

## Studies on the Reduction of $\beta$ -Enamino Ketones

Melina A. Machado, Maria Inês N. C. Harris and Antonio C. H. Braga\*

Instituto de Química, Universidade Estadual de Campinas CP 6154, 13084-971 Campinas-SP, Brazil

A redução de  $\beta$ -enamino cetonas **1** com  $\text{NaBH}(\text{OAc})_3$  em ácido acético glacial produziu  $\beta$ -amino cetonas **3** em 65% a 67% de rendimento. Esses resultados, juntamente com outros, obtidos nas reduções de  $\beta$ -enamino cetonas **1** a  $\gamma$ -amino álcoois **2**, preferencialmente *syn*, com  $\text{NaBH}_4/\text{HOAc}$ , sugerem que o curso reacional desta última reação passa inicialmente pela redução de  $\beta$ -enamino cetonas **1** a  $\beta$ -amino cetonas **3** e estas são reduzidas posteriormente a  $\gamma$ -amino álcoois **2**. Com esses resultados podemos dizer que a diastereosseletividade da redução de  $\beta$ -enamino cetonas **1**, a  $\gamma$ -amino álcoois **2** dando preferencialmente produtos *syn* pode ser analisada como o resultado de uma competição entre um estado de transição tipo bote e um estado de transição tipo cadeira, obtidos a partir das  $\beta$ -amino cetonas **3**.

Reduction of  $\beta$ -enamino ketones **1** with  $\text{NaBH}(\text{OAc})_3$  in glacial acetic acid gave  $\beta$ -amino ketones **3** in 65% to 67% yield. These data and others observed in the reduction of  $\beta$ -enamino ketones **1** to preferentially *syn*  $\gamma$ -amino alcohols **2** with  $\text{NaBH}_4/\text{HOAc}$  suggest that in this last reaction we have firstly the reduction of the  $\beta$ -enamino ketones **1** to produce the  $\beta$ -amino ketones **3**, and then this compound is reduced to the  $\gamma$ -amino alcohols **2**. We can say from this results that the diastereoselectivity of the reduction of  $\beta$ -enamino ketones **1** to mainly *syn*  $\gamma$ -amino alcohols **2**, can be analysed as a competition between a chair-like transition state and a boat-like transition state, obtained from the  $\beta$ -amino ketones **3**.

**Keywords:** amino alcohols, enamino ketones, amino ketones, Mannich base

### Introduction

Recently, we reported an easy and efficient method to produce  $\gamma$ -amino alcohols **2** by reduction of  $\beta$ -enamino ketones **1** with  $\text{NaBH}_4$  in glacial acetic acid, which has been successfully used in our laboratory.<sup>1</sup> Our results showed that the reaction of  $\beta$ -enamino ketones **1** with  $\text{NaBH}_4$  in glacial acetic acid (3 hours at room temperature) produces a mixture of *syn/anti*  $\gamma$ -amino alcohols **2** in 70% to 98% yield with diastereomeric excesses preferentially for the *syn* product, from 44% to 90%. The use of  $\text{NaBH}_4$  in a carboxylic acid medium is well known,<sup>2</sup> but its use in the reduction of  $\beta$ -enamino ketones **1** has not been explored. To continue our studies on the reduction of  $\beta$ -enamino ketones **1**, and to understand the diastereoselectivity observed in the reduction to  $\gamma$ -amino alcohols **2** and the real reducing agent, we wish to report herein our results obtained with the reduction of  $\beta$ -enamino ketones **1** using  $\text{NaBH}(\text{OAc})_3/\text{HOAc}$ .

### Results and Discussion

The reaction of  $\text{NaBH}_4$  with neat carboxylic acids leads to the formation of acyloxyborohydrides.<sup>2</sup> Reaction with glacial acetic acid leads to the formation of acetoxyborohydrides of different hydride-donating abilities. Presumably the reactivity order ( $^-\text{BH}_3\text{OAc} > ^-\text{BH}_2(\text{OAc})_2 > ^-\text{BH}(\text{OAc})_3$ ) is a consequence of both the inductive electron-withdrawing ability of the acetoxy group and the steric bulk surrounding the B-H bond.<sup>3</sup> Although the reaction of  $\beta$ -enamino ketones **1** with  $\text{NaBH}_4$  in glacial acetic acid for 3 hours at room temperature leads to products from total reduction ( $\gamma$ -amino alcohols **2**),<sup>1</sup> under the same conditions, using  $\text{NaBH}(\text{OAc})_3$  as a reducing agent we have the Mannich base **3** as a product (Scheme 1, Table 1). These results are obtained when we add commercial  $\text{NaBH}(\text{OAc})_3$  to a solution of  $\beta$ -enamino ketone **1** in glacial acetic acid or when firstly we add  $\text{NaBH}_4$  to glacial acetic acid and then add the  $\beta$ -enamino ketones **1**,<sup>4,5</sup> and shows that in the reduction of the  $\beta$ -enamino ketones **1** to  $\gamma$ -amino alcohols **2**, the reducing agent is not the  $\text{NaBH}(\text{OAc})_3$  as it is normally interpreted in this type of reaction.<sup>7</sup> These data

\*e-mail: herrera@iqm.unicamp.br

imply that sodium borohydride added directly to acetic acid, as it is used in the total reduction of  $\beta$ -enamino ketones **1** to  $\gamma$ -amino alcohols **2**, does not quantitatively give sodium triacetoxyborohydride.<sup>6</sup>

**Table 1.** Products obtained by reduction of  $\beta$ -enamino ketones **1** with  $\text{NaBH}(\text{OAc})_3/\text{HOAc}$

<b>1</b>	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	% <b>3</b> <sup>c</sup>
<b>a</b>	Me	Ph	H	67
<b>b</b>	Me	Bn	H	65
<b>c</b>	Me	<sup>i</sup> Pr	H	67
<b>d</b>	Ph	<sup>i</sup> Pr	H	<sup>a</sup>
<b>e</b>	Me	-(CH <sub>2</sub> ) <sub>4</sub> -	H	65
<b>f</b>	<sup>t</sup> Bu	Bn	H	<sup>b</sup>
<b>g</b>	Ph	Bn	H	<sup>a</sup>

<sup>a</sup>The product was identified as the corresponding  $\alpha,\beta$ -unsaturated ketone; <sup>b</sup>decomposition during treatment; <sup>c</sup>isolated yield.

Early information showed that, when the reduction reaction of  $\beta$ -enamino ketones **1** to  $\gamma$ -amino alcohols **2** with  $\text{NaBH}_4/\text{HOAc}$  is carried out without temperature control, the reaction produces the corresponding  $\alpha,\beta$ -unsaturated ketone, while at 0 °C (using hexane/HOAc,  $\text{CH}_2\text{Cl}_2/\text{HOAc}$  or HOAc as solvent) the product is a mixture of reactant **1**,  $\gamma$ -amino alcohol **2** and the corresponding Mannich base **3**.<sup>1</sup> This information suggests that the Mannich base **3** acts as an intermediate in this reaction. The partial reduction of

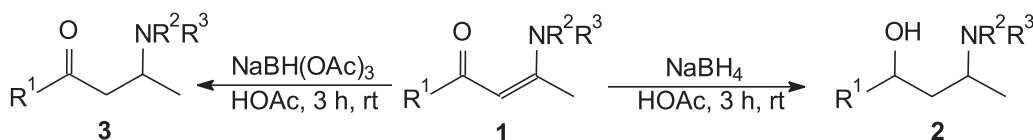
$\beta$ -enamino ketones **1** to  $\beta$ -amino ketones **3** with  $\text{NaBH}(\text{OAc})_3/\text{HOAc}$  and the observation in some cases the corresponding  $\alpha,\beta$ -unsaturated ketones reinforces this suspicion. The  $\beta$ -amino ketones **3** obtained are very unstable and decompose rapidly to the corresponding  $\alpha,\beta$ -unsaturated ketones. They were immediately analysed on a Shimadzu GC/MS Class 500 chromatograph equipped with a Simplicity-1 (SUPELCO) column. All the chromatograms presented only one compound with the MS showing a typical fragmentation, as seen in Figure 1 and Table 2.

Another important observation is that it is not possible to reduce 3-(N-benzylamino)-2-cyclohexen-1-one using either  $\text{NaBH}_4/\text{HOAc}$  or  $\text{NaBH}(\text{OAc})_3/\text{HOAc}$ .

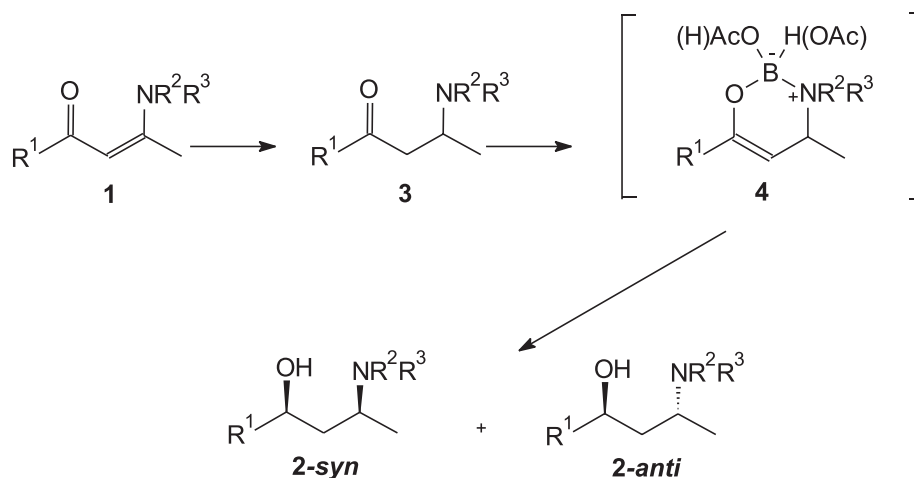
In conclusion, these observations suggest that in the reduction of  $\beta$ -enamino ketones **1** to  $\gamma$ -amino alcohol **2** we have firstly the reduction of the  $\beta$ -enamino ketones **1** to  $\beta$ -amino ketones **3**, then this compound is further reduced to

**Table 2.** Typical fragmentation observed in the  $\beta$ -amino ketones **3**

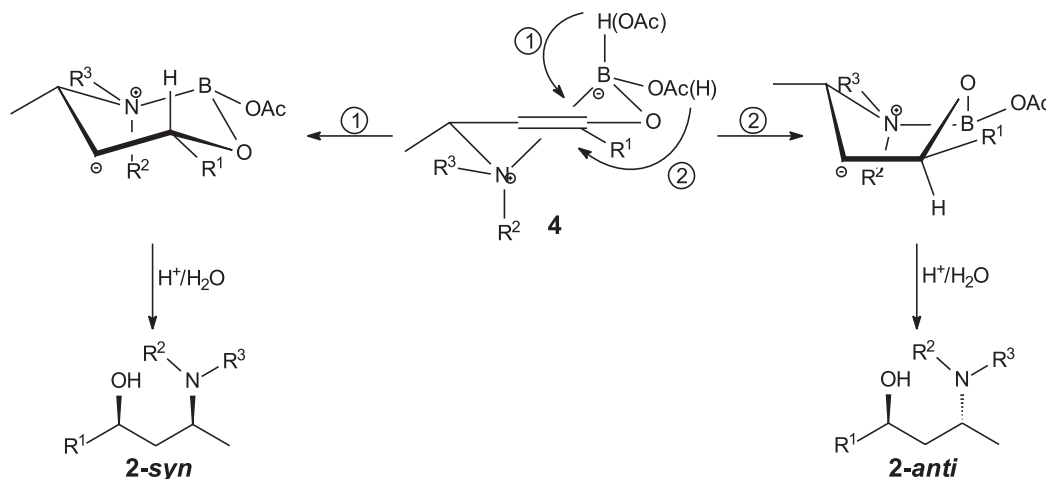
<b>3</b>	<b>5</b> ( <i>m/z</i> )	<b>6</b> ( <i>m/z</i> )
<b>a</b>	43 (67%)	120 (100%)
<b>b</b>	43 (57%)	134 (9%)
<b>c</b>	43 (67%)	86 (16%)
<b>e</b>	43 (74%)	98 (100%)



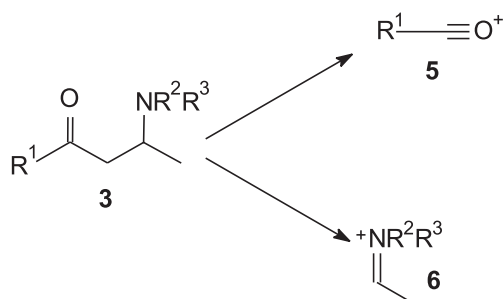
**Scheme 1.**



**Scheme 2.**



Scheme 3.

Figure 1. Typical fragmentation observed with the  $\beta$ -amino ketones **3**.

the  $\gamma$ -amino alcohols **2** (Scheme 2). The stereochemical course of these reductions, producing preferentially the *syn*- $\gamma$ -amino alcohols **2**, may be rationalised via the different energies of the diastereomeric transition states resulting in a competition between a chair-like transition state and a boat-like transition state (Scheme 3), when the *syn* product is obtained by the lower energy route.

## Experimental

### General procedure to obtain $\beta$ -amino ketones (**3**)

To a solution of  $\beta$ -enamino ketone (**1**, 1 mmol) in glacial acetic acid (6 mL), was slowly added  $\text{NaBH}(\text{OAc})_3$  (4 mmol). The reaction was kept at 18–20 °C. The reaction was stirred for 3 hours, and then neutralized with an aqueous solution of 30% NaOH (approximately 12 mL) in an ice bath. The reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$  and the organic phases were combined, dried over  $\text{MgSO}_4$ , and concentrated. The products were immediately analysed.

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- For a better understanding of this reactivity, theoretical studies are in progress.
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