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New and Efficient Synthesis of Amides from Acid Chlorides Using Diisobutyl(amino)aluminum

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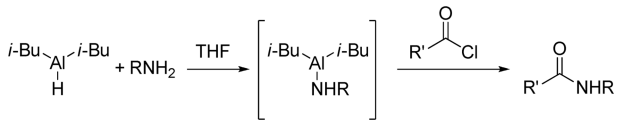
Amides are valuable functional groups in biological, agrochemical, and pharmaceutical molecules.[1] Several amides such as Weinreb amides,[2] morpholine amides,[3] and pyrrolidine amides[4] are useful intermediates for the synthesis of aldehydes or ketones. Among them, morpholine amides are a cheap and good substitute for Weinreb amides.

A large number of synthetic methods for making amides from various carboxylic acid derivatives have been reported. Among these, the aminolysis of acid chlorides in the presence of non-nucleophilic tertiary amines is generally considered to be the method of choice.[5] Amides can also be synthesized using metals such as zinc, indium and samarium instead of tertiary amines from acid chlorides.[6]

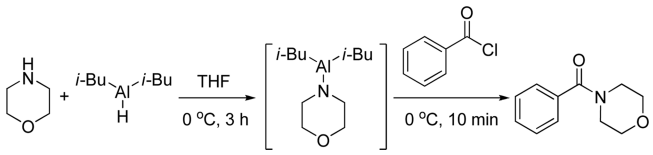
Herein, we wish to report an alternative direct conversion of acid chlorides to secondary and tertiary amides (including morpholine amides), which proceeds under mild reaction conditions (0 °C) with an almost stoichiometric amount of amine and a short reaction time, and gives very good to excellent yields (Scheme 1).

To demonstrate the feasibility of performing the desired reaction under a variety of conditions, we first carried out the synthesis of tertiary amides from benzoyl chloride. The corresponding morpholine amides could be obtained in 99% yield by reaction with benzoyl chloride under optimized reaction conditions in the presence of diisobutyl(morpholino)aluminum, which was easily prepared from morpholine and diisobutylaluminum hydride (DIBALH). The results are summarized in Table 1.



Scheme 1. New synthetic method for production of amides from acid chlorides.

Table 1. Optimization of reaction conditions for the synthesis of tertiary amides from acid chlorides



Entry	Acid Chloride	Morpholine (eq)	DIBALH (eq)	Yield (%)[a]
1	Benzoyl chloride	1.05	1.0	73
2		1.25	1.2	99
3		1.45	1.4	96

[a]Yields were determined by GC.

We next synthesized various secondary and tertiary amides from other acid chlorides under the optimal conditions deduced from the previous experimental results. The results obtained for the reaction of benzoyl chloride with various primary and secondary amines are summarized in Table 2.

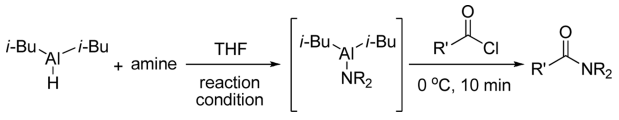
As shown in Table 2, various noncyclic and cyclic primary amines underwent smooth conversion to the corresponding secondary amides in 90-99% yields (entries 1-5). Furthermore, the secondary amines also afforded the corresponding tertiary amides in 75-99% yields under similar reaction conditions (entries 6-10).

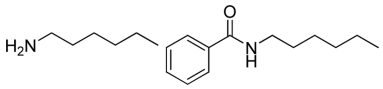
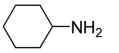
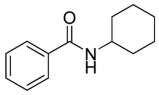
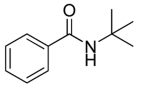
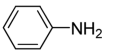
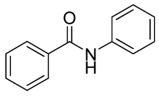
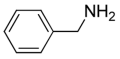
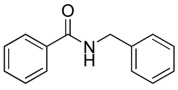
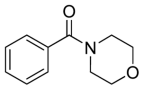
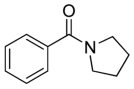
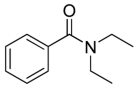
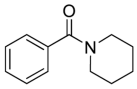
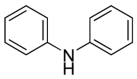
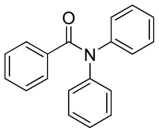
From these results, we anticipated that the treatment of diisobutyl(morpholino)aluminum with representative acid chlorides would be effective for the direct synthesis of morpholine amides. Table 3 summarizes the results of the one-pot synthesis of morpholine amides from various acid chlorides.

As expected, various aromatic acid chlorides with electron-withdrawing and electron-donating substituents underwent the conversion to the corresponding morpholine amides smoothly, in 89-99% yields (entries 1-7). A polyaromatic acid chloride such as naphthoyl chloride and a heterocyclic aromatic acid chloride such as furoyl chloride gave the corresponding morpholine amides in 92% and 91% yields, respectively, *via* the same methodology (entries 8 and 9). Furthermore, aliphatic acid chloride such as caproyl chloride smoothly afforded the corresponding morpholine amide in 96% under the same reaction conditions (entry 10).

A proposed mechanism for this reaction is shown in Scheme 2 for the conversion of benzoyl chloride to the corresponding piperidine amide. Initially, the intermediate **2** is produced through the attack on the acid chloride by the secondary amino anion in diisobutyl(piperidino)aluminum **1** to give intermediate **3**, with the release of an aluminum complex from intermediate **2**. Finally, the hydrolysis of the

Table 2. Synthesis of various amides from benzoyl chloride[a]



Entry	Amine	Product	Reaction Condition		Yield (%)[b]
			Temp	Time (h)	
1			0 °C	3	98
2			0 °C	3	90
3			0 °C	3	97
4			0 °C	3	99
5			0 °C	3	94
6			0 °C	3	99
7			0 °C	3	97
8			0 °C	3	97
9			RT	6	84
10			RT	6	75

[a]Benzoyl chloride:morpholine:DIBALH = 1.0:1.25:1.2. [b]Isolated yield after column chromatography.

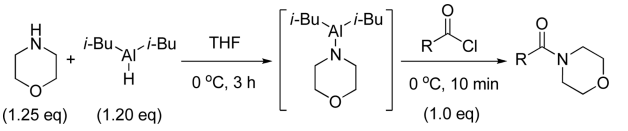
adduct **3** affords the corresponding amide.

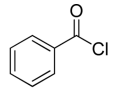
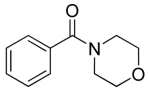
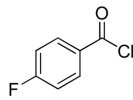
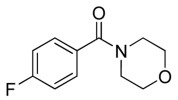
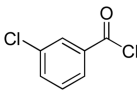
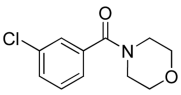
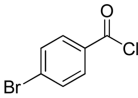
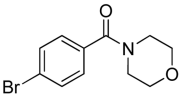
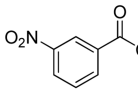
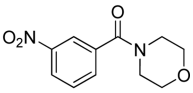
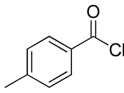
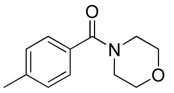
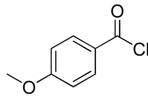
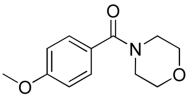
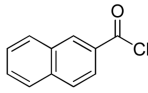
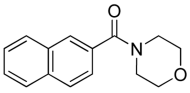
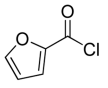
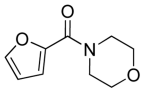
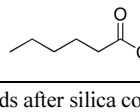
In conclusion, we have developed a facile, alternative method for the formation of secondary and tertiary amides including morpholine amides from acid chlorides by using diisobutyl(amino)aluminum under mild reaction conditions. The advantages of the present method include the high product yields, simple experimental procedure, short reaction time (10 min), and the fact that an excess amount of amine is not required. This result suggests that our new method can provide an alternative method for the synthesis of useful amides from acid chlorides.

Experimental

General. All glassware used was dried thoroughly in an

Table 3. Synthesis of morpholine amides from representative acid chlorides



Entry	Acid Chloride	Product	Yield (%)[a]
1			99
2			97
3			99
4			98
5			96
6			98
7			89
8			92
9			91
10			96

[a]Isolated yieds after silica column chromatography.

Scheme 2. Proposed mechanism.

oven, 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 using standard techniques for the handling of air-sensitive materials. All chemicals were commercial products of the highest purity, which were further purified before use by using standard methods. THF was dried over sodium-benzophenone and distilled. DIBALH, acid chlorides, and amines were purchased from Aldrich Chemical Company. ^{1}H-NMR spectra were measured at 300 or 400 MHz with $CDCl_3$ as a solvent at ambient temperature unless otherwise indicated, and the chemical shifts were recorded in parts per million downfield from tetramethylsilane ($\delta = 0$ ppm) or based on residual $CHCl_3$ ($\delta = 7.26$ ppm) as an internal standard. ^{13}C NMR spectra were recorded at 75 or 100 MHz with $CDCl_3$ as a solvent and referenced to the central line of the solvent ($\delta =$ 77.0 ppm). The coupling constants (J) are reported in hertz. Analytical thin-layer chromatography (TLC) was performed on glass precoated with silica gel (Merck, silica gel 60 F_{254}). Column chromatography was carried out using 70-230 mesh silica gel (Merck) at normal pressure. GC analyses were performed on a Donam DS 6200 FID chromatograph, using an HP-1 capillary column (30 m). All GC yields were determined with the use of a suitable internal standard and authentic mixture.

Synthesis of Amides from Acid Chlorides Using Diisobutyl(amino)aluminum. The Following Experimental Procedure for the Synthesis of *N*-Benzoylmorpholine is Representative. A dry and argon-flushed flask, equipped with a magnetic stirring bar and a septum, was charged with morpholine (0.12 mL, 1.25 mmol) and THF (10 mL). After cooling to 0 °C, DIBALH (1.2 mL, 1.0 M in hexane, 1.2 mmol) was added dropwise, and the mixture was stirred for 3 h at the same temperature. Benzoyl chloride (0.12 mL, 1.0 mmol) was added slowly to the reaction mixture, which was stirred for 10 min. The reaction was stopped with aqueous 1 N HCl (10 mL) and extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel yielded *N*-benzoylmorpholine (189 mg, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.48-3.70 (m, 8H), 7.39-7.44 (m, 5H). All products in Tables 2 and 3 were confirmed through comparison with NMR data reported in the literature.[7]

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