Convenient synthesis of chiral α,β-acetylenic γ-amino acid derivatives and γ-aminobutyric acid analogues *via* stabilised ylides

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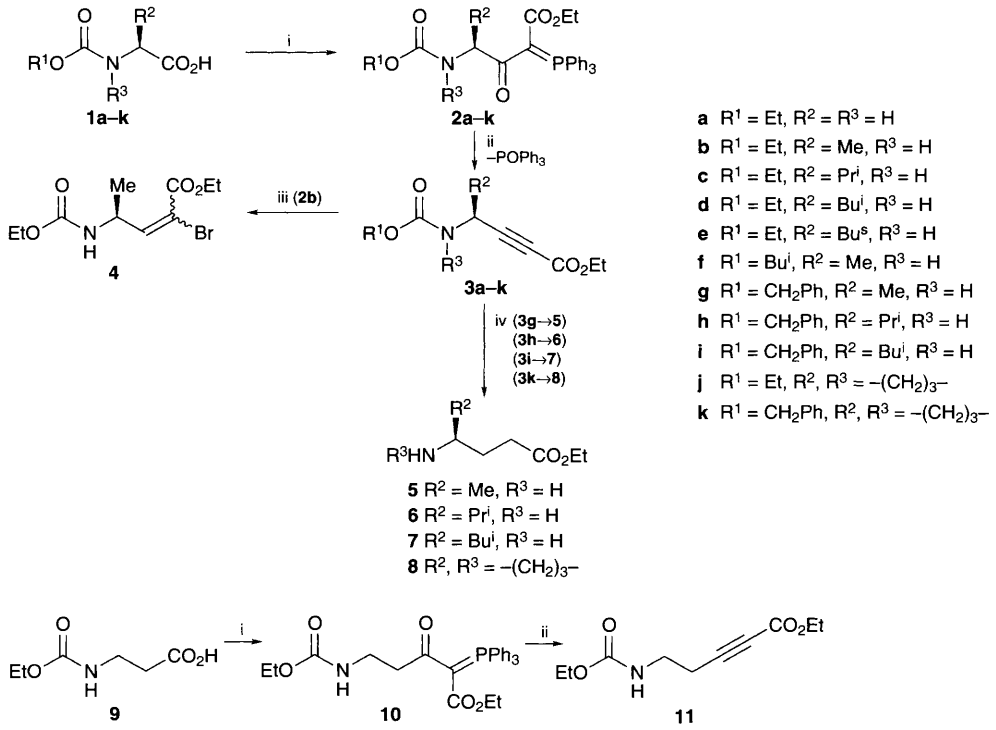
Twelve examples of protected acetylenic amino acids are readily prepared in a two-step procedure involving formation and flash vacuum pyrolysis of chiral aminoacyl phosphorus ylides.

In a recent paper[1] we described an attempt to apply the thermal extrusion of Ph_3PO from suitable α-amino acid-derived stabilised phosphorus ylides to the formation of derivatives of the α,β-acetylenic γ-amino acids. This was frustrated by preferential elimination of an oxygen of the phthalimido group, used to protect nitrogen, to give pyrroloisoindolones. Relatively few compounds of this type have been prepared before,[2] but they are of considerable importance as potential mechanism-based inhibitors of medicinally important enzymes. In particular, 4-aminotetrolic acid and a number of *N*-substituted analogues have been shown to be effective γ-aminobutyric acid (GABA) mimics,[3] and related compounds have been proposed for the therapeutic treatment of alcoholism and as anti-tumour agents.[4] In addition, the relationship between α-amino acids and the analogues extended by insertion of a C≡C unit, a concept recently generalised by Chauvin[5] and termed 'carbomers', makes the latter of interest for the formation of modified peptides. We report here the application of the ylide pyrolysis method to formation of acetylenic amino acid derivatives and some reactions of these products. While our work was in progress, Reetz and co-workers described a different and somewhat longer route for carrying out the same transformation using the Corey–Fuchs procedure.[6]

The required ylides **2a–k** and **10** were readily obtained in moderate yield following Wasserman's method,[7] which involved reaction of *N*-alkoxycarbonyl-protected amino acids **1a–k** and **9** and $Ph_3P{=}CHCO_2Et$ with the carbodiimide peptide-coupling reagent EDCI† in the presence of DMAP (Scheme 1). The ylides are stable crystalline solids which could be readily purified by column chromatography and gave all the expected analytical and spectroscopic data.‡ This included clear evidence for the existence of carbamate rotamers in some of the ^{13}C and ^{31}P NMR spectra, and this was quantified for **2e** and **j** by means of a variable temperature study giving estimated free energy barriers to rotation of 74.8 and 70.9 kJ mol^{-1}, respectively.

When the ylides were subjected to flash vacuum pyrolysis (FVP) at 600 °C and 10^{-2} Torr in a flow system using the previously reported method,[8] the expected extrusion took place and chromatographic purification of the material in the cold trap gave the acetylenic amino esters **3a–k** and **11** in low to moderate yield (Table 1). In addition to the acyclic examples **3a–i**, this method also provided convenient access to the cyclic derivatives **3j** and **k** from proline, and the δ-amino-α,β-acetylenic ester **11** from β-alanine. These products were obtained as yellow oils whose structure was confirmed by ^{13}C NMR signals for –C≡ at δ_C 70–76 and 81–88. Again the compounds were present as a 1 : 1 mixture of carbamate rotamers in most cases,



Scheme 1 *Reagents and conditions*: i, $Ph_3P{=}CHCO_2Et$, EDCI, cat. DMAP; ii, FVP, 600 °C; iii, HBr, AcOH; iv, H_2, Pd/C

as shown by ^{13}C NMR.‡ Although we have not yet found a satisfactory general method for the direct estimation of the enantiomeric purity of either **3** and **11** or **2** and **10**, the absence of significant diastereoisomer signals in the NMR spectra of **3e** show that there has been little racemisation during the pyrolysis and from the substantial optical rotations obtained in the other cases, the products are certainly not racemic. This is also supported by the high enantiomeric excess (ee) values obtained for the GABA analogues **5–8** derived from **3g**, **h**, **i** and **k**. These results provide a good demonstration of the mild nature of the FVP technique, something which is often not appreciated.

The value of the products **3** and **11** as synthetic intermediates was demonstrated by reaction of **3b** with HBr in acetic acid which gave the α-bromoacrylate **4** as a 1 : 1 mixture of *E* and *Z* isomers, and by catalytic hydrogenation of the *N*-*Z* examples **3g**, **h**, **i** and **k** which gave the γ-alkylated GABA analogues **5–8** directly in good yield (Table 2). The ees of these products were determined by formation of their Mosher amide derivatives and analysis by ^{13}C and ^{19}F NMR spectroscopy.[9]

Table 1 Formation of aminoacyl ylides **2a–k** and **10** and their conversion to acetylenic amino acid derivatives **3a–k** and **11**

	Aminoacyl ylide				Acetylenic amino acid		
Starting material	No.	Yield (%)	δ_P	$[\alpha]_D$	No.	Yield (%)	$[\alpha]_D$
1a	**2a**	51	17.8	—	**3a**	39	—
1b	**2b**	50	18.0	+17.5	**3b**	32	−91.0
1c	**2c**	45	17.8	+22.6	**3c**	34	−49.5
1d	**2d**	45	17.9	+17.1	**3d**	36	−74.5
1e	**2e**	48	18.7/18.6[a]	+5.9	**3e**	38	+9.1
1f	**2f**	45	18.0	+13.8	**3f**	33	−9.1
1g	**2g**	46	17.5	+20.3	**3g**	29	−30.3
1h	**2h**	49	17.8	+28.7	**3h**	30	−34.4
1i	**2i**	44	17.5	+21.7	**3i**	30	−26.7
1j	**2j**	44	17.4/17.2[a]	−33.8	**3j**	48	−137.7
1k	**2k**	49	17.6/17.4[a]	−45.0	**3k**	48	−114.4
9	**10**	52	18.1	—	**11**	49	—

[a] Separate signals due to carbamate rotamers.

Table 2 Hydrogenation of acetylenic esters **3g–i**, **k** to give GABA derivatives **5–8**

	GABA derivative			
Starting material	No.	Yield (%)	$[\alpha]_D$	ee (%)[a]
3g	**5**	74	−2.5	70
3h	**6**	72	+7.2	85
3i	**7**	70	+6.9	>85
3k	**8**	78	−8.6	>95

[a] Determined by NMR analysis of Mosher amides.

Footnotes

† EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

‡ All new compounds gave satisfactory microanalytical data. *Selected spectroscopic data* for **2i**: colourless crystals; mp 152–154 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67–7.61 (5 H, m, Ph), 7.64–7.44 (10 H, m, Ph), 7.30–7.26 (5 H, m, Ph), 5.61 (2 H, m, NH and CH), 5.07 (2 H, s, OCH_2Ph), 3.81 (2 H, m, OCH_2), 1.77 (2 H, m, CH_2CH), 1.36 (1 H, m, CH_2CH), 1.12 (3 H, d, *J* 6, $CHMe$), 0.94 (3 H, d, *J* 6, $CHMe$) and 0.72 (3 H, t, *J* 7, CH_2Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2 (d, *J* 3, P=C–*C*O), 166.8 (d, *J* 15, CO_2Et), 156.2 (NHCO), 137.1 (C-1 of Ph), 128.5 (d, *J* 12, 6 × C-3 of PPh), 133.1 (d, *J* 10, 6 × C-2 of PPh), 131.8 (d, *J* 2, 3 × C-4 of PPh), 128.3 (2 C, Ph), 127.7 (3 C, Ph), 126.2 (d, *J* 94, 3 × C-1 of PPh), 69.3 (d, *J* 110, P=C), 66.1 (OCH_2Ph), 58.7 (OCH_2), 55.1 (d, *J* 8, *C*HNH), 43.6 (CH_2CH), 25.1 (*C*HMe), 21.9 ($CHMe$), 21.8 ($CHMe$) and 13.9 (OCH_2Me); *m/z* (CI) 596 (M + H^+, 100%). For **3i**: yellow oil; ^1H NMR: δ 7.35 (5 H, s, Ph), 5.12 (2 H, s, OCH_2Ph), 4.93 (1 H, br s, NH), 4.68 (1 H, m, NHC*H*), 4.22 (2 H, q, *J* 7, OCH_2), 1.78 (1 H, m, CH_2CH), 1.62 (2 H, m, $CHCH_2$), 1.30 (3 H, t, *J* 7, Me) and 0.94 (6 H, d, *J* 7, $CHMe_2$); ^{13}C NMR: δ 155.3 (CO_2), 153.3 (NHCO), 136.1 (C-1 of Ph), 128.6 (2 C, Ph), 128.3 (1 C, Ph), 128.2 (2 C, Ph), 86.5 and 83.4* ($OCC{\equiv}C$), 75.0 and 71.2* ($OCC{\equiv}C$), 67.2 (OCH_2Ph), 62.1 (OCH_2Me), 44.3 (CH_2), 41.8 (NCH), 24.9 ($CHMe_2$), 22.4 ($CHMe$), 22.1 ($CHMe$) and 14.0 (OCH_2Me) [* indicates signal due to minor carbamate rotamer]; *m/z* (CI) 318 (M + H^+, 26%) and 274 (100). For **7**: colourless crystals; mp 124–125 °C; ^1H NMR: δ 8.93 (2 H, br s, NH_2), 4.14 (2 H, q, *J* 7, OCH_2), 3.37 (1 H, m, NCH), 2.59 (2 H, t, *J* 7, $COCH_2$), 2.04 (2 H, m, CH_2), 1.88 and 1.70 (2 H, 2 × m, CH_2), 1.49 (1 H, m, CH), 1.25 (3 H, t, *J* 7, OCH_2Me) and 0.95 (6 H, d, *J* 7, $CHMe_2$); ^{13}C NMR δ 172.5 (CO_2), 60.7 (OCH_2), 50.2 (NCH), 42.1 ($CHCH_2$), 30.1 ($COCH_2$), 28.2 (CH_2), 24.4 (CH), 22.4 ($CHMe$), 22.2 ($CHMe$) and 14.2 (OCH_2Me); *m/z* (CI) 188 (M + H^+, 100%).

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