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The Diels–Alder reactions of polymer bound dehydroalanine derivatives

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Abstract

The synthesis and Diels–Alder cycloadditions of a number of polymer bound dehydroalanine derivatives are described. The studies compare methodologies for accessing polymer bound dehydroalanines and establish the versatility and efficiency of solid phase Diels–Alder reactions in the synthesis of carbocyclic amino acids. These studies nicely complement the growing repertoire of methodologies for the functionalisation of amino acid derivatives.

Keywords: dehydro amino acids; Diels–Alder; solid phase.

In recent years, solid phase synthesis has emerged as an important methodology for the rapid synthesis of organic molecules.[1,2] The ease of work-up and purification procedures in solid phase as compared to solution phase chemistry, as well as the scope for combinatorial synthesis provides impetus for further development in this field. In view of the chemical and biological importance of novel amino acids,[3] development of new methodologies for the efficient functionalisation of amino acids remains a challenge. Recently, the solid phase synthesis of functionalised α-amino acids via reactions of polymer supported *N*-acetyl dehydroalanine were reported.[4,5] The methodologies employ Michael and radical reactions for new carbon–carbon bond formation and the yields of *N*-acetyl functionalised amino acids ranged from moderate to good. Our interests in recent years[6] have exploited dehydroalanines in cycloaddition reactions as a route to the biologically important cycloaliphatic amino acids and peptides.[7,8] In this study, we report the first solid phase synthesis of this class of compounds, thus demonstrating the versatility and efficiency of dehydroalanines in the synthesis of a variety of *N*-protected carbocyclic amino acids. Furthermore, the potential for direct incorporation of these conformationally constrained amino acids into peptides is illustrated.

The attachment of dehydroamino acids was achieved following the procedures shown in Scheme 1. In our initial attempts, the hydroxy functionality of the Wang resin was firstly converted to the chloride and

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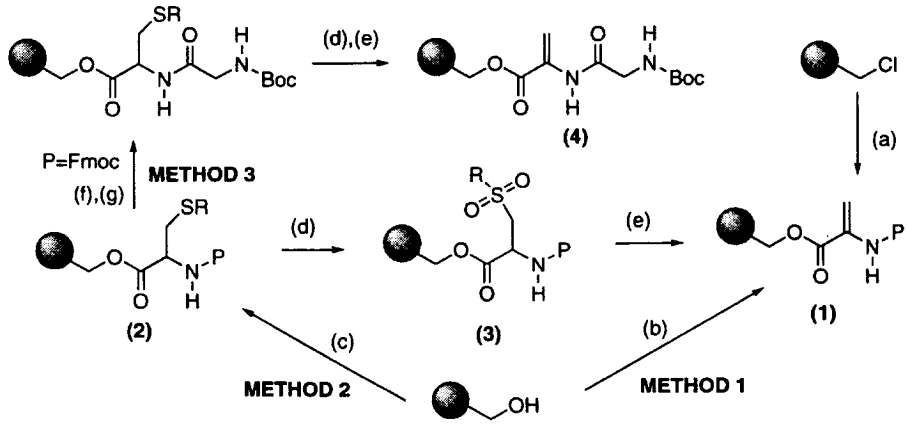
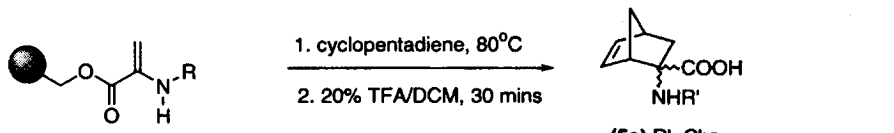
coupling was achieved via treatment of the dehydroamino acid with Cs_2CO_3.[9] The transformation can be readily followed using IR spectroscopy by monitoring the appearance of the ester C=O stretch at ~1740 cm^{-1}. A more direct route can alternatively be employed in which the corresponding dehydroamino acids were coupled to the hydroxyl functionality of the Wang resin under Mitsonobu conditions.[4] Conventional DCC procedures for coupling of amino acids to Wang resin were problematic and similar observations have recently been noted.[4]



Scheme 1. (a) *N*-Protected dehydroalanine (1.5 equiv.), Cs_2CO_3 (3 equiv.), KI (0.5 equiv.), DMF, 16 hours, 80°C; (b) *N*-protected dehydroalanine (5 equiv.), DEAD (5 equiv.), PPh_3 (5 equiv.), THF, rt, 24 hours; (c) *N*-protected-*S*-protected cysteine (1.5 equiv.), DCC (1.6 equiv.), DMAP (1.5 equiv.), 4:1 CH_2Cl_2/DMF, rt, 6 hours; (d) *m*CPBA (2 equiv.), CH_2Cl_2, 0°C, 3 hours; (e) DBU (1 equiv.), CH_2Cl_2, rt, 10 min; (f) 50% piperidine/DMF, 5 min; (g) Boc-glycine (6 equiv.), HBTU (6 equiv.), DIPEA (6 equiv.), DMF, rt, 30 min

The direct synthesis of polymer supported dehydroalanine derivatives were also investigated. Initial studies in which *N*-protected serine derivatives were coupled to the Wang resin gave poor coupling yields. When *N*- and *O*-protected serine derivatives were employed, problems were encountered with the transformation of the latent hydroxyl functionality to the double bond. A more successful approach utilising *N*-protected-*S*-protected cysteine derivatives was subsequently employed. In a typical procedure, Boc-Cys(Acm)-OH was coupled to the Wang resin using DCC and DMAP. Oxidation of the sulfide (**2**) to the sulfone using *m*CPBA was readily monitored by IR spectroscopy where new S=O stretches at ~1115 and ~1326 cm^{-1} appear.[10] Treatment of the polymer bound sulfone (**3**) with DBU for 10 min clearly shows the disappearance of the sulfone stretches and the appearance of a characteristic IR stretch at ~1320 cm^{-1} indicative of dehydroalanine (**1**). Similar protocols were also attempted for the synthesis of polymer supported Fmoc dehydroalanine starting from the commercially available Fmoc *S*-benzyl cysteine. However in this case, elimination of the intermediate sulfone to the dehydroalanine derivative was problematic, despite the variety of conditions attempted, which resulted in the cleavage of the Fmoc protecting group. Despite this, the use of polymer supported Fmoc *S*-benzyl cysteine allows an important extension to the methodologies above. In particular, further chain elongation via peptide coupling can be readily achieved and polymer supported dehydrodipeptides such as (**4**) can be rapidly synthesised (Scheme 1).

With the polymer supported dehydroalanines in hand, cycloadditions were carried out in the presence of cyclopentadiene in toluene at 80°C (Scheme 2). The cycloadducts were cleaved from the resin (20% TFA in DCM, 30 min) and the *exo*/*endo* selectivities of cycloadditions were determined by ^1H NMR spectroscopy as well as HPLC analysis. The selectivities and yields of the cycloadditions are summarised in Table 1.



(5a) R'=Cbz
(5b) R'=Ac
(5c) R'=H, as the TFA salt
(5d) R'=H-Gly, as the TFA salt

Scheme 2.

Table 1

Dehydroalanine derivative	Method	*Exo/endo*[a]	Yields of cycloadducts[b] (5a-d)
(1a) P= Cbz	1	4:1	73%
(1b) P= NAc	1	2:1	67%
(1c) P= Boc	1	4:1	72%
	2	4:1	51%
(4)	3	2:1	81%

[a] *Exo/endo* ratios were determined by careful integration of olefinic resonances in the ^{1}H NMR spectra of the cleaved cycloadducts .

[b] Yields reported are isolated yields and are based on the theoretical loading per gram of resin. All new compounds gave satisfactory analysis.

In the case with *N*-Boc protected cycloadducts, conditions for cleavage from the Wang resin also resulted in the deprotection of the Boc group, leading directly to the bicyclic amino acid derivatives. The *exo/endo* selectivities of the cycloadditions are compared with solution phase studies of the corresponding methyl esters of dehydroalanines. The *exo/endo* selectivities in both solution and solid phase are similar for a particular *N*-protected dehydroalanine.[6,11–13]

Attempts to release the bicyclic amino acids directly as the corresponding esters via nucleophilic cleavage under a variety of conditions failed.[14,15] These results suggest that these sterically hindered cycloadducts do not undergo nucleophilic substitution at the carbonyl group of the C-terminus easily. Despite this, the range of compounds that could be synthesised demonstrates the versatility of solid phase cycloadditions of dehydroalanine derivatives. In view of the importance of dehydroalanine derivatives as precursors in new carbon–carbon bond forming reactions, the current studies clearly outline the scope and limitations of these compounds in solid phase reactions. Further work exploring the synthetic utility of these compounds on solid phase is currently in progress.

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