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A NOVEL ROUTE TO N-ALKYLATED DERIVATIVES OF AZIRIDINE-2-CARBOXYLIC ACID. AN ALTERNATIVE SYNTHESIS OF (S,S)-Bz-Azy-Val-OMe

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Abstract. A novel method for N-alkylation of azyridine-2-carboxylic acid derivatives with benzyl chloride under phase-transfer conditions or using KF/Al_2O_3 as a base was developed. The latter variant of this method was applied to carry out the key step of the alternative synthesis of the dipeptide (S,S)-Bz-Azy-Val-OMe.

Recently, using asymmetric reaction between methyl esters of 2,3-dibromopropionylamino acids and primary amines a series of diastereoisomeric azyline-containing dipeptides [azyline(Azy) = aziridine-2-carboxylic acid] has been obtained.[1] The dipeptide Bz-Azy-Val-OMe (**1**) prepared from methyl-2,3-dibromopropionyl valinate and

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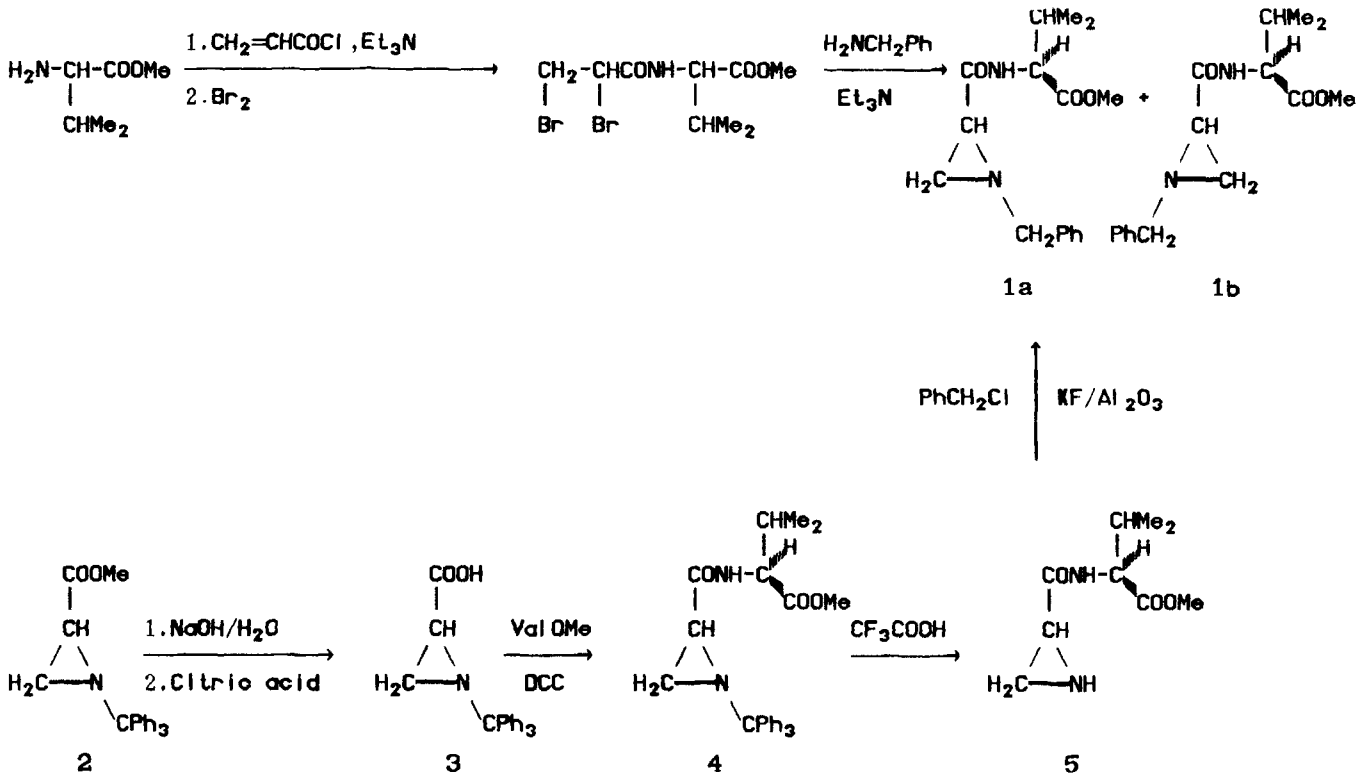
benzylamine by the Gabriel-Cromwell reaction (Scheme 1) was separated into individual diastereoisomers by means of preparative HPLC.

Alternative synthesis of (S,S)-Bz-Azy-Val-OMe was performed in the present work in order to determine the absolute configuration of the predominant diastereoisomer.

The choice of the synthetic route to diastereoisomer **1a** was based on the use of (S)-methyl-N-tritylazylinate (**2**)[2,3] as starting material. Compound **2** was saponified (1. aqueous NaOH, 2. citric acid) to give Tri-Azy-OH (**3**) in 94% yield. The reaction of 3 with Val-OMe using the carbodiimide method afforded an optically pure dipeptide - (S,S)-Tri-Azy-Val-OMe (**4**) in 90% yield. Detritylation of **4** with trifluoroacetic acid led to (S,S)-Azy-Val-OMe (**5**) in 54% yield (Scheme 1). The final step of the alternative synthesis of dipeptide **1a** presented N-benzylation of **5**.

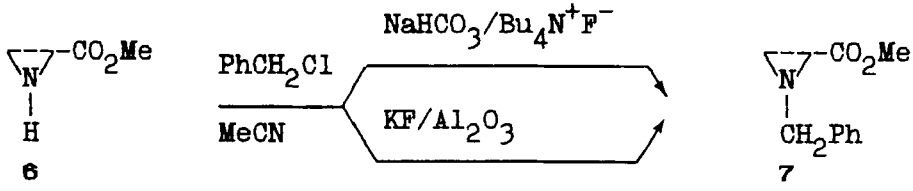
As the N-alkylation of azyline derivatives has not been described until presently, we first exazimined the opportunity of carrying out this reaction for methyl azylinate (**6**). N-alkylation of aziridines by alkyl halides is known to proceed in the presence of Et_3N or inorganic bases[4] and also under phase-transfer catalysis (PTC) conditions using aqueous alkali as a base.[5]



DCC - Dicyclohexylcarbodiimide

Scheme 1

However, all attempts to carry out N-benzylation of **6** in $CHCl_3$ in the presence of Et_3N or in acetone in the presence of K_2CO_3 were unsuccessful. Under liquid/liquid or solid/liquid PTC conditions, using aqueous or solid NaOH as a base, N-benzylation of **6** also fails to occur, although GLC control indicates gradual disappearance of **6**, obviously owing to saponification of the ester group. Using a weaker base ($NaHCO_3$) in MeCN under solid/liquid PTC conditions (catalyst - $Bu_4N^+F^-$, 5 mol.%) (Method A) the azylinate **6** is smoothly alkylated to give the desirable **7** isolated in 72% yield.



The use of KF/Al_2O_3 (Method B) was found even more effective. Benzylation of **6** in acetonitrile in the presence of KF/Al_2O_3 affords N-alkylated derivative **7** in 75% yield, the reaction time being decreased almost twice, as compared with PTC alkylation.

Dipeptide **5** was successfully benzylated using Method B. In this way, diastereoisomerically pure (S,S)-Bz-Azy-Val-OMe (**1a**) was synthesized in 63% yield. This diastereoisomer was identical by its physico-chemical charac-

teristics (^{1}H NMR spectrum, HPLC retention time, optical rotation) with those of the predominant diastereoisomer obtained in the asymmetric reaction of methyl-2,3-dibromopropionyl valinate with benzylamine.[1] Thus, asymmetric atoms of this diastereoisomer possess (S)-configuration.

EXPERIMENTAL

^{1}H NMR spectra were obtained on a Bruker WH-90/DS (90 MHz) or WH-360 (360 MHz) spectrometers for solutions in $CDCl_3$ with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 580-B instrument in nujol. Silufol UV-254 plates were used for TLC. GLC analysis was conducted on a Chrom-5 instrument equipped with a flame-ionization detector using a glass column (1.2 m x 3 mm) packed with 5% OV-17 on Chromosorb W-HP (80-100 mesh). Helium (50 cm^3/min) was used as carrier gas, analysis temperature 170°. The angles of optical rotation were determined on a Perkin-Elmer 141 polarimeter. Melting points were determined on a Fisher Digital Melting Point Analyser.

In this work we used amino acids purchased from Reanal. Methyl esters of amino acids,[6] methyl-(S)-N-trityl azylinate [(S)-Tri-Azy-OMe (2)][7] and methyl azylinate[8]

were obtained following the procedures described previously. $Bu_4N^+F^-\cdot 3H_2O$ and KF/Al_2O_3 (~5.5 mmol F^-/g) were Fluka products.

(S)-N-Tritylazyline, (S)-Tri-Azy-OH (3). To a solution of 2 (3.4 g, 10 mmol) in MeCN (10 ml) was added a solution of NaOH (0.6 g, 15 mmol) in water (10 ml) at 0°C. After 1 h, the solution was evaporated under reduced pressure, supplemented with water (20 ml) and a solution of citric acid (4.2 g, 20 mmol) in ethyl acetate (70 ml). The reaction mixture was then stirred for 0.5 h. The organic layer was removed and washed with water and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue after usual work up was recrystallized from hexane to give 3 (3.22 g, yield: 94%), m.p. 145°C, $[\alpha]_D^{20}$ -56.3° (c=1.25, ethanol). Found: C 80.5, H 5.9, N 4.1. $C_{12}H_{19}NO_2$; requires: C 80.2, H 5.8, N 4.3. IR: ν, cm^{-1} (nujol): 1208 ($\overset{C-C}{\diagdown N \diagup}$), 1736 (C=O), 3080 (CH of aziridine cycle). H^1NMR (90 MHz), δ, ppm: 1.51, 2.00 and 2.25 (each dd, 1H, ABC system, $^3J_{AB}$=6.2 Hz, $^2J_{BC}$=1.1 Hz, $^3J_{AC}$=2.2 Hz), 7.04-7.58 (m, 15H, CPh_3).

(S,S)-Metyl-N-tritylazylilvalinate, (S,S)-Tri-Azy-Val-OMe (4). To a solution of 3 (2.6 g, 8 mmol) and (S)-Val-OMe (1.3 g, 8 mmol) in absolute $CHCl_3$ (20 ml)

at -5°C was added a solution of DCC (1.8 g, 85 mmol) in absolute $CHCl_3$ (7 ml). The reaction mixture was stirred for 8 h and kept overnight in a refrigerator. Then the precipitate consisting of dicyclohexylurea was separated and the filtrate was washed with 0.01 N $NaHCO_3$, 0.01 M citric acid and water and dried over Na_2SO_4. The usual procedure gives **4** (3.2 g, yield: 90%), mp 62-3°C, $[\alpha]_D^{20}$ -77.2° (c=0.61, ethanol). Found: C 76.5, H 6.6, N 6.5 $C_{28}H_{30}N_2O_3$; requires: C 76.0, H 6.8, N 6.3. IR : ν, cm^{-1} (nujol): 1209 ($\overset{C-C}{\diagdown N \diagup}$), 1672 (C=O), 3075 (CH of aziridine cycle). ^1H NMR (360 MHz) δ, ppm: 0.96 and 0.98 (each 2d, 6H, CMe_2, ^3J=7.1 Hz), 1.50 (d, 1H) and 2.00 (covering dd and d, 2H) (ABC system, $^3J_{AB}$=6.5, $^2J_{BC}$=0.0, $^3J_{AC}$=2.9 Hz), 2,24 (dd, 1H, H_β, $^3J_{\alpha\beta}$=4.5 Hz), 3.80 (s, 3H, OMe), 4.54 (dd, 1H, H_α, $^3J_{H_\alpha NH}$=9.4 Hz), 7.19-7.94 (m, 16H, CPh_3 and NH).

(S,S)-Methylazylyl valinate, (S,S)-Azy-Val-OMe (5)

To a solution of **4** (2.65 g 6 mmol) in absolute MeOH (30 ml) at -20°C was added CF_3COOH (20 ml). The reaction mixture was kept for 2 h at -20° until the starting **4** dissappeared from the mixture (TLC-control, eluent hexane-EtOAc, 1:1). The reaction mixture was neutralized with $NaHCO_3$. After filtration the solvent was removed under reduced pressure. The residue was purified by co-

lumn chromatography on silica gel (40 x 100 m). Elution was carried out with ethyl acetate and then with EtOH. The ethanol fraction was collected and after solvent removing viscous oil - **5** was obtained (0.65 g, yield: 54%), $[\alpha]_D^{20}$ -42.6° (c=0.43, ethanol).

Methyl-N-benzyl-2-carboxylate (7)

Method A. To a solution of **6** (1.0 g, 10 mmol) in MeCN (50 ml) were added benzyl chloride (2.53 g, 20 mmol), $NaHCO_3$ (4.2 g, 50 Mmol) and $Bu_4N^+F^- 3H_2O$ (0.13 g, 0.5 mmol). The reaction mixture was refluxed for 20 h until the starting substance **6** disappeared (GLC-control). Then the reaction mixture was cooled, filtered, the solvent and the excess of benzyl chloride were removed under vacuum at ambient temperature. The residue was distilled in high vacuum to give **7** (1.38 g, yield: 72%), bp 80°C (bath temperature)/10^{-2} mm Hg identical, by its IR and NMR spectra, to that described previously.[7]

Method B. To a solution of **6** (1.0 g, 10 Mmol) in MeCN (50 ml) were added benzyl chloride (2.53 g, 20 mmol), and KF/Al_2O_3 (2.9 g, 50 mmol KF). The reaction-mixture was refluxed for 10 h until disappearance of the starting **6** (GLC control). Then the reaction mixture was worked up as described above to give **7** (1.43 g, yield: 75%).

(S,S)-Methyl-N-benzylazylyl valinate, (S,S)-Bz-Azy-Val-OMe (1a). To a solution of 5 (0.4 g, 4 mmol) and benzyl chloride (0.5 g, 4 mmol) in MeCN (20 ml) was added KF/Al_2O_3 (0.6 g, 10 mmol KF). The reaction mixture was refluxed for 10 h (TLC control, eluent hexane-EtOAc, 1:1), cooled, filtered and evaporated under vacuum (10^{-2} mm Hg). The resultant viscous oil was **1a** (0.37 g, yield: 63%), $[\alpha]_D^{20}$ -21° (c=0.79, EtOH). ^1H NMR spectrum (360 MHz), δ, ppm: 0.84 and 0.87 (each d, 3H, ^3J =6.8 Hz, CMe_2), 1.81 (d, 1H), 1.99 (d, 1H), 2,21 (dd, 1H) (ABC system, $^3J_{AB}$=6.9, $^2J_{BC}$=0.0, $^3J_{AC}$=3.1 Hz), 2.12 (dd, 1H, H_β, $^3J_{\alpha\beta}$=5.1 Hz), 3.56 (s, 2H, CH_2), 3.72 (s, 3H, OMe), 4.45 (d, 1H, H_a), 7.05 (bs, H, NH), 7.3-7.4 (m, 5H, Ph).

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