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DIBAL–H–H_2NR and DIBAL–H–HNR^1R^2·HCl complexes for efficient conversion of lactones and esters to amides

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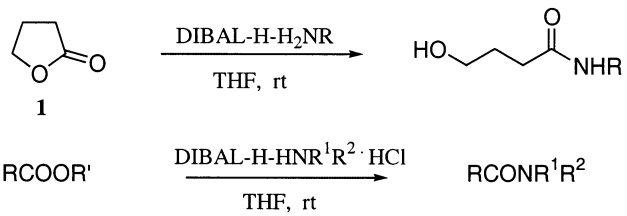
Abstract—The reaction of a lactone or an ester with organoaluminum species generated from DIBAL–H–H_2NR or DIBAL–H–HNR^1R^2·HCl complexes provided efficient methods for preparation of amides. Conditions were defined for the preparation of both secondary and tertiary amides, including Weinreb amides in excellent yields.

Since the first report in 1981, *N*-methoxy-*N*-methyl amides (Weinreb amides)[1] have been recognized as reliable and widely used intermediates for the preparation of aldehydes and ketones.[2] Nevertheless, there is continuing interest in the development of new methods for the transformation of amides to aldehydes and ketones.[3] While a number of methods are available for the preparation of amides from carboxylic acids,[4] the direct conversion of inactivated carboxylic esters and lactones to the corresponding amides still remains a highly desirable transformation in modern organic synthesis.[5,6] Among known ester aminolysis methods,[5,6] the one based on the use of the Weinreb reagents prepared by reaction of trimethylaluminum with an amine (Me_3Al–HNR_2)[5a] or an amine hydrochloride (Me_3Al–HNR_2·HCl),[5b] is the most popular.[7] Recently, Shimizu et al reported[8a] the use of Me_2AlCl–HN(OMe)Me[8] as an efficient amidating agent. In this paper, we describe the successful use of DIBAL–H–H_2NR and DIBAL–H–HNR^1R^2·HCl complexes as efficient amidating agents for the conversion of lactones and esters to amides (Scheme 1).



2: R = CH_3, R' = Bu-*n*
3: R = Ph, R' = Et

Scheme 1.

The aminolysis of γ-butyrolactone **1** was studied first. The effect of DIBAL–H in lactone aminolysis was clearly demonstrated in the reaction between benzylamine and γ-butyrolactone. After heating a mixture of γ-butyrolactone and benzylamine at 45°C for 20 h, the desired γ-hydroxy amide **4** was obtained in only 28% yield (Table 1, entry 1). When using 1.1 mol equiv. of the organoaluminum species generated by the reaction of DIBAL–H with benzylamine (*i*-Bu_2AlH–$BnNH_2$), the desired aminolysis reaction proceeded smoothly at room temperature, and the isolated yield of amide **4** was 98% after just 30 min.

As can be seen from entries 2, 3 and 4 (Table 1), primary amines showed higher reactivities compared with those of secondary amines. For example, the organoaluminum reagents derived from primary amines such as benzylamine and *i*-pentylamine reacted smoothly with γ-butyrolactone at rt (entries 2 and 3), while in the case of a secondary amine (entry 4), gentle heating was necessary to ensure a reasonable yield of amide **6**. Gratifyingly, when the organoaluminum reagents were generated from the HCl salts of secondary amines, the aminolysis of the lactone was significantly accelerated (entries 5 and 6). In this way, tertiary amides, such as the Weinreb amide **7** (entry 6) were obtained in excellent yields.

The general applicability of this aminolysis methodology is further demonstrated in entries 7–15. The lactone aminolysis methodology was extended to aliphatic esters. As outlined in entries 7–12, *n*-butyl acetate **2** showed similar reactivity to that of γ-butyrolactone **1**. Treatment of *n*-butyl acetate with *i*-Bu_2AlH–RNH_2 afforded the corresponding amides in 91–94% yield,

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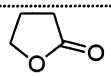
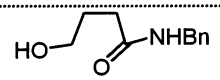
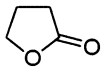
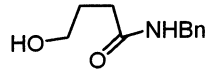
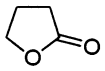
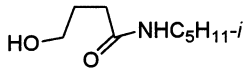
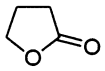
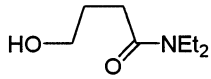
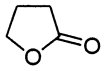
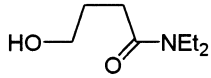
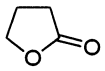
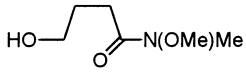
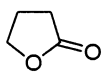
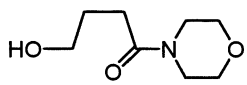
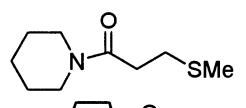
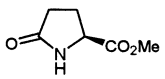
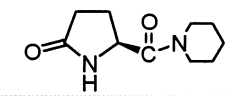
Table 1. The aminolysis of lactones or esters with DIBAL–H–H_2NR or DIBAL–H–HNR^1R^2·HCl

Entry	Ester	Method	Reagent equiv.	Reaction conditions	Product		Yield (%)
1		A [a]	1.1	~45°C, 20 h		**4**	28
2		B [b]	1.1	rt, 0.5 h		**4**	98
3		B	2.3	rt, 1 h		**5**	95
4		B	2.5	~45°C, 2 h		**6**	72
5		C [c]	2.5	rt, 0.5 h		**6**	94
6		C	2.0	rt, 0.5 h		**7**	92
7	CH_3CO_2Bu-*n*	B	2.3	rt, 2 h	$CH_3CONHPr$-*i*	**8**	91
8	CH_3CO_2Bu-*n*	B	2.3	rt, 2 h	$CH_3CONHC_5H_{11}$-*i*	**9**	94
9	CH_3CO_2Bu-*n*	B	2.3	rt, 2 h	$CH_3CONHBn$	**10**	91
10	CH_3CO_2Bu-*n*	B	2.8	~45°C, 2 h	CH_3CONEt_2	**11**	72
11	CH_3CO_2Bu-*n*	C	2.0	rt, 2 h	CH_3CONEt_2	**11**	90
12	CH_3CO_2Bu-*n*	C	2.0	rt, 2 h	$CH_3CON(OMe)Me$	**12**	91
13	$PhCO_2Et$	B	5.0	rt, 2 h	$PhCONHC_5H_{11}$-*i*	**13**	94
14	$PhCO_2Et$	B	5.0	rt, 2 h	$PhCONHBn$	**14**	95
15	$PhCO_2Et$	C	5.0	~45°C, 20 h	$PhCONEt_2$	**15**	76
16		C	2.0	rt, 0.5h		**16**	82
17	$MeS(CH_2)_2CO_2Me$	C	3.0	~45°C, 2 h		**17**	89
18		C	4.0	~45°C, 2 h		**18**	52

a. Method A: using amine as amidating reagent; b. Method B: using DIBAL-H-H_2NR complexes as amidating reagent; c. Method C: using DIBAL-H-HNR^1R^2·HCl complexes as amidating reagent.

after 2 h at rt (entries 7–9), while in the reaction of *n*-butyl acetate with *i*-Bu_2AlH–$HNEt_2$, the yield was only 72% (entry 10). However, the aminolysis of *n*–butyl acetate with *i*-Bu_2AlH–$HNEt_2$·HCl proceeded in high yield (entry 11). In such a way, the Weinreb amide **12** was prepared in a yield of 91% (entry 12).

Next, we examined the aminolysis of less reactive aromatic esters. Treatment of ethyl benzoate **3** with 5 mol equiv. of *i*-Bu_2AlH–$NH_2C_5H_{11}$-*i* or *i*-Bu_2AlH–NH_2Bn yielded amide **13** or **14** in 94 and 95% yields, respectively. For the aminolysis of ethyl benzoate with *i*-Bu_2AlH–$HNEt_2$·HCl, a prolonged reaction time (20 h at 45°C) was necessary to ensure a reasonable yield of amide **15**.

Finally, the method was extended to cyclic amines (entries 16–18). In this way, fasoracetam **18**, a novel cognition enhancer, was prepared from (*S*)-methyl pyroglutamate in a yield of 52%.

In summary, we have developed convenient and mild methods for amide synthesis by aminolysis of lactones or esters with DIBAL–H–H_2NR or DIBAL–H–HNR^1R^2·HCl.[9] Conditions have been defined for the preparation of both secondary and tertiary amides, including Weinreb amides in excellent yields. The major advantage of the present method resides on the successful substitution of Me_3Al or Me_2AlCl by *i*-Bu_2AlH (DIBAL–H). Compared with other organoaluminium reagents such as Me_3Al or Me_2AlCl, DIBAL–H, a routinely used reducing reagent, is much more popular. Hence, the present method constitutes an important modification to the well known Weinreb methodology. The nature of the reactive species in the present aminolysis reaction is being investigated in these laboratories.

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9. **General procedure**: A solution of DIBAL–H (1.5 M in toluene, 2.58 mL, 3.87 mmol) was added to a cooled (0–5°C) solution of *i*-pentylamine (0.47 mL, 4.0 mmol) in THF (1.7 mL) under nitrogen. The mixture was allowed to warm up and stirred at rt for 2 h. The concentration of the prepared DIBAL–H–*i*-$C_5H_{11}NH_2$ complex was about 0.88 M, and was used directly for aminolysis. To a solution of ethyl benzoate (0.095 mL, 0.67 mmol) in THF (2.5 mL) was added, under nitrogen at rt, the DIBAL–H–*i*-$C_5H_{11}NH_2$ complexes (3.8 mL, ~3.35 mmol). After stirring at rt for 2 h, the reaction was cooled to 0°C, and then quenched with H_2O (1.5 mL) and a 1 M aqueous solution of $KHSO_4$ (4 mL). The resulting mixture were extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (EtOAc/PE: 1/4) to give amide **13** (120 mg, yield 94%) as white crystals. Mp 52~53°C. IR: 3317, 3065, 3027, 2957, 2930, 2870, 1639, 1603, 1579, 1543, 1491, 1468, 1368, 1310, 1224, 1153, 1076, 1025, 805, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 0.98 (d, $J=6.6$ Hz, 6H, $2CH_3$), 1.48–1.56 (m, 2H, H-3′), 1.64–1.75 (m, 1H, H-4′), 3.44–3.52 (m, 2H, H-2′), 7.40–7.79 (m, 5H, Ph-H). HRESIMS calcd for $[C_{12}H_{17}NO+H]^+$ 192.1383, found 192.1385. Anal. calcd for $C_{12}H_{17}NO$: C, 75.39; H, 8.90; N, 7.33; found: C, 75.38; H, 9.00; N, 7.28.