

Transformation of Carboxylic Acid Salts to Aldehydes by Stepwise Reduction with Borane and Oxidation with Pyridinium Chlorochromate

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The stepwise reduction-oxidation method has been successfully applied to conversion of carboxylic acid salts to the corresponding aldehydes. Thus, both sodium and lithium salts of carboxylic acid were readily converted to aldehydes in essentially quantitative yields by stepwise treatment with borane and dimethyl sulfate, and followed by oxidation with PCC. Alternatively, the treatment of acid salts with two equivalents of borane in THF, and followed by the oxidation also provided the same results.

Keywords: Stepwise reduction-oxidation, Borane reduction, PCC oxidation, Conversion of carboxylic acid salts to aldehydes, Aldehyde synthesis.

Introduction

The development of general, facile and convenient methods for transformation of carboxylic acid and its derivatives into the corresponding aldehydes is one of the most desirable subjects in organic synthesis. There have appeared several useful methods using metal hydride reducing systems for such purpose in the literature. Thus, carboxylic acid itself¹ and its derivatives, such as acid chlorides,² esters,³ amides,⁴ and nitriles,⁵ have been readily converted to the corresponding aldehydes.

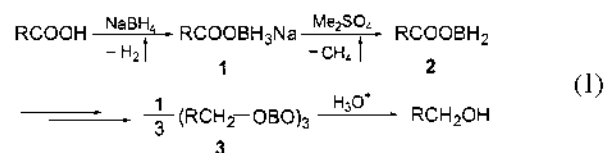
In addition to that, we reported that carboxylic acid metal salts are converted to the corresponding aldehydes in moderate to high yields by two equivalents of the hexylborane-methyl sulfide ($\text{Thx}(\text{BHBr} \cdot \text{SMe}_2)$)⁶ or 9-borabicyclo-[3.3.1]nonane (9-BBN).⁷ Although these procedures provided promising routes to convert carboxylic acid salts to aldehydes, a really clean conversion has escaped us. Thus, the yields of aromatic aldehydes are significantly lower than those in the aliphatic series and appear to be influenced by substituents on the aromatic ring.

Recently, we have found that the stepwise reduction-oxidation method provides an apparently ideal procedure for conversion of carboxylic acid⁸ and its derivatives such as esters⁹ and acid chlorides¹⁰ to the corresponding aldehydes. This procedure involves the complete reduction of such derivatives to an alcohol stage with a suitable reducing agent, followed by oxidation of the resultant intermediate with pyridinium chlorochromate (PCC) or pyridinium dichromate (PDC). This method intrigued us, because we can get aldehydes from carboxylic acid salts if any pertinent reducing system, which can convert such a reduction-resistant carboxylic acid salt to alcohol stage, is available. This paper describes such an equally facile conversion of carboxylic acid salts to aldehydes.

A portion of our results has appeared in the form of preliminary report.¹¹ We now describe in full a new, convenient method which effects such transformation.

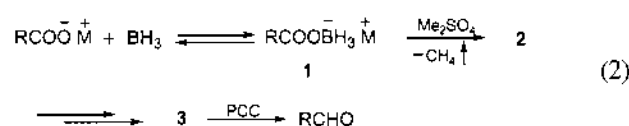
Results and Discussion

Stepwise Reduction-Oxidation with Borane-Dimethyl Sulfate and PCC. Carboxylic acids are readily reduced to alcohols by stepwise treatment with sodium borohydride and dimethyl sulfate (eq. 1).¹² This method involves the reaction of carboxylic acid with sodium borohydride to form acyloxyborohydride **1**, followed by the treatment of **1** with dimethyl sulfate to yield acyloxyborane **2**, a reactive intermediate. The initial reaction product in such reduction has been identified as the corresponding trialkoxyboroxine **3**.¹³



On the basis of this mechanistic point of view, if a carboxylate reacts with borane in THF to form an ate complex, which is the same species **1** as depicted in eq. 1, we should expect that in the presence of dimethyl sulfate the system follows the exactly same reduction pathway until the boroxine **3** forms.

Actually carboxylate readily reacts with borane in THF to form ate complex (acyloxyborohydride **1**), the equilibrium being driven over to the right by the reaction with dimethyl sulfate and hence evolution of methane gas to yield acyloxyborane **2**. Finally, the oxidation of the resultant boroxine **3** with PCC yields aldehydes (eq. 2).



This procedure converts both sodium and lithium salts of most aliphatic carboxylic acids to aldehydes in essentially quantitative yields, as shown in Table 1, except α,β -

Table 1. Conversion of Carboxylic Acid Metal Salts to Aldehydes by Stepwise Reduction-Oxidation with Borane and Pyridinium Chlorochromate (PCC) in Tetrahydrofuran

Acid salt	Yield of aldehyde, ^a %			
	BH ₃ -Me ₂ SO ₄ ^{b,d}		Two equiv BH ₃ ^{c,d}	
	Na salt	Li salt	Na salt	Li salt
butyric	98	100	99	100
hexanoic	98(81) ^f	100(82) ^f	~100	~100
decanoic	99	100	99	100
stearic	98	99	99	99
isobutyric	98	96	99	100
pivalic	100	100	100	100
cyclohexanecarboxylic	98	99	99	99
diphenylacetic	99	99	–	–
6-bromohexanoic	99	100	99	100
α-camphoric	98	99	–	–
cinnamic	8	9	7	8
crotonic	5	–	–	–
benzoic	100(80) ^f	100(81) ^f	100	100
<i>o</i> -chlorobenzoic	98	100	98	99
<i>p</i> -chlorobenzoic	99	100	99	100
<i>p</i> -methoxybenzoic	99	100	99	99
<i>p</i> -nitrobenzoic	100	99	–	–
<i>m</i> -toluic	99	100	99	100
<i>p</i> -toluic	99	100	100	100
<i>p</i> -cyanobenzoic	10	15	8	12
terephthalic ^e	35	40	50	56

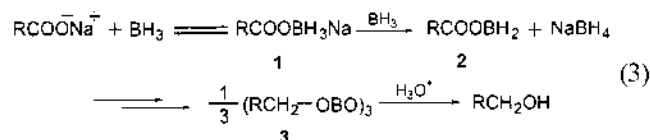
^aGC yields. ^bReacted with 10% excess BH₃-THF and dimethyl sulfate at 25 °C, except that Na salts of aliphatic acids run at 15 °C, followed by treatment with 10% excess PCC for 6 h at 25 °C for aromatic and for 3 h under reflux for aliphatic acid salts. ^cReacted with 2 equiv BH₃-THF at 25 °C, followed by treatment with 2.1 equiv PCC for 3 h under reflux or for 12 h at 25 °C. ^dAldehyde products were confirmed by authentic samples and GC yields were estimated by internal standards. ^eIsolated yields of distilled product. ^fDouble quantity of reagents utilized.

unsaturated acids such as cinnamic and crotonic acids. In all cases there is no bias in yields between sodium and lithium salts. The reduction proceeds readily as the mixture of a carboxylate and 1.1 equiv of borane in the presence of dimethyl sulfate in THF; the oxidation also proceeds readily *in situ* in the reaction mixture with 10% excess PCC.

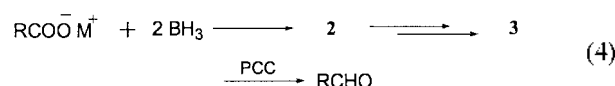
Just as in the reaction of aliphatic carboxylic acid salts by this procedure, the reaction of both sodium and lithium salts of aromatic series gives the corresponding aldehydes in essentially quantitative yields. Moreover, there is no variance in yields with the substituents on the benzene ring. However, the derivatives bearing a readily reducible cyano group by borane, such as *p*-cyanobenzoic acid salts, afford very low yields of aldehydes. Dicarboxylic acid salts such as disalts of terephthalic acid also fail to provide satisfactory yields of dialdehyde (35-40%). Apparently, this process provided an ideal procedure for such transformation. However, there is a precaution in the reaction of sodium derivatives. Free borane itself, apparently exists in equilibrium as depicted in eq. 2, could react with dimethyl sulfate, that might result in a significant loss of aldehyde product. In order to

overcome this difficulty, the reaction temperature should be maintained below 15 °C.

Stepwise Reduction-Oxidation with Two Equivalents of Borane and PCC in THF. About two decades ago, Yoon and Cho reported that carboxylic acid sodium salts are reduced rapidly to the corresponding alcohols with two molar equivalents of borane-THF, while the reduction with one molar equivalent of borane-THF is quite sluggish.¹⁴ The authors concluded that the reduction proceeds *via* acyloxyborane **2** which is formed from the reaction of acyloxyborohydride **1** and borane (eq. 3). In this reaction, the second mole of borane behaved as a Lewis acid.



On the basis of this mechanistic point of view, we adopted this procedure to our reaction. Thus, carboxylic acid metal salts are treated with one more equivalent of borane (*i.e.*: two equivalents) in place of dimethyl sulfate. Actually, carboxylate readily reacts with two equivalents of borane in THF to form acyloxyborane **2**, and the reductive process follows. In this reaction, there is no limitation in the reaction temperature: both sodium and lithium derivatives are readily reduced to the corresponding alcohol stages at 25 °C. Finally, the oxidation of the resultant boroxine with PCC yields aldehydes (eq. 4).



This procedure converts both sodium and lithium salts of most aliphatic and aromatic carboxylic acids to aldehydes in essentially quantitative yields, as shown in Table 1. In all cases there is no bias in yields between sodium and lithium salts. Moreover, no variance in yields with the substituents on the benzene ring is realized. However, the derivatives bearing readily reducible functional groups, such as cyano and alkenyl functions, by borane and sodium borohydride afford very low yields of aldehyde. Dicarboxylic acid salts such as disalts of terephthalic acid provide relatively low yields of dialdehyde (50-56%). The reduction proceeds readily as the mixture of a carboxylate and two equivalents of borane in THF; the oxidation also proceeds readily *in situ* in the reaction mixture with two equivalents of PCC.

Conclusion

Carboxylic acid metal salts are readily converted to the corresponding aldehydes in essentially quantitative yields by stepwise treatment with borane and dimethyl sulfate, and followed by oxidation with PCC. Alternatively, the treatment of acid salts with two equivalents of borane, and followed by the oxidation also provides the same results.

These processes are broadly applicable so far as the

borane-sensitive groups,¹³ such as cyano and alkenyl functions, are absent. The mild nature of both borane and PCC makes these methods simple, general and practical. Consequently, these new processes, based on the reductive oxidation method, provide an apparently ideal procedure for conversion of carboxylic acid salts to the corresponding aldehydes.

Experimental Section

Techniques for handling air-sensitive compounds have been previously described.¹⁵ All glassware used in this study was oven-dried, assembled hot and cooled to room temperature in a stream of nitrogen.

All reactions were performed under a dry nitrogen atmosphere. The liquids were transferred with syringes or double-ended needles. All chemicals used were commercial products of the highest purity available. CH_2Cl_2 was stirred under a nitrogen atmosphere for 1 day over P_4O_{10} and distilled; THF was dried over 4-Å molecular sieves and distilled from sodium-benzophenone ketyl prior to use. The Na and Li salts of carboxylic acid were prepared by standard methods using NaOH and LiH. A solution of BH_3 in THF was prepared by the reaction NaBH_4 and Me_2SO_4 in THF. The aldehyde products were confirmed by authentic sample and the GC yields were estimated by internal standards.

Reduction of Carboxylic Acid Salts with Borane-Dimethyl Sulfate. The following procedure for the reduction of lithium hexanoate is illustrative for both GC analysis and the larger scale reaction. An oven-dried, 250-mL flask, fitted with a side arm capped by a rubber septum and attached to a gas meter, was charged with 7.57 g (62 mmol) of lithium hexanoate and 62 mL of THF. The flask was maintained at 25 °C with a circular water bath. A 1.2 M solution of BH_3 in THF (56.9 mL, 68.2 mmol) was added slowly with stirring, and the slurry was stirred for 1 h at 25 °C. To this mixture, 6.4 mL (68.2 mmol) of dimethyl sulfate was added slowly at 25 °C.¹⁶ Methane gas was liberated in approximately 3 h. A small portion of the reaction mixture was withdrawn and hydrolyzed with 2 N HCl. GC analysis of the dried organic layer using an internal standard (dodecane) indicated the presence of hexanol in a yield of 100%.

Oxidation of Intermediate Formed from Reduction by Borane-Dimethyl Sulfate. To a well-stirred suspension of PCC (14.4 g, 67 mmol) in CH_2Cl_2 (100 mL) taken in a 500-mL flask was added dropwise the above reaction mixture (61 mmol) using a cannula, the mixture was stirred for 3 h under gentle reflux.¹⁷ A small portion of this mixture was withdrawn and tridecane was added as an internal standard. The mixture was then filtered through Florisil[®]. GC analysis indicated the presence of hexanal in a yield of 100%.

Isolation of Product Aldehydes. After the GC analysis, the rest of the reaction mixture (60 mmol) was diluted with ethyl ether (200 mL). The supernatant liquid was filtered through Florisil[®] (200 g) contained on a 300-mL sintered glass funnel. The insoluble solid residue was triturated with

ethyl ether (3 × 50 mL) and passed through the same Florisil[®] column. The combined filtrate was concentrated and distilled to give pure hexanal (4.93 g, 82%); bp 129-130 °C (755 mmHg); n_D^{20} 1.4037.

Reduction of Carboxylic Acid Salts with Two Equivalents of Borane in THF. The following procedure for the reduction of sodium hexanoate is illustrative for quantitative GC analysis. An oven-dried, 250-mL flask, fitted with a side arm capped by a rubber septum and attached to a mercury bubbler, was charged with 0.75 g (5 mmol) of sodium hexanoate and 5 mL of THF. The flask was maintained at 25 °C with a circular water bath. A 1.2 M solution of BH_3 in THF (9 mL, 11 mmol) was added slowly with stirring, and the slurry was stirred for 3 h at 25 °C. GC analysis of the small portion of dried organic layer using an internal standard (dodecane) indicated the presence of hexanol in a yield of 100%.

Oxidation of Intermediate Formed from Reduction by Two Equivalents of Borane. To a well-stirred suspension of PCC (1.9 g, 9 mmol) in CH_2Cl_2 (14 mL) taken in a 100-mL flask was added dropwise the above reaction mixture (4 mmol) using a cannula, and the mixture was stirred for 3 h under gentle reflux.¹⁸ To this was added tridecane as an internal standard, and the mixture was then filtered through Florisil[®]. GC analysis of the dried solution indicated the presence of hexanal in an almost quantitative yield (~100%).

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16. In the case of Na salts of aliphatic carboxylic acid, the reaction temperature should be maintained below 15 °C; the yields of aldehydes drops significantly above that temperature.
17. The oxidation requires 3 hrs under reflux or 12 hrs at room temperature for the aliphatic series; 6 hrs at room temperature for the aromatic series.
18. The oxidation requires 3 hrs under reflux or 12 hrs at room temperature.