Solid-Phase Synthesis of Peptide Mimetics with (*E*)-Alkene Amide Bond Replacements Derived from Alkenylaziridines

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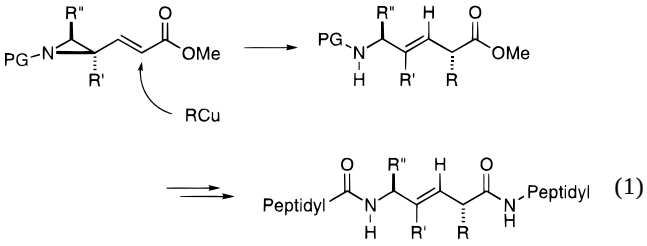
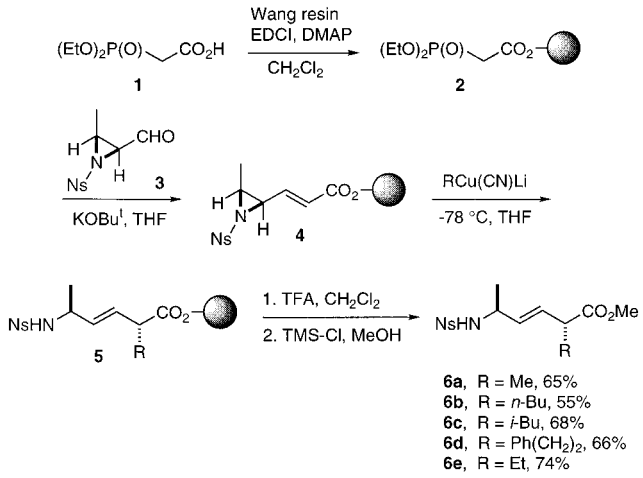
The systematic substitution of amide groups in a biologically active peptide sequence by isosteric but nonhydrolyzable functions continues to be an important design motif in medicinal chemistry.[1] Hydroxyethylene (ψ[CHOHCH$_2$]), methylenethio (ψ[CH$_2$S]), aminomethylene (ψ[CH$_2$NH$_2$]), and *trans*-alkene (ψ[(*E*)-CH=CH]) are among the most popular amide bond replacements.[1,2] In particular, the nonhydrolyzable, rigid (*E*)-alkene moiety effectively mimics the three-dimensional structure of the amide bond, especially the C(α)$_n$ − C(α)$_{n+1}$ distance. We[3] and others[4] have recently reported the S$_N$2′-opening of alkenylaziridines for the preparation of alkene isosteres.[5] Further progress in this area has been hampered by a lack of readily removable protective group functions (PG) for effective aziridine activation and, especially, a straightforward integration of this methodology with the standard Fmoc- and resin-based peptide synthesis techniques. In this paper, we report the first preparation of alkene isosteres on solid support that is immediately amenable to iterative peptide synthesis.



(1)

We envisioned that attachment of the alkenylaziridine to a polymeric support through an ester linkage would lead to a C-terminal-linked dipeptide isostere directly suitable for further chain elongation. The readily available Wang resin[6] was selected because its usefulness for peptide synthesis has been well documented,[7] and more recently, it has also proved quite versatile for solid-phase organic chemistry.[8] The appropriate protection of the aziridine nitrogen proved critical for the ultimate success of this methodology. Although both the tosyl and Boc groups have been shown to be effective protecting/activating groups in the solution-phase alkenylaziridine opening,[3,4] neither was deemed appropriate for the corresponding solid-phase protocol. The former is often difficult to remove, and deprotection of the latter is not compatible with the acid-sensitive Wang linker. However, Fukuyama and co-workers recently reported the use of the 2-nitrophenylsulfonyl (Ns−) group as a tosyl analog that could be readily cleaved with thiophenoxide.[9] These mild conditions appeared compatible with the functionality of the (*E*)-alkene peptide isostere as well as the Wang resin. Indeed, our work demonstrates that the Ns group can serve as an effective orthogonal protective group in solid-phase peptide chemistry (*vide infra*).

Scheme 1



Preparation of the polymer-supported alkenylaziridine entailed a solid-phase olefination as a key step. Coupling of the Wang resin with (diethylphosphono)acetic acid yielded the novel polymeric Horner−Wadsworth−Emmons reagent **2** (Scheme 1).[10] Reaction with a 3-fold excess of the aldehyde **3**[11] in the presence of potassium *tert*-butoxide provided the polymer-supported alkenylaziridine **4**. Reaction of **4** with alkylcyanocuprates occurred readily and cleanly. Swelling of the resin in THF at room temperature followed by cooling to −78 °C, addition of a preformed, cold (−78 °C) solution of cuprate, and quenching after 1 h was established as the most

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(10) A similar reagent, leading to α,β-unsaturated amides, was recently reported: Johnson, C. R.; Zhang, B. *Tetrahedron Lett.* **1995**, *36*, 9253.

(11) Preparation of **3** is described in the Supporting Information.

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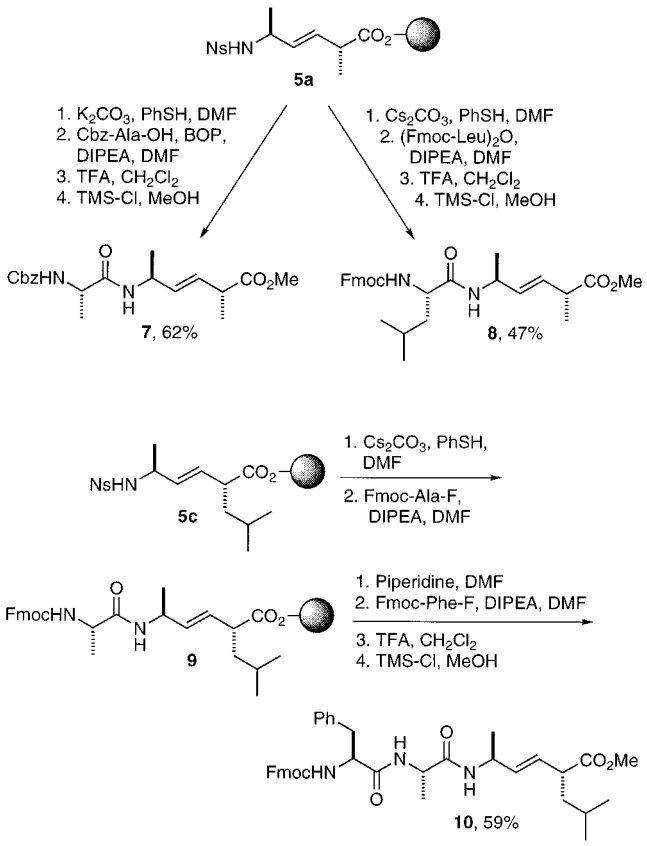
Scheme 2



general reaction protocol for the S_N2' reaction. After cleavage from the resin and esterification,[12] the protected dipeptide isosteres **6a**−**e** were directly obtained in excellent purity and in good yields (based on the original loading of **1** on the Wang resin (ca. 0.81 mmol/g)). Copper reagents derived from organolithium, -magnesium, and -zinc precursors were equally effective. Since the purity of the isolated compounds after filtration through a short plug of SiO_2 was >90% according to ^1H and ^{13}C NMR, the less than quantitative overall yields for **6a**−**e** are probably due to some cleavage of the carboxylate **2** from the resin during the Wadsworth−Emmons reaction.

After the optimization of the solid-phase cuprate chemistry, incorporation of the polymer-bound dipeptide isosteres **5** into longer peptide sequences was now readily achieved as shown in Scheme 2. Cleavage of the nosyl group according to Fukuyama's protocol and iterative coupling of *N*-protected amino acid residues yielded tri- and tetrapeptide analogs **7**, **8**, and **10** in high yields and in >90% purity after cleavage from the resin. Due to the high level of reaction optimization in this sequence, no further chromatographic separation steps were required.[13]

In summary, we have developed the first solid-phase protocol for the synthesis of peptides containing (*E*)-alkene amide isostere linkages.[14] This efficient method should prove useful for structure−activity studies of biologically active peptide sequences in medicinal chemistry as well as the combinatorial synthesis of peptidomimetics. Novel features of this methodology include the use of a polymer-bound Horner−Wadsworth−Emmons reagent for the synthesis of alkenylaziridines and the S_N2'-reaction of organocopper reagents on solid support. In addition, the compatibility of the nosyl group with alkylcyanocuprates and the Wang resin has been demonstrated.

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Supporting Information Available: Experimental procedures and compound characterization data (29 pages).

JO9701039

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(13) Resin-cleaved products were fully characterized by ^1H, ^{13}C NMR, IR, MS, and HRMS.

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