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Synthesis of 2-Acylamino-1,2-Dihydropyrrolizin-3-ones from Pyrrole‡

Thomas L. Gilchrist* and Américo Lemos

Chemistry Department, University of Liverpool, P.O. Box 147, Liverpool L69 3BX, U.K.

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Abstract: *The pyrrolizidin-3-ones* ***5, 7 and 10*** *have been prepared from pyrrole by making use of its reaction with ethyl bromopyruvate oxime in the presence of sodium carbonate to introduce the side chain. The 5-substituents were introduced into the pyrrole ester* ***2*** *before hydrolysis and dehydrative cyclization. The X-ray crystal structure of compound* ***10*** *has been determined and this shows that the C-3 to N-4 bond is longer than in normal tertiary amides, as has been obsered with other* N*-acylated azoles.*

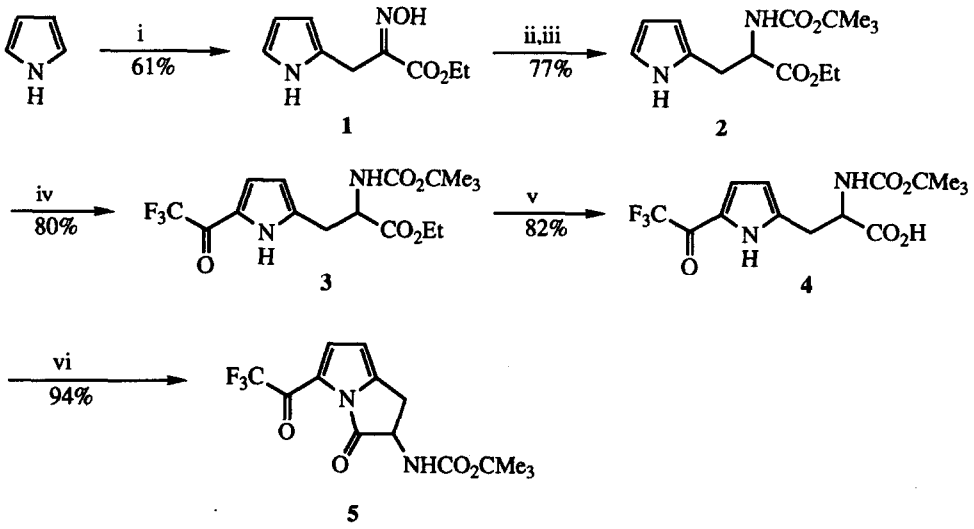
There has recently been renewed interest in the potential use of fused γ-lactams as antibacterial agents.[1] As part of an investigation into methods of preparation of new compounds of this type we have synthesised 1,2-dihydropyrrolizin-3-ones bearing an acylamino substituent at C-2. In this paper we describe a new route to these compounds starting from pyrrole. This route is intended to be sufficiently flexible to allow a variety of functional groups to be introduced at C-5 and, eventually, at other positions.

Methods of synthesis of pyrrolizines, including pyrrolizin-3-ones and partly saturated derivatives, have been reviewed[2] and further recent examples have been described.[3] We have used a variant of one of the literature approaches, namely the dehydrative cyclization of a pyrrole-2-propanoic acid. 2-Acylamino-2,3-dihydropyrrolizin-3-ones have previously been synthesised by a cyclization of this type in which the Mannich base 2-(dimethylamino)methylpyrrole was condensed with acylaminomalonic esters.[4] In the present work the side chain was introduced directly into pyrrole by reaction with ethyl bromopyruvate oxime in the presence of sodium carbonate.[5]

The reaction sequence used is shown in the Scheme. Ethyl pyrrole-2-(2-oximino)propanoate **1** was isolated in 61% yield from the reaction of ethyl bromopyruvate oxime with pyrrole in excess in the presence of sodium carbonate. This reaction can be interpreted as an electrophilic substitution of pyrrole by the transient intermediate ethyl 2-nitrosopropenoate, although the possibility that the oxime **1** is formed by [4 + 2] cycloaddition of the vinylnitroso intermediate across C-2 and C-3 of pyrrole followed by ring opening cannot be ruled out. The oxime was reduced by reaction with aluminium amalgam and the amine was converted into the t-butoxy urethane **2** in good overall yield. Attempts to cyclize the ester by reaction with sodium hydride and other bases were unsuccessful and resulted in decomposition of the urethane **2**. Attempts to cyclize the corresponding acid (formed by mild basic hydrolysis of **2**) gave unsatisfactory results, the reactions being incomplete and complicated by attack of the electrophilic dehydrating agents at C-5 of the pyrrole. An alternative approach was therefore adopted in which C-5 was blocked, and the NH group simultaneously activated, by the introduction of a conjugative electron withdrawing group at C-5. Several such substituents were introduced; this procedure makes it possible to incorporate a variety of activating substituents at the position equivalent to that which bears

‡ *Dedicated to Professor Charles W. Rees, FRS, on his 65th birthday.*

the carboxyl group in carbapenems. The simplest and most efficient substitution took place with trifluoroacetic anhydride at room temperature, a reaction which gave the ketone **3** in good yield.

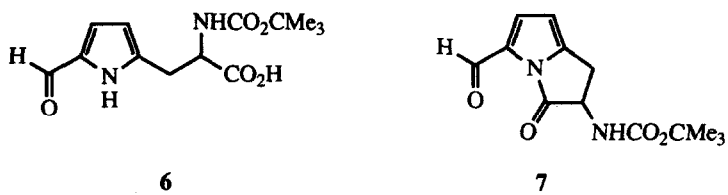


Scheme

Reagents: i, $BrCH_2C(=NOH)CO_2Et$, Na_2CO_3; ii, Al/Hg; iii, $(Me_3COCO)_2O$, NEt_3; iv, $(CF_3CO)_2O$, Na_2CO_3; v, KOH, aq. EtOH, then HCl; vi, 2-chloro-4,6-dimethoxy-1,3,5-triazine, *N*-methylmorpholine.

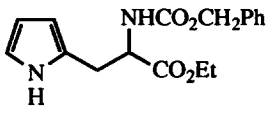
Compound **3** was hydrolyzed to the carboxylic acid **4** which was then cyclized in mild conditions to the pyrrolizinone **5**. With dicyclohexylcarbodiimide compound **5** was isolated in only 22% yield, since the carbodiimide also reacted at the carboxyl group to give a urea. The cyclization was, however, achieved in excellent yield by the use of 2-chloro-4,6-dimethoxy-1,3,5-triazine[6] as the dehydrating agent.

The ester **2** was also formylated in high yield at C-5 by means of the Vilsmeier-Haack reagent. The product was hydrolyzed *in situ* to the carboxylic acid **6**. This was cyclized to the pyrrolizinone **7** by reaction with dicyclohexylcarbodiimide, but again the yield with this reagent was low (20%). In this case other dehydrating agents were not used.



6 **7**

Attempts were made to produce crystals of **5** or **7** for X-ray structure determination but these were unsuccessful. A reaction sequence analogous to that in the Scheme was then carried out to produce the benzyloxycarbonyl protected aminopyrrolizinone **10** by way of the isolated intermediates **8** and **9**. The X-ray crystal structure of the pyrrolizinone **10** was determined and is shown in the Figure. Selected intramolecular distances (crystallographic numbering of atoms) are given in Table 1 and selected bond angles are in Table 2.



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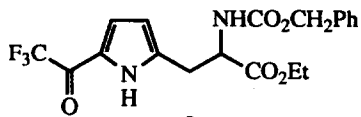

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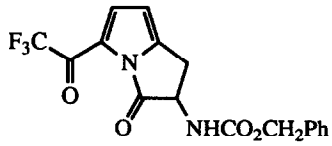

10

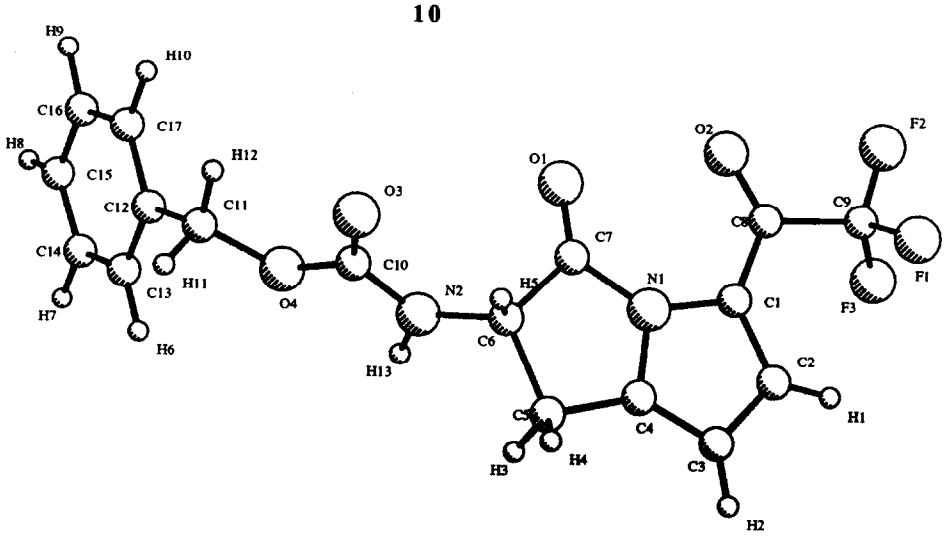

Figure. Structure of the pyrrolizinone **10**.

The C-3 to nitrogen bond length (atoms labelled C7 and N1 in the crystal structure) is 1.423(7) Å. McNab and his co-workers have previously determined the crystal structure of 6-bromopyrrolizin-3-one[3b]: the molecule was shown to be planar and with a C-3 to nitrogen bond length of 1.419 (9) Å, which is significantly greater than that of a normal cyclic tertiary amide [1.335(9) Å].[8] It has been pointed out that the long bond is typical of *N*-acylated azoles in which the normal amide delocalization is reduced.[3b] In the structure of compound **10** the carbon-oxygen bond length of 1.182(7) Å is also unusually small. An unexpected feature is the abnormally long 4-5 bond in the pyrrole ring (linking atoms labelled N1 and C1 in the Figure). The bond distance of 1.418(7) Å is much greater than any corresponding bond distances in monocyclic pyrroles.[9]

γ-Lactam analogues of β-lactam antibiotics must be accommodated in the active sites of bacterial penicillin-binding proteins in order to display antibacterial activity. Molecular modelling studies have shown that compounds which display activity are nonplanar and have structures in which the substituents are in a similar spatial arrangement to those in penicillins and cephalosporins.[10] As derivatives of aromatic pyrroles it is to be expected that the pyrrolizinones **5**, **7** and **10** are essentially planar about the central nitrogen atom. Indeed the crystal structure of compound **10** shows that the nitrogen is essentially planar but that the carbonyl oxygen atom is slightly displaced from the plane: the conformation angle O1-C7-N1-C1 (crystal structure numbering) is 6°. We are currently investigating the reduction of these and related bicyclic pyrrole derivatives as a route to bicyclic lactams in which the bridgehead nitrogen is nonplanar.

Table 1. Selected Intramolecular Bond Distances (Å) in Crystal of **10**.

atom	atom	distance	atom	atom	distance
O1	C7	1.182(7)	C1	C2	1.377(8)
O2	C8	1.202(8)	C1	C8	1.435(9)
N1	C1	1.418(7)	C2	C3	1.388(8)
N1	C4	1.381(7)	C3	C4	1.371(8)
N1	C7	1.423(7)	C4	C5	1.482(8)

Table 2. Selected Intramolecular Bond Angles (°) in Crystal Structure of **10**.

atom	atom	atom	angle	atom	atom	atom	angle
C1	N1	C4	108.9(5)	C3	C4	C5	140.2(6)
C1	N1	C7	138.8(6)	C4	C5	C6	103.3(5)
C4	N1	C7	112.3(6)	N2	C6	C5	113.7(5)
N1	C1	C2	105.0(6)	N2	C6	C7	111.7(5)
N1	C1	C8	123.9(6)	C5	C6	C7	106.8(5)
C2	C1	C8	131.0(6)	O1	C7	N1	126.6(7)
C1	C2	C3	110.4(6)	O1	C7	C6	128.1(6)
C2	C3	C4	107.3(6)	O2	C8	C1	128.3(7)
N1	C4	C3	108.3(6)	O2	C8	C9	116.0(8)

EXPERIMENTAL

General. ^{1}H NMR spectra were recorded on a Bruker ACE200 spectrometer operating at 200MHz or on a Bruker AMX400 instrument operating at 400 MHz. The solvent is deuteriochloroform except where indicated otherwise. Signals are singlets where no multiplicity is shown. Mass spectra where recorded under electron impact at 70 meV or under chemical ionisation (NH_3) on a VG Micromass 7070E instrument. M.p.'s were recorded on a Reichert hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase.

Ethyl pyrrole-2-(2-hydroxyimino)propanoate **1**.—Ethyl bromopyruvate oxime[5] (5.36 g, 25.5 mmol) was added to a stirred solution of pyrrole (13.2 mL, 190 mmol) in dichloromethane (120 mL) containing a suspension of anhydrous sodium carbonate (16.11 g, 120 mmol). The mixture was stirred at 20 °C under nitrogen for 16 h then filtered through Celite. The filtrate was evaporated to small volume and the excess of pyrrole was distilled off at 50 °C and 0.2 mmHg. Column chromatography [silica; dichloromethane-ethyl acetate (3:2)] gave the oxime **1** (3.07 g, 61%) as a light tan solid, m.p. 118-120 °C (from ethanol-hexane) (lit.,[5] m.p. 118-120 °C); d (400 MHz) 1.35 (3 H, t), 3.95 (2 H), 4.31 (2 H, q), 6.05 (1 H, d, 3-H of pyrrole), 6.08-6.10 (1 H, m, 4-H of pyrrole), 6.67-6.68 (1 H, m, 5-H of pyrrole) and 10.38 (1 H, br, NH). This compound was earlier reported to be a mixture which contained the 3-substituted pyrrole as a minor component[5] but in this preparation only the title compound was detected.

Ethyl pyrrole-2-(2-t-butoxycarboxamido)propanoate **2**.—The oximino ester **1** (1.0 g, 5.1 mmol) in aqueous THF (1:10; 44 mL) was reduced by reaction with aluminium amalgam prepared from aluminium foil.[7]

The reaction was monitored by TLC until the starting material had been consumed (1.5 h). The mixture was then filtered through Celite, the filter pad washed well with ethyl acetate, and the combined filtrate and washings were evaporated to small volume. Dichloromethane (25 mL) was added and the solution was dried over magnesium sulfate. The drying agent was filtered off, the filtrate was cooled to 0 °C, and triethylamine (0.71 mL, 5.0 mmol) was added followed by di-t-butyl dicarbonate (1.11 g, 5.0 mmol). The reaction mixture was stirred at 0 °C for 0.5 h then at 20 °C for 0.5 h, when TLC showed that all the amine had been consumed. The solution was washed with water and with aqueous sodium chloride, then dried ($MgSO_4$) and evaporated to leave a solid. This was washed with cold hexane to remove unreacted di-t-butyl dicarbonate Crystallization of the residue gave the *pyrrole* **2** (1.08 g, 77%) as a colourless solid, m.p. 106-108 °C (from dichloromethane-hexane) (Found: C, 59.5; H, 7.8; N, 9.9; m/z, 282.1580. $C_{14}H_{22}N_2O_4$ requires C, 59.6; H, 7.85; N, 9.9%; M, 282.1580); $\nu_{max.}$(KBr) 3 350, 1 736 and 1 690 cm^{-1}; δ (200 MHz) 1.26 (3 H, t), 1.44 (9 H), 3.11 (2 H, d, *J* 5.4), 4.19 (2 H, q), 4.48 (1 H, br), 5.13 (1 H, d, *J* 8.0, NH), 5.94-5.96 (1 H, m, 3-H of pyrrole), 6.09-6.12 (1 H, m, 4-H of pyrrole), 6.67-6.70 (1 H, m, 5-H of pyrrole) and 7.26 (1 H, br, NH).

Ethyl 5-trifluoroacetylpyrrole-2-(2-t-butoxycarboxamido)propanoate **3**.—To a stirred solution of the ester **2** (0.30 g, 1.1 mmol) in dry dichloromethane (10 mL) was added sodium carbonate (0.23 g, 2.1 mmol) and trifluoroacetic anhydride (0.18 mL, 1.3 mmol). There was an exothermic reaction. The mixture was stirred under nitrogen for 20 min. The solid was then filtered off and the filtrate was washed with water and dried ($MgSO_4$). The solvent was removed to leave a brown oil which crystallised on standing. Recrystallization gave the *pyrrole* **3** (0.32 g, 80%), m.p. 110-111.5 °C (from dichloromethane-hexane) (Found: C, 50.8; H, 5.6; N, 7.4. $C_{16}H_{21}F_3N_2O_5$ requires C, 50.8; H, 5.6; N, 7.4%); $\nu_{max.}$(KBr) 3 380, 3 200, 1 740 and 1 680 cm^{-1}; δ (200 MHz) 1.24 (3 H, t), 1.43 (9 H), 3.13 (1 H, dd, *J* 15.0 and 6.4, H of 3-CH_2), 3.28 (1 H, dd, *J* 15.0 and 5.3, H of 3-CH_2), 4.23 (2 H, q), 4.56-4.58 (1 H, m), 5.29 (1 H, br, NH), 6.17-6.20 (1 H, m, 3-H of pyrrole), 7.12-7.14 (1 H, m, 4-H of pyrrole) and 10.1 (1 H, br, NH); ^{19}F δ [376.32 MHz, $(CD_3)_2CO$] 4.04 (d, *J* 1.80); m/z (CI) 396 $(M + NH_4)^+$.

5-Trifluoroacetylpyrrole-2-(2-t-butoxycarboxamido)propanoic acid **4**.—Concentrated aqueous potassium hydroxide was added dropwise until in excess to a stirred solution of the ester **3** (0.80 g, 2.1 mmol) in ethanol (15 mL) at room temperature. After 10 min. TLC showed that the ester had completely reacted. The solution was diluted with water (30 mL) and the aqueous solution was washed with dichloromethane, then made acid with dilute hydrochloric acid. The product was extracted with ethyl acetate (3 x 20 mL) and the combined organic extracts were dried ($MgSO_4$). The solvent was evaporated off to give the *pyrrole* **4** (0.61 g, 82%), m.p. 156-157 °C (from dichloromethane-hexane) (Found: C, 48.0; H, 4.9; N, 8.0. $C_{14}H_{17}F_3N_2O_5$ requires C, 48.0; H, 4.9; N, 8.0%); $\nu_{max.}$(KBr) 3 470, 3 370, 3 310, 1 695 and 1 640 cm^{-1}; δ (200 MHz) 1.34 (9 H), 3.15 (1 H, dd, *J* 15.0 and 9.6, H of 3-CH_2), 3.37 (1 H, dd, *J* 15.0 and 4.8, H of 3-CH_2), 4.49-4.60 (1 H, m), 6.34 (1 H, br, NH), 6.35-6.37 (1 H, m, 3-H of pyrrole), 7.12-7.14 (1 H, m, 4-H of pyrrole) and 11.43 (1 H, br, NH); ^{19}F δ [376.32 MHz, $(CD_3)_2CO$] 4.08 (d, *J* 1.93); m/z (CI) 368 $(M + NH_4)^+$.

2-t-Butoxycarboxamido-1,2-dihydro-5-trifluoroacetylpyrrolizin-3-one **5**.—2-Chloro-4.6-dimethoxy-1,3,5-triazine[6] (0.144 g, 0.822 mmol) was added to a solution of the carboxylic acid **4** (0.240 g, 0.685 mmol) and *N*-methylmorpholine (0.09 mL, 0.82 mmol) in dry dichloromethane (15 mL) and THF (5 mL) at -10 °C. The reaction mixture was stirred under nitrogen and was allowed to warm to room temperature. After 4 h TLC showed that the starting material had been consumed. The solvent was evaporated off and the residue was dissolved in dichloromethane (40 mL). The solution was washed with dilute hydrochloric acid and with aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed to leave a solid which on crystallization gave the *pyrrolizinone* **5** (0.213 g, 94%), m.p. 165-166 °C (from dichloromethane-hexane) (Found: C, 50.6; H, 4:5; N, 8.45. $C_{14}H_{15}F_3N_2O_4$ requires C, 50.6; H, 4.55; N, 8.4%); $\nu_{max.}$(nujol) 3 350, 1 780 and 1 700 cm^{-1}; δ (400 MHz) 1.45 (9 H), 3.18 (1 H, dd, *J* 17.6 and 5.5, H of 1-CH_2), 3.57 (1 H, dd, *J* 17.6 and 8.7, H of 1-

CH_2), 4.61-4.64 (1 H, dd, br, 2-H), 5.29 (1 H, br, NH), 6.24 (1 H, d, *J* 3.8, 7-H) and 7.55 (1 H, approx. dd, *J* 3.8 and 1.8, 6-H); m/z (CI) 350 $(M + NH_4)^+$.

5-Formylpyrrole-2-(2-t-butoxycarboxamido)propanoic acid **6**.—Phosphorus oxychloride (0.30 mL, 3.2 mmol) was added to dry DMF (0.31 mL, 4.0 mmol) at 0 °C under nitrogen. The reaction mixture was kept at 0 °C for 5 min. then at 20 °C for 40 min. Dry dichloromethane (3 mL) was then added and the solution was cooled to 0 °C. A solution of the ester **3** (0.91 g, 3.2 mmol) in dichloromethane (7 mL) was added dropwise. After the addition was complete the reaction mixture was allowed to attain room temperature, the reaction being complet (TLC) after 15 min. Ethanol (20 mL) was added and aqueous potassium hydroxide (40%; 10 mL) was added dropwise. After 1.5 h the solution was diluted with water (30 mL) and the organic solvents were removed under reduced pressure. The aqueous solution was acidified with dilute hydrochloric acid and the product was extracted with dichloromethane (2 x 20 mL). The organic extracts were dried ($MgSO_4$) and evaporated to leave an oil which slowly solidified. Crystallization gave the *pyrrole* **6** (0.785 g, 87%), m.p. 79-81 °C (from dichloromethane-hexane) (Found: C, 55.7; H, 6.6; N, 9.8. $C_{13}H_{18}N_2O_5$ requires C, 55.3; H, 6.4; N, 9.9%); $\nu_{max.}$(KBr) 3 300-2800br, 3 310, 1 683 and 1 622 cm^{-1}; δ (200 MHz) 1.44 (9 H), 3.20-3.35 (2 H, br, 3-CH_2), 4.69 (1 H, br), 5.30-5.50 (1 H, m), 6.21(1 H, br, 3-H of pyrrole), 6.99 (1 H, br, 4-H of pyrrole), 9.18 (1 H, CHO) and 11.10 (1 H, br, NH); m/z (CI) 283 $(M + H)^+$.

2-t-Butoxycarboxamido-5-formyl-1,2-dihydropyrrolizin-3-one **7**.—Dicyclohexylcarbodiimide (0.50 g, 2.4 mmol) was added to a solution of the acid **6** (0.36 g, 1.27 mmol) in THF (15 mL) at 0 °C. The reaction mixture was stirred under nitrogen for 0.5 h and was allowed to warm to room temperature. After a further 0.5 h TLC showed that the starting material had been consumed and that two products had been formed. The dicyclohexylurea was filtered off and the fitrate was subjected to flash chromatography {silica; ethyl acetate-hexane (4:1)] which gave (R_f 0.62) a solid (0.058 g) which was tentatively identifiedas an acylurea derivative of the carboxylic acid and (R_f 0.45) a pale yellow solid which on crystallization gave the *pyrrolizinone* **7** (0.068 g, 20%), m.p. 162-164 °C (from dichloromethane-hexane) (Found: C, 59.0; H, 6.1; N, 10.6. $C_{13}H_{16}N_2O_4$ requires C, 59.1; H, 6.1; N, 10.6%); $\nu_{max.}$(KBr) 3 361, 1 769 and 1 674 cm^{-1}; δ (400 MHz) 1.46 (9 H), 3.16 (1 H, poorly resolved dd, H of 1-CH_2), 3.54 (1 H, dd, *J* 17.2 and 8.6, H of 1-CH_2), 4.59-4.62 (1 H, dd, br, 2-H), 5.34 (1 H, br, NH), 6.18 (1 H, d, *J* 3.5, 7-H), 7.55 (1 H, d, *J* 3.5, 6-H) and 10.20 (1 H, CHO); m/z (CI) 282 $(M + NH_4)^+$.

Ethyl pyrrole-2-(2-benzyloxycarboxamido)propanoate **8**.—The oximino ester **1** (4.85 g, 24.7 mmol) in aqueous THF (1:10; 110 mL) was reduced by reaction with aluminium amalgam prepared from aluminium foil.[7] The reaction was monitored by TLC until the starting material had been consumed (1.5 h). The mixture was then filtered through Celite and the filter pad was washed well with THF. To the filtrate was added sodium carbonate (8.0 g, 75 mmol) and benzyl chloroformate (7.0 mL, 4.94 mmol). The reaction mixture was stirred at 20 °C for 0.5 h, when TLC showed that all the amine had been consumed. The reaction mixture was filtered and the filtrate was subjected to flash chromatography which gave the *pyrrole* **8** (4.71 g, 60%) as an oil (Found: C, 64.2; H, 6.5; N, 8.5; m/z, 316.1420. $C_{17}H_{20}N_2O_4$ requires C, 64.5; H, 6.4; N, 8.85%; M, 316.1423); $\nu_{max.}$(KBr) 3 367 and 1 718 cm^{-1}; δ (400 MHz) 1.21 (3 H, t), 3.10 (2 H, d, *J* 5.3), 4.15 (2 H, q), 4.66 (1 H, br, 2-H), 5.08 (2 H), 5.51 (1 H, d, *J* 8.0, NH), 5.90-5.93 (1 H, m, 3-H of pyrrole), 6.08 (1 H, dd, *J* 5.6 and 2.5, 4-H of pyrrole), 6.61 (1 H, dd, *J* 2.5 and 2.0, 5-H of pyrrole), 7.31 (5 H) and 8.42 (1 H, br, NH).

Ethyl 5-trifluoroacetylpyrrole-2-(2-benzyloxycarboxamido)propanoate **9**.—To a stirred solution of the ester **8** (0.50 g, 1.6 mmol) in dry dichloromethane (30 mL) was added sodium carbonate (1.67 g, 15.8 mmol) and trifluoroacetic anhydride (0.27 mL, 2.0 mmol). There was an exothermic reaction. The mixture was stirred under nitrogen for 20 min. The solid was then filtered off and the filtrate was washed with water and dried ($MgSO_4$). The solvent was removed to leave a brown oil which crystallized on standing. Recrystallization gave the *pyrrole* **9** (0.45 g, 70%), m.p. 123-124 °C (from dichloromethane-hexane) (Found: C, 55.2; H, 4.6; N, 6.8;

m/z, 412.1247. $C_{19}H_{19}F_3N_2O_5$ requires C, 55.3; H, 4.6; N, 6.8%; M, 412.1246); $\nu_{max.}$(KBr) 3 292, 3 200, 1 746, 1 692 and 1 646 cm^{-1}; δ (200 MHz) 1.25 (3 H, t), 3.10-3.30 (2 H, m), 4.21 (2 H, q), 4.65-4.75 (1 H, m), 5.11 (2 H), 5.57 (1 H, br, NH), 6.14 (1 H, dd, *J* 3.7 and 2.7, 3-H of pyrrole), 7.10 (1 H, approx t, *J* 2.2, 4-H of pyrrole), 7.33 (5 H) and 9.95 (1 H, br, NH).

2-Benzyloxycarboxamido-1,2-dihydro-5-trifluoroacetylpyrrolizin-3-one **10**.—The ester **9** (0.19 g, 0.46 mmol) was hydrolyzed to the corresponding carboxylic acid (0.164 g, 93%), which was characterized only by NMR; δ [400 MHz, $(CD_3)_2CO$] 1.18 (3 H, t), 3.22 (1 H, dd, *J* 15.0 and 9.1, H of 3-CH_2), 3.38 (1 H, dd, *J* 15.0 and 4.3, H of 3-CH_2), 4.63 (1 H, br), 5.04 (2 H), 6.31 (1 H, 3-H of pyrrole), 6.75 (1 H, br, NH), 7.10 (1 H, 4-H of pyrrole), 7.28 (5 H) and 11.47 (NH). 2-Chloro-4.6-dimethoxy-1,3,5-triazine[8] (0.060 g, 0.33 mmol) was added to a solution of the carboxylic acid (0.0.10 g, 0.26 mmol) and *N*-methylmorpholine (0.04 mL, 0.33 mmol) in dry dichloromethane (15 mL) and THF (5 mL) at -10 °C. The reaction mixture was stirred under nitrogen and was allowed to warm to room temperature. After 4 h TLC showed that the starting material had been consumed. The solvent was evaporated off and the residue was dissolved in dichloromethane (40 mL). The solution was washed with dilute hydrochloric acid and with aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed to leave a solid which on crystallisation gave the *pyrrolizinone* **10** (0.076 g, 80%), m.p. 192-194 °C (from dichloromethane-hexane) (Found: C, 55.8; H, 3.55; N, 7.6. $C_{17}H_{13}F_3N_2O_4$ requires C, 55.7; H, 3.6; N, 7.65%); $\nu_{max.}$(KBr) 3 343, 1 786 and 1 700 cm^{-1}; δ [400 MHz, $(CD_3)_2CO$] 3.20 (1 H, dd, *J* 17.5 and 5.9, H of 1-CH_2), 3.65 (1 H, dd, *J* 17.5 and 8.4, H of 1-CH_2), 4.98 (1 H, dt, *J* 11.4 and 5.6, 2-H), 5.10 (2 H), 6.38(1 H, d, *J* 4.0, 7-H) 7.31 (1 H, d, *J* 4.0, 6-H), 7.36 (5 H) and 7.64 91 H, br, NH); m/z (EI) 366 (M^+, 0.2%), 275 (35) and 91(100).

Crystal data for $C_{17}H_{13}F_3N_2O_4$, **10**. M = 366.30, monoclinic, space group $P2_1/c$ (#14), a = 5.012(7), b = 10.529(7), c = 30.822(8), V = 1625(2) $Å^3$, Z = 4, D_c = 1.497 g cm^{-3}, F_{000} = 752, μ (Mo-Kα) = 1.23 cm^{-1}, T = 297 K. Number of independent intensities = 2979 from clear prism, 0.300 x 0.100 x 0.200 mm. R = 0.061, R_W = 0.059 for 1155 observed reflections [$I > 3.00\sigma(I)$] and 235 variable parameters.

X-Ray intensity measurements were made using the omega scan technique to a maximum 2Θ value of 45.0° on a Rigaku AFC6S diffractometer. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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