An Easy and Efficient Method to Produce γ-Amino Alcohols by Reduction of β-Enamino Ketones

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A redução de β-enamino cetonas 2 com NaBH₄ em ácido acético glacial produziu γ-amino álcoois 1 em 70% a 98% de rendimento, com excessos diastereoméricos, preferencialmente o produto syn, de 44% a 90%. A estereoquímica desses compostos foi confirmada pela análise de seus derivados tetrahydro-1,3-oxazinas 3.

Reduction of β-enamino ketones 2 with NaBH₄ in glacial acetic acid gave γ-amino alcohols 1 in 70% to 98% yield with diastereomeric excesses, preferentially the syn product, from 44% to 90%. The stereochemistry of these compounds was confirmed by analysis of their tetrahydro-1,3-oxazine derivatives 3.

Keywords: amino alcohols, enamino ketones, oxazines, stereoselective reduction

Introduction

The synthesis of γ-amino alcohols 1 is of great interest due to the pharmacology of these compounds and their derivatives. This functionality is found in several antibiotics and other biologically active natural products. Several synthetic methods have been described for the synthesis of γ-amino alcohols 1 from diols, hydroxazols, lactams and lactones, but the more important methods are those where one can obtain γ-amino alcohols 1 by reduction of 1,3-difunctionalized unsaturated compounds containing nitrogen and oxygen, such as β-hydroxy oximes, β-enamino ketones and, more frequently, by the reduction of β-amino ketones.

γ-Amino alcohols 1, mainly syn, can be synthesized by reduction of β-enamino ketones 2 with Na in PrOH/tetrahydrofuran or with CeCl₃/LiBH₄/tetrahydrofuran. On the other hand, the combination of NaBH₄ in a carboxylic acid medium has yielded an efficient reducing reagent.

We wish to report herein a simple and efficient method to produce γ-amino alcohols 1 through the reduction of β-enamino ketones 2 with NaBH₄ in glacial acetic acid, which has been successfully used in our laboratory.

Results and Discussion

Difficulties in reduction of β-enamino ketones 2 have been reported. The use of NaBH₄ in a carboxylic acid medium is well known, but its use in the reduction of β-enamino ketones 2 has not been explored. Our results show that the reaction of β-enamino ketones 2 with NaBH₄ in glacial acetic acid (3 hours at room temperature, Scheme 1), produces a mixture of syn/anti γ-amino alcohols 1, the syn isomer being the major product (Table 1).

Table 1. Diastereomeric ratios of γ-amino alcohols 1 in the reduction of β-enamino ketones 2

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>% I syn</th>
<th>syn/anti</th>
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<tr>
<td>a</td>
<td>Me</td>
<td>H</td>
<td>Ph</td>
<td>87/13</td>
</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>H</td>
<td>Bn</td>
<td>80/20</td>
</tr>
<tr>
<td>c</td>
<td>Me</td>
<td>H</td>
<td>'Pr</td>
<td>72/28</td>
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<tr>
<td>d</td>
<td>Ph</td>
<td>H</td>
<td>'Pr</td>
<td>90/10</td>
</tr>
<tr>
<td>f</td>
<td>'Bu</td>
<td>H</td>
<td>Bn</td>
<td>&gt; 95/5</td>
</tr>
<tr>
<td>e</td>
<td>Me</td>
<td>-</td>
<td>(CH₂)₄-</td>
<td>75/25</td>
</tr>
</tbody>
</table>

* Diastereomeric ratio determined in the mixtures of the tetrahydro-1,3-oxazine derivatives 3 using ¹H NMR (75.1 MHz), and confirmed by CG/MS. If was not isolated; it was transformed immediately into 3f; 4 isolated yield.

When the reaction is carried out without temperature control, the reaction produces the α,β-unsaturated ketone 6 while at 0 °C (hexane/HOAc, CH₂Cl₂/HOAc or HOAc as
solvent) the product is a mixture of reactant 2, γ-amino alcohol 1 and the corresponding Mannich base 5. Another important observation is that, by this methodology, it is impossible to reduce 3-(N-benzylamino)-2-cyclohexen-1-one.

A mechanism is suggested where chelated intermediate 4 is reduced to produce β-amino ketone 5 and γ-amino alcohol 1 (Scheme 2).

Quantitative conversion of γ-amino alcohols 1 to the corresponding tetrahydro-1,3-oxazine derivatives 3 (formal in diethyl ether, Scheme 3), allow us to assign the syn stereochemistry to the major γ-amino alcohol 1 after inspection of their 1H and 13C NMR spectra. Using the syn-3a compound as an example (Scheme 4), we can see the hydrogen atoms H4 and H6 as a double quartet of doublets at 3.27 ppm (J 3.3, 6.3, 11.1 Hz) and 3.68 ppm (J 2.7, 6.3, 12.3 Hz) respectively. These hydrogen atoms and H5e are in a axial-equatorial situation (θ ≈ 60°), with coupling constants 2.7 Hz (JH4-H5e) and 3.3 Hz (JH6-H5e). The 1H NMR spectrum shows the axial-axial (θ ≈ 180°) relation between H5a and hydrogen atoms H4 and H6 (JH4-H5a 11.1 Hz; JH6-H5a 12.5 Hz). Furthermore we can see H5e and H5a as a double triplet at 1.57 ppm (J 2.7, 13.5 Hz) and 1.42 ppm (J 11.1, 13.0 Hz), respectively. The analysis of the 13C NMR spectrum (Scheme 5) allows the assignment of the secondary carbons at 40.03 ppm and 85.76 ppm (C5 and C2 respectively), and the tertiary carbons at 53.43 ppm and 73.45 ppm (C4 and C6 respectively). The chemical shifts of the methyl groups were assigned mainly based on the protective anisotropic effect of the phenyl group at C4. The chemical shift of the carbon C6 in the syn-3a isomer and in the anti-3a isomer are 73.43 and 68.14 ppm respectively. This upfield shift (ca. 5 ppm) is compatible with a γ-gauche exocyclic interaction, showing the axial methyl group at C4.

In conclusion, the reduction of β-enamino ketones 2 with NaBH4 in acetic acid is a very simple and fast method to obtain γ-amino alcohols 1 (with preferential syn configuration) in good chemical yields.

**Experimental**

**General**

1H NMR and 13C NMR spectra were recorded on a GEMINI-300 MHz instrument, using CDCl3 as a solvent and TMS as internal reference. The IR spectra were recorded on a Perkin Elmer 1600-FTIR (film in NaCl cell) instrument. Elemental analyses were performed on a Perkin Elmer 2400 instrument. The mass spectra were recorded on a HP 5988A instrument. The gas chromatographic analysis were performed on a Shimadzu GC/MS Class 5000 chromatograph equipped with a Simplicity-1 (SUPELCO) column. The products were purified by flash chromatography or PLC using SiO2 as a stationary phase.

**General procedure to obtain γ-amino alcohol, (1).** To a solution of β-enamino ketone (2, 1 mmol) in glacial acetic acid (6 mL), was slowly added NaBH4 (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 CH₂Cl₂, the organic phases were combined, dried over MgSO₄, and concentrated.

4-(N-Phenylamino)-pentan-2-ol, (1a). IR (neat) νmax/cm⁻¹: 3350, 3050, 3025, 2970, 2925, 1600, 1500, 1320, 1250, 1130, 750, 690. MS m/z (%): 179(37), 164(15), 120(100), 104(7.6), 93(24), 77(22), 45(24). ¹H NMR syn-1a δ: 1.14(d, J 6.2 Hz, 3H), 1.18(d, J 6.2 Hz, 3H), 1.57(A'X'Y', 2H), 3.41(s, large, 2H), 3.66(sext, J 6.5 Hz, 1H), 4.01(sext, J 6.0 Hz, 1H), 6.57-6.79(m, 3H), 7.12-7.24(m, 2H). ¹³C NMR syn-1a δ: 147.13, 129.46, 118.98, 115.29, 67.97, 49.89, 45.76, 23.98, 21.46. ¹H NMR anti-1a δ: 1.17(2 d, 6H), 1.43-1.70(m, 2H), 3.20(s, large, 2H), 3.76(m, 1H), 3.91(m, 1H), 6.49-6.67(m, 3H), 7.00-7.10(m, 2H). ¹³C NMR anti-1a δ: 147.73, 129.37, 117.61, 113.73, 67.25, 46.05, 45.70, 24.04, 21.32. Anal. Calc. for C₁₂H₁₉NO: C 73.70; H 9.56; N 7.82%. Found: C 73.91; H 9.56; N 7.62%.

4-(N-Benzylamino)-pentan-2-ol, (1b). IR (neat) νmax/cm⁻¹: 3346, 3286, 3076, 2964, 2925, 1452, 1374, 1165, 1129, 1088, 742, 698. MS m/z (%): 193(5), 178(15), 134(83), 106(28), 91(100). ¹H NMR syn-1b δ: 1.12(d, J 6.3 Hz, 3H), 1.17(d, J 8.1 Hz, 3H), 1.20-1.55(m, 2H), 2.92(dqd, J 2.7, 6.3, 10.6 Hz, 1H), 3.71(d, J 13.0 Hz, 1H), 3.90(s, large, 1H), 3.93(d, J 13.0 Hz, 1H), 3.94(dqd, J 2.3, 5.8, 17.0 Hz, 1H), 7.20-7.36(m, 5H). ¹³C NMR syn-1b δ: 139.24, 128.72, 128.49, 127.48, 68.94, 54.08, 50.64, 44.91, 23.87, 20.82. ¹H NMR anti-1b δ: 1.15(d, J 8.1 Hz, 3H), 1.21(d, J 6.6 Hz, 3H), 1.43(ddd, J 2.7, 5.1, 14.4 Hz, 1H), 1.70(ddd, J 3.3, 9.0, 14.4 Hz, 1H), 3.12(dqd, J 3.2, 3.9, 6.6 Hz, 1H), 3.50(s, large, 2H), 3.74(d, J 12.6 Hz, 1H), 3.86(d, J 12.6 Hz, 1H), 4.15(dqd, J 3.0, 6.2, 9.0 Hz, 1H), 7.20-7.37(m, 5H). ¹³C NMR anti-1b δ: 139.51, 128.73, 128.43, 127.45, 65.03, 51.48, 51.97, 45.06, 23.56, 19.76. Anal. Calc. for C₁₃H₂₁NO: C 75.32; H 10.21; N 6.75%. Found: C 75.10; H 10.22; N 6.26%.

4-(N-Pyrrolidinyl)-pentan-2-ol, (1e). IR (neat) νmax/cm⁻¹: 3400, 2980, 2940, 2870, 2830, 1455, 1160, 1150. MS m/z (%): 157(4.2), 142(9), 96(100), 70(24), 56(20), 45(24). ¹H NMR syn-1e δ: 0.97(d, J 6.6 Hz, 3H), 1.13(d, J 6.2 Hz, 3H), 1.34(ddd, J 1.8, 3.6, 14.5 Hz, 1H), 1.52(d, J 10.9, 14.0 Hz, 1H), 1.70-1.80(A'X'B', 4H), 2.57-2.80(A'X'B', 4H), 3.17(dqd, J 3.3, 6.9, 10.5 Hz, 1H), 3.96(dqd, J 2.0, 6.2, 10.3 Hz, 1H), 6.24(s, large, 1H). ¹³C NMR syn-1e δ: 69.08, 55.56, 46.70, 41.94, 23.67, 23.23, 12.43. ¹H NMR anti-1e δ: 1.21(d, J 6.2 Hz, 3H), 1.25(d, J 6.6 Hz, 3H), 1.55(ddd, J 2.6, 7.0, 14.0 Hz, 1H), 1.83(ddd, J 6.1, 10.6, 14.0 Hz, 1H), 1.94-2.20(m, 4H), 3.09(t, J 6.5 Hz, 4H), 3.50 sext(J, 6.6 Hz, 1H), 3.90(dqd, J 1.8, 5.6, 11.0 Hz, 1H), 5.20(s, large, 1H). ¹³C NMR anti-1e δ: 64.43, 57.62, 51.48, 41.05, 23.52, 23.28, 17.28.

General procedure to obtain tetrahydro-1,3-oxazines, (3). To a solution of γ-amino alcohol (1, 1mmol) in diethyl ether (1 mL), was added a solution of 40% formaldehyde (0.1 mL). The reaction was stirred for 16-20 hours at room temperature. After this time, diethyl ether (approximately 5 mL) was added, and the solution was dried over MgSO₄, filtered and concentrated in vacuo. The yield was quantitative.

3-Phenyl-4,6-dimethyl-tetrahydro-1,3-oxazine, (3α). IR (neat) νmax/cm⁻¹: 2960, 2920, 1600, 1485, 1370, 1250, 1240, 1175, 1100, 1000, 700. MS m/z (%): 192(7), 191(50), 190(11), 176(58), 132(83), 120(50), 119(83), 118(22), 106(33), 105(83), 104(91), 91(14), 77(100). ¹H NMR syn-3α δ: 1.02(d, J 6.3 Hz, 3H), 1.26(d, J 6.3 Hz, 3H), 1.42(dt, J 11.1, 13.0 Hz, 1H), 1.57(dt, J 2.7, 13.5 Hz, 1H), 3.73(dqd, J 3.3, 6.3, 11.1 Hz, 1H), 3.68(dqd, J 2.7, 6.3, 12.3 Hz, 1H), 4.39(d, J 9.3 Hz, 1H), 4.73(d, J 9.3 Hz, 1H), 7.06-7.33(m, 5H). ¹³C NMR syn-3α δ: 147.57, 129.02, 126.32, 124.83,
10.2 Hz, 1H), 7.20-7.40(AA'BBC, 5H). 13C NMR δ: 150.88, 129.35, 120.65, 119.08, 74.85, 68.14, 52.79, 35.76, 22.07, 17.07. Anal. Calc. for C_{12}H_{17}NO: C, 76.06; H, 9.33; N, 6.60%.  

3-Benzyl-4,6-dimethyl-tetrahydro-1,3-oxazine, (3b). IR (neat) ν_{max}/cm^{-1}: 2956, 2869, 1188, 1105, 1027, 734, 698. MS m/z (%): 232(9), 190(12), 146(15), 118(4), 91(100). 1H NMR syn-3f: δ: 0.71(s, 9H), 1.02(d, J = 6.6 Hz, 3H), 1.12(dt, J = 2.8, 11.3 Hz, 1H), 1.29(AAXY, 1H), 2.79(dq, J = 3.0, 6.6, 11.3 Hz, 1H), 2.87(dd, J = 11.3, 2.6 Hz, 1H), 3.35(d, J = 13.5 Hz, 1H), 3.65(d, J = 13.5 Hz, 1H), 3.83(dd, J = 0.9, 9.8 Hz, 1H), 4.20(d, J = 9.8 Hz, 1H), 6.93-7.21(m, 5H). 13C NMR syn-3f: δ: 139.34, 128.74, 127.95, 126.56, 84.55, 83.34, 55.07, 48.26, 34.01, 29.41, 25.64, 20.44.

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References


18. It is well known that the reaction of NaBH₄ with neat carboxylic acids or solutions of carboxylic acids in nonprotonic solvents leads to the formation of acyloxyborohydrides.¹⁶ In order to understand the real nature of the reducing agent, studies with sodium triacetoxyborohydride are in progress.

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