Chemistry of 5-oxodihydroisoxazoles. Part 17.[1] Acylation of 5-oxodihydroisoxazoles

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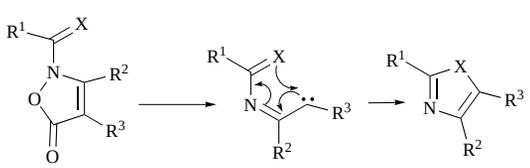
2-Unsubstituted isoxazol-5(4*H*)-ones and -5(2*H*)-ones may be acylated by acid chlorides, anhydrides or carboxylic acids in the presence of carbodiimides, to give *O*- and *N*-acylated products. The solvent, the presence of base and the temperature are found to alter the product ratios dramatically, but the substituents present at C-3 have the greatest effect. Aliphatic acid anhydrides and chlorides generally react at nitrogen, but aroyl halides give significant proportions of *O*-acylated products. Limited success in converting *O*-aroyl to *N*-aroyl isoxazolones is reported.

Introduction

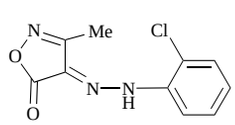
For a number of years our group has investigated the chemistry of isoxazolones **1**,[1] particularly their propensity to extrude carbon dioxide to give iminocarbenes **2** either by pyrolytic[2] or photochemical[3] means. The iminocarbene **2** can be captured by nucleophiles in an intermolecular reaction giving enamines,[4] or intramolecularly to give imidazoles **3** (X = N)[5] and oxazoles **3** (X = O)[6] (Scheme 1).



1 **2** **3**

Scheme 1

Although methods have been found to achieve high yields in these reactions, with oxazoles the overall effectiveness of the procedure depends on the ready availability of *N*-acylisoxazolones. No detailed study of a procedure to achieve this aim has been reported, although a number of *N*-acylisoxazolones have been reported before this present study. Rabe[7] reported the benzoylation of 3-phenylisoxazol-5(4*H*)-one in 1897, obtaining mixtures of the *N*- and *O*-acylated materials by the Schotten–Baumann procedure, and *O*-acylated material with benzoyl chloride in pyridine. He was unable to assign structures with certainty, but correctly ruled out the occurrence of *C*-acylation. Posner[8] acetylated the same isoxazolone, assuming the product to be the *N*-acetyl derivative, but Korte and Storiko obtained the same compound with acetyl chloride in picoline[9] and claimed it was the 5-acetoxy derivative without offering any evidence. Kohler and Blatt[10] benzoylated 3,4-diphenylisoxazol-5(2*H*)-one, but again were unable to assign a structure to the product. Eckhard *et al.*[11] *N*-acylated the isoxazolone fungicide drazoxolon **4** with a number of aliphatic



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and aromatic acid chlorides, and assigned structures to the products on the basis of infrared and ultraviolet spectroscopy. More recently Kurkov[12] reported the formation of *N*- and *O*-acylated materials from the reaction of 3-alkylisoxazol-5(4*H*)-ones with substituted benzoyl chlorides, and claimed the chromatographic separation of the products. The *N*-acyl compounds showed promising fungicidal activity.

Although acylation of a number of ambident anions has been thoroughly investigated in the past,[13] especially in relation to *O*- versus *C*-acylation of enolates,[14] much less attention has been given to acylation of the pyridone–hydroxypyridine tautomers, which should serve as models for studies of the isoxazol-5-ones. Effenberger *et al.*[15] studied the acylation of 4-pyridones and found that *N*-acyl derivatives could be isolated only when the 4-pyridone was reacted with aliphatic acid chlorides and anhydrides. 4-Acyloxypyridines were the major products when aryl acid chlorides and anhydrides were used, and it was reported that the *N*- and *O*-acyl compounds were in equilibrium in solution, with the equilibrium position depending on the structure of the acyl group, solvent and temperature.

Discussion

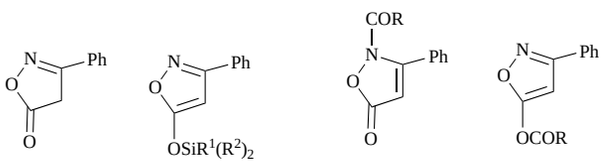
3-Phenylisoxazol-5(4*H*)-one **5** was chosen as the model compound on which to trial various acylation procedures, as Rabe[7] had already established that both *N*- and *O*-acylation occurred readily, and we found it was one of the most challenging substrates for *N*-acylation. This substrate clearly also has the possibility of undergoing *C*-acylation at C-4, but such reactions have generally been reported only when acid ortho esters are used,[7,9,16] although Korte and Storiko[9] achieved acylation of **5** at C-4 with boiling acetic anhydride in the presence of sodium acetate. The relative proportions of acylation products obtained from **5** under a variety of conditions are shown in Table 1. Inspection of Table 1 suggests that *N*-acylation with aliphatic acyl groups is relatively easily achieved, and that aromatic acid chlorides are more likely to acylate on oxygen. The Schotten-Baumann procedure gave the best ratio of *N*- to *O*-acylated materials, but the total yield was unacceptably low (34%). The use of the mixed anhydride benzoic trifluoroacetic anhydride[17] unexpectedly gave a mixture of *O*-benzoyl and *N*-trifluoroacetyl derivatives. Williams[18] overcame non selective acylation of triazoles by first making a trimethylsilyl derivative, but our *O*-silylated isoxazoles **6** and **7** gave essentially only *O*-benzoylation with benzoyl chloride or benzoyl fluoride, while ether **8** failed to react.

Sodium,[9] silver[19,20] and tetrabutylammonium salts of **5** were reacted in non-polar solvents with benzoyl chloride in the hope of achieving significant *N*-acylation,[9,21] but again only *O*-acylation was observed.

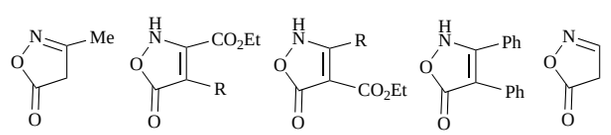
Table 1 *N*- and *O*-Acylation of 3-phenylisoxazol-5(4*H*)-one **5**

Reaction conditions	Total Yield (%)	Ratio of *O*-: *N*-acylation
MeCOCl, CH_2Cl_2, 40 °C	92	0:100
$(MeCO)_2O$, 130 °C	94	0:100
$(MeCO)_2O$, 35 °C	95	0:100
PhCOCl, OH^-, H_2O, 20 °C	34	20:80
PhCOCl, $(CH_2)_2Cl_2$, 80 °C	90[b]	80:20
PhCOCl, pyridine, CH_2Cl_2, 20 °C	90[b]	95:5
PhCOCl, pyridine	90	95:5
$PhCO_2H$, DCC[a]	85	90:10
PhCOF	N/R	
(i) Bu^tPh_2SiCl (ii) PhCOF, PhH, 80 °C	40	85:15
(i) Me_3SiCl, NEt_3 (ii) PhCOF, 20 °C	95[b]	95:5
PhCOCl, NBu_4^+ salt, PhH, 20 °C	95	87:13
PhCOCl, Ag^+ salt, PhH, 80 °C	90[b]	100:0
PhCOCl, Na^+ salt, acetone, 20 °C	90[b]	100:0
(i) Bu^tMe_2SiCl (ii) PhCOCl, 20 °C	90[b]	95:5
PhCOBr, pyridine, CH_2Cl_2, 20 °C	95	85:15
$(CF_3CO)_2O$, 40 °C	100	0:100
Pyrrole-2-carbonyl Cl, pyridine, 20 °C	70	0:100

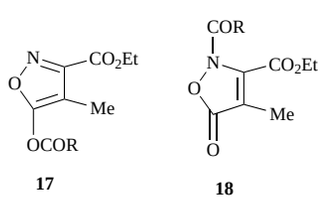
[a] Dicyclohexylcarbodiimide. [b] Determined by ^{1}H NMR spectral analysis.



5 **6** $R^1 = R^2 = Me$ **7** $R^1 = Bu^t$, $R^2 = Me$ **8** $R^1 = Bu^t$, $R^2 = Ph$ **9** **10**



11 **12** **13** R = H **14** R = Me **15** **16**



17 **18**

The isolation of the two acylation products from **5** allowed us to establish spectroscopic criteria that clearly differentiated the *N*-acylated material **9** from the *O*-acylated compound **10**. In this pair, the position of H-4 in the ^{1}H NMR spectrum was diagnostic: H-4 in **9** was generally seen around δ 5.4, and H-4 in **10** around δ 6.1. Additionally, the infrared spectrum of **9** would be expected to show two carbonyl bands and **10** only one.[22] Thus the *N*-acylated compounds showed lactone stretching around 1760 cm^{-1} and *N*-acyl bands at 1695 cm^{-1} (**9**; R = Ph) and 1719 cm^{-1} (**9**; R = Me), while the *O*-acylated compounds exhibited a strong band at 1770 cm^{-1}. The ^{13}C resonance for C-4[23] proved to be the most generally diagnostic: C-4 in the *N*-acylated isomer resonated at higher field than in the *O*-acylated isomer.

In an attempt to ascertain if steric or electronic factors bore the major responsibility for the poor *N*-acylation yields, the 3-methylisoxazolone **11** was investigated next. Again, *N*-acylation with aliphatic anhydrides or acid chlorides was extremely efficient, and benzoylation in the presence of triethylamine now gave a 55:45 ratio of *N*- to *O*-acylation. If **11** was first brominated at C-4, benzoylation now gave more than 90% of *N*-benzoylated material. The isoxazolone-3-carboxylate **12** (R = Me) showed a preference for acylation on nitrogen with aliphatic acid chlorides (90% *N*-acylation) but not with all aroyl chlorides (benzoyl: 40% *N*-acylation; 2,5-dimethyloxazole-4-carbonyl: 85% *N*-acylation); **12** (R = H) generally was acylated on nitrogen.

The isoxazolone-4-esters **13** and **14** showed decreased nucleophilicity due to the presence of the additional carbonyl group. Again, reaction of **13** with aliphatic anhydrides or acid chlorides occurred exclusively on nitrogen. Benzoyl chloride and other aromatic acyl halides also reacted with **13** to give high yields of *N*-acylated products, but required several hours at 80 °C. A number of examples of *N*-acylated products are collected in Table 2. The more hindered isoxazolone **14** gave *N*-benzoylation to the extent of 60% in the absence of base, but only 30% in the presence of base. Finally, acylation of the highly substituted isoxazolone **15** was investigated: benzoylation gave 50% of the *N*-benzoyl and 35% of the *O*-benzoyl derivative, whereas acetylation occurred completely on nitrogen. By contrast isoxazol-5(4*H*)-one **16** gave 60% *N*-benzoylated material, with only a trace of *O*-benzoylation.

The acylation results reported herein are somewhat similar to those observed by Effenberger *et al.* with 4-pyridones.[15] In those studies it was reported that equilibrium between *O*- and *N*-acylated material was readily achieved in solution. None of the acylated isoxazolones prepared by us underwent any change in solution. However, limited success in converting a typical 5-acyloxyisoxazole **17**, derived from isoxazol-5(2*H*)-one **12**, to the corresponding *N*-acyl derivative **18** was achieved in two ways. When the *O*-acylisoxazole **17** (R = Ph) was treated with benzoyl chloride for a brief period at 150 °C, 25% was converted to the *N*-acyl derivative **18** (R = Ph), but decomposition occurred on prolonged heating. When a 1:1 mixture of the *O*-acylisoxazole **17** (R = 2,5-dimethyl-1,3-oxazol-4-yl) and the *N*-acylisoxazole **18** (R = 2,5-dimethyl-1,3-oxazol-4-yl) was heated to 150 °C in sulfolane,[18] equilibration occurred, favouring **18** to the extent of 90%. While this was a general phenomenon, it was noted unfortunately that many of the *N*-acylated compounds were hydrolysed during the extensive washing with water required to remove the sulfolane.

Experimental

Freshly distilled solvents were used throughout, and anhydrous solvents were dried according to Perin and Armarego.[24] Light petroleum refers to the fraction boiling between 40–60 °C. Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR measurements were determined on a Gemini Varian 300 nuclear magnetic resonance spectrometer in deuteriochloroform with tetramethylsilane as an internal standard and coupling constants *J*, are measured in Hz. Infrared spectra were recorded on a Perkin Elmer 1600 FT-infrared spectrophotometer, using fused sodium chloride cells. Solids were measured as Nujol mulls and liquids as films. Mass spectra and high resolution mass spectra were recorded on a Kratos MS25RF spectrometer. Microanalyses were performed by the Australian Microanalytical Service, Melbourne and the Chemical & Micro Analytical Services Pty. Ltd, Essendon North.

Acylation of 3-phenylisoxazol-5(4*H*)-one 5

2-Benzoyl-3-phenylisoxazol-5(2*H*)-one 9 (R = Ph) and 3-phenylisoxazol-5-yl benzoate 10 (R = Ph). Benzoyl chloride (4 ml) was added to a well stirred solution of 3-phenylisoxazolone[8] (2.5 g) in aqueous 2 M sodium hydroxide (15 ml). After 2 h, further benzoyl chloride (2 ml) was added and stirring was continued for 2 h. The mixture was extracted with diethyl ether (2 × 100 ml), and the dried extract evaporated to give a yellow semi-solid. Fractional crystallisation from benzene gave 2-benzoyl-3-phenylisoxazol-5(2*H*)-one **9** (R = Ph) (1.01 g, 29%)

Table 2 Ethyl 2-acyl-5-oxo-2,5-dihydroisoxazole-4-carboxylate **1** ($R^3 = CO_2Et$, X = O)[a]

R^1	R^2	mp (°C)	Yield (%)	δ_H	δ_C	ν_{max}/cm^{-1} (C=O)
Bz	H	160–162	89	1.35 (3 H, t, *J* 7), 4.10 (2 H, s), 4.36 (2 H, q, *J* 7), 7.20–7.57 (5 H, m) and 9.01 (1 H, s)		1800, 1774, 1739
Pr^i	H	57–58	95	1.27 (6 H, d, *J* 7), 1.33 (3 H, t, *J* 7), 4.35 (2 H, q, *J* 7), 9.07 (1 H, s)		1786, 1741, 1702
Ph	H	108–110	93	1.40 (3 H, t, *J* 7), 4.43 (2 H, q, *J* 7), 7.53–7.83 (3 H, m), 7.97–8.23 (2 H, m) and 9.23 (1 H, s)	14.1, 61.5, 100.1, 128.1, 128.8, 130.4, 134.5, 147.7, 159.9, 160.0 and 162.7	1794, 1721
2-ClC_6H_4	H	146–147	88	1.37 (3 H, t, *J* 7), 4.39 (2 H, q, *J* 7), 7.53–7.70 (4 H, m) and 8.98 (1 H, s)		1781, 1717
4-ClC_6H_4	H	99–100	87	1.41 (3 H, t, *J* 7), 4.38 (2 H, q, *J* 7), 7.25 (2 H, d, *J* 9), 8.08 (2 H, d, *J* 9) and 9.25 (1 H, s)		1791, 1708
2-$MeOC_6H_4$	H	115–116	91	1.35 (3 H, t, *J* 7), 3.89 (3 H, s), 4.37 (2 H, q, *J* 7), 7.00–7.78 (4 H, m) and 8.90 (1 H, s)		1810, 1703
4-$MeOC_6H_4$	H	119–120	88	1.37 (3 H, t, *J* 7), 3.91 (3 H, s), 4.38 (2 H, q, *J* 7), 7.03 (2 H, d, *J* 9), 8.12 (2 H, d, *J* 9) and 9.25 (1 H, s)	14.3, 55.8, 61.5, 99.3, 114.4, 120.0, 133.4, 148.0, 159.2, 160.2, 163.2 and 164.9	1800, 1689
2-$NO_2C_6H_4$	H	155–156	85	1.39 (3 H, t, *J* 7), 4.41 (2 H, q, *J* 7), 8.28 (2 H, d, *J* 13), 8.43 (2 H, d, *J* 13) and 9.26 (1 H, s)	14.3, 62.0, 123.9, 131.7, 133.6, 147.4, 158.5, 159.6; C-4[b]	1790, 1718
$PhCH_2CH_2$	H	104–106	80	1.35 (3 H, t, *J* 7.14), 3.03–3.15 (4 H, m), 4.34 (2 H, q, *J* 7.14), 7.15–7.35 (5 H, m) and 8.95 (1 H, s)	14.2, 29.2, 35.1, 61.5, 100.1, 126.8, 128.3, 128.7, 138.8, 145.2, 159.9, 162.3 and 164.9	1804, 1738
pyrrol-2-yl	H	182–184	85	1.40 (3 H, t, *J* 7), 4.42 (2 H, q, *J* 7), 6.65 (1 H, m), 7.40 (1 H, m), 7.60 (1 H, m), 9.38 (1 H, s) and 10.5 (NH, br s)	13.7, 63.3, 98.2, 114.0, 119.2, 124.5, 131.1, 151.3, 162.1 and 165.9	1802, 1684
Ph	Me	108–111	60[c]	1.27 (3 H, t, *J* 7), 2.93 (3 H, s), 4.26 (2 H, q, *J* 7), 7.39 (2 H, t, *J* 7), 7.54 (1 H, t, *J* 7) and 7.77 (2 H, d, *J* 7)	13.9, 14.7, 60.9, 97.8, 128.3, 129.8, 129.9, 133.7, 161.2, 162.1, 162.9 and 164.5	1789, 1716
Me	H	104–105	91	1.39 (3 H, t, *J* 7), 2.53 (3 H, s), 4.38 (2 H, q, *J* 7) and 9.04 (1 H, s)	14.2, 21.1, 61.0, 100.3, 145.2, 160.0 and 162.5[d]	1785, 1744, 1694
Me	Me	oil	95	1.22 (3 H, t, *J* 7), 2.37 (3 H, s), 2.82 (3 H, s) and 4.20 (2 H, q, *J* 7)	13.9, 14.2, 22.8, 60.8, 97.4, 161.1, 161.8, 162.7 and 165.2	1785, 1746, 1709

[a] All compounds gave satisfactory CHN analyses (solids) or high resolution mass spectral data (liquids). [b] C-4 ester or lactone resonances not observed. [c] 30% of ethyl 3-methyl-5-benzoyloxyisoxazole-4-carboxylate. [d] Amide not observed.

and the more soluble 3-phenylisoxazol-5-yl benzoate **10** (R = Ph) (0.18 g, 5%).

Recrystallisation of **9** from benzene–light petroleum gave white needles, mp 158–160 °C (lit., α-isomer,[7] 161 °C) (Found: $M^+ - 44$, 221.0840. Calc. for $C_{15}H_{11}NO$: *M*, 221.0841); δ_H 5.83 (1 H, s), 7.47–7.7 (8 H, m) and 7.93–8.17 (2 H, m,); δ_C 96.8, 127.8, 128.1, 128.5, 128.6, 130.4, 130.6, 131.6, 133.8, 163.2, 164.7 and 166.7; ν_{max}/cm^{-1} 1759, 1692, 1605 and 1283; *m*/*z* 221 (M − 44, 28%), 193 (20), 165 (4) and 105 (100).

Recrystallisation of **10** from benzene gave white needles, mp 112–113 °C (lit., β-isomer,[7] 115 °C) (Found: $M^+ - 28$, 237.0195. Calc. for $C_{15}H_{11}NO_2$: *M*, 237.0190); δ_H 6.57 (1 H, s), 7.28–8.0 (8 H, m) and 8.19–8.34 (2 H, m); ν_{max}/cm^{-1} 1771, 1599 and 1575; *m*/*z* 237 (M − 28, 18%), 192 (6), 122 (60) and 105 (100).

2-Acetyl-3-phenylisoxazol-5(2*H*)-one 9 (R = Me). This was prepared in 90% yield (114 mg) by heating **5** (100 mg) with acetic anhydride (3 ml) at 100 °C for 4 h and evaporating the solvent, mp 137–139 °C (lit.,[8] 137–138 °C) (Found: M^+, 203.0582. Calc. for $C_{11}H_9NO_3$: *M*, 203.0582); δ_H 2.47 (3 H, s), 5.60 (1 H, s) and 7.51 (5 H, s); δ_C 23.0, 96.2, 127.3, 128.1, 128.5, 131.4, 161.0, 165.1 and 165.8; ν_{max}/cm^{-1} 1774, 1719, 1607 and 1562; *m*/*z* 203 (M, 22%), 161 (73), 144 (7), 130 (10) and 103 (100).

3-Phenyl-2-trifluoroacetylisoxazol-5(2*H*)-one 9 (R = CF_3). *Method A*.—Isoxazolone **5** (200 mg) was refluxed in trifluoroacetic anhydride for 2 h as above. Removal of solvent gave the oily N-*trifluoroacetyl compound* **9** (R = CF_3) (315 mg) which was spectroscopically pure, but decomposed readily in moist air (Found: M^+, 257.0304. $C_{11}H_6F_3NO_3$ requires *M*, 257.0299); δ_H 5.92 (1 H, s) and 7.54 (5 H, s); δ_C 99.1, 114.6, (q, *J* 286), 121.8, 128.6, 128.8, 132.7, 159.3 (q, *J* 57), 162.0 and 165.66; ν_{max}/cm^{-1} 1809, 1701 and 1162; *m*/*z* 257 (M, 30%), 213 (5), 189 (8), 172 (4), 144 (26), 102 (48), 49 (38) and 44 (100).

Method B.—Isoxazolone **5** (200 mg) was refluxed in anhydrous benzene (20 ml) and benzoic trifluoroacetic anhydride[17] (2 ml) for 8 h. Removal of solvent gave a mixture (1:1) of the *O*-acyl **10** (R = Ph) and *N*-trifluoroacetyl **9** (R = CF_3) derivatives, as determined by comparison of the ^1H and ^{13}C NMR spectra with those of the authentic samples prepared above.

3-Phenyl-2-(pyrrol-2-ylcarbonyl)isoxazol-5(2*H*)-one 9 (R = pyrrol-2-yl). Reaction of **5** (100 mg) with pyrrole-2-carbonyl chloride (100 mg) in pyridine at 20 °C for 14 h gave 3-*phenyl*-2-(*pyrrol*-2-*ylcarbonyl*)*isoxazol*-5(2H)-*one* **9** (R = pyrrol-2-yl) (178 mg, 70%) after crystallisation from benzene–light petroleum, mp 181–183 °C (Found: M^+, 254.0682. $C_{14}H_{10}N_2O_3$ requires *M*, 254.0691); δ_H 5.65 (1 H, s), 6.39 (1 H, dt, *J* 4, 2.6), 7.04 (1 H, dq, *J* 2.5, 1.4), 7.44–7.58 (6 H, m) and 9.55 (NH, s); δ_C 95.9, 112.0, 120.7, 121.9, 126.1, 128.2, 128.4, 131.3, 154.9, 162.9 and 166.7; ν_{max}/cm^{-1} 3315, 1777 and 1645; *m*/*z* 254 (M, 4%), 210 (7), 94 (100) and 66 (18).

O-Silylation of 3-phenylisoxazol-5(4*H*)-one 5

Isoxazolone **5** (100 mg, 0.62 mmol) was treated with the corresponding silyl chloride (1.0 mmol) in dichloromethane (10 ml) and triethylamine (63 mg) at 20 °C for 24 h. Removal of solvent and excess reagents, and extraction into diethyl ether gave the crude silyl ethers **6**–**8**, whose identity was confirmed by ^1H NMR spectroscopy. Benzoyl chloride or benzoyl fluoride (0.75 mmol) was added to a benzene solution (10 ml) of the silyl ether. The results of the reactions are collected in Table 1.

2-Acetyl-4-methyl-3-phenylisoxazol-5(2*H*)-one 1 ($R^1 = R^3 =$ Me, R^2 = Ph, X = O)

4-Methyl-3-phenylisoxazol-5-(2*H*)-one[25,26] (200 mg) was acetylated as above. Distillation (142 °C/1 mm Hg) gave a viscous *pale yellow oil* (248 mg, 89%) (Found: C, 66.2; H, 5.3; N, 6.4%; M^+, 217.0745. $C_{12}H_{11}NO_3$ requires C, 66.4; H, 5.1; N, 6.5%; *M*, 217.0739); δ_H 1.85 (3 H, s), 2.40 (3 H, s) and 7.44 (5 H, s); ν_{max}/cm^{-1} 1762, 1722 and 1624; *m*/*z* 217 (M, 3%), 173 (63), 158 (11), 146 (6), 131 (22), 115 (11) and 103 (100).

Acylation of 3-methylisoxazol-5(4*H*)-one 11

3-Methylisoxazol-5-yl benzoate and 2-benzoyl-3-methylisoxazol-5(2*H*)-one 1 (R^1 = Ph, R^2 = Me, R^3 = H, X = O). 3-Methylisoxazol-5-one[27] (2.0 g, 0.02 mol), benzoyl chloride (3.0 g, 0.021 mol) and triethylamine (2.10 g, 0.021 mol) were stirred at room temperature for 24 h in dichloromethane (50 ml). The solvent was evaporated and the resulting oil was dissolved in diethyl ether and washed with 1 M hydrochloric acid (2 × 10 ml), water (2 × 10 ml), and evaporated. Purification by silica gel column chromatography (diethyl ether–light petroleum) afforded two compounds. 3-*Methylisoxazol*-5-*yl benzoate* (1.70 g, 42%) was recrystallised from acetone–water as white crystals, mp 43–45 °C (Found: C, 65.3; H, 4.6; N, 7.0. $C_{11}H_9NO_3$ requires C, 65.0; H, 4.5; N, 6.9%); δ_H 2.33 (3 H, s), 6.08 (1 H, s), 7.54–7.71 (3 H, m) and 8.23 (2 H, dd, *J* 6, 2); ν_{max}/cm^{-1} 1762, 1604 and 1447; *m*/*z* 159 (M − 81, 7%), 139 (3), 122 (58) and 105 (100).

2-Benzoyl-3-methylisoxazol-5(2*H*)-one **1** (R^1 = Ph, R^2 = Me, R^3 = H, X = O) (2.10 g, 51%) was recrystallised from diethyl ether–light petroleum as white needles, mp 74–75 °C (lit.,[12] 59–66 °C) (Found: C, 65.2; H, 4.5; N, 6.8%; M^+ − 44, 159.0688. Calc. for $C_{11}H_9NO_3$: C, 65.0; H, 4.5; N, 6.9%. Calc. for $C_{10}H_9NO$: *M*, 159.0684); δ_H 2.66 (3 H, d, *J* 1.2), 5.40 (1 H, d, *J* 1.2), 7.33–7.70 (3 H, m) and 7.8–8.0 (2 H, m); δ_C 15.6, 95.2, 128.1, 129.6, 130.6, 133.0, 160.1, 162.8 and 166.0; ν_{max}/cm^{-1} 1762, 1698 and 1599; *m*/*z* 159 (M, 19%), 130 (11), 122 (21), 105 (100) and 77 (71).

In pyridine, 60% of the *O*-benzoyl and 20% of the *N*-benzoyl derivatives could be isolated. The Schotten–Baumann procedure gave 25% of the *O*-benzoyl and 65% of the *N*-benzoyl derivative.

2-Acetyl-3-methylisoxazol-5(2*H*)-one 1 ($R^1 = R^2$ = Me, R^3 = H, X = O). Acetyl chloride (1.15 ml) was added slowly to a stirring solution of 3-methylisoxazolone (1 g, 10 mmol) and pyridine (0.8 g, 12 mmol) in dichloromethane (20 ml). After 30 min at room temperature the solvent was removed and the residue diluted with diethyl ether (50 ml). Pyridinium hydrochloride was removed by filtration and the filtrate was reduced to give an oil which was identified as 2-acetyl-3-methylisoxazol-5(2*H*)-one **1** ($R^1 = R^2$ = Me, R^3 = H, X = O) (1.28 g, 90%); δ_H 2.44 (3 H, s), 3.08 (3 H, d, *J* 1) and 5.32 (1 H, q, *J* 1); δ_C 15.3, 22.4, 94.7, 158.6, 164.8 and 165.9; ν_{max}/cm^{-1} 1764, 1712 and 1598.

4-Bromo-3-methylisoxazol-5(2*H*)-one

3-Methylisoxazol-5(2*H*)-one (2 g) was reacted with bromine (3.39 g) in chloroform (20 ml) in the dark at 20 °C. After 10 min the solvent was removed and the product recrystallised from benzene–light petroleum to give 4-*bromo*-3-*methylisoxazol*-5(2*H*)-*one*, mp 78–80 °C (2.91 g, 81%) (Found: M^+, 178.9399; 176.9380. Calc. for $C_4H_4BrNO_2$: *M*, 178.9406; 176.9426); δ_H 2.27 (3 H, s) and 4.89 (1 H, s); ν_{max}($CHCl_3$)/cm^{-1} 1816 and 1767; ν_{max}(Nujol)/cm^{-1} 3410, 1683 and 1550; *m*/*z* 179 (M, 3%), 177 (M, 3), 151 (12), 141 (36), 99 (10) and 77 (100).

2-Benzoyl-4-bromo-3-methylisoxazol-5(2*H*)-one 1 (R^1 = Ph, R^2 = Me, R^3 = Br, X = O)

A sample (1.00 g) of 4-bromo-3-methylisoxazol-5(2*H*)-one was treated with benzoyl chloride (1.0 g) in 1,2-dichloroethane at 80 °C for 10 h as above. The crude product was recrystallised from *tert*-butyl methyl ether–light petroleum to afford the *title compound* (1.43 g, 91%) as white crystals, mp 94–95 °C (Found: C, 47.1; H, 2.9; N, 5.0%; M^+ − 44, 236.9796; 238.9987. $C_{11}H_8BrNO_3$ requires C, 47.1; H, 2.9; N, 5.3%; $C_{10}H_8BrNO$ requires *M*, 236.9770; 238.9970); δ_H 2.71 (3 H, s), 7.42–7.67 (3 H, m) and 7.85 (2 H, dd, *J* 8, 2); δ_C 15.5, 88.9, 128.4, 129.9, 129.3, 130.1, 133.5, 133.7, 157.1, 162.9 and 177.2; ν_{max}/cm^{-1} 1771, 1703 and 1594; *m*/*z* 239 (M, 1%), 237 (M, 1%), 211 (1), 209 (1), 159 (23), 130 (11) and 105 (100).

Acylation of isoxazolones 12

3-Ethoxycarbonyl-4-methylisoxazol-5-yl acetate 17 (R = Me) and ethyl 2-acetyl-4-methyl-5-oxo-2,5-dihydroisoxazole-3-carboxylate 18 (R = Me). The isoxazolone **12** (R = Me)[28] (250 mg) was treated with acetyl chloride (115 mg) and triethylamine (148 mg) in dichloromethane for 2 h at 20 °C as above. The crude product was purified by chromatography to remove 16 mg (5%) of the *O*-acetyl derivative, 3-*ethoxycarbonyl*-4-*methylisoxazol*-5-*yl acetate* **17** (R = Me), which was isolated as a colourless oil (Found: M^+, 213.0620. $C_9H_{11}NO_5$ requires *M*, 213.0637); δ_H 1.35 (3 H, t, *J* 7), 2.05 (3 H, s), 2.43 (3 H, s) and 4.41 (2 H, q, *J* 7); δ_C 6.4, 14.0, 20.0, 61.9, 100.6, 159.6, 159.9, 160.6 and 165.4; ν_{max}/cm^{-1} 1800 and 1650.

Ethyl 2-*acetyl*-4-*methyl*-5-*oxo*-2,5-*dihydroisoxazole*-3-*carboxylate* **18** (R = Me) (280 mg, 90%) was isolated as a colourless oil (Found: M^+, 213.0628. $C_9H_{11}NO_5$ requires *M*, 213.0637); δ_H 1.37 (3 H, t, *J* 7), 1.95 (3 H, s), 2.40 (3 H, s) and 4.42 (2 H, q, *J* 7); δ_C 6.8, 13.8, 21.4, 63.3, 108.2, 144.6, 158.5, 164.4 and 167.0; ν_{max}/cm^{-1} 1788, 1746, 1709 and 1582; λ_{max}(EtOH)/nm 206 (ε/dm^3 mol^{-1} cm^{-1} 43 000 and 290 (89 000); *m*/*z* 213 (M, 26%), 180 (16), 171 (57), 143 (100), 125 (61), 67 (60), 51 (31) and 40 (47).

The isoxazolone **12** (R = Me) (150 mg) was treated with benzoyl chloride (124 mg) and triethylamine (90 mg) in dichloromethane for 14 h at 20 °C to give two fractions after chromatography (CH_2Cl_2–light petroleum). The first was identified as the O-*benzoyl derivative* **17** (R = Ph) (48 mg, 20%) obtained as an oil; δ_H 1.39 (3 H, t, *J* 7), 2.08 (3 H, s), 4.42 (2 H, q, *J* 7), 7.50 (3 H, m) and 8.15 (2 H, m); δ_C 6.4, 13.9, 61.8, 101.0, 126.3, 128.3, 130.0, 133.6, 156.4, 159.9 and 161.3; ν_{max}/cm^{-1} 1774, 1734 and 1701; *m*/*z* 122 (48%), 105 (100), 77 (99) and 51 (48).

The second was identified as the N-*benzoyl derivative* **18** (R = Ph) (96 mg, 40%) obtained as a solid, mp 70–72 °C (Found: C, 61.1; H, 4.7; N, 5.0. $C_{14}H_{13}NO_5$ requires C, 61.01; H, 4.76; N, 5.09%); δ_H 1.34 (3 H, t, *J* 7), 2.02 (3 H, s,), 4.42 (2 H, q, *J* 7), 7.46 (2 H, m), 7.58 (1 H, m) and 7.91 (2 H, m); δ_C 7.1, 13.7, 62.9, 110.9, 128.3, 128.4, 130.2, 133.9, 146.6, 158.5, 164.1 and 167.6; ν_{max}/cm^{-1} 1777, 1736 and 1699; *m*/*z* 231 (M − 44, 1%), 122 (53), 105 (100) and 77 (81).

The isoxazole **17** (R = Ph) (100 mg) was heated in benzoyl chloride (2 ml) at 150 °C for 1 h. On cooling the mixture was diluted with copious amounts of light petroleum and cooled to 0 °C. The product (85 mg) was collected as fine pale yellow crystals, mp 70–73 °C, identical with the *N*-benzoyl derivative **18** above.

Ethyl 2-dichloroacetyl-4-methyl-5-oxo-2,5-dihydroisoxazole-3-carboxylate 18 (R = $CHCl_2$). This was obtained as a *pale yellow semi-solid* (158 mg from 100 mg, 96%) using the procedure given above for the preparation of **18** (R = Me), but was stable only if kept below 5 °C in the absence of air (Found: M^+, 282.9821. $C_9H_9{}^{35}Cl_2NO_5$ requires *M*, 282.9828); δ_H 1.41 (3 H, t, *J* 7.14), 2.04 (3 H, s), 4.48 (2 H, q, *J* 7.14) and 6.52 (1 H, s); δ_C 7.3, 13.8, 62.7, 63.9, 111.7, 157.1, 157.5, 165.6 and 167.3; ν_{max}/cm^{-1} 1793 and 1740; *m*/*z* 283/281 (M, 2%), 218 (17) and 171 (24).

Acylation of **12** (R = Me) (100 mg) as above, with ethyl oxalyl chloride (120 mg) led to 90% (171 mg) *N*-acylation and 10% (19 mg) *O*-acylation. Pyridine-2,6-dicarbonyl chloride gave 80% bis *N*-acylation, 10% *O*,*N*-acylation and 10% bis *O*-acylation.

Ethyl 4-methyl-5-oxo-2-(phthalimidoacetyl)-2,5-dihydroisoxazole-3-carboxylate 18 (R = phthalimidomethyl). Reaction of the isoxazolone **12** (R = Me) (100 mg) with phthalimidoacetyl chloride (140 mg) and triethylamine (60 mg) in dichloromethane at 20 °C for 4 h gave a product from which *ethyl* 4-*methyl*-5-*oxo*-2-(*phthalimidoacetyl*)-2,5-*dihydroisoxazole*-3-*carboxylate* **18** (R = phthalimidomethyl) (84 mg, 40%) could be obtained by direct crystallisation from diethyl ether, mp 148–151 °C (Found: C, 56.7; H, 4.0; N, 7.6%; $M^+ - 44$, 314.0896. $C_{17}H_{14}N_2O_7$ requires C, 57.0; H, 3.9; N, 7.8%; $C_{16}H_{14}N_2O_5$ requires *M*, 314.0902); δ_H 1.31 (3 H, t, *J* 7.14), 1.99 (3 H, s), 4.36 (2 H, q, *J* 7.14), 4.85 (2 H, s), 7.75 (2 H, dd, *J* 5.5, 2.9) and 7.88 (2 H, dd, *J* 5.5, 2.9); δ_C 7.0, 13.8, 39.3, 63.5, 109.8, 123.8, 131.8, 134.4, 144.6, 157.8, 160.9, 166.4 and 167.1; ν_{max}/cm^{-1} 1789, 1725 and 1376.

Ethyl 2-acetyl-5-oxo-2,5-dihydroisoxazole-3-carboxylate 1 (R^1 = Me, R^2 = CO_2Et, R^3 = H, X = O). Acetyl chloride (100 mg) was added dropwise to the isoxazolone **12** (R = H) (150 mg) at 20 °C, and the mixture kept for 30 min. A dark brown oil was obtained on evaporation, which was shown by ^{1}H NMR spectral analysis to consist of 88% *N*-acylated material. Further purification resulted in decomposition although storage under nitrogen in a cool dark place was satisfactory; δ_H 1.39 (3 H, t, *J* 7.14), 2.46 (3 H, s), 4.43 (2 H, q, *J* 7.14) and 5.80 (1 H, s), δ_C 13.4, 21.1, 63.4, 96.5, 149.2, 157.7, 163.7 and 165.2; *m*/*z* 157 (M − 42, 5%), 129 (100), 124 (19) and 112 (23).

Ethyl 2-ethoxycarbonyl-5-oxo-2,5-dihydroisoxazole-3-carboxylate 1 (R^1 = OEt, R^2 = CO_2Et, R^3 = H, X = O). The isoxazolone **12** (R = H) (120 mg) was treated with ethyl chloroformate (90 mg) at 20 °C to give a dark brown oil containing 93% *N*-acylated material by ^{1}H NMR spectral analysis. Further purification resulted in decomposition although storage under nitrogen in a cool dark place was satisfactory; δ_H 1.40 (3 H, t, *J* 7.14), 1.41 (3 H, t, *J* 7.14), 4.43 (2 H, q, *J* 7.14), 4.44 (2 H, q, *J* 7.14) and 5.82 (1 H, s); δ_C 13.5, 13.7, 63.4, 65.4, 97.3, 146.5, 151.5, 157.4 and 165.5.

3-Ethoxycarbonyl-4-methylisoxazol-4-yl 2,5-dimethyl-1,3-oxazole-4-carboxylate 17 (R = 2,5-dimethyl-1,3-oxazol-4-yl) and ethyl 2-(2,5-dimethyl-1,3-oxazol-4-ylcarbonyl)-4-methyl-5-oxo-2,5-dihydroisoxazole-3-carboxylate 18 (R = 2,5-dimethyl-1,3-oxazol-4-yl). Isoxazolone **12** (R = Me) (100 mg, 0.585 mmol) was dissolved in anhydrous benzene (5 ml) and dry pyridine (0.052 ml, 0.643 mmol) under a nitrogen atmosphere. The mixture was then heated under reflux, and 2,5-dimethyl-4-chlorocarbonyl-1,3-oxazole (103 mg, 0.643 mmol) in 1,2-dichloroethane (2 ml) was added dropwise. After 5 min the solvent was removed and the residue diluted with diethyl ether and washed with water. ^{1}H NMR spectral analysis showed the residue (175 mg) to consist of **18** (R = 2,5-dimethyl-1,3-oxazol-4-yl) (85%) and **17** (R = 2,5-dimethyl-1,3-oxazol-4-yl) (15%). Chromatographic purification resulted in decomposition. The use of triethylamine as base resulted in a 1:1 mixture of the above products. This mixture (100 mg) was heated in anhydrous sulfolane (2 ml) at 150 °C for 2 h. On cooling, the mixture was diluted with a 1:1 mixture of light petroleum and ethyl acetate and washed with water. The structure of the product **18** (R = 2,5-dimethyl-1,3-oxazol-4-yl) (90 mg) was confirmed by ^{1}H NMR spectral analysis; δ_H 1.37 (3 H, t, *J* 7.14), 2.07 (3 H, s), 2.49 (3 H, s), 2.59 (3 H, s) and 4.42 (2 H, q, *J* 7.14); δ_C 7.2, 13.5, 13.7, 62.8, 111.4, 127.1, 146.1, 157.7, 158.3, 158.5, 159.8 and 167.7.

General synthesis of 2-acyl-4-ethoxycarbonylisoxazol-5(2*H*)-ones

Ethyl 5-oxo-2,5-dihydroisoxazole-4-carboxylate **13**[29] (0.5 g, 3.18 mmol) or the 3-methyl analogue **14**[30,31] (dried under high vacuum for 8 h) and an acid chloride (1.3 equiv.) were heated at reflux in anhydrous dichloroethane–benzene (8:1) (50 ml) in the dark under an atmosphere of nitrogen. The reactions were monitored by TLC (diethyl ether), with most requiring 10–24 h for completion. Data for compounds made by this procedure are collected in Table 2.

Acylation of 3,4-diphenylisoxazol-5(2*H*)-one, 15

2-Acetyl-3,4-diphenylisoxazol-5(2*H*)-one 1 (R^1 = Me, R^2 = R^3 = Ph, X = O). The isoxazolone[32] (150 mg) was heated with acetic anhydride (2 ml) for 1 h at 100 °C. The N-*acetyl derivative* **1** (R^1 = Me, R^2 = R^3 = Ph, X = O) (159 mg, 90%), mp 169–172 °C separated as colourless needles on cooling (Found: C, 73.1; H, 4.7; N, 5.05. $C_{17}H_{13}NO_3$ requires C, 73.15; H, 4.7; N, 5.0%); δ_H 2.46 (3 H, s) and 7.23–7.48 (10 H, m); δ_C 23.1, 108.1, 127.5, 128.2, 128.4, 128.6, 128.9, 129.0, 130.7, 153.7, 164.6 and 165.7; ν_{max}/cm^{-1} 1765, 1725 and 1451; *m*/*z* 235 (M − 44, 100%), 193 (12), 178 (21), 165 (27), 104 (31), 89 (23) and 77 (29).

2-Benzoyl-3,4-diphenylisoxazol-5(2*H*)-one 1 (R^1 = R^2 = R^3 = Ph, X = O) and 3,4-diphenylisoxazol-5-yl benzoate. The isoxazolone (100 mg) was treated with benzoyl chloride (100 mg) and pyridine (55 mg) in dichloromethane (2 ml) for 14 h at 20 °C. The two products were separated by radial chromatography [dichloromethane–light petroleum (1:1)]. The first product was 3,4-*diphenylisoxazol*-5-*yl benzoate* (50 mg, 35%), mp 69–71 °C after crystallisation from benzene–light petroleum (Found: C, 77.6; H, 4.4; N, 4.2. $C_{22}H_{15}NO_3$ requires C, 77.4; H, 4.4; N, 4.1%); δ_H 7.24–7.73 (13 H, m) and 8.04–8.18 (2 H, m); δ_C 104.0, 126.8, 127.9, 128.0, 128.4, 128.6, 128.8, 128.9, 129.0, 129.1, 129.9, 130.8, 134.9, 162.2, 162.2 and 163.3; ν_{max}/cm^{-1} 1769, 1639 and 1413; *m*/*z* 341 (M, 1%), 192 (3), 105 (100) and 77 (25).

The second fraction (72 mg, 50%) was the *N*-benzoyl derivative **1** (R^1 = R^2 = R^3 = Ph, X = O), mp 139–141 °C (lit.,[10] 138–139 °C); δ_H 7.28–7.36 (5 H, m), 7.41–7.54 (7 H, m), 7.60–7.67 (1 H, m) and 7.95–7.99 (2 H, m); δ_C 108.9, 127.4, 128.3, 128.3, 128.4, 128.5, 128.5, 128.8, 130.2, 130.7, 131.0, 133.6, 155.8, 164.5 and 166.4; ν_{max}/cm^{-1} 1760, 1703 and 1304; *m*/*z* 341 (M, 2%), 297 (27), 165 (19), 105 (100) and 77 (30).

2-Benzoylisoxazol-5(2*H*)-one

Benzoyl chloride (230 mg) was reacted with isoxazol-5(4*H*)-one[33] **16** (130 mg), in the presence of triethylamine as above. The first chromatographic fraction was the *O*-benzoyl derivative (72 mg, 25%), and the second was the *title compound*, mp 87–89 °C (173 mg, 60%) (Found: M^+, 189.0428. $C_{10}H_7NO_3$ requires *M*, 189.0428); δ_H 5.65 (1 H, d, *J* 4), 7.51 (2 H, m), 7.64 (1 H, m), 7.96 (2 H, m) and 8.63 (1 H, d, *J* 4); δ_C 95.3, 128.6, 129.1, 130.1, 133.8, 144.5, 160.4 and 167.7; ν_{max}/cm^{-1} 1769 and 1682; *m*/*z* 189 (M, 1%), 145 (1), 122 (3), 105 (100), 77 (66) and 51 (23).

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