

## Preparation of Aldehydes from Carboxylic Esters by Reductive Oxidation with Lithium Aluminum Hydride and Pyridinium Chlorochromate or Pyridinium Dichromate

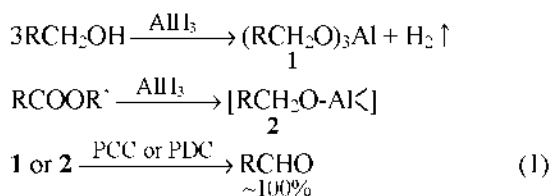
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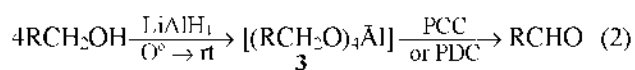
The reduction of carboxylic esters to aldehydes is one of the most useful synthetic transformation in organic synthesis. Therefore, many useful reduction methods have been reported for such conversions.<sup>1</sup> However, common reducing agents such as aluminum hydride usually reduce carboxylic esters to alcohols.<sup>2,3</sup> Very recently, we reported that the oxidation of alkoxyaluminum intermediates, which are formed by reduction of primary alcohols<sup>4</sup> or carboxylic esters<sup>5</sup> with aluminum hydride, by pyridinium chlorochromate (PCC) or pyridinium dichromate (PDC) gives almost quantitative yields of the corresponding aldehydes (Eq. 1). These results indicate that both alkoxyaluminum intermediates (**1** and **2**) are structurally same: the intermediates are composed of primary alkoxy group bonded to aluminum atom. Therefore, we can assume that any primary alkoxy moiety attached to aluminum atom may undergo the oxidation to afford



the corresponding aldehyde function. From this structural point of view, we decided to utilize lithium aluminum hydride (LAH) instead of aluminum hydride in such procedure for the conversion of carboxylic esters to aldehydes. Herein, we introduce a new method, which effects the transformation of carboxylic esters to aldehydes in high yields at room temperature.

### Result and Discussion

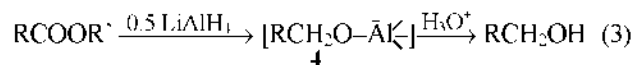
First of all, we examined the possibility of the alkoxyaluminum intermediate (**3**), which is formed by the reaction of primary alcohols with LAH, being oxidized by PCC or PDC to the corresponding aldehydes (Eq. 2). Benzyl alcohol and 1-hexanol were examined as representative of primary alcohol.



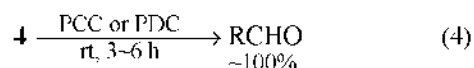
Tetraalkoxyaluminates are readily prepared from the reaction of alcohols with LAH at 0 °C. Both aromatic and aliphatic alkoxyaluminates examined were readily oxidized with

PCC or PDC in a mixed solvent of THF and methylene chloride at room temperature, providing essentially quantitative yields of aldehydes determined by GC analysis.

Such results accelerated us to examine the conversion of carboxylic ester to aldehyde by this procedure. If carboxylic ester is reduced to the alcohol stage by LAH under these reaction conditions,<sup>6</sup> the resulting intermediate in the reaction mixture would contain alkoxy moiety as in **3**. Actually, carboxylic esters were readily reduced to the corresponding alcohol stage by LAH (0.5 equiv) at room temperature (Eq. 3).<sup>6</sup> Even though the final reduction intermediate has not been identified, it is believed that **4** could be the possible structure.



The method involves the rapid reduction of carboxylic ester with LAH, followed by oxidation of the resultant alkoxyaluminum intermediate (**4**) (without isolation) with PCC or PDC at room temperature (Eq. 4).



As listed in Table 1, the procedure converts aliphatic esters to aldehydes in 6 h at room temperature in yields of 92-97%. Actually, there is no difference in the yields of aldehydes with PCC or PDC. Similarly,  $\alpha,\beta$ -unsaturated carboxylic esters, such as ethyl crotonate and ethyl cinnamate, afford the olefinic aldehydes in 94-96% yields. The conversion of aromatic esters by this procedure provides the corresponding aldehydes in 92-99% yields. The unsubstituted benzoates with a variety of alcohol portions are converted to benzaldehyde in yields of 96-99%, showing no bias in the yields. Alkyl-substituted benzoate, such as 3- and 4-methylbenzoates, afford the corresponding aldehydes in 94-96% yields. Finally, chloro and nitro groups on the benzene ring are readily accommodated and gave aldehydes in better than 92% yield.

This reaction is broadly applicable tolerating many substituents, such as chloro, nitro, and alkene groups. The reactivities of LAH toward a carboxylic ester function and of PCC and PDC toward alkoxyaluminum intermediate (**4**) are quite similar to the case of aluminum hydride. However, the general reduction patterns of these two reducing agents are quite different.<sup>2,5,7</sup> The difference is basically derived from the fact that lithium aluminum hydride is basic and alumi-

**Table 1.** Conversion of Carboxylic Esters to Aldehydes by Oxidation of Alkoxyaluminate Intermediate (**4**) with Pyridinium Chlorochromate (PCC) or Pyridinium Dichromate (PDC) at Room Temperature<sup>a,b</sup>

Ester	Product	Reac- tion time (h)	PCC	PDC
			Yield (%) <sup>c</sup>	Yield (%) <sup>c</sup>
Ethyl butyrate	Butyraldehyde	6	92	93
Ethyl caproate	Hexanal	6	95(80)	95
Ethyl caprylate	Octanal	6	96	97
Ethyl isobutyrate	Isobutyraldehyde	6	95	94
Ethyl isovalerate	Isovaleraldehyde	6	94	96
Ethyl crotonate	Crotonaldehyde	6	96	94
Ethyl cinnamate	Cinnamaldehyde	6	95	95
Methyl benzoate	Benzaldehyde	3	97	99
Ethyl benzoate	Benzaldehyde	3	98(82)	97(78)
Phenyl benzoate	Benzaldehyde	3	96	98
Methyl 3-methylbenzoate	3-Methylbenzaldehyde	3	96	94
Ethyl 4-methylbenzoate	4-Methylbenzaldehyde	3	95	95
Methyl 4-chlorobenzoate	4-Chlorobenzaldehyde	3	97	95
Ethyl 4-nitrobenzoate	4-Nitrobenzaldehyde	3	94	92

<sup>a</sup>Ester: oxidant = 1 : 2.2. <sup>b</sup>In a THF-methylene chloride mixture solvent. <sup>c</sup>GC yields. The numerals in parentheses are isolated yields.

num hydride is acidic.<sup>8</sup> For example, the reduction of capronitrile with AlH<sub>3</sub> results in the clean conversion to hexylamine without any hydrogen evolution, whereas the reduction with LAH evolves *ca.* 0.2 equiv of hydrogen and undesirable side reaction occurs. Therefore, when a carboxylic ester function in a complex molecule is applied to this reductive oxidation procedure, one must consider which reducing agent is amenable. However, in the case where the difference in the reduction pattern between lithium aluminum hydride and aluminum hydride is not a problem, the use of lithium aluminum hydride must be more convenient and economical than the use of aluminum hydride: all four equivalents of hydride in lithium aluminum hydride are utilized for the reduction.

It is worthwhile to compare this reductive oxidation procedure with the reduction procedure using diisobutylaluminum hydride (DIBAL),<sup>1-a</sup> the most widely used method in organic synthesis: the present procedure is performed at ambient temperature, but the DIBAL reduction runs at -70°. Furthermore, the aldehyde yields obtained by DIBAL are not general (50-90%), whereas the yields achieved by the present procedure are higher than 95%. Consequently, this reductive oxidation procedure must be far superior to the DIBAL reduction.<sup>1-a</sup>

### Experimental Section

All reactions were performed under a dry N<sub>2</sub> atmosphere. All chemicals used were commercial products of the highest purity available; THF was dried over 4 Å molecular sieve and distilled from sodium-benzophenone ketyl prior to use. Methylene chloride was also dried over P<sub>2</sub>O<sub>5</sub> and distilled. <sup>1</sup>H NMR spectra were recorded on a Bruker AMX 300 spectrometer. Gas chromatographic analyses were carried out with a Varian 3300 Chromatograph.

### Reduction of Esters with Lithium Aluminum Hydride.

The following procedure for the reaction of ethyl benzoate with PCC is representative. An oven-dried, 250 mL flask, fitted with a side arm and a reflux condenser connected to a mercury bubbler, was flushed with dry nitrogen and then maintained under a static pressure of nitrogen. The flask was charged with a 1.0 M solution of lithium aluminum hydride (31 mL, 31 mmol) in THF. To the stirred solution at 0 °C, ethyl benzoate (9.61 g, 61 mmol) was added dropwise and the reaction mixture was stirred further for 3 h at room temperature. To a well-stirred suspension of PCC (29 g, 134 mmol) in methylene chloride (200 mL) taken in a 500 mL flask equipped as described above, is added dropwise the above solution of alkoxyaluminate intermediate (**4**) in THF using a cannula. The mixture was stirred for 3 h at room temperature. The small portion of this mixture was transferred to a vial and dodecane was added as an internal standard. GC analysis using a capillary column of Carbowax 20 M indicated the presence of benzaldehyde in a yield of 98%.

**Isolation of Aldehyde Products.** The rest of the reaction mixture (60 mmol) was diluted with ethyl ether (120 mL). The supernatant liquid is filtered through Florisil® (120 g) contained in a 300 mL sintered glass funnel; the solid residue is triturated with ethyl ether (3 × 30 mL) and passed through the same Florisil column. The filtrate is concentrated and distilled under reduced pressure to give pure benzaldehyde (5.22 g, 82%); bp 62-63 °C (15 mm). The <sup>1</sup>H NMR spectrum agreed with that of an authentic sample.

Analogous procedures are used for the synthesis of the other aldehydes listed in Table 1. In the case of PDC as an oxidant used, actually the same procedure was adopted.

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