Chinese Chemical Letters Vol. 11, No. 5, pp. 391–393, 2000

The Synthesis of Some Novel N-[α-(Isoflavone-7-O-) Acetyl] Amino Acid Derivatives

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Abstract: A series of novel N-[α-(isoflavone-7-O-)acetyl] amino acid methyl esters were prepared from the efficient and regioselective alkylation of isoflavones with chloroacetyl amino acid derivatives under mild condition.

Keywords: Isoflavone analogues, N-[α-(isoflavone-7-O-)acetyl] amino acid methyl ester, synthesis.

Isoflavonoids are biologically important natural products occurring mainly in species of the Leguminosae family and have shown a wide spectrum of biological activities including estrogenic, anticancer, insecticidal, pisciadal and antifungal property[1]. These isoflavonoid phytoestrogens are rich in some plant diet such as soybean[2]. Animal experiments had shown that soybean diet inhibit radiation- and chemical-induced tumor of the mammary[3], skin[4], and liver[5]. A study conducted by Barnes *et al.*[6] suggested that soybean isoflavones may be responsible for the anticarcinogenic effect of soy. However, the pharmaceutical forms of purified isoflavones did not show such activity in clinic trial[7]. Some researchers proposed that the beneficial effect of soybean came from the combination of the protein and the isoflavones. This prompted us to synthesize a series of compounds constructed by the attachment of an amino acid or an oligopeptide to a synthetic isoflavone to test if they have above activities.

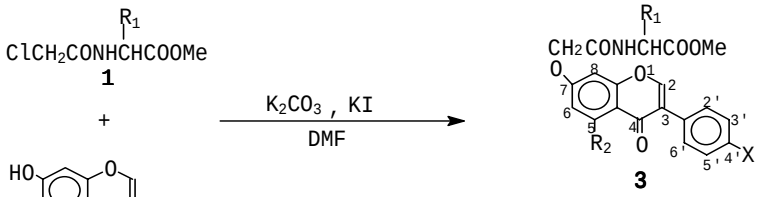
In addition, it is believed that the introduction of an amino acid or an oligopeptide subunit into a biological active molecule might provide a new compound, which shares in the potentialities of the amino acids to enhance the interaction and selectivity towards the target-cells, facilitate the permeation of the cell walls and improve the bioavailability[8].

Herein, we report a selective and efficient approach to synthesize a class of new compounds *via* modifying isoflavones with glycine, valine, nor-leucine or aspartic acid respectively at C-7 hydroxyl by etheral bond **(scheme 1)**.

In essence, our synthetic approach to compound **3,** consisting of treating isoflavones **2** with easily accessible chloroacetyl amino acid methyl ester **1** in DMF at 75-80℃ for 5 hours, was based upon the efficient and regioselective O-alkylation of

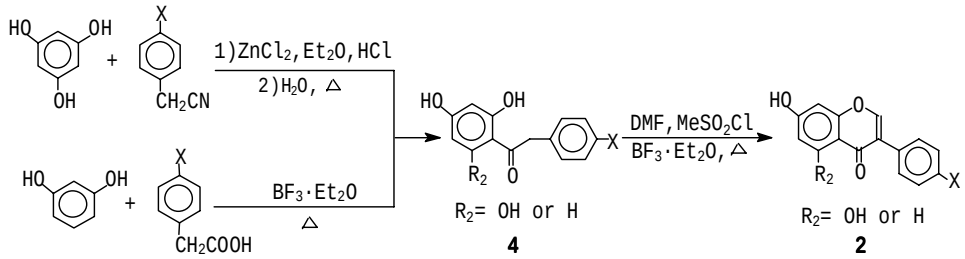
chromanones[9]. The isoflavones **2** were prepared by the ring closure of the corresponding deoxybenzoins **4** with boron trifluoride etherate and methansulphonyl chloride in dry dimethylformamide at 60-70℃[10]. The deoxybenzoins **4** were prepared in two ways **(scheme 2)**: resorcinol was treated with the appropriately substituted phenyl acetic acid using boron trifluoride etherate both as catalyst and solvent to afford 2,4-dihydroxydeoxybenzoin derivatives[11], while the preparation of 2,4,6-trihydroxy deoxybenzoins through Hoesch reaction of phloroglucinol with a variety of *p*-substituted phenyl acetonitriles[12] seems to be a necessary approach[13].

Scheme 1



a. R_1=H, R_2=OH, X=Cl, 95%
b. R_1=$CH_3(CH_3)CH$-, R_2=H, X=H, 78%
c. R_1=$CH_3(CH_3)CH$-, R_2=OH, X=Cl, 82%
d. R_1=$CH_3(CH_3)CH$-, R_2=OH, X=Br, 75%
e. R_1=$CH_3(CH_2)_3$-, R_2=OH, X=F, 90%
f. R_1=$CH_3(CH_2)_3$-, R_2=OH, X=OMe, 80%
g. R_1=CH_3OOCCH_2-, R_2=OH, X=F, 72%
h. R_1=CH_3OOCCH_2-, R_2=H, X=F, 70%

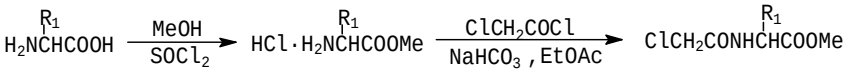
Scheme 2



The chloroacetyl amino acid methyl esters **1** were obtained in two steps beginning with the esterification of amino acids with methanol-thionyl chloride[14] to give the amino acid methyl ester hydrochlorides **5** that was treated with chloroacetyl chloride in dry ethyl acetate in the presence of sodium hydrogen carbonate at room temperature for two days to afford compounds **1** in yields over 90% **(Scheme 3)**.

Alternatively, compounds **3** were also prepared by the O-alkylation of compounds **2** with **1** at room temperature for 1 day. If the optically active amino acid is employed, we obtained optically active compound **3**.

Scheme 3



In summery, we have described an efficient approach to synthesize the isoflavone analogues containing amino acid residues and prepared a series of novel N-[α-(isoflavone-7-O-)acetyl] amino acid methyl esters. The evaluation of their biological activities is in proceeding.

References and Notes

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15. All new compounds gave satisfactory ^{1}H and ^{13}C NMR and mass spectral data. Representative data includes: **3a**: mp 180-181℃; ^{1}HNMR (400MHz, CD_3SOCD_3) δ 8.67 (t, J=5.6Hz, 1H, NH), 8.59 (s, 1H, 2-H), 7.63 (d, J=8.4Hz, 2H, 2'-and 6'-H), 7.53 (d, J=8.4Hz, 2H, 3'-and 5'-H), 6.73 (d, J=2Hz, 1H, 6-H), 6.50 (d,J=2Hz, 1H, 8-H), 4.73 (s, 2H, OCH_2), 3.93 (d, J=5.6Hz, 2H, $NHCH_2$), 3.65 (s, 3H, $COOCH_3$); ^{13}C NMR (400Hz, CD_3COCD_3) δ 180.09, 170.18, 167.65, 163.75, 161.81, 157.49, 155.96, 133.10, 130.92, 129.75, 128.47, 121.62, 105.97, 99.19, 93.65, 67.23, 51.98, 40.58; MS (EI) *m/z*: 417 (M^+), 358 (M^+-COOMe). **3b**: mp 106-107℃; ^{1}HNMR (400MHz, CD_3COCD_3) δ 8.30 (s, 1H, 2-H), 8.15 (d, J=8.8Hz, 1H, NH), 7.60-7.70 (m, 3H, 5-H , 2'- and 6'-H), 7.30-7.50 (m, 3H, 3'-,4'- and 5'-H), 7.18 (d-d J_o=8.8Hz, J_m=2.4Hz, 1H, 6-H), 7.14 (d, J=2.4Hz, 1H, 8-H), 4.81 (s, 2H, OCH_2), 4.44-4.50 (m, 1H, NHCH), 3.70 (s, 3H,$COOCH_3$), 2.13-2.30 (m, 1H, Me_2 CH), 0.94 (d, J=4.0Hz, 3H,CH_3), 0.92 (d, J=4.0Hz, 3H,CH_3); ^{13}C NMR (400Hz, CD_3COCD_3) δ 175.23, 172.36, 167.71, 162.93, 158.40, 154.30, 133.06, 129.72, 128.82, 128.54, 128.10, 125.39, 119.64, 115.66, 102.37, 67.99, 57.80,52.13,31.35,19.23,18.21; MS (EI) *m/z*: 409 (M^+),350 (M^+-COOMe). **3c**: mp 142-144℃; ^{1}HNMR (400MHz, CD_3COCD_3) δ 8.39 (s,1H,2-H),7.66 (d,J=8.8Hz,2H,2'-and 6'-H), 7.60 (d,J=1.6Hz,1H,NH), 7.49 (d,J=8.8Hz,2H,3'-and 5'-H), 6.66 (d, J=2.4Hz, 1H, 6-H), 6.47 (d, J=2.4Hz, 1H, 8-H), 4.77 (s,2H,OCH_2), 4.44-4.48 (m,1H,NHCH), 3.70 (s,3H,$COOCH_3$), 2.10-2.30 (m,1H,Me_2CH), 0.94 (d,J=3.2Hz,3H,CH_3), 0.92 (d,J=3.2Hz,3H,CH_3); ^{13}C NMR (400Hz, CD_3COCD_3) δ 181.03, 172.35, 167.61, 164.61, 163.07, 158.59, 155.73, 134.31, 131.72, 130.62, 129.05, 123.06, 106.99, 99.58, 93.97, 67.86, 57.84, 52.13, 31.33, 19.22, 18.20; MS (EI) *m/z*: 459 (M^+),400 (M^+-COOMe). **3d**: mp 150-152℃; ^{1}HNMR (400MHz, CD_3COCD_3) δ 8.41 (s, 1H, 2-H), 7.16 (d, J=8.4Hz, 1H, NH), 7.65 (d, J=8.4Hz, 2H,2'-and 6'-H),7.60

(d,J=8.4Hz,2H,3'-and 5'-H), 6.68 (d,J=2.4Hz,1H,6-H), 6.49 (d, J=2.4Hz,1H,8-H), 4.79 (s, 2H, OCH_2), 4.49-4.51 (m,1H,NHCH), 3.72 (s,3H,$COOCH_3$), 2.10-2.30 (m, 1H,Me_2CH), 0.96 (d, J=2.4Hz, 3H, CH_3), 0.92 (d, J=2.4Hz, 3H, CH_3) ;^{13}C NMR (400Hz, CD_3COCD_3) δ 180.97, 172.35, 167.59, 164.61, 163.07, 158.60, 155.71, 132.05, 131.72, 131.06, 123.10, 122.52, 106.99, 99.59, 93.97, 67.86, 57.83, 52.13, 31.33, 19.22, 18.20; MS (EI) *m/z*: 503 (M^+), 505 ($M^{+\cdot}$+2). **3e** : mp 106-108℃; ^{1}HNMR (400MHz, CD_3COCD_3) δ 8.36 (s, 1H, 2-H), 7.77 (d, J=7.6Hz, 1H, NH), 7.60-7.70 (m, 2H, 2'-and 6'-H), 7.20-7.28 (t, $J_{FH}\approx J_O\approx$8.8Hz, 2H, 3'-and5'-H), 6.65 (d, J=2.0Hz, 1H, 6-H), 6.45 (d, J=2.0Hz, 1H, 8-H), 4.73 (s, 2H, OCH_2), 4.50-4.54 (m, 1H, CH), 3.68 (s, 3H, $COOCH_3$), 1.65-1.91 (m, 2H, $CHCH_2$), 1.2-1.4 (m, 4H, CH_2CH_2), 0.83-0.87 (m, 3H, CH_3); ^{13}C NMR (400Hz, CD_3COCD_3) δ 181.21, 172.94, 167.60, 164.56, 163.10, 162.20, 158.67, 155.47, 131.90, 131.82, 128.04, 123.37, 115.89, 115.67, 107.10, 99.64, 93.95, 68.01, 52.60, 52.22, 31.84, 28.39, 22.71, 13.98; MS (EI) *m/z*: 457 ($M^{+\cdot}$), 398 ($M^{+\cdot}$-COOMe). **3f**: mp 62-64℃; ^{1}HNMR (400MHz, CD_3COCD_3) δ 8.29 (s, 1H, 2-H), 7.75 (d, J=7.6Hz, 1H, NH), 7.55 (d, J=8.8Hz, 2H, 2'-and 6'-H), 7.02 (d, J=8.8Hz, 2H, 3'-and 5'-H), 6.63 (d, J=2.4Hz, 1H, 6-H), 6.44 (d, J=2.4Hz, 1H, 8-H), 4.73 (s, 2H, OCH_2), 4.45-4.67 (m, 1H, CH), 3.83 (s, 3H, $COOCH_3$), 3.68 (s, 3H, 4'-OCH_3), 1.67-1.92 (m, 2H, $CHCH_2$), 1.20-1.40 (m, 4H, CH_2CH_2), 0.85 (t, 3H, CH_3); ^{13}C NMR (400Hz, CD_3COCD_3) δ 181.49, 172.93, 167.61, 164.35, 163.08, 160.55, 158.61, 154.81, 130.94, 123.92, 123.78, 114.36, 107.09, 99.46, 93.77, 67.92, 55.42, 52.54, 52.22, 31.78, 22.70, 13.99; MS (EI) *m/z*: 469 (M^+), 410 (M^+-COOMe). **3g** : mp 64-66℃; ^{1}HNMR (400MHz, CD_3COCD_3) δ 8.37 (s,1H,2-H), 7.96 (d, J=8.0Hz, 1H, NH), 7.65-7.69 (m, 2H, 2'-and 6'-H), 7.23 (t, $J_{FH}\approx J_O\approx$8.8Hz, 2H, 3'-and5'-H), 6.65 (d, J=2.4Hz, 1H, 6-H), 6.44 (d, J=2.4Hz, 1H, 8-H), 4.90-4.94 (m, 1H, CH), 4.73 (s, 2H, OCH_2), 3.69 (s, 3H, $COOCH_3$), 3.63 (s, 3H, $COOCH_3$), 2.90-2.95 (m, 2H, $CHCH_2$); ^{13}C NMR (400Hz, CD_3COCD_3) δ 181.20, 171.47, 167.40, 164.60, 164.35, 163.07, 162.16, 158.64, 155.53, 131.90, 131.82, 127.98, 123.32, 115.88, 115.66, 107.12, 99.56, 93.92, 67.89, 52.66, 51.99, 48.99, 36.16; MS (EI) *m/z*: 473 (M^+), 414 (M^+-COOMe). **3h** : mp 149.5-151℃; ^{1}H NMR (400MHz, CD_3COCD_3) δ 8.34 (s, 1H, 2-H), 8.14 (d, J=8.8Hz, 1H, 5-H), 8.00 (d, J=8.0Hz, 1H, NH), 7.65-7.70 (m, 2H, 2'-and 6'-H), 7.17-7.22 (t, $J_{FH}\approx J_O\approx$8.8Hz, 2H, 3'-and 5'-H), 7.12-7.17 (m, 2H, 6-H and 8-H), 4.92-4.95 (m, 1H, CH), 4.77 (s, 2H, OCH_2), 3.69 (s, 3H, $COOCH_3$), 3.62 (s, 3H, $COOCH_3$), 2.91-2.94 (m, 2H, $CHCH_2$) ;^{13}C NMR (400Hz, CD_3COCD_3) δ 175.18, 171.47, 167.55, 167.49, 164.42, 162.76, 161.99, 158.40, 154.32, 131.75, 131.67, 129.25, 128.10, 124.39, 119.58, 115.70, 115.48, 102.38, 67.99, 52.66, 51.98, 49.08, 36.17; MS (EI) *m/z*: 457 (M^+), 398 (M^+-COOMe).

Received 6 January 2000