

(Chlorosulfinyloxy)-*N,N*-dimethylmethaniminium Chloride Mediated Direct and Chemoselective Conversion of Carboxylic Acids into Aldehydes[†]

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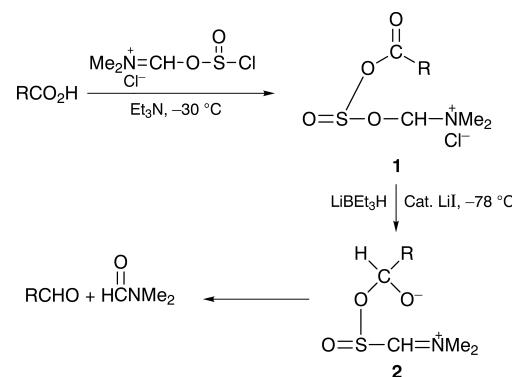
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A new method for the direct conversion of carboxylic acids into aldehydes using (chlorosulfinyloxy)*N,N*-dimethylmethaniminium chloride and lithium triethylhydroborate (super-hydride) was established which provides a convenient way for the chemoselective reduction of carboxylic acids even with such functional groups as halide, ester, nitrile, olefin and ketone.

Aldehydes often play an important role in organic synthesis. In general, carboxylic acids are transformed into aldehydes after first converting them into carboxylic acid derivatives which are more easily reduced or designed to produce stable intermediates of similar reducibility. Several processes have been employed to effect aldehyde synthesis: the Rosenmound reduction¹ or hydride reduction of acid halides,² tertiary amides,³ esters and lactones⁴ and other derivatives.⁵ It is very difficult to obtain aldehydes by direct reduction of carboxylic acids⁶ because of the easier reduction of the aldehydes. A few methods for the direct reduction have been reported which use lithium methylamide,⁷ bis(*N*-methylpiperidinyl)aluminium hydride,⁸ thexyborane⁹ or Grignard reagents catalysed by dichlorobis(η -cyclopentadienyl)titanium.¹⁰ However, they seem to be lacking in general applicability and chemoselectivity because of the different reaction conditions. On the other hand a process which involves activation of carboxylic acids *in situ* and then attack of nucleophiles was used to give the esters, amides and acid chlorides selectively. Accordingly the reduction of selectively activated intermediates of carboxylic acids *in situ* can provide a chemoselective synthetic method for aldehydes by easier reduction of the activated carboxylic acids than that of other functional groups. We report herein an example of a simple and chemoselective method to convert carboxylic acids into aldehydes using (chlorosulfinyloxy)*N,N*-dimethylmethaniminium chloride and LiBEt₃H in a one-pot operation, which enlarges the range of application of this concept and suggests a variety of new synthetic possibilities.

(Chlorosulfinyloxy)*N,N*-dimethylmethaniminium chloride¹¹ is known to activate carboxylic acid groups for the preparation of acid chlorides,¹² alkyl chlorides¹³ *gem*-dichlorides¹⁴ and ketones.¹⁵ Accordingly chemoselective conversion of carboxylic acids into aldehydes could be achieved when active carboxysulfinyloxymethaniminium chloride **1** derived *in situ* from chlorosulfinyloxy-methaniminium chloride and carboxylic acids was reduced with metal hydride to yield a stable betaine **2** as an intermediate which was in turn converted into aldehydes. Thus, a mixture of carboxylic acids and freshly prepared (chlorosulfinyloxy)*N,N*-dimethylmethaniminium chloride in the presence of triethylamine was added 10 mol% LiI and LiBEt₃H at -78 °C. Usual work-up gave the corresponding aldehydes as shown in Table 1.

When lithium carboxylates were used in place of the carboxylic acid–triethylamine system the yields decreased



because of their solubility. Addition of lithium catalyst increases the yield. The best solvent system was a mixture of acetonitrile and THF; independent use of other solvents resulted in decreased yield of the aldehydes. Other reductants such as NaBH₄ and NaBH(OMe)₃ resulted in further reduction to give alcohols. Both aliphatic and aromatic aldehydes were obtained in high yields from the corresponding carboxylic acids in a one-pot operation. Aromatic carboxylic acids with halogen, nitro or methoxy substituents were reduced chemoselectively to the corresponding aldehydes. Although heteroaromatic carboxylic acids such as furoic acid and nicotinic acid gave the corresponding aldehydes, the yield was low in the case of the nicotinaldehyde due to poor solubility.

Olefins, which react with boron hydrides, are tolerant and geranic acid was easily converted into geranal with retention of stereochemistry (experiment 16). The characteristics of the reduction with the mild reductant LiBEt₃H were also seen in the aliphatic series and other various type 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. Carboxylic acids with such groups were converted chemoselectively into the corresponding aldehydes in high yield. Furthermore, 6-oxooctanoic acid, a carboxylic acid with a second carbonyl group, gave 6-oxooctanal in high yield. This result shows that the carboxyiminium salt can be reduced more easily than a carbonyl group and that this technique should be useful for the reduction of complex molecules in natural product synthesis.

The good results obtained in the present method are achieved by a combination of a reductant and the activation of the carboxylic acids. The high chemoselectivity and easy transformation into aldehydes by the reduction of carboxylic acids using the iminium salt makes the method attractive and widely applicable.

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Table 1 Yields of aldehydes obtained by the reduction of various carboxylic acids^a

Expt. No.	Acid	Aldehyde	Yield (%) ^b
1	C ₆ H ₅ CO ₂ H	C ₆ H ₅ CHO	80 ^c
2	p-ClC ₆ H ₄ CO ₂ H	p-ClC ₆ H ₄ CHO	81 ^c
3	p-O ₂ NC ₆ H ₄ CO ₂ H	p-O ₂ NC ₆ H ₄ CHO	82
4	p-MeOC ₆ H ₄ CO ₂ H	p-MeOC ₆ H ₄ CHO	75 ^c
5	C ₆ H ₅ (CH ₂) ₂ CO ₂ H	C ₆ H ₅ (CH ₂) ₂ CHO	82
6	CH ₃ (CH ₂) ₅ CO ₂ H	CH ₃ (CH ₂) ₅ CHO	90 ^c
7	C ₆ H ₅ CH=CHCO ₂ H	C ₆ H ₅ CH=CHCHO	82
8			84 ^c
9			70 ^c
10			55
11	BrCH ₂ (CH ₂) ₄ CO ₂ H	BrCH ₂ (CH ₂) ₄ CHO	70
12	NCC ₂ (CH ₂) ₄ CO ₂ H	NCC ₂ (CH ₂) ₄ CHO	75
13			62
14	CH ₃ CH ₂ C(CH ₂) ₄ CO ₂ H	CH ₃ CH ₂ C(CH ₂) ₄ CHO	70
15	(CH ₃) ₂ =CH(CH ₂) ₂ CH(CH ₃)CH ₂ CO ₂ H	(CH ₃) ₂ =CH(CH ₂) ₂ CH(CH ₃)CH ₂ CHO	78
16			80 ^d

^aAll reductions were performed on a 2 mmol scale with the procedure described in the text. ^bThe products isolated by silica gel TLC were identified by IR and ¹H NMR spectra. ^cDetermined by GLC. ^dE:Z = 9:1.

Experimental

A representative procedure for the reduction of 3-phenylpropionic acid is as follows: (chlorosulfonyloxy)*N,N*-dimethylmethaniminium chloride was prepared by adding *N,N*-dimethylformamide (2 mmol) to thionyl chloride (2.1 mmol) in benzene, essentially according to the reported procedure.¹¹ The solvent was removed under reduced pressure. To the residue in acetonitrile (3 ml) and THF (5 ml) was added a solution of 3-phenylpropionic acid (2 mmol) and triethylamine (2 mmol) in THF (5 ml) at -30 °C and the mixture was stirred for 1 h at the same temperature. Then a suspension of 10 mol % of lithium iodide in THF and a solution of LiBEt₃H (4.0 ml of 1 M THF solution, 4 mmol) were added at -78 °C. After being stirred for 15 min the mixture was quenched by the addition of aqueous 2 M HCl. The organic layer was extracted with diethyl ether, washed with aqueous NaHCO₃ solution and dried with Na₂SO₄. After removal of the solvent, 3-phenylpropanal was obtained by silica gel TLC (hexane-ether, 3:2) in 82% yield.

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