HETEROCYCLES, Vol. 71, No. 4, 2007, pp. 761 - 798. © The Japan Institute of Heterocyclic Chemistry
Received, 18th December, 2006, Accepted, 1st February, 2007, Published online, 6th February, 2007. REV-06-616

# PYRROLO[2,1-*b*]THIAZOLES

**Anton V. Tverdokhlebov**

Enamine Ltd., Alexandra Matrosova str. 23, 01103, Kiev, UKRAINE; E-mail: atver@univ.kiev.ua

**Abstract** – Synthesis and properties of pyrrolo[2,1-*b*]thiazoles have been reviewed. The literature from 1940 to 2005 is covered. Bibliography comprises 136 references.

## 1. INTRODUCTION

Pyrrolo[2,1-*b*]thiazole system (Figure 1) is known for about 70 years. However their chemistry has not been reviewed hitherto. Partially it was covered in the monographs devoted to fused bicyclic heterocycles.[1,2] Also some aspects of pyrrolothiazoles chemistry were mentioned in the reviews on thiazoles[3-5] and in the monographs on penicillins.[6,7] Nevertheless within all these works[1-7] pyrrolo[2,1-*b*]thiazoles were described episodically and unsystematically. Nowadays a lot of data gathered in the field should be reviewed and summarized. The present paper is aimed to do it and covers the literature from 1940 to 2005.

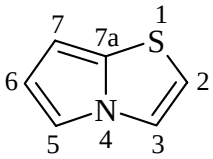


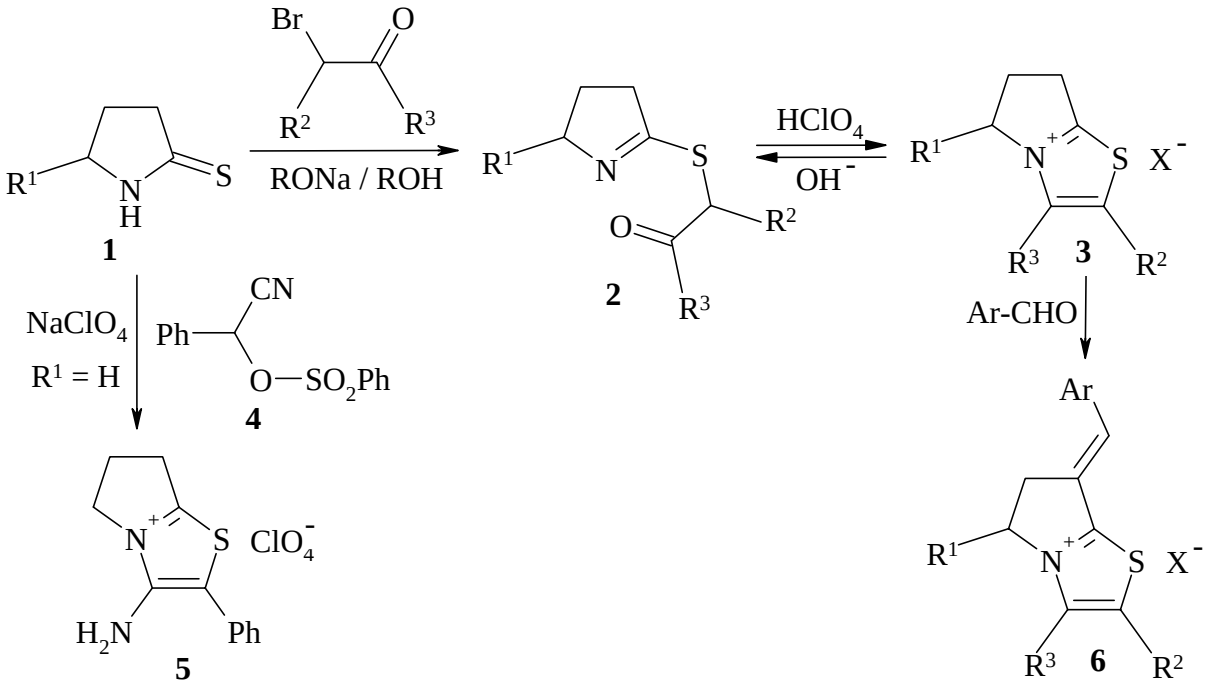

Figure 1

## 2. SYNTHESIS OF PYRROLO[2,1-*b*]THIAZOLES

### 2.1. Thiazole Ring Annulation to Pyrrole Derivatives

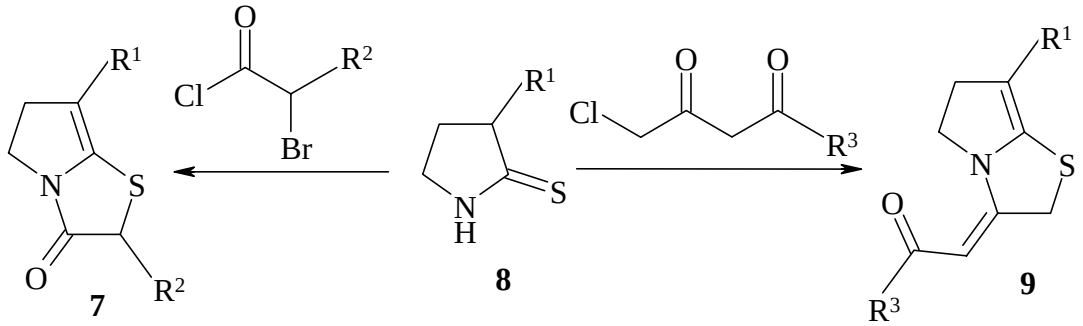
#### 2.1.1. Hantzsch reaction

2-Pyrrolidinethione derivatives **1** upon heating with α-bromoketones in alcohols, benzene or in melt were found to give pyrrolothiazolium salts **3** (X = Br) in moderate yields[8-12,18] (Scheme 1). When the reaction was carried out at rt in the presence of alkoxide the intermediate compounds **2** were isolated almost quantitatively.[9,11] Their treatment with perchloric acid caused ring closure and formation of derivatives **3** (X = $ClO_4$). In turn, saponification of the salts **3** led to the corresponding precursors **2**.[9,11] Apparently, the present reaction is the particular case of the well known Hantzsch thiazole synthesis. Methylene group at the position 7 of pyrrolothiazoles **3** was shown to be active enough for condensation with aldehydes resulted in arylidene derivatives **6**.[11] Noteworthy, O-sulfonyl derivative of benzaldehyde cyanohydrine **4** was successfully employed instead of the bromoketones affording 3-aminopyrrolo[2,1-*b*]thiazolium perchlorate **5** in 81 % yield.[13]



Scheme 1. $R^1$, $R^2$ = H, Alkyl; $R^3$ = Alkyl, subst. Ph.

3-Substituted pyrrolidinethiones **8** usually react with halocarbonyls avoiding the charged products due to deprotonation of initial pyrrolothiazolium adducts from the position 7. Thus, treatment of the thioamides **8** with α-bromo acid chlorides afforded derivatives **7** in good yields[14-16] (Scheme 2). An interesting result was obtained during alkylation of compounds **8** with γ-chloroacetoacetic acid esters and amides. Along with expected formation of the uncharged pyrrolothiazole moiety the water elimination was found to proceed in exocyclic manner giving the products of structure **9**.[17]

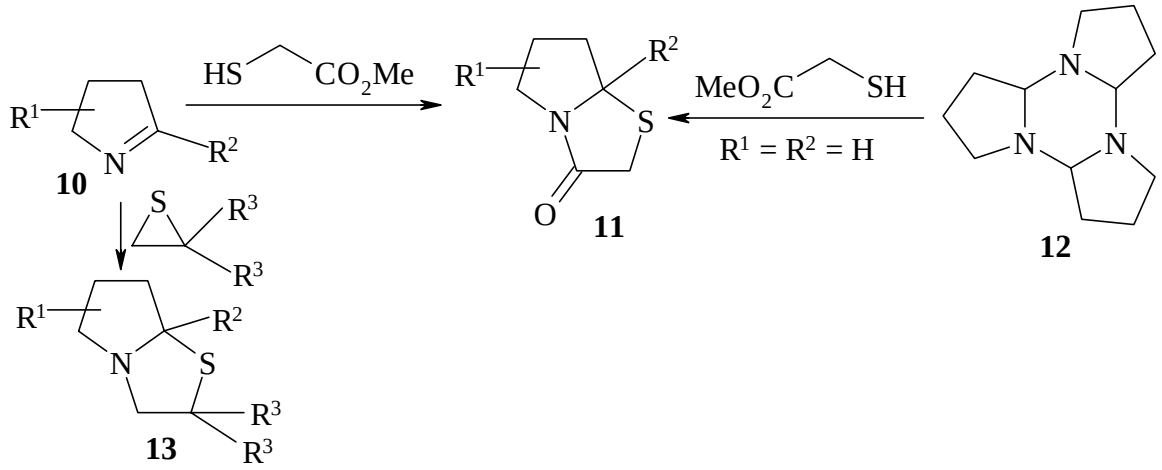


Scheme 2. $R^1$ = Alkyl, $CO_2R$; $R^2$ = H, Alkyl; $R^3$ = OR, NHR.

**2.1.2. Syntheses from 3,4-dihydro-2*H*-pyrroles and their equivalents**

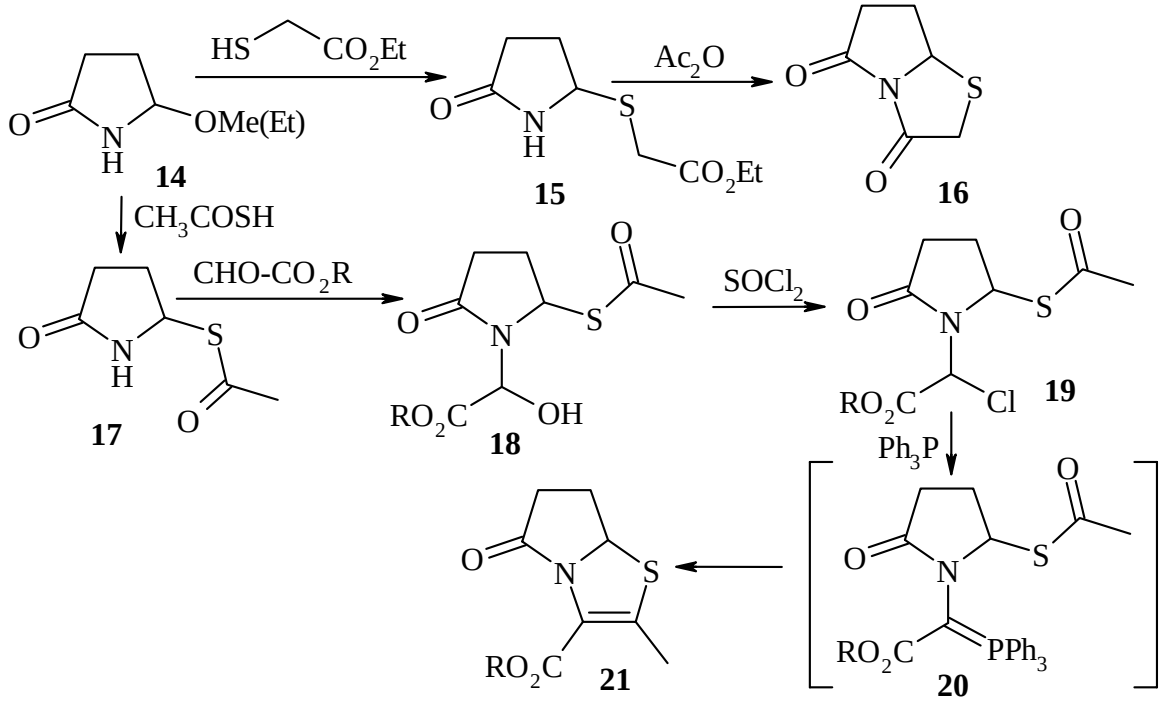
Addition of mercaptoacetic acid esters to imines with formation of 4-thiazolidinones is well known. 3,4-Dihydro-2*H*-pyrroles **10** as the cyclic imines were shown to react similarly yielding pyrrolothiazoles **11**[19] (Scheme 3). Certain compounds **10**, especially with $R^2$ = H, are inclined to polymerization and, hence, are hardly to be stored. However, the appropriate stable trimers **12** appeared to react in a similar fashion allowing to overcome this obstacle.[20] Moreover, derivatives **10** were found to give

pyrrolothiazoles **13** with thiiranes.[21] In the case of substituted thiiranes the reaction occurred regioselectively affording 2-substituted derivatives **13**.



Scheme 3. $R^1$, $R^3$ = H, Me; $R^2$ = H, Me, Ph, $PhCH_2$.

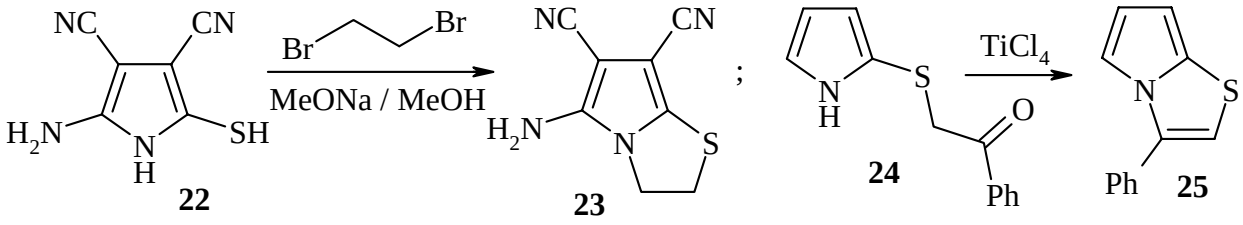
Alkoxypyrrolidinone **14** readily available by reduction of succinimide is known to be the synthon of cyclic imine. It reacts smoothly with a mercaptoacetic ester yielding derivative **15**, which undergoes easy cyclization into pyrrolothiazole **16**[22] (Scheme 4). Furthermore, the multi-step synthesis of pyrrolo[2,1-*b*]thiazole-3-carboxylic acids **21** starting from the **14** was reported.[23,24] It includes the alkoxy group substitution with thioacetic acid, two-step insertion of α-chloroalkyl residue to the nitrogen atom and, finally, intramolecular Wittig reaction of the intermediate **20** generated by treatment of the precursor **19** with triphenylphosphine.



Scheme 4

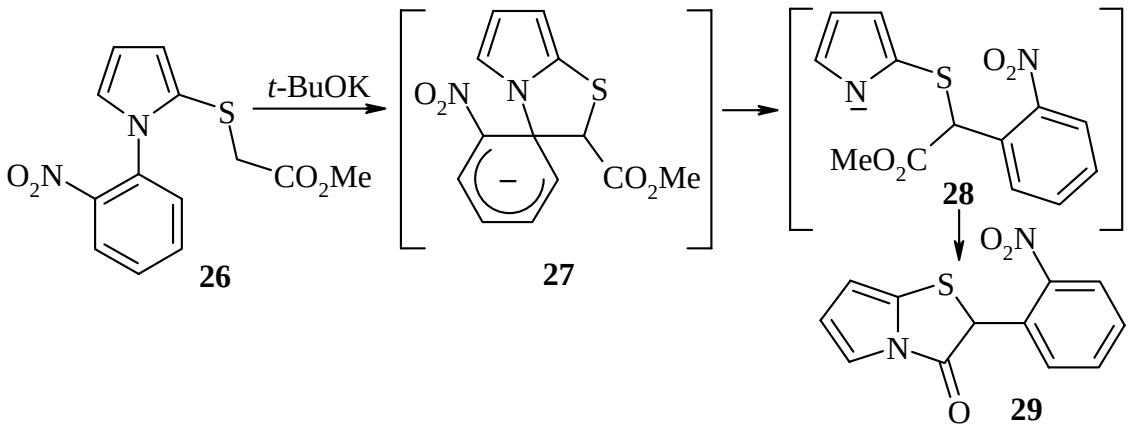
### 2.1.3. Miscellaneous

Alkylation of 2-pyrrolethiol **22**, available from tetracyanoethene and hydrogen sulfide, with dibromoethane was found to give pyrrolothiazole **23** in 65% yield[25] (Scheme 5). Treatment of (2-pyrrolylthio)acetophenone **24**, prepared in low yield by one-pot reductive cleavage and further alkylation of 2-pyrrolyl thiocyanate, with $TiCl_4$ afforded derivative **25**.[26] Certain resemblance with Hantzsch synthesis can be noted.



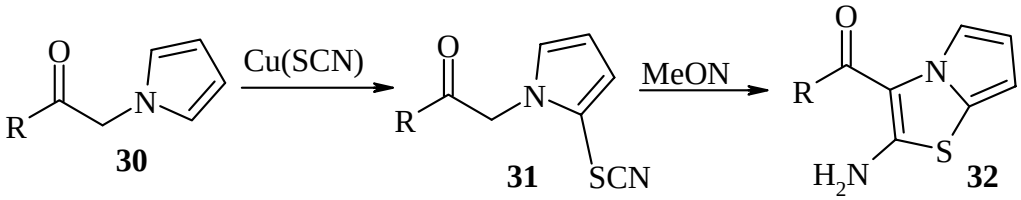

Scheme 5

(2-Pyrrolylthio)acetic acid ester **26**, also obtained from the appropriate thiocyanate, unexpectedly gave compound **29** in 30% yield[27] upon treatment with *tert*-butoxide (Scheme 6). The reaction was assumed to proceed via Smiles rearrangement of initially produced methylene anion affording intermediate **28**, which underwent spontaneous intramolecular acylation of the pyrrole nitrogen with ester group.



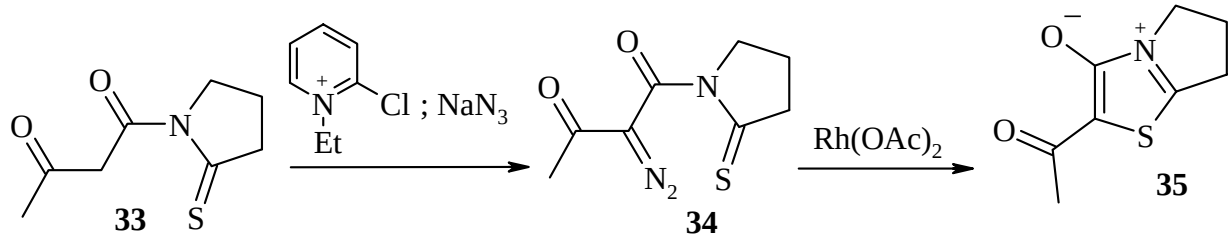

Scheme 6

An attempt to cleave thiocyano group in the pyrrole **31** by methanolysis in the presence of sodium methoxide failed to give corresponding thiol. Instead, it resulted in intramolecular Thorpe addition of the methylene to the nitrile thus leading to the product **32** in 81% yield[28] (Scheme 7).



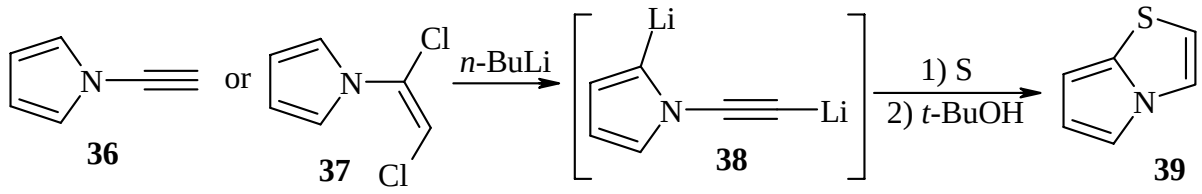

Scheme 7. R = 2-$FC_6H_4$

Thioamide **33** obtained by acylation of pyrrolidinethione with diketene was converted into diazo compound **34** by means of diazo group transfer reaction (Scheme 8). Derivative **34** in the presence of catalytic amount of rhodium acetate afforded betainic pyrrolothiazole **35**.[29,30] It turned out to be stable enough to be isolated and completely characterized.



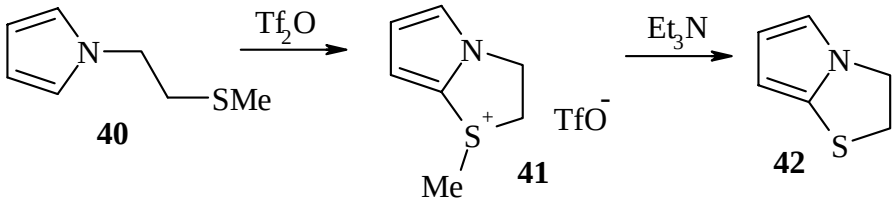

Scheme 8

An elegant method was developed for preparation of parent unsubstituted pyrrolo[2,1-*b*]thiazole (**39**). It includes a double lithiation of either *N*-ethynyl- or *N*-dichlorovinylpyrroles **36, 37** followed by the treatment of dilithio intermediate **38** with sulfur[31] (Scheme 9).




Scheme 9

Triflic anhydride induced electrophilic cyclization of *N*-[(2-methylthio)ethyl]pyrrole **40** into sulfonium salt **41** was reported[32] (Scheme 10). The salt **41** was stable and was isolated in pure state and characterized completely. It was readily demethylated by action of triethylamine into pyrrolothiazole **42**. The overall yield of compound **42** based on the pyrrole **40** reached 63%.



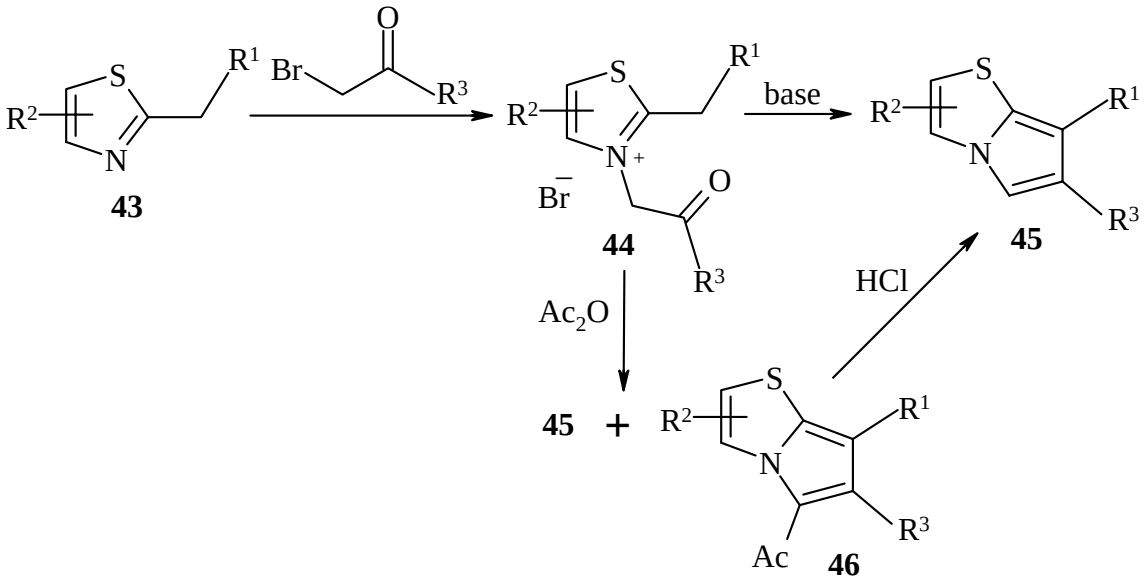

Scheme 10. Tf = $CF_3SO_2$

## 2.2. Pyrrole Ring Annulation to Thiazole Derivatives

### 2.2.1. Chichibabin reaction

Following analogy with the well-known indolizines synthesis from 2-picoline and phenacyl bromides the 2-alkylthiazoles **43** also react with α-bromo ketones yielding pyrrolothiazoles **45**[33-41] (Scheme 11). Both protocols with[33-36] and without[37-41] isolation of the intermediate salts **44** were described. Several bases

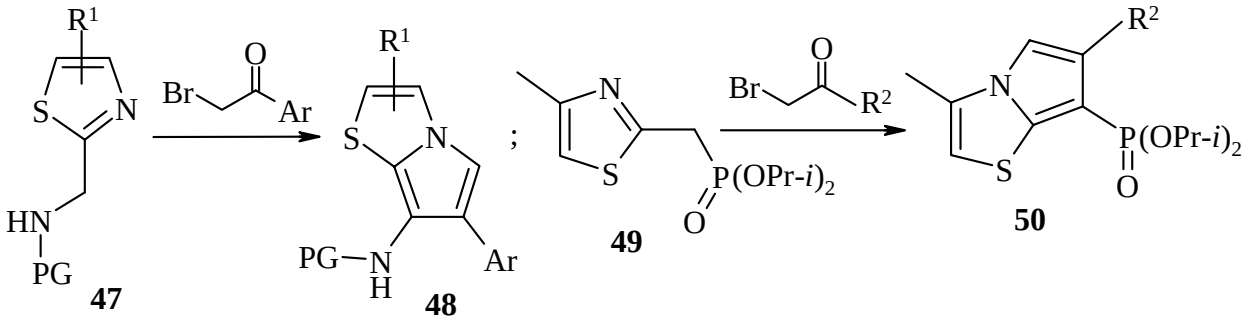
such as sodium hydroxide,[37] sodium carbonate[33-35] and triethylamine[36] were employed to achieve conversion of **44** into **45**. The thermal cyclization without a base was used as well.[38-41] The yields of derivatives **45** strongly depended on a substitution pattern and reaction conditions and generally were in the range of 40-80%.




Scheme 11. $R^1$, $R^2$ = H, Alkyl; $R^3$ = Me, subst. Ph.

Reid with co-workers proposed to perform cyclization of the salts **44** by heating in acetic anhydride. It resulted in the mixture of desired products **45** and their 5-acetyl derivatives **46**.[42,43] Nevertheless compounds **46** were found to undergo easily protodeacetylation with acids. So, treatment of the obtained mixture with hydrochloric acid afforded pure derivatives **45**. The method appeared to be the most universal.

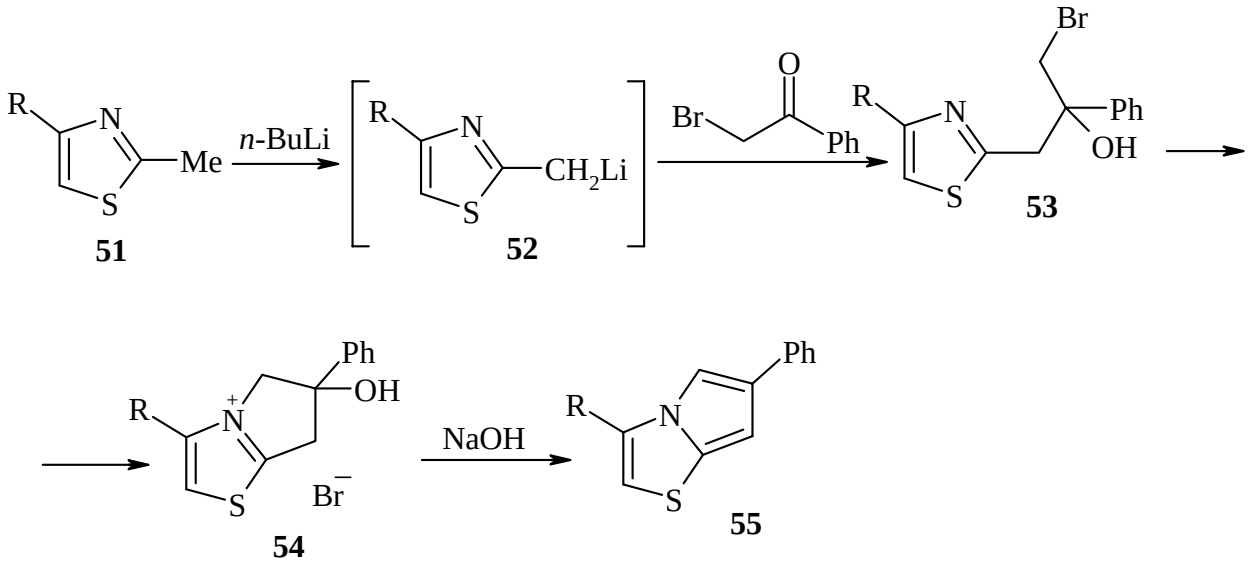
A wide variety of alkylthiazoles was applied in the Chichibabin pyrrolothiazoles synthesis, whereas the bromo ketone components, except a few cases,[38,43] were limited predominantly by substituted phenacyl bromides and bromoacetone. As for the thiazoles bearing additional functionalities the preparation of protected 7-amino derivatives **48**[44] and phosphonates **50**[45] can be mentioned (Scheme 12).




Scheme 12. $R^1$ = H, Me, Ph; PG = COPh, $SO_2Ph$; $R^2$ = Me, subst. Ph.

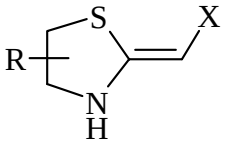
An interaction of the lithiated 2-methylthiazole **52** with bromoacetophenone at -55°C was found to give

compound **53**[46] (Scheme 13). Upon heating it was converted into the salt **54**, which treatment with alkali afforded pyrrolothiazole **55** identical with the sample obtained through the typical Chichibabin reaction. So this scheme can be considered as Chichibabin synthesis with inverted steps sequence.




Scheme 13. R = Me, 4-$ClC_6H_4$.

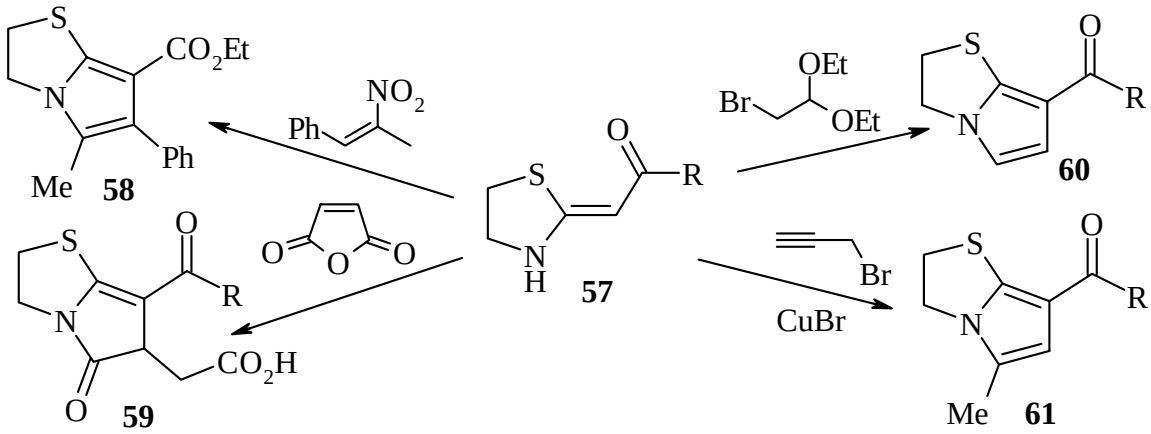
### 2.2.2. Reactions of 2-methylidenethiazolidines and related derivatives




**56**

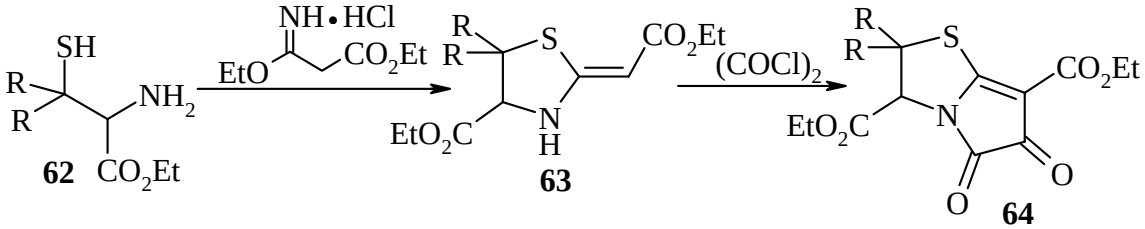
Figure 2

Thiazolidines of general structure **56** (Figure 2), where X is CN, $CO_2Et$, COR or related electron-withdrawing groups, were shown to be suitable precursors of pyrrolo[2,1-*b*]thiazoles. Reactions of derivatives **56** with various 1,2-bielectrophiles usually gave the target system in moderate or high yields. Thus, Michael addition of the enamine **57** (R = OEt) to (2-nitropropen-1-yl)benzene followed by nitrous acid elimination afforded compound **58** in 49% yield[47] (Scheme 14). Similar reaction with maleic anhydride led to the acids **59** in 80-90% yield.[48] Alkylation of compounds **57** with bromoacetaldehyde diethylacetal was found to give pyrrolothiazoles **60**.[49] Finally, interaction of derivatives **57** with 3-bromopropyne in the presence of CuBr allowed to obtain compounds **61** in 55-65% yields.[50] It is considered that derivatives **57** initially react with electrophiles at the enamine carbon atom and then a ring closure with participation of the nitrogen occurs. This assumption is confirmed by the structures of the products formed with unsymmetrical bielectrophiles.[47,48]



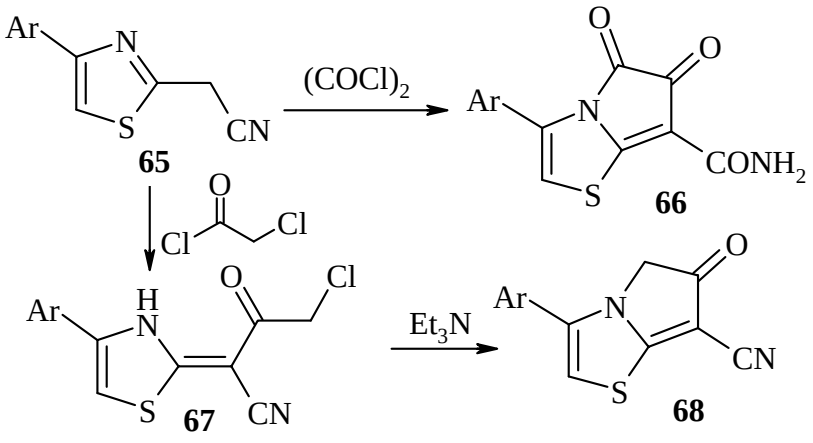
Scheme 14. R = OEt, Me, subst. Ph.

Thiazolidines **63** with additional functionality were prepared from a cysteine ester and its 3,3-dimethyl derivative **62** (Scheme 15). Acylation of compounds **63** with oxalyl chloride resulted in pyrrolothiazoles **64** in 45-55% yields.[51,52] Both enantiomers of **64** were obtained starting from *D*- and *L*-cysteine esters, respectively.



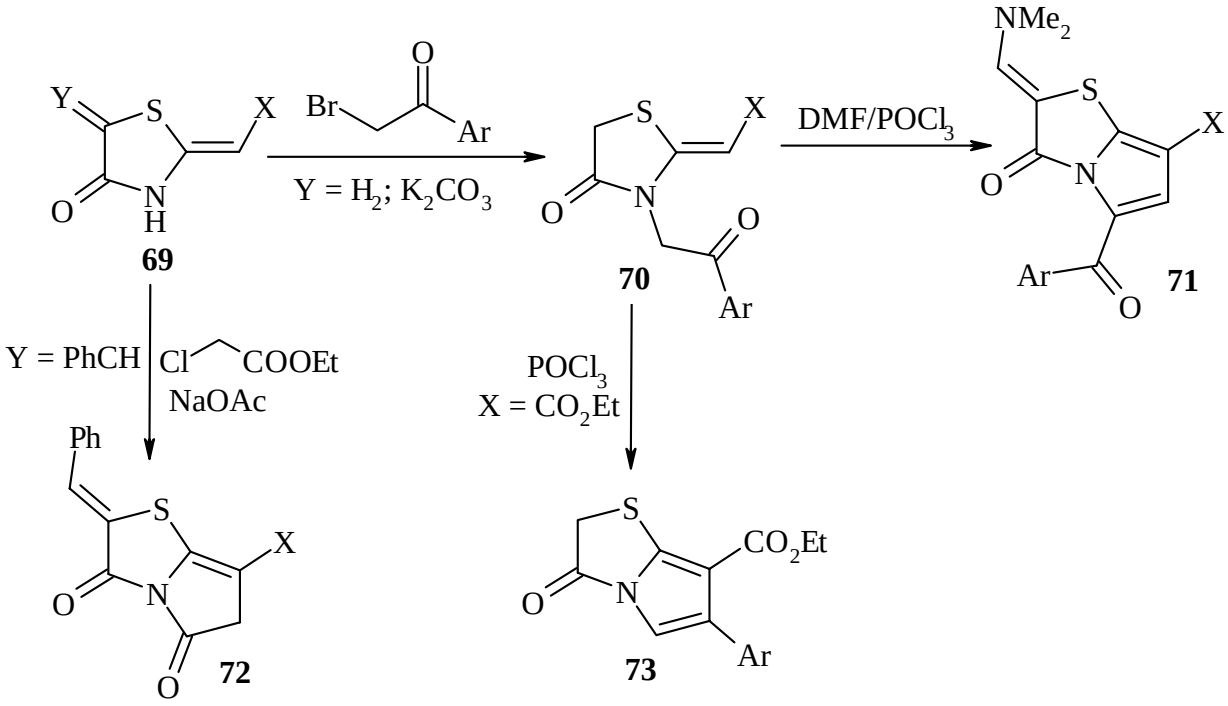
Scheme 15. R = H, Me.

A similar cyclization with oxalyl chloride was reported for thiazolylacetonitriles **65** (Scheme 16). In this case, the nitrile group hydrolysis into carboxamide one is followed leading to compounds **66**.[53] Furthermore, thiazoles **65** were shown to undergo acylation with chloroacetyl chloride at the active methylene. Treatment of the chloroacetyl derivatives **67** with triethylamine effected intramolecular alkylation yielding compounds **68**.[54]



Scheme 16. Ar = Ph, 4-$ClC_6H_4$, 4-$BrC_6H_4$.

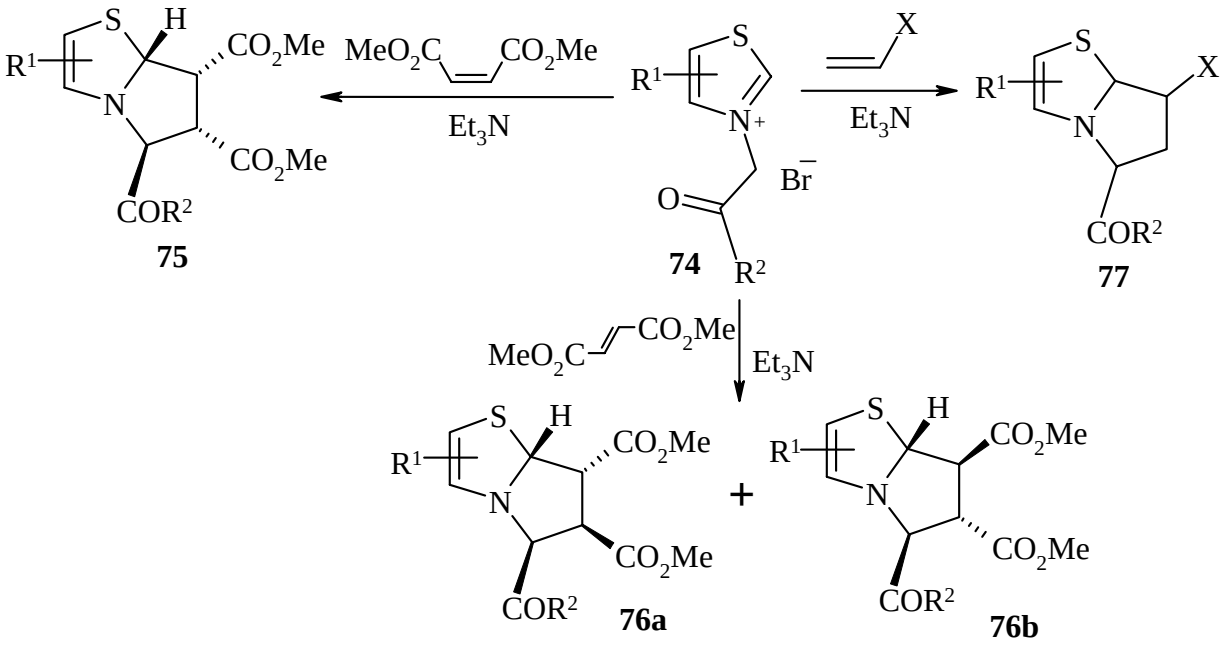
Contrary to thiazolidines **57,** in the case of corresponding 4-oxo derivatives **69** the direction of initial interaction with electrophiles depends on substitution pattern and reaction conditions. Thus alkylation of 5-arylidene derivative **69** (Y = PhCH, X = $CO_2Et$) with ethyl chloroacetate in the presence of NaOAc was reported to give compound **72**[55] formed, apparently, via initial C-alkylation (Scheme 17). At the same time alkylation of thiazolidinones **69** (Y = $H_2$) unsubstituted at position 5 with phenacyl bromides in the presence of $K_2CO_3$ was found to proceed selectively at the nitrogen atom leading to derivatives **70**. The latter upon refluxing in $POCl_3$ afforded pyrrolothiazoles **73**.[56] Vilsmeyer-Haack formylation of compounds **70** resulted in derivatives **71** formed at the expense of one-carbon unit introduction into position 6 of the system.[57-59]




Scheme 17. X = $CO_2Et$, CN, $SO_2Ar$, 2-benzothiazolyl.

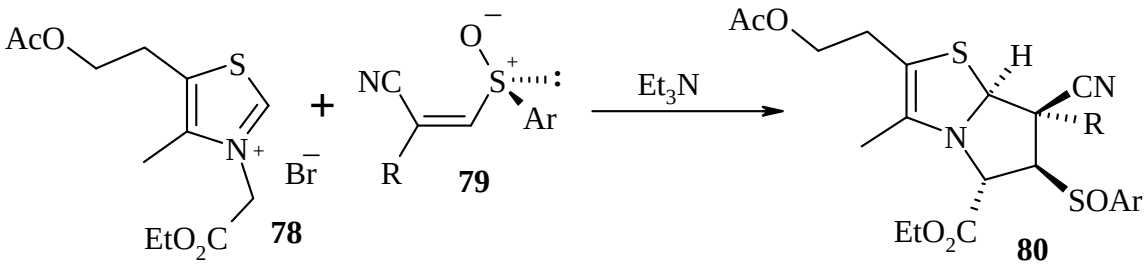
### 2.2.3. Cycloaddition reactions of thiazolium ylides

Thiazolium ylides readily generated from the salts **74** by action of bases were shown to react with typical dienophiles like maleic ester yielding pyrrolothiazoles **75** (Scheme 18). The process occurred stereoselectively as *cis*-addition leading to compounds of structure **75** in the case of maleic ester or to the 1:1 mixture of stereoisomers **76a** and **76b** for fumaric ester.[60,61] Unsymmetrical alkenes afforded 7-substituted adducts **77**.[62,63] Except a few cases[62] the stereochemistry of derivatives **77** was not determined. The most popular base used for generation of thiazolium ylides was triethylamine,[60,61,63] but sodium methoxide[62] and DBU[64] were also employed.



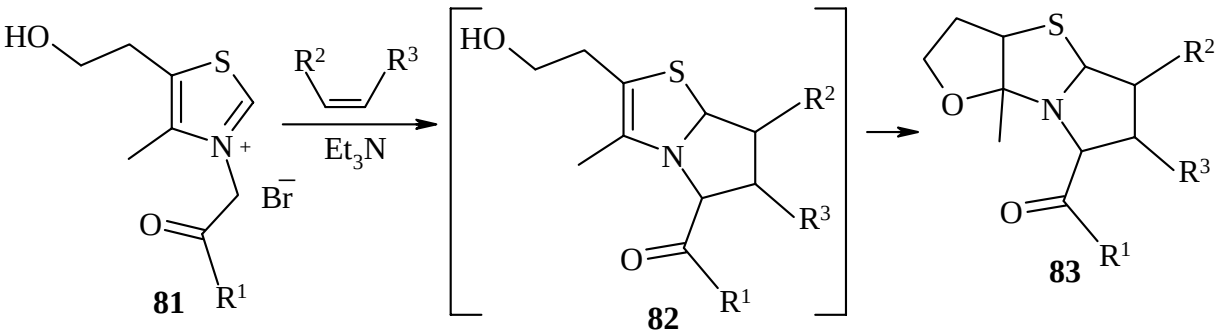
Scheme 18. $R^1$ = H, Alkyl; $R^2$ = Me, OMe, Ar; X = CN, $CO_2Et$, COR.

An interesting example of cycloaddition reaction with alkenes **79** bearing chiral sulfoxide substituent was described[64] (Scheme 19). It was found to proceed with high regio- and stereoselectivity yielding enantiopure derivatives **80**.



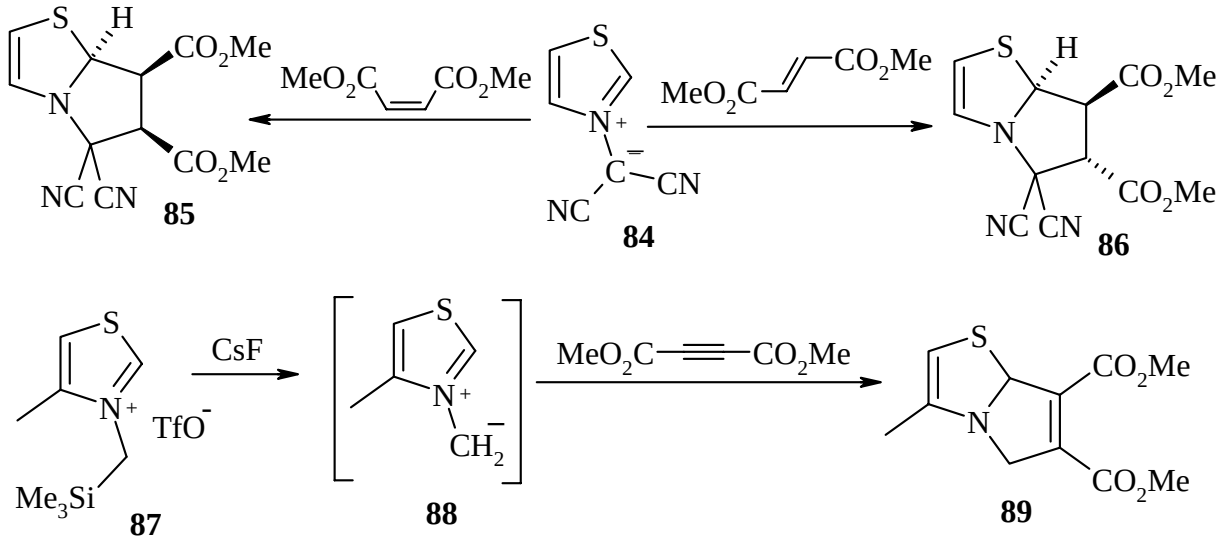
Scheme 19. R = H, *n*-Bu; Ar = 4-$CH_3C_6H_4$.

Cycloaddition of compounds **81** with tethered hydroxy group was shown not to stop at the corresponding adducts **82** (Scheme 20). Instead the more complex system **83** was obtained at the expense of intramolecular addition of hydroxy group to the double bond.[65,66]



Scheme 20. $R^1$ = Me, OEt; $R^2$ = $R^3$ = $CO_2Me$; $R^2$ = CN, $CO_2Et$ when $R^3$ = H.

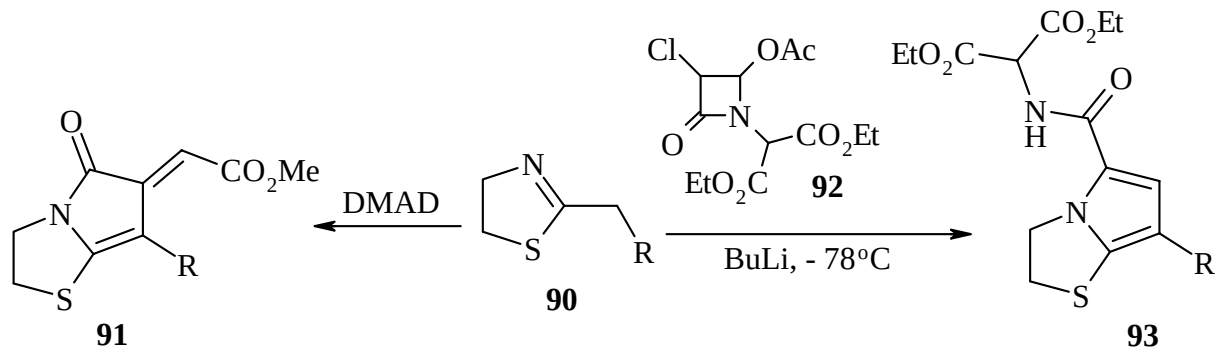
Several unusual thiazolium ylides were reported (Scheme 21). Thus, the very stable ylide **84** nevertheless reacted with maleic and fumaric esters resulting in compounds **85** and **86** respectively.[67] Unsubstituted at the negatively charged carbon ylide **88** was produced from the salt **87** by means of fluoride-induced silyl group scission. It was trapped with dimethyl acetylenedicarboxylate to give derivative **89**.[68]




Scheme 21. Tf = $CF_3SO_2$

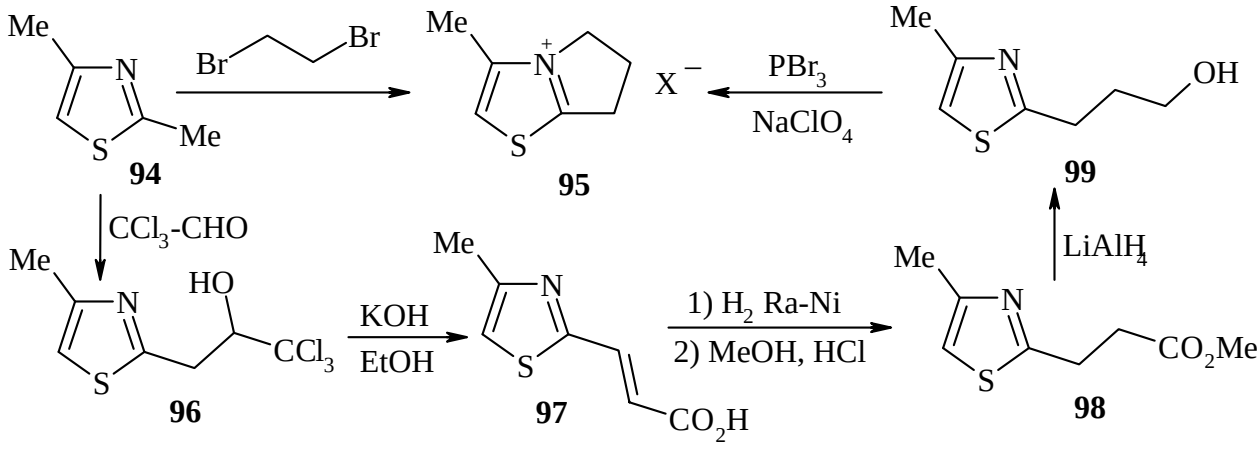
### 2.2.4. Miscellaneous

2-Alkyl-4,5-dihydrothiazoles **90** were reported to react with dimethyl acetylenedicarboxylate (DMAD) yielding pyrrolothiazoles **91**[69] (Scheme 22). In turn, the lithiated derivatives of **90** were shown to give compounds **93** upon treatment with azetidines **92**.[70]



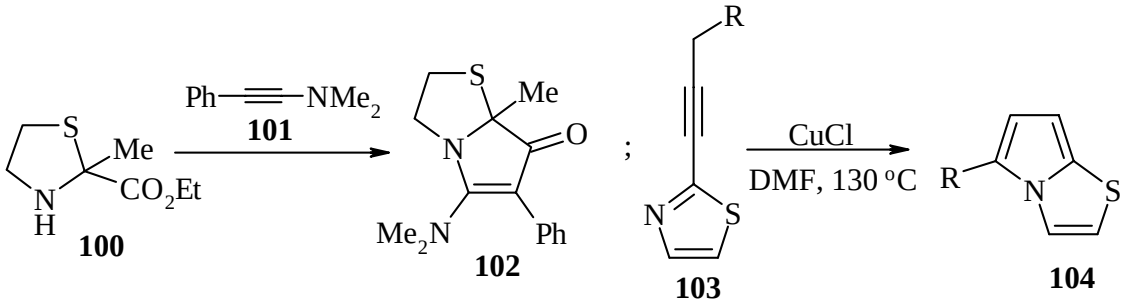

Scheme 22. R = H, Me.

Alkylation of the thiazole **94** with dibromoethane afforded pyrrolothiazolium salt **95** (X = Br).[71] Alternatively, perchlorate of the same cation **95** (X = $ClO_4$) was obtained from the alcohol **99** by *in situ* generation of the corresponding bromide and further intramolecular alkylation.[10] The alcohol precursor **99** was prepared starting from the thiazole **94** through a four-step sequence outlined in the Scheme 23.



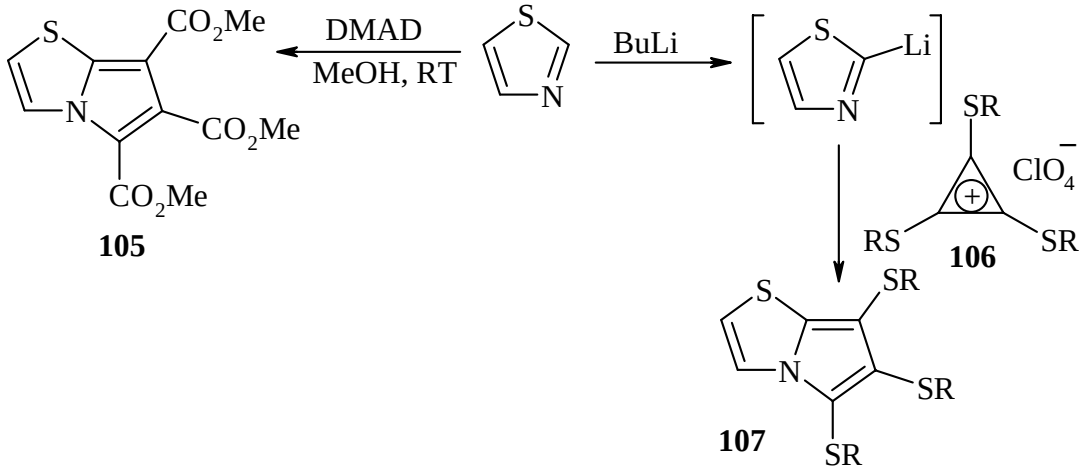

Scheme 23. X = Br, $ClO_4$.

Condensation of thiazolidinecarboxylic ester **100** with ynamine **101** resulted in pyrrolothiazole derivative **102** in 58 % yield[72] (Scheme 24). A CuCl mediated ring closure of 2-ethynylthiazoles **103** readily available via Sonogashira protocol was found to give compounds **104** in at about 60 % yields.[73]



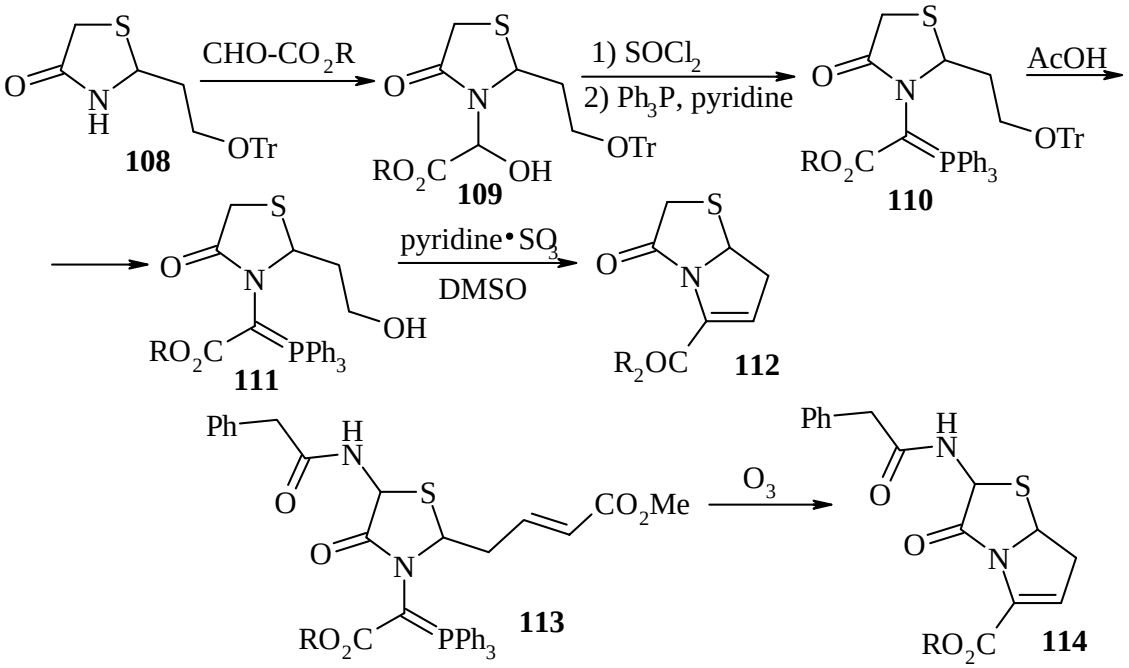

Scheme 24. R = alkyl.

Keeping the thiazole with excess of DMAD in methanol at room temperature afforded a complex mixture of products where compound **105** was isolated from in a poor yield[74] (Scheme 25). An interesting reaction of 2-lithiothiazole with the relatively stable cyclopropenium perchlorate **106** was shown to lead to pyrrolothiazole derivative **107** in 71 % yield.[75]



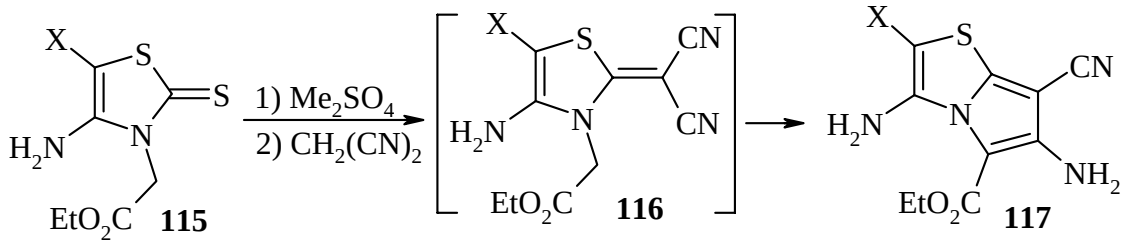

Scheme 25. R = *i*-Pr.

An intramolecular Wittig reaction based approach to pyrrolo[2,1-*b*]thiazole-5-carboxylic acids **112, 114** was developed (Scheme 26). Thus compound **108** was converted into phosphorane **110** in three steps. Deprotection of the hydroxy group and further oxidative generation of aldehyde resulted in derivative **112**.[76] The same authors prepared corresponding 2-amino derivatives **114** through the similar pathway. However in this case the carbonyl moiety was produced by ozonolysis of alkene.[76] Noteworthy, the present method should be compared with the above mentioned synthesis (Scheme 4, section 2.1.2.) also utilizing the Wittig reaction. Although in the both approaches the phosphorane moiety was introduced in the same manner, it served for different rings formation, namely thiazoles or pyrroles.



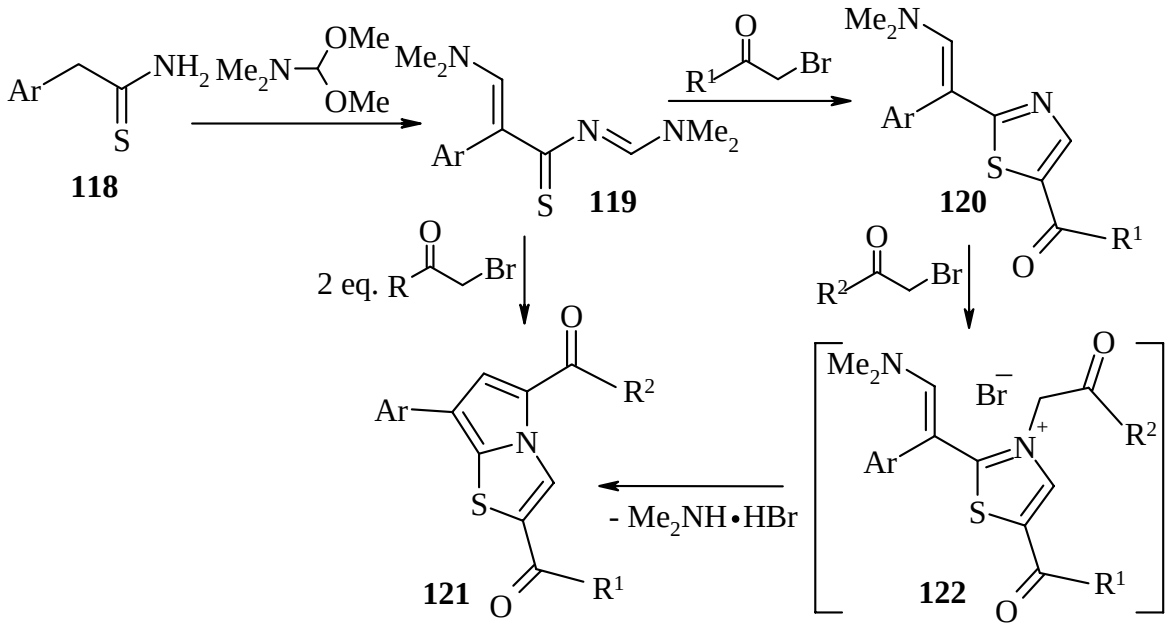

Scheme 26. Tr = $Ph_3C$; R = 4-$MeOC_6H_4CH_2$.

Methylation of the thiazoles **115** at the exocyclic sulfur atom and further substitution of the formed methylthio group with malonodinitrile afforded intermediates **116** (Scheme 27). The latter underwent spontaneous intramolecular Thorpe addition of the methylene to the nitrile group thus leading to pyrrolothiazoles **117** in 50-65 % yields.[77] Notably, when the Thorpe reaction was employed for thiazole ring formation (see Scheme 7, section 2.1.3.), the appropriate precursor **31** was isolated and the strongly basic conditions were required for cyclization.




Scheme 27. X = CN, $CO_2Et$.

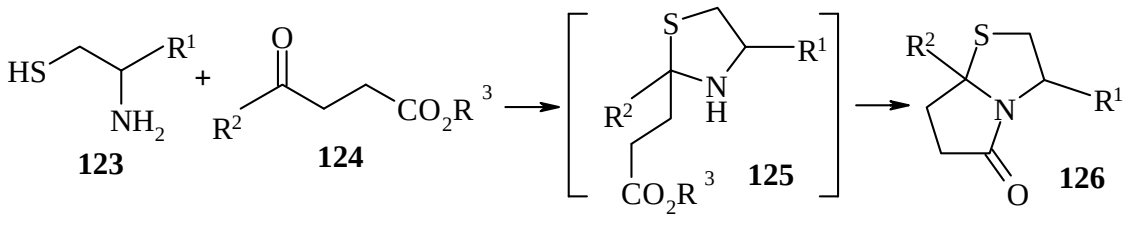
Finally, a graceful method of pyrrolothiazole framework construction by introduction of a one-carbon unit into position 5 was described by Liebsher (Scheme 28). Thus, alkylation of thiazoles **120**, prepared in two steps from arylacetic acids thioamides **118**, with α-bromo ketones yielded compounds **121** through the intermediate salts **122**.[78] Furthermore pyrrolothiazoles **121** with $R^1$=$R^2$ could be obtained directly from the appropriate precursors **119** using two equivalents of the bromo ketone.




Scheme 28

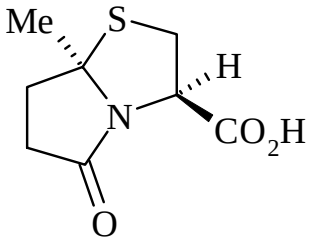
## 2.3. Formation of the Both Rings at Once. Reaction of 2-Aminoethanethiol Derivatives with 4-Oxo Carboxylic Acids

One of the simplest and very popular approaches to pyrrolo[2,1-*b*]thiazole core includes interaction of mercapto amines **123** with 4-oxo acids or their esters **124** (Scheme 29). A wide variety of different derivatives **124** was successfully used in this reaction,[79-90] whereas the second component usually was represented by cysteamine **123** ($R^1$ = H),[79-84] cysteine or its esters **123** ($R^1$ = $CO_2H$, $CO_2Me$),[83-88] and 3-mercaptovaline.[88-90] Isotopically labeled cysteine was also employed.[88] As a rule the target compounds **126** were obtained directly after heating of the reagents, but sometimes the intermediates of type **125** could be isolated and then cyclized.[87] The yields of pyrrolothiazoles **126** depended on reaction conditions and substitution pattern and were in the range 20-100 %.



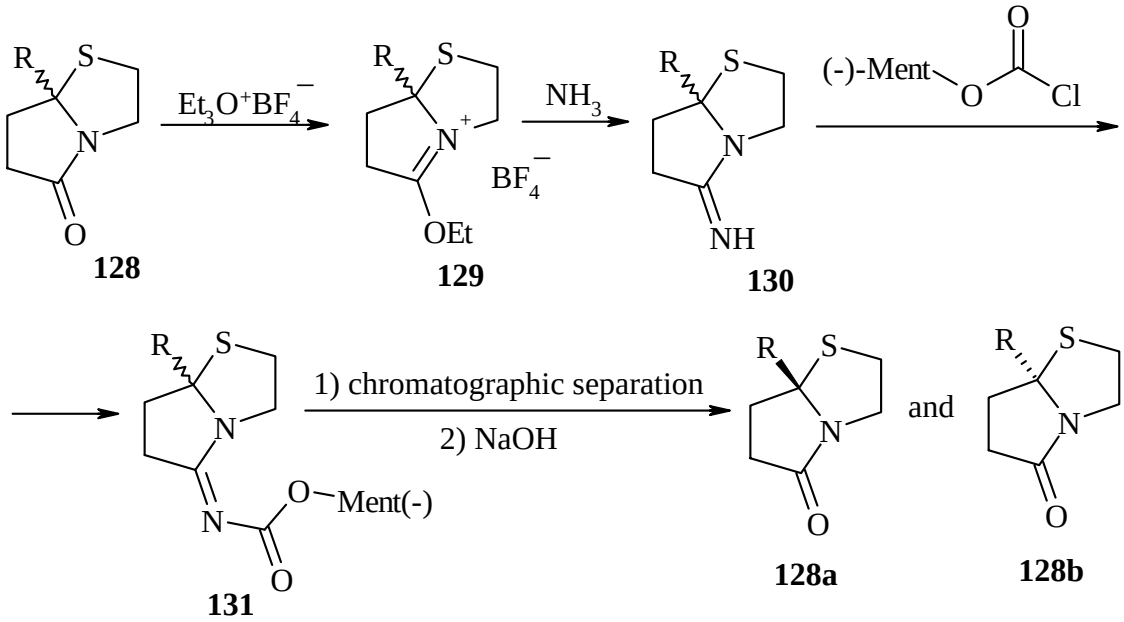

Scheme 29. $R^1$ = H, $CO_2H$, $CO_2Me$; $R^2$ = H, Me, Ar; $R^3$ = H, Me.

In the case of chiral cysteine and 3-mercaptovaline a diastereoselectivity was observed and stereochemistry of the products **126** was driven by the structure of the starting material **123**. For example, *L*-cysteine and levulinic acid afforded derivative **127** as the major stereoisomer[85] (Figure 3). At the same time for the cysteamine racemic compounds **128** were obtained. Since pharmaceutical needs required optically pure materials the separation method was elaborated[81] (Scheme 30). Thus, derivatives **128** were converted into amidines **130** via Meyerwein's reaction. The latter were acylated with (-)-menthyloxycarbonyl chloride to give compounds **131**. Chromatographic separation of diastereomers of **131** followed by amidine moiety cleavage allowed to obtain optically pure isomers **128a** and **128b**.[81] (+)-Camphor-10-sulfonyl chloride also can be used instead of the menthol derivative.[81]




**127**

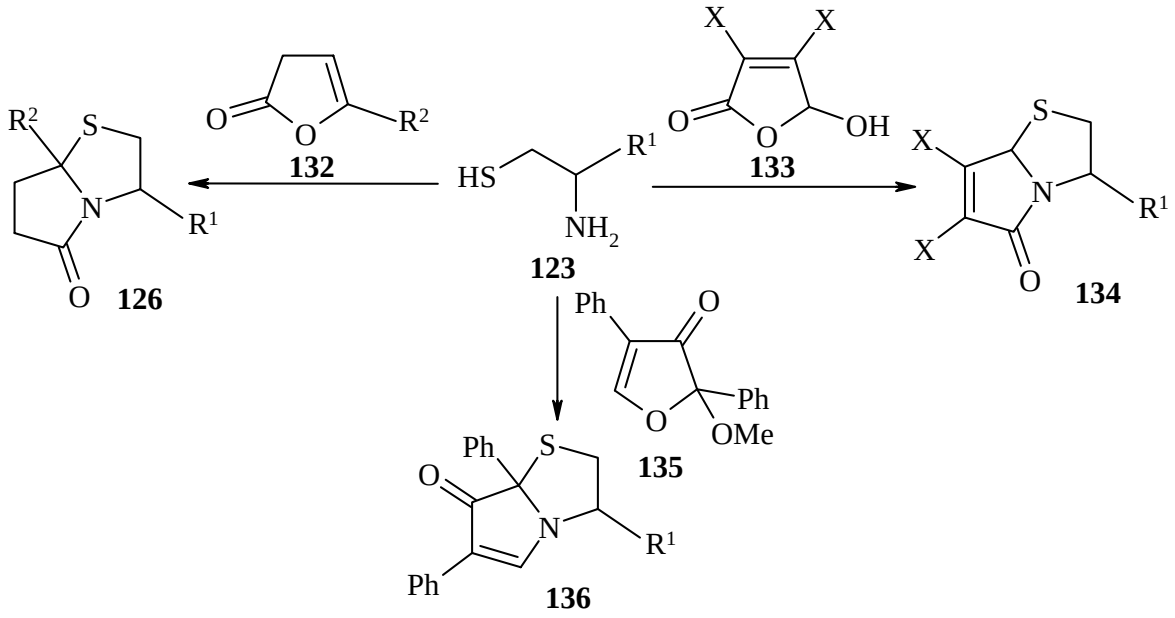
Figure 3




**128** **129** **130** **131** **128a** **128b**

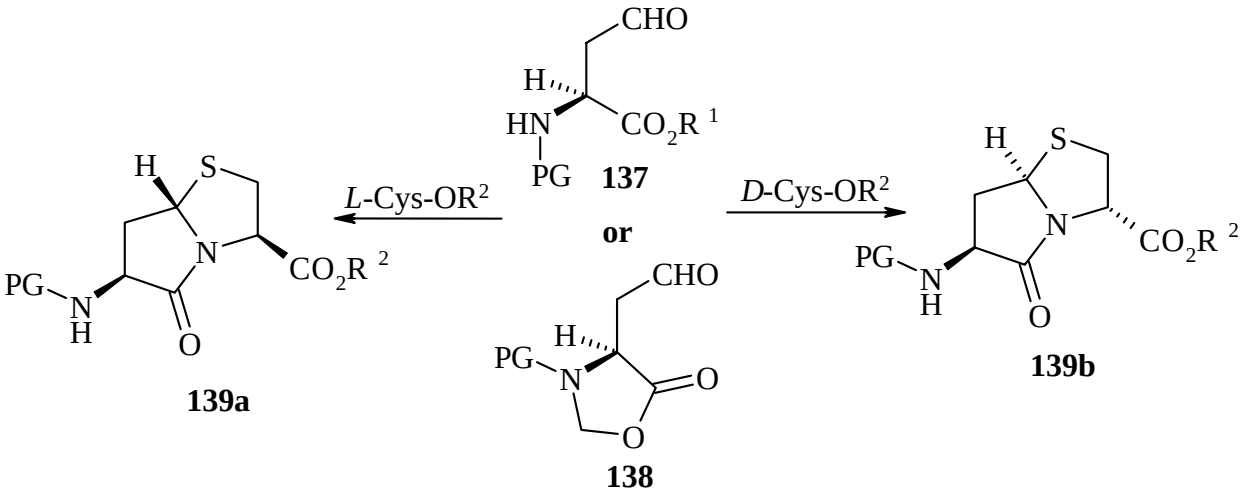
Scheme 30. Ment = menthyl.

Certain masked oxo acids were found to react similarly with cysteine and cysteamine (Scheme 31). Thus, lactones **132** yielded compounds **126** identical with those obtained from the appropriate acids **124**.[86,91] Mucochloric and mucobromic acids **133** afforded corresponding pyrrolothiazoles **134**.[92,93] Finally, reaction with masked oxo aldehyde **135** resulted in derivative **136**.[94]



Scheme 31. $R^1$ = H, $CO_2H$, $CO_2Me$; $R^2$ = H, Me, Ar; X = Cl, Br.

Cysteine derived pyrrolothiazoles **139** bearing amino group at position 6 are of especial interest for peptidomimetics chemistry because this scaffold imitates a β-turn in *Leu-Gly* moiety. The simplest amino substituted oxo esters **137** and **138**, both available from *L*-aspartic acid, were shown to react with *L*- and *D*-cysteine derivatives with high stereoselectivity yielding compounds **139a** and **139b**, respectively[23,95-98] (Scheme 32). Analogous oxo esters produced from *D*-aspartic acid behaved similarly thus providing access to corresponding epimers of **139a,b** at position 6.[99] Deprotection of either amino or carboxyl group of **139** followed by introduction of a suitable amino acid residue at the appropriate side leads to peptidomimetics. For instance, compound **140** (Figure 4) prepared in four steps from the corresponding derivative **139** mimics the natural peptide *Pro-Leu-Gly-NH₂* and exhibits 5 times more potent biological activity.[99] The solid phase supported approach to this type peptidomimetics was also developed.[102,136]



Scheme 32. $R^1$ = Me, $PhCH_2$; $R^2$ = H, Me; PG = Boc, $CO_2CH_2Ph$.

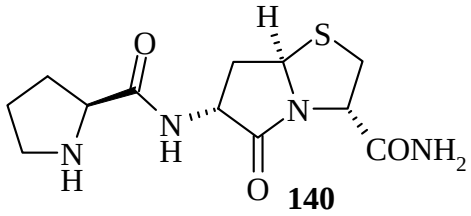
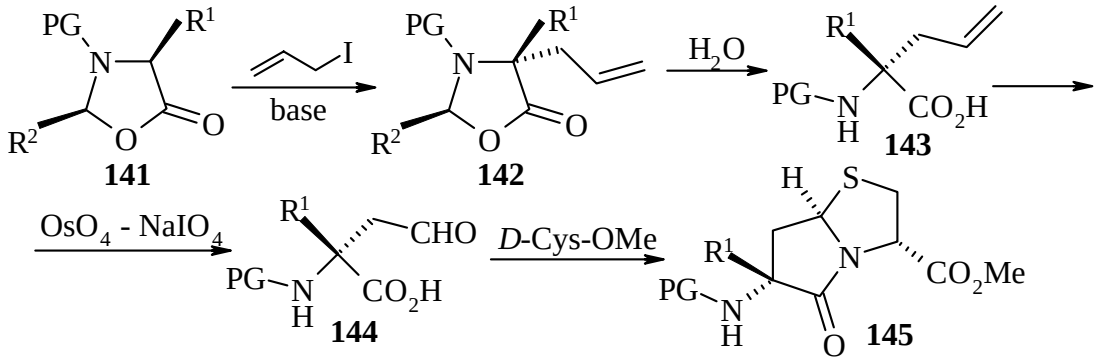


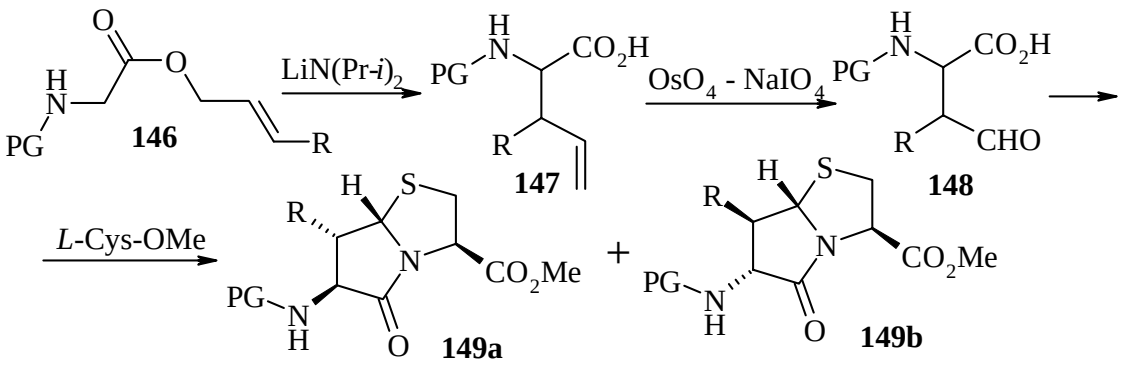

Figure 4

Recently significant efforts have been made to bring in different substituents into position 2 of the oxo esters **137**. It is aimed to obtain derivatives of type **139** either mimicking other aminoacids sequences or imitating *Leu-Gly* moiety more precisely. For this purpose oxazolidinones **141** available from the appropriate amino acids were alkylated with allyl iodide yielding derivatives **142** with retention of configuration (Scheme 33). Cleavage of oxazolidine and further oxidation of alkene by means of $OsO_4$-$NaIO_4$ system afforded the target aldehydes **144**. The latter were transformed into pyrrolothiazoles **145** suitable for mimicking *Phe-Gly*, *Leu-Gly* and *Nle(norleucine)-Gly* fragments, dependently on the $R^1$ nature.[100,101]

Alternatively, the 3-substituted racemic oxo acids **148** were prepared via Claisen rearrangement of glycine esters **146** followed by oxidation of the formed alkenes **147** (Scheme 34). Treatment of compounds **148** with *L*-cysteine methyl ester resulted in the separable mixture of stereoisomers **149a** and **149b**, which also mimicked properly *Phe-Gly* and *Nle-Gly* sequences.[103,104]

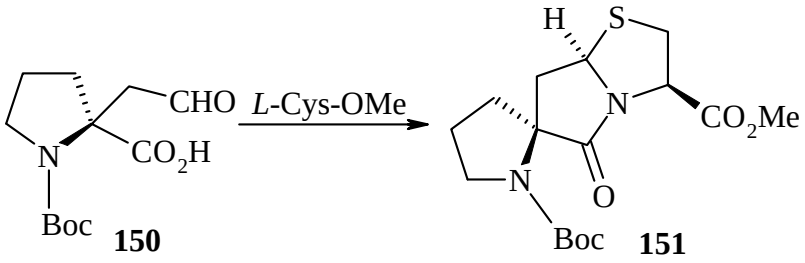



Scheme 33. $R^1$ = $PhCH_2$, *i*-Bu, *n*-Bu; $R^2$ = *t*-Bu; PG = Boc, $CO_2CH_2Ph$, Fmoc.



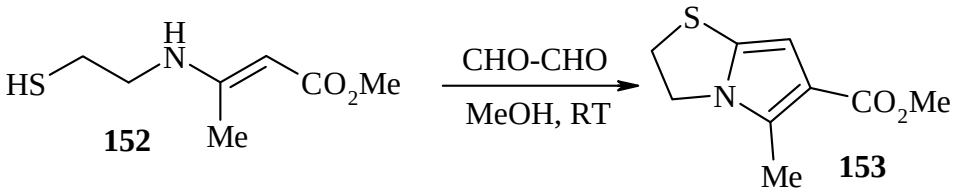

Scheme 34. R = Ph, *n*-Pr; PG = Boc, $CO_2CH_2Ph$

Spirocyclic pyrrolothiazole **151** was synthesized as the more rigid core for peptidomimetics starting from *L*-proline derived oxo acid **150** (Scheme 35).[105]




Scheme 35

Finishing the section a singular case of pyrrolothiazole preparation by formation of both rings at once, but utilizing another strategy should be mentioned (Scheme 36). Thus, the enamine **152** was reported to react with glyoxal affording derivative **153** in 8 % yield.[106]

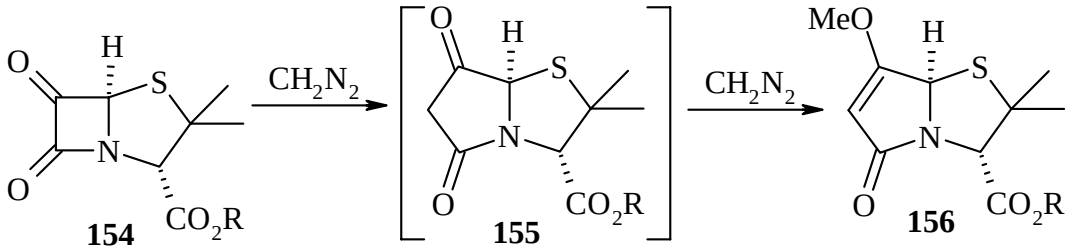



Scheme 36

## 2.4. Synthesis of Pyrrolo[2,1-*b*]thiazoles from Other Heterocyclic Systems

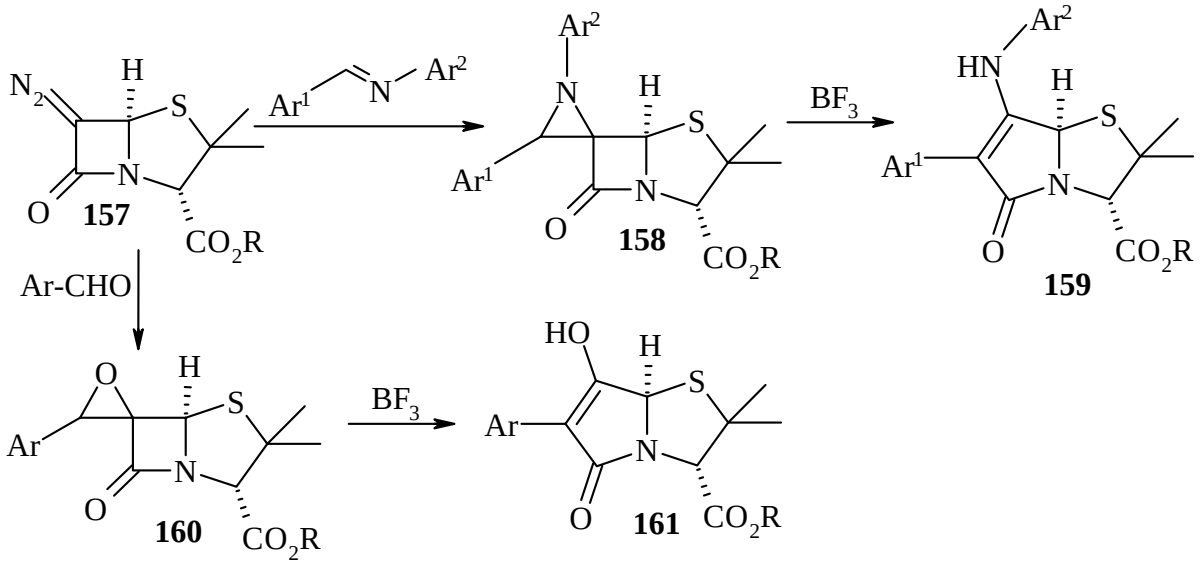
### 2.4.1. Ring expansion of penicillin derivatives

Carbene insertion into benzyl 6-oxopenicillanate **154** was found to give intermediate **155**, which immediately underwent *O*-alkylation with excess of diazomethane yielding pyrrolothiazole derivative **156** (Scheme 37).[107,108]



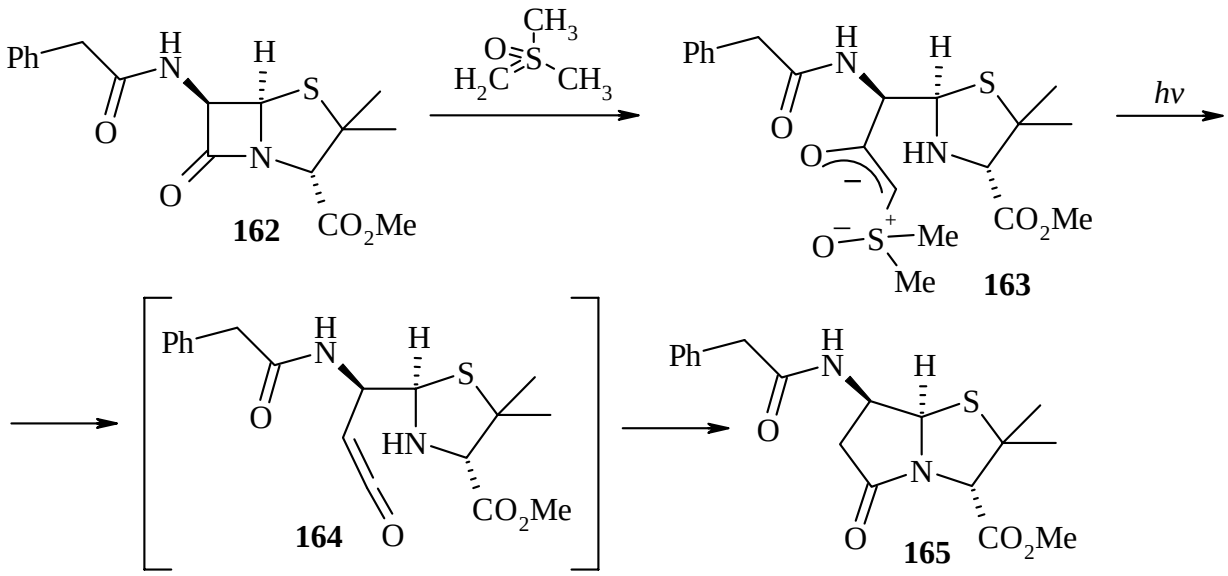

Scheme 37. R = $CH_2Ph$.

6-Diazopenicillin derivative **157** was shown to react with Schiff bases with formation of spiroaziridines **158** (Scheme 38). Boron trifluoride induced rearrangement of compounds **158** afforded pyrrolothiazoles **159**.[109] Similar reaction with aldehydes allowed to obtain pyrrolothiazoles **161** via intermediacy of oxiranes **160**. Noteworthy, the structures of both aziridines **158** and pyrrolothiazoles **159,161** were confirmed unambiguously by X-ray crystallographic study.[109]



Scheme 38. R = $CH_2CCl_3$.

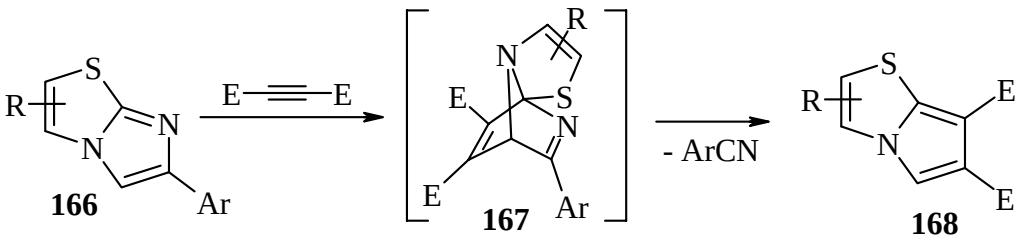
Reaction of penicillin derivative **162** with dimethylsulfoxonium methylide resulted in the stable ylide **163** isolated in 90 % yield (Scheme 39). Photochemically induced elimination of DMSO followed by Wolf rearrangement of the formed carbene afforded ketene intermediate **164**, which underwent ring closure to give pyrrolothiazole **165** in 47 % yield.[110]



Scheme 39

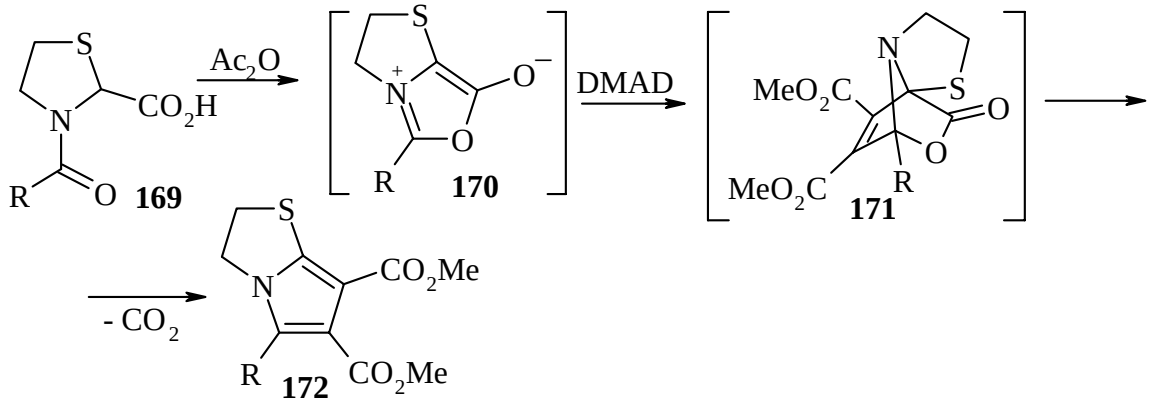
### 2.4.2. Cycloaddition – elimination reactions

Refluxing of imidazo[2,1-*b*]thiazoles **166** with acetylenic dienophiles in toluene or xylene was reported to give pyrrolothiazoles **168** in 50-70 % yields[111-113] (Scheme 40). The reaction was assumed to occur through initial [2+4]cycloaddition and further elimination of benzonitrile derivatives from the intermediate adduct **167**.



Scheme 40. R = H, Me; E = $CO_2Me$, $CO_2Et$, COPh.

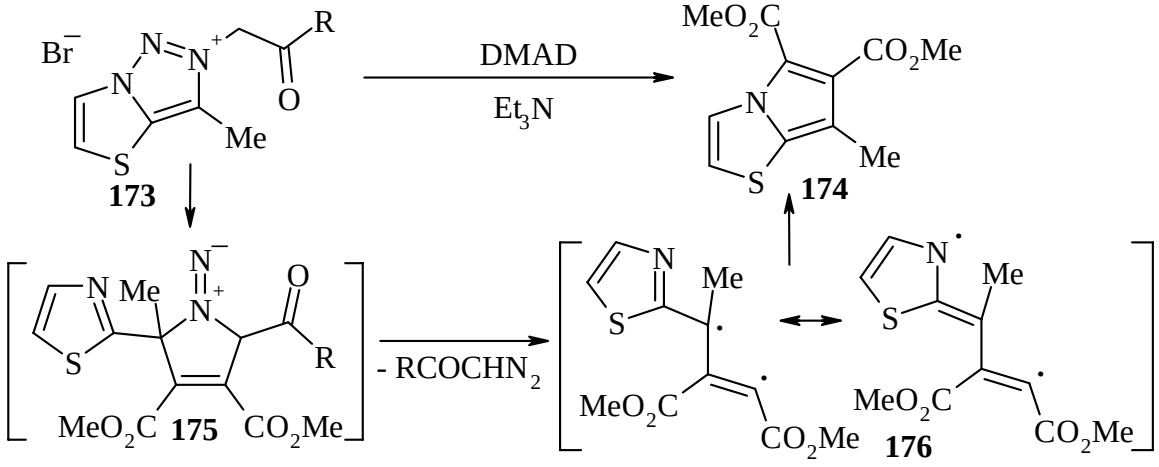
Betaines **170** were produced by heating of compounds **169** in acetic anhydride (Scheme 41). They were trapped with DMAD resulting in pyrrolothiazoles **172** formed, apparently, after elimination of $CO_2$ from the initial adducts **171**.[114,115]



Scheme 41. R = Ph, 4-$FC_6H_4$, 4-$ClC_6H_4$, 3,4-$Cl_2C_6H_3$.

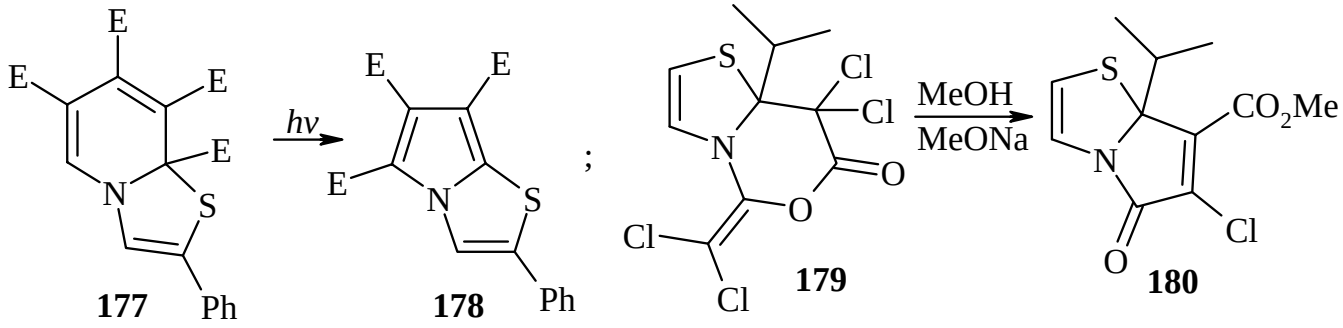
### 2.4.3. Miscellaneous

Treatment of thiazolo[3,2-*c*][1,2,3]triazolium salts **173** with DMAD in the presence of triethylamine was found to give compound **174** in 15-20 % yield[116,117] (Scheme 42). Authors suggested a pathway including the biradical intermediate **176** formed at the expense of diazo ketone extrusion from the initial adduct **175**.[116]



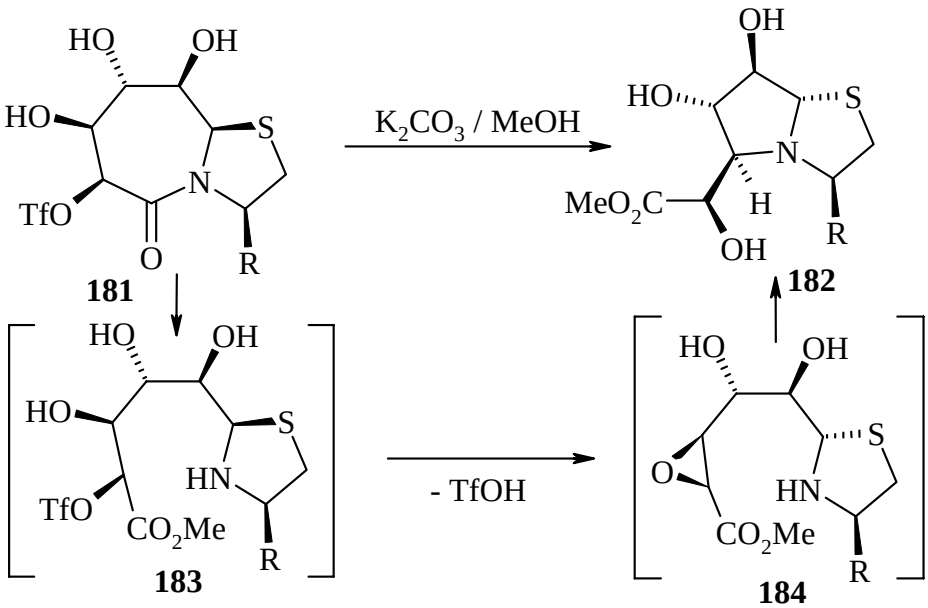
Scheme 42. R = Ph, OMe.

Photochemical transformation of thiazolo[3,2-*a*]pyridine **177** into pyrrolothiazole **178** was reported[118] (Scheme 43). Furthermore conversion of thiazolo[3,2-*c*][1,3]oxazine **179** into derivative **180** upon treatment with sodium methoxide was described as well.[119]




Scheme 43. E = $CO_2Me$.

Highly stereoselective transformation of thiazolo[3,2-*a*]azepines **181** into compounds **182**, accompanied with inversion of configuration at 7a-C of the products, was observed[120] (Scheme 44). The reaction was assumed to proceed via initial methanolysis of the amide bond leading to the intermediates **183**, further formation of epoxides **184** and, finally, intramolecular alkylation of the nitrogen. Inversion of configuration at 2-C of thiazolidine could occur at the expense of ring-chain tautomerism of thiazolidine moiety both in intermediates **183** and **184**.




Scheme 44. R = H, $CO_2Me$, $CO_2Et$; Tf = $SO_2CF_3$.

## 3. PROPERTIES OF PYRROLO[2,1-*b*]THIAZOLES

### 3.1. Electrophilic Substitution

#### 3.1.1. Protonation and deuterium exchange

Simple alkyl substituted pyrrolo[2,1-*b*]thiazoles were found to give stable crystalline salts with perchloric acid.[121] Their $^{1}H$ and $^{13}C$ NMR study revealed them to be 5-protonated derivatives **185** (Figure 5). However, upon keeping in $CF_3CO_2D$ pyrrolothiazoles underwent deuterium exchange both at positions 5 and 7.[121] Therefore, the 7-protonated adducts of type **186** were also present in the equilibrium, but in the concentrations lower than NMR sensitivity level. Kinetic measurements were performed for deuteriation of 6-methylpyrrolo[2,1-*b*]thiazole and the rate constants were determined as $6.1\times10^{-3}$ and $4.3\times10^{-6}$ for substitution at positions 5 and 7, respectively.[122] So, according to these data electrophilic substitution in pyrrolo[2,1-*b*]thiazoles should proceed at position 5 and could occur at position 7, if position 5 is occupied.

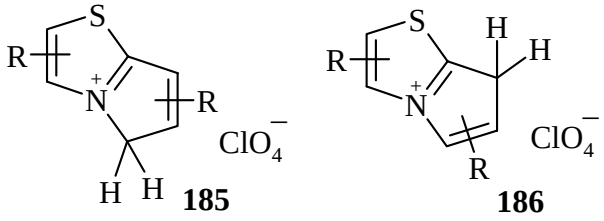
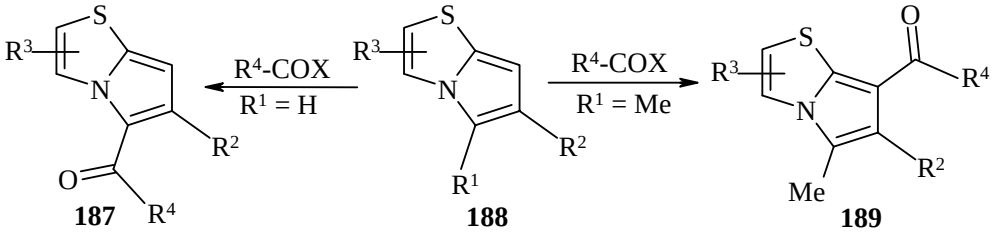



Figure 5. R = H, Me.

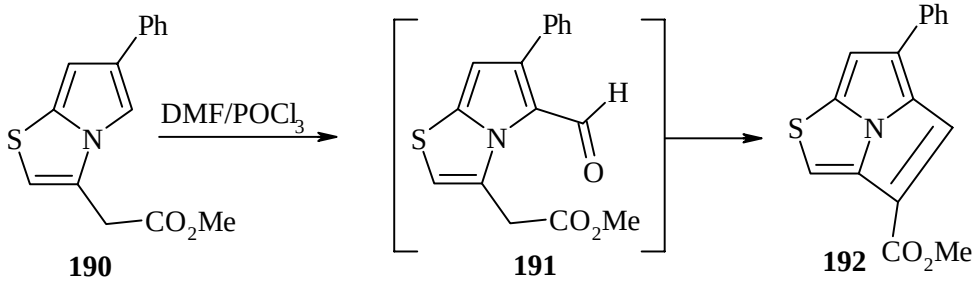
### 3.1.2. Reactions with carbon electrophiles

Acylation of pyrrolothiazoles **188** with acid chlorides or anhydrides was shown to occur at position 5 to give derivatives **187** in 20-100 % yields[37,123] (Scheme 45). When position 5 was occupied by methyl group the 7-acyl derivatives **189** were obtained.[123]



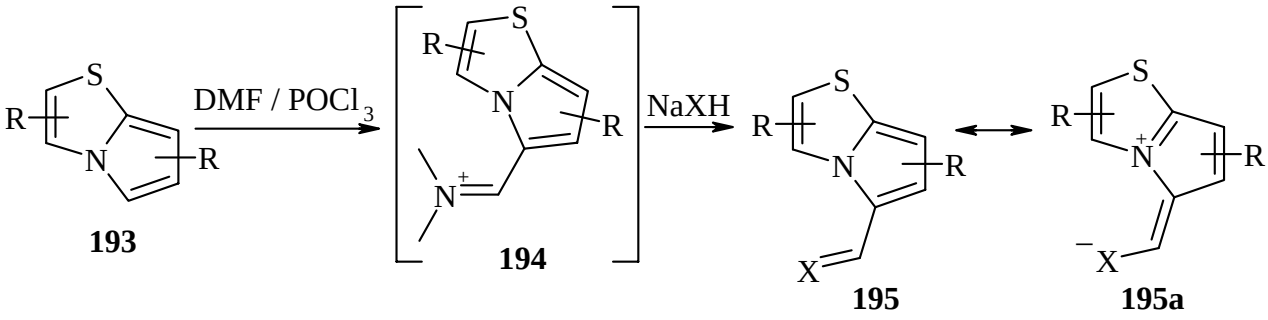

Scheme 45. $R^1$ = H, Me; $R^2$ and $R^3$ = H, Me, subst. Ph; X = Cl, O(CO)$R^4$; $R^4$ = Me, $CF_3$, Ph.

Vilsmeyer-Haack formylation of compounds **188** occurred similarly affording appropriate aldehydes **187** or **189** ($R^4$ = H).[35,46] Noteworthy, formylation of the suitably substituted pyrrolothiazole **190** resulted in the tricyclic system **192** formed via intermediate aldehyde **191**[40,41] (Scheme 46).



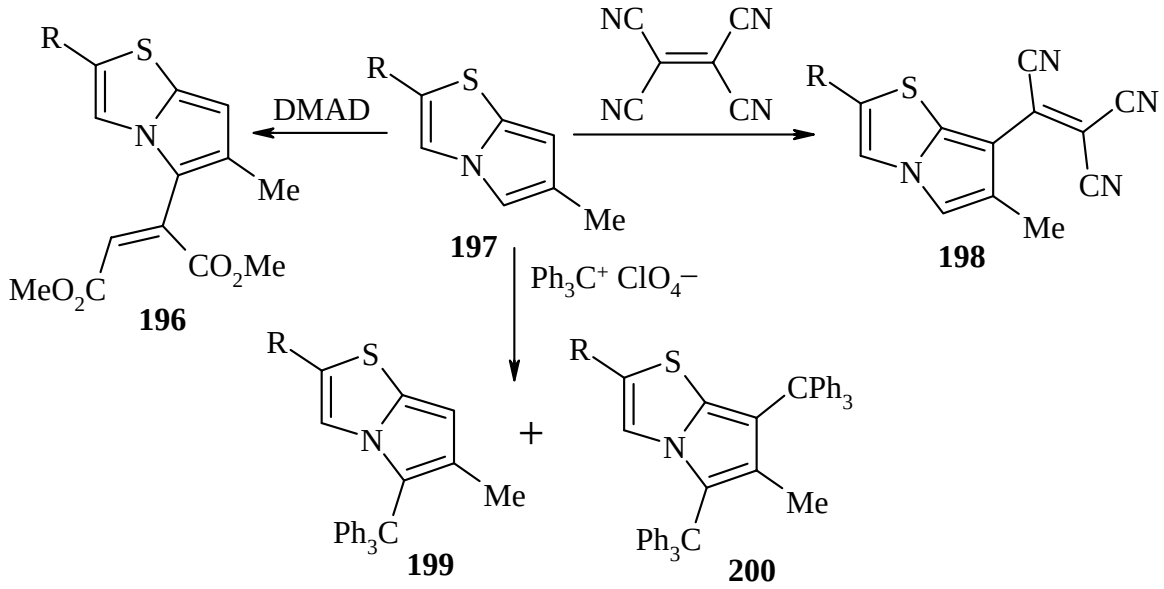

Scheme 46

Treatment of initial Vilsmeyer adducts **194** with NaSH or NaSeH instead of usual hydrolysis allowed to obtain thio- and selenoformyl derivatives **195**[42,124,125] (Scheme 47). As a rule thioaldehydes are very reactive and inclined to polymerization, but in the present case compounds **195** appeared to be stable. Their X-Ray crystallographic study exhibited significant contribution from the canonic structure **195a**, thus explaining the unusual stability.[126-128] Appropriate 7-thio- and selenoformyl derivatives were prepared similarly starting from the 5-methyl substituted pyrrolothiazoles.[42,125]




Scheme 47. R = H, $CH_3$; X = S, Se.

As for other carbon electrophiles addition of compounds **197** to DMAD was reported to give derivatives **196**[129] (Scheme 48). Unexpectedly reaction with tetracyanoethene appeared to proceed at position 7 yielding compounds **198**.[129] Satisfactory explanation of this fact was not offered. Finally, alkylation of pyrrolothiazoles **197** with trityl cation was shown to result in the mixture of mono- and disubstituted products **199** and **200** in almost 1:1 ratio.[123]

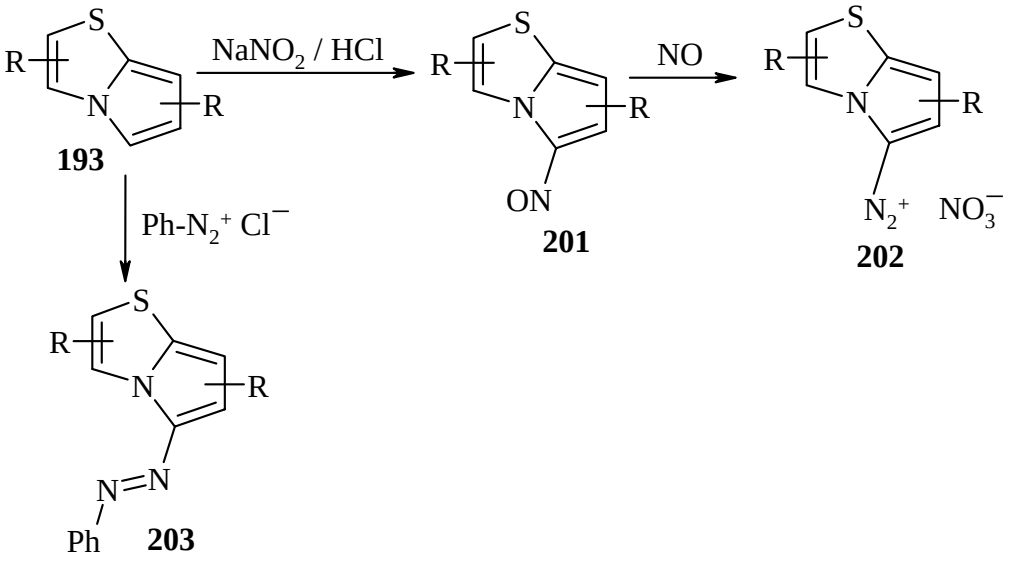



Scheme 48. R = H, Me.

### 3.1.3. Reactions with non-carbon electrophiles

Pyrrolothiazoles **193** were reported to undergo nitrosation and coupling with diazonium salts at position 5 yielding compounds **201**, **203** (Scheme 49).[35,38,123] When the position 5 was occupied, the same reactions

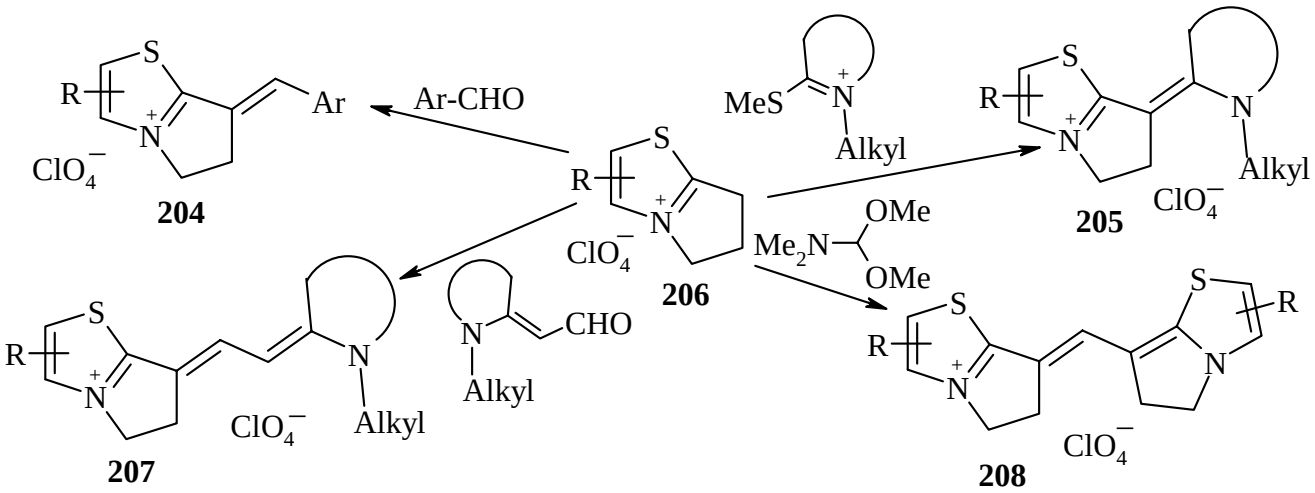
occurred at position 7. It is interesting to note that treatment of nitroso derivatives **201** with excess of gaseous nitrogen monoxide afforded diazonium nitrates **202** unavailable through other methods.[38]




Scheme 49. R = H, Me, subst. Ph.

### 3.2. Reactions of Active Methylene Groups and Synthesis of Cyanine Dyes

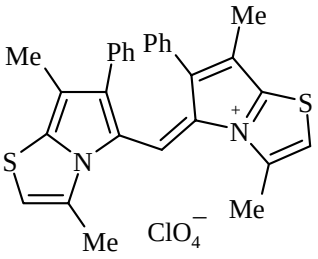
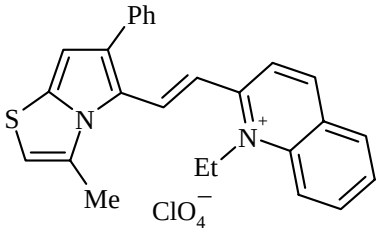
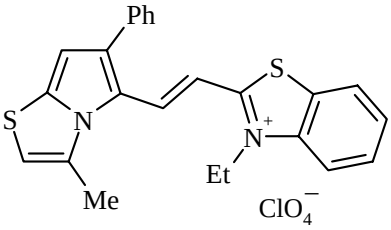
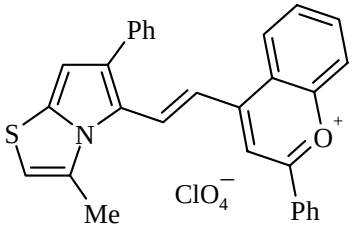
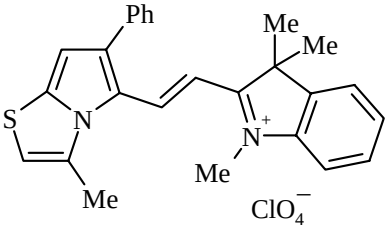
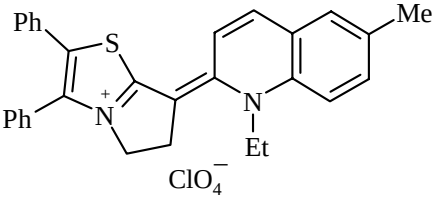
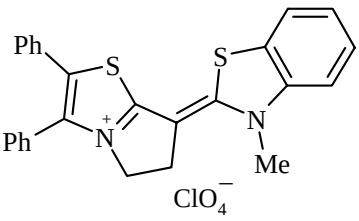
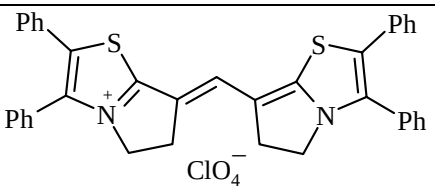
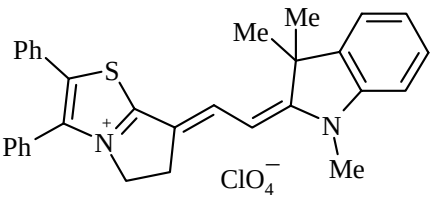
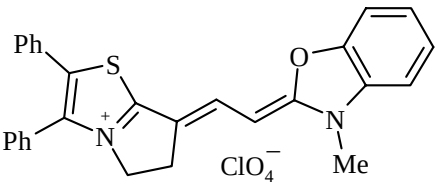
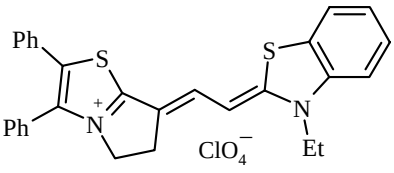
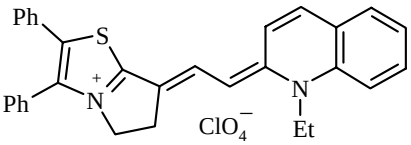
Pyrrolothiazolium salts **206** consisting of the active methylene group at position 7 were shown to react with aldehydes yielding derivatives **204**[11,71] (Scheme 50). Use of the suitable heterocyclic aldehydes led to the cyanine dyes **207**.[130] Another type of dyes **205** was obtained by condensation of the salts **206** with 1-alkyl-2-methylthio- heterocycles.[71,130,131] Furthermore, the symmetrical cyanines **208** were prepared with DMFDMA or triethyl orthoformate.[71,131] The structures and absorption maxima of the dyes are listed in the Table 1.



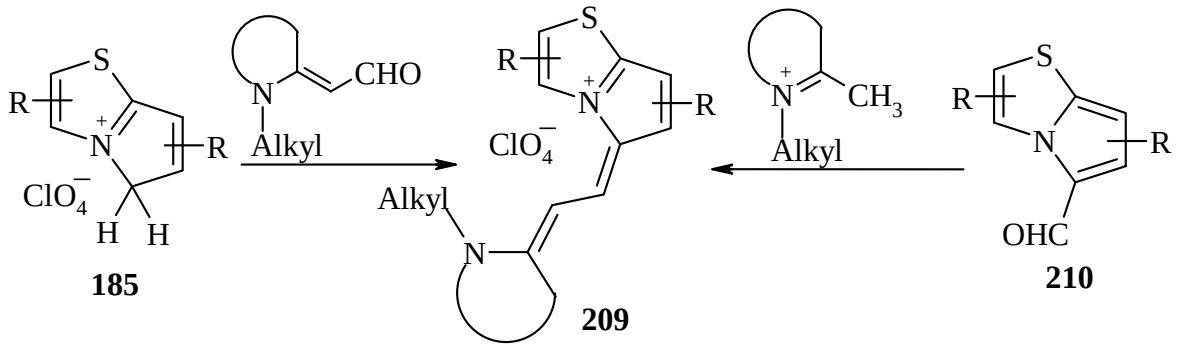

Scheme 50. R = Me, Ph; Alkyl = Me, Et.

Pyrrolothiazolium perchlorates **185** (see section 3.1.1.) also contain the active methylene at position 5 and were reported to give the dyes **209** with appropriate heterocyclic aldehydes[132] (Scheme 51). Alternatively

Table 1. Pyrrolo[2,1-*b*]thiazole based cyanine dyes.

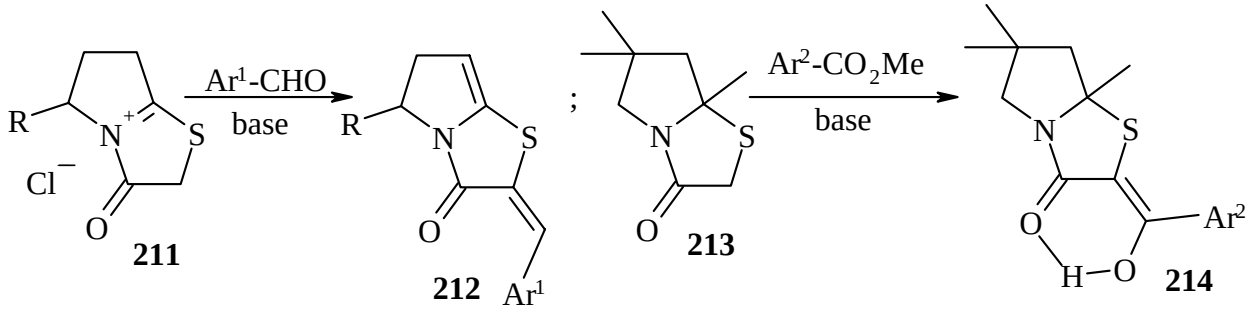
| Structure | $\lambda_{max}$, nm | Ref. | Structure | $\lambda_{max}$, nm | Ref. |
|---|---|---|---|---|---|
|  | 597 | 132 |  | 560 | 132 |
|  | 555 | 132 |  | 595 | 132 |
|  | 550 | 132 |  | 521 | 131 |
|  | 452 | 131 |  | 608 | 131 |
|  | 540 | 130 |  | 525 | 130 |
|  | 563 | 130 |  | 606 | 130 |

compounds **209** can be obtained by condensation of pyrrolo[2,1-*b*]thiazole-5-carboxaldehydes **210** with 1-alkyl-2-methyl- heterocycles.[132,133] The structures and absorption maxima of the dyes **209** are also present in the Table 1. Noteworthy, some of these dyes were found to be useful as photographic sensitizers.[71,133]




Scheme 51. R = Me, subst. Ph; Alkyl = Me, Et.

Finally, the last type of active methylene containing pyrrolothiazoles is the 3-oxo derivatives **211, 213**. Although compounds **211, 213** have no relation to cyanines, they were reported to react with aldehydes and to undergo Claisen condensation yielding derivatives **212** and **214**, respectively[12,134] (Scheme 52).




Scheme 52. R = *n*-Pr; $Ar^1$ = 4-$(Me_2N)C_6H_4$; $Ar^2$ = 4-$ClC_6H_4$.

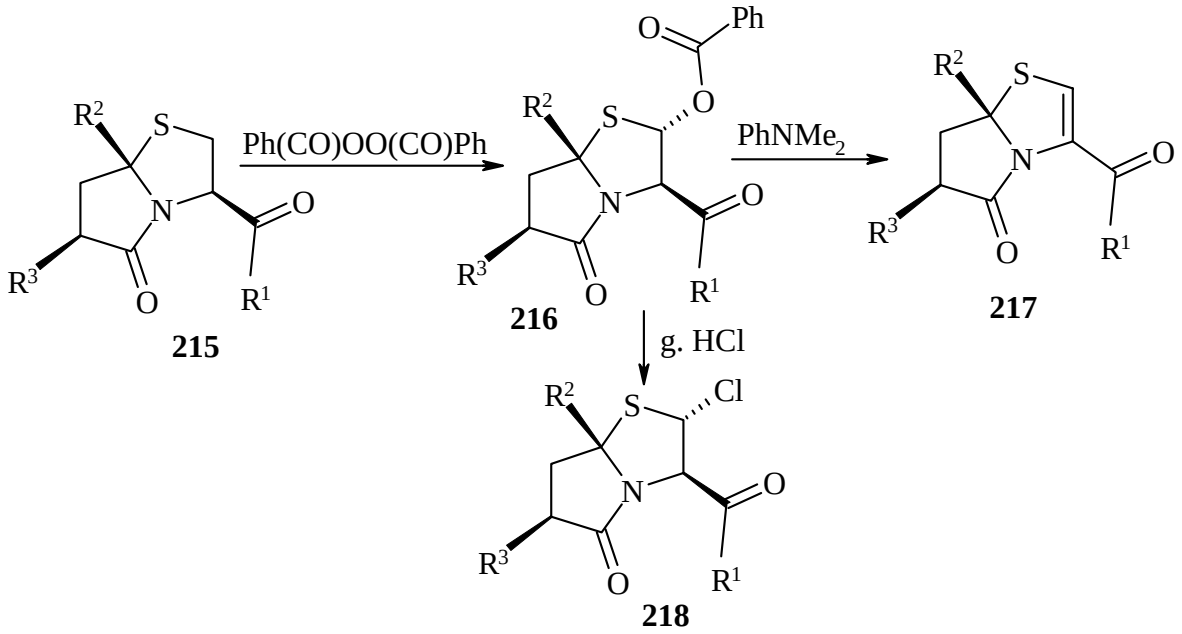
### 3.3. Miscellaneous

There are several reactions of pyrrolothiazoles represented by a few number of examples. Therefore, the degree of their generality is unclear and it is hardly to classify them in separate groups. These reactions are collected here and are divided in two subgroups, namely the processes occurring with retention of pyrrolothiazole core, and the reactions including transformations or cleavage of the rings system. Of course, the typical transformations of functional groups are not the matter of consideration.

#### 3.3.1. Reactions with retention of pyrrolo[2,1-*b*]thiazole moiety

For the cysteine derived pyrrolothiazoles **215** (see section 2.3.) the free radical introduction of benzoyloxy group at position 2 was reported[23,85,95,96] (Scheme 53). Usually the benzoyloxy substituent adopted *anti*-configuration in the respect of carboxyl functionality,[85,95,96] but sometimes the absence of stereoselectivity was observed.[23,95,96] Benzoic acid elimination caused by treatment with

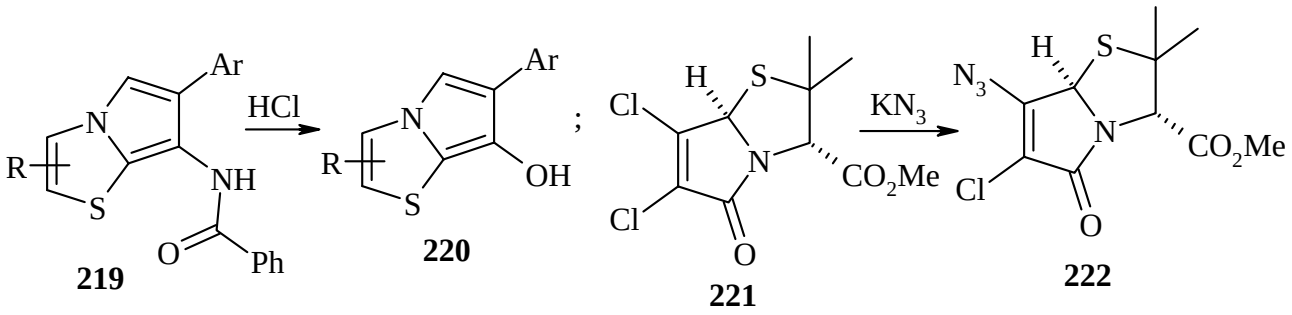
N,N-dimethylaniline led to the 2,3-dehydro derivatives **217**.[23,95,96] Furthermore, the benzoyloxy group could be replaced by chlorine using gaseous HCl.[85]




Scheme 53. $R^1$ = OR, NHR; $R^2$ = H, Me; $R^3$ = H, NH-Cbz, NH-Boc.

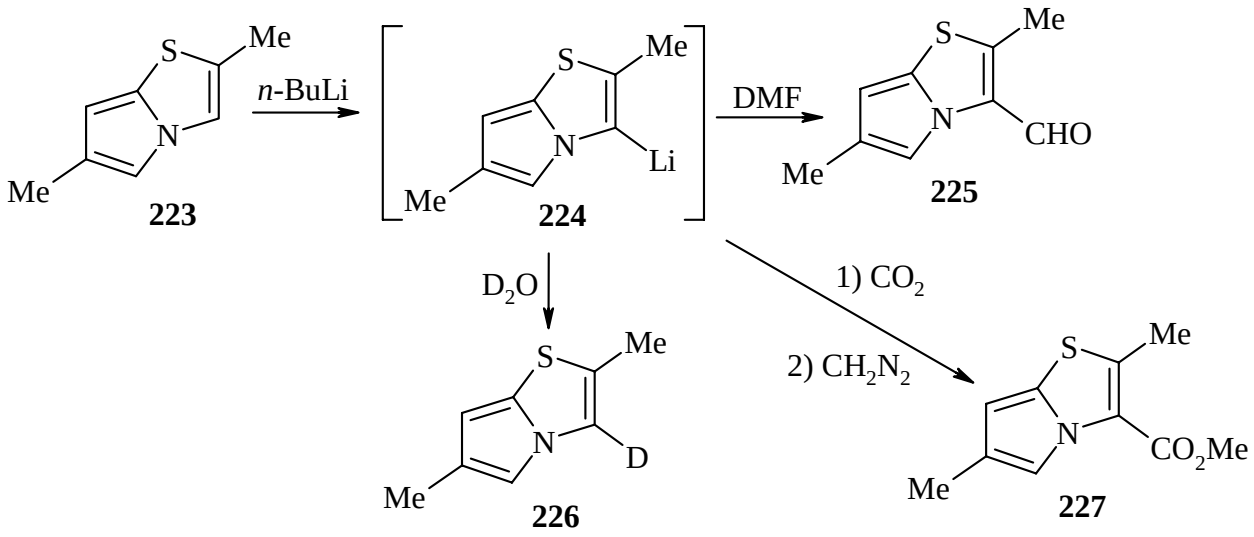
The sulfur atom of pyrrolo[2,1-*b*]thiazoles consisting of completely hydrogenated thiazole moiety can be readily oxidized both into sulfoxide[20,76,79] and sulfone.[20,110] Periodic acid,[79] *m*-chloroperbenzoic acid[76] and hydrogen peroxide[20,110] were employed as oxidants.

Generally a nucleophilic substitution is not inherent to pyrrolothiazoles. Nevertheless, the two cases were described (Scheme 54). Thus, refluxing of compounds **219** in hydrochloric acid resulted in the benzamide residue substitution by hydroxyl group.[44] Also replacement of chlorine by potassium azide was reported for derivative **221**.[93]



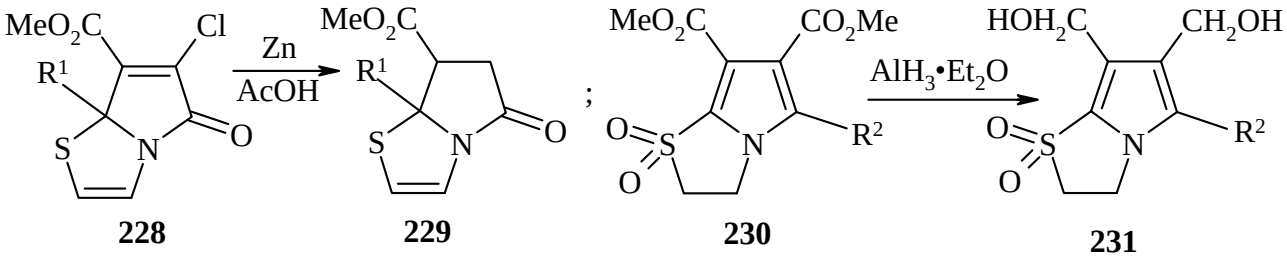

Scheme 54. R = H, Me, Ph.

Lithiation of 2,6-dimethylpyrrolo[2,1-*b*]thiazole **223** was found to occur at position 3[129] (Scheme 55). The metalated intermediate **224** was transformed into appropriate formyl, carboxyl and deuterium substituted derivatives **225-227**. Corresponding 3,6-disubstituted analogue of **223** was shown to undergo lithiation at position 2 followed by the same transformations.[129]




Scheme 55

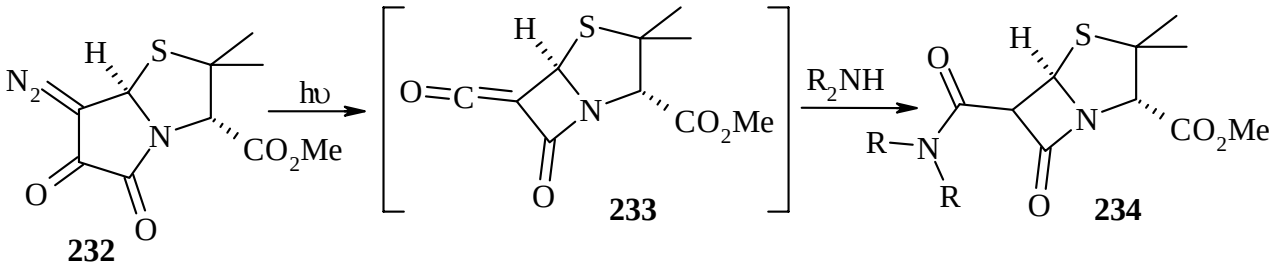
Lastly, the two unusual reductions of pyrrolothiazole derivatives should be mentioned. Thus, reductive dechlorination with zinc in acetic acid was reported for compound **228**[119] (Scheme 56). Furthermore, the two ester groups of compound **230** were reduced with aluminum hydride ether complex saving the sulfone moiety.[114]




Scheme 56. $R^1$ = *i*-Pr; $R^2$ = Me, subst. Ph.

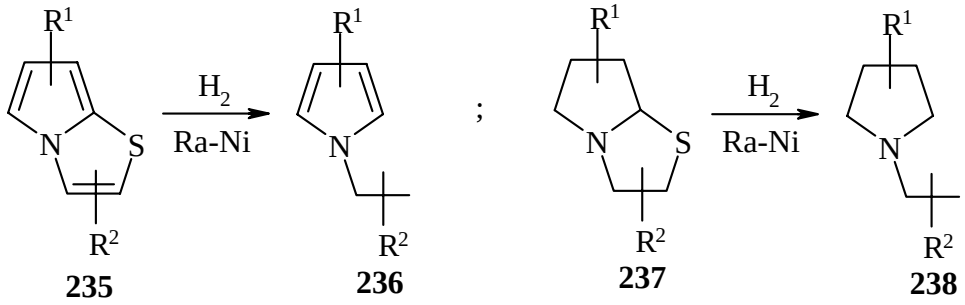
### 3.3.2. Transformations and cleavages of pyrrolo[2,1-*b*]thiazole core

Most of the reactions in this section are the cleavages of one of the rings. The sole example of pyrrolothiazole conversion into another bicyclic system reported to date is the ring fusion of 7-diazo derivative **232** via the Wolf rearrangement leading to compound **234**[93] (Scheme 57).



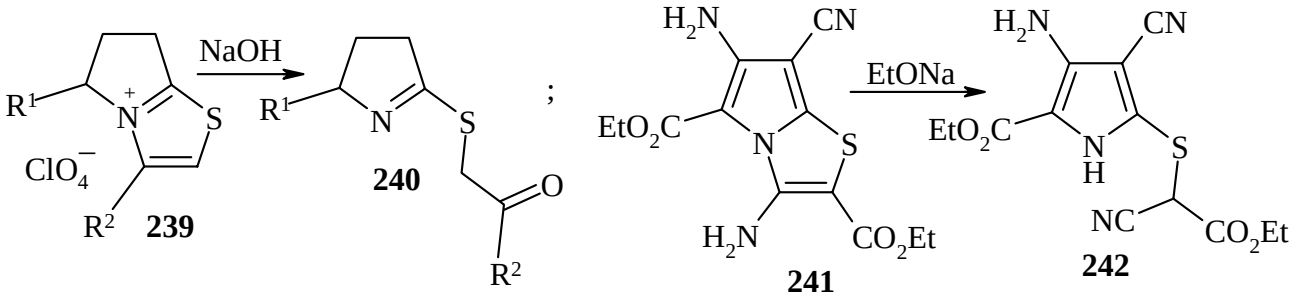

Scheme 57. R = *i*-Pr.

Reduction of both aromatic and perhydro- pyrrolothiazoles **235** and **237** with hydrogen over Raney nickel resulted in desulfurization and formation of pyrrole or pyrrolidine derivatives **236** and **238**, respectively[65,79,129] (Scheme 58). Apparently, if the substituents $R^1$, $R^2$ consisted of reducible moieties, they were also hydrogenated.[129] This reaction had not found preparative applications but sometimes turned out to be useful for identification and structure assignment purposes.



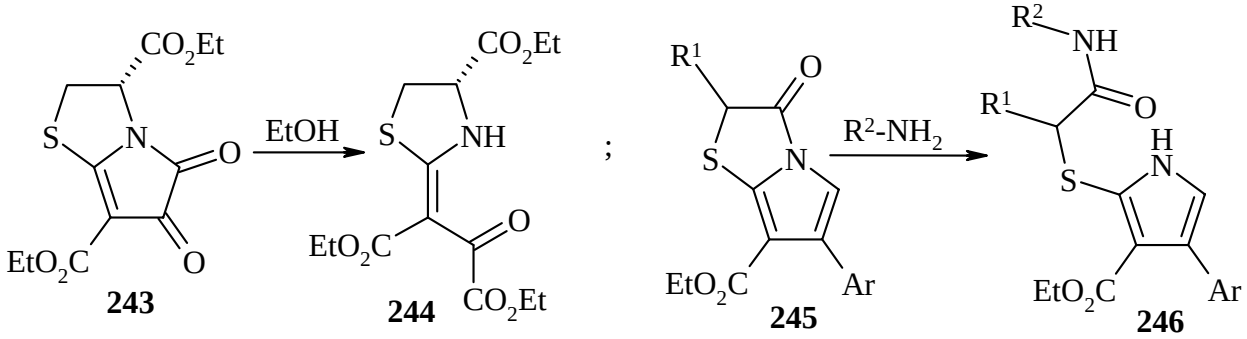

Scheme 58

The several cases of the cleavage along C3-N4 bond were reported (Scheme 59). Thus, treatment of the salts **239** with alkali yielded derivatives **240**,[9,11] whereas pyrrolothiazole **241** was converted into pyrrole **242** by action of sodium ethoxide.[77]



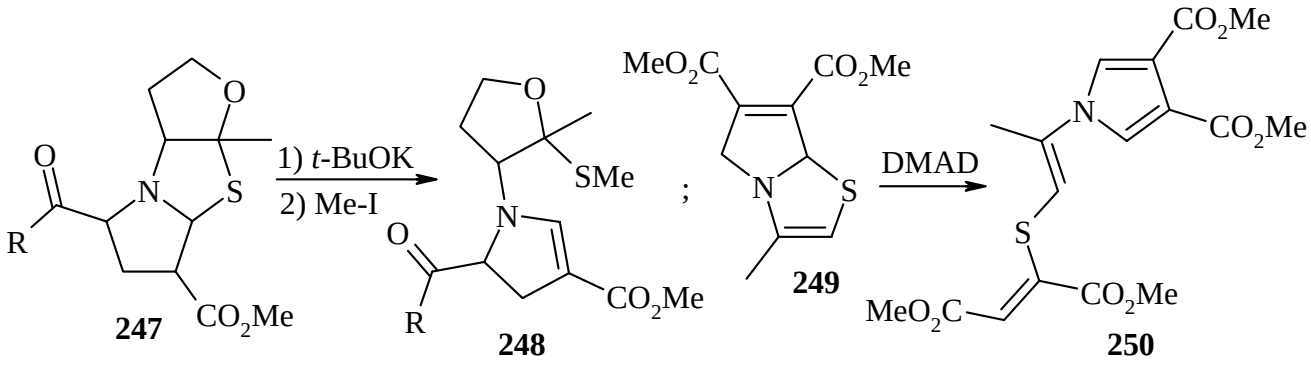

Scheme 59. $R^1$ = $C_3$-$C_6$ alkyl; $R^2$ = Me, Ph.

Pyrrolo[2,1-*b*]thiazol-4,5-dione **243** was found to undergo alkoholysis of the amide moiety to give compound **244**[52] (Scheme 60). On the other hand, the 3-oxo derivatives **245** also containing amide bond were shown to be mild acylating agents and reacted with primary amines yielding pyrroles **246**.[56]

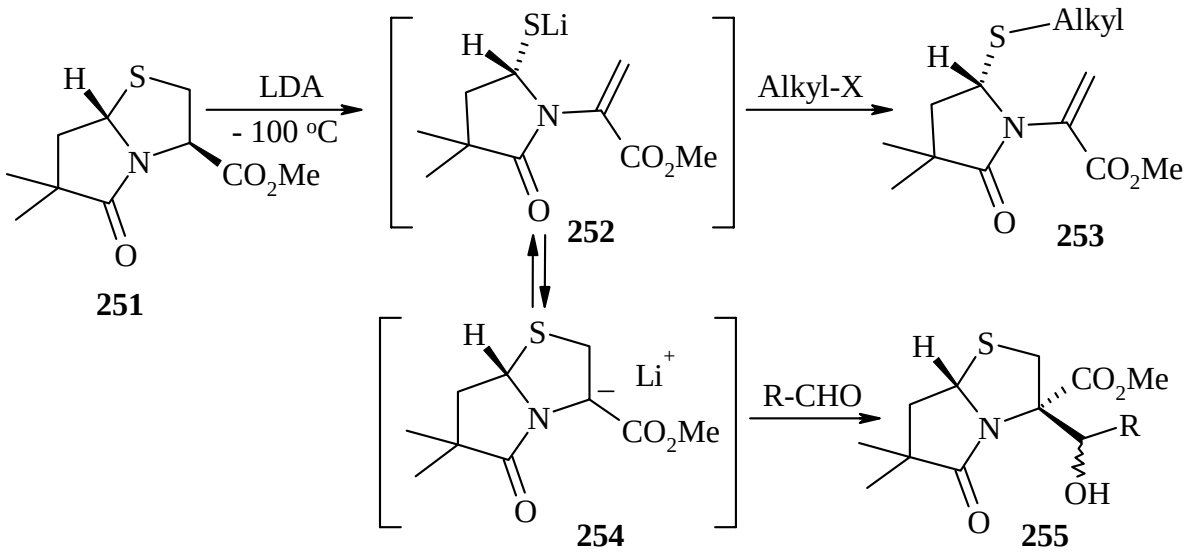



Scheme 60. $R^1$ = H, Me; $R^2$ = $PhCH_2$, 3,4-$(MeO)_2C_6H_3CH_2$; Ar = Ph, 4-$ClC_6H_4$, 4-$BrC_6H_4$.

A few examples of mercapto group elimination were noted for certain partially or completely hydrogenated pyrrolothiazoles (Schemes 61, 62). Thus, *tert*-butoxide induced β-elimination followed by alkylation of the formed thiolate afforded derivative **248**.[66] Compound **249** underwent 1,4-elimination of thiol driven by pyrrole aromatization. Trapping of the formed thiol with DMAD resulted in derivative **250**.[68] Finally, another case of β-elimination was observed upon treatment of pyrrolothiazole **251** with lithium diisopropylamide. Alkylation of intermediate thiolate **252** yielded derivatives **253**.[105] However, reaction with aldehydes afforded the carbon adducts **255**. Hence, an equilibrium between the cleaved and cyclic intermediates **252** and **254** was present.[105]




Scheme 61. R = Me, OEt.




Scheme 62. Alkyl-X = $PhCH_2Cl$ and related halides; R = Ph, Ph-CH=CH-.

## 4. UTILITY OF PYRROLO[2,1-*b*]THIAZOLES

Applications of pyrrolo[2,1-*b*]thiazoles in dyes and photography, as well as in peptidomimetics chemistry have been already discussed in the sections 3.2 and 2.3 respectively. Additionally there is a number of pyrrolothiazole derivatives possessing different biological activities. Thus, several compounds with bactericidal and antibiotic activities[11,18,24,95,96] are shown in the Figure 6.

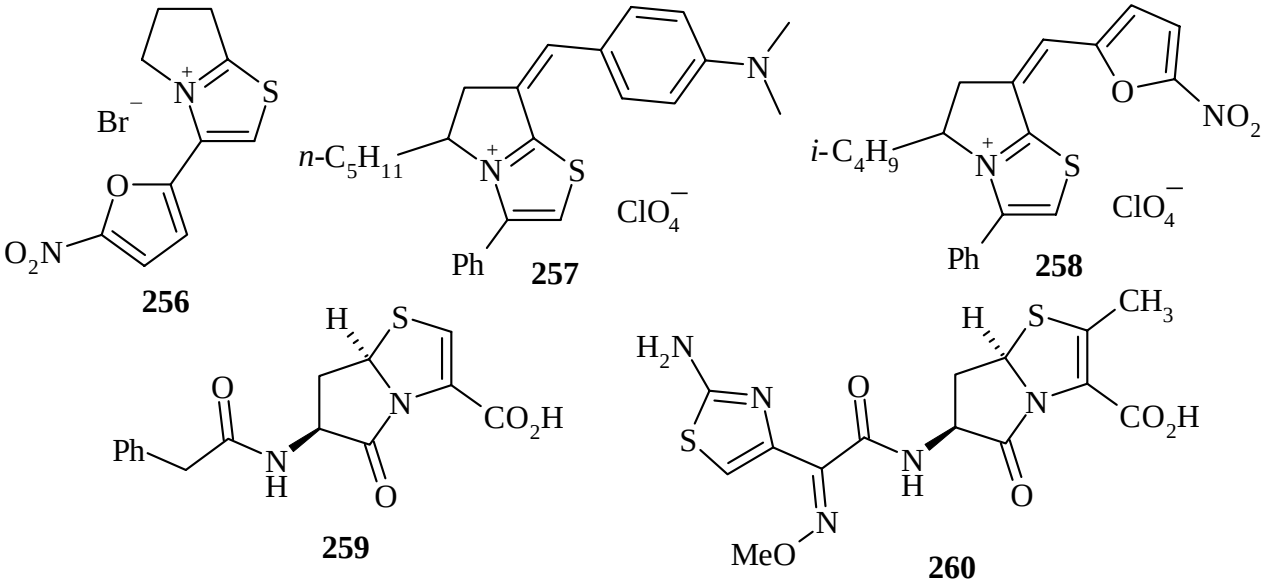



Figure 6. Pyrrolo[2,1-*b*]thiazoles with bactericidal and antibiotic properties.

Moreover, antiinflammatory properties were found for derivatives **261**,[19] and the substances **262**-**264** with high antileucemic[91] and anticonvulsant[84,135] activities were described as well (Figure 7). Furthermore, hepatoprotective[17] and antidiabetic[81,82] pyrrolothiazoles **265, 266** were discovered. Finally, derivative **267** appeared to be useful for prevention and treatment of human cognitive disorders such as mental retardation and Alzheimer's disease.[22]

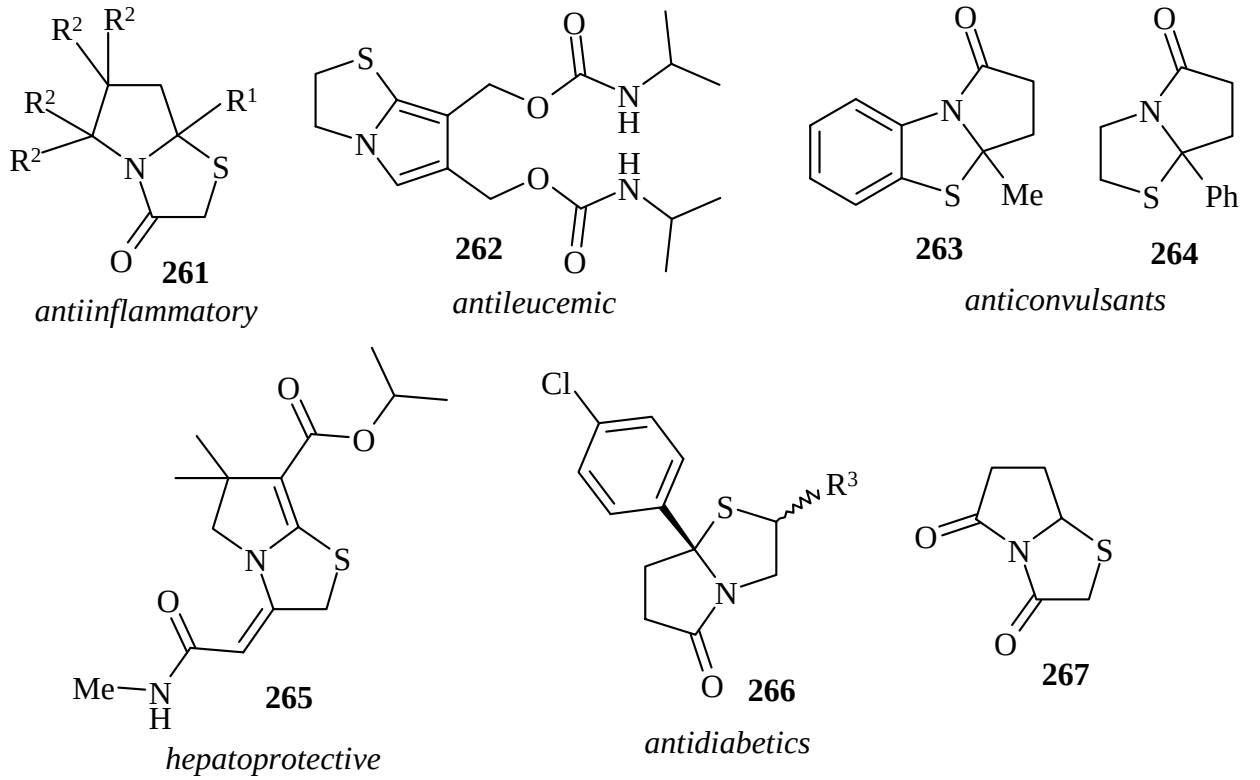



Figure 7. $R^1$ = H, Me, Ph, $CH_2Ph$; $R^2$ = H, Me; $R^3$ = H, $CH_2OC_6H_4Cl$-*p*.

## REFERENCES


1. K. H. Pilgram, 'Comprehensive Heterocyclic Chemistry: Two Fused Five-Membered Heterocyclic Rings: (i) Classical Systems,' Vol. 6, ed. by A. R. Katrizky and C. W. Rees, Pergamon Press, Oxford, 1984, p. 973.
2. C. A. Ramsden, 'Comprehensive Heterocyclic Chemistry: Two Fused Five-Membered Heterocyclic Rings: (ii) Non-classical Systems,' Vol. 6, ed. by A. R. Katrizky and C. W. Rees, Pergamon Press, Oxford, 1984, p. 1027.
3. A. Dondoni, *Phosphorus Sulfur Silicon Relat. Elem.*, 1985, **24**, 1.
4. J. Liebscher, 'Heteroarenes III, Part 2: 1,3-Thiazoles,' Vol. E8b, ed. by Schaumann, Georg Thieme Verlag, Stuttgart, 1994, pp. 1-398.
5. D. Kikelj and U. Urleb, 'Hetarenes and Related Ring Systems: Five-Membered Hetarenes with One Chalcogen and One Additional Heteroatom,' Vol. 11, ed. by Schaumann, Georg Thieme Verlag, Stuttgart – New York, 2002, pp. 627-833.
6. 'The Chemistry of Penicillins,' ed. by H. T. Clarke, J. R. Johnson, and R. Robinson, Princeton University Press, Princeton, NJ, 1949.
7. D. N. McGregor, 'Comprehensive Heterocyclic Chemistry: Penicillins,' Vol. 7, ed. by A. R. Katrizky and C. W. Rees, Pergamon Press, Oxford, 1984, p. 299.
8. M. Roth, P. Dubs, E. Götschi, and A. Eschenmoser, *Helv. Chim. Acta*, 1971, **54**, 710.
9. G. V. Bespalova, V. A. Sedavkina, and V. G. Kharchenko, *Khim. Geterotsikl. Soedin*., 1979, 1648; *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1979, **15**, 1323.
10. F. S. Babichev, V. A. Bogolyubsky, V. K. Kibirev, and F. A. Mikhajlenko, *Zh. Obshch. Khim*., 1962, **32**, 2793; *J. Gen. Chem. USSR (Engl. Transl.)*, 1962, **32**, 2750.
11. V. A. Sedavkina, G. V. Bespalova, V. G. Garanzha, and L. K. Kulikova, *Khim. Farm. Zh.*, 1976, **10**, 66; *Pharm. Chem. J. (Engl. Transl.)*, 1976, **10**, 58.
12. G. V. Bespalova, V. A. Sedavkina, E. V. Ponomareva, A. D. Shebaldova, and V. I. Labunskaya, *Khim. Geterotsikl. Soedin.*, 1986, 1690; *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1986, **22**, 1370.
13. W. Friedrichsen and M. König, *Synthesis*, 1983, 582.
14. A. Padwa and Z. J. Zhang, *Heterocycles*, 1994, **37**, 441.
15. T. M. Heidelbaugh, B. Liu, and A. Padwa, *Tetrahedron Lett.*, 1998, **39**, 4757.
16. A. Padwa, L. S. Beall, T. M. Heidelbaugh, B. Liu, and S. M. Sheehan, *J. Org. Chem.*, 2000, **65**, 2684.
17. M. Hasegawa, A. Nakayama, S. Yokohama, T. Hosokami, Y. Kurebayashi, T. Ikeda, Y. Shimoto, S. Ide, Y. Honda, and N. Suzuki, *Chem. Pharm. Bull.*, 1995, **43**, 1125.
18. H. R. Snyder and L. E. Benjamin, *J. Med. Chem*., 1970, **13**, 164.

19. T. Burgemeister, G. Dannhardt, E. Graf, and R. Obergrusberger, *Arch. Pharm*., 1987, **320**, 799.
20. Y. Terao, Y. Yasumoto, K. Ikeda, and M. Sekiya, *Chem. Pharm. Bull*., 1986, **34**, 105.
21. A. A. Potekhin, V. V. Sokolov, K. A. Ogloblin, and S. M. Esakov, *Khim. Geterotsikl. Soedin*., 1983, 776; *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1983, **19**, 622.
22. D. E. Butler, J. D. Leonard, B. W. Caprathe, Y. J. L'Italien, M. R. Pavia, F. M. Hershenson, P. H. Poschel, and J. G. Marriott, *J. Med. Chem*., 1987, **30**, 498.
23. N. E. Allen, D. B. Boyd, J. B. Campbell, J. B. Deeter, T. K. Elzey, B. J. Foster, L. D. Hatfield, J. N. Hobbs, W. J. Hornback, D. C. Hunden, N. D. Jones, M. D. Kinnick, J. M. Morin, J. E. Munroe, J. K. Swartzendruber, and D. G. Vogt, *Tetrahedron*, 1989, **45**, 1905.
24. D. B. Boyd, T. K. Elzey, L. D. Hatfield, M. D. Kinnick, and J. M. Morin, *Tetrahedron Lett*., 1986, **27**, 3453.
25. W. J. Middleton, V. A. Engelhardt, and B. S. Fisher, *J. Am. Chem. Soc*., 1958, **80**, 2822.
26. R. L. N. Harris and H. G. McFadden, *Austr. J. Chem*., 1986, **39**, 887.
27. G. W. H. Cheeseman and A. A. Hawi, *J. Heterocycl. Chem*., 1983, **20**, 591.
28. G. Campiani, V. Nacci, S. Bechelli, S. M. Ciani, A. Garofalo, I. Fiorini, H. Wikström, P. de Boer, Y. Liao, P. G. Tepper, A. Cagnotto, and T. Mennini, *J. Med. Chem*., 1998, **41**, 3763.
29. A. Padwa, F. R. Kinder, W. R. Nadler, and L. Zhi, *Heterocycles*, 1993, **35**, 367.
30. A. Padwa, S. R. Harring, D. L. Hertzog, and W. R. Nadler, *Synthesis*, 1994, 993.
31. A. G. Mal'kina, R. den Besten, A. C. H. T. M. van der Kerk, L. Brandsma, and B. A. Trofimov, *J. Orgamonet. Chem.*, 1995, **493**, 271.
32. N. E. Shevchenko, V. G. Nenajdenko, and E. S. Balenkova, *Synthesis*, 2003, 1191.
33. H. Erlenmeyer, O. Weber, P. Schmidt, G. Kung, C. Zinsstag, and B. Prijs, *Helv. Chim. Acta*, 1948, **31**, 1142.
34. W. Traupel, M. Erne, and E. Sorkin, *Helv. Chim. Acta*, 1950, **33**, 1960.
35. V. K. Kibirew and F. S. Babichev, *Ukr. Khim. Zh*., 1964, **30**, 488.
36. C. Galera, J. J. Vaquero, J. L. Garcia, and J. Alvarez-Builla, *J. Heterocycl. Chem*., 1986, **23**, 1889.
37. T. Pyl, H. Gille, and D. Nusch, *Justus Liebigs Ann. Chem*., 1964, **679**, 139.
38. J. M. Tedder, K. H. Todd, and W. K. Gibson, *J. Chem. Soc. (C)*, 1969, 1279.
39. H. Kondo and F. Nagasawa, *J. Pharm. Soc. Jpn*., 1937, **57**, 1050 (*Chem. Abstr*., 1938, **32**, 3398.)
40. K. G. Untch and J. O. Gardner, US Pat. 4033978, 1977 (*Chem. Abstr*., 1977, **87**, 152180.)
41. K. G. Untch and J. O. Gardner, US Pat. 3920672, 1975 (*Chem. Abstr*., 1976, **84**, 121807.)
42. R. K. Mackie, S. McKenzie, D. H. Reid, and R. G. Webster, *J. Chem. Soc., Perkin Trans. 1*, 1973, 657.
43. B. B. Molloy, D. H. Reid, and F. S. Skelton, *J. Chem. Soc*., 1965, 65.

44. T. Pyl, H.-D. Dinse, and O. Sietz, *Justus Liebigs Ann. Chem*., 1964, **676**, 141.
45. B. A. Baimashev, N. A. Polezhaeva, and E. N. Klimovitskii, *Phosphorus Sulfur Silicon Relat. Elem*., 1998, **132**, 251.
46. J. C. Brindley, D. G. Gillon, and G. D. Meakins, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1255.
47. H. Meyer, *Justus Liebigs Ann. Chem*., 1981, 1534.
48. A. K. Gupta, H. Ila, and H. Junjappa, *Synthesis*, 1988, 284.
49. A. K. Gupta, R. T. Chakrasali, H. Ila, and H. Junjappa, *Synthesis*, 1989, 141.
50. A. K. Gupta, K. R. Reddy, H. Ila, and H. Junjappa, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1725.
51. G. M. Davies, P. B. Hitchcock, D. Loakes, and D. W. Young, *Tetrahedron Lett*., 1996, **37**, 5601.
52. S. H. Bhattia, G. M. Davies, P. B. Hitchcock, D. Loakes, and D. W. Young, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2449.
53. H. Schäfer and K. Gewald, *J. prakt. Chem*., 1974, **316**, 684.
54. Yu. M. Volovenko, T. A. Volovnenko, and A. V. Tverdokhlebov, *Khim. Geterotsikl. Soedin*., 2001, 1101; *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2001, **37**, 1011.
55. A. K. El-Shafei, A. M. El-Sayed, H. Abdel-Ghany, and A. M. El-Saghier, *Gazz. Chim. Ital*., 1990, **120**, 193.
56. A. V. Tverdokhlebov, A. P. Andrushko, E. V. Resnyanska, and A. A. Tolmachev, *Synthesis*, 2004, 2317.
57. A. V. Tverdokhlebov, E. V. Resnyanska, A. A. Tolmachev, and A. P. Andrushko, *Synthesis*, 2003, 2632.
58. A. V. Tverdokhlebov, A. P. Andrushko, A. A. Tolmachev, A. N. Kostyuk, A. N. Chernega, and E. B. Rusanov, *Monatsh. Chem*., 2005, **136**, 1781.
59. A. V. Tverdokhlebov, A. P. Andrushko, and A. A. Tolmachev, *Synthesis*, 2006, 1433.
60. O. Tsuge, S. Kanemasa, and S. Takenaka, *Heterocycles*, 1983, **20**, 1907.
61. O. Tsuge, S. Kanemasa, and S. Takenaka, *Bull. Chem. Soc. Jpn*., 1985, **58**, 3137.
62. J. Fröhlich, U. Habermalz, and F. Kröhnke, *Tetrahedron Lett*., 1970, 271.
63. O. Tsuge, S. Kanemasa, and S. Takenaka, *Bull. Chem. Soc. Jpn*., 1985, **58**, 3320.
64. J. L. G. Ruano, A. M. M. Castro, and J. H. R. Ramos, *Heteroatom Chem*., 2002, **13**, 453.
65. G. A. Kraus and J. O. Nagy, *Tetrahedron Lett*., 1981, **22**, 2727.
66. G. A. Kraus and J. O. Nagy, *Tetrahedron*, 1985, **41**, 3537.
67. O. Tsuge, Y. Shimizu, H. Shimoharada, and S. Kanemasa, *Heterocycles*, 1982, **19**, 2259.
68. A. Padwa, U. Chiacchio, and M. K. Venkatramanan, *J. Chem. Soc., Chem. Commun*., 1985, 1108.
69. C. Divorne, P. Joly, and J. Roggero, *Compt. Rend. Acad. Sci*., 1970, **271**, 763.
70. T. Kametani, S. Hirata, H. Nemoto, M. Ihara, and K. Fukumoto, *Heterocycles*, 1979, **12**, 523.

71. P. de Smet and G. Schwartz, *Natuurw. Tijdschr*., 1940, **21**, 271 (*Chem. Abstr*., 1940, **34**, 3603.)
72. R. Fuks and H. G. Viehe, *Tetrahedron*, 1969, **25**, 5721.
73. A. V. Kel'in, A. W. Sromek, and V. Gevorgyan, *J. Am. Chem. Soc*., 2001, **123**, 2074.
74. D. H. Reid, F. S. Skelton, and W. Bonthrone, *Tetrahedron Lett*., 1964, 1797.
75. H. Kojima, K. Yamamoto, Y. Kinoshita, and H. Inoue, *J. Heterocycl. Chem*., 1992, **29**, 1473.
76. S. Coulton and R. Southgate, *J. Chem. Soc., Perkin Trans. 1*, 1992, 961.
77. K. Gewald, U. Hain, and P. Hartung, *Monatsh. Chem*., 1981, **112**, 1393.
78. A. Knoll and J. Liebsher, *Z. Chem*., 1988, **28**, 214.
79. R. G. Hiskey and S. J. Dominianni, *J. Org. Chem*., 1965, **30**, 1506.
80. J. R. Geigy, Belg. Pat. 659528, 1965 (*Chem. Abstr*., 1966, **64**, 3545).
81. T. D. Aicher, D. C. Knorr, and H. C. Smith, *Tetrahedron Lett*., 1998, **39**, 8579.
82. T. D. Aicher, B. Balkan, P. A. Bell, L. J. Brand, S. H. Cheon, R. O. Deems, J. B. Fell, W. S. Fillers, J. D. Fraser, J. Gao, D. C. Knorr, G. G. Kahle, C. L. Leone, J. Nadelson, R. Simpson, and H. C. Smith, *J. Med. Chem*., 1998, **41**, 4556.
83. G. L. Oliver, J. R. Dann, and J. W. Gates, *J. Am. Chem. Soc*., 1958, **80**, 702.
84. G. Trapani, M. Franco, A. Latrofa, G. Genchi, G. Brigiani, M. Mazzoccoli, M. Persichella, M. Serra, G. Biggio, and G. Liso, *Eur. J. Med. Chem*., 1994, **29**, 197.
85. J. E. Baldwin and M. A. Christie, *J. Am. Chem. Soc*., 1978, **100**, 4597.
86. N. Hellström, S.-O. Almqvist, M. Aamisepp, and S. Rodmar, *J. Chem. Soc. (C)*, 1968, 392.
87. I. T. Strukow, *Zh. Obshch. Khim*., 1952, **22**, 521.
88. J. E. Baldwin, R. M. Adlington, N. G. Robinson, and H.-H. Ting, *J. Chem. Soc., Chem. Commun*., 1986, 409.
89. H. H. Wasserman, B. Suryanarayana, R. C. Koch, and R. L. Tse, *Chem. Ind. (London)*, 1956, 1022.
90. H. Rapoport, Ger. Offen. 2130730, 1971 (*Chem. Abstr*., 1972, **70**, 99688).
91. J. B. Jones and J. M. Young, *J. Med. Chem*., 1968, **11**, 1176.
92. H. H. Wasserman, F. M. Precopio, and T.-C. Liu, *J. Am. Chem. Soc*., 1952, **74**, 4093.
93. H. W. Moore and M. J. Arnold, *J. Org. Chem*., 1983, **48**, 3365.
94. J. P. Freeman and M. K. Fettes-Fields, *Heterocycles*, 1985, **23**, 1073.
95. J. E. Baldwin, R. T. Freeman, C. Lowe, C. J. Schofield, and E. Lee, *Tetrahedron*, 1989, **45**, 4537.
96. J. E. Baldwin, C. Lowe, C. J. Schofield, and E. Lee, *Tetrahedron Lett*., 1986, **27**, 3461.
97. J. E. Baldwin and E. Lee, *Tetrahedron*, 1986, **42**, 6551.
98. J. E. Baldwin, W. J. Norris, R. T. Freeman, M. Bradley, R. M. Adlington, S. Long-Fox, and C. J. Schofield, *J. Chem. Soc., Chem. Commun*., 1988, 1128.
99. N. L. Subasinghe, R. J. Bontems, E. McIntee, R. K. Mishra, and R. L. Johnson, *J. Med. Chem*., 1993,

**36**, 2356.

100. J. E. Baldwin, V. Lee, and C. J. Schofield, *Heterocycles*, 1992, **34**, 903.
101. E. M. Khalil, A. Pradhan, W. H. Ojala, W. B. Gleason, R. K. Mishra, and R. L. Johnson, *J. Med. Chem*., 1999, **42**, 2977.
102. P. Johannesson, M. Erdelyi, G. Lindeberg, P.-A. Frändberg, F. Nyberg, A. Karlen, and A. Hallberg, *J. Med. Chem*., 2004, **47**, 6009.
103. W. Qiu, X. Gu, V. A. Soloshonok, M. D. Carducci, and V. J. Hruby, *Tetrahedron Lett*., 2001, **42**, 145.
104. J. M. Ndungu, X. Gu, D. E. Gross, J. P. Cain, M. D. Carducci, and V. J. Hruby, *Tetrahedron Lett*., 2004, **45**, 4139.
105. N. L. Subasinghe, E. M. Khalil, and R. L. Johnson, *Tetrahedron Lett*., 1997, **38**, 1317.
106. E. Caballero, P. Puebla, M. Domercq, M. Medarde, J.-L. Lopez, and A. San Feliciano, *Tetrahedron*, 1994, **50**, 7849.
107. J. E. Baldwin, M. F. Chan, G. Gallacher, M. Otsuka, P. Monk, and K. Prout, *Tetrahedron*, 1984, **40**, 4513.
108. J. E. Baldwin, M. F. Chan, G. Gallacher, P. Monk, and K. Prout, *J. Chem. Soc., Chem. Commun*., 1983, 250.
109. V. J. Jephcote, D. I. John, and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1986, 2195.
110. Y. Maki, M. Sako, N. Kurahashi, and K. Hirota, *J. Chem. Soc., Chem. Commun*., 1988, 110.
111. N. Abe, T. Nishiwaki, and N. Komoto, *Chem. Lett*., 1980, 223.
112. N. Abe, T. Nishiwaki, and N. Komoto, *Bull. Chem. Soc. Jpn*., 1980, **53**, 3308.
113. N. Abe, T. Nishiwaki, T. Omori, and E. Harada, *Bull. Chem. Soc. Jpn*., 1982, **55**, 200.
114. W. K. Anderson and R. H. Mach, *Synth. Commun*., 1986, **16**, 911.
115. I. Lalezari and E. L. Schwartz, *J. Med. Chem*., 1988, **31**, 1427.
116. B. Abarca, R. Ballesteros, M. J. Del Rincon-Guaita, and G. Jones, *Heterocycles*, 1994, **38**, 2017.
117. B. Abarca, R. Ballesteros, N. Houari, and A. Samadi, *Tetrahedron*, 1998, **54**, 3913.
118. S. Ito, M. Maeda, and M. Kojima, *Heterocycles*, 1977, **8**, 455.
119. A. Dondoni, G. Fantin, M. Fogagnolo, and A. Medici, *Heterocycles*, 1984, **22**, 2341.
120. K. Agoston and A. Geyer, *Tetrahedron Lett*., 2004, **45**, 1895.
121. B. B. Molloy, D. H. Reid, and S. McKenzie, *J. Chem. Soc*., 1965, 4368.
122. W. Engewald, M. Mühlstädt, and C. Weiss, *Tetrahedron*, 1971, **27**, 4171.
123. S. McKenzie, B. B. Molloy, and D. H. Reid, *J. Chem. Soc. (C)*, 1966, 1908.
124. S. McKenzie and D. H. Reid, *J. Chem. Soc., Chem. Commun*., 1966, 401.
125. D. H. Reid, R. G. Webster, and S. McKenzie, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2334.

126. R. C. G. Killean, J. L. Lawrence, J. U. Cameron, and A. Sharma, *Acta Crystallogr., Sect. B*, 1975, **B31**, 1217.
127. A. Sharma and R. C. G. Killean, *Acta Crystallogr., Sect. B*, 1974, **B30**, 2869.
128. A. Sharma, J. L. Lawrence, and R. C. G. Killean, *Acta Crystallogr., Sect. B*, 1982, **B38**, 962.
129. O. Ceder and B. Beijer, *Tetrahedron*, 1972, **28**, 4341.
130. F. S. Babichev, V. K. Kibirew, F. A. Mikhajlenko, and V. A. Bogolyubsky, *Ukr. Khim. Zh.*, 1966, **32**, 991.
131. F. S. Babichev, F. A. Mikhajlenko, V. K. Kibirew, and V. A. Bogolyubsky, *Ukr. Khim. Zh.*, 1966, **32**, 204.
132. F. S. Babichev, V. K. Kibirew, and L. G. Khil'ko, *Ukr. Khim. Zh.*, 1966, **32**, 64.
133. H. Depoorter and F. J. Moelants, Ger. Offen. 2419071, 1974 (*Chem. Abstr*., 1975, **85**, 105183).
134. G. Dannhardt and T. Debaerdemaeker, *Arch. Pharm*., 1987, **320**, 1278.
135. G. Trapani, M. Franco, A. Latrofa, A. Carotti, S. Cellamare, M. Serra, C. A. Ghiani, G. Tuligi, G. Biggio, and G. Liso, *J. Pharm. Pharmacol*., 1996, **48**, 834.
136. T. E. Nielsen, S. Le Quement, and M. Meldal, *Org. Lett*., 2005, **7**, 3601.