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A MILD, GENERAL METHOD FOR CONVERSION OF ESTERS TO AMIDES

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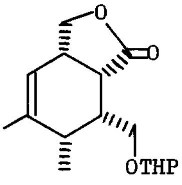
Although the direction conversion of esters to amides is potentially a useful synthetic operation, the practical application of this method has been somewhat limited for a number of reasons.[2] In general, aminolysis of esters requires high temperatures and/or long reaction times,[3] and the strong alkali metal catalysts sometimes used[4-7] are not compatible with senesitive functionality. Milder catalysts have been reported such as 2-pyridone[8] and boron tribromide,[9] but the generality of these reagents has not been tested. Some work has also appeared on the use of tin, and titanium amides in this transformation.[10] In 1970 Ishii et al. found that diethylaluminum dimethylamide will open propiolactone and butyrolactone to the ω-hydroxydimethylamides. We now wish to report that dimethylaluminum amides react in high yield under very mild reaction conditions with a wide variety of esters to produce carboxamides.

$$\underset{\mathbf{1}}{(CH_3)_2AlNRR_1} \quad + \quad \wr\!-COOR_2 \quad \xrightarrow[25\text{-}41^{o}]{CH_2Cl_2} \quad \wr\!-CONRR_1$$

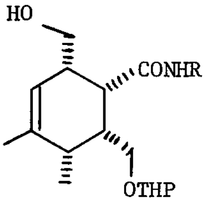
$R, R_1 = H$, alkyl, aryl

Trimethylaluminum reacts with ammonia and primary or secondary amines in a 1:1 ratio at room temperature in methylene chloride with evolution of methane to give dimethylaluminum amides **1**.[11-13] These reagents can be generated in situ as needed, or one molar stock solutions may be prepared and stored for long periods under refrigeration. Addition of an ester to one of these reagents, followed by gentle warming at 25-41° for 5 to 48 hours produces an amide in high yield. We have tested this procedure on a number of representative esters with several dimethylaluminum amides and yields of the isolated carboxamides which were prepared are listed in the Table. In general, one equivalent of dimethylaluminum amide was sufficient for high conversion in a relatively short reaction time. In the case of the ammonia-derived reagent, optimum results were obtained when two equivalents were used. We have also investigated some diethylaluminum amides in this transformation, but the rates of reaction were considerably slower than with the dimethylaluminum reagents, perhaps for steric reasons.

The reactions of hindered lactone **2** further illustrate the utility and mildness of the method. On treatment with several equivalents of benzylamine in refluxing xylene for nine days, lactone 2 gave only a trace of hydroxyamide 3. On warming 2 at 41° with 2 equiv of dimethylaluminum benzylamide for 24 hr, 3 was isolated in 80% yield. Similarly, lactone 2 was inert to sodium amide in liquid ammonia, but was converted on treatment with 2.2 equivalents of dimethylaluminum amide for 26 hr at 41° to hydroxy amide 4 in 83% yield.



2



3 R = $CH_2C_6H_5$
4 R = H

In a typical experiment 0.8 ml (2.0 mmol) of a 2.5 M solution of trimethylaluminum in hexane (Alfa Inorganics) was slowly added at room temperature to a solution of 2.0 mmol of amine or ammonia in 5 ml of dry methylene chloride under nitrogen. The mixture was stirred at room temperature for 15 min and 2.0 mmole of ester was added. The mixture was warmed at 25-41° under nitrogen until TLC indicated that the reaction had gone to completion. The reaction was carefully quenched with dilute HCl and extracted with methylene chloride. The organic extract was dried ($MgSO_4$) and concentrated to afford the carboxamide which could be recrystallized, if necessary.

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References and Notes

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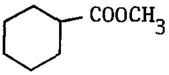
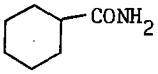
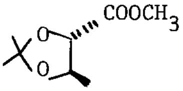
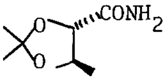
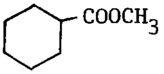
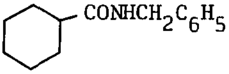
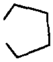
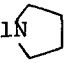
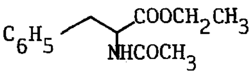
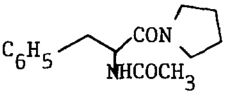
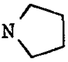
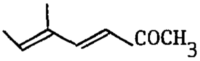
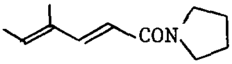
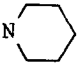
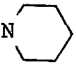
Table. Preparation of Carboxamides from Dimethylaluminum Amides and Esters.

Aluminum Reagent (equiv)	Ester Used	Amide Product	Reaction Time/Temp	Isolated Yield (%)
$(CH_3)_2AlNH_2$ (2.2)	$C_6H_5COOCH_3$	$C_6H_5CONH_2$	17hr/41°	77
$(CH_3)_2AlNH_2$ (2.2)	$C_6H_5CH_2COOCH_3$	$C_6H_5CH_2CONH_2$	17hr/41°	75
$(CH_3)_2AlNH_2$ (2.0)	$C_6H_5CH{=}CHCOOCH_3$	$C_6H_5CH{=}CHCONH_2$	12hr/38°	86
$(CH_3)_2AlNH_2$ (2.2)			17hr/35-40°	78
$(CH_3)_2AlNH_2$ (2,0)			16hr/40	69
$(CH_3)_2AlNHC(CH_3)_3$ (1.1)	$Cl(CH_2)_3COOCH_2CH_3$	$Cl(CH_2)_3CONHC(CH_3)_3$	45 hr/41°	79
$(CH_3)_2AlNHCH_2C_6H_5$ (2.0)			17hr/35-40°	78
$(CH_3)_2AlNHCH_2C_6H_5$ (1.1)	$CH_3COOCH_2(CH_2)_2CH_3$	$CH_3CONHCH_2C_6H_5$	24hr/40°	95
$(CH_3)_2AlNHCH_2C_6H_5$ (1.1)	$C_6H_5CH_2COOCH_2CH_3$	$C_6H_5CH_2CONHCH_2C_6H_5$	25hr/25°	100
$(CH_3)_2AlNHCH_2C_6H_5$ (1.1)	$C_6H_5COOCH_3$	$C_6H_5CONHCH_2C_6H_5$	20hr/25°	95
$(CH_3)_2AlNHCH_2C_6H_5$ (1.1)	$CH_3OOC(CH_2)_8COOCH_3$	$CH_3OOC(CH_2)_8CONHCH_2C_6H_5$	25hr/40°	88
$(CH_3)_2AlNHCH_2C_6H_5$ (1.1)	$C_6H_5COOCH_2CH_3$	$C_6H_5CONHCH_2C_6H_5$	25hr/40°	93
$(CH_3)_2AlN$  (1.1)	$C_6H_5COOCH_3$	C_6H_5CON 	5hr/40°	94
$(CH_3)_2AlN$  (1.1)			40hr/40°	77
$(CH_3)_2AlN$  (2.0)			45hr/40°	74
$(CH_3)_2AlN$  (1.1)	$C_6H_5COOCH_3$	C_6H_5CON 	34hr/40°	74
$(CH_3)_2AlNHC_6H_5$ (1.1)	$CH_3COOCH_2(CH_2)_2CH_3$	$CH_3CONHC_6H_5$	40hr/40°	78
$(CH_3)_2AlNHC_6H_5$ (1.1)	$C_6H_5COOCH_2CH_3$	$C_6H_5CONHC_6H_5$	40hr/40°	79
$(CH_3)_2AlNHsecBu$ (1.1)	$Cl(CH_2)_3COOCH_2CH_3$	$Cl(CH_2)_3CONHsecBu$	48 hr/41°	76
$(CH_3)_2AlNHsecBu$ (1.1)	$C_6H_5CHOHCOOCH_3$	$C_6H_5CHOHCONHsecBu$	18 hr/40°	78