BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 52 (10), 3111—3112 (1979)

A Synthetic Method for *N*-Benzyloxycarbonyl Hydroxy Amino Acid *t*-Butyl Esters

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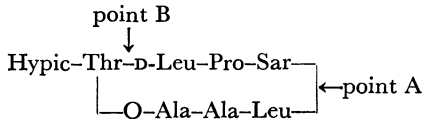
(Received September 13, 1978)

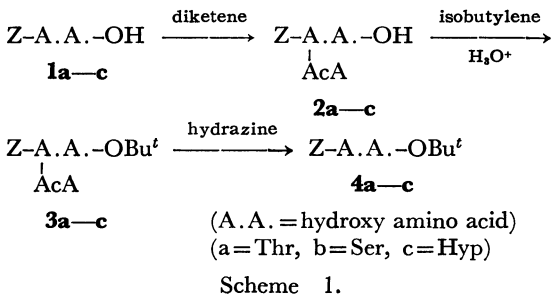
Synopsis. A preparative method for the *N*-benzyloxycarbonyl hydroxy amino acid *t*-butyl esters using the acetoacetyl group as a protecting group for the hydroxyl group of hydroxy amino acids is described. The acetoacetyl group is readily introduced into the hydroxyl group with diketene and effectively deprotected from the O-protected compounds using hydrazine.

Recently, a new method for the synthesis of a peptide lactone as exemplified in the preparation of *N*-(3-hydroxypicolinyl) threonyl-D-leucyl-propylsarcosyl-leucyl-alanyl-alanine threonine lactone, *via* peptide cyclization between sarcosine and leucine (Fig. point A) has been reported.[1] The peptide lactone has also been synthesized by an alternative route, in which peptide cyclization was achieved by peptide bond formation between threonine and D-leucine (Fig. point B).[2] In the latter case it was necessary to prepare *N*-benzyloxycarbonyl threonine *t*-butyl ester (**4a**) as a starting material.

N-benzyloxycarbonyl amino acids are readily esterified by treating the acid with isobutylene in the



presence of an acid catalyst. In the case of *N*-benzyloxycarbonyl hydroxy amino acids, however, this method is accompanied by simultaneous *O*-alkylation. A novel preparation of *t*-butyl ester of the hydroxy amino acids **4a**—**c** *via* protection of the hydroxyl group of **1a**—**c** effectively overcomes this problem. For the O-protection the acetoacetyl (AcA) group proved very effective for this purpose, the synthetic route of which is shown in Scheme 1. A practical example will be given to illustrate the route for the case of threonine derivatives. The reaction of Z-Thr-OH (**1a**) with diketene was conducted in dichloromethane in the presence of an equimolar amount of triethylamine at room temperature to give Z-Thr(AcA)-OH (**2a**) in 96% yield. Esterification of **2a** with isobutylene in the presence of a catalytic amount of concd sulfuric acid gave the *t*-butyl ester **3a** in 65% yield.



Scheme 1.

Similarly, but without isolation of **2b**—**c**, compounds **1b**—**c** were converted into the corresponding esters **3b**—**c**. Attempts to protect the hydroxyl group of **1a**—**c** by acetylation gave unsatisfactory results.

Removal of the protecting group from compound **3a** was achieved by treatment with a twicemolar amount of hydrazine in ethanol for 30 min, the yield of deprotected product **4a** being 94%. Similarly, the deacylated products **4b**—**c** were prepared from compounds **3b**—**c**, the results of which are listed in Table 1.

Table 1. Preparation of *N*-benzyloxycarbonyl hydroxy amino acid *t*-butyl esters **4a**—**c** from *N*-benzyloxycarbonyl hydroxy amino acids **1a**—**c**

Starting material	Yield/%	
	3a—**c**	**4a**—**c**
Z-Thr-OH (**1a**)	65[a]	94
Z-Ser-OH (**1b**)	65[b]	96
Z-Hyp-OH (**1c**)	80[b]	quant.

a) Yield based on **2a**. b) Yields based on the corresponding **1b**—**c**.

Experimental

All melting points are uncorrected. The NMR spectra were recorded on a JEOL/MH-60. The chemical shifts are reported on the δ scale relative to TMS as an internal standard. The IR spectra were measured with a JASCO IRA-1 diffraction grating infrared spectrometer. The optical rotation values were measured with a JASCO DIP-SL polarimeter.

Z-Thr(AcA)-OH (2a). To a suspension of Z-Thr-OH (**1a**) (506 mg, 2 mmol) in dichloromethane (10 ml) was added triethylamine (202 mg, 2 mmol). To the resulting clear solution, diketene (168 mg, 2 mmol) was added. After stirring at room temperature for several hours, the reaction mixture was evaporated to dryness under reduced pressure. The residual oil was dissolved in ethyl acetate and the organic layer washed with 1M HCl (2.2 ml) and water, and dried over Na_2SO_4. After evaporation of the solvent, the desired product was obtained as an oil (96% yield; 646 mg): IR (neat) 3300, 2990, 1710, 1530, 1060 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (d, 3H, J=7 Hz), 2.14 (s, 3H), 3.36 (s, 2H), 4.30—4.65 (dd, 1H, J=9 Hz), 5.07 (s, 2H), 5.27—5.90 (m, 2H), 7.24 (s, 5H), 8.75 (bs, 1H). DCHA salt of **2a**: mp 140—141 °C; $[\alpha]_D^{25}$ +3.0° (0.67, absEtOH); Found: C, 64.80; H, 8.26; N, 5.26%. Calcd for $C_{28}H_{42}N_2O_7$: C, 64.84; H, 8.16; N, 5.40%.

Z-Thr(AcA)-OBut (3a). Compound **2a** (337 mg, 1 mmol) was dissolved in dichloromethane (10 ml) and the solution saturated with isobutylene in the presence of concd sulfuric acid (0.05 ml). The reaction mixture was allowed to stand at room temperature for 65 h, evaporated *in vacuo* and the residue dissolved in ethyl acetate. The organic layer was washed with 10% $NaHCO_3$ and water, dried over Na_2SO_4

and filtered. Then it was evaporated to dryness *in vacuo* to give the crude product. The crude oil was subjected to preparative TLC using benzene–ethanol (10: 1 v/v) as solvent to give the desired product **3a** as an oil in 65% yield (254 mg): IR (neat) 3320, 2960, 1720, 1510, 1150, 1060 cm^{-1}; NMR (CCl_4) δ 1.25 (d, 3H, J=7 Hz), 1.37 (s, 9H), 2.09 (s, 3H), 3.22 (s, 2H), 4.10—4.42 (bd, 1H, J=9 Hz), 5.00 (s, 2H), 5.17—5.75 (m, 2H), 7.20 (s, 2H).

*Z-Ser(AcA)-OBu^t (**3b**)*: Oil, IR (neat) 3320, 2960, 1715, 1420, 1050 cm^{-1}; NMR (CCl_4) δ 1.39 (s, 9H), 2.08 (s, 3H), 3.25 (s, 2H), 4.32 (m, 3H), 4.97 (s, 2H), 5.62—5.95 (m, 1H), 7.19 (s, 5H).

*Z-Hyp(AcA)-OBu^t (**3c**)*: Oil, IR (neat) 2960, 1740, 1700, 1050 cm^{-1}; NMR (CCl_4) δ 1.39 (d, 9H, J=8 Hz), 2.12 (s, 2H), 2.30 (m, 2H), 3.29 (s, 2H), 3.65 (m, 2H), 4.18 (t, 1H, J=7 Hz), 5.01 (s, 2H), 5.22 (bs, 1H), 7.20 (s, 5H).

*Z-Thr-OBu^t (**4a**).* To a solution of **3a** (100 mg, 0.25 mmol) in ethanol (2 ml), was added a solution of hydrazine hydrate (25 mg, 0.50 mmol) in ethanol. The reaction mixture was stirred at room temperature for 30 min, and evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate and filtered. After evaporation of the solvent, the residue was subjected to preparative TLC using benzene–ethanol (10: 1 v/v) as solvent to give the desired product **4a** (74 mg, 94%), which was recrystallized from benzene–hexane: mp 66—67 °C; $[\alpha]_D^{26}$ −20.6° (1.07, absEtOH); IR (KBr) 3400, 3180, 1738, 1705, 1220, 1090, 1065 cm^{-1}; NMR (CCl_4) δ 1.15 (d, 3H, J=7 Hz), 1.43 (s, 9H), 2.70 (d, 1H, J=4 Hz), 3.29—4.23 (m, 2H), 5.03 (s, 2H), 5.64 (bd, 1H, J=9 Hz), 7.26 (s, 5H); Found: C, 61.90; H, 7.32; N, 4.68%. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53%.

*Z-Ser-OBu^t (**4b**)*: Mp 93—95 °C; $[\alpha]_D^{26}$ −16.5° (1.03, absEtOH); IR (KBr) 3400, 3260, 1710, 1704, 1235, 1045 cm^{-1}; NMR (CCl_4) δ 1.46 (s, 9H), 2.60 (s, 1H), 3.83 (d, 2H, J=4 Hz), 4.20 (m, 1H), 5.03 (s, 2H), 5.70 (d, 1H, J=8 Hz), 7.86 (s, 5H); Found: C, 61.32; H, 7.04; N, 4.58%. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74%.

*Z-Hyp-OBu^t (**4c**)*: Mp 62—63 °C; $[\alpha]_D^{27}$ −68.6° (1.09, absEtOH); IR (KBr) 3440, 1730, 1665, 1370, 1040 cm^{-1}; NMR (CCl_4) δ 1.31 (d, 9H, J=7 Hz), 2.20 (m, 2H), 3.39 (m, 2H), 3.73—4.38 (m, 3H), 4.89 (s, 2H), 7.02 (s, 5H); Found: C, 63.66; H, 6.96; N, 4.31%. Calcd for $C_{17}H_{23}NO_5$: C, 63.53; H, 7.21; N, 4.36%.

References

1) H. Kinoshita and H. Kotake, *Bull. Chem. Soc. Jpn.*, **50**, 280 (1977).

2) H. Kinoshita, H. Ishikawa, and H. Kotake, 36th National Meeting of the Chemical Society of Japan, Higashi-oosaka, April 1977, Abstr. No. 3U37.

3) The abbreviations used in this work are those recommended by the IUPAC-IUB commission on Biochemical Nomenclature, as published in *J. Biol. Chem.*, **247**, 977 (1972): Hypic for 3-hydroxypicolinyl.