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Amination of α,β-unsaturated (2-trimethylsilanylmethyl) carboxylic esters

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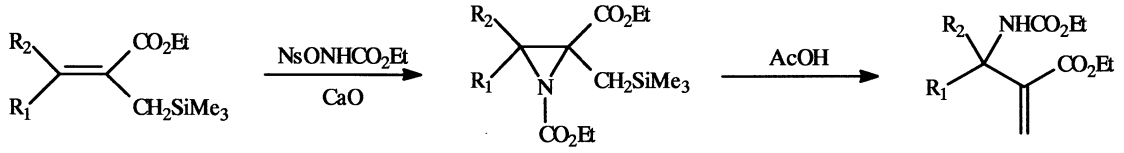
Abstract—The reactions of (2-trimethylsilanylmethyl) α,β-unsaturated carboxylic ethyl esters with $NsONHCO_2Et$ and CaO produce, after treatment with AcOH, α-methylene *N*-(ethoxycarbonyl) β-amino carboxylic esters through ring opening and elimination of the trimethylsilyl group from the intermediate aziridine. By ozonization and subsequent reductive cleavage these products give the corresponding *N*-(ethoxycarbonyl) β-amino α-hydroxy esters. © 2002 Elsevier Science Ltd. All rights reserved.

The chemistry of β-amino acids[1] has been of growing interest in recent years. In particular, α-substituted β-amino acids are an important class of compounds not only as components of natural products,[2] but also for their presence in medicinally useful molecules.[3] Representatives of this class are taxol, an anti-tumor agent[4] and bestatin, an immunological response modifier.[5] Furthermore, α-substituted β-amino acids and their derivatives are the object of constant research as precursors of β-lactams.[6]

A variety of routes to obtain β-amino acids is available,[7] many of which involve highly regiocontrolled ring-opening of aziridine-2-carboxylates.[8]

For many years our research group has been involved in a study of aziridination through a particular reagent: the ethyl *N*-{[(4-nitrobenzene)sulphonyl]oxy}carbamate ($NsONHCO_2Et$) **1**. It shows good reactivity with electron-rich alkenes in the presence of Et_3N.[9] The use of **1** and an inorganic insoluble base such as CaO or K_2CO_3 allows also the aziridination of electron poor double bonds such as α,β-unsaturated esters[10] and nitro olefins.[11] Using the same aminating reagent **1**, allylsilane derivatives have been used as starting material to obtain *N*-ethoxycarbonyl allylamines,[12] β,γ-unsaturated α-amino carboxylic esters[13] and α-methylene β-amino phosphonic esters.[14]

Pursuing this work, we have tested the aziridination of (2-trimethylsilanylmethyl) α,β-unsaturated esters **2** with the above reagent in order to obtain α-methylene β-amino carboxylates **4** by ring opening of the intermediate aziridines **3**. Compounds **4** are precursors of β-amino α-hydroxy esters and, in principle, of all the functionalities obtainable by chemical elaboration of the double bond. In this communication we report the first results we have obtained[15] (Scheme 1).



2 **3** **4**

Scheme 1. Synthesis of α-methylene *N*-(ethoxycarbonyl)-β-amino carboxylic ethyl esters **4**.

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Table 1. Synthesis of aziridines **3** and *N*-(ethoxycarbonyl)-β-amino α-methylene carboxylates **4**

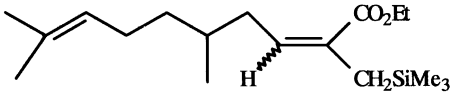
Entry	R_1	R_2	Molar ratio **2**:$NsONHCO_2Et$:CaO	Aziridines **3** ^1H NMR for aziridine protons	Molar ratio **2**:AcOH	Products **4** Yield (%)
a	H	H	1:3:3	δ 2.17 (d, 2H, $J=1.3$ Hz)	1:6	46
b	CH_3	H	1:4:4	δ 2.88 (q, 1H, $J=5.7$ Hz)	1:6	61
c	Ph	H	1:8:8	δ 4.03 (s, 1H)	1:6	58
d	CH_2-$(CH_2)_3$-CH_2		1:3:3	None	1:10	50

While ethyl 2-(trimethylsilanylmethyl)acrylate **2a** is commercially available, the known substrates **2b**,[16] **2c**[17] and **2d**[18] and the novel silyl derivative **2e** have been prepared, by extension of the procedure reported for **2b**,[16] through alkylation of the triethylphosphonacetate with iodomethyltrimethylsilane and subsequent Horner–Emmons reaction using the appropriate carbonyl compound. All compounds were isolated by chromatography on silica gel (hexane:diethyl ether). Substrates **2b**, **2c** and **2e** showed to be a *Z*/*E* mixture (*Z* isomer prevalent) and this affected the aziridination reactions, but had no effect on the final products **4**.

The aziridination reactions were carried out by treating a solution of substrates **2** in CH_2Cl_2 with $NsONHCO_2Et$ and CaO in excess following the general procedure reported below and reaching the molar ratio showed in Table 1 to obtain the best results. The expected aziridine derivatives **3a–d** were not isolated but detected in the crude reaction mixture by ^1H NMR (Table 1) and GC–MS spectral data. Aziridines **3b–c** were a *cis*/*trans* mixture, but only ^1H NMR data for the more abundant *cis*-isomer are shown in Table 1.

By treating the crude reaction mixtures containing the aziridines **3a–d** with AcOH in the molar ratios reported in Table 1 for 24 h, the α-methylene *N*-(ethoxycarbonyl)-β-amino carboxylic esters **4** were obtained because of the elimination of the silyl group and the ring-opening reaction. Obviously, ring opening eliminated the *cis*/*trans* isomerism present in aziridines **3b–c**. All products **4** have been easily isolated by flash chromatography and characterized by GC–MS, IR, ^1H NMR and ^{13}C NMR analysis.[19]

At variance with the behavior of substrates **2a–d**, the aziridination of **2e**, which is characterized by the presence of two double bonds, resulted in attack at the double bond far from the ester function and it was not further investigated.



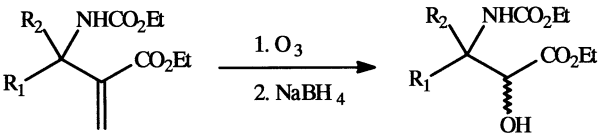
2e

The α-methylene-β-amino carboxylates **4** can be converted, in principle, into α-methylene-β-lactams and into β-amino acids having at the α-position the functionalities obtainable from a C=C bond as already reported, for example, by Yamamoto et al.[21] for the synthesis of α-methyl-β-amino acid derivatives and the corresponding β-lactams.

Therefore, to obtain β-amino α-hydroxy ester derivatives, we treated the α-methylene-derivatives **4a–c** with ozone (Scheme 2) and the resulting ozonides were reduced by $NaBH_4$[22] *one-pot*. Spectral data[23] of reaction mixtures showed the presence of the expected *N*-(ethoxycarbonyl)-β-amino α-hydroxy esters **5a–c**, namely two diastereomers for **5b** and only one for **5c**, this is likely to be because of the steric hindrance of phenyl group.

General procedure. *For compounds **4***: To a stirred solution of the substrate **2** (2.7 mmol) in 2.1 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, 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 24 h, 10 mL of a hexane–CH_2Cl_2 mixture (9:1) was added. After filtration, the organic phase containing the aziridine **3** was concentrated in vacuo and treated with AcOH (6–10 equiv., see Table 1) for 24 h. The mixture was washed with a saturated solution of sodium bicarbonate, then extracted with a mixture of hexane and CH_2Cl_2 (9:1) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the product **4** was isolated by flash chromatography on silica gel (hexane:ethyl acetate) in the yields reported in Table 1.

*For compounds **5***: The α-methylene-β-amino carboxylate **4** (0.4 mmol) in 2.0 mL of anhydrous CH_2Cl_2 was added to a saturated solution of ozone in 3.5 mL of anhydrous MeOH at −78°C. More ozone was added until the blue color persisted. Ozone bubbling was then terminated and the excess of ozone was displaced by passing a stream of oxygen through the solution. An excess of $NaBH_4$ (2.5 equiv.) was added and the solution was stirred at −78°C for 2.5 h and additional 3 h at room temperature. The reaction was then quenched with 7.5 mL of saturated solution of NH_4Cl. After the work-up the solvent was evaporated in vacuo giving the product **5**.



4 **5**

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

Scheme 2. One-pot ozonization–$NaBH_4$ reduction of **4a–c**.

Acknowledgements

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References

1. (a) Drey, C. N. C.; Barret, G. C. *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London, 1985; (b) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3–11; (c) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517–9582; (d) Cardillo, G.; Tommasini, C. *Chem. Soc. Rev.* **1996**, *23*, 117–128; (e) Juaristi, E. *Enantioselective Synthesis of β-amino Acids*; Wiley-VCH: New York, 1997.
2. (a) Pettit, G. R.; Kamano, Y.; Kizu, H.; Dufresne, C.; Herald, C. L.; Bontems, R. J.; Schmidt, J. M.; Boettner, F. E.; Nieman, R. A. *Heterocycles* **1989**, *28*, 553–558; (b) Carter, D. C.; Moore, E. R.; Mynderse, J. S.; Niemczura, W. D.; Todd, J. S. *J. Org. Chem.* **1984**, *49*, 236–241; (c) Cativela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 529–536.
3. (a) Palomo, C.; Aizpurua, J. M.; Cuevas, C. *J. Chem. Soc., Chem. Commun.* **1994**, 1957–1958; (b) Seebach, D.; Gademann, K.; Ernst, M.; Hoyer, D. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1223–1226; (c) Davis, S. G.; Dixon, D. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2635–2643.
4. (a) Reddy, S. H. K.; Lee, S.; Datta, A.; Georg, G. I. *J. Org. Chem.* **2001**, *66*, 8211–8214 and references cited therein; (b) Nicolau, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15–44.
5. (a) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852–2859 and references cited therein; (b) Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1976**, *29*, 97–99.
6. (a) Page, M. I. *The Chemistry of β-Lactams*; Chapman and Hall: London, 1992; (b) Craig, W. A.; Ebert, S. C. *Antimicrob. Agents Chemother.* **1992**, *36*, 2577–2583; (c) Georg, G. I. *The Organic Chemistry of β-Lactams*; Verlag Chemie: New York, 1993; (d) Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 613–618; (e) Mayachi, N.; Shibasaki, M. *J. Org. Chem.* **1990**, *55*, 1975–1976; (f) Murayama, T.; Kobayashi, T.; Miura, T. *Tetrahedron Lett.* **1995**, *36*, 3703–3706.
7. (a) Seebach, D.; Estermann, H. *Tetrahedron Lett.* **1987**, *28*, 3103–3106; (b) Juaristi, E.; Quintana, D.; Lamatsh, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553–2557; (c) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull.* **1978**, *26*, 260–263; (d) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Heterocycles* **1977**, *6*, 1323; (e) Farina, V.; Hauck, S. I.; Walker, D. G. *Synlett* **1992**, 761–763; (f) Terent'ev, A. P.; Gracheva, R. A.; Dedenko, T. F. *Dokl. Akad. Nauk. SSSR* **1965**, *163*, 686–689.
8. (a) Dubois, L.; Mehta, A.; Tourette, E.; Dodd, R. H. *J. Org. Chem.* **1994**, *59*, 434–441; (b) Molander, G. A.; Stengel, P. J. *J. Org. Chem.* **1995**, *60*, 6660–6661; (c) Righi, G.; D'Achille, R.; Bonini, C. *Tetrahedron Lett.* **1996**, *37*, 6893–6896; (d) McCoull, W.; Davis, F. A. *Synthesis* **2000**, *10*, 1347–1365; (e) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599–619.
9. Lwowski, W.; Maricich, T. J. *J. Am. Chem. Soc.* **1965**, *87*, 3630–3637.
10. Carducci, M.; Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **1996**, *37*, 3777–3778.
11. Fioravanti, S.; Pellacani, L.; Stabile, S.; Tardella, P. A.; Ballini, R. *Tetrahedron* **1998**, *54*, 6169–6176.
12. Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Raimondi, S.; Tardella, P. A. *Tetrahedron Lett.* **1993**, *34*, 4101–4104.
13. Loreto, M. A.; Pompei, F.; Tardella, P. A.; Tofani, D. *Tetrahedron* **1997**, *53*, 15853–15858.
14. Loreto, M. A.; Pompili, C.; Tardella, P. A. *Tetrahedron* **2001**, *57*, 4423–4427.
15. A preliminary account has been presented at The 12th European Symposium on Organic Chemistry (ESOC 12), Groningen, The Netherlands, July 13–18, 2001; abstract p. 2–209.
16. Henning, R.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1982**, *23*, 2305–2308.
17. Pornet, J.; Rayadh, A.; Miginiac, L. *Tetrahedron Lett.* **1986**, *27*, 5479–5482.
18. Kuroda, C.; Hirono, Y. *Tetrahedron Lett.* **1994**, *35*, 6895–6896.
19. Spectral data: **4a**:[20] ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, 3H, CH_2CH_3); 1.34 (t, 3H, CH_2CH_3); 4.03 (br d, $J=6.4$ Hz, 2H, CH_2); 4.14 (q, 2H, OCH_2CH_3); 4.25 (q, 2H, OCH_2CH_3); 5.20 (br t, $J=6.4$ Hz, 1H, NH); 5.82 (s, 1H, $=CH_2$); 6.28 (d, $J=0.9$ Hz, 1H, $=CH_2$); ^{13}C NMR (50 MHz, $CDCl_3$): 14.1, 14.5, 21.0, 49.1, 60.8, 126.3, 137.2, 156.4, 166.1; IR (CCl_4): 3446, 1727 cm^{-1}; GC–MS: m/z 201 [M$^+$] (8%), 128 (100%). **4b**: ^{1}H NMR: δ 1.19 (t, 3H, CH_2CH_3); 1.29 (t, 3H, CH_2CH_3); 1.32 (d, $J=6.9$ Hz, 3H, CH_3CH); 4.06 (q, 2H, OCH_2CH_3); 4.19 (q, 2H, OCH_2CH_3); 4.58 (m, 1H, CH); 5.33 (br d, $J=7.8$ Hz, 1H, NH); 5.71 (s, 1H, $=CH_2$); 6.14 (d, $J=0.8$ Hz, 1H, $=CH_2$); ^{13}C NMR: 14.1, 14.5, 20.9, 49.1, 60.7, 60.8, 124.9, 141.7, 155.6, 165.8; IR: 3442, 1733, 1707 cm^{-1}; GC–MS: m/z 215 [M$^+$] (3%), 82 (100%). **4c**: ^{1}H NMR: 1.51 (t, 3H, CH_2CH_3); 1.59 (t, 3H, CH_2CH_3); 4.45 (q, 2H, OCH_2CH_3); 4.48 (q, 2H, OCH_2CH_3); 5.95–6.10 (br m, 2H, CHN, NH); 6.23 (s, 1H, $=CH_2$); 6.71 (d, $J=0.8$, 1H, $=CH_2$); 7.56–7.67 (m, 5H, CH arom.); ^{13}C NMR: 13.9, 14.5, 56.6, 60.8, 61.1, 126.4, 127.4, 128.6, 139.8, 155.8, 165.6; IR: 3441; 1722 cm^{-1}; GC MS: m/z 277 [M$^+$] (7%), 174 (100%). **4d**: ^{1}H NMR: 1.18 (t, 3H, CH_2CH_3); 1.26 (t, 3H, CH_2CH_3); 1.45–1.71 (m, 8H); 2.24–2.42 (m, 2H); 4.01 (q, 2H, OCH_2CH_3); 4.15 (q, 2H, OCH_2CH_3); 4.92 (br s, 1H, NH); 5.73 (s, 1H, $=CH_2$); 6.18 (s, 1H, $=CH_2$); ^{13}C NMR: 14.1, 14.5, 21.5, 25.5, 34.2, 55.9, 60.2, 60.4, 124.0, 145.0, 157.9, 166.7; IR: 3435, 1734, 1720 cm^{-1}; GC–MS: m/z 269 [M$^+$] (5%), 167 (100%).
20. Barluenga, J.; Canteli, R.; Florez, J. *J. Org. Chem.* **1994**, *59*, 1586–1588.
21. Yamamoto, K.; Takagi, M.; Tsuji, J. *Bull. Chem. Soc. Jpn.* **1998**, *61*, 319–321.
22. (a) Sousa, J. A.; Bluhm, A. L. *J. Org. Chem.* **1959**, *25*, 108–111; (b) Blay, G.; Cordona, L.; Garcia, B.; Lahoz, L.; Monje, B.; Pedro, J. R. *Tetrahedron* **2000**, *56*, 6331–6338.

23. **5a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.20 (t, 3H, CH_2CH_3); 1.28 (t, 3H, CH_2CH_3); 3.38–3.62 (m, 2H, CHOH, OH); 4.07 (q, 2H, OCH_2CH_3); 4.22 (q, 2H, OCH_2CH_3); 4.18–4.40 (m, 2H, CH_2NH); 5.19 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): 14.1, 14.5, 44.2, 61.1, 62.1, 70.1, 156.3, 166.1; IR: 3532, 3459, 1735, 1729 cm^{-1}; GC–MS m/z 205 [M$^+$] (0.1%), 102 (100%). **5b**: (mixture *syn–anti*) ^{1}H NMR δ: 1.08 (d, $J=6.8$ Hz, 3H, CH_3CH); 1.17–1.4 (m, 15H); 2.89–3.36 (br s, 2H, OH); 4.02–4.36 (m, 12H); 4.82–5.00 (br d, $J=9.6$ Hz, 1H, NH); 5.00–5.18 (br d, $J=7.6$ Hz, 1H, NH); ^{13}C NMR: 14.0, 14.1, 14.4, 14.5, 18.1, 48.9, 60.9, 62.0, 62.2, 72.7, 73.1, 155.8, 155.9, 166.1; IR 3530, 3446, 1734, 1719 cm^{-1}; GC–MS m/z 219 [M$^+$] (0.1%), 44 (100%). **5c**: ^{1}H NMR δ: 1.25 (t, 6H, CH_2CH_3); 2.81–3.29 (br s, 1H, OH); 3.99–4.26 (m, 4H, CH_2CH_3); 4.60 (d, $J=3$, 1 Hz 1H, CHOH); 5.17 (dd, $J=9.1$ Hz, $J=3.1$ Hz, 1H, CHNH); 5.85 (br d, $J=9.1$ Hz, 1H, NH); 7.02–7.50 (m, 5H, CH arom.); ^{13}C NMR: 14.0, 14.5, 56.8, 61.1, 62.1, 73.1, 127.5, 128.2, 128.4, 128.6, 136.8, 155.8, 171.7; IR 3522, 3442, 1739, 1729 cm^{-1}; GC–MS m/z 281 [M$^+$] (0.2%), 178 (100%).