Stereoselectivity of sodium borohydride reduction of saturated steroidal ketones utilizing conditions of Luche reduction

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A B S T R A C T
A series of keto steroids were reduced with sodium borohydride in the presence of cerium(III) chloride or samarium(III) iodide (Luche reduction). The ratios of axial and equatorial alcohols were determined by HPLC and the results were compared with those obtained by a standard sodium borohydride reduction. The best results were obtained with the 2-keto derivative, 7-keto derivatives and 12-keto derivative where the cerium(III) ion addition resulted in the inversion of the axial/equatorial ratios. The Luche reduction of the 20-keto derivative improved the proportion of the (20S)-alcohol in a mixture of (20S)/(20R) alcohols up to 35% from 5% in a standard sodium borohydride reduction.

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1. Introduction

Luche published [1] an efficient method for the regioselective reduction of α,β-unsaturated ketones based on treatment of an equimolecular amount of ketone and lanthanoid chloride in methanol with sodium borohydride (1 molar equivalent). During this reaction, hydrogen gas is evolved, and in 5–10 min a quantitative yield of the corresponding alcohol is obtained. Lanthanoid addition allows a highly regioselective 1,2-reduction which competes with the undesirable 1,4-reduction. Few examples can be found in the literature that use this method [2] for the reduction of saturated ketones to promote the formation of an equatorial over an axial alcohol [3–6]. This effect is most important in the case of sterically crowded ketones [7].

The mechanistic, synthetic, and stereochemical aspects of the Luche reduction have been studied and discussed [2]. The attack by a cerium ion on the carbonyl oxygen allows the formation of a cerium–steroid complex that distinctively enhances the axial attack of borohydride and the subsequent formation of an equatorial alcohol. The vigorous hydrogen gas evolution indicates the formation of alkoxyborohydrides, the actual reducing species.

Our goal was to determine the effects of Ln3+ ions on the sodium borohydride reduction of selected steroidal ketones in order to map the effects on various positions on the steroid skeleton. This method is in some cases useful for the synthesis of rare steroidal alcohols of potential biological activity.

2. Experimental

2.1. General

NMR spectra were measured on a FT NMR spectrometer Bruker AVANCE-400 (at 400 MHz for 1H and 100 MHz for 13C nuclei) in CDCl3 with tetramethylsilane as the internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (J) are given in Hz. Anhydrous methanol was obtained by treatment with magnesium turnings and distillation, anhydrous THF by distillation with LiAlH4 immediately prior to use. Before evaporation on a rotary evaporator in vacuo (bath temperature 50 °C, pressure 1.5 kPa), solutions in organic solvents were dried over anhydrous sodium sulfate. For column chromatography, Silica gel 60 (Merck, 63–100 μm) was used. Sodium borohydride (>96%, Fluka), CeCl₃·7H₂O (99%, Janssen Chimica, Belgium) and anhydrous SmI₃ (Sigma–Aldrich) were used without further purification. Anhydrous CeCl₃ was prepared by the dehydration of CeCl₃·7H₂O in a vacuum dryer at 50 °C and 2 kPa for 24 h. Other reagents were purchased from commercial sources and used without further purification. Steroidal ketones utilized in this study were obtained by generally known methods (for references see Table 1).

The identities of all steroidal ketones were examined by 1H NMR spectra and the purity by GC/MS with electron impact ionization of 70 eV on a 6890N network GC System and 5975B inert XL MSD instruments (Agilent Technologies) fitted with a capillary column (J and W 122-0132 DB-1ms) of nominal length 30 m and diameter 250 μm. The purity of all used steroids was >98%, as determined by the HPLC system consisted of High Pressure Pump (model 361, Gilson), Inject Valve Rheodyne, Preparative Column

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2.2. General procedure for NaBH₄ reduction

Sodium borohydride (5 mg, 0.13 mmol) was added to a stirred solution of a ketone (0.13 mmol) in MeOH/THF (2:1, 2.5 mL per 50 mg). The progress of the reaction was monitored by TLC. After completion (5–10 min), 5% aqueous HCl was added and the mixture was extracted with EtOAc (25 mL). The extract was washed with a saturated aqueous solution of KHCO₃, water, and was dried and evaporated in vacuo. The crude mixture of epimeric steroidal alcohols was analyzed by means of ¹H NMR spectroscopy and HPLC (for details see Section 2.2). For results see Table 1.

2.3. General procedure for Luche reduction using CeCl₃·7H₂O

Cerium(III) chloride hepthydrate (53 mg, 0.14 mmol) was added to a stirred solution of a steroidal ketone (0.13 mmol) in MeOH/THF (2:1, 2.5 mL per 50 mg). The mixture was allowed to stir at room temperature until all the chloride dissolved. Then, NaBH₄ (5 mg, 0.13 mmol) was added in small portions over 5 min. Vigorous hydrogen gas evolution occurred and the progress of the reaction was monitored by TLC. The reaction was worked up (after 10–30 min) as described in Section 2.2. For results see Tables 1 and 2.

2.4. General procedure for Luche reduction using SmI₃

Anhydrous samarium(III) iodide (37 mg, 0.14 mmol), steroidal ketone (0.13 mmol), anhydrous MeOH/THF (2:1, 2.5 mL per 50 mg), and NaBH₄ (5 mg, 0.13 mmol) under argon afforded a mixture of equatorial and axial alcohols according to Section 2.2. For results see Table 2.

2.5. General procedure for Luche reduction using anhydrous CeCl₃

Anhydrous cerium(III) chloride (35 mg, 0.14 mmol), steroidal ketone (0.13 mmol), anhydrous MeOH/THF (2:1, 2.5 mL per 50 mg), and NaBH₄ (5 mg, 0.13 mmol) under argon afforded a mixture of equatorial and axial alcohols according to Section 2.2. For results see Table 2.

2.6. Selected ¹H NMR data [chemical shifts, multiplicity, coupling constants] and compositions of mobile phases used for analysis of the alcohols produced by the reduction of steroidal ketones

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ref.</th>
<th>C=O position</th>
<th>NaBH₄</th>
<th>NaBH₄/CeCl₃</th>
<th>7H₂O</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>[20]</td>
<td>2</td>
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<tr>
<td>2</td>
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<td>3b</td>
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<td>10</td>
<td>[31]</td>
<td>17</td>
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<td>100</td>
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<tr>
<td>11</td>
<td>[32]</td>
<td>20</td>
<td>5</td>
<td>15d</td>
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</tr>
</tbody>
</table>

α Determined by HPLC analysis. Starting ketones completely converted to alcohols; axial alcohols represent complements to 100%. For details see Section 2.

β Compound 7 did not react completely.

γ Pseudoequatorial alcohols.

δ (20S)-Alcohols.

(10 mm × 250 mm) with silica gel (Biospher PSI 200, 7 μm; Labio), and a preparative ELSD Detector (Gilson) connected to a PC (software Trilution LC, Gilson).

1: ¹H NMR: 3.75 tt, J = 10.8, J = 4.5 (H-2β, ax.), HPLC in EtOAc/hexanes (7:93).
2: ¹H NMR: 3.64 p, J = 3.0 (H-3α, ax.); 3.63 tt, J = 11.1, J = 4.8, (H-3β, eq.), HPLC in EtOAc/hexanes (30:70).
3a: ¹H NMR: 3.80 m (H-6α, eq.); 3.42 m (H-6β, ax.), HPLC in EtOAc/hexanes (60:40).
3b: ¹H NMR: 3.80 m (H-6α, eq.); 3.40 m (H-6β, ax.), HPLC in EtOAc/hexanes (40:60).
4a: ¹H NMR: 3.75 q, J = 2.9 (H-6α, eq.); 3.39 m (H-6β, eq.), HPLC in EtOAc/hexanes (60:40).
4b: ¹H NMR: 3.73 m (H-6α, eq.); 3.38 m (H-6β, ax.), HPLC in EtOAc/hexanes (30:70).
4c: ¹H NMR: 3.72 q, J = 2.7 (H-6α, eq.); 3.38 m (H-6β, ax.), HPLC in EtOAc/hexanes (5:95).
5: ¹H NMR: 3.84 bm (H-7β, eq.); 3.41 ddd, J = 10.9, J = 9.2, J = 5.2 (H-7α, ax.), HPLC in EtOAc/hexanes (20:80).
6: ¹H NMR: 3.82 bm (H-7β, eq.); 3.37 ddd, J = 10.6, J = 9.5, J = 5.3 (H-7α, ax.), HPLC in EtOAc/hexanes (50:50).
7: Not completed reaction.
8: ¹H NMR: 3.98 m (H-12β, eq.); 3.42 bm (H-12α, ax.), HPLC in EtOAc/hexanes (5:95).
9: ¹H NMR: 4.45 bm (H-16β); 4.38 tdd, J = 7.8, J = 5.6, J = 2.3 (H-16α), HPLC in ether/light petroleum (30:70).
10: ¹H NMR: 3.65 t, J = 8.5 (H-17α, ps. eq.), HPLC in ether/light petroleum (30:70).
11: ¹H NMR: 3.73 dq, J = 9.8, J = 6.1 (H-20(γ/R)) 0.77 s (H-18(γ)); 3.71 dq, J = 8.3, J = 6.2 (H-20(δ)), 0.68 s (H-18(δ)), HPLC in EtOAc/hexanes (16:84).

2.7. (20R)- and (20S)-20-hydroxy-5β-pregn-3β-yl acetate (14 and 15)

Anhydrous CeCl₃ (380 mg, 1.54 mmol) was added to a solution of ketone 12 (500 mg, 1.39 mmol, Ref. [8]) in a mixture of THF (8 mL) and methanol (16 mL). After all the CeCl₃ was completely dissolved, NaBH₄ (55 mg, 1.45 mmol) was added in five portions over 5 min at room temperature. After 30 min the reaction was complete (TLC), and the mixture was poured into 5% aqueous HCl and extracted with EtOAc (50 mL). The EtOAc extract was washed with saturated aqueous KHCO₃ (2x), water, and dried. Solvents were evaporated and a crude mixture of products (500 mg) was chromatographed on a silica gel column (50 g) in a mixture of benzene/acetone (50:1). Mixed fractions were rechromatographed in a mixture of petroleum ether/acetone (50:1) to (10:1) to give 310 mg (62%) of (20R)-isomer 14 and 115 mg (23%) of (20S)-isomer 15. For
followed by 1 molar equivalent of sodium borohydride (see Section 2).

were treated either with 1 molar equivalent of sodium borohydride under standard or Luche conditions.

by 1H NMR spectroscopy, and the ratios of epimeric alcohols were determined.

and the preparation of a 6β-α alcohol in the cholestane series by Luche conditions was also described by Brunel et al. [3].

Table 1. The ratios of equatorial/axial alcohols were comparable for both the 3α- and 3β-series. In the case of 3-hydroxy (3α and 4α) and 3-acetoxy group (3β and 4β), formation of axial 6β-alcohols was favored, with the equatorial 6α-alcohols comprising only 16–20% of the mixture. No equatorial alcohols were detected in reductions of the corresponding tert-butylidimethylsilyl derivatives 3c and 4c.

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were synthesized from ketone (500 mg, 1.38 mmol, 24%) and did not change the ratio of epimers.

reported reductions with sodium borohydride alone or with the addition of alkali hydroxide required a huge excess of the reagent and several hours of boiling [14,15], conditions that should not be compatible with Luche reductions.

The reduction results of 12-ketones were similar to the 7-ketones; namely, the ratio of products was completely reversed. Reduction of 12-keto steroid 4 with sodium borohydride afforded 85% of the axial 12α-alcohol. On the contrary, when cerium(III) chloride heptahydrate was added to the reaction mixture, the ratio changed to 71% in favor of the equatorial 12β-alcohol.

D-ring ketones did not lead to any unexpected results. The addition of cerium(III) chloride heptahydrate into the reaction mixture of 16-ketone 3 did not change the ratio of epimers significantly, but a shift from 3% to 9% was observed for the 16α-alcohol. However, a notable effect was found in the presence of a vicinal 17α-hydroxy group [16].

3. Results and discussion

3.1. Sodium borohydride reduction with and without cerium(III) chloride heptahydrate

In our screening, we initially compared the stereoselectivity of the reduction of steroidal ketones 1–11 (Fig. 1) with sodium borohydride under standard or Luche conditions.

Ketones dissolved in a mixture of tetrahydrofuran/methanol were treated either with 1 molar equivalent of sodium borohydride, or with 1.1 equivalents of cerium(III) chloride heptahydrate followed by 1 molar equivalent of sodium borohydride (see Section 2). After work up, crude mixtures of alcohols were analyzed by 1H NMR spectroscopy, and the ratios of epimeric alcohols were determined by HPLC (Table 1).

Reduction of the 2-keto steroid 1 with sodium borohydride produced only 11% of the equatorial alcohol in the mixture of epimers. Under Luche conditions, the proportion of the equatorial alcohol formed increased to 55%. Luche mentioned the effect of cerium(III) on the reduction in position 3 for dihydrotestosterone [2] with the ratio changing from 81% to better than 95% in favor of the equatorial product. We obtained similar results in the 5β-series: for keto 2, the proportion of the equatorial alcohol increased from 84% to 97%.

Steric hindrance of the C-6 keto group in 3a by the C-19 methyl group led to equatorial attack by sodium borohydride and the subsequent exclusive formation of the axial 6β-alcohol. This effect was partially overcome by the addition of cerium(III) chloride heptahydrate, and the equatorial 6α-alcohol was formed in 16% of the epimeric mixture. The preparation of a 6β-α alcohol in the cholestane series by Luche conditions was also described by Brunel et al. [3].

We investigated the impact of different 3α- and 3β-substituents on the reduction of 6-keto steroids: compounds with hydroxy, acetoxy, and tert-butylidimethylsilyl group were studied (3a–4c, see Table 1). The ratios of equatorial/axial alcohols were comparable for both the 3α- and the 3β-series. In the case of 3-hydroxy (3α and 4α) and 3-acetoxy group (3β and 4β), formation of axial 6β-alcohols was favored, with the equatorial 6α-alcohols comprising only 16–20% of the mixture. No equatorial alcohols were detected in reductions of the corresponding tert-butylidimethylsilyl derivatives 3c and 4c.

In the case of the Luche reduction of 7-ketones, the ratio of products was completely reversed when compared to the standard sodium borohydride reduction: the addition of cerium(III) into the reaction mixture of 7-keto steroids 5 and 6 increased the proportion of the equatorial alcohol from 16% to 83% and 23% to 85%, respectively. This effect was used preparatively [4,5] but without details about the minor axial alcohol.

With 11-keto steroid 7, the reaction did not go to the completion in either sodium borohydride or Luche reduction conditions. Only traces of the reduction products were noticed, and increasing the amount of reagent or prolonging the reaction time had no effect. Reported reductions with sodium borohydride alone or with the addition of alkali hydroxide required a huge excess of the reagent and several hours of boiling [14,15], conditions that should not be compatible with Luche reductions.

The reduction results of 12-ketones were similar to the 7-ketones; namely, the ratio of products was completely reversed. Reduction of 12-keto steroid 8 with sodium borohydride afforded 85% of the axial 12α-alcohol. On the contrary, when cerium(III) chloride heptahydrate was added to the reaction mixture, the ratio changed to 71% in favor of the equatorial 12β-alcohol.

D-ring ketones did not lead to any unexpected results. The addition of cerium(III) chloride heptahydrate into the reaction mixture of 16-ketone 9 did not change the ratio of epimers significantly, but a shift from 3% to 9% was observed for the 16α-alcohol. However, a notable effect was found in the presence of a vicinal 17α-hydroxy group [16]. The reduction of 17-ketone 10 afforded only pseudoequatorial 17β-alcohol as in the case of standard borohydride reduction.

In the case of the 20-keto steroid 11, only a small increase in the formation of the minor (20S)-alcohol was observed (15% vs. 5%). Higher shifts were obtained when anhydrous Ce(III) and Sm(III) salts were used (see below).

3.2. Sodium borohydride reduction with anhydrous samarium(III) iodide or anhydrous cerium(III) chloride

The replacement of Ce(III) by Sm(III) in the borohydride reduction of ketones 1, 3a, 6 and 11 resulted in a significant increase of the equatorial or (20S)-alcohol (Table 2). Samarium(III) iodide addition in the reduction of the 2-keto steroid 1, the 6-keto steroid 3a, and the 7-keto steroid 6 gave 68%, 33%, and 96% of the equatorial alcohol, respectively. Most notable for its potential synthetic utility was the increased formation of (20S)-alcohol from the reduction of 20-
keto steroid 11 from 15% to 35%. The disadvantage of samarium(III) iodide is its air and moisture sensitivity compared to cerium(III) chloride heptahydrate.

In cerium(III) chloride heptahydrate, seven molecules of water compose 34% of the reagent weight. This raises the question whether water has an effect on the selectivity of the reduction. Therefore, 2-keto steroid 1, 6-keto steroid 3a, 7-keto steroid 6, and 20-keto steroid 11 were reduced in the presence of anhydrous cerium(III) chloride in anhydrous solvents (Table 2). It was found that molecules of water in cerium(III) chloride heptahydrate indeed did have an effect on the selectivity of the reduction (Table 2). In the case of 2-keto steroid 1 and 6-keto steroid 3a, reduction led to a decrease of the proportion of the equatorial alcohol from 55% to 42% and 16% to 6%, respectively. Here the use of anhydrous cerium(III) chloride resulted in a shift towards the axial alcohols, in contrast to the 7-keto steroid 6 where the formation of equatorial alcohol was nearly the same (93% vs. 85%). In contrast, reduction of 20-keto steroid 11 gave double the amount of the (20S)-alcohol, from 15% with heptahydrate, up to 31% with anhydrous cerium(III) chloride. This corresponds well with the results obtained using anhydrous samarium(III) iodide.

(20S)-Alcohol was found as an endogenous metabolite of progesterone and related compounds [17]. In addition, it is an important intermediate in the synthesis of 18-functionalized steroids using the Barton reaction [18]. Therefore, the promising result of forming a higher proportion of the (20S)-alcohol using Luche conditions, led us to analyze the reduction products formed from the reduction of 20-ketones of the 5α- and 5β-pregnane series: 20-oxo-5α-pregn-3β-yl acetate (12) and 20-oxo-5β-pregn-3α-yl acetate (13) as well (Fig. 1).

Ketones 12 and 13 were reduced similar to the 5-ene derivative 11 with the addition of anhydrous cerium(III) chloride and the desired (20S)-alcohols 15 and 17 (Fig. 2) formed 25% and 26% of the mixture of epimers, respectively. These experiments were scaled up and products were separated and characterized (See Section 2). Isolated yields were in accord with the analyses of small scale experiments: we were able to achieve 23% and 24% yields of the minor (20S)-isomers 15 and 17, respectively. It must be noted, however, that borane reductions with chiral directors were reported to give (20S)-alcohols nearly exclusively [19].

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Fig. 1. Steroidal ketones used in this study.

Fig. 2. Reduction products from 20-ketones 12 and 13.
4. Conclusions

Application of Luche reaction conditions to the reduction of a series of saturated steroidal ketones has shown in several cases a notable change of epimer ratio when compared to standard borohydride reductions. A significant influence of the cerium ion on the formation of equatorial alcohols was found especially for 2-, 7-, and 12-ketones (1, 5, 6, and 8). Reductions of 20-ketones are also affected: the increased proportion of rare (20S)-isomers provides a useful preparative application.

In our opinion, this simple and mild method may lead to cleaner reaction mixtures in some cases, and in others may give good yields of less accessible epimers. The stereochemical differentiation mediated by Luche conditions is a useful synthetic tool and deserves broader utilization.

Acknowledgments

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References

[31] Commercial product from Steraloids, m.p. 168–170°C.
[32] Commercial product from Steraloids, m.p. 140–150°C.