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Allyloxycarbonyl—a useful protecting group for phenolic amino acids and applications on solid support

Andrew D. Morley*,†

Aventis Pharma Ltd., Rainham Road South, Dagenham, Essex RM10 7XS, UK

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Abstract

Bis-protection of phenolic amino acids can be achieved in a one-pot procedure using allyl chloroformate. Subsequent immobilisation via the free acid onto solid support then permits the carbonate protecting group to be selectively removed under mild conditions.

Keywords: solid-phase synthesis; protecting group; amino acids and derivatives.

The preparation of small organic molecules on solid-phase is now a powerful tool that allows the synthesis and screening of diverse arrays of compounds. Templates possessing multiple functionality that are amenable to derivatisation are useful for generating libraries of this type. Unfortunately, this usually requires multistep reaction sequences, including protecting group strategies in order to obtain products with acceptable purity profiles.

We recently required a series of phenolic amino acids, **1**, to be immobilised on solid support, to generate SAR for a medicinal chemistry programme. It was essential that functionalisation of both the hydroxyl and amino groups could be achieved selectively in order to maximise the diversity of the library. Initial attempts to couple Fmoc-tyrosine to Wang resin, were not encouraging, giving multi-component mixtures, presumably due to the presence of the free hydroxyl group of the phenol. Protection was therefore deemed necessary. Although orthogonally protected analogues of **1** are known in the literature, their large-scale synthesis is tedious and can require chromatographic purification.[1,2]

A strategy to overcome these problems is shown in Scheme 1. By employing the same group to protect both the hydroxyl and amino moieties, a template such as **2** would be available from **1** in a single step. Attachment to the solid support, via the free acid, should then be straightforward, using conventional methodology.[3] The differences in reactivity between the two protecting groups would then allow selective mono-deprotection, generating phenol **3**. Functionalisation of the

* Corresponding author.

† Present address: AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK. Tel: +44(0)1625 582828; fax: +44(0)1625 516667; e-mail: andymorley@astrazeneca.com

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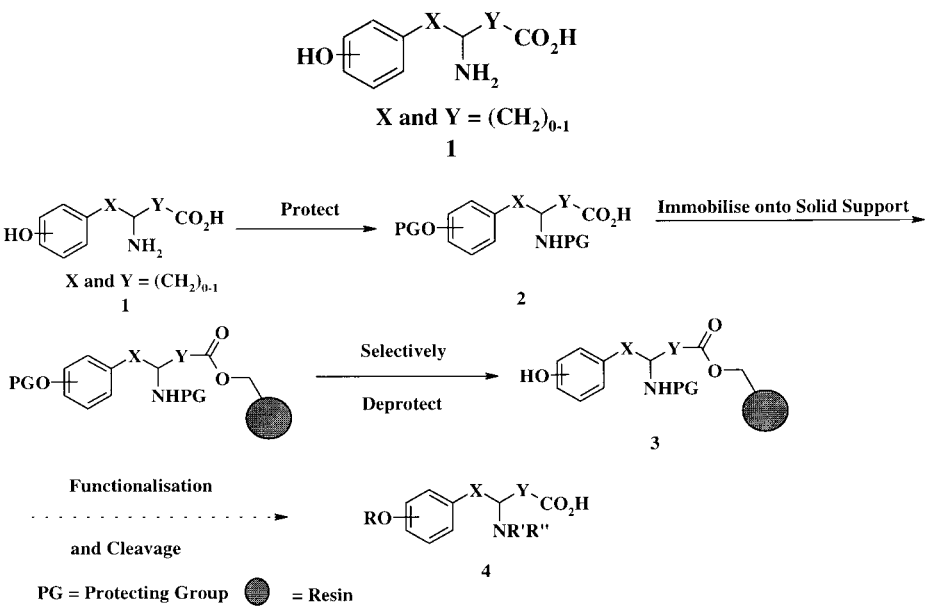


Scheme 1.

phenol, deprotection of the carbamate, derivatisation of the resulting amine and finally cleavage from the resin would provide the requisite products **4**.

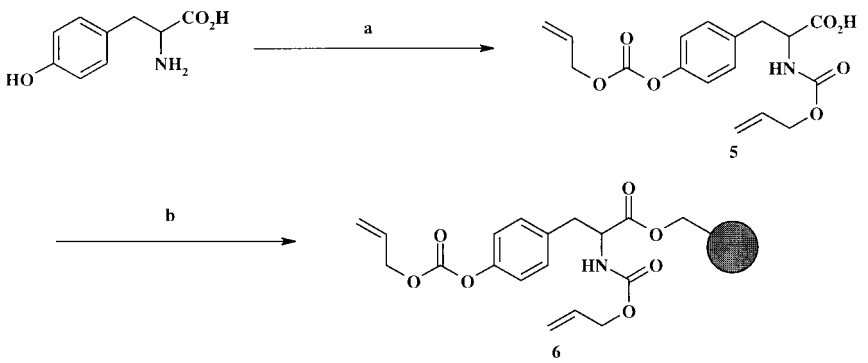
The allyloxycarbonyl group was chosen as the dual protecting group. Allyl chloroformate is cheap and readily available, enabling conversion of the amino and hydroxyl functions to the allylcarbamate and carbonate, respectively. Differential deprotection of these two groups should be possible, as literature precedent exists for the cleavage of phenylcarbonates under conditions that allylcarbamates are inert to.[4,5] The carbamate could then be deprotected later in the synthetic sequence with catalytic $Pd(PPh_3)_4$ (standard deprotection conditions for this group, which is compatible with solid-phase synthesis).[6,7]

N,*O*-Bis-alloctyrosine, **5**, and related analogues were prepared following the methodology of Stevens.[8] Several conditions were initially evaluated to immobilise the acid on Wang (*p*-benzyloxybenzyl alcohol) resin (Polymer Labs.–1.7 mmol/g). Optimal conditions required 3 equiv. each of **5** and diisopropylcarbodiimide (DIC) plus 0.1 equiv. of dimethylaminopyridine (DMAP) in DMF (Scheme 2). This reaction can routinely be carried out on a 30 g scale of resin. Compound **5** can also be immobilised onto 2-chlorotrityl chloride resin (Advanced Chemtech.–2.1 mmol/g) using CsI and diisopropylethylamine (DIPEA) in DMF.

The infra red spectrum of **6** showed carbonyl stretches at 1724 cm^{-1} (broad) for the ester and carbamate and at 1750 cm^{-1} for the phenylcarbonate. Weighed samples were cleaved and quantified in one of two ways:

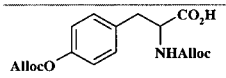
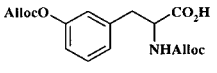
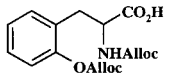
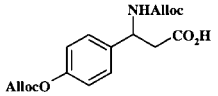
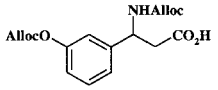
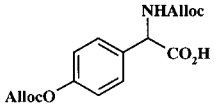
(i) LC/MS employing evaporative light scattering (ELS) detection using **5** as a standard;
(ii) ^1H NMR using bis-*p*-tolylsulphone as an integration standard.

By these methods loadings of 0.8–1.1 mmol/g (66–90% theoretical) were obtained with purity $>95\%$. Similar results were also obtained using weight analysis for loading determinations. Five additional templates were also synthesised and loaded onto Wang resin using the protocol described above. Results are shown in Table 1.



Scheme 2. Conditions: (a) 3 equiv. 4 M NaOH, 2 equiv. allylchloroformate; (b) 0.33 equiv. Wang resin, 1 equiv. DIC, 0.033 equiv. DMAP, DMF or 1 equiv. 2-chlorotrityl chloride resin, 1 equiv. CsI, 1.5 equiv. DIPEA, DMF

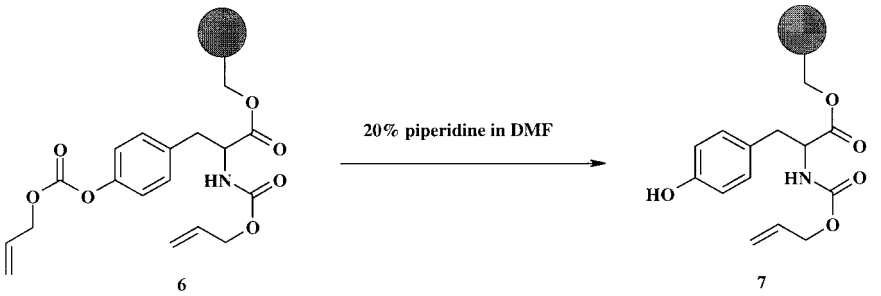
Table 1
Yields and loading of phenolic amino acids to Wang resin

Structure	Yield[a]	Loading[bc]
	91%	0.9mmol/g
	98%	0.81mmol/g
	88%	1.06mmol/g
	85%	1.07mmol/g
	93%	0.96mmol/g
	87%	1.15mmol/g

[a]Yield for preparation of *N,O*-bis-alloc derivative.
[B]Employing Wang resin (Polymer Labs, 1.7mmol/g)
[c] Determined by LC/MS employing evaporative light scattering (ELS) detection and using **6** as an internal standard or ^{1}H nmr using bis-*p*-tolylsulphone as an integration standard.

Attention then focused on the selective removal of one of the alloc groups. It was hoped that cleavage of the phenylcarbonate group could be achieved under nucleophilic conditions. However, as the attachment point to the resin is an ester, careful choice of reaction conditions would be necessary so as to avoid detachment of the template from the solid support. A solution of 20% piperidine in DMF is frequently used in solid-phase chemistry for the removal of the fluorenyloxycarbonyl (Fmoc) protecting group. These are mild conditions to which a number of functional groups, including esters and allylcarbamates, are stable. Treatment of tyrosine resin **6** under these conditions for 24 hours resulted in complete removal of one of the protecting groups (as determined by ^{1}H NMR and mass spectroscopy of a cleaved resin sample) The reaction

occurred in 90% yield, with >98% purity. The infra red spectrum showed the disappearance of the carbonyl stretch at 1750 cm^{-1} and the NMR spectrum showed an upfield shift of the aromatic doublet from δ 7.3 to 6.7. These indicated that the carbonate had been removed to form **7** (Scheme 3). This was confirmed by detailed NMR studies using hetero multiple bond coherence (HMBC), showing cross correlation's from the *N*-alpha methine proton to the carbamate carbonyl. Time course studies showed the reaction to be complete after 90 min. Prolonged treatment did not effect purity or resin loading.



Scheme 3.

In conclusion, phenolic amino acids can be suitably protected and loaded on to resins as esters. Selective removal of the phenolic protecting group can be achieved to leave intermediates that are suitable for constructing diverse libraries. Examples of such libraries are described in the following paper.[9]

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