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UNNATURAL AMINO ACIDS. 3*. AZIRIDINYL KETONES FROM ESTERS AND AMIDES OF AZIRIDINE-2-CARBOXYLIC ACIDS

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A series of N-substituted amides and esters of aziridine-2-carboxylic acids have been prepared and have been subjected to deprotonation with lithium diisopropylamide. The intermediate carbanions reacted more readily with the carbonyl groups of the substrates than with methyl iodide. So, in place of the expected amides or esters of methylaziridine-2-carboxylic acids, amides or esters of 2-aziridinylcarbonylaziridine-2-carboxylic acids were isolated.

Keywords: aziridinyl ketones, esters and amides of aziridin-2-carboxylic acids, deprotonation.

Esters and amides of aziridine-2-carboxylic acids are suitable starting materials for the preparation of derivatives of α- and β-amino acids after opening the aziridine ring [2,3]. Unlike other esters of α-amino acids, aziridine-2-carboxylates do not have a tendency to dimerize to form diketopiperazines. Our interest in esters and amides of aziridine-2-carboxylic acids is connected with the study of the conditions for deprotonation of the α-center of the aziridine ring to prepare sterically hindered cyclic unnatural α-amino acids, required for the synthesis of different derivatives of α- and β-amino acids.

Deprotonation of esters of aziridine-2-carboxylic acid was first carried out by Seebach [4,5]. However isolation of the reaction products was unsuccessful. Only after moving to thiol esters was isolation of the products from the reactions with electrophiles successful [4]. In this paper [4]it was first postulated that carbanions were configurationally stable at low temperatures. In 1997 Vedejs published a paper on lithiated complexes of aziridines with BH_3 [6]. It was shown that the increased *s*-character of the CH bonds in the aziridine ring accelerated lithiation in position 2 of the aziridine ring, facilitating the reaction with electrophiles.

The stability of carbanions in a series of esters of aziridine-2-carboxylic acids has been demonstrated recently [7, 8]. A methoxymethyl protecting group on the aziridine nitrogen atom stabilizes the intermediate carbanion and permits the preparation of a series of 2-substituted esters of aziridine-2-carboxylic acids [8]. Alkylation of 3-substituted esters of 1-(diphenylmethyl)aziridine-2-carboxylic acids gave a mixture of 2-alkylated aziridines and diaziridinyl ketones [9].

We have studied the deprotonation of derivatives of aziridine-2-carboxylic with different substituents in the aziridine ring to determine the limits of use of this reaction. As substituents we chose well known protecting groups which are readily removed after the reaction was completed. We have developed a method for synthesis of the 1-substituted dimethylamides of the aziridine-2-carboxylic acids **2a-c** (scheme 1) required for this study.

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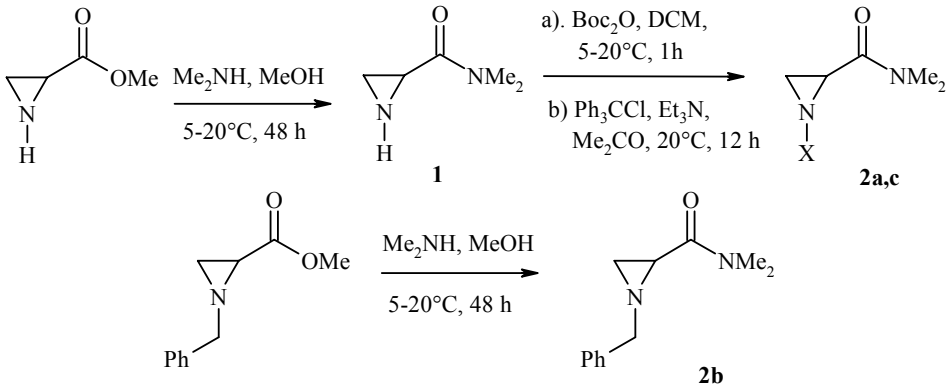
Scheme 1



1 **2a,c** **2b**

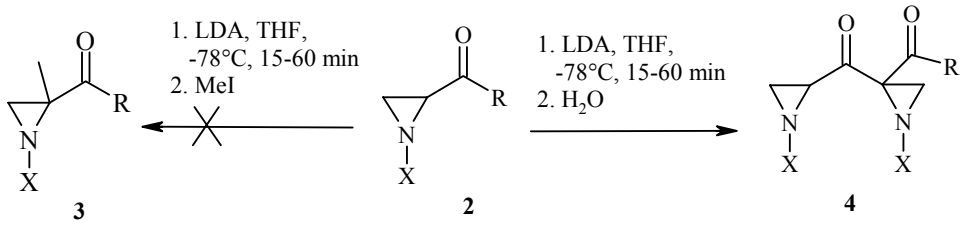
2 a X = COOBu-*t*, **c** X = Ph_3C

The methyl ester of aziridine-2-carboxylic acid [10] and the dimethylamide of aziridine-2-carboxylic acid [11] were prepared by known methods. The methyl ester of 1-benzylaziridine-2-carboxylic acid (**2d**) reacted readily with dimethylamine even at low temperature to give the dimethylamide **2b** in 73% yield. However the methyl esters of 1-*tert*-butoxycarbonyl- and 1-tritylaziridine-2-carboxylic acids gave difficult to separate reaction mixtures. An alternative reaction scheme was therefore used in the dimethylamide of aziridine-2-carboxylic acid (**1**) as the starting material. The dimethylamides **2a** and **2c** prepared by this method were readily isolated in yields of 71 and 91% and were suitable for the reactions studied.

In the initial study we carried out deprotonation of the amides **2a-c** with the aim of trapping the carbanions formed with the simple electrophile – methyl iodide – to obtain the 2-methyl-substituted compounds **3** (Scheme 2). However after addition of methyl iodide to the reaction mixture only aziridine **4c** (33% yield) was isolated. The same product **4c** (58% yield) was isolated after treatment of the mixture with water.

We used the same conditions for deprotonation of the esters **2d-g**. The corresponding aziridinyl ketones **4d** and **4f** were formed from 1-benzyl-substituted **2d** and **2f**. The aziridinyl ketones **4** are difficult to make by other methods.

Scheme 2

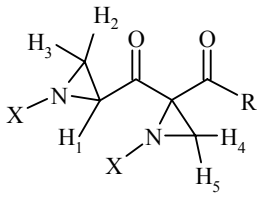


3 **2** **4**

a R = NMe_2, X = COOBu-*t*; **b** R = NMe_2, X = Bn; **c** R = NMe_2, X = CPh_3, **d** R = OMe, X = Bn, **e** R = OMe, X = CPh_3; **f** R = OBu-*t*, X =Bn, **g** R = OBu-*t*, X = CPh_3

It should be noted that not all of these reactions gave only the aziridinyl ketones. For example, the dimethylamide of 1-*tert*-butoxycarbonylaziridine-2-carboxylic acid (**2a**) gave a mixture of ketone **4a** and another bisaziridine, the structure of which was not established, which was difficult to separate. In the synthesis of

TABLE 1. ^{1}H NMR Spectra of aziridinyl ketones **4**



Com-pound	X	R	Chemical shifts, δ, ppm (*J*, Hz)
4c	CPh_3	NMe_2	1.44 (1H, dd, ^2J = 1.6, $^3J_{cis}$ = 6.6, *cis*-H-3); 1.91 (1H, unresolved dd, *trans*-H-3); 2.05 (1H, d, *J* = 6.8, H-5); 2.38 (3H, s, $N(CH_3)_2$); 2.50 (1H, d, *J* = 6.8, H-4); 2.54 (3H, s, $N(CH_3)_2$); 2.89 (1H, dd, $^3J_{trans}$ = 2.3, $^3J_{cis}$ = 6.6, H-2); 7.05-7.28 (20H, m, arom,.); 7.36-7.54 (10H, m, arom,.)
4d	Bn	OMe	1.75 (1H, unresolved dd, $^3J_{cis}$ = 6.5, *cis*-H-3); 2.13-2.17 (1H, m, H-5); 2.26-2.29 (1H, m, H-4); 2.37 (1H, unresolved dd, *trans*-H-3); 2.59 (1H, dd, $^3J_{trans}$ = 2.7, $^3J_{cis}$ = 6.5, H-2); 3.41 and 3.56 (1H and 1H, AB system, *J* = 13.4, $C_6H_5CH_2$); 3.64 (3H, s, CH_3); 3.79 and 3.95 (1H and 1H, AB system, *J* = 13.6, $C_6H_5CH_2$); 7.20-7.38 (10H, m, arom,.)
4f	Bn	OBu-*t*	1.41 (9H, s, $(CH_3)_3C$-*t*; 1.71 (1H, dd, ^2J = 1.2, $^3J_{cis}$ = 6.5, *cis*-H-3); 2.15-2.19 (1H, m, H-5); 2.25-2.28 (1H, m, H-4); 2.30 (1H, unresolved dd, *trans*-H-3); 2.52 (1H, dd, $^3J_{trans}$ = 3.0, $^3J_{cis}$ = 6.5, H-2); 3.41 and 3.55 (1H and 1H, AB system, *J* = 13.9, $PhCH_2$); 3.78 and 3.96 (1H and 1H, AB system, *J* = 13.8, $PhCH_2$); 7.17-7.50 (10H, m, arom,.)

ketone **4e** an inseparable reaction mixture was formed, which contained the corresponding aziridinyl ketone **4e**, the methyl 1-tritylaziridine-2-carboxylate starting material (**2e**) with a small amount (<5%) of the diisopropylamide of 1-tritylaziridine-2-carboxylic acid.

The carbanions obtained from the amide **2b** and the *tert*-butyl ester **2g** (observed by the characteristic orange-red color of the reaction mixture) captured water to form the corresponding starting materials. In its turn, ketone **4c** was formed only by raising the temperature to room temperature for 3 h with subsequent treatment with water.

Hence, the bulky trityl substituent on the nitrogen atom decreased the reactivity of the substrates **2**. Formation of the aziridinyl ketones occurred only with the dimethylamides and not the esters of the 1-tritylaziridine-2-carboxylic acid.

In the future we shall extend the investigation of the behavior of carbanions generated from N-substituted esters and amides of aziridine-2-carboxylic acids.

EXPERIMENTAL

^{1}H NMR spectra of $CDCl_3$ solutions with TMS as internal standard were recorded with a Varian Mercury (200 MHz) spectrometer. Elemental analyses were determined with Carlo Erba EA-1108 machine. Mass spectra were obtained with a Micromass Q-ToF micro. Melting points were recorded with a Gallenkamp heating block and were not corrected. TLC was carried out on DC Aluflien strips with Kiesel-60 absorbent. HPLC of compounds **2** was carried out on a Gilson chromatographic system with an Ultrasphere Si (4.6×250 mm) column with 96:4 hexane-isopropanol eluant (10 ml/min), 254 nm UV detector). Dry methylene chloride was distilled from CaH_2. Dry THF was distilled twice over sodium (the second time in the presence of benzoquinone). Dry isopropanol was prepared by distillation twice from CaH_2. Dry dimethylamine was prepared heating an aqueous solution of dimethylamine and passing the product through dry NaOH.

Dimethylamide of aziridine-2-carboxylic acid (1). Absolute methanol (100 ml) was added to methyl aziridine-2-carboxylate [10] (10.1 g, 100 mmol). The solution was cooled to 5°C and saturated with dry dimethylamine for 20 min. The mixture obtained was stirred at room temperature for 48 h under argon. The methanol was evaporated at low pressure and the residue was purified by chromatography on silica gel (eluant 9:1 chloroform-methanol) to give compound **1** (10.0 g, 88%), mp 85-87°C (in [14] compound 1 was prepared by aziridination of the dimethylamide of acrylic acid in 40% yield). ^{1}H NMR Spectrum, δ, ppm: 1.40 (1H, br. s, NH), 1.67-1.83 (2H, m, H-3), 2.5-2.68 (1H, m, H-2), 2.95 (3H,s, $N(CH_3)_2$), 3.13 (3H,s, $N(CH_3)_2$).

Dimethylamide of 1-benzylaziridine-2-carboxylic acid (2b) [13] was obtained from methyl 1-benzylaziridine-2-carboxylate [12] was made analogously to amidation by method [11]. Yield 73%. ^{1}H NMR Spectrum, δ, ppm: 1.69 (1H, unresolved, dd, $^3J_{cis}$ = 6.2, *cis*-H-3), 2.23-2.35 (2H, m, *trans*-H-2,3), 2.94 (3H, s, $N(CH_3)_2$), 2.99 (3H, s, $N(CH_3)_2$), 3.50 and 3.65 (1H and 1H, AB system, J = 13.4, $PhCH_2$), 7.2-7.43 (5H, M, arom).

Dimethylamide of 1-(*tert*-butoxycarbonyl)aziridine-2-carboxylic acid (2a). Dry methylene chloride (20 ml) was added with stirring to dimethylamide **1** (11.4 g, 100 mmol). The mixture was cooled to 5°C and (t-BuOCO)$_2$O) (21.8 g, 100 mmol) in dry methylene chloride (10 ml) was added over 5 min. The mixture obtained was stirred for 1 h at room temperature under argon. Methylene chloride was evaporated at reduced pressure. The residue was purified by chromatography on silica gel with 1:1 petroleum ether-ethyl acetate as eluant to give compound **2a** (15.2 g, 71%, oil) (the optically active analog of **2a** was prepared by the Mitsunoba method from the L-serine derivative [15]). ^{1}H NMR Spectrum, δ, ppm, (J, Hz): 1.25 (9H, s, $C(CH_3)_3$), 2.15 (1H, dd, ^2J = 1.2, $^3J_{cis}$ = 5,3, *cis*-H-3), 2.42 (1H, dd, ^2J = 1.2, $^3J_{trans}$ = 3.1, *trans*-H-3), 2.79 (3H, s, $N(CH_3)_2$), 3.05 (1H dd, $^3J_{trans}$ = 3.1, $^3J_{cis}$ =5.3), 3.08 (3H, s, $N(CH_3)_2$.

Dimethylamide of 1-tritylaziridine-2-carboxylic acid (2c). Acetone (20 ml) triethylamine (7.0 ml, 50 mmol), and a solution of trityl chloride (13.9 g, 50 mmol) in acetone (10 ml) were added with stirring to the dimethylamide **1**. The mixture was stirred at room temperature for 12 h in an atmosphere of argon. The mixture was then poured into ice water (20 ml) and extracted with ether (3×20 ml). The ether extracts were combined, washed with water (2×20 ml) and saturated NaCl solution (20ml), dried over Na_2SO_4, filtered and the solvent was removed at low pressure. The product was purified by chromatography on silica gel with 3:1 petroleum ether-ethyl acetate as eluant to give compound **2c** (16,2 g, 91%), mp 141°C (from 2:1 petroleum ether-ethyl acetate). ^{1}H NMR Spectrum, δ, ppm (J, Hz): 1.35 (1H, unresolved dd, $^3J_{cis}$ = 6.0, *cis*-H-3), 1.94 (1H, dd, $^3J_{trans}$ = 2.9, $^3J_{cis}$ = 6.0, H-2), 2.36 (1H, unresolved dd, *trans*-H-3), 2.80 (3H, s, $N(CH_3)_2$), 2.99 (3H, s, $N(CH_3)_2$), 7.15-7.34 (9H, m, arom), 7.50-7.59 (6H, m, arom). Found, %: C 80.44, H 6.79, N 7.71. Calculated for $C_{24}H_{24}N_2O$, %: C 80.87, H 6.79, N 7.86.

Esters of aziridine-2-carboxylate acid 2d-g are described in the literature. Methyl ester **2d** was obtained by method [12]. The *tert*-butyl esters **2f** and **2g** were prepared from the corresponding methyl esters **2d** and **2e** and have been characterized by us previously [1].

Methyl 1-tritylaziridine-2-carboxylate (2e) was made previously by a different method, a 97% yield being obtained by cyclization of O-methylsulfonyl derivatives of serine [16]. Triethylamine (4.5 ml, 32 mmol) and trityl chloride (9.0 g, 32 mmol) were added with stirring at 0-5°C to a solution of methyl aziridine-2-carboxylate (2.9 ml, 32 mmol) in acetone (40 ml). Within a minute of the dissolution of trityl chloride precipitation of triethylammonium chloride began. The mixture was stirred for 12h and then filtered. The filtrate was evaporated at low pressure to give compound **2e** (10.0 g, 91%), m.p. 133°C (from 5:1 ether-hexane). ^{1}H NMR Spectrum, δ, ppm (J, Hz): 1.41 (1H, dd, ^2J = 1.9, $^3J_{cis}$ =6.0, *cis*-H-3), 1.89 (1H, dd, $^3J_{trans}$ = 2.6, $^3J_{cis}$ = 6.1, H-2), 2.26 (1H, dd, ^2J = 1.9, $^3J_{trans}$= 2.6, *trans*-H-3), 3.76 (3H, s, OCH_3), 7.16-7.33 (9H, m, arom), 7.46-7.54 (6H, m, arom). Found, %: C 80.51, H 6.16, N 4.10. Calculated for $C_{23}H_{21}NO_2$, %: C 80.44, H 6.16, N 4.08.

Condensation of derivatives of esters and dimethylamides of aziridine-2-carboxylic acids in the presence of lithium diisopropylamide and methyl iodide or dimethyl sulfate (general method A). A round-bottomed flask (100 ml) was heated at 150°C for 5 h and then cooled to room temperature in a stream of argon. Absolute THF (10 ml was placed in the flask and dry diisopropylamine (0,51 g, 5 mmol) was added. The solution was cooled to -20°C in a stream of argon and *n*-BuLi (2.0 ml, 5 mmol) as a 2.5 M hexane solution was added drop wise. The solution of lithium diisopropylamide obtained was stirred for 15 min at -20°C and then cooled to -78°C in a stream of argon and solution of an ester r a dimethyl amide of an aziridine-2-carboxylic acid **2a-g** in abs. THF (5 ml) was added drop wise. The reaction mixture was then stirred for 15-60 min at -78°C and the mixture became orange red in color. Then methyl iodide (1.42 g, 10 mmol) (in experiments with esters of aziridine-2-carboxylic acids) or dimethyl sulfate (1.26 g, 10 mmol) (in experiments with dimethylamides of aziridine-2-carboxylic acids) was added to the reaction mixture. Then 1:1 H_2O-TYF (10 ml) was added.

After the color had disappeared the solution was heated to room temperature, poured into ice water (20 ml), and extracted with ether (3×20 ml). The ether extracts were combined, washed with water (2×20 ml) and saturated NaCl solution (20 ml), dried over Na_2SO_4 (20 ml), filtered, and evaporated under low pressure. The products were purified by chromatography on silica gel with petroleum ether-ethyl acetate as eluant. Only condensation products **4** were obtained. The ^{1}H NMR Spectra are given in the Table.

Condensation of derivatives of esters and dimethylamides of aziridine-2-carboxylic acids in the presence of lithium diisopropylamide (general method B). A round-bottomed flask (100 ml) was heated at 150°C for 5 h and then cooled to room temperature in a stream of argon. Absolute THF (10 ml was placed in the flask and dry diisopropylamine (0,51 g, 5 mmol) was added. The solution obtained was cooled to -20°C in a stream of argon and *n*-BuLi (2.0 ml, 5 mmol) as a 2.5 M hexane solution was added drop wise. The solution of lithium diisopropylamide formed was stirred at -20°C for 15 min and then cooled to -78°C in a stream of argon. An ester or a dimethylamide of an aziridine-2-carboxylic acid (**2a-g**) (5 mmol) in absolute THF (5 ml) was then added drop wise. The reaction mixture was then stirred for 15-60 min at -78°C, and the mixture became orange-red in color. The 1:1 H_2O-THF (10 ml) was added. After the color had disappeared the solution was raised to room temperature, poured into ice water (20 ml), and extracted with ether (3×20 ml). The ether extracts were combined, washed with water (2×20 ml) and saturated NaCl solution (20 ml), and dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The condensation products were purified chromatographically on silica gel with petroleum ether–ethyl acetate as eluant.

Dimethylamide of 1-trityl-2-(1-tritylaziridine-2-carbonyl)aziridine-2-carboxylic acid (4c) was obtained from compound **2c** (1.78 g) by either general method A or B. The reaction took 60 min. No product was obtained by "extinguishing" the reaction mixture with water at -78°C. In a second experiment, after slowly raising the temperature of the reaction mixture to room temperature over 3 h with subsequent "extinction" with water, product **4c** was obtained as an oil (1.10 g, 33%) by method A or (1.94 g, 58%) by method B Found: *m/z*: 690.3132 $[M + Na]^-$, $C_{46}H_{41}N_3O_2$. M + Na = 690.3096.

Methyl 1-benzyl-2-(1-benzylaziridine-2-carbonyl)aziridine-2-carboxylate (4d) was obtained from compound **2d** (0.96 g, 5 mmol) by either method A or B. Length of reaction 50 min. Yield 0.54 g (31%, oil)(general method A) or 0.90 g (46%, oil) (general method B). Found: *m/z*: 350.1736 $[M + H]^-$ $C_{21}H_{22}N_2O_3$. M + H = 350.1756

***Tert*-Butyl 1-benzyl-2-(1-benzylaziridine-2carbonyl)aziridine-2-carboxylate (4f)** was obtained from *tert*-butyl 1-tritylaziridin-2-carboxylate (**2f**) (1.17 g 5 mmol) by either method A or B. Reaction time 15 min. Yield 0.82 g (42%, oil) (general method A) or 0.90 g (46%, oil) (general method B). Found, *m/z*: 393.2165 $[M + H]^-$ $C_{24}H_{28}N_2O_3$ M + H = 393.2178.

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