New Chemistry of Pyrrolizin-3-one: a Concise Route to 3,8-Didehydroheliotridin-5-one†

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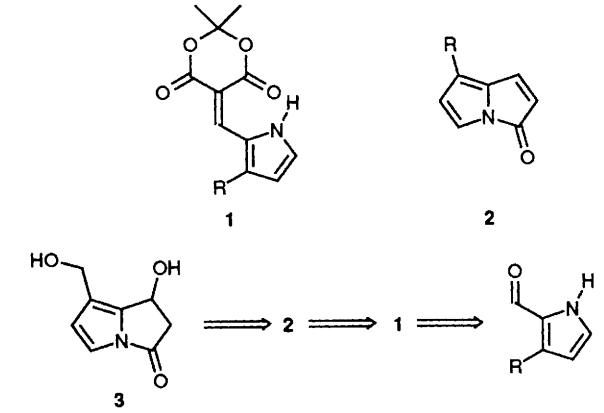
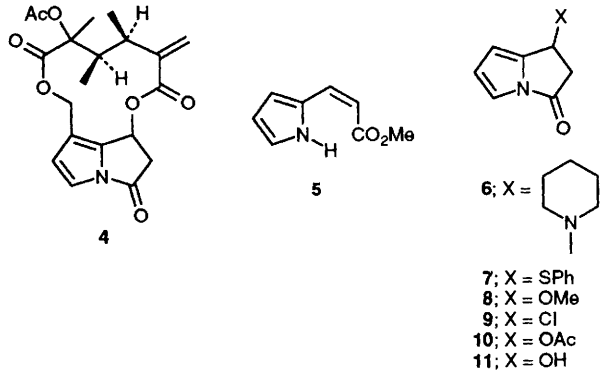
1-Substituted 1,2-dihydropyrrolizin-3-ones can be obtained from pyrrolizin-3-one **2** by conjugate nucleophilic addition or electrophilic addition reactions; the 1-chloro compound **9** obtained by the latter method is used as a key intermediate in a six-step synthesis of the title compound **3** from 4-acetoxymethylpyridine-*N*-oxide.

In 1981, we reported that flash vacuum pyrolysis (FVP) of the Meldrum's acid derivative **1** (R = H) leads to a highly efficient synthesis of the pyrrolizin-3-one system **2** (R = H).[1] This nucleus occurs as the heterocyclic unit 5,7a-didehydroheliotridin-3-one in **3** in a range of pyrrolizidine alkaloids such as pterophoron **4**,[2] which have been isolated from the *Senecio* species of Chile, Australia and South Africa.[3] In order to apply our route to such targets, we required methods of functionalising the 1,2-positions of pyrrolizin-3-one. However, very little is known about the chemistry of such ring systems.[4] A direct route to 3-substituted pyrrole-2-aldehydes would also be preferable (Scheme 1), since previous syntheses have relied on multi-step methods to create the required substitution pattern of the pyrrole ring.[5,6] We now report preliminary results of a fundamental study of pyrrolizinone chemistry which have allowed us to realise both of these objectives.

The 1-hydroxy-1,2-dihydropyrrolizinone functionality present in the alkaloids may be formally derived from **2** by conjugate addition of H_2O across the enone system, and so we first investigated the reaction of the parent compound **2** (R = H) with simple nucleophiles. Pyrrolizin-3-one proved to be inert to water or methanol under neutral conditions, but, as previously reported,[4] was rapidly ring opened by methoxide ion to give a quantitative yield of the *Z*-propenoate **5**.



Scheme 1



7; X = SPh
8; X = OMe
9; X = Cl
10; X = OAc
11; X = OH

† Heliotridine = 2,3,5,7a-tetrahydro-1-hydroxy-7-hydroxymethyl-1*H*-pyrrolizine; 5,7a-didehydroheliotridin-3-one was used for the title compound in ref. 6.

However, softer nucleophiles such as piperidine or thiophenol readily underwent the required conjugate addition in methanol solution to give **6**‡ (90%) or **7** (74%), respectively: the regiochemistry of this process was confirmed by an NOE (nuclear Overhauser effect) experiment on the phenylthio derivative **7** (Fig. 1). These reactions suggest possible routes to sulfur or nitrogen analogues of the natural products, but clearly nucleophilic addition methods cannot be applied to give the required hydroxy function.

On the basis of a minor pyrolysis byproduct,[7] we have previously suggested that the 1,2-double bond of pyrrolizin-3-one may be susceptible to electrophilic addition, even though it is deactivated by the carbonyl group. Possible complications due to acid hydrolysis of the formal lactam unit might also be anticipated. Surprisingly, the lactam function of **2** (R = H) proved to be completely inert under protic acid conditions. Thus, in 10% methanolic hydrogen chloride the addition product **8** was obtained, though only in low yield (22%). The reaction was dramatically improved by the use of non-protic solvents, and treatment of **2** (R = H) with dry hydrogen chloride in methylene dichloride gave the 1-chloro compound **9** (93%). This substituent proved to be particularly labile, and quenching with methanol, sodium acetate in glacial acetic acid, or even water (room temp., 20–30 min) gave the 1-methoxy- **8**, 1-acetoxy- **10**, or 1-hydroxy-**11** derivatives respectively in >85% yield. This simple two-step procedure has proved to be our method of choice for formal addition of water across the 1,2-position of pyrrolizin-3-ones, and is both more convenient and more efficient than an alternative hydrogenation–oxidation method which has been employed previously.[5]

Access to the previously unknown 7-substituted pyrrolizinones **2** required for the synthesis of the alkaloids necessitated the direct preparation of 3-substituted pyrrole-2-aldehydes. This proved possible by a copper sulfate mediated photochemical ring contraction of pyridine-*N*-oxides discovered by Streith and Bellamy[8] (*e.g.* Scheme 2, R = Me). Though yields

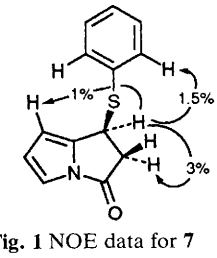
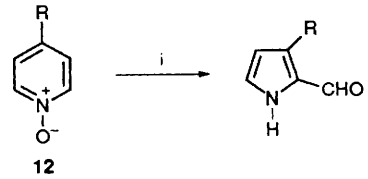


Fig. 1 NOE data for **7**



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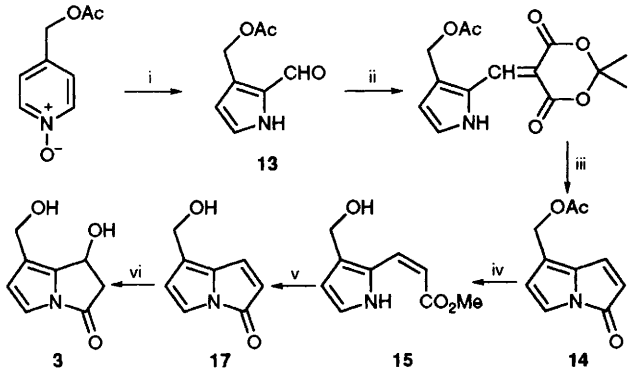
Scheme 2 *Reagents and conditions*: i, *hv*, $CuSO_4$, H_2O

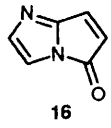
‡ All new compounds were characterised by elemental analysis or by accurate mass measurement.



Scheme 3 *Reagents and conditions*: i, *hν*, $CuSO_4$, H_2O (27%); ii, Meldrum's acid, piperidinium acetate (60%); iii FVP (600 °C) (90%); iv, K_2CO_3, MeOH (99%): v, FVP (650 °C) (60%); vi, HCl, CH_2Cl_2 then H_2O (63%)

were low (25–30%), the required aldehyde was obtained isomerically pure as the only significant product after continuous extraction of the aqueous photolysate followed by dry-flash chromatography. For this example, condensation with Meldrum's acid gave the 3-methyl derivative **1** (R = Me) which yielded the model 7-methylpyrrolizin-3-one **2** (R = Me) upon pyrolysis, in 66% overall yield. As expected,[9] cyclisation to the nitrogen atom is favoured over alternative cyclisation at the methyl group.[10]

With these results in hand, we were in a position to attempt a synthesis of **3** by the route shown in Scheme 3. Direct photolytic ring contraction of 4-hydroxymethylpyridine-*N*-oxide **12** (R = CH_2OH) was not successful, and so *O*-acetate protection was employed to give the previously unknown aldehyde **13** (27%). Condensation with Meldrum's acid was less efficient than usual, presumably for steric reasons, but FVP under the standard conditions gave the pyrrolizin-3-one **14** in 90% yield. Removal of the acetate protecting group was achieved with potassium carbonate in methanol, but even under these mild conditions the pyrrolizinone underwent ring opening to produce the *Z*-propenoate **15** in quantitative yield. Regeneration of the lactam ring was conveniently effected by FVP (650 °C); it is worth noting in passing that thermolysis of *Z*- (or *E*-) propenoates has proved to be a useful complement to the Meldrum's acid route to pyrrolizinones and related



systems, expecially for relatively involatile substrates. Thus, pyrrolo[1,2-*a*]imidazol-5-one **16** was made in 90% yield by this method, whereas the yield by the Meldrum's acid route was just 5%.[11]

Functionalisation of the enone unit of **17** was achieved as above by hydrochlorination followed by quenching with water. The product **3** had identical ^1H NMR parameters with those described in the literature,[6] and was obtained in 20% overall yield for the five steps from the aldehyde **13**. Further work will be required to optimise in particular the protection–deprotection steps, and it is hoped to report these in detail in a full paper.

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