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RESEARCH ARTICLE

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Synthesis of α-amino-β-keto-esters (β-oxodipeptides)

Abstract The synthesis of α-amino-β-keto-esters (β-oxo dipeptides) was studied. Corresponding α-amino-β-keto-esters were prepared from BOC-(L)-Valine and BOC-(L)-isoleucine by coupling with (D,L)-threonine hydrochloride and oxidation with Dess-Martin periodinane (DMP) with a total yield of 48% and 38%, respectively.

Keywords α-amino-β-keto-esters, dipeptide, oxidation, Dess-Martin Periodinane (DMP)

In recent years, a wide variety of natural cyclopeptides characterized by an alternating sequence of oxazole and thiazole moieties have been isolated from marine sources, mainly sponges and ascidians. These compounds have usually been identified as secondary metabolites of marine organisms possessing good cytotoxicity and antibacterial activity. This has prompted many chemists to study the structure and synthesis of these compounds [1,2]. The imidazole unit plays a major role in the biological functions of many peptides and proteins. However, no cyclopeptides containing imidazole units have yet been found in nature. Thus, some recent studies focused on the synthesis of the imidazole analogs of cyclopeptides [3,4]. As the key segments of the cyclopeptides mentioned above, the syntheses of these 5-membered heterocyclic dipeptide mimetics **1** were studied by Gorden T D (Scheme 1) [5]. They found that α-amino-β-keto-esters (β-oxo-dipeptides) of general structure **2** are useful intermediates in the synthesis of oxazole **1a**, thiazole **1b** and imidazole **1c** dipeptide mimetics through different synthetic routes.

In this paper, α-amino-β-keto-esters are the synthetic target molecules. Amino ketones **3** and **4** were prepared from BOC-(L)-Valine **5** and BOC-(L)-isoleucine **6**, which were coupled with (L)-threonine methyl ester hydrochloride **7** and the resulting secondary alcohols **8** and **9** were then oxidized with the Dess-Martin periodinane (DMP) [6] giving 48% yield and 38% yield (Scheme 2).

1 Experiments

1.1 Apparatus and reagents

Specific rotations were measured on a WZZ-3 polarimeter. Infrared spectra were obtained using a BIO-BAD EXALIBUR FTS3000 series FT-IR instrument. ^{1}H and ^{13}C-NMR spectra were recorded employing a Bruker AV360 instrument and chemical shifts (δ) are in ppm relative to TMS used as internal standard. Mass spectra were recorded on a Finnigan MAT 95 spectrometer using fast atom bombardment (HR-FABMS). All chemicals and solvents were of analytical grade. All reactions were monitored by TLC using glass sheets coated with silica gel (type GF254, Qingdao Haiyang). Flash column chromatography was carried out using 200–300 mesh silica gel. The oxidant, DMP, was prepared according to reference [6].

1.2 BOC-(L)-Val-(D, L)-Thr-OMe 8

N-Methylmorpholine (NMM, 1.5 mL, 12.9 mmol), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl, 2.5 g, 12.9 mmol) and N-hydroxybenzotriazole (HOBt, 1.7 g, 12.9 mmol) were added to a stirred solution of BOC-(L)-valine **5** (2.5 g, 11.8 mmol) in dichloromethane (DCM, 10 mL) at 0°C under nitrogen. The mixture was stirred at 0°C for 20 min and then a precooled solution of (D, L)-threonine methyl ester hydrochloride **7** (1.9 g, 11.8 mmol) deprotonated with NMM (1.5 mL, 12.9 mmol) in DCM (5 mL) was slowly added dropwise. The mixture was stirred at 0°C for 1 h and then at room temperature for 14 h. Water (50 mL) was added and the separated aqueous layer was then extracted with ethyl acetate (6 × 50 mL). The combined organic extracts was washed with sodium hydrogen carbonate solution (3 × 40 mL) and brine (3 × 40 mL) then dried ($MgSO_4$) and evaporated in vacuo to leave the dipeptide **8** (3.75 g, 96%) as a pale yellow oil without further purification.

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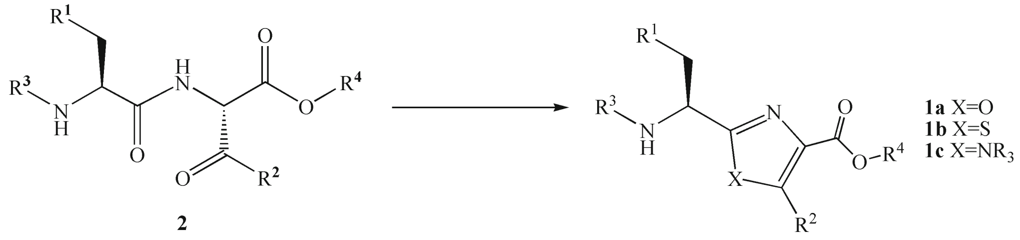
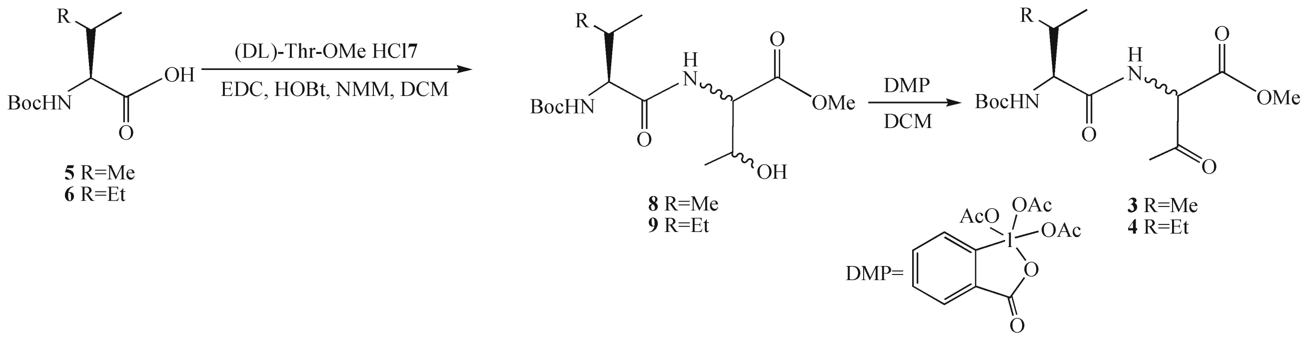


Scheme 1



Scheme 2

$[\alpha]_D^{23} = -7.2$ (*c* 1.0 in MeOH); ^{1}H-NMR (360 MHz, $CDCl_3$): δ 6.86(1H, br s, NH), 5.19(1H, br s, NH), 4.63 (1H, dd, $J = 2.5$, 9.0 Hz, $C\underline{H}CHCH_3OH$), 4.37(1H, dq, $J = 2.5$, 6.4 Hz, $C\underline{H}CH_3OH$), 3.98–3.91(1H, m, $C\underline{H}CH(CH_3)_2$), 3.78(3H, s, OCH_3), 2.09–2.04(1H, m, $C\underline{H}(CH_3)_2$), 1.44(9H, s, Bu^t), 1.21(3H, d, $J = 6.4$ Hz, $CHC\underline{H}_3OH$), 0.99(3H, s, $CHC\underline{H}_3CH_3$), 0.96(3H, s, $CHCH_3C\underline{H}_3$). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 171.3, 171.2, 156.1, 79.9, 68.0, 60.1, 57.4, 52.4, 30.8, 28.2(3C), 21.0, 14.1; IR (solution $CHCl_3$, cm^{-1}): 3432, 2977, 1732, 1682.

1.3 Methyl 2-{[(*s*)-2-(*tert*-butoxycarbonylamino)-3-methylbutanoyl]-amino}-3-oxobutanoate 3

The DMP (0.9 g, 2.1 mmol) was added in one portion to a solution of dipeptide **8** (0.62 g, 1.9 mmol) in DCM (15 mL) at room temperature. The resulting yellow solution was stirred for 4 h at room temperature. The reactant was quenched with 15 mL of 1:1 10% $Na_2S_2O_3$: saturated aqueous $NaHCO_3$. The aqueous layer was extracted with DCM (3 × 30 mL) and the combined organic layers was washed with water (30 mL) and brine (30 mL) then dried with Na_2SO_4 and concentrated. The residue was purified by chromatography on silica using 50% ethyl acetate in petrol ether (40°C–60°C) as eluent to give the amino ketone **3** (0.31 g, 50%) as a yellow oil. $[\alpha]_D^{23} = -8.6$ (*c* 2.8 in $CHCl_3$); ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.30(1H, br s, NH), 5.26–5.23(1H, m, $C\underline{H}COCH_3$), 5.20(1H, br s, NH), 4.10–4.08(1H, m, $C\underline{H}CH(CH_3)_2$), 3.76(3H, s, OCH_3), 2.34 (3H, s, $COCH_3$), 2.18–2.06(1H, m, $C\underline{H}(CH_3)_2$), 1.39(9H, s, Bu^t), 0.93(3H, d, $J = 6.8$ Hz, $CHC\underline{H}_3CH_3$), 0.88(3H, d, $J = 6.8$ Hz, $CHCH_3C\underline{H}_3$). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 198.2, 198.1, 171.6, 166.3, 166.3, 155.7, 79.9, 62.8, 62.7, 59.3, 53.2, 53.1, 30.9, 30.7, 28.2, 27.9, 27.8, 19.1, 19.0, 17.4, 17.3. IR ($CHCl_3$ solution, cm^{-1}): 3360, 3404, 2968, 2933, 1756, 1737, 1713, 1652. HRMS $[M+Na]^+$ *m/z* 353.1664 (calcd for $C_{15}H_{26}N_2O_6Na$ 353.1688)

1.4 BOC-(L)-Ile-(L)-Thr-OMe 9

Using the same method in Subsection **1.2**, the dipeptide **9** was obtained (0.89 g, 51%) as a pale yellow oil without further purification. $[\alpha]_D^{23} = -15.8$ (*c* 1.2 in $CHCl_3$), ([5], $[\alpha]_D^{29} = -14.9$ (*c* 1.32 in $CHCl_3$)); ^{1}H-NMR (360 MHz, $CDCl_3$): δ 6.86(1H, d, $J = 9.0$ Hz, NH), 5.17(1H, d, $J = 8.8$ Hz, NH), 4.63(1H, dd, $J = 2.5$, 9.0 Hz, $NHC\underline{H}$-$CHCH_3OH$), 4.37(1H, dq, $J = 2.4$, 6.3 Hz, $C\underline{H}CH_3OH$), 4.00–3.95(1H, m, $C\underline{H}CHCH_3(CH_2CH_3)$), 3.77(3H, s, OCH_3), 1.85–1.83(1H, m, $C\underline{H}CH_3(CH_2CH_3)$), 1.48–1.47 (1H, m, $CHCH_3(C\underline{H}_2CH_3)$), 1.43(9H, s, Bu^t), 1.21(3H, d, $J = 6.4$ Hz, $CHC\underline{H}_3OH$), 1.26–1.12(1H, m, $CHCH_3$-$(C\underline{H}_2CH_3)$), 0.96(3H, d, $J = 6.7$ Hz, $CHC\underline{H}_3(CH_2CH_3)$, 0.92(3H, t, $J = 7.4$ Hz, $CHCH_3(CH_2C\underline{H}_3)$); IR ($CHCl_3$ solution, cm^{-1}): 3434, 2970, 2933, 2879, 1743, 1712, 1682, 1491, 1456, 1368, 1314, 1156, 1092, 1000, 908.

1.5 Methyl 2-{[(*s*)-2-(*tert*-butoxycarbonylamino)-3-ethylbutanoyl]-amino}-3-oxo-butanoate 4

Using the same method in Subsection **1.3**, the amino ketone **4** was obtained (0.65 g, 75%) as a yellow oil.

$[\alpha]_D^{23} = -14.3$ (c 2.8 in $CHCl_3$); ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.16(1H, br s, NH), 5.23(1H, br s, NH), 5.10–5.05(1H, m, $NHC\underline{H}COCH_3$), 4.14–4.08(1H, m, $C\underline{H}CHCH_3(CH_2CH_3)$), 3.80(3H, s, OCH_3), 2.38(3H, s, $COCH_3$), 1.98–1.89(1H, m, $C\underline{H}CH_3(CH_2CH_3)$), 1.50–1.46(1H, m, $CHCH_3(C\underline{H}_2CH_3)$), 1.44(9H, s, Bu^t), 1.24–1.14(1H, m, $CHCH_3(C\underline{H}_2CH_3)$), 0.94(3H, d, $J = 6.8$ Hz, $CHC\underline{H}_3(CH_2CH_3)$), 0.90(3H, t, $J = 7.4$ Hz, $CHCH_3(CH_2C\underline{H}_3)$). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 198.1, 198.0, 171.5, 171.5, 166.4, 166.3, 155.7, 80.1, 80.0, 62.9, 62.9, 59.0, 58.9, 53.3, 53.3, 37.4, 37.2, 28.0, 27.9, 24.6, 24.5, 15.9, 15.5, 11.5. IR ($CHCl_3$ solution, cm^{-1}): 3418, 2968, 2932, 2877, 1751, 1727, 1711, 1680, 1490, 1457, 1368, 1156, 909. HRMS $[M+Na]^+$ m/z 367.1816 (calcd for $C_{15}H_{26}N_2O_6Na$ 367.1845)

2 Results and discussion

2.1 Synthetic route

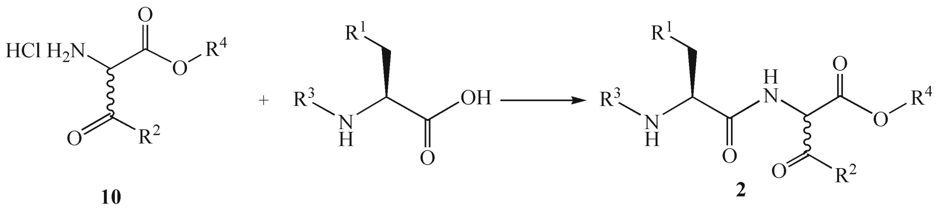
Singh had described an efficient route for the general synthesis in which the α-amino-β-keto-esters hydrochloride **10** was coupled with BOC- or CBZ-ptotected α-amino acids to provide the oxo-dipeptides **2** (Scheme 3) [8]. The α-amino-β-keto-ester hydrochlorides **10** were obtained through alkylation of the Schiff base of an α-amino-ester with acyl chloride and then acidification with hydrochloric acid. Due to the low temperature (−78°C) requirement and the numerous steps involved, this synthetic method was not used in this paper. In 1973, Suzuki had reported that α-amino-β-keto-esters hydrochlorides could be prepared in good yields by the acid hydrolysis of α-acyl-α-isocyanoacetate analogs and oxazole-4-carboxylate derivatives which, in turn, can be easily obtained by the reaction of α-isocyanoacetate analogs with acyl halides or acid anhydrides in the presence of metallic or organic bases [9]. Because the starting material, the α-isocyanoacetate analog, is not easily obtained, this synthetic method was not used widely.

If we consider coupling the N-protected amino acids and amino esters with hydroxy group, the dipeptides with hydroxy group could be obtained. Then, the hydroxy group could be oxidized to yield the target compounds, oxo-dipeptides. This synthetic method could shorten the synthetic route and simplify the operation. We studied this synthetic method choosing BOC-(L)-Valine **5** and BOC-(L)-Isoleucine **6** as starting materials. First, we coupled the N-BOC-amino acid **5** or **6** with (D, L)-threonine methyl ester hydrochloride **7** to get dipeptide **8** or **9** with a secondary alcohol. After oxidation of the secondary alcohol, the α-amino-β-keto-esters were successfully obtained in 48% yield and 38% yield which proved that this two-step method is feasible. The oxidation of the secondary alcohol to the ketone is introduced in the next section.

2.2 Oxidation of alcohols

There are a lot of methods for the oxidation of alcohols to ketones or aldehydes. The PCC oxidation, Swern oxidation, 2-iodoxybenzoic acid (IBX) oxidation and DMP oxidation are in common use. In this paper, we studied the oxidation of dipeptide, BOC-(L)-val-(D, L)-thr-OMe **8** using PCC oxidation, Swern oxidation, IBX oxidation and DMP oxidation. The results are shown in Table 1.

The results (Table 1) showed that the PCC oxidation and Swern oxidation were ineffective in the oxidation of dipeptide **8**. Some product was obtained through IBX oxidation but the reaction was not complete even with prolonged reaction time. Only through DMP oxidation was the product **3** obtained in good yield (50%). Oxidation of the dipeptide **9** using DMP gave the α-amino-β-keto-ester **4** also in good yield (75%). Consequently, DMP is an effective oxidant for the oxidation of a hydroxy group in the dipeptides.



Scheme 3

Table 1 Results of oxidation of dipeptide BOC-(L)-Val-(D, L)-Thr-OMe 8 with four methods

method	PCC oxidation	swern oxidation	IBX oxidation	DMP oxidation
yield(%)	no product	no product	14%	50%
$[\alpha]_D^{23}$			−7.0 (c 1.0 in $CHCl_3$)	−8.6 (c 2.8 in $CHCl_3$)

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