1-Methoxycarbonylpyrrolizin-3-one and related compounds†

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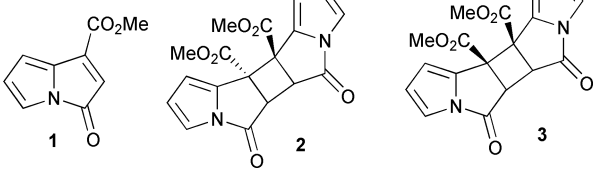
Flash vacuum pyrolysis (FVP) of dimethyl *E*- or *Z*-pyrrol-2-ylbut-2-enedioate **5** at 700 °C gave 1-methoxycarbonylpyrrolizin-3-one **1**. The sequence involves *E*- to *Z*-isomerisation (if necessary), elimination of methanol and cyclisation; the elimination step is rate determining. The pyrrolizinone **1** is stable at low temperatures, but at room temperature dimerises spontaneously across the 1,2-bond to give a mixture of *trans*- and *cis*- cyclobutanes **2** and **3**, respectively. In this process **1** behaves as a captodative alkene. The dimerisation can be reversed at >100 °C. Related pyrrolizinones such as the esters **14** and **22** and the amide **15** are stable to dimerisation. The diacid **12** and the amide **10** do not cyclise to pyrrolizinones under FVP conditions, but instead give the anhydride **19** and the maleimide **18**, respectively; at high furnace temperatures, 2-ethynylpyrrole **17** is obtained from **12** and from **19**.

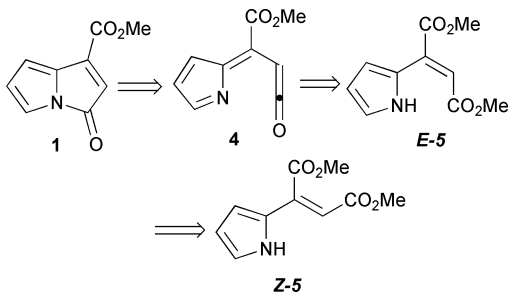
Introduction

In this paper we present full details of results published in a preliminary communication[1] where we showed that 1-methoxycarbonylpyrrolizin-3-one **1**, synthesised in the gas-phase by flash vacuum pyrolysis (FVP), spontaneously dimerises at room temperature to the cyclobutanes **2** and **3**. We discuss the mechanism of formation of **1**, which differs in some details from the 'normal' pyrolytic formation of pyrrolizinones and related compounds from acrylate esters.[2] We report the syntheses of several analogues of **1**, and complete the series of possible pyrrolizin-3-one monocarboxylic esters. Compound **1** is the only pyrrolizinone we have discovered which shows spontaneous dimerisation behaviour (though pyrrolizinone itself has been shown to dimerise under photochemical conditions[3]).

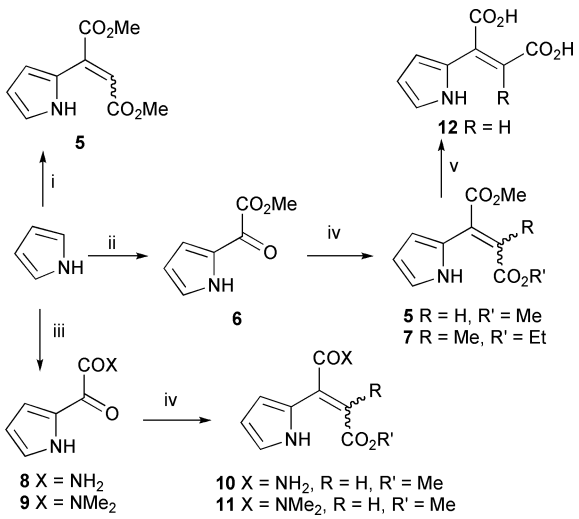


Results and discussion

Thermal formation and subsequent collapse of pyrrolylketenes from pyrrolylacrylate esters[4] provides a general route to the pyrrolizin-3-one ring system.[5] Equilibration of the *E*- and *Z*-isomers of the precursor takes place under the FVP conditions, prior to ketene generation. In order to generate the ketene **4** *en route* to methoxycarbonylpyrrolizin-3-ones such as **1**, the diesters **5** were required (Scheme 1) and two routes were used for their synthesis (Scheme 2).



Scheme 1



Scheme 2 *Reagents and conditions:* (i) DMAD, 4 days, 20 °C; (ii) $(COCl)_2$, −78 °C, then NaOMe; (iii) $(COCl)_2$, −78 °C, then NH_3 or Me_2NH; (iv) $Ph_3P{=}C(R)CO_2R'$, toluene or xylene, reflux; (v) NaOH, $MeOH/H_2O$, reflux.

First, the known[6] treatment of pyrrole with DMAD gave **5** as a mixture of *E*- and *Z*-isomers (36 and 28%, respectively) which could be separated by chromatography. The configuration of the alkene was best assigned by the chemical shift of the NH proton. When the pyrrole and the ester group are on the same side of the

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molecule (the *E*-isomers‡), hydrogen bonding causes substantial deshielding of the NH (δ_H >12 p.p.m.). In the *Z*-isomer of **5**, the NH resonates at *ca.* 9 p.p.m.

The diesters **5** can also be made by Wittig reactions of methyl pyrrol-2-ylglyoxylate **6**, itself readily formed by reaction of pyrrole with oxalyl chloride at −78 °C,[7] followed by quenching with sodium methoxide (Scheme 2). In practice, this second route had few advantages over the DMAD method for the preparation of **5** itself, but the use of different Wittig reagents allowed the introduction of substituents into the acrylate chain (*e.g.* **7**). In addition, application of different quenching reagents provided a route to the amides **10** and **11** (*via* **8** and **9**, respectively) which could not be accessed by the DMAD method. The diacid *Z*-**12** was obtained by hydrolysis of the diester *Z*-**5**.

Small-scale FVP of **5**, at 700 °C in the absence of special precautions at the liquid nitrogen trap and with rapid analysis of the pyrolysate, gave a mixture of three compounds. The first was readily identified as the pyrrolizinone **1** by NMR spectroscopic comparison with other pyrrolizinones.[5] The other two products, which were obtained exclusively if a solution of the pyrolysate was allowed to stand at room temperature for *ca.* 24 h, could be separated by chromatography; they were identified by mass spectrometry as dimers of **1**. Their constitutions as the *trans*- and *cis*- isomers, **2** and **3**, respectively, formed in 2:1 ratio in 66% overall yield, were best determined unambiguously by X-ray crystallography (Fig. 1 and 2).[1] The pyrrolizinone **1** can be obtained in reasonable purity on a preparative scale by modification of the FVP trap design to keep the pyrolysate as cold as possible during work-up (see Experimental section); under these conditions the dimerisation process is slow.

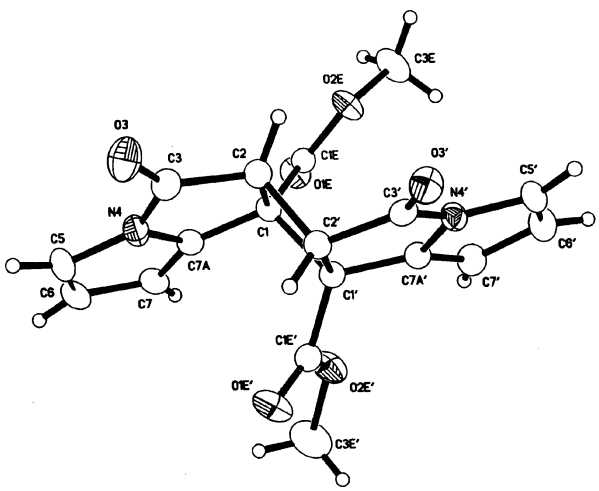


Fig. 1 X-Ray crystal structure of **2** showing crystallographic numbering scheme. See ref. 1 for details.

Initially, it proved difficult to obtain a crystal of the *cis*-isomer **3** and, on one occasion a single crystal of trimethyl 6-oxo-5,5a,10b,10c-tetrahydro-3*H*-pyrrolizino[1,2-*e*]indole-4,5,10b-tricarboxylate **13** was selected (Fig. 3).[8] In principle, this compound

‡ Note that due to the Cahn–Ingold–Prelog priority rules, the *Z*-isomers of the acrylates that lack an ester group in the 3-position, have the same relative configuration to the pyrrole moiety as the *E*-isomer of **5**.

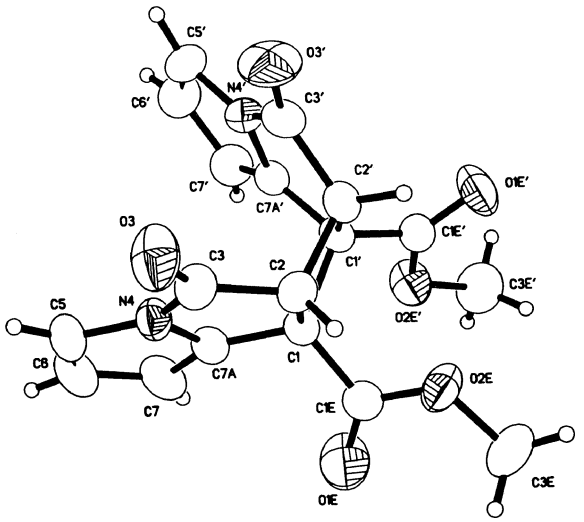


Fig. 2 X-Ray crystal structure of **3** showing crystallographic numbering scheme. See ref. 1 for details.

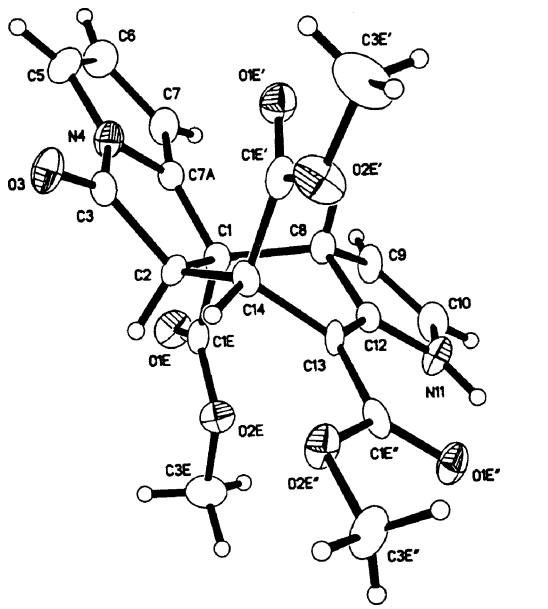
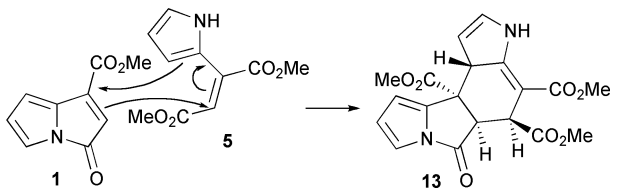


Fig. 3 X-Ray crystal structure of **13** showing crystallographic numbering scheme. See ref. 8 for details.

is a [4+2] cycloadduct of **1** (acting as the dienophile) and **5** (acting as the diene) (Scheme 3). It is known that 2-vinylpyrroles can behave as dienes in appropriate circumstances.[9] Initial attempts to replicate this reaction preparatively were unsuccessful.



Scheme 3

Formation of **2** and **3** clearly takes place by head-to-head dimerisation across the 1,2-bond of two pyrrolizinone moieties. The reaction rate is qualitatively independent of solvent, exposure to light and of the presence of a radical inhibitor. The mechanism must therefore be quite different from the photochemical dimerisation of pyrrolizin-3-one itself.[3] Spontaneous dimerisation of alkenes in the absence of light usually takes place only when the double bond contains both a powerful electron withdrawing group and a powerful electron donating group attached to the same carbon atom (a so-called captodative olefin[10]). These requirements are met by **1**, in which the pyrrole unit is able to act as the donating group.

We have previously found that FVP conditions for the transformation of 3-(azol-2-yl)acrylate esters into pyrrolizin-3-ones and their analogues are dependent on the configuration of the alkene.[2] Transformation of *Z*-isomers‡ is complete at around 700 °C, whereas the *E* isomers require *ca.* 850 °C for total conversion to products. This shows that formation of the *Z*-isomers is needed for reaction, consistent with the intramolecular nature of the elimination step. *E*- to *Z*-isomerisation is clearly the rate determining step for these transformations, followed by rapid elimination and cyclisation. The cyclisation step is likely to be a pseudopericyclic process with a low (or non-existent) barrier.[11] However, the temperature profiles for the FVP reactions of both *E*- and *Z*-isomers of **5** are identical within experimental error (Fig. 4) with complete transformation to cyclised products at 700 °C.

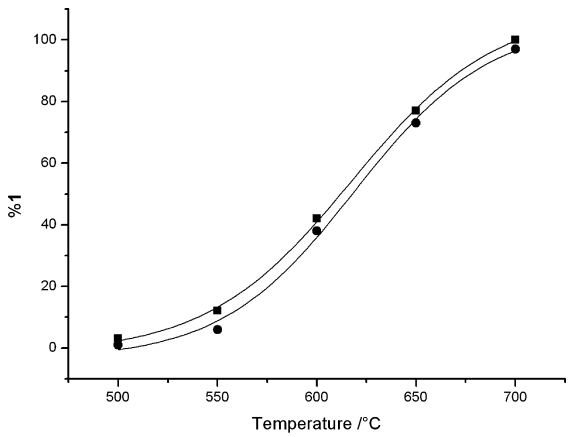
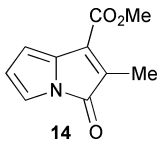


Fig. 4 Temperature–conversion plot for the formation of **1** by FVP of *E*-**5** (squares) and *Z*-**5** (circles).

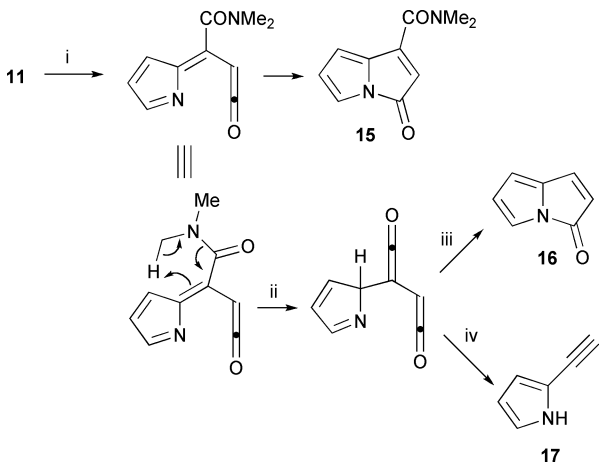
This result suggests that the presence of the second ester group facilitates the *E*- to *Z*-isomerisation process so that the elimination becomes the rate determining step. However, equilibration of dimethyl fumarate and dimethyl maleate is incomplete below 800 °C in our apparatus (see ESI†), so the pyrrole unit and the ester group in **5** must have a synergistic effect in lowering the barrier for the interconversion. The captodative alkene concept may again be relevant here.[10] This result nevertheless has the synthetic advantage that either the *E*- or the *Z*-isomer of **5**, or a mixture of both, can be used to prepare the pyrrolizinone **1** under identical FVP conditions at the relatively low furnace temperature of 700 °C.

The position of the equilibrium of monomer **1** with dimers **2** and **3**, was studied by heating the *trans* dimer **2** in solution. Structure **2** is stable for up to 15 min at 91 °C, but the *trans*-dimer to monomer equilibrium is established after *ca.* 25 min at 101 °C (36% **1**). The ratio of monomer **1** : *trans*-dimer **2** : *cis*-dimer **3** after 15 min at 106 °C was found to be 48 : 49 : 3 though it is not clear whether the equilibrium position of **3** has been established after this period. The monomer **1** is therefore kinetically stable to dimerisation only below room temperature (see above) but is thermodynamically stable at high temperatures.



14

The dimerisation process was surprisingly sensitive to minor structural modifications in the region of the ester group. Thus, the 1-carbomethoxy-2-methylpyrrolizinone **14** was obtained in 73% yield by FVP of **7** at 625 °C and was stable as the monomer. FVP of the amide **11** proved more complex, but under optimised conditions (650 °C) a 17% yield of the pure pyrrolizinone **15** could be obtained by Kugelrohr distillation and it was also stable for weeks at room temperature. Minor products included pyrrolizinone itself **16** and 2-ethynylpyrrole **17** (see below). Their proportions increased at higher furnace temperatures and they are probably formed by retro-ene elimination of $MeN{=}CH_2$ followed by sequential loss of CO (Scheme 4). Similar retro-ene processes have been previously reported.[12]

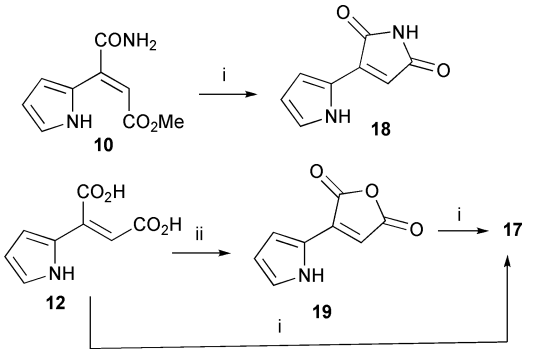


Scheme 4 *Reagents and conditions:* (i) FVP 600–700 °C; (ii) $-MeN{=}CH_2$; (iii) –CO and H-shift; (iv) –2CO and H-shift.

Both **14** and **15** are, in principle, captodative alkenes, yet neither has any tendency to dimerise. In the first case, dimerisation may be hindered by the presence of the methyl substituent and in the second, the electron withdrawing effect of the amide function is apparently insufficient to cause the reaction.

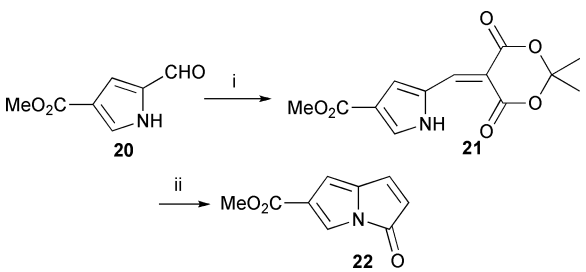
FVP of the *N*-unsubstituted amide **10** (700 °C) or of the diacid **12** (400 °C) caused the formation of the maleimide **18** and the maleic anhydride **19** respectively rather than cyclisation to the pyrrolizinones. At higher temperatures (700 °C), both the diacid **12** and an authentic sample of the maleic anhydride **19** gave 2-ethynylpyrrole **17** as the only product (Scheme 5). FVP of phenylmaleic anhydride similarly provided phenylacetylene. The

mechanism of these reactions involves concomitant decarbonylation and decarboxylation of the anhydride moiety.



Scheme 5 *Reagents and conditions:* (i) FVP 700 °C; (ii) FVP 400 °C.

Pyrrolizin-3-ones with methyl or ethyl carboxylic ester substituents in the 1-,[1] 2-,[4] 5-[4] and 7-positions[4] are now known and all except the 1-isomer are stable. In order to complete the series of possible pyrrolizinone monocarboxylic esters, the 6-substituted-derivative **22** was made by the standard Meldrum's acid route[4,5] using the known[13] 4-methoxycarbonylpyrrole-2-carboxaldehyde **20** as starting material (Scheme 6 and Experimental section). The FVP step gave 6-methoxycarbonylpyrrolizin-3-one **22** (88%) as a stable solid which, as expected, showed no tendency to dimerise.



Scheme 6 *Reagents and conditions:* (i) Meldrum's acid, piperidinium acetate, 24 h, 20 °C; (ii) FVP 650 °C.

Conclusions

1-Methoxycarbonylpyrrolizin-3-one **1** has been prepared under FVP conditions and is kinetically stable at –20 °C. Unlike the formation of pyrrolizinones by FVP of other 3-(pyrrol-2-yl)acrylate esters, the alcohol elimination stage of the mechanism is rate determining. At room temperature **1** behaves as a captodative olefin and dimerises spontaneously in head-to-head fashion to provide the cyclobutanes **2** and **3**. No dimers are formed under these conditions from 1-dimethylaminocarbonylpyrrolizin-3-one **15** or from 1-methoxycarbonyl-2-methylpyrrolizin-3-one **14**, or from any other carboxylic ester derivatives of pyrrolizinone, so the structural and electronic requirements for the dimerisation process are stringent. The dimerisation reaction of **1** can be reversed at >100 °C. The methods described here provide the pyrrolizinone skeleton with carbon-based functionality in the 1-position which creates the possibility of a pyrrolizinone approach to simple pyrrolizidine alkaloids. This approach has been successful and will be reported in a future paper.

Experimental

^{1}H and ^{13}C NMR spectra were recorded at 200 (or 250) and 50 (or 63) MHz respectively for solutions in [^{2}H]chloroform unless otherwise stated. Coupling constants are quoted in Hz. Mass spectra were recorded under electron impact conditions.

Methyl pyrrol-2-ylglyoxylate 6

A solution of pyrrole (3.35 g, 50 mmol) in dry ether (20 cm^3) was added over 1 h to a stirred solution of oxalyl chloride (7.40 g, 58 mmol) in ether (50 cm^3) kept at –78 °C. The solution became yellow. Stirring was continued for 1 h at –78 °C and the cold reaction mixture was then poured slowly onto a vigorously stirred solution of sodium methoxide [from sodium (1.55 g, 67 mmol)] in methanol (100 cm^3) at –78 °C. The resulting white suspension was warmed up to 0 °C and a solution of sodium hydrogen carbonate (10 g, 120 mmol) in water (150 cm^3) was added. The solution was then concentrated and extracted with dichloromethane (3 × 100 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvents were removed to yield, after recrystallisation from chloroform, methyl pyrrol-2-ylglyoxylate **6** (4.38 g, 57%) as colourless crystals, mp 66–67 °C (from chloroform) (lit.,[14] 69–70 °C); ν_{max} (nujol) 3297, 1724 and 1636; δ_H 10.41 (1H, br, NH), 7.37 (1H, m), 7.19 (1H, m), 6.30 (1H, m) and 3.89 (3H, s); δ_C 171.33 (quat), 162.41 (quat), 129.03 (quat), 128.75, 122.78, 112.07 and 52.71.

Pyrrol-2-ylglyoxylamide 8

A solution of pyrrole (3.05 g, 45 mmol) in dry ether (50 cm^3) was added over 1 h to a stirred solution of oxalyl chloride (6.31 g, 50 mmol) in ether (40 cm^3) kept at –78 °C. Stirring was continued for 1 h at –78 °C and the cold reaction mixture was then poured slowly onto a vigorously stirred solution of liquid ammonia (*ca.* 20 cm^3) in ether (100 cm^3), kept at –78 °C in a flask equipped with a dry ice condenser and a calcium chloride trap. The trap was then replaced by a tube connected to an inverted funnel placed in a water bath, and the system was allowed to reach room temperature overnight. Water was added, the ether layer was separated and the aqueous layer was continuously extracted with dichloromethane over 3 days. The combined ether and dichloromethane fractions were concentrated to give pyrrol-2-ylglyoxylamide **8** (4.41 g, 70%) as a white solid, mp 125 °C (from chloroform) (lit.,[15] 126–127 °C); ν_{max} (nujol) 3452, 3295, 1705 and 1622; δ_H ([$^2H_6$]acetone) 11.47 (1H, br, NH), 7.78 (1H, br, NH), 7.49 (1H, m), 7.31 (1H, m), 7.20 (1H, br, NH) and 6.33 (1H, m). The ^{13}C spectrum was complicated by exchange processes but the following peaks were resolved at 63 MHz (297 K): δ_C ([$^2H_6$]acetone) 164.10 (quat), 164.05 (quat), 128.20 (quat), 128.04 (quat), 127.13, 126.96 (quat), 120.76 (br CH) and 110.22.

N,N-Dimethyl-pyrrol-2-ylglyoxylamide 9

A solution of pyrrole (1.52 g, 23 mmol) in dry ether (10 cm^3) was added over 1 h to a stirred solution of oxalyl chloride

(3.13 g, 25 mmol) in ether (25 cm^3) kept at −78 °C. Stirring was continued for 1 h at −78 °C and the cold reaction mixture was then poured slowly onto a vigorously stirred solution of anhydrous dimethylamine (25 cm^3) in ether (50 cm^3) at −78 °C. After warming to room temperature, the white precipitate which had formed was filtered off and washed thoroughly with dichloromethane. The filtrate was concentrated, dried ($MgSO_4$) and purified by dry flash chromatography to give *N,N*-dimethyl-pyrrol-2-ylglyoxylamide **9** (2.64 g, 70%) as white crystals, mp 110 °C (from ethyl acetate) (Found: C, 57.9; H, 6.05; N, 16.8. $C_8H_5NO_3$ requires C, 57.8; H, 6.05; N, 16.85%); ν_{max} (nujol) 1639 and 1627; δ_H 10.62 (1H, br, NH), 7.11 (1H, m), 6.98 (1H, m), 6.26 (1H, m) 3.02 (3H, s) and 2.97 (3H, s); δ_C 179.73 (quat), 166.51 (quat), 128.96 (quat), 127.75, 120.87, 111.53, 37.25 and 34.18; *m/z* 166 (M^+, 15%), 109 (21), 94 (100), 72 (46) and 66 (21).

Propenoic acid ester derivatives

A solution of the appropriate pyrrol-2-ylglyoxylic acid derivative and ylide was heated at reflux in the solvent reported (unless otherwise stated) for the time stated. The solvent was removed and the products were separated from residual starting material and triphenylphosphine oxide by careful dry flash chromatography, using hexane and ethyl acetate as eluents. The carbonylic compound, ylide, solvent, volume of solvent, reaction time and recovered starting material are quoted.

Dimethyl *(E)*- and *(Z)*-pyrrol-2-ylbut-2-enedioate 5. [from methyl pyrrol-2-yl glyoxylate **6** (72 mg, 0.5 mmol) and methyl (triphenylphosphoranylidene)acetate (186 mg, 0.6 mmol), toluene, 3 cm^3, 3.5 h, 0 mg recovered starting material]; dimethyl *(E)*-pyrrol-2-ylbut-2-enedioate *E*-**5** (54 mg, 49%) and dimethyl (*Z*)-pyrrol-2-ylbut-2-enedioate *Z*-**5** (16 mg, 15%) (data identical to those reported above).

Ethyl (*E*)- and (*Z*)-3-methoxycarbonyl-2-methyl-3-(pyrrol-2-yl)propenoate 7. [from methyl pyrrol-2-yl-glyoxylate **6** (630 mg, 4.1 mmol) and ethyl 2-(triphenylphosphoranylidene)propionate (1.78 g, 4.9 mmol), *p*-xylene, 30 cm^3, 36 h, 186 mg recovered starting material] ethyl (*E*)-3-methoxycarbonyl-2-methyl-3-(pyrrol-2-yl)propenoate *E*-**7** (35 mg, 4%), bp 105–110 °C (0.3 Torr) (Found: M^+ 237.1001. $C_{12}H_{15}NO_4$ requires *M* 237.1001); δ_H 11.95 (1H, br, NH), 6.90 (1H, m), 6.22 (2H, m), 4.24 (2H, q, ^3J 7.1), 3.89 (3H, s), 1.99 (3H, s) and 1.30 (3H, t, ^3J 7.1); δ_C 169.48 (quat), 169.02 (quat), 135.88 (quat), 125.30 (quat), 121.65, 116.38 (quat), 115.14, 109.75, 61.23, 52.22, 18.14 and 13.87; *m/z* 237 (M^+, 40%), 205 (22), 191 (53), 177 (54), 176 (55), 155 (66), 154 (64), 128 (56), 127 (100), 126 (80), 105 (70), 104 (71), 99 (67), 83 (68), 77 (62), 55 (80), 43 (83) and 39 (66); ethyl (*Z*)-3-methoxycarbonyl-2-methyl-3-(pyrrol-2-yl)propenoate *Z*-**7** (382 mg, 39%), bp 145–150 °C (1 Torr) (Found: M^+ 237.0999. $C_{12}H_{15}NO_4$ requires *M* 237.1001); δ_H 8.96 (1H, br, NH), 6.87 (1H, m), 6.43 (1H, m), 6.28 (1H, m), 4.21 (2H, q, ^3J 7.1), 3.80 (3H, s), 2.15 (3H, s) and 1.29 (3H, t, ^3J 7.1); δ_C 169.62 (quat), 167.74 (quat), 132.66 (quat), 124.57 (quat), 124.41 (quat), 120.64, 113.44, 110.10, 61.11, 52.51, 15.71 and 13.92; *m/z* 237 (M^+, 77%), 205 (49), 191 (60), 177 (87), 176 (78), 163 (37), 105 (100), 104 (84) and 94 (30).

Methyl (*E*)-3-aminocarbonyl-3-(pyrrol-2-yl)propenoate 10. [from pyrrol-2-yl-glyoxylamide **8** (1.48 g, 11 mmol) and methyl (triphenylphosphoranylidene)acetate (4.81 g, 14 mmol), toluene, 130 cm^3, 3.5 h, 0 mg recovered starting material] methyl (*E*)-3-aminocarbonyl-3-(pyrrol-2-yl)propenoate *E*-**10** (687 mg, 33%) yellow crystals, mp 152–153 °C (from chloroform/hexane) (Found: C, 55.65, H, 5.15, N, 14.3. $C_9H_{10}N_2O_3$ requires C, 55.65, H, 5.15, N, 14.45%); δ_H ([$^2H_6$]acetone) 12.44 (1H, br, NH), 7.30 (1H, br, NH), 7.21 (1H, m), 6.98 (1H, br, NH), 6.70 (1H, m), 6.26 (1H, m), 5.68 (1H, s) and 3.78 (3H, s); δ_C ([$^2H_6$]acetone) 169.06 (quat), 168.34 (quat), 143.80 (quat), 125.41 (quat), 122.97, 117.05, 109.11, 105.23 and 50.62; *m/z* 194 (M^+, 81%), 177 (32), 118 (31) and 91 (100). A very minor fraction, strongly fluorescent, was isolated from the column and characterised as methyl [5-oxo-4-(pyrrol-2-yl)-1*H*-pyrrole-2(5*H*)-ylidene]acetate (5 mg, 0.2%), (Found: M^+ 218.0690. $C_{11}H_{10}N_2O_3$ requires *M* 218.0691); δ_H 10.39 (1H, br, NH), 9.23 (1H, br, NH), 6.95 (1H, m), 6.73 (1H, m), 6.71 (1H, d, ^nJ 1.5), 6.31 (1H, m), 5.38 (1H, s) and 3.77 (3H, s); δ_C 171.38 (quat), 167.51 (quat), 149.69 (quat), 128.48 (quat), 123.61 (quat), 121.88, 119.86, 111.73, 110.80, 98.96 and 51.61; *m/z* 218 (M^+, 58%), 187 (31), 186 (26), 125 (20), 119 (22), 111 (38), 97 (66), 95 (44), 91 (26), 85 (40), 83 (65), 55 (89) and 43 (100).

Methyl (*E*)- and (*Z*)-3-(*N,N*-dimethylaminocarbonyl)-3-(pyrrol-2-yl)propenoate 11. [from *N,N*-dimethyl-pyrrol-2-yl-glyoxylamide **9** (610 mg, 3.7 mmol) and methyl (triphenylphosphoranylidene)acetate (1.64 g, 4.9 mmol), *p*-xylene, 55 cm^3, 44 h, 94 mg recovered starting material] methyl (*E*)-3-(*N,N*-dimethylaminocarbonyl)-3-(pyrrol-2-yl)propenoate *E*-**11** (360 mg, 44%) yellow oil, bp 95–100 °C (0.3 Torr) (Found: M^+ 222.1000. $C_{11}H_{14}N_2O_3$ requires *M* 222.1004); δ_H 12.49 (1H, br, NH), 7.03 (1H, m), 6.40 (1H, m), 6.26 (1H, m) 5.49 (1H, s), 3.75 (3H, s), 3.08 (3H, s) and 2.94 (3H, s); δ_C 168.93 (quat), 168.89 (quat), 143.41 (quat), 125.60 (quat), 123.66, 117.00, 110.44, 105.28, 51.71, 38.46 and 34.38; *m/z* 222 (M^+, 92%), 190 (19), 178 (23), 151 (81), 150 (78), 119 (33), 118 (28), 116 (50), 92 (30) and 91 (100). A second column (alumina, using hexane/ethyl acetate as eluant) was necessary to separate the *(Z)*-isomer from triphenylphosphine; methyl (*Z*)-3-(*N,N*-dimethylaminocarbonyl)-3-(pyrrol-2-yl)propenoate *Z*-**11** (126 mg, 15%) yellow crystals, mp 147–149 °C (from ethyl acetate) (Found: C, 59.35; H, 6.45; N, 12.2. $C_{11}H_{14}N_2O_3$ requires C, 59.45; H, 6.35; N, 12.6%); δ_H 9.44 (1H, br, NH), 6.83 (1H, m), 6.48 (1H, m), 6.20 (1H, m), 6.00 (1H, s), 3.68 (3H, s), 3.11 (3H, s) and 2.88 (3H, s); δ_C 168.80 (quat), 166.25 (quat), 142.96 (quat), 126.23 (quat), 123.84, 113.48, 110.26, 106.51, 51.24, 37.57 and 34.33; *m/z* 222 (M^+, 100%), 178 (22), 151 (90), 150 (85), 119 (29), 118 (25), 116 (50), 92 (29) and 91 (92).

FVP experiments

The precursors were distilled under vacuum through a silica pyrolysis tube (35 × 2.5 cm), which was heated by a laboratory tube furnace. Unless otherwise stated, products were collected in a U-tube trap cooled by liquid nitrogen and situated at the exit point of the furnace. Upon completion of the pyrolysis the trap was allowed to warm up to room temperature under nitrogen and the product was generally removed from the trap by dissolution in acetone. Removal of the solvent(s) followed by bulb-to-bulb distillation, sublimation or recrystallisation afforded the pure pyrrolizin-3-ones. Pyrolysis parameters are quoted as follows:

furnace temperature (T_f), inlet temperature (T_i), pressure (range if appropriate) (P) and reaction time (t).

FVP of dimethyl *E*- and *Z*-pyrrol-2-ylbut-2-enedioate 5

E-**5** or *Z*-**5** or a mixture of both, were used interchangeably (see below for justification).

Method 1—isolation of **1**. Upon completion of the FVP of dimethyl pyrrol-2-ylbut-2-enedioate **5** [70 mg, T_f 700 °C, T_i 80 °C, P 0.005 Torr, t 15 min], the trap was kept cold and slowly warmed to −30 °C/−20 °C (bath of dry ice/acetone) and [^{2}H]chloroform was added. ^{1}H and ^{13}C NMR spectra were recorded immediately at 253 K and were characteristic of 1-methoxycarbonylpyrrolizin-3-one **1**; δ_H (253 K) 6.91 (1H, d, ^3J 3.1), 6.29 (1H, d, ^3J 3.1), 6.21 (1H, s), 6.02 (1H, t, ^3J 3.1) and 3.87 (3H, s); δ_C (253 K) 163.77 (quat), 161.40 (quat), 140.88 (quat), 133.93 (quat), 126.34, 119.82, 116.28, 114.11 and 52.77; λ_{max} (methanol) 313 (log$\varepsilon \geq$ 3.51) and 438 (log$\varepsilon \geq$ 2.72).

In order to obtain **1** for further reactions, a cold-finger trap was situated as close as possible to the exit point of the furnace. The connection between the furnace silica tube and the cold finger trap was wrapped in aluminium foil so that 1-methoxycarbonylpyrrolizin-3-one **1** condensed almost exclusively on the cold finger. Under nitrogen, it was washed from the trap, using ice-cold acetone and kept below 0 °C before use.

Method 2—isolation of **2** and **3**. Using a U-tube trap, the products of pyrolysis [from dimethyl pyrrol-2-ylbut-2-enedioate (231 mg, 1.1 mmol), T_f 700 °C, T_i 60 °C, P 0.0005 Torr, t 15 min] were dissolved in acetone (50 cm^3). The solution was filtered and set aside for 4 days. The solvent was then removed to give a mixture of *trans*- and *cis*- dimethyl 7,8-dioxo-7,7a,7b,8-tetrahydro-6a,8a-diaza-cyclobuta[1,2-*a*;4,3-*a*′]dipentalene-3b,3c dicarboxylate **2** and **3** (129 mg, 66%), respectively in a 2:1 ratio (determined by ^{1}H NMR spectroscopy). Dry flash column chromatography on silica (using ethyl acetate and hexane as eluants) allowed the separation of the two dimers. The first to elute was the major *trans*-isomer **2** as colourless crystals, mp 178 °C (from toluene) (Found: C, 61.15; H, 3.95; N, 7.85. $C_{18}H_{14}N_2O_6$ requires C, 61.0; H, 3.95; N, 7.9%) (Found: M$^+$ 354.0846. $C_{18}H_{14}N_2O_6$ requires *M* 354.0851); δ_H 7.17 (2H, dd, ^3J 3.2 and ^4J 1.1), 6.54 (2H, t, ^3J 3.2), 6.37 (2H, dd, ^3J 3.2 and ^4J 1.1), 4.03 (2H, s) and 3.57 (6H, s); δ_C 167.30 (quat), 166.48 (quat), 133.09 (quat), 120.11, 113.71, 109.00, 55.02 (quat), 52.96 and 47.52; *m*/*z* 354 (M$^+$, 8%), 322 (12), 290 (9), 178 (12), 177 (100), 118 (33) and 91 (20): followed by the *cis*-isomer **3** as colourless crystals mp 160–162 °C (from hexane) (Found: M$^+$ 354.0871. $C_{18}H_{14}N_2O_6$ requires *M* 354.0851); δ_H 6.90 (2H, d, ^3J 3.1), 6.33 (2H, t, ^3J 3.1), 6.13 (2H, d, ^3J 3.1), 4.36 (2H, s) and 3.80 (6H, s); δ_C 168.07 (quat), 165.85 (quat), 133.09 (quat), 119.77, 113.30, 108.99, 53.40 (quat), 53.18 and 47.12; *m*/*z* 354 (M$^+$, 4%), 322 (8), 290 (7), 178 (11), 177 (100), 118 (54), 91 (42), 90 (20), 63 (13) and 39 (13).

Dimerisation of 1-methoxycarbonylpyrrolizin-3-one 1

Various solutions of 1-methoxycarbonylpyrrolizin-3-one **1** were monitored by ^{1}H NMR spectroscopy. The solvent and particular conditions included the following: [^{2}H]chloroform; [$^2H_6$]acetone; [$^2H_4$]methanol; [^{2}H]chloroform in the dark; [^{2}H]chloroform with 2,4,6-tri-*tert*-butylphenol (15 eq). The rates of dimerisation were qualitatively identical, the reaction being complete in just over 1 day.

Formation of trimethyl 6-oxo-5,5a,10b,10c-tetrahydro-3*H*-pyrrolizino[1,2-*e*]indole-4,5,10b-tricarboxylate 13

During recrystallisation trials of a fraction which was predominantly the *cis*-dimer **3**, a single crystal of trimethyl 6-oxo-5,5a,10b,10c-tetrahydro-3*H*-pyrrolizino[1,2-*e*]indole-4,5,10b-tricarboxylate **13** was selected for X-ray crystallography after slow recrystallisation from isopropyl alcohol.[8] (Found: M$^+$ 386.1136. $C_{19}H_{18}N_2O_7$ requires *M* 386.1114); *m*/*z* 386 (M$^+$, 1.6%), 354 (11), 322 (8), 290 (10), 178 (13), 177 (100), 149 (11), 118 (42) and 91 (20).

2-Methyl-1-methoxycarbonylpyrrolizin-3-one 14

The pyrolysate from FVP of ethyl (*Z*)-3-methoxycarbonyl-2-methyl-3-(pyrrol-2-yl)propenoate **7** [(141 mg, 0.6 mmol), T_f 625 °C, T_i 120–150 °C, P 0.02–0.05 Torr, t 20 min] was dissolved in dichloromethane. Removal of the solvents and bulb-to-bulb distillation afforded 2-methyl-1-methoxycarbonylpyrrolizin-3-one **14** (83 mg, 73%) as the major product, bp 110–120 °C (0.3 Torr) (Found: M$^+$ 191.0574. $C_{10}H_9NO_3$ requires *M* 191.0582); δ_H 6.86 (1H, ddq, ^3J 3.1, ^4J 0.8 and ^6J 0.5), 6.14 (1H, ddq, ^3J 3.1, ^4J 0.8 and ^6J 0.5), 5.99 (1H, t, ^3J 3.1), 3.87 (3H, s) and 2.15 (3H, t, ^6J 0.5); δ_C 164.90 (quat), 162.43 (quat), 139.63 (quat), 132.56 (quat), 124.53 (quat), 118.77, 116.06, 111.76, 52.01 and 10.32; *m*/*z* 191 (M$^+$, 55%), 176 (50), 132 (19), 105 (84), 104 (100), 77 (41) and 51 (63).

1-(*N,N*-Dimethylaminocarbonyl)pyrrolizin-3-one 15

The pyrolysate from FVP of methyl (*E*)-3-(*N,N*-dimethyl-aminocarbonyl)-3-(pyrrol-2-yl) propenoate **11** [(190 mg, 0.8 mmol), T_f 650 °C, T_i 100–120 °C, P 0.01–0.05 Torr, t 35 min] was rinsed with dichloromethane and the solvents were removed under vacuum to yield a dark liquid (101 mg) containing 3 products: 1-(*N,N*-dimethylaminocarbonyl)pyrrolizin-3-one **15** (46%), bp 180–185 °C (0.6 Torr) (partial decomp.) (Found: M$^+$ 190.0744. $C_{10}H_{10}N_2O_2$ requires *M* 190.0742); δ_H 6.93 (1H, dd, ^3J 3.1 and ^4J 0.8), 6.10 (1H, dd, ^3J 3.1 and ^4J 0.8), 6.04 (1H, td, ^3J 3.1 and ^6J 0.7), 5.67 (1H, d, ^6J 0.7), 3.11 (3H, s) and 3.06 (3H, s); δ_C 164.11 (quat), 162.75 (quat), 145.47 (quat), 134.95 (quat), 119.37, 119.28, 115.85, 112.54, 38.27 and 34.78; *m*/*z* 190 (M$^+$, 100%), 147 (42), 119 (38), 118 (32), 91 (93), 90 (44), 72 (44), 63 (24), 44 (12), 42 (19) and 39 (22), pyrrolizin-3-one **16** (8%); δ_H 7.05 (1H, d, ^3J 5.9), 6.87 (1H, d, ^3J 3.1), 5.97 (2H, m) and 5.64 (1H, d, ^3J 5.9) and 2-ethynylpyrrole **17** (11%); δ_H 6.73 (1H, m), 6.49 (1H, m), 6.14 (1H, m) and 3.16 (1H, s) (data compatible with the spectrum of an authentic sample[16]). Distillation of the entire fraction gave pure 1-(*N,N*-dimethylaminocarbonyl)pyrrolizin-3-one **15** (28 mg, 17%) which is stable in solution for weeks at room temperature.

At 600 °C, 20% of the starting material was recovered.

At 700 °C, 1-(*N,N*-dimethylaminocarbonyl)pyrrolizin-3-one **15**, pyrrolizin-3-one **16** and 2-ethynylpyrrole **17** were formed in the ratio 38 : 31 : 31.

FVP of methyl (*E*)-3-aminocarbonyl-3-(pyrrol-2-yl)propenoate 10

FVP of methyl (*E*)-3-aminocarbonyl-3-(pyrrol-2-yl)propenoate **10** [(56 mg, 0.3 mmol), T_f 700 °C, T_i 120 °C, P 0.02 Torr, t 35 min] gave a red pyrolysate which was washed with acetone. Removal of the solvents yielded 3-(pyrrol-2-yl)-pyrrole-2,5-dione **18** (30 mg, 64%) which decomposed on attempted distillation. (Found: M^+ 162.0430. $C_8H_6N_2O_2$ requires *M* 162.0429); δ_H ([$^2H_6$]acetone) 11.17 (1H, br, NH), 9.93 (1H, br, NH), 7.24 (1H, m), 7.14 (1H, m), 6.49 (1H, s) and 6.32 (1H, dt, ^nJ 3.8 and ^nJ 2.4); δ_C ([$^2H_6$]acetone) 171.00 (quat), 170.80 (quat), 135.09 (quat), 124.06, 121.22 (quat), 114.63, 112.69 and 109.96; *m/z* 162 (M^+, 4%) and 91 (100). A trace of a minor by-product was identified as 1-aminocarbonylpyrrolizin-3-one on the basis of its ^1H NMR spectrum; δ_H ([$^2H_6$]acetone) 7.76 (1H, br, NH), 7.37 (1H, br, NH), 7.09 (1H, d, ^3J 3.2), 6.38 (1H, d, ^3J 3.2), 6.22 (1H, s) and 6.14 (1H, t, ^3J 3.2).

Synthesis and pyrolysis of (*Z*)-(pyrrol-2-yl)but-2-enedioic acid 12

To a solution of dimethyl (*Z*)-(pyrrol-2-yl)but-2-enedioate *Z*-**5** (1.94 g, 9 mmol) in methanol (100 cm^3) was added a solution of aqueous sodium hydroxide (5 M, 20 cm^3) and the reaction mixture was heated under reflux for 5 h. Methanol was removed under vacuum leaving a light brown residue to which was added water (60 cm^3) and hydrochloric acid (5%, 60 cm^3). After extraction with ether (3 × 100 cm^3), the combined organic layers were dried ($MgSO_4$) and concentrated to give (*Z*)-pyrrol-2-ylbut-2-enedioic acid **12** (1.28 g, 76%) as a yellow solid which quickly becomes brown-black at room temperature. (Found: C, 52.4; H, 4.2; N, 7.2. $C_8H_7NO_4$, 0.2 H_2O requires C, 52.0; H, 4.0; N, 7.6%) (Found: M^+ 181.0361. $C_8H_7NO_4$ requires *M* 181.0375); ν_{max} (nujol) 3373, 1715 and 1664; δ_H ([$^2H_6$]acetone) 10.80 (1H, br, NH), 5.6–8.4 (2H, br, $2CO_2H$), 7.06 (1H, m), 6.49 (1H, m), 6.23 (1H, m) and 6.14 (1H, s); δ_C ([$^2H_6$]acetone) 166.76 (quat), 165.23 (quat), 140.90 (quat), 125.71 (quat), 122.68, 113.09, 109.34 and 106.06; *m/z* 181 (M^+, 1%), 164 (16), 163 (81), 137 (3), 119 (9), 92 (23) and 91 (100).

FVP of (*Z*)-pyrrol-2-ylbut-2-enedioic acid **12** (50 mg, T_f 400 °C, T_i 135–150 °C, P 0.0006 Torr, t 25 min) gave exclusively 3-(pyrrol-2-yl)furan-2,5-dione **19** characterised by its ^1H NMR spectrum, identical with that of an authentic sample (see below).

FVP of (*Z*)-pyrrol-2-ylbut-2-enedioic acid **12** at 700 °C (24 mg, T_f 700 °C, T_i 120–150 °C, P 0.005–0.01 Torr, t 10 min) gave 2-ethynylpyrrole **17**, characterised as above.[16]

Synthesis and pyrolysis of 3-(pyrrol-2-yl)furan-2,5-dione 19

A solution of (*Z*)-(pyrrol-2-yl)but-2-enedioic acid **12** (240 mg, 1.3 mmol) and acetic anhydride (3 cm^3) was heated at reflux for 1.5 h. Acetic acid and acetic anhydride were then removed under vacuum to leave a black residue, which was dissolved in dichloromethane and heated under reflux with decolourising charcoal for 0.5 h. Filtration through Celite and removal of the solvent gave 3-(pyrrol-2-yl)furan-2,5-dione **19** (89 mg, 41%) as a yellow oil which slowly solidified, mp 110–112 °C (from ethyl acetate) (Found: M^+ 163.0267. $C_8H_5NO_3$ requires *M* 163.0269); δ_H 10.02 (1H, br, NH), 7.18 (1H, m), 7.04 (1H, m), 6.45 (1H, s) and 6.42 (1H, m); δ_C 166.95 (quat), 164.43 (quat), 136.97 (quat), 126.50, 120.95 (quat), 117.94, 113.00 and 112.12; *m/z* 163 (M^+, 30%), 92 (8), 91 (100), 64 (15) and 63 (17).

FVP of 3-(pyrrol-2-yl)furan-2,5-dione **19** (20 mg, T_f 700 °C, T_i 105 °C, P 0.005 Torr, t 5 min) gave 2-ethynylpyrrole **17**, characterised as above.[16]

Similarly pyrolysis of phenylmaleic anhydride (25 mg, T_f 750 °C, T_i 135 °C, P 0.005 Torr, t 10 min) gave ethynylbenzene; δ_H 7.3–7.5 (5H, m) and 3.02 (1H, s) (compatible with literature data[17]).

2,2-Dimethyl-5-(4-methoxycarbonylpyrrol-2-ylidene)-1,3-dioxan-4,6-dione 21

Reaction of 4-methoxycarbonylpyrrole-2-carboxaldehyde[12] **20** (0.55 g, 4 mmol) with Meldrum's acid (0.58 g, 4 mmol) in toluene (8 cm^3) containing glacial acetic acid (4 drops) and piperidine (4 drops) gave, after 24 h at room temperature 2,2-dimethyl-5-(4-methoxycarbonylpyrrol-2-ylidene)-1,3-dioxan-4,6-dione **21** (0.68 g, 68%) as yellow crystals, mp 239–241 °C (dec.) (from methanol) (Found: C, 55.85; H, 4.5; N, 5.1. $C_{13}H_{13}NO_6$ requires C, 55.9; H, 4.65; N, 5.0%); δ_H 12.76 (1H, br, NH), 8.26 (1H, d, ^5J 0.7), 7.84 (1H, br s), 7.45 (1H, d, ^5J 0.7), 3.84 (3H, s) and 1.76 (6H, s); δ_C 163.89 (quat), 163.22 (quat), 143.91, 133.07, 129.39, 128.46 (quat), 120.71 (quat), 104.68 (quat), 103.53 (quat), 51.59 and 27.24 (one quaternary signal not apparent); *m/z* 279 (M^+, 17%), 248 (2), 221 (20), 177 (48), 146 (100), 118 (20), 90 (14), 63 (16), 44 (25) and 43 (27).

6-Methoxycarbonylpyrrolizin-3-one 22

FVP of 2,2-dimethyl-5-(4-methoxycarbonylpyrrol-2-ylidene)-1,3-dioxan-4,6-dione **21** (236 mg, 0.8 mmol) (T_f 650 °C, T_i 180–200 °C, P 0.01 Torr, t 25 min) gave 6-methoxycarbonylpyrrolizin-3-one **22** (131 mg, 88%), mp 111–112 °C (from ethyl acetate/hexane) (Found: C, 61.05; H, 3.85; N, 7.9. $C_9H_7NO_3$ requires C, 61.0; H, 3.95; N, 7.9%); δ_H 7.49 (1H, t, ^4J and ^5J 0.7), 7.18 (1H, dd, ^3J 6.0 and ^5J 0.7), 6.39 (1H, d, ^4J 0.7), 5.77 (1H, dd, ^3J 6.0 and ^nJ 0.3) and 3.78 (3H, s); δ_C 165.05 (quat), 163.62 (quat), 138.90, 136.29 (quat), 123.11, 122.84 (quat), 122.50, 110.74 and 51.42; *m/z* 177 (M^+, 98%), 146 (100), 134 (48), 118 (51), 90 (24) and 63 (66).

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