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An investigation of structure-reactivity relationships of δ-alkenyl oximes; competitive thermal reactions leading to cyclic nitrones and/or *N*-unsubstituted bicyclic isoxazolidines

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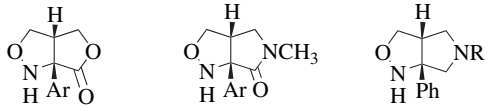
ABSTRACT

Thermal reactions of *C*-aryl δ-alkenyl oximes give *N*-unsubstituted bicylic lactone, lactam and pyrrolidine fused isoxazolidines by an intramolecular oxime olefin cycloaddition pathway (IOOC) and/or cyclic nitrones by an azaprotio cyclotransfer (APT) route; a number of factors, including the nature of the aryl group, the oxime geometry and the structure of the linker between the oxime and the terminal alkene, contribute to the competition.

1. Introduction

The isoxazolidine nucleus has long been recognized in its own right as a key structural component in biologically active molecules,[1,2] as an important synthon for the construction of 1,3-aminoalcohols or saturated nitrogen heterocycles[3–5] and as a chiral auxiliary.[6] Recently, isoxazolidines have attracted attention as nucleoside analogues[7a,8] and as synthetic transcriptase activators.[9] However, our current interests are concerned with the preparation of a family of isoxazolo-bicycles with potential as organocatalysts. 1,3-Dipolar cycloaddition of nitrones to alkenes represents a key route to the isoxazolidine framework.[10] However, *N*-substituted nitrones produce isoxazolidines with *N*-substituents, which are often difficult to remove without simultaneous cleavage of the labile N–O bond. In addition to those systems formed by intramolecular oxime olefin cycloaddition (IOOC) routes[11–14] approaches to *N*-unsubstituted isoxazolidines have frequently exploited Vasella's carbohydrate-derived auxiliaries;[15] a more recent contribution to this area is Partridge's easily hydrolyzed *N*-nosyl auxiliary.[16] In certain cases the resonate tetrahydropyran,[17] diphenyl methyl,[18] trityl,[19] Boc,[20] benzyl[21] or Troc[21] groups from *N*-substituted heterocycles has been demonstrated.

We were interested in 5,5-bicycles incorporating an *N*-unsubstituted isoxazolidine with a second ring, fused proximal to the nitrogen and report herein the synthesis of lactone, lactam and pyrrolidine fused systems **1**–**3** (Fig. 1).



1
a. Ar = Ph
b. Ar = 2-furyl
c. Ar = 2-thienyl
d. Ar = 2-$(NO_2C_6H_4)CH_2$
e. Ar = CH_2Ph
f. Ar = 2,4,6-$(CH_3)_3C_6H_2$

2
a Ar = Ph
b Ar = 2-furyl
c Ar = 2-thienyl

3
a R = Me
b R = Ph

Figure 1. Isoxazolo-fused bicycles **1**–**3**.

We have previously reported the preparation of two members of these families, **1a** and **2a**, from δ-alkenyl oximes and have reported a relationship between the oxime geometry and the observed reactivity.[22–24] The reterosynthetic analysis outlined in Scheme 1 summarises our approach to the target bicycles. The δ-alkenyl oximes **4** were to be accessed from their parent ketones **5** in turn

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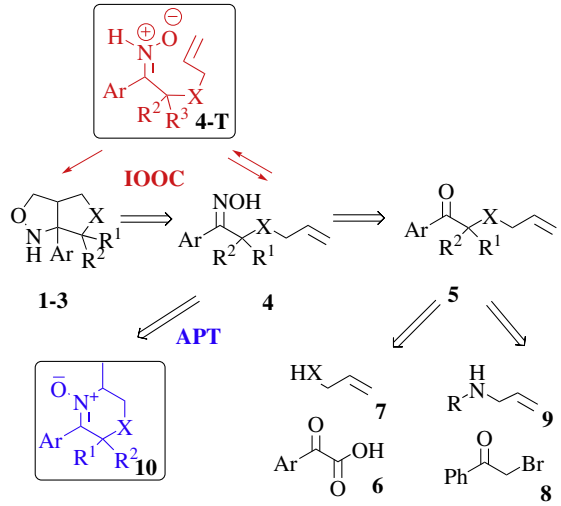
obtained from the condensation between the α-ketoacids **6** with either allyl alcohol (X=O) or *N*-methyl allylamine (X=NMe) **7**, or by reaction between bromoacetophenone **8** and allylamine **9**. Competition between the desired IOOC reaction pathway, furnishing **1**–**3** and an alternative azaprotio cyclotransfer (APT) route,[25] leading to the cyclic nitrones **10**, depends on a number of parameters including a favourable equilibrium between the oximes **4** and the unsubstituted heteroaryl nitrones, their NH-tautomers, **4**-**T**. Whilst heteroaryl nitrones are known to be excellent peroxyl free radical absorbance agents and potentially useful neuroprotective agents,[26,27] there are relatively few reports on their utility as building blocks for the construction of isoxazolidines. In particular, heteroaryl *N*-unsubstituted isoxazolidines are rare and direct access to this framework has been realized by either thermal[28] or Pd(II) assisted cascade cycloadditions,[29] indirect access by N-deprotection strategies,[30] and by reaction of 2-isoxazolines with arylorganolithium reagents[2, 31] have been successful.



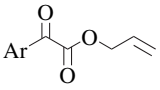
4/5/10(I) R^1R^2 = (=O), X = O;
4/5/10(II) R^1R^2 = (=O), X = NMe;
4/5(III) R^1 = R^2 = H, X = NR

Scheme 1. Retrosynthetic approach to isoxazolo-fused bicycles **1**-**3** including optional reaction pathways for alkenyl oximes **4**.

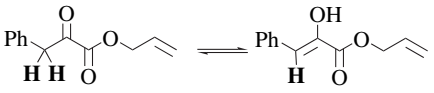
2. Results and discussions

The lactone-fused isoxazolidines **1b**–**f** were targeted by a route directly parallel to that described previously.[22,24] In all cases esterification of the commercially available ketoacids with allyl alcohol proceeded to yield **5**(**I**)**b**–**f** in good yield (81–91%). The benzyl substituted ester **5**(**I**)**e** initially seemed difficult to purify, however ^{1}H NMR spectroscopy ($CDCl_3$) subsequently revealed it to exist as a mixture of keto and enol tautomers in solution. The enol CHPh proton resonated at ~6.62 ppm whilst the benzylic protons of the keto tautomer appeared at 4.16 ppm, minor signals in the spectrum are consistent with the presence of isomers about the enol double bond (Fig. 2). This phenomenon was not observed with the 2-($NO_2C_6H_4$)CH_2 analogue **5**(**I**)**d**.

Conversion to the oximes **4**(**I**) was effected by treatment with NH_2OH (Fig. 3); the ensuing yields and geometrical make-up[†] of



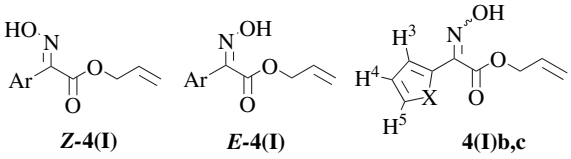
5(I)
a. Ar = Ph; b. Ar = 2-furyl,
c. Ar = 2-thienyl, d. Ar = 2-($NO_2C_6H_4$)CH_2,
e. Ar = CH_2Ph, f. Ar = 2,4,6-$(CH_3)_3C_6H_2$



5(I)e (keto) **5(I)e** (enol)

Figure 2. Key ^{1}H NMR data for the tatuomers of **5**(**I**)**e**.

the products are summarised in Table 1. For substrates **5**(**I**)**b**–**e** reaction proceeded rapidly in EtOH at reflux and **4**(**I**)**b**,**c** presented as a mixture of geometrical isomers whilst **4**(**I**)**d**[39],**e** formed as single isomers. The mesityl substrate **5**(**I**)**f** was more sluggish to react and heating in ^{i}PrOH at reflux for 56 h furnished the desired products, in 70% yield. A freshly prepared sample of the oximes **4**(**I**)**f** existed as an ~1:8 mixture of geometrical isomers, however, upon standing in solution ($CDCl_3$) a gradual conversion of the major to the minor isomer, completed after 17 days, at rt, was observed. However, pure samples of **4**(**I**)**f** stored at −20 °C proved to be conformationally stable.



***Z*-4(I)** ***E*-4(I)** **4(I)b,c**

a. Ar = Ph; b. Ar = 2-furyl,
c. Ar = 2-thienyl, d. Ar = 2-($NO_2C_6H_4$)CH_2,
e. Ar = CH_2Ph, f. Ar = 2,4,6-$(CH_3)_3C_6H_2$

Figure 3. Structures of the geometrical oxime isomers **4**(**I**).

Table 1
Yields and Geometrical ratios of the oximes **4**(**I**), **4**(**II**) and **4**(**III**)

Compound No.	*Z*/*E*-ratio	Isolated yield, % *Z*, *E*-isomers	Compound No.	*Z*/*E*-ratio	Isolated yield, % *Z*,*E*-isomers
4(**I**)**b**	1:1.4[a]	99[a]	**4**(**II**)**b**	1:1.1[a,c]	76[a,d]
4(**I**)**c**	~1:1	40, 43	**4** (**II**)**c**	1:1.2[c]	20,[d] 24[d]
4(**I**)**e**		75			
4(**I**)**f**	~1:8	8, 62[b]	**4**(**III**)**a**	2:5	17, 45
			4(**III**)**b**	1:1.3[a]	100[a]

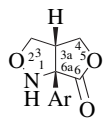
[a] Geometrical isomers could not be separated.
[b] Oxime isomers were not stable at rt.
[c] Two rotamers presented for each oxime isomer.
[d] It was not possible to separate individual rotameric forms.

In the case of the oxime **4**(**I**)**b** geometrical isomers, present in a 1:1.4 ratio, were inseparable by flash column chromatography, however, for **4**(**I**)**c** it was possible to obtain individual samples of each oxime isomer.[‡] The aryl protons of the furyl and thienyl oximes are readily assigned on the basis of their different coupling constants; thus for a typical furan $^2J_{3,4}$ is ~3.5 Hz whilst $^2J_{4,5}$ is smaller at ~1.5 Hz; corresponding values for a thiophene are $^2J_{3,4}$ ~3.4 Hz and $^2J_{4,5}$ ~4.7 Hz.[32] A comparison of the ^{1}H NMR spectral

[†] In the interest of uniformity, the *C*- phenyl, furyl and thienyl oxime isomers of **4**(**I**), **4**(**II**) and **4**(**III**) are designated *Z*- if the hydroxyl group is on the same side as the aryl group and *E*- if the aryl and the hydroxyl groups are on opposite sides of the oxime C=N.

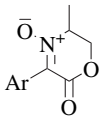
[‡] Overlaps with the other conformer.

data, for the geometrical isomers of **4**(**I**)**b** with that of the precursor **5**(**I**)**b** show a marked upfield shift (~1 ppm) in the resonance position of H-3 for one isomer only. The same pattern, also observed for the resonance position of the H-3 protons of the thienyl analogues, *Z*- and *E*-**4**(**I**)**c**, is mirrored in the ^{13}C resonance position of the corresponding carbon atoms (Ar–C^3). Whilst one can assume the upfield shift correlates with oxime configuration the ability to distinguish between geometrical oxime isomers is more reliably based on the shielding effects of the oxime oxygen atom on the α-carbon atom where the oxime hydroxyl group is *Z* to that carbon atom.[33] In the case of the isomers of **4**(**I**)**b** the α-carbon/carbon atom, Ar–C^2 of the *Z*-isomer resonates at 140 ppm upfield by ~3 ppm of the corresponding carbon atom in the *E*-isomer. For the *Z*-isomer, the α′-carbon atom (*C*=O) appears downfield, ~0.6 ppm, from the same atom in the *E*-isomer. The resonance position of the oxime carbon atom (*C*=N) of the *E*-isomer is also found ~3 ppm downfield of its *Z*-analogue. The oximes of **4**(**I**)**c** display the same pattern, pertinent chemical shifts are summarised in Table 2.



1

a. Ar = Ph
b. Ar = 2-furyl
c. Ar = 2-thienyl



10(I)

a. Ar = Ph; b. Ar = 2-furyl,
c. Ar = 2-thienyl, d. Ar = 2-($NO_2C_6H_4$)CH_2,
e. Ar = CH_2Ph, f. Ar = 2,4,6-$(CH_3)_3C_6H_2$

Figure 4. Structures of the bicycles **1** and the cyclic nitrones **10**(**I**) arising from reaction of oximes **4**(**I**).

We had previously observed that upon thermal activation the individual oxime isomers of **4**(**I**)**a** reacted chemospecifically, with the *Z*-isomer cyclising to the nitrone **10**(**I**)**a** by an APT route and the *E*-isomer yielding the isoxazole-bicycle **1a** by the IOOC pathway (Fig. 4).[22,24] Thus, in search of analogous bicycles **1b**–**f** we wished to establish if the oximes **4**(**I**)**b**–**f** shared the reactivity profile of **4**(**I**)**a**. As the oximes **4**(**I**)**b** were inseparable, a solution of a 1:1.4 (*Z*/*E*-) mixture was heated to reflux in xylenes under an N_2 atmosphere. Following purification by flash column chromatography the nitrone **10**(**I**)**b** and the bicycle **1b**, were isolated in 56 and 20% yield, respectively, together with unreacted oxime (15%) (Table 3). The relationship between the relative amounts of the starting oxime isomers and the composition of the reaction products rules out a simple correlation between oxime geometry and reactivity for **4**(**I**)**b**.

The individual isomers of the analogous thienyl oximes **4**(**I**)**c** were separately heated in xylenes at reflux in. The *Z*-isomer converted solely to the nitrone **10**(**I**)**c** in 79% yield. However, the *E*-isomer of **4**(**I**)**c** reacted to furnish the desired bicycle **1c** (22%) as the minor component in a product mixture, which included the nitrone **10**(**I**)**c** (41%), together with unreacted oxime. Thus it is apparent that replacing the phenyl substituent in **4**(**I**)**a** with a thienyl group has a significant influence on the balance of reactivity. Thus, whilst *Z*-**4**(**I**)**c** does react chemospecifically by the APT route, *E*-**4**(**I**)**c** does not share the conformational stability displayed by *E*-**4**(**I**)**a**.

Both **1b** and **1c** formed regio- and diastereospecifically and similarities in their pmr data with that reported for **1a**[22] permit assignment of the 5,5-bicycles as having the expected cis-ring stereochemistry.

Table 2
Selected NMR spectral data for the ketones **5**(**I**), **5**(**II**) and **5**(**III**) and the oximes **4**(**I**), **4**(**II**) and **4**(**III**)

Compound Number	H-3/C-3	H-4/C-4	H-5/C-5	α-Ar–C^Q	C=N	α-C=O	OH
5(**I**)**b**	7.73/124.8	6.64/113.1	7.78/149.6	149.7	—		
Z-**4**(**I**)**b**	7.45/119.8	6.57/111.9	7.57/144.1	140.0	142.3	161.9	10.23
E-**4**(**I**)**b**	6.68/113.1	6.48/111.8	7.52/144.9	142.6	145.1	161.3	10.21
5(**I**) **c**	8.12/130.7	7.19/128.7	7.83/137.3	139.1	—	161.3	
Z-**4**(**I**)**c**	8.16/133.5	7.15/126.5	7.62/131.1	127.9	141.8	162.9	10.69
E-**4**(**I**)**c**	7.19/129.1	7.05/127.5	7.37/128.4	133.7	146.9	162.7	9.37
5(**II**)**b**	7.15/122.3, 121.9	6.43/112.8, 112.9	7.57/148.9, 148.8	150.1, 149.9	—	165.6 165.2	
Z-**4**(**II**)**b** and *E*-**4**(**II**)**b**	7.44 and 6.62 119.7 and 119.6	6.54 and 6.47 122.3, 112.8 and 111.7	7.50 and 7.48 144.8, 155.7, 143.6 and 143.5–143	146.0–142.5 (8 signals)		163.8, 163.6, 162.8	9.30 and 8.89
5(**II**) **c**	7.80/136.5, 135.4	7.22/128.7, 128.6	7.80/136.2, 136.1	140.3, 140.2			
Z-**4**(**II**)**c**	7.40/131.8, 131.8	7.11/126.2, 126.1	7.58/131.1, 130.9	128.8, 128.7	146.8, 146.7	165.1 164.8	10.22
E-**4**(**II**)**c**	7.17/127.8, 127.6	7.00/126.5, 126.4	7.30/126.8, 126.7	133.7, 133.5	147.9	163.3	9.89
5(**III**)**a**				136.7	—	3.69/63.1[a]	—
Z-**4**(**III**)**a**				132.6	155.5	3.38/60.3[a]	8.75
E-**4**(**III**)**a**				135.7	154.2	3.77/54.8[a]	12.38

[a] ^1H and ^{13}C NMR positions of the C(=NOH)CH_2 atoms.

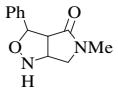
Table 3
Reactivity profiles of the oximes **4**(**I**), **4**(**II**) and **4**(**III**)[a]

Oxime No	Geometry	Bicycle (%)	Nitrone (%)	Oxime No	Geometry	Bicycle (%)	Nitrone (%)
4(**I**)**a**[22]	*Z*-		**10**(**I**)**a** (85)	**4**(**II**)**a**[23]	*E*	**2a** (91)	
4(**I**)**a**[22]	*E*-	**1a** (66)		**4**(**II**)**b**	*Z*/*E*-1:1.1	**2b** (44)	**10**(**II**)**b**[b,c]
4(**I**)**b**	*Z*/*E*-1:1.4	**1b** (20)	**10**(**I**)**b** (56)	**4**(**II**)**c**	*Z*		**10**(**II**)**c** (71)
4(**I**)**c**	*E*-	**1c** (22)	**10**(**I**)**c** (41)	**4**(**II**)**c**	*E*	**2c** (86)	
4(**I**)**c**	*Z*-		**10**(**I**)**c** (79)				
4(**I**)**d**	*Z*-		**10**(**I**)**d** (50)	**4**(**III**)**a**	*Z*/*E*- 1:1.6	**3a** (62)[c]	—
4(**I**)**e**	*Z*-		**10**(**I**)**e** (24)	**4**(**III**)**b**[c]	*Z*/*E*- 1:1	**3b** (89)[11b]	
4(**I**)**f**	*Z*-		**10**(**I**)**f** (89)				

[a] A solution of the oxime(s) was heated to reflux in xylene under an N_2 atmosphere.
[b] Nitrone **10**(**II**)**b** could not be obtained pure and was found in an enriched mixture together with bicycle.
[c] Reaction conducted in boiling toluene.

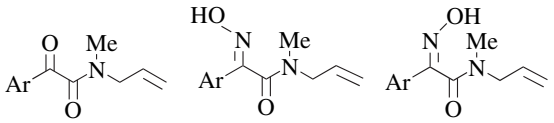
In keeping with the observation for **4**(**I**)**c**, the *Z*-oximes of **4**(**I**)**d**, **e**,**f** upon heating in xylenes at reflux chemospecifically cyclised to yield the corresponding nitrones. Whilst yields could be poor **10**(**I**)**d**, 50%; **10**(**I**)**e**, 24%; **10**(**I**)**f** 89% in no case was there evidence for any reactivity by way of an IOOC pathway. As may have been anticipated on the grounds of its ease of geometrical isomerisation in solution under ambient conditions, a pure sample of *E*-**4**(**I**)**f** also failed to furnish the corresponding bicycle. Thus, of the anticipated lactone-fused isoxazolidine series the interplay between the geometrical make-up and the differential reactivity of the oxime isomers of **4**(**I**), conspired to facilitate access only to the furyl- and thienyl bearing bicyclic isoxazolidines **1b**,**c** (Table 3).

An IOOC approach to the synthesis of lactam-fused isoxazolidines has previously been demonstrated with substrates bearing an amido functionality tethered either directly[7b] or more remotely[23] to the alkene bond affording isomeric 5,5-bicycles illustrated, respectively, by **11** and **2a**.



11

The lactam-fused isoxazolidines **2b**,**c** were accessed by a parallel route to that described for **2a**. Condensation between the acid chloride derivatives of the commercially available α-ketoacids **6b**,**c** prepared by reaction with α,α-dichloromethly methyl ether[34] and *N*-methylamine furnished the amides **5**(**II**)**b**,**c** in good yield. In both cases, ^{1}H NMR spectroscopy ($CDCl_3$) revealed the amides to exist as an ~1:1.1 mixture of rotamers in solution. Conversion to the oximes **4**(**II**)**b**,**c** followed from treatment with NH_2OH, in refluxing EtOH (Fig. 5). The ^{1}H and ^{13}C NMR spectra for the reaction products were quite busy as in both cases the products presented as a mixture of *Z*- and *E*-oxime isomers with each isomer showing evidence for both rotameric forms in solution. The geometrical isomers of **4**(**II**)**b** were inseparable and the ^{1}H NMR data shows multiple resonance signals for many of the protons, for example, the *N*-methyl protons present as four singlets at 3.06, 3.05, 2.93 2.92 ppm, in ~1.1:1:1:1.1 ratio; four distinct signals represent the corresponding *C*-atom in the ^{13}C NMR data (32.4, 31.4, 35.5, 34.6 ppm). It was not possible to deconvolute the NMR data to unambiguously assign the observed resonances to the individual conformers present (Table 2). In keeping with the analogous thienyl ester oximes **4**(**I**)**c** the amido oximes **4**(**II**)**c** could be obtained as individual compounds. A comparison of the ^{1}H/^{13}C NMR spectral data for each oxime of **4**(**II**)**c** with the data for *Z*- and *E*-**4**(**I**)**c** reveals a similar pattern. Specifically, the α-carbon carbon atom, Ar–C^{Q}, of the *Z*-isomer resonates at ~129 ppm, ~5 ppm upfield of the corresponding carbon atom in the *E*-isomer. For the *Z*-isomer the α′-carbon atom (*C*=O) appears downfield, 1.7 ppm, from the same atom in the *E*-isomer. The resonance position of the oxime carbon atom of the *E*-isomer is also found 1 ppm downfield of its *Z*-analogue (Table 2).

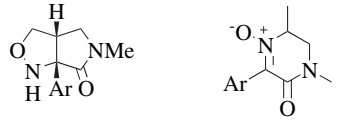


5(II) ***Z*-4(II)** ***E*-4(II)**

a. Ar = Ph; b. Ar = 2-furyl; c. Ar = 2-thienyl

Figure 5. Structures of the amido esters **5**(**II**) and the geometrical oxime isomers **4**(**II**).

As the furyl bearing oximes **4**(**II**)**b** were impossible to separate by flash column chromatography, thermal activation was performed on the mixture of *E*-and *Z*-isomers. The resulting reaction products comprised both the desired bicycle **2b**, as a single diastereoisomer and the nitrone **10**(**II**)**b** (Fig. 6). The crude products, together with unreacted oxime, were found in an ~5:2:3 ratio. Bicycle **2b** was isolated in 44% yield and the relative stereochemistry is assigned with reference to **2a**;[23] the nitrone **10**(**II**)**b** was obtained as an enriched sample together with bicycle (Table 3). The relationship between the relative amounts of the starting oxime isomers and the composition of the crude reaction products does not permit any conclusion regarding structure and reactivity for the oximes of **4**(**II**)**b**. In sharp contrast, the individual isomers of the thienyl analogues **4**(**II**)**c** react chemoselectively upon heating to reflux in xylene; thus, the *Z*-isomer furnished the nitrone **10**(**II**)**c** in 71% yield by the APT pathway, whilst the *E*-isomer delivered the desired bicycle **2c** (86%) by the IOOC route (Table 3). This observation demonstrates the importance of the structure of the tether connecting the oxime and the terminal alkene in determination of the preferred mode of reactivity. Thus, replacement of the ester tether of the thienyl oxime *E*-**4**(**I**)**c** with the amide tether of *E*-**4**(**II**)**c** is sufficient to restore chemospecific reactivity to the *C*-thienyl oxime.

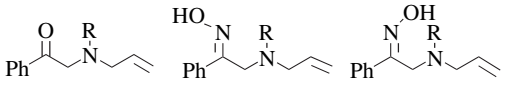


2 **10(II)**

a. Ar = Ph; b. Ar = 2-furyl; c. Ar = 2-thienyl

Figure 6. Structures of the bicycles **2** and the cyclic nitrones **10**(**II**) arising from reaction of **4**(**II**).

Allylamines possessing an appropriately positioned oxime are known to undergo a thermally-induced IOOC sequence to give bicyclic pyrrolidine fused isoxazolidines.[11,35,36] Olefin bearing *O*-*tert*-butyldimethylsilyl oximes, under the influence of $BF_3{\cdot}OEt_2$, also react efficiently to generate *N*-unsubstituted bicycles.[37,38] Stirring a solution of 2-bromoacetophenone **9** and *N*-methyl allylamine in DCM for 10 min furnished the desired tertiary amine **5**(**III**)**a** in quantitative yield, the already known **5**(**III**)**b** required longer to reach the same extent of conversion (30 h).[11b] Each substrate reacted with $NH_2OH{\cdot}HCl$ in ethanolic $NaHCO_3$ to furnish the corresponding oximes as pairs of geometrical isomers (Fig. 7). Analytical samples of *Z*- and *E*-isomers of the *N*-methyl amino oximes **4**(**III**)**a** were obtained. Geometrical assignment is based on the ^{13}C NMR resonance data. In the case of the *Z*-isomer the α-carbon carbon atom, Ar–C^{Q}, resonates at ~132 ppm upfield by ~3 ppm of the corresponding carbon atom in the *E*-isomer. For the *Z*-isomer the α′-carbon atom (NCH_2) appears downfield, ~6 ppm, from the same atom in the *E*-isomer. The resonance position of the α′-protons (NCH_2) reflect this pattern with the methylene protons of *E*-isomer resonating ~0.4 ppm downfield of those in the *Z*-analogue (Table 2). Flash column chromatography was not able to separate the *N*-phenyl amido oximes **4**(**III**)**b**, which we obtained as a 1:1.3 mixture of *Z*- and *E*-isomers. This ratio reflects a slight preference for the *E*-isomer over an earlier synthesis conducted in H_2O.[11b]



5(III) ***Z*-4(III)** ***E*-4(III)**

a. R = Me; b. R = Ph

Figure 7. Structures of the amido esters **5**(**III**) and the geometrical oxime isomers **4**(**III**).

The *N*-methylpyrrolidine fused isoxazolidine **3a** (Fig. 1) resulted in 62% yield following heating to reflux a toluene solution of the mixed oximes *Z*-/*E*-**4**(**III**)**a**, Table 3. As has been observed for the *N*-phenyl analogue **3b**[11b] pmr spectroscopy revealed an equilibrium between two major conformers. Spectra of **3a** were very broad at ambient temperature whilst sharp signals representing individual conformers, in a ratio of ~6:1, were evident at −50 °C. The individual conformers are most likely associated with pyramidal inversion of both *N*-atoms and flipping of the two five-membered rings.[11b]

3. Conclusion

Facile thermal oxime/NH-nitrone tautomerisation is a requisite for IOOC reactivity and appropriately positioned functional groups within the rest of the molecule, for example, a carbonyl oxygen atom capable of forming of a stabilizing H-bond with the new dipole, are known to facilitate this process.[28] Whilst the oximes **4**(**I**) and **4**(**II**) do bear this type of functionality they are not conformationally constrained molecules and it may be the case that, even if dipole formation is facilitated by the proximal ester or amide carbonyl group, that it is difficult to attain the necessary alignment for an intramolecular cycloaddition between the transient NH-nitrone and the pendant alkene moiety. In addition to the possibility of presenting as geometrical isomers about the C=N double bond the oximes **4**(**I**)**b**,**c** and **4**(**II**)**b**,**c** and their tautomeric NH-nitrones **4**(**I**)**b**,**c**-**T** and **4**(**II**)**b**,**c**-**T**, have additional restrictions to their conformational freedom. *S*-cis- or *S*-trans-relationships are possible about the C–C single bond connecting the heteroaryl and the oxime functionalities, and about the bond connecting the oxime carbon atom to the adjacent carbonyl group. The presentation of distinct rotameric forms about the amide functionality adds a further layer of structural complexity for the oximes of **4**(**II**), Figure 8. Whilst our results demonstrate enhanced chemoselectivity for the amide tethered alkenyl oximes over their ester analogues, the multitude of possible reacting conformations makes it difficult to be prescriptive about any relationship between oxime structure and reactivity. However, this survey does indicate that thermal activation of amino or amido linked δ-alkenyl oximes can be an acceptable route to *N*-unsubstituted bicyclic isoxazolidines overcoming the difficulties associated with the most commonly employed routes to the *N*-unsubstituted hetrocycle, i.e., removal of *N*-substituent from those isoxazolidines prepared from cycloaddition of *N*-alkyl nitrones.

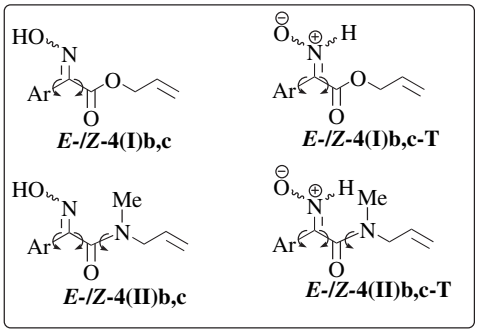


Figure 8. Degrees of conformational freedom for ester and amido linked heteroaryl oximes **4**(**I**) and **4**(**II**).

4. Experimental

4.1. General

All ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded in $CDCl_3$, with TMS as internal standard, on a Bruker Avance spectrometer at a probe temperature of 25 °C, unless otherwise stated, operating at 300 MHz for the ^{1}H nucleus and 75.5 MHz for the ^{13}C nucleus. Coupling constants are measured in hertz. Mass spectra were obtained on a LC/TOF-MS model 6210. Infrared spectra were recorded on a Perkin Elmer System 2000 FT spectrometer as thin films or as Nujol mulls. Melting points were measured on a Stuart Scientific (Bibby) Melting Point SMPI apparatus and are uncorrected. Microanalytical data were recorded on an Exeter Analytical CE-440 elemental analyser. Flash column chromatography was performed using silica gel 60 (Merck, 0.040–0.063 mm) on a Buchi Automated Flash system. Analytical thin layer chromatography was carried out on aluminium sheets pre-coated with Merck TLC Silica gel 60 F_{254}. Developed chromatograms were visualised using a portable UVItec CV-006 lamp (λ 254). Mixed, and not individual xylene isomers were used in all reactions.

4.2. General procedure for preparation of allyl esters of α-ketoacids, 5(I)

A solution of the α-keto acid **6** (18.0 mmol) and allyl alcohol **7** (X=O) (27.0 mmol) in toluene (75 mL) in the presence of a catalytic amount of *p*-TsOH was stirred with heating at reflux using a Dean–Stark apparatus for 15 min-20 h. The solution was washed with satd aq $NaHCO_3$ (20 mL) and H_2O (20 mL) and the organic layer was dried ($MgSO_4$), filtered and evaporated to yield the crude product.

*4.2.1. Allyl 2-(2-furyl)-2-oxoacetate, **5**(**I**)**b**.* Prepared from **6b**, the product **5**(**I**)**b** was obtained as a dark yellow oil (2.80 g, 87%) after a reaction time of 20 h and was used without further purification; R_f (10% EtOAc/Hex) 0.25; ν_{max} (Nujol) 5793, 2951, 1675, 1576, 1457 cm^{-1}; δ_H 7.78–7.77 (1H, dd *J* 1.6 and 0.6, Ar–H^5), 7.73–7.72 (1H, dd *J* 3.7 and 0.6 Ar–H^3), 6.64–6.63 (1H, dd *J* 3.7 and 1.6, Ar–H^4), 6.09–5.95 (1H, m, C*H*=CH_2), 5.49–5.32 (2H, m, CH=CH_2), 4.85 (2H, d, *J* 5.9, OCH_2); δ_C, 170.8 (ArC=O), 160.7 (C=O), 149.7 (Q ArC), 149.6 (ArC^5), 130.6 (*C*H=CH_2), 124.8 (ArC^3), 120.1 (CH_2=CH), 113.1 (ArC^4) 67.0 (OCH_2); LC/TCOF-MS found 181.0495$(M+NH_4)^+$; $C_9H_8O_4$ requires 181.0501.

*4.2.2. Allyl 2-oxo-2-(2-thienyl)acetate, **5**(**I**)**c**[39].* Prepared from **6c**, the product **5**(**I**)**c** was obtained as a yellow oil (1.06 g, 84%). δ_H 8.13–8.11 (1H, dd *J* 3.9 and 1.1, Ar–H^3), 7.84–7.82 (1H, dd *J* 4.9 and 1.1, Ar–H^5), 7.21–71.18 (1H, dd *J* 4.9 and 3.9, Ar–H^4), 6.09–5.96 (1H, m, C*H*=CH_2), 5.48–5.42 (1H, dd *J* 17.2 and 1.3, H C=CH *trans*), 5.37–5.33 (1H, dd *J* 10.4 and 1.3, H C=CH *cis*), 4.85 (2H, d, *J* 5.9, OCH_2); δ_C 176.1 (ArC=O), 161.3 (C=O), 139.1 (Q ArC), 137.5 (*C*H=CH_2), 137.3, 130.7, 128.7 (3×ArC), 120.1 (CH_2=CH), 67.0 (OCH_2).

*4.2.3. Allyl 2-oxo-3-phenylpropanoate, **5**(**I**)**e**.* Prepared from **6e**, the product **5**(**I**)**e** was obtained as a dark yellow oil (3.11 g, 81%) after a reaction time of 25 min and was used without further purification; ν_{max} (Nujol) 3225, 2952, 2587, 1736, 1455, 1274, 1177 cm^{-1}; δ_H 7.85–7.26 (10H, m, ArH[keto and enol]), 6.63 (1H, br s, OH[enol]), 6.62 (1H, s, C*H*Ph[enol]), 6.11–5.88 (2H, m, C*H*=CH_2[keto and enol]), 5.48–5.30 (4H, CH_2=CH [keto and enol]), 4.85–4.73 (4H, OCH_2[keto and enol]), 4.16 (2H, s, CH_2Ph[keto]); δ_C 190.1 (COH [enol]), 164.9, 159.5 (OC=O[keto and enol]), 156.3 (CH_2*C*=O[keto]), 143.8 (*C*HPh[enol]), 138.1, 137.5 (Q ArC[keto and enol]), 131.4, 130.6 (*C*H=CH_2[keto and enol]), 130.4, 130.1, 129.4, 129.2, 129.1, 128.8, 128.5, 128.1, 128.0, 127.6 (10×ArC[keto and enol]), 111.4 (CHPh [enol]), 118.8, 118.2 (CH_2=CH [keto and enol]), 66.4, 66.1 (OCH_2[-keto and enol]), 44.8 (CH_2Ph[keto]).

*4.2.4. Allyl 2-mesityl-2-oxoacetate, **5**(**I**)**f**.* Prepared from **6f**, the product **5**(**I**)**f** was obtained as a yellow oil (90%) after a reaction time of 15 min and was used without further purification; [found: C, 72.19; H, 6.90. $C_{14}H_{16}O_3$ requires, C, 72.39; H, 6.95%]; R_f (25% EtOAc/Hex) 0.33; ν_{max} (Nujol) 2854, 1737, 1610, 1460, 1377, 1297, 1201 cm^{-1}; δ_H 6.86 (2H, s, ArH), 5.99–5.88 (1H, m, C*H*=CH_2), 5.40–5.34 (1H, dd, *J*

17.2 and 1.0, C=CH *trans*), 5.30–5.26 (1H, dd, *J* 10.4 and 1.0, C=CH *cis*), 4.75 (2H, d, *J* 5.9, OCH_2), 2.27 (3H, s, *p*-$ArCH_3$), 2.24 (6H, s, 2×*o*-$ArCH_3$); δ_C 191.7 (Ar*C*=O), 162.4 (C=O), 141.1 (*p*-ArC), 136.3 (*o*-ArC), 133.1 (Q ArC), 130.7 (*C*H=CH_2), 129.1 (*m*-ArC), 120.0 (CH_2=CH), 66.8 (CH_2O), 21.2 (*p*-$ArCH_3$), 19.4 (*o*-$ArCH_3$); LC/TCOF-MS found 233.1182 $(M+H)^+$ $C_{14}H_{16}O_3$ requires 233.1172.

4.3. General procedures for oxime formation

Method A. A solution of the allyl ester **5**(**I**) (15 mmol), $NH_2OH·HCl$ (1.61 g, 23.0 mmol) and pyridine (2.71 g, 23.0 mmol) in EtOH (140 mL) was stirred with heating at reflux for 3 h. Following cooling to rt the solution was evaporated and the residue taken up in DCM (50 mL), washed with satd aq $NaHCO_3$ (50 mL) and H_2O (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to yield the crude product, which was purified as noted below.

Method B. A mixture of the allyl ester **5**(**I**) (2.4 mmol), pyridine (0.42 g, 5.3 mmol) and $NH_2OH·HCl$ (0.37 g, 5.3 mmol) in ^{i}PrOH (11 mL) was heated with stirring at reflux for 56 h. The mixture was allowed to cool to rt prior to evaporation to dryness. The residue was taken up in DCM (10 mL), washed with satd aq $NaHCO_3$ (5 mL) and H_2O (5 mL), dried ($MgSO_4$), filtered and evaporated to yield the crude product, which was purified as described below.

*4.3.1. Allyl 2-(2-furyl)-2-(hydroxyimino)acetates, Z-**4**(**I**)**b** and E-**4**(**I**)**b***. Prepared by method A. The product, a brown oil (2.90 g, 99%), comprised *Z*- and *E*-oxime isomers (*Z*/*E* 1:1.4), which could not be separated by flash column chromatography; R_f 0.39 (40% EtOAc/Hex) 0.39; ν_{max} 3152, 2854, 1737, 1649, 1461, 1377, 1308, 1225, 1157, 1052 cm^{-1}; δ_H *Z*-**4**(**I**)**b** 10.23 (1H, br s, OH), 7.57 (1H, d, *J* 1.5, Ar–H^5), 7.45 (1H, d, *J* 3.5, Ar–H^3), 6.58–6.56 (1H, dd, *J* 3.5 and 1.5, Ar–H^4), 6.08–5.94 (1H, m, C*H*=CH_2), 5.46–5.40 (1H, dd, *J* 17.2 and 1.3, C=CH *trans*), 5.33–5.29 (1H, dd *J* 10.4 and 1.3, C=CH *cis*), 4.84 (2H, d, *J* 5.8, OCH_2); δ_C *Z*-**4**(**I**)**b** 161.9 (C=O), 144.1 (ArC^5), 142.3 (C=N), 140.0 (Q ArC), 131.2 (CH_2=*C*H), 119.8 (ArC^3), 119.4 (*C*H_2=CH), 111.9 (ArC^4), 66.7 (CH_2O); δ_H *E*-**4**(**I**)**b** 10.21 (1H, br s, OH), 7.52 (1H, d, *J* 1.5, Ar–H^5), 6.68 (1H, d, *J* 3.5, Ar–H^3), 6.49–6.47 (1H, dd, *J* 3.5 and 1.5, Ar–H^4), 6.08–5.94 (1H, m, C*H*=CH_2), 5.48–5.43 (1H, dd, *J* 17.2 and 1.3, C=CH *trans*), 5.35–5.31 (1H, dd *J* 10.4 and 1.3, C=CH *cis*), 4.88 (2H, d, *J* 5.8, OCH_2); δ_C *E*-**4**(**I**)**b** 161.3 (C=O), 145.1 (C=N), 144.9 (ArC^5), 142.6 (Q ArC), 130.9 (CH_2=*C*H), 119.7 (*C*H_2=CH), 113.1 (ArC^3), 111.8 (ArC^4), 66.8 (CH_2O); LC/TCOF-MS found 219.0464; $(M+Na)^+$ requires 219.0456.

*4.3.2. Allyl 2-(hydroxyimino)-2-(2-thienyl)acetates, Z-**4**(**I**)**c** and E-**4**(**I**)**c***[39]. The *Z*- (0.21 g, 40%) and *E*-oximes **4**(**I**)**c** (0.23 g, 43%) were purified by flash column chromatography; δ_H *Z*-**4**(**I**)**c** 10.69 (1H, br s, OH), 8.18–8.15 (1H, dd, *J* 4.0 and 0.9, Ar–H^3), 7.63–7.61 (1H, dd, *J* 5.0 and 0.9, Ar–H^5), 7.17–7.14 (1H, dd, *J* 5.0 and 4.0, Ar–H^4), 6.12–6.01 (1H, m, C*H*=CH_2), 5.49–5.42 (1H, dd, *J* 17.2 and 1.2, C=CH *trans*), 5.36–5.32 (1H, dd, *J* 10.4 and 1.2, C=CH *cis*), 4.86 (2H, d, *J* 5.9, OCH_2); δ_C *Z*-**4**(**I**)**c** 162.9 (C=O), 141.8 (C=N), 133.5 (Ar–C^3), 131.1 (Ar–C^5), 131.2 (*C*H=CH_2), 127.9 (Q ArC), 126.5 (Ar–C^4), 119.7 (*C*H_2=CH), 66.9 (OCH_2); δ_H *E*-**4**(**I**)**c** 9.37 (1H, br s, OH), 7.37–7.35 (1H, dd, *J* 5.1 and 1.0, Ar–H^5), 7.21–7.19 (1H, dd, *J* 3.8 and 1.0, Ar–H^3), 7.05–7.02 (1H, dd, *J* 5.1 and 3.8, Ar–H^4), 6.08–5.95 (1H, m, C*H*=CH_2), 5.45–5.42 (1H, dd, *J* 17.2 and 1.3, C=CH *trans*), 5.35–5.31 (1H, dd, *J* 10.4 and 1.3, C=CH *cis*), 4.89 (2H, d, *J* 5.9, OCH_2); δ_C *E*-**4**(**I**)**c** 162.7 (C=O), 146.9 (C=N), 133.7 (Q ArC), 130.9 (*C*H=CH_2), 129.1 (Ar–C^3), 128.4 (Ar–C^5), 127.5 (Ar–C^4), 119.9 (*C*H_2=CH), 66.7 (OCH_2).

*4.3.3. Allyl 2-(hydroxyimino)-3-phenylpropanoate, Z-**4**(**I**)**e***. Prepared by method A. The crude product was purified by flash column chromatography (50% Hex/Et_2O) to yield the title oxime as a white solid (1.27 g, 75%); [found: C, 68.08; H, 7.21; N, 5.15. $C_{12}H_{13}NO_3$ requires C, 67.98; H, 6.93; N, 5.66%; mp 59–62 °C; ν_{max} (KBr) 3243, 1726, 1449, 1311 cm^{-1}; δ_H 9.45 (1H, br s, NOH), 7.33–7.21 (5H, m, 5×ArH), 5.98–5.89 (1H, m, C*H*=CH_2), 5.36–5.30 (1H, dd, *J* 17.0 and 1.1, C=CH *trans*), 5.28–5.25 (1H, dd, *J* 10.6 and 1.1, C=CH *cis*), 4.71 (2H, d, *J* 5.8, CH_2O), 3.99 (2H, s, CH_2Ph); δ_C 163.0 (C=O), 151.1 (C=N), 135.6 (Q ArC), 131.3 (*C*H=CH_2), 129.2, 128.6, 126.7 (3×ArC), 119.3 (CH_2=CH), 66.5 (OCH_2), 30.6 (*C*H_2Ph); LC/TCOF-MS found 242.0779 $(M+Na)^+$ $C_{12}H_{13}NO_3$ requires 242.0787.

*4.3.4. Allyl 2-(hydroxyimino)-2-mesitylacetates, Z-**4**(**I**)**f** and E-**4**(**I**)**f***. Prepared by method B. The crude product was purified by flash column chromatography (5% EtOAc/Hex) to yield *Z*-**4**(**I**)**f** as a cream solid (42.0 mg, 8%) and *E*-**4**(**I**)**f** as a yellow oil (0.31 g, 62%); *Z*-**4**(**I**)**f** [found: C, 68.10; H, 7.04; N, 5.62; $C_{14}H_{17}NO_3$ requires C, 67.98; H, 6.93; N, 5.66; mp 83–87 °C; ν_{max} (KBr) 3258, 2923, 1735, 1410, 1199 cm^{-1}; δ_H 8.65 (1H, br s, NOH), 6.91 (2H, s, 2×ArH), 6.00–5.87 (1H, m, C*H*=CH_2), 5.34–5.28 (1H, dd, *J* 17.2 and 1.3, C=CH *trans*), 5.27–5.23 (1H, dd, *J* 10.4 and 1.3, C=CH *cis*), 4.75 (2H, d, *J* 5.8, OCH_2), 2.30 (3H, s, *p*-CH_3), 2.14 (6H, s, *o*-CH_3); δ_C 162.8 (*C*=O), 151.9 (*C*=N), 139.2 (*p*-ArC), 135.6 (*o*-ArC), 131.3 (*C*H=CH_2), 128.2 (*m*-ArC), 126.6 (Q ArC), 119.2 (*C*H_2=CH), 66.4 (OCH_2), 21.2 (*p*-CH_3), 19.5 (*o*-CH_3); LC/TCOF-MS found 248.1285 $(M+Na)^+$ $C_{14}H_{17}NO_3$ requires 248.1281. Compound *E*-**4**(**I**)**f** R_f (20% EtOAc/Hex) 0.40; ν_{max} (Nujol) 3266, 2924, 1736, 1612, 1456, 1287 cm^{-1}; δ_H 11.11 (1H, br s, NOH), 6.89 (2H, s, *m*-ArH), 5.93–5.80 (1H, m, *C*H=CH_2), 5.30–5.26 (1H, dd, *J* 12.7 and 1.4, C=CH *trans*), 5.24–5.22 (1H, dd, *J* 5.9 and 1.4, C=CH *cis*), 4.72 (2H, d, *J* 5.7, OCH_2), 2.29 (3H, s, *p*-$ArCH_3$), 2.23 (6H, s, *o*-CH_3).; δ_C 163.0 (C=O), 148.7 (C=N), 139.1 (*p*-ArC), 137.4 (*o*-ArC), 130.6 (*C*H=CH_2), 128.5 (*m*-ArC), 128.0 (Q ArC), 119.5 (CH_2=CH), 66.2 (OCH_2), 21.1 (*p*-$ArCH_3$), 19.8 (*o*-$ArCH_3$); LC/TCOF-MS found 270.1108 $(M+Na)^+$ found 270.1101, $C_{14}H_{17}NO_3$ requires 270.1108.

4.4. General procedure for thermal reactivity of oximes, 4(I)b–f

A solution of the oxime **4**(**I**)**b**–**f** (5.0 mmol) in xylenes (300 mL) was heated with stirring at reflux in the presence of hydroquinone (1.0%, w/v, 3.0 g) under N_2 for 24–46 h. The solution was allowed to cool to rt, the solvent was removed under vacuum and the crude product was taken up in $CHCl_3$ (150 mL) and left to stand at rt for 30 min. After any remaining hydroquinone had precipitated the solution was filtered and evaporated to yield the crude products, which were purified as detailed below.

*4.4.1. 6a-(2-Furyl)tetrahydro-3H,6H-furo[3,4-c]isoxazol-6-one, **1b** and 5-(2-furyl)-5-methyl-6-oxo-3,6-dihydro-2H-1,4-oxazin-4-ium-4-olate, **10**(**I**)**b***. Title products **1b**, a brown solid (0.20 g, 20%) and **10**(**I**)**b**, also a brown solid (0.55 g, 56%), were obtained following heating a 1:1.4 mixture of *Z*- and *E*-**4**(**I**)**b** for 24 h, Separation was achieved by flash column chromatography (50% Hex/EtOAc); **1b** mp 69–74 °C; ν_{max} (KBr) 3384, 2849, 1766, 1377, 1194 cm^{-1}; δ_H 7.46 (1H, d, *J* 1.9, Ar–H^5), 6.64 (1H, d, *J* 3.3, Ar–H^3), 6.43–6.41 (1H, dd, *J* 3.3 and 1.9, Ar–H^4), 5.79 (1H, br s, NH), 4.62–4.56 (1H, dd, *J* 9.6 and 8.3, H^4), 4.33–4.26 (2H, m, $H^{3\text{ and }4}$), 4.20–4.14 (1H, dd, *J* 9.1 and 6.5, H^3), 3.75–3.67 (1H, m, H^{3a}); δ_C 173.1 (C=O), 144.2 (C^{6a}), 143.9 (Ar–C^5), 111.3 (Ar–C^4), 110.8 (Ar–C^3), 70.2 (Q ArC), 69.9 (C^4), 48.1 (C^{3a}), 29.7 (C^3); LC/TCOF-MS found 196.0540 $(M+H)^+$ $C_9H_9NO_4$ requires 196.0540 g. Compound **10**(**I**)**b** [found: C, 55.78; H, 4.76; N, 6.94; $C_9H_9NO_4$ requires C, 55.37; H, 4.65; N, 7.18%]; mp 68–72 °C; ν_{max} (KBr) 3426, 2837, 1716, 1526, 1286, 1280, 1207; δ_H 7.80 (1H, d, *J* 3.5, Ar–H^3), 7.63 (1H, d, *J* 1.6, Ar–H^5), 6.57–6.56 (1H, dd, *J* 3.5 and 1.6, Ar–H^4), 4.70–4.63 (1H, m, C*H*CH_3), 4.37–4.26 (2H, m, CH_2), 1.61 (3H, d, *J* 6.7, CH_3); δ_C 156.5 (C=O), 144.7 (Ar–C^5), 143.6 (C=N), 127.2 (Q ArC), 118.3 (Ar–C^3), 111.6 (Ar–C^4), 67.0 (CH_2), 64.0 (*C*HCH_3), 14.2 (CH_3); LC/TCOF-MS found 196.0613 $(M+H)^+$ $C_9H_9NO_4$ requires 196.0604.

*4.4.2. 6a-(2-Thienyl)tetrahydro-3H,6H-furo[3,4-c]isoxazol-6-one, **1c** and 3-methyl-6-oxo-5-(2-thienyl)-3,6-dihydro-2H-1,4-oxazin-4-ium-4-*

olate, ***10(I)c***. Title products **1c**, a pale brown solid (51.0 mg, 22%) and **10(I)c**, also a brown solid (96.0 mg, 41%), were obtained following heating *E*-**4(I)c** for 46 h, Separation was achieved by flash column chromatography (22% Hex/EtOAc); **1c** mp 135–140 °C; ν_{max}(KBr) 3197, 3070, 2923, 1764, 1481, 1384, 1234, 983 cm^{-1}; δ_H 7.40–7.38 (1H, dd, *J* 5.1 and 1.2, Ar–H^5), 7.29–7.27 (1H, br dd, *J* 3.5 and 1.2, Ar–H^3), 7.07–7.04 (1H, dd, *J* 5.1 and 3.8, Ar–H^4), 5.76 (1H, br s, NH), 4.65–4.59 (1H, dd, *J* 9.7 and 7.1, H^3), 4.39–4.34 (1H, dd, *J* 9.7 and 2.4, H^3), 4.30–4.19 (2H, m, H^4), 3.63–3.57 (1H, m, H^{3a}); δ_C 175.3 (C=O), 134.6 (Q ArC), 127.7 (Ar–C^4), 127.3 (Ar–$C^{3\ and\ 5}$), 78.7 (C^4), 72.5 (C^{6a}), 70.6 (C^3), 50.51 (C^{3a}); LC/TCOF-MS found 249.9937 $(M+K)^+$ $C_9H_9NO_3S$ requires 249.9935. Compound **10(I)c** mp 119–123 °C; δ_H 8.49–8.47 (1H, dd, *J* 4.2 and 1.1, Ar–H^3), 7.53–7.51 (1H, dd, *J* 5.1 and 1.1, Ar–H^5), 7.24–7.21 (1H, dd, *J* 5.1 and 4.2, Ar–H^4), 4.70–4.64 (2H, m, CH_2), 4.44–4.33 (1H, m, C*H*CH_3), 1.66 (3H, d, *J* 6.6, CH_3); δ_C 157.5 (C=O), 132.8 (Ar–C^3), 130.6 (C=N^+), 129.2 (Ar–C^5), 129.0 (Q ArC), 127.2 (Ar–C^4), 67.0 (*C*HCH_3), 63.2 (CH_2), 14.4 (CH_3); LC/TCOF-MS found 234.0202 $(M+Na)^+$ $C_9H_9NO_3S$ requires 234.0195.

4.4.3. 3-Methyl-6-oxo-5-(2-thienyl)-3,6-dihydro-2H-1,4-oxazin-4-ium-4-olate, ***10(I)c***. The nitrone **10(I)c** was obtained as a brown solid (0.16 g, 79%) following heating *Z*-**4(I)c** for 24 h.

4.4.4. 3-Methyl-5-(2-nitrobenzyl)-6-oxo-3,6-dihydro-2H-1,4-oxazin-4-ium-4-olate, ***10(I)d***. The nitrone **10(I)d** was obtained as a yellow solid (0.15 g, 50%) following heating *Z*-**4(I)d** for 24 h. Purification was by flash column chromatography (50% Hex/EtOAc); mp 68–74 °C; ν_{max} (KBr) 2923, 1727, 1520, 1342, 1265 cm^{-1}; δ_H 7.94–7.91 (1H, dd, *J* 8.7 and 1.7, Ar–H^3), 7.55–7.52 (1H, ddd *J* 9.4, 7.5 and 1.7, Ar–H^5), 7.42–7.37 (2H, m, Ar–$H^{4\ and\ 6}$), 4.63–4.58 (1H, dd, *J* 12.2 and 3.6, H^2), 4.35 (2H, s, CH_2Ar), 4.32–4.26 (1H, dd, *J* 12.2 and 5.9, H^2), 4.20–4.10 (1H, m, C*H*CH_3), 1.53 (3H, d, *J* 6.8, CH_3); δ_C 159.0 (C=O), 149.6 (Q ArC), 135.7 (C=N^+), 133.0 (Ar–$C^{5'}$), 131.7 and 128.0 (Ar–$C^{4/6}$), 130.2 (QAr–C), 124.8 (Ar–C^3), 67.3 (C^2), 63.7 (*C*HCH_3), 28.6 (CH_2Ph), 14.3 (CH_3); LC/TCOF-MS found 288.0678 $(M+Na)^+$ $C_{12}H_{12}N_2O_5$ requires 288.0669.

4.4.5. 5-Benzyl-3-methyl-6-oxo-5,6-dihydro-2H-1,4-oxazin-4-ium-4-olate, ***10(I)e***. The nitrone **10(I)e** was obtained as a yellow solid (38.0 mg, 24%) following heating *Z*-**4(I)e** for 24 h. Purification was by flash column chromatography (20% Hex/EtOAc); mp 88–94 °C; ν_{max} (KBr) 3402, 1703, 1553, 1495, 1453, 1382, 1362 cm^{-1}; δ_H 7.37–7.19 (5H, m, ArH), 4.57–4.52 (1H, dd, *J* 12.0 and 3.5, H^2), 4.26–4.20 (1H, dd, *J* 12.0 and 5.8, H^2), 4.19–4.11 (1H, m, C*H*CH_3), 4.02 (2H, s, CH_2Ph), 1.53 (3H, d, *J* 6.8, CH_3); δ_C 158.2 (C=O), 134.6 (C=N^+), 133.7 (Q ArC), 128.6, 127.6, 124.7 (3×ArC), 66.6 (C^2), 62.8 (*C*HCH_3), 29.9 (*C*H_2Ph), 13.4 (CH_3); LC/TCOF-MS found 220.0964 $(M+H)^+$ $C_{12}H_{13}NO_3$ requires 220.0968.

4.4.6. 5-Mesityl-3-methyl-6-oxo-3,6-dihydro-2H-1,4-oxazin-4-ium-4-olate, ***10(I)f***. The nitrone **10(I)f** was obtained as a pale brown solid (45.0 mg, 89%) following heating *Z*-**4(I)f** for 24 h; mp 101–109 °C; ν_{max} (KBr) 3415, 2920, 1722, 1611, 1722, 1534, 1464, 1350, 1282, 1201, 1142 cm^{-1}; δ_H 6.92 (2H, s, *m*-ArH), 4.74–4.68 (1H, dd, *J* 12.2 and 3.4, H^2), 4.38–4.23 (1H, dd, *J* 12.2 and 4.0, H^2), 4.29–4.20 (1H, m, C*H*CH_3), 2.29 (3H, s, *p*-CH_3), 2.12 (3H, s, *o*-CH_3), 2.09 (3H, s, *o*-CH_3), 1.66 (3H, d, *J* 6.9, CHC*H*$_3$); δ_C 157.6 (C=O), 139.2 (C=N^+), 136.2, 135.6, 134.9 (4×Q ArC), 127.9 (ArCH), 66.1 (CH_2), 63.6 (*C*HCH_3), 20.2 (*p*-CH_3), 18.3, 17.9 (2×*o*-CH_3), 13.8 (CH_3); LC/TCOF-MS found 239.1304 $(M+H)^+$ $C_{14}H_{17}NO_3$ requires 249.1314.

4.5. General procedure for formation of α-keto amides, 5(II)

Step 1—Preparation of the acid chlorides of **6b** and **6c**. α-Oxo-2-furanacetic acid **6b** or thiophene-2-glyoxylic acid **6c** was stirred neat under Ar or N_2 at rt for 10–15 min. α,α-Dichloromethylmethyl ether (4.0 equiv) was added dropwise, addition was accompanied by evolution of HCl. The mixture was heated in an oil bath at 50 °C for 30 min and then allowed to cool to rt. Methyl formate was removed on a rotatory evaporator using an ice-cooled water bath to afford the products in quantitative yield as a pungent brown oils, which were immediately used without further purification. Obtained from **6b**, 2-(chlorooxy)-1-(2-furyl)-2-oxo-1-ethanone 0.226 g; from **6c** 2-(chlorooxy)-1-(2-thienyl)-2-oxo-1-ethanone 1.126 g.

Step 2. To a mixture of *N*-methyl allylamine (1.44 g, 20.0 mmol) and $NaHCO_3$ (1.71 g, 20.0 mmol) in DCM (30 mL) at 0 °C was added dropwise a solution of freshly prepared acid chloride (15.0 mmol) in DCM (8 mL). The mixture was stirred at rt for 1 h prior to washing with H_2O (20 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent was removed by rotary evaporation to yield the crude product, which required no further purification.

4.5.1. N-Allyl-2-(2-furyl)-N-methyl-2-oxo acetamide, ***5(II)b***. The title product was obtained as a brown oil (2.66 g, 88%); rotamer ratio: 1.1:1; R_f 0.31 (20% EtOAc/Hex); ν_{max} (Nujol) 2854, 1654, 1568, 1462, 1377 cm^{-1}; δ_H 7.57–7.56 (2.1H, m, Ar–H^5), 7.15 (2.1H, d, *J* 3.5, Ar–H^3), 6.44–6.42 (2.1H, m, Ar–H^4), 5.65–5.50 (2.1H, m, C*H*=CH_2), 5.48–4.97 (4.2H, m, CH_2=CH), 3.90 (2.2H, d, *J* 5.8, NCH_2 major rot.), 3.68 (2H, d, *J* 5.8, NCH_2[minor rot.]), 2.81 (3H, s, NCH_3[minor rot.]), 2.75 (3.3H, s, NCH_3 major rot.); δ_C 178.4 and 178.3 (ArC=O), 165.6 and 165.2 (NC=O), 150.1 and 149.9 (2×Q ArC), 148.9, 148.8 (Ar–C^5), 131.9 and 131.6 (*C*H=CH_2), 122.3, 121.9 (Ar–C^3), 119.3 and 119.2 (CH_2=CH), 112.8, 112.9 (Ar–C^4), 52.1 (NCH_2 major rot.), 48.8 (NCH_2[minor rot.]), 34.5 (NCH_3[minor rot.]), 31.7 (NCH_3 major rot.); LC/TCOF-MS found 216.0639 $(M+Na)^+$ $C_{10}H_{11}NO_3$ requires 216.0631.

4.5.2. N-Allyl-N-methyl-2-oxo- 2-(2-thienyl)acetamide, ***5(II)c***. The title product was obtained as a brown oil (1.01 g, 75%); rotamer ratio: 1.1:1; R_f (10% EtOAc/Hex) 0.33; ν_{max} (Nujol) 3286, 3086, 2932, 1852, 1760, 1659, 1408, 1355, 1287 cm^{-1}; δ_H 7.83–7.78 (4.2H, m, Ar–$H^{3\ and\ 5}$), 7.28–7.16 (2.1H, m, Ar–H^4), 5.89–5.73 (2.1H, m, C*H*CH_2), 5.32–5.18 (4.2H, m, CH_2=CH), 4.13 (2H, d, *J* 6.0, NCH_2[minor rot.]), 3.90 (2.2H, d, *J* 5.9, NCH_2 major rot.), 3.05 (3.3H, s, CH_3 major rot.), 2.98 (3H, s, CH_3[minor rot.]); δ_C 183.4, 183.3 (Ar*C*=O), 166.1, 165.7 (NC=O), 140.3, 140.2 (2×Q ArC), 136.5, 136.4 (Ar–C^3), 136.2, 136.1 (Ar–C^5), 132.2, 131.4 (*C*H=CH_2), 128.7, 128.6 (Ar–C^4), 119.0, 118.7 (CH_2=CH), 52.5, 49.1 (NCH_2), 34.8, 32.0 (NCH_3); LC/TCOF-MS found 248.0148 $(M+K)^+$ $C_{10}H_{11}NSO_2$ requires 248.0142.

4.6. General procedure for formation of oximes, 4(II)

A mixture of the α-keto amide **5(II)** (2.6 mmol), pyridine (2.24 g, 2.8 mmol) and $NH_2OH{\cdot}HCl$ (1.97 g, 2.8 mmol) in EtOH (500 mL) was stirred with heating at reflux in for 18–20 h. The solution was cooled to rt prior to evaporation under reduced pressure. The residue was taken up in DCM (150 mL) and the organics were washed with satd aq $NaHCO_3$ (50 mL) and H_2O (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to yield the crude product, which was purified as detailed below.

4.6.1. N-Allyl-2-(2-furyl)-2-(hydroxyimino)-N-methylacetamides, Z- ***4(II)b*** *and E-* ***4(II)b***. The title products, obtained as a brown oil (4.09 g, 76%) after 20 h reaction time, presented a pair of geometrical oxime isomers in a 1:1.1 ratio. Each oxime presented as a pair of rotamers. The oximes were inseparable by flash column chromatography. R_f (30% EtOAc/Hex) 0.18, 0.41; ν_{max} (Nujol) 2924, 1654, 1463, 1377, 1154, 963 cm^{-1}; δ_H 9.30 and 8.89 (1.1H and 1H br s, major and minor NOH), 7.51–7.47 (2.1H, m, major and minor Ar–H^5), 7.45–7.43, 6.64–6.61 (2.1H, 2×m, major and minor Ar–H^3), 6.56–6.45 (2.1H, m, major and minor Ar–H^4), 5.91–5.76 (1.1H, m, major C*H*=CH_2) 5.75–6.62 (1H, m, minor C*H*=CH_2) 5.33–5.15 (4.4H, m, major and minor CH_2=CH) 4.17 (2.2H, d, *J* 5.5, major

NCH_2) 3.84 (2H, dd, *J* 6.2, minor NCH_2) 3.06 and 3.05 (3H, s, NCH_3) 2.93 and 2.92 (3.3H, s, major NCH_3); δ_C 163.8, 163.6, 162.8 (C=O), 146.0, 145.9, 145.8, 145.6, 143.55, 143.3, 142.6, 142.5 (C=N and Q ArC), 144.8, 144.7, 143.6, 143.5 (Ar–C^5), 131.9, 131.6; 132.6, 132.4 (*C*H=CH_2), 119.1, 118.6 (major *C*H_2=CH), 117.9, 117.8 (minor *C*H_2=CH), 119.7, 119.6 (Ar–C^3), 112.8, 122.3, 111.7 (Ar–C^4), 49.6, 49.0 (major NCH_2), 53.4, 53.0 (minor NCH_2), 35.5, 34.6 (major NCH_3) 32.4, 31.4 (minor NCH_3); LC/TCOF-MS found 247.0488 $(M+K)^+$ $C_{12}H_{13}NO_3$ requires 247.0480.

*4.6.2. N-Allyl-2-(hydroxyimino)-N-methyl-2-(2-thienyl)acetamides, Z-**4(II)c** and E-**4(II)c**.* The title products were obtained after 20 h reaction time. Following separation by flash column chromatography (30% Hex/EtOAc) individual samples of each oxime isomer were obtained, *Z*-**4**(**II**)**c**, a yellow oil (0.23 g, 20%) and *E*-**4**(**II**)**c**, a brown oil, (0.29 g, 24%). Each oxime presented as a pair of rotamers; *Z*-**4**(**II**)**c** rotamer ratio: 1:1; *E*-**4**(**II**)**c** rotamer ratio: 1.3:1; *Z*-**4**(**II**)**c** R_f (50% Hex/EtOAc) 0.27; ν_{max} (Nujol) 3233, 1737, 1627, 1394, 1417, 1342, 982 cm^{-1}; δ_H 10.22 (1H, br s, OH), 7.58 (1H, d, *J* 5.1, Ar–H^5), 7.40 (1H, d, *J* 3.8, Ar–H^3), 7.11–7.06 (1H, m, Ar–H^4), 5.94–5.81 (0.5H, m, C*H*=CH_2 rot. a), 5.74–5.61 (0.5H, m, C*H*=CH_2 rot. b), 5.31–5.13 (2H, m, *C*H_2=CH), 4.17 (1H, d, *J* 5.9, NCH_2 rot. a), 3.88 (1H, d, *J* 6.0, NCH_2 rot. b), 3.08 (1.5H, s, NCH_3 rot. a), 2.93 (1.5H, s, NCH_3 rot. b); δ_C 165.1 and 164.8 (C=O), 146.8 and 146.7 (C=N), 132.5 (*C*H=CH_2 rot. b), 132.0 (*C*H=CH_2rot. a), 131.9 and 131.8 (Ar–C^3), 131.1 and 130.9 (Ar–C^5), 128.8 and 128.7 (Q ArC) 126.2 and 126.1 (Ar–C^4), 118.9 and 118.3 (*C*H_2=CH), 53.7 (NCH_2 rot. a), 49.8 (NCH_2rot. b), 35.9 (NCH_3 rot. a), 32.5 (NCH_3 rot. b); LC/TCOF-MS found 225.0702 $(M+H)^+$ $C_{10}H_{12}N_2O_2S_2$ requires 225.0692.

E-**4**(**II**)**c** R_f (50% Hex/EtOAc) 0.33; ν_{max} (Nujol) 3244, 2246, 1622, 1488, 1416, 1348, Compound 1265 cm^{-1}; δ_H 9.89 (2.3H, br s, OH), 7.31–7.29 (2.3H, dd, *J* 4.7 and 1.0, Ar–H^5), 7.17–7.16 (2.3H, dd, *J* 3.4 and 1.0, Ar–H^3), 7.02–6.98 (2.3H, m, Ar–H^4), 5.88–5.75 (1.3H, m, C*H*=CH_2 major rot.), 5.72–5.54 (1H, m, C*H*=CH_2 minor rot.), 5.32–5.11 (4.6H, m, *C*H_2=CH), 4.16 (2.6H, d, *J* 5.3, NCH_2 major rot.), 3.80 (2H, d, *J* 5.9, NCH_2 minor rot.), 3.04 (3H, s, NCH_3 minor rot.), 2.88 (3.9H, s, CH_3 major rot.); δ_C 163.3 (C=O), 147.9 (C=N), 133.7 and 133.5 (Q ArC) 131.5 (*C*H=CH_2 minor rot.), 130.2 (*C*H=CH_2 major rot.), 127.8 and 127.6 (Ar–C^3), 126.8 and 126.7 (Ar–C^5), 126.5 and 126.4 (Ar–C^4), 118.2 and 117.0 (*C*H_2=CH), 52.1 (NCH_2 minor rot.), 48.0 (NCH_2 major rot.), 33.6 (NCH_3 major rot.), 30.5 (NCH_3 minor rot.); LC/TCOF-MS found 225.0702 $(M+H)^+$ $C_{10}H_{12}N_2O_2S_2$ requires 225.0692.

*4.6.3. 6a-(2-Furyl)-5-methylhexahydro-6H-pyrrolo[3,4-c]isoxazol-6-one, **2b** and 6-(2-furyl)-2,4-dimethyl-5-oxo-2,3,4,5-tetrahydropyrazin-1-ium-1-olate, **10(II)b**.* A solution of *Z*- and *E*-**4**(**II**)**b** (1.00 g, 4.8 mmol) in toluene (310 mL) was heated to reflux under a N_2 atmosphere for 100 h. The solution was allowed to cool to rt prior to evaporation. The crude products were purified by flash column chromatography (20% DCM/EtOAc) to afford the bicycle **2b** as a orange solid (0.441 g, 44%) and the nitrone **10**(**II**)**b** as an enriched sample together with the bicycle. **2b**; mp 109–115 °C; ν_{max} (KBr) 3435, 3224, 3118, 2876, 1676, 1496, 1403 cm^{-1}; δ_H 7.41–7.40 (1H, dd, *J* 1.9 and 0.8, Ar–H^5), 6.60 (1H, d, *J* 3.3, Ar–H^3), 6.38–6.36 (1H, dd, *J* 3.3 and 1.9, Ar–H^4), 5.74 (1H, br s, NH), 4.15–4.11 (2H, m, H^3), 3.75–3.68 (1H, dd, *J* 10.1 and 8.3, H^4), 3.65–3.44 (1H, m, H^{3a}), 3.28–3.24 (1H, dd, *J* 10.1 and 2.6, H^4), 2.92 (3H, s, NCH_3); δ_C 170.2 (C=O), 148.2 (Q ArC), 143.0 (Ar–C^5), 110.9 (Ar–C^4), 109.8 (Ar–C^3), 79.2 (C^3), 72.8 (C^{6a}), 52.5 (C^4), 44.8 (C^{3a}), 30.3 (NCH_3); LC/TCOF-MS found 247.0280 $(M+K)^+$ $C_{10}H_{12}N_2O_3$ requires 247.0280; **10**(**II**)**b** δ_H 7.81 (1H, d, *J* 3.5, Ar–H^3), 7.62 (1H, d, *J* 1.8, Ar–H^5), 6.55–6.53 (1H, dd, *J* 3.5 and 1.8, Ar–H^4), 4.28–4.18 (1H, m, C*H*CH_3), 3.91–3.86 (1H, dd, *J* 13.7 and 4.3, H^2), 3.37–3.30 (1H, dd, *J* 13.7 and 5.2, H^2), 3.17 (3H, s, NCH_3), 1.57 (3H, d, *J* 6.8, CH*CH*$_3$); δ_C 153.8 (C=O), 144.5 (C=N^+), 143.0 (Ar–C^3), 129.8 (Q ArC), 118.1 (Ar–C^5), 110.5 (Ar–C^4), 64.9 (*C*HCH$_3$), 52.9 (NCH_2), 34.8 (NCH_3), 15.6 (CCH_3).

*4.6.4. 5-Methyl-6a-(2-thienyl)hexahydro-6H-pyrrolo[3,4-c]isoxazol-6-one, **2c**.* A solution of *E*-**4**(**II**)**c** (0.08 g, 3.5 mmol) in xylenes (24 mL) was heated at reflux under N_2 in the presence of hydroquinone (0.240 g, 1 mol % w/v). After 90 h reaction time the solution was allowed to cool to rt prior to evaporation. The residue was taken up in $CHCl_3$ (15 mL) and left at rt for 30 min. After any remaining hydroquinone, which precipitated was filtered and the solvent was evaporated to yield the crude product, which was purified by flash column chromatography (20% Hex/EtOAc) to yield **2c** as a brown oil (0.067 g, 86%); R_f (20% Hex/EtOAc) 0.36; ν_{max} (KBr) 3436, 3183, 2924, 1677, 1503, 1404, 1678 cm^{-1}; δ_H 7.32–7.30 (1H, dd, *J* 5.1 and 1.0, Ar–H^5), 7.22–7.21 (1H, br d, *J* 3.7, Ar–H^3), 7.01–6.98 (1H, dd, *J* 5.1 and 3.7, Ar–H^4), 4.19–4.08 (2H, m, H^3), 3.79–3.73 (1H, dd, *J* 10.3 and 7.8, H^4), 3.41–3.37 (1H, m, H^{3a}), 3.32–3.27 (1H, dd, *J* 10.3 and 2.0, H^4), 2.91 (3H, s, NCH_3); δ_C 170.4 (C=O), 136.9 (Q ArC), 126.2 (Ar–C^4), 125.0 (Ar–C^5), 123.1 (Ar–C^3), 79.4 (C^3), 73.1 (C^{6a}), 51.4 (C^4), 47.1 (C^{3a}), 29.8 (NCH_3); LC/TCOF-MS found 242.0951 $(M+NH_4)^+$ $C_{10}H_{12}N_2O_2S$ requires 242.0958.

*4.6.5. 2,4-Dimethyl-5-oxo-6-(2-thienyl)-2,3,4,5-tetrahydropyrazin-1-ium-1-olate, **10(II)c**.* A solution of *Z*-**4**(**II**)**c** (0.08 g, 3.5 mmol) in xylenes (24 mL) was heated to reflux under N_2 in the presence of hydroquinone (0.240 g, 1 mol % w/v). After 90 h reaction time the solution was allowed to cool to rt and left to stand prior to evaporation. The residue was taken up in $CHCl_3$ (15 mL) and left at rt for 30 min. After any remaining hydroquinone had precipitated the solution was filtered and the solvent evaporated to yield the crude product. Separation by flash column chromatography (20% Hex/EtOAc) yielded **10**(**II**)**c** as a brown oil (0.056 g, 71%); R_f 0.27 (12.5% Hex/EtOAc); ν_{max} (KBr) 3585, 2980, 2244, 1652, 1485, 1389, 1056, 913 cm^{-1}; δ_H 8.66 (1H, d, *J* 4.2, Ar–H^3), 7.46 (1H, d, *J* 5.1, Ar–H^5), 7.20–7.17 (1H, dd, *J* 5.1 and 4.2, Ar–H^4), 4.36–4.26 (1H, m, *C*HCH_3), 3.89–3.83 (1H, dd, *J* 13.5 and 4.4, H^2), 3.36–3.30 (1H, dd, *J* 13.5 and 5.4, H^2), 3.19 (3H, s, NCH_3), 1.59 (3H, d, *J* 6.8, CH_3); δ_C 158.5 (C=O), 133.0 (C=N^+), 132.8 (Ar–C^3), 130.4 (Q ArC), 128.7 (Ar–C^5), 126.8 (Ar–C^4), 63.6 (*C*HCH$_3$), 49.9 (CH_2), 35.2 (NCH_3), 15.6 (CH*C*H$_3$); LC/TCOF-MS found 226.0720 $(M+H)^+$ $C_{10}H_{12}N_2SO_2$ requires 225.0698.

*4.6.6. 2-[Allyl(methyl) amino]-1-phenyl-1-ethanone, **5(III)a**.* A solution of 2-bromoacetophenone **9** (2.03 g, 10.2 mmol) in DCM (23 mL) was injected slowly to a stirred solution of *N*-methyl allylamine (5.00 g, 70.4 mmol) in DCM (68 mL) at rt. After complete addition and a further 10 min stirring at rt the solution was washed with H_2O (3×30 mL), dried ($MgSO_4$), filtered and evaporated to yield the title product as a yellow oil (1.82 g, 98%), which required no further purification; R_f (40% EtOAc/Hex) 0.27, 0.41; ν_{max} (Nujol) 3451, 2960, 2572, 1741, 1647, 1455, 1169, 1040 cm^{-1}; δ_H 7.89–7.85 (2H, m, *m*-ArH), 7.44–7.38 (1H, m, *p*-ArH), 7.34–7.25 (2H, m, *o*-ArH), 5.88–5.74 (1H, m, C*H*=CH_2), 5.13–5.03 (2H, m, *C*H_2=CH), 3.69 (2H, s, NCH_2CO), 3.05 (2H, d, *J* 6.6, NCH_2CH), 2.25 (3H, s, NCH_3); δ_C 197.3 (C=O), 136.7 (Q ArC), 135.5 (CH_2=*C*H), 132.7 (*p*-ArC), 128.8 (*o*-ArC), 128.4 (*m*-ArC), 118.2 (*C*H_2=CH), 63.1 (*C*H_2C(O)), 60.9 (NCH_2CH), 42.7 (NCH_3); LC/TCOF-MS found 190.1219 $(M+H)^+$ $C_{12}H_{15}NO$ requires 190.1226.

*4.6.7. 2-[Allyl(methyl) amino]-1-phenyl-1-ethanone oximes, Z-**4(III)a** and E-**4(III)a**.* To a solution of **5**(**III**)**a** (0.314 g, 1.7 mmol) in EtOH (5 mL) was added $NH_2OH{\cdot}HCl$ (0.128 g, 1.8 mmol) and $NaHCO_3$ (0.157 g, 1.8 mmol). The mixture was heated at 80 °C for 3.5 h. The solution was cooled to rt, concentrated in vacuo and the residue taken up in DCM (10 mL). The organic layer was washed with H_2O

(2×10 mL), dried ($MgSO_4$), filtered and concentrated to yield the title product as a yellow oil (0.289 g, 85%). The oximes presented as a 1:2 mixture of *Z*- and *E*-isomers, separation was achieved by flash column chromatography (30% EtOAc/Hex). Compound *Z*-**4**(**III**)**a**, a yellow oil (0.026 g, 17%), *E*-**4**(**III**)**a** (0.152 g, 45%) also a yellow oil; *Z*-**4**(**III**)**a**; R_f (50% Hex:EtOAc) 0.32; ν_{max} (Nujol) 2854, 1463, 1377, 1154 cm^{-1}; δ_H 8.75 (1H, br s, OH), 7.58–7.50 (2H, m, *o*-ArH), 7.44–7.36 (3H, m, *m*- and *p*-ArH), 5.86–5.72 (1H, m, C*H*=CH_2), 5.16–5.09 (2H, m, CH_2=CH), 3.38 (2H, s, CH_2C=N), 3.03 (2H, d, *J* 6.5, NCH_2CH), 2.24 (3H, s, NCH_3); δ_C 155.5 (C=N), 135.4 (*C*H=CH_2), 132.6 (Q ArC), 129.0, 128.1 (*m*- and *p*-ArC), 126.5 (*o*-ArC), 117.8 (CH_2=CH), 60.6 (NCH_2CH), 60.3 (NCH_2C=N), 42.1 (NCH_3); LC/TCOF-MS found 227.1164 $(M+Na)^+$ $C_{12}H_{16}N_2O$ requires 227.1155; *E*-**4**(**III**)**a**; R_f (40% EtOAc/Hex 3:2) 0.39; ν_{max} (Nujol) 2854, 1463, 1377, 1154 cm^{-1}; δ_H 12.38 (1H, br s, OH), 7.66–7.60 (2H, m, *o*-ArH), 7.38–7.33 (3H, m, *m*- and *p*-ArH), 5.96–5.82 (1H, m, C*H*=CH_2), 5.26–5.20 (2H, m, CH_2=CH), 3.77 (2H, s, CH_2C=N), 3.13 (2H, d, *J* 6.7, NCH_2CH), 2.34 (3H, s, NCH_3); δ_C 154.2 (C=N), 135.7 (Q ArC), 133.5 (*C*H=CH_2), 129.1, 128.5 (*m*- and *p*-ArCH), 126.5 (*o*-ArCH), 119.6 (CH_2=CH), 60.3 (NCH_2), 54.8 (NCH_2C=N), 41.8 (NCH_3); LC/TCOF-MS found 227.1603 $(M+NH_4)^+$ $C_{12}H_{16}N_2O$ requires 222.1601.

*4.6.8. 2-(Allylanilino)-1-phenyl-1-ethanone oximes, E-**4**(**III**)**b** and Z-**4**(**III**)**b**.* To a stirred solution of **5**(**III**)**b** (0.310 g, 1.0 mmol) in EtOH (8 mL) were added $NH_2OH{\cdot}HCl$ (0.109 g, 2.0 mmol) and $NaHCO_3$ (0.132 g, 2.0 mmol). The mixture was stirred with heating at reflux for 3 h, following cooling to rt, the solution was concentrated and the residue dissolved in DCM (10 mL). The organic layer was washed with H_2O (2×5 mL), dried ($MgSO_4$), filtered and evaporated to yield the title products as a yellow solid (0.325 g, 100%); *Z*-**4**(**III**)**b** and *E*-**4**(**III**)**b** were obtained in a ratio of 1:1.3. ^1H NMR spectral data were in agreement with the literature.[11b]

*4.6.9. 5-Methyl-6a-phenylhexahydro-1H-pyrrolo[3,4-c]isoxazole, **3a**.* A solution of *Z*- and *E*-**4**(**III**)**a** (1.08 g, 5.3 mmol) in toluene (370 mL) was heated at reflux. After 15 h it was cooled to rt and concentrated to yield the crude product, purification was achieved by flash column chromatography (10% MeOH/Et_2O) and **3a** was obtained as a yellow solid (0.660 g, 62%). [Found: C, 70.40; H, 7.63; N, 13.43; $C_{12}H_{16}N_2O$ requires C, 70.55; H, 7.90;N, 13.72%]; mp 77–80 °C; ν_{max} (KBr) 3420, 2972, 2795, 1663, 1448, 1264, 1164 cm^{-1}; δ_C 142.3 (Q ArC), 128.4, 127.0, 125.6 (3×ArC), 78.4 (CH_2), 77.9 (C^{6a}), 65.4, 60.5 (2×CH_2), 55.0 (C^{3a}), 40.1 (NCH_3), 28.6; LC/TCOF-MS found 205.1335 $(M+H)^+$ $C_{12}H_{16}N_2O$ requires 205.1335. NMR spectral data was poorly resolved at rt and signals, in an ~6:1 ratio, attributable to two distinct conformers emerged at −50 °C. δ_H (300 MHz, $CDCl_3$, −50 °C) major conformer 7.61–7.27 (5H, 3×m, 5×ArH‡), 5.48 (1H, s, NH), 4.60–4.55 (1H, dd, *J* 8.4 and 8.4, H^3), 3.62–3.57 (1H, dd, *J* 8.4 and 8.0, H^3), 3.25–3.18 (2H, m, $H^{3a\text{ and }4}$‡), 3.14 (1H, d, *J* 10.8, H^6), 3.01 (1H, d, *J* 10.8, H^6), 2.62–2.57 (1H, dd, *J* 9.7 and 6.8, H^4‡), 2.42 (3H, s, NCH_3); minor conformer 7.62–7.27 (5H, 3×m, 5×ArH‡), 5.22 (1H, s, NH), 4.22 (1H, d, *J* 9.0, H^3), 3.83–3.78 (1H, dd, *J* 9.0 and 7.7, H^3), 3.45–3.39 (1H, m, H^{3a}), 3.25–3.18 (1H, m, $H^{4/6}$‡), 2.92 (2H, m, $H^{4/6}$), 2.62–2.57 (1H, m, $H^{4/6}$‡), 2.35 (3H, s, NCH_3).

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Supplementary data

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