

Studies on the Reduction of β -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 β -enamino cetonas **1** com $\text{NaBH}(\text{OAc})_3$ em ácido acético glacial produziu β -amino cetonas **3** em 65% a 67% de rendimento. Esses resultados, juntamente com outros, obtidos nas reduções de β -enamino cetonas **1** a γ -amino álcoois **2**, preferencialmente *syn*, com $\text{NaBH}_4/\text{HOAc}$, sugerem que o curso reacional desta última reação passa inicialmente pela redução de β -enamino cetonas **1** a β -amino cetonas **3** e estas são reduzidas posteriormente a γ -amino álcoois **2**. Com esses resultados podemos dizer que a diastereosseletividade da redução de β -enamino cetonas **1**, a γ -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 β -amino cetonas **3**.

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

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

Introduction

Recently, we reported an easy and efficient method to produce γ -amino alcohols **2** by reduction of β -enamino ketones **1** with NaBH_4 in glacial acetic acid, which has been successfully used in our laboratory.¹ Our results showed that the reaction of β -enamino ketones **1** with NaBH_4 in glacial acetic acid (3 hours at room temperature) produces a mixture of *syn/anti* γ -amino alcohols **2** in 70% to 98% yield with diastereomeric excesses preferentially for the *syn* product, from 44% to 90%. The use of NaBH_4 in a carboxylic acid medium is well known,² but its use in the reduction of β -enamino ketones **1** has not been explored. To continue our studies on the reduction of β -enamino ketones **1**, and to understand the diastereoselectivity observed in the reduction to γ -amino alcohols **2** and the real reducing agent, we wish to report herein our results obtained with the reduction of β -enamino ketones **1** using $\text{NaBH}(\text{OAc})_3/\text{HOAc}$.

Results and Discussion

The reaction of NaBH_4 with neat carboxylic acids leads to the formation of acyloxyborohydrides.² 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.³ Although the reaction of β -enamino ketones **1** with NaBH_4 in glacial acetic acid for 3 hours at room temperature leads to products from total reduction (γ -amino alcohols **2**),¹ 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 β -enamino ketone **1** in glacial acetic acid or when firstly we add NaBH_4 to glacial acetic acid and then add the β -enamino ketones **1**,^{4,5} and shows that in the reduction of the β -enamino ketones **1** to γ -amino alcohols **2**, the reducing agent is not the $\text{NaBH}(\text{OAc})_3$ as it is normally interpreted in this type of reaction.⁷ 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 β -enamino ketones **1** to γ -amino alcohols **2**, does not quantitatively give sodium triacetoxyborohydride.⁶

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

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

^aThe product was identified as the corresponding α,β -unsaturated ketone; ^bdecomposition during treatment; ^cisolated yield.

Early information showed that, when the reduction reaction of β -enamino ketones **1** to γ -amino alcohols **2** with $\text{NaBH}_4/\text{HOAc}$ is carried out without temperature control, the reaction produces the corresponding α,β -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**, γ -amino alcohol **2** and the corresponding Mannich base **3**.¹ This information suggests that the Mannich base **3** acts as an intermediate in this reaction. The partial reduction of

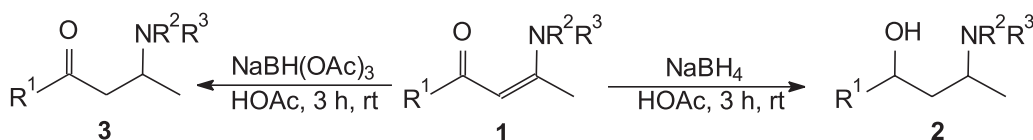
β -enamino ketones **1** to β -amino ketones **3** with $\text{NaBH}(\text{OAc})_3/\text{HOAc}$ and the observation in some cases the corresponding α,β -unsaturated ketones reinforces this suspicion. The β -amino ketones **3** obtained are very unstable and decompose rapidly to the corresponding α,β -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 $\text{NaBH}(\text{OAc})_3/\text{HOAc}$.

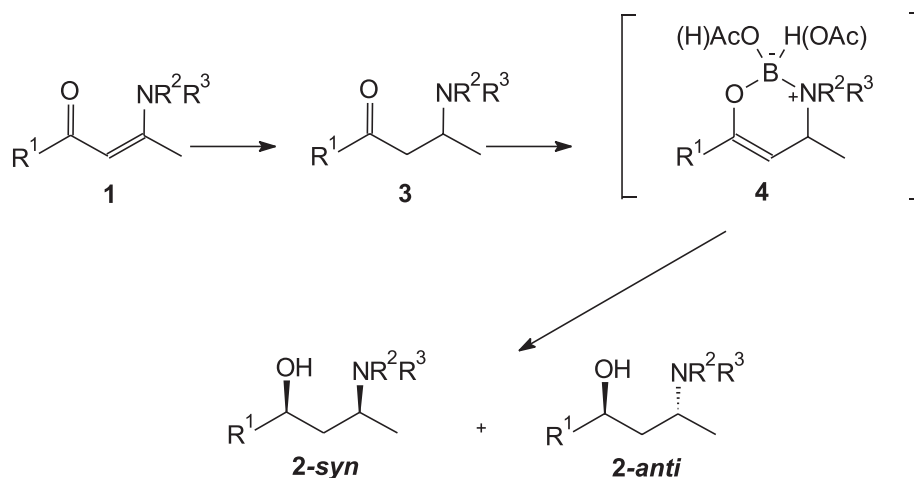
In conclusion, these observations suggest that in the reduction of β -enamino ketones **1** to γ -amino alcohol **2** we have firstly the reduction of the β -enamino ketones **1** to β -amino ketones **3**, then this compound is further reduced to

Table 2. Typical fragmentation observed in the β -amino ketones **3**

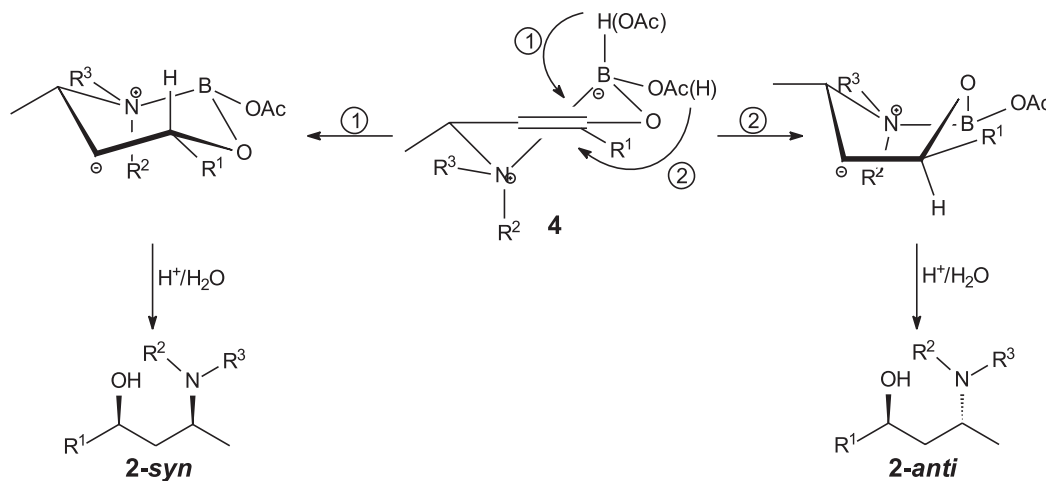
3	5 (<i>m/z</i>)	6 (<i>m/z</i>)
a	43 (67%)	120 (100%)
b	43 (57%)	134 (9%)
c	43 (67%)	86 (16%)
e	43 (74%)	98 (100%)



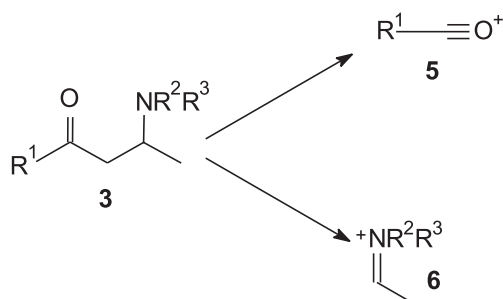
Scheme 1.



Scheme 2.



Scheme 3.

Figure 1. Typical fragmentation observed with the β -amino ketones **3**.

the γ -amino alcohols **2** (Scheme 2). The stereochemical course of these reductions, producing preferentially the *syn*- γ -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 β -amino ketones (**3**)

To a solution of β -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 CH_2Cl_2 and the organic phases were combined, dried over MgSO_4 , and concentrated. The products were immediately analysed.

Acknowledgments

The authors thank FINEP-Financieira de Estudos e Projetos for financial support, FAPESP-Fundação de Amparo à Pesquisa do Estado de São Paulo for a scholarship to Melina A. Machado, Dr. Ronaldo Aloise Pilli for reagents and lab facilities and Prof. Dr. Carol H. Collins for her kind attention in revising this manuscript.

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- For a comprehensive review of uses of borohydrides in carboxylic acid media see: Gribble, G. W.; Nutaitis, C. F.; *Org. Prep. Proced. Int.* **1985**, *17*, 317; Gribble, G. W.; *Chem. Soc. Rev.* **1998**, *27*, 395.
- For a better understanding of this reactivity, theoretical studies are in progress.
- When sodium borohydride is added to excess acetic acid, hydrogen is liberated rapidly. The species in this reaction has been suggested to be sodium triacetoxyborohydride.
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Received: March 28, 2006

Published on the web: August 30, 2006

FAPESP helped in meeting the publication costs of this article.