Nitrogen-containing heterocycles: 1,3-dipolar cycloaddition of stabilized nitrones with alkynes; primary cycloadducts, first and second generation rearrangement processes

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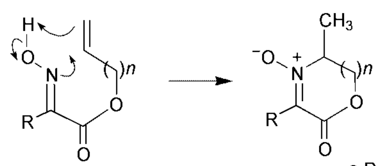
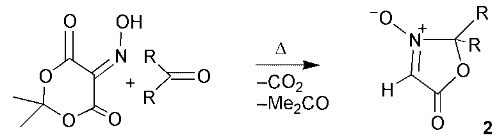
[4.3.0]- and [5.3.0]Bicyclic ring systems containing a nitrogen atom at the bridgehead position were prepared by a [3+2] addition of acetylenic dipolarophiles to the conformationally locked cyclic α-alkoxycarbonylnitrones **1a**–**c** and **18**. Reaction proceeded with a high degree of diastereofacial selectivity with cycloaddition taking place to the face of the dipole opposite the C-5 methyl group. Reaction with the *C*-phenyl nitrones, **1b** and **1c**, was straightforward and the structure of **12b**, arising from reaction of **1b** with dimethyl acetylenedicarboxylate has been determined by single crystal X-ray diffraction. The identity of the product(s) from reaction of *C*-methyl nitrones, **1a** or **18**, with dimethyl acetylenedicarboxylate varies with reaction duration; **12a** and **20** are the primary cycloaddition products and the pyrrolooxazinones **14** and **22** appear after prolonged reaction duration. A similar pattern of reactivity is observed when the same dipoles react with methyl propiolate. The structure of **14** has been confirmed following X-ray crystallographic analysis. The primary cycloadducts, **12a**, **20**, **24a** and **30**, bearing a C3a-methyl group had poor thermal stability and rearranged to the pyrrolooxazinones **13**, **21**, **25** and **31** respectively. A mechanistic proposal for the origin of the fused pyrroles is included. A C-6 methyl substituent on the dipole **18** had no determining influence on the stereochemical course or the rate of the cycloaddition reaction established by its unsubstituted analogues **1a** and **1b**. In addition to its mechanistic findings, this paper reports two significant synthetic advances: access to a range of unusually substituted hetero-fused pyrroles and to isoxazolooxazepinones, a rare bicyclic ring system.

Introduction

The 1,3-dipolar cycloaddition reaction of nitrones and nitrile oxides is amongst the most important methodologies for the construction of *N*-containing heterocycles.[1] We have recently reported the ready preparation of the *E*-geometry fixed cyclic dipoles **1** by thermal cyclization of the corresponding *E*-alkenyl oximes.[2] "Lactone" containing nitrones like **1** are relatively rare, however synthesis of their 5-membered analogues has been reported; reaction of isonitroso Meldrum's acid with ketones forms **2** in moderate yield.[3] Tamura's group have prepared the C-5 phenyloxazinone *N*-oxide **4** by indirect oxidation of *R*-phenylglycinol followed by condensation with methyl glyoxylate,[4] whilst Baldwin and co-workers report formation of the same dipole by direct oxidation (dimethyldioxirane, 3–4 equivalents) of oxazinone **3**.[5a] Looper and Williams report the success of Davis' oxaziridine for oxidation of analogues of **3**,[5b] and finally, **6**, the lactam analogue of **1** has been accessed by oxidation (H_2O_2, Na_2WO_4) of the pyrazinone **5**.[6] Related dipoles, the azomethine ylides **7** have been extensively studied by Harwood *et al.*[7] and preparation and cycloaddition of the azomethine imine **8** has recently been reported.[8] Ali and Wazeer have shown earlier that the introduction of an α-keto substituent lowers the reactivity of the cyclic nitrone **9** compared to the parent **10**,[9]† whilst the presence of a β-heteroatom makes **11a** more reactive than the carbocyclic analogue.[10a]‡ Finally, a γ-heteroatom, as in **11b**, appears to have little influence on reactivity.[10b,c] The influence of the lactone/lactam moiety on the cycloadditive potential of the dipoles **4**, **6**, **7** and **8** has been to reduce their reactivity and high pressure, long reaction times or Lewis acid catalysts have generally been employed to promote reaction. The nitrones **1** and **18**, unlike their sister dipoles **2**, **4**, **6** and **7**, are *C*-substituted and consequently cycloaddition could be slow, but it should lead to highly substituted isoxazolo-oxazinones. We now report our findings on the reaction of **1** and **18** with electron poor acetylenes and the tendency of the primary cycloadducts to participate in rearrangement reactions.



1
a R = Me, *n* = 1
b R = Ph, *n* = 1
c R = Ph, *n* = 2



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Results and discussion

Following stirring in boiling $CHCl_3$ (30 h) the dipole **1a** reacts with dimethyl acetylenedicarboxylate (1.5 eq.) in a diastereofacially specific manner furnishing **12a** as the only reaction

† It is reported that bond opposition strain in the transition state leading to cycloaddition and a lower dipole moment combine to render the α-keto dipole a less reactive species.
‡ It is proposed that the skeletal oxygen atom may have a defining influence on the conformation of the heterocyclic dipole and that the torsional strain relieved when it undergoes cycloaddition will be greater than that associated with addition to the carbocyclic analogue.

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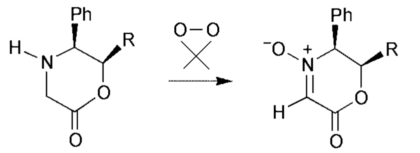
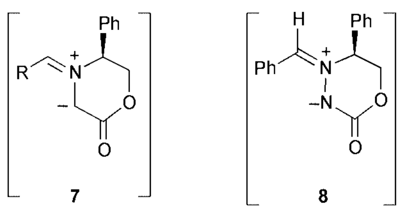
Table 1 Selected ^1H NMR spectral data for the isoxazolooxazinones **12**, **15**, **23**, **24** and **23c**

Adduct	^1H NMR position (ppm) [$^3J_{6,7}$, $^3J_{6,6}$/Hz]			
	6a-H	6b-H	7-H	2-H/3-H
12a	4.30 [2.93, 12.02]	4.10 [9.40, 12.02]	3.45	—
12b	4.14 [3.17, 11.96]	3.85 [10.99, 11.96]	3.62	—
15	4.33 [3.17, 11.72]	4.68 [9.52, 11.72]	3.72	—
23a	4.46 [2.69, 12.02]	4.16 [6.84, 12.02]	3.48	7.38
24a	4.25 [2.93, 11.96]	4.05 [11.96, 11.96]	3.32	6.00
23b	4.05 [3.17, 11.96]	3.73 [11.23, 11.96]	3.57	7.48
24b	4.20 [2.93, 11.96]	4.04 [10.74, 11.96]	3.54	6.26
23c	4.24 [3.05, 11.60]	4.57 [9.77, 11.60]	3.65	7.19

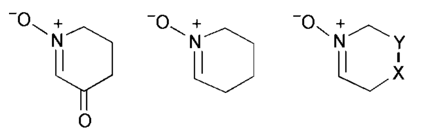


3 **4**

5 **6**



7 **8**



9 **10** **11a** X = O, Y = CH_2
b X = CH_2, Y = O

product. Nuclear Overhauser enhancement difference spectroscopy (NOEDS) experiments gave only a weak indication as to the relative stereochemistry of **12a**, which, following comparison with ^1H NMR spectral data of the analogous adducts **12b** and **15** (Table 1), is tentatively assigned as shown in the drawing. Although **12a** is stable either as a solid or in solution at rt, efforts to recrystallise it [from $CHCl_3$ (*wet* or *dry*) or C_6H_6] alerted us to its very limited thermal stability. It was subsequently found that following heating alone in boiling $CHCl_3$ (25 h) **12a** completely disappeared and the pyrrolo-fused bicycle **13** was isolated in 80% yield. Δ^4-Isoxazolines are well recognised as labile heterocycles[11a] and their ring opening reactions have been synthetically exploited.[11b] Recent experiments support the involvement of acylaziridines and azomethine ylides as intermediates in the ring transformation of isoxazolines,[11c,d] and one possible route to the pyrrole nucleus from the aziridine is detailed in Scheme 1. In an effort to obtain **13** directly from reaction of **1a** with dimethyl acetylenedicarboxylate, the original reaction was repeated extending the time to 48 h. Following purification of the product mixture two adducts were isolated: the primary cycloadduct **12a** (25%) and a second compound (31%), not **13**, but rather a new product with ^1H NMR spectral data similar to **13** with two exceptions—the loss of the "aromatic" pyrrole H signal (δ_H 7.29 ppm) and the presence of an additional methoxy resonance signal. To the new adduct we assigned structure **14**. A crystal of **14** suitable for X-ray analysis was obtained following slow evaporation of C_6H_6 and confirmation that it has a 1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]-oxazinone framework rests with this structure determination. The ORTEX drawing of **14** is shown in Fig. 1. The pyrrole ring,

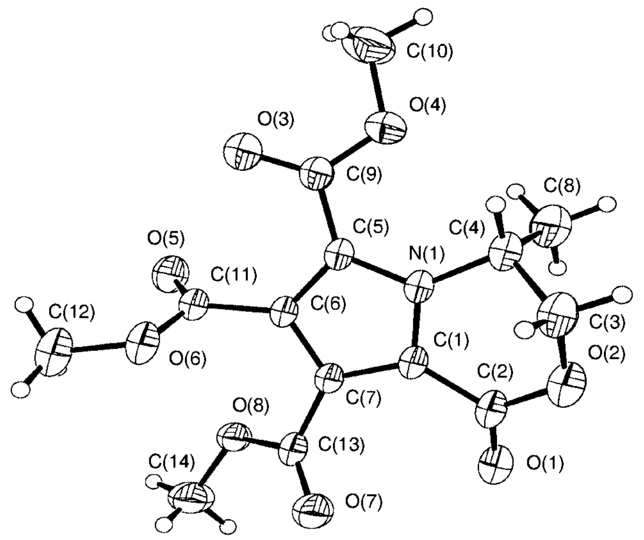
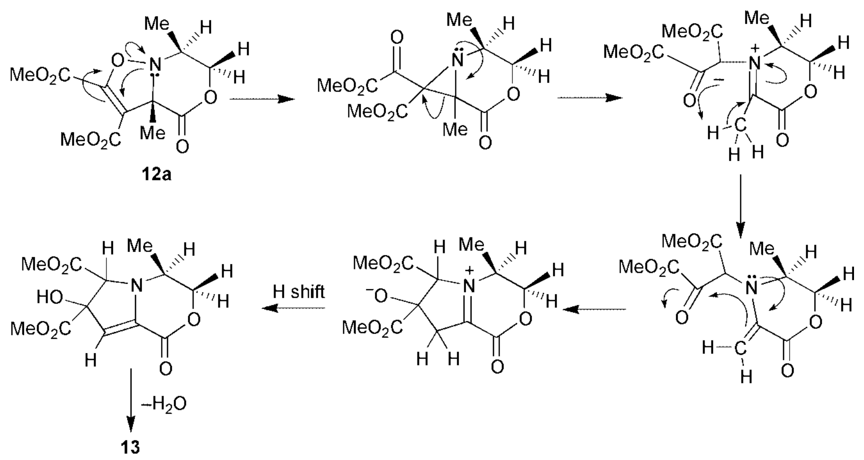


Fig. 1 ORTEX drawing of compound **14**.

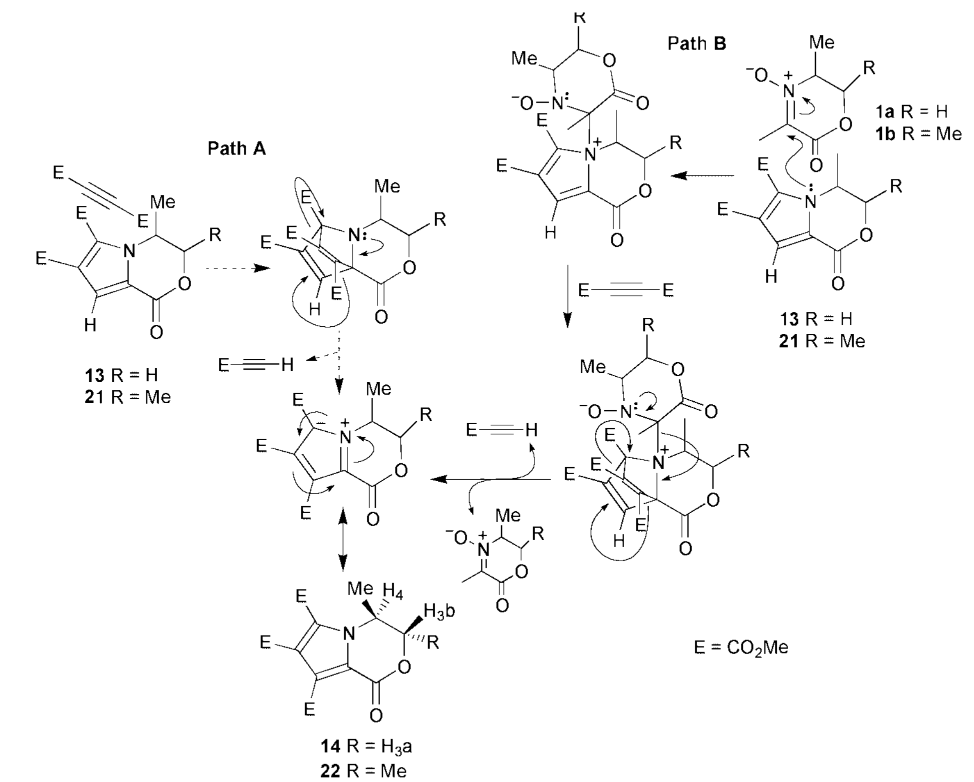
as expected, is planar (mean deviation from planarity 0.04 Å), and 4-C and 2-C (crystal numbering system) are on opposite sides of the plane by just 0.9 Å. The estimated dihedral angles 3aH–C–C–4H, −63.32° (0.32) and 3bH–C–C–4H, 54.73° (0.32) are not as would be expected from analysis of the vicinal coupling constants $^3J_{3,4}$ of **14**. The apparent failure of the NMR and crystallographic data to correlate simply means that the six-membered ring adopts a different conformation in solution than in the solid state. The 1-oxo-3,4-dihydro-1*H*-pyrrolo-[2,1-*c*][1,4]oxazinone framework of **14** has previously been accessed by Harwood and Lilly following aromatisation of the reaction product of azomethine ylide **7** (R = CO_2Et) with methyl propiolate.[7b]

Initially, it seemed likely that **14** may arise *via* **13** by way of a direct cycloaddition–cycloreversion sequence involving a [4+2] addition of the pyrrole nucleus to a second equivalent of dimethyl acetylenedicarboxylate, followed by elimination of a molecule of methyl propiolate (Scheme 2, path A). Dimethyl acetylenedicarboxylate is a reactive dienophile and the involvement of **13** in a Diels–Alder reaction could be considered to be facilitated by the following structural features. The 2- and 5-positions of the pyrrole ring are already substituted, therefore, Michael type addition is not an attractive option. The pyrrole nitrogen atom is substituted thus lowering the activation energy for the [4+2] cycloaddition. Finally the conjugating substituents in **13** lower the aromaticity of the pyrrole nucleus further permitting it to function as a diene in a Diels–Alder reaction.[12] Despite these characteristics it was discovered that independent heating of **13** with dimethyl acetylenedicarboxylate failed to furnish any **14**. This result suggests a critical role for unreacted nitrone in the formation of **14** and our revised mechanism (Scheme 2, path B) follows from a series of reactions with **21**, the 3-methyl analogue of **13**; these observations will be discussed below.

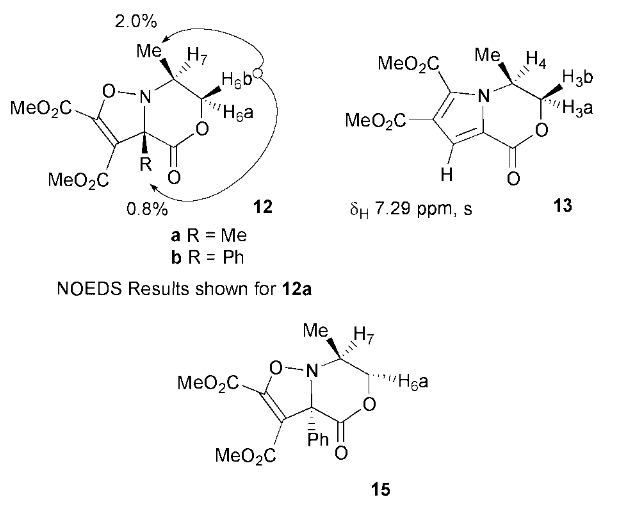
The reaction of *C*-phenyl dipole **1b** with dimethyl acetylenedicarboxylate progressed more slowly than its methyl analogue and some unreacted nitrone (26%) was present even after 40 h heating. The diastereomeric products **12b** and **15** were obtained in a ratio of 10 : 1. The C-3a position carries a phenyl substituent and hence there exists no opportunity for **12b** or **15** to form pyrrolo-fused adducts in an analogous fashion to **13** or **14**. As



Scheme 1



Scheme 2



was observed for **12a**, NOEDS results were inconclusive (0.8% NOE between 7-Me and the 3a-ArH). However, the relative stereochemistry of **12b** was confirmed following a single crystal X-ray analysis. A crystal suitable for structure determination was obtained following slow solvent evaporation ($CHCl_3$–hexane) and the ORTEX drawing of **12b** is shown in Fig. 2. The isoxazoline ring is quite flat with a mean deviation from planarity of 0.1 Å and the angle this ring makes with the plane defined by C(10)–N(1)–C(1)–C(8) (crystal numbering system) is 63.0°. The dihedral angles 9bH–C–C–10H and 9aH–C–C–10H are estimated as −69.53° (0.53) and 172.95° (0.41), respectively. These angles correlate well with the observed vicinal coupling in **12b** $^3J_{6a,7}$ (3.17 Hz) and $^3J_{6b,7}$ (10.99 Hz) suggesting that in this adduct the oxazinone ring adopts a similar conformation in the solid and the solution state. From the product structure it is clear that **12b** arises *via* addition of the dipolarophile to the least hindered (α) face of the dipole. The same facial specificity has previously been observed in the addition of olefinic substrates to the chiral dipoles **4** and **7**. In the reported cases the C-5 "directing" group is a bulky phenyl substituent,[4,5a,7c–e,13] but in the current example the smaller methyl substituent is quite effective in shielding one π-face of the dipole. NOEDS results on the minor diastereomer **15** were also inconclusive, however, it must, by default, have the C-3a and the C-7 substituents on

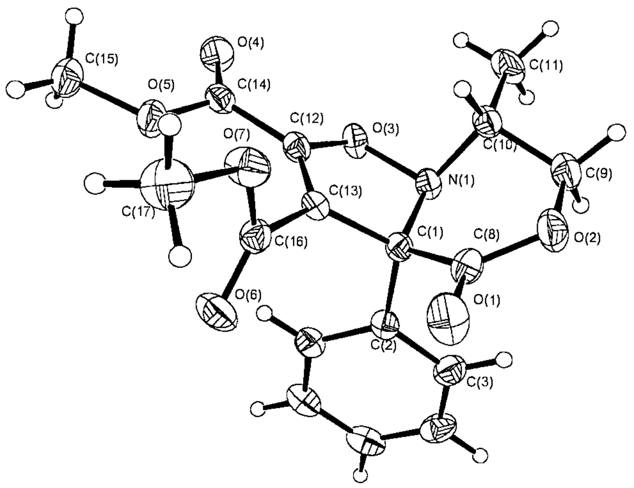
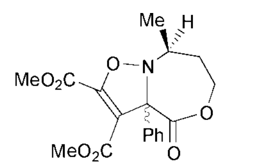


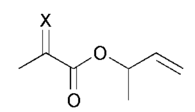
Fig. 2 ORTEX drawing of compound **12b**.

opposite faces. The change in relative stereochemistry between **12b** and **15** is reflected in the resonance position of the 6b-proton; in **12b** this proton is shielded by the phenyl ring (*δ* 3.85 ppm) whilst in **15** it resonates further downfield (*δ* 4.68 ppm) (Table 1).

The 7-membered cyclic nitrone **1c** reacted with dimethyl acetylenedicarboxylate (1.3 eq.) in a diastereofacially specific manner and the isoxazolooxazepinone **16** was isolated in 87% yield ($CHCl_3$, 32 h). Apart from our previous report, the 7,5-bicyclic skeleton of **16** remains unknown.[2]

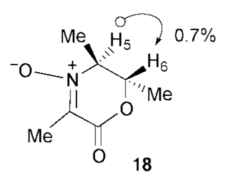


16

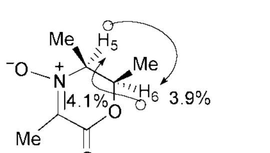


17

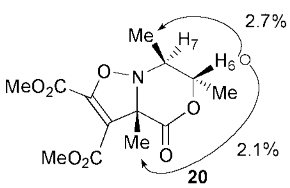
a X = O
b X = NOH



18



19



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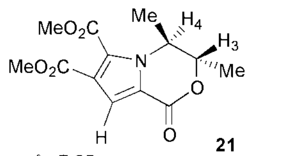
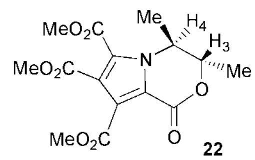


21



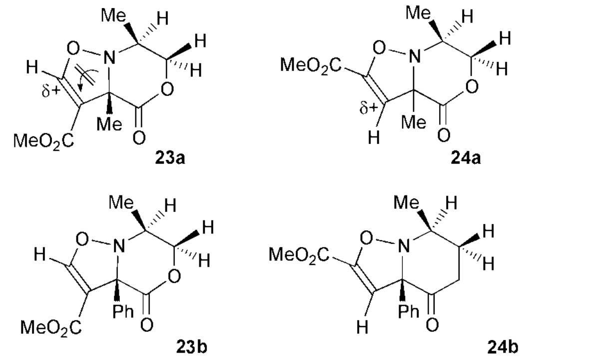
22

The nitrone **18** was prepared in order to observe the influence of a C-6 dipole substituent on the diastereoselectivity of the cycloaddition reaction. Pyruvic acid was allowed to react with but-3-en-2-ol and the resulting ester **17a** upon treatment with NH_2OH afforded the oxime **17b**. Thermal cyclisation (xylene, 140 °C, 51 h) of **17b** proceeded with a moderate degree of facial selectivity, generating the diastereomeric dipoles **18** and **19** in the ratio 10 : 3. The major nitrone, **18**, has the C-5 methyl group shielding one face of the dipole and the C-6 substituent shielding the opposite face (NOEDS results are summarised in the drawings). The cycloaddition of **18** with dimethyl acetylenedicarboxylate gave **20** in 74% yield after 7.5 h heating in boiling $CHCl_3$. As expected, reaction at rt was much slower, however, almost quantitative yield resulted after 7 d. Analysis of the NOEDS results for **20** clearly indicates that the dipolarophile added to the face of the dipole opposite the C-5 substituent. The rate and diastereoselectivity of reaction of **18** with dimethyl acetylenedicarboxylate compare favourably with those observed for the C-6 unsubstituted analogues **1a** and **1b**. In contrast, Baldwin *et al.*[5a] note a much reduced reaction rate and almost complete loss of stereoselectivity when cycloaddition to the diphenyl nitrone **4b** is compared to reaction with the monosubstituted dipole **4a**.

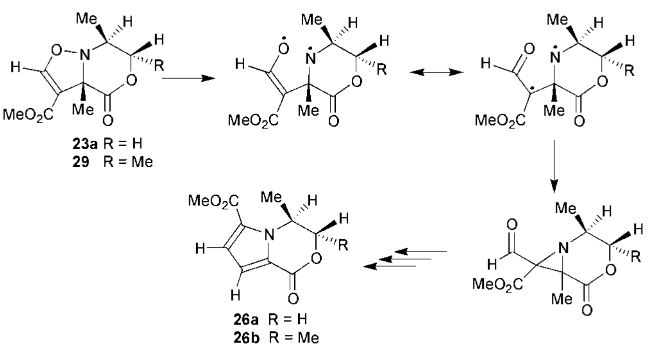
The primary adduct **20** has limited thermal stability and heating in the minimum amount of boiling $CHCl_3$ effects rearrangement to the pyrrolo-fused oxazinone **21** (76%). If reaction between nitrone **18** and dimethyl acetylenedicarboxylate is allowed to continue for 24 h at reflux or 10 d at rt the pyrrolo-fused adduct **22** accompanies the primary cycloadduct **20**. We believe that **20** relates to **21** and **22** in the same way as **12a** relates to **13** and **14**. It is our proposal that **21**, the initial product of a thermal rearrangement of the primary cycloadduct **20**, subsequently serves as a precursor to **22**. The original proposal that **21** would lead directly to **22** (Scheme 2, path A) was revised when simple heating of **21** with dimethyl acetylenedicarboxylate failed to give any new product. It was only when free nitrone **18** (10 mol%) was added to an equimolar mixture of **21** and dimethyl acetylenedicarboxylate that any trace of the pyrrole **22** became evident. After heating for 28 h in boiling $CHCl_3$ the ^1H NMR spectrum of the crude reaction mixture shows signals characteristic of the tris(methoxycarbonyl)pyrrole **22** (5.03 ppm, m, 3-H and 3.91, s, OMe); the relative intensities of the diagnostic signals for **21** and **22** suggest they are present in a ~7 : 1 ratio. These experimental results suggest that, despite the structural attributes listed above, the pyrrole nucleus of **21** (or **13**) is too unreactive to form a Diels–Alder adduct with dimethyl acetylenedicarboxylate and the first step in the generation of **22** (or **14**) is likely the quaternisation of the pyrrole nitrogen atom by nucleophilic attack on the nitrone. The *N*-protonated species is more susceptible to a cycloaddition–cycloreversion process, which ultimately leads to **22** (Scheme 2, path B). The origin of **14** likely mirrors that of **22** and the prolonged reaction of dipoles like **1a** and **18** with dimethyl acetylenedicarboxylate may represent a useful route to unusually substituted hetero-fused pyrroles.

One interesting feature of the ^1H NMR spectrum ($CDCl_3$) of **21** is the appearance of the signals for 3-H and 4-H as quartets rather than the expected doublet of quartets. The implication is that each of these protons is spin coupled only to the adjacent Me group with there being zero coupling between 3-H and 4-H and indeed decoupling experiments are in complete agreement with this conclusion. Clearly when in solution in $CDCl_3$ **21** must adopt a conformation where the dihedral angle 3-H–C–C–4-H would result in $J = 0$. Interestingly, no changes were observed in the general appearance of the spectrum upon changing the NMR solvent to C_6D_6.

The dipoles **1a**, **1b** and **1c** all reacted with methyl propiolate in boiling $CHCl_3$ giving regioisomeric 4- and 5-substituted Δ^4-isoxazolines. For all of the dipoles reaction with methyl propiolate was more sluggish than with dimethyl acetylenedicarboxylate and a larger excess of dipolarophile was employed to promote cycloaddition. In the case of **1a** reaction was complete after heating for 32 h and the adducts **23a** (56%) and **24a** (23%) were obtained. Their regiochemical assignment is obvious from the resonance position of the isoxazoline proton, 2-H/3-H (Table 1). Cycloaddition took place in a facially specific manner and only one diastereomer of each regioisomer is found. For this series of compounds the stereochemical relationship between 6a/6b-H and 7-H is based on the magnitude of the vicinal coupling constants $J_{6,7}$ where $J_{ax,eq} < J_{ax,ax}$[14] (Table 1). That this generalisation holds for the current structures is supported by comparison between the crystallographic and the NMR spectral measurements for **12b**. NOEDS experiments on **23a** indicate a small enhancement (~0.5%) on 6b-H following irradiation of 3a-Me, and as 6b-H is *cis* to 7-Me it follows that the 3a- and 7-methyl groups lie on the same face of the molecule. Regioselective formation of the 4-substituted adduct (isoxazolidine numbering) is in keeping with literature precedent for the addition of acetylenes to *C*-substituted nitrones.[15] The relative stereochemistry of the minor adduct **24a** remains unknown as NOEDS results were inconclusive.



The adduct **24a**, by virtue of the direction of polarisation of the conjugated "double bond" of its isoxazoline ring, is activated to acylaziridine formation, and on thermal activation it converts to the pyrrolooxazinone **25**. The rate and extent of the transformation are significantly reduced (40%, 56 h), but it most likely proceeds by a mechanism parallel to that outlined for **12a** (80%, 25 h) in Scheme 1. The adduct **23a** is not activated toward acylaziridine formation in the same way as its regioisomer and it is thermally stable after 24 h heating in boiling $CHCl_3$. However, inspection of the crude ^{1}H NMR spectrum of the mixture after 82 h heating it is clear that very little of **23a** remains intact and whilst much decomposition has occurred one new compound can be seen. This material, present in a 5 : 1 ratio with **23a** has been isolated and characterised as the pyrrole **26a**. The pyrrolooxazinone **26a** likely arises from **23a** as shown in Scheme 3, a homolytic cleavage of the isoxazoline N–O bond



Scheme 3

of **23a** generates a diradical species which is a precursor to the acylaziridine, the mechanism for formation of the pyrrole ring from the acylaziridine intermediate is as delinated for **13** in Scheme 1.

As previously observed in the reaction of *C*-methyl dipoles with dimethyl acetylenedicarboxylate, the composition of the products of reaction between **1a** and methyl propiolate is dependent on reaction duration. After 82 h at reflux the ^{1}H NMR spectrum of the crude mixture clearly shows signals characteristic of the primary adduct **24a** (6.00 ppm, s, 3-H) as well as a pair of doublets, 7.49 and 7.52 ppm each with a small *J* value (~1.5 Hz) characteristic of the *meta*-coupled aromatic protons of **25**. A second pair of doublets in the Ar–H region of the spectrum points to the presence of a further reaction product which we propose to have structure **25i**. The primary cycloadduct **23a** has its 2-H signal at 7.48 ppm in the ^{1}H NMR spectrum and this signal has all but disappeared from the spectrum of the crude reaction mixture (82 h) and a new signal presented at 7.36 ppm. Following flash chromatography it became evident that the aforementioned signal was representative of an inseparable mixture of isomeric pyrroles identified as **13** and **13i**. Integration of signals characteristic of each compound suggests the components to be present in the following approximate ratios **24a** : **23a** : **25** : **25i** : **13** plus **13i** 3 : trace : 15 : 4 : 25.

The pyrrole **25** could have its origins in a straightforward thermal rearrangement of **24a**, akin to the observed transformation of **12a** to **13**. However, this is probably not the case since the corresponding reaction of dipoles **1a** and **18** with dimethyl acetylenedicarboxylate did not stop with the products of a simple thermal reaction (**13** and **21**), but rather continued in a more complex process furnishing instead **14** and **22**. This apparent anomaly is satisfied by considering that if pyrrole **25** were to participate in an activation–addition–elimination sequence of the type proposed for **13** and **21** (Scheme 2, path B), the unsymmetrical nature of methyl propiolate should result in the formation of two regioisomeric Diels–Alder cycloadducts **A** and **B**. Elimination from **A** would return **25** and therefore the process would be degenerate. However, elimination from **B** would afford the isomeric compound **25i**. Evidence to support the structure of **25i** lies with the crude ^{1}H NMR spectral data which clearly show a pair of doublets, 7.05 and 6.96 ppm with *J* 4.4 Hz, typical of *ortho*-related protons on a pyrrole ring.

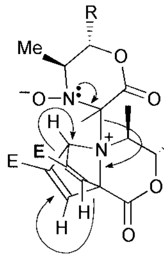
The pyrrolooxazinones **13** and **13i** likely arise from **23a** in a parallel fashion *i.e.* an initial thermal rearrangement of **23a** to the pyrrolo-fused adduct **26a** followed by an activation, Diels–Alder cycloaddition sequence generating regioisomeric intermediates C and D, methyl propiolate elimination affords **13** and **13i** respectively.

As observed with dimethyl acetylenedicarboxylate the phenyl substituted dipole **1b** reacts more slowly with methyl propiolate than its counterpart and 43% nitrone remained after a reaction time of 40 h. Further **1b** does not exhibit high diastereoselectivity in reaction with methyl propiolate and the diastereomeric 4-substituted isoxazolines **23b** (31%) and **23c** (13%) are isolated with the 5-substituted adduct **24b** (17%). For each of **23b** and **24b** an ~3% enhancement was observed on Ar-H upon irradiation of 6b-H, and taken together with the coupling constant data for $J_{6,7}$ the relative stereochemistry of **23b** and **24b** is thus assigned as shown in the diagrams. The relative stereochemistry of **23c** must be opposite to that of **23b** and it is assigned by default. Again it is worth noting the deshielding experienced by 6b-H when the relative configuration at the stereogenic centres is changed: thus, for **23b** and **24b** 6b-H resonates at $\sim\delta$ 4.0 ppm whilst the same proton in **23c** appears at δ 4.57 ppm (Table 1).

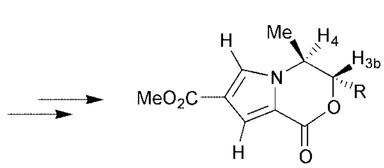
To encourage reaction of **1c** with methyl propiolate it was necessary to employ a great excess of dipolarophile and accordingly methyl propiolate was used as both reactant and solvent. After 36 h the regioisomeric 4- and 5-substituted Δ^4-isoxazolines **27** and **28** were formed in 24 and 60% yield respectively. The similarity between the ^{1}H NMR spectral data of the three [5.3.0]bicyclic adducts **16**, **27** and **28** suggests that all the cycloadditions took place with the same stereochemical sense (Table 2).

Table 2 Selected ^{1}H NMR spectral data for the isoxazolooxazepinones **16**, **27** and **28**

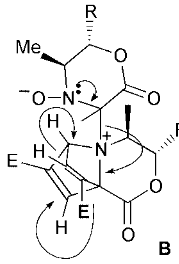
	δ_H (ppm)			
Adduct	6a-H and 6b-H	7a-H	7b-H	8-H
16	3.88 (2H)	2.24	1.67	3.60
27	3.86 (2H)	2.21	1.64	3.50
28	4.10 (1H) and 3.90 (1H)	2.23	1.75	3.52



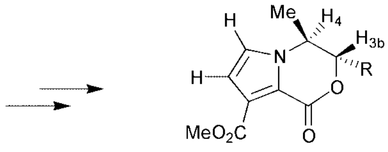
A



25, R = H δ_H Ar-H, 7.50 and 7.52 ppm, 2 x d, *J* 1.46 Hz
31, R = Me δ_H Ar-H, 7.48 and 7.53 ppm, 2 x d, *J* 1.46 Hz

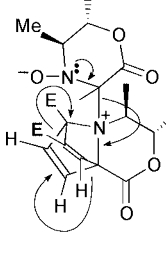


B

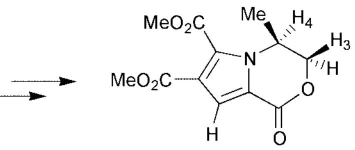


25i, R = H δ_H Ar-H, 6.96 and 7.05 ppm, 2 x d, *J* 4.39 Hz
31i, R = H δ_H Ar-H, 6.96 and 7.03 ppm, 2 x d, *J* 4.15 Hz

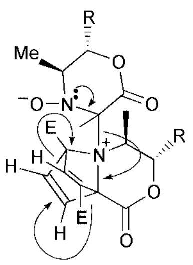
E = CO_2Me

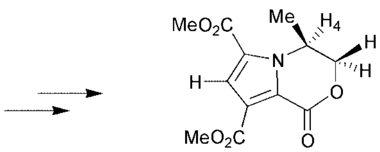


C

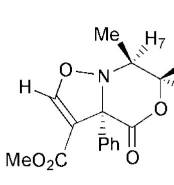


13 δ_H Ar-H, 7.36; 4-H, 5.04

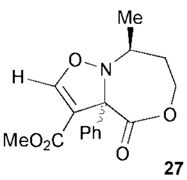




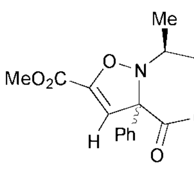
13i δ_H Ar-H, 7.36; 4-H, 5.35 ppm



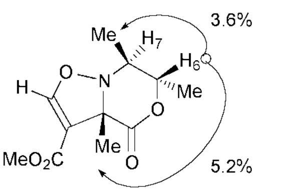
23c



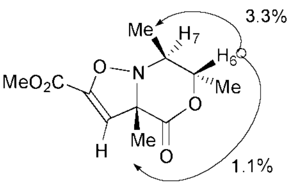
27



28



29



30

To promote reaction between the fully substituted nitrone **18** and methyl propiolate, the reactants were heated in refluxing $CHCl_3$ (30 h). As with **1a**, the 4-substituted isoxazoline is the major regioisomer and **29** and **30** were isolated in the ratio 3 : 2. NOEDS results indicate that the new adducts have the same relative stereochemistry and that in each case cycloaddition proceeded through a transition state involving the dipolarophile approaching the dipole on the face opposite the C-5 methyl group. The direction of polarisation of the isoxazoline C=C bond makes regioisomer **30** a good candidate for thermally induced acylaziridine formation and in keeping with the reactivity of its sister compounds **12a**, **20** and **24a**, it rearranges to the pyrrole **31** (67%) following heating in boiling $CHCl_3$. The isomeric adduct **29**, like its sister compound **23a**, is less prone to thermal rearrangement, remaining intact after 24 h ($CHCl_3$, 63 °C). Following heating for 82 h some decomposition became evident, however a single new compound, the pyrrolooxazinone **26b** was isolated from the reaction mixture. A proposed mechanistic origin of **26b** is outlined in Scheme 3. When reaction between **18** and methyl propiolate was extended to 84 h and the products were analysed by ^1H NMR spectroscopy, it was found that the regioisomeric primary cycloadducts **29** and **30** were accompanied by the pyrrole **31** and what is believed to be its isomer **31i**. The pyrroles **31** and **31i** are analogous with **25** and **25i** and presumably share the same mechanistic origin.

It is clear from the reaction of the 3,5,6-trimethyl nitrone **18** with dimethyl acetylenedicarboxylate and with methyl propiolate that the stereochemical mode of reaction is the same as that observed with the less substituted nitrones **1**. The C-6 substituent on **18** is more remote from the dipole reacting site and it is apparent that if it is to have a chance to invert the diastereoselectivity of the cycloaddition reaction it needs to be much larger than the C-5 group. Work is progressing in this direction.

Conclusion

In conclusion, 1,3-dipolar cycloaddition of the oxazinone

N-oxides **1a**,**b** to acetylenic dipolarophiles proceeded to afford cycloadducts predominately through addition to the less substituted face of the dipole. The phenyl substituted dipole **1b** with its enhanced conjugation is a more sluggish reactant than its methyl analogue **1a**; this was reflected in longer reaction times and incomplete conversion to cycloadducts. Adducts arising from reaction of **1a**, with a C-3a methyl substituent are prone to primary and secondary rearrangement processes opening a route to highly substituted pyrrolo-fused oxazinones. The seven-membered dipole **1c** on trapping with the acetylenes furnished novel isoxazolooxazepinones: examples of a rare bicyclic ring system. The trapping of the trisubstituted nitrone **18** with acetylenic dipolarophiles indicates that the additional C-6 substituent had no role to play in influencing the stereochemical course of the cycloaddition. It remains to be seen if a group larger than methyl is able to override the control of the C-5 substituent. The high regio- and diastereoselectivities of the cycloaddition chemistry of **1** and **18** encourage us in future investigations of their chiral, non-racemic derivatives in search of enantiopure products.

Experimental

Mps were determined on an Electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer model 240 CHN analyser. IR spectra (Nujol mull and liquid film) were measured on a Perkin Elmer 1600 series (FT) or a Perkin Elmer 983G spectrometer. ^{1}H and ^{13}C NMR spectra were recorded using a JEOL EX270 FT NMR spectrometer and a JEOL JNM-LA400 FT NMR spectrometer at probe temperatures with tetramethylsilane as internal reference and deuteriochloroform as solvent; *J* values are given in hertz. Flash column chromatography was carried out on silica gel 60 (Merck 9385, 70–230 mesh) and analytical TLC plates were purchased from Merck. Samples were located by UV illumination using a portable Spectroline Hanovia lamp (λ = 254 nm) or by the use of iodine staining. Mass spectra were recorded on a Profile Kratos Analytical Instrument.

Dimethyl 3a,7-dimethyl-4-oxo-3a,4,6,7-tetrahydroisoxazolo-[3,2-*c*][1,4]oxazine-2,3-dicarboxylate 12a

The nitrone **1a** (0.11 g, 0.78 mmol) and dimethyl acetylenedicarboxylate (0.16 g, 1.2 mmol) were stirred in $CHCl_3$ (24 cm^3) at reflux under a nitrogen atmosphere for 30 h. The reaction mixture was cooled to rt and the solvent removed under reduced pressure. The yellow oily residue was purified by flash chromatography (Et_2O–petroleum spirit 40–60 °C, 2 : 1) giving **12a**, colourless needles (0.18 g, 81%), mp 99–101 °C (from $CHCl_3$–petroleum spirit) (Found: C, 50.45; H, 5.16; N, 4.78. $C_{12}H_{15}NO_7$ requires: C, 50.53; H, 5.26; N, 4.91%); δ_H (400 MHz) 1.29 (3H, d, *J* 6.35, 7-Me), 1.83 (3H, s, 3a-Me), 3.45 (1H, m, 7-H), 3.83 and 3.87 (2 × 3H, 2 × s, 2 × OMe), 4.10 (1H, dd, *J* 12.02 and 9.40, 6b-H), 4.30 (1H, dd, *J* 12.02 and 2.93, 6a-H); δ_C (100 MHz) 14.84 (7-Me), 27.03 (3a-Me), 52.63 and 53.14 (OMe), 55.73 (7-C), 67.96 (6-C), 74.49 (3a-C), 114.66 (3-C), 146.34 (2-C), 158.01, 161.92 and 167.27 (C=O and 2 × CO_2Me); DEPT 135 (400 MHz) 14.83 (7-Me), 27.02 (3a-Me), 52.64 (OMe), 53.17 (OMe), 55.73 (7-C), 67.67 (6-C) and unreacted nitrone (0.025 g, 11%).

NOEDS results: irradiation of 6b-H caused a 19% enhancement on its partner 6a-H, 2% enhancement on 7-Me and 0.8% on 3a-Me. Back irradiation of 3a-Me caused a 0.6% enhancement on 6b-H. Irradiation of 6a-H caused an enhancement of 5.8% on 7-H and 23% on its partner 6b-H.

Dimethyl 4-methyl-1-oxo-3,4,6,7-tetrahydro-1*H*-pyrrolo[2,1-*c*]-[1,4]oxazine-6,7-dicarboxylate 13

The adduct **12a** (100 mg, 0.35 mmol) was stirred in $CHCl_3$ (10 cm^3) at reflux under a nitrogen atmosphere for 25 h. The mixture was allowed to cool to rt and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (Et_2O–petroleum spirit, 1 : 2) yielding **13**, colourless needles (75 mg, 80%), mp 116–119 °C (from Et_2O–petroleum spirit) (Found: C, 53.88; H, 4.94; N, 4.74. $C_{12}H_{13}NO_6$ requires: C, 53.93; H, 4.87; N, 5.24%); δ_H (400 MHz) 1.56 (3H, d, *J* 6.59, Me), 3.87 and 3.94 (2 × 3H, 2 × s, 2 × OMe), 4.44 (1H, d, *J* 11.96, 3b-H), 4.66 (1H, dd, *J* 11.96 and 3.17, 3a-H), 5.06 (1H, m, 4-H), 7.36 (1H, s, Ar-H); δ_C (100 MHz) 18.83 (Me), 49.15 (4-C), 52.20 and 52.71 (OMe), 70.76 (3-C), 118.35 (8-C), 118.52 (7-C), 120.90, 121.54 (8a-C, 6-C), 157.42, 160.43 and 163.62 (2 × CO_2Me and C=O); DEPT 135 (400 MHz) 18.83 (Me), 49.15 (4-C), 52.20 and 52.71 (OMe), 70.76 (−ve, 3-C), 118.35 (8-C), ν_{max}/cm^{-1} 3138, 2359, 2340 (Ar-CH), 1732, 1714, 1706 (3 × C=O), 1463 (Ar C=C), 1226 (C–O).

Trimethyl 4-methyl-1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]-oxazine-6,7,8-tricarboxylate 14

The nitrone **1a** (0.30 g, 2.1 mmol) and dimethyl acetylenedicarboxylate (0.40 g, 2.8 mmol) were stirred in $CHCl_3$ (40 cm^3) at reflux under a nitrogen atmosphere for 48 h. The reaction mixture was allowed to cool to rt and the solvent was removed under reduced pressure. The yellow oily residue was purified by flash chromatography (Et_2O–petroleum spirit, 1 : 1) yielding **12a** (148 mg, 25%, spectral data as previously reported), **14** (209 mg, 31%) and unreacted nitrone (32 mg, 11%). Compound **14**: colourless needles, mp 99–101 °C (from C_6H_6) (Found: C, 51.62; H, 4.40; N, 4.22. $C_{14}H_{15}NO_8$ requires: C, 51.69; H, 4.62; N, 4.31%); δ_H (400 MHz) 1.59 (3H, d, *J* 6.83, 4-Me), 3.90 (6H, s, 2 × OMe), 3.91 (3H, s, OMe), 4.43 (1H, d, *J* 10.99, 3b-H), 4.65 (1H, br dd, 3a-H), 5.20 (1H, m, 4-H); δ_H (400 MHz, d$_6$-acetone) 1.78 (3H, d, *J* 6.59, Me), 3.98, 3.99 and 4.07 (3 × 3H, 3 × s, 3 × OMe), 4.75 (1H, dd, *J* 11.99 and 1.10, 3b-H), 5.05 (1H, dd, *J* 11.99 and 2.75, 3a-H), 5.36 (1H, m, 4-H); δ_C (C_6D_6, 100 MHz) 17.23 (Me), 49.46 (4-C), 51.88 (OMe), 52.09 (OMe), 52.22 (OMe), 69.41 (3-C), 120.71 (7-C), 121.98 (8-C), 122.87 (6-C), 123.63 (8a-C), 155.10, 159.39, 162.99, 163.46 (3 × CO_2Me and C=O), ν_{max}/cm^{-1} 1716, 1721, 1737, 1755, (4 × C=O), 1554 (C=N); *m/z* 325 ($M^{\bullet+}$), 294 (base), 236.

X-Ray crystal structure determination of 14.§ The structure was solved by direct methods, SHELXS-97,[16] and refined by full matrix least squares using SHELXL-97.[17] SHELX operations were rendered paperless using ORTEX which was also used to obtain the drawings.[18] Data were corrected for Lorentz and polarization effects but not for absorption. Hydrogen atoms were included in calculated positions with thermal parameters 30% larger than the atom to which they were attached. The non-hydrogen atoms were refined anisotropically. All calculations were performed on a Pentium PC. Crystal data for **14** are given in Table 3.

Dimethyl 7-methyl-4-oxo-3a-phenyl-3a,4,6,7-tetrahydro-isoxazolo[3,2-*c*][1,4]oxazine-2,3-dicarboxylates 12b and 15

Freshly recrystallised nitrone **1b** (0.19 g, 0.93 mmol) and dimethyl acetylenedicarboxylate (0.18 g, 1.27 mmol) were stirred in $CHCl_3$ (23 cm^3) at reflux under a nitrogen atmosphere for 40 h. The reaction mixture was allowed to cool to rt and the solvent was removed under reduced pressure. The yellow oily residue was purified by flash chromatography (Et_2O–petroleum spirit, 1 : 1), yielding **12b** (178 mg, 56%), **15** (17.5 mg, 6%) and unreacted nitrone (0.05 g, 26%). Compound **12b**: colourless cubic crystals, mp 159–162 °C (from $CHCl_3$–hexane) (Found: C, 58.82; H, 4.99; N, 4.40. $C_{17}H_{17}NO_7$ requires: C, 58.79; H, 4.90;

§ CCDC reference numbers 168302 and 168303. See http://www.rsc.org/suppdata/p1/b1/b106832f/ for crystallographic files in .cif or other electronic format.

Table 3 Crystal data and structure refinement[a] for **14**

Empirical formula	$C_{14}H_{15}NO_8$
Formula weight	325.27
Temperature/K	293(2)
Crystal system	Monoclinic
Space group	$P2_1/a$
Unit cell dimensions	a = 9.917(2) Å
	b = 11.620(3) Å
	c = 13.983(4) Å
	β = 107.40(2)°
Volume	1537.4(7) Å^3
Z	4
Density (calculated)	1.405 Mg m^{-3}
Absorption coefficient	0.117 mm^{-1}
Independent reflections	1880 [R(int) = 0.0150]
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0365, wR_2 = 0.0934

[a] R indices: $R_1 = [\Sigma||F_o| - |F_c||/\Sigma|F_o|$ (based on F), $wR_2 = [[\Sigma_w(|F_o^2 - F_{2\text{-C}}|)^2]/[\Sigma_w(F_o^2)^2]]^{1/2}$ (based on F^2). $w = 1/[(\sigma F_o)^2 + (0.0569P)^2]$. Goodness-of-fit = $[\Sigma_w(F_o^2 - F_{2\text{-C}})^2/(N_{obs} - N_{parameters})]^{1/2}$.

Table 4 Crystal data and structure refinement[a] for **12b**

Empirical formula	$C_{17}H_{17}NO_7$
Formula weight	347.32
Temperature/K	293(2)
Crystal system	Orthorhombic
Space group	$P2_1$
Unit cell dimensions	a = 9.023(3) Å
	b = 11.0408(16) Å
	c = 16.112(3) Å
	β = 89.976(19)°
Volume	1605.1(6) Å^3
Z	4
Density (calculated)	1.437 Mg m^{-3}
Absorption coefficient	0.113 mm^{-1}
Independent reflections	1823 [R(int) = 0.0583]
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0501, wR_2 = 0.1127

[a] R indices: $R_1 = [\Sigma||F_o| - |F_c||/\Sigma|F_o|$ (based on F), $wR_2 = [[\Sigma_w(|F_o^2 - F_{2\text{-C}}|)^2]/[\Sigma_w(F_o^2)^2]]^{1/2}$ (based on F^2). $w = 1/[(\sigma F_o)^2 + (0.0569P)^2]$. Goodness-of-fit = $[\Sigma_w(F_o^2 - F_{2\text{-C}})^2/(N_{obs} - N_{parameters})]^{1/2}$.

N, 4.04%); δ_H (400 MHz) 1.32 (3H, d, J 6.35, Me), 3.62 (1H, m, 7-H), 3.66 (3H, s, OMe), 3.85 (1H, dd, J 11.96 and 10.99, 6b-H), 3.89 (3H, s, OMe), 4.14 (1H, dd, J 11.96 and 3.17, 6a-H), 7.42 (3H, m, *m*- and *p*-Ar-H), 7.60 (2H, m, *o*-Ar-H); δ_C (100 MHz) 15.73 (Me), 52.16 and 53.27 (2 × OMe), 58.62 (7-C), 67.40 (6-C), 79.59 (3a-C), 111.86 (3-C), 127.10, 128.63, 128.97 (Ar-C), 137.84 (quaternary *n*-Ar-C), 149.18 (2-C), 158.39, 161.66 and 167.82 (2 × *C*O$_2$Me and C=O).

NOEDS results for **12b**: irradiation of 7-Me caused a 4.9% enhancement on 7-H and 1.2% on 6a-H and 0.8% on each of the Ar-H signals.

X-Ray crystal structure determination of 12b.§ As for compound **14**. Crystal data for **12b** are given in Table 4.

Compound **15**: a brown–orange gum which solidified on standing (decomposed 118 °C) (combustion analysis is obtained as an enriched mixture of **12b** with **15**. Found: C, 58.80; H, 4.64; N, 3.84. $C_{16}H_{17}NO_7$ requires: C, 58.78; H, 4.89; N, 4.03%); δ_H (400 MHz) 1.31 (3H, d, J 6.60, 7-Me), 3.63 (3H, s, OMe), 3.72 (1H, m, 7-H), 3.93 (3H, s, OMe), 4.33 (1H, dd, J 11.90 and 3.30, 6a-H), 4.68 (1H, dd, J 11.90 and 9.52, 6b-H), 7.37 (3H, m, *m*- and *p*-Ar-H), 7.54 (2H, m, *o*-Ar-H); δ_C (100 MHz, obtained for an enriched mixture of **12b** with **15**) 13.40 (7-Me), 52.98 and 53.74 (2 × OMe), 58.96 (7-C), 68.90 (6-C), 79.77 (3a-C), 111.65 (3-C), 128.13, 128.21, 128.81 (Ar-C), 137.09 (quaternary *n*-Ar-C), 153.09 (2-C), 158.61, 162.01 and 166.64 (2 × *C*O$_2$Me and C=O).

NOEDS results for **15**: irradiation of 7-H gave an enhancement of 8.10% onto 7-Me and 2.17% onto 6a-H. Irradiation of 6a-H gave an enhancement of 26.76% onto its partner 6b-H.

2,3-Dimethoxycarbonyl-8-methyl-3a-phenyl-7,8-dihydro-6*H*-isoxazolo[3,2-*c*][1,4]oxazepin-4(3a*H*)-one 16

The nitrone **1c** (0.55 g, 2.50 mmol) and dimethyl acetylenedicarboxylate (0.46 g, 3,25 mmol) were stirred in $CHCl_3$ (20 cm^3) at reflux under a nitrogen atmosphere for 32 h. The reaction mixture was allowed to cool to rt and the reaction solvent removed under reduced pressure. The yellow oily residue was purified by flash chromatography (Et_2O–petroleum spirit, 1.5 : 1.0) to give **16** (0.79 g, 87%) and unchanged nitrone (0.07 g, 12%). Compound **16**: colourless cubic crystals (from C_6H_6–petroleum spirit), mp 145–146 °C (Found: C, 60.08; H, 7.12; N, 5.22%. $C_{18}H_{19}NO_7$ requires: C, 59.83; H, 7.28; N, 5.36%); δ_H (270 MHz) 1.42 (3H, d, J 5.87, Me), 2.24 and 1.67 (2 × 1H, 2 × m, 7a-H and 7b-H), 3.60 (1H, m, 8-H), 3.85 and 3.67 (2 × 3H, 2 × s, 2 × OMe), 3.88 (2H, m, 6a-H and 6b-H), 7.40 (3H, m, *m*- and *p*-Ar-H), 7.62 (2H, m, *o*-Ar-H); δ_C (67.5 MHz) 19.6 (Me), 36.6 (7-C), 51.9 and 53.2 (2 × OMe), 57.2 (8-C), 64.0 (6-C), 86.7 (3a-C), 113.1 (3-C), 126.3–134.8 (Ar-C), 138.0 (2-C), 159.7, 164.3 and 168.6 (2 × *C*O$_2$Me and C=O).

1-Methylprop-2-enyl 2-oxopropanoate 17a

Pyruvic acid (5.07 g, 57.6 mmol) and but-3-en-2-ol (4.98 g, 69.2 mmol) were heated for 5 h at reflux in C_6H_6 (200 cm^3) in the presence of a catalytic amount of *p*-TsOH (0.55 g, 2.89 mmol) using a Dean–Stark apparatus. The reaction was allowed to cool to rt and was washed with sat. $NaHCO_3$ (2 × 150 cm^3) and then with water (2 × 150 cm^3). The organic layers were collected and dried (anhydrous Na_2SO_4), filtered and concentrated to yield the crude product as a yellow, pungent, mobile oil (6.56 g, 80.2%) which was not purified further. δ_H (400 MHz) 1.35 (3H, dd, J 6.21 and 2.01, OCMe), 2.39 (3H, s, Me), 5.14 (1H, dd, J 1.10 and 10.62, =CH$_2$), 5.25 (1H, dd, J 1.10 and 17.21, =CH$_2$), 5.37 (1H, M, CH=), 5.81 (1H, m, OCH).

1-Methylprop-2-enyl 2-(hydroxyimino)propanoate 17b

The α-keto ester **17a** (6 g, 42.2 mmol), pyridine (5.01 g, 63.4 mmol) and $NH_2OH{\cdot}HCl$ (4.40 g, 63.3 mmol) were stirred in EtOH (600 cm^3) at rt for 15 h. The mixture was concentrated and taken up in CH_2Cl_2 (300 cm^3) and washed with water (2 × 150 cm^3). The organic layers were collected, dried (anhydrous Na_2SO_4), filtered and concentrated to yield the product, colourless plates (5.97 g, 90%), mp 56.5–58.5 °C (from C_6H_6–hexane) (Found: C, 53.72; H, 6.79; N, 8.69. $C_7H_{11}NO_3$ requires: C, 53.50; H, 7.01; N, 8.92%); δ_H (400 MHz) 1.38 (3H, d, J 6.22, OCMe), 2.09 (3H, s, Me), 5.16 (1H, dd, J 10.62 and 0.91, =CH$_2$), 5.28 (1H, dd, J 17.21 and 0.91, =CH$_2$), 5.47 (1H, m, OCH), 5.87 (1H, m, CH=), 10.64 (1H, br s, OH); δ_C (100 MHz) 10.42 (OC*Me*), 19.81 (Me), 72.75 (OC), 116.57 (=CH$_2$), 136.91 (CH=), 149.18 (C=N), 162.85 (C=O).

2,3,5-Trimethyl-6-oxo-3,6-dihydro-2*H*-1,4-oxazin-4-ium-4-olates 18 and 19

Oxime **17b** (1.2 g, 7.64 mmol) was heated at reflux in xylene (410 cm^3) in the presence of hydroquinone (1% w/v, 4.1 g) under a nitrogen atmosphere for 51 h. The reaction mixture was allowed to cool to rt and the precipitated hydroquinone was filtered off. The filtrate was concentrated and taken up in $CHCl_3$ (10 cm^3), and further hydroquinone precipitated, which was again removed by filtration. The filtrate was concentrated to yield the crude product, a black viscous oil. Purification by flash chromatography (Et_2O–petroleum spirit, 4 : 1) afforded **18** (624 mg, 52%), **19** (190 mg, 16%) and unreacted oxime **17b** (260 mg, 22%).

Compound **18**: colourless cubic crystals, mp 82–84 °C (from $CHCl_3$–hexane) (Found: C, 53.76; H, 7.01; N, 8.59. $C_7H_{11}NO_3$ requires: C, 53.50; H, 7.01; N, 8.92%); δ_H (400 MHz) 1.51 (3H, d, J 6.59, 6-Me), 1.53 (3H, d, J 6.60, 5-Me), 2.22 (3H, s, 3-Me), 3.91 (1H, m, 5-H), 4.45 (1H, m, 6-H); δ_C (100 MHz) 11.95 (6-Me), 14.29 (5-Me), 18.41 (3-Me), 67.74 (5-C), 75.05 (6-C), 134.83 (3-C), 159.03 (C=O).

NOEDS results for **18**: irradiation of 5-H caused a 0.68% enhancement on 6-H and 5.14% enhancement on the signal representing 5-Me and 6-Me. *m*/*z* 57 (base), 68, 85, 113, 157 (M^+).

Compound **19**: a brown mobile oil which solidified on standing (Found: C, 53.55; H, 6.83; N, 8.67. $C_7H_{11}NO_3$ requires: C, 53.50; H, 7.01; N, 8.92%); δ_H (400 MHz) 1.42 (3H, d, *J* 6.59, 6-Me), 1.47 (3H, d, *J* 6.96, 5-Me), 2.20 (3H, s, 3-Me), 3.97 (1H, m, 5-H), 4.82 (1H, m, 6-H); δ_C (100 MHz) 11.61 (6-Me), 11.83 (5-Me), 15.69 (3-Me), 68.30 (5-C), 72.37 (6-C), 134.23 (3-C), 159.62 (C=O).

NOEDS results for **19**: irradiation of 5-H caused a 3.93% enhancement on 6-H and irradiation of 6-H caused a 4.11% enhancement on the signal representing 5-H.

Dimethyl 3a,6,7-trimethyl-4-oxo-3a,4,6,7-tetrahydroisoxazolo-[3,2-*c*][1,4]oxazine-2,3-dicarboxylate 20 and trimethyl 3,4-dimethyl-1-oxo-3,4,6,7-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]-oxazine-6,7,8-tricarboxylate 22

(i) Nitrone **18** (0.050 g, 0.318 mmol) and dimethyl acetylenedicarboxylate (0.090 g, 0.63 mmol) were stirred in $CHCl_3$ (5 cm^3) at reflux under a nitrogen atmosphere for 7.5 h. The reaction mixture was allowed to cool to rt, was concentrated under reduced pressure and purified by flash chromatography (Et_2O–petroleum spirit, 1 : 2) yielding **20** (134 mg, 74%). Compound **20**: colourless needle-like crystals, mp 157–159.5 °C (from $CHCl_3$–hexane) (Found: C, 51.81; H, 5.53; N, 4.23. $C_{13}H_{17}NO_7$ requires: C, 52.17; H, 5.68; N, 4.68%); δ_H (400 MHz) 1.28 (3H, d, *J* 5.86, 7-Me), 1.40 (3H, d, *J* 6.59, 6-Me), 1.82 (3H, s, 3a-Me), 3.07 (1H, m, 7-H), 3.83 (3H, s, OMe), 3.85 (3H, s, OMe), 4.21 (1H, m, 6-H); δ_C (100 MHz) 15.14 (7-Me), 17.47 (6-Me), 26.94 (3a-Me), 52.71 (OMe), 53.10 (OMe), 61.21 (7-C), 74.71 (3a-C), 75.26 (6-C), 115.55 (3-C), 145.32 (2-C), 158.01, 162.13 and 167.65 (2 × CO_2Me and C=O).

NOEDS results for **20**: irradiation of 3a-Me caused a 1.27% enhancement of 6-H and 0.2 on 7-H. Irradiation of 6-H caused the following enhancements 4.30% on 6-Me, 2.73 on 7-Me, 2.07 on 3a-Me and 1.63 on 7-H. Irradiation of the signal for 7-H caused the following enhancements 1.95% on 6-Me, 4.53 on 7-Me and 1.60 on 6-H.

(ii) When the reaction was repeated, on twice the scale of (i) above, and extending the reaction time to 24 h, adduct **20** (134 mg, 72%) and trimethyl 3,4-dimethyl-1-oxo-3,4,6,7-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-6,7,8-tricarboxylate **22** (27 mg, 15%) were obtained; data for **20** as reported above.

Compound **22**: a yellow amorphous solid, mp 103–108 °C ($CHCl_3$–hexane) (Found: C, 52.74; H, 5.37; N, 3.57. $C_{15}H_{17}NO_8$ requires: C, 53.10; H, 5.01; N, 4.13%); δ_H (400 MHz) 1.39 (3H, d, *J* 6.96, 4-Me), 1.58 (3H, d, *J* 6.59, 3-Me), 3.91 (9H, s, 3 × OMe), 4.72 (1H, m, 4-H), 5.03 (1H, m, 3-H); δ_C (100 MHz) 19.21 (4-Me), 20.32 (3-Me), 52.71 (4-C), 52.80 and 53.69 (OMe), 76.70 (3-C), 120.27, 121.45, 122.03, 124.17, (6-C, 7-C, 8-C, 8a-C), 154.38, 159.41, 162.43 and 164.00 (3 × CO_2Me and C=O); *m*/*z* 55, 236, 308 (base), 339 (M^+).

(iii) Nitrone **18** (0.05 g, 0.318 mmol) and dimethyl acetylenedicarboxylate (0.09 g, 0.64 mmol) were stirred in $CHCl_3$ (5 cm^3) at rt under a nitrogen atmosphere for 7 d. The reaction mixture was concentrated and purified by flash chromatography (Et_2O–petroleum spirit, 1 : 2) yielding **20** (90.3 mg, 95%) which crystallised as colourless needle-like crystals, data agree with those reported above.

(iv) When the reaction was repeated, at rt, on twice the scale of (iii) above, extending the reaction time to 10 d, adduct **20** (157.5 mg, 83%) and trimethyl 3,4-dimethyl-1-oxo-3,4,6,7-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-6,7,8-tricarboxylate **22** (15.3 mg, 8%) were obtained; data as reported above.

Dimethyl 3,4-dimethyl-1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*]-[1,4]oxazine-6,7-dicarboxylate 21

The adduct **20** (50 mg, 0.167 mmol) was stirred with heating under vigorous reflux in the minimum amount of $CHCl_3$ (1 cm^3) for 48 h. The reaction was allowed to cool to rt and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (Et_2O–petroleum spirit; 1 : 2) yielding **21** (35.5 mg, 76%), which crystallised as colourless needles, mp 118–120 °C (from Et_2O–petroleum spirit) (Found: C, 55.84; H, 5.26; N, 4.81. $C_{13}H_{15}NO_6$ requires: C, 55.52; H, 5.34; N, 4.98%); δ_H (400 MHz) 1.38 (3H, d, *J* 6.87, 4-Me), 1.56 (3H, d, *J* 6.78, 3-Me), 3.87 (3H, s, OMe), 3.95 (3H, s, OMe), 4.71 (1H, q, *J* 6.87, 4-H), 4.86 (1H, q, *J* 6.78, 3-H), 7.35 (1H, s, 8-H); δ_C (100 MHz) 19.34 (4-Me), 20.61 (3-Me), 52.20 (4-C), 52.71 (OMe), 53.18 (OMe), 78.10 (3-C), 117.97 (8-C), 120.65, 121.79 and 125.75 (7-C, 6-C and 8a-C), 156.87, 159.67 and 163.66 (2 × CO_2Me and C=O); *m*/*z* 281 ($M^{\bullet+}$), 250.

Methyl 3a,7-dimethyl-4-oxo-3a,4,6,7-tetrahydroisoxazolo[3,2-*c*][1,4]oxazine-3-carboxylate 23a and methyl 3a,7-dimethyl-4-oxo-3a,4,6,7-tetrahydroisoxazolo[3,2-*c*][1,4]oxazine-2-carboxylate 24a

The nitrone **1a** (0.10 g, 0.69 mmol) and methyl propiolate (0.29 g, 3.49 mmol) were stirred in $CHCl_3$ (10 cm^3) at reflux under a nitrogen atmosphere for 25 h. The reaction mixture was allowed to cool to rt and the reaction solvent and unreacted dipolarophile were removed under reduced pressure, yielding the crude product as an orange–brown oil. The residue was purified by flash chromatography (Et_2O–petroleum spirit, 1 : 2), yielding **24a** (36.5 mg, 23%), **23a** (88.5 mg, 56%) and unreacted dipole (19 mg, 19%).

Compound **24a**: colourless cubic crystals, mp 88–90 °C (from $CHCl_3$–hexane) (Found: C, 52.57; H, 5.96; N, 6.09. $C_{10}H_{13}NO_5$ requires: C, 52.86; H, 5.73; N, 6.16%); δ_H (400 MHz) 1.28 (3H, d, *J* 6.35, 7-Me), 1.66 (3H, s, 3a-Me), 3.32 (1H, m, 7-H), 3.85 (3H, s, OMe), 4.05 (1H, dd, *J* 11.96 and 2.93, 6a-H), 4.25 (1H, dd, *J* 11.96 and 2.93, 6a-H), 6.00 (1H, s, 3-H); δ_C (100 MHz) 14.93 (7-Me), 27.58 (3a-Me), 52.54 (OMe), 54.96 (7-C), 68.21 (6-C), 73.82 (3a-C), 112.67 (3-C), 144.89 (2-C), 158.73 and 168.84 (*C*O_2Me and C=O); DEPT 135 (400 MHz) 14.93 (7-Me), 27.58 (3a-Me), 52.54 (OMe), 54.96 (7-C), 68.21 (6-C), 112.67 (3-C).

NOEDS results for **24a**: irradiation of 6a-H caused an enhancement of 4.1% on 7-H, 2.9% onto 7-Me and 22.5% on its partner 6b-H. Irradiation of 6b-H caused an 18.8% enhancement on its partner 6a-H, 2% enhancement on 7-H and no enhancement on either 7-Me or 3a-Me.

Compound **23a**: a viscous yellow oil (Found: C, 52.74; H, 5.68; N, 6.34. $C_{10}H_{13}NO_5$ requires: C, 52.86; H, 5.73; N, 6.16%); δ_H (400 MHz) 1.29 (3H, d, *J* 6.84, 7-Me), 1.82 (3H, s, 3a-Me), 3.48 (1H, m, 7-H), 3.75 (3H, s, OMe), 4.16 (1H, dd, *J* 12.02 and 6.71, 6b-H), 4.46 (1H, dd, *J* 12.02 and 2.69, 6a-H), 7.48 (1H, s, 2-H); δ_C (100 MHz) 15.18 (7-Me), 26.86 (3a-Me), 51.40 (OMe), 57.68 (7-C), 67.15 (6-C), 70.12 (3a-C), 109.31 (3-C), 154.53 (2-C), 162.47 and 167.86 (*C*O_2Me and C=O); DEPT 135 (400 MHz) 15.18 (7-Me), 26.86 (3a-Me), 51.40 (OMe), 57.68 (7-C), 67.15 (6-C), 154.53 (2-C).

NOEDS results for **23a**: irradiation of 6b-H caused a 19% enhancement on its partner 6a-H, and a 1.8% enhancement on 7-Me. Irradiation of 3a-Me caused a 0.55% enhancement on 6b-H. Irradiation of 6a-H caused an enhancement of 4% on 7-H and 20% on its partner 6b-H.

(ii)When the above reaction was repeated extending the duration to 82 h heating crude ^{1}H NMR spectral analysis showed **24a**, **23a**, **25**, **25i**, **13** plus **13i** present in a 3 : trace : 15 : 4 : 25 ratio. **25** is characterised by a separate experiment (see below) and **25i** is proposed on the basis of a pair of doublets, 6.96 and 7.05 ppm each with *J* value (~4.4 Hz) characteristic of the *ortho*-coupled aromatic protons. Adducts **13** and **13i** are characterised as a mixture δ_H (400 MHz) 1.56 (6H, 2 × overlapping d, Me [**13** and **13i**]), 3.87 & 3.94 (2 × 3H, 2 × s, 2 × OMe [**13**]), 3.89 & 3.90 (2 × 3H, 2 × s, 2 × OMe [**13i**]), 4.44 (1H, 2 × overlapping d, 3b-H [**13** and **13i**]), 4.65 (2H, m, 3a-H [**13** and **13i**]), 5.05 (1H, m, 4-H [**13**]), 5.35 (1H, m, 4-H [**13**]), 7.36 (2H, s, Ar-H [**13** and **13i**]).

Methyl 4-methyl-1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]-oxazine-7-carboxylate 25

The adduct **24a** (59 mg, 0.26 mmol) in $CHCl_3$ (1 cm^3) was held at vigorous reflux under a nitrogen atmosphere for 56 h. The resulting mixture was concentrated under reduced pressure and purification by flash chromatography (Et_2O–petroleum spirit, 1 : 1) yielded **25** as fine colourless needles (21.6 mg, 40%), mp 127.5–128.0 °C (from C_6H_6–petroleum spirit) (Found: C, 57.42; H, 5.55; N, 6.38. $C_{10}H_{11}NO_4$ requires: C, 57.42; H, 5.26; N, 6.70%); δ_H (400 MHz) 1.59 (3H, d, *J* 6.59, Me), 3.84 (3H, s, OMe), 4.29 (1H, dd, *J* 11.53 and 7.87, 3b-H), 4.42 (1H, m, 4-H), 4.55 (1H, dd, *J* 11.53 and 3.48, 3a-H), 7.49 and 7.52 (2 × 1H, 2 × d, *J* 1.46, 6-H and 8-H); δ_C (100 MHz) 15.94 (Me), 49.23 (4-C), 51.52 (OMe), 71.01 (3-C), 118.06 (7-C), 118.69 (8-C), 119.76 (8a-C), 126.00 (6-C), 157.88 and 163.83 (CO_2Me and C=O).

Methyl 4-methyl-1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]-oxazine-6-carboxylate 26a

The adduct **23a** (63 mg, 0.28 mmol) was stirred in $CHCl_3$ (3 cm^3) with heating at reflux under a N_2 atm for 82 h. The mixture was allowed to cool to rt and the solvent removed under reduced pressure. Purification of the crude mixture by flash chromatography (petroleum spirit–Et_2O, 2 : 1) afforded the title compound **26a** (14 mg, 24%) and returned **23a** (8 mg, 12%). **26a**, colourless cubic crystals, mp 138–140 °C (from $CHCl_3$). (R_f 0.676, Et_2O); δ_H (400 MHz) 1.54 (3H, d, *J* 6.83, 4-Me), 3.89 (3H, s, OMe), 4.43 (1H, d, *J* 11.71, 3a-H), 4.65 (1H, dd, *J* 11.71 and 3.90, 3b-H), 5.29 (1H, m, 4-H), 6.95 (1H, d, *J* 3.90, 8-H), 7.05 (1H, d, *J* 3.90, 7-H); δ_C(100 MHz) 18.79 (4-Me), 48.64 (4-C), 51.86 (OMe), 71.01 (3-C), 116.57 (7-C), 117.46 (8-C), 123.20 (8a-C), 124.30 (6-C), 158.27 (1-C), 160.69 (CO_2Me).

Methyl 7-methyl-4-oxo-3a-phenyl-3a,4,6,7-tetrahydroisoxazolo-[3,2-*c*][1,4]oxazine-2-carboxylate 24b and methyl 7-methyl-4-oxo-3a-phenyl-3a,4,6,7-tetrahydroisoxazolo[3,2-*c*][1,4]oxazine-3-carboxylates 23b and 23c

Freshly recrystallised nitrone **1b** (0.11 g, 0.54 mmol) and methyl propiolate (0.25 g, 3.02 mmol) were stirred in $CHCl_3$ (15 cm^3) at reflux under a nitrogen atmosphere for 40 h. The reaction mixture was allowed to cool to rt and the solvent removed under reduced pressure yielding the crude product, a viscous yellow oil which was purified by flash chromatography (Et_2O–petroleum spirit, 1 : 2), yielding **24b** (26.1 mg, 17%), **23b** (48.8 mg, 31%) and **23c** (19.2 mg, 13%) and unreacted nitrone (47 mg, 43%).

Compound **24b**: colourless cubic crystals, mp 122–125 °C (from $CHCl_3$–hexane) (Found: C, 62.08; H, 4.94; N, 4.96. $C_{15}H_{15}NO_5$ requires: C, 62.28; H, 5.19; N, 4.84%); δ_H (400 MHz) 1.40 (3H, d, *J* 6.35, 7-Me), 3.54 (1H, m, 7-H), 3.82 (3H, s, OMe), 4.04 (1H, dd, *J* 11.96 and 10.74, 6b-H), 4.20 (1H, dd, *J* 11.96 and 2.93, 6a-H), 6.26 (1H, s, 3-H), 7.34–7.42 (3H, m, *o*- and *p*-Ar-H), 7.67 (2H, m, *m*-Ar-H); δ_C (100 MHz) 15.67 (7-Me), 52.65 (OMe), 57.06 (7-C), 67.98 (6-C), 79.6 (3a-C), 111.75 (3-C), 126.27, 128.35, 128.78 and 129.03 (Ar-C), 144.61 (2-C), 158.75 and 167.50 (CO_2Me and C=O).

NOEDS results for **24b**: irradiation of 6b-H caused a 3.5% enhancement on the Ar-H signal, 21% enhancement on its partner 6a-H and 2% enhancement on 7-Me. Irradiation of 7-Me caused a 0.6% enhancement on Ar-H. Irradiation of 6a-H caused an enhancement of 3.9% on 7-H and 11% on its partner 6b-H.

Compound **23b**: a colourless viscous oil (Found: C, 61.92; H, 5.09; N, 4.84. $C_{15}H_{15}NO_5$ requires: C, 62.28; H, 5.19; N, 4.84%); δ_H (400 MHz) 1.30 (3H, d, *J* 6.35, 7-Me), 3.57 (1H, m, 7-H), 3.59 (3H, s, OMe), 3.73 (1H, dd, *J* 11.96 and 11.23, 6b-H), 4.05 (1H, dd, 11.96 and 3.17, 6a-H), 7.40 (3H, m, *o*- and *p*-Ar-H), 7.48 (1H, s, 2-H), 7.60 (2H, m, *m*-Ar-H); δ_C (67.5 MHz) 16.26 (7-Me), 51.19 (OMe), 59.85 (7-C), 66.94 (6-C), 76.87 (3a-C), 110.47 (quaternary *n*-Ar-C), 127.30–128.63 (5 × Ar-C), 138.31 (3-C), 152.86 (2-C), 162.41 and 168.48 (CO_2Me and C=O).

NOEDS results for **23b**: irradiation of 6b-H caused a 3% enhancement on the Ar-H signal and 20% enhancement on its partner 6a-H.

Compound **23c**: a brown–orange viscous oil (Found: C, 62.20; H, 5.06; N, 4.61. $C_{15}H_{15}NO_5$ requires: C, 62.28; H, 5.19; N, 4.84%); δ_H (400 MHz) 1.22 (3H, d, *J* 6.71, 7-Me), 3.57 (3H, s, OMe), 3.65 (1H, m, 7-H), 4.24 (1H, dd, *J* 11.60 and 3.05, 6a-H), 4.57 (1H, dd, *J* 9.77 and 11.60, 6b-H), 7.19 (1H, s, 2-H), 7.34 (3H, m, *o*- and *p*-Ar-H), 7.42 (2H, d, *J* 1.22, *m*-Ar-H); δ_C (100 MHz) 13.52 (7-Me), 51.48 (7-C), 52.84 (OMe), 68.51 (6-C), 75.64 (3a-C), 110.75 (3-C), 127.78–128.67 (Ar-C), 137.38 (quaternary *n*-Ar-C), 155.89 (2-C), 162.21 and 166.67 (CO_2Me and C=O).

3-Methoxycarbonyl-8-methyl-3a-phenyl-7,8-dihydro-6*H*-isoxazolo[3,2-*c*][1,4]oxazepin-4(3a*H*)-one 27 and 2-methoxy-carbonyl-8-methyl-3a-phenyl-7,8-dihydro-6*H*-isoxazolo[3,2-*c*]-[1,4]oxazepin-4(3a*H*)-one 28

Freshly recrystallised nitrone **1c** (0.46 g, 2.10 mmol) was stirred in neat methyl propiolate (5 cm^3, 4.73 g, 56.0 mmol) under a nitrogen atmosphere at 65 °C for 36 h. Unreacted dipolarophile was removed under reduced pressure (100 °C, 15 mmHg) to leave a viscous yellow oil. The crude products were separated by flash chromatography (Et_2O–petroleum spirit, 1.0 : 1.8) yielding **28** (0.38 g, 60%), **27** (0.15 g, 24%) and unreacted dipole (0.06 g, 13%).

Compound **28**: colourless prisms, mp 133–134 °C (from C_6H_6–petroleum spirit) (Found: C, 63.09; H, 5.76; N, 4.48. $C_{16}H_{17}NO_5$ requires: C, 63.37; H, 5.61; N, 4.62%); δ_H (270 MHz) 1.44 (3H, d, *J* 5.86, Me), 1.75 (1H, m, 7b-H), 2.23 (1H, m, 7a-H), 3.52 (1H, m, 8-H), 3.78 (3H, s, OMe), 3.90 (1H, m, *J* 12.45 and 6.60, 6b-H), 4.10 (1H, m, 6a-H), 6.19 (1H, s, 3-H), 7.38 (3H, m, *m*- and *p*-Ar-H), 7.62 (2H, m, *o*-Ar-H); δ_C (67.5 MHz) 19.8 (Me), 36.8 (7-C), 52.6 (OMe), 55.9 (8-C), 63.9 (6-C), 86.5 (3a-C), 113.6 (3-C), 125.0–138.5 (Ar-C), 142.5 (2-C), 159.0 and 169.7 (CO_2Me and C=O).

Compound **27**: colourless rods, mp 130–131 °C (from C_6H_6–petroleum spirit) (Found: C, 63.20; H, 5.49; N, 4.49. $C_{16}H_{17}NO_5$ requires: C, 63.37; H, 5.61; N, 4.62%); δ_H (270 MHz) 1.44 (3H, d, *J* 5.86, Me), 1.64 (1H, m, 7b-H), 2.21 (1H, m, 7a-H), 3.50 (1H, m, 8-H), 3.60 (3H, s, OMe), 3.86 (2H, m, 6b-H, 6a-H), 7.35 (4H, m, *m*- and *p*-Ar-H and 2-H), 7.65 (2H, m, *o*-Ar-H); δ_C (67.5 MHz) 18.9 (Me), 36.4 (7-C), 53.3 (OMe), 55.6 (8-C), 64.1 (6-C), 86.9 (3a-C), 110.4 (3-C), 125.9–138.5 (Ar-C), 152.9 (2-C), 158.6 and 168.6 (CO_2Me and C=O).

Methyl 3a,6,7-trimethyl-4-oxo-3a,4,6,7-tetrahydroisoxazolo-[3,2-*c*][1,4]oxazine-3-carboxylate 29 and methyl 3a,6,7-trimethyl-4-oxo-3a,4,6,7-tetrahydroisoxazolo[3,2-*c*][1,4]oxazine-2-carboxylate 30

Nitrone **18** (0.2 g, 1.27 mmol) and methyl propiolate (0.535 g, 6.37 mmol) were heated at reflux in $CHCl_3$ (20 cm^3) under a nitrogen atmosphere for 30 h. The reaction was allowed to cool to rt and the solvent and excess dipolarophile were removed under reduced pressure. The resulting mixture was purified by flash chromatography (Et_2O–petroleum spirit, 1 : 2) yielding

30 (60.7 mg, 20%), **29** (117.7 mg, 38%) and unreacted nitrone (57.9 mg, 29%).

Compound **30**: a colourless oil which solidified in the cold, mp 89–92 °C (Found: C, 54.96; H, 6.13; N, 5.65. $C_{11}H_{15}NO_5$ requires: C, 54.77; H, 6.22; N, 5.81%); δ_H (400 MHz) 1.28 (3H, d, *J* 6.22, 7-Me), 1.38 (3H, d, *J* 6.59, 6-Me), 1.64 (3H, s, 3a-Me), 2.97 (1H, m, 7-H), 3.83 (3H, s, OMe), 4.17 (1H, m, 6-H), 6.01 (1H, s, 3-H); δ_H (400 MHz) (C_6D_6) 0.73 (3H, d, *J* 6.39, 7-Me), 0.83 (3H, d, *J* 6.39, 6-Me), 1.45 (3H, s, 3a-Me), 2.41 (1H, m, 7-H), 3.25 (3H, s, OMe), 3.45 (1H, m, 6-H), 6.00 (1H, s, 3-H); δ_C (100 MHz) 15.31 (7-Me), 17.47 (6-Me), 27.45 (3a-Me), 52.54 (OMe), 60.65 (7-C), 73.65 (3a-C), 75.51 (6-C), 112.92 (3-C), 144.59 (2-C), 158.86 and 169.26 (CO_2Me and C=O); *m/z* 110, 142 (base), 154, 170, 182, 198, 241 (M^+), 242 (M + 1).

NOEDS results for **30** (recorded in C_6D_6): irradiation of 3a-Me caused a 1.14% enhancement on 6-H and 0.9 on 3-H. Irradiation of 7-H caused the following enhancements 3.39% on 6-Me and 4.06 on 7-Me. Irradiation of the signal for 6-H caused the following enhancements 3.26% on 7-Me, 1.05 on 3a-Me and 1.27 on 7-H.

Compound **29**: brown needles, mp 98–102 °C (from $CHCl_3$–hexane) (Found: C, 54.82; H, 6.18; N, 5.55. $C_{11}H_{15}NO_5$ requires: C, 54.77; H, 6.22; N, 5.81%); δ_H (400 MHz) 1.25 (3H, d, *J* 6.22, 7-Me), 1.38 (3H, d, *J* 6.22, 6-Me), 1.83 (3H, s, 3a-Me), 3.01 (1H, m, 7-H), 3.75 (3H, s, OMe), 4.24 (1H, m, 6-H), 7.34 (1H, s, 2-H); δ_C (100 MHz) 15.99 (7-Me), 17.56 (6-Me), 26.86 (3a-Me), 51.40 (OMe), 63.97 (7-C), 71.06 (3a-C), 73.69 (6-C), 109.57 (3-C), 152.96 (2-C), 162.89 and 169.39 (CO_2Me and C=O).

NOEDS results for **29**: irradiation of 3a-Me caused a 2.54% enhancement on 6-H and 0.2% on 7-H. Irradiation of 7-H caused the following % enhancements: 2.42 on 6-Me, 5.23 on 7-Me and 1.18 on 6-H. Irradiation of the signal for 6-H caused the following % enhancements: 3.55 on 7-Me, 4.79 on 6-Me, 5.17 on 3a-Me and 0.73 on 7-H.

(ii) When the above reaction was repeated, extending the duration to 84 h crude ^1H NMR spectral analysis showed **29**, **30**, **31** and **31i** present in the ratio 10 : 6 : 2.6 : 2.

Methyl 3,4-dimethyl-1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]-oxazine-8-carboxylate 31

The adduct **30** (58 mg, 0.24 mmol) was stirred with heating at vigorous reflux in $CHCl_3$ (1 cm^3) for 80 h. The reaction was allowed to cool to rt and the solvent removed under reduced pressure. The crude mixture was purified by flash chromatography (Et_2O–petroleum spirit, 1 : 1) yielding **31** (36 mg, 67%) and unreacted **30** (9.6 mg, 17%). Compound **31** crystallised to yellow cubic crystals, mp 129–132 °C (from C_6H_6–petroleum spirit) (Found: C, 58.82; H, 5.79; N, 5.65. $C_{11}H_{13}NO_4$ requires: C, 59.19; H, 5.83; N, 6.28%); δ_H (400 MHz) 1.52 (3H, d, *J* 6.59, 4-Me), 1.60 (3H, d, *J* 6.59, 3-Me), 3.84 (3H, s, OMe), 4.07 (1H, dq, *J* 8.24 and 6.59, 4-H), 4.46 (1H, dq, *J* 8.24 and 6.59, 3-H), 7.48 (1H, d, *J* 1.46, 6-H), 7.53 (1H, d, *J* 1.46, 8-H); δ_C (100 MHz) 15.77 (4-Me), 17.77 (3-Me), 51.22 (OMe), 54.50 (4-C), 78.70 (3-C), 118.06 (7-C), 118.44 (8-C), 120.05 (8a-C), 125.79 (6-C), 157.73 and 163.91 (CO_2Me and C=O).

Methyl 3,4-dimethyl-1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]-oxazine-6-carboxylate 26b

The adduct **29** (0.12 g, 0.49 mmol) was stirred in $CHCl_3$ (4 cm^3) with heating at reflux under a N_2 atm for 84 h. The mixture was allowed to cool to rt and the solvent removed under reduced pressure. Purification of the crude mixture by flash chromatography (petroleum spirit–Et_2O, 2 : 1) afforded title compound (14 mg, 12.8%) and returned **29** (38 mg, 32%). **26b**, colourless cubic crystals, mp 155–156 °C (from $CHCl_3$–hexane) (Found: C, 58.90; H, 6.06; N, 5.98. $C_{11}H_{13}NO_4$ requires: C, 59.19; H, 5.87; N, 6.27%); δ_H (400 MHz) 1.36 (3H, d, *J* 6.35, 4-Me), 1.53 (3H, d, *J* 6.35, 3-Me), 3.89 (3H, s, OMe), 4.70 (1H, quartet, *J* 6.67, 4-H), 5.12 (1H, quartet, *J* 6.67, 3-H), 6.95 (1H, d, *J* 4.39, 8-H), 7.03 (1H, d, *J* 4.39, 7-H); δ_C (100 MHz) 19.43 (4-Me), 20.57 (3-Me), 51.82 (4-C), 52.59 (OMe), 78.27 (3-C), 116.10 (7-C), 117.42 (8-C), 122.94 (8a-C), 124.64 (6-C), 157.42 (1-C), 161.37 (CO_2Me).

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