The influence of oxime stereochemistry in the generation of nitrones from \(\omega\)-alkenyloximes by cyclization or 1,2-prototropy

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Thermally induced cyclization of the anti-alkenyl oximes \(E\)-7a,b and \(E\)-17a,b affords cyclic \(\alpha\)-alkoxy carbonylnitrones 8 and the 6,7-bicyclic nitrones 18, respectively. The syn-oximes \(Z\)-7b and \(Z\)-17b react via an alternate pathway to give exclusively the fused isoxazolidine derivatives 10b and 19b, respectively. These oximes are configurationally stable at high temperatures with the energy barrier to isomerization being greater than that to cyclization/cycloaddition. Neither the tert-butyl derivative 7c nor the \(\omega\)-alkenyl oxime 7d share this characteristic and in these cases the products of thermal activation are independent of the geometry of the starting oxime. For 7c the energy barriers to oxime rotation and cyclization or cycloaddition are sufficiently close to allow all three reactions to proceed. With 7d, cis–trans isomerization and cyclization are the only observed reactions.

Introduction

The 1,3-dipolar cycloaddition can accomplish the synthesis of a range of highly functionalised stereochemically complex five-membered rings. The isoxazolidines/isoxazolines which are the primary adducts from reaction between nitrones and alkynes/alkynes have a labile \(N\)-O bond easily cleaved under reductive or oxidative conditions, consequently this reaction is often used as a key step in targeted syntheses. The most general methods for nitrene preparation include oxidation of secondary amines (useful for the preparation of both cyclic and acyclic nitrones) and condensation between an \(N\)-substituted hydroxylamine and a carbonyl compound. Many nitrones are isolable, stable compounds especially those with a \(C\)-aryl substituent and in the absence of any stabilizing substituent the nitrene may dimerize or trimerize and so may be best generated \textit{in situ}. In a recent communication we have described the preparation of highly functionalized cyclic nitrones from alkenyloximes. \(\omega\)-Alkenyloximes may form nitrones by one of two routes; they may tautomerize to form an acyclic \(NH\)-nitrene 1, the dipolar structure represents the less stable tautomer and to date no examples of the unsubstituted dipole have been isolated, their existence being substantiated through the formation of an intramolecular cycloaddition product 2. This tandem process has been named the intramolecular oxime olefin cycloaddition reaction (IOOC) [Scheme 1(a)]. Secondly alkenyloximes may

\[
\begin{array}{ccc}
\text{(a)} & & \\
\begin{array}{c}
\text{Scheme 1 Dipole formation from oximes; (a) intramolecular oxime–olefin cycloaddition (IOOC) and (b) intramolecular 1,3-azaprotio cyclotransfer reaction (APT)}
\end{array}
\end{array}
\]

undergo an intramolecular cyclization reaction [1,3-azaprotio cyclotransfer (APT)] forming the cyclic nitro 3. Numerous examples exist where the olefinic moiety is activated (electron deficient), \(\text{H}^4\)-unassisted cyclization is much less common and to date has generally involved only aldoximes [Scheme 1(b)]. Alkynylhydroxylamines \(4\) undergo a related pericyclic reaction effective for the formation of 5-, 6- and 7-membered cyclic nitrones 5. An initial ene-like cyclization (reverse Cope elimination) \(7\) is followed by proton transfer and tautomerism (Scheme 2). In the current example the \(N\)-O–H unit of the oxime adds across the internal C=C double bond in a concerted fashion giving the cyclic dipole. For certain oximes the two modes of reactivity illustrated in Scheme 1 are in competition and the preferred reaction path in any given case will be that of lowest energy.

Results and discussion

The oximes \(7\) were prepared in two steps from their parent \(\alpha\)-keto acids; esterification with the corresponding alcohol proceeded in high yield to give the \(\alpha\)-oxo esters \(6\) which were converted to the oximes \(7\) following reaction with hydroxylamine (Tables 1 and 2). Transformation of \(6a\) gave a single diastereoisomer \(E\)-7a (65%) whilst \(6b,c,d\) each gave both

\[
\begin{array}{ccc}
\text{Scheme 2 Dipole formation from alkynylhydroxylamines}
\end{array}
\]

anti and syn isomers, with the \(E\)– and \(Z\)-isomers being easily separated by flash chromatography. Oxime stereochemical assignment can be made in a number of ways; by \(\text{H}^1\)NMR...
Table 1: Selected UV–Visible and $^{13}$C NMR data for the oximes 7

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\lambda_{	ext{max}}$/nm</th>
<th>MeOH</th>
<th>0.03% Methanolic NaOH</th>
<th>$^{13}$C NMR resonance of imino carbon atom (δ/ppm)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-7a</td>
<td>221.77</td>
<td>260.11</td>
<td>149.2</td>
<td></td>
</tr>
<tr>
<td>E-7b</td>
<td>243.44, 233.44, 218.43</td>
<td>273.44, 243.44, 225.11</td>
<td>151.6</td>
<td></td>
</tr>
<tr>
<td>Z-7b</td>
<td>209.45</td>
<td>210.11</td>
<td>149.6</td>
<td></td>
</tr>
<tr>
<td>E-7c</td>
<td>—</td>
<td>—</td>
<td>151.4</td>
<td></td>
</tr>
<tr>
<td>Z-7c</td>
<td>—</td>
<td>—</td>
<td>148.7</td>
<td></td>
</tr>
<tr>
<td>E-7d</td>
<td>243.44, 208.44</td>
<td>273.44, 225.11, 206.78</td>
<td>151.8</td>
<td></td>
</tr>
<tr>
<td>Z-7d</td>
<td>250.10, 213.44</td>
<td>256.78, 208.44</td>
<td>149.8</td>
<td></td>
</tr>
</tbody>
</table>

* $^{13}$C NMR spectra were taken in CDCl$_3$.

Table 2: Analytical data for the $\alpha$-oxo esters 6 and 16 and the corresponding oximes 7 and 17

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molecular formula</th>
<th>Yield (%)</th>
<th>Physical properties</th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>6b</td>
<td>C$_4$H$_5$NO$_2$</td>
<td>81</td>
<td>bp: 126–128°C, 0.1 mmHg</td>
<td>69.19</td>
<td>5.40</td>
<td>0</td>
</tr>
<tr>
<td>6d</td>
<td>C$_4$H$_5$NO$_2$</td>
<td>90</td>
<td>bp: 90–94°C, 0.3 mmHg</td>
<td>70.37</td>
<td>5.94</td>
<td>0</td>
</tr>
<tr>
<td>16a</td>
<td>C$_4$H$_5$O$_2$</td>
<td>85</td>
<td>bp: 93–95°C, 2.0 mmHg</td>
<td>75.21</td>
<td>6.84</td>
<td>0</td>
</tr>
<tr>
<td>16b</td>
<td>C$_4$H$_5$O$_2$</td>
<td>90</td>
<td>mp: 29–30°C</td>
<td>75.00</td>
<td>6.82</td>
<td>0</td>
</tr>
<tr>
<td>Z-7b</td>
<td>C$_4$H$_5$NO$_2$</td>
<td>38</td>
<td>bp: 110–112°C, 0.3 mmHg</td>
<td>80.54</td>
<td>5.72</td>
<td>0</td>
</tr>
<tr>
<td>E-7b</td>
<td>C$_4$H$_5$NO$_2$</td>
<td>55</td>
<td>mp: 90–94°C (benzene–pet. spirit)</td>
<td>64.17</td>
<td>5.07</td>
<td>6.84</td>
</tr>
<tr>
<td>Z-7c</td>
<td>C$_4$H$_5$NO$_2$</td>
<td>45</td>
<td>$R$, 0.88 (Et$_2$O–pet. spirit, 1:4)</td>
<td>64.59</td>
<td>5.37</td>
<td>6.87</td>
</tr>
<tr>
<td>E-7c</td>
<td>C$_4$H$_5$NO$_2$</td>
<td>20</td>
<td>mp: 110–111°C (benzene–pet. spirit)</td>
<td>69.08</td>
<td>7.32</td>
<td>5.33*</td>
</tr>
<tr>
<td>Z-7d</td>
<td>C$_4$H$_5$NO$_2$</td>
<td>49</td>
<td>bp: 138°C, 0.025 mmHg</td>
<td>65.48</td>
<td>5.67</td>
<td>6.21*</td>
</tr>
<tr>
<td>E-7d</td>
<td>C$_4$H$_5$NO$_2$</td>
<td>47</td>
<td>mp: 46–48°C (benzene–pet. spirit)</td>
<td>65.75</td>
<td>5.94</td>
<td>6.39</td>
</tr>
<tr>
<td>E-17a</td>
<td>C$_4$H$_5$NO$_2$</td>
<td>94</td>
<td>mp: 69–71°C (benzene–pet. spirit)</td>
<td>69.33</td>
<td>7.08</td>
<td>7.59</td>
</tr>
<tr>
<td>Z-17b</td>
<td>C$_4$H$_5$NO$_2$</td>
<td>70</td>
<td>mp: 100–101°C (benzene–hexane)</td>
<td>75.77</td>
<td>6.04</td>
<td>5.81*</td>
</tr>
<tr>
<td>E-17b</td>
<td>C$_4$H$_5$NO$_2$</td>
<td>23</td>
<td>mp: 123–124°C (benzene–hexane)</td>
<td>75.89</td>
<td>5.93</td>
<td>5.53</td>
</tr>
</tbody>
</table>

* Microanalytical data reported for the major oxime isomer only; satisfactory data have also been obtained for the minor isomer.

utilization of through-space effects, by $^{13}$C or $^{14}$N NMR spectra studies, and by examination of $J_{CH}$ coupling constants for aldoximes. In this case assignment was based largely on UV π→π* absorption; (E)-1,2-hydroxymino ketones are known to exhibit a bathochromic shift when their spectra, recorded in basic solution (MeOH–NaOH), are compared with those measured in neutral solution (MeOH), whereas Z-isomers show no such effect. The anti oximes E-7a,b,c showed a shift of ca. 30 nm under these conditions whilst the syn-isomers Z-7b,c showed very little change. Additionally in each case the $^{13}$C-resonance signal for the hydroxymino carbon atom for the E-isomers appeared downfield of the corresponding signal for the Z-isomers. Finally irradiation of the hydroxymino proton gave a positive enhancement on to the Cu-substituent in the E-oxime series whilst no effect was observed with the Z-isomers (Table 1).

The propensity for (E)-prop-2-enyl 2-(hydroxymino)propanoate to behave as a dipole precursor was investigated: heating a solution of E-7a in each of MeOH, DMF or C$_6$H$_6$ at reflux temperature resulted only in returned starting material. In boiling xylene reaction was slow, however heating in boiling mesitylene effected complete conversion of the substrate to products. The dipole 8a was isolated in 85% yield and mixed isomers of the dimeric compounds 9a in 5% yield. None of the alternative bicyclic furoisoxazolone 10a was detected. 1,3-Oxazolin-5-one 3-oxides 11, the 5-ring analogues of 8, have been generated from reaction of isonitroso Meldrum’s acid with various ketones. The separated oxime isomers E- and Z-7b were independently heated in boiling xylene. After 30 h the anti-oxime E-7b had reacted exclusively in a 6-exo-trig cyclization affording 8b in 85% yield whilst the syn-oxime Z-7b reacted more slowly yielding the furoisoxazolone 10b (70% conversion of starting material after 36 h) (Tables 3 and 4). Evidently each oxime is geometrically stable under the reaction conditions and the Z-isomer reacts only by path (a), whilst the E-oxime reacts specifically via path (b), Scheme 1. That oxime geometry may have a defining influence on reactivity has been observed in many cases, for example in a recent report Tiecco et al. have shown that, depending on its geometry, the oxime group can act as either an oxygen or a nitrogen nucleophile in the intra-
molecular selenium-induced cyclizations of \( \alpha \)-alkenyl oximes generating 1,2-oxazines or cyclic nitrones respectively,\(^{13a}\) and Noguchi’s group have demonstrated that only the \( \text{E} \)-oxime ethers \( 12 \) participate in an intramolecular azepine-forming reaction whilst \( \text{Z} \)-isomers remain unchanged under the same experimental conditions.\(^{13b}\)

In an effort to probe the generality of the reaction (\( E \rightarrow 8 \) and \( Z \rightarrow 10 \)) and in particular its tolerance to substitution and ring size the oximes \( 7c,d \) were prepared. It was anticipated that the introduction of a tert-butyl substituent on the alkenyl chain in the oximes \( 7 \) e may invoke diastereoselectivity in both the APT reaction (leading to \( 8 \)) and in the IOOC reaction (leading to \( 10c \)). The separated oxime isomers \( E \)-7c and \( Z \)-7c were heated in boiling xylene and the following points noted (i) the isomers were shown to be devoid of thermal stability and (ii) in each case reaction was slower than that observed for the unsubstituted analogue \( 7b \). Following the heating of \( E \rightarrow 7c \) the reaction products comprised a 5:3:1:5 mixture of the \( \text{syn-oxime Z-7c} \), returned \( \text{anti-oxime E-7c} \), furoisoxazoline \( 10c \) and the cyclic dipole \( 8c \). The same products were obtained in a 4:1:1:2 ratio following reaction with the \( Z \)-oxime \( Z \)-7c.

That oxime interconversion occurs directly rather than by retrocyclization of the dipole \( 8c \) is evident from the thermal stability of the latter which remains unchanged after heating in boiling xylene for 24 h. The cycloadduct \( 10c \) is also stable under these reaction conditions. Significantly the cyclization and cycloaddition products are formed diastereoscopically; for the dipole \( 8c \) NOEDS studies indicate the methyl and tert-butyl substituents are in an 4:1:1:2 ratio following reaction with the \( \text{E} \)-oxime \( E \)-7c. Indeed 7-membered nitrones have been prepared by Holmes and co-workers by cyclization of alk-6-ynylhydroxylamines by the general mechanism outlined in Scheme 2.\(^2a\) Following heating of \( E \rightarrow 7d \) in refluxing xylene, \( 8d \) was formed in 32% yield with unreacted oxime present as a 1:1:1 mixture of \( E \) and \( Z \)-isomers, and a trace amount of the dimeric adducts \( 9d \) accounting for the rest of the reaction material. The low yield of dipole may be attributed to a combination of the following: the increased entropy of activation required for the formation of a 7-membered ring, the reversible nature of dipole formation and/or the influence of the allyl- and butenyl-oxy carbonyl group on the relative reactivity of the olefinic centres in \( 7b \) and \( 7d \). In contrast to the stability of the 6-membered dipole \( 8c \), simply heating a solution of \( 8d \) in boiling mesitylene generated a 1:2 ratio of the isomeric oximes \( E \) and \( Z \)-7d. When the syn-oxime \( Z \)-7d was heated in boiling xylene the reaction products comprised unreacted oxime (75%), as a 2:5 mixture of \( E \) and \( Z \)-isomers, and the cyclic dipole \( 8d \) (15%); none of the anti-

### Table 3 Analytical data for the cyclic nitrones 8 and 18

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molecular formula</th>
<th>Yield (%)</th>
<th>Physical properties</th>
<th>Found (%) (Requires)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>( \text{C}_7\text{H}_7\text{NO}_3 )</td>
<td>85</td>
<td>bp: 115–120 °C, 0.5 mmHg</td>
<td>50.20 (50.35) 6.44 (6.34) 9.67 (9.79)</td>
</tr>
<tr>
<td>8b</td>
<td>( \text{C}_7\text{H}_7\text{NO}_3 )</td>
<td>85</td>
<td>mp: 94–95 °C (benzene–pet. spirit)</td>
<td>64.56 (64.68) 5.37 (5.35) 6.83 (6.78)</td>
</tr>
<tr>
<td>8c</td>
<td>( \text{C}_7\text{H}_7\text{NO}_3 )</td>
<td>33</td>
<td>mp: 93–95 °C (benzene–pet. spirit)</td>
<td>69.07 (68.97) 7.34 (7.28) 5.49 (5.36)</td>
</tr>
<tr>
<td>8d</td>
<td>( \text{C}_7\text{H}_7\text{NO}_3 )</td>
<td>32</td>
<td>mp: 105–110 °C (benzene–pet. spirit)</td>
<td>65.56 (65.75) 6.04 (5.94) 6.21 (6.39)</td>
</tr>
<tr>
<td>18a</td>
<td>( \text{C}_7\text{H}_7\text{NO}_3 )</td>
<td>98</td>
<td>bp: 119–123 °C, 0.6 mmHg</td>
<td>68.91 (69.11) 6.74 (6.81) 7.54 (7.33)</td>
</tr>
<tr>
<td>18b</td>
<td>( \text{C}_7\text{H}_7\text{NO}_3 )</td>
<td>92</td>
<td>bp: 119–120 °C (benzene–pet. spirit)</td>
<td>75.79 (54.77) 7.77 (6.22) 5.63 (5.53)</td>
</tr>
</tbody>
</table>

### Table 4 Analytical data for the isoxazolo-fused adducts 10 and 19

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molecular formula</th>
<th>Yield (%)</th>
<th>mp°C*</th>
<th>Found (%) (Requires)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10a</td>
<td>( \text{C}_7\text{H}_7\text{NO}_3 )</td>
<td>4</td>
<td>80–81</td>
<td>50.43 (50.35) 6.44 (6.34) 10.02 (9.79)</td>
</tr>
<tr>
<td>10b</td>
<td>( \text{C}_7\text{H}_7\text{NO}_3 )</td>
<td>66</td>
<td>133–136</td>
<td>64.66 (64.39) 5.15 (5.37) 6.68 (6.83)</td>
</tr>
<tr>
<td>10c</td>
<td>( \text{C}_7\text{H}_7\text{NO}_3 )</td>
<td>7</td>
<td>136–137</td>
<td>68.99 (68.97) 7.44 (7.28) 5.29 (5.36)</td>
</tr>
<tr>
<td>19b</td>
<td>( \text{C}_7\text{H}_7\text{NO}_3 )</td>
<td>58</td>
<td>110–112</td>
<td>75.69 (75.89) 5.66 (5.93) 5.34 (5.53)</td>
</tr>
</tbody>
</table>

\* From benzene–pet. spirit.
pated pyranooxazolone 10d resulted. Clearly both oximes E- and Z-7d suffer partial isomerization under the reaction conditions studied. The failure of Z-7d to partake in the IOOC reaction sequence is consistent with Hassner’s observations that whilst the unsaturated aldoximes 14a underwent smooth trans-formation to the furooxazoles 15a the homologous 14b failed to form the corresponding pyranooxazoles 15b under the same experimental conditions.34 These results suggest that the transition state required for the formation of the 6,5-bicyclic skeleton is more difficult to attain than the corresponding 5,5-skeleton. That this difficulty can be overcome by judicious positioning of the aldoxime and alkene functions is suggested from Oppolzer’s observation that 2-allyloxybenzaldehyde underwent smooth trans-formation to the corresponding pyranoisoxazoles 18a,b, c,5 and unchanged oxime (25%). The cycloadduct was obtained as a single diastereoisomer with cis stereochemistry at the BC ring junction assigned on the basis of NOEDS results.

Conclusions

In all the cyclization reactions hydroquinone (1% w/v) was added to the reaction solvent to prevent its decomposition on prolonged heating and since both the dipoles (8 and 18) and the cycloadducts (10 and 19) form in such high yields under these conditions a radical based reaction mechanism is not favoured in either reaction path (Scheme 1). Formation of the cyclic nitrones is via a concerted pericyclic mechanism and the anti-oxime isomers E-7a,b readily attain the necessary geometry for the 6,5-bicyclic transition state (Scheme 3), therefore the APT reaction does not suffer competition from oxime isomerization or tautomerism to the corresponding NH-dipole under the reaction conditions (E1 < E2, Scheme 4). The oxime E-7c on the other hand with its bulky tert-butyl substituent displays remarkable sensitivity to substitution and oxime isomerization and cycloaddition (IOOC) compete effectively with the proposed APT reaction (E1′ = E2′ = E3). In the case of the ϵ-alkenyl oxime E-7d a 7,5-bicyclic transition state must be reached to allow formation of the oxazeinone N-oxide 8d (Scheme 3), this requirement places significant demands on the open chain structure and consequently dipole generation is accompanied by EIZ oxime isomerization, however the Z-7d so

geometrical isomers E-17b and Z-17b are distinguished on the basis of their 14C NMR data with the E-isomer having the more downfield imino carbon signal (CDCl3, 155.7 vs. 158.6 ppm).

The oxime E-17a underwent quantitative conversion to the 6,7-bicyclic dipole 18a following heating (14 h) in boiling xylene, E-17b reacted similarly giving 18b after just 5 h heating. Clearly the incorporation of the aryl ring in the chain linking the oxime to the alkene significantly reduces the conformational mobility of the reacting centres in E-17 making dipole formation facile compared to that previously observed with the open chain substrate E-7d. The syn-oxime Z-17b also reacted in a chemospecific manner and after 50 h heating in refluxing xylene the reaction products comprised the benzofuroisoxazole 19b (58%) and unchanged oxime (25%).
formed is unable to undergo the IOOC reaction as the energy barrier to the formation of the 6,5-bicyclic adduct 10d is too great (\(E_a \sim E_Z = E_E > E_b\)). The conformationally constrained analogues E-17 more easily attain the necessary approach of reacting centres for the 7-endo-trig cyclization (Scheme 3) and they thermally cyclize to the corresponding benzoxazepine N-oxides 18 in excellent yield.

With the \(\alpha\)-oxime isomers Z-7b and Z-17b attainment of the transition state for direct formation of cyclic dipoles is impossible to achieve. Therefore there are only two reaction paths available to these substrates viz., isomerization to the E-oxime (and then possible cyclization) or a tautomerism to the corresponding NH-dipole and intramolecular cycloaddition (IOOC). The open chain \(\alpha\)-alkenyl oxime Z-7b and the conformationally restricted \(\alpha\)-alkenyl oxime Z-17b reacted chemoselectively via the IOOC route giving single stereoisomeric isoxazolone fused adducts in each case, no oxime isomerization occurring (\(E_a < E_E < E_Z\)). On the contrary, the tert-butyl substituted \(\alpha\)-alkenyl oxime Z-7c and the open chain \(\alpha\)-alkenyl oxime Z-7d suffered from facile oxime interconversion and when equilibrium had been reached the products from thermal activation of these \(\alpha\)-oximes were identical to those obtained from the corresponding \(\alpha\)-anti-isomers under the same experimental conditions.

Analogously, whilst an attempt to isomerize E-7a to the Z-isomer by heating in boiling water resulted in the loss of much of the reaction material, the furiosoxazolone 10a was isolated in small yield (4%) together with unchanged starting oxime (16%). Similar treatment of E-23b gave the adduct 10b in 67% yield together with both E- and Z-oxime isomers (10 and 15%, respectively). These observations suggest that oxime isomerization is more facile in water and indeed it has earlier been noted that the relative stability of iminoxyl radicals from benzaldehyde oxime shows a remarkable solvent dependency.13e

The relatively slow rate of oxime isomerization compared with simple imines has recently been exploited in a study of the effect of \(E/Z\) isomerization on the asymmetric hydrogenation of prochiral C=N bonds.14c The enantioselectivity of the reaction was shown to reflect the \(E/Z\) ratio of 1-acectonaphthone oxime. The oximes 7 and 17 chosen in this study, like 1-acectonaphthone oxime, are conjugated ketoximes and therefore the barrier to rotation is expected to be high and the products of reaction likely to reflect the geometry of the starting oxime. In contrast the oximes 14 employed in Hassner’s thermal IOOC study are all unconjugated aldoximes carrying a single substituent on the \(\alpha\)-carbon atom, the barrier to geometrical inversion would therefore be expected to be much lower thus explaining why in this case the products of reaction are independent of the stereochemistry of the starting oximes.15d

Thermal cyclization of the conjugated \(\alpha\)-alkenyl oximes E-7a,b and E-17 provides easy access to geometry fixed \(\alpha\)-alkoxyacarborylnitrones 8 and benzoazepine N-oxides 18, respectively. These interesting nitrones are reactive 1,3-dipoles and their cycloadditive behaviour will be discussed in a forthcoming paper.

**Experimental**

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer model 240 CHN analyser. 1H NMR spectra were recorded using a JEOL EX90 FT NMR and a JEOL EX270 FT NMR spectrometer at probe temperatures with tetramethylsilane as internal reference and deuteriochloroform as solvent. J Values are given in Hz. Flash column chromatography was carried out on silica gel 60 (Merck 9385, 70–230 mesh or 40–60 mesh), analytical TLC plates were purchased from Merck. Samples were located by UV illumination using a portable Spectroline Hanovia lamp (\(\lambda =254\) nm) or by the use of iodine staining. All solvents used were purified by standard procedures and pet. spirit refers to that fraction of petroleum spirits boiling between 40–60°C.

**Prop-2-alkyl benzoxazepine 6b**

A solution of benzoic acid (4.0 g, 27 mmol), prop-2-en-1-ol (2.35 g, 40 mmol) and a catalytic amount of toluene-p-sulfonic acid in benzene (100 cm³) was boiled in reflux (16 h) using a Dean-Stark apparatus. The reaction mixture was allowed to cool to room temp., washed firstly with sat. aq. NaHCO₃ (2 × 150 cm³) and then H₂O (150 cm³). The organic layer was collected, dried (Na₂SO₄) and concentrated to furnish the crude product as a yellow oil. Following fractional distillation the title compound was obtained as a colourless oil (4.1 g, 81%). \(\delta_\text{H} = 4.87\) (d, 2H, OCH₃), 5.40 (m, 2H, CH₂=CH₂), 6.02 (m, 2H, CH₂=CH₂), 7.49 (m, 2H, p-Ar-H), 7.50 (m, 2H, m-Ar-H), 7.68 (t, 1H, p-Ar-H), 8.01 (d, 2H, o-Ar-H); \(\delta_\text{C} = 66.2\) (OCH₃), 119.5 (CH=CH₂), 128.7 (2 × m-Ar-C), 129.7 (2 × o-Ar-C), 130.6 (p-Ar-C), 133.1 (Ar-C), 134.7 (CH=CH₂), 163.2 (C=O, ester), 185.9 (C=O, ketone).

**4,4-Dimethylpent-1-en-3-yl benzoxazepine 6c**

Benzoylformic acid (1.60 g, 11 mmol), 4,4-dimethylpent-1-en-3-ol17 (1.48 g, 13 mmol) and a catalytic amount of toluene-p-sulfonic acid were stirred in benzene (60 cm³) at reflux using a Dean-Stark apparatus for 13 h (care was taken to ensure that the temperature of the oil bath did not rise above 100°C). The reaction mixture was allowed to cool to room temp. before washing firstly with sat. aq. NaHCO₃ solution (2 × 100 cm³) and then H₂O (100 cm³). After drying (Na₂SO₄) the organic layer was concentrated to yield the crude product, a yellow oil (2.04 g, 75%), which was used without further purification.

(Duration of the concentration step, the temperature of the water bath was not allowed to rise above 65°C.) \(\delta_\text{H} = 1.04\) (s, 9H, 3 × Me), 4.83 (d, 1H, OCH, J 6.60), 5.50 (m, 2H, CH=CH₂), 5.90 (m, 1H, CH=CH₂), 6.75–6.77 (2 × m, 3H, 2 × m and p-Ar-H), 7.39 (m, 2H, o-Ar-H); \(\delta_\text{C} = 26.6\) (3 × Me), 34.4 (CMe₂), 66.2 (OCH₃), 119.5 (CH=CH₂), 130.0–128.8 (4 × Ar-C), 134.8 (CH=CH₂), 163.6 (C=O, ester), 186.6 (C=O, ketone).

**But-3-enyl benzoxazepine 6d**

A solution of benzoic acid (11.80 g, 79 mmol), but-3-en-1-ol (8.64 g, 120 mmol) and a catalytic amount of toluene-p-sulfonic acid in benzene (325 cm³) was boiled under reflux (9 h) using a Dean-Stark apparatus. The reaction mixture was allowed to cool to room temp, washed firstly with sat. aq. NaHCO₃ (2 × 100 cm³) and then H₂O (2 × 100 cm³). The organic layer was collected, dried (Na₂SO₄) and concentrated to furnish the crude product as a yellow oil. Following fractional distillation, 6d was obtained as a colourless oil (14.4 g, 90%). \(\delta_\text{H} = 2.40\) (m, 2H, OCH₂CH₂), 4.38 (t, 2H, OCH₃), 5.08 (m, 2H, CH=CH₂), 5.77 (m, 1H, CH=CH₂), 7.39 (t, 2H, m-Ar-H), 7.59 (1H, p-Ar-H), 7.98 (d, 2H, o-Ar-H); \(\delta_\text{C} = 32.5\) (OCH₂CH₂), 64.7 (OCH₃), 117.5 (CH=CH₂), 128.5 (2 × m-Ar-C), 129.6 (2 × o-Ar-C), 132.9 (p-Ar-C), 134.5 (Ar-C), 134.6 (CH=CH₂), 163.2 (C=O, ester), 186.0 (C=O, ketone).

(E)-Prop-2-alkyl-2-(hydroxyimino)propanoate E-7a

The title compound was prepared according to literature procedure1a and was obtained as colourless plates (5.11 g, 65%), mp 86°C (lit.,18 84–86°C).

**Prop-2-alkyl-2-(hydroxyimino)-2-phenylacetate Z-7b and E-7b**

The \(\alpha\)-keto ester 6b (1.20 g, 6.3 mmol), hydroxylamine hydrochloride (0.66 g, 9.5 mmol) and sodium acetate (0.78 g, 9.5 mmol) were stirred in H₂O (50 cm³) at 70°C for 14 h. The reaction mixture was allowed to cool to room temp. and with \(\delta_\text{H} (\text{CH}_3) (2 \times 50 \text{ cm}^3)\). The organic layers were combined, washed with H₂O (2 × 50 cm³), dried (Na₂SO₄) and concentrated to yield the crude products as a yellow gum. Separation by flash chromatography (EtO₂/pet. spirit, 1:2:2)


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gave the syn-isomer Z-7b a colourless oil (0.49 g, 38%) and the anti-isomer E-7b a white solid which crystallized to colourless needles (0.71 g, 55%). Z-7b: δ_H 0.97 (d, 2H, OCH_2), 3.92 (m, 3H, C=CH), 7.42 (m, 3H, 5- and 7-ar-H). 7.52 (m, 2H, ox-Ar-H), 10.18 (br s, 1H, OH); δ_C 29.1 (3 × Me), 33.3 (CMe_2), 67.0 (OCH_3), 118.0 (CH=CH), 130.2–130.6 (4 × Ar-C), 135.5 (CH=CH), 148.7 (C=O), 163.5 (C=O). E-7c: δ_H 0.97 (s, 9H, 3 × Me), 4.70 (d, 1H, OCH, J 6.59), 5.52 (m, 1H, CH=CH), 5.81 (d, 2H, CH=CH, J 15.39), 7.42 (3m, 3H, m- and p-ar-H), 7.52 (m, 2H, ox-Ar-H), 10.18 (br s, 1H, OH); δ_C 29.1 (3 × Me), 34.0 (CMe_2), 67.3 (OCH_3), 118.0 (CH=CH), 129.9–128.1 (4 × Ar-C), 130.1 (CH=CH), 151.4 (C=O), 163.6 (C=O).

But-3-enyl-2-(hydroximino)-2-phenylacetate Z-7d and E-7d

The α-keto ester 6d (11.12 g, 55 mmol) of hydroxylamine hydrochloride (0.83 g, 12.0 mmol) and sodium acetate (11.1 g, 135.30 mmol) were stirred in H_2O (60 cm^3) at 65°C for 25 h. The reaction mixture was cooled to room temp, before extracting with CH_2Cl_2 (4 × 80 cm^3). The organic layers were combined, washed with water (50 cm^3), dried (Na_2SO_4) and concentrated to yield the crude products as a colourless gum. Purification by flash chromatography (EtO_2:pet. spirit, 1:6) gave recovered starting material (0.59 g, 30%), syn-isomer Z-7c a colourless oil (0.99 g, 48%), E-7c a white solid, which crystallized to colourless needles (0.43 g, 20%). Z-7c: δ_H 1.02 (s, 9H, 3 × Me), 4.86 (d, 1H, OCH, J 6.59), 5.59 (m, 1H, CH=CH), 5.89 (d, 2H, CH=CH, J 15.38), 7.39 (m, 3H, m- and p-ar-H), 7.55 (m, 2H, ox-Ar-H), 9.02 (br s, 1H, OH); δ_C 29.1 (3 × Me), 33.3 (CMe_2), 67.0 (OCH_3), 118.0 (CH=CH), 130.2–130.6 (4 × Ar-C), 135.5 (CH=CH), 148.7 (C=O), 163.5 (C=O). E-7c: δ_H 0.97 (s, 9H, 3 × Me), 4.70 (d, 1H, OCH, J 6.59), 5.52 (m, 1H, CH=CH), 5.81 (d, 2H, CH=CH, J 15.39), 7.42 (3m, 3H, m- and p-ar-H), 7.52 (m, 2H, ox-Ar-H), 10.18 (br s, 1H, OH); δ_C 29.1 (3 × Me), 34.0 (CMe_2), 67.3 (OCH_3), 118.0 (CH=CH), 129.9–128.1 (4 × Ar-C), 130.1 (CH=CH), 151.4 (C=O), 163.6 (C=O).

4,4-Dimethylpent-1-en-3-yl 2-(hydroxyimino)-2-phenylacetate Z-7e and E-7e

A solution of the oxime E-7a (2.31 g, 22.50 mmol) in H_2O (90 cm^3) at 100 °C was stirred for 48 h. The reaction mixture was cooled to room temp, and was extracted with CH_2Cl_2 (4 × 100 cm^3). The organic layers were combined, dried (Na_2SO_4) and concentrated to yield a yellow solid (0.65 g, 20%), which was purified by flash chromatography (EtO_2) to give unchanged oxime E-7a (0.50 g, 16%) and the adduct 10a (0.13 g, 4%), which crystallized to colourless cubic crystals. Careful evaporation (70 °C, 15 mmHg) of the aqueous layer gave a brown gummy residue (0.19 g, 6%) which was decomposed organic material. δ_H 1.58 (s, 3H, Me), 3.08 (m, 1H, H_3), 3.99 (dd, 1H, H_β, J_α,β 6.9, J_β,δ 9.0, J_δ,α 8.0), 4.15 (dd, 1H, H_δ, J_δ,α 8.0, J_δ,β 9.0), 4.22 (dd, 1H, ox-Ar-H, J 11.5, J 16.0), 7.40 (m, 1H, CH=CH, J 16.0), 7.76 (d, 1H, ox-Ar-H, J 15.5), 8.06 (m, 1H, ox-Ar-H), 8.29 (s, 1H, NH); δ_C 17.0 (Me), 47.8 (C_3), 66.4 (C_6), 69.4 (C_7), 77.6 (C_8), 176.1 (C=O). NOEDS experimental results indicate cis stereochirality at the ring junction, irradiation of H_α caused a 2.9% enhancement on the methyl group.

5,6-Dihydro-5-methyl-1,4-oxazin-2-one N-oxide 8b

A solution of the oxime E-7b (0.90 g, 4.39 mmol) in xylene (250 cm^3) was stirred at 138 °C under a nitrogen atmosphere for 30 h in the presence of hydroquinone (1.0% w/w). The reaction mixture was cooled to room temp, and the solvent was removed under reduced pressure (100 °C, 0.25 mmHg). The solid residue was taken up in CHCl_3 (3 cm^3) and allowed to stand at room temp (0.5 h). The precipitated hydroquinone was removed by filtration in vacuo and the filtrate was concentrated under reduced pressure. Purification of the crude mixture by flash chromatography (EtO_2:pet. spirit, 2:1) gave unchanged starting oxime E-7b (0.02 g, 2%), a dimeric adduct 9b (0.06 g, 7%, colourless cubic crystals, mp 135–158 °C; benzene-pet. spirit) and the dipole 8b (0.77 g, 85%). δ_H 9.63 (s, 1H, ox-Ar-H), 6.35 (m, 1H, CH=CH, J 15.5), 7.42 (3m, 3H, Ar-H), 7.5 (2H, 2 × ox-Ar-H), 10.1 (br s, 1H, OH); δ_C 32.8 (OCH_3), 65.1 (OCH_3), 117.7 (CH=CH), 128.0 (m-ar-C), 128.5 (Ar-C), 129.4 (Ar-C), 132.3 (CH=CH), 149.8 (C=O), 163.3 (C=O).

5,6-Dihydro-3,5-dimethyl-1,4-oxazin-2-one N-oxide 8a

A solution of the oxime E-7a (2.75 g, 19 mmol) in mesitylene (500 cm^3) at 165 °C was stirred under a nitrogen atmosphere for 28 h in the presence of hydroquinone (1/1 w/v). The reaction mixture was cooled to room temp, and the solvent removed under reduced pressure (100 °C, 0.50 mmHg) to give a brown gummy residue which was taken up in CHCl_3 (3 cm^3) and allowed to stand at room temp (0.5 h), the precipitated hydroquinone was removed by filtration in vacuo, and the filtrate was concentrated under reduced pressure. Purification of the crude mixture by flash chromatography (EtO_2:pet. spirit, 2:1) gave unchanged starting oxime E-7b (0.02 g, 2%), a dimeric adduct 9b (0.06 g, 7%, colourless cubic crystals, mp 135–158 °C; benzene-pet. spirit) and the dipole 8b (0.77 g, 85%). δ_H 9.63 (s, 1H, ox-Ar-H), 6.35 (m, 1H, CH=CH, J 15.5), 7.42 (3m, 3H, Ar-H), 7.5 (2H, 2 × ox-Ar-H), 10.1 (br s, 1H, OH); δ_C 32.8 (OCH_3), 65.1 (OCH_3), 117.7 (CH=CH), 128.0 (m-ar-C), 128.5 (Ar-C), 129.4 (Ar-C), 132.3 (CH=CH), 149.8 (C=O), 163.3 (C=O).

10.15 (br s, 1H, OH); δc 15.9 (Me), 45.8 (C6), 56.6 (C5), 65.5 (OCH3), 68.6 (C4), 74.3 (C3), 74.6 (C2), 140.0–126.2 (8 × Ar-C), 149.5 (C-N), 162.9 (C=O, C-O), 171.1 (C=O, ester).

Method A. A solution of the oxime Z-7b (0.76 g, 3.7 mmol) in xylene (225 cm3) was stirred at 138 °C under a nitrogen atmosphere for 36 h in the presence of hydroquinone (1.0% w/w). The reaction mixture was cooled to room temp. and the solvent removed under reduced pressure (100 °C, 0.5 mmHg). The yellow residue was taken up in CHCl3 (2.5 cm3) and allowed to stand at room temp. (0.5 h), the precipitated hydroquinone removed by filtration in vacuo, and the filtrate concentrated. Purification of the crude products by flash chromatography (EtOAc:pet. spirit, 1:0.2) gave unchanged starting oxime Z-7b (0.22 g, 29%), and the adduct 10b, a viscous yellow oil which solidified upon tituration (pet. spirit) (0.5 g, 66%). 10b-δδ 3.57 (m, 1H, H3); 4.21 (m, 2H, H4 and H5); 4.40 (dd, 1H, H6); 6.64 (d, 2H, J3,3′ = 11.6 Hz); 7.22 (m, 7H, 2 × Ar-H); 7.44 (m, 7H, 2 × Ar-H); δc 14.7 (Me), 64.8 (C6), 66.9 (C5), 134.5–127.5 (4 × Ar-C), 136.2 (C3, C=O), 158.9 (C2, C=O).

(3aS,6aS)-Tetrahydro-6a-phenylfurano[3,4-c]isoxazol-6-one 10b

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collected, dried (MgSO₄) and concentrated to yield the crude product as a yellow oil. Following fractional distillation 16a (151.5 g, 78%) was obtained as a colourless oil which solidified upon standing giving colourless plates. δ₂ 2.62 (s, 3H, Me), 4.62 (d, 2H, OCH₂), 5.35 (m, 2H, CH=CH₂), 6.06 (m, 1H, CH=CH₂), 6.95 (m, 2H, Ar-H), 7.39 (m, 1H, Ar-H), 7.75 (m, 1H, Ar-H); δ₃ 31.9 (Me), 69.4 (OCH₂), 112.9 (Ar-C), 118.2 (CH=CH₂), 120.8 (Ar-C), 128.8 (Ar-C), 130.4 (Ar-C), 132.7 (Ar-C), 133.5 (CH=CH₂), 158.0 (Ar-C), 199.9 (C=O).

2-(Prop-2-enyloxy)benzophenone 16b
2-Hydroxybenzophenone (3.96 g, 20 mmol), allyl bromide (3.6 g, 20 mmol) and potassium carbonate (4.15 g, 0.3 mmol) were stirred in EtOH (150 cm³) at 78 °C for 50 h in the presence of hydroquinone (1% w/v). The reaction mixture was cooled to room temp., and the solvent was removed under reduced pressure. To the yellow oily residue was added H₂O (100 cm³) and the resulting aqueous solution was extracted with EtO₂ (4 × 75 cm³). The organic layers were combined, dried (MgSO₄) and concentrated to furnish the crude product. Following fractional distillation 16b (4.0 g, 90%) was obtained as a colourless oil, δ₁ 4.46 (m, 2H, OCH₂), 5.05 (m, 2H, CH=CH₂), 5.72 (m, 1H, CH=CH₂), 7.0 (m, 2H, Ar-H), 7.49 (m, 5H, Ar-H), 7.84 (m, 2H, Ar-H); δ₂ 69.9 (OCH₂), 112.7 (Ar-C), 116.9 (Ar-C), 119.8 (Ar-C), 123.9 (Ar-C), 129.9 (Ar-C), 132.9 (Ar-C), 132.3 (Ar-C), 132.8 (CH=CH₂), 138.1 (Ar-C), 156.3 (Ar-C), 196.6 (C=O).

(E)-2-(Prop-2-enyloxy)acetophenone oxime E-17a
The ketone 16a (6.00 g, 34.00 mmol), hydroxylamine hydrochloride (2.84 g, 40.00 mmol) and pyridine (3.16 g, 40.00 mol) were stirred in EtOH (150 cm³) at 78 °C for 13 h. The reaction mixture was allowed to cool to room temp., and after standing overnight, the reaction solvent was removed under reduced pressure, leaving a yellow gummy residue which was taken up in CH₂Cl₂ (5 × 200 cm³) and dried (Na₂SO₄). The organic layer was concentrated to furnish the crude product which solidified upon trituration with pet. spirit (61 g, 94%). δ₁ 2.17 (s, 3H, Me), 4.48 (d, 2H, OCH₂), 5.25 (m, 2H, CH=CH₂), 5.95 (m, 1H, CH=CH₂), 6.85 (m, 2H, Ar-H), 7.23 (m, 2H, Ar-H), 9.35 (br s, 1H, OH); δ₂ 15.5 (Me), 69.2 (OCH₂), 117.3 (CH=CH₂), 133.5 (CH=CH₂), 154.6–112.8 (6 × Ar-C), 155.0 (C=N).

(2′-Prop-2-enyloxy)benzophenone oxime Z-17b and E-17b
The ketone 16b (4.45 g, 20 mmol), hydroxylamine hydrochloride (1.67 g, 24 mmol) and pyridine (5.56 g, 70 mmol) were stirred in EtOH (150 cm³) at reflux for 16 h. The reaction mixture was cooled to room temp., and left to stand overnight. The solvent was removed under reduced pressure leaving a yellow viscous oil which was taken up in CH₂Cl₂ (150 cm³) and transferred to a separated funnel. The organic layer was washed with H₂O (5 × 100 cm³), dried (Na₂SO₄) and concentrated to yield the isomeric oximes which were purified by flash chromatography (EtO₂:pet. spirit, 1:1) to give the ketone 16b (0.12 g, 12%) as a viscous pale yellow oil, unchanged oxime E-17b (0.90 g, 92%) was obtained as a colourless oil which solidified upon trituration and gave colourless cubic crystals (1.05 g, 21%).

(3aS*,9bS*)-9b-Phenyl-1,3a,4b,9b-tetrahydro-3H-benzofuro-[4,3-c]isoxazole 19b
A solution of the oxime Z-17b (1.04 g, 4.11 mmol) in refluxing xylene (350 cm³) was stirred under an atmosphere of nitrogen for 50 h in the presence of hydroquinone (1% w/v). The reaction mixture was cooled to room temp., and the solvent was removed under reduced pressure. The crude products were purified by flash chromatography (EtO₂:pet. spirit, 1:1) to give the ketone 16b (0.26 g, 25%), and the cycloduct 19 as a yellow gum which solidified upon trituration and gave colourless cubic crystals from benzene–pet. spirit (0.6 g, 58%), δ₁ 3.14 (m, 1H, H²a), 3.78 (dd, 1H, H²b,2A); δ₂ 8.06, 5.33 (3 × Ar-C), 3.95 (dd, 1H, H²b,2A), 11.73 (J₂A,2B), 9.52, 4.17 (dd, 1H, H¹b,3a), 8.06, 7.48, 7.33, 4.32 (dd, 1H, H¹b,3a), 11.72, 7.48, 4.40, 5.61 (br s, 1H, NH), 7.00–6.82 (2 × m, 3H, Ar-H), 7.35–6.82 (3 × m, 4H, Ar-H), 7.49 (m, 2H, o-Ar•••H); δ₂ 50.1 (C=O), 67.3 and 66.0 (C₃ and C₄), 72.4 (C₅), 145.1–117.3 (10 × Ar-C). NOEDS experimental results indicate cis stereochemistry at the ring junction; irradiation of H¹b caused a 4.2% enhancement on the cross ring ArH.

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