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Crystallisation-Induced Dynamic Resolution of Dipeptide-Derived 5(4*H*)-Oxazolones

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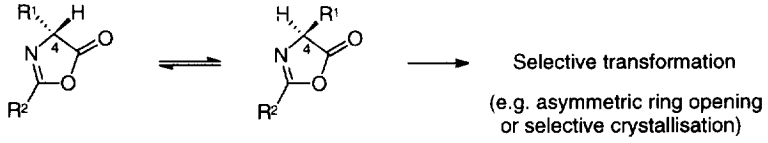
Abstract: Crystallisation-induced dynamic resolution of a diastereomeric mixture of dipeptide-derived 5(4*H*)-oxazolones is reported. By this method 5(4*H*)-oxazolones are obtained in very high d.e.'s. These compounds were converted to peptido-alcohols without epimerisation.

Dynamic kinetic resolution has received much attention in recent years.[1] It combines kinetic resolution with *in situ* epimerisation of the starting material, thus giving access to enantiomerically (or diastereomerically) enriched products in greater than 50% yield. Most dynamic kinetic resolution processes involve asymmetric transformations catalysed by chiral ligand complexes[2] or enzymes.[3] A successful dynamic kinetic resolution requires the substrate to be configurationally labile and thereby epimerise under the applied reaction conditions. The rate of epimeristion should be faster than the rate of product formation from the slower reacting stereoisomer. In addition, the product should be stable with respect to epimerisation and the desired stereoisomer should be formed at a faster rate than the undesired stereoisomer.

Alternatively, dynamic resolution processes can be achieved through crystallisation.[4] This method has been applied to resolve enantiomers[5] as well as diastereomers[6] in greater than 50% yield. The products thus resolved are usually configurationally stable as crystals, but rapidly racemise or epimerise again when redissolved. Therefore this method is only synthetically useful when the products can be converted to products which are stable with respect to epimerisation. In this paper we wish to report an example of crystallisation-induced dynamic resolution followed by epimerisation-free conversion to a configurationally stable derivative.

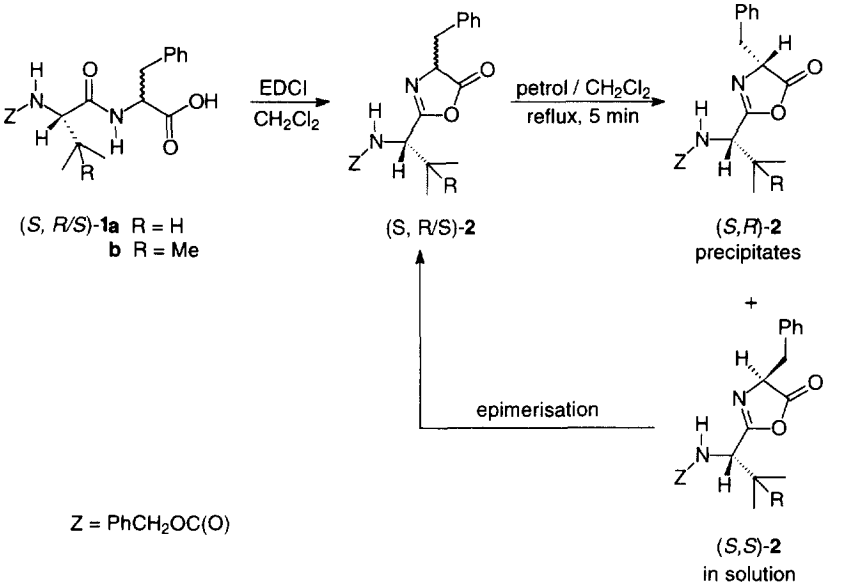
Recently we have become interested in the 5(4*H*)-oxazolone[7] system with regard to dynamic resolutions (Scheme 1). Due to the relative acidity of the proton at C-4 (pKa ~ 8.9),[8] 5(4*H*)-oxazolones epimerise under very mild conditions. We[9] and others[10] have applied this system to enzyme-catalysed resolutions.



Scheme 1

5(4*H*)-oxazolones are easily prepared by dehydration of N-acyl derivatives of amino acids. Thus treatment of dipeptides **1a** and **1b** with N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide (EDCI) gave

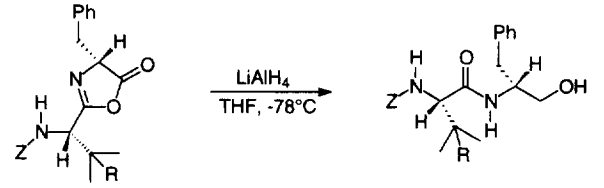
5(4*H*)-oxazolones **2a** and **2b** in 84 and 78% yield, respectively (Scheme 2). During our studies on C-alkylation of dipeptide-derived 5(4*H*)-oxazolones (**2**)[11] we observed that crystallisation of an epimeric mixture of **2** resulted in dynamic resolution. When a sample of **2a** (d.e. 12%) was refluxed in petrol (40-60) / CH_2Cl_2 (100:1) for 5 min, a single diastereomer[12] precipitated in 73% yield (Scheme 2). The configuration at C-4 of the precipitated **2a** was confirmed to be *R*, as determined by comparison with independently prepared (*S,S*)-**2a**.[13] Analogue **2b** showed similar behaviour. Heating to reflux of a suspension of **2b** (d.e. 7%) in petrol / CH_2Cl_2 gave (*S,R*)-**2b** in 93% d.e. and 70% yield.[14] The yield can approach 100% when it is taken into account that the product in the mother liquor can be introduced into the next crystallisation cycle. The fact that the "unnatural" *R*-configuration on C-4 is obtained makes this method versatile for accessing D-amino acid derivatives.



Scheme 2

When resolved (*S,R*)-**2a** (d.e. >99%) was dissolved in $CDCl_3$, slow epimerisation occurred. After 5 days at room temperature the solution had equilibrated and contained (*S,S*)-**2a** as the major diastereomer (20% d.e.). To preserve the high diastereomeric excess obtained *via* crystallisation of **2** we searched for a method to convert (*S,R*)-**2** into a derivative which is less prone to epimerisation. Although nucleophilic ring opening of **2** appeared attractive, reactions involving basic conditions are precarious since traces of base can cause epimerisation.[15] Ring opening of (*S,R*)-**2b** with methanol, in the presence of triethylamine as a base, resulted in formation of the methyl ester of **1b** in very low d.e. (< 20%). Attempts to convert **2** into **1** under neutral conditions, by sonication of a suspension of **2** in water[16], failed to give product. After sonication of (*S,R*)-**2b** (d.e. 93%) for 30 h at room temperature starting material was recovered quantitatively and had partially epimerised to 58% d.e. under the reaction conditions. Sonication of a solution of **2b** in methanol resulted in formation of a complex reaction mixture.

Ring opening of **2a** and **2b** under reductive conditions yielded peptido-alcohols **3a** and **3b**. When **2b** was reduced with $NaBH_4$ / LiCl, at room temperature, **3b** was obtained in 93% yield. However, the long reaction time (24 h) required for completion of this reaction resulted in low d.e. (20%) for **3b**. When $LiAlH_4$ was applied the ring opening was much faster. After 15 min at -78°C conversion was complete and **3a** and **3b** were obtained without detectable epimerisation in 77 and 73% yield, respectively (Scheme 3).



(*S,R*)-**2a** R = H (d.e. >99%)
b R = Me (d.e. 93%)

(*S,R*)-**3a** R = H c.y. 77%; d.e. >99%
b R = Me c.y. 73%; d.e. 93%

Scheme 3

The crystallisation-induced dynamic resolution process described in this communication, combined with a fast reductive ring opening reaction, gives access to configurationally stable peptide derivatives in very high diastereomeric excess and in good yield. The obvious advantages of this method are that no external chiral auxiliaries are required and that it can be scaled-up easily. Further research is needed to determine the scope and limitations of this process.

ACKNOWLEDGEMENTS

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All new compounds reported in this communication exhibited satisfactory spectroscopic data.

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12. The diastereomeric excesses of **2a** and **2b** were determined by ^{1}H NMR *via* integration of the *iso*-propyl and *tert*-butyl signals, respectively: (*S,S*)-**2a** δ 0.78 ppm (t, 6H, J = 6.5 Hz); (*S,R*)-**2a** δ 0.55 ppm (d, 3H, J = 6.8 Hz), 0.78 ppm (d, 3H, J = 6.8 Hz); (*S,S*)-**2b** δ 0.84 (s, 9H); (*S,S*)-**2b** δ 0.77 ppm (s, 9H). Chiroptical data: (*S,R*)-**2a** (d.e. > 99%): $[\alpha]_D$: + 23.7 (c=0.49, $CHCl_3$); (*S,R*)-**2b** (92% d.e.): $[\alpha]_D$: + 41.1 (c=0.55, $CHCl_3$).
13. To be sure that no epimerisation or kinetic resolution of (*S,S*)-**2a** occurred during its formation it was prepared under mild conditions from (*S,S*)-**1a** by stirring with EDCI for 15 min in CH_2Cl_2 at 0°C. These conditions are known to give enantiomerically pure oxazolin-5(4*H*)-ones: Chen, F.M.F.; Kuroda, K.; Benoiton, N.L. *Synthesis* **1979**, 230.
14. Experimental procedure: 5.12 g of **2b** (d.e. 7%) was refluxed in a mixture of petrol (40-60) (50 mL) and CH_2Cl_2 (4 mL) for 5 min. After cooling to room temperature the precipitate was filtered off, giving 3.59 g (70%) of (*S,R*)-**2b** (d.e. 93%). The mother liquor contained (*S,R*)-**2b** (d.e. 13%) together with some minor impurities.
15. The extent of epimerisation of enantiomerically pure 5(4*H*)-oxazolones, when subjected to nucleophilic ring opening under basic conditions, depends on the ratio between the rate of substitution and the rate of epimerisation. It is known that hydrazine, although basic, reacts with 5(4*H*)-oxazolones to give ring opening without epimerisation (see ref. 13).
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