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Synthetic Methods

Synthesis of Complex Thiazoline-Containing Peptides by Cyclodesulfhydration of *N*-Thioacyl-2-Mercaptoethylamine Derivatives

Marat Meleshin, Lukas Koch, Christoph Wiedemann, and Mike Schutkowski*

Abstract: Herein we report a mild, efficient, and epimerization-free method for the synthesis of peptide-derived 2-thiazolines and 5,6-dihydro-4*H*-1,3-thiazines based on a cyclodesulfhydration of *N*-thioacyl-2-mercaptoethylamine or *N*-thioacyl-3-mercaptopropylamine derivatives. The described reaction can be easily carried out in aqueous solutions at room temperature and it is triggered by change of the pH, leading to complex thiazoline or dihydrothiazine derivatives without epimerization in excellent to quantitative yields. The new method was applied in the total synthesis of the marine metabolite mollamide F, resulting in the revision of its stereochemistry.

Bacteria, fungi, and some marine organisms (e.g., invertebrates) use thiazoline formation to fine-tune the molecular properties of peptide-based metabolites (e.g., conformational rigidity, metal coordination, and proteolytic stability).[1] Subsequent thiazoline transformation into thiazole or thiazolidine provides additional structural and chemical diversity.[2] A plethora of bioactive natural thiazoline-containing compounds have been isolated and characterized from different organisms (e.g., siderophores: yersiniabactin,[3] desferrithiocin,[4] pyochelin;[5] antibiotics: bacitracin,[6] vioprolides,[7] thiangazole,[8] micacocidines;[9] cytotoxic compounds: apratoxin A,[10] cycloforskamide,[11] grassypeptolides,[12] marthiapeptide A,[13] trunkamide A[14]). Some of them are depicted in Figure 1.

The most common methods for the synthesis of thiazolines are based on dehydrative cyclizations of *N*-acylated cysteine derivatives via activation of the amide group using electrophilic reagents or catalysts.[15] Other common precursors are *N*-thioacylated serine or threonine derivatives, the hydroxyl groups of which are converted to leaving groups, followed by an intramolecular alkylation of the sulfur atom of the thioamide group.[16] A general disadvantage of these cyclodehydrations is their lack of selectivity that prohibits the formation of a single thiazoline ring in the presence of unprotected cysteine- or serine/threonine residues, respectively, and therefore careful choice of protecting groups is highly important.[16f]

Another useful method is the reaction of nitriles with cystamine- or cysteine derivatives. This method has been known for almost 70 years and has many modern variations.[17] It is very well suited for many aromatic nitriles, but in the case of aliphatic and some aromatic nitriles prolonged heating is often required and commonly lower yields of thiazolines are obtained.[17b,e,18] Most of these reactions are limited to relatively small compounds and

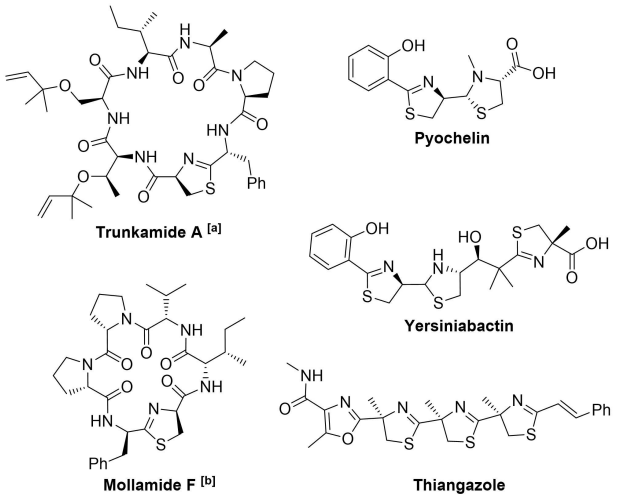


Figure 1. Thiazoline-containing natural products. [a] Revised structure according to Wipf and Uto.[14b] [b] Structure originally proposed to mollamide F according to Lu et al.[26]

[*] Dr. M. Meleshin, L. Koch, Prof. Dr. M. Schutkowski
Department of Enzymology, Institute of Biochemistry and Biotechnology, Martin Luther University Halle-Wittenberg, Charles Tanford Protein Center
Kurt-Mothes-Str. 3a, 06120 Halle (Saale) (Germany)
E-mail: marat.meleshin@biochemtech.uni-halle.de

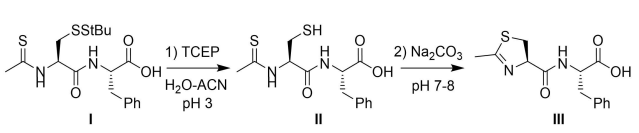
L. Koch
Department of Pharmaceutical Biology and Pharmacology, Institute of Pharmacy, Martin Luther University Halle-Wittenberg
Hoher Weg 8, 06120 Halle (Saale) (Germany)

Dr. C. Wiedemann
Faculty of Chemistry and Earth Sciences, Institute of Organic Chemistry and Macromolecular Chemistry, Friedrich Schiller University Jena
Humboldtstraße 10, 07743 Jena (Germany)

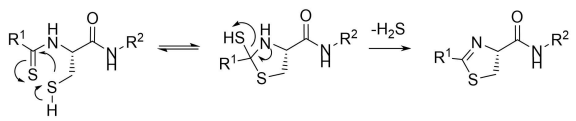
building blocks. In one recent work it was demonstrated that the cyclization of linear peptides with an N-terminal cysteine and a C-terminal amino acid derivative bearing a cyano group is reasonably fast only in the case of aromatic nitriles and gives low yields and slow reaction rates in case of aliphatic nitriles.[19] In addition, peptides bearing a C-terminal cyano group are not readily accessible by solid-phase peptide synthesis (SPPS).

Despite these and many other available methods,[20] the synthesis of complex thiazoline-containing compounds remains challenging. It is well known that the C2-exomethine stereocenter of the thiazoline ring is prone to epimerization at different rates depending on the solvent, pH value, temperature, and additives, limiting further synthetic manipulations.[16c,21] Thus, thiazoline rings with a chiral C2-exomethine center should ideally be introduced in the last step of a synthesis under mild conditions in order to retain their stereochemical integrity.[22] Since existing methods are often limited in scope, incompatible with many functional groups, require strong electrophilic reagents, catalysts, elevated temperatures, or anhydrous conditions, more efficient methods are needed to overcome these limitations. During our investigations on thioxylated peptides we discovered that compounds containing *N*-thioacylated cysteine residues are not stable. For instance, tris-carboxyethylphosphine (TCEP)-mediated reductive cleavage of the *S*-tert-butylthio (StBu) group of thioacetylated dipeptide **I** afforded the expected reduced dipeptide **II** which was stable in acetonitrile (ACN)-H_2O solution at pH 3 for hours, but adjustment of the pH with sodium carbonate to 7–8 caused a rapid and virtually quantitative conversion to another compound. According to HPLC-MS analysis, the mass of the new compound was 34 units less than that of the peptide with the free mercapto group **II**. NMR spectroscopy confirmed the absence of the thiocarbonyl group and the H^N-proton of the cysteine residue (see Figure S4, S5). We concluded that a cyclization-desulfhydration reaction sequence had occurred and the new compound is thiazoline derivative **III** (Scheme 1).

We also suggested a possible mechanism of the reaction which involves an intramolecular nucleophilic attack of the thiolate anion at the thiocarbonyl group, leading to the formation of a cyclic intermediate. Expulsion of hydrogen sulfide furnishes the thiazoline ring formation (Scheme 2).



Scheme 1. Thiazoline formation from *N*-thioacetyl-Cys-Phe-OH.



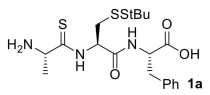
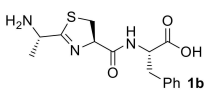
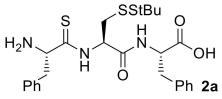
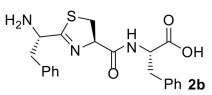
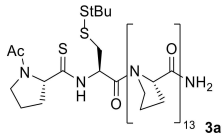
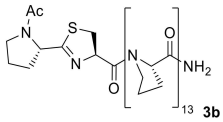
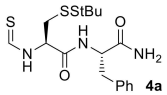
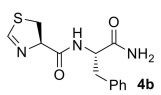
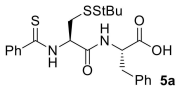
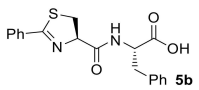
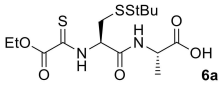
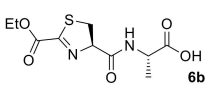
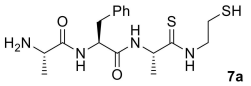
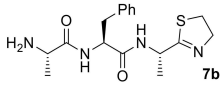
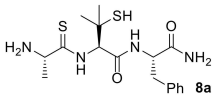
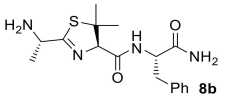
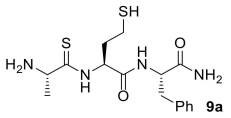
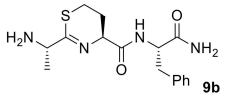
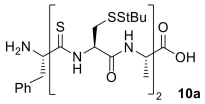
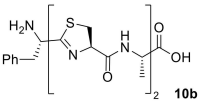
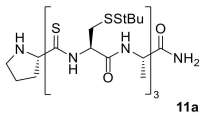
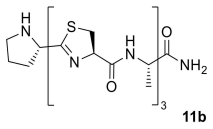
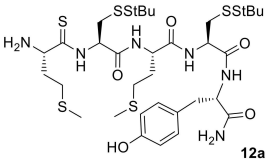
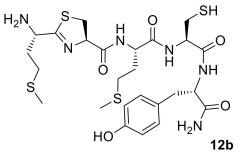
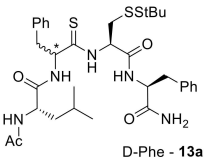
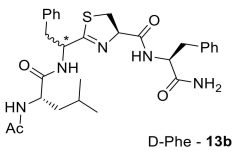
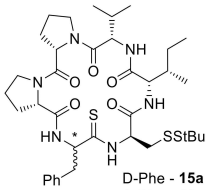
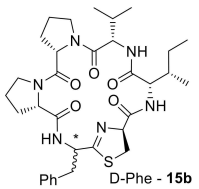
Scheme 2. Proposed mechanism of thiazoline formation.

While we were preparing the manuscript, a similar reaction was published as a method to generate H_2S from *N*,*N*-bis-thioacyl-(seleno)cystamine derivatives in the presence of glutathione in aqueous solutions and in HeLa cells in culture.[23]

In order to evaluate the scope and limitations of this reaction in the synthesis of thiazolines, we prepared a set of model peptide derivatives using SPPS. For the introduction of thioacyl residues 1-(Fmoc-α-aminothioacyl)-6-nitrobenzotriazoles[24] or dithioesters were used. The preparation of the thioformyl dipeptide **4a** was accomplished by selective thioxylation of the resin-bound, sterically less hindered *N*-formyl amide group with Lawesson's reagent. In most of the model compounds the thiol groups were StBu-protected, while compounds **7a**–**9a** were used in the free thiol form since only *S*-triphenylmethyl-protected precursors are commercially available.

According to HPLC-MS analysis, the thiazoline ring formation for StBu-protected derivatives was completed in 1–3 hours in sodium phosphate buffer (pH 7.5, containing 3 equivalents of TCEP) at room temperature. Nearly quantitative yields were obtained for the thiazolines **1b**–**3b** from the thioxylated tripeptides **1a**–**2a** and the polyproline-derived thioxopeptide **3a** (Table 1). According to analytical HPLC, the thioformylated dipeptide **4a** formed the expected product **4b** in a poor yield of 11 % along with a compound with the mass corresponding to the hydrolysis product of the thiazoline ring (*N*-formyl-Cys-Phe-NH_2). Rapid hydrolysis of the 2-unsubstituted thiazoline in the acidic eluent containing 0.1 % formic acid would explain this result.[25] Thiobenzoylamide **5a** cyclized in the same time range as the aliphatic thioamides, leading to thiazoline **5b** in quantitative yield. Thiazoline **6b**, bearing an ethoxycarbonyl group at C2, was rapidly formed from thiooxalyl derivative **6a** together with 5 % of another product isobaric to **6b**. However, we found that this product was arising from the starting thioamide, which also had an impurity with the same mass as **6a**. Elongation of the reaction time invariably lead to the hydrolysis of the thiazoline ring of **6b** (data not shown). The purified thioamide derivatives with a free thiol group **7a**–**9a** were partially converted to thiazolines **7b** and **8b** or 5,6-dihydro-4*H*-1,3-thiazine **9b** already during lyophilization from an ACN-H_2O mixture containing 0.1 % TFA. We found that the compounds **7a** and **9a** contained approximately 4 % and 11 % of **7b** and **9b**, respectively, directly after lyophilization (HPLC, 220 nm). In the case of penicillamine derivative **8a**, a conversion of almost 90 % to the thiazoline derivative **8b** was observed. Such an easiness of the heterocyclization even in acidic solutions can be attributed to the gem-dimethyl effect. Along with **8b** and starting material **8a**, we observed a small amount (< 4 %) of S/O exchange product (oxoamide). To complete cyclization, **7a**–**9a** were dissolved in sodium phosphate buffer with TCEP. A rapid reaction with release of H_2S occurred, completing the formation of the expected thiazolines **7b** and **8b** in very good yields. The homocysteine derivative **9a** also cyclized efficiently in the buffer solution, leading to an excellent yield of the dihydrothiazine derivative **9b**. To explore the scope of this reaction in more sophisticated

Table 1: Synthesis of thiazolines and dihydrothiazines by the cyclodesulfhydration of *N*-thioacyl-2(3)-mercaptoethyl(propyl)amine derivatives.[a]

Starting thioxopeptide	Product	Yield [%][b]	Starting thioxopeptide	Product	Yield [%][b]
 **1a**	 **1b**	99	 **2a**	 **2b**	99
 **3a**	 **3b**	98[c]	 **4a**	 **4b**	11[e]
 **5a**	 **5b**	97	 **6a**	 **6b**	85[e]
 **7a**	 **7b**	95	 **8a**	 **8b**	97
 **9a**	 **9b**	99	 **10a**	 **10b**	97
 **11a**	 **11b**	94[d]	 **12a**	 **12b**	97
 D-Phe - **13a** L-Phe - **14a**	 **13b** 98 **14b** 97 D-Phe - **13b** L-Phe - **14b**		 D-Phe - **15a** L-Phe - **16a**	 D-Phe - **15b** L-Phe - **16b**	**15b** 79(68)[f] **16b**: 94(55)[f]

[a] Reaction conditions: 1 mM thioxopeptide, 3 mM TCEP in phosphate buffer (100 mM, pH 7.5) 1–2 h, room temperature. [b] Yields were determined by HPLC (area under curve at 220 nm). Isolated yields are given in parentheses. [c] Prolonged reaction time (4 h) was required to complete conversion. [d] 10 equiv of TCEP in ACN-ammonium formate buffer (50 mM, pH 7.5) was used. [e] The products are unstable toward hydrolysis in the reaction solution (see text). [f] Reactions were performed using 7.5 equiv of TCEP in 50% ACN-sodium phosphate buffer mixture at 40 °C for 2–3 h.

models, we tested thioamides **10a** and **11a** containing two and three *N*-thioacyl cysteine fragments, respectively. Compound **10a** readily afforded the corresponding dithiazoline **10b** in excellent yield. In contrast, the cyclization of compound **11a** in a slightly modified reaction solution (40% ACN solution was used to dissolve the starting material) lead to an unidentified side product, reducing the yield to 75%. However, replacing ACN by 20% of dimethylformamide (DMF) or using ACN-ammonium formate buffer increased the yield of **11b** to 94%. To our gratification, reduction of the sulfur-rich thioxopentapeptide **12a** that contains an additional cysteine residue yielded a single product, highlighting the regioselectivity of the reaction. The structure of the product **12b** was confirmed by tandem mass spectrometry (see Figure S45).

Even though the reduction and cyclization of StBu-protected thioacylated cysteine derivatives proceeded without formation of side products, we decided to study the epimerization at the C2- exomethine center. As model compounds, we prepared the acetylated thioxotetrapeptide **13a** and its diastereomer **14a**.

The reduction of these peptide derivatives with 3 equivalents of TCEP was sluggish but use of 6 equivalents of TCEP increased the rate of deprotection of the cysteine side chain. After 2 hours of incubation the samples were analyzed with HPLC-MS. We found that less than 0.5% of

the diastereomeric peptides **13b** and **14b** formed. Therefore, our method is successfully applicable for the synthesis of thiazoline derivatives with epimerizable C2-stereocenters.

To demonstrate the synthetic utility of the method, we attempted the total synthesis of mollamide F (**15b**), a cyclic thiazoline-containing natural compound with anti-HIV activity isolated from the ascidian *Didemnum molle*.[26] We prepared the linear precursor H-D-Phe-ψ[CSNH]-D-Cys-(StBu)-Ile-Val-Pro-Pro-OH using Fmoc-based SPPS on a 2-chlorotrityl resin. Cleavage from solid support and subsequent cyclization in dichloromethane (DCM)-DMF solution using 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide (EDC) and *N*-hydroxybenzotriazole (HOBt) followed by preparative HPLC afforded the cyclic thioxylated peptide **15a** which was treated with TCEP in aqueous sodium phosphate buffer (pH 7.5). Due to the very slow reduction of the disulfide bond the reaction required a prolonged incubation time (2–3 hours) together with mild heating of the reaction mixture to 40 °C and 7.5-fold excess of TCEP for completion. However, the reaction of **15a** was complex and a more hydrophobic byproduct with the same molecular mass was formed along with a minor amount of hydrolysis product (Figure 2a). Moreover, **15b** partially hydrolyzed during the HPLC run, as it was judged by baseline hump. Nevertheless, we successfully isolated the product via preparative HPLC using ACN-ammonium formate buffer as eluent. Surprisingly, the ^{1}H NMR spectrum of **15b** was inconsistent with the respective spectrum of mollamide F reported in literature (see Figure S8).[26]

Considering the observed fast formation of another product with the same molecular mass, we decided to synthesize the thiazoline C2-exomethine epimer of **15b** starting from an L-phenylalanine building block. Using the same reaction sequence, **16a** was prepared, purified, and treated with TCEP, yielding **16b** in a very good yield and purity (Figure 2b). The ^{1}H NMR spectrum and MS/MS data of **16b** were identical with those reported for natural mollamide F (see Figure S8, S13).[26] Of note, the solution of pure **15b** in DMSO-d6 left in the fridge for several months contained up to 30 % of **16b** according to HPLC-MS (data not shown), indicating instability of the *epi*-mollamide F **15b**. Therefore, we conclude that, in contrast to the previously published data, the absolute configuration of the phenylalanine residue in the naturally occurring mollamide F is (*S*) and that its structure must be revised to **16b**.

In the original publication the absolute configurations of the amino acid residues in natural mollamide F were determined using the advanced Marfey's method.[27b] The configuration of the phenylalanine residue, however, remained ambiguous as about 60 % of D-Phe and 40 % of L-Phe were detected after derivatization.[26] Based on the enantiomeric excess of D-Phe and because no configurational isomers were detectable by NMR, the phenylalanine residue was assigned as D-Phe. In an attempt to reproduce this experiment, we found that acidolysis of both **15b** and **16b** yields D-Phe and L-Phe in the same ratio of about 60:40 (Figure S1). Based on this observation and considering the rapid hydrolysis of **15b** under acidic conditions as well as its spontaneous epimerization to **16b**, we propose that exposure of these compounds to concentrated hydrochloric acid establishes an equilibrium between the two epimers. Since the thiazoline ring of **15b** appears to be more susceptible to hydrolysis than that of **16b**, D-Phe would be formed in excess over L-Phe. The efficiency and robustness of the new method prompted us to investigate a rapid synthesis of mollamide F. Thus, we omitted the purification of intermediates and performed macrocyclization of the crude linear peptide, disulfide reduction and heterocyclization in situ. Starting from the linear peptide, our optimized synthetic strategy afforded a solution of the crude product in only 3–4 hours (Scheme 3). After preparative HPLC, we obtained mollamide F in 33.8 % overall yield based on the proline-preloaded 2-chlorotrityl resin.

In summary, we developed a mild and efficient epimerization-free method for the synthesis of complex thiazolines and dihydrothiazines in aqueous solutions. Starting from readily accessible thioxopeptide precursors, our approach thus enables ring formation in the final step of the synthesis. Moreover, we demonstrated the utility and robustness of the new method on a rapid synthesis of the cyclic thiazoline-

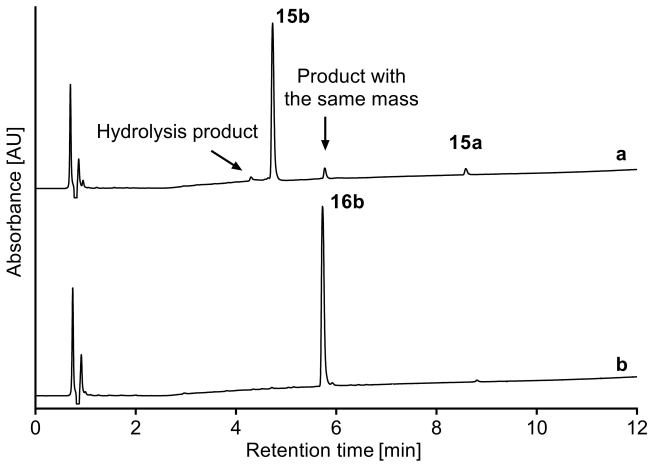
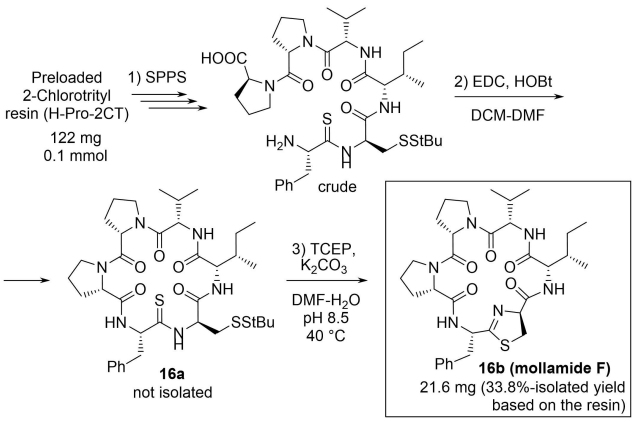


Figure 2. HPLC profiles of reaction mixtures containing crude thiazoline a) **15b**; b) **16b**. UV detection at 220 nm.



Scheme 3. Rapid synthesis of mollamide F.

containing natural product mollamide F, leading to revision of its stereochemistry. We are sure that our approach will find broad application in the straightforward and efficient synthesis of complex thiazoline- and dihydrothiazine-containing natural products.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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