JOC*Note*

Diastereoselective Aziridination of Chiral α-Carbonyl Enoates[1]

Stefania Fioravanti,* Alberto Morreale, Lucio Pellacani,* and Paolo A. Tardella*

Dipartimento di Chimica, Università "La Sapienza", P.le Aldo Moro 2, I-00185 Roma, Italy

lucio.pellacani@uniroma1.it

Received March 1, 2002

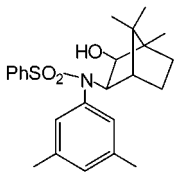
Abstract: Nosyloxycarbamates very efficiently aziridinate optically active α-carbonyl enoates with high levels of diastereoselectivity under mild conditions and in a straightforward process.

Aziridines receive continuous and increasing interest in organic synthesis[2] as they can possess both biological and pharmacological activities.[3] Nevertheless, despite their importance, the dearth of single-step preparation methods of aziridines limits their applicative use.

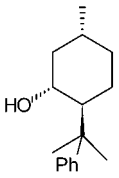
Direct aziridination of alkenes by carbamates has proved to be a useful reaction.[4] We have proposed the use of ethyl nosyloxycarbamate ($NsONHCO_2Et$, Ns = 4-nitrobenzenesulfonyl) in the presence of inorganic bases to obtain aziridines starting from different kinds of substituted alkenes.[5]

Recently, we reported a simple and efficient synthesis of *N*-protected aziridines, starting from 1,1-dicarbonyl-substituted olefins using either ethyl or *tert*-butyl nosyloxycarbamate in the presence of calcium oxide.[6] Moreover, the stereoselective amination of analogous substrates by conjugate addition of hydroxylamino reagents in the presence of Evans' catalyst[7] has been recently reported.[8] A variation of this procedure in two steps giving aziridines from the same starting materials was then reported by the same authors.[9]

Continuing our studies, we report here the aziridination of optically active α-carbonyl enoates derived from the commercially available alcohols (R*OH) Helmchen's auxiliary[10] (**1a**) and (−)-8-phenylmenthol (**1b**).



1a



1b

All substrates were easily prepared; aziridination reactions were carried out in dichloromethane at 0 °C. Calcium oxide and ethyl or *tert*-butyl nosyloxycarbamate were added to the solution of the enoates **2**−**4**. The expected aziridines **5**−**10** were obtained after flash chromatography on silica gel, in the yields displayed in the Table 1.

No significant differences in reactivities were observed using both carbamates, and all reactions proceeded in high yields. Moreover, the aziridinations took place with a very high asymmetric induction using both chiral auxiliaries, as shown by ^1H and ^{13}C NMR and HPLC analyses.[11]

Substrates **2a** and **3a** were already reported to undergo asymmetric conjugate nucleophilic addition from the less hindered prochiral *si*-face to give 5-alkyl-substituted derivatives with a high level of diastereoselection.[12] On the basis of these results, we suggest the configuration (*S*,*S*) for the major diastereomers of aziridines **5a**−**8a**.

We also observed a very good diastereoselectivity using (−)-8-phenylmenthol as the chiral auxiliary. On the other hand, it has been reported that α,β-unsaturated esters derived from (−)-8-phenylmenthol gave other conjugate additions with a low asymmetric induction.[13]

In conclusion, we believe that this method offers considerable advantages for the development of a direct diastereoselective synthesis of chiral substituted aziridines in high yields under very mild conditions and with operational simplicity.

Experimental Section

General. GC analyses were performed on a capillary column (methyl silicone, 12.5 m × 0.2 mm). GC MS was performed using a quadrupole mass spectrometer on a capillary column (phenyl methyl silicone, 30 m × 0.25 mm). IR spectra were recorded on

* Phone: +39 06 49913673. Fax: +39 06 490631.

(1) Presented in part at the 12th European Symposium on Organic Chemistry (ESOC 12), Groningen, The Netherlands, July 13−18, 2001. Abstract P2-105.

(2) For reviews, see: (a) Tanner, D. *Angew. Chem.* **1994**, *6*, 625−646; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599−619. (b) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693−1715. (c) Stamm, H. *J. Prakt. Chem.* **1999**, *4*, 319−331. (d) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519−1559. (e) Dodd, R. H. *Molecules* **2000**, *5*, 293−298. (f) McCoull, W.; Davis, F. A. *Synthesis* **2000**, *10*, 1347−1365.

(3) (a) Armstrong, R. W.; Tellew, J. E.; Moran, E. J. *Tetrahedron Lett.* **1996**, *37*, 447−450. (b) Katoh, T.; Itoh, E.; Yoshino, T.; Terashima, S. *Tetrahedron Lett.* **1996**, *37*, 3471−3474. (c) Ngo, E. O.; Nutter, L. M.; Sura, T.; Gutierrez, P. L. *Chem. Res. Toxicol.* **1998**, *11*, 360−368. (d) Skelly, J. V.; Sanderson M. R.; Suter, D. A.; Baumann, U.; Read, M. A.; Gregory, D. S. J.; Bennett, M.; Hobbs, S. M.; Neidle, S. *J. Med. Chem.* **1999**, *42*, 4325−4330. (e) Dvorakova, K.; Payne, C. M.; Tome, M. E.; Briehl, M. M.; McClure, T.; Dorr, R. T. *Biochem. Pharmacol.* **2000**, *60*, 749−758. (f) Brown, F. *Vaccine* **2000**, *20*, 322−327.

(4) Lwowski, W.; Maricich, T. J. *J. Am. Chem. Soc.* **1965**, *87*, 3630−3637.

(5) (a) Barani, M.; Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **1994**, *50*, 3829−3834. (b) Fioravanti, S.; Pellacani, L.; Tabanella, S.; Tardella, P. A. *Tetrahedron* **1998**, *54*, 14105−14112.

(6) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Synthesis* **2001**, 1975−1978.

(7) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134−9142.

(8) Cardillo, G.; Gentilucci, L.; Gianotti, M.; Kim, H.; Perciaccante, G.; Tolomelli, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2395−2398.

(9) Cardillo, G.; Gentilucci, L.; Gianotti, M.; Perciaccante, G.; Tolomelli, A. *J. Org. Chem.* **2001**, *25*, 8657−8660.

(10) Helmchen, G.; Wegner, G. *Tetrahedron Lett.* **1985**, *26*, 6051−6054.

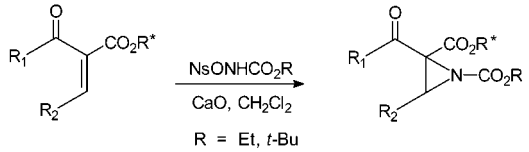
(11) A further test using simple (−)-menthol as the chiral auxiliary gave a very low induction, as nearly equimolar mixtures of both diastereomeric aziridines were obtained.

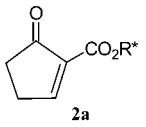
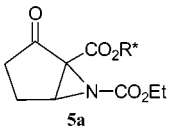
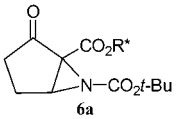
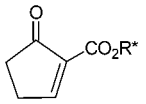
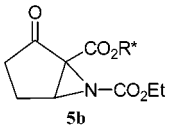
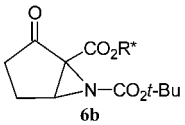
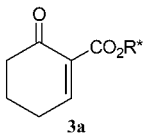
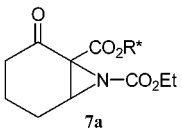
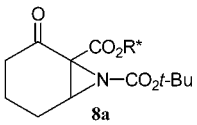
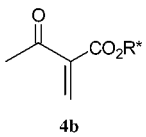
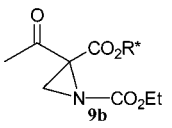
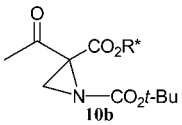
(12) (a) Urban, E.; Knühl, G.; Helmchen, G. *Tetrahedron Lett.* **1995**, *36*, 7229−7232. (b) Urban, E.; Riehs, G.; Knühl, G. *Tetrahedron* **1995**, *51*, 11149−11164.

(13) Kotsuki, H.; Arimura, K.; Ohishi, T.; Maruzasa, R. *J. Org. Chem.* **1999**, *64*, 3770−3773.

10.1021/jo025670x CCC: $22.00
Published on Web 05/16/2002

TABLE 1. Aziridination of Optically Active α-Carbonyl Enoates by Nosyloxycarbamates



entry	substrate	time (h)	product	yield (%)	de (%)
1	 **2a**	2	 **5a**	91	99
			 **6a**	90	99
2	 **2b**	2.5	 **5b**	92	97
			 **6b**	90	98
3	 **3a**	2	 **7a**	90	99
			 **8a**	88	99
4	 **4b**	3	 **9b**	78	96
			 **10b**	79	96

a FTIR spectrophotometer in CCl_4 as the solvent. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 or 300 and 50 or 75 MHz, respectively. $CDCl_3$ was used as the solvent and $CHCl_3$ as the internal standard. ESI MS analyses were performed using a triple-quadrupole mass spectrometer equipped with an ESI source and a syringe pump. The experiments were conducted in the positive ion mode. HPLC analyses were performed with an instrument equipped with a differential refractometer, using an analytical column (3.9 × 300 mm, 80:20 hexane/ethyl acetate, flow rate 1.3 mL/min). Eluents were HPLC grade. Optical rotations were recorded at the sodium D line with a polarimeter at room temperature. NaH (55/65% suspension in mineral oil) was washed twice with pentane and dried under nitrogen. Anhydrous THF and toluene were used as such. Substrates **2a**, **2b**, and **3a** were easily prepared following reported procedures.[12,14]

Synthesis of 4b. According to a reported procedure,[15] 8-phenylmenthyl 2-methyl-3-oxobutanoate[16] (0.68 g, 2.0 mmol) was added slowly to a stirred suspension of NaH (0.07 g, 3.0 mmol)

(14) Pan, L. R.; Tokoroyama, T. *Tetrahedron Lett.* **1992**, *33*, 1469−1472.

(15) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434−5447.

(16) Zhang, Q.; Mohan, R. M.; Cook, L.; Kazanis, S.; Peisach, D.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1993**, *58*, 7640−7651.

in 40 mL of anhydrous THF at 0 °C. After 1 h, a solution of PhSeCl (0.38 g, 2.0 mmol) in 5 mL of anhydrous THF was added dropwise. After 30 min, the solution was diluted with diethyl ether, washed with saturated $NaHCO_3$ and saturated NaCl, and dried over Na_2SO_4. The solvents were evaporated under reduced pressure. The crude mixture was dissolved in 20 mL of CH_2Cl_2 and stirred with 40% H_2O_2 (0.6 mL, 8 mmol) for 3 h at 0 °C. Then, the mixture was washed with saturated $NaHCO_3$ and saturated NaCl and dried over Na_2SO_4. After solvent evaporation, **4b** was obtained (0.63 g, yield 96%) and used without further purification: $[\alpha]_D$ −21.46 (*c* 4.8, $CHCl_3$); IR 1715, 1630 cm^{-1}; ^1H NMR δ 0.64−2.18 (m, 8 H), 0.93 (d, J = 6.6 Hz, 3 H), 1.26 (s, 3 H), 1.32 (s, 3 H), 2.38 (s, 3 H), 4.83−5.08 (m, 1 H), 5.74 (d, J = 1.5 Hz, 1 H), 6.15 (d, J = 1.5 Hz, 1 H), 7.06−7.50 (m, 5 H); ^{13}C NMR δ 21.7, 24.3, 26.4, 28.5, 31.2, 31.9, 34.8, 39.7, 45.4, 54.2, 75.3, 125.2, 125.7, 128.0, 133.6, 140.9, 151.5, 163.5, 196.6; GC MS *m*/*z* 328 (M^+, <1), 120 (10), 119 (100), 118 (26), 91 (23), 43 (10). Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 77.01; H, 8.47.

Typical Experimental Procedure of Aziridination. To a stirred solution of the substrate (2.0 mmol) in 5 mL of CH_2Cl_2 were added batchwise CaO (6.0 mmol) and $NsONHCO_2R$ (3.0 mmol) at 0 °C. The reaction was monitored by TLC until completion (see Table 1), and then the crude mixture was diluted with 10 mL of CH_2Cl_2 and filtered. After solvent evaporation under reduced pressure, the residue was purified by flash chromatography on silica gel (70:30 hexane/ethyl acetate).

5a: mp 133−134 °C (pentane/$CHCl_3$); $[\alpha]_D$ +72.3 (*c* 4.8, $CHCl_3$); IR 1767, 1733, 1723 cm^{-1}; ^1H NMR δ 0.52 (s, 3 H), 0.79 (s, 3 H), 0.84 (s, 3 H), 0.94−2.58 (m, 9 H), 1.22 (t, J = 7.2 Hz, 3 H), 1.97 (s, 3 H), 2.29 (s, 3 H), 3.76 (d, J = 7.2 Hz, 1 H), 4.11−4.31 (m, 2 H), 4.29−4.36 (m, 1 H), 5.28 (d, J = 7.2 Hz, 1 H), 5.56−5.64 (br, 1 H), 6.82 (s, 1 H), 7.02−7.52 (m, 6 H); ^{13}C NMR δ 11.1, 13.9, 14.2, 19.2, 20.6, 21.0, 27.9, 31.6, 32.7, 47.2, 48.2, 50.1, 50.7, 51.9, 62.9, 67.0, 81.8, 128.1, 129.5, 132.5, 136.6, 138.0, 157.7, 162.6, 200.5; ESI MS *m*/*z* 609 (M^+ + 1). Anal. Calcd for $C_{33}H_{40}N_2O_7S$: C, 65.11; H, 6.62; N, 4.60; S, 5.27. Found: C, 65.18; H, 6.69; N, 4.62; S, 5.32.

6a: mp 164−165 °C (pentane/$CHCl_3$); $[\alpha]_D$ +100.8 (*c* 4.9, $CHCl_3$); IR 1766, 1720 cm^{-1}; ^1H NMR δ 0.53 (s, 3 H), 0.79 (s, 3 H), 0.82 (s, 3 H), 1.00−2.58 (m, 9 H), 1.42 (s, 9 H), 1.98 (s, 3 H,), 2.29 (s, 3 H), 3.79 (d, J = 7.2 Hz, 1 H), 4.22−4.31 (m, 1 H), 5.28 (d, J = 7.2 Hz, 1 H), 5.52−5.68 (br, 1 H), 6.83 (s, 1 H), 7.26−7.55 (m, 6 H); ^{13}C NMR δ 10.9, 13.9, 19.1, 20.7, 21.1, 27.7, 28.0, 31.6, 32.9, 47.2, 48.2, 50.1, 51.1, 52.1, 67.0, 81.8, 82.0, 128.2, 129.5, 132.5, 136.8, 137.9, 156.3, 162.9, 200.9; ESI MS *m*/*z* 637 (M^+ + 1). Anal. Calcd for $C_{35}H_{44}N_2O_7S$: C, 66.01; H, 6.96; N, 4.40; S, 5.03. Found: C, 66.12; H, 6.98; N, 4.46; S, 5.10.

5b: viscous oil; $[\alpha]_D$ −44.8 (*c* 5.2, $CHCl_3$); IR 1769, 1738 cm^{-1}; ^1H NMR δ 0.85 (d, J = 6.3 Hz, 3 H), 0.95−1.78 (m, 15 H), 1.84−2.55 (m, 4 H), 2.20−2.38 (m, 2 H), 3.01−3.08 (m, 1 H), 3.95−4.42 (m, 2 H), 4.95 (dt, J_d = 4.5 Hz, J_t = 10.5 Hz, 1 H), 7.09−7.20 (m, 1 H), 7.25−7.36 (m, 4 H); ^{13}C NMR δ 14.2, 19.6, 21.7, 26.6, 26.9, 29.7, 31.4, 32.9, 34.4, 40.0, 41.5, 49.8, 49.9, 63.2, 76.6, 125.1, 125.5, 127.8, 150.9, 157.4, 162.7, 200.1; ESI MS *m*/*z* 428 (M^+ + 1). Anal. Calcd for $C_{25}H_{33}NO_5$: C, 70.23; H, 7.78; N, 3.26. Found: C, 70.34; H, 7.56; N, 3.30.

6b: mp 58−59 °C (pentane); $[\alpha]_D$ −10.6 (*c* 5.1, $CHCl_3$); IR 1762, 1724 cm^{-1}; ^1H NMR δ 0.84 (d, J = 6.6 Hz, 3 H), 0.97−1.81 (m, 12 H), 1.42 (s, 9 H), 1.83−2.28 (m, 4 H), 2.27−2.46 (m, 2 H), 3.05−3.23 (m, 1 H), 4.94 (dt, J_d = 4.5 Hz, J_t = 10.5 Hz, 1 H), 7.05−7.20 (m, 1 H), 7.21−7.38 (m, 4 H); ^{13}C NMR δ 19.3, 21.7, 26.4, 27.0, 27.5, 27.9, 31.4, 33.1, 34.3, 40.1, 41.5, 49.6, 50.1, 50.4, 76.5, 82.8, 125.1, 125.6, 127.7, 150.7, 156.0, 163.2, 200.1; ESI MS *m*/*z* 456 (M^+ + 1). Anal. Calcd for $C_{27}H_{37}NO_5$: C, 71.18; H, 8.19; N, 3.07. Found: C, 71.14; H, 8.11; N, 3.03.

7a: mp 167−168 °C (pentane/$CHCl_3$); $[\alpha]_D$ −22.1 (*c* 2.9, $CHCl_3$); IR 1750, 1736, 1721 cm^{-1}; ^1H NMR δ 0.52 (s, 3 H), 0.69 (s, 3 H), 0.83 (s, 3 H), 0.98−2.45 (m, 11 H), 1.25 (t, J = 7.2 Hz, 3 H), 2.02 (s, 3 H), 2.29 (s, 3 H), 3.81 (d, J = 7.2 Hz, 1 H), 3.89−3.92 (m, 1 H), 4.18 (q, J = 7.2 Hz, 2 H), 5.35 (d, J = 7.2 Hz, 1 H), 5.64−5.73 (br, 1 H), 6.85 (s, 1 H), 7.10−7.53 (m, 6 H); ^{13}C NMR δ 11.2, 14.1, 17.3, 20.5, 21.0, 21.3, 22.1, 28.0, 32.0, 38.5, 45.2, 46.8, 47.2, 48.4, 50.3, 62.8, 67.0, 82.9, 128.0, 128.7, 129.6, 132.7, 136.3, 138.2, 158.1, 164.8, 196.9; ESI MS *m*/*z* 623 (M^+ + 1). Anal. Calcd for $C_{34}H_{42}N_2O_7S$: C, 65.57; H, 6.80; N, 4.50; S, 5.15. Found: C, 65.63; H, 6.85; N, 4.52; S, 5.22.

8a: mp 206−207 °C (pentane/$CHCl_3$); $[\alpha]_D$ −27.1 (*c* 2.1, $CHCl_3$); IR 1740, 1718, 1708 cm^{-1}; ^1H NMR δ 0.52 (s, 3 H), 0.72 (s, 3 H), 0.84 (s, 3 H), 0.98−2.45 (m, 11 H), 1.41 (s, 9 H), 2.02 (s, 3 H), 2.24 (s, 3 H), 3.51−3.64 (m, 1 H), 3.84 (d, J = 7.2 Hz, 1 H), 5.29 (d, J = 7.2 Hz, 1 H), 5.63−5.85 (br, 1 H), 6.82 (s, 1 H), 7.10−7.62 (m, 6 H); ^{13}C NMR δ 11.2, 17.2, 20.7, 21.0, 21.2, 21.3, 27.7, 28.1, 31.6, 37.9, 44.8, 47.2, 47.7, 48.2, 50.3, 66.5, 82.0, 82.5, 128.0, 128.5, 129.4, 132.4, 136.7, 138.1, 156.5, 165.2, 197.0; ESI MS *m*/*z* 651 (M^+ + 1). Anal. Calcd for $C_{36}H_{46}N_2O_7S$: C, 66.44; H, 7.12; N, 4.30; S, 4.93. Found: C, 66.49; H, 7.15; N, 4.38; S, 5.02.

9b: bp 169−170 °C (7 mmHg); $[\alpha]_D$ +27.4 (*c* 4.6, $CHCl_3$); IR 1747, 1735, 1723 cm^{-1}; ^1H NMR δ 0.75−1.11 (m, 4 H), 0.84 (d, J = 6.5 Hz, 3 H), 1.18 (s, 3 H), 1.24 (t, J = 7.3 Hz, 3 H), 1.30 (s, 3 H), 1.38−1.48 (m, 1 H), 1.55−1.66 (m, 2 H), 1.82−1.87 (m, 1 H, CH), 2.08 (d, J = 1.3 Hz, 1 H), 2.11 (d, J = 1.3 Hz, 1 H), 2.30 (s, 3 H), 4.04−4.19 (m, 2 H), 4.94 (dt, J_d = 4.5 Hz, J_t = 10.7 Hz, 1 H), 7.10−7.15 (m, 1 H), 7.22−7.27 (m, 4 H); ^{13}C NMR δ 14.1, 21.6, 25.6, 26.6, 27.4, 28.3, 31.3, 34.2, 36.3, 39.7, 41.3, 49.5, 50.1, 62.9, 77.3, 125.3, 128.0, 151.2, 158.9, 164.9, 199.0; GC MS *m*/*z* 415 (M^+, 12), 201 (70), 157 (14), 156 (23), 129 (100), 128 (32), 119 (42), 111 (59), 110 (10), 105 (48), 91 (37), 84 (21), 83 (21), 55 (10), 43 (13), 41 (13). Anal. Calcd for $C_{24}H_{33}NO_5$: C, 69.37; H, 8.00; N, 3.37. Found: C, 69.41; H, 8.07; N, 3.40.

10b: bp 193−194 °C (7 mmHg); $[\alpha]_D$ +15.7 (*c* 4.2, $CHCl_3$); IR 1736, 1722 cm^{-1}; ^1H NMR δ 0.72−1.75 (m, 6 H), 0.85 (d, J = 6.6 Hz, 3 H), 1.24 (s, 3 H), 1.34 (s, 3 H), 1.46 (s, 9 H), 1.87−2.08 (m, 2 H), 2.24 (d, J = 2.2 Hz, 1 H), 2.26 (d, J = 2.2 Hz, 1 H), 2.34 (s, 3 H), 4.95 (dt, J_d = 4.4 Hz, J_t = 11.0 Hz, 1 H), 7.10−7.20 (m, 1 H), 7.24−7.31 (m, 4 H); ^{13}C NMR δ 21.6, 26.3, 26.8, 27.2, 27.9, 28.6, 31.3, 34.3, 37.0, 40.0, 41.3, 49.6, 50.2, 77.6, 82.4, 125.3, 125.5, 128.1, 150.8, 157.5, 165.3, 199.2; GC MS *m*/*z* 342 (M^+ − 101, <1), 128 (88), 120 (10), 119 (100), 118 (55), 109 (57), 91 (33), 41 (10). Anal. Calcd for $C_{26}H_{37}NO_5$: C, 70.40; H, 8.41; N, 3.16. Found: C, 70.33; H, 8.34; N, 3.11.

Acknowledgment. This research was carried out within the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie e Applicazioni", supported by the Italian Ministero dell'Istruzione dell'Università e della Ricerca (MIUR) and by the Università di Roma "La Sapienza".

JO025670X