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

Jin Soon Cha,* Joong Hyun Chun, Jong Mi Kim, Oh Oun Kwon, Sang Yong Kwon, and Jae Cheol Lee†

Department of Chemistry, Yeungnam University, Kyongsan 712-749, Korea
†Department of General Education, Samchok National University, Samchok 245-080, Korea

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Recently, we reported that the oxidation of alkoxyaluminum intermediates, which are formed by reduction of primary alcohols[1] or carboxylic acids[2] 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 acids to aldehydes. Herein, we introduce a new method, which effects the transformation of carboxylic acids to aldehydes in high yields at room temperature.

$$3\ \mathrm{RCH_2OH} \xrightarrow{\mathrm{AlH_3}} \underset{\mathbf{1}}{(\mathrm{RCH_2O})_3\mathrm{Al}} + 3\ \mathrm{H_2}\uparrow$$

$$\mathrm{RCOOH} \xrightarrow{\mathrm{AlH_3}} \underset{\mathbf{2}}{[\mathrm{RCH_2O\text{-}Al}{<}]} + \mathrm{H_2}\uparrow$$

$$\mathbf{1}\ \text{or}\ \mathbf{2} \xrightarrow{\text{PCC or PDC}} \underset{\sim 100\%}{\mathrm{RCHO}} \qquad (1)$$

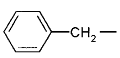
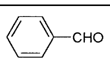
First of all, we examined the possibility of the alkoxyaluminate intermediate (**3**), which is formed by the reaction of primary alcohols with LAH, being oxidized by PCC or PDC to the corresponding aldehydes (Eq. 2). Benzyl alcohol and 1-hexanol were examined as representative of primary alcohol.

$$4\ \mathrm{RCH_2OH} \xrightarrow[0^{\circ}\rightarrow \mathrm{RT}]{\mathrm{LiAlH_4}} \underset{\mathbf{3}}{[(\mathrm{RCH_2O})_4\mathrm{Al}^-]} \xrightarrow[\text{or PDC}]{\text{PCC}} \mathrm{RCHO} \qquad (2)$$

Tetraalkoxyaluminates are readily prepared from the reaction of alcohols with LAH at 0 °C. As summarized in Table 1, 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 acid itself to aldehyde by this procedure. If carboxylic acid is reduced to the alcohol stage by LAH under these reaction conditions,[3] the resulting intermediate in the reaction mixture would contain alkoxy moiety as in **3**. Actually, carboxylic acids were readily reduced to the corresponding alcohol stage with immediate evolution of 1 equiv hydrogen by LAH (0.75 equiv) at 0 °C (Eqs. 3-4).[3] Even though the final reduction intermediate has not been identified, it is believed that **4** could be the possible structure.

Table 1. Oxidation of Tetraalkoxyaluminate (**3**) with PCC and PDC in Tetrahydrofuran and Methylene Chloride at Room Temperature

Alkyl group of $(\mathrm{RO})_4\mathrm{Al}^-$	Oxidant	Reaction time(h)	Product	Yield of aldehyde(%)[a]
	PCC	3		94[b], 98[c]
	PDC	1		97[b], 99[c]
$n\text{-}\mathrm{C_6H_{13}}$–	PCC	6	$n\text{-}\mathrm{C_5H_{11}\text{-}CHO}$	89[b], 95[c]
	PDC	3		98[b], 97[c]

[a] GC yields. [b] **3** : oxidant = 1 : 4.4. [c] **3** : oxidant = 1 : 8.

$$\mathrm{RCOOH} \xrightarrow[0^{\circ}]{0.75\ \mathrm{LiAlH_4}} \mathrm{RCOO{-}\overset{-}{Al}{<}{-}} + 1/2\ \mathrm{H}\uparrow \qquad (3)$$

$$\mathrm{RCOO{-}\overset{-}{Al}{<}{-}} \xrightarrow[0^{\circ}\rightarrow \mathrm{RT}]{} \underset{\mathbf{4}}{[\mathrm{RCH_2O{-}\overset{-}{Al}{<}{-}}]} \xrightarrow{\mathrm{H_3O^+}} \mathrm{RCH_2OH} \qquad (4)$$

The method involves the rapid reduction of carboxylic acid with LAH, followed by oxidation of the resultant alkoxyaluminate intermediate (**4**) (without isolation) with PCC or PDC at room temperature (Eq. 5).

$$\mathbf{4} \xrightarrow[\text{RT, 6\textasciitilde 12 h}]{\text{PCC or PDC}} \underset{\sim 100\%}{\mathrm{RCHO}} \qquad (5)$$

As listed in Table 2, this procedure provides clean, convenient conversion. There were actually no significant difference in yields of aldehydes between oxidants applied, PCC and PDC. Both oxidants convert aliphatic carboxylic acids to aldehydes in yields of 92-98%. Alicyclic derivative, such as cyclohexanecarboxylic acid, works equally well. Derivatives are readily accommodated. Thus, diphenylacetic acid was converted to the corresponding aldehyde in yields of 92-93%. Cinnamic acid was also readily converted to the corresponding α,β-unsaturated aldehyde in yields of 95-96%.

The transformations of aromatic acids into the corresponding aldehydes with this procedure were also essentially quantitative. The oxidation of aromatic intermediates was

Table 2. Conversion of Carboxylic Acids to Aldehydes by Oxidation of Alkoxyaluminate (**4**) with PCC and PDC at Room Temperature[a]

Acid	Product	Reaction time(h)	PCC[b]	PDC[b]
			Yield(%)[c]	Yield(%)[c]
Hexanoic	Hexanal	12	97[d](79)[d,e]	94
Decanoic	Decyl aldehyde	12	96	98
Isobutyric	Isobutyraldehyde	12	92	94
Trimethylacetic	Trimethylacetaldehyde	12	95	96
Cyclohexanecarboxylic	Cyclohexanecarboxaldehyde	12	96	95
Diphenylacetic	Diphenylacetaldehyde	12	93	92
Cinnamic	Cinnamaldehyde	12	95	96
Benzoic	Benzaldehyde	6	99(81)[e]	98(80)[e]
1-Naphthoic	1-Naphthaldehyde	12	98	98
o-Toluic	*o*-Tolualdehyde	6	96	97
p-Toluic	*p*-Tolualdehyde	6	96	96
p-Anisic	*p*-Anizaldehyde	6	98	97
4-Chlorobenzoic	4-Chlorobenzaldehyde	6	96	95

[a] In a THF-methylene chloride mixture (1 : 1). [b] Acid : oxidant = 1 : 1.1. [c] GC yields. [d] The yield reacted with BMS and PCC procedure was 97(77)[e]: see ref. 7. [e] Isolated yields.

much faster than that of aliphatic ones: the reaction was completed within 6 h at room temperature. Although PDC is more reactive than PCC, there is no bias toward oxidizing agents examined in giving quantitative yields of aldehydes.

This reaction is broadly applicable tolerating many substituents, such as halogeno, methoxy, and alkene groups. The reactivities of LAH toward a carboxylic acid function and of PCC and PDC toward alkoxyaluminate intermediate (**4**) are quite similar to the case of aluminum hydride. However, the general reduction patterns of these two reducing agents are quite different.[3,4] The difference is basically derived from the fact that lithium aluminum hydride is basic and aluminum hydride is acidic.[5] For example, the reduction of capronitrile with AlH$_3$ 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 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. In addition, it is noteworthy that there appears one example in which a modified aluminum reagent, bis(dialkylamino)aluminum hydride, was utilized for the direct conversion of carboxylic acids to aldehydes. However, this method afforded relatively lower yields of aldehydes.[6] Consequently, this method provides another useful procedure for the direct conversion of carboxylic acids to the corresponding aldehydes.[7,8]

The following procedure for the reaction of hexanoic acid is representative. An oven-dried, 250-mL, round-bottom flask with sidearm, equipped with a magnetic stirring bar and a reflux condenser, was attached to a mercury bubbler. The flask was flushed with dry nitrogen and then maintained under a static pressure of nitrogen. The flask was charged with hexanoic acid (6.97 g, 60 mmol) and 15 mL of THF. The flask was immersed in an ice-water bath and a precooled 1.0 M solution of LiAlH$_4$ (45 mL, 45 mmol) in THF was added dropwise with vigorous stirring. After the complete evolution of the hydrogen, the ice-water bath was removed and the reaction mixture was stirred for 30 min at room temperature.

To a well-stirred suspension of pyridinium chlorochromate (PCC) (14.3 g, 66 mmol) in methylene chloride (100 mL) taken in a 500-mL flask equipped as described above, was added dropwise the above solution of alkoxyaluminum intermediate in THF using a cannula. The mixture was stirred for 12 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 Carbowax 20 M capillary column (20 m) showed the presence of hexanal in a yield of 97%. The reaction mixture was diluted with 100 mL of diethyl ether and the supernatant liquid was filtered through Florisi® (100 g) contained in a 300-mL sintered glass funnel. The solid residue was washed with diethyl ether (3×30 mL) and passed through the same Florisil column. The filtrate was concentrated and distilled to afford pure hexanal (4.75 g, 79% yield); b.p. 129-130 °C (754 mmHg).

Analogous procedures were used for the synthesis of the other aldehydes listed in Table 2. In the case of PDC as an oxidant used, actually the same procedure was adopted except the oxidation time.

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