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SYNTHESIS OF L-β-(ISOXAZOLIN-5-ONE-2-YL)-ALANINE: A NOVEL METHOD FOR THE SYNTHESIS OF N-SUBSTITUTED 3,4-UNSUBSTITUTED ISOXAZOLIN-5-ONES[1]

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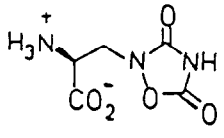
Abstract: A mild new general method for the synthesis of the isoxazolin-5-one-2-yl ring system (4) via a favoured 5-endo-dig cyclisation is described; this methodology has been successfully applied for the first chemical enantio-efficient synthesis of L-β-(isoxazolin-5-one-2-yl)-alanine (3).

We have recently described a general method for the enantiospecific synthesis of β-amino alanine derivatives,[2] as exemplified by a total synthesis of the neuroexcitatory amino acid quisqualic acid (1) from the known β-lactam 2. We now wish to report the first synthesis of L-β-(isoxazolin-5-one-2-yl)-alanine (3), a highly base labile amino acid isolated from the roots of pea seedlings, [3,4] from the same β-lactam precursor 2 and describe a novel method for the construction of the heterocyclic moiety of this amino acid.



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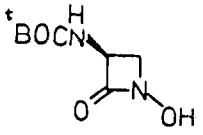

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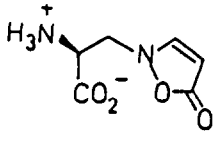

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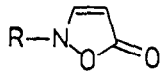
There are few reports concerning the synthesis of N-substituted, 3,4- unsubstituted isoxazolin-5-ones (4). Most satisfactory is the alkylation of the anion 5[5], which gave modest yields (13-50%) of 4 when alkylated with good alkylating agents such as dimethylsulphate (R=Me). However the authors attempts to synthesise 3 via displacement on a β-substituted alanine (6) failed, presumably due to the facility with which such substrates undergo β-elimination to give dehydroalanines (7). Reaction of N-substituted hydroxylamines with propiolic esters or β-ketoesters by refluxing in pyridine has led to 3- or 4-substituted isoxazolin-5-ones,[6] but no report has been made for the 3,4-unsubstituted case. Any potential synthesis of 3 must also be mild, due to the lability of the heterocyclic ring towards dilute alkali or strong acid.[3,6]



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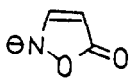

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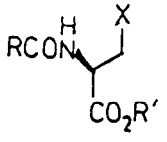

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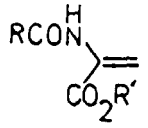

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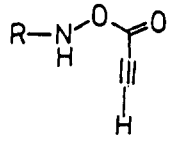
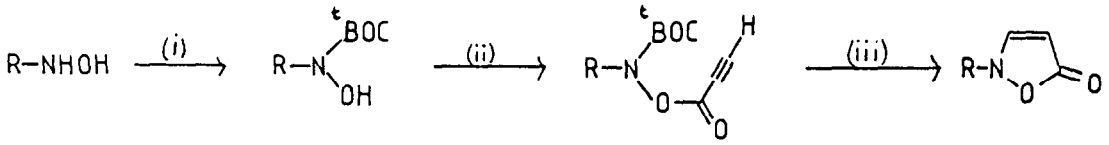


8

A new approach to this system was therefore sought. It was considered that N-substituted, O-propiolated hydroxylamines (8) could furnish isoxazolin-5-ones (4) in a 5-endo-dig manner.[7] To this end, a series of N-substituted hydroxylamines (9 a-d) were treated with di-tert-butylpyrocarbonate (BOC_2O) prior to acylation on oxygen with propiolic acid and dicyclohexylcarbodiimide (DCC), to produce 11 a-d (~70% following chromatography). Treatment of crude or chromatographed 11 a-d with neat formic acid afforded the isoxazolin-5-ones (4) directly in 53-66% overall yield from the hydroxylamines 9 a-d (Scheme 1) (Table 1). All gave characteristic[5] ^1H NMR spectra (5 and 8 p.p.m., d, J 3.5Hz) and showed strong absorption in both the UV (λ_{max} ~ 265 nm, ε ~ 10^4) and IR ($CHCl_3$) ($\nu_{C=O}$ 1730 cm^{-1}) spectrum.



9 a-d 10 a-d 11 a-d 4 a-d

Scheme 1

Reagents and Conditions: (i) BOC_2O/1,4-dioxan/20°/30 mins
(ii) H-C≡C-CO_2H/DCC (1 equiv.)/CH_2Cl_2/20°/12h (iii) HCO_2H/20°C/4h.

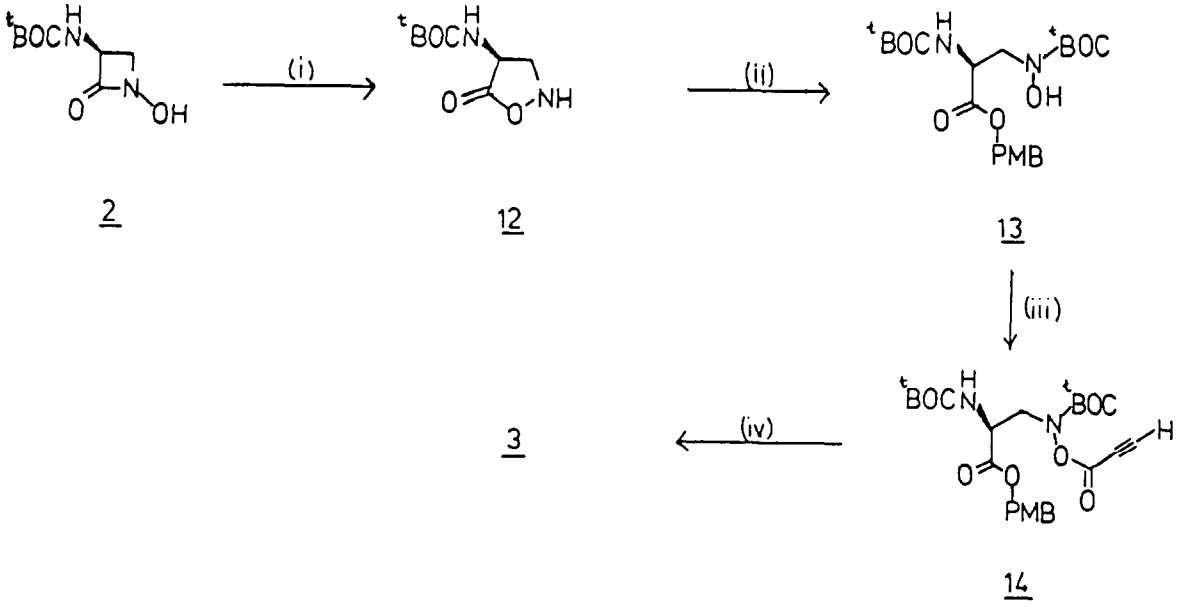
	R	yield 4
a	tert-butyl †	63%
b	cyclopentyl	53%
c	methyl	66%
d	benzyl	57%

Table 1

The utility of this methodology has been exemplified by the synthesis of the amino acid 3. Thus the β-lactam 2[8] was isomerised to the known isoxazolidin-5-one 12[2,9] by treatment with catalytic sodium ethanethiolate (83%). 12 was converted to 13 in one pot by treatment with aqueous caesium carbonate[10], followed by addition of BOC_2O and esterification (after freeze-drying) with p-methoxybenzyl chloride. 13 was obtained in 53% yield from 12 following chromatography. Acylation of 13 with propiolic acid and DCC gave the O-propiolyl-hydroxylamine 14 (77%) which underwent deprotection and spontaneous cyclisation on exposure to neat formic acid to give the amino acid 3.‡ Purification by H.P.L.C. (reverse phase octadecasilane, using 1% formic acid in water as eluant) afforded pure 3 (61% from 14), $[\alpha]^{2}\beta$ -57.5° (C 0.4 in H_2O) [Lit.,[11] -62.7° (C 1.4 in H_2O)]; ν_{max} (KBr disc) 3500-2500 mbr, 1700s, 1630-1590s, and 1530s cm^{-1} (Lit.[3] identical); δ_H (500 MHz, D_2O) 3.98 (1H, t, J 5Hz), 4.19 (2H, d, J 5Hz), 5.15 (1H, d, J 3.5Hz) and 8.11 p.p.m. (1H, d, J 3.5Hz); δ_C (125 MHz, D_2O) 55.0 (t), 55.8 (d), 90.3 (d), 157.1 (d), 173.3 (s) and 177.2 (s) p.p.m.; m/z (positive argon fast atom bombardment) 173 (MH^+, base peak). The synthetic sample thus obtained was identical by ^1H NMR, λ_{max} and m.p. (and mixed m.p.) to an authentic sample of the natural material.[11]

† Synthesised without recourse to initial protection on nitrogen, viz N-t-butylhydroxylamine/ H-C≡C-CO_2H/DCC/CH_2Cl_2/20°C/12 hours, then usual DCC work up.

‡ NMR yield prior to H.P.L.C. ca 81%.



2 12 13 14 3

PMB = p-methoxybenzyl

Scheme 2

Reagents and Conditions: (i) $EtS^{\ominus}Na^{\oplus}$ (2.5 mol %, THF, 20°C, 72h); (ii) (a) Cs_2CO_3 [1 mol equivalent, THF/H_2O (1:1), 20°C, 4h] (b) BOC_2O (1eq, 1 h) then freeze-dry (c) PMB-Cl [1·1 equiv., NaI(cat), DMF, 40°C, 24 h]; (iii) HC≡C-CO_2H (1 equiv.) DCC (1 equiv., CH_2Cl_2, 20°C, 12 h); (iv) HCO_2H (neat, 20°C, 8 h) then water/ether partition and freeze-drying.

References

1. In honour of Professor H. Wasserman on the occasion of his 65th birthday.

2. J. E. Baldwin, R. M. Adlington, and D. J. Birch, J.Chem.Soc.Chem.Commun., 1985, 256.

3. F. Lambein, N. Schamp, L. Vandendriessche, and R. Van Parijs, Biochem.Biophys. Res.Commun., 1969, 37, 375.

4. F. Lambein, Yu Haey Kuo, and R. Van Parijs, Heterocycles, 1976, 4, 567.

5. L. Van Rompuy, N. Schamp, N. De Kimpe, and R. Van Parijs, J.Chem.Soc. Perkin Trans.I., 1973, 2503.

6. F. De Sarlo, L. Fabbrini, and G. Renzi, Tetrahedron, 1966, 22, 2989.

7. J. E. Baldwin, R. C. Thomas, L. I. Kruse, and L. Silberman, J.Org.Chem., 1977, 42, 3846; cf. footnote 13.

8. P. G. Mattingly and M. J. Miller, J.Org.Chem., 1980, 45, 410.

9. T. Hirose, K. Chiba, S. Mishio, J. Nakano, and H. Uno, Heterocycles, 1982, 19, 1019.

10. P. E. Pfeffer and L. S. Silbert, J.Org.Chem., 1976, 41, 1373.

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