

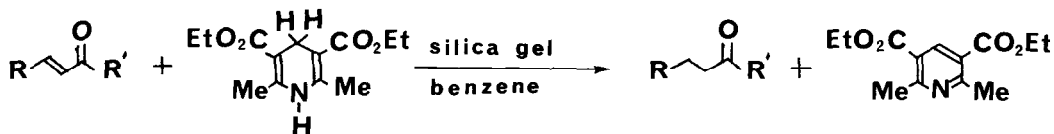
NAD(P)<sup>+</sup>-NAD(P)H MODEL. 52. REDUCTION OF OLEFINS BY HANTZSCH ESTER  
ON SILICA GEL

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*Summary:* Olefinic double bonds in  $\alpha,\beta$ -unsaturated carbonyl or nitro compounds are reduced chemoselectively by Hantzsch ester on silica gel in excellent yields.

There are several biological examples in which an enzyme catalyzes the reduction of olefinic double bond with NADH or NADPH.(1) The corresponding mimetic reduction with a model of NAD(P)H, however, has been studied much less extensively than the reduction of carbon-oxygen double bond, and the olefins so far reduced have been limited to those that are strongly electron-deficient ones.(2) Two reports have contributed to extend the scope of reduction by the aid of photoirradiation.(3) Although the photochemical process seems to be promising to extend the substrate for reduction, it usually results in the formation of an adduct of the olefin and the reductant. Namely, in the reduction of benzalacetone, the adduct is the sole product.(3b) Since most NAD(P)H models so far studied have redox potentials comparable to NADH or NADPH (4) and these coenzymes reduce olefins in enzymic systems, our effort should be concentrated for finding a suitable catalyst that behaves as a *mimetic* enzyme.

In this letter, we wish to report that silica gel is such a good catalyst as to promote the reduction of carbon-carbon double bonds in simple  $\alpha,\beta$ -unsaturated ketones and aldehydes or in  $\alpha,\beta$ -unsaturated nitro compounds. In a typical run, a mixture of 1 mmole of a substrate, 1.5 mmoles of 3,5-dicarboethoxy-2,6-dimethyl-1,4-dihydropyridine (Hantzsch ester, HEH), and 1 g of



silica gel (5) in 15 mL of benzene was kept at 80°C for 17 hr under an argon

atmosphere in the dark. Then, the solvent was evaporated from the reaction mixture and the residue was subjected either to a column chromatography on silica gel with an eluent of benzene-hexane mixture or to a preparative GLPC (PEG 20 m, 70 - 160°C), yielding the corresponding product ( $\beta$ ). Results are summarized in the Table.

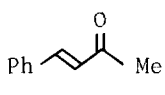
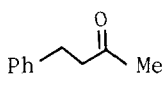
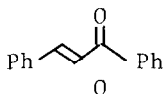
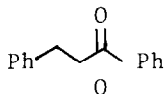
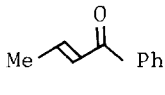
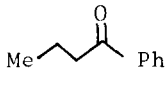
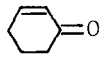
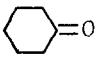
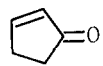
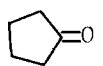
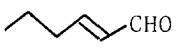
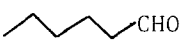
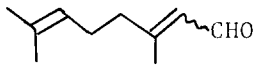
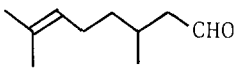
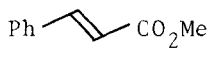
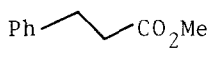


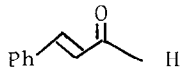
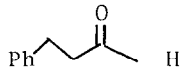


Chemoselectivity of the present reduction is quite unique: no functional groups other than carbon-carbon double bond adjacent to a carbonyl or nitro group are susceptible to the reduction. In other words, in addition to a carbonyl group itself, nitro-, cyano-, sulfinyl-, sulfonyl-, and other unsaturated functional groups are inert to the reduction. Ester function(s) is not enough to activate an olefin, which forms a striking contrast to the behavior in the photochemical reduction. Thus, the stability of composite enolate formed from the addition of a (net) hydride onto the olefinic double bond of a substrate ( $\gamma$ ) seems to be important for the reactivity of the substrate in the reduction on silica gel, whereas, in the photochemical reduction, it is known that the reactivity of a substrate is directly correlated with its one-electron reduction potential. ( $\beta b$ ) Another comparison can be made with the reduction of an  $\alpha, \beta$ -enone with 2-propanol on alumina (Meerwein-Ponndorf-Verley type reduction), where the substrate is reduced to the corresponding  $\alpha, \beta$ -unsaturated alcohol. ( $\beta$ ) Therefore, by selecting the reducing method, one can obtain either a saturated carbonyl compound or an unsaturated alcohol starting from a particular  $\alpha, \beta$ -enone under quite mild reaction conditions.

N-benzyl-1,4-dihydronicotinamide (BNAH) has frequently been used as an NAD(P)H model to reduce ketones. However, an attempt to use BNAH in place of HEH in the present system was unsuccessful, because the decomposition of BNAH was much faster than its reaction with an olefin. Although the silica gel employed for the reduction was commercially available one and subjected to the reaction without further treatment, dried material seems to be recommended because the addition of 10 weight percent of water to silica gel lowered the yield of the product remarkably (compare entry 1 with entry 4). The reaction also seems to be inhibited by oxygen: the reaction under air lowered the yield of benzylacetone to only 12%.

Although detailed mechanism of the reduction has not yet been clarified, the role of silica gel in the present reduction may be as followings: Firstly, silica gel adsorbs both HEH and a substrate to set the reductant in close proximity to the substrate. Secondly, silica gel activates the substrate as an acid catalyst. Finally, silica gel stabilizes the resulting enolate anion with a proton from water on the surface of silica gel.

Acidic, basic, and neutral alumina could also promote the reduction, although the efficiencies of these catalysts were not so good as that of silica gel (yields of benzylacetone were 79, 60, and 40%, respectively). The fact that Amberlyst H-15, a solid acid-catalyst, could not promote the reduction

Table. Reduction of Carbon-Carbon Double Bonds by Hantzsch Ester on Silica Gel<sup>a)</sup>

Entry	Substrate	Product	Yield, % <sup>b, c)</sup>	Starting Material Recovered, % <sup>b)</sup>
1			100 (97)	0
2 <sup>d)</sup>			100	0
3 <sup>e)</sup>			0	99
4 <sup>f)</sup>			42	32
5			100 (94)	0
6			82 (56)	18
7			88	12
8			100	0
9			96	3
10			67 (57)	7
11			0	100
12			20	54
13			83 (56)	15
14			100 (84)	0

- a) Reaction condition: [substrate] = 0.5 mmol, [HEH] = 0.75 mmol, silica gel = 0.5 g; 17 hr at 80°C in benzene (2 mL) under an argon atmosphere in the dark.
- b) Determined on GLPC. c) Numbers in parentheses are isolated yields after column chromatography or preparative GLPC. d) *m*-Dinitrobenzene (0.1 mmol) was added. e) *N*-Benzyl-1,4-dihydronicotinamide (BNAH) was used in place of Hantzsch ester. f) Ten weight percent of water (to silica gel) was added.

supports the above proposal on the role of silica gel; silica gel and alumina can adsorb the reactants, but Amberlyst cannot. Thus, silica gel can act not only as an acid-catalyst but also as an adsorbent to increase local concentrations of reactants. This role of silica gel resembles that of an enzyme.

A chain process involving an anion radical or a free radical as an intermediate is discarded because the addition of dinitrobenzene or hydroquinone to the reaction system exerted no effect.

It should be noted that the present reduction system has synthetic utility in the following points; a) Preparation of Hantzsch ester (HEH) is easy and HEH is stable against light and air; b) The procedure is simple. The reaction mixture can be subjected directly to a column chromatography; c) The reduction proceeds chemoselectively. Citral has two carbon-carbon double bonds but only the one adjacent to an aldehyde is reduced selectively, while the other olefinic function remains unreduced (see entry 9).

Further studies on extending the scope and limitations of the reaction, application to organic synthesis, and reaction mechanism including the search on the origin of hydrogens in the product are in progress in our laboratory.

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