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Building Functionalized Peptidomimetics: New Electroauxiliaries and the Use of a Chemical Oxidant for Introducing *N*-Acyliminium Ions into Peptides

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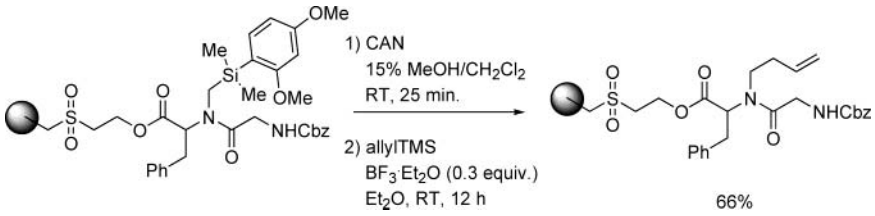
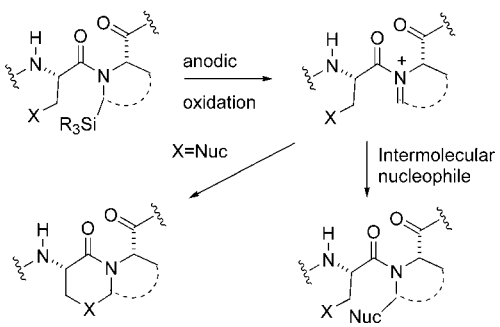
ABSTRACT



The removal of electroauxiliaries from peptide substrates with chemical oxidants has been examined as a method for inserting *N*-acyliminium ions into the peptides. To this end, it was found that both 4-methoxyphenyldimethylsilyl and 2,4-dimethoxyphenyldimethylsilyl electroauxiliaries were readily cleaved with the use of ceric ammonium nitrate. Of the two groups, the 2,4-dimethoxyphenyldimethylsilyl electroauxiliary was the most labile under the oxidative conditions. The oxidation reactions were shown to be compatible with the use of a solid-phase substrate.

Peptide libraries that include conformationally constrained peptidomimetics can potentially provide an attractive means for gathering information about the three-dimensional requirements of ligand−receptor binding.[1] But how does one conveniently build a peptide library that contains conformationally constrained analogues? As part of an effort to answer this question, we recently showed that silylated amino acids can be used to selectively insert *N*-acyliminium ions into peptides.[2] The *N*-acyliminium ions were used to trigger either the formation of a conformational constraint or introduce an external nucleophile to the peptide (Scheme 1). This chemistry worked because a silyl substituent on the carbon α to the nitrogen of an amide serves as an electroauxiliary[3] and lowers the oxidation potential of the amide by 0.5 V.[4] Therefore, the insertion of a silyl substituent into the peptide enabled the selective oxidation of the neighboring amide relative to any of the other amides in the peptide. In these cases, the oxidation was accomplished using anodic electrochemistry.

Scheme 1



(1) Burgess, K. *Acc. Chem. Res.* **2001**, *34*, 826.
(2) Sun, H.; Moeller, K. D. *Org. Lett.* **2002**, *4*, 1547.
(3) (a) Yoshida, J.; Isoe, S. *Tetrahedron Lett.* **1987**, *28*, 6621. (b) Yoshida, J. *Top. Curr. Chem.* **1994**, *170*, 39. (c) For a recent application, see: Kamada, T.; Oku, A. *J. Chem. Soc., Perkin Trans 1* **1998**, 3381. Kamada, T.; Oku, A. *J. Chem. Soc., Perkin Trans 1* **2002**, 1105.

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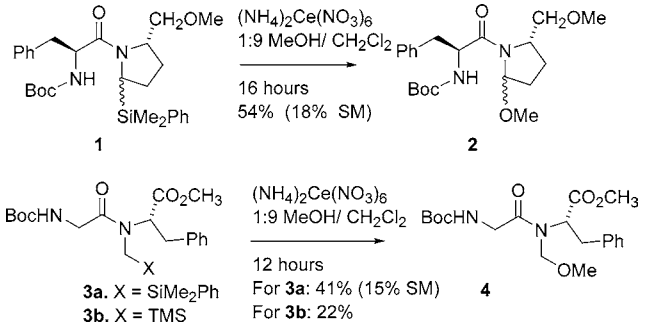
While this strategy enabled the rapid synthesis of a variety of peptide analogues, the use of electrochemistry for the oxidation limited its applicability to the construction of solid-phase peptide libraries. Such a scenario would require the oxidation of a solid-phase substrate using a solid-phase reagent (the electrode). For this reason, a directly analogous strategy that used a solution-phase chemical oxidant for the key step was needed. Normally, routes to *N*-acyliminium ion intermediates using chemical oxidants[5] are limited in scope due to the high oxidation potential of the starting amide and the lack of selectivity between oxidation of the amide substrate and oxidation of the methoxylated or hydroxylated product. However, by reducing the oxidation potential of the amide substrate, the presence of a silyl electroauxiliary in the molecule should eliminate both of these problems. For example, Mariano and co-workers studied the chemical oxidation of simple trimethylsilyl-substituted amides and carbamates and utilized the subsequent *N*-acyliminium ions for the synthesis of alkaloid ring skeletons.[6] Yet while these reactions were successful, the yields of the oxidations ranged from 25 to 86% and were sensitive to changes in the nature of the substrate. On the basis of these efforts, it was not clear that a chemical oxidant could be used to efficiently insert *N*-acyliminium ions into a series of more difficult to oxidize peptide substrates.[7] With this in mind, an investigation was undertaken in order to determine the viability of using chemical oxidants for selectively functionalizing peptide substrates. We report herein that peptides containing modified silyl-based electroauxiliaries can be selectively oxidized in high yield using a solution-phase chemical oxidant.

Initial efforts to oxidize peptides with a chemical reagent focused on the oxidation of substrates **1** and **3a** (Scheme 2).

Scheme 2

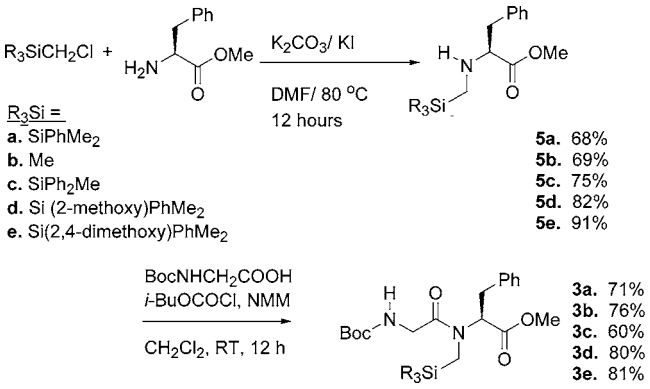


In these cases, a phenyl dimethylsilyl electroauxiliary was utilized along with ceric ammonium nitrate as the oxidant. The oxidation of **1** led to the desired methoxylated product in a 54% isolated yield along with 18% of the recovered starting material. The oxidation of **3a** gave rise to a 41% yield of the desired methoxylated compound along with 15% of the recovered starting material. While both reactions afforded the desired product, it was clear that a method for raising the yield was needed if the reactions were to prove useful for solid-phase synthesis. A potential solution to this problem suggested itself when we observed that the reaction using the acyclic substrate was very sensitive to the nature of the electroauxiliary. When a trimethylsilyl electroauxiliary (substrate **3b**) was used for this reaction, only a 22% yield of the methoxylated product was obtained. For comparison, the corresponding electrolysis of **3b** afforded a 92% isolated yield of the methoxylated product **4**. This observation was consistent with a chemical oxidation that was occurring near the oxidation potential limit for ceric ammonium nitrate. This made the chemical oxidation sensitive to variations in the structure, and hence oxidation potential, of the substrate. The corresponding electrochemical reaction was not adversely effected because the reaction automatically adjusted to the oxidation potential of the substrate.

In principle, there were two ways to solve this problem. Either the strength of the chemical oxidant could be increased or the electroauxiliary could be altered in order to further lower the oxidation potential of the substrates.

Since the oxidation of the amide needed to be not only selective relative to other amides in the backbone but also selective relative to the side chains of the peptide, the strategy taken was to alter the electroauxiliary. The plan called for studying a series of electroauxiliaries in a dipeptide model system. As in the synthesis of **3a** and **3b** (Scheme 3), each new substrate for this study was synthesized by alkylating phenyl alanine methyl ester with an appropriately substituted silyl methyl chloride derivative and then coupling the resulting alkylated amine with a Boc-protected glycine.

Scheme 3



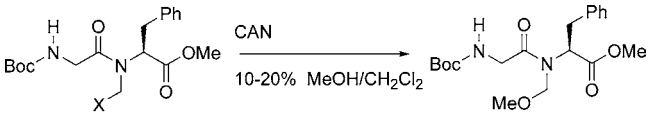
Once the substrates were in hand, they were oxidized using ceric ammonium nitrate in a solution of 15−20% methanol in dichloromethane (Table 1). The reactions originating from **3a** and **3b** are included as the first three entries in Table 1 so that direct comparisons with the new electroauxiliaries can be made. Our first attempt to improve the reaction

(4) Yoshida, J.; Wtanabe, M.; Toshioka, H.; Imagawa, M.; Suga, S. In *Novel Trends in Electroorganic Synthesis*; Torii, S., Ed.; Springer: Tokyo, 1998; p 99.

(5) Murahashi, S. I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2443.

(6) (a) Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841. (b) Kim, H.-J.; Yoon, U.-C.; Jung, Y.-S.; Park, N. S.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 860.

Table 1.



3a-e 4

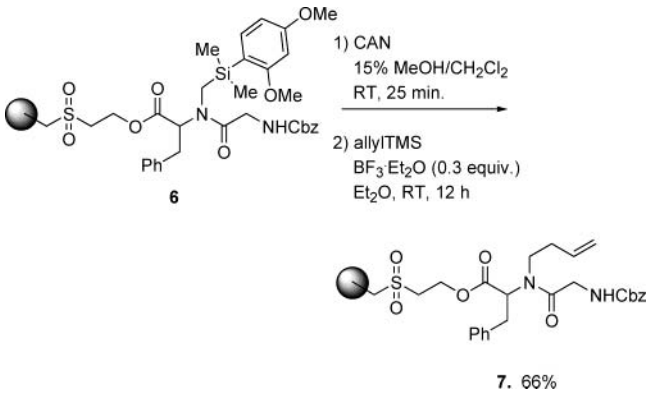
	X	$E_{p/2}$[a]	time	temp	yield 4
3a	$PhMe_2Si$	+1.67 V	12 h	25 °C	41%[b]
3b	Me_3Si	+1.63 V	12 h	25 °C	22%
3b	Me_3Si	+1.63 V	30 min	25 °C	0%[c]
3c	Ph_2MeSi		12 h	25 °C	0%[c]
3d	(2-methoxy-phenyl)Me_2Si	+1.64 V	30 min	25 °C	87%
3d	(2-methoxy-phenyl)Me_2Si	+1.64 V	90 min	−40 °C	0%[c]
3e	(2,4-dimethoxy-phenyl)Me_2Si	+1.38 V	15 min	25 °C	80%
3e	(2,4-dimethoxy-phenyl)Me_2Si	+1.38 V	35 min	0 °C	82%
3e	(2,4-dimethoxy-phenyl)Me_2Si	+1.38 V	90 min	−40 °C	86%

[a] Measured by cyclic voltammetry using a silver/silver chloride reference electrode, a solution of tetrabutylammonium perchlorate in acetonitrile electrolyte, and Pt electrodes. [b] Product was isolated along with 15% of recovered starting material. [c] No reaction was observed for this substrate using the conditions indicated.

involved the addition of a second phenyl ring to the electroauxiliary (substrate **3c**). This change was found to interfere with the oxidation process, and none of the desired product was obtained. Fortunately, varying the nature of the phenyl ring in substrate **3a** proved to be more rewarding. A dramatic improvement in the oxidation reaction was observed when an electron-donating oxygen substituent was added to the phenyl ring. In this case, the oxidation of substrate **3d** led to an 87% isolated yield of the desired oxidized product after only 30 min. For comparison, no product was obtained from a similar oxidation using a trimethylsilyl electroauxiliary (entry 3). Cyclic voltammetry indicated that the improvement in the reaction was not a result of the methoxy group lowering the oxidation potential of the substrate. Apparently, the electron-rich aromatic ring on the silyl substituent aids in the elimination step once the radical cation is formed from the oxidation. The addition of a second methoxy group to the phenyl ring on the silyl substituent led to a further improvement in the reaction (**3e**). In this case, the yield of the oxidation improved as the temperature was lowered. Even at −40 °C, the ceric ammonium nitrate oxidation led to an 86% isolated yield of the methoxylated compound. For comparison, the oxidation of **3d** led to no reaction at −40 °C. Interestingly, one of the side products from the oxidation of substrate **3e** was 1,3-dimethoxybenzene. The formation of this product would appear to be the result of an initial oxidation of the phenyl ring followed by elimination of the silyl group and hydrogen atom abstraction from solvent. This suggestion was consistent with the lower oxidation potential measured for substrate **3e**. In any event, the ease with which the dimethoxylated electroauxiliary could be removed relative to either the 2-methoxylphenyldimethylsilyl or the trimethylsilyl electroauxiliary suggested that more than one site for *N*-acyliminium ion generation can be inserted into a peptide and then selectively unmasked.

Having established that electroauxiliaries can be used in conjunction with chemical oxidants, we sought to demonstrate the compatibility of the reactions with solid-phase substrates. For this reason, the Merrifield resin-based substrate **6** was synthesized[8] and then oxidized using ceric ammonium nitrate (Scheme 4). Since the methoxylated product was not compatible with cleavage from the resin, the methoxy group of the product was exchanged for an allyl substituent. The allylated product could be readily cleaved from the resin and identified. The combined yield for the oxidation and subsequent allylation reaction on the solid-phase substrate was 66%.

Scheme 4



6

7. 66%

The yield for this reaction was obtained by dividing substrate **6** into two fractions. For the first fraction, the substrate was oxidized, the resulting methoxylated product used to introduce an allyl nucleophile, and then the peptide cleaved from the resin.[9] For the second fraction, the substrate was simply cleaved from the resin. By comparing the yield of product obtained from the two fractions, success of the oxidation/trapping sequence could be ascertained. Since the exchange of the methoxy group for the allyl substituent is known to proceed in about 80% yield,[10] it would appear that the oxidation of the solid-phase substrate produced the methoxylated amide in approximately 80% yield.

In conclusion, it has been found that an electroauxiliary can be used in conjunction with a chemical oxidant to selectively insert *N*-acyliminium ion precursors into peptides. This work is compatible with the use of solid-phase-bound

(7) For difficulties associated with the oxidation of amides having heteroatoms α to the carbonyl group, see: (a) Li, W.; Hanau, C. E.; d'Avignon, A.; Moeller, K. D. *J. Org. Chem.* **1995**, *60*, 8155. Selected dipeptides can be oxidized using high current densities: (b) Cornille, F.; Fobian, Y. M.; Slomczynska, U.; Beusen, D. D.; Marshall, G. R.; Moeller, K. D. *Tetrahedron Lett.* **1994**, *35*, 6989 and (c) Cornille, F.; Slomczynska, U.; Smythe, M. L.; Beusen, D. D.; Moeller, K. D.; Marshall, G. R. *J. Am. Chem. Soc.* **1995**, *117*, 909. The success of these reactions is highly dependent upon the nature of the substitutents.

(8) Peptide was added to the solid-phase resin using the standard protocol. Tesser, G. I.; Buis, J. T.; Wolters, E. T. M.; Bothe-Helmes, E. G. *Tetrahedron* **1976**, *32*, 1069.

(9) Product was cleaved off of the resin using sodium hydroxide in a 10:3 ratio of dioxane and water for 2 min.

(10) (a) Beal, L. M.; Liu, B.; Chu, W.; Moeller, K. D. *Tetrahedron* **2000**, *56*, 10113. (b) Tong, Y.; Fobian, Y. M.; Wu, M.; Boyd, N. D.; Moeller, K. D. *J. Org. Chem.* **2000**, *65*, 2484.

substrates. Studies aimed at utilizing this methodology in the synthesis of peptide libraries containing constrained peptidomimetics are currently underway.

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Supporting Information Available: Sample experimental procedure for the oxidation reaction along with characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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