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Synthesis of α-amino γ-butyrolactone derivatives by aziridination of α-ylidene γ-butyrolactones

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Abstract—The reactions of exocyclic α,β-unsaturated γ-lactones with $NsONHCO_2Et$ and CaO produce *N*-(ethoxycarbonyl) spiroaziridino γ-lactones. By reaction with acetic acid these products give ring opening reaction and acetylated *N*-protected α-amino γ-butyrolactones are obtained. The ring opening reaction is quantitative and highly regioselective.

Aziridines are versatile synthetic intermediates for the synthesis of many biologically active molecules such as antitumor agents,[1] cysteine protease[2] or squalene synthase inhibitors.[3] The ability of aziridines to undergo highly regio and stereoselective ring opening reactions gives them a great value in the field of amino acids, heterocycles and alkaloids.[4] Spiroaziridines are investigated to obtain functionalized branched-chain amino derivatives.[5] In recent years our research group has focused attention on the use of the ethyl *N*-{[(4-nitrobenzene)sulphonyl]oxy}carbamate ($NsONHCO_2Et$)[6] in the presence of an inorganic insoluble base, such as CaO in CH_2Cl_2, to aziridinate electron poor olefins such as α,β-unsaturated carboxylates[7] and phosphonates.[8] Now we are interested to obtain spiroaziridines from exocyclic α,β-unsaturated γ-lactones **2**, and to investigate the ring opening reaction to get amino lactone derivatives.

The scaffold of these compounds, homoserine lactones, is a common feature in certain biological analogs including immunosuppressant, antiallergy and antineoplastic agent.[9] Furthermore α-amino γ-lactones are precursors of several non-proteinogenic amino acids and building blocks of polypirrolynone asymmetric synthesis.[10]

α-Ylidene γ-lactones **2** were synthesized by the Horner–Wadsworth–Emmons procedure, starting from the α-diethoxyphosphonyl-γ-butyrolactone **1**[11] and different aldehydes or ketones,[12,13] using K_2CO_3 as base. The substrates **2b**, **2f** and **2c**, **2e** were obtained as mixtures of *E* and *Z* isomers easily separated by flash chromatography on silica gel.

The aziridination reactions were carried out adding $NsONHCO_2Et$ and CaO portionwise, reaching the molar ratio reported in Table 1. Starting from substrates **2a**–**e**,

Table 1. Aziridination of α-ylidene γ-butyrolactones **2**

Entry	R_1	R_2	Molar ratio **2**: $NsONHCO_2Et$:CaO	Products and yield (%)[a]
2a	H	H	1:2:2	**3a** (39%)
2b (*E*)	CH_3	H	1:3:3	**3b** (45%)
2c (*E*)	$CH_2(CH_2)_3CH_3$	H	1:5:5	**3c** (47%)
2d (*E*)	Ph	H	1:5:5	**3d** (60%)
2e	CH_3	CH_3	1:3:3	**3e** (52%)
2f (*Z*)	CH_3	H	1:3:3	**3f** (42%)+**3b** (39%)
2g (*Z*)	$CH_2(CH_2)_3CH_3$	H	1:5:5	**3g** (28%)+**3c** (24%)

[a] Yield of isolated, purified products.

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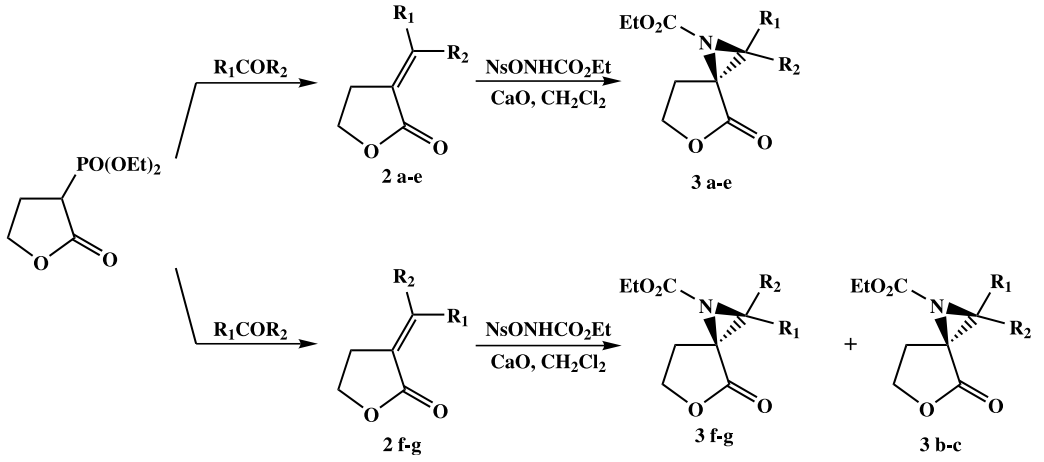
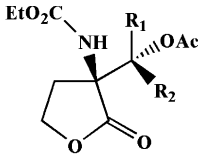


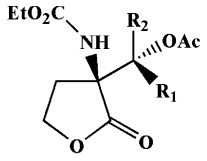
Scheme 1.

only one *N*-(ethoxycarbonyl)spiroaziridine (**3a**–**e**) was obtained, while aziridination of **2f** and **2g** led to two *N*-protected diastereomeric spiroaziridines in the ratio 1:1 (**3f** and **3b**, **3g** and **3c**, Scheme 1). The products were isolated by chromatography on silica gel and characterized by GC–MS, IR, ^{1}H, ^{13}C NMR analysis.[14] Also using ethyl *N*-[(trifluoromethanesulfonyl)oxy]-carbamate[15] as an aminating agent, it was possible to obtain the *N*-(ethoxycarbonyl)spiroaziridine **3a** in good yield from **2a**.

The hypothesis that aziridine ring opening[16] gives amino lactones, led us to test the reactivity with a nucleophile such as AcOH.[17] Compounds **3a**–**g** were allowed to react with acetic acid at 80°C.[18] The ring opening reactions for **3a**–**c** and **3e**–**g** seemed to be quantitative giving only the acetylated *N*-protected α-amino γ-butyrolactones **4a**–**c** and **4e**–**g**. From spectral data **4b** and **4f** appear to be different stereomers as well as **4c** and **4g**.



4 a-e

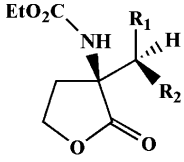


4 f-g

Even if a mixture of compounds was obtained starting from **3d**, the α-amino γ-butyrolactones **4d** was isolated as the main product (80%). This clearly shows that the ring opening reaction is regioselective and stereoselective.

All products **4** have been characterized by GC–MS, IR, ^{1}H, ^{13}C NMR analysis and spectroscopic data are in agreement with the reported structure.[19]

Our first attempts at reductive ring opening of **3** by catalytic transfer hydrogenation in the presence of 10% Pd(0)/C and ammonium formate[16h] was successful for aziridines **3a**, **3d** and **3e** giving as single products the *N*-(ethoxycarbonyl) α-amino γ-butyrolactones **5a**, **5d** and **5e**.[20]



5a, 5 d-e

We tested aziridination on *endocyclic* α,β-unsaturated γ-lactones such as **6**, known to be unreactive toward other aminating agents.[21] Compounds **6a**–**b** gave only traces of aziridines though the molar ratio substrate:$NsONHCO_2Et$:CaO reached 1:6:6. Meanwhile **6c** showed a good reactivity in the presence of 5 equiv. of reagent **1** and the base. The aziridine **7c** was isolated in a yield of 30% (Scheme 2).[22]

In conclusion, an efficient synthesis of *N*-(ethoxycarbonyl)spiroaziridino-γ-lactones has been developed based on the reaction with $NsONHCO_2Et$ of α-ylidene γ-butyrolactones. The following regioselective and stereoselective ring opening reaction leads to α-amino γ-butyrolactone derivatives, biologically interesting molecules. Efforts to extend the scope of this process to chiral α-ylidene γ-butyrolactones are currently in progress. Moreover we are pursuing studies on the aziridination reaction by different aminating reagent.

a: R_1 = H, R_2= H;
b: R_1 = OCH_3, R_2= H;
c: R_1 = H, R_2= CH_3.

Scheme 2.

General procedure. *For compounds **3** and **6c***. To a stirred solution of the substrate **2** (10.2 mmol) in 2.0 mL of CH_2Cl_2, $NsONHCO_2Et$ (10.2 mmol, 1 equiv.) and CaO were added every hour, reaching the molar ratio substrate:$NsONHCO_2Et$:CaO reported in Table 1. Because the reaction is exothermic, during the addition the flask was cooled in a water bath to avoid overheating. After 6 h, 10 mL of hexane was added. After filtration, the organic mixture containing the aziridine **3** was concentrated in vacuo. The product was isolated by flash chromatography on silica gel (hexane:ethyl acetate) in the yields reported in Table 1.

*For compounds **4***: The aziridines **3** were stirred at 80°C in the presence of acetic acid as a solvent. Different substrates needed different heating times to reach the complete conversion.[18] The reaction mixture was evaporated under reduced pressure, and then $CHCl_3$ was added. The organic layer was washed with a saturated solution of $NaHCO_3$ then dried over Na_2SO_4. After the work-up, the solvent was evaporated in vacuo giving the products **4**.[19]

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14. Spectral data: **3a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, 3H, CH_2CH_3); 2.51 (d, 1H, C*H*N, $J=1.2$ Hz); 2.38–2.67 (m, 2H, OCH_2CH_2); 2.81 (d, 1H, C*H*N, $J=1.2$ Hz); 4.18 (q, 2H, CH_2CH_3); 4.43–4.65 (m, 2H, OCH_2CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): 14.2, 26.8, 36.3, 42.0, 63.1, 65.6, 159.9, 172.8; IR: (CCl_4): 1794, 1748 cm^{-1}; GC–MS: m/z 185 [M$^+$] (<1%), 69 (100%). **3b**: ^{1}H NMR: δ 1.21 (t, 3H, CH_2CH_3); 1.29 (d, 3H, $CHCH_3$, $J=5.6$ Hz); 2.31–2.43 (m, 2H, OCH_2CH_2); 2.95 (q, 1H, C*H*N, $J=5.6$ Hz); 4.12 (q, 2H, CH_2CH_3); 4.36–4.64 (m, 2H, OCH_2CH_2); ^{13}C NMR: 14.1, 14.2, 24.1, 42.0, 45.8, 62.7, 65.7, 159.9, 173.0; IR: 1785, 1749 cm^{-1}; GC–MS: m/z 199 [M$^+$] (<1%), 54 (100%). **3c**: ^{1}H NMR: δ 1.25 (t, 3H, CH_2CH_3); 1.20–1.64 (m, 11H, $CH_2(CH_2)_3CH_3$); 2.26–2.34 (m, 2H, OCH_2CH_2); 2.91 (t, 1H, CHN, $J=5.6$ Hz); 4.17 (q, 2H, OCH_2CH_3); 4.37–4.67 (m, 2H, OCH_2CH_2); ^{13}C NMR: 13.8, 14.1, 22.1, 24.4, 26.4, 29.0, 31.1, 45.8, 46.7, 62.7, 65.0, 65.7, 159.9, 173.0; IR: 1790, 1735 cm^{-1} GC–MS: m/z 255 [M$^+$] (7.2%), 55 (100%). **3d**: ^{1}H NMR: δ 1.29 (t, 3H, CH_2CH_3); 1.97 (ddd, 1H, OCH_2CHH, $J=5.0$, 8.6, 14.0 Hz); 2.44 (ddd, 1H, OCH_2CHH, $J=7.0$, 9.2, 14.0 Hz); 4.05 (s, 1H, CHN); 4.25 (q, 2H, CH_2CH_3); 4.21–4.40 (m, 1H, $OCHHCH_2$); 4.57 (ddd, 1H, $OCHHCH_2$, $J=5.0$, 9.2, 9.2 Hz); 7.27–7.44 (m, 5H, CH arom.); ^{13}C NMR: 14.2, 23.8, 48.6, 48.7, 63.2, 65.6, 127.1, 128.6, 128.7, 132.9, 159.5, 172.2; IR: 1785, 1735 cm^{-1} GC–MS: m/z 261 [M$^+$] (<1%), 173 (100%). **3e**: ^{1}H NMR: 1.23 (t, 3H, CH_2CH_3); 1.35 (s, 3H, CCH_3); 1.55 (s, 3H, CCH_3); 2.33 (ddd, 1H, OCH_2CHH, $J=4.7$, 8.1, 13.8 Hz); 2.50–2.67 (m, 1H, OCH_2CHH); 4.14 (q, 2H, CH_2CH_3); 4.18–4.40 (m, 1H, $OCHHCH_2$); 4.50 (ddd, 1H, $OCHHCH_2$, $J=4.7$, 9.0, 9.0 Hz); ^{13}C NMR: 14.3, 16.4, 22.4, 25.1, 47.5, 48.3, 62.2, 64.6, 157.8, 171.7; IR: 1781, 1730 cm^{-1} GC–MS: m/z 213 [M$^+$] (<1%), 140 (100%). **3f**: ^{1}H NMR: 1.28 (t, 3H, CH_2CH_3); 1.49 (d, 3H, $CHCH_3$, $J=5.7$ Hz); 2.17 (ddd, 1H, OCH_2CHH, $J=3.4$, 7.3, 13.5, Hz); 2.73–2.90 (m, 1H, OCH_2CHH); 2.87 (q, 1H, $CHCH_3$, $J=5.7$ Hz); 4.19 (q, 2H, CH_2CH_3); 4.42 (ddd, 1H, $OCHHCH_2$, $J=7.3$, 9.2, 9.2 Hz); 4.56 (ddd, 1H, $OCHHCH_2$, $J=3.4$, 9.2, 9.2 Hz); ^{13}C NMR: 11.6, 14.3, 26.4, 44.6, 45.1, 62.8, 65.0, 159.1, 171.3; IR: 1788, 1723 cm^{-1}; GC–MS: m/z 199 [M$^+$] (0.3%), 54 (100%). **3g**: ^{1}H NMR: 1.28 (t, 3H, OCH_2CH_3); 1.22–1.68 (m, 11H, $CH_2(CH_2)_3CH_3$); 2.11 (ddd, 1H, OCH_2CHH, $J=3.0$, 7.1, 13.3, Hz); 2.69–2.96 (m, 1H, OCH_2CHH); 4.19 (q, 2H, CH_2CH_3); 4.44 (ddd, 1H, $OCHHCH_2$, $J=7.0$, 9.2, 9.2 Hz); 4.56 (ddd, 1H, $OCHHCH_2$, $J=3.0$, 9.2, 9.2 Hz); ^{13}C NMR; 13.8, 14.1, 22.1, 24.4, 26.4, 29.0, 31.1, 45.8, 46.7, 62.7, 65.0, 65.7, 159.9, 173.0; IR: 1788, 1731 cm^{-1} GC–MS: m/z 255 [M+] (7.2%), 55 (100%).
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18. **3a**: 15 h; **3b**: 45 h; **3c**: 30 h; **3d**: 7 h; **3e**: 15 h; **3f**: 95 h; **3g**: 25 h.
19. For example: **4b**: ^{1}H NMR: 1.24 (t, 3H, CH_2CH_3); 1.35 (d, 3H, $CHCH_3$, $J=6.4$ Hz); 2.08 (s, 3H, CH_3CO); 2.50 (ddd, 1H, OCH_2CHH, $J=3.5$, 7.9, 13.6 Hz); 2.61–2.85 (m, 1H, OCH_2CHH); 4.12 (q, 2H, CH_2CH_3); 4.20–4.40 (m, 1H, $OCHHCH_2$); 4.50 (ddd, 1H, $OCHHCH_2$, $J=3.4$, 9.2 Hz); 5.15 (q, 1H, $CHCH_3$, $J=6.4$ Hz); 5.27 (br s, 1H, NH); ^{13}C NMR; 14.4, 14.7, 20.9, 29.8, 61.6, 62.0, 65.5, 70.8, 155.2, 169.5, 174.5; IR: 3421, 1794, 1755, 1723 cm^{-1}; GC–MS: m/z 259 [M$^+$] (<1%), 173 (100%). **4f**: ^{1}H NMR: 1.25 (t, 3H, CH_2CH_3); 1.31 (d, 3H, $CHCH_3$, $J=6.5$ Hz); 2.11 (s, 3H, CH_3CO); 2.50–2.72 (m, 2H, OCH_2CH_2); 4.11 (q, 2H, CH_2CH_3); 4.19–4.35 (m, 1H, $OCHHCH_2$); 4.40–4.59 (m, 1H, $OCHHCH_2$); 5.30 (q, 1H, $CHCH_3$, $J=6.5$ Hz); 5.60 (br s, 1H, NH); ^{13}C NMR; 14.4, 15.0, 21.8, 61.5, 62.0, 66.1, 72.0, 155.2, 170.9, 175.1; IR: 3424, 1780, 1752, 1725 cm−^{1}; GC–MS: m/z 259 [M$^+$] (0.2%), 173 (100%).
20. For example: **5d**: ^{1}H NMR: 1.25 (t, 3H, CH_2CH_3); 2.54–2.80 (m, 2H, OCH_2CH_2), 3.05 (d, 1H, $CHHPh$, $J=13.2$ Hz), 3.17 (d, 1H, $CHHPh$, $J=13.2$ Hz), 4.12 (q, 2H, CH_2CH_3); 4.16–4.32 (m, 2H, OCH_2CH_2); 5.26 (br s, 1H, NH); 7.16–7.40 (m, 5H, CH arom.). GC–MS: m/z 263 [M$^+$] (0.2%), 100 (100%).
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22. **7c**: ^{1}H NMR: 1.27 (t, 3H, CH_2CH_3); 1.59 (s, 3H, CCH_3); 3.50 (d, 1H, OCH_2CH, $J=2.6$ Hz); 4.05 (q, 2H, CH_2CH_3); 4.12–4.38 (m, 2H, OCH_2CH); GC–MS: m/z 185 [M$^+$] (0.2%), 68 (100%).