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N-Fmoc-dehydroalanine: a versatile molecular scaffold for the rapid solid-phase synthesis of cycloaliphatic amino acids

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Abstract

The synthesis of polymer-supported *N*-Fmoc-dehydroalanine starting from *S*-protected cysteine via an oxidation/elimination strategy is described. Cycloaddition with a range of dienes afforded a range of conformationally constrained amino acids in moderate yields. The potential applications of this methodology to combinatorial libraries is discussed. \bigcirc 2000 Elsevier Science Ltd. All rights reserved.

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Conformationally constrained α -amino acid derivatives such as carbocyclic α -amino acids have applications in biological chemistry as enzyme inhibitors and peptidomimetics.^{1–3} Historically, these amino acids are synthesised via the Strecker or Bucherer–Lieb synthesis,^{4,5} but recent strategies employ cycloaddition reactions of dehydroalanine derivatives.^{6–9} In view of the potential therapeutic uses of conformationally constrained amino acids and mindful of the possible combinatorial applications, we recently reported the solid-phase synthesis of the bicyclic norbornene α -amino acids from polymer-supported dehydroalanine derivatives.¹⁰ Whilst useful for the synthesis of cycloaliphatic amino acids and peptides, the reported methodology lacked versatility in that the *N*-protecting groups utilised were not orthogonal to the acid-labile polymer support. In this report, the synthesis of polymer-supported *N*-Fmoc-dehydroalanine is described and applications to the rapid synthesis of carbocyclic amino acids are outlined.

Although synthetic routes to polymer-bound dehydroalanine derivatives have been reported, these methods are generally not applicable to the synthesis of polymer-bound *N*-Fmoc-dehydroalanine.^{10–12} Thus, in order to circumvent this problem the procedure as outlined in Scheme 1 was implemented. The key step in this synthesis employs thermal elimination of the β -sulfoxide derived from *N*-Fmoc-*S*-benzylcysteine (1) for the installation of the α , β -unsaturated system.¹³

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Scheme 1. (i) DCC (1.6 equiv.), DMAP (1.5 equiv.), 4:1 dichloromethane:DMF, 5.5 h. (ii) MCPBA (1.05 equiv.), dichloromethane, 0°C, 3 h. (iii) toluene, 110°C, 16 h

Coupling of *N*-Fmoc-*S*-benzylcysteine to Wang resin (1.22 mmol/g) under standard coupling procedures (DCC) gave the polymer-bound amino acid **2** in 76% yield as determined by photometric analysis.¹⁴ Subsequent treatment of polymer-bound *N*-Fmoc-*S*-benzylcysteine (**2**) with careful stoichiometric amounts of MCPBA afforded the sulfoxide **3**.

As the characteristic IR sulfoxide S=O vibration (typically $\sim 1030 \text{ cm}^{-1}$) was partially obscured by polystyrene backbone vibrations, the oxidation reaction was monitored by ¹H NMR analysis on a small portion of cleaved product. Conversion to the polymer-supported *N*-Fmoc-dehydroalanine **4** was readily achieved by heating the polymer-bound sulfoxide **3** at 100°C for 16 h. The polymer-supported dehydroalanine derivative **4** was then reacted with dienes **5a**–**d** (Scheme 2) to afford cycloadducts **6a**–**d** following cleavage with TFA, as summarised in Table 1.



Scheme 2. (i) Diene 5a-d (10 equiv.), toluene, 110°C, sealed tube, 16-72 h. (ii) 20% TFA/dichloromethane, 30 min

With the exception of furan, cycloadditions with the dienes (**5a**,**b**,**d**) proceeded to give moderate to good isolated yields of the desired cycloadducts.[†] Deprotection and hydrogenation of **6a** confirmed the preferential formation of the *exo* cycloadduct by comparison with literature ¹H NMR data.⁷ The Diels–Alder reaction of polymer-supported *N*-Fmoc-dehydroalanine with furan was sluggish and, during the extended period of heating, degradation of the polymer support ensued. For ease of characterisation, the *N*-Fmoc group of the cycloadduct resulting from the Diels–Alder reaction of **4** with diene **5d**, was removed prior to cleavage with TFA, which in turn resulted

[†] All new compounds gave satisfactory spectroscopic and analytical data. Representative ¹H NMR data for **6a** (300 MHz, CD₃OD): (*exo*) δ 1.43 (dd, *2J* 12.5 Hz, *3J* 3 Hz, 1H, cycloaliphatic CHaHb), 1.56 (dm, *2J* 9 Hz, 1H, bridge CHaHb), 1.93 (dm, *2J* 9 Hz, 1H, bridge CHaHb), 2.52 (dd, *2J* 12.5 Hz, *3J* 3 Hz, 1H, cycloaliphatic CHaHb), 2.96 (br m, 1H, CH), 3.43 (br m, 1H, CH), 4.20–4.50 (m, 3H, fluorenyl CH₂ and CH), 6.11 (m, 1H, olefinic CH), 6.42 (m, 1H, olefinic CH), 7.30–8.00 (8H, aromatics); (*endo*) δ 1.30–2.30 (multiple signals, 4H, cycloaliphatic CH), 6.40 (m, 1H, olefinic CH), 7.30–8.00 (8H, aromatics).

 Table 1

 Isolated yields of cycloadducts following Diels–Alder reaction of 4 with dienes 5a–d

Diene	Product	Conditions ^a	Yield	Exo:Endo ^b
5a	HO ₂ C NHFmoc	а	50%	4:1
Sb	HO ₂ C NHFmoc	b	48%	1:1
5 c	HO ₂ C NHFmoc 6c	c		
otms 5d	MeO ₂ C // NHFmoc	b	56%	3:1

^a Conditions: a) toluene, 110°C, 16 hours. b) toluene, 100°C, sealed tube, 72 hours. c) toluene, 100°C, 7 days.

^b Selectivity determined by integration of the olefinic resonances in ¹H NMR spectra of the cleaved cycloadducts.

^c Isolated as the methyl ester following treatment of the crude cleavage mixture with diazomethane. Note that only the relative stereochemistry is shown.

in the concomitant removal of the TMS protecting group. Two cycloadducts in the ratio of 3:1 were observed in the ¹H NMR spectrum of the crude cleavage mixture. The major product was identified as the 1,2- or *ortho*-adduct as determined by 2D $^{1}H^{-1}H$ NMR spectroscopy. The cleaved material was then hydrogenated to afford the corresponding cyclohexane derivatives and comparison of the ¹H NMR data with those in the literature¹⁵ identified the major product from the cycloaddition as the *exo*-cycloadduct.

In order to demonstrate the potential of utilising *N*-Fmoc-dehydroalanine derivatives for the synthesis of novel amino acids and peptides of therapeutic interest, the *N*-Fmoc group of the polymer-supported cycloadduct **7** was deprotected and then functionalised under a variety of conditions. Thus, elaboration of the polymer-bound cycloadduct **8** into the dipeptide **9** was achieved via standard peptide coupling conditions followed by cleavage from the Wang resin (Scheme 3a). Alternatively, the polymer-bound cycloadduct **8** may be readily acylated, which upon cleavage affords *N*-acyl cycloaliphatic amino acids such as **10** (Scheme 3b). *N*-Alkylation of the polymer-bound cycloadduct **8** was treated with benzaldehyde under standard conditions, the *N*-benzyl cycloaliphatic amino acid **11** was isolated in 63% yield following cleavage from the resin (Scheme 3c). In view of the extensive range of commercially available aldehydes, reductive alkylation reactions are particularly well suited to combinatorial methodologies, leading to the synthesis of diverse libraries of potentially biologically active compounds. In addition, polymer-supported *N*-alkylated cycloaliphatic amino acids may be further functionalised by simple peptide coupling techniques to afford the corresponding peptoids.

These studies nicely illustrate the utility of polymer-supported *N*-Fmoc-dehydroalanine in the solid phase synthesis of carbocyclic amino acids. The use of the base-labile *N*-Fmoc functionality allows further manipulation of the N-terminus of the amino acid, enabling a number of *N*-functionalised



Scheme 3. (i) 1:1 Piperidine:DMF, 10 min. (ii) *N*-Fmoc-glycine (3 equiv.), HBTU (3 equiv.), DIPEA (3 equiv.), DMF, 1 h. (iii) 20% TFA/dichloromethane. (iv) Ac₂O (6 equiv.), DMAP (1 equiv.), DMF, 3 h. (v) PhCHO (1 equiv.), NaCNBH₃ (0.95 equiv.), 90:5:5 THF:H₂O:AcOH, 3 h. (Note: only the *exo*-cycloadduct is shown in each case. In each case the functionalised cycloadducts were obtained as a 4:1 mixture of *exo:endo* isomers)

products to be accessed from a single precursor. In addition, a variety of carbocyclic frameworks are accessible via Diels–Alder methodologies, enabling large libraries of potentially biologically active amino acids to be generated from a readily accessible, inexpensive molecular scaffold.

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