CSIRO PUBLISHING

Full Paper

www.publish.csiro.au/journals/ajc

Aust. J. Chem. **2004**, *57*, 455–460

Intramolecular Interactions in Carbenes Derived During the Pyrolysis of *N*-Alkenylisoxazolones

Matthew Cox,[A] *Michael Dixon*,[A] *Troy Lister*,[A] *and Rolf H. Prager*[A,B]

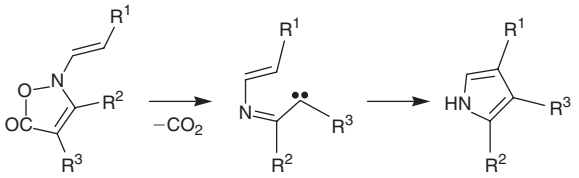
[A] School of Chemistry, Physics and Earth Sciences, Flinders University, Adelaide SA 5001, Australia.
[B] Author to whom correspondence should be addressed (e-mail: rolf.prager@flinders.edu.au).

Flash vacuum pyrolysis of ethyl 3-(3-methyl-5-oxo-2,5-dihydroisoxazole-2-yl)-3-phenylpropenoate yields 4-ethoxy-3-hydroxy-2-methyl-5-phenylpyridine in addition to the expected pyrrole. The structure assignment is based on two-dimensional NMR and computational evidence. The pyrolysis of the corresponding dimethyl amide gives a mixture of three 3-hydroxypyridines, in addition to the pyrrole. Evidence is presented for the formation of intermediate 1,4-oxazepines by a six-electron electrocyclic reaction of a carbene with ester or amide carbonyl groups.

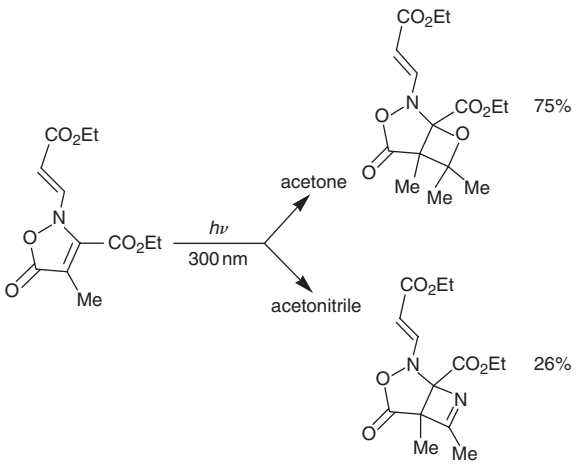
Manuscript received: 17 June 2003.
Final version: 13 October 2003.

Introduction

While the pyrolysis or photolysis of *N*-(1-alkenyl)isoxazolones (Scheme 1) generally proceeds through a carbene intermediate and gives pyrroles,[1,2] several alternate pathways were observed involving solvent capture by the triplet state of the isoxazolone (Scheme 2),[3] rearrangement of the initially formed carbene to a more stable one and subsequent cyclization,[1] or more complicated pathways involving a [1,4]-migration to form a ketenimine, followed by a [1,3]-alkoxide migration forming a ketene which underwent cyclization to the quinolone product (Scheme 3).[1]



Scheme 1.



Scheme 2.

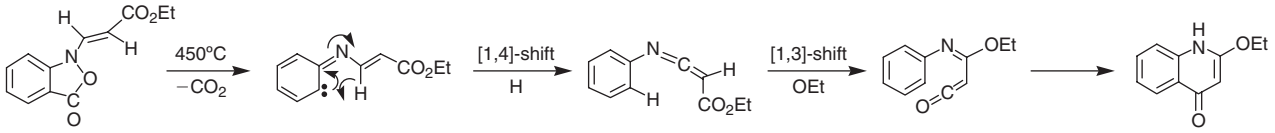
In a previous paper[2] we reported that flash vacuum pyrolysis (FVP) of the alkenylisoxazolone **1** gave the expected pyrrole **2** from the intermediate carbene **3** (Scheme 4) as only the minor product, the major product being an unidentified isomer. The present paper describes an investigation of this isomer and related reaction products, which concludes it to have the structure **4**.

Discussion

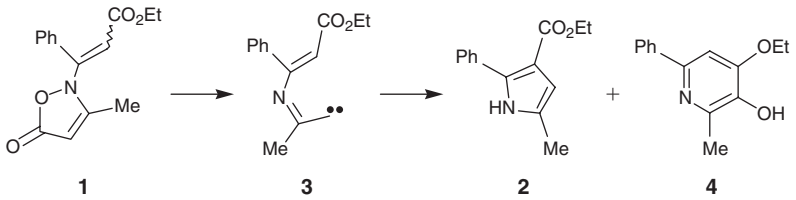
FVP of the isoxazolone **1** at 450°C gave two products, separable by chromatography. The first was ethyl 5-methyl-2-phenylpyrrole-3-carboxylate **2** (19%) and the second (38%) was an isomer, to which we ascribe the structure **4**. The product **4** was weakly acidic but no longer contained an ester group (IR data); ^{1}H and ^{13}C NMR spectra suggested the presence of an ethyl ether. The singlet at 7.04 ppm in the ^{1}H NMR spectrum, and the other substituents present, require the presence of a pyridine ring. The ^{13}C chemical shift of the pyridine carbon atom at 103.6 ppm is consistent only with a pyridine unsubstituted at C-5. Plausible pathways for three possible pyridine structures, **4**–**6**, can be envisaged (Scheme 5).

The assignment of structure for the pyridine **4** rests on the combination of theoretical and two-dimensional NMR evidence. The pyrolysis product **4**, because of its low solubility, was methylated with MeI/K_2CO_3, to give a single methylation product, for which structures **7**–**11** could be envisaged, based on the above. Unfortunately, both **4** and **7** were obtained as microcrystalline powders, unsuitable for X-ray determination. The methylation product appeared to be an *O*-methyl derivative, based on the ^{13}C resonance at 60.2 ppm; *N*-methylpyridones would be expected to have

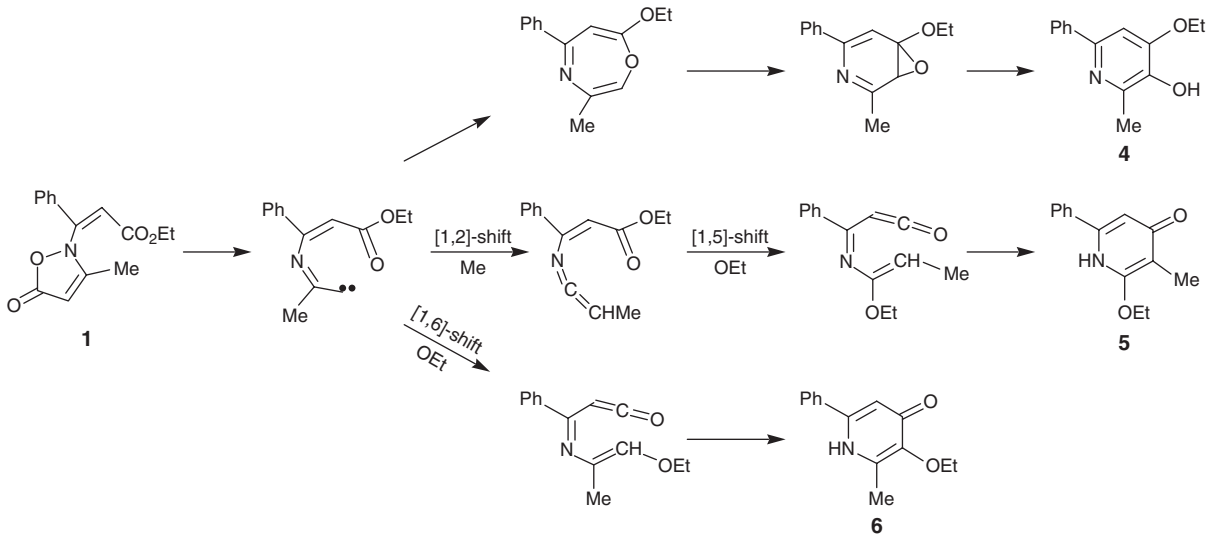
 10.1071/CH03154 0004-9425/04/050455



Scheme 3.



Scheme 4.



Scheme 5.

resonances around 40 ppm. Since 4-pyridones undergo predominantly *N*-methylation,[4–6] structures **5** and **6**, leading to **8**–**11**, appeared unlikely. Nonetheless, we have calculated (*Gaussian 98*, restricted Hartree–Fock) the ^{1}H and ^{13}C NMR spectra of the four methylated compounds **8**–**11**: those for **7** should be very similar to those of **8** (Tables 1 and 2).

The *N*-methylated 4-pyridone structures **10** and **11** are clearly incompatible with the methylation product, in addition to the ^{13}C *N*-Me resonances around 40 ppm, the pyridone carbonyl group resonates around 180 ppm, whereas the pyrolysis product and its methylated derivative have their highest chemical shift around 157.9 ppm. This also rules out structures **8** and **9** for the methylated product; their precursors **5** and **6** also require pyridone carbonyl resonances. Only structure **7** remains consistent with the one-dimensional ^{13}C NMR spectrum. While the calculated chemical shifts, using the less accurate Hartree–Fock theory rather than the density functional theory (DFT), do not allow for the effect of solvent or possible intermolecular stacking, the calculated values for **8** are all uniquely in the same order as those observed for **7** and eliminate structures **9**–**11**.

Two-dimensional NMR data measured at 600 MHz allowed the confirmation of structure **7** for the methylation product, and hence **4** for the pyrolysis product. The pulse sequences gHMBC and gHMQC (Varian) allowed assignment of all carbon resonances and the connectivity of the aromatic *C*-methyl with C-2 and C-3, the *O*-methyl group with C-3, the *O*-ethyl group with C-4, and the positioning of H-5 relative to C-4, C-3, C-6, and C-1′. NOESY and ROESY spectra showed the nuclear Overhauser interaction of the pyridine H-5 with both the O—CH_2—CH_3 and H-2′ atoms of the phenyl group, unequivocally placing these groups.

We have used *MacSpartan* semi-empirical calculations to seek to understand the reason for the differences in pyrolysis outcome for the cinnamate isoxazolone **1** compared to the crotonate isoxazolone **12**.[2] We suggest that while **12** is more stable in the (*E*)-configuration on electronic grounds, **1** will prefer the (*Z*)-configuration for steric reasons. It could be anticipated that the pyrolysis of (*Z*)- and (*E*)-isoxazolones **1** would lead ultimately to the carbenes (*Z*)-**3** and (*E*)-**3*** respectively.[7] Hickson and McNab[8] have shown that significant (*E*)- to (*Z*)-isomerization of simple

The terms (*Z*) and (*E*) here refer to the geometry of the double bond of the conjugated ester.

Table 1. Comparison of calculated ^{1}H chemical shifts for pyridines 8–11 with those observed for 7

	8	9	10	11	Methylated product 7
H-5	7.84	6.91	6.59	6.53	7.00
H-2′	9.31	9.16	8.51	8.55	7.80
H-3′	7.95	7.95	8.51	8.49	7.37
H-4′	7.88	7.90	8.51	8.49	7.30
H-5′	7.89	7.87	8.45	8.44	7.37
H-6′	8.23	8.16	8.32	8.36	7.80
OCH_3 (NCH_3)	4.15	4.04	3.60	3.58	3.78
OCH_2CH_3	4.00	4.45	4.46	4.44	4.11
OCH_2CH_3	1.70	1.68	2.11	2.24	1.43
$ArCH_3$	2.80	2.42	2.98	2.63	2.47

Table 2. Comparison of calculated ^{13}C chemical shifts for pyridines 8–11 with those observed for 7

	8	9	10	11	Methylated product 7
C-2	161.2	169.1	145.8	159.5	152.4
C-3	145.8	107.4	144.1	113.2	142.6
C-4	163.4	168.8	177.7	183.1	157.9
C-5	116.4	100.5	119.2	118.0	103.7
C-6	161.3	161.2	159.5	158.3	153.5
C-1′	141.3	141.8	141.8	141.5	139.9
C-2′	130.5	133.6	134.6	134.6	126.9
C-3′	131.6	131.6	133.6	133.7	128.6
C-4′	132.6	132.7	134.0	134.1	128.4
C-5′	130.6	130.6	132.4	132.3	128.6
C-6′	129.9	129.9	133.6	133.4	126.9
OCH_3 (NCH_3)	55.8	50.6	40.4	39.1	60.2
OCH_2CH_3	62.3	58.0	63.2	66.8	64.0
OCH_2CH_3	16.5	15.5	23.4	22.7	14.6
$ArCH_3$	21.2	9.9	20.3	17.0	19.2

alkenes, including those with conjugating phenyl and nitrile groups, occurs above 650°C under FVP conditions, but we feel such isomerization would be minimal at the low temperatures (450°C) used herein. AM1 calculations suggest that carbene (*E*)-**3** will collapse spontaneously to the cyclic precursor of pyrrole **2**, but the carbene (*Z*)-**3** has its lowest energy state in a conformation which allows neither the cinnamate double bond nor the ester carbonyl group to interact with the carbenoid centre. However, simple rotations about the 3,4 and 5,6 single bonds leads to an apparent conformation of (*Z*)-**3a** (see Fig. 1), which is only 48 kJ mol^{-1} higher in energy, and has the carbonyl oxygen atom lying 1.40 Å above the carbene centre, the angle C-1—O—C-6 being 114°, which indeed corresponds to the oxazepine **13**, a precursor known to readily form 3-hydroxypyridines under mild thermal conditions,[9,10] as shown in Scheme 6. Whereas reaction of 3-methylisoxazol-5(4*H*)-one with ethyl butynoate gives a single product **12**, which gives the corresponding pyrrole in 93% yield on pyrolysis,[1] reaction with ethyl phenylpropiolate gives a mixture of the esters (*E*)-**1** and (*Z*)-**1** (ratio 1 : 3.5), which cannot be separated by chromatography and are possibly the precursors of the pyrrole and pyridine products respectively. It is interesting to note that we have been

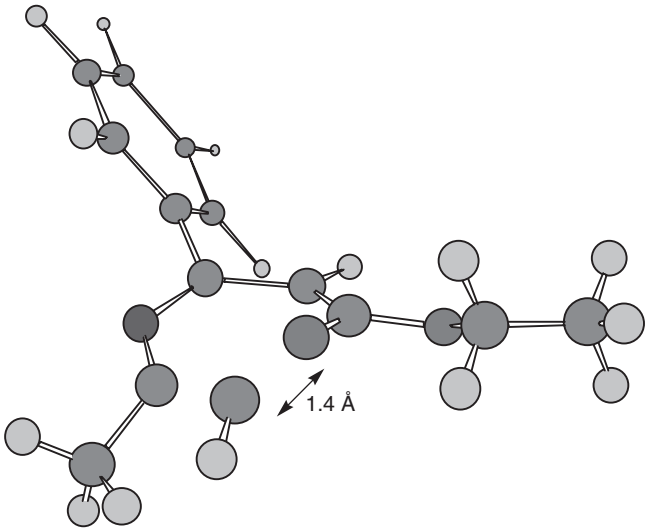
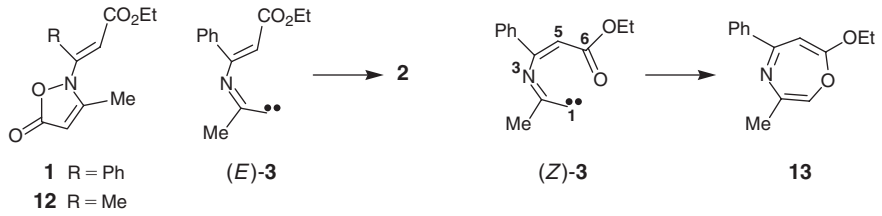


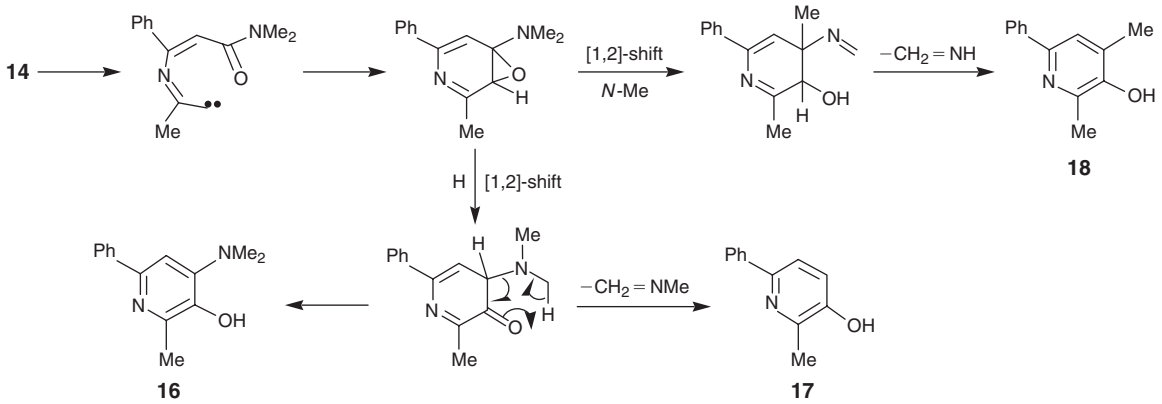
Fig. 1. Calculated low-energy conformation (*Z*)-**3a**, corresponding to **13**.

unable to detect any evidence of alternative reactions of carbene **3**, such as insertion into the benzene ring, which would lead to isoquinoline derivatives.

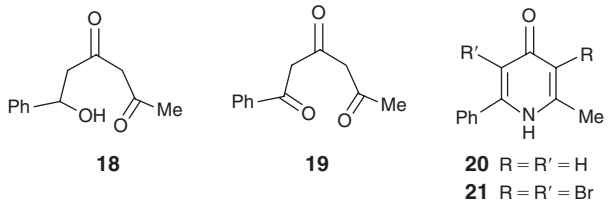
In order to probe the generality of this pyrolytic rearrangement leading to pyridines, the ester group in **1** was changed to the dimethyl amide. We were aware of the observations of Wentrup et al.,[11] that group migrations to carbenes or electron-deficient centres were dictated by electron density, and hence we reasoned that amide analogues of **1** might undergo additional pyrolysis pathways, perhaps akin to those in Scheme 6. 3-Methylisoxazolone could not be induced to react with the piperidide or other amides of phenylpropiolic acid under the usual conditions. Accordingly, the isoxazolone **1** was hydrolyzed to the corresponding acid, which was converted to the amide **14** with dimethylamine in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. Pyrolysis of **14** at 450°C gave a mixture of products, of which the four major components were separated by radial chromatography. The minor product (5%) was the pyrrole **15**, easily recognizable as it was the only product with nonequivalent *N*-methyl groups in the ^{1}H NMR spectrum, typical of amides. The most polar was the 3-hydroxypyridine **16** (18%), whose spectral data were as expected from those of **4**, its analogue. Again, the infrared spectrum showed the absence of an amide group. Two other products were isolated in significant yields, and mass spectral evidence suggested that both were also 3-hydroxypyridines. Structures **17** (33%) and **18** (16%) were assigned to these compounds. Both retained the oxygen atom of the dimethylamide but not the amino group: in **18** a methyl group (δ_C 18.4 or 16.2 ppm) has been transferred from nitrogen to the pyridine ring. We tentatively suggest these compounds arise by the pathways shown in Scheme 7. While [1,2]-alkyl shifts from carbon to carbon are well known in the gas phase, resulting from cationic[12] or radical[13] intermediates, migrations from nitrogen to carbon appear to be unknown. Alternative mechanisms to those above, involving radical opening of the epoxide, can be drawn.



Scheme 6.



Scheme 7.



Scheme 8.

Unfortunately we are unable to complete this study by the unambiguous synthesis of structure **4**, but wish to report some preliminary investigations. Reaction of benzaldehyde with the dianion of acetylacetone gave the hydroxyketone **18**,[14–16] Scheme 8, which could be oxidized to the triketone **19** with MnO_2, but reaction with ammonia failed to give satisfactory yields of the pyridone **20**, which we hoped to convert to both **7** and **8**. However, the procedure of Koshima and coworkers,[17] in which acetylacetone dianion is treated with benzonitrile, proceeded to **20** directly. We hoped to achieve monobromination of this compound at C-3, but several mild reagents, including KBr_3,[18] gave only the dibromide **21**, as might have been expected from literature precedent.[19]

Conclusions

Flash vacuum pyrolysis of derivatives of *N*-carboxyethenyl isoxazolones leads to carbenes which undergo cyclization forming either pyrroles or pyridines, depending on the configuration of the alkene. Carbenes from (*E*)-alkenes give mainly pyrrole derivatives, while those from (*Z*)-alkenes lead to conformations with the ester or amide carbonyl groups within bonding distance of the carbenoid centre. The resulting oxazepines rearrange to the observed 3-hydroxypyridines.

Experimental

All solvents used were freshly distilled and dried according to the methods of Perrin et al.[20] Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^1H (300 MHz) and ^{13}C (75.5 MHz) NMR measurements were recorded on a Gemini Varian 300 spectrometer in deuteriochloroform with tetramethylsilane as internal standards, unless otherwise stated. 2D NMR spectra were determined on a Varian Unity 600 MHz spectrometer, using the pulse sequences gHMBC, gHMQC, gCOSY, ROESY, and TOCSY. Infrared spectra were recorded on a Perkin–Elmer 1600 FT-infrared spectrophotometer, using fused sodium chloride cells, measured as Nujol mulls or films. Mass spectra and high-resolution mass spectra were recorded on a Kratos MS25RF spectrometer. Microanalyses were performed by Chemical & Micro Analytical Services, Melbourne. Flash vacuum pyrolyses were carried out by slowly subliming the substrate through a silica tube (400 mm × 25 mm), packed with silica chips, and heated to the quoted temperature under reduced pressure. The products were collected in a liquid nitrogen cold trap. The NMR calculations were carried out on a Sun 64-SVR4-Unix system, using *Gaussian 98*, *Rev. A.11.3*.

*FVP of Ethyl 3-(3-methyl-5-oxo-2,5-dihydroisoxazol-2-yl)-3-phenylpropenoate **1***

Pyrolysis (450°C, 150°C, 0.01 mmHg) of **1** (65 mg, 0.23 mmol) gave a pale brown oil (50 mg), which was purified by radial chromatography (10% ethyl acetate/light petroleum) to give two fractions.

The first fraction was *ethyl 5-methyl-2-phenylpyrrole-3-carboxylate* **2**, which was obtained as a colourless oil (10 mg, 19%). (Found: M^+ 229.1102. $C_{14}H_{15}NO_2$ requires M^+ 229.1103). ν_{max}/cm^{-1} 1672. δ_H 8.13 (1H, bs, NH), 7.55–7.59 (2H, m), 7.29–7.41 (3H, m), 6.40 (1H, dq, *J* 0.82, 3), 4.19 (2H, q, *J* 7.0), 2.28 (3H, d, *J* 0.82), 1.24 (3H, t, *J* 7.0). δ_C 165.0, 135.9, 132.3, 128.8, 128.0, 127.9, 127.6, 112.2, 109.6, 59.5, 14.3, 12.7. *m*/*z* 229 (M^+, 90%), 201 (23), 184 (100), 170 (3), 156 (13), 141 (3), 128 (10), 104 (7), 77 (10).

The second fraction was *4-ethoxy-3-hydroxy-2-methyl-6-phenylpyridine* **4** (20 mg, 38%), colourless microcrystals, mp 130–132°C. (Found: M^+ 229.1092. $C_{14}H_{15}NO_2$ requires M^+ 229.1103). ν_{max}/cm^{-1} 3110, 1473, 1078. δ_H 7.84–7.87 (2H, m), 7.29–7.44 (3H, m), 7.04 (1H, s), 4.21 (2H, q, *J* 7.0), 2.56 (3H, s), 1.48 (3H, t, *J* 7.0), (OH unsighted). δ_C 152.1, 149.6, 144.4, 139.6, 139.3, 128.6, 128.2, 126.8, 102.5, 64.7, 18.2, 14.6. *m*/*z* 229 (M^+, 100%), 214 (6), 201 (56), 185 (17), 172 (29), 156 (5), 131 (9), 115 (6), 102 (10), 77 (9).

Methylation of ***4***

Methyl iodide (84 mg, 0.6 mmol) was added to a solution containing **4** (68 mg, 0.3 mmol) and potassium carbonate (41 mg, 0.3 mmol) in acetone (5 mL), and the mixture was stirred at room temperature for 3d. The solvent was evaporated, and the residue extracted with ethyl acetate (20 mL). The product was purified by radial chromatography (10% EtOAc/light petroleum), to give *4-ethoxy-3-methoxy-2-methyl-6-phenylpyridine* **7** (53 mg, 74%) as a white powder, mp 39°C. (Found: M^+ 243.1270. $C_{15}H_{17}NO_2$ requires M^+ 243.1259). ν_{max}/cm^{-1} 1578, 1469, 1343, 1245, 1206, 1113, 1076. δ_H (600 MHz) 7.81 (2H, dd, *J* 5.9, 3.0), 7.36 (2H, dt, *J* 5.9, 3), 7.27 (1H, dt, *J* 6, 3), 7.00 (1H, s), 4.11 (2H, q, *J* 7.1), 3.78 (3H, s), 2.47 (3H, s), 1.43 (3H, t, *J* 7.1). δ_C 157.9, 153.5, 152.4, 142.6, 139.9, 128.6, 128.4, 126.9, 103.7, 64.0, 60.2, 19.2, 14.6.

N,N-*Dimethyl-3-(3-methyl-5-oxo-2,5-dihydroisoxazol-2-yl)-3-phenylpropenamide* ***14***

Isoxazolone **1** (0.825 g, 3 mmol) was stirred with sodium hydroxide (0.121 g, 3 mmol) in ethanol (9.2 mL) and water (9.2 mL) for 2 h at 0°C. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL). The aqueous phase was acidified with conc. HCl to pH 3, and extracted with ethyl acetate (2 × 30 mL) to give the *carboxylic acid* as a dark orange oil (0.609 g, 82%). (Found: M^+ 245.0686. $C_{13}H_{11}NO_4$ requires M^+ 245.0688). ν_{max}/cm^{-1} 1777, 1719, 1628, 1577, 1449, 1278. δ_H 8.84 (1H, bs), 7.38–7.52 (5H, m), 6.26 (1H, s), 5.17 (1H, q, *J* 0.82), 2.03 (3H, d, *J* 0.82). δ_C 170.4, 167.5, 161.5, 145.7, 133.9, 132.1, 129.5, 127.8, 115.1, 89.3, 13.1. *m*/*z* 245 (M^+, 42%), 227 (17), 201 (33), 184 (19), 172 (30), 147 (100), 115 (28), 103 (62), 77 (68), 69 (76), 51 (20), 44 (40).

The carboxylic acid above (0.609 g, 2.5 mmol), dimethylamine hydrochloride (0.223 g, 2.73 mmol), pyridine (0.216 g, 2.73 mmol), and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (0.768 g, 3.73 mmol) were stirred in dichloromethane (30 mL) and DMF (3 mL) for 3 h at 0°C and then at room temperature for 16 h. The solvent was evaporated, and the residue was redissolved in ethyl acetate (50 mL) and then washed with 1 M HCl (2 × 20 mL) and water (20 mL). The organic layer was dried (Na_2SO_4) and evaporated to give an orange oil (0.493 g), which was purified by radial chromatography (ethyl acetate) to give *the title compound* as an orange/brown glass (0.15 g, 23%). (Found: M^+ 272.1164. $C_{15}H_{16}N_2O_3$ requires M^+ 272.1161). ν_{max}/cm^{-1} 1760, 1732, 1640, 1396. δ_H 7.36–7.42 (5H, m), 6.48 (1H, s), 5.12 (1H, q, *J* 0.82), 3.07 (3H, s), 2.97 (3H, s), 1.99 (3H, d, *J* 0.82). δ_C 170.1, 164.7, 163.3, 139.4, 134.0, 130.4, 129.1, 126.4, 121.7, 89.2, 38.0, 34.6, 12.7. *m*/*z* 272 (M^+, 8%), 255 (2), 228 (100), 213 (10), 200 (5), 184 (29), 169 (11), 156 (7), 144 (35), 129 (12), 105 (12), 82 (13), 72 (41).

FVP of ***14***

Pyrolysis (450°C, 175°C, 0.1 mmHg) of **14** (120 mg, 0.44 mmol) gave a dark brown oil (100 mg, 83%), which was purified by radial chromatography (beginning at 30% ethyl acetate/light petroleum), to give four fractions.

The first fraction was tentatively assigned as *3-hydroxy-2-methyl-6-phenylpyridine* **17** (30 mg 33%) as white needles, mp 45°C (Found: $[M+H]^+$ 186.0919. $C_{12}H_{12}NO$ requires $[M+H]^+$ 186.0918). ν_{max}/cm^{-1} 2917, 1667, 1633, 1584, 1557, 1499. δ_H ($CDCl_3$/TFA) 7.93 (1H, d, *J* 8.79), 7.70 (1H, d, *J* 8.79), 7.50–7.61 (5H, m), 2.67 (3H, s). δ_C ($CDCl_3$/TFA) 153.3, 144.4, 143.3, 131.7, 131.6, 130.2, 129.7, 127.1, 123.9, 14.3. *m*/*z* (GC-MS) 186 ($[M+H]^+$, 100%), 156 (19), 115 (15), 89 (5).

The second fraction, tentatively assigned as *3-hydroxy-2,3-dimethyl-6-phenylpyridine* **18** (15 mg, 16%), was obtained as a pale yellow oil. (Found: $[M+H]^+$ 200.1084. $C_{13}H_{14}NO$ requires $[M+H]^+$ 200.1075). ν_{max}/cm^{-1} 1605, 1536. δ_H 7.84–7.87 (2H, m), 7.34–7.44 (5H, m, ArH and H-5), 4.55 (1H, bs, OH), 2.59 (3H, s), 2.33 (3H, s). δ_C 149.1, 148.0, 144.1, 138.0, 134.9, 128.6, 128.3, 126.8, 121.7, 18.3, 16.1. *m*/*z* (GC-MS) 200 ($[M+H]^+$, 100%), 170 (7), 129 (4).

The third fraction was N,N-*dimethyl-5-methyl-2-phenylpyrrole-3-carboxamide* **15** (5 mg, 5%), which was obtained as a brown oil. (Found: M^+ 228.1254. $C_{14}H_{16}N_2O$ requires M^+ 228.1263). ν_{max}/cm^{-1} 1656, 1599, 1449. δ_H 8.33 (1H, bs, NH), 7.28–7.40 (5H, m), 5.99 (1H, dq, *J* 0.82, 2.75), 3.02 (3H, bs), 2.72 (3H, bs), 2.28 (3H, d, *J* 0.82). δ_C 169.4, 132.4, 129.0, 128.8, 128.4, 126.6, 125.5, 111.8, 108.1, 38.6, 34.9, 12.8. *m*/*z* 228 (M^+, 38%), 184 (100), 156 (9), 128 (10), 105 (22), 72 (21), 43 (6).

The fourth fraction was *3-hydroxy-4-dimethylamino-2-methyl-6-phenylpyridine* **16** (16 mg, 18%), obtained as a brown oil. (Found: M^+ 228.1262. $C_{14}H_{16}N_2O$ requires M^+ 228.1263). ν_{max}/cm^{-1} 1478, 1092. δ_H 7.81–7.87 (2H, m), 7.29–7.46 (4H, m, ArH and OH), 7.11 (1H, s), 2.84 (6H, s), 2.56 (3H, s). δ_C 148.8, 148.6, 144.9, 143.5, 138.9, 128.8, 128.5, 126.9, 109.3, 43.6, 18.6. *m*/*z* 228 (M^+, 100%), 213 (77), 199 (15), 185 (33), 170 (6), 144 (10), 128 (13), 115 (8), 102 (13), 83 (10), 59 (6), 43 (5).

*Bromination of 2-Methyl-6-phenylpyridin-4(1*H*)-one* ***20***

A solution of bromine (52 mg, 0.29 mmol) in 1 M aqueous KBr (2 mL) was added over 5 min to a stirred suspension of *2-methyl-6-phenyl-4-pyridone* **20**[17] (50 mg, 0.29 mmol) in 1 M KBr (2 mL). After 24 h the solid precipitate was collected and recrystallized from acetonitrile to give *3,5-dibromo-2-methyl-6-phenylpyridin-4(1*H*)-one* **21** as small white crystals (70 mg), mp 290–292°C. (Found: C 42.4, H 2.7, N 4.3%. $C_{12}H_9Br_2NO$ requires C 42.0, H 2.6, N 4.1%). δ_H ($CDCl_3$/TFA) 7.64–7.74 (5H, m), 2.88 (3H, s). δ_C ($CDCl_3$/TFA) 166.0, 154.5. 154.0, 132.5, 130.0, 129.8, 128.9, 110.0, 109.5, 20.5.

Bromination as above under more dilute conditions, or with NBS in chloroform, or with bromine in various solvents, all gave predominantly the 3,5-dibromo compound above, with small quantities of the desired mono brominated species, as determined by the pyridine H-3 and H-5 resonances at 7.1 and 6.8 ppm.

Acknowledgments

The authors are grateful to the Australian Research Grants Committee for support of this work.

References

[1] M. Cox, F. Heidarizadeh, R. H. Prager, *Aust. J. Chem.* **2000**, *53*, 665. doi:10.1071/CH00098
[2] M. Cox, R. H. Prager, D. M. Riessen, *Arkivoc* **2001**, *2*, Part 5.
[3] K. H. Ang, M. Cox, W. D. Lawrance, R. Prager, J. A. Smith, W. Staker, *Aust. J. Chem.* **2003**, *56*, 101. doi:10.1071/CH03140
[4] J. L. Janin, J. Chiki, M. Legraverend, C. Huel, E. Bisagni, *Tetrahedron* **1999**, *51*, 12 797. doi:10.1016/S0040-4020(99)00755-3
[5] L. F. Lee, Y. L. Sing, *J. Org. Chem.* **1990**, *55*, 380.
[6] A. Basak, M. K. Nayak, A. K. Chakraborti, *Tetrahedron Lett.* **1998**, *39*, 4993.
[7] D. W. Jeffery, T. Lister, R. H. Prager, *Aust. J. Chem.* **2004**, *57*, 491. doi:10.1071/CH03139
[8] C. L. Hickson, H. McNab, *J. Chem. Res.* **1989**, 176.
[9] J. Kurita, K. Iwata, T. Tsuchiya, *J. Chem. Soc., Chem. Commun.* **1986**, 1188.
[10] J. Kurita, K. Iwata, T. Tsuchiya, *Chem. Pharm. Bull. Jpn.* **1987**, *35*, 3166.
[11] A. Ben Cheikh, J. Chuche, N. Manisse, J. C. Pommelet, K. Netsch, P. Lorencak, C. Wentrup, *J. Org. Chem.* **1991**, *56*, 970.

[12] A. Filippi, G. Roselli, G. Renzi, F. Grandinetti, M. Speranza, *Chem Eur. J.* **2003**, *9*, 2072. doi:10.1002/CHEM.200204281
[13] J. J. Gajewski, *J. Am. Chem. Soc.* **1970**, *92*, 3688.
[14] J. R. Peterson, T. J. Winter, C. P. Miller, *Syn. Commun.* **1988**, *18*, 949.
[15] S. N. Huckin, L. Weiler, *Tetrahedron Lett.* **1971**, 4835. doi:10.1016/S0040-4039(01)97628-2
[16] B. Lygo, *Tetrahedron* **1995**, *51*, 12 859. doi:10.1016/0040-4020(95)00820-X
[17] C. Koshima, M. Yamomoto, S. Kobayashi, N. Sugiyama, *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2389.
[18] O. S. Tee, M. Paventi, *J. Am. Chem. Soc.* **1982**, *104*, 4142.
[19] M. A. Elkaschef, M. H. Nosseir, *J. Am. Chem. Soc.* **1960**, *82*, 4344.
[20] D. D. Perrin, W. L. F. Armarego, D. R. Perrin, *Purification of Laboratory Chemicals, 2nd edn* **1980** (Pergamon: Oxford).