STEREOSELECTIVE SODIUM BOROHYDRIDE REDUCTIONS OF CYCLOPENTANONES: INFLUENCE OF CERIC CHLORIDE ON THE STEREOCHEMISTRY OF REACTION

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In this paper we describe the reduction by NaBH$_4$ of some cyclopentanones containing an oxygenated function at the side chain position β to the carbonyl group, both in the presence and in the absence of CeCl$_3$. Some suggestions for the rationalization of the results are discussed, considering the stereochemical course of the reactions.

Keywords: cyclopentanones; stereoselective reduction; sodium borohydride; ceric chloride.

In the course of our studies on the synthesis of natural products we came across the problem of stereoselectively reducing some cyclopentanones with a quaternary α-carbon atom and containing an oxygenated function at the side chain position β to the carbonyl group (general structure **A**, Figure **1**).
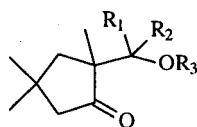
A

R$_3$ = H or alkyl

Figure 1.

As no simple solution to this problem could be found in the literature, we undertook a detailed study of the reduction of compounds **1, 2, 3** and **4** (see Scheme **1** and Table **1**). This led to a number of useful results and conclusions which we now disclose.

Gallagher *et al.*[1] demonstrated that the reduction of a cyclopentanone bearing an α-side chain containing a hydroxyl group β to the ring carbonyl function (cf. structure **A**) can be effected with low stereoselectivity by NaBH$_4$ and with high stereoselectivity by NaBH(OAc)$_3$; both reagents gave the same main product, and the results can be rationalized by assuming the generally accepted mechanism of hydroxyl group complexation to the reagent followed by intramolecular delivery of hydride to the ketone.

Luche *et al.*[2] have used CeCl$_3$ as a catalyst for regioselective 1,2 - reductions of α-enones by NaBH$_4$. They proposed that the major effect of Ce^{3+} is to catalyse the formation of alkoxyboro-hydrides, and they found low stereoselectivity in their reductions. However, Maycock *et al.*[3] have reduced a number of prostaglandin precursors, *ie.* substituted cyclopentenones, and obtained considerable stereoselectivity in some cases. There are also a few other examples of stereocontrol during reduction by the addition of CeCl$_3$ to NaBH$_4$[4].

In this paper we describe the reduction of some cyclopentanones (see Table **1**) with NaBH$_4$ in the absence (reaction conditions **A**) or in the presence (reaction conditions **B**) of CeCl$_3$. The oxygenated group β to the ring ketone function is either a hydroxyl group (compounds **2** and **3**) or an alkoxy group (compounds **1** and **4**). A remarkable difference between these two cases can be noted in the results: when a β-hydroxyl group is present, the major product of the reaction is always the isomer **a**, the addition of CeCl$_3$ having the main effect of lowering the yield. However, when a β-alkoxy group is present, CeCl$_3$ has a pronounced effect on the ratio of isomers, roughly reversing it and giving isomer **b** as the major product[5]. This selectivity is to be expected considering the near planar conformation of the five membered ring and the affinity between NaBH$_4$ (or any of its possible methoxylated derivatives) and the oxygenated functions. After complexation (and resultant activation), NaBH$_4$ should deliver the hydride from the same face as the OH or OR groups, thus producing isomer **a**. Compound **1** could give a slightly different result as a consequence of competition between steric hindrance and complexation[6]. Further evidence supporting this conclusion is given by the LiAlH$_4$ reduction of compound **1**, which produced a 3:1 ratio of isomers **5a**:**5b**, presumably due to stronger complexation between the LiAlH$_4$ and the OMe groups.

The role of CeCl$_3$ can be rationalized in at least two different ways: it can be assumed *either* that the salt forms a complex with the oxygenated functions, thus reducing the importance of NaBH$_4$ complexation and introducing additional steric hindrance, *or* that the salt acts only as a catalyst for the formation of alkoxyborohydrides from NaBH$_4$ and the solvent, enhancing the reactivity and the bulk of the reducing agent and lowering its tendency towards complexation with substrate oxygenated functions. However, the difference between the results obtained with hydroxyl and alkoxy groups would be better explained by assuming that it is due to the unequal tendency for complex formation between these groups and NaBH$_4$: the hydroxyl group would form a strong complex with NaBH$_4$, while the complex formed with alkoxy groups would be weak. It should be noted that Maycock *et al.*[3] considered, and discarded, the idea of chelation control to explain the stereochemistry of their reductions; however, their results are not really inconsistent with this interpretation, and it must be noted that they did not compare results obtained in the presence of Ce^{3+} to those obtained using only NaBH$_4$.
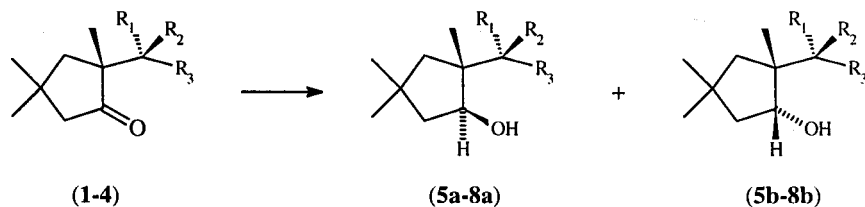
Scheme 1.

Table 1. Reduction of Cyclopentanones

starting material	R_1	R_2	R_3	reaction conditions	product[§] %	yield[¶]	ratio a:b
1	OMe	H	OMe	A	**5a** + **5b**	90	1:1[†]
				B		90	1:6[‡]
2	OH	H	CH_2CO_2Me	A	**6a** (+**6b**)	84	**6a** only
				B		75	**6a** only
3	H	OH	CH_2CO_2Me	A	**7a** + **7b**	62	**7a** only
				B		56	3:1[†]
4	OEt	H	CH_2CO_2Me	A	**8a** + (**8b**)	49	4:1[‡]
				B		90	1:5[‡]

reaction conditions: A: $NaBH_4$/MeOH/-78°C, 2h (in the case of compound **1**, the reaction temperature was 0°C). B: $NaBH_4$/MeOH/$CeCl_3 \cdot 7\ H_2O$/-78°C, 2h.

§ compound **6b** was not formed; compound **7b** slowly lactonizes to form compound **12**, but it could be isolated and characterized; compound **8b** was never isolated, as it rapidly lactonizes to give compound **13**, which was the actual indicator of the amount of **8b** obtained in the reduction.

¶ yield of crude product, calculated as if it consisted only of the mentioned isomeric products.

† ratio determined by ^{1}H NMR.

‡ ratio determined by yields after column chromatography.

Compounds **1** - **4** were prepared from the keto-aldehyde **9**[7] (Figure **2**). Treatment of **9** with trimethyl orthoformate and PTSA gave compound **1** in 77% yield[8]. We have already described the details for the preparation and analyses of compounds **2** - **4**[9]: a Reformatsky reaction on compound **9** with methyl bromoacetate and zinc in Et_2O/C_6H_6 at reflux furnished a mixture of products **2** and **3** in a ratio of 2:1, and a yield of 60%; compound **4** was obtained in 56% yield by treating **2** with $Et_3O^+BF_4^-$ and K_2CO_3 in CH_2Cl_2 at room temperature for 24 h.

9

10 : $R_1 = OH, R_2 = H$
11 : $R_1 = H, R_2 = OH$

12 : $R_1 = H, R_2 = OH$
13 : $R_1 = OEt, R_2 = H$

14 : α - H (*trans* - fused rings)
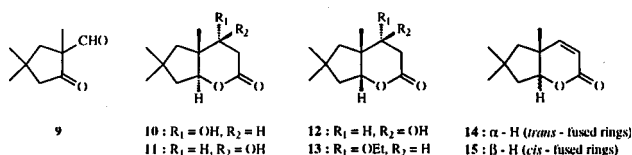**15** : β - H (*cis* - fused rings)

Figure 2.

The relative stereochemistry of compounds **5a** and **5b** was determined with the aid of NOE experiments, which showed that the carbinolic proton of isomer **5b** had a stronger signal enhancement by irradiation of the methyl group at the asymmetric carbon when compared to the carbinolic proton of isomer **5a**.

The relative stereochemistry of compounds **2**, **3**, **4** and their reduction products has already been unambiguously established by an X-ray crystallographic analysis of lactone **10**[9], obtained by treatment of compound **6a** with PPTS in benzene. Treated in a similar way, compounds **7a** and **7b** gave lactones **11** and **12**, respectively. Elimination of water from lactones **10** - **12** to produce unsaturated lactones **14** and **15** helped to establish the relative stereochemistry, because the *cis*-fused lactone **15** has a W-coupling between the hydrogen on the ring junction and the β-enone hydrogen.

EXPERIMENTAL

Reaction Conditions A

Reduction of Compound 1. A solution of compound **1** (251 mg, 1.25 mmol) in CH_3OH (10 mL) was cooled to 0°C, $NaBH_4$ (472 mg, 1.25 mmol) was added and the mixture was stirred at 0°C for 2 h. Water was then added, and the resulting mixture was diluted with water and ether, the layers were separated, and the aqueous layer was extracted with ether (5 times). The organic phase was washed with saturated NaCl solution, dried with $MgSO_4$ and concentrated under vacuum. The residue (228 mg, 90%), a pale yellow oil, consisted of a 1:1 mixture (by ^{1}H NMR) of compounds **5a** and **5b**. This mixture was separated by column chromatography (silica gel) eluting with hexane at the beginning and then adding gradually ethyl acetate to reach a maximum of 20% of ethyl acetate in hexane.

Note: Compounds **2**, **3** and **4** were reduced in a similar manner, except that the reaction temperature was -78°C.

Reaction Conditions B

Reduction of Compound 1 in the Presence of $CeCl_3$. A solution of compound **1** (54.6 mg, 0.27 mmol) in CH_3OH (5 mL) was cooled to -78°C, $CeCl_3 \cdot 7\ H_2O$ (201 mg, 0.54 mmol) was added and the mixture was stirred at -78°C for 10 min, $NaBH_4$ (12.0 mg, 0.32 mmol) was added and stirring was continued at -78°C for a further 2 h. The temperature was then raised to 0°C and the reaction was quenched and extracted as described under *reaction conditions A*. After evaporation of the solvent, a colorless oil (49.6 mg, 90%) was obtained, consisting of a 1:6 mixture of compounds **5a** and **5b**, as determined by the yields after column chromatography.

Note: Compounds **2**, **3** and **4** were reduced in a similar manner.

ACKNOWLEDGMENTS

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5. In the case of compound **1** it was not exactly a reversion, as $NaBH_4$ alone gave no stereoselectivity.[6]

6. It is also possible that the lack of stereoselectivity observed in the reduction of **1** with $NaBH_4$ is, at least partly, due to the comparatively high temperature ($0^{\circ}C$) used in this case.

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10. Spectroscopic data for compounds **1**, **5a** and **5b**. **Compound 1**: IR (liquid film) 1737, 1371, 1194, 1092, 1073 cm^{-1}; ^1H NMR (CCl$_4$, 80 MHz) d 4.01 (s, 1H), 3.38 (s, 3H), 3.34 (s, 3H), 2.29 (d, 1H, J=13.8 Hz), 2.10 (d, 1H, J=16 Hz), 1.99 (dd, 1H, J$_1$=16.0 Hz and J$_2$=1.5 Hz), 1.39 (dd, 1H, J$_1$=13.8 Hz and J$_2$=1.5 Hz), 1.16 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (CCl$_4$, 20 MHz) d 217.5, 110.1, 57.7, 56.5, 54.6, 53.7, 44.5, 32.7, 30.3, 22.2; MS *m/z* (rel. intensity) 169 (M-31)$^+$ (10), 129 (20), 115 (21), 101 (8), 75 (100), 55 (9). **Compound 5a**: IR (liquid film) 3454, 1368, 1188, 1104, 1070 cm^{-1}; ^1H NMR (CDCl$_3$, 80 MHz) d 4.04; (dd, 1H, J$_1$=7.7 Hz and J$_2$=10.1 Hz), 3.91 (s, 1H), 3.46 (s, 3H), 3.43 (s, 3H), 2.16 (br. s, 1H), 1.64 (dd, 1H, J$_1$=12.7 Hz and J$_2$=7.7 Hz), 1.53 (dd, 1H, J$_1$=12.7 Hz and J$_2$=10.1 Hz), 1.55 (d, 1H, J=13.9 Hz), 1.26 (d, 1H, J=13.9 Hz), 1.07 (s, 3H), 0.99 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (CDCl$_3$, 20 MHz) d 113.4, 74.7, 58.0, 56.6, 50.4, 48.6, 46.3, 33.1, 32.6, 32.4, 16.1; MS *m/z* (rel. intensity) 202 (M$^+$)(8), 135 (40), 111 (12), 95 (16), 85 (29), 75 (100), 69 (17). **Compound 5b**: IR (liquid film) 3466, 1372, 1186, 1107, 1070 cm^{-1}; ^1H NMR (CDCl$_3$, 80 MHz) d 4.27 (s, 1H),3.92 (t, 1H, J=5.0 Hz), 3.52 (s, 3H), 3.50 (s, 3H), 2.98 (br. s, 1H), 1.85 (d, 1H, J=13.5 Hz), 1.25 (d, 1H, J=13.5 Hz), 1.82 (dd, 1H, J$_1$=13.0 Hz, J$_2$=5.0 Hz), 1.57 (dd, 1H, J$_1$=13.0 Hz, J$_2$=5.0 Hz), 1.13 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (CCl$_4$, 20 MHz) d 110.8, 81.1, 57.5, 56.7, 52.0, 48.9, 48.6, 36.4, 33.0, 32.7, 21.2