A versatile approach to pyrimidin-4-yl substituted α-amino acids from alkynyl ketones; the total synthesis of L-lathyrine

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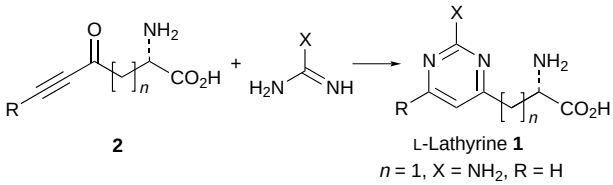
A range of pyrimidin-4-yl substituted α-amino acids has been synthesised by the reaction of amidines with α-amino acid alkynyl ketones.

The stereoselective synthesis of α-amino acids is an active field of research.[1] In particular heterocyclic substituted non-proteinogenic amino acids show a diverse range of biological activities. Examples of these include azatyrosine,[2] mimosine,[3] lathyrine **1**[4,5] and discadenine.[6] In view of the wide range of biological activities shown we wished to develop a versatile route to these types of compounds, which may also be applicable to parallel and/or combinatorial syntheses, thus providing families of related compounds.

Our initial target was to introduce alkynyl ketones as a versatile reactive group for the construction of heterocycles into the side chain of α-amino acids. Alkynyl ketones have been used in the synthesis of a range of heterocyclic systems[7] and very recently have been condensed with amidines to give pyrimidines.[8] As our approach offered the possibility of three different groups on the heterocyclic ring, one of which being an α-amino acid, a large range of structurally related families should be readily accessible (Scheme 1).

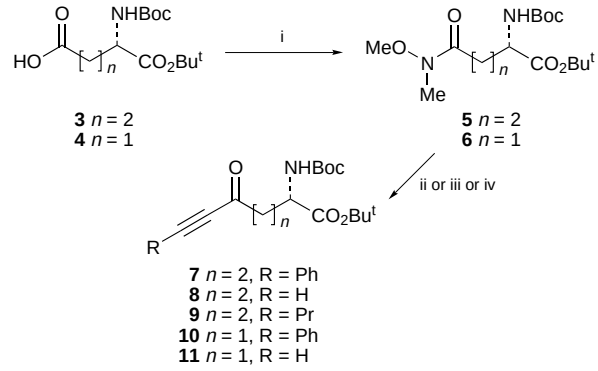
Glutamic acid and aspartic acid were considered as suitable precursors to **2**, where the side chain acid could be activated and reacted with a lithium acetylide. The activation chosen was the 'Weinreb' amide, which has been used to synthesise aryl ketone amino acids.[9,10] Thus α-*tert*-butyl *N*-*tert*-butoxycarbonyl-glutamate **3** was prepared following a five step procedure from L-glutamic acid,[11,12] which was then converted to the amide **5** by reaction of *N*,*O*-dimethylhydroxylamine *via* a mixed anhydride in satisfactory yield.[10] Subsequent reaction of the amide **5** with a five-fold excess of lithium phenylacetylide, ethynylmagnesium bromide or lithium propylacetylide at −78 °C in THF afforded the ethynyl ketones **7**, **8** and **9** in good yields (Scheme 2).

Trial cyclocondensations between **8** and benzamidine hydrochloride showed that optimal conditions for the formation of the desired pyrimidinyl substituted amino acid **12** were stirring an MeCN or EtOAc solution of the ethynyl ketone with benzamidine hydrochloride and solid Na_2CO_3 with a catalytic amount of water at reflux. Acetylenic ketones **7**, **8** and **9** containing aryl, hydrogen and alkyl functionalities respectively then underwent a series of cyclocondensations with a range of hetero, aryl, alkyl and hydrogen functionalised amidines to generate the pyrimidines **12**–**19** (Scheme 3 and Table 1). The enantiomeric purity of these compounds was determined by conversion of their N-deprotected forms (Boc deprotection carried out by azeotropic distillation with $TsOH·H_2O$–PhMe) to both (*R*)- and (*S*)-Mosher's amides and proved to be greater than 98% ee.[13]



2 L-Lathyrine **1**
n = 1, X = NH_2, R = H

Scheme 1

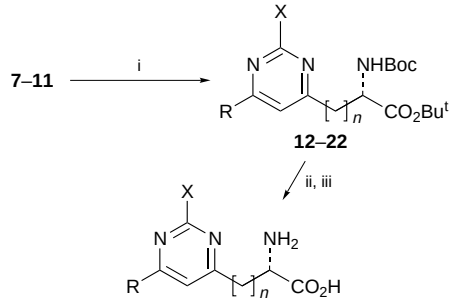


3 n = 2
4 n = 1
5 n = 2
6 n = 1
7 n = 2, R = Ph
8 n = 2, R = H
9 n = 2, R = Pr
10 n = 1, R = Ph
11 n = 1, R = H

Scheme 2 *Reagents and conditions*: i, NMM,Bu^{i}OCOCl, THF, −15 °C; HN(OMe)Me·HCl, NEt_3, DMF, 74% (**5**), 76% (**6**); ii, PhCCLi (5 equiv.), THF, −78 °C, 79% (**7**), 62% (**10**); iii, HCCMgBr (5 equiv.), Et_2O, −78 °C, 61% (**8**), 78% (**11**); iv, PrCCLi (5 equiv.), THF, −78 °C, 95% (**9**)

Thus from a key precursor **5** a large family of diverse structures can be built up incorporating hydrogen, alkyl, aryl and hetero functionality. The amidine used allows control at the 2 position of the resulting pyrimidine whilst the choice of acetylide controls the 6 position.

To allow further variation in the substitution at the pyrimidine 4 position, the chemistry was expanded to L-aspartic acid. The α-*tert*-butyl *N*-*tert*-butoxycarbonylaspartate **4** was prepared and converted to the 'Weinreb' amide **6** as previously for **5**. The acetylenic ketones **10** and **11** were then formed by reaction of **6** with a five-fold excess of ethynylmagnesium bromide or lithium phenylacetylide respectively (Scheme 2). The ketones **10** and **11** underwent high yielding condensations to produce **20**, **21** and **22** (Scheme 3 and Table 1). Investigation



30 n = 2, R = Ph, X = Ph
31 n = 2, R = Ph, X = Me
32 n = 2, R = Ph, X = H
33 n = 2, R = Ph, X = SMe
34 n = 2, R = H, X = SMe
35 n = 2, R = H, X = NH_2
36 n = 2, R = Pr, X = SMe
37 n = 2, R = Pr, X = Me
38 n = 1, R = Ph, X = SMe
39 n = 1, R = Ph, X = 4-ClC_6H_4
40 n = 1, R = H, X = SMe

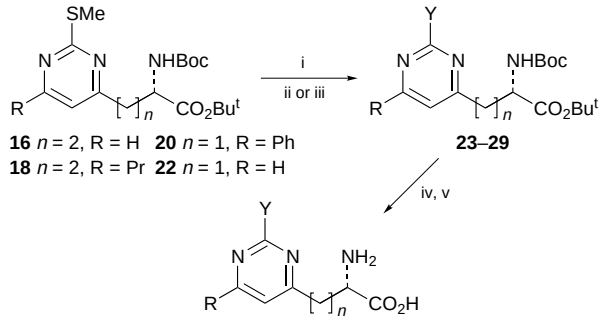
Scheme 3 *Reagents and conditions*: i, HN(CX)NH_2·HCl or 0.5 H_2SO_4, EtOAc or MeCN, Na_2CO_3, H_2O (cat.), reflux (or 40 °C for n = 1); ii, TFA, anisole; iii, Dowex 50X8-100 ion-exchange resin

Table 1 Pyrimidin-4-yl substituted protected α-amino acids from the cyclocondensations of ethynyl ketones with amidines

Compound	*n*	R	X	Yield (%)
12	2	Ph	Ph	87
13	2	Ph	Me	90
14	2	Ph	H	40
15	2	Ph	SMe	79
16	2	H	SMe	82
17	2	H	NH_2	28
18	2	Pr	SMe	95
19	2	Pr	Me	83
20	1	Ph	SMe	91
21	1	Ph	4-ClC_6H_4	89
22	1	H	SMe	87

of the enantiomeric purity of these pyrimidines by Mosher's amide formation showed up to 5% racemisation when the cyclocondensations were carried out at reflux temperatures; however, this was reduced by carrying out the condensations at 40 °C affording enantiomeric purity greater than 98% ee.

One compound of note is pyrimidine **17**, which is a homologue of the naturally occurring amino acid L-lathyrine.[4] The condensation of **8** with guanidine to give **17** had, however, given a disappointingly low yield. In order to attempt the synthesis of L-lathyrine itself as well as other analogues and to further diversify the functionality at the pyrimidine 2 position it was decided to undertake nucleophilic aromatic substitutions of suitable leaving groups. It was expected that the existing thiomethyl functionality, derived from cyclisations of ethynyl ketones with 2-methyl-2-thiopseudourea, if oxidised to the corresponding sulfone, would be susceptible to substitution by nucleophiles.[14] Reaction of the pyrimidines **16**, **18**, **20** and **22** with 2 equiv. of MCPBA resulted in the corresponding sulfones **23**–**26**. Substitution of the methylsulfonyl group using liquid ammonia was then possible. Good yields of the corresponding pyrimidines **27**–**29** were thus achieved, **29** being protected L-lathyrine. When 1 M NaOH was used in the substitution reaction with **23**, followed by mild acidic work up (KH_2PO_4–H_2O) and purification by ion-exchange chromatography, pyrimidone **45** was obtained in 71% yield (Scheme 4 and Table 2).



16 *n* = 2, R = H **20** *n* = 1, R = Ph
18 *n* = 2, R = Pr **22** *n* = 1, R = H

41 *n* = 2, R = H, Y = SO_2Me **45** *n* = 2, R = H, Y = OH
42 *n* = 2, R = Pr, Y = SO_2Me **46** *n* = 2, R = Pr, Y = NH_2
43 *n* = 1, R = Ph, Y = SO_2Me **47** *n* = 1, R = Ph, Y = NH_2
44 *n* = 1, R = H, Y = SO_2Me **1** *n* = 1, R = H, Y = NH_2

Scheme 4 *Reagents and conditions*: i, MCPBA (2 equiv.), CH_2Cl_2, room temp.; ii, 1,4-dioxane, 1 M NaOH, room temp.; iii,NH_3 (1), THF, room temp.; iv, TFA, anisole; v, Dowex 50X8-100 ion exchange resin

Table 2 Results for oxidation of **16**, **18**, **20** and **22** and subsequent nucleophilic substitutions

Compound	*n*	R	Y	Yield (%)
Oxidation				
23	2	H	SO_2Me	86
24	2	Pr	SO_2Me	88
25	1	Ph	SO_2Me	76
26	1	H	SO_2Me	100
Substitution				
27	2	Pr	NH_2	75
28	1	Ph	NH_2	87
29	1	H	NH_2	93

Deprotection of the protected pyrimidin-4-yl amino acids was achieved by dissolution in TFA–anisole. The free amino acids **30**–**32**, **34**–**38**, **40**–**47** and **1** were obtained by ion-exchange chromatography as solids in high yields (90–100%). A lower yield was observed for the deprotection/purification of **33** due to the low solubility of its TFA salt and **39** was preferentially isolated as its TFA salt (Schemes 3 and 4). The optical rotation of **1** (synthetic L-lathyrine) had a value of $[\alpha]_D^{21}$ −55.4 (*c* 1.2, H_2O), consistent with that reported for the naturally occurring amino acid [lit.,[5] −55.9 (*c* 1.2, H_2O)].

In conclusion we have developed a versatile approach, applicable to parallel synthesis, to a family of pyrimidin-4-yl substituted α-amino acids, the chemistry allowing diversification by control of the 2, 4 and 6 positions of the pyrimidine. This route allows the total synthesis of non-proteinogenic amino acids in approximately 20% overall yield from aspartic or glutamic acids. Further routes to other families of natural product derivatives will be reported in due course.

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Footnote and References

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