NAD(P)$^+$-NAD(P)H Models. 59. 1,2- Versus 1,4-Reduction of β,γ-Unsaturated α-Keto Ester

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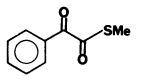
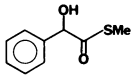
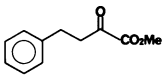
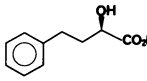
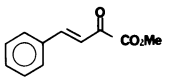
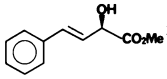
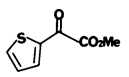
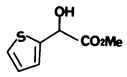
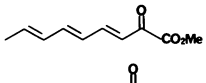
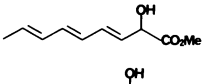
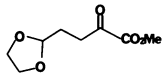
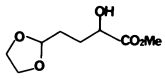
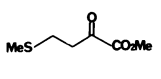
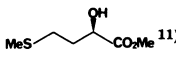
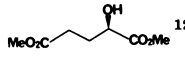
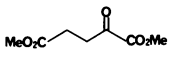
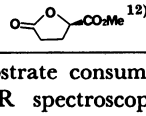
Synopsis. Depending on the reactivity of the reducing agent, β,γ-unsaturated α-keto ester is reduced into either β,γ-unsaturated α-hydroxy ester or saturated α-keto ester as the result of 1,2- or 1,4-reduction.

It has been reported that the asymmetric reduction by a chiral NAD(P)H model, *N*-(α-methylbenzyl)-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (Me_2-PNPH), is a useful tool in obtaining a chiral alcohol as a building block of natural products and many other bio-active compounds.[1] Namely, the reduction of α-keto esters results in excellent enantio-specificity. In order to extend the scope of this interesting asymmetric reduction, we further studied the reduction of α-keto esters that have various functional groups.

Table 1. Reduction of β,γ-Unsaturated and Other α-Keto Esters with 4*R*, 9*R*-Me_2PNPH

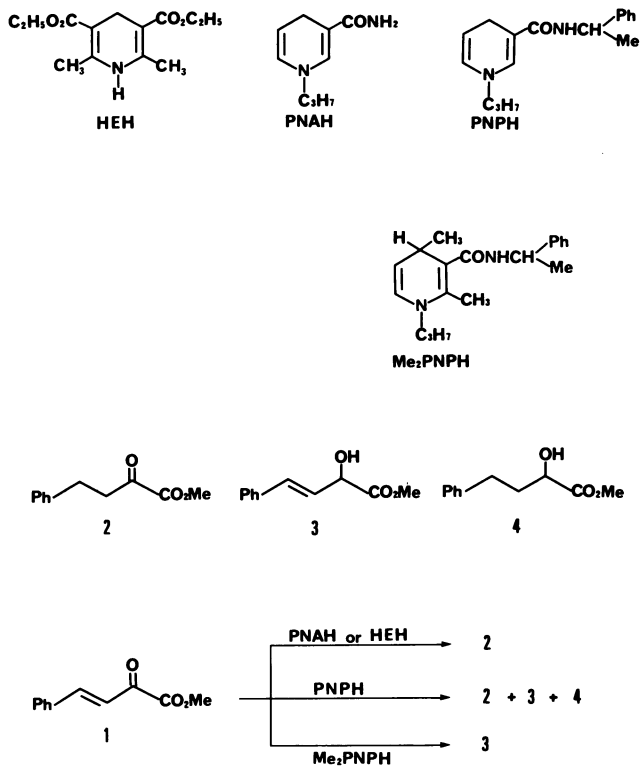
Substrate	Product	Conv. %[a]	Chem. Yield/%	e.e. %[b]
		—[c]	71[d]	86.6
		91	80[e]	63.1
		100	89[d]	95.2
		100	—[c]	93.5
		97	—[c]	76.9
		95	—[c]	75.4
		100	65[e]	95.4
		—[c]	60[e]	62.5
				
		—[c]	30[e]	62.5

a) Amount of substrate consumed. b) Determined by 400 MHz ^{1}H NMR spectroscopy and/or on VPC of the *R*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetates (MTPA esters). When the absolute configurations of the products are known, they are indicated on the structures. c) Not observed. d) Isolation yield. e) Yield measured on VPC.

Results and Discussion

The results are summarized in Table 1, which apparently shows that the presence of various functional groups in the substrate does not interfere the reduction both in chemical yield and in enantio-specificity.

Among these, the reduction of methyl (*E*)-2-oxo-4-phenyl-3-butenoate (**1**) is especially interesting. The reduction of this keto ester with 1-propyl-1,4-dihydronicotinamide (PNAH) or with the Hantzsch ester (HEH) was recently studied by Meijer and Pandit[2] and it was reported that the sole product was the corresponding saturated α-keto ester (**2**) as a result of the 1,4-reduction. Since Me_2PNPH is more reactive reducing agent than PNAH due to electron-releasing substituents, two methyl groups on the 1,4-dihydropyridine ring and an α-methylbenzyl group on the amide nitrogen, the difference in the product seems to stem from the difference in reactivity of these reagents. Therefore, we also studied the reduction with *N*-(α-methylbenzyl)-1-propyl-1,4-dihydronicotinamide (PNPH), which is expected to have medium reactivity and found that the reaction affords **2**, methyl (*E*)-2-hydroxy-4-phenyl-3-butenoate (**3**) and methyl 2-



Scheme 1.

hydroxy-4-phenylbutanoate (**4**) in 14, 14, and 7% yields, respectively (Scheme 1). Since it is known that PNPH has no ability to reduce an α-hydroxy olefin, there remains no doubt that **4** is the reduction product from **2**.

The origin of the reactivity-selectivity relationship is not known at present. However, the present result seems to support our prvious proposal that the reduction is composed of succesive transfers of an electron, a proton, and an electron: The reactivity of the reducing agent is defined by its ability for the initial electron transfer. When the activation energy for this process becomes small, the activation energy for the proton-transfer process overwhelms the former and the reaction becomes to appear as if it proceeded with the transfer of a hydrogen atom or a hydride.[3,4] Since the transfer of an electron is the orbital-controlled process, the reaction takes place at the soft reaction center, the olefinic carbon, to result in the 1,4-reduction, whereas the hydride-like species prefers to attack harder reaction center, the carbonyl-carbon, through the charge-density-controlled reaction to result in the 1,2-reduction.

Experimental

Materials. General procedures for the preparation of the 1,4-dihydronicotinamide derivatives were described in the previous papers.[1,3]

Methyl 2-oxo-4-phenyl-3-butenoate[2,5] and methyl 2-oxo-3,5,7-nonatrienoate[6] were respectively prepared according to the literature procedures. Methyl 2-oxo-4-phenylbutanoate, methyl 2-oxo-2-(2-thienyl)acetate, and methyl 2-oxo-4-(1,3-dioxolan-2-yl)butanoate were synthesized by the reaction of the corresponding Grignard reagents and dimethyl oxalate in tetrahydrofuran according to the general procedure.[7]

Methyl 2-oxo-4-(methylthio)butanoate was obtained by methylation of 2-oxo-4-(methylthio)butanoic acid, which was prepared from D,L-methionine by oxidation with D-amino acid oxidase.[8] Dimethyl 2-oxoglutalate was obtained by methylation of 2-oxoglutalic acid. *S*-Methyl 2-oxo-2-phenylethane-thioate is a kind gift from Prof. K. Ogura of Chiba University.

Procedure. The reaction was run with 1.1 equivalent amount of PNAH, PNPH, or Me_2PNPH in the presence of 1 equivalent amount of magnesium perchlorate in acetonitrile for appropriate period (about a day) under an argon atmosphere in the dark at room temperature.

Isolation of the reaction products and the method to determine the enantiomer excess by ^{1}H NMR spectroscopy and on VPC were described in the previous papers.[1,3]

References

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