An Efficient Synthesis of (4*S*)-(−)-4-Isopropyl-2-oxazolidinone

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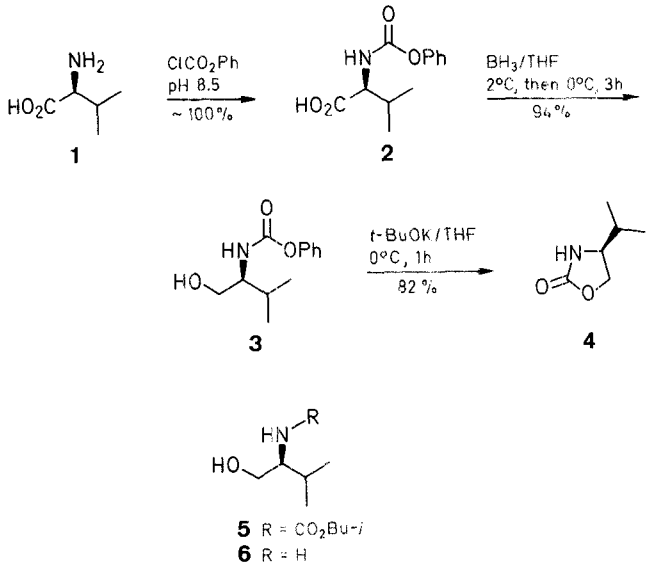
A new, efficient, cost-effective method for the preparation of the Evans' chiral auxiliary (4*S*)-4-isopropyl-2-oxazolidinone **(4)** is described. A Schotten–Baumann acylation of valine with phenyl carbonochloridate quantitatively affords the protected valine, which is then reduced with borane in tetrahydrofuran to give an alcohol. Cyclization with a catalytic amount of potassium *tert*-butoxide gives **4** in 81% overall yield and in 41–43% after crystallization from ethyl acetate/*n*-hexane.

Since the initial publication by Evans[1] on the use of (4*S*)-4-isopropyl-2-oxazolidinone **(4)** as a chiral auxiliary for effecting asymmetric alkylations and aldol condensations, this auxiliary has seen wide spread use in the synthesis of a variety of substrates. The main disadvantages of this auxiliary are its high cost if purchased commercially[2] or that its preparation involves a reduction of (*S*)-valine **(1)** to the water soluble (*S*)-valinol **(6)**, which is difficult to isolate and requires a high vacuum distillation not always practical on an industrial scale.[3] In this note we wish to describe an alternative synthesis, which is easily carried out on a large scale and does not involve the use of water soluble intermediates.

The synthesis begins with a Schotten–Baumann acylation of (*S*)valine **(1)** with phenyl carbonochloridate in aqueous sodium hydrogen carbonate at pH 8.5. The pH is maintained with the slow addition of 50% sodium hydroxide and the temperature is maintained between 20 and 25 °C. The acid **2** is then isolated by an acid-base extraction to remove some nonpolar impurities. Borane reduction of **2** in tetrahydrofuran affords alcohol **3**,



which is not purified further.[4] Treatment of **3** with a catalytic amount of potassium *tert*-butoxide in tetrahydrofuran then cleanly affords the crystalline oxazolidinone **4** in 81% yield. Recrystallization from ethyl acetate/*n*-hexane gives the pure product in 41–43% overall yield from (*S*)-valine **(4)**. The key to the success of this scheme lies in the use of phenyl carbonochloridate. When we examined the use of isobutyl carbonochloridate as an acylating agent the first two steps proceeded smoothly but the final cyclization of **5** failed to give a clean product. This is presumably due to the fact that phenol is a much better leaving group than isobutyl alcohol. In fact, the isobutyl derivative **5** must be heated to reflux for cyclization to occur, whereas the phenyl derivative **3** cyclizes rapidly at room temperature. We have also looked at an alternative approach, in which **1** is reduced with borane/boron trifluoride,[5] and then the (*S*)-valinol **(6)** is trapped *in situ* with phenyl carbonochloridate to give **3**. Cyclization of the crude **3** to the oxazolidinone **4** gave only a 40% yield of a low quality material, which could not be induced to crystallize and therefore this latter route was abandoned in favor of the more efficient discrete three-step approach.

In conclusion we have developed an efficient and cost-effective synthesis of (4*S*)-(−)-4-isopropyl-2-oxazolidinone **(4)**, a now widely utilized chiral auxiliary. This sequence of reactions should be sufficiently general that other oxazolidinones may be prepared similarly.

(2*S*)-3-Methyl-2-phenoxycarbonylaminobutanoic Acid (2):
A 250 mL flask fitted with a mechanical stirrer, thermometer, nitrogen inlet and a pH probe is charged with valine (**1**; 5 g, 42.7 mmol), potassium hydrogen carbonate (6.4 g, 64 mmol) and water (30 mL). To the stirred suspension is added phenyl carbonochloridate (5.6 mL, 44.8 mmol). The pH is adjusted from 8.15 to 8.6 with 50% NaOH and kept between pH 8.5 and 8.7 with the periodic addition of 50% NaOH. When the pH stabilizes at 8.6–8.7, the mixture is stirred at room temperature for 90 min. If the pH becomes too high the reaction becomes exothermic and results in a reduced yield. The pH is adjusted to 8.9 and the solution is diluted with methyl *tert*-butyl ether (30 mL) and filtered to remove solids. The aqueous layer is added to 30% aq. H_2SO_4 (100 mL) and extracted with methyl *tert*-butyl ether (50 mL). The organic layer is dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a clear viscous oil; yield: 10 g (100%);

$C_{12}H_{15}NO_4$	calc.	C 60.75	H 6.37	N 5.90
(237.3)	found	60.61	6.42	5.98

IR (Film): ν = 3300, 1740, 1590, 1525, 1485, 1388, 1367, 1205, 1150, 1065, 1019, 840, 775, 757, 716, 682 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.0 [d, 3H, J = 6.5 Hz, $CH(CH_3)_2$]; 1.07 [d, 3H, J = 6.5 Hz, $CH(CH_3)_2$]; 2.3 [m, 1H, $CH(CH_3)_2$]; 4.38 (dd, 1H, J = 4.5, 9.0 Hz, CHN); 5.77 (d, 2H, J = 9.0 Hz, NH_2); 7.23 (m, 5H, C_6H_5); 8.8 (br s, 1H, CO_2H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 17.33, 18.99, 31.11, 58.96, 121.48, 125.44, 129.27, 150.83, 154.72, 176.06.

(2*S*)-3-Methyl-2-phenoxycarbonylamino-1-butanol (3):
A 500 mL three-neck flask fitted with a mechanical stirrer, septum, nitrogen inlet and a temperature probe is charged with a 1 N THF solution of BH_3–THF complex (103 mL, 103 mmol) and cooled to 0 °C. To the stirred solution is slowly added acid **2** (8.1 g, 34 mmol) in dry THF (35 mL) maintaining the temperature at 2 °C. Upon complete addition, the mixture is stirred at 0 °C for 3 h. The reaction is quenched with 10% methanolic HCl maintaining the temperature at ~ 0 °C. The mixture is warmed to room temperature, concentrated under reduced pressure and the resulting slurry is partitioned between EtOAc (80 mL) and water (80 mL). The organic layer is washed with 10% HCl. The aqueous phase is extracted with EtOAc (30 mL). The combined organic layer is washed with 5% Na_2CO_3 (80 mL), and brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford clear viscous oil; yield: 7.2 g (94%);

$C_{12}H_{17}NO_3$	calc.	C 64.56	H 7.68	N 6.24
(233.3)	found	64.49	7.81	6.18

IR (Film): ν = 3605, 3420, 1740, 1590, 1502, 1480, 1230, 1183, 1158, 1065, 1020 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.97 [d, 6H, J = 7.0 HZ, $CH(CH_3)_2$]; 1.88 [m, 1H, $CH(CH_3)_2$]; 3.62 m, 3H, CH_2O + CHN); 5.62 (d, 2H, J = 9.0 Hz, NH_2); 7.2 (m, 5H, C_6H_5).

^{13}C-NMR ($CDCl_3$/TMS): δ = 18.53, 19.00, 29.11, 58.67, 63.10, 121.52, 125.22, 129.18, 150.97, 155.42.

(4*S*)-(−)-4-Isopropyl-2-oxazolidinone (4):
A 250 mL three-necked flask fitted with a mechanical stirrer, septum, nitrogen inlet and a temperature probe is charged with a solution of the

alcohol **3** (6.6 g, 29.6 mmol) in THF (30 mL) and cooled to 0 °C. A 1.6 M solution of *t*-BuOK in THF (4.6 mL, 7.4 mmol) is then added slowly and the mixture is stirred at 0 °C for 1 h. The mixture is concentrated under reduced pressure, the residue is dissolved in EtOAc (30 mL) and extracted with 10% NaOH (2 × 15 mL). The combined aqueous phase is extracted with EtOAc (10 mL), the organic layers are combined and dried (Na_2SO_4). Evaporation of the solvent affords an oil, which solidifies upon seeding, yield: 3.13 g (82%). Recrystallization from EtOAc/*n*-hexane affords pure **4**; yield: 1.44 g (41% from **1**); mp 70.5–72.2 °C; Lit.[6] mp 69–70 °C; $[\alpha]_D^{18}$ – 18.5 °C (*c* = 6, EtOH); Lit.[6] $[\alpha]_D^{18}$ – 16.6° (*c* = 5.81, EtOH).

IR (Film): ν = 3450, 3250, 2950, 1740, 1400, 1375, 1215, 1078, 1062, 1045, 1010, 930 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.9 [d, 3 H, *J* = 7.0 Hz, $CH(CH_3)_2$]; 1.0 [d, 3 H, *J* = 7.0 Hz, $CH(CH_3)_2$]; 1.72 [m, 1 H, *J* = 7.0 Hz, $CH(CH_3)_2$]; 3.60 (m, 1 H, CHN); 4.10 (dd, 1 H, *J* = 6.0, 8.0 Hz, H-5); 4.40 (t, 1 H, *J* = 8.0 Hz, H-5).

^{13}C-NMR ($CDCl_3$/TMS): δ = 17.45, 17.82, 32.52, 58.28, 68.46, 160.63.

Received: 27 February 1989

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