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APPLICATION OF $AlMe_3$-MEDIATED AMIDATION REACTIONS TO SOLUTION PHASE PEPTIDE SYNTHESIS

Stephen F. Martin*, Michael P. Dwyer, and Christopher L. Lynch
Department of Chemistry and Biochemistry, The University of Texas at Austin
Austin, Texas 78712 USA

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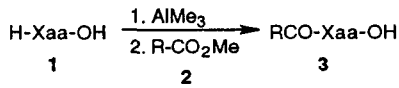
Abstract. A practical modification of the Weinreb amidation protocol employing amino acids as the amine reaction partner has been developed that allows for the facile synthesis of oligopeptides in solution.

Due to the abundance of the amide function in natural products and peptides, the conversion of carboxylic esters to amides is a reaction of critical import to organic synthesis. Although many methods are available to effect this transformation,[1] there remains the opportunity to develop new techniques that may be more efficient and less expensive. A major advance in the area of amide bond formation was the protocol developed by Weinreb in which trimethylaluminum is used as a condensing agent in amidation reactions.[2] Since its discovery, this procedure and variants thereof have been widely employed to construct hydroxamic acids,[3] ureas,[4] hydroxyalkyl isosteres,[5] and natural products.[6]

As part of a general program toward the synthesis of peptide mimics, we have implemented modifications of the Weinreb protocol to construct cyclopropane-derived pseudopeptides by opening cyclopropyl lactones with amino acids and their derivatives.[7] As an extension of this methodology, we became interested in its potential use for the construction of small oligopeptides from readily available, amino acids as starting materials. The approach involves the coupling of a protected, amino acid or peptide ester with a zwitterionic amino acid or peptide in the presence of $AlMe_3$. Several potential advantages of such a coupling method can be envisioned. For example, the amino acid serving as the nucleophilic reactant is incorporated as the free acid, thereby allowing for facile elaboration at the *C*-terminus without subsequent deprotection. Moreover, the condensing agent $AlMe_3$ is much less expensive than the more commonly used carbodiimide coupling reagents, which are also toxic.

The general approach begins with preactivation of the zwitterionic, *C*-terminal reaction partner **1**, which may be an amino acid or an oligopeptide, with $AlMe_3$, followed by addition of the methyl ester of the *N*-terminal subunit **2**, which may be a monofunctional ester, a lactone or an ester of an amino acid (Scheme 1).[8] It is

Scheme 1



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necessary to use one equivalent of $AlMe_3$ for each acidic proton in both starting fragments in order to solubilize the reactants. Although the reactions are sluggish at room temperature, they proceed readily at 80 °C. The results in Table 1 clearly indicate that the $AlMe_3$-mediated coupling of various esters with amino acids and dipeptides constitutes a useful protocol for the production of peptide derivatives. Although benzene can be used as a solvent for some reactions, dichloroethane is generally the solvent of choice owing to solubility considerations.

Table 1. The $AlMe_3$-Mediated Coupling of Esters and Amino Acid Derivatives.[9]

Entry	Ester	H-Xaa-OH	R-CO-Xaa-OH	% Yield[a]
1	$PhCO_2Me$	Phe	PhCO-Phe-OH	77
2	$PrCO_2Me$	Phe	PrCO-Phe-OH	69
3	γ-butyrolactone	Pro	$HO(CH_2)_3CO$-Pro-OH	64
4	"	Phe	$HO(CH_2)_3CO$-Phe-OH	67
5	"	Phe-Leu	$HO(CH_2)_3CO$-Phe-Leu-OH	59
6	$MeCO_2$-Phe-OMe	Phe	$MeCO_2$-Phe-Phe-OH	60
7	Boc-Phe-OMe	Val	Boc-Phe-Val-OH	50
8	"	Phe	Boc-Phe-Phe-OH	45(<1)[b]
9	Boc-Val-OMe	Val	Boc-Val-Val-OH	37
10	"	Phe	Boc-Val-Phe-OH	31
11	Boc-Phe-OMe	Phe-Leu	Boc-Phe-Phe-Leu-OH	42(<3%)[c]

[a] Unoptimized. [b] Less than 1% of the epimer detected by reverse phase HPLC analysis.
[c] Less than 3% of the epimer could be detected by ^1H NMR analysis

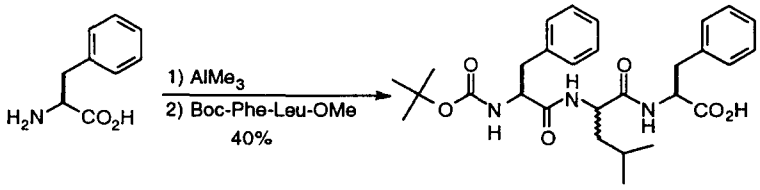
Several trends are evident upon examination of the entries in Table 1. Firstly, the presence of β-branching in either of the reactants led to decreased yields, presumably owing to the increased steric demands at the reacting centers (entries 7-10). Secondly, the reactions involving simple amino acids (entries 7-10) were complete within 6-10 h, whereas the assembly of larger peptide fragments in which a dipeptide serves as the nucleophilic partner (entry 11) was more sluggish and required longer reactions times (16-20 h). Lastly, when an ester of an amino acid was used as the electrophilic partner, the yields of coupled product varied with the nature of the amino protecting group. The lower yield in entry 8 may be attributed to partial loss of the Boc protecting group at the *N*-terminus under the Lewis-acidic conditions. Consistent with this hypothesis, is the observation that higher yields of dipeptides were obtained when a methyl carbamate moiety was employed as the nitrogen protecting group in place of the Boc group as illustrated by comparing the yields in entries 6 and 8.

Examination of the literature reveals that historically there has not been a significant problem with epimerization at vulnerable stereocenters in reactants during $AlMe_3$-mediated amidations.[3,4] However, because activated amino acids may undergo facile epimerization under certain coupling conditions, it was necessary to

examine whether the configurational integrity of the stereocenter alpha to the carbonyl function in the *N*-terminal subunit was maintained during the amidation. To address this issue, Boc-Phe-Phe-OCH_3 and its diastereomer Boc-D-Phe-Phe-OCH_3 were prepared by conventional carbodiimide coupling techniques;[10] hydrolysis of the *C*-terminal ester group then provided authentic samples of Boc-Phe-Phe-OH and Boc-D-Phe-Phe-OH for HPLC analysis.[11] Comparison of the HPLC chromatogram of the crude reaction mixture of entry 8 with these authentic samples showed that less 1% epimerization had occurred under the conditions of the amidation. Similarly, treatment of a *N*-protected amino acid methyl ester with a preactivated dipeptide gave the expected tripeptide in modest yield, and no epimerization was detected by careful ^1H NMR analysis of authentic samples of both diastereomers (entry 11).

On the other hand, when *N*-protected dipeptide esters were employed as the electrophilic partners in these couplings, significant epimerization at the center alpha to the ester function was observed (10-20%) during the construction of tri- and tetrapeptide subunits. For example, treatment of L-phenylalanine (**4**) with $AlMe_3$ followed by addition of Boc-Phe-Leu-OCH_3 afforded the protected tripeptide **5** in 42% yield as a mixture (8:1) of diastereomers epimeric at the leucine sidechain (Scheme 2). It is possible that $AlMe_3$ directly catalyzes partial racemization alpha to the methyl ester group. However, because carbamate-protected amino acid esters do not suffer loss of stereochemistry, a more likely mechanism would seem to involve formation of an oxazolone intermediate from the Boc-Phe-Leu-OCH_3 dipeptide, enolization of which prior to addition of the nucleophilic amino acid component leads to some epimerization.

Scheme 2



4 **5**

In summary, we have found that $AlMe_3$-mediated amidations may be used in a number of instances to construct oligopeptides in good yields. As is observed with other coupling methods, some epimerization may be observed when *N*-acyl amino acid esters are used as the electrophilic partners, although urethane protected amino esters may be coupled without epimerization. The inexpensive nature of the condensing agent and the ability to use unprotected amino acids as the nucleophiles lend to the attractiveness of the method. Because the reaction may be conducted under homogeneous conditions, it may be possible to extend this protocol to solid phase peptide synthesis. Further applications of this methodology to the synthesis of biologically active pseudopeptides will be reported in due course.

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8. **General Procedure for Construction of Dipeptides.** To a solution of the amino acid (3 equiv) in dichloroethane (0.24 M) was added dropwise a 2.0 M solution of $AlMe_3$ in hexane (7 equiv). The solution was stirred at rt for 30 min, whereupon the *N*-protected peptide ester (1 equiv) in dichloroethane (0.12 M) was added slowly. The reaction mixture was heated at reflux until the reaction was judged to be complete by TLC (6-10 h). The mixture was diluted with CH_2Cl_2 (1 volume), cooled to 0 °C and quenched with 3 N HCl (2 volumes). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 1 volume). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The crude dipeptide was purified by flash chromatography eluting with CH_2Cl_2/MeOH/HOAc to afford pure dipeptides.
9. The structure assigned to each compound was in accord with its spectral (^1H and ^{13}C NMR, ir and mass) characteristics. Yields cited are for compounds judged to be >95% pure by ^1H NMR. Analytical samples of all new compounds were obtained by distillation, recrystallization, preparative HPLC or flash chromatography and gave satisfactory identification by high resolution mass spectrometry.
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