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Stereoselective Introduction of Hydroxyl Groups via Hydrazones

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Synopsis. Reduction of tosylhydrazones by hydride reagents in wet alcohol gave predominantly alcohols whose stereochemistries are opposite to those of the major reduction products of the corresponding ketones with sodium borohydride.

Stereoselective introduction of hydroxyl groups is one of important reactions in organic synthesis. Particularly, interest has been focused on the diastereoselective reduction of the carbonyl group close to chiral centers. These ketones are usually attacked by hydrides from the less hindered side to give an epimer of alcohols.[1—5] In the reduction of alkylcyclohexanones by complex hydride reagents,[6,7] corresponding axial alcohols are obtained as main products, whereas soluble metal reduction of ketones has been investigated to yield equatorial alcohols in several conditions.[8,9] In the course of our investigation on the stereoselective introduction of a hydroxyl group, we found that the reduction of a tosylhydrazone by sodium borohydride in wet alcohol gives predominantly an epimer of the alcohols which is usually obtained as a minor product in the reduction of the corresponding alcohol with sodium borohydride.

Ketones were converted to corresponding tosylhydrazones with tosylhydrazide.[10] A solution of the tosylhydrazone in 2-propanol–H_2O (10 : 1) was stirred with $NaBH_4$ (7.0 equiv) for 16 h under air atmosphere at room temperature to yield alcohols. The alcohols were determined by GLC or separated by silica-gel column chromatography.

Table 1 shows the results of the reductive hydrolysis of ketone tosylhydrazones. In the reductive hydrolysis of the tosylhydrazone, the stereochemistry of the major product alcohol is inversed to that of the product in the sodium borohydride reduction of the ketone in most cases. 2-Decanone **1** was reduced to 2-decanol via the tosylhydroazone by $NaBH_4$ in the presence of H_2O in 2-propanol. Tosylhydrazone of 3,3,5-trimethylcyclohexanone **2** was reduced to 3,3,5-trimethylcyclohexanols in a ratio **2a** (eq-OH) : **2b** (ax – OH) = 75 : 25. On the other hand, $NaBH_4$ reduction of **2** gave the axial alcohol **2b** as a major product. Pregnenolone **4** was reduced via the tosylhydrzaone to yield 20-ol[α (20S) : β (20R) = 71 : 29]. Direct reduction of **4** by $NaBH_4$ gave the α-alcohol **4a** predominantly ($\alpha:\beta=11:89$), and the configuration was confirmed by comparing the chemical shift of C-21 methyl group ($\alpha:\delta=1.22$, $\beta:\delta=1.14$) with that of 5β-pregnane-3α, 20α-diol ($\delta=1.22$) by ^{1}H NMR. As the tosylhydrazone of norbornanone **5** scarcely dissovled in wet alcohol, the reduction was performed in a heterogeneous system in PhH–2-propanol–H_2O (10 : 10 : 1).

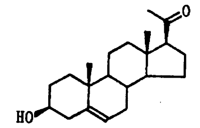
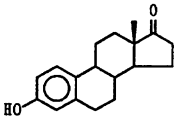
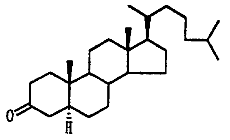
It is known that ketones can be converted into the corresponding alkanes via the hydrazones by treating $NaBH_4$ in refluxing dry MeOH.[11] On the other hand, tosylhydrazones derived from α,β-unsaturated ketones give allyl methyl ethers by the reduction with $NaBH_4$ in refluxing dry MeOH.[12] The present reductive hydrolysis of the tosylhydrozones, however, occurred just in the presence of water in alcohol. In addition, neither allyl methyl ether nor allyl alcohol was obtained from α,β-unsaturated ketone via tosylhydrazone in our reaction condition. The conversion ratio lowered in the condition of Ar atmosphere in comparison with that of air atmosphere. These results suggest that the reaction is initiated by the attack of hydride from the less hindered side and by protonation to the tosyl group with the evolution of *p*-toluenesulfinic acid. It should involve the air oxidation of diazene intermediate and the inversion of the stereochemistry by the S_N2 reaction by H_2O accompanied by the elimination of N_2 (Fig. 1).

Experimental

NMR spectra were measured with a JEOL GX-270 spectrometer in a $CDCl_3$ solution containing tetramethylsilane as an internal standard. IR spectra were measured with a JASCO IR-810 spectrometer. Volatile products were determined by GLC (Ohkura GC-202, PEG-6000, TCD).

General Procedure. Ketone (3 mmol) was converted to the corresponding tosylhydrazone by *p*-toluenesulfonylhydrazide in the presence of *p*-toluenesulfonic acid in MeOH.[10] The ketone tosylhydrazone was purified by silica-gel column chromatography (yield 50—80 %). The tosylhydrazone (1 mmol) except for that of **5** was dissolved in 30 ml of 2-propanol–H_2O (10 : 1). After $NaBH_4$ (7 mmol) was added, the reaction mixture was stirred for 16 h under air atmosphere at room temperature. Tosylhydrazone of **5** was dissolved in PhH–2-propanol–H_2O (10 : 10 : 1) and reduced in the same procedure. The alcohols obtained from **1**, **4**, **5**, **6**, and **7** were separated by silica-gel column chromatography as the mixture of α and β (or equatorial and axial) alcohols. The ratios were determined by ^{1}H NMR. The determination of alcohols derived from **2** and **3** were performed by GLC, and their structures were confirmed with ^{1}H NMR and IR spectra. ^{1}H NMR (signals for $\underline{H}$COH); **2a**: $\delta=3.75$ (1H, tt, $J=11.3$, 4.3 Hz), **2b**: $\delta=4.13$ (1H, quin, $J=3.2$ Hz), **3a**: $\delta=4.09$ (1H, br.s), **3b**: $\delta=3.38$ (1H, dt, $J=9.5$, 5.7 Hz), **5a**: $\delta=3.75$ (1H, d, $J=6.8$ Hz), **5b**: $\delta=4.26$ (1H, dt, $J=10.3$, 3.0 Hz), **6a**: $\delta=3.82$ (1H, d, $J=5.8$ Hz), **6b**: 3.67 (1H, t, $J=8.6$ Hz), **7a**: $\delta=4.03$ (1H, m), **7b**: $\delta=3.60$ (1H, tt, $J=10.8$, 5.1 Hz : (signals for $C\underline{H}_3$CHOH); **4a**: $\delta=1.22$ (3H, d, $J=6.2$ Hz), **4b**: $\delta=1.14$ (3H, d, $J=6.2$ Hz).

Table 1. Reduction of Ketone Tosylhydrazones and Ketones

		Tosylhydrazone (NaBH$_4$/2-propanol/H$_2$O) a b α-OH : β-OH (eq : ax)	yield(%)	Ketone[a)] (NaBH$_4$/2-propanol) a b α-OH : β-OH (eq : ax)
2-Decanone	**1**	—	88	—
3,3,5-Trimethylcyclohexanone	**2**	(75 : 25)	76[b)]	(14 : 86)
Menthone	**3**	(74 : 26)	57[b)]	(48 : 52)
	**4**	71 : 29	95	19 : 81
	**5**	29 : 71	49	81 : 19
	**6**	50 : 50	78	: >99
	**7**	53 : 47	87	15 : 85

a) Yields were more than 95%. b) Determined by GLC.

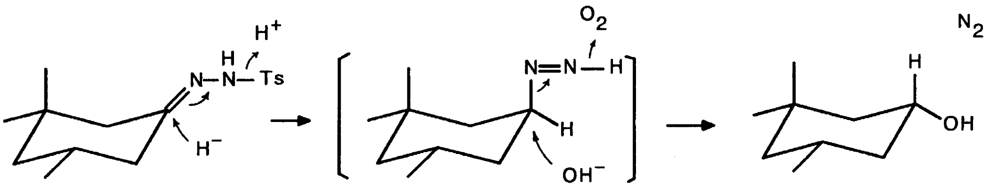


Fig. 1. Proposed reaction mechanism of the reductive hydrolysis of tosylhydrazone.

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