Chinese Chemical Letters Vol. 12, No. 6, pp. 475 – 476, 2001

No-solvent Condensation Reaction of Amino Acids and their Derivatives with Pyrandione

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Abstract: Synthesis of a novel series of N-pyrandione substituted amino acids and their esters **3** *via* a condensation reaction between pyrandione and amino acid or their derivatives in excess ethyl orthoformate without solvent is described. The stereochemistry of **3** has been discussed.

Keywords: Pyrandione, amino acid, condensation reaction, Z/E isomer, green chemistry.

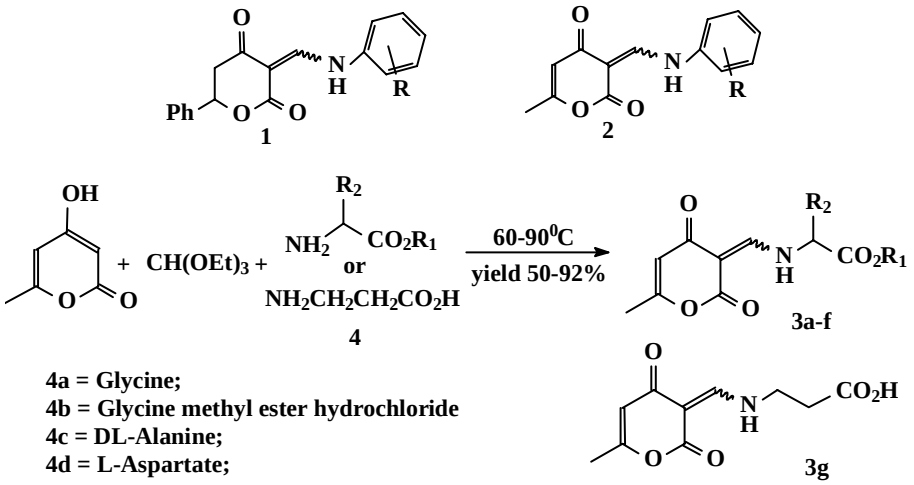
Pyrandione rings are contained within a number of natural products[1], pharmaceutical intermediates[2] and agrochemicals[3]. They have drawn great interest recently because some of them have high activity of inhibiting HIV protease[4]. We have reported the fungicidal activity of **1**[5]. Later we found that **2** also could inhibit *S. Sclerotiorum* (85.7% at a concentration of 500 ppm). This result led us to study the biological activity of the derivatives of this kind of compounds. We have synthesized a series of compound **3a-3g**, introduced natural L- amino acids, unnatural D-amino acids, β-amino acid and their esters to the pyrandione ring in 3-position instead of amino-phenyl group (**Scheme 1**).

Typical procedure: 4-Hydroxy-6-methyl-2H-pyran-2-one (310 mg, 2.46 mmol), DL-alanine **4c** (225 mg, 2.46 mmol) and ethyl orthoformate (1 mL) were heated at 60^0C for 4 hours without solvent. After recovering orthoformate in *vacuo*, the residue was purified by flash chromatography to give **3c** as a white solid, mp. 200°C (dec.), yield 81%. ^{1}HNMR (200MHz, DMSO-d_6) δ 1.47 (m, 3H, CH_3), 2.09 (m, 3H, CH_3), 4.61 (m, 1H, CH), 5.73 (m, 1H, C=CH), 8.32 (m, 1H, CH), 10.20 (br m, 0.2 H, NH), 11.80 (br m, 0.8 H, NH). MS (*m/z*): 225 (M^+). **3a~g** were synthesized with the same method but at different temperatures. The reactivity of amino acids are as follows: β-Alanine＞ DL-Alanine, Glycine＞Glycine methyl ester hydrochloride.

The ^{1}HNMR showed that **3c** existed Z/E isomers in ratio about 1:4 according to the ratio of intensities of two peacks of NH in the ^{1}H NMR spectrum[6].

Above method can be expected to apply in the synthesis of peptides and other complex molecules of derivatives of **3**. The reaction was carried out in no-solvent condition and ethyl orthoformate can be recovered. No materials go to waste. In the environment point of view, this method also has its merit.

Scheme 1 Synthesis of compound **3a-3g**



4a = Glycine;
4b = Glycine methyl ester hydrochloride
4c = DL-Alanine;
4d = L-Aspartate;
4e = L-Lysine;
4f = DL-Threonine;
4g = $NH_2CH_2CH_2CO_2H$

The biological test of these derivatives is in progressing.

Acknowledgment

We thank the National Natural Science Foundation of China for the project support (No.29832050) and Prof. Yu Fen HAN for her helpful bioassay.

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6. The spectral date of **3a-b, 3d-g** were submitted to editorial department of CCL.

Received 31 October, 2000