Notes

Selective Hydrogenations Promoted by Copper Catalysts. 2. Hydrogen-Transfer Reactions Leading to Stereoselective Hydrogenation of Δ^5-3β-Sterols to 5β-Derivatives[1]

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Introduction

Catalytic hydrogenation of 3-oxo 4-ene and 3-oxo 1,4-diene derivatives is the main route to 5β-steroids. Palladium-based systems are widely used for this purpose owing to their activity and stereoselectivity. However, in the presence of these catalysts the 5β/5α ratio strongly depends on the nature and stereochemistry of substituents as well as on the reaction medium.[2] In particular, an oxygen function at C-11 or C-17 can effectively decrease the stereoselectivity for 5β-derivatives.[3,4]

In the preceding paper of this series,[1] we reported that Cu/Al_2O_3 is an effective catalyst for the hydrogenation of 3-oxo 4-ene steroids under very mild conditions with fairly good stereoselectivity for 5β-derivatives. However, androstenedione and progesterone, having a C-17 and a C-20 oxo group, respectively, gave the lowest yield of the 5β-isomer.

In order to test also the influence of the alcoholic function at C17 on the stereoselectivity at C5, we carried out the hydrogenation of 4-androsten-17β-ol-3-one (testosterone, 1). By studying this reaction we found evidence that a hydrogen-transfer reaction takes place between the 17-hydroxyl group and the Δ^4-3-keto moiety of the molecule, both in the presence and in the absence of molecular H_2. These results suggested the use of different alcohols as donors in order to avoid the use of molecular H_2 and the possibility to modulate the products stereochemistry only by changing the hydrogenation conditions.

Here we report results obtained in the hydrogenation of some Δ^5-3β-ols in the presence and in the absence of molecular H_2 and by using secondary alcohols as hydrogen donors. They show that both hypotheses proved to be true: our system can allow for hydrogenation in the absence of molecular H_2, and very high stereoselectivity values were achieved in the hydrogenation of Δ^5-3β and $\Delta^{5,7}$-3β sterols.

Results

Hydrogenation of 1 in the presence of Cu/Al_2O_3 in toluene proceeds smoothly at 60 °C and 1 atm of H_2. However, the product distribution found after absorption of 1 equiv of H_2 is quite anomalous as only a minor amount of the expected product 17-hydroxyandrostan-3-one (2), deriving from selective addition of H_2 to the olefinic moiety of the enone function, can be found. The major products were instead 3-hydroxyandrostan-17-one (3), coming from a formal exchange between the 17β-hydroxy and the 3-oxo functional groups of 2 (Scheme I). This hydrogen-transfer reaction takes place also in the absence of molecular hydrogen. Thus, when testosterone (1) was stirred under an inert atmosphere at 60 °C in the presence of Cu/Al_2O_3, saturated diones 4 were obtained in 91% yield, while Al_3O_3 alone was found to be inactive in these conditions. It should be noted that a different product stereochemistry was found when the reaction was carried out in the absence of molecular H_2.

In order to investigate a possible hydrogen exchange in other steroidal alcohols where the Δ^4-3-keto moiety is absent, we focused our attention on Δ^5-3β-ols 5–7. These molecules are scarcely reactive toward reduction. Thus, the olefinic bond of these steroids is reduced very slowly in the presence of Pd catalysts, giving selectively the 5α isomer, whereas homogeneous systems are inactive.[2]

Results are shown in Table I. The hydrogenation of 5 and 6 in the presence of prereduced Cu/Al_2O_3 in toluene at 60 °C and 1 atm of H_2 is slow and unselective, leading to unsaturated diols as the main products. Cholesterol (7) was recovered unchanged after 24 h in these conditions. Upon raising the reaction temperature to 90 °C, we obtained not only the hydrogenation products but also saturated cholestanones.

The reaction of these substrates with the catalyst under an inert atmosphere at 60 °C for several hours confirmed the presence of an effective hydrogen exchange in all the molecules: 5 and 6 were totally converted into the corresponding saturated ketones, whereas 7 was transformed into the hydrogenated product in 76% yield at 90 °C. In every case, small amounts of 4-en-3-one derivatives were detected in the reaction products.

As a first hypothesis, we can assume that Δ^5-3-ol steroids are dehydrogenated to Δ^5-3-ones which undergo a facile isomerization to the conjugated isomers (Scheme II). Alcohol dehydrogenation in the presence of copper catalysts at high temperature has long been known.[5] In our case the presence of a good hydrogen acceptor, the enone moiety, could be the driving force to allow the reaction to occur under very mild conditions.

However, we cannot rule out that the original alcohol undergoes isomerization and dehydrogenation of the allylic alcohol formed, and a detailed investigation of the behavior of homoallylic alcohols in the presence of Cu catalysts

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Scheme I

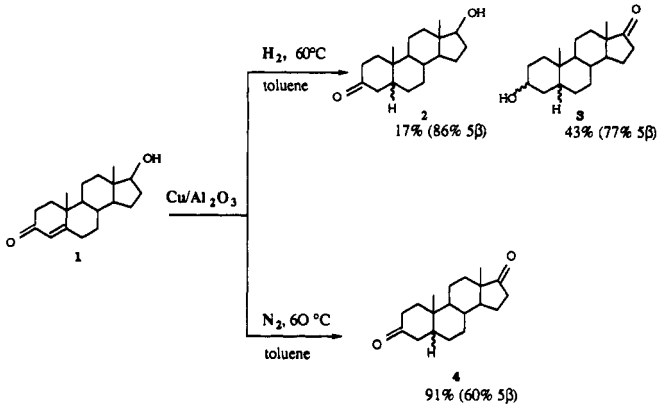
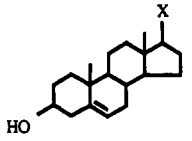


Table I. Reactivity of Δ^5-3β-Ols in the Presence of Cu/Al_2O_3 under H_2 and under N_2

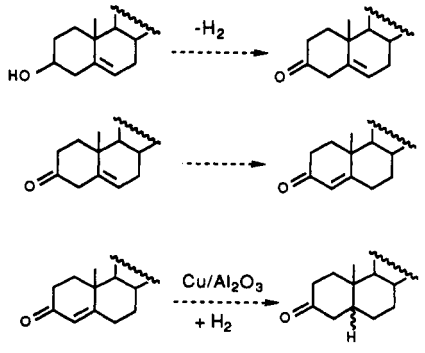


5 X= O=
6 X= β-$COCH_3$
7 X= β-C_8H_{17}

steroid	atm	solvent	T/°C	convn/%	SA[a]	SK[a]	CK[a]	UD[a]	% 5β
5	H_2	toluene	60	84	22			62	41
	N_2	toluene	60	100		88	12		72
6	H_2	toluene	60	88	41			47	12
	N_2	toluene	60	100[b]		72	5		78
7	H_2	toluene	90	97	76[c]	21			86
	N_2	toluene	90	76	34	33	9		86
	N_2[d]	toluene	90	29[e]			17		
	N_2	2-propanol	90	100	100				40
	N_2	2-octanol	140	100	100				78
	N_2	1-phenyl-ethanol	140	100	100				85
	N_2	cyclohexanol	140	100	100				95

[a] SA = saturated alcohol, SK = saturated ketone, CK = conjugated ketone, UD = unsaturated diol. [b] 23% nonidentified products. [c] 81% 3α (equatorial) epimer. [d] Catalyst Al_2O_3. [e] 12% dehydration products.

Scheme II



needs to be carried out. On the other hand, it is known that heterogeneous copper catalysts convert allyl alcohol to propanal, acrolein, and H_2 at 180–280 °C,[6] and recent surface studies show that dihydrogen is formed in stoichiometric amounts during this reaction.[7]

It is worth noting that the products obtained from 5 and 6 in the presence of molecular H_2 show different stereochemistry from those obtained under an inert atmosphere. Thus, H_2 addition to the Δ^5 olefinic bond gives mainly the 5α-isomer, whereas under N_2 the 5β-derivative is the major one, as is to be expected for molecular H_2 addition to a Δ^4-3-keto derivative in the presence of Cu/Al_2O_3.[1] In the case of 7 the same stereochemistry at C5 was found both under H_2 and under a N_2 atmosphere, suggesting that the reaction takes place always through hydrogen transfer, as supported by the presence of saturated ketones among the products and by epimerization at C3. This can be essentially due to the inertness of the Δ^5 olefinic bond of 7 toward molecular hydrogen, which requires a preliminary isomerization step also in the presence of molecular H_2.

These results suggested the possibility of modulating the product stereochemistry by moving from H_2 addition conditions to hydrogen-transfer conditions in the hydrogenation at Δ^5-3β-ols and by exploiting the isomerization reaction. We also thought it of interest to investigate whether the hydrogen-transfer reaction could be carried out using alcohols different from the substrate as hydrogen donors.

Therefore we carried out the hydrogenation of 7 under N_2 with different secondary alcohols as hydrogen donors (Table I), and we found in particular that cyclohexanol gave almost specifically the 5β-derivative. The product stereochemistry found with most of the donors is close to that observed in the hydrogenation of 4-cholesten-3-one with molecular H_2 in the presence of Cu/Al_2O_3 (84% 5β),[1] thus suggesting the occurrence of a three-step mechanism: dehydrogenation of the donor alcohol, Δ^5-3-ol to Δ^4-3-keto oxidative isomerization of the steroid, and H_2 addition to the Δ^4-3-keto derivative. Small differences in product stereochemistry can be due to solvent effect. Participation of the hydroxy group via solvation or interaction with the carbonyl group can modify the participation of the carbonyl group in adsorption on the catalyst with the double bond, as was proposed by Augustine et al. for the hydrogenation of β-octalone in the presence of Pd catalysts.[8]

Only for 2-propanol a different mechanism should be taken into account. According to Bowker and Madix the probability of alcohol dehydrogenation on the Cu surface increases with the stability of the intermediate alkoxy species and is very low for 2-propanol.[9] Thus, in this case a direct surface hydrogen-transfer reaction may take place, as was demonstrated by Burwell for the reaction between 2-propanol and 2-butanone on copper oxide.[10]

As an application of these results, we carried out the hydrogenation of ergosterol (8) (Scheme III). In this molecule a conjugated diene is present in ring B and, according to the selectivity known for copper catalysts, one of the olefinic bonds should be reduced selectively. However, such a substrate is also a Δ^5-3β-ol and therefore it should be hydrogenated from the β-face by means of isomerization and hydrogen-transfer reaction with a suitable choice of the alcohol donor. Thus, under conditions of high hydrogen availability on the catalyst surface, the Δ^5 olefinic bond was selectively reduced from the α face, whereas with cyclohexanol under N_2 pure 5β-ergosta-7,22-dien-3-ol (10) was obtained. In this latter case the

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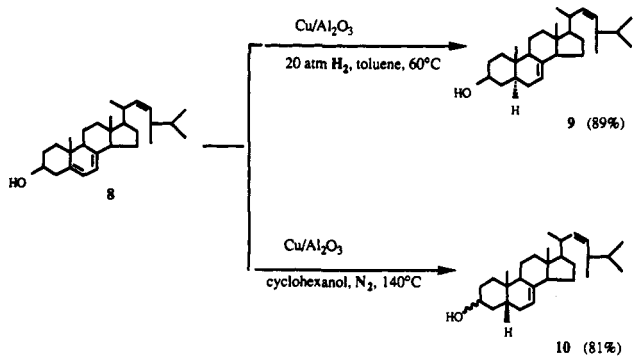
Scheme III



intermediate formation of a 3-oxo derivative is apparent from epimerization at C3.

It should be noted that this reaction is chemospecific as only the conjugated dienic moiety is hydrogenated, leaving the isolated olefinic bond at C22 unaffected. Moreover, not only is the Δ^5 olefinic bond regioselectively reduced but we can move from >98% 5α-product to >95% 5β-product by only changing the hydrogenation conditions. Analogous results were obtained in the hydrogenation of 7-dehydrocholesterol (another $\Delta^{5,7}$-3β-sterol).

The synthetic value of this reaction should also be outlined. Thus, current production of 5β-steroids from Δ^5-3-ols, readily available and cheap starting materials, requires a preliminary Oppenauer oxidation or fermentation of the Δ^4-3-keto derivative followed by catalytic hydrogenation under alkaline conditions.[11] The use of Cu/Al_2O_3 allows one to produce pure 5β-derivatives in one step.

Work is in progress now to show that these findings can be applied to a wide series of unsaturated alcohols.

Experimental Section

Solvents, RPE-ACS grade, were used without further purification. Steroids were purchased from Sigma Chemical Co. and Fluka A.G. IR spectra were recorded on a Perkin-Elmer 577 instrument; ^1H and ^{13}C NMR spectra were recorded on a Varian XL 200 instrument. GC analyses were performed on a Hewlett-Packard 5880 instrument, FI detector, equipped with (a) a methyl silicone fluid capillary column (30 m) or (b) a 35% diphenyl:65% dimethylpolysiloxane capillary column (30 m) and using *n*-hexadecane as internal standard. GC-MS analyses were performed using a Hewlett-Packard 5995 C instrument.

Reaction products were identified by comparison of their GC retention times and IR, ^{13}C NMR,[12] and MS spectra[13] with those of commercial samples or those reported in the literature. The purity of all title compounds were judged to be ≥90% by GC and ^{13}C NMR spectral determination.

Catalyst Preparation. Cu/Al_2O_3 was prepared and activated as previously reported.[1]

Hydrogenation Procedure. The steroid (0.2 mmol) was dissolved in toluene (6 mL) and the solution was heated to 60 °C and then transferred under H_2 into the reaction vessel where the catalyst (150 mg) had been previously pretreated. The final charge of H_2 was adjusted to 1 atm with a mercury leveling bulb, stirring was begun, and H_2 uptake was measured through a mercury-sealed gas burette.

After absorption of 1 equiv of H_2 (GC monitoring) on a 0.5-g scale experiment, the reaction mixture was eluted on silica with ethyl ether/hexane or toluene/hexane and the products identified.

Reactions under Inert Atmosphere. After activation and cooling of the catalyst (200 mg), the reaction vessel was evacuated and filled five times with N_2, and then the substrate solution (200 mg in 6 mL), previously prepared under N_2, was added. The solution was heated to the required temperature, and stirring was begun. For substrate 7 conversion to saturated alcohols was complete for reaction times ranging from 70 to 100 h. As 5β- and 5α-isomers give well-separated GC peaks, the stereoisomeric ratio was determined by GC analysis (column a, carrier, He; 15 psi; *T*, from 150 to 250 °C at 7 °C/min; retention times, 5β 21.1 min, 5α 22.2 min).

Hydrogenation of 7 with Cyclohexanol. The above procedure was used. After 90 h at 140 °C, GC analysis showed the 5α product to be <5%. Centrifugation of the catalyst, distillation of the solvent, and two recrystallizations from methanol gave 158 mg of pure 5β-cholestan-3-ol. Integration of the ^1H NMR spectrum showed the product to be 26% axial alcohol (3β) and 74% equatorial (3α): δ 4.09 (0.257 H, C*H* OH eq), 3.60 (0.742 H, C*H* OH ax).

5α-7,22-Ergostadien-3β-ol (9). Cu/Al_2O_3 (200 mg) was activated and transferred under N_2 into a stainless steel (AISI 316) autoclave. A solution of 8 (200 mg) in toluene (7 mL) was added under N_2. The autoclave was closed, flushed two times with H_2, and charged with 20 atm of H_2. Finally it was heated to 90 °C, and stirring was begun. After 2 h the autoclave was vented, the catalyst was removed by centrifugation, and the solvent was evaporated under reduced pressure. Recrystallization from methanol gave 178 mg of pure 5α-7,22-ergostadien-3β-ol:[14] mp 176–177 °C (lit.[15] mp 176 °C).

5β-7,22-Ergostadien-3-ol (10). The general procedure for reaction under inert atmosphere was used (200 mg Cu/Al_2O_3, 200 mg of 8, 6 mL of cyclohexanol) at 140 °C. After 4 days (about 100 h) GC analysis of the reaction mixture showed the 5α-product to be 4% of the total. The catalyst was removed by centrifugation and the solvent distilled. Recrystallization three times from methanol gave 162 mg of pure 5β-7,22-ergostadien-3-ol.[16] Integration of the ^1H NMR spectrum showed the product to be 29% axial alcohol (3β) and 71% equatorial (3α): δ 4.08 (0.287 H, C*H* OH eq), 3.63 (0.712 H, C*H* OH ax). ^{13}C NMR of the 3α isomer ($CDCl_3$): 137.4 (C8), 135.7 (C22), 131.8 (C23), 115.2 (C7), 71.3 (C3α), 55.9 (C17), 55.1 (C14), 43.6 (C13), 42.8 (C24), 40.9 (C12), 40.5 (C20), 39.8 (C9), 37.6 (C5), 36.7 (C4), 34.7 (C1), 33.5 (C10), 33.1 (C25), 31.4 (C2), 28.6 (C6), 28.2 (C16), 24.5 (C19), 22.8 (C15), 21.6 (C11), 21.1 (C21), 19.9 (C27), 19.6 (C26), 17.6 (C28), 12.1 (C18) ppm.

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Supplementary Material Available: ^{13}C NMR spectrum of compound 10 (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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