

LiAlH₄/Silica Chloride as a New Chemoselective System for Reduction of Carbonyl Compounds and Phosphine Oxides

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LiAlH₄/silica chloride system was used as an efficient and chemoselective reductant for organic substrates. The reduction of phosphine oxides was achieved with this system. Good chemoselectivity in reduction of aldehydes and ketones in the presence of other carbonyl compounds was observed.

Keywords: Lithium aluminium hydride, Silica chloride, Reduction, Carbonyl compounds, Phosphine oxides

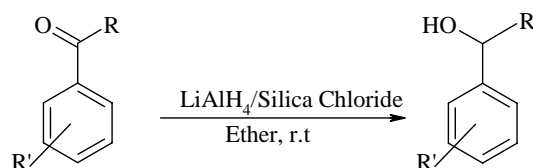
INTRODUCTION

The reduction of carbonyl compounds is one of the most useful synthetic transformations in organic synthesis [1] and a variety of methods have been developed for this purpose [2]. Lithium aluminum hydride is an important reducing agent which is used for reduction of organic compounds in laboratories and industries. It is a strong reducing agent which does not show selectivity towards reduction of functional groups. In addition, it is very sensitive to moisture which restricts its uses as an easy handling agent. The high reactivity of LiAlH₄ decreases its synthetic utility and as such cannot be used easily for reduction of multifunctional organic compounds. In this regard various modifications have been made to produce a reactive but more stable reducing agent [3].

LiAlH₄ is also used for the reduction of phosphine oxides [4]. Various phosphine oxides are efficiently reduced by the use of a methylation reagent and lithium aluminum hydride [5]. Diisobutylaluminum hydride (DIBAL-H) and triisobutylaluminum hydride have found to be outstanding reductants for secondary phosphine oxides (SPOs) [6] and

triphenylphosphine oxide [7]. On the other hand, polymer-supported reducing agents have received considerable attention in recent years and a variety of them, while exhibiting the advantages of polymeric reagents, have been used in the mild and selective reduction of organic compounds [8-10].

Along this line, we found that silica chloride is an effective supporting polymer in modification of LiAlH₄ as it can raise the stability and selectivity of this compound. The utility of silica chloride in organic synthesis has been well recognized [11]. We now report that LiAlH₄ on solid silica chloride can be employed as a selective and mild reagent for the reduction of carbonyl compounds under heterogeneous conditions (Scheme 1).



R = H, Alkyl, -O-Alkyl, Cl, OH

Scheme 1

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EXPRIMENTAL

Chemicals and Apparatus

Chemicals were purchased from Merck or Fluka chemical companies. All products were known and identified by comparison of their physical and spectroscopic data with those of authentic samples.

General Procedure

To a solution of silica chloride (0.5 mmol), dry diethyl ether (10 ml) and LiAlH_4 (0.5 mmol) was added carbonyl compounds or phosphine oxides (1 mmol) and stirred at room temperature for the time specified in the Tables 1 and 3. The progress of reaction was monitored by TLC or gas chromatography. The reaction mixture was filtered, and washed with 5 ml diethyl ether. Successively, 0.5 ml water and 0.5 ml of 1 molar NaOH were added. The suspension was stirred at room temperature for 1 h. After MgSO_4 was added, the suspension was stirred for another 30 min and filtered. The residue was washed three times with 10 ml of ether. The combined filtrates were concentrated *in vacuo*. The crude product was then collected. The ratio of substrate:silica chloride: LiAlH_4 was 1:1:1, except for the case of carboxylic acids and acid chlorides, which were reduced in 2:2:1 molar ratio. Competitive reductions were carried out under preceding procedure with a ratio of 1:1 silica chloride: LiAlH_4 and 1 mmol of substrates.

RESULTS AND DISCUSSION

Our first goal was to determine the reactivity of LiAlH_4 /silica chloride toward various types of carbonyl compounds, and this was done by monitoring the progress of the reactions by gas chromatography. The results are summarized in Table 1. The data clearly demonstrate differences in reactivity for the various classes of carbonyl derivatives, as summarized by the following order of decreasing reactivity: aldehydes \geq ketones > esters > acid chlorides > carboxylic acids. The reaction times of aldehydes, in all cases, were relatively decreased when we used silica chloride (quantitative conversions by TLC) with the exception of substrates bearing electron-withdrawing groups that required approximately the same reaction time in the absence

of silica chloride (Table 1). Except aldehydes and some ketones, other carbonyl compounds (Table 1, entries 17-33) undergo reduction at rates which are useful for synthetic purpose. Unless otherwise noted, carbonyl compounds were reduced quantitatively after appropriate time (monitored by TLC or GC).

Various ketones were reduced efficiently under reaction conditions (Table 1, entries 9-16). Application of this system to α,β -unsaturated ketone (entry 11) produced the corresponding allylic alcohol, uncontaminated with 1,4 reduction product. Reduction of benzyl (entry 16) afforded a mixture of 80% 2-hydroxy-1,2-diphenyl-ethanone and 20% of 1,2-diphenyl-ethane-1,2-diol after 30 min. LiAlH_4 in the absence of silica chloride reduced benzyl in 50 min in diethyl ether and gave only 1,2-diphenyl-ethane-1,2-diol.

In the application of LiAlH_4 /silica chloride to the reduction of esters, we modified the relative ratios of reagent and substrate. While maintaining a 1:1 molar ratio of silica chloride to ester, the amount of LiAlH_4 was varied between 1 and 1.6 mmol. Within this range, the rate of reduction steadily increases with the quantity of reagent used, and we found that the 1:1:1 ratio of LiAlH_4 :silica chloride:ester is the best from synthetic point of view (Table 1, entries 17-21).

Despite of their high reactivities, acid chlorides were reduced at longer reaction times than aldehydes and ketones (Table 1, entries 22-27). To optimize the reduction of acid chlorides, we tried different molar ratio of reagent and acid chlorides and found that suitable rate is furnished in 2:2:1 ratio of silica chloride: LiAlH_4 :acid chloride. In the absence of silica chloride, LiAlH_4 reduced acid chloride in less than 15 min in diethyl ether at room temperature. Carboxylic acids showed a more resistance to reduction using LiAlH_4 /silica chloride, as indicated in the Table 1 (entries 28-33). This is probably related to deprotonation of acid in first step which then decreases the reactivity of the resulting carboxylate anion. This was further confirmed by the fact that the reduction of 4-hydroxy benzoic acid was not completed after even 10 h (Table 1, entry 33).

In order to show the chemoselectivity of this reducing system, we examined the reduction of mixtures of different carbonyl compounds, and the results are also included in Table 2. As indicated in this Table, aldehydes are reduced selectively in the presence of esters (Table 2, entries 1-3), acid chlorides

Table 1. Reduction of Carbonyl Substrates with LiAlH₄/Silica Chloride in Diethyl Ether at Room Temperature^a

Entries	Substrate	Product ^b	Time (min)
1	Benzaldehyde	Benzyl alcohol	10
2	4-Methylbenzaldehyde	4-Methylbenzyl alcohol	15
3	2-Benzylideneacetaldehyde	2-Benzylideneethanol	12
4	Phenylacetaldehyde	2-Phenylethanol	10
5	4-Hydroxybenzaldehyde	4-Hydroxybenzyl alcohol	25
6	4-Chlorobenzaldehyde	4-Chlorobenzyl alcohol	6
7	Cynamaldehyde	Cynamyl alcohol	15
8	4-Benzyloxybenzaldehyde	4-Benzyloxybenzyl alcohol	15
9	Acetophenone	1-Phenylethanol	20
10	Phenylpropanone	Phenyl-2-propanol	20
11	2-Cyclohexen-1-one	2-Cyclohexenol	15
12	2-Chlorodiphenylketone	2-Chlorodiphenylmethanol	12
13	4-Chlorodiphenylketone	4-Chlorodiphenylmethanol	12
14	4-Methylacetophenone	4-Methyldiphenylmethanol	30
15	4-Methoxyacetophenone	4-Methoxydiphenylmethanol	50
16	Benzil	2-Hydroxy-1,2-diphenyl-ethanone+diol ^c	30
		1,2-Diphenylethane-1,2-diol	
		1,2-Diphenylethane-1,2-diol ^d	50
17	Methylbenzoate	Benzyl alcohol	80
18	4-Chloromethyl benzoate	4-Chlorobenzyl alcohol	70
19	Benzylbenzoate	Benzyl alcohol	60
20	Iso-propylbenzoate	Benzyl alcohol	80
21	3-Methylmethylbenzoate	3-Methylbenzyl alcohol	120
22	Benzoyl chloride ^e	Benzyl alcohol	600
23	Phenylacetylchloride	Phenylethanol	330
24	4-Nitrobenzoyl chloride	4-Nitrobenzyl alcohol	180
25	4-Chlorobenzoyl chloride	4-Chlorobenzyl alcohol	300
26	3-Chlorobenzoyl chloride	3-Chlorobenzyl alcohol	480
27	2-Chlorobenzoyl chloride	2-Chlorobenzyl alcohol	420
28	Benzoic acid ^f	Benzyl alcohol	1200
29	4-Methylbenzoic acid	4-Methylbenzyl alcohol	1800
30	4-Nitrobenzoic acid	4-Nitrobenzyl alcohol	300
31	2-Nitrobenzoic acid	4-Nitrobenzyl alcohol	375
32	4-Chlorobenzoic acid	4-Chlorobenzyl alcohol	390
33	4-Hydroxybenzoic acid	4-Hydroxybenzyl alcohol	1800 ^g

^aThe ratio of LiAlH₄:silica chloride:ketone or aldehyde was 1:1:2. ^bAll the products obtained quantitatively. ^cA mixture comprises of 80% ketohydroxy and 20% diol was obtained after 30 min. ^dAfter 50 min diol was obtained as sole product. ^eThe ratio of LiAlH₄:silica chloride: acid chlorides was 2:2:1. ^fThe ratio of LiAlH₄:silica chloride: carboxylic acid was 2:2:1. ^gAfter 30 h reduction was not completed.

(Table 2, entries 4-6) and carboxylic acids (Table 2, entries 10,11). Ketones also selectively reduced in the presence of acid chlorides (Table 2, entries 7-9).

Reduction of aldehydes in the presence of ketones was examined (Table 2, entries 10-13). Inspection of the Table reveal that our reagent has a relatively good chemoselectivity toward reduction of aldehydes, as benzaldehyde was reduced both in the presence of 4-methyl and 4-methoxy acetophenone

but a mixture of product was obtained when cynamaldehyde or phenyl acetaldehyde beside 4-methoxy acetophenone were subjected to reduction.

As shown in the Table 3, triphenylphosphine oxide is reduced to triphenyl phosphine after 20 min at room temperature. Similarly, diethoxy phosphine oxide reduced to diethoxy phosphine in 50 min (Table 3, entry 2). However, when dibenzyloxy phosphine oxide was subjected to reduction, only

Table 2. Chemoselective Reduction of Carbonyl Compounds with $\text{LiAlH}_4/\text{Silica Chloride}$ at Room Temperature

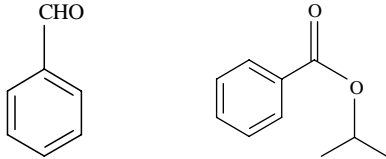
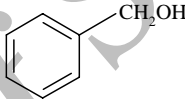
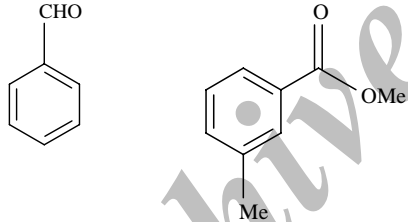
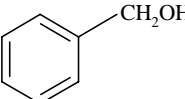
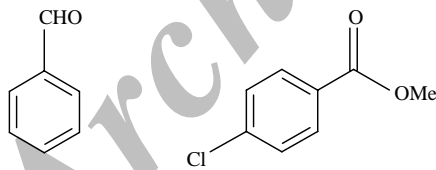
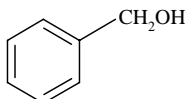
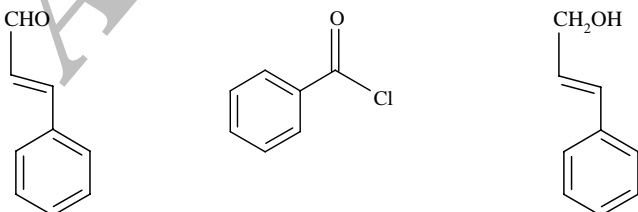
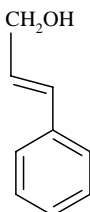
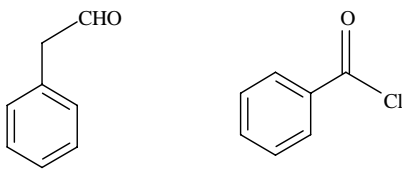
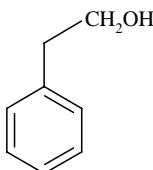
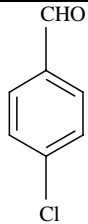
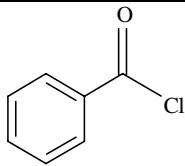
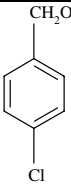
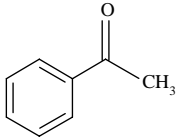
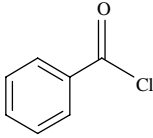
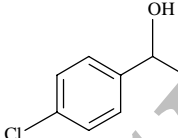
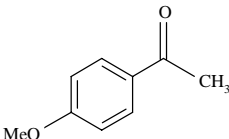
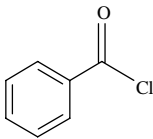
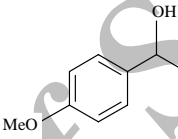
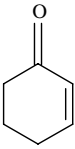
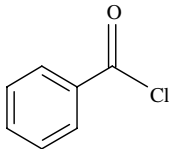
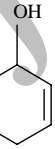
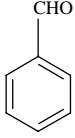
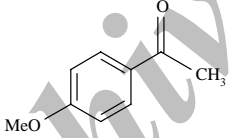
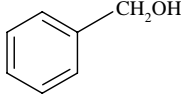
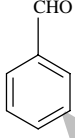
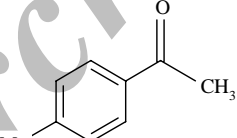
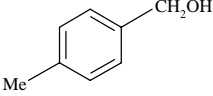
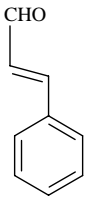
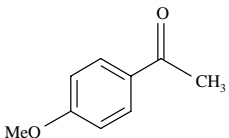
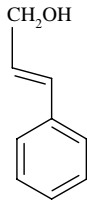
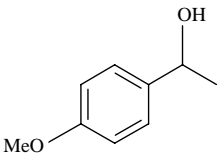
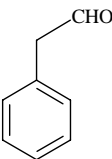
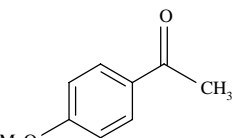
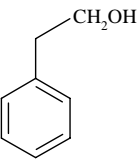
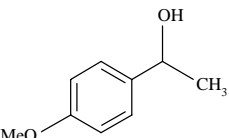
Entries	Substrates	Products ^a	Time (min)	Conversion (%)
1			15	100:0
2			15	100:0
3			12	100:0
4			20	100:0
5			18	100:0

Table 2. Continued

6				9	100:0	
7				10	100:0	
8				70	100:0	
9				15	100:0	
10				30	100:0	
11				30	100:0	
12					90	100:20
13					70	100:30

^aProducts were obtained quantitatively.

Table 3. Reduction of Phosphine Oxides with LiAlH₄/Silica Chloride^a in Diethyl Ether at Room Temperature

Entries	Substrates	Products ^b	Time (min)
1	(Ph) ₃ PO	(Ph) ₃ P	20
2	(EtO) ₂ HPO	(EtO) ₂ HP	50
3	(PhCH ₂ O) ₂ HPO	PhCH ₂ OH	30

^aThe ratio of LiAlH₄:silica chloride:phosphine oxides was 1:1:1. ^bAll the products obtained quantitatively.

benzyl alcohol was obtained (Table 3, entry 3).

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