Reaction of Pyrroles with Ethyl 2-Nitroso- and 2-Azo-propenoates, and with Ethyl Cyanoformate *N*-Oxide: A Comparison of the Reaction Pathways

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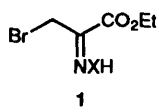
The reaction of ethyl 2-nitrosopropenoate **2a** with 1-methylpyrrole, 2,5-dimethylpyrrole and 2,5-diphenylpyrrole has been investigated. In every case the products result from highly regioselective attack at C-2 of the pyrrole by the electrophile. The azopropenoate esters **2b** and **2c** react similarly with pyrroles, to the extent that even 1-(triisopropylsilyl)pyrrole is attacked exclusively at the 2-position by the azo ester **2b**. In contrast, the nitrile oxide ethyl cyanoformate *N*-oxide **12** reacts at the 3-position of 2,5-dimethyl- and of 2,5-diphenyl-pyrrole. The reactions of the nitroso and azo esters with pyrroles are interpreted as Diels–Alder cycloadditions with inverse electron demand.

Reaction of Pyrroles With Vinylnitroso- and Vinylazo-esters.— Ethyl bromopyruvate oxime **1a** and the hydrazones **1b** and **1c** react in organic solvents with sodium carbonate in suspension to produce transient vinylnitroso and vinylazo esters **2**.[1,2] These intermediates act as heterodienes in Diels–Alder reactions with alkenes and they react with electron-rich heterocycles including furan, pyrrole and indole. With indoles the products result from exclusive attack at the 3-position, even if it is substituted, and either cycloadducts or 3-substituted indoles are isolated.[1,2] Pyrrole reacts with the intermediate **2a** to give the hydroxyimino ester **3a**.[3]

In this paper we describe the reactions of the nitroso ester **2a**, and of the azo esters **2b** and **2c**, with a variety of pyrroles. The main objectives were to determine the scope of the reaction and its regioselectivity with pyrroles in which the 2- and 5- positions are substituted, in order to develop the method as a route to new α-amino esters.[3]



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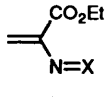

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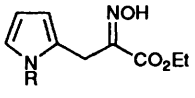
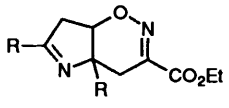
a; X = O
b; X = $NC_6H_3(NO_2)_2$-2,4
c; X = NCO_2Bu^t



3a; R = H
b; R = Me

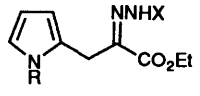


4a; R = Me
b; R = Ph

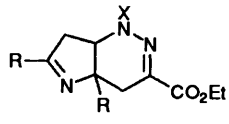
The reaction of the intermediate **2a** with 1-methylpyrrole was investigated first. This reaction was previously reported by us to give the 2-substituted pyrrole **3b** together with the 3-isomer as an inseparable mixture in a ratio of 4:1.[1] We have concluded after a careful re-examination of the reaction that the exclusive product is the pyrrole **3b**: none of the isomer was detected, its presence having been inferred in the earlier work from signals in the NMR spectrum.

With 2,5-disubstituted pyrroles reaction also occurred at the 2-position, the products being the formal cycloadducts **4**. The oxazine **4a** was isolated (70%) from the reaction with 2,5-dimethylpyrrole as a clear yellow oil, stable to flash chromatography and distillation; with 2,5-diphenylpyrrole the oxazine **4b** was obtained in 36% yield as colourless crystals (the low yield may, to some extent, reflect the fact that we were unable to use 2,5-diphenylpyrrole in large excess; instead we used a small excess of the oxime). Both compounds were assigned the structures **4** on the basis of their ^1H NMR spectra. Thus, the spectrum of compound **4a** shows signals for two methyl groups at δ 1.22 (4a-Me) and 1.99 (6-Me). The methylene groups at positions 4 and 7 both appear as AB systems, the signals for the hydrogens attached to C-7 being further split by coupling to 7a-H. An analogous set of signals is present in the spectrum of compound **4b**. Both thus exist as the imine tautomers shown. We were unable to isolate any products from the reaction of ethyl nitrosopropenoate with 1-benzyl- and 1-phenyl-2,5-dimethylpyrroles where this enamine–imine tautomerism is blocked. This may be due to further reaction of the enamine intermediates with the nitroso ester, which could result in the formation of unstable 1:2 adducts.

When substituents were present which diminished the electron-rich character of the pyrrole ring the nitroso ester **2a** failed to react. This was the case with the *N*-trialkylsilyl- and *N*-*p*-tolylsulfonyl-pyrroles and with pyrrole-2-carbaldehyde.



5a; R = H, X = $C_6H_3(NO_2)_2$-2,4
b; R = Me, X = $C_6H_3(NO_2)_2$-2,4
c; R = $SiPr^i_3$, X = $C_6H_3(NO_2)_2$-2,4
d; R = H, X = CO_2Bu^t
e; R = Me, X = CO_2Bu^t

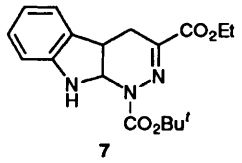


6a; R = Me, X = $C_6H_3(NO_2)_2$-2,4
b; R = Me, X = CO_2Bu^t
c; R = H, X = CO_2Bu^t

In order to investigate further the scope of the reaction of these activated esters with pyrroles we performed similar reactions with ethyl 2-(2,4-dinitrophenylazo)propenoate **2b** and with ethyl 2-(*tert*-butoxycarbonylazo)propenoate **2c**. Earlier work with indoles showed that the reactions of these azo esters are generally analogous to those of the nitroso ester **2a** but that the yields of adducts are often higher.[2] Ethyl 2-(2,4-dinitrophenylazo)propenoate **2b** gave the open-chain hydrazones **5a** and **5b**, respectively, in reactions with pyrrole and 1-methylpyrrole. The yields were high and no 3-substituted regioisomers were observed. With 2,5-dimethylpyrrole the expected pyridazine **6a** was isolated in 96% yield as a yellow solid. As with the nitrosoalkene **2a**, no stable adducts were obtained with 1-substituted 2,5-dimethylpyrroles. It was possible to precipitate a solid at the end of the reaction by addition of ether, but this solid quickly became an intractable tar.

1-(Triisopropylsilyl)pyrrole was used as a substrate because of its known tendency to give mainly or exclusively 3-substituted pyrroles in electrophilic substitution.[4] When treated with the azoalkene **2b** this pyrrole gave a single product which was isolated in 12% yield. This was not, as we had expected, the 3-substituted compound, but the 2-substituted hydrazone **5c**. This was established when the compound was desilylated by reaction with tetrabutylammonium fluoride: the product was the hydrazone **5a**. This observation is in striking contrast to that reported with a standard electrophilic alkylating agent, Eschenmoser's salt, which resulted in substitution at both the 3- and 4-positions.[5]

The azoalkene **2c** gave analogous products **5d** and **5e** with pyrrole and with 1-methylpyrrole, and the formal cycloadduct **6b** with 2,5-dimethylpyrrole. Two points deserve brief comment. First, after reaction of the azoalkene **2c** with pyrrole for 12 h it was possible to detect in the ^{1}H NMR spectrum of the crude product some signals which could indicate the presence of a bicyclic structure **6c**. In particular, four double doublets were present, the chemical shifts and coupling constants of which were consistent with those expected for the two 4-H and the two 7-H signals (by analogy with those observed for compound **6b**). A singlet at δ 7.70 was assigned to 6-H. However, flash chromatography gave only the open hydrazone **5d**. Although such a cycloadduct has never previously been observed with pyrrole, a cycloadduct **7** was isolated from the analogous reaction of this azo ester with indole.[2] The second point of note is the abnormally low yield of the product **5e** from 1-methylpyrrole: although the experiment was carried out several times under differing conditions the yield was never higher than 8%. This could again be related to the formation of a possible cycloadduct, but, because the enamine–imine tautomerism is blocked, further addition to the transient enamine could be faster than the ring opening to the open-chain hydrazone **5e**.



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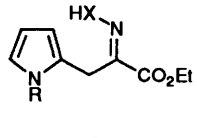

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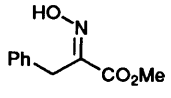

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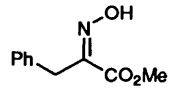

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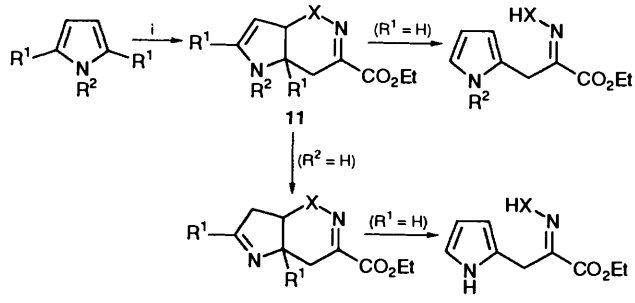
In all the reactions in which open-chain oximes or hydrazones were obtained only a single stereoisomer was formed. These have been assigned as the *anti* isomers **8** for the following reason. A study of the oximes **9** and **10** showed significant differences in their IR spectra and in the rates of hydrogen–deuterium exchange in the NMR.[6] The *syn* oxime **10** shows no free OH absorption band in the IR spectrum because of intramolecular hydrogen bonding whereas the *anti* oxime **9** has an OH absorption at 3250 cm^{-1}; in the NMR spectrum of the *syn* oxime the hydrogen–deuterium exchange of the OH signal in chloroform–deuterium oxide is very slow (10 days) whereas in the spectrum of the *anti* oxime exchange is fast (5 min). All the IR spectra of the oximes and hydrazones obtained from the reactions with pyrroles showed OH and NH absorptions, and hydrogen–deuterium exchange was fast in the NMR spectrum of the oxime **3a**. Although it was not established unequivocally that the products isolated always resulted from kinetic control, this seems likely because of the mild reaction conditions; the *anti* isomers are the ones required by a cycloaddition–ring opening mechanism.

In view of these observations our tentative conclusion is that we are observing cycloadditions (*i.e.*, Diels–Alder reactions with inverse electron demand) and not conjugate addition. Cycloadducts of the general type **11** are then the primary products of the reactions (Scheme 1) but if no 2- and 5-

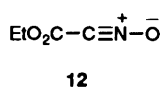


11

Scheme 1 *Reagents and conditions:* i, $BrCH_2C(=NXH)CO_2Et$, Na_2CO_3, CH_2Cl_2, room temp.

substituents are present (R^1 = H) the six-membered ring opens to give the oximes **3** or the hydrazones **5**. In the presence of 2- and 5-substituents the primary cycloadducts tautomerise to the imines **4** and **6**; if the pyrrole is 1,2,5-trisubstituted, this tautomerisation is blocked and further additions occur leading to more complex products. A two-step alkylation and ring-closure sequence cannot definitely be ruled out, however: there are examples of 2-alkylation of 2,5-dimethylpyrrole[7,8] including a recent study in which α-chloro sulfides were shown to react with 2,5-dimethylpyrrole predominantly at the 2-position in the presence of alumina.[8]

Reaction of Pyrroles With Ethyl Cyanoformate N-*Oxide.*— There is superficial similarity between the reactions of vinylnitroso compounds with nucleophilic alkenes and electron-rich heterocycles and the reactions of nitrile oxides with these substrates. Both types of intermediate undergo regioselective cycloadditions with nucleophilic alkenes and with furan. Very few reactions of nitrile oxides with pyrroles have been reported, however.[9] We undertook a brief investigation of the reactions of ethyl cyanoformate *N*-oxide **12** with pyrroles to determine whether they are analogous to those of the vinylnitroso ester **2a**.



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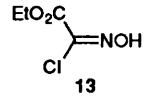

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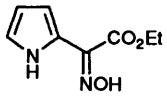

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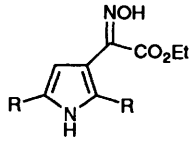
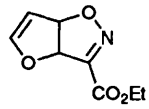


15a; R = Me
b; R = Ph



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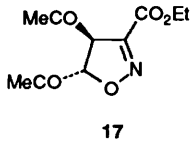

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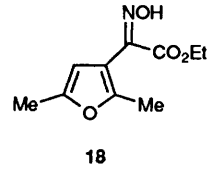

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The nitrile oxide **12** was generated *in situ* from the chloro oxime **13**. Reaction with pyrrole gave the expected 2-substituted hydroxyimino ester **14** in moderate yield. With 2,5-disubstituted pyrroles no cycloadducts were detected; only the 3-substituted hydroxyimino esters **15a** and **15b** were isolated. Thus, in

contrast to the vinylnitroso ester **2a**, the nitrile oxide **12** appears to act as a conventional electrophile with these pyrroles. The intermediate **12** also gave a cycloadduct **16** with furan, as has been shown previously for other nitrile oxides.[10] 2,5-Dimethylfuran reacted with difficulty with the nitrile oxide, the main product being identified as the isoxazole **17** which was probably formed by cycloaddition of **12** to an oxidation product of dimethylfuran, (*E*)-hex-3-ene-2,5-dione, present as an impurity (although attempts to detect such an impurity, or to remove it, failed). The 3-substituted furan **18** was also formed but in very low yield. No adducts were formed when the nitrile oxide **12** was generated in the presence of 3-methylindole. Both 3-methylindole and 2,5-dimethylfuran give cycloadducts in high yield with the nitroso ester **2a**.[1,11] Dehaen and Hassner have reported an example of an intramolecular cycloaddition of a nitrile oxide across across the 2- and 3-positions of a 2-substituted furan[9] but we are not aware of any intermolecular cycloadditions of nitrile oxides to 2,5-disubstituted furans or to 3-substituted indoles.

Conclusions.—We have found that pyrroles react exclusively at the 2-position with the vinylnitroso and vinylazo esters **2** and that these reactions provide a useful route to new functionalised pyrrole esters. In contrast, 2,5-disubstituted pyrroles react at position 3 with the nitrile oxide ethyl cyanoformate *N*-oxide **12**. These results can be rationalised as involving cycloadditions with the intermediates **2** but electrophilic substitutions with the nitrile oxide **12**. Reactions of other 1,3-dipoles with 2,5-disubstituted pyrroles and furans would merit a more detailed investigation.

Experimental

General.—^{1}H NMR spectra were recorded either on a Bruker AC 200 (200 MHz) or on a Bruker AMX 400 (400 MHz) spectrometer. Multiplicities are recorded as broad peaks (br), doublets (d), triplets (t), quartets (q) and multiplets (m); other signals are singlets; *J* values are in Hz. IR spectra were recorded either on a Perkin-Elmer 298 or on a Perkin-Elmer 1720-X FTIR spectrometer. Solid samples were run as KBr discs unless indicated otherwise, and liquids as thin films. Mass spectra were recorded on a VG micromass 7070E as electron impact or chemical ionisation spectra. Microanalyses were performed in the University of Liverpool Microanalysis Laboratory. M.p.s were determined on a Kofler hot-stage apparatus. Flash column chromatograhy was carried out using Mackerey Nagel MN-Kieselgel 60 and hand bellows or an air line to supply the pressure to the column. Thin layer chromatography (TLC) was carried out on Merck 10 × 2 cm aluminium-backed plates with a 0.2 mm layer of Kieselgel 60 F_{254}. Ether refers to diethyl ether.

Ethyl 2-(2-*Hydroxyimino*)-3-(1-*methylpyrrol*-2-*yl*)*propanoate* **3b**.—The oxime **1a**[1] (0.75 g, 3.57 mmol) and 1-methylpyrrole (3.17 cm^3, 35.7 mmol) were stirred for 24 h in dichloromethane (35 cm^3) containing a suspension of sodium carbonate (3.0 g, 28.56 mmol). Flash chromatography [dichloromethane then dichloromethane–ethyl acetate (3:1) after removal of the excess of pyrrole] gave the hydroxyimino ester **3b** as a light brown solid (0.50 g, 67%), m.p. 103–105 °C (lit.,[1b] m.p. 98–101 °C); ν_{max}/cm^{-1} 3220, 1718, 1213, 1129, 1025 and 703; δ(400 MHz) 1.32 (3 H, t), 3.63 (3 H, s), 3.92 (2 H), 4.28 (2 H, q), 5.96–5.98 (1 H, m, 3-H of pyrrole), 6.02–6.03 (1 H, m, 4-H of pyrrole), 6.51–6.52 (1 H, m, 5-H of pyrrole) and 9.79 (1 H, br).

Ethyl 4a,6-*Dimethyl*-4,4a,7,7a-*tetrahydropyrrolo*[2,3-*e*]-1,2-*oxazine*-3-*carboxylate* **4a**.—The oxime **1a** (1.0 g, 4.76 mmol) and 2,5-dimethylpyrrole (4.84 cm^3, 47.6 mmol) in dichloromethane (45 cm^3) containing a suspension of sodium carbonate (4.04 g, 38.08 mmol) gave, after removal of the excess of dimethylpyrrole by distillation followed by flash chromatography [dichloromethane–ethyl acetate–ethanol (3:1:1)], the *oxazine* **4a** as a yellow oil (0.744 g, 70%); b.p. 165 °C at 0.5 mmHg (Kugelrohr oven temperature) (Found: C, 58.6; H, 7.2; N, 12.4%; M$^+$, 224.1165. $C_{11}H_{16}N_2O_3$ requires C, 58.9; H, 7.2; N, 12.5%; *M*, 224.1161); ν_{max}/cm^{-1} (film) 2980, 1725, 1650, 1385, 1280, 1015 and 733; δ(200 MHz) 1.22 (3 H, 4a-Me), 1.32 (3 H, t), 1.99 (3 H, 6-Me), 2.57 (1 H, d, 4-H, $J_{4,4'}$ 16.1), 2.68 (1 H, d, 4'-H), 2.78 (1 H, d, 7-H, $J_{7,7'}$ 18.7, $J_{7,7a}$ 0), 2.98 (1 H, dd, 7'-H, $J_{7',7a}$ 5.9), 4.11 (1 H, d, 7a-H) and 4.33 (2 H, q); *m*/*z* 224 (M$^+$, 1.5%), 179 (8), 151 (35), 96 (75) and 42 (100).

Ethyl 4a,6-*Diphenyl*-4,4a,7,7a-*tetrahydropyrrolo*[2,3-*e*]-1,2-*oxazine*-3-*carboxylate* **4b**.—The oxime **1a** (5.5 g, 26.2 mmol) and 2,5-diphenylpyrrole (4.07 g, 18.6 mmol) in dichloromethane (120 cm^3) containing a suspension of sodium carbonate (10.09 g, 95.2 mmol) gave, after flash chromatography [dichloromethane–ethyl acetate (39:1)], the *oxazine* **4b** (2.33 g, 36%), m.p. 94–95 °C (from dichloromethane–hexane) (Found: C, 72.5; H, 5.8; N, 8.0%; M$^+$, 348.1469. $C_{21}H_{20}N_2O_3$ requires C, 72.4; N, 5.8; N, 8.0%; *M*, 348.1474; ν_{max}/cm^{-1} (Nujol) 1718, 1615, 1449, 1295, 1063 and 812; δ(400 MHz) 1.36 (3 H, t), 3.12 (1 H, d, $J_{4,4'}$ 16.5, 4-H), 3.20 (1 H, d, 4'-H), 3.23 (1 H, d, $J_{7,7'}$ 18.3, $J_{7,7a}$ 6.3, 7-H), 3.38 (1 H, dd, $J_{7',7a}$ 1.3, 7'-H), 4.36 (2 H, q), 4.74 (1 H, dd, 7a-H), 7.25–7.32 (1 H, m), 7.34–7.36 (4 H, m), 7.43–7.52 (3 H, m) and 7.92 (2 H, dd, *J* 1.6 and 8.3); *m*/*z* 348 (M$^+$, 2%), 275 (61), 219 (73) and 103 (100).

Reactions of Ethyl 2-(2,4-*Dinitrophenylazo*)*propenoate* **2b** *with Pyrroles.*—*General procedures.* The hydrazone **1b** and the pyrrole in dichloromethane or tetrahydrofuran containing a suspension of anhydrous sodium carbonate were stirred together at room temperature for 16 h. The reaction mixture was filtered through Celite and the filtrate was evaporated to dryness. The products were isolated as indicated.

Ethyl 2-(2,4-*Dinitrophenylhydrazono*)-3-*pyrrol*-2-*ylpropanoate* **5a**.—The hydrazone **1b** (0.5 g, 1.3 mmol) and pyrrole (0.9 cm^3, 13.0 mmol) in dichloromethane (30 cm^3) containing a suspension of sodium carbonate (1.3 g, 13.0 mmol) gave by flash chromatograhy (dichloromethane) the *dinitrophenylhydrazone* **5a** (0.41 g, 89%), m.p. 152–154 °C (from dichloromethane–hexane) (Found: C, 49.65; H, 4.25; N, 19.15. $C_{15}H_{15}N_5O_6$ requires C, 49.85; H, 4.2; N, 19.4%); ν_{max}/cm^{-1} 3395, 3303, 1723, 1613, 1504 and 1137; δ([H_6]acetone, 200 MHz) 1.44 (3 H, t), 4.10 (2 H), 4.38 (2 H, q), 6.02–6.08 (1 H, m, 4-H), 6.17 (1 H, br, 3-H), 6.70–6.76 (1 H, m, 5-H), 8.16 (1 H, d, 6'-H), 8.39 (1 H, dd, 5'-H), 9.09 (1 H, d, 3'-H), 9.59 (1 H, br) and 11.44 (1 H, br s).

Ethyl 2-(2,4-*dinitrophenylhydrazono*)-3-(1-*methylpyrrol*-2-*yl*)-*propanoate* **5b**.—The hydrazone **1b** (0.75 g, 1.99 mmol) and 1-methylpyrrole (1.78 cm^3, 19.9 mmol) in dichloromethane (35 cm^3) containing a suspension of sodium carbonate (1.69 g, 16.0 mmol) gave, after flash chromatograhy [dichloromethane–hexane (3:1)], the *dinitrophenylhydrazone* **5b** (0.629 g, 84%), m.p. 45–47 °C (from ether) (Found: C, 50.9; H, 4.6; N, 18.5%; M$^+$, 375.1181. $C_{16}H_{17}N_5O_6$ requires C, 51.2; H, 4.6; N, 18.7%; *M*, 375.1179); ν_{max}/cm^{-1} 1713, 1618, 1591, 1505, 1332, 1267 and 1137; δ(200 MHz) 1.40 (3 H, t), 3.62 (3 H), 4.06 (2 H), 4.38 (2 H, q), 5.95–5.99 (2 H, m, 3-H and 4-H), 6.59–6.61 (1 H, m, 5-H), 8.11 (1 H, d, 6'-H), 8.35 (1 H, dd, 5'-H), 9.02, (1 H, d, 3'-H) and 11.27 (1 H, NH); *m*/*z* 375 (M$^+$, 24%), 193 (42), 119 (75) and 94 (100).

Ethyl 2-(2,4-*dinitrophenylhydrazono*]-3-[1-(*triisopropylsilyl*)-*pyrrol*-2-*yl*]*propanoate* **5c**.—The hydrazone **1b** (2.54 g, 6.77

mmol) (added in four portions of 0.635 g) and 1-(triisopropylsilyl)pyrrole (2.247 g, 10.0 mmol) in tetrahydrofuran (60 cm^3) containing a suspension of sodium carbonate (2.86 g, 27.0 mol) gave, after evaporation of the solvent and precipitation with ether, the *dinitrophenylhydrazone* **5c** as a yellow solid (0.19 g, 12%), m.p. 130 °C (from ether–hexane) (Found: C, 55.7; H, 6.8; N, 13.5. $C_{24}H_{35}N_5O_6Si$ requires C, 55.7; H, 6.8; N, 13.5%); ν_{max}/cm^{-1} 2952, 2870, 1726, 1620, 1585, 1498, 1359, 1347, 1270, 1136 and 1076; (400 MHz) 1.20 (18 H, d), 1.38 (3 H, t), 1.57–1.74 (3 H, m), 4.18 (2 H), 4.36 (2 H, q), 5.83 (1 H, 3-H of pyrrole), 6.11 (1 H, t, 4-H of pyrrole), 6.89 (1 H, 5-H of pyrrole), 8.20 (1 H, d, 6′-H), 8.42 (1 H, dd, 5′-H), 9.10 (1 H, d, 3′-H) and 11.34 (1 H, NH); *m/z* (CI) 518 [$(M + H)^+$, 14%] and 337 (100).

The structure of the dinitrophenylhydrazone **5c** was established by desilylation as follows. To the hydrazone **5c** (0.060 g, 0.13 mmol) in dry tetrahydrofuran (5 cm^3) was added a solution of tetrabutylammonium fluoride in tetrahydrofuran (1 mol dm^{-3}; 0.05 cm^3, 0.5 mmol) and the mixture was stirred under nitrogen for 20 min. Evaporation of the solvent and flash chromatography [dichloromethane–ethyl acetate (5:1] gave the dinitrophenylhydrazone **5a** as a yellow solid (0.031 g, 66%), m.p. 152–154 °C. This was identified by comparison with the specimen prepared previously.

Ethyl 1-(2,4-*Dinitrophenylhydrazono*)-4a,6-*dimethyl*-4,4a,7,7a-*tetrahydropyrrolo*[3,2-c]*pyridazine*-3-*carboxylate* **6a**.—The hydrazone **1b** (2.1 g, 5.6 mmol) and 2,5-dimethylpyrrole (2.64 g, 27.7 mmol) in dichloromethane (50 cm^3) containing a suspension of sodium carbonate (4.75 g, 45 mmol) gave, by flash chromatography [ethyl acetate–dichloromethane–ethanol (2:1:1)], a thick yellow oil which on treatment with ether precipitated the *pyridazine* **6a** as a yellow solid (2.10 g, 96%), m.p. 112–114 °C (from dichloromethane–hexane) (Found: C, 52.6; H, 4.9; N, 17.8%; M^+, 389.1332. $C_{17}H_{19}N_5O_6$ requires C, 52.4; H, 4.9; N, 18.0%; *M*, 389.1335); ν_{max}/cm^{-1} 2979, 2933, 1709, 1634, 1608, 1369, 1319, 1249, 1207 and 1153; δ(200 MHz) 1.35 (3 H, t), 1.40 (3 H, 4a-Me), 2.02 (3 H, 6-Me), 2.63 (1 H, dd, $J_{7,7'}$ 17.4, $J_{7,7a}$ 5.4, 7-H), 2.64 (2 H, 4-H and 4′-H), 3.17 (1 H, dd, $J_{7',7a}$ 7.4, 7′-H), 4.18 (1 H, dd, 7a-H), 4.22–4.31 (2 H, m, OCH_2CH_3), 7.25 (1 H, d, 6-H of 2,4-dinitrophenyl), 8.32 (1 H, dd, 5-H) and 8.50 (1 H, d, 3-H); *m/z* 389 (M^+, 10%), 107 (19), 95 (71) and 94 (100%).

Reactions of Ethyl 2-(tert-*Butoxycarbonylazo*)*propenoate* **2c** *with Pyrroles.—General procedure.* Ethyl bromopyruvate *tert*-butoxycarbonylhydrazone **1c** and the appropriate pyrrole were stirred together in dichloromethane or tetrahydrofuran with anhydrous sodium carbonate at room temperature for 16 h. The reaction mixture was filtered through Celite and the filtrate was evaporated to dryness. The products were isolated as indicated.

Ethyl 2-(tert-*Butoxycarbonylhydrazono*)-3-*pyrrol*-2-*ylpropanoate* **5d**.—The hydrazone **1c** (0.75 g, 2.45 mmol) and pyrrole (1.36 cm^3, 19.6 mmol) in dichloromethane (40 cm^3) containing a suspension of sodium carbonate (2.15 g, 19.6 mmol) gave, by flash chromatography [ethyl acetate–dichloromethane (1:1)], the *hydrazone* **5d** (0.54 g, 75%), m.p. 141 °C (colourless crystals from dichloromethane–hexane) (Found: C, 56.8; H, 7.15; N, 14.2%; M^+, 295.1535. $C_{14}H_{21}N_3O_4$ requires C, 56.9; H, 7.2; N, 14.2%; *M*, 295.1532); ν_{max}/cm^{-1} 3450, 3410, 3200, 1700 and 161; δ(200 Mz) 1.34 (3 H, t), 1.49 (9 H) 3.68 (2 H), 4.31 (2 H, q), 6.05 (1 H, br), 6.09–6.13 (1 H, m), 6.70 (1 H, br), 8.54 (1 H, NH) and 8.71 (1 H, NH); *m/z* 295 (M^+, 2.5%), 239 (56) and 57 (100).

In a separate experiment an NMR spectrum of the crude reaction product was obtained after 12 h and this showed, in addition to the signals for the hydrazone **5d**, signals of a minor component (*ca.* 20% of the total) which were ascribed to the pyridazine **6c**: δ(200 MHz) 2.43 (1 H, dd, *J* 17.1 and 6.3, 4-H), 2.59 (1 H, dd, *J* 18.3 and 6.0, 7-H), 2.93 (1 H, dd, *J* 17.1 and 5.9, 4′-H), 3.11 (1 H, dd, *J* 18.3 and 7.4, 7′-H) and 7.70 (1 H, 6-H). Signals for 4a-H and 7a-H were obscured. Flash chromatography of the reaction mixture gave only the hydrazone **5d**. (We thank Emma S. Tomlinson for repeating this experiment.)

Ethyl 2-tert-*butoxycarbonylhydrazono*-3-(1-*methylpyrrol*-2-*yl*)*propanoate* **5e**. The hydrazone **1c** (0.9 g, 2.91 mmol) and 1-methylpyrrole (2.6 cm^3, 29.1 mmol) in dichloromethane (40 cm^3) containing a suspension of sodium carbonate (2.47 g, 23.38 mmol) gave, by flash chromatography [dichloromethane first, and after removal of the excess of 1-methylpyrrole, dichloromethane–ethyl acetate (3:2], the *hydrazone* **5e** (0.068 g, 7.6%), m.p. 139–140 °C (from ether) (Found: C, 58.2; H, 7.5; N, 13.6%; M^+, 309.1683. $C_{15}H_{23}N_3O_4$ requires C, 58.2; H, 7.5; N, 13.6%; *M*, 309.1689); ν_{max}/cm^{-1} 3192, 1708, 1545, 1253, 1202 and 1147; δ([$^2H_6$]acetone, 200 MHz) 1.24 (3 H, t), 1.40 (9 H), 3.48 (3 H), 3.88 (2 H), 4.17 (2 H, q), 5.65 (1 H, br, 3-H of pyrrole), 5.82 (1 H, t, 4-H), 6.50 (1 H, *ca.* t, 5-H) and 9.29 (1 H, br, NH); *m/z* 309 (M^+, 1%), 253 (23), 209 (28), 119 (100) and 94 (78).

Ethyl 1-(tert-*butoxycarbonylhydrazono*)-4a,6-*dimethyl*-4,4a,7,7a-*tetrahydropyrrolo*[3,2-c]*pyridazine*-3-*carboxylate* **6b**. The hydrazone (1.1 g, 3.56 mmol) and 2,5-dimethylpyrrole (3.95 cm^3, 38.8 mmol) in tetrahydrofuran (50 cm^3) containing a suspension of sodium carbonate (3.29 g, 31.0 mmol) gave, after distillation of the excess of pyrrole followed by flash chromatography [dichloromethane–ethyl acetate–ethanol (6:4:1)], the *pyridazine* **6b** (1.05 g, 91%), m.p. 109–110 °C (from dichloromethane–hexane) (Found: C, 59.55; H, 7.8; N, 13.0%; M^+, 323.1843. $C_{16}H_{25}N_3O_4$ requires C, 59.4; H, 7.8; N, 13.0%; *M*, 323.1845); ν_{max}/cm^{-1} 1704, 1596, 1549, 1326, 1257, 1177 and 1150; δ(200 MHz) 1.31 (3 H, 4a-Me), 1.39 (3 H, t), 1.60 (9 H), 2.03 (3 H, 6-Me), 2.31 (1 H, d, $J_{4,4'}$ 17.1, 4-H), 2.47 (1 H, dd, $J_{7,6'}$ 17.6, $J_{7,7a}$ 8.0, 7-H), 2.76 (1 H, d, 4′-H), 3.13 (1 H, dd, $J_{7',7a}$ 6.9, 7′-H), 4.17 (1 H, *ca.* 5, 7a-H) and 4.32 (2 H, q); *m/z* 324 [$(M + H)^+$, 0.2%], 323 (M^+, 0.2), 223 (7), 150 (23) and 57 (100).

Reactions of Ethyl Cyanoformate N-*Oxide* **12** *with Pyrroles and Furans.—General procedure.* To the substrate in dichloromethane containing anhydrous sodium carbonate was added the oxime **13**[12] in dichloromethane by means of a syringe pump over a period of 14–16 h (except where indicated). The reaction mixture was filtered through Celite and the filtrate was evaporated to dryness. The products were isolated as indicated.

Ethyl hydroxyimino(*pyrrol*-2-*yl*)*acetate* **14**. Pyrrole (2.29 cm^3, 33.0 mmol) in dichloromethane (35 cm^3) with sodium carbonate (1.4 g, 13.2 mmol) and the oxime **13** [(0.5 g, 3.3 mmol) added in one portion] gave, after removal of the excess of pyrrole by distillation and recrystallisation of the solid redidue, the *acetate* **14** (0.34 g, 57%) as a pale yellow solid, m.p. 148–150 °C (from dichloromethane–hexane) (Found: C, 52.5; H, 5.5; N, 15.3. $C_8H_{10}N_2O_3$ requires C, 52.7; H, 5.5; N, 15.4%); ν_{max}/cm^{-1} 3427, 3187, 1703, 1382, 1126, 1025 and 738; δ(400 MHz, [$^2H_6$]acetone) 1.32 (3 H, t), 4.32 (2 H, q), 6.20–6.22 (1 H, m, 3-H of pyrrole), 6.91–6.93 (1 H, m, 4-H of pyrrole), 7.02–7.06 (1 H, m, 5-H of pyrrole), 11.11 (1 H, br) and 11.36 (1 H, br); *m/z* 182 (M^+, 75%) and 106 (100).

Ethyl 2,5-*dimethylpyrrol*-3-*yl*(*hydroxyimino*)*acetate* **15a**. 2,5-Dimethylpyrrole (3.36 cm^3, 33.0 mmol) in dichloromethane (35 cm^3) with sodium carbonate (1.4 g, 13.2 mmol) and the oxime **13** (0.5 g, 3.3 mmol) in dichloromethane (10 cm^3) added by syringe pump gave, after removal of the excess of dimethylpyrrole followed by flash chromatography [dichloromethane–ethyl acetate (3:1)], *acetate* **15a** (0.362 g, 52%), m.p. 123–124 °C (from dichloromethane–hexane) (Found: C, 57.2; H, 6.7; N, 13.4%; M^+, 210.1006. $C_{10}H_{14}N_2O_3$

requires C, 57.1; H, 6.7; N, 13.3%; *M*, 210.1004); ν_{max}/cm^{-1} 3343, 1697, 1316, 1192 and 1000; δ(400 MHz, [$^2H_6$]acetone) 1.29 (3 H, t), 2.12 (3 H), 2. 16 (3 H), 4.24 (2 H, q), 6.17 (1 H), 9.72 (1 H, br) and 10.62 (1 H); *m/z* 210 (M^+, 55%), 193 (89), 121 (82), 120 (93) and 119 (100).

Ethyl 2,5-*diphenylpyrrol*-3-*yl*(*hydroxyimino*)*acetate* **15b**. 2,5-Diphenylpyrrole (1.23 g, 5.61 mmol) in ether (20 cm^3) with sodium carbonate (2.16 g, 20.4 mmol) and the oxime (0.78 g, 5.1 mmol) in dichloromethane (10 cm^3) added by syringe pump gave, by flash chromatography [ethyl acetate–hexane (1:3)], the *acetate* **15b** (0.349 g, 20%), m.p. 211–212 °C (from dichloromethane–hexane) (Found: C, 71.7; H, 5.4; N, 8.4%; M^+, 334.1321. $C_{20}H_{18}N_2O_3$ requires C, 71.8; H, 5.4; N, 8.4%; *M*, 334.1321); ν_{max}/cm^{-1} 3410, 3220 and 1171; δ(400 MHz) 0.97 (3 H, t), 3.82 (2 H, q), 7.01 (1 H, d, *J* 2.7, 4-H of pyrrole), 7.21–7.47 (8 H, m), 7.77 (2 H, d, *J* 8.2), 10.72 (1 H, br) and 11.07 (1 H); *m/z* 334 (M^+, 100%).

Ethyl 3a,6a-*dihydrofuro*[2,3-d]*isoxazole*-3-*carboxylate* **16**. Furan (3.6 cm^3, 49.5 mmol) in dichloromethane (30 cm^3) with sodium carbonate (4.0 g, 39.6 mmol) and the oxime **13** (0.75 g, 4.95 mmol) in dichloromethane (10 cm^3) added by syringe pump gave, by flash chromatography, the *ester* **16** (0.263 g, 29%) as a colourless oil, b.p. 135 °C at 0.4 mmHg (Kugelrohr oven temp.) (Found: C, 52.7; H, 5.0; N, 7.9. $C_8H_9O_4$ requires C, 52.5; H, 4.95; N, 7.65%); ν_{max}/cm^{-1} (film) 1723, 1607, 1245, 1114 and 1056; δ(200 MHz) 1.36 (3 H, t), 4.36 (2 H, q), 5.35 (1 H, t, *J* 2.5, 6-H), 6.03–6.13 (2 H, m, 3a-H and 6a-H) and 6.61 (1 H, d, *J* 2.5, 5-H); *m/z* (CI) 201 [$(M + NH_4)^+$, 100] and 184 [$(M + H)^+$, 28].

Reaction with 2,5-*dimethylfuran*. 2,5-Dimethylfuran (5.23 cm^3, 49.5 mmol) in dichloromethane (40 cm^3) with sodium carbonate (4.20 g, 39.6 mmol) and the oxime **13** (0.75 g, 4.95 mmol) in dichloromethane (10 cm^3) added by syringe pump over 24 h gave, by flash chromatography (dichloromethane), *ethyl* trans-4,5-*diacetyl*-4,5-*dihydroisoxazole*-3-*carboxylate* **17** (0.165 g) as a colourless oil (Found: C, 53.3; H, 5.8; N, 6.5. $C_{10}H_{13}NO_5$ requires C, 52.9; H, 5.8; N, 6.2%); ν_{max}/cm^{-1} (film) 1723, 1361, 1216, 1125 and 936; δ(200 MHz) 1.37 (3 H, t), 2.38 (3 H), 2.43 (3 H), 4.73 (1 H, d, *J* 6.95) and 5.24 (1 H, d, *J* 6.95); *m/z* 227 (M^+, 17%), 142 (58) and 43 (100).

Further elution gave *ethyl* 2,5-*dimethyl*-3-*furyl*(*hydroxyimino*)*acetate* **18** (0.032 g, 3%) as an oil (Found: M^+, 211.0844. $C_{10}H_{13}NO_4$ requires *M*, 211.0845); ν_{max}/cm^{-1} (CH_2Cl_2) 1727, 1378, 1168 and 1036; δ(200 MHz, [$^2H_6$]acetone) 1.24 (3 H, t), 2.16 (3 H), 2.21 (3 H), 4.24 (2 H, q), 6.19 (1 H) and 11.30 (1 H, br); *m/z* 211 (M^+, 11%), 194 (20), 138 (22), 122 (19), 121 (39), 120 (40) and 43 (100).

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