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Synthesis of β,β-branched β-amino ester derivatives through spiroaziridination of (α-trimethylsilanylmethyl)cyclohexylidene esters

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Abstract—The reaction of (α-trimethylsilanylmethyl)cyclohexylidene esters with $NsONHCO_2Et$ and CaO produces the *N*-(ethoxycarbonyl)spiroaziridines which, after ring-opening, gives the corresponding β,β-disubstituted β-amino ester derivatives. The stereochemical outcome of the reaction is influenced by substituents on the cyclohexyl group.

α-Substituted β-amino acids have been the subject of considerable interest because of their direct involvement in the chemistry of various bioactive compounds.[1] They are common features of naturally occurring peptides[2] and they occur in many molecules with important pharmacological properties.[3] Furthermore, it has been shown that replacement of α-amino acid residues with β-amino acid residues at specific positions in some peptides leads to improved biological activity due to increased metabolic stability against peptidases.[4]

Moreover, other studies on β-peptide oligomers have revealed new opportunities for the development of specific helical conformations.[5] Some research groups are interested in the study of amino acids incorporating cycloalkane structures as models for conformationally restricted β,β-branched β-amino acids.[6]

The synthesis of β-amino acids has been extensively studied.[7] One very direct route is the addition of a suitable amino compound to α,β-unsaturated ester.[8] Recently, our research has been addressing the preparation of β-amino ester derivatives[9] by aziridination of β-(ethoxycarbonyl)allylsilanes with ethyl *N*-{[(4-nitrobenzene)sulphonyl]oxy}carbamate ($NsONHCO_2Et$) **1**,[10] in the presence of CaO as base. The intermediate *N*-(ethoxycarbonyl)aziridines ring-open upon treatment with AcOH to give the corresponding β-amino ester derivatives. The isolated *N*-(ethoxycarbonyl) β-amino α-methylene esters are precursors of β-amino α-hydroxy[9] esters, and in principle, of compounds obtainable by elaboration of the double bond.[11]

In this paper we extend this procedure to (α-trimethylsilanylmethyl)cyclohexylidene esters in order to synthesise β,β-disubstituted β-amino ester derivatives (Scheme 1) and to study the influence of substituents on the cyclohexyl group.

The β-(ethoxycarbonyl)allylsilanes **2a**–**d** were prepared from triethylphosphonoacetate using the appropriate cyclohexanones, following a modification of Hoffman's method.[9] The ^1H NMR and ^{13}C NMR analysis of compounds **2a**–**d** were in agreement with the structures and the spectral data of substrates **2a**, **2b** and **2d** reported by Kuroda et al.[12] The mixture of *E*/*Z* (1:1) isomers **2a** was used in the subsequent aziridination reaction without separation.

Aziridination of **2** was carried out in CH_2Cl_2 with an excess of $NsONHCO_2Et$ and CaO, using the molar ratio shown in Table 1. After purification, the mixtures of diastereomeric aziridines **3a**–**d** and **4a**–**d** were treated with AcOH in large excess (20 equiv.) at room temperature. The α-methylene *N*-(ethoxycarbonyl)-β-amino carboxylic esters **5** and **6** were obtained as a result of

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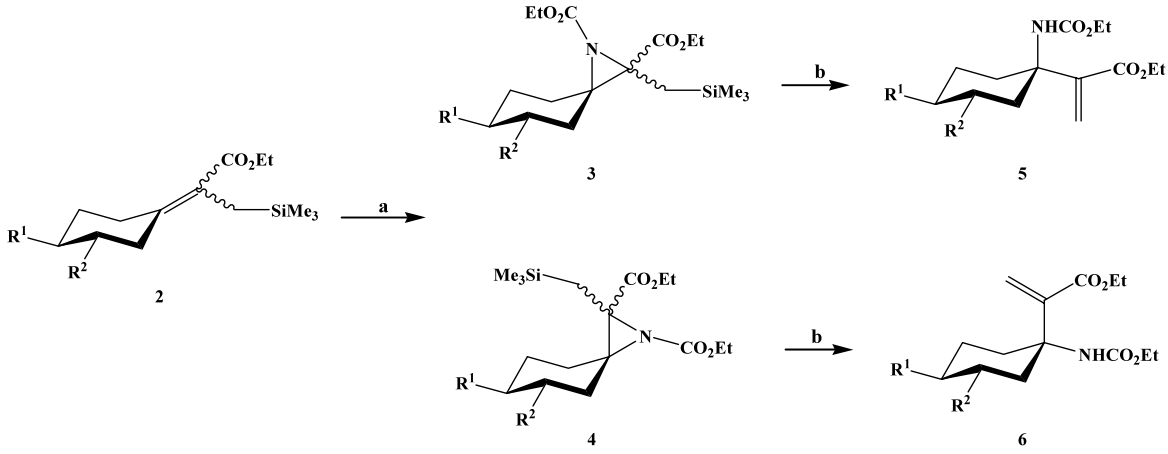

Scheme 1. *Reagents and conditions*: (a) *N*-{[(4-nitrobenzene)sulphonyl]oxy}carbamate ($NsONHCO_2Et$), CaO, CH_2Cl_2; (b) AcOH, CH_2Cl_2, rt.

Table 1. β-amino ester derivatives by spiroaziridination of (α-trimethylsilanylmethyl)cyclohexylidene esters

Entry	R^1	R^2	Molar ratio **2**:**1**:CaO	Aziridines **3** ^{13}C NMR δ of: *C*N; *C*N; CH_2Si; CH_3Si	Aziridines **4** ^{13}C NMR δ of: *C*N; *C*N; CH_2Si; CH_3Si	d.r. of products **5**:**6**	Yield of **5** (%)	Yield of **6** (%)
a$_{(E+Z)}$	H	CH_3	1:6:6	51.4; 50.8; 16.3; −0.8	51.5; 50.2; 16.2; −0.6	86:14	56	9
b	CH_3	H	1:6:6	51.4; 50.3; 16.2; 0.7	51.4; 52.8; 16.3; −0.7	67:33	48	23
c	Ph	H	1:7:7	51.4; 50.5; 16.4; −0.8	51.5; 49.5; 16.3; −0.5	67:33	42	21
d	*t*-Bu	H	1:8:8	51.4; 50.2; 16.2; −0.6	51.4; 51.0; 16.3; −0.8	60:40	44	30

ring-opening[13] and elimination of the silyl group. The ^1H NMR spectra showed that the diastereomeric ratios, determined by the integration of the vinyl proton signals, were always in favour of the same stereoisomer. Products **5** and **6** were isolated by flash chromatography (hexane/ethyl acetate = 95/5) in the yields reported (Table 1).

In order to investigate the stereochemistry of the process, we separated the aziridines **3** and **4** via several chromatographic purifications on silica gel. We observed that subsequent ring-opening reactions of the isolated spiroaziridines led to a single diastereomer in each reaction. Furthermore, the entire amination sequence on substrates **2a** (*E*) and **2a** (*Z*), separated through HPLC (hexane/Et_2O = 98/2), gave the same amino esters with the same d.e. without any effect of the double bond geometry on the final products.

We believe that all the major diastereomer derivatives are the amino esters **5**. Indeed, the above results suggest that the overall stereochemistry is the result of a preference for an axial attack by the aminating agent, as observed by Fleming and co-workers in the epoxidation of 4-substituted-cyclohexylidene silyl derivatives.[14] They observed a preference for axial attack by the epoxidising species which led to axial and equatorial alcohols in a ratio of 2:1 upon treatment with TBAF. Moreover, this kind of attack for **2a** will also be preferred because it is always *anti* with respect to the methyl group in position 3. When the substituent is in position 4, axial attack is *syn* to this group and the stereoselectivity becomes lower, as shown by the lower diasteromeric ratios in series **b**–**d**.

In conclusion, we have analyzed the effect of substituents on the stereochemistry of aziridation reactions of (α-trimethylsilanylmethyl)cyclohexylidene esters and we have been able to synthesise β,β-disubstituted β-amino ester derivatives. To the best of our knowledge, only a few methods appear to be appropriate for the generation of a quaternary centre at the β-position,[15] while the majority of investigations in this area have dealt with the synthesis of α,β-disubstituted β-amino acids.[13] Furthermore, the *N*-(ethoxycarbonyl)-spiroaziridines obtained in the first step of our procedure could be regarded as versatile tools in organic synthesis due to their ability to undergo facile and regioselective ring-opening.[16]

General procedure *For compounds **3** and **4**:* To a stirred solution of the substrate **2** (2.7 mmol) in 2 mL of CH_2Cl_2, $NsONHCO_2Et$ (2.7 mmol, 1 equiv.) and CaO (2.7 mmol, 1 equiv.) were added every 1.5 h, until the molar ratios **2**:$NsONHCO_2Et$:CaO reported in Table 1 was reached. After 24 h, 10 mL of a pentane–CH_2Cl_2

mixture (9/1) was added. The organic phase was filtered, concentrated in vacuo and flash chromatographed on silica gel (hexane/Et_2O = 8/2) to give a mixture of aziridines **3** and **4**.

*For compounds **5** and **6**:* To a stirred solution of the aziridines **3** and **4** in 2 mL of CH_2Cl_2 was added AcOH (20 equiv.) and the resulting solution was stirred for 96 h. The mixture was washed with a saturated solution of sodium bicarbonate, then extracted with CH_2Cl_2 and dried (Na_2SO_4). The solvent was evaporated in vacuo and the products **5** and **6** were separated by flash chromatography on silica gel (hexane/ethyl acetate = 95/5).[17]

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17. Spectral data: **5a** ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (d, 3H, J = 6.4 Hz), 1.18 (t, 3H, J = 7.1 Hz), 1.29 (t, 3H, J = 7.1 Hz), 1.36–1.78 (m, 7H), 2.58–2.66 (m, 1H), 2.66–2.74 (m, 1H), 4.00 (q, 2H, J = 7.1 Hz), 4.19 (q, 2H, J = 7.1 Hz), 5.14 (brs, 1H), 5.87 (s, 1H), 6.35 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): 14.1; 14.5; 22.3; 28.7; 34.5; 34.9; 41.9; 43.11; 56.3; 60.0; 60.5; 127.6; 140.0; 154.8; 167.1; IR: (CCl_4): 3432; 1733; 1710 cm^{-1}; GC-MS: m/z 283 [M$^+$] (<1%), 194 (100%); **6a**: 0.89 (d, 3H, J = 6.4 Hz), 1.18 (t, 3H, J = 7.1 Hz), 1.29 (t, 3H, J = 7.1 Hz), 1.33–1.89 (m, 7H), 2.36–2.55 (m, 2H), 4.02 (q, 2H, J = 7.1 Hz), 4.18 (q, 2H, J = 7.1 Hz), 4.92 (brs, 1H), 5.74 (s, 1H), 6.18 (s, 1H); ^{13}C NMR 14.1; 14.56; 22.4; 27.6; 33.5; 34.3; 41.3; 42.6;

56.5; 60.2; 60.5; 130.4; 145.6; 157.3; 170.1; IR: (CCl_4): 3438; 1757; 1730 cm^{-1}; GC-MS: m/z 283 [M^+] (<1%), 194 (100%); **5b** 0.89 (d, 3H, $J=6.5$ Hz), 1.19 (t, 3H, $J=7.1$ Hz), 1.29 (t, 3H, $J=7.1$ Hz), 1.29–1.85 (m, 7H), 2.32–2.51 (m, 2H), 4.01 (q, 2H, $J=7.1$ Hz), 4.18 (q, 2H, $J=7.1$ Hz), 5.08 (brs, 1H), 5.88 (s, 1H), 6.32 (s, 1H); ^{13}C NMR: 14.1; 14.6; 22.1; 29.9; 30.0; 30.1; 32.4; 34.1; 55.6; 60.2; 60.4; 123.5; 148.1; 155.2; 166.9; IR: (CCl_4): 3433; 1730; 1710 cm^{-1}; GC-MS: m/z 283 [M^+] (<1%), 180 (100%); **6b** 0.91 (d, 3H, $J=5.9$ Hz), 1.18 (t, 3H, $J=7.1$ Hz), 1.29 (t, 3H, $J=7.1$ Hz), 1.47–1.87 (m, 7H), 2.32–2.51 (m, 2H), 4.03 (q, 2H, $J=7.1$ Hz), 4.17 (q, 2H, $J=7.1$ Hz), 4.88 (brs, 1H), 5.74 (s, 1H), 6.18 (s, 1H); ^{13}C NMR 14.1; 14.6; 22.1; 29.9; 30.5; 32.4; 32.7; 34.1; 55.6; 60.2; 60.4; 123.5; 145,5; 155.5; 166.7; IR: (CCl_4): 3436; 1731; 1712 cm^{-1}; GC-MS: m/z 283 [M^+] (<1%), 180 (100%); **5c** 1.27 (t, 3H, $J=7.1$ Hz), 1.29–1.47 (m, 7H), 1.38 (t, 3H, $J=7.1$ Hz), 2.61–2.93 (m, 2H), 4.09 (q, 2H, $J=7.1$ Hz), 4.26 (q, 2H, $J=7.1$ Hz), 5.29 (brs, 1H), 6.02 (s, 1H), 6.50 (s, 1H); 7.15–7.42 (m, 5H); ^{13}C NMR 14.2; 14.4; 28.8; 31.2; 32.4; 32.8; 43.6; 55.6; 60.15; 60.6; 126.2; 126.8; 127.8; 128.3; 128.4; 128.5; 139.9; 146.2; 154.9; 166.9; IR (CCl_4): 3434; 1730; 1714 cm^{-1};GC-MS: m/z 345 [M^+] (<1%), 91 (100%); **6c** 1.21 (t, 3H, $J=7.1$ Hz), 1.30 (t, 3H, $J=7.1$ Hz), 1.41–2.09 (m, 7H), 2.36–2.72 (m, 2H), 4.04 (q, 2H, $J=7.1$ Hz), 4.18 (q, 2H, $J=7.1$ Hz), 5.00 (brs, 1H), 5.79 (s, 1H), 6.23 (s, 1H); 7.15–7.35 (m, 5H); ^{13}C NMR 14.1; 14.5; 29.8; 31.6; 33.2; 34.3; 43.5; 55.5; 60.3; 60.5; 123.8; 126.1; 126.4; 126.8; 128.3; 128.5; 146.6; 157.4; 170.0; IR: (CCl_4): 3438; 1732, 1709 cm^{-1}; GC-MS: m/z 345 [M^+] (<1%), 91 (100%); **5d** 0.81 (s, 9H), 1.00–1.71 (m, 7H), 1.18 (t, 3H, $J=7.1$ Hz), 1.29 (t, 3H, $J=7.1$ Hz), 2.69–2.77 (m, 1H), 2.77–2.85 (m, 1H), 4.00 (q, 2H, $J=7.1$ Hz), 4.18 (q, 2H, $J=7.1$ Hz), 5.16 (brs, 1H), 5.91 (s, 1H), 6.39 (s, 1H); ^{13}C NMR: 14.1; 14.5; 23.5; 23.6; 27.4; 32.2; 34.4; 35.2; 48.2; 55.7; 60.0; 60.5; 128.0; 139.5; 154.9; 167.0; IR (CCl_4): 3428; 1736; 1715 cm^{-1}; GC-MS: m/z 325 [M^+] (<1%), 180 (100%); **6d**; 0.86 (s, 9H), 1.00–1.71 (m, 7H), 1.20 (t, 3H, $J=7.1$ Hz), 1.28 (t, 3H, $J=7.1$ Hz); 2.46–2.53 (m, 1H), 2.53–2.61 (m, 1H), 3.99 (q, 2H, $J=7.1$ Hz), 4.17 (q, 2H, $J=7.1$ Hz), 4.88 (brs, 1H), 5.73 (s, 1H), 6.17 (s, 1H); ^{13}C NMR 14.1; 14.5; 23.2; 23.6; 27.5; 32.3; 33.1; 34.6; 46.7; 55.6; 60.5; 61.7; 123.5; 140.5; 156.8; 170.0 IR: (CCl_4): 3426; 1732; 1712 cm^{-1}; GC-MS: m/z 325 [M^+] (<1%), 180 (100%).