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An effective one-pot conversion of acid chlorides to aldehydes and ketones

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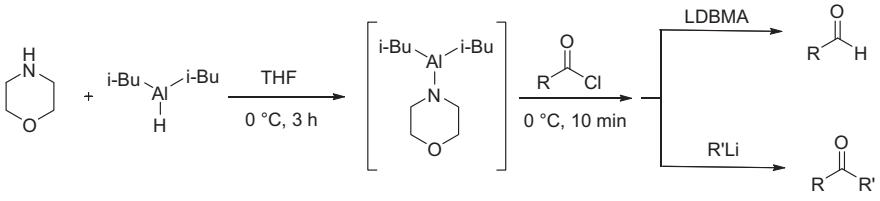
ABSTRACT

Aldehydes and ketones were synthesized from their respective acid chlorides via a one-pot protocol. Morpholine amide intermediates that were readily prepared by the aminolysis of various acid chlorides with diisobutyl(morpholino)aluminum smoothly reacted with the reducing agent LDBMA and the organolithium reagents under mild reaction conditions (0 °C), giving almost excellent product yields of up to 95%.

Aldehydes and ketones are highly valuable building blocks and reactive intermediates in a wide variety of organic syntheses. The establishment of a simple, general, and practical method for preparing these molecules is one of the most important and highly desirable objectives in the synthesis field. Weinreb amides,[1] which are generally synthesized from acid chlorides, are recognized as reliable intermediates for the preparation of aldehydes and ketones from carboxylic acid derivatives, and their synthetic utility has been widely demonstrated.[2] However, reactions involving Weinreb amides are not always suited to large-scale practical applications because of the high cost factor involved. Further, the yields of the desired aldehydes are fairly low (67–76%) even at −78 °C, in contrast to those of ketones, which can reach 90%.

Herein, we report a new and improved method for the one-pot synthesis of aldehydes and ketones from acid chlorides. As an alternative to the use of Weinreb amides, this approach involves the reaction of a reducing agent and organolithium reagents with morpholine amide intermediates under mild conditions (0 °C), resulting in excellent yields (Scheme 1).

We previously carried out the synthesis of tertiary amides from the reaction of benzoyl chloride and diisobutyl(morpholino)aluminum. The corresponding morpholine amides could be obtained in 99% yield. And we found that the morpholine amide was an effective precursor to the synthesis of aldehydes and ketones through the reaction of morpholine amide with DIBALH and *n*-BuLi. Furthermore, to demonstrate the feasibility of performing the desired reaction under a variety of conditions, various reducing agents[3] were employed in the one-pot synthesis of benzaldehyde via amide intermediates prepared by the reaction of a diisobutyl(amino)aluminum reagent and benzoyl chloride. Diisobutyl(morpholino)aluminum was the most effective reagent for synthesizing the amide intermediate, with lithium diisobutylmethoxy



Scheme 1. New synthetic method of aldehydes and ketones from acid chlorides.

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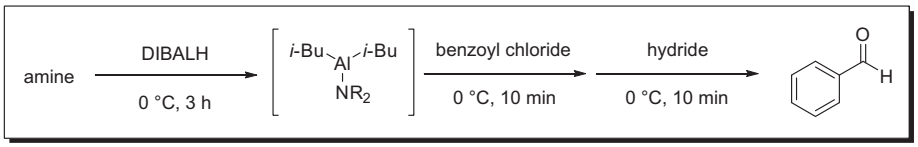
aluminum hydride (LDBMA)[4] being the best reducing agent for the partial reduction of benzoyl chloride to benzaldehyde at 0 °C (Table 1).

The next step was to synthesize different aldehydes from their respective aromatic and aliphatic acid chlorides using the conditions optimized in the first set of experiments. The results for a number of representative esters are summarized in Table 2.

As shown in Table 2, various aromatic acid chlorides with electron-withdrawing and electron-donating substituents were observed to smoothly undergo conversion to the corresponding aldehydes in 92–99% yields at mild reaction temperature (entries 1–11). The polyaromatic compound, 2-naphthoyl chloride, and the heterocyclic aromatic compound, 2-furoyl chloride, gave the corresponding aldehydes in 92% and 83% yields, respectively (entries 12 and 13). Furthermore, aliphatic acid chlorides were smoothly reduced to the corresponding aldehydes in 98% and 90% yields, respectively, under similar reaction conditions (entries 14 and 15).

From these results, it was anticipated that treatment of morpholine amide intermediates with *n*-BuLi or PhLi would be effective for the one-pot synthesis of ketones from their respective aromatic and aliphatic acid chlorides. As expected, the corresponding ketones were isolated in 85–99% yields; however, with bromo-substituted esters, metal–halogen exchange products were obtained instead of the desired ketones. Table 3 summarizes the

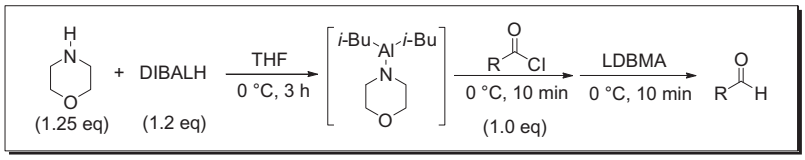
Table 1
Partial reduction of benzoyl chloride under a variety of reaction conditions

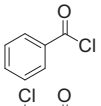
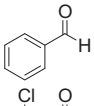
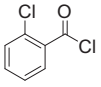
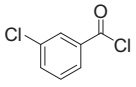
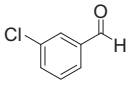
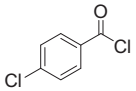
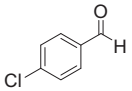
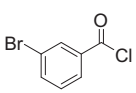
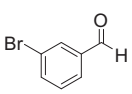
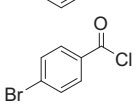
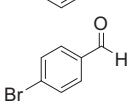


Entry	Amine (equiv)	Amine (equiv)	DIBALH (equiv)	Hydride	Hydride (equiv)	Yield[d] (%)
1	Morpholine	1.25	1.2	DIBALH	1.5	75
2				LDBMA[a]		99
3				LDBMA[b]		91
4				LDBMA[c]		72
5				LDBMA		98
6	Piperidine			LDBMA		15
7	Diethyl amine			LDBMA		18

[a] Lithium diisobutylethoxy aluminum hydride.
[b] Lithium diisobutylisopropoxy aluminum hydride.
[c] Lithium diisobutyl-*t*-butoxy aluminum hydride.
[d] Yields were determined by GC with naphthalene as internal standard.

Table 2
Yields of aldehydes from representative acid chlorides in a one-pot reaction[5]



Entry	Acid chloride	Product	LDBMA (equiv)	Yield[a] (%)
1			1.5	99
2			1.5	97
3			1.5	98
4			1.5	96
5			1.5	98
6			1.5	92