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A GENERAL PROCEDURE FOR THE SYNTHESIS OF ISOXAZOLIDIN-5-ONES

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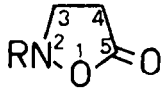
Abstract Conjugate addition of N-substituted hydroxylamines to α,β-unsaturated esters followed by cyclisation of the adducts with lithium bis (trimethylsilyl)amide provides the first general means of synthesising isoxazolidin-5-ones, the N-benzyl derivatives of which may be hydrogenolised to β-aminoacids.

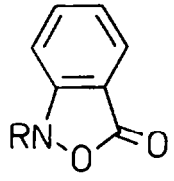
The literature contains few reports of the synthesis of compounds possessing the isoxazolidin-5-one skeleton (1).



(1)

The majority of the examples recorded have been prepared by condensation of ester enolates, or their equivalents, with nitrones.[1] Other methods include the thermal cyclisation of N-methyl O-cinnamylhydroxylamine[2] and also treatment of cinnamate esters with hydroxylamines, when the initial 1,4-adducts undergo concomitant cyclisation.[3] 2,1-Benzisoxazolone (2a) has been prepared by zinc reduction of o-nitrobenzoates[4] and a recent publication[5] has described the synthesis and antibacterial properties of the N-hydroxymethyl derivative (2b).

a R = H
b, R = CH_2OH



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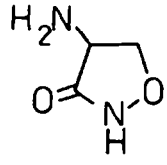
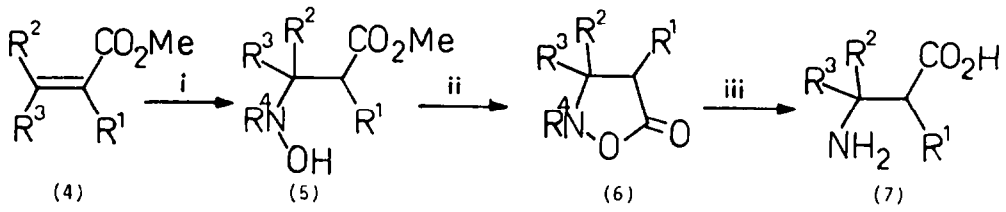


(3)

In view of the potential pharmacological interest in structural analogues of cycloserine[6] (3) we decided to approach the synthesis of a series of isoxazolidin-5-ones, in particular those lacking substituents at C-3 and C-4 which have not been previously reported. The approach which seemed most likely to be successful was the conjugate addition-cyclisation route which had been reported for isolated cases.[3]



Reagents i R^4NHOH; ii Base; iii H_2, Pd/C

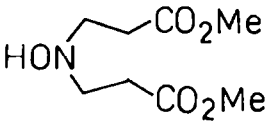
	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
a	H	H	H	$PhCH_2$	i	H	H	H	Ph
b	H	H	H	Me	j	H	H	Me	$PhCH_2$
c	H	H	H	Hexyl	k	Me	H	H	$PhCH_2$
d	H	H	H	iPr	l	H	CO_2Me	H	$PhCH_2$
e	H	H	H	cyclopentyl	m	Me	Me	H	$PhCH_2$
f	H	H	H	cyclohexyl	n	H	H	H	(S)-PhCHMe
g	H	H	H	cyclododecyl	o	Me	H	H	(S)-PhCHMe
h	H	H	H	tBu	p	H	CO_2Me	H	(S)-PhCHMe
					q	H	H	Me	(S)-PhCHMe

Preparation of adducts (5), isoxazolidin-5-ones (6) and β-aminoacids (7)

	Isolated yield %		
Entry	5	6[a]	7
a	84	91	85
b	79[b]	80(0)	
c	75	79(61)	
d	84	83	
e	91	82(63)	
f	91	85	
g	77	76(61)	
h	84	72	
i	66	0[c]	
j	86	86	
k	83	79[g]	95
l	83	61	95
m	-	76[d]	
n	93	60	
o	86	74[e]	87
p	84	72	93
q	93	77	94[f]

[a] Yields in brackets refer to reactions using LDA as base. [b] Hydroxylamine generated *in situ* from the hydrochloride and Et_3N. [c] Phenyl isocyanide obtained in a 20% yield. [d] Prepared by methylation of 5j. [e] Prepared in an alternative manner by methylation of 5n (77% yield). [f] Pure dioxan used as hydrogenation solvent. [g] Prepared in an alternative manner by methylation of 5a (74% yield).

The 1,4-adducts (5) were simply prepared by addition of the appropriate hydroxylamine to a solution of the α,β-unsaturated ester (4) in diethyl ether, or by generation of the hydroxylamine in situ from its hydrochloride with triethylamine. The yields of adducts were uniformly good, (Table) except with 3,3-disubstituted-α,β-unsaturated esters as substrates when no addition was observed. The addition of hydroxylamine to methyl acrylate led to the isolation of the bis-adduct (8) even under the conditions of inverse addition of methyl acrylate to a large excess of hydroxylamine indicating that the initial adduct readily attacks a second equivalent of ester. In no case was spontaneous cyclisation of the adducts (5 a-q) observed, in contrast to

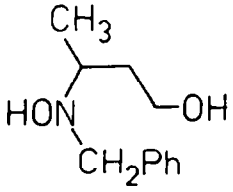


(8)

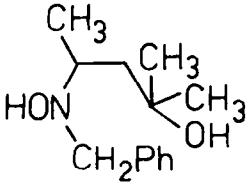
the results reported for the adducts with cinnamate esters.[3]

A wide variety of basic conditions failed to yield isolable quantities of cyclised material although in some instances lithium diisopropylamide was effective. (Table) However lithium bis(trimethylsilyl)amide[7] was found to give high and reproduceable yields of the required isoxazolidinones (6 a-q). It is difficult to rationalise the marked reagent dependence of the cyclisation but the greater efficiency of bis(trimethylsilyl)amide bases compared with others, such as lithium diisopropylamide or potassium tert-butoxide, in promoting sterically hindered condensations[8] and cyclisations[9] has been noted previously. In the case of the N-phenyl adduct (5l) cyclisation was not observed on treatment with base, but a low yield of phenyl isocyanide was obtained.

The isoxazolidin-5-ones typically exhibited carbonyl absorptions at 1760-1775 cm^{-1}. The most notable feature of the N.M.R. spectra of those compounds lacking substitution at C-3 was the very low resolution of the absorptions due to the relatively slow nitrogen inversion at room temperature.[10†] The system behaved in the expected manner with hydride reducing agents and carbon nucleophiles. For example, (6j), gave the alcohol (9) with lithium aluminium hydride and on reaction with excess methyl magnesium iodide furnished the tertiary carbinol (10).



(9)



(10)

The latent acidity of the C-4 methylene group permitted methylation of (6a) and (6j) to produce (6k) and (6m) respectively. The 3,4-dimethyl derivative (6m) was obtained as a 3.5:1.0 mixture of diastereomers as measured by N.M.R. In this instance the additional substitution of the ring inhibits the conformational mobility of the system sufficiently to permit a resolved N.M.R. spectrum to be obtained at room temperature.

Hydrogenolysis of the N-benzylisoxazolidin-5-ones (6a), (6k) and (6l) smoothly furnished the corresponding β-aminoacids (7a,k,l) in excellent yields. β-Aminoacids, although less ubiquitous in living systems than α-aminoacids, nonetheless are widely distributed. (+)-3-Amino-2-methyl propanoic acid has been isolated from human urine[11] and β-aminoacids are

† Details of the variable temperature studies on the dynamic N.M.R. spectra of these compounds will be presented elsewhere.

important building blocks in antibiotics such as blasticidin S[12] as well as some polypeptide antibiotics[13].

With this in mind several enantioselective approaches towards α- and β-substituted β-aminoacids were investigated which used a chiral benzylic nitrogen protecting group in an attempt to control the absolute stereochemistry of the isoxazolidin-5-ones.

In the first instance (S)-1-phenylethylhydroxylamine (11) was added to methyl acrylate and the adduct cyclised to yield (-)(6n). Methylation and hydrogenolysis led to the isolation of (+)-3-amino-2-methylpropanoic acid (+)-(7k) ($[\alpha]_D^{19}$ +1.4°, Lit[14] 14°, 10% ee). In a second approach to (+)-(7k), (S)-(11) was added to methyl methacrylate and the diastereomeric mixture of adducts (5o) cyclised and hydrogenolysed to produce (+)-(7k). ($[\alpha]_D^{19}$ = +2.4°, 16.5% ee). The optical yields of these routes are disappointingly low. In another instance the conditions for cyclisation to the isoxazolidinone permitted an enhancement of the diastereomeric ratio in the final product. Reaction of (11) with dimethyl maleate led to a 1.6:1.0 ratio of diastereomeric 1,4-adducts (5p). However, after cyclisation the ratio of isoxazolidin-5-one diastereomers (6p) was 3.0:1 and this mixture on hydrogenolysis gave (+)-aspartic acid α-methylester (7l) ($[\alpha]_D^{19}$ -10.5°, Lit.[15] 37.5°, 28% ee). Addition of (11) to E-methyl crotonate gave a 2.5:1 mixture of diastereomeric adducts (5q) from which the major diastereomer (5q) could be obtained pure by chromatography in 50% yield. Cyclisation and hydrogenolysis led to the formation of (+)-3-aminobutanoic acid (7j) 72% yield from (+)-(5q) ($[\alpha]_D^{19}$ = +34.2°, Lit.[16] = 38.8°, 88% ee).

The general procedure for the preparation of isoxazolidin-5-ones herein described has thus permitted access to a wide range of previously inaccessible structures. The N-O bond may be hydrogenolysed smoothly and permits the direct synthesis of β-aminoacids. With a chiral nitrogen protecting group some chiral induction is possible, either in the formation of the adducts (5) or in the alkylation subsequent to isoxazolidine formation.

EXPERIMENTAL

I.R. spectra were recorded with a Perkin-Elmer 681 spectrometer either as the neat liquid or in chloroform solution as stated. Mass spectra were obtained using a VG-16F instrument using chemical ionisation (NH_3) or electron ionisation. ^1H N.M.R. spectra were run on a Bruker WH 300 operating at 300 MHz. Chemical shifts (δ) were measured in deuterochloroform except where stated. Peak multiplicities are quoted as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (b). Melting points were taken using a Buchi 510 melting point apparatus and are uncorrected. Optical rotations were recorded using a Perkin-Elmer 281 polarimeter. Microanalyses were carried out by D. F. B. Strauss of the Dyson Perrins Laboratory.

Preparation of 1,4-adducts (5)

Method A: The appropriate hydroxylamine (1.0 eq) was added to a stirred solution of the α,β-unsaturated ester (2.5eq.) in diethyl ether and stirred overnight at room temperature. The solvent was removed in vacuo to give the crude product which was purified by column chromatography (dichloromethane: ether).

Method B: The hydroxylamine hydrochloride (1.0 eq) was added to a stirred solution of triethylamine (2.5 eq) and the α,β-unsaturated ester (2.5 eq) in dichloromethane and stirred overnight at room temperature. The solution was filtered and the solvent removed in vacuo to give the crude product which was purified by column chromatography (dichloromethane: ether).

Preparation of isoxazolidin-5-ones (6): Lithium bis(trimethylsilyl)amide (0.95 eq) was added to a solution of the hydroxylamine adduct (5) (1.0 eq) in dry tetrahydrofuran (THF) at -78°C. The solution was stirred for 1 hr at -78°C, quickly warmed to 0°C and stirred for 15 min at 0°C. Water (2 ml) was added followed by dichloromethane. The solution was dried ($MgSO_4$) and the solvent removed in vacuo to give the crude isoxazolidin-5-one (6) which was purified by column chromatography (dichloromethane: ether). The preparations were performed on 5-50 mmol scale. Attempted purification by distillation invariably led to decomposition of the product.

4-Methylation of isoxazolidin-5-ones: Lithium bis(trimethylsilyl)amide (1.0 eq) was added to a stirred solution of the isoxazolidin-5-one (1.0 eq) in dry THF at -78°C and stirred for 15 min. Methyl iodide (10 eq) was added and the solution allowed to warm upto room temperature over 3 hr. Water (50 ml) was added and the solution extracted with dichloromethane. The extract was dried ($MgSO_4$) and evaporated in vacuo to give the crude product which was purified by column chromatography (dichloromethane: ether).

Hydrogenolysis of 2-benzyl and 2-(S)-α-methylbenzylisoxazolidin-5-ones (6,a,k,l,o,p,q): The isoxazolidin-5-ones (10% solution in aqueous dioxan (10% v/v); 6q pure dioxan was used as solvent) were added to a stirred suspension of 10% Palladium on Carbon in dioxan. The sample was placed in a low pressure hydrogenator and stirred at 60°C for 16 hr (85°C in the case of the α-methyl benzyl isoxazolidinones). The solution was filtered through celite, washing with hot water. The solvents were removed in vacuo to give the crude product which was purified by recrystallisation.

Reduction of isoxazolidin-5-one (6j) with Lithium Aluminium Hydride: 2-Benzyl-3-methyl-isoxazolidin-5-one (6j) (760 mg, 4 mmol) was added to a stirred suspension of Lithium aluminium hydride (1.4g, 40 mmol) and stired for 3 hr at room temperature. Sodium sulphate (10 ml of a saturated aqueous solution) was added dropwise. Dichloromethane (250 ml) was added and the solution dried ($MgSO_4$). The solvent was removed in vacuo to give the hydroxylamine (9) (720 mg, 95%) as a white solid, (m.p. 75-6°C), (from light petroleum (b.p. 40-60°C), (Found: C, 67.90; H, 8.61; N, 6.90: $C_{11}H_{17}NO_2$ requires C, 67.65; H, 8.78; N, 7.15%), ν($CHCl_3$) 3 580, 3 250, 3 010, 1 600 cm^{-1}, δ($CDCl_3$) 7.35(5H, m), 3.9(2H, AB quartet), 3.6(2H, m), 3.1(1H, m), 1.9(2H, m), 1.15(3H, d J 7Hz), m/e NH_3 C.I. 196(100%), 150(30%), 91(60%).

2-Methyl-4-(N-benzyl-N-hydroxy)aminopentan-2-ol(10). - 2-Benzyl-3-methylioxazolidin-5-one (6j) (1.9 g, 10 mmol) was added to a stirred solution of Methyl magnesium iodide (16.4 g, 100 mmol) in dry THF (150 ml), and stirred for 1 hr at room temperature. Water (50 ml) was added and the solution extracted with ethyl acetate. The extract was dried ($MgSO_4$) and the solvent removed in vacuo to give the product (10) (780 mg, 35%) as a white solid, m.p. 99-101°C (from light petroleum (b.p 40-60°C)), (Found:C, 69.50; H, 9.39; N, 6.30; $C_{13}H_{21}NO_2$ requires C, 69.90; H, 9.48; N, 6.25%), ν($CHCl_3$) 3 560, 3 250, 2 980, 1 610 cm^{-1}, δ($CDCl_3$) 7.35(5H, m), 4.0(2H, AB quartet), 3.9(1H, m), 3.25(2H, b), 1.95(2H, m), 1.1(3H,s J 7Hz), 1.0(6H,s), m/e C.I. (NH_3), 224(100%), 205(20%), 91(35%).

NN-(Bis-(2-carbomethoxyethyl)hydroxylamine (8). - Hydroxylamine hydrochloride (2.0 g, 30 mmol) was added to a solution of triethylamine (7.5 g, 75 mmol) and methyl acrylate (6.5 g, 75 mmol) in dichloromethane (200 mls) and stirred overnight at room temperature. The solution was then filtered and the solvent removed in vacuo to give the crude hydroxylamine (4.55 g, 75%) as an oil which was purified by column chromatography (dichloromethane: ether) (Found: C, 47.25; H, 7.47; N, 7.00 $C_8H_{15}NO_5$ requires C, 46.80; H, 7.37; N, 6.85 %), ν(film) 3 460, 2 960, 1 730, 1 200 cm^{-1}, δ($CDCl_3$) 3.7(6H, s) 3.0(4H, t J 7Hz), 2.6(4H, t J 7Hz) m/e E.I. 206(1%), 173(6%), 55(10%).

Methyl 3-(N-benzyl-N-hydroxy)aminopropanoate (5a). - Yield 84%, (Method A), mp. 55-7°C (from light petroleum (b.p. 40-60°C)) (Found: C, 62.90; H, 7.19; N, 6.50: $C_{11}H_{15}NO_3$ requires C, 63.15; H, 7.23; N, 6.50 %), ν($CHCl_3$) 3 580, 1 725 cm^{-1}, δ($CDCl_3$), 7.3(5H, m), 4.10(2H, s), 3.8(3H, s), 3.0(2H, t J 7Hz), 2.6(2H, t J 7Hz), m/e E.I. 209(3%), 192(2%), 177(10%), 91(100%).

Methyl 3-(N-hydroxy-N-methyl)aminopropanoate (5b). - Yield 79%, (Method B), (Found: C, 45.40; H, 7.96; N, 10.30: $C_5H_{11}NO_3$ requires C, 45.10; H, 8.33; N, 10.50 %), ν(film) 3 440, 1 725 cm^{-1}, δ($CDCl_3$), 3.6(3H, s), 2.9(2H, t J 7Hz), 2.6(3H, s), 2.55(2H, t J 7Hz), m/e E.I. 101(70%), 87(70%), 60(100%).

Methyl 3-(N-hexyl-N-hydroxy)aminopropanoate (5c). - Yield 75%, (Method A), mp. 42-4°C from light petroleum, (Found: C, 59.20; H, 10.45; N, 6.85: $C_{10}H_{21}NO_3$ requires C, 59.10; H, 10.41; N, 6.90 %), ν($CHCl_3$) 3 430, 3 280, 2 950, 1 730 cm^{-1}, δ ($CDCl_3$), 4.5(1H, b), 3.7(3H, s), 2.95(2H, t J 7Hz), 2.9(2H, t J 7Hz), 2.6(2H, J 7Hz), 1.6-1.25(8H, m), 0.9(3H, t J 7Hz), m/e E.I. 203(21%), 186(2%), 171(10%), 100(100%).

Methyl 3-(N-hydroxy-N-isopropyl)aminopropanoate (5d). - Yield 84%, (Method A), ν(film) 3 425, 1 720 cm^{-1}, δ($CDCl_3$), 3.7(3H, s), 2.9(2H, t J 7Hz), 2.85(1H, m), 2.6(2H, t J 7Hz), 1.5(6H d J 7Hz), m/e C.I.(NH_3) 162(100%), 130(25%). Acc. mass, found: 161.105: $C_7H_{15}NO_3$ requires 161.105.

Methyl 3-(N-cyclopentyl-N-hydroxy)aminopropanoate (5e). - Yield 91%, (Method A), (Found: C, 57.50; H, 8.99; N, 7.45; $C_9H_{17}NO_3$ requires C, 57.75; H, 9.15; N, 7.50 %), ν(film) 3 440, 3 230, 2 975, 2 860, 1 720 cm^{-1}, δ ($CDCl_3$), 6.2(1H, b), 3.7(3H, s), 3.00(2H, t J 7Hz), 2.9(1H, m), 2.6(2H, t J 7Hz), 1.6-1.5(8H, m), m/e E.I. 187(10%), 170(5%), 155(25%), 97(100%).

Methyl 3-(N-cyclohexyl-N-hydroxy)aminopropanoate (5f). Yield 91% (Method A) (Found: C, 60.00; H, 9.31; N, 7.20; $C_{10}H_{19}NO_3$ requires C, 59.70; H, 9.52; N, 6.95 %), ν(film) 3 450, 3 275, 2 940, 2 860, 1 730 cm^{-1}, δ ($CDCl_3$) 3.65(3H, s), 3.0(2H, t J 7Hz), 2.6(2H, t J 7Hz), 2.55(1H, m), 2.0-1.1(10H, m), m/e E.I. 201(30%), 184(10%), 169(55%), 87(100%), 83(70%).

Methyl 3-(N-cyclododecyl-N-hydroxy)aminopropanoate (5g). Yield 77% (Method A), m.p. 64-7°C (from methanol), (Found: C, 67.25; H, 10.79; N, 4.80: $C_{16}H_{31}NO_3$ requires C, 67.35; H, 10.95; N, 4.80 %), ν($CHCl_3$) 3 585, 2 940, 1 720 cm^{-1}, δ ($CDCl_3$) 4.95(1H, b), 3.7(3H, s), 3.0(2H, t J 7Hz), 2.7(1H, m), 2.6(2H, t J 7Hz), 1.65-1.3(22H, m), m/e E.I. 285(15%), 268(12%), 254(10%), 158(100%).

Methyl 3-(N-tert butyl-N-hydroxy)aminopropanoate (5h). Yield 84% (Method A), (Found: C, 54.60; H, 9.63; N, 7.85: $C_8H_{17}NO_3$ requires C, 54.85; H, 9.78; N, 8.00 %), ν(film) 3 580, 3 010, 2 980, 1725 cm^{-1}, δ($CDCl_3$) 6.5(1H, b), 3.67(3H, s), 3.00(2H, t J 7Hz), 2.65(2H, t J 7Hz), 1.10(9H, s), m/e E.I. 175(5%), 160(10%), 97(60%), 57(100%).

Methyl 3-(N-hydroxy-N-phenyl)aminopropanoate (5i). Yield 66% (Method A), (Found: C, 61.65; H, 6.52; N, 7.25: $C_{10}H_{13}NO_3$ requires C, 61.55; H, 6.71; N, 7.15 %), ν(film) 3 410, 1 730, 1 600 cm^{-1}, δ($CDCl_3$) 7.4-7.1(5H, m), 3.8(3H, s), 3.6(2H, t J 7Hz), 2.8(2H, t J 7Hz), m/e E.I. 195(40%), 163(60%), 77(50%), 55(100%).

Methyl 3-(N-benzyl-N-hydroxy)aminobutanoate (5j). Yield 86% (Method A), (Found: C, 64.50; H, 7.49; N, 6.10: $C_{12}H_{17}NO_3$ requires C, 64.55; H, 7.67; N, 6.25 %), ν(film) 3 440, 1 735 cm^{-1}, δ ($CDCl_3$) 7.3(5H, m), 3.75(2H, AB quartet), 3.7(3H, s), 3.2(1H, m), 2.6(1H, dd), 2.4(1H, dd), 1.15(3H, d J 7Hz), m/e E.I. 223(1%), 191(9%), 91(100%).

Methyl 2-methyl 3-(N-benzyl-N-hydroxy)aminopropanoate (5k). Yield 83% (Method A except stirred for 72 hr at room temperature), (Found: C, 64.95; H, 7.55; N, 6.49: $C_{12}H_{17}NO_3$ requires C, 64.55; H, 7.67; N, 6.25%), ν($CHCl_3$) 3 430, 2 960, 1 730 cm^{-1}, δ ($CDCl_3$) 7.3(5H, m), 6.5(1H, b), 3.9(2H, AB quartet), 3.7(3H, s), (3.0(1H, dd), 2.9(1H, dd), 1.2(3H, t J 7Hz), m/e E.I. 191(10%), 91(100

Dimethyl 3-(N-benzyl-N-hydroxy)aminobutandioate (5l). Yield 83% (Method A) as a white solid, mp.59-61°C (from light petroleum (b.p.40-60°C)), (Found: C, 58.40; H, 6.33; N, 5.30: $C_{13}H_{17}NO_3$ requires C, 58.40; H, 6.41; N, 5.25 %), ν(film) 3 460, 2 960, 1 735 cm^{-1}, δ($CDCl_3$) 7.3(5H, m), 6.1(1H, b), 4.05(2H, AB quartet), 4.0(1H, m), 3.8(2H, s), 3.65(3H, s), 2.9(2H, m), m/e E.I. 267(10%), 208(20%), 91(100%).

Methyl 3-[N-hydroxy-N-(S)-(1-phenylethyl)]aminopropanoate (5n). Yield 93% (Method A), (Found: C, 64.50; H, 7.61; N, 6.20: $C_{12}H_{17}NO_3$ requires C, 64.55; H, 7.67; N, 6.25 %), ν($CHCl_3$) 3 580, 1 730 cm^{-1}, δ($CDCl_3$) 7.3(5H, m), 3.8(1H, q J 7Hz), 3.65(3H, s), 2.9(2H, t K 7Hz), 2.6(2H, t J 7Hz), 1.45(3H, d J 7Hz), $[\alpha]_D^{19}$ (C=1.0) -19.5°C, m/e C.I. (NH_3), 224(100%), 208(30%), 192(15%), 105(10%).

Methyl 2-methyl 3-[N-hydroxy-N-(S)-(1-phenylethyl)]aminopropanoate (5o). Prepared by a method similar to the general procedure except that it was stirred for 72 hr. Yield 86% (Method A), (Found: C, 65.85; H, 7.88; N, 6.10: $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90 %), ν ($CHCl_3$) 3 580, 2990, 1730 cm^{-1}, δ ($CDCl_3$) 7.3(5H, m), 5.30(1H, b), 3.85(1H, q J 7Hz), 3.7(3H, s), 2.9(2H, m), 2.6(1H, m), 1.4(3H, d J 7Hz), 1.1(3H, d J 7Hz), 1.1(3H, d J 7Hz) major diastereomer, m/e E.I., 237(3%), 206(3%), 105(100%).

Dimethyl 3-[N-hydroxy N-(S)-(1-phenylethyl)]aminobutanedioate (5p). Yield 84% (Method A), m.p. 64-5°C (from light petroleum (b.p. 40-60°C)), (Found: C, 59.60; H, 6.57, N, 5.20: $C_{14}H_{19}NO_5$ requires C, 59.75; H, 6.81; N, 5.00 %), ν($CHCl_3$) 3 480, 1 725 cm^{-1}, δ($CDCl_3$) 7.3(5H, m), 5.2(1H, b), 4.2(1H, q J 7Hz), 3.8(1H, m), 3.75(3H, s), 3.7(3H, s), 2.9(1H, m), 1.4(3H, d J 7Hz), m/e E.I. 105(100%).

Methyl-3[N-hydroxy-N-(S)-(1-phenylethyl)]aminobutanoate (5q). - Yield 93%, (Method A), ν ($CHCl_3$) 3 575, 3 420, 2 980, 1 725, 1 600 cm^{-1}, δ($CDCl_3$) 7.3(5H, m), 4.95(1H, b), 4.0(1H, q J 7Hz), 3.7(3H, s), 3.5(1H, m), 2.7(1H, m), 2.5(1H, m), 1.3(3H, d J 7Hz), 1.1(3H, d J 7Hz), m/e E.I 238 (60%), 206(60%), 105(100%), Acc. mass; found: 237.137: $C_{13}H_{19}NO_3$ requires 237.137.

N-Benzylisoxazolidin-5-one (6a). - Yield 91%, (Found: C, 67.65; H, 6.18; N, 7.90: $C_{10}H_{11}NO_2$ requires C, 67.80; H, 6.26; N, 7.90 %), ν(film) 3 010, 2 925, 1 765 cm^{-1}, δ(toluene d_8, 105°C) 7.15(5H, m), 3.72(2H, s), 2.6(2H, t J 7Hz), 2.1(2H, t J 7Hz), m/e E.I 177(30%), 91(100%).

N-Methylisoxazolidin-5-one (6b). - Yield 80%, (Found: C, 47.20; H, 6.86; N, 13.55: $C_4H_7NO_2$ requires C, 47.50; H, 6.98; N, 13.85 %), ν(film) 1 760 cm^{-1}, δ(toluene d_8, -80°C) 2.4(1H, ddd), 2.15(3H, s), 1.95(1H, ddd), 1.70(1H, ddd), 1.5(1H, ddd), m/e E.I 101(50%), 55(100%), 42(45%).

N-Hexylisoxazolidin-5-one (6c). - Yield 79%, (Found: C, 63.55; H, 10.35; N, 7.95: $C_9H_{17}NO_2$ requires C, 63.15; H, 10.00; N, 8.20 %), ν(film) 2 960, 1 760 cm^{-1}, δ(toluene d_8, 105°C) 2.6(2H, t J 7Hz), 2.5(2H, t J 7Hz), 2.1(2H, t J 7Hz), 1.5-1.1(8H, m), 0.8(3H, t J 7Hz), m/e E.I 171(15%), 100(100%), 55(65%).

N-Isopropylisoxazolidin-5-one (6d). - Yield 83%, (Found: C, 55.70; H, 8.44; N, 10.55: $C_6H_{11}NO_2$ requires C, 55.80; H, 8.58; N, 10.85 %), ν(film) 2 950, 1 765 cm^{-1}, δ($CDCl_3$) 3.7(1H, b), 3.1-2.5(4H, m), 1.1(6H, d), m/e E.I 129(10%), 114(40%), 55(100%).

N-Cyclopentylisoxazolidin-5-one (6e). - Yield 82%, ν(film) 2 950, 2 880, 1 765 cm^{-1}, δ (toluene d_8, 105°C) 2.9(1H, m), 2.8(2H, t J 7Hz), 2.2(2H, t J 7Hz), 1.7-1.3(8H, m), m/e E.I 155(25%), 87(75%), 69(50%), 55(100%), Acc. mass; found 155.095: $C_8H_{13}NO_2$ requires 155.095.

N-Cyclohexylisoxazolidin-5-one (6f). - Yield 85%, (Found: C, 63.75; H, 8.79; N, 8.25: $C_9H_{15}NO_2$ requires C, 63.85; H, 8.93; N, 8.25 %), ν (film) 2 940, 2 860, 1 765 cm^{-1}, δ(toluene d_8, 105°C) 2.8(2H, t J 7Hz), 2.4(1H, m), 2.2(2H, t J 7Hz), 1.5-1.0(10H, m), m/e E.I 169(35%), 126(55%), 86(60%), 55(100%).

N-Cyclododecylisoxazolidin-5-one (6g).- Yield 76%, ν(film) 2 930, 2 850, 1 760 cm^{-1}, δ (toluene d_8, 105°C) 2.75(2H, t J 7Hz), 2.65(1H, m), 2.2(2H, t J 7Hz), 1.5-0.9(22H, m), m/e E.I 253 (30%), 126(100%), 97(90%),83(85%), 69(75%), 55(85%), Acc.mass; Found: 253.204: $C_{15}H_{27}NO_2$ requires 253.204.

N-tert-butylisoxazolidin-5-one (6h). - Yield 72%, (Found: C, 58.70; H, 9.20; N, 9.90: $C_7H_{13}NO_2$ requires C, 58.70; H, 9.15; N, 9.75 %), ν(film) 2 960, 1 760 cm^{-1}, δ($CDCl_3$) 3.2(2H, b), 2.8(2H, b), 1.09(9H, s), m/e E.I 143(50%), 128(15%), 57(100%).

N-Benzyl-3-methylisoxazolidin-5-one (6j). - Yield 86%, m.p. 64-5°C (from diethyl ether), (Found: C, 69.05; H, 6.71; N, 7.05: $C_{11}H_{13}NO_2$ requires C, 69.10; H, 6.85; N, 7.30 %), ν ($CHCl_3$) 2 980, 1 760 cm^{-1}, δ($CDCl_3$) 7.3(5H, m), 4.1(2H, AB quartet), 3.45(1H, b), 2.8(1H, dd), 2.6(1H, dd), 1.3(3H, d J 6.5Hz), m/e E.I 191(15%), 91(100%).

2-Benzyl-4-methylisoxazolidin-5-one (6k). - Yield 79%, from Methyl-2-methyl-3-(N-hydroxy-N-benzyl)aminopropanoate. Yield 74% from 2-benzylisoxasolidin-5-one. (Found: C, 69.15; H, 6.73; N, 7.10: $C_{11}H_{13}NO_2$ requires C, 69.10; H, 6.85; N, 7.30 %), ν($CHCl_3$) 3 010, 1 770, 1 600 cm^{-1}, δ ($CDCl_3$) 7.4(5H, m), 4.1(2H, AB quartet), 3.8-2.8(3H, b), 1.3(3H, d), m/e E.I 191(15%), 91(100%).

2-Benzyl-3-carbomethoxyisoxazolidin-5-one (6l). - Prepared according to the general method except it was only stirred for 45 min at -78°C and then quenched. Yield 61%, m.p. 43-5°C (from diethyl ether), (Found: C, 61.25; H, 5.57; N, 5.95: $C_{12}H_{13}NO_4$ requires C, 61.25; H, 5.57; N, 5.95 %), ν(film) 2 950, 1 775, 1 730 cm^{-1}, δ($CDCl_3$) 7.4(5H, m), 4.35(2H, AB quartet), 4.1(1H, m), 3.75(3H, s), 3.0(2H, m), m/e E.I 235(20%), 176(15%), 91(100%).

2-Benzyl-3,4-dimethylisoxazolidin-5-one (6m). - Yield 76% as a 3:1 mixture of diastereomer, (Found: C, 70.30; H, 7.19; N, 6.95: $C_{12}H_{15}NO_2$ requires C, 70.20; H, 7.37; N, 6.80 %), ν(film) 2 973, 1 765 cm^{-1}, δ($CDCl_3$) 7.4(5H, m), 4.1(2H, AB quartet), 3.6(1H, b), 2.9(1H, b), 1.25(3H, d J 7Hz), 1,2(3H, d J 7Hz), m/e E.I 205(5%), 91(100%), 65(20%).

N-((S)-1-phenylethyl)isoxazolidin-5-one (6n). - Yield 60%. (Found: C, 69.20; H, 6.70; N, 7.00: $C_{11}H_{13}NO_2$ requires C, 69.10; H, 6.85; N, 7.30 %), ν($CHCl_3$) 3 010, 2 990, 1 770 cm^{-1}, δ ($CDCl_3$) 7.3(5H, m), 3.95(1H, b), 3.3-2.5(4H, b), 1.3(3H, b), $[\alpha]_D^{19}$ (C=1.0)($CHCl_3$) -13.5°C, m/e E.I 191(5%), 105(100%).

4 Methyl-N-(S)-1-phenylethylisoxazolidin-5-one (6o). - 74% yield from methyl 2-methyl-3-[N-hydroxy-N-(S)-(1-phenylethyl]aminopropanoate. 77% yield from N-(S)-phenylethyl-isoxazolidin-5-one. Both methods gave a 55:45 mixture of diastereomers. (Found: C, 69.85; H, 7.25; N, 6.80: $C_{12}H_{15}NO_2$ requires C, 70.20; H, 7.37; N, 6.80 %), ν ($CHCl_3$) 2 995, 1 770 cm^{-1}, δ ($CDCl_3$) 7.35(5H, m), 3.9(1H, b), 3.3-2.5(3H, b), 1.6-1.2(6H, b), m/e E.I 205(20%), 105(100%).

3-Carbomethoxy-N-(S)-(phenylethyl)isoxazolidin-5-one (6p). - 72% yield, (Found: C, 62.60; H, 5.83; N, 5.45: $C_{13}H_{15}NO_4$ requires C, 62.65; H, 6.07; N, 5.60 %), ν($CHCl_3$) 1 770, 1 725 cm^{-1}, δ ($CDCl_3$) 7.35(5H, m), 4.1(1H, q J 7Hz), 4.0(1H, m), 3.5(3H, s), 2.9(2H, m), 1.6(3H, d J 7Hz), m/e C.I (NH_3) 250(100%).

3-Methyl-N-(S)-(1-phenylethyl)isoxazolidin-5-one (6q). - 77% yield, (Found: C, 69.90; H, 7.49; N, 6.90: $C_{12}H_{15}NO_2$ requires C, 70.20; H, 7.37; N, 6.80 %), ν($CHCl_3$) 3 015, 2 990, 1 780 cm^{-1}, δ($CDCl_3$) 7.35(5H, m), 4.0(1H, q J 7Hz), 3.5(1H, m), 2.9(1H, dd), 2.4(1H, dd), 1.55(3H, d J 7Hz), 1.0(3H, d K 7Hz) major diastereomer, m/e E.I 205(3%), 105(100%).

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