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Selective Reduction of Carbon-Carbon Double Bonds with an NAD(P)H Model-Acetic Acid System

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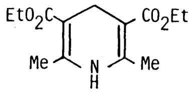
Synopsis. The carbon-carbon double bond in conjugated nitro and certain carbonyl compounds was reduced smoothly and selectively by Hantzsch ester (HEH), an NAD(P)H model, in the presence of a small amount of acetic acid.

Normally the reducing ability of NAD(P)H models is so modest that only strongly electron-deficient olefins are reduced[1)] in contrast to certain enzymatic systems where NAD(P)H reduces smoothly the carbon-carbon double bond in a conjugated carbonyl compound with the aid of dehydrogenase.[2)] In model systems, some cationic species such as proton,[3)] Lewis acid,[4)] or magnesium ion[5)] have been used as an activator. For example, an NAD(P)H model, 3,5-bis(ethoxycarbonyl)-1,4-dihydro-2,6-dimethylpyridine (Hantzsch ester: HEH) was demonstrated to reduce the carbon-carbon double bond in nitroalkenes smoothly with the aid of silica gel in benzene without any side reaction.[6)]

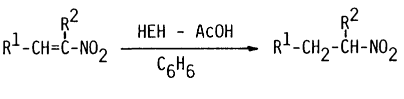

HEH

Nitroalkanes are useful intermediates because the nitro group can be easily converted to other functional groups, e.g., carbonyl,[7)] nitrile oxide,[8)] and amino group.[9)] The synthetic method used widely for nitroalkanes is the reduction of conjugated nitroalkenes with $NaBH_4$.[10)] The reaction proceeds smoothly for aliphatic nitroalkenes usually. However for aromatic nitroalkenes, side reactions such as dimerization take place affording low yields of the desired product.

In this paper we present another example of the selective reduction of conjugated aromatic nitroalkenes to nitroalkanes with HEH-acetic acid system[11)] and also describe the extension of the scope to α,β-unsaturated carbonyl compounds.

Results and Discussion

The reduction of aromatic nitroalkene **1** to nitroalkane **2** was performed usually in benzene at 80 °C using 1.3 equivalent amounts of HEH under a nitrogen atmosphere. Other solvents such as ethanol and acetonitrile could be used in place of benzene.


$$R^1\text{-CH=}\overset{R^2}{\overset{|}{C}}\text{-NO}_2 \xrightarrow[C_6H_6]{\text{HEH - AcOH}} R^1\text{-CH}_2\text{-}\overset{R^2}{\overset{|}{C}}\text{H-NO}_2$$

As shown in Table 1, even a catalytic amount of acetic acid is enough as an activator for the selective reduction of various nitroalkenes. Besides acetic acid (pK_a=4.76), several carboxylic acids such as benzoic (pK_a=4.21), formic (pK_a=3.75), and chloroacetic (pK_a=2.87) acids showed efficient activation effects in catalytic amounts whereas dichloroacetic (pK_a=1.26) and trifluoroacetic (pK_a=0.3) acids did not exert sufficient effects in the reduction of β-nitrostyrene.

Table 1. Reduction of Nitroalkene **1**

1		AcOH/HEH	Yield of **2**[a)]
R^1	R^2	molar ratio	%
C_6H_5	H	0	28
		0.04	73
		0.23	(100)[b)]
		2.30	(90)[b)]
p-$CH_3C_6H_4$	H	0.23	95
m-$CH_3OC_6H_4$	H	0.23	96
p-$CH_3OC_6H_4$	H	0.23	(95)[b)]
p-ClC_6H_4	H	0.23	95
p-$NO_2C_6H_4$	H	0.23	97
C_6H_5	CH_3	0.23	70
m-$CH_3OC_6H_4$	CH_3	0.23	85

1; 1.0 mmol, HEH; 1.3 mmol: 80 °C, 15 h in benzene.
a) Isolated yield. b) GLC yield.

The products were obtained in excellent yields irrespective of the kind of the aromatic substituent in nitrostyrenes. In every case, no formation of dimer or other side products were observed.

To clarify the substituent effect, the reactions of substituted β-nitrostyrenes were carried out with HEH-trifluoroacetic acid system. Results are shown in Fig. 1. Apparently the yield of products increased with the increase in electron-withdrawing effect of the aromatic substituent.

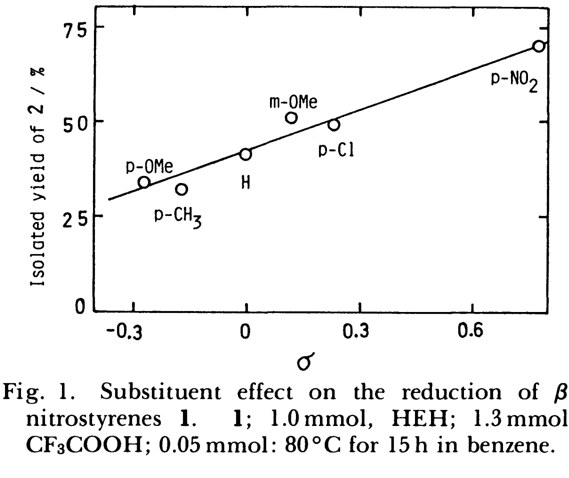


Fig. 1. Substituent effect on the reduction of β-nitrostyrenes **1**. **1**; 1.0 mmol, HEH; 1.3 mmol, CF_3COOH; 0.05 mmol: 80 °C for 15 h in benzene.

Reduction of α,β-unsaturated carbonyl compounds required more severe conditions than those of nitroalkene reduction in terms of reaction temperature and acid concentration. Thus the reactions were performed in toluene at 100 °C for 15 h using 2.3 equivalent amounts of acetic acid to HEH under a nitrogen atmosphere.

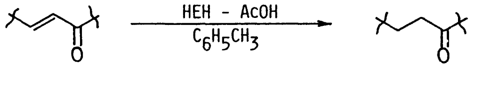


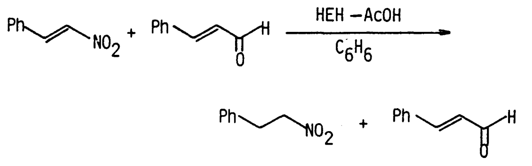
Table 2. Reduction of α,β-Unsaturated Carbonyl Compounds

Carbonyl compound	AcOH/HEH molar ratio	Yield[a] %
PhCH=CHCHO	0	9[b]
	0.3	32[b]
	2.3	61[b]
	2.3	76
$CH_3(CH_2)_2CH$=CHCHO	2.3	83
PhCH=$CHCOCH_3$	2.3	54
	(0.05)[c]	33
$(CH_3)_2C$=$CHCOCH_3$	(0.05)[c]	35
2-Cyclohexen-1-one	2.3	trace
2-Cyclopenten-1-one	2.3	13

Carbonyl compound; 1.0 mmol, HEH; 1.3 mmol: 100 °C for 15 h in toluene. a) GLC yield. b) The reaction was run in benzene at 80 °C. c) The reaction was performed in benzene at 80 °C for 5 h employing CF_3COOH instead of CH_3COOH.

Results are given in Table 2. α,β-Unsaturated aldehydes were reduced smoothly yielding saturated aldehydes. α,β-Unsaturated linear ketones were moderately reactive whereas cyclic ketones such as 2-cyclohexenone reacted only scantily. Esters like methyl cinnamate, butyl acrylate, dimethyl fumarate, dimethyl maleate, and coumarin did not take part in the reaction.

The chemoselectivity between nitroalkene and α,β-unsaturated aldehyde is noteworthy. Thus an equimolar mixture of β-nitrostyrene and cinnamaldehyde was allowed to react with 0.9 equivalent amounts of HEH in the presence of a small amount of acetic acid (acetic acid/HEH=0.3) at 80 °C in benzene for 15 h. The reduction of the β-nitrostyrene to (2-nitroethyl)benzene took place selectively in 82% yield while the cinnamaldehyde was recovered unchanged in 98%.



As a whole, the present HEH-acetic acid system exhibited somewhat weaker reducing ability than that of HEH-silica gel system[6] in the reduction of a carbon-carbon double bond. In terms of this mildness, HEH-acetic acid system revealed the marked difference in reactivity toward the linear and cyclic α,β-unsaturated ketones. Since HEH is stable and obtained easily the present method has synthetic utility.

Experimental

HEH[12] and nitrostyrene derivatives[13] were prepared according to the literature. Other materials were commercially obtained. The structures of the products were confirmed by ^{1}H NMR and IR spectra.

General Procedure for the Reduction of Nitrostyrenes. Into a 50 cm^3 flask containing nitroalkene (1.0 mmol) and HEH (1.3 mmol) were added benzene (5 cm^3) and acetic acid (0.3 mmol) under a nitrogen atmosphere. The mixture was agitated at 80 °C for 15 h. After cooling, the reaction mixture was submitted to column chromatography on silica gel eluting with hexane-ethyl acetate to afford the reduced product. The results are given in Table 1.

General Procedure for the Reduction of α,β-Unsaturated Carbonyl Compounds. Into a 50 cm^3 flask containing α,β-unsaturated carbonyl compound (1.0 mmol) and HEH (1.3 mmol) were added toluene (5 cm^3) and acetic acid (3.0 mmol) under a nitrogen atmosphere. The mixture was agitated at 100 °C for 15 h. The product was analyzed by GLC. On the employment of trifluoroacetic acid (0.05 mmol), the reaction was performed in benzene (10 cm^3) at 80 °C for 5 h. The results are shown in Table 2.

Competitive Reaction of β-Nitrostyrene and Cinnamaldehyde. β-Nitrostyrene (1.0 mmol) and cinnamaldehyde (1.0 mmol) were agitated in the presence of HEH (0.9 mmol) and acetic acid (0.27 mmol) in benzene (5 cm^3) at 80 °C for 15 h under a nitrogen atmosphere. GLC analysis revealed the formation of (2-nitroethyl)benzene in 82% yield (based on HEH). The formation of 3-phenylpropionaldehyde was negligible (ca. 2%) and the most of the cinnamaldehyde remained unchanged (ca. 98%).

References

1) B. E. Norcross, P. E. Klinedinst, Jr., and F. H. Westheimer, *J. Am. Chem. Soc.*, **84**, 797 (1962); Y. Ohnishi, M. Kagami, T. Numakunai, and A. Ohno, *Chem. lett.*, **1976**, 915; S. Fukuzumi, Y. Kondo, and T. Tanaka, *J. Chem. Soc., Perkin Trans. 2*, **1984**, 673.

2) For example: G. Weeks and S. J. Wakil, *Methods Enzymol.*, **14**, 66 (1969); C. C. Levy and G. D. Weinstein, *Biochemistry*, **3**, 1944 (1964); P. D. Show, *Biochemistry*, **6**, 2253 (1967).

3) S. Shinkai, H. Hamada, and O. Manabe, *Tetrahedron Lett.*, **1979**, 1397.

4) A. Ohno, Y. Ishihara, S. Ushida, and S. Oka, *Tetrahedron Lett.*, **23**, 3185 (1982).

5) A. Ohno, M. Ikeguchi, T. Kimura, and S. Oka, *J. Am. Chem. Soc.*, **101**, 7036 (1979).

6) K. Nakamura, M. Fujii, S. Oka, and A. Ohno, *Chem. Lett.*, **1985**, 523; K. Nakamura, M. Fujii, A. Ohno, and S. Oka, *Tetrahedron Lett.*, **25**, 3983 (1984); S. Yasui, M. Fujii, K. Nakamura, and A. Ohno, *Bull. Chem. Soc. Jpn.*, **60**, 963 (1987); M. Fujii, K. Nakamura, S. Yasui, S. Oka, and A. Ohno, *Bull. Chem. Soc. Jpn.*, **60**, 2423 (1987); S. Yasui, M. Fujii, and A. Ohno, *Bull. Chem. Soc. Jpn.*, **60**, 4019 (1987).

7) M. R. Galobardes and H. W. Pinnick, *Tetrahedron Lett.*, **22**, 5235 (1981), and references cited therein.

8) C. Grundman and P. Grunanger, "The Nitrile Oxides," Springer-Verlag, New York (1971), p. 51.

9) O. Von Schickh, G. Apel, H. G. Padeken, H. H. Schwarz, and A. Segnitz, "Houben-Weyl-Müller: Methoden der Organischen Chemie," Thieme, Stuttgart (1971), Vol. X/1.

10) H. Shechter, D. E. Ley, and E. B. Roberson, Jr., *J. Am.*

Chem. Soc., **78**, 4984 (1956); A. I. Meyers and J. C. Sircar, *J. Org. Chem.*, **32**, 4134 (1967).

11) Reduction of nitrostyrene by *N*-benzyl-1,4-dihydronicotinamide–acetic acid system has been described with unsatisfactory results; K. Wallenfels, W. Ertel, A. Hockendorf, J. Rieser, and K. H. Uberschar, *Naturwissenschaften*, **62**, 459 (1975).

12) V. Baliah, V. Gopalakrishnan, and T. S. Govindarajan, *J. Ind. Chem. Soc.*, **31**, 832 (1954).

13) D. E. Worrall, *Org. Synth.*, Coll. Vol., I, 413 (1941); H. B. Hass, A. G. Susie, and R. L. Herder, *J. Org. Chem.*, **15**, 8 (1950); S. Miyano, H. Hokari, and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, **55**, 534 (1982); B. M. Vanderbilt and H. B. Hass, *Ind. Eng. Chem.*, **32**, 34 (1940).