Thermal cyclisation of β-hydroxyamides to oxazolines

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Thermal conversion is described of amides derived from erythro and threo ephedrines yields stereospecific oxazolines.

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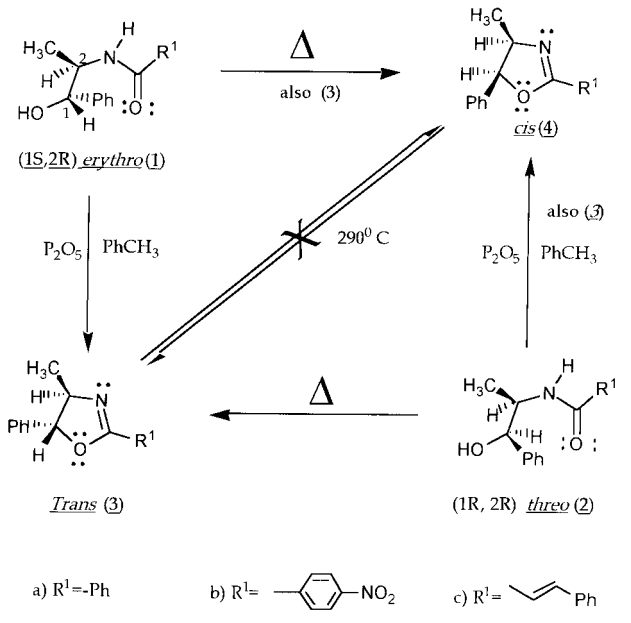
A common approach to the synthesis of oxazolines is ring closure of hydroxyamides using a dehydrating agent such as $SOCl_2$, P_2O_5, $EtO_2CN{=}NCO_2Et/PPh_3$ and, more recently, Burgess reagent.[1–5] The mechanism for this ring closure is believed to involve an internal S_N2 displacement of an alcohol derived leaving group, for example, a phosphate group, with accompanying inversion at the carbon carrying the hydroxyl group.[3]

An alternative mechanistic pathway for oxazoline synthesis would be an initial hydroxyl group attack on the amide carbonyl followed by elimination of water leading to the oxazoline, but this has never been established. Such a process would involve retention of configuration at the carbon carrying the hydroxyl group, opposite to what is observed when a chemical dehydrating agent is used. Such a mechanism might take place under thermal conditions, in the absence of a dehydrating agent, to give other stereospecific oxazolines. To establish this mechanism we selected norephedrine (*erythro*) and norpseudoephedrine (*threo*) as our precursors to the β-hydroxyamides (**1**,**2**). In our work, reaction of the β-hydroxyamide (**1**) derived from norephedrine (*erythro***)** with P_2O_5 in refluxing toluene gave only the *trans*-oxazoline (**3**) with inversion at C-1, while the norpseudoephedrine (*threo*) derived hydroxyamide (**2**) gave the *cis*-oxazoline (**4**) as the major product; *trans*-oxazoline (**3**) was always less than 15%.



However, thermal cyclization (heating to 290°C, 2 min) of *threo*-(**2**) gave only *trans*-oxazoline (**3**)**,** *i.e.*, retention of configuration at C-1; similar treatment of *erythro*-(**1**) gave *cis*-oxazoline (**4**) as the major product, again retention of configuration at C-1, along with *trans*-(**3**) (33–40%). The *trans* and *cis*-oxazolines were clearly distinguished from each other by proton-NMR (*trans*-(**3a**), 5.08 ppm, $J_{4,5}$=8.3 Hz; *cis*-(**4a**), 5.78 ppm, $J_{4,5}$=10 Hz).[6]

That the same β-hydroxyamide gives two different oxazolines with opposite configurations, depending on the conditions used (chemical or thermal), clearly supports our assumption that, under thermal conditions, the hydroxyl group initially attacks the carbonyl carbon, followed by elimination of water to give the oxazoline. The formation of mixtures of oxazolines (*cis* and *trans)* in the reaction *threo* (**2**) with P_2O_5 and *erythro* (**1**) under thermal conditions may arise from a dual mechanistic pathway (S_N2 and S_N1). This aspect is under study.

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