

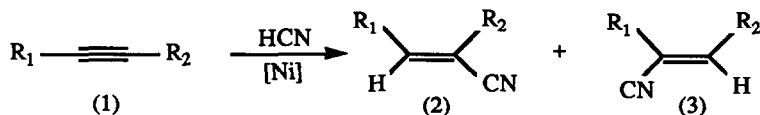
**THE HYDROCYANATION ROUTE TO β - AND γ -AMINO ACIDS.
A SYNTHESIS OF α -METHYLENE- β -ALANINE**

W. Roy Jackson, Patrick Perlmutter and Andrew J. Smalbridge

Department of Chemistry, Monash University, Clayton, Victoria 3168, Australia

Hydrocyanation of several phthalimidoalkynes proceeds with good regioselection yielding products which were easily converted into unsaturated and saturated β - and γ -amino acids.

Recently, we showed that the nickel(0)-catalysed hydrocyanation of a range of protected hydroxy-alkylalkynes gave unsaturated nitriles with good regioselection.¹ It seemed likely that the corresponding amines might behave similarly, yielding useful precursors to amino acids. A variety of phthalimidoalkynes was prepared by a well defined literature method.² The phthalimidoalkynes (10 mmol) were reacted with hydrogen cyanide (10.4 mmol) with tetrakis(triphenylphosphite)nickel (0.17 mmol) in the presence of triphenylphosphite (0.65 mmol) in benzene (20 ml) for 18 hours in a stainless steel autoclave (similar conditions to those used in the hydrocyanation of other alkynes.^{3,4}) Unsaturated nitrile products (Scheme 1) were obtained in good yield and with good regioselection in most cases[†] (Table 1). The major product in each case was purified either by crystallisation or radial chromatography. Catalytic hydrogenation followed by hydrolysis gave the saturated derivatives in excellent overall yield (Table 1).



Scheme 1

Alternatively, direct hydrolysis provided the unsaturated amino acids in moderate yields (Scheme 2). One of these products, α -methylene- β -alanine (4; $\text{R}_1=\text{H}$) is a naturally occurring compound. It occurs both as the free amino acid in the Red Sea sponge, *Fasciospongia cavernosa*⁴ and as a series of N-acyl derivatives of its methyl ester from a black Hawaiian sponge, *Spongia cf. zimocca*.⁵ Holm and Scheuer synthesised the amino acid in four steps from (*bis*-bromomethyl)acetic acid.⁵ Our synthesis proceeded in 38% overall yield in four steps from propargyl alcohol. Thus, our methodology makes this natural product and its congeners readily available.

Finally, this simple route to stereochemically pure dehydro- β -amino acids, which our method now provides invites an investigation into their asymmetric hydrogenation. Such an investigation is underway in our laboratories.

[†] All new compounds reported here gave satisfactory spectroscopic and elemental analysis.

Table 1: Hydrocyanation of phthalimidoalkynes (1) and conversion into the corresponding amino acids (4) and (6)

| R ₁ | R ₂ | % Yield ^{a,b} | | Ratio | |
|-----------------|------------------------------------|------------------------|-----------|-----------------|-----------------|
| | | (2) + (3) | (2) : (3) | (4) | (6) |
| H | CH ₂ Ft ^c | 88 | 4 : 1 | 48 ^d | 65 ^e |
| CH ₃ | CH ₂ Ft | 72 | 1 : 1 | | 86 |
| Ph | CH ₂ Ft | 76 | 9 : 1 | 30 ^d | 90 |
| H | (CH ₂) ₂ Ft | 88 | 9 : 1 | | 75 |

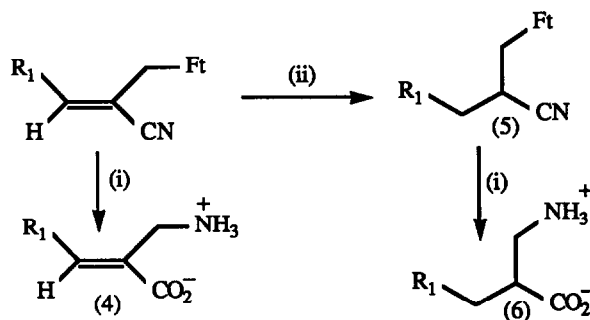
a Reaction conditions were as described in text and in ref. 3 except for the first entry for which the reaction time was 66 and not 18 h

b Yield of product after purification by either crystallisation or radial chromatography.

c Ft = N-phthalimido

d Isolated as the hydrochloride salt.

e Isolated as the N-benzyloxycarbonyl (cbz) derivative



Scheme 2: (i) conc. HCl, reflux 4 to 18 h; (ii) Pd/CaCO₃, H₂ (140 psi), 4 h

Acknowledgements

We thank Professor P.J. Scheuer, University of Hawaii, for the generous sample of authentic α -methylene- β -alanine. We also thank the Australian Research Grants Scheme and the Australian Government, Department of Education, for a Postgraduate Research Award (to A.J.S.)

References

1. W.R. Jackson, P. Perlmutter and A.J. Smallridge, *J. Chem. Soc. Chem. Commun.*, 1985, 1509.
2. Prepared in 80-92% yield by phase transfer catalysed displacement of the corresponding mesylate with potassium phthalimide (see Landini, D. and Rello, F., *Synthesis*, 1976, 389).
3. N.J. Fitzmaurice, W.R. Jackson and P. Perlmutter, *J. Organomet. Chem.*, 1985, 285, 375.
4. Y. Kashman, L. Fishelson and I. Neeman, *Tetrahedron*, 1973, 29, 3655.
5. A. Holm and P.J. Scheuer, *Tetrahedron Letts.*, 1980, 1125.

(Received in UK 24 February 1988)