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An easy route to 4-substituted 2-oxazolidinones from prochiral-1,3-diols

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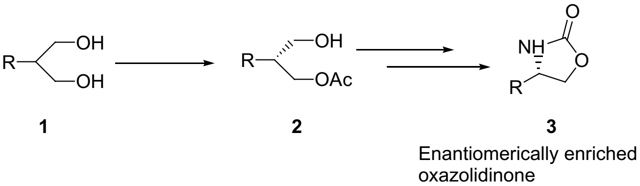
Abstract—A novel synthesis of 4-substituted 2-oxazolidinones starting from prochiral-1,3-diols has been developed. After enzymatic desymmetrisation the resulting monoacetyled diols were transformed into amides. A Hofmann rearrangement of these amides led to 2-oxazolidinones.

1. Introduction

A large number of examples have emerged in recent years that demonstrate the use of 2-oxazolidinones as chiral auxiliaries in organic synthesis. Methodologies have been described for the preparation of chiral substituted 2-oxazolidinones mainly from natural aminoacids.[1] Two recent examples reported preparation of chiral substituted oxazolidinones, one of these[2] used baker's yeast reduction of β-ketoesters followed by a Curtius degradation to give 4,5-substituted 2-oxazolidinones, and the other[3] started from serinol, which was subjected to an enzymatic desymmetrisation before treatment with thionyl chloride to afford 4-substituted 2-oxazolidinones. Previous work[4] in our research group had dealt with desymmetrisation of prochiral-1,3-diols **1**. The good results in this area encouraged us to develop a new synthesis of chiral 4-substituted-2-oxazolidinones **3** from chiral monoacetates of these diols **2** (Scheme 1). Thus this class of compounds seemed to be good intermediates for an oxidation step followed by an amidification, the resulting amides being subjected to a Hofmann rearrangement.



Scheme 1. General approach to preparation of oxazolidinones.

2. Results and discussion

Chiral hydroxy acetates **2a** and **b** previously described[4,5] were used as chiral precursors. These compounds were easily obtained from achiral diols **1a** and **b** by an enzymatic acetylation with the advantage that, in this kind of reaction, all of the product could be converted into one stereoisomer, and thus be obtained in a high yield. In addition, the enantiomeric excess (ee) was generally high. The alcohols (*S*)-(+)-**2a** and (*S*)-(+)-**2b** were obtained in 97% and 87% ee, respectively. Primary alcohols **2a** and **b** were oxidised, using PDC,[6] to afford acids **4a** and **b** (Scheme 2) in satisfactory ee (measured by GC). When Jones' reagent was used in this step we observed better yields but a very significant racemisation occurred with **4b** (the ee felt to 7%). In the case of **4a** this effect was limited (the ee felt to 88%). The acid **4a** had previously been obtained from (*R*)-(−)-2-phenylpropanoic acid.[7] Treatment of acids successively with methyl chloroformate then ammonia[8] gave amides **5a** and **b** in good yields. The key step of the synthesis, conversion of amides **5a** and **b** into 2-oxazolidinones **3a** and **b**, was achieved using diacetoxyiodobenzene in basic medium.[9] After the Hofmann rearrangement, the spontaneous

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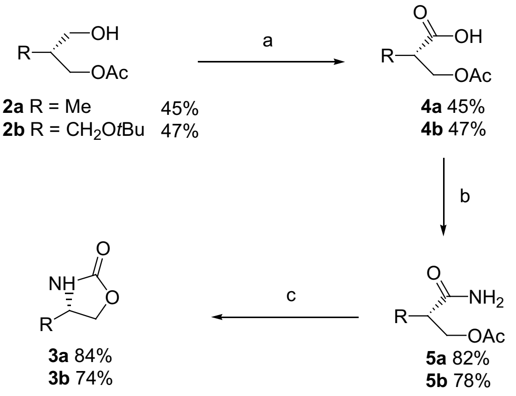

Scheme 2. (a) PDC, DMF; (b) Et_3, ClCOOMe then NH_3, MeOH; (c) $PhI(OAc)_2$, KOH, MeOH.

cyclisation of the intermediate amine occurred to give the 2-oxazolidinone in good yield.

In conclusion we prepared 5-substituted 2-oxazolidinones from the chiral diol monoacetates easily available in good yields from the corresponding prochiral-diols by enzymatic acylation. This acetate led to the expected oxazolidinones in three steps and in fair to good ee.

3. Experimental

3.1. General

NMR spectra were recorded on a Bruker AC 400 spectrometer at 400 and 100.6 MHz, respectively. All melting points were uncorrected. Elemental analyses were performed by the service of microanalyses, CNRS, ICSN, Gif sur Yvette. High resolution mass spectra were recorded on a Varian Mat 311 or ZabSpec TOF Micromass spectrometer at the CRMPO, Rennes. Infrared spectra were measured with a FT infrared spectrometer Genesis Matteson instrument. Enantiomeric excesses were determined by gas phase chromatography with a Hewlett–Packard HP 6890 Series apparatus equipped either with a Restek-β Dex Sm (25 m × 0.25 mm) column or with a R+βDEXCST (25 m × 0.25 mm) column.

3.2. (−)-(*R*)-3-(Acetyloxy)-2-(methyl) propanoic acid 4a

To a solution of alcohol (+)-(*S*)-**2a**[5] (1.55 g, 11.72 mmol) in DMF (30 mL) PDC (15.3 g, 41 mmol) was added portionwise. The reaction was stirred for 24 h at room temperature. Water (4 mL) was added and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography to give acid **4a**[7] (774 mg, 45%) as an oil. $[\alpha]_D^{20} = -17.3$ (*c* 1.07, $CHCl_3$), ee = 95%, ^1H NMR ($CDCl_3$): δ ppm 1.25 (d, 3H, $J = 6.89$ Hz); 2.07 (s, 3H); 2.84 (m, 1H); 4.19 (dd, 1H, $J = 10.83$ and 5.41 Hz); 4.25 (dd, 1H, $J = 10.83$ and 7.38 Hz); 8–9 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 13.59; 20.75; 38.85; 65.23; 170.97; 179.65. IR ν (cm^{-1}) (film): 1739, 1714.

3.3. (+)-(*S*)-3-(Acetoxy)-2-(*tert*-butoxymethyl) propanoic acid 4b

To a solution of alcohol (+)-(*S*)-**2b**[4] (130 mg, 0.88 mmol) in DMF (2.5 mL) PDC (1.16 g, 3.08 mmol) was added portionwise. The reaction was stirred for 24 h at room temperature. Water (4 mL) was added and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography to give acid **4b** (83 mg, 43%) as an oil. $[\alpha]_D^{20} = +1.1$ (*c* 2, $CHCl_3$), ee = 87%. ^1H NMR ($CDCl_3$): δ ppm 1.19 (s, 9H); 2.07 (s, 3H); 2.92 (m, 1H); 3.62 (dd, 1H, $J = 9.60$ and 6.40 Hz); 3.66 (dd, 1H, $J = 9.60$ and 5.91 Hz); 4.33 (dd, 1H, $J = 11.32$ and 5.41 Hz); 4.38 (dd, 1H, $J = 11.32$ and 6.40 Hz); 10–11 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 20.74; 27.16; 45.28; 58.95; 61.72; 73.65; 170.87; 176.72. IR ν (cm^{-1}) (film): 1743; 1714. Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.94; H, 8.41.

3.4. (−)-(*R*)-2-(Carbamoyl) propyl acetate 5a

To a solution of acid **4a** (1.2 g, 5.5 mmol) in THF (20 mL) at −5 °C were added successively triethylamine (4.75 mmol, 577 μL) and methyl chloroformate (4.75 mmol, 367 μL). The mixture was stirred for 0.5 h at −5 °C and a saturated solution of ammonia in methanol (25 mL) was added. After 0.5 h at −5 °C and 1 h at room temperature the solution was filtered, the solvents were removed under reduced pressure and the residue was purified by column chromatography to give amide **5a** as white crystals (468 mg, 79%). Mp = 56.1 °C, $[\alpha]_D^{20} = -26.7$ (*c* 1.0, $CHCl_3$), ^1H NMR ($CDCl_3$): δ ppm 1.20 (d, 3H, $J = 6.89$ Hz); 2.07 (s, 3H); 2.67 (m, 1H); 4.13 (dd, 1H, $J = 10.83$ and 5.41 Hz); 4.21 (dd, 1H, $J = 10.83$ and 8.37 Hz); 5.90 (1H, br s); 6.24 (1H, br s). ^{13}C NMR ($CDCl_3$): δ ppm 14.18; 20.82; 39.73; 65.97; 170.83; 176.28. IR ν (cm^{-1}) (KBr): 1731, 1649. Anal. Calcd for $C_6H_{11}NO_3$: C, 49.64; H, 7.63. Found: C, 49.73; H, 7.71.

3.5. (−)-(*S*)-3-(*tert*-Butoxy)-2-(carbamoyl) propyl acetate 5b

To a solution of acid **4b** (1.2 g, 5.5 mmol) in THF (50 mL) at −5 °C were added successively triethylamine (1.4 mL, 11.56 mmol) and methyl chloroformate (0.893 mL, 11.56 mmol). The mixture was stirred for 0.5 h at −5 °C and a saturated solution of ammonia in methanol (60 mL) was added. After 0.5 h at −5 °C and 1 h at room temperature the solution was filtered, the solvents were removed under reduced pressure and the residue was purified by column chromatography to give amide **5b** as white crystals (933 mg, 78%). Mp = 52.9 °C, $[\alpha]_D^{20} = -3.6$ (*c* 1.50, $CHCl_3$). ^1H NMR ($CDCl_3$): δ ppm 1.20 (s, 9H); 2.06 (s, 3H); 2.76 (m, 1H); 3.57 (d, 2H,

$J = 6.40$ Hz); 4.28 (dd, 1H, $J = 10.83$ and 6.4 Hz); 4.33 (dd, 1H, $J = 10.83$ and 6.89 Hz); 6.34 (1H, br s); 6.67 (1H, br s). ^{13}C NMR ($CDCl_3$): δ ppm 20.73; 27.18; 45.90; 59.62; 62.47; 73.67; 170.70; 174.40. IR ν (cm^{-1}) (film): 1740, 1692. Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81. Found: C, 55.21; H, 8.86.

3.6. (−)-(*R*)-4-(Methyl) oxazolidin-2-one 3a

To a solution of potassium hydroxide (394 mg, 7.04 mmol) in methanol (20 mL) was added carboxamide **5a** (409 mg, 2.82 mmol) with good stirring. Diacetoxyiodobenzene (907 mg, 2.82 mmol) was then added portionwise at 5 °C. The mixture was stirred for 15 min at 5 °C and 2 h at room temperature. Methanol was removed under reduced pressure and a water/chloroform mixture (7/3, 50 mL) was added to the residue. The aqueous layer was extracted with dichloromethane and the combined organic layers were washed with water (15 mL) and brine (15 mL). After drying ($MgSO_4$) the solvent was removed under reduced pressure and the residue purified by column chromatography to give oxazolidinone **3a**[10] as a white solid (254 mg, 89%). Mp = 45.9 °C; $[\alpha]_D^{20} = -8.1$ (*c* 2.0, $CHCl_3$), ee = 94%. ^{1}H NMR ($CDCl_3$): δ ppm 1.24 (d, 3H, $J = 5.91$ Hz); 3.89 (dd, 1H, $J = 8.37$ and 6.40 Hz); 3.97 (m, 1H); 4.45 (t, 1H, $J = 8.37$ Hz); 6.69 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 20.60; 48.15; 71.54; 160.18. IR ν (cm^{-1}): 1745.

3.7. (−)-(*S*)-4-(*tert*-Butoxymethyl) oxazolidin-2-one 3b

To a solution of potassium hydroxide (477 mg, 8.51 mmol) in methanol (25 mL) was added carboxamide **5b** (740 mg, 3.41 mmol) with good stirring. Diacetoxyiodobenzene (1.11 g, 3.41 mmol) was then added portionwise at 5 °C. The mixture was stirred for 15 min at 5 °C and 2 h at room temperature. Methanol was removed under reduced pressure and a water/chloroform mixture (7/3, 50 mL) was added to the residue. The aqueous layer was extracted with dichloromethane and the combined organic layers were washed with water (15 mL and brine (15 mL). After drying ($MgSO_4$) the solvent was removed under reduced pressure and the residue purified by column chromatography to give oxazolidinone **3b** as an oil (436 mg, 74%). $[\alpha]_D^{20} = -55.1$ (*c* 2.0, $CHCl_3$), ee = 80%. ^{1}H NMR ($CDCl_3$): δ ppm 1.18 (s, 9H); 3.36 (dd, 1H, $J = 8.86$ Hz and 5.91 Hz); 3.40 (dd, 1H, $J = 8.86$ and 6.40 Hz); 3.95 (m, 1H); 4.16 (dd, 1H, $J = 8.86$ and 4.92 Hz); 4.46 (t, 1H, $J = 8.86$ Hz); 6.58 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ ppm: 27.16; 52.25; 63.58; 67.48; 73.33; 159.98. IR ν (cm^{-1}): 1747. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.72. Found: C, 55.35; H, 8.65.

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