Diastereoselective Synthesis of *N*-Substituted Ethyl 4-Phenyloxazolidine-2-carboxylates†

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(*S*)-2-Phenylglycinol, ethyl glyoxylate, formaldehyde and benzotriazole formed stereospecifically ethyl (2*S*,4*S*)-*N*-(benzotriazol-1-yl)methyl-4-phenyloxazolidine-2-carboxylate (**1**) which was converted into chiral *N*-substituted oxazolidines, *via* regiospecific substitutions of the benzotriazolyl residue.

N-Substituted-1,3-oxazolidines derived from chiral β-amino alcohols are valuable chiral templates,[1] and show mydriatic[2] or anorectic[3] pharmacological activity. We have previously applied benzotriazole as a synthetic auxiliary[4] in the chiral syntheses of 2-substituted- and 2,5-disubstituted pyrrolidines,[5] 2-substituted- and 2,6-disubstituted piperidines[6] and indolo[3,2,1-*de*][1,5]naphthyridines.[7] We have now prepared diverse chiral *N*-substituted-oxazolidines (**3a**–**e**, **4**, **5**) with an α-aminoester substructure by regiospecific nucleophilic replacement of the benzotriazolyl group from ethyl (2*S*,4*S*)-3-(1*H*-benzotriazol-1-yl)methyl-4-phenyl-1,3-oxazolidine-2-carboxylate (**1**).

Chiral oxazolidine **1** was prepared from benzotriazole, ethyl glyoxylate, (*S*)-2-phenylglycinol and formaldehyde in toluene by removing water with a Dean–Stark apparatus (see Scheme 1 below). The crude ^{1}H NMR spectrum indicated a mixture of Bt-1 and Bt-2 isomers in a 9:1 ratio. Oxazolidine **1** (Bt-1 isomer) crystallized in 80% yield from ethanol. Structure **1** was confirmed by X-ray crystallography, and shows that the 2-ethoxycarbonyl group is *cis* to the C-4 phenyl substituent (Fig. 1). By contrast, the reaction between (*R*)-phenylglycinol and cyclohexylcarbaldehyde was reported[8] to afford the corresponding oxazolidine as a mixture of diasteromers in a 3:2 ratio.

Compound **1** has two reactive centres, each, in the presence of a Lewis acid, can form an imminium salt which is prone to nucleophilic attack.[4,9] In the presence of an excess of the mild Lewis acid $ZnBr_2$ at 0 °C, regiospecific nucleophilic substitution of the benzotriazolyl group in compound **1** by allyltrimethylsilane (**2a**, R = H) was observed (without any attack on the oxazolidine ring) to give ethyl

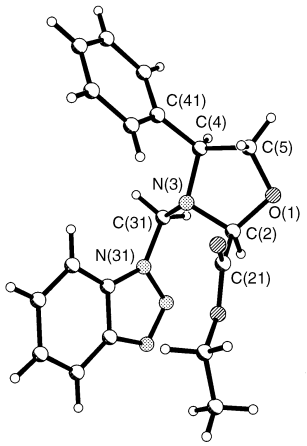
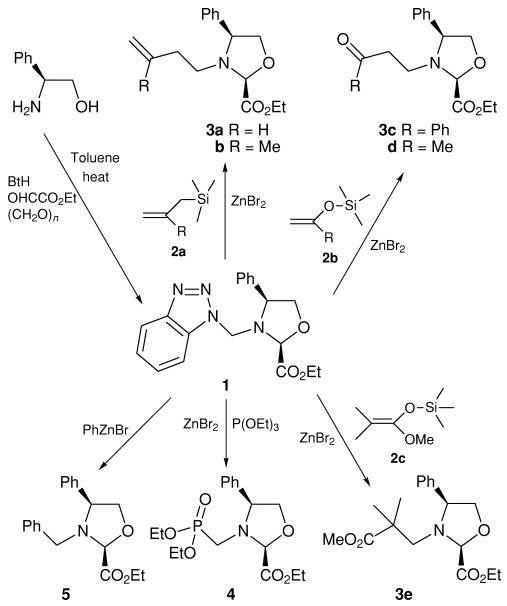


Fig. 1 Perspective view of the X-ray crystal structure of **1**



Scheme 1

(2*S*,4*S*)-3-(but-3-enyl)-4-phenyl-1,3-oxazolidine-2-carboxylate (**3a**) in 66% yield (Scheme 1). Similar treatment of **1** with (β-methylallyl)trimethylsilane (**2a**, R = Me) afforded **3b** in 69% yield. Compounds **3a,b** are potential precursors for chiral substituted pyrrolidines *via* amino-zinc-enolate cyclization.[10]

Reaction of **1** with the vinyl trimethylsilyl ethers **2b** (R = Ph and Me) and **2c** under the above conditions afforded ketones **3c** and **3d**, and ester **3e**, respectively, in good yields. Treatment of compound **1** with triethoxyphosphine gave the α-aminophosphate **4** in 78% yield under similar conditions.

Phenylzinc bromide also effected regiospecific nucleophilic substitution of the benzotriazolyl group in compound **1** at 0 °C in THF to afford compound **5** in 57% yield. However, the reaction failed with butyl and pentyl aliphatic organozinc reagents.

In summary, the synthesis of oxazolidine derivatives **3a**–**e**, **4** and **5** from the regiospecific reaction of oxazolidine **1** with different nucleophiles provides a convenient route of this class of *N*-functionalized α-aminoesters.

Experimental

General.—^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ with TMS and $CDCl_3$ as the internal references, respectively. Elemental analyses were performed on a Carlo Erba-1106 instrument. High resolution mass spectra were measured on a Kratos/AE1-MS 30 mass spectrometer. The $[\alpha]_D$ were recorded on a Perkin Elmer 341 polarimeter at 20 °C, $c = 1$ g/100 ml in methylene chloride. Gas chromatographic analyses were run on a Hewlett Packard 5890 Gas Chromatograph.

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Synthesis of Ethyl (2*S*,4*S*)-3-(1*H*-1,2,3-*Benzotriazol*-1-*yl methyl*)-4-*phenyl*-1,3-*oxazolidine*-2-*carboxylate* (**1**).—Ethyl glyoxylate (11 mol) and benzotriazole (11 mmol) were heated to reflux temperature for 15 min in toluene (30 ml) and cooled to room temperature. Then (*S*)-phenylglycinol (10 mmol) and paraformaldehyde (10 mol) were added to the above mixture, which was heated to reflux in toluene (30 ml) with a Dean–Stark trap for 30 min. The solvent was removed to give 3.64 g of crude product, which was fractionally crystallized from ethanol to yield 2.81 g (80%) of crystalline compound **1**, Mp 94–96 °C, $[\alpha]_D = +28.4°$. δ_H 1.35 (t, $J = 7.1$ Hz, 3 H), 4.00 (t, $J = 7.7$ Hz, 1 H), 4.15–4.40 (m, 4 H), 5.17 (s, 1 H), 5.52 (d, $J = 14.4$ Hz, 1 H), 5.79 (d, $J = 14.4$ Hz, 1 H), 7.25–7.50 (m, 8 H), 8.08 (d, $J = 8.2$ Hz, 1 H). δ_C 14.1, 59.8, 61.5, 63.5, 75.0, 87.9, 109.4, 119.9, 124.0, 127.8, 128.1, 128.6, 128.8, 134.0, 136.1, 145.6, 170.3. (Found: C, 64.6; H, 5.9; N, 6.0. $C_{19}H_{20}N_4O_3$ requires C, 64.75; H, 5.7; N, 15.9%.)

General Procedure for the Syntheses of **3a**–**e**, **4**.—To a mixture of compound **1** (1 mmol, 0.35 g) and either an organosilane reagent **2a**–**e** or triethoxyphosphine (1.1 mmol) in acetonitrile (5 ml), zinc bromide (anhydrous, 1.2 mmol, 0.28 g) was added at 0 °C under nitrogen. The mixture was stirred at this temperature for several hours until the starting material had reacted. The reaction mixture was then quenched with water (5 ml) and extracted with ether (2×10 ml). The combined organic layers were washed with aqueous NaOH (2 M, 2×5 ml) and ammonium chloride (saturated, 2×5 ml) and dried over anhydrous sodium sulfate. After removal of solvents, the residue was purified (as necessary) by silica gel column chromatography to give the products.

Ethyl (2*S*,4*S*)-3-(3-*Butenyl*)-4-*phenyl*-1,3-*oxazolidine*-2-*carboxylate* (**3a**).—With allyltrimethylsilane, **1** gave an oil, yield 66%, $[\alpha]_D = +75.9°$. δ_H 1.31 (t, $J = 7.1$ Hz, 3 H), 2.15 (q, $J = 7.2$ Hz, 2H), 2.93 (td, $J = 3.5$ and 7.4 Hz, 1 H), 3.95–4.05 (m, 2 H), 4.23–4.35 (m, 3 H), 4.78 (s, 1 H), 4.90 (s, 1 H), 4.95 (d, $J = 5.0$ Hz, 1 H), 5.60–5.75 (m, 1 H), 7.25–7.45 (m, 5 H). δ_C 14.2, 33.2, 53.8, 61.0, 68.5, 75.2, 93.1, 115.8, 127.5, 127.7, 128.4, 135.9, 139.1, 171.3. (Found: C, 69.5; H, 8.15; N, 5.4. $C_{16}H_{21}NO_3$ requires C, 69.8; H, 7.7; N, 5.1%.)

Ethyl (2*S*,4*S*)-3-(3-*Methylbut*-3-*enyl*)-4-*phenyl*-1,3-*oxazolidine*-2-*carboxylate* (**3b**).—With 2-methyl-3-trimethylsilylpropene, **1** gave an oil, yielded 69%, $[\alpha]_D = +66.1°$. δ_H 1.34 (t, $J = 7.1$ Hz, 3 H), 1.60 (s, 3 H), 2.05–2.20 (m, 2 H), 2.91 (t, $J = 7.8$ Hz, 2 H), 3.95–4.05 (m, 2 H), 4.20–4.35 (m, 3 H), 4.57 (s, 1 H), 4.67 (s, 1 H), 4.80 (s, 1 H), 7.25–7.45 (m, 5 H). δ_C 14.1, 22.5, 36.7, 52.6, 60.9, 68.4, 75.1, 93.1, 110.9, 127.5, 127.7, 128.4, 139.1, 143.2, 171.3. (Found: C, 70.0; H, 8.3; N, 5.1. $C_{17}H_{23}NO_3$ requires C, 70.55; H, 8.0; N, 4.8%).

Ethyl (2*S*,4*S*)-3-(3-*Oxo*-3-*phenylpropyl*)-4-*phenyl*-1,3-*oxazolidine*-2-*carboxylate* (**3c**).—With 1-phenyl-1-trimethylsilyloxyethene, **1** gave an oil, yield 70%, $[\alpha]_D = +31.5°$. δ_H 1.30 (t, $J = 7.1$ Hz, 3 H), 2.95–3.35 (m, 4 H), 3.95–4.05 (m, 2 H), 4.20–4.32 (m, 3 H), 4.84 (s, 1 H), 7.20–7.30 (m, 3 H), 7.30–7.55 (m, 5 H), 7.70 (d, $J = 7.9$ Hz, 2 H). δ_C 14.1, 38.1, 49.0, 61.0, 68.7, 75.2, 93.2, 127.5, 127.8, 128.4, 128.5, 132.9, 136.8, 138.9, 171.1, 198.1. (Found: C, 71.05; H, 6.8; N, 4.1. $C_{21}H_{23}NO_4$ requires C, 71.4; H, 6.6; N, 4.0%.)

Ethyl (2*S*,4*S*)-3-(3-*Oxobutyl*)-4-*phenyl*-1,3-*oxazolidine*-2-*carboxylate* (**3d**).—With 2-trimethylsilyloxypropene, **1** gave an oil, yield 56%, $[\alpha]_D = +44.8°$. δ_H 1.35 (t, $J = 7.1$ Hz, 3 H), 1.94 (s, 3 H), 2.45–2.65 (m, 2 H), 3.00–3.20 (m, 2 H), 3.90–4.05 (m, 2 H), 4.25–4.35 (m, 3 H), 4.76 (s, 1 H), 7.25–7.40 (m, 5 H). δ_C 14.0, 29.7, 42.8, 48.6, 60.9, 68.5, 75.1, 93.1, 127.4, 127.7, 128.4, 138.8, 171.0, 206.7. (Found: C, 65.6; H, 7.5; N, 4.8. $C_{16}H_{21}NO_4$ requires C, 66.0; H, 7.3; N, 4.8%.)

Ethyl (2*S*,4*S*)-3-(2-*Methoxycarbonyl*-2-*methylpropyl*)-4-*phenyl*-1,3-*oxazoline*-2-*carboxylate* (**3e**).—With 1-methoxy-2-methyl-1-trimethylsilyloxypropene, **1** gave an oil, yield 80%, $[\alpha]_D = +26.9°$. δ_H 1.01 (s, 3 H), 1.06 (s, 3 H), 1.32 (t, $J = 7.2$ Hz, 3 H), 2.90 (d, $J = 13.7$ Hz, 1 H), 3.18 (d, $J = 13.7$ Hz, 1 H), 3.41 (s, 3 H), 3.94 (t, $J = 8.3$ Hz, 1 H), 4.04–4.09 (m, 1 H), 4.20–4.30 (m, 3H). 4.90 (s, 1 H), 7.20–7.35 (m, 3 H), 7.42 (d, $J = 7.36$ Hz, 2 H). δ_C 14.1, 23.5, 24.3, 44.1, 51.5, 61.0, 66.5, 71.4, 74.1, 95.7, 127.5, 127.7, 128.2, 140.0, 170.6, 177.1. (Found: C, 64.0; H, 7.8; N, 4.4. $C_{18}H_{25}NO_5$ requires C, 64.45; H, 7.5; N, 4.2%.)

Ethyl (2*S*,4*S*)-3-[(*Diethoxyphosphoryl*)*methyl*]-4-*phenyl*-1,3-*oxazolidine*-2-*carboxylate* (**4**).—With triethoxyphosphine, **1** gave an oil, yield 78%, $[\alpha]_D = +37.8°$. δ_H 1.20–1.40 (m, 9 H), 3.13 (dd, $J = 6.15$ and 15. Hz, 1 H), 3.27 (dd, $J = 15.7$ and 15.8, 1 H), 3.85–3.96 (m, 1 H), 4.02 (t, $J = 7.2$ Hz, 2 H), 4.11 (t, $J = 7.2$ Hz, 2 H), 4.22–4.35 (m, 4 H), 5.13 (s, 1 H), 7.25–7.40 (m, 3 H), 7.48 (d, $J = 6.9$ Hz, 2 H). δ_C 14.2, 16.3 (d, $J = 5.5$ Hz), 16.35 (d, $J = 5.5$ Hz), 46.0 (d, $J = 151.5$ Hz), 61.0, 61.65 (d, $J = 6.7$ Hz), 52.15 (d, $J = 6.8$ Hz), 67.7 (d, $J = 8.9$ Hz), 74.2, 91.6, 127.8, 128.0, 128.4, 137.8, 170.1. (Found: C, 54.8; H, 7.7; N, 4.2. $C_{17}H_{26}NO_6P$ requires C, 5.0; H, 7.1; N, 3.8%.)

Ethyl (2*S*,4*S*)-3-*Benzyl*-4-*phenyl*-1,3-*oxazolidine*-2-*carboxylate* (**5**).—To a suspension of zinc bromide (anhydrous, 1.2 mmol, 0.28 g) in 5 ml of dry THF at 0 °C under nitrogen, phenylmagnesium bromide (1.2 ml of 1 M solution in THF) was added dropwise, and the mixture was then stirred at room temperature for 1 h. Afterwards, the above mixture was cooled to 0 °C and a solution of compound **1** (1 mmol) in 5 ml of dry THF was added dropwise. The resulting mixture was then stirred at this temperature for one day. The reaction mixture was then quenched with water (5 ml) and extracted with diethyl ether (2×10 ml). The combined organic layers were washed with aqueous NaOH (2 M, 2×5 ml) and ammonium chloride (saturated, 2×5 ml), and then dried over anhydrous sodium sulfate. After removal of the solvents, the residue was purified by silica gel column chromatography to give product **5**. Oil, yield 57%, $[\alpha]_D = +15.7°$. δ_H 1.16 (t, $J = 7.15$ Hz, 3 H), 3.76 (d, $J = 7.15$ Hz, 3 H), 3.76 (d, $J = 3.7$ Hz, 1 H), 3.90–4.15 (m, 5 H), 4.25–4.30 (m, 1 H), 4.79 (s, 1 H), 7.15–7.40 (m, 8 H), 7.51 (d, $J = 7.4$ Hz, 2 H). δ_C 13.8, 55.7, 60.8, 67.1, 74.8, 91.7, 127.1, 127.7, 127.8, 127.9, 128.1, 128.5, 129.0, 137.0, 138.1, 170.8. (Found: C, 73.1; H, 7.0; N, 4.8. $C_{19}H_{21}NO_3$ requires C, 73.3; H, 6.8; N, 4.5%.)

X-Ray Crystallography.—Intensity data for **1** were collected with a Siemens SMART CCD area detector using monochromatized MoKα ($\lambda = 0.71073$ Å) radiation. The crystal used was a colourless block of dimensions $0.65 \times 0.54 \times 0.34$ mm. A total of 14734 reflections were collected which, after merging, ($R_{int} = 0.0187$) gave 3533 unique reflections. The intensities were corrected for Lorentz and polarization effects and for absorption ($T_{max} = 0.970$, $T_{min} = 0.944$).

The structure was solved by direct methods using SHELXS90,[11] and refined on F^2 by full-matrix least-squares procedures using SHELXL96.[12] All non-hydrogen atoms were refined with anisotropic displacement coefficients. Hydrogen atoms were included in calculated positions with isotropic displacement coefficients equal to 1.2 times the isotropic equivalent of their carrier carbons. The function minimized was $\Sigma w(F_o^2 - F_c^2)$, with $w = [\sigma^2(F_o^2) + 0.0508P^2 + 0.160P]^{-1}$, where $P = [\max(F_o^2) + 2F_c^2]/3$. A final difference map showed no features greater or less than $0.24\ e^-\ Å^{-3}$. Full crystallographic details, excluding structure factors, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Research* (*S*), 1999, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 423/18.

Crystal Data at −115 °C.—$C_{19}H_{20}N_4O_3$, $M_r = 352.39$; orthorhombic, space group $P2_12_12_1$; $a = 9.0198(8)$, $b = 10.3420(9)$, $c = 19.2633(16)$ Å; $U = 1796.9(3)$ Å^3; $F(000) = 744$; $Z = 4$; $D_c = 1.303$ g cm^{-3}; $\mu(\text{MoK}\alpha) = 0.091$ mm^{-1}; $2\theta_{max} = 53°$; 235 parameters, $wR_2 = 0.0806$ for all 3533 data; $R1 = 0.0315$ for 3295 data with $F_o > 4\sigma(F_o)$.

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