Pergamon

Tetrahedron 56 (2000) 811–816

TETRAHEDRON

The Synthesis and Activity of Oxazole and Thiazole Analogues of Urocanic Acid

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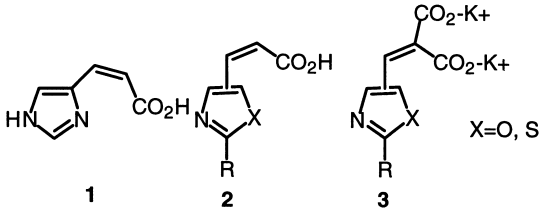
Received 18 October 1999; revised 6 December 1999; accepted 23 December 1999

Abstract—Direct exposure of human skin to sunlight leads to suppression of the immune system, believed to be mediated by urocanic acid. The synthesis of oxazole and thiazole analogues of urocanic acid is reported, as is their effect on biological markers of the human immune system.

Introduction

UV-A (320–400 nm) and UV-B (290–320 nm) light has been shown to suppress the immune system.[1] Subsequent research has identified (*Z*)-urocanic acid (UCA) **1** as a chemical mediator responsible for inducing immunosuppression.[2]

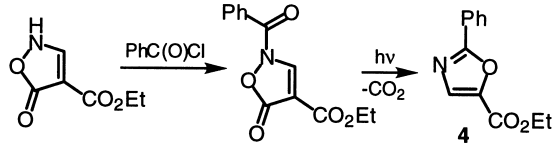


(*E*)-UCA arises from the deamination of the amino acid histidine, and is generally present to the extent of about 0.7% in human skin;[3] the immunosuppressive (*Z*)-UCA is formed upon UV irradiation of the (*E*)-isomer. In an attempt to discover the molecular structure necessary for immunosuppressive activity, Norval and co-workers[4] tested several analogues of **1** for their ability to suppress the immune system. They concluded that the heteroaromatic ring, together with the side chain, is necessary to induce immunosuppression. However, even when the side chain was reduced or the carboxyl group replaced by amino, the compound retained its activity. Since then further analogues have been synthesised and tested, with somewhat ambiguous results.[5–7] This paper aims to probe further the structure necessary for immunosuppressive activity by synthesising oxazole and thiazole analogues **2** and **3** of UCA and to evaluate them as potential agonists or antagonists of the (*Z*)-UCA receptor site.

Results and Discussion

Recent work in our group has led to the development of a novel route to oxazoles[8] and thiazoles[9] from isoxazol-5(2*H*)-ones, and we envisaged that the oxazoles and thiazoles required in this project could be derived in this way. Due to its ease of formation[8] (Scheme 1), ethyl 2-phenyloxazole-5-carboxylate **4** was chosen as the model starting compound for the synthesis of the analogues of UCA.

Transformations on the oxazole ester **4**, as depicted in Scheme 2, gave the desired compounds **8** and **9**. Direct reduction of the ester **4** to aldehyde **5** with diisobutylaluminium hydride proceeded poorly. Hence the aldehyde was obtained by reduction of **4** with lithium aluminium hydride to afford **6**, followed by Swern oxidation of **6** to give the aldehyde in 83% overall yield. Reaction of **5** with malonic acid in refluxing pyridine delivered **7**, which gave essentially a 1:1 mixture of (*Z*)-**9** and (*E*)-**7** isomers upon exposure to UV light; further irradiation of this mixture did not improve the yield of the (*Z*)-isomer. The dicarboxylate compound **8** was prepared by adapting the procedure of



Scheme 1.

Keywords: oxazoles; thiazoles; anti-inflammatory compounds.
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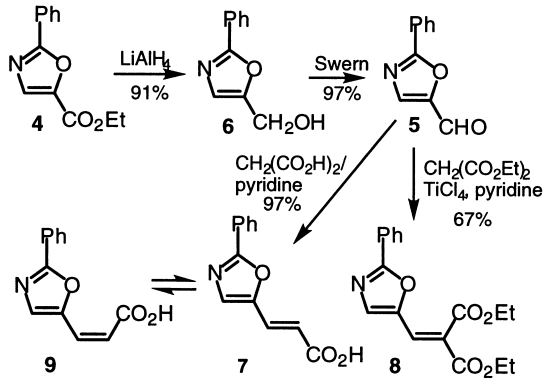
PII: S0040-4020(00)00019-3



Scheme 2.

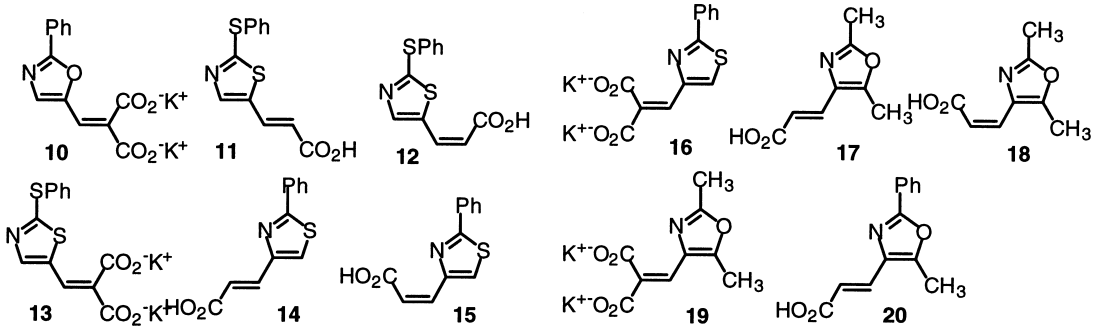
Lehnert[10] followed by base hydrolysis to give **10**. The analogues **10**–**20** were synthesised by similar procedures.

Biological Experimentation

The UCA analogues **7**, **9**, **10**–**20** were tested in vitro for their ability to stimulate human peripheral blood monocyte prostaglandin E2 (PGE2) production and their ability to suppress lipopolysaccharide (LPS) induced tumour necrosis factor-α (TNF-α) levels. The procedure was adapted from the work carried out by Hart and co-workers,[11] in which (*Z*)-UCA induced PGE2 synthesis and suppressed TNF-α levels in human monocytes. It was concluded that the reduction of TNF-α, by a PGE2-dependent mechanism, may be implicated in the suppression of the immune system by (*Z*)-UCA.

The biological data are summarised in Table 1, and all trends (average of three determinations) have been replicated at least twice. It is apparent that the (*E*)-isomer of each UCA analogue **7**, **11**, **14** and **20**, except **17**, induced PGE2 synthesis and reduced LPS induced TNF-α levels suggesting that they may be acting as anti-inflammatory agents. Analogue **20** increased PGE2 levels and dramatically reduced TNF-α levels, relative to **17**, and so it was concluded that the necessary functionality at C-2 of the five membered ring was a phenyl group, suggesting that hydrophobicity plays a role in the activity of each respective compound. Compound **20** decreased the production of TNF-α to 34% of the control, being more active than (*Z*)-UCA (62% of control), and the suppression was additive (23% of control when 1:1). However, this suppression appears to occur by a mechanism less dependent on PGE2 production than that of (*Z*)-UCA, as it was only partially restored by the addition of indomethacin, a cyclooxygenase inhibitor. In addition, production of PGE2 was only mildly stimulated (24% of that by (*Z*)-UCA).

Table 1. Effect on LPS-induced production of TNF-α and PGE 2



Compound[a]	TNF-α (%) Control[b]	PGE 2 (%) Control[b]
(*E*)-UCA	102	64
(*Z*)-UCA	62[c]	1105
7	39[d]	782
7+**9** (1:1)	196	281
10	101	93
11	83[e]	691
11+**12** (3:2)	137	376
13	138	57
14	82	410
14+**15** (1:2)	207	119
16	129	152
17	84	163
17+**18** (2:3)	99	133
19	138	97
20	34[f]	265
20+(*Z*)-UCA	23	774

[a] All concentrations 0.1 mg mL^{-1}, ca. 5×10^{-4} M.
[b] Production induced by lipopolysaccharide (LPS) alone.
[c] Returned to 138% in the presence of indomethacin (10^{-5} M).
[d] Returned to 110% in the presence of indomethacin.
[e] Returned to 94% in the presence of indomethacin.
[f] Returned to 72% in the presence of indomethacin.

The mixture of (*E*)- and (*Z*)-isomers **7**/**9**, **11**/**12**, **14**/**15** and **17**/**18** obtained from the UV isomerisation of each (*E*)-isomer could not be separated by reverse phase HPLC or ion exchange chromatography, except on an analytical scale, and so each was tested as a mixture (see Table 1). Although the isomer ratio of the mixtures **7**/**9**, **11**/**12**, **14**/**15** and **17**/**18** appeared to be stable under ordinary laboratory conditions, assay samples were protected from light. While the (*E*)-isomers **7**, **11**, **14** and **20** significantly reduced TNF-α (production, the corresponding (*E*)/(*Z*) mixtures actually increased TNF-α levels. Similarly, the level of induced PGE2 synthesis due to the (*E*)-isomers was reduced in the presence of the (*Z)* isomer. The dicarboxylate compounds **10**, **13**, **16** and **19** affected PGE2 or TNF-α levels in a way suggesting that they were acting as both (*E*)- and (*Z*)-isomers, supporting the supposition that the (*E*)- and (*Z*)-isomers were antagonistic.

Conclusions

In contrast to what we initially envisaged, the (*E*)-isomers **7**, **11**, **14**, and **20** act in the same way as (*Z*)-UCA and appear to be synergistic with it. While (*E*)-UCA has little effect on the production of TNF-α, the (*Z*)-isomers of the above analogues are clearly antagonistic to the effect of their (*E*)-isomers and to (*Z*)-UCA. The (*E*)-isomers **7**, **11**, **14**, and **20** may act as anti-inflammatory agents.

Experimental

Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded with a Varian Gemini spectrometer at 300 and 75.5 MHz, respectively. Spectra were measured in deteuriochloroform ($CDCl_3$) unless otherwise indicated and coupling constants were recorded in Hertz. Infrared spectra were recorded on a Perkin–Elmer 1600 Fourier-transform IR spectrometer, with samples measured as a nujol mull (solid) or as a neat film (oil). Mass spectra and high-resolution mass spectra were recorded on a Kratos MS25RF spectrometer operating at an electron ionising energy of 70 eV. Melting points were determined on a Reichert hot-stage apparatus and remain uncorrected. Analytical thin-layer chromatography was carried out with Merck silica gel 60 F254 aluminium backed sheets. Radial chromatography was performed with silica gel PF254 coated glass rotors using a Chromatotron 7924T. All organic extracts were dried with anhydrous sodium sulphate. Microanalyses were performed by the Microanalytical Service, University of Otago.

5-Hydroxymethyl-2-phenyloxazole 6. To a stirred solution of lithium aluminium hydride (0.19 g; 5 mmol) in ether (100 mL) was added a solution of ethyl 2-phenyloxazole-5-carboxylate[8] **4** (1.00 g; 4.61 mmol) in ether (20 mL) dropwise. The mixture was stirred for 16 h at 20°C and then excess lithium aluminium hydride was quenched by dropwise addition of saturated ammonium chloride solution. The mixture was filtered and the solvent dried and evaporated affording a pale yellow solid, which was recrystallised from ether–light petroleum as white needles (0.73 g; 91%), mp 72–74°C. Anal for $C_{10}H_9NO_2$, calcd C, 68.6; H, 5.2; N, 8.0%; found C, 68.7; H, 5.3; N, 8.1%. ^{1}H NMR δ: 4.43 (bs, 1H); 4.68 (s, 2H); 7.00 (s, 1H); 7.36–7.44 (m, 3H); 7.92–8.00 (m, 2H). ^{13}C NMR δ: 54.7, 125.4, 126.3, 127.0, 128.8, 130.6, 151.5, 162.1. IR ν_{max}: 3192, 1549, 1452, 1361, 1026 cm^{-1}. Mass spectrum *m*/*z*: 175 (M, 100%), 158 (16), 144 (94), 116 (97), 105 (40), 89 (47). HRMS calcd for $C_{10}H_9NO_2$ 175.0633, found 175.0634.

2-Phenyloxazole-5-carboxaldehyde 5. To a solution of oxalyl chloride (1.16 g; 0.80 mL; 9.14 mmol) in dichloromethane (20 mL) at −78°C was added a solution of dimethyl sulphoxide (1.26 g; 1.14 mL; 0.016 mol) in dichloromethane (10 mL). The mixture was maintained at −78°C for 10 min and then a solution of the alcohol **6** (0.40 g; 2.28 mmol) in dichloromethane (10 mL) was added dropwise over 5 min and then stirring was continued for 30 min at −78°C. Triethylamine (3.00 g; 4.14 mL; 0.03 mol) was added dropwise over 5 min. The solution was allowed to warm to 0°C and was then quenched with saturated ammonium chloride solution. The solvent was evaporated and the residue diluted with ether (50 mL) and washed twice with 2 M HCl (20 mL) and the solvent removed to give a pale yellow solid. The solid was recrystallised from ether–light petroleum affording the title compound[12] **5** as white needles (0.36 g; 91%), mp 66–68°C. Anal for $C_{10}H_7NO_2$, calcd C, 69.4; H, 4.1; N, 8.1%; found C, 69.3; H, 4.4; N, 8.3%. ^{1}H NMR δ: 7.48–7.60 (m, 3H); 7.96 (s, 1H); 8.14–8.21 (m, 2H); 9.83 (s, 1H). ^{13}C NMR δ: 126.0, 127.8, 129.2, 132.4, 139.2, 149.8, 165.7, 176.5. IR ν_{max}: 1683, 1531, 1454, 1378, 1148 cm^{-1}. Mass spectrum *m*/*z*: 173 (M, 94%), 144 (100), 116 (96), 89 (43). HRMS calcd for $C_{10}H_7NO_2$ 173.0477, found 173.0478.

(*E*)-3-(2-Phenyloxazol-5-yl)propenoic acid 7. Malonic acid (0.09 g; 0.87 mmol) was added to a solution of the aldehyde **5** (0.15 g; 0.87 mmol) in pyridine (10 mL) and piperidine (2 drops) and the solution refluxed for 2 h. The solvent was evaporated and the residue acidified with 10 M HCl and extracted twice with ethyl acetate (40 mL) and the extract dried and evaporated to give a pale yellow solid, which was recrystallised from ethyl acetate–light petroleum, affording pale brown needles of the title compound **7** (0.18 g; 97%), mp 188–190°C. Anal for $C_{12}H_9NO_3$, calcd C, 66.9; H, 4.0; N, 6.5%; found C, 67.0; H, 4.2; N, 6.5%. ^{1}H NMR ($CDCl_3$/$(CD_3)_2SO$) δ: 6.46 (d, J=15.9 Hz, 1H); 7.39 (s, 1H); 7.46–7.54 (m, 4H); 8.06–8.12 (m, 2H). ^{13}C NMR ($CDCl_3$/$(CD_3)_2SO$) δ: 118.7, 126.4, 126.5, 127.5, 128.7, 131.0, 131.3, 148.0, 162.8, 168.1. IR ν_{max}: 1699, 1685, 1646, 1465, 1303 cm^{-1} Mass spectrum *m*/*z*: 215 (M, 6%), 84 (25), 79 (100). HRMS calcd for $C_{12}H_9NO_3$ 215.0582, found 215.0581.

(*Z*)-3-(2-Phenyloxazol-5-yl)propenoic acid 9. The propenoic acid **7** (0.10 g; 0.47 mmol) was dissolved in methanol (200 mL) and irradiated through pyrex (300 nm) for 1 h. The solvent was evaporated affording a yellow solid (0.10 g), which was shown to be a mixture (55:45) of the (*Z*)-**9** and (*E*)-propenoic acid **7** by NMR analysis. Further irradiation did not change the (*Z*) to (*E*) ratio. Attempts to separate the mixture by silica gel column chromatography (ethyl acetate–methanol, 1:4), anion exchange (acetate form) column chromatography (water–0.2 M acetic acid gradient elution), and reverse phase HPLC (methanol–water, 4:96)

were unsuccessful. (*Z*)-propenoic acid **9**: ^{1}H NMR ($CDCl_3$/$(CD_3)_2SO$) δ: 5.96 (d, J=12.9 Hz, 1H); 6.88 (d, J=12.9 Hz, 1H); 7.44–7.56 (m, 3H); 8.04–8.14 (m, 2H); 8.37 (s, 1H). ^{13}C NMR ($CDCl_3$/$(CD_3)_2SO$) δ: 117.9, 126.6, 126.7, 127.8, 128.8, 131.5, 134.2, 161.9, 168.5.

Diethyl 2-(2-phenyloxazol-5-yl)methylenemalonate 8. A solution of titanium tetrachloride (0.44 g; 0.25 mL; 2.31 mmol) in carbon tetrachloride (10 mL) was added to THF (20 mL), and then a mixture of the aldehyde **5** (0.20 g; 1.16 mmol) and diethyl malonate (0.19 g; 1.16 mmol) in THF (10 mL) was added. A solution of pyridine (0.37 g; 0.37 mL; 4.67 mmol) in THF (20 mL) was then added dropwise over 1 h. The reaction mixture was stirred at 20°C for 16 h and then water (20 mL) was added and the reaction mixture extracted twice with ether (40 mL) and the extract dried and evaporated to give a colourless oil. The oil was chromatographed on silica by radial chromatography (ether–dichloromethane–light petroleum, 1:2:7) affording a colourless oil, which solidified on standing. The solid was recrystallised from ether–light petroleum as white cubes (0.24 g; 67%), mp 56–57°C. Anal for $C_{17}H_{17}NO_5$, calcd C, 64.8; H, 5.4; N, 4.4%; found C, 64.6; H, 5.3; N, 4.4%. ^{1}H NMR δ: 1.34 (t, J=7.0 Hz, 3H); 1.36 (t, J=7.0 Hz, 3H); 4.32 (q, J=7.0 Hz, 2H); 4.47 (q, J=7.0 Hz, 2H); 7.44–7.52 (m, 3H); 7.55 (s, 2H); 8.00–8.06 (m, 2H). ^{13}C NMR δ: 13.7, 13.8, 61.6, 61.7, 123.9, 124.4, 126.3, 126.8, 128.8, 131.4, 134.8, 146.1, 163.6, 164.0, 165.7. IR ν_{max}: 1728, 1711, 1459, 1278, 1225, 1207 cm^{-1}. Mass spectrum *m*/*z*: 315 (M, 95%), 270 (21), 184 (28), 156 (18), 138 (31), 105 (100). HRMS calcd for $C_{17}H_{17}NO_5$ 315.1107, found 315.1107.

5-Hydroxymethyl-2-phenylsulphanylthiazole. The title compound was prepared from ethyl 2-phenylsulphanylthiazole-5-carboxylate[9] as was **6**. The product was purified by radial chromatography (ether–dichloromethane, 1:1) on silica as a pale orange oil (0.73 g; 67%). ^{1}H NMR δ: 4.63 (s, 2H); 4.80 (bs, 1H); 7.31–7.40 (m, 4H); 7.50–7.56 (m, 2H). ^{13}C NMR δ: 56.5, 129.5, 129.6, 131.2, 133.5, 139.9, 140.9, 166.6. IR ν_{max}: 3296, 1475, 1441, 1398, 1041, 1024 cm^{-1}. Mass spectrum *m*/*z*: 223 (M, 50%), 222 (65), 49 (100). HRMS calcd for $C_{10}H_9NOS_2$ 223.0126, found 223.0122.

2-Phenylsulphanylthiazole-5-carboxaldehyde. Oxidation of the above-mentioned product, as for **5**, gave a pale yellow oil which was purified by radial chromatography on silica (ether–dichloromethane, 1:4) as a pale yellow oil (0.64 g; 99%). ^{1}H NMR δ: 7.47–7.59 (m, 3H); 7.66–7.72 (m, 2H); 8.20 (s, 1H); 9.81 (s, 1H). ^{13}C NMR δ: 128.9, 130.3, 131.1, 135.2, 138.7, 152.14 180.1, 180.9. IR ν_{max}: 1657, 1508, 1388, 1345, 1271, 1233, 1165, 1050 cm^{-1}. Mass spectrum *m*/*z*: 221 (M, 100%), 220 (96), 192 (14), 109 (25), 89 (18), 86 (11). HRMS calcd for $C_{10}H_7NOS_2$ 220.9969, found 220.9973.

(*E*)-3-(2-Phenylsulphanylthiazol-5-yl)propenoic acid 11. Acid **11** was obtained following the above procedure, and was recrystallised from ethyl acetate–light petroleum as pale yellow needles (116 mg; 97%), mp 142–144°C. Anal for $C_{12}H_9NO_2S_2$, calcd C, 54.8; H, 3.4; N, 5.3%; found C, 54.5; H, 3.1; N, 5.3%. ^{1}H NMR δ: 5.92 (d, J=15.6 Hz, 1H); 7.45–7.57 (m, 3H); 7.66–7.79 (m, 4H). ^{13}C NMR δ: 118.5, 129.8, 130.3, 130.9, 134.7, 135.2, 135.6, 147.1, 171.4, 172.8. IR ν_{max}: 1690, 1616, 1465, 1377, 1315, 1259 cm^{-1}. Mass spectrum *m*/*z*: 263 (M, 100%), 262 (84), 140 (13), 128 (10), 110 (16), 100 (16). HRMS calcd for $C_{12}H_9NO_2S_2$ 263.0075, found 263.0071.

(*Z*)-3-(2-Phenylsulphanylthiazol-5-yl)propenoic acid 12. Photolysis of **11** as above for 1 h gave a yellow-brown oil (0.10 g), which later solidified and was identified as a mixture (2:3) of the (*Z*)-**12** and (*E*)-propenoic acid **11**. (*Z*)-propenoic acid **12**: ^{1}H NMR δ: 5.77 (d, J=12.1 Hz, 1H); 7.04 (d, J=12.1 Hz, 1H); 7.36–7.58 (m, 3H); 7.62–7.80 (m, 2H); 7.89 (s, 1H). ^{13}C NMR δ: 114.2, 129.9, 130.1, 132.7, 134.3, 134.6, 150.7, 170.4, 175.0.

Diethyl 2-(2-phenylsulphanylthiazol-5-yl)methylenemalonate. 2-Phenylsulphanylthiazole-5-carboxaldehyde was reacted with diethyl malonate as above. After 16 h, water (20 mL) was added and the mixture extracted twice with ether (40 mL) and the extract dried and evaporated to give a colourless oil (0.40 g). The oil was then purified on silica by radial chromatography (ether–dichloromethane–light petroleum, 1:2:7) as a pale yellow oil, which solidified on standing and was recrystallised from ether–light petroleum as white cubes (0.22 g; 61%), mp 77–79°C. Anal for $C_{17}H_{17}NO_4S_2$, calcd C, 56.2; H, 4.7; N, 3.9%; found C, 56.0; H, 4.7; N, 3.8%. ^{1}H NMR δ: 1.19 (t, J=7.2 Hz, 3H); 1.30 (t, J=7.2 Hz, 3H); 4.16 (q, J=7.2 Hz, 2H); 4.26 (q, J=7.2 Hz, 2H); 7.40–7.52 (m, 3H); 7.64–7.71 (m, 2H); 7.73 (s, 1H); 7.86 (s, 1H). ^{13}C NMR δ: 13.6, 13.9, 61.6, 61.7, 123.3, 129.6, 130.2, 130.7, 131.4, 132.1, 135.1, 150.6, 164.1, 165.6, 175.2. IR ν_{max}: 1729, 1716, 1614, 1465, 1379, 1283 cm^{-1}. Mass spectrum *m*/*z*: 363 (M, 48%), 180 (16), 155 (17), 133 (54), 115 (96), 93 (24), 91 (87), 71 (100). HRMS calcd for $C_{17}H_{17}NO_4S_2$ 363.0599, found 363.0598.

4-Hydroxymethyl-2-phenylthiazole. The starting thiazole was prepared by the procedure of Badr and co-workers.[13] The crude material was purified by radial chromatography on silica (ether–dichloromethane, 1:4) as a pale yellow oil, which solidified on standing (0.65 g; 56%), mp 53–54°C (lit.[14] mp 67–68°C). ^{1}H NMR δ: 4.20 (bs, 1H); 4.78 (s, 2H); 7.13 (s, 1H); 7.35–7.45 (m, 3H); 7.80–7.90 (m, 2H). ^{13}C NMR δ: 60.4, 114.6, 126.4, 128.8, 130.0, 133.2, 157.5, 168.8. IR ν_{max}: 3297, 3084, 1464, 1033, 1003 cm^{-1}. Mass spectrum *m*/*z*: 191 (M, 100%), 190 (58), 162 (38), 121 (13), 104 (31). HRMS calcd for $C_{10}H_9NOS$, 191.0405, found 191.0410.

2-Phenylthiazole-4-carboxaldehyde. Swern oxidation as above gave a yellow oil which was purified by radial chromatography on silica (dichloromethane) as a pale yellow oil that solidified on standing and was not further purified (0.59 g; 99%) (lit.[15] mp 52°C). ^{1}H NMR δ: 7.43–7.50 (m, 3H); 7.96–8.04 (m, 2H); 8.17 (s, 1H); 10.08 (s, 1H). ^{13}C NMR δ: 126.8, 127.3, 129.1, 130.9, 132.5, 155.6, 169.6, 184.9. IR ν_{max}:1683, 1469, 1440, 1133, 1006 cm^{-1}. Mass spectrum *m*/*z*: 189 (M, 72%), 150 (89), 128 (28), 104 (21), 86 (24). HRMS calcd for $C_{10}H_7NOS$ 189.0248, found 189.0252.

(*E*)-3-(2-Phenylthiazol-4-yl)propenoic acid 14. The crude product, obtained as above with **7**, was recrystallised from

ethyl acetate–light petroleum as a pale brown powder (0.30 g; 98%), mp 188–190°C (lit.[16] mp 192–194°C). Anal for $C_{12}H_9NO_2S$, calcd C, 62.3; H, 3.9; N, 6.1%; found C, 61.8; H, 3.9; N, 6.4%. ^{1}H NMR ($CDCl_3$/$(CD_3)_2SO$) δ: 6.87 (d, J=15.5 Hz, 1H); 7.42–7.54 (m, 4H); 7.67 (d, J=15.5 Hz, 1H); 7.94–8.04 (m, 2H). ^{13}C NMR ($CDCl_3$/$(CD_3)_2SO$) δ: 120.7, 121.7, 126.8, 129.1, 130.7, 133.0, 137.3, 152.44 169.1, 169.9. IR ν_{max}: 3097, 1667, 1435, 1321 cm^{-1}. Mass spectrum *m*/*z*: 231 (M, 10%), 187 (100). HRMS calcd for $C_{12}H_9NO_2S$ 231.0354, found 231.0357.

(*Z*)-3-(2-Phenylthiazol-4-yl)propenoic acid 15. Photolysis for 1 h gave a yellow-brown solid, which was identified as a mixture (2:1) of the (*Z*)-**15** and (*E*)-propenoic acid **14**. (*Z*)-propenoic acid **15**: ^{1}H NMR ($CDCl_3$/$(CD_3)_2SO$) δ: 6.11 (d, J=13.1 Hz, 1H); 6.86 (d, J=13.1 Hz, 1H); 7.42–7.60 (m, 3H); 7.62 (s, 1H); 7.86–7.94 (m, 2H). ^{13}C NMR ($CDCl_3$/$(CD_3)_2SO$) δ: 123.3, 124.1, 126.8, 129.0, 129.5, 130.7, 131.9, 149.5, 166.4, 169.9.

Dimethyl 2-(2-phenylthiazol-4-yl)methylenemalonate. The crude product was purified by radial chromatography on silica (ether–dichloromethane–light petroleum, 1:2:7) as a pale yellow oil that solidified on standing, and was recrystallised from ether–dichloromethane–light petroleum as a white powder (0.26 g; 81%), mp 88–89°C. Anal for $C_{15}H_{13}NO_4S$, calcd C, 59.4; H, 4.3; N, 4.6%; found C, 59.4; H, 4.3; N, 4.6%. ^{1}H NMR δ: 3.86 (s, 3H); 3.95 (s, 3H); 7.42–7.49 (m, 3H); 7.58 (s, 1H); 7.66 (s, 1H); 7.88–7.95 (m, 2H). ^{13}C NMR δ: 52.6, 52.7, 125.0, 126.0, 126.9, 129.1, 130.8, 133.1, 133.1, 150.2, 164.8, 167.0, 169.0. IR ν_{max}: 3123, 1729, 1629, 1459, 1255, 1232, 1213 cm^{-1}. Mass spectrum *m*/*z*: 303 (M, 100%), 272 (65), 244 (54), 215 (11), 204 (13), 189 (14). HRMS calcd for $C_{15}H_{13}NO_4S$ 303.0565, found 303.0575.

2,5-Dimethyl-4-hydroxymethyloxazole. The starting oxazole was prepared by the procedure of Treibs and Sutter[17] as a pale yellow solid that was recrystallised from ether–light petroleum as pale orange cubes (1.86 g; 57%), mp 76–78°C (lit.[18] 82–84°C). ^{1}H NMR δ: 2.28 (s, 3H); 2.39 (s, 3H); 4.46 (s, 2H); 4.72 (bs, 1H). ^{13}C NMR δ: 9.7, 13.4, 55.1, 130.0, 144.7, 160.0. IR ν_{max}: 3253, 1585, 1456, 1378, 1284, 1025, 816 cm^{-1}. Mass spectrum *m*/*z*: 127 (M, 48%), 110 (22), 98 (11), 86 (21), 43 (100). HRMS calcd for $C_6H_9NO_2$ 127.0633, found 127.0633.

2,5-Dimethyloxazole-4-carboxaldehyde. The crude product was purified by radial chromatography on silica (dichloromethane–light petroleum, 1:1) as a pale yellow oil[18] (0.71 g; 80%). ^{1}H NMR δ: 2.48 (s, 3H); 2.60 (s, 3H); 9.90 (s, 1H). ^{13}C NMR δ: 11.0, 13.2, 134.7, 156.4, 160.2, 184.8. IR ν_{max}: 1699, 1614 cm^{-1}. Mass spectrum *m*/*z*: 125 (M, 95%), 110 (55), 84 (48), 82 (44), 43 (100). HRMS calcd for $C_6H_7NO_2$ 125.0477, found 125.0480.

(*E*)-3-(2,5-Dimethyloxazol-4-yl)propenoic acid 17. The usual procedure gave the title compound **17** (0.26 g; 64%), mp 150–152°C. Anal for $C_8H_9NO_3$, calcd C, 57.5; H, 5.4; N, 8.4%; found C, 57.6; H, 5.5; N, 8.2%. ^{1}H NMR δ: 2.40 (s, 3H); 2.46 (s, 3H); 6.52 (d, J=15.6 Hz, 1H); 7.52 (d, J=15.6 Hz, 1H). ^{13}C NMR δ: 10.2, 13.5, 117.4, 131.8, 134.1, 150.4, 161.0, 172.1. IR ν_{max}: 3570, 1699, 1654, 1590, 1458, 1309, 1275, 1186 cm^{-1}. Mass spectrum *m*/*z*: 167 (M, 48%), 149 (55), 123 (52), 111 (29), 80 (34), 43 (100). HRMS calcd for $C_8H_9NO_3$ 167.0582, found 167.0587.

(*Z*)-3-(2,5-Dimethyloxazol-4-yl)propenoic acid 18. Photolysis for 1 h gave a cream solid that contained a 3:2 mixture of (*Z*)-**18** and (*E*)-propenoic acid **17**. (*Z*)-propenoic acid **18**: ^{1}H NMR δ: 2.43 (s, 3H); 2.53 (s, 3H); 5.92 (d, J=13.1 Hz, 1H); 6.60 (d, J=13.1 Hz, 1H). ^{13}C NMR δ: 9.8, 13.3, 121.1, 125.3, 129.8, 151.2, 159.6, 166.8.

Diethyl 2-(2,5-dimethyloxazol-4-yl)methylenemalonate. 2,5-Dimethyloxazole-4-carboxaldehyde and diethyl malonate were reacted as above. After 16 h at 20°C water (20 mL) was added and the mixture extracted twice with ether (40 mL). The resulting pale yellow oil was diluted with light petroleum (10 mL) and cooled to −5°C for 16 h to give a solid, which was washed twice with light petroleum (20 mL) and recrystallised from ether–light petroleum as white cubes (0.47 g; 63%), mp 50–51°C. Anal for $C_{13}H_{17}NO_5$, calcd C, 58.4; H, 6.4; N, 5.2%; found C, 58.5; H, 6.2; N, 5.3%. ^{1}H NMR δ: 1.32 (t, J=7.2 Hz, 3H); 1.37 (t, J=7.2 Hz, 3H); 2.37 (s, 3H); 2.39 (s, 3H); 4.28 (q, J=7.2 Hz, 2H); 4.40 (q, J=7.2 Hz, 2H); 7.40 (s, 1H). ^{13}C NMR δ: 10.3, 13.7, 13.8, 14.0, 61.3, 124.3, 128.8, 130.7, 152.14 160.1, 164.5, 166.7. IR ν_{max}: 1729, 1708, 1463, 1286, 1247, 1199 cm^{-1}. Mass spectrum *m*/*z*: 267 (M, 14%), 221 (100), 149 (15), 123 (15). HRMS calcd for $C_{13}H_{17}NO_5$ 267.1107, found 267.1104.

5-Methyl-2-phenyl-4-hydroxymethyloxazole. The oxazole was prepared by the procedure of Smith[19] as white needles (1.43 g; 82%), mp 111–112°C (lit.[20] 118–119°C). ^{1}H NMR δ: 2.17 (s, 3H); 3.20 (bs, 1H); 4.66 (s, 2H); 7.37–7.45 (m, 3H); 7.93–9.02 (m, 2H). ^{13}C NMR δ: 11.2, 53.9, 126.2, 127.1, 128.7, 130.34 134.8, 145.6, 160.5. IR ν_{max}: 3203, 1461, 1551, 1446, 1017, 783 cm^{-1}. Mass spectrum *m*/*z*: 189 (M, 100%), 172 (79), 130 (71), 105 (90), 77 (66). HRMS calcd for $C_{11}H_{11}NO_2$ 189.0790, found 189.0788.

5-Methyl-2-phenyloxazole-4-carboxaldehyde. Swern oxidation as above gave pale green needles of the title compound (0.37 g; 53%), mp 103–104°C (lit.[21] mp 90.5–91.5°C). ^{1}H NMR δ: 2.56 (s, 3H); 7.43–7.62 (m, 3H); 8.08–8.22 (m, 2H). ^{13}C NMR δ: 12.6, 125.8, 127.5, 128.9, 132.0, 145.0, 150.1, 163.8, 176.3. IR ν_{max}: 1673, 826 cm^{-1}. Mass spectrum *m*/*z*: 187 (M, 100%), 158 (53), 130 (82), 104 (35). HRMS calcd for $C_{11}H_9NO_2$ 187.0633, found 187.0633.

(*E*)-3-(5-Methyl-2-phenyloxazol-4-yl)propenoic acid 20. Reaction of the above aldehyde with malonic acid gave a solid that was recrystallised from ethyl acetate–light petroleum as a pale brown powder (235 mg; 96%), mp 150–152°C. ^{1}H NMR δ: 2.38 (s, 3H); 6.36 (d, J=15.4 Hz, 1H); 7.38–7.60 (m, 3H); 7.59 (d, J=15.4 Hz, 1H); 8.00–8.20 (m, 2H). ^{13}C NMR δ: 12.0, 115.0, 126.4, 126.9, 128.9, 131.3, 143.0, 143.4, 162.3, 171.8. IR ν_{max}: 3063, 1716, 1704, 1638, 1457, 1258, 1174 cm^{-1}. Mass spectrum *m*/*z*: 229 (M, 100%), 126 (63), 105 (70). HRMS calcd for $C_{13}H_{11}NO_3$ 229.0739, found 229.0738.

Potassium dicarboxylate compounds 10, 13, 16 and 19. The dicarboxylate compounds **10**, **13**, **16** and **19** were prepared from the diester compounds by stirring each with two molar equivalents of potassium hydroxide in ethanol for 1 h at 20°C. The solvent was evaporated to give a white solid confirmed to be the potassium salt by NMR spectroscopy.

Acknowledgements

The authors are grateful to the Australian Research Council for support of this work. D.S.M. acknowledges the Australian Post-graduate Award.

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