Tetrahedron Letters,Vol.23,No.44,pp 4585-4588,1982 0040-4039/82/444585-04$03.00/0
Printed in Great Britain

SELECTIVE REDUCTION OF KETOESTERS TO HYDROXYESTERS WITH THE USE OF LITHIUM ALUMINUM HYDRIDE IN THE PRESENCE OF SILICA GEL

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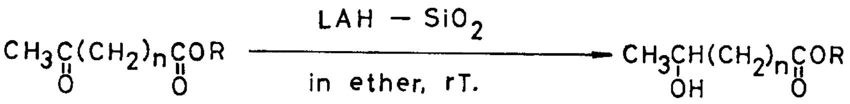
Abstract: Lithium aluminum hydride, in the presence of a small amount of silica gel, has been found to be a versatile and highly selective reagent for reduction of various ketoesters to the corresponding hydroxyesters in fair yields.

Recently we reported a series of new synthetic reactions[1~7)] with the use of silica gel as a versatile catalyst. In some of these reactions[2)] silica gel was used by itself as a mild and therefore very selective Lewis acid catalyst. In the other cases[1, 3~6)] where silica gel was used in combination with other reagents such as sulfuryl chloride, nature of the reagents was completely changed by silica gel and new reactions occurred. Later on, several oxidizing reagents[8)] which are tightly bound on silica gel were reported to be very selective oxidizing reagents, where silica gel effectively controls intrinsic activity of the reagents. In contrast, little is known about selective reductions in the presence of silica gel.

Lithium aluminum hydride has long been known as a specific reagent for reducing carbonyl compounds and carboxy esters to alcohols, and it is now widely used in organic syntheses. However, its selectivity is not sufficient to discriminate these two types of compounds. In fact ketoesters are invariably reduced to diols by this reagent. During the study on some problems in this laboratory some hydroxyesters became necessary and their syntheses prompted us to check for enhanced selectivity of lithium aluminum hydride when it is used in the presence of silica gel.

We now wish to report in this paper a new highly selective reducing agent, lithium aluminum hydride on silica gel (LAH-SiO_2). Experiments so far revealed that a small amount of added silica gel effectively increased selectivity of lithium aluminum hydride and various ketoesters were converted into corresponding hydroxyesters in fair yields.



$$CH_3\underset{\underset{O}{\|}}{C}(CH_2)_n\underset{\underset{O}{\|}}{C}OR \xrightarrow[\text{in ether, rT.}]{LAH - SiO_2} CH_3\underset{\underset{OH}{|}}{C}H(CH_2)_n\underset{\underset{O}{\|}}{C}OR$$

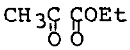
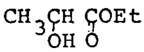
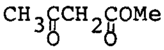
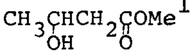
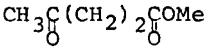
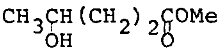
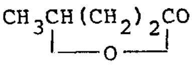
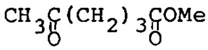
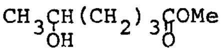
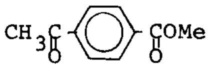
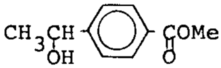
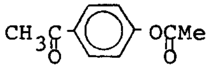
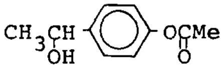
n = 0 ~ 3

The reaction proceeds quite cleanly at room temperature and the raw products were practically pure hydroxyesters. No diol was detected by ^{1}H-NMR. Work-up process of this reaction is very simple; the reaction can be carried out in the same manner as in usual lithium aluminum hydride reduction except that the hydride is mixed well with silica gel in ether just before introducing substrates. Amounts of silica gel, reaction time and temperature are all not critical in this reaction; in varying conditions essentially the same results were obtained. Data for the selective reduction of some ketoester by LAH-SiO_2 are summarized and shown in Table I.

Typical procedure for this reaction is as follows. Commercial grade silica gel (Waco gel C-300, for column chromatography) was dried at 150 ~ 170°C for 3 h under reduced pressure (5 torr.). To a mixture of silica gel (750 mg) thus prepared and LAH (1.4 mmol) was added 5 ml of dry ether under atmosphere of nitrogen. There occurred spontaneous evolution of some hydrogen. After stirring for 2 h, 1 mmol of methyl 4-acetylbutyrate was added to the mixture and stirring was continued for another 3 h. The whole mixture was then heated9) to reflux temperature and kept for 15 min. After cooling and quenching with few drops of saturated aqueous solution of ammonium chloride, the mixture was filtered and the silica gel was washed thoroughly with ether. The filtrate and washings were combined and the solvent was removed to give 84 % yield of methyl 5-hydroxyhexanoate as colorless oil. This product was found to be practically pure by ^{1}H-NMR and neither starting material nor the diol was detected. In control experiments where no silica gel was added, considerable amounts of the diol was found in the raw product, even if quantity of LAH was reduced to 1/4 equivalent of the starting material.

Selective reductions by LAH-SiO_2 were successfully performed with ethyl pyruvate, methyl acetoacetate and methyl levulinate to afford corresponding hydroxyesters in similar conditions (No. 1 ~ 4). In the case of methyl levulinate (No. 3), however, about a half of the product was obtained as the corresponding lactone. Since no hydrolysis occurred during reductions of other ketoesters, this lactone would be resulted *via* formation of the hydroxyester followed by intramolecular attack of the hydroxyl on the ester group during the reaction. Selective reduction was further examined with two types of

Table I Selective Reduction of Ketoesters to Hydroxyesters by LAH - SiO_2.

No.	Substrate	Product	Yield* (%)	IR (ν_{CO};cm^{-1})	^{1}H-NMR (δ;ppm)
1	 $CH_3\underset{\underset{O}{\|}}{C}\underset{\underset{O}{\|}}{C}OEt$	 $CH_3\underset{OH}{CH}\underset{\underset{O}{\|}}{C}OEt$ 10)	61	1743 (1740) 17)	4.25 (q, 3H, OCH_2, CH) 1.43 (d, 3H, $CHC\underline{H}_3$) 1.29 (t, 3H, $CH_2C\underline{H}_3$)
					[4.26 (q, OCH_2, CH) 1.44 (d, $CHC\underline{H}_3$) 1.30 (t, $CH_2C\underline{H}_3$)] 18)
2	 $CH_3\underset{\underset{O}{\|}}{C}CH_2\underset{\underset{O}{\|}}{C}OMe$	 $CH_3\underset{OH}{CH}CH_2\underset{\underset{O}{\|}}{C}OMe$ 11)	75	1732	4.20 (se, 1H, CH) 3.70 (s, 3H, OCH_3) 2.46 (d, 2H, CH_2) 1.24 (d, 3H, CH_3)
3	 $CH_3\underset{\underset{O}{\|}}{C}(CH_2)_2\underset{\underset{O}{\|}}{C}OMe$	 $CH_3\underset{OH}{CH}(CH_2)_2\underset{\underset{O}{\|}}{C}OMe$ 12)	42 16)	1733 (1735) 13)	3.83 (se, 1H, CH) 3.70 (s, 3H, OCH_3) 2.47 (t, 2H, CH_2CO) 2.00 ~ 1.57(m, 2H, CH_2) 1.22 (d, 3H, CH_3)
		 $CH_3CH(CH_2)_2CO$ 13)	44	1782 (1780) 13)	4.90 ~ 4.40 (m, 1H, CH) 2.80 ~ 1.57 (m, 4H, CH_2) 1.43 (d, 3H, CH_3)
					[4.90 ~ 4.40 (m, CH) 2.80 ~ 1.60 (m, CH_2) 1.44 (d, CH_3)] 19)
4	 $CH_3\underset{\underset{O}{\|}}{C}(CH_2)_3\underset{\underset{O}{\|}}{C}OMe$	 $CH_3\underset{OH}{CH}(CH_2)_3\underset{\underset{O}{\|}}{C}OMe$ 13)	84	1738	3.80 (se, 1H, CH) 3.70 (s, 3H, OCH_3) 2.37 (t, 2H, CH_2CO) 2.00 ~ 1.03 (m, 4H, CH_2) 1.17 (d, 3H, CH_3)
5		 14)	84	1718	7.79, 7.38 (q, 4H, Ar) 4.92 (q, 1H, CH) 3.88 (s, 3H, OCH_3) 1.49 (d, 3H, CH_3)
6		 15)	82	1755	7.48 ~ 6.58 (m, 4H, Ar) 4.82 (q, 1H, CH) 2.23 (s, 3H, CH_3CO) 1.46 (d, 3H, CH_3)

* Isolated yield. All raw products proved essentially pure by ^{1}H-NMR.

aromatic ketoesters (No 5 and 6), too. In both cases expected hydroxyesters were obtained as sole products.

The high keto-ester selectivity produced by the presence of silica gel seems surprising and LAH -SiO_2 will be used as an alternative versatile reagent for preparing hydroxyesters. Further works including possibility of this reagent for another use in organic synthesis are now in progress in this laboratory.

References and notes

1) M. Hojo and R. Masuda, *Synth. Comm.,* 5, 173 (1975).
2) M. Hojo and R. Masuda, *ibid.,* 5, 169 (1975).
3) M. Hojo and R. Masuda, *Tetrahedron Lett.,* 613 (1976).
4) M. Hojo and R. Masuda, *Synthesis,* 678 (1976).
5) M. Hojo, R. Masuda, T. Saeki, K. Fujimori and S. Tsutsumi, *Tetrahedron Lett.,* 3883 (1977).
6) M. Hojo, R. Masuda and K. Hakotani, *Tetrahedron Lett.,* 1121 (1978).
7) For reviews, see M. Hojo and R. Masuda, *J. Synth. Org. Chem., Japan,* 37, 557; 37, 689 (1979); A. McKillop and D. W. Young, *Synthesis,* 401 (1979).
8) For example, S. L. Regen and C. Koteel, *J. Am. Chem. Soc.,* 99, 3837 (1977); E. Santaniello, E. Ponti and A. Manzocchi, *Synthesis,* 534 (1978); Z. Cohen, E. Keinan, Y. Mazur and T. H. Varkony, *J. Org. Chem.,* 40, 2141 (1975).
9) In one experiment without this heating, essentially the same result was obtained.
10) A. W. Smith and C. E. Boord, *J. Am. Chem. Soc.,* 48, 1512 (1926).
11) E. Fischer and H. Scheibler, *Chem. Ber.,* 42, 1219 (1909).
12) I. Hayashi, *Kogyo Kagaku Zasshi,* 60, 280 (1957).
13) H. Machleidt, E. Cohnen and R. Tscheche, *Justus Liebigs Ann. Chem.,* 655, 70 (1962).
14) W. S. Emerson, J. W. Heyd, V. E. Lucas, E. C. Chapin, G. R. Owens and R. W. Shortridge, *J. Am. Chem. Soc.,* 68, 674 (1946).
15) Satisfactory elemental analysis was given for this compound; calc'd. for $C_{10}H_{10}O_3$: C, 66.65; H, 6.71. Found: C, 66.92; H, 6.75 %.
16) Hydrolysis of this ester in 1 N aqueous solution of KOH followed by acidification with dil. HCl to pH 1~2 afforded γ-valerolactone.
17) " The Aldrich Library of Infrared Spectra", 3rd Ed., 388 F.
18) " The Aldrich Library of NMR Spectra", 3, 49 B.
19) " The Aldrich Library of NMR Spectra", 3, 72 C.

(Received in Japan 12 July 1982)