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# NAD(P)$^+$-NAD(P)H Models 70. Reduction of Imines with Hantzsch Ester in the Presence of Silica Gel

Masayuki Fujii,* Tetsuo Aida, Masakuni Yoshihara,† and Atsuyoshi Ohno††
Department of Industrial Chemistry, Faculty of Engineering, Kinki University in Kyushu, Iizuka, Fukuoka 820
†Department of Applied Chemistry, Faculty of Science and Engineering, Kinki University, Higashi-Osaka 577
††Institute for Chemical Research, Kyoto University, Uji, Kyoto 611

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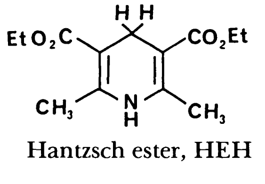
Imines are reduced into the corresponding amines in high yields by Hantzsch ester in the presence of silica gel. The reduction shows high chemoselectivity and stereoselectivity. Reduction of $\alpha,\beta$-unsaturated imines proceeds with high regioselectivity to yield allylic amines (1,2-reduction products).

The reduction of imines is very important in organic synthesis[1] and has been studied intensively, especially in connection with the syntheses of alkaloids[2]and amino acids.[3] Although there has been many investigations contributing to this subject, the procedures generally employed at the present time seem to involve certain problems to be improved. For example, a carbonyl group will be reduced into hydroxyl group by hydride reagents and a carbon-carbon double bond will be saturated by catalytic hydrogenation. These poor chemoselectivities seem to make it difficult to apply these methods to the reduction of such molecules that bear various functional groups along with an imino group.

On the other hand, from the viewpoint of biomimetic reactions of NAD$^+$-coenzymes,[4] reduction of imines[5–11] and iminium salts[12–14] as well as that of carbonyl compounds has been studied intensively. It is shown that reduction of imines with NAD(P)H models is susceptible to acid-catalysis such as proton[5–8] or metal cation.[9–11]

Recently, it was found that diethyl 2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylate (Hantzsch ester, HEH) acted as a mild and selective reducing agent for electron-defficient olefins in the presence of silica gel.[15–19] The HEH-$SiO_2$ reduction has some unique characteristic features. For example, it shows an excellent chemoselectivity, that is, olefins conjugated with a nitro, a formyl, or a keto group are reduced in quantitative yields whereas those conjugated with an alkoxycarbonyl, or a cyano group are not affected at all.[15–17] It also shows a high regioselectivity in the reduction of conjugated dienones.[18] The reduction proceeds in a manner of 1,4-reduction to afford $\gamma,\delta$-unsaturated ketones. These features of HEH-$SiO_2$ reduction system seem to be very attractive for the syntheses of certain natural products that bear various functional groups susceptible to reduction. In fact, the system was applied to the convenient syntheses of some natural products.[19] In the present paper, application of this HEH-$SiO_2$ system to the reduction of imines is described.



Hantzsch ester, HEH

## Results and Discussion

The HEH-$SiO_2$ system has been proved to be effective for the reduction of imines into the corresponding amines (Scheme 1) as it was in the reductions of certain carbon-carbon double bonds. Table 1 shows that the reduction of *N*-benzylideneaniline (**1a**) with HEH was highly accelerated by silica gel. Without silica gel, the reduction gave **2a** only in 15% yield after 12 h, whereas the reaction completed within 1 h in the presence of silica gel. Solvent effect was so significant and only nonpolar solvents such as hexane or benzene gave satisfactory results. It can be considered that polar solvents retard the adsorption of HEH and imine **1a** onto the silica gel surface. Aluminum oxide (basic or acidic) was also proved to be a good catalyst for the reduction.[20] A variety of imines derived from ketones and aldehydes were also reduced smoothly in high yields as shown in Table 2. It is

$$\underset{1}{R^1R^2C{=}NR^3} \xrightarrow[\text{benzene, 25°C or 60°C}]{\text{HEH(1.1eq.), }SiO_2} \underset{2}{R^1R^2CHNHR^3}$$

Scheme 1.

Table 1. Reduction of **1a** with HEH-$SiO_2$ or $Al_2O_3$[a]

| Catalyst[b] | Solvent | Time/h | Yield[c]/% |
|---|---|---|---|
| None | Benzene | 12 | 15 |
| $SiO_2$ | Benzene | 1 | 100 |
| $SiO_2$ | Hexane | 1 | 100 |
| $SiO_2$ | THF | 12 | 17 |
| $SiO_2$ | Acetonitrile | 12 | 51 |
| $Al_2O_3$ (Merck, basic) | Benzene | 1 | 93 |
| $Al_2O_3$ (Merck, acidic) | Benzene | 1 | 96 |

a) Reaction conditions: **1a**, 0.10 mmol; HEH, 0.11 mmol; $SiO_2$, 100 mg; solvent, 1.0 ml; 25 °C; $N_2$. b) Dried at 80 °C for several days. c) Determined on GLC analysis.

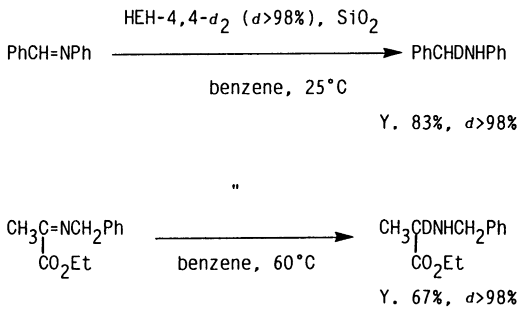
Table 2. Reduction of Imines with HEH-$SiO_2$[a)]

| 1/2 | $R^1$ | $R^2$ | $R^3$ | Time/h | Yield[b)]/% |
|---|---|---|---|---|---|
| **a** | Ph | H | Ph | 1 | 86 |
| **b** | Et | H | Ph | 3 | 78 |
| **c** | Ph | H | Bu | 3 | 83 |
| **d** | Et | H | Bu | 3 | 68 |
| **e** | Ph | $CH_3$ | Ph | 3 | 85 |
| **f** | Ph | $CH_3$ | Bu | 3 | 64 |
| **g** | $CH_3$ | $CO_2Et$ | $PhCH_2$ | 3 | 58 |
| **h** | $(CH_3)_2C{=}CH(CH_2)_2\underset{\underset{\displaystyle CH_3}{|}}{C}H-$ | H | Ph | 3 | 72 |

a) Reaction temperature: 25 °C for a, b, c, d, h. 60 °C for e, f, g. b) Isolated yield.

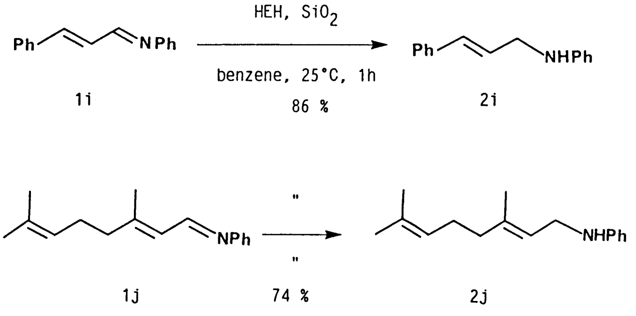
notable to find that the reductions of aldimines (**1a**—**d**, **h**) completed within 3 h at 25 °C, whereas the reductions of ketimines (**1e**—**g**) required higher temperature of 60 °C. *N*-(1-Ethoxycarbonylethylidene)benzylamine (**1g**) and *N*-(2,6-dimethyl-5-heptenylidene)aniline (**1h**) was reduced chemoselectively into *N*-benzylalanine ethyl ester and *N*-(2,6-dimethyl-5-heptenyl)aniline (**2h**) respectively. The high chemoselectivity of the HEH-$SiO_2$ system was further demonstrated by the following competition reactions. Reduction of a mixture of **1a** and 4-phenyl-3-buten-2-one (**3**), or a mixture of **1a** and *N*-(α-methylbenzylidene)aniline (**1e**) was carried out with 1.1 equivalent amounts of HEH at 25 °C. In the former reaction, **1a** was converted into **2a** in 95% yield (on GLC) in 1 h whereas most of **3** remained unchanged. An apparent predominance of **1a** over **1e** was also observed in the latter reaction. The aldimine **1a** was reduced to give **2a** in 86% yield after 1 h while only a trace amount of the ketimine **1e** was converted into **2e** within the same reaction time.

Preparation of α-deuteriated amines and α-deuteriated amino esters can be easily performed with HEH-4,4-$d_2$ ($d$>98%) (Scheme 2). Reduction of **1a** and **1g** with HEH-4,4-$d_2$ indicates that the deuterium atom was regioselectively transferred onto the carbon atom in the imine moiety without any contamination.



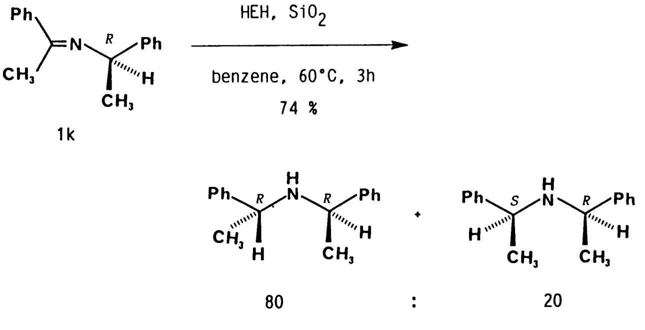
Scheme 2.

Investigation on the regioselectivity of the reduction of α,β-unsaturated imines **1i** and **1j** revealed that the reduction with the HEH-$SiO_2$ system proceeded in a manner of 1,2-reduction to afford allylic amines **2i** and **2j** (Scheme 3) which is in a flat contrast to the reduction of α,β-unsaturated ketones.[19] In the reduction of α,β-unsaturated ketones, it was reported that the 1,4- vs. 1,2-regioselectivity is affected by the reactivity of the reducing agents.[21] In the present system, since the reducing agent is kept unchanged, the difference in the regioselectivity between the α,β-unsaturated imines and ketones may reflect the difference in reactivity of the substrate.



Scheme 3. Regioselectivity in the reductions of α,β-unsaturated imines.

Substituent effect on the stereochemical properties of the present reduction were also examined. As an example of acyclic imines, reduction of (*R*)-*N*-(α-methylbenzylidene)-α-methylbenzylamine (**1k**) was carried out and the product was characterized on ${}^1$H NMR analysis[11] to contain 80% of the (*R*,*R*)-isomer and 20% of the (*S*,*R*)-isomer (Scheme 4). Reductions of methyl-substituted *N*-(cyclohexylidene)benzylamines (**1l**—**n**) represents the stereoselectivity for the cyclic systems (Table 3). The results revealed that thermodynamically more stable isomer was preferred in each case, which suggests that the reduction under-



Scheme 4. Stereoselectivity in the reduction of **1k**.

Table 3. Stereoselectivity in the Reductions of *N*-(Methylcyclohexylidene)benzylamines[a)]

| 1/2 | Substituent | Yield[b)]/% | Cis/Trans[c)] |
|---|---|---|---|
| l | 2-$CH_3$ | 85 | 18/82 |
| m | 3-$CH_3$ | 73 | 72/28 |
| n | 4-$CH_3$ | 89 | 4/96 |

a) Reactions were run in benzene at 60 °C for 3 h. b) Isolated yields. c) Determined on GLC analysis.

goes through the product-like transition state. It is notable that stronger steric effect was observed for methyl substituent at the 4-position than that at the 2 or 3-position.

Applications of the present reduction system to certain natural products are now in progress in our laboratory.

## Experimental

**Instruments.** $^1$H NMR srectra were measured at 90 MHz with a Hitachi R-90H FT-NMR spectrometer, and at 400 MHz with a JEOL GX400 Fourier Transfer NMR spectrometer. IR spectra were recorded on a JASCO IR-810 infrared spectrophotometer. Gas chromatography analyses were performed on a Shimadzu GC-12A gas chromatograph. GC-Mass spectra were measured with a Hitachi M-80A GC-Mass spectrometer.

**Materials.** Hantzsch ester (HEH) and its 4,4-dideuteriated analog (HEH-4,4-$d_2$) were prepared as reported in a previous paper.22) The deuterium content in HEH-4,4-$d_2$ was confirmed to be over 98% by 400 MHz $^1$H NMR analysis. Imines **1a**—**n** were prepared as described in the literature.23) Solvents were distilled immediately prior to the use. Silica gel (Nakarai Silica Gel 60, 35—70 mesh) was activated in an oven at 80 °C for a few days and stored in a desiccator. Other chemicals were purchased from Wako Pure Chemicals Industries Ltd. and Nakarai Chemicals Ltd.

**Reduction of Imine.** A mixture of 1.0 mmol of an imine, 293 mg (1.1 mmol) of HEH, 1.50 g of silica gel and 10 ml of absolute benzene was stirred at 25 °C (**1a**, **1b**, **1c**, **1d**, **1h**, **1i**, **1j**), or at 60 °C (**1e**, **1f**, **1g**, **1k**, **1l**, **1m**, **1n**) under a nitrogen atmosphere for an appropriate reaction time (1—3 h). The silica gel was removed by filtration and the residue was subjected to a column chromatography on silica gel using dichloromethane as an eluent to afford the corresponding amine. Chemical yields were: **2a**, 86%; **2b**, 78%; **2c**, 83%; **2d**, 68%; **2e**, 85%; **2f**, 64%; **2g**, 58%; **2h**, 72%; **2i**, 86%; **2j**, 74%; **2k**, 74%; **2l**, 85%; **2m**, 73%; **2n**, 89%.

***N*-Benzylaniline-*α*-*d* and *N*-Benzylalanine-2-*d* Ethyl Ester.** Reduction of **1a** and **1g** with HEH-4,4-$d_2$ was carried out by the same procedure as described above. The analysis of the 400 MHz $^1$H NMR spectrum revealed that the deuterium was incorporated in the α-position of the product. The deuterium content determined was 98%. Chemical yields were 83% for **2a** and 67% for **2g**.

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