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THIOFUNCTIONALIZED γ-LACTAMS

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Abstract – This review summarizes and analyzes literature data concerning the methods of preparation and some aspects of synthetic and biomedical applications of 3-, 4-, and 5-thiosubstituted γ-lactams. The material is systematized for each type of structure according to the prevalence and importance of synthetic methods. Practical application aspects are combined in a section that includes all types of compounds. The bibliography of the review involves 120 sources, from the appearance of the first publications till now.

CONTENTS

6. Conclusions

1. INTRODUCTION

γ-Lactams (pyrrolidin-2-ones) belong to the most common types of pyrrole derivatives and have been key objects of chemical and biomedical research for many years. The γ-lactam scaffold is the basis for a significant number of biologically active natural and synthetic compounds and is rightfully considered to be a privileged molecular platform for the creation of various pharmacologically attractive structures.[1] Systematic study of γ-lactam-containing natural compounds resulted in the discovery of the anticonvulsant Brivaracetam (**1**),[2] a promising candidate for the treatment of multiple myeloma salinosporamid A (**2**),[3] antitumor preparate pseurotin A (**3**),[4] nootropic agent clausenamide (**4**),[5,6] microbial metabolite lactacystin (**5**),[7] and also in isolation of cyclic alkaloids family (42 products) from *Stenoma tuberosa* plants, the simplest representative of which is (-)-stemoamide (**6**) (Figure 1).[8] The presence of a γ-lactam fragment in the structure of synthetic organic compounds has also proved to be essential for giving them a pronounced pharmacological profile. In this context, a special attention should be given to the nootropic drug Piracetam (**7**),[9] antidepressant Roliprom (**8**),[10] antiemetic Rolapitant (**9**)[11] and the drug for the treatment of acute myeloid leukemia Ivosidenib (**10**).[12]

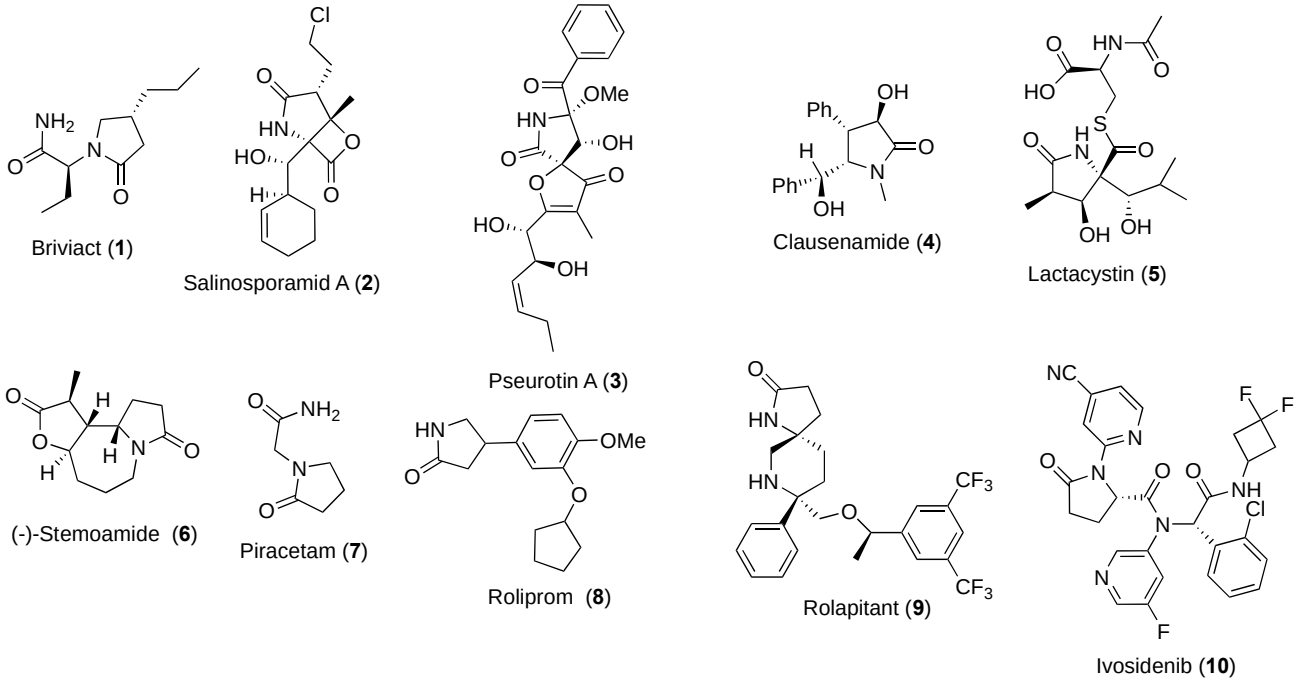
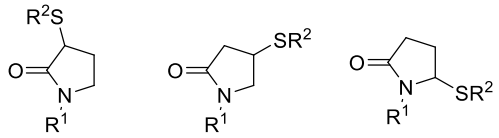


Figure 1. Selected examples of drugs and bioactive substances with a γ-lactam nucleus

A special role in the modern chemistry of heterocyclic compounds is played by γ-lactams additionally modified with various functional groups. Due to their reactivity and a wide range of highly selective transformations, they serve as valuable building blocks for the design of original molecular architectures

of various degrees of complexity.[13-19] The pronounced synthetic and biological potential of these types of γ-lactams was accompanied by accumulation of a large scope of original research, which in turn stimulated their generalization. Over the past few years, a number of interesting review articles have been published covering modern methodologies for the construction and structural transformations of γ-lactam compounds of synthetic and natural origin.[1,20-25] It should be underlined that some types of synthetically important γ-lactam structures, including their thiofunctionalized derivatives, remain unsystematic and not generalized. The latter are the subject of this review.

Structural features of the γ-lactam cycle suppose the existence of three types of its thiofunctionalized representatives, 3-, 4-, and 5-substituted derivatives (**11-13**) (Figure 2), which have been synthesized and have been the subject of the detailed studies.



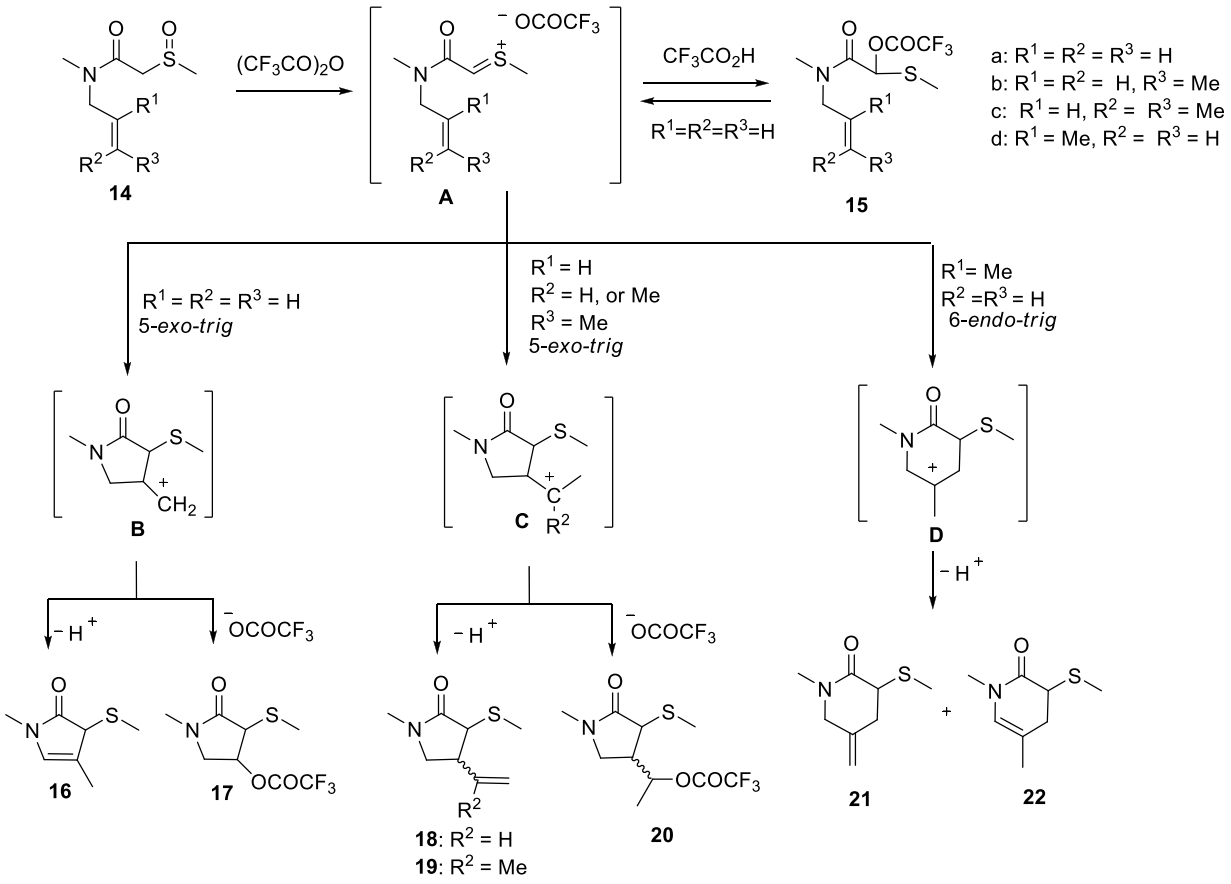
11 **12** **13**

Figure 2. Types of thiofunctionalized γ-lactams

2. SYNTHESIS OF 3-THIOSUBSTITUTED γ-LACTAMS

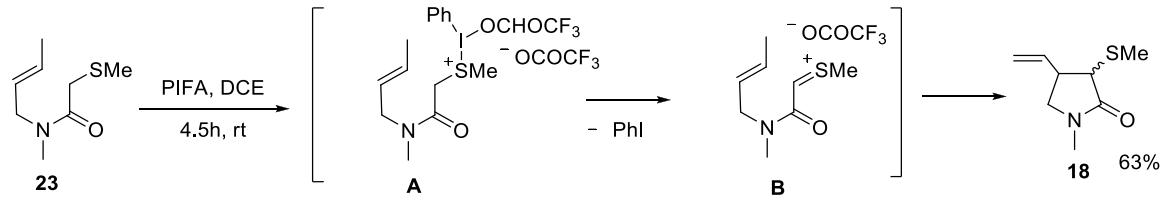
2-1. Intramolecular Cyclization of N,S-Containing Acyclic Substrates

The substrates found to be successfully used for the synthesis of 3-sulfanyl-substituted γ-lactams are N-2-alkenyl-N-methyl-α-(methylsulfinyl)acetamides (**14**), which under the action of trifluoroacetic anhydride generate Pummerer-type intermediates α-carbamoyl-α-thiocarbocations **A** (Scheme 1). The latter, depending on the nature of the substituents R^2 and R^3, undergo Pummerer rearrangement into α-trifluoroacetyloxy sulfides (**15**) or intramolecular attack of the allylic fragment, which results in 5-*exo*-*trig* or 6-*endo*-*trig* cyclization with the formation of **B**-**D** cations. The result of their stabilization, which occurs due to proton elimination or addition of an external nucleophile, is the formation of methylthio-containing γ-lactams (**16-20**) or δ-lactams (**21**,**22**).[26-29]



Scheme 1. The synthesis of methylthiosubstituted γ- and δ-lactams (**16**-**22**) from N-2-alkenyl-N-methyl-α-(methylsulfinyl)acetamides (**14**)

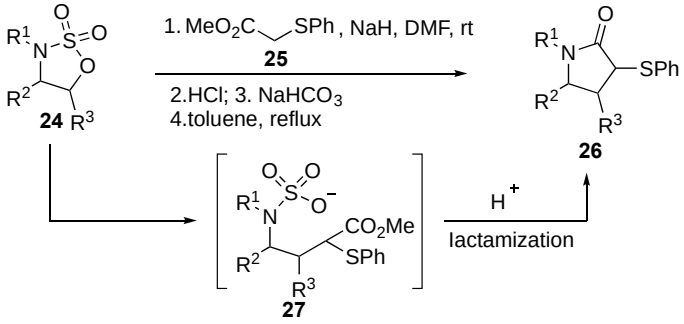
It is most likely that interaction of α-(methylthio)-N-allylacetamide (**23**) with such a common oxidizing reagent as phenyliodine bis(trifluoroacetate) (PIFA) also proceeds through the Pummerer reaction intermediate (**B**), which leads to 3-(methylthio)-4-vinylpyrrolidin-2-one (**18**) (Scheme 2).[30]



Scheme 2. The synthesis of 3-(methylthio)-4-vinylpyrrolidin-2-one (**18**) by PIFA-initiated Pummerer-type reaction

The substituted 1,2,3-oxathiazolidine S,S-dioxides (**24**) react with enolate derived from α-thioester (**25**) to form α-thiosubstituted lactams (**26**).[31] The reaction proceeds according to the scheme of nucleophilic opening of the oxathiazolidine ring and the formation of intermediate N-sulfates (**27**), acid hydrolysis of which initiates lactamization into the target products. In the case of enantiomerically pure oxathiazolidine

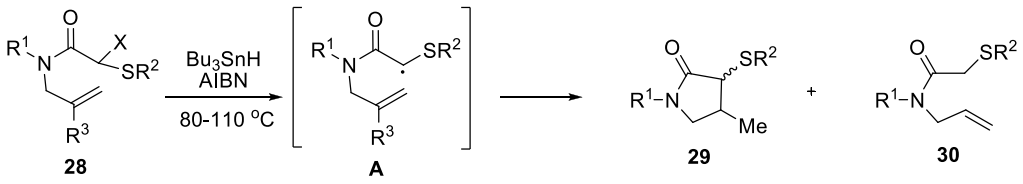
S,S-dioxides, an inversion was observed at the ring opening stage near the carbon atom which is the center of the nucleophilic attack (Scheme 3).



a: $R^1 = R^2$ = Bn, R^3 = H (4*S*)-**24** (3*R*,5*S*)-2 : (3*S*,5*S*)-**26** = 2 : 1 98% yield
b: $R^1 = R^2$ = Me, R^3 = Ph (4*S*,5*R*)-**24** (3*R*,4*S*,5*S*)-**26** : (3*S*,4*S*,5*S*)-**26** = 10 : 1 83% yield
c: $R^1 = R^2$ = Me, R^3 = Ph (4*R*,5*R*)-**24** (3*R*,4*S*,5*R*)-**26** : (3*S*,4*S*,5*R*)-**26** = 1 : 1 83% yield
d: $R^1 = R^3$ = Bn, R^2 = H rac-**24** 3 : 2 mixture of diastereomers 23% yield

Scheme 3. The synthesis of α-thiosubstituted lactams (**26)** from 1,2,3-oxathiazolidine S,S-dioxides (**24)**

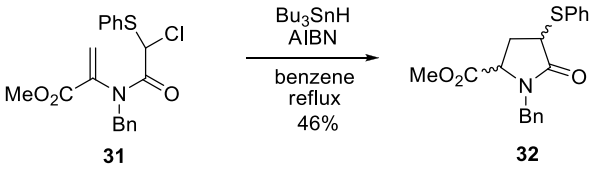
Bu_3SnH-AIBN-induced radical cyclization of N-alkenyl-α-chloro-α-(methylthio)acetamides proved to be a good method for the synthesis of a number of 3-thiosubstituted γ-butyrolactams.[32-36] For instance, these conditions are suitanle for 5-*exo*-cyclization of N-allyl(methallyl)-α-chloro-α-(methylthio)acetamides (**28**) into methyl-3-methylthiopyrrolidin-2(l*H*)-ones (**29**), obtained in 68-90% yields as a mixture of *trans/cis* stereoisomers, along with the classical reduction products (**30**) (Scheme 4). It was found that stabilization of the radical intermediate **A** by a sulfanyl substituent is crucial in the realization of such cyclization of **28**. The nature of the substituents at nitrogen atom of the amides (**28**) was determined influences the reaction, and it was shown that no cyclization product is formed in case of R^1=H, whereas an increase in the substituent size positively affects the yield of the target products (**29**).[33] Since phenylthio group is also a good leaving group in radical reactions, dithioacetal (**28**) (SR^2 = X = SPh) tested under similar conditions is also transformed into a mixture of *trans*- and *cis*-lactams (**29**) (SR^2 = SPh) in 48 and 14% yields, respectively.



R^1 = Me, CH_2Ph, Ph, H
R^2 = Me, Ph
R^3 = H, Me
X = Cl, SPh

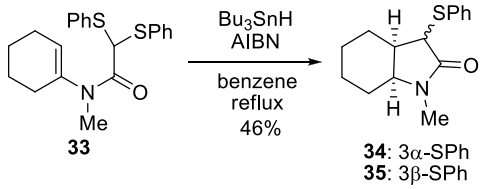
Scheme 4. The synthesis of methyl-3-methylthiopyrrolidin-2(l*H*)-ones (**29**) *via* Bu_3SnH-AIBN-induced radical cyclization

Bu_3SnH-AIBN-induced radical 5-*endo-trig* cyclization of methyl 2-(N-benzyl-2-chloro-2-(phenylthio)acetamido)acrylate (**31**) was successful in the synthesis of 4-phenylthiopyroglutamate (**32**) which is formed as a mixture of diastereomers in a ratio of 1.5:1 (Scheme 5).[35]



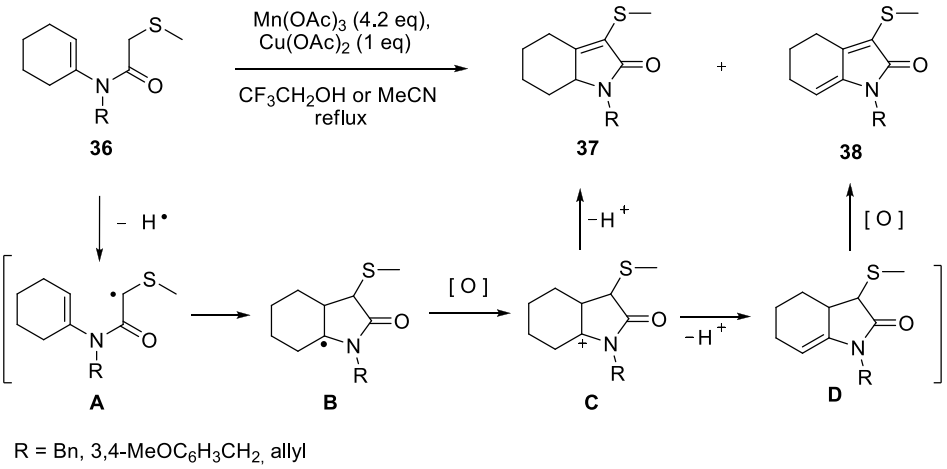
Scheme 5. The synthesis of 4-phenylthiopyroglutamate (**32**) *via* Bu_3SnH-AIBN-induced radical cyclization

A similar reaction involving N-cyclohexenyl-N-methyl-2,2-bis(phenylthio)acetamide (**33**) proceeds according to the 5-*endo-trig* scheme and results in 3-thiosubstituted carboannelated butyrolactams (**34**) and (**35**) as epimer pair with 30 and 29% yields, respectively (Scheme 6).[36]



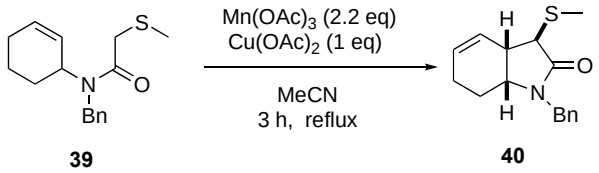
Scheme 6. The synthesis of (*3aR,7aS*)-1-methyl-3-(phenylthio)hexahydro-1*H*-indol-2(3*H*)-ones (**34**,**35**)

Ishibashi et al.[37] proposed to use a mixture of Mn(III) and Cu(II) acetates as a promoter of radical cyclization of N-(1-cyclohexen-1-yl)-α-(methylthio)acetamides (**36**) into carboannelated thiolactams (**37**) and (**38**) (Scheme 7). The plausible reaction mechanism involves the generation of carbamoylmethyl radical **A**, its subsequent cyclization to form α-acylamino radical **B**, which is then oxidized to acyliminium cation **C**. Deprotonation of the latter leads to lactams (**37**) and unstable tetrahydroindolones **D**, oxidized more deeply to products (**38**).



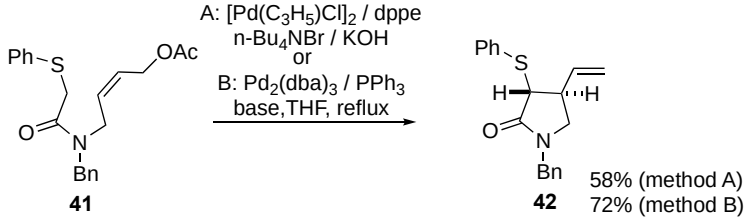
Scheme 7. The synthesis of 3-(methylthio)-5,6,7,7a-tetrahydro-1*H*-indol-2(4*H*)-ones (**37**) and 3-(methylthio)-5,6-dihydro-1*H*-indol-2(4*H*)-ones (**38**) by $Mn(OAc)_3/Cu(OAc)_2$ initiated radical cyclization

This method was also productive for N-(1-cyclohexen-1-yl)-α-(methylthio)acetamide (**39**), which under similar reaction conditions was cyclized according to the 5-*exo*-*trig* type to lactam (**40**) in 71% yield (Scheme 8).[37]



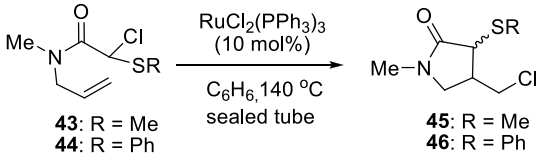
Scheme 8. The synthesis of (*3R*,*3aS*,*7aR*)-1-benzyl-3-(methylthio)-3,3a,7,7a-tetrahydro-1*H*-indol-2(6*H*)-one (**40**) by $Mn(OAc)_3/Cu(OAc)_2$ initiated radical cyclization

The authors[38,39] have developed the efficient route of the construction of 3-phenylthiosubstituted γ-lactam (**42**) *via* intramolecular Pd(0)-catalyzed allyl alkylation of unsaturated α-phenylthioacetamide (**41**) (Scheme 9). It was found that the reaction under conditions of heterogeneous catalysis with$[Pd(C_3H_5)Cl]_2$/dppe/KOH/n-$Bu_4NBr/CH_2Cl_2/H_2O$ (method A) is characterized by a higher yield of the target product compared to the catalysis by the $Pd_2(dba)_3/PPh_3$/base/THF system (method B).



Scheme 9. The synthesis of (*3RS*,*4SR*)-1-benzyl-3-(phenylthio)-4-vinylpyrrolidin-2-one (**42**) by intramolecular Pd(0)-catalyzed allyl alkylation of **41**

Another approach to synthesis of 4-chloromethyl-3-thiolactams (**45**,**46**) is ruthenium-catalyzed cyclization of N-allyl-α-chloro-α-thioacetamides (**43**,**44**)[40,41] that was performed at 140 °C and is accompanied by the transfer of chlorine atom to the terminal carbon atom of the double bond (Scheme 10). In this case, the target products (**45**,**46**) are formed in 57-62% yields as a mixture of *cis*- and *trans*-isomers in the ratio of 3:7 (6:4), respectively.



43: R = Me
44: R = Ph

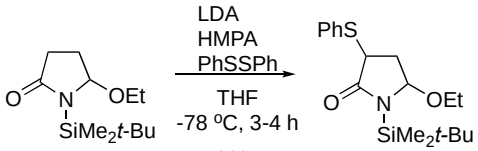
45: R = Me
46: R = Ph

Scheme 10. The synthesis of 3-thiosubstituted 4-(chloromethyl)-1-methylpyrrolidin-2-ones (**45**,**46**) by ruthenium-catalyzed cyclization of N-allyl-α-chloro-α-thioacetamides (**43**,**44**)

2-2. 3-Thiofunctionalization of γ-Lactams

Another appropriate strategy for obtaining of 3-thiosubstituted γ-lactams is based on the selective exo-functionalization of an already formed lactam framework with a sulfanyl group. The advantage of this approach is the possibility of diversifying S-alkyl substituents.

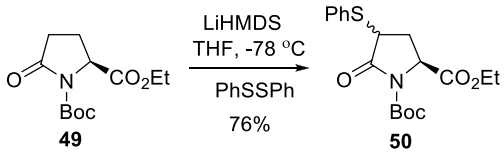
The direct introduction of a sulfanyl substituent into the 3-position of the pyrrolidone nucleus is possible due to increased acidity of the corresponding protons caused by the influence of the neighboring carbonyl group. The action of strong lithium bases on γ-lactams with a pre-protected nitrogen atom leads to α-deprotonation with formation of lithium enolate which is then attacked by a sulfanyl-containing electrophile. For instance, the treatment of N-silylated lactam (**47**) consecutively with lithium diisopropylamide (LDA) and diphenyl disulfide leads to 3-(phenylthio)pyrrolidone (**48**) in high yields (Scheme 11).[42]



47 **48**

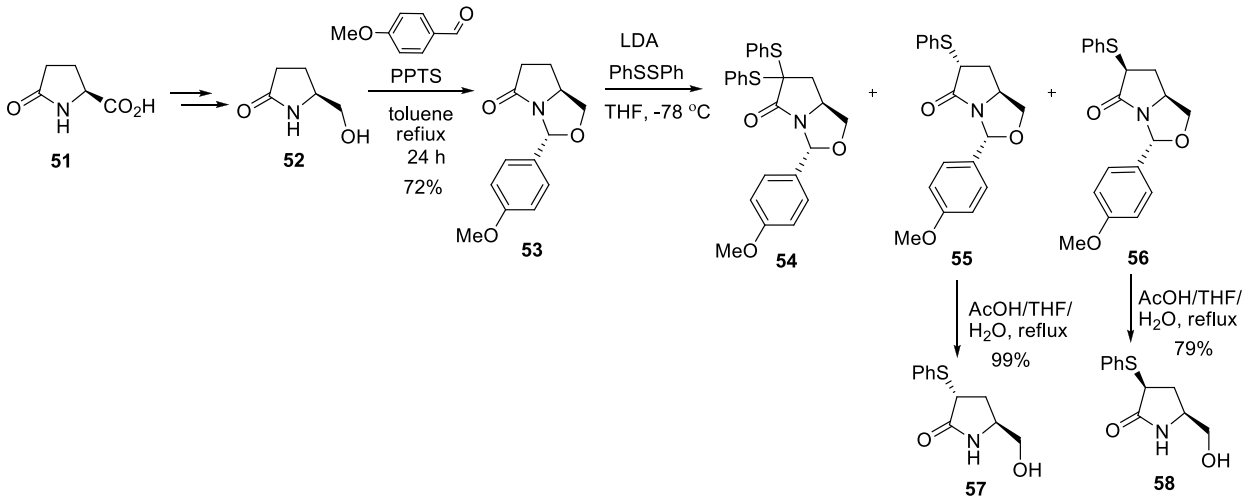
Scheme 11. The synthesis of 1-(*tert*-butyldimethylsilyl)-5-ethoxy-3-(phenylthio)pyrrolidin-2-one (**48**)

Ethyl N-Boc-(L)-pyroglutamate (**49**) is a convenient substrate for the preparation of optically active 3-phenylsulfanylbutyrolactams (Scheme 12).[43,44] The enolate of **49** was generated by action of LiHMDS in THF at -78 °C, with subsequent addition of PhSSPh which resulted in a mixture of diastereomeric 4-phenylthiopyroglutamates (**50**) (2:1) in 76% yield.



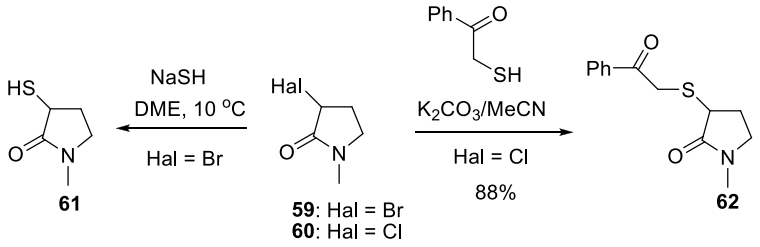
Scheme 12. The synthesis of diastereomeric ethyl N-Boc-4-phenylthiopyroglutamates (**50**)

An approach to chiral 3-phenylthiopyrrolidinones based on the use of easily available (S)-pyroglutamic acid (**51**) was developed (Scheme 13).[45] To avoid racemization during the reactions, it was converted in two steps to the 5-(S)-hydroxymethyl derivative (**52**) followed by its N,O-acetal protection with p-methoxybenzaldehyde, resulting in pyrrolooxazolone (**53**). Further interaction of **53** with 3 eq. of PhSSPh in the presence of LDA (3 eq.) led to di- and monosulfanylated products (**54-56**) in a ratio of 2:1:1, respectively. At the same time, when using 1.2 equivalents of PhSSPh and LDA, mainly epimers (**55**) and (**56**) were formed in a ratio of 4:3. Deprotection of **55**,**56** by boiling in AcOH/THF/water (3:7:1) afforded optically active (*3R,5S*)- and (*3S,5S*)-hydroxymethyl-3-phenylthiopyrrolidinones (**57**) and (**58**).



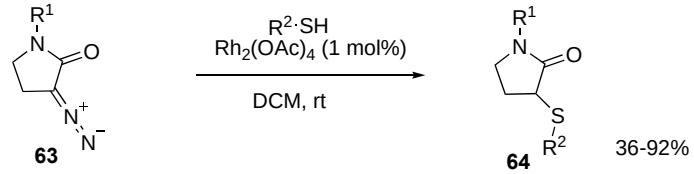
Scheme 13. The synthesis of (*3R,5S*)- and (*3S,5S*)-hydroxymethyl-3-phenylthiopyrrolidinones (**57**) and (**58**) from (*S*)-pyroglutamic acid (**51**)

Another synthesis version of 3-thiofunctionalized lactams is the substitution of a halogen atom in halogenolactams with nucleophilic sulfur-containing reagents, although this method is not widely used.[47-49] For example, 3-mercaptobutyrolactam (**61**) was obtained in 78% yield by reaction of lactam (**59**) with sodium hydrosulfide (Scheme 14).[46] Likewise, sulfide (**62**) was synthesized from 3-chloro-N-methylbutyrolactam (**60**) and phenacylmercaptan in the presence of potassium carbonate.[49]



Scheme 14. The synthesis of 3-mercapto-1-methylpyrrolidin-2-one (**61**) and 1-methyl-3-(2-oxo-2-phenylethylthio)pyrrolidin-2-one (**62**) from halogenolactams (**59**,**60**)

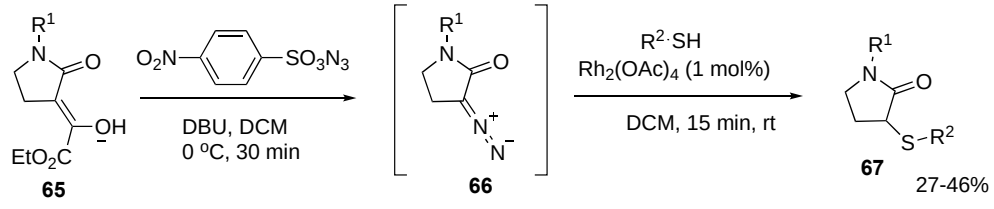
Recently,[48,49] an elegant method of introducing sulfanyl substituents at position 3 of γ-lactams by $Rh_2(OAc)_4$-catalyzed coupling of the corresponding N-aryldiazo derivatives (**63**) with various thiols was proposed (Scheme 15). It was found that such transformations occur in high or moderate yields that are almost independent of the electronic parameters of the N-aryl substituent and are tolerant to sterically hindered thiols.



R^1 = Ph, 4-$MeOC_6H_4CH_2$, 4-CNC_6H_4, 3-$CF_3C_6H_4$, 4-BrC_6H_4, thiazol-2-yl
R^2 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, Cy, CH_2CO_2Me, Bn, *t*-Bu, CH_2CH_2SH, $CH_2(CH_2)_2SH$, benzo[*d*]thiazol-2-yl

Scheme 15. 3-Thiofunctionalization of N-aryl-γ-lactams (**64**) by $Rh_2(OAc)_4$-catalyzed coupling of N-aryldiazo-γ-lactams (**63**) with thiols

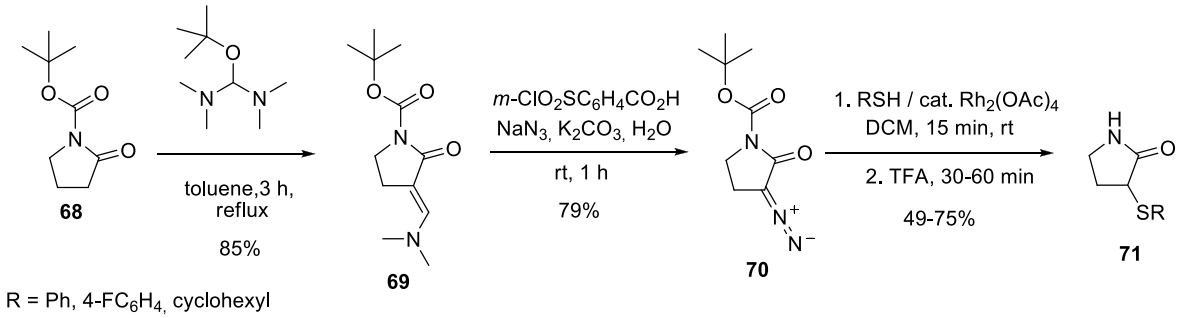
Indeed, in the case of less stable N-alkyl-α-diazo-γ-lactams (**66**), a protocol for their *in situ* use in the reaction with thiols was developed.[50] Accordingly, N-alkyl-α-alkenyl-γ-lactams (**65**) were treated with 4-nitrobenzenesulfonyl azide in the presence of DBU, and after rapid filtration of diazo compounds (**66**) through a plug of alumina, thiol was added together with $Rh_2(OAc)_4$ catalyst, producing α-thiosubstituted γ-lactams (**67**) in moderate yields (Scheme 16).



R^1 = Me, *i*-Pr, 4-$MeOC_6H_4CH_2$; R^2 = Ph, Cy, CH_2CO_2Me, Bn, 4-C_6H_5

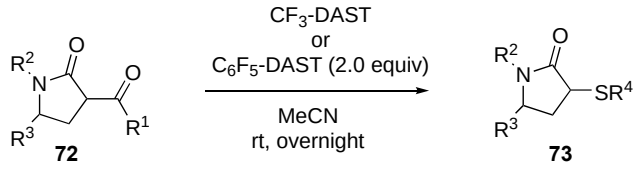
Scheme 16. The synthesis of 3-thiosubstituted N-alkyl-γ-lactams (**67**) by $Rh_2(OAc)_4$-catalyzed coupling of N-alkyl-α-diazo-γ-lactams (**66**) with thiols

N-Boc-protected 3-diazo-2-oxopyrrolidine (**70**) synthesized in two steps from lactam (**68**) proved to be a convenient substrate for the preparation of N-unsubstituted 3-thiolactams (**71**).[51] Its interaction with thiols under $Rh_2(OAc)_4$ catalysis and subsequent deprotection leads to compounds (**71**) (Scheme 17).



Scheme 17. The synthesis of 3-thiosubstituted pyrrolidin-2-ones (**71**)

Tokunaga *et al.*[52] reported the synthesis of 3-trifluoromethyl(perfluorophenyl)thiolactams (**73**) *via* deacylative fluorothiolation of 3-acylpyrrolidinones (**72**) with CF_3- or C_6F_5-analogs of diethylaminosulfur trifluoride (CF_3-DAST or C_6F_5-DAST) (Scheme 18). It was established that the acyl variety (R^1=Ph, *i*-propyl, *n*-propyl) in the N-Boc substrate (**72**) does not significantly affect the yield of the target product (**73**), unlike the nitrogen substituent R^2 (84% for R^2=Boc, 61% for R^2=Ts, 26% for R^2=Bn).



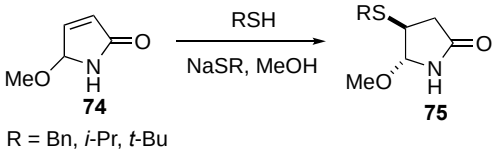
1: R^1 = Ph, *n*-Pr, *i*-Pr; R^2 = Boc, Ts, Bn; R^3 = H, CO_2Me
2: R^2 = Boc, Ts, Bn; R^3 = H, CO_2Me, R^4 = CF_3, C_6F_5

Scheme 18. The synthesis of 3-trifluoromethyl(perfluorophenyl)thiolactams (**73**) *via* deacylative fluorothiolation of 3-acylpyrrolidinones (**72**)

3. SYNTHESIS OF 4-THIOSUBSTITUTED γ-LACTAMS

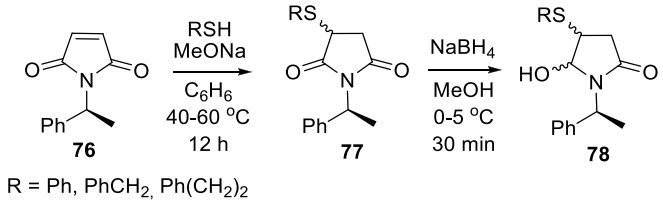
3-1. Thiofunctionalization of 2-Oxopyrrolines and 2-Oxopyrrolidines

One of the widely used approaches to introduce a sulfanyl function into the structure of a heterocycle is the addition of a corresponding thiol to the activated multiple C=C bond. The success of this method of synthesis of 4-thiosubstituted pyrrolidinones is associated with the unambiguous regiochemistry of the conjugated nucleophilic addition to pyrrol-2(5*H*)-ones.[53-55] For instance, the addition of thiols to 5-substituted pyrrolidinones (**74**) in the presence of the corresponding sodium thiolate leads to 4-alkylthiofunctionalized pyrrolidinones (**75**) with *trans*-stereochemistry of 4,5-substituents in 63-90% yields (Scheme 19).[53]



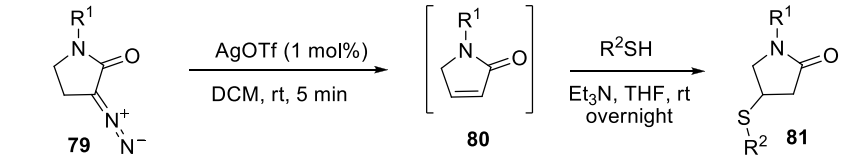
Scheme 19. The synthesis of *trans*-5-methoxy-4-(alkylthio)pyrrolidin-2-ones (**75**) by addition of thiols to 5-methoxy-1*H*-pyrrol-2(5*H*)-one (**74**)

The regioselective reduction of chiral succinimide (**77**) obtained by thiolation of (1-phenylethyl)maleimide (**76**) produced 5-hydroxy-4-thiolactams (**78**) as a mixture of diastereomers in 69-82% yields (Scheme 20).[56]



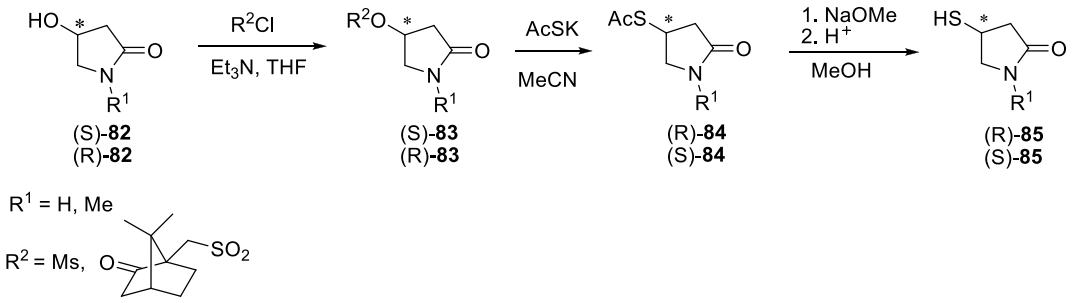
Scheme 20. The synthesis of diastereomeric 5-hydroxy-4-(methylthio)-1-(1-phenylethyl)pyrrolidin-2-ones (**78**)

A one-pot two-step synthesis of β-aryl(alkyl)thiolactams (**81**) from α-diazo-γ-lactams (**79**) was proposed (Scheme 21).[48] In the first stage of this process, in the presence of catalytic amounts of silver triflate, 3-pyrrolin-2-ones (**80**) were formed, which then were treated with thiols without isolation.



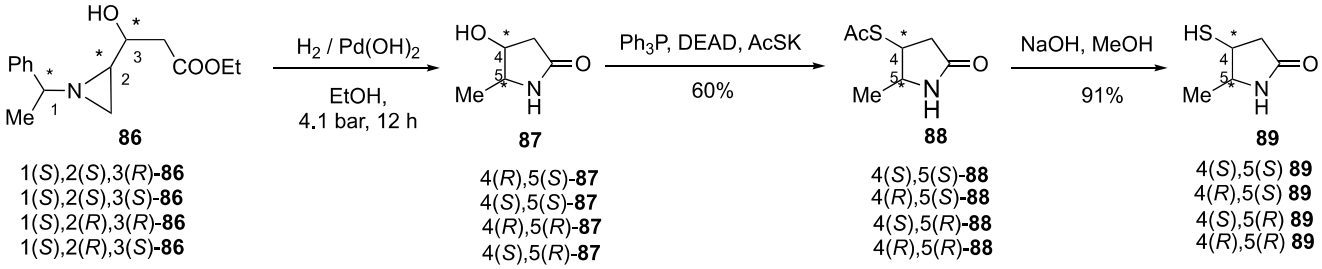
Scheme 21. The synthesis of 4-aryl(alkyl)thiolactams (**81**) from 3-diazopyrrolidin-2-ones (**79**)

The 4-sulfanyl substituent can also be introduced into the structure of an already formed lactam ring by stereoselective substitution of the hydroxyl group through intermediate sulfonates or under Mitsunobu reaction conditions.[57-61] Thus, the reaction of chiral 5-oxopyrrolidin-3-yl methanesulfonate[57,58] or camphorsulfonates[59] (**83**) with potassium thioacetate followed by deacetylation of products (**84**) resulted in optically pure (*R*)- and (*S*)-4-mercapto derivatives (**85**) (Scheme 22).



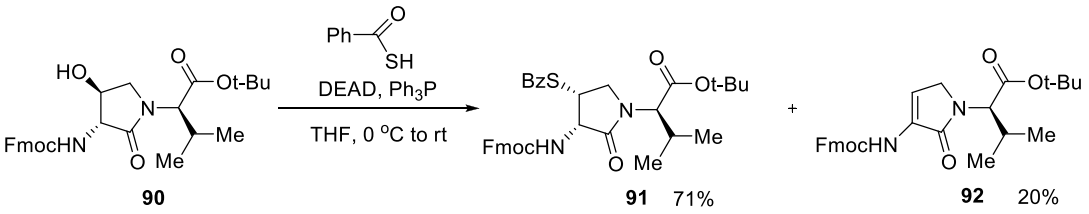
Scheme 22. The synthesis of (*R*)- and (*S*)-4-mercapto-1-methylpyrrolidin-2-ones (**85**) from (*S*)- and (*R*)-4-hydroxypyrrolidin-2-one (**82**)

The authors[60] described a somewhat similar synthesis of chiral 4-thiofunctionalized γ-lactams (**89**) which is based on regioselective reductive cleavage-cyclization by Pd-catalyzed hydrogenation of diastereomeric hydroxyaziridine (**86**) to 4-hydroxypyrrolidinones (**87**) (Scheme 23). Further Mitsunobu thioesterification of (**87**) followed by deacetylation of thioacetates (**88)** gave the target mercaptolactams (**89**) in 91% yields.



Scheme 23. The synthesis of chiral 4-mercapto-5-methylpyrrolidin-2-ones (**89**) from hydroxyaziridine (**86**)

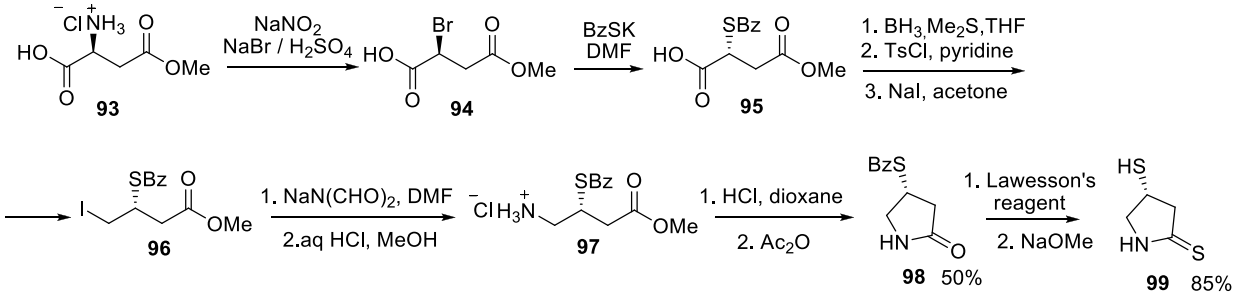
The Mitsunobu reaction was also used for the stereoselective synthesis of β-thiosubstituted α-N-(Fmoc)amino-γ-lactam dipeptide (**91**) from (3*R*,4*S*)-hydroxylactam (**90**), since it is characterized by minor side reaction of β-elimination with the formation of pyrrolinone (**92**) (Scheme 24).[61]



Scheme 24. The synthesis of *tert*-butyl-2-((3*S*,4*R*)-3-((Fmoc)amino)-4-(benzoylthio)-2-oxopyrrolidin-1-yl)-3-methylbutanoate (**91**) from (3*R*,4*S*)-hydroxylactam (**90**)

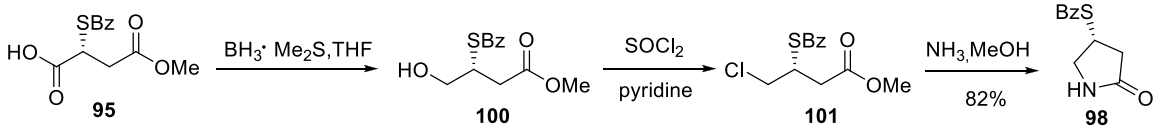
3-2. Lactamization of Sulfanyl-Containing Substrates

The synthesis of linear thiofunctionalized substrates was important to implement this approach, especially with a defined configuration of chiral centers. Natural chiral compounds were most often used as starting substances for this purpose, and the resulting optically active thiopyrrolidinones served as building blocks for the preparation of pharmacologically valuable objects. In particular, aspartic acid was proposed as an available substrate for a number of simple stereoselective reactions leading to β-acylthio-γ-lactams and their mercapto analogues which are promising molecular platforms for the design of carbapenem antibiotics.[62,63] For instance, the stepwise transformation of the (*L*)-aspartic acid esterhydrochloride (**93**) through intermediate esters (**94-96**) yielded (*R*)-4-amino-3-benzoylthiobutyric acid (**97**), the cyclization of which in acetic anhydride led to (*R*)-4-benzoylthio-γ-lactam (**98**) (Scheme 25).[62] Thionation of the latter with Lawesson's reagent followed by removal of the S-benzoyl group with sodium methylate resulted in mercaptopyrrolidine-2-thione (**99**).



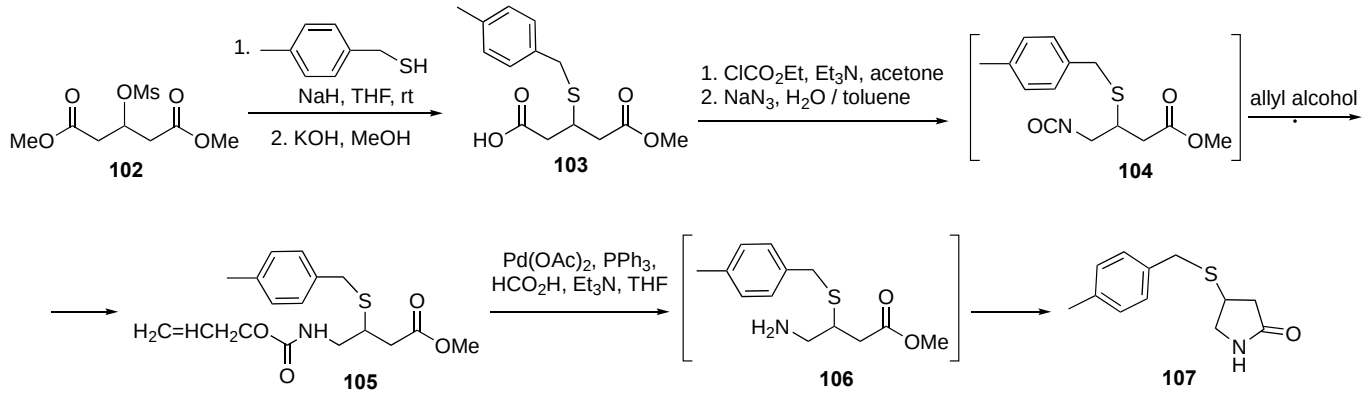
Scheme 25. The synthesis of (*R*)-S-5-oxopyrrolidin-3-yl benzothioate (**98**) and (*R*)-4-mercaptopyrrolidine-2-thione (**99**) by (*R*)-4-amino-3-benzoylthiobutyric acid (**97**) lactamization

Alternatively, reduction followed by nucleophilic substitution of (*R*)-benzoylthiomonomethyl succinate (**95**) yielded 4-chlorobutanoic acid derivative (**101**), which is easily cyclized in a methanolic ammonia solution resulting in thiolactam (**98**) (Scheme 26).[63]



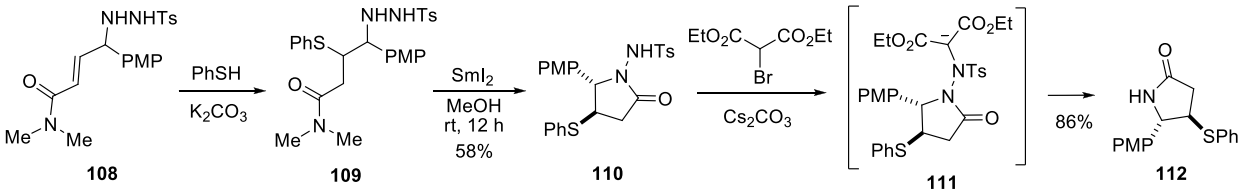
Scheme 26. The synthesis of (*R*)-S-5-oxopyrrolidin-3-yl benzothioate (**98**) from (*R*)-benzoylthiomonomethylsuccinate (**95**)

Hirai et al. reported the synthesis of carbamate (**105**) by thiolation of dimethyl 3-mesyloxyglutarate (**102**), with subsequent Curtius rearrangement of the intermediate azide and treatment of the resulting isocyanate (**104**) with allyl alcohol (Scheme 27).[64] The 4-amino-3-(4-methylbenzyl)thiobutyric acid methyl ester (**106**) generated from **105** easily underwent lactamization to 4-thiosubstituted lactam (**107**).



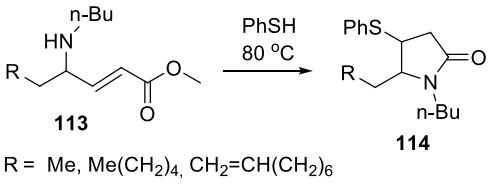
Scheme 27. The synthesis of 4-(4-methylbenzylthio)pyrrolidin-2-one (**107**) from 3-mesyloxy glutaric acid (**102**)

The synthesis of the sulfanyl-containing derivative (**109**) of butanoic acid as 2:1 mixture of diastereomers was achieved by the conjugate addition of thiophenol to enamide (**108**) (Scheme 28).[65] Its treatment with SmI_2 as Lewis acid resulted in cyclization to 4-phenylthiopyrrolidinone (**110**) obtained as a single diastereomer. Further N–N bond cleavage in tosylhydrazine fragment *via* alkylation with bromomalonic ester followed by E1cb-elimination produced thiolactam (**112**) in 86% yield.



Scheme 28. The synthesis of 5-(4-methoxyphenyl)-4-(phenylthio)pyrrolidin-2-one (**112**) from enamide (**108**)

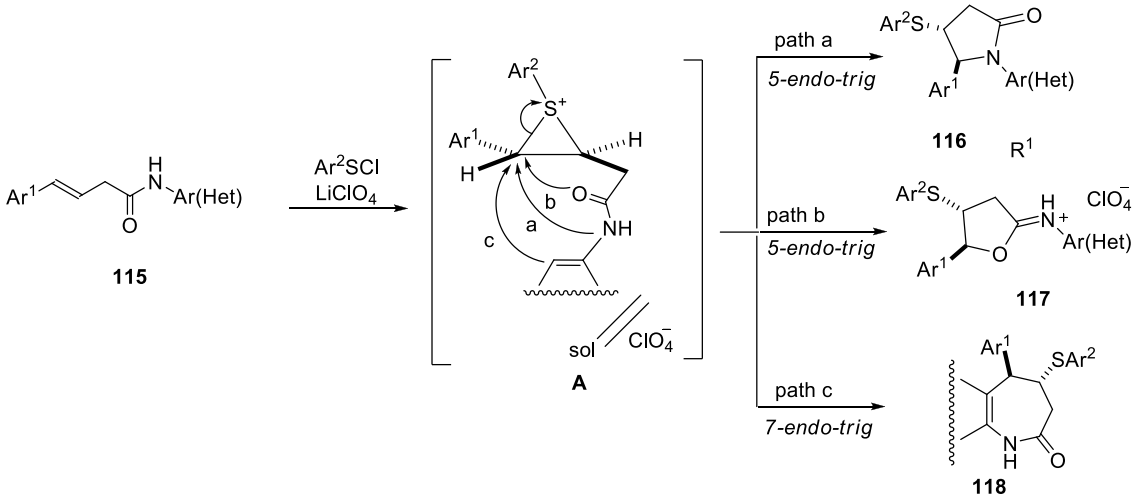
The reaction of thiophenol with enaminoesters (**113**) at 80 °C did not stop at the stage of the formation of addition products but was followed by their further lactamization to 4-phenylthiopyrrolidinones (**114**) (Scheme 29).[68]



Scheme 29. The synthesis of 1-butyl-4-(phenylthio)pyrrolidin-2-ones (**114**) from (*E*)-methyl 4-(butylamino)pent-2-enoates (**113**)

3-3. Cyclothiofunctionalization of Carboxylic Acid Derivatives

Intramolecular cyclization of unsaturated carboxylic acid amides induced by sulfanyl-containing electrophiles has become a convenient tool for the synthesis of thiofunctionalized heterocycles.[67,68] The most successful substrates for the preparation of β-sulfanyl-containing γ-lactams in such reactions were aryl(heteryl)amides of styrylacetic acids (**115**) (Scheme 30).[69-71] Their peculiarity in $LiClO_4$-promoted reactions with arylsulfenyl chlorides is the competing directions of cyclization to N, O, and C atoms to form lactams (**116**), iminolactones (**117**), and azepinones (**118**). High diastereoselectivity of cyclosulfenylation is due to the reaction mechanism which proceeds through the formation of a cyclic episulfonium intermediate followed by *trans*-attack by an internal nucleophile.

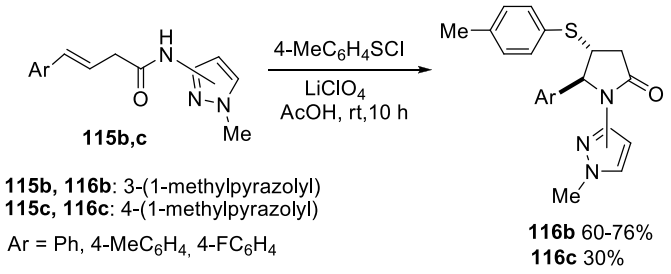


Scheme 30. Three pathways of intramolecular cyclization of aryl(heteryl)amides of styrylacetic acids (**115**) with arylsulfenyl chlorides

The regioselectivity of cyclization is largely determined by the nature of the substrate and electrophilic reagent. For instance, the formation of *trans*-1,5-diaryl-4-arylthiopyrrolidin-2-ones (**116a**) according to the 5-*endo-trig* cyclization scheme in 60-66% yields is typical of the reaction of phenyl- and 4-tolylsulfenyl chlorides with styrylacetanilides (**115a**) with donor *para*-substituents in the N-arylamide fragment (Scheme 31).[69]

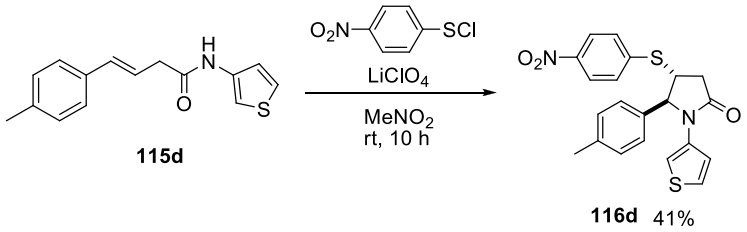
Scheme 31. The synthesis of *trans*-1,5-diaryl-4-arylthiopyrrolidin-2-ones (**116a**) by intramolecular cyclization of styrylacetanilides (**115a**) with ArSCl

Cyclization to nitrogen atom with formation of thiopyrrolidinones (**116b**) was also the main direction in the interaction of 4-tolylsulfenyl chloride with N-(3-pyrazolyl)styrylacetamides (**115b**) (Scheme 32).[70] Whereas for their 4-pyrazolyl-substituted analogs (**115c**), the cyclization to oxygen atom was dominant, and the yields of γ-lactams (**116c**) were only 30%.



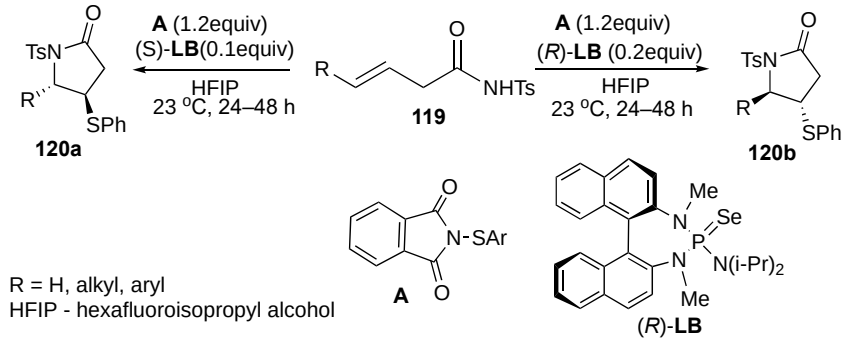
Scheme 32. The synthesis of 1-(1-methylpyrazolyl)-5-aryl-4-(*p*-tolylthio)pyrrolidin-2-ones (**116b**,**c**) by intramolecular cyclization of N-(pyrazolyl)styrylacetamides (**115b**,**c**) with 4-MeC_6H_4SCl

The predominant formation of 4-arylthiolactam (**116d**) was also achieved by the interaction of N-(3-thienyl)methylstyrylacetamide (**115d**) with 4-nitrophenylsulfenyl chloride (Scheme 33).[71]



Scheme 33. The synthesis of *trans*-4-(4-nitrophenylthio)-1-(thiophen-3-yl)-5-*p*-tolylpyrrolidin-2-one (**116d**) from N-(thiophen-3-yl)-4-*p*-tolylbut-3-enamide (**115d**)

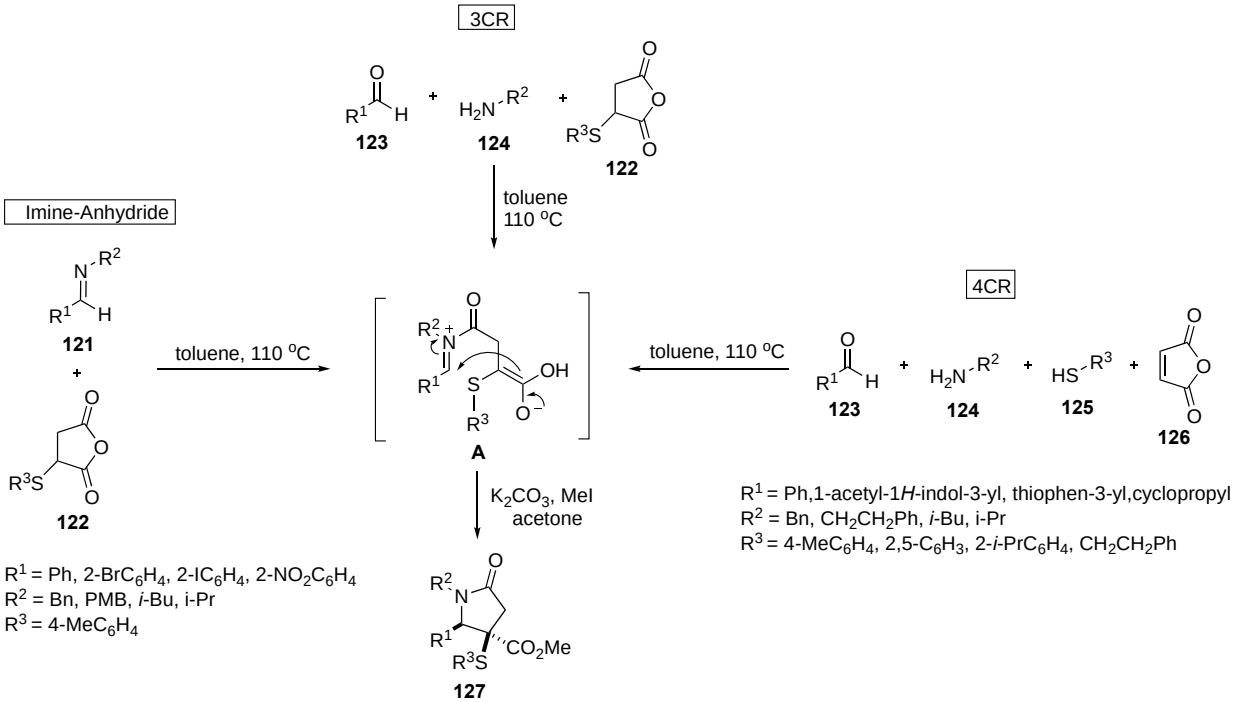
Panger and Denmark have recently developed a catalytic enantioselective variant of the cyclosulfenylation of alkenylamides (**119**) with N-arylsulfenylphthalimides (Scheme 34).[72] The use of a chiral selenophosphoramidate Lewis base catalyst (LB) resulted in optically active 4-arylthio-γ-lactams (**120a**,**b**) with 80-96% ee.



Scheme 34. The enantioselective synthesis of (4*R*,5*S*)- and (4*S*,5*R*)-4-(arylthio)-1-tosylpyrrolidin-2-ones (**120a**,**b**)

3-4. Modified Castagnoli-Cushman Reaction

Shaw et al. developed an efficient diastereoselective method for the preparation of 4-arylthiosubstituted 4-carboxy-γ-lactams (**127**) by the interaction of aldimines (**121**) with 2-arylthiosubstituted succinic anhydrides (**122**)[73] which is a modified version of the Castagnoli-Cushman reaction (Scheme 35).[74-76] Later, the method was modified into multicomponent variants: condensation of amines (**123**) with aldehydes (**124**) and 2-arylthiosuccinic anhydrides (**122**) (three-component reaction, 3CR) or the precursors of the latter, thiols (**125**) and maleic anhydride (**126**) (four-component reaction, 4CR).[77] It is suggested that high diastereoselectivity of the process is determined by the steric and electronic effects of the thiolsubstituent which stabilizes the enol intermediate **A**.



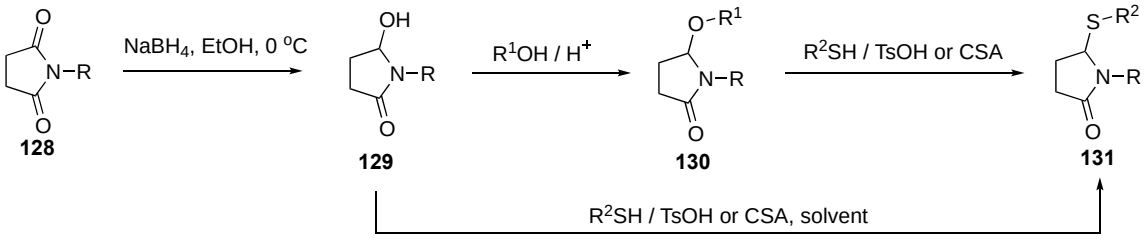
Scheme 35. The synthesis of (2*RS*,3*RS*)-methyl 1-methyl-5-oxo-2-aryl-3-(aryl(alkyl)thio)pyrrolidine-3-carboxylates (**127**) by modified Castagnoli-Cushman Reaction

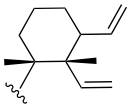
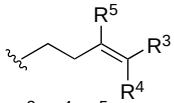
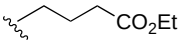
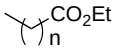
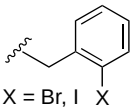
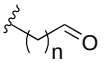
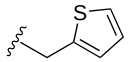
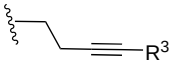
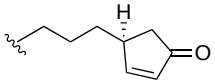
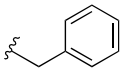
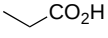
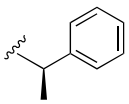
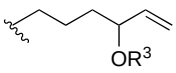
The proposed 4CR also makes it possible to obtain N-unsubstituted analogs of lactams (**127**) using NH_4OAc as an amino component, although in this case the process lacks high yields.[78] A study to evaluate the effectiveness of chiral thiols on the stereocontrol of 4CR and its imino anhydride variant deserves attention.[79] High *syn/anti*-selectivity in the formation of two lactam stereogenic centers was found, although the products were isolated in low yields and moderate selectivity for the chiral center near the thiol group (dr = 51:49 to 64:36).

4. SYNTHESIS OF 5-THIOSUBSTITUTED γ-LACTAMS

4-1. Sulphenylation of 5-Hydroxy-Substituted Pyrrolidinones

Convenient substrates for the synthesis of 5-thiolactams (**131**) are 5-alkoxypyrrolidinones (**130**) which were obtained from succinimides (**128**) *via* hydroxy derivatives (**129**) (Scheme 36).[80-86] The interaction of alkoxylactams (**130**) with thiols in the presence of a catalytic amount of camphorsulfonic acid (CSA) or *para*-toluenesulfonic acid (TsOH) resulted in the formation of the target sulfides (**131**) in high yields. It was demonstrated that thiolactams (**131**) can also be prepared by direct nucleophilic substitution of hydroxypyrrolidinones (**129**) with thiols (Scheme 36).[87-93] The availability of reagents, ease of manipulation, and high yields allow the synthesis of 5-sulfanyl-γ-lactams by these protocols in quantities sufficient for their use as building blocks in the total synthesis of many natural compounds. Recently a modified solvent-free method for the sulfenylation of alkoxylactams using CsF (5 mol%) as a catalyst in a moderate vacuum (30 mm Hg) at 80 °C was proposed.[94,95]

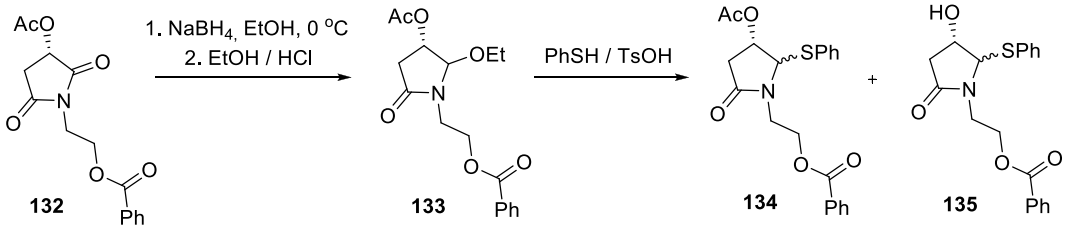


R	R^1	R^2	Substrate for synthesis **131**	yeild, %	Reference
	Et	Ph	from **130**	61%	80
 R^3, R^4, R^5 = H or Me	Et	Ph	from **130**	83-88%	81
	Et	Ph	from **130**		82,83
H	Et	 n = 1, 2	from **130**		84
 X = Br, I	Et	Me, t-Bu	from **130**		85
 n = 2, 3	Me	Ph	from **130**		86
	–		from **129**		87
 R^3 = H, *n*-Pr, *i*-Pr, $SiMe_3$,$C(Me)_2OMe$	–	Ph	from **129**	77-94%	88
	–	Ph	from **129**	70%	89
	–		from **129**	89%	90
	–	Ph	from **129**	92%	91
 1-3: R^3 = TBS; 4: R^3 = H	–	Ph	from **129**	87%	92, 93

Scheme 36. The synthesis of 5-thiosubstituted pyrrolidin-2-ones (**131**) from succinimides (**128**)

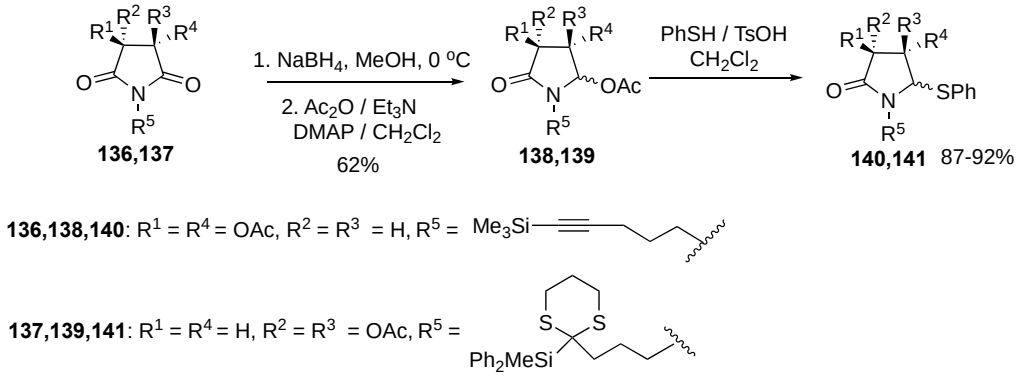
The general nature of the above method was successfully applied in the synthesis of optically active 5-phenylsulfanylpyrrolidinones based on malic acid imides (**132**) (Scheme 37).[96-103] An interesting

example of such reactions is the selective substitution of the ethoxy group of chiral 4-acetyloxy-5-ethoxypyrrolidinone (**133**) under the action of thiophenol with formation of sulfanyl-substituted products (**134**) and (**135**) in a ratio of 1:1.9 in 76.2% yield.[98,99]



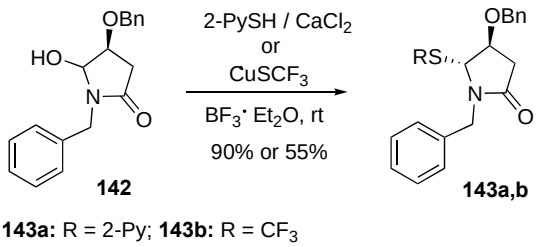
Scheme 37. The synthesis of 2-(5-oxo-2-(phenylthio)pyrrolidin-1-yl)ethyl benzoates (**134**,**135**)

Likewise, *via* triacetyloxypyrrolidinones (**138**,**139**) derived from D- and L-tartaric acid imides (**136**,**137**) 5-thiolactams (**140**,**141**) were obtained (Scheme 38).[97,102]



Scheme 38. The synthesis of (3*S*,4*S*)- and (3*R*,4*R*)-2-oxo-5-(phenylthio)pyrrolidine-3,4-diyl diacetates (**140**,**141**) from imides (**136**,**137**)

The authors[103] proposed to use Lewis acid ($BF_3 \cdot OEt_2$) activation instead of Brønsted acid for the sulfanylation of hydroxylactam (**142**). Such an interaction of **142** with 2-mercaptopyridine yielded 2-pyridyl sulfide (**143a**) as a mixture of diastereomers in a 2:1 ratio (90% yield) with 4,5-*trans* geometry of the main product (Scheme 39). Trifluoromethylthiopyrrolidinone (**143b**) was synthesized by a similar procedure using $CuSCF_3$.[104]

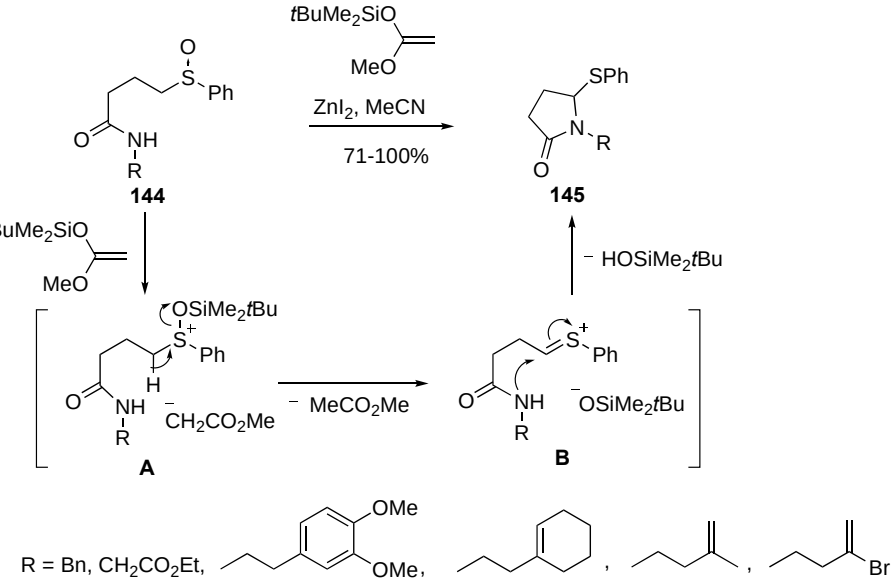


143a: R = 2-Py; **143b:** R = CF_3

Scheme 39. The synthesis of (4*S*,5*R*)-1-benzyl-4-(benzyloxy)-5-thiopyrrolidin-2-ones (**143a**,**b**) from hydroxylactam (**142**)

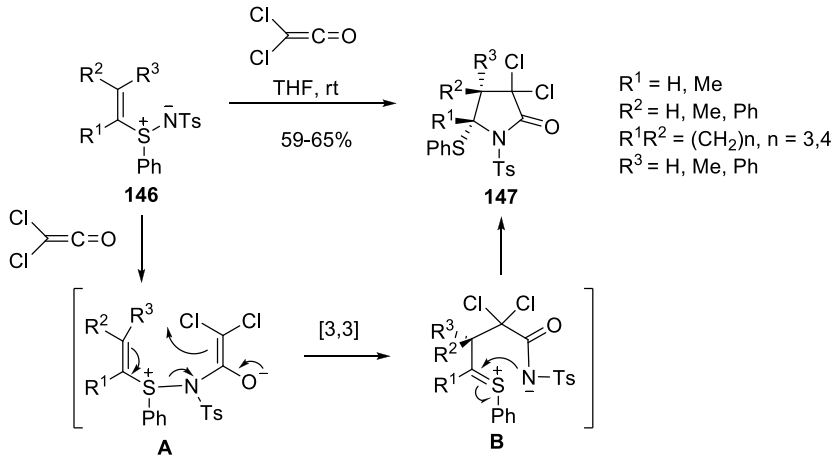
4-2. Intramolecular Cyclization of N,S-Containing Acyclic Substrates

The effective methods for the synthesis of 5-phenylthio-substituted lactams (**145**) include the intramolecular Pummerer reaction of amido-sulfoxides (**144**) induced by 1-(*tert*-butyldimethylsiloxy)-1-methoxyethylene in the presence of catalytic amounts of ZnI_2 (Scheme 40).[105-107] This organosilicon additive has been found to play a key role in the lactamization process, since the formation of classical products of the intermolecular Pummerer reaction or complex mixtures was observed when the reaction was held in an acetic anhydride or in the TMSOTf/NEt_3 system. The proposed mechanism of this interaction involves the formation of silyloxysulfonium salt **A** and the subsequent generation of Pummerer intermediate **B**. Further cyclization occurs due to the attack of the nitrogen atom as an internal nucleophile on the α-carbon atom.



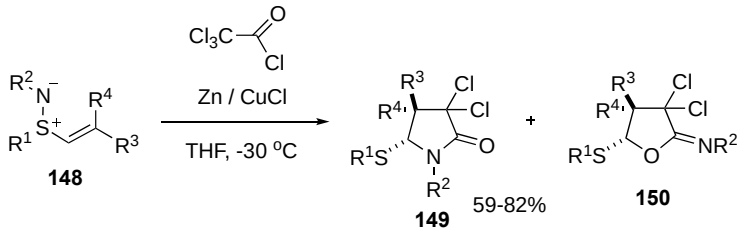
Scheme 40. The synthesis of 5-phenylthiolactams (**145**) *via* intramolecular Pummerer reaction of amido-sulfoxides (**144**)

Another approach to 5-thiosubstituted γ-lactams (**147**) is the reaction of dichloroketene with vinyl sulfilimines (**146**), nitrogen analogues of sulfoxides (Scheme 41).[108] At the first stage of this transformation, the sulfilimine is attached to ketene to form a zwitterionic intermediate **A**. The latter is transformed, in the [3,3]-sigmatropic rearrangement scheme, to a Pummerer-type thionium intermediate **B**, which is cyclized into the target pyrrolidinones (**147**). The reaction proceeds through a highly ordered pericyclic reaction transition state which ensures complete stereospecificity of the cyclization process resulting in the formation of different diastereomeric products from *Z*- and *E*-phenylstyrylsulfilimines (**146**).



Scheme 41. The synthesis of 3,3-dichloro-5-phenylthio-1-tosylpyrrolidin-2-ones (**147**) by reaction of vinyl sulfilimines (**146**) with dichloroketene

When studying the influence of electronic effects of N,S-substituents of vinyl sulfilimines (**148**) in the reaction with *in situ* generated dichloroketene on the yields and ratios of products of competitive lactamization and lactonization processes (**149**) and (**150**), respectively, it was found that S-alkyl and N-tosyl substituents usually direct the reaction towards the formation of lactams (**149**) (Scheme 42).[109] Taking into account the found trend, a series of polyfunctionalized 5-alkylthiopyrrolidinones (**149**) were synthesized in 59-82% yields.



R^1 = Ph, Tol, 4-ClC_6H_4, 4-$MeOC_6H_4$, *n*-C_6H_{13}, *c*-C_6H_{11} (Cy), *t*-Bu, Bn
R^2 = Ts, 4-$ClC_6H_4SO_2$, 4-$MeOC_6H_4SO_2$, 4-$NO_2C_6H_4SO_2$, Cbz
R^3 = Ph, *t*-Bu, OTBS, CH_2OAc, morpholyl, Me, H
R^4 = H, Ph, *t*-Bu

Scheme 42. The synthesis of 5-alkylthiopyrrolidinones (**149**) from vinyl sulfilimines (**148**)

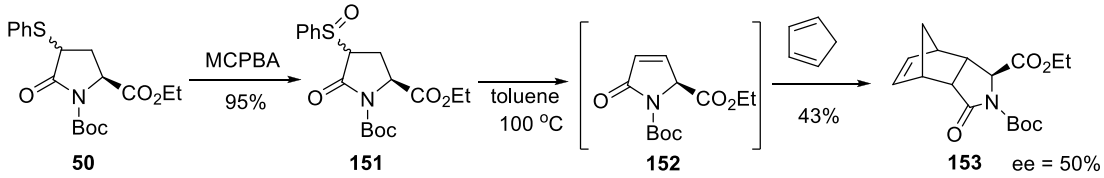
5. SYNTHETIC AND BIOMEDICAL POTENTIAL OF THIOFUNCTIONALIZED γ-LACTAMS

5-1. Aspects of Synthetic Transformations

The presence of a sulfanyl substituent in γ-lactam compounds creates necessary preconditions for its involvement in a number of important structural transformations, which significantly enriched the synthetic potential of lactams. These include oxidation reactions of the sulfur atom, reactions involving additional functional groups in the sulfanyl substituent, homolytic cleavage of the S–C bond, and

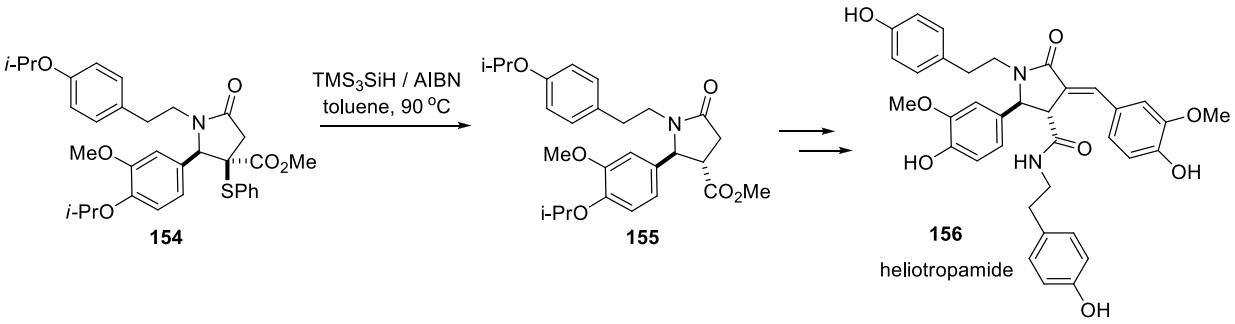
interactions with carbenes (carbenoids) with the primary formation of S-ylides.

For instance, the oxidation of 3-phenylsulfanyl pyroglutamate (**50**) with *meta*-chloroperbenzoic acid (mCPBA) was used to synthesize sulfoxide (**151**) which, when heating to 100 °C in toluene, underwent *syn*-elimination with *in situ* generation of dehydropyroglutamate (**152**) (Scheme 43).[44,45] The latter, as an active chiral dienophile, readily participated in the Diels-Alder reaction with cyclopentadiene to form *endo*-adduct (**153**) with a moderate enantiomeric excess due to the epimerization of **152**.



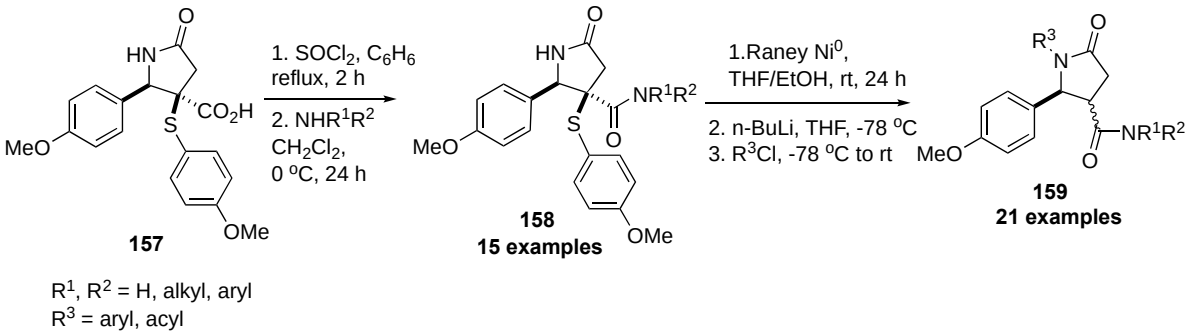
Scheme 43. The synthesis of ethyl N-Boc-5-oxo-4-azatricyclo[5.2.1.$0^{2,6}$]decan-8-en-3-yl carboxylate (**153**) from of ethyl N-Boc-4-phenylthiopyroglutamate (**50**)

4-Phenylthiolactam (**154**), obtained by a diastereoselective multicomponent Castagnoli-Cushman reaction was used as a key substrate for the preparation of heliotropamide (**156**), a natural 2-oxopyrrolidine isolated from *Heliotropium ovalifolium* (Scheme 44).[110] The developed synthesis methodology involved the step of radical desulfurization of pyrrolidinone (**154**) with tris(trimethylsilyl)silane TMS_3SiH into **155**, followed by amidation of the ester group and aryl vinylation of position 3 of the pyrrolidine nucleus.



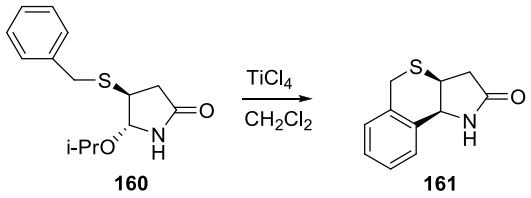
Scheme 44. The synthesis of heliotropamide (**156**) from 4-phenylthiolactam (**154**)

Compounds (**157**) obtained by the Castagnoli-Cushman reaction became convenient scaffolds for the creation of a library of "lead-like" γ-lactams.[111] For example, their amides (**158**) and (**159**) were synthesized by simple structural modifications (Scheme 45).



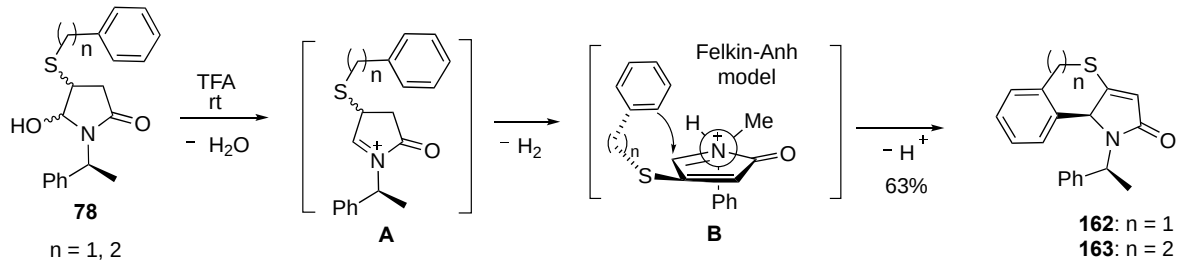
Scheme 45. The synthesis of 2-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxamides (**158**) and (**159**) from 2-(4-methoxyphenyl)-3-(4-methoxyphenylthio)-5-oxopyrrolidine-3-carboxylic acid (**157**)

The action of $TiCl_4$ on 4-benzylthio-5-isopropoxypyrrolidin-2-one (**160**) results in a mild intramolecular alkylation of the benzene nucleus, which leads to isothiochromeno[4,3-*b*]pyrrol-2(5*H*)-one (**161**) (Scheme 46).[57]



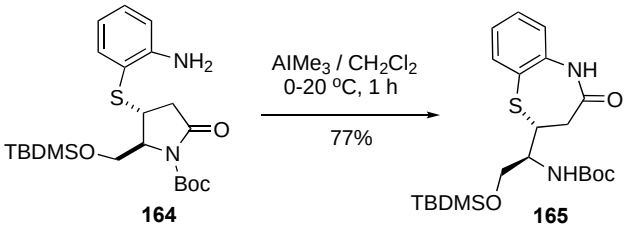
Scheme 46. The synthesis of *(*3*aS*,9*bS*)-1,3,3a,9b-tetrahydroisothiochromeno[4,3-*b*]pyrrol-2(5*H*)-one (**161**) from (4*S*,5*R*)-4-(benzylthio)-5-isopropoxypyrrolidin-2-one (**160**)

In turn, 4-benzyl(phenylethyl)thio-5-hydroxylactams (**78**), when subjected to neat TFA, undergo successive dehydration (intermediate **A**) and dehydrogenation (intermediate **B**) to form pyrroloisothiochromene (**162**) and pyrrolobenzo[*d*]thiopine (**163**) in 63% yield (Scheme 47).[58] The high stereoselectivity of the π-cyclization of 5-hydroxylactams is likely due to the attack of the nucleophile from the side of hydrogen as a small substituent in the Felkin-Anh model of adduct **B**.



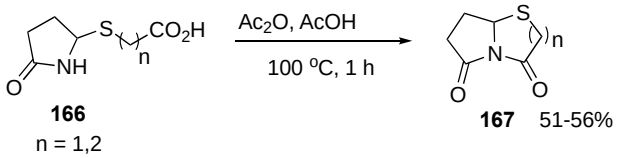
Scheme 47. The synthesis of pyrroloisothiochromene (**162**) and pyrrolobenzo[*d*]thiopine (**163**) from 4-benzyl(phenylethyl)thio-5-hydroxylactams (**78**)

Thiolactam (**164**) with an *ortho*-amino group in the thioaryl moiety by intramolecular reamidation in the presence of trimethylaluminium were converted to 1,4-thiazepin-5-one derivative (**165**) (Scheme 48).[56]



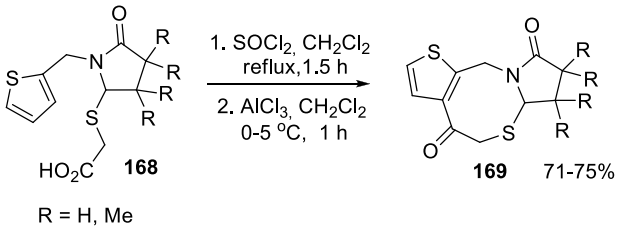
Scheme 48. The synthesis benzo[*b*][1,4]thiazepin-4(5*H*)-one (**165**) from 4-(2-aminophenylthio)pyrrolidin-2-one (**164**)

Cyclocondensations are also typical for γ-lactams bearing thioacetic or thiopropanoic acid fragments at position 5. For instance, NH-pyrrolidinones (**166**) when heated in acetic anhydride gave pyrrolo[2,l-*b*]thiazole (thiazine) derivatives (**167**) in satisfactory yields (Scheme 49).[84]



Scheme 49. The synthesis of pyrrolo[2,l-*b*]thiazole (thiazine) (**167**) from 2-(5-oxopyrrolidin-2-ylthio)acetic(propanoic) acid (**166**)

Another striking example of such transformations is the Friedel-Crafts cyclodehydration of 1-(thien-2'-ylmethyl)-2-pyrrolidinone-5-thioglycolic acids (**168**), which is a kind of an effective method for the synthesis of pyrrolo[2,1-*b*]thieno[2,3-*e*][1,3]thiazocinediones (**169**) (Scheme 50).[87]

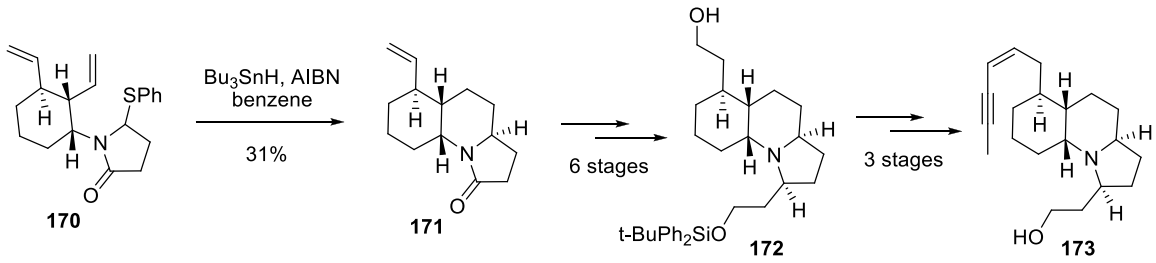


Scheme 50. The synthesis of pyrrolo[2,1-*b*]thieno[2,3-*e*][1,3]thiazocinediones (**169**) from 2-(5-oxo-1-(thiophen-2-ylmethyl)pyrrolidin-2-ylthio)acetic acids (**168**)

A peculiarity of thiosubstituted γ-lactams is that they can be considered as compounds with latent α-acylamino radical functionality. Their treatment with tri-*n*-butyltin hydride in the presence of AIBN results in homolytic C–-S bond cleavage; if the substrate features an appropriately located multiple

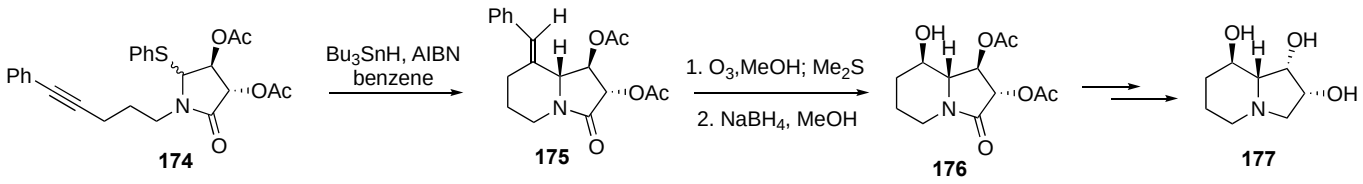
carbon-carbon bond[81,85,88,89,93,96,97,100] or a carbonyl group,[86,102] intramolecular radical cyclization with formation of pyrrolizidinones or indolizidinones can take place. These reactions proved to be very useful for the synthesis of compounds of natural origin.

Specifically, Bu_3SnH/AIBN-induced radical cyclization of sulfide (**170**) was successfully used to construct the framework of the gephyrotoxin alkaloid (**171**) with appropriately located substituents. Further transformations of scaffold (**171**) via intermediate (**172**) resulted in the synthesis of the target alkaloid (**173**).[80]



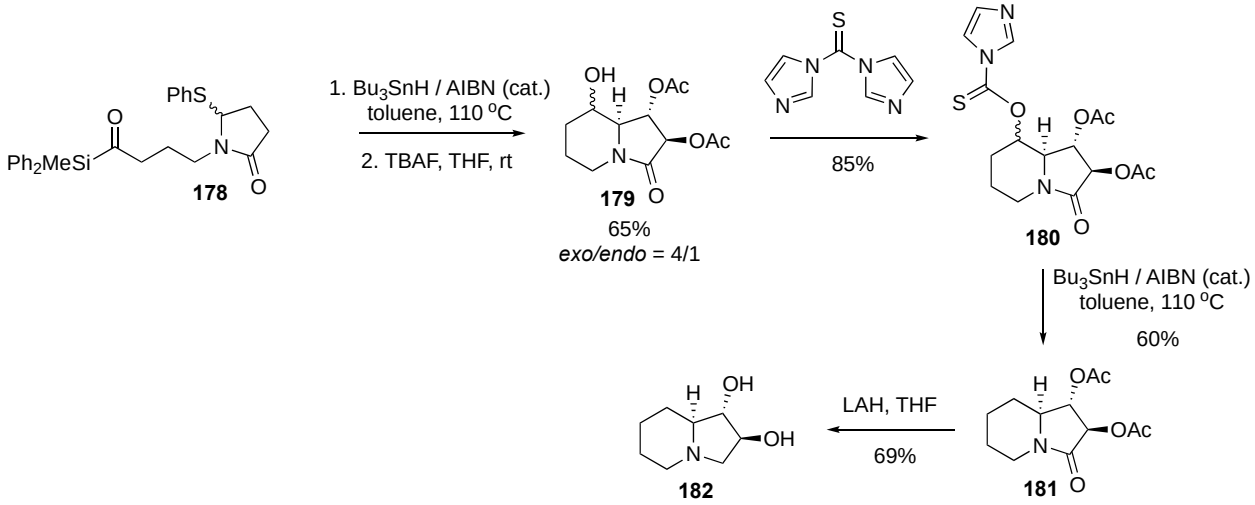
Scheme 51. The synthesis of gephyrotoxin alkaloid (**173**) from 5-(phenylthio)pyrrolidin-2-one (**170**)

N-Alkynyl-substituted 5-phenylthio-γ-lactam (**174**) derived from D-tartaric acid is a convenient building block for the synthesis of the polyhydroxylated swainsonine alkaloid (**177**).[97] At the first stage, lactam (**174**) was converted to *trans*-indolizidinone (**175**) in 80-85% yield by the Bu_3SnH/AIBN-initiated radical cyclization scheme. Its ozonolysis with subsequent treatment with dimethyl sulfide and sodium borohydride led to hydroxyindolizinone (**176**) in 74% overall yield. The latter was converted to product (**177**) in several steps.



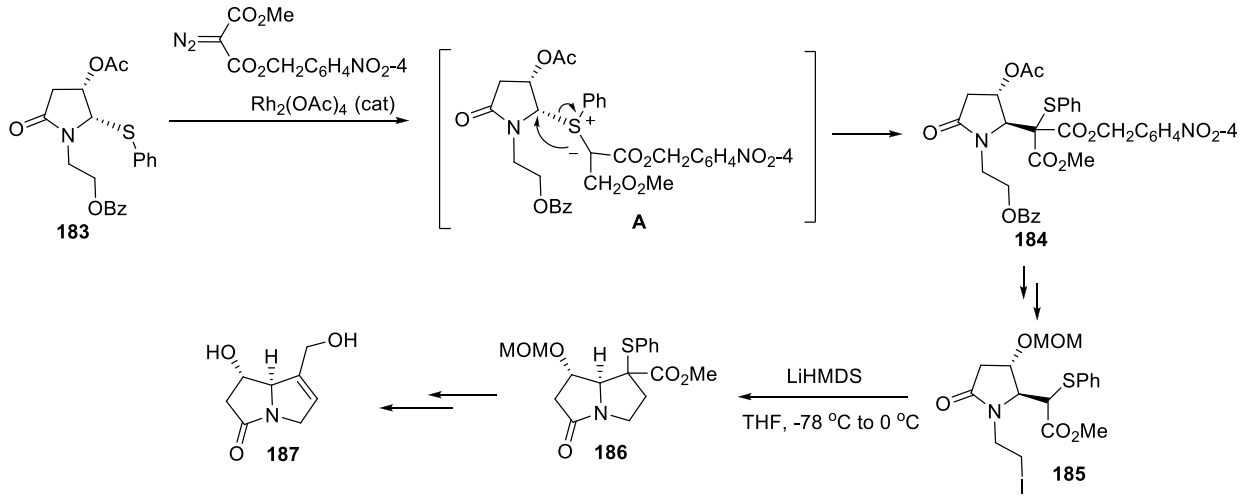
Scheme 52. The synthesis of swainsonine (**177**) from N-(5-phenylpent-4-ynyl)-substituted 5-(phenylthio)pyrrolidin-2-one (**174**)

Radical cyclization of polyfunctional phenylthiosubstituted lactam (**178**) was also a key step in the synthesis of hydroxyindolizinone (**179**) as a mixture of *exo*- and *endo*-isomers in 65% yield. A series of subsequent simple protocols *via* intermediates (**180**) and (**181**) afforded the indolizine alkaloid (+)-lentiginosine (**182**) in high yield.[102]



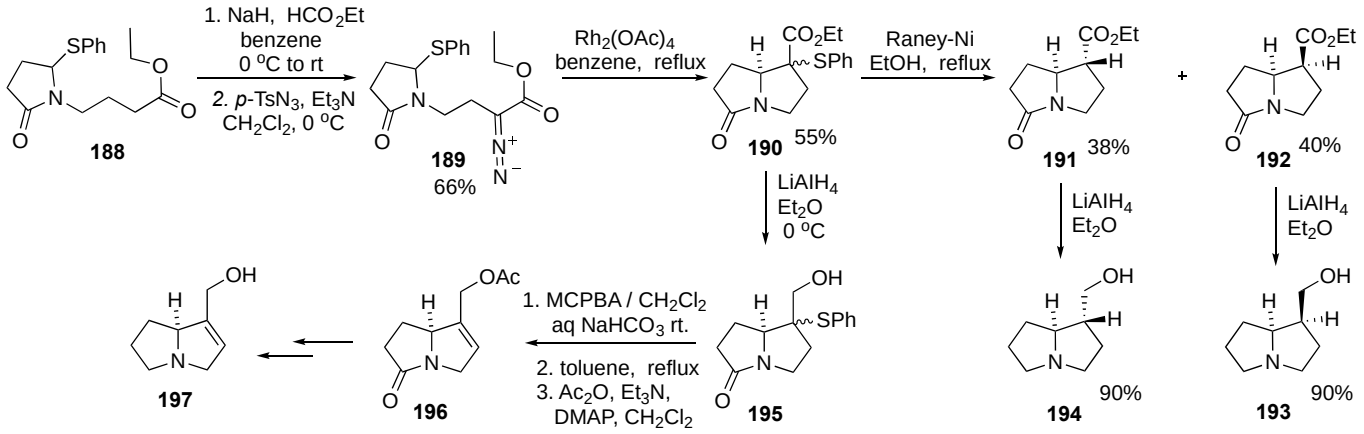
Scheme 53. The synthesis of (+)-lentiginosine (**182**) from N-(4-(methyldiphenylsilyl)-4-oxobutyl)-substituted 5-(phenylthio)pyrrolidin-2-one (**178**)

The reaction of intermolecular carbenoid substitution of sulfanyl groups in 5-thiolactams which is realized through the formation of S-ylides deserves attention. It serves as an effective option for the formation of a new carbon-carbon bond and was widely used in the synthesis of natural compounds. For example, the interaction of acetoxysulfide (**183**) with methyl *p*-nitrobenzyl α-diazomalonate in the presence of catalytic amounts of $Rh_2(OAc)_4$ in boiling benzene leads via the intermediate S-ylide **A** to the *trans*-2,3-substituted product (**184**) in high yield. A series of its further transformations results in the synthesis of the alkaloid (+)-heliotridine (**187**).[99]



Scheme 54. The synthesis of (+)-heliotridine (**187**) from 2-((2*S*,3*S*)-3-acetoxy-5-oxo-2-(phenylthio)pyrrolidin-1-yl)ethyl benzoate (**183**)

Diazo compound (**189**), obtained by the stepwise treatment of 5-phenylthiopyrrolidinone (**188**) with ethyl formate and tosyl azide, under $Rh_2(OAc)_4$-catalyzed conditions undergoes intramolecular carbenoid substitution to form pyrrolizidine derivative (**190**). Its subsequent desulfurization with Raney nickel gives diastereomeric esters (**191**) and (**192**), which are precursors of the pyrrolizidine alkaloids isoretronecanol (**193**) and trachelanthamide (**194**). In addition, the alcohol (**195**), obtained by the reduction of ester (**190**), was converted by oxidative elimination of the sulfide group and subsequent acetylation to acetate (**196**), a precursor of supinidine alkaloid (**197**).[82,83]



Scheme 55. The synthesis of pyrrolizidine alkaloids isoretronecanol (**193**), trachelanthamide (**194**) and supinidine (**197**) from 5-phenylthiopyrrolidinone (**188**)

5-2. Biological Activity of Thiosubstituted γ-Lactams

In addition to a number of synthetically useful properties, thiofunctionalized γ-lactams are interesting objects for biomedical research. It should be mentioned that thiosubstituted lactam derivatives are characterized by a pronounced pharmacological profile (Figure 3). For instance, lactam (**198**), functionalized at position 4 with a thioalanine fragment, is an inhibitor of matrix metalloproteinase, exhibits anti-inflammatory properties and may be useful in the treatment of osteoarthritis and rheumatoid arthritis.[112,113] The hybrid compound (**199**), in which the basic pyrazine cycle is structurally modified by 4-thiopyrrolidone fragment, has recently been patented as a potent adenosine receptor antagonist.[114] Among 3-thiolactams, a number of important compounds are worth highlighting, in particular for the treatment of diabetes (**200**),[115] treatment of diseases associated with hyperglycemia (**201**)[116] and the treatment of HIV-1 (**202**).[117] In turn, 3-arylthiolactam (**203**) is a sodium channel blocker,[118] and its pyrimidinyl analog (**204**) is a kinase inhibitor.[119]

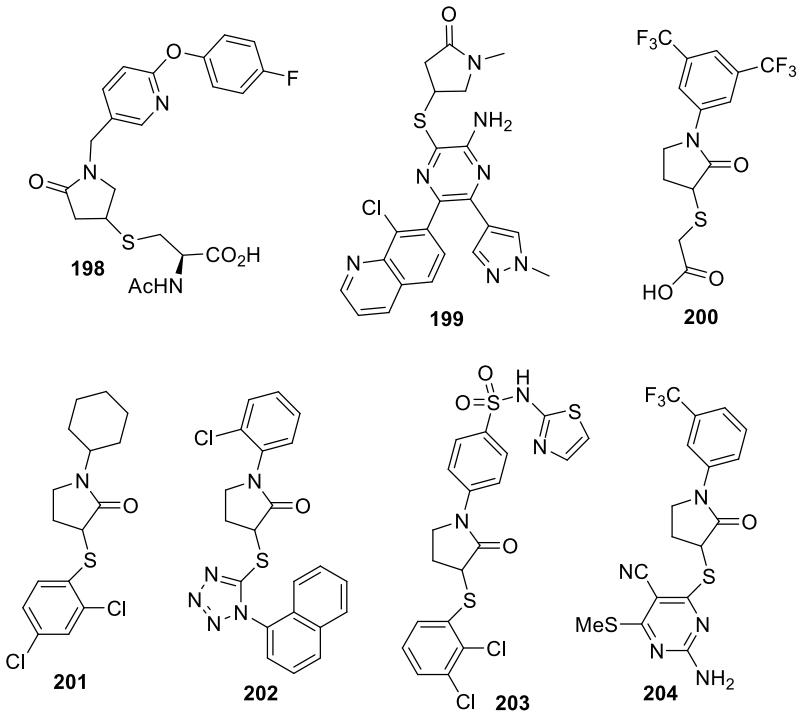


Figure 3. Some bioactive thiosubstituted γ-lactams

Helicide-pyrrolidone derivatives (**205**) and (**206**) synthesized by a modified Castagnoli-Cushman reaction demonstrated high antitumor activity against human SKOV3 cell (Figure 4).[120]

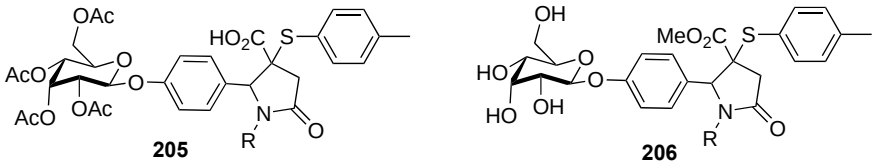


Figure 4. Helicide-pyrrolidone derivatives (**205**) and (**206**) with antitumor activity

To optimize the characteristics of carbapenem antibiotics and to increase their resistance to dehydropeptidase-1 (DHP-1), their 4-mercaptopyrrolidin-2-one analogues R-82301 (**207a**), CS-834 (**207b**) and N-methylated forms (**207c**,**d**) were synthesized and tested (Figure 5).[57,58] The modified carbopenems (**207a-d**) were not inferior to such well-known predecessors as imipenem, ertapenem, meropenem, doripenem in terms of efficacy and chemical resistance, and showed better results on certain strains.

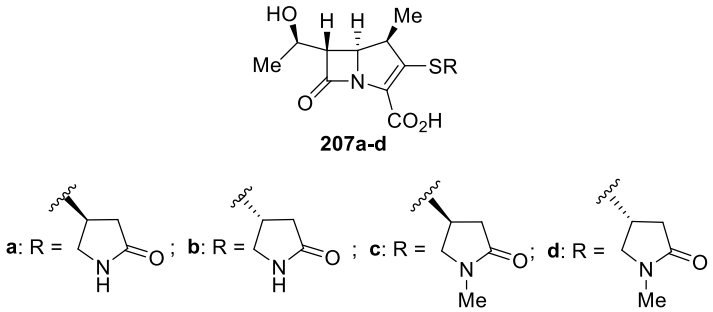


Figure 5. 4-Mercaptopyrrolidin-2-one analogues of carbapenem antibiotics

6. CONCLUSIONS

The results of the literature analysis show that thiosubstituted γ-lactams are very promising heterocyclic structures in both synthetic and biological aspects. For their synthesis, the methods of directed functionalization of the corresponding position of the γ-lactam cycle and intramolecular cyclization of N,S-containing acyclic compounds have become widespread. A newly developed approach based on the combination of tandem cyclothiofunctionalization processes of alkenyl carboxylic acid derivatives deserves special attention. The practical significance of thiofunctionalized γ-lactams is largely due to their ability to homogeneously cleave the C-S bond of a sulfanyl substituent with a pyrrolidone nucleus, which played a key role in the synthesis of various natural compounds on their basis. Of equal importance are the results of biomedical studies, which indicate the prospects of thiofunctionalized γ-lactams for the creation of pharmacologically attractive substances.

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