

Amide bond formation using an air-stable source of AlMe₃

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Abstract—Synthesis of amides from coupling esters with a range of primary amines can be conveniently achieved in moderate to excellent yields (69–99%) using an air-stable adduct of trimethylaluminium (AlMe₃)₂-DABCO (DABCO is 1,4-diazobicyclo[2.2.2]octane), referred to as DABAL–Me₃. Reactions can be run without requiring the exclusion of atmospheric oxygen or the drying of solvents.

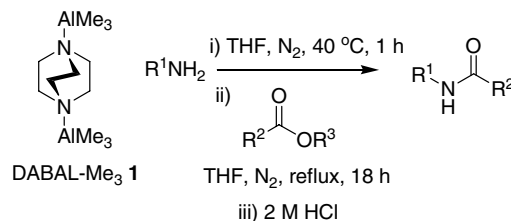
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Direct formation of amides from the corresponding *unactivated* esters and lactones is a desirable synthetic operation as hydrolysis to the parent carboxylic acid and its subsequent activation is avoided.^{1–3} Amine activation is most easily achieved by the formation of an aluminium amide⁴ (R₂AlNR₂) from exposure of amines or their HCl salts to AlMe₃,⁵ or DIBAL–H.⁶ Subsequent ester aminolysis delivers the desired amides in excellent yields. The power of this methodology is illustrated by its application to numerous modern syntheses of complex organic molecules.⁷ A major drawback to this chemistry is the pyrophoric nature of the aluminium reagents used and the subsequent need for strict exclusion of air and moisture. Recently, we demonstrated that the remarkably air-stable AlMe₃ adduct (AlMe₃)₂-DABCO (DABCO = 1,4-diazobicyclo[2.2.2]octane) **1**, which we call DABAL–Me₃,⁸ could be formed in one step from DABCO and AlMe₃, and although somewhat moisture sensitive this can be easily handled without the need for an inert atmosphere.⁹ We were pleased to observe that while DABAL–Me₃ **1** is an extremely convenient source of methyl carbanions,^{9–11} it retains sufficient Lewis acidity to render it capable of amine activation.

A brief optimization study on the aminolysis of ethyl benzoate with benzylamine revealed that using 1.5 equiv of both amine and DABAL–Me₃ **1** gave a quantitative

conversion of the ester to *N*-benzylbenzamide.¹² In comparison to the aminolysis of esters with Me₂Al–HNR that are commonly run at ambient temperature in CH₂Cl₂,⁵ reactions utilizing the air-stable DABAL–Me₃ **1** reagent favour THF as solvent. Use of THF allows complete solubility of reagent **1** and enables the use of elevated temperatures to promote complete conversion of the reaction (Scheme 1). In the absence of the DABAL–Me₃ reagent **1** no coupling was observed.

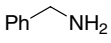
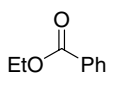
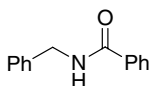
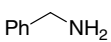
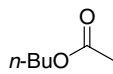
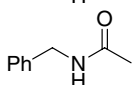
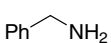
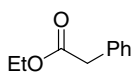
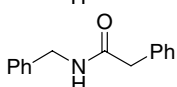
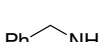
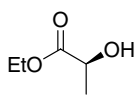
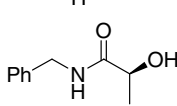
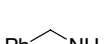
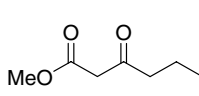
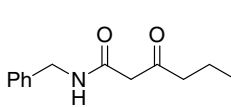
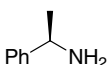
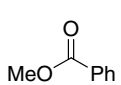
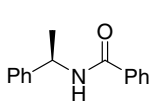

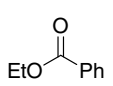
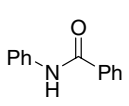

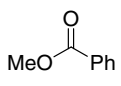
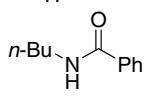

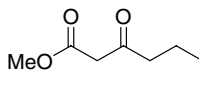
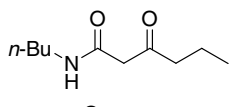

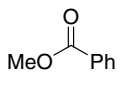
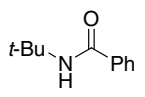
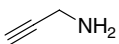
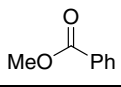
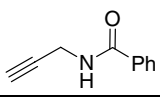
Application of this methodology to the aminolysis of a range of amines revealed excellent generality with benzylic, aromatic and aliphatic primary amines exhibiting good reactivity (Table 1).¹³ A variety of simple esters participated well in the reaction including β-keto and α-hydroxy esters. Previously we have found that exposure of DABAL–Me₃ **1** to substrates possessing enolizable protons led to undesirable side reactions.^{9–11} Interestingly, the use of a β-keto ester gave the desired amides in good yield (entries 5 and 9). We postulate that formation of the enolate, due to the presence of



Scheme 1. Aminolysis of esters using DABAL–Me₃ **1**.

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Table 1. Synthesis of amides using DABAL–Me₃ **1**^a

Entry	Amine	Ester	Amide	Yield ^b (%)
1				99 (99 ^c)
2				69 (70 ^c)
3				88
4				99
5				90
6				98
7				91
8				99 (99 ^c)
9				89
10				97
11				86

^a Reactions performed on a 0.50 mmol scale using amine (1.5 equiv), DABAL–Me₃ **1** (1.5 equiv), anhydrous THF, N₂, 40 °C, 1 h followed by ester (1 equiv), reflux, 18 h.

^b Isolated products.

^c Reactions performed on a 0.50 mmol scale using amine (1.5 equiv), DABAL–Me₃ **1** (1.5 equiv), undried THF, open to air, 40 °C, 1 h followed by ester (1 equiv), reflux, 18 h.

DABCO, acts by deactivating the more reactive carbonyl group allowing aminolysis to occur smoothly. Unfortunately, the presence of an aldehyde functionality was not tolerated. The use of γ -formyl esters resulted in the formation of several unidentified products while methyl 4-formyl benzoate was recovered quantitatively, presumably through C=N formation via preferential attack of aluminium amide at the more reactive carbonyl centre and subsequent hydrolysis of the imine back to aldehyde upon aqueous workup.

In attempts to further simplify the experimental procedure we were pleased to discover that the reaction can be performed without adhering to a strictly anhydrous protocol. Simply running reactions in commercial undried THF and open to the atmosphere made little to no difference in the yield of amide attained.¹⁴ Our method is complimentary to the recent approaches to

amide bond formation.¹⁵ Additionally, it is particularly suited to the preparation of small scale amide libraries.

In summary we have developed a convenient and highly practical method for the direct aminolysis of esters with aluminium amides, utilizing an air-stable form of AlMe₃. The reactions require no precautions to exclude air or moisture and in all cases the reactions result in full conversion of the starting esters with analytically pure amides being attained without the need for further purification.

Acknowledgements

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12. Reactions to form secondary amides, including Weinreb amides, do not give acceptable yields under the present procedure.
13. *Representative procedure:* To a stirred solution of DABAL–Me₃ **1** (194 mg, 0.75 mmol) in anhydrous THF (4 mL) under an inert atmosphere, benzylamine (82 μL, 0.75 mmol) was added. The solution was stirred and warmed to 40 °C for 1 h. To this ethyl benzoate (62 μL, 0.50 mmol) was added and the solution was refluxed for 18 h. The reaction mixture was cooled to ambient temperature and quenched with aqueous HCl (2 M, 5 mL) dropwise, followed by extraction with diethyl ether (2 × 10 mL). The organic phase was separated and filtered through a small plug of silica. Removal of the solvent under reduced pressure gave *N*-benzylbenzamide (105 mg, 99%) as a colourless powder. Use of lower stoichiometries of DABAL–Me₃ (e.g., Table 1, entry 1, but 1.0 equiv) led to a reduction in the yield of amide to 70%. Below 1.0 equiv of DABAL–Me₃ amide coupling yields became unacceptable.
14. Reaction performed as in the general procedure using standard undried glassware and all stages carried out in air. Lower specification grades of THF (containing up to 0.05% w/w water) were used directly from the bottle as supplied without the need for pre-drying.
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