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Base Induced C-5 Epimerisation of 4-Methyl-5-phenyl Oxazolidinones: Chiral Auxiliaries Derived from Norephedrine and Norpseudoephedrine.

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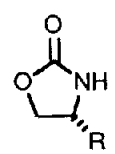
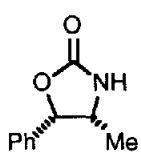
Abstract: Treatment of *cis*- and *trans*-4-methyl-5-phenyl oxazolidinones **2** and **3** with excess butyllithium at 0°C results in C-5 epimerisation, *via* a common intermediate *N,C*-5-dianion, generating after protonation a 1:4 mixture of **2**:**3**.

Introduction:

Oxazolidinone chiral auxiliaries **1** pionecred by Evans *et al* have proved very popular for directing the stereoselectivity of the reactions of attached enolates.[1] In some instances however the *cis*-4-methyl-5-phenyl oxazolidinone **2** derived from norephedrine is preferred.[2] Surprisingly the use of the corresponding *trans*-4-methyl-5-phenyl oxazolidinone **3** derived from norpseudoephedrine as chiral auxiliary has not been reported. We describe herein the base promoted epimerisation of the *cis*- and *trans*-4-methyl-5-phenyl oxazolidinones **2** and **3**.



1 R = iPr, Bn



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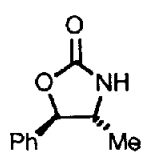

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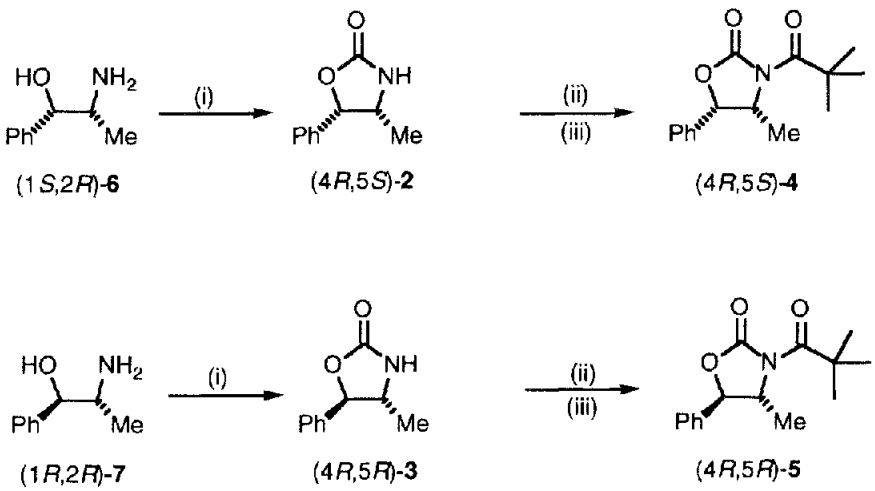
Results and Discussion:

An important feature of any chiral auxiliary is its ability to be removed efficiently after the stereoselective reaction without compromising the stereochemical integrity within the desired product. With oxazolidinones it is important to achieve selective nucleophilic cleavage of the attached elaborated acyl fragments while minimising competing opening of the oxazolidinone *via* nucleophilic attack at the oxazolidinone carbonyl. As part of an ongoing study in this area we needed, for comparison purposes, the unknown *N*-pivaloyl oxazolidinone derivatives **4** and **5**.

Treatment of (1*S*,2*R*)-norephedrine **6** with diethylcarbonate and potassium carbonate generated (+)-(4*R*,5*S*)-4-methyl-5-phenyl oxazolidinone **2** $[\alpha]_D^{21}$ +161.7 (c = 2.2, $CHCl_3$).[3] Treatment at -78°C of (+)-(4*R*,5*S*)-**2** with 1 equivalent of butyllithium followed by addition of pivaloyl chloride generated the *N*-pivaloyl oxazolidinone (+)-(4*R*,5*S*)-**4** $[\alpha]_D^{21}$ +34.1 (c = 1.75, $CHCl_3$) (Scheme 1). In an exactly analogous manner (1*R*,2*R*)-norpseudoephedrine **7** was converted to (-)-(4*R*,5*R*)-4-methyl-5-phenyl oxazolidinone **3** $[\alpha]_D^{21}$ -29.5 (c = 2.32, $CHCl_3$) [4] and thence to the *N*-pivaloyl derivative (-)-(4*R*,5*R*)-**5** $[\alpha]_D^{21}$ +28.8 (c = 3.5, $CHCl_3$) (Scheme 1).

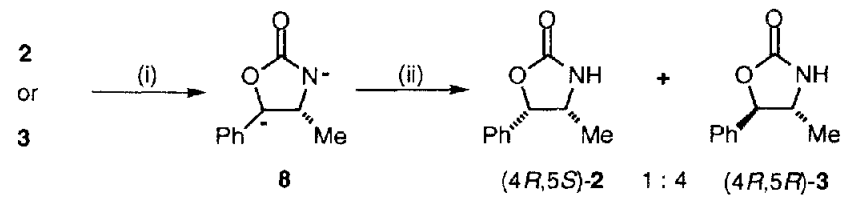
If more than 1 equivalent of butyllithium at 0°C was used in the above *N*-acylation reactions then the *N*-pivaloyl oxazolidinone **4** was contaminated with its epimer **5** and *vice versa*. We first considered that this



Scheme 1: Reagents (i) $(EtO)_2CO$, K_2CO_3; (ii) BuLi; (iii) tBuCOCl

epimerisation might be due to C-5 deprotonation of the product *N*-pivaloyl oxazolidinones **4** and **5** by the excess base present. However, treatment of **4** with butyllithium (<2 equiv.) followed by proton quench resulted in cleavage of the *N*-pivaloyl moiety to regenerate **2** (uncontaminated by **3**) and form $BuCO^tBu$ and $Bu_2C(OH)^tBu$, but with none of the epimeric *N*-pivaloyl derivative **5** being detected in the recovered **4**.

Treatment of (+)-(4*R*,5*S*)-**2** with 5 equivalents of butyllithium at 0°C followed by proton quench generated a 1:4 mixture of **2** and **3**. The major *trans*-isomer **3** was separated from **2** and shown to have a specific rotation corresponding to (4*R*,5*R*)-**3**. The epimerisation reaction is therefore occuring at the benzylic position C-5 of the oxazolidinone with the most reasonable mechanism involving formation of the *N*,*C*-5-dianion **8** (Scheme 2). This was confirmed by treatment of (4*R*,5*R*)-**3** with excess butyllithium, which on protonation also generated a 1:4 mixture of **2** and **3** as expected if both reactions proceed through the common intermediate, dianion **8** (Scheme 2).



Scheme 2: Reagents (i) BuLi; (ii) pH 7 buffer solution

The predominant formation of the *trans*-epimer **3** suggests that the protonation is under product development rather than reagent approach control.

Conclusions:

The *cis*- and *trans*-4-methyl-5-phenyl oxazolidinones **2** and **3** undergo C-5 epimerisation in the presence of excess base *via* a common intermediate dianion **8**. Avoidance of excess base when these chiral auxiliaries are acylated as a prelude to asymmetric synthesis is therefore advisable.

Experimental: Melting points are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1750 FT spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WH-300 (300MHz) spectrometer. Mass spectra were obtained on a VG masslab TRIO 1. Specific rotations were measured on a Perkin Elmer 241 polarimeter. Elemental analyses were performed by Mrs. V. Lamburn of the Dyson Perrins Laboratory. Tetrahydrofuran (THF) was dried and distilled from sodium benzophenone ketyl. Norephedrine **6** and norpseudoephedrine **7** were obtained from their commercially available hydrochloride salts : (+)-(1*S*,2*R*)-norephedrine. HCl $[\alpha]_D^{23}$ = +33.4 (c 7, H_2O) and (-)-(1*R*,2*R*)-norpseudoephedrine. HCl $[\alpha]_D^{23}$ = -41.7 (c 7, H_2O).

(4*R*, 5*S*)-(-)-4-Methyl-5-phenyl-2-oxazolidinone 2: The *title compound* was prepared according to the literature procedure.[3] Norephedrine **6** (3.00 g, 19.8 mmol), potassium carbonate (0.276 g, 2.0 mmol) and freshly distilled diethyl carbonate (6.0 ml, 49.5 mmol) were mixed and heated to 150°C. Distillation of ethanol was performed until all the ethanol was removed from the reaction mixture (approximately 2.5 h). After cooling, removal of the volatiles from the reaction mixture left a white solid residue which was subsequently dissolved in methylene chloride (50 ml). The organic solution was washed with water (2 x 20 ml), dried over $MgSO_4$ and evaporated to furnish the crude product as a white solid. Recrystallisation in ethyl acetate-hexane solution afforded the *title compound* **2**, (2.91 g, 83%), as colourless crystals. mp 116-118°C; $\nu_{max.}$ (CH_2Cl_2) : 3346, 3019, 2983, 1767, 1453 and 1220 cm^{-1} ; $[\alpha]_D^{21}$ = +161.7 (c 2.2, $CHCl_3$) ; δ_H ($CDCl_3$, 300 MHz) : 0.81 (3H, d, *J* 6.5), 4.22 (1H, m), 5.72 (1H, d, *J* 8.0), 6.13 (br-s, 1H), 7.36 (5H, m) ; *m/z* (CI^+, NH_3) : 195 (M^++18), 178 (M^++1), 136 and 134.

(4*R*, 5*S*)-(+)-1-(2',2'-Dimethyl-1'-oxopropyl)-4-methyl-5-phenyl-2-oxazolidinone 4: The oxazolidinone **2** (2.00 g, 11.3 mmol) was dissolved in THF (25 ml) and this solution was cooled to -78°C. BuLi as a 1.6 M solution in hexane (7.06 ml, 11.3 mmol) was added dropwise and the resulting colourless solution was stirred at -78°C for 15 min. Freshly distilled pivaloyl chloride (1.81 ml, 14.7 mmol) was then added and the solution was stirred at this temperature for 0.5 h. The reaction mixture was then poured on to water and the product was extracted with diethyl ether. The combined extracts were washed successively with saturated aquous hydrogen carbonate solution and brine, and then dried over $MgSO_4$. Removal of the solvent left the desired product **4** as a colourless crystalline solid (2.77 g, 94%). $\nu_{max.}$ (CH_2Cl_2) : 3057, 1783, 1687 and 1192 cm^{-1} ; $[\alpha]_D^{21}$ = +34.1 (c 1.75, $CHCl_3$) ; (Found : C, 69.49 ; H, 7.65 ; N, 5.18. $C_{15}H_{19}NO_3$ requires C, 68.94 ; H, 7.32 ; N, 5.36%) ; δ_H ($CDCl_3$, 300 MHz) : 0.90 (3H, d, *J* 6.5), 1.41 (9H, s), 4.79 (1H, m), 5.66 (1H, d, *J* 7.0), 7.39 (5H, m) ; *m/z* (CI^+, NH_3) : 279 (M^++18), 262 (M^++1), 218, 162, 134 and 118.

(4*R*, 5*R*)-(-)-4-Methyl-5-phenyl-2-oxazolidinone 3: Following the same experimental procedure as for the preparation of the oxazolidinone **2**, reaction of norpseudoephedrine **7** (3.6 g, 23.8 mmol), potassium carbonate (0.332 g, 2.4 mmol) and freshly distilled diethyl carbonate (7.22 ml, 54.9 mmol) furnished the *title compound* **3**, as a white solid which was recrystallised in ethyl acetate-hexane solution (3.97 g, 94%). mp 117-119°C. $\nu_{max.}$ (CH_2Cl_2) : 3447, 3030, 1763 and 1234 cm^{-1}, $[\alpha]_D^{21}$ = -29.5 (c 2.3, $CHCl_3$) ; (Found : C, 67.63 ; H, 6.29 ; N, 7.83. $C_{10}H_{11}NO_2$ requires C, 67.78 ; H, 6.25 ; N, 7.90%) ; δ_H ($CDCl_3$, 300 MHz) : 1.39 (3H, d, *J* 6.2), 3.34 (1H, m), 5.04 (1H, d, *J* 7.3), 6.07 (1H, br-s), 7.39 (5H, m) ; *m/z* (CI^+, NH_3) : 195 (M^++18), 178 (M^++1), 136 and 134.

(4*R*,5*R*)-(+)-1-(2',2'-Dimethyl-1'-oxopropyl)-4-methyl-5-phenyl-2-oxazolidinone 5: The oxazolidinone **3** (2.00 g, 11.3 mmol) was dissolved in THF (25 ml) and this solution was cooled to -78°C. A solution of BuLi in hexane (1.6 M, 7.06 ml, 11.3 mmol) was added dropwise and the resulting colourless mixture was left to

stir at -78°C for 15 min. Freshly distilled pivaloyl chloride (1.81 ml, 14.7 mmol) was added and the solution was stirred at this temperature for 0.5 h. The reaction mixture was then poured on to water and the product was extracted with diethyl ether. The combined extracts were washed successively with saturated aquous hydrogen carbonate solution and brine, and then dried over $MgSO_4$. Removal of the solvent left the desired product **5** as a clear colourless oil (2.80 g, 95%). $\nu_{max.}$ (CH_2Cl_2) : 3053, 1780, 1692 and 1194 cm^{-1} ; $[\alpha]_D^{21}$ = +28.8 (c 3.5, $CHCl_3$) ; (Found : C, 69.14 ; H, 7.61 ; N, 5.18. $C_{15}H_{19}NO_3$ requires C, 68.94 ; H, 7.32 ; N, 5.36%) ; δ_H ($CDCl_3$, 300 MHz) : 1.39 (9H, s), 1.48 (3H, d, *J* 6.2), 4.43 (1H, m), 5.05 (1H, d, *J* 6.0), 7.40 (5H, m) ; *m/z* (CI^+, NH_3) : 279 (M^++18), 262 (M^++1), 218, 162, 134 and 118.

Epimerisation of 2 with BuLi.: To a solution of oxazolidinone **2** (0.600 g, 3.4 mmol) in dry THF (40 ml) cooled to 0°C, was slowly added a solution of BuLi in hexane (1.4 M, 12.1 ml, 16.9 mmol). The dark red resulting solution was stirred at 0°C for 1 h and then quenched by the addition of pH 7 buffer phosphate solution. After removal of the solvent, methylene chloride was added (30 ml) and the organic solution was washed with brine (15 ml) and dried over $MgSO_4$. ^1H NMR spectroscopic analysis of the residue indicated the presence of both products **2** and **3** in a ratio 1:4. Filtration on small column of silica and two successive recrystallisations in ethyl acetate-hexane, afforded a pure sample of **3** for characterisation purposes. This material was spectroscopically identical to that prepared above $[\alpha]_D^{21}$ = -23.4 (c 0.42, $CHCl_3$).

Epimerisation of 3 with BuLi: A solution of the oxazolidinone **3** (0.700 g, 3.95 mmol) in dry THF (40 ml) cooled to 0°C, was treated with BuLi (19.7 mmol) in a similar way as above. After 1 h of stirring at 0°C the resulting dark red solution was quenched by the addition of pH 7 buffer phosphate solution. Once again, ^1H NMR spectroscopic analysis of the residue indicated the presence of both **2** and **3** in a ratio 1:4.

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