ORGANIC LETTERS

2002
Vol. 4, No. 9
1547−1550

Silyl-Substituted Amino Acids: New Routes to the Construction of Selectively Functionalized Peptidomimetics

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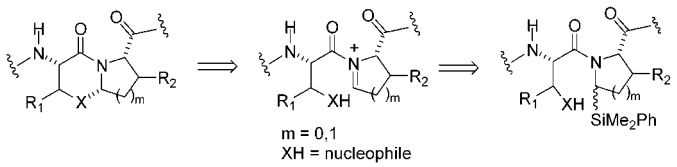
Received February 25, 2002

ABSTRACT

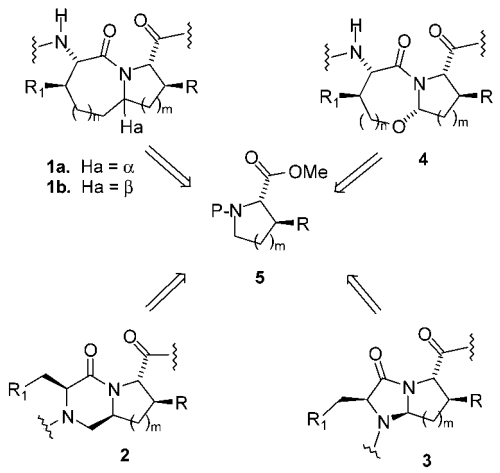


Silylated amino acids have been incorporated into peptides and then converted into *N*-acyliminium ions with the use of an anodic oxidation reaction. The result is a method for selectively incorporating conformational constraints or external nucleophiles within the peptide.

The anodic oxidation of amides[1] has proven to be a valuable tool for synthesizing lactam-based peptidomimetics[2] because it enables the selective functionalization of amino acid starting materials.[3] For example, constrained peptide analogues **1**−**4** have all been made by using an anodic electrolysis reaction to effect the net annulation of a ring onto an amino acid derivative such as **5** (Scheme 1).[4]

Although the electrolysis reactions have proven to be quite versatile, taking full advantage of the chemistry's potential for rapidly synthesizing monocyclic ($m = 0$) and bicyclic peptidomimetics has proven to be an elusive goal. Consider

Scheme 1



(1) For reviews of anodic amide oxidations, see: (a) Shono, T.; Matsumura, Y.; Tsubata, K. In *Organic Synthesis*; Saucy, G. Ed.; Organic Synthesis Inc.: Bloomington, 1984; Vol. 63, p 206 and references therein. (b) Shono, T. In *Topics in Current Chemistry*; Steckhan, E. Ed., Springer-Verlag: Berlin, Heidelberg, New York, 1988; Vol. 148, p 131.

(2) For a recent review concerning the use of lactam based peptidomimetics, see: (a) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. For more recent references, see: (b) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 5937. (c) Curran, T. P.; Marcaurell, L. A.; O'Sullivan, K. M. *Org. Lett.* **1999**, *1*, 1998. Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **2000**, *65*, 2163 and references therein.

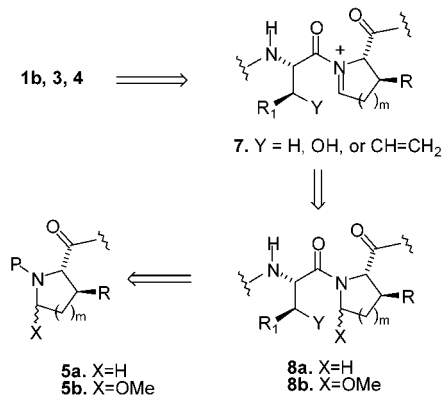
(3) For a review, see: Moeller, K. D. *Topics in Current Chemistry* **1997**, *185*, 49 and in particular ref 13 therein. Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527.

(4) (a) For the syntheses of **1a** and **1b**, see: Li, W.; Moeller, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 10106. Beal, L. M.; Liu, B.; Chu, W.; Moeller, K. D. *Tetrahedron* **2000**, *56*, 10113 and references therein. (b) For the synthesis of **2,** see: Tong, Y.; Fobian, Y. M.; Wu, M.; Boyd, N. D.; Moeller, K. D. *J. Org. Chem.* **2000**, *65*, 2484. (c) For the synthesis of **3**, see: Cornille, F.; Fobian, Y. M.; Slomczynska, U.; Beusen, D. D.; Marshall, G. R.; Moeller, K. D. *Tetrahedron Lett.* **1994**, *35*, 6989. (d) For the synthesis of **4,** see: Cornille, F.; Slomczynska, U.; Smythe, M. L.; Beusen, D. D.; Moeller, K. D.; Marshall, G. R. *J. Am. Chem. Soc.* **1995**, *117*, 909.

10.1021/ol025776e CCC: $22.00
Published on Web 03/28/2002

the intramolecular cyclization strategy used to build analogues such as **1b**,[5] **3**, and **4** (Scheme 2). In this route, amino

Scheme 2

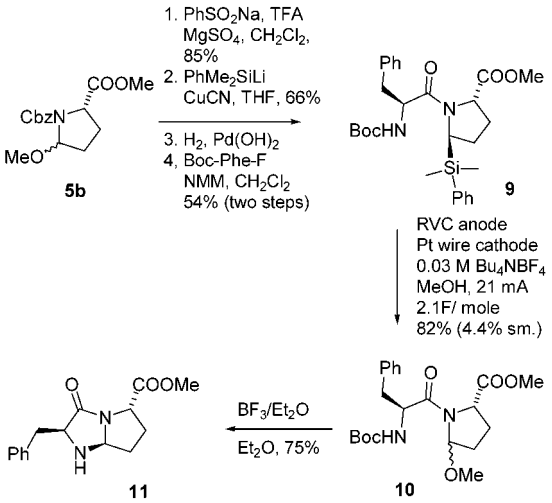


acid starting materials are converted into *N*-acyliminium ion precursor **8b**. Peptide **8b** is then cyclized to form the desired constrained peptidomimetic. On the surface, the strategy appears ideal for synthesizing libraries of constrained molecules. However, synthesizing substrate **8b** can be a challenging task. If the leaving group needed to make *N*-acyliminium ion **7** is introduced into the initial monomer (**5b**), then it is readily eliminated during the deprotection and coupling steps needed to incorporate the functionalized amino acid into **8b**. On the other hand, introduction of the leaving group following construction of the polypeptide **8a** requires the selective oxidation of a substrate having more than one nitrogen atom. While such oxidation reactions can be accomplished for specific dipeptides,[4c,d] they are highly dependent on the nature of the substrate. There is little hope for chemoselectively oxidizing just one nitrogen in a polypeptide like **8a**.[6]

Fortunately, chemistry developed by Yoshida and coworkers would appear to provide an ideal solution to this dilema.[7−9] These authors showed that the presence of a silyl substituent on the carbon α to an amide nitrogen lowered the oxidation potential of the amide by +0.5 V. Oxidation of the α-silated amide led to loss of the silyl group and generation of an *N*-acyliminium ion. Hence, if a silyl group could be selectively incorporated into **8b** (X = SiR_3), then a subsequent oxidation reaction would in principle selectively oxidize the nitrogen proximal to the silyl group, lead to the chemoselective formation of an *N*-acyliminium ion, and allow for the approach to peptidomimetics outlined in Scheme 2.

To test the feasibility of this approach, the chemistry outlined in Scheme 3 was investigated. This example was

Scheme 3



selected as a starting point for the study because the anodic oxidation of a dipeptide analogous to **9** having no silyl substituent had failed to afford any methoxylated product.[10] Substrate **9** was synthesized by first oxidizing a simple proline derivative in order to form the methoxylated product and then converting the product into the phenyl sulfonyl proline derivative in 85% yield.[11] A cuprate reagent was then employed to introduce the silyl moiety.[12] Once the silyl group was in place, the Cbz group was removed and the amino acid was coupled to a *t*-Boc protected phenylalanine. The oxidation of **9** was performed in an undivided cell using a reticulated vitreous carbon anode, a 0.03 M Et_4NOTs in MeOH electrolyte solution, and constant current conditions. Current was passed until 2.0 F/mol of charge had been passed.[13] The reaction led to the formation of the methoxylated product in an 82% yield along with 4.4% of the recovered starting material. The intramolecular cyclization was then completed with the use of $BF_3{\cdot}Et_2O$ and the stereochemistry of the bicyclic product assigned with the use of a NOESY experiment.

A similar oxidation−cyclization sequence was accomplished using substrate **12a** (another case in which the unsilated alternative failed to afford a bicyclic product). In this experiment the oxidation afforded a methoxylated product (76%) that was cyclized using TFA in dichloro-

(5) For intramolecular cyclizations leading to stereoselective syntheses of peptidomimetics such as **1b**, see: (a) Robl, J. A. *Tetrahedron Lett.* **1994**, *35*, 393. (b) Flynn, G. A.; Beight, D. W.; Mehdi, S.; Koehl, J. R.; Giroux, E. L.; French, J. F.; Hake, P. W.; Dage, R. C. *J. Med. Chem.* **1993**, *36*, 2420. Flynn, G. A.; Giroux, E. L.; Dage, R. C. *J. Am. Chem. Soc.* **1987**, *109*, 7914.

(6) Murahashi, S.-I.; Mitani A.; Kitao, K. *Tetrahedron Lett.* **2000**, *41*, 10245.

(7) (a) Yoshida, J.; Isoe, S. *Tetrahedron Lett.* **1987**, *28*, 6621. (b) For a review, see: Yoshida, J. *Topics Curr. Chem.* **1994**, *170*, 39.

(8) (a) For a recent application to a simple amide, see: Kamada, T.; Oku, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3381.

(9) For the use of α-silylamines to direct the generation of iminium ions, see: (a) Yoon, U. C.; Mariano, P. S. *Acc. Chem. Res.* **1992**, *25*, 233.

(10) For an experimental procedure, see ref 4b.

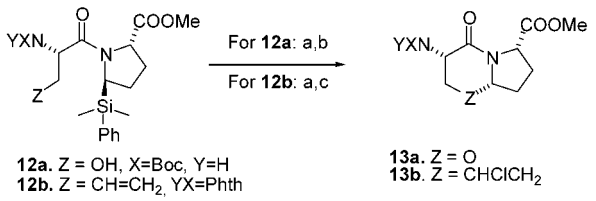
(11) Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V. *Tetrahedron* **1991**, *47*, 1311.

(12) For a review, see: Fleming, I. In *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; pp 257−292.

(13) The oxidations were conducted using a model 630 coulometer, a model 410 potentiostatic controller, and a model 420A power supply purchased from The Electrosynthesis Co., Inc.

methane to yield an 81% yield of **13a**. In a related carbon-based example, **12b** was oxidized to afford a 73% isolated yield of the methoxylated product. The methoxylated product was cyclized using $TiCl_4$ in order to generate a 64% yield of the target ring system **13b** having *cis* stereochemistry about the original proline ring. The stereochemistry of the bridgehead carbon was again established with the use of a NOESY experiment (Scheme 4).

Scheme 4[a]



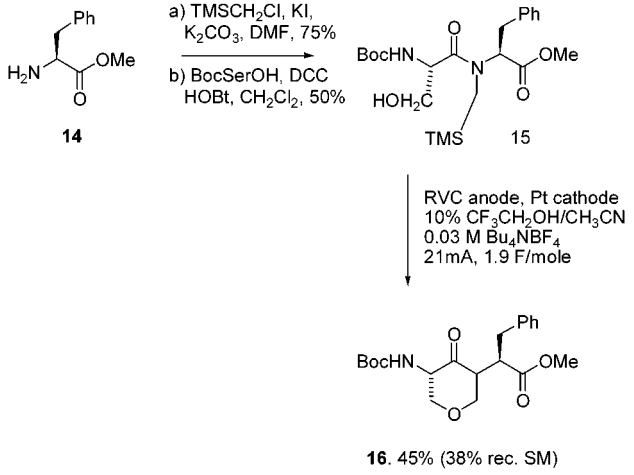
12a. Z = OH, X=Boc, Y=H
12b. Z = CH=CH_2, YX=Phth

13a. Z = O
13b. Z = $CHClCH_2$

[a] Reagents: (a) RVC anode, Pt cathode. 0.03 M Bu_4NBF_4, MeOH, 21 mA, 2.1 F/mol. For **12a**: 76%. For **12b**: 73%. (b) 1% TFA, CH_2Cl_2, 81%. (c) $TiCl_4$, CH_2Cl_2, −78 °C → rt, 64%

The use of the silyl group was not restricted to analogues that contained a proline moiety. As outlined in Scheme 5, a

Scheme 5

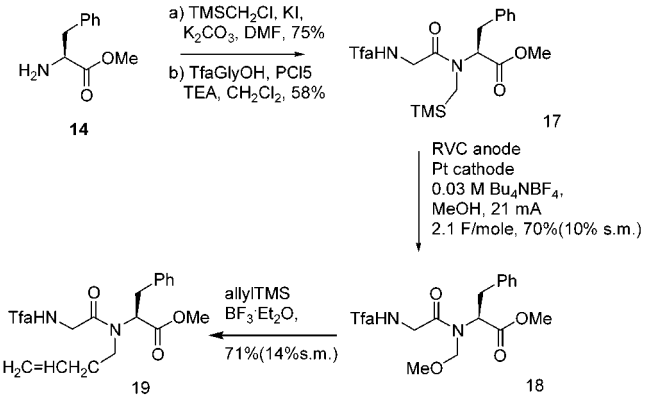


16. 45% (38% rec. SM)

silylated phenylalanine building block was synthesized using an alkylation reaction. The alkylated amino acid was then coupled to serine, and the dipeptide was oxidized. In this experiment, the oxidation was performed using trifluoroethanol as the cosolvent so that the intramolecular alcohol nucleophile would have the time to directly trap the *N*-acyliminium ion generated from the oxidation. A 45% isolated yield of the product was obtained along with 38% of the recovered starting material. The reaction was stopped after 2 F/mol of charge had been passed in order to avoid side reactions that made the reaction less clean.

The oxidations could also be used to selectively introduce intermolecular nucleophiles into the peptide analogues

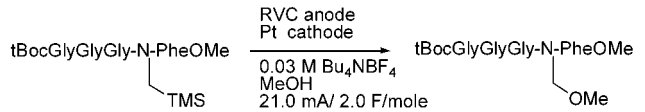
Scheme 6



(Scheme 6). For example, the silyl group of **17** was replaced with a methoxy group, and then an allyl group was introduced using $BF_3{\cdot}Et_2O$ and allyltrimethylsilane in order to form **19**. In this case, it was found that a higher yield for the addition reaction was obtained when the N-terminal amine was protected as the trifluoroacetate ester. Interestingly, a cyclization reaction analogous to the bicyclic example illustrated in Scheme 3 did not compete with the intermolecular addition. Even when a substrate having a N-terminal *t*-Boc protecting group was treated with $BF_3{\cdot}Et_2O$ in Et_2O in the absence of the allylsilane nucleophile, none of the cyclic product was generated. Apparently, the less substituted *N*-acyliminium ion was not stable enough to allow for a 5-*endo-trig* cyclization.

Finally, the use of the silated amino acid was shown to be compatible with the use of larger peptide-based starting materials. As illustrated in Scheme 7, the use of a silyl

Scheme 7



20 **21**. 78%

substituent allowed for the selective incorporation of an *N*-acyliminium ion into a tetrapeptide.

In conclusion, the use of a silated amino acid building block allows for the selective incorporation of an *N*-acyliminium ion precursor into a peptide. The result is that either constrained peptidomimetics or external nucleophiles can be systematically introduced into the peptide, a development that should greatly expand our ability to rapidly construct modified peptides from readily available amino acid starting materials.

Acknowledgment. We thank the National Science Foundation (CHE-9023698) for their generous support of our work. We also gratefully acknowledge the Washington University High Resolution NMR facility, partially supported

by NIH grants RR02004, RR05018, and RR07155, and the Washington University Mass Spectrometry Resource Center, partially supported by NIHRR00954, for their assistance.

Supporting Information Available: A sample method for the electrochemical procedure is included along with characterization data for the electrochemical substrates and corresponding products. This material is available free of charge via the Internet at http://pubs.acs.org.

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