SELECTIVE REDUCTION OF ALDEHYDES TO THE CORRESPONDING PRIMARY ALCOHOLS
BY LITHIUM ENOLATE OF ACETALDEHYDE

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Abstract – Reaction of lithium enolate of acetaldehyde(obtained by cyclore-
version of THF in the presence of n-BuLi) with a number of nonenolizable
aldehydes (aromatic, heteroaromatic, cinnamaldehyde) in THF and room tempe-
rature affords good to quantitative yields of the corresponding primary al-
cohols, instead of other products commonly reported for similar conditions.
Reduction of the carbonyl group is the main reaction even in the presence
of other reducible groups or parts of the same group. A possible mechanism
of reaction is also proposed.

The aldol condensation represents a highly useful synthetic tool for forming new carbon-carbon
bonds. In particular, reactions converting aldehydes or ketones into α,β-unsaturated aldehydes with
chain extension by two carbon atoms are of considerable interest.[1] In this case a simple aldol
condensation directly using acetaldehyde (in presence of a base) and a carbonyl partner cannot
be utilized because of the facile self-condensation and polimerization of acetaldehyde when its
conversion into the corresponding enolate ion is attempted.[2] Thus, a number of alternative precur-
sors and procedures of the cited enolate ion have been proposed.[1,3] Within these, an interesting
procedure is the cycloreversion of THF in the presence of n-butyllithium,[4] allowing the quantita-
tive conversion to the lithium enolate of acetaldehyde without any of the above-mentioned compli-
cations.

On the other hand, concerning the use of lithium enolates in the aldol condensation, other
aspects must be pointed out. In fact, good results in ethereal solvents are obtained only in con-
ditions in which an efficient metal chelate formation (stabilizing the aldolate ion intermediate)
occurs, i.e., at low temperatures and/or by adding a divalent metal salt, such as $MgBr_2$ or $ZnCl_2$.[5]

If only the lithium cation is present, as the reaction temperature raises to 0° or above, a
number of side reactions are observed (retrograde aldol, enone formation followed by Michael
addition, polycondensation).

During our investigation concerning the reaction of a number of nonenolizable aldehydes with the
enolate ion of acetaldehyde (obtained as above described), we have discovered, however, that the
main (and, in some cases, the only) observed reaction at room temperature is the reduction of al-
dehydes to the corresponding primary alcohols. This unusual and (to our knowledge) unprecedented
behaviour is the object of the present paper.

RESULTS AND DISCUSSION

A number of nonenolizable aldehydes (aromatic or heteroaromatic, as well as cinnamaldehyde) have been allowed to react with lithium enolate of acetaldehyde (obtained by cycloreversion of THF in the presence of $\underline{n}$-buthyllithium) in THF at room temperature. In some cases both reagents were mixed (and the reaction mixture kept for some time) at low temperature (-35°C) before heating at room temperature as above indicated. In these cases, however, the results were not much different from those observed when reactions are directly performed at room temperature. On the contrary, when the reactions were entirely carried out at low temperatures (experiments made in only a few cases), a different behaviour was observed.

Results obtained at room and at low temperatures are summarized in Table 1 and 2, respectively.

As it can be seen, at low temperatures substantial amounts of the expected products of aldol condensation (and subsequent dehydration) are actually isolated after quenching the reaction mixtures with NH_4Cl/H_2O. Excepted for the case of furaldehyde, however, the observed yields are low. This is not surprising since, a) reaction conditions were not optimized and, b) it has been reported that good results in the aldol condensation with preformed lithium enolates in ethereal solvents and in the absence of added $ZnCl_2$ (or $MgBr_2$) can sometimes be achieved only if the reactions are performed in Et_2O solution at low temperatures (-20 to -50°C).[5]

Table 1

Products of the reaction of aldehydes with lithium enolate of acetaldehyde in THF at room temperature [a]

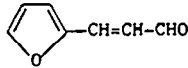| G in G-C≤H O	$\left[G-C{<}^H_{\cdot O}\right]/\left[=\!/^{O^-}\right]$	G-CH$_2$OH Yield %
C_6H_5-CH=CH-	1 : 1	quantitative
C_6H_5-	4 : 1 [b]	94
$\underline{o}$-NO_2-C_6H_4-.	1 : 1	75
$\underline{m}$-NO_2-C_6H_4	1 : 1	68
$\underline{p}$-NO_2-C_6H_4-	1 : 1	97
$\underline{o}$-Cl-C_6H_4-	1 : 1	54
$\underline{m}$-Cl-C_6H_4-	1 : 1	71
2-furyl-	1 : 1	40 [c]

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[a] Reaction times varied from ca. 30' (for cinnamaldehyde) to ca. 30[h] (for o-chlorobenzaldehyde).

[b] More complex mixtures were obtained for equimolar ratios.

[c] Besides other unidentified products, 3-(2-furyl)-acrolein (ca.20%) was also isolated.

Table 2

Products of the reaction of aldehydes with lithium enolate of acetaldehyde at low temperatures

G in G-C$\overset{\nwarrow H}{\underset{\searrow O}{}}$	$\left[G-C\overset{\nwarrow H}{\underset{\searrow O}{}} \right] / \left[\overset{O^-}{=\!\!\!\diagup} \right]$	t, °C	Condensation Product [*]	Yield %
C_6H_5-	1 : 2	- 35	$C_6H_5-CH=CH-CHO$	15
$\underline{p}-NO_2-C_6H_4-$	1 : 1	- 35	$\underline{p}-NO_2-C_6H_4-CH=CH-CHO$	28
(furan ring)	1 : 1	- 60	(furan ring)—CH=CH–CHO	66

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[*] Appreciable amounts of the primary alcohols corresponding to the starting aldehydes could in some cases also be observed.

If more polar solvents are used (DME or, especially, THF), then the addition of salts providing metal cations with a small ionic radius similar to lithium (0.78 Å)[6] but with a greather positive charge (like Mg^{2+} or Zn^{2+}, ionic radius 0.78 Å and 0.69 Å, respectively)[6] is almost always required in order to better (compared to lithium) intercept the initially formed aldolates as metal chelates
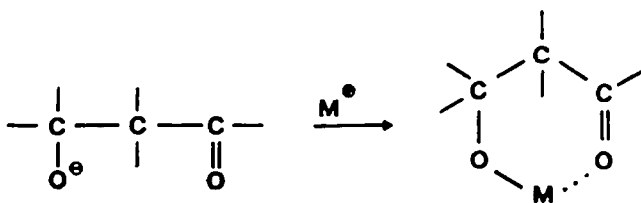
and so prevent the above mentioned typical side reactions of aldol condensation (retrograde aldol, polycondensation, and enone formation followed by Michael addition).

Thus the latter reactions become important when only lithium cation is present and as the temperature raises to 0°C or above.

However, observation of Table 1 indicates that the main (or the only) products that can be isolated when the reactions of the considered aldehydes with the lithium enolate of acetaldehyde in THF are performed at room temperature (and, in little amounts, even at low temperatures: footnote in Table 2) are the primary alcohols correaponding to the starting aldehydes. The yields are high even in the presence of other reducible groups (e.g., NO_2,Cl) or parts of the same group (i.e., C=C conjugated with C=O, by considering their combination as a single functional group).[7] Thus the observed reduction is also a chemo- and regio-selective reaction.

Selectivity in reduction reactions has been the object of great attention by numerous authors. In particular, in the case of α, β-unsaturated carbonyl derivatives, it is important to obtain only products of carbonyl reduction without concomitant reduction of C=C double bond, and, for this aim, various reagents have been proposed such as AlH_3,[8] $NaBH_4$ in the presence of lanthanide

chlorides (LaCl$_3$, CeCl$_3$, SmCl$_3$),[9] 9-BBN,[10] Et$_3$SiH,[11] lithium n-butylborohydride[12] or diisobutyl-aluminum hydride.[13]

As it can be seen in Table 2, cinnamaldehyde, which is a typical example of α, β-unsaturated aldehyde, subject to our procedure can be converted into cinnamol in virtually quantitative yield and in a relatively short time.

Further, good results are observed, with a few exceptions, also in the other cases examined, in which other reducible groups are present in the molecule. Therefore, the reaction discovered by us seems to be an interesting procedure for the chemo- or regio-selective reduction of nonenolizable aldehydes.

Some experiments (not reported) carried out on nonenolizable ketones (benzophenone, trifluoro-acetophenone) did not afford equally good results, a maximum yield of ca. 30% in the corresponding secondary alcohol having been observed in the case of trifluoroacetophenone. So, synthetic utility in the case of ketones seems to be less appreciable. Besides synthetic utility, however, mechanistic aspects seem also to be worthy of consideration. With this aim we have made further investigations in order to establish the fate of the enolate ion of acetaldehyde, and so discovered that it is very likely converted into ketene. We have in fact detected in the aqueous phase (separated after quenching the reaction mixture with NH$_4$Cl/H$_2$O) substantial amounts of acetic acid (see EXPERIMENTAL), and this, in our view, could in turn just be formed from ketene by the known facile reaction with water,[14] as depicted in Scheme 1

Scheme 1
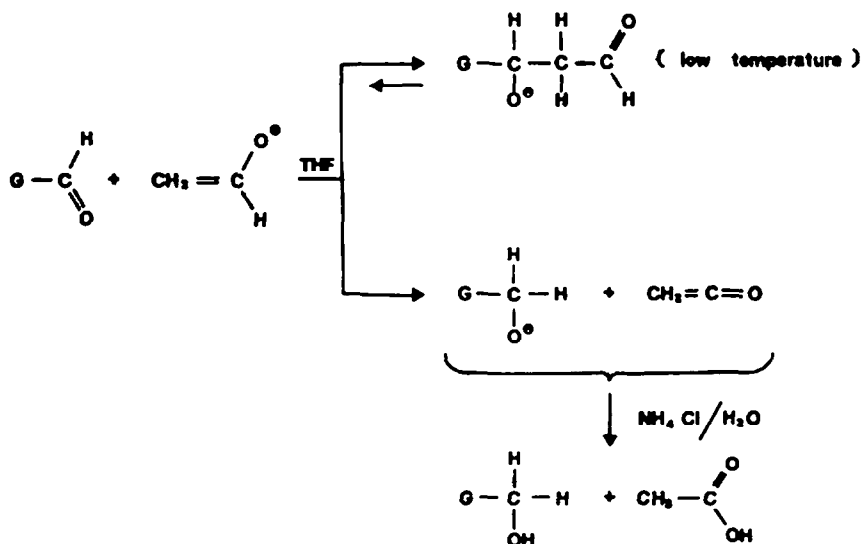
On the other hand, as the formation of ketene formally involves hydride migration from the enolate ion to the carbonyl derivative in a manner that resembles reduction by alkoxides (aluminum isopropoxide), then a similar mechanism (Meerwein-Ponndorf-Verley) could also be hypothesized.

Scheme 2
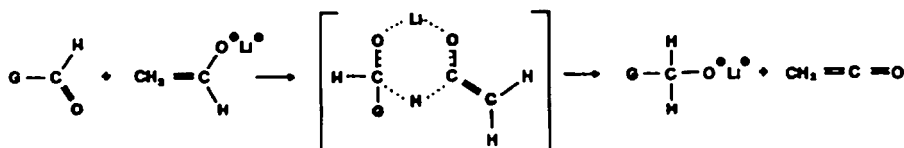
It is well known, in fact, that such a mechanism can operate in various cases[15] (even though some occurrence of a single-electron transfer SET mechanism has sometimes been demonstrated),[16] being commonly accepted also for the carbonyl reduction by a number of other reagents, such as Grignard reagents[17] and lithium amides.[18]

Further investigations, however, are in progress on this point.

EXPERIMENTAL

MPS taken on a Electrothermal apparatus were uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 390 spectrometer. IR spectra were recorded on a Perkin Elmer 681 spectrometer.

Thin-layer chromatography (TLC) was performed on silica gel sheets with fluorescent indicator (stratocrom SIF, Carlo Erba). Column chromatography was carried out by using 70-230 mesh silica gel from Merck. Flash chromatography was conducted by using silica gel, average particle size 60 µm, particle size distribution 40-63 µm, 230-400 ASTM.

Materials. Tetrahydrofuran (THF) from commercial source (RS, Carlo Erba) was purified by distillation (twice) from sodium wire in N_2 atmosphere.

Standardized (2.4 N) n-butyllithium in hexane was from Aldrich Chemical Co.. All other chemicals (starting aldehydes, as well as the corresponding primary alcohols and other substances used for comparison with the reaction products) were commercial grade further purified by distillation or crystallization prior to use.

Reaction of aldehydes with the enolate ion of the acetaldehyde : general procedure

To a mixture containing lithium enolate of the acetaldehyde (32 mmole) in anhydrous THF (25 ml), prepared by allowing to stand THF in the presence of butyllithium at room temperature for ca. 16 hrs as previously reported,[4,19] was added dropwise and at ca. 20°C a solution of aldehyde (usually, 32 mmole: see Table 1) using a nitrogen-flushed, three necked flask, equipped with a magnetic stirrer, a nitrogen inlet and a dropping funnel. After the reaction was completed, the reaction mixture was quenched by adding aqueous NH_4Cl, the organic layer separated and washed with H_2O. The extracts were then dried over Na_2SO_4 and evaporated under reduced pressure. When a single product (4-nitrobenzyl alcohol and cinnamyl alcohol) was obtained, the residue was simply purified by recrystallization or distillation. In the other cases the products mixture was separated by flash chromatography(ether-petrol 8:2 as eluent) before purification. All the isolated

products (Tables 1 and 2) were identical (mps for solid substances, IR, ^{1}H NMR) to authentical samples (commercial).

Detection of acetic acid was made directly on the aqueous layer (from the quenched reaction mixture) by gas chromatography using a GP 10% SP-1200/ 1% H_3PO_4 on 80/100 Chromosorb W AW column from Supelco, suitable for the analysis of volatile (C_2-C_5) fatty acids in water.

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