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Bridgehead Nitrogen Thiazolopyrimidines

Abdel-Zaher Abdel-Aziz Elassar[a]
[a] Chemistry Department, Faculty of Science, Helwan University, Cairo, Egypt

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BRIDGEHEAD NITROGEN THIAZOLOPYRIMIDINES

ABDEL-ZAHER ABDEL-AZIZ ELASSAR

Chemistry Department, Faculty of Science, Helwan University, Ain Helwan, Cairo, Egypt

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This review article includes a recent development in the chemistry of bridgehead nitrogen thiazolpoyrimidines. Synthetic approaches with respect to the four different ring systems were reported. Chemical reactivity, experimental structural methods, biological activity, basicity of thiazole heterocyclic compounds, and applications were also reported. This review includes 126 references.

Keywords: Thiazolopyrimidine; Thiazole; Pyrimidine

CONTENTS

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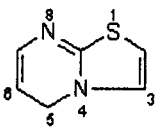
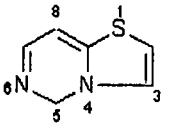
1. INTRODUCTION

This reviews the literature appearing in the last ten years, on the thiazolopyrimidine ring systems with one ring junction nitrogen atom. The parent ring systems of known derivatives are shown in structures **1–4**. The literature on thiazolo[3,2-a]pyrimidines has been reviewed [1–3] and has received a lot of attention in literature mainly due to the interesting biological and pharmaceutical activities associated with this ring system.



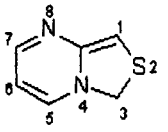
5H-Thiazolo[3,2-a]pyrimidine

1



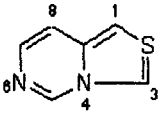
5H-Thiazolo[3,2-c]pyrimidine

2



6H-Thiazolo[3,4-a]pyrimidine

3



3H-Thiazolo[3,4-c]pyrimidine

4

2. METHOD OF PREPARATION

2.1. General consideration

The synthesis of the thiazolopyrimidines has already been reported in the literature [4–10]. The following routes have been employed:

1. Azole Approach: Starting from the thiazole ring and subsequent construction of the pyrimidine ring in the terminal step.

2. Azine Approach: Starting from pyrimidine ring and subsequent construction of the thiazole in the terminal step.
3. Retro Diels-Alder reaction: both azole and azine approaches were considered as major methods for synthesis of the thiazolopyrimidines. Whereas, the retro Diels-Alder reaction was considered a minor method. Other reported methods include: i) cyclization of propargylthiopyrimidines in the presence of Pd(II) salts, ii) metabolism of a *N*-allylpyrimidine and iii) reaction of thiazole derivative with isocyanates.

2.2. Preparation of Thiazolo[3,2-a]pyrimidines

2.2.1. Azole Approaches

Thiazolo[3,2-a]pyrimidine **7** was prepared in 30% yield by the reaction of 2-aminothiazole **5** with ethyl cyanoacetate **6** in a sodium ethoxide/ethanol mixture or using polyphosphoric acid [4] or acetic acid [5,6]. However, oxothiazolopyrimidine **9** was obtained upon treatment with phosphorous pentoxide and methanesulfonic acid **8** [4].

The reaction of **5** with ethyl acetoactate **10** at 140–150°C resulted in the formation of **11** that was then converted to the Z-isomer upon heating at 250°C and cyclized to give **12** [7]. 2-Aminothiazole **5** cyclized with acetylacetone **13** at 100°C, in the presence of methanesulfonic acid-phosphorus pentoxide or formic acid–phosphorus pentoxide, followed by treatment with 70% perchloric acid, to give the thiazolopyrimidin-4-ium salt **14** [8]. The ester **16** was obtained from 2-aminothiazole **5** with an excess of methyl methanetricarboxylate **15** in 61% yield [9]. Cyclocondensation of **5** with diethyl ethoxymethylene malonate **17** in acetic acid followed by hydrolysis of the ester **18** gave **19** [10,11]. Similarly, 2-aminothiazole **5** reacted with **20** in ethanol to give **21** [12]. Stanovink *et al.*, [13–17] reported the synthesis of a series of thiazolopyrimidine derivatives upon reacting 2-aminothiazole with a variety of different reagents. Thus, dimethylaminobut-2-enoate (or pentenoate), **22a–d**, reacted with **5** to give thiazolopyrimidines **23a–d** (cf. Chart 1).

The reaction of 2-aminothiazole **5** with 2-hydropolyfluoroalk-2-enoate **24** in basic medium gave two isomers, 7-oxo **25** and its isomeric 5-oxo **26**. The structure of both **25** and **26** was established through ^{1}H NMR, ^{19}F NMR and mass spectra [18]. 2-Aminothiazole derivatives **5**, (R^1 = H, CO2Et; R^2 = Ph, aryl, Me), reacted with the acetylenic derivative **27** and ester derivative **28** in ethanol and polyphosphoric acid, respectively, to give the isomeric oxothiazolopyrimidine derivatives **29** and **30**, in 5–32% and 8–97 % yield, respectively [19]. Condensation of 2-aminothiazole **5** in absolute ethanol with the sodium salt of ethyl oximinocyanoacetate **31** gave after acidification (pH 6) with diluted hydrochloric acid, the nitroso derivative **32** in 92% yield [20]. Treatment of the 2-aminothiazaole derivatives **5** with the hydrazone derivatives **33** gave the oxothiazolo [3,2-a] pyrimidine derivatives **34** [21]. Compound **37** was prepared in 70–95% yield by thermal (160°C) condensation of arylaminobisthiazole **35** with two equivalents of bis(2,4,6-trichlorophenyl)methyl malonate **36** [22] (cf. Chart 2).

Heating 2-aminothiazole **5** with the isoxazole-4-carboxylates **38a,b** in the absence of solvent gave the oxothiazolopyrimidine derivatives **40a** and **40b** in 24 and 22% yield, respectively, via the ring opening intermediate **39** [23].

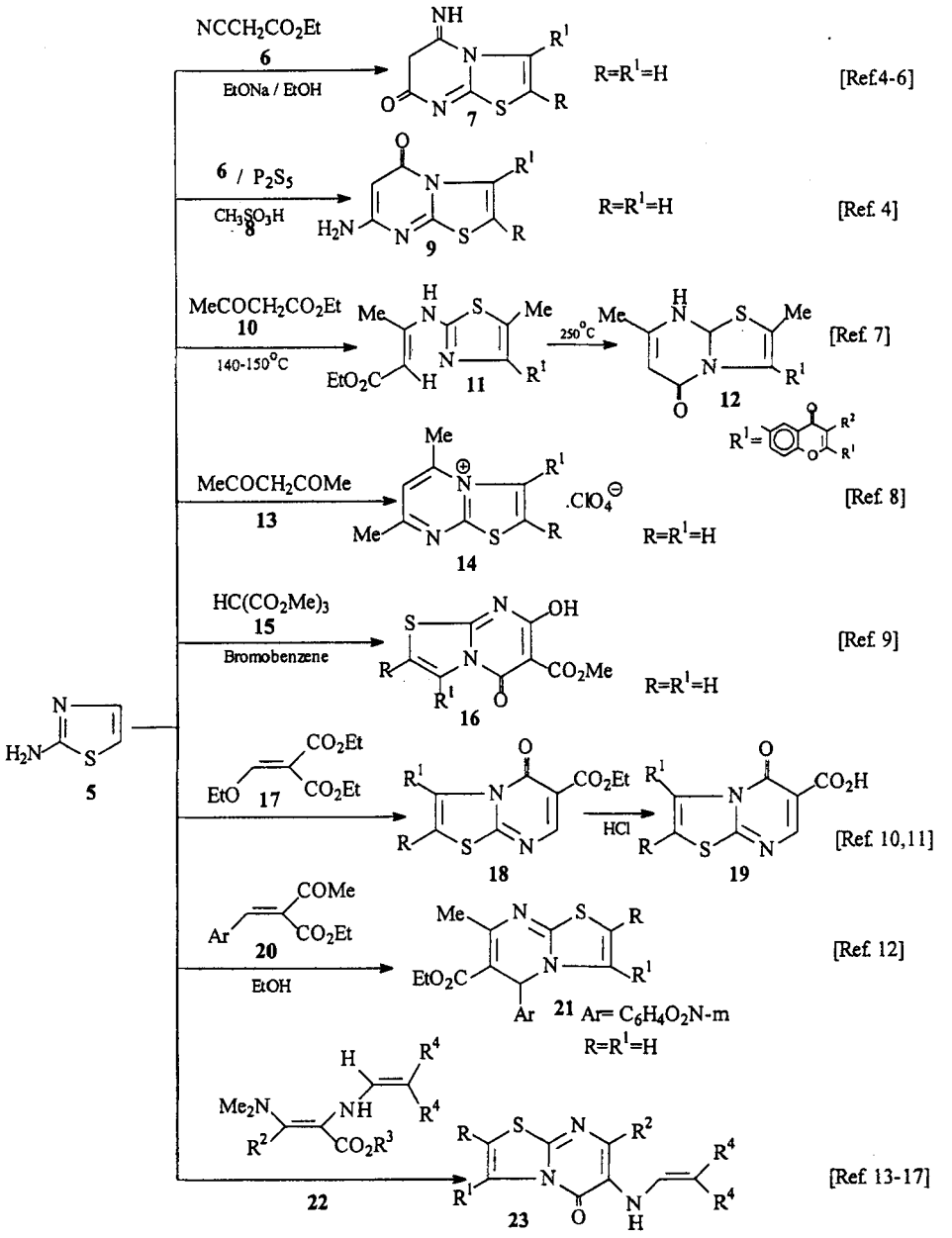


Chart 1

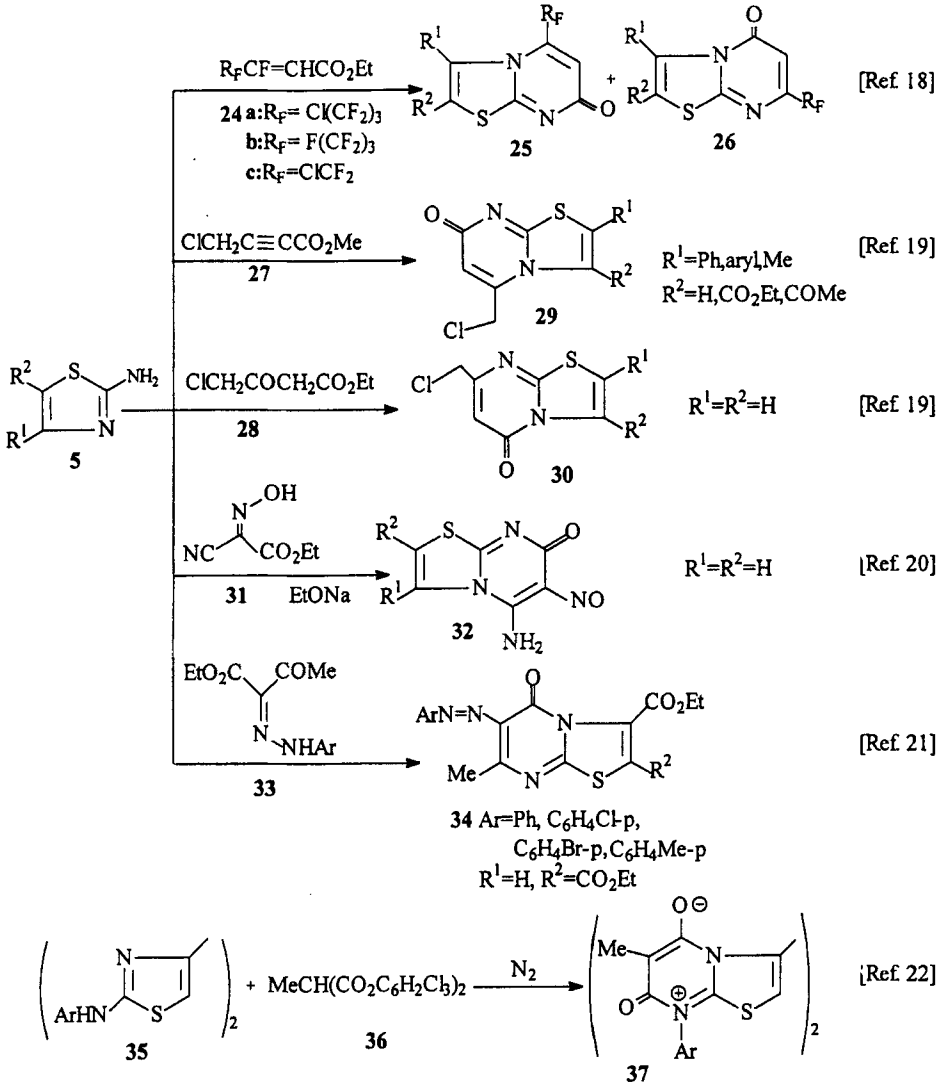
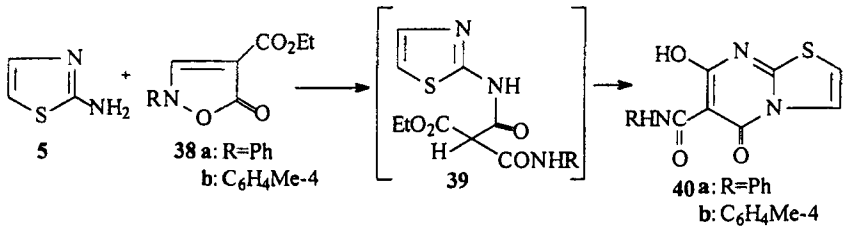
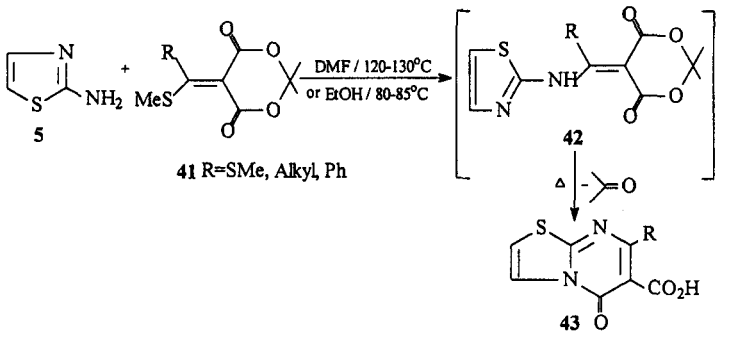


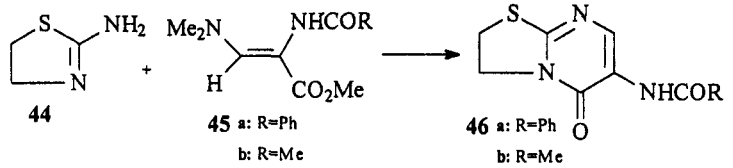
Chart 2



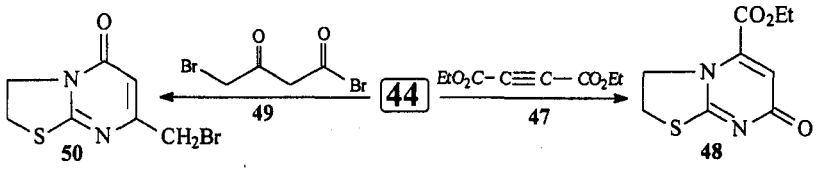
Upon heating in dimethylformamide (DMF) or ethanol, the Meldrum acid derivative **41** readily reacted with 2-aminothiazole **5** to give the cyclocondensation product **43** in a single step, via the intermediate **42** [24].



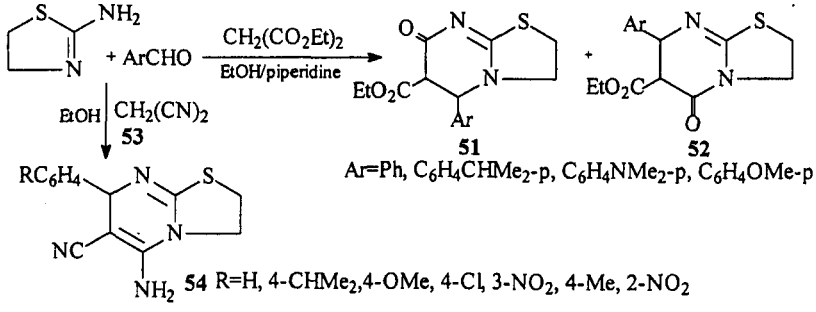
2-Amino-2-thiazoline **44** reacted with 2-acylamino-3-dimethylamino-propenoates **45a,b** in acetic acid to yield 6-acylamino-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-a]pyrimidines **46a** and **46b** in 73 and 12% yields, respectively [25]. Although, Stanovink *et al.* have published about five papers in this area, his nomenclature is incorrect, the correct nomenclature is [3,2-a] not [3,2-b].



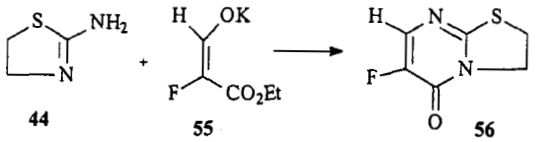
2-Amino-2-thiazoline **44** reacted with acetylenecarboxylate **47** to give 7-oxothiazolo [3,2-a]pyrimidine **48**. Furthermore, 2-amino-2-thiazoline **44** reacted with γ-bromo-acetoacetyl bromide **49** to give 5-oxothiazolo[3,2-a]pyrimidine derivative **50** [26].



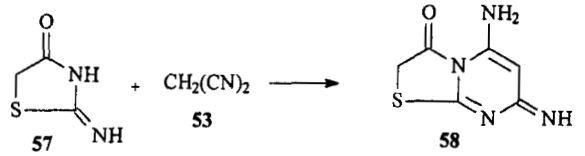
Moreover, 2-amino-2-thiazoline **44** reacted with an aromatic aldehyde and diethyl malonate, to give a mixture of thiazolidino[3,2-a]pyrimidines **51** and **52** [27,28]. Furthermore, malononitrile **53** reacted with **44** to give **54** [27,28].



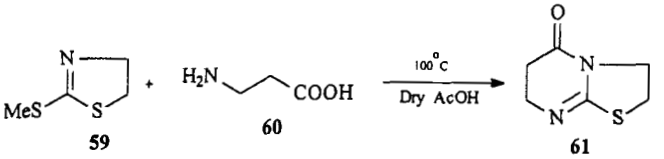
2-Amino-2-thiazoline **44** reacted with potassium 2-ethoxycarbonyl-2-fluorovinyl alcoholate **55** in a sodium methoxide/methanol mixture to give 6-fluoro-2,3-dihydro-5-oxothiazolo[3,2-a]pyrimidine **56** [29].



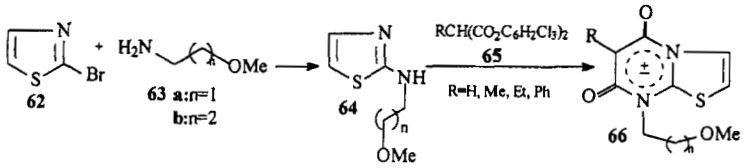
2-Imino-4-thiazolidinones **57** reacted with nitrile **53** to give the thiazolo-[3,2-a]pyrimidine derivative **58** [30].



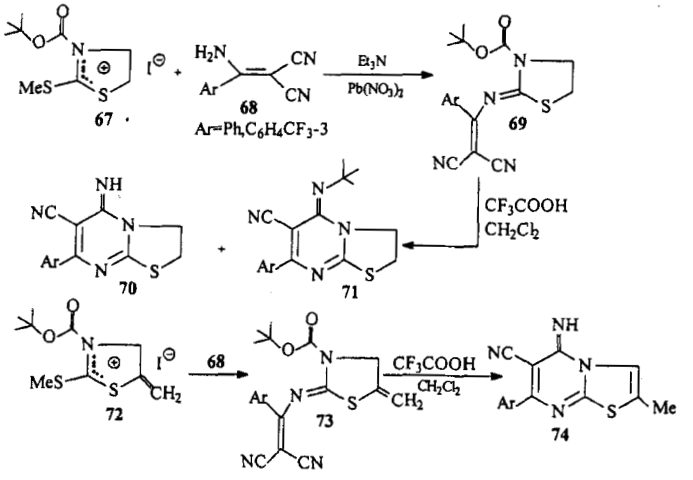
2-(Methylthio)-2-thiazoline **59** reacted with β-alanine **60** to give a 5-oxothiazolo[3,2-a]-pyrimidine derivative **61** in 23% yield [31].



2-Bromothiazole **62** and 2-methoxyethylamine **63a** or 3-methoxypropylamine **63b** underwent a nucleophilic substitution reaction to afford the corresponding **64a** ($n=1$) and **64b** ($n=2$), respectively. Thermal condensation of the aminothiazole derivatives **64a,b** with bis(2,4,6-trichlorophenyl)malonate **65** gave **66** in good yield [32].

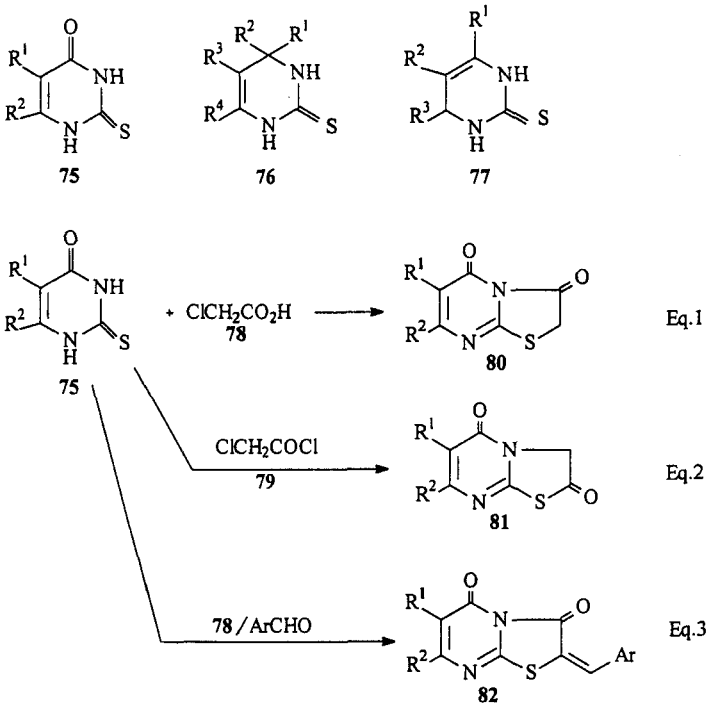


2-Methylthiothiazolium iodide **67** reacted with 3-amino-2-cyano-arylacrylonitriles **68** to give the cyclic isothioureas **70** and **71**. Interestingly, after removal of the N-protecting group, spontaneous cyclization of **69** gave the thiazolopyrimidine derivatives **70** and **71**. Similarly, compound **72** reacted with **68** to give **74**, through a similar intermediate **73** [33].



2.2.2. *Azine Approaches*

Pyrmidinethione derivatives **75–77** were alkylated with monochloroacetic acid or chloroacetyl chloride and then cyclized to give thiazolopyrimidine derivatives [34–48]. Thus, pyrimidinethione **75** reacted with **78** or **79** in DMF [34] or in an acetic anhydride/pyridine mixture [36,38] to give thiazolo-pyrimidines **80** and **81**. Alkylation with **78** in the presence of an aromatic aldehyde [34–36,39,41–44,46], gave the ylidene derivatives **82** (cf. Eqs. 1–3). Similarly, pyrimidinethione derivatives **76** and **77** reacted with monochloroacetic acid in acetic acid/acetic anhydride/sodium acetate mixture [39,40] or with chloroacetyl chloride in dry dioxane to give the corresponding thiazolo-pyrimidines. Table I summarizes the pyrimidine-thione derivatives **75–77** used in the synthesis of various thiazolopyrimidines.



The Hantzsch-type condensation of dihydropyrimidines **77c** with a substituted 2-bromophenylacetaldehyde **83** led to the thiazolopyrimidine derivatives **84** [49,50].

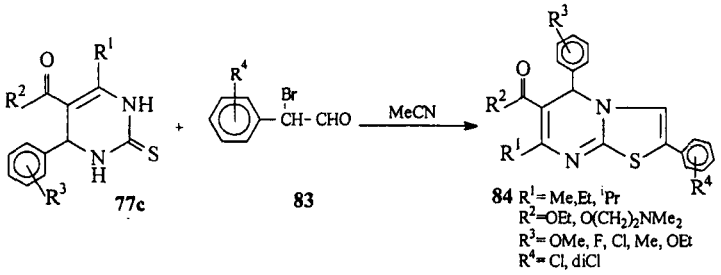
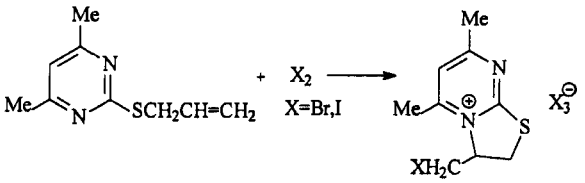


TABLE I Pyrimidinethione derivatives used in the synthesis of Thiazolopyrimidines and the corresponding references

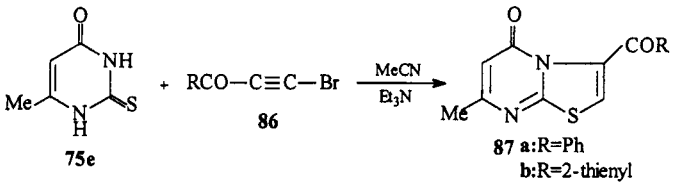
Cpd. No.	R^1	R^2	R^3	R^4	*Reference*
75a	CN	2,4-$C_6H_3Cl_2$	–	–	34
b	CN	2-thienyl	–	–	35
c	CN	2-furyl	–	–	35
d	CN	4-$MeOC_6H_4$	–	–	36, 37
e	H	Me	–	–	38
76a	H	Ph	H	4-$NH2C_6H_4$	39
b	H	4-ClC_6H_4	H	4-$NH2C_6H_4$	39
c	H	Ph	H	2-OH-5-MeC_6H_3	40
d	H	Ph	Me	CO_2Et	41
	H	Ph	H	CH::CHPh	42
f	H	4-$MeOC_6H_4$	H	CH::CHPh	42
g	H	4-ClC_6H_4	H	CH::CHPh	42
h	H	2-ClC_6H_4	H	CH::CHPh	42
i	H	Ph	CONHPh	Me	43
j	H	2-$MeOC_6H_4$	CONHPh	Me	43
k	H	4-$MeOC_6H_4$	CONHPh	Me	43
l	H	2-ClC_6H_4	CONHPh	Me	43
m	H	4-ClC_6H_4	CONHPh	Me	43
n	H	4-$NO2C_6H_4$	CONHPh	Me	43
o	H	4-$NMe2C_6H_4$	CONHPh	Me	43
p	H	4-BrC_6H_4	CO_2Me	Me	44
q	H	4-$MeOC_6H_4$	CO_2Me	Me	44
r	H	4-MeC_6H_4	CO_2Me	Me	44
s	H	2-FC_6H_4	CO_2Me	Me	44
77a	Me	CO2Et	Ph	–	45
b	Me	CO2Et	3,4-diMeC_6H_3	–	45
c	Me	CO2Et	4-$MeOC_6H_4$	–	45
d	Me	CO2Et	3-MeC_6H_4	–	45
e	Ph	H	Ph	–	46, 47

Reaction of allylthiopyrimidine with iodine and bromine gave the corresponding thiazolopyrimidine halogenides **85** in 67% yield [51–53].



85

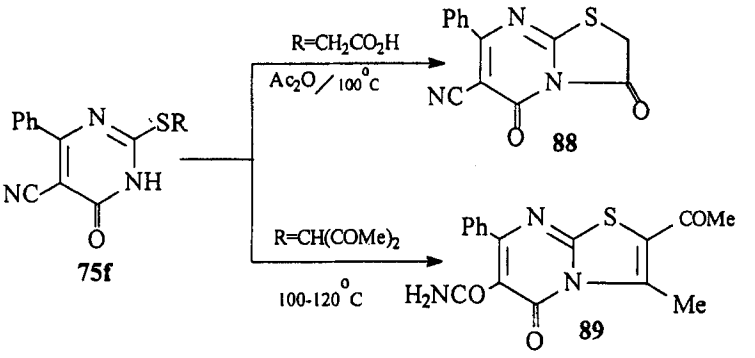
5-Oxothiazolo[3,2-a]pyrimidine derivatives **87a,b** were prepared by reaction of pyrimidinethione **75e** with the acetylenic derivative **86** in DMF, dioxane or acetonitrile in the presence of triethylamine [54,55].



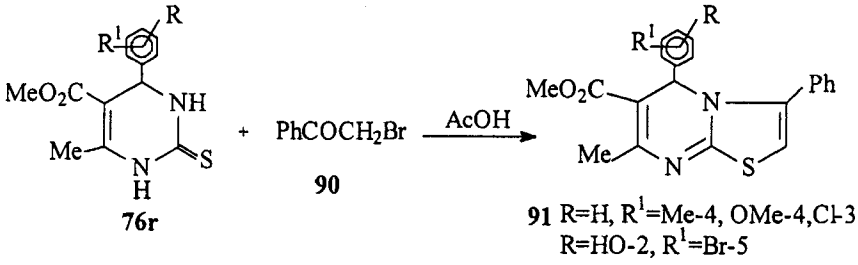
75e **86**

87 a:R=Ph
b:R=2-thienyl

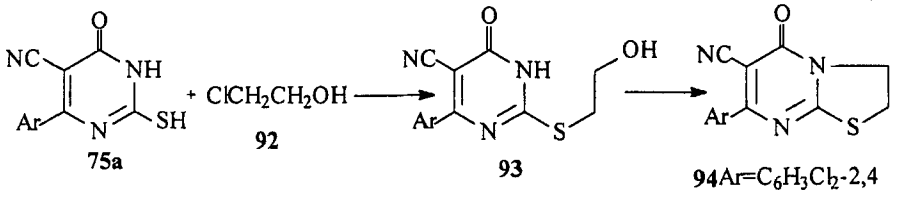
The alkylthiopyrimidine **75f** readily cyclized to give thiazolopyrimidine derivative **88** upon heating at 100°C in acetic anhydride. Alternatively, heating with polyphosphoric acid, at 100–120°C resulted in hydrolysis of the cyanide function to give **89** [56].



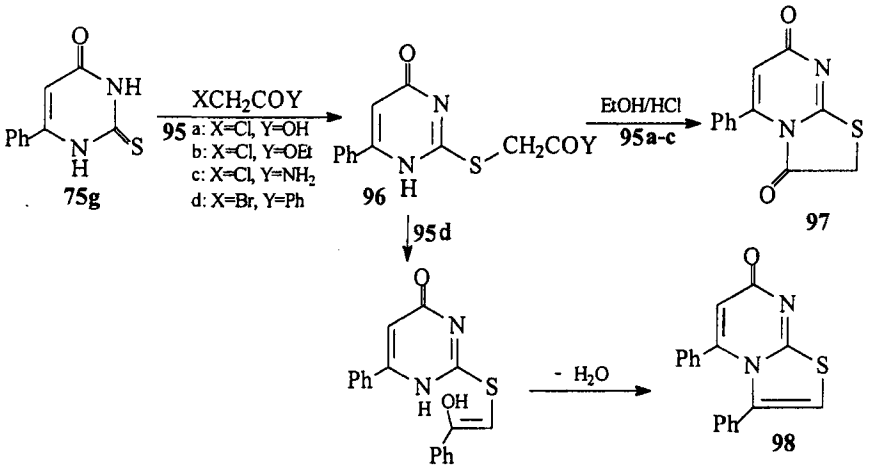
Thiazolo[3,2-a]pyrimidine derivatives **91** were prepared by refluxing pyrimidinethione derivative **76r** with phenacyl bromide **90** in glacial acetic acid [57–59].



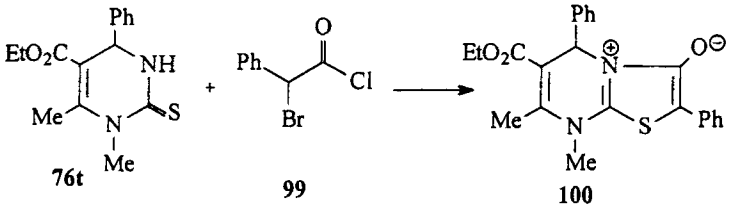
Treatment of mercaptopyrimidine derivative **75a** with 2-chloroethanol in DMF gave the asymmetrical thioether **93** which underwent cyclization on refluxing with a mixture of acetic anhydride–pyridine, to give the oxothiazolopyrimidine **94** [59].



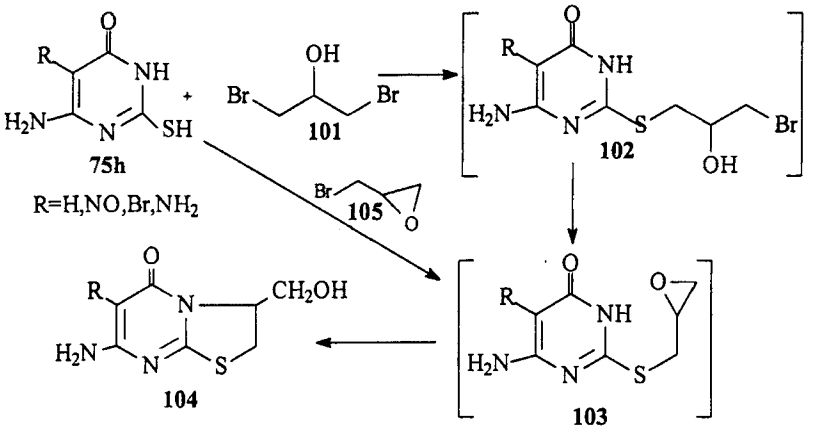
Furthermore, pyrimidinethione **75g** reacted with **95a–d** in ethanolic-sodium ethoxide to give products of dehydrochlorination **96a–d**. Compound **96** was cyclized in ethanolic-hydrochloric acid mixture to afford **97** and **98** in 89 and 60%, respectively [60].



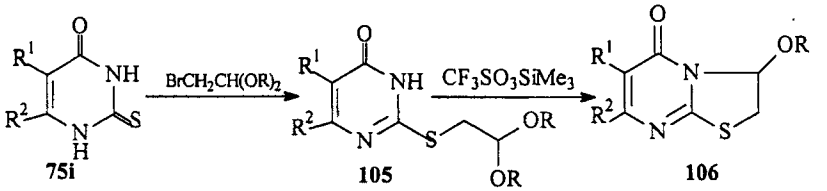
Compound **100** was obtained in 86% yield as a stable, orange-red solid by sequential addition of α-bromophenylacetyl chloride **99** and triethylamine to a solution of pyrimidinethione **76t** in chloroform [61].



1,3-Dibromopropan-2-ol **101** reacted with mercaptopyrimidine derivative **75h** to give **104** through the non isolated intermediates **102** and **103**. The same reaction product was obtained by reacting **75h** with 1-bromomethyloxirane **105** via intermediate **103** [62].

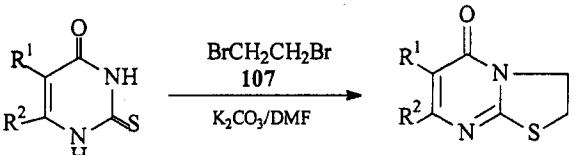


S-Alkylation of pyrimidinethione **75i** with 2-bromo-acetaldehyde acetals gave the *S*-[bis(alkoxy)ethyl] derivative **105**. Thiazolopyrimidine **106** were obtained by an N^1 regioselective intramolecular cyclization reaction using trimethylsilyl trifluoromethanesulfonate, $CF_3SO_3SiMe_3$, as the catalyst [63]. Similarly, the *S*-allyl derivatives cyclized to the corresponding thiazolopyrimidine derivatives [63].

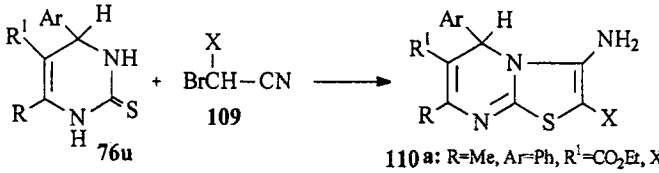


R=Me, Et, CH_2CH_2OH; R^1=Et, $CHMe_2$; R^2= CH_2Ph, $CH_2C_6H_3Me_2$-3,5

Reaction of pyrimidinethiones **75j,k** with 1,2-dibromoethane **107** gave the oxothiazolopyrimidine derivatives **108** in the presence of DMF/K_2CO_3 at 70–80°C [64,65],

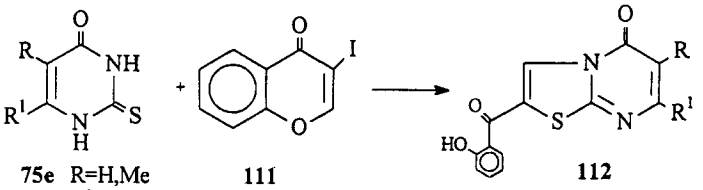


When a solution of the pyrimidinethione **76u** in ethanol containing potassium hydroxide was treated with bromomalononitrile **109**, a single product **110a–d** was isolated in high yield 88–91% [66]. Pyrimidinethione derivative **76u** reacted with bromoethylcyanoacetate to give thiazolopyrimidine derivative **110e** [67,68].

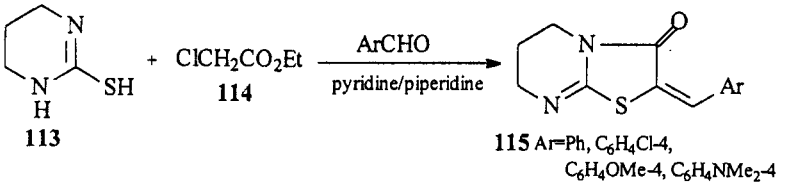


110a: R=Me, Ar=Ph, R^1=CO_2Et, X=CN
b: R=Me, Ar=C_6H_4OMe-4, R^1=CO_2Et, X=CN
c: R=Me, Ar=C_6H_4Cl, R^1=CO_2Et, X=CN
d: R=Ph, Ar=Ph, R^1=CO_2Et, X=CN
e: Ar,H=O, R=Ph, R^1=H, X=CO_2Et

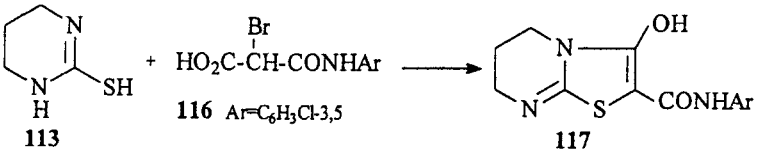
Michael addition of 3-iodochromone **111** or iodo-4H-1-benzopyran-4-one with pyrimidinethione nucleophile **75e** in DMF/K_2CO_3 solution gave the thiazolopyrimidines **112** in 58–72% yield [69,70].



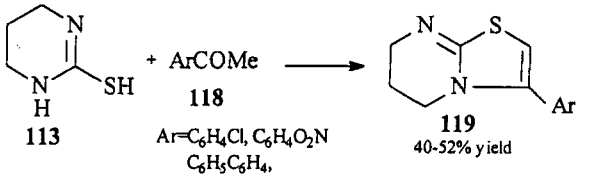
Tetrahydromercaptopyrimidine **113** on condensation with ethyl chloroacetate **114** and an aromatic aldehyde, in the presence of pyridine and piperidine, gave oxothiazolo[3,2-a]pyrimidines **115** [71].



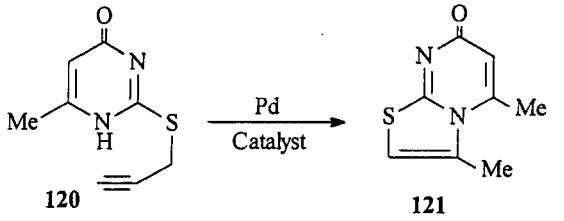
The brominated acid derivative **116** cyclocondensed with tetrahydromercaptopyrimidine **113** to give the thiazolopyrimidine **117** [72].



Tetrahydromercaptopyrimidine **113** also reacted with acetophenone derivatives **118** to give **119**, in the presence of [hydroxy(p-tosyloxy)iodo]benzene, which generated the α-haloketone in *situ* [73].



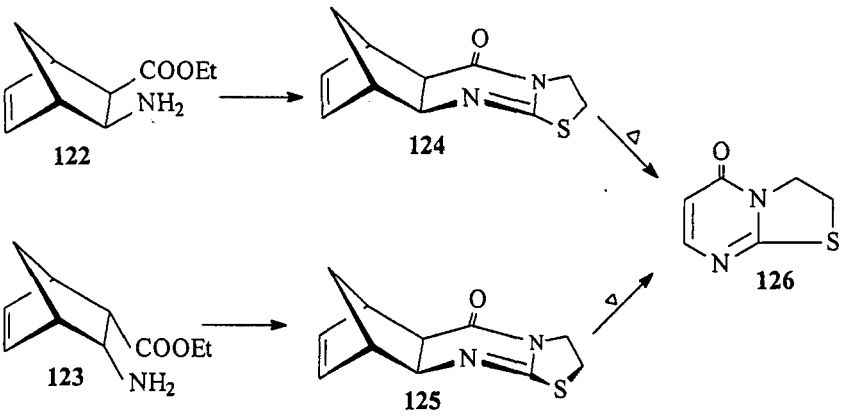
The transformation of 2-propargylthio-6-methyl-4-oxopyrimidine **120** to 7H-thiazolo [3,2-a]pyrimidine **121** was performed with base catalysis [74]. Palladium catalyzed cyclization was also reported [74]. In addition, it was also reported [75] that the synthesis of variety of thiazolopyrimidines was carried out by the catalytic action of a Cu(II) salt on the corresponding propargylthio derivatives.



2.2.3. By The Retro Diels-Alder Reaction

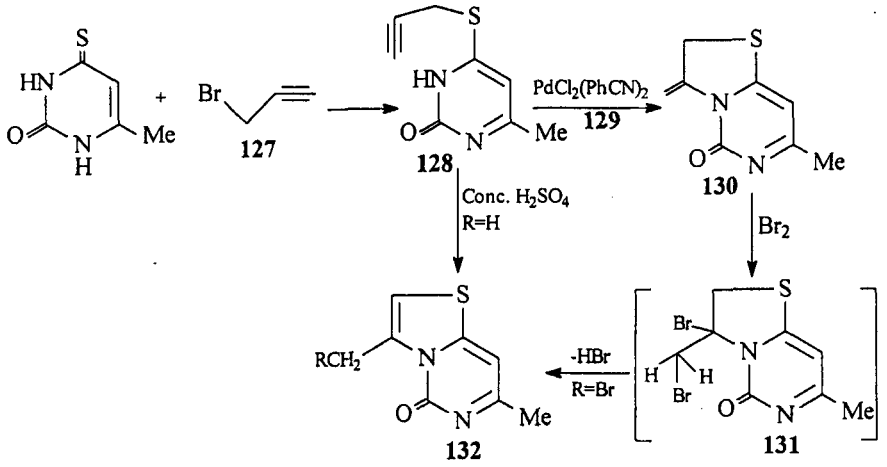
The reaction of ethyl 3-exo-aminobicyclo[2.2.1]hept-5-ene-2-exo-carboxylate **122** and the diendo counterpart **123** with chloroethyl isothiocyanate yielded the tetracycles **124**

and **125**, respectively. When compounds **124** and **125** were melted at 140°C for 20 min, bicycles **126** were formed in good yield, by eliminating cyclopentadiene [76].

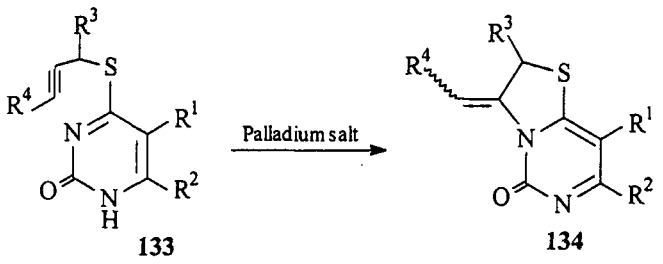


2.3. Preparation of Thiazolo[3,2-c]pyrimidines

6-Methyl-2-oxo-4-thioxopyrimidine was alkylated with propargyl bromide **127** to give the corresponding 4-propargylmercapto derivative **128** which was then transformed to 5H-thiazolo[3,2-c]pyrimidine derivative **130** by the action of the palladium salt **129** in methanol. In this reaction the Pd(II) salt catalyzes the nucleophilic addition of the amide to the acetylene. When compound **130** was treated with an excess of bromine in chloroform, the 5H-thiazolo[3,2-c]pyrimidine derivative **132** was formed via the intermediate **131**. In addition, when compound **128** was treated with concentrated sulfuric acid at 50°C, compound **132** resulted [77].

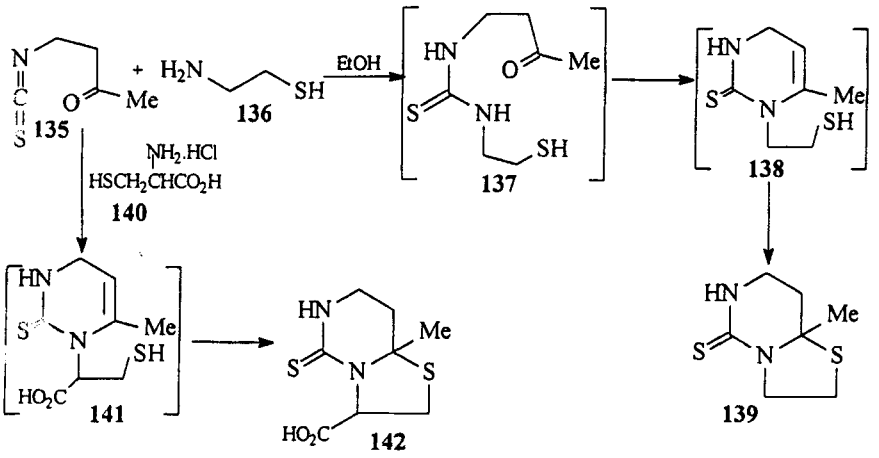


Propargylthiopyrimidines **133** gave thiazolo[3,2-c]pyrimidines **134** under the catalytic action of a Pd(II) salt. The reaction proceeds via addition of the amide nitrogen to the acetylene triple bond [78].



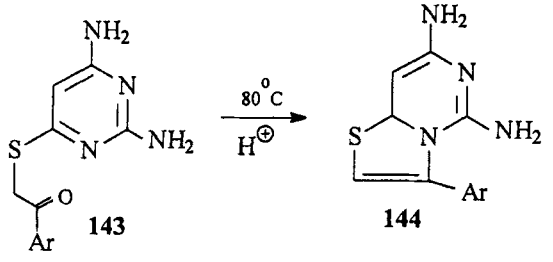
133 134

4-Isothiocyanatobutan-2-one **135** reacted with 2-mercaptoethylamine **136** to give the hexahydrothiazolo[3,2-c]pyrimidinethione **139** in a single-pot reaction, via the intermediates **137** and **138** [79]. In addition, compound **135** reacted with cysteine hydrochloride **140** to give **142** through the non isolated intermediate **141** [79].



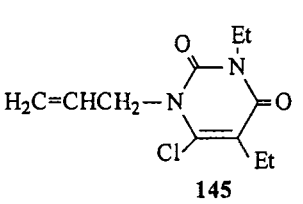
135 136 137 138 139 140 141 142

2,4-Diamino-6-(p-bromophenacylthio)pyrimidine **143** when heated on steam bath, with exclusion of moisture, with 0.5 M sulfuric acid gave the thiazolo[3,2-c]pyrimidine derivative **144** [80].

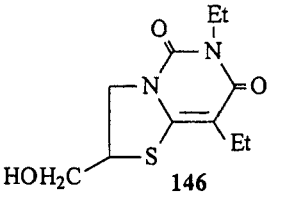


143 144

Kaul *et al.* [81] reported that the N-allylpyrimidine derivative **145** was metabolized to give 5,7-dioxothiazolo[3,2-c]pyrimidine derivative **146** and confirmed this by comparison with the synthetic product.

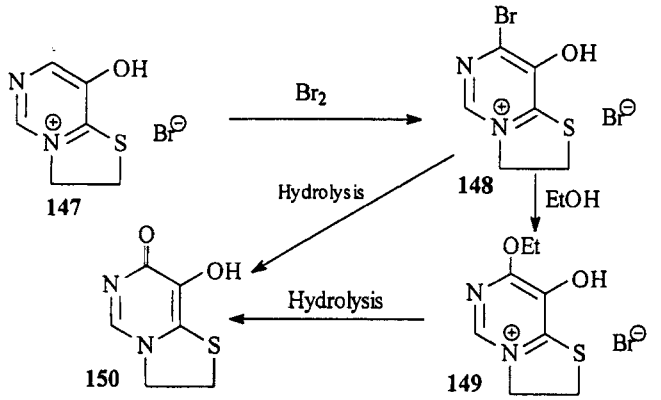


145

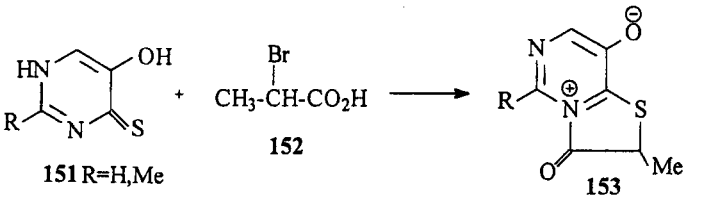


146

Bromination of thiazolo[3,2-c]pyrimidinium bromide **147** gave the monobromo derivative **148**. Nucleophilic substitution of **148** with ethanol gave **149**, which on hydrolysis gave the thiazolo[3,2-c]pyrimidine **150** [82].

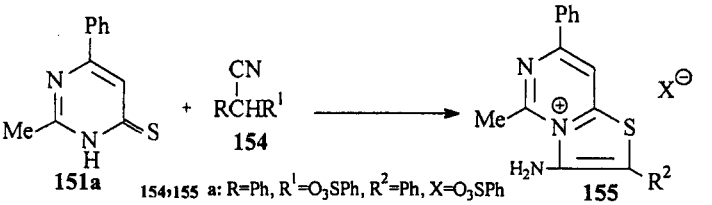


It was reported [83] that 2,3-dihydrothiazolo[3,2-c]pyrimidinium-8-olate **153** was prepared by the reaction of 5-hydroxy-4-pyrimidinethione **151** with 2-bromopropanoic acid **152**.



151 R=H,Me

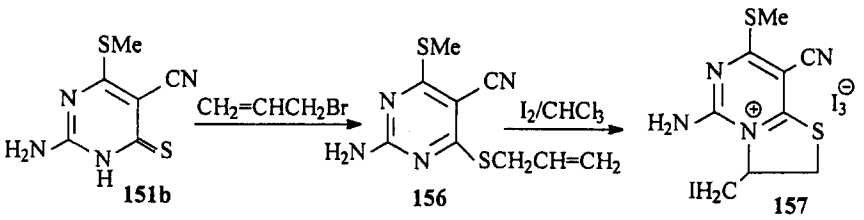
Pyrimidinethione derivative **151a** reacted with the nitriles **154a–c** to give the corresponding thiazolo[3,2-c]pyrimidinium salts **155a–c** in a 52–83% yield [84].



151a

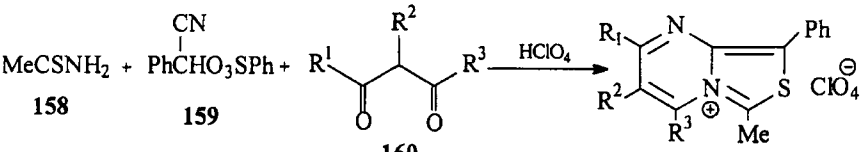
154,155 a: R=Ph, R^1=O_3SPh, R^2=Ph, X=O_3SPh
b:R=Br, R^1=H, R^2=H, X=Br
c: R=Br, R^1=Me, R^2=Me, X=Br

Pyrimidinethione **151b** underwent allylation with allyl bromide to give **156** in 69% yield. The latter was cyclized by iodine-chloroform to give the thiazolo[3,2-c]pyrimidinium salt **157** in 67% yield [85].



2.4. Preparation of Thiazolo[3,4-a]pyrimidine

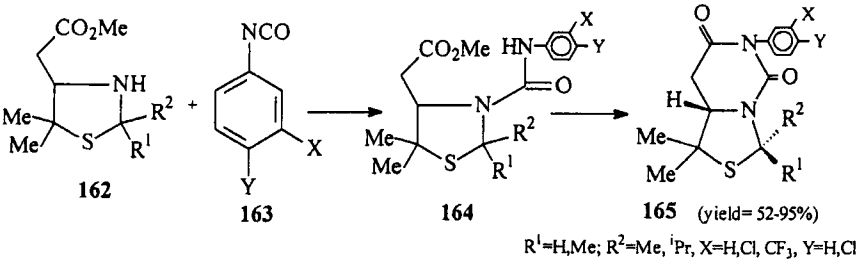
Romanov *et al.* [86] reported that the thioacetamide **158** cyclocondensed with the nitrile compound **159** and diketone **160** at 100–110°C in perchloric acid to give thiazolo[3,4-a]pyrimidinium perchlorate derivatives **161a–c** in 28–34% yield.



The syntheses of thiazolo[3,4-a]pyrimidinium polymethine dyes were also reported [87,88].

2.5. Preparation of Thiazolo[3,4-c]pyrimidine

The β-amino esters **162** reacted with isocyanates **163** in dry dichloromethane in an exothermic manner (in most cases the reaction temperature increased < 10°C) to form the carbomoyl compounds **164** in 55–90% yields as colourless crystals. Compounds **164** were heated in triethylamine under reflux to give **165** in 54–95% yield [89]. This is the only published report for the synthesis of this ring system.



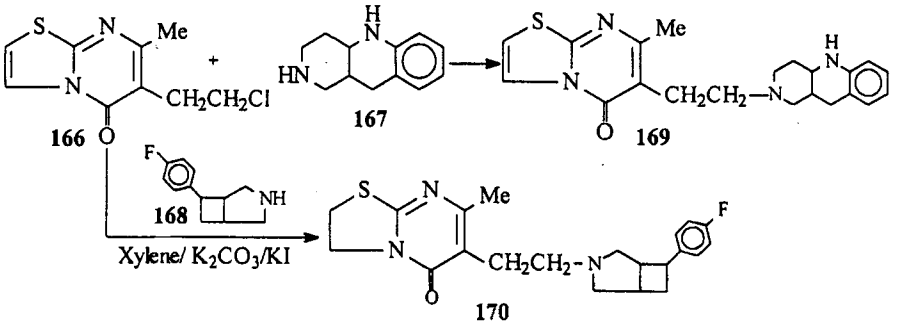
3. CHEMICAL REACTIVITY

3.1. General Consideration

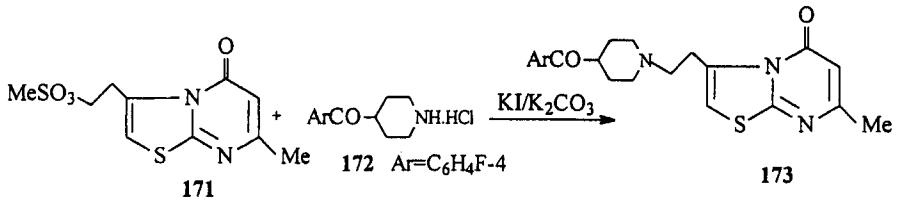
Most of the observed chemical reactivity of the thiazolopyrimidines in the literature covers the chemical reactions of the substituents attached to the ring carbon atoms. Little literature exists for ring opening or ring transformation reactions.

3.2. Reaction with Amines

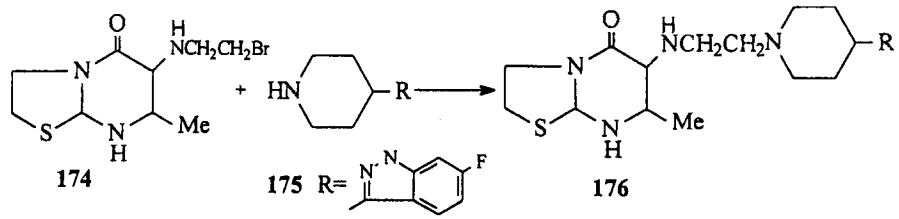
Thiazolopyrimidine derivative **166** reacted with **167** and **168** to give the tricyclicalkyl substituent **169** and **170**, respectively [90,91].



Thiazolopyrimidine derivative **171** reacted with 4(4-fluorobenzoyl) piperidine hydrochloride **172**, in the presence of potassium iodide and potassium carbonate, to give the benzoylpiperidine derivative **173** [92].

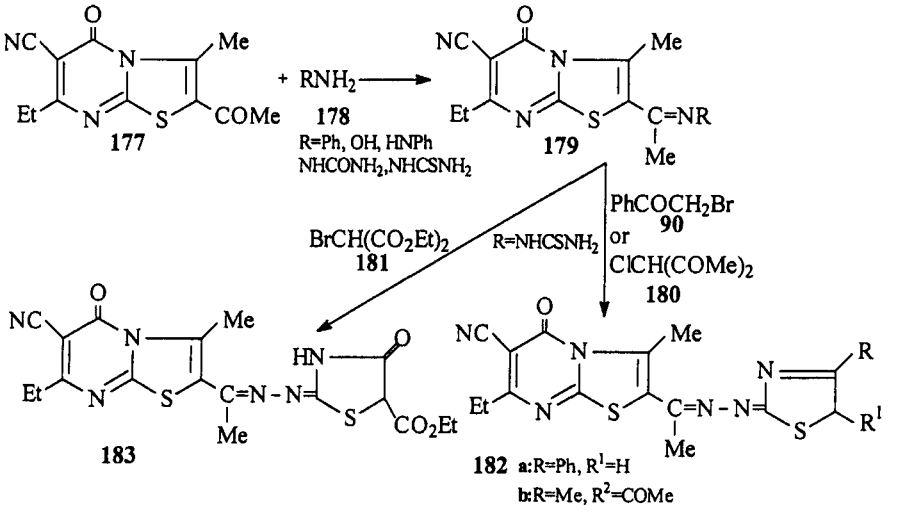


Oxotetrahydrothiazolopyrimidine **174** reacted with 3-piperidinylindazole **175** to give the antihypertensive compound **176** [93].

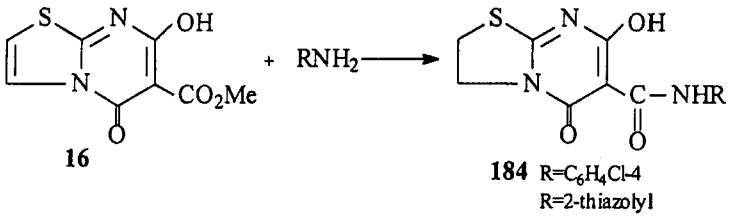


Thiazolopyrimidine derivative **177** reacted with the amine derivatives **178** to give **179**. The latter reacted with phenacyl bromide **90**, chloroacetylacetone **180**, and bromodiethyl

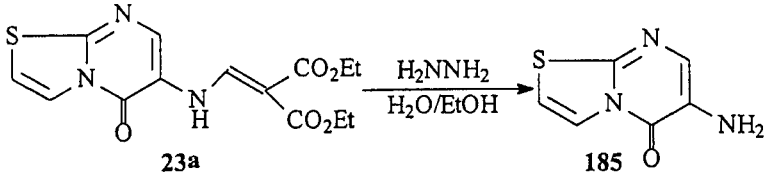
malonate **181** in a refluxing ethanol/sodium acetate mixture to give **182a, 182b** and **183**, respectively [94].



Thiazolopyrimidinecarboxylate **16** reacted with 4-chloroaniline in refluxing bromobenzene to give compound **184** [9].

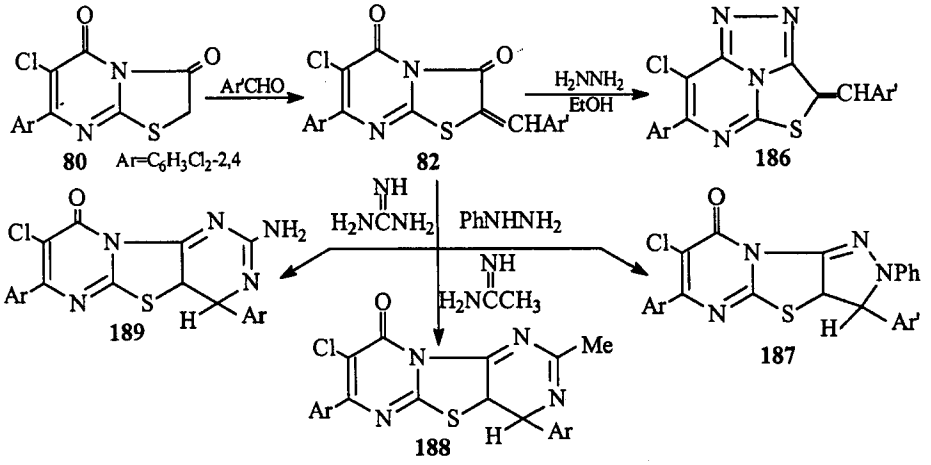


The N-protecting group can be easily removed upon treating **23a** with hydrazine hydrate in ethanol at reflux to give the corresponding 6-aminothiazolopyrimidine **185** [13].

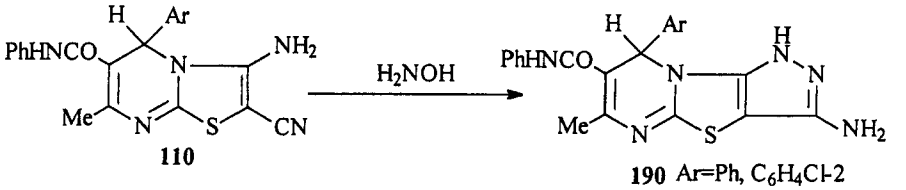


The active methylene in the thiazolopyrimidine derivative **80** readily condensed with an aromatic aldehyde [34–37,39,41–44,56,66,71] in acidic medium to give an ylidene derivative **82**. In addition, the α,β-unsaturated ketone obtained was used to synthesize fused heterocyclic systems in order to give conclusive proof for ylidene structure [34]. Thus, the ylidene derivative **82** reacted with hydrazine hydrate, phenylhydrazine,

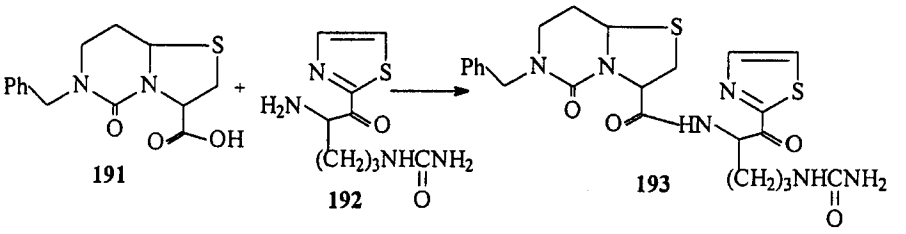
acetamidine hydrochloride and guanidine hydrochloride to give **186, 187, 188** and **189**, respectively [34].



A solution of thiazolopyrimidine **110**, (R = Me, R^1 = CONHPh, X = CN), in pyridine was heated under reflux with hydroxylamine hydrochloride in ethanolic sodium ethoxide give to **190** [43].



Oxothiazolopyrimidine derivative **191** was amidated by the arginine derivative **192** to give **193** [95].



The isocyanate **194** reacted with the morpholine **195**, aminothiazole **196**, aminoisoxazole **197**, and 2-aminopyridine **198** to give the ureas **199–202**, respectively (cf. Chart 3) [10].

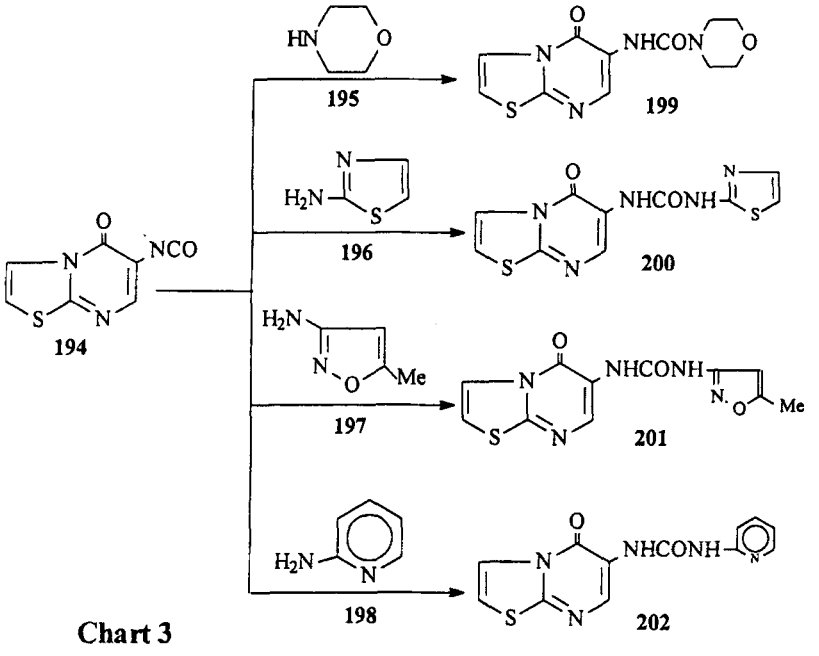
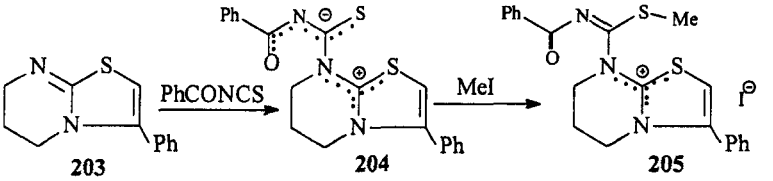


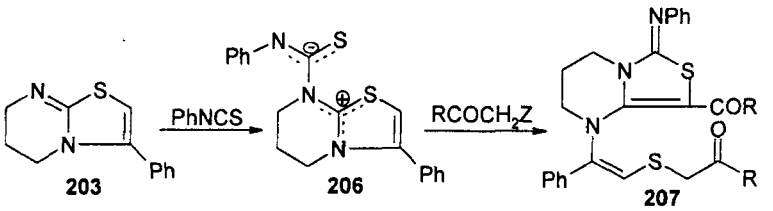
Chart 3

3.3. Reaction with Isothiocyanates

Betaines **204** were easily prepared by reaction of the N-bridged thiazolo compound **203** with benzoyl isothiocyanate in acetone at room temperature. Subsequent reaction with methyl iodide in acetone or acetonitrile gave the *S*-alkylated quarternary ammonium salt **205** [96].



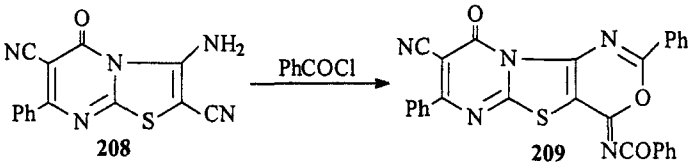
Compound **203** reacted with phenylisothiacyanate to give **206**. The latter was alkylated with an α-haloketone or α-haloester to give **207** via a ring transformation reaction [96,97].



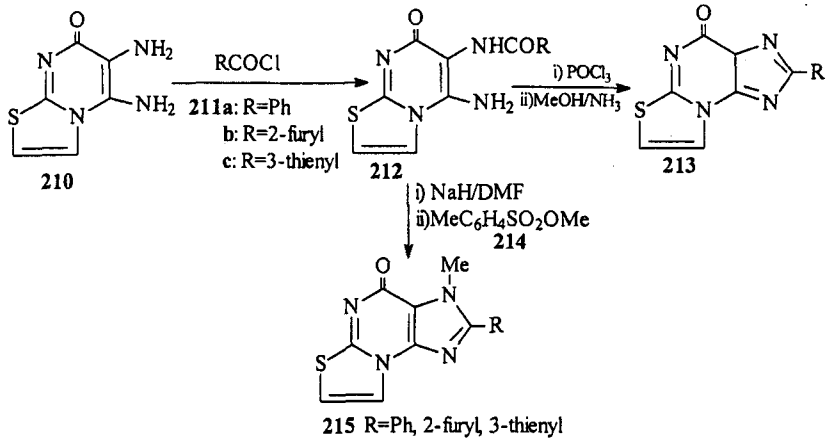
R=OEt , Me , $EtCO_2CH_2$
Z=Br , Cl

3.4. Reaction with Acid chloride Derivatives

Cyclocondensation of thiazolopyrimidine derivative **208** with benzoylchloride gave the oxazinothiazolopyrimidine **209** [67].

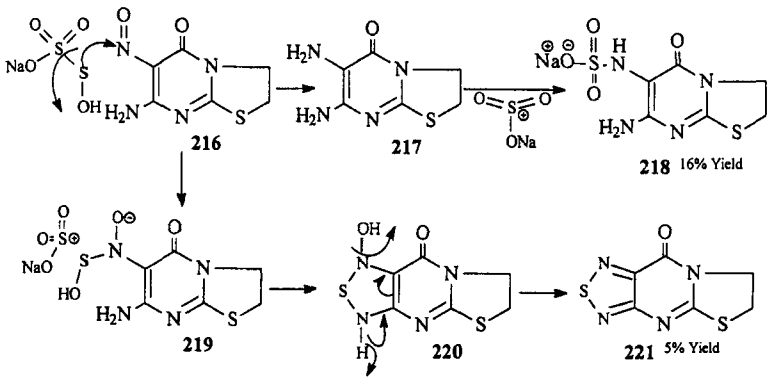


5,6-Diaminothiazolopyrimidine **210** was easily acylated by **211a–c** in pyridine. The resulting acylamino derivatives **212** cyclized to compounds **213** in the presence of $POCl_3$ and methanolic or cyclized to compounds **215** in the presence of NaH/DMF followed by treatment with methyl 4-toluenesulfonate **214** [20].



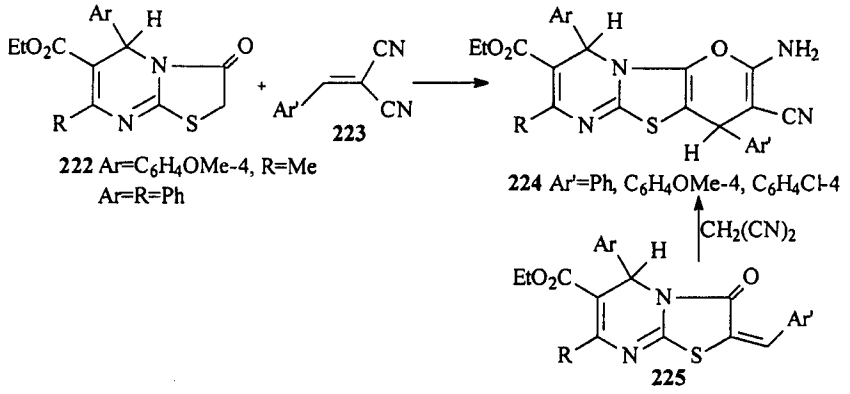
3.5. Reduction Reactions

Reduction of 6-nitrosothiazolopyrimidine **216** with sodium hydrosulfite yielded **218** and **221** in low yield via the intermediates **217, 219** and **220** [20,98,99].



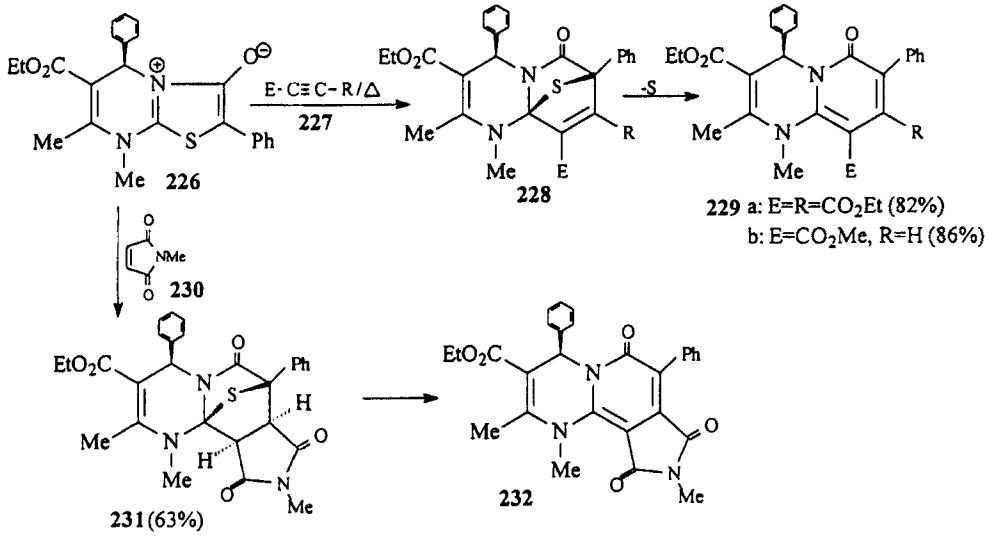
3.6. Michael Addition Reactions

Thiazolopyrimidines **222** reacted with cinnamonitrile derivatives **223** in refluxing pyridine to give **224**. Alternatively the reaction of malononitrile with **225** in refluxing ethanolic piperidine gave the same reaction product **224** [66].



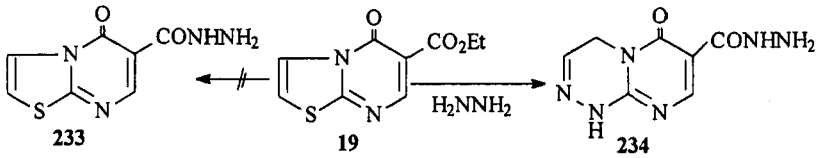
3.7. Cycloaddition Reactions

Fused pyrimidine derivative **226** reacted smoothly with dimethyl acetylenedicarboxylate **227** and methyl propiolate at ~100°C to produce pyridopyrimidine **229a,b** via the intermediate **228** in high yield [61]. The reaction of **226** with the olefinic dipolarphiles **230** resulted in the formation of cycloadduct **231** in 63% isolated yield and **232** as a by product. Cycloadduct **231** is relatively stable, however, on prolonged standing, a chloroform solution at room temperature or in the presence of silica gel, conversion to **232** occurred [61].



3.8. Ring Transformations

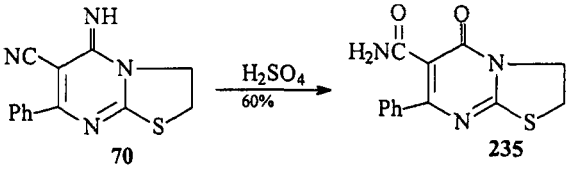
Although it was reported [13,34] that oxothiazolopyrimidine reacted with hydrazine hydrate to give the cyclized amino derivative, Shridhar *et al.*, [10] reported that the hydrazinolysis of ethyl thiazolopyrimidine carboxylate **19** instead of giving **233**, led to the formation of pyrimidinotriazine hydrazide **234**. This was believed to take place through the initial opening of thiazole ring in **19** with hydrazine hydrate followed by recyclization with the elimination of hydrogen sulfide [10].



233 **19** **234**

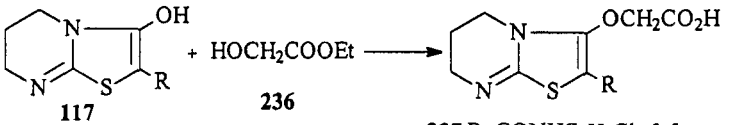
3.9. Miscellaneous

The hydrolysis of the imino, in addition to the nitrile function in **70** was accomplished using 60% sulfuric acid under reflux to give **235** [33].



70 **235**

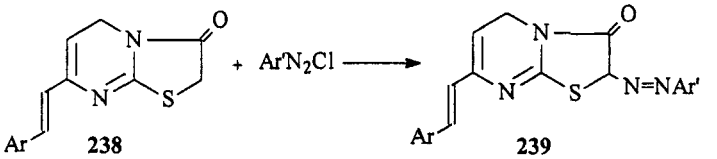
Treatment of hydroxythiazolopyrimidine **117** with hydroxyethyl acetate **236** gave **237** [72].



117 **236**

237 R=$CONHC_6H_3Cl_2$-3,5

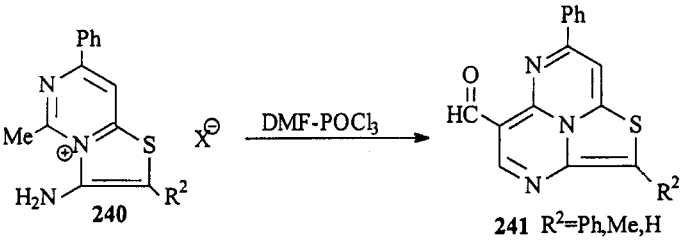
Arylstyrylthiazolopyrimidine **238** readily coupled with aryl diazonium salts to give **239** [42,66].



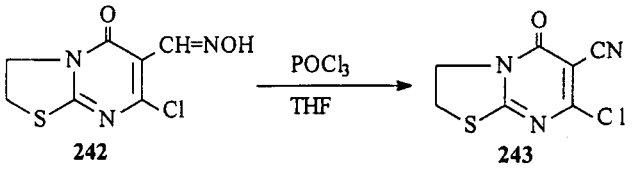
238 **239**

Ar'=Ph,C_6H_4-Br,C_6H_4-Cl

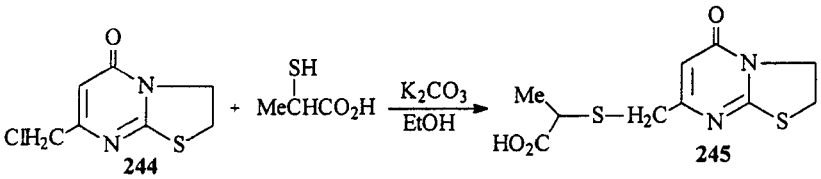
Thiazolopyrimidinium salt **240** cyclized with DMF-$POCl_3$ to give the tricyclic adducts **241** in 55–77% yield [84].



Treatment of thiazolopyrimidine **242** with $POCl_3$ in THF at room temperature for 1 h gave **243** in 86% yield [100].



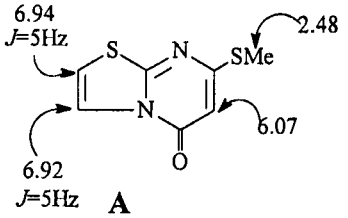
7-Chloromethylthiazolopyrimmidine derivative **244** reacted with α-mercaptopropionic acid in ethanolic potassium carbonate to give the thioether derivative **245** [101].

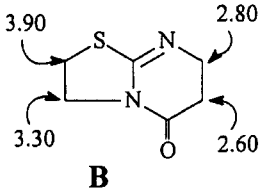


4. EXPERIMENTAL STRUCTURAL METHODS

4.1. ^1H, ^{13}C NMR and ^{15}N NMR Spectroscopy

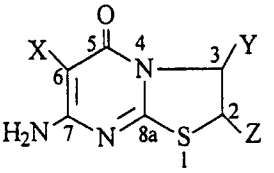
There are miscellaneous collections of chemical shift data available for select examples of all these systems [24,25,29,31,45,102]. Some of the selected example are indicated below (e.g. structures **A**[24] and **B**[31]). Furthermore, ^1H; ^{13}C; H,H-cosy; H,C-cosy; DEPT 90° and 135°C NMR spectroscopic method were also reported [103].





^{13}C NMR Spectroscopy

The chemical shifts for the thiazolopyrimidines were reported [31,50,76,102]. Table II shows the chemical shift (δ) values for compound 246.



246 **a**:X=NH_2, Y=Z=H
b:X=NH_2, Y=CH_2OH, Z=H
c: X=Y=H, Z=Ph

^{15}N NMR Spectroscopy

The chemical shift of ^{15}N NMR spectra for thiazolopyrimidines with one nitrogen in common were reported [102]. The ^{15}N NMR, chemical shifts for compounds **246a–c** fall into the general range reported for amidic nitrogen atoms, (N-4) from (−210 to −180 ppm) and iminic nitrogen atoms, (N-8) from (−154.6 to −167.4 ppm). However, in compound **246b** a strong β-effect due to the polar substituent, CH_2OH, on (N-4) Table III gave the same chemical shifts of compounds **246a–c**.

4.2. UV Spectroscopy

The UV spectra of compounds with the thiazole ring are characterized by an electronic band in 220–290 nm range. It was reported that substitution at the 5-position induced a bathochromic effect on the band at higher λ_{max}. This effect is in accordance with the following order: 5-H < 5-Br < 5-NH_2 < 5-NO. No effect was observed for the 3-OH and 3-CH_2OH substitution [62]. Table IV shows different values λmax for different derivatives of thiazolopyrimidine **246** [62].

TABLE II ^{13}C NMR chemical shifts δ (ppm) relative to TMS

Cpd. No.	*C-2*	*C-3*	*C-5*	*C-6*	*C-7*	*C-8a*
246a	26.89	48.78	156.39	105.89	151.68	148.40
246b	28.93	61.79	156.11	105.89	151.75	148.50
246c	45.80	54.79	164.13	80.97	163.84	160.87

TABLE III ^{15}N NMR Chemical shifts (ppm) relative to $MeNO_2$

Cpd. No.	*N-4*	*N-8*	*NH_2*
246a	−206.6	−162.6	−300.6
246b	−188.7	−162.4	−300.2
246c	−206.1	−164.1	−289.9

TABLE IV λ_{max} for the thiazolopyrimidines (246, Z = H)

X	Y	λ_{max} (log ε) in ethanol
H	H	271 (3.62), 220 (4.30)
H	$-CH_2OH$	273 (3.84), 223 (4.50)
NO	$-CH_2OH$	342 (4.17), 277 (sh, 3.68), 211 (4.19)
Br	$-CH_2OH$	289 (3.86), 224 (4.42)
NH_2	$-CH_2OH$	308 (sh, 3.85), 290 (3.87), 221 (4.29)

4.3. Mass Spectrometry

Mass spectrometry has been used for the identification of isomers having groups in the position 7 (or 5) of pyrimidine ring [104]. Direct distinction between the thiazolo [3,2-a] [4,8,105,106] and [3,2-c]pyrimidine [105] containing carbonyl groups on thiazole ring has been reported. Different fragment patterns were also reported.

4.4. X-ray Diffraction

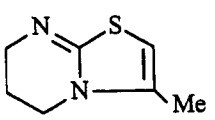
The X-ray molecular structure of 7-amino-2,3-dihydro-2-phenylthiazolo[3,2-a]pyrimidin-5-one **246c** was reported [102].

5. BIOLOGICAL ACTIVITY

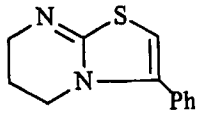
Thiazolopyrimidines have generated recent interest due to their interesting biological and pharmaceutical activities. Thus, these ring systems have antimicrobial [70] activity and have been found useful as insecticides and in addition, they have been reported to be active against virulent Lewis lung tumor in mice [65]. Furthermore, thiazolopyrimidines were used as *in vitro* test for activity against human cytomegalovirus [107]. They have also been used as psychotropic agents [108,109], antiviral agents against herpes simplex virus Type 1 [110], gram negative and gram positive antibacteria affects [110–114], anti-inflammatory [115–117], analgesic, antipyretic and gastrointestinal toxicity of a new anti-inflammatory drug [110]. The influence of substitutents at positions 6 and 7 as well as the substitution pattern of the two phenyl rings in positions 2 and 5 on activity is also reported [48]. Thiazolopyrimidines were also investigated as antifungal [114], inhibitors of trypanosome musculi development in mice [118], and as an antiallergic agent [119].

6. BASICITY OF THIAZOLE HETEROCYCLIC COMPOUNDS

The potentiometric titration method of Albert and Serjeant has been used in this determination, so that the pKa's have been corrected for ionic-strength effects. Because of their poor solubilities in water, the pKa of the phenyl derivative has been measured in 50% aqueous ethanol. The pKa's values of thiazolo[3,2-a]pyrimidine with methyl and phenyl substituents are shown below.



pKa = 10.31 ± 0.06



pKa = 9.11±0.04

Both derivatives show high basicities considering that the pKa value of pyridine and triethylamine is 5.27 and 10.72, respectively. The pKa values of the methyl substituted thiazole are higher than those of the corresponding phenyl substituents. These observations may be interpreted as being mainly due to polar effects. The methyl group is electron donating and, therefore, the ion is expected to be stabilized to a greater degree by methyl substitution and increasing ring size [120].

7. APPLICATIONS

Thiazolopyrimidines have been used as a coating dye for optical recording materials [88–121]. On the material comprising a support coated with silver halide, the layer containing the thiazolopyrimidinium salt shows a clear reversal image on high luminance [122]. Cyanine dyes based on mesoionic thiazolo[3,2-a]pyrimidine derivatives [123–125] or thiazolo[3,4-a]pyrimidine have been reported [78,88,126].

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