

Reductive Oxidation of Acid Chlorides to Aldehydes with Sodium Borohydride and Pyridinium Chlorochromate

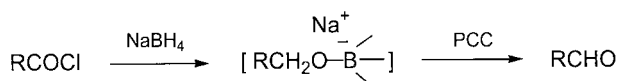
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The establishment of a simple, general and practical method to get aldehydes from acid chlorides is one of the most desirable objects in organic synthesis. Recently, we reported that the oxidation of alkoxyaluminum intermediates, which are formed by reduction of acid chlorides with aluminum hydride, with pyridinium chlorochromate (PCC) or pyridinium dichromate (PDC), affords aldehydes in excellent yields.¹ But this method did not provide a really simple and practical procedure. The reducing agent, aluminum hydride, exhibits a very strong reducing power which results in attacking almost all of the organic functional groups.² In addition to this, the reagent should be prepared just prior to use.^{2a}

Recently, we successfully applied sodium borohydride, a very mild and economical reducing agent, to the reductive oxidation for conversion of carboxylic acids to aldehydes.³ On the basis of these results, we decided to utilize sodium borohydride as a reducing agent to carry out reductive oxidation to convert acid chlorides to aldehydes. Herein, we introduce a new method, which effects the transformation of acid chlorides to aldehydes in excellent yields.



Although there has already been reported that sodium borohydride reduces acid chlorides to alcohols readily,⁴ we reexamined such reductions in THF or THF-DMF. The reagent reduce both aromatic and aliphatic acid chlorides to the corresponding alcohols in refluxing THF (*Procedure A*) or in THF-DMF (1 : 1) at 25° (*Procedure B*) both in 24h : the yields of alcohols from both procedures were higher than 98%. We applied such procedures to reduction of acid chlorides to the corresponding alkoxyborates stage, and the resultant borates are then subjected to the oxidation procedure with PCC.

As shown in Table 1, this procedure provides a clean and convenient conversion of acid chlorides to aldehydes. Both aliphatic and aromatic acid chlorides are readily converted to the corresponding aldehydes in excellent yields. The oxidation of aliphatic borates requires 2.5 equivalents of PCC, while the oxidation of aromatic borates needs only 10% excess. However, the oxidation in THF-DMF-CH₂Cl₂ (1 : 1 : 2) appears to be more effective than the procedure in THF-CH₂Cl₂ (1 : 1). Therefore, it appears that the reduction of acid chlorides in THF-DMF (1 : 1) at 25° (*Procedure B*) followed by oxidation of the resultant alkoxyborates with PCC in THF-DMF-CH₂Cl₂ (1 : 1 : 2) is recommendable for conversion of acid chlorides to aldehydes.

This reaction is broadly applicable as many substituents, such as chloro, methoxy, nitro and alkenyl groups are tolerated. The tolerance of sodium borohydride toward a wide variety of functional groups as well as its ease of handling and low cost, combined with the mild nature of PCC as an oxidizing agent, makes this method simple, general and practical. It is noteworthy that the use of sodium borohydride can provide more selective reactions than the use of aluminum hydride, because sodium borohydride is milder and hence more selective than aluminum hydride.² Moreover, we are now free from preparing a solution of aluminum hydride prior to use. Consequently, this method provides another useful procedure for direct conversion of acid chlorides to the corresponding aldehydes.^{5,6}

Experimental Section

All glassware used was dried thoroughly in a drying oven at 130°, assembled hot, and cooled under a stream of dry nitrogen prior to use. All reactions and manipulations of air and moisture-sensitive materials were carried out under a dry nitrogen atmosphere. All chemicals were commercial products of the highest purity which were carefully purified by standard methods before use. The acid chlorides were commercial products and purified by distillation. Tetrahydrofuran (THF) was distilled from benzophenone-sodium ketyl. Sodium borohydride (NaBH₄) and pyridinium chlorochromate (PCC) were used as received from Aldrich Chemical Co. Yields reported in all cases are of analytically pure compounds. GC analyses were carried out on a Varian 3300 FID chromatograph equipped with a Varian 4400 integrator using Carbowax 20M capillary column.

Reduction of Acid Chlorides (Formation of Alkoxyborate Intermediates). The following two different procedures for the reduction of acid chlorides to alkoxyborate intermediates are listed in Table 1.

Procedure A: Into an oven-dried, 100-mL, round-bottomed flask with a side-arm, fitted with a silicon rubber cap, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler was introduced 0.38 g (10 mmol) of sodium borohydride, followed by 18 mL of THF. To this slurry, 1.40 g (10 mmol) of benzoyl chloride was added. The reaction mixture was then brought to a gentle reflux for 24h with vigorous stirring. The reaction mixture was subjected to oxidation (*vide infra*).

Procedure B: Into a 100-mL flask equipped as described above (*Procedure A*), was added 0.38 g (10 mmol) of sodium borohydride, followed by 9 mL of THF and 9 mL of

Table 1. Conversion of Acid Chlorides to Aldehydes by Reductive Oxidation with Sodium Borohydride (NaBH₄) and Pyridinium Chlorochromate (PCC)

Acid Chloride	Product	Reduction Procedure ^{a,b}		Oxidation ^{c,d}	Yield (%) ^e
		A or B		Time (h)	
Butyryl	Butyraldehyde	B		6	95
Isobutyryl	Isobutyraldehyde	B		6	96
Hexanoyl	Hexanal	A		6	92
		B		24	94
Trimethylacetyl	Trimethylacetaldehyde	B		6	71 ^f , 97(80)
		A		6	93
		B		6	61 ^f , 96
Trichloroacetyl	Trichloroacetaldehyde	B		6	95
Cyclopropanecarbonyl	Cyclopropanecarboxaldehyde	B		6	97
Cyclohexanecarbonyl	Cyclohexanecarboxaldehyde	B		6	98
Cinnamoyl	Cinnamaldehyde	B		6	97
Benzoyl	Benzaldehyde	A		6	98
		B		24	99
		B		6	94, 99 ^f
				24	99(81)
1-Naphthoyl	1-Naphthaldehyde	B		6	98
2-Naphthoyl	2-Naphthaldehyde	B		6	97
<i>o</i> -Toluoyl	<i>o</i> -Tolualdehyde	B		6	96
<i>p</i> -Toluoyl	<i>p</i> -Tolualdehyde	A		6	94
		B		6	99
2-Chlorobenzoyl	2-Chlorobenzaldehyde	A		6	91
		B		6	97
4-Chlorobenzoyl	4-Chlorobenzaldehyde	A		6	90
		B		6	98
<i>o</i> -Anisoyl	<i>o</i> -Anisaldehyde	A		6	90
		B		6	97
<i>p</i> -Anisoyl	<i>p</i> -Anisaldehyde	A		6	90
		B		6	98
4-Nitrobenzoyl	<i>p</i> -Nitrobenzaldehyde	A		6	92
		B		6	97

^aTreated with 1 equiv NaBH₄. ^bProcedure A: reacted for 24h in refluxing THF; Procedure B: reacted for 24h at 25° in a THF-DMF (1 : 1) mixture solvent. ^cIn a THF-CH₂Cl₂ (1 : 1) or THF-DMF-CH₂Cl₂ (1 : 1 : 2) mixture solvent. ^dReacted with 2.5 equiv PCC for aliphatic acid chlorides and 1.1 equiv for aromatic acid chlorides at room temperature. ^eGC yields; the values in parentheses are isolated yields. ^fReacted with 2 equiv PCC at room temperature.

DMF. Finally, 1.40 g (10 mmol) of benzoyl chloride was added to this solution of sodium borohydride with stirring. The reaction mixture was stirred for 24h at room temperature, and then subjected to oxidation (*vide infra*).

Oxidation of Alkoxyborate Intermediate. To a well-stirred suspension of PCC (2.4 g, 11 mmol) in methylene chloride (18 mL) taken in a 100-mL flask, was added dropwise the above reaction mixture (from procedure A or B) using a cannula. The mixture was stirred for 24h at room temperature. GC analysis of an aliquot using tridecane as an internal standard indicated a yield of 99%.

Isolation of Product Aldehydes. The procedure for the isolation of benzaldehyde in the reaction mixture is illustrative. In the usual setup, 60 mmol of benzoyl chloride was reduced with 60 mmol of sodium borohydride in a THF-DMF (1 : 1) mixture solvent (108 mL) at room temperature for 24h, the same as the procedure B described above. The reaction mixture was then oxidized with PCC (14.3 g, 66 mmol) in methylene chloride (108 mL) at room temperature

for 24h. The mixture was diluted with ethyl ether (200 mL) and the supernatant liquid was filtered through Florisil® (110 g) contained in a 300-mL sintered glass funnel. The solid residue was triturated with ethyl ether (3 × 50 mL) and passed through the same Florisil column. The filtrate was then concentrated and distilled under reduced pressure to give 5.16 g (81%) of pure benzaldehyde, bp. 63-65° (16 mm). The ¹H NMR spectrum agreed with that of an authentic sample.

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