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Concise and Efficient Synthesis of Dehydropeptide Analogues from Unsaturated 5(4H)-Oxazolone

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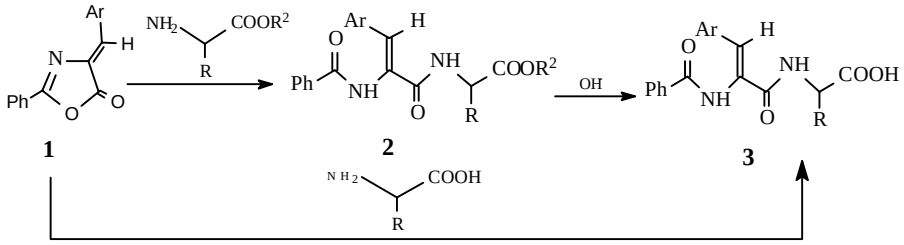
Abstract: Some dehydropeptide analogues were directly synthesized by the reaction of unsaturated oxazolones with free amino acids.

Keywords: Azlactone, free amino acid, dehydrodipeptide.

For improving the bioactivity and bioavailability of peptides, one of the approaches is to introduce a dehydroamino acid residue into the peptide sequence without adversely affecting the bioactivity[1]. The Erlenmeyer reaction[2] was most frequently employed to prepare dehydroamino acids with aromatic and heterocyclic substituent[3].

However, the presence of double bond in a dehydroamino acid dramatically decreases both the nucleophilicity of the amino group and the reactivity of carboxylic group, making the acylation of dehydroamino acids is not a satisfactory method for the preparation of dehydropeptide[4].

Scheme 1



The unsaturated oxazolone can be converted into the corresponding dipeptide by two reaction sequences (**Scheme 1)**. One is to condense **1** with the amino acid ester to form **2**. The resulting dipeptide ester **2** was hydrolyzed to afford **3**[5]. Another reaction sequence is direct condensation of **1** with free amino acid without esterification and saponification. This method would be more favorable.

In the present study, the possibility of ring-cleavage of oxazolone **1** with free amino acid was explored. Considering the reluctant solubility of free amino acid in organic solvents, the water mixing organic solvents like acetone, pyridine, dioxane,

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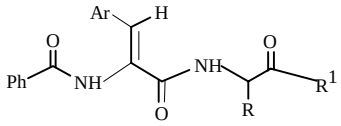
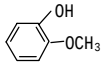
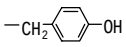
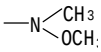
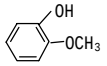
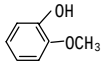
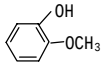
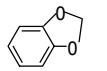
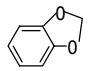
tetrahydrofuran were used as reaction media. Among them, the mixed solvent of THF-water (4:1) has been proved particularly efficient to dissolve all related reactants and to give reasonable yields of products (68 ~ 80%).

Table 1 The physical and chemical data of the target compounds **3a~f**



No.	Ar	R	R′	Mp (°C)	H^1NMR(δ ppm)
3a				145-147	1.40 (t, 2H, -CH_2-), 3.45 (m, 3H, N-CH_3), 3.80 (s, 3H, OCH_3),3.84 (m, 3H, $NOCH_3$) 5.26 (t, 1H, -CH-), 6.90 - 8.0 (m, 13H, Ar-H)
3b			—OH	114-117	3.19 (d, 2H, -CH_2-), 3.58 (s, 3H, OCH_3), 4.87 (dd, 1H, -CH-), 6.8 - 7.8 (m, 14H, Ar-H)
3c		H	—NH_2	149-151	3.55 (s, 3H, OCH_3), 3.67 (d, 2H, -CH_2-), 7.05 - 8.45 (m, 9H, Ar-H)
3d		—$CH(CH_3)_2$	—OH	144-146	0.95 (dd, 6H, CH_3), 87 (m, 1H, -CH-), 3.64 (s, 3H, OCH_3), 4.48 (s, 1H, N-CH-COOH), 6.91 - 8.64 (m, 9H, Ar-H),
3e			—OH	212-215	3.03 (m, 2H, CH_2), 4.49 (m, 1H, N-CH-COOH) 5.99 (s, 2H, O-CH_2-O), 6.89 - 7.99 (m14H, Ar-H)
3f		—$CH(CH_3)_2$	—OH	165-167	0.94 (dd, 6H, CH_3), 2.19 (m, 1H, CH), 4.50 (dd, 1H, N-CH-COOH), 5.98 (s, 2H, O-CH_2-O), 6.83 - 8.06 (m, 9H, Ar-H)

Experimental

To a solution of oxazolone **1**[4] (1 mmol) in THF (5 ml) was added a suspension of amino acid (1.1 mmol) and TEA (1.1 mmol) in THF/H_2O (7:3) (10 ml). After 12 hours of stirring at room temperature, the solvent was removed in vacuum and the residue was partitioned between 10% Na_2CO_3 and diethyl ether. The aqueous layer was washed twice with ether, then chilled to 0°C and acidified to pH 2 with saturated $KHSO_4$ solution. The precipitate was filtered, washed with cold water, and recrystallized from ethonal/ H_2O (1:1).

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