Synthesis of cis- and trans-3-Aminocyclohexanols by Reduction of β-Enaminoketones

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Abstract: We describe a protocol developed for the preparation of β-enaminoketones derived from 1,3-cyclohexanediones, and their subsequent reduction by sodium in THF-isopropyl alcohol to afford cis- and trans-3-aminocyclohexanols.

Keywords: 1,3-amino alcohols; 3-aminocyclohexanols; β-enaminoketones; reduction of β-enaminoketones

1. Introduction

Amino alcohols are of great interest because of their biological and structural importance. For example, acyclic 1,3-amino alcohols are key structural components of numerous natural products [1-6], potent drugs [7,8], and components of numerous medicinal compounds such as HIV-protease inhibitors [9], μ-opioid receptor antagonists [10], potent antibiotic negamycin [11-13], serotonin reuptake inhibitor, and antidepressants [14]. Additionally, 1,3-amino alcohols are useful chiral building blocks in asymmetric synthesis functioning as chiral ligands and auxiliaries [15-23]. Despite their prevalence and the importance of acyclic 1,3-amino alcohols [24-27], there are only a few synthetic methods reported in the literature to access to this important class of compounds [28-31], and even fewer reports exist regarding the synthesis of 1,3-aminocyclohexanols [32-34]. We wish to report
herein our results on the reduction of β-enaminoketones, leading to the synthesis of both cis- and trans-3-aminocyclohexanols.

2. Results and Discussion

Our method starts with the condensation reaction of 4,4-dimethyl-1,3-cyclohexanediione with either benzylamine or (S)-α-methylbenzylamine in toluene at reflux, conditions that lead to the β-enaminoketones 1 and 2 in 85 and 87% yield, respectively (Scheme 1) [35,36]. Both products were fully characterized by NMR spectroscopy and the stereochemistry was corroborated by their X-ray crystal structure [37] (Figure 1).

Scheme 1. Preparation of β-enaminoketones 1 and 2.

Figure 1. X-Ray structure of β-enaminoketone 2.

In a subsequent step, the reduction of β-enaminoketones 1 and 2 was carried out following a procedure described in the literature [38-45]. Thus, the reaction of 1 and 2 with sodium in a mixture of THF/isopropyl alcohol at room temperature afforded the corresponding diasteromeric mixture of amino alcohols 3 and 4 in 77 and 75% yield, respectively (Scheme 2).
Scheme 2. Reduction of β-enaminoketones 1 and 2.

A percolation of the reaction mixture followed by GC-MS analysis using a cyclosil-B chiral column revealed the presence of four major stereoisomers in identical ratio for compound 3 and two stereoisomers for compound 4 (cis and trans in 89:11 ratio). The diastereoisomeric separation of 3 was not attempted; however, column chromatography separation of 4 afforded the cis-4 and trans-4 in 69 and 6% yield, respectively.

Considering the X-ray structure of β-enaminoketone 2, a reasonable explanation of the high cis:trans diastereoselectivity in its reduction step can be explained assuming that the allyl anion A obtained by successive electron-transfers from the sodium to the conjugate system of enaminone, is the more stable conformation, because it avoids the interaction of C-10 or Ph with C2-H observed in conformation B. Thus, protonation with isopropyl alcohol of the corresponding allyl anion in the conformation A takes place selectively from the bottom-face, since the top-face is hindered by the methyl group (Figure 2).

Figure 2. Plausible explanation of the diastereoselectivity in the reduction of 2.

Additionally, structural elucidation for cis-4 and trans-4 was accomplished through 1H- and 13C-NMR, as well as 2D NMR spectra like COSY, HSQC and NOESY. Spectra data for cis-4 and trans-4 are shown in Table 1. In the 1H-NMR spectra of compound cis-4, protons H1 and H3 exhibit a triplet of triplets multiplicity, with coupling constants of 11.2, 4.8 Hz and 11.6, 4.0 Hz, respectively. Analysis of these coupling constants confirms the axial disposition of both protons establishing then an equatorial distribution of the OH and NHR groups. Additionally, proton H2b presents a quadruple signal (\( J = 11.6 \) Hz) which determines its axial position whereas H2a is occupies an equatorial position. The multiplicity of H4a (ddt) shows three couplings constants \( ^2J = 12.8 \) Hz, \(^3J_{ec/ax} = 3.6 \) Hz and \(^4J_{H4a/H6a} = 2 \) Hz, this scalar coupling establishes that H1 and H3 occupy axial positions (Figure 3).
Table 1. $^1$H And $^{13}$C-NMR chemical shifts for the compounds cis-4 and trans-4.

| Proton   | cis-4 $^1$H δ(ppm), $J$ (Hz) | Carbon | cis-4 $^{13}$C δ (ppm) | trans-4 $^1$H δ(ppm), $J$ (Hz) | trans-4 $^{13}$C δ (ppm) |
|----------|-------------------------------|--------|-------------------------|--------------------------------|--------------------------|
| H1       | 3.65 (tt, $J = 11.2, 4.8, 1$H) | C1     | 66.8                    | 3.64 (tt, $J = 10.8, 4.4, 1$H) | 67.1                     |
| H2a      | 2.13 (m, $J_{gon} = 11.6, 1$H) | C2     | 43.3                    | 2.35 (ddddd, $J = 11.6, 5.6, 4.2, 1$H) | 42.6                     |
| H2b      | 1.07 (q, $J = 11.6, 1$H)      | C2     | 43.3                    | 0.94 (bq, $J = 10.2, 1$H)       |                          |
| H3       | 2.53 (tt, $J = 11.6, 4.0, 1$H) | C3     | 49.5                    | 2.59 (tt, $J = 11.6, 4.0, 1$H)   | 49.3                     |
| H4a      | 1.70 (dddt, $J = 12.8, 3.6, 2.0, 1$H) | C4 | 44.7                    | 1.50 (m, 1H)                  | 46.5                     |
| H4b      | 0.97 (t, $J = 12.0, 1$H)      | C4     | 44.7                    | 0.99 (t, $J = 12.0, 1$H)       |                          |
| H5       | - -                           | C5     | 31.8                    | - -                            | 31.7                     |
| H6a      | 1.63 (dddt, $J = 12.4, 4.0, 2.0, 1$H) | C6 | 48.1                    | 1.63 (dddt, $J = 12.4, 4.0, 2.0, 1$H) | 48.4                     |
| H6b      | 0.97 (t, $J = 11.8, 1$H)      | C6     | 48.1                    | 1.04 (bq, $J = 12.0, 1$H)       |                          |
| H7       | 0.97 (s, 3H)                  | C7     | 33.3                    | 0.93 (s, 3H)                  | 33.2                     |
| H8       | 0.70 (s, 3H)                  | C8     | 26.0                    | 0.75 (s, 3H)                  | 26.2                     |
| H9       | 4.00 (q, $J = 6.4, 1$H)       | C9     | 55.1                    | 4.03 (q, $J = 6.8, 1$H)       | 54.8                     |
| H10      | 1.42 (d, $J = 6.4, 3$H)       | C10    | 24.3                    | 1.40 (d, $J = 6.8, 3$H)       | 24.9                     |
| C6H5     | 7.30–7.38 (m, 5H)             | Cipso  | 144.3, 128.7, 127.3, 126.8 | 7.32–7.35 (m, 5H)             | 145.4, 128.7, 127.1, 126.7 |
| NH, OH   | 2.37 (bs, 2H)                 | - -    | 2.01 (bs, 2H)           | - -                            |                          |

The coupling pattern shown by compound cis-4 establishes a syn diequatorial distribution of the OH and NHR groups. A NOESY experiment (Figure 4) carried out on this compound, shows that H1 interacts with H3 and both protons are close to the equatorial H2a. In addition, H2b, H6b and H4b show dipolar couplings confirming the analysis of the coupling constants described previously.

The $^1$H-NMR spectra of the compound trans-4 displays similar data to those observed for the cis-4 stereoisomer, the main difference being the chemical shift for protons H2a, H2b, and H4a. On the other hand, its $^{13}$C-NMR data shows that C4 is shifted downfield by 2.0 ppm. This can be attributed to a lesser ring strain around this atom. In addition, the coupling pattern for proton H2a is different due to dihedral angles variations (Figure 5).
Figure 4. NOESY experiments for cis-4 (CDCl₃, 400 MHz).

Figure 5. Multiplicity of the protons H₂ec for compounds cis-4 and trans-4.

Compound trans-4 shows a triplet of triplets for the H₁ and H₃ protons (\( J = 11.8, 4.4 \) Hz and \( J = 11.6, 4.0 \) Hz respectively), which are similar to those observed for cis-4. However, in the NOESY experiment (Figure 6) these two protons do not interact spatially, suggesting an anti-arrangement of the hydroxyl and amino groups.
In order to establish the relative configuration at C-1 and C-3 of compound 4, we also carried out a NOESY experiment (Figure 7). If a chair conformation is considered for compound trans-4 (A), the fact that H₃ has a dihedral angle below 60° with respect to H₂a, H₂b, H₄a and H₄b, would generate coupling constants with magnitude around ~3–5 Hz according to the Karplus rule, however, this is not observed in the spectrum of this compound.

These experimental data thus confirm that the compound trans-4 does not adopt a chair conformation as its isomer cis-4 does. Therefore, we carried out an additional NOESY experiment in order to establish the relative configurations at C-1 and C-3, analyzing the coupling constants and spatial interactions of the two possible conformations C and D (Table 2).
Table 2. NOE interactions for H1, H3, H4eq and H6eq.

| Proton | cis-4                           | trans-4                        |
|--------|---------------------------------|--------------------------------|
| 1      | 3, 2eq, 4eq, Meupfield           | 2eq, 6eq                       |
| 3      | 1, 2eq, 4eq, 7ax                | Meupfield, 4eq                 |
| 6eq    | -                               | 6eq, Medownfield               |
| 4eq    | -                               | Me-7, Me-8                     |

In conformation D, proton H3 shows a dihedral angle larger than 120° with H2a and H4a, this spatial arrangement exhibits coupling constants of ~12.0 Hz, and the coupling with H2b and H4b of 4.0 Hz. On the other hand the NOESY experiment shows the spatial proximity of H4b to both methyl groups at C5, and of proton H1 to both H2a and H6a. In addition the fact that proton H3 shows a proximity to H4b, suggests a boat conformation for compound trans-4. The shielding of H4a is caused by the proximity of the NHR substituent, the torsional effect and the steric hinderance of the boat conformation explains the variation of the chemical shift of C4 in comparison to that of compound cis-4.

3. Experimental

Reagents were obtained from commercial suppliers and were used without further purification. Melting points were determined in a Fischer-Johns apparatus and are uncorrected. NMR studies were carried out with Varian Gemini 200 and Varian Inova 400 instruments using TMS as a standard (1H, 13C). Chemical shifts are stated in parts per million. IR spectra have been recorded on a Bruker Vector 22 FT spectrophotometer. The diastereoisomeric composition were determined by GC-MS on the HP 5989A, Cyclosil-B column, 30 m, 0.25 mm (ID), 0.25 μm (film), transfer line 220 °C, injection 220 °C, and HRMS in Jeol JMS 700 equipment. X-ray diffraction studies were performed on a Bruker-APEX diffractometer with a CCD area detector at 100 K (λMo Kα = 0.71073 Å, monochromator: graphite). Specific rotations were measured in a Perkin-Elmer 341 polarimeter at room temperature and λ = 589 nm.

3.1. General Experimental Procedures

5,5-Dimethyl-3-benzylaminocyclohexen-2-one (1). A solution of 4,4-dimethyl-1,3-cyclohexanedione (1.0 g, 7.13 mmole) and benzylamine (0.86 mL, 7.84 mmole) was refluxed in toluene (30 mL) for 3 h, while the water formed was azeotropically removed using a Dean-Stark trap. After this time, the solvent was removed under reduced pressure and the resulting yellow solid was purified by recrystallization (CH2Cl2/hexane) affording 1 (1.39 g, 85%), mp = 122–125 °C. IR (film CH2Cl2, cm⁻¹): 3,252, 3,062, 1,800, 1,545. 1H-NMR (400 MHz, CDCl3): δ 1.05 (s, 6H), 2.14 (s, 2H), 2.25 (s, 2H), 4.23 (d, J = 10.8 Hz, 2H), 5.14 (s, 1H), 5.77 (bs, 1H), 7.30 (m, 5H). 13C-NMR (100 MHz, CDCl3): δ 28.5(2), 33.0, 43.5, 47.3, 50.2, 95.9, 127.6(2), 127.9(2), 128.9, 136.9, 163.5, 196.7. HRMS Cl⁺ calcd. for C15H20NO (M⁺+1): 230.1545. Found: 230.1538.

(S)-5,5-Dimethyl-3-(α-methylbenzylamino)cyclohexen-2-one (2). A solution of 4,4-dimethyl-1,3-cyclohexanedione (1.0 g, 7.13 mmole) and (S)-α-methylbenzylamine (1.0 mL, 7.84 mmole) was refluxed in toluene (30 mL) during 3.5 h, while the water formed was removed azeotropically using a Dean-Stark trap. After this time, the solvent was removed and the yellow solid obtained was purified by crystallization (CH₂Cl₂/hexane) to give compound 2 (1.51 g, 87%), mp = 135–137 °C.
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$[\alpha]_D = -243.26$ ($c = 1, \text{CHCl}_3$). IR (KBr, cm$^{-1}$): 3,270, 3,059, 1,750, 1,542 cm$^{-1}$. $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ 1.01 (s, 3H), 1.06 (s, 3H), 1.47 (d, $J = 6.6$ Hz, 3H), 2.12 (s, 2H), 2.23 (s, 2H), 4.47 (q, $J = 6.6$ Hz, 1H), 4.97 (s, 1H), 5.62 (d, $J = 6$ Hz, 1H), 7.26 (m, 5H). $^{13}$C-NMR (50 MHz, CDCl$_3$): $\delta$ 23.6, 28.5(2), 33.1, 43.6, 50.1, 53.0, 97.1, 125.7(2), 127.5, 128.9(2), 142.9, 162.5, 196.5. HRMS Cl$^+$ calcd. for C$_{16}$H$_{22}$NO (M$^+$+1): 244.1701, found: 244.1695.

3.2. General Procedure for the Reduction of $\beta$-Enaminoketones 1 and 2

The $\beta$-enaminoketones (2.0 mmol) were dissolved in a mixture of isopropyl alcohol (2 mL) and THF (5 mL). The resulting solution was treated with an excess of small pieces of metallic sodium (0.27 g, 12.0 g-atoms) and stirred from 0 °C to room temperature until the reaction was complete (TLC). After removal of the unreacted sodium, the reaction mixture was poured into a saturated aqueous solution of NH$_4$Cl and extracted with AcOEt. The organic layers were combined, dried over Na$_2$SO$_4$ filtered and evaporated under reduced pressure. The resulting materials were submitted to an initial percolation and then were submitted to HPLC-MS analysis. The materials were separated by column chromatography (silica gel, 230–400) eluting with 65:25:10 proportions of hexane/ethyl acetate/isopropyl alcohol or 95:5, CH$_2$Cl$_2$/CH$_3$OH.

5,5-Dimethyl-3-benzylaminocyclohexanols (3a, b). Compound 3a: (97 mg, 48%). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 0.85 (s, 3H), 0.99 (s, 3H), 1.09 (m, 3H), 1.67 (m, 2H), 2.31 (m, $J_{\text{gem}} = 11.6$ Hz, 1H), 2.79 (tt, $J = 11.2, 4$ Hz, 1H), 3.75 (tt, $J = 11.2, 4.4$ Hz, 1H), 3.83 (d, $J = 12.8$ Hz, 1H), 3.85 (d, $J = 13.2$ Hz, 1H), 7.3 (m, 5H). $^{13}$C-NMR (50 MHz, CDCl$_3$): $\delta$ 26.3, 31.8, 33.3, 42.7, 45.3, 48.2, 50.9, 51.7, 66.6, 127.2, 128.4, 128.6, 139.7. MS, Cl$^+$ (M$^+$+1): 234, 216, 162, 91. HRMS calcd. for C$_{15}$H$_{24}$NO (M$^+$+1): 234.1858, found 234.1891. Compound 3b: (59 mg, 29%). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 0.89 (s, 3H), 0.99 (s, 3H), 1.04 (m, 3H), 1.6 (bs, 2H), 1.65 (ddt, $J = 12.8, 4, 2$ Hz, 1H), 1.70 (ddt, $J = 12.8, 4, 2$ Hz, 1H), 2.29 (ddd, $J = 11.6, 4, 2$ Hz, 1H), 2.76 (tt, $J = 11.2, 4$ Hz, 1H), 3.79 (m, 1H), 3.8 (d, $J = 12.8$ Hz, 1H), 3.84 (d, $J = 12.8$ Hz, 1H), 7.3 (m, 5H). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 25.9, 31.8, 33.1, 41.3, 43.2, 47.8, 49.7, 49.5, 51.7, 66.5, 128.2, 128.9, 129.3, 136.3. MS, Cl$^+$ (M$^+$+1): 234, 216, 162, 108, 106, 91. HRMS calcd. for C$_{15}$H$_{24}$NO (M$^+$+1): 234.1858, found 234.1852.

5,5-Dimethyl-3-[(S)-$\alpha$-methylbenzylamino]cyclohexanol (cis-4 and trans-4). Compound cis-4: (352 mg, 69%), $[\alpha]_D = -48$ ($c = 3.26, \text{CHCl}_3$). IR (KBr, cm$^{-1}$): 3439, 3257, 3028, 1646. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 0.70 (s, 3H), 0.97 (s, 3H), 0.97 (t, $J = 11.8$ Hz, 1H), 0.97 (t, $J = 12$ Hz, 1H), 1.07 (q, $J = 11.6$ Hz, 1H), 1.42 (d, $J = 6.4$ Hz, 3H), 1.63 (ddt, $J = 12.4, 4.2$ Hz, 1H), 1.70 (ddt, $J = 12.8, 3.6, 2.0$ Hz, 1H), 2.13 (m, $J_{\text{gem}} = 11.6$ Hz, 1H), 2.37 (bs, 2H), 2.53 (tt, $J = 11.6, 4.0$ Hz, 1H), 3.65 (tt, $J = 11.2, 4.8$ Hz, 1H), 4.00 (q, $J = 6.4$ Hz, 1H), 7.30–7.38 (m, 5H). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 24.3, 26.0, 31.8, 33.3, 43.3, 44.7, 48.1, 49.5, 55.1, 66.8, 126.8, 127.3, 128.7, 144.3. MS Cl$^+$ (M$^+$+1): 248, 247, 232, 230, 176, 105. HRMS Cl$^+$ calcd. for C$_{16}$H$_{26}$NO (M$^+$+1): 248.2014, found 248.2132. Compound trans-4: (32 mg, 6%) $[\alpha]_D = -28$ ($c = 0.24, \text{CHCl}_3$). IR (KBr, cm$^{-1}$): 3,376, 3,067, 3,029, 1,633. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 0.75 (s, 3H), 0.93 (s, 3H), 0.94 (bs, $J = 10.2$ Hz, 1H), 0.99 (t, $J = 12$ Hz, 1H), 1.04 (bs, $J = 12$ Hz, 1H), 1.40 (d, $J = 6.8$ Hz, 3H), 1.50 (m, 1H), 1.63 (ddt, $J = 12.4, 4.2$ Hz, 1H), 2.01 (bs, 2H), 2.35 (ddd, $J = 11.6, 5.6, 4.2$ Hz, 1H), 2.59 (tt, $J = 11.6, 4.1$ Hz, 1H), 3.64 (tt, $J = 10.8, 4.4$ Hz, 1H), 4.03 (q, $J = 6.8$ Hz, 1H), 7.32–7.35 (m, 5H). $^{13}$C-NMR (50 MHz, CDCl$_3$): $\delta$ 24.9, 26.2, 31.7, 33.2,
4. Conclusions

In conclusion, 1,3-amino alcohols 3 and 4 were obtained as diastereoisomeric mixtures in good yield by reduction of the corresponding β-enaminoketones 1 and 2, which were analyzed by gas chromatography/mass spectrometry using a chiral column. Two diastereomeric pairs were identified for compound 3 and two diasteromeric pairs, cis-4 and trans-4, for compound 4. Chromatographic techniques allowed the separation of cis-4 and trans-4. On the other hand, NMR NOESY experiments enabled us to establish a chair conformation and a syn-orientation of the hydroxyl and amino groups for cis-4 and a boat conformation with anti-orientation of the hydroxyl and amino groups for trans-4.

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36. Crystal data for C_{16}H_{21}NO (2), M_t = 243.34 g mol^{-1}, 0.41 × 0.34 × 0.16 mm^3, monoclinic, space group P2(1), a = 9.6513(16), b = 7.0546(11), c = 21.462(4) Å, α = 90, β = 93.259(3), γ = 90°, V = 1458.9(4) Å^3, Z = 4, ρ_{calc} = 1.108 g cm^{-3}, ϴ_{max}=25°, 5149 independent reflections, R_1 = 0.0700 for 14134 reflections with I > 2σ(I) and wR_2 = 0.1455 for all data, 2 parameters. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 841749.

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\textit{Sample Availability}: Not available.

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