Allenes. Part 42.[1] Nucleophilic Addition of Hydroxylamine to Allenic and Acetylenic Nitriles; Synthesis of 3-Alkyl-5-amino, 5-Amino-3-phenyl-, and 3-Amino-5-phenyl-isoxazoles

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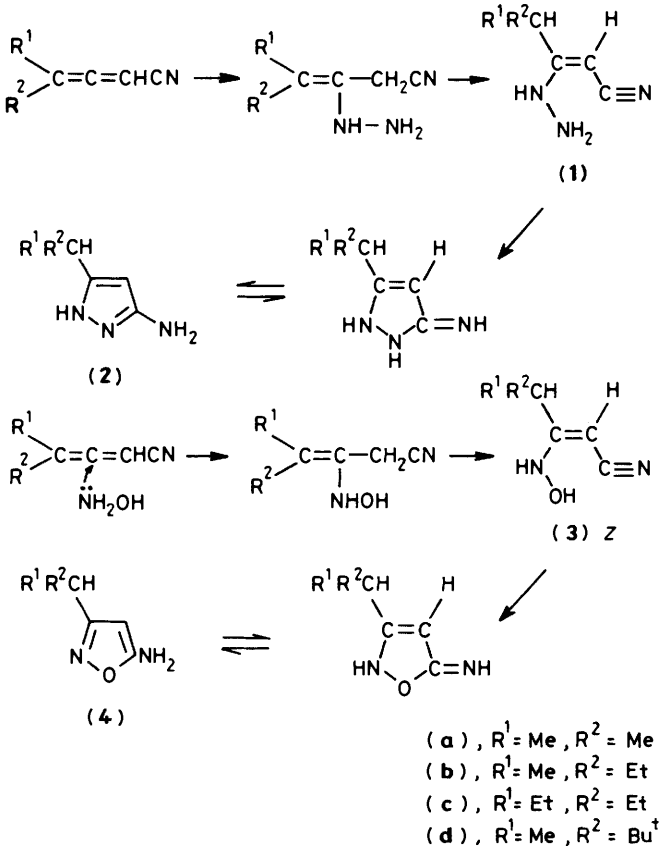
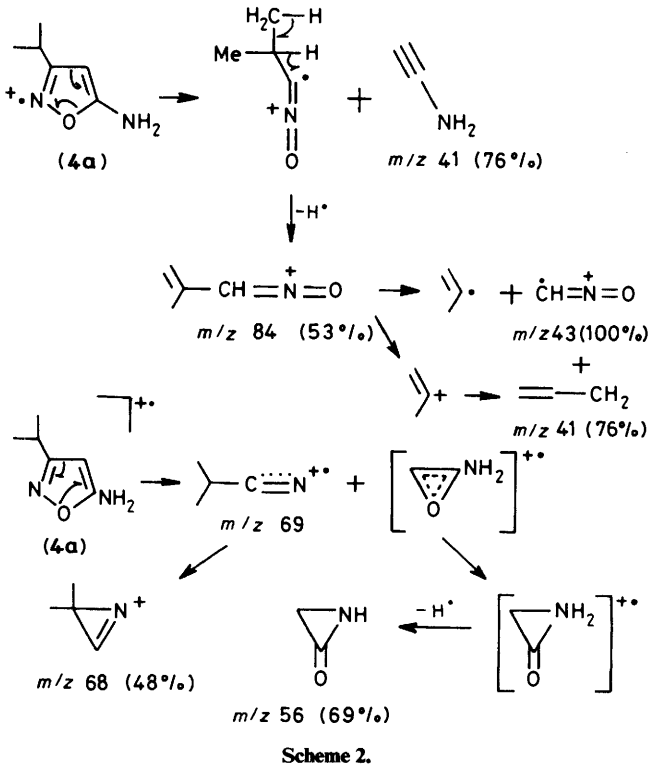
Hydroxylamine adds to allenic nitriles to give 3-alkyl-5-aminoisoxazoles in excellent yield. Hydroxyacetylenic nitriles similarly give 5-amino-3-(1-hydroxyalkyl)isoxazoles. Phenylpropynenitrile under varying conditions of temperature and solvent yields mainly 5-amino-3-phenylisoxazole with varying amounts of 3-amino-5-phenylisoxazole as a by-product.

Amines have been shown to add to allenic nitriles to give enaminic nitriles.[2] If a 1,2-dinucleophile like hydrazine or a substituted hydrazine is used in the reaction, the initially formed Michael adduct (**1**) undergoes 5-*Exo-Dig*[3] ring closure by nucleophilic attack of the second amino group at the carbon of the nitrile to give 3-alkyl-5-amino-2*H*-pyrazoles (**2**) (Scheme 1).[4] Using hydroxylamine, the parallel ring-closure step involving the weakly nucleophilic hydroxy group nevertheless proceeds smoothly and attack at the carbon of the nitrile of the conjugated adduct (**3**) gives 3-alkyl-5-aminoisoxazoles (**4**) after 24 h reflux in tetrahydrofuran (THF) in 88—92% yield.[5] The yields are slightly lower in refluxing methanol or ethanol as solvent. Only the *Z* form can undergo ring closure but, although *E* forms predominate with adducts formed from primary amino groups,[2] we have previously postulated[4] that *E* and *Z* forms of enaminic nitriles are readily interconvertible under the reaction conditions used and that yields of 90% and over are thus obtainable.



Scheme 1.

The u.v. spectra of these 3-alkyl-5-amino-2*H*-isoxazoles [$\lambda_{max.}$(EtOH) 242—243 nm, ε 10 000—12 000] are in good agreement with the u.v. spectrum of 3-methyl-5-aminoisoxazole described by Boulton and Katritzky[6] [$\lambda_{max.}$(H_2O) 239 nm, ε 9 200]. Only one product is obtained in each case as shown by the n.m.r. spectrum of the crude material,† and the isomeric 3-amino-5-alkylisoxazoles, which would be expected to absorb at



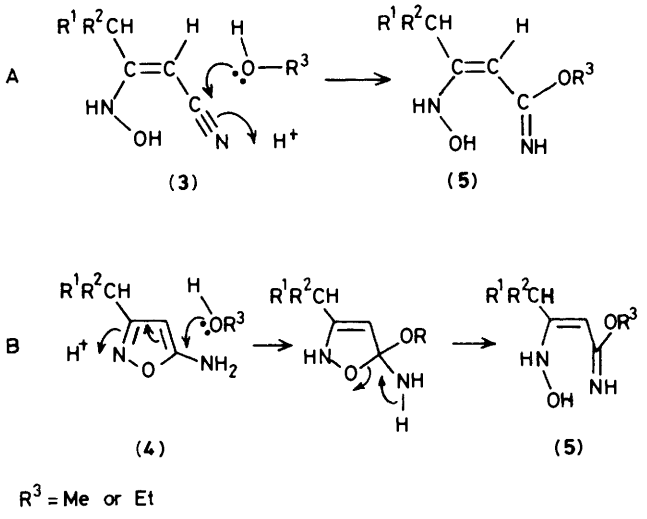
Scheme 2.

† The only exception was 5-amino-3-(1,2,2-trimethylpropyl)isoxazole (**4d**) where the n.m.r. spectrum indicated that a small quantity (<10%) of isomeric 3-amino-5-(1,2,2-trimethylpropyl)isoxazole was present but which was lost during work-up. Steric hindrance to Michael attack is likely to lead to some reaction at the carbon of the nitrile; *cf.* hydrolysis of allenic nitriles (P. M. Greaves, P. D. Landor, S. R. Landor, and O. O. Odyek, *Tetrahedron*, 1974, **30**, 1427, and unpublished work).

much shorter wavelengths in the u.v. [3-amino-5-methylisoxazole: $\lambda_{max.}(H_2O)$ 209 nm, ε 6 820 [6]] were not detected.

The mass spectra of 3-alkyl-5-aminoisoxazoles show weak molecular ions which is unusual for heterocycles; *e.g.* 5-amino-3-isopropylisoxazole (**4a**) gives the molecular ion M^+, 126 (29%) which readily fragments as shown in Scheme 2.

Hydroxylamine was usually generated *in situ* from hydroxylamine hydrochloride by means of two equivalents of sodium carbonate. However, if only one equivalent of sodium carbonate was added to the reaction mixture in methanol or ethanol, approximately 20% of the corresponding imino ester (**5**; R^3 = Me or Et) was obtained as a by-product together with the isoxazole (68%). Two alternative mechanistic pathways may be envisaged for the formulation of imino esters as shown in Scheme 3.

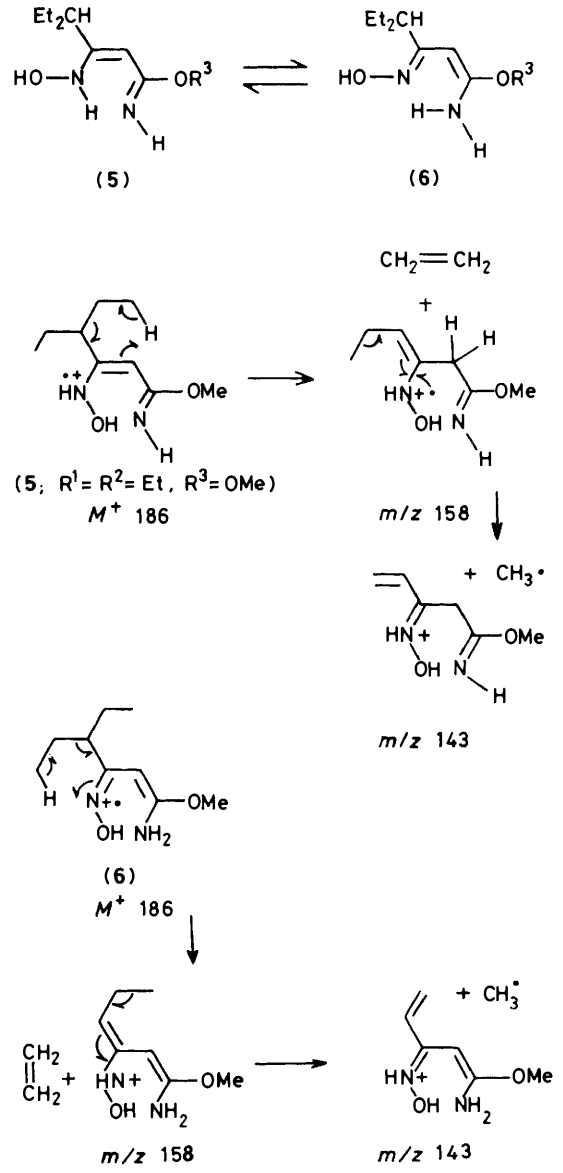


Scheme 3.

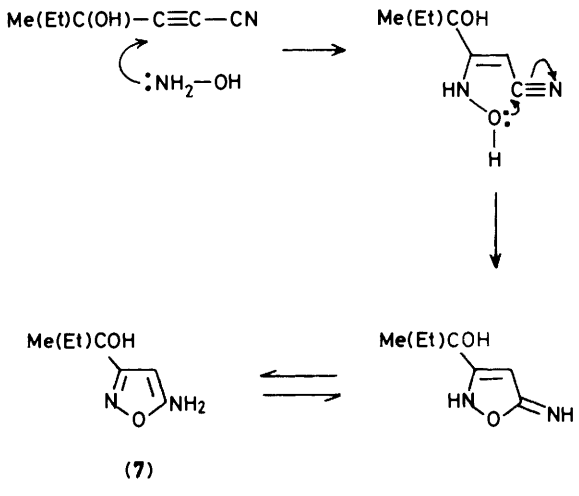
Alternative pathways. A The enaminic nitrile (**3**) in the presence of a trace of acid adds the alcohol at the carbon of the nitrile to give the imino ester (**5**). B The isoxazole (**4**) in the presence of a trace of acid nucleophilically adds the alcohol at C-5, followed by ring fission to give the imino ester (**5**).

However, the isoxazole (**4**), under comparable conditions, does *not* add alcohols and we therefore believe the reaction proceeds by path A. Both *E* and *Z* forms of the imino ester (**5**) could be formed by path A and, by equilibration under reflux, *via* path B, but the hydrogen-bonded *Z* form shown in Scheme 3 is more stable and probably preferred. Furthermore, analysis of the i.r. and n.m.r. spectra suggests that we may have a mixture of tautomers consisting of imino ester (**5**) and alkoxy enamine (**6**) as shown by non-integral, broad signals for exchangable protons at τ 5.20—4.70 and 3.30—2.60 for (**5**; $R^1 = R^2$ = Et, R^3 = Me). Mass spectra do not distinguish between tautomers as a McLafferty rearrangement $M^+(186) - 28$ gives the base peak at *m/z* 158 with a metastable ion at *m/z* 134.2 and loss of a methyl radical gives an ion *m/z* 143 with a metastable peak at *m/z* 129.4 which can be explained by fission of either (**5**) or (**6**) (R^3 = Me) (Scheme 4).

The addition of hydroxylamine to an acetylenic nitrile with a functionalised side-chain gave the corresponding 3-alkyl-5-aminoisoxazole (**7**) ($\lambda_{max.}$ 244 nm, ε 8 300) in 85% yield, suggesting that acetylenic nitriles also add the amino group in the Michael position and ring close by nucleophilic attack of the oxygen onto the carbon of the nitrile (Scheme 5). However, phenylpropynenitrile and hydroxylamine under reflux in ethanol gave a mixture of two products in the ratio 76:24 as



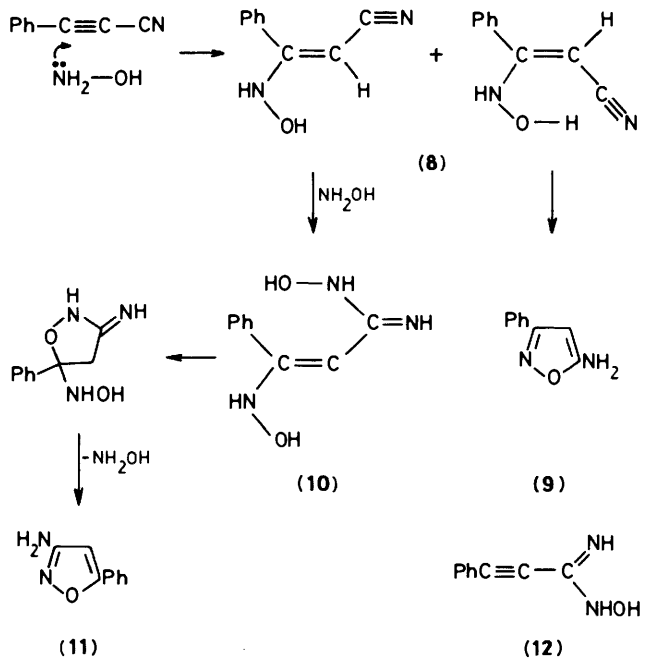
Scheme 4.



Scheme 5.

shown by n.m.r. spectroscopy. Separation by chromatography on alumina gave 5-amino-3-phenylisoxazole (**9**) (65%) and 3-amino-5-phenylisoxazole (**11**) (18.5%). Previously, Lopez and Barrans[7] had obtained three products from a similar reaction of phenylpropynenitrile at room temperature, *viz.* the two isoxazoles (**9**) and (**11**) and a low melting compound described as 'phenylpropiol-amidoxime' (**12**).* We have not been able to isolate any product corresponding to the *N*-hydroxyamidine (**12**) under the French workers' conditions and a series of modified conditions, the only products isolated being the 5-amino-3-phenylisoxazole (**9**) always as the main product, together with varying amounts of 3-amino-5-phenylisoxazole (**11**). Lopez and Barrans extracted their crude product in diethyl ether with dilute hydrochloric acid leaving most, but not all, of the less basic, major component, isoxazole (9), in the ethereal solution. On basification of the acid solution a low melting mixture of isoxazoles (**9**) and (**11**) must have been obtained and erroneously believed to be compound (**12**) which, on vacuum sublimation, gave the minor product (**11**) in pure form.

A plausible mechanistic scheme is shown in Scheme 6. Michael addition of the amino group in hydroxylamine to the phenylpropynenitrile gives *E*- and *Z*-enaminic nitrile (**8**), the *Z* form of which undergoes ring closure to give the major product 5-amino-3-phenylisoxazole (**9**). The *E* form either isomerises to the *Z* form which ring closes to give (**9**) or adds a second mole of hydroxylamine at the carbon of the nitrile. The bis-adduct (**10**) then ring closes with elimination of hydroxylamine to give the minor product 3-amino-5-phenylisoxazole (**11**). The ratio of



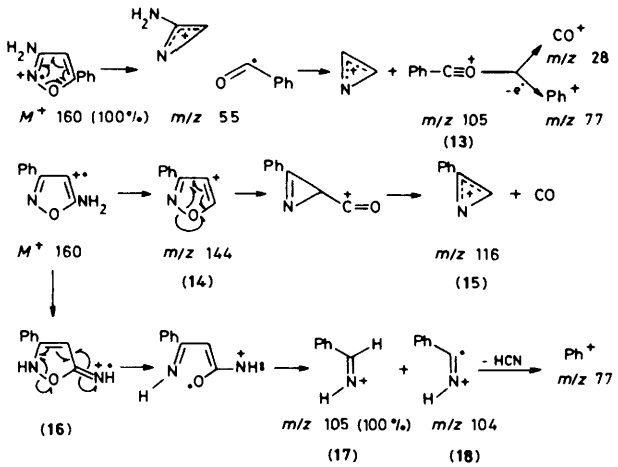
Scheme 6.

isoxazoles (**9**):(**11**) varies with temperature and solvent as does the ratio of *E* and *Z* isomers of the enaminic nitriles.[8] An alternative mechanism involves addition of hydroxylamine to the carbon of the nitrile to give *N*-hydroxyamidine (**12**) which then ring closes at C-3 of the propyne. However, as all previous examples[4] of the addition of substituted amines to propynenitrile always resulted in Michael addition at C-3 and never addition to the carbon of the nitrile this route seems less likely.

* *N*-Hydroxyphenylpropiolamidine.

The u.v. absorption pattern of the two isomeric amino-(phenyl)isoxazoles is opposite to that of corresponding alkyl(amino)isoxazoles with 5-amino-3-phenylisoxazole absorbing at shorter wavelengths ($\lambda_{max.}$ 233 nm) than 3-amino-5-phenylisoxazole ($\lambda_{max.}$ 260 nm) but this may readily be explained by the more extended conjugation of the styryl-imine chromophore in (**11**) as compared with the cross-conjugated system in (**9**). Furthermore, the proton at C-4 in (**9**) resonates at higher field (τ 4.62) due to the enaminic shielding by the NH_2 at C-5 than it does in (**11**) where it resonates at τ 3.82 due to the relatively deshielding amidine structure at C-3. The integrated signals of the C-4 proton are used to determine the ratio of the two isomeric isoxazoles (**9**) and (**11**) in the mixture of products obtained under different reaction conditions (see Experimental section).

The fission pattern of the two amino(phenyl)isoxazoles (**9**) and (**11**) provides further evidence for their respective structures. For the 5-phenylisoxazole (**11**) the molecular ion at M^+, 160 is also the base peak which loses aminoazirine (*m/z* 55, 45%) leaving $PhC{\equiv}O^+$ (**13**) (*m/z* 105, 55%), with the normal breakdown to phenyl (*m/z* 77, 44%) and $C{\equiv}O^+$ (*m/z* 28, 34%) (Scheme 7).



Scheme 7.

For 3-phenyl-5-aminoisoxazole (**9**) a strong molecular ion M^+, 160 is 91% of base peak which loses the amino group to give 3-phenylisoxazole (**14**) (*m/z* 144, 59%). Loss of CO (*m/z* 28, 31%) leads to phenylazirine (**15**) (*m/z* 116, 44%) which then undergoes fission to phenyl (*m/z* 77, 98%) followed by the usual loss of acetylene to give $C_4H_3^+$ (*m/z* 51, 46%). Alternatively, the 5-imino-tautomer (**16**) gives benzaldimine (**17**) (*m/z* 105, base peak) and protonated benzonitrile (**18**) (*m/z* 104, 76%) which loses HCN to give phenyl (*m/z* 77, 98%).

Experimental

I.r. spectra were determined with Perkin-Elmer 257 and 337 spectrophotometers. U.v. spectra were obtained for ethanolic solutions with a Pye-Unicam 1800, Perkin-Elmer 137, or a Beckman 25 spectrophotometer. ^{1}H N.m.r. spectra were determined with Varian T60 and Perkin-Elmer R12A spectrometers for solutions in deuteriochloroform unless otherwise stated, with tetramethylsilane as internal standard. Chemical shifts are expressed as τ values. The allenic nitriles were prepared as previously described.[2]

5-Amino-3-isopropylisoxazole (**4a**).—(*a*) A solution of 4-methylpenta-2,3-dienenitrile (1.86 g, 20 mmol) in ethanol (25

ml; 95%) was added to a mixture of hydroxylamine hydrochloride (1.39 g, 20 mmol) and sodium carbonate (2.12 g, 20 mmol) and the solution was refluxed for 20 h. Removal of the solvent, followed by column chromatography (neutral alumina, activity 2; 200 g) and elution with methylene dichloride–hexane (9:1) gave a crystalline compound which was recrystallized from chloroform–hexane to give *5-amino-3-isopropylisoxazole* (**4a**) (2.14 g, 85%), m.p. 65 °C (Found: C, 57.1; H, 8.0; N, 22.15. $C_6H_{10}N_2O$ requires C, 57.14; H, 7.94; N, 22.22%); $\nu_{max.}$ 3 400, 3 300 (NH_2), 1 640 (C=N), 1 590 (C=C), and 1 510 cm^{-1} (N–H def.); $\lambda_{max.}$ 243 nm (ε 11 400); τ 8.80 (6 H, d, $CHMe_2$), 7.14 (1 H, septet, $CHMe_2$), 5.55 (2 H, br s, NH_2, disappears on deuteriation), and 5.05 (1 H, s, $NH_2C{=}CH$); *m/z* M^+, 126 (29%) ($C_6H_{10}N_2O$ requires M^+, 126), 111 (65), 84 (53), 68 (48), 56 (69), 55 (33), 43 (100), 41 (76), 28 (45), and 27 (57).

(*b*) A solution of 4-methylpenta-2,3-dienenitrile (1.86 g, 20 mmol) in methanol (25 ml) containing sodium carbonate (2.12 g, 20 mmol) and hydroxylamine hydrochloride (1.39 g, 20 mmol) was refluxed for 20 h. Work-up gave 5-amino-3-isopropylisoxazole (2.17 g, 86%), m.p. 65 °C.

(*c*) A solution of 4-methylpenta-2,3-dienenitrile (1.86 g, 20 mmol) in THF (25 ml) containing sodium carbonate (2.12 g) was added to hydroxylamine hydrochloride (1.39 g, 20 mmol) and the mixture was refluxed for 20 h. Work-up gave 5-amino-3-isopropylisoxazole (2.27 g, 88%), m.p. 65 °C.

5-Amino-3-s-butylisoxazole (**4b**).—(*a*) 4-Methylhexa-2,3-dienenitrile (4.28 g, 40 mmol) was refluxed in ethanol (95%; 50 ml) with hydroxylamine hydrochloride (2.78 g, 40 mmol) and sodium carbonate (4.24 g, 40 mmol) for 24 h to give, after column chromatography (neutral alumina, activity 2; 300 g), *5-amino-3-s-butylisoxazole* (**4b**) (4.87 g, 87%), m.p. 71 °C (Found: C, 60.5; H, 8.8; N, 20.2. $C_7H_{12}N_2O$ requires C, 60.43; H, 8.63; N, 20.14%); $\nu_{max.}$ 3 350, 3 200 (NH_2), 1 660 (C=N), 1 600 (C=C), and 1 500 cm^{-1} (N–H def.); $\lambda_{max.}$ 243 nm (ε 9 800); τ 9.15 (3 H, t, CH_3CH_2CHMe), 8.85 (3 H, d, CH_3CHEt), 8.49 (2 H, quintet, CH_3CH_2CHMe), 7.36 (1 H, sextet, CH_3CH_2CHMe), 5.40 (2 H, br s, NH_2, disappears on deuteriation), and 5.06 (1 H, s, $NH_2C{=}CH$); *m/z* M^+, 140 ($C_7H_{12}N_2O$ requires *M*, 140).

(*b*) A solution of 4-methylhexa-2,3-dienenitrile (4.28 g, 40 mmol) in methanol (50 ml) was refluxed with hydroxylamine hydrochloride (2.78 g, 40 mmol) and sodium carbonate (4.24 g, 40 mmol) for 24 h to give 5-amino-3-s-butylisoxazole (4.76 g, 85%), m.p. 71 °C.

(*c*) 4-Methylhexa-2,3-dienenitrile (4.28 g, 40 mmol) was refluxed in THF (25 ml) with hydroxylamine hydrochloride (2.78 g, 40 mmol) and sodium carbonate (4.24 g, 40 mmol) for 24 h to give 5-amino-3-s-butylisoxazole (5.0 g, 90%), m.p. 71 °C.

5-Amino-3-(1-ethylpropyl)isoxazole (**4c**).—4-Ethylhexa-2,3-dienenitrile (1.21 g, 10 mmol) was refluxed in THF (50 ml) with hydroxylamine hydrochloride (0.70 g, 10 mmol) and sodium carbonate (1.06 g, 10 mmol) for 24 h to give, after column chromatography (neutral alumina, activity 2; 200 g), *5-amino-3-(1-ethylpropyl)isoxazole* (**4c**) (1.42 g, 92%), m.p. 35 °C. T.l.c. gave one spot [R_F 0.56, benzene–ethyl acetate (3:2)] (Found: C, 62.2; H, 9.25; N, 18.2. $C_8H_{14}N_2O$ requires C, 62.32; H, 9.09; N, 18.18%); $\nu_{max.}$ 3 340, 3 180 (NH_2), 1 640 (C=N), 1 600 (C=C), and 1 500 cm^{-1} (N–H def.); $\lambda_{max.}$ 242 nm (ε 12 000); τ 9.15 [6 H, t, $(CH_3CH_2)_2CH$], 8.70—8.30 [4 H, m, $(CH_3CH_2)_2CH$], 7.85—7.30 [1 H, m, $(CH_3CH_2)_2CH$], 5.57 (2 H, br s, NH_2, disappears on deuteriation), and 5.10 (1 H, s, $NH_2C{=}CH$).

5-Amino-3-(1-ethylpropyl)isoxazole (**4c**) *and* *4-Ethyl-3-hydroxyamino-1-imino-1-methoxyhex-2-ene.**—4-Ethylhexa-2,3-dienenitrile (4.84 g, 40 mmol) was refluxed in methanol (50 ml) with hydroxylamine hydrochloride (2.74 g, 40 mmol) and sodium carbonate (2.12 g, 20 mmol) for 21 h to give, after column chromatography [neutral alumina, activity 2; elution with methylene dichloride–hexane (9:1)], 5-amino-3-(1-ethylpropyl)isoxazole (**4c**) (5.0 g, 68%), m.p. 35 °C. Elution with methylene dichloride then gave a solid which was recrystallized from chloroform–hexane to give *4-ethyl-3-hydroxyamino-1-imino-1-methoxyhex-2-ene* (**5**; $R^1 = R^2 = Et$, $R^3 = Me$) (1.17 g, 19%), m.p. 116 °C (Found: C, 58.2; H, 9.55; N, 15.25. $C_9H_{18}N_2O_2$ requires C, 58.06; H, 9.68; N, 15.05%); $\nu_{max.}$ 3 500, 3 440, 3 240 (NH, =NH, OH), 1.630 (C=N), 1 580 (C=C), and 1 530 cm^{-1} (N–H def.); $\lambda_{max.}$ 281 nm (ε 13 800); τ 9.25 [6 H, t, $(CH_3CH_2)_2CH$], 8.60—8.10 [5 H, m, $(CH_3CH_2)_2CH$], 6.90 (3 H, s, OCH_3), 5.63 (1 H, s, =CH, disappears on deuteriation), 5.20—4.70 (1.7 H, m, =NH, NH, and OH, disappears on deuteriation), and 3.30—2.60 (1.3 H, m, =NH, NH, and OH, disappears on deuteriation); *m/z* 186 (M^+), 158 (100%), and 143 (40), *m** at *m/z* 134.2 and 129.4.

5-Amino-3-(1-ethylpropyl)isoxazole (**4c**) *and* *1-Ethoxy-4-ethyl-3-hydroxyamino-1-iminohex-2-ene.*†—4-Ethylhexa-2,3-dienenitrile (4.84 g, 40 mmol) was refluxed in ethanol (25 ml; 95%) with hydroxylamine hydrochloride (2.74 g, 40 mmol) and sodium carbonate (1.12 g, 20 mmol) for 8 h to give, after chromatography (neutral alumina, activity 2; 300 g) and elution with methylene dichloride–hexane (9:1), 5-amino-3-(1-ethylpropyl)isoxazole (**4c**) (4.0 g, 66%). Elution with methylene dichloride then gave *1-ethoxy-4-ethyl-3-hydroxyamino-1-iminohex-2-ene* (1.6 g, 20%), m.p. 132 °C (Found: C, 59.9; H, 10.15; N, 13.95. $C_{10}H_{20}N_2O_2$ requires C, 60.00; H, 10.00; N, 14.00%); $\nu_{max.}$ 3 490, 3 440, 3 350, 3 300, and 3 200 (NH_2, NH, OH), 1 630 (C=N), 1 580 (C=C), and 1 525 cm^{-1} (N–H def.); $\lambda_{max.}$ 281 nm (ε 12 600); τ 9.25 [6 H, t, $(CH_3CH_2)_2CH$], 8.84 (3 H, t, CH_3CH_2O), 8.60—8.10 [5 H, m, $(CH_3CH_2)_2CH$], 6.74 (2 H, q, CH_3CH_2O), 5.18 (1 H, s, =CH), 5.40—4.85 (1.3 H, m, =NH, NH, and OH, disappears on deuteriation), and 3.15—2.75 (1.7 H, m, =NH, NH, and OH, disappears on deuteriation); *m/z*, M^+, 200 ($C_{10}H_{20}N_2O_2$ requires *M*, 200), 172 (62%), and 156 (100).

5-Amino-3-(1,2,2-trimethylpropyl)isoxazole (**4d**).—(With G. W. B. Mpango). A solution of 4,5,5-trimethylhexa-2,3-dienenitrile (0.68 g, 5 mmol) in ethanol (75 ml) was added to a mixture of hydroxylamine hydrochloride (0.35 g, 5 mmol), water (2 ml), and potassium carbonate (1.0 g). The precipitated potassium chloride was filtered off and the filtrate was refluxed for 6 h. The aqueous ethanol was distilled off and the residue was extracted with methylene dichloride (5 × 20 ml). The combined extracts were washed with water (3 × 10 ml) and dried ($MgSO_4$). Removal of solvent gave a crude product which solidified at room temperature, τ 4.33 (0.1 H, s, CH=C) and 6.55 (0.2 H, s, NH_2) due to 3-amino-5-(1,2,2-trimethylpropyl)-isoxazole (10%) and τ 4.97 (0.9 H, s, CH=C) and 5.77 (1.8 H, s, NH_2) due to 5-amino-3-(1,2,2-trimethylpropyl)isoxazole (90%). Recrystallization from carbon tetrachloride–pentane gave *5-amino-3-(1,2,2-trimethylpropyl)isoxazole* (**4d**) (0.53 g, 71%), m.p. 103—104 °C (Found: C, 64.1; H, 9.7; N, 16.8. $C_9H_{16}N_2O$ requires C, 64.3; H, 9.5; N, 16.7%); $\nu_{max.}$ 3 360, 3 270 (N–H), and 1 640 cm^{-1} (C=C, C=N); $\lambda_{max.}$ 240 nm (ε 8 800); τ (CCl_4) 9.08 (9 H, s, CMe_3), 8.87 (3 H, d, $CHCH_3$), 7.67—7.30 (1 H, q, $CHCH_3$), 5.77 (2 H, s, NH_2, disappears on deuteriation), and 4.97 (1 H, s, CH=C).

5-Amino-3-(1-hydroxy-1-methylpropyl)isoxazole (**7**).—A mixture of 4-hydroxy-4-methylhex-2-ynenitrile[9] (1.61 g, 13 mmol), hydroxylamine hydrochloride (0.90 g, 13 mmol), and sodium carbonate (1.38 g, 13 mmol) was refluxed in ethanol (50

* Methyl 4-ethyl-3-hydroxyaminohex-2-enimidate (**5**; $R^1 = R^2 = Et$, $R^3 = Me$).

† Ethyl 4-ethyl-3-hydroxyaminohex-2-enimidate (**5**; $R^1 = R^2 = R^3 = Et$).

ml) for 22 h to give, after column chromatography (neutral alumina, activity 4; 130 g), *5-amino-3-(1-hydroxy-1-methylpropyl)isoxaole* (**7**) (1.67 g, 85%), m.p. 100 °C (Found: C, 53.7; H, 7.7; N, 18.05. $C_7H_{12}N_2O_2$ requires C, 53.85; H, 7.69; N, 17.95%); $\nu_{max.}$ 3 400, 3 330, 3 275 (OH, NH_2), 1.642 (C=N), 1 595 (C=C), and 1 540 cm^{-1} (N–H def.); $\lambda_{max.}$ 244 nm (ε 8 300); τ($CDCl_3$–DMSO) 9.18 [3 H, t, $CH_3CH_2C(OH)CH_3$], 8.59 [3 H, s, $CH_3CH_2C(OH)CH_3$], 8.30 [2 H, q, $CH_3CH_2C(OH)CH_3$], 5.90 (1 H, s, OH, disappears on deuteriation), 5.02 (1H, s, C=CH) and 4.46 (2 H, br s, NH_2, disappears on deuteriation).

5-Amino-3-phenylisoxazole (**9**) *and 3-Amino-5-phenylisoxazole* (**11**).—(a) *Synthesis in refluxing ethanol* (With G. W. B. Mpango). A solution of 3-phenylpropynenitrile[10] (2.54 g, 20 mmol) in ethanol (absolute; 190 ml) was added dropwise to a stirred mixture of hydroxylamine hydrochloride (1.39 g, 20 mmol), water (8 ml), and potassium carbonate (2 g). The precipitated potassium chloride was filtered off and the filtrate was refluxed for 6 h, the solvent was evaporated off, and the solid residue was dissolved in methylene dichloride (100 ml), washed with water (2 × 100 ml), and dried (Na_2SO_4). Removal of the solvent gave a crude product (3.01 g, 94%) which was a solid mixture of 5-amino-3-phenylisoxazole (**11**) (76%) and 3-amino-5-phenylisoxazole (**9**) (24%). T.l.c. gave two spots, R_F 0.55 and 0.50 [benzene–ethyl acetate (3:2)]; τ($CDCl_3$–DMSO) 4.62 [0.76 H, s, C=CH of (**9**)] and 3.82 [0.24 H, s, C=CH of (**11**)]. Separation of the mixture (2.7 g) by column chromatography (alumina, activity 2; 340 g) and elution with hexane–ethyl acetate (1:4) gave a solid which was recrystallized from carbon tetrachloride–methylene dichloride to give 5-amino-3-phenylisoxazole (**9**) (1.75 g, 65%), m.p. 110 °C (lit.,[7] 110—112 °C) (Found: C, 67.3; H, 5.0; N, 17.8. Calc. for $C_9H_8N_2O$: C, 67.50; H, 5.00; N, 17.50%); $\nu_{max.}$ 3 460, 3 300 (NH_2), 1 650 (C=N), 1 580 (C=C), and 1 535 cm^{-1} (N–H def.); $\lambda_{max.}$ 206 (ε 16 800) and 233 nm (12 000); τ($CDCl_3$–DMSO) 4.62 (1 H, s, C=CH), 3.80 (2 H, br s, NH_2, disappears on deuteriation), 2.75—2.50 (3 H, m, ArH), and 2.45—2.20 (2 H, m, ArH); *m/z*, M^+, 160 (91%) (Calc. for $C_9H_8N_2O$: *M*, 160), 144 (59), 116 (44), 132 (50), 116 (44), 105 (100), 104 (76), 89 (47), 77 (98), 51 (46), and 28 (31).

Elution with ethyl acetate gave a second compound which was recrystallized from carbon tetrachloride–methylene dichloride to give 3-amino-5-phenylisoxazole (**11**) (0.5 g, 18.5%), m.p. 136 °C (lit.,[7] 136—137 °C) (Found: C, 67.6; H, 4.9; N, 17.45. Calc. for $C_9H_8N_2O$: C, 67.50; H, 5.00; N, 17.50%); $\nu_{max.}$ 1 660 (C=N), 1 600 (C=C), and 1 520 cm^{-1} (N–H def.); $\lambda_{max.}$ 206 (ε 15 900) and 260 nm (14 600); τ($CDCl_3$–DMSO) 4.72 (2 H, s, NH_2, disappears on deuteriation), 3.82 (1 H, s, C=CH), 2.75—2.45 (3 H, m, ArH), and 2.40—2.20 (2 H, s, ArH); *m/z*, M^+, 160 (100%) (Calc. for $C_9H_8N_2O$: *M*, 160), 105 (55), 77 (44), 55 (45), 51 (19), and 28 (34).

(b) *Synthesis in ethanol at room temperature.* A solution of 3-phenylpropynenitrile (1.27 g, 10 mmol) in ethanol (absolute; 95 ml) was added dropwise to a stirred mixture of hydroxylamine hydrochloride (0.7 g, 10 mmol), water (4 ml), and potassium carbonate (1 g). The precipitated potassium chloride was filtered off and the filtrate was kept at room temperature for 24 h. The solvent was evaporated off and the solid residue was dissolved in methylene dichloride (50 ml), washed with water (2 × 50 ml), and dried (Na_2SO_4). Removal of the solvent gave a crude product (1.52 g, 95%) consisting of a mixture of 5-amino-3-phenylisoxazole (**9**) (70%) and 3-amino-5-phenylisoxazole (**11**) (30%) as determined by the ratio of the signals at τ 4.62 and 3.82 respectively.

(c) *Synthesis in ethanol at* 0 °C. 3-Phenylpropynenitrile (1.27 g, 10 mmol), hydroxylamine hydrochloride (0.7 g, 10 mmol), and potassium carbonate (1 g) were mixed in ice-cold ethanol and the mixture was kept at 0 °C for 48 h. Work-up as in (b) gave a crude product (1.49 g, 93%) which was a mixture of 5-amino-3-phenylisoxazole (**9**) (95%) and 3-amino-5-phenylisoxazole (**11**) (5%), based on the ratio of the signals at τ 4.62 and 3.82 respectively.

(d) *Synthesis in methanol under reflux.* 3-Phenylpropynenitrile (2.54 g, 20 mmol), hydroxylamine hydrochloride (1.39 g, 20 mmol), absolute methanol (200 ml), and potassium carbonate (2 g) were refluxed for 6 h to give a crude product (3.0 g, 93.7%) consisting of 5-amino-3-phenylisoxazole (**9**) (61%) and 3-amino-5-phenylisoxazole (**11**) (39%), based on the ratio of signals at τ 4.62 and 3.82 respectively.

(e) *Synthesis in methanol at room temperature.* Experiment (d) was repeated at room temperature for 24 h to give a crude mixture (2.98 g, 93%) consisting of 5-amino-3-phenylisoxazole (**9**) (68%) and 3-amino-5-phenylisoxazole (**11**) (32%), based on the ratio of signals at τ 4.62 and 3.82 respectively.

(f) *Synthesis in methanol at* 0 °C. Experiment (d) was repeated at 0 °C for 43 h to give a crude product (2.9 g, 90.6%) consisting of 5-amino-3-phenylisoxazole (**9**) (82%) and 3-amino-5-phenylisoxazole (**11**) (18%), based on the ratio of signals at τ 4.62 and 3.82 respectively.

(g) *Repeat of the synthesis under the conditions used by Lopez and Barrans.*[7] A solution of 3-phenylpropynenitrile (7.62 g, 60 mmol) in absolute ethanol (15 ml) was added to a solution of hydroxylamine hydrochloride (4.30 g, 60 mmol) in ethanol (absolute; 75 ml). The free base was liberated by the addition of sodium ethoxide (4.10 g, 60 mmol) at 0 °C. The solid precipitate was filtered off and the filtrate was kept at room temperature for 24 h. The solvent was removed under reduced pressure and the solid thus obtained was dissolved in hydrochloric acid (150 ml; 2M) at 0 °C. 5-Amino-3-phenylisoxazole (**9**) was extracted with diethyl ether (6 × 100 ml) and the extracts were washed in turn with aqueous sodium carbonate (2 × 100 ml) and water (1 × 100 ml), and then dried ($CaCl_2$). Evaporation of the solvent gave a crystalline compound which was recrystallized from chloroform–hexane to give 5-amino-3-phenylisoxazole (**9**) (5.76 g, 60%), m.p. 110 °C, having identical spectral data with those of the sample obtained in (a).

After extraction of the 5-amino-3-phenylisoxazole, aqueous sodium hydroxide (100 ml; 5M) was added at 0 °C to the aqueous acid solution which was then extracted with diethyl ether (3 × 100 ml), and the extracts were washed with water (200 ml) and dried ($CaCl_2$). Evaporation of the solvent gave a crystalline compound which was recrystallized from chloroform–hexane to give 3-amino-5-phenylisoxazole (**11**) (2.28 g, 24%), m.p. 136 °C, having identical spectral data with those of the sample obtained in (a).

No other products were isolated or detected in this reaction.

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