

Synthesis of Peptidyl Aldehydes from Thiazolidines

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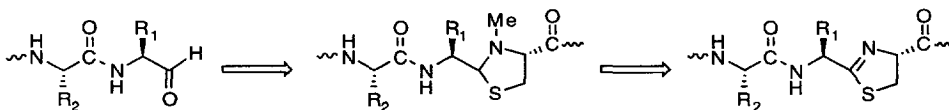
Abstract: Peptidyl aldehydes were synthesized using thiazolidine peptides as precursors. Hydrolysis of the heterocycles is easily accomplished using copper salts to furnish the peptidyl aldehydes with very good yield and with no epimerization. © 1997 Published by Elsevier Science Ltd.

There is growing evidence which suggests that intracellular proteases are involved in cell homeostasis. Peptidyl aldehydes represent one of the most specific classes of serine and cysteine protease inhibitors.¹ These compounds are of great value for identifying the role of proteolytic activity in normal or pathological cellular processes (e.g.: apoptosis, tumor metastasis, bone resorption, arthritis).

One strategy for preparing peptidyl aldehydes is based on the reduction of the C-terminal carboxylic acid or ester followed by oxydation of the corresponding amino alcohol or peptide alcohol. Kawamura² used this procedure on preformed tripeptides, whereas Woo³ elongated the peptides starting from the C-terminal amino alcohol. An alternative method is based on the reduction of the Weinreb amide.⁴ Accordingly, Fehrentz synthesized peptidyl hydroxamates on solid phase, generating the aldehyde by LiAlH₄ reduction.⁵ The conditions for reduction and oxydation used in these two methods are incompatible with certain amino acid functionalities. An alternative procedure is based on the transient protection of the aldehyde function as a semicarbazone.⁶ Using this method, several peptidyl aldehydes have been synthesized by elongation from the α -amino semicarbazone in solution⁷⁻⁹ or on solid support.¹⁰ Two specific methods have been described for the synthesis of peptidyl aspartal¹¹ and arginal¹² involving respectively an aminor or an acylal obtained by internal cyclization of the amino aldehyde with the lateral function. These building blocks can be efficiently condensed with a peptide by fragment coupling and the masked aldehyde regenerated under mild conditions.

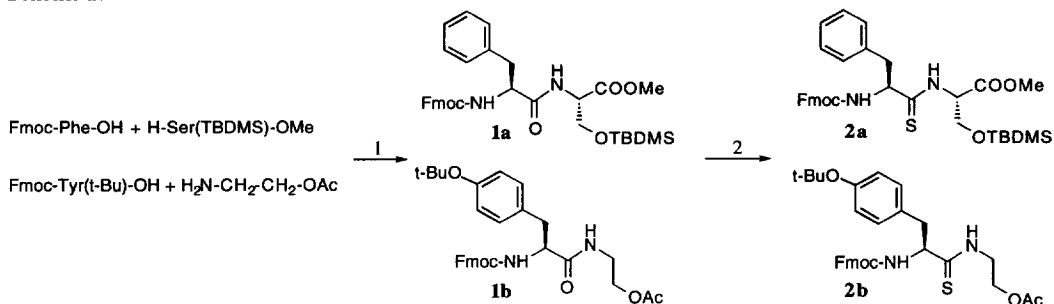
We report here a method for the synthesis of peptidyl aldehydes using a thiazolidine precursor which is hydrolyzed to produce an aldehyde using a mercuric¹³⁻¹⁵ or copper¹⁶ salt under neutral conditions (Scheme 1). The thiazolidine was prepared by reduction of the corresponding thiazoline according to Dondoni.^{16,17} The thiazoline ring was obtained following a β -hydroxy thioamide cyclization previously described.^{18,19}

Scheme 1:



The thioamide bond in compounds **2a,b** was introduced by using Lawesson's reagent²⁰ on dipeptides **1a,b** whose hydroxyl function was protected (yield 75-85%) (Scheme 2).

Scheme 2:

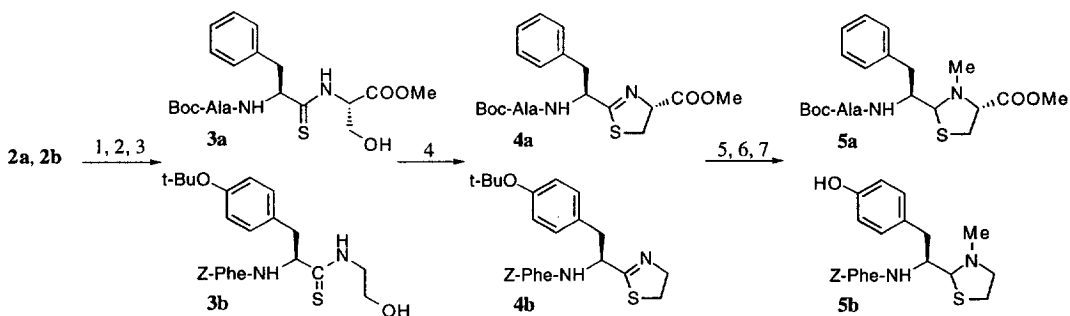


1) BOP, CH_2Cl_2 ; 2) Lawesson's reagent, dioxane.

Starting from β -hydroxy thiodipeptides, we investigated two pathways for the synthesis of peptidyl aldehydes. First, we elongated the pseudopeptide from **2a,b** and formed the thiazolidine at the end of the synthesis. The second pathway involved the preliminary formation of the amino thiazolidine, followed by elongation of the pseudopeptide.

Following the first route, pseudopeptides **2a,b** were elongated and their hydroxyl function deprotected to furnish compounds **3a,b**. Cyclization of these β -hydroxy thiopeptides **3a,b**, by the Mitsunobu reaction was accomplished with a yield of 70% (Scheme 3). Reduction of thiazolines **4a,b** was performed following a two-step procedure¹⁶ (methylation and reduction with NaBH_4) to give the N-methyl thiazolidine **5a,b** with a yield of 70-85%.

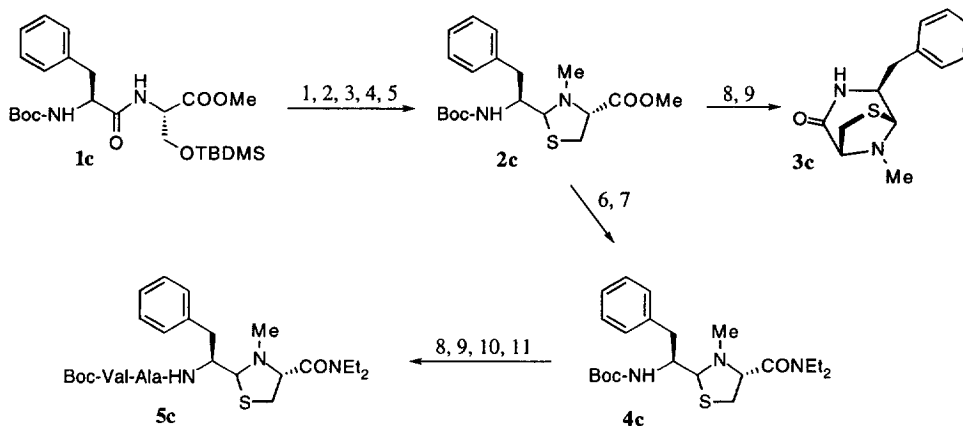
Scheme 3:



1) Et_2NH , DMF; 2) Boc-Ala-OH, BOP, CH_2Cl_2 for **2a**; Z-Phe-OH, BOP, CH_2Cl_2 for **2b**; 3) Bu_4NF , THF for **a**; K_2CO_3 , MeOH for **b**; 4) Ph_3P , DEAD, THF; 5) $\text{F}_3\text{CSO}_3\text{Me}$, CH_3CN ; 6) NaBH_4 , MeOH; 7) TFA for **b**.

We next investigated the second route in which the pseudopeptide was elongated from the preformed thiazolidine **2c** (Scheme 4). Because of the formation in large amounts of compound **3c** during the coupling reaction of the ester **2c**, stepwise peptide synthesis was done from **4c**.

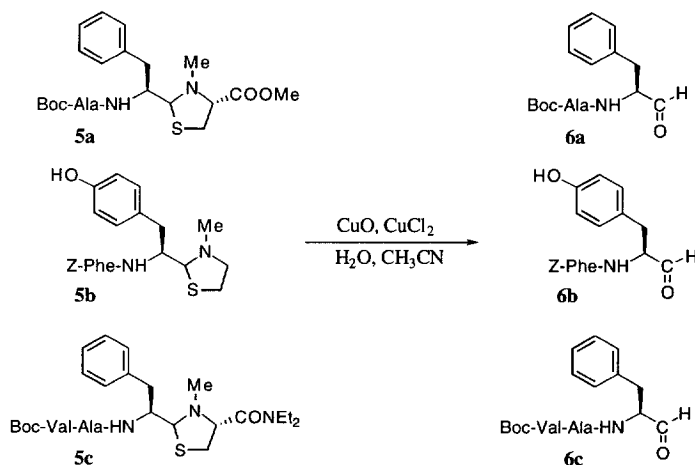
Scheme 4:



1) Lawesson's reagent, dioxane; 2) Bu₄NF, THF; 3) Ph₃P, DEAD, THF; 4) F₃CSO₃Me, CH₃CN; 5) NaBH₄, MeOH; 6) NaOH, MeOH; 7) Et₂NH, BOP, DIEA, CH₂Cl₂; 8) TFA; 9) Boc-Ala-OH, BOP, DIEA, CH₂Cl₂; 10) TFA; 11) Boc-Val-OH, BOP, DIEA, CH₂Cl₂.

Thiazolidine pseudopeptides **5a-c** were easily (a few minutes) hydrolyzed by using copper salts (CuO, CuCl₂) under the reducing conditions described by Dondoni (Scheme 5).^{16,21} The peptidyl aldehydes **6a-c** were obtained as solid products in high yield (90-95%).

Scheme 5:



Following our isolation procedure²¹, only one isomer was obtained after having verified that the diastereomer Boc-L-Ala-D-Phe-H synthesized by an alternative method,⁴ presented distinct ¹H NMR data from the L,L-isomer **6a**.

In conclusion, we present here the synthesis of peptidyl aldehydes using thiazolidine peptides as precursors. Thanks to the mild conditions of thiazoline reduction, the synthesis of functionalized side chain peptidyl aldehydes is now investigated. We also envisage adapting the strategy reported in this paper to solid phase synthesis.

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References and Notes

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- Workup described by Dondoni (ref.16) was modified: CH₃CN was evaporated and the aqueous phase was extracted with AcOEt. The organic phase was dried and the solvent was removed to give the aldehydes as solid products.

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