

Letter

# *N,N*-Dimethyl(chlorosulphenyl)methaniminium chloride mediated direct and chemoselective conversion of carboxylic acids to aldehydes

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**Abstract**

A new method for the direct conversion of carboxylic acids to aldehydes using *N,N*-dimethyl(chlorosulphenyl)methaniminium chloride and lithium triethyl-borohydride (super-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. © 1998 Elsevier Science B.V. All rights reserved.

*Keywords:* Carboxylic acid; Aldehyde; *N,N*-Dimethyl(chlorosulphenyl)methaniminium chloride

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Aldehydes play often an important role in organic synthesis. In general carboxylic acids were transformed to aldehydes after they were converted into carboxylic acid derivatives which are more easily reduced than carboxylic acid 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 [2–4], *t*-amides [5,6], esters and lactones [7,8] and examples of the reduction for other carboxylic acid derivatives are shown in Refs. [9–12]. It is very difficult to obtain aldehydes by the direct reduction of carboxylic acids [13] because of easier reduction of aldehydes than carboxylic acids [13]. A few methods for the direct reduction of carboxylic acids into aldehydes have been reported to use lithium methylamine [14], bis(*N*-methylpiperidynyl) aluminium hydride [15], thexylborane [16] or Grignard reagents catalysed by dichlorobis- $[\eta$ -cyclopentadienyl]-titanium [17]. However, these methods seem to be lacking in general applicability and chemoselectivity because of several reaction conditions. On the other hand, a process which involves an 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 the selectivity 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 report herein an

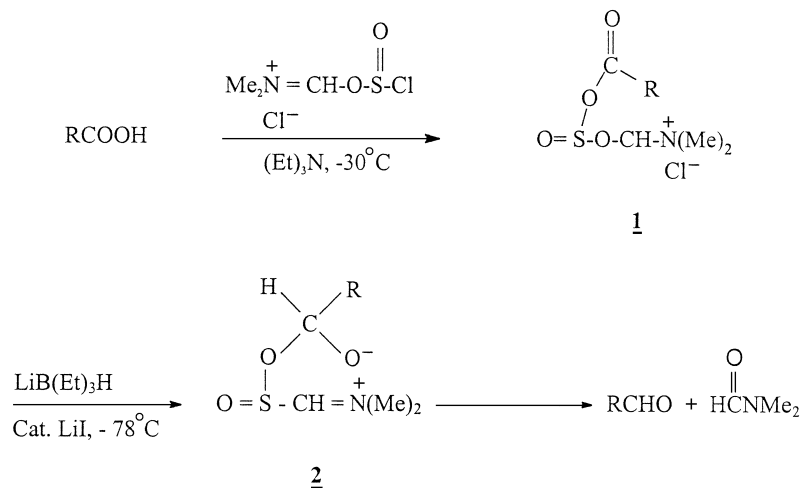
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example of a simple and chemoselective synthetic method of aldehydes by easier reduction of the activated carboxylic acids than other functional groups. We report herein an example of a simple and chemoselective method to convert carboxylic acids into aldehydes using *N,N*-dimethyl(chlorosulphenyl)methaniminium chloride and  $\text{LiB}(\text{Et})_3\text{H}$  in one pot operation, that enlarges the range of application of this concept and suggests a variety of new synthetic possibilities.

*N,N*-Dimethyl(chlorosulphenyl)methaniminium chloride<sup>1</sup> is known for activation of carboxylic acid groups for the preparation of acid chlorides [20], alkyl chlorides [21,22] *gem*-dichlorides [23] and ketones [24].

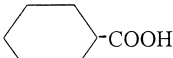
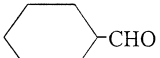
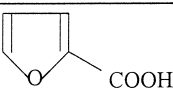
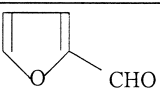
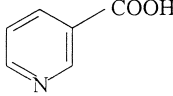
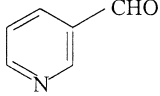
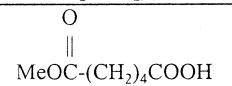
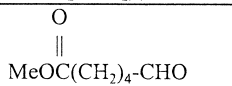
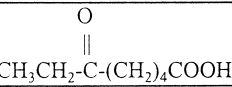
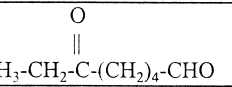
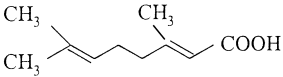
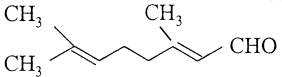
Accordingly chemoselective conversion of carboxylic acids into aldehydes could be achieved when active carboxylsulphenylmethaniminium chloride **1** derived in situ from chlorosulphenylmethaniminium chloride and carboxylic acids are reduced with metal hydride to yield a stable betaine **2** as an intermediate which is in turn converted into aldehydes. Although the betaine formation was not yet verified experimentally, Entwistle et al. had speculated it as an intermediate of the reduction of carboxymethyleniminium salt with  $\text{NaBH}_4\text{-CdCl}_2$  [25]. Thus, a reaction mixture of carboxylic acids and freshly prepared *N,N*-dimethyl(chlorosulphenyl)methaniminium chloride in the presence of triethylamine was added 10 mol%  $\text{LiI}$  and  $\text{LiB}(\text{Et})_3\text{H}$  at  $-78^\circ\text{C}$ . The 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. An effect of addition of lithium catalyst causes the increase of 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  $\text{NaBH}_4$  and  $\text{NaBH}(\text{OMe})_3$  resulted in the further reduction to give alcohols. Both aliphatic and aromatic aldehyde were obtained in high yields from the corresponding carboxylic acids in a one pot operation by the present method. Aromatic carboxylic acids with substituent of halogen, nitro or methoxy group were 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.

<sup>1</sup> For preparation and some of the applications of the reagent see Refs. [18,19].

Table 1  
Yields of aldehydes by the reduction of various carboxylic acids<sup>a</sup>

Sl. No.	Acid	Aldehyde	Yield (%) <sup>b</sup>
1.	C <sub>6</sub> H <sub>5</sub> COOH	C <sub>6</sub> H <sub>5</sub> CHO	80 <sup>c</sup>
2.	pCl-C <sub>6</sub> H <sub>4</sub> COOH	pCl-C <sub>6</sub> H <sub>4</sub> CHO	81 <sup>c</sup>
3.	pNO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> COOH	pNO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> CHO	82
4.	pMeO-C <sub>6</sub> H <sub>4</sub> COOH	pMeO-C <sub>6</sub> H <sub>4</sub> CHO	75 <sup>c</sup>
5.	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub> COOH	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub> CHO	82 <sup>c</sup>
6.	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> COOH	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> CHO	90 <sup>c</sup>
7.	C <sub>6</sub> H <sub>5</sub> -CH=CH-COOH	C <sub>6</sub> H <sub>5</sub> -CH=CH-CHO	82
8.			84 <sup>c</sup>
9.			70 <sup>c</sup>
10.			55
11.	Br-CH <sub>2</sub> (CH <sub>2</sub> ) <sub>4</sub> -COOH	Br-CH <sub>2</sub> (CH <sub>2</sub> ) <sub>4</sub> -CHO	70
12.	NC-CH <sub>2</sub> (CH <sub>2</sub> ) <sub>4</sub> -COOH	NC-CH <sub>2</sub> (CH <sub>2</sub> ) <sub>4</sub> -CHO	75
13.			62
14.			70
15.	(CH <sub>3</sub> ) <sub>2</sub> C=CH-(CH <sub>2</sub> ) <sub>2</sub> -CH(CH <sub>3</sub> )CH <sub>2</sub> COOH	(CH <sub>3</sub> ) <sub>2</sub> C=CH-(CH <sub>2</sub> ) <sub>2</sub> -CH(CH <sub>3</sub> )-CH <sub>2</sub> CHO	78
16.			80 <sup>d</sup>

<sup>a</sup>All reductions were performed in 2 mmol scales with the sample procedure as described in the text.

<sup>b</sup>The products which were isolated by silica gel TLC were identified by IR and <sup>1</sup>H NMR spectra and compared with authentic samples.

<sup>c</sup>Determined by GLC.

<sup>d</sup>E:Z = 9:1.

Olefins, which react with boron hydrides are tolerant and geranic acid has easily converted to geranial with retention of stereochemistry (run 16). The characteristics of the reduction with the mild reduction LiB(Et)<sub>3</sub>H, 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. The carboxylic acids with those groups were also converted chemoselectively to 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 carboxyiminium salt can be reduced more easily 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: *N,N*-dimethyl(chlorosulphenyl)methaniminium chloride was prepared by adding *N,N*-dimethylformamide

(2 mmol) to thionyl chloride (2.1 mmol) in benzene, essentially according to reported procedure [18,19]. The solvent was removed under reduced pressure. To this 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  $-30^{\circ}\text{C}$  and the reaction mixture was stirred for 1 h at the same temp. Then to reaction mixture was added a suspension of 10 mol% of lithium iodide in THF and a solution of  $\text{LiB}(\text{Et})_3\text{H}$  (4.0 ml of 1 M THF solution, 4 mmol) at  $-78^{\circ}\text{C}$ . After being stirred for 15 min. the reaction was quenched by the addition of 2 N HCl aq. solution. The organic layer was extracted with ether, washed with aq.  $\text{NaHCO}_3$  solution and dried with  $\text{Na}_2\text{SO}_4$ . After removal for the solvent, 3-phenyl-propanol was obtained by silica gel TLC (hexane:ether = 3:2) in 82% yield.

The good results by the present method are obtained from the combination of 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.

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