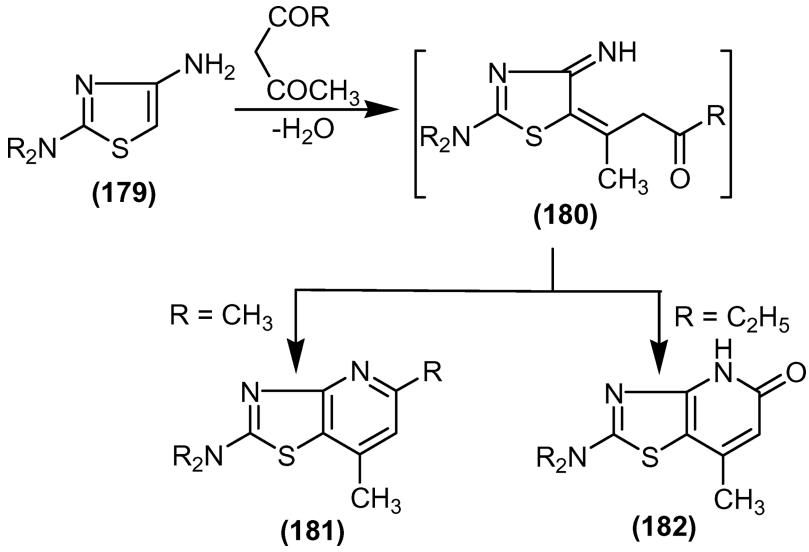
The 2-oxothiazolo[4,5-b]pyridine-3-(2H)acetates (**176**) were prepared from(**175**) by treatment with mercuric trifluoroacetate.[89] Compound **175** (Ar=CF_3) was hydrolyzed to the corresponding acid (**177**) by treatment with sodium hydroxide.[89] Alkylation[89] of (**177**) with ethyl 2-brom-opropionate in the presence of potassium carbonate gave the lactate ester (**178**) (Scheme 69).

2,4-diaminothiazoles (**179**) were allowed to react with ketomethylene compounds at their carbonyl group to give intermediates (**180**), which



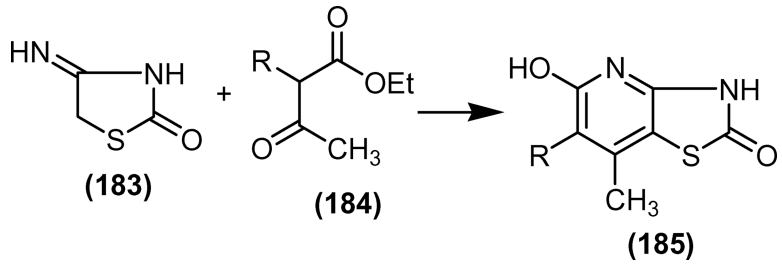
SCHEME 69

cyclize, in turn, at their terminal carbonyl group to the final products thiazolo[4,5-b]pyridines (**181**) and(**182**)[90] (Scheme 70).



SCHEME 70

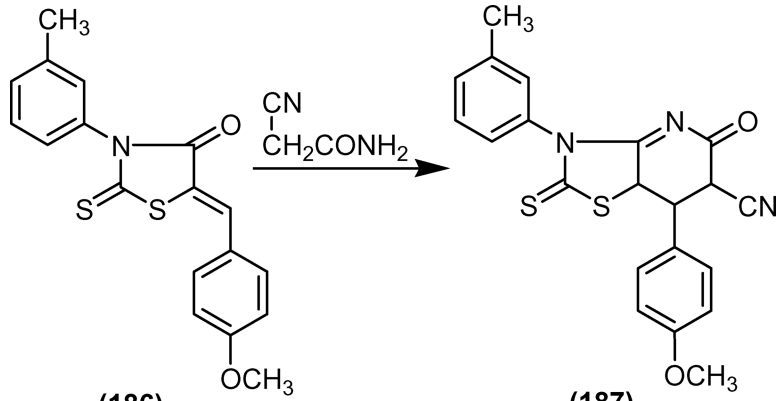
Cyclocondensation[91] of 4-imino-2-thiazolidinone (**183**) with acetoacetic esters (**184**) in methanol containing sodium methoxide gave thiazolo[4,5-b]pyridines (**185**) (Scheme 71).



SCHEME 71

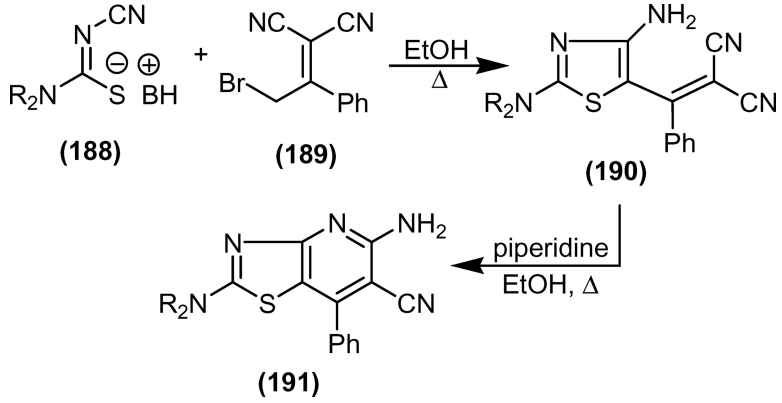
The addition of cyanoacetamide to compound (**186**) resulted in the formation of 7-anisyl-6-cyano-2-thione-3-(m-tolyl)thiazolo[4,5-b]pyridine-5-one (**187**)[92] (Scheme 72).

The piperidinium salts of N-substituted-N′-cyanothio-ureas (**188**) reacted with 2-bromo-1-phenylethylidenemalononitrile (**189**) in ethanol at 50–60°C, forming the substituted thiazoles (**190**). Subsequent treat-



SCHEME 72

ment of these compounds by a catalytic quantity of piperidine in ethanol under heating afforded thiazolo[4,5-b]pyridines (**191**)[93,94] (Scheme 73).

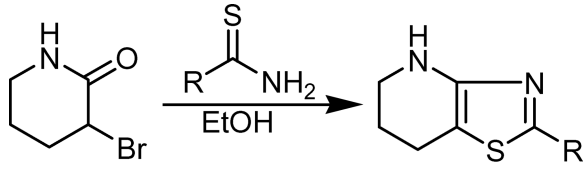


SCHEME 73

Synthesis from Pyridine Derivatives

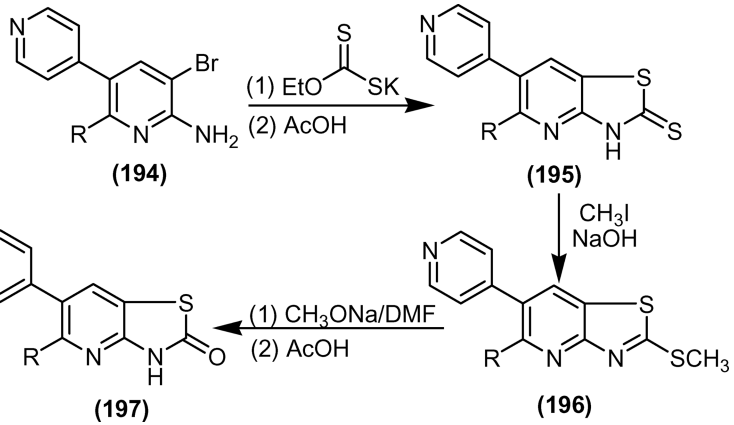
The reaction of an α-bromolactam(**192**) with thio-amides was found to give cyclic thiazolo[4,5-b]pyridine derivatives (**193**)[95] (Scheme 74).

Thiazolo[4,5-b]pyridine-2(3*H*)-ones (**197**) were prepared from 5-bromo[3,4′-bipyridin]-6-amines (**194**) via a four-step sequence[96] (Scheme 75).

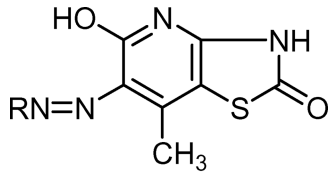


(192) **(193)**

SCHEME 74

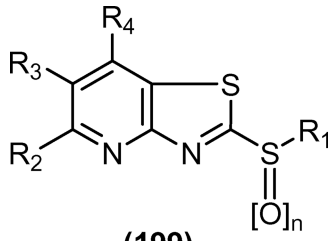


SCHEME 75



(198)

SCHEME 76



(199)

SCHEME 77

Applications of Thiazolo[4,5-b]pyridines

Potent antibacterial activity was found for 6-arylazo-7-methyl-5-hydroxy-2,3-dihydrothiazolo[4,5-b]pyridine-2-ones (**198**).[97]

2-(substitutedthio)thiazolo[4,5-b]pyridines (**199**) were patented as fungicides,[98] pesticides, and parasitcides.[99,100]

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