5-Amino-3-imino-2,3-dihydrofurans and 3-Amino-5-imino-2,5-dihydrofurans from 4,4-Dialkyl-4-hydroxybut-2-ynenitriles

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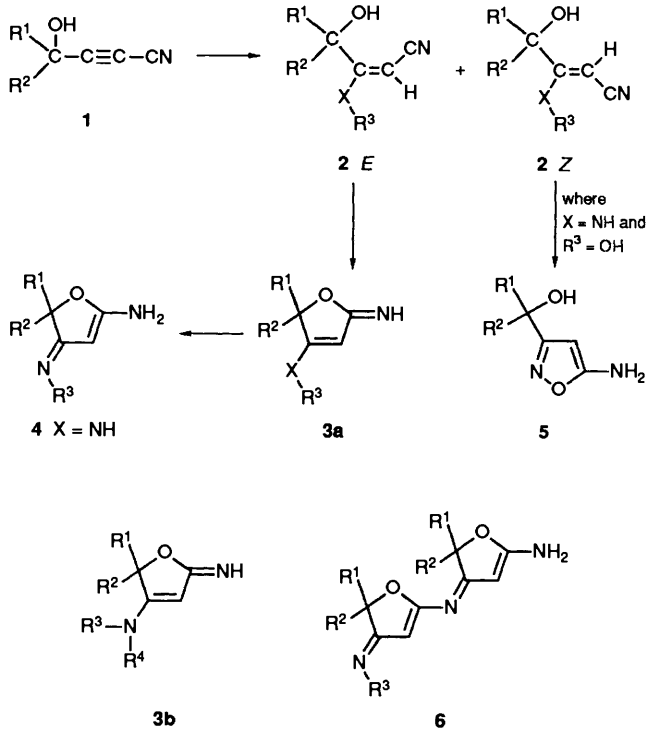
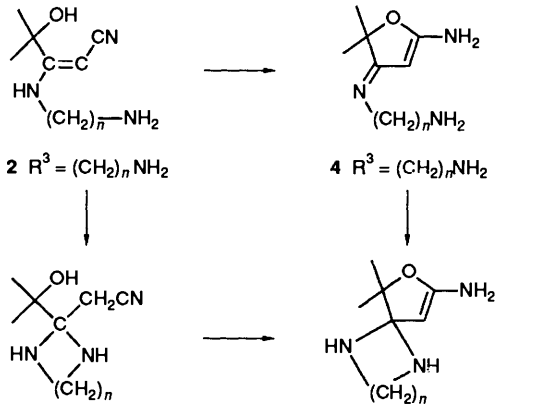
A novel general synthesis of the dihydrofurans **4** and **3b** with nitrogen substituents in the 3- and 5-positions from 4,4-dialkyl-4-hydroxybut-2-ynenitriles **1** and primary and secondary amines is described. A 5-amino group reacts further with unchanged, or an excess of, hydroxybutynenitrile to give the difurylimines **6**.

The readily available 4-hydroxybut-2-ynenitriles **1** [1] (prepared here by a modified literature method, see Experimental section) undergo a Michael addition with nucleophiles HXR^3 under mild conditions to give the conjugated adducts **2** which may be isolated under basic conditions (where X = O or S and where X = NH and R^3 is a bulkyl group) or under neutral conditions (where X = NH and R^3 is small). Under basic conditions, where X = NH and R^3 = alkyl, hydroxyalkyl or aminoalkyl, the adducts cyclise spontaneously to give 5-amino-3-imino-2,3-dihydrofurans **4** in 85–95% yield.[2] Similarly, secondary amines (R^{5}R^{4}NH) form adducts which ring close spontaneously to give 3-amino-5-imino-2,5-dihydrofurans **3b**.[2] After removal of



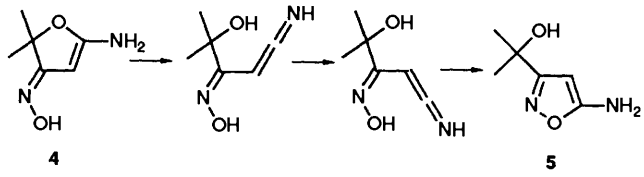
Scheme 1

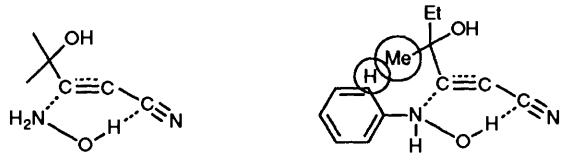
solvent, quantitative yields of oily products were obtained at 0 °C for 3 h with dichloromethane as solvent. On being kept in a refrigerator most of the oils crystallised after 1–3 d, some after months and a few remained as oils. Crystallisation is probably inhibited by traces of adduct **2**, difurylimine **6** and unchanged amine. Recrystallisation gave 88–93% yields. The oils which did not crystallise gave correct elemental analyses and spectroscopic analysis showed that they were essentially pure. Chromatography was unsuccessful as aminofurans stick on columns and tail on TLC. Sterically hindered amines gave some difurylimines **6**. With one exception, a second functional group present in the starting amine does not lead to products from alternative or additional ring closure. Although an equilibrium is probably established for 5- or 6-membered rings, it favours the open-chain structure (**2** or **4**). The exception was hydroxylamine which always gave the isoxazole **5** in *ca.* 80% yield with no evidence of furan formation either as an intermediate or as a by-product, even under the mildest conditions. This contraindicates the mechanism tentatively proposed in our preliminary communication[2,†] and may be rationalised by postulating a transition state in which the nitrile is held in the *Z* configuration **7**. However, phenylhydroxylamine under reflux in dichloromethane gave only furans in *ca.* 20% yield and neither isoxazoles nor quinolines[4] could be detected in the rest of the product, which consisted of decomposition products from phenylhydroxylamine. Here interference between the phenyl group and the bulky side chain destabilises the transition state with a *Z* configuration **8a** and favours *E*-isomer **8b** and furan formation.



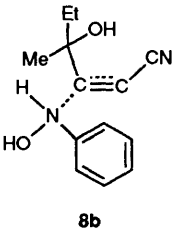
Oxygen or sulphur adducts are formed under basic conditions but do not cyclise to furans either spontaneously or

† It was proposed that furan **4** is always formed first followed by ring fission to ketimine and ring closure to isoxazole **5**

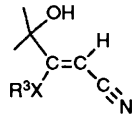




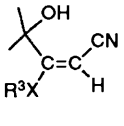
7 8a



8b

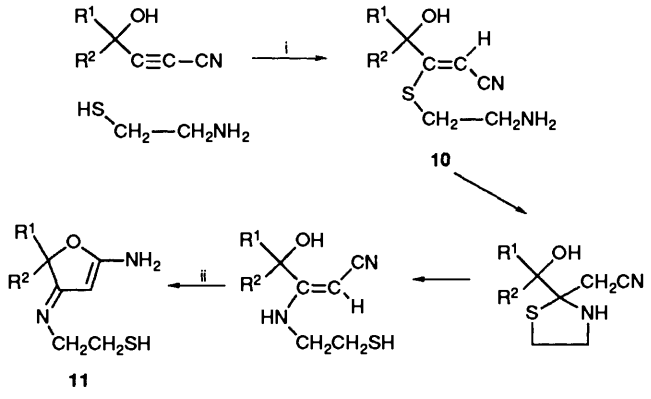


9 X = O; δ 5.28
X = S; δ 6.00



X = O; δ 5.00
X = S; δ 5.28

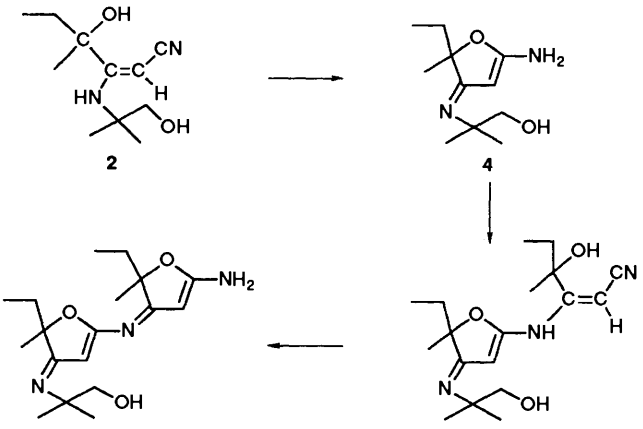
under reflux. NMR spectroscopy shows that the adducts are 70% in the *Z* configuration **9** and that the sulphur adducts equilibrate to form >99% *Z*-form after 5 d at reflux in ethanol or *N*,*N*-dimethylformamide (DMF). However we have no explanation for the total lack of furan formation. The specificity of the formation of aminofurans from enaminic nitrile intermediates is demonstrated by the reaction of aminoethanethiol with 4-hydroxybutynenitriles (Scheme 2). At room temperatures (25 °C in chloroform) the *S*-adduct **10** is completely formed in 15 min as shown by λ_{max}/nm 274 and the NMR signal at δ 5.96 (ene sulphide proton) reading a maximum. Evaporation of solvent leaves *S*-adduct of >95% purity as an oil. Kept neat* at room temperature (25 °C) for 18 h completes the two-stage transformation to the aminofuran **11** with the disappearance of the δ 5.96 signal and appearance of the dihydrofuran olefinic proton at δ 4.7 and λ_{max}/nm 270. A derivative of the *N*-adduct may be isolated if furan formation is prevented by using the 4-tetrahydropyranyloxybutynenitrile.



Scheme 2 *Reagents and conditions:* i, Na_2CO_3, 25 °C, 15 min; ii, 18 h

Sterically hindered amines required longer times and produce variable quantities of less soluble difurylimines **6**, which may be separated by fractional crystallisation. Diagnostic spectroscopic constants are λ_{max}/nm 270–274 (ε 18 000–22 000) and the enaminic shielded proton at C-4 of the 5-amino-3-imino-2,3-dihydrofurans **4** at δ 4.7–5.0, λ_{max}/nm 280–284 (ε 22 000–

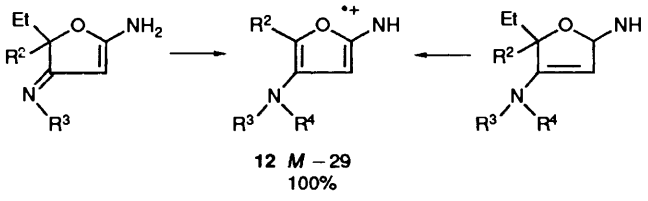
* Refluxing in $CHCl_3$–EtOH gave 30% bis adduct[5] 70% furan.



2 4

6 a R^1 = Me; R^2 = Et; R^3 = CMe_2CH_2OH
b R^1 = Me; R^2 = Et; R^3 = $HCEtCH_2OH$

30 000) and the enamic shielded proton at C-4 of 3-amino-5-imino-2,5-dihydrofurans **3b** at δ 4.85–5.15. Difurylimines **6** show longer UV absorption for the oxotetraene system at λ_{max}/nm 370–372 (ε 36 000–42 000) and two enamimic protons at C-4 and C-4′ at δ 4.65–4.99 and 5.30–5.57. Both 5-amino-3-imino- and 3-amino-5-iminodihydrofurans undergo fission of the strong molecular ion by losing an ethyl radical from C-2 to give the stable furan radical ion **12** either as a base or principal peak. Difurylimines **6** give either: strong molecular



12 *M* − 29
100%

R^4 = H or alkyl

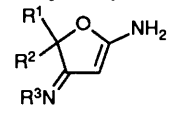
ions with preferred McLafferty rearrangement to ethyl radical fission followed by a second McLafferty and fission (pathway **A**), or the same steps in reverse order (pathway **B**). Both pathways shown involve side-chain loss of hydrogen (Scheme 3). Amino or iminodihydrofuran formation is a general reaction of 3-amino-4-hydroxy-2-enenitriles and applications to the synthesis of fused ring aminofuran systems will be described elsewhere.

Experimental

IR spectra were determined with Perkin-Elmer 257 and 337 spectrometers, UV spectra for ethanolic solutions with Perkin-Elmer 137, Beckman 25 and Cary spectrometers and NMR with Perkin-Elmer R12 and Jeol 60 instruments.

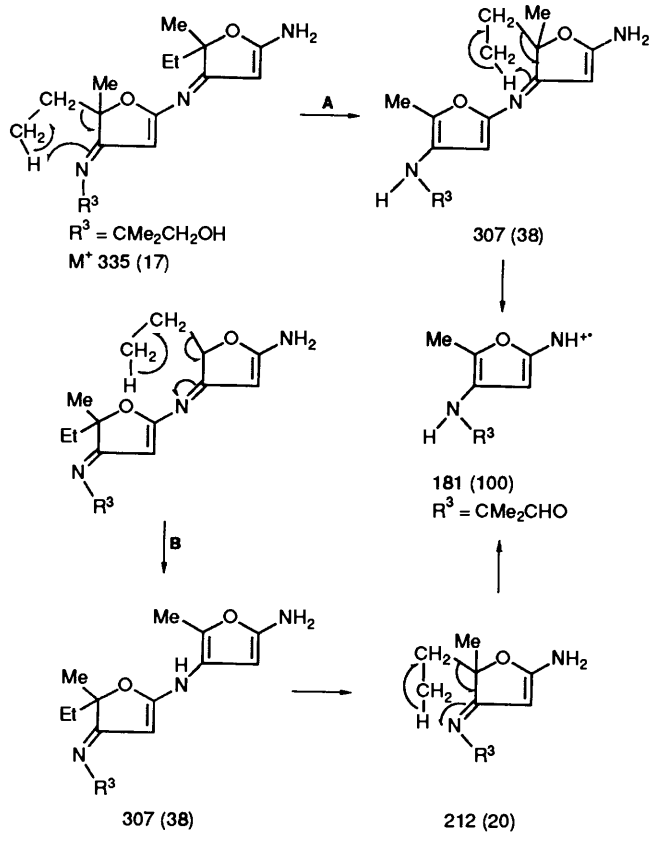
4-Ethyl-4-hydroxyhex-2-ynenitrile.—To a vigorously stirred suspension of anhydrous, finely ground copper(I) cyanide (34 g, 0.38 mmol) in dry *N*,*N*-dimethylformamide (DMF, 200 cm^3) 1-bromo-3-ethylpent-1-yn-3-ol was added dropwise under nitrogen the temperature not being allowed to exceed 50 °C. The mixture was stirred at 50 °C for 3 h after which it was cooled; aqueous DMF (100 cm^3 in H_2O, 200 cm^3) was then added to the vigorously stirred reaction mixture and stirring continued until the precipitated solids became granular. The precipitate was filtered off and washed with dichloromethane (3 × 200 cm^3) and the filtrate was extracted (CH_2Cl_2, 4 × 200 cm^3). The combined extracts were washed with water (15 × 200 cm^3), dried (Na_2SO_4), and distilled to give the title compound (23.3 g, 59%), b.p. 80–81 °C at 5 mmHg.

Table 1 5-Amino-2,2-dialkyl-3-(alkylimino)-2,3-dihydrofurans from primary amines



Entry	R^1	R^2	R^3	Reaction conditions h at °C	A[a]	B[e]	Yield (%)	M.p. (°C)	UV λ_{max}/nm	ε	Required C	H	N	Found C	H	N	M^+
1	Et	Et	Bu	24 at 0 °C			100	*a*	270	18 600	68.57	10.48	13.33	68.4	10.3	13.2	210
2	Me	Et	Bu	24 at 40 °C			100	*a*	271	19 200	—	—	—	—	—	—	196[c]
3	Me	Et	$(CH_2)_2OH$	3 at 0 °C	3	ac	93	86	271	21 800	58.70	8.70	15.22	58.6	8.7	15.3	184
4	Et	Et	$(CH_2)_2OH$	3 at 0 °C	1	ch	89	112	271	22 900	60.61	9.09	14.14	60.45	9.2	14.3	198
5	Me	Et	$(CH_2)_3OH$	3 at 0 °C			100	*a*	271	20 200	60.61	9.09	14.14	60.4	9.3	14.2	198
6	Et	Et	$(CH_2)_3OH$	3 at 0 °C	1	ch	90	130	271	22 900	62.26	9.43	13.21	62.3	9.55	13.3	212
7	Me	Et	$(CH_2)_4OH$	3 at 0 °C			100	*a*	272	20 000	62.26	9.43	13.21	62.5	9.3	13.0	212
8	Et	Et	$(CH_2)_4OH$	3 at 0 °C			100	*a*	272	21 000	63.72	9.73	12.39	63.6	9.6	12.4	—
9	Me	Et	$(CH_2)_5OH$	3 at 0 °C	60	ac	93	108	270	21 500	63.72	9.74	12.39	63.6	9.8	12.25	226
10	Et	Et	$(CH_2)_5OH$	3 at 0 °C	60	ac	89	118	274	22 000	64.95	9.99	11.66	64.9	10.15	11.5	240
11	Me	Et	$CHEtCH_2OH$	22 at 40 °C	*b*		86	*a*	274	20 100	62.26	9.43	13.21	62.1	9.6	13.1	—
12	Et	Et	$CHEtCH_2OH$	30 at 40 °C	30[b]	ac	81	179	273	22 600	63.72	9.74	12.39	63.5	9.65	12.5	226
13	Me	Et	CMe_2CH_2OH	37 at 40 °C	30[b]	ac	85	234	274	22 100	62.26	9.43	13.21	62.35	9.5	13.3	212
14	Me	Et	$(CH_2)_2NH_2$	52 at 25 °C	270	ct	90	130	271	18 500	59.02	9.29	22.95	59.2	9.4	23.1	—
15	Me	Et	$(CH_2)_3NH_2$	52 at 25 °C	270	ct	88	135	272	19 500	60.91	9.64	21.32	60.8	9.8	21.45	—
16	Et	Et	$(CH_2)_2NH_2$	52 at 25 °C			100	*a*	271	22 600	62.56	9.95	19.91	62.75	10.15	20.0	—

[a] Obtained as an oil. [b] Difurylimine by-product also obtained. [c] Spectroscopic evidence showed these to be >98% pure. [d] A, days to effect crystallisation. [e] B, recrystallised from solvent: ac = acetone, ch = chloroform, ct = carbon tetrachloride.



Scheme 3

5-Amino-2-ethyl-3(2-hydroxyethylimino)-2-methyl-2,3-dihydrofuran **4** (R^1 = Me, R^2 = Et, R^3 = CH_2CH_2OH).—Redistilled 2-aminoethanol (1.22 g, 20 mmol) in dichloromethane (25 cm^3) and 4-hydroxy-4-methylhex-2-ynenitrile (2.46 g, 20 mmol) in dichloromethane (25 cm^3) were vigorously stirred at 0 °C and stirring continued at 0 °C for 3 h. Removal of solvent gave an oil which crystallised either after 1 d in the refrigerator or 3 d at 25 °C. Recrystallisation from acetone gave the title compound (3.42 g, 93%), m.p. 86 °C (compound **3** in Table 1); λ_{max}/nm 271 (21 800); δ_H 0.85 (3 H, t, CH_3CH_2), 1.45 (3 H, s, CH_3C), 1.80 (2 H, q, CH_3CH_2), 3.15 (2 H, t, NCH_2), 3.64 (2 H, t, CH_2OH), 4.58 (1 H, s, =CH) and 5.20 (3 H, s, NH_2 and OH exchanges D_2O); *m/z* 184 (M^+, 93%).

The following compounds were prepared similarly. Table 1: **1**, **2**, **4–10**, **14**, **15**, **16** and Table 3: **20**, **21**, **22**. All have ^1H NMR and mass spectra in complete accord with their different sidechains.

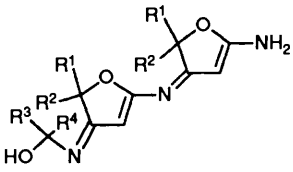
5-Amino-2-ethyl-3-(3-hydroxy-2-methylpropan-2-ylimino)-2,3-dihydrofuran **4** (R^1 = Me, R^2 = Et, R^3 = CMe_2CH_2OH) and *[2-ethyl-3-(3-hydroxy-2-methylpropan-2-ylimino)-2-methyl-2,3-dihydro-5-furylimino]-5′-amino-2′-ethyl-2′-methylfuran* **6** (R^1 = Me, R^2 = Et, R^3 = CMe_2CH_2OH).—Redistilled 2-amino-2-methylpropan-1-ol (1.78 g, 20 mmol) in dichloromethane (50 cm^3) and 4-hydroxy-4-methylhex-2-ynenitrile (2.46 g, 20 mmol) in dichloromethane (50 cm^3) were rapidly mixed and refluxed for 37 h, to precipitate a solid. Filtration and recrystallisation gave the title compound **6** (0.2 g, 6%) (compound **17** in Table 2).

Evaporation of solvent from the filtrate gave an oil which crystallised after 1 month at 0 °C. Recrystallisation from acetone gave the title compound **4** (compound **13** in Table 1) (3.5 g, 85%), m.p. 234 °C; δ_H 4.98 [1 H, s, $O(NH_2)C{=}CH$].

Compounds **11** (Table 1) and **19** (Table 2) and compounds **12** (Table 1) and **18** (Table 2) were prepared similarly and have ^1H NMR and mass spectra in complete accord with their different side chains.

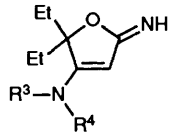
2-Ethyl-3-(N-hydroxyanilino)-5-imino-2-methyl-2,5-dihydrofuran **3b** (R^1 = Me, R^2 = Et, R^3 = Ph, R^4 = OH).—4-Hydroxy-4-methylhex-2-ynenitrile (2.1 g, 17 mmol) in dichloromethane (25 cm^3) was heated under reflux with phenylhydroxylamine (1.8 g, 17 mmol) in dichloromethane (25 cm^3) for 24 h. Removal of solvent gave a dark brown oily product which, after column chromatography (neutral alumina, II, 350 g, ethyl acetate–hexane, 8:2), gave the *title compound* **36** (0.86 g, 22%), m.p. 216 °C (Found: C, 67.45; H, 6.55; N, 12.5%. $C_{13}H_{16}N_2O_2$ requires C, 67.24; H, 6.90; N, 12.07%); ν_{max}/cm^{-1} 3250, 3200 (OH

Table 2 Difurylimines



Entry	R^1	R^2	R^3	R^4	Yield (%)	M.p. (°C)	δ_H 4'-CH	δ_H 4-CH	UV λ_{max}/nm	UV ε	Required C	Required H	Required N	Found C	Found H	Found N	Found M^+
17	Et	Me	Me	Me	6	124	4.99	5.50	372	42 200	64.48	8.66	12.54	64.05	8.45	12.1	335
18	Et	Et	Et	H	7	168	4.98	5.57	371	42 100	66.12	9.09	11.57	65.9	9.1	11.7	—
19	Et	Me	Et	H	5	118	4.66	5.30	370	35 700	64.48	8.66	12.54	64.3	8.95	12.4	335

Table 3 2,2-Diethyl-3-dialkylamino-5-imino-2,3-dihydrofurans from secondary amines



Entry	R^3	R^4	Reaction conditions h at °C	M.p. (°C)	Yield (%)	UV λ_{max}/nm	UV ε	Required C	Required H	Required N	Found C	Found H	Found N	Found M^+
20	Me	CH_2CH_2OH	24 at 40 °C	150	90	284	30 200	62.26	9.43	13.21	62.1	9.5	13.05	212
21	Bu	CH_2CH_2OH	24 at 40 °C	93	95	284	24 600	66.14	10.24	11.02	66.05	10.3	11.2	254
22	Et	Et	24 at 40 °C	140	89	280	22 000	68.57	10.48	13.33	68.65	10.6	13.5	210

and NH), 1620 and 1600 (C=N and C=C); λ_{max}/nm 205 (10 200), 214 (9300) and 282 (16 800); δ_H($CDCl_3$–[$^2H_6$]DMSO) 0.85 (3 H, t, CH_3CH_2), 1.58 (3 H, s, CH_3), 1.95 (2 H, q, CH_3CH_2), 3.30 (1 H, s, NH exchanges D_2O), 5.10 (1 H, s, =CH), 7–7.50 (5 H, m, aromatic) and 8.88 (1 H, s, NOH exchanges D_2O); *m/z* 232 (M^+).

2,2-*Diethyl*-3-(N-*hydroxyaniline*)-5-*imino*-2,5-*dihydrofuran* **3b** (R^1 = R^2 = Et, R^3 = Ph, R^4 = OH).—Similarly 4-ethyl-4-hydroxyhex-2-ynenitrile (4.11 g, 30 mmol) in ethanol (25 cm^3) with phenylhydroxylamine (3.27 g, 30 mmol) refluxed for 60 h gave the *title compound* (0.79 g, 10.7%), m.p. 208 °C (Found: C, 68.2; H, 6.6; N, 12.9. $C_{14}H_{18}O_2$ requires C, 68.29; H, 7.32; N, 11.38%); ν_{max}/cm^{-1} 3275, 3220 (OH and NH), 1620 and 1600 (C=N, C=C); λ_{max}/nm 205 (16 100), 214 (14 000) and 283; δ_H 0.81 (6 H, t, CH_3CH_2 × 2) 1.90 (4 H, g, CH_3CH_2 × 2), 2.98 (1 H, s, NH exchanges D_2O), 5.11 (1 H, s, =CH), 6.95–7.50 (5 H, m, aromatic), 8.60 (1 H, s, NOH exchanges D_2O); *m/z* 246 (M^+).

3-(2-*Aminoethylthio*)-4-*hydroxy*-4-*methylhex*-2-*enenitrile* **10** (R_2 = Me, R_2 = H).—2-Aminoethanethiol hydrochloride (1.14 g, 10 mmol) in chloroform (25 cm^3) was added to 4-hydroxy-4-methylhex-2-ynenitrile (1.33 g, 10 mmol) in chloroform (25 ml) followed by sodium carbonate (1.06 g, 10 mmol). The mixture was stirred briskly and continuously monitored λ/nm 272. Absorption reached a maximum after 15 min. Work-up gave the title compound as an oil (1.91, 95.5%). ν_{max}/cm^{-1} 3500–3000 (br OH NH_2) and 2200 (CN); λ_{max}/nm 274 (14 700); δ_H 5.96 (1 H, s, SC=CH).

5-*Amino*-2-*ethyl*-3-(2-*mercaptoethylimino*)-2-*methyl*-2,3-*dihydrofuran* **11** (R^1 = Me, R^2 = Et).—The *S*-adduct above (1.8 g, 9 mmol) was kept for 18 h at 25 °C when δ_H 5.96 (SC=CH) was replaced by δ_H 4.70 (NH_2C=CH) of the dihydrofuran (1.80, 100%); ν_{max}/cm^{-1} 3325, 3250 (NH_2) and 1660 (C=N); λ_{max}/nm 270 (18 000); δ_H($CDCL_3$–[$^2H_6$]DMSO) 4.70 (1 H, s, NH_2C=CH) 5.14 (3 H, br s, NH_2, SH exchanges D_2O); *m/z* 200 (M^+, 34), 198 (80), 153 (100) (M − CH_2SH).

5-*Amino*-3-(1-*hydroxy*-1-*methylpropyl*)*isoxazole* **5** (R^1 = Me, R^2 = Et).[3]—Anhydrous sodium carbonate (0.82 g, 6 mmol), hydroxylamine hydrochloride (0.45 g, 6 mmol) and 4-hydroxy-4-methylhex-2-ynenitrile (0.80 g, 6 mmol) when stirred at 0 °C for 6 h showed λ_{max}/nm 240 but no peak at λ_{max}/nm 270. When the mixture was allowed to warm up to the 18 °C overnight with stirring, work-up gave the isoxazole (0.73 g, 78%), m.p. 101–102 °C; λ_{max}/nm 244 (9000); δ_H 5.00 (1 H, s, NH_2C=CH); (lit.,[3] constants m.p. 100 °C; λ_{max}/nm 244 (8300), δ_H 5.02).

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