Synthesis and unexpectedly facile dimerisation of 1-methoxycarbonylpyrrolizin-3-one

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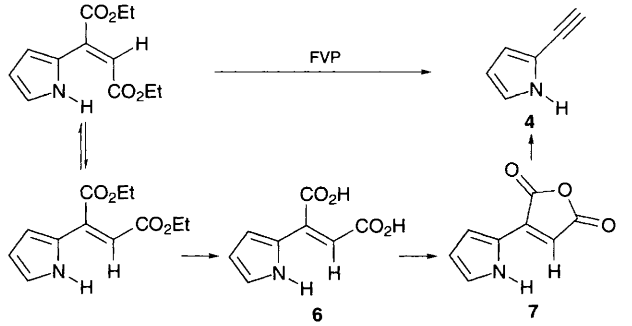
Flash vacuum pyrolysis of the diethyl esters 2 gives 2-ethynylpyrrole *via* the anhydride 7; the corresponding dimethyl esters 3 give, under similar conditions, the pyrrolizinone 5, which is remarkably unstable and spontaneously dimerises to give the [2 + 2] cycloadducts 8 and 9 whose structures are proved by X-ray crystallography.

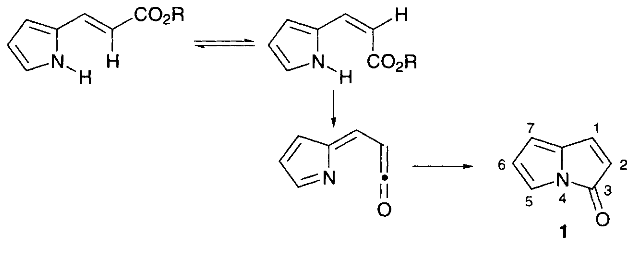
Flash vacuum pyrolysis (FVP) of 2-pyrrolylacrylate esters is a useful general synthetic route to the pyrrolizin-3-one ring system **1** and related aza-analogues (Scheme 1).[1,2] In an extension of this work to the synthesis of unknown pyrrolizinone 1-carboxylic esters, we have now found that the appropriate diethyl esters **2** undergo an unprecedented thermal degradation to 2-ethynylpyrrole **4**, and that although the dimethyl esters **3** give the expected 1-methoxycarbonylpyrrolizin-3-one **5** in good yield, this compound is remarkably unstable and spontaneously dimerises under mild conditions.

The diesters **2** and **3** were prepared by the literature method[3] by reaction of pyrrole with the appropriate acetylenedicarboxylic ester, and were purified, if required, by chromatography on silica. Pyrolysis of a mixture of the (*E*)- and (*Z*)-diethyl esters **2** at 700–750 °C and 0.001 Torr (1 Torr = 133.322 Pa) gave 2-ethynylpyrrole **4** as the major product, identified by comparison with an authentic sample,[4] together with a small amount of the parent pyrrolizin-3-one **1**. The mechanism of the alkyne formation probably involves *E*–*Z* isomerisation[5] of the alkene (if required), with concomitant elimination of ethylene from one (or both) of the ester functions (Scheme 2). The diacid **6** can dehydrate thermally to the anhydride **7**, and well precedented[6] cleavage of CO and CO_2 from the anhydride gives the observed alkyne. The mechanism is strongly supported by independent preparation and pyrolysis of the maleic acid **6** [prepared by basic hydrolysis of the (*Z*)-diester] and of the anhydride **7** (prepared either by dehydration or by mild thermolysis of the diacid **6**†), both of which lead to 2-ethynylpyrrole **4** under the same conditions as the diesters **2** (Scheme 2). No significant amounts of the parent pyrrolizinone were obtained in either of these reactions, and so it probably formed from **2** by the standard route (Scheme 1) followed by ester elimination and decarboxylation.

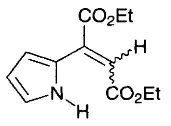
Diversion of the ester elimination process by pyrolysis of either the (*E*)- or (*Z*)-dimethyl esters **3** at 700 °C (0.001 Torr) led to quite different results. If the products of the FVP were quenched at a low temperature, 1-methoxycarbonylpyrrolizin-3-one **5** [δ_H($CDCl_3$, −20 °C) 6.91 (1 H, d), 6.29 (1 H, d), 6.21 (1 H, s), 6.02 (1 H, t) and 3.87 (3 H, s)] was obtained as expected (Scheme 3). The pyrrolizinone was relatively stable in dilute solution at low temperatures, and could be stored for some days at −20 °C. However, in marked contrast to all other reported pyrrolizin-3-ones this compound spontaneously dimerises in solution at room temperature within *ca.* 24 h to give a 66% yield (based on **3**) of just two isomers in a ratio of 2 : 1. These products were separated by chromatography and shown to be symmetrical dimers of the pyrrolizinone by ^1H and ^{13}C NMR spectroscopy and by mass spectrometry [δ_H ($CDCl_3$, major isomer) 7.17 (2 H, d), 6.54 (2 H, t), 6.37 (2 H, d), 4.03 (2 H, s) and 3.57 (6 H, s); δ_H($CDCl_3$, minor isomer) 6.90 (2 H, d), 6.33 (2 H, t), 6.13 (2 H, d), 4.36 (2 H, s) and 3.80 (6 H, s)]. These dimers are also the major products from the FVP of **3**, if no



Scheme 2



Scheme 1



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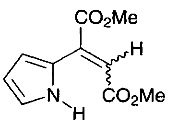

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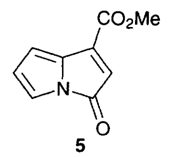

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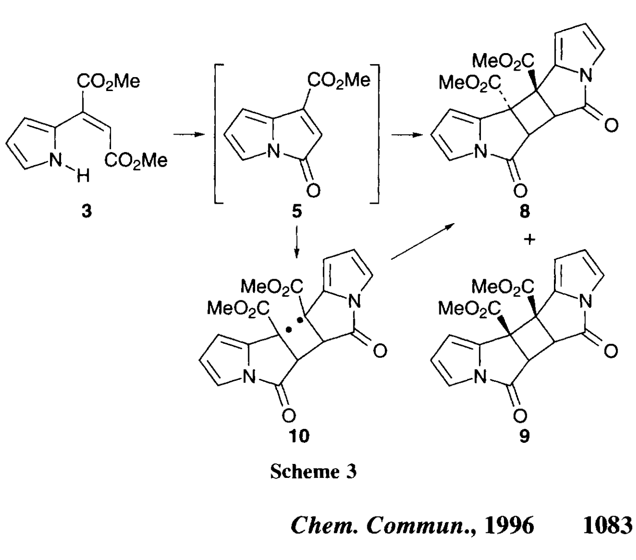

Scheme 3

special precautions are taken to keep the pyrolysis products cold.

The structures of the major and minor dimers were found by X-ray crystallography‡ to be the *trans* and *cis* head-to-head [2 + 2] dimers **8** and **9** respectively (Fig. 1 and Scheme 3). Spontaneous dimerisation of this type is unprecedented in pyrrolizinone chemistry; pyrrolizinones bearing carboxylic ester substituents at the 2-, 5- and 7-positions are known[2,7,8] and are stable. However, captodative olefins, in which a single position of an alkene is substituted with both an electron-withdrawing and an electron-donating group, are well known to dimerise, probably *via* an intermediate stabilised diradical.[9] The 1-ester substituent and the pyrrole ring, respectively, can act in this fashion with respect to the 1,2-double bond of the pyrrolizinone structure **5**, to give the corresponding diradical **10** (Scheme 3). In agreement with this mechanism, the dimerisation of the pyrrolizinone appears to proceed qualitatively at a similar rate in a range of solvents (chloroform, acetone or methanol), or in the presence or absence of light, or in the presence of an excess of a radical chain inhibitor (tri-*tert*-butylphenol), and no trace of head-to-tail dimers were detected. Solution thermolysis of a pure sample of **8** at 110 °C in refluxing toluene generates a mixture consisting of the pyrrolizinone **5** and the two dimers **8** and **9**, as found for other captodative alkene dimers.[9]

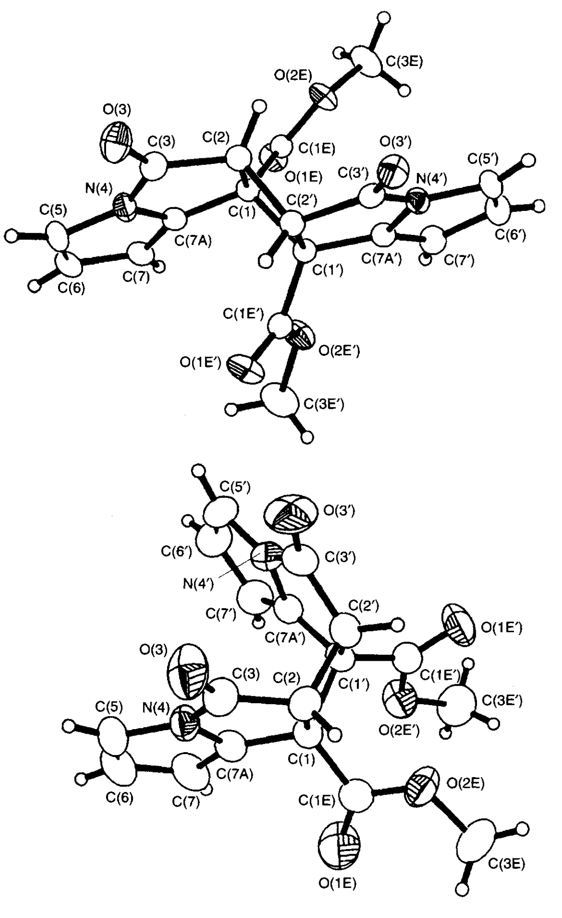

Fig. 1 Thermal ellipsoid plots of the pyrrolizinone dimers **8** and **9** showing the crystallographic numbering system. (Thermal ellipsoids are drawn at the 50% probability level).

We are grateful to the SERC for the provision of a four-circle diffractometer and to Glaxo Wellcome for financial support.

Footnotes

† All new compounds were characterised by their spectra and by elemental analysis or accurate mass measurement.

‡ *Crystal data* for **8**: $C_{18}H_{14}N_2O_6$, M = 354.31, monoclinic, $P2_1/c$, a = 13.129(3), b = 9.622(4), c = 12.836(3) Å, β = 99.28(2) °, V = 1600.3 Å^3 [from 2θ values for 40 reflections measured at ±ω (28 < 2θ < 31 °), λ = 0.71073 Å]. Z = 4, D_{calc} = 1.471 g cm^{-3}, F(000) = 736, T = 298 K, μ(Mo-Kα) = 0.112 mm^{-1}. Colourless block, 0.56 × 0.39 × 0.36 mm^3. For **9**: $C_{18}H_{14}N_2O_6$, M = 354.31, triclinic, $P\bar{1}$, a = 9.4414(18), b = 9.6252(15), c = 10.0047(15) Å, α = 113.228(13) °, β = 95.960(15) °, γ = 90.487(16) °, V = 829.8 Å^3 [from 2θ values for 24 reflections measured at ±ω (30 < 2θ < 32 °), λ = 0.71073 Å]. Z = 2, D_{calc} = 1.418 g cm^{-3}, F(000) = 368, T = 298 K, μ(Mo-Kα) = 0.108 mm^{-1}. Colourless block, 0.77 × 0.58 ×0.39 mm^3. Both data sets were collected on a Stoe Stadi-4 four-circle diffractometer; data were collected in the range 5 < 2θ < 50 ° using ω-2θ scans. The structures were solved by direct methods[10] and refined by full-matrix least squares.[11] Hydrogen atoms were placed in calculated positions and treated with a riding model during refinement. At convergence for **8**: $R1$ = 3.41% [based on F and all 2359 unique data with $F > 4\sigma(F)$], $wR2$ = 8.74% (based on F^2 and all 2820 unique data) for 238 parameters; ΔF max. and min. were 0.283 and −0.169 eÅ^{-3}, respectively. For **9**: $R1$ = 5.57% [based on 2158 data with $F > 4\sigma(F)$], $wR2$ = 15.64% (based on all 2918 data) for 236 parameters; ΔF max. and min. were +0.30 and −0.29 eÅ^{-3}, respectively. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/33.

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