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Introduction of the Aib-Pro unit into peptides by means of the 'azirine/oxazolone method' on solid phase

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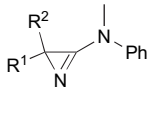
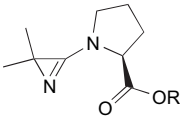
Abstract—A method for the direct introduction of Aib-Pro into peptides on solid phase was developed. The Aib-Pro unit was introduced by means of the 'azirine/oxazolone method' using allyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate as the synthon. After the reaction of the resin-bound amino or peptide acid with allyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate, the allyl protecting group of the resulting extended peptide could be removed by a mild Pd^0-promoted procedure. Cleavage of the peptide from the resin was performed with UV light at 352 nm and yielded C-terminal protected peptides. The method found a successful application in the syntheses of different Aib-Pro containing peptaibol segments. Furthermore, a protected derivative of the peptide antibiotic *Trichovirin I 1B* was prepared by segment condensation.

1. Introduction

2*H*-Azirin-3-amines are highly strained systems with versatile reactivity.[1] One very interesting and useful reaction is their application in peptide synthesis. In the 'azirine/oxazolone method', 2*H*-azirin-3-amines such as **1** or **2** are used as synthons for the introduction of sterically demanding α,α-disubstituted α-amino acids into peptides.[1–3] Thus, the reaction of 2*H*-azirin-3-amines, e.g., the α-aminoisobutyric acid (Aib) synthon **1a**, with amino or peptide acids leads to peptide amides, the terminal amide bonds of which can be hydrolyzed selectively to give extended peptide acids. In solution-phase chemistry, the 'azirine/oxazolone method' has proven to be successful for the introduction of a variety of sterically demanding α,α-disubstituted α-amino acids into oligopeptides,[4–13] endothiopeptides,[14–16] cyclic peptides,[17–18] and cyclic depsipeptides.[19–23]



1a $R^1 = R^2 = Me$
1b $R^1 - R^2 = -(CH_2)_4-$
1c $R^1 - R^2 = -(CH_2)_2O(CH_2)_2-$
1d $R^1 = Me$, $R^2 = PhCH_2$



2a R = Me
2b $R = CH_2CHCH_2$
2c $R = PhCOCH_2$

Recently, we adapted the 'azirine/oxazolone method' to solid-phase conditions, in order to additionally benefit from their advantages,[24] e.g., the rapid access to peptides without the need for the isolation of the sometimes cumbersome peptide acid intermediates. In this method, the growing peptide was attached through a carbamate linker to a [4-(hydroxymethyl)phenyl]acetamidomethyl (PAM) polystyrene resin (**3**) (Scheme 1). After deprotection of ^{t}Bu ester **4a**, resin-bound amino acid **4b** was treated with a solution of **1a**. It is worth mentioning that unconsumed **1a** could easily be recovered and re-used. The terminal amide **5a** was selectively hydrolyzed with 3 M HCl in THF/H_2O to provide the resin-bound peptide acid **5b**. Further extension of the peptide chain could be achieved either with a ^{t}Bu-protected amino acid and a coupling reagent or with **1a**. Cleavage of the peptide from the resin was achieved with HBr (33%) in acetic acid, and yielded the tripeptide **6**. In a recent paper, we showed that the method is not restricted to the Aib synthon **1a**, and that it was successfully extended to the 1-aminocyclopentane-1-carboxylic acid synthon **1b**, the 4-amino-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylic acid synthon **1c**, and the α-methylphenylalanine synthon **1d**.[25]

Peptaibols are linear, amphiphilic oligopeptides from fungal sources with a high proportion of α,α-disubstituted α-amino acids, primarily, Aib.[26–27] Peptaibols show antibiotic properties due to self-association in lipid membranes forming ion channels.[28] Several peptaibols, or segments thereof, were synthesized by means of the 'azirine/oxazolone method'.[4,8–13] The 2*H*-azirin-3-amine **2a** played an important role in these syntheses, since **2a** allowed the direct

Keywords: α-Aminoisobutyric acid; Azirine/oxazolone method; Peptaibols; Peptide synthesis; Photocleavable linker.
Abbreviations: Aib, α-aminoisobutyric acid; DIPEA, *N*,*N*-diisopropylethylamine; HOBt, 1-hydroxybenzotriazole; PyBOP, (1*H*-benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate; TBTU, *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; TFA, trifluoroacetic acid; TIPS, triisopropylsilane; Z, benzyloxycarbonyl; Z-ONSu, *N*-[(benzyloxycarbonyl)oxy]succinimide.
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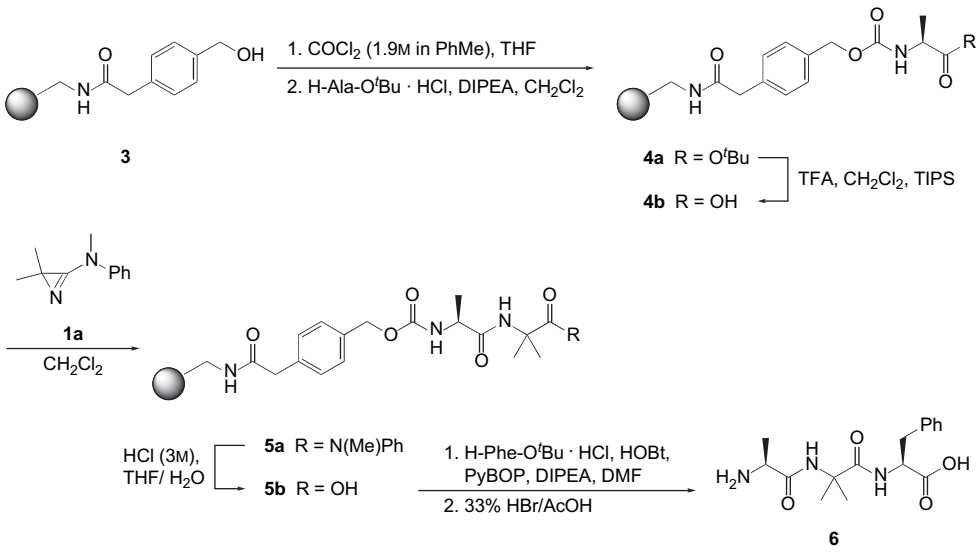


Scheme 1.

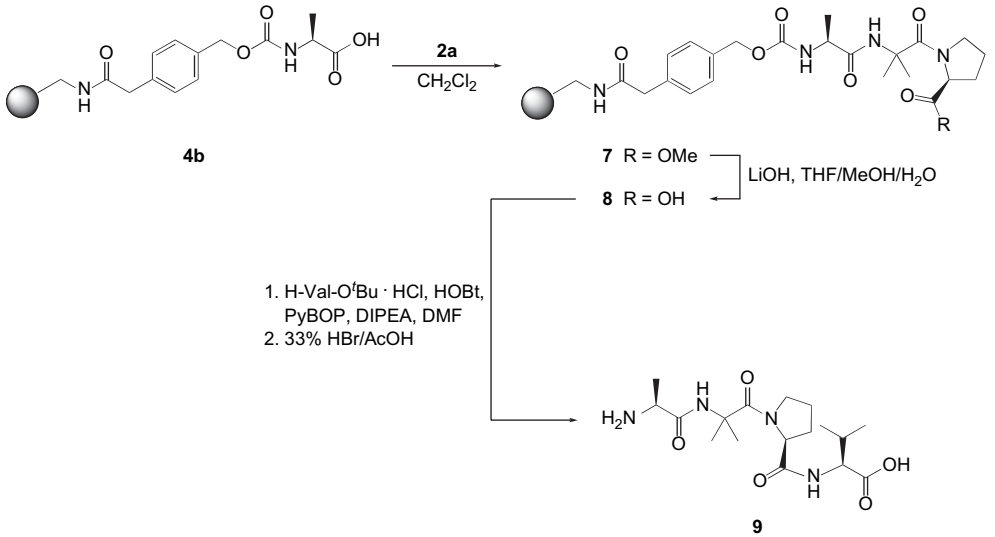
introduction of the frequently present, but relatively acid labile, Aib-Pro unit.[9] Unexpectedly, the use of **2a** on solid phase was not successful (vide infra).

Herein we report a method for the introduction of the Aib-Pro unit into peptides on solid phase, using a photolabile linker and a new Aib-Pro synthon (**2b**), which was especially developed for this purpose.[29]

2. Results and discussion

The most obvious approach to the introduction of the Aib-Pro unit was the use of synthon **2a** in analogy to the method outlined in Scheme 1. In doing so, the resin-bound amino acid **4b** was treated with a solution of **2a**, and the resulting resin-bound tripeptide methyl ester **7** was saponified with LiOH in a mixture of THF, MeOH, and H_2O (Scheme 2). After coupling with H-Val-O^{t}Bu by using PyBOP as the coupling reagent, the peptide was cleaved from the resin with HBr (33%) in acetic acid to give H-Ala-Aib-Pro-Val-OH (**9**) in 20% yield. In order to guarantee proper swelling of the resin during the saponification, the experiment was repeated with a Tentagel resin. However, the yield of 21% was still conspicuously lower in comparison with the introduction of the synthons **1a–d** (37–50%). The problem was recognized, when the synthesis of the model peptide H-Ala-Aib-Pro-Leu-Aib-Val-OH (on Tentagel resin) and the peptaibol segment (A8–A14 of *Trichovirin Ia*) H-Val-Aib-Gly-Aib-Aib-Pro-Leu-OH (on polystyrene resin) failed. Only peptide fragments, which are caused by Aib-Pro fissions, were detected. The analysis of the fragments revealed that the cleavage of the Aib-Pro amide bond occurred during the HBr-promoted cleavage of the peptide from the resin, and not during the hydrolysis of the terminal amide, which was necessary after the incorporation of **1a**.

Thus, a linker was required, which can be cleaved under milder conditions, but is still stable in TFA (50%) and HCl (3 M). Some years ago, Kunz introduced a Pd^0-labile allyl



Scheme 2.