

An Effective One-pot Synthesis of Aldehydes from Acid Chlorides

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The establishment of a simple, general and practical method to get aldehydes from acid chlorides is one of the most important and highly desirable objectives in organic synthesis, and a number of reducing agents for this purpose have been reported. It has been reported that several reducing agents for partial reduction of acid chlorides, such as Li(*t*-BuO)₃AlH,¹ NaBH₄-DMF,² [(PPh₃)₂CuBH₃CN]₂,³ (PPh₃)₂CuBH₄,⁴ and sodium diethyldihydroaluminumate (SDDA)-piperidine,⁵ can be used. Among these, the SDDA-piperidine system with acid chlorides is usually considered to be the method of choice. However, the yields of aldehydes from various acid chlorides are moderate to good (61-93%) and this method has a great problem in that the use of SDDA is not commercially feasible now.

We have recently reported that lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA),^{6a} sodium diisobutyl-*t*-butoxyaluminum hydride (SDBBA),^{6b} and potassium diisobutyl-*t*-butoxyaluminum hydride (PDBBA),^{6c} the *t*-butoxy 'ate' complexes of DIBAL, are new effective partial reducing agents which can convert various esters to aldehydes in very good yields.

With these results in hand, we anticipated that treatment of several acid chlorides with metal diisobutyl-*t*-butoxyaluminum hydrides (LDBBA, SDBBA and PDBBA) would be effective in developing an efficient method for partial reduction of acid chlorides. However, we could not get the corresponding aldehydes by these reducing agents only, but alcohols. Next, we tried the similar reactions of benzoyl

chloride with the reducing agents and secondary amines such as morpholine for obtaining benzaldehyde from benzoyl chloride. Among these, we could find the best results with PDBBA at room temperature (Table 1).

Also, as shown in Table 2, we examined partial reduction of benzoyl chloride to benzaldehyde with PDBBA in the presence of various secondary amines such as diethylamine, dicyclohexylamine, piperidine, pyrrolidine, pyrrole and indole. However, we could not find better results than those with morpholine. Finally, we applied PDBBA in the pre-

Table 2. One-pot reduction of benzoyl chloride with PDBBA in the presence of various secondary amines^a

Entry	<i>sec</i> -Amine	Hydride	Yield of aldehyde (%) ^b
1	morpholine	PDBBA	95
2	piperidine		87
3	pyrrolidine		81
4	diethylamine		0
5	dicyclohexylamine		1
6	pyrrole		6
7	indole		23

^aBenzoyl chloride:*sec*-amine = 1.0:2.0:2.0. ^bDetermined yields by GC after reacted 6 h.

Table 3. Yields of aldehydes in the reduction of representative acid chlorides with PDBBA in the presence of morpholine at room temperature^{8,9}

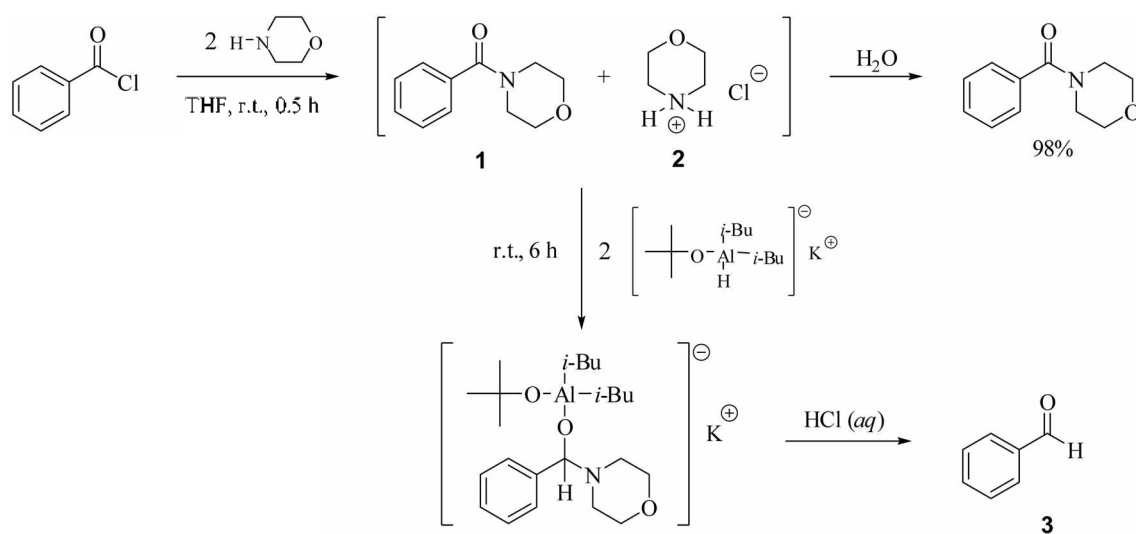
Entry	Compound	Reaction condition			Yield of aldehyde (%) ^a
		<i>sec</i> -amine	H ⁺	time (h)	
1	benzoyl chloride	2.0	2.0	6	95
2	4-fluorobenzoyl chloride	2.0	2.0	6	92
3	3-chlorobenzoyl chloride	2.0	2.0	6	96 (86) ^b
4	4-chlorobenzoyl chloride	2.0	2.0	6	94
5	4-bromobenzoyl chloride	2.0	2.0	6	96
6	4-nitrobenzoyl chloride	2.0	2.0	6	99 (88) ^b
7	4-methylbenzoyl chloride	2.0	2.0	6	93
8	4-methoxybenzoyl chloride	2.0	2.0	6	95
9	2-naphthoyl chloride	2.0	2.0	6	96 (83) ^b
10	2-furoyl chloride	2.0	2.0	6	94
11	hexanoyl chloride	2.0	2.0	6	97
12	undecanoyl chloride	2.0	2.0	6	92
13	cinnamoyl chloride	2.0	2.0	6	94

^aYields were determined by GC. ^bIsolated yields.

Table 1. One-pot reduction of benzoyl chloride to benzaldehyde with various reducing agents in the presence of morpholine

Entry	Hydride	Reaction condition				Yield of aldehyde (%) ^a
		morpholine	H ⁺	time (h)	temp.	
1	DIBAL	2.0	2.0	3	r.t.	34
2		2.0	2.0	12	r.t.	40
3	LDBBA	2.0	2.0	3	r.t.	82
4		2.0	2.0	6	r.t.	86
5		2.0	2.0	12	r.t.	88
6	SDBBA	2.0	2.0	3	r.t.	86
7		2.0	2.0	6	r.t.	87
8		2.0	2.0	12	r.t.	88
9	PDBBA	2.0	2.0	3	r.t.	81
10		2.0	2.0	6	r.t.	95
11		2.0	2.0	12	r.t.	89

^aYields were determined by GC.



sence of morpholine for the synthesis of aldehydes from representative acid chlorides at room temperature. Table 3 summarizes the results of successive treatment of various acid chlorides.

As shown in Table 3,⁷ in addition to benzoyl chloride (entry 1 in Table 3), acid chlorides with electron-withdrawing substituents such as 4-fluorobenzoyl chloride, 3-chlorobenzoyl chloride, 4-chlorobenzoyl chloride, 4-bromobenzoyl chloride and 4-nitrobenzoyl chloride, and electron-donating substituents such as 4-methoxybenzoyl chloride and 4-methylbenzoyl chloride were readily reduced to the corresponding aldehydes in 92–99% yields (entries 2–8 in Table 3). Similarly, reduction of other aromatic acid chlorides such as 2-naphthoyl chloride and 2-furoyl chloride gave the corresponding aldehydes in 96% and 94% yield, respectively (entries 9 and 10 in Table 3). Furthermore, aliphatic acid chlorides such as hexanoyl chloride and undecanoyl chloride were smoothly reduced to the corresponding aldehydes in 97% and 92% yield, respectively (entries 11 and 12 in Table 3). Also, cinnamoyl chloride, an α,β -unsaturated acid chloride, gave 94% yield of cinnamaldehyde (entry 13 in Table 3).

A proposed mechanism of this reaction is as follows (Scheme 1). Reaction of one equivalent of benzoyl chloride and morpholine rapidly forms more stable tertiary amide intermediate 1. Also, quaternary amine salt 2 was produced by the reaction of remaining one equivalent of the morpholine with the hydrochloride that is a side product for the prepared amide. Then, one of two equivalent of PDBBA reacted with the resulting amide 2 at room temperature to form the benzaldehyde 3 in 95% yield after acidic work-up, and another of PDBBA reacted with a proton in the amine salt to evolve hydrogen gas.

In summary, an effective and useful method for synthesizing aldehydes from acid chlorides has been developed. This method is believed to be the best synthetic tool for the synthesis of aldehydes from acid chlorides up to now.

References and Notes

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- All glassware used was dried thoroughly in an oven, assembled hot, and cooled under a stream of dry nitrogen prior to use. All reactions and manipulation of air- and moisture sensitive materials were carried out by standard techniques for handling air-sensitive materials. All chemicals were commercial products of the highest pure which were purified further by standard methods before use. THF was dried over sodium-benzophenone and distilled. Diisobutylaluminum hydride (DIBALH) and sodium *t*-butoxide were purchased from Aldrich Chemical Company. GC analyses were performed on a Donam DS 6200 FID chromatograph using a HP-1 (crosslinked methyl siloxane) capillary column (30 m). All GC yields were determined with the use of a suitable internal standard and authentic mixture.
- Preparation of PDBBA.** To a solution of potassium *t*-butoxide (5.89 g, 52.5 mmol) in THF (25 mL) was added dropwise DIBALH (50 mL, 1.0 M in hexane, 50 mmol) at 0 °C and the mixture was stirred for 2 h at room temperature to give a colorless homogeneous solution. The concentration of PDBBA solution in THF-hexane was measured gasometrically by hydrolysis of an aliquot of the solution with a hydrolyzing mixture of *t*-butyl alcohol-THF (1:1) at 0 °C.
- Reduction of acid chlorides to aldehydes.** The following procedure for the reduction of benzoyl chloride with PDBBA is representative. To a solution of benzoyl chloride (0.058 mL, 0.5 mmol) in THF (5 mL) containing naphthalene as an internal standard was added morpholine (0.087 mL, 1.0 mmol) at room temperature. Stirring was continued for 30 min; to this was added dropwise PDBBA (2.17 mL, 0.46 M in THF-hexane). After being stirred for 6 h at the same temperature, the reaction mixture was hydrolyzed with 5 mL of 1 N HCl (aq) and the product was extracted with 10 mL of diethyl ether. The ether layer was dried over anhydrous magnesium sulfate. GC analysis showed a 95% yield of benzaldehyde.