COMMUNICATION

The synthesis of novel heterocyclic substituted α-amino acids; further exploitation of α-amino acid alkynyl ketones

Robert M. Adlington, Jack E. Baldwin,* David Catterick, Gareth J. Pritchard and Lam T. Tang

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY. E-mail: jack.baldwin@chem.ox.ac.uk

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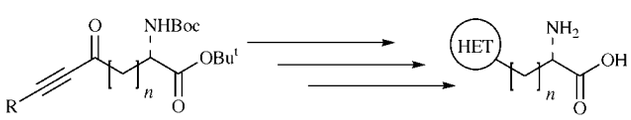
A range of novel heterocyclic substituted α-amino acids has been synthesised by cyclocondensations of (*S*)-2-*tert*-butoxycarbonylamino-4-oxohex-5-ynoic acid *tert*-butyl ester with enamines, phenylhydrazine, hydroxylamine and phenyl azide.

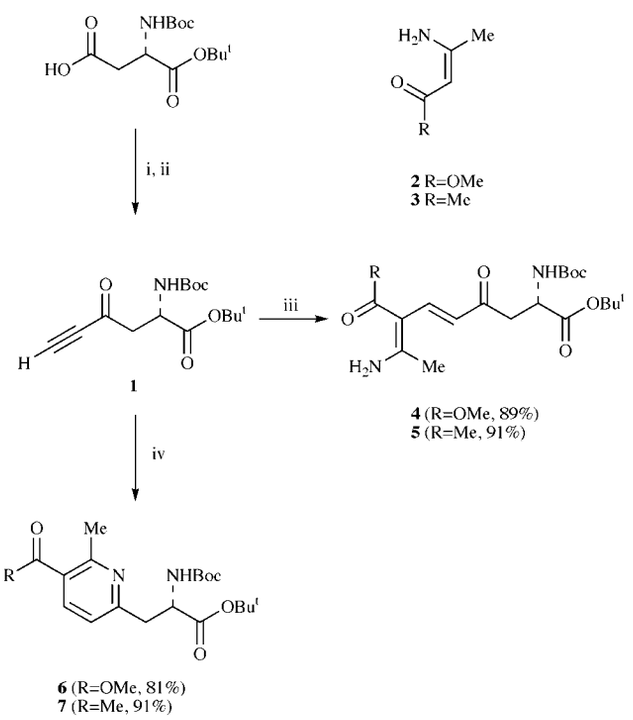
Interest in heterocyclic substituted non-proteinogenic α-amino acids has arisen due to the diverse range of biological and toxicological properties many of these compounds display, for example lathyrine,[1] azatyrosine,[2] and mimosine.[3] We have therefore recently developed a versatile synthetic route towards compounds of this type, which is applicable to a parallel–combinatorial synthesis, to allow the formation of analogue families.[4,5] This was achieved by the formation of a range of α-amino acid alkynyl ketones, by the introduction of alkynyl ketone moieties into the side chains of L-aspartic and L-glutamic acids. These reactive substrates were then shown to undergo high yielding cyclocondensations with a range of amidines to allow a diverse family of pyrimidin-4-yl substituted α-amino acids to be generated. The alkynyl ketone moiety, being an analogue of the β-dicarbonyl, is however a flexible reactive building block capable of varied heterocyclic construction.[4–10] It was therefore decided to further exploit this reactive group in the generation of a range of heterocyclic substituted α-amino acids (Scheme 1).



Scheme 1

The reactive substrate (*S*)-2-*tert*-butoxycarbonylamino-4-oxohex-5-ynoic acid *tert*-butyl ester **1** was selected as a representative α-amino acid alkynyl ketone for exploring cyclocondensation reactions. Selective protection of the α-amino and α-carboxylic acid functionalities of L-aspartic acid, followed by conversion of the free side chain acid to the 'Weinreb' amide and reaction with ethynylmagnesium bromide thus allowed **1** to be generated, as outlined previously.[4,5]

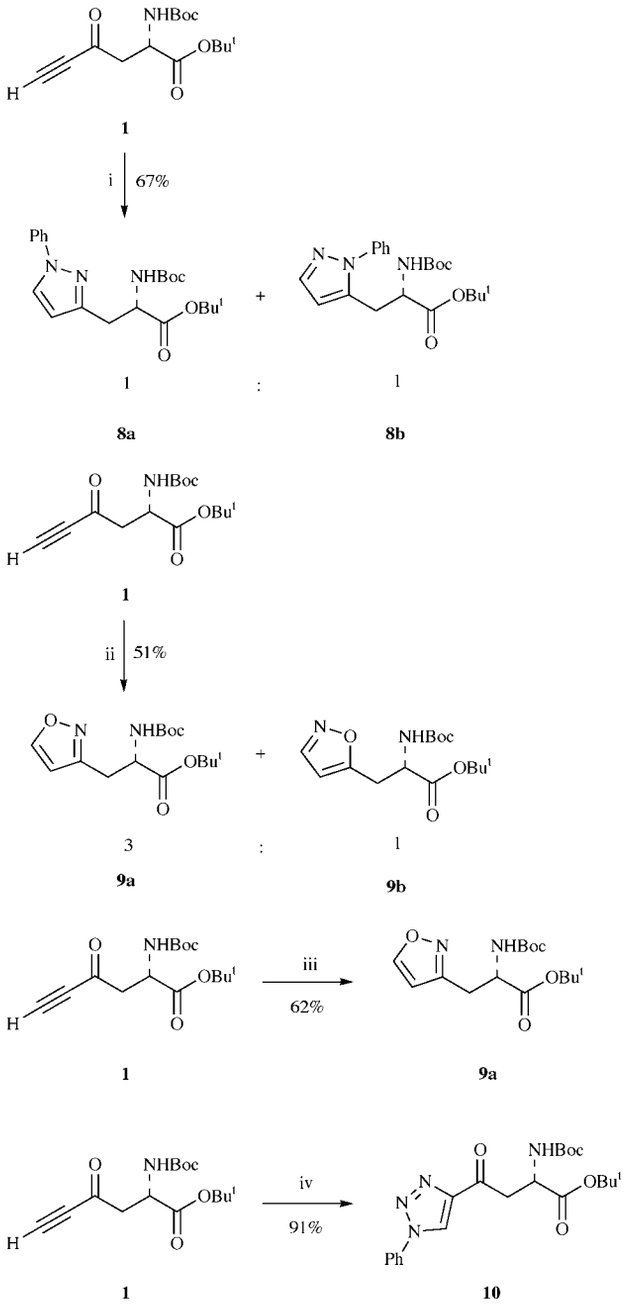
Bohlmann and Rahtz reported that cyclocondensations between alkynyl ketones and suitable enamines allowed the generation of functionalised pyridines in excellent yields.[6] In order to access pyridine substituted amino acids, which would bear relation to the naturally occurring amino acid L-azatyrosine, condensation reactions between **1** and 3-amino-but-2-enoic acid methyl ester **2** and 4-aminopent-3-en-2-one **3**, prepared by literature procedures,[11,12] were therefore carried out. Initial reactions between **1** and either **2** or **3**, carried out in ethanol at room temperature, led to almost quantitative conversion to single products. ^{1}H NMR analysis of these products indicated that instead of a cyclocondensation to form the desired pyridines, the disubstituted *trans*-alkenes **4** and **5** had formed (olefinic $^3J = 15.5$ Hz compared to *ca.* 8.0 Hz for pyridines). This observed *trans* addition to the triple bond of the alkynyl ketone was consistent with that reported by Bromidge *et al.*,[13] with the *Z*-geometry of the enamine double bond expected due to the possibility of hydrogen bonding. Bohlmann and Rahtz had however carried out their cyclocondensations at elevated temperatures and it was subsequently found that stirring an ethanolic solution of **1** with either enamine **2** or **3**, at reflux, then resulted in high conversion to the pyridin-6-yl substituted, protected, β-alanines **6** and **7** (Scheme 2).



Scheme 2 *Reagents and conditions*: i, NMM, Bu^{i}OCOCl, THF, −15 °C, HN(OMe)Me·HCl, NEt$_3$, DMF, 74%; ii, HCCMgBr (5 equiv.), Et$_2$O, −78 °C; iii, **2** or **3**, EtOH, RT; iv, **2** or **3**, EtOH, reflux.

Literature evidence also suggested that cyclocondensation of **1** with hydrazines and hydroxylamine should allow access to both pyrazole and isoxazole substituted amino acids.[7,8] Reaction of (*S*)-2-*tert*-butoxycarbonylamino-4-oxohex-5-ynoic acid *tert*-butyl ester **1** with hydrazines was therefore investigated by stirring an ethanol solution of **1** and phenylhydrazine hydrochloride with solid sodium carbonate. This allowed the desired pyrazolyl substituted protected α-amino acids **8a/b** to be isolated in satisfactory yield, as an inseparable mixture of regioisomers, in a 1 : 1 ratio by ^{1}H NMR (Scheme 3).

Cyclocondensations of **1** with hydroxylamine were then attempted to investigate a similar preparation of isoxazoles. The expected products from our condensation reaction appeared attractive targets, with interest in isoxazolyl α-amino acids having arisen due to non-protein amino acids such as ibotenic acid being regarded as conformationally restricted glutamic acid analogues.[14,15] Thus reaction of **1** with hydroxyl-



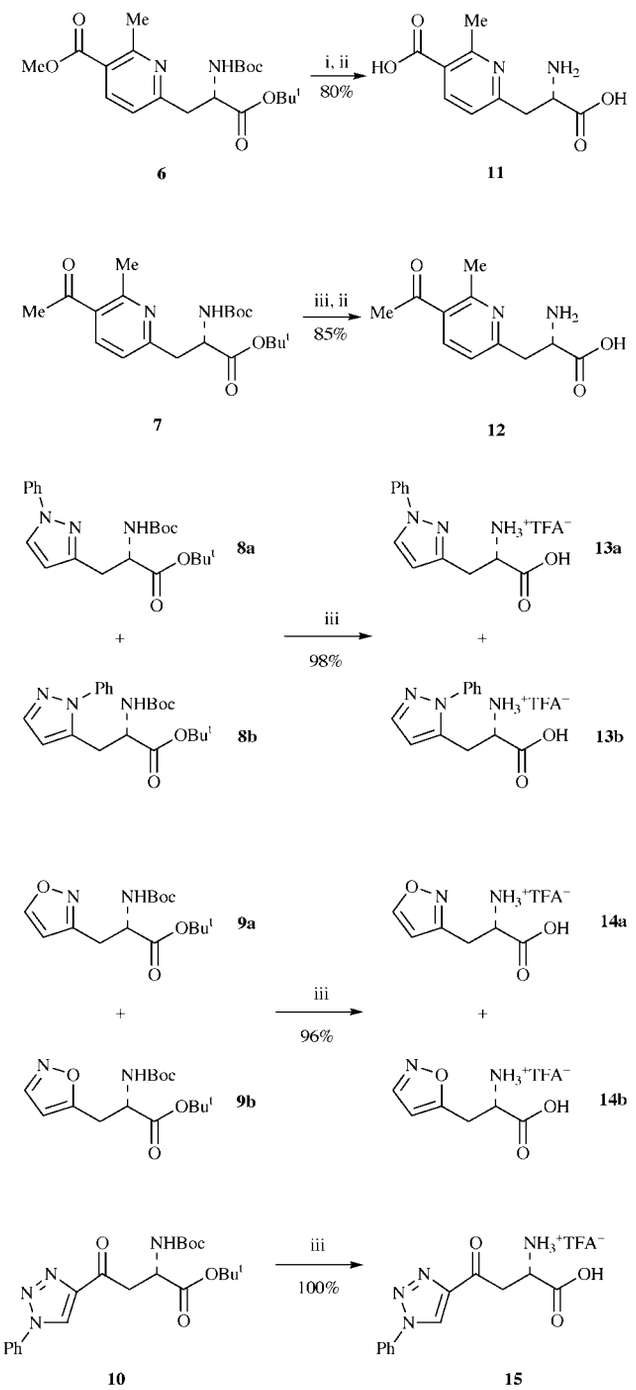
Scheme 3 *Reagents and conditions*: i, H_2N–NHPh·HCl, Na_2CO_3, H_2O, EtOH, reflux; ii, H_2N–OH·HCl, EtOH, pyridine, reflux; iii, H_2N–OH·HCl, EtOH, reflux; iv, Ph–N_3, Et_2O, reflux.

amine hydrochloride in an ethanol solution with solid sodium carbonate only allowed isolation of the isoxazole **9a** in a poor 13% yield.[7] Variation of the solvent and base employed, to ethanol and 1.2 equivalents of pyridine, subsequently allowed the regioisomeric isoxazoles **9a/b** to be obtained in a 51% yield, as a 3:1 separable mixture of regioisomers.[16] Giacomelli *et al.* however had reported a successful condensation of hydroxylamine upon an enamino ketone, albeit in low yield, by a simple reaction with the hydrochloride salt in refluxing methanol.[17] We therefore investigated the possibility of cyclocondensations that were not subject to the hydroxlamine being released by the addition of base. Hydroxylamine hydrochloride was thus refluxed in ethanol with **1** and the isoxazole **9a** isolated exclusively in a respectable 62% yield (Scheme 3).

It was next decided to attempt the formation of a 1,2,3-triazolyl substituted α-amino acid by a cycloaddition with an azide. It had been shown that reaction of azides with alkynyl ketones had led to exclusive addition at the acetylene and therefore reaction of **1** with phenyl azide was carried out in refluxing diethyl ether.[8] This generated the triazol-4-yl, protected, amino acid **10**, in almost quantitative yield, as a single regioisomer (Scheme 3). ^{1}H NMR (CD_3OD) analysis indicated that presumably only the regioisomer **10** was formed owing to the high ppm value (δ_H 9.11 ppm) of the C-5 aromatic proton (usually *ca.* 8.5–9.0 ppm).[8,16]

The enantiomeric purity of this range of heterocyclic amino acids was then determined by conversion of their *N*-deprotected forms (Boc deprotection was carried out by azeotropic distillation with TsOH·H_2O–PhMe) to both their (*R*)- and (*S*)-Mosher's amides and shown, by ^{19}F NMR analysis, to be greater than 98% ee.[18]

Facile deprotection of the amino acids **7**, **8a/b**, **9a/b** and **10** was carried out by their dissolution in TFA–anisole; full deprotection of **6** being carried out by refluxing in 1 M HCl. The free amino acids **11** and **12** were then obtained, by ion-exchange chromatography, as solids in high yields and the amino acids **13a/b**, **14a/b** and **15** were isolated as their TFA salts, after diethyl ether trituration, due to their low solubilities (Scheme 4).



Scheme 4 *Reagents and conditions*: i, 1 M HCl, reflux; ii, Dowex 50X8-100 ion exchange resin; iii, TFA, anisole, DCM.

In summary we have shown that our methodology can be readily expanded to other novel heterocyclic systems. Further exploitation of the alkynyl ketone reactive group has allowed efficient construction of a range of representative heterocyclic non-proteinogenic amino acids. This has further highlighted the flexibility and power of our approach with pyridinyl, pyrazolyl, isoxazolyl and 1,2,3-triazolyl substituted β-alanines being generated in approximately 15% yield from L-aspartic acid. Further routes to novel heterocyclic non-protein amino acids will be reported in due course.

Acknowledgements

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