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Wang-aldehyde resin as a recyclable support for the synthesis of α,α-disubstituted amino acid derivatives

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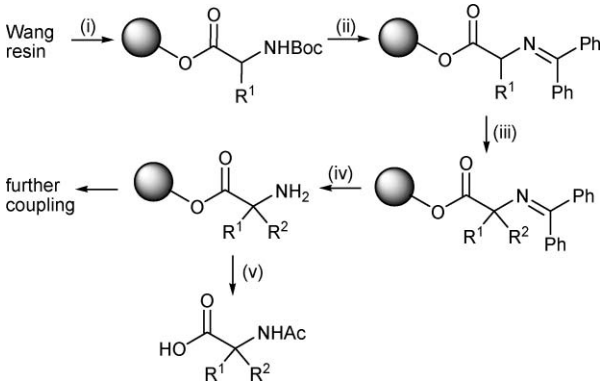
Merrifield resin was functionalised with hydroxybenzaldehyde under microwave irradiation. The resultant resin was used as a means for immobilisation and activation of α-amino acid esters for alkylation reactions. α,α-Disubstituted and cyclic amino acid esters were prepared in good yields.

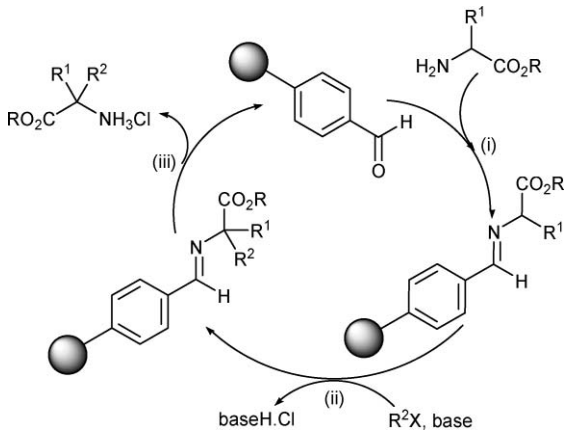
Introduction

Schiff base esters are widely employed as precursors in the synthesis of unnatural α,α-disubstituted amino acids.[1] Transposition of these reactions on to the solid-phase has since been achieved, notably by O'Donnell, who developed a methodology for unnatural peptide synthesis (UPS) using polymer supports (Scheme 1).[2,3] In these reactions, *N*-Boc protected amino acids are tethered onto the support *via* the *C*-terminus (ester linkage). Hence, removal of the *N*-protecting group and activation of the α-carbon by the formation of a benzophenone imine is necessary prior to reaction. Following α-alkylation, removal of the activating group and cleavage of the product from the support required two separate steps.



Scheme 1 O'Donnell's tandem UPS methodology: (i) immobilisation; (ii) deprotect and activate; (iii) alkylation; (iv) hydrolysis; (v) *N*-acylation and cleavage.

Wang-aldehyde resin has been widely used as an efficient scavenger for primary amines through the formation of aldimine (CH=N) bonds.[4] We envisaged that such a linkage may also be used to temporarily immobilise and activate amino acid residues, such that α-alkylation may be achieved. Product cleavage can be accomplished by acid hydrolysis, to regenerate the functionalised resin (Scheme 2). Recently, Park *et al.* have reported the use of Wang-aldehyde polymer resin to support glycineimine *tert*-butyl ester, for the synthesis of racemic and optically active α-amino acids by monoalkylation of the supported glycine derivative.[5,6] In light of these reports, we wish to disclose our work on the synthesis of (±)-α,α-disubstituted amino acid residues using this methodology. The regeneration and reuse of the polymer resin will also be demonstrated.



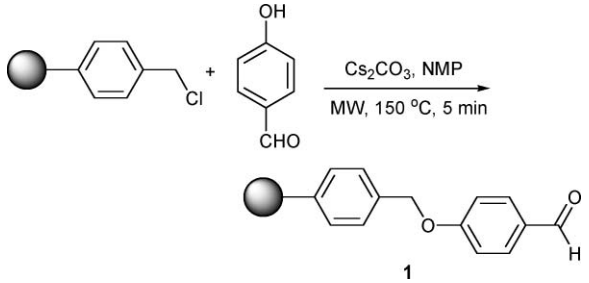
Scheme 2 Proposed route for the synthesis of α,α-disubstituted amino acid esters: (i) imine formation (activation/immobilisation); (ii) alkylation; (iii) acid hydrolysis/regeneration of resin.

Result and discussion

Functionalisation of polymer resins[7]

The required functionalised polymer was prepared by treating HL Merrifield resin (1.3 mmol g^{-1}, 100–200 mesh, 1% cross-link) with 4-hydroxybenzaldehyde and K_2CO_3 in the presence of KI at 80 °C. The substitution was slow under thermal conditions—two treatments (lasting three days each) were required to achieve total displacement of the Cl from the resin (%Cl analysis).

To speed up this transformation, a mixture of the Merrifield resin, 4-hydroxybenzaldehyde, Cs_2CO_3 and NMP was subjected to microwave-irradiation. Employing a temperature of 150 °C, total Cl displacement can be reduced to just 5 minutes (Scheme 3).



Scheme 3 Preparation of benzaldehyde-functionalised resin **1** by MW irradiation.

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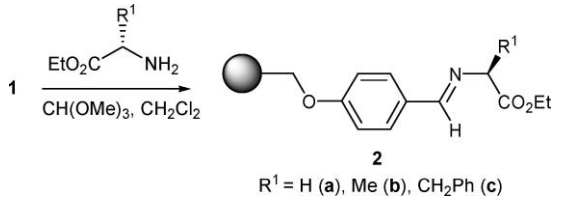
Resins prepared by either methods are identical in their physical and chemical properties, and have similar loadings of *ca.* 1.10 mmol g^{-1}, corresponding to 95% yield. They are characterised by on-bead techniques—aldehyde absorption bands were observed in the transmittance FTIR spectrum (2734, 1685 cm^{-1}), further verified by the characteristic aldehydric resonance at 9.8 ppm in the ^1H MAS-NMR spectrum.

Immobilisation/activation of amino acid esters

Glycine, alanine and phenylalanine ethyl esters were immobilised and activated in one synthetic step, by treating **1** with an excess of the corresponding amino acid ester in the presence of trimethyl orthoformate (Scheme 4). The progress of the reaction was monitored on-bead using transmittance FTIR spectroscopy, by observing the disappearance of the aldehyde (1685 cm^{-1}) and concurrent emergence of the imine and ester (1640 and 1740 cm^{-1}) absorption bands. The ^1H MAS-NMR spectrum of the final product resin showed a distinctive imine CH=N resonance at 8.3 ppm. The amount of the immobilised amino acid on the beads was calculated from %N analysis, verified by the amount of amino acid recovered from the beads upon acid hydrolysis. The reaction is dependent on the steric nature of the substituent on the amino acid. Whilst the immobilisation of alanine and phenylalanine were achieved at 50 °C in three days,



Scheme 4 Immobilisation of amino acid esters: R = H (**2a**), rt, 5 days, 91% (0.96 mmol g^{-1}); R = Me (**2b**), 50 °C, 3 days, 89% (0.93 mmol g^{-1}); R = CH_2Ph (**2c**), 50 °C, 3 days, 77% (0.75 mmol g^{-1}).

the reaction was unsuitable for the attachment of glycine—the product resin showed an unusually high %N content, accompanied by the observation of an unexpected IR (amide) absorption peak at 1689 cm^{-1}, corresponding to the formation of polymerised products. This competitive reaction may be eliminated by conducting the reaction at room temperature in an orbital shaker. Using these procedures, immobilisation of glycine and alanine proceeded with good to excellent yields, while phenylalanine gave a lower yield of 77%.

Attempts to employ microwave irradiation for the immobilisation of the amino acids were unsuccessful. Treatment of a mixture of **1** with phenylalanine and trimethyl orthoformate gave either very low yield (CH_2Cl_2, 140 °C, 30 minutes, 40%), or led to uncontrollable polymerisation (NMP, 200 °C, 30 minutes).

Synthesis of α,α-disubstituted amino acid esters

The alkylation of supported glycine **2a** was examined initially, using benzyl bromide as the electrophile in the presence of different bases (Table 1, entries 1–5). Neutral phosphazene bases such as BEMP and BTPP, previously employed in the UPS methodology,[2] were assessed along with weak bases (K_2CO_3, NEt_3, pyridine) and strong, non-nucleophilic bases (LDA and LHMDS). After a suitable period of time (14 h), the resin was filtered off and washed repeatedly with several organic solvents and water. Finally, by treating the resin with 2 M aq. HCl (5 h), the product was collected in the aqueous phase and isolated as their HCl salts. These were subsequently analysed by ^1H NMR spectroscopy and mass spectrometry.

Unsurprisingly, weak bases were found to be totally ineffective for the alkylation (entries 1–3)—only starting material was recovered. In contrast, reactions employing phosphazene reagents gave a mixture of mono- and di-alkylated products. Interestingly, different product distributions were observed—BTPP, the more basic and slightly less sterically bulky, gave dialkylated amino acid as the major product, whereas the opposite was observed with BEMP (entries 4 and 5).

Table 1 Alkylation of **2a, 2b** and **2c** employing different bases[a]

Entry	R^1 (resin)	Base[b]	R^2X	Product	Yield (%)[c]
1	H (**2a**)	Pyridine (5)	$PhCH_2Br$ (5)	**3a**	—
2		NEt_3 (5)	$PhCH_2Br$ (5)	**3a**	—
3		K_2CO_3 (5)	$PhCH_2Br$ (5)	**3a**	—
4		BEMP (5)	$PhCH_2Br$ (5)	**3a**	75 (25)[d]
5		BTPP (5)	$PhCH_2Br$ (5)	**3a**	10 (90)[d]
6	Me (**2b**)	LDA[e](5)	$CH_2=CHCH_2Br$ (5)	**3b**	—
7		LHMDS[e] (5)	$CH_2=CHCH_2Br$ (5)	**3b**	90
10		BEMP (5)	$CH_2=CHCH_2Br$ (5)	**3b**	25
11			$PhCH_2Br$ (5)	**3c**	50
12		BTPP (5)	$CH_2=CHCH_2Br$ (5)	**3b**	90
13			$PhCH_2Br$ (5)	**3c**	90
14	$PhCH_2$ (**2c**)	LDA[e] (5)	$PhCH_2Br$ (5)	**3d**	20
15		LHMDS[e] (5)	$PhCH_2Br$ (5)	**3d**	75
18		BEMP (5)	$CH_2=CHCH_2Br$ (5)	**3e**	15
19			$PhCH_2Br$ (5)	**3d**	25
20		BTPP (5)	$CH_2=CHCH_2Br$ (5)	**3e**	85
21			$PhCH_2Br$ (5)	**3d**	90
22	Me (**2b**)	BTPP (2)	$CH_2=CHCH_2Br$ (2)	**3b**	90
23		BTPP (5)	$CH_2=CHCH_2Br$ (5)	**3b**	90
24		BTPP (10)	$CH_2=CHCH_2Br$ (10)	**3b**	90
25	$PhCH_2$ (**2c**)	BTPP (2)	$CH_2=CHCH_2Br$ (2)	**3e**	70
26		BTPP (5)	$CH_2=CHCH_2Br$ (5)	**3e**	85
27		BTPP (10)	$CH_2=CHCH_2Br$ (10)	**3e**	90
28		BTPP (2)	$PhCH_2Br$ (2)	**3d**	70
29		BTPP (5)	$PhCH_2Br$ (5)	**3d**	90
30		BTPP (10)	$PhCH_2Br$ (10)	**3d**	85

[a] Typical reaction conditions: The resin, base and electrophile were allowed to react in anhydrous NMP, at room temperature for 14 h. Equivalents of reagents given in parentheses. LDA = lithium diisopropylamide, LHMDS = lithium hexamethyldisilazane, BEMP = 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine, BTPP = *tert*-butylimino-tri(pyrrolidino)phosphorane. [b] H NMR integration of product mixture obtained after hydrolysis. [c] Value in parentheses corresponds to yield of dialkylated product **3c**. [d] Reaction was performed in anhydrous THF at −78 °C, then warmed to room temperature and stirred for 14 h.

Table 2 Synthesis of α,α-disubstituted amino acid esters (Scheme 2)[a]

Entry	R^1 (resin)	R^2X	Product	Additive (equiv.)	Yield (%)[b]
1	Me (**2b**)	CH_2=$CHCH_2Br$	**3b**	—	90 (100)
2					80[c]
3		CH_2=$CHCH_2Cl$	**3b**	—	30
4				TBAI (5)	85
5		$PhCH_2Br$	**3c**	—	90 (100)
6					90[c]
7		$PhCH_2Cl$	**3c**	—	45
8				TBAI (5)	80
9		MeI	—	—	—(100)
10		*n*-$C_6H_{13}I$	**3f**	—	95 (97[d])
11					90[c]
12		$naphthCH_2Cl$	**3g**	TBAI (5)	90 (98)
13		CH_2=$CHCH_2CH_2Br$	—	—	—(5)
14		*tert*-C_4H_9Br	—	—	—
15	$PhCH_2$(**2c**)	CH_2=$CHCH_2Br$	**3e**	—	85 (96)
16					85[e]
17		CH_2=$CHCH_2Cl$	**3e**	—	50
18				TBAI (5)	90
19		$PhCH_2Br$	**3d**	—	90 (100)
20					90[e]
21		$PhCH_2Cl$	**3d**	—	55
22				TBAI (5)	90
23		MeI	**3c**	—	5 (98)
24		*n*-$C_6H_{13}I$	**3h**	—	95 (75[d])
25					95[e]
26		$naphthCH_2Cl$	**3i**	TBAI (5)	95 (99)
27		CH_2=$CHCH_2CH_2Br$	—	—	—(2)
28		*tert*-C_4H_9Br	—	—	—
29	H (**2a**)	CH_2=$CHCH_2Br$	**3j**	—	20 [80][e]
30		CH_2=$CHCH_2Cl$	**3j**	TBAI (5)	15 [85]
31		$PhCH_2Br$	**3a**	—	10 [90]
32		$PhCH_2Cl$	**3a**	—	35 [55][f]
33				TBAI (5)	5 [95]

[a] Typical reaction conditions: the resin was reacted with 5 equiv. of BTPP and 5 equiv. of electrophile in anhydrous NMP, at room temperature for 14 h. TBAI = tetra-*n*-butyl ammonium iodide, equivalents given in parentheses. [b] ^1H integration of product mixture obtained after hydrolysis. Value in parentheses (x) refers to that reported by using the UPS methodology.[8] Value in square brackets [x] refers to yield of the dialkylated product. [c] Yield obtained with recovered resin. [d] Value obtained with *n*-octyl iodide. [e] Diallylated product = **3k**. [f] 10% glycine ester recovered.

Alkylation of **2b** and **2c** gives amino acid derivatives with a quaternary α-carbon centre. For this part of the study, allyl bromide was also used as an electrophile. LHMDS is better than LDA for the reaction (entries 6, 7, 14 and 15), but the deprotonation has to be performed at low temperatures. In contrast, the phosphazene bases may be employed at room temperature. This is more practical as this enables the deployment of parallel synthesiser (Argonaut QUEST 210) for the latter part of our investigations. Again, the structure of the phosphazene base was observed to have a dramatic effect. The use of BTPP gave cleaner and higher yield of products (entries 10–13, 18–19).

For the alkylation of **2b** containing the less sterically demanding alanine, the amount of reagents may be reduced to 2 equivalents (entries 22–24), but at least 5 equivalents of each reagent were required for the alkylation of **2c**, whilst the use of 10 equivalents did not lead to any noticeable improvement (entries 25–30).

The optimal reaction conditions established were subsequently adopted to prepare a number of α,α-dialkylated amino acid derivatives from alanine and phenylalanine (Table 2). In general, yields comparable to those obtained using the UPS methodology were achieved (entries 1, 5, 9, 10, 12, 15, 19, 24 and 26).

The nature of the electrophile is important in the alkylation step. Activated benzyl and allyl bromides afforded good yields of products (entries 1, 5, 15 and 19), whereas the corresponding chlorides gave much lower yield of the same products without the assistance of iodide (entries 3 *vs.* 4, 7 *vs.* 8, 17 *vs.* 18, and 19 *vs.* 20). Methyl iodide gave very little or no product (entries 9 and 23), which is in contrast to the good yields obtained with *n*-hexyl iodide (entries 10 and 24). We attribute this to the volatility of the methyl iodide (bp 41–3 °C), which is clearly not compatible with deployment of the parallel reaction synthesiser (Argonaut Quest 210). As was observed earlier in the UPS method, the reaction of 1-bromobut-3-ene gave little or no products (entries 13 and 27). This could be due to the slow rate of alkylation, which allowed base-induced elimination of the electrophile (to butadiene) to become competitive under these conditions.

The reaction is also clearly sensitive to steric and electronic effects-*tert*-butyl bromide is unreactive (entries 14 and 28), whereas 1-naphthylmethyl chloride–TBAI gave a good yield of products (entries 12 and 26).

As was observed before, the alkylation of immobilised glycine derivative **2a** is susceptible to competitive formation of dialkylated products. Attempts to alkylate glycine led to the formation of dialkylated products in all our attempts (entries 29–33). On the other hand, employment of reduced amounts of base and/or electrophile, mixtures of products and starting material were obtained.

Regeneration and recycling

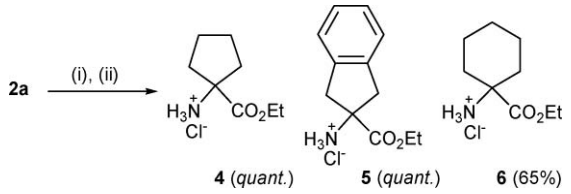
One of the major impetuses for the development of the current strategy is the potential recovery of **1** for subsequent reuse. Following acid-cleavage of the product, the resins were washed repeatedly with organic solvents. Transmittance FTIR and ^1H NMR spectra of the recovered polymer beads showed the restoration of the aldehyde functional group, with a loading similar to the original value.

The recovered beads were subsequently used to immobilise/activate amino acid esters for further alkylation reactions.

In all cases, the product yields obtained with the recovered beads were similar, if not identical, to the results obtained with freshly prepared beads (Table 2, entries 1/2, 5/6, 10/11, 15/16, 19/20 and 24/25). The products obtained were of high purity—no cross-contamination was detectable (by ^{1}H and MS) when the recovered beads were used in the support of a different amino acid ester and/or reacted with a different electrophile.

Synthesis of cyclic amino esters

Given the propensity of the glycine residue to form dialkylated products under these reaction conditions, we investigated the use of **2a** for the synthesis of cyclic amino esters by the reaction with dielectrophiles. Reactions of **2a** with 1,4-dibromobutane, 1,5-dibromopentane and α,α′-dibromo-*o*-xylene furnished the required amino acid esters **4, 5** and **6** respectively (Scheme 5). The formation of the 1-aminopentanecarboxylate ring **4** was the most facile, the reaction was completed by a single treatment with the base and dielectrophile (absence of %Br in the resin). The corresponding reactions with 1,5-dibromopentane and 1,2-dibromomethylbenzene were slower. In these cases, a second treatment with the base were needed for the complete displacement of Br.



Scheme 5 Synthesis of cyclic amino acid derivatives: (i) dielectrophile, BTPP, rt; (ii) 2 M aq. HCl.

Following acid hydrolysis, the cyclic amino acid residues **4** and **5** were obtained in quantitative yields, whereas the yield of the cyclohexyl derivative **6** was lower.

In summary, we demonstrate that a number of unnatural α,α-disubstituted amino acid derivatives can be synthesised using the Wang aldehyde resin **1** as a solid support, with good to excellent yields. The current methodology reduces immobilisation/activation and deprotection/recovery into single-steps. Additionally, resin **1** is reusable, hence the overall atom and economic efficiency of the process can be improved significantly. New ways of improving and extending the synthetic scope of the methodology, either through the modification of polymer support and/or reaction conditions are currently under investigation.

Experimental

Merrifield resin HL (1.3 mmol g^{-1}, 1% cross-linked, 100–200 mesh) was purchased from Novabiochem. Anhydrous DMF, trimethyl orthoformate and NMP were bought from Aldrich (in Sure Seal bottles) and dichloromethane was freshly distilled from calcium hydride under nitrogen. Commercially available chemicals were purchased from Aldrich, Avocado, Fluka or Lancaster, and were used as received, unless otherwise stated.

Microwave reactions were conducted using a CEM Discover Synthesis Unit. Reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. The semi-automated synthesiser used is a Quest 210 purchased from Argonaut Technologies and contains twenty reactors with an internal volume of 5 mL. It is combined with an automated solvent wash unit, which is usually programmed as follows: acetone–CH_3OH–H_2O (1 : 1 : 1) (5 mL × 5), acetone–CH_3OH (1 : 1) (5 mL × 5), acetone (5 mL × 5), ethyl acetate (5 mL × 5), CH_2Cl_2 (3 mL × 5) and HPLC-grade pentane (5 mL × 5).

Elemental analysis was carried out by the Elemental Analysis Services at the University of North London (CHN) or University College London (halides). Mass spectra (MS) were recorded using the Mass Spectrometry Service within the Department of Chemistry (Imperial College). CI-MS were run in a Micromass Platform II. This instrument is a single quadrupole, and is used to provide the nominal mass EI and CI service for masses up to 800 Da. Infra-red spectra and single bead FT-IR spectra (transmittance) were recorded on a Perkin Elmer Spectrum One spectrometer with a beam-condensing accessory (BCA), using a diamond compressor to flatten the bead.

^{1}H and ^{13}C NMR spectra were recorded using JEOL 270, Bruker AM 360 and AVANCE 400 spectrometers. High resolution magic angle spinning (HR-MAS) NMR spectra were recorded using a Bruker AVANCE 400 spectrometer with special HR-MAS probe and the resin was placed in a 4 mm rotor. Chemical shifts were recorded in parts per million (δ: ppm) referenced to TMS (δ:0) as an internal standard. Coupling constants (J) are given in Hertz (Hz). The following abbreviations are used to describe multiplicity: br—broad, s—singlet, d—doublet, t—triplet, q—quartet, m—multiplet, dd—double doublet.

Synthesis of Wang-aldehyde resin 1 by thermal heating

4-Hydroxybenzaldehyde (1.5 equiv.), K_2CO_3 (5 equiv.) and KI (2 equiv.) were placed in an oven-dried three-neck round bottom flask equipped with an overhead stirrer and a condenser and purged with N_2, containing Merrifield resin HL resin (1 equiv., 1.3 mmol g^{-1}). Anhydrous DMF (200 mL) was added *via* syringe and the mixture was stirred (60 rpm) and heated at 80 °C for 3 days. After cooling to room temperature, the beads were transferred to a sintered tube and washed successively with acetone–CH_3OH–H_2O (1 : 1 : 1) (5 mL × 5), acetone–CH_3OH (1 : 1) (5 mL × 5), acetone (5 mL × 5), ethyl acetate (5 mL × 5), CH_2Cl_2 (3 mL × 5) and HPLC-grade pentane (5 mL × 5). A second treatment for 3 more days was carried out to bring the reaction to completion. After cooling to room temperature, the beads were transferred to a sintered tube and washed as before, then dried under vacuum at 50 °C for 2 hours to give pale yellow–white beads. After two treatments, %Cl = 0% (100% Cl displacement). Theoretical loading = 1.1 mmol g^{-1}. ν_{max}/cm^{-1} 2734 (O=C-H), 1685 (C=O); δ_H (400 MHz, $CDCl_3$) 9.82 (1H, s, CHO), 7.76 (2H, br s, H-Ar), 7.00 (br s, PS), 6.55 (br s, PS), 4.91 (2H, br s, OCH_2), 1.60 (br s, PS), 1.35 (br s, PS).

Synthesis of Wang-aldehyde resin 1 using microwave irradiation

Merrifield resin HL (100 mg, 1.3 mmol g^{-1}, 0.13 mmol) was placed in a reaction vessel and allowed to swell in dry NMP (0.5 mL) under N_2. 4-Hydroxybenzaldehyde (24 mg, 0.195 mmol) and Cs_2CO_3 (85 mg, 0.26 mmol) were dissolved in dry NMP (2.5 mL) and added *via* syringe to the reaction vessel. The mixture was stirred and heated in the microwave at 150 °C for 5 minutes. After cooling to room temperature, the beads were transferred to a sintered tube and washed as above. %Cl = 0% (100% Cl displacement).

General procedure for the immobilisation of amino acid esters

Alanine or phenylalanine ethyl ester hydrochloride (10 equiv.) were respectively dissolved in water (10 mL). 2 M aqueous NaOH was added until pH between 9 and 10 was obtained. The solution was extracted with DCM (3 × 10 mL). The organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give an oil. Wang-aldehyde resin **1** (1 equiv.) was placed in an oven-dried three-neck round bottom flask purged with N_2 and equipped with an overhead stirrer and a condenser. Anhydrous dichloromethane (20 mL), anhydrous trimethyl orthoformate (20 mL) and the alanine or phenylalanine ethyl ester were added and the flask was stirred (60 rpm) at 50 °C for 3 days. After cooling to room temperature, the beads were transferred to a sintered tube and washed as above. The beads were dried under vacuum at 50 °C for 2 hours to give pale yellow beads.

Wang alanine ethyl ester resins, 2b. 89% of attachment to the resin, based on %N analysis of 1.3%. Loading = 0.93 mmol g^{-1}. ν_{max}/cm^{-1} 1740 (C=O), 1640 (C=N); δ_H (400 MHz, $CDCl_3$) 8.27 (1H, s, CH=N), 7.76 (2H, br s, H-Ar), 7.08 (br s, PS + H-Ar), 6.60 (br s, PS), 5.00 (2H, br s, OCH_2), 4.23 (2H, br s, CH_2CH_3), 4.14 (1H, br s, CH), 1.90 (br s, PS), 1.56 (br s, PS + CH_3), 1.30 (br s, CH_3).

Wang phenylalanine ethyl ester resins, 2c. 77% of attachment to the resin, based on %N analysis of 1.05%. Loading = 0.75 mmol g^{-1}. ν_{max}/cm^{-1} 1740 (C=O), 1640 (C=N); δ_H (400 MHz, $CDCl_3$) 8.02 (1H, s, CH=N), 7.95 (br s, H-Ar), 7.77 (br s, H-Ar), 7.18 (br s, PS + H-Ar), 6.71 (br s, PS), 5.11 (2H, br s, OCH_2), 4.32 (3H, br s, CH + CH_2CH_3), 3.49 (1H, br s, CH_2Ph), 3.28 (1H, br s, CH_2Ph), 1.98 (br s, PS), 1.57 (br s, PS), 1.45 (br s, CH_3).

General procedure for the immobilisation of glycine ethyl ester

Glycine ethyl ester hydrochloride (10 equiv.) was dissolved in water. 2 M aqueous NaOH was added until pH between 9 and 10 was obtained. The solution was extracted with DCM (3 × 10 mL). The organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give an oil. Wang-aldehyde resin **1** (1 equiv.) was placed in an oven-dried three-neck round bottom flask purged with N_2. Anhydrous dichloromethane (20 mL), anhydrous trimethyl orthoformate (20 mL) and the glycine ethyl ester were added. The flask was shaken at room temperature for 5 days. The beads were transferred to a sintered tube and washed as above. The beads were dried under vacuum at 50 °C for 2 hours to give pale yellow beads.

Wang glycine ethyl ester resins, 2a. 91% of attachment to the resin, based on %N analysis of 1.35%. Loading = 0.96 mmol g^{-1}. ν_{max}/cm^{-1} 1740 (C=O), 1645 (C=N); δ_H (400 MHz, $CDCl_3$) 8.18 (1H, s, CH=N), 7.72 (2H, br s, H-Ar), 7.04 (br s, PS + H-Ar), 6.56 (br s, PS), 4.95 (2H, br s, OCH_2), 4.34 (2H, br s, CH_2), 4.22 (2H, br s, CH_2), 1.85 (br s, PS), 1.43 (br s, PS), 1.28 (br s, CH_3).

General procedure for the synthesis of α,α-dialkylated amino ethyl ester hydrochlorides (using the semi-automated synthesiser)

The appropriate resin-bound amino ester **2a–c** (100 mg, 1 equiv.) was swollen in dry NMP (2–3 mL) in a 5 mL reaction vessel fitted into the Quest 210 semi-automated synthesiser under N_2. Corresponding RX (5 equiv.) and Bu_4NI (5 equiv.) were added, and the reaction mixture was subjected to magnetic agitation for 1 hour, before BTPP (5 equiv.) was added. Agitation was continued at room temperature overnight (14 hours). The resin was then collected by filtration and washed with the programmed washing rinsing protocol. The resin was then swollen in a mixture of THF : H_2O (2 : 1) (2–3 mL) and aqueous 2 M HCl (5 equiv.) was added. The mixture was stirred for 5 hours. The resin was then filtered and rinsed with THF : H_2O (2 : 1) (2–3 mL × 3). The combined filtrate was collected and evaporated to remove THF from the mixture. The pH of the aqueous solution was neutralised by the addition of aqueous 2 M NaOH (until pH 5–6). The solvent was eventually evaporated to give the crude product as white or pale yellow solids. Yield was calculated as % conversion by ^1H NMR, and product formation further verified by ^{13}C NMR and MS analysis. The resin was recovered by filtration and washed using the automated solvent wash unit and dried in a vacuum oven for 3 hours at 50 °C.

Phenylalanine ethyl ester hydrochloride, 3a. ν_{max}/cm^{-1} 1739 (C=O); δ_H (270 MHz, D_2O) 7.25–7.10 (5H, m, H-Ar), 4.21 (1H, dd, *J* 7.2 Hz and 6.1 Hz, CH), 4.10 (2H, q, *J* 7.2 Hz, CH_2CH_3), 3.16 (1H, dd, *J* 14.5 Hz and 6.1 Hz, CH_2Ph), 3.06 (1H, dd, *J* 14.5 Hz and 7.3 Hz, CH_2Ph), 1.07 (3H, t, *J* 7.2 Hz, CH_2CH_3); δ_C (90.5 MHz, D_2O) 169.9 (C=O), 134.1 (C), 129.8 (CH), 129.6 (CH), 128.5 (CH), 63.9 (CH_2), 54.5 (CH), 36.0 (CH_2), 13.5 (CH_3); *m/z* (EI) 194 ([M − Cl]$^+$, 100%), 177 (28%), 135 (32%), 134 (22%).

Allylalanine ethyl ester hydrochloride, 3b. ν_{max}/cm^{-1} 1739 (C=O); δ_H (270 MHz, D_2O) 5.67–5.52 (1H, m, $CH=CH_2$), 5.19–5.12 (2H, m, $CH=CH_2$), 4.16 (2H, q, *J* 7.2, CH_2CH_3), 2.62 (1H, dd, *J* 14.5 Hz and 7.1 Hz, CH_2Allyl), 2.45 (1H, dd, *J* 14.5 Hz and 8.0 Hz, CH_2Allyl), 1.44 (3H, s, CH_3), 1.15 (3H, t, *J* 7.2 Hz, CH_2CH_3); δ_C (90.5 MHz, D_2O) 172.8 (C=O), 130.2 (CH), 123.6 (CH_2), 65.0 (CH_2), 60.8 (C), 42.1 (CH_2), 22.3 (CH_3), 14.3 (CH_3); *m/z* (CI) 158 ([M − Cl]$^+$, 100%), 159 (14%), 118 (14%), 100 (20%), 90 (32%), 58 (66%).

Methylphenylalanine ethyl ester hydrochloride, 3c. ν_{max}/cm^{-1} 1743 (C=O); δ_H (270 MHz, D_2O) 7.30–7.10 (5H, m, H-Ar), 4.16 (2H, q, *J* 7.2 Hz, CH_2CH_3), 3.26 (1H, d, *J* 14.3 Hz, CH_2Ph), 3.02 (1H, d, *J* 14.3 Hz, CH_2Ph), 1.53 (3H, s, CH_3), 1.15 (3H, t, *J* 7.2 Hz, CH_2CH_3); δ_C (90.5 MHz, D_2O) 171.5 (C=O), 130.5 (CH), 129.5 (CH), 128.7 (CH), 64.3 (CH_2), 61.3 (C), 42.9 (CH_2), 21.9 (CH_3), 13.5 (CH_3); *m/z* (CI) 208 ([M − Cl]$^+$, 100%), 209 (44%), 134 (9%), 118 (10%).

Diphenylalanine ethyl ester hydrochloride, 3d. ν_{max}/cm^{-1} 1737 (C=O); δ_H (270 MHz, D_2O) 7.29–7.07 (10H, m, H-Ar), 4.13 (2H, q, *J* 7.2 Hz, CH_2CH_3), 3.42 (2H, d, *J* 14.5 Hz, CH_2Ph), 3.05 (2H, d, *J* 14.5 Hz, CH_2Ph), 1.11 (3H, t, *J* 7.2 Hz, CH_2CH_3); *m/z* (CI) 284 ([M − Cl]$^+$,100%), 285 (57%), 234 (16%), 194 (11%), 192 (18%).

Allylphenylalanine ethyl ester hydrochloride, 3e. ν_{max}/cm^{-1} 1737 (C=O); δ_H (270 MHz, D_2O) 7.24–7.04 (5H, m, H-Ar), 5.67–5.51 (1H, m, $CH=CH_2$), 5.18–5.12 (2H, m, $CH=CH_2$), 4.13 (2H, q, *J* 7.2 Hz, CH_2CH_3), 3.26 (1H, d, *J* 14.5 Hz, CH_2Ph), 2.98 (1H, d, *J* 14.5 Hz, CH_2Ph), 2.75 (1H, dd, *J* 14.5 Hz and 6.7 Hz, CH_2Allyl), 2.49 (1H, dd, *J* 14.5 Hz and 8.1 Hz, CH_2Allyl), 1.10 (3H, t, *J* 7.2 Hz, CH_2CH_3); δ_C (90.5 MHz, D_2O) 168.7 (C=O), 130.5 (CH), 129.6 (CH), 129.2 (CH), 128.8 (CH), 123.3 (CH_2), 64.4 (CH_2), 41.5 (CH_2), 40.3 (CH_2), 13.5 (CH_3); *m/z* (CI) 234 ([M − Cl]$^+$, 100%), 235 (29%), 194 (8%).

***n*-Hexylalanine ethyl ester hydrochloride, 3f.** ν_{max}/cm^{-1} 1738 (C=O); δ_H (270 MHz, D_2O) 4.17 (2H, q, *J* 7.2 Hz, CH_2CH_3), 1.90–1.60 (2H, m, CH_2), 1.44 (3H, s, CH_3), 1.20–1.00 (11H, m, 4 × CH_2 + CH_2CH_3), 0.71 (3H, t, *J* 6.8 Hz, CH_3); *m/z* (CI) 202 ([M − Cl]$^+$, 100%), 203 (18%), 128 (18%), 118 (14%), 52 (55%).

Naphthylalanine ethyl ester hydrochloride, 3g. ν_{max}/cm^{-1} 1743 (C=O); δ_H (270 MHz, D_2O) 7.91–7.81 (3H, m, H-Ar), 7.52–7.31 (4H, m, H-Ar), 3.80 (2H, q, *J* 7.2 Hz, CH_2CH_3), 3.66 (1H, d, *J* 14.7 Hz, CH_2Naphth), 3.57 (1H, d, *J* 14.7 Hz, CH_2Naphth), 1.55 (3H, s, CH_3), 0.85 (3H, t, *J* 7.2 Hz, CH_2CH_3); *m/z* (EI) 258 ([M − Cl]$^+$, 66%), 158 (100%), 141 (19%), 118 (19%), 116 (78%), 85 (20%), 84 (87%).

***n*-Hexylphenylalanine ethyl ester hydrochloride, 3h.** ν_{max}/cm^{-1} 1744 (C=O); δ_H (270 MHz, D_2O) 7.24–7.03 (5H, m, H-Ar), 4.13 (2H, q, *J* 7.2 Hz, CH_2CH_3), 3.23 (1H, d, *J* 14.4 Hz, CH_2Ph), 2.97 (1H, d, *J* 14.4 Hz, CH_2Ph), 2.03–1.66 (2H, m, CH_2), 1.19 (11H, m, CH_2CH_3 + 4 × CH_2), 0.67 (3H, t, *J* 6.7 Hz, CH_3); δ_C (90.5 MHz, D_2O) 171.7 (C=O), 130.5 (CH), 129.5 (CH), 128.7 (CH), 68.2 (CH_2), 64.2 (CH_2), 54.5 (C), 41.9 (CH_2), 30.8 (CH_2), 28.5 (CH_2), 25.4 (CH_2), 22.9 (CH_2), 22.1 (CH_3), 13.6 (CH_3); *m/z* (CI) 278 ([M − Cl]$^+$, 100%), 279 (20%), 194 (9%), 76 (31%), 59 (46%).

Naphthylphenylalanine ethyl ester hydrochloride, 3i. ν_{max}/cm^{-1} 1746 (C=O); δ_H (360 MHz, pyr-d_5) 8.64 (1H, d, *J* 8.6 Hz, H-Ar), 7.82–7.10 (11H, m, H-Ar), 4.15–3.95 (4H, m, CH_2CH_3 + CH_2Naphth), 3.71–3.62 (2H, m, CH_2Ph), 1.05 (3H, t, *J* 7.2, Hz CH_2CH_3); δ_C (90.5 MHz, pyr-d_5) 177.0 (C=O), 138.2 (C), 135.3 (C), 134.7 (C), 134.5 (C), 131.7 (CH), 129.9 (CH), 129.8 (CH), 129.5 (CH), 128.9 (CH), 128.1 (CH), 126.9 (CH), 126.8 (CH), 126.6 (CH), 126.4 (CH), 64.9 (C), 62.0 (CH_2), 47.5 (CH_2), 43.2 (CH_2), 14.9 (CH_3); *m/z* (EI) 334

([M − Cl]$^+$, 4%), 333 (4%), 262 (21%), 261 (63%), 260 (73%), 244 (8%), 243 (38%), 242 (46%), 206 (27%), 205 (33%), 194 (24%), 193 (81%), 192 (100%), 142 (11%), 141 (31%), 119 (19%), 118 (31%), 91 (39%).

Diallylglycine ethyl ester hydrochloride, 3k. ν_{max}/cm^{-1} 1741 (C=O); δH (270 MHz, D_2O) 5.68–5.53 (1H, m, C*H*=CH_2), 5.21–5.15 (2H, m, CH=CH_2), 4.19 (2H, q, *J* 7.2 Hz, CH_2CH$_3$), 2.67 (1H, dd, *J* 14.5 Hz and 7.1 Hz, CH_2Allyl), 2.50 (1H, dd, *J* 14.5 Hz and 8.1 Hz, CH_2Allyl), 1.16 (3H, t, *J* 7.2 Hz, CH_2CH_3); *m*/*z* (CI) 184 ([M − Cl]$^+$, 100%), 185 (13%), 144 (41%), 90 (17%), 52 (31%).

General procedure for the synthesis of α,α-dialkylated amino ethyl ester hydrochlorides using lithiated bases

The appropriate resin-bound amino ester (100 mg, 1 equiv.) was washed with anhydrous THF and placed in a two-neck flask under N_2. Anhydrous THF (2 mL) was added to the resin and the flask was cooled down to −40 °C. LHMDS (1 M in THF, 5 equiv.) or LDA (2 M in THF–pentane, 5 equiv.) was added dropwise. After 45 minutes, corresponding RX (5 equiv.) and anhydrous THF (1 mL) were added. The reaction mixture was stirred at −40 °C (1 h), −20 °C (1 h), 0 °C (1 h) and then left at room temperature and stirred overnight (14 h). The resin was then filtered off and washed, following same procedure described above.

General procedure for the synthesis of cyclic amino ethyl ester hydrochlorides (using the semi-automated synthesiser)

Immobilised glycine ethyl ester (100 mg, 1 equiv.) was swollen in dry NMP (2–3 mL) in a reaction flask under N_2. Corresponding RX (5 equiv.) was added. The reaction mixture was subjected to magnetic agitation for 1 hour. BTPP (5 equiv.) was then added and the agitation was continued at room temperature overnight (14 h). The resin was then collected by filtration and washed in the automated washing unit using the usual program. A second treatment, if required, was carried out by swelling the beads in anhydrous NMP (2–3 mL) and adding BTPP (5 equiv.). The reaction mixture was stirred for further 5 hours. The resin was filtered off and washed. The resin was finally swollen in a mixture of THF : H_2O (2 : 1) (2–3 mL), to which aqueous 2 M HCl (5 equiv.) was added and the mixture was stirred at room temperature for 5 hours. The resin was then filtered off and rinsed with THF : H_2O (2 : 1) (2–3 mL × 3). The combined filtrate was then evaporated to remove THF from the mixture. To the aqueous solution was added aq. 2 M NaOH to adjust the pH to 5–6 (pH meter). The solvent was evaporated to give the crude product as a white or pale yellow residue, which was analysed by IR, ^{1}H NMR spectroscopy and MS.

1-Amino-cyclopentanecarboxylic acid ethyl ester hydrochloride, 4. ν_{max}/cm^{-1} 1745 (C=O); δ_H (400 MHz, D_2O) 4.10 (2H, q, *J* 7.0 Hz, CH_2CH$_3$), 2.14 (2H, m, CH_2), 1.77–1.67 (6H, m, 3 × CH_2), 1.09 (3H, t, *J* 7.0 Hz, CH_2CH_3); δ_C (100 MHz, D_2O) 169.0 (C=O), 68.2 (C), 66.5 (CH_2), 39.3 (CH_2), 28.0 (CH_2), 16.0 (CH_3); *m*/*z* (CI) 158 ([M − Cl]$^+$, 100%), 176 (30%), 90 (17%), 52 (34%), 44 (21%).

2-Amino-indan-2-carboxylic acid ethyl ester hydrochloride, 5. ν_{max}/cm^{-1} 1751 (C=O); δ_H (400 MHz, D_2O) 7.27 (4H, m, H-Ar), 4.23 (2H, q, *J* 7.1 Hz, CH_2CH$_3$), 3.67 (2H, d, *J* 17.4 Hz, CH_2Ar), 3.26 (2H, d, *J* 17.4 Hz, CH_2Ar), 1.18 (3H, t, *J* 7.1 Hz, CH_2CH_3); δ_C (100 MHz, D_2O) 174.8 (C=O), 138.2 (C), 128.3 (CH), 125.2 (CH), 65.2 (C), 64.4 (CH_2), 42.6 (CH_2), 13.5 (CH_3); *m*/*z* (CI) 206 ([M − Cl]$^+$, 100%), 207 (15%), 132 (9%), 100 (4%), 52 (7%).

1-Amino-cyclohexanecarboxylic acid ethyl ester hydrochloride, 6. ν_{max}/cm^{-1} 1747 (C=O); δ_H (400 MHz, D_2O) 4.14 (2H, q, *J* 7.1 Hz, CH_2CH$_3$), 1.90–1.20 (10H, m, 5 × CH_2), 1.14 (3H, t, *J* 7.1 Hz, CH_2CH_3); δ_C (100 MHz, D_2O) 173.3 (C=O), 62.8 (C), 66.4 (CH_2), 32.4 (CH_2), 26.6 (CH_2), 23.1 (CH_2), 16.2 (CH_3); *m*/*z* (CI) 172 ([M − Cl]$^+$, 100%), 208 (24%), 190 (14%), 173 (10%), 98 (8%), 52 (9%).

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