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Synthesis of stable tetrahedral intermediates (hemiaminals) and kinetics of their conversion to thiazol-2-imines

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ABSTRACT

Tetrahedral intermediates (hemiaminals) during thiazol-2-imine formation reactions have been isolated as stable compounds from the $LiAlH_4$ reduction of the corresponding 2-arylimino-3-aryl-thiazolidine-4-ones and identified by ^1H NMR spectroscopy. In solution, the hemiaminals have been found to slowly convert to the corresponding thiazol-2-imines over time. The first order rate constants for the conversion processes have been determined by time dependent ^1H NMR spectroscopic analyses. The half-lives of the hemiaminals were found to be in the range of 2.5–160 days. The hemiaminals owed their ease of formation mainly to the imine conjugation of the amide nitrogen N3, which is expected to increase the electrophilicity of the amide carbonyl by shifting the lone pair of electrons on the amide nitrogen towards the imine side. The stabilities of the hemiaminals were due to the amidine conjugation of the hemiaminal nitrogen and an intramolecular H-bonding interaction for the *o*-methoxyphenyl derivative as verified by computational studies. The reaction mechanism was investigated by DFT/M06-2X/6-31+G(d,p) method. The computational and experimental data are in agreement with an acid catalyzed water elimination mechanism for the conversion of hemiaminal to thiazol-2-imine. Axial chirality of the hemiaminal 2-*o*-methoxyphenylimino-3- *o*-methoxyphenyl-thiazolidine-4-ol, the derivative **2a**, was modeled in DMF and in chloroform with DFT/M06-2X/6-31+G(d,p) method. Interestingly, a solvent induced conformational switching between *P* and *M* atropisomers has been observed by means of 2D-NOESY and verified by computation, which may provoke future research studies targeting the design of solvent-driven or medium-driven molecular devices as well as chiral reagents.

1. Introduction

Hemiaminals (N,*O*-hemiacetals) are tetrahedral intermediates during imine and enamine formations and are usually not isolable.[1] Thus, the synthesis of hemiaminals is a challenging task for organic chemists. Evans[2] et al. synthesized stable hemiaminals from *N*-acylpyroles and Rebek[3,4] et al. stabilized the tetrahedral hemiaminal intermediates by using a synthetic receptor. Other groups obtained relatively stable hemiaminals by conjugating the hemiaminal structure with dendrimers,[5] with a triazole ring,[6] and by making the nitrogen atom part of an aromatic pyrrole ring.[7] H-bonding interactions together with electron withdrawal due to unsaturated groups bonded to the amide carbonyl were also found to have stabilizing effects on hemiaminals in *N*-methoxy amides.[8] Hemiaminals have been postulated to be tetrahedral intermediates during some enzymatic reactions, that involve cleavage of biochemically important amides,[9] and during some natural product syntheses.[10–13] Therefore, a detailed knowledge of the factors responsible for hemiaminal stability would be of paramount importance for understanding the related biochemical processes. We have previously synthesized hemiaminal enantiomers from oxazolidinediones by $NaBH_4$ reduction, and found that the resolved enantiomers racemized via a ring-chain tautomerization through an imine intermediate.[14,15] It has been argued by several groups[16,17] that by preventing the conjugation of the lone pair of electrons on the amide nitrogen with the carbonyl bond by means of forming twisted bridged amides, the amide carbonyl will gain a keto carbonyl character and thus reactivity of the amide towards nucleophilic addition reactions will increase. Szostak et al. synthesized stable hemiaminals from such twisted amides via hydride reduction reactions.[10,18] Recently bicyclic iminosugars with a hemiaminal functionality have been synthesized as drug molecules and found to be stable molecules.[19] Increased reactivities have also been shown for sterically congested amides towards nucleophilic species.[20–22] We hypothesized that withdrawal of the lone

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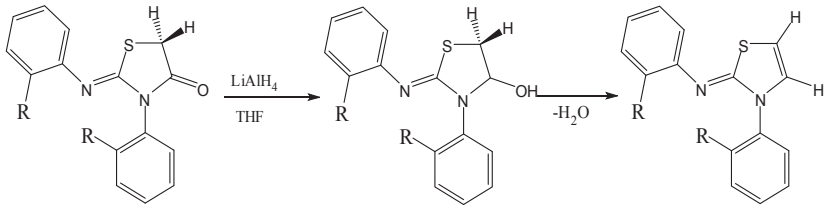
pair of electrons towards the imine nitrogen in amides **1a**–**d** (Scheme 1) will increase the reactivity of the amide carbonyl towards nucleophilic addition by the hydride anion and will have a stabilizing effect on the hemiaminals produced. In the present paper, we show the synthesis of iminophenyl substituted hemiaminals **2a**–**d** via $LiAlH_4$ reduction of the amides **1a**–**d** and show for the first time the conversion of hemiaminals to thiazol-2-imines[23,24] over time together with the kinetics of the process followed by a time dependent ^1H NMR spectroscopic analysis, the results being verified by computational tools.

these results, the conversion of **1a** to **2a** seems to be stereoselective. However a non-selective reduction and a rapid rotation around the C-N bond would also account for these observations (Scheme 2). For the $NaBH_4$ reduction of structurally similar axially chiral oxazolidinediones with an *o*-methyl substituent,[14,15] it has previously been shown that after the *anti* attack to C-4 according to the Felkin-Ahn model a fast rotation around the C_{aryl}-N_3 chiral axis took place to relieve the steric interactions between the OH and the *o*-methyl groups. In this work the OH and the OCH_3 groups were shown to stay *cisoid* due to an H-bonding interaction through 2D-NOESY experiments.



1a. R=OCH_3
1b. R=H
1c. R=CH_3
1d. R=benzo

2a. R=OCH_3
2b. R=H
2c. R=CH_3
2d. R=benzo,

3a. R=OCH_3
3b. R=H
3c. R=CH_3
3d. R=benzo

Scheme 1. Synthesis of the compounds **2a**–**d** and **3a**–**d**.

2. Results and discussion

2.1. Chemoselective reduction of 2-methoxyphenylimino-3-methoxyphenyl-thiazolidine-4-one with $LiAlH_4$ to yield a stable hemiaminal

We have previously described the synthesis of axially chiral **1a** which was shown to exist as a racemic mixture of *M* and *P* enantiomers.[25] Reduction of the axially chiral racemate **1a** was carried out using $LiAlH_4$ in THF at room temperature. The reaction took place chemoselectively reducing only the C-4 carbonyl and not the C-2 imine to yield the hemiaminal **2a**. Compound **2a**, in addition to its chiral axis (Scheme 1) has also a chiral center at C-4. Thus it would, in principle, be expected to exist in four stereoisomers: *M*-*S*, *P*-*R*, *P*-*S* and *M*-*R*. However, in the ^1H NMR spectrum of the hemiaminal **2a**, only one set of signals was observed, indicating the presence of one enantiomeric pair (Fig. 1). HPLC analysis of **2a** on Chiralpak IB also showed the presence of only one enantiomeric pair (Fig. 1). Based on

A detailed analysis of the ^1H NMR spectrum of **2a** is important because its conversion to the corresponding thiazol-2-imine **3a** has been followed by this method. The H_c proton at C-4 gave a signal at δ 5.55 ppm and showed a coupling with the H_a ($^3J_{HaHc}$=4.8 Hz) which is *cis* to H_c, but not with H_b which is *trans* to it ($^3J_{HbHc}$=~0 Hz) (Fig. 1). The H_a proton appeared at δ 3.57 ppm (dd) giving a geminal coupling with H_b ($^2J_{HaHb}$=11.6 Hz) and a vicinal coupling with H_c ($^3J_{HaHc}$=4.8 Hz) (Fig. 1). The H_b proton showed coupling with only the H_a ($^2J_{HaHb}$=11.6 Hz and $^3J_{HbHc}$=~0 Hz) and appeared as a doublet at δ 3.24 ppm (Fig. 1).

In order to elucidate the stereochemistry of the hemiaminal **2a**, a 2D-NOESY spectrum was taken in $CDCl_3$. When the hemiaminal **2a** has a *P*-*R*/*M*-*S* stereochemistry, a crosspeak between the OH at C-4 and the OCH_3 of *o*-anisyl at N_3 would be expected, whereas in the case of *P*-*S*/*M*-*R*, a crosspeak between the hydrogen at C-4 and the OCH_3 group *o*-anisyl at N_3 would be observed. Unfortunately, the peak for the OH at δ 4.01 ppm was found to coincide with that of the *ortho* OCH_3 on N_3 at 3.94 ppm (Fig. 1) and thus, a crosspeak

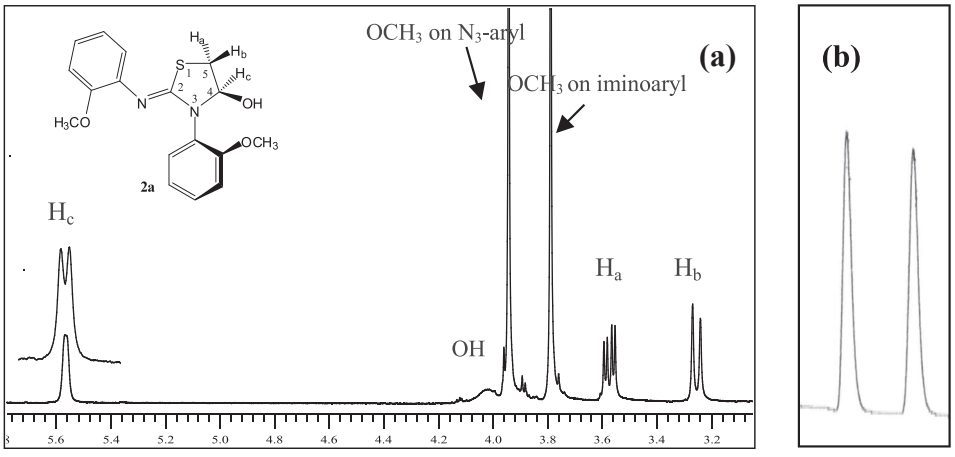


Fig. 1. (a) Partial ^1H NMR spectrum of the hemiaminal **2a** in $CDCl_3$ and (b) the HPLC chromatogram of **2a** (column: Chiralpak IB, eluent: Hexane:Ethanol (99:1), flow rate: 0.6 mL/min, retention times: t_1: 31.8 min, t_2: 36.5 min, column temperature: 280 K).