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A novel highly stereoselective synthesis of chiral 5- and 4,5-substituted 2-oxazolidinones

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Abstract—A novel highly stereoselective synthesis of chiral mono- and bicyclic 4- and 4,5-substituted 2-oxazolidinones starting from β-keto esters was developed. After bioreduction with *S. cerevisiae* the resulting homochiral β-hydroxy esters are transformed into their hydrazides. Treatment with $NaNO_2/H^+$ then furnishes 2-oxazolidinones in high e.e. (~99%) and d.e. (>99%). The ring formation proceeds via a highly concerted sextet rearrangement with full retention of configuration at the stereocentres. Enantiopure 1,2-amino alcohols can subsequently be obtained by saponification of the 2-oxazolidinone products.

1. Introduction

In modern drug synthesis chiral oxazolidinones serve as synthetic tools and also as essential subunits of pharmacons, as in the antidepressant befloxatone,[1–3] and in fungicides.[4] There exist several synthetic methodologies for the preparation of 5-substituted chiral 2-oxazolidinones.[5–8] Herein, with regard to the preparative effort, we report a new synthetic variant using diastereomerically pure β-hydroxy esters **1a**–**1e** as easily accessible chiral synthons (Scheme 1).

Homochiral β-hydroxy esters are provided with high stereoselectivity by the baker's yeast reduction of the respective β-keto esters and are characterised structurally by an intramolecular proton bridge between the hydroxyl group and the carbonyl oxygen (Scheme 2).[9,10]

Thus, this class of ester emerged as an ideal candidate for an intramolecular Curtius-degradation–cyclisation (the diastereoselectivity of which should benefit from fixed conformation of the substituents). As the Curtius-degradation preserves the configuration of the stereogenic center α to the carboxylic acid group, this procedure should also be well suited for the synthesis of oxazolidinones containing two stereogenic centres.[11]

The intention was to start with the baker's yeast reduction of a β-keto ester to the corresponding β-hydroxy ester **A**, and to convert this into its hydrazide **B**. Nitrosation would then lead to an intermediary azide, from which elimination of nitrogen furnishes the isocyanate **C**. The latter can cyclise to the oxazolidinone **D** or can give the 1,2-amino alcohol **E** by decarboxylation. Reaction conditions which allow for a sufficient discrimination between intramolecular ring-closure reaction to afford **D** and carbamic acid formation to afford **E** are key to the success of this synthesis (Scheme 2).

Scheme 1.

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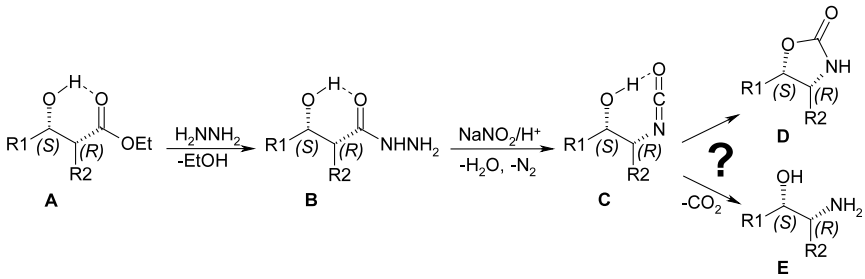


Scheme 2.

Many 2-oxazolidinone syntheses require noxious reagents like phosgene. With the sequence **A→D** an elegant approach to diastereomerically pure oxazolidinones which avoids the use of such hazardous reagents would be at hand.

2. Results and discussion

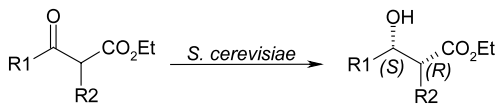
Chiral β-hydroxy esters **2a**–**2e** were prepared by the baker's yeast reduction of the keto esters **1a**–**e** (Table 1).[3,9,10,12–15]

In the next step the β-hydroxy esters **2a**–**2e** were reacted with hydrazine hydrate (80%) in ethanol, which furnished the corresponding hydrazides **3a**–**3e** in high yields with the exception of **3c** (Table 2).[16] The reasons for the low yield in the step **2c→3c** remain unclear. Using a less concentrated hydrazine hydrate solution resulted in a significant decrease in yield.

The conversion of hydrazides **3a**–**3e** with $NaNO_2$ in acidic medium is the key step of the synthesis as the reaction conditions govern whether intramolecular cyclisation to the 2-oxazolidinone **6a**–**6e** occurs or whether the 1,2-amino alcohol **8a**–**8e** is preferred. In order to demonstrate the effects involved, the process is exemplified best with the cyclic hydrazide **3e** (Scheme 3).

From hydrazide **3e** azide **4e** is formed by nitrosation. Accompanied by the liberation of nitrogen gas, the azide rearranges in a highly concerted process to the isocyanate **5e**. At this stage, temperature has proven to be essential for the fate of the intermediate. At room temperature, cyclisation to the 2-oxazolidinone **6e** occurs, while at elevated temperature (up to 50°C), the reaction is less selective and up to 38% of 1,2-amino alcohol **8e** is formed. When temperature is raised above 50°C, the reaction becomes increasingly unselective. This is assigned to nitrene formation at elevated temperature levels, while at lower temperature the process is highly concerted and highly selective. On the other hand, the rates of the reactions are very low at 0°C.

Table 1. Enantioselective baker's yeast reduction of keto esters **1a**–**1e**



Entry	Substrate	Yield (%)[a]	% e.e.[b] (conf.)[c]	% d.e.[b] (conf.)[c]
1	Ethyl acetoacetate **1a**	67	98.4 (*S*)	–
2	Ethyl 4-chloro-acetoacetate **1b**	95	92.8 (*R*)	–
3	Ethyl 4,4,4-trifluoro-acetoacetate **1c**	35	62.1 (*R*)	–
4	Ethyl 2-oxocyclopentanecarboxylate **1d**	86	99.3 (1*R*,2*S*)	97.3 (1*R*,2*S*)
5	Ethyl 2-oxocyclohexanecarboxylate **1e**	84	93.9 (1*R*,2*S*)	97.4 (1*R*,2*S*)

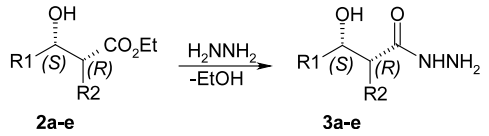
[a] Representative procedure: Baker's yeast (*Saccharomyces cerevisiae*)[d] (250 g) was suspended in a solution of sucrose (250 g) in tap water (2.0 L) in a 3 L flask. The mixture was maintained at 30°C and stirred for 30 min. **1a** (19.53 g, 150 mmol) was added and the suspension was stirred at 30°C for 20 h (GLC control). The reaction mixture was centrifuged, the yeast was washed with water and the aqueous phase was extracted with *tert*-butyl methylether (3×250 mL). Problems due to emulsions were overcome by centrifugation. The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Distillation of the crude residue under reduced pressure yielded the carbinols **2a**–**2e** as colourless liquids.

[b] Determined by GLC with Macherey&Nagel Lipodex A column.

[c] Absolute configurations were determined by comparison of specific rotations with literature values.

[d] Baker's yeast was the product of Societé de levure FALA S.A., Strasbourg, France.

Table 2. Conversion of β-hydroxy esters **2a**–**2e** into hydrazides **3a**–**3e**



2a-e **3a-e**

Entry	Substrate	Yield (%)[a]
1	**2a**	94
2	**2b**	92
3	**2c**	12
4	**2d**	96
5	**2e**	97

[a] Representative procedure: To a solution of **2a** (9.91 g, 75 mmol) in ethanol (6 mL) 80% aqueous hydrazine hydrate (7.3 mL, 120 mmol) was added. The solution was stirred under reflux conditions until TLC (CH_2Cl_2/ethyl acetate, 9:1) showed that conversion was complete (1 h). After cooling to ambient temperature the solution was concentrated in vacuo (60°C, 25 mbar). The solid residue was crystallised from methylene chloride, affording **3a** (8.39 g, 94%) as colourless crystals.

The selectivity of the intramolecular cyclisation is affected positively by the conformation of the starting material and the acidic reaction conditions. It is known from early studies that there is no change in the configuration of the stereogenic carbon α to the carboxylic acid group during the concerted sextet rearrangement **4e**→**5e** (Scheme 4).[11] Consequently, the isocyanate residue will be positioned *cis* to the hydroxyl group and the isocyanate oxygen is fixed by hydrogen bonding in the position nearest to the hydroxyl group. As a consequence of the acidic conditions, the resonance-stabilised protonated species **5e** exhibits a partial positive charge at the NCO-carbon. Due to these electronic and steric factors, the interaction between the hydroxyl oxygen and NCO-carbon allows for a fast nucleophilic attack to give the 2-oxazolidinone **6e**. The proton bridging further polarises the NCO-residue, thus additionally catalyzing the cyclisation step (Scheme 4).

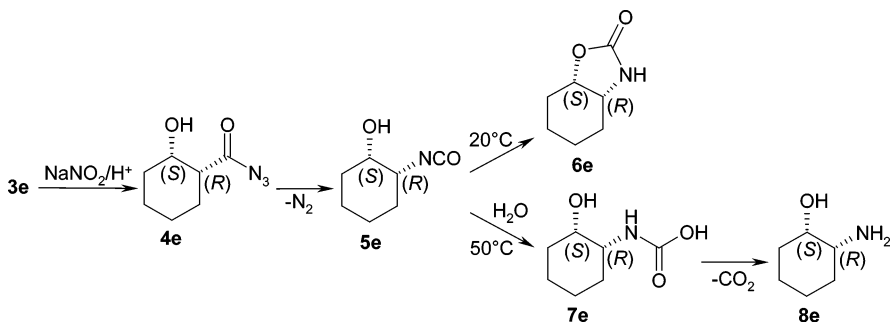
At elevated temperature the rotational freedom of the substrate is increased due to thermal hydrogen bond breakage. Hence, the isocyanate possesses the ability to react either intramolecularly to afford the cyclic product **6e** or to react intermolecularly with water to give the carbamic acid **7e**, which spontaneously decarboxylates to the 1,2-amino alcohol product **8e** (Scheme 3). This behaviour demonstrates that the intramolecular process is kinetically highly favoured and therefore very fast.

A comparison of 2-oxazolidinone yields confirms this interpretation (Table 3). The cyclic species **6d** and **6e** gave the best results, which is probably a result of high order in the respective transition states.

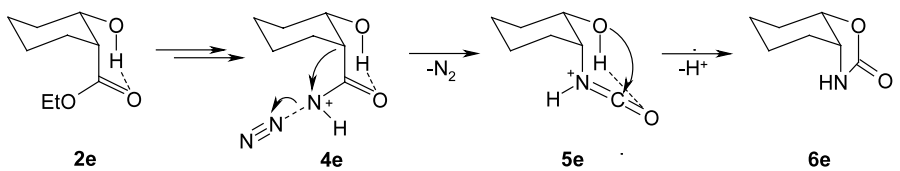
The high selectivity of this process is shown in the e.e. (>99%) and d.e. (>99%) of the product **6e**.

Alongside 2-oxazolidinone synthesis, an enrichment of the desired stereoisomer is encountered (Table 3). This finding is explained by the different reactivities of the diastereomeric substrates and a depletion of the undesired stereoisomers as a result of the purification steps. Possibly due to the trifluoromethyl substituent, the reaction of **3c** proceeds essentially unselectively. This needs further clarification.

Preparation of chiral *N*-substituted 2-oxazolidinones such as the *N*-phenyl derivative **11e** using substituted hydrazines are matters of current research (Scheme 5).[17–20]

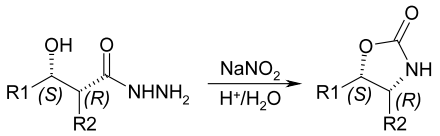


Scheme 3.



Scheme 4.

Table 3. Formation of 2-oxazolidinones **6a**, **6b**, **6d** and **6e** from β-hydroxy-hydrazides **3a**, **3b**, **3d** and **3e**



2a,b,d,e **5a,b,d,e**

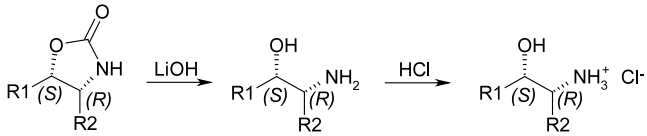
Entry	Substrate	Yield (%)[a]	% e.e.[b] (conf.)[c]	% d.e.[b] (conf.)[c]
1	**3a**	61	98.9 (*S*)	–
2	**3b**	71	99.0 (*R*)	–
3	**3d**	88	>99.0 (1*R*,2*S*)	>99.0 (1*R*,2*S*)
4	**3e**	89	>99.0 (1*R*,2*S*)	>99.0 (1*R*,2*S*)

[a] Representative procedure: At 0°C a solution of $NaNO_2$ (5.5 g, 89 mmol) in 5% aqueous sulfuric acid (110 mL) was added to the hydrazide **3a** (5.91 g, 50 mmol) under an inert gas atmosphere. While stirring, the solution was allowed to warm up to 20°C within 2 h. After TLC (ethyl acetate/CH_2Cl_2, 9:1) had shown that conversion was complete, the solution was neutralised by portionwise addition of Na_2CO_3 (pH control). NaCl (7.0 g) was added and the aqueous phase was extracted with methylene chloride (3×50 mL). The combined organic extracts were washed with water (50 mL), dried over $MgSO_4$ and concentrated in vacuo. The solid residue was crystallised from methylene chloride, yielding **6a** (2.62 g, 61%) as colourless crystals.

[b] Determined by GLC with Macherey&Nagel Lipodex A column.

[c] Absolute configurations were determined by comparison of specific rotations with literature values.

Table 4. Preparation of 1,2-amino alcohol hydrochlorides **9a**, **9d** and **9e** from 2-oxazolidinones **6a**, **6d** and **6e**



6a,d,e **8a,d,e** **9a,d,e**

Entry	Substrate	Yield (%)[a]	% e.e.[b] (conf.)[c]	% d.e.[b] (conf.)[c]
1	**6a**	27	98.6 (*S*)	–
2	**6d**	50	>99.0 (*S*)	99.0 (*R*)
3	**6e**	47	>99.0 (*S*)	98.9 (*R*)

[a] Representative procedure: To a 10% aqueous solution of LiOH (50 mL), **6a** (5.06 g, 50 mmol) was added and stirred at 80°C for 15 min. The reaction mixture was saturated with NaCl and extracted with ethyl acetate (3×30 mL). Total extraction was confirmed by GLC. After washing the organic extract with water (30 mL) the volatile components were removed in vacuo. The crude material was dissolved in ethanol/diethyl ether, 10:1 (10 mL) and HCl gas was passed through the solution until precipitation was complete. After filtration and concentration in vacuo **6a** (0.98 g, 27%) was obtained as colourless crystals.

[b] Determined by GLC with Macherey&Nagel Lipodex A column.

[c] Absolute configurations were determined by comparison of specific rotations with literature values.

From the diastereomerically pure 2-oxazolidinones **6a**, **6d** and **6e**, the respective chiral 1,2-amino alcohols **8a**, **8d** and **8e** can be obtained by saponification with aqueous alkali hydroxide. Due to their sensitivities towards oxygen, the 1,2-amino alcohols **8a**, **8d** and **8e** were isolated as their amine hydrochloride salts **9a**, **9d** and **9e** (Table 4).

However, the isolated yields are rather poor, owing to side reactions such as elimination. These are favoured by the highly basic conditions and the strongly electrophilic Li^+ cation, which may not only polarise the carbonyl, but also the carbinolic C–O bond. As a consequence, the enantiopurity of the amino alcohols is slightly affected (Table 4).

The 3-chloro-amino alcohol **8b** was not accessible in satisfactory yields. This is mainly attributed to a Li^+-catalysed competition between saponification of the 2-oxazolidinone and Lewis acid-assisted nucleophilic substitution of the halogen by hydroxide, as well as the aforementioned elimination reactions.

3. Conclusions

We have presented herein a novel and effective method for facile and highly stereoselective access to mono- and bicyclic 2-oxazolidinones starting from β-keto esters. Subsequent saponification renders this methodology a facile and efficient process for the preparation of 1,2-amino alcohols.

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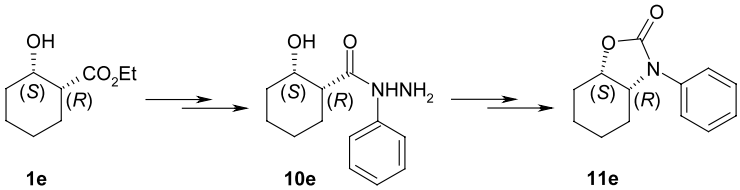

1e **10e** **11e**

Scheme 5.

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