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STEREOSELECTIVE HYDROGENATION OF UNHINDERED CYCLOHEXANONES TO AXIAL ALCOHOLS WITH RHODIUM CATALYST

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Hydrogenation of unhindered cyclohexanones with rhodium catalyst in isopropyl alcohol or tetrahydrofuran in the presence of hydrochloric acid gives excellent yields of axial alcohols. Steroidal 3,17- and 3,20-diones are selectively hydrogenated at C-3 to give the corresponding 3-axial-hydroxy ketones in high yields.

The hydrogenation of cyclohexanones with platinum catalysts in strongly acidic media has been widely applied to the synthesis of axial alcohols.[1-6] This method, however, has the following disadvantages: (a) the hydrogenation is accompanied by the hydrogenolysis to give hydrocarbons, particularly in the cases of unhindered ketones;[7] (b) the stereoselectivities are not always very high;[2,3,5,7,8] (c) when acetic acid is used as a solvent, acetylated products may be formed and neutralization of the solvent and hydrolysis of the products are often required to isolate the alcohols.[4,5,8]

Another promising method using a heterogeneous catalyst is the hydrogenation by rhodium metal. As has been reported with 4-methyl-[9] and 4-t-butylcyclohexanones[10] and 5α- and 5β-cholestan-3-ones, [11] hydrogenation with rhodium catalyst in ethanol at atmospheric pressure yields the axial alcohols in high stereoselectivities. The selectivities are further enhanced by the presence of hydrochloric acid.[12] However, under these conditions significant amounts (4-16%) of the corresponding ethoxy derivatives and small amounts of hydrogenolysis products are produced as by-products.[9,11,13] We have improved this method by using isopropyl alcohol, instead of ethanol, as the solvent.[13] By this improvement the side reactions could be depressed to the extent of less than 1% without losing the high stereoselectivities. Subsequently, the use

of tetrahydrofuran and hydrochloric acid as the medium has been found to give even better results, with almost complete depression of hydrogenolysis which is the only side reaction in this solvent. In contrast to isopropyl alcohol, with tetrahydrofuran the addition of hydrochloric acid in only very small amounts is sufficient for obtaining high stereoselectivities and excess hydrochloric acid retards the hydrogenation greatly. In Table 1 are shown the examples of the hydrogenations of typical unhindered cyclohexanones in isopropyl alcohol or tetrahydrofuran as the solvent. Thus, hydrogenation of 4-t-butylcyclohexanone with a rhodium catalyst at 25°C and atmospheric pressure gave the axial alcohol in greater than 99% yields. The yields compare with that recently reported by Krishnamurthy and Brown using lithium trisiamylborohydride.[14] Hydrogenation of 5α- and 5β-cholestan-3-ones in isopropyl alcohol/hydrochloric acid afforded the respective axial alcohol in 95.4 and 96.3% yields. The yields were improved to 97.5 and 96.6%, respectively, using tetrahydrofuran as the solvent. The yields are higher than any of those reported in the literature employing other methods.[2,3,6,15-18] In general, the hydrogenation of unhindered cyclohexanones with rhodium catalyst proceeds rather fast and can usually be completed within a few hours. Besides the high stereoselectivities, easy isolation of the products from the catalyst and solvent is another advantage of the present method.

The hydrogenation of hindered cyclohexanones with rhodium catalyst is known to proceed very slowly.[7,12,19] This nature of the rhodium catalyst can successfully be applied to the selective hydrogenation of steroidal 3,17- and 3,20-diones to the corresponding 3-axial-hydroxy ketones. Thus the 17-oxo groups of 5α- and 5β-androstane-3,17-diones were practically not hydrogenated under the present conditions and 3-axial-hydroxy-17-ones were produced in high yields as shown in Table 1. Similarly, 5α-pregnane-3,20-dione gave 3α-hydroxy-20-one in 94.8% yield. There was no indication of the epimerization at C-17 of the β-acetyl group which was reported to occur under the Henbest reduction conditions.[20,21]

The tetrahydrofuran used in this study had been treated with lithium aluminum hydride or with a ruthenium catalyst and hydrogen, followed by distillation over sodium. When an untreated tetrahydrofuran was used as the solvent, the hydrogenation proceeded very slowly and resulted in higher stereoselectivities.[22] The rhodium catalyst was prepared by reduction of rhodium hydroxide with hydrogen in water as described previously.[23]

Table 1. Stereoselective Hydrogenation of Unhindered Cyclohexanones to Axial Alcohols with Rhodium Catalyst[a)]

Ketone	Amount (mg)	Catalyst (mg)	Solvent, ml	Conc.HCl[b)] added (ml)	Reac. time (hr)	Composition of product (%)[c)] Alcohol		Other products
						Axial	Equatorial	
4-Methylcyclohexanone	100	5	THF, 2	0.001	4	90.1	9.9	0.0
4-t-Butylcyclohexanone	100	5	Pr^iOH, 2.5	0.02	3	99.2	0.5	0.3
4-t-Butylcyclohexanone	500	20	THF, 5	0.006	3	99.3[d)]	0.7	0.0
5α-Cholestan-3-one	500	10	Pr^iOH, 30	0.16	4.5	95.4[e)]	3.8	0.8
5α-Cholestan-3-one	200	20	THF, 3.5	0.004	3	97.5	2.3	0.2
5β-Cholestan-3-one	500	10	Pr^iOH, 12	0.08	4	96.3	2.7	1.0
5β-Cholestan-3-one	200	20	THF, 3	0.004	3	96.6	3.2	0.2
17β-Hydroxy-5α-androstan-3-one	30	12	THF, 2	0.002	1.3	92.0	7.9	0.1
5α-Androstane-3,17-dione	200	10	THF, 2.5	0.002	2	96.6[f)]	2.7	0.7[g)]
5β-Androstane-3,17-dione	100	6	Pr^iOH, 3	0.02	1.7	98.8[h)]	0.2	1.0
5α-Pregnane-3,20-dione	100	10	THF, 2	0.002	2.5	94.8[i)]	2.6	2.6[g)]

a) All hydrogenations were performed at 25°C and atmospheric pressure. The ketone was added after the catalyst had been shaken with hydrogen in the solvent and hydrochloric acid. b) 37% aqueous hydrochloric acid. c) Analyzed by glpc using the columns of OV-17 for the steroids with trimethylsilylation and PEG 20M for 4-methyl- and 4-t-butylcyclohexanones. In all cases no starting ketones were found in the products. d) Recrystallization of the product from 40% aqueous ethanol, as recommended by Eliel et al., in Org. Synth., 50, 13 (1970), gave pure cis-4-t-butylcyclohexanol in 73% yield (mp 82-82.3°C, greater than 99.9% purity by glpc analysis). e) When 320 mg of the product was chromatographed on silica gel, 300 mg of pure 5α-cholestan-3α-ol was obtained (mp 188-189°C, 99.8% purity by glpc analysis). f) 3α-Hydroxy-5α-androstan-17-one. g) Mostly the corresponding diols. h) 3β-Hydroxy-5β-androstan-17-one. i) 3α-Hydroxy-5α-pregnan-20-one.

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22) As an example, 17β-hydroxy-5α-androstan-3-one was hydrogenated in 24 hr with an untreated tetrahydrofuran and hydrochloric acid to give 5α-androstane-3α,17β-diol in 96.9% yield under the conditions comparable to those in Table 1.

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