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Optimisation and synthesis of libraries derived from phenolic amino acid scaffolds

Andrew D. Morley*,†

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

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Abstract

Functionalisation of a series of resin bound phenolic amino acids is described, employing Irori technology to produce multidimensional libraries.

Keywords: solid-phase synthesis; Mitsunobu reactions; acylation; reductive amination.

In the accompanying paper, the facile protection and loading of a series of phenolic amino acids onto resin was described.[1] In this communication, the subsequent functionalisation of these resin bound intermediates is presented, enabling the preparation of diverse multifunctional libraries.

Having successfully developed a facile synthetic route to **1** (and related analogues) in multigramme quantities (Scheme 1), the subsequent functionalisation of the phenolic group and the revealing and derivatisation of the amino function was investigated. In order to incorporate maximum diversity into the libraries, reactions that would tolerate a variety of substituents were reviewed. The proposed sequence for the construction of the library is outlined in Scheme 2 (tyrosine resin shown for example).

The Mitsunobu reaction was chosen to prepare a series of diverse ethers from the phenolic group, as it fulfilled the above criteria. The reaction is well-documented in the literature for the preparation of ethers on solid-phase and occurs under mild conditions. The allyloxycarbonyl group, as mentioned previously, had been chosen as the protecting group, since it can easily be removed to reveal the primary amine under mild conditions to which the majority of functional groups are inert.[2,3] Alkylation of the resulting amine could then be achieved by reductive amination and finally primary or secondary amines capped as amides or sulphonamides.

In order to maximise the utility of this multidimensional approach, all the subsequent work was undertaken employing Irori technology.[4] Trainer sets, were carried out using MicroKans™

* 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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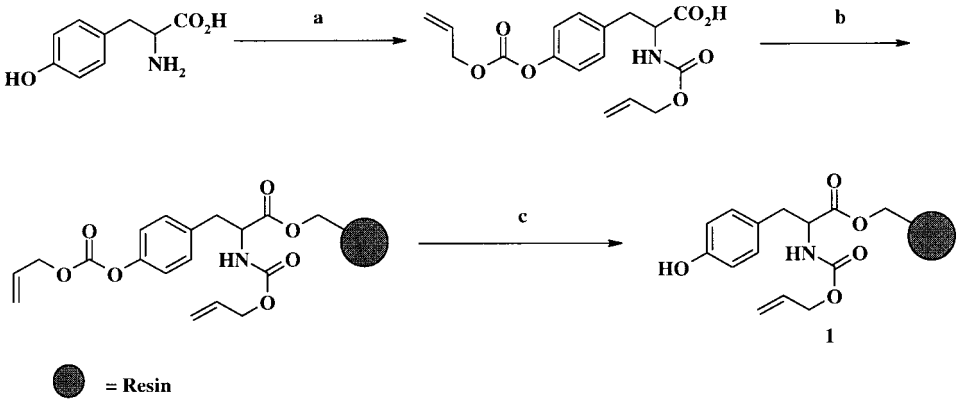
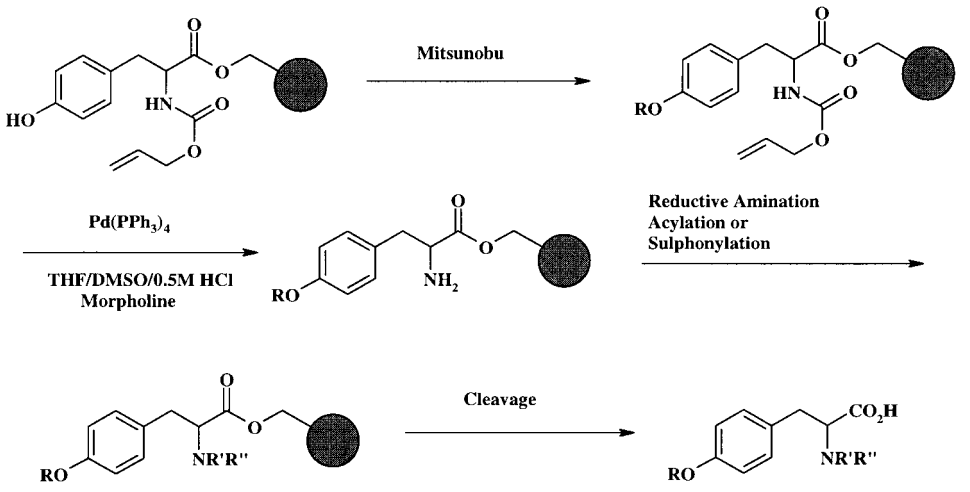


Scheme 1. *Conditions*: (a) 3 equiv. 4 M NaOH, 2 equiv. allylchloroformate; (b) 0.33 equiv. Wang resin, 1 equiv. DIC, 0.033 equiv. DMAP, DMF; (c) 20% piperidine in DMF



Scheme 2.

to mimic the conditions that would be required for library synthesis. The optimum conditions for each step were as follows:

Mitsunobu reaction: Alcohol, PPh_3 and diethyl diazodicarboxylate (20 equiv. each) in a 1:1 mixture of DCM:THF (0.2 M solution) room temperature for 24 h.

In order to achieve consistently high yields and ensure complete reaction across a range of substrates, 20 equiv. of ylid (PPh_3/DEAD complex) and alcohol were required. No effort was made to optimise these quantities by manipulation of the temperature or concentration at which the reaction was carried out.

Alloc deprotection: Pd $(PPh_3)_4$ (0.1 equiv.), THF:DMSO:0.5 M HCl:morpholine (20:20:10:1 ratio) room temperature for 24 h.

The deprotection of the allylcarbamate was achieved using a variation of a literature protocol[2] and worked well with all substrates. It was found essential to wash the resin with 0.1 M solution of dimethyldithiocarbamic acid in addition to standard washing protocols in order to remove all

traces of catalyst from the resin. If this step was not carried out the purity of final products was compromised.

Reductive amination: Aldehyde (15 equiv.), dichloromethane:trimethylorthoformate (1:1) at room temperature for 24 h. Drain. $NaCNBH_3$ (10 equiv.) in trimethylorthoformate, plus 1% of either AcOH or MeOH (depending on the nature of the aldehyde) at room temperature for 24 h.

A two-step procedure gave the most reproducible results for this reaction. Treatment of the resin with 15 equiv. of aldehyde in a 1:1 mixture of dichloromethane:trimethylorthoformate gave the intermediary imine.[5] Excess reagents were then drained and the resin was then treated with a 0.06 M solution of sodium cyanoborohydride in trimethyl orthoformate containing 1% acetic acid for aromatic and 1% methanol for aliphatic aldehydes[6] and stirred at room temperature for 24 h.

Acylation (with acid chlorides): Acid chloride (3 equiv.), diisopropylethylamine (DIPEA) (4 equiv.) in DCM at room temperature for 24 h.

Acylations (with acids): Acid (3 equiv.), HATU[7] (3 equiv.), DIPEA (12 equiv.) in DMF at room temperature for 24 h.

Acylation (with anhydrides): Anhydride (3 equiv.), DIPEA (4 equiv.) in DCM at room temperature for 24 h.

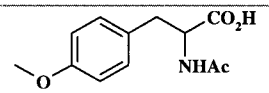
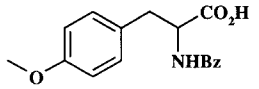
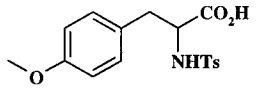
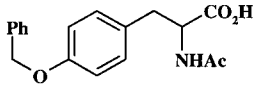
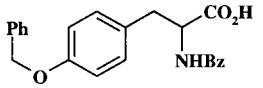
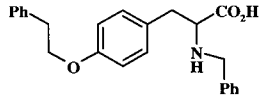
Sulphonylations: Sulphonyl chloride (3 equiv.), DIPEA (4 equiv.) in DCM at room temperature for 24 h.

Acylations/sulphonylations all worked well using standard literature procedures.

Deprotection: TFA:DCM (3:7) at room temperature for 1 h.

Data for selected examples are given below in Table 1. Yields are generally excellent as determined by either AUC comparisons (ELSD—evaporative light scattering detection) from HPLC analysis

Table 1
Yields and purity of representative compounds

Structure	Yield(%)[a]	Purity[b]
	86 (102)	>98%
	88 (110)	>98%
	83 (87)	>98%
	87 (97)	>98%
	96 (106)	>98%
	85 (107)	>98%

[a] yield determined by AUC comparisons (ELS detection) of samples with standard (20mM solution of *N*-acetyltyrosine). Values in parentheses are for yields determined by weight.
[b] determined by LC/MS employing ELS detection

against a standard (20 mM solution of *N*-acetyltyrosine) or by weight determination. The products were of sufficient purity (HPLC analysis) to make purification unnecessary.

Employing this methodology a library of 1932 members was constructed (4×23×21 matrix), using only 45 reactions, highlighting the utility of the Irori technology for the synthesis of libraries of this type.

In conclusion, functionalisation of a variety of phenolic amino acids has been optimised, enabling diverse multidimensional libraries to be accessed. Biological activity and subsequent work based on these templates will be published elsewhere.

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