An unusual ring expansion from the Zav'yalov pyrrole synthesis: formation of oxacino[2,3-*c*]pyrroles

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Enamino acids 2 and 5 undergo a facile cyclisation to afford the pyrrole 3 and isoindole 6 ring systems; a novel two atom ring expansion ensues when derivatives 5b,d are subjected to the cyclisation conditions, resulting in the formation of the new oxacino[2,3-c]pyrrole system, the structure of which is confirmed by X-ray crystallography.

The pyrrole unit¹ occurs in a diversity of natural products, pharmaceutical agents and polymers.² The synthesis of this ring system has been the subject of intense activity and has featured in a number of review articles.^{3,4} Despite such activity, routes to 2,5-unsubstituted pyrroles and routes which involve the formation of the C-2–C-3 bond are particularly rare.⁴ There are several routes to pyrroles that utilise 1,3-dicarbonyl compounds and α -amino acids as the starting components, but in all of these examples the resulting pyrrole retains a carboxylate function at C-2.⁵ In 1973, Zav'yalov reported an efficient route to the pyrrole system (Scheme 1),⁶ which has been scarcely utilised in the last 25 years.⁷ We now report the application of this methodology to the synthesis of some novel substituted pyrroles and fused analogues and describe a unique ring expansion reaction to afford the new oxacino[2,3-*c*]pyrrole system.

Dimethylaminomethylene ketones 1 and 4 were obtained by standard protocols.⁸ Their addition–elimination reaction with a range of α -amino acids in aq. EtOH containing NaOAc gave the crystalline enamino acids 2 and 5 in high yields (Scheme 2).[†]

Heating a solution of enamino acids 2a, b and 5a, c in Ac₂O containing Et₃N proceeded with the instantaneous formation of a deep red colour which was accompanied by the vigorous evolution of CO₂ (lime water bubbler) as the internal reaction temperature reached reflux. In the case of **5b**, d, however, evolution of CO₂ was only slight. After *ca*. 30 min the reaction mixture was allowed to cool and was subjected to an aqueous work-up. TLC examination of the crude reaction mixtures typically revealed the presence of a fast running major component contaminated with dark base line material rendering initial purification by flash chromatography easy.

The cyclisation of enamino acid **2a** proceeded with the expected regioselectivity of cyclisation on to the more electrophilic ketonic carbonyl group rather than the ester function to afford a single pyrrole, **3a**, confirmed by the presence of signals in its ¹H NMR spectrum associated with the ethyl ester moiety. Of particular note is the efficient preparation of **3b**. Existing routes to compounds of this type are often laborious and low yielding.^{3c,f,h,4} Formation of the pyrroles **3** and isoindoles **6** and **9** is chemoselective, and in no instances did we observe the presence of any α -amino ketones resulting from a Dakin–West reaction.⁹

The ¹³C NMR spectra of **7** (from **5b**) and **8** (from **5d**) contained an additional low field signal at δ 168.9 (OAc) and



192.8 (C=O), respectively, when compared to the isoindoles **6a** and **b**. Elemental analysis and HRMS for **7** and **8** confirmed that both contained an additional CO₂ unit. The structure of **8**^{\ddagger} was established as the oxacino[2,3-*c*]pyrrole by X-ray crystallography (Fig. 1). The ¹H NMR spectrum of **8**^{\ddagger} displayed marked broadening of the signals associated with the aliphatic functions indicating that the molecule is undergoing conformational interconversion. The resolution of the spectrum was improved when it was recorded at low temperature (253 K).

It is evident from the ¹H NMR data that the eight-membered ring of **8** is in equilibrium between a number of conformers.¹⁰ However, **7** does not display this behaviour, probably as a



Scheme 2 Reagents and conditions: i, α -amino acid (1.05 equiv.) NaOAc.3H₂O (1.05 equiv.) eq. EtOH, Δ ; ii, Ac₂O, Et₃N (1.1 equiv.), Δ .



Fig. 1 X-Ray crystallographic structure of the oxacino[2,3-c]pyrrole 8.

consequence of the rigidity imparted to the ring by the enol acetate function.

Scheme 3 depicts a possible mechanism for the formation of the isoindoles $\hat{\mathbf{6}}$ and oxacinopyrrole 8. It is well established that the acylation of N-substituted amino acids proceeds with the formation of mesoionic 1,3-oxazolium-5-olates (munchnones) and evidence has accrued that these are tautomeric with N-acyl ketenes.¹¹ The mesoionic heterocycle 10 may react by two distinct pathways. We propose that, when R = phenyl, the extended conjugation imparts stability to the munchnone tautomer which then attacks the proximal C=O group. The alkoxide species thus generated forms the lactone 11 with concomitant oxazole ring cleavage. Cycloreversion of CO2 and subsequent O-acylation completes the route to the dihydroisoindoles **6a**,**b**. Conversely, $\hat{10}$ is destabilised when R = alkyl and the munchnone undergoes ring-chain tautomerism to the Nacyl ketene 12. Intramolecular acylation of the enamine function affords the spirocycle 13. Oxetane ring formation and subsequent ring cleavage of 14 effects the ring expansion to the oxacinopyrrole system. It is noteworthy that the formation of the oxacinopyrroles only occurs with the combination of an α alkyl amino acid and a cyclohexane-1,3-dione; replacement of either one of these components results in the formation of the pyrrole or isoindole as, for example, 9 which is derived from 2-hydroxymethylene-1-tetralone and glutamic acid 5-methyl ester.



In conclusion, this pyrrole synthesis is highly versatile and permits access to 2,5-unsubstituted pyrroles, 3-hydroxypyrrole derivatives, isoindoles and the novel oxacino[2,3-*c*]pyrroles.

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Notes and references

[†] All new compounds were fully characterised by ¹H and ¹³C NMR, HRMS and elemental analyses.

‡ Crystal data for **8**: C₁₇H₂₃NO₄, M = 305.36, triclinic, space group $P\overline{1}$, a = 7.7540(11), b = 8.8328(12), c = 12.476(2) Å, $\alpha = 78.530(14)$, $\beta = 89.250(12)$, $\gamma = 81.025(9)^\circ$, U = 827.0(2) Å³, $D_c = 1.226$ g cm⁻³, Z = 2, Cu-Kα radiation ($\lambda = 1.54184$ Å), $\mu = 0.71$ mm⁻¹, T = 160 K, R1 = 0.0471 ($F^2 > 2\sigma$), wR2 = 0.1095 (all data) for 2778 unique data and 205 parameters. CCDC 182/1130. Crystallographic data is available in CIF format from the RSC web site, see: http://www.rsc.org/suppdata/cc/1999/289/

§ *Selected data* for **8**: from **5d** (49.5%) after elution from silica with 40% EtOAc in hexane, as colourless cubes from EtOAc–hexane, mp = 152.5–153.5 °C, v_{max} (KBr)/cm⁻¹ 2962, 1766, 1742, 1670, 1594, 1524, 1274, 1189 cm⁻¹; $\delta_{\rm H}$ (CDCl₃, 253 K) 0.82 (3H, d, *J* 6.6, CHC*H*₃), 0.94 (3H, d, *J* 6.6, CHC*H*₃), 1.07 (3H, s, 7-CH₃), 1.27 (3H, s, 7-CH₃), 1.87 [1H, m, *J* 6.6, CH(CH₃)₂], 2.25 (1H, d, *J* 12.3, CH₂), 2.37 (1H, d, *J* 12.3, CH₂), 2.64–2.70 [1H, m, C*H*₂C*H*(CH₃)₂], 2.65 (3H, s, NAc), 2.79–2.83 [1H, m, *CH*₂CH(CH₃)₂], 2.92 (1H, d, *J* 12.3, CH₂), 2.99 (1H, d, *J* 12.3, CH₂), 7.70 (1H, s, 1-H); $\delta_{\rm C}$ (CDCl₃, 299 K) 22.1, 23.5, 28.2, 29.4, 33.2, 34.6, 42.5, 53.4, 120.0, 122.3, 126.5, 137.4, 169.0, 169.4, 192.8. Found C, 66.85; H, 7.60; N, 4.55; M⁺ 305.1627. C₁₇H₂₃NO₄ requires C, 66.85; H, 7.60; N, 4.60%; M⁺ 305.1627.

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