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Synthesis of Peptidyl Aldehydes from Thiazolidines

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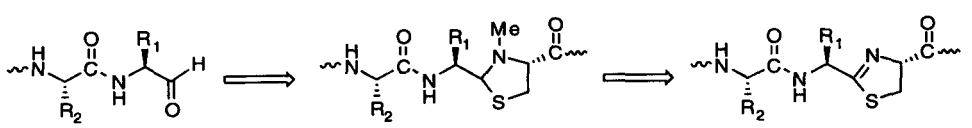
Abstract: Peptidyl aldehydes were synthesized using thiazolidine peptides as precursors. Hydrolysis of the heterocycles is easily accomplished using cupper salts to furnish the peptidyl aldehydes with very good yield and with no epimerization. © 1997 Published by Elsevier Science Ltd.

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. Kawamura[2] used this procedure on preformed tripeptides, whereas Woo[3] 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 $LiAlH_4$ 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 solution[7-9] or on solid support.[10] Two specific methods have been described for the synthesis of peptidyl aspartal[11] and arginal[12] involving respectively an aminal 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.

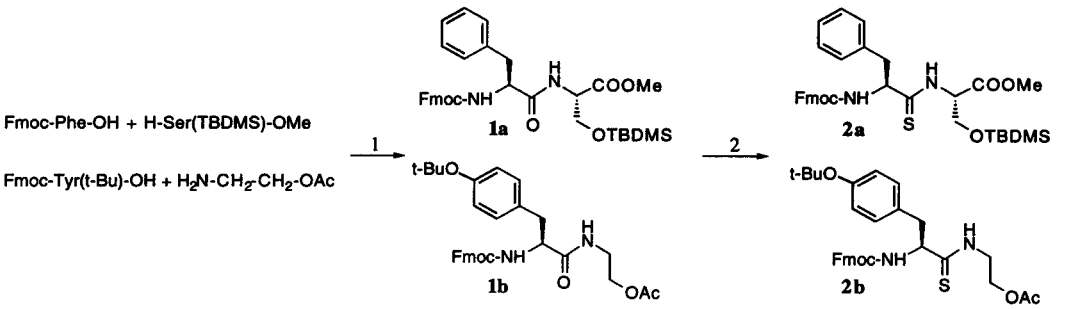
We report here a method for the synthesis of peptidyl aldehydes using a thiazolidine precursor which is hydrolyzed to produce an aldehyde using a mercuric[13-15] or cupper[16] salt under neutral conditions (Scheme 1). The thiazolidine was prepared by reduction of the corresponding thiazoline according 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 reagent[20] on dipeptides **1a,b** whose hydroxyl function was protected (yield 75-85%) (Scheme 2).

Scheme 2:

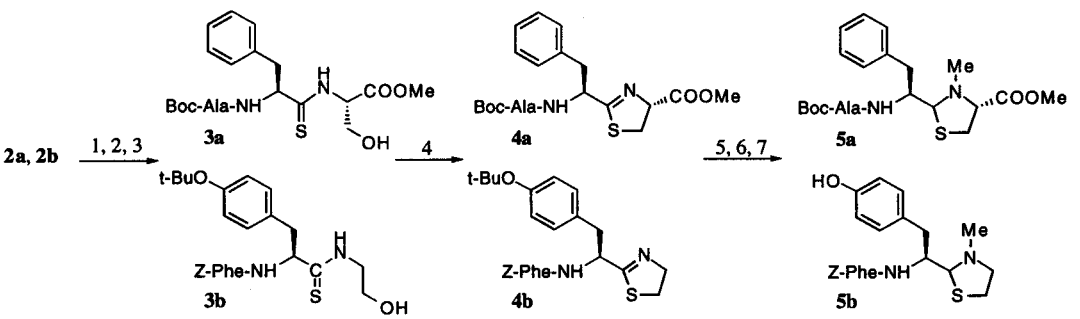


1) BOP, CH_2Cl_2; 2) Lawesson's reagent, dioxane.

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 procedure[16] (methylation and reduction with $NaBH_4$) to give the N-methyl thiazolidine **5a,b** with a yield of 70-85%.

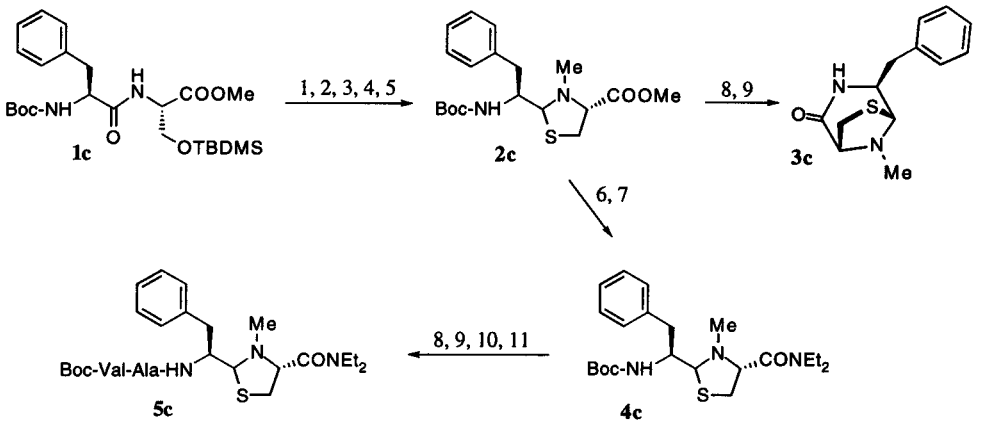
Scheme 3:



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) F_3CSO_3Me, 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.**

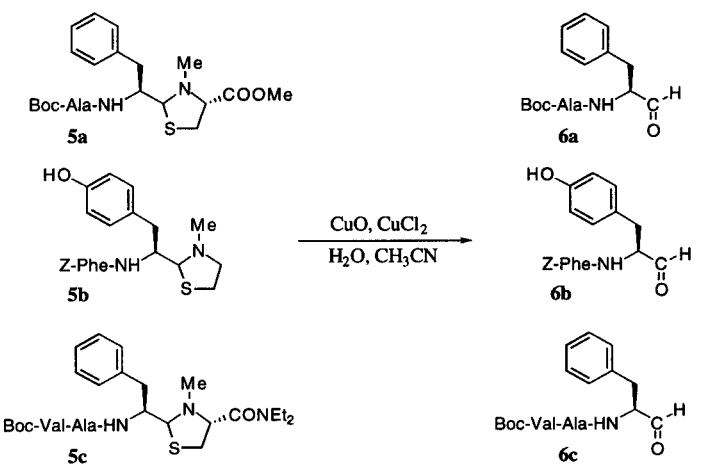
Scheme 4:



1) Lawesson's reagent, dioxane; 2) Bu_4NF, THF; 3) Ph_3P, DEAD, THF; 4) F_3CSO_3Me, CH_3CN; 5) $NaBH_4$, MeOH; 6) NaOH, MeOH; 7) Et_2NH, BOP, DIEA, CH_2Cl_2; 8) TFA; 9) Boc-Ala-OH, BOP, DIEA, CH_2Cl_2; 10) TFA; 11) Boc-Val-OH, BOP, DIEA, CH_2Cl_2.

Thiazolidine pseudopeptides **5a-c** were easily (a few minutes) hydrolyzed by using cupper salts (CuO, $CuCl_2$) under the reducting 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 procedure[21], 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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21. Workup described by Dondoni (ref.16) was modified: CH_3CN was evaporated and the aqueous phase was extracted with AcOEt. The organic phase was dried and the solvant was removed to give the aldehydes as solid products.

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