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Oxidation, With Chiral Retention, of Benzyloxycarbonyl Threonine Methyl Ester

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OXIDATION, WITH CHIRAL RETENTION, OF BENZYLOXYCARBONYL THREONINE METHYL ESTER

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ABSTRACT : A simple oxydative procedure converted Z-L-threonine methyl ester into the corresponding (2S)-β-keto ester : Starting material for the synthesis of labelled threonine derivatives.

In connection with our work on an original procedure for labelling the human insulin and studying carboxypeptidase (1), we intend to obtain tritiated L-threoninates 5 and threoninamides.

Catalytic reduction by tritium gas is the usual way of tritiation, so the oxidative precursors, the methyl (2S)-2-benzyloxycarbonylamino-acetoacetate 2 and its amide derivative 4 were our objectives.

Structurally connected molecules of type 6, valuable intermediates for the preparation of β-lactam antibiotics (2), have been prepared by acylation of lithium enolate of dibenzylamino acetate (3), or by reduction of the ethyl 2-hydroxyimino-3-oxobutanoate, followed by acylation *in situ* of the free amine (4). But these methods led to racemic mixtures.

The reaction of oxidative reagents with threonine or its derivatives has been reported. Lead tetracetate cut the side-chain of some threonine derivatives, e.g. Z-Thr-OEt, to the corresponding secondary alcohols 7 (5).

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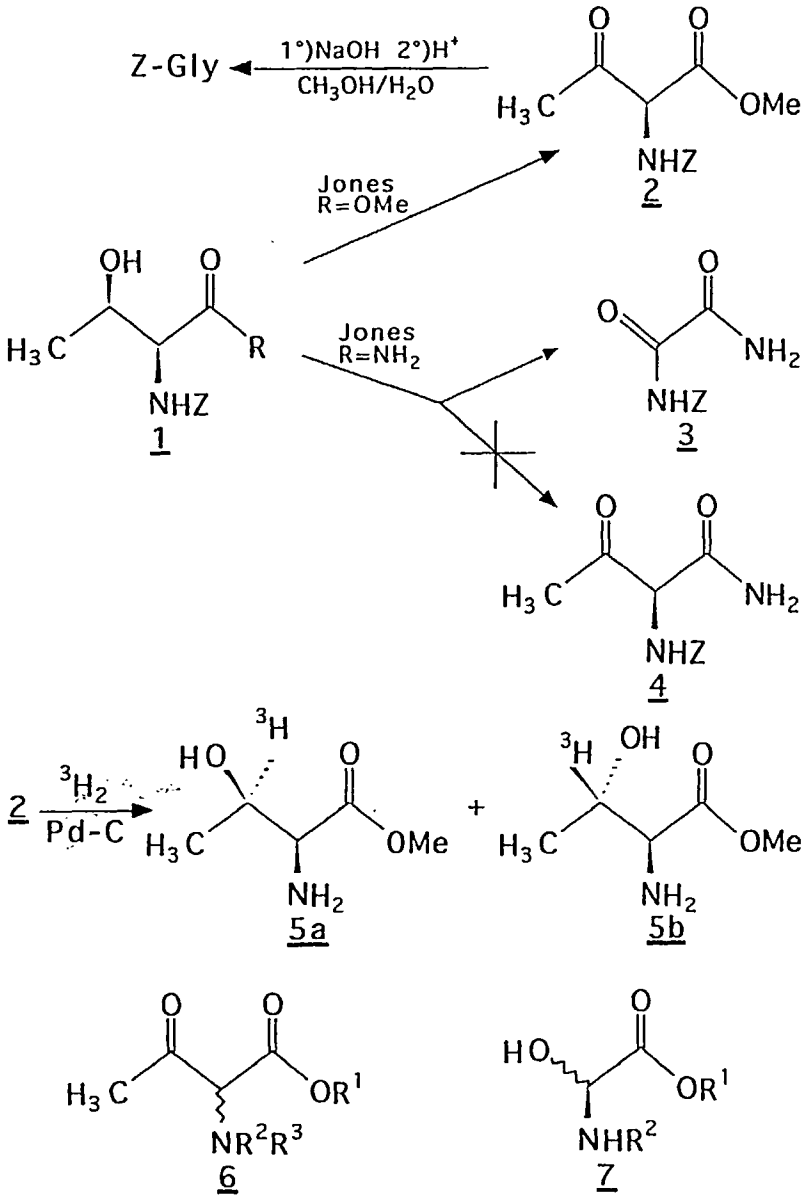

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A more complete oxidation occured, that lead to a carbonyl function, when using chromium (VI) salt on Z-D-thr-OMe (6). With pyridinium chlorochromate, NMR spectrum of the reaction mixture presented some characteristic signals of compound 2; the little quantity detected was not sufficient for isolation (6).

We focused our attention on Jones method (7a,b). Several products arose when oxidazing Z-L-Thr-OH. The treatement of Z-L-threoninamide (1: R=NH_2), resulting from the amidation of Z-L-Thr-OH with NH_3, DCC and N-hydroxysuccinimide [procedure better than direct amidation (NH_3/EtOH) of the commercially available Z-L-Thr-OMe (1: R=OMe)], according to Jones oxidatively cut the side chain to derivative 3. It will be noted that this product is the amidated analogue of the methyl ester obtained when oxidizing Z-D-Thr-OMe with CrO_3-pyridine (6).

Yet, in varying the parameters (duration, temperature, reagents concentration) of the reaction, we selected the experimental conditions (see below) that turn the Z-L-Thr-OMe (1: R=OMe) into pure 2 isolated in 45% yield. The obtention of a chiral β-keto ester was unexpected. The (2S) configuration of compound 2 was proved by the quantity of each [^{3}H]-threonine isomer, resulting from its tritiation (tritium gas and Pd-C) that led to 5, followed by acid hydrolysis. Only 5% possess the D relative configuration.

Reactivity of 2 do not permit the obtention of the corresponding amide 4. The amidation (NH_3/EtOH) of the ester 2 led to several products and the saponification brought Z-Gly-OH, characterised by its mass, NMR and IR spectra.

Experimental

General : Instruments included a Brücker A-C 270 NMR spectrometer, a Perkin-Elmer 157 G IR spectrophotometer, a Nermag R 10-10 C mass spectrometer, a perkin-Elmer 241 polarimeter and a Perkin-Elmer CHN analyser. Materials for tritiation are detailed in reference (1).

N-(benzyloxycarbonyl)threoninamide 1 (R=NH_2): m.p. 82 °C. $[\alpha]_D$ +4.13 (c 8.10^{-3}, CH_3OH). IR (KBr): 3500 and 3480 (OH), 3380 (NH), 3340 and 3220 (NH_2) and 1710-1640 cm^{-1}(CO). ^{1}H NMR ($CDCl_3$) δ 1.17 (3H, d, J 6.8 Hz, CH_3), 1.80 (1H, s, exchanged with D_2O, NH), 4.14 (1H, d, J 8 Hz, CH), 4.38 (1H, m, OCH), 5.12 (2H, s, $ArCH_2$), 5.80 (1H, br s, exchanged with D_2O, NH_2), 5.89 (1H, d, J 8 Hz, exchanged with D_2O, OH), 6.61 (1H, br s, exchanged with D_2O, NH) and 7.34

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(5H, s, Ar). MS (CID, NH_3) *m/z* 253 $(M+H)^+$ and 270 $(M+NH_4)^+$. Found: C, 55.40; H, 6.51; N, 10.69. Calcd for $C_{12}H_{16}N_2O_4$, 0.5 H_2O: C, 55.17; H, 6.51; N, 10.73.

Methyl (2S)-2-benzyloxycarbonylamino-acetoacetate 2: To a solution of methyl L-(benzyloxycarbonyl)threoninate 1 (R=OMe) (1.07 g, 4 mM) in acetone (165 ml) maintained in an ice bath, was added dropwise Jones reagent (7a) (4.5ml). Then, the reaction mixture was stirred at room temperature for 3.5 h. After reduction of the excess of the chromium salt with sodium bisulfite, acetone was removed. Aqueous phase was extracted with ethyl ether. Evaporation of the organic solvent under reduced pressure left a colourless solid. The crude product was washed three times with ethyl ether to give the white crystals of compound 2. Yield: 45 %. m.p. 212 °C. $[\alpha]_D$ -0.75 (c 8.10^{-3}, CH_3OH). IR (KBr): 3380 (NH), 1755, 1730 and1710 cm^{-1}(CO). ^1H NMR ($CDCl_3$) δ 1.59 (1H, br s, exchanged with D_2O, NH), 2.38 (3H, s, $COCH_3$), 3.82 (3H, s, OCH_3), 5.10 (1H, s, CH), 5.12 (2H, s, CH_2) and 7.33 (5H, s, Ar). MS (CID, NH_3) *m/z* 283 $(M+NH_4)^+$ and 266 $(M+H)^+$. Found: C, 58.79; H, 5.80; N, 5.24. Calcd for $C_{13}H_{15}NO_5$: C, 58.87; H, 5.66; N, 5.26.

Benzyl (carbamoylcarbonyl)carbamate 3: It was obtained from the reaction of the amide 1 with Jones reagent (7a) (2.5 ml) in acetone (80 ml), following the procedure above described for the synthesis of the compound 2. At the end of the preparation, aqueous phase was filtered. The white solid was washed three times with water to give the pure product 3. Yield: 48%. m.p. 206 °C. IR (KBr): 3390 (NH), 3240 and 3180 (NH_2), 1805, 1780, 1710 and 1685 cm^{-1}(CO). ^1H NMR (DMSO-D_6) δ 5.13 (2H, s, $ArCH_2$), 7.34 (5H, m, Ar), 7.90 (1H, s, exchanged with D_2O, NH_2), 8.12 (1H, s, exchanged with D_2O, NH_2) and 10.74 (1H,s, exchanged with D_2O, NH). MS (CID, NH_3) *m/z* 240 $(M+NH_4)^+$. Found: C, 53.98; H, 4.32; N, 12.62; O, 28.43. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.50; N, 12.61; O, 28.83.

[^{3}H]-threonine isomers : Palladium (10%) on charcoal (11 mg) was added to a solution of threonine precursor 2 (4.3mg, $1.62.10^{-2}$ mM) in 1 ml of methanol-water (60-40). The reacting vial was connected to the automatic tritium gas transfert unit (8). Tritium gas was introduced and the reaction mixture was kept at ambiant temperature under magnetic stirring for 3.5 h. After separation from palladium on charcoal and elimination of the labile tritium atoms, the crude material (29.6 mCi ; 1.09 GBq) was analysed and purified by TLC on cellulose with the BAW (20-10-10) solvent system. The radiochromatogram and ^{3}H-scanning revealed two major peaks : one of them (Rf 0.75) was by-products, while the other one (Rf 0.68) commigrated

with L-threonine methyl ester (spot detection : ninhydrine). This product was again chromatographyed in the same manner so that the radioactivity finally recovered was 6.0 mCi (222 MBq). After hydrolysis (HCl 6N, 110°C, 17h), quantitative and comparative estimation by amino-acids analysis indicated that the specific activity was 56 Ci/mM (2.072 TBq/mM). Enantiomeric separation was performed on a Chiralpak WH column with an aqueous solution of $CuSO_4$ (0.25 M) as an eluant (2ml/mn) and an UV (230 nm) detection. The radiochromatogram revealed three peaks commigrating with L-allo-threonine (55%), L-threonine (40%) and D-threonine (5%). No significant presence of D-allo-threonine was detected.

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