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Quantitative ring contraction of 5-hydroxy-1,3-oxazin-2-ones into 5-hydroxymethyl-1,3-oxazolidin-2-ones: A DFT study

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Abstract

The ring contraction of *trans*-5-hydroxy-1,3-oxazin-2-ones **1** into *cis*-5-hydroxymethyl-oxazolidinones **3** was studied with different bases and nucleophiles and it was found that it is the basicity and not the nucleophilicity the factor responsible for the ring contractions. A DFT study was made for the proposed mechanism.
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Keywords: 1,3-Oxazin-2-ones; 1,3-Oxazolidin-2-ones; Ring contraction; DFT study

1. Introduction

The heterocyclic ring systems, 1,3-oxazin-2-ones [1] and 1,3-oxazolidin-2-ones [2] are present in many biologically important natural products and they have been used as a key intermediates in synthesis of aminoalcohols and as chiral auxiliaries [3].

In previous works [4–6] we reported the preparation of *trans*-5-hydroxy-1,3-oxazin-2-ones and *cis* and *trans*-5-hydroxymethyl-1,3-oxazolidin-2-ones from (2,3-*anti*)-3-amino-1,2-diols and the results were studied theoretically.

In this work, we report the quantitative ring contraction of *trans*-5-hydroxy-1,3-oxazin-2-ones into *cis*-5-hydroxymethyl-1,3-oxazolidin-2-ones, observed in experiments carried out in the preparation of derivatives of such compounds.

2. Results and discussion

In the course of a project of synthesis of new amino acids for biological screening, we used as starting materials different 1,3-oxazin-2-ones derivatives **1a**, **2a**, and **2b** (Scheme 1) prepared by our group in previous works [4–6].

In one of these synthetic experiments we attempted the elongation of the carbon chain at C-5 of the oxazinone **1a**, by tosylation of the hydroxyl group and replacement by cyanide. When the alcohol **1a** was reacted with TsCl in pyridine, the tosyl derivative **4a** was obtained after purification by column chromatography with low yield (45%) along with the unreacted alcohol **1a** (30%). In the reaction of **4a** with potassium cyanide in DMSO we obtained a complex mixture. At the same time we had performed an experiment with the crude mixture containing **4a** and **1a**, and in this case in the reaction with potassium cyanide in DMSO, the ring contracted product, *cis*-5-hydroxymethyl-1,3-oxazolidin-2-one **3a** (30%), was isolated from the crude reaction mixture.

In other series of chemical assays, we obtained similar ring contraction reaction products. So, when we attempted the deprotection of the TBDMS derivatives **2a** and **2b** with KF-methanol at reflux, the oxazolidinones **3a** and **3b** were obtained, respectively.

According to the results of these experiments we thought that the observed ring contractions occurred on products containing the *trans*-5-hydroxy-1,3-oxazin-2-one moiety. In the reaction of the mixture **4a** and **1a**, with

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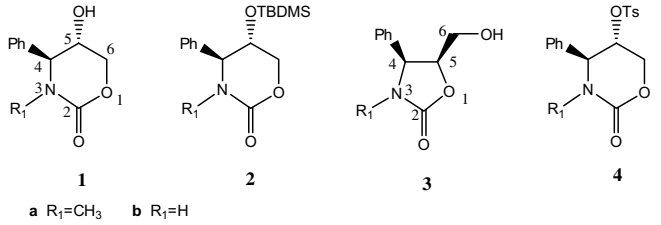


Scheme 1.

potassium cyanide in DMSO, the ring contraction should take place on **1a** and in the deprotection reaction of **2a** and **2b** with KF-methanol, the ring contraction would occur on **1a** and **1b**.

The results of these experiments agree with a major thermodynamic stability of the oxazolidinones **3** in comparison with the oxazinones **1**. The ring contraction could be induced by the reagents or solvents used in the reactions.

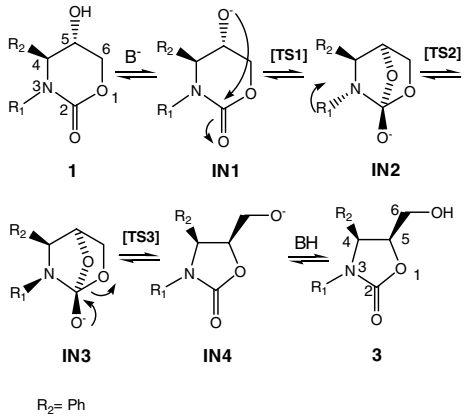
In order to confirm the extent of this ring contraction we studied the reaction of **1a** (easier preparation) with different bases and nucleophiles under different reaction conditions (Table 1).

As it can be seen in entries 1–4, the reactivity follows the order $F^- > Cl^- > Br^- > I^-$, so it is the basicity of the reagent, and not the nucleophilicity (inverse order) [7] the factor responsible for the ring contraction. In the reactions with KCN we observe the effect of the temperature and as it can be seen in Table 1, quantitative transformations using KCN, can be obtained at lower temperatures with longer reaction times (entries 5–7). The ring contraction does not depend on the solvent (entries 8 and 11).

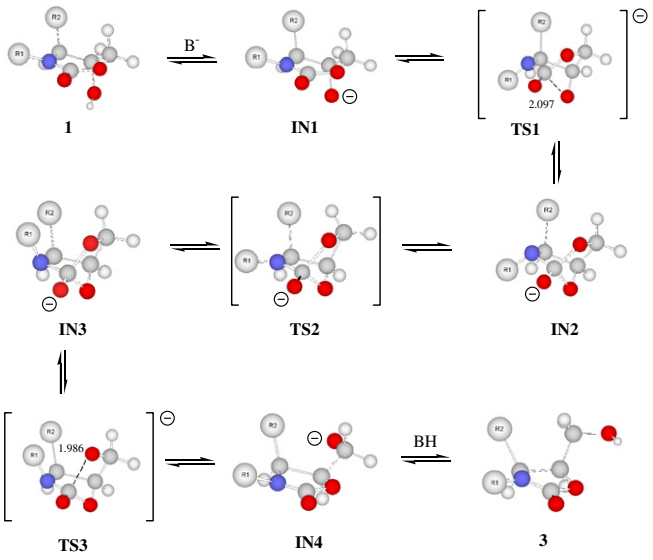
We suggest a mechanism to explain the ring contraction of the 5-hydroxy-1,3-oxazin-2-ones **1** into the 5-hydroxymethyl-1,3-oxazolidin-2-ones **3** and it is shown in Schemes 2 and 3. An initial acid–base equilibrium between the oxazinone **1** and its alcoxyde **IN1** should be generated in the presence of a base. The intramolecular attack of the alcoxyde oxygen atom to the carbonyl of the carbamate would afford the intermediate **IN2**, through the transition state **TS1**. The Walden inversion of the asymmetric N through the **TS2** would afford a new intermediate **IN3**. The subsequent C2–OC6 bond breaking through **TS3** would afford a new alcoxyde **IN4**, whose protonated species are the oxazolidinones **3** [8].

Table 1
Reactions of 1,3-oxazin-2-one **1a** with bases and nucleophiles

Entry	Reactant	T (°C)	Solvent	Time (h)	Yield (%) **3a**: recovered **1a**
1	KF	Reflux	Methanol	18	100:0
2	NaBr	Reflux	Methanol	36	15:85
3	NaCl	Reflux	Methanol	39	4:96
4	KI	Reflux	Methanol	48	0:100
5	KCN	25	Methanol	192	100:0
6	KCN	40	Methanol	24	100:0
7	KCN	Reflux	Methanol	3	100:0
8	KCN	100	DMSO	24	100:0
9	HCOONa	Reflux	Methanol	24	100:0
10	Na_2CO_3	Reflux	Methanol	16 h	94:6
11	NaH	25	Toluene	0.5	100:0



Scheme 2.



Scheme 3. Mechanism of the ring contraction of oxazinones **1** to oxazolidinones **3** with geometries of species involved. The interatomic distances between centers directly involved in the bond-forming processes are given in angstroms.

A DFT study of the proposed mechanism was made in order to determine the factors controlling the ring contraction. As in previous works [6,9] we have made an extensive conformational study for oxazinones **1b**, **1a** and oxazolidinones **3b**, **3a** but we only show the results of the most stable conformations for each compound (Scheme 3, Table 2). As it can be see in Table 2, the oxazolidinones **3b**, **3a** are more stable than the corresponding oxazinones **1b**, **1a** (1.05 and 3.50 kcal/mol, respectively) in agreement with experimental results.

For the theoretical calculations of the species **IN1**–**IN4** we have used a simplified model ($R_1 = H$ and $R_2 = Me$). The stepwise conversion of the intermediate **IN1** into **IN4** has a barrier 14.78 kcal mol^{-1}, being the Walden inversion the rate-determining of the ring contraction (**TS2**).

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