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DIRECT AND CHEMOSELECTIVE CONVERSION OF CARBOXYLIC ACIDS INTO ALDEHYDES

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Summary: *A new method for the direct conversion of carboxylic acids to aldehydes using N,N-dimethylchloromethyleniminium chloride and lithium tri-t-butoxyaluminum hydride was established. This method provides a convenient way for the chemoselective reduction of carboxylic acids even with such a functional group as halide, ester, nitrile, olefin, and ketone.*

Aldehydes play often an important role in organic synthesis. In general, carboxylic acids were transformed to aldehydes after they are converted into carboxylic acid derivatives which are more easily reduced than carboxylic acids themselves, or designed to produce stable intermediates of aldehyde equivalent by reduction. Several examples of processes effect aldehyde synthesis; the Rosenmund reduction[1] or hydride reduction of acid halides,[2] *t*-amides,[3] esters and lactones,[4] and so on.[5] It is very difficult to obtain aldehydes by the direct reduction of carboxylic acids, because of easier reduction of aldehydes than that of carboxylic acids.[6] A few methods for the direct reduction of carboxylic acids into aldehydes have been reported to use lithium-methylamine,[7] bis(*N*-methylpiperidynyl)aluminum hydride,[8] thexylborane,[9] or Grignard reagents catalyzed by dichlorobis[π-cyclopentadienyl]titanium.[10] However, these methods seem to be lacking in general applicability and chemoselectivity because of severe reaction conditions. On the other hand, a process which involves an activation of carboxylic acids *in situ* and then the attack of nucleophiles was used to give esters, amides and acid chlorides selectively. Accordingly the reduction of the selectively activated intermediate of carboxylic acids *in situ* can provide a chemoselective synthetic method of aldehydes by easier reduction of the activated carboxylic acids than other functional groups. We describe herein an example of a simple and chemoselective method to convert carboxylic acids into aldehydes using *N*,*N*-dimethylchloromethyleniminium chloride and $LiAlH(OBu^t)_3$ in one-pot operation, that enlarges the range of application of this concept and suggests a variety of new synthetic possibilities.

N,*N*-Dimethylchloromethyleniminium chloride derived easily from *N*,*N*-dimethylformamide is famous not only as a formylating reagent of the Vielsmeyer-Haack reaction, but also as an activating reagent for carboxylic acids to give esters, amides, acid chlorides, and acyl azides.[11] Accordingly chemoselective conversion of carboxylic acids into aldehydes could be achieved when active carboxymethyleniminium chloride 1 derived *in situ* from chloromethyleniminium chloride and carboxylic acids are reduced with a metal hydride to yield a stable betaine 2 as an intermediate which is in turn converted to aldehydes. Although the betaine formation was not yet verified experimentally, Johnstone *et al.* had speculated it as an intermediate of reduction of carboxymethyleniminium salt with $NaBH_4$-$CdCl_2$.[2f] Thus, to a reaction mixture of carboxylic acids and freshly prepared *N,N*-dimethylchloromethyleniminium chloride in the presence of pyridine was added 10 mol% of CuI and then $LiAlH(OBu^t)_3$ at -78 °C. An usual workup gave the corresponding aldehydes as shown in the Table. When lithium carboxylates were used in place of the carboxylic acids-pyridine system, the yields decreased because of their solubility. An effect of addition of copper catalyst causes the increase of the yield. The best solvent system was a mixture of acetonitrile and THF, and an independent use of other solvents resulted in decreasing the yield of the aldehydes. The use of other reductants such as $NaBH_4$ and $NaBH(OMe)_3$ resulted in the further reduction to give alcohols. Both aliphatic and aromatic aldehydes were obtained in high yields from the corresponding carboxylic acids in one-pot operation by the present method. Although the yields were lowered in aliphatic series in the case of reduction of acid chlorides with $LiAlH(OBu^t)_3$,[2a] primaly, secondary and tertialy aliphatic carboxylic acids were easily converted into the corresponding aldehydes in high yields. In addition, the hydride has been

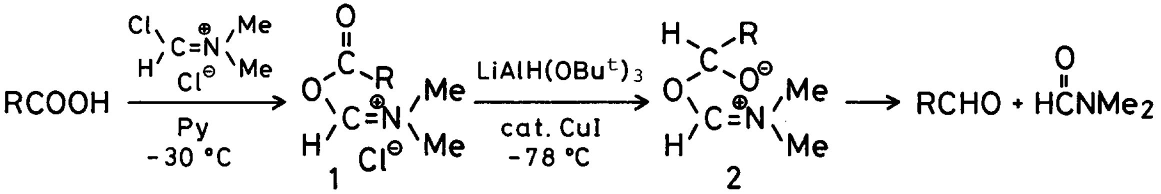
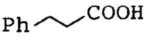
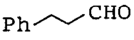
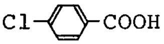
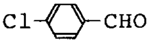
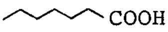
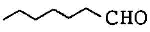
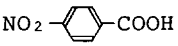
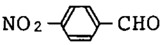
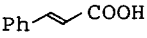
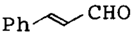
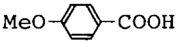
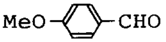
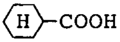
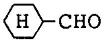
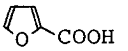
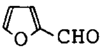
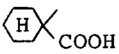
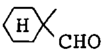
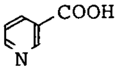
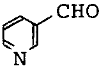
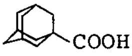
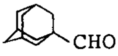
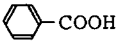
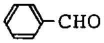


Table. Yields of Aldehydes by the Reduction of Various Carboxylic Acids[a]

Acid	Aldehyde	Yield(%)[c]	Acid	Aldehyde	Yield(%)[c]
		81			79[b]
		90[b]			81
		83			70[b]
		84[b]			70[b]
		82[b]			55
		60			
		78[b]			

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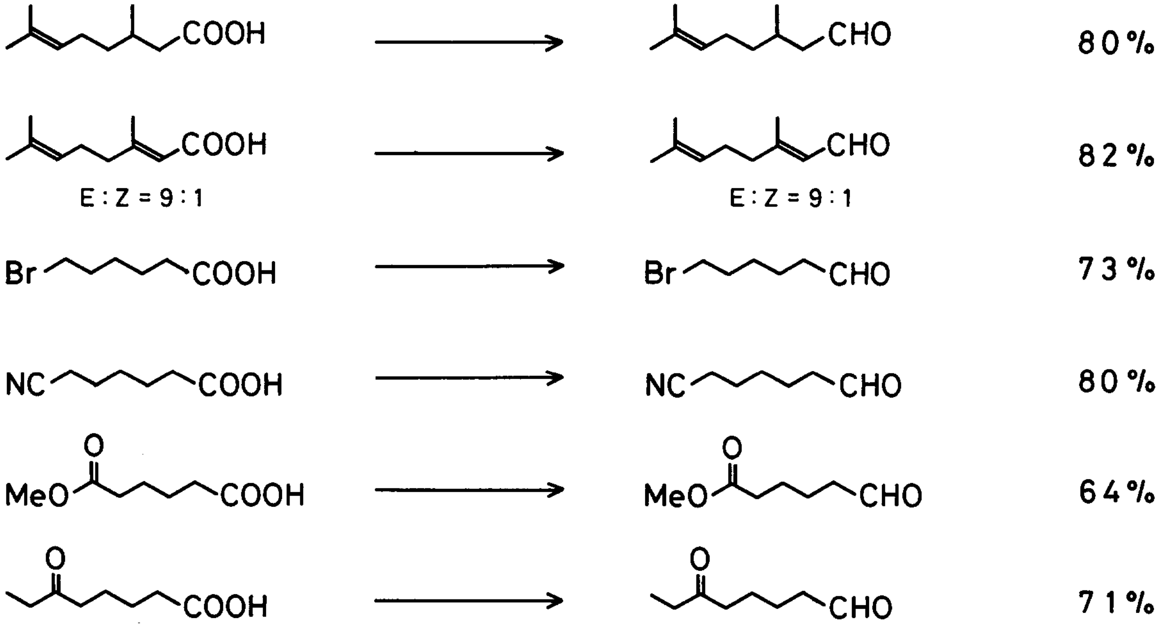
[a] All reductions were performed on 2 mmol scales with the same procedure as described in the text.
[b] Determined by GLC. [c] The products which were isolated by silica gel TLC were identified by IR and NMR spectra.

reported not to reduce aromatic carboxylic acids, slowly to reduce the alkyl ester, and easily to reduce the phenolic ester,[4c] and the amine-metal reduction[7] is reported to accompany with the reduction of aromatic ring, while the present method using the iminium chloride and $LiAlH(OBu^t)_3$ easily reduced aromatic carboxylic acids to give the corresponding aldehydes in high yields without such a trouble. Furthermore aromatic carboxylic acids with a substituent of halogen, nitro, or methoxy group was reduced chemoselectively to the corresponding aldehydes. Although heteroaromatic carboxylic acids such as furoic acid and nicotinic acid gave the corresponding aldehydes, the yield decreased in the case of the nicotinaldehyde due to poor solubility.

This rapid reduction of carboxyiminium salt by the present method provides a means for chemoselective reduction. Olefins, which react with boron hydrides, are tolerant, and geranic acid was easily converted to geranial with retention of the stereochemistry. The characteristics of the reduction with the mild reductant, $LiAlH(OBu^t)_3$, are also seen in the aliphatic series, and other various types of substituents can also be tolerated, even those which might be considered susceptible to reduction by complex hydrides, such as bromo, cyano and ester groups. The carboxylic acids with those groups were also converted chemoselectively to the corresponding aldehydes in high yields. Furthermore, 6-oxooctanoic acid, a carboxylic acid with carbonyl group, gave 6-oxooctanal in high yield. This result shows that carboxyiminium salt can be reduced easier than carbonyl group, and this technique is useful for the reduction of complex molecules in the natural product synthesis.



The representative procedure for the reduction of 3-phenylpropionic acid is as follows. Oxalyl chloride (0.5 ml) was added to a solution of *N*,*N*-dimethylformamide (2 mmol) in dichloromethane (3 ml) at 0 °C. After the solution was stirred for 1 h, the solvent was removed under a reduced pressure. To the residual white powder in acetonitrile (3 ml) and THF (5 ml) was added a solution of 3-phenylpropionic acid (2 mmol) and pyridine (2 mmol) in THF (3 ml) at -30 °C, and the reaction mixture was stirred for 1 h at the same temperature. Then, to the reaction mixture was added a suspension of 10 mol% of copper(I) iodide in THF and a solution of $LiAlH(OBu^t)_3$ (2.6 ml of 1.54M THF solution, 4 mmol) at -78 °C. After stirring for 10 min, the reaction was quenched by the addition of 2N HCl aq solution. The organic layer was extracted with ether, washed with $NaHCO_3$ aq solution and dried over $MgSO_4$. After removal of the solvent, 3-phenylpropanal was obtained by silica gel TLC (hexane:ether = 3:2) in 81% yield.

The good results by the present method are obtained from the combination of the reductant and the activating reagent of carboxylic acids. This high chemoselectivity and easy transformation into aldehydes by the reduction of carboxylic acids using iminium salt makes the present method attractive and widely applicable.[12]

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