# Electrochemical and yeast-catalysed ring-opening of isoxazoles in the synthesis of analogues of the herbicide Grasp®

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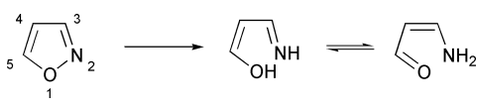
Isoxazoles substituted with an electron-withdrawing group at the 4-position undergo electrochemical and yeast-catalysed N–O bond cleavage. The electrolysis is much more efficient and, with acyl- and alkoxycarbonyl-substituted isoxazoles, it affords the enolised dicarbonylimine functionality characteristic of the herbicide Grasp®. Regioisomeric 4- and 5-substituted isoxazoles are accessible through nitrile oxide cycloaddition chemistry, using halogen as a steric auxiliary to control the regiochemistry of reaction. Crystal data for compounds **11** and **19b** are presented.

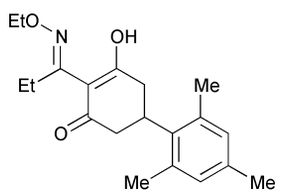
## Introduction

Isoxazoles are aromatic heterocycles as reflected in their electrophilic substitution reactions.[1] However, the aromatic ring is readily disrupted through cleavage of the N–O bond, under reductive conditions (Scheme 1). Most often this transformation



**Scheme 1**

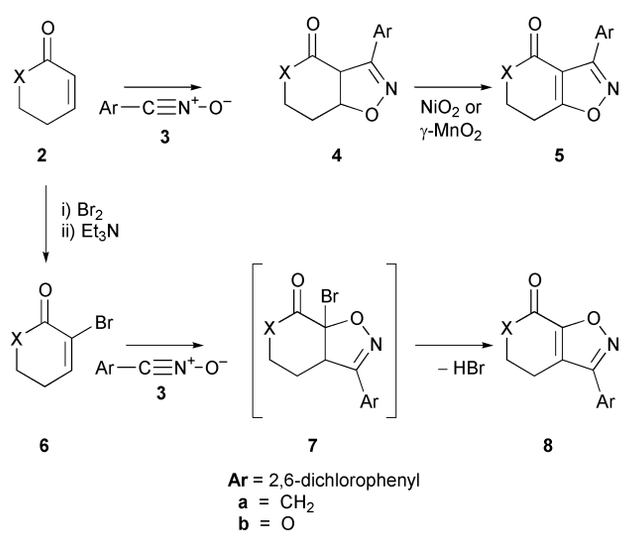
is accomplished through hydrogenolysis[2] but reagents such as sodium,[3] sodium amalgam,[4] Grignard reagents[5] and metal-carbonyl compounds[6] have also been used. Several years ago we reported the only example of yeast-catalysed cleavage of either an aromatic ring or a single bond, with the ring-opening of 4-acyl- and alkoxycarbonyl-substituted isoxazoles.[7] It seemed likely that the reaction occurred *via* an electron transfer process, analogous to that thought to be involved in the yeast-catalysed reduction of aldehydes and ketones. On this basis we envisaged that the transformation might also be accomplished electrochemically. We now report our confirmation of this hypothesis, together with full details of the synthesis of isomeric 4- and 5-acyl- and alkoxycarbonyl-substituted isoxazoles,[8] which were prepared using nitrile oxide cycloaddition reactions and bromine as a steric auxiliary to control the regiochemistry of cycloaddition. Overall, the reaction sequence provides a route for the synthesis of the enolised dicarbonylimine motif of the herbicide Grasp® **1**.[9] The method is complementary to that developed by Jones *et al*.,[10] for the preparation of structurally related compounds through the cycloaddition of nitrile oxides to enamines derived from β-ketoesters.



**1**

## Results and discussion

The ring-opening of isoxazoles catalysed by yeast had been investigated using the bicyclic ketones **5a** and **8a**, and the corresponding lactones **5b** and **8b**, which were consequently employed in this study. The 4-acyl- and alkoxycarbonyl-substituted isoxazoles **5a** and **5b** were obtained through reaction of the nitrile oxide **3** with the 1,2-disubstituted dipolarophiles **2a** and **2b**, respectively, followed by oxidation of the corresponding isoxazolines **4a** and **4b** with either nickel peroxide or γ-activated manganese dioxide (Scheme 2). The



**Scheme 2**

cycloaddition reactions were regiospecific and the regiochemistry may be attributed to the electronic effect of the carbonyl substituent.[11] In order to access the 5-carbonyl-substituted

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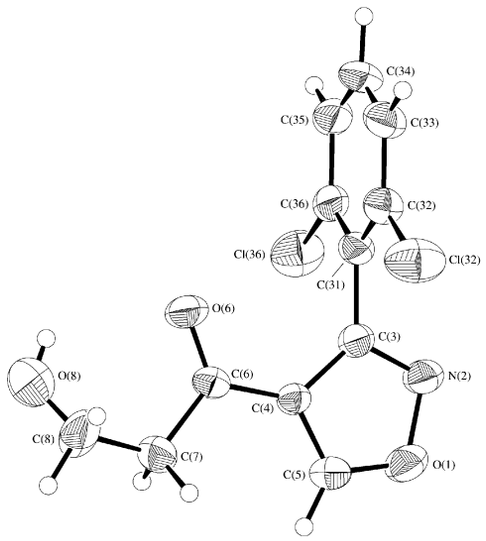



**Fig. 1** Molecular structure and crystallographic numbering scheme employed for the isoxazole **11**.

isoxazoles, it was necessary to reverse the regioselectivity of cycloaddition. This was accomplished by halogenation of the cyclohexenone **2a** and the pyranone **2b** using a variation of the method of Posner *et al.*[12] to give the corresponding bromides **6a** and **6b**, which reacted with the nitrile oxide **3** to afford the isoxazoles **8a** and **8b**, respectively (Scheme 2). Presumably these reactions involve formation of the isoxazolines **7a** and **7b**. In their formation the bromine is acting as a steric auxiliary. It controls the regiochemistry of cycloaddition, which for the 1,1,2-trisubstituted dipolarophiles **6a** and **6b** is determined by steric effects,[13] and is then lost by spontaneous elimination of hydrogen bromide. The structures of compounds **4a**,[14] **5a**[15] and **8a**[16] were confirmed using X-ray crystallographic analysis. The structures of the corresponding pyranones **4b**, **5b** and **8b** were assigned by comparing their $^1$H NMR spectra and other data with those of the analogous ketones **4b**, **5b** and **8b**.

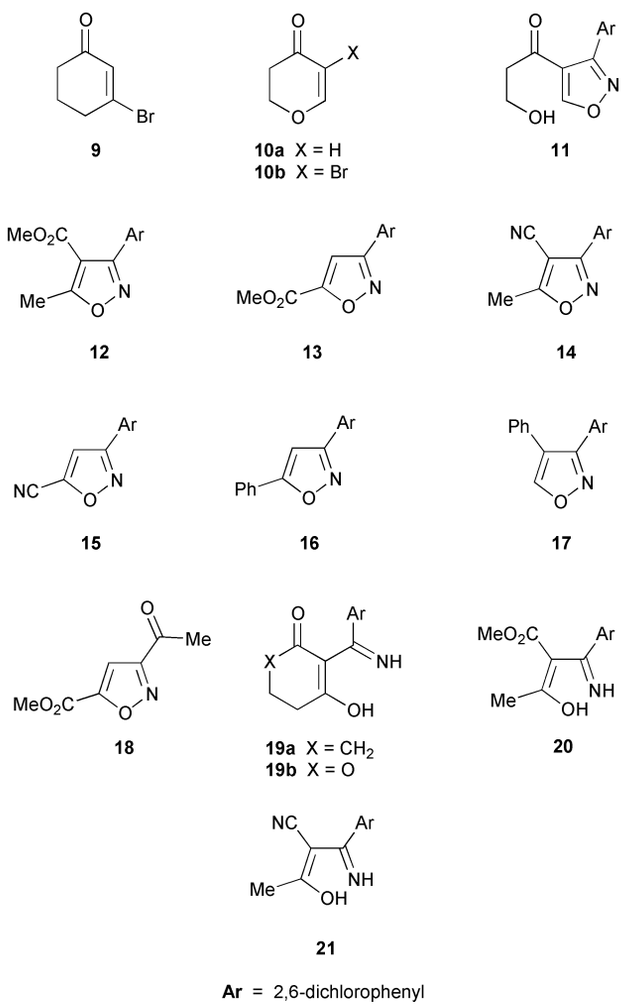
In competitive experiments, with limiting amounts of the nitrile oxide **3**, the relative reactivity of the alkenes **2a**, **2b**, **6a** and **6b** was found to be 1.0 : 1.3 : 0.2 : 0.3. Thus the bromine reduces the reactivity of the dipolarophiles **6a** and **6b**, but not sufficiently to prevent cycloaddition. The bromoenone **9**[17] was approximately half as reactive as its regioisomer **6a**, and reacted with the nitrile oxide **3** to give the isoxazole **5a**. By contrast, the bromopyran-4-one **10b**, prepared by bromination of the pyranone **10a**, was inert to cycloaddition, even though the parent pyranone **10a** reacted with the nitrile oxide **3** to give the isoxazole **11** (Fig. 1). The reactivity of the pyran-4-one **10a** was 0.7 times that of the isomer **2b**.

The electrochemical behaviour of the isoxazoles **12**–**18** was also investigated. The synthesis of several of these compounds had already been reported[18–23] but different methods were used in the present work. The isoxazoles **12** and **13** were prepared through reaction of the nitrile oxide **3** with methyl but-2-ynoate and methyl propiolate, using the procedure reported previously for reaction of benzonitrile oxide.[24] The nitriles **14** and **15** were obtained using crotononitrile and acrylonitrile as dipolarophiles, and oxidation of the intermediate isoxazolines with either nickel peroxide or γ-activated manganese dioxide. The 5-methyl substituents of the isoxazoles **12** and **14** were used as a tool to manipulate the regioselectivity of the cycloaddition reactions which afforded these species.[24] The isoxazoles **16** and **17** were prepared using styrene and β-bromostyrene as dipolarophiles. In the former case the intermediate isoxazoline was oxidised with γ-activated manganese dioxide. In the latter, the bromine acts as a steric auxiliary, to control the regiochemistry of cycloaddition, and is then lost through hydrogen bromide elimination from the intermediate isoxazoline. Reaction of

**Table 1** Reduction potentials of the isoxazoles **5a,b**, **8a,b** and **12**–**18**[a]

| Isoxazole | Reduction potential/V |
|---|---|
| **5a** | −2.2 |
| **5b** | −2.1 |
| **8a** | −2.5 |
| **8b** | −2.5 |
| **12** | −2.3 |
| **13** | −2.4 |
| **14** | −1.4 |
| **15** | −1.7 |
| **16** | −2.0 |
| **17** | −2.4 |
| **18** | −1.4 |

[a] At RT in acetonitrile (0.1 mol dm$^{-3}$ tetrabutylammonium hexafluorophosphate), referenced to Ag/AgCl.




acetylnitrile oxide with methyl propiolate afforded the isoxazole **18**.

Electrolysis of the isoxazoles **5a,b**, **8a,b** and **12**–**18** was carried out at room temperature in acetonitrile (0.1 mol dm$^{-3}$ tetrabutylammonium hexafluorophosphate) under argon, using a mercury coated platinum mesh electrode. The first reduction potential of each compound, relative to Ag/AgCl, is shown in Table 1. These values are only approximate since the reductions are complicated by multiple electron transfer, possibly coupled to chemical steps, and are not chemically reversible. Bulk electrochemical reductions were performed at a potential 0.1–0.2 V more negative than the first reduction potential, as determined by a cyclic voltammetric scan.

Our earlier studies showed that the 4-acyl- and alkoxycarbonyl-substituted isoxazoles **5a** and **5b** underwent yeast-

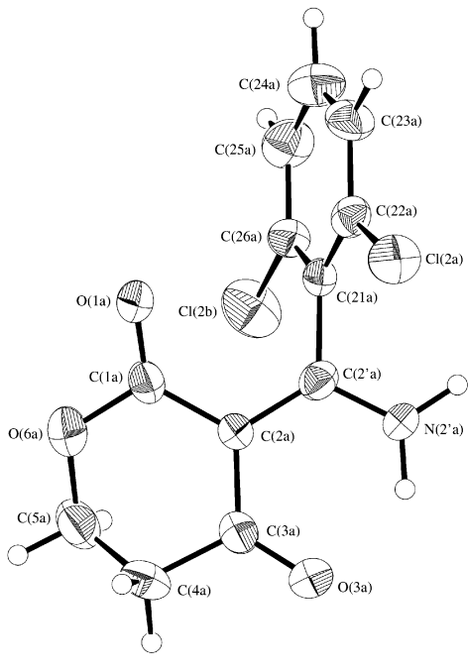



**Fig. 2** Molecular structure and crystallographic numbering scheme employed for molecule *a* of the enolised dicarbonylimine **19b**; the numbering scheme for molecule *b* follows that for *a*.

catalysed ring-opening to give the enolised dicarbonylimines **19a** and **19b**, in yields of 23 and 21%, respectively. By contrast, the corresponding 5-carbonyl-substituted compounds **8a** and **8b** were inert. On electrolysis, the isoxazoles **5a** and **5b** afforded the ring-opened species **19a** and **19b**, in yields of 61 and 66%, respectively. By comparison, the 5-carbonyl-substituted compounds **8a** and **8b** were more resistant to electrochemical reduction than their corresponding regioisomers **5a** and **5b**, as reflected by the reduction potentials. When reduced, the isoxazoles **8a** and **8b** decomposed to give complex mixtures of compounds from which it was impractical to isolate discrete species. Thus, the isoxazoles **5a** and **5b** which were cleaved by yeast also underwent electrolysis to give the ring-opened species **19a** and **19b**, whereas the isoxazoles **8a** and **8b** which did not react with yeast were more resistant to electrolysis and did not give clean products.

The reactivity of the isoxazoles **5a,b** and **8a,b** is therefore dependent on the location of the carbonyl substituent. This is reflected in the electrolysis of the esters **12** and **13** and the nitriles **14** and **15**, where the 4-methoxycarbonyl- and cyano-isoxazoles **12** and **14** gave the ring-opened species **20** and **21**, in 58 and 68% yield, respectively, while the 5-methoxycarbonyl- and cyano-substituted species **13** and **15** were more resistant to reduction and afforded complex product mixtures. Neither of the phenylisoxazoles **16** nor **17** afforded a clean ring-opened species and of these compounds the 4-substituted isomer was the more resistant to electrolysis. The 3,5-dicarbonylisoxazole **18** also failed to give a discrete ring-opened product. These substituent effects indicate that an electron-withdrawing group at the 4-position of an isoxazole makes the ring susceptible to N–O bond cleavage, possibly as a result of conjugation of the ring-oxygen with the 4-substituent through C4 and C5. The effect is therefore seen with acyl-, alkoxycarbonyl- and cyano-groups, but not with phenyl substituents. Instead a phenyl substituent at the 5-position facilitates reduction, as indicated by the electrochemical potentials of the isoxazoles **16** and **17**. This is consistent with the observation that the other reports of electrochemical ring-opening of isoxazoles involve 3-methyl-5-phenyl- and 3,5-diphenyl-substituted species.[25]

The structures of the ring-opened species **19a**[26] and **19b** (Fig. 2) were confirmed through X-ray crystallographic analysis. In non-polar solution these compounds exist as the enolised dicarbonylimines but in the solid state they are present as the corresponding tautomeric dicarbonylenamines, which are stabilised by intermolecular hydrogen bonds. This combination of functional groups is similar to that found in Grasp® **1**, indicating that the methodology outlined above may be suitable for the synthesis of this and related compounds.

## Experimental

Melting points were determined on a Kofler hot-stage apparatus under a Reichert microscope and are uncorrected. $^1$H NMR spectra were recorded on either a Bruker ACP-300, a Varian Gemini 300 or a Varian Mercury 300 spectrometer, as dilute solutions in $CDCl_3$. Electron impact mass spectra were recorded on either a VG Micromass 7070F or an AEI MS-30 spectrometer, operating at an ionisation potential of 70 eV. Elemental analyses were performed by either the Microanalytical Laboratory, Research School of Chemistry, Australian National University, or Chemical and Microanalytical Services Pty. Ltd., Melbourne, Australia. Chromatography was performed using Merck-Keiselgel 60 (230–400 mesh ASTM). Cyclohex-2-en-1-one (**2a**) was purchased from Aldrich Chemical Co. Nickel peroxide,[27] γ-activated manganese dioxide,[28] 5,6-dihydro-2*H*-pyran-2-one (**2b**),[29] 3-bromocyclohex-2-en-1-one (**9**)[17] and 2,3-dihydro-4*H*-pyran-4-one (**10a**)[30] were prepared using literature procedures. 2,6-Dichlorobenzohydroximoyl chloride was prepared as reported previously.[31] Usually it was converted to the nitrile oxide **3** *in situ* by treatment with triethylamine but on some occasions the nitrile oxide **3** was isolated.

### *cis*-3-(2,6-Dichlorophenyl)-5,6,7,7a-tetrahydro-1,2-benzisoxazol-4(3a*H*)-one 4a

A solution of 2,6-dichlorobenzohydroximoyl chloride (1.0 g, 4.5 mmol) in dry THF (3.6 mL) was added dropwise to a mixture of cyclohex-2-en-1-one (**2a**) (0.43 g, 4.5 mmol) and triethylamine (0.68 mL, 4.9 mmol) in dry THF (7.3 mL). The mixture was stirred at RT for 1 h, then at reflux for 3 h. After the solvent was removed under reduced pressure, the residue was taken up in $CHCl_3$ (20 mL), and the solution was washed with $H_2O$ (3 × 20 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes–EtOAc (1 : 1), afforded the title compound **4a** (0.51 g, 40%) as large, rhomboid, colourless crystals, after recrystallisation from hexanes–EtOAc, mp 150–151 °C (Found: C, 55.13; H, 3.98; N, 4.89. $C_{13}H_{11}Cl_2NO_2$ requires C, 54.95; H, 3.90; N, 4.93%); $\delta_H$ 1.98–2.56 (6 H, m), 4.41 (1 H, d, *J* 11), 5.26 (1 H, dt, *J* 11 and 4.5), 7.27–7.39 (3 H, m); *m*/*z* 287 ($M^+$, 4%), 285 ($M^+$, 17), 283 ($M^+$, 24), 214 (100).

The structure of the benzisoxazole **4a** was confirmed using X-ray crystallographic analysis.[14]

### *cis*-3-(2,6-Dichlorophenyl)-3a,6,7,7a-tetrahydro-4*H*-pyrano-[3,4-*d*]isoxazol-4-one 4b

Using the procedure described above for synthesis of the benzisoxazole **4a**, 5,6-dihydro-2*H*-pyran-2-one (**2b**) (0.50 g, 5.1 mmol) and 2,6-dichlorobenzohydroximoyl chloride (1.14 g, 5.1 mmol) afforded the title compound **4b** (0.94 g, 64%) as large, rhomboid, colourless crystals, mp 161–163 °C (Found: C, 50.69; H, 3.17; N, 4.87. $C_{12}H_9Cl_2NO_3$ requires C, 50.37; H, 3.17; N, 4.90%); $\delta_H$ 2.28 (2 H, m), 4.48 (1 H, m), 4.71 (1 H, ddd, *J* 3, 11 and 11), 4.75 (1 H, d, *J* 11), 5.33 (1 H, m), 7.32–7.42 (3 H, m); *m*/*z* 289 ($M^+$, 3%), 287 ($M^+$, 9), 285 ($M^+$, 14), 250 (58), 212 (100).

### 3-(2,6-Dichlorophenyl)-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one 5a

**Method 1.** The benzisoxazole **4a** (3.0 g, 10.6 mmol) was added to a suspension of nickel peroxide (30.0 g) in dry benzene

(300 mL) and the mixture was heated at reflux overnight, then it was cooled and filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was recrystallised from hexanes–EtOAc to give the title compound **5a** (1.46 g, 49%) as colourless crystals, mp 205–207 °C (Found: C, 55.36; H, 3.21; N, 5.20. $C_{13}H_9Cl_2NO_2$ requires C, 55.34; H, 3.22; N, 4.97%); $\delta_H$ 2.30 (2 H, quintet, *J* 6.5), 2.56 (2 H, t, *J* 6.5), 3.14 (2 H, t, *J* 6.5), 7.33–7.44 (3 H, m); *m*/*z* 285 ($M^+$, 1%), 283 ($M^+$, 3), 281 ($M^+$, 4), 247 (35), 245 (100).

The structure of the benzisoxazole **5a** was confirmed using X-ray crystallographic analysis.[15]

**Method 2.** The dihydrobenzisoxazole **4a** (0.10 g, 0.35 mmol) was added to a suspension of γ-activated manganese dioxide (0.50 g) in dry benzene (10 mL) and the mixture was heated at reflux overnight, then it was cooled and filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was recrystallised from hexanes–EtOAc to give the title compound **5a** (70 mg, 71%) as colourless crystals, identical in all respects with the sample obtained as described above.

**Method 3.** Using the procedure described above for synthesis of the benzisoxazole **4a**, 3-bromocyclohex-2-en-1-one (**9**) (1.56 g, 8.9 mmol) and 2,6-dichlorobenzohydroximoyl chloride (1.0 g, 4.5 mmol) afforded the title compound **5a** (0.65 g, 51%) as colourless crystals, identical in all respects with the sample obtained as described above.

### 3-(2,6-Dichlorophenyl)-6,7-dihydro-4*H*-pyrano[3,4-*d*]isoxazol-4-one 5b

Treatment of the pyranoisoxazole **4b** with either nickel peroxide or γ-activated manganese dioxide, as described above for synthesis of the benzisoxazole **5a**, afforded the title compound **5b** as colourless crystals, in 65% yield in both cases, mp 175–177 °C (Found: C, 50.72; H, 2.42; N 4.90. $C_{12}H_7Cl_2NO_3$ requires C, 50.73; H, 2.48; N, 4.93%); $\delta_H$ 3.34 (2 H, t, *J* 6), 4.69 (2 H, t, *J* 6), 7.39–7.47 (3 H, m); *m*/*z* 287 ($M^+$, 1%), 285 ($M^+$, 3), 283 ($M^+$, 4), 250 (38), 248 (100), 212 (53), 210 (79).

### 2-Bromocyclohex-2-en-1-one 6a

A solution of bromine (0.51 mL, 10.0 mmol) in $CH_2Cl_2$ (10 mL) was added over 10 min to a stirred solution of cyclohex-2-en-1-one (**2a**) (0.96 g, 10 mmol) in $CH_2Cl_2$ (35 mL). The mixture was stirred at RT for 2 h, after which triethylamine (1.4 mL, 10.0 mmol) was added. After a further 3 h, the mixture was poured into $H_2O$ (40 mL) and the organic layer was separated. The aqueous fraction was extracted twice with $CH_2Cl_2$. The organic solutions were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallised from aqueous EtOH to afford the title compound **6a** (1.06 g, 61%) as large colourless platelets, mp 72–75 °C (Found 173.9684. $C_6H_7{}^{79}BrO$ requires 173.9680); $\delta_H$ 2.08 (2 H, m), 2.45 (2 H, m), 2.64 (2 H, m), 7.44 (1 H, t, *J* 4.5); *m*/*z* 176 ($M^+$, 48%), 174 ($M^+$, 50), 67 (100), 39 (70).

### 3-Bromo-5,6-dihydro-2*H*-pyran-2-one 6b

Using the procedure described above for the synthesis of the bromocyclohexenone **6a**, reaction of the dihydropyranone **2b** (0.98 g, 10 mmol) afforded the title compound **6b** (1.33 g, 75%), as colourless, crystalline platelets, after flash column chromatography eluting with hexanes–$Et_2O$ and recrystallisation from hexanes–$Et_2O$, mp 32–34 °C (Found 175.9471. $C_5H_5{}^{79}BrO_2$ requires 175.9473); $\delta_H$ 2.57 (2 H, dt, *J* 4.5 and 6), 4.49 (2 H, t, *J* 6), 7.27 (1 H, t, *J* 4.5); *m*/*z* 178 ($M^+$, 33%), 176 ($M^+$, 33), 53 (50), 39 (100).

### 3-(2,6-Dichlorophenyl)-5,6-dihydro-1,2-benzisoxazol-7(4*H*)-one 8a

Using the procedure described above for the synthesis of the benzisoxazole **4a**, 2-bromocyclohex-2-en-1-one (**6a**) (0.76 g, 4.3 mmol) and 2,6-dichlorobenzohydroximoyl chloride (1.0 g, 4.5 mmol) afforded the title compound **8a** (0.65 g, 54%) as pale orange crystals, mp 108.5–110.5 °C (Found: C, 54.96; H, 3.25; N, 4.97. $C_{13}H_9Cl_2NO_2$ requires C, 55.34; H, 3.22; N, 4.97%); $\delta_H$ 2.23 (2 H, quintet, *J* 6), 2.61 (2 H, t, *J* 6), 2.70 (2 H, t, *J* 6), 7.37–7.46 (3 H, m); *m*/*z* 285 ($M^+$, 8%), 283 ($M^+$, 31), 281 ($M^+$, 53), 248 (14), 246 (47), 197 (100).

The structure of the benzisoxazole **8a** was confirmed using X-ray crystallographic analysis.[16]

### 3-(2,6-Dichlorophenyl)-4,5-dihydro-7*H*-pyrano[4,3-*d*]isoxazol-7-one 8b

Using the procedure described above for the synthesis of the benzisoxazole **4a**, 3-bromo-5,6-dihydro-2*H*-pyran-2-one (**6b**) (0.43 g, 2.4 mmol) and 2,6-dichlorobenzohydroximoyl chloride (0.79 g, 3.5 mmol) afforded the title compound **8b** (0.34 g, 50%) as pale orange crystals, mp 106–107 °C (Found: C, 50.86; H, 2.49; N, 4.93. $C_{12}H_7Cl_2NO_3$ requires C, 50.73; H, 2.48; N, 4.93%); $\delta_H$ 2.89 (2 H, t, *J* 6), 4.68 (2 H, t, *J* 6), 7.43–7.47 (3 H, m); *m*/*z* 287 ($M^+$, 3%), 285 ($M^+$, 14), 283 ($M^+$, 21), 250 (7), 248 (23), 211 (100), 197 (33).

### 5-Bromo-2,3-dihydro-4*H*-pyran-4-one 10b

Using the procedure described above for the synthesis of the bromocyclohexenone **6a**, reaction of the dihydropyranone **10a** (0.20 g, 2.0 mmol) afforded the title compound **10b** (0.23 g, 65%), as pale yellow needles, after flash column chromatography, eluting with hexanes–EtOAc, and recrystallisation from hexanes–$Et_2O$, mp 92–96 °C (Found 175.9468. $C_5H_5{}^{79}BrO_2$ requires 175.9473); $\delta_H$ 2.83 (2 H, t, *J* 6.5), 4.59 (2 H, t, *J* 6.5), 7.71 (1 H, s); *m*/*z* 178 ($M^+$, 100%), 176 ($M^+$, 100), 150 (99), 148 (99).

### 3-Hydroxy-1-[3-(2,6-dichlorophenyl)isoxazol-4-yl]propan-1-one 11

Using the procedure described above for the synthesis of the benzisoxazole **4a**, 2,3-dihydro-4*H*-pyran-4-one (**10a**) (0.10 g, 1.0 mmol) and 2,6-dichlorobenzohydroximoyl chloride (0.46 g, 2.0 mmol) afforded the title compound **11** (124 mg, 43%) as a colourless crystalline solid, mp 101–102.5 °C (Found: C, 50.18; H, 3.19; N, 4.84. $C_{12}H_9Cl_2NO_3$ requires C, 50.38; H, 3.17; N, 4.90%); $\delta_H$ 1.87 (1 H, br s), 2.92 (2 H, t, *J* 5), 3.91 (2 H, t, *J* 5), 7.38–7.48 (3 H, m), 9.14 (1 H, s).

The structure of the propanone **11** was confirmed using X-ray crystallographic analysis (Fig. 1).

### 3-(2,6-Dichlorophenyl)-5-methylisoxazole-4-carboxylic acid methyl ester 12

Using the procedure described above for synthesis of the benzisoxazole **4a**, methyl but-2-ynoate (0.57 g, 5.8 mmol) and 2,6-dichlorobenzohydroximoyl chloride (1.2 g, 5.3 mmol) afforded the title compound **12** as a 22 : 1 mixture with its regioisomer, 3-(2,6-dichlorophenyl)-4-methylisoxazole-5-carboxylic acid methyl ester [$\delta_H$ 2.16 (3 H, s), 4.01 (3 H, s), 7.34–7.43 (3 H, m)]. Compound **12** (1.32 g, 87%) was isolated by flash column chromatography, eluting with hexanes–EtOAc, and obtained as a colourless solid, mp 112–115 °C (lit.,[18] mp 116–117 °C); $\delta_H$ 2.80 (3 H, s), 3.69 (3 H, s), 7.34–7.43 (3 H, m).

### 3-(2,6-Dichlorophenyl)isoxazole-5-carboxylic acid methyl ester 13

Using the procedure described above for the synthesis of the benzisoxazole **4a**, methyl propiolate (0.47 g, 5.6 mmol) and

2,6-dichlorobenzohydroximoyl chloride (1.0 g, 4.5 mmol) afforded the title compound **13** as a 3 : 1 mixture with its regioisomer 3-(2,6-dichlorophenyl)-4-isoxazolecarboxylic acid methyl ester [$\delta_H$ 3.76 (3 H, s), 7.20–7.56 (3 H, m), 9.08 (1 H, s)]. Compound **13** (0.70 g, 57%) was isolated by flash column chromatography, eluting with hexanes–EtOAc, and obtained as colourless crystals after recrystallisation from hexanes–EtOAc, mp 114–116 °C (Found 270.9803. $C_{11}H_7{}^{35}Cl_2NO_3$ requires 270.9806); $\delta_H$ 4.03 (3 H, s), 7.08 (1 H, s), 7.38–7.47 (3 H, m); *m*/*z* 275 ($M^+$, 9%), 273 ($M^+$, 30), 271 ($M^+$, 38), 216 (31), 214 (80), 212 (100), 186 (34), 184 (46).

### 4-Cyano-3-(2,6-dichlorophenyl)-5-methylisoxazole 14

Using the procedure described above for synthesis of the benzisoxazole **4a**, a *ca*. 1 : 1.5 mixture of the *cis*- and *trans*-isomers of crotononitrile (0.32 g, 4.8 mmol) reacted with 2,6-dichlorobenzonitrile oxide (1.2 g, 5.3 mmol) to give a mixture of isoxazoline cycloadducts. This was treated with nickel peroxide (10.0 g), as described above for synthesis of the benzisoxazole **5a**, to give the title compound **14** (0.12 g, 10%) as a colourless solid, after flash column chromatography, eluting with hexanes–EtOAc, and recrystallisation from hexanes–EtOAc, mp 98–100 °C (lit.,[19] mp 99–100 °C); $\delta_H$ 2.75 (3 H, s), 7.43–7.46 (3 H, m).

### 5-Cyano-3-(2,6-dichlorophenyl)isoxazole 15

Using the procedure described above for synthesis of the benzisoxazole **4a**, acrylonitrile (0.26 g, 4.9 mmol) and 2,6-dichlorobenzonitrile oxide (1.2 g, 5.3 mmol) afforded 5-cyano-3-(2,6-dichlorophenyl)-4,5-dihydroisoxazole (0.55 g, 47%), as a pale yellow oil; $\delta_H$ 3.67 (2 H, m), 5.47 (1 H, dd, *J* 5 and 5.5), 7.40 (3 H, m).

Treatment of 5-cyano-3-(2,6-dichlorophenyl)-4,5-dihydroisoxazole (0.52 g, 2.2 mmol) with nickel peroxide (5.0 g), as described above for synthesis of the benzisoxazole **5a**, afforded the title compound **15** (0.23 g, 44%) as a colourless solid after recrystallisation from hexanes–EtOAc, mp 114–117 °C (lit.,[20] mp 115–117 °C); $\delta_H$ 7.15 (1 H, s), 7.29–7.36 (3 H, m).

### 3-(2,6-Dichlorophenyl)-5-phenylisoxazole 16

Using the procedure described above for synthesis of the benzisoxazole **4a**, styrene (0.55 g, 5.3 mmol) and 2,6-dichlorobenzohydroximoyl chloride (1.0 g, 4.5 mmol) afforded 3-(2,6-dichlorophenyl)-4,5-dihydro-5-phenylisoxazole (1.18 g, 98%) as a colourless powder, mp 63–65 °C (lit.,[21] mp 64–65 °C); $\delta_H$ 3.28 (1 H, dd, *J* 9 and 17), 3.73 (1 H, dd, *J* 11 and 17), 5.82 (1 H, dd, *J* 9 and 11), 7.23–7.48 (8 H, m).

Treatment of 3-(2,6-dichlorophenyl)-4,5-dihydro-5-phenylisoxazole (0.5 g, 1.7 mmol) with γ-activated manganese dioxide (2.5 g), as described above for synthesis of the benzisoxazole **5a**, afforded the title compound **16** (57 mg, 12%) as a colourless solid, mp 75–76 °C (lit.,[22] 75–76 °C); $\delta_H$ 6.63 (1 H, s), 7.30–7.52 (6 H, m), 7.86 (2 H, d, *J* 8).

### 3-(2,6-Dichlorophenyl)-4-phenylisoxazole 17

Using the procedure described above for synthesis of the benzisoxazole **4a**, a *ca*. 1 : 4 mixture of the *cis*- and *trans*-isomers of β-bromostyrene (2.75 g, 15.1 mmol) reacted with 2,6-dichlorobenzohydroximoyl chloride (3.4 g, 15.2 mmol) to give a *ca*. 7 : 5 : 1 mixture of the title compound **17**, 3-(2,6-dichlorophenyl)-5-phenylisoxazole [$\delta_H$ 6.56 (1 H, s), 7.16–7.41 (8 H, m)] and *trans*-4-bromo-3-(2,6-dichlorophenyl)-4,5-dihydro-5-phenylisoxazole [$\delta_H$ 5.52 (1 H, d, *J* 3.5), 6.02 (1 H, d, *J* 3.5), 7.16–7.41 (8 H, m)]. A portion of the title compound **17** (0.30 g, 7%) was isolated by flash column chromatography, eluting with hexanes–EtOAc, and obtained as a colourless powder after recrystallisation from hexanes–EtOAc, mp 89–90 °C (lit.,[23] 90–92 °C); $\delta_H$ 7.16–7.43 (8 H, m), 8.73 (1 H, s).

### 3-Acetylisoxazole-5-carboxylic acid methyl ester 18

A solution of methyl propiolate (0.69 g, 8.2 mmol) and triethylamine (0.63 mL, 4.5 mmol) in dry THF (100 mL) was added dropwise to a solution of 1-chloro-1-(hydroxyimino)acetone[32] (0.50 g, 4.1 mmol) in dry THF (25 mL). The mixture was stirred at RT for 1 h and at reflux for 3 h, then it was cooled and concentrated under reduced pressure. The residue was taken up in $CHCl_3$ and the solution was washed with $H_2O$, dried ($MgSO_4$) and concentrated. Flash column chromatography of the residue, eluting with hexanes–EtOAc, and recrystallisation from hexanes–EtOAc, afforded the title compound **18** (0.15 g, 22%) as a colourless powder, mp 95–96 °C [Found 170.0451 ($M+H^+$). $C_7H_7NO_4$ requires 170.0453 ($M+H^+$)]; $\delta_H$ 2.71 (3 H, s), 3.99 (3 H, s), 7.26 (1 H, s); *m*/*z* 169 ($M^+$, 5%), 154 (100), 138 (31).

### General procedure for electrolysis

Voltammetric experiments were conducted using a PAR model 273A potentiostat/galvanostat controlled by standard PAR electrochemical software through a PC interface. Cyclic voltammograms were performed at RT in acetonitrile (0.1 mol $dm^{-3}$ tetrabutylammonium hexafluorophosphate) under argon, using a 1 mm planar mercury coated Pt working electrode and Pt auxiliary electrode, in conjunction with a Ag/AgCl reference electrode.

The general procedure for performing the synthetic scale electrolysis experiments involved first obtaining the reduction potential of the substrate. This was achieved by performing a cyclic voltammogram and the results are shown in Table 1. The constant potential electrolyses were then conducted in a two compartment electrolytic cell using a mercury coated platinum-mesh working electrode and, at varying intervals, the electrolysis was paused and cyclic voltammograms were performed until none of the substrates could be detected electrochemically. Under these conditions the isoxazoles **8a,b**, **13** and **15**–**18** afforded complex product mixtures from which it was not practical to isolate discrete species.

### 2-[(2,6-Dichlorophenyl)iminomethyl]-3-hydroxycyclohex-2-en-1-one 19a

The crude mixture obtained by electrolysis of the benzisoxazole **5a** (0.30 g, 1.0 mmol) was concentrated under reduced pressure, and the residue was subjected to flash column chromatography, eluting with hexanes–EtOAc, to give the title compound **19a** (0.18 g, 63%) as a colourless powder, mp 228–231 °C (Found: C, 54.92; H, 3.98; N, 4.92. $C_{13}H_{11}Cl_2NO_2$ requires C, 54.95; H, 3.90; N, 4.93%); $\delta_H$ 1.95 (2 H, quintet, *J* 6.5), 2.41 (2 H, t, *J* 6.5), 2.65 (2 H, t, *J* 6.5), 6.02 (1 H, br s), 7.23–7.37 (3 H, m), 12.02 (1 H, br s); *m*/*z* 287 ($M^+$, 1%), 285 ($M^+$, 3), 283 ($M^+$, 4), 249 (37), 247 (100).

The structure of the enolised dicarbonylimine **19a** was confirmed using X-ray crystallographic analysis.[26]

### 3-[(2,6-Dichlorophenyl)iminomethyl]-5,6-dihydro-4-hydroxy-2*H*-pyran-2-one 19b

The crude mixture obtained by electrolysis of the pyranoisoxazole **5b** (0.30 g, 1.1 mmol) was concentrated under reduced pressure, and the residue was subjected to flash column chromatography, eluting with hexanes–EtOAc, to give the title compound **19b** (0.2 g, 64%) as a colourless powder, mp 216–218 °C (Found: C, 50.46; H, 3.48; N, 4.65. $C_{12}H_9Cl_2NO_3$ requires C, 50.38; H, 3.17; N, 4.90%); $\delta_H$ 2.73 (2 H, t, *J* 6), 4.35 (2 H, t, *J* 6), 6.34 (1 H, br s), 7.25–7.39 (3 H, m), 11.50 (1 H, br s); *m*/*z* 289 ($M^+$, 0.2%), 287 ($M^+$, 0.7), 285 ($M^+$, 1), 252 (33), 250 (100).

The structure of the enolised dicarbonylimine **19b** was confirmed using X-ray crystallographic analysis (Fig. 2).

### α-Acetyl-β-amino-2,6-dichlorocinnamic acid methyl ester 20

The crude mixture obtained by electrolysis of the isoxazole **13** (0.23 g, 0.80 mmol) was concentrated under reduced pressure, and the residue was subjected to flash column chromatography, eluting with hexanes–EtOAc, to give the title compound **20** (130 mg, 58%) as a colourless powder, mp 155–157 °C (lit.,[19] 155–156.5 °C); $\delta_H$ 2.49 (3 H, s), 3.46 (3 H, s), 5.50 (1 H, br s), 7.29–7.40 (3 H, m), 11.35 (1 H, br s).

### α-Acetyl-β-amino-2,6-dichlorocinnamonitrile 21

The crude mixture obtained by electrolysis of the isoxazole **15** (82 mg, 0.32 mmol) was concentrated under reduced pressure, and the residue was subjected to flash column chromatography, eluting with hexanes–EtOAc, to give the title compound **21** (56 mg, 68%) as a colourless powder, mp 229–232 °C (lit.,[19] 231–232 °C); $\delta_H$ 2.44 (3 H, s), 5.87 (1 H, br s), 7.36–7.47 (3 H, m), 10.80 (1 H, br s).

### Crystallography [33] †

**Crystal data for 11.** $C_{12}H_9Cl_2NO_3$, $M = 286.1$, orthorhombic, $a = 11.131(4)$, $b = 25.771(4)$, $c = 8.699(3)$ Å, $V = 2495(1)$ Å$^3$, $T = 293$ K, space group *Pbca*, $Z = 8$, $\mu$(Mo-Kα) = 5.18 cm$^{-1}$, 2635 reflections measured on a Rigaku AFC6R diffractometer on a plate (0.05 × 0.23 × 0.39 mm), $\theta_{max}$ 25.3°, 994 with $I \geq 2.0\sigma(I)$ were used in subsequent calculations: final $R = 0.059$ and $R_w = 0.048$. The O–H atom was located from a difference map and refined but not in the final cycles. The structure determination (Fig. 1) establishes the molecular connectivity, is consistent with the microanalytical and spectroscopic results but is not of high precision. In particular, high thermal motion is noted for the $CH_2CH_2OH$ residue so that the C–C and C–O distances are shorter than expected. The aryl ring is approximately orthogonal to the planar five-membered heterocycle as seen in the respective N(2)–C(3)–C(31)–C(32), O(1)–N(2)–C(3)–C(4) and O(1)–C(5)–C(4)–C(3) torsion angles of −89.3(7), −0.6(6) and –0.8(7)°. The side-chain adopts a *syn* configuration but steric strain precludes a significant intramolecular O–H · · · O contact: the H(8) · · · O(6) separation is 2.31 Å. This hydroxy group is involved in a weak intermolecular contact with a centrosymmetrically related hydroxy group such that O–H(8) · · · O(8)$^{i}$ is 2.55 Å [O(8) · · · O(8)$^{i}$ is 3.059(6) Å and the angle at H is 126.2°; symmetry operation i: $-x, -y, -1-z$]. A methylene H atom also forms a close contact with O(8) with C(7)–H(7b) · · · O(8)$^{ii}$ being 2.46 Å [C(7) · · · O(8)$^{ii}$ is 3.335(7) Å, the angle at H 150.0° and symmetry operation ii: $\frac{1}{2}-x, -y, \frac{1}{2}+z$]. The closest intermolecular contact in the lattice involves the carbonyl O(6) atom and occurs between C(5)–H(5) · · · O(6)$^{iii}$ with H(5) · · · O(6)$^{iii}$ 2.26 Å, C(5) · · · O(6)$^{iii}$ 3.230(5) Å, angle at H 174.3° and symmetry operation iii: $\frac{1}{2}+x, y, -\frac{1}{2}-z$.

**Crystal data for 19b.** $C_{12}H_9Cl_2NO_3$, $M = 286.1$, monoclinic, $a = 14.092(4)$, $b = 8.212(5)$, $c = 21.719(4)$ Å, $\beta = 93.06(2)°$, $V = 2510(1)$ Å$^3$, $T = 293$ K, space group $P2_1/c$, $Z = 8$, $\mu$(Mo-Kα) = 5.15 cm$^{-1}$, 4987 reflections measured as for **11** on a block (0.10 × 0.16 × 0.36 mm), $\theta_{max}$ 25.1°, 2090 with $I \geq 2.0\sigma(I)$ were used: final $R = 0.063$ and $R_w = 0.050$. Two independent molecules comprise the crystallographic asymmetric unit with only minor conformational differences between them with only molecule *a* illustrated in Fig. 2. The molecule exists as the C–$NH_2$/C(3)=O(3) tautomer and the aryl group is approximately orthogonal to the enamine residue as seen in the C(2)–C(2)–C(21)–C(22) torsion angle of 109.8(7)° [95.3(7)° for molecule *b*]. An intramolecular N(2′)–H · · · O(3) contact of 1.88 Å [1.84 Å for molecule *b*] is formed with N(2′) · · · O(3) of 2.609(5) Å [2.576(5) Å] and angle at H of 130.3° [130.7°]. The second amine H atom forms an intermolecular interaction with the carbonyl O(1)$^{i}$ atom of the other independent molecule with H · · · O(1b)$^{i}$ of 1.84 Å, N(2′a) · · · O(b)$^{i}$ 2.776(5) Å and angle at H of 162.6° (symmetry operation i: $x, \frac{1}{2}-y, -\frac{1}{2}+z$); the comparable parameters for molecule *b* are 1.99 Å, 2.921(5) Å, and 160.0° ($x, y, z$). The carbonyl O(3) atom forms an additional interaction. In the case of molecule *a*, this is with H(24b) of the aryl ring so that H(24b) · · · O(3a)$^{ii}$ is 2.50 Å, C(24b) · · · O(3a)$^{ii}$ is 3.365(8) Å, the angle at H 148.0° and symmetry operation ii is $1-x, \frac{1}{2}+y, \frac{1}{2}-z$. For molecule *b*, the contact occurs with a methylene H, *i.e.* C(4b)–H(4b) · · · O(3b) with parameters 2.48 Å, 3.350(7) Å, 148.8°, and $2-x, -1-y, 1-z$.

† CCDC reference number(s) 161209 and 161209. See http://www.rsc.org/suppdata/p1/b0/b008081k for crystallographic files in .cif or other electronic format.

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## References

1 (*a*) N. K. Kochetkov and S. D. Sokolov, in *Advances in Heterocyclic Chemistry*, Academic Press, New York, 1963, vol. 2, p. 365; (*b*) A. Quilico, in *The Chemistry of Heterocyclic Compounds*, ed. A. Weissberger, John Wiley & Sons, New York, 1962, vol. 17, p. 1; (*c*) A. Quilico and R. Justoni, *Gazz. Chim. Ital.*, 1940, **70**(1), 11.
2 (*a*) G. Stork, S. Danishefsky and M. Ohashi, *J. Am. Chem. Soc.*, 1967, **89**, 5459; (*b*) M. Ohashi, H. Kamachi, H. Kakisawa and G. Stork, *J. Am. Chem. Soc.*, 1967, **89**, 5460; (*c*) G. Stork and J. E. McMurry, *J. Am. Chem. Soc.*, 1967, **89**, 5461; G. Stork and J. E. McMurry, *J. Am. Chem. Soc.*, 1967, **89**, 5463; G. Stork and J. E. McMurry, *J. Am. Chem. Soc.*, 1967, **89**, 5464; (*d*) P. Pino, F. Piacenti and G. Fatti, *Gazz. Chim. Ital.*, 1960, **90**, 356; (*e*) P. Bravo, G. Gaudiano, A. Quilico and A. Ricca, *Gazz. Chim. Ital.*, 1961, **91**, 47; (*f*) G. Stagno d'Alcontres, *Gazz. Chim. Ital.*, 1950, **80**, 441; (*g*) G. Shaw and G. Sugowdz, *J. Chem. Soc.*, 1954, 665; (*h*) S. Auricchio, S. Morrocchi and A. Ricca, *Tetrahedron Lett.*, 1974, 2793; (*i*) R. V. Stevens, *Tetrahedron*, 1976, **32**, 1599; (*j*) A. A. Akhrem, F. A. Lakhvich, V. A. Khripach and I. B. Klebanovich, *Tetrahedron Lett.*, 1976, 3983; (*k*) S. Plescia, S. Petruso and V. Sprio, *J. Heterocycl. Chem.*, 1974, **11**, 623; (*l*) C. Kashima, Y. Yamamoto and Y. Tsuda, *J. Org. Chem.*, 1975, **40**, 526.
3 (*a*) L. Claisen, *Chem. Ber.*, 1891, **24**, 3900; (*b*) G. Büchi and J. C. Vederas, *J. Am. Chem. Soc.*, 1972, **94**, 9128.
4 J. Thiele and H. Landers, *Liebigs. Ann.*, 1909, **369**, 300.
5 (*a*) L. Claisen, *Chem. Ber.*, 1926, **59**, 144; (*b*) E. P. Kohler and N. K. Richtmyer, *J. Am. Chem. Soc.*, 1928, **50**, 3092.
6 (*a*) M. Nitta and T. Kobayashi, *Tetrahedron Lett.*, 1982, **23**, 3925; M. Nitta and T. Kobayashi, *J. Chem. Soc., Chem. Commun.*, 1982, 877; M. Nitta and T. Kobayashi, *Chem. Lett.*, 1983, 51; (*b*) M. Nitta, A. Yi and T. Kobayashi, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 991; (*c*) P. G. Baraldi, A. Barco, S. Benetti, M. Guarneri, S. Manfredini, G. P. Pollini and D. Simoni, *Tetrahedron Lett.*, 1985, **26**, 5319.
7 C. J. Easton, C. Merrîcc Hughes, K. D. Kirby, G. P. Savage, G. W. Simpson and E. R. T. Tiekink, *J. Chem. Soc., Chem. Commun.*, 1994, 2035.
8 C. J. Easton, C. Merrîcc Hughes, E. R. T. Tiekink, C. E. Lubin, G. P. Savage and G. W. Simpson, *Tetrahedron Lett.*, 1994, **35**, 3589.
9 K. G. Watson, *Chem. Aust.*, 1988, **55**, 193.
10 (*a*) R. C. F. Jones, G. Bhalay, P. A. Carter, K. A. M. Duller and S. I. E. Vulto, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2513; (*b*) R. C. F. Jones, G. Bhalay, P. A. Carter, K. A. M. Duller and S. I. E. Vulto, *Synlett*, 1995, 149.
11 (*a*) G. Bianchi, C. De Micheli, R. Gandolfi, P. Grünanger, P. Vita Finzi and O. Vajna de Pava, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1148; (*b*) L. Fisera, N. D. Kozina, L. A. Badovskaya and L. Stibranyi, *Chem. Pap.*, 1986, **40**, 685; (*c*) L. Fisera and P. Oravec, *Collect. Czech. Chem. Commun.*, 1987, **52**, 1315; (*d*) P. Oravec, L. Fisera and R. Gazo, *Monatsh. Chem.*, 1991, **122**, 165; (*e*) E. Malamidou-Xenikaki, E. Coutouli-Argyropoulou and N. E. Alexandrou, *Tetrahedron Lett.*, 1985, **26**, 4105; (*f*) M. Nitta and N. Kanomata, *Chem. Lett.*, 1986, 1925; (*g*) E. Coutouli-Argyropoulou and E. Malamidou-Xenikaki, *J. Heterocycl. Chem.*, 1986, **23**, 1681; (*h*) S. Kanemasa, T. Hayashi, H. Yamamoto, E. Wada and T.

Sakurai, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 3274; (*i*) A. J. Blake, T. A. Cook, A. C. Forsyth, R. O. Gould and R. M. Paton, *Tetrahedron*, 1992, **48**, 8053; (*j*) M. Schubert-Zsilavecz, D. Gusterhuber and W. Likussar, *Monatsh. Chem.*, 1993, **124**, 1201; (*k*) C. Baldoli, F. Gioffreda and G. Zecchi, *J. Heterocycl. Chem.*, 1994, **31**, 251; (*l*) C. J. Easton, C. M. M. Hughes, G. P. Savage and G. W. Simpson, in *Advances in Heterocyclic Chemistry*, Academic Press, New York, 1994, vol. 60, p. 261.
12 (*a*) G. H. Posner, T. D. Nelson, C. M. Kinter and K. Afarinkia, *Tetrahedron Lett.*, 1991, **32**, 5295; (*b*) G. H. Posner, personal communication.
13 (*a*) N. Almirante and L. Forti, *J. Heterocycl. Chem.*, 1984, **21**, 1121; (*b*) T. Minami, T. Hanamoto and I. Hirao, *J. Org. Chem.*, 1985, **50**, 1278; (*c*) M. D. Taylor, R. J. Himmelsbach, B. E. Kornberg, J. Quin, III, E. Lunney and A. Michel, *J. Org. Chem.*, 1989, **54**, 5585; (*d*) O. Arjona, C. Domínguez, R. F. de la Pradilla, A. Mallo, C. Manzano and J. Plumet, *J. Org. Chem.*, 1989, **54**, 5883.
14 C. J. Easton, C. M. Hughes, E. R. T. Tiekink, G. P. Savage and G. W. Simpson, *Z. Kristallogr.*, 1994, **209**, 771.
15 C. J. Easton, C. M. M. Hughes, E. R. T. Tiekink, G. P. Savage and G. W. Simpson, *Z. Kristallogr.*, 1996, **211**, 193.
16 C. J. Easton, C. M. Hughes, E. R. T. Tiekink, G. P. Savage and G. W. Simpson, *Z. Kristallogr.*, 1994, **209**, 767.
17 A. W. Crossley and P. Haas, *J. Chem. Soc.*, 1903, **83**, 494.
18 J. C. Hanson, A. A. W. Long, J. H. C. Nayler and E. R. Stove, *J. Chem. Soc.*, 1965, 5976.
19 D. N. McGregor, U. Corbin, J. E. Swigor and L. C. Cheney, *Tetrahedron*, 1969, **25**, 389.
20 R. G. Micetich, *Can. J. Chem.*, 1970, **48**, 3753.
21 Y. Tokunaga, M. Ihara and K. Fukumoto, *Heterocycles*, 1996, **43**, 1771.
22 A. Dondoni and G. Barbaro, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1591.
23 G. Bianchetti, D. Pocar and C. Torricelli, *Gazz. Chim. Ital.*, 1981, **111**, 315.
24 M. Christl, R. Huisgen and R. Sustmann, *Chem. Ber.*, 1973, **106**, 3275.
25 (*a*) I. Surov and H. Lund, *Acta Chem. Scand., Ser. B*, 1986, **40**, 831; (*b*) I. G. Markova, M. K. Polievktov and S. D. Sokolov, *J. Gen. Chem. USSR (Engl. Transl.)*, 1976, **46**, 394; (*c*) H. Lund and I. Tabakovic, in *Advances in Heterocyclic Chemistry*, Academic Press, Orlando, 1984, vol. 36, p. 235.
26 C. J. Easton, C. M. Hughes, E. R. T. Tiekink, K. Kirby, G. P. Savage and G. W. Simpson, *Z. Kristallogr.*, 1995, **210**, 231.
27 K. Nakagawa, R. Konaka and T. Nakata, *J. Org. Chem.*, 1962, **27**, 1597.
28 (*a*) A. Barco, S. Benetti, G. P. Pollini and P. G. Baraldi, *Synthesis*, 1977, 837; (*b*) A. Barco, S. Benetti, G. P. Pollini and B. Veronesi, *Synth. Commun.*, 1978, **8**, 219; (*c*) G. Diamantini, E. Duranti and A. Tontini, *Synthesis*, 1993, 1104; (*d*) A. J. Fatiadi, *Synthesis*, 1976, 65.
29 (*a*) M. Nakagawa, M. Tonozuka, M. Obi, M. Kiuchi and T. Hino, *Synthesis*, 1974, 510; (*b*) R. N. McDonald and C. E. Reineke, *Org. Synth.*, **Coll. Vol. VI**, 1988, 462.
30 S. Danishefsky and R. R. Webb II, *J. Org. Chem.*, 1984, **49**, 1955.
31 K.-C. Lui, B. R. Shelton and R. K. Howe, *J. Org. Chem.*, 1980, **45**, 3916.
32 G. Hesse and G. Krehbiel, *Chem. Ber.*, 1955, **88**, 130.
33 *Programs used for X-ray analysis: TEXSAN, Structure Analysis Package*, Molecular Structure Corporation, TX, 1992; C. K. Johnson, *ORTEP II, Report ORNL-5136*, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.