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Expeditious amide-forming reactions using thiol esters

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Abstract

The reaction of a 2-pyridylthiol ester with a dimethylaluminum amide leads to the rapid formation of the corresponding amide. The tolylthiol esters can be activated with silver trifluoroacetate and coupled even with poorly reactive amino compounds.

The direct conversion of esters into amides is an ideal method in the syntheses of peptides in terms of the reduction of the deprotection step(s) at the C-terminus needed for usual peptide-forming reactions. Thiol esters are versatile intermediates in natural product syntheses; e.g. Lewis acid-catalyzed asymmetric aldol-type reactions,[1] kinetic resolutions,[2] synthesis of aldehydes,[3] esters,[4] lactons,[5] and ketones.[6] However, application of thiol esters in peptide-forming reactions has not been thoroughly investigated.[7] In peptide synthesis, it is essential to prevent base-catalyzed racemization during coupling reactions. The conditions to circumvent this problem are: (1) reducing the lifetime of the racemization prone species; and (2) omission of *tertiary* amines from the reaction mixture.

2-Pyridylthiol esters are stable to Brønsted acids (e.g. TFA in CH_2Cl_2 at 0°C to deprotect *N*-Boc groups), as well as to Lewis acids (e.g. diethylaluminum chloride in CH_2Cl_2). They are highly reactive with nucleophiles under basic conditions.

Taking advantage of the nature of trimethylaluminum, which reacts with primary or secondary amines with the evolution of methane to give dimethylaluminum amides,[8] the reactivity of 2-pyridylthiol ester **1**[9] to the dimethylaluminum amide generated from H-L-Phe-OMe[10] (**3**) was examined. This reaction was completed at 0°C within 10 min to afford Z-L-Val-L-Phe-OMe (**4**). The expeditious peptide-formation observed would result in the dual activation of amino group and 2-pyridylthiol ester by aluminum species. Interestingly, the dimethylaluminum amide of **3** did not react with tolylthiol ester **2** under the same conditions. On the other hand, tolylthiol ester **2**[11] could be coupled with H-L-Phe-OMe (**3**) in the presence of silver trifluoroacetate in toluene at 60°C within 20 min to afford dipeptide **4**. In a competition reaction between 2-pyridylthiol ester **1** and tolylthiol ester **2** with the dimethylaluminum amide of **3**, after **1** was completely consumed, 95% of **2** was recovered. In the same competition reaction using $AgOCOCF_3$, **1** was recovered in 90% yield after the reaction (Scheme 1).

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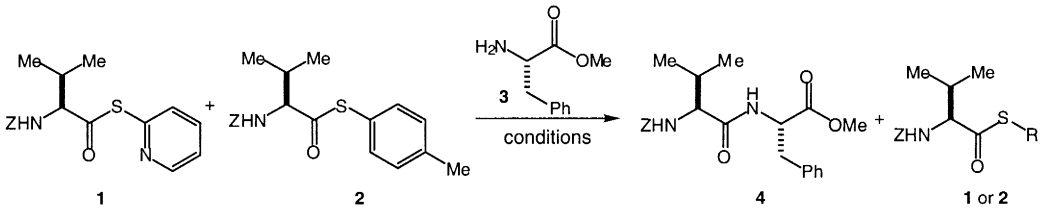


conditions	time	product (yield %)	recovered S.M (yield %)
Me_3Al / CH_2Cl_2 / 0 °C	10 min.	**4** (75%)	**2** (95%)
$AgOCOCF_3$ / Toluene 60 °C	20 min.	**4** (90%)	**1** (90%)

Scheme 1.

These competition reaction studies are given to show the applicability of thiol esters as a protecting group for the C-terminus of amino acids and the utility of this rapid and simple method for the formation of peptide bond under mild conditions. More conveniently, Me_3Al promoted coupling reactions were accomplished by the addition of two equivalents of Me_3Al into a mixture of the amino acid ester hydrochloride and the 2-pyridylthiol ester. The peptide formation with thiol esters of urethane-protected amino acids was verified and is summarized in Table 1.[12]

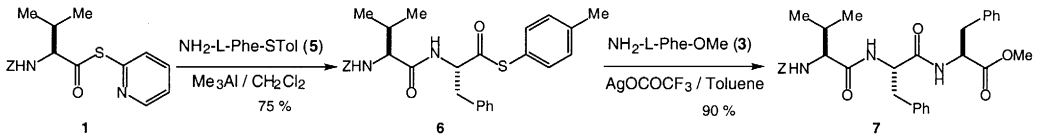
Table 1

thioester	amino acid	condition	time	product yield (%)
Z-L-Val-SPy	Me_2Al-L-Phe-OMe	no additive	10 min	70
Z-L-Val-SPy	HCl•H-L-Phe-OMe	Me_3Al (2eq)[a]	10 min	75
Z-L-Val-SPy	H-L-Phe-OMe	Me_3Al (1eq)[a]	10 min	80
Z-L-Val-SPy	HCl•H-L-Pro-OMe	Me_3Al (2eq)[a]	10 min	70
Z-L-Phe-SPy	HCl•H-L-Phe-OMe	Me_3Al (2eq)[a]	10 min	70
Boc-L-Val-SPy	HCl•H-L-Phe-OMe	Me_3Al (2eq)[a]	10 min	75
Boc-L-Tyr(Me)-SPy	HCl•H-L-Phe-OMe	Me_3Al (2eq)[a]	10 min	70
Boc-L-Tyr(Me)-STol	H-L-Phe-OMe	$AgOCOCF_3$[b]	20 min	85
Z-L-Val-STol	H-L-Phe-OMe	$AgOCOCF_3$[b]	20 min	90
Boc-L-Phe-STol	H-L-Phe-OMe	$AgOCOCF_3$[b]	20 min	90

[a] All reactions were carried out at 0 °C in CH_2Cl_2. [b] The reactions were conducted at 60 °C in Toluene.
Z = benzyloxycarbonyl, Boc = *tert*-butoxycarbonyl

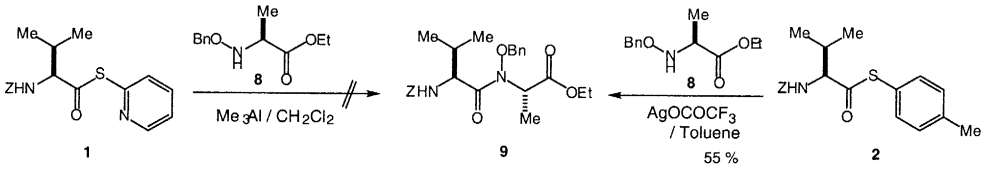
The usefulness of these protocols was demonstrated by the synthesis of tripeptide **7** as illustrated in Scheme 2. The coupling reaction between Z-L-Val-SPy (**1**) and H-L-Phe-STol (**5**) with one equivalent of Me_3Al at 0°C for 10 minutes afforded dipeptide **6** in 75%, which was subsequently coupled with H-L-Phe-OMe (**3**) using $AgOCOCF_3$ at 60°C to give tripeptide **7** in 90% yield.

In order to assess how powerful these peptide-forming reactions are, H-*N*-OBn-L-Ala-OEt (**8**)[13,14] was chosen as an acceptor amino acid. 2-Pyridylthiol ester **1** and **8**, using Me_3Al, did not afford the coupling product **9**; starting material was recovered after the reaction. In contrast, tolylthioester **2** reacted with H-*N*-OBn-L-Ala-OEt in the presence of $AgOCOCF_3$ to afford the desired dipeptide **9** in 55% yield when 2 equivalents of **8** were used (Scheme 3). *N*-Hydroxy-α-amino acids show no reactivity to conventional



Scheme 2.

peptide forming reactions using DCC or BOP.[15] This method is shown to be a powerful peptide forming reaction. It is especially useful for the reaction of amino acids having the diminished nucleophilicity on nitrogen.



Scheme 3.

In conclusion, it has been demonstrated that the reactions of thiol esters (2-pyridylthiol ester and tolylthiol ester) with different promoters (trimethylaluminum and silver trifluoroacetate, respectively) constitute an efficient method for rapid synthesis of peptides. Significantly, the generated peptides from two different types of thiol amino acid esters can be utilized directly to the next coupling reaction. The application of these protocols for the synthesis of apoptosis-inducing cyclic depsipeptide polyoxypeptin A[16] is in progress.

General Procedure for Z-L-Val-L-Phe-OMe. Method A (Me_3Al promoted coupling reaction): To a stirred suspension of Z-L-Val-SPy (100 mg, 0.279 mmol) and HCl·H-L-Phe-OMe (120 mg, 0.558 mmol) in CH_2Cl_2 (2 mL) at 0°C was added Me_3Al (0.558 mL, 1.116 mmol, 2 M in toluene). After 10 min at 0°C, the reaction mixture was quenched with *t*-butanol and acidified with 0.1N HCl. The aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude dipeptide was purified by silica gel chromatography (2:1:1, hexanes:EtOAc:CH_2Cl_2) to afford Z-L-Val-L-Phe-OMe (89.2 mg, 75%). Method B ($AgOCOCF_3$ promoted coupling reaction): To a stirred solution of Z-L-Val-STol (100 mg, 0.283 mmol) and H-L-Phe-OMe (101 mg, 0.566 mmol) in toluene (2 mL) was added $AgOCOCF_3$ (62.5 mg, 0.283 mmol). The reaction mixture was warmed to 60°C. After 20 min, the reaction mixture was cooled, and quenched with aqueous NH_4OH. The aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by the same conditions as Method A afforded Z-L-Val-L-Phe-OMe (108 mg, 90%).

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12. In order to examine the extent of racemization, a diastereomixture of Boc-DL-Tyr(Me)-L-Phe-OMe was synthesized from Boc-DL-Tyr(Me)-SPy and HCl·H-L-Phe-OMe using Me_3Al. Comparison of this mixture with Boc-L-Tyr(Me)-L-Phe-OMe, synthesized from Boc-L-Tyr(Me)-SPy and HCl·H-L-Phe-OMe in the same manner, using ^1H NMR revealed that no detectable racemization occurred. Boc-L-Tyr(Me)-L-Phe-OMe synthesized by the $AgOCOCF_3$ promoted peptide-forming reaction with Boc-L-Tyr(Me)-STol and H-L-Phe-OMe showed a single diastereomer by ^1H NMR.
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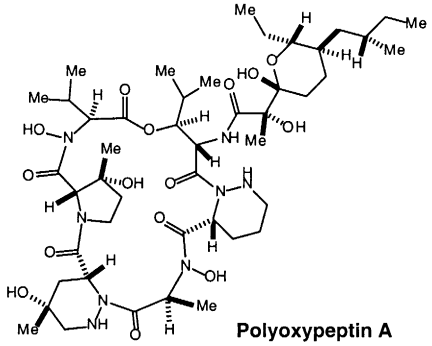

Polyoxypeptin A