Site selectivity in the addition of ketoximes to activated allenes and alkynes; *N- versus O*-alkylation

Frances Heaney,* Bronwyn M. Kelly, Sharon Bourke, Oliver Rooney, Desmond Cunningham and Patrick McArdle

Department of Chemistry, National University of Ireland, Galway, Ireland

Received (in Cambridge) 21st October 1998, Accepted 18th November 1998

Reaction of ketoximes with methyl propiolate afforded geometrical isomers of the methyl 3-(hydroxyimino)-propanoates **4** and of the *O*-vinyl oximes **5** as well as the 2-isoxazoline **6**. With dimethyl penta-2,3-diendioate **8c** reaction progressed *via* an *O*-alkylation to give the *O*-oxime ethers **9**, only in the case of cyclopentanone oxime was the spirocyclic dihydroazepinol **11** also obtained, its identity has been confirmed by an X-ray structure determination.

Introduction

The preparation of nitrones from oximes falls into three broad categories; i. thermal or catalytic proton transfer (generating an *NH*-nitrone);[1] ii. intramolecular cyclisation of a δ- or ε-alkenyl-(alkynyl) oxime (generating a cyclic nitrone);[2] iii. inter- or intramolecular reaction with an electrophilic species (generating acyclic or cyclic dipoles).[2b,3,4] When the electrophilic species is an electron deficient olefin the dipole forming reaction follows a 1,3-azaprotio cyclotransfer (APT) mechanism, a concerted equivalent of the Michael addition reaction[2b] and since activated acetylenes and allenes make excellent Michael acceptors (with carbon and heteronucleophiles),[5] it was postulated that they ought to react with oximes to furnish *N*-vinyl nitrones (**2** and **10**). The current paper reports an investigation of this hypothesis.

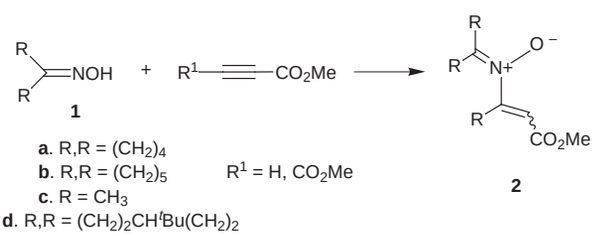
It is known that activated alkynes are more susceptible to nucleophilic attack than the corresponding olefins[6] and the nitrone forming power of the intramolecular oxime–alkyne cyclisation reaction has been shown to be considerably greater than the comparative oxime–alkene process.[7] Further, Holmes and co-workers have reported that an enynylhydroxylamine preferentially cyclises on the alkyne moiety to give an alkenyl substituted dipole.[8] Thus it was anticipated that methyl propiolate and dimethyl acetylenedicarboxylate may be potent substrates in an intermolecular APT reaction and that the *N*-vinyl nitrones **2** may thus be readily accessible.

Reported intermolecular reactions between oximes and acetylenic substrates, in the presence of base, lead to products from an initial *O*-alkylation.[9]† Further, it has recently been reported that conjugate addition of an oxime to ethyl propiolate, in neutral conditions, under the influence of triphenylphosphine, gives *E O*-vinyl oximes.[10] Only one example of a bimolecular oxime–alkyne reaction resulting in the formation of nitrones has been reported. Winterfeldt and Krohn have found that each of cyclohexanone and acetone oxime react with 2 mol equivalents of dimethyl acetylenedicarboxylate (DMSO, room temperature) to afford the 4-isoxazolines **3b**,**c** by a two step, one pot, dipole formation–cycloaddition sequence.[11]

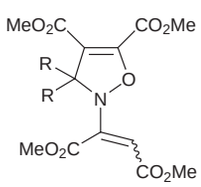
Results and discussions

a. Reactions with methyl propiolate

Following the reaction between the monoactivated acetylene, methyl propiolate and each of the symmetrical oximes, cyclopentanone oxime, cyclohexanone oxime and acetone oxime, **1a**–**c** (MeOH, 55–60 °C, 3 d) three groups of products were isolated

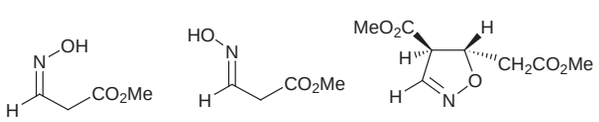


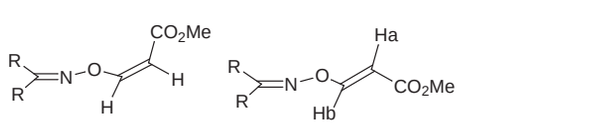
a. R,R = $(CH_2)_4$
b. R,R = $(CH_2)_5$ R^1 = H, CO_2Me
c. R = CH_3
d. R,R = $(CH_2)_2CH^tBu(CH_2)_2$



3b,c

from the crude mixture. For each oxime the major products were the isomeric oximes **4**, present as a 1 : 1 mixture in 60–75% yield, the stable *E*–*Z O*-addition products (**5a**–**c**) which were

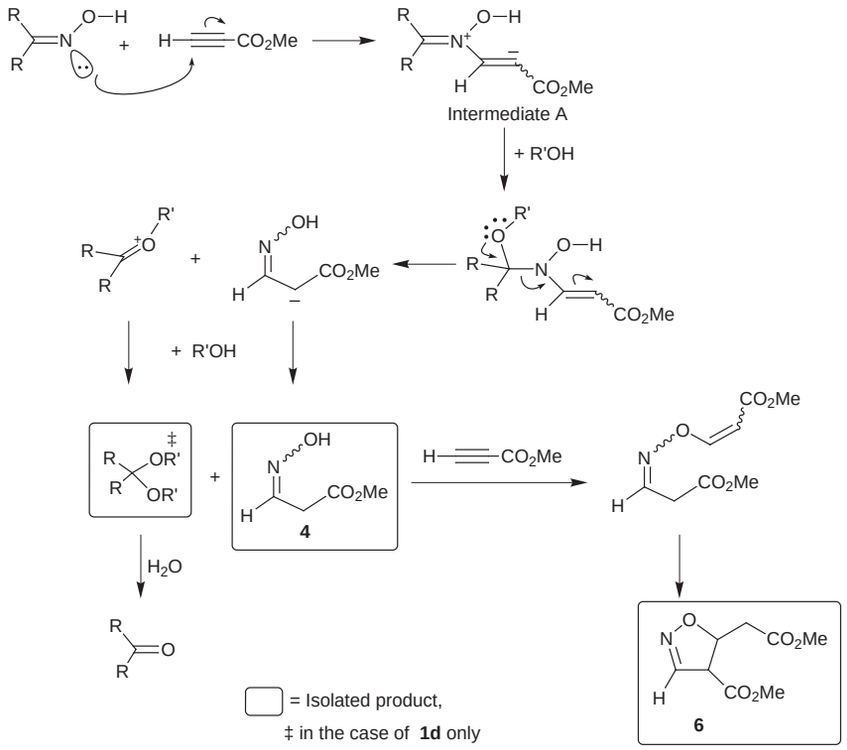




a. R,R = $(CH_2)_4$
b. R,R = $(CH_2)_5$
c. R = R = CH_3
d. R,R = $(CH_2)_2CH^tBu(CH_2)_2$

obtained in 10–16% yield, and the 2-isoxazoline **6** in 6–10% yield. (*E*)–(*Z*) Methyl 3-(hydroxyimino)propanoates **4** were inseparable by flash chromatography, accordingly, stereochemical assignment is based on the deshielding of the hydroxyimino proton of the *Z*-isomer (9.38 *versus* 8.92) due to its proximity (and potential hydrogen-bonding) to the ester carbonyl group, further, in the *E*-isomer the imino proton is deshielded by the proximate hydroxy group and resonates at 7.42 ppm, ~0.3 ppm

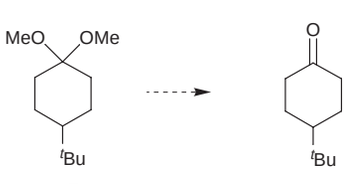
† The addition of base favours *O*-addition by enhancing the nucleophilicity of the oxygen atom. In the absence of base the equilibrium concentration of the nitrone form may be expected to be greater.



Scheme 1

downfield of its *Z*-analogue. The *O*-vinyl oximes **5a**–**c** were also inseparable, their stereochemical assignment is reliably based on the magnitude of the vicinal coupling constant between the olefinic protons [*E*-8 ^3J ~ 12 Hz; *Z*-8 ^3J ~ 7 Hz]. The assignment of the third product as the 2-isoxazoline **6** is based on its ^{1}H and ^{13}C NMR spectral data and the proposed structure is supported by microanalytical data. Diagnostic spectral signals include the C-3 proton which appears downfield at 7.19 ppm (1H, d, *J* 1.95) and the corresponding C-3 carbon signal at 143 ppm. Irradiation of the C-4 hydrogen atom failed to effect an enhancement on the signal for the C-5 proton suggesting these protons have a *trans* relationship; measurement of the coupling constant, $J_{4,5}$, as ~7.5 Hz does not help in stereochemical assignment since coupling constants in 2-isoxazolines are not diagnostic.[12]

Whilst the mechanistic route to the oximes **4** and the 2-isoxazoline **6** is not obvious it is clear that their formation is independent of the structure of the starting oxime (cyclopentanone, cyclohexanone and acetone oxime all give the same products in similar relative yields). Analysis of the structures of **4** and **6** show that they are constructed from the hydroxyimino portion of the oxime with one and two moles respectively of methyl propiolate. A plausible mechanism, shown in Scheme 1, requires the expulsion of one mole of carbonyl compound, however, in no case could this be found amongst the reaction products, perhaps this can be explained by the volatility of the ketones arising from the deoximation of **1a**–**c**. 4-*tert*-Butylcyclohexanone, the parent carbonyl of the oxime **1d** has a bp of 113–116 °C at 20 mmHg and so, if formed in the reaction of **1d** with methyl propiolate, it should be easily detectable. Methyl propiolate and **1d** were heated in anhydrous methanol for 3 d at 65 °C; following flash chromatographic analysis of the reaction mixture 1,1-dimethoxy-4-*tert*-butylcyclohexane **7** was isolated in 27% yield together with the oximes **4** (1 : 1 mixture, 24%), the *O*-vinyl ethers (*E*)- and (*Z*)-**5d**, (combined yield 17%) and the 2-isoxazoline **6** (3%). The isolation of **7** (which hydrolyses on standing to its parent ketone) implies that the nucleophile attacking the intermediate **A** is a solvent molecule (methanol) and not an extraneous water molecule. That the dimethyl acetal **7** arises from **1d** by a route more convoluted than straightforward methanolysis followed by transfer of the hydroxylamine functionality is supported by the observed stability of **1d** following heating with cyclohexanone in boiling methanol. That the oximes **4** are the precursors to the 2-isoxazoline **6** has been illustrated by an independent experiment, thus heating **4** with methyl propiolate (1.4 equiv.) furnished **6** in 29% isolated yield (MeOH, 2 d, 65 °C).



7

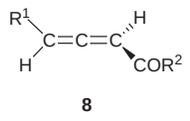
The suggested mechanism involves a critical role for the solvent in determining the product distribution, indeed acetone oxime **1c** reacts with methyl propiolate in dry C_6H_6 (80 °C) slowly, but specifically, to give (*E*)-**5c** only (14%) whilst in water quantitative transformation to the *O*-vinyl adducts **5c** was observed (*E* : *Z* 1 : 3). In anhydrous ethanol, the reaction proceeded as with methanol but with a much reduced rate of conversion. The nature and relative quantities of the products from the reaction in $CHCl_3$ appeared very sensitive to the method by which the solvent was purified and dried, however, in each case, following the reaction with cyclohexanone oxime, inspection of the crude ^{1}H NMR spectra revealed the presence of the isoxazoline **6** and (*E*)-**5b**. Methyl but-2-ynoate, a disubstituted acetylene, failed to take part in reaction with any of the chosen oximes. The observed lack of reactivity is presumably due to problems of steric access between the reactants.

b. Reactions with electron deficient allenes

Nitrone generation from the reaction between oximes and allenes has thus far been demonstrated only in the intramolecular variant; Lathbury and Gallagher have shown that ω-allenyl oximes undergo a Ag(I) promoted cyclisation yielding 5- and 6-membered cyclic dipoles.[13a,b] The success of the reaction is related to the geometry of the oxime and the length of the tether connecting the oxime and allene functionalities with

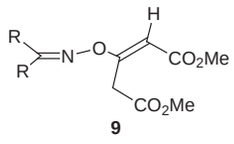
certain oximes preferentially reacting *via* their oxygen atom to give the corresponding oxazepines.[13b,c]

The allenes **8** were prepared according to literature



8

a. R^1 = H, R^2 = OMe
b. R^1 = H, R^2 = Me
c. R^1 = CO_2Me, R^2 = OMe



9

a. R,R = $(CH_2)_4$
b. R,R = $(CH_2)_5$
c. R = CH_3

methods,[14a–c] and their reaction with the ketoximes **1a**–**c** studied. The monoactivated allenes **8a**,**b** failed to give any useful results in this investigation and products from reaction with oximes in various solvents, over a range of temperatures, varied between returned starting material and complicated mixtures of unidentifiable compounds. However heating a solution of the symmetrically activated allene **8c**,[14d] [recognised as a superior Michael acceptor due to the strong cationic nature of the centre (sp) carbon atom] and cyclopentanone oxime (0.5 equiv.) in each of C_6H_6, $CHCl_3$, MeOH and DMSO resulted in greater reactivity and the *O*-alkylation product **9a** was formed in 0, 30, 35 and 42% yield respectively. Analogous behaviour was observed for cyclohexanone and acetone oxime and in DMSO the adducts **9b** and **9c** were formed in 55 and 43% yield respectively. ^{1}H NMR measurements indicated that in each case the alkylation proceeded stereospecifically and indeed π-facial selectivity in the addition of nucleophiles to allene carboxylates is a recognised characteristic.[15] *E*-Geometry is assigned to the adducts **9** following comparison of the resonance position of the vinylic proton (δ_H 5.81–5.84 ppm) with that observed for the corresponding proton (H_a) in the acetylenic adducts (*E*)- and (*Z*)-**5**. In (*E*)-**5**, where the terminal vinylic proton is *cis* to the oxygen atom, resonance is in the range 5.45–5.55 ppm whilst for the *Z*-adducts the analogous proton resonates upfield at 4.77–4.84 ppm. No trace of *N*-alkylated products (nitrones, **10**) or the corresponding cycloadducts could be detected in any of the crude reaction mixtures and only in the case of cyclopentanone oxime was any other reaction product noted. A yellow solid, isolated in 14% yield, has tentatively been identified as the spirocyclic dihydroazepine **11**. Microanalytical data indicate it is made up of two moles of the allene and one mole of the oxime. The ^{1}H NMR spectrum displays two exchangeable protons, at 12.4 and 4.8 ppm, assigned as the enolic OH and the NH signals respectively. The CH methine proton resonates as a singlet (3.46 ppm) and the methylene protons as doublets at 4.04 and 3.41 ppm (J ~ 16 Hz), their magnetic non-equivalence is attributed to restricted rotation of the side chain in the highly substituted spirocyclic ring skeleton. In the ^{13}C NMR spectrum there are eight downfield signals, representing four ester carbonyl groups and four olefinic carbon atoms, two of which are deshielded and two which are not. Confirmation of the structure as the spirocyclic dihydroazepine rests with a single crystal X-ray structure analysis of a triclinic crystal grown from CH_2Cl_2–hexane (Fig. 1). The 2,3-dihydro-1*H*-azepin-4-ol ring skeleton is rare and heretofore has been seen only as part of a benzo fused bicyclic ring system.[16] Examination of the structure gives evidence for an intramolecular hydrogen bond between the enolic hydrogen atom H-3 and the adjacent carbonyl oxygen atom O-4, the O-4–O-3 distance is 2.524(3) Å, this hydrogen bond is the likely stabilising factor in the adoption of the enolic structure. A second interesting structural feature is the extent of planarity in the dihydroazepine ring with five ring atoms C-1, N-1, C-16, C-13 and C-10 falling in a plane. We postulate that formation of **11** may involve the *N*-vinyl nitrone **10**, which following cycloaddition to a second molecule of **8c**[17] gives the spirocyclic isoxazolidine **12**; being a 1,5-diene

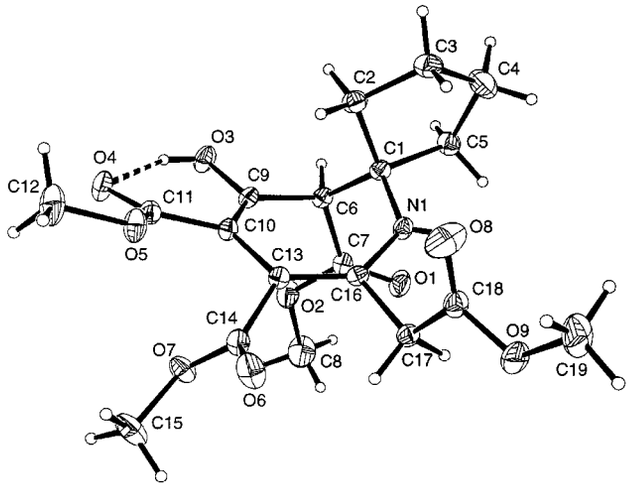
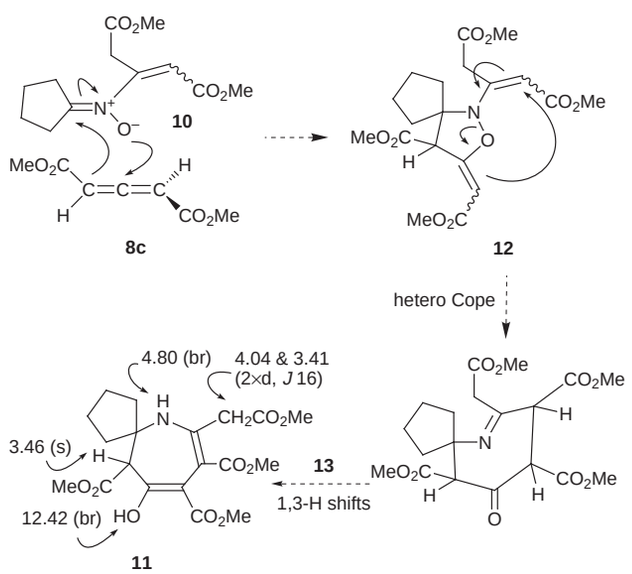


Fig. 1 X-Ray crystallographic projection of **11**.

12 may undergo a 3,3-sigmatropic shift (hetero Cope) to the spirocyclic azepinone **13**, which following two 1,3-proton transfers (keto ⇌ enol and imine ⇌ enamine] results in the conjugated dihydroazepine **11** (Scheme 2). 1-Aza-1′-oxa Cope



Scheme 2

rearrangements are known for *O*-aryl oximes and *O*-vinyl *N*-phenylhydroxylamines (preparative routes to benzofurans and indoles respectively). There is also precedent for this rearrangement with substrates like **12** where the N–O bond is within a ring, an *in situ* rearrangement of 5-methylene-*N*-phenylisoxazoline is reported to afford *Z*-configured 2-vinylindoles.[18] The factors promoting the formation of **11** from cyclopentanone oxime and **8c** appear not to operate with cyclohexanone or acetone oxime, the explanation for this divergence of reactivity between the three ketoximes is not clear.

Conclusions

The ambifunctional nucleophilicity of oximes is well known and, in contrast to their behaviour with simple electron deficient olefins, ketoximes react with a symmetrically activated allene to form products arising from oxa- and not aza-addition. It may be that the different topological requirements of the transition states leading to *N*- and *O*-alkylation dictate chemoreactivity (Fig. 2). The APT mechanism,[2b] leading to **10**, involves a 5-membered cyclic framework with initial attack of the oxime nitrogen atom on the central carbon of the allene and the steric

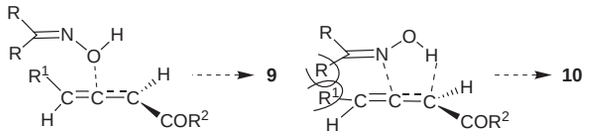


Fig. 2

hindrance encountered in this transtition state may be sufficient to prohibit nitrone formation. On the other hand generation of the *O*-addition product **9** involves a two step process and is sterically uninhibited. Formation of the spirocyclic dihydroazepinol **11** was unexpected and its unusual structure has been confirmed by a single crystal X-ray structure determination. Reaction between methyl propiolate and ketoximes in MeOH is complex and the simple *O*-addition products **5**, present in rather small yield, are accompanied by the isomeric oximes **4** (the major products) and the 2-isoxazoline **6** as the reaction products. A mechanism postulating the origin of these unexpected products is presented in Scheme 1. Since the allene and the alkyne are electronically activated towards nucleophilic attack, the disparate reactivity encountered with these species with respect to similarly activated alkenes, is a likely consequence of the differing topological requirements for the interaction of the oxime with the allenic (sp hybridised), alkynic (sp hybridised), and olefinic carbon atoms (sp^2 hybridised). In particular, aza attack, to result in nitrone formation, requires a 5-membered cyclic transition state (APT mechanism) and is more spatially demanding than the alternate conjugate (two step) addition. The latter mechanism can proceed with either the oxime *O*- or *N*-atom as the attacking centre.

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. NMR Spectra were recorded using JEOL JNM-LA400 and JEOL EX270 FT NMR spectrometers at probe temperatures with tetramethylsilane as internal reference and $CDCl_3$ as solvent, *J* values are given in Hertz. Flash column chromatography was carried out on silica gel (200–400 mesh; Kieselgel 60, E Merck) with air pump pressure; 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. All solvents used were purified by standard procedures and pet. spirit refers to that fraction of light petroleum boiling between 40–60 °C.

General procedure for the reaction of ketoximes with methyl propiolate. Preparation of (*E*)- and (*Z*)-methyl 3-[(alkylideneamino)oxy]prop-2-enoates 5, (*E*)- and (*Z*)-methyl 3-(hydroxyimino)propanoates 4 and 4,5-dihydro-4-methoxycarbonyl-5-methoxycarbonylmethylisoxazole 6

A solution of methyl propiolate (2 mmol) and the oxime (1 mmol) in anhydrous MeOH (3 cm^3) was heated to 55–65 °C under a N_2 atmosphere for 3 d. The cooled reaction solution was concentrated to yield the crude products, the *O*-vinyl oxime ethers **5**, the oximes **4** and the 2-isoxazoline **6**. Purification by flash chromatography [SiO_2, ethyl acetate–pet. spirit (for reaction of **1a**, 2:3; **1b**, 2:3; **1c**, 1:1)] afforded the products.

Reaction of cyclopentanone oxime **1a** with methyl propiolate afforded the methyl 3-[(cyclopentylideneamino)oxy]prop-2-enoates **5a** (10%), as an inseparable mixture of *E*- and *Z*-isomers (1:1.5), mixed melting point 99–104 °C (Found: C 58.77; H 7.90; N 7.66. $C_9H_{13}NO_3$ requires C 59.00; H 7.10; N 7.64%). (*E*)-**5a** δ_H (270 MHz), 7.27 (d, 1H, *J* 12.45, H-a), 5.45 (d, 1H, *J* 12.45, H-b), 3.71 (s, 3H, OMe), 2.65 (m, 4H, CH_2-(C=N)CH_2), 1.72 (m, 4H, CH_2CH_2); δ_C (67.5 MHz), 173.1, 162.3, 136.8, 95.8, 50.1, 29.7, 27.8, 24.9, 23.4; (*Z*)-**5a** δ_H (270 MHz), 7.23 (d, 1H, *J* 7.33, H-a), 4.77 (d, 1H, *J* 7.33, H-b), 3.71 (s, 3H, OMe), 2.56 (m, 4H, CH_2(C=N)CH_2), 1.75 (m, 4H, CH_2CH_2); δ_C (67.5 MHz), 172.6, 159.9, 134.1, 92.8, 50.3, 29.3, 27.7, 25.3, 23.5. The isomeric oximes **4** were obtained as an inseparable mixture of *E*- and *Z*-isomers (1:1.5) 65% (Found: C 43.69; H 6.39; N 6.42. $C_4H_7NO_3$ requires C 43.33; H 6.40; N 6.36%). (*E*)-**4** δ_H (400 MHz), 8.92 (br s, 1H, OH), 7.42 (t, 1H, *J* 6.13, HC=N), 3.69 (s, 3H, OMe), 3.12 (d, 2H, *J* 6.13, CH_2); δ_C (100 MHz), 168.4, 146.2, 52.1, 31.9; (*Z*)-**4** δ_H (400 MHz), 9.38 (br s, 1H, OH), 7.13 (t, 1H, *J* 6.03, HC=N), 3.71 (s, 3H, OMe), 3.44 (d, 2H, *J* 6.13, CH_2); δ_C (100 MHz), 169.2, 144.0, 52.2, 30.3. The isoxazoline **6** was obtained as a pale yellow oil (10%) (Found: C 47.88; H 5.13; N 6.25. $C_8H_{11}NO_5$ requires C 47.76; H 5.47; N 6.96%). δ_H (400 MHz), 7.19 (d, 1H, *J* 3.2, H-2), 5.17 (q, 1H, *J* 7.67, H-5), 4.21 and 4.19 (2 × d, 2 × 1H, *J* 7.67, CH_2), 3.79 and 3.71 (2 × s, 2 × 3H, 2 × OMe), 2.75 (m, 1H, H-4); δ_C (100 MHz), 169.3, 167.3, 144.2, 58.2, 52.3, 37.2, 29.4; IR 1739.9, 1628.0, 1602.8 1202.4 cm^{-1}.

Reaction of cyclohexanone oxime **1b** with methyl propiolate afforded the methyl 3-[(cyclohexylideneamino)oxy]prop-2-enoates **5b** (10%) as an inseparable mixture of *E*- and *Z*-isomers (1.1:2), mixed melting point 114–118 °C (Found: C 61.10; H 7.30; N 7.40. $C_{10}H_{15}NO_3$ requires C 60.90; H 7.66; N 7.10%). (*E*)-**5b** δ_H (270 MHz), 7.88 (d, 1H, *J* 12.45, H-a), 5.45 (d, 1H, *J* 12.45, H-b), 3.63 (s, 3H, OMe), 2.42 (m, 2H, CH_2(C=N)), 2.22 (m, 2H, CH_2(C=N)), 1.90 (m, 6H $(CH_2)_3$); δ_C (67.5 MHz), 168.3, 166.5, 159.9, 95.9, 51.2, 32.8, 32.0, 29.8, 26.9, 25.8; (*Z*)-**5b** δ_H (270 MHz), 7.25 (d, 1H, *J* 7.33, H-a), 4.77 (d, 1H, *J* 7.33, H-b), 3.63 (s, 3H, OMe), 2.56 (m, 2H, CH_2(C=N)), 2.20 (m, 2H, CH_2(C=N)), 1.90 (m, 6H, $(CH_2)_3$); δ_C (67.5 MHz), 166.6, 162.4, 159.9, 92.8, 51.0, 32.7, 31.8, 29.3, 26.7, 25.5. The isomeric oximes **4** were obtained as an inseparable mixture of *E*- and *Z*-isomers (1:1) (75%) and the isoxazoline **6** was obtained as a pale yellow oil (6%).

Reaction of acetone oxime **1c** with methyl propiolate afforded the methyl 3-[(methylethylideneamino)oxy]prop-2-enoates **5c** (10%) as an inseparable mixture of *E*- and *Z*-isomers (1:1), mixed melting point 96–100 °C (Found: C 53.22; H 7.01; N 8.80. $C_7H_{11}NO_3$ requires C 53.49; H 7.05; N 8.90%). (*E*)-**5c** δ_H (270 MHz), 7.89 (d, 1H, *J* 12.53, H-a) 5.49 (d, 1H, *J* 12.53, H-b), 3.73 (s, 3H, OMe), 2.00 and 1.99 (2 × s, 2 × 3H, 2 × Me); δ_C (67.5 MHz), 168.3, 162.2, 144.3, 96.0, 51.2, 22.2, 21.4; (*Z*)-**5c** δ_H (270 MHz), 7.26 (d, 1H, *J* 7.26, H-a), 4.83 (d, 1H, *J* 7.26, H-b), 3.73 (s, 3H, OMe), 2.00 and 1.99 (2 × s, 2 × 3H, 2 × Me); δ_C (67.5 MHz), 168.3, 163.3, 144.9, 94.3, 51.2, 17.1, 16.4. The isomeric oximes **4** were obtained as an inseparable mixture of *E*- and *Z*-isomers (1:1.3) (60%) and the isoxazoline **6** was obtained as a pale yellow oil (6%).

Reaction of 4-*tert*-butylcyclohexanone oxime 1d with methyl propiolate

4-*tert*-Butylcyclohexanone oxime **1d** (0.500 g, 2.95 mmol) and methyl propiolate (0.496 g, 5.90 mmol) were heated at reflux in dried methanol (65 °C) for 3 d under a nitrogen atmosphere. The reaction was monitored by TLC (pet. spirit–diethyl ether; 10:3). Removal of the solvent yielded a brown oil. Purification by flash chromatography (silica gel, pet. spirit–diethyl ether; 10:2) afforded the pure products. 1,1-Dimethoxy-4-*tert*-butylcyclohexane **7** was isolated as a clear oil (160 mg, 27.1%) (Found: C 71.63; H 12.74. $C_{12}H_{24}O_2$ requires C 72.00; H 12.00%); δ_H (400 MHz), 3.16 (s, 3H, OMe), 3.11 (s, 3H, OMe), 2.05 (d, 2H, *J* 11.1, 2 × C*H*C(OMe)$_2$), 1.61 (d, 2H, *J* 11.1, 2 × C*H*C(OMe)$_2$), 1.21 (m, 2H, 2 × C*H*CH$_2$C(OMe)$_2$), 1.10 (m, 2H, 2 × CHCH$_2$C(OMe)$_2$), 1.00 (m, 1H, CH$_2$C*H*CH$_2$), 0.82 (s, 9H, 3 × CH_3); δ_C (100 MHz), 47.51, 47.28, 32.71, 32.21, 27.57, 23.52. Methyl (*E*)-3-[(4-*tert*-butylcyclohexylideneamino)oxy]-prop-2-enoate (*E*)-**5d** was isolated as a clear oil (70 mg, 9.6%) (Found: C 66.51; H 8.53; N 5.23. $C_{18}H_{19}N_3O_6$ requires C 66.66; H 8.73; N 5.55%); δ_H (400 MHz), 7.95 (d, 1H, *J* 12.2, OCH=C),

5.55 (d, 1H, *J* 12.2, C*H*CO_2Me), 3.71 (s, 3H, OMe), 2.44 (m, 2H, 2 × C*H*C=N), 2.24 (m, 2H, 2 × C*H*C=N), 2.01 (m, 5H, 2 × C*H*(CH_2)$_2$), 0.88 (s, 9H, 3 × CH_3); δ_C (100 MHz), 168.33, 162.23, 144.49, 96.11, 51.24, 47.15, 31.49, 27.44, 26.45, 26.02. Methyl (*Z*)-3-[(4-*tert*-butylcyclohexylideneamino)oxy]prop-2-enoate, (*Z*)-**5d** was isolated as a clear oil (50 mg, 7.3%) (Found: C 66.32; H 8.45; N 5.33. $C_{18}H_{19}N_3O_6$ requires C 66.66; H 8.73; N 5.55%); δ_H (400 MHz), 7.32 (d, 1H, *J* 7.32, OCH=C), 4.84 (d, 1H, *J* 7.32, C*H*CO_2Me), 3.70 (s, 3H, OMe), 2.43 (m, 2H, 2 × C*H*C=N), 2.24 (m, 2H, 2 × C*H*C=N), 2.00 (m, 5H, 2 × C*H*(CH_2)$_2$), 0.86 (s, 9H, 3 × CH_3); δ_C (100 MHz), 168.33, 163.31, 144.73, 95.12, 51.23, 47.11, 31.44, 27.40, 26.41, 25.00. The oximes **4** (1 : 1, 24%) and the isoxazoline **6** (3%) were isolated, data agreed with that reported above.

General procedure for the reaction of ketoximes with dimethyl penta-2,3-dienedioate. Preparation of dimethyl (*Z*)-3-[(cyclopentylideneamino)oxy]pent-2-enedioate, 9a, dimethyl (*Z*)-3-[(cyclohexylideneamino)oxy]pent-2-enedioate, 9b and dimethyl (*Z*)-3-[(1-methylethylideneamino)oxy]pent-2-enedioate, 9c

A solution of the allene[14] **8c** (2 mmol) and the oxime **1a**–**c** (1 mmol) in anhydrous DMSO (12 cm^3) was heated to 55 °C under a N_2 atmosphere for 15 h. To the cooled reaction solution was added distilled water (10 cm^3) and the aqueous layer was extracted with CH_2Cl_2 (10 cm^3). The organic layer was collected, washed with water (2 × 8 cm^3), dried ($MgSO_4$) and concentrated to yield a brown coloured residue which was purified by flash chromatography (SiO_2; **9a**, ethyl acetate–hexane 3 : 7; **9b**, ethyl acetate–hexane 1 : 1; **9c**, diethyl ether–hexane 3 : 7). The following *O*-vinyl oximes were prepared; **9a** colourless oil (43%) (Found: C 56.52; H 6.69; N 5.50. $C_{12}H_{17}NO_5$ requires C 56.46; H 6.71; N 5.48%); δ_H (270 MHz), 5.81 (s, 1H, C=CH), 3.83 (s, 2H, CH_2), 3.65 and 3.60 (2 × s, 2 × 3H, 2 × OMe), 2.43 (m, 4H, CH_2(C=N)CH_2), 1.72 (m, 4H, CH_2CH_2); δ_C (67.5 MHz), 168.2, 167.3, 166.2, 161.5, 95.3, 52.4, 51.1, 36.5, 31.6, 27.2, 25.0, 23.4; **9b** colourless oil (42%) (Found: C 58.33; H 7.52; N 5.00. $C_{13}H_{19}NO_5$ requires C 57.96; H 7.10; N 5.20%); δ_H (270 MHz), 5.85 (s, 1H, C=CH), 3.87 (s, 2H, CH_2), 3.74 and 3.63 (2 × s, 2 × 3H, 2 × OMe), 2.49 (m, 2H, CH_2C=N), 2.27 (m, 2H, CH_2C=N), 1.60 (m, 6H, (CH_2)$_3$); δ_C (67.5 MHz), 169.5, 168.2, 167.1, 165.4, 94.5, 52.3, 50.7, 36.1, 31.7, 26.6, 26.1, 25.5, 25.1; **9c** colourless oil (55%) (Found: C 52.00; H 6.83; N 6.26. $C_{10}H_{15}NO_5$ requires C 52.40; H 6.60; N 6.10%); δ_H (270 MHz), 5.84 (s, 1H, C=CH), 3.85 (s, 2H, CH_2), 3.66 and 3.61 (2 × s, 2 × 3H, 2 × OMe), 1.92 and 1.91 (2 × s, 2 × 3H, 2 × Me); δ_C (67.5 MHz), 169.4, 168.3, 165.5, 162.3, 95.1, 52.2, 51.0, 36.4, 22.6, 21.8.

In the reaction of **1a** with **8c**, trimethyl 10-hydroxy-7-(2-methoxy-2-oxoethyl)-6-azaspiro[4.6]undeca-7,9-diene-8,9,11-tricarboxylate **11** was isolated in 14% yield, mp 139–140 °C (diethyl ether–pet. spirit) (Found: C 55.16; H 6.19; N 3.46. $C_{19}H_{25}NO_9$ requires C 55.47; H 6.08; N 3.41%); δ_H (400 MHz), 12.42 (br s, 1H, OH), 4.80 (br s, 1H, NH), 4.04 (d, 1H, *J* 15.7, C*H*$_2$$CO_2$Me), 3.75 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.60 (s, 3H, OMe), 3.46 (s, 1H, C*H*CO_2Me), 3.41 (d, 1H, *J* 15.7, C*H*$_2$$CO_2$Me), 2.09 (m, 2H, 2 × C*H*CN), 1.65 (m, 6H, 2 × C*H*N and CH_2CH_2); δ_C (100 MHz), 172.7, 170.8, 170.0, 168.0, 167.8, 143.1, 100.9, 93.9, 71.0, 58.5, 52.2, 52.0, 51.3, 42.2, 40.1, 39.6, 23.8, 22.5.

Crystal data for 11

$C_{19}H_{25}NO_9$, M = 411.40, λ 0.71069 Å, triclinic, space group $P\bar{1}$, a = 8.7445(11), b = 10.6180(12), c = 12.083(2) Å; α = 69.045(12), β = 78.645(12), γ = 82.861(11)°, V = 1025.4(2) $Å^3$, Z = 2, D_c 1.332 Mg m^{-3}, μ = 0.107 mm^{-1}, F(000) = 436, crystal size 0.54 × 0.20 × 0.14 mm, unique reflections = 4006 [R(int) = 0.0253], observed $I > 2\sigma I$ = 2563, data/restraints/parameters = 4006/0/267, observed data R_1 = 0.0462, wR_2 = 0.1338, all data R_1 = 0.0785, wR_2 = 0.1446, max peak/hole 0.371 and −0.208 e $Å^{-3}$, software used, SHELXS-97,[19] SHELXL-97[20] and ORTEX.[21] 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 (see Table 1).‡

Table 1 Crystal data and structure refinement for **11**

Identification code	**11**
Empirical formula	$C_{19}H_{25}NO_9$
Formula weight	411.40
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 8.7445(11) Å, α = 69.045(12)°
	b = 10.6180(12) Å, β = 78.645(12)°
	c = 12.083(2) Å, γ = 82.861(11)°
Volume	1025.4(2) $Å^3$
Z	2
Density (calculated)	1.332 Mg m^{-3}
Absorption coefficient	0.107 mm^{-1}
F(000)	436
Crystal size	0.54 × 0.20 × 0.14 mm
θ range for data collection	2.06 to 25.97°
Index ranges	$0 \leqslant h \leqslant 10$; $-12 \leqslant k \leqslant 13$;
	$-14 \leqslant l \leqslant 14$
Reflections collected	4434
Independent reflections	4006 [R(int) = 0.0253]
Reflections observed (>2σ)	2563
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4006/0/267
Goodness-of-fit on F^2	1.071
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0462, wR_2 = 0.1338
R indices (all data)	R_1 = 0.0785, wR_2 = 0.1446
Largest diff. peak and hole	0.371 and −0.208 e $Å^{-3}$

R indicies; $R_1 = [\Sigma||F_o| - |F_c||]/\Sigma|F_o|$ (based on F), $wR_2 = [[\Sigma_w(|F_o^2 - F_c^2|)^2]/[\Sigma_w(F_o^2)^2]]^{\frac{1}{2}}$ (based on F^2). $w = 1/[(\sigma F_o)^2 + (0.0842P)^2]$. Goodness-of-fit = $[\Sigma_w(F_o^2 - F_c^2)^2/(N_{obs} - N_{parameters})]^{\frac{1}{2}}$.

Acknowledgements

We acknowledge Forbairt grants for postgraduate research (B. K. and S. B.) and a Forbairt Basic Science Grant SC/97/517 (F. H., O. R.), support from Galway County Co. (B. K., O. R.), Mayo County Co. (S. B.) and the Chemistry Department, University College, Galway.

‡ Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/285.

References

1 R. Grigg, F. Heaney, J. Markandu, S. Surendrakumar, M. Thornton-Pett and W. J. Warnock, *Tetrahedron*, 1991, **47**, 4007; A. Hassner, R. Maurya, A. Padwa and W. H. Bullock, *J. Org. Chem.*, 1991, **56**, 2775.

2 (*a*) R. Grigg, J. Markandu, T. Perrior, S. Surendrakumar and W. J. Warnock, *Tetrahedron Lett.*, 1990, **31**, 559; (*b*) R. Grigg, J. Markandu, T. Perrior, S. Surendrakumar and W. J. Warnock, *Tetrahedron*, 1992, **47**, 6929; (*c*) C. O'Mahony and F. Heaney, *Chem. Commun.*, 1996, 167.

3 R. Grigg, J. Markandu and S. Surendrakumar, *Tetrahedron Lett.*, 1990, **31**, 1191; R. Grigg and J. Markandu, *Tetrahedron Lett.*, 1989, **30**, 5489; R. Grigg, M. Hadjisoteriou, P. Kennewell, J. Markandu and M. Thornton-Pett, *J. Chem. Soc., Chem. Commun.*, 1992, 1388; R. Grigg, M. Hadjisoteriou, P. Kennewell and J. Markandu, *J. Chem. Soc., Chem. Commun.*, 1992, 1537; M. Frederickson, R. Grigg, J. Markandu and J. Redpath, *J. Chem. Soc., Chem.*

Commun., 1994, 2225; H. A. Dondas, R. Grigg and C. S. Frampton, *Tetrahedron Lett.*, 1997, **38**, 5719.
4 R. Grigg, F. Heaney, S. Surendrakamar and W. J. Warnock, *Tetrahedron*, 1991, **47**, 4477.
5 S. R. Landor, in *The Chemistry of the Allenes*, ed. S. R. Landor, Academic Press, London, 1982, vol. 2, pp. 361–397; H. F. Schuster and G. M. Coppola, *Allenes in Organic Synthesis*, Wiley Interscience, New York, 1984; P. Perlmutter, in *Conjugate Addition Reactions in Organic Synthesis*, Tetrahedron Organic Chemistry Series, Volume 9, Pergamon Press, Ltd., 1992.
6 J. March, *Advanced Organic Chemistry*, Wiley Interscience, New York, 1985, 3rd edn., pp. 664–672.
7 R. Grigg, T. R. Perrior, G. J. Sexton, S. Surendrakumar and T. Suzuki, *J. Chem. Soc.*, *Chem. Commun.*, 1993, 372.
8 M. E. Fox, A. B. Holmes, I. T. Forbes and M. Thompson, *J. Chem. Soc.*, *Perkin Trans. 1*, 1994, 3379.
9 G. A. Pinna, M. A. Pirisi and G. Paglietti, *J. Chem. Res.* (*S*), 1990, 360; G. A. Pinna, M. A. Pirisi and G. Paglietti, *J. Chem. Res.* (*S*), 1993, 210; S. E. Korostova, S. G. Shevchenko and V. V. Shcherbakov, *Zh. Org. Khim*, 1993, **29**, 1639 (*Chem. Abstr.*, 1994, **121**, 255563v); V. Gómez, A. Pérez-Medrano and J. M. Muchowski, *J. Org. Chem.*, 1994, **59**, 1219; P. S. Branco, S. Prabhakar, A. M. Lobo and D. J. Williams, *Tetrahedron*, 1992, **48**, 6335.
10 I. Yavari and A. Ramazani, *Synth. Commun.*, 1997, **27**, 1449.
11 E. Winterfeldt and W. Krohn, *Angew. Chem.*, *Int. Ed. Engl.*, 1967, **6**, 709.
12 R. Huisgen and M. Christl, *Chem. Ber.*, 1973, **106**, 3291.
13 (*a*) D. Lathbury and T. Gallagher, *Tetrahedron Lett.*, 1985, **26**, 6249; (*b*) D. Lathbury and T. Gallagher, *J. Chem. Soc.*, *Chem. Commun.*, 1986, 1017; (*c*) J. Grimaldi and A. Cormons, *Tetrahedron Lett.*, 1985, **26**, 825.
14 (*a*) R. W. Lang and H.-J. Hansen, *Helv. Chim. Acta*, 1980, **63**, 483; (*b*) G. Buono and J. R. Llinas, *J. Am. Chem. Soc.*, 1981, **103**, 4532; (*c*) K. N. Houk, in *Pericyclic Reactions*, ed. A. March and R. E. Lehr, Academic Press, New York, 1977, vol. 11, p. 181; (*d*) A much improved synthetic route to allene-1,3-dicarboxylates has appeared during the preparation of this manuscript—M. Node, T. Fujiuara, S. Ichihashi and K. Nishide, *Tetrahedron Lett.*, 1998, 6331.
15 Y. Naruse, S. Katita and A. Tsunekawa, *Synlett*, 1995, 711.
16 W. Verboom, E. O. M. Orlemans, H. J. Berga, M. W. Scheltinga and D. N. Reinhoudt, *Tetrahedron*, 1986, **42**, 5053; M. S. El-Hossini, K. J. McCullough and G. R. Proctor, *Tetrahedron Lett.*, 1986, **27**, 3783.
17 1,3-Dipolar cycloaddition to allenes has been the subject of two recent reviews; A. Padwa, M. Meske and Z. Ni, *Tetrahedron*, 1995, **51**, 89; G. Broggini and G. Zecchi, *Gazz. Chim. Ital.*, 1996, **126**, 479.
18 S. Blechert, *Synthesis*, 1989, 71.
19 G. M. Sheldrick, *Acta Crystallogr.*, *Sect. A*, 1990, **46**, 467.
20 G. M. Sheldrick, SHELXL-97 a computer program for crystal structure determination, University of Göttingen, 1997.
21 P. McArdle, *J. Appl. Crystallogr.*, 1995, **28**, 65.

Paper 8/08167K