Reaction of heterocyclic enamines with nitrile oxide and nitrilimine precursors†

Cevher Altuğ,[a,b] Yasar Dürüst,[b] Mark C. Elliott,*[a] Benson M. Kariuki,[a] Tillique Rorstad[a] and Mark Zaal[a]

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Alkylidenepyrrolidines **1**, **21**, **24** and **26** undergo reactions with nitrile oxides and nitrilimines or their precursors to give a range of novel heterocyclic compounds. With alkylidenepyrrolidine ester **1**, nitrolic acids give products in which the liberated nitrous acid reacts with the alkylidenepyrrolidine, followed by two cycloadditions to give adducts **3**. In contrast, hydroximoyl chlorides give isoxazoles **10**, presumably by cycloaddition/elimination. With hydrazonyl chlorides, simple acylation of the alkylidenepyrrolidine occurs to give compounds **17**. With sulfonyl alkylidenepyrrolidines **24** and **26**, cycloaddition onto the imine tautomer is the preferred pathway, with a stereoselective reaction taking place in the latter case.

Introduction

Nitrile oxides[1] and nitrilimines[2] are versatile 1,3-dipoles,[3] undergoing cycloaddition reactions with a wide range of alkenes and alkynes. Nitrile oxides are generally prepared by treatment of hydroxamic acid chlorides with base, or by oxidation of aldoximes, although their formation by elimination of HNO_2 from nitrolic acids has also been reported.[4] This latter method has not yet seen widespread application. There are a small number of reports of reactions of nitrilimines and their hydrazonyl chloride precursors with heterocyclic enamines, with both acylation[5] and cycloaddition products[6] being reported. Alkylidenepyrrolidines are versatile synthetic intermediates, and have been converted into a broad range of compounds of biological interest.[7] As part of our continued interest in this class of compound,[8] we have investigated the reactions of alkylidenepyrrolidines with nitrile oxide and nitrilimine precursors, and now report the results of this investigation in full.[9]

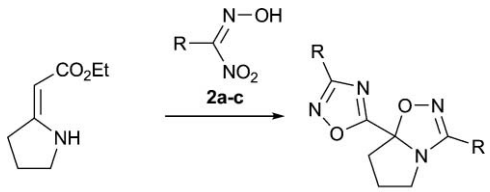
Results and discussion

The reactions of nitrolic acids **2** with alkylidenepyrrolidine **1** give compounds **3** in good yield (Table 1). The structural assignment of compound **3a** was confirmed by single-crystal X-ray diffraction (Fig. 1), with other compounds being assigned by analogy.

For the formation of compound **3a**, simply heating the precursors in benzene is sufficient, while the reaction to produce compound **3c** requires a slightly higher temperature. Reaction of nitrolic acid **2b** was considerably slower, but was accelerated by microwave irradiation (Table 1). In all cases, complete consumption of the alkylidenepyrrolidine reagent **1** was observed.

The formation of these products was rationalised by the mechanism shown in Scheme 1. The nitrous acid liberated upon heating compound **2a** is trapped by the alkylidenepyrrolidine, giving nitrosoalkene **4** or its oxime tautomer **5**. The presence of the oxime will presumably render the ester more susceptible to hydrolysis, and there is precedent for the decarboxylation of oximinocarboxylic acids, albeit on the corresponding *O*-acyl compounds,[10] so that ester hydrolysis and decarboxylation to give the nitrile **6** is not unreasonable (ester hydrolysis/decarboxylation to give the aldoxime, followed by nitrile oxide cycloaddition/dehydration is also a possibility[11]). From this point, cycloaddition of the nitrile oxide **7** onto the nitrile[12] and imine[13] bonds will give the observed product **3**.

Table 1 Formation of adducts **3**



1 **3a-c**

Compound	R	Conditions	Yield (%)
3a	6-Chloro-3-pyridyl	Benzene, reflux, 2 h	76
3b	4-Pyridyl	110 °C, 100 W, 10 min[a]	58
3c	Me	Toluene, reflux, 2 h	65

[a] CEM Discover microwave reactor

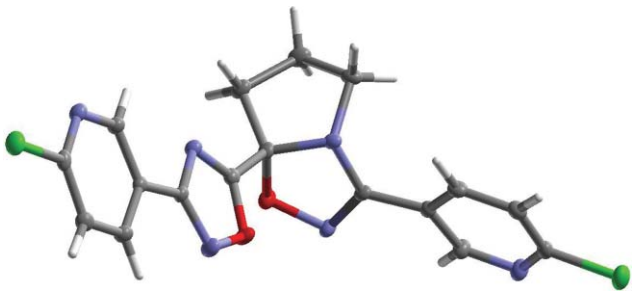


Fig. 1 Structure of compound **3a** from single crystal X-ray data.

[a]*School of Chemistry, Cardiff University, Park Place, Cardiff, UK, CF10 3AT. E-mail: elliottmc@cardiff.ac.uk; Fax: +44 29 20874030; Tel: +44 29 20874686*
[b]*Department of Chemistry, Abant İzzet Baysal University, TR-14280 Bolu, Turkey*

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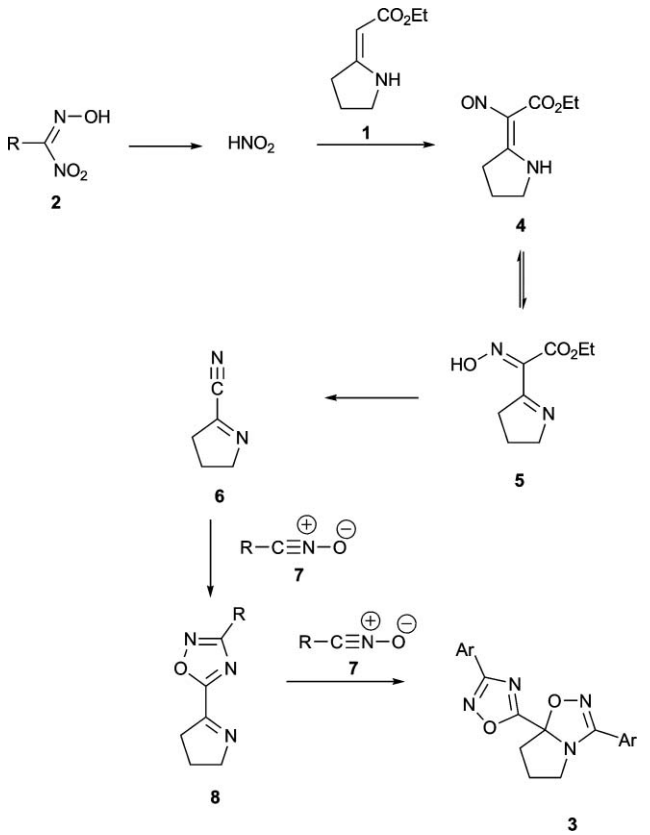
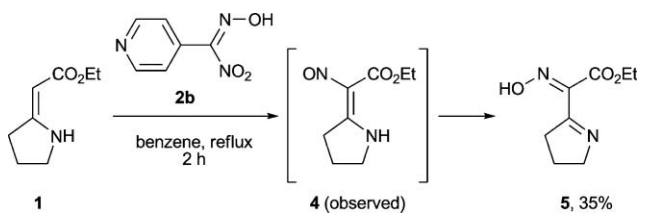


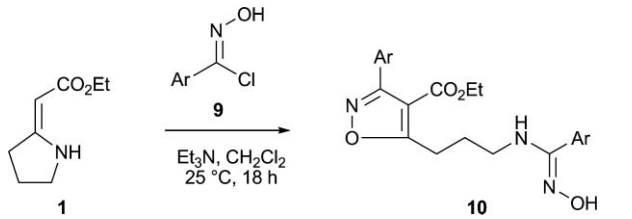
Scheme 1

Upon examination of crude reaction mixtures, particularly for the slower reactions, a by-product was observed in which the alkylidenepyrrolidine was clearly present, but lacking its alkene hydrogen. This therefore appeared to be consistent with either structure **4** or **5**. Upon chromatography, compound **5** was obtained (Scheme 2), this being similar, but not identical to, the compound observed in the crude reaction mixtures. We therefore assign the product observed in the crude reaction mixtures to be compound **4**, which undergoes tautomerisation to give the more stable compound **5** upon purification. The modest yield of this compound is due to its isolation from the crude reaction mixture under milder conditions which led to lower conversion. The oxime carbon in compound **5** resonates at 143.1 ppm, whereas the corresponding carbon in alkylidenepyrrolidine **1** resonates at 76.5 ppm. Nitrosation of the alkene, as in compound **4**, is unlikely to lead to such a dramatic increase, whereas related α-oximinoesters show very similar chemical shifts.[10,14] Reaction of phenylnitrolic acid only gave compound **4**, with compound **3** not observed even under forcing conditions.



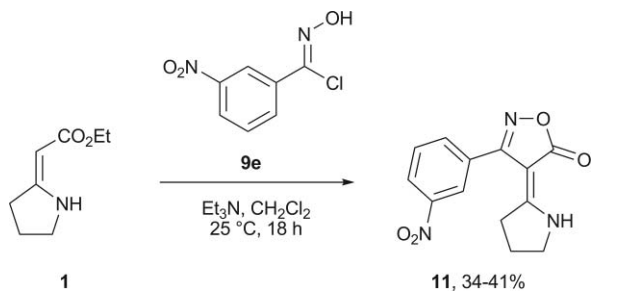
Scheme 2

Table 2 Formation of adducts **10**



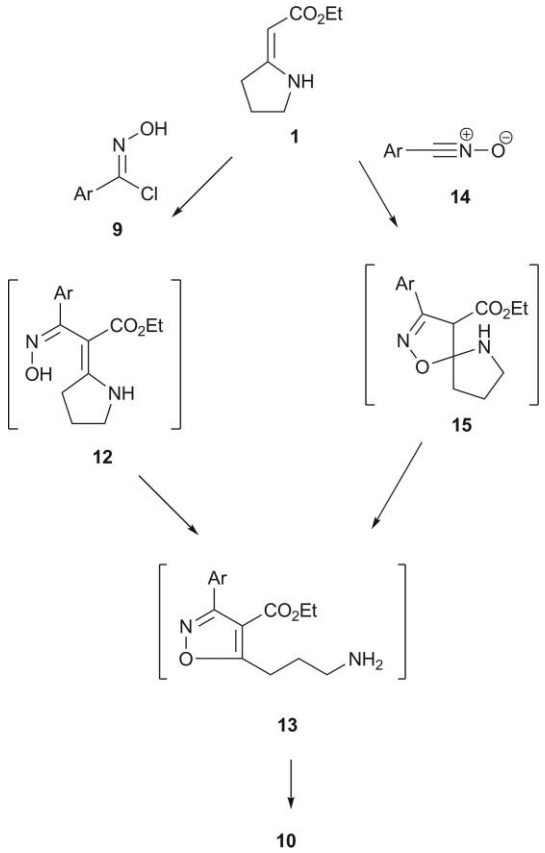
Compound	Ar	Yield (%)
10a	Phenyl	68
10b	2,6-Dichlorophenyl	69
10c	2,4-Dichlorophenyl	67
10d	2-Nitrophenyl	56

These reactions give interesting products with a considerable increase in molecular complexity. However, the reactions do not involve direct reaction of the nitrile oxide with the alkylidenepyrrolidine, and so we elected to investigate reactions of the corresponding α-chlorooximes **9** under basic conditions to form the nitrile oxides without this added complexity. In this case, isoxazoles **10** were formed (Table 2). Use of a single equivalent of the α-chlorooxime gave the same products, but in lower yield and with some alkylidenepyrrolidine left unreacted. However, when the 3-nitrophenyl chlorooxime **9e** was used, compound **11** was obtained as the sole product (Scheme 3).

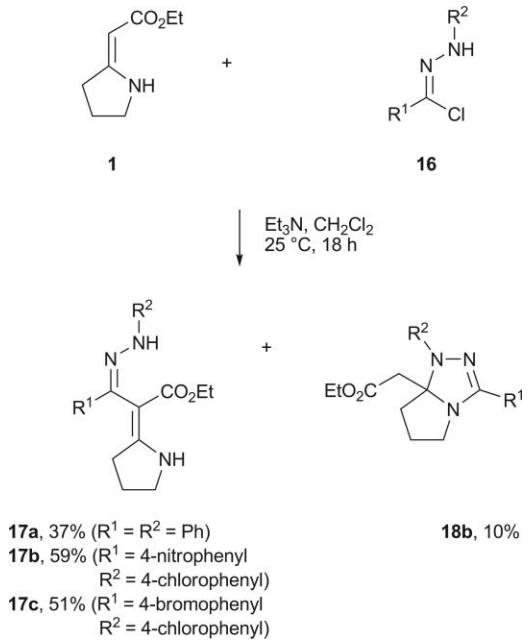


Scheme 3

There are two possible distinct mechanisms for the formation of compounds **10**. Initial *C*-acylation of compound **1**[15] could lead to the formation of compound **12**. This would then undergo isomerisation to compound **13** followed by a second rapid acylation. Alternatively, cycloaddition of nitrile oxide **14** onto the alkylidenepyrrolidine **1** would give spirocyclic compound **15** which could undergo elimination to give the same compound **13**. There is some precedent for the isomerisation of compounds **12** to give the isoxazoles in the work of Dannhardt on the reaction of alkylidenepyrrolidine ketones with hydroxylamine.[16] The reverse of the ring transformation in Scheme 4 is known, leading to the formation of aromatic pyrrole compounds from suitably substituted isoxazoles.[17] However, Dadiboyena and co-workers have recently reported[6] the cycloaddition/elimination pathway for the corresponding nitrilimines. Since cyclisation of intermediate **12** would require the oxime geometry shown, and would be a disfavoured 5-*endo-trig* cyclisation, we would also tend to favour the cycloaddition/elimination pathway for the formation of compounds **10**. It is not clear why compound **11** is formed from α-chlorooxime **9e**. It is conceivable that the nitrile oxide



Scheme 4



Scheme 5

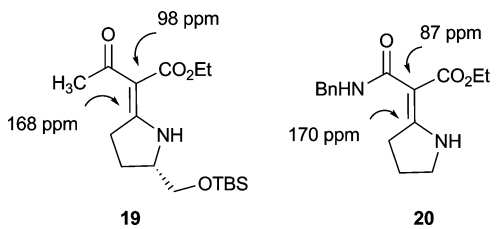


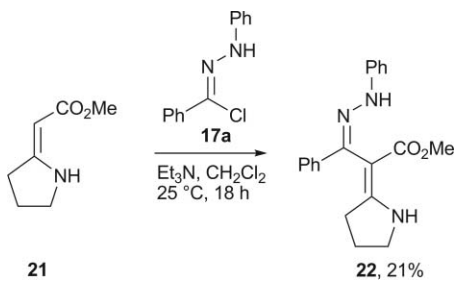
Fig. 2

14 would be formed more rapidly from compounds **9b–d** due to steric acceleration. However, rapid formation of cycloadducts from compound **9e** has been reported,[18] and if this was the explanation, we would also expect to observe a similar product from α-chlorooxime **9a**.

The reaction of alkylidenepyrrolidines, including compound **1**, with α-chlorohydrazones **16** has been reported to give products **17** by simple acylation of the alkylidenepyrrolidine double bond.[5] The possibility that the products **17** could isomerise to give the corresponding pyrazoles was mentioned by the authors, but only to exclude these compounds as possible reaction products. We were intrigued by the difference between the behaviour of α-chlorooximes and α-chlorohydrazones, and therefore reacted alkylidenepyrrolidine **1** with several α-chlorohydrazones (Scheme 5).

In each case, the major product (**17**) obtained has NMR data broadly in line with that reported by Miao *et al.*[5] In one case we obtained an additional product **18b**, formed by 1,3-dipolar cycloaddition onto the imine tautomer of the alkylidenepyrrolidine. We were initially surprised by some aspects of the NMR data for compounds **17**. In particular, the two hydrogen atoms at position 4 of the pyrrolidine ring are clearly in different environments, and we were also rather surprised that the ^{13}C chemical shift of C-α in compound **17c** is 79.8 ppm, compared to 76.6 ppm in compound **1**. Acylation will typically increase the chemical shift of this carbon further, for example to 97.7 ppm in compound **19**[19] and 86.6 ppm in compound **20**[20] (Fig. 2).

We therefore sought unambiguous proof of these structural assignments, and obtained an X-ray structure of compound **22**, prepared from the alkylidenepyrrolidine methyl ester **21** in the same manner (Scheme 6, Fig. 3). It is clear from this structure that the hydrazone group is almost perpendicular to the alkylidenepyrrolidine double bond, which explains the apparent diastereotopicity as well as the relatively minor effect of the hydrazone on the alkene carbon chemical shift. The low yield in this case is more likely attributable to losses on purification rather than any fundamental problem with the reaction.



Scheme 6

The isolation of compounds **17** and **22** rather than the pyrazole **23** (analogous to compounds **10**) is surprising. If these reactions proceeded by nitrilimine cycloaddition followed by fragmentation (Scheme 7) it seems unlikely that compounds **17**/**22** would be formed exclusively, at the expense of the aromatic pyrazole. We

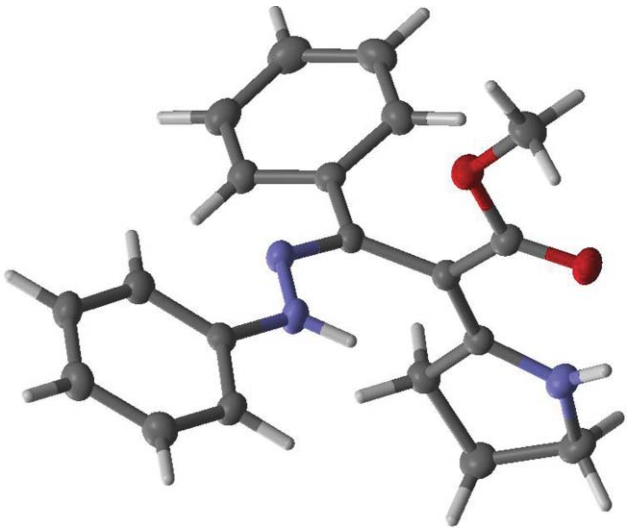
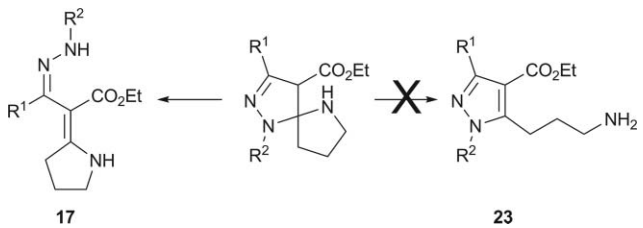


Fig. 3 Structure of compound **22** from single crystal X-ray data.



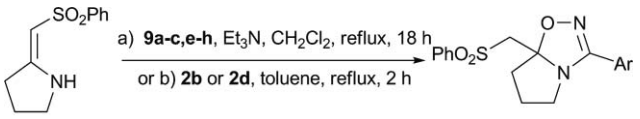
Scheme 7

would therefore favour a simple acylation mechanism in this instance.

The formation of compound **18b** presents an interesting opportunity. We considered the possibility that with alkylidenepyrrolidines with substituents that are less able to stabilise the enamine tautomer, this type of reaction could become the predominant pathway. With the sulfone **24**, this is indeed the case, with the reaction being high-yielding and general for the formation of compounds **25** (Table 3) using either nitrolic acids or hydroximoyl chlorides as nitrile oxide precursors.

These results then presented a further opportunity; the use of chiral alkylidenepyrrolidines to deliver diastereoselective cycloaddition chemistry. Alkylidenepyrrolidine **26** was prepared by a method previously developed in the Elliott group.[21] Reaction of this compound with a representative range of hydroximoyl chlorides gave the corresponding cycloadducts **27**, all as single diastereoisomers. Although we were unable to obtain diagnostic nOe enhancements that would confirm the stereochemistry, the stereochemistry shown in Table 4 seems most likely as a result of approach of the nitrile oxide to the least hindered face of the imine tautomer. Compound **27b** shows evidence of hindered rotation of the 2,6-dichlorophenyl ring (broadening of peaks in the ^{13}C NMR spectrum) which was not observed for compound **25b**. Molecular modelling[22] shows that the 2,6-dichlorophenyl ring is close to the ester in both possible diastereoisomers, and therefore we are unable to assign stereochemistry based on this observation.

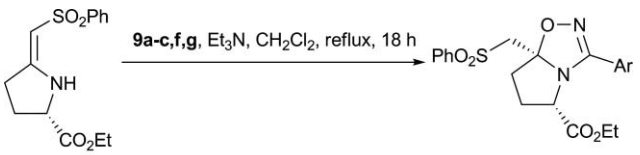
Table 3 Formation of adducts **25**



24 25a-c,e-j

Product	Method	Ar	Yield (%)
25a	a	Phenyl	69
25b	a	2,6-Dichlorophenyl	75
25c	a	2,4-Dichlorophenyl	44
25e	a	3-Nitrophenyl	76
25f	a	4-Fluorophenyl	73
25g	a	4-Bromophenyl	66
25h	a	Thien-2-yl	78
25i	b	4-Pyridyl	68
25j	b	3-Pyridyl	58

Table 4 Formation of adducts **27**



26 27a-c,f,g

Product	Ar	Yield (%)
27a	Phenyl	46
27b	2,6-Dichlorophenyl	51
27c	2,4-Dichlorophenyl	65
27f	4-Fluorophenyl	56
27g	4-Bromophenyl	29[a]

[a] = 47% based on recovered **26**.

Conclusion

A range of interesting heterocyclic systems has been obtained by the reaction of alkylidenepyrrolidines with 1,3-dipoles and/or their precursors. The differing products obtained with quite similar systems would have made it difficult to predict the outcome of these reactions.

Experimental section

General experimental points

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a Fisons VG Platform II spectrometer and on a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C at 25 °C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (J) are reported in Hz. Crystallographic data were recorded on a Nonius KappaCCD diffractometer equipped with an Oxford Cryosystem cryostat. The structures were solved by direct methods with additional light atoms found by Fourier methods. Hydrogen atoms were added at calculated positions and refined using a riding model. Anisotropic displacement parameters

were used for all non-H atoms; H-atoms were given isotropic displacement parameters equal to 1.2 or 1.5 times the equivalent isotropic displacement parameter of the atom to which the H-atom is attached. Alkylidenepyrrolidines **1** and **24** were prepared according to a literature procedure;[21] compound **21** was prepared by a similar method. The nitrolic acids,[23] α-chlorooximes[24] and α-chlorohydrazones[25] used in this study were all prepared by standard methods.

3-(6-Chloropyridin-3-yl)-7a-[3-(6-chloropyridin-3-yl)-1,2,4-oxadiazol-5-yl]-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (3a)

6-Chloropyridin-3-nitrolic acid (**2a**) (2.0 eq., 201 mg, 1.0 mmol) was added to ethyl 2-pyrrolidin-2-ylidene acetate (**1**) (77.5 mg, 0.5 mmol) in dry benzene (10 mL) and the mixture was heated to reflux for 2 h. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent 1 : 1 petroleum ether–ethyl acetate) to give the *title compound* (154 mg, 76%) as a yellow solid, m.p. 162–163 °C ($CDCl_3$); $\nu_{max.}$ (KBr) 3060, 2980, 1597, 1584, 1382, 1134, 1113, 840 and 740 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 9.03 (1 H, dd, *J* 2.4, 0.6, pyridine 2-H), 8.71 (1 H, d, *J* 2.4, 0.6, pyridine 2-H), 8.27 (1 H, dd, *J* 8.4, 2.4, pyridine 4-H), 8.02 (1 H, dd, *J* 8.4, 2.4, pyridine 4-H), 7.40 (1 H, dd, *J* 8.4, 0.6, pyridine 5-H), 7.38 (1 H, dd, *J* 8.4, 0.6, pyridine 5-H), 3.43–3.40 (2 H, m, CH_2N), 2.88 (1 H, ddd, *J* 14.2, 10.7, 6.9, one of CH_2C), 2.72 (1 H, ddd, *J* 14.2, 7.1, 3.3, one of CH_2C), 2.15–2.07 (1 H, m, one of CH_2CH_2N) and 2.05–1.98 (1 H, m, one of CH_2CH_2N); δ_C (100 MHz; $CDCl_3$) 178.2 (C), 166.3 (C), 156.8 (C), 154.7 (C), 154.5 (C), 149.3 (CH), 149.2 (CH), 138.3 (CH), 137.9 (CH), 125.2 (CH), 125.1 (CH), 122.0 (C), 121.1 (C), 104.4 (C), 54.1 (CH_2), 37.7 (CH_2) and 25.6 (CH_2); *m*/*z* (TOF ES^+) 446 (MH^+ + CH_3CN, 67%), 444 (MH^+ + CH_3CN, 100), 405 (M^+, 16) and 403.0 (M^+, 25). Selected crystallographic data: $C_{17}H_{12}Cl_2N_6O_2$, FW = 403.23, *T* = 150(2) K, λ = 0.71073 Å, Monoclinic, $P2_1/c$, *a* = 6.8900(3) Å, *b* = 13.7810(5) Å, *c* = 18.1120(9), β = 94.5030(10)°, *V* = 1714.45(13) $Å^3$, *Z* = 4, ρ(calc) = 1.562 Mg m^{-3}, crystal size = 0.50 × 0.12 × 0.12 mm^3, reflections collected = 6624, independent reflections = 3885, *R*(int) = 0.0569, parameters = 244, R_1 [$I > 2\sigma(I)$] = 0.0848, wR_2 [$I > 2\sigma(I)$] = 0.188, R_1 (all data) = 0.117, wR_2 (all data) = 0.205. Full crystallographic data for this compound have been deposited with the CCDC, reference number 731459.†

3-(Pyridin-4-yl)-7a-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (3b)

Pyridine-4-nitrolic acid (**2b**) (334 mg, 2 mmol) was added to ethyl 2-pyrrolidin-2-ylidene acetate (**1**) (155 mg, 1 mmol) in dry toluene (4 mL) and the mixture was heated in a CEM Discover microwave reactor for 10 min (100 W, 110 °C, 240 Psi). The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent 20 : 20 : 1 petroleum ether–ethyl acetate–methanol) to give the *title compound* (193 mg, 58%) as a pale oil (Found: M^+, 334.1183; $C_{17}H_{14}N_6O_2$ requires M, 334.1178); $\nu_{max.}$ (neat) 2924, 1679, 1599, 1375, 1257, 835 and 799 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.73–8.67 (4 H, m), 7.92 (2 H, app. broad d, *J* 6.1), 7.63–7.59 (2 H, m), 3.53–3.29 (2 H, m, CH_2N), 2.89 (1 H, ddd, *J* 14.2, 10.8, 6.9, one of CH_2C), 2.73 (1 H, ddd, *J* 14.2 7.1, 3.1, one of CH_2C), 2.15–2.06 (1 H, m, one of CH_2CH_2N) and 2.05–1.99 (1H, m, one of CH_2CH_2N); δ_C (100 MHz; $CDCl_3$) 177.8 (C), 167.0 (C), 157.6 (C), 150.5 (4 × CH), 133.8 (C), 132.8 (C), 121.7 (2 × CH), 121.4 (2 × CH), 104.3 (C), 53.7 (CH_2), 37.2 (CH_2) and 25.0 (CH_2); *m*/*z* (TOF AP^+) 376 (MH^+ + CH_3CN, 100%) and 335 (MH^+, 45).

3-Methyl-7a-(3-methyl-1,2,4-oxadiazol-5-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (3c)

Acetonitrolic acid (**2c**) (208 mg, 2 mmol) was added to ethyl 2-pyrrolidin-2-ylidene acetate (**1**) (155 mg, 1 mmol) in dry toluene (10 mL) and the mixture was heated under reflux for 2 h. The reaction mixture was concentrated *in vacuo* and the crude residue purified by flash column chromatography (eluent 1 : 1 petroleum ether–ethyl acetate) to give the *title compound* (135 mg, 65%) as a yellow oil; $\nu_{max.}$ (neat) 2982, 1622, 1561, 1436, 1396, 1302, 1105 and 853 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.45 (1 H, ddd, *J* 11.3, 6.9, 3.5, one of CH_2N), 3.18 (1 H, ddd, *J* 11.3, 9.5, 6.1, one of CH_2N), 2.62 (1 H, ddd, *J* 14.0, 9.4, 7.1, one of CH_2C), 2.46 (1 H, ddd, *J* 14.0, 7.5, 4.4, one of CH_2C), 2.36 (3 H, s, CH_3), 2.08–1.84 (2 H, m, CH_2CH_2N) and 1.96 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 177.4 (C), 167.3 (C), 155.7 (C), 102.4 (C), 50.9 (CH_2), 37.3 (CH_2), 24.8 (CH_2), 11.6 (CH_3) and 10.2 (CH_3); *m*/*z* (TOF EI^+) 208 (M^+, 22%), 178 (100), 111 (38) and 85 (95).

Ethyl 2-(3,4-dihydro-2*H*-pyrrol-5-yl)-2-(hydroxyimino)acetate (5)

Pyridine-4-nitrolic acid (**2b**) (334 mg, 2 mmol) was added to ethyl (2-pyrrolidin-2-ylidene acetate (**1**) (155 mg, 1 mmol) in dry benzene (10 mL) and the mixture was heated under reflux for 2 h. The reaction was concentrated *in vacuo*, and the crude residue (expansion of proton NMR spectrum provided in ESI†) was purified by flash column chromatography (2 : 1 petroleum ether–ethyl acetate) to give the *title compound* (65 mg, 35%) as a yellow oil; $\nu_{max.}$ (neat) 3546, 2988, 1739, 1608, 1291, 1205, 1029 and 946 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.33 (2 H, q, *J* 7.1, OCH_2), 3.89 (2 H, t, *J* 7.7, NCH_2), 3.14 (2 H, t, *J* 8.1, CH_2), 1.97 (2 H, app. quintet, *J* 7.9, CH_2) and 1.33 (3 H, t, *J* 7.1, CH_3); δ_C (100 MHz; $CDCl_3$) 167.8 (C), 164.5 (C), 143.1 (C), 61.3 (CH_2), 54.5 (CH_2), 36.0 (CH_2), 19.6 (CH_2) and 14.2 (CH_3); *m*/*z* (TOF AP^+) 248 (MNa^+ + CH_3CN, 61%), 185 (MH^+, 100) and 152 (38).

General experimental procedure for the formation of isoxazoles (10)

The alkylidenepyrrolidine **1** (155 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added to a solution of α-chlorooxime **9** (2 mmol) in CH_2Cl_2 (5 mL). Triethylamine (250 mg, 2.5 mmol) was added dropwise and reaction mixture stirred at ambient temperature for 18 h. The crude reaction mixture was filtered through a short plug of silica gel to remove triethylamine hydrochloride, then concentrated *in vacuo* and purified as described below.

Ethyl 5-(3-(*N*′-hydroxybenzimidamido)propyl)-3-phenylisoxazole-4-carboxylate (10a). The crude product was purified by flash column chromatography (eluent 2 : 1 petroleum ether–ethyl acetate) to give the *title compound* (267 mg, 68%) as a yellow oil (Found: M^+, 393.1690. $C_{22}H_{23}N_3O_4$ requires M, 393.1689); $\nu_{max.}$ (neat) 3372, 3063, 2980, 1722, 1627, 1447, 1306, 767 and 698 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.49 (2 H, dd, *J* 7.8, 1.7), 7.38–7.25

(8 H, m), 5.45 (1 H, broad s, NH), 4.09 (2 H, q, *J* 7.1, OCH_2), 3.09–2.94 (4 H, m, $CH_2CH_2CH_2N$), 1.79 (2 H, app. quintet, *J* 7.2, $CH_2CH_2CH_2N$) and 1.05 (3 H, t, *J* 7.1, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 178.0 (C), 162.5 (C), 161.7 (C), 156.2 (C), 131.1 (C), 129.7 (CH), 129.6 (CH), 129.3 (2 × CH), 128.4 (2 × CH), 128.4 (2 × CH), 128.3 (C), 127.9 (2 × CH), 108.2 (C), 60.8 (CH_2), 42.7 (CH_2), 28.8 (CH_2), 24.5 (CH_2) and 13.8 (CH_3); *m*/*z* (TOF ES$^+$) 393 (M^+, 3%), 245 (12), 144 (26) and 104 (100).

Ethyl 5-(3-(2,6-dichloro-*N*′-hydroxybenzimidamido)propyl)-3-(2,6-dichlorophenyl)isoxazole-4-carboxylate (10b). The crude product was purified by flash column chromatography (eluent 2 : 1 petroleum ether–ethyl acetate) to give the *title compound* (366 mg, 69%) as a colourless solid, m.p. 122–123 °C (Found: MH^+, 530.0182. $C_{22}H_{20}N_3O_4{}^{35}Cl_4$ requires M, 530.0208); $\nu_{max.}$ (neat) 3372, 2922, 1721, 1644, 1457, 1377, 1297, 910, 784 and 732 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.39–7.11 (6 H, m, aromatic CH), 5.57 (1 H, broad s, NH), 4.01 (2 H, q, *J* 7.1, OCH_2), 3.13 (2 H, t, *J* 7.4, $CH_2CH_2CH_2N$), 2.88 (2 H, poorly resolved app. q, *J* 5.1, $CH_2CH_2CH_2N$), 1.88 (2 H, app. quintet, *J* 7.0, $CH_2CH_2CH_2N$) and 0.90 (3 H, t, *J* 7.1, CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 177.9 (C), 160.7 (C), 158.3 (C), 150.2 (C), 135.7 (2 × C–Cl), 135.0 (2 × C–Cl), 131.0 (CH), 130.8 (CH), 129.4 (C), 127.9 (C), 127.8 (2 × CH), 127.4 (2 × CH), 109.0 (C), 60.5 (CH_2), 41.7 (CH_2), 27.8 (CH_2), 24.1 (CH_2) and 13.4 (CH_3); *m*/*z* (TOF ES$^+$) 532 (MH^+, 100%) (isotopic distribution consistent with 4 × Cl).

Ethyl 5-(3-(2,4-dichloro-*N*′-hydroxybenzimidamido)propyl)-3-(2,4-dichlorophenyl)isoxazole-4-carboxylate (10c). The crude residue was purified by flash column chromatography (eluent 2 : 1 petroleum ether–ethyl acetate) to give the *title compound* (179 mg, 67% using 0.5 mmol of compound **1**) as an orange oil (Found: MH^+, 530.0205. $C_{22}H_{20}N_3O_4{}^{35}Cl_4$ requires M, 530.0208); $\nu_{max.}$ (neat) 3383, 3090, 2980, 1723, 1634, 1594, 1433, 1372, 1308, 1246, 1102 and 825 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.43 (1 H, d, *J* 1.3), 7.39 (1 H, d, *J* 1.8), 7.31–7.21 (4 H, m), 5.52 (1 H, app. broad t, *J* 5.7, NH), 4.07 (2 H, q, *J* 7.1, OCH_2), 3.09 (2 H, t, *J* 7.4, $CH_2CH_2CH_2N$), 2.93 (2 H, app. q, *J* 6.5, CH_2N), 1.87 (2 H, app. quintet, *J* 7.2, $CH_2CH_2CH_2N$) and 1.01 (3 H, t, *J* 7.1, CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 177.7 (C), 161.3 (C), 160.0 (C), 152.5 (C), 136.3 (C), 136.3 (C), 134.9 (C), 134.8 (C), 132.4 (CH), 131.8 (CH), 129.6 (CH), 129.3 (CH), 129.0 (C), 127.4 (CH), 127.2 (C), 127.0 (CH), 109.6 (C), 61.0 (CH_2), 42.1 (CH_2), 28.5 (CH_2), 24.3 (CH_2) and 13.7 (CH_3); *m*/*z* (TOF ES$^+$) 532 (MH^+, 100%) (isotopic distribution consistent with 4 × Cl).

Ethyl 5-(3-(*N*′-hydroxy-2-nitrobenzimidamido)propyl)-3-(2-nitrophenyl)isoxazole-4-carboxylate (10d). The crude product was purified by flash column chromatography (eluent 2 : 1 petroleum ether–ethyl acetate) to give the *title compound* (135 mg, 56% using 0.5 mmol of compound **1**) as a yellow oil (Found: MH^+, 484.1479. $C_{22}H_{22}N_5O_8$ requires M, 484.1468); $\nu_{max.}$ (neat) 3382, 2980, 1718, 1637, 1529, 1348, 1315, 912 and 855 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.16 (1 H, dd, *J* 8.0, 1.3), 7.96 (1 H, dd, *J* 8.1, 1.0), 7.66 (1 H, app. td, *J* 7.5, 1.5), 7.62–7.57 (2 H, m), 7.52 (1 H, app. td, *J* 7.7, 1.5), 7.47 (1 H, dd, *J* 7.5, 1.4), 7.44 (1 H, dd, *J* 7.5, 1.4), 5.53 (1 H, broad s, NH), 4.04 (2 H, q, *J* 7.1, OCH_2), 3.10 (2 H, t, *J* 7.4, $CH_2CH_2CH_2N$), 2.95 (2 H, app. q, *J* 6.4, $CH_2CH_2CH_2N$), 1.89 (2 H, app. quintet, *J* 7.1, $CH_2CH_2CH_2N$) and 0.95 (3 H, t, *J* 7.1, OCH_2CH_3); δ_C (100 MHz; $CDCl_3$) 177.6 (C), 161.0 (C), 160.7 (C), 152.6 (C), 148.7 (C), 148.2 (C), 133.4 (CH), 133.2 (CH), 132.1 (CH), 131.8 (CH), 130.7 (CH), 130.5 (CH), 126.3 (C), 124.7 (C), 124.5 (CH), 124.4 (CH), 108.6 (C), 60.9 (CH_2), 42.5 (CH_2), 28.0 (CH_2), 24.2 (CH_2) and 13.5 (CH_3); *m*/*z* (TOF ES$^+$) 506 (MNa^+, 46%) and 484 (MH^+, 100).

3-(3-Nitrophenyl)-4-(pyrrolidin-2-ylidene)isoxazol-5(4*H*)-one (11)

The alkylidenepyrrolidine **1** (155 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added to a solution of *N*-hydroxy-3-nitrobenzimidoyl chloride (**9e**) (400 mg, 2 mmol) in CH_2Cl_2 (5 mL). Triethylamine (250 mg, 2.5 mmol) was added dropwise and the reaction mixture stirred at ambient temperature for 18 h. The crude reaction mixture was filtered through a short plug of silica gel to remove triethylamine hydrochloride, then concentrated *in vacuo* and purified by flash column chromatography (eluent 1 : 1 petroleum ether–ethyl acetate) to give the *title compound* (193 mg, 41%) as a yellow solid, m.p. 144–146 °C (Found: M^+, 273.0750; $C_{13}H_{11}N_3O_4$ requires M, 273.0750); $\nu_{max.}$ (KBr disk) 3284, 2926, 1691, 1599 and 1351 cm^{-1}; δ_H (400 MHz; d_6-DMSO) 10.11 (1 H, broad s, NH), 8.38 (1 H, dd, *J* 8.2, 2.3), 8.31 (1 H, app. broad s), 8.00 (1 H, d, *J* 7.6), 7.80 (1 H, app. t, *J* 8.0), 3.62 (2 H, t, *J* 7.0, CH_2N), 2.53–2.47 (2 H, m, CH_2C) and 1.89 (2 H, app. quintet, *J* 7.2, CH_2CH_2N); δ_C (100 MHz; d_6-DMSO) 173.4 (C), 169.5 (C), 160.7 (C), 147.7 (C), 135.3 (CH), 132.1 (C), 130.2 (CH), 124.5 (CH), 123.4 (CH), 84.6 (C), 49.1 (CH_2), 33.3 (CH_2) and 20.3 (CH_2); *m*/*z* (TOF EI$^+$) 273 (M^+, 58%), 230 (100), 200 (93) and 184 (73).

General experimental procedure for the formation of compounds 17a, 17b, 18b, 17c and 22

The alkylidenepyrrolidine **1** (39 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) was added to a solution of α-chlorohydrazone **16** (0.5 mmol) in CH_2Cl_2 (5 mL). Triethylamine (75 mg, 0.75 mmol) was added dropwise and reaction mixture stirred at ambient temperature for 18 h. The crude reaction mixture was filtered through a short plug of silica gel to remove triethylamine hydrochloride, then concentrated *in vacuo* and purified as described below.

Ethyl 3-phenyl-3-(2-phenylhydrazono)-2-(pyrrolidin-2-ylidene)-propanoate (17a). The crude product was purified by flash column chromatography (eluent 2 : 1 petroleum ether–ethyl acetate) to give the *title compound* (32 mg, 37%) as a pale yellow solid, m.p. 122–124 °C (lit.[5] 127–129 °C) (Found: MH^+, 350.1854; $C_{21}H_{24}N_3O_2$ requires M, 350.1869); $\nu_{max.}$ (KBr) 3362, 3273, 1649, 1601, 1501, 1234, 1057 and 748 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.67 (1 H, broad s, NH), 7.84 (1 H, broad s, NH), 7.73 (2 H, app. broad d, *J* 7.1, aromatic CH), 7.32 (2 H app. broad t, *J* 7.4, aromatic CH), 7.29–7.24 (3 H, m, aromatic CH), 7.17 (2 H, app. broad d, *J* 7.5, aromatic CH), 6.84 (1 H, app. tt, *J* 7.4, 1.1, aromatic CH), 4.10–4.01 (2 H, m, OCH_2), 3.64 (2 H, app. td, *J* 7.2, 3.6, CH_2N), 2.42 (1 H, app. dt, *J* 17.2, 7.8, one of CH_2), 2.31 (1 H, app. dt, *J* 17.2, 7.9, one of CH_2), 1.93 (2 H, app. quintet, *J* 7.4, CH_2) and 1.03 (3 H, t, *J* 7.1, CH_3); *m*/*z* (TOF ES$^+$) 350 (MH^+, 100%).

Ethyl 3-(2-(4-chlorophenyl)hydrazono)-3-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)propanoate (17b) and ethyl [2-{1-(4-chlorophenyl)-3-(4-nitrophenyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]-triazol-7a-yl}acetate (18b). The crude product was purified by flash column chromatography (eluent 2 : 1 petroleum ether–ethyl

acetate) to give compound **17b** (63 mg, 59%) as an orange solid and compound **18b** (10 mg, 10%) as a pale oil.

*Data for compound **17b**.* Orange solid (63 mg, 59%), m.p. 151–153 °C (Found: MH^+, 429.1337. $C_{21}H_{22}N_4O_4{}^{35}Cl$ requires M, 429.1300); $\nu_{max.}$ (KBr) 3368, 3248, 1649, 1572, 1336, 1238, 852 and 821 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.69 (1 H, broad s, NH), 8.11 (2 H, d, *J* 8.9, aromatic CH), 7.97 (1 H, broad s, NH), 7.77 (2 H, d, *J* 8.9, aromatic CH), 7.18 (2 H, d, *J* 9.1, aromatic CH), 7.06 (2 H, d, *J* 9.1, aromatic CH), 4.04–3.92 (2 H, m, OCH_2), 3.61 (2 H, app. broad t, *J* 6.6, CH_2N), 2.32 (1 H, app. dt, *J* 17.2, 7.8, one of CH_2C), 2.20 (1 H, app. dt, *J* 17.2, 7.8, one of CH_2C), 1.91 (2 H, app. quintet, *J* 7.5, CH_2) and 0.96 (3 H, t, *J* 7.1, CH_3); *m*/*z* (TOF ES$^+$) 470 ($MH^+ + CH_3CN$, 68%) and 429 (MH^+, 100).

*Data for compound **18b**.* Pale oil (10 mg, 10%) (Found: MH^+, 429.1346. $C_{21}H_{22}N_4O_4{}^{35}Cl$ requires M, 429.1300); $\nu_{max.}$ (KBr) 2924, 1726, 1591, 1489, 1340, 1091, and 856 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.24 (2 H, d, *J* 9.0, aromatic CH), 7.93 (2 H, d, *J* 9.0, aromatic CH), 7.23 (2 H, d, *J* 9.1, aromatic CH), 7.12 (2 H, d, *J* 9.0, aromatic CH), 4.09–3.96 (2 H, m, CH_2O), 3.44 (1 H, ddd, *J* 10.2, 7.5, 6.4, one of CH_2N), 3.26 (1 H, ddd, *J* 10.2, 6.8, 5.5, one of CH_2N), 3.06 (1 H, d, *J* 14.5, one of CH_2), 2.91 (1 H, d, *J* 14.5, one of CH_2), 2.65–2.52 (2 H, m, CH_2), 2.09–1.99 (1 H, m, one of CH_2), 1.93–1.82 (1 H, m, one of CH_2) and 1.18 (3 H, t, *J* 7.1, CH_3); δ_C (100 MHz; $CDCl_3$) 169.3 (C), 150.5 (C), 147.7 (C), 140.5 (C), 135.0 (C), 129.1 (CH), 127.3 (CH), 124.9 (C), 123.9 (CH), 115.6 (CH), 92.2 (C), 60.7 (CH_2), 53.2 (CH_2), 42.9 (CH_2), 37.2 (CH_2), 26.0 (CH_2) and 14.1 (CH_3); *m*/*z* (TOF ES$^+$) 429 (MH^+, 95%), 391 (100) and 341 (94).

Ethyl 3-(4-bromophenyl)-3-(2-(4-chlorophenyl)hydrazono)-2-(pyrrolidin-2-ylidene)propanoate 17c). The crude product was purified by flash column chromatography (eluent 2 : 1 petroleum ether–ethyl acetate) to give the *title compound* (59 mg, 51%) as a pale yellow solid, m.p. 134–136 °C (Found: MH^+, 462.0561. $C_{21}H_{22}N_3O_3{}^{35}Cl^{79}Br$ requires M, 462.0584); $\nu_{max.}$ (KBr) 3356, 3267, 1657, 1595, 1497, 1483, 1244, 1086, 824 and 783 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.68 (1 H, broad s, NH), 7.83 (1 H, broad s, NH), 7.58 (2 H, d, *J* 8.7, aromatic CH), 7.44 (2 H, d, *J* 8.7, aromatic CH), 7.21 (2 H, d, *J* 8.9, aromatic CH), 7.08 (2 H, d, *J* 8.9, aromatic CH), 4.11–4.00 (2 H, m, OCH_2), 3.65 (2 H, app. td, *J* 7.3, 2.4, CH_2N), 2.41–2.21 (2 H, m, CH_2), 1.94 (2 H, app. quintet, *J* 7.3, CH_2) and 1.03 (3 H, t, *J* 7.1, CH_3); δ_C (100 MHz; $CDCl_3$) 168.5 (C), 167.6 (C), 143.2 (C), 141.0 (C), 138.0 (C), 131.2 (CH), 129.0 (CH), 127.4 (CH), 124.3 (C), 121.6 (C), 114.1 (CH), 79.8 (C), 59.3 (CH_2), 47.7 (CH_2), 31.5 (CH_2), 21.5 (CH_2) and 14.5 (CH_3); *m*/*z* (TOF ES$^+$) 505 ($MH^+ + CH_3CN$, 41%) and 464 (MH^+, 100) (isotopic distribution consistent with 1 × Br and 1 × Cl).

Methyl 3-phenyl-3-(2-phenylhydrazono)-2-(pyrrolidin-2-ylidene)propanoate (22)

The crude product was purified by flash column chromatography (eluent 2 : 1 petroleum ether–ethyl acetate) to give the *title compound* (20 mg, 21% from 0.28 mmol of alkylidenepyrrolidine **21**) as a pale yellow solid, m.p. 165–170 °C (hexane–Et_2O) (Found: MH^+, 336.1718; $C_{20}H_{22}N_3O_2$ requires M, 336.1712); $\nu_{max.}$ (Nujol) 3389, 3273, 1653, 1601, 1575 and 1505 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.66 (1 H, broad s, NH), 7.86 (1 H, broad s, NH), 7.74 (2 H, d, *J* 7.3, aromatic CH), 7.33 (2 H app. t, *J* 7.5, aromatic CH), 7.29–7.23 (3 H, m, aromatic CH), 7.17 (2 H, d, *J* 7.6, aromatic CH), 6.84 (1 H, app. t, *J* 7.2, aromatic CH), 3.69–3.60 (2 H, m, CH_2N), 3.56 (3 H, s, OCH_3), 2.47–2.26 (2 H, m, CH_2), and 1.93 (2 H, app. quintet, *J* 7.6, CH_2); δ_C (100 MHz; $CDCl_3$) 169.7 (C), 168.1 (C), 145.3 (C), 141.5 (C), 139.5 (C), 129.6 (2 × CH), 128.7 (2 × CH), 128.0 (CH), 126.2 (2 × CH), 120.1 (CH), 113.5 (2 × CH), 80.4 (C), 51.4 (CH_3), 48.2 (CH_2), 31.9 (CH_2) and 22.0 (CH_2); *m*/*z* (TOF ES$^+$) 336 (MH^+, 100%) and 304 (20). Selected crystallographic data: $C_{20}H_{21}N_3O_2$, FW = 335.40, *T* = 150(2) K, λ = 0.71073 Å, Monoclinic, $P2_1/n$, *a* = 10.4390(7) Å, *b* = 8.2177(7) Å, *c* = 20.2299(13) Å, β = 102.142(4)°, *V* = 1696.6(2) Å^3, *Z* = 4, ρ(calc) = 1.313 Mg m^{-3}, crystal size = 0.35 × 0.15 × 0.04 mm^3, reflections collected = 3780, independent reflections = 2266, *R*(int) = 0.0557, parameters = 227, R_1 [$I > 2\sigma(I)$] = 0.059, wR_2 [$I > 2\sigma(I)$] = 0.124, R_1 (all data) = 0.092, wR_2 (all data) = 0.139. The low data to parameter ratio for this compound is due to the weakness of the data from the crystals which could only be obtained as thin plates. Full crystallographic data for this compound have been deposited with the CCDC, reference number 776572.†

3-Phenyl-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25a)

Triethylamine (30 mg, 0.3 mmol) was added to a solution of (*Z*)-2-(phenylsulfonylmethylene)pyrrolidine (**24**) (56 mg, 0.25 mmol) and α-chlorooxime **9a** (39 mg, 0.25 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was heated under reflux for 18 h. The solution was then washed with water (3 × 15 mL), dried over magnesium sulfate and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent 3 : 1 petroleum ether–ethyl acetate) to give the *title compound* (59 mg, 69%) as a yellow oil (Found: MH^+, 343.1121. $C_{18}H_{19}N_2SO_3$ requires M, 343.1116); $\nu_{max.}$(neat) 2974, 1593, 1562, 1447, 1371, 1308, 1143, 1082, 751 and 690 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.87 (2 H, d, *J* 7.1, aromatic CH), 7.56 (1 H, app. tt, *J* 7.4, 2.1, aromatic CH), 7.47 (2 H, app. t, *J* 7.6, aromatic CH), 7.36–7.30 (3 H, m, aromatic CH), 7.24 (2 H, app. broad tt, *J* 7.4, 1.3, aromatic CH), 3.69 (1 H, d, *J* 14.8, one of CH_2SO_2), 3.67 (1 H, d, *J* 14.8, one of CH_2SO_2), 3.21–3.01 (2 H, m, CH_2N), 2.73 (1 H, ddd, *J* 14.1, 11.7, 7.0, one of CH_2C), 2.38 (1 H, ddd, *J* 14.1, 7.1, 1.0, one of CH_2C), 1.89–1.79 (1 H, m, one of CH_2CH_2N) and 1.78–1.67 (1 H, m, one of CH_2CH_2N); δ_C (100 MHz; $CDCl_3$) 159.4 (C), 140.8 (C), 133.5 (CH), 130.9 (CH), 129.1 (2 × CH), 128.5 (2 × CH), 127.7 (2 × CH), 127.6 (2 × CH), 125.5 (C), 105.5 (C), 60.9 (CH_2), 52.8 (CH_2), 36.5 (CH_2) and 24.8 (CH_2); *m*/*z* (TOF ES$^+$) 343 (MH^+, 100%) and 224 (7).

Compounds **25b–25h** were prepared by a similar procedure, as detailed in the ESI.†

7a-(Phenylsulfonylmethyl)-3-(pyridin-4-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole (25i)

A solution of the nitrolic acid **2b** (42 mg, 0.25 mmol) and (*Z*)-2-(phenylsulfonylmethylene) pyrrolidine (**24**) (56 mg, 0.25 mmol) in dry toluene (5 mL) was heated under reflux for 2 h. The solvent was removed *in vacuo* and the crude product purified by flash column chromatography on silica gel (eluent 2 : 1 petroleum ether–ethyl acetate) to give the *title compound* (58 mg, 68%) as a pale oil (Found: MH^+, 343.1074. $C_{17}H_{18}N_3SO_3$ requires M, 344.1069); $\nu_{max.}$

(neat) 3059, 1590, 1447, 1374, 1307 and 1143 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.56 (2 H, d, *J* 6.0, pyridine 2-H and 6-H), 7.87 (2 H, broad app. d, *J* 7.3, aromatic CH), 7.59 (1 H, app. tt, *J* 7.4, 1.9, aromatic CH), 7.50 (2 H, app. t, *J* 7.6, aromatic CH), 7.26 (2 H, d, *J* 6.0, pyridine 3-H and 5-H), 3.69 (1 H, d, *J* 14.8, one of CH_2SO_2), 3.64 (1 H, d, *J* 14.8, one of CH_2SO_2), 3.20–3.10 (2 H, m, CH_2N), 2.75 (1 H, ddd, *J* 14.2, 11.7, 6.9, one of CH_2C), 2.42 (1 H, ddd, *J* 14.2, 7.3, 1.7, one of CH_2C), 1.95–1.86 (1 H, m, one of CH_2CH_2N) and 1.82–1.68 (1 H, m, one of CH_2CH_2N); δ_C (100 MHz; $CDCl_3$) 157.8 (C), 150.3 (2 × CH), 140.8 (C), 133.8 (CH), 133.4 (C), 129.3 (2 × CH), 127.7 (2 × CH), 121.5 (2 × CH), 106.9 (C), 61.0 (CH_2), 53.1 (CH_2), 36.7 (CH_2) and 25.0 (CH_2); *m*/*z* (TOF ES$^+$) 385 (MH^+ + CH_3CN, 41%) and 344 (MH^+, 100%).

Compound **25j** was prepared by a similar procedure, as detailed in the ESI.†

(*S*,*Z*)-Ethyl 5-(phenylsulfonylmethylene)pyrrolidine-2-carboxylate (26)

A solution of *n*-BuLi (1.6M in hexanes, 3.8 mL, 6.1 mmol was added to a solution of diisopropylamine (0.84 mL, 6 mmol) in THF (40 mL) at 0 °C. A solution of phenyl methyl sulfone (925 mg, 6 mmol) in THF (5 mL) was added dropwise over 30 min and the solution allowed to stir for a further 30 min. (2*S*)-1-*tert*-butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate (1.54 g, 6 mmol) in THF (5 mL) was added over 30 min and the solution allowed to warm to 25 °C and stirred for 18 h. Saturated aqueous NH_4Cl solution (25 mL) was added and the organic layer extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (5 mL) and trifluoroacetic acid (1.37 g, 12 mmol) added. The resulting solution was stirred for 18 h at 25 °C before being concentrated *in vacuo*. Saturated aqueous sodium bicarbonate solution (20 mL) was added and the organic materials extracted into CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by flash column chromatography (eluent 2 : 1 petroleum ether–ethyl acetate) gave the *title compound* (885 mg, 51%) as a pale oil (Found: MH^+, 296.0945. $C_{14}H_{18}NO_4S$ requires M, 296.0957); $\nu_{max.}$ (neat) 3395, 2981, 1735, 1607, 1446, 1279, 1199, 1078, 847 and 717 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.83 (2 H, broad d, *J* 7.0), 7.53–7.37 (3 H, m), 4.68 (1 H, s, alkene CH), 4.30 (1 H, dd, *J* 8.4, 4.8, CHN), 4.14 (2 H, q, *J* 7.1, OCH_2), 2.64–2.49 (2 H, m, CH_2C), 2.27–2.16 (1 H, m, one of CH_2CHN), 2.06–1.96 (1 H, m, one of CH_2CHN) and 1.22 (3 H, t, *J* 7.1, CH_3CH_2); δ_C (100 MHz; $CDCl_3$) 171.6 (C), 160.4 (C), 144.8 (C), 131.9 (CH), 128.8 (2 × CH), 125.7 (2 × CH), 85.3 (CH), 61.6 (CH_2), 60.5 (CH), 31.7 (CH_2), 25.7 (CH_2) and 14.1 (CH_3); *m*/*z* (TOF MS AP$^+$) 296 (MH^+, 100%).

(5*S*,7a*S*)-Ethyl 3-phenyl-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-*d*][1,2,4]oxadiazole-5-carboxylate (27a)

Triethylamine (30 mg, 0.3 mmol) was added to a solution of (*S*,*Z*)-ethyl 5-(phenylsulfonylmethylene)pyrrolidine-2-carboxylate (**26**) (74 mg, 0.25 mmol) and α-chlorooxime **9a** (39 mg, 0.25 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was heated under reflux for 18 h. The solution was then washed with water (3 × 15 mL), dried over magnesium sulfate and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent 3 : 1 petroleum ether–ethyl acetate) to give the *title compound* (48 mg, 46%) as a yellow oil (Found: MH^+, 415.1338. $C_{21}H_{23}N_2SO_5$ requires M, 415.1328); $\nu_{max.}$ (neat) 2980, 1732, 1608, 1447, 1370, 1309, 1084, 750 and 688 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.91 (2 H, app. broad d, *J* 7.1), 7.60–7.54 (3 H, m), 7.48 (2 H, app. broad t, *J* 7.5), 7.38 (1 H, app. tt, *J* 7.4, 1.4), 7.31 (2 H, app. broad t, *J* 7.3), 4.18 (2 H, q, *J* 7.1, OCH_2), 3.98 (1 H, dd, *J* 7.2, 2.2, CHN), 3.88 (1 H, d, *J* 14.7, one of CH_2SO_2), 3.62 (1 H, d, *J* 14.7, one of CH_2SO_2), 2.65–2.60 (2 H, m, CH_2C), 2.15–2.04 (2 H, m, CH_2CHN) and 1.25 (3 H, t, *J* 7.1, CH_3CH_2); δ_C (100 MHz; $CDCl_3$) 171.2 (C), 158.2 (C), 140.4 (C), 133.8 (CH), 131.5 (CH), 129.1 (2 × CH), 129.0 (2 × CH), 128.3 (2 × CH), 128.0 (2 × CH), 125.1 (C), 106.2 (C), 64.5 (CH), 63.2 (CH_2), 61.8 (CH_2), 35.7 (CH_2), 29.1 (CH_2) and 14.2 (CH_3); *m*/*z* (TOF MS ES$^+$) 415 (MH^+, 64%) and 296 (100).

Compounds **27b,c,f,g** were prepared by a similar procedure, as detailed in the ESI.†

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